Techniques in Organic Chemistry

Third Edition

Compatible with
Standard Taper Miniscale
14/10 Standard Taper Microscale
Williamson Microscale.
Includes Modern Spectroscopy

Jerry R. Mohrig
Christina Noring Hammond
Paul F. Schatz

Chemical resistance of common types of gloves to various compounds

	Glove type		
Compound	**Neoprene**	**Nitrile**	**Latex**
Acetone	good	fair	good
Chloroform	good	poor	poor
Dichloromethane	fair	poor	poor
Diethyl ether	very good	good	poor
Ethanol	very good	excellent	excellent
Ethyl acetate	good	poor	fair
Hexane	excellent	excellent	poor
Methanol	very good	fair	fair
Nitric acid (conc.)	good	poor	poor
Sodium hydroxide	very good	excellent	excellent
Sulfuric acid (conc.)	good	poor	poor
Toluene	fair	fair	poor

Common organic solvents

Name	**Boiling point (°C)**	**Density ($g \cdot ml^{-1}$)**	**Dielectric constant**	**Miscible with H_2O**
Acetone (2-propanone)	56.5	0.792	21	yes
Dichloromethane	40	1.326	9.1	no
Diethyl ether	35	0.713	4.3	no
Ethanol (95% aq. azeotrope)	78	0.816	27	yes
Ethanol (anhydrous)	78.5	0.789	25	yes
Ethyl acetate	77	0.902	6.0	slightly
Hexane	69	0.660	1.9	no
Methanol	65	0.792	33	yes
Pentane	36	0.626	1.8	no
2-Propanol (Isopropyl alcohol)	82.5	0.785	18	yes
Toluene	111	0.866	2.4	no

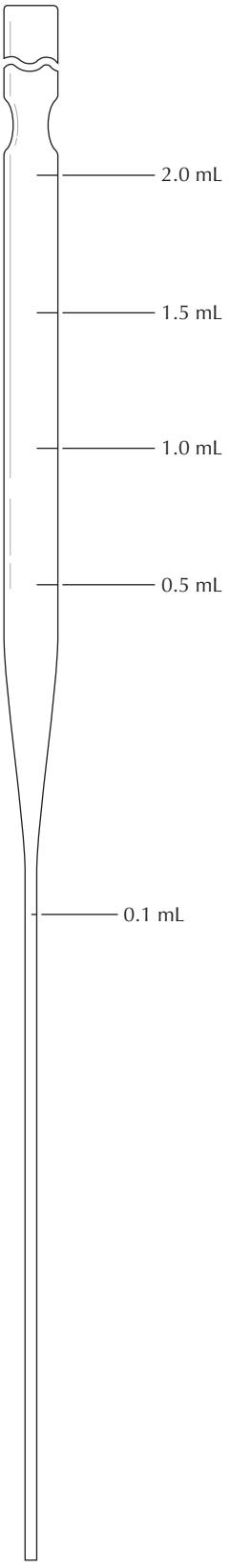
Selected data on common acid and base solutions

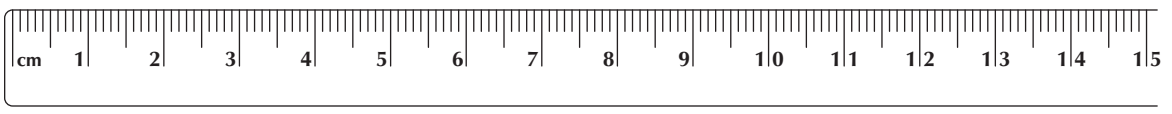
Compound	**Molarity**	**Density ($g \cdot ml^{-1}$)**	**% by weight**
Acetic acid (glacial)	17	1.05	100
Ammonia (concentrated)	15.3	0.90	28.4
Hydrobromic acid (concentrated)	8.9	1.49	48
Hydrochloric acid (concentrated)	12	1.18	37
Nitric acid (concentrated)	16	1.42	71
Phosphoric acid (concentrated)	14.7	1.70	85
Sodium hydroxide	6	1.22	20
Sulfuric acid (concentrated)	18	1.84	95–98

Quick reference for other important tables

Quick reference for other important figures

Quick reference for sections on sources of confusion





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Techniques in Organic Chemistry

Miniscale, Standard Taper Microscale, and Williamson Microscale

Third Edition

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Contents

Preface

The major focus of the Third Edition of *Techniques in Organic Chemistry* is the same as the focus of the earlier editions: the fundamental techniques that students encounter in the organic chemistry laboratory. However, we have also expanded our emphasis on the areas that students need to develop their skills in the critical interpretation of their experimental data and to successfully carry out guided-inquiry experiments.

Organic chemistry is an experimental science, and students learn its process in the laboratory. Our primary goal should be to teach students how to carry out well-designed experiments and draw reasonable conclusions from their results—a process at the heart of science. We should work to find opportunities that engage students in addressing questions whose answers come from their experiments, in an environment where they can succeed. These opportunities should be designed to catch students' interest, transporting them from passive spectators to active participants. A well-written and comprehensive textbook on the techniques of experimental organic chemistry is an important asset in reaching these goals.

Changes in the Third Edition

The Third Edition of *Techniques in Organic Chemistry* includes a number of new features. Entirely new sections have been added on planning a chemical reaction, computational chemistry, and ^{13}C nuclear magnetic resonance spectroscopy. A new chapter on UV-visible spectroscopy has been added. Many sections concerning basic techniques have been brought up to date and reorganized to better meet the practical needs of students as they encounter laboratory work.

A short essay introduces each of the five major parts of the Third Edition, on topics from the role of the laboratory to the spectroscopic revolution. Perhaps most important, the essay Intermolecular Forces in Organic Chemistry provides the basis for subsequent discussions on organic separation and purification techniques.

Many important features of earlier editions have been retained in the Third Edition. Subsections on sources of confusion again walk students through the pitfalls that could easily discourage them if they did not have this practical support. For easy reference, commonly used data on solvents and acids and bases, as well as quick references to frequently used techniques, are located inside the front cover. Data tables for IR and NMR spectroscopy appear inside the back cover and on the back foldout. We believe that these features will assist active learning as students encounter the need for this information during their laboratory work.

Who Should Use This Book?

The book is intended to serve as a laboratory textbook of experimental techniques for all students of organic chemistry. It can be used in conjunction with any lab experiments to provide the background and skills necessary for mastering the organic

chemistry laboratory. The book is written to provide effective support for guided-inquiry and design-based experiments and projects. It can also serve as a useful reference for laboratory practitioners and instructors.

Flexibility

Techniques in Organic Chemistry offers a great deal of flexibility. It can be used in any organic laboratory with any glassware. The basic techniques for using standard taper miniscale glassware as well as 14/10 standard taper microscale and Williamson microscale glassware are all covered. The miniscale glassware that is described is appropriate with virtually any 14/20 or 19/22 standard taper glassware kit.

Modern Instrumentation

Modern instrumental methods play a crucial role in supporting guided-inquiry experiments, which provide the active learning opportunities many instructors seek for their students. We feature instrumental methods that offer quick, reliable, quantitative data. NMR spectroscopy and gas chromatography are particularly important. Our emphasis is on how to acquire good data and how to read spectra efficiently and with real understanding. Chapters on ^{1}H and ^{13}C NMR, IR, and mass spectrometry stress the practical interpretation of spectra and how they can be used to answer questions posed in an experimental context. They describe how to deal with real laboratory samples and include case studies of analyzed spectra.

Organization

The book is divided into five parts:

- Part 1 has chapters on safety, green chemistry, and the lab notebook.
- Part 2 discusses glassware, measurements, heating methods, computational chemistry, and planning a chemical reaction.
- Part 3 introduces filtration, extraction, drying organic liquids, distillation, melting points, recrystallization, and a chapter on specialized techniques—sublimation, refractometry, measurement of optical activity, and inert atmosphere techniques.
- Part 4 presents the three chromatographic techniques widely used in the organic laboratory—thin-layer, liquid, and gas chromatography.
- Part 5 discusses IR, ^{1}H and ^{13}C NMR, MS, and UV-visible spectra in some detail.

Traditional organic qualitative analysis is available on our Web site: www.whfreeman.com/mohrig.

Modern Projects and Experiments in Organic Chemistry

The accompanying laboratory manual, *Modern Projects and Experiments in Organic Chemistry*, comes in two complete versions:

- *Modern Projects and Experiments in Organic Chemistry: Miniscale and Standard Taper Microscale* (ISBN 0-7167-9779-8)
- *Modern Projects and Experiments in Organic Chemistry: Miniscale and Williamson Microscale* (ISBN 0-7167-3921-6)

Modern Projects and Experiments is a combination of inquiry-based and traditional experiments, plus multiweek inquiry-based projects. It is designed to provide quality content, student accessibility, and instructor flexibility. This laboratory manual introduces students to the way the contemporary organic lab actually functions and allows them to experience the process of science.

Custom Publishing

All experiments and projects are available through LabPartner for Chemistry, Freeman Custom Publishing's newest offering. LabPartner provides instructors with a diverse database of experiments, selected from the extensive array published by W. H. Freeman and Hayden-McNeil Publishing. Instructors can use LabPartner to create their own customized lab manual by selecting specific experiments from *Modern Projects and Experiments,* adding experiments from other WHF or H-M titles, and incorporating their own original material so that the manual is organized to suit their course. Visit http://www.whfreeman.com/labpartner to learn more.

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We hope that teachers and students of organic chemistry find our approach to laboratory techniques effective, and we would be pleased to hear from those who use our book. Please write to us in care of the Chemistry Acquisitions Editor at W. H. Freeman and Company, 41 Madison Avenue, New York, NY 10010, or e-mail us at chemistry@whfreeman.com.

PART

1

Introduction to the Organic Laboratory

Essay — The Role of the Laboratory

Organic chemistry is an experimental science, and the laboratory is where you learn about "how we know what we know about it." The laboratory deals with the processes of scientific inquiry that organic chemists use. It demonstrates the experimental basis of what your textbook presents as fact. The primary goal of the laboratory is to help you understand how organic chemistry is done by actually doing it. Learning how to obtain and interpret experimental results and draw reasonable conclusions from them is at the heart of doing science. Your laboratory work will give you the opportunity to exercise your critical thinking abilities, to join in the process of science—to observe, to think, and to act.

To learn to do experimental organic chemistry, you need to master an array of techniques for carrying out and interpreting chemical reactions, separating products from their reaction mixtures, purifying products, and analyzing the results. *Techniques in Organic Chemistry* is designed to provide you with a sound fundamental understanding of the techniques that organic chemists use and the chemical principles they are based on. Mastering these techniques involves attention to detail and careful observations that will enable you to obtain accurate results and reach reasonable conclusions in your investigations of chemical phenomena.

While you are in the laboratory, you will have a variety of experiences—from learning basic techniques to running chemical reactions. Interpretation of your experimental results will involve consideration of the relationship between theory and experiment and provide reinforcement of what you are learning in the classroom. You may have the opportunity to do guided-inquiry experiments that ask you to answer a question or solve a problem by drawing conclusions from your experiments. You may also have the opportunity to synthesize an interesting organic compound by adapting a generic experimental procedure from the chemical literature.

Science is often done by teams of people working together on problems, and your experiments may involve teamwork with other students in your lab section. Some of your lab work may involve multiweek related experiments, which have a flexibility that may allow you to repeat a reaction procedure successfully if it didn't work well the first time. In fact, virtually all experimental results that are reported in chemical journals have been repeated many times before they are published.

Part of learning how to do organic chemistry in the laboratory includes learning how to do it safely. Technique 1 discusses laboratory safety and safe handling practices for the chemicals you will use. We urge you to read it carefully before you begin laboratory work.

TECHNIQUE 1

SAFETY IN THE LABORATORY

As you begin your study of experimental organic chemistry, you need a basic understanding of safety principles for handling chemicals and equipment in the laboratory. Consider this chapter to be required reading before you perform any experiments.

The organic chemistry laboratory is a place where accidents can and do occur and where safety is everyone's business. While working in the laboratory, you are protected by the instructions in an experiment and by the laboratory itself, which is designed to safeguard you from most routine hazards. However, neither the experimental directions nor the laboratory facilities can protect you from the worst hazard—your own or your neighbors' carelessness.

In addition to knowledge of basic laboratory safety, you need to learn how to work safely with organic chemicals. Many organic compounds are flammable or toxic. Some can be absorbed through the skin; others are volatile and vaporize easily into the air in the laboratory. Despite the hazards, organic compounds can be handled with a minimum of risk if you are adequately informed about the hazards and necessary safe handling procedures and if you use common sense while you are in the laboratory.

At the first meeting of your lab class, local safety issues will be discussed—the chemistry department's policies on safety goggles and protective gloves, the location of safety showers and eye wash stations, and the procedures to be followed in emergency situations. The information in this chapter is intended to complement your instructor's safety rules and instructions.

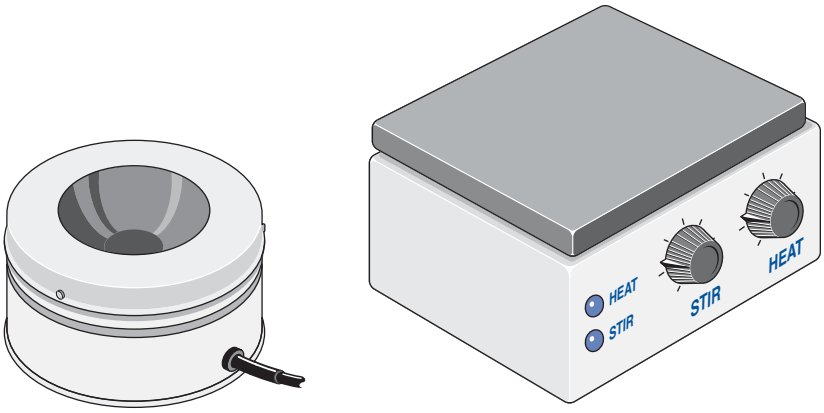
1.1 Causes of Laboratory Accidents

Laboratory accidents are of three general types: accidents involving fires and explosions, accidents producing cuts or burns, and accidents occurring from inhalation, absorption through the skin, or ingestion of toxic materials.

Fires and Explosions

Fire is the chemical union of a fuel with an oxidizing agent, usually molecular oxygen, and is accompanied by the evolution of heat and flame. Most fires involve ordinary combustible materials—hydrocarbons or their derivatives. Such fires are *extinguished* by removing oxygen or the combustible material or by decreasing the heat of the fire. Fires are *prevented* by keeping flammable materials away from a flame source or from oxygen (obviously, the former is easier).

Four sources of ignition are present in the organic laboratory: *open flames, hot surfaces* such as hot plates or heating mantles, *faulty electrical equipment,* and *chemicals.* The most obvious way to prevent a fire is to prevent ignition.



Ceramic heating mantle Hot plate/stirrer

FIGURE 1.1
Heating devices.

Open flames. Open-flame ignition of organic vapors or liquids is easily prevented: **Never bring a lighted Bunsen burner or a match near a low-boiling-point flammable liquid.** Furthermore, because vapors from organic liquids can travel over long distances at bench or floor level (they are heavier than air), an open flame within 10 ft of diethyl ether, pentane, or other low-boiling organic solvents is an unsafe practice. In fact, the use of a Bunsen burner or any other flame in an organic laboratory should be a rare occurrence and done only with the permission of your instructor.

Hot surfaces. A hot surface, such as a hot plate or heating mantle, presents a trickier problem (Figure 1.1). An organic solvent spilled or heated recklessly on a hot plate surface may burst into flames. The thermostat on most hot plates is not sealed and can spark when it cycles on and off. The spark can ignite flammable vapors from an open container such as a beaker. Remove any hot heating mantle or hot plate from the vicinity before pouring a volatile organic liquid because the vapors from the solvent can be ignited by the hot surface of a hot plate or a heating mantle.

Faulty electrical equipment. Do not use appliances with frayed or damaged electrical cords as their use could lead to an electrical fire.

Chemical fires. Chemical reactions sometimes produce enough heat to cause a fire and explosion. For example, in the reaction of metallic sodium with water, the hydrogen gas that forms in the reaction can explode and ignite a volatile solvent that happens to be nearby.

Cuts and Injuries

Cuts and mechanical injuries are hazards anywhere, including the laboratory.

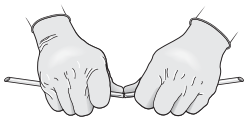


FIGURE 1.2
Breaking a glass rod properly.

Breaking glass rods or tubing. When you purposely break a glass rod or a glass tube, do it correctly. Score (scratch) a small line on one side of the tube with a file. Wet the scored line with a drop of water. Then, holding the tube on both sides with a paper towel and with the scored part away from you, quickly snap it by pulling the ends toward you (Figure 1.2).

Inserting glass into stoppers. Insert thermometers or glass tubes into corks, rubber stoppers, and thermometer adapters carefully and correctly. First, lubricate the end of the glass tube with a drop of water or glycerol. Then, while holding the tube with a towel **close** to the lubricated end, insert it slowly by firmly rotating it into the stopper. Never hold the thermometer by the end away from the stopper—it may break and the shattered end may be driven into your hand.

Chipped glassware. Check the rims of beakers, flasks, and other glassware for chips. Discard any piece of glassware that is chipped because you could be cut very easily by the sharp edge.

Inhalation, Ingestion, and Skin Absorption

Inhalation. The hoods in the laboratory protect you from inhalation of noxious fumes, toxic vapors, or dust from finely powdered materials. A hood is an enclosed space with a continuous flow of air that sweeps over the bench top, removing vapors or fumes from the area.

Because many compounds used in the organic laboratory are at least potentially dangerous, the best practice is to run every experiment in a hood, if possible. Your instructor will tell you when an experiment *must* be carried out in a hood. **Make sure that the hood is turned on before you use it.** Position the sash for the optimal airflow through the hood. If the optimum sash position is not indicated on the hoods in your laboratory, consult your instructor about how far to open the sash.

Ingestion. Ingestion of chemicals by mouth is easily prevented. **Never taste any substance or pipet any liquid by mouth.** Wash your hands with soap and water before you leave the laboratory. **No food or drink of any sort should be brought into a laboratory or eaten there.**

Absorption through the skin. Many organic compounds are absorbed through the skin. Wear the appropriate gloves while handling reagents and reaction mixtures. If you spill any substance on your skin, notify your instructor immediately, and wash the affected area thoroughly with water for 10–15 min.

1.2 Safety Features in the Laboratory

Organic laboratories contain many safety features for the protection and comfort of the people who work in them. It is unlikely that you will have to use the safety features in your lab, but in the event that you do, you must know what and where they are and how they operate.

Fire Extinguishers

Colleges and universities all have standard policies regarding the handling of fires. Your instructor will inform you whether evacuation of the lab or the use of a fire extinguisher takes priority at

your institution. **Learn where the exits from your laboratory are located.**

Fire extinguishers are strategically located in your laboratory. There may be several types, and your instructor may demonstrate their use. Your lab is probably equipped with either class BC or class ABC dry chemical fire extinguishers suitable for solvent or electrical fires.

Fire Blankets

Fire blankets are used for one thing and one thing only—to smother a fire involving a person's clothing. Fire blankets are available in most labs.

Safety Showers

Safety showers are for acid burns and other spills of corrosive, irritating, or toxic chemicals on the skin or clothing. If a safety shower is nearby, it can also be used when a person's clothing or hair is ablaze. The typical safety shower dumps a huge volume of water in a short period of time and thus is effective for both fire and acid spills, when speed is of the essence. **Do not use the safety shower routinely, but do not hesitate to use it in an emergency.**

Eye Wash Stations

You should always wear safety goggles while working in a laboratory, but if you accidentally splash something in your eyes, *immediately* use the eye wash station to rinse them with copious quantities of slightly warm water for 10–15 min. Learn the location of the eye wash stations in your laboratory and examine the instructions on them during the first (check-in) lab session.

First Aid Kits

Your laboratory or a nearby stockroom may contain a basic first aid kit consisting of such items as adhesive bandages, sterile pads, and adhesive tape for treating a small cut or burn. **All injuries, no matter how slight, should be reported to your instructor immediately.** Your instructor will indicate the location of the first aid station and instruct you in its use.

1.3 Preventing Accidents

Accidents can largely be prevented by common sense and knowledge of simple safety rules.

Personal Safety

1. Think about what you are doing while you are in the laboratory. Read the experiment before the laboratory session starts and perform laboratory operations with careful forethought.
2. It is a law in many states and common sense in the remainder to **wear safety glasses or goggles at all times in the laboratory.** Your institution may have a policy regarding wearing contact lenses in the laboratory; learn what it is and follow it. Wear clothing that covers and protects your body. **Shorts, tank tops, and sandals (or bare feet) are not suitable attire for the lab.** Avoid loose clothing and loose long hair, which are fire hazards or could become entangled in an apparatus. Laboratory aprons or lab coats may be required by your instructor. Always wash

your hands with soap and water at the end of the laboratory period.

3. **Never eat, chew gum, drink beverages, or apply cosmetics in the lab.**
4. Be aware of what your neighbors are doing. Many accidents and injuries in the laboratory are caused by other people. Often the person hurt worst in an accident is the one standing next to the place where the accident occurred. Make yourself aware of the procedures that should be followed in case of any accident. [See Technique 1.4].
5. **Never work alone in the laboratory.** Being alone in a situation in which you may be helpless can be life threatening.
6. Women who are pregnant or who become pregnant should discuss with the appropriate medical professionals the advisability of working in the organic chemistry laboratory.

Precautions When Handling Reagents

Never taste, ingest, or sniff directly any chemical. Always use the hood when working with volatile, toxic, or noxious materials. Handle all chemicals carefully, and remember that many chemicals can enter the body through the skin and eyes, as well as through the mouth and lungs.

Protective attire. Wear a lab coat or apron when working with hazardous chemicals. Cotton is the preferred fabric because synthetic fabrics could melt in a fire or undergo a reaction that causes the fabric to adhere to the skin and cause a severe burn.

Disposable gloves. Disposable gloves are available in all laboratories. **Wear gloves** to prevent chemicals from coming into contact with your skin unnecessarily. Table 1.1 lists a few common chemicals

TABLE 1.1 Chemical resistance of common types of gloves to various compounds

	GLOVE TYPE		
Compound	**Neoprene**	**Nitrile**	**Latex**
Acetone	good	fair	good
Chloroform	good	poor	poor
Dichloromethane	fair	poor	poor
Diethyl ether	very good	good	poor
Ethanol	very good	excellent	excellent
Ethyl acetate	good	poor	fair
Hexane	excellent	excellent	poor
Methanol	very good	fair	fair
Nitric acid (conc.)	good	poor	poor
Sodium hydroxide	very good	excellent	excellent
Sulfuric acid (conc.)	good	poor	poor
Toluene	fair	fair	poor

The information in this table was compiled from the Web site http://www.inform.umd.edu/CampusInfo/Departments/EnvirSafety/Is/gloves.html and from "Chemical Resistance and Barrier Guide for Nitrile and Natural Rubber Latex Gloves," Safeskin Corporation, San Diego, CA, 1996.

and the chemical resistance to each one provided by three common types of gloves. A more extensive chemical resistance table for types of gloves may be posted in your laboratory. Additional information on disposable gloves and tables listing glove types and their chemical resistance are also available from many Internet Web sites, for example:

http://www.microflex.com
http://www.ansellpro.com
http://www.des.umd.edu/ls/gloves
http://www.hazmat.msu.edu:591/glove_guide
http://www.admin.cam.ac.uk/offices/safety

Chemical hazards. Consult your instructor if you are in doubt about the safe handling procedures for any chemical. If you are handling a particularly hazardous compound, wear the appropriate type of gloves and know what the safe handling procedures for it are *before* you begin the experiment.

Flammable solvents. Flammable solvents with boiling points of less than 100°C, such as diethyl ether, methanol, pentane, hexane, and acetone, should be distilled, heated, or evaporated on a steam bath or heating mantle, **never on a hot plate or with a Bunsen burner**. Use an Erlenmeyer flask fitted with a cork—**never an open beaker**—for temporarily storing flammable solvents at your work area.

Order in the Laboratory

Keep your laboratory space clean and neat. In addition to your own bench area, the balance and chemical dispensing areas should be left clean and orderly. **If you spill anything while measuring out your chemicals, notify your instructor and clean it up immediately.** After weighing a chemical, replace the cap on the container and dispose of the weighing paper in the appropriate receptacle. Keep gas and water valves closed whenever they are not in use. Floors can become very slippery if water is spilled; wipe up any spill immediately.

Burns and Other Injuries

Remember that both glass and the tops of hot plates look the same when hot as when cold. When heating glass, do not touch the hot spot. Do not put hot glass on a bench where someone else might pick it up.

Steam and boiling water cause severe burns. Turn off the steam source before removing containers from the top of a steam bath or steam cone. The screw attached to the rounded handle that controls a steam line can become very hot; be careful not to touch it when you turn the steam on or off. Handle containers of boiling water very carefully.

Explosions

Never heat a closed system! Also, never completely close off an apparatus in which a gas is being evolved: always provide a vent in order to prevent an explosion.

1.4 What to Do if an Accident Occurs

If an accident occurs, act quickly, but think first. The first few seconds after an accident may be crucial. Acquaint yourself with the following instructions so that you can be of immediate assistance.

Fire

Your laboratory instructor will inform you on the first day of lab about the proper response to a fire. **It is important to know the policy of your institution concerning when to evacuate the building and when to use a fire extinguisher.**

In case of a fire in the lab, get out of danger and then immediately notify your instructor. If possible, remove any containers of flammable solvents from the fire area.

Know the location of the fire extinguishers and how they operate. A fire extinguisher will always be available. If you use one, aim low and direct its nozzle first toward the edge of the fire and then toward the middle. Tap water is not always useful for extinguishing chemical fires and can actually make some fires worse, so always use the fire extinguisher.

Be sure you know where the fire blanket and safety showers are located. If a person's clothing catches fire, **drop the person to the floor** and roll the person's body tightly in a fire blanket. If the blanket is wrapped around a person who is standing, it may direct the flames toward the person's face. If your clothing is on fire, do not run. Rapid movement fans flames.

General Policy Regarding Accidents

Always inform your instructor immediately of any accident that happens to you or your neighbors. **Let your instructor decide whether a physician's attention is needed.** If a physician's attention is necessary, an injured person should always be accompanied to the medical facility; the injury may be more serious than it initially appears.

Minor Cuts and Burns

Learn the location of the first aid kit and the materials it contains for the treatment of simple cuts and burns. **Notify your instructor immediately if you are cut or burned or if any chemical is spilled on your skin. Seek immediate medical attention** for anything except the most trivial cut or burn.

Cuts. Press on the cut to help slow the bleeding. Apply a bandage when the bleeding has ceased. If the cut is large or deep, seek immediate medical attention.

Heat burns. Apply cold water for 10–15 min to any heat burn. Seek immediate medical attention for any extensive burn.

Chemical burns. The first thing to do if any chemical is spilled on your skin, unless you have been specifically told otherwise, is to wash the area well with water for 10–15 min. This treatment will rinse away the excess chemical reagent. For acids, bases, and toxic chemicals, thorough washing with water will save pain later. Skin contact with a strong base usually does not produce immediate pain

or irritation, but serious tissue damage (especially to the eyes) can occur if the affected area is not immediately washed with copious amounts of water. Specific treatments for chemical burns are published in *The Merck Index*. Seek immediate medical treatment for any serious chemical burn.

Chemical splash in the eyes. If a chemical gets into your eyes, immediately go to the eye wash station and wash your eyes with a copious amount of slightly warm water. Position your head so that the stream of water from the eye wash fountain is directed at your eyes. **Hold your eyes open** to allow the water to flush the eyeballs for 10–15 minutes. Because this position is difficult, assistance may be required. Do not hesitate to call for help. Do not use very cold water because it can damage the eyeballs. Seek medical treatment immediately after using the eye wash for *any* chemical splash in the eyes.

If you are wearing contact lenses, they must be removed for the use of an eye wash station to be effective, an operation that is extremely difficult if a chemical is causing severe discomfort to your eyes. Therefore, **it is prudent not to wear contact lenses in the laboratory.**

1.5 Chemical Toxicology

Most substances are toxic at some level, but the level varies over a wide range. A major concern in chemical toxicology is quantity or dosage. It is important that you understand how toxic compounds can be handled safely in the organic laboratory.

The toxicity of a compound refers to its ability to produce injury once it reaches a susceptible site in the body. A compound's toxicity is related to its probability of causing injury and is a species-dependent term. What is toxic for people may not be toxic for other animals and vice versa. A substance is ***acutely toxic*** if it causes a toxic effect in a short time; it is ***chronically toxic*** if it causes toxic effects with repeated exposures over a long duration.

Fortunately, not all toxic substances that accidentally enter the body reach a site where they can be deleterious. Even though a toxic substance is absorbed, it is often excreted rapidly. Our body protects us with various devices: the nose, scavenger cells, metabolism, and rapid exchange of good air for bad. Many foreign substances are detoxified and discharged from the body very quickly.

Action of Toxic Substances on the Body

Although many substances are toxic to the entire system (arsenic, for example), many others are site specific. Carbon monoxide, for example, forms a complex with the hemoglobin in our blood, diminishing the blood's ability to absorb and release oxygen; it also poisons the action of mitochondrial aerobic metabolism.

In some cases, the metabolites of a compound are more toxic than the original compound. An example is methanol poisoning. The formic acid that is formed in the body's metabolism of methanol affects the optic nerve, causing blindness. The metabolism of some relatively harmless polycyclic aromatic hydrocarbons produces

potent carcinogenic compounds. As far as the body is concerned, it does not matter whether the toxicity is due to the original substance or to a metabolic product of it.

Toxicity Testing and Reporting

Consumers are protected by a series of laws that define toxicity, the legal limits and dosages of toxic materials, and the procedures for measuring toxicities.

Acute oral toxicity is measured in terms of LD_{50} (***LD*** stands for "lethal dose"). $\boldsymbol{LD_{50}}$ represents the dose, in milligrams per kilogram of body weight, that will be fatal to 50% of a certain population of animals. Other tests include dermal toxicity (skin sensitization) and irritation of the mucous membranes (eyes and nose). *The Merck Index* is a useful reference for the toxicity of organic compounds and lists the LD_{50} of many compounds.

The toxicity of virtually all chemical compounds that are commercially available has been reported, and every year the toxicities of many more compounds become known. Chemists and biologists have learned a great deal about toxicities in the past few decades. A wall chart of toxicities for many common organic compounds may be hanging in your laboratory or near your stockroom.

1.6 Where to Find Chemical Safety Information

Material Safety Data Sheets

All laboratories must make available a Material Safety Data Sheet (MSDS) for every chemical used in the laboratory. Every MSDS contains information on a list of topics required by law that describe the physical properties, hazards, safe handling and storage practices, and first aid information for the chemical. Manufacturers are required to prepare an MSDS for every chemical sold; the content is the same for a specific chemical, but the format in which the information is presented differs from one company to another. An MSDS from one company may be easy to read while that from another may be more difficult to understand.

MSDS information for thousands of compounds can be obtained easily on the Internet. The Web sites for chemical companies provide MSDSs for specific compounds as free, downloadable PDF files. Example companies are Sigma-Aldrich and Acros Organics:

http://www.sigmaaldrich.com

http://www.acros.com

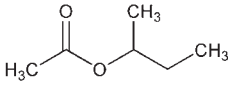
If your college or university subscribes to them, the following Web sites have downloadable PDF files of MSDSs:

http://www.MSDSonline.com

http://www.chemwatch.na.com

In addition to a complete MSDS, Chemwatch also provides mini MSDSs that briefly summarize the essential safety information for compounds in clear, concise language and pictograms.

1536. *sec*-Butyl Acetate. [105-46-4] Acetic acid 1-methylpropyl ester; acetic acid *sec*-butyl ester. $C_6H_{12}O_2$; mol wt 116.16. C 62.04%, H 10.41%, O 27.55%. Prepd from *sec*-butanol and acetic anhydride: R. Altschul, *J. Am. Chem. Soc.* **68**, 2605 (1946). Prepn of *d*- and *l*-form: J. Kenyon *et al., J. Chem. Soc.* **1935**, 1072. Manuf: *Faith, Keyes & Clark's Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 171-177.



***dl*-Form.** Liquid. d_{27} 0.865. bp_{761} 111-111.5°. n_D^{27} 1.3848. Flash pt, open cup: 88°F (31°C). Slightly sol in water; sol in alcohol, ether.

***d*-Form.** [66610-38-6] Acetic acid (1*S*)-1-methylpropyl ester. $[\alpha]_{546.1}^{18}$ +10.52° (neat).

***l*-Form.** [54657-08-8] Acetic acid (1*R*)-1-methylpropyl ester. Liquid, bp 116-117°. d_4^{19} 0.873. $[\alpha]_{546.1}^{19}$ −20.19° (neat). $[\alpha]_{546.1}^{19}$ −18.86° (c = 5.046 in ethanol). n_D^{18} 1.3899.

Caution: Potential symptoms of overexposure are irritation of eyes; headache; drowsiness; narcosis; dryness of upper respiratory system and skin. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 38.

FIGURE 1.3
Monograph 1536, for *sec*-Butyl acetate from page 256 of *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals,* 14th ed. (Reproduced with permission from *The Merck Index,* Fourteenth edition. Copyright © 2006 by Merck & Co., Inc., Whitehouse Station, NJ, USA. All rights reserved.)

The Merck Index

A brief synopsis of safety information for common organic compounds can be found in *The Merck Index*. The entry for sec-butyl acetate lists the caution information at the end (Figure 1.3).

Hazardous Materials Identification Systems

The labels on chemical containers carry warnings about the hazards involved in handling and shipping the compounds. The four-diamond symbol and a globally harmonized system of pictograms are the most commonly used hazardous materials identification systems.

Four-diamond symbol. Chemical suppliers put a color-coded, four-diamond symbol—developed by the National Fire Protection Association—on the container label of all reagents they sell (Figure 1.4). The four diamonds provide information on the hazards associated with handling the compounds:

fire hazard (top, red diamond)
reactivity hazard (right, yellow diamond)
specific hazard (bottom, white diamond)
health hazard (left, blue diamond)

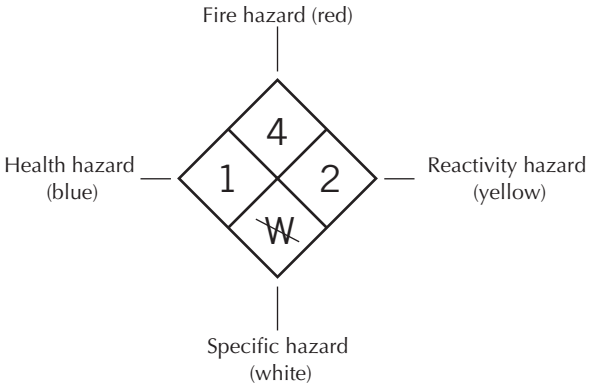


FIGURE 1.4
Four-diamond label for chemical containers indicating health, fire, reactivity, and special hazards. The symbol in the specific hazard diamond indicates that the compound is reactive with water and should not come into contact with it.

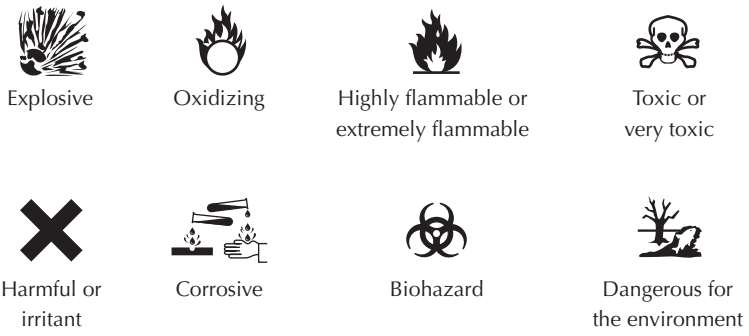


FIGURE 1.5
Globally Harmonized System (GHS) pictograms indicating chemical hazards.

The numerical values in the diamonds range from 0 to 4—0 indicates no chemical hazard and 4 indicates extreme chemical hazard.

Globally Harmonized System (GHS) of pictograms. Many chemical suppliers also indicate hazards by printing the universally understandable pictograms approved at the UN-sponsored Rio Earth Summit in 1992 on the labels of their reagents (Figure 1.5). Since then the pictograms have become a widely accepted standard on chemical labels around the world.

Other warnings found on chemical labels. Chemical labels may also include warnings such as "Irritant," "Lachrymator," "Cancer suspect agent," "Mutagen," or "Teratogen." Definitions of these terms follow:

Irritant: Substance causes irritation to skin, eyes, or mucous membranes.
Lachrymator: Substance causes irritation and watering of the eyes (tears).
Cancer suspect agent: Substance is carcinogenic in experimental animals at certain dose levels, by certain routes of administration, or by certain mechanisms considered relevant to human exposure. Available epidemiological data do not confirm an increased cancer risk in exposed humans.
Mutagen: Substance induces genetic changes.
Teratogen: Substance induces defects in a developing fetus.

Further Reading

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O'Neill, M. J.; Heckelman, P. A.; Koch, C. B.; Roman, K. J. (Eds.) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals;* 14th ed.; Merck & Co., Inc.: Whitehouse, NJ, 2006.

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TECHNIQUE 2

PROTECTING THE ENVIRONMENT

What you do in the laboratory extends beyond the laboratory itself. Every person working in a laboratory must also be aware of the impact that he or she has on the environment. Before disposing of anything in the lab, you should be conscious of how the disposal will affect the environment. Although zero waste is impossible, minimum waste is essential. Industries are now required to account for almost every gas, liquid, or solid waste they put into the environment. In the undergraduate laboratory, we should do the same.

2.1 Green Chemistry

One way to protect the environment is to reduce or eliminate the waste and by-products from chemical reactions and manufacturing processes that use chemical reagents and solvents. The term ***green chemistry*** has been given to new chemical reactions and processes that replace existing methods and that have the following characteristics:

- Use fewer and safer reagents and solvents.
- Reduce energy requirements.
- Utilize renewable resources whenever possible.
- Minimize or prevent the formation of waste.

The goal of green chemistry is to be as environmentally friendly as possible in the synthesis and utilization of chemicals both in the laboratory and in industrial and manufacturing applications.

How can an existing chemistry procedure be changed to one that could be called green chemistry? The first step is to ascertain the safety information on the reagents and solvents that are currently being used, as well as information on any toxic by-products that would remain after completion of the reaction. The next steps are to consider what would be safer, less toxic alternatives for the reactants and solvents and to ascertain whether another method would give the desired product using less hazardous materials. For example, consider replacement solvents that pose fewer health and environmental hazards.

Water

In the quest for solvents that minimize health hazards and risks to the environment, water would appear to be ideal because it is readily available and nonhazardous. But a requirement for most reaction solvents is that they dissolve the reagents used in the reaction, and a very large percentage of organic compounds are insoluble or only slightly soluble in water. However, reactions in aqueous solutions can be promoted in several ways with water-insoluble organic compounds, such as using vigorous stirring or phase-transfer catalysts.

Supercritical Carbon Dioxide

Carbon dioxide is a gas under normal conditions. Solid CO_2 (dry ice) ***sublimes,*** or vaporizes, from the solid to gaseous state without melting. When CO_2 is subjected to conditions of temperature and pressure that exceed its critical point, 31.1°C and 73 atm pressure, it becomes a single phase with properties intermediate between the properties of its gaseous and liquid states. A fluid above its critical-point temperature and pressure is called a ***supercritical fluid.***

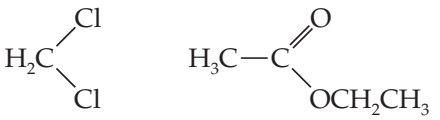
Supercritical CO_2 is a very good solvent with properties similar to many common organic solvents. The high-pressure equipment necessary to contain supercritical CO_2, however, makes its use in academic laboratories impractical. Supercritical CO_2 can replace traditional and hazardous solvents in industrial-scale chemical processes, include decaffeinating coffee, dry-cleaning clothing, cleaning electronic and industrial parts, and chemical reactions. At the end of these processes, the pressure is released and the escaping CO_2 gas can be easily recovered and recycled.

2.2 How Can a Laboratory Procedure Be Made Greener?

The following examples illustrate how an organic lab procedure can be made "greener" by the use of alternative solvents and reagents.

Example 1. Extraction of an Organic Compound from an Aqueous Mixture

The organic chemist frequently needs to separate an organic compound from an aqueous mixture using the process of ***extraction,*** in which the higher solubility of the organic compound in an organic solvent selectively transfers it from an aqueous mixture. Consider a procedure that specifies dichloromethane as a solvent for extracting caffeine from tea leaves. Assuming that both solvents dissolve the caffeine adequately, would ethyl acetate be a "greener" alternative?



Dichloromethane Ethyl acetate

We need to ascertain and evaluate the properties of ethyl acetate relative to those of dichloromethane to decide whether ethyl acetate would be a greener alternative.

Safety information. The safety information on the MSDS for dichloromethane indicates that the compound is a cancer suspect agent, toxic, a neurological hazard, and an irritant to the skin, eyes, and mucous membranes. The MSDS for ethyl acetate states that it is an irritant to the skin, eyes, and mucous membranes. Ethyl acetate certainly looks safer.

Relative volatilities of dichloromethane and ethyl acetate. Dichloromethane has a high volatility (evaporation rate) related to its low boiling point (40°C). The boiling point of ethyl acetate is 77°C. The higher boiling point of ethyl acetate gives it a lower volatility than

dichloromethane at room temperature, thus ethyl acetate does not evaporate as readily during the handling and transfers that occur while the extraction is in progress. However, the higher boiling point of ethyl acetate means that it requires more heat (energy) to remove the solvent and recover the caffeine than would dichloromethane.

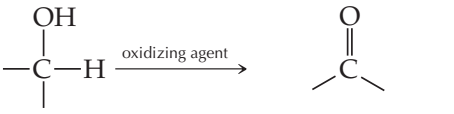
Solubility of water in the extraction solvent. For an extraction to be successful, the organic solvent and the aqueous phase must have a low solubility in one another. The solubility of water in ethyl acetate is five times greater than its solubility in dichloromethane. If we want to substitute ethyl acetate for dichloromethane as the extraction solvent, we need a way to decrease the solubility of water in ethyl acetate. The decrease can be accomplished by saturating the caffeine-containing aqueous mixture with sodium chloride, which reduces the amount of water that dissolves in ethyl acetate.

Relative costs of waste disposal. What happens to the solvent when the extraction of caffeine from tea is completed? It can be removed and recovered from the caffeine by distillation and possibly recycled for use in another application, but eventually the solvent becomes a waste that requires disposal either by burning in a process where the heat energy is recovered or by incineration where the heat is not recovered. Complete combustion of ethyl acetate produces carbon dioxide and water, whereas complete combustion of dichloromethane produces carbon dioxide, water, and hydrogen chloride. The HCl needs to be removed from the combustion gases before they are released to the atmosphere, a process that increases the disposal costs for chlorinated compounds relative to nonhalogenated compounds.

Justification for the substitution of ethyl acetate for dichloromethane. Using ethyl acetate instead of dichloromethane is less hazardous both to the person doing the procedure and to the environment. In addition, lower waste disposal costs make substitution of ethyl acetate a greener alternative than dichloromethane as the extraction solvent, despite the higher energy costs incurred with ethyl acetate.

Example 2. Oxidation of Alcohols to Ketones

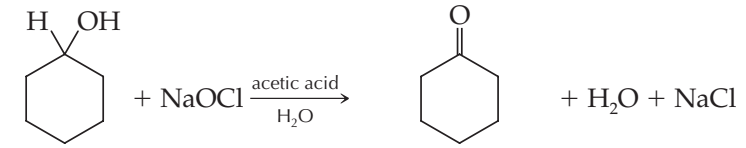
Chromium(VI) oxide (CrO_3) has been a traditional reagent for oxidizing an alcohol to a ketone.



Alcohol Carbonyl compound

The MSDS for CrO_3 indicates that it is highly toxic and a cancer suspect reagent. In addition, at the end of the reaction an equivalent amount of chromium(III) oxide is present as a by-product, requiring expensive disposal to prevent it from becoming an environmental contaminant. Household bleach, a 5.25% or 6.00% aqueous sodium hypochlorite (NaOCl) solution, is a green alternative for chromium(VI) oxide in oxidation reactions.

Oxidation of cyclohexanol. The oxidation of cyclohexanol with aqueous sodium hypochlorite solution in the presence of acetic acid is an example of green chemistry oxidation.[1]



Cyclohexanol Cyclohexanone

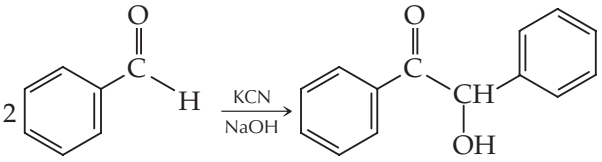
Stirring to facilitate the reaction. Cyclohexanol is a liquid at room temperature and is relatively insoluble in water. The water in the sodium hypochlorite solution provides the reaction medium. Even though cyclohexanol is largely insoluble in the aqueous sodium hypochlorite/acetic acid solution, vigorous stirring of the two phases increases the surface area of one liquid in contact with the other and greatly enhances the reaction rate.

Elimination of the extraction solvent. Cyclohexanone has traditionally been recovered from the two-phase reaction mixture by extraction with an organic solvent, such as diethyl ether. Steam distillation (codistillation of the organic compound with water) is a green alternative for separating the cyclohexanone from the inorganic salts in the aqueous reaction mixture. The tradeoffs for not using extractions to recover the product are a lower yield (50–60%) instead of the 70–80% that is possible using extractions, as well as higher energy costs, versus no organic solvent waste that would require disposal.

Nonhazardous by-products. This synthesis also qualifies as green chemistry because the by-products of the reaction, water and sodium chloride, are nonhazardous wastes that can be washed down the sink. Any excess acetic acid remaining in the aqueous solution can be neutralized with sodium carbonate to form acetate ion, also a nonhazardous waste that can be washed down the sink.

Example 3. Biochemical Catalysis

Biochemical catalysis is a green alternative to traditional catalysis in organic synthesis. Using thiamine (vitamin B_1) is a green alternative to using potassium cyanide (KCN), the traditional catalyst in the condensation of two benzaldehyde molecules to form benzoin.[2]



Benzaldehyde Benzoin

[1]Mohrig, J. R.; Neinhuis, D. M.; Linck, C. F.; Van Zoeren, C.; Fox, B. G.; Mahaffy, P. G. *J. Chem. Educ.* **1985,** *62,* 519–521.
[2]Mohrig, J. R.; Neckers, D. C. *Laboratory Experiments in Organic Chemistry;* 2nd ed.; Van Nostrand: New York, 1973, 184–187.

The MSDS for potassium cyanide indicates that it is highly toxic and readily absorbed through the skin. Its contact with acids produces highly toxic hydrogen cyanide gas. Vitamin B_1, in the form of thiamine, provides a far safer catalytic reagent for this reaction and eliminates the hazards and waste disposal costs of potassium cyanide. Thiamine is a naturally occurring compound and a renewable resource. The MSDS for thiamine indicates that it may be harmful when ingested in high concentrations, and it may cause allergic reactions.

Overview of Greening a Chemical Process

These three examples are a brief introduction to the ways in which chemical processes can be made greener. They are part of a continuing effort toward the goal of green chemistry—using chemistry in the synthesis and utilization of chemicals in as environmentally friendly a manner as possible. New manufacturing processes and chemical syntheses using green chemistry are being developed every day.

2.3 Fewer Reaction By-Products

In addition to finding greener alternatives for solvents and reagents, green chemistry is about finding ways to minimize or eliminate waste by generating fewer by-products in chemical reactions. Chemists generally regard the percentage yield of a chemical reaction as the measure of its success. However, the percentage yield does not indicate how much mass of the original reagents remains as by-products at the end of the reaction.

Atom Economy

The concept of atom economy was developed as a quantitative measure of how efficiently atoms of the starting materials and reagents are incorporated into the desired product.[3] Atom economy is defined as the percentage of atomic mass of all starting materials that appears in the final product, assuming 100% yield in the reaction. The balanced equation for the reaction is used in the calculation of atom economy.

Example 1. Consider the synthesis of 1-ethoxybutane, a substitution reaction in which an ethoxy group replaces the bromine atom of 1-bromobutane.

$$\underset{\substack{\text{1-Bromobutane}\\ \text{MW 137}}}{CH_3CH_2CH_2CH_2{-}Br} + \underset{\substack{\text{Sodium ethoxide}\\ \text{MW 68}}}{CH_3CH_2{-}O^-Na^+} \xrightarrow{CH_3CH_2OH} \underset{\substack{\text{1-Ethoxybutane}\\ \text{MW 102}}}{CH_3CH_2CH_2CH_2{-}O{-}CH_2CH_3} + NaBr$$

[3]Trost, B. M. *Science* **1991,** *254,* 1471–1477.

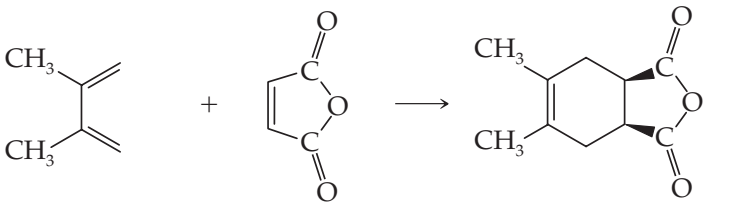
The atom economy for the reaction can be calculated as follows:

$$\text{atom economy} = \frac{\text{MW}_{\text{1-ethoxybutane}}}{\text{MW}_{\text{1-bromobutane}} + \text{MW}_{\text{sodium ethoxide}}} \times 100\%$$

$$= \frac{102}{137 + 68} \times 100\% = 50\%$$

Thus, only 50% of the atomic mass of the starting materials is incorporated into the product. The other 50% of the atomic mass of the starting materials is the by-product sodium bromide.

Example 2. Addition reactions are inherently high in atom economy because both reagents in the reaction are incorporated into the product. The Diels-Alder reaction is an example of an addition reaction.



2,3-Dimethyl-1,3-butadiene
MW 82.1

Maleic anhydride
MW 98.1

4,5-Dimethylcyclohex-4-ene-*cis*-1,2-dicarboxylic anhydride
MW 180.2

The atom economy for this synthesis is 100% because the sum of atomic mass of the reagents (82.1 + 98.1) is equal to the atomic mass of the product (180.2).

Reaction Efficiency

The concept of reaction efficiency was developed as a measure of the mass of reactant atoms actually contained in the final product.[4] If the 1-ethoxybutane from the synthesis described in Example 1 were obtained in a 65% yield, the reaction efficiency would be

$$\text{Reaction efficiency} = \%\ \text{yield} \times \text{atom economy}$$
$$= 65\% \times 0.50 = 33\%$$

The reaction efficiency indicates that only 33% of the mass of reactants was recovered as product in the synthesis and the other 67% became waste, making the synthesis less than ideal from an environmental perspective. If the yield for the Diels-Alder reaction in Example 2 were 80%, the reaction efficiency would also be 80%, indicating that only 20% of the total mass of reagents became waste in the synthesis, a much lower percentage than in the substitution reaction of Example 1. One goal of green chemistry is to design synthetic pathways that improve both the atom economy of a reaction and the percentage yield in order to minimize the waste produced by chemical reactions.

[4]Cann, M. C.; Dickneider, T. A. *J. Chem. Educ.* **2004**, *81*, 977–980.

2.4 Handling Laboratory Waste

Any person using chemicals in a laboratory has a legal and ethical responsibility to handle them properly from the moment of purchase and during storage and use and to follow appropriate disposal procedures. The common term for this mandate is "cradle to grave" responsibility.

At the end of every experiment you may have a number of reaction by-products, such as aqueous solutions from extractions, filter paper and used drying agent coated with organic liquids, the filtrate from the reaction mixture or a recrystallization, and possibly a metal catalyst or other materials that need proper disposal. It is your legal obligation, as well as that of your instructor, the stockroom personnel, and your institution, to collect and handle all laboratory wastes in a manner consistent with federal and state requirements.

Labels on Waste Containers

Your instructor will inform you of the locations of all waste containers in your laboratory. There may be a list posted in the lab or on the waste containers themselves stating what by-product or other waste from your experiment goes into each container. Placing a waste in the wrong type of container may lead to additional waste disposal costs. For example, if a halogenated compound is put into the flammable waste container, the entire contents of the container now become halogenated waste, which has higher disposal costs than flammable waste. In the worst-case scenario, placing a waste in the wrong container may cause a dangerous reaction to occur. **It is your responsibility to check carefully—and then double-check—the label on a waste container BEFORE you place any by-product in it.** If you are in doubt about what to do with something remaining from your experiment, consult your instructor.

In general, an organic laboratory has a hazardous waste container for liquid halogenated waste, one for flammable waste, one for aqueous waste, and one or more for solid waste, depending on what kind(s) of solid waste will be generated by the experiment. A ***halogenated waste*** container is *only* for disposal of organic waste containing fluorine, chlorine, bromine, or iodine. Nonhalogenated organic waste, such as solvents or filtrate from a recrystallization, is placed in a ***flammable waste*** container. An ***aqueous waste*** container is used for *neutralized* (pH 7) aqueous solutions such as the acidic or basic solutions remaining from extractions and any other aqueous solutions that cannot be poured into a sink. ***Solid waste*** containers are for such things as spent drying agents, filter paper coated with solvents, filter paper used in recrystallizations, and a specific solid material remaining after a reaction. All waste containers should be kept closed when not in use.

Compatibility of Waste with Its Container

A container for storing chemical waste needs to be compatible with the waste it will hold. For example, if waste that contains hexane is placed in a polyethylene container, it will soften the polyethylene and compromise the integrity of the container. If an acidic or

corrosive waste is placed in a metal container, the waste can react with the metal and cause the container to leak. In general, glass containers with tight-fitting caps are best for accumulating chemical waste in the laboratory before their removal to the campus site for storage of hazardous chemical waste.

Sink Disposal

Be aware of what your instructor says about which, if any, reaction by-products can be discarded into the sink. In the organic laboratory few reaction by-products or chemicals should be poured into a sink.

Further Reading

Green Chemistry

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National Research Council, *Prudent Practices in the Laboratory: Handling and Disposal of Chemicals;* National Academy Press: Washington, DC, 1995.

TECHNIQUE 3

LABORATORY NOTEBOOKS AND PRELABORATORY INFORMATION

Your laboratory notebook is the primary record of your experimental work. Keeping an accurate record of what you do and observe while working in the lab is a vital part of your laboratory experience. As part of your prelab preparation in setting up your notebook, you will need to find physical constants, such as melting and boiling points, densities, and other useful information on the organic compounds you will be using and synthesizing. Information on the physical constants and other properties of organic compounds is published in a number of handbooks and is also available from databases on the Internet.

3.1 The Laboratory Notebook

A few general comments are in order about the laboratory notebook. **All entries about your work must be made directly in your laboratory notebook in ink.** Although many campus bookstores sell notebooks that are specifically designed as lab notebooks, any

notebook with bound pages is usually sufficient. Spiral and three-ring binders are inappropriate for lab notebooks because pages can be easily removed or torn out. **Recording data on scraps of paper is an unacceptable practice** because the papers can easily be lost; this practice is probably strictly forbidden in your laboratory.

Set aside the first two or three pages of your lab notebook for a table of contents. The rest of the pages should be numbered sequentially, and **no page should ever be torn out** of your laboratory notebook. The notebook must be written with accuracy and completeness. It must be organized and legible, but it does not need to be a work of art.

Some flexibility in format and style may be allowed, but proper records of your experimental results must answer certain questions.

- ***When*** did you do the work?
- ***What*** are you trying to accomplish in the experiment?
- ***How*** did you do the experiment?
- ***What*** did you observe?
- ***How*** do you explain your observations?

A lab record needs to be written in three steps: **prelab, in lab, and postlab.** It should contain the following sections for each experiment you do.

Prelaboratory Preparation

The basic notebook setup discussed here is designed to help you prepare for an effective and safe experiment. Your instructor will undoubtedly provide specific guidelines for lab notebook procedures at your institution, but the notebook should generally have the following information:

Experiment title: Use a title that clearly identifies what you are doing in this experiment or project.

Date(s): Use the date on which an experiment is actually carried out. In some research labs, where patent issues are important, a witnessed signature of the date is required.

Statement of purpose: Write a brief statement of purpose for the experiment with a few words on any synthesis objective, as well as major analytical or conceptual approaches.

Safety information: Briefly list the safety precautions for all reagents and solvents you will use in the experiment [see Technique 1.6].

Waste disposal: If the procedure states how to dispose of the waste remaining from the experiment, briefly summarize the instructions in your notebook.

Balanced chemical reactions: Write balanced chemical equations that show the overall process. Any necessary details of reaction mechanisms go into the postlab summary section.

List the techniques to be used: For example: reflux, filtration, drying agents, distillation. You might want to list the page in your lab manual or techniques book where the figure of a particular glassware setup is shown, particularly if this is the first time you will be using it.

Table of reagents and solvents: This table normally lists molecular weights and the number of moles and grams of reagents. It also includes pertinent physical constants for the reagents, solvents, and product(s), such as the densities of liquid compounds, boiling points of compounds that are liquids at room temperature, and melting points of organic solids.

Method of yield calculation: Outline the computations to be used in a synthesis experiment, including calculation of the theoretical yield [see Technique 3.2].

Procedure outline: Write a procedural outline in sufficient detail so that the experiment could be done without reference to your lab textbook. This outline is especially important in experiments where you have designed the procedure.

Prelab questions: Answer any assigned prelab questions.

In the Laboratory

Recording observations during the experiment is a crucial part of your laboratory record. If your observations are incomplete, you cannot interpret the results of your experiments once you have left the laboratory. It is difficult, if not impossible, to reconstruct them at a later time.

Observations **must be recorded in your lab notebook in ink while you are doing an experiment.** You must record the **actual quantities** of all reagents as they are used, as well as the amounts of crude and purified products you obtain. Mention which measurements (temperature, time, melting point, and so on) you took and which spectra you recorded or which samples you prepared for later analysis.

Because organic chemistry is primarily an experimental science, your observations are crucial to your success. Things that seem insignificant may be important in understanding and explaining your results later. Typical laboratory observations might be as follows:

- A white precipitate appeared, which dissolved when sulfuric acid was added.
- The solution turned cloudy when it was cooled to 10°C.
- An additional 10 mL of solvent were required to completely dissolve the yellow solid.
- The reaction was heated at 50°C for 25 min on a water bath.
- A small puff of white smoke appeared when sodium hydroxide was added to the reaction mixture.
- The NMR sample was prepared with 20 mg of product, using 0.7 mL of $CDCl_3$.
- A capillary OV–101 GC column heated to 137°C was used.
- The infrared spectrum was obtained from a cast-film sample.

Your observations may be recorded in a variety of ways. They may be written on right-hand pages across from the corresponding section of the experimental outline on a left-hand page, or the page may be divided into columns with the left column used for procedure and the right column for observations. It is a good idea to cross-index your observations to specific steps in the procedure

that you have written. Your instructor will probably provide specific advice on how you should record your observations during the laboratory.

Be aware of the physical properties of the reagents and solvents that you included in your prelab preparations while you are carrying out an experiment. For example, the low boiling point of diethyl ether (34.6°C) indicates high volatility at room temperature.

Postlaboratory Interpretation of Your Experimental Results

In this section of the notebook you summarize and interpret your experimental data. Entries include a section on interpretation of physical and spectral data, a summary of your conclusions, calculation of the percent yield, and answers to any assigned postlab questions.

Conclusions and summary: In an inquiry-based project or experiment, return to the question being addressed and discuss the conclusions you can draw from analysis of your data. For both inquiry-based experiments and those where you learned about laboratory techniques and the design of organic syntheses, discuss how your experimental results support your conclusions. Include a thorough interpretation of NMR and IR spectra and other analytical results, such as TLC and GC analyses. Properly labeled spectra and chromatograms should be stapled into your notebook. Cite any reference sources that you used.

Percent yield: The single most important measure of success in a chemical synthesis is the quantity of product that is produced. To be sure, the purity of the product is also crucial, but if a synthetic method produces very small amounts of the needed product, it is not much good. Reactions on the pages of textbooks are often far more difficult to carry out in good yield than the books suggest. Calculation of the percent yield is discussed in Technique 3.2.

3.2 Calculation of the Percent Yield

When you report the results of a synthesis reaction, the percent yield is always stated. The percent yield is defined as the ratio of the mass of product obtained to the theoretical yield (maximum amount possible), multiplied by 100:

$$\%\ \text{yield} = \frac{\text{actual yield of product}}{\text{theoretical yield}} \times 100$$

You calculate the theoretical yield from the balanced chemical equation and the amount of limiting reagent, assuming 100% conversion of the starting materials to product(s). For example, consider the synthesis of 1-ethoxybutane from 1-bromobutane and sodium ethoxide. Notice that in the balanced reaction one mole of product is

produced from one mole of 1-bromobutane and one mole of sodium ethoxide.

$$\underset{\substack{\text{1-Bromobutane}\\ \text{MW 137}\\ \text{density 1.27 g}\cdot\text{mL}^{-1}}}{CH_3(CH_2)_3{-}Br} + \underset{\text{Sodium ethoxide MW 68.1}}{CH_3CH_2{-}O^-Na^+} \xrightarrow{\text{ethanol}} \underset{\text{1-Ethoxybutane MW 102}}{CH_3(CH_2)_3{-}O{-}CH_2CH_3} + NaBr$$

The procedure specifies 4.50 mL of 1-bromobutane, 3.70 g of sodium ethoxide, and 20 mL of anhydrous ethanol. To calculate the theoretical yield, it is necessary to ascertain whether 1-bromobutane or sodium ethoxide is the limiting reagent by calculating the moles of each reagent present in the reaction mixture:

$$\text{moles of 1-bromobutane} = \frac{4.50\ \text{mL} \times 1.27\ \text{g}\cdot\text{mL}^{-1}}{137\ \text{g}\cdot\text{mol}^{-1}} = 0.0417\ \text{mol}$$

$$\text{moles of sodium ethoxide} = \frac{3.70\ \text{g}}{68.1\ \text{g}\cdot\text{mol}^{-1}} = 0.0543\ \text{mol}$$

Therefore, 1-bromobutane is the limiting reagent.

According to the balanced equation, equimolar amounts of the two reactants are required. Thus the theoretical yield, the maximum amount of product that is possible from the reaction assuming that it goes to completion and that no experimental losses occur, is 0.0417 mol or 4.25 g of ethoxybutane:

$$\begin{aligned}\text{theoretical yield} &= 0.0417\ \text{mol} \times 1.02\ \text{g}\cdot\text{mol}^{-1}\\ &= 4.25\ \text{g of 1-ethoxybutane}\end{aligned}$$

The percent yield for a synthesis that produced 2.70 g of 1-ethoxybutane is 63.5%:

$$\%\ \text{yield} = \frac{2.7\ \text{g}}{4.2\ \text{g}} \times 100 = 64\%$$

3.3 Sources of Prelaboratory Information

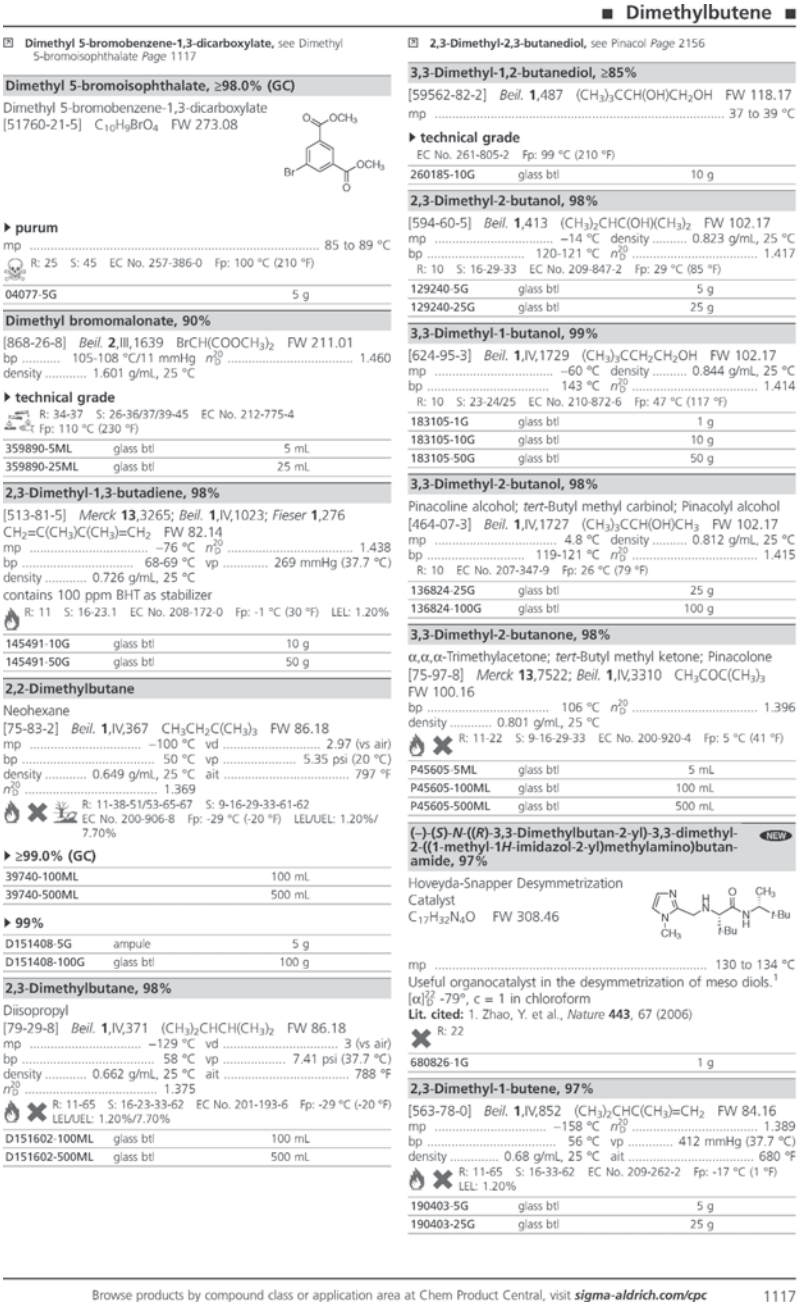
The traditional sources of prelaboratory information on physical constants and safety information about chemicals have been handbooks. Today, there are many Internet Web sites where this type of information is also readily accessed. Both handbooks and the Internet are useful sources of prelaboratory information.

Handbooks

Three handbooks are particularly useful for physical constants of organic compounds: the *Aldrich Handbook of Fine Chemicals*, the *CRC Handbook of Chemistry and Physics*, and *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.*

Aldrich Handbook of Fine Chemicals. The *Aldrich Handbook of Fine Chemicals* is published biennially by the Aldrich Chemical Company of Milwaukee, Wisconsin. It lists thousands of organic and inorganic compounds and includes the chemical structure for each one, a brief

summary of its physical properties, references on IR, UV, and NMR spectra, plus safety and disposal information. There are also references to *Beilstein's Handbook of Organic Chemistry* and to *Reagents for Organic Synthesis* by Fieser and Fieser [see Technique 9.5 for more information about these reference works]. Figure 3.1 shows a page from the 2009–2010 *Aldrich Handbook of Fine Chemicals.*



■ Dimethylbutene ■

Dimethyl 5-bromobenzene-1,3-dicarboxylate, see Dimethyl 5-bromoisophthalate *Page* 1117

Dimethyl 5-bromoisophthalate, ≥98.0% (GC)

Dimethyl 5-bromobenzene-1,3-dicarboxylate
[51760-21-5] $C_{10}H_9BrO_4$ FW 273.08

▸ **purum**
mp ..... 85 to 89 °C
R: 25 S: 45 EC No. 257-386-0 Fp: 100 °C (210 °F)

04077-5G		5 g

Dimethyl bromomalonate, 90%

[868-26-8] *Beil.* **2**,III,1639 $BrCH(COOCH_3)_2$ FW 211.01
bp ..... 105-108 °C/11 mmHg n_D^{20} 1.460
density ..... 1.601 g/mL, 25 °C

▸ **technical grade**
R: 34-37 S: 26-36/37/39-45 EC No. 212-775-4
Fp: 110 °C (230 °F)

359890-5ML	glass btl	5 mL
359890-25ML	glass btl	25 mL

2,3-Dimethyl-1,3-butadiene, 98%

[513-81-5] *Merck* **13**,3265; *Beil.* **1**,IV,1023; *Fieser* **1**,276
$CH_2=C(CH_3)C(CH_3)=CH_2$ FW 82.14
mp ..... −76 °C n_D^{20} 1.438
bp ..... 68-69 °C vp ..... 269 mmHg (37.7 °C)
density ..... 0.726 g/mL, 25 °C
contains 100 ppm BHT as stabilizer
R: 11 S: 16-23.1 EC No. 208-172-0 Fp: -1 °C (30 °F) LEL: 1.20%

145491-10G	glass btl	10 g
145491-50G	glass btl	50 g

2,2-Dimethylbutane

Neohexane
[75-83-2] *Beil.* **1**,IV,367 $CH_3CH_2C(CH_3)_3$ FW 86.18
mp ..... −100 °C vd ..... 2.97 (vs air)
bp ..... 50 °C vp ..... 5.35 psi (20 °C)
density ..... 0.649 g/mL, 25 °C ait ..... 797 °F
n_D^{20} 1.369
R: 11-38-51/53-65-67 S: 9-16-29-33-61-62
EC No. 200-906-8 Fp: -29 °C (-20 °F) LEL/UEL: 1.20%/7.70%

▸ **≥99.0% (GC)**

39740-100ML		100 mL
39740-500ML		500 mL

▸ **99%**

D151408-5G	ampule	5 g
D151408-100G	glass btl	100 g

2,3-Dimethylbutane, 98%

Diisopropyl
[79-29-8] *Beil.* **1**,IV,371 $(CH_3)_2CHCH(CH_3)_2$ FW 86.18
mp ..... −129 °C vd ..... 3 (vs air)
bp ..... 58 °C vp ..... 7.41 psi (37.7 °C)
density ..... 0.662 g/mL, 25 °C ait ..... 788 °F
n_D^{20} 1.375
R: 11-65 S: 16-23-33-62 EC No. 201-193-6 Fp: -29 °C (-20 °F)
LEL/UEL: 1.20%/7.70%

D151602-100ML	glass btl	100 mL
D151602-500ML	glass btl	500 mL

2,3-Dimethyl-2,3-butanediol, see Pinacol *Page* 2156

3,3-Dimethyl-1,2-butanediol, ≥85%

[59562-82-2] *Beil.* **1**,487 $(CH_3)_3CCH(OH)CH_2OH$ FW 118.17
mp ..... 37 to 39 °C

▸ **technical grade**
EC No. 261-805-2 Fp: 99 °C (210 °F)

260185-10G	glass btl	10 g

2,3-Dimethyl-2-butanol, 98%

[594-60-5] *Beil.* **1**,413 $(CH_3)_2CHC(OH)(CH_3)_2$ FW 102.17
mp ..... −14 °C density ..... 0.823 g/mL, 25 °C
bp ..... 120-121 °C n_D^{20} 1.417
R: 10 S: 16-29-33 EC No. 209-847-2 Fp: 29 °C (85 °F)

129240-5G	glass btl	5 g
129240-25G	glass btl	25 g

3,3-Dimethyl-1-butanol, 99%

[624-95-3] *Beil.* **1**,IV,1729 $(CH_3)_3CCH_2CH_2OH$ FW 102.17
mp ..... −60 °C density ..... 0.844 g/mL, 25 °C
bp ..... 143 °C n_D^{20} 1.414
R: 10 S: 23-24/25 EC No. 210-872-6 Fp: 47 °C (117 °F)

183105-1G	glass btl	1 g
183105-10G	glass btl	10 g
183105-50G	glass btl	50 g

3,3-Dimethyl-2-butanol, 98%

Pinacoline alcohol; *tert*-Butyl methyl carbinol; Pinacolyl alcohol
[464-07-3] *Beil.* **1**,IV,1727 $(CH_3)_3CCH(OH)CH_3$ FW 102.17
mp ..... 4.8 °C density ..... 0.812 g/mL, 25 °C
bp ..... 119-121 °C n_D^{20} 1.415
R: 10 EC No. 207-347-9 Fp: 26 °C (79 °F)

136824-25G	glass btl	25 g
136824-100G	glass btl	100 g

3,3-Dimethyl-2-butanone, 98%

α,α,α-Trimethylacetone; *tert*-Butyl methyl ketone; Pinacolone
[75-97-8] *Merck* **13**,7522; *Beil.* **1**,IV,3310 $CH_3COC(CH_3)_3$
FW 100.16
bp ..... 106 °C n_D^{20} 1.396
density ..... 0.801 g/mL, 25 °C
R: 11-22 S: 9-16-29-33 EC No. 200-920-4 Fp: 5 °C (41 °F)

P45605-5ML	glass btl	5 mL
P45605-100ML	glass btl	100 mL
P45605-500ML	glass btl	500 mL

(−)-(*S*)-*N*-((*R*)-3,3-Dimethylbutan-2-yl)-3,3-dimethyl-2-((1-methyl-1*H*-imidazol-2-yl)methylamino)butanamide, 97% NEW

Hoveyda-Snapper Desymmetrization Catalyst
$C_{17}H_{32}N_4O$ FW 308.46

mp ..... 130 to 134 °C
Useful organocatalyst in the desymmetrization of meso diols.[1]
$[\alpha]_D^{22}$ -79°, c = 1 in chloroform
Lit. cited: 1. Zhao, Y. et al., *Nature* **443**, 67 (2006)
R: 22

680826-1G		1 g

2,3-Dimethyl-1-butene, 97%

[563-78-0] *Beil.* **1**,IV,852 $(CH_3)_2CHC(CH_3)=CH_2$ FW 84.16
mp ..... −158 °C n_D^{20} 1.389
bp ..... 56 °C vp ..... 412 mmHg (37.7 °C)
density ..... 0.68 g/mL, 25 °C ait ..... 680 °F
R: 11-65 S: 16-33-62 EC No. 209-262-2 Fp: -17 °C (1 °F)
LEL: 1.20%

190403-5G	glass btl	5 g
190403-25G	glass btl	25 g

Browse products by compound class or application area at Chem Product Central, visit ***sigma-aldrich.com/cpc*** 1117

D

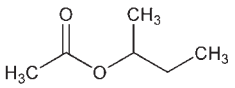
FIGURE 3.1 Page 1117 from the 2009–2010 *Sigma-Aldrich Handbook of Fine Chemicals.* Listings provide a summary of the physical properties for each compound. (Reprinted with permission from Aldrich Chemical Co., Inc., Milwaukee, WI.)

CRC Handbook of Chemistry and Physics. The *CRC Handbook of Chemistry and Physics* is a commonly used handbook that is published annually. The *CRC Handbook* contains a wealth of information, including extensive tables of physical properties and solubilities, as well as structural formulas, for more than 12,000 organic and 2400 inorganic compounds.

To locate an organic compound successfully, you must pay close attention to the nomenclature used in the tables. In general, IUPAC nomenclature is followed, but a compound usually known by its common name may be listed under both names or even only under the common name. For example, the primary name of CH_3CO_2H is listed in the *CRC Handbook* as acetic acid, with ethanoic acid (its IUPAC name) given as the secondary name. No entry for ethanoic acid is listed. Conversely, the listing for $CH_3(CH_2)_5Br$ has 1-bromohexane as the primary name of the compound and *n*-hexyl bromide as the secondary name (synonym). In earlier editions of the *CRC Handbook* substituted derivatives of compounds were listed under the heading of the parent compound rather than simply in alphabetical order by the first letter of the compound's name. For example, 1-bromohexane was listed under the parent alkane as "Hexane, 1-bromo-". A brief explanation of the nomenclature system, plus definitions of abbreviations and symbols, precedes the tables of organic compounds in all editions of the *CRC Handbook.*

The Merck Index. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals,* currently in its 14th edition, has over 10,000 organic compound entries that give physical properties and solubilities, as well as references to syntheses, safety information, and uses. *The Merck Index* is particularly comprehensive for organic compounds of medical and pharmaceutical importance. Figure 3.2

1536. *sec*-Butyl Acetate. [105-46-4] Acetic acid 1-methylpropyl ester; acetic acid *sec*-butyl ester. $C_6H_{12}O_2$; mol wt 116.16. C 62.04%, H 10.41%, O 27.55%. Prepd from *sec*-butanol and acetic anhydride: R. Altschul, *J. Am. Chem. Soc.* **68**, 2605 (1946). Prepn of *d*- and *l*-form: J. Kenyon *et al., J. Chem. Soc.* **1935**, 1072. Manuf: *Faith, Keyes & Clark's Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 171-177.



***dl*-Form.** Liquid. d_{27} 0.865. bp_{761} 111-111.5°. n_D^{27} 1.3848. Flash pt, open cup: 88°F (31°C). Slightly sol in water; sol in alcohol, ether.

***d*-Form.** [66610-38-6] Acetic acid (1*S*)-1-methylpropyl ester. $[\alpha]_{546.1}^{18}$ +10.52° (neat).

***l*-Form.** [54657-08-8] Acetic acid (1*R*)-1-methylpropyl ester. Liquid, bp 116-117°. d_4^{19} 0.873. $[\alpha]_{546.1}^{19}$ −20.19° (neat). $[\alpha]_{546.1}^{19}$ −18.86° (c = 5.046 in ethanol). n_D^{18} 1.3899.

Caution: Potential symptoms of overexposure are irritation of eyes; headache; drowsiness; narcosis; dryness of upper respiratory system and skin. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 38.

FIGURE 3.2
Monograph 1536: *sec*-Butyl Acetate from page 256 of *The Merck Index*: *An Encyclopedia of Chemicals, Drugs, and Biologicals,* 14th edition.

shows the entry for *sec*-butyl acetate from the 14th edition of *The Merck Index*.

Online Resources

The Internet provides access to many sites that have information about organic compounds; the number of Web sites changes frequently. At the time of publication, the following sites provided useful information on physical constants and other properties of organic compounds.

http://www.sigmaaldrich.com/sigma-aldrich/home.html

http://chembiofinderbeta.cambridgesoft.com

http://www.acros.com

http://www.chemspider.com

If your college or university subscribes to them, the following Web sites have downloadable PDF files of material safety data sheets (MSDSs) that provide information about a compound's properties as well as safety information about its handling, use, and disposal:

http: //www.MSDSonline.com

http://www.chemwatch.na.com

In addition to a complete MSDS, Chemwatch also has a mini MSDS that briefly summarizes the essential physical properties and safety information for a compound in clear, concise language and pictograms.

PART

2

Carrying Out Chemical Reactions

Essay — Learning to Do Organic Chemistry

Learning to do organic chemistry involves learning how to use new types of equipment and mastering the techniques of assembling the specialized glassware setups that are used for organic reactions. You will also acquire techniques for measuring and handling reagents, and the methods of heating and cooling organic reactions. Finally, you may have the opportunity to learn how to predict reaction outcomes using computational chemistry and how a chemical reaction can be designed based on a published procedure. The techniques in Part 2 will guide you in acquiring these skills. Think through the purpose of each lab operation while carrying out your experiments.

Organic chemists have developed specialized equipment to carry out chemical reactions, separate mixtures of compounds, and purify reaction products, so it is understandable if you feel bewildered at first by the large variety of equipment found in your lab drawer(s). Technique 4 has pictures of thirty different pieces of glassware, plus pictures of porcelain and plastic funnels, drying tubes, and spatulas. Individual pieces of glassware have names that make perfect sense to a chemist but not necessarily to a person new to the lab. Round-bottomed flasks are self-explanatory, but Erlenmeyer flasks, Buchner funnels, and Claisen connecting adapters may be less so. Just as reactions in organic chemistry are named after the chemists who discovered or popularized them, pieces of equipment are named after the chemists who invented them—in this case, Emil Erlenmeyer, Ernst Büchner, and Ludwig Claisen. Much of the glassware has standardized interconnections, called ***standard taper joints***, which allow a few pieces to be assembled in a variety of ways for many different lab operations.

Although the many specialized pieces of equipment can be confusing at the outset, they make doing organic chemistry a good deal easier. Organic chemistry is concerned with compounds that have a variety of physical properties, so equipment to handle both liquids and solids is necessary. Liquids form a thin, almost invisible, coating on glass surfaces, and it is necessary to use glassware appropriate for the scale of the work being carried out. For example, if the glassware is too large for the amounts of reagents

being used, inadvertent loss of chemicals can occur on the glassware surface and reduce the product yield. If the glassware is too small for the amounts of reagents, a reaction mixture could overflow. Developing a sense of scale and using the kind of equipment appropriate for the scale at which you are working is a skill you will need to develop in the organic lab.

The large, macroscale equipment used until thirty or forty years ago for most chemistry in academic laboratories is now largely gone, replaced by smaller equipment that has safety and environmental advantages. We call the most common standard taper glassware "miniscale" to reflect this newer practice. When the quantity of reagents is very small, "microscale" glassware is used. Your lab may use miniscale or microscale or even both types of standard taper glassware.

Specialized techniques are used for measuring the volumes of liquids and quantities of solids used in reactions (Technique 5). A graduated cylinder is often adequate for miniscale work, while a syringe is used for microscale work to measure and transfer a volume of liquid. You may encounter dispensing pumps and automatic delivery pipets for measuring volumes of liquids—their misuse can wreak havoc with your experimental results. Pasteur pipets are commonly used to transfer small amounts of liquids. A top-loading balance is often used for miniscale work, but a more precise analytical balance is necessary to weigh accurately the solids used in microscale work.

Organic reactions often require a period of heating to reach completion (Technique 6). Heating a reaction mixture at its boiling point under reflux is a common method for preventing loss of volatile reagents and solvents during the heating period. A variety of heating devices—hot plates, heating mantles, and water or steam baths—may be available to you, but the days of Bunsen burners are largely past because of the flammability of most organic compounds. Again, the scale of your experiments will often determine which heating method is most appropriate. Technique 7 is a discussion of how glassware is assembled to carry out chemical reactions.

The last two techniques in Part 2 are a change of pace. Technique 8 deals with computational chemistry. The power and rapid computational capabilities of computers have made it feasible to carry out calculations relating to the experimental chemistry you are studying even before you step into the laboratory. These calculations provide insights that can be helpful in guiding your experimental work.

Technique 9 discusses strategies for success when you have the opportunity to design a chemical reaction. This type of experiment or project often involves adapting published reaction procedures to the scale you want to use. Naturally, it involves using the chemical literature. The thoroughness or brevity of a published experimental procedure depends in part on the guidelines for the journal or monograph in which it was published. If it is a primary research journal written for experienced chemists, filling in the many details implied—but not actually described—in an experimental procedure can be a challenging but rewarding experience, linking what you have learned in the classroom to the action of the laboratory.

If you have not already done so, we urge you to read carefully Technique 1 on laboratory safety before you begin your laboratory work. Doing organic chemistry safely should be a constant consideration while you are working in the laboratory.

TECHNIQUE

4 LABORATORY GLASSWARE

You will find an assortment of glassware and equipment in your laboratory desk; some items will be familiar to you from your earlier lab experiences and other items may not. If your laboratory is equipped for miniscale experimentation, you will find specialized glassware called ***standard taper glassware,*** which has carefully constructed ground glass joints designed to fit together tightly and interchangeably. Standard taper glassware is available in a variety of sizes. If you will be carrying out microscale experimentation, you will use scaled-down glassware designed for the milligram and milliliter quantities of reagents used in microscale work. There are two types of microscale glassware commonly used in the undergraduate organic laboratory—microscale standard taper glassware with threaded screw cap connectors and the Kontes/Williamson microscale glassware that fastens together with flexible elastomeric connectors.

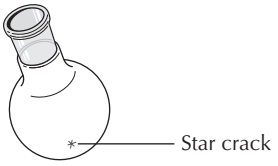


FIGURE 4.1
Round-bottomed flask with a star crack.

SAFETY PRECAUTION

Before you use any glassware in an experiment, check it carefully for cracks or chips. Glassware with spherical surfaces, such as round-bottomed flasks, can develop small, star-shaped cracks (Figure 4.1). Replace damaged glassware. When cracked glassware is heated, it can break and ruin your experiment and possibly cause a serious spill or fire.

4.1 Desk Equipment

A typical student desk contains an assortment of beakers, Erlenmeyer flasks, filter flasks, thermometers, graduated cylinders, test tubes, funnels, and other items. Your desk or drawer will probably have most, if not all, of the equipment items shown in Figure 4.2. Make sure that all glassware is clean and has no chips or cracks. Replace damaged glassware.

4.2 Standard Taper Miniscale Glassware

Standard taper glassware is designated by the symbol ⅋. All the joints in standard taper glassware have been carefully ground so that they are exactly the same size, and all the pieces fit together interchangeably. We recommend the use of ⅋ 19/22 or ⅋ 14/20 glassware for miniscale experiments. The numbers, in millimeters, represent the diameter and the length of the ground glass surfaces (Figure 4.3). A typical set of ⅋ 19/22 glassware found in introductory organic laboratories is shown in Figure 4.4.

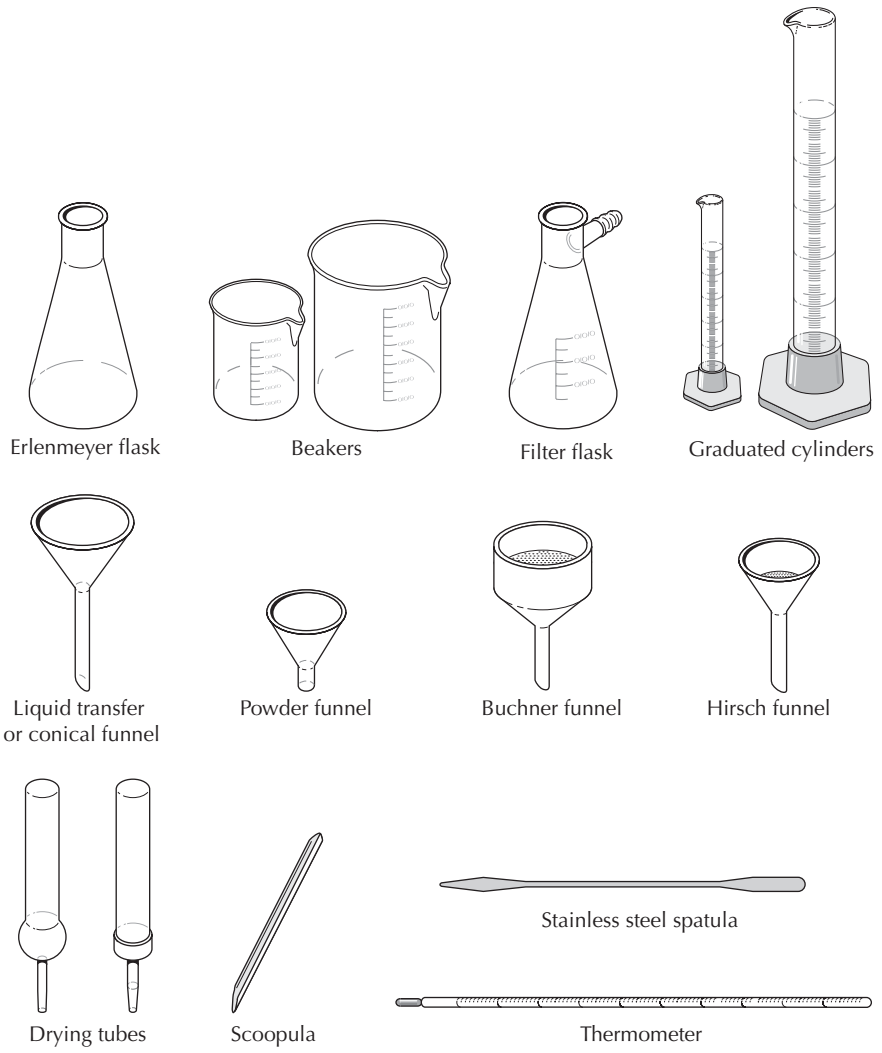


FIGURE 4.2 Typical equipment in a student desk.

Greasing Ground Glass Joints

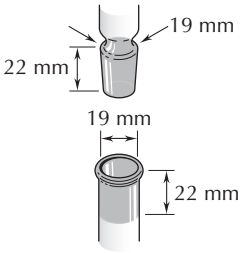


FIGURE 4.3 Dimensions of ⅋ 19/22 ground glass joints.

Because standard taper joints fit together tightly, they are not always put together dry but are often coated with a lubricating grease. The grease prevents interaction of the ground glass joints with the chemicals used in the experiment that can cause the joints to "freeze," or stick together. Taking apart stuck joints, although not impossible, is often not an easy task, and standard taper glassware (which is expensive) frequently is broken in the process. **Note:** Microscale glassware with ground glass joints is never greased unless the reaction involves strong bases such as sodium hydroxide or sodium methoxide.

Types of grease for ⅋ joints. Several greases are commercially available. For general purposes in an undergraduate laboratory, a hydrocarbon grease, such as Lubriseal, is preferred because it can be

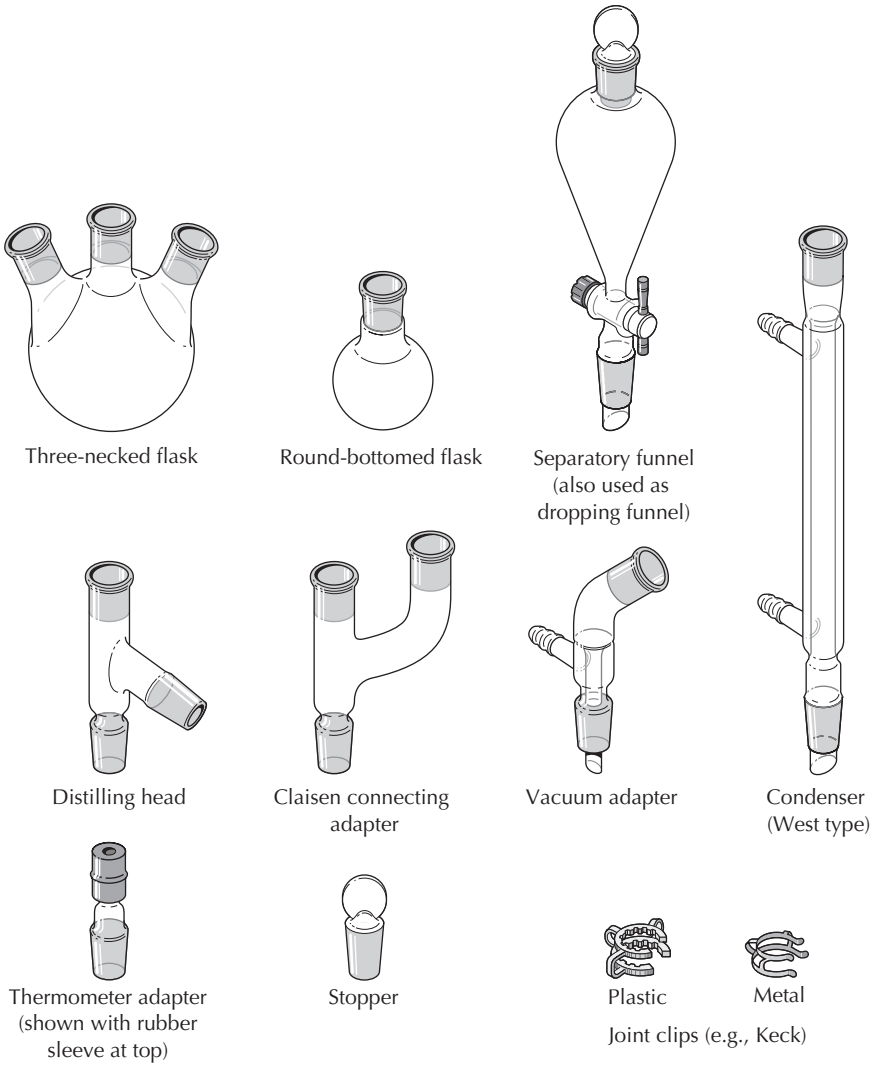


FIGURE 4.4 Standard taper glassware for miniscale experiments.

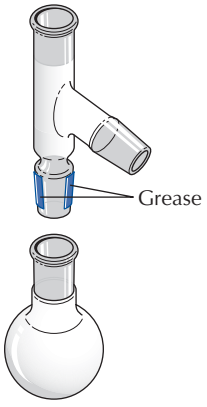


FIGURE 4.5
Apply two *thin* strips of grease almost the entire length of the inner joint about 180° apart.

removed easily. Silicone greases have a very low vapor pressure and are intended for sealing a system that will be under vacuum. Silicone greases are nearly impossible to remove completely because they do not dissolve in detergents or organic solvents.

Sealing a standard taper joint with grease. To seal a standard taper joint, apply two thin strips of grease almost the entire length of the inner joint about 180° apart, as shown in Figure 4.5. Gently insert the inner joint into the outer joint and rotate one of the pieces. The joint should rotate easily and the grease should become uniformly distributed so that the frosted surfaces appear clear.

Using excess grease is bad practice. Not only is it messy, but worse, it may contaminate the reaction or coat the inside of reaction

flasks, making them difficult to clean. Just enough grease to coat the entire ground surface thinly is sufficient. If grease oozes above the top or below the bottom of the joint, you have used too much. Take the joint apart, wipe off the excess grease with a towel or tissue, and assemble the pieces again.

Removing grease from standard taper joints. When you have finished an experiment, clean the grease from the joints by using a brush, detergent, and hot water. If this scrubbing does not remove all the grease, dry the joint and clean it with a towel (for example, a Kimwipe) moistened with toluene or hexane.

SAFETY PRECAUTION

Toluene and hexane are irritants and pose a fire hazard. Wear gloves and work in a hood. Place the spent solvent in the appropriate waste container.

4.3 Microscale Glassware

When the amounts of reagents used for experiments are in the 100–300-mg or 0.1–2.0-mL range, microscale glassware is used. Recovering any product from an operation at this scale would be difficult if you were using 19/22 or 14/20 standard taper glassware; much of the material would be lost on the glass surfaces. Two types of microscale glassware are commonly used in undergraduate organic laboratories—standard taper glassware with threaded screw cap connectors or Kontes/Williamson glassware that fastens together with flexible elastomeric connectors. Your instructor will tell you which type of microscale glassware is used in your laboratory.

Standard Taper Microscale Glassware

The pieces of microscale standard taper glassware needed for typical experiments in the introductory organic laboratory are shown in Figure 4.6. The pieces fit together with 14/10 standard taper joints.

Grease is NOT used with microscale glassware, except when the reaction mixture contains a strong base, because its presence could cause significant contamination of the reaction mixture. Instead, a threaded cap and O-ring ensure a tight seal and hold the pieces together, thus eliminating the use of clamps or joint clips. Place the threaded cap over the inner joint; then slip the O-ring over the tapered portion. Fit the inner joint inside the outer joint and screw the threaded cap tightly onto the outer joint (Figure 4.7). A securely screwed connection effectively prevents the escape of vapors and is also vacuum tight.

Kontes/Williamson Microscale Glassware

The various pieces of Kontes/Williamson microscale glassware used in typical experiments in the organic laboratory are shown in

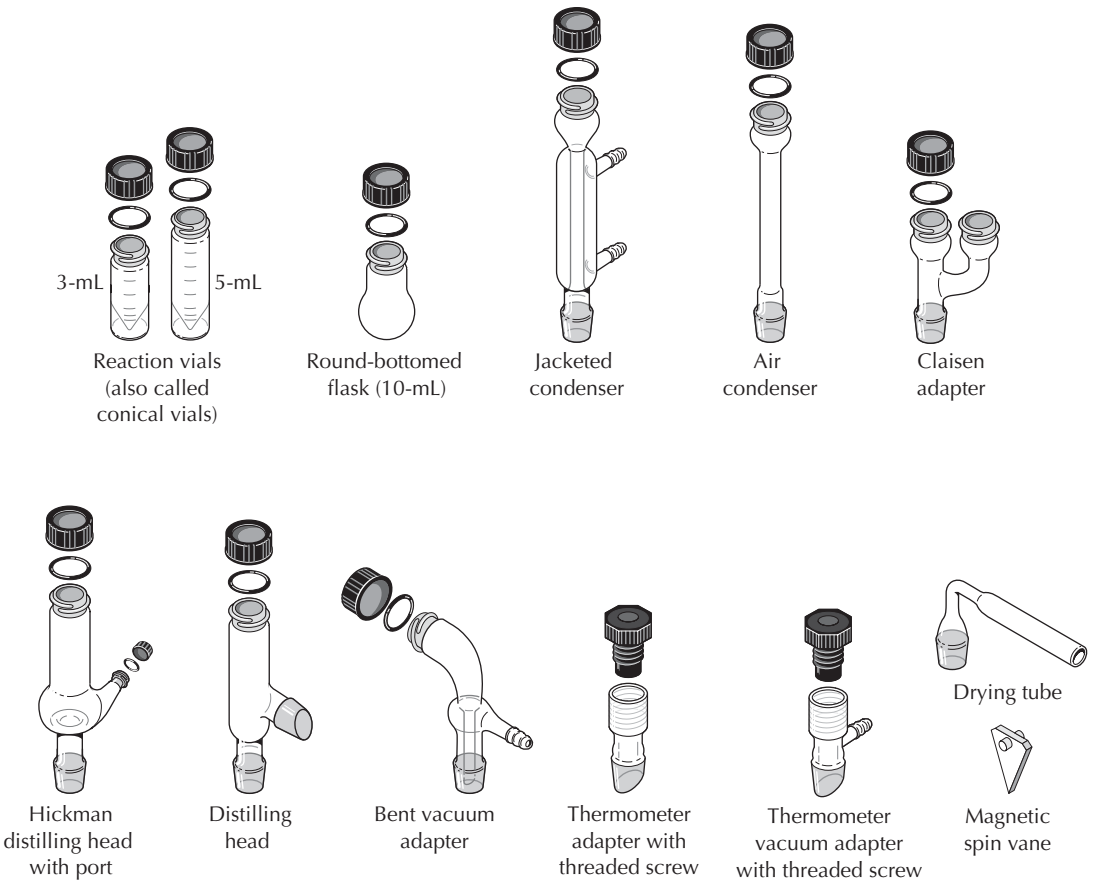


FIGURE 4.6 Standard taper microscale glassware.

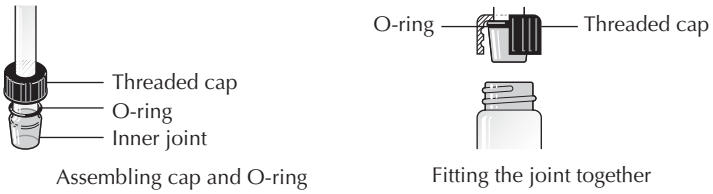


FIGURE 4.7 Assembling a standard taper joint on standard taper microscale glassware.

Figure 4.8. This type of microscale glassware fits together with flexible elastomeric connectors that are heat and solvent resistant.

Grease is NOT used with this type of glassware connector. A flexible connector with an aluminum support rod fastens two pieces of glassware together and provides attachment of the apparatus by way of a two-way clamp to a ring stand or vertical support rod. One piece of glassware is pushed into the flexible connector, and then the second piece is pushed into the other end of the connector, as shown in Figure 4.9. The flexible connector effectively seals the joint and prevents the escape of vapors.

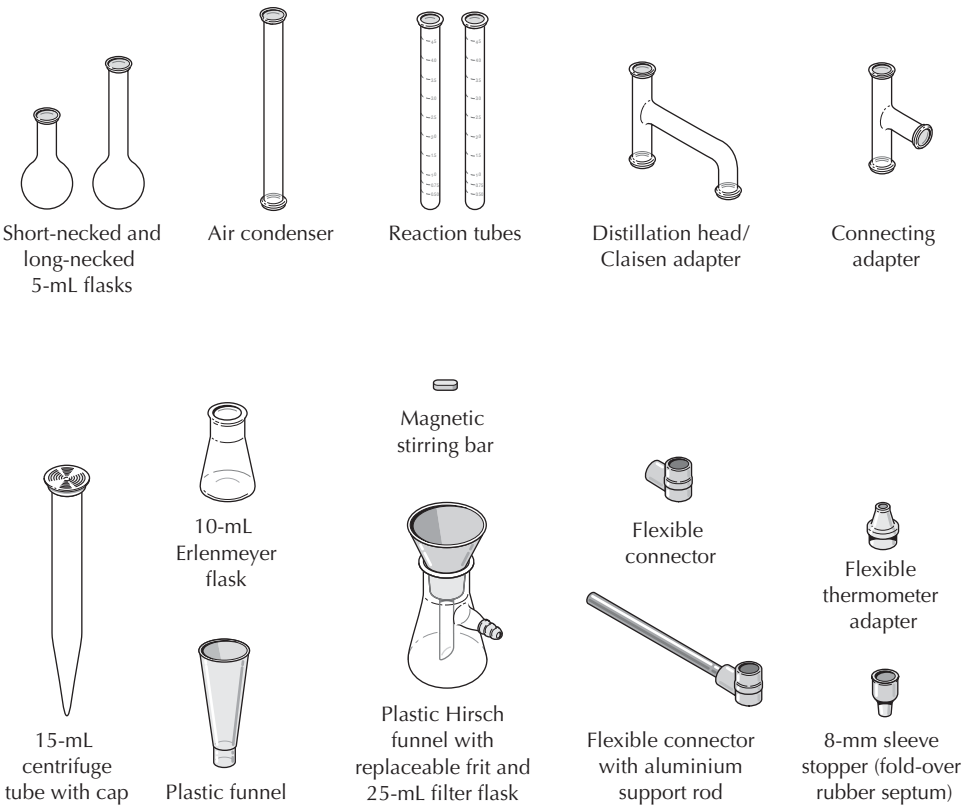


FIGURE 4.8 Williamson microscale glassware and other microscale apparatus. (Manufactured by Kontes Glass Co., Vineland, NJ.)

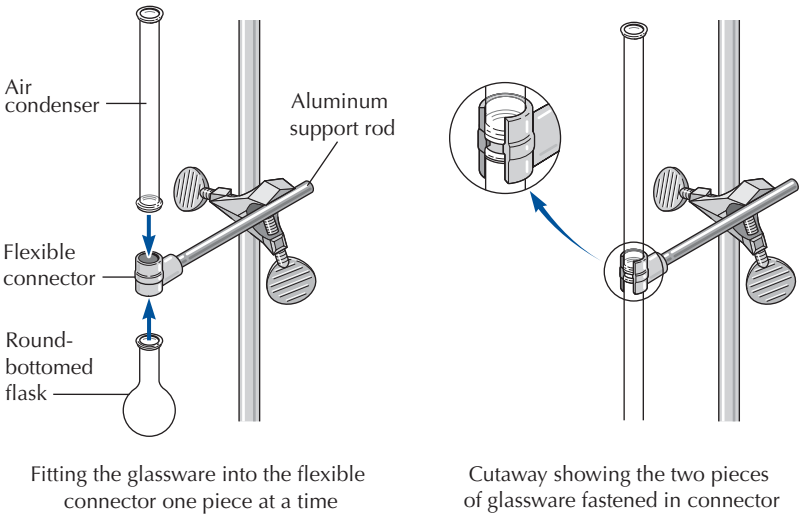


FIGURE 4.9 Assembling Williamson microscale glassware with a flexible connector.

4.4 Cleaning and Drying Laboratory Glassware

Part of effective laboratory technique includes cleaning the glassware before you leave the laboratory, a practice that ultimately saves time and reduces everyone's exposure to chemicals. Clean glassware is essential for maximizing the yield in any organic reaction, and in many instances glassware also must be dry. Try not to have to wash something immediately before using it, because then you will waste time while it dries in the oven.

Cleaning Glassware

Strong detergents and hot water are the ingredients needed to clean most glassware used for organic reactions. Scrubbing with a paste made from water and scouring powder, such as Ajax or Bon Ami, removes many organic residues from glassware. Organic solvents, such as acetone or hexane, help dissolve the polymeric tars that sometimes coat the inside of a flask after a distillation. You may want to wear gloves when cleaning glassware. A final rinse of clean glassware with distilled water prevents water spots.

SAFETY PRECAUTION

Solvents such as acetone and hexane are irritants and flammable. Wear gloves, use the solvents in a hood, and dispose of them in the flammable (nonhalogenated) waste container.

A solution of alcoholic sodium hydroxide* is usually an effective cleanser for removing grease and organic residues from flasks and other glassware.

SAFETY PRECAUTION

Strong bases, such as sodium hydroxide, cause severe burns and eye damage. Skin contact with alkali solutions starts as a slippery feel to the skin followed by irritation. Wash the affected area with copious amounts of water. Wear gloves and eye protection while cleaning glassware with alcoholic NaOH solution.

Drying Glassware

Dry glassware is needed for most organic reactions. The easiest way to ensure dry glassware is to leave all glassware washed and clean at the end of each lab session. It will be dry and ready to use by the next laboratory period.

Oven drying of glassware. Wet glassware can be dried by heating it in an oven at 120°C for 20 min. Remove the dried glassware from the oven with tongs and allow it to cool to room temperature before using it for a reaction.

*Made by dissolving 120 g of NaOH in 120 mL of water and diluting to 1 L with 95% ethanol.

Drying wet glassware with acetone. Glassware that is wet from washing can be dried more quickly by rinsing it in a hood with a few milliliters of acetone. Acetone and water are completely miscible, so the water is removed from the glassware. The acetone is collected as flammable (nonhalogenated) waste; any residual acetone on the glassware is allowed to evaporate into the atmosphere. There is an environmental cost, as well as the initial purchase price and later waste disposal costs, in using acetone for drying glassware.

TECHNIQUE 5

MEASUREMENTS AND TRANSFERRING REAGENTS

Whether you are carrying out miniscale or microscale experiments, you need to accurately measure both solid and liquid reagents as well as the temperature in reaction and purification procedures. Methods for weighing solids and liquids, measuring liquid volumes, transferring solids and liquids without loss, and measuring temperature are described in this chapter.

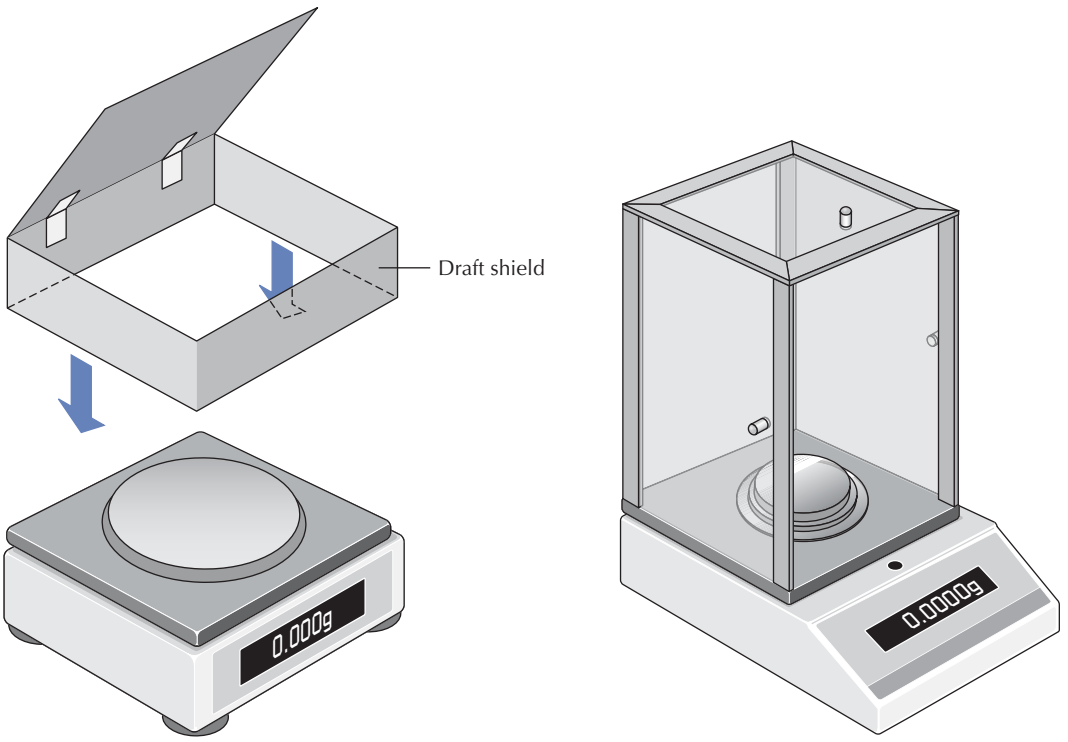
5.1 Using Electronic Balances

Your laboratory is probably equipped with several types of electronic balances for weighing reagents. How do you decide which one to use to determine the mass of a reagent or product? As a general rule, a top-loading balance that weighs to the nearest centigram (0.01 g) is satisfactory for miniscale reactions using more than 2–3 g of a substance. However, in miniscale reactions where reagent quantities of less than 2 g are used, as well as for the small quantities of reagents used in microscale reactions (100–300 mg), all reagent quantities should be determined on a balance that weighs to the nearest milligram (0.001 g). A top-loading milligram balance has a draft shield to prevent air currents from disturbing the weighing pan while a sample is being weighed (Figure 5.1a).

When a quantity of less than 50 mg is required in a microscale reaction, its mass should be determined on an analytical balance (Figure 5.1b) that weighs to the nearest 0.1 mg (0.0001 g). Close the doors of the balance while weighing the sample.

Care of Electronic Balances

Electronic top-loading and analytical balances are expensive precision instruments that can be rendered inaccurate very easily by corrosion from spilled reagents. If anything spills on the balance or the weighing pan, clean it up immediately. Notify your instructor right away if the spill is extensive or the substance is corrosive.



(a) Milligram top-loading balance with draft shield

(b) Analytical balance

FIGURE 5.1 Two types of balances

Weighing Solids

No solid reagent should ever be weighed directly on a balance pan, nor should a reagent be weighed directly into a round-bottomed flask or test tube, which are not stable on the balance pan. Weigh the solid in a glass container (vial or beaker), in an aluminum or plastic weighing boat, in a crinkle cup, or on glazed weighing paper. Then transfer it to the reaction vessel.

Tare mass. The mass of the container or weighing paper used to hold the sample being weighed is called the ***tare mass*** or just the ***tare***. When weighing a specific quantity of reagent, the tare mass of the container or weighing paper is simply subtracted by pressing the tare or zero button before the sample is added. Then the solid is added until the desired mass appears on the readout screen.

If the mass of the container is not ***tared*** (subtracted) using the zero button before the sample is added, the container mass should be determined and recorded **after** the sample is transferred from it. A vial or flask—with its label and cap or cork—that will be used to hold a purified reaction product should be weighed **before the product is placed in it.** Be sure to record the tare mass of the container in your lab notebook.

How to weigh a solid. To weigh a specific quantity of a solid reagent, place a weighing boat, crinkle cup, or piece of diagonally

folded glazed weighing paper on the balance pan and press the zero or tare button. Use a spatula to add small portions of the reagent until the desired mass (within 1–2%) is shown on the digital display. For example, the mass of a sample would not need to be exactly the 0.300 g specified, but normally it should be within ±0.005 g of that amount. **Record the actual amount you use** in your notebook. If the compound you are weighing is the limiting reagent, calculate the theoretical yield based on the actual amount used, not on the amount specified in the experimental procedure.

Weighing Liquids

Be very careful that liquid does not spill on the balance while you are weighing a liquid sample. Should a spill occur, clean it up immediately.

To weigh a liquid, the mass of the container (tare) must be ascertained and recorded, or else subtracted by using the zero button on the balance, **before** the liquid is placed in it. If the liquid is volatile, a cap or cork for the container must be included in the tare mass so that the sample will not evaporate during the weighing process. To weigh a specific amount of a liquid compound, determine the volume of the required sample from its density and transfer that volume to a tared container. Ascertain the mass of the tared container and its cap, plus the liquid, to determine the mass of the liquid sample. If the mass of liquid needed is less than 1 g, an alternative to measuring the volume is to add the liquid drop by drop to the tared container until the desired mass is obtained.

5.2 Transferring Solids to a Reaction Vessel

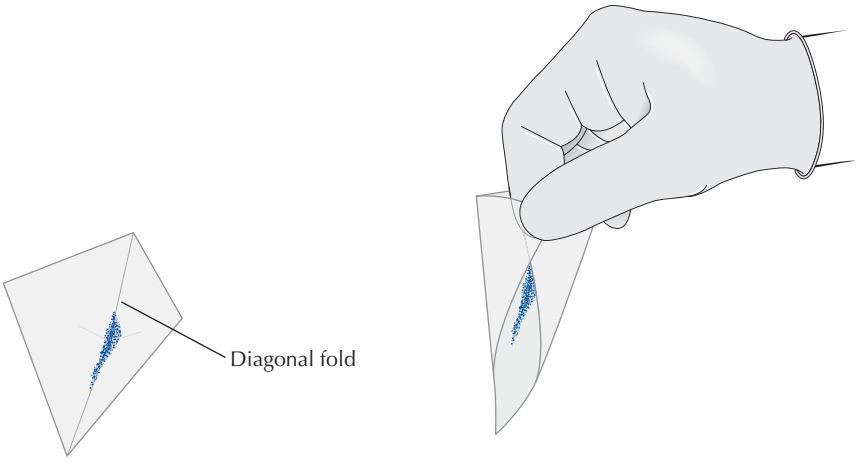
Once the mass of a solid reagent has been determined, the reagent must be transferred to the reaction vessel without mishap. If the sample is in a weighing boat, fold the boat diagonally before transferring the sample. If the sample is in a crinkle cup, pinch the edges of the cup together leaving a small opening so that the solid can slide out of it easily but not spill. If the sample is on a piece of glazed weighing paper with a diagonal fold (Figure 5.2a), overlap the two outside edges and firmly hold them between your thumb and index finger while transferring the solid (Figure 5.2b). A spatula can be used to aid in transferring the solid if it sticks to the weighing paper.

Using a Powder Funnel

For reactions being run in miniscale round-bottomed flasks, transferring solids using a powder funnel serves to keep the solid from spilling and prevents any solid from sticking to the inside of the joint at the top of the flask (Figure 5.3a). The stem of a powder funnel has a larger diameter than that of a funnel used for liquid transfers so that solids will not clog it. Use of a powder funnel is essential with Williamson microscale glassware because of the very small opening at the top of the round-bottomed flasks and reaction tubes (Figure 5.3b).

Transferring Solids to a Standard-Taper Microscale Vial

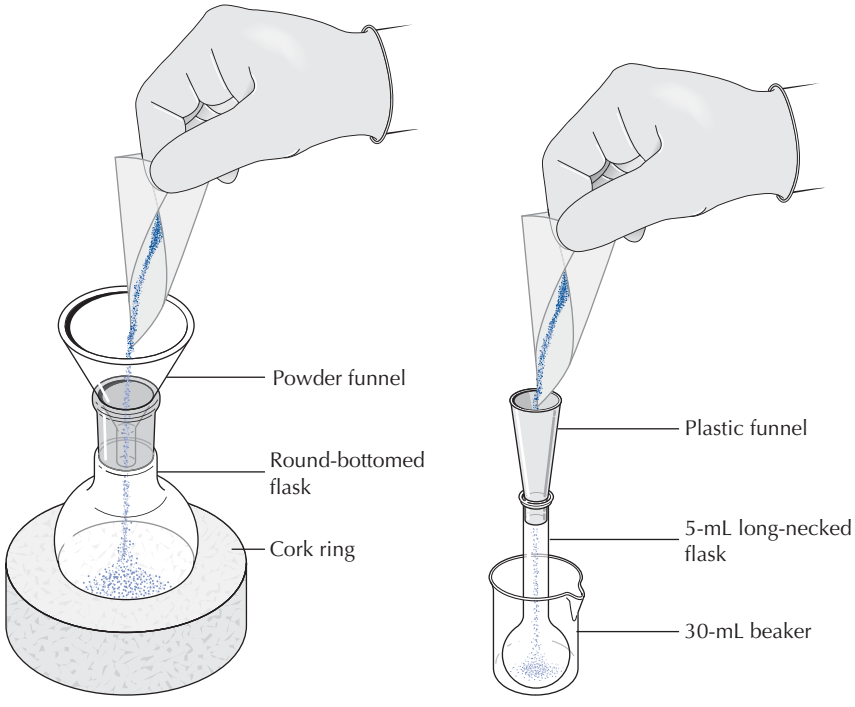
Set the standard-taper microscale vial in a small beaker so it will not tip. Pick up the weighing paper (see Figure 5.2a and b.). Slide the overlapped edges further together to decrease the size of the opening



(a) Diagonally folded weighing paper with a solid sample

(b) Overlap opposite diagonal corners and hold firmly between thumb and index finger.

FIGURE 5.2 Preparing to transfer a solid sample from a weighing paper.



(a) Miniscale apparatus

(b) Williamson microscale apparatus

FIGURE 5.3 Transferring solids with a powder funnel.

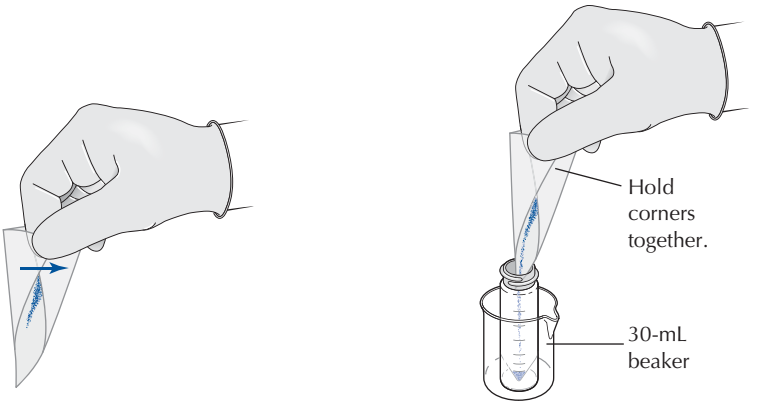


FIGURE 5.4
Transferring solids with a weighing paper into a conical vial.

(a) Hold the weighing paper as shown, and slide the overlapping edges further together as shown in (b).

(b) Insert tip of paper into conical vial.

at the bottom of the weighing paper (Figure 5.4a). Insert the tip of the paper into the conical vial and allow the solid to slide from the paper into the vial (Figure 5.4b).

5.3 Measuring Volume and Transferring Liquids

Several liquid volume measuring devices are used in the laboratory, including graduated cylinders, pipets, burets, dispensing pumps, syringes, and beakers and flasks with volume markings on them. The equipment used for measuring a specific volume of liquid depends on the accuracy with which the volume needs to be known. For example, the volume of a liquid reagent that is the limiting factor in a miniscale reaction may need to be measured with a graduated pipet or a dispensing pump and then weighed to know the exact amount.

If the liquid is a solvent or present in excess of the limiting reagent, volume measurement can be done with a graduated pipet for microscale work and with either a graduated pipet or a graduated cylinder for miniscale work. The volume markings on beakers and flasks can be used only to estimate an approximate volume and should never be used for measuring a reagent that will go into a reaction.

Graduated Cylinders

Graduated cylinders do not provide high accuracy in volume measurement and should be used only to measure quantities of liquids other than limiting reagents. The volume contained in a graduated cylinder is correctly read from the bottom of the meniscus, as shown in Figure 5.5.

Graduated cylinders are not used to measure reagents for microscale reactions. However, a 5- or 10-mL graduated cylinder can be used for measuring volumes of extraction solvents greater than 1 mL.

Dispensing Pumps

Dispensing pumps fitted to glass bottles come in a variety of sizes designed to deliver a preset volume of liquid (>0.1 mL). Pumps in

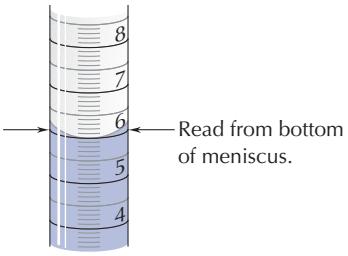


FIGURE 5.5
The meniscus in a graduated cylinder.

the 1-, 2-, and 5-mL range may sometimes be used in microscale work for dispensing solvents, but they should not be used for limiting reagents.

Before you begin to measure a sample, check that the spout of the pump is filled with liquid and contains no air bubbles that could cause a volume less than the preset one to be delivered. If air bubbles are present in the spout, pull up the plunger and discharge one or two samples into another container until the spout is completely filled with liquid. (Place the discarded samples in the appropriate waste container.) Dispense the sample *directly* into the container in which it will be used. If an accurate mass of the sample is necessary, dispense it into a preweighed container and then weigh the container and sample.

The operation of a dispensing pump consists of slowly pulling the plunger up until it reaches the preset volume stop (Figure 5.6). Hold the receiving container or reaction vessel under the spout and then gently push the plunger down as far as it will go to discharge the preset volume. Be sure that the last drop of liquid on the spout is transferred.

Graduated Pipets

The small volumes used in microscale and many miniscale reactions are conveniently and accurately measured with graduated pipets of 1.00-, 2.00-, and 5.00-mL size. A syringe attached to the pipet with a short piece of latex tubing or a pipet pump serves to fill the pipet and

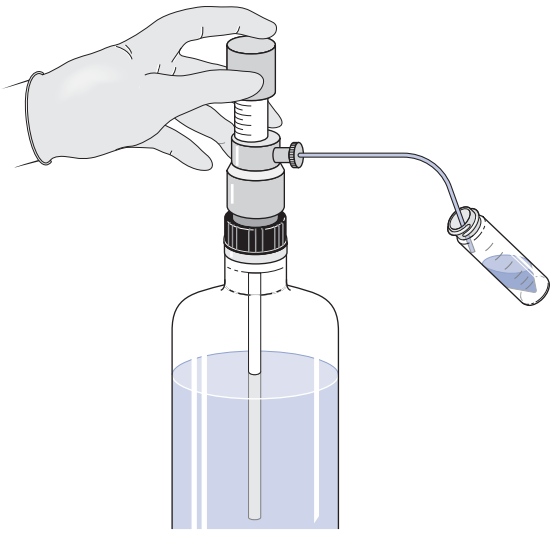
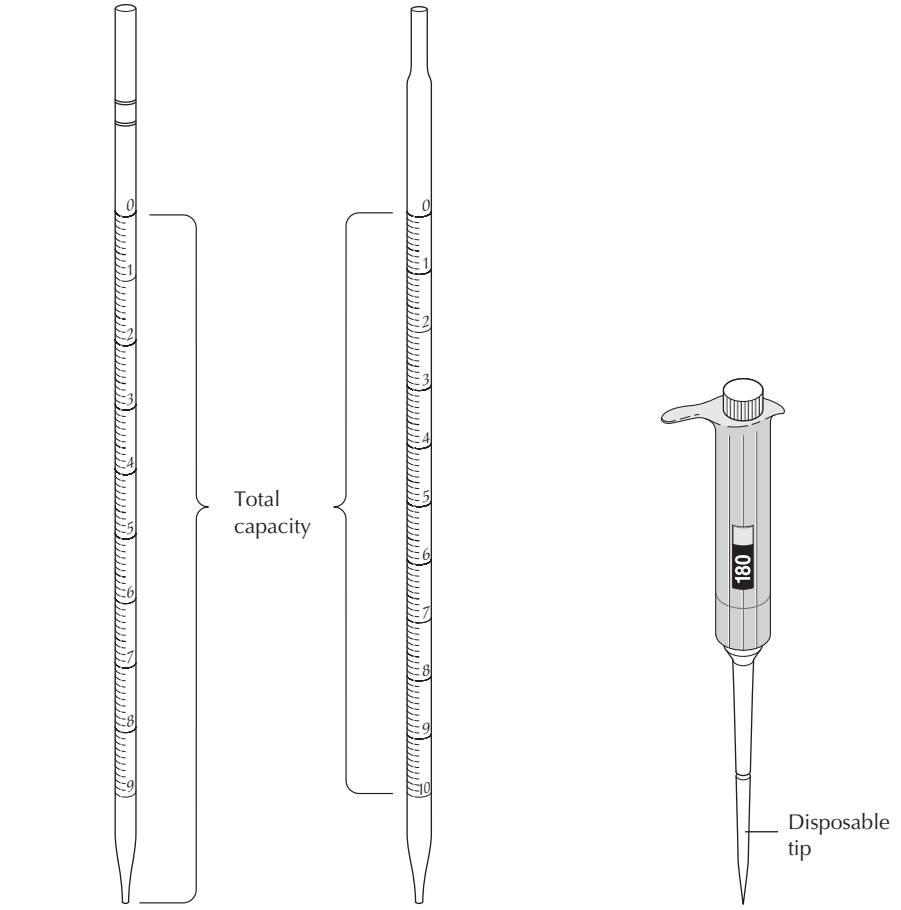


FIGURE 5.6
Dispensing pump.

expel the requisite volume. The most accurate volumes are obtained by difference measurement—that is, filling the pipet to a convenient specific mark and then discharging the liquid until the required volume has been dispensed. The volume contained in a graduated pipet is correctly read from the bottom of the meniscus. The excess liquid remaining in the pipet should be placed in the appropriate waste container.

Two types of graduated pipets are available: one delivers its total capacity when the last drop is expelled (Figure 5.7a), and the other delivers its total capacity by stopping the delivery when the meniscus reaches the bottom graduation mark (Figure 5.7b). However, both kinds of graduated pipets are more frequently used to deliver a specific volume by stopping the delivery when the meniscus reaches the desired volume.



(a) Expel entire contents to deliver total capacity.

(b) Deliver total capacity by draining until the bottom of the meniscus is at 10.00 mL.

(c) Automatic delivery pipettor

FIGURE 5.7 (a and b) Types of graduated pipets. (c) Automatic delivery pipettor.

Automatic Delivery Pipets

Small volumes of 10–1000 μL (0.010–1.000 mL) can be measured very accurately and reproducibly with automatic delivery pipets or pipettors. Automatic pipets have disposable plastic tips that hold the preset volume of liquid; no liquid actually enters the pipet itself, and the pipet should never be used without a disposable tip in place (Figure 5.7c). Automatic pipets are very expensive, and your instructor will demonstrate the specific operating technique for the type in your laboratory.

Automatic pipets must be properly calibrated before use. **Never assume that an automatic delivery pipet is calibrated accurately unless your instructor assures you that this is the case.** Calibrate a pipet by delivering the preset amount of water from the pipet to a small, weighed flask. Then weigh the flask to determine the exact amount of water. If the automatic pipet needs to be recalibrated, consult your instructor.

Syringes

A syringe with a needle attached works well for measuring and transferring the small amounts of reagents used in microscale reactions. Syringes are also utilized for measuring and transferring anhydrous reagents from a septum-sealed reagent bottle to the reaction vessel when inert atmospheric conditions are employed [see Technique 16].

SAFETY PRECAUTION

A syringe needle can cause puncture wounds. Handle it carefully, keep the shield on it except when using it, and dispose of it **only** in a special "sharps" container.

Pasteur Pipets and Plastic Transfer Pipets

Pasteur pipets are particularly useful for transferring liquids in microscale reactions and extractions. There are also times when it is helpful to know the approximate volume of liquid in a Pasteur pipet.

SAFETY PRECAUTION

Glass Pasteur pipets are puncture hazards. They should be handled and stored carefully. Dispose of Pasteur pipets in a "sharps" box or in a manner that does not present a hazard to lab personnel or housekeeping staff. Check with your instructor about the proper disposal method in your laboratory.

Approximating volumes with a Pasteur pipet. Pasteur pipets are suitable for measuring only approximate volumes because they do not have volume markings. An approximate volume calibration of a Pasteur pipet is shown inside the front cover of this book. Attaching a 1- or 3-mL Luer-lock syringe with a short piece of latex tubing to a Pasteur pipet also allows an approximate volume of the liquid to be estimated from the position of the plunger in the syringe as the liquid is drawn into the pipet (Figure 5.8).

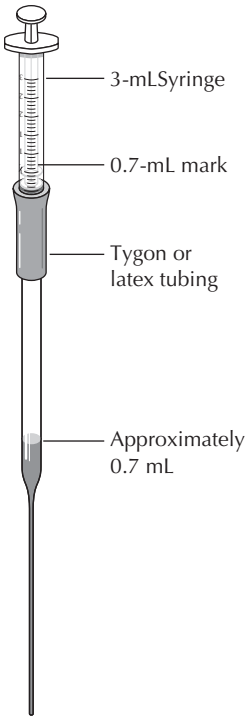


FIGURE 5.8
Using a syringe to estimate the volume of liquid drawn into a Pasteur pipet.

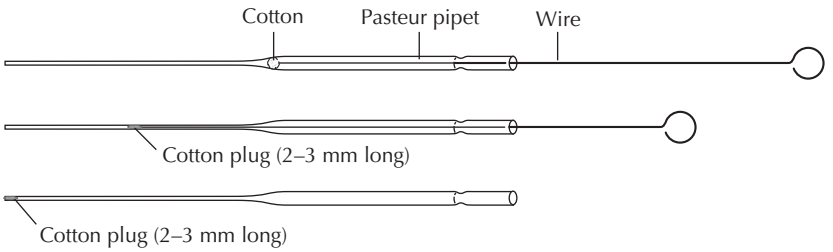


FIGURE 5.9 Preparing a Pasteur filter-tip pipet.

Pasteur filter-tip pipets. Volatile organic liquids tend to drip from a Pasteur pipet during transfers because the vapor pressure increases as your fingers warm the rubber bulb. If a small plug of cotton is pushed into the tip of the pipet, a liquid can be transferred from one container to another without dripping.

Pasteur filter-tip pipets are prepared by using a piece of wire that has a diameter slightly less than the inside diameter of the capillary portion of the pipet to push a tiny piece of cotton into the tip of the Pasteur pipet (Figure 5.9). A piece of cotton of the appropriate size should offer only slight resistance to being pushed by the wire. If there is so much resistance that the cotton cannot be pushed into the tip of the pipet, then the piece is too large. If this is the case, remove the wire and insert it through the tip to push the cotton back out of the upper part of the pipet, and tear a bit off the piece of cotton before putting it back into the pipet. The finished cotton plug in the tip of the pipet should be 2–3 mm long and should fit snugly but not too tightly. If the cotton is packed too tightly in the tip, liquid will not flow through it; if it fits too loosely, it may be expelled with the liquid. With a little practice, you should be able to prepare a filter-tip pipet easily.

Plastic transfer pipets. Graduated plastic transfer pipets, available in 1- and 2-mL sizes, are suitable for measuring the volume of aqueous washing solutions used for microscale extractions and for estimating the volume of solvent added in a microscale recrystallization (Figure 5.10). Most plastic transfer pipets are made of polyethylene and are chemically impervious to aqueous acidic or basic solutions, alcohols such as methanol or ethanol, and diethyl ether. They are not suitable for use with halogenated hydrocarbons because the plasticizer leaches from the polyethylene into the liquid being transferred.

Beakers, Erlenmeyer Flasks, Conical Vials, and Reaction Tubes

The volume markings found on beakers and Erlenmeyer flasks are only approximations and are not suitable for measuring any reagent that will be used in a reaction. However, the markings may be sufficient for measuring the amount of solvents in large-scale recrystallizations. The volume markings on conical vials and reaction tubes are also approximations and should be used only to estimate

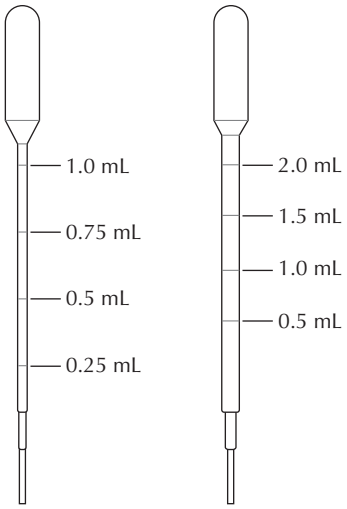


FIGURE 5.10
Graduated plastic transfer pipets.

the volume of the contents, such as the final volume of a recrystallization solution, not for measuring the volume of a reagent used in a reaction.

5.4 Measuring Temperature

A number of temperature measurements must be made while carrying out chemical reactions. For example, it may be necessary to maintain a constant temperature with a cooling or heating bath, to monitor the temperature of a reaction mixture, to determine the boiling point when carrying out a distillation, or to determine the melting point of a reaction product. There are numerous types of thermometers available, some suitable for a variety of tasks and others designed for specific purposes.

Types of Thermometers

Until recently, mercury thermometers were the type of thermometer found in chemistry laboratories. However, concern for the environment, the toxicity of mercury, and the hazards of cleaning up a mercury spill from a broken thermometer have caused a number of states to ban the use of mercury thermometers in schools, colleges, and universities. They have been replaced by other types of temperature-measuring devices, such as nonmercury thermometers, metal probe thermometers, and digital thermometers that can be used with different types of temperature probes.[1]

Nonmercury Thermometers

Nonmercury thermometers filled with alcohol or other organic liquids are now available; some of them can measure to 300°C. Like

[1]Everett, T. S. *J. Chem. Educ.* **1997,** *74,* 1204. Foster. B. L. *J. Chem. Educ.* **2005,** *82,* 269. Ongley, L. K.; Kern, C. S.; Woods, B. S. *J. Chem. Educ.* **2008,** *85,* 1263–1264.

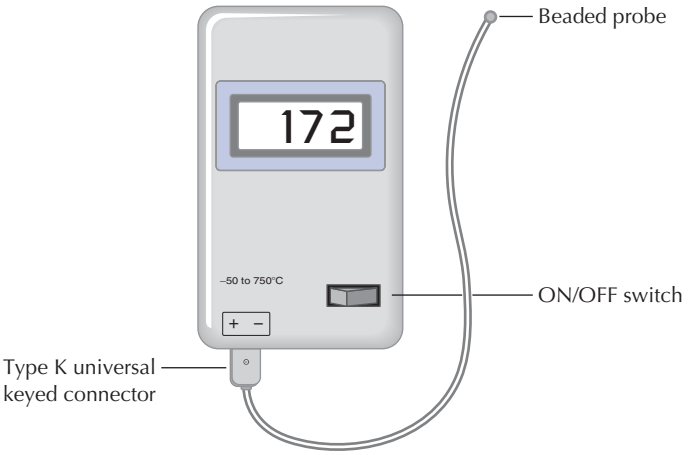


FIGURE 5.11
Digital thermometer.

mercury thermometers, nonmercury thermometers also need to be calibrated before using them for any temperature measurement where accuracy is essential, for example, when determining a melting or boiling point.

Digital Thermometers

Many types of temperature probes are available for use with digital thermometers. For example, the bead probe attached to the digital thermometer in Figure 5.11 can be used with the Mel-Temp melting point apparatus (Figure 14.2). The use of a stainless steel or a Teflon-coated metal temperature probe with a digital thermometer is an alternative for a mercury thermometer in a distillation. However, uncoated metal probes can react with hot organic vapors, particularly if they can be oxidized easily or are acidic or corrosive; the use of an uncoated metal probe is not recommended for distillations of such compounds.

The length of a temperature probe that is positioned below the side arm of a distilling head needs to be determined experimentally by a series of distillations using pure compounds. Consult your instructor about the correct position within the distilling head for the type of probe used in your laboratory.

Thermometer Calibration

The accuracy of a temperature determination is no better than the accuracy of the thermometer. You cannot assume that a thermometer has been accurately calibrated. Although frequently this is the case, it is not always true. Thermometers may give high or low temperature readings of 2°–3° or more.

A thermometer can be calibrated with a series of pure compounds whose melting points are relatively easy to reproduce. The observed melting point corrections for the standard compounds in Table 5.1 can be plotted to determine the necessary temperature corrections (Figure 5.12). Interpolate from the graph to ascertain the correction needed for any subsequent melting point determined with **this thermometer.**

TABLE 5.1 Compounds suitable for thermometer calibration*

Compound	Melting point, °C
Benzophenone	48
Acetamide	81
Benzil	95
Benzoic acid	122
Phenacetin	135
Salicylic acid	160
Succinic acid	189
4-Fluorocinnamic acid	210
Anthraquinone	285

*A kit of compounds for melting-point standards for Mel-Temp calibration is available from the Aldrich Chemical Co.

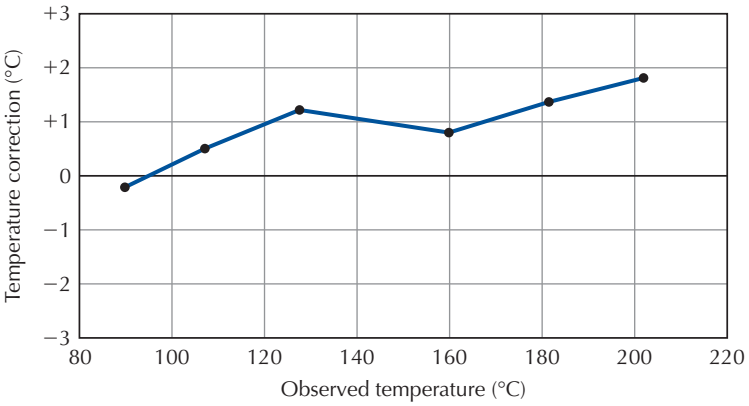


FIGURE 5.12 Thermometer calibration graph.

TECHNIQUE 6

HEATING AND COOLING METHODS

Many organic reactions do not occur spontaneously when the reactants are mixed together but require a period of heating to reach completion. On the other hand, exothermic organic reactions require removal of the heat generated during a reaction by using a cooling bath. Cooling baths are also used to ensure the maximum recovery of crystallized product from a solution or to cool the contents of a reaction flask. Heating and cooling methods are also utilized in other techniques of the organic lab, for example distillation [Technique 13] and recrystallization [Technique 15].

6.1 Preventing Bumping of Liquids

Liquids heated in laboratory glassware tend to boil by forming large bubbles of superheated vapor, a process called ***bumping.*** The inside surface of the glass is so smooth that no tiny crevices exist where air bubbles can be trapped, unlike the surfaces of metal pans used for cooking. Bumping can be prevented by the addition of inert porous material—a boiling stone or boiling stick—to the liquid or by mechanically stirring the liquid while it is heated. Without the use of boiling stones or stirring, ***superheating*** can occur, a phenomenon caused by a temperature gradient in the boiling liquid—lower temperatures near the surface and higher temperatures at the bottom of the liquid near the heat source. Superheating can lead to loss of product and a potentially dangerous situation if the superheated liquid spatters out of the container and causes burns.

A heated liquid enters the vapor phase at the air-vapor interface of a pore in the boiling stone or stick. As the volume of vapor nucleating at the pore increases, a small bubble forms, is released, and continues to grow as it rises through the liquid. Because of the air trapped in the pores of a boiling stone or boiling stick, multiple small bubbles form instead of only a few large ones. The sharp edges on boiling stones also catalyze bubble formation in complex ways not fully understood.

The ***boiling stones*** commonly used in the laboratory are small pieces of carborundum, a chemically inert compound of carbon and silicon. Their black color makes them easy to identify and remove from the product if they have not been removed earlier by filtration.

Boiling sticks are short pieces of wooden applicator sticks and can be used instead of boiling stones. Boiling sticks should not be used in reaction mixtures, with any solvent that might react with wood, or in a solution containing an acid.

Using Boiling Stones

You should always add boiling stones or a boiling stick to any unstirred liquid ***before*** *boiling it—unless instructed otherwise.*

One or two boiling stones suffice for smooth boiling of most liquids. **Boiling stones should always be added before heating the liquid.** Adding boiling stones to a hot liquid may cause the liquid to boil violently and erupt from the flask because superheated vapor trapped in the liquid is released all at once. If you forget to add boiling stones before heating, **the liquid must be cooled well below the boiling point before putting boiling stones into it.**

If a liquid you have boiled requires cooling and reheating, an additional boiling stone should be added before reheating commences. Once boiling stones cool, their pores fill with liquid. The liquid does not escape from the pores as readily as air does when the boiling stone is reheated, rendering the boiling stone less effective in promoting smooth boiling.

Magnetic Stirring

Magnetic stirring is frequently used instead of boiling stones or boiling sticks. The agitation provided by stirring drives the vapor bubbles to the surface of the liquid before they grow large enough to cause bumping. Stirring is also a common method for preventing superheating.

6.2 Heating Devices

SAFETY PRECAUTION

These safety precautions pertain to all electrical heating devices.

1. The hot surface of a hot plate, the inside of a hot heating mantle, or the hot nozzle of a heat gun are fire hazards in the presence of volatile, flammable solvents. An organic solvent spilled on the hot surface can ignite if its flash point is exceeded. Remove any hot heating device from your work area before pouring a flammable liquid.
2. Never heat a flammable solvent in an open container on a hot plate; a buildup of flammable vapors around the hot plate could result. The thermostat on most laboratory hot plates is not sealed and it arcs each time it cycles on and off, providing an ignition source for flammable vapors. Steam baths, oil baths, and heating mantles are safer choices.

Flash point or ***autoignition temperature*** *is the minimum temperature at which a substance mixed with air ignites in the absence of a flame or spark.*

Heating Mantles

Many reactions and other operations are carried out in round-bottomed flasks heated with electric heating mantles shaped to fit the bottom of the flask. Several types of heating mantles may be available in your laboratory. One type consists of woven fiberglass with the heating element embedded between the layers of fabric. Fiberglass heating mantles come in a variety of sizes to fit specific sizes of round-bottomed flasks; a mantle sized for a 100-mL flask will not work well with a flask of another size. A different type of heating mantle, called a Thermowell, has a metal housing and a ceramic well covering the heating element. Thermowell heating mantles can be used with flasks smaller than the designated size of the mantle because of radiant heating from the surface of the well.

Many types of heating mantles have no controls and must be plugged into a variable transformer (or rheostat) or other variable controller to adjust the rate of heating (Figure 6.1). The variable transformer is then plugged into a wall outlet.

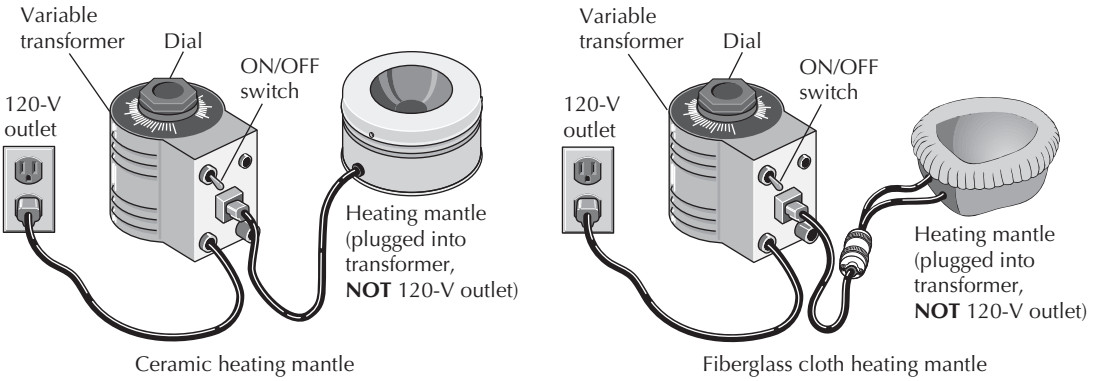
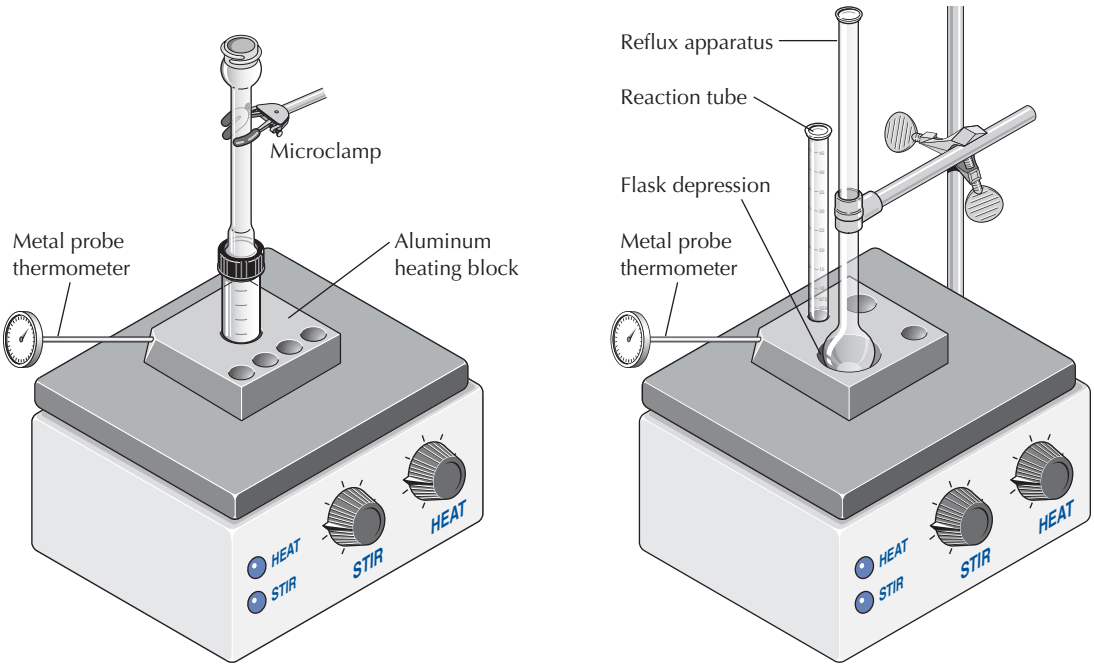


FIGURE 6.1 Heating mantle and variable transformer. (**Note:** The transformer dial is calibrated in percentage of line voltage, **not** in degrees.)



(a) Typical standard taper reaction apparatus with a conical vial and an air condenser

(b) Heating a Williamson reflux apparatus and a reaction tube

FIGURE 6.2 Aluminum blocks used for heating microscale glassware.

Heating mantles are supported underneath a round-bottomed flask by an iron ring or lab jack [see Technique 6.4]. Fiberglass heating mantles should not be used on wooden surfaces because the bottom of the heating mantle can become hot enough to char the wood.

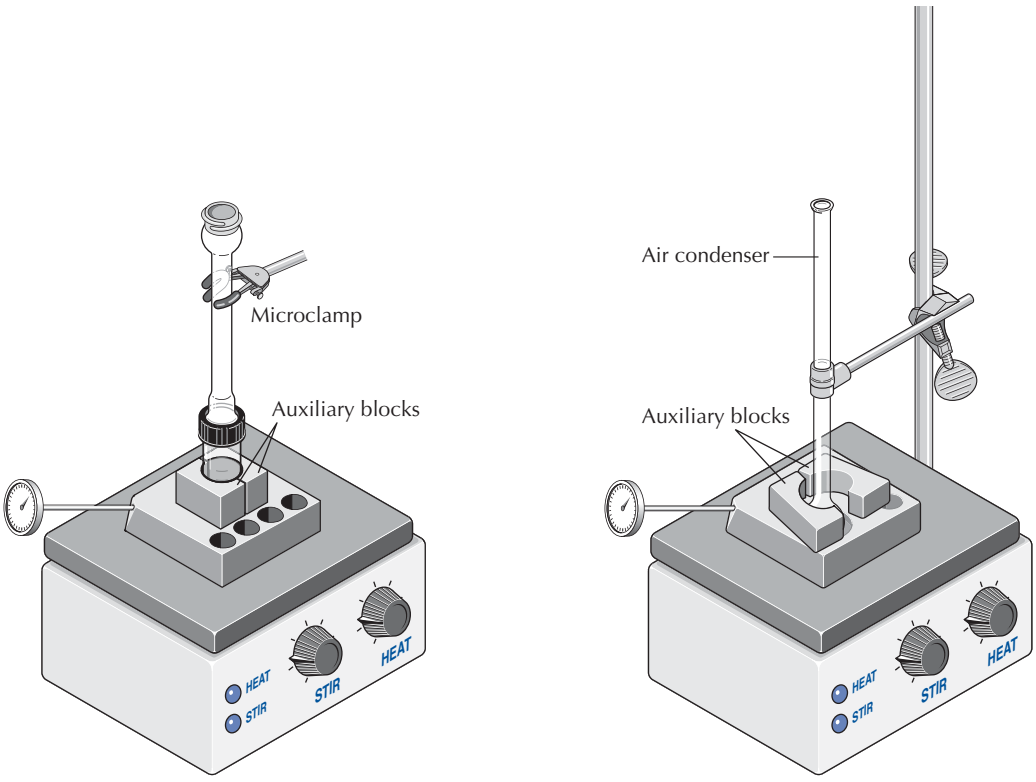
Hot Plates

Hot plates work well for heating flat-bottomed containers such as beakers, Erlenmeyer flasks, and crystallizing dishes used as water baths or sand baths.

Hot plates also serve to heat the aluminum blocks used with microscale glassware.[1] Figure 6.2a shows a microscale setup for heating a standard-taper conical vial fitted with an air condenser; Figure 6.2b shows a microscale setup for heating a Williamson reaction tube and a round-bottomed flask fitted with an air condenser. Several types of aluminum heating blocks are available commercially. The blocks have holes sized to fit microscale reaction tubes or vials and a depression or hole for a 5- or 10-mL microscale round-bottomed flask. The blocks also have a hole designed to hold a metal probe thermometer so that the temperature of the block can be monitored.

Auxiliary aluminum blocks designed in two sections can be placed on top of the aluminum block around a vial or round-bottomed flask to provide extra radiant heat, as shown in Figure 6.3.

[1]Lodwig, S. N. *J. Chem. Educ.* **1989,** *66,* 77–84.



Auxiliary blocks used around a standard taper conical vial fitted with an air condenser

Auxiliary blocks used around a Williamson reflux apparatus for extra radiant heat

FIGURE 6.3 Using auxiliary aluminum blocks to provide extra radiant heat with microscale glassware.

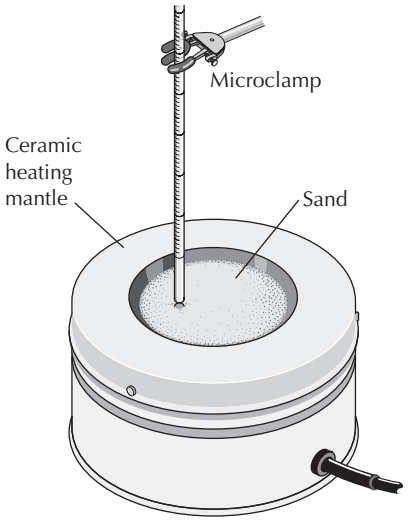
Sand Baths

A sand bath provides another method for heating microscale reactions. Sand is a poor conductor of heat, so a temperature gradient exists along the various depths of the sand, with the highest temperature occurring at the bottom of the sand and the lowest temperature near the top surface.

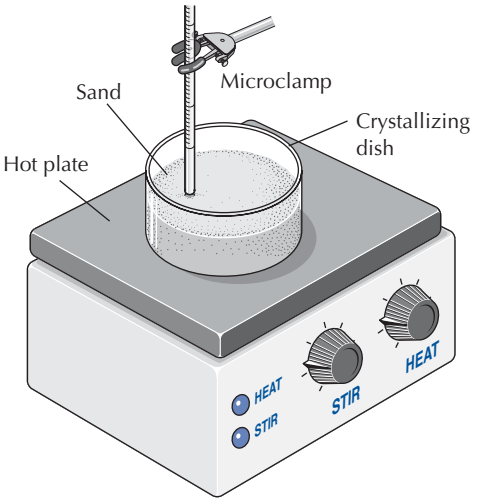
One method of preparing a sand bath uses a ceramic heating mantle, such as a Thermowell, about two-thirds full of washed sand (Figure 6.4a). A second method employs a crystallizing dish, heated on a hot plate, containing 1–1.5 cm of washed sand (Figure 6.4b); the sand in the dish should be level, not mounded. A thermometer is inserted in the sand so that the bulb is completely submerged at the same depth as the contents of the reaction vessel. The heating of a reaction vessel can be closely controlled by raising or lowering the vessel to a different depth in the sand as well as by changing the heat supplied by the heating mantle or hot plate.

SAFETY PRECAUTION

Sand in a crystallizing dish should not be heated above 200°C, nor should the hot plate be turned to high heat settings. Either situation could cause the crystallizing dish to crack.



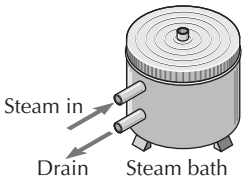
(a) Sand bath in ceramic heating mantle



(b) Sand bath in crystallizing dish on hot plate

FIGURE 6.4 Sand baths.

Steam Baths



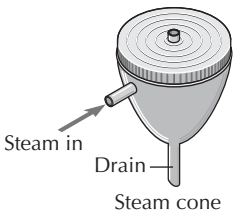


FIGURE 6.5
Steam baths.

Steam baths or steam cones provide a safe and efficient way of heating low-boiling flammable organic liquids (Figure 6.5). Steam baths are used in the organic laboratory for heating liquids below 100°C and in situations where precise temperature control is not required. The concentric rings on the top of the steam bath can be removed to accommodate containers of various sizes. A round-bottomed flask should be positioned so that the rings cover the flask to the level of the liquid it contains. For an Erlenmeyer flask, remove only enough rings to create an opening that is slightly larger than one-half of the bottom diameter of the flask.

SAFETY PRECAUTION

Steam is nearly invisible and can cause severe burns. Turn off the steam before placing a flask on a steam bath or removing it. (**Note:** The metal screw on the valve handle may be hot enough to cause burns.) Grasp the neck of a hot flask with flask tongs. **Do not use** a test tube holder or a towel.

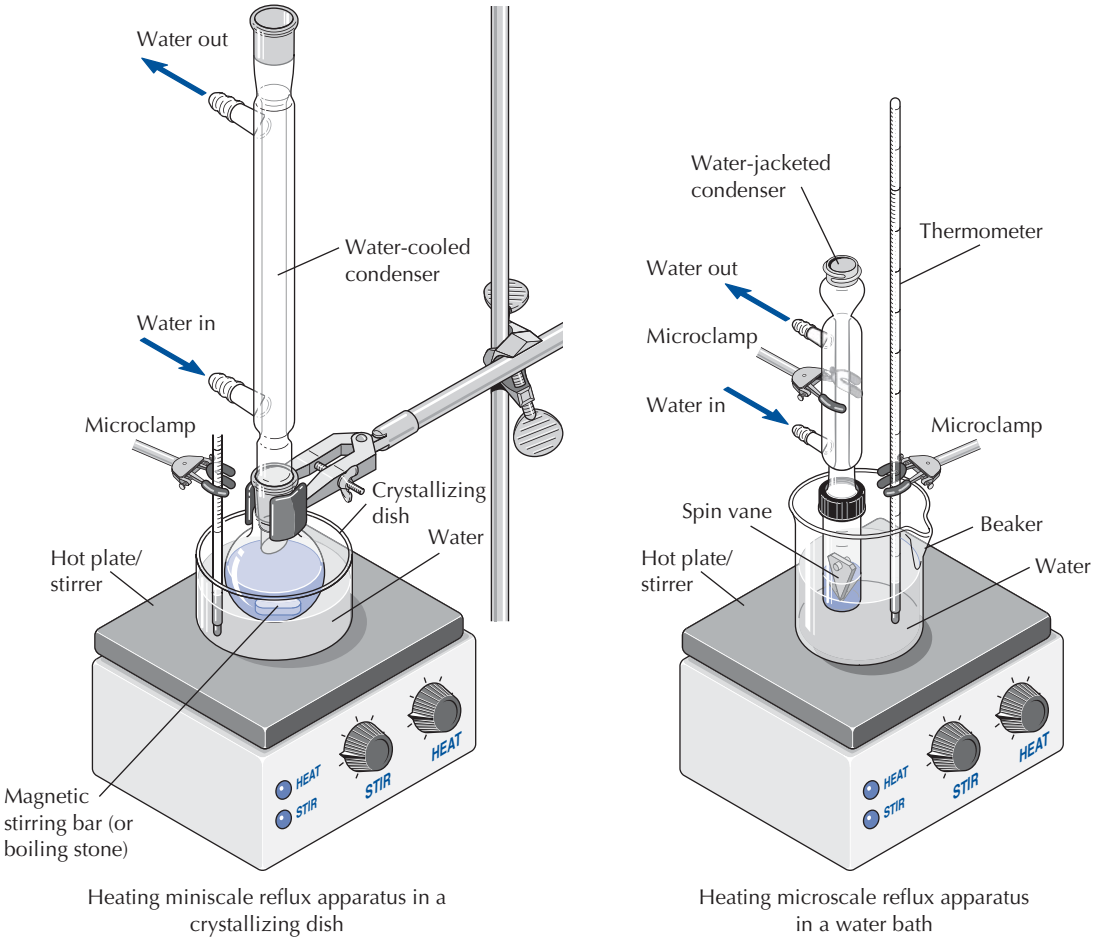
Steam baths operate at only one temperature, approximately 100°C. Increasing the rate of steam flow does not raise the temperature, but it does produce clouds of moisture within the laboratory or hood and in your sample. Adjust the steam valve for a **slow to moderate rate of steam flow** when using a steam bath.

A steam bath has two disadvantages. First, it cannot be used to boil any liquid with a boiling point above 100°C. Second, water vapor from the steam may contaminate the sample being heated on the steam bath unless special precautions are taken to exclude moisture.

Water Baths

When a temperature of less than 100°C is needed, a water bath allows for closer temperature control than can be achieved with the heating methods discussed previously. The water bath can be contained in a beaker or crystallizing dish. Once the desired temperature of the water bath is reached, the water temperature can be maintained by using a low heat setting on a hot plate. Magnetic stirring of the water bath prevents temperature gradients and maintains a uniform water temperature.

The thermometer used to monitor the temperature of a water bath should **always be held by a clamp** so that it does not touch the wall or bottom of the vessel holding the water (Figure 6.6). It is very easy to bump a thermometer that is merely set in a beaker and propped against its lip, perhaps breaking it or upsetting the water bath. In addition, if a thermometer is at the bottom of the water bath, it may give a temperature reading that does not accurately reflect the temperature in the reaction vessel. The reaction vessel should be submerged in the water bath no farther than the depth of the reaction mixture it contains.



Heating miniscale reflux apparatus in a crystallizing dish

Heating microscale reflux apparatus in a water bath

FIGURE 6.6 Water baths.

If magnetic stirring of a reaction mixture is needed, the reaction vessel should be clamped as close to the stirring motor as possible and centered on the hot plate/stirrer surface. A crystallizing dish may be a better choice than a beaker for the water bath, particularly if the reaction vessel is a round-bottomed flask. The wide, shallow crystallizing dish allows a round-bottomed flask to be clamped closer to the magnetic stirrer than does a beaker.

Oil Baths

Distillations of high-boiling liquids often need a heating bath of greater than 150°C [see Technique 13]. Water baths are limited to temperatures below 100°C, and a heating mantle may not offer fine enough temperature control for a successful distillation. In these cases magnetically stirred oil baths, heated on a hot plate, can provide the solution. The preceding discussion on using water baths also applies to using oil baths.

Both mineral oil (a mixture of high-boiling alkanes) and silicone oil are available commercially. Extremely stable, medium-viscosity silicone oil is ideal for heating baths, but it is quite expensive. Silicone oil is available in two temperature ranges—low temperature (designed for use up to 180°C) and high temperature (up to 230°C). Mineral oil that can be used for oil baths is less expensive but also poses a safety hazard: it is flammable. Mineral oil should not be heated over 175°C. Consult your instructor about using an oil bath if you are in a situation where one may be appropriate.

SAFETY PRECAUTION

Mineral oil is flammable. Care must be taken not to spill any on a hot plate. In addition, if any water gets into a mineral-oil heating bath, there is the danger of hot oil spattering out when the temperature gets over 100°C when the denser water begins to boil.

Heat Guns

A heat gun allows hot air to be directed over a fairly narrow area (Figure 6.7). A heat gun is particularly useful as a heat source for heating thin-layer chromatographic plates after they have been dipped in

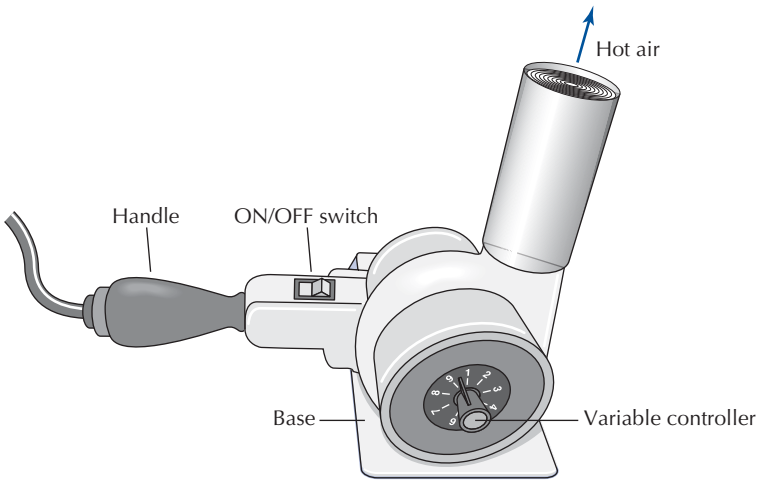


FIGURE 6.7
Heat gun.

a visualizing reagent that requires heat to develop the color. Heat guns usually have two heat settings as well as a cool air setting. If the heat gun does not have an integral stand, it should be suspended in a ring clamp with the heat setting on cool for a few minutes to allow the nozzle to cool before the gun is set on the bench.

Another use of heat guns is the rapid removal of moisture from glassware where dry but not strictly anhydrous conditions are needed.

Bunsen Burners

The use of Bunsen burners in the organic laboratory poses an extreme fire hazard because volatile vapors of organic compounds can ignite when mixed with air. Use of a Bunsen burner or other source of an open flame should be a very rare event in an organic laboratory and should never be undertaken without your instructor's supervision.

6.3 Cooling Methods

Cooling baths are frequently needed in the organic laboratory to control exothermic reactions, to cool reaction mixtures before the next step in a procedure, and to promote recovery of the maximum amount of crystalline solid from a recrystallization. Most commonly, cold tap water or an ice/water mixture serves as the coolant. Effective cooling with ice requires the addition of just enough water to provide complete contact between the ice and the flask or vial being cooled. Even crushed ice does not pack well enough against a flask for efficient cooling because the air in the spaces between the ice particles is a poor conductor of heat.

Temperatures from 0° to −10°C can be achieved by mixing solid sodium chloride into an ice/water mixture. The amount of water mixed with the ice should be only enough to make good contact with the vessel being cooled.

Dewar Flasks

A cooling bath of 2-propanol and chunks of solid carbon dioxide (dry ice) can be used for temperatures from −30° to −70°C. (**Caution:** Foaming occurs as solid carbon dioxide chunks are added to 2-propanol.) The 2-propanol/dry ice mixture should be contained in a Dewar flask, a double-walled vacuum chamber that insulates the contents from ambient temperature (Figure 6.8).

SAFETY PRECAUTION

The inside silvered glass surface of a Dewar flask is very fragile and must be handled with care. There is a vacuum between the two glass walls of a Dewar flask. If the silvered glass is broken, an implosion occurs and shards of glass are released. Never use a Dewar flask that does not have a protective metal case on the outside. **Always** use eye protection when using a Dewar flask.

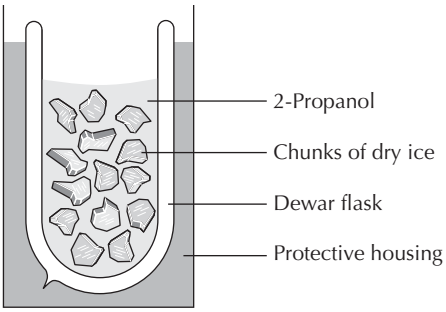


FIGURE 6.8
Dewar flask with a mixture of 2-propanol and dry ice.

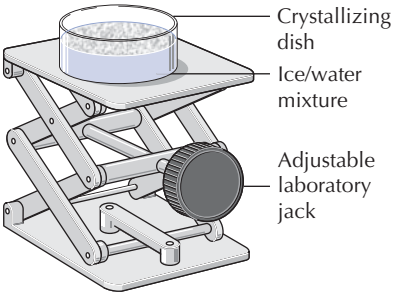


FIGURE 6.9
Laboratory jack with ice bath.

6.4 Laboratory Jacks

Laboratory jacks are adjustable platforms that are useful for holding heating mantles, magnetic stirrers, and cooling baths under reaction flasks (Figure 6.9). The reaction apparatus is assembled with enough clearance between the bottom of the reaction or distillation flask and the bench top to position the heating or cooling device under the flask by raising the platform of the lab jack. At the end of the operation, the heating or cooling device can be removed easily by lowering the lab jack.

TECHNIQUE 7

ASSEMBLING A REACTION APPARATUS

When carrying out organic reactions, it may be necessary to prevent loss of volatile compounds while maintaining a reaction mixture at the boiling point, to make additions of reagents to the reaction mixture, to keep atmospheric moisture from entering a reaction apparatus, and to prevent noxious vapors from entering the laboratory. Assembly of the apparatus necessary for each of these reaction conditions is described in this technique.

7.1 Refluxing a Reaction Mixture

Most organic reactions do not occur quickly at room temperature but require a period of heating. If the reaction were heated in an open container, the solvent and other liquids would soon evaporate; if the system were closed, pressure could build up and an explosion could occur. Chemists have developed a simple method of heating a reaction mixture for extended time periods without loss of reagents. This process is called ***refluxing,*** which simply means boiling a solution while continually condensing the vapor by cooling it and returning the liquid to the reaction flask.

A condenser mounted vertically above the reaction flask provides the means of cooling the vapor so that it condenses and flows back into the reaction flask. Condensers are available for either water cooling or air cooling. When the boiling point of a reaction mixture is less than 150°C, a water-jacketed condenser is used to transfer heat from the vapor to the water running through the outer jacket of the condenser. For efficient heat transfer, water must be flowing through the outer jacket, but if the flow is too fast, the rubber hose may pop off the condenser's water inlet and a minor flood will occur. For reaction mixtures with boiling points above 150°C, an air condenser is sufficient because the vapor loses heat rapidly enough to the surrounding atmosphere to condense before it can escape from the top of the condenser.

Rate of Heating

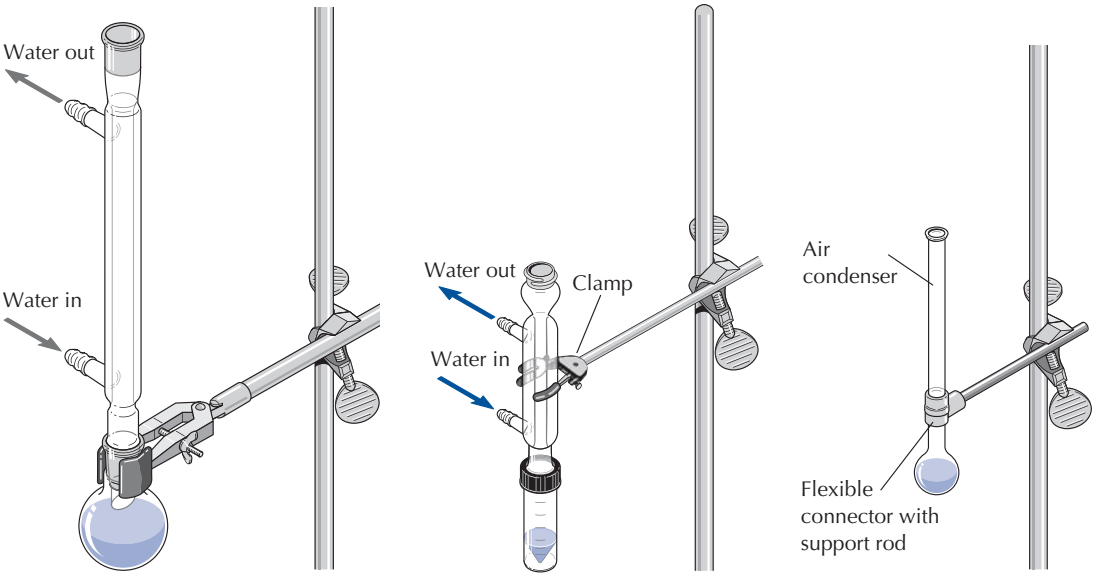
The rate of heating a reflux apparatus is not critical as long as the liquid in the reaction mixture boils at a moderate rate. With more heat, faster boiling occurs, but the temperature of the liquid in the flask cannot rise above the boiling point of the solvent or solution. If the system is boiling at too rapid a rate, the capacity of the condenser to cool the vapors may be exceeded and reagents (or product!) may be lost from the top of the condenser.

Miniscale Reflux Apparatus

A funnel keeps the reagents from coating the inside of the ground glass joint.

Begin the assembly of a reflux apparatus by firmly clamping a round-bottomed flask to a ring stand or vertical support rod. Position the clamp holder far enough above the bench top so that a ring or a lab jack can be placed underneath the flask to hold a heating mantle. Add the reagents to the reaction flask with the aid of a conical funnel for liquids and a powder funnel for solids. Add a boiling stone or magnetic stirring bar to the flask.

If grease is being used on the standard taper joint, apply it to the lower joint of the condenser before fitting it into the top of the flask. Attach rubber tubing to the water jacket outlets as shown in Figure 7.1a. **Water must flow into the water jacket at the bottom inlet and out at the top outlet** to ensure that a column of water without any air bubbles surrounds the inside tube. Raise the heating mantle, supported on an iron ring or a lab jack, until it touches the bottom of the round-bottomed flask. At the end of the reflux period, lower the heating mantle away from the reaction flask.



(a) Miniscale apparatus **(b)** ⅓ microscale apparatus **(c)** Williamson microscale apparatus

FIGURE 7.1 Apparatus for simple reflux.

Standard Taper Microscale Glassware

Place the reagents for the reaction in a conical vial or 10-mL round-bottomed flask sitting in a small beaker so that it will not tip over. Put a boiling stone or a magnetic spin vane into the reaction vessel. Grease is not used on the joints of microscale glassware except when the reaction mixture contains a strong base such as sodium hydroxide. Fit the condenser to the top of the conical vial or round-bottomed flask with a screw cap and an O-ring as shown in Technique 4, Figure 4.7. Fasten the apparatus to a vertical support rod or a ring stand with a microclamp attached to the condenser. Attach rubber tubing to the water jacket outlets (Figure 7.1b). **Water must flow into the water jacket at the bottom inlet and out at the top outlet** to ensure that a column of water without any air bubbles surrounds the inside tube. Lower the apparatus into an aluminum heating block, sand bath, or water bath heated on a hot plate or into a sand-filled Thermowell heater. At the end of the reflux period, raise the apparatus out of the heat source.

Williamson Microscale Glassware

Place a 5-mL round-bottomed flask in a 30-mL beaker and use the plastic funnel to add the reagents to the flask. Add a boiling stone or magnetic stirrer. Attach the air condenser to the flask using the flexible connector with the support rod. Clamp the apparatus to a vertical support rod or a ring stand as shown in Figure 7.1c. Wrap the air condenser with a wet paper towel or wet pipe cleaners to prevent loss of vapor when refluxing reaction mixtures containing solvents or reagents that boil under 120°C. Lower the apparatus into an aluminum heating block, sand bath, or water bath that is heated on a hot plate or into a sand-filled Thermowell heater. At the end of the reflux period, raise the apparatus out of the heat source.

7.2 Anhydrous Reaction Conditions

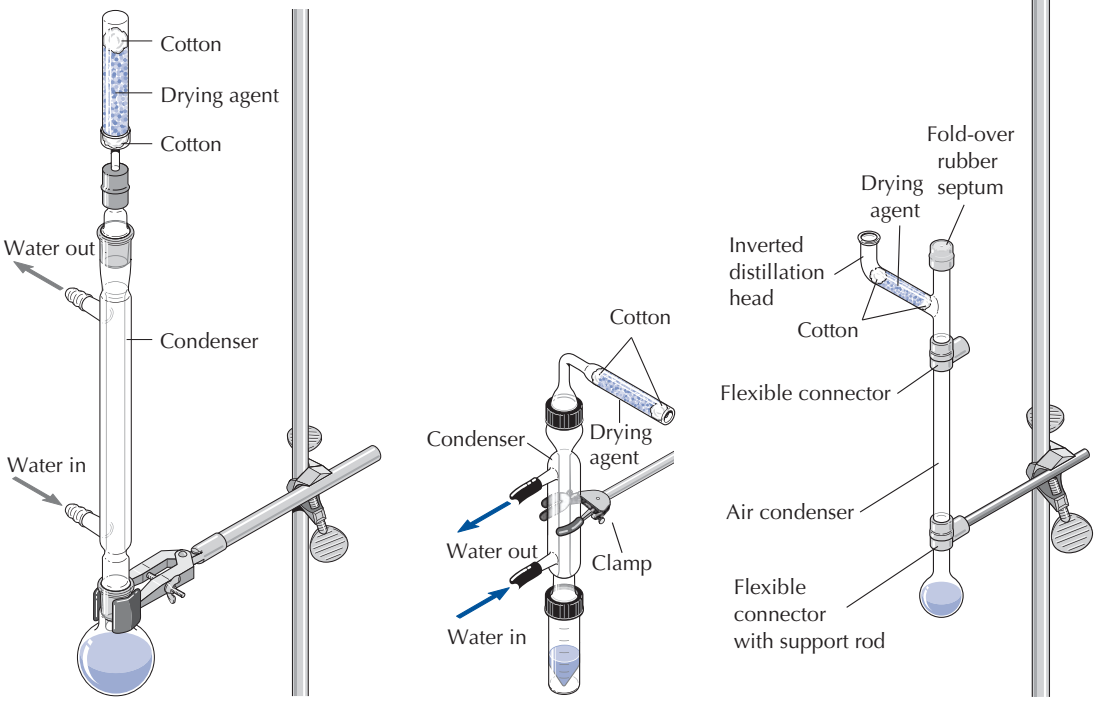
Sometimes it is necessary to prevent atmospheric moisture from entering a reaction vessel during the reflux period. In this case, a drying tube filled with a suitable drying agent, often anhydrous calcium chloride, is placed at the top of the condenser.

Miniscale Glassware

For miniscale glassware, a thermometer adapter with a rubber sleeve serves to hold the plastic drying tube (Figure 7.2a). A small piece of cotton is placed at the bottom of the drying tube to prevent drying agent particles from plugging the outlet of the tube; a piece of cotton is also placed over the drying agent at the top of the drying tube to keep the particles from spilling.

Standard Taper Microscale Glassware

The L-shaped standard taper microscale drying tube has a ground glass inner joint that fits into the outer ground glass joint at the top of the condenser and is secured with an O-ring and screw cap (Figure 7.2b). A small piece of cotton is pushed into the drying tube to prevent the drying agent particles from falling into the reaction vessel; cotton is also placed near the open end of the drying tube to hold the drying agent in place.



(a) Miniscale apparatus **(b)** ⅓ microscale apparatus **(c)** Williamson microscale apparatus

FIGURE 7.2 Refluxing under anhydrous conditions.

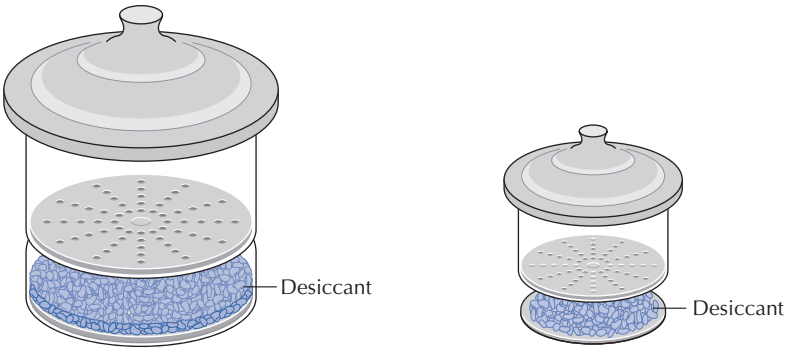


FIGURE 7.3
Desiccators.

(a) Large desiccator for storing oven-dried glassware

(b) Small desiccator for storing reagents

Williamson Microscale Glassware

Figure 7.2c shows how the Williamson microscale Claisen adapter/distilling head can be used as a drying tube. A small piece of cotton is pushed to the bottom of the side arm using the tip of a flexible plastic disposable pipet, a suitable drying agent, such as anhydrous calcium chloride, is added, and a second piece of cotton is placed at the top to keep the drying agent from spilling. The other opening is closed with a fold-over rubber septum. The drying tube is fitted to the top of the air condenser with a flexible connector.

Handling Glassware and Reagents for Anhydrous Conditions

The glassware used for reactions carried out under anhydrous conditions is usually dried in an oven and, if it will not be used as soon as it cools, placed in a desiccator (Figure 7.3a). It will probably be necessary to slide the lid of the desiccator open slightly several times during the cooling process to relieve the increased air pressure inside the chamber caused by the heat from the glassware. Assembly of the reaction apparatus and addition of reagents should be accomplished as rapidly as possible to minimize their exposure to atmospheric moisture.

The reagents used for anhydrous reactions also need to be anhydrous. Solid reagents can be stored in small desiccators such as the one shown in Figure 7.3b. Anhydrous liquid reagents as sold by the manufacturer usually have a sealed cap with a septum in the top or other type of tight seal to exclude moisture. If a liquid reagent has been opened, it may need to be stored over a suitable drying agent for a period of time prior to using the reagent in an anhydrous reaction.

7.3 Addition of Reagents During a Reaction

Miniscale Glassware

When it is necessary to add reagents during the reflux period, a separatory funnel can be used as a dropping funnel. If the round-bottomed flask has only one neck, a Claisen adapter provides a second opening into the flask, as shown in Figure 7.4a. For a three-necked flask, the third neck is closed with a ground glass stopper, as shown in Figure 7.4b. If it is also necessary to maintain anhydrous conditions [see Technique 7.2] during the reflux period, both the condenser and

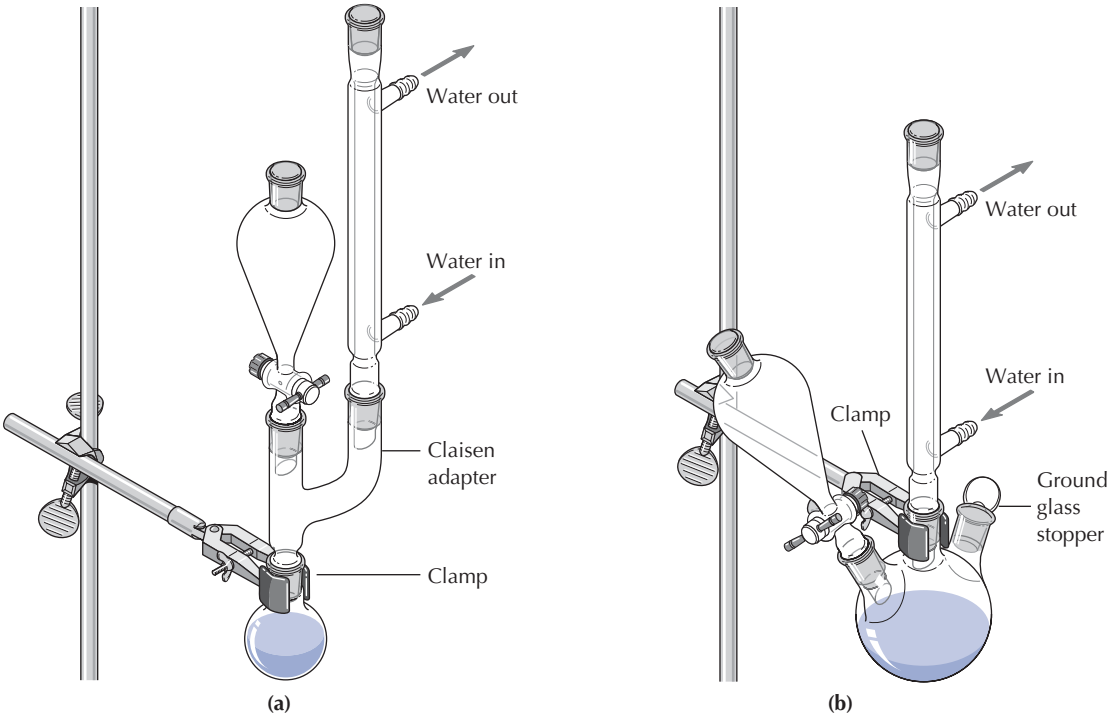


FIGURE 7.4 Assemblies for adding reagents to a reaction heated under reflux in (a) a one-necked reaction flask and (b) a three-necked flask.

the separatory funnel can be fitted with drying tubes filled with a suitable drying agent.

Standard Taper Microscale Glassware

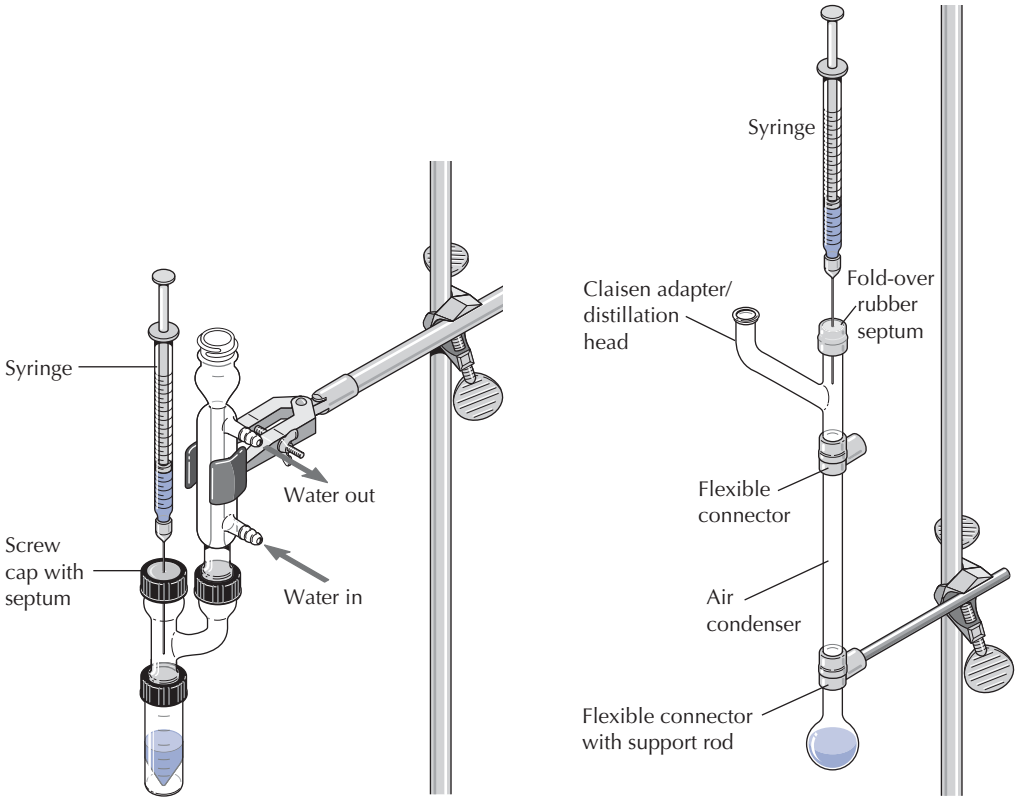
The addition of reagents to a microscale reaction is done with a syringe. Figure 7.5a shows a standard taper microscale apparatus assembled for reagent addition using a syringe. The Claisen adapter provides two openings into the system. The opening used for the syringe can be capped either with a screw cap and Teflon septum or with a fold-over rubber septum. The top of the condenser is left open.

Williamson Microscale Glassware

The addition of reagents to a microscale reaction is done with a syringe. For Williamson microscale glassware, the Claisen adapter/distilling head provides two openings in the system. The vertical opening used for the syringe is capped with a fold-over rubber septum and the side-arm opening is left uncovered, as shown in Figure 7.5b.

7.4 Removal of Noxious Vapors

When a noxious acidic gas such as nitrogen dioxide, sulfur dioxide, or hydrogen chloride forms during a reaction, it must be prevented from escaping into the laboratory. Acidic or basic gases, such as HCl



(a) Microscale apparatus **(b)** Williamson microscale apparatus

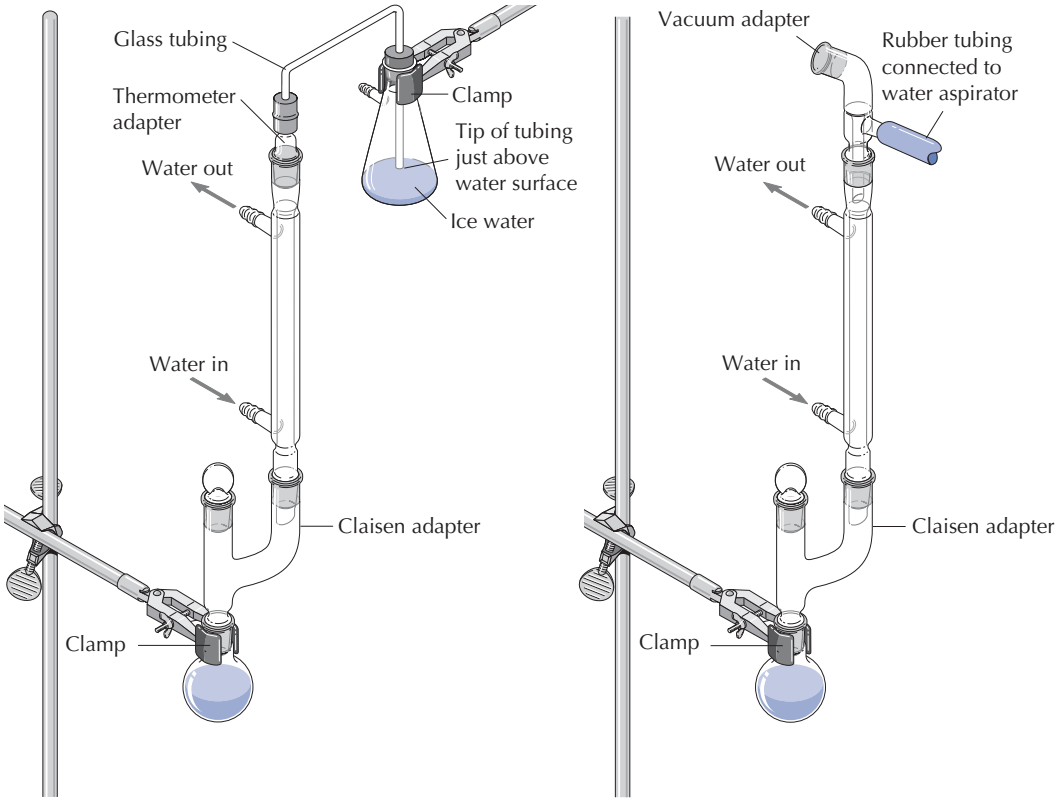
FIGURE 7.5 Using a syringe to add reagents to a microscale reaction.

or NH_3, are readily soluble in water, so a gas trap containing either water or dilute aqueous sodium hydroxide for HCl vapors, or dilute hydrochloric acid solution for NH_3 vapors, effectively traps them. **Any reaction that emits noxious vapors should be performed in a hood.**

Miniscale Apparatus

Attach a U-shaped piece of glass tubing to the top of a reflux condenser by means of a one-hole rubber stopper or a thermometer adapter. Carefully fit the other end of the U tube through a one-hole rubber stopper sized for a 125-mL filter flask. Place about 50 mL of ice water or dilute sodium hydroxide solution in the filter flask and position the open end of the U tube **just above** the surface of the liquid, as shown in Figure 7.6a.

In laboratories equipped with water aspirators, a gas trap can be made by placing a vacuum adapter at the top of a condenser. The side arm of the vacuum adapter is connected by heavy-walled rubber tubing to the side arm of the water aspirator and the water turned on at a moderate flow rate. The noxious gases are pulled



(a) Gas trap attached to reaction apparatus **(b)** Noxious vapors exhausted through a water aspirator

FIGURE 7.6 Miniscale apparatus used to trap water-soluble noxious vapors.

from the reaction apparatus and dissolved in the water passing through the aspirator (Figure 7.6b).

Standard Taper Microscale Apparatus

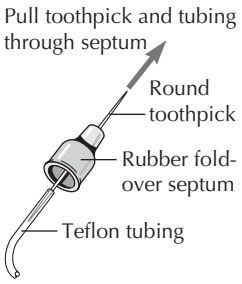
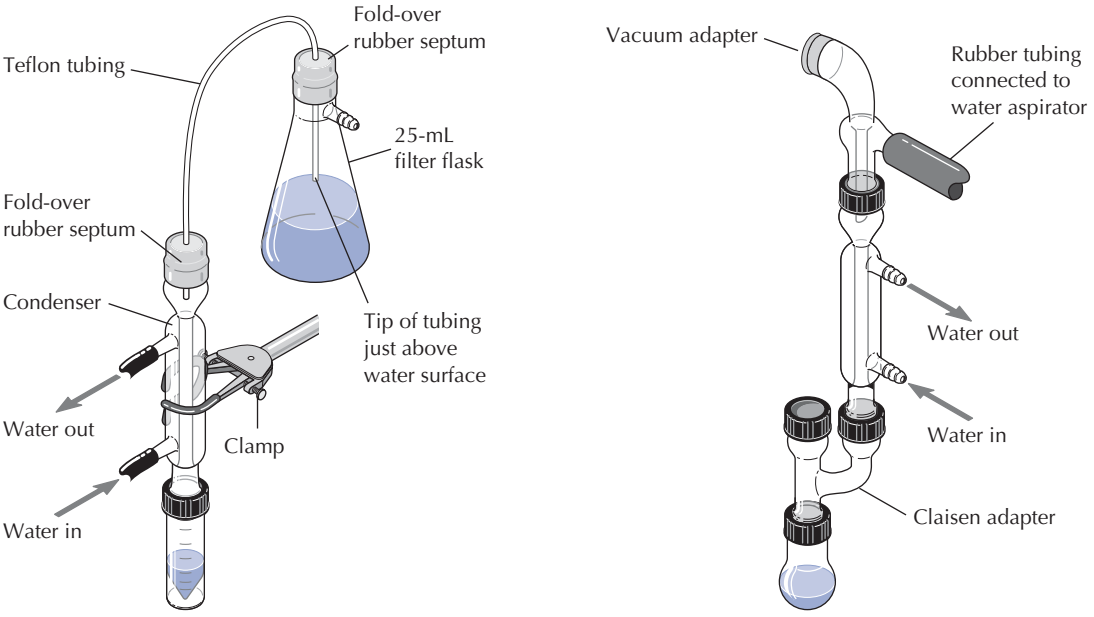


FIGURE 7.7 Threading Teflon tubing through a rubber septum.

A gas trap for microscale reactions can be prepared with fold-over rubber septa, Teflon tubing (1/16 inch in diameter), and a 25-mL filter flask. To insert the Teflon tubing through a rubber septum, carefully punch a hole in the septum with a syringe needle and push a round toothpick through the hole. Fit the tubing over the point of the toothpick and pull the toothpick (with tubing attached) back through the septum, as shown in Figure 7.7. Repeat this process to place a rubber septum on the other end of the tubing.

Half fill a 25-mL filter flask with ice water, or a dilute aqueous solution of acid or base if needed, and close the top with one septum. Push the tubing down until the open end is **just above** the surface of the water or sodium hydroxide solution. Attach the other septum to the top of the condenser. The side arm of the filter flask serves as a vent (Figure 7.8a).

In laboratories equipped with water aspirators, a gas trap for standard taper microscale glassware can be made by placing a vacuum adapter at the top of a condenser. The side arm of the vacuum



(a) Gas trap attached to reaction apparatus

(b) Bent vacuum adapter

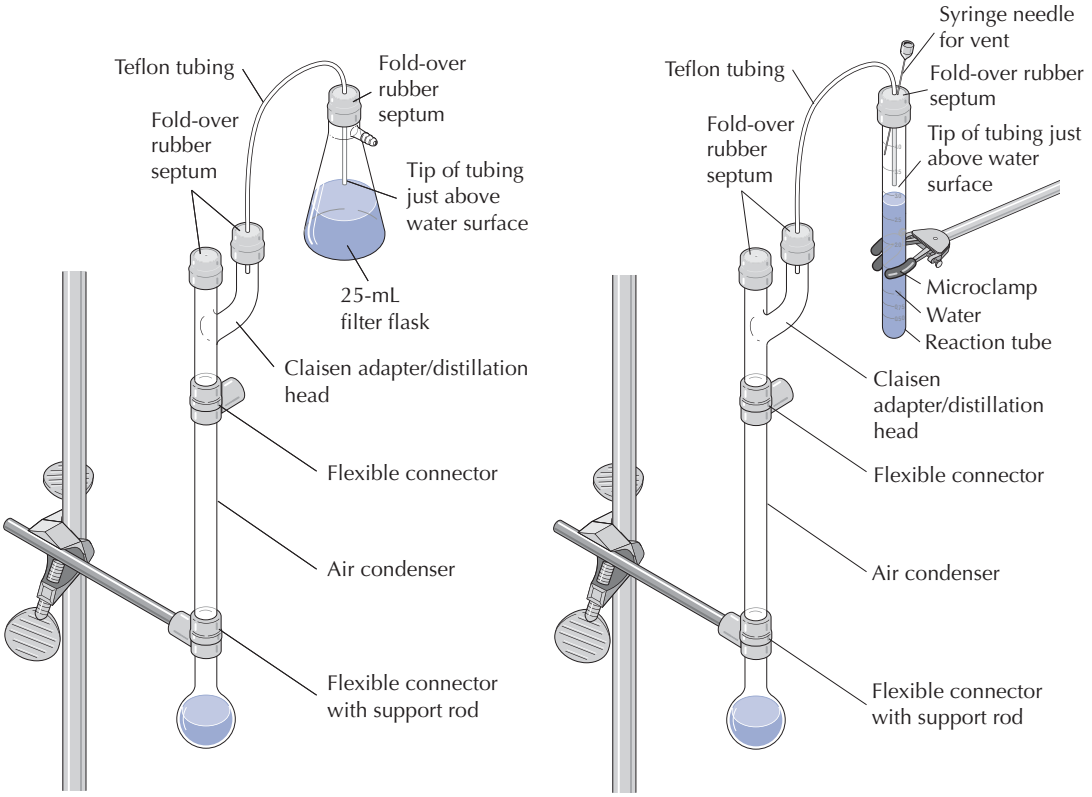
FIGURE 7.8 Standard taper microscale apparatus used to trap water-soluble noxious vapors.

adapter is connected to the side arm of the water aspirator with heavy-walled rubber tubing and the water turned on at a moderate flow rate. The noxious gases are pulled from the reaction apparatus and dissolved in the water passing through the aspirator (Figure 7.8b).

Williamson Microscale Glassware

A gas trap for microscale reactions using Williamson glassware can be prepared with three fold-over rubber septa, Teflon tubing (1/16 inch in diameter), and a 25-mL filter flask or a reaction tube. To insert the Teflon tubing through a rubber septum, carefully punch a hole in one septum with a syringe needle and push a round toothpick through the hole. Fit the tubing over the point of the toothpick and pull the toothpick (with tubing attached) back through the septum, as shown in Figure 7.7. Repeat this process to place a rubber septum on the other end of the tubing.

Half fill a 25-mL filter flask or a Williamson reaction tube with ice water or dilute sodium hydroxide solution and close the top with one septum attached to the tubing. Push the tubing down until the open end is **just above** the surface of the water or sodium hydroxide solution. Attach the other septum to the top of the Claisen adapter. Close the other opening of the Claisen adapter with the third septum. If a filter flask serves as the trap, the side arm provides a vent (Figure 7.9a); if the trap is a Williamson reaction tube, then a syringe needle **must** be inserted into the septum attached to the reaction tube to provide a vent (Figure 7.9b)



(a) Gas trap using a 25-mL filter flask

(b) Gas trap using a reaction tube and syringe needle vent

FIGURE 7.9 Williamson microscale apparatus used to trap water-soluble noxious vapors.

TECHNIQUE

8 COMPUTATIONAL CHEMISTRY

Computational chemistry is the calculation of physical and chemical properties of compounds using mathematical relationships derived from theory and observation to picture the structures of molecules. It is often referred to as ***molecular modeling.*** However, we use the term *computational chemistry* to avoid confusion with molecular model sets, which you may have already used to create three-dimensional structures of molecules. Once the exclusive domain of mainframe and supercomputers, computational chemistry has migrated to desktop and laptop computers. Advances in computer hardware provide massive amounts of memory, high computational speed, and high-resolution graphics displays.

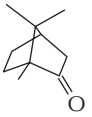
Carrying out these calculations is often most useful before you go into the laboratory to perform your experiments. The calculation results can inform a chemist about how to design and carry out experiments and in the process save a good deal of time.

8.1 Picturing Molecules on the Computer

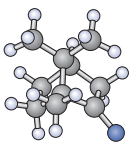
Computational chemistry can be used to create three-dimensional images and two-dimensional projections of chemical structures. The computer images that result are completely interactive. In this way they are similar to a molecular model set, but computational chemistry is also much more. In molecular model sets, the bond lengths and bond angles are fixed at certain "standard values," such as 109.5° for the bond angle of a tetrahedral (sp^3) carbon atom. Anyone who has built a molecule containing a cyclopropane ring is well aware of the limitations of using a 109.5° bond angle for its "tetrahedral" carbon atoms. The structure of a molecule created on the computer can be optimized by changing bond lengths and angles until the structure represents the lowest energy conformation of the molecule. Optimization means that the bond lengths and bond angles of the structure are allowed to deviate from their "standard values." Thus, the molecule created on the computer is a more accurate picture of the actual molecule than can be obtained from using a molecular model set.

Computational Chemistry Programs

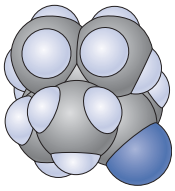
Most computational chemistry programs consist of interacting modules that carry out specialized tasks such as building a molecule, optimizing the molecular structure, and extracting physical properties from the calculation. The computer image of a molecule can be shown in a variety of ways—wire frame, ball and stick, and space filling, to mention a few. Wire frame images are best to represent bond angles, lengths, and direction. A molecule's size and shape are probably best represented by a space-filling model. The rendering methods can be mixed to emphasize steric interactions in a specific portion of a molecule. The electron density surface can be displayed, providing a view of its overall shape. The electrostatic potential can be mapped onto the molecular surface, highlighting regions of potential reactivity within the molecule. Molecular orbitals can also be superimposed onto a molecular structure.



Camphor
wire frame model



Camphor
ball-and-stick model



Camphor
space-filling model

Many physical and chemical properties can be extracted from an optimized molecular structure. These properties include bond lengths, bond angles, dihedral angles, interatomic distances, dipole moments, electron densities, and heats of formation. The computed properties are often very good approximations of the values determined by experiments.

Computational Methods

There are two major types of computational methods. The first, called ***molecular mechanics***, is derived from a classical mechanical model, which treats atoms as balls and bonds as springs connecting the balls. In general, molecular mechanics methods pay attention to nuclei, while paying little attention to electrons. The second and more rigorous group of methods is based on ***quantum mechanics***, which can be used to describe the physical behavior of matter on a very small scale. Quantum mechanics methods pay attention to both nuclei and electrons.

Following are some computational chemistry packages available for modern microcomputers:

- MacSpartan and PC Spartan from Wavefunction
- ChemBio3D from CambridgeSoft
- CAChe for Macintosh and CAChe for PC from Fujitsu
- HyperChem from HyperCube

We will describe in general terms and give examples of the types of calculations that are possible using these computational packages and their limitations. Because the operation of a program and its calculation modules differs from one package to another, the details of these packages will not be discussed. Materials included with the packages provide comprehensive descriptions of the specific methods the programs use.

8.2 Molecular Mechanics Method

The ***molecular mechanics (MM)*** method was developed in the 1970s. It treats a molecule as an assemblage of classical balls (atoms) and springs (bonds, bond angles, and so on) connecting the balls. The ***total energy*** of a molecule, often called the ***steric energy*** or ***strain energy,*** is the sum of energy contributions from bond stretching, angle strain, strain resulting from improper torsion, steric or van der Waals interactions, and electronic charge interactions.

$$E_{\text{steric}} = E_{\text{bond stretching}} + E_{\text{angle bending}} + E_{\text{torsion}} + E_{\text{van der Waals}} + E_{\text{electrostatic interactions}}$$

The contributions are described by empirically derived equations. For example, the energy of bond stretching is approximated by the energy of a spring described by Hooke's Law from classical physics,

$$E_{\text{bond stretching}} = 1/2k\,(x - x_0)^2$$

in which k is a force constant related to bond strength and $(x - x_0)$ is

the displacement of an atom from its equilibrium bond length (x_0). If a bond is stretched or compressed, its potential energy will increase, and there will be a restoring force that tries to restore the bond to its equilibrium bond length. The force constants for various types of bonds can be derived from experimental data and are incorporated into the molecular mechanics parameter set. The energy of the bond stretching in the molecule is the sum of the contributions from all of its bonds.

$$E_{\text{bond stretching}} = \sum_{i=1}^{i=n \text{ bonds}} 1/2k_i(x - x_0)_i^2$$

Other energy contributions are developed in a similar fashion. For example, an angle has a force constant, k, which resists a change in the size of the bond angle. As with the energy of bond stretching, $E_{\text{angle bending}}$ must be systematically varied until it is minimized. Molecular mechanics calculations give good estimates for the bond lengths and angles in a molecule.

The collections of equations describing the various energies and their associated parameter sets are called ***force fields.*** Following are some frequently used force fields:

- MM2, MM3, MM4
- MMX
- MMFF
- SYBYL

The kinds of energy outputs from a molecular mechanics calculation are listed here. These data come from using the ChemBio3D computational package with an MM2 force field, and they involved 19 iterations.

Stretch:	0.3406
Bend:	0.3720
Stretch-Bend:	0.0893
Torsion:	2.1529
Non-1,4 VDW	−1.0609
1,4 VDW	4.6632
Total (steric energy):	**6.5571**

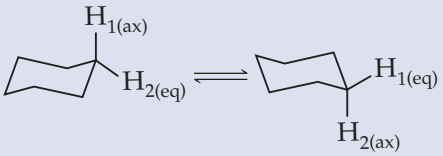
The absolute value of the steric energy of a molecule has no meaning by itself. Its calculated value can vary greatly from one force field parameter set to another. Steric energies are useful only for comparison purposes. The comparisons are most useful for conformers, such as chair and twist-boat cyclohexane, and diastereoisomers, such as *cis*- and *trans*-1,3-dimethylcyclohexane.

In the calculation of the total energy each atom type is associated with an unstrained heat of formation. The relative heat of formation of each isomer is then the sum of the heats for the unstrained atom types plus the strain energy.

Energies of Cyclohexane Conformers

WORKED EXAMPLE

The axial and equatorial conformers of cyclohexanes can be interchanged by way of a ring flip. In the simplest example, the axial hydrogen atoms of cyclohexane become equatorial hydrogen atoms and the equatorial hydrogen atoms become axial hydrogen atoms. Construct an energy profile for converting one chair conformer into its flipped chair conformer.



To perform this feat of molecular gymnastics, the cyclohexane ring twists and bends into several conformers. Starting at the chair conformer, it proceeds through a half-chair, then a twist-boat, then a boat conformation, then through another twist-boat and half-chair to the flipped chair conformer.

Calculate the steric energies of each of these conformers and construct an energy profile for converting one chair conformer into its flipped chair conformer. The computational chemistry package actually used to obtain the desired energies was Spartan 06, using an MMFF force field parameter set.

Construction and optimization of chair cyclohexane

1. If the computational chemistry package has a fragment library, select the chair cyclohexane. Otherwise, construct a ring of six carbons that roughly approximates a chair conformation.
2. Optimize the geometry (or minimize the energy) using the molecular mechanics module of the program. If the optimized structure is not in the chair conformation, judicious editing of the structure and optimization will usually afford the chair conformation.
3. Record its steric energy (−14.9 kJ/mol).

Construction and optimization of boat cyclohexane

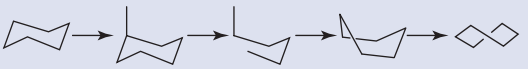
1. If the computational chemistry package has a fragment library, select the cyclopentane. Otherwise, construct a ring of five carbons.
2. Attach sp^3 carbons to the 1 and 3 positions of the cyclopentane ring. The attached carbons must be on the same side of the ring.
3. Make a bond between the two methyl groups to form bicyclo [2.2.1]heptane.
4. Optimize the geometry (or minimize the energy) using the molecular mechanics module of the program.

5. Delete the carbon atom that forms the one carbon bridge of bicyclo[2.2.1]heptane. Optimize the geometry (or minimize the energy) using the molecular mechanics module of the program. This structure should be the boat conformation of cyclohexane.

6. Record the steric energy (13.0 kJ/mol).

Construction and optimization of twist-boat cyclohexane

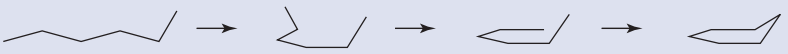
1. Construct a chair cyclohexane.
2. Attach an sp^3 carbon atom to an axial position of the cyclohexane ring to create *axial*-methylcyclohexane.
3. Delete the ring carbon atom that is directly adjacent to the ring carbon bearing the methyl group.
4. Make a bond between the terminal carbons of the resulting six carbon atom chain.
5. Optimize the geometry (or minimize the energy) using the molecular mechanics module of the program. This structure should be twist-boat cyclohexane.



6. Record the steric energy (9.9 kJ/mol).

Construction and optimization of half-chair cyclohexane. To construct this conformer it is necessary to force five carbons of the cyclohexane ring to lie in the same plane.

1. Build a chain of six sp^3 carbon atoms.
2. Define the dihedral angle described by C2, C3, C4, and C5 to be 0° and lock the angle to that value.
3. Define the dihedral angle described by C1, C2, C3, and C4 to be 0° and lock the angle to that value.
4. Connect the terminal carbons, C1 and C6, with a bond.



5. Optimize the geometry (or minimize the energy) using the molecular mechanics module of the program. Make sure the program respects the constraints. With Spartan 06 there is a Constraints box that must be checked.
6. Record the steric energy (28.2 kJ/mol).

Using the calculated steric energies, an energy profile connecting each conformation of cyclohexane can be constructed, as shown in Figure 8.1.

To recap, the steric energies are: chair, −14.9 kJ/mol; half-chair, 28.2 kJ/mol; twist-boat, 9.9 kJ/mol; boat, 13.0 kJ/mol.

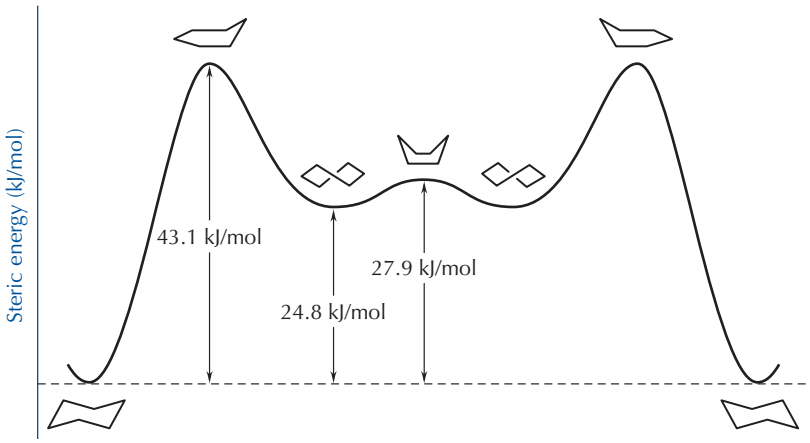
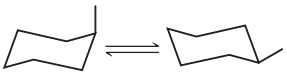


FIGURE 8.1
Energy profile for interconversion of the chair conformers of cyclohexane.

Equilibrium Constants for Axial and Equatorial Cyclohexane Conformers

Differences in steric energies can also be used to estimate equilibrium constants between interconverting conformers. At room temperature methylcyclohexane is a mixture of *axial*-methylcyclohexane and *equatorial*-methylcyclohexane that are rapidly interconverting by way of a ring flip.



The relative amount of each conformer at equilibrium can be determined by the difference in energy between the two conformers, which is related to the equilibrium constant, K_{eq}, by the following relationships:

$$K_{eq} = \frac{\text{number of } eq\text{-methylcyclohexane molecules}}{\text{number of } ax\text{-methylcyclohexane molecules}}$$

$$\Delta G^0 = -RT \ln K_{eq} = -2.303\, RT \log K_{eq}$$

where ΔG^0 is the change in Gibbs standard free energy in going from *axial*-methylcyclohexane to *equatorial*-methylcyclohexane, R is the gas constant (1.986 cal $deg^{-1} \cdot mol^{-1}$) and T is the absolute temperature in degrees Kelvin (K).

Using the MM2 force field with CAChe, the steric energy of *axial*-methylcyclohexane is calculated to be 8.69 kcal/mol, and the steric energy of *equatorial*-methylcyclohexane is calculated to be 6.91 kcal/mol. If the difference in steric energy approximates the difference in free energy between the conformers, the free energy difference is –1.78 kcal/mol. The negative value for $\Delta G°$ signifies a release of energy in going from *ax*-methylcyclohexane to *eq*-methylcyclohexane. At room temperature (25°C, 298 K), the preceding equation becomes

$$-1.78 = -1.36 \log K_{eq}$$

$$\log K_{eq} = 1.31$$

$$K_{eq} = 20.4$$

At equilibrium, there would be approximately 20 molecules of *equatorial*-methylcyclohexane present for each molecule of *axial*-methylcyclohexane—close to the experimental value.

FOLLOW-UP ASSIGNMENT

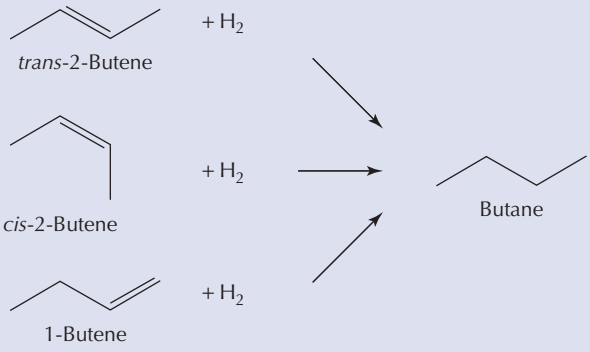
Calculate the steric energies for *equatorial-tert*-butylcyclohexane and *axial-tert*-butylcyclohexane and use them to calculate the composition of their equilibrium mixture at 25°C. Construct the chair cyclohexane using the method on p. 71 and then replace an equatorial hydrogen with a *tert*-butyl group. For the construction of *axial-tert*-butylcyclohexane replace an axial hydrogen with a *tert*-butyl group. Optimize the geometries using the molecular mechanics module of your computational chemistry package. Record the two energies and calculate the equilibrium constant.

Energies of Butene Isomers: Limitations of Molecular Mechanics

WORKED EXAMPLE

Molecular mechanics methods work well for comparing the energies of conformers, but less well for isomeric compounds that are not conformers. Consider the case of the isomeric butanes: 1-butene, *cis*-2-butene and *trans*-2-butene. The disubstituted 2-butenes are known to be more stable than 1-butene, and the *trans*-isomer of 2-butene is more stable than the *cis*-isomer. A quantitative experimental perspective comes from heats of formation as well as heats of hydrogenation.

The hydrogenation of all three butenes produces butane.



Thus, the differences in the heats of hydrogenation are a measure of the relative energy levels of the alkenes (Figure 8.2).

The heats of hydrogenation and heats of formation follow:

	$\Delta H_{hydrogenation}$ (kJ/mol)	($\Delta H°$)	ΔH_f° (kJ/mol)
1-Butene	126.8	(0.0)	0.1
cis-2-Butene	119.7	(−7.1)	−9.2
trans-2-Butene	115.5	(–11.3)	−14.0

Both data sets indicate that *trans*-2-butene is more stable than the *cis* isomer by 4–5 kJ/mol and 1-butene is the least stable of the three isomers.

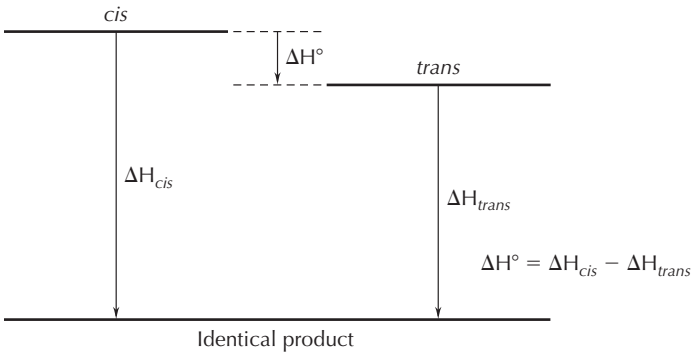


FIGURE 8.2
Energy diagram for the conversion of two isomers to a common product.

How well do the steric energies of these three butenes match the experimental data? With Spartan 06 using the MMFF parameter set, the following results were obtained:

	Steric energy (kJ/mol)
1-Butene	22.7
cis-2-Butene	25.9
trans-2-Butene	20.3

The calculated steric energies indicate that the most stable isomer is *trans*-2-butene and the least stable isomer is *cis*-2-butene. This result does not agree with the experimental results. The molecular mechanics calculation is not reliable in comparing the energies of the butene isomers. However, calculations using the quantum mechanical methods described in Section 8.3 are far more reliable. Optimizing the geometry of the butenes using the AM1 parameter set (MOPAC) of the semi-empirical quantum mechanical method in Spartan 06 gives the following results:

	ΔH_f° (kJ/mol)
1-Butene	0.7
cis-2-Butene	−7.1
trans-2-Butene	−11.4

Now the order of stability is correct and the differences in the calculated energies of the three isomers are close to the experimental results.

8.3 Quantum Mechanics Methods: *Ab Initio,* Semiempirical, and DFT Methods

Quantum mechanical molecular orbital (MO) methods are based on solving the ***Schrödinger wave equation,*** $\hat{H}\Psi = E\Psi$, in which $\hat{H}$ is the Hamiltonian operator describing the kinetic energies and electrostatic interactions of the nuclei and electrons that make up a molecule, E is the energy of the system, and Ψ is the wavefunction of the system. Although simple in expression, the solution is exceedingly

complex and requires extensive computational time. Even an organic molecule as simple as methane defies exact solution. The key to obtaining useful information from the Schrödinger relationship in a reasonable length of time lies in choosing approximations that simplify the solution. There are tradeoffs, however. When more approximations are used, the calculation is faster but the accuracy of the result may be degraded.

Ab Initio *Quantum Mechanical Molecular Orbital (MO) Methods*

Quantum mechanical MO models with the least degree of approximation are called **ab initio *methods***. *Ab initio* is a Latin phrase that means "from the beginning" or "from first principles." Following are some common approximations that are used even in *ab initio* MO theory:

1. Nuclei are stationary relative to electrons, which are fully equilibrated to the molecular geometry (Born-Oppenheimer approximation).
2. Electrons move independently of each other, and the motion of any single electron is affected by the average electric field created by all the other electrons and nuclei in the molecule (Hartree-Fock approximation).
3. A molecular orbital is constructed as a linear combination of atomic orbitals (LCAO approximation).

Ab initio calculations use a collection of atomic orbitals called a ***basis set*** to describe the molecular orbitals of a molecule. There are numerous basis sets of varying complexity in use. The choice affects the accuracy of the calculation and the amount of time required for a solution. Normally, you should use the lowest degree of complexity that will answer your question or solve the problem.

The smallest basis set in common use is STO-3G, so called because it is a Slater-type orbital (STO) built from three Gaussian functions to describe each orbital. STOs have the same angular terms and overall shape as the hydrogen-like orbitals 1*s*, 2*s*, 2*p* and so on, but are different in that they have no radial nodes. The STO-3G basis set works reasonably well with first- and second-row elements that incorporate *s*- and *p*-orbitals. An *ab initio* calculation using an STO-3G basis set can often provide good equilibrium geometries.

Much of the time, the medium-sized 3-21G basis set is a good starting point. The 3-21G symbolism signifies that three Gaussian functions are used for the wavefunction of each core electron, but the wavefunctions of the valence electrons are "split" two to one between inner and outer Gaussian functions, allowing the valence shell to expand or contract in size. The 6-31G* basis set, using more Gaussian functions and a polarization function on heavy atoms, provides better answers and is more flexible. However, it requires more calculation time, typically ten to twenty times more than the same calculation using an STO-3G basis set.

Semiempirical Molecular Orbital (MO) Approach

The geometries and energies of organic molecules can be optimized by the *ab initio* MO method using a 3-21G basis set with a desktop computer, but the calculation can take many minutes for the

optimization of even a small organic molecule. For most practical purposes, a faster method of calculation is needed. The ***semiempirical molecular orbital approach*** introduces several more approximations that dramatically speed up the calculations. A geometry optimization using a semiempirical molecular orbital method is typically 300 or more times faster than one using an *ab initio* MO method with a 3-21G basis set.

The approximations generally used with semiempirical molecular orbital methods are as follows:

1. Only valence electrons are considered. Inner shell electrons are not included in the calculation (this is also an option with *ab initio* MO calculations).
2. Only selected interactions involving at most two atoms are considered. This is called the *neglect of diatomic differential overlap*, or NDDO.
3. Parameter sets are used to calculate interactions between orbitals. The parameter sets are developed by fitting calculated results with experimental data.

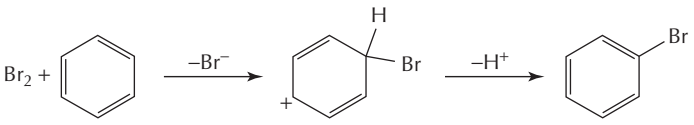
Several popular versions of semiempirical methods follow:

- MNDO or **m**inimum **n**eglect of **d**ifferential **o**verlap
- AM1 or **A**ustin **m**ethod 1
- PM3 or **p**arameterized **m**odel 3

In many cases, AM1 is the method of choice for organic chemists; it should be used whenever possible before resorting to an *ab initio* calculation. Using an Apple Macintosh G-5 computer, for example, the optimization of 2-bromoacetanilide, which you will soon see in a worked example, takes almost 18 minutes in an *ab initio* calculation using a 3-21G basis set; using the AM1 semiempirical method the optimization takes 1.7 seconds. The PM3 method is often used for inorganic molecules because it has been parameterized for more chemical elements. The ***MOPAC*** or **m**olecular **o**rbital **pac**kage combines these three semiempirical methods in a single program. As you become more familiar with computational chemistry, you will be able to experiment with the various methods to find the one that works best for the molecules you are working with.

WORKED EXAMPLE

The bromination of a benzene ring is an example of an electrophilic aromatic substitution reaction, which involves the reaction of Br_2 with the benzene ring to form a bromobenzenium cation in the rate-determining step. The bromobenzenium ion subsequently loses a proton to yield a bromobenzene product.



Bromobenzenium cation

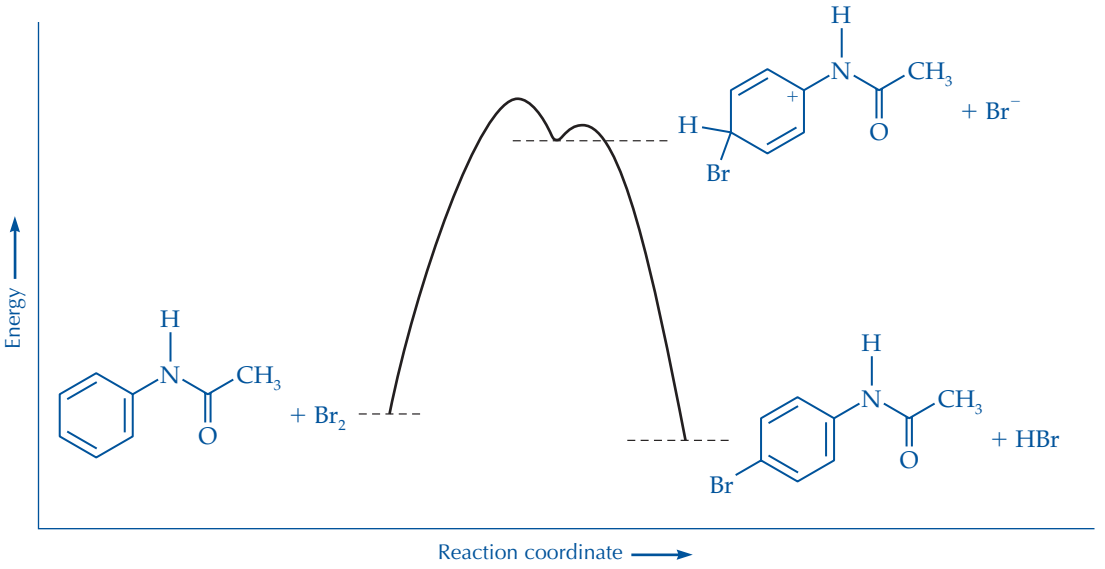
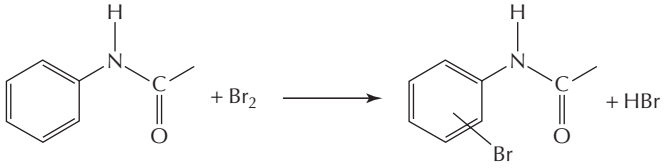


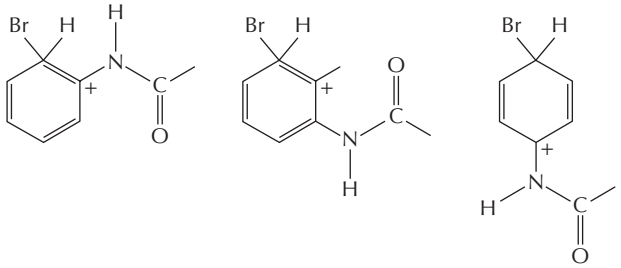
FIGURE 8.3 Energy profile for the bromination of acetanilide.

In the case of a monosubstituted benzene, such as acetanilide, there are three possible monosubstituted products, the *ortho*-, *meta*-, and *para*-bromoacetanilides.



The reaction pathway with the lowest activation energy for the formation of the bromobenzenium ion will be favored. Because the formation of this cation is endothermic, the most stable bromobenzenium ion correlates with the rate-determining transition state. The energy profile for the formation of *para*-bromoacetanilide is shown in Figure 8.3.

Use the semiempirical molecular orbital method (MOPAC) with the AM1 parameter set to calculate the heats of formation of the intermediate benzenium cations 1–3, which would lead to the *ortho*-, *meta*-, and *para*-bromoacetanilides.



(1) **(2)** **(3)**

CONSTRUCTION AND OPTIMIZATION OF THE BROMOBENZENIUM ION

1. Construct a 1, 4-cyclohexadiene molecule. Attach a bromine atom to one of the sp^3 carbon atoms of the molecule. At the other sp^3 carbon atom, delete one of the valences (or hydrogen atoms). Before optimizing the geometry, indicate that the molecule has a charge of +1 and is in the singlet state (all its electron spins are paired).
2. Optimize the geometry using the semiempirical method (MOPAC) with the AM1 parameter set.
3. Record the heat of formation (ΔH_f = 923.2 kJ/mol).

CONSTRUCTION AND OPTIMIZATION OF THE INTERMEDIATE BROMOBENZENIUM IONS 1–3

1. Use a copy of the bromobenzenium ion to build the reactive intermediates **1–3**. For bromobenzenium ion 1 attach an acetanilide group to the carbon *ortho* to the sp^3 carbon bearing the bromine atom.
2. Optimize the geometry using the semiempirical method (MOPAC) with the AM1 parameter set.
3. Record the heat of formation.

The intermediates leading to 3-bromoacetanilide and 4-bromoacetanilide can be created in a similar fashion. Record the heats of formation for these intermediates.

Using Spartan 06, the heats of formation are as follows:

ΔH_f (2-bromoacetamidobenzenium ion) = 695.6 kJ/mol
ΔH_f (3-bromoacetamidobenzenium ion) = 761.6 kJ/mol
ΔH_f (4-bromoacetamidobenzenium ion) = 681.6 kJ/mol

These results indicate that the lowest-energy, favored reaction pathway is the one that yields 4-bromoacetanilide.

USE OF $\Delta\Delta H_f$ VALUES TO DETERMINE REACTIVITY

We can also use MOPAC with the AM1 parameter set to gain insight into whether the acetamido group activates or deactivates the aromatic ring in the bromination reaction.

1. Build molecules of benzene and acetanilide.
2. Optimize the geometry of each molecule using the semiempirical method (MOPAC) with the AM1 parameter set.
3. Record the heat of formation for benzene and for acetanilide.

$$\Delta H_f \text{ (benzene)} = 92.1 \text{ kJ/mol}$$

$$\Delta H_f \text{ (acetanilide)} = -64.2 \text{ kJ/mol}$$

Now we can calculate the energy difference for the formation of the bromobenzenium ion intermediate in the bromination of benzene.

$$\Delta\Delta H_f \text{ (benzene to bromobenzenium ion)}$$
$$= 923.2 \text{ kJ/mol} - 92.1 \text{ kJ/mol}$$
$$= 831.1 \text{ kJ/mol}$$

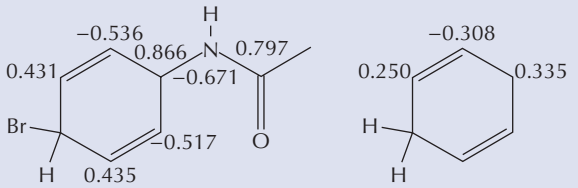
The bromobenzenium ion is 831.1 kJ/mol higher in energy than the starting material.

For the bromination of acetanilide, the reactive intermediate is 745.7 kJ/mol higher in energy than the starting material.

$$\Delta\Delta H_f \text{ (acetanilide to 4-bromoacetamidobenzenium ion)}$$
$$= 681.6 \text{ kJ/mol} - (-64.2 \text{ kJ/mol})$$
$$= 745.8 \text{ kJ/mol}$$

The activation energy is lower for the bromination of acetanilide. Thus, the acetamido group activates the benzene ring toward electrophilic aromatic substitution.

You can also use the MOPAC package to calculate the positive charge distribution in the benzenium ion intermediates. The program can provide a color representation of the charge distribution. Because we do not have a palette of colors at our disposal, here are the electrostatic charge distributions at the ring carbon atoms of two relevant benzenium ions, as calculated by the AM1 parameter set of Spartan 06.



You can see that even in the benzenium ion itself the positive charge is greater at the carbon atoms *ortho* and *para* to the sp^3 carbon. The positive charge density is substantially greater at the *para*-position of the bromoacetamidobenzenium ion, where the electron donating characteristics of the acetamido group stabilize this nearby positive charge.

Density Functional Theory (DFT)

In contrast to molecular orbital theory, the quantum mechanical ***density functional theory (DFT)*** optimizes an electron density rather than a wave function. Because the electron correlation energy as a function of the electron density can be included in the functional, DFT is more robust than MO theory with respect to calculating the electron-electron interaction term. DFT has become increasingly popular in the computational chemistry community within the last decade and is now a part of the standard packages that are available. The use of wave functions has slightly broader utility, but DFT is often the method of choice to achieve a particular level of accuracy in the least amount of time for an average problem.

To determine a particular molecular property using DFT, such as the energy of a molecule, one needs to know how the property depends on the electron density.

$$E[\rho(r)] = T_{ni}[\rho(r)] + V_{ne}[\rho(r)] + V_{ee}[\rho(r)] + E_{xc}[\rho(r)]$$

In this equation, $\rho(r)$ is the electron density at a specific position in space, and $E[\rho(r)]$ is called the ***energy functional***. The electron density integrated over all space gives the total number of electrons. The

equation allows the electrons to interact with one another and with an external potential, the attraction of the electrons to the nuclei.

$T_{ni}[\rho(r)]$ = the kinetic energy of the noninteracting electrons.
$V_{ne}[\rho(r)]$ = the interaction of the nucleus and the electron.
$V_{ee}[\rho(r)]$ = the classical electron-electron repulsion.
$E_{xc}[\rho(r)]$ = the exchange-correlation energy, a combination of the correction to the kinetic energy deriving from the interacting nature of the electrons and all nonclassical corrections to the electron-electron repulsion energy.

As with MO calculations, a basis set or sets for DFT is chosen to construct the density and a molecular geometry is selected. Then one guesses an initial electron density matrix and iteratively solves the basic DFT equation. After repeated iterations to minimize the ground state electronic energy and optimization of the molecular geometry, the desired molecular property can be calculated.

8.4 Which Computational Method Is Best?

The best computational method depends on the question you are asking and the resources at your disposal. Determination of molecular geometry is one of the easier aspects of computational chemistry. If you are simply trying to find the optimum (lowest energy) structures of organic molecules, molecular mechanics provides reasonable structures, and it is very fast. Good values for bond angles, bond lengths, dihedral angles, and interatomic distances can be determined from an optimized structure. In general, you are limited to typical organic compounds; for instance, there are few good parameter sets for carbon-metal bonds.

The energy differences between conformers determined by molecular mechanics are often very close to experimentally determined values, and they can be used to determine equilibrium ratios of the conformers. Because the calculations are fast, the energies of many conformers can be determined in a short time. This is especially useful when examining ***rotamers,*** conformations related by rotation about a single bond. As a classical mechanical model, however, molecular mechanics says nothing about electron densities and dipole moments. It also says nothing about molecular orbitals. However, the optimized structure from molecular mechanics can provide input data for other programs. Using a molecular mechanics calculation is often an efficient way to get an approximation that can be further refined with a quantum mechanical method, often saving computational time.

Semiempirical methods, which are significantly faster than *ab initio* calculations, provide reliable descriptions of structures, stabilities, and other properties of organic molecules. They often do a good job in calculating thermodynamic properties, such as heats of formation. The heats of formation can be used to compare energies of isomers, such as 2-methyl-1-butene and 2-methyl-2-butene, with greater accuracy than molecular mechanics may provide. The

calculated heats of formation can also be used to approximate the energy changes in balanced chemical equations.

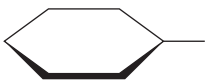
8.5 Sources of Confusion

Computational chemistry is inherently complex, but most of the commercially available packages have been "human engineered," making it relatively easy to get started. When you get to a point in the process where you have a choice, a default option is usually provided. It is beneficial to acquaint yourself with the information provided with the package so that you can make the best choices.

Two things can cause a good deal of confusion and should be avoided. The first occurs if you start with the wrong structure, and the second deals with the problem of local rather than global energy minima. A third warning is that a grip on reality must always accompany computational chemistry calculations.

Starting the Computation with the Correct Structure

Starting with the correct structure is closely related to the method you use in building a molecule. In many packages, the user draws a two-dimensional projection, similar to the line formulas printed in a book, and the program translates it into a rough three-dimensional structure. However, if the projection is ambiguous, the program may create an unsuitable structure. For example, suppose you wanted to create *axial*-methylcyclohexane. The projection entered on the computer might look like this:



Viewing the structure created by this projection on the computer screen and then rotating it, you would probably observe a flat molecule, clearly unsuitable for optimizing the molecule's structure. To turn this projection into a three-dimensional structure usually requires invoking some sort of "cleanup" or "beautifying" routine. The routine creates a three-dimensional structure using "normal" bond lengths and bond angles. In the case of methylcyclohexane, the structure typically becomes a cyclohexane in the chair conformation with a methyl group in an equatorial position.

Building a cyclohexane with a methyl group in the axial position usually requires the creation of the structure in stages. In this case, you need to create a chair cyclohexane and then replace one of the axial hydrogens with a methyl group. As you can see, the process involves building the framework first and then adding the necessary attachments at specific locations. Most computational chemistry packages contain templates or molecular fragments to assist in creating complex structures.

Local and Global Minima

Another potential source of confusion encountered in attempting optimization of a structure is the ***global minimum*** problem. During the optimization of the geometry, the program tries to find the structural conformation with the lowest energy. At each point, it calculates the gradient or first derivative of the energy with respect to the motion of each atom in each Cartesian direction, and the geometry is perturbed in the direction of the resulting gradient vector. Each individual perturbation depends on the history of the energies and gradients from prior steps. This process is repeated until the gradient is computed to be zero, at which point a ***local minimum*** is likely to have been found (Figure 8.4).

The energy surface is often uneven, with lumps, bumps, ridges, and several low spots. The low spot that a minimization falls into depends on where you start on the energy surface. In Figure 8.4, a start from point A or B will end up at the local minimum. A start at point C or D will end up at the desired global minimum. The calculation of *axial*- and *equatorial*-methylcyclohexane illustrates this point. The two structures are conformers that can be interconverted by way of a ring flip. *axial*-Methylcyclohexane is a local minimum and *equatorial*-methylcyclohexane is the global minimum. The barrier represents the strain energy required to flip the ring.

Systematic creation of starting structures. How does one know if a structure built with a computational chemistry package represents a local minimum or a global minimum? This question has led to many research projects. For our purposes, the answer is to create several different starting structures, carry out minimizations on each of them, and use the lowest energy as the global minimum. One of the several methods for systematically creating possible starting structures is conformational searching. Several conformations of a structure are created by rotating portions of the molecule connected by single bonds. Some modeling packages have routines called *sequential searching* which automate this process; in ChemBio3D this is called the *dihedral driver*. Other packages have methods such as Monte Carlo routines for generating random structures.

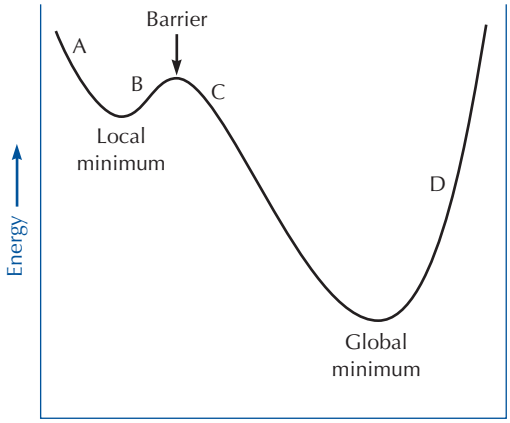


FIGURE 8.4
Local and global minima resulting from energy minimization, showing that an energy profile is usually not a smooth curve with one minimum.

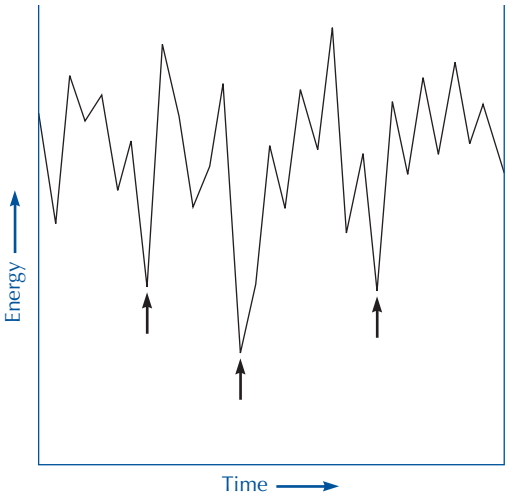


FIGURE 8.5
Output of a molecular dynamics simulation plotted as a graph of energy versus the conformation of the structure, changing with time.

Molecular dynamics simulation. Yet another method of generating candidate structures for minimization is to use a molecular dynamics simulation program. This program simulates the motions of atoms within a structure. The molecule is given increased kinetic energy, the amount depending on the designated temperature. As the atoms move around, energy "snapshots" are taken at regular intervals. The structures with the lowest energies are used as starting structures for minimization. This method often propels molecules over energy barriers that are caused by steric interactions, bond strain, and torsional strain. The results of a molecular dynamics simulation can be plotted as the internal energy of a molecule versus time. In Figure 8.5, structures corresponding to low-energy conformers are designated with arrows. These conformers can be used as initial structures for energy minimizations by molecular mechanics or quantum mechanical calculations. Even using these methods, there is no guarantee that the global minimum will always be found with systems of fairly modest size. The situation is completely hopeless with a large molecule, such as a protein.

Computational Chemistry and Physical Reality

Computational chemistry is based on theoretical models using approximations and parameter sets derived from theory and experiment. Thus, it is important to keep a firm grip on reality at all times. You need to evaluate the result, especially a surprising result, and determine whether it makes sense chemically and physically and not just accept the results of calculations as physical truth. In spite of this caveat, computational chemistry is a highly valuable tool for gaining insights into organic chemistry.

Further Reading

Cramer, C. J. *Essentials of Computational Chemistry: Theories and Models;* 2nd ed.; Wiley: New York, 2004.

Goodman, J. M. *Chemical Applications of Molecular Modeling;* Royal Society of Chemistry: Cambridge, 1998.

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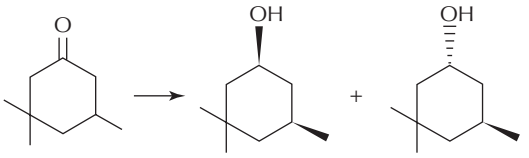
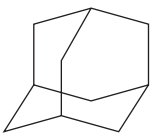
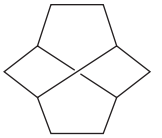
Questions

1. Reduction of 3,3,5-trimethylcyclohexanone with sodium borohydride yields a mixture of *cis*-3,3,5-trimethylcyclohexanol and *trans*-3,3,5-trimethylcyclohexanol. Use molecular mechanics to determine the most stable conformer of each product.



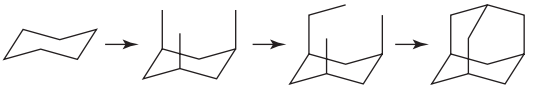
2. Adamantane is a tetracyclic hydrocarbon, $C_{10}H_{16}$, incorporating four chair cyclohexane rings. Twistane is an isomeric tetracyclic hydrocarbon incorporating four twist-boat cyclohexane rings. Use semi-empirical MOPAC calculations with the AM1 parameter set to optimize the geometries of adamantane and twistane. Record their heats of formation.


Adamantane

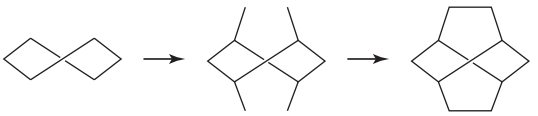

Twistane

Hints for construction of the molecules

Adamantane: Start with chair cyclohexane. Attach carbon atoms to the three axial positions on the same side of the cyclohexane, attach a carbon atom to one of the three axial carbons atoms, and then make bonds between the newly attached carbon atom and the remaining two axial carbon atoms.



Twistane: Start with twist-boat cyclohexane. Attach carbon atoms to the pseudo-axial positions at the 1,2,4,5 carbons of the ring, make a bond between the carbon atoms added at the 1 and 4 positions, and finally make a bond between the carbon atoms added at the 2 and 5 positions.



TECHNIQUE 9

DESIGNING A CHEMICAL REACTION

As you gain experience in organic chemistry, you may have the opportunity to plan and carry out a chemical reaction where you are not given explicit experimental directions. For example, you may be using a published experimental procedure from the chemical literature and need to modify the scale of the reaction. Projects where you develop your own lab procedures can be great fun, but they can also be frustrating if you don't plan carefully before beginning your experimental work. Consult with your lab instructor about your planning and final detailed written procedure before beginning any experimental work.

Often a project focuses on the synthesis of a specific organic compound. Usually, you would begin by searching the chemical literature to find a synthesis of the compound. If you cannot find one, you can look for a synthesis of a structurally similar compound to use as a guide. The material presented in this chapter provides you with practical advice for planning a synthesis procedure from precedents in the literature.

9.1 Importance of the Library

There is a maxim in experimental chemistry: "An hour in the library is worth at least a day in the laboratory." Before attempting any laboratory work, search the chemical literature for examples of the reaction you wish to carry out. You may find several different methods for preparing the desired compound or one similar to it. Compare the various methods critically and carefully in terms of scale, availability of starting materials, availability and complexity of equipment, ease of workup, and safety issues.

A good place to start is *Organic Syntheses,* a compilation of carefully checked procedures with full experimental details. The detailed footnotes at the end of each procedure are especially useful. Another good resource is the multivolume series *Fieser's Reagents for Organic Synthesis* by Ho. This series provides information on improvements in the preparation and purification of organic compounds. Many newer reagents are safer and easier to handle than older traditional reagents. Full bibliographical information for both these series as well as other suggestions for information resources appear in Technique 9.5, The Literature of Organic Chemistry. In an early phase of your library searching, it will be worthwhile to look at *Comprehensive Organic Transformations: A Guide to Functional Group Preparations* by Larock [also listed in Technique 9.5], which lists ways to carry out specific classes of reactions for the synthesis of specific functional groups and gives references to the primary journal literature. Last but by no means least is the invaluable database *Scifinder Scholar,* an excellent search engine. If *Scifinder Scholar* is available on your campus, you have at your disposal perhaps the most efficient way there is to survey the chemistry journal literature for the synthesis of particular organic compounds.

9.2 Modifying the Scale of a Reaction and Carrying It Out

Very often, a synthesis procedure found in the literature does not prepare the amount of compound that you wish to make. Methods from literature published prior to the 1960s and those found in *Organic Syntheses* are usually on a larger scale than most of the reactions carried out in the modern organic chemistry laboratory. These procedures will need to be scaled down. Conversely, if a synthetic

method is of recent vintage, it may be on the microscale level and need to be scaled up.

At first approximation, the scale-up or scale-down is simply a matter of direct proportionality. If a procedure produces only one-half the material you want, the quantities of all the reagents and solvents should be doubled to produce enough of the product. If the amount you want is only one-tenth the amount produced in the procedure, divide the quantities of all the reagents and solvents by ten. However, when scaling up or down by a large factor, the simple proportionality often needs to be adjusted for some of the reaction components, particularly the solvent volumes.

Also keep in mind that many published synthetic procedures report optimum product yields that were achieved only after a number of iterations. The yield on the first attempt is likely to be less than that reported, perhaps only 50% as much. If you propose to carry out a synthesis in three steps, lower yields may result by a factor of $50\% \times 50\% \times 50\% = 13\%$ of what has been reported. When a reaction procedure looks particularly challenging, it can be useful to try it out on a smaller scale before attempting it on the scale you need.

Once you have determined the scale of a reaction, you are ready to consider the specific details of carrying it out:

- Amount of solvent to use
- Size of reaction apparatus
- How the reagents will be added
- How to determine the reaction time
- Whether and how the reaction should be stirred
- How to provide temperature control
- Whether the reaction requires anhydrous or inert atmosphere conditions
- How to purify the reaction product

Amount of Solvent to Use

In scaling down a very large-scale reaction to miniscale or microscale, reducing the solvent volume by the same factor you're using to reduce the reagents may not provide enough solvent for an effective reflux of the reaction mixture. The capacity of the apparatus should probably be substantially larger proportionately than that used for the large-scale reaction. Otherwise, when the reaction is refluxed, almost all the solvent might vaporize, leaving little or none for dissolving the reaction mixture and for providing a constant reaction temperature. In such cases, extra solvent must be used for the scaled-down reaction.

Conversely, when scaling up a microscale reaction by a large factor, the proportion of solvent can often be decreased, thus avoiding the use of extremely large volumes of solvent, which can be cumbersome to handle and can lead to increased waste disposal costs.

Size of the Reaction and Purification Apparatus

Use apparatus of a size appropriate for the scale of the reaction. Large-scale apparatus has a much larger surface area than small-scale equipment. Using a large-scale apparatus for a small-scale reaction usually leads to excessive loss of liquid material, which adheres to the surface

of the glassware as an almost invisible film. With small-scale reactions, flasks with conical bottoms are recommended because they focus the material into a more manageable volume.

The capacity of the reaction flask should be two to three times the total combined volumes of the reagents and solvent(s). This practice allows for the usual increase in volume as a mixture is heated, and it allows room for vaporization of the solvent during reflux. If the mixture is known to foam during reflux or if a gas is evolved during the reaction, a flask five or more times the volume of the reaction mixture is recommended.

Working with small quantities of solids is easier than working with small quantities of liquids. However, you will need to scale down the size of flasks and vacuum funnels when carrying out a recrystallization of less than 300 mg of a solid. If you have scaled down a reaction that will produce less than 5 g of a liquid product, which must be purified by distillation, you need to use a short-path distillation apparatus with a cow receiver and a conical-bottomed distillation flask; standard taper 14/20 ground glass joints are preferable [see Technique 13, Figure 13.24].

Addition of Reagents

Some reactions give optimal results if one of the reagents is added gradually to the reaction mixture. With large-scale reactions, this slow addition is best accomplished using a dropping funnel for solutions and liquid reagents. For miniscale reactions, the most convenient method is to use a pipet to gradually drip the reagent into the reaction mixture through the reflux condenser attached to the top of the reaction flask. The addition of reagents can be done this way if the reaction is being either heated at reflux or simply stirred at room temperature. Care must be taken not to lose too much of the reagent on the walls of the condenser. If the reaction system is sealed to isolate it from the atmosphere, a liquid reagent or solution can be added from a syringe through a rubber septum.

Reaction Time

The time required for a scaled-up or scaled-down reaction should be approximately the same as that for the model reaction. That being said, there can be great variation in optimal reaction times due to many variables that cannot be scaled along with the reagents, for example, heating or cooling efficiency. Miniscale and microscale reactions can take less time than their large-scale counterparts because the small scale makes mass transport more efficient.

The best way to determine when a reaction has reached completion is to monitor it, usually by thin-layer chromatography of samples taken from the reaction mixture during the course of the reaction [see Technique 17]. The reaction is stopped when one of the starting materials is no longer present or when the desired product begins to decrease due to a further reaction. Gas chromatography can also be used for monitoring reactions [see Technique 19]. Sometimes other visual clues can be used to decide when to stop a reaction, for example, color change, disappearance of a solid, or appearance of a solid.

Stirring Reactions

Magnetic stirring is normally used for miniscale and microscale reactions to avoid concentration gradients and uneven heating. Stirring is especially important for mixtures of solids and liquids or immiscible liquids, which are not homogeneous. Large-scale reactions have traditionally been stirred mechanically because magnetic stirring may not be powerful enough to be efficient.

Temperature Control

Many organic chemical reactions require heating to drive them to completion in a reasonable amount of time. The exact method of heating—water bath, steam bath, heating mantle, or oil bath—depends on the equipment available in the laboratory. If a variable transformer for the heating source is available, it can provide a convenient method for controlling the temperature of the reaction. Alternatively, the temperature can be controlled by the choice of solvent. In a refluxing reaction mixture, the temperature is close to the boiling point of the solvent; for example, the temperature of a reaction carried out in refluxing ether is close to 35°C and the temperature of a reaction carried out in refluxing hexane is close to 70°C.

Exothermic reactions require external methods for dissipating the generated heat, a process often accomplished with a solvent that refluxes into a water-cooled condenser as the reaction heats up. Thus, it is the water running through the condenser that is the heat-transfer agent. With miniscale and microscale reactions, the surface area of the apparatus often provides efficient and rapid transfer of heat to the surrounding atmosphere. Many microscale reactions can be carried out in 20 × 150 mm test tubes; the wall of the test tube is high enough to provide the condensing surface for the refluxing solvent.

With very exothermic or large-scale exothermic reactions, it is often necessary to use a water or ice-water bath to cool the reaction flask. Another method for controlling the temperature of exothermic reactions is by slow addition of one of the reagents to the stirred reaction mixture. If the reaction becomes too vigorous, addition is stopped or slowed until the reaction rate subsides.

Some reactions must be cooled well below 0°C. A 2-propanol/dry ice bath in a low-form Dewar flask works well for reactions that must be carried out in the −30° to −70°C temperature range; Dewar flasks also allow for magnetic stirring [see Technique 6.3].

Using Anhydrous and Inert Atmosphere Reaction Conditions

The presence of water is deleterious to many organic reactions and the use of dry equipment and a drying tube with an anhydrous drying agent are essential. Even though there may be no visible evidence of water, the glassware surface can absorb considerable amounts of moisture. All glassware for the reaction should be placed in a 120°C oven to remove any surface moisture, then cooled in a desiccator [see Technique 7.2]. Because of the relatively large surface area of the glassware relative to the size of the reaction, it is especially important to dry the equipment used for microscale reactions. Inert atmosphere conditions are discussed in Technique 16.

Separating and Purifying Products

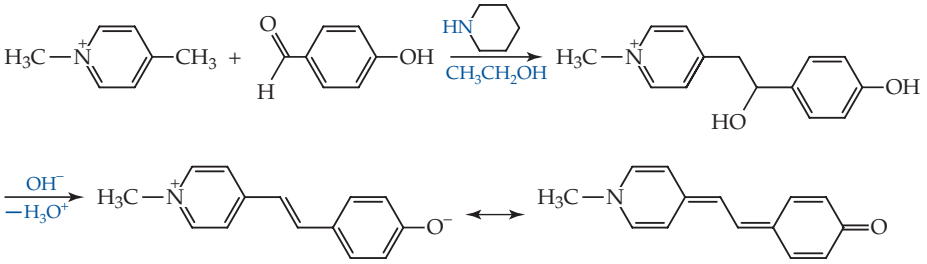
The thoroughness of a published experimental procedure depends in part on the guidelines for the journal or monograph in which it was published. Published procedures can be especially terse about the specific details of working up a reaction mixture; for example, amounts of recrystallization solvents or chromatographic elution solvents may not be given, or volumes of extraction solvents and the steps used to separate by-products may be omitted. Most chemistry journals now have detailed supplemental experimental information available online.

If an experimental procedure has been written for experienced chemists, filling in the many details implied but not actually described in the procedure can be a challenging but rewarding experience, linking what you have learned in the classroom to the action of the laboratory.

9.3 Case Study: Synthesis of a Solvatochromic Dye

Over 30 years ago the synthesis of a dye whose color changes dramatically when the solvent is changed was published in the *Journal of Chemical Education* (Minch, M. J.; Shah, S. S. *J. Chem. Educ.*, **1977**, *54*, 709). This property, called solvatochromism, is not uncommon in ultraviolet and visible spectroscopy and is discussed in Technique 24.3. The change in solvent polarity causes a solvatochromic compound to change color. The dye—given the acronym MOED—is reported to be yellow in water solution, red in ethanol, and violet in acetone. Solvatochromism has potential applications in molecular electronics for the construction of molecular switches.

Procedure for Synthesis of MOED



MOED
1-Methyl-4-[(oxocyclohexadienylidene)ethylidene-]-1,4-dihydropyridine

1,4-Dimethylpyridinium iodide (28.4 g, 0.12 mol), freshly recrystallized (EtOH-H_2O, 2:1), 4-hydroxybenzaldehyde (14.5 g, 0.12 mol), and piperidine (10 mL, 0.10 mole) are dissolved in 150 mL dry ethanol and heated at reflux for 24 h. Cooling the reaction mixture yields a red precipitate, which is removed by filtration. This solid is suspended in 700 mL of 0.2 *M* KOH and heated (without boiling) for 30 min. The cool solution yields blue-red crystals, which are recrystallized three times from hot water. Yield: 22 g (86.3%), mp 220°C.

Analyzing the Procedure

1,4-Dimethylpyridinium iodide is commercially available from the Aldrich Chemical Company. However, it can also readily be synthesized from methyl iodide and 4-methylpyridine, as outlined in the published article. If you have read the article by Minch and Shah in the *Journal of Chemical Education*, you might have noticed that there is no mention of safety considerations. This omission would definitely not happen today, when we have learned to respect the toxicities of organic compounds. Methyl iodide, which is used in the synthesis of 1,4-dimethylpyridinium iodide, is very toxic and must be handled with caution.

Although nothing is stated in the procedure about the purification of 4-hydroxybenzaldehyde, it is well known that aldehydes undergo free-radical oxidation in the presence of oxygen. Therefore, it would be best to use a new bottle of 4-hydroxybenzaldehyde that hasn't been open to the atmosphere many times before. If the only available stock is an old bottle, it would be wise to take an infrared spectrum of it to make sure that it has not been oxidized to 4-hydroxybenzoic acid. If oxidation has occurred, not only will the amount of the limiting reagent available be reduced, which will lower the percentage yield, but 4-hydroxybenzoic acid will react with piperidine in an acid/base reaction, thereby removing some of the active catalyst.

Even though you might expect that a procedure would be optimized when it is published in the *Journal of Chemical Education* and designed to be carried out by undergraduate students, it is always a good idea to check the literature cited in the article to see what conditions were used by others. For example, in the 1949 *Journal of Organic Chemistry* article by Phillips, the heating period was only 1 to 4 hours in methanol. Following the course of the reaction by thin-layer chromatography would be useful.

Scale of the Reaction

The scale of the MOED synthesis needs to be reduced to be useful in a laboratory with microscale glassware. This scale makes sense because the solutions of MOED used to study the color variation in different solvents are very dilute (5×10^{-5} *M*). Only a few milligrams of MOED is needed for each color experiment.

A reaction scale appropriate for microscale equipment would be one-hundredth of the size described in the *Journal of Chemical Education* article. The amounts of reagents will be 1,4-dimethylpyridinium iodide (0.284 g, 1.2 mmol), 4-hydroxybenzaldehyde (0.145 g, 1.2 mmol), and piperidine (0.10 mL, 1.0 mmol). The amount of ethanol that is used might be increased from the proportionate amount used for the larger-scale reaction to allow for a proportionately larger vapor volume; perhaps 2–4 mL of ethanol should be used. The appropriate-size vessel for this microscale reaction is a 10-mL flask.

The Next Step: Framing and Answering a Question

Solvatochromism depends on the difference in dipole moments of the MOED molecule in its ground state and excited state (see Technique 24.3). The authors of the *Journal of Chemical Education* article suggest that color changes are most striking when aqueous

solutions of MOED in 0.01 *M* NaOH are diluted with various portions of an organic cosolvent, producing colors that vary across the whole visible spectrum.

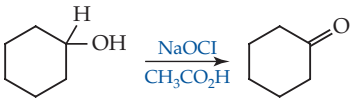
An interesting path for the exploration of this synthesis might be to use a different hydroxybenzaldehyde. One obvious molecule to consider is 4-hydroxy-3-methoxybenzaldehyde (vanillin). Numerous 4-hydroxybenzaldehydes are available from chemical suppliers as alternative substrates. Another path of exploration might be to use 2-hydroxybenzaldehydes.

9.4 Case Study: Oxidation of a Secondary Alcohol to a Ketone Using NaOCl Bleach

One experiment found in virtually all organic chemistry laboratory programs 25 years ago was the oxidation of a secondary alcohol to a ketone with chromium (VI), usually in the form of CrO_3 or $Na_2Cr_2O_7$. This kind of experiment had been widely used in organic chemistry labs since the 1940s.

In 1980 Stevens, Chapman, and Weller reported in the *Journal of Organic Chemistry* that using "swimming pool chlorine" as the oxidizing agent is a convenient and inexpensive method of producing ketones in good yields from secondary alcohols (Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980,** *45,* 2030–2032). One of the authors of this book was teaching a junior-level synthesis course at Carleton College at that time and decided to use the experimental procedure from the *Journal of Organic Chemistry* article as a way to engage students by using synthetic reactions from the primary chemical literature. The students were given the following procedure and no other advice except to scale down the reaction by tenfold and use magnetic rather than mechanical stirring.

Procedure for NaOCl Oxidation of Cyclohexanol



Cyclohexanol (99.0 g, 0.988 mol) was dissolved in glacial acetic acid (660 mL) in a 2-L three-necked flask fitted with a mechanical stirring apparatus and thermometer. Aqueous sodium hypochlorite (660 mL of 1.80 M solution, 1.19 mol) was added one drop at a time over 1 h. The reaction was cooled in an ice bath to maintain the temperature in the 15°–25°C range. The mixture was stirred for 1 h after the addition was complete. A potassium iodide–starch test was positive. Saturated aqueous sodium bisulfite solution (3 mL) was added until the color of the reaction mixture changed from yellow to white and the potassium iodide–starch test was negative. The mixture was then poured into an ice/brine mixture (2 L) and extracted six times with ether. The organic layer was washed with aqueous sodium hydroxide (5% by weight) until the aqueous layer was basic (pH test paper). The aqueous washes were then combined and extracted five

times with ether. The ether layers were combined and dried over magnesium sulfate. The ether was distilled through a 30-in Vigreux column until less than 300 mL of solution remained. The remainder was fractionally distilled through a 12-in Vigreux column. After a forerun of ether, cyclohexanone (bp 155°C) was distilled to give 92.9 g (95.8%) of a colorless liquid that had ^{1}H NMR and IR spectra and GC retention time identical with those of an authentic sample.

Experimental Results

The following week the ten students reported their results to one another. The results were not encouraging. Every student had an intense, broad peak in the O–H stretching region (~2800 cm^{-1}) of the infrared spectrum.

After careful examination of their experimental results, the students realized that their product contained a significant amount of acetic acid, which had been the reaction solvent. The students had the opportunity to repeat the reaction and everyone got a high yield of pure cyclohexanone.

The problem that every student experienced in the first trial had been an incomplete extraction of acetic acid from ether into the aqueous layer. Although they had neutralized the last aqueous wash with 5% NaOH, earlier aqueous washes were still acidic. Even though the experimental procedure from the *Journal of Organic Chemistry* was more complete than many others in chemistry journals, there was still some ambiguity in the details. This situation was a classic case of the necessity for reading between the lines. To get a pure product, all the aqueous washes had to be made basic with NaOH solution before the back extractions with ether were performed.

The positive student experience with the NaOCl oxidation of cyclohexanol led to recrafting the reaction to one that was less expensive and far safer and greener (Mohrig, J. R.; Mahaffy, P. G.; Nienhuis, D. M.; Linck, C. F.; Van Zoeren, C.; Fox, B. G. *J. Chem. Educ.* **1985,** *62,* 519–521). First, the "swimming pool chlorine," which cannot be stored from one class to the next, was replaced by household bleach (5.25% NaOCl). Then the reaction was carried out in a stirred water/cyclohexanol mixture with only enough acetic acid to provide the appropriate pH for the oxidation to proceed. The workup eliminated the need for ether extractions by using a steam distillation to separate the cyclohexanone product from the water/salt mixture. The bleach oxidation of secondary alcohols has replaced the old Cr (VI) method in virtually all undergraduate organic laboratories.

9.5 The Literature of Organic Chemistry

The great change in chemistry libraries within the last few years is the transition from printed to electronic materials. Electronic access has revolutionized the way many libraries do business and the way scientists access information. Journal articles and reference works can now be delivered directly to a scientist's desktop computer.

Electronic searches of the chemistry literature can be completed far more rapidly and comprehensively than manual searches.

Three types of information sources are found in all chemistry libraries: reference works, chemistry journals, and chemical databases. Chemical databases are invaluable for locating journal articles on a topic or compound and for looking up specific information about chemical compounds.

Reference Works

General

Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structures;* 6th ed.; Wiley: New York, 2007.

Handbooks

1. Lide, D. R. (Ed.) *CRC Handbook of Chemistry and Physics*; 90th ed.; CRC Press: Boca Raton, FL, 2009.
2. O'Neill, M. J.; Smith, A.; Heckelman, P. E.; Oberchain, J. R. Jr. (Eds.) *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*; 14th ed.; Merck & Co., Inc.: Whitehouse, NJ, 2006.
3. *Aldrich Handbook of Fine Chemicals*; Aldrich Chemical Co.: Milwaukee, WI, published biennially.
4. Speight, J. (Ed.) *Lange's Handbook of Chemistry*; 16th ed.; McGraw-Hill: New York, 2004.
5. Gordon, A. J.; Ford, R. A. *The Chemist's Companion: A Handbook of Practical Data, Techniques and References*; Wiley: New York, 1973.

Spectral Information

1. Pouchert, C. J.; Behnke, J. (Eds.) *Aldrich Library of* ^{13}C *and* ^{1}H *FT-NMR Spectra;* 3 vols.; Aldrich Chemical Co.: Milwaukee, WI, 1993. Print or CD-ROM.
2. *Aldrich Library of FT-IR Spectra;* 2nd ed.; 3 vols.; Aldrich Chemical Co.: Milwaukee, WI, 1997.
3. *Sadtler Collection of High-Resolution (NMR) Spectra;* Sadtler Research Laboratories: Philadelphia, 1992.
4. *Sadtler Reference (IR) Spectra;* Sadtler Research Laboratories: Philadelphia, 1992.

Reactions, Synthetic Procedures, and Techniques

1. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R.; Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry;* 5th ed.; Prentice Hall: Upper Saddle River, NJ, 1996.
2. Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations;* 2nd ed.; Wiley: New York, 1999.
3. Mackie, R. D. *Guidebook to Organic Synthesis;* 3rd ed.; Prentice Hall: Upper Saddle River, NJ, 2000.
4. Ho, T.-L. *Fieser's Reagents for Organic Synthesis;* 24 vols.; Wiley: New York, 1967–2008.
5. *Organic Syntheses;* Wiley: New York, 1932–present. Collective Volumes 1–11 (2009) combine and index five or ten volumes each through Volume 85, 2008. The preparations have been carefully checked in two separate research laboratories.

6. Harrison, I. T.; Wade, L. G., Jr.; Smith, M. B. (Eds.) *Compendium of Organic Synthetic Methods;* 11 vols.; Wiley: New York 1971–2004.
7. Sandler, S. R.; Karo, W. *Sourcebook of Advanced Organic Laboratory Preparations;* Academic Press: San Diego, CA, 1992.
8. Loewenthal, H. J. E. *A Guide for the Perplexed Organic Experimentalist;* 2nd ed.; Wiley: New York, 1992.
9. Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry;* 2nd ed.; Blackie Academic and Professional: London, 1995.
10. Sharp, J. T.; Gosney, I.; Rowley, A. G. *Practical Organic Chemistry, A Student Handbook of Techniques;* Chapman and Hall: London, 1989.

Chemistry Journals

Important current journals that publish original papers in organic chemistry include the following:

Journal of the American Chemical Society
Journal of Heterocyclic Chemistry
Journal of Medicinal Chemistry
Journal of Organic Chemistry
Organic & Biomolecular Chemistry
Organic Letters
Synthesis
Synthetic Communications

All these journals are available online, and in all of them there is supplemental information that provides electronic access to detailed experimental procedures and data.

Electronic Abstracts and Indexes

Because the literature of chemistry is so vast, finding specific information, such as the preparation of a particular compound, is difficult and time consuming without a survey of the entire literature of chemistry. *Chemical Abstracts (CA),* published by the American Chemical Society, is such a survey and is the most complete source of information on chemistry in the world.

Chemical Abstracts condenses the content of journal articles into abstracts and indexes the abstracts by research topic, author's name, chemical substance or structure, molecular formula, and patent numbers. Each chemical compound is assigned a number, called a ***registry number,*** which can facilitate finding references to the compound. In evaluating an abstract you need to keep in mind that it gives only a brief summary of an article; you should always consult the original journal article as the final source.

Chemical Abstract Services (CAS), the publishers of *Chemical Abstracts,* provides a number of databases. The newest of these databases, called *SciFinder Scholar,* is an excellent search engine (Figure 9.1). If it is available on your campus, you will find it invaluable. In addition to *SciFinder Scholar,* CAS provides *STN,* a more limited but nonetheless helpful database for *Chemical Abstracts.* Today, most college and university libraries are equipped to search *Chemical Abstracts* using these computerized databases. Consult the library at your college or university to obtain assistance and training before undertaking an online search.

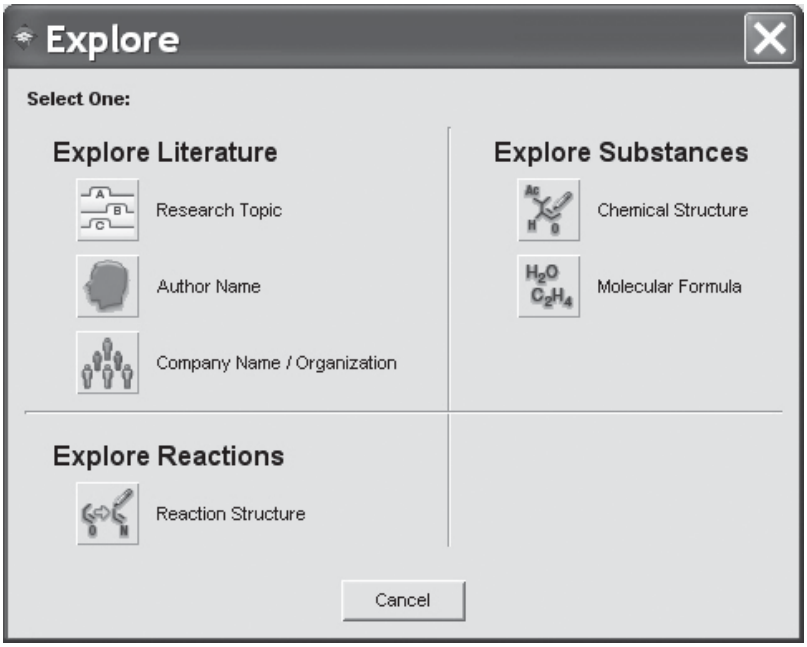


FIGURE 9.1
Initial search menu of *Scifinder Scholar.* (*SciFinder Scholar* and the SciFinder Scholar logo are trademarks and/or registered trademarks of the American Chemical Society. All graphics relating to *SciFinder Scholar* software have been reproduced with permission of the American Chemical Society. All rights are reserved.)

Science Citation Index Expanded contains all articles published in prominent journals and also lists all the articles that were cited or referred to in current articles. It is available in the online *ISI Web of Knowledge* through its Web of Science, which can be searched by subject, author, journal, and cited references.

The *Beilstein CrossFire* databases are drawn from *Beilstein's Handbook of Organic Chemistry* and over 170 leading journals. *Beilstein* is an excellent though expensive database for locating information about organic compounds. It contains records on almost 10 million organic substances. For each compound, the database contains the name (or names), formula, physical properties, methods of synthesis, chemical reactions, and biological properties. Every piece of information has a reference to the primary literature so that data may be checked. The database continues to add information on many compounds that were reported in the earlier print versions of *Beilstein's Handbook.* Thus, corrections and updating continue. The entry for an organic compound in the *CRC* and *Aldrich Handbooks* also gives the location of the compound in *Beilstein*. If *Beilstein CrossFire* is available at your university, it is well worth learning how to use it effectively.

It is difficult to provide complete current database information in this book because many databases regularly undergo changes. However, the *Journal of Chemical Education* in its *JCE Online* site (www.jce.divched.org) maintains a list of reviewed Web sites.

More Information About the Chemistry Library

We urge you to consult the library at your college or university for assistance in conducting a search for information in books and journals and online. The following books and journal articles contain

more information about chemistry information sources, how to use them, and how to plan and carry out an online search.

1. Maizell, R. E. *How to Find Chemical Information: A Guide for Practicing Chemists, Educators, and Students;* 4th ed.; Wiley: New York, 2009.
2. Poss, A. J. *Library Handbook for Organic Chemists;* Chemical Publishing Company: New York, 2000.
3. Smith, M. B.; March, J. *March's Advanced Organic Chemistry;* 6th ed.; Wiley: New York, 2007, Appendix A.
4. Wienbroer, D. R. *Guide to Electronic Research and Documentation;* McGraw-Hill: New York, 1997.
5. *Using CAS Databases on STN: Student Manual*; American Chemical Society: Washington, DC, 1995.

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PART

3

Separation and Purification Techniques

Essay — Intermolecular Forces in Organic Chemistry

The structures of organic molecules and the making and breaking of covalent bonds in chemical reactions are the major focus of classroom work in organic chemistry. After a discussion of intermolecular forces, mainly in the context of boiling points, the emphasis is on covalent bond chemistry. Except for hydrogen bonds, weak intermolecular forces may seem largely unimportant. However, many experimental techniques of organic chemistry—for example, the separation and purification of organic compounds—depend almost entirely on the weak forces between molecules.

Several categories of weak intermolecular interactions are listed here from strongest to weakest:

- Hydrogen bonding
- Dipole-dipole interactions
- Dipole-induced dipole interactions
- Induced dipole-induced dipole interactions

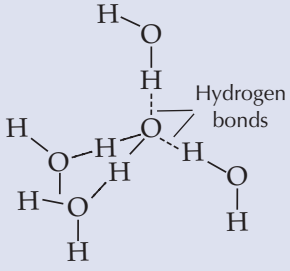
These electrostatic intermolecular forces are all concerned with favorable enthalpy changes that occur when molecules attract one another.

Hydrogen Bonding

Hydrogen bonding, often called H-bonding, occurs when hydrogen atoms are covalently attached to highly electronegative elements. Hydrogen atoms attached to atoms of these elements—most important are oxygen and nitrogen—can have reasonably strong electrostatic interactions, as well as weak orbital overlap, with electronegative atoms in nearby molecules. These interactions form intermolecular hydrogen bonds, whose energies are on the order of 15–20 kJ/mol (3.5–5 kcal/mol). This range of energies

is only about 5% of the energy associated with covalent bonds, but it is enough to make hydrogen bonds the strongest of the weak intermolecular forces.

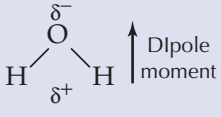
Perhaps the most dramatic example of intermolecular interactions by hydrogen bonding occurs between molecules of water. The high boiling point of water is an indication of the substantial intermolecular forces between water molecules. H_2O boils at 100°C whereas CH_4, which is approximately the same size, boils at −162°C. H_2O also boils over 160° higher than H_2S, which has a higher molecular weight and surface area. An intermolecular H-bonding network gives ice an open tetrahedral structure, which makes ice a very unusual solid: it floats because it is less dense than the liquid phase of water. Planet Earth would be a very different place without liquid water and floating ice.



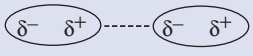
Organic molecules that have hydrogen atoms covalently bonded to oxygen or nitrogen can also form H-bonds with water molecules or with other organic molecules that have oxygen or nitrogen atoms in them.

Dipole-Dipole and Dipole-Induced Dipole Interactions

Water is also distinguished by its polarity due to the relatively large charge separation in the polar O—H covalent bonds in water molecules. Just as bonds can be polar, entire molecules can be polar, depending on their shape and the nature of their bonds. Water has a large permanent dipole moment as well as a high dielectric constant, which gives it the ability to dissolve many inorganic and organic salts but not the ability to dissolve most organic molecules. Organic molecules that dissolve in water are usually those that can also hydrogen bond, particularly low molecular-weight alcohols, carboxylic acids, and amines.



Molecules that have dipole moments can attract one another when their dipoles align so that there is an electrostatic attraction between them.



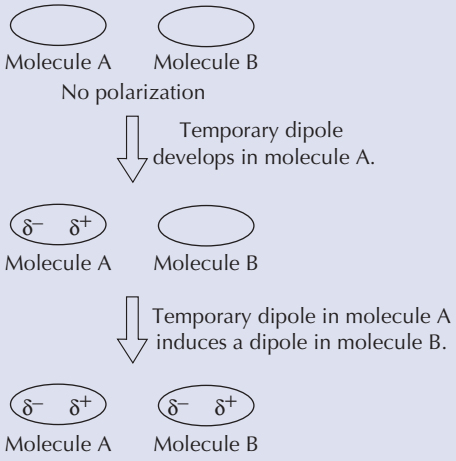
Some molecules, such as dimethyl sulfoxide (CH_3SOCH_3) and acetonitrile (CH_3CN), even though they have no hydrogen atoms that can H-bond with other molecules, have significant dipoles, which makes them polar solvents and miscible

with water. In addition, each of them is able to accept an H-bond from a molecule of water.

Molecules that have dipole moments can also induce dipoles in other nearby molecules that do not have dipole moments of their own. This process provides an attractive force, although it is usually not as great as the one provided by dipole-dipole interactions.

Induced Dipole-Induced Dipole Interactions

The weakest intermolecular interactions are induced dipole-induced dipole interactions, often called London dispersion forces. These intermolecular forces result from temporary charges on molecules due to fluctuations in the electron distribution within them. Because all covalent molecules have electrons, they exhibit this induced dipole-induced dipole polarization. The magnitude of these dispersion forces depends on how easily the electrons in a molecule can move in response to a temporary dipole in a nearby molecule, called *polarizibility*.



London dispersion forces are the only intermolecular interactions that attract alkane molecules to their neighbors. They play a major role in the structure of lipid bilayer membranes, where fatty acids having linear alkane chains of 11–19 CH_2 groups closely pack together to form the membrane.

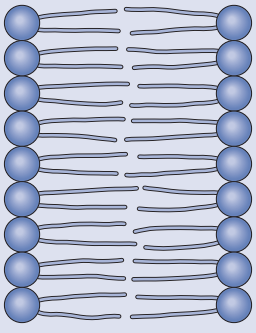


Diagram of a bilayer membrane. The fatty acid chains are attached as esters to molecules of glycerol, which also have ionic phosphates attached, shown as blue circles.

Van der Waals Forces

All weak intermolecular forces, with the exception of hydrogen bonds, are often referred to as van der Waals forces. The magnitude of van der Waals interactions depends on the surface areas of the interacting molecules. Thus, larger molecular-weight compounds have higher boiling points, and isomers whose shapes lead to larger surface area also have higher boiling points.

When very large molecules interact, a combination of many hydrogen bonds and van der Waals electrostatic forces can produce a large cumulative effect with strong association between the molecules. These intermolecular forces can also occur between different portions of very large molecules. For example, they determine the three-dimensional shapes of proteins and nucleic acids (DNA and RNA).

Solubility

Water and an organic solvent, such as hexane, do not dissolve in one another because water has extensive hydrogen bonding as well as dipole-dipole forces. To dissolve hexane in water would involve breaking apart these favorable electrostatic interactions between water molecules. In addition, the alkane molecules have their own attractive van der Waals forces which would be disrupted by foreign water molecules. Thus, water is not soluble in hexane.

The insolubility of organic and inorganic salts in hexane can be understood by recognizing that for salts to dissolve, the positive and negative ions in the salt crystals must be separated from each other. The electrostatic ion-ion attraction is strong, and the weak interactions between the ions and hexane molecules cannot begin to compensate for the energy required to separate the ions from one another. However, water has quite strong ion-dipole forces with both positive and negative ions, which can often compensate for the energy required to separate the ions from one another. Thus, ionic salts are much more soluble in water than in hexane.

The solubility of many organic compounds in relatively nonpolar organic solvents can be understood by the compensating intermolecular forces that produce a favorable enthalpy and often more so by the favorable entropy of mixing, which is related to the greater disorder that results when a solid dissolves in a liquid or two liquids dissolve in one another.

Intermolecular Forces in Separation and Purification

Part 3 is concerned mainly with the techniques that organic chemists use to separate liquids from other liquids by extraction and distillation and to separate solids from liquids by crystallization and filtration. Understanding the techniques of separation and purification of organic compounds depends on understanding the weak intermolecular interactions of liquids and solids.

Extraction is a technique for separating a water-insoluble organic compound from water-soluble salts and polar organic compounds by mixing an organic solvent with an aqueous mixture. Carrying out two or three extractions of a water mixture with an organic solvent usually serves to separate and purify a desired organic compound.

We have already briefly discussed the importance of intermolecular forces in determining the boiling points of organic compounds. The stronger the intermolecular forces, the more energy it takes to pull the molecules away from each other and the higher the boiling point. The technique of distillation utilizes the difference in boiling points of compounds in a mixture to effect their separation.

Crystallization is often carried out by adding water to an organic reaction mixture to decrease the solubility of a solid organic product, which can then be filtered from the aqueous mixture. The technique of recrystallization uses differential solubility to purify a solid. In general, organic compounds become more soluble at higher temperatures. A recrystallization solvent of the right polarity is chosen so that the solid dissolves in hot solvent but is largely insoluble in cold solvent. Impurities remain dissolved in the cold solution when the recrystallized solid is filtered.

TECHNIQUE

10 FILTRATION

Filtration is an important technique for the physical separation of solids and liquids. It has several purposes in the organic laboratory:

- To separate a solid product from a reaction mixture or recrystallization solution
- To remove solid impurities from a solution
- To separate a product solution from a drying agent after an aqueous extraction

The miniscale filtrations commonly performed in the organic laboratory use conical funnels and Erlenmeyer flasks for gravity filtrations and either Buchner or Hirsch funnels and filter flasks for vacuum filtrations. All three types of funnels require the use of filter paper to separate the solid from the liquid in the mixture undergoing filtration. The liquid that passes through the filter paper is called the ***filtrate***. Microscale gravity filtrations are usually done with a Pasteur pipet packed with either cotton or glass wool. Microscale vacuum filtrations use smaller versions of the miniscale equipment. When and how to use each filtration method is explained in this technique.

Although they are not strictly filtration techniques, decantation and centrifugation can also be used to separate solids from liquids in the organic laboratory.

10.1 Filtering Media

In any filtration, there needs to be a filtering medium that traps the solid being separated from its accompanying liquid. A variety of filtering media—filter paper, cotton, glass wool, micropore filters, and finely powdered solids called filter aids—are described in this section.

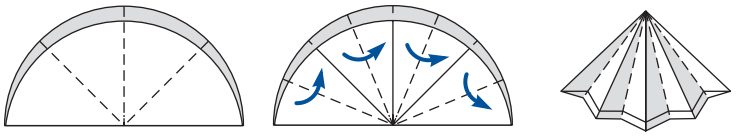
Filter Paper

Filter paper is used for both gravity and vacuum filtrations. For most filtrations performed in the introductory organic lab, a paper that provides medium filtering speed is satisfactory. Whatman is the major producer of filter paper for qualitative applications, and its various grades are listed in Table 10.1. Whatman No. 2 filter paper works well for both gravity and vacuum filtrations.

TABLE 10.1 Some Whatman Qualitative Filter Paper Types with Their Approximate Relative Speed and Retentivity

Type Number	Relative Speed	Particle Retention (μm)
Whatman 2	medium	> 8
Whatman 3[a]	medium-slow	> 6
Whatman 4	very fast	> 20–25
Whatman 5	slow	> 2.5
Whatman S & S 595	medium-fast	> 4–7

a. Thick—good for Buchner and Hirsch funnels.



(a) Crease filter paper. **(b)** Fold each quarter inward. **(c)** Fluted filter paper.

FIGURE 10.1
Fluting filter paper.

Special-purpose filter papers are also available. For example, when the filtrate contains the desired product and the solid being filtered is a by-product, a fast, hardened filter paper, such as Whatman 54, can be used. When an emulsion forms during an extraction, vacuum filtration through phase separator filter paper, such as Whatman 1PS, will usually break the emulsion.

Fluted Filter Paper

Fluted filter paper provides a larger surface for liquid-solid separations, which facilitates faster gravity filtration than does the usual filter paper cone. Speed of filtration is especially important when filtering insoluble impurities from a hot recrystallization solution in order to prevent the solid from crystallizing as the solution cools during the filtration. Vacuum filtration does not work well for a hot solution because much of the solvent can be lost to evaporation and because the solution cools too rapidly, leading to premature crystallization.

To make a fluted filter, crease a regular filter paper in half four times (Figure 10.1a). Then fold each of the eight sections of the filter paper inward, so that it looks like an accordion (Figure10.1b). Finally, open the paper to make a fluted cone, as illustrated in Figure 10.1c. Alternatively, commercially available filter paper already folded in this manner can be used.

Glass Fiber Filters

Glass fiber filter circles can be used instead of paper filters for vacuum filtration with a Buchner or Hirsch funnel. The filters are available in a wide range of sizes: 13–24-mm circles work well with Hirsch funnels; larger sizes can be used with Buchner funnels. Although glass fiber filters are more expensive than cellulose filter papers, they are particularly useful if the particles of the solid being filtered are very small.

Cotton and Glass Wool

Cotton or glass wool can be packed into a Pasteur pipet to make a useful filter in small-scale and microscale filtrations. The preparation and use of Pasteur filter pipets are described in Technique 10.3.

Micropore Filters

Samples for instrumental analysis by NMR spectroscopy, polarimetry, or high-pressure liquid chromatography may contain very fine particles that would interfere with obtaining a correct measurement. The use of a micropore filter will remove particles as small as 0.5 μm.

Draw a liquid sample into a syringe, and then attach a micropore filter to its end. Invert the syringe so that the filter points upward, and

push the syringe plunger just enough to force a few drops through the filter. Then reposition the filter pointing down and place it over a receiving vial. Press the plunger to force the solution through the filter into the vial. This filtered sample is ready for analysis.

Use of a Filter Aid

Occasionally, you may encounter a mixture containing very fine particles of a by-product or other unwanted solid material that passes through filter paper or clogs the filter paper pores and prevents or impedes filtration of the desired material. The use of a filter aid such as Celite facilitates the separation. Celite is a trade name for diatomaceous earth—a finely divided inert material derived from phytoplankton skeletons—which neither clogs the pores of filter paper nor passes through it. A filter aid should be used **only** for a mixture where the filtrate will contain the desired material and the solid adhering to the filter aid will be discarded.

In miniscale procedures, Celite may be added to a reaction mixture before vacuum filtration if the mixture contains a large quantity of unwanted fine particles that could clog the filter paper. In microscale procedures, the separation of fine particles of unwanted material from a liquid mixture is more easily carried out with a Pasteur pipet packed with silica gel or alumina as the filter aid.

10.2 Miniscale Gravity Filtration

Miniscale gravity filtrations are used in the organic laboratory for several purposes—to remove a drying agent from an organic solution, during a recrystallization where the desired product is completely dissolved in a hot solution but insoluble impurities remain, and when colored impurities are present in a hot recrystallization solution. In the latter instance, the mixture is treated with activated charcoal and then gravity-filtered to remove the charcoal.

Carrying Out a Miniscale Gravity Filtration

The following procedure requires a minimum of 15 mL of liquid. Place a fluted filter paper [see Technique 10.1] in a clean, short-stemmed funnel and put the funnel into the neck of a clean Erlenmeyer flask or, if the liquid will be distilled after filtration, into a round-bottomed flask. Wet the filter paper with a small amount of the solvent in the mixture being filtered so that the paper adheres to the conical funnel. When the liquid volume is less than 15 mL, the Pasteur filter pipet method described in Technique 10.3 will prevent significant losses.

Filtering a room-temperature liquid. If the mixture to be filtered is at room temperature, it can simply be poured into the filter paper and allowed to drain through the paper into an Erlenmeyer flask. Then add a few milliliters of the solvent to wash through any product that may have adhered to the filter paper.

Filtering a hot solution. If the mixture being filtered is a hot solution containing a dissolved solid, precautions must be taken to prevent

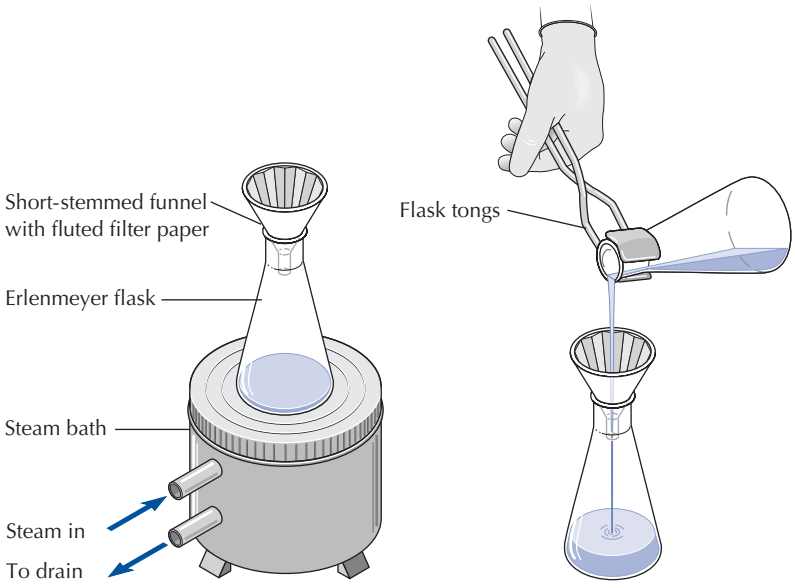


FIGURE 10.2
Filtering solid impurities from a recrystallization solution.

the solid from crystallizing during the filtration process. Add a small amount of the recrystallization solvent to the receiving flask (1–10 mL depending on the size of the flask). Then heat the flask, funnel, and solvent on a steam bath (Figure 10.2, step 1) or clamp the flask in a water bath that is being heated on a hot plate in a hood. The hot solvent warms the funnel and helps prevent premature crystallization of the solute during filtration. If the steam bath is large enough, keep both flasks hot during the filtration process; if it is too small for both, keep the unfiltered solution hot and set the receiving flask on the bench top. Next pour the hot recrystallization solution through a fluted filter paper (Figure 10.2, step 2).

SAFETY PRECAUTION

Lift a hot Erlenmeyer flask with flask tongs.

Be sure that the hot solution is added in small quantities to the fluted filter paper, because cooling at this stage may cause premature crystallization. Keep the unfiltered solution hot at all times. If you have difficulty keeping the solution from crystallizing on the filter paper, add additional hot solvent to the flask containing the unfiltered solution and reheat it to the boiling point before continuing the filtration. When the filtration is complete, add a boiling stone or stick and boil away the extra solvent you added.

When all the hot solution has drained through the filter paper, check to see whether any crystallization occurred in the Erlenmeyer receiving flask due to rapid cooling during the filtration step. If it has, reheat the mixture to dissolve the solid completely before allowing the solute to crystallize slowly.

Using Activated Charcoal to Remove Colored Impurities

If the compound you are recrystallizing is known to be colorless and if the recrystallization solution is deeply colored after the compound dissolves, treatment with activated charcoal (Norit, for example) may remove what is probably a small amount of intensely colored impurity. Activated charcoal has a large surface area and a strong affinity for highly conjugated colored compounds, allowing it to readily adsorb these impurities from the recrystallization solution. Using too much charcoal, however, may cause some of the compound you are purifying to be adsorbed by the charcoal and reduce your yield.

SAFETY PRECAUTION

Cool the hot solution briefly before adding the charcoal. Adding charcoal to a boiling solution can cause the solution to foam out of the flask.

Add 40–50 mg of Norit activated-carbon decolorizing pellets to the **hot but not boiling** recrystallization solution. Then heat the mixture to just under boiling for a few minutes. (Boiling actually hinders decolorization, but heating to keep the compound in solution is necessary.) While the solution is still very hot, gravity filter it through a fluted filter paper.

10.3 Microscale Gravity Filtration

Pasteur pipets are used to filter a small quantity of liquid by packing the tapered portion of the pipet with glass wool or cotton.

SAFETY PRECAUTION

Glass Pasteur pipets are puncture hazards. They should be handled and stored carefully. Dispose of Pasteur pipets in a "sharps" box or in a manner that does not present a hazard to lab personnel or housekeeping staff. Check with your instructor about the proper disposal method in your laboratory.

Pasteur Filter Pipets

When a small amount of an organic liquid or solution needs to be separated from a solid reaction by-product or a drying agent, a Pasteur filter pipet provides the necessary filtration with minimal loss of the organic liquid. The tapered portion of the pipet is packed with either cotton or glass wool. If the solid to be separated contains very fine particles, such as a powdered catalyst, using glass wool or cotton alone often does not provide sufficient filtration and a Celite filter pad is added.

Preparing and Using a Pasteur Filter Pipet

To prepare a filter pipet, use a pair of tweezers to pick up a small amount of cotton and then push it down into the pipet with a wooden applicator stick. Pack the cotton firmly into the bottom of the tapered portion of the pipet as shown in Figure 10.3. Use a

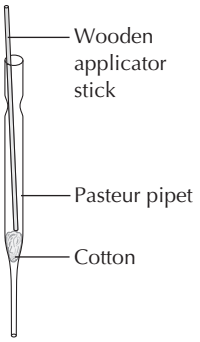


FIGURE 10.3
Pasteur filter pipet.

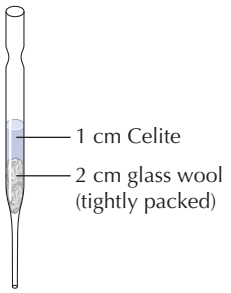


FIGURE 10.4
Pasteur filter pipet packed with a Celite filter pad.

microclamp to hold the filter pipet in a vertical position for the filtration and place a small Erlenmeyer flask underneath it. Use another Pasteur pipet to transfer the mixture being filtered to the filter pipet. The drying agent or solid impurities will adhere to the cotton. Use a clean Pasteur pipet to add 1–2 mL of fresh solvent to the filter pipet to rinse all desired material from it and collect the rinse in the same Erlenmeyer flask.

Preparing a Celite Filter Pad in a Pasteur Pipet

SAFETY PRECAUTION

Wear gloves and use tweezers to handle glass wool.

Pick up a small amount of glass wool with tweezers and tightly pack it into the tapered portion of a Pasteur pipet using a wooden applicator stick as shown in Figure 10.3. Continue packing small portions until approximately a 2-cm depth is reached. Add approximately 1 cm of Celite on top of the glass wool to ensure efficient entrapment of very fine particles (Figure 10.4). Use a microclamp to hold the pipet and position the receiving container underneath it.

10.4 Vacuum Filtration

Vacuum filtration is used to rapidly and completely separate a solid from the liquid with which it is mixed. The recovery of the crystallized product from a recrystallization procedure is a common application of vacuum filtration in the organic chemistry lab. Vacuum filtration is also employed when it is necessary to use a filter aid, such as Celite, to remove very finely divided insoluble solids from a solution. In this instance, it is the solution, not the solid, that is the desired product.

The vacuum source for a filtration can be either a water aspirator or a compressor-driven vacuum system. **Heavy-walled tubing must be used in vacuum filtration** so that it will not collapse from atmospheric pressure on the outside when the vacuum is applied. If the tubing collapses, the vacuum filtration will not work.

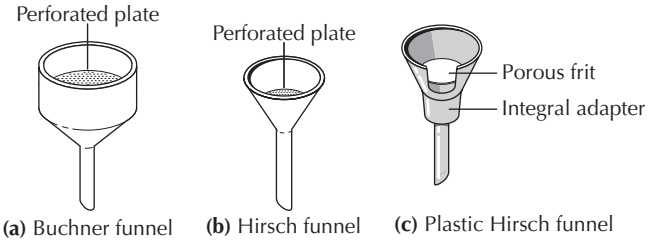


FIGURE 10.5
Funnels used for vacuum filtration.

Funnels for Vacuum Filtration

The funnels used for vacuum filtration have a flat, perforated or porous plate that holds filter paper to retain the solid being separated from its accompanying liquid. They are made from porcelain, glass, or plastic. Figure 10.5 shows a porcelain Buchner funnel, a porcelain Hirsch funnel, and a plastic Hirsch microscale funnel with an integral adapter. Both Buchner and Hirsch funnels are available in a variety of sizes—select a size appropriate for the amount of material you will be collecting. For example, if you are filtering a mixture that contains 1–3 g of solid, use a 78- or 100-mm diameter Buchner funnel. For filtering a mixture containing 0.2–1 g of solid, select a 43-mm diameter Buchner funnel or a 16-mm Hirsch funnel. For microscale filtrations, use an 11-mm Hirsch funnel or a microscale plastic Hirsch funnel.

When using a Buchner or Hirsch funnel with perforations, **it is crucial to select the correct size of filter paper** for the funnel you are using. The paper must lie flat on the perforated plate and **just cover** all the holes in the plate but not curl up the side.

Miniscale Apparatus for Vacuum Filtration

The apparatus for a miniscale vacuum filtration consists of a Buchner funnel (or medium-size Hirsch funnel), neoprene adapter, filter flask, and trap flask or bottle (Figure 10.6). A trap flask is placed between the vacuum source and the filter flask to prevent back flow of water into the filter flask when a water aspirator is the vacuum source. With a compressor-driven vacuum system, the trap

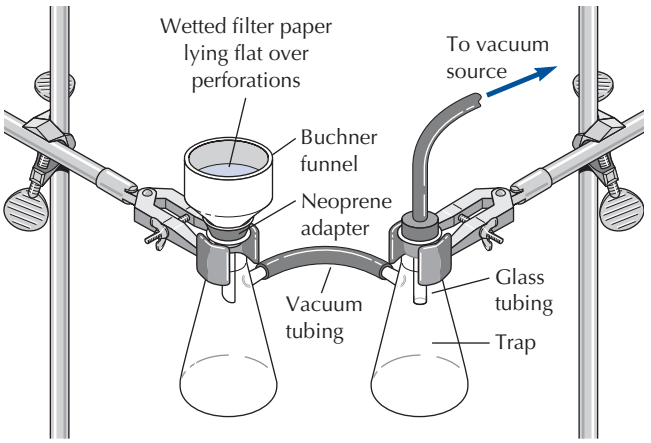


FIGURE 10.6
Apparatus for vacuum filtration.

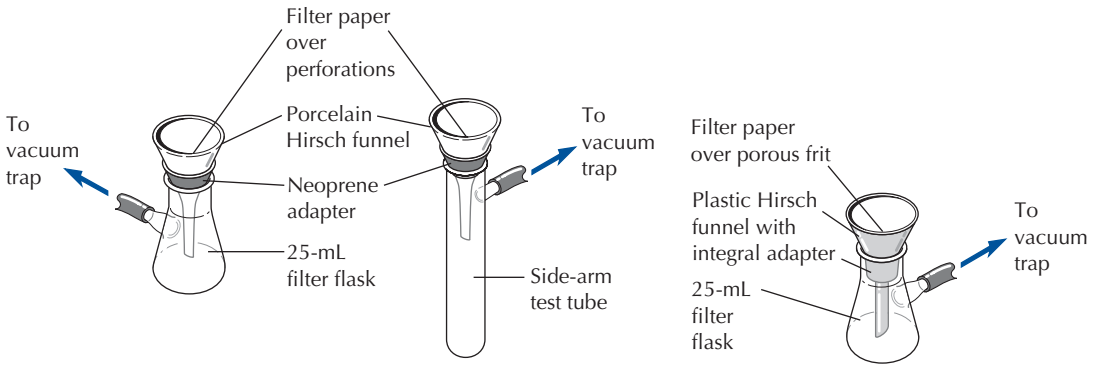
flask keeps any overflow from the filter flask out of the vacuum line or vacuum pump. Both the filter flask and the trap flask must be firmly clamped to prevent the apparatus from tipping over. The neoprene adapter insures a tight seal between the filter flask and the Buchner funnel. Heavy-walled tubing is used to connect the vacuum line and filtration flask in order to prevent collapse of the tubing from atmospheric pressure when the vacuum is applied.

Place a piece of appropriate-sized filter paper in the Buchner funnel and wet the paper with a small amount of the solvent present in the mixture being filtered. Turn on the vacuum source to pull the paper tightly over the holes in the funnel, and then **immediately** pour the mixture being filtered into the funnel. At the end of the filtration, hold the filter flask firmly with one hand and use the other hand to tip the Buchner (or Hirsch) funnel **slightly** to the side to break the seal before turning off the vacuum source.

Microscale Apparatus for Vacuum Filtration

Microscale vacuum filtrations use a small, porcelain Hirsch funnel, a 25-mL filter flask and an 18- × 150-mm side-arm test tube with a neoprene adapter assembled as shown in Figure 10.7a. When a plastic Hirsch funnel with an integral adapter is used, the funnel is simply inserted into a 25-mL filter flask—no neoprene adapter is used (Figure 10.7b).

A microscale filtration apparatus should always be firmly clamped at the neck of the filter flask; the apparatus tips very easily when it is attached to the heavy-walled rubber tubing leading to the vacuum source. Place an appropriate-sized filter paper or glass fiber filter in the Hirsch funnel so that it lies flat and just covers the holes in the funnel. Wet the paper with a small amount of the solvent present in the mixture being filtered. Turn on the vacuum source to pull the paper tightly over the holes in the funnel, and then **immediately** pour the mixture being filtered into the funnel. At the end of the filtration, hold the filter flask firmly with one hand and use the other hand to tip the Hirsch funnel **slightly** to the side to break the seal before turning off the vacuum source.



(a) Using a Hirsch funnel **(b)** Using a plastic Hirsch funnel

FIGURE 10.7 Microscale apparatus for vacuum filtration.

10.5 Other Liquid-Solid and Liquid-Liquid Separation Techniques

Decantation and centrifugation can also be used to separate solids from liquids.

Decantation

A liquid can be separated from a few large particles by carefully pouring away the liquid above the particles—a process called ***decanting.*** The large, solid particles will stay in the bottom of the original container. For example, decanting can be used to separate a liquid from boiling stones. However, if the sample contains a large number of solid particles or the particles are fine, filtration is a better separation method.

Centrifugation

When a sample contains suspended particles, centrifugation may be more effective than filtration in separating the solid and the liquid. Centrifugation is also useful for breaking liquid-liquid emulsions in microscale extractions. In fact, a microscale extraction is frequently carried out in a centrifuge tube to facilitate removing the lower layer with a Pasteur pipet, and if an emulsion forms, the tube can be spun in a centrifuge to separate the liquid phases.

In operating a centrifuge, the sample tube **must** be counterbalanced by another centrifuge tube filled with an equal volume of water. A centrifuge containing unbalanced tubes vibrates excessively and noisily and may move around on the bench top. A balanced centrifuge makes a steady, uniform noise at full speed.

10.6 Sources of Confusion

Much of the confusion regarding filtration arises in knowing which method to select for a specific situation. As a general guide, if a solution contains unwanted solid material, use gravity filtration to separate the mixture. If the desired product is a solid in a liquid mixture, use vacuum filtration to recover it.

Solid Particles Pass Through the Filter Paper

Incomplete separation in a gravity filtration is probably caused by using the wrong type of filter paper. Tiny solid particles can go through filter paper designed for coarse solids. In vacuum filtrations, using wrong-size filter paper can allow both the liquid and the solid particles to creep around the edges, which will lead to incomplete separation.

Liquid in the Funnel Ceases to Run Through the Filter

Having liquid in the funnel that won't pass through the filter in a gravity filtration is perhaps the most frustrating part of any filtration. The pores in the filter paper can become clogged if wrong-porosity

paper is used. The answer to the problem usually is to interrupt the filtration and start over, using filter paper designed for the size of particles the solid contains. In some cases, using a centrifuge for the separation may be more feasible.

The Vacuum Filtration Won't Suck the Liquid Through the Funnel

Lack of suction in a vacuum filtration is usually caused by the collapse of thin-walled rubber tubing not designed for use with a vacuum. Replace the hoses with thick-walled vacuum tubing. The phenomenon could also be due to an inefficient vacuum system caused by insufficient power in the vacuum pump or water aspirator or by a leak in the system.

A Liquid in the Filter Flask of a Vacuum Filtration Is Boiling

Vacuum filtrations can't easily be carried out with very low-boiling solvents such as ether or pentane. Their vapor pressures are too great at room temperature.

Questions

1. Why would a Hirsch funnel be more effective than a Buchner funnel for a small-scale vacuum filtration?
2. Pasteur pipets are often used for microscale gravity filtrations but seldom for miniscale filtrations. Why?
3. Explain the advantage that fluted filter paper has in a gravity filtration.
4. Why should a hot recrystallization solution be filtered by gravity rather than by vacuum filtration?
5. Explain why the filter flask can become quite cold to the touch during a vacuum filtration.
6. Why must the seal be broken in a vacuum filtration before the flow of water to a water aspirator is turned off?
7. In each of the following situations, which type of filtration apparatus would you use?
   a. Remove about 0.3 g of solid impurities from 5 mL of a liquid.
   b. Collect crystals obtained from recrystallizing an organic solid from 20 mL of solvent.
   c. Remove dissolved colored impurities from 35 mL of an ethanol solution.

TECHNIQUE 11

EXTRACTION

Extraction is a technique used for selectively separating a compound from a mixture. For example, a relatively water-insoluble organic compound can be separated from an aqueous mixture by extracting it into a water-insoluble organic solvent. Extractions are often part of the workup procedure for isolating and purifying the products of organic reactions.

11.1 Understanding How Extraction Works

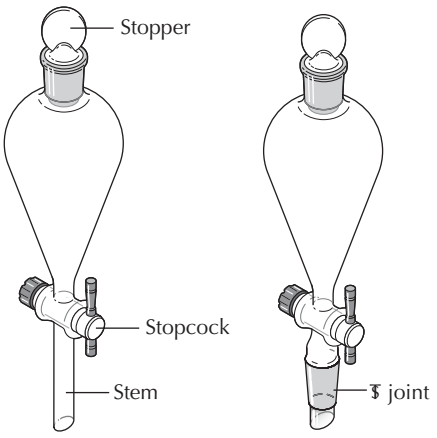
The process of ***liquid-liquid extraction*** involves the distribution of a compound **(*solute*)** between two solvents that are ***immiscible* (*insoluble*)** in each other. Generally, although not always, one of the solvents in an extraction is water and the other is a much less polar organic solvent, such as diethyl ether, ethyl acetate, hexane, or dichloromethane. By taking advantage of the differing solubilities of a solute in a pair of solvents, compounds can be selectively transported from one liquid phase to the other during an extraction.

You will find it helpful to read the essay on intermolecular forces in organic chemistry on pages 99–103 that are the foundation of our understanding of extraction. This essay describes the dipole-dipole forces between molecules and the structural factors that determine the solubility characteristics of organic compounds.

Aqueous Extractions

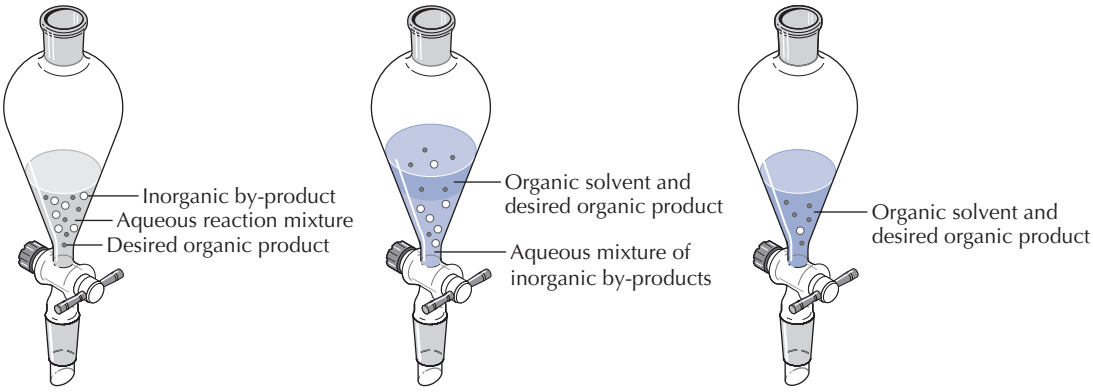
In a typical extraction procedure, an ***aqueous phase (water)*** and an immiscible organic solvent, often called the ***organic phase,*** are gently shaken in a separatory funnel (Figure 11.1). The solutes distribute themselves between the aqueous layer and the organic layer according to their relative solubilities. Inorganic salts generally prefer the aqueous phase, whereas most organics dissolve more readily in the organic phase. Two or three extractions of an aqueous mixture often suffice to quantitatively transfer a nonpolar organic compound, such as a hydrocarbon or a halocarbon, to an organic solvent. Separation of low-molecular-weight alcohols or other polar organic compounds may require additional extractions or a different approach.

If at the end of an organic reaction you have an aqueous mixture containing the desired organic product and a number of inorganic by-products, extraction with an organic solvent immiscible with water can be used to separate the organic product from the by-products. The separatory funnel initially contains the aqueous reaction mixture (Figure 11.2a). When an organic solvent less dense than



(a) Separatory funnel **(b)** Dropping funnel, which can be used as a separatory funnel

FIGURE 11.1 Funnels for extractions.



(a) Aqueous mixture of organic product and inorganic by-products

(b) Most of the desired organic product has been transferred to the organic solvent.

(c) After the aqueous mixture of inorganic by-products has been drained from the separatory funnel, the organic solvent solution of the desired product remains in the separatory funnel.

FIGURE 11.2 Using extraction to separate an organic compound from an aqueous mixture.

water is added to the separatory funnel and the funnel is stoppered and shaken to mix the two phases, the separated phases would appear as shown in Figure 11.2b. Then the lower aqueous layer can be drained from the separatory funnel, leaving the organic layer containing the desired product in the funnel (Figure 11.2c). The separation of organic product and inorganic by-products normally is not entirely complete because the organic compound may have a slight solubility in water and the inorganic by-products may have a slight solubility in the organic solvent.

Distribution Coefficient

When an organic compound is distributed or partitioned between an organic solvent and water, the ratio of solute concentration in the organic solvent, C_1, to its concentration in water, C_2, is equal to the ratio of its solubilities in the two solvents. The distribution of an organic solute, either liquid or solid, can be expressed by

$$K = \frac{C_1}{C_2} = \frac{\text{g compound per mL organic solvent}}{\text{g compound per mL water}} \qquad \text{(Eq. 1)}$$

K is defined as the ***distribution coefficient,*** or ***partition coefficient.***

Any organic compound with a distribution coefficient greater than 1.5 can be separated from water by extraction with a water-insoluble organic solvent. As you will soon see, working through the mathematics of the distribution coefficient shows that a series of extractions using small volumes of solvents is more efficient than a single large-volume extraction. A volume of solvent about one-third the volume of the aqueous phase is appropriate for each extraction. Commonly used extraction solvents are listed in Table 11.1.

If the distribution coefficient K of a solute between water and an organic solvent is large, a single extraction may suffice to extract the compound from water into the organic solvent. Most often,

TABLE 11.1 Common extraction solvents

Solvent	Boiling point, °C	Solubility in water, g/100 mL	Hazard	Density, g/mL^{-1}	Fire hazard[a]
Diethyl ether	35	6	Inhalation, fire	0.71	++++
Pentane	36	0.04	Inhalation, fire	0.62	++++
Petroleum ether[b]	40–60	Low	Inhalation, fire	0.64	++++
Dichloromethane	40	2	LD_{50}[c], 1.6 mL/kg	1.32	+
Hexane	69	0.02	Inhalation, fire	0.66	++++
Ethyl acetate	77	9	Inhalation, fire	0.90	++

a. Scale: extreme fire hazard = ++++.
b. Mixture of hydrocarbons.
c. LD_{50}, lethal dose orally in young rats.

however, the distribution coefficient is less than 10, making multiple extractions necessary.

In general, the fraction of solute remaining in the original water solvent is given by

$$\frac{(\text{Final mass of solute})_{\text{water}}}{(\text{Initial mass of solute})_{\text{water}}} = \left(\frac{V_2}{V_2 + V_1K}\right)^n \qquad \text{(Eq. 2)}$$

where

V_1 = volume of organic solvent in each extraction
V_2 = original volume of water
n = number of extractions
K = distribution coefficient

How Many Extractions Should Be Used?

Consider a simple case of extraction from water into ether, assuming a distribution coefficient of 5.0 for the organic compound being extracted. As an illustration, we use 1.0 g of compound dissolved in 50 mL of water. Would the recovery of the desired compound be better if the water solution were extracted once with 45 mL of ether or 2–3 times with 15-mL portions of ether? The final mass of solute remaining in the water after extraction can be calculated using equation 2.

One extraction. Calculation of the amount of organic compound (solute) remaining in the water solution after one extraction using 45 mL of ether using equation 2 ($n = 1$):

$$(\text{Final mass of solute})_{\text{water}} = x \text{ g}$$
$$(\text{Initial mass of solute})_{\text{water}} = 1.0 \text{ g}$$
$$V_1 = 45 \text{ mL ether}$$
$$V_2 = 50 \text{ mL water}$$

$$\frac{(\text{Final mass of solute})_{\text{water}}}{(\text{Initial mass of solute})_{\text{water}}} = \frac{x \text{ g}}{1.0 \text{ g}} = \left(\frac{V_2}{V_2 + V_1K}\right)^n = \left(\frac{50}{50 + (45 \times 5.0)}\right) \qquad \text{(Eq. 3)}$$

$x = 0.18$ g solute remaining in water layer after extraction

Thus, 0.82 g of solute was extracted into the ether layer and 0.18 g of solute remains in the water layer.

Two extractions. Calculation for two extractions, each using 15 mL of ether ($n = 2$):

$$(\text{Final mass of solute})_{\text{water}} = x \text{ g}$$
$$(\text{Initial mass of solute})_{\text{water}} = 1.0 \text{ g}$$
$$V_1 = 15 \text{ mL ether}$$
$$V_2 = 50 \text{ mL water}$$

$$\frac{(\text{Final mass of solute})_{\text{water}}}{(\text{Initial mass of solute})_{\text{water}}} = \frac{x \text{ g}}{1.0 \text{ g}} = \left(\frac{V_2}{V_2 + V_1 K}\right)^n = \left(\frac{50}{50 + (15 \times 5.0)}\right)^2 \quad \text{(Eq. 4)}$$

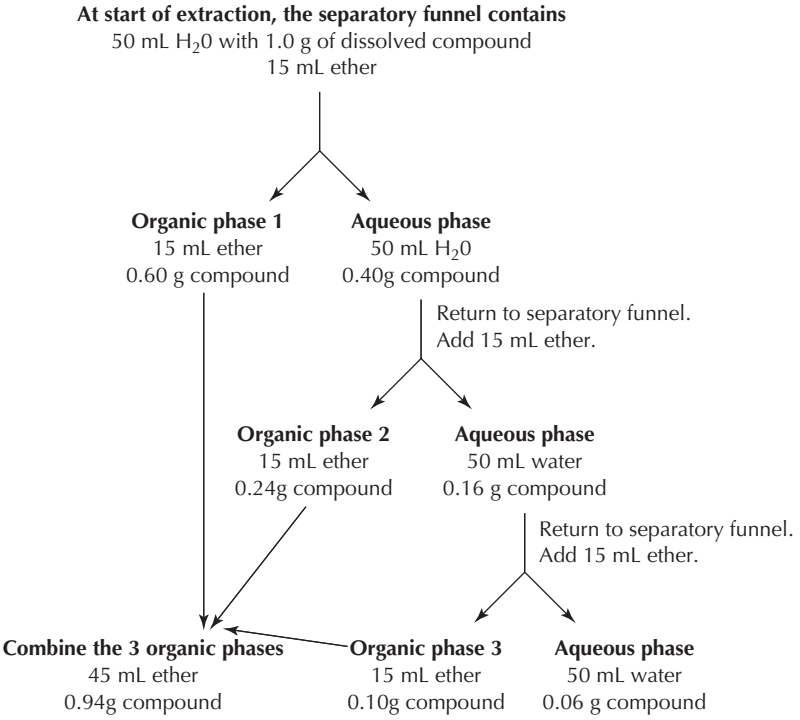
$x = 0.16$ g solute remaining in water layer after second extraction

After two extractions with 15 mL of ether, a total of 0.84 g of solute has been extracted into the ether layers. The amount of solute separated by two extractions is comparable to that of the single extraction, but the process was carried out more effectively and economically with the use of only 60% as much ether.

Three extractions. If a third extraction of the residual aqueous layer with 15 mL of ether were done, an additional 0.10 g of solute (10%) would be transferred from the aqueous layer to the ether layer, giving a total recovery of 0.94 g of solute. Only 6% of the organic compound would remain in the aqueous layer; most of it could be extracted with one more 15-mL portion of ether.

Drawing a flowchart of the extractions. It can be helpful to draw a flowchart that shows the steps in an extraction, particularly when multiple steps are involved. The flowchart shown here illustrates the three steps in separating 0.94 g of organic compound from a solution of 1.0 g of the compound in 50 mL of water as described by the previous calculations. Recall that the distribution coefficient (K = 5) is relatively small; thus, three extractions are needed for satisfactory recovery of the organic compound.

At the end of the three extractions, the three ether solutions of the organic compound are combined before subsequent operations are used to purify and dry the combined ether solution and recover the purified organic compound. If further steps in the procedure involve more extractions, they can be illustrated by extending the flowchart below the point where the three ether solutions are combined into one product solution.



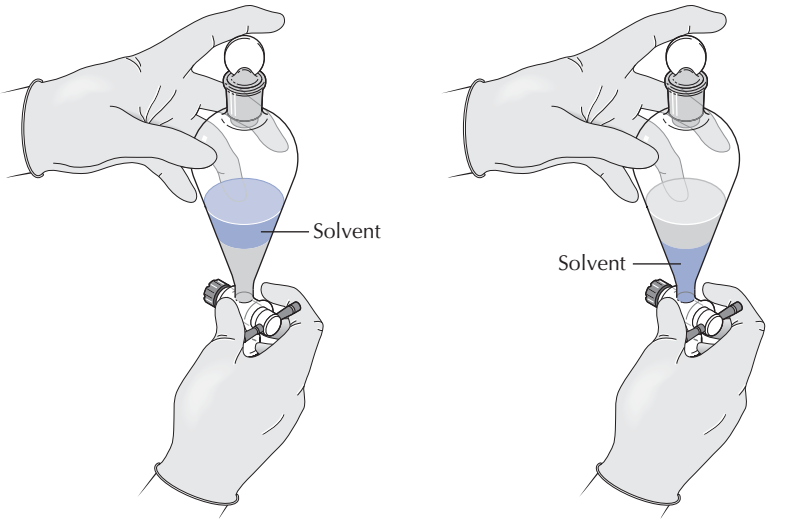
11.2 Practical Advice on Extractions

A number of practical details need to be taken into account while carrying out an extraction:

- Density of the solvent used for the extraction
- Temperature of the extraction mixture
- Venting the separatory funnel and why it is necessary
- What happens when an acid or base is present in the aqueous phase
- What is meant by "washing the organic phase"
- Improving the efficiency of an extraction by salting out if the distribution coefficient is less than 2.0
- Preventing and dispersing emulsions
- Caring for the separatory funnel after an extraction

Density of the Solvent

Before you begin any extraction, look up the density of the organic solvent in Table 11.1 or use a handbook to determine whether the extraction solvent you are using is more dense or less dense than water. **The more dense layer is always on the bottom.** Organic solvents that are less dense than water form the upper layer in the separatory funnel (Figure 11.3a), whereas solvents that are denser than water form the lower layer (Figure 11.3b). Occasionally, sufficient material is extracted from the aqueous phase to the organic phase or vice versa to change the relative densities of the two phases enough for them to exchange places in the separatory funnel.



(a) Organic solvent less dense than water **(b)** Organic solvent more dense than water

FIGURE 11.3 Solvent densities.

Temperature of the Extraction Mixture

Be sure that the aqueous extraction solution is at room temperature or slightly cooler before you add the organic extraction solvent. Most organic solvents used for extractions have low boiling points and may boil if added to a warm aqueous solution. A few pieces of ice can be added to cool the aqueous solution.

Venting the Separatory Funnel

SAFETY PRECAUTION

Do not point a separatory funnel at yourself or your neighbor. Point the separatory funnel toward the back of the hood when venting it.

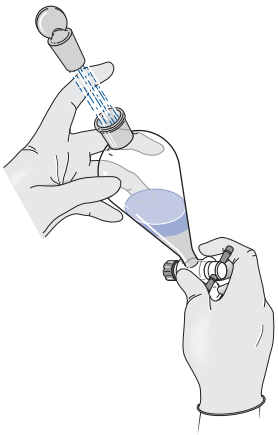


FIGURE 11.4
Failure to vent the separatory funnel when extracting with Na_2CO_3 or $NaHCO_3$ solution can cause the stopper to pop out.

Work in a hood while carrying out an extraction. Be sure that you vent an extraction mixture by carefully inverting the stoppered separatory funnel and immediately opening the stopcock before you begin the shaking process. If you do not do this, the stopper may pop out of the funnel and liquids and gases may be released (Figure 11.4). Pressure buildup in the separatory funnel is always a problem when using low-boiling extraction solvents such as diethyl ether, pentane, and dichloromethane.

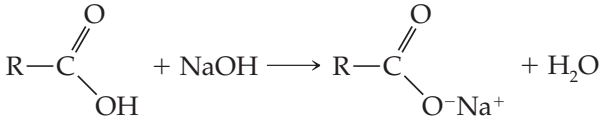
Venting extraction mixtures is especially important when you use a dilute sodium carbonate or bicarbonate solution to extract an organic phase containing traces of an acid. Carbon dioxide gas is given off in the neutralization process. The CO_2 pressure buildup can easily force the stopper out of the funnel, cause losses of solutions, and possibly injure you or your neighbor. When using sodium carbonate or bicarbonate to extract or wash acidic contaminants from an organic solution, **vent the extraction mixture immediately after the first inversion and subsequently after every three or four inversions.**

Removing Acids and Bases

When inorganic acids or bases are present in an organic phase, extraction with water, followed by extraction with a base or an acid, will usually remove the acid or base. Chemists often use the term ***wash*** to describe this type of extraction. For example, if HBr were used in a reaction, the organic phase could be *washed* with water and then with a dilute sodium bicarbonate solution. The reaction between HBr and sodium bicarbonate effectively removes HBr from the organic phase to the aqueous phase by converting it to the ionic salt sodium bromide.

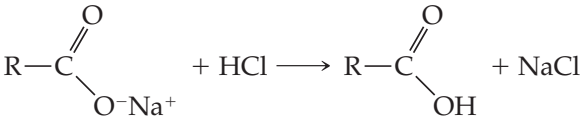
$$HBr + NaHCO_3 \longrightarrow NaBr + H_2O + CO_2(g)$$

An acid/base extraction can also be used to separate an acidic organic product from a reaction mixture. For example, in the synthesis of a carboxylic acid (RCO_2H), the product can be purified by first extracting an ether solution of the reaction mixture with a dilute solution of sodium hydroxide. The carboxylic acid is converted to the water-soluble carboxylate anion, which dissolves in the aqueous sodium hydroxide solution, while nonacidic impurities remain in the organic phase.



Carboxylic acid Sodium carboxylate

Later, the basic solution of the sodium carboxylate can be acidified, and the purified carboxylic acid can be extracted back into an organic solvent to recover it.



Sodium carboxylate Carboxylic acid

Washing the Organic Phase

After an extraction is completed and the two immiscible liquids are separated, the organic layer is often extracted, or washed, with water or perhaps a dilute aqueous solution of an acid or a base. For example, a chemical reaction involving alkaline (basic) reagents often yields an organic extract that still contains some alkaline material. This alkaline material can be removed by washing the organic phase with a 5% solution of hydrochloric acid. Similarly, an organic extract obtained from an acidic solution should be washed with a 5% solution of sodium carbonate or sodium bicarbonate (see preceding section on venting). The salts formed in these extractions are very soluble in water but not in typical organic solvents, so they are easily transported into the aqueous phase. If acid or base washes are required, they are done in the same manner as any other extraction and are usually followed by a final water wash.

Improved Efficiency of Extraction by Salting Out

If the distribution coefficient for a substance to be extracted from water into an organic solvent is lower than 2.0, a simple extraction procedure is not effective. In this case, a salting out procedure can help. ***Salting out*** is done by adding a saturated solution of NaCl (sometimes called brine) or Na_2SO_4, or the salt crystals themselves, to the aqueous layer. The presence of a salt in the water layer decreases the solubility of the organic compound in the aqueous phase. Therefore, the distribution coefficient increases, allowing more of the organic compound to be transferred from the aqueous phase to the organic layer. Salting out can also help to separate a homogeneous solution of water and a water-soluble organic compound into two phases.

Emulsions

The formation of an ***emulsion***—a suspension of insoluble droplets of one liquid in another liquid—is sometimes encountered while doing an extraction. When an emulsion forms, the entire mixture has a milky appearance, with no clear separation between the immiscible layers, or there may be a third milky layer between the aqueous and the organic phases. Emulsions are not usually formed during diethyl ether extractions, but they frequently occur when aromatic or chlorinated organic solvents are used. An emulsion often disperses if the separatory funnel and its contents are allowed to sit in a ring stand for a few minutes.

Prevention of emulsions. Preventing emulsions is simpler than dealing with them. When using aromatic or chlorinated solvents to extract organic compounds from aqueous solutions, very gentle mixing of the two phases may reduce or eliminate emulsion formation. Instead of shaking the mixture vigorously, invert the separatory funnel and gently swirl the two layers together for 2–3 min. However, use of this swirling technique may mean that you need to extract an aqueous solution with an extra portion of organic solvent for maximum recovery of the product.

What to do if an emulsion forms. Should an emulsion occur, it can often be dispersed by vacuum filtration through a pad of the filter aid Celite. Prepare the Celite pad by pouring a slurry of Celite and water onto a filter paper in a Buchner funnel [see Technique 10.1]. Remove the water from the filter flask before pouring the emulsion through the Buchner funnel. Return the filtrate to the separatory funnel and separate the two phases. Another method, useful when the organic phase is the lower layer, involves filtering the organic phase by vacuum filtration through a phase separator filter paper, such as Whatman 1PS. For microscale extractions [Technique 11.5], centrifugation of an emulsified mixture usually separates the two liquid phases.

Caring for the Separatory Funnel

When the entire extraction is complete, clean the funnel immediately and regrease the glass stopcock to prevent a "frozen" stopcock later. Grease is not necessary with Teflon stopcocks, but they may also freeze if not loosened prior to storage.

11.3 Miniscale Extractions

Read Techniques 11.1 and 11.2 before undertaking a miniscale extraction for the first time.

Before you begin an extraction, assemble and **label** a series of Erlenmeyer flasks for the aqueous phase and the organic phase for the number of extractions you will be doing. (Do **not** use beakers for the organic phase, because the solvent will evaporate rapidly.) The solutions in an extraction tend to be colorless, so if the flasks are not clearly labeled, it is very easy to become confused about the contents of a particular flask by the end of the procedure.

Extraction with an Organic Solvent Less Dense Than Water

SAFETY PRECAUTION

Wear gloves and work in a hood while doing extractions. Point the separatory funnel toward the back of the hood when venting it.

Place a separatory funnel large enough to hold three to four times the total solution volume in a metal ring firmly clamped to a ring stand or upright support rod (Figure 11.5, step 1). **The stopcock must fit tightly and be closed.** If the separatory funnel has a glass stopcock, make sure that the stopcock is adequately greased. If the separatory funnel has a Teflon stopcock, as shown in Figure 11.2, no grease is necessary. However, the nut on the threaded end of the stopcock must be tightened so that the stopcock fits snugly and yet can still be rotated with ease.

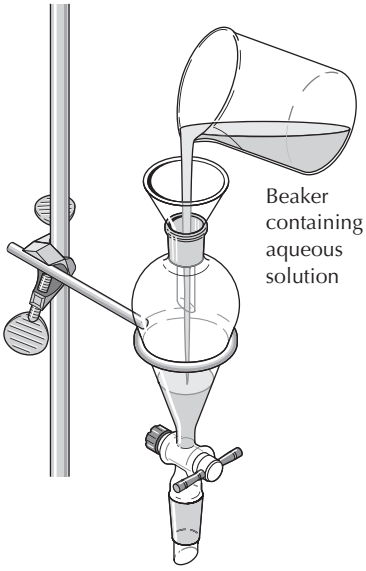
Pour the cooled aqueous solution to be extracted into the separatory funnel. Add a volume of organic solvent equal to approximately one-third the total volume of the aqueous solution (Figure 11.5, step 2), and put the stopper in place.

Remove the funnel from the ring and grasp its neck with one hand, holding the stopper down firmly with your index finger (Figure 11.5, step 3). Invert the funnel, and **open the stopcock immediately** to release the pressure from solvent vapors (Figure 11.5, step 4). Close the stopcock, and thoroughly mix the two liquid phases by shaking the mixture while inverting the separatory funnel four or five times. Then release the pressure by opening the stopcock. Repeat this shaking and venting process five or six times to ensure complete mixing of the two phases. Shaking too gently does not effectively mix the two phases; shaking too vigorously may lead to the formation of emulsions.

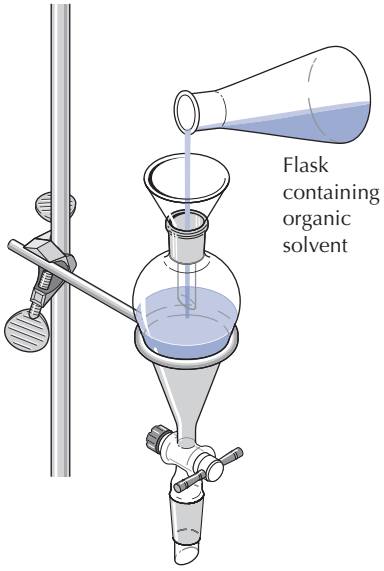
Pour the top layer out of the top of the funnel so that it is not contaminated by the residual bottom layer adhering to the stopcock and tip.

Place the separatory funnel in the ring once more and wait until the layers have completely separated (Figure 11.5, step 5). **Remove the stopper and open the stopcock** to draw off the bottom layer into a labeled Erlenmeyer flask (Figure 11.5, step 6). Pour the remaining organic layer out of the funnel through the top into a separate labeled Erlenmeyer flask (Figure 11.5, step 7). Do this entire procedure each time you carry out an extraction.

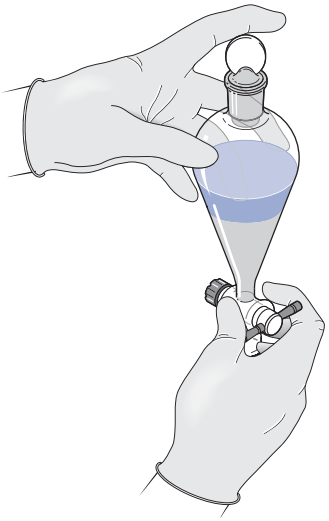
If you are in doubt as to which layer is the organic phase and which is the aqueous phase, you can check by adding a few drops of the layer in question to 1–2 mL of water in a test tube and observing whether it dissolves or not. **Do not discard any solution until**



1. Add aqueous solution.



2. Add organic solvent.



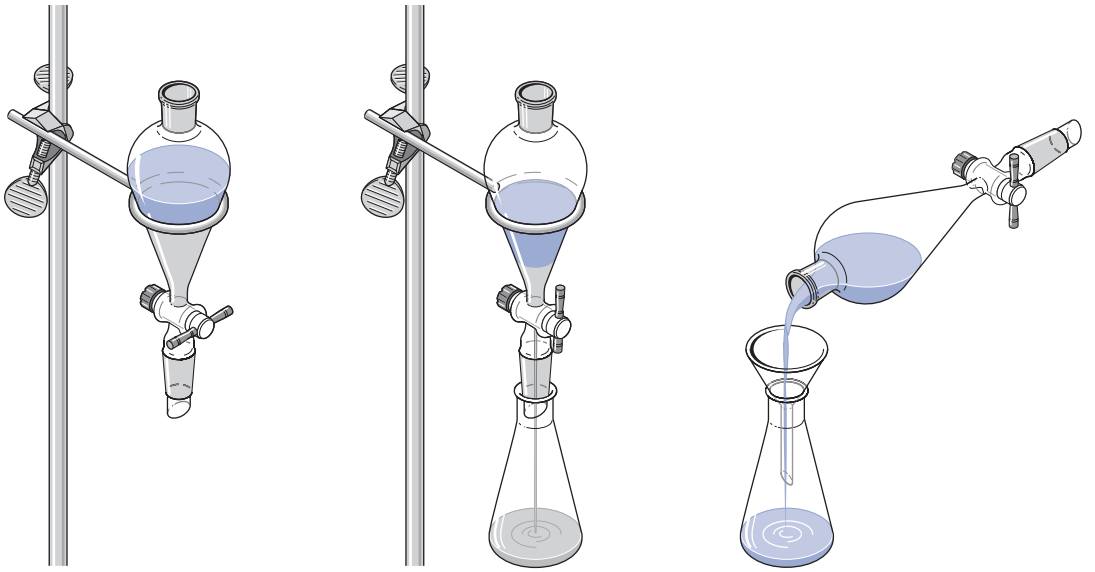
3. Insert stopper and hold stopper with your finger.

4. Invert funnel and immediately open stopcock to release pressure, close the stopcock, and mix the layers by shaking the funnel.

FIGURE 11.5 Using a separatory funnel. *(Continued on next page.)*

you have completed the entire extraction procedure and are certain which flask contains the desired product.

After the last extraction and separation of the lower aqueous phase, pour the remaining organic layer from the top of the separatory funnel into a clean, dry Erlenmeyer flask. The organic solution is now ready for the addition of an anhydrous drying agent [see Technique 12.1].



5. Use a ring stand to hold separatory funnel until layers separate.

6. Draw off bottom layer.

7. Pour off top layer.

FIGURE 11.5 (*Continued*).

Extraction with an Organic Solvent Denser Than Water

SAFETY PRECAUTION

Wear gloves and work in a hood while doing extractions. Point the separatory funnel toward the back of the hood when venting it.

When extracting an aqueous solution several times with a solvent denser than water, it is not necessary to pour the upper aqueous layer out of the separatory funnel after each extraction. Simply drain the lower organic phase out of the separatory funnel into a labeled Erlenmeyer flask. Then add the next portion of organic solvent to the aqueous phase remaining in the funnel. At the end of the extraction procedure, drain the organic layer into a clean, dry Erlenmeyer flask. The organic solution is now ready for the addition of an anhydrous drying agent [see Technique 12.1].

11.4 Summary of the Miniscale Extraction Procedure

1. Close the stopcock; pour the aqueous mixture into a separatory funnel with a capacity 3–4 times the amount of the mixture.
2. Add a volume of immiscible organic solvent approximately one-third the volume of the aqueous phase. **You must know the density of the organic solvent.**
3. Invert the funnel, grasping the neck with one hand and firmly hold down the stopper with your index finger. Open the stopcock to release any pressure buildup.
4. Close the stopcock, and shake the mixture while inverting the separatory funnel four or five times before releasing the pressure

by opening the stopcock; repeat this shaking and venting process five or six times to ensure complete mixing of the two phases (see precautions about emulsions in Technique 11.3).
5. Allow the two phases to separate.
6. *For an organic solvent less dense than water,* draw off the lower aqueous phase into a labeled Erlenmeyer flask; pour the organic phase from the top of the funnel into a second labeled Erlenmeyer flask. Return the aqueous phase to the separatory funnel. *For an organic solvent denser than water,* draw off the lower organic phase into a labeled Erlenmeyer flask; the upper aqueous phase remains in the separatory funnel.
7. Extract the original aqueous mixture twice more with fresh organic solvent.
8. Combine the organic extracts in one Erlenmeyer flask and pour this solution into the separatory funnel. Extract the organic solution with dilute acid or base, if necessary, to neutralize any bases or acids remaining from the reaction.
9. Wash the organic phase with water or saturated NaCl.
10. Dry the organic phase with an anhydrous drying agent [see Technique 12.1].

11.5 Microscale Extractions

Read Techniques 11.1 and 11.2 before undertaking a microscale extraction for the first time.

The small volumes of liquids used in microscale reactions should not be handled in a separatory funnel because much of the material would be lost on the surface of the glassware. Instead, use a conical vial or a centrifuge tube to hold the two-phase system and a Pasteur pipet to separate one phase from the other and transfer it to another container (Figure 11.6). The V-shaped bottom of a conical vial or a centrifuge tube enhances the visibility of the interface between the two phases in the same way that the conical shape of a separatory funnel just above the stopcock enhances the visibility of the interface. Centrifuge tubes are particularly useful for extractions with combinations of organic and aqueous phases that form emulsions. The tubes can be spun in a centrifuge to produce a clean separation of the two phases.

11.5a Equipment and Techniques Common to Microscale Extractions

Before discussing specific types of extractions, we need to consider the equipment and techniques common to all microscale extractions.

Extractions involve the use of several containers. Before you begin an extraction, **carefully label all the conical vials and centrifuge tubes that will hold aqueous and organic solutions.** The solutions in an extraction tend to be colorless, so if the containers are not clearly labeled, it is easy to become confused about their contents during the procedure. **Do not discard any solution until the entire extraction procedure is complete and you are certain** which vessel contains the product.

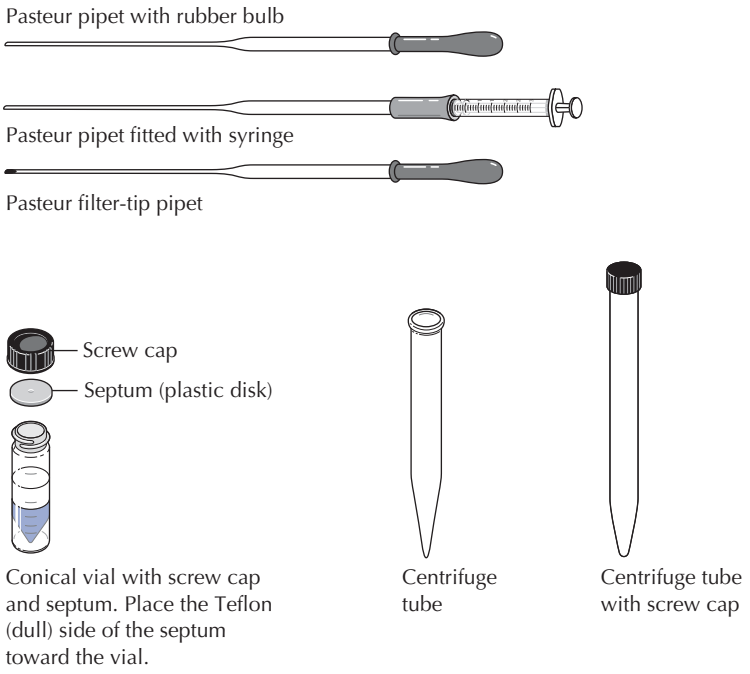


FIGURE 11.6 Equipment for microscale extractions.

Conical Vials

Conical vials, with a capacity of 5 mL, work well for extractions in which the total volume of both phases does not exceed 4 mL. Conical vials tip over very easily. **Always place the vial in a small beaker.** The plastic septum used with the screw cap on a conical vial has a chemically inert coating of Teflon on one side. The Teflon looks dull and should be positioned toward the vial. (The shiny side of the septum is not inert to all organic solvents.)

Centrifuge Tubes

Centrifuge tubes with a 15-mL capacity and tight-fitting caps serve for extractions involving a total volume of up to 12 mL. Set centrifuge tubes in a test tube rack to keep them upright.

Mixing the Two Phases

As with extractions performed in a separatory funnel, thorough mixing of the two phases is essential for complete transfer of the solute from one phase to the other. Mix the two phases by capping the conical vial or centrifuge tube and shaking it vigorously 8–10 times. Slowly loosen the cap to vent the vial or centrifuge tube. Repeat the shaking and venting process four to six times.

Alternatively, or for a centrifuge tube without a screw cap, you can use the ***squirt method***. Draw the two phases into a Pasteur pipet (with no cotton plug in the tip) and squirt the mixture back into the centrifuge tube five or six times to mix the two phases thoroughly. The use of a vortex mixer is another way of mixing the two phases.

Separation of the Phases with a Pasteur Filter-Tip Pipet

A Pasteur filter-tip pipet [see Technique 5, Figure 5.9] provides better control for transferring volatile solvents such as dichloromethane or ether during a microscale extraction than does a Pasteur pipet

without the cotton plug. The lower layer is more easily removed from a conical vial or centrifuge tube than the upper layer. **Expel the air from the rubber bulb before inserting the pipet to the bottom of the conical vial or centrifuge tube.** Slowly release the pressure on the bulb and draw the lower layer into the pipet. Maintain a steady pressure on the rubber bulb while transferring the liquid to another container—another conical vial, a centrifuge tube, or a test tube. Hold the receiving container close to the extraction vial or centrifuge tube so that the transfer can be accomplished smoothly without any loss of liquid (Figure 11.7).

Separation of the Phases with a Pasteur Pipet and Syringe

A Pasteur pipet fitted with a small syringe can also be used to remove the lower layer [see Technique 5, Figure 5.8]. Place the tip of the pipet at the bottom of the V in the conical vial or centrifuge tube. Draw the lower layer into the pipet with a steady pull on the syringe plunger until the interface between the layers reaches the bottom of the vial or tube. **Do not exceed the capacity of the Pasteur pipet (approximately 2 mL); no liquid should be drawn into the syringe.** Remove the Pasteur pipet from the extraction vessel and transfer the contents of the pipet to the receiving container—another conical vial, a centrifuge tube, or a test tube. Hold the receiving container close to the extraction vessel so that the transfer can be accomplished quickly without any loss of liquid (see Figure 11.7). Depress the syringe plunger to empty the pipet.

What to Do If the Upper Phase Is Drawn into the Pasteur Pipet

The interface between the two phases in a conical vial or centrifuge tube can be difficult to see in some instances, and a small amount of the upper layer may be drawn into the Pasteur pipet. If this situation occurs, maintain a steady pressure on the Pasteur pipet with the rubber bulb or syringe and allow the two phases in the pipet to separate. Slowly expel the lower layer into the receiving container until the interface between the phases is at the bottom of the pipet. Then move the pipet to the original container and add the upper layer in the pipet to the remaining upper phase.

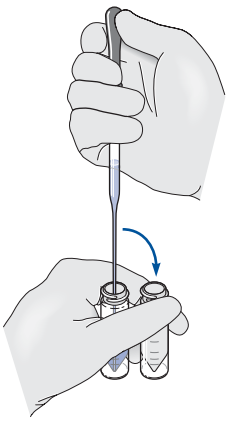


FIGURE 11.7
Holding vials while transferring solutions.

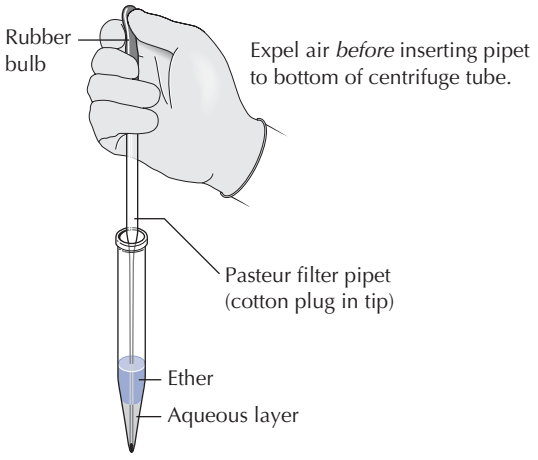
11.5b Microscale Extractions with an Organic Phase Less Dense Than Water

The microscale extraction of an aqueous solution with an organic solvent that is less dense than water and washing an ether solution with aqueous reagents are examples of this type of extraction.

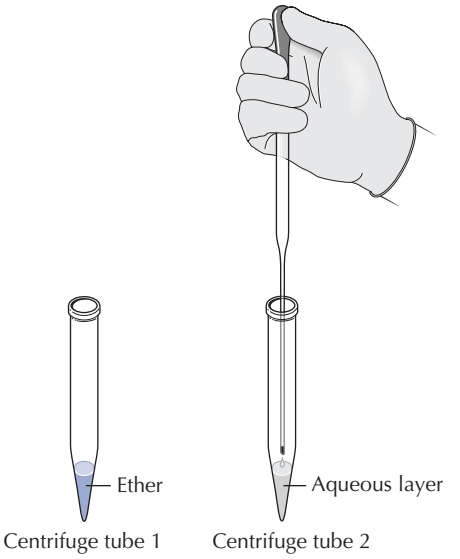
SAFETY PRECAUTION

Wear gloves and work in a hood while doing extractions.

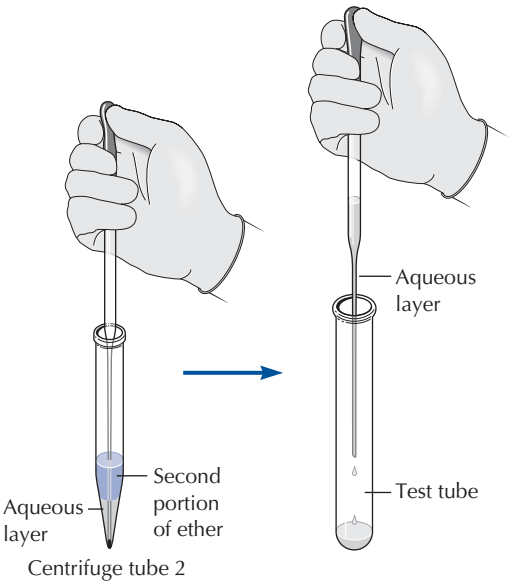
Two centrifuge tubes or conical vials and a test tube are needed for the extraction of an aqueous solution with a solvent less dense than water. Place the aqueous solution in the first centrifuge tube or conical vial, and add the organic solvent—diethyl ether in



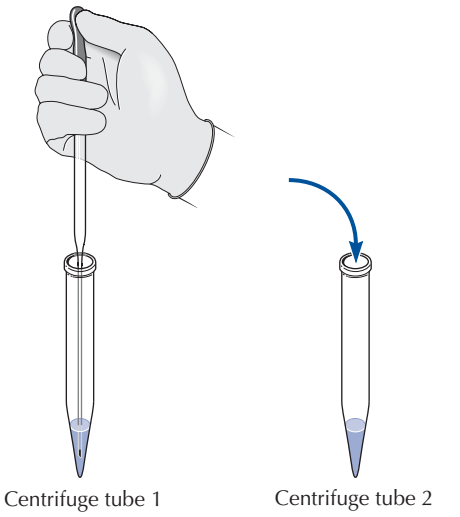
1. Remove lower aqueous phase with Pasteur pipet.



2. Transfer aqueous phase to tube 2.



3. Remove aqueous phase and transfer to a test tube.



4. Combine ether solution from tube 1 with ether solution in tube 2.

FIGURE 11.8 Extracting an aqueous solution with an organic solvent less dense than water.

this example. Cap the tube or vial and shake it to mix the layers. Vent the tube by slowly releasing the cap and allow the phases to separate. Repeat the shaking and venting four to six times. Alternatively, use the squirt method (five or six squirts) [see Technique 11.5a] or a vortex mixer to mix the phases. Allow the layers to separate completely.

Put a Pasteur filter-tip pipet or a Pasteur pipet fitted with a syringe [see Technique 11.5a] into the tube or vial with the tip

touching the bottom of the cone (Figure 11.8, step 1). Slowly draw the aqueous layer into the pipet until the interface between the ether and the aqueous solution is at the bottom of the V. Transfer the aqueous solution to the second centrifuge tube or conical vial (Figure 11.8, step 2). The ether solution remains in the first tube.

Add a second portion of ether to the aqueous phase in the second tube, cap the tube, and shake it to mix the phases. Repeat the shaking and venting four to six times. After the phases separate, again remove the lower aqueous layer and place it in a test tube (Figure 11.8, step 3). Transfer the ether solution in the first tube to the ether solution in the second tube with the Pasteur pipet (Figure 11.8, step 4). Repeat the procedure if a third extraction is necessary.

In any extraction, no material should be discarded until you are certain which container holds the desired product.

Washing the Organic Liquid

If an experiment specifies washing an organic solution that is less dense than water with an aqueous solution, place the organic solution in a centrifuge tube or conical vial. Add the requisite amount of water or aqueous reagent solution, cap the tube (or vial), and shake it to mix the phases. Repeat the shaking and mixing four to six times. Open the cap to release any built-up vapor pressure and allow the layers to separate. Transfer the lower aqueous layer to a test tube with a Pasteur filter-tip pipet or a Pasteur pipet fitted with a syringe [see Technique 5, Figure 5.9]. The upper organic phase remains in the extraction tube (or conical vial) ready for the next step (Figure 11.9), which may be washing with another aqueous reagent solution or, if the extractions are completed, drying with an anhydrous salt [see Technique 12.1].

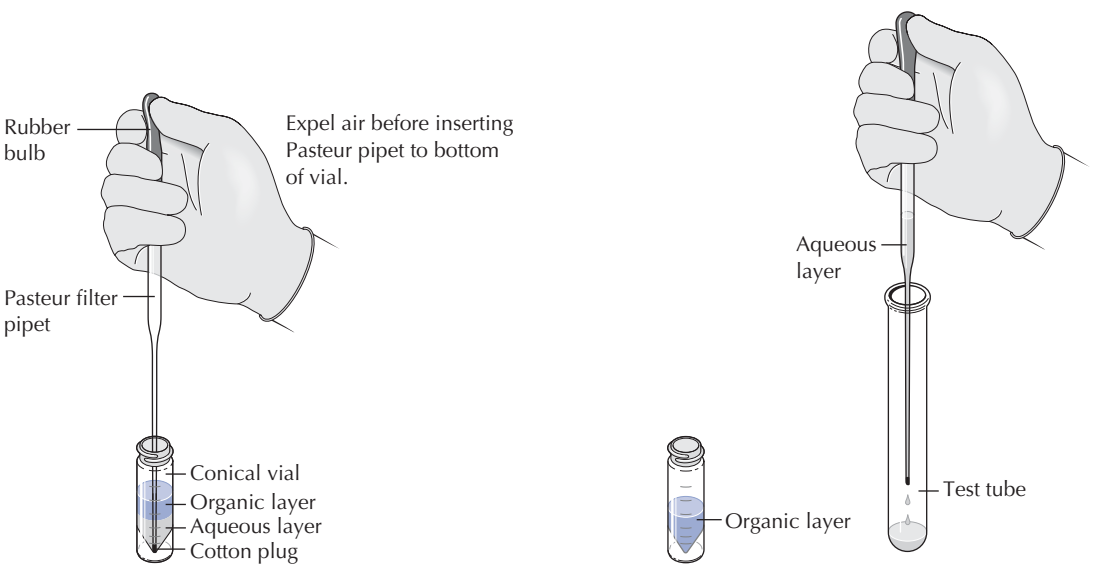


FIGURE 11.9 Washing an organic phase less dense than water.

11.5c Microscale Extractions with an Organic Phase Denser Than Water

Extraction of an aqueous solution with a solvent that is denser than water, such as dichloromethane (CH_2Cl_2), and washing a dichloromethane/organic product solution with water are examples of this type of extraction. The dichloromethane solution (lower phase) needs to be removed from the conical vial or centrifuge tube in order to separate the layers.

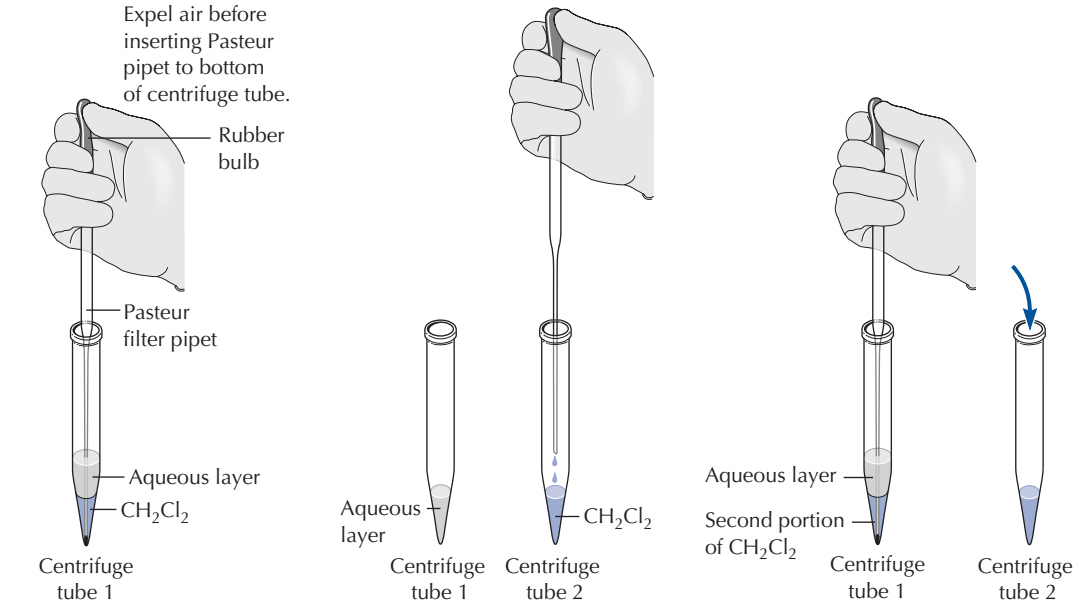
SAFETY PRECAUTION

Wear gloves and work in a hood while doing extractions.

Place the aqueous solution and the specified amount of organic solvent in a labeled conical vial or centrifuge tube. Tightly cap the vial or tube and shake the mixture thoroughly. Loosen the cap slightly to release the pressure. Repeat the shaking and venting process four to six times. Alternatively, use the squirt method (five or six squirts) [see Technique 11.5a] or a vortex mixer to mix the phases. Allow the layers to separate completely.

In any extraction, no material should be discarded until you are certain which container holds the desired product.

Put a Pasteur filter-tip pipet or a Pasteur pipet fitted with a syringe [see Technique 11.5a] into the conical vial or centrifuge tube with the tip touching the bottom of the cone (Figure 11.10, step 1). Slowly draw the lower layer into the pipet until the interface between the two layers is exactly at the bottom of the V. Transfer the



1. Draw lower layer into pipet.

2. Transfer organic layer to centrifuge tube 2 (or a test tube).

3. Repeat extraction procedure, transfer organic layer from tube 1, and combine it with CH_2Cl_2 solution in tube 2.

FIGURE 11.10 Extracting an aqueous solution with an organic solvent denser than water.

pipet to another centrifuge tube, conical vial, or test tube and expel the dichloromethane solution into the second container (tube 2) (Figure 11.10, step 2). The aqueous layer remains in the extraction tube and can be extracted a second time with another portion of CH_2Cl_2. The second dichloromethane solution is added to the second centrifuge tube after the separation (Figure 11.10, step 3).

Washing the Organic Liquid

If the organic phase transferred to tube or vial 2 is being washed with an aqueous solution, the aqueous reagent is added to tube 2. Cap the tube or vial, shake it to mix the phases, and then loosen the cap to release any pressure buildup. The lower organic phase is separated and transferred to another centrifuge tube (or conical vial) if more washings are necessary. Otherwise, the organic phase is transferred to a dry test tube for treatment with a drying agent [see Technique 12.1].

11.6 Sources of Confusion in Extractions

Which Layer Is the Organic Phase?

Before beginning any extraction, ascertain the density of the organic solvent that you will be using. If the extraction involves dilute aqueous solutions of inorganic reagents, you can assume that their density is close to the density of water, 1.0 g/mL. If the density of the organic solvent is less than 1.0 g/mL, the organic phase will be the upper layer in the separatory funnel. If the density of the organic solvent is greater than 1.0 g/mL, the organic phase will be the lower layer.

Three Layers Are Present

After mixing the two phases in a separatory funnel, three instead of two layers are visible. The middle layer is probably an emulsion of the organic and aqueous phases. The section "Emulsions" in Technique 11.2 describes procedures for breaking up emulsions.

No Separation of Phases Is Visible

Several scenarios can lead to no discernible interface between the liquid phases in an extraction.

Solvent added to solvent. This problem occurs in the extraction of an aqueous solution with an organic solvent less dense than water. If the upper organic phase is not removed from the separatory funnel (or microscale vial) and the aqueous solution is not returned to the extraction vessel before the subsequent portion of organic solvent is added, no interface appears because the second portion of solvent is the same as the first one.

The upper layer is too small to be easily visible. Occasionally, the volume of the upper layer in a separatory funnel is too small for the interface to be clearly visible. Draining some of the lower layer will increase the depth of the upper layer as the liquid moves toward the narrower conical portion of the funnel, and the interface will become visible. Another approach to this problem is to add some additional solvent that will become part of the upper layer.

The refractive index of the two solutions is very similar. In rare instances, the refractive index of each solution is so similar that the interface is not visible. Usually adding more water to the aqueous phase will dilute the solution enough to change its refractive index and make the interface visible.

Which Container Holds the Product?

When carrying out a series of extractions, many containers may be used for the various solutions involved. It is **imperative** that all containers be clearly labeled to indicate their contents.

If you are in doubt about the contents of any container, add a few drops of the solution in question to 1–2 mL of water in a small test tube and observe whether it dissolves or not. The organic phase will be insoluble.

A Prudent Practice

Never discard any solution during an extraction until you are certain that you know which container holds your product.

Questions

1. An extraction procedure specifies that an aqueous solution containing dissolved organic material be extracted twice with 10-mL portions of diethyl ether. A student removes the lower layer after the first extraction and adds the second 10-mL portion of ether to the upper layer remaining in the separatory funnel. After shaking the funnel, the student observes only one liquid phase with no interface. Explain.
2. A crude nonacidic product mixture dissolved in diethyl ether contains acetic acid. Describe an extraction procedure that could be used to remove the acetic acid from the ether.
3. What precautions should be observed when an aqueous sodium carbonate solution is used to extract an organic solution containing traces of acid?
4. When two layers form during a petroleum ether/water extraction, what would be an easy, convenient way to tell which layer is which if the densities were not available?
5. You have 100 mL of a solution of benzoic acid in water; the amount of benzoic acid in the solution is estimated to be 0.30 g. The distribution coefficient of benzoic acid in diethyl ether and water is approximately 10. Calculate the amount of benzoic acid that would be left in the water solution after four 20-mL extractions with ether. Do the same calculation using one 80-mL extraction with ether to determine which method is more efficient.

TECHNIQUE 12

DRYING ORGANIC LIQUIDS AND RECOVERING REACTION PRODUCTS

Most organic separations involve extractions from an aqueous solution; no matter how careful you are, some water usually remains in the organic liquid. A small amount of water dissolves in most extraction solvents, and the physical separation of the layers in the extraction process may be incomplete. As a result, the organic layer usually needs to be dried with an anhydrous drying agent before recovering an organic

product. After the drying procedure, the organic liquid needs to be separated from the drying agent and the solvent removed to recover the product. These operations are described in Technique 12.

12.1 Drying Agents

The most common way to ***dry*** (remove the water from) an organic liquid is to add an ***anhydrous*** (deprived of water) drying agent that binds with water. Anhydrous drying agents react with water to form crystalline ***hydrates,*** which are insoluble in the organic phase and can be removed by filtration:

$$n\mathrm{H_2O} + \text{drying agent} \rightarrow \text{drying agent} \cdot n\mathrm{H_2O}$$

Drying agents for organic liquids are usually anhydrous inorganic salts.

Factors in Selecting a Drying Agent

Table 12.1 lists common drying agents used for organic liquids. Following are the factors that need to be considered in selecting a drying agent:

- Capacity
- Efficiency
- Speed
- Chemical inertness

Capacity for removing water. The maximum number of moles of water bound in the hydrated form of the salt is called its ***capacity;*** the capacity is the amount of water that can be taken up per unit weight of drying agent.

TABLE 12.1 Common anhydrous chemical drying agents

Drying agent	Acid/Base properties	Capacity	Efficiency[a]	Speed of drying	Comments
$MgSO_4$	neutral	high	2.8	fairly rapid	good general drying agent
$CaCl_2$	neutral	medium to high	1.5	fairly slow	reacts with many organic compounds
Silica gel	neutral	high	low	medium	good general drying agent but somewhat expensive
Na_2SO_4	neutral	very high	25	slow	good for predrying; hydrate is unstable above 32°C
K_2CO_3	basic	low	moderate	fairly rapid	reacts with acidic compounds
$CaSO_4$ (Drierite)	neutral	low	0.004	fast	fast and efficient but low capacity
KOH	basic	very high	0.1	fast	used to dry amines

a. Efficiency = measure of equilibrium residual water [mg/L of air] at 25°C

TABLE 12.2 Drying Agents

Class of compounds	Recommended drying agents
Alkanes and alkyl halides	$MgSO_4$, $CaCl_2$, $CaSO_4$
Hydrocarbons and ethers	$CaCl_2$, $MgSO_4$, $CaSO_4$
Aldehydes, ketones, and esters	Na_2SO_4, $MgSO_4$, $CaSO_4$, K_2CO_3
Alcohols	$MgSO_4$, K_2CO_3, $CaSO_4$
Amines	KOH
Acidic compounds	Na_2SO_4, $MgSO_4$, $CaSO_4$

Efficiency. The ***efficiency*** expresses how much water the drying agent *leaves behind* in the organic liquid. The lower the efficiency value, the smaller the amount of water left in the organic liquid; thus, the drying agent is more efficient.

Speed. The ***speed*** with which the hydrate forms determines how long the drying agent needs to be in contact with the organic solution. A good general drying agent, such as $MgSO_4$, usually requires 5–10 minutes to remove water from an organic liquid. $CaCl_2$ and Na_2SO_4 usually require 15–30 minutes.

Chemical inertness. Drying agents must be ***chemically inert*** (unreactive) to both the organic solvent and any organic compound dissolved in the solvent. For example, bases such as K_2CO_3 and KOH are not suitable for drying acidic organic compounds because they undergo chemical reactions with these compounds. $MgSO_4$ is generally considered to be a neutral salt, but in the presence of water it is slightly acidic. Therefore, $MgSO_4$ is not suitable for drying solutions containing compounds that are especially acid sensitive.

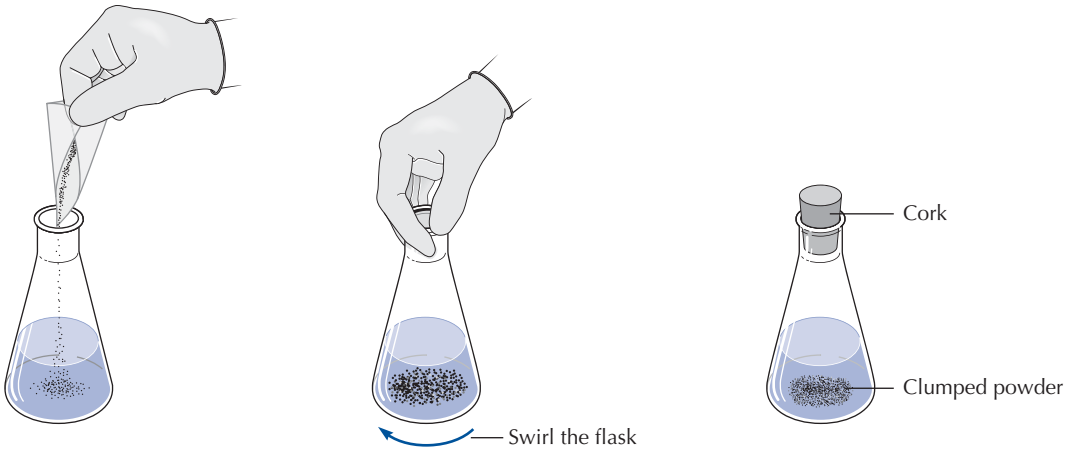
Which Drying Agent Should I Use?

Table 12.2 lists suitable drying agents to use with various classes of organic compounds. Use it as a guide for selecting an appropriate drying agent if one is not specified in a procedure.

Some drying agents have a high capacity but leave quite a bit of water in the organic solution. Na_2SO_4 is a good example, as you can see from Table 12.1. It is particularly useful as a preliminary drying agent, but it is also widely used as a general-purpose drying agent because it is inexpensive and can be used with many types of compounds. However, the hydrate does not form quickly; it needs 15–30 minutes to form.

$MgSO_4$ is a good general-purpose drying agent, suitable for nearly all compounds. It has a high capacity for water and a reasonable efficiency, and it works fairly quickly. However, its exothermic reaction with water in the solution being dried sometimes causes the solvent to boil if the drying agent is added too rapidly. Slow addition of the drying agent prevents this problem.

$CaSO_4$ leaves little water behind, but it has a low capacity, which means that it works better after a preliminary drying of the liquid with Na_2SO_4 or $MgSO_4$.



(a) Adding powdered drying agent to solution

(b) Swirling the mixture of solution and drying agent

(c) Drying agent clumped at bottom of flask

FIGURE 12.1 Adding drying agent to a solution.

Using a Drying Agent

To remove water from an organic liquid, add about 1 g of powdered or granular anhydrous drying agent per 25 mL of solution for a miniscale procedure. For microscale procedures, weigh the drying agent and use about 40 mg of drying agent per milliliter of solution.

Always place the organic liquid being treated with drying agent in an Erlenmeyer flask closed with a cork to prevent evaporation losses.

Add the drying agent to the solution to be dried (Figure 12.1a). Swirl the flask to mix the drying agent with the liquid (Figure 12.1b). If you are using anhydrous $MgSO_4$ to dry an organic solution, the first bit of drying agent you add will clump together (Figure 12.1c). You have added enough drying agent when some of it moves freely in the mixture while the flask is gently swirled.

The anhydrous form of indicating Drierite ($CaSO_4$) is blue, whereas the hydrated form is pink. If blue Drierite turns pink, you need to add more drying agent. The solution may be stirred with a magnetic stirring bar or simply swirled occasionally by hand to ensure as much contact with the surface of the drying agent as possible.

Often a preliminary drying period of 30–60 s, followed by removal of the drying agent, is useful. Then allowing a second portion of drying agent to stand in the liquid for 10 min or more removes the water more completely than the use of a single portion.

12.2 Methods for Separating Drying Agents from Organic Liquids

After the drying agent has absorbed the water present in the organic liquid, it must be separated from the liquid by filtration [see Technique 10]. The container receiving the liquid should be clean and dry and have a volume about two or three times the volume of the organic liquid.

Miniscale Separation of Drying Agents

Miniscale methods used to separate the drying agent from an organic liquid depend on whether the product is dissolved in a solvent or not. All glassware used in these procedures must be clean and dry.

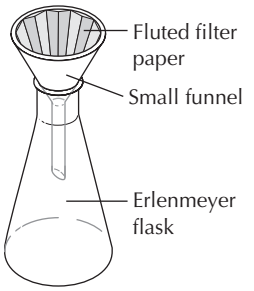


FIGURE 12.2
Filtration of drying agent from a solution when the solvent will be evaporated.

The product is dissolved in solvent. If the solvent will be evaporated to recover the product, place fluted filter paper in a small funnel and set the funnel in an Erlenmeyer flask (Figure 12.2). If the solvent will be distilled from the compound, use a round-bottomed flask as the receiving container and set it on a cork ring. Decant the solution slowly into the filter paper, leaving most of the drying agent in the flask. Rinse the drying agent with a few milliliters of dry solvent and also pour this rinse into the filter paper. The filtered organic liquid is ready for the removal of the solvent.

A liquid product is not dissolved in solvent. This method is not usually used for samples of less than 7–8 g because a significant amount of product can be lost on the surface of the glassware and drying agent. However in some extraction procedures, the organic liquid is ***neat,*** not dissolved in a solvent. In this situation, you must minimize the loss of liquid product during the removal of the drying agent. Instead of filter paper, tightly pack a small plug of cotton or glass wool about 5–6 mm in diameter into the outlet of the funnel. If the drying agent is powdery rather than granular, make sure the cotton plug is rolled very tightly. The plug traps the drying agent and absorbs only a small amount of the organic liquid (Figure 12.3). Slowly decant the liquid from the drying agent. The organic liquid is ready for the final distillation.

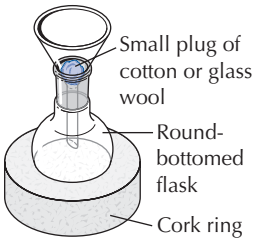


FIGURE 12.3
Filtration of drying agent from an organic liquid when no solvent is present.

The drying agent is granular or chunky. If the drying agent is granular or chunky, for example $CaCl_2$ or Drierite, the cotton plug can be omitted and the liquid carefully decanted into the funnel, keeping all the drying agent in the original flask. The drying agent may or may not be rinsed with a few milliliters of solvent in this procedure. The organic liquid is ready for the final distillation or evaporation of the solvent.

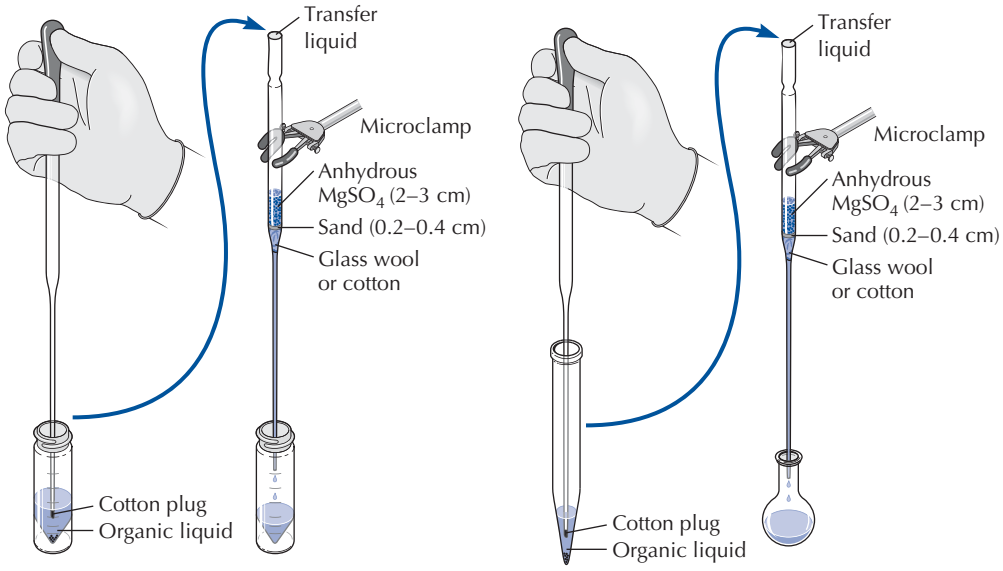
Microscale Separation of Drying Agents

The separation methods that follow use Pasteur pipets in two different ways:

- Pasteur filter-tip pipets [see Technique 5, Figure 5.9] fitted with a rubber bulb for the transfer of a liquid
- Pasteur filter pipets [see Technique 10, Figure 10.3] held by a clamp for the filtration

Method 1: Filtration of the organic liquid from the drying agent. After a microscale extraction, the organic liquid can be dried with drying agent in a conical vial, a centrifuge tube, or a test tube. If the drying agent has large particles, such as calcium chloride, simply use a Pasteur filter-tip pipet to remove the liquid from the drying agent and transfer it to a clean, dry container.

For granular or powdered drying agents, a Pasteur filter pipet is clamped in an upright position and used as a filter funnel



(a) Standard taper microscale equipment **(b)** Williamson microscale equipment

FIGURE 12.4 Using microscale equipment and a Pasteur filter pipet containing anhydrous $MgSO_4$ to dry an organic liquid or solution.

[see Technique 10, Figure 10.3]. A Pasteur filter-tip pipet is used to transfer the liquid to the filtering funnel. Collect the filtered organic liquid in a clean, dry conical vial or small, round-bottomed flask.

Method 2: Drying and filtration in one step. In this method, useful for a powdered drying agent such as magnesium sulfate, both drying and filtration are done simultaneously as the organic liquid passes through a Pasteur filter pipet containing anhydrous $MgSO_4$. A cotton or glass wool plug is packed into a Pasteur pipet and covered with a layer of sand (0.2–0.4 cm) and then with a layer of $MgSO_4$ (2–3 cm), as shown in Figure 12.4. The solution to be dried is transferred from its original container to the filtering pipet with a Pasteur filter-tip pipet.

12.3 Recovery of an Organic Product from a Dried Extraction Solution

Once the extraction solution has been dried, the solvent must be removed to recover the desired organic product. Evaporation of the solvent to the atmosphere has been a traditional method of recovering a product; however, concern for the environment and environmental laws now limit and sometimes prohibit this practice. Removing solvents by distillation or with a rotary evaporator are alternatives to evaporation; both methods allow the solvents to be recovered. Your instructor will advise you whether evaporation of solvents is allowed in your laboratory or if a method where the solvent is recovered must be used.

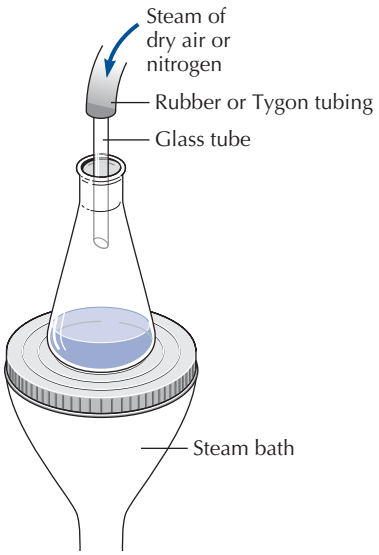


FIGURE 12.5
Using a stream of nitrogen or dry air to evaporate an organic liquid.

Evaporation Methods

In experiments in which the amount of solvent is small (less than 25 mL), it can be removed by evaporation on a steam bath in a hood or by blowing it off with a stream of nitrogen or air in a hood.

Boiling the solvent. Place a boiling stick or boiling stone in the Erlenmeyer flask containing the solution to be evaporated and heat the flask on a steam bath in a hood. The product will be the liquid or solid residue left in the flask when the boiling ceases. The last of the solvent can be blown off in a hood with a stream of nitrogen or air.

Evaporation with a stream of air or nitrogen. Evaporation is a cooling process; therefore, gently heating the container holding the solution to be evaporated will speed the process. However, the liquid should not boil. Instead, the evaporation rate can be enhanced by directing a gentle stream of dry air or nitrogen **above** the liquid in the container. **Note:** If the end of the tube is close to or in the solution or the flow rate of gas is too rapid, the liquid may spatter and some of the product will be lost.

Figure 12.5 shows the apparatus for a miniscale evaporation with a stream of nitrogen while heating with a steam bath adjusted for a very slow rate of steam flow. A glass tube attached to rubber or Tygon tubing that leads to the nitrogen source should be clamped so the end is well above the liquid level.

In microscale evaporations, warm water suffices as the heat source and the air or nitrogen flow is directed above the liquid through a Pasteur pipet attached to rubber or Tygon tubing. Figure 12.6a shows a standard taper conical vial held by auxiliary aluminum blocks set in a small beaker of warm water. Figure 12.6b shows a Williamson reaction tube held by a microclamp in a small beaker of warm water.

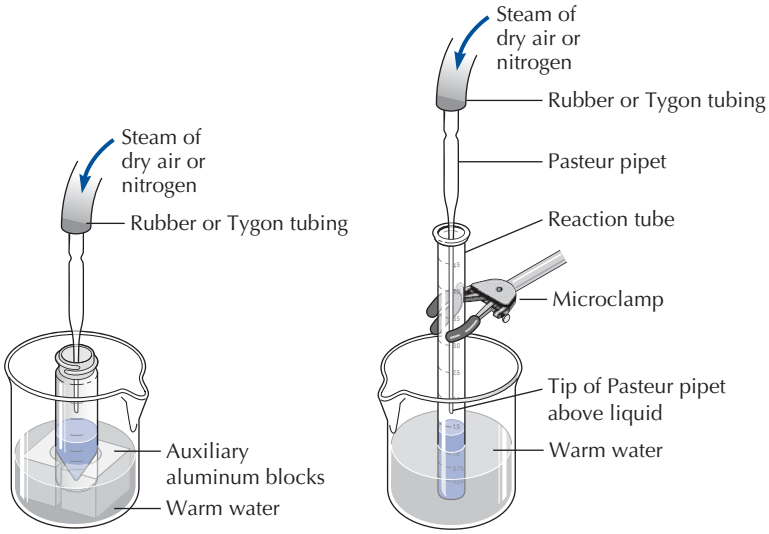


FIGURE 12.6
Microscale apparatus for using a stream of nitrogen or dry air to evaporate an organic liquid.

Distillation

Assemble the simple distillation apparatus shown in Technique 13, Figure 13.7. If the solvent is ether, pentane, or hexane, work in a hood and use a steam bath or a water bath on a hot plate as a heat source to eliminate the fire hazard an electric heating mantle poses with the very flammable vapors from these solvents. Continue the distillation until the solvent has completely distilled, an endpoint indicated by a drop in the temperature reading on the thermometer. The drop in temperature occurs because there is no longer any hot vapor surrounding the thermometer bulb. The product and a small amount of solvent will remain in the distilling flask. The solvent can be removed by evaporation with a stream of dry air or nitrogen.

Using a Rotary Evaporator

A rotary evaporator is an apparatus for removing solvents rapidly in a vacuum (Figure 12.7). No boiling stones or sticks are necessary because the rotation of the flask minimizes bumping. Rotary evaporation is usually done in a round-bottomed flask that is no more than half filled with the solution being evaporated. A receiving flask (also called a trap) is placed between the round-bottomed flask and the vacuum source so that the evaporated solvent can be recovered.

The following protocol is a generalized outline of the steps in using a rotary evaporator; consult your instructor about the exact operation of the rotary evaporators in your laboratory.

Select a round-bottomed flask of a size that will be only half full or less with the solution undergoing evaporation. Connect the flask to the rotary evaporator with a joint clip. Use an empty trap and be sure that it is also clipped tightly to the rotary evaporator housing. Position a room-temperature water bath under the flask containing the solution so that the flask is approximately one-third submerged in the water bath. Turn on the water to the condenser and then turn

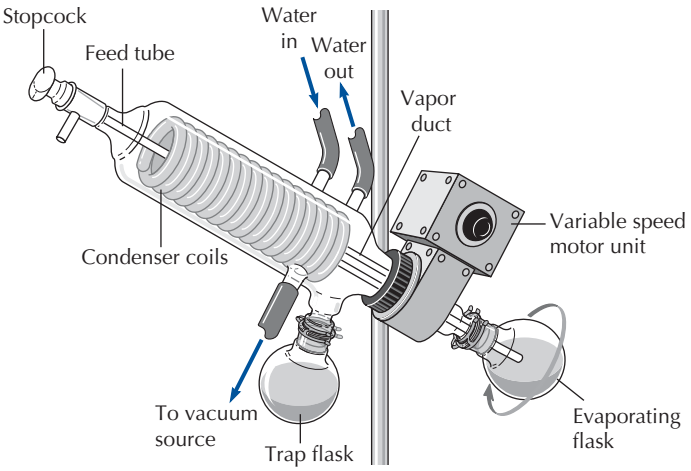


FIGURE 12.7
Diagram of a rotary evaporator.

on the vacuum source. Make sure the stopcock is closed. As the vacuum develops, turn on the motor that rotates the evaporating flask. When the vacuum stabilizes at 20–30 torr or lower, begin to heat the water bath. A temperature of 50°–60°C will quickly evaporate solvents with boiling points under 100°C.

When the liquid volume in the round-bottomed flask no longer decreases, the evaporation is complete. Stop the rotation of the flask and remove the water bath. Open the stopcock slowly to release the vacuum and allow air to bleed slowly into the system. Hold the flask with one hand, take off the clip holding it to the evaporator, and remove the flask from the rotary evaporator. Turn off the vacuum source and the condenser water. Disconnect the trap from the rotary evaporator housing and empty the solvent in the trap into the appropriate waste or recovered solvent container.

12.4 Sources of Confusion in Drying Liquids

Amount of Drying Agent to Use

The amount of drying agent necessary to remove residual water from the organic liquid cannot be specified exactly; it depends on how much water is present in the liquid. You need to learn to judge when enough drying agent has been added. When using anhydrous $MgSO_4$ or Na_2SO_4, if all the drying agent particles are clumped together, not enough has been used. Continue adding small amounts from the tip of a spatula until there is a thin layer of particles that look very similar to the original particles of the drying agent and that move freely in the flask. If indicating Drierite ($CaSO_4$) is the drying agent and it has turned a pink color, more blue anhydrous Drierite must be added.

Remember that the use of too much drying agent can cause a loss of product by its adsorption on the drying agent. If you have to add quite a bit of drying agent to reach the clumping point, you must have had a large amount of water present initially. In this case you may wish to add more organic solvent to minimize the loss of product.

Is the Organic Liquid Dry?

Drying agents do not absorb water instantaneously. Allow a minimum of 10 min for the drying agent to become hydrated. When an organic liquid is dry, it will be clear and at least a portion of the drying agent will still have the particle size and appearance of the anhydrous form. If all the drying agent has become clumped or the organic liquid is still cloudy after 10 min, decant the organic liquid into a clean Erlenmeyer flask and add another portion of drying agent. Allow the mixture to stand for another 10 min.

A White Liquid Surrounds the Drying Agent

When the drying agent is added to the organic liquid, a milky white liquid may appear around the drying agent particles, particularly when anhydrous calcium chloride in pellet form is being used. The pellets do not provide as much surface area for reaction with water as powder or granules do. The white liquid is a saturated water solution of calcium chloride. Continue adding pellets until the liquid is absorbed and some of the pellets move freely in the organic liquid. Allow at least 15 min for the drying agent to be effective.

Questions

1. Which would be a more effective drying agent, $CaCl_2$ or $CaCl_2 \cdot 6\ H_2O$? Explain.
2. (a) What are the disadvantages of using too little drying agent?
   (b) What are the disadvantages of using too much drying agent?
3. Which drying agent would you choose to dry a solution of 2-octanone (a ketone) in hexane? Explain your reasoning.
4. KOH is an excellent drying agent for some organic compounds. Would it be a better choice for an acid (RCO_2H) or an amine (RNH_2)? Why?

TECHNIQUE

13 BOILING POINTS AND DISTILLATION

Distillation is a method for separating two or more liquid compounds by taking advantage of their boiling-point differences. Unlike the liquid-liquid and liquid-solid separation techniques of extraction and crystallization, distillation is a liquid-gas separation in which vapor pressure differences are used to separate different compounds.

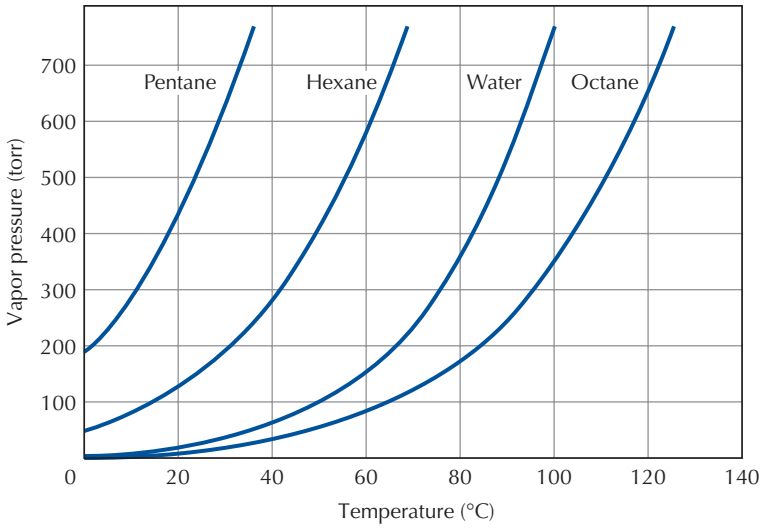


FIGURE 13.1 Examples of the dependence of vapor pressure on temperature.

A liquid at any temperature exerts a pressure on its environment. This ***vapor pressure*** results from molecules leaving the surface of the liquid to become vapor.

$$\text{Molecules}_{\text{liquid}} \rightleftharpoons \text{molecules}_{\text{vapor}}$$

As a liquid is heated, the kinetic energy of its molecules increases. The equilibrium shifts to the right and more molecules move into the gaseous state, thereby increasing the vapor pressure. Figure 13.1 shows the relationship between vapor pressure and temperature for pentane, hexane, water, and octane.

13.1 Determination of Boiling Points

Boiling Point

The boiling point of a pure liquid is defined as the temperature at which the vapor pressure of the liquid exactly equals the pressure exerted on it by the atmosphere. At an external pressure of 1.0 atm (760 torr), the boiling point is reached when the vapor pressure equals 760 torr. However, at other pressures the boiling point of the liquid will be different. Table 13.1 gives boiling points of several common solvents at different elevations. When the boiling point of a substance is determined, both the atmospheric pressure and the experimental boiling point need to be recorded.

Every pure and thermally stable organic compound has a characteristic boiling point at atmospheric pressure. The boiling point reflects its molecular structure, specifically the types of weak intermolecular interactions that bind the molecules together in the liquid state, which must be overcome for molecules to enter

TABLE 13.1 Boiling points (°C) of common compounds at different elevations (pressures)

Compound	Death Valley, CA Elevation –285 ft P = 1.01 atm	New York City Elevation 0 ft P = 1.00 atm	Laramie, WY Elevation 7165 ft P = 0.75 atm
Water	100.3	100.0	92.2
Diethyl ether	35.0	34.6	26.7
Ethyl acetate	77.4	77.1	68.6
Acetic acid	118.2	117.9	108.7

the vapor state. Intermolecular hydrogen bonding and dipole-dipole interactions always produce higher boiling points. Thus, polar compounds have higher boiling points than nonpolar compounds of similar molecular weight. In addition, increased molecular weight usually produces a larger molecular surface area and greater van der Waals interactions, again leading to a higher boiling point.

Miniscale Determination of Boiling Points

The boiling point of 5 mL or more of a pure liquid compound can be determined by a simple distillation using miniscale standard taper glassware. The procedure for setting up a simple miniscale distillation is described in Technique 13.3. When distillate is condensing steadily and the temperature stabilizes, the boiling point of the substance has been reached.

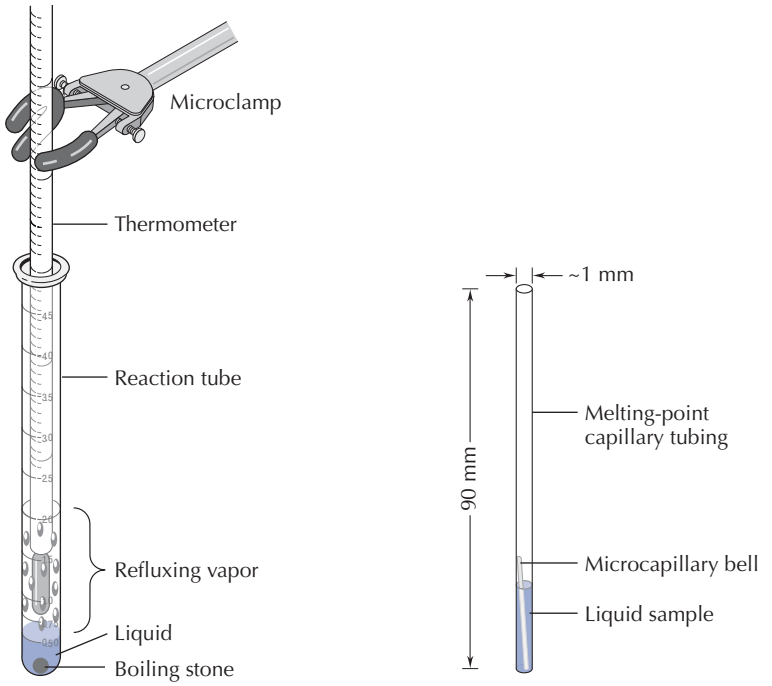
The microscale methods described next are an alternative for determining the boiling point of any pure liquid when only a very small sample of the liquid is available.

Microscale Determination of Boiling Points

Using a Williamson reaction tube. Place 0.3 mL of the liquid and a boiling stone in a reaction tube. Set the tube in the appropriate-size hole of an aluminum heating block [see Technique 6.2]. Alternatively, heat may be supplied by a sand bath [see Technique 6.2], in which case the tube and the thermometer need to be held by separate clamps. Clamp the thermometer so that the bottom of the bulb is 0.5–1.0 cm above the surface of the liquid; be sure that the thermometer does not touch the wall of the tube (Figure 13.2a).

Gradually heat the sample to boiling and continue to increase the rate of heating *slowly* until the ring of condensate is 1–2 cm above the top of the thermometer bulb. When the temperature reaches a maximum and stabilizes for at least 1 min, you have reached the boiling point of the liquid. Rapid or excessive heating of the tube can lead to superheating of the vapor and can also radiate heat from the tube to the thermometer bulb, causing the observed boiling point to be too high.

Using a capillary tube. When only a few drops of a pure liquid are available, its boiling point can be determined with the same type of capillary tube that is used for melting points. A 10-μL syringe of the



(a) Williamson reaction tube or small test tube **(b)** Capillary tube boiling point apparatus

FIGURE 13.2 Apparatus for microscale boiling-point determinations.

type used with a gas chromatograph works well for transferring a 4–5-μL sample into the capillary tube. If the liquid does not flow to the bottom of the tube, place the capillary tube in a centrifuge tube and spin it briefly in a centrifuge.

To prepare a microcapillary bell, obtain a 10-μL microcapillary tube that is about 40 mm long and cut the tube in half with a file or glass scorer. Hold the uncut end with tweezers and rotate the cut end in a small flame just long enough for the glass to melt and form a seal. Allow the tube to cool before inserting it **with the open end down** into the capillary tube containing the liquid sample (Figure 13.2b).

Determine the boiling point of the liquid by placing the capillary tube in a melting-point apparatus, such as a Meltemp. Use the same heating procedure as for a melting-point determination [see Technique 14.3]. Increase the rate of heating fairly rapidly until the temperature is 15°–20°C below the known boiling point of the compound; then decrease the rate of heating to about 2°C/min until a fine stream of bubbles emerges from the bottom of the microcapillary bell. At this point, turn the heat controller down to decrease the rate of heating. Carefully watch the stream of bubbles emerging from the bell and record the temperature when the last bubble emerges; this temperature is the boiling point of the compound. To verify it, **immediately** repeat the determination by increasing the rate of heating to 2°C/min to produce a second stream of bubbles.

13.2 Distillation and Separation of Mixtures

The boiling point of a mixture depends on the vapor pressures of its components. Impurities can either raise or lower the observed boiling point. Consider, for example, the boiling characteristics of a mixture of pentane and hexane. The two compounds are mutually soluble, and their molecules interact with one another only by van der Waals forces. A solution composed of both pentane and hexane boils at temperatures between their two boiling points.

Raoult's and Dalton's Laws

If pentane alone were present, the vapor pressure above the liquid would be due only to pentane. However, when pentane is only a fraction of the solution, the ***partial pressure*** (P_{pentane}) exerted by pentane is equal to only a fraction of the vapor pressure of pure pentane ($P°_{\text{pentane}}$). The fraction is determined by X_{pentane}, the ***mole fraction*** of pentane, which is the ratio of moles of pentane to the total number of moles of pentane and hexane in the solution.

$$\text{Mole fraction of pentane:} \quad X_{\text{pentane}} = \frac{\text{moles}_{\text{pentane}}}{\text{moles}_{\text{pentane}} + \text{moles}_{\text{hexane}}}$$

$$\text{Partial pressure of pentane:} \quad P_{\text{pentane}} = P°_{\text{pentane}} \cdot X_{\text{pentane}} \qquad (1)$$

The hexane present in the solution also exerts its own independent partial pressure.

$$\text{Mole fraction of hexane:} \quad X_{\text{hexane}} = \frac{\text{moles}_{\text{hexane}}}{\text{moles}_{\text{pentane}} + \text{moles}_{\text{hexane}}}$$

$$\text{Partial pressure of hexane:} \quad P_{\text{hexane}} = P°_{\text{hexane}} \cdot X_{\text{hexane}} \qquad (2)$$

The vapor pressure–mole fraction relationships expressed in equations 1 and 2 are valid only for ideal liquids in the same way that the ideal gas law strictly applies only to ideal gases. Equations 1 and 2 are applications of Raoult's law, named after the French chemist François Raoult, who studied the vapor pressures of solutions in the late nineteenth century.

Using Dalton's law of partial pressures, we can now calculate the total vapor pressure of the solution, which is the sum of the partial pressures of the individual components:

$$P_{\text{total}} = P_{\text{pentane}} + P_{\text{hexane}} \qquad (3)$$

Figure 13.3 shows the partial pressure curves for pentane and hexane at 25°C using Raoult's law and the total vapor pressure of the solution using Dalton's law. The boiling point of a pentane/hexane mixture is the temperature at which the individual vapor pressures of both pentane and hexane add up to the total pressure exerted on the liquid by its surroundings.

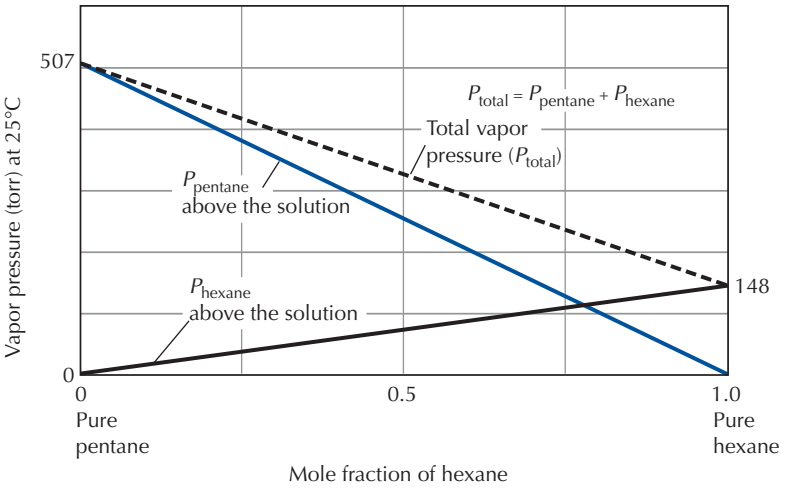


FIGURE 13.3
Vapor pressure-mole fraction diagram for pentane/hexane solutions at 25°C.

Composition of the Vapor Above the Solution

Being able to calculate the total vapor pressure of a solution can be extremely useful, but knowing the composition of the vapor above a solution is just as important. Qualitatively, it is not hard to see that the vapor above a 1:1 molar pentane/hexane solution will be richer in pentane as a result of its greater vapor pressure. Quantitatively, we can predict the composition of the vapor above a solution for which Raoult's law is valid simply by knowing the vapor pressures of its volatile components and the composition of the liquid solution.

Here is an illustration of how it is done. A single expression for the total vapor pressure (equation 4) can be derived easily from equations 1, 2, and 3, because

$$X_{hexane} = 1.0 - X_{pentane}$$

$$P_{total} = X_{pentane}(P^{\circ}_{pentane} - P^{\circ}_{hexane}) + P^{\circ}_{hexane} \qquad (4)$$

Applying the ideal gas law to the mixture of gases above a solution of pentane and hexane leads to equation 5. The quantity $Y_{pentane}$ is the fraction of pentane molecules in the vapor above the solution.

$$Y_{pentane} = \frac{P_{pentane}}{P_{total}} \qquad (5)$$

Finally, substituting equations 1 and 4 into equation 5 allows the calculation of the mole fraction of pentane in the vapor state (equation 6).

$$Y_{pentane} = \frac{P^{\circ}_{pentane} X_{pentane}}{X_{pentane}(P^{\circ}_{pentane} - P^{\circ}_{hexane}) + P^{\circ}_{hexane}} \qquad (6)$$

Equation 6 can be used to construct a ***temperature/composition diagram*** (sometimes called a phase diagram) like the one shown in

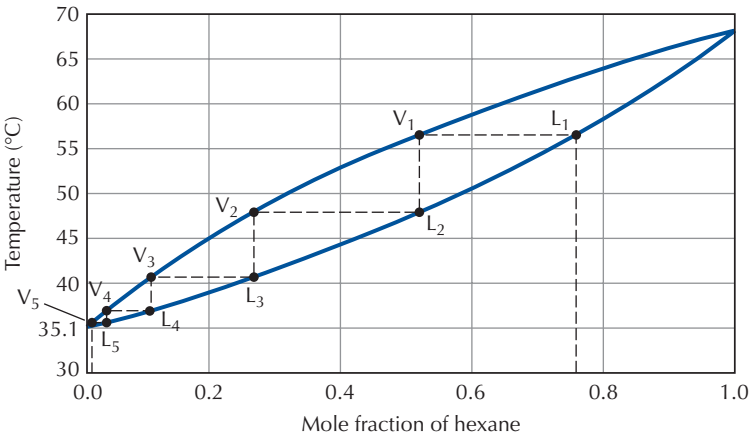


FIGURE 13.4
Calculated temperature/composition diagram for pentane/hexane solutions at 1.0 atm pressure.

Figure 13.4. A similar diagram can also be constructed directly from experimental data.

It is useful to follow the dashed line in Figure 13.4, beginning at an initial liquid composition L_1, which has the molar composition of 75% hexane and 25% pentane. This mixture boils at 57°C, producing the vapor V_1, which has a molar composition of 52% hexane and 48% pentane. The mole fraction of the component with the lower boiling point is greater in the vapor than in the liquid. The new liquid that forms from the condensation of the vapor V_1 is L_2, which has the same composition as V_1. If liquid L_2 is vaporized, the new vapor will be even richer in pentane, shown by point V_2. Repeating the boiling and condensing processes a few more times allows us to obtain essentially pure pentane.

Fractional and Simple Distillation

As pentane-enriched vapor is removed, the remaining liquid contains a decreasing proportion of pentane. The liquid, originally at L_1, now is richer in hexane (the component with the higher boiling point). As the mole fraction of hexane in the liquid increases, the boiling point of the liquid also increases until the boiling point of pure hexane, 69°C, is reached. In this way pure hexane can also be collected. The process of repeated vaporizations and condensations, called ***fractional distillation,*** allows us to separate liquid components of a mixture by exploiting the vapor pressure differences of the components [see Technique 13.4].

In a ***simple distillation,*** perhaps only two or three vaporizations and condensations occur. The condensed liquid is called the ***distillate*** or condensate**.** Figure 13.4 shows that a simple distillation would not effectively separate a 1:3 molar solution of pentane and hexane. As the distillation proceeds, the remaining pentane/hexane solution does become increasingly more concentrated in hexane and the boiling point of the solution increases, but the separation of pentane and hexane is not nearly complete. Figure 13.5 shows a distillation curve of vapor temperature versus volume of distillate for the simple distillation of a 1:1 pentane/hexane solution. The initial

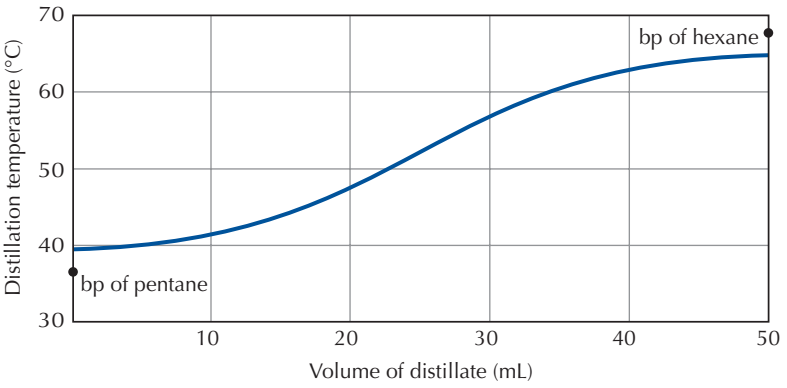


FIGURE 13.5
Distillation curve for simple distillation of a 1:1 molar solution of pentane and hexane.

distillate is collected at a temperature above the boiling point of pure pentane and the final distillate never quite reaches the boiling point of pure hexane.

Now compare the temperature/composition diagram of the pentane/hexane system with that of a pentane/octane mixture. Whereas the boiling points of pentane (bp 36°C) and hexane (bp 69°C) differ by only 33°C, the boiling points of pentane and octane (bp 126°C) differ by 90°C, making it much easier to separate pentane from octane by distillation. Figure 13.6 shows that even with a 3:1 molar solution of octane and pentane only two vaporizations and condensations are necessary to separate the two compounds, and thus a simple distillation would be reasonably successful in separating them. As the boiling point difference between two liquids becomes greater, simple distillation becomes increasingly more effective in their separation.

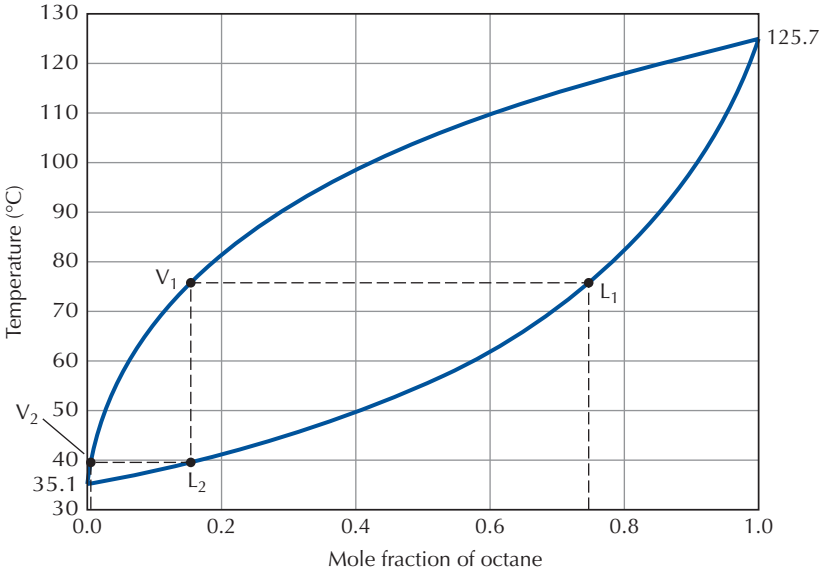


FIGURE 13.6 Calculated temperature/composition diagram for pentane/octane solutions at 1.0 atm pressure.

Even though simple distillation does not effectively separate a mixture of liquids whose boiling points differ by less than 60°–70°C, organic chemists use simple distillations in two commonly encountered situations: (1) the last step in the purification of a liquid compound and (2) to remove a volatile solvent from an organic compound with a high boiling point.

13.3 Simple Distillation

In a simple distillation, **the distilling flask should be only one-third to one-half full of the liquid being distilled.** With a flask that is too full, liquid can easily bump over into the condenser. If the flask is nearly empty, a substantial fraction of the material will be needed just to fill the flask and distilling head with vapor. When the desired liquid is dissolved in a large quantity of a solvent with a lower boiling point, the distillation should be interrupted after almost all of the solvent has been distilled and the higher-boiling liquids should be poured into a smaller distilling flask before continuing the distillation.

13.3a Miniscale Distillation

Figure 13.7 shows the miniscale apparatus for a simple distillation. The assembly of the apparatus is explained in detail in the following steps.

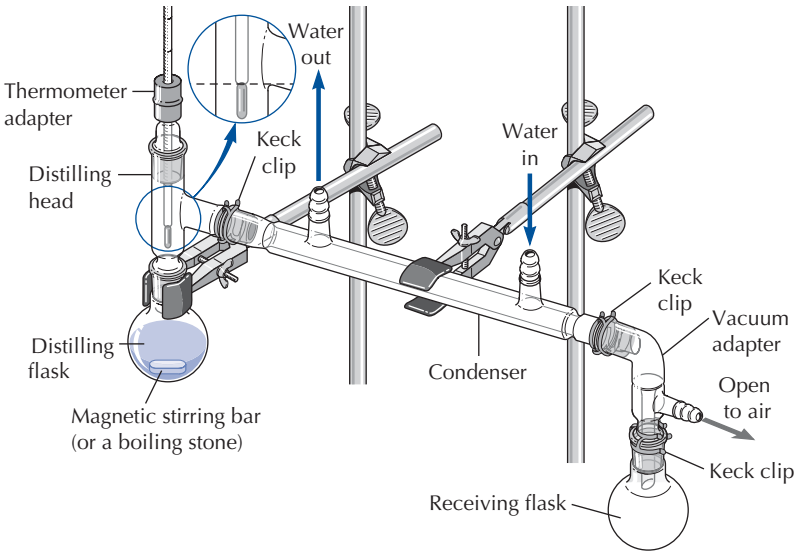


FIGURE 13.7
Simple miniscale distillation apparatus. The enlargement shows the correct placement of a thermometer bulb for accurate measurement of the boiling point. If you are using a digital thermometer, consult your instructor about the correct placement of the temperature probe in the distilling head.

Steps in Assembling a Miniscale Apparatus for Simple Distillation

A funnel keeps the ground glass joint from becoming coated with the liquid and prevents loss of product.

1. Select a round-bottomed flask of a size that will be one-third to one-half filled with the liquid being distilled. Place a clamp firmly on the neck of the flask and attach the clamp to a ring stand or support rod. Using a conical funnel, pour the liquid into the flask. Add one or two boiling stones.

SAFETY PRECAUTION

Boiling stones should **never** be added to a hot liquid because they may cause a superheated liquid to boil violently.

2. *Lightly* grease the bottom joint and the side-arm joint [see Technique 4.2] on the distilling head. Fit the distilling head to the round-bottomed flask and twist the joint to achieve a tight seal. Finish assembling the rest of the apparatus before inserting the thermometer adapter and thermometer. **Note: The distilling flask and distilling head need to be in a completely vertical position so that the condenser is positioned with a downward slant.**
3. Attach rubber tubing to the outlets on the condenser jacket. Wire hose clamps are often used to prevent water hoses from being blown off the outlets by a surge in water pressure. Grease the inner joint at the bottom of the condenser, attach the vacuum adapter, and while the pieces are still lying on the desktop, place a Keck clip over the joint.
4. Clamp the condenser to another ring stand or upright support rod, as shown in Figure 13.7. If the clamp used to support the condenser has a stationary and a movable jaw, position it with the stationary jaw underneath the condenser and the movable jaw above. Fit the upper joint of the condenser to the distilling head, twist to spread the grease, and place a Keck clip over the joint.

The use of Keck clips ensures that ground glass joints do not come apart.

5. Lightly grease the inner joint at the bottom of the vacuum adapter and attach a round-bottomed flask to serve as the receiving vessel. Twist the joint to achieve a tight seal and immediately attach a Keck clip. Although without a clip the receiver flask may stay attached to the vacuum adapter for a time, gravity will soon win out and the flask will fall and perhaps break.

It is usually necessary to have at least two receiving vessels at hand; the first container is for collecting the initial distillate that consists of impurities with lower boiling points before the expected boiling point of the desired fraction is attained.

SAFETY PRECAUTION

Grasp the thermometer close to the bulb and push it gently 1–2 cm into the adapter. Move your hand several centimeters up the thermometer stem and repeat the pushing motion. Continue this process until the thermometer is properly positioned. Holding the thermometer by the upper part of the stem while inserting it through the rubber sleeve of the thermometer adapter could break the thermometer and force a piece of broken glass into your hand.

6. Gently push the thermometer through the rubber sleeve on the thermometer adapter. Alternatively, a thermometer with a standard taper fitting may be used instead of the thermometer and rubber-sleeved adapter.

Proper positioning of the thermometer bulb is crucial.

7. Grease the joint on the thermometer adapter and fit it into the top joint of the distilling head. Adjust the position of the thermometer to **align the top of the thermometer bulb with the bottom of the side arm** on the distilling head (see detail in Figure 13.7).

A slow to moderate water-flow rate suffices and lessens the chance of blowing the rubber tubing off the condenser.

8. Check to ensure that the rubber tubing is tightly attached to the condenser and that **water flows in at the bottom and out at the top. Slowly turn on the water.**
9. Place a heating mantle or other heat source under the distillation flask, using an iron ring or lab jack to support the mantle, and begin heating the flask.

If you use an Erlenmeyer flask or graduated cylinder to collect the distillate, position the outlet of the vacuum adapter slightly inside the mouth of the receiving vessel. A **beaker should never be used as the receiving vessel** because its wide opening readily allows vapors to escape.

Carrying Out the Distillation

The expected boiling point of the liquid being distilled determines the heat input, controlled by a variable transformer [see Technique 6.2]; vaporization of a liquid with a high boiling point requires more heat than does a low-boiling liquid. Heat the liquid slowly to a gentle boil. A ring of condensate will begin to move up the inside of the flask and then up the distilling head. The temperature observed on the thermometer will not rise appreciably until the vapor reaches the thermometer bulb because it is measuring the vapor temperature, not the temperature of the boiling liquid. If the ring of condensate stops rising before it reaches the thermometer, increase the setting on the variable transformer.

When the vapor reaches the thermometer, the temperature reading should increase rapidly. To achieve satisfactory separation of liquids that boil within 100°C of one another, adjust the heat input to maintain a collection rate of 1 drop every 1–2 s. It may be necessary to increase the heat input during the distillation if the rate of collection slows.

Collect any liquid that condenses below the expected boiling point as the first fraction, or forerun—which is usually discarded—then change to a second receiving vessel to collect the desired fraction when the temperature stabilizes at or slightly below the expected boiling point of the liquid. Record the temperature at which you begin to collect the desired fraction.

As the end of a distillation approaches, it is essential to lower the heat source BEFORE the distillation flask reaches dryness [see Safety Precaution on the next page]. If the temperature begins to drop, it signifies that vapor is no longer reaching the thermometer bulb and that the distillation should be discontinued. Record the temperature at which the last drop of distillate is collected; the initial and final temperatures are the boiling range of a liquid fraction.

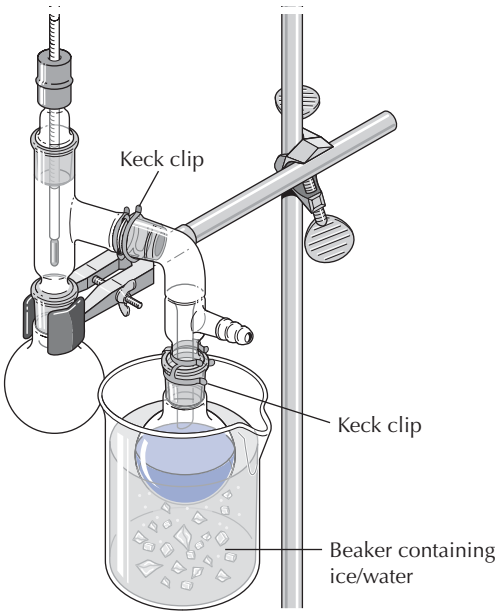
SAFETY PRECAUTION

By leaving a small residue of liquid in the boiling flask, you will not overheat the flask and break it, nor will you char the last drops of residue, which causes cleaning difficulty. Moreover, some compounds, such as ethers, secondary alcohols, and alkenes form peroxides by air oxidation. If a distillation involving one of these compounds is carried to dryness, the peroxides could explode.

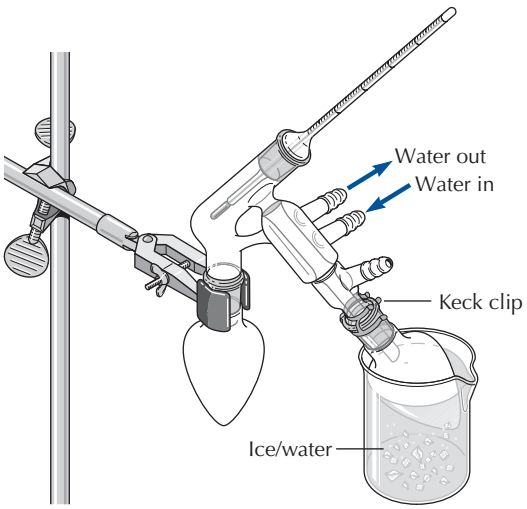
13.3b Miniscale Short-Path Distillation

When only 4–6 mL of liquid are distilled, a simple distillation apparatus can be modified to a short path by reducing the size of the glassware and shortening the condenser, as shown in Figure 13.8. The short path reduces the ***holdup volume,*** the volume of the distilling flask and fractionating column, which is filled with vapor during and after completion of a distillation. Short-path distillation also prevents distillate from being lost on the walls of a long condenser. A beaker or crystallizing dish of water surrounding the receiving flask replaces the condenser. If the liquid boils below 100°C, the beaker should contain an ice/water mixture. If the liquid boils above 100°C, a water bath provides sufficient cooling. For liquids that boil above 150°C, air cooling of the receiving flask suffices.

Figure 13.8b shows an even more efficient short-path distillation apparatus than the one shown in Figure 13.8a. In this apparatus the distilling head, a short condenser, and the vacuum adapter are



(a) ℨ 19/22 short-path apparatus



(b) ℨ 14/20 one-piece distilling head and condenser with flasks

FIGURE 13.8 Two types of short-path distillation apparatus.

combined in one piece of standard taper glassware. Using a pear-shaped distilling flask also leads to less loss of a valuable product. Despite the presence of a condenser, an ice/water bath is usually placed around the receiving flask for maximum cooling efficiency.

Carry out the distillation as described in Technique 13.3a for a simple distillation, but do the short-path distillation at a rate of less than 1 drop per second. While changing receiving flasks it may be necessary to stop the distillation by removing the heat source.

13.3c Microscale Distillation Using Standard Taper 14/10 Apparatus

Microscale apparatus is required when the volume of a liquid to be distilled is less than 5 mL. For the distilling vessel, use a conical vial for 1–3 mL or a 10-mL round-bottomed flask for 4–5 mL of liquid. Set the vial or flask in a small beaker before putting the liquid to be distilled into it. Add a magnetic spin vane to the vial or a magnetic stirring bar to the round-bottomed flask.

Assembly of a Short-Path Distillation Apparatus

Assemble standard taper microscale glassware into a short-path distillation apparatus with a 14/10 distillation head, a thermometer adapter (Figure 13.9), and a bent vacuum adapter, as shown in Figure 13.10. Begin by putting the thermometer through the

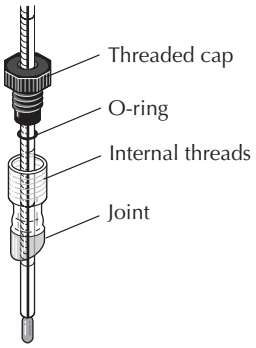


FIGURE 13.9
Thermometer adapter for 14/10 microscale glassware.

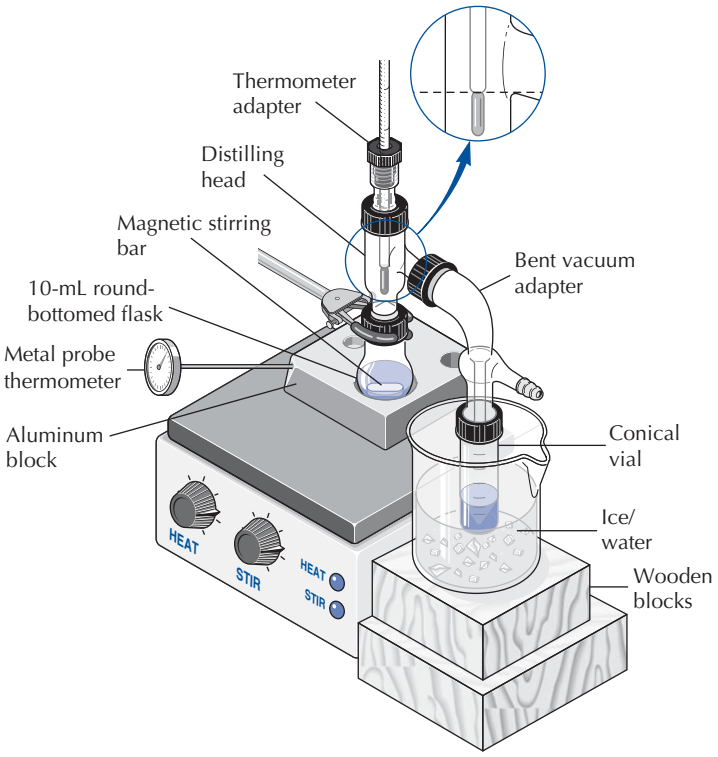


FIGURE 13.10
Short-path standard taper microscale distillation apparatus.

threaded cap of the thermometer adapter, then push a small O-ring up the thermometer as shown in Figure 13.9. Fit a screw cap, and a large O-ring over the ground glass joint at the bottom of the thermometer adapter. Place the thermometer adapter in the top of the distilling head and tighten the screw cap. Adjust the position of the thermometer in the adapter until **the top of the thermometer bulb is aligned with the bottom of the side arm of the distilling head** [See enlargement, Figure 13.10]. Attach the bent vacuum adapter to the distilling head and the receiving vial to the open end of the bent adapter. Last, attach the conical vial or round-bottomed flask holding the liquid to be distilled to the distilling head with a screw cap and O-ring; firmly clamp the apparatus to a ring stand or upright post.

Place an aluminum heating block on a hot plate. Lower the distilling vessel into the heating block. The conical vial collecting the distillate should be half submerged in an ice/water bath for efficient condensation of the vapor.

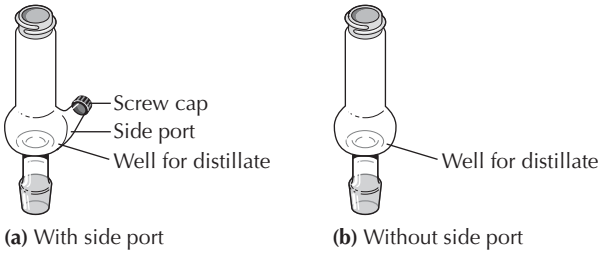
For distillation of very volatile liquids, a water-jacketed condenser can be inserted between the distilling head and the vacuum adapter. Attach rubber tubing to the condenser so that water enters at the lower outlet and exits at the upper outlet.

Carrying Out the Distillation

The procedure for carrying out a microscale distillation is the same as that for a miniscale distillation. Follow the procedure described in Technique 13.3a, p. 151. Have two conical vials available for the distillate: one for the forerun before the expected boiling point is reached, the other for the final product. Heat the aluminum block slowly to a temperature 20°–30°C above the boiling point of the liquid being distilled. Do the distillation at a rate of less than 1 drop per second. While changing the receiving vial, it may be necessary to stop the distillation by removing the heat source.

Using a Hickman Distilling Head

Another type of standard taper microscale distillation apparatus consists of a Hickman distilling head (Figure 13.11) and a 3-mL or 5-mL conical vial or a 10-mL round-bottomed flask. The Hickman distilling head also serves as the receiving vessel, an arrangement that considerably reduces the holdup volume. Vapors condense on the upper portion of the Hickman still and drain into the bulbous collection well. One version of the Hickman still has a port at the side for easy removal of the condensate (Figure 13.11a).



(a) With side port **(b)** Without side port

FIGURE 13.11
Hickman distilling heads. The condensate collects in the well at the bottom of the head in both versions.

Grease is not used on ground glass joints of microscale glassware because its presence could contaminate the product.

Setting up the apparatus. To carry out a microscale distillation, select a conical vial or 10-mL round-bottomed flask appropriate for the volume of liquid to be distilled; the vessel should be no more than two-thirds full. Use a Pasteur pipet to place the liquid in the vial and add a magnetic spin vane or a boiling stone. Attach the Hickman distilling head to the vial with a screw cap and O-ring. Usually an air condenser or a water-cooled condenser (for particularly volatile liquids) is placed above the Hickman distilling head to minimize the loss of vapor (Figure 13.12). Clamp the assembled apparatus at the Hickman distilling head, and place the vial in an aluminum heating block. If you are using a spin vane, turn on the magnetic stirrer.

It may be necessary to wrap the distillation vial loosely with glass wool to prevent rapid heat loss, but do not wrap the well of the Hickman distilling head.

Carrying out the distillation. Begin heating the aluminum block slowly to a temperature 20°–30°C above the boiling point of the liquid being distilled. Position a thermometer inside the condenser and the Hickman distilling head, with the top of the thermometer bulb aligned with the bottom of the head's collection well, as shown in Figure 13.12. Clamp the thermometer firmly above the condenser.

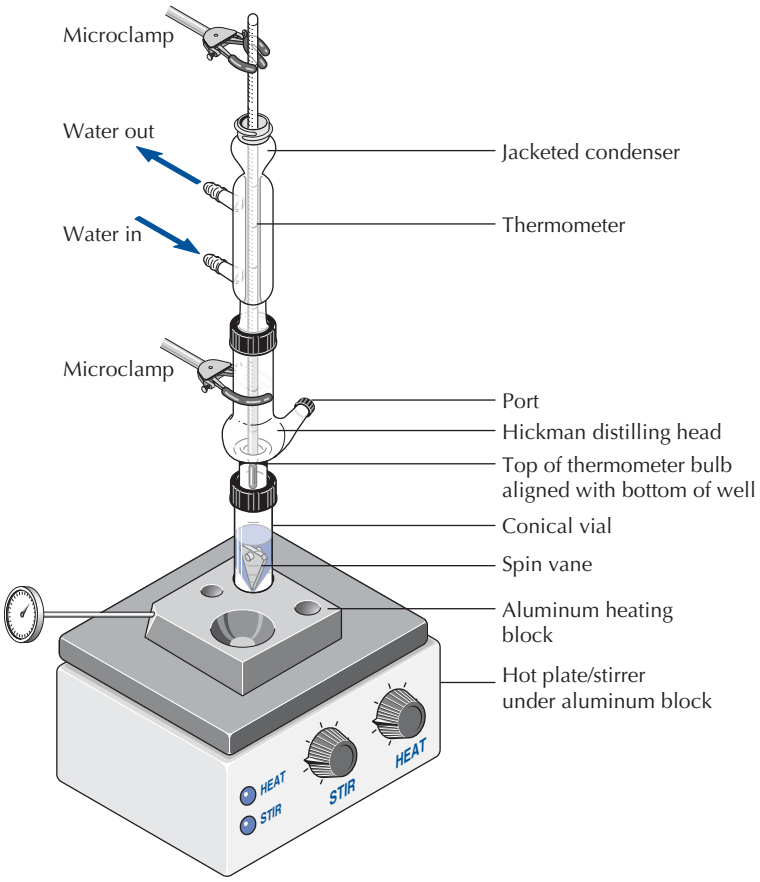


FIGURE 13.12
Standard taper apparatus for a microscale distillation using a Hickman distilling head with a side port.

Removing the distillate. After the liquid in the vial boils, you should see a ring of condensate slowly moving up the vial and into the Hickman distilling head. The temperature observed on the thermometer rises as the vapor reaches the thermometer bulb. You may also see the upper neck of the Hickman distilling head become wet and shiny as the vapor condenses and begins to fill the well. The distillation must be done at a rate slow enough to allow the vapor to condense and not evaporate out of the condenser.

The collection well has a capacity of about 1 mL, so the distillate may need to be removed once or twice during a distillation. Open the port and quickly remove the distillate with a clean Pasteur pipet. Alternatively, withdraw the distillate using a syringe inserted through the plastic septum in the screw cap of the port.

13.3d Microscale Distillation Using Williamson Apparatus

The Williamson microscale distillation apparatus is essentially a miniature version of the standard taper short-path distillation apparatus [see Technique 13.3b]. The apparatus consists of a 5-mL round-bottomed flask and a distillation head connected by a flexible connector with a support rod. The thermometer is held in place by the flexible thermometer adapter, as shown in Figure 13.13. The distillate is collected in a small vial that is at least three-fourths submerged in a 50-mL beaker of ice and water.

Assembling the Apparatus

Using a Pasteur pipet, transfer the liquid (no more than 3 mL) to the 5-mL round-bottomed flask and add a magnetic stirring bar or a boiling stone. Attach the flexible connector with a support rod to the

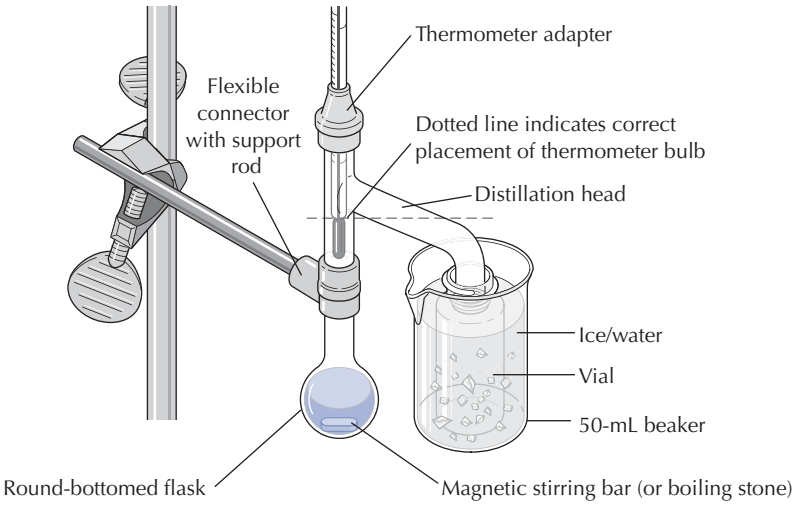


FIGURE 13.13
Williamson microscale distillation apparatus.

flask and clamp the rod to a vertical support rod or ring stand. Fit the flexible thermometer adapter to the top of the distilling head and carefully push a thermometer through the adapter.

SAFETY PRECAUTION

Grasp the thermometer close to the bulb and push it gently 1–2 cm into the adapter. Move your hand several centimeters up the thermometer stem and repeat the pushing motion; continue this process until the thermometer is properly positioned. Holding the thermometer by the upper part of the stem while inserting it through the rubber sleeve of the thermometer adapter could break the thermometer and force a piece of broken glass into your hand.

Place the top of the thermometer bulb just below the side arm, as shown by the dashed line drawn across the distillation head in Figure 13.13. Fit the distillation head into the flexible connector holding the distillation flask. Place the receiving vial in a 50-mL beaker of ice and water, and position the vial under the outlet of the distillation head as far as it will go. Put a sand bath or an aluminum heating block with a flask depression under the round-bottomed flask. The temperature of the sand bath or aluminum block needs to be 20°–50°C above the boiling point of the liquid being distilled.

Carrying Out the Distillation

After the liquid in the flask boils, you should notice a ring of condensate slowly moving up the flask and into the distillation head. The temperature observed on the thermometer rises as the vapor reaches the thermometer bulb. The distillation should be done at a rate slow enough for the vapor to condense and not evaporate out of the system. It may be necessary to wrap a wet pipe cleaner or wet paper towel around the side arm of the distillation head to increase its cooling efficiency, particularly for the distillation of compounds that boil below 100°C.

13.4 Fractional Distillation

Fractionating Columns

In a ***fractional distillation*** many vaporizations and condensations take place before the distillate is collected. As shown in Figure 13.4 (page 147), each vaporization and condensation cycle causes the vapor to become enriched in the more volatile compound. If a number of vaporization/condensation cycles are carried out in a ***fractionating column,*** the components of a mixture can be efficiently separated based on their vapor pressure differences. The fractionating column is inserted between the distillation flask and the distilling

head of the distillation apparatus and provides a large surface area over which a number of separate liquid-vapor equilibria can occur. As vapor travels up a column, it cools, condenses into a liquid, then vaporizes again after it comes into contact with hotter vapor rising from below. The process can be repeated many times. If the fractionating column is efficient, the vapor that finally reaches the distilling head at the top of the column is composed entirely of the component with the lower boiling point.

Efficiency of a fractionating column. The efficiency of a fractionating column is expressed as its number of ***theoretical plates***—a term best defined with the help of Figure 13.4 (page 147). Assume that the original solution being distilled has a molar composition of 75% hexane and 25% pentane. A fractionating column would have one theoretical plate if the liquid that is collected from the top of the column has the molar composition of 52% hexane and 48% pentane (L_2). In other words, a fractionating column has one theoretical plate if one complete vaporization of the original solution occurs in the column, followed by condensation of the vapor.

The column would have two theoretical plates if the liquid that distills has the molar composition L_3, which is 27% hexane and 73% pentane. Figure 13.4 indicates that a column with five theoretical plates would seem sufficient to obtain essentially pure pentane from the 1:3 pentane/hexane mixture present at the start of the distillation. However, as the distillation progresses, the residue in the boiling flask becomes richer in hexane, so a few more theoretical plates are required for complete separation of the two compounds.

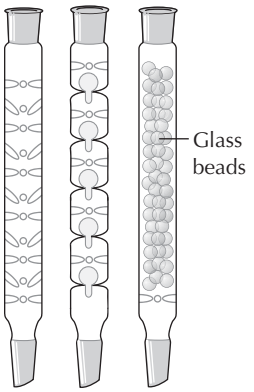


FIGURE 13.14
Examples of fractionating columns.

Types of fractionating columns. Fractionating columns that can be used to separate two liquids boiling at least 25°C apart are shown in Figure 13.14. The larger the column surface area on which liquid-vapor equilibria can occur, the more efficient the column will be. The fractionating columns shown in Figure 13.14 have from six to eight theoretical plates. A fractionating column with eight theoretical plates can separate liquids boiling only 25°C apart.

A more efficient column can be made by packing a simple fractionating column with a wire spiral, glass helixes, metal sponge, or thin metal strips. These packings provide additional surface area on which liquid-vapor equilibria can occur. Care must be used in selecting packing materials to ensure that the packing does not undergo chemical reactions with the hot liquids in the fractionating column.

Effective Fractional Distillation

Figure 13.15 shows the separation of molecules of two compounds with different boiling points in a fractional distillation column. If the fractionating column has enough theoretical plates to completely separate a mixture of pentane and hexane, for example, the initial condensate will appear when the temperature is very close to 36°C, the boiling point of pentane. The observed boiling point will remain

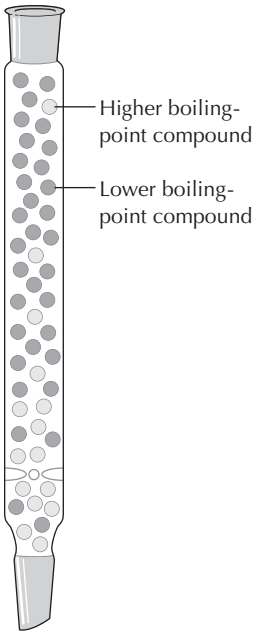


FIGURE 13.15 Separation of two compounds with different boiling points in a fractional distillation column.

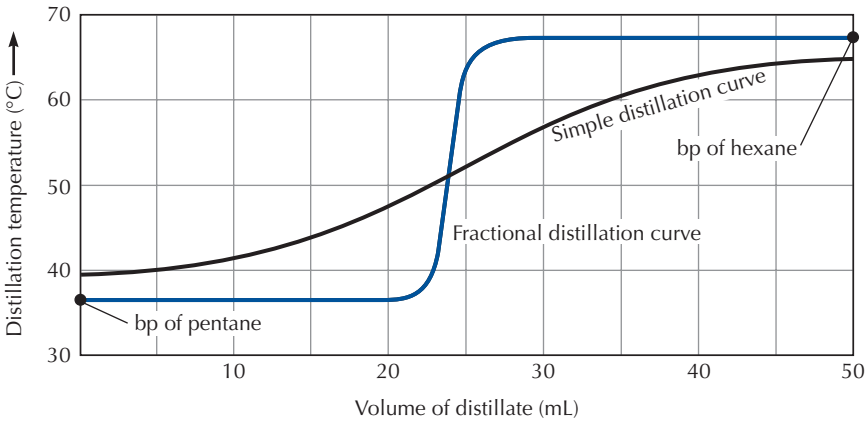


FIGURE 13.16 Distillation curve for the fractional distillation of a solution of pentane and hexane. The dashed line represents the distillation curve for a simple distillation of the same solution.

essentially constant at 36°C while all the pentane distills into the receiving vessel. Then the boiling point will rise rapidly to 69°C, the boiling point of hexane. Figure 13.16 shows a distillation curve for the fractional distillation of pentane and hexane. The abrupt temperature increase in boiling point at approximately 22–24 mL of distillate demonstrates an efficient fractional distillation.

Miniscale Fractional Distillation Apparatus

As in simple distillation, the distilling flask capacity should be about two times the volume of liquid being distilled. When the desired material is contained in a large quantity of a solvent with a lower boiling point, the distillation should be interrupted after the solvent has distilled, and the liquids with higher boiling points (the solution that remains in the boiling flask) should be transferred to a smaller flask before continuing the distillation.

Figure 13.17 shows the apparatus for a fractional distillation. Follow the steps listed in Technique 13.3a for assembling a simple distillation apparatus, except for the addition of the fractionating column between the distillation flask and the distilling head. Be sure to add one or two boiling stones to the distilling flask, and be sure that the thermometer is placed correctly, as shown in the circled detail in Figure 13.7.

Carrying Out a Fractional Distillation

Rate of heating. Control of heating in a fractional distillation is extremely important; the heat needs to be increased gradually as the distillation proceeds. Applying too much heat causes the distillation to occur so quickly that the repeated liquid-vapor equilibria required to bring about maximum separation cannot occur. On the other hand, if too little heat is applied, the column may lose heat faster than it can

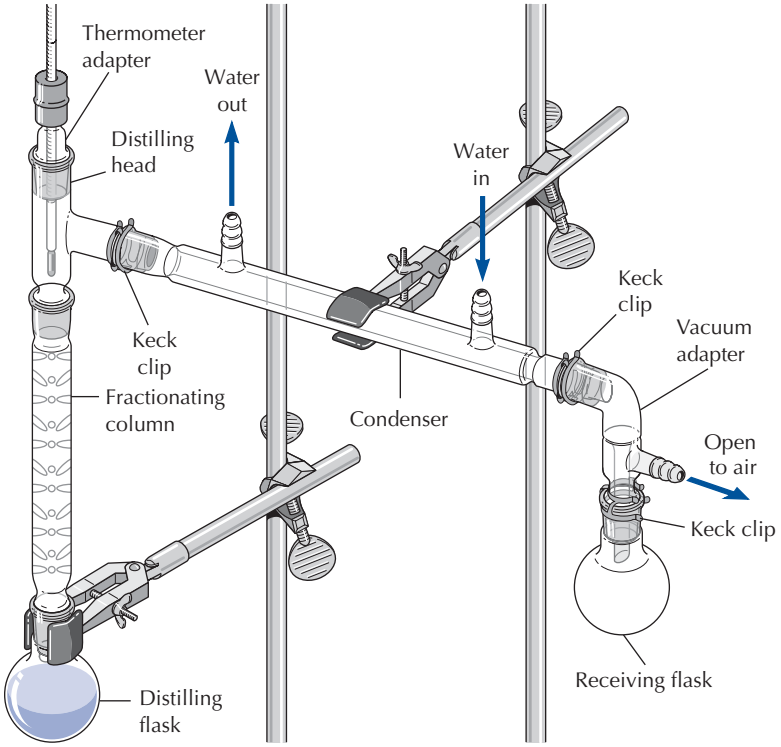


FIGURE 13.17
Miniscale fractional distillation apparatus. The fractionating column is inserted between the distilling flask and the distilling head.

be warmed by the vapor, thus preventing the vapor from reaching the top of the column. Thus, too little heat causes the thermometer reading to drop below the boiling point of the liquid, simply because vapor is no longer reaching the thermometer bulb.

Rate of distillation. The rate of distillation is always a compromise between the time the distillation takes and the efficiency of the fractionation. For an easy separation, 1–2 drops per second can be collected. Generally a slow, steady distillation where 1 drop is collected every 2–3 s is a better rate. Difficult separations (when the boiling points of the distilling compounds are close together) require a slower distillation rate as well as a more efficient fractionating column—one with more theoretical plates. The distillation rate can be increased during collection of the last fraction, when all the lower boiling compounds have already been distilled.

Collecting the fractions. You will need a labeled receiving container (round-bottomed flask, vial, or Erlenmeyer flask) for each fraction you plan to collect. The cutoff points for the fractions are the boiling points (at atmospheric pressure) of the substances being separated. For example, in a fractional distillation of a solution of pentane (bp 36°C) and hexane (bp 69°C), the first fraction would be collected when the temperature at the distilling head reaches 35°–36°C. The temperature would stay at 36°C for a period of time while the pentane distills.

Eventually the temperature either rises or drops several degrees; a drop indicates that there is no longer enough pentane vapor to maintain the temperature at the thermometer bulb. At this point, increase the heat input and change to the second receiving flask. Liquid then begins to distill again. Leave the second receiver in place until the temperature reaches 68°–69°C, the boiling point of hexane; then change to the third receiving flask. The second receiver should contain only a small amount of distillate. Continue collecting fraction 3 (hexane) until only 1 mL of liquid remains in the distillation flask.

SAFETY PRECAUTION

A distillation flask should **never** be allowed to boil dry.

Summary of a Miniscale Fractional Distillation Procedure

1. Use a round-bottomed flask that has a capacity about two times the volume of the liquid mixture you wish to distill. Clamp the flask to a ring stand or upright support rod. Pour the liquid into the flask and add one or two boiling stones.
2. Set up the rest of the apparatus as shown in Figure 13.17.
3. Heat the mixture to boiling and collect the distillate in fractions based on the boiling points of the individual components in the mixture. Use a separate labeled receiving container for each fraction.

Microscale Fractional Distillation

Among the most efficient fractionating columns for microscale distillation are those with helical bands of Teflon mesh that spin at many rotations per minute. A microscale spinning band distillation apparatus has a Teflon rod with a spiral molded along its axis, extending from the bottom of the column to the top (Figure 13.18). The spinning band wipes the condensate on the side of the column

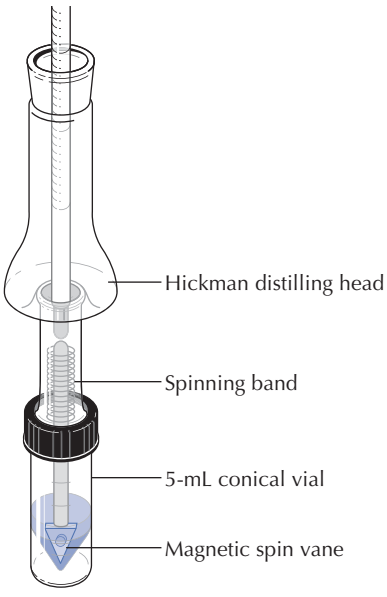


FIGURE 13.18
Hickman distilling head with spinning band apparatus.

into a thin film and forces the rising vapors into contact with the descending condensate. The result is a large increase in the number of vaporization/condensation equilibria in the column. Spinning-band columns can have more than 100 theoretical plates and can be used to separate liquids that have a boiling-point difference of only a few degrees.

13.5 Azeotropic Distillation

The systems described up to this point are solutions whose compounds interact only slightly with one another and thus approximate the behavior of ideal solutions. Most liquid solutions, however, deviate from ideality. The deviations result from intermolecular interactions in the liquid state—hydrogen bonding, for example. In the distillation of some solutions, mixtures that boil at a constant temperature are produced. Such constant-boiling mixtures, called ***azeotropes,*** or ***azeotropic mixtures,*** cannot be further purified by distillation.

One of the best-known binary mixtures that forms an azeotrope during distillation is the ethanol/water system, shown in Figure 13.19. The azeotrope boils at 78.2°C and consists of 95.6% ethanol and 4.4% water by weight. The liquid that has this azeotropic composition will vaporize to a gas that has exactly the same composition because the liquid and vapor curves intersect at this point. No matter how many more liquid-vapor equilibria take place as the vapor travels up the column, no further separation will occur. Continued distillation never yields a liquid that contains more than 95.6% ethanol. Pure ethanol must be obtained by other means.

More detailed discussion about the formation of azeotropes from nonideal solutions can be found in the Further Reading references at the end of the chapter. Extensive tables of azeotropic data are available in references such as the *CRC Handbook of Chemistry and Physics.* Table 13.2 lists a few azeotropes formed by common solvents.

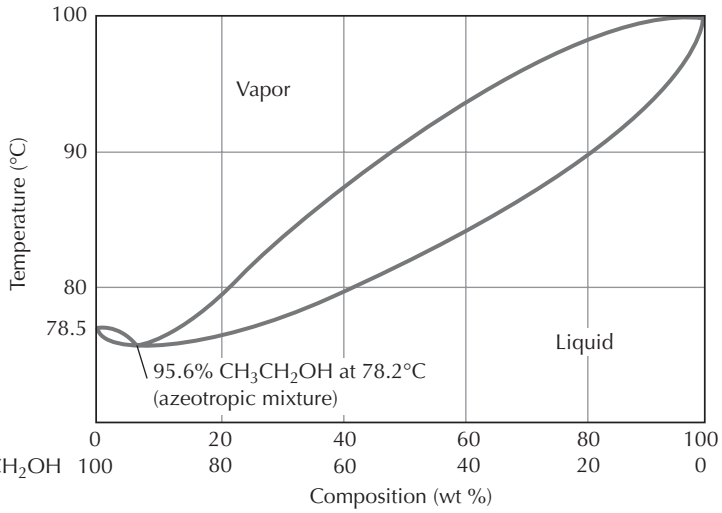


FIGURE 13.19
Temperature/composition diagram for ethanol/water solutions.

TABLE 13.2 Azeotropes formed by common solvents

Component *X* (bp)	% by wt	Component *Y* (bp)	% by wt	Azeotrope bp
Water (100)	13.5	Toluene (110.7)	86.5	84.1
Water (100)	1.4	Pentane (36.1)	98.6	34.6
Methanol (64.7)	12.1	Acetone (56.1)	87.9	55.5
Methanol (64.7)	72.5	Toluene (110.7)	27.5	63.5
Ethanol (78.3)	68.0	Toluene (110.7)	32.0	76.7
Water (100)	1.3	Diethyl ether (34.5)	98.7	34.2

Azeotropic distillation is a useful way to remove a product, such as water, from a reaction mixture by codistillation with an immiscible organic liquid; removing the water will shift the reaction equilibrium toward the product side. If the reaction were carried out in toluene, which is less dense than water, the vapor in the reflux condenser would contain an azeotropic mixture of toluene and water. When this mixture condenses, it falls into the Dean-Stark trap and separates into a layer of liquid toluene on top of the lower water layer (Figure 13.20). When the liquid level in the Dean-Stark trap

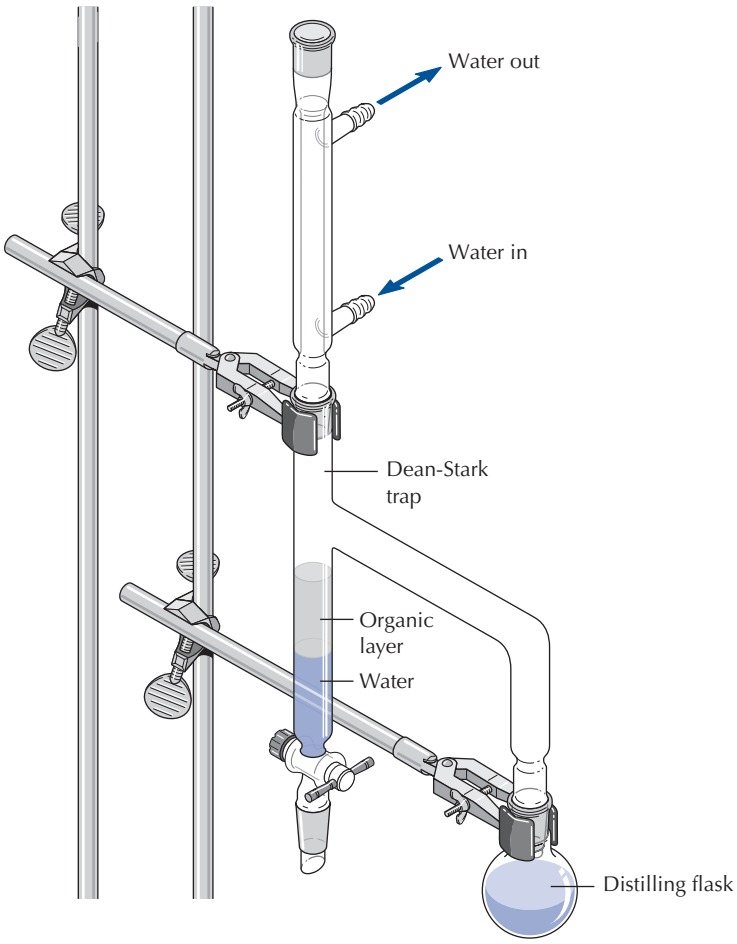


FIGURE 13.20
Dean-Stark apparatus for azeotropic removal of water from a reaction.

reaches the top of the side arm, the toluene flows back into the reaction flask. The water can be removed through the stopcock at the bottom of the Dean-Stark trap.

13.6 Steam Distillation

Codistillation with water, called ***steam distillation,*** allows distillation of relatively nonvolatile organic compounds without using vacuum systems. Steam distillation can be thought of as a special kind of azeotropic distillation; it is especially useful for separating volatile organic compounds from nonvolatile inorganic salts or from the leaves and seeds of plants. Indeed, the process has found wide application in the flavor and fragrance industries as a means of separating essences or flavor oils from plant material. For example, limonene (oil of orange) can be separated from ground orange peels by steam distillation.

Mutual Insolubility and Vapor Pressure

Steam distillation depends on the mutual insolubility or immiscibility of many organic compounds with water. In such two-phase systems, at any given temperature each of the two components exerts its own full vapor pressure. The total vapor pressure above the two-phase mixture is equal to the sum of the vapor pressures of the pure components independent of their relative amounts.

Consider the codistillation of iodobenzene (bp 188°C) and water (bp 100°C). The vapor pressures ($P°$) of both substances increase with temperature, but the vapor pressure of water will always be higher than that of iodobenzene because water is more volatile. At 98°C,

$$P°_{\text{iodobenzene}} = 46 \text{ torr}$$

$$P°_{\text{water}} = 714 \text{ torr}$$

$$P°_{\text{iodobenzene}} + P°_{\text{water}} = 760 \text{ torr}$$

Therefore, a mixture of iodobenzene and water codistills at 98°C.

An ideal gas law calculation shows that the mole fraction of iodobenzene in the vapor at the distilling head is 0.06 (46 torr/760 torr), and the mole fraction of water in the vapor is 0.94. However, because iodobenzene has a much higher molecular weight than water (204 g/mol versus 18 g/mol), its weight percentage in the vapor is much larger than 0.06, as the following calculation shows:

$$\frac{\text{moles}_{\text{iodobenzene}}}{\text{moles}_{\text{water}}} = \frac{P°_{\text{iodobenzene}}}{P°_{\text{water}}}$$

$$\frac{\text{grams}_{\text{iodobenzene}}/\text{MW}_{\text{iodobenzene}}}{\text{grams}_{\text{water}}/\text{MW}_{\text{water}}} = \frac{P°_{\text{iodobenzene}}}{P°_{\text{water}}}$$

Rearranging this expression and substituting for the molecular weights and vapor pressures allow us to calculate the weight ratio of iodobenzene to water in the distillate from the steam distillation:

$$\frac{g_{\text{iodobenzene}}}{g_{\text{water}}} = \frac{0.73}{1.00}$$

In other words, the distilling liquid contains 42% iodobenzene and 58% water by weight. In any steam distillation, a large excess of water is used in the distilling flask so that virtually all the organic compound can be distilled from the mixture at a temperature well below the boiling point of the pure compound.

The steam distillation of most reasonably volatile organic compounds that are insoluble in water occurs between 80°C and 100°C. For example, at 1.0 atm, octane (bp 126°C) steam distills at 90°C, and 1-octanol (bp 195°C) steam distills at 99°C. The lower distillation temperature has the added advantage of preventing decomposition of the organic compounds during distillation.

Procedure for Steam Distillation

Use more water than the amount of organic mixture being distilled and select a distilling flask that will be no more than half filled with this organic/water mixture. Add one or two boiling stones to the flask. Modify a simple distillation apparatus by adding a Claisen connecting tube or adapter between the distillation flask and the distilling head. This adapter provides a second opening into the system to accommodate the addition of extra water without stopping the distillation (Figure 13.21).

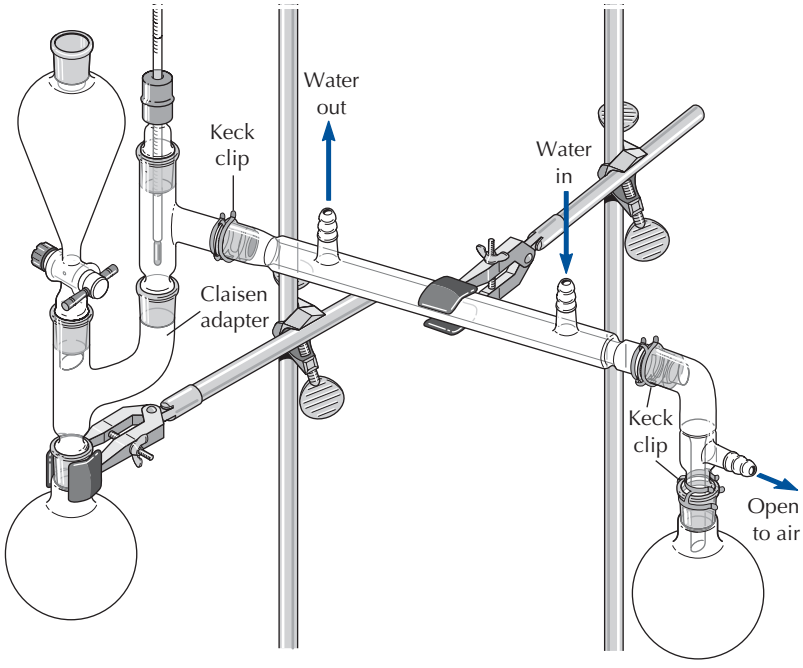


FIGURE 13.21
Steam distillation apparatus.

Steps in a Steam Distillation

1. Set up the distillation apparatus.
2. Pour the organic mixture and an excess of water into a firmly clamped distilling flask at least twice as large as the combined organic/water volume. Add one or two boiling stones.
3. Heat the mixture until the entire top organic layer has distilled into the receiving flask. Sometimes it is worthwhile to collect some additional water after the organic material is no longer apparent in the distilling flask.
4. Separate the organic phase of the distillate from the aqueous phase in a separatory funnel.

13.7 Vacuum Distillation

Many organic compounds decompose at temperatures below their atmospheric boiling points. These compounds can be distilled at temperatures lower than their atmospheric boiling points when a partial vacuum is applied to the distillation apparatus. Distillation at reduced pressure, called vacuum distillation, takes advantage of the fact that the boiling point of a liquid is a function of the pressure under which the liquid is contained [see Technique 13.1]. Although vacuum distillation is inherently less efficient than fractional distillation at atmospheric pressure, it is often the only feasible way to distill compounds with boiling points above 200°C.

A partial vacuum can be obtained in the laboratory with either a vacuum pump or a water aspirator. Vacuum pumps can easily produce pressures of less than 0.5 torr. The pressure obtained with a water aspirator can be no lower than the vapor pressure of water, which is approximately 13 torr at 15°C. In practice, an efficient water aspirator produces a partial vacuum of 15–25 torr.

The boiling point of a compound at any given pressure other than 760 torr is difficult to calculate exactly. As a rough estimate, a 50% drop in pressure lowers the boiling point of an organic liquid 15°–20°C. Below 25 torr, reducing the pressure by one-half lowers the boiling point approximately 10°C (Table 13.3).

A nomograph provides a good way of estimating the boiling points of relatively nonpolar compounds at either reduced or atmospheric pressure (Figure 13.22). For example, if the boiling point of a compound at 760 torr is 200°C and the vacuum distillation is being done at 20 torr, the approximate boiling point is found by aligning a straightedge on 200 in column B with 20 in column C;

TABLE 13.3 Boiling points (°C) at reduced pressures

Pressure (torr)	Water	Benzaldehyde	Diphenyl ether
760	100	179	258
100	51	112	179
40	34	90	150
20	22	75	131

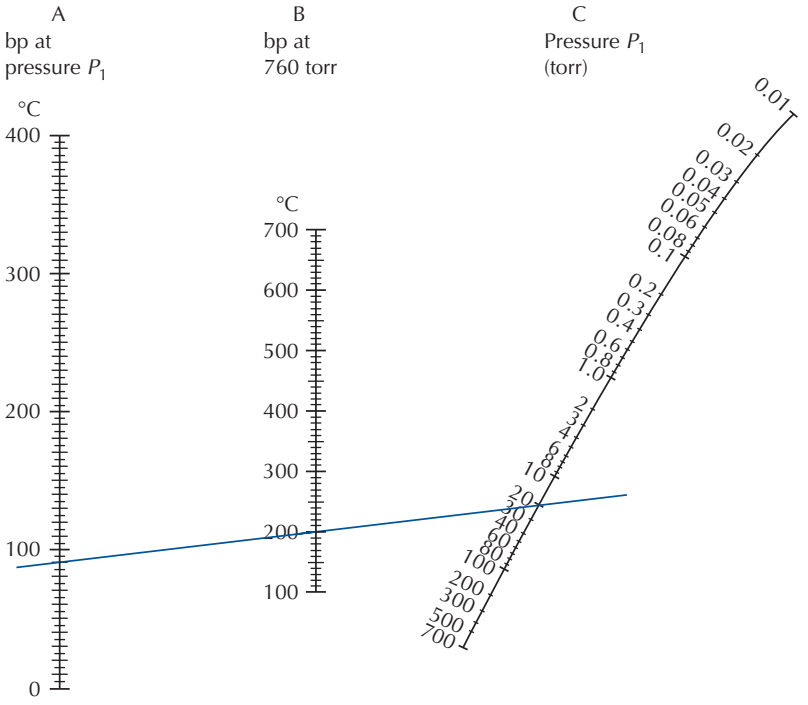


FIGURE 13.22
Nomograph for estimating boiling points at different pressures.

the straightedge intersects column A at 90°C, the approximate boiling point of the compound at 20 torr, as shown by the line on Figure 13.22. Similarly, the boiling point at atmospheric pressure can be estimated if the boiling point at a reduced pressure is known. By aligning the boiling point in column A with the pressure in column C, a straightedge intersects column B at the approximate atmospheric boiling point. The graph gives a less accurate estimate of boiling points for polar compounds that associate strongly in the liquid phase.

Monitoring the Pressure During a Vacuum Distillation

The pressure can be continuously monitored with a manometer (Figure 13.23) or read periodically with a McLeod gauge (Figure 13.24). If a water aspirator is used as the vacuum source, a trap bottle or flask must be used to prevent any back flow of water from entering the distillation apparatus.

When a vacuum pump is used as the vacuum source, a cold trap, kept at the temperature of isopropyl alcohol/dry ice (−77°C) or liquid nitrogen (−196°C), must be placed between the distillation system and the pump. The trap collects any volatile materials that could otherwise get into the pump oil and cause a rise in the vapor pressure of the oil, which would decrease the efficiency of and possibly damage the pump. A pressure relief valve serves to close the system from the atmosphere and to release the vacuum after the system has cooled following the distillation. Consult your instructor before you do a distillation using a vacuum pump.

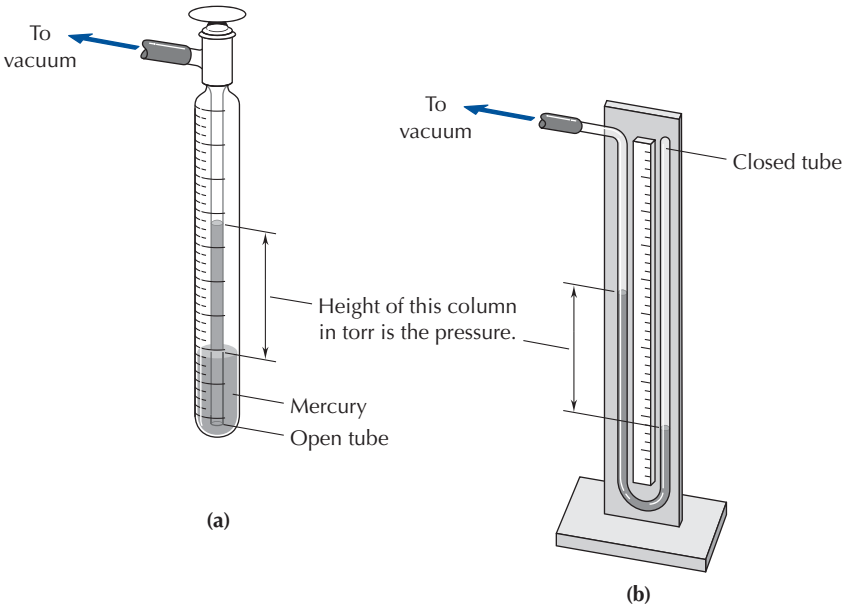


FIGURE 13.23 Two types of closed-end manometers used in vacuum distillations.

A McLeod gauge is often used to measure pressures below 5 torr. It works by compressing the gas inside the gauge into a closed capillary tube with a pressure great enough to be measured with a mercury column. Initially the gauge must be in the horizontal, resting position with the mercury in the reservoir. When the pressure inside the distillation apparatus has stabilized, the gauge is slowly rotated until the open-ended reference capillary tube is in the vertical position (Figure 13.24). The pressure is indicated by the scale on the closed-end capillary tube when the mercury level in the reference capillary tube reaches the calibration mark. After the pressure has been read, the gauge must be returned to the horizontal, resting position.

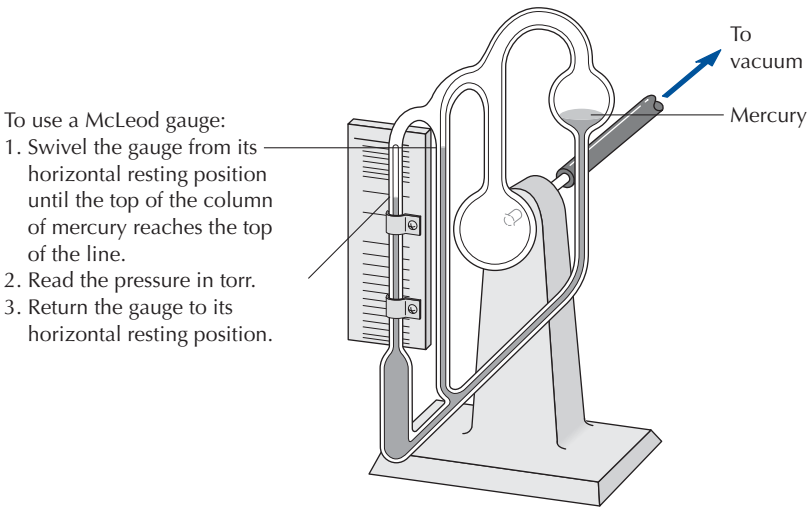


FIGURE 13.24
McLeod gauge used in vacuum distillations, shown in the vertical measuring position.

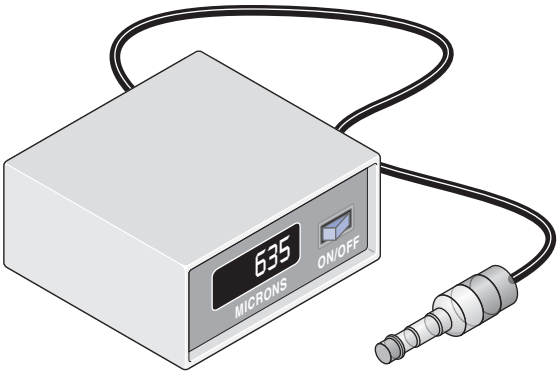


FIGURE 13.25
Digital, nonmercury vacuum gauge.

When distillations are carried out at high vacuum, the distillation apparatus can be connected to a vacuum manifold, which has multiple ports equipped with stopcocks. To minimize leaks and for safety reasons, vacuum manifolds are mounted securely on metal racks. The pressure inside the vacuum system is often measured with a digital electronic gauge such as the one shown in Figure 13.25, which measures the pressure in microns (10^{-3} torr). Consult your instructor before using a McLeod gauge or a vacuum manifold.

Apparatus for Miniscale Vacuum Distillation

The vacuum distillation apparatus shown in Figure 13.26 works adequately for most vacuum distillations, although a fractionating column may be needed to provide satisfactory separation of

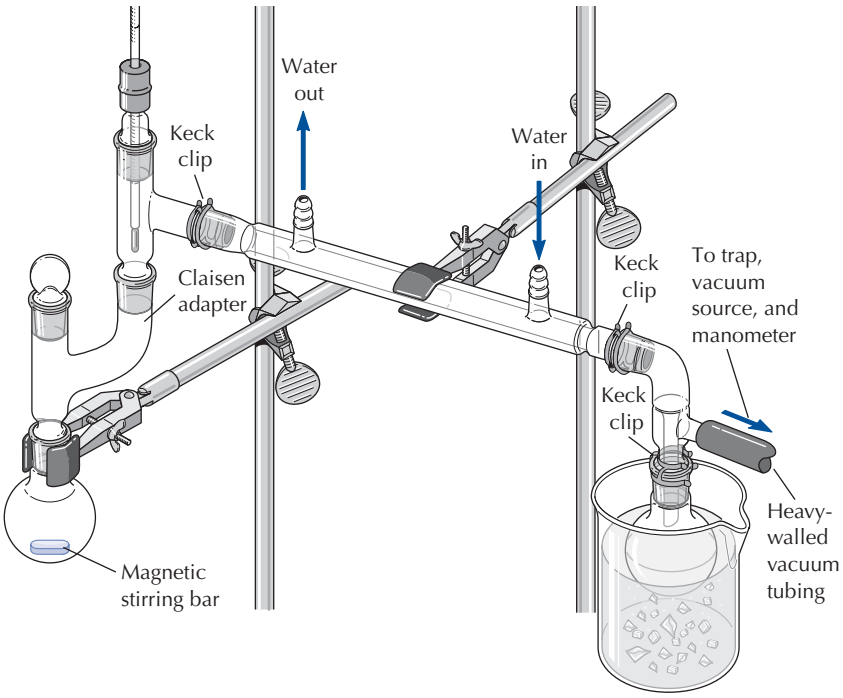


FIGURE 13.26 Vacuum distillation apparatus.

some mixtures. Because liquids often boil violently at reduced pressures, a Claisen connecting adapter is always used in a vacuum distillation to lessen the possibility of liquid bumping up into the condenser. If undistilled material jumps through the Claisen adapter into the condenser, you must begin the distillation again. Uncontrolled bumping during a vacuum distillation can be lessened by using a large distillation flask, by adding small pieces of wood splints in place of boiling stones, or by magnetic stirring.

If a satisfactory vacuum is to be maintained, each connecting surface must be greased with high-vacuum silicone grease, and **the rubber tubing to the aspirator or vacuum pump must be thick-walled** so that it does not collapse under vacuum. Care must be exercised to use a thin film of grease applied only at the top half of the inner joints. If the partial vacuum is not as low as expected, carefully check all connections for possible leaks.

To change the receiving flask using the apparatus shown in Figure 13.26, you must allow air into the distillation assembly to bring it back to atmospheric pressure. This often requires cooling down the distillation flask somewhat before allowing the air back in.

Figure 13.27 shows a "cow" receiver, which allows the collection of four distillation fractions without breaking the vacuum. This apparatus is an efficient setup for vacuum distillations; the receiver can simply be rotated to change the receiver arm when a new distillation fraction is called for. Figure 13.27 also shows how a very finely drawn-out capillary can provide a steady stream of very small bubbles to enhance the steadiness of a distillation. The bottom of the capillary-tube bubbler should be just above the bottom surface of

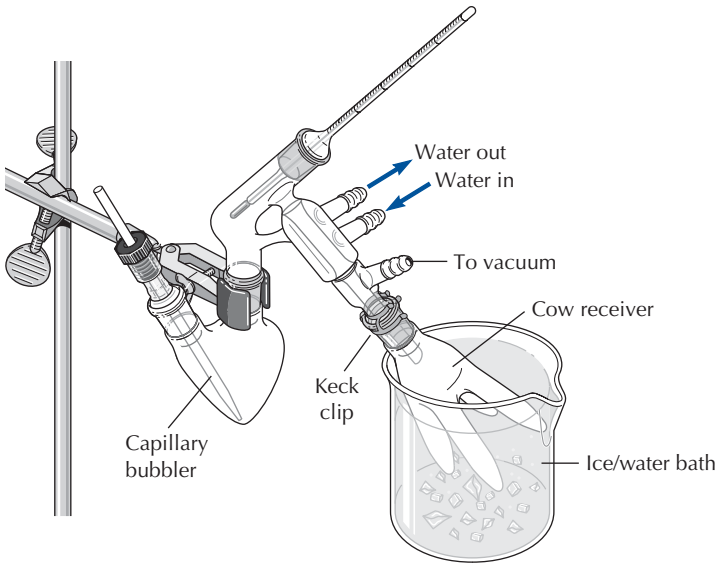


FIGURE 13.27
Short-path standard taper apparatus for vacuum distillation with capillary bubbler and cow receiver.

the distilling flask and must always be below the liquid's surface. Do not use wood splints or boiling stones when you use a capillary bubbler; their violent motions may break the fragile tip of the bubbler, making it useless.

Steps in a Miniscale Vacuum Distillation

SAFETY PRECAUTION

Safety glasses must be worn at all times while carrying out a vacuum distillation because of the danger of an implosion, which can shatter the glassware.

1. Add the liquid to be distilled to a round-bottomed flask sized so that it will be less than half filled. Add some wood splints or a magnetic stirring bar and set up the apparatus as shown in Figure 13.26, or use a capillary bubbler, as shown in Figure 13.27.
2. Attach a trap and a manometer [see Figure 13.23], a McLeod gauge [see Figure 13.24], or a digital pressure gauge [see Figure 13.25] to the system and connect the apparatus to the vacuum source with thick-walled rubber tubing.
3. Close the pressure release valve and turn on the vacuum.
4. When the vacuum has reached an appropriate level, heat the distilling flask cautiously to obtain a moderate distillation rate. Periodically monitor the pressure during the distillation.
5. When the distillation is complete, remove the heat source and allow the apparatus to cool nearly to room temperature before allowing air into the apparatus. **Turn off the aspirator or vacuum pump only after the vacuum has been broken. If you have used a cold trap, empty its contents immediately.**

Standard Taper Microscale Apparatus for Vacuum Distillation

For a volume of 2–5 mL of liquid, a 10-mL round-bottomed flask and the microscale 14/10 apparatus shown in Figure 13.28 can be used for a vacuum distillation. If the volume of liquid to be distilled is less than 2 mL, the microscale apparatus shown in Figure 13.29 can be used. In both cases thick-walled rubber tubing must connect the distillation apparatus to the vacuum source.

The ground glass joints of microscale glassware should not be greased. Usually clean standard taper joints are completely sealed by compression of the O-ring when the cap is screwed down tightly. Only if the requisite reduced pressure cannot be obtained should microscale joints be greased with high-vacuum silicone grease. Care must be exercised to use a very thin film of grease applied only at the top of the inner joints. No grease should be allowed to seep from the bottom of any joint because the grease might contaminate the liquid being distilled.

The well in a Hickman distilling head has a capacity of only 1 mL.

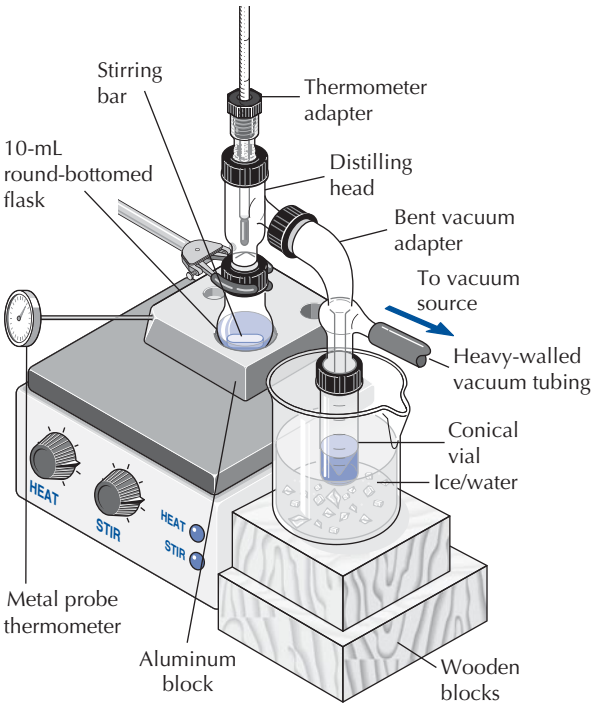


FIGURE 13.28 Short-path standard taper microscale apparatus for vacuum distillation.

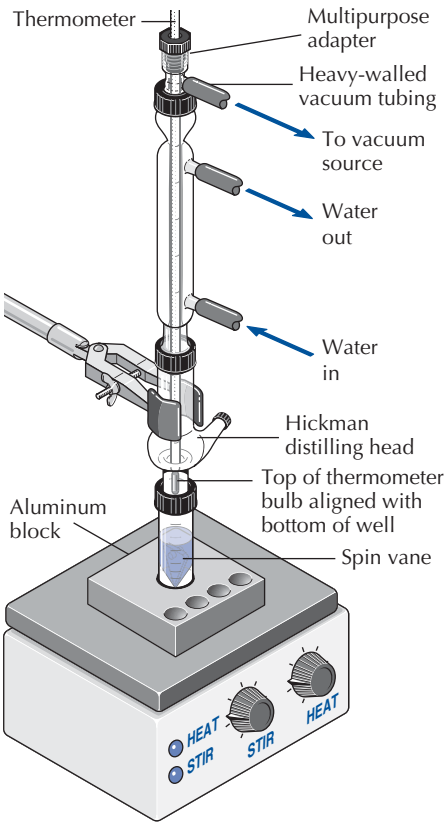


FIGURE 13.29 Standard taper microscale apparatus for distillation with a Hickman distilling head.

13.8 Sources of Confusion

Distillation is an important method for separating and purifying organic liquids. However, successful distillations require careful attention to a number of factors.

What Type of Distillation Should I Use?

Simple distillation. Simple distillation is used in two commonly encountered situations: (1) to remove a low-boiling solvent from an organic compound with a high boiling point; (2) as the last step in the purification of a liquid compound to obtain a pure product and determine its boiling point.

Fractional distillation. Fractional distillation is used for the separation of a mixture of two or more liquid compounds whose boiling points differ by less than 60°–75°C.

Steam distillation. Steam distillation is used to separate volatile compounds from a complex mixture. It can also be used to separate an organic product from an aqueous reaction mixture containing inorganic salts.

Vacuum distillation. When the boiling point of a liquid compound is over 200°C, the compound may decompose thermally before its atmospheric boiling point is reached. The reduced atmospheric pressure of a vacuum distillation allows the compound to boil at a lower temperature and thus distill without decomposition.

The Thermometer Reading Seems Too Low

If the liquid in the distilling flask is boiling but the temperature recorded on the thermometer in the distilling head is still 25°–30°C, it is likely that the vapor has not yet reached the thermometer bulb. The space between the boiling liquid and the thermometer bulb in the distilling head must become filled with vapor before a temperature increase can be observed. Filling the space above the boiling liquid with vapor may require several minutes, depending on the rate of heating.

If the distillation is well under way and liquid is collecting in the receiving flask, yet the thermometer reading is still near room temperature, it is likely that the thermometer bulb is improperly positioned above the side arm (see Figure 13.7).

The Temperature Drops Suddenly During a Fractional Distillation

A sudden drop in temperature before all the liquid has distilled indicates a break between fractions. There is not enough vapor of the higher-boiling compound reaching the thermometer bulb to register on the thermometer. Increase the rate of heating until vapor again envelops the thermometer bulb.

When Do I Change Receiving Flasks?

Simple distillation. If you are conducting a simple distillation of a liquid that previously was dissolved in a low-boiling solvent, any liquid that distills at a temperature less than 5°C below the product's reported boiling point should be collected in a separate receiving flask. At 5°C or less from the expected boiling point of the liquid at the atmospheric pressure in your lab, change the receiving flask to the tared (weighed) receiving flask.

Fractional distillation. In a fractional distillation, the receiving flasks are changed soon after a sudden increase in temperature is noted, after a wait only long enough to allow the lower-boiling fraction to be washed out of the condenser. The sharp increase in temperature indicates that distillation of the lower-boiling component of the mixture is complete.

Further Reading

Lide, D. R. (Ed.) *Handbook of Chemistry and Physics;* 90th ed. CRC Press: Boca Raton, FL, 2009.

Perry, E. S.; Weissberger, A. (Eds.) *Techniques of Organic Chemistry;* 2nd ed.; Wiley-Interscience: New York, 1965, Vol. 4.

Questions

1. Explain why the observed boiling point for the first drops of distillate collected in the simple distillation of a 1:1 molar solution of pentane and hexane, illustrated in Figure 13.5, will be above the boiling point of pentane.

2. The molar composition of a mixture is 80% hexane and 20% pentane. Use the phase diagram in Figure 13.4 to estimate the composition of the vapor over this liquid. This vapor is condensed and the resulting liquid is heated. What is the composition of the vapor above the second liquid?
3. A student carried out a simple distillation on a compound known to boil at 124°C and reported an observed boiling point of 116°–117°C. Gas chromatographic analysis of the product showed that the compound was pure, and a calibration of the thermometer indicated that it was accurate. What procedural error might the student have made in setting up the distillation apparatus?
4. The directions in an experiment specify that the solvent, diethyl ether, be removed from the product by using a simple distillation. Why should the heat source for this distillation be a steam bath, not an electrical heating mantle?
5. The boiling point of a compound is 300°C at atmospheric pressure. Use the nomograph (Figure 13.22) to determine the pressure at which the compound would boil at about 150°C.
6. Azeotropes can be used to shift chemical equilibria by removing products. Treatment of 1-butanol with acetic acid in the presence of sulfuric acid as a catalyst results in formation of butyl acetate and water. The mixture of 1-butanol/butyl acetate/water forms a ternary azeotrope that boils at 90.7°C. This azeotrope separates into two layers; the upper layer is largely butyl acetate, along with 11% 1-butanol, and the lower layer is largely water. Butyl acetate forms by an equilibrium reaction that does not especially favor product formation.
   a. Describe an apparatus by which azeotrope formation can be used to drive the equilibrium toward the products, thus maximizing the yield.
   b. How would you separate the 1-butanol/butyl acetate mixture that forms the upper azeotropic layer?

TECHNIQUE 14

MELTING POINTS AND MELTING RANGES

Molecules in a crystal are arranged in a regular pattern. Melting occurs when the fixed array of molecules in the crystalline solid rearranges to the more random, freely moving liquid state. The transition from solid to liquid requires energy in the form of heat to break down the crystal lattice. The temperature at which this transition occurs is the solid's ***melting point,*** an important physical property of any solid compound. The melting point of a compound is useful in establishing its identity and as a criterion of its purity. Until the advent of modern chromatography and spectroscopy, the melting point was the primary index of purity for an organic solid. Melting points are still used as a preliminary indication of purity.

14.1 Melting-Point Theory

The melting point, or more correctly the melting range, of a crystalline organic compound is determined by the strength of the intermolecular forces between its molecules—hydrogen bonds, dipole-dipole interactions, and van der Waals interactions. These forces hold the molecules together in an orderly crystalline array and must be overcome for the molecules to enter the less orderly liquid phase. Large molecular surface area and high molecular symmetry are associated with greater intermolecular forces and higher melting points. Intermolecular forces are discussed in more detail in the essay at the beginning of Part 3, page 99.

Melting Behavior

The melting point is generally reproducible for a pure compound. Relatively pure compounds normally melt over a narrow temperature range of 0.5°–1.5°C, whereas impure substances often melt over a much larger range. However, the presence of even small amounts of impurities usually depresses the melting point a few degrees and causes melting to occur over a relatively wide temperature range. Adding greater amounts of an impurity generally causes a greater decrease in the melting point.

Solid and liquid phases exist in equilibrium at their melting points as shown by the solid curved line in Figure 14.1. This phase diagram plots the observed melting curve for mixtures of compounds A and B ranging from 100 mol % A with 0 mol % B to 0 mol % A with 100 mol % B. A pure sample of compound A melts at temperature T_A whereas pure compound B melts at temperature T_B. At T_A and T_B, pure samples of A and B melt sharply over a narrow temperature range.

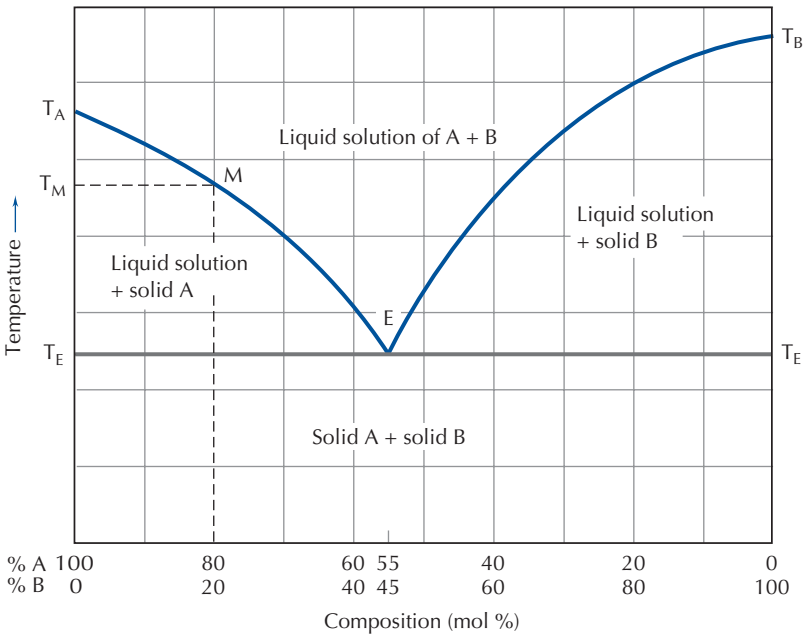


FIGURE 14.1
Melting-point composition diagram for the binary mixture A + B. T_A is the melting point of pure solid A, T_B of pure solid B, and T_E of eutectic mixture E. The temperature range $T_E - T_M$ is the melting range of a solid containing 80 mol % A and 20 mol % B.

Figure 14.1 shows that the melting range of A/B mixtures is depressed and becomes wider. Consider the behavior of a solid consisting of 80% of compound A and 20% of compound B. The melting point of this mixture is T_M at point M on the diagram. Thus, adding 20% B to A lowers the melting point from T_A to T_M. In addition, the melting range also becomes greater; T_M is the upper limit of the melting range for the 80/20 mixture of A and B. As the temperature increases and A begins to soften, it dissolves B. As B dissolves, the melting point is lowered. B continues to dissolve and the lowering continues until all the B has dissolved or when the liquid phase becomes saturated with B. Then actual melting begins at T_E and the first liquid appears. Because all the B has dissolved, the melting point begins to rise as more A melts. While all this is happening, the melting-point sample contains both solid and liquid phases. As more A melts, the composition reaches point M on the curve and the mixture finally melts sharply, producing a clear liquid. Melting occurs along curve EM in Figure 14.1, giving an observed melting range of $T_E - T_M$.

Another way to look at this phenomenon is to compare freezing points with melting points. An impurity depresses the melting point of a solid just as the freezing point of a liquid is depressed by an impurity. The freezing point and melting point are identical, although accurate freezing points are more challenging to obtain because liquids often supercool before they freeze. One practical application of this behavior is salting roads to melt ice at a temperature lower than 0°C.

Eutectic Composition

The limit to how far a melting point can be lowered is reached when the liquid solution of A and B becomes saturated in B. Until point E is reached in Figure 14.1, all the B dissolves in melting A. After point E—when all A is melted—a portion of solid B remains. Point E defines the composition of a saturated solution of B in liquid A and is called the ***eutectic point.*** A solid mixture with the eutectic composition (55% A and 45% B) will melt sharply at the eutectic temperature, T_E.

Not all binary mixtures form eutectics and some mixtures may form more than one. There can be two eutectic points, for example, when two compounds interact to form a molecular compound of definite composition. In spite of these variations, the melting point and its range are useful indications of a compound's purity.

14.2 Apparatus for Determining Melting Ranges

Two types of electrically heated melting-point devices are commonly used in introductory organic chemistry laboratories—the Mel-Temp apparatus and the Fisher-Johns hot-stage apparatus.

Mel-Temp Apparatus

A Mel-Temp apparatus is shown in Figure 14.2. The heating block with sample chambers and a thermometer well are located within the surrounding safety shield. A thin-walled glass capillary tube

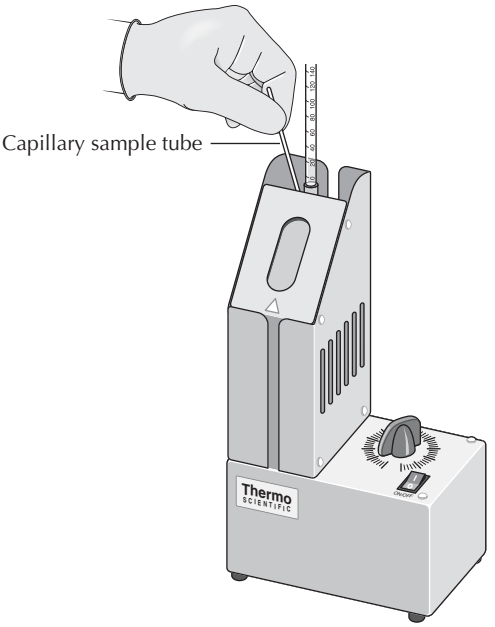


FIGURE 14.2
Mel-Temp apparatus.
(Reprined with permission from Thermo Fisher Scientific, Asheville, NC.)

holds the sample. The capillary tube fits into one of three sample chambers in the heating block; multiple chambers allow simultaneous determinations of three melting points. A cylindrical cavity in the top of the heating block holds the thermometer, a light illuminates the sample chamber, and an eyepiece containing a small magnifying lens facilitates observation of the sample. A digital thermometer can also be used with a Mel-Temp apparatus.

A rheostat controls the rate of heating by allowing continuous adjustment of the voltage. The higher the rheostat setting, the faster the rate of heating. However, the rate of heating at any particular setting increases more rapidly at the start and then slows as the temperature increases. The decreasing rate of heating at the higher temperatures allows for the slower heating needed as the melting point is approached.

Fisher-Johns Apparatus

The Fisher-Johns hot-stage apparatus is another device for the determination of melting points (Figure 14.3). The crushed sample is

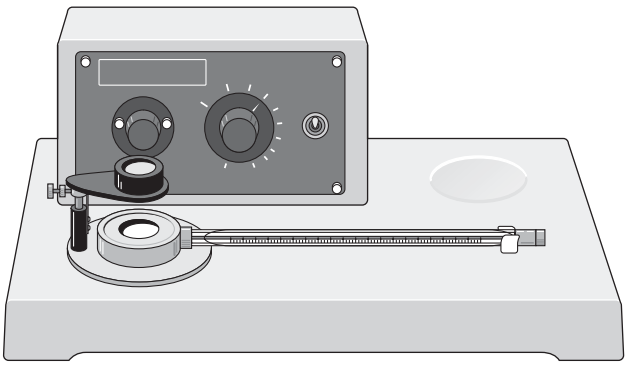


FIGURE 14.3
Fisher-Johns hot-stage melting-point apparatus.
(Courtesy of Fisher Scientific, Pittsburgh, PA.)

placed between thin, circular, microscope coverslips rather than in a capillary tube. The coverslips fit in a depression in the metal block surface. A rheostat controls the rate of heating, and the lighted sample area is viewed through a small magnifying glass.

SAFETY PRECAUTION

1. If the heater on a Fisher-Johns apparatus is not turned off after the sample melts, the high heat may ruin the thermometer calibration or even break the thermometer. The latter event may lead to a spill of toxic mercury in the laboratory.
2. Never use ice to cool the hot stage. The sudden decrease in temperature may break the thermometer and cause a spill of toxic mercury.

14.3 Determining Melting Ranges

Sample Preparation

The melting range of an organic solid can be determined by introducing a small amount of the substance between two coverslips or into a capillary tube with one sealed end. Such capillary tubes, which are approximately 1 mm in diameter, are commercially available.

Filling a capillary tube. Place a few milligrams of the dry solid on a piece of smooth-surfaced paper and crush it to a fine powder by rubbing a spatula over the solid while pressing down. Introduce the solid into the capillary tube by tapping the open end of the tube in the powdered substance. A small amount of material will stick in the open end. Invert the capillary tube so that the sealed end is down, and holding it very near the sealed end, tap it lightly with quick motions against the bench top.

SAFETY PRECAUTION

Care must be taken while tapping the capillary tube against the bench top; the tube could break and cause a cut.

The ideal sample for a melting point is only 1–2 mm in height in the capillary tube.

The solid will fall to the bottom of the tube. Repeat this operation until the amount of solid in the tube is 1–2 mm in height. A small sample is essential for accurate melting points. Melting-point determinations made with too much sample lead to a broad melting range because more time is required to melt the complete sample and the temperature continues to rise while the sample melts.

An alternative method for getting the solid to the bottom of a capillary tube is to drop the tube down a piece of glass tubing about 1 m in length or down the inside tube of a condenser, the bottom end of which is resting on the lab bench. After a few trips down the glass tubing, the solid will usually have fallen to the bottom of the capillary tube.

Wet samples. If a solid is still wet from recrystallization, it will not fall to the bottom of a capillary tube but will stick to the capillary wall. This failure to behave properly is probably a good thing, because melting points of wet solids are always low and thus nearly worthless. If your sample is still wet, allow it to dry completely before continuing with the melting-range determination.

Samples for the Fisher-Johns apparatus. Samples for the Fisher-Johns apparatus also need to be finely powdered. Place a few grains of the powdered sample on one coverslip and set it in the metal heating block. Place a second coverslip over the sample and gently flatten the powder until the two glass surfaces just touch each other; contact between the two coverslips ensures good heat transfer to the sample.

Thermometer Calibration

The accuracy of a melting-point determination can be no better than the accuracy of the thermometer. You cannot assume that a thermometer has been accurately calibrated—although that may be the case, it is not always true. Thermometers can give high or low temperature readings of 1°–2° or more. Technique 5.4, page 48, describes a procedure for calibrating a thermometer.

Heating the Sample to the Melting Point

The melting-point apparatus can be heated rapidly until the temperature is about 20°C below the expected melting point. Then decrease the rate of heating so that the temperature rises only 1°–2° per minute and the sample has time to melt before the temperature rises above the true melting point. When you are taking successive melting points, remember that the apparatus needs to cool to at least 20° below the expected melting point before it can be used for the next determination.

Approximate melting point. If you do not know the melting point of a solid sample, you can make a quick preliminary determination by heating the sample rapidly and watching for the temperature at which melting begins. In a more accurate second determination, you can then carefully control the temperature rise to 1°–2° per minute when you get within 15°–20° of the expected melting point.

Use a fresh sample for each determination. Always prepare a fresh sample for each melting-point determination; many organic compounds decompose at the melting point, making reuse of the solidified sample a poor idea. Moreover, many low-melting compounds (mp 30°–80°C) do not easily resolidify with cooling.

Digital thermometers. Digital thermometers have a metal probe that responds more rapidly than a mercury-filled glass thermometer to temperature changes. The rate of heating near the melting point must be 1°–2° per minute or else the observed melting-point range will very probably be above the true melting point. Consult your instructor before using a digital thermometer.

Reporting the Melting Range

Unless you have an extraordinarily pure compound in hand, you will always observe and report a melting range—from the temperature at which the first drop of liquid appears to the temperature at which the

solid is completely melted and only a clear liquid is present. This melting range is usually 1°–2° or slightly more. For example, salicylic acid usually gives a melting range of 157°–159°C. An extremely pure sample of salicylic acid, however, melts over less than a 1° range (for example, 160.0°–160.5°C) and it may have 160°C listed as its melting point. Published melting points are usually the highest values obtained after several recrystallizations; the values you observe will probably be slightly lower.

14.4 Summary of Mel-Temp Melting-Point Determinations

1. Introduce the powdered, dry solid sample to a height of 1–2 mm into a capillary tube that is sealed at one end.
2. Place the capillary tube in the melting-point apparatus.
3. Adjust the rate of heating so that the temperature rises at a moderate rate. The rate can be faster if, for example, the melting point is 170°C rather than 70°C.
4. When a temperature 15°–20° below the expected melting point is reached, decrease the rate of heating so that the temperature rises only 1°–2° per minute. **Note:** There will be a time lag before the rate of heating changes.
5. If the temperature is rising more than 1°–2° per minute at the time of melting, determine the melting point again using a new sample.
6. Record the melting range as the range of temperatures between the onset of melting and the temperature at which only liquid remains in the tube.

14.5 Using Melting Points to Identify Compounds

We have already discussed how impurities can lower the melting point of a compound. This behavior can be useful not only in evaluating a compound's purity but also in helping to identify the compound. Assume that two compounds have virtually identical melting ranges. Are the compounds identical? Possibly, but not necessarily, because the identical melting ranges may be a coincidence. The use of a mixture melting point is one way of answering this question.

Mixture Melting Point

If roughly equal amounts of the two compounds are finely ground together with a spatula, the melting range of the resulting mixture can provide useful information. If there is a melting-point depression or if the melting range is expanded by a number of degrees, it is reasonably safe to conclude that the two compounds are not identical. One compound has acted as an impurity toward the other by lowering the melting range. If there is no lowering of the mixture's melting range relative to that for each separate compound, the two are probably the same compound.

Sometimes only a modest melting-point depression is observed. To know whether this change is significant, the mixture melting point and the melting point of one of the two compounds should be determined simultaneously in separate capillary tubes. This experiment allows simultaneous identity and purity checks. Infrequently, a eutectic point (point E in Figure 14.1) can be equal to the melting point of the pure compound of interest. In a case where you have accidentally used the eutectic mixture, a mixture melting point would not be a good indication of purity or identity. Errors of this type can be discerned by testing various mixtures other than a 1:1 composition. The subsequent use of 1:2 and 2:1 mixtures can avoid eutectic-point-induced misinterpretation.

Other Ways of Determining Identity

Other ways of determining the identity of a solid organic compound involve spectroscopic methods [see Techniques 20–23] and thin-layer chromatography [see Technique 17].

14.6 Sources of Confusion

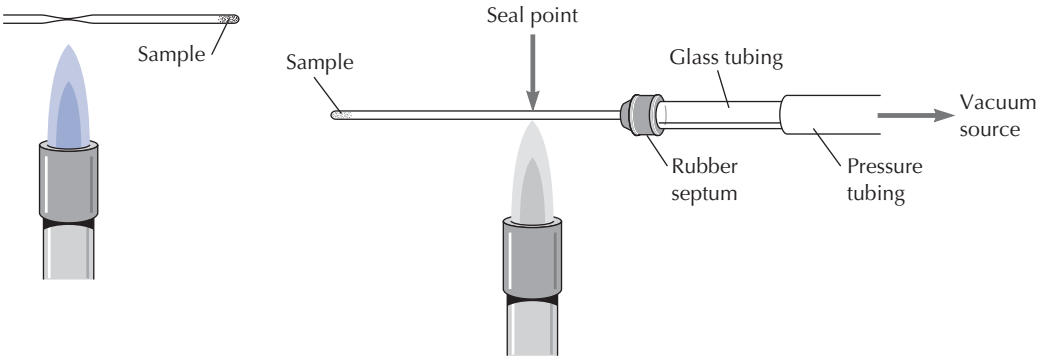
When you heat a sample for a melting-point determination, you may see some strange and wonderful things happen before the first drop of liquid actually appears. The compound may soften and shrivel up as a result of changes in its crystal structure. It may "sweat out" some solvent of crystallization. It may decompose, changing color as it does so. None of these changes should be called melting. **Only the appearance of liquid indicates the onset of true melting.** Even so, it can be difficult to distinguish exactly when melting starts. In fact, even with careful heating, two people may disagree on the melting point by as much as 1°–2°.

Rate of Heating

Heating faster than 1°–2° per minute may lead to an observed melting range that is higher than the correct one, particularly when using a digital thermometer with a metal probe. And if the rate of heating is extremely rapid (>10°C per minute), you may also observe thermometer lag with a liquid-filled thermometer, a condition caused by failure of the liquid's temperature to increase as rapidly as the temperature of the metal heating block. This error causes the observed melting range to be lower than it actually is. Determining accurate melting points requires patience.

Sublimation

Another possible complication in melting-point determinations occurs if the sample sublimes. Sublimation is the change that occurs when a solid is transformed directly to a gas, without passing through the liquid phase [see Technique 16]. If the sample in the capillary tube sublimes, it can simply disappear as it is heated. Many common substances sublime, for example, camphor and caffeine. You can determine their melting points by sealing the open end of the capillary tube in a Bunsen burner flame before it is placed in the melting-point apparatus (Figure 14.4a).



(a) Sealing a capillary tube **(b)** Evacuating and sealing a capillary tube

FIGURE 14.4 Methods for sealing a capillary tube with a Bunsen burner.

Decomposition

Some compounds decompose as they melt, a behavior usually indicated by a change in color of the sample to dark red or brown. The melting point of such a compound is reported in the literature with the letter **d** after the temperature. For example, 186°C **d** means that the compound melts at 186°C with decomposition.

Sometimes decomposition occurs as a result of a reaction between the compound and oxygen in the air. If this is the case, when the air is evacuated from the capillary tube and the tube is sealed, the melting point can be determined without decomposition (Figure 14.4b).

Place the sample in the capillary tube as directed earlier. Punch a hole in a rubber septum, insert the closed end of the capillary tube through the inside of the septum, then gently push most of the capillary through the septum. Fit the septum over a piece of glass tubing that is connected to a vacuum line. Turn on the vacuum source, and while heating the upper portion of the capillary tube in a Bunsen burner flame, hold and pull on the sample end of the capillary tube until it seals.

SAFETY PRECAUTION

Be sure no flammable solvents are in the vicinity when you are using a Bunsen burner.

Further Reading

Skau, E. L.; Arthur, J. C. Jr. In *Physical Methods of Chemistry,* A. Weissberger and B. W. Rossiter (Eds.); Wiley-Interscience: New York, 1971, vol. 1, Part V.

Questions

1. A student performs two melting-point determinations on a crystalline product. In one determination, the capillary tube contains a sample about 1–2 mm in height and the melting range is found to be 141°–142°C. In the other determination, the sample height is 4–5 mm and the melting range is found to be 141°–145°C.

Explain the broader melting-point range observed for the second sample. The reported melting point for the compound is 143°C.

2. Another student reports a melting range of 136°–138°C for the compound in Question 1 and mentions in her notebook that the rate of heating was about 12°/min. NMR analysis of this student's product does not reveal any impurities. Explain the low melting point.
3. A compound melts at 120°–122°C on one apparatus and at 128°–129°C on another. Unfortunately, neither apparatus is calibrated. How might you check the identity of your sample without calibrating either apparatus?
4. Why does sealing the open end of a melting-point capillary tube allow you to measure the melting point of a compound that sublimes?
5. A white crystalline compound melts at 111°–112°C and the melting-point capillary is set aside to cool. Repeating the melting-point analysis with the same capillary reveals a much higher melting point of 140°C. Yet repeated recrystallization of the original sample yields sharp melting points no higher than 114°C. Explain the behavior of the sample that was cooled and then remelted.

TECHNIQUE 15

RECRYSTALLIZATION

A pure organic compound is one in which there are no detectable impurities. Because experimental work requires an immense number of molecules (Avogadro's number per mole), it is not true that 100% of the molecules in a "pure" compound are identical to one another. Seldom is a pure compound purer than 99.99%. Even if it were that pure, one mole would still contain more than 10^{19} molecules of other compounds. Nevertheless, we want to work with compounds that are as pure as possible, and recrystallization is one of the major techniques for purifying solid compounds.

15.1 Introduction to Recrystallization

What Is Recrystallization?

When a crystalline material (solute) dissolves in a hot solvent and then returns to a solid again by crystallizing (precipitating) in a cooled solvent, the process is called ***recrystallization.*** Its success depends on the increasing solubility of the crystals in hot solvent and their decreasing solubility when the solution cools, thereby causing the compound to recrystallize. Impurities in the original crystalline material are usually present at a lower concentration than in the substance being purified. Thus, as the mixture cools, the impurities tend to remain in solution while the highly concentrated product crystallizes.

Crystal Formation

Crystal formation of a solute from a solution is a selective process. When a solid crystallizes at the right speed under the appropriate conditions of concentration and solvent, an almost perfect crystalline material can result because only molecules of the right shape fit into the crystal lattice. In recrystallization, dissolution of the impure solid in a suitable hot solvent destroys the impure crystal lattice, and recrystallization from the cold solvent selectively produces a new, more perfect (purer) crystal lattice. Slow cooling of the saturated solution promotes formation of pure crystals because the molecules of the impurities, which do not fit as well into the newly forming crystal lattice, have time to return to the solution. Therefore, crystals that form slowly are larger and purer than ones that form quickly. Indeed, rapid crystal formation traps the impurities because the lattice grows so quickly that the impurities are simply surrounded by the crystallizing solute as the crystals form.

Solvent Properties

In general, a solvent with a structure similar to that of the solute will dissolve more solute than will solvents with dissimilar structures. Although the appropriate choice of a recrystallization solvent is a trial-and-error process, a relationship exists between the solvent's structure and the solubility of the solute. This relationship is simply described as **like dissolves like.** In a recrystallization, the polarity of the solvent and that of the compound being recrystallized should be similar.

High-polarity solvents. Among the more polar organic solvents, both methanol and ethanol are commonly used for recrystallization because they dissolve a wide range of both polar and nonpolar compounds to the appropriate degree. Ethanol and methanol also evaporate easily and possess water solubility, which allows recrystallization from an alcohol/water mixture.

Nonionic compounds generally dissolve in water only when they can associate with the water molecules through hydrogen bonding [see Essay on Intermolecular Forces, page 99]. Carboxylic acids, which readily form hydrogen bonds, are often recrystallized from water solution. Molecules that associate with water through hydrogen bonds include carboxylic acids, alcohols, and amines. Carboxylic acids hydrogen bond to a lone pair of electrons of water through the acidic proton; alcohols do likewise. Amines hydrogen bond primarily through the lone pair on nitrogen and a hydrogen atom of water.

Low-polarity solvents. Organic solvents of low polarity also dissolve many nonionic organic compounds with ease. Even polar organic compounds can dissolve in solvents of low polarity if the ratio of polar functional groups per carbon atom is not too high and if hydrogen bonding can occur between the solute and the solvent.

Among the low-polarity solvents, diethyl ether and ethyl acetate appear to provide the best solvent properties, although the low boiling point of diethyl ethyl (35°C) is a disadvantage and its extreme

TABLE 15.1 Common recrystallization solvents

Solvent	Boiling point, °C	Miscibility[a] in water	Solvent polarity	Comments
Diethyl ether	35	–	low	Good solvent, but low bp limits its use
Acetone	56	+	intermediate	Good general solvent, but low bp
Petroleum ether[b]	60–80	–	nonpolar	Good solvent for less polar compounds
Methanol	65	+	high	Good solvent for moderately polar compounds
Hexane	69	–	nonpolar	Good solvent for less polar compounds
Ethyl acetate	77	–	low	Good general solvent
Ethanol	78.5	+	high	Excellent general solvent
Cyclohexane	80.6	–	nonpolar	Good solvent for less polar compounds[c]
Water	100		very high	Solvent of choice for polar compounds
Toluene	111		nonpolar	Good solvent for aromatic compounds, slow to evaporate

a. Infinite solubility = +
b. Petroleum ether (or ligroin) is a mixture of isomeric alkanes. The term "ether" refers to volatility, not the presence of an ether functional group.
c. May freeze if the cooling bath is less than 6.5°C.

flammability requires careful attention to safety. Diethyl ether in combination with hexane or methanol has excellent solvent properties for recrystallizations.

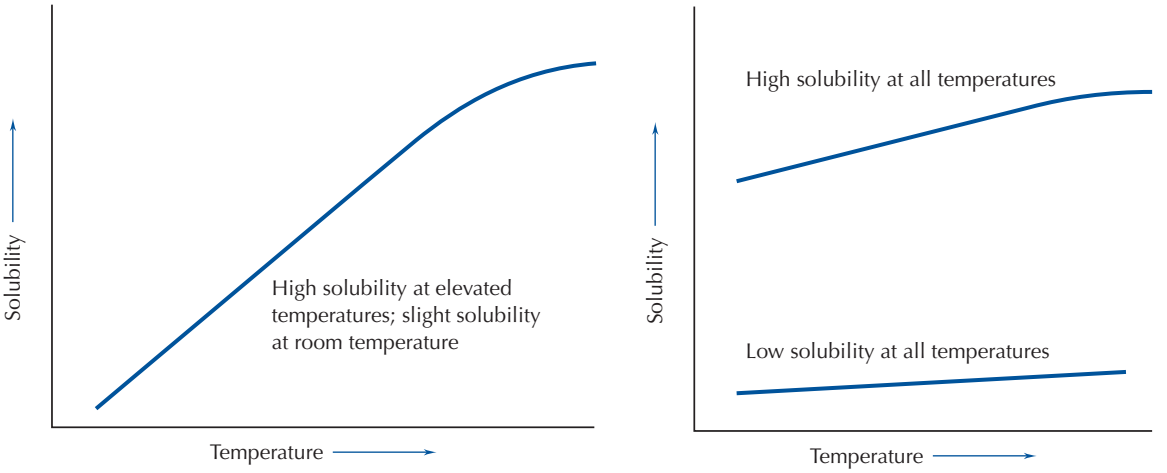
SAFETY PRECAUTION

Ether, hexane, and petroleum ether are very flammable and should be heated with a steam or hot-water bath. They should **never** be heated with a flame or on a hot plate.

Boiling point of the solvent. The boiling point of the solvent is another important property because the solvent needs to be volatile enough to evaporate fairly quickly from the crystals after they are recovered from the recrystallization solution. Therefore, most commonly used recrystallization solvents have boiling points at or below 100°C (Table 15.1).

Choice of a Recrystallization Solvent

The most crucial aspect of a recrystallization procedure is the choice of solvent, because **the solute should have a maximum solubility in the hot solvent and a minimum solubility in the cold solvent.** Figure 15.1a shows the solubility curve for a good recrystallization solvent with low solubility at lower temperatures and high solubility



(a) A good recrystallization solvent

(b) Poor recrystallization solvents

FIGURE 15.1 Solubility graphs.

at higher temperatures. For recrystallization to work effectively, the solubility of the organic solid should not be too large or too small in the recrystallization solvent. If the solubility is too large, it is difficult to recover the compound, as illustrated by the upper curve in Figure 15.1b. If the solubility is too small, a very large volume of solvent will be needed to dissolve the compound or it simply may not dissolve sufficiently for recrystallization to be effective, as shown in the lower curve of Figure 15.1b.

15.2 Carrying Out Successful Recrystallizations

There are several important factors in carrying out successful recrystallizations that apply to both miniscale and microscale recrystallizations. When you are recrystallizing a compound, attention to these details will make the process proceed more smoothly and successfully.

Scale of the Recrystallization

Beakers are not used for recrystallizations because the solvent would evaporate too rapidly during heating.

The amount of solid to be recrystallized will determine the size of the container used for the recrystallization and the volume of solvent needed. For miniscale recrystallizations you will probably never use an Erlenmeyer flask of smaller capacity than 50 mL. A 125- or 250-mL Erlenmeyer flask is usually appropriate for recrystallizations of 1–10 g. A good rule of thumb is to use a flask two to three times larger than the amount of solvent you think you will need. Microscale recrystallizations are usually done in 10- or 25-mL Erlenmeyer flasks or small test tubes.

The amount of solvent needed for the recrystallization will naturally differ if you are purifying 400 mg or 4.0 g of a compound. For example, you would not want to recrystallize 4.0 g of compound in 10 mL of solvent because it would be difficult to achieve much

purification. You will probably want to use twenty to forty times the amount of solvent as compound being recrystallized.

Add a boiling stone or boiling stick to the recrystallization flask. Adding the solvent incrementally and then allowing the mixture to boil before adding more solvent is crucial. You want to use only the amount of solvent needed to just dissolve all the solute in boiling solvent, thereby insuring maximum recovery of the solute when the solution cools. If you are using approximately 20 mL of solvent, it works best to make incremental additions of solvent with a Pasteur pipet. If you are using a larger amount of solvent, pour small portions of warm solvent directly from the flask holding the solvent into the recrystallization flask.

Insoluble Impurities

Consider a situation where you have added 40 mL of warm solvent to your compound. When you heat the mixture to just under the boiling point of the solvent, most of the solid dissolves immediately. With the addition of another 5 mL of solvent, more of the solid dissolves. But after you add another 10 mL of solvent and heat the mixture again to the boiling point, no more solid has gone into solution. Now is the time to consider that your compound contains an insoluble impurity that needs to be removed by filtration of the hot solution [see Technique 10.2, Figure 10.2.]. In this situation you have to make accurate experimental observations and then act on them if necessary.

Seed Crystals

Always set aside a small amount of the crude crystalline product to use as seeds for catalyzing the formation of crystals in the event that recrystallization does not occur. If no crystals appear in the cooled solution, it could mean that the solution is not saturated with your compound. But it could also mean that the solution is supersaturated and won't form crystals until an appropriate surface is present on which crystal growth can occur. Deciding which situation pertains can be difficult, but adding two or three small crystals of the compound will tell you.

Maximum Recovery of Product

Many students recover a smaller amount of product from a recrystallization than they should because of mechanical losses on the walls of oversized flasks or during the filtration step. Losses also occur because (1) too much solvent is added, (2) premature crystallization occurs during a gravity filtration, or (3) the crystals are filtered before recrystallization is complete.

Ensuring Dry Crystals

When a higher-boiling-point solvent, such as ethyl alcohol, water, or toluene, is used as the recrystallization solvent, the recrystallized product dries slowly and should be allowed to dry at least overnight before determining its mass and melting point. If water has been used as the recrystallization solvent, the drying procedure can be hastened by placing the crystals on a watch glass in a 50°C oven for 15–20 min. Solids recrystallized from organic solvents **should not be oven dried** because of the potential for a fire.

15.3 How to Select a Recrystallization Solvent

A recrystallization is straightforward if you are told what solvent to use and are given explicit directions about the ratio of solvent to solute. But when you have to determine these factors yourself, recrystallization is more challenging, especially if you use a mixed-solvent recrystallization. To be successful, you must consider the choices and then pay careful attention to your experimental observations and what they tell you. Use Table 15.1 and the background essay on intermolecular forces on page 99 to decide on suitable candidates for the recrystallization solvent. Begin by carefully selecting what seems to be a good recrystallization solvent using the following procedure.

Testing a Solvent

Careful measurements and observation are essential when testing potential solvents.

Place a small sample (20–30 mg) of the compound to be recrystallized in a test tube, and add 5–10 drops of a trial solvent. Shake the tube to mix the materials. If the compound dissolves immediately, it is probably too soluble in the solvent for recrystallization to be effective. If no solubility is observed, heat the solvent to its boiling point. If complete solubility is observed, cool the solution to induce crystallization. The formation of crystals in 10–20 min suggests that you have a good recrystallization solvent.

When you scale up a recrystallization from the test quantities, you need to be flexible enough to question your solvent choice if the recrystallization does not seem to be working. For example, if most of the crystals dissolve immediately in a small volume of solvent, you may have to boil away the solvent you are using and start again with a different solvent.

Two-Solvent Recrystallizations

When no single solvent seems to work for a recrystallization, a pair of ***miscible solvents***—solvents that are very soluble in one another—can often be used. Mixed-solvent pairs usually include one solvent in which a particular solute is very soluble and another in which its solubility is marginal to poor. Typical mixed-solvent pairs are listed in Table 15.2.

TABLE 15.2 Solvent pairs for mixed-solvent recrystallizations[a]

Solvent 1	Solvent 2	Solvent 1	Solvent 2
Ethanol	Acetone	Ethyl acetate	Hexane
Ethanol	Petroleum ether	Methanol	Diethyl ether
Ethanol	Water	Methanol	Water
Acetone	Water	Diethyl ether	Hexane (or petroleum ether)
Ethyl acetate	Cyclohexane		

a. Properties of these solvents are given in Table 15.1.

Record the exact amount of each solvent used for the tests.

Mixed-solvent tests. To select a suitable mixed-solvent pair, place 20–30 mg of the solute in a test tube and add 5–10 drops of the solvent in which you expect it to be more soluble. Warm the solution nearly to its boiling point. When the solid dissolves completely, add the other solvent drop by drop until a slight cloudiness appears and persists as mixing continues, indicating that the hot solution is saturated with the solute. If no cloudiness appears, the compound is too soluble in this solvent pair for an effective recrystallization and another solvent pair should be tested.

If you are working with less than 0.5 g of compound, the solid used for the tests can be recovered by evaporating the solvents.

If cloudiness appears, add the first solvent again in small portions until the cloudiness just disappears and then add a little more to ensure an excess. Let the solution cool slowly. The formation of crystals in 10–20 min suggests that you have found a good solvent pair.

Scaling up a mixed-solvent method. If one of the tests for a mixed solvent is more successful than those using a single solvent, scale it up for the recrystallization of your compound. Use approximately the same proportions of the two solvents in the scaled-up procedure as you used in the test.

In a mixed-solvent recrystallization the solute usually is dissolved in just enough of the solvent in which it is more soluble; then a small excess of that solvent (about 10%) is added to prevent premature crystallization. The second solvent, in which the solute is sparingly soluble, is added in small portions until the hot solution becomes cloudy, indicating the saturation point of the solute. Then a small amount of the first solvent is added until the cloudiness completely disappears and the solution is set aside to cool slowly.

If the solute is very soluble in the first solvent, the volume of solvent compared to the amount of sample may be so small that the crystals will separate as a pasty mass that is difficult to filter. In this situation, you need to use more of the first solvent than will just dissolve the solute and then add a correspondingly larger amount of the second solvent. However, avoid using so much of the first solvent that no amount of the second solvent will produce crystal formation. Should this situation occur, the solvents need to be partially evaporated before cooling again; if crystallization still does not occur, remove all the solvents and test another solvent pair. If the solid is more soluble in the solvent with the lower boiling point, any excess solvent can simply be boiled away in the hood until cloudiness is reached.

15.4 Miniscale Procedure for Recrystallizing a Solid

The procedure for recrystallizing a solid involves three main steps:

- Dissolving the solid and removing insoluble impurities
- Cooling the solution to allow for crystal growth
- Collecting the recrystallized solid by vacuum filtration

SAFETY PRECAUTIONS

1. Most organic solvents used for recrystallizations are volatile and flammable. Therefore, they should be heated on a steam bath or in a hot-water bath, not on a hot plate or with an open flame.
2. Lift a hot Erlenmeyer flask with flask tongs. **Note:** Test tube holders are not designed to hold an Erlenmeyer flask securely and the flask may fall onto the bench top.

If you are doing a mixed-solvent recrystallization, refer to the section on two-solvent recrystallizations in Technique 15.3.

Step 1. Dissolving the Solid

Always set aside a small amount of the crude crystals to use as seeds in the event that recrystallization does not occur.

Boiling a mixed solvent [see Technique 15.3] can preferentially remove the lower-boiling solvent and affect the solubility of the solute.

Place the solid to be recrystallized on a creased weighing paper and carefully pour it into an Erlenmeyer flask (Figure 15.2a). Alternatively, a plastic powder funnel may be set in the neck of the Erlenmeyer flask to prevent spillage (Figure 15.2b). Add one or two boiling stones or a boiling stick. Heat an appropriate volume of the solvent in another Erlenmeyer flask (see Figure 15.3). Then add small portions of hot (just below boiling) solvent to the solid being recrystallized. Begin heating the solid/solvent mixture, allowing it to boil briefly between additions, until the solid dissolves; then add some excess solvent. Remember that some impurities may be completely insoluble, so do not add too much solvent in trying to dissolve the last bit of solid.

With particularly volatile organic solvents, such as ether or hexane, it is often easier to add a small amount of cold solvent and then heat the mixture nearly to boiling. Slowly add more cold solvent to the heated mixture until the solid just dissolves when the solution is boiling; then add a small excess of solvent.

If you have no insoluble material or highly colored impurities in your hot recrystallization solution, cool the solution as described in step 2.

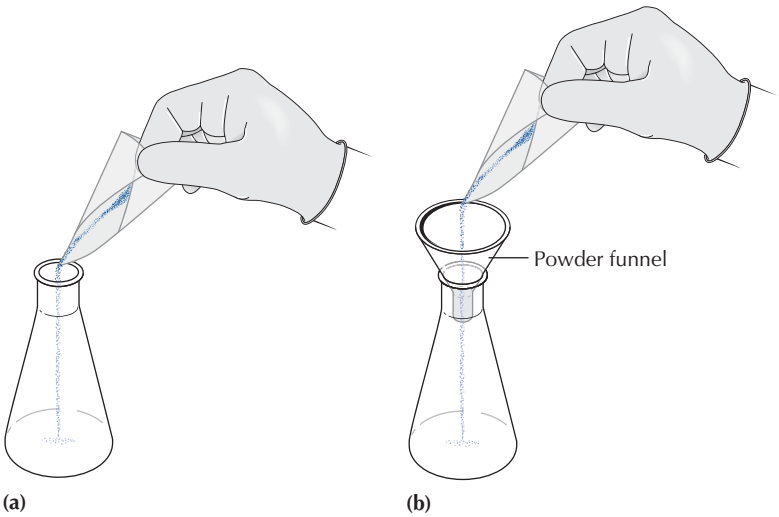


FIGURE 15.2
Two ways to add a solid to an Erlenmeyer flask for recrystallization.

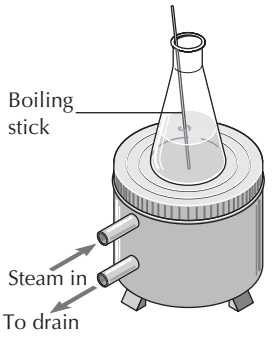


FIGURE 15.3
Heating a solution on a steam bath.

If you have **insoluble material or colored impurities** in the hot recrystallization solution, they need to be removed before cooling the solution. Carry out the procedure described in Technique 10.2 for filtering insoluble material or treating hot solutions with charcoal to remove colored impurities.

Step 2. Cooling the Solution

The size and purity of the crystals obtained will depend on the rate at which the solution cools: the slower the cooling, the larger the crystals. Cork the Erlenmeyer flask while the solution cools. Allow the hot solution to stand on the bench top until crystal formation begins and the flask reaches room temperature. Occasionally, it may take 30 min or more before crystals appear. This slow cooling usually produces crystals of a reasonable purity and intermediate size. The cooling process will take at least 20 min. Once crystal growth appears to be complete, cool the solution for 10–15 min in an ice-water bath before recovering the crystals from the solution as described in step 3.

What to do if no crystals appear in the cooled solution. If no crystals appear in the solution after at least 15 min of cooling in an ice-water bath, add one or two seed crystals. If you do not have any seed crystals, scratch the bottom of the flask vigorously with a glass stirring rod. Tiny particles of glass scratched from the flask can initiate crystallization. If crystallization still does not occur, there is probably too much solvent. Boil off a small portion of the solvent in the hood and cool the solution again.

Careful attention to detail and slow cooling of the hot solution often result in the formation of beautiful, pure crystals. Beautiful crystals are to an organic chemist what a home run is to a baseball player!

Step 3. Collecting the Recrystallized Solid

To recover the recrystallized solid after crystallization appears to be complete, collect the solid by vacuum filtration [see Technique 10.4], using a Buchner funnel, neoprene adapter, filter flask, heavy-walled rubber tubing, and trap bottle or flask (Figure 15.4). The trap flask avoids backflow of water from a water aspirator coming into contact with your remaining recrystallization solution; with a house

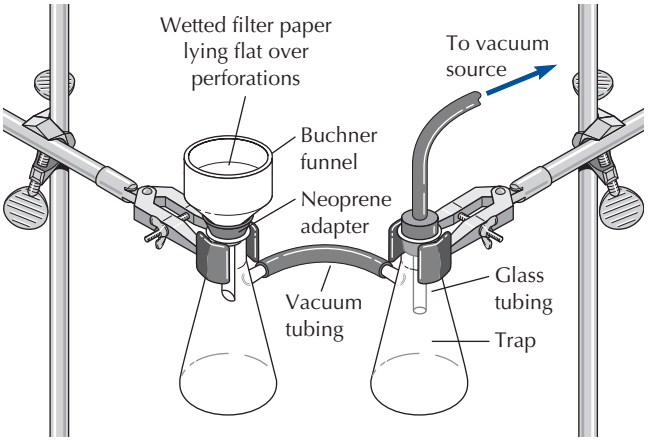


FIGURE 15.4
Apparatus for vacuum filtration. The second filter flask serves as a backflow trap.

vacuum system or vacuum pump, the trap flask keeps any overflow from the filter flask out of the vacuum line.

Choose the correct type and size of filter paper [see Technique 10.1], one that will fit flat on the bottom of the Buchner funnel and just cover all the holes. Turn on the vacuum source and wet the paper with the recrystallizing solvent to pull it tightly over the holes in the funnel. Pour a slurry of crystals and solvent into the funnel.

Wash the crystals on the Buchner funnel with a small amount of cold recrystallization solvent (1–5 mL, depending on the amount of crystals) to remove any supernatant liquid adhering to them. To wash the crystals, allow air to enter the filtration system by removing the rubber tubing from the water aspirator nipple or vacuum system. Then turn off the water (to prevent backup of water into the system), or turn off the vacuum line. Loosen the neoprene adapter connecting the Buchner funnel to the filter flask. Cover the crystals with the cold solvent, reconnect the vacuum, and draw the liquid off the crystals. Initiate the crystal drying process by pulling air through the crystals for a few minutes. Again disconnect the vacuum as described earlier. Place the crystals on a ***tared (preweighed)*** watch glass. You will probably need to leave the crystals open to the air in your desk for a time to dry them completely. Remove any boiling stones or sticks before you weigh the crystals.

A Second Crop of Crystals

A second "crop" of crystals can sometimes be obtained by evaporating about half the solvent from the filtrate and again cooling the solution. This crop of crystals should be kept separate from the first crop of crystals until the melting points of both crops [see Technique 14.3] have been determined. If the two melting points are the same, indicating that the purity is the same, the crops may be combined. Usually the second crop has a slightly lower melting point and a larger melting range, indicating that some impurities crystallized with the desired product.

15.5 Summary of the Miniscale Recrystallization Procedure

1. Dissolve the solid sample in a minimum volume of hot solvent with a boiling stone or boiling stick present.
2. If the color of the solution reveals impurities, add a small number of Norit carbon-decolorizing pellets to the hot but not boiling solution. If insoluble impurities are present or charcoal treatment is used, gravity filter the hot solution through a fluted filter paper.
3. Cool the solution slowly to room temperature and then in an ice-water bath to induce crystallization.
4. Recover the crystals from the cooled recrystallization mixture by vacuum filtration.
5. Wash the crystals with a small amount of cold solvent.
6. Allow the crystals to air-dry completely on a watch glass before weighing them and determining their melting point.

15.6 Microscale Recrystallization

Read Techniques 15.1 and 15.2 before you undertake your first microscale recrystallization.

Always save a few crude crystals to use as seeds in the event that recrystallization does not occur.

Microscale methods are used for recrystallizations of less than 300 mg of solid. If you are doing a mixed-solvent recrystallization, also refer to the section on two-solvent recrystallizations in Technique 15.3.

In a microscale recrystallization, a 10- or 25-mL Erlenmeyer flask holds the recrystallization solution and a Hirsch funnel replaces the Buchner funnel for collecting the crystals. If the amount of solid being recrystallized is less than 150 mg, a 10-mL Erlenmeyer flask or a test tube can be used. The following steps outline the procedure for a microscale recrystallization.

Step 1. Dissolving the Solid and Removing Insoluble Impurities

Place the solid in a 25-mL or 10-mL Erlenmeyer flask or a test tube, depending on the mass of crude product to be recrystallized; add a boiling stick or boiling stone. With a Pasteur pipet, add only enough solvent to just cover the crystals. Use a hot-water or steam bath to heat the contents of the flask or test tube to the boiling point, then add additional solvent drop by drop, allowing the mixture to boil briefly after each addition. Continue this process until just enough solvent has been added to dissolve the solid. Be aware that some impurities may not dissolve.

Colored impurities. If colored impurities are present, cool the mixture slightly and add 10 mg of Norit carbon-decolorizing pellets (about 10 pellets). Keep the mixture heated to just under the boiling point. If the color is not removed after 1–2 min, add a few more Norit pellets and heat briefly. Prepare a Pasteur filter-tip pipet [see Technique 5.3, Figure 5.9]. Warm the Pasteur pipet by immersing it in a test tube of hot solvent and drawing the hot solvent into it

several times. Then use the heated pipet to separate the hot recrystallization solution from the Norit pellets and transfer it to another test tube or flask. If crystallization begins in the solution with the carbon pellets during this process, add a few more drops of solvent and warm the mixture to boiling to redissolve the crystals before completing the transfer.

Insoluble impurities. If the recrystallization mixture contains insoluble impurities, use a Pasteur filter-tip pipet as outlined in step 3 to separate the solution from the insoluble impurities.

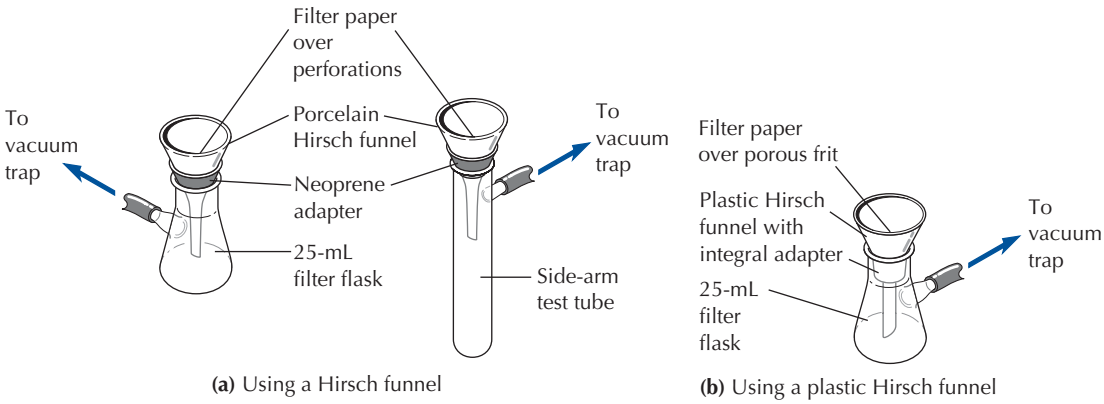
Step 2. Cooling the Solution

The size of the crystals obtained will depend on the rate at which the solution cools: the slower the cooling, the larger and purer the crystals. Slow cooling usually produces crystals of a reasonable purity and intermediate size. To facilitate slow cooling, set the flask on a paper towel and cover the flask with a beaker; if the recrystallization was done in a test tube, place the test tube in an Erlenmeyer flask for the cooling period. Allow the solution to cool slowly to room temperature. The recrystallization process may take 20 min or more. Then chill the container in an ice-water bath to complete the crystallization process.

Step 3. Collecting the Recrystallized Solid

Assemble a filtration apparatus as shown in Figure 15.5a or b, using heavy-walled rubber tubing. Choose the correct size of filter paper—a size that fits flat on the Hirsch funnel and just covers the holes of the porcelain Hirsch funnel or the frit of the plastic Hirsch funnel. Clamp the filter flask firmly at the neck to a ring stand or apparatus rack. Connect the filter flask to a vacuum trap as shown in Figure 15.4. Turn on the vacuum source and wet the paper with a few drops of the recrystallization solvent to pull it tightly to the funnel. Pour a slurry of crystals and solvent into the funnel.

Wash the crystals on the Hirsch funnel with a few drops of cold recrystallization solvent to remove any supernatant liquid adhering



(a) Using a Hirsch funnel

(b) Using a plastic Hirsch funnel

FIGURE 15.5 Vacuum filtration using a Hirsch funnel.

to them. To wash the crystals, allow air to enter the filtration system by removing the rubber tubing from the water aspirator nipple or vacuum line. Then turn off the water (to prevent backup of water into the system), or turn off the vacuum line and carefully loosen the neoprene adapter (or the plastic Hirsch funnel) from the filter flask. Add cold solvent one drop at a time to just cover the crystals, reconnect the vacuum, and draw the liquid off the crystals. Initiate the crystal drying process by pulling air through the crystals for a few minutes. Again disconnect the vacuum as described earlier.

Place the crystals on a ***tared (preweighed)*** watch glass. Allow the crystals to air-dry completely on the watch glass before weighing them and determining their melting point. Remove any boiling stones before you weigh the crystals.

15.7 Summary of Microscale Recrystallization Procedure

1. Dissolve the solid in a minimum volume of hot solvent in a 10- or 25-mL Erlenmeyer flask or a test tube; use a boiling stick or boiling chip to prevent bumping.
2. If colored impurities are present, heat the mixture briefly with 8–10 Norit pellets.
3. If insoluble impurities are present or Norit pellets were used, transfer the hot recrystallization solution to another test tube or flask, using a warm Pasteur filter-tip pipet.
4. Cool the solution slowly to room temperature to induce crystallization; then complete the cooling in an ice-water bath.
5. Collect the crystals by vacuum filtration on a Hirsch funnel.
6. Allow the crystals to air-dry completely on a watch glass before weighing them.

15.8 Sources of Confusion

It is worthwhile to recall Technique 15.2, which discusses the importance of scale, volume of solvent, insoluble impurities, the use of seed crystals, maximum recovery factors, and ensuring dry crystals. Technique 15.3 pointed out the need for flexibility in doing a recrystallization and the need to make good observations, form hypotheses from them, and be willing to test the hypotheses.

Did I Use the Proper Recrystallization Solvent?

Probably the most confusing part of recrystallization is deciding how to choose the most effective recrystallization solvent by the methods of Technique 15.3. This is the stage where careful observations and thoughtful analysis of your experimental results can save a great deal of time in the long run. If loss of the crystals that you use for the solubility tests must be minimized, you can recover them by evaporation of the solvents.

How Much Solvent Should I Use?

The answer to this question depends on the solubilities of the compound in the hot and cold solvent and the amount of material being recrystallized. General recrystallization guidelines are always somewhat ambiguous because they cannot be applied in a straightforward manner for every one of the many thousands of organic compounds you might be recrystallizing.

A recrystallization is usually started with only enough solvent to cover the crystals in the recrystallization flask. After heating the solvent to boiling in a separate flask, it is added in small increments, 1–5 mL for miniscale recrystallizations and a few drops for microscale recrystallizations. Reheat the recrystallization flask after adding **each** solvent increment. Add only enough solvent to just dissolve the crystals when the solvent is boiling, plus another increment to provide a modest excess of solvent.

I Added Solvent but the Volume Did Not Change

If the rate of heating is too rapid, solvent may be evaporating from the recrystallization flask as fast as you are adding it. Evaporation is a particular problem when working with a mixed-solvent recrystallization. Rapid heating in this instance probably results in preferential loss of the lower-boiling solvent. The rate of heating should be at a setting that just maintains the solvent at its boiling point.

No Crystallization Occurred in the Cooled Solution

In many instances, recrystallization fails because too much solvent is used in the process. In these cases, you need to boil off a portion of the solvent and try the recrystallization again. If crystallization still does not occur from the supersaturated solution, the best approach is to add one or two seed crystals. If you do not have a few seed crystals available, it may be possible to promote crystal formation by scratching the inside of the bottom of the flask vigorously with a glass stirring rod. Tiny particles of glass scratched from the flask can serve as centers for crystallization.

Formation of Oils

The formation of oils may be the most frustrating outcome of an attempted recrystallization. The presence of impurities lowers the melting point, making "oiling out" especially prevalent during recrystallization of a solute with a melting point near the boiling point of the solvent. Oiling out also occurs if too little recrystallization solvent has been used so that the compound becomes insoluble at too high a temperature. The presence of an insoluble oil allows impurities to distribute themselves between the solvent and the oil before crystallization can occur. This means that impurities are trapped in the oil when it cools; it often hardens into a viscous, glasslike substance.

If you have an oil rather than crystals, you can add more solvent so that the compound does not come out of solution at so high a temperature. It may also help to switch to a solvent with a lower boiling point (consult Table 15.1).

Some oils can be crystallized by dissolving them in a small amount of diethyl ether or hexane and allowing the solvent to

evaporate slowly in a hood. Crystallization often occurs as the solution slowly becomes more concentrated. Once crystals form, seed crystals are available to assist further purification.

Questions

1. Describe the characteristics of a good recrystallization solvent.
2. The solubility of a compound is 59 g per 100 mL in boiling methanol and 30 g per 100 mL in cold methanol, whereas its solubility in water is 7.2 g per 100 mL at 95°C and 0.22 g per 100 mL at 2°C. Which solvent would be better for recrystallization of the compound? Explain.
3. Explain how the rate of crystal growth can affect the purity of a recrystallized compound.
4. In what circumstances is it necessary to filter a hot recrystallization solution?
5. Why should a hot recrystallization solution be filtered by gravity rather than by vacuum filtration?
6. Low-melting solids often "oil out" of a recrystallization solution rather than crystallizing. If this were to happen, how would you change the recrystallization procedure to ensure good crystals?
7. An organic compound is quite polar and is thus much more soluble in methanol than in pentane (bp 36°C). Why would methanol and pentane be an awkward solvent pair for recrystallization? Consult Table 15.1 to assist you in deciding how to change the solvent pair so that recrystallization would proceed smoothly.

TECHNIQUE

16 SPECIALIZED TECHNIQUES

This chapter contains four important techniques that are not commonly used in the introductory organic chemistry laboratory but that may be needed in specialized situations.

- ***Sublimation*** is used for the purification of solids that have exceptionally high vapor pressures and high melting points. Sublimation converts solids directly into the gas phase.
- ***Refractometry*** is the measurement of the refractive index of a liquid for evaluating its purity or for determining the composition of a solution. Measurement of the refractive index is a simple, inexpensive technique, which can be very useful in some situations.
- ***Polarimetry*** has been of great importance in the development of structural organic chemistry. However, specialized modern polarimeters that can accurately measure the optical activity of small samples are expensive.
- ***Inert atmosphere reaction setups*** are increasingly important in modern organic synthesis.

SUBLIMATION

Before most solid organic compounds evaporate, they melt, a process that usually requires a reasonably high temperature. However, some substances, such as iodine, camphor, and 1,4-dichlorobenzene (mothballs), exhibit appreciable vapor pressure below their melting points. You may already have seen iodine crystals evaporate to a purple gas during gentle heating and smelled the characteristic odors of camphor or mothballs. These substances all change directly from the solid phase to the gas phase without forming an intermediate liquid phase by a process called ***sublimation.***

The process of sublimation seems somewhat unusual in that, unlike normal phase changes from solid to liquid to gas, no liquid phase forms between the solid and gas phases. The conversion of the solid form of carbon dioxide (also called *dry ice*) directly into CO_2 gas may be the best-known example of sublimation. Carbon dioxide does not have a melting point at atmospheric pressure. The sublimation point for CO_2 at atmospheric pressure is $-78°C$, well below room temperature. More than 5 atm of pressure must be used to produce liquid CO_2.

Purification by Sublimation

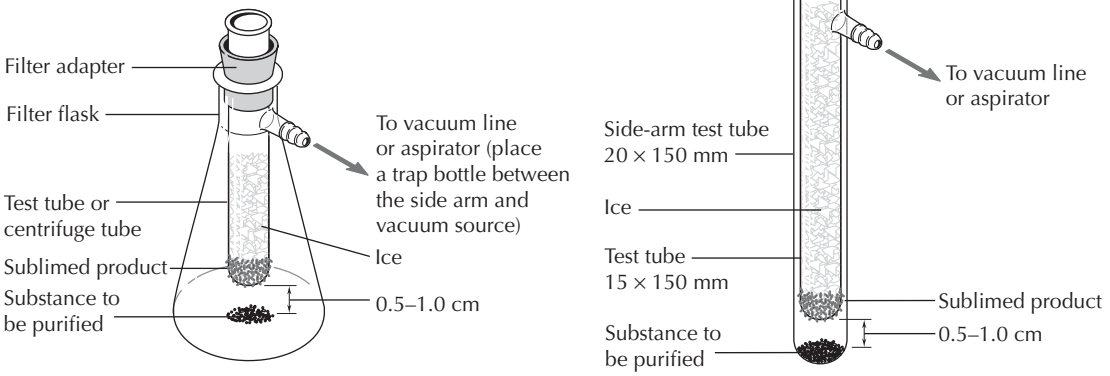
In the laboratory sublimation is used as a purification method for an organic compound (1) if it can vaporize without melting, (2) if it is stable enough to vaporize without decomposition, (3) if the vapor can be condensed back to the solid, and (4) if the impurities present do not also sublime. Many organic compounds that do not sublime at atmospheric pressure sublime appreciably at reduced pressure, thus enabling their purification by sublimation. Use of reduced pressure, supplied by a vacuum source, also makes decomposition and melting less likely to occur during the sublimation.

16.1 Assembling the Apparatus for a Sublimation

The apparatus for a sublimation consists of an outer vessel and an inner vessel. The outer vessel holds the sample being purified and is connected to a vacuum source. An inner container, sometimes called a "cold finger," provides a cold surface on which the vaporized compound can recondense as a solid.

Two simple arrangements for sublimation under reduced pressure are shown in Figure 16.1. The inner test tube, which contains cold water or ice and water, serves as a condensation site for the sublimed solid. The outer vessel, a side-arm test tube or a filter flask, holds the substance being purified, and the side arm provides a connection to the vacuum source. The inner and outer vessels are sealed together by a neoprene filter adapter. The distance between the bottom surfaces of the inner tube and the outer tube or filter flask should be 0.5–1.0 cm.

If the vapor has to travel a long distance, a higher temperature is needed to keep it in the gas phase, and decomposition of the solid



(a) Microscale or macroscale apparatus, depending on the sizes of the flask and the test tube

(b) Microscale apparatus

FIGURE 16.1 Two simple apparatuses for sublimation.

sample may very well occur. If the surfaces are too close, impurities can spatter and contaminate the condensed solid on the surface of the inner tube. Connect the side arm of the test tube or filter flask to a water aspirator or vacuum line with heavy-walled rubber tubing, using a trap bottle or flask between the aspirator and the sublimation apparatus.

The side-arm test tube apparatus serves well for 10−150 mg of material. The filter flask apparatus can be sized to suit the amount of material being purified. For example, microscale quantities of 10−150 mg can be sublimed in a 25-mL filter flask, whereas 1 g of material would require a 125-mL filter flask with a correspondingly larger test tube for the cold finger.

16.2 Carrying Out a Sublimation

SAFETY PRECAUTION

The lip of the inner test tube must be large enough to prevent it from being pushed through the bottom of the filter adapter by the difference in pressure created by the vacuum. Slippage of the inner test tube could cause both vessels to shatter as the inner test tube hits the outer test tube or flask. Placing a microclamp on the inner test tube above the filter adapter helps keep the test tube from moving once it is positioned in the filter adapter.

Place the sample (10–150 mg) to be sublimed in a 25-mL filter flask or a side-arm test tube. Fit the inner test tube through the filter adapter and adjust the position of the inner tube so that it is 0.5–1.0 cm above the bottom of the flask or side-arm test tube. Turn on the water aspirator or vacuum line. After a good vacuum has been

*Ice and water are placed in the inner test tube **after** the vacuum is applied to prevent condensation of moisture from the air on the tube before sublimation takes place.*

achieved, fill the inner test tube with ice and water, then proceed to heat the sublimation vessel gently using a sand bath [see Technique 6.2]. If a filter flask (25 mL for 10–150 mg, 125 mL for 0.25–1.0 g) is used as the outer container, heat it gently on a hot plate or with a sand bath.

During sublimation, you will notice material disappearing from the bottom of the outer vessel and reappearing on the cool outside surface of the inner test tube. If the sample begins to melt, briefly withdraw the heat source from the apparatus. If all the ice melts, remove half the water from the inner test tube with a Pasteur pipet and then add additional ice.

After sublimation is complete, remove the heat source and slowly let air back into the system by gradually removing the rubber tubing from the water aspirator or other vacuum source. Then turn off the water flow in the aspirator or turn off the vacuum source and slowly disconnect the rubber tubing from the side arm of the filter flask or test tube. Carefully remove the inner test tube and scrape the purified solid onto a tared weighing paper. After weighing the sublimed solid, store it in a tightly closed vial.

REFRACTOMETRY

A beam of light traveling from a gas into a liquid undergoes a decrease in its velocity. If the light strikes the horizontal interface between gas and liquid at an angle other than 90°, the beam bends downward as it passes from the gas into the liquid. Application of this phenomenon allows the determination of a physical property known as the ***refractive index,*** a measure of how much the light is bent, or ***refracted,*** as it enters the liquid. The refractive index can be determined quite accurately to four decimal places, making this physical property useful for assessing the purity of liquid compounds. The closer the experimental value approaches the value reported in the literature, the purer the sample. Even trace amounts of impurities (including water) change the refractive index, so unless the compound has been extensively purified, the experimentally determined value may not agree with the literature value past the second decimal place.

The refractive index, ***n***, represents the ratio of the velocity of light in a vacuum (or in air) to the velocity of light in the liquid being studied. The variables of temperature and the wavelength of the light being refracted influence the refractive index for any substance. The temperature of the sample affects its density. A density change, in turn, affects the velocity of the light beam as it passes through the sample. Therefore, the temperature (20°C in the following example) at which the refractive index was determined is always specified by a superscript in the notation of n:

$$n_D^{20} = 1.3910$$

The wavelength of light used also affects the refractive index because light of differing wavelengths refracts at different angles.

The two bright yellow, closely spaced lines of the sodium spectrum at 589 and 589.6 nm, commonly called the ***sodium D line,*** usually serves as the standard wavelength for refractive index measurements and is indicated by the subscript D on the symbol *n*. If light of some other wavelength is used, the specific wavelength in nanometers appears as the subscript.

16.3 The Refractometer

The instrument used to measure the refractive index of a compound is called a ***refractometer*** (Figure 16.2). This instrument includes a built-in thermometer for measuring the temperature at the time of the refractive index reading, as well as a system for circulating water at a constant temperature around the sample holder. This type of refractometer uses a white light source instead of a sodium lamp and contains a series of compensating prisms that give a refractive index equal to that obtained with 589-nm light (the D line of sodium).

When the upper part of the hinged prism is lifted and tilted back, a few drops of sample can be placed on the lower prism. After the upper part of the hinged prism is set back on the lower prism, the light passes through the sample and is reflected by an adjustable mirror. When the mirror is properly aligned, the light is reflected

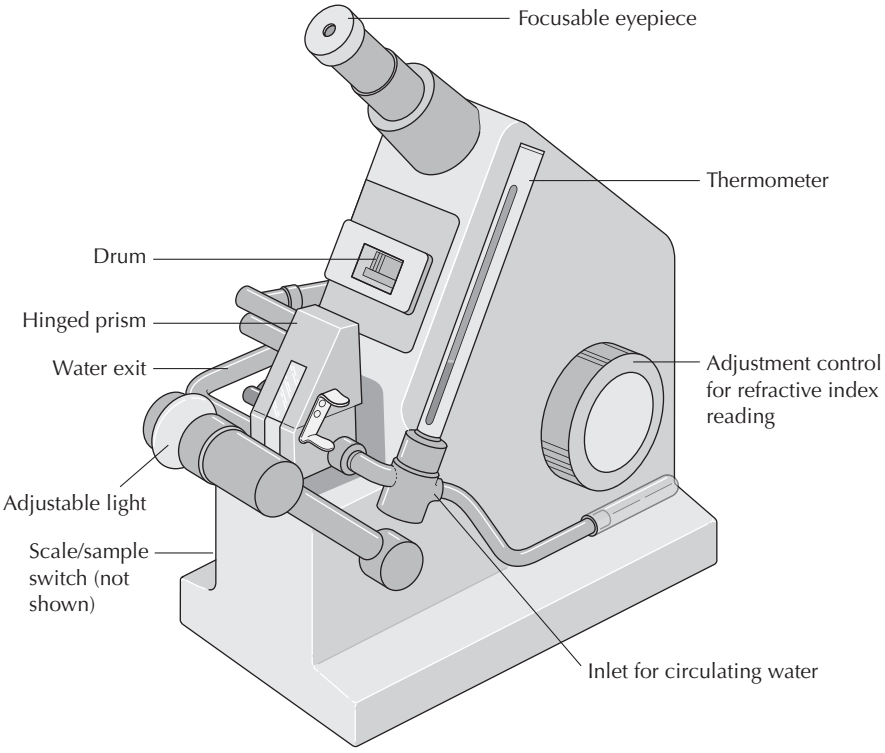


FIGURE 16.2 Abbé-3L refractometer.

through the compensating prisms and finally through a lens with crosshairs to the eyepiece.

16.4 Determining a Refractive Index

The sample used for a refractive index measurement needs to be free of water and other contaminants. Four or five drops of liquid are needed for a measurement. The temperature at which the refractive index is measured needs to be recorded and a temperature correction applied to the experimental value before comparing it with a reported value.

Steps in Determining a Refractive Index

Do not use acetone to clean the refractometer prisms because it can dissolve the adhesive holding them in place.

The following directions apply to the use of a refractometer such as the one shown in Figure 16.2. Consult your instructor about using an automated refractometer if your laboratory has one.

1. Check the surface of the prisms for residues from previous determinations. If the prisms need cleaning, place a few drops of methanol on the surfaces and blot (do not rub) the surfaces with lens paper. Allow the residual methanol to evaporate completely.
2. With a Pasteur pipet held 1–2 cm above the prism, place 4–5 drops of the sample on the measuring (lower) prism. Do not touch the prism with the tip of the pipet because the highly polished surface can scratch very easily, and scratches ruin the instrument. Lower the illuminating (upper) prism carefully so that the liquid spreads evenly between the prisms.
3. Rotate the adjustment control until the dark and light fields are exactly centered on the intersection of the crosshairs in the eyepiece (Figure 16.3). If color (usually red or blue) appears as a horizontal band at the interface of the fields, rotate the chromatic adjustment drum or dispersion correction wheel until the interface is sharp and uncolored (achromatic). Occasionally the sample evaporates from the prisms, making it impossible to produce a sharp, achromatic interface between the light and dark fields. If evaporation occurs, apply more sample to the prism and repeat the adjustment procedure.
4. Press the read display button and record the refractive index in your notebook. Then record the temperature.
5. Open the prisms, blot up the sample with lens paper, and follow the cleaning procedure with methanol outlined in step 1.

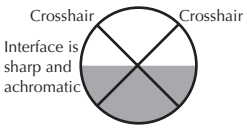


FIGURE 16.3
View through the eyepiece when the refractometer is adjusted correctly.

Temperature Correction

Values reported in the literature are often determined at a number of different temperatures, although 20°C has become the standard. To compare an experimental refractive index with a value reported at a different temperature, a correction factor must first be calculated. The refractive index for a typical organic compound decreases by 4.5×10^{-4} for each 1° increase in temperature. Refractive index values vary inversely with temperature because the density of a liquid almost always decreases as the temperature increases. This decrease in density produces an increase in the velocity of light in the liquid, causing a corresponding decrease in the refractive index at higher temperatures.

To compare an experimental refractive index measured at 25°C to a reported value at 20°C, a temperature correction needs to be calculated:

$$\Delta n = 4.5 \times 10^{-4} \times (T_1 - T_2)$$

where T_1 is the observation temperature in degrees Celsius and T_2 is the temperature reported in the literature in degrees Celsius.

The correction factor, including its sign, is then added to the experimentally determined refractive index. For example, if your experimental refractive index is 1.3888 at 25°C, then you obtain a corrected value at 20°C of 1.3911 by adding the correction factor of 0.0023 to the experimental refractive index.

$$\Delta n = [4.5 \times 10^{-4} \times (25 - 20)] = 0.00225 \text{ (round to } 0.0023)$$

$$n^{20} = n^{25} + 0.0023 = 1.3888 + 0.0023 = 1.3911$$

The correction needs to be applied before comparing the experimental value to a literature value reported at 20°C. If an experimental refractive index is determined at a temperature lower than that of the literature value to which it is being compared, the correction has a negative sign and the corrected refractive index is lower than the experimental value.

Unless a compound has been extensively purified, you may not be able to reproduce the last two decimal places of a refractive index given in a handbook. It is not uncommon that a 1% impurity can change the refractive index of an organic liquid by 0.0010.

OPTICAL ACTIVITY AND ENANTIOMERIC ANALYSIS

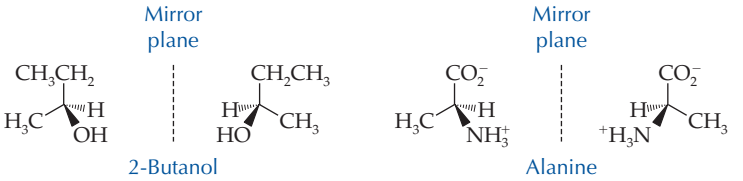
Optical activity, the ability of substances to rotate plane-polarized light, played a crucial role in the development of chemistry as the link between the molecular structures chemists write and the real physical world. A major development in the structural theory of chemistry was the concept of the three-dimensional shape of molecules. When Jacobus van't Hoff and Joseph le Bel noted the asymmetry possible in tetrasubstituted carbon compounds, they claimed that their "chemical structures" were identical to the "physical structures" of the molecules. Not only was the structural theory of the organic chemist useful in explaining the facts of chemistry, it also happened to be "true." Van't Hoff and le Bel could make this claim because their theories of the tetrahedral carbon atom accounted not only for chemical properties but also for the physical property of optical activity.

16.5 Mixtures of Optical Isomers: Separation/Resolution

A molecule that possesses no internal mirror plane of symmetry and that is not superimposable on its mirror image is said to be chiral, or "handed." ***Chirality,*** a molecular property, is normally indicated by

the presence of a ***stereocenter***—a tetrahedral atom bearing four different substituents. A stereocenter is sometimes called a ***chiral*** or ***asymmetric center.***

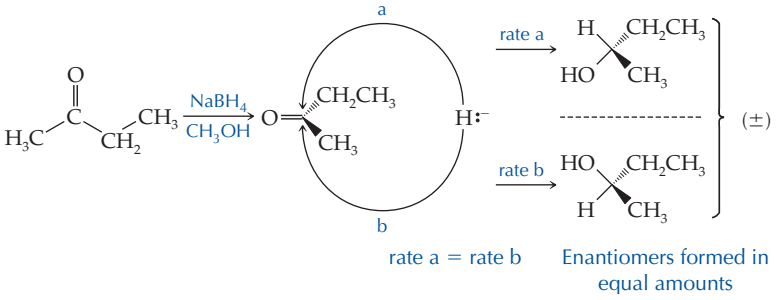
Chiral compounds possess the property of enantiomerism. ***Enantiomers*** are stereoisomers that have ***nonsuperimposable mirror images.*** Chiral compounds such as 2-butanol and the amino acid alanine, which contain only one stereocenter, are simple examples of enantiomers.



Enantiomers and Racemic Mixtures

The enantiomers of 2-butanol have identical physical properties, including boiling points, IR spectra, NMR spectra, refractive indices, and TLC R_f values, except for the direction in which they rotate plane-polarized light. Both enantiomers are optically active—one of them rotates polarized light in a clockwise direction and is called the ***(+)-isomer.*** The other enantiomer rotates polarized light counterclockwise and is called the ***(−)-isomer.*** The rotational power of (+)-2-butanol is exactly the same in the clockwise direction as that of (−)-2-butanol in the counterclockwise direction. Unfortunately, there is no simple theoretical way to predict the direction of the rotation of plane-polarized light on the basis of the configuration at a carbon stereocenter. Thus, it is not apparent which structure of 2-butanol or alanine is the (+)- or the (−)-enantiomer.

Usually, simple compounds obtained from the stockroom are optically inactive, even when their molecules are chiral. For example, you would normally find that a sample of 2-butanol is optically inactive. To understand this apparent paradox, consider the reduction of 2-butanone with sodium borohydride. This reaction can proceed in two ways. Hydride can react with 2-butanone from either the top side or the bottom side of the carbonyl double bond. The reaction occurs both ways at equal rates, giving rise to a 50:50 mixture of the enantiomers of 2-butanol—a product that is optically inactive:



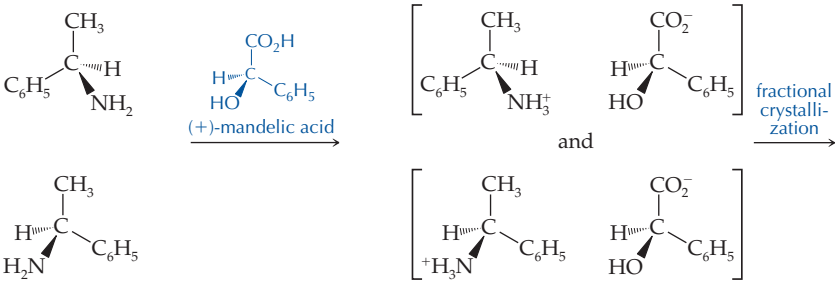
An equal mixture of (+)- and (−)-enantiomers is called a ***racemic mixture.*** In the separation or ***resolution*** of a racemic mixture, the

enantiomers are transformed into a pair of ***diastereomers***—stereoisomers that have different physical and chemical properties. A mixture of two diastereomers is prepared from a racemic mixture by its reaction with an optically active substance. The diastereomers can then be separated by recrystallization, for example, because of the differential solubility of the two diastereomers.

Resolution with Acids or Bases

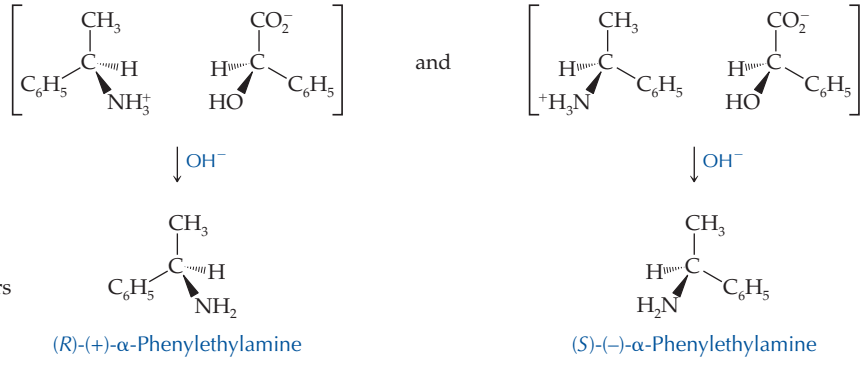
The simplest reaction for preparing diastereomers from racemic mixtures is that of an acid with a base to form a salt. For resolution or separation of the two enantiomers to occur, the added reagent in the acid/base reaction must be optically active. Reaction of a racemic amine, for example, with an optically active carboxylic acid is a method for resolving the amine. Similarly, reaction of a carboxylic acid with an optically active amine is a way of resolving the acid. Two different diastereomeric salts are produced in each of these reactions. These salts differ in their solubilities in various solvents and can be separated by fractional crystallization. The less soluble diastereomeric salt is the more easily obtained. The process for resolution of an amine with an optically active carboxylic acid is represented in the following reactions:

(a) Formation of diastereomeric salts from a racemic amine



(b) Separation of the diastereomeric salts produced by fractional crystallization

(c) Isolation of resolved enantiomers



If you examine the diastereomeric salts in (a) and (b), you will see that each salt has two stereocenters. When you compare their structures, you will find that the carbon stereocenters bearing the —OH group have the identical configuration in each salt, whereas the stereocenters bearing the $—NH_3^+$ group have opposite configurations. Thus the two salts are stereoisomers that are not mirror images; they are diastereomers.

TABLE 16.1 Optically active acids and bases used for resolutions

Bases	Acids
Brucine	Tartaric acid
Strychnine	Mandelic acid
Quinine	Malic acid
Cinchonine	Camphor-10-sulfonic acid
α-Phenylethylamine	

Optically active acids and bases, often isolated from plant materials, are frequently used for the resolution of racemic mixtures (Table 16.1). However, the diastereomers necessary for resolution do not need to be salts. For example, diastereomeric esters, formed by reaction of the enantiomers of an alcohol with an optically active carboxylic acid, can also be used.

Enzymatic Resolution

An increasingly useful method for the resolution of racemic mixtures utilizes an enzyme that selectively catalyzes the reaction of one enantiomer. Because all enzymes are chiral molecules, the transition states for the reaction of an enzyme with two enantiomers are diastereomeric and the energies of these two transition states differ. Thus one of the enantiomers reacts faster than the other one. In many cases an enzyme reacts so much faster with one enantiomer that the specificity provides an excellent method for resolving a racemic mixture. For example, one enantiomer of an ester in a racemic mixture can be selectively hydrolyzed to a carboxylic acid by an esterase, whereas the other enantiomer is untouched. It is a straightforward matter to separate the optically active carboxylic acid from the unreacted ester.

The synthesis of pharmaceuticals that are important to the success of modern medicine places great emphasis on the production of optically active drugs, which can be more effective and have fewer side effects than racemic drugs. Enzymes are particularly useful in making the optically active chiral precursors from which the drugs can be synthesized.

Resolution by Chiral Chromatography

Resolution of a racemic mixture can also be carried out using a chiral chromatographic separation, by either gas chromatography [see Technique 19] or liquid chromatography [see Technique 18]. When a mixture of enantiomers passes through a chiral chromatographic column, each enantiomer has a different attraction for the chiral stationary phase—differences that lead to separation of the enantiomers. Typical stationary phases that produce this effect are proteins or β-cyclodextrins, often immobilized by bonding to silica gel. The less tightly coordinated enantiomer passes through the column more rapidly than the enantiomer that is selectively retained by the chiral stationary phase.

16.6 Polarimetric Techniques

The traditional way to measure optical activity is with a polarimeter, a schematic description of which is shown in Figure 16.4. All commercially available polarimeters have the same general features. The analyzer of a simple polarimeter is adjusted manually, whereas all the components of an automated polarimeter are housed in the instrument case and produce a digital readout of the observed rotation.

How a Polarimeter Works

The light beam approaching the polarizer in Figure 16.4 has wave oscillations in all planes perpendicular to the direction in which the beam is traveling. When the light beam hits the polarizer, which has ranks and files of molecules arranged in a highly ordered fashion, only the light whose oscillations are in one plane is transmitted through the polarizer. The light that gets through is called ***plane-polarized light.*** The remaining waves are refracted away or absorbed by the polarizer. In a rough analogy, the light beam hits the polarizer, whose molecules are ordered like the slats of wood in a picket fence. Only the light waves whose oscillations are parallel to the slats pass through the polarizer and into the sample tube.

The analyzer is a second polarizer whose ranks and files of molecules must also be lined up for the polarized light waves to be transmitted. If the polarized light has been rotated by an optically active substance in the sample tube, the analyzer must be rotated the same amount to let the light through. The rotation is measured in degrees, indicated by α in Figure 16.4.

Use of Monochromatic Light

Monochromatic light is preferred in polarimetric measurements because the optical activity or rotatory power of chiral compounds depends on the wavelength of the light used. For example, the rotation of 431-nm (blue) light is 2.8 times greater than the rotation of 687-nm (red) light. A common light source is a sodium lamp, which has two very intense emission lines at 589 and 589.6 nm. This closely spaced doublet is called the ***sodium D line.*** A mercury lamp is another common light source; it uses the intense 546.1-nm emission line. The human eye is

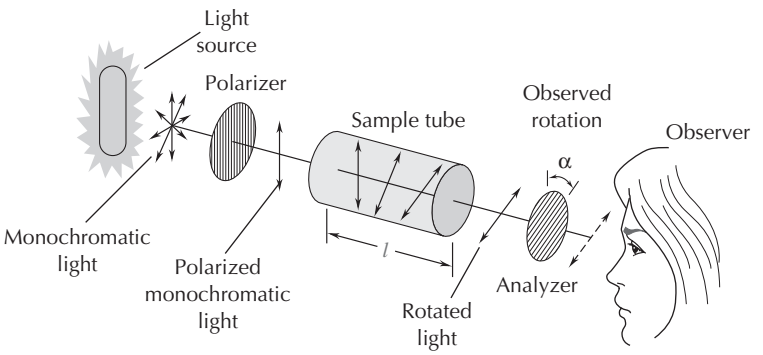


FIGURE 16.4 Schematic diagram of a polarimeter.

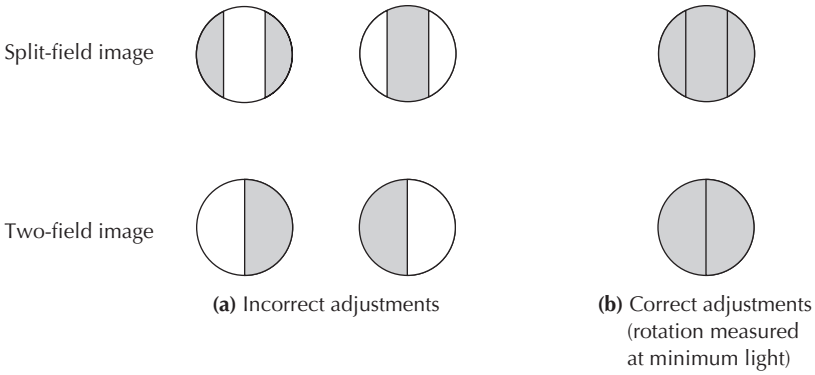


FIGURE 16.5 Representative images in the light field of a manual polarimeter.

more sensitive to the mercury emission in the green region than to the sodium line in the yellow region of the visible spectrum.

Reading a Manual Polarimeter

A number of techniques are used to detect the rotation of polarized light with a manual polarimeter. The simplest way is to rotate the analyzer until no light at all comes through the eyepiece. However, this method depends not only on the sensitivity of our eyes but also on our ability to remember quantitatively the amount of brightness we have just seen. In practice, this is difficult to do.

Various optical devices can be used to make the measurement of rotation easier. They depend on a sudden change of contrast when the minimum amount of light is transmitted by the analyzer. Manual polarimeters have a split-field image or two fields divided through the middle (Figure 16.5a). The analyzer is rotated in a clockwise or counterclockwise direction until a point is reached where every field is of equal minimum intensity and the divided fields are no longer visible (Figure 16.5b).

Using Polarimeter Tubes

Polarimeter tubes are expensive and must be handled carefully. They come in different lengths; 1-dm and 2-dm tubes are the most common. The periscope tube allows removal of any air bubbles from the light path that can be tedious to remedy when using a straight tube. The tubes shown in Figure 16.6 are closed with a glass plate and a rubber washer, both held in place by a one- or two-part screw cap. Be careful not to screw the cap too tightly, because strain in the glass end plate can produce an apparent optical rotation.

Cleaning a polarimeter tube. Unless the polarimeter tube is clean and dry, you should first clean the tube with some care. When the tube is clean, rinse it with the solvent you plan to use for the

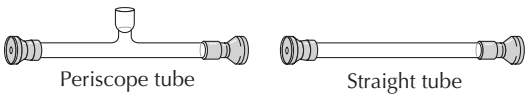


FIGURE 16.6 Polarimeter tubes.

solution of your optically active compound. After the tube has been well drained, rinse it with two or three small portions of your solution to ensure that the concentration of the solution in the polarimeter tube is the same as the concentration of the solution you have prepared. You may want to save these optically active rinses, because your chiral compound can be recovered from them later.

Air bubbles and suspended particles. When you fill a polarimeter tube with a solution, make sure that the tube has no air bubbles trapped in it; bubbles will refract the light coming through. Also make sure that there are no suspended particles in a solution whose rotation you wish to measure, or you may get so little transmitted light that measurement of the rotation will be very difficult. If you have a solution that you suspect may be too turbid for polarimetry measurements, filter it through a micropore filter using a syringe or by gravity through a small plug of glass wool [see Technique 10.1].

Standardizing the polarimeter. A polarimeter can be standardized by filling a tube with an optically inactive solvent such as distilled water or with the solvent being used for your sample. Adjust the instrument to the minimum-light position (see Figure 16.5).

If you are using a manual polarimeter, check your ability to use it properly by analysing a 5.00% or 10.00% solution of sucrose in water. Determine the specific rotation of your sample based on the average of five to seven readings of the optical rotation. Automatic polarimeters normally do not require multiple determinations of the experimental rotation. Consult your instructor about the operation of the polarimeter in your laboratory.

16.7 Analyzing Polarimetric Readings

Specific Rotation

The magnitude of the optical rotation depends on the concentration of the optically active compound in the solution, the length of the light path through the solution, the wavelength of the light, the nature of the solvent, and the temperature. A typical rotation of common table sugar (sucrose) is written in the following manner:

$$[\alpha]_D^{20} = +66.4°(H_2O)$$

The symbol $[\alpha]_\lambda^{T°}$ is called the ***specific rotation*** and is an inherent property of a pure optically active compound. T° signifies the temperature of the measurement in degrees Celsius, and λ is the wavelength of light used. In the sucrose example, the sodium D line was used. The specific rotation is calculated from the observed angle of rotation:

$$[\alpha]_\lambda^{T°} = \frac{\alpha}{l \cdot c}$$

where α is the observed angle of rotation, l is the length of the light path through the sample in decimeters, and c is the concentration of the sample ($g \cdot mL^{-1}$).

The cell length is always given in decimeters (dm, 10^{-1} m) in the calculation of specific rotation. When a pure, optically active liquid is used as the sample, its concentration is simply the density of the liquid.

Sometimes a rotation of an optically active substance is given as a ***molecular rotation:***

$$[M]_{\lambda}^{T^\circ} = \frac{M}{100}[\alpha]$$

where M is the molecular weight of the optically active compound.

The value of the specific rotation can change considerably from solvent to solvent. It is even possible for an enantiomer to have a different sign of rotation in two different solvents. Such solvent effects are due to specific solvent/solute interactions. The four most common solvents for polarimetry are water, methanol, ethanol, and chloroform.

The intrinsic specific rotation of a compound is generally considered to be a constant in dilute solutions at a particular temperature and wavelength. However, if you wish to compare the optical activity of a sample with that obtained by other workers, you should use the same concentration in the same solvent. Sucrose makes an excellent reference compound for polarimetry because its intrinsic specific rotation in water is essentially independent of concentration up to 5−10% solutions.

A change in the specific rotation due to temperature variation may be caused by a number of factors, including changes in molecular association, dipole-dipole interactions, conformation, and solvation. When nonpolar solutes are dissolved in nonpolar solvents, variation in the specific rotation with temperature may not be large. But for some polar compounds, the specific rotation varies markedly with temperature. Near room temperature, the specific rotation of tartaric acid may vary by more than 10% per degree Celsius.

Enantiomeric Excess

The purity of optically active compounds is reported in terms of enantiomeric excess. ***Enantiomeric excess (% ee)*** is calculated from the expression

$$\%\ \text{ee} = \left(\frac{[\alpha]_{\text{observed}}}{[\alpha]_{\text{pure}}}\right) \times 100\%$$

Thus, if we determine a specific rotation of 6.5° for 2-butanol, we can calculate the enantiomeric excess (% ee) of the sample if we know the specific rotation of pure (+)-2-butanol ([α] = +13.00):

$$\%\ \text{ee} = \left(\frac{6.5}{13.00}\right) \times 100\% = 50\%$$

It is instructive to examine the composition of 100 molecules of a mixture of (+)- and (−)-2-butanol with a % ee = 50%. We have an excess of 50 (+)-2-butanol molecules, which causes the optical activity. The remaining 50 molecules, because they have no net optical activity, are composed of 25 (+)-2 -butanol molecules and 25 (−)-2 -butanol molecules. Thus we have a total of 75 (+)-2-butanol molecules and 25 (−)-2-butanol molecules.

16.8 Modern Methods of Enantiomeric Analysis

Rather than using polarimetry, it can be useful to convert a mixture of enantiomers to a corresponding mixture of diastereomers and use high-performance liquid chromatography (HPLC) [see Technique 18.9] or nuclear magnetic resonance (^{1}H NMR) spectroscopy [see Technique 21] for measuring the composition. These methods can be used to determine how successful a resolution has been or how stereoselective a chemical reaction is. They have the advantage of needing much smaller samples to determine enantiomeric excess than polarimetry usually requires.

Use of Chiral Acid/Base Chemistry for NMR Analysis

If the enantiomers of a chiral carboxylic acid undergo reaction with an optically active amine in an NMR tube, a mixture of diastereomeric salts is produced; these diastereomers can have subtly different ^{1}H NMR spectra. Neutralization of a mixture of enantiomers of a chiral amine by an optically active carboxylic acid can serve the same purpose. The NMR spectra will be fairly complex, and the chiral enantiomers generally need to have a clean singlet for one of its NMR signals so that integration can be used reliably to determine the enantiomeric composition.

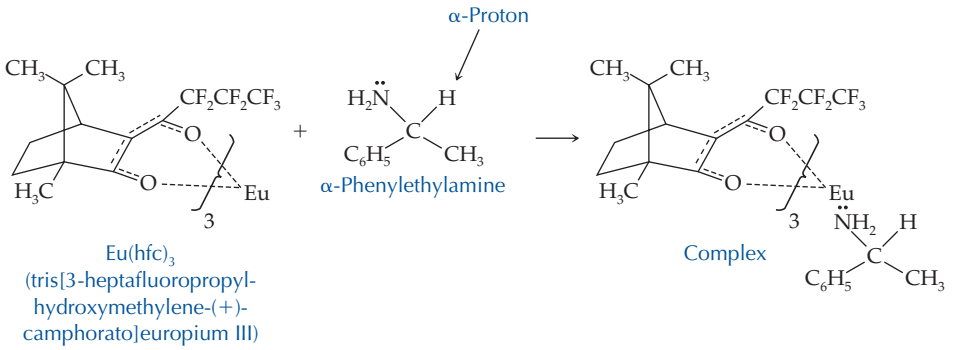
Chiral Shift Reagents for NMR Analysis

Chiral lanthanide shift reagents are often used to produce a diastereomeric mixture for NMR analysis. Derivatives of camphor provide shift reagents that are rich in chiral character. Eu(hfc)$_3$, called tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III), is such a compound. This compound undergoes rapid and reversible coordination with Lewis bases, (B:), establishing the following equilibrium:

$$\text{Eu(hfc)}_3 + \text{B:} \rightleftharpoons \text{B: Eu(hfc)}_3$$

The complex B: Eu(hfc)$_3$ brings a paramagnetic ion, Eu^{3+}, into close proximity to the chiral organic base (B:), which induces changes in the ^{1}H NMR chemical shifts of the chiral base. The chemical shifts are different in each of the two coordinated enantiomers because the formation of the diastereomeric pair causes the protons of the two enantiomers to become nonequivalent.

Identification of the ^{1}H NMR signals of the α-protons and integration of their areas allows determination of the composition of the B: Eu(hfc)$_3$ complex, which equals the enantiomeric composition of the original mixture.



Chiral HPLC

Another modern approach to the determination of enantiomeric excess is the use of chiral high-performance liquid chromatography [see Technique 18.9]. As discussed in Technique 16.5 in the section on chiral chromatography, when a mixture of enantiomers passes through a chiral chromatographic column, different interactions occur between each enantiomer and the chiral stationary phase, which lead to separation of the enantiomers.

INERT ATMOSPHERE REACTION CONDITIONS

Many useful reagents react quickly and vigorously with molecular oxygen, as well as with moisture in the air. Reactions using these reagents must be conducted in an inert atmosphere with air excluded from the system. Examples of air-sensitive reagents include borane complexes, organoboranes, metal hydrides, and organometallic compounds such as Grignard reagents, organoaluminums, organolithiums, and organozincs. Reactions with these reagents are usually carried out in an atmosphere of nitrogen or argon.

Several special techniques and apparatuses are used for inert atmosphere reactions. Consult your instructor before using any of these specialized techniques:

- Inert atmosphere reaction apparatus
- Balloon assembly
- Transferring reagents using syringe techniques
- Transferring liquid from a reagent bottle with a syringe
- Transferring liquid from a reagent bottle with a cannula

16.9 Reaction Apparatus

Reactions can be run under inert atmosphere conditions using common standard taper ground glass apparatus. Additional equipment needed includes a bubbler, a source of nitrogen (or argon), rubber septa, and syringes fitted with suitable needles. If the volume of reagent to be added during the reaction is larger than the available syringes will hold, a pressure-equalizing funnel should be included

in the reaction apparatus (Figure 16.7). A bubbler partially filled with mineral oil provides an outlet for nitrogen from the reaction apparatus (Figure 16.8). All glassware and syringes used for inert atmosphere reactions need to be oven-dried. Consult your instructor about drying the apparatus for your reaction.

Assembly of Reaction Apparatus

Standard taper joints in an apparatus used for inert atmosphere conditions should have a light coating of grease and Keck clips attached to keep the joints firmly in place. Nitrogen enters the system through a syringe needle placed in a rubber septum fitted over one neck of the reaction apparatus.

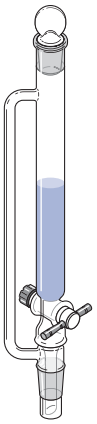


FIGURE 16.7
Pressure-equalizing funnel.

SAFETY PRECAUTIONS

1. Tanks of inert gases at high pressure must be handled with caution. Consult your instructor on how to handle them safely before using them.
2. All reaction assemblies described in the following techniques use syringe needles, which have sharp tips and can cause puncture wounds. Handle the needles with caution.

Assemble an oven-dried round-bottomed flask, Claisen adapter, and condenser, as shown in Figure 16.9a. Close the tops of the Claisen adapter and the condenser with fold-over rubber septa. Insert a syringe needle into the septum at the top of the condenser and insert the needle attached to the nitrogen source into the septum on the Claisen adapter. The nitrogen source is usually a pressurized tank of N_2.

Flushing the Reaction Apparatus with Nitrogen

The reaction apparatus may be flushed (purged) with nitrogen either before or after the reagents and solvent are placed in the reaction flask, depending on their air and moisture sensitivity. Turn on the nitrogen flow so that a reasonably rapid stream of bubbles passes through the liquid in the bubbler. Flush the apparatus with a gentle flow of nitrogen delivered through the needle in the Claisen adapter; the needle in the top of the condenser serves as the gas exit during purging. When you have finished purging the system, you can remove both needles from the septa unless the reaction will be heated.

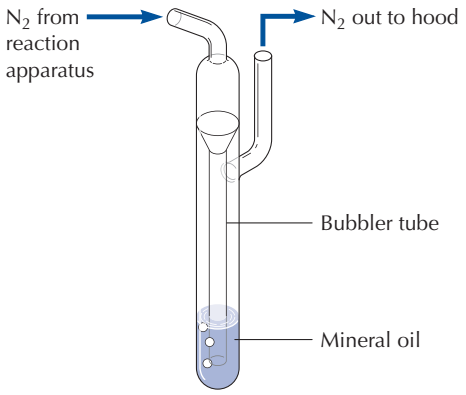
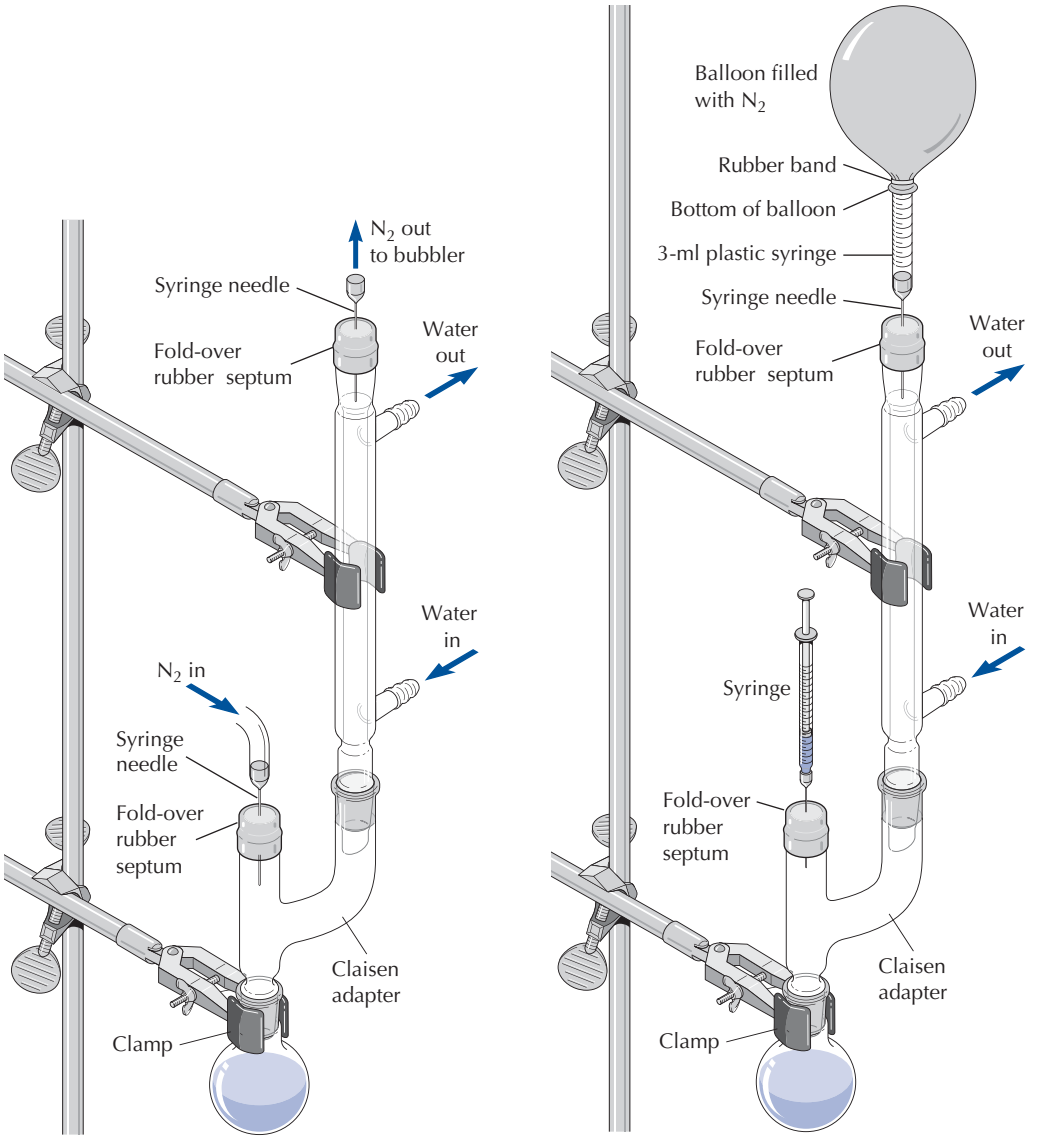


FIGURE 16.8
Bubbler for measuring the flow of an inert gas.



(a) Flushing reaction apparatus with N_2

(b) Reaction apparatus with balloon assembly in place.

FIGURE 16.9 Miniscale reaction setups for inert atmosphere reaction conditions.

SAFETY PRECAUTION

Never heat a closed system!

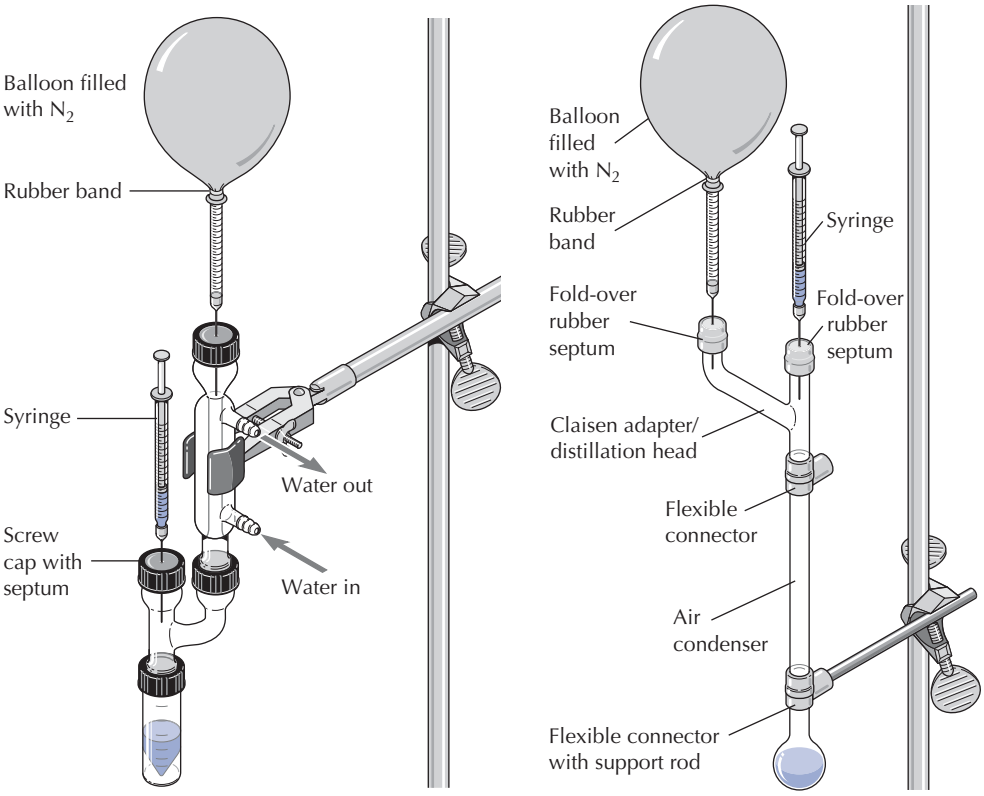
If the N_2 flow is continued during a reaction that is heated, increase the flow rate as soon as you remove the heat source from the reaction flask. This precaution prevents air from being drawn into the system through the bubbler as the vapors inside the apparatus cool and contract.

Preparing Balloon Assemblies

For small-scale and microscale reactions, you can often use a balloon assembly to provide an inert atmosphere (Figure 16.9b). Prepare the balloon assembly by removing the plunger and cutting the top off a 3-mL disposable plastic syringe. Fasten a small balloon to the top of the syringe with a small rubber band that is doubled to make a tight seal. Carefully fill the balloon with N_2 through a needle attached to the syringe, using plastic tubing to connect to the nitrogen source. When the balloon is inflated, tightly pinch its neck just above the top of the syringe barrel, remove the plastic tubing connected to the gas source from the needle, and immediately push the needle into a solid rubber stopper. The balloon will remain inflated, but it should be used as soon as possible after filling with nitrogen; otherwise, diffusion of oxygen from the atmosphere will contaminate it.

Insert the needle attached to the gas-filled balloon into the septum at the top of the condenser. Add reagent(s) to the reaction with a syringe inserted into the septum on the Claisen adapter (Figure 16.9b).

Figure 16.10a shows a standard taper microscale apparatus and Figure 16.10b shows a Williamson microscale apparatus for inert atmosphere conditions using a balloon assembly.



(a) ⅓ microscale apparatus **(b)** Williamson microscale apparatus

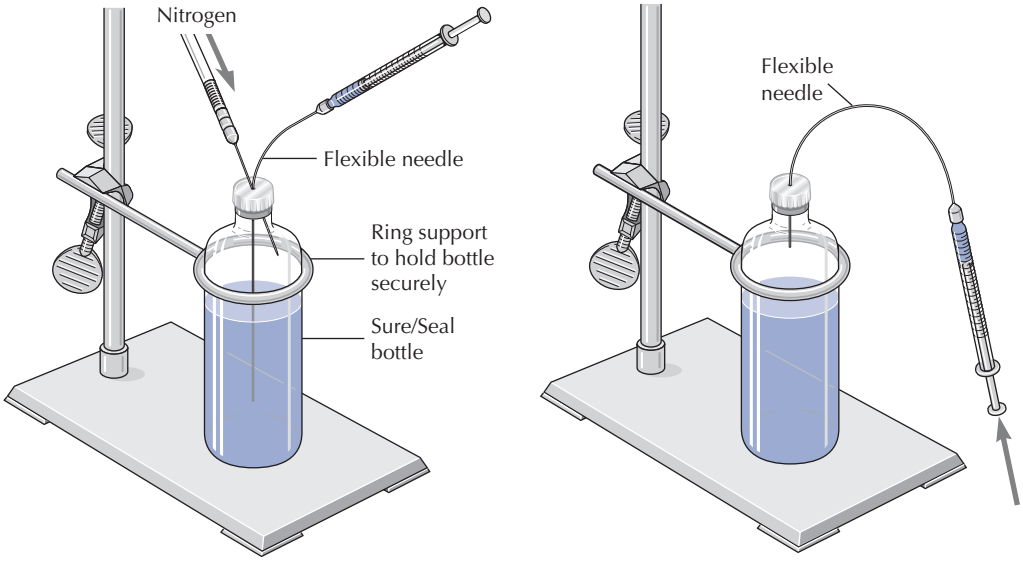
FIGURE 16.10 Microscale reaction apparatus with balloon assembly for inert atmosphere conditions.

16.10 Transfer of Reagents Using Syringe Techniques

Air-sensitive reagents and the dry solvents necessary for their use require special techniques for transferring from reagent bottles to the reaction apparatus without exposure to atmospheric oxygen and moisture. Small quantities (up to 40 mL) may be transferred from a reagent bottle to the reaction apparatus with a syringe fitted with a long (12–24 in) flexible needle. A glass syringe and needle should be cleaned, dried in an oven, and cooled in a desiccator before use. Purge the syringe and needle with nitrogen before filling the syringe with reagent (consult your instructor). After purging the syringe and the needle, insert the tip of the needle into a solid rubber stopper unless it will be immediately filled with reagent.

Transferring Liquid from a Reagent Bottle with a Syringe

The reagent bottle should be firmly clamped so that it cannot move. Insert a short syringe needle connected to a nitrogen source into the septum that seals the reagent bottle, and pressurize the bottle to a small degree. Then insert the long flexible needle of the transfer syringe so that the open end is below the surface of the liquid in the bottle (Figure 16.11a). Allow the nitrogen pressure in the reagent bottle to assist in filling the syringe until it contains a liquid volume slightly larger than required. Do not pull on the plunger because this may cause leaks or generate gas bubbles. Push the plunger slowly to expel any gas bubbles and adjust the volume of reagent to the desired amount (Figure 16.11b). Hold the syringe with one hand. Use the



(a) Filling syringe using nitrogen pressure

(b) Removing gas bubbles and returning excess reagent to the Sure/Seal bottle

FIGURE 16.11 Filling a syringe with an air-sensitive reagent.
Reprinted with permission from Aldrich Chemical Co., Inc., Milwaukee, WI.

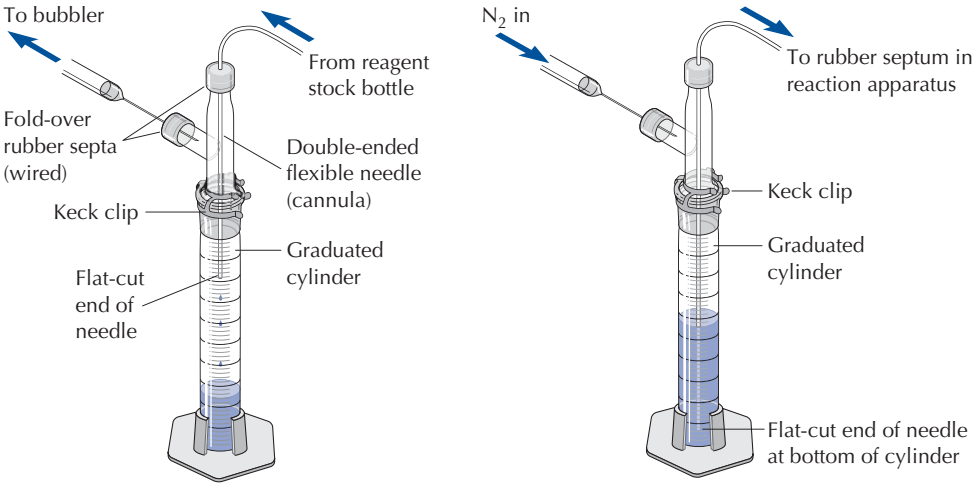
other hand to pull the needle out of the reagent bottle and quickly insert it through the rubber septum on the reaction apparatus.

Transferring Liquid from a Reagent Bottle with a Cannula

If larger quantities than will fit in a syringe are needed, a standard taper graduated cylinder can be used to measure the reagent. The transfer from the reagent bottle to a graduated cylinder is best accomplished with a ***cannula,*** a long double-ended needle. The transfer of liquid from a reagent bottle using a cannula is a complex operation for which consultation with your instructor is essential.

The procedure entails two preliminary steps. The reagent bottle should be firmly clamped as shown in Figure 16.11. Second, the graduated cylinder needs to be purged with N_2. A ground glass adapter fitted with two septa-covered ports is placed in the top of the graduated cylinder (Figure 16.12a) and a Keck clip is positioned over the ground glass joint. The side outlet of the adapter is connected to a bubbler by a short syringe needle. With a syringe needle in the second septum, the graduated cylinder is then flushed with nitrogen.

After the graduated cylinder has been prepared, insert a short syringe needle connected to a nitrogen source into the septum seal of the reagent bottle and pressurize the bottle. Then flush the cannula with nitrogen and insert one end of it into the reagent bottle so that the needle point is above the level of the liquid. The flow of nitrogen through the cannula will purge it of any remaining air. Insert the other end of the cannula into the septum at the top of the adapter on the graduated cylinder to a depth that is less than the height of liquid to be delivered (Figure 16.12a). Push the end of the cannula that is in the reagent bottle into the liquid to begin the transfer of reagent. When the level of liquid in the graduated cylinder reaches the desired height, immediately pull the cannula out of the reagent



(a) Transfer of liquid from stock bottle to graduated cylinder

(b) Transfer of liquid from graduated cylinder to reaction apparatus

FIGURE 16.12 Transfer of a liquid reagent (a) to a graduated cylinder and (b) from a graduated cylinder under inert atmosphere conditions.

bottle and insert it into the reaction apparatus with the tip of the needle above the surface of the reaction mixture.

Transferring Liquid to the Reaction Flask with a Cannula

To transfer the reagent from the graduated cylinder to the reaction apparatus, remove the syringe needle attached to the bubbler from the side arm of the adapter on the graduated cylinder and replace it with a syringe needle attached to a nitrogen source. Push the cannula needle tip to the bottom of the graduated cylinder and adjust the nitrogen flow so that the reagent drips slowly into the reaction flask (Figure16.12b).

Further Reading

The following sources provide additional details and information on a wide variety of reaction setups and methods for carrying out reactions under inert atmosphere conditions.

Aldrich Technical Bulletin AL-134, Handling Air-Sensitive Reagents, Aldrich Chemical Co., Inc., Milwaukee, WI.

Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry;* 2nd ed.; Blackie Academic and Professional: London, 1995.

Questions

Sublimation

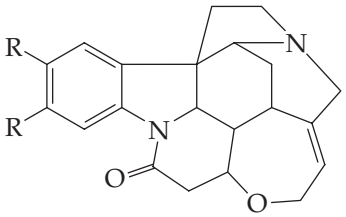
1. Which of the following three compounds—polyethylene, menthol, or benzoic acid—is the most likely to be amenable to purification by sublimation?
2. A solid compound has a vapor pressure of 65 torr at its melting point of 112°C. Give a procedure for purifying this compound by sublimation.
3. Hexachloroethane has a vapor pressure of 780 torr at its melting point of 186°C. Describe how solid hexachloroethane would behave while carrying out a melting-point determination at atmospheric pressure (760 torr) in a capillary tube open at the top.

Refractometry

4. A compound has a refractive index of 1.3191 at 20.1°C. Calculate its refractive index at 25.0°C.
5. To clean the glass surfaces of a refractometer, ethanol or methanol but not acetone or water is usually recommended. Why?

Optical Activity and Enantiomeric Analysis

6. A sample of 2-butanol has a specific rotation of +3.25°. Determine the % ee and the molecular composition of this sample. The specific rotation of pure (+)-2-butanol is +13.0°.
7. A sample of 2-butanol (see question 6) has a specific rotation of −9.75°. Determine the % ee and the molecular composition of this sample.
8. An optical rotation study gives $\alpha = +140°$ as the result. Suggest a dilution experiment to test whether the result is indeed +140°, not −220°.
9. The structures of strychnine (R = H) and brucine (R = CH_3O) are examples of alkaloid bases that can be used for resolutions. These molecules are rich sources of chirality (respectively, $[\alpha]_D = -104°$ and −85° in absolute ethanol). Assume that nitrogen inversion is slow and identify the eight stereocenters in each of the two nitrogen heterocyclic compounds.



R = H, strychnine
R = CH_3O, brucine

10. Only one of the two nitrogens in strychnine and brucine acts as the basic site for the necessary acid/base reaction for a resolution. Which nitrogen, and why?

PART

4

Chromatography

Essay — Modern Chromatographic Separations

Few experimental techniques rival chromatography for purifying organic compounds and separating complex mixtures. Chromatography got its name from the fact that it was originally used to separate mixtures of colored substances—the pigments in green leaves. Once chemists realized that chromatography could be used to separate colorless substances as well, its development took off. The British chemists Archer Martin and Richard Synge were awarded the 1952 Nobel Prize in Chemistry for their invention of partition chromatography, which has revolutionized the practice of chemistry, biochemistry, and many areas of modern biology.

Principles of Chromatography

The International Union of Pure and Applied Chemistry (IUPAC) defines chromatography as a physical method of separation in which the components to be separated are distributed between two phases, the immobile stationary phase and the mobile phase. The ***mobile phase*** moves in a definite direction and passes over the ***stationary phase.***

The substances being separated are attracted to the stationary phase by intermolecular forces; the stronger the attraction the slower they migrate through the mobile phase. Separation results from the different migration rates. The adsorption-desorption process with the stationary phase occurs many times as a molecule moves through a chromatography column or on a plate. The time required to move through the mobile phase depends mainly on the proportion of time it is adsorbed on the stationary phase and held immobile. The movement of compounds that have stronger intermolecular forces with the stationary phase is retarded in proportion to their interaction.

All chromatographic methods depend on the distribution of the compounds being separated between the mobile and stationary phases. A dynamic equilibrium exists between the sample components dissolved in the stationary phase and those dissolved in the mobile phase. The most commonly used polar stationary phase in liquid and thin-layer chromatography is silica gel, finely ground silica (SiO_2) particles that are coated

with a thin layer of water molecules. Intermolecular hydrogen bonding and dipole-dipole interactions allow polar organic compounds to be attracted by the water-coated silica gel much more than nonpolar organic compounds [see Essay—Intermolecular Forces in Organic Chemistry, page 99]. Therefore, polar organic compounds are carried more slowly by the mobile solvent phase through the stationary phase and leave a chromatography column later than nonpolar compounds. In the same manner, polar organic solvents move compounds faster through a chromatography column and on a TLC plate than nonpolar solvents do.

Because the layer of liquid coating on the stationary phase is very thin, much of the interaction takes place near the surface of the liquid. Rather than absorption into the bulk liquid, a process of surface ***adsorption*** onto the stationary phase occurs. Absorption can be compared to eating a pie and adsorption to a pie hitting your face and clinging to it.

When the compounds being separated adsorb onto the liquid coating of the stationary phase, they ***partition*** themselves between the stationary liquid phase and a mobile liquid or gas phase. The partitioning occurs in the same way a solute partitions itself between two immiscible solvents used for an extraction [see Technique 11]. The compounds being separated adsorb onto and desorb from a liquid stationary phase many, many times as the solvent passes through. The tighter they adsorb to the stationary phase, the slower they travel through the chromatography column.

Chromatography in the Organic Lab

Three modern chromatographic methods used in organic chemistry are carried out in glass or metal columns:

- Liquid chromatography (LC), which uses either a gravity flow of solvent through a stationary phase or a modest pressure to force the solvent through the column at a faster rate (flash chromatography). Usually silica gel, which has a thin film of water on its surface, is the stationary phase.
- High-performance liquid chromatography (HPLC), which uses high-pressure pumps to force the mobile phase through a very small diameter column that contains the stationary phase.
- Gas-liquid chromatography (GC), where the mobile phase is a stream of an inert gas.

Rather than using a column, thin-layer chromatography (TLC) is carried out on small glass, aluminum, or plastic plates covered with a thin coating of silica gel. Capillary action on the thin surface allows the mobile phase to ascend the plate.

In gas-liquid chromatography (GC) the mobile phase is an inert gas such as helium or nitrogen. The stationary phase is a thin film of a nonvolatile liquid. The column is heated and the compounds pass through the chromatography column somewhat in the order of their volatilities, although specific intermolecular forces with the stationary phase also play a role in the separation. In GC, the mobile phase does not interact with the compounds being separated and does not appreciably cause them to desorb from the stationary phase. It simply carries them down the column when they are in the vapor state. In LC, the mobile-phase liquids compete actively with the stationary phase to attract the compounds moving through the column.

TECHNIQUE

17 THIN-LAYER CHROMATOGRAPHY

If Technique 17 is your introduction to chromatographic analysis, read the Essay "Modern Chromatographic Separations" on pages 219–220 before you read Technique 17.

Thin-layer chromatography (TLC) has become a widely used analytical technique. It is simple, inexpensive, fast, and efficient, and it requires only milligram quantities of material. TLC is especially useful for determining the number of compounds in a mixture, for helping to establish whether or not two compounds are identical, and for following the course of a reaction.

In TLC, glass, metal, or plastic plates are coated with a thin layer of adsorbent, which serves as the ***stationary phase.*** The stationary phase is usually polar—silica gel is most widely used. The ***mobile phase*** is a pure solvent or a mixture of solvents; the appropriate composition of the mobile phase depends on the polarities of the compounds in the mixture being separated. Most nonvolatile solid organic compounds can be analyzed by thin-layer chromatography. However, TLC does not work well for many liquid compounds because their volatility can lead to loss of the sample by evaporation from the TLC plate.

Overview of TLC Analysis

To carry out a TLC analysis, a small amount of the mixture being separated is dissolved in a suitable solvent and applied or spotted onto the adsorbent near one end of a TLC plate. Then the plate is placed in a closed chamber, with the edge nearest the applied spot immersed in a shallow layer of the mobile phase called the ***developing solvent*** (Figure 17.1). The solvent rises through the stationary phase by capillary action, a process called ***developing the chromatogram.***

As the solvent ascends the plate, the sample is distributed between the mobile phase and the stationary phase. Separation during the development process occurs as a result of many equilibrations taking place between the mobile and stationary phases and the compounds being separated. **The more tightly a compound binds to the adsorbent, the more slowly it moves on the TLC plate** (Figure 17.2). When silica gel is the stationary phase, the developing solvent moves nonpolar substances up the plate most rapidly. As the chromatogram develops, polar substances travel up the plate slowly or not at all.

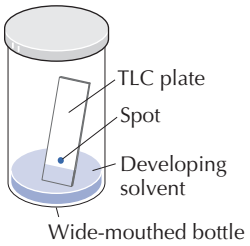


FIGURE 17.1
Developing chamber containing a thin-layer plate.

The TLC plate is removed from the developing chamber when the ***solvent front*** (leading edge of the solvent) is 1−1.5 cm from the top of the plate. The position of the solvent front is marked immediately, before the solvent evaporates, with a pencil line. The plate is then placed in a hood to dry.

Several methods are available for ***visualizing*** the compounds in the sample. Some compounds are colored and their spots can easily be seen. If the TLC plate is impregnated with a fluorescent indicator, the plate can be visualized by exposure to ultraviolet light. Alternatively, the compounds can be visualized using a reagent that produces colored spots. The developed and visualized plate is then ready for analysis of the chromatogram.

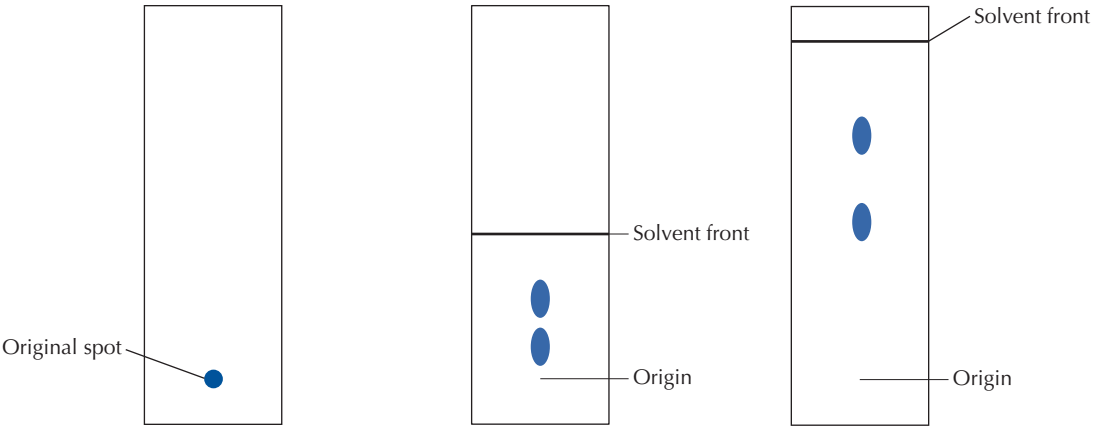


FIGURE 17.2 Steps in development of a TLC plate.

17.1 Plates for Thin-Layer Chromatography

Thin-layer chromatographic plates consist of a solid support, such as glass, metal, or plastic with a thin layer of an adsorbent coating the solid surface, which provides the stationary phase.

Adsorbents

Silica gel ($SiO_2 \cdot xH_2O$) is the most commonly used general-purpose adsorbent for partition chromatography of organic compounds. Aluminum oxide (Al_2O_3, also called alumina) can also be used as a polar adsorbent. Cellulose is used to separate highly polar compounds. Several intermolecular forces cause organic molecules to bind to these polar stationary phases. Only weak van der Waals forces bind nonpolar compounds to the adsorbent, but polar molecules can also adsorb by dipole-dipole interactions, hydrogen bonding, and coordination to highly polar metal oxide surfaces. The strength of the interaction varies for different compounds, but one generality can be stated: **the more polar the compound, the more strongly it binds to silica gel or alumina.** Another type of silica gel adsorbent—used for reverse-phase chromatography—has a nonpolar surface that adsorbs less polar compounds more strongly than polar compounds.

Silica gel and aluminum oxide. Silica gel and alumina adsorbents are prepared from activated, finely ground powders. Activation usually involves heating the powder to remove some of the adsorbed water. Silica gel is somewhat acidic, and usually it effectively separates acidic and neutral compounds that are not too polar. Aluminum oxide is available in acidic, basic, and neutral formulations for the separation of relatively nonpolar compounds.

If the plastic seal on a package containing precoated silica gel or alumina TLC sheets has been broken for some time, the TLC plates should be activated before use to remove some of the adsorbed water.

Activation is done simply by heating the sheets in a clean oven for 15–30 min at the temperature recommended by the manufacturer.

Cellulose. Cellulose is less polar than silica gel and alumina and is used for the partition chromatography of water-soluble and quite polar organic compounds, such as sugars, amino acids, and nucleic acid derivatives. Cellulose can adsorb up to 20% of its weight in water; the substances being separated partition themselves between the developing solvent and the water molecules that are hydrogen-bonded to the cellulose particles. Paper chromatography is an example of using cellulose as a stationary phase.

Adsorbents for reverse-phase TLC. The adsorbents used on plates for reverse-phase thin-layer chromatography are based on silica gel modified by replacing the hydroxyl groups normally attached to silicon atoms with alkoxy groups and with long-chain alkyl groups, such as $—(CH_2)_{17}CH_3$. The alkyl chains provide a nonpolar liquid stationary phase. The solvents used in reverse-phase TLC are quite polar, for example, methanol or acetonitrile, often mixed with water. In reverse-phase TLC, the order of movement up the TLC plate is reversed; more polar compounds travel faster up the TLC plate than less polar compounds, which bind more tightly to the nonpolar adsorbent surface.

Backing for TLC Plates

A number of manufacturers sell TLC plates that are precoated with a layer of adsorbent.

Plastic backing. Plastic-backed silica gel plates are usually the least expensive. They can be cut to any desired size with a paper cutter or sharp scissors. The adsorbent surface is of uniform thickness, usually 0.20 mm. Results are quite reproducible, and sharp separation is normal. The plastic backing is generally a solvent-resistant polyester polymer. The adsorbent is bound to the plastic by solvent-resistant polyvinyl alcohol, which binds tightly to both the adsorbent and the plastic. Precoated plastic plates impregnated with a fluorescent indicator are also available; these plates facilitate the visualization of many colorless compounds with a UV lamp [see Technique 17.4].

We suggest using TLC plates of 2.5 × 6.7 cm; 24 plates can be cut from a standard 20 × 20 cm sheet.

Glass and aluminum backing. TLC plates with a glass or aluminum backing are also available in the standard 20 × 20 cm sheets. Both types can be heated without melting the backing—an important property if the plate is to be visualized with a reagent that requires heating [see Technique 17.4]. Aluminum sheets can be cut with scissors into convenient sizes for TLC plates. Glass sheets can be cut with a special diamond-tipped tool.

17.2 Sample Application

For TLC analysis, dissolve 10–20 mg of the solid in 1 mL of solvent.

The sample must be dissolved in a volatile organic solvent; a very dilute (1–2%) solution works best. Because the atmosphere in the developing chamber must be saturated with solvent vapor, the solvent needs a high volatility so that it will evaporate easily at room

temperature. Anhydrous reagent-grade acetone or ethyl acetate is commonly used. If you are analyzing a solid, dissolve 10–20 mg of it in 1 mL of the solvent. If you are analyzing a nonvolatile liquid, dissolve about 10 μl of it in 1 mL of the solvent.

Micropipets for Spotting TLC Plates

Commercial micropipets are available in 5- and 10-μL sizes and work well for applying samples onto plastic-backed plates. Glass and aluminum-backed plates require micropipets of a smaller interior diameter. Narrow capillary tubes of 0.7 mm internal diameter are commercially available.

A micropipet can be made easily from an open-ended, thin-walled, melting-point capillary tube. The capillary tube is heated at its midpoint. A microburner is ideal because only a small flame is required, but a Bunsen burner may be used. (If you do not know how to use a microburner or Bunsen burner, consult your instructor.) The softened glass tube is stretched and drawn into a narrower capillary.

SAFETY PRECAUTION

Be sure there are no flammable solvents in the vicinity when you are using a microburner or Bunsen burner.

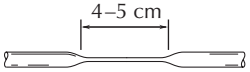


FIGURE 17.3
Constricted capillary tube.

While heating the tube, rotate it until it is soft on all sides over a length of 1–2 cm. When the tubing is soft, remove it from the heat and quickly draw out the heated part until a constricted portion 4–5 cm long is formed (Figure 17.3). After cooling the tube for a minute or so, score it gently at the center with a file and break it into two capillary micropipets. The diameter at the end of a micropipet needs to be tiny, just a little larger than the diameter of a human hair, about 0.2–0.3 mm. The break must be a clean one, at right angles to the length of the tubing, so that when the tip of the micropipet is touched to the plate, liquid is pulled out by the adsorbent.

Spotting a TLC Plate

Tiny spots of the dilute sample solution are carefully applied with a micropipet near one end of the plate. Keeping the spots small assures the cleanest separation. It is important not to overload the plate with too much sample, which leads to large tailing spots and poor separation.

No type of pen should be used for marking TLC plates because components of the ink separate during development and may obscure the samples.

Preparing the plate. Before spotting a TLC plate, measure 1.0 cm from the bottom edge of the plate and *lightly* mark both edges with a 0.3-cm or shorter pencil mark (Figure 17.4). The imaginary line between these marks indicates the compound's starting point for your analysis after the TLC has been completed.

Number of lanes per plate. If you are using 2.5 × 6.7 cm TLC plates, two spots can be applied to one plate (Figure 17.4); the spot in each lane should be one-third of the distance from the side of the plate. Three spots require a 3.0-cm-wide plate. The spots become larger by diffusion during development, and if they are too close to each other or to the edge of the plate, the chromatograms are likely to become difficult to interpret.

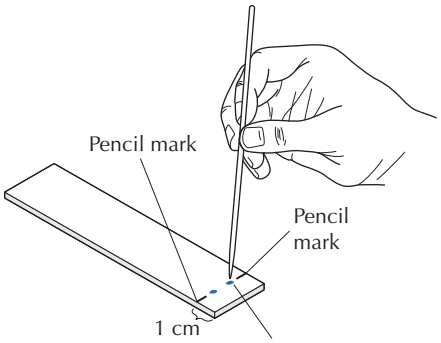


FIGURE 17.4
Spotting a thin-layer plate.

Applying the samples. The micropipet is filled by dipping one end of the capillary tube into the solution to be analyzed. Only 1–5 μL of the sample solution are needed for most TLC analyses. Hold the micropipet vertically and apply the sample by **touching the micropipet gently and briefly to the plate** on the imaginary line between the two pencil marks (Figure 17.4). It is important to touch the micropipet to the plate very lightly so that no hole is gouged in the adsorbent and to remove it quickly so that only a very small drop is left on the adsorbent. The spot delivered should be no more than 2 mm in diameter to avoid excessive broadening of the spot during the development. If you apply very small spots, you will probably need to apply more sample by touching the micropipet to the plate a second time *at exactly the same place.* Allow one spot to dry before applying the next. The spotting procedure may be repeated numerous times, if necessary.

Testing the amount of sample to spot. You can quickly test for the proper amount of solution to spot on the plate by spotting two different amounts on the same plate. If you have used plates with a fluorescent indicator, visualize the spots by using a UV lamp [see Technique 17.4] before developing the plate. Otherwise, develop the plate as directed in Technique 17.3 and decide which spot gives better results.

Using known standards. If available, an authentic standard should be included on the TLC plate for comparison. If two compounds travel up the plate the same distance, they may be the same compound; if the distances differ significantly, they most definitely are not the same compound. If the distances the two compounds travel are quite close, it is best to run the chromatogram again, using a different solvent or a longer TLC plate.

Accurate record keeping. Accurate record keeping is essential while doing a TLC analysis. **Before spotting the plate,** draw a sketch in your notebook of the TLC plate with a line drawn across it to indicate the initial position of the sample. Set up a key underneath

the sketch with the position and name of each sample that will be spotted. Most samples are colorless, and identifying which sample is spotted in a specific position is impossible without a detailed record.

17.3 Development of a TLC Plate

Development of a TLC plate is carried out in a closed developing chamber containing a developing solvent. If a developing solvent is not specified for the system you are analyzing, read Technique 17.7 on how to choose a suitable developing solvent before undertaking your TLC analysis.

Preparing the Developing Chamber

To ensure good chromatographic resolution, the developing chamber **must be saturated with solvent vapors** to prevent the evaporation of solvent from the TLC plate as the solvent rises up the plate. If the solvent mobile phase evaporates, the compounds in the sample can end up unseparated near the top of the TLC plate. Inserting a piece of filter paper three-quarters of the way around the inside of the developing chamber helps to saturate its atmosphere with solvent vapor by wicking solvent into the upper region of the chamber (Figure 17.5). The paper wick should be a little shorter than a TLC plate so that the plate does not touch the paper. After adding the correct amount of developing solvent, shake the capped TLC chamber briefly to ensure that the paper wick is saturated with solvent.

*The solvent depth in the developing chamber **must be less** than the height of the spots on the TLC plate.*

Use enough developing solvent to allow a shallow layer (3–4 mm) to remain on the bottom after the closed chamber has been shaken to saturate the filter paper with the solvent. If the solvent level in the jar is too high, the spots on the plate may be below the solvent level. Under these conditions, the spots leach into the solvent, thereby ruining the chromatogram.

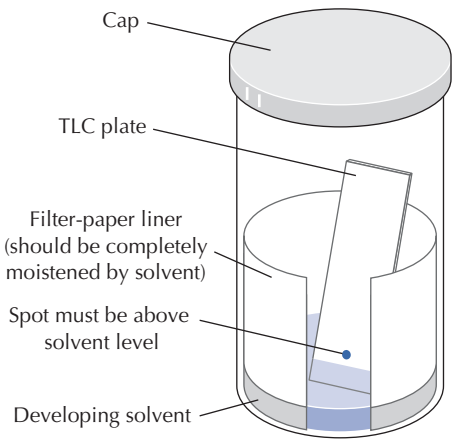


FIGURE 17.5
Developing a TLC plate.

Carrying Out the TLC Development

Do not touch the adsorbent side of the TLC plate with your fingers. Hold the plate by the top edge with a pair of tweezers.

Uncap the developing chamber and carefully place the TLC plate inside with a pair of tweezers, taking care that it is level and not touching the paper wick. Recap the chamber, and allow the solvent to move up the plate. The adsorbent will become visibly moist. **Do not lift or otherwise disturb the chamber while the TLC plate is being developed.**

The development of a chromatogram usually takes 5–10 min if the chamber is saturated with solvent vapor. When the solvent front is 1–1.5 cm from the top of the plate, remove it from the developing chamber with a pair of tweezers and immediately mark the adsorbent at the solvent front with a pencil. The final position of the solvent front must be marked before any evaporation occurs. Analysis of the chromatogram requires accurate knowledge of the distance the compounds have traveled up the TLC plate relative to the distance the solvent has traveled. Allow the developing solvent to evaporate from the plate before visualizing the results.

SAFETY PRECAUTION

Evaporate the solvent from a developed chromatogram in a fume hood.

17.4 Visualization Techniques

Chromatographic separations of colored compounds usually can be seen directly on the TLC plate, but colorless compounds require indirect methods of visualization. Fluorescence and visualization reagents are commonly used to visualize TLC plates.

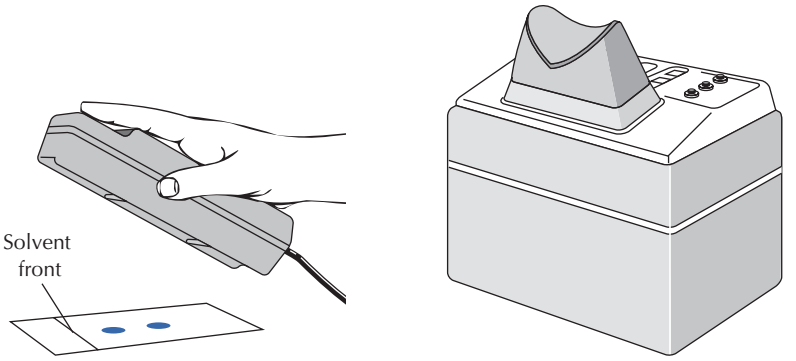
Fluorescence

The simplest visualization technique involves the use of adsorbents that contain a fluorescent indicator. The insoluble inorganic indicator rarely interferes in any way with the chromatographic results and makes visualization straightforward. When the output from a short-wavelength ultraviolet lamp (254 nm) is used to illuminate the adsorbent side of the plate in a darkened room or dark box, the plate fluoresces visible light.

SAFETY PRECAUTION

Never look directly at an ultraviolet radiation source. Like the sun, UV radiation can cause eye damage.

The separated compounds appear as dark spots on the fluorescent field because the substances forming the spots usually quench the fluorescence of the adsorbent, as shown in Figure 17.6a. Sometimes substances being analyzed are visible by their own fluorescence, producing a brightly glowing spot. Outline each spot with a pencil while the plate is under the UV source to give a permanent record, which will allow the analysis of your chromatogram.



(a) Using an ultraviolet lamp

(b) Using an ultraviolet lamp with dark box

FIGURE 17.6 UV visualization.

Visualization Reagents

Not all substances are visible on fluorescent silica gel, so visualization by one of the following methods should also be tried on any unknown sample.

Dipping reagents for glass or aluminum plates. Glass or aluminum TLC plates can be dipped briefly in visualizing solutions containing reagents that react to form colored compounds upon heating. Alternatively, the TLC plates can be sprayed with the visualizing solution. Visualization occurs by heating the dipped or sprayed TLC plates with a heat gun or on a hot plate for a few minutes. Three common visualizing solutions are *p*-anisaldehyde, vanillin, and phosphomolybdic acid.* The colors fade with time, so the spots should be outlined with a pencil soon after the visualization process.

Iodine visualization. Another way to visualize colorless organic compounds uses their absorption of iodine (I_2) vapor. A plastic wash bottle containing a thin layer of iodine crystals is used for this visualization method.

SAFETY PRECAUTION

Iodine vapor is toxic and corrosive. Wear gloves and work in a hood while using iodine visualization.

Lay the TLC plate on a clean piece of paper or paper towel. Hold the tip of the wash bottle containing the iodine about 1 cm above the plate and gently squeeze the sides of the bottle as you

*_p_-Anisaldehyde visualizing solution: 2 mL of *p*-anisaldehyde in 36 mL of 95% ethanol, 2 mL of concentrated sulfuric acid, and 5 drops of acetic acid.

Vanillin visualizing solution: 6.0 g of vanillin in 100 mL of 95% ethanol and 1.0 mL of concentrated sulfuric acid. Store the vanillin reagent in an amber-colored bottle covered with aluminum foil; discard the solution when it acquires a blue color.

Phosphomolybdic acid visualizing solution: 20% phosphomolybdic acid by weight in ethanol.

move it from the bottom to the top of the plate; repeat the motion two or three times. The spots on the plate should appear within 30–60 sec. Yellow-brown colored spots are produced from the reaction of the substances with iodine vapor. If no spots appear, repeat the application of iodine vapor several more times. The colored spots disappear in a short period of time, so they must be outlined with a pencil immediately after they appear. The spots will reappear if the plate is again treated with iodine vapor.

Further information on visualization reagents. Consult the references at the end of the Technique 17 for detailed discussions of visualization reagents.

17.5 Analysis of a Thin-Layer Chromatogram

Once the spots on the chromatogram are visualized, you are ready to analyze the chromatogram. The analysis of a thin-layer chromatogram consists of determining the ratio of the distance each compound has traveled on the plate relative to the distance the solvent has traveled.

Determination of the R_f

Under a constant set of experimental conditions, a given compound always travels a fixed distance relative to the distance traveled by the solvent front (Figure 17.7). This ratio of distances is called the ***R_f (ratio to the front)*** and is expressed as a decimal fraction:

$$R_f = \frac{\text{distance traveled by compound}}{\text{distance traveled by developing solvent front}}$$

The R_f value for a compound depends on its structure as well as the adsorbent and mobile phase used. It is a physical characteristic of the compound, just as its melting point is a physical characteristic. Whenever a chromatogram is done, the R_f value should be calculated for each substance and the experimental conditions recorded. The

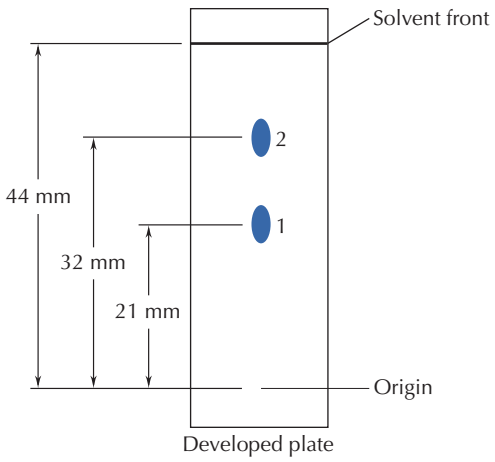


FIGURE 17.7
Measurements for the R_f value.

important data that need to be recorded include the following:

- Brand, type of backing, and adsorbent on the TLC plate
- Developing solvent
- Method used to visualize the compounds
- R_f value for each substance

Calculation of an R_f Value

To calculate the R_f value for a given compound, measure the distance the compound has traveled from where it was originally spotted and the distance the solvent front has traveled from where the compound was spotted (see Figure 17.7). The measurement is made from the center of a spot. The best data are obtained from chromatograms in which the spots are less than 5 mm in diameter. If a spot shows "tailing," measure from the densest point of the spot. The R_f values for the two substances shown on the developed TLC plate in Figure 17.7 are calculated as follows:

$$\text{Compound 1:} \quad R_f = \frac{21 \text{ mm}}{44 \text{ mm}} = 0.48$$

$$\text{Compound 2:} \quad R_f = \frac{32 \text{ mm}}{44 \text{ mm}} = 0.73$$

Identical R_f Values

When two samples have identical R_f values, you should not conclude that they are the same compound without doing further analysis. There are perhaps 100 possible R_f values that can be distinguished from one another, whereas there are greater than 10^8 known organic compounds. Further analysis by infrared (IR) or nuclear magnetic resonance (NMR) spectroscopy would be needed to provide definitive evidence about whether the compounds are identical or not. You could conclude that the samples are different compounds if subsequent TLC analyses with different developing solvents reveal different R_f values for each sample.

17.6 Summary of TLC Procedure

1. Obtain a precoated TLC plate of the proper size for the developing chamber.
2. Lightly mark the edges of the origin line with a pencil. Spot the plate with a small amount of a 1–2% solution containing the compounds to be separated.
3. Add a filter-paper wick to the developing jar. Then add a suitable solvent, cap the jar, and shake it briefly to saturate the paper with solvent and the air in the chamber with solvent vapors.
4. Place the spotted TLC plate into the developing jar, taking care that it doesn't touch the wick, and quickly recap the jar.
5. Develop the chromatogram until the solvent front is 1–1.5 cm from the top of the plate.

6. Mark the solvent front immediately after removing the plate from the developing chamber.
7. Visualize the chromatogram and outline the separated spots.
8. Calculate the R_f value for each compound.

17.7 How to Choose a Developing Solvent When None Is Specified

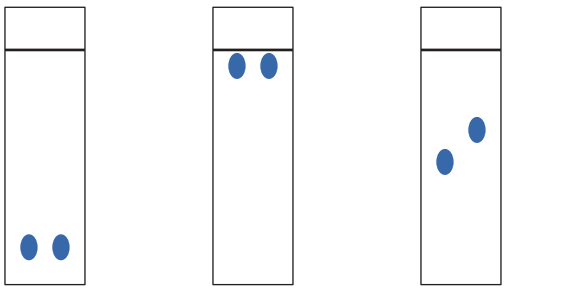
Finding a Suitable Developing Solvent

Chromatographic behavior is the result of competition by the stationary phase (adsorbent) and the mobile-phase (developing solvent) for the compounds being separated.

Solvent considerations. In general, you should use a nonpolar developing solvent for nonpolar compounds and a polar developing solvent for polar compounds. Selecting a suitable solvent is often, however, a trial-and-error process, particularly if a mixture of solvents is required to give good separation. A solvent that does not cause any compounds to move from the original spot is not polar enough, whereas a solvent that causes all the spotted material to move with the solvent front is too polar (Figure 17.8a and b). An appropriate solvent for a TLC analysis gives R_f values of 0.20–0.70, with ideal values in the range 0.30–0.60, as shown in Figure 17.8c.

With a silica gel plate, nonpolar hydrocarbons should be developed with hydrocarbon solvents, but a mixture containing an alcohol and an ester might be developed with a hexane/ethyl acetate mixture. Highly polar solvents are seldom used with silica gel plates, except in the case of reverse-phase TLC.

Testing developing solvents. If you know the compounds in the mixture you want to separate, use Table 17.1 to select solvents to test. It shows the relative polarity of common TLC developing solvents and organic compounds by functional group class. If the composition of the mixture is unknown, begin by testing with a nonpolar solvent such as hexane and then with a medium-polarity solvent such as ethyl



(a) Hexane **(b)** Ethyl acetate **(c)** 30% ethyl acetate/ 70% hexane

FIGURE 17.8 TLC results with different developing solvents.

TABLE 17.1 Relative polarities of common TLC solvents and organic compounds

Common developing solvents	Increasing polarity ↓	Organic compounds by functional group class
Alkanes, cycloalkanes		Alkanes
Toluene		Alkenes
Dichloromethane		Aromatic hydrocarbons
Diethyl ether		Ethers, halocarbons
Ethyl acetate		Aldehydes, ketones, esters
Acetone		Amines
Ethanol		Alcohols
Methanol		Carboxylic acids
Acetonitrile		
Water		

acetate. When testing mixed solvents, you might start by testing a 50:50 mixture to see how much separation occurs and how far up the plate the two compounds travel. If they travel more than halfway up the plate, test a solvent mixture with a higher percentage of hexane; conversely, if they travel less than halfway up the plate, test a solvent mixture with a higher percentage of ethyl acetate.

If a very polar solvent is required. If a very polar solvent is required to move spots on a particular TLC adsorbent, better results may be obtained by switching to a less active adsorbent and a less polar solvent. Silica gel is less polar than most grades of alumina.

Rapid Method for Testing Developing Solvents

As a rapid way to determine the best TLC developing solvent among several possibilities, three or four samples can be spotted along the length of the same plate (Figure 17.9). Fill a micropipet with the solvent to be tested and gently touch one of the spots. The solvent will diffuse outward in a circle, and the sample will move out with it. Mixtures of compounds will be partially separated and approximate R_f values can be estimated. Ideal R_f values should be in the range 0.30–0.60.

Consider the separation of an alcohol and an ester. Start with a relatively nonpolar solution of 90:10 (v/v) hexane/ethyl acetate. If the R_f values are below 0.2, test a second spot with 70:30 (v/v) hexane/ethyl acetate, then test other spots with 50:50 (v/v) hexane/ethyl acetate and with pure ethyl acetate. If an ethyl acetate system does not produce R_f values in the satisfactory range, select a

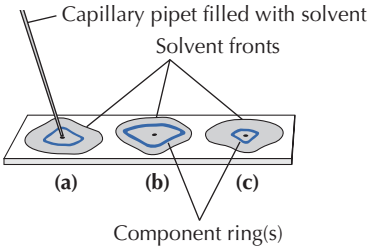


FIGURE 17.9
Rapid method for determining an effective TLC solvent: (a) good development; (b) and (c) poor development.

more polar solvent system such as a mixture of diethyl ether and acetone and repeat the test with various proportions.

17.8 Using TLC Analysis in Synthetic Organic Chemistry

In the synthesis of an organic compound you may have multiple compounds in the reaction mixture and the starting reagents may be the only known compounds available. TLC analysis has proved extremely useful both in determing when the limiting reagent is consumed—thus, the reaction is complete—and in ascertaining how many compounds are formed during the reaction.

Following the Course of a Reaction

A TLC plate is spotted with the limiting reagent in one lane and the reaction mixture in another lane. An initial TLC should be run on the reaction mixture as soon as all reagents are combined. Samples of the reaction mixture are then withdrawn from the reaction flask with a long micropipet at periodic intervals and analyzed by TLC. The reaction is complete when the lane with the reaction mixture no longer shows a spot with the same R_f as the limiting reagent in the other lane.

How Many Products Are Formed in the Reaction?

TLC analysis can be used to determine how many products are present in a reaction mixture where multiple products can be formed. Again, one lane is spotted with the limiting reagent for reference. Developing solvents of different polarities will need to be tested to ascertain how many compounds are in the mixture, because all the compounds present will not likely separate completely in every solvent.

17.9 Sources of Confusion

The R_f Values Are Very Similar

If the R_f values for two compounds are very similar—within ±0.05—then another solvent or mixture of solvents should be tested in order to distinguish between them.

Multiple Overspotting

A question that often arises is how many times to spot a sample on a TLC plate. The answer depends on several factors: the concentration of the spotting solution, the diameter of the capillary spotting tube, how long the capillary tube is in contact with the adsorbent, and the thickness of the adsorbent on the TLC plate. Do a quick trial to determine how many times to spot the sample solution by spotting two different amounts on the same plate and examining the spots under a UV lamp or by developing the TLC plate. Decide which gives the best results.

Purity of the Developing Solvent

The purity of the developing solvent is an important factor in the success of a TLC analysis and in obtaining reproducible R_f values. The presence of a soluble impurity can dramatically affect the developing power of the resulting solution compared with that of the pure solvent. For example, the presence of water in acetone changes its developing power appreciably, and therefore the R_f values will differ from values obtained with pure acetone.

No Spots Are Apparent on the Developed Plate

There are several possible reasons why no spots are seen on a developed plate—the origin line may have been submerged in the developing solvent, not enough sample was spotted on the TLC plate, the UV lamp was set on the wrong wavelength, the wrong side of the plate was irradiated, the dipped plate was not heated long enough to visualize the spots, or the compounds being analyzed are volatile and they evaporated from the plate.

The solvent level in the developing jar was too high. Check the solvent level in the developing jar. Was the depth of the solvent high enough to submerge the origin line containing the spots? If so, the spots probably leached into the developing solvent instead of moving up the plate as the solvent ascended.

Not enough sample was spotted. If the sample solution is too dilute or too little spotting is used, the developed spot might not be visible because there is not enough material to see.

The UV lamp was set at the wrong wavelength. Most UV lamps have two switches—one for short-wavelength light and one for long-wavelength light. Short-wavelength light is necessary for visualizing TLC plates. Check that you selected the correct switch.

The wrong side of the TLC plate was irradiated by the UV light. The spots will be visible only if you irradiate the side of the plate containing the TLC adsorbent.

The dipped plate was not heated long enough. A few minutes of heating are necessary to visualize the spots when *p*-anisaldehyde, vanillin, or phosphomolybdic acid visualizing solutions are being used.

The compounds being analyzed are volatile. A liquid sample with a boiling point below 160°C may evaporate from the TLC plate before the plate is visualized. A solid compound that sublimes could also do so before the plate is visualized.

Large, Overlapping, or Tailing Spots

The developed TLC plate may show very large spots, two spots that overlap at the center of the plate, or a spot that shows a long oval tail instead of being circular. Tailing spots, in particular, lead to poor reproducibility of R_f values. These problems are likely to arise because too large a sample of the spotting solution was applied to the TLC plate. Prepare another plate using smaller spots and less overspotting.

If the spots are still too large or if they tail, prepare a more dilute spotting solution.

Can I Get Quantitative Information from a TLC Analysis?

The size and intensity of the spots can be used as a rough measure of the relative amounts of the substances. These parameters can be misleading, however, especially with fluorescent visualization. Some organic compounds interact much more intensely with ultraviolet radiation than do others, making one spot appear to be more concentrated than another when that may not reflect their relative quantities. Quantitative information is not one of the strengths of thin-layer chromatography.

Further Reading

Fried, B.; Sherma, J. *Thin-Layer Chromatography: Techniques and Applications;* 4th ed.; Chromatographic Science Series, Vol. 81, Marcel Dekker: New York, 1999.

Hahn-Deinstrop, Elke, *Applied Thin-Layer Chromatography: Best Practices and Avoidance of Mistakes;* 2nd ed.: Wiley, New York, 2007.

Sherma, J.; Fried, B. (Eds.) *Handbook of Thin-Layer Chromatography;* 3rd ed.; Chromatographic Science Series, Vol. 89, Marcel Dekker: New York, 2003.

Touchstone, J. C. *Practice of Thin Layer Chromatography;* 3rd ed.; Wiley: New York, 1992.

Questions

1. When 2-propanol was used as the developing solvent, two substances moved with the solvent front (R_f = 1) during TLC analysis on a silica gel plate. Can you conclude that they are identical? If not, what additional experiment(s) would you perform?
2. The R_f value of compound A is 0.34 when a TLC plate is developed in hexane and 0.44 when the plate is developed in diethyl ether. Compound B has an R_f value of 0.42 in hexane and 0.60 in diethyl ether. Which solvent would be better for separating a mixture of A and B by TLC? Explain.
3. A student needs to analyze a mixture containing an alcohol and a ketone by silica gel TLC. After consulting Table 17.1, suggest a likely developing solvent.

TECHNIQUE

18 LIQUID CHROMATOGRAPHY

If Technique 18 is your introduction to chromatographic analysis, read the Essay "Modern Chromatographic Separations" on pages 219–220 before you read Technique 18.

Liquid chromatography (LC), also called column chromatography, and the related methods of flash chromatography and high-performance liquid chromatography (HPLC) are part of the chromatographic methods so important in experimental organic chemistry. Liquid chromatography is generally used to separate compounds of low volatility, whereas gas chromatography (GC) works only for volatile mixtures. Unlike thin-layer chromatography (TLC) and GC, liquid chromatography can be carried out with a wide range of sample quantities, ranging from a few micrograms for HPLC up to 10 g or more for column chromatography. Most liquid chromatography is carried out under partition conditions.

Overview of Liquid Chromatography (LC)

In liquid chromatography the stationary phase is a solid adsorbent with a liquid coating, packed into a column. An ***elution solvent*** serves as the mobile phase and consists of either a pure liquid compound or a solution of liquids. Gravity draws the elution solvent down the column. Separation occurs by selective interactions of the compounds in the sample with the stationary phase and the mobile phase. The relative polarities of these two phases determine the order in which compounds in the sample elute from the column. Figure 18.1 illustrates how a mixture of two compounds separates on a chromatographic column. With a polar adsorbent such as silica gel, the compound represented by A would be less polar than compound B. In reverse-phase chromatography, a relatively nonpolar adsorbent would be used, and the compound represented by A would be more polar than compound B.

18.1 Adsorbents

Most chromatographic separations today use silica gel ($SiO_2 \cdot xH_2O$) because it allows the separation of compounds with a wide range of polarities. Aluminum oxide (alumina, Al_2O_3) is also sometimes used for separations of compounds of low to medium polarity. Silica gel, however, has the advantage of being less likely than alumina to cause a chemical reaction with the substances being separated. Both adsorbents produce a polar stationary phase (aluminum oxide is more polar), and both are generally used with nonpolar to moderately polar elution solvents as the mobile phase.

Liquid chromatography at atmospheric or slightly higher pressure is used for the purification of samples that require only modest resolution. It uses relatively large—greater than 37 μm—adsorbent particles, which allow a reasonably fast flow of the mobile phase under these low-pressure conditions. In HPLC much smaller adsorbent particles are used, which requires high pressure to force the elution solvent through the column.

Silica Gel

For a simple gravity liquid chromatography column, 63–210 μm (70–230 mesh) particle size silica gel is usually used. Chromatographic silica gel has 10–20% adsorbed water by weight and acts as the solid support for this water under the conditions of partition chromatography. Compounds separate by partitioning themselves between the elution solvent and the water that is strongly adsorbed on the silica surface. The partition equilibria depend on the relative solubilities of the compounds in the two liquid phases. The adsorptive properties of silica gel may vary considerably from one manufacturer to another or even within different lots of the same grade from one manufacturer. Therefore, the solvent system previously used for a particular analysis may not work exactly the same way for another separation of the same sample mixture.

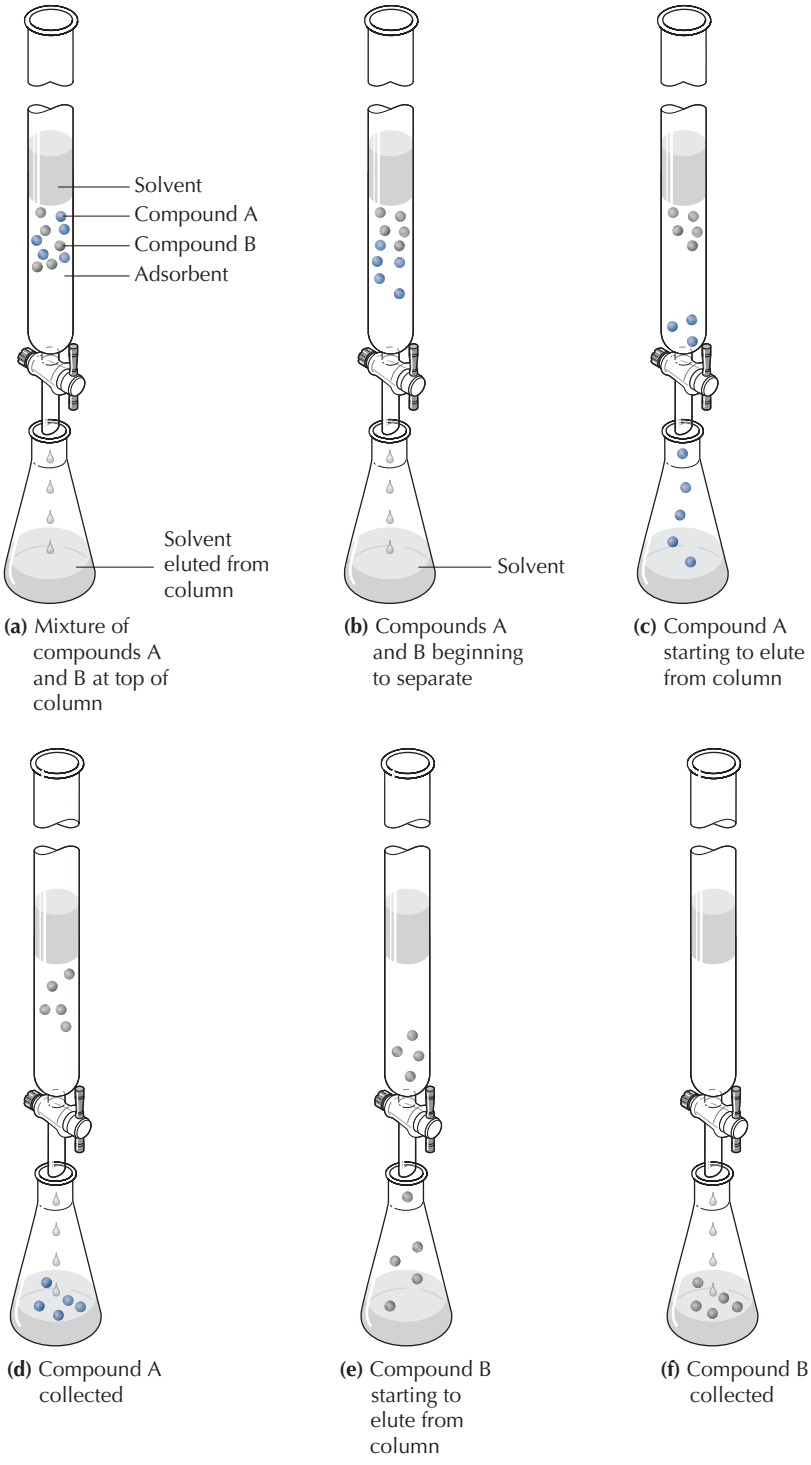


FIGURE 18.1 Stages in liquid chromatographic separation of a mixture containing compound A and compound B. Compound A moves faster than does compound B, which is more strongly adsorbed on the stationary phase.

Alumina

Activated alumina, made explicitly for chromatography, is available commercially as a finely ground powder in neutral (pH 7), basic (pH 10), and acidic (pH 4) grades. Different brands and grades vary enormously in adsorptive properties, mainly because of the amount of water adsorbed on the surface. The strength of the adsorption holding a substance on aluminum oxide depends on the strength of the bonding forces between the substance and the polar surface of the adsorbent.

Adsorbents for Reverse-Phase Chromatography

Reverse-phase chromatography is used most often for HPLC separations [see Technique 18.9]. The liquid stationary phase is less polar than the mobile phase and the separation of most nonvolatile organic compounds is very effective. Under reverse-phase conditions, elution of the more polar compounds occurs first, with the less polar compounds adsorbed more tightly to the stationary phase. For reverse-phase chromatography, the surface of silica particles is rendered less polar by replacing the Si—OH hydroxyl groups with alkoxy groups and long-chain alkyl groups (C_{12}–C_{18}).

18.2 Elution Solvents

In liquid chromatography, the ***elution solvents*** used to dislodge the compounds adsorbed on the column are made increasingly more polar as the separation progresses. Nonpolar compounds bind less tightly than polar compounds on a polar adsorbent, such as silica gel, and dislodge more easily with nonpolar solvents. Therefore, the nonpolar compounds in a mixture exit from the column first. The more polar compounds must be eluted, or washed out of the column, with more polar solvents.

Selecting an Elution Solvent

Silica gel usually works well as the adsorbent for separating most organic compounds. Thin-layer chromatography on silica gel plates [see Technique 17.7] can be used to determine a good solvent system for separating a mixture by liquid chromatography on silica gel. The separation on a silica gel TLC plate with a particular solvent or combination of solvents reflects the separation that the mixture will undergo with a silica gel column if the same solvent is used. A solvent that moves the desired compound to an R_f of approximately 0.3 should be a good elution solvent.

The proper choice of elution solvents and the amounts to use are, in part, a trial-and-error process. Polar compounds always require more polar elution solvents than do nonpolar compounds. For example, the separation of 1-decene from 2-chlorodecane requires elution solvents of low polarity, such as alkanes. However, the separation of the alcohol 2-decanol from its oxidation product, 2-decanone, requires more polar solvents, such as a hexane/diethyl ether mixture. If poor separation occurs because the compounds elute too rapidly, the elution solvent is too polar. Table 18.1 lists common elution solvents and organic compounds by functional group class in

TABLE 18.1 Relative polarities of common LC solvents and organic compounds on silica gel

Common elution solvents	Increasing polarity	Organic compounds by functional group class
Alkanes, cycloalkanes	↓	Alkanes
Toluene		Alkenes
Dichloromethane		Aromatic hydrocarbons
Diethyl ether		Ethers, halocarbons
Acetone (anhydrous)		Aldehydes, ketones, esters
Ethyl acetate		Amines
Ethanol (anhydrous)		Alcohols
Methanol		Carboxylic acids

order of increasing polarity. There is no universal series of eluting strengths because this property depends not only on the activity of the adsorbent but also on the compounds being separated.

Purity of Elution Solvents

Elution solvents for column chromatography must be rigorously purified and dried for best results. Small quantities of polar impurities can radically alter the eluting properties of a solvent. For example, the presence of water in a solvent can significantly increase its eluting power. Wet acetone may have an eluting power greater than anhydrous ethanol.

18.3 Determining the Column Size

The size of the column used for a liquid chromatography separation depends on how much material you want to separate. After deciding which adsorbent to use for a separation, you must decide how much adsorbent to use. In general, for a moderately challenging separation, you should use about ten to twenty times as much silica gel or alumina by weight as the material to be separated. More adsorbent should be used for a difficult separation, less for an easy one. If too little adsorbent is used, the column will be overloaded and the separation will be poor. If too much adsorbent is used, the chromatography will take longer, require more elution solvent, and be no more efficient.

Amount of Adsorbent

A height of 10–20 cm of silica gel often works well, and an 8:1 or 10:1 ratio of the adsorbent height to the inside column diameter is normal. Thus, a 1.5–2.5-cm column diameter is common for liquid chromatography on silica gel. A short, fatter column often produces worse separation, while a tall, thinner column can retain the compounds so tenaciously that the polar solvents required for their elution do not discriminate well between the various compounds on the column.

Calculation of Column Diameter

If you were carrying out a chromatographic separation on a 1.0-g sample, 15 g of silica gel would be appropriate. Silica gel has a bulk

density of about 0.3 g/cm^3, so 15 g would occupy a volume of 45–50 cm^3 (45–50 mL); this quantity is called the ***column volume.*** Aiming for a column height of 15 cm of silica gel, we can calculate the inside diameter of the necessary chromatography column. The column of silica gel is a cylinder with a volume of $\pi r^2 h$. If h = 15 cm and V = 50 cm^3, then r = 1.0 cm. Thus, a chromatography column with a 2-cm inside diameter would be appropriate. Common inside diameters for commercially available glass columns used in miniscale liquid chromatography are 1.9 cm and 2.5 cm.

Column Height

Usually one- to two-column volumes of elution solvent above the adsorbent are used to push the liquid through the silica gel column. Therefore, the chromatographic separation of 1.0 g of material on silica gel would require a glass column 2 cm in diameter and 40 cm long. Either a commercial chromatography column of 2.5-cm diameter and 30-cm length or one of 1.9-cm diameter and 40-cm length would be appropriate for the separation of a 1.0-g sample.

18.4 Miniscale Liquid Chromatography

After selecting a chromatography column and weighing the requisite amount of adsorbent, you are ready to prepare the column.The packing of a column is just as crucial to the success of the chromatographic separation as is the choice of adsorbent and elution solvents. If the column of adsorbent has cracks or channels or if the top surface is not flat, separation will be poor.

Figure 18.2 shows additional solvent above a completed chromatographic column. **It is essential that the column never be allowed to dry out once it is prepared,** so the solvent level should never be allowed to fall below the top of the sand above the adsorbent. If the adsorbent becomes dry, it may pull away from the walls of the column and form channels. **Once you begin a chromatographic separation, finish it without interruption.**

Preparation of a Miniscale Column

Clamp the chromatography column in an upright position on a ring stand or vertical support rod, and with the stopcock closed, fill it approximately one-half full either with the first developing solvent you plan to use or with a less polar solvent. Add a small piece of glass wool as a plug, and push it to the bottom of the column with a long glass rod, making sure all the air bubbles are out of the glass wool. Cover the glass wool plug with 3–4 mm of clean white sand. The glass wool plug and sand serve as a level support base to keep the adsorbent in the column and prevent it from clogging the stopcock. The adsorbent can be added to the column by either the dry method or the slurry method.

Dry adsorbent method. Place a powder funnel in the top of the column, and with the stopcock closed, pour the adsorbent slowly into the solvent-filled column. Take care that the adsorbent falls uniformly

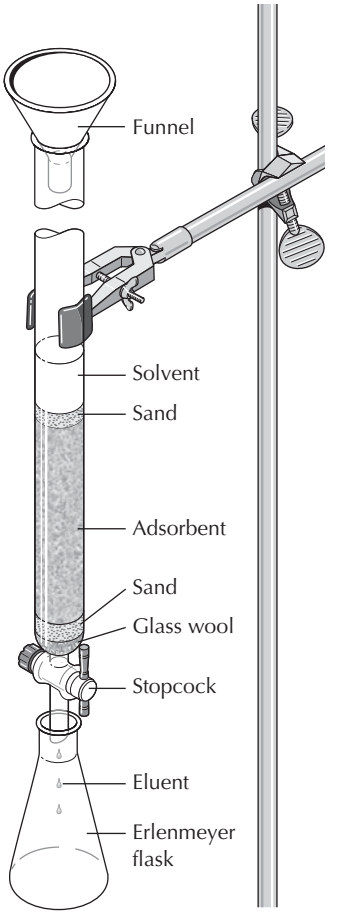


FIGURE 18.2
A completed chromatographic column.

to the bottom. Do not add the adsorbent too quickly or clumping may occur. The adsorbent column should be firm, but if it is packed too tightly, the flow of elution solvents becomes too slow.

The top of the adsorbent must always be horizontal. Gentle tapping on the side of the column as the adsorbent falls through the solvent prevents the formation of bubbles in the adsorbent. If large bubbles or channels develop in the column, the adsorbent should be discarded and the column should be repacked. Any irregularities in the adsorbent column may cause poor separation because part of the advancing sample will move faster than the rest. The time consumed in repacking will be much less than the time wasted trying to make a poor column function efficiently.

After all the adsorbent has been added, carefully pour 3–4 mm of white sand on top to protect the adsorbent from mechanical disturbances when solvents are poured into the column. Allow solvent to drip through the stopcock until only a small amount of solvent is above the sand and close the stopcock.

Slurry method. If you are using a liquid more polar than an alkane in packing the column, you may need to prepare a slurry of the adsorbent and solvent in an Erlenmeyer flask by **slowly** adding the

requisite amount of adsorbent to an excess of solvent. The use of a slurry prevents the formation of clumps or gas bubbles in the column, which can form from the heat produced by the interaction between polar solvents and the surface of the adsorbent.

Place a powder funnel in the top of the column and half fill the column with the same solvent used to prepare the slurry. Partially open the stopcock so that the solvent drains slowly into an Erlenmeyer flask. Swirl the flask containing the slurry and pour a portion of it into the column. Tap the side of the column constantly while the slurry is settling. Swirl the slurry thoroughly before each portion is added to the column. Add more solvent as needed so that the solvent level never falls below the level of the adsorbent at any time during the packing procedure. The solvent drained from the column can be reused for this purpose. Once all the adsorbent is in the column, return the collected solvent to the column once or twice to firmly pack the adsorbent.

Even packing of the adsorbent is essential to ensure that no cracks, air bubbles, or channels form while preparing the column.

After all the adsorbent has settled, carefully pour 3–4 mm of white sand on top. The layer of sand protects the adsorbent from mechanical disturbances when new solvents are poured into the column during the separation process. Be sure that there is a small amount of solvent above the sand and close the stopcock.

Application of Sample

Liquid samples can be applied directly onto the column, but a mixture of solids must be added to the column, either dissolved in a solvent or preadsorbed onto a small amount of silica gel. Before a liquid or solution sample is applied to a column, the solvent used in packing the column should be allowed to drain until its level is just at the top of the upper sand layer. Then close the stopcock.

Preparation of a sample solution. The solvent used in packing the column or another solvent of similar polarity is preferred for dissolving a solid sample. If the sample's components do not dissolve in the first elution solvent, a small amount of a more polar solvent can be used to prepare the sample solution. However, the sample solution should be as concentrated as possible, preferably less than 5 mL in volume. Poor separation will occur if the sample volume is too large—the compounds will begin to move down the column while the sample is still entering at the top.

Sample adsorbed on silica gel. Instead of preparing a sample solution, preadsorb the sample onto a small amount of silica gel, remove the solvent, and carefully pour the dry mixture onto the top of the column. For a miniscale sample, add 1–2 g of silica gel to a solution of the sample, remove the solvent using a rotary evaporator [see Technique 12.3]. Carefully add the dry powder to the top of the column.

Application of a liquid sample or sample solution onto a column. Draw the sample into a 9-in Pasteur pipet, hold the pipet with the tip just above the level of the sand, and add the sample **one drop at a time to**

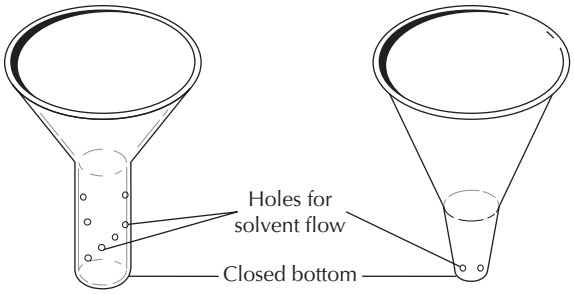


FIGURE 18.3
Chromatography funnels.

the center of the sand. Reopen the stopcock and allow the upper level of the sample solution to just reach the top of the sand; then close the stopcock again.

Final layer of sand. A thin layer of white sand, added to the column after the sample is applied, keeps the surface of the column from being disturbed when the elution solvent is added.

Elution of the Column

Fill the column with elution solvent carefully so that the upper layer of the column is not disturbed. The use of a chromatography funnel with a closed bottom and small holes in the stem wall provides a gentle flow of solvent down the wall of the tube that does not disturb the sand and adsorbent (Figure 18.3).

Fresh solvent needs to be added to the top of the column continuously during the elution process. **Do not allow the level of solvent to drop below the top of the adsorbent column** or the top surface of the adsorbent to be disturbed by the addition of solvents; if possible, use the type of funnel shown in Figure 18.3. Elution of the compounds in the sample is done by using a series of increasingly polar elution solvents. The less polar compounds elute first with the less polar solvents. Polar compounds usually come out of a column only after a switch to a more polar solvent. As the elution proceeds, the compounds in the mixture separate into a series of bands in the column (Figure 18.4). With colorless compounds, the bands are invisible; with colored compounds, the bands are seen.

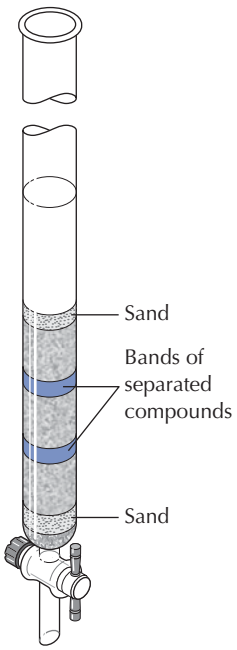


FIGURE 18.4
Chromatography column during elution.

Changing elution solvents during a separation. A mixture of two solvents is commonly used for elution. Addition of small amounts of a polar solvent to a less polar one increases the eluting power in a gentle fashion. For example, the development of the column can begin with hexane, and if nothing elutes from the column with this solvent, a 2–5% solution of diethyl ether in hexane can be used next, followed by a 10% solution of diethyl ether, then a 25% solution of diethyl ether, and then pure diethyl ether for the most polar compounds.

If the change of solvent is made too abruptly, enough heat may be generated from adsorbent/solvent bonding to cause cracking or channeling of the adsorbent column. In some cases, a low-boiling

elution solvent may actually boil on the column. The bubbles that form will degrade the efficiency of the column.

Flow rate of elution solvent. A greater solvent height above the adsorbent layer provides a faster flow rate through the column. An optimum flow rate is about 2–3 mL · min^{-1}. If the flow is too slow, poor separation may result from diffusion of the compound bands as they travel down the column. A reservoir at the top of a column can be used to maintain a proper height of elution solvent above the adsorbent so that an adequate flow rate is maintained. A separatory funnel makes a good reservoir. It can be filled with the necessary amount of solvent and clamped directly above the column. The stopcock of the separatory funnel can be adjusted so that elution solvent flows into the column as fast as it flows out at the bottom.

Size of elution solvent fractions. The size of the elution solvent fractions collected at the bottom of the column depends on the particular experiment. Common fraction sizes range from 10 to 50 mL for miniscale columns. If the separated compounds are colored, it is a simple matter to tell when the different fractions should be collected. However, column chromatography is not limited to colored materials.

With an efficient adsorbent column, each compound in the mixture being separated is eluted separately. After one compound has come through the column, there is a time lag before the next one appears. Hence, there are times when only solvent drips out of the column. To ascertain when you should collect a new fraction of eluent, either note the presence of crystals forming on the tip at the bottom of the column as the solvent evaporates or collect a few drops of liquid on a watch glass and evaporate the solvent in a hood. Any relatively nonvolatile compounds that are being separated will remain on the watch glass.

Removing the Adsorbent from the Column

When you are finished eluting the sample from the column, allow any remaining solvent to drain out. The chromatography tube can then be emptied by opening the stopcock, inverting the column over a beaker, and using gentle air pressure at the tip to push out the adsorbent.

Recovery of Separated Compounds

Ascertain the purity of each fraction by GC or TLC analysis and combine the fractions containing each pure component. Recover the compounds by evaporation of the solvent. Evaporation methods include using a rotary evaporator [see Technique 12.3] or blowing off the solvent with a stream of nitrogen or air in a hood.

18.5 Microscale Liquid Chromatography

Microscale liquid chromatography methods are used for samples of 100 mg or less.

18.5a Preparation and Elution of a Microscale Column

A column suitable for separating 50–100 mg of a mixture can be prepared in a large-volume Pasteur pipet.* Regular-size Pasteur pipets ($5\frac{3}{4}$ in) can be used for separating a 10–30-mg sample. **Prepare the sample solution and assemble all equipment and reagents for the entire chromatographic procedure before you begin to prepare the column.** The entire procedure of preparing the column and collecting the fractions must be done without interruption.

Preparation of the Sample

Dissolve the mixture being separated in a small test tube using 0.5–1 mL of the elution solvent or another solvent that is less polar than the elution solvent. Cork the tube until you are ready to apply the sample to the column.

Alternatively, add 300 mg of silica gel to the sample solution, and in a hood, evaporate the solvent by warming the sample container in a hot-water bath while stirring the mixture with a microspatula to prevent bumping. The dried solid is ready for addition to the column.

Test Tubes for Sample Collection

Label a series of 10 test tubes (13 × 100 mm) for fraction collection. Pour 5 mL of elution solvent into one test tube and mark the liquid level on the outside of the tube. Place a corresponding mark on the outside of the other 9 test tubes.

Packing the Column

Pour about 50 mL of hexane (or other nonpolar solvent) into an Erlenmeyer flask and cork the flask. Pack a small plug of glass wool into the stem of the large-volume Pasteur pipet, using a wooden applicator stick or a thin stirring rod (Figure 18.5, step 1). Clamp the pipet in a vertical position. Add a 2–3-mm layer of sand. Place a 25-mL Erlenmeyer flask underneath the column to collect the drained solvent. Place 1.7–1.8 g of silica gel adsorbent in a 50-mL Erlenmeyer flask; add approximately 15 mL of hexane to make a thin slurry. Transfer the adsorbent slurry to the Pasteur pipet column using a 9-in Pasteur pipet (Figure 18.5, step 2). Continue adding slurry until the column is two-thirds full of adsorbent. Fill the column four to five times with hexane to pack the adsorbent well. The eluted hexane can be reused for this purpose. **Note: Do not let the solvent level fall below the top of the adsorbent.** After the adsorbent is packed, add a 2–3-mm layer of sand above the adsorbent by letting it settle through the hexane.

Addition of the Sample and Elution of the Column

Allow the solvent level to almost reach the top of the adsorbent and place the test tube labeled "Fraction 1" under the column. Draw the sample mixture into a 9-in Pasteur pipet, hold the pipet tip just above the surface of the sand, and add the sample one drop at a time to the center of the column. When the entire sample is on the

*Available from Fisher-Scientific, catalog item 22-378-893; the pipets have a capacity of 4 mL.

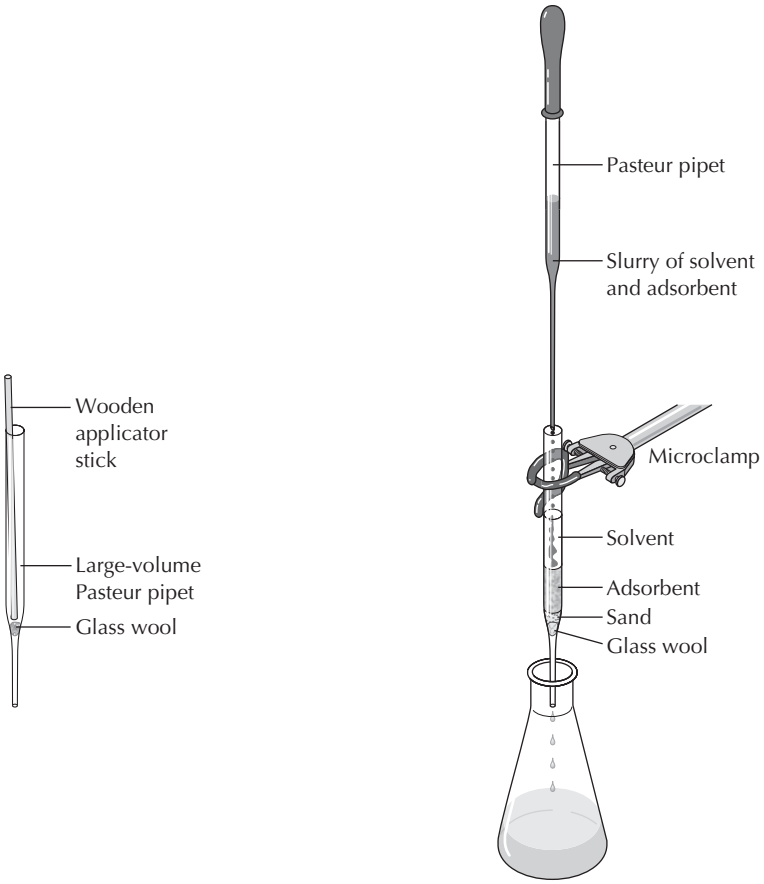


FIGURE 18.5 Setting up a microscale column.

column, use a 9-in Pasteur pipet to add the elution solvent by *gently running it down the interior wall of the pipet*. Maintain a column of solvent above the silica gel while you collect fractions of approximately 2–4 mL in the 10 labeled test tubes.

Recovery of Separated Compounds

Ascertain the purity of each fraction by GC or TLC analysis and combine the fractions containing each pure component. Recover the compounds by evaporation of the solvent either by using a rotary evaporator [see Technique 12.3] or by blowing off the solvent with a stream of nitrogen or air in a hood.

18.5b Preparation and Elution of a Williamson Microscale Column

The Williamson microscale chromatography apparatus is similar to the miniscale apparatus, except that it consists of several pieces fitted together. **Before you start to prepare the column, collect all the reagents and equipment you will need for the entire procedure.** Prepare 10 test tubes for sample collection as directed on page 245.

Preparation of the Sample

Dissolve the mixture being separated in a small test tube using 1 mL of the elution solvent or another solvent that is less polar than the elution solvent. Cork the tube until you are ready to apply the sample to the column.

Alternatively, add 300 mg of silica gel to the sample solution. In a hood, evaporate the solvent by warming the mixture in a hot-water bath while stirring with a microspatula to prevent bumping. The dried solid is ready for addition to the column.

Packing the Column

Assemble the plastic funnel, glass column, Buchner microfunnel with a polyethylene frit, and plastic stopcock as shown in Figure 18.6. With the stopcock closed, fill the column with hexane (or other nonpolar solvent) nearly to the top. Weigh approximately 3.0–3.5 g of silica gel adsorbent in a tared 50-mL beaker. Add enough hexane to make a thin slurry and swirl the beaker gently to thoroughly wet the adsorbent. Gently swirl the beaker to suspend the adsorbent and pour the mixture into the funnel. Place an Erlenmeyer flask under the column and open the stopcock to collect the solvent as it drains.

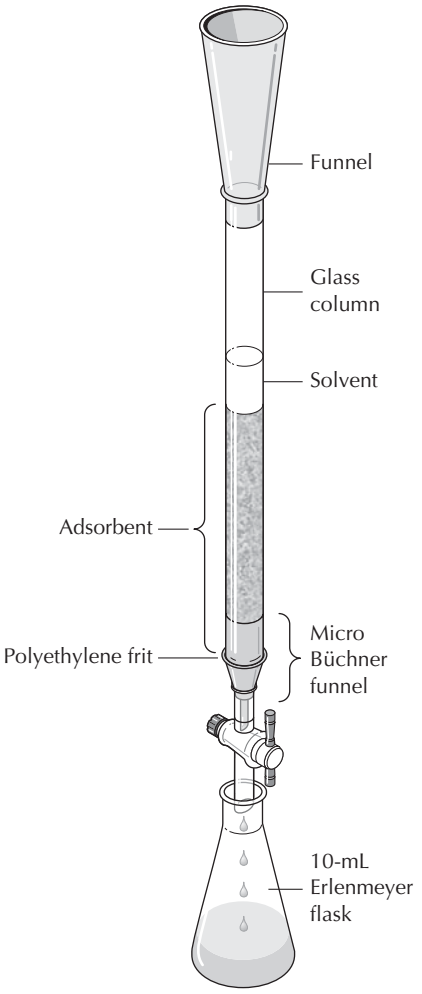


FIGURE 18.6
Williamson microscale column.

Use a few milliliters of solvent to rinse the remaining adsorbent from the flask and add the slurry to the funnel. Tap the side of the column gently to help pack the adsorbent. Close the stopcock when the solvent level is *just slightly* above the top of the adsorbent.

Addition of the Sample

Draw a liquid sample mixture into a 9-in Pasteur pipet, hold the pipet tip just above the surface of the adsorbent, and add the sample one drop at a time to the center of the column. Open the stopcock slightly to drain the solvent to *just above* the top of the adsorbent.

For a sample adsorbed on silica gel, drain the solvent to *exactly* the top of the adsorbent. Place the sample mixture on diagonally folded weighing paper and transfer it slowly into the funnel at the top of the column. After the sample is applied, add a 1–2-mm layer of white sand to the column. The sand prevents disturbance of the surface of the column when the elution solvent is added.

Elution of the Column

Fill the column with elution solvent by allowing the liquid to run down the side of the funnel slowly, open the stopcock, and begin collecting 2–4-mL fractions in labeled test tubes. Do not allow the solvent level to fall below the top of the column at any time during the elution. Continue to add solvent while collecting fractions.

Recovery of Separated Compounds

Ascertain the purity of each fraction by GC or TLC analysis and combine the fractions containing the pure components. Recover the compounds by evaporation of the solvent. Evaporation methods include using a rotary evaporator [see Technique 12.3] or blowing off the solvent with a stream of nitrogen or air in a hood.

18.6 Summary of Column Chromatography Procedures

1. Prepare a properly packed column of adsorbent.
2. Carefully add the sample mixture to the column as a small volume of solution or liquid, or as a solid adsorbed on silica gel.
3. Elute the column with progressively more polar solvents.
4. Collect the eluted compounds in fractions from the column.
5. Evaporate the solvents to recover the separated compounds.

18.7 Flash Chromatography

Gravity liquid chromatography, described in Techniques 18.1–18.4, can be quite time consuming, and it has been largely replaced by flash chromatography in research laboratories. However, it is important for you to read and understand Techniques 18.1–18.4 before you embark on flash chromatography. In ***flash chromatography,***

pressure is used to push the elution solvent through the adsorbent column. The flash technique is not only much faster but is also more efficient because the silica gel adsorbent has a smaller particle size, 38–63 μm (230–400 mesh), compared with 63–210 μm (70–230 mesh) for gravity columns. The total time to prepare and elute a column can be less than 30 min. The smaller particle size of the stationary phase requires pressures up to 20 pounds per square inch (psi), thus necessitating a chromatography column that does not leak and a source of nitrogen gas or compressed air. Although it is desirable to have an R_f difference of ≥0.35 for the compounds being separated, it is possible to separate compounds with an R_f difference of ~0.15.

Gas pressure controls the flow rate of the elution solvent through the column. One type of apparatus consists of a glass column topped by a variable bleed device (Figure 18.7). The bleed device has at its top a Teflon needle valve that controls the pressure applied to the top of the solvent in the column. Table 18.2 provides column and solvent dimensions for preparation of a flash silica gel column of 12–15 cm in height. Either the available flash column determines the range of sample sizes that can be accommodated or the size of the sample to be separated indicates the column size needed. Table 18.2 also shows that a smaller column diameter requires that the collected fraction sizes be correspondingly smaller. In addition, the smaller the difference in R_f values, the smaller the size of the sample that can be placed on the column. Elution fractions must be analyzed by TLC or GC.

Before running a flash column, the TLC characteristics of the sample's components should be determined. Ideally a solvent system that provides an R_f difference of ≥0.35 should be used. Systems that have been found useful include petroleum ether (30°–60°C)

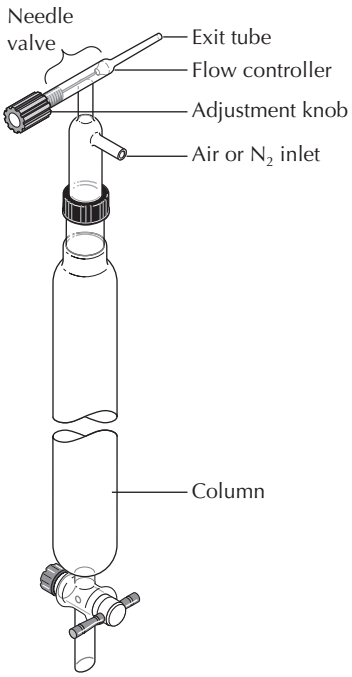


FIGURE 18.7
Apparatus for flash chromatography.

TABLE 18.2 Column dimensions and solvent volumes for flash chromatography

Column diameter, mm	Volume of eluent, mL	Typical sample size, mg		Recommended fraction size, mL
		$\Delta R_f \geq 0.2$	$\Delta R_f \geq 0.1-0.2$	
10	100	100	40	5
20	200	400	160	10
30	400	900	360	20
40	600	1600	600	30
50	1000	2500	1000	50

Source: Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43,* 2923–2925.

mixed with one of the following: diethyl ether, ethyl acetate, or anhydrous acetone. As in gravity liquid chromatography, the composition of the elution solvent can be changed during the course of elution.

Preparation of the Column

A flash chromatography column is prepared very much like a gravity column. The necessary calculation for finding the mass of silica gel to use for the column height you expect to use is discussed in Technique 18.3. Begin by placing a glass wool plug at the bottom of the flash column (a long glass tube may be used to insert the plug) and covering it with a thin layer (3–4 mm) of 50–100-mesh clean white sand. With the stopcock open, add, with tapping, 12–15 cm of 230–400-mesh silica gel to the solvent-filled column.* Alternatively, the adsorbent can be packed by the slurry method [see Technique 18.4]. Add a second layer of sand (3–4 mm) at the top of the silica gel and level it with gentle tapping.

Fill the column with the elution solvent. Use of a chromatography funnel, which has a closed bottom and small holes in the stem wall, provides a gentle flow of solvent down the wall of the column that does not disturb the packing of the sand and adsorbent (see Figure 18.3). Insert the flow controller, and with the needle valve open, gently turn on the flow of pressurized gas. Control the pressure by placing your finger (wear gloves) over the end of the exit tube, and manipulate the pressure so that the column is packed tightly. When the solvent has just reached the level of the sand, close the stopcock, and remove the flow controller.

Application of the Sample

Prepare a concentrated solution of the sample (25% or more) dissolved in the elution solvent. If the sample is not very soluble in the elution solvent, use a small amount of a more polar solvent. Draw the sample solution into a 9-in Pasteur pipet, hold the pipet with the tip just above the level of the sand, and add the sample **one drop at a time to the center of the sand.**

*Aldrich and other suppliers indicate whether the silica gel is suitable for flash chromatography.

Elution of the Column

After the sample is on the column, fill the column with the first elution solvent, using a chromatography funnel. Reinsert the flow controller and adjust the needle valve to reach an equilibrium pressure that causes the level of solvent to drop at a rate of 5 cm · min^{-1}. **Never let the column run dry**—the solvent must never go below the level of the top sand layer. Collect the proper fraction volumes of eluent solution (see Table 18.2) until all the solvent you planned to use has passed through the column of adsorbent or until fraction monitoring indicates that the desired components have been eluted.

Recovery of Separated Compounds

The purity of each fraction can be ascertained by GC or TLC analysis. Each of the fractions containing the same pure component should be combined before the compounds are recovered by evaporation of the solvent. As an evaporation method, you might use a rotary evaporator [see Technique 12.3] or blow off the solvent in the hood with a stream of nitrogen or air.

18.8 Sources of Confusion

Polarity of Elution Solvent

If the elution solvent is too polar, the sample mixture will elute too quickly and poor separation will result. If the solvent is not polar enough, the sample will elute too slowly and the bands of compounds will broaden by diffusion, again resulting in poor separation along with a waste of time and solvent. An elution solvent that produces an R_f of about 0.3 for the desired compound on silica gel TLC is best if the separation of the other components is adequate.

Packing the Column Unevenly

For a chromatography column to work successfully in separating a mixture, the adsorbent must be packed uniformly without air bubbles, gaps, or surface irregularities. If the packing is not satisfactory, the sample mixture will not separate well.

Nonhorizontal bands. Nonhorizontal bands result if the adsorbent surface at the top of the column is not flat and horizontal, if the column is not clamped in a perfectly vertical position, or if the sample is not evenly applied to the column (Figure 18.8a). If nonhorizontal bands are present, poor separation can result because the lower part of one band can coelute with the upper part of the next band.

Channeling. If a depression or other irregularity is present at the top of the adsorbent surface, if cracks occur in the adsorbent, or if an air bubble is trapped in the column, part of the advancing front of a band will move ahead of the rest of the band, a process called ***channeling*** (Figures 18.8b and 18.8c). If the fronts of two bands are close together, they may elute together, rendering the chromatographic separation ineffective.

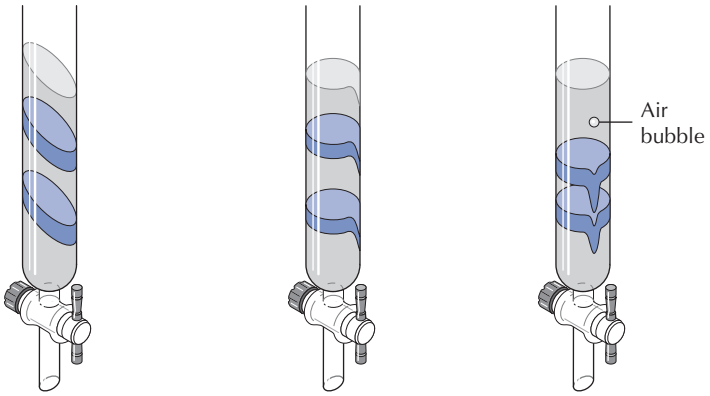


FIGURE 18.8
Problems that occur as a result of a poorly packed column.

(a) Nonhorizontal bands

(b) Channeling caused by irregular surface

(c) Channeling caused by air bubble

Applying the Sample Improperly

Achieving a good separation with a chromatography column depends on how the sample mixture is prepared and applied to the column. It is essential not to disturb the surface of the adsorbent column while the sample is applied. A liquid sample should be applied with a 9-in Pasteur pipet one drop at a time to the center of the column, with the tip of the pipet just above the adsorbent surface.

Overloading the column. If the amount of sample is too large for the amount of adsorbent used in packing the column, the column will be overloaded and incomplete separation of the mixture's components will occur. Calculate the correct amount of adsorbent to use with the information in Technique 18.3 for gravity chromatography or the information in Table 18.2 for flash chromatography.

Too much solvent in the sample solution. Prepare the sample in a minimal amount of solvent. If too much solvent is used to dissolve the sample, the excess will behave as an elution solvent and start to carry the mixture's components down the column. Separation will be incomplete because the entire sample was not on the column before its components started to move down the column.

The Column Becomes Dry

If the level of solvent falls below the top of the column, the adsorbent can become dry and pull away from the column wall. The channels that form compromise the effectiveness of the column. Be sure that the adsorbent is covered with solvent throughout the chromatographic procedure. Have all solvents at hand before starting the elution so that the separation can be completed without interruption.

Changing the Solvent Polarity Too Quickly

The polarity of the elution solvent often needs to be increased as the elution proceeds. However, the increase in polarity must be made gradually. If the polarity change is made too rapidly, enough heat may be generated from adsorbent/solvent bonding to cause gas bubbles that lead to channeling or even open cracks in the adsorbent column. The first change in polarity should add only 2–5% of the more polar solvent to the original elution solvent.

Diffuse Bands or Tailing

If the elution solvent flows through the column at too slow a rate or if it is not polar enough to displace the desired compounds at a reasonable rate, poor separation may result from diffusion of the bands at a faster rate than the substance moves down the column. The optimum flow rate is about 2–3 mL · min^{-1} for a gravity column and 15–20 mL · min^{-1} for a flash column.

18.9 High-Performance Liquid Chromatography

High-performance liquid chromatography (HPLC) is one of the most widely used analytical separation techniques. It allows analyses to be completed quickly with superior separation and sensitivity compared with other liquid chromatography methods. In this regard HPLC is comparable to gas chromatography. Like GC, HPLC utilizes small samples and is often used for the analysis of mixtures. Unlike GC, however, HPLC can be used equally well with volatile and non-volatile compounds. However, because of its high cost and demanding instrumental requirements, HPLC is not nearly as common in organic laboratory courses as GC. Virtually all organic chemistry research labs have access to HPLC instruments.

HPLC Columns and Injection Systems

HPLC is carried out with packed columns rather than the open-tubular columns used in GC capillary columns [see Section 19.2]. Diffusion in liquids is many times slower than diffusion in gases, so as molecules pass through an HPLC column in the mobile liquid phase they cannot diffuse quickly enough for effective adsorption equilibria to occur with a liquid stationary phase coating the column wall. The liquid stationary phase in packed HPLC columns has a particle size of only 3–10 μm. This small particle size produces efficient partition of compounds between the mobile phase and the liquid stationary phase on the very large surface area of the particles. However, particles of this small size pack very tightly, a condition that severely restricts the flow of solvent through the column. Consequently, pressures of 50–200 atmospheres are required to force solvent through an HPLC column at a reasonable rate.

The instrumentation for high-performance liquid chromatography consists of a column, a sample injection system, a solvent reservoir, a pump, a detector, and a recorder or computer readout. Figure 18.9 is a diagram of a typical HPLC setup.

At the onset of an HPLC run, an automated injection system (autosampler) is often used to inject a tiny amount of sample solution into the column. There is generally a short ***guard column*** in position before the more expensive main column. The guard column retains fine particles and strongly adsorbed compounds that would degrade the main column; it must be replaced periodically.

The length of the main column can range from 5 to 30 cm with an inner diameter of 1–5 mm for analytical HPLC of 0.01–1.0 mg samples. HPLC columns usually have a liquid stationary phase that is covalently bonded to microporous spherical silica (SiO_2) particles. These particles are permeable to solvent and have a very large surface area.

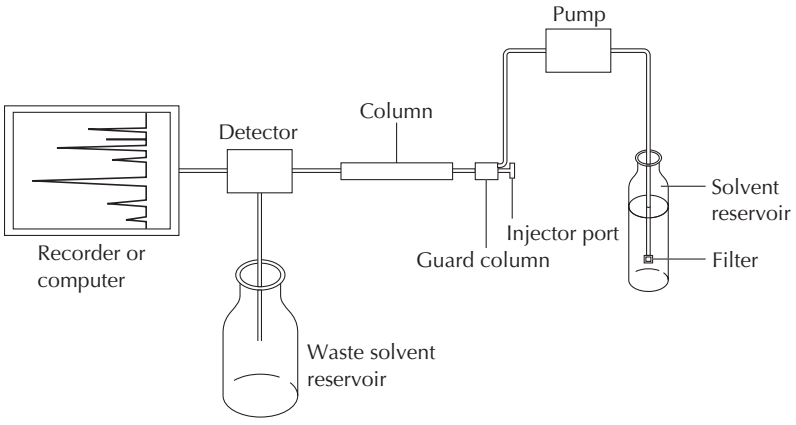


FIGURE 18.9
Schematic representation of a typical high-performance liquid chromatograph.

Reverse-Phase HPLC Columns

Most HPLC is done using ***reverse-phase*** chromatography, in which the mobile phase is polar and the stationary phase that covers the surface of the silica particles is a very thin layer of a nonpolar organic compound bonded to the particles. In reverse-phase chromatography the most polar compounds elute from the column first because they do not compete effectively for the nonpolar stationary phase. If inorganic salts and buffers are present in the sample, they are eluted very quickly. A generalized diagram of how a hydrophobic organic stationary phase is covalently bonded to the silica is shown in Figure 18.10.

By far the most popular bonded stationary phase in reverse-phase HPLC columns is the nonpolar C_{18} octadecyl group, which adsorbs organic compounds by van der Waals interactions. Other R groups, such as $(CH_2)_7CH_3$ and $(CH_2)_3C_6H_5$, can also be used. Reverse-phase columns are especially useful in separating moderately polar to polar compounds, but they can be used to separate most nonvolatile organic compounds. The more polar compounds elute first because the solvent is more polar than the nonpolar stationary phase.

Detectors

Simple HPLC systems use a fixed-wavelength, low-pressure 254-nm mercury vapor ultraviolet lamp as the detector. However, the most common type of detector is the sensitive diode-array UV/visible detector [see Technique 24 for the principles and practice of UV spectroscopy]. Diode-array detectors use 500–1000 individual detectors, each covering a discrete spectral region of 1–2 nm to accumulate an entire UV spectrum almost simultaneously as each compound emerges from the column. Analog signals from the detector are then

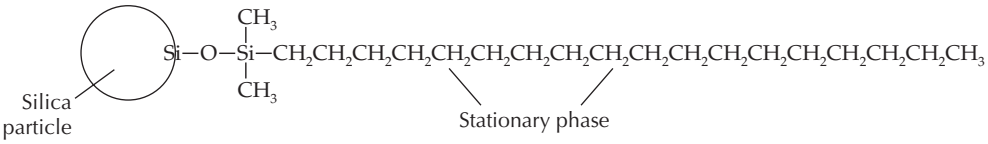


FIGURE 18.10 One mode of covalent attachment of a common liquid stationary phase to a microporous silica particle in reverse-phase HPLC.

digitized for computer manipulation. The only limitation of the photodiode-array detector is that compounds must have measurable UV absorbance above 210 nm to be detected. However, a majority of organic compounds fulfill this criterion.

HPLC is very useful for quantitative analysis if standards are available for constructing a calibration curve for the dependence of the detector signal on concentration. The measurements should be carried out under conditions where the measured absorbance is less than 1.0 and definitely no greater than 2.0. The photodiode-array detector generally has a good linear range over five orders of magnitude in which the Beer-Lambert law is followed (see Technique 24.1).

Sometimes refractometry detectors are utilized for HPLC. These detectors measure changes in the refractive index of the eluent as a sample's components move off the column and through the detector. Refractometry detectors are not as sensitive as diode-array UV detectors and cannot easily be used with gradient elution. However, they bypass the requirement that HPLC solvents and the compounds being analyzed must absorb UV light.

HPLC Solvents

The two most useful elution solvents for reverse-phase HPLC are methanol and acetonitrile ($CH_3C{\equiv}N$), which are usually mixed with water. Neither of these polar solvents absorbs UV radiation above 210 nm, so either one can be used with a photodiode-array UV detector. Combinations of $CH_3C{\equiv}N$ or CH_3OH with water are sufficient to separate most organic compounds. HPLC columns are easily degraded by dust and particles in the sample or the solvent. Consequently, the pressure necessary to push the solvent through the column can double during the life of a column because of progressive clogging. To minimize this problem, the solvent, which is stored in the solvent reservoir, is passed through a 0.5 μm pore filter before being pumped through the injector port.

Solvents used for HPLC must be of high purity because impurities can degrade the column by irreversible adsorption onto the stationary phase. Before use, solvents must also be purged with helium or by a vacuum to remove dissolved air. Dissolved O_2 absorbs ultraviolet radiation in the 200–250 nm wavelength range, which interferes with UV detectors.

Many HPLC instruments can accommodate a gradient elution system, allowing the composition of the solvent to be changed during the course of a separation. During gradient elution, the mobile phase is changed from a more polar solvent, which is less able to move compounds through the column, to a less polar solvent; this change gives improved sensitivity and shorter analysis times.

Sample Preparation

The ideal solvent for sample preparation is the same solvent as that used for the mobile liquid phase. Approximately 10–150 μL of a very dilute solution (0.0001–0.001 M) are normally used for the injection sample. A solution of 1 mg or less of the sample is prepared in approximately 5 mL of solvent. The sample solution must be filtered through a micropore filter of about 0.5 μm pore size to remove any solid impurities that could clog the HPLC column. The filtration is

done by taking up about 1 mL of the sample solution into a syringe and injecting it through the micropore filter into a small vial. After filtration, the vial is usually capped with a rubber septum. The vial is placed in the correct position in the HPLC instrument, and the automatic injection system often used does the rest when the chromatography run is initiated. Consult your instructor about specific operating procedures for the HPLC instrument in your laboratory.

Further Reading

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Questions

1. Once the adsorbent is packed in a liquid chromatography column, it is important that the level of the elution solvent not drop below the top of the adsorbent. Why?
2. What precautions must be taken when you introduce a mixture of compounds to be separated onto a liquid chromatography adsorbent column?
3. What effect will the following factors have on a liquid chromatographic separation? (a) too strong an adsorbent (b) collection of large elution fractions (c) very slow flow rate of the mobile phase
4. Arrange the following compounds in order of decreasing ease of elution from a column of silica gel. (a) 2-octanol (b) 1,3-dichlorobenzene (c) *tert*-butylcyclohexane (d) benzoic acid
5. Why do silica gel columns having smaller particle size produce more effective chromatographic separations?

TECHNIQUE 19

GAS CHROMATOGRAPHY

If Technique 19 is your introduction to chromatographic analysis, read the Essay "Modern Chromatographic Separations" on pages 219–220 before you read Technique 19.

Few techniques have altered the analysis of volatile organic chemicals as much as gas chromatography (GC), also called gas-liquid chromatography (GLC). Before GC became widely available just over fifty years ago, organic chemists usually looked for ways to convert liquid compounds into solids in order to analyze them. Gas chromatography changed all that by providing a quick, easy way for both qualitative and quantitative analysis of volatile organic mixtures. In addition, GC has a truly fantastic ability to separate complex mixtures.

Gas chromatography does, however, have limitations. It is useful only for the analysis of small amounts of compounds that have vapor pressures high enough to allow them to pass through a GC column, and, like thin-layer chromatography (TLC), gas chromatography does not identify compounds unless known samples are available. Coupling a gas chromatograph with a mass spectrometer (GC-MS) combines the superb separation capabilities of GC with the superior identification methods of mass spectrometry [see Technique 23].

Overview of Gas Chromatography

GC is an example of partition chromatography, where the compounds being analyzed adsorb on the stationary phase. The stationary phase consists of a nonvolatile liquid, usually a polymer, with a high boiling point. The mobile phase is an inert gas, generally helium or nitrogen. Unlike LC and TLC, where the mobile phase actively competes with the stationary phase for the compounds being analyzed, in GC the mobile phase does not interact with the compounds. The inert gas simply carries them down the column when they are in the vapor state.

In capillary columns, the stationary phase is a thin, uniform, liquid film applied either to the interior wall of a long, narrow capillary tube or to a thin layer of solid support lining the capillary tube. In either case, a clear channel through the center is left for passage of a carrier gas and molecules of the sample (Figure 19.1a). For older, packed-column chromatographs, the liquid is coated on a porous, inert solid support that is then packed into a tube (Figure 19.1b). Packed GC columns have nonuniform films of the stationary phase in the pores of the solid particles.

When the mixture being separated is injected into the heated injection port, the components vaporize and are carried by the carrier gas into the column, where separation occurs. The compounds in the mixture partition themselves between the gas phase and the liquid phase in the column, in an equilibrium that depends on the temperature, the rate of gas flow, and the solubility of the components in the liquid phase (Figure 19.2)

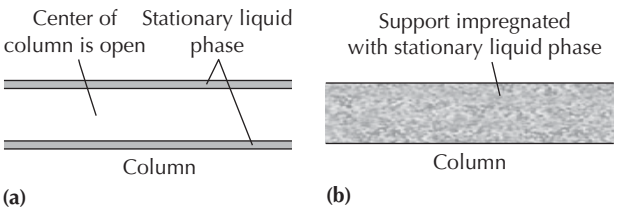


FIGURE 19.1 Microview of (a) a wall-coated open tubular capillary column and (b) a packed column.

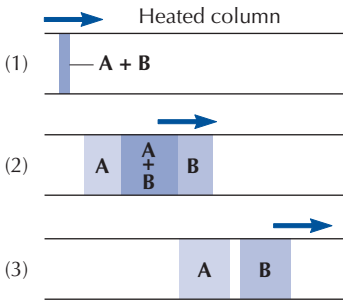


FIGURE 19.2 Stages in the separation of a two-component (**A, B**) mixture as it moves through a packed column.

Mixtures separate during gas chromatography because their components interact in different ways with the liquid stationary phase. A GC column has thousands of theoretical plates as a result of the huge surface area on which the gas and liquid phases can interact [see Technique 13.4, page 157, for a discussion of theoretical plates]. The partitioning of a substance between the liquid and gas phases depends on both its relative attraction for the liquid phase and its vapor pressure. The greater a compound's vapor pressure, the greater its tendency to go from the liquid stationary phase into the mobile gas phase. So, in the thousands of liquid-gas equilibria that take place as substances travel through a GC column, a more volatile compound spends more time in the gas phase than does a less volatile compound. In general, lower-boiling compounds with higher vapor pressures travel through a GC column faster than higher-boiling compounds.

19.1 Instrumentation for GC

The basic parts of a gas-liquid chromatograph are as follows:

- Source of high-pressure pure ***carrier gas***
- ***Flow controller***
- Heated ***injection port***
- ***Column*** and ***column oven***
- ***Detector***
- ***Recording device*** or ***data station***

These components are shown schematically in Figure 19.3.

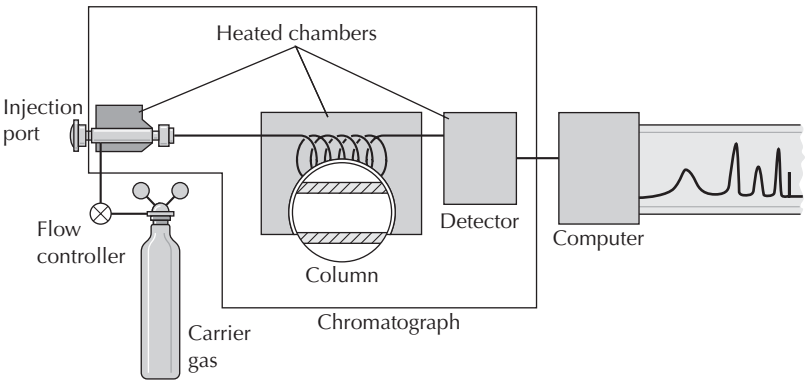


FIGURE 19.3 Schematic diagram of a gas-liquid chromatograph.

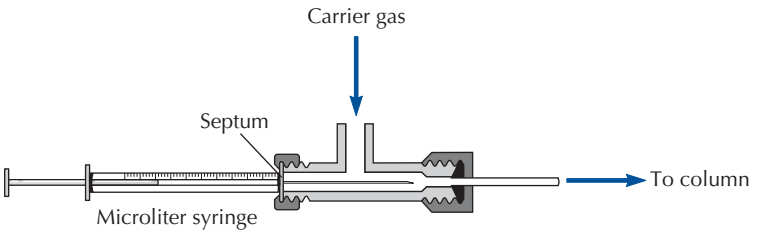


FIGURE 19.4
Injection port during sample injection.

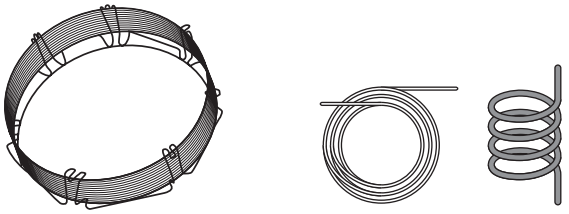


FIGURE 19.5
GC columns.

A small hypodermic syringe is used to inject the sample through a sealed rubber septum or gasket into the stream of carrier gas in the heated injection port (Figure 19.4). The sample vaporizes immediately and the carrier gas sweeps it into the column—a metal, glass, or fused-silica tube that contains the liquid stationary phase (Figure 19.5). The column is enclosed in an oven whose temperature can be regulated from just above room temperature to greater than 200°C. After the sample's components are separated by the column, they pass into a detector, where they produce electronic signals that can be amplified and recorded.

19.2 Types of Columns and Liquid Stationary Phases

A gas chromatograph can have either capillary or packed columns. Capillary columns, also called open tubular columns, have an interior diameter of only 0.2–0.5 mm and a length of 10–100 m. A packed column typically has an interior diameter of 2–4 mm and a length of 2–3 m. Capillary columns usually give much better separation than do packed columns. The greater length of capillary columns and the better diffusion of sample molecules in and out of the liquid phase provide more theoretical plates whereby equilibration of the sample molecules with the liquid stationary phase and the gas phase can occur. Capillary columns not only give better separations, they also do it in a much shorter analysis time.

Types of Columns

Capillary columns. Several types of capillary columns are available. In a ***wall-coated open tubular column (WCOT),*** the liquid phase coats the interior surface of the tube, leaving the center open. In a ***support-coated open tubular column (SCOT),*** the liquid phase coats a thin layer of solid support that is bonded to the capillary wall, again leaving the center of the column open.

Packed columns. The solid support in packed columns (and SCOT capillary columns) consists of a porous, inert material that has a very large surface area. The most commonly used substance is calcined diatomaceous earth, which contains the crushed skeletons of algae, especially diatoms. Its major component is silica. The efficiency of separation increases with decreasing particle size as a consequence of the expanded surface area available for the liquid coating. With packed columns, however, there is a practical lower limit to the particle size because increased gas pressure is necessary to push the mobile phase through a column packed with smaller particles. The liquid stationary phase coats the pores of the solid stationary phase.

Nature of the Liquid Stationary Phase

The liquid stationary phase interacts with the substances being separated by a number of intermolecular forces: dipolar interactions, van der Waals forces, and hydrogen bonding [see the Essay "Intermolecular Forces in Organic Chemistry" on pages 99–103]. These intermolecular forces determine the relative volatility of the adsorbed compounds and play important roles in the separation process.

As a general rule, a liquid phase provides the best separation if it is chemically similar to the compounds being separated. Nonpolar liquid coatings are used to separate nonpolar compounds, and polar liquid phases are best for separating polar compounds. In part, this rule is simply a manifestation of the adage "Like dissolves like." Unless the sample dissolves well in the liquid phase, little separation occurs as the sample passes through the column. Table 19.1 lists some commonly used liquid stationary phases for both packed and capillary columns and gives their chemical composition.

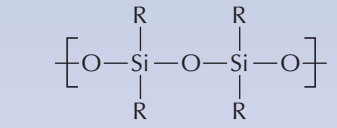
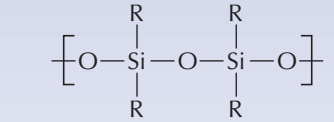
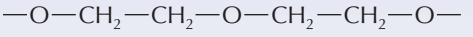
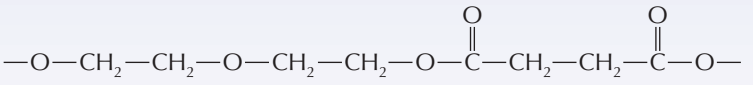
Silicones, or polysiloxanes, are polymers with a silicon/oxygen backbone, which can have variation in the R groups attached to the silicon atoms. If all the R groups are methyl, the liquid phase is nonpolar. Substituting benzene rings (phenyl groups) for 5–10% of the methyl groups increases the polarity somewhat. Substitution of other functional groups for the methyl groups of polydimethylsiloxane provides a wide variety of stationary phases suited to almost any application.

Polyethylene glycol, commonly called Carbowax, and diethylene glycol succinate are polymers frequently used as liquid phases for separating polar compounds, which they dissolve in part by being good hydrogen bond acceptors.

Useful Temperature Range of a Liquid Phase

An important characteristic of a liquid phase is its useful temperature range. A stationary phase cannot be used under conditions in which it decomposes or in which its vapor pressure is high enough that it vaporizes from the column. All liquid stationary phases evaporate, or "bleed," if they are heated to a high enough temperature; this vaporized material then fouls the detector. Therefore, GC columns have specified temperature maxima.

TABLE 19.1 Common GC liquid stationary phases

Polarity of column	Maximum temperature (°C)	Chemical composition
Nonpolar	225	 R = CH_3 Polydimethylsiloxane (methyl silicone)
Medium polarity	300	 R = CH_3 or C_6H_5 Polymethylphenylsiloxane (methylphenyl silicone) Typically, 5–50% of the R groups are phenyl
Polar	250	 Polyethylene glycol (Carbowax)
	200	 Diethylene glycol succinate (DEGS polyester)

Selecting a Liquid Phase

The proper choice of a liquid stationary phase is often a trial-and-error process. Published experimental procedures usually specify the type of column used for a GC analysis, but eventually you might have to make your own choices. Tables of appropriate liquid phases for specific classes of compounds can be found in the Further Reading references at the end of the technique.

19.3 Detectors

Two kinds of detectors are most often used in gas-liquid chromatography: ***flame ionization detectors*** and ***thermal conductivity detectors.*** The function of a detector is to "sense" a material and convert the sensing into an electrical signal.

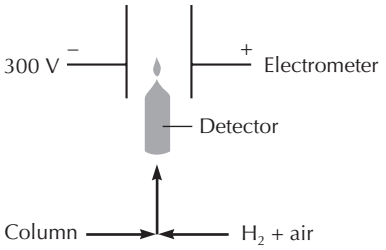


FIGURE 19.6 Flame ionization detector.

Flame Ionization Detectors (FIDs)

Flame ionization is a highly sensitive detector system that is commonly used with capillary columns, where the amount of sample reaching the detector is substantially less than that emanating from a packed column. In a flame ionization detector, the organic substances leaving the column are burned in a hydrogen/air flame (Figure 19.6). The combustion process produces ions that alter the current output of the detector.

$$H_2 + O_2 + \text{organic} \xrightarrow{\Delta} CO_2 + H_2O + 2(\text{ions})^+ + (\text{ions})^- + e^-$$

$$\Sigma(\text{ions})^- + \Sigma e^- \rightarrow \text{electric current}$$

In the chromatograph, the electrical output of the flame is fed to an electrometer, where the response can be recorded.

Thermal Conductivity Detectors (TCDs)

The older thermal conductivity detectors operate on the principle that heat is conducted away from a hot body at a rate that depends on the composition of the gas surrounding it. In other words, heat loss is related to gas composition. The electrical component of a thermal conductivity detector is a hot wire or filament. Most of the heat loss from the hot wire of the detector occurs by conduction through the gas and depends on the rate at which gas molecules can diffuse to and from the metal surface. Helium, the carrier gas most often used with thermal conductivity detectors, has an extremely high thermal conductivity. Larger organic molecules are less efficient heat conductors because they diffuse more slowly. With only carrier gas flowing, a constant heat loss is maintained and there is a constant electrical output. When an organic compound reaches the detector, the gas composition changes and causes the hot filament to heat up and its electrical resistance to increase. The change in electrical resistance creates an imbalance in the electrical circuit that can be recorded.

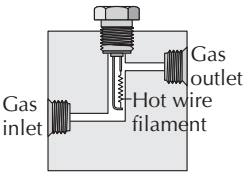


FIGURE 19.7 Thermal conductivity detector.

In practice, the filament of a thermal conductivity detector, a tungsten/rhenium or platinum wire, operates at temperatures from 200°C to over 400°C. An enlarged view of a common thermal conductivity detector is shown in Figure 19.7. Thermal conductivity detectors have the advantages of stability, simplicity, and the option of recovery of the separated materials but the disadvantage of low sensitivity. Because of their low sensitivity, they are unsuitable for use with capillary columns.

19.4 Recorders and Data Stations

The recorded response of the detector's electrical signal as the sample passes through it over time is called a ***chromatogram.*** A typical chromatogram for a mixture of alcohols, which plots the intensity of the detector response against time, is shown in Figure 19.8. The chromatogram shows the changes in the electrical signal as each component of the mixture passes through the detector. You will notice that the later peaks are somewhat broader. This pattern is typical; the longer a compound remains on the column, the broader its peak will be when it passes through the detector.

Most modern gas chromatographs are equipped with a computer-based data station that allows manipulation of the results and their display on the recorder. Not only can the computer print out the chromatogram, but it automatically prints out a table containing the following data:

- Retention time in minutes
- Area under each peak
- Percentage of the total area

Retention Time

Under a definite set of experimental conditions, a compound always travels through a GC column in a fixed amount of time, called the ***retention time.*** The retention time for a compound, like the R_f value in thin-layer chromatography, is an important number, and it is reproducible if the same set of instrumental parameters is maintained from one analysis to another.

Figure 19.9 shows how retention times are determined from a chromatogram. The distance from the time of injection to the time at which the peak maximum occurs is the retention time for a compound. Most computer-based data stations label the top of each peak on the chromatogram with its retention time. If you are not using a data station, you can determine the retention time manually by measuring the distance from the injection to the peak on the chromatogram and dividing it by the recorder chart speed.

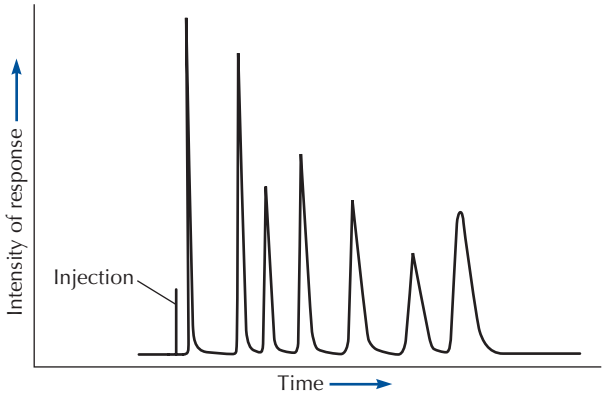


FIGURE 19.8
GC of a complex mixture of alcohols.

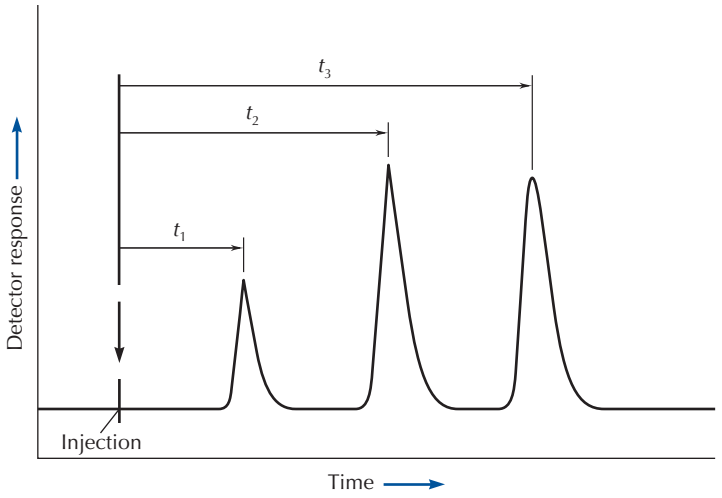


FIGURE 19.9
Measuring retention times.

The retention time depends on many factors. Of course, the compound's structure is one of them. Beyond that, the kind and amount of stationary liquid phase used in the column, the length of the column, the carrier gas flow rate, the column temperature regimen, the solid support, and the column diameter are most important. To some extent, the sample size can also affect the retention time. **Always record these experimental parameters when you note a retention time in your lab notebook**.

Peak Areas

If you are not using a modern, computer-based data station, see Technique 19.8 for the determination of peak areas. If you are using a GC instrument with a data station, tick marks on the chromatogram show the limits of what is included in each calculated area printed out in the data table and a two- or three-letter code on the table of results tells which method was used to calculate each peak area.

There may be small peaks that are not included in the data table because their areas are smaller than the area rejection setting of the data station. This feature makes it possible to ignore the noise that is present on any gas chromatogram. If it is important to know the area of a small peak, the area rejection setting can easily be changed.

Most computer-based data stations present data to many significant figures past the decimal point. In fact, the data are not nearly as precise as the number of significant figures implies and they cannot be duplicated to such a precise extent. **You should report the areas on data station printouts to only three or at most four significant figures**.

If a solvent is included in the sample being analyzed, its area may be a large part of the total integration area. If you are interested in only the relative percentages of two peaks on the chromatogram, you can calculate their relative amounts by using only their two areas, as well as their sum.

19.5 Practical GC Operating Procedures

Modern GCs have great analytical power, but they are also complex. You need to learn the functions of many buttons, switches, and dials, and you need to learn the sequential steps in the procedure for readying the gas chromatograph for an analysis. Your instructor or lab technician will probably have already set a number of the instrumental parameters, but you should always check to ensure that they have been set correctly. Your instructor will show you how to do these operations; the procedures vary for different instruments.

Turning on the GC and Adjusting the Carrier Gas

First make sure that the chromatograph and the detector are heated and ready to go and that the carrier gas is on and its pressure is properly set. The necessary pressure depends on the instrument and columns you are using, so check with your instructor before changing the pressure setting. Capillary-column chromatographs have built-in flowmeters. Flow rates for capillary columns generally range from 60 to 70 mL/min.

With a packed column that is 2 m long and 3 mm in diameter, a flow rate of 20–30 mL/min is common; for a 6-mm column of the same length, 60–70 mL/min is usual. A convenient measure of the carrier gas flow rate in a packed-column chromatograph is made at the exit port by using a soap-film (bubble) flowmeter.

Choosing the Correct GC Column and Temperatures

Most modern gas chromatographs have two different columns, only one of which is operational at any time. You can activate the column of your choice with the flick of a switch. Decide whether a polar or nonpolar column is needed to separate the sample being analyzed and send the signal for that column to the detector. You also need to see that the GC column oven temperature is set properly for your sample and that the detector and the injector port are at the correct temperatures. Temperature equilibration of the column can require 20–30 min for a given set of operating parameters.

The column temperature can be programmed to increase during an analysis on modern capillary-column GCs. This feature gives the instrument far greater flexibility compared with the older isothermal gas chromatographs where a constant column temperature is used. Having the option of temperature programming allows you to begin a GC run at 50°C or so and then increase the column temperature at a selected rate per minute until it reaches a selected maximum temperature. Using temperature programming allows the efficient and quick separation and analysis of organic mixtures whose components have widely different volatilities.

Turning on the Detector

If you are using a flame ionization detector, the hydrogen and air tanks must be regulated with the correct flow rates, and the flame must be lit. It's likely that your instructor will carry out this operation.

Before the sample is injected, the detector circuit must be balanced and the proper sensitivity (attenuation) chosen for the analysis. If you are using a thermal conductivity detector, you must turn on the inert carrier gas flow 2–3 min before the detector current is turned on. The thin metal filament of the detector can oxidize and burn out in the presence of oxygen, much like a tungsten lightbulb.

Sample Size and Microliter Syringes

When the instrument is ready and the sample is prepared, you can inject the sample. Gas chromatographs take very small samples; if too much sample is injected, poor separation will occur from overloading the column. **Injecting the proper amount of sample is the most important operation in obtaining a useful gas chromatogram.** Consult with your instructor about sample preparation and size for the chromatographs in your laboratory.

Capillary-column GC. For a capillary-column GC, the sample must be in a dilute solution. A 2–5% solution in a volatile solvent, such as diethyl ether, works best. Usually 1 drop of a liquid or 20–50 mg of a solid sample diluted with 1 mL of the solvent is sufficient. Then only 0.5–1.0 μL of this dilute sample solution is injected into the GC with a microliter syringe. Even this amount of sample can overload a capillary column, so the injected mixture is split into two highly unequal flows and the smaller one is actually introduced into the column. A split ratio of 1:50 is not uncommon.

For some capillary chromatographs, it may be necessary to pull the plunger back until the entire sample is inside the syringe barrel before inserting the needle. Ask your instructor if this step is necessary for the chromatographs in your laboratory.

Packed-column GC. For a packed-column GC, 1–3 μL of a volatile mixture are directly injected through the rubber septum with a microliter hypodermic syringe.

Injection Technique

Proper injection technique is important if you want to get well-formed peaks on the chromatogram. Using both hands, insert the needle all the way into the injection port and immediately push the plunger with a smooth, rapid motion (Figure 19.10). **Withdraw the syringe needle immediately after completing the injection.** This procedure ensures that the entire sample reaches the column at one time and that there is minimal disturbance of the gas flow. If your GC is equipped with a computer-driven, automatic digital integrator, simply press the start button after withdrawing the syringe needle.

If you are using a noncomputerized packed-column GC, the time of injection can be recorded in several ways. A mark can be made on the recorder base line just after the sample has been injected, but this action may be difficult to do reproducibly. If the GC has a thermal conductivity detector, a better way is to include several microliters of air in your syringe. The air is injected at the same time as the sample, and it comes through the column very quickly as the first tiny peak. Retention times can then be calculated using this

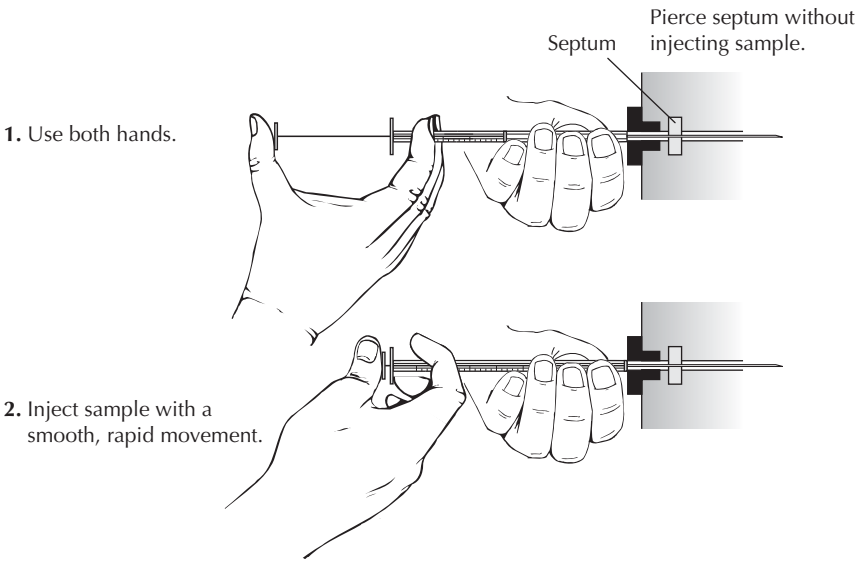


FIGURE 19.10 Injecting the sample into the column.

air peak as the injection time. It is worth noting that an air peak cannot be used to mark injection time with a flame ionization detector because air does not burn and thus gives no peak.

Completion of a Chromatographic Separation

After injection, wait for the peaks to appear on the moving chromatogram. If you are analyzing mixtures with a known number of components, you need wait only until the last component has come through the column before terminating the chromatographic run. If the analysis involves an unknown mixture, it is sometimes difficult to know exactly how long to wait before injecting another sample because components with unexpectedly long retention times may still be present in the column. Determination of the total analysis time for unknown mixtures is a matter of trial and error. Refer to Technique 19.4 for interpretation of retention times and integration data on computer-driven data stations.

Keeping Microliter Syringes Clean

A microliter syringe has a tiny bore that can easily become clogged if it is not rinsed after use. If viscous organic liquids or solutions containing acidic residues are allowed to remain in the syringe, you may find that it is almost impossible to move the plunger. For this reason, a small bottle of acetone is often kept beside each GC instrument. One or two fillings of the syringe with acetone will normally suffice to clean it, if done directly after an injection.

During a series of analyses, it is unnecessary to rinse the syringe with acetone after each injection. This practice may even cause confusion if traces of acetone show up on the chromatogram. For multiple analyses, it is best to rinse the syringe several times with the next sample to be analyzed before filling the syringe with the injection sample.

When you have finished your analyses, thoroughly rinse out the microliter syringe with acetone.

Record Keeping

Attach your GC printouts firmly in your lab notebook, along with a notation of the experimental conditions under which the chromatograms were run. Record the following experimental parameters:

- Injection port temperature
- Column temperature and programmed temperature ramp (if applicable)
- Detector temperature
- Carrier gas flow rate
- Injection sample size
- Length of column and identity of its liquid stationary phase

19.6 Sources of Confusion

Modern GCs have great analytical power but they are also complex, and to get good results many factors require careful attention. Using a GC requires thinking and problem-solving skills. Mastering the operation of a gas chromatograph—with the various adjustments of the column, injector port, and detector temperatures, the carrier gas flow rate, the hydrogen/air fuel mixture, and the sensitivity controls—can seem formidable. Yet it is worth the challenge, because there are few other ways to get quantitative data on the composition of organic mixtures quickly.

Instrumental Parameters

A number of the instrumental parameters are likely to be set by your instructor or lab manager, but you should always check to ensure that they have been set correctly. It pays to be careful and systematic in setting up the chromatograph, because if a key factor is overlooked, you have to make the somewhat frustrating decision of how long to wait before you decide to abort a questionable experimental run that is under way. Remember also that compounds from an earlier aborted run may still be in the GC column. They may then come through the detector at unexpected times in the next chromatographic run.

Poor Separation of a Mixture

If the components of your mixture are not well separated, a number of factors can be adjusted. You may have injected too much sample into the column, the column temperature may be too high, or the wrong liquid stationary phase may have been used. Adjust only one parameter at a time until you have achieved a good separation of the mixture.

Trace Amounts of Impurities

If you are using a capillary-column GC, you will probably see many small peaks on your chromatogram that indicate the presence of trace impurities, even if you are analyzing a "pure" compound. There are virtually always tiny amounts of impurities in pure compounds. A GC chromatogram can be a vivid reminder of the immense size of Avogadro's number. Many trillions of molecules pass through the detector of a GC in every chromatographic run. If the detector is sensitive enough, the trace impurities will show up. Usually, you can safely ignore them.

Injection Technique

Developing good injection technique with a microliter syringe is probably the biggest challenge for the GC beginner.

What happens if the plunger is pushed too slowly. If the plunger of the syringe is pushed too slowly, the leading edge of the sample reaches the column before the entire sample has vaporized in the injector port. The components of the sample then move through the column as a series of fronts that overlap with the components that have longer retention times. As a result, the chromatogram shows multiple overlapping peaks and the run must be repeated.

Overlapping and repeating patterns. Overlapping peaks and repeating patterns of peaks can also occur if the sample solution is not drawn into the barrel of the syringe before the injection is made. Otherwise, the solution in the needle can vaporize into the injection port before the rest of the sample is injected. A series of overlapping and repeating peak patterns on the chromatogram signifies that the analysis will have to be done again.

Is the Microliter Syringe Working Properly?

The correct size of the injections and concentration of the sample are crucial to success. You do not want to overload the column with too large a sample. It is also possible to inject virtually no sample because the very narrow bore of the microliter syringe has become plugged. Determining whether a microliter syringe is drawing properly can sometimes be difficult. The use of packed columns makes it easier to know if the syringe is working properly because a larger sample volume is injected.

19.7 Identification of Components Shown on a Chromatogram

GC analysis can quickly assess the purity of a compound, but as with thin-layer chromatography, a compound cannot be identified by GC unless a known sample is available to use as a standard. Comparison of retention times, peak enhancement, and spectroscopy are among the methods used to identify the components of a mixture.

Comparison of Retention Times

One method of identification compares the retention time of a known compound with the peaks on the chromatogram of the sample mixture. If the operating conditions of the instrument are unchanged, a match of the reference compound's retention time to one of the sample peaks may serve to identify it. This method will not work for a mixture in which the identity of the components is totally unknown, because several compounds could have identical retention times.

Peak Enhancement

When mixtures containing known compounds are being analyzed, ***peak enhancement*** serves as a method for identifying a peak in the

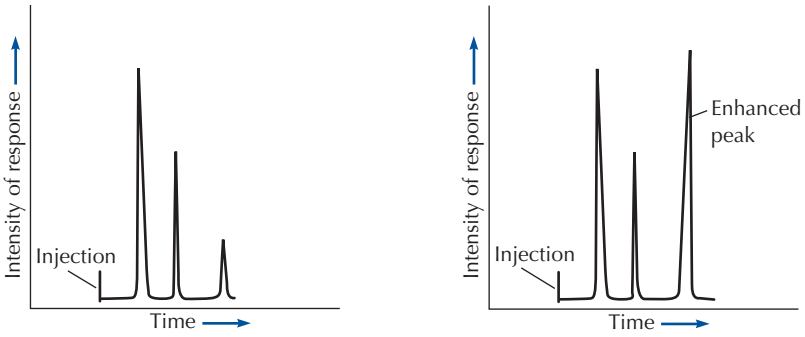


FIGURE 19.11 Identification by the peak enhancement method.

(a) Original chromatogram

(b) Chromatogram after addition of a known compound identical to a compound in the sample

chromatogram. The sample being analyzed is "spiked" with a drop of the known compound and the mixture injected into the chromatograph. If the known that is added is identical to one of the compounds in the mixture, its peak area is enhanced relative to the other peaks on the chromatogram (Figure 19.11).

Spectroscopic Methods

Positive identification of the compounds in a completely unknown mixture requires the pairing of GC methods with a spectroscopic method such as mass spectrometry (MS), where the mass spectrometer serves as the GC detector. In a GC-MS the two instruments are interfaced so that the separated components pass directly from the chromatograph into the spectrometer [see Technique 23.1].

19.8 Quantitative Analysis

Gas-liquid chromatography is particularly useful for quantitative analysis of the components in volatile mixtures. A comparison of relative peak areas on the chromatogram often gives a good approximation of relative amounts of the compounds.

Determination of Peak Areas

One great advantage of GC over other chromatographic methods is that approximate quantitative data are almost as easy to obtain as information on the number of components in a mixture. If we assume equal response by the detector to each compound, then the relative amounts of compounds in a mixture are proportional to their peak areas. Most peaks are approximately the shape of either an isosceles or a right triangle, whose areas are simply $A = ½$ base $\times$ height. Measuring the base of most GC peaks is difficult because abnormalities in their shapes usually occur there. A more accurate

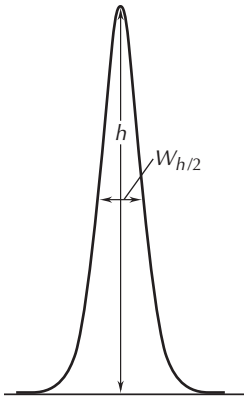


FIGURE 19.12
Determining peak area: *h*, height; $W_{h/2}$, width at half-height.

estimate of peak area is A = height × width at half-height (Figure 19.12).

Electronic digital integrators, common on most modern chromatographs, determine peak areas. Chromatograms produced by these recorders include a table of data that lists both retention times and relative peak areas.

Internal normalization is the easiest method for calculating the percentage composition of a mixture. **The percentage of a compound in a mixture is its peak area divided by the sum of all peak areas.** If you have a two-component mixture,

$$\%\ \text{compound 1} = \frac{\text{area}_1}{\text{area}_1 + \text{area}_2} \times 100$$

$$\%\ \text{compound 2} = \frac{\text{area}_2}{\text{area}_1 + \text{area}_2} \times 100$$

Relative Response Factors

For accurate quantification of a GC analysis, the response of each component to the detector must be determined from known samples. Each compound has a unique response in a detector, but the detector response varies between classes of compounds. For accurate quantitative interpretation of a chromatogram, analysis of standard mixtures of known concentration must be carried out and a correction factor, called a ***response factor (f),*** must be determined for each compound. The area under a chromatographic peak, A, is proportional to the concentration, C, of the sample producing it; the response factor is the proportionality constant.

$$A = fC \tag{1}$$

Response factors can be determined as either weight factors or mole factors, depending on the units of concentration used for the standard sample.

In chromatographic analyses, the samples being analyzed usually have more than one component; therefore, the relative response factors of one compound to the other compounds in the sample are usually determined. For a two-component system, the response-factor equation for each component is

$$A_1 = f_1 C_1 \tag{2}$$

$$A_2 = f_2 C_2 \tag{3}$$

The relative response factor of compound 1 to compound 2 can be determined by dividing equation 2 by equation 3:

$$\frac{A_1}{A_2} = \frac{f_1}{f_2} \times \frac{C_1}{C_2} \tag{4}$$

Rearranging equation 4 gives the ratio of response factors, f_1/f_2, the relative response factor of compound 1 to compound 2:

$$\frac{f_1}{f_2} = \frac{A_1}{A_2} \times \frac{C_2}{C_1} \tag{5}$$

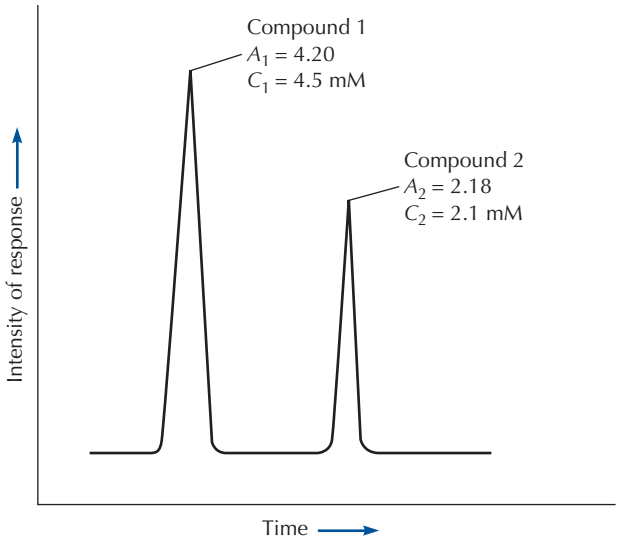


FIGURE 19.13 Chromatogram of a standard mixture containing known concentrations of two compounds.

Using data from the chromatogram shown in Figure 19.13 as an example, equation 5 can be used to calculate the molar response factor of compound 1 relative to compound 2; compound 2 is arbitrarily assigned a response factor of 1.00.

$$\frac{f_1}{f_2} = \frac{4.20}{2.18} \times \frac{2.1}{4.5} = \frac{0.90}{1.00}$$

Therefore, the molar response factor for compound 1 is 0.90 relative to 1.00 for compound 2.

Once relative molar response factors have been determined, the composition of a mixture can be calculated from the areas of the peaks on a chromatogram. Table 19.2 shows how molar response factors (designated M_f) can be used to determine the corrected mole percentage composition of a sample containing compound 1 and compound 2; Table 19.2 also compares these results to the uncorrected composition that was calculated. The differences between the uncorrected and corrected compositions illustrate the necessity of using response-factor corrections for accurate quantitative analysis.

TABLE 19.2 **Molar percentage composition data for a two-compound mixture uncorrected and corrected for molar response factors, M_f**

Compound	Area (A) (arbitrary units)	Uncorrected % (A/118.4) × 100	M_f	A/M_f	Corrected mol % (A/M_f) × (100/124.0)
Compound 1	50.2	**42.4**	0.90	55.8	**45.0**
Compound 2	68.2	**57.6**	1.00	68.2	**55.0**
Total	118.4	100	—	124.0	100

Further Reading

Grob, R. L.; Barry, E. F. *Modern Practice of Gas Chromatography;* 4th ed.; Wiley: New York, 2004.

Miller, J. M. *Chromatography: Concepts and Contrasts;* 2nd ed.; Wiley: Hoboken, NJ, 2005.

Ravindranath, B. *Principles and Practice of Chromatography;* Wiley: New York, 1989.

Skoog, D. A.; Holler, F. J.; Crouch, S. R. *Principles of Instrumental Analysis;* 6th ed.; Thomson Brooks/Cole: New York, 2007.

Questions

1. Why is a GC separation more efficient than a fractional distillation?
2. What characteristics must the liquid stationary phase have?
3. How do (a) the flow rate of the carrier gas and (b) the column temperature affect the retention time of a compound on a GC column?
4. Describe a method for identifying a compound using GC analysis.
5. Describe a method for identifying a compound purified by and collected from a gas chromatograph.
6. If the resolution of two components in a GC analysis is mediocre but shows some peak separation, what are two adjustments that can be made in the operating parameters to improve the resolution (without changing columns or instruments)?
7. Suggest a suitable liquid stationary phase for the separation of (a) ethanol and water; (b) cyclopentanone (bp 130°C) and 2-hexanone (bp 128°C); (c) phenol (bp 182°C) and pentanoic acid (bp 186°C).

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PART

5

Spectroscopic Methods

Essay — The Spectroscopic Revolution

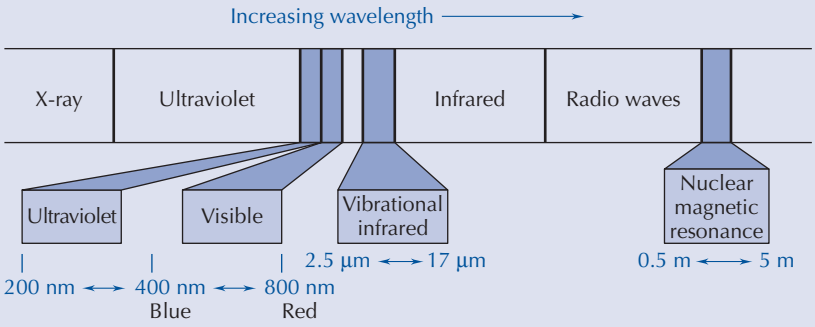
Throughout the study of organic chemistry, you are asked to think in terms of molecular structure because structure determines the properties of molecules. The connection between structure and reactivity is a central principle of organic chemistry. The experienced organic chemist can anticipate many of the physical and chemical properties of various compounds by simply looking at their structures.

Sixty years ago, the structure of an organic compound was discovered largely by time-consuming and sometimes ambiguous chemical methods. Determination of the structures of important compounds such as cholesterol and morphine took decades to achieve. Modern organic spectroscopic methods have produced a revolution in determining the structures of complex organic molecules. What used to take years or months can now often be done in a few days. For organic molecules with molecular weights of 300 or less, the job can often be done within an hour or so. The spectroscopic revolution has had a pronounced effect on how organic chemistry is done.

The new techniques are based in large part on the absorption of radiation from various portions of the electromagnetic spectrum. In effect, spectroscopic techniques provide "snapshots" of molecular structure.

NMR

Arguably the most useful portion of the electromagnetic spectrum is the radio frequency region. Using radio waves in the presence of a strong magnetic field is the basis for nuclear magnetic resonance (NMR) spectroscopy, which came into extensive use fifty years ago. Thanks to modern computer advances, major improvements in NMR methodology have taken place in recent decades. It is virtually impossible to do organic chemistry nowadays without access to an NMR spectrometer. The two most important NMR techniques are ^{1}H NMR and ^{13}C NMR, which can ascertain the interrelated connectivity of hydrogen and carbon atoms in organic compounds. NMR



Portions of the electromagnetic spectrum used in organic chemistry.

chemical shifts, spin-spin coupling patterns, and integration can be invaluable in organic structure determination and for the study of biopolymers, such as nucleic acids, proteins, and carbohydrates. The NMR technique is also at the heart of magnetic resonance imaging (MRI), a powerful medical diagnostic probe of soft tissue. It should be no surprise that NMR is the major focus of this spectroscopic methods section.

Infrared

The infrared region of the electromagnetic spectrum provides quick and valuable information on functional groups present in a molecule. In some ways the newer NMR spectroscopy and mass spectrometry have outshone IR vibrational spectroscopy, but IR can pin down the functional groups that are present—an important piece of structural information. In addition, IR spectra can be used as fingerprints to identify particular compounds.

UV and Visible

Ultraviolet and visible spectroscopy continue to be important methodologies in organic chemistry, but less so for structure determination than for the analyses of organic and biochemical mixtures, especially as high-performance liquid chromatography (HPLC) detectors.

MS

Mass spectrometry (MS) differs from the other spectroscopic methods in Part 5 in that it irradiates substances not with light but with highly energetic electrons, which ionize the molecules. The ions are then separated in a magnetic field. MS allows chemists to determine the molecular weight of a compound, and high-resolution MS can determine a compound's molecular formula as well. The fragmentation pattern of an ionized molecule also provides data that can assist in the identification of the compound. Like IR spectroscopy, MS can be used to provide a fingerprint that can pin down the structure of a molecule. MS is particularly useful when complex samples are separated in a gas chromatograph and a mass spectrometer is used as the detector (GCMS).

Integrating Spectral Data

Integrating the data obtained from the different spectroscopic methods discussed in Part 5 is important in the characterization of an organic compound. One spectral method may reveal features about a compound that may not be clear from another method, or one spectral method may confirm the existence of a structural unit suggested by another method.

TECHNIQUE

20 INFRARED SPECTROSCOPY

If Technique 20 is your introduction to spectroscopic analysis, read the Essay "The Spectroscopic Revolution" on pages 275–276 before you read Technique 20.

Infrared (IR) spectroscopy is the oldest of the three important spectroscopic techniques for determination of the structures of organic molecules; it provides a rapid and effective method for identifying the presence or absence of simple functional groups. When infrared energy is passed through a sample of an organic compound, absorption bands are observed. The positions of these IR absorption bands have been correlated with types of chemical bonds, which can provide key information about the nature of functional groups in the sample.

The ***mid-infrared,*** extending from 4000 to 600 cm^{-1}, is the region of most interest to organic chemists because it is the region in which absorptions from typical organic compounds appear. When coupled with other spectroscopic techniques, such as nuclear magnetic resonance [see Technique 21], infrared spectroscopy allows organic chemists to systematically and confidently determine the molecular structures of organic compounds.

20.1 IR Spectra

In an IR spectrum, energy measured as frequency or wavelength is plotted along the horizontal axis, and the intensity of the absorption is plotted along the vertical axis. There are several different formats for plotting the data depending on the scales used for the axes. Figure 20.1 shows examples of IR spectra of cyclopentanone recorded on two different IR spectrometers.

The horizontal scale in Figure 20.1a is linear in wavelength of the infrared radiation, which is the default axis used by older IR spectrometers. Many of the original libraries of infrared spectra were plotted using this format. The horizontal scale in Figure 20.1b is linear in wavenumbers, the standard frequency scale for infrared radiation used by most modern IR spectrometers. Microcomputers incorporated into modern IR spectrometers can quickly interchange data between the two formats. The shapes of the absorption bands appear quite different in Figures 20.1a and 20.1b, but their actual positions in the spectrum are the same. In the two IR spectra of cyclopentanone, the major absorption band appears at 5.72 μm in Figure 20.1a and at 1747 cm^{-1} in Figure 20.1b. These IR bands are characteristic of the carbonyl group (C═O), one of the major functional groups in organic chemistry.

20.2 Molecular Vibrations

The atoms making up a molecule are in constant motion, much like balls at the ends of springs. Covalent bonds act as the springs that connect the nuclei. The movements of the atoms relative to each other can be described as vibrations, and in fact infrared spectroscopy has

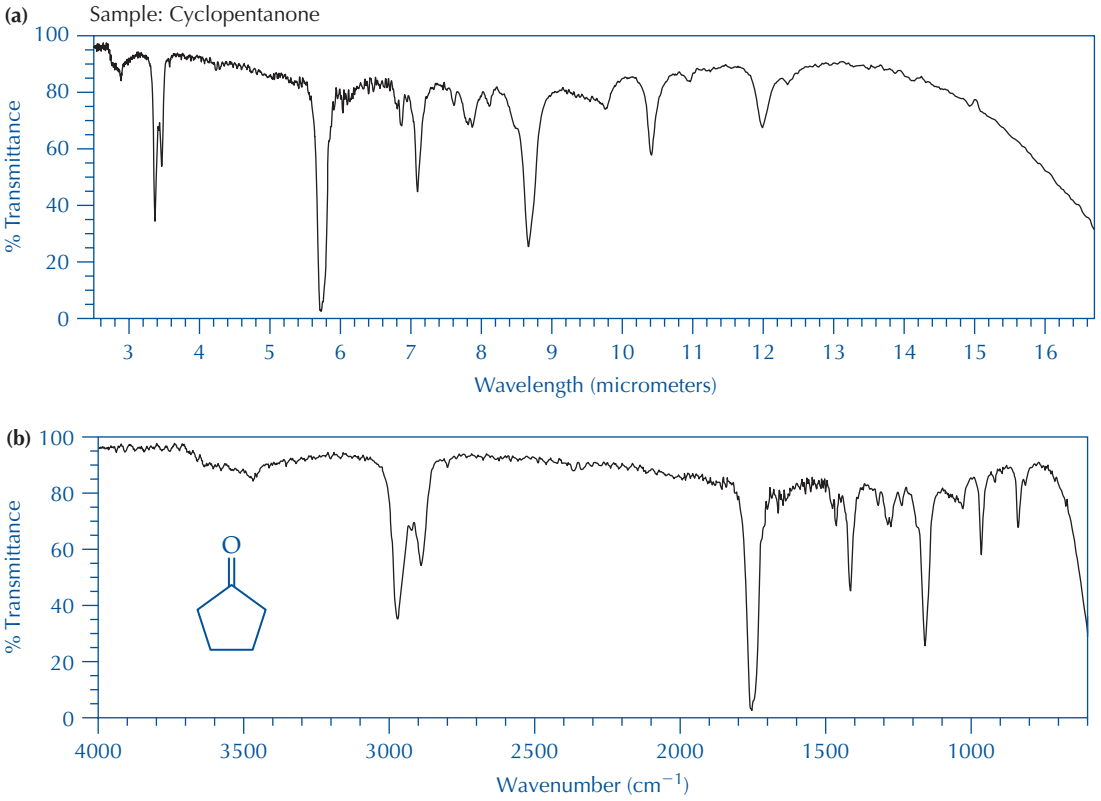


FIGURE 20.1 Infrared spectra of cyclopentanone recorded with (a) the horizontal (energy) scale linear in wavelength (micrometers) and (b) the horizontal scale linear in wavenumbers (frequency).

been called ***vibrational spectroscopy***. The photons of IR radiation absorbed by an organic molecule have just the right amount of energy to stretch or bend its covalent bonds. The energy of infrared radiation is on the order of 8–40 kJ/mole (2–10 kcal/mole). This amount is not enough energy to break a covalent bond, but it is enough to increase the amplitude of bond vibrations. When infrared radiation is absorbed, the sample becomes warm as its molecules increase their kinetic energy. This is how infrared heat lamps work.

An absorption band appears in an infrared spectrum at a frequency where a molecular vibration occurs in the molecule. Energy levels of molecular vibrations are quantized, which means that only infrared energy with the same frequencies as the molecular vibrations can be absorbed. The energy levels available to a molecular vibration are expressed as

$$E = h\nu_0(\nu + \tfrac{1}{2}) \text{ for } \nu = 0, 1, 2, 3 \ldots$$

where h = Planck's constant and ν_0 = the zero-point vibrational level of the bond. The energy (ΔE) of the absorbed radiation that will promote a vibration of frequency (ν) from one energy level to the next energy level is

$$\Delta E = h\nu$$

The frequency (ν) and wavelength (λ) of light are related by

$$\nu = c/\lambda$$

where c = the speed of light. Substituting this relationship into the equation for the absorbed radiation yields

$$\Delta E = hc(1/\lambda)$$

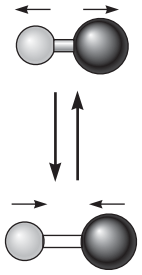


FIGURE 20.2 Fundamental stretching vibrational mode of a diatomic molecule.

The quantity $(1/\lambda)$ is called the ***wavenumber*** ($\bar{\nu}$) and is usually expressed in units of reciprocal centimeters (cm^{-1}). A wavenumber defines the number of wave crests per unit length. It is proportional to the frequency as well as to the energy of an IR absorption.

$$\Delta E = hc\bar{\nu}$$

An IR absorption band is often called a ***peak,*** and its maximum is defined as the position of maximum absorption in wavenumber units. Frequency in units of wavenumbers, cm^{-1}, and wavelengths in units of micrometers, μm (10^{-6} meters, called microns in the older literature), can be interconverted by the following relationship:

$$cm^{-1} = \frac{10{,}000}{\mu m}$$

Fundamental Molecular Vibrations

There are two kinds of fundamental molecular vibrations: stretching and bending. In a ***stretching vibration,*** the distance between two atoms increases and decreases in a rhythmic manner, but the atoms remain aligned along the bond axis. Figure 20.2 shows a ***symmetric stretching vibration*** in which the atoms stretch in and out simultaneously. In a ***bending vibration,*** the positions of atoms change relative to the bond axis, as shown in Figure 20.3. A nonlinear molecule made up of n atoms has $3n - 6$ possible fundamental stretching and bending vibrations.

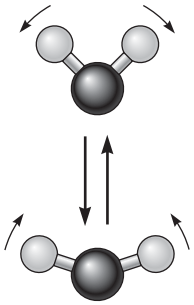


FIGURE 20.3 Fundamental bending vibrational mode of a triatomic molecule.

EXERCISE

Water (H_2O) is a nonlinear molecule consisting of three atoms. (a) How many fundamental vibrations does it have? (b) Describe them.

Answer: (a) Water has three fundamental vibrations. Two are stretching vibrations and one is a bending vibration. (b) The vibrations are shown in Figure 20.4. The first is a symmetric stretching vibration. The second stretching vibration is an ***asymmetric stretching vibration*** in which one hydrogen atom moves out as the other hydrogen atom moves in. The bending vibration involves a kind of scissoring motion in which the H—O—H bond angle changes back and forth.

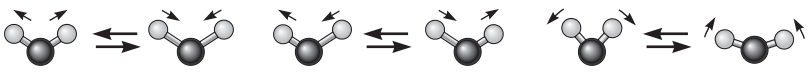


FIGURE 20.4 The three fundamental vibrational modes of water.

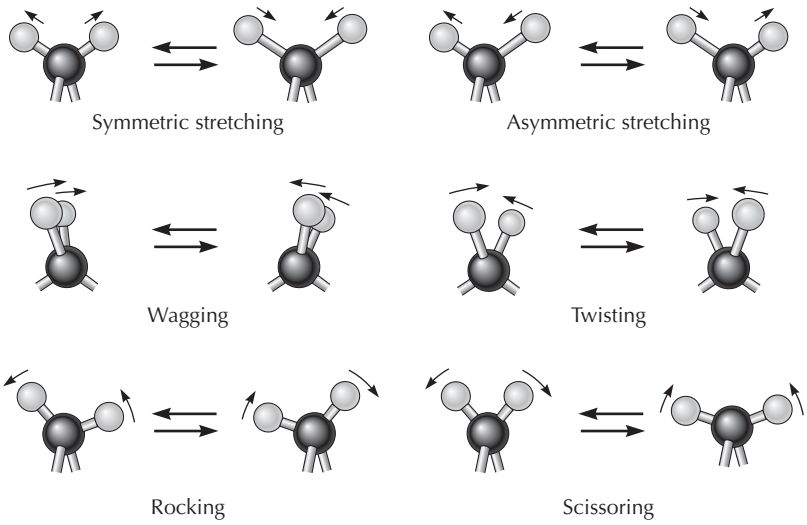


FIGURE 20.5 Vibrational modes of the methylene group (CH_2).

For molecules containing many atoms, there are numerous fundamental vibrations. The stretching and bending vibrations of a methylene (CH_2) group are shown in Figure 20.5.

Complexity of IR Spectra

Organic compounds, which contain 10 or 20 atoms or more, can manifest substantial numbers of IR peaks, and the spectra of organic compounds can be complex. The total number of observed absorption bands is generally different from the total number of possible fundamental vibrations. Some fundamental vibrations are not IR active and do not absorb energy. However, additional absorption bands, which occur as a result of overtone vibrations, combination vibrations, and the coupling of vibrations more than make up for the decrease.

Overtone bands are observed when fundamental vibrations produce intense absorption bands. Overtone frequencies are multiples of the fundamental frequency, and they result from the change of more than one vibrational energy level.

Combination bands appear at frequencies that correspond to sums and differences of two or more fundamental vibrational frequencies. The intensities of overtone and combination absorption bands are usually less than the intensities of fundamental vibrations.

A coupling interaction called ***Fermi resonance*** can occur in compounds where an absorption band due to an overtone or combination band is close to the frequency of a fundamental vibration. The interaction of the overtone and the vibration causes the intensity of the fundamental vibration to decrease and the intensity of the overtone or combination band to increase. This results in two peaks of roughly equal intensity in the IR spectrum.

Fortunately, many of the peaks in an IR spectrum can usually be ignored. The large number of fundamental vibrations, their overtones, and combinations of vibrations make it far too difficult to understand quantitatively entire IR spectra of most organic compounds. But, as you will see, IR spectra can easily yield a great deal

of qualitative information about functional groups. Moreover, the complexity of an IR spectrum imparts a unique pattern for each compound, allowing the spectrum to be used as a "fingerprint" for identification.

Correlation of Peaks with Specific Bond Vibrations

The absorptions corresponding to specific molecular vibrations appear in definite regions of the IR spectrum, regardless of the particular compound. For example, the stretching region of O—H bonds in all alcohols appears at nearly the same frequency. In the same way, the C═O vibrations of all carbonyl compounds appear within a narrow frequency range.

What determines the frequency and intensity of IR peaks? Following are the most important factors:

- Type of vibration, stretching or bending
- Strength of the bond connecting the atoms, particularly the bond order
- Masses of the atoms attached by the covalent bonds
- Electronegativity difference between the two atoms or groups of atoms in a bond

Type of vibration. In general, the stretching of covalent bonds takes more energy than bending vibrations. Stretching vibrations in the infrared appear at higher frequencies.

Type of vibration	Frequency (cm^{-1})
C—H stretching	3000–2800
—CH_2— bending	1470–1430

Bond order. Bond order is simply the amount of bonding between two atoms. For example, the bond order between carbon atoms increases from one to two to three for ethane (CH_3—CH_3), ethene (ethylene, CH_2═CH_2), and ethyne (acetylene, HC≡CH), respectively. In general, the higher the bond order, the greater the energy required to stretch the bond. Higher bond order produces a higher-frequency IR absorption.

Bond order	Type of bond	Stretching frequency (cm^{-1})
1	C—C, C—O, C—N	1300–800
2	C═C, C═O, C═N	1900–1500
3	C≡C, C≡N	2300–2000

Atomic mass. The frequency of the IR absorption also relates to the atomic masses of the vibrating atoms. Covalent bonds to hydrogen occur at high frequencies compared to bonds between heavier atoms—a light weight on a spring tends to oscillate faster than a heavy weight.

Type of bond	Stretching frequency (cm^{-1})
O—H	3650–2500
N—H	3500–3150
C—H	3300–2850

Electronegativity differences and peak intensities. Bond polarity does not significantly affect the position of IR absorption, but it greatly influences the intensity of IR peaks. If a vibration (stretching or bending) induces a significant change in the dipole moment, an intense IR band will result. Thus, when bonds are between atoms having different electronegativities, such as C—O, C═O, and O—H, the IR stretching vibrations are very intense. A symmetric molecule such as ethylene, on the other hand, does not show any absorption band for the C═C stretching vibration.

The intensity (peak size) of an IR absorption can be reported in terms of either transmittance (T) or absorbance (A). ***Transmittance*** is the ratio of the amount of infrared radiation transmitted by the sample to the intensity of the incident beam. Percent transmittance is $T \times 100$. In practice, peak intensities are reported in a more qualitative fashion.

A properly prepared sample produces an IR spectrum in which the most intense peak nearly fills the vertical height of the chart. Peaks of that magnitude are termed ***strong (s);*** smaller peaks are called either ***medium (m)*** or ***weak (w).*** Peaks can also be described as ***broad (br)*** or sharp. It is important that the most intense peak in an IR spectrum be above 0% transmittance (5–10% is good) so that its peak maximum can be measured accurately.

20.3 IR Instrumentation

There are two major classes of instruments used to measure IR absorption: dispersive spectrometers and Fourier transform (FT) spectrometers. ***Dispersive spectrometers*** were developed first and for a long time were the standard infrared instruments. The advent of computers allowed the development of ***Fourier transform infrared (FTIR) spectrometers*** in the 1960s. In recent years, instruments incorporating powerful and relatively inexpensive microcomputers have allowed most laboratories to convert to FTIR instruments.

Dispersive Spectrometers

In a dispersive IR spectrometer, the source of radiation, often a heated filament, provides a beam of IR radiation that is split into two beams. The beams are directed by mirrors through both sample and reference cells. The sample and reference beams are alternately selected for measurement by means of a special rotating sector mirror, which allows the selected beam components to be recombined into a single beam. This beam is then focused onto a diffraction grating, which separates the beam into a continuous band of infrared frequencies. A slit allows only a narrow range of these frequencies to reach the detector. By continuously changing the angle of the diffraction grating, the entire infrared spectrum can be scanned, and the instrument records the intensity of the radiation as a function of frequency.

Fourier Transform Spectrometers

Unlike the older dispersive instruments, FTIR spectrometers gather data at all IR wavelengths at the same time. A simplified diagram of

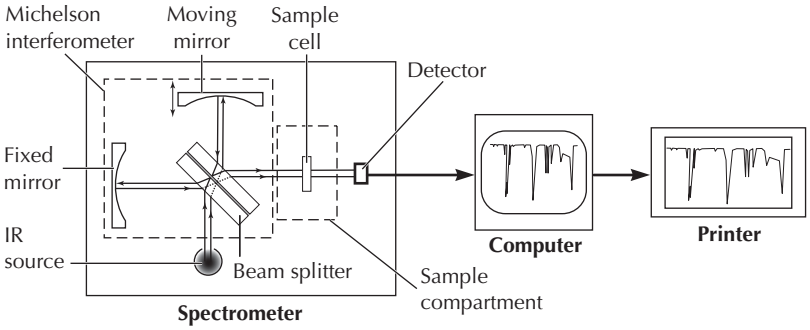


FIGURE 20.6 Diagram of a single-beam FTIR spectrometer. The interior of the instrument is isolated from the ambient environment by purging with dry nitrogen or dry, carbon dioxide-free air.

an FTIR spectrometer is shown in Figure 20.6. Infrared radiation from a heated source is directed to a ***beam splitter,*** a thin film of the element germanium sandwiched between two highly polished plates of potassium bromide. The beam splitter separates the radiation into two beams. One beam is reflected off the beam splitter and directed to a fixed mirror. The other beam is transmitted through the beam splitter and directed to a moving mirror, which is controlled by a laser. The mirrors reflect their respective beams of infrared energy back to the beam splitter, where the beams recombine. The two beams travel different distances to the mirrors, so their frequencies are now out of phase. The constructive and destructive combination of the out-of-phase frequencies produces an ***interferogram.*** The beam splitter and mirror assembly is known as a ***Michelson interferometer.***

The interferogram is an array of signal intensities that reveals the difference in the two optical paths. Information about every infrared frequency is contained in the interferogram. The beam of infrared energy, encoded as an interferogram, is directed through a sample to the detector. On interacting with the sample, specific frequencies of infrared energy are absorbed through excitation of molecular vibrations. Fourier transform mathematics is then used to sort out the frequencies of infrared energies encoded in the modified interferogram. The result is an infrared spectrum plotted as an array of intensities versus frequencies measured in cm^{-1}.

In actual practice, two scans are required—a scan of the empty sample compartment referred to as the ***background*** scan and a scan with the sample in the beam of infrared energy. The background scan contains signals due to water vapor and gaseous carbon dioxide in the atmosphere, the emission profile of the source, and film coatings of the optics, among other things. The background spectrum is subtracted from the sample spectrum to produce a spectrum displaying only absorptions due to the sample. The steps involved in creating a spectrum from the data are outlined in Figure 20.7.

Although it is more complicated than dispersive IR spectroscopy, there are numerous advantages to the FTIR method. Results of multiple scans can be combined to average out random

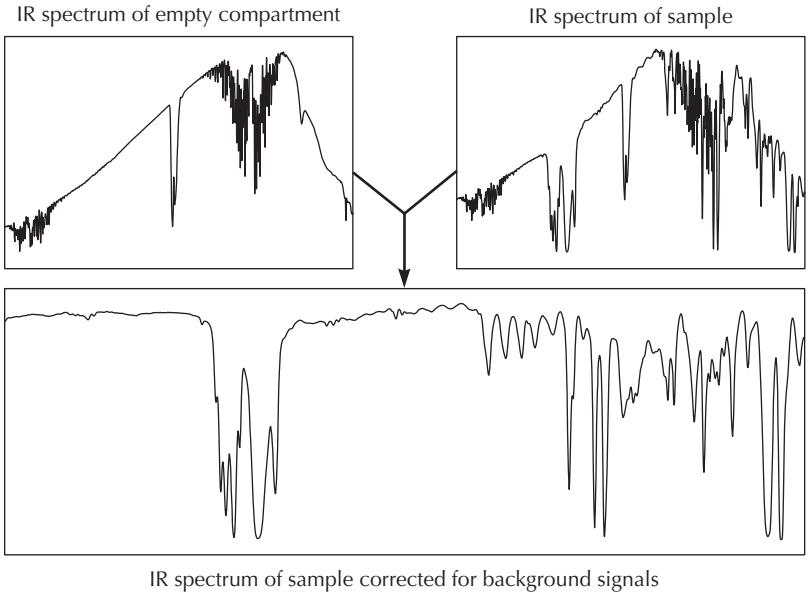


FIGURE 20.7 The collection and processing of data required for the creation of an infrared spectrum with a single-beam FTIR spectrometer.

noise, and excellent spectra can be obtained rapidly from very small samples. FTIR spectrometers have few mirror surfaces, and because more energy gets to the detector, they are much more sensitive. Also, the resolution of the spectrum from an FTIR spectrometer is much higher. FTIR data are digitized; the quality of a spectrum can often be improved by baseline correction or the subtraction of peaks resulting from impurities.

20.4 Operating an FTIR Spectrometer

An FTIR spectrometer is a robust, modern instrument with many capabilities, but it must be used with care and respect. The most difficult step in taking the IR spectrum of a sample is often the preparation of the sample.

If you are using the attenuated total reflectance (ATR) accessory, see Technique 20.6, otherwise use the following operating procedure.

1. Prepare the sample. Methods for preparing samples for transmittance IR spectra are described in Technique 20.5.
2. Briefly open the sample compartment and confirm that there is nothing in the sample beam. Close the compartment.
3. Run a background scan. The data are collected, processed, and stored in the instrument's computer memory. The instrument indicates when this operation is completed.
4. Briefly open the sample compartment and place the sample in the sample beam. Close the compartment.

5. Run a sample scan. The data are collected and processed. The background scan is automatically subtracted from the sample scan. The result, an infrared spectrum of the sample, is displayed on the monitor.
6. Use the instrument's software to mark the frequency of each major peak in the region of 4000–1500 cm^{-1}. Having the exact frequencies (wavenumbers) of these peaks on the printed spectrum can be helpful in analyzing it.
7. Format the spectrum and print out a copy for analysis and for inclusion in your laboratory notebook.

20.5 Sample Preparation for Transmittance IR Spectra

IR spectra can be obtained from liquid, solid, or gas samples. Traditionally, IR spectra have been obtained by means of transmitting the radiation directly through the sample. Almost all the IR spectra shown in this book are ***transmission spectra.*** Solid and liquid compounds are often prepared as thin films that allow infrared radiation to pass through them. Various additional methods for preparing samples of solids and liquids for transmission IR spectra are also described in this section. A newer method for obtaining IR spectra—attenuated total reflectance (ATR)—works in quite a different manner and makes the preparation of IR samples, particularly solids, much easier [see Technique 20.6]. Gas samples require a special gas cell for sampling. Gas samples are encountered infrequently in organic chemistry and are not included in the discussion.

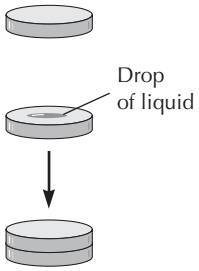
Sample Cells for IR Transmittance Spectra

The windows of the sample cells used for transmittance spectra must be transparent to IR radiation in the mid-infrared region. Because glass absorbs IR radiation, it cannot be used to make IR sample cells. Most cells are made from alkali halides, in particular polished sodium chloride disks that, for the most part, are transparent in the mid-infrared region.

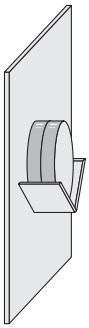
It is important to be aware that **alkali halide sample cells are very susceptible to water damage** and that care must be taken to ensure that all samples are completely dry. Water etches and clouds the surface of cells and disks, rendering them useless. Also, touching the polished surfaces of salt disks with fingers leaves indelible fingerprints from skin moisture and oils. **NaCl disks should be handled only by the edges.** The disks are much softer than glass and they break easily if dropped even a short distance. When preparing an IR sample, avoid touching the polished surface of a sodium chloride disk with a glass pipet because the pipet will nick and scratch the surface. The only way to remove nicks, scratches, and fingerprints is to repolish the disk.

Thin Films for Liquid Compounds

A thin film pressed between NaCl disks is the most convenient method for preparing a liquid for IR analysis (Figure 20.8). A drop of ***neat*** sample (liquid with no added solvent) is placed on one disk;



(a) Preparing sample



(b) Disk holder with sample

FIGURE 20.8 Preparation of thin-film sample for IR spectroscopy.

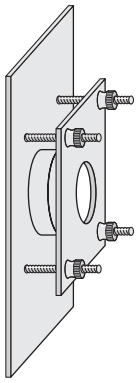


FIGURE 20.9 IR sample disk holder for low-viscosity liquids. The holder slips into a bracket on the IR spectrometer.

the other disk is placed on top of the drop. The disks are gently rotated and then gently squeezed together to form a film approximately 0.01 mm in thickness. The sandwich is placed in a holder that is subsequently positioned in the sample compartment of the IR spectrometer. When the sample has a low viscosity, the holder shown in Figure 20.9 is a better choice because it keeps the sample film tightly in contact with the salt disks.

Steps in Preparing and Using a Thin Film

SAFETY PRECAUTION

Wear gloves and handle all solvents only in a hood.

1. Clean the disks with a **dry** solvent—acetone or dichloromethane.
2. Place a folded tissue on the lab bench. Place one disk on top of the tissue pad.
3. Using a Pasteur pipet, place 1 drop of the liquid sample on the center of the disk. Be careful not to touch the surface of the disk with the pipet.
4. Place the second disk on top of the first and gently rotate it; then gently press the disks together.
5. Obtain the IR spectrum.
6. Clean the disks with a **dry** solvent—acetone or dichloromethane. Store the disks in a desiccator to protect them from moisture.

Cast Films for Solid Compounds

A thin film of solid can be prepared by placing a drop of a concentrated solution of the compound in the center of a clean sodium chloride disk. The best solvent to use for this solution is one that has a high vapor pressure at room temperature and does not dissolve NaCl. Diethyl ether, dichloromethane, and ethyl acetate work well; methanol, ethanol, and water must be avoided. For best results the salt disk must have a smooth, polished surface because scratched and pitted disks lead to uneven distribution of the sample.

Steps in Preparing and Using a Cast Film IR Sample

SAFETY PRECAUTION

Wear gloves and handle all solvents only in a hood.

1. In a small test tube, prepare 0.3–0.5 mL of a 10–20% sample solution in a volatile organic solvent. Cork the test tube.
2. Clean a NaCl disk with a **dry** solvent—acetone or dichloromethane.
3. Place a folded tissue on the lab bench. Place the clean disk on top of the tissue pad. Make sure the disk is level.
4. Using a Pasteur pipet, place 1 drop of the sample solution at the center of the disk. Be careful not to touch the surface of the disk with the pipet.
5. Allow the solvent to completely evaporate. It may be necessary to repeat steps 4 and 5 up to four or five times to build up a film of the compound thick enough to produce an acceptable IR spectrum.
6. Place the NaCl disk in a sample holder like that shown in Figure 20.8 or Figure 20.9.
7. Obtain the IR spectrum.
8. Clean the disks with a **dry** solvent—acetone or dichloromethane. Store the disks in a desiccator to protect them from moisture.
9. If your sample compound is especially valuable, you can wash the sample from the NaCl disk into the sample test tube and then evaporate the solvent from the remaining solution to recover the compound.

KBr Pellets for Solid Compounds

Potassium bromide (KBr) does not absorb mid-region IR radiation. Thus, a solid compound can be prepared for IR spectroscopy by grinding the sample with anhydrous KBr powder and pressing the mixture into a thin, transparent disk. Potassium bromide disks are excellent for IR analysis, but their preparation is challenging and requires great care. It may take several attempts to prepare KBr disks that are suitable for IR analysis, especially if you have not made them before.

The solid sample must be ground exceedingly fine because large particles scatter IR radiation—exhibited on the spectrum as a dramatically sloping baseline. The sample is ground with a polished mortar and pestle made of agate or some other nonporous material or by vibrating the mixture in a small ball mill, similar to the mills that have been used by dentists to mix amalgam fillings.

Care must be taken to maintain anhydrous conditions. The smallest trace of water in the disk can disrupt homogeneous sample preparation and can also produce spurious O—H peaks in the IR spectrum at 3450 cm^{-1} and 1640 cm^{-1}. The ground mixture is pressed into transparent disks with a special press. In a research laboratory, the KBr/compound mixture may be subjected to 14,000–16,000 psi in a high-pressure disk press. A convenient alternative to a high-pressure press is the minipress shown in Figure 20.10.

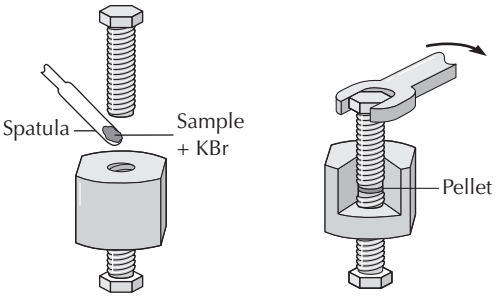


FIGURE 20.10
Preparation of a KBr pellet with a minipress.

Steps in Preparing a KBr Pellet Using a Minipress

1. Using a small, nonporous mortar and pestle, grind a small quantity of the solid compound (0.5–2.0 mg) until it is an exceedingly fine powder. Use a small, flat spatula to scrape the ground solid from the surface of the mortar and grind it thoroughly with 100 mg of completely dry potassium bromide.
2. Thread one bolt halfway into the minipress die.
3. Add the sample/KBr mixture to the minipress die. Tap the side of the minipress to encourage all the solid mixture to fall to the bottom of the die. Try to cover the bottom of the die with a thin, even coating of the mixture. Too much material can produce poor-quality pellets, which are thick and opaque.
4. Thread the second bolt into the minipress die by hand as far as it will go.
5. Secure the minipress die in a vise or similar device.
6. Apply pressure to the sample using a wrench to tighten the second bolt.
7. Remove the bolts.
8. Place the minipress die containing the KBr pellet into a sample holder like the one used for the thin film sample, shown in Figure 20.8.
9. Obtain the IR spectrum.
10. Clean the minipress die and bolts and store them in a container to protect them from moisture.
11. Clean the equipment used for grinding the sample.

Mulls for Solid Compounds

A ***mull*** used for IR samples is not a true solution but is a fine dispersion of a solid organic compound in a viscous liquid. The most common liquids used for IR mulls are Nujol (a brand of mineral oil, which is a mixture of long-chain alkanes) and Fluorolube (a mixture of completely fluorinated alkanes). The fluorinated mulling substances are often used for more polar compounds. Unfortunately, neither Nujol nor Fluorolube are transparent over the entire IR region. Both display IR peaks that may obscure peaks due to the dispersed compound (Table 20.1). The spectrum of Nujol, which is a mixture of alkanes, exhibits only C—H stretching and bending absorptions. Thus, Nujol does not obscure most IR peaks due to the functional groups found in organic compounds. However, the preparation of a

TABLE 20.1 Absorption regions of common mulling compounds

Carrier	Absorption region (cm^{-1})
Fluorolube	1300–1080
	1000–920
	910–870
	<670
Nujol	3000–2800
	1490–1450
	1420–1360
	750–720

good Nujol mull requires care and practice to prevent the problems discussed in Technique 20.10, page 308.

Steps in Preparing and Using a Mull

SAFETY PRECAUTION

Wear gloves and handle all solvents only in a hood.

1. Using a small agate or nonporous ceramic mortar and pestle, grind 10–15 mg of the solid until the sample is exceedingly fine and has a caked, glassy appearance. Use a small flat spatula to scrape the ground solid from the surface of the mortar.
2. Add 1 drop of mulling liquid to the ground solid in the mortar. **Be careful!** Err on the side of adding too little mulling liquid because it is impossible to remove it if you add too much. Grind the mixture to make a uniform paste with the consistency of toothpaste; it should not be grainy but must not be runny.
3. Transfer the paste to the center section of a NaCl disk with a small flat spatula, as in Figure 20.8. Press the disks together gently, rotate the top disk, and place them in a sample holder.
4. Obtain the IR spectrum.
5. Clean the disks with a **dry** solvent—acetone or dichloromethane. Store the disks in a desiccator to protect them from moisture.
6. Clean the equipment you used for grinding the sample.

Sample Cards for Solid Compounds

A relatively new innovation in IR spectroscopy is the use of a disposable sampling card. The sample is applied to an inert, microporous matrix in the middle of the card, but first the sample card is scanned in the FTIR spectrometer and its IR spectrum saved in the instrument's memory. Liquids are applied neat (without solvent). Solids are applied in solution and the solvent is allowed to evaporate. The card is placed in the sample beam and scanned. The spectrum of the blank sample card is then subtracted from that of the card with the applied compound by software provided with the FTIR instrument. This subtraction produces the spectrum of the compound itself.

Polyethylene or polytetrafluoroethylene is usually used for the solid support matrix on the card. Polyethylene has strong absorptions in the regions 2918–2849 cm^{-1}, 1480–1430 cm^{-1}, and 740–700 cm^{-1}. Polytetrafluoroethylene has strong absorptions in the regions 1270–1100 cm^{-1} and 660–460 cm^{-1}. As is the case with the mulling agent in IR mulls, the infrared peaks of the sample card matrix may obscure peaks due to your sample.

A technique analogous to sample cards using Teflon tape as a solid support for an IR sample has been described by Oberg and Palleros.*

20.6 Sample Preparation for Attenuated Total Reflectance (ATR) Spectra

FTIR instruments are extremely sensitive, and FTIR techniques using specialized sampling accessories have been developed that make obtaining IR spectra of solids much easier. When an ***attenuated total reflectance (ATR)*** accessory is used, it is unnecessary to prepare KBr disks, Nujol mulls, or cast films or even to use sodium chloride disks in IR sample preparation. With ATR, the infrared radiation is passed through an infrared transmitting crystal with a high refractive index, which allows the radiation to reflect within the crystal.

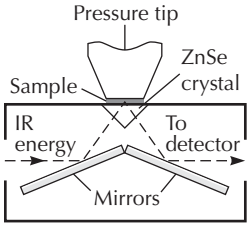


FIGURE 20.11
Cross section of single-reflection attenuated total reflectance (ATR) accessory.

A single-reflection ATR accessory, such as the one shown in Figure 20.11, often works best for the IR spectra of solids. The solid is powdered and then pressed into intimate contact with the top surface of the crystal, usually zinc selenide (ZnSe) or germanium (Ge), by screwing down a pressure tip onto the sample. After entering the ATR crystal, the beam of infrared energy reflects off the surface of the solid sample, effectively penetrating a small distance (0.5−5 μm) into the sample before being reflected. The IR beam becomes attenuated (becomes less intense) in regions of the IR spectrum where the sample absorbs. The beam then exits from the opposite end of the crystal and passes to the IR detector, and an IR spectrum is generated.

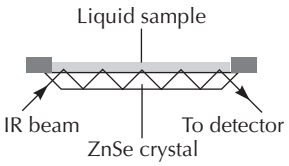


FIGURE 20.12
Multiple-reflection ATR crystal and sample.

For high-quality IR spectra of liquids, multiple-reflection ATR with a long crystal and a trough that can be filled with the liquid sample is often used. With each reflection, the IR beam becomes attenuated in regions of the IR spectrum where the sample absorbs. The IR beam reflects off the liquid five to ten times, as shown in Figure 20.12.

An IR spectrum from an ATR accessory is similar to a transmission IR spectrum, but there are some differences. The frequencies of the absorptions are the same, but the relative intensities of the peaks may differ. A comparison of the transmission spectrum and the ATR spectrum of solid polystyrene is shown in Figure 20.13. The differences occur because lower-frequency infrared energy penetrates farther into the sample than higher-frequency IR energy. Because the lower frequencies interact with more sample, their absorbance bands are more intense.

*Oberg, K. A.; Palleros, D. R. *J. Chem. Educ.* **1995,** *72,* 857–859.

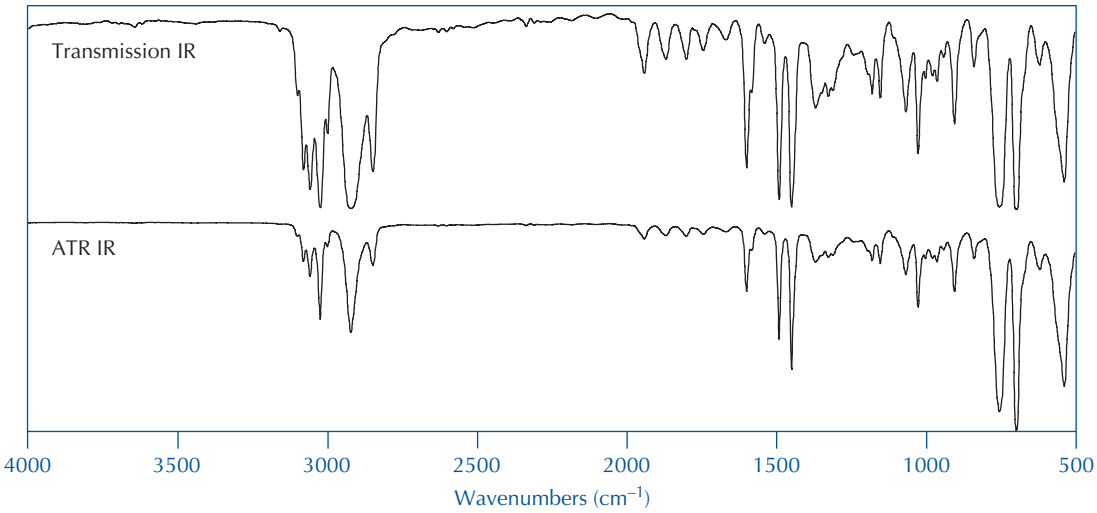


FIGURE 20.13 Comparison of (top) a transmission spectrum of polystyrene with (bottom) an ATR spectrum of polystyrene.

Software is available that can correct for the different intensities at different wavelengths. Use of this software produces IR spectra that more closely resemble transmission spectra, which makes it easier to compare ATR and transmission spectra.

Steps in Obtaining an ATR-IR Spectrum of a Solid

1. Carefully clean the surface of the ATR crystal with a lint-free tissue.
2. Place a small amount of powered solid sample on the crystal. Use just enough sample to cover the crystal area. The sample height should not be more than a few millimeters. Use a wooden stick or other nonabrasive tool for this operation because a metal spatula can easily scratch the surface of a ZnSe crystal.
3. Lower the pressure tip so that it is in contact with the solid. (**Note:** To avoid contamination of the tip, a small piece of paper can be placed between the tip and the sample.)
4. Apply approximately 10 psi of pressure to the sample. The mechanism and appropriate pressure vary for different ATR accessories, so find out from your instructor the procedure for your accessory.
5. Obtain the IR spectrum.
6. Raise the pressure tip from the sample. Gently wipe the sample from the crystal and from the pressure tip with a tissue. Then wipe the crystal and pressure tip with a methanol-soaked tissue.

20.7 Interpreting IR Spectra

Confirming the identity of a compound is one of the most important uses of IR spectroscopy. Because of the numerous and interactive vibrations of a typical organic molecule, no two compounds are

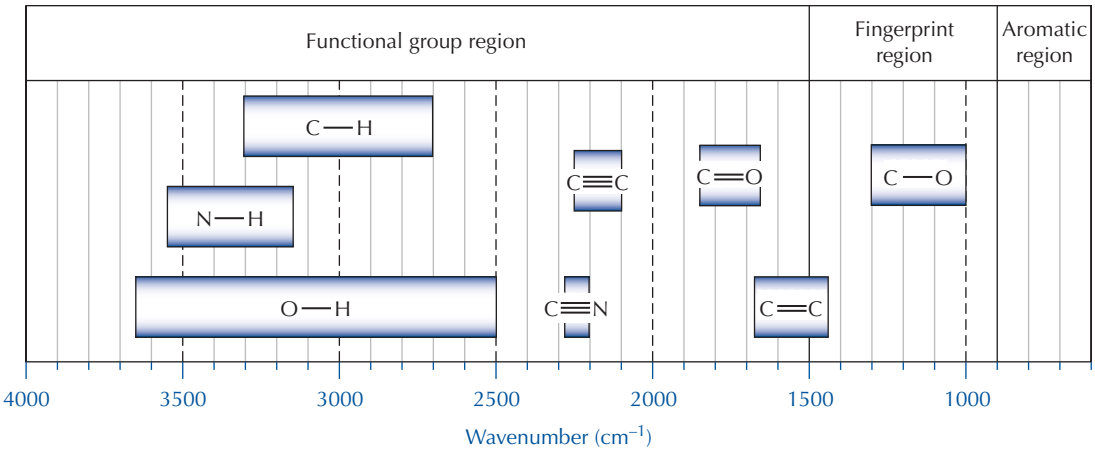


FIGURE 20.14 Approximate regions of chemical bond stretches in an IR spectrum.

known to have identical IR spectra. The unique pattern of each compound allows an IR spectrum to be used as a "fingerprint" for identification. Databases of IR spectra of known compounds can be searched for a match with the spectrum of an unknown compound—an identification method frequently used in forensic and quality control laboratories. Comparing an IR spectrum obtained in the laboratory to the spectra available in a compendium of IR spectra can be useful;* however, it can also be time consuming.

Often there is no sample spectrum available for comparison and it is necessary to interpret the IR spectrum. The most basic interpretation consists of an inventory of the functional groups in the molecule. Systematic examination of the IR spectrum and identification of absorption bands due to fundamental stretching vibrations are used to construct a functional group inventory. Combining IR data with structural information from other techniques, such as nuclear magnetic resonance (NMR) spectroscopy, usually allows unequivocal assignment of a molecular structure to an organic compound.

Regions of the IR Spectrum

As shown in Figure 20.14, an IR spectrum can be broken down into three regions:

- Functional group region
- Fingerprint region
- Aromatic region

Functional group region. The functional group region (4000–1500 cm^{-1}) provides unambiguous, reasonably strong peaks for most major functional groups. Figure 20.14 shows the approximate regions in which peaks appear as a result of important bond-stretching vibrations. Structurally similar compounds that contain the same functional groups are virtually identical in this region. For example,

**The Aldrich Library of FT-IR Spectra;* 2nd ed.; Aldrich Chemical Company: Milwaukee, WI, 1992; 3 volumes.

the absorption bands for the carbonyl groups of 2-butanone and 3-hexanone both appear at the same frequency, 1715 cm^{-1}. Since many functional groups, such as C═C, C≡C, C≡N, N—H, O—H, and C═O bonds, show IR bands in the 4000–1500 cm^{-1} region, **both the presence and absence of peaks in this region are significant.** The absence of an appropriate IR band in the functional group region argues against the presence of that functional group, except in the rare cases when a stretching vibration has no associated dipole change.

Fingerprint region. The fingerprint region (1500–900 cm^{-1}) is normally complex because of the many bending vibrations and combination bands that appear in this region. Before the development of NMR spectroscopy, when IR spectroscopy was the major structural probe available to organic chemists, much effort went into analyzing and assigning characteristic vibrations in this region. NMR spectroscopy now provides detailed structural information more directly and reliably. Except for a few intense absorptions, such as C—O stretching vibrations, IR peaks in the fingerprint region are now primarily used for fingerprint pattern matching.

Aromatic region. The aromatic region (900–600 cm^{-1}) provides information about the substitution pattern of benzenes and other aromatic compounds, although it is generally easier to determine these aromatic substitution patterns by NMR spectroscopy.

EXERCISE

All organic compounds have IR absorptions because of C—H and C—C stretching and bending vibrations. For each of the following compounds, identify the additional bond-stretching vibrations that should be observed. Using Figure 20.14 as a guide, identify regions of the IR spectrum where you would expect to see characteristic absorptions for each compound.

(a) 2-propanol (c) phenylethyne (e) 4-methylphenylamine
(b) propanoic acid (d) 1-hexene (f) benzonitrile

Answer

(a) 2-propanol (O—H, 3650–2500 cm^{-1}; C—O, 1300–1000 cm^{-1})
(b) propanoic acid (O—H, 3650–2500 cm^{-1}; C═O, 1850–1650 cm^{-1})
(c) phenylethyne (C≡C, 2250–2100 cm^{-1}; C═C, 1680–1440 cm^{-1})
(d) 1-hexene (C═C, 1680–1440 cm^{-1})
(e) 4-methylphenylamine (N—H, 3550–3150 cm^{-1}; C═C, 1680–1440 cm^{-1})
(f) benzonitrile (C≡N, 2280–2200 cm^{-1}; C═C, 1680–1440 cm^{-1})

FOLLOW-UP ASSIGNMENT

Using Figure 20.14 as a guide, identify regions of the IR spectrum in which you would expect to see characteristic functional group absorptions for each of the following compounds: (a) cyclopentanone, (b) methyl acetate, (c) methoxybenzene, (d) acetamide, (e) 1-aminohexane.

Where to Begin?

An efficient approach to interpreting an IR spectrum usually starts with a survey of the 4000–1500 cm^{-1} functional group region and the creation of an inventory of bond types present in the molecule. This inventory allows you to get a good idea of which functional groups are in the compound and which functional groups are not.

The functional group region can be subdivided into narrower frequency regions that are characteristic of specific bond types. Table 20.2 lists the positions of characteristic IR absorption peaks of various functional groups. It is fairly accurate for ***strong(s)*** and ***broad (br)*** peaks. However, because the intensities of IR absorptions can vary a good deal, the use of Table 20.2 has limitations, particularly for peaks listed as ***m (medium)*** and ***w (weak)*** intensity. As in the analysis of other experimental data, you must think about the significance of your conclusions, rather than assuming that an algorithm will lead to the correct answer every time.

In the following pages, each important IR region is described and examples of spectra illustrating the fundamental stretching bonds are given. Besides correlating a stretching vibration with a frequency (wavenumber), it is important to consider the general appearance of the signal. Is it sharp? Is it broad? Is it weak? Is it strong?

O—H and N—H Stretch of Alcohols and Amines ($3650–3200\ cm^{-1}$)

Alcohols and phenols show strong IR bands due to oxygen-hydrogen bond stretching and amines show medium intensity IR bands due to nitrogen-hydrogen bond stretching. The appearance of absorptions in this region is highly varied, which can actually add to their usefulness.

Alcohols. If an alcohol is prepared for IR analysis in any form other than a dilute solution, the hydroxyl group hydrogen bonds with neighboring molecules and the signal caused by the O—H stretch appears as a broad band between 3550 and 3200 cm^{-1}. The IR spectrum of a thin film of 2-propanol, shown in Figure 20.15, exhibits a broad, strong O—H stretching absorption at 3365 cm^{-1}.

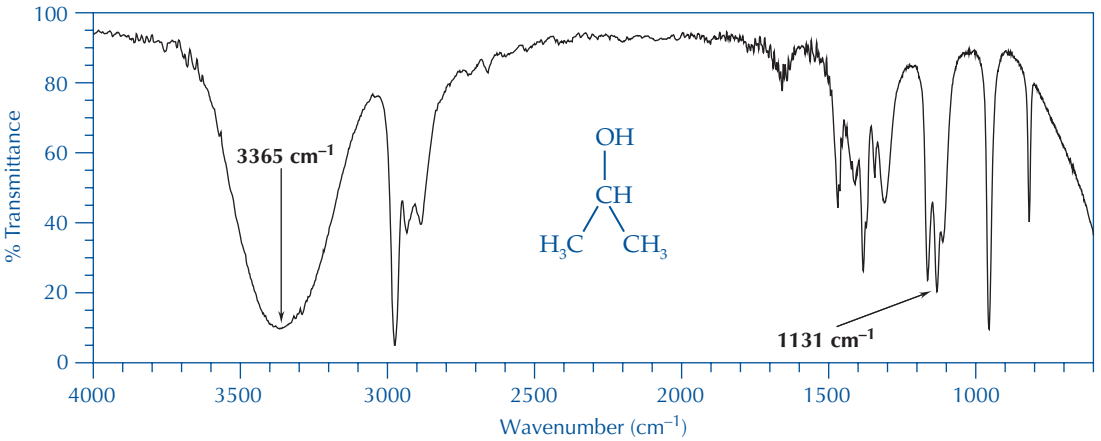


FIGURE 20.15 IR spectrum of 2-propanol (thin film).

TABLE 20.2 Characteristic infrared absorption peaks of functional groups

Vibration	Position (cm^{-1})	Intensity[a]	
Alkanes			
C—H stretch	2990–2850	m to s	
C—H bend	1480–1430 and 1395–1340	m to w	
Alkenes			
=C—H stretch	3100–3000	m	
C=C stretch	1680–1620 (sat.)[b], 1650–1600 (conj.)[b]	w to m	
=C—H bend	995–685	s	See Table 20.3 for detail
Alkynes			
≡C—H stretch	3310–3200	s	
C≡C stretch	2250–2100	m to w	
Aromatic Compounds			
C—H stretch	3100–3000	m to w	
C=C stretch	1620–1440	m to w	
C—H bend	900–680	s	See Table 20.3 for detail
Alcohols			
O—H stretch	3650–3550	m	Non-hydrogen bonded
	3550–3200	br, s	Hydrogen bonded
C—O stretch	1300–1000	s	
Amines			
N—H stretch	3550–3250	br, m	1° (two bands), 2° (one band)
Nitriles			
C≡N stretch	2280–2200	s	
Aldehydes			
C—H stretch	2900–2800 and 2800–2700	w	H—C=O, Fermi doublet
C=O stretch	1740–1720 (sat.), 1715–1680 (conj.)		
Ketones			
C=O stretch	1750–1705 (sat.), 1700–1650 (conj.)	s	
Esters			
C=O stretch	1765–1735 (sat.), 1730–1715 (conj.)	s	
C—O stretch	1300–1000	s	
Carboxylic Acids			
O—H stretch	3200–2500	br, m to w	
C=O stretch	1725–1700 (sat.), 1715–1680 (conj.)	s	
C—O stretch	1300–1000	s	
Amides			
N—H stretch	3500–3150	m	1° (two bands), 2° (one band)
C=O stretch	1700–1630	s	
Anhydrides			
C=O stretch	1850–1800 and 1790–1740	s	
C—O stretch	1300–1000	s	
Acid chlorides			
C=O stretch	1815–1770	s	
Nitro compounds			
NO_2 stretch	1570–1490 and 1390–1300	s	

a. s = strong, m = medium, w = weak, br = broad b. sat. = saturated, conj. = conjugated

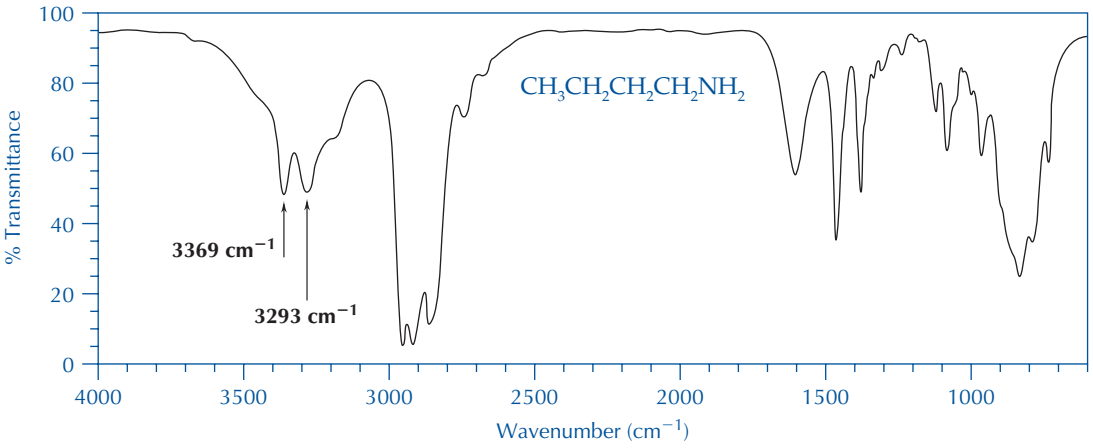
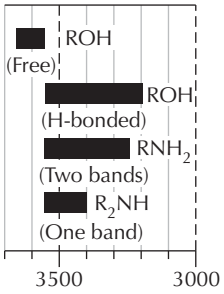
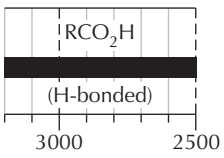


FIGURE 20.16 IR spectrum of 1-aminobutane (thin film).

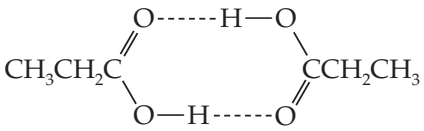


Amines. The medium intensity N—H stretching vibrations of primary and secondary amines also appear in 3550–3200 cm^{-1} region. The number of signals depends on the number of hydrogen atoms attached to the nitrogen atom. Primary amines show two peaks and secondary amines show only one. The IR spectrum of 1-aminobutane is shown in Figure 20.16. Because it is a primary amine, there are two absorptions (at 3369 and 3293 cm^{-1}) from symmetric and asymmetric H—N—H stretching vibrations. Amines are capable of hydrogen bonding, so the position and shape of the absorption may vary. The higher the concentration of the amine and the better it can hydrogen bond, the broader the absorption will be. Hydrogen bonding shifts N—H stretching absorptions to lower frequencies. Alkyl amines are stronger bases than aromatic amines and tend to form stronger hydrogen bonds.

O—H Stretch of Carboxylic Acids (3200–2500 cm^{-1})



As a result of extensive intermolecular hydrogen bonding, carboxylic acids generally show an unusually broad O—H stretching absorption, with the band often tailing from about 3200 cm^{-1} all the way down to 2500 cm^{-1}. The intensity of this band is medium to weak. The spectrum of propanoic acid shown in Figure 20.17 illustrates this behavior. In this spectrum the O—H stretching band is so broad that the sharper C—H stretch at approximately 3000 cm^{-1} is superimposed on it. This superimposition is not uncommon with the O—H and C—H stretching vibrations of carboxylic acids. The structure of the intermolecular hydrogen-bonded propanoic acid dimer is



C—H Stretch (3310–2850 cm^{-1})

Because most organic compounds contain hydrogen atoms, you can expect to find C—H stretching signals in most IR spectra. The

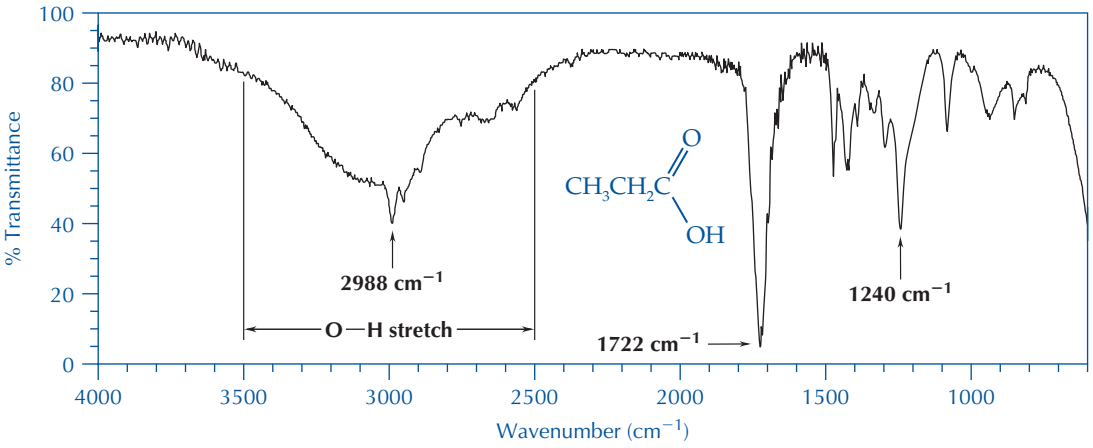
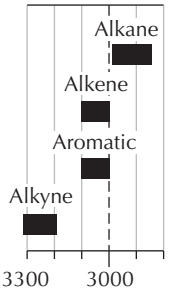


FIGURE 20.17 IR spectrum of propanoic acid (thin film).



position of the C—H stretch depends on the hybridization of the carbon atom to which the hydrogen is bound.

***sp* Hybridization.** If the carbon atom is *sp* hybridized, the absorption appears near 3300 cm^{-1}. A good example is found in the spectrum of phenylacetylene shown in Figure 20.18. The C—H stretch of the acetylene appears at 3277 cm^{-1}. This band could be confused with a signal resulting from an O—H or N—H stretch, were it not for its shape. The C—H band is much sharper than the typical hydrogen-bonded O—H or N—H stretch found in this region.

sp*^{2} *Hybridization. Peaks that occur when hydrogen atoms are attached to *sp*^{2}-hybridized carbon atoms of alkenes and aromatic compounds appear in the region 3100–3000 cm^{-1}. In the spectrum of phenylacetylene (see Figure 20.18), the aromatic hydrogen stretching vibrations appear from 3066 to 3006 cm^{-1}. In the spectrum of 1-hexene shown in Figure 20.19, the vinyl-hydrogen stretch appears at 3084 cm^{-1}.

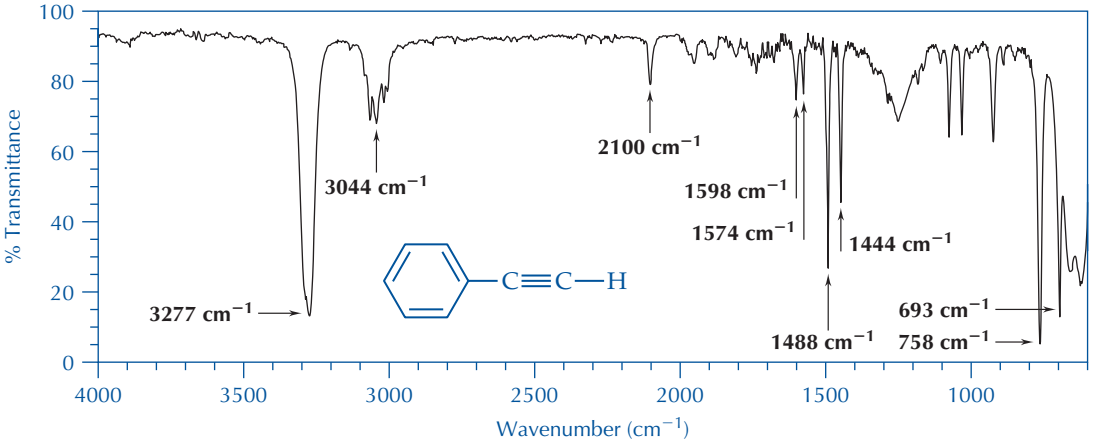


FIGURE 20.18 IR spectrum of phenylacetylene (thin film).

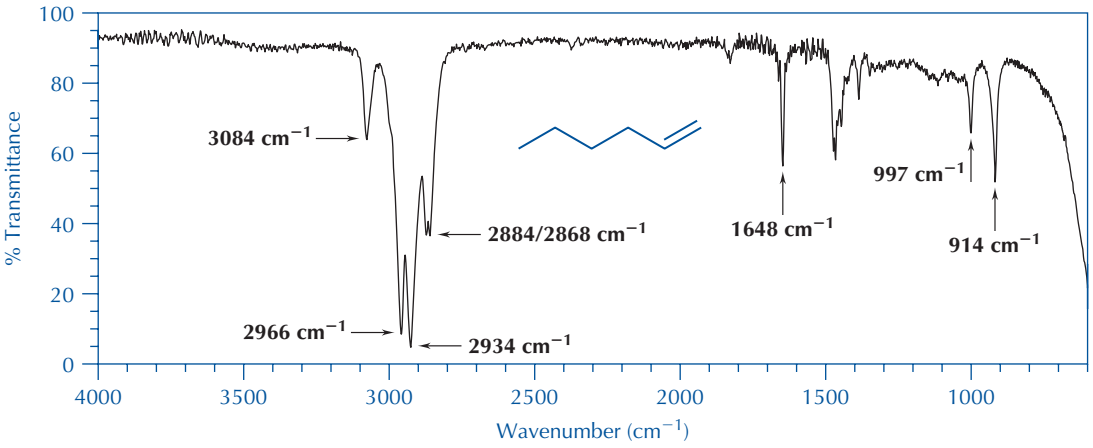
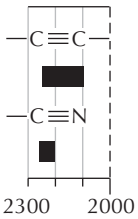


FIGURE 20.19 IR spectrum of 1-hexene (thin film).

sp³ Hybridization. Hydrogen atoms attached to sp^3-hybridized carbon atoms exhibit absorption bands in the 2990–2850 cm^{-1} region. There are usually several alkyl C—H stretching vibration bands in an IR spectrum. In the spectrum of 1-hexene, there are four distinct peaks from 2966 to 2868 cm^{-1} because of C—H stretching vibrations of hydrogen atoms attached to sp^3 carbon atoms.

C≡C and C≡N Stretch (2280–2100 cm⁻¹)



Only the triple bonds of nitriles and alkynes have absorptions in this region. If it is a strong absorption, it is likely to be that of a nitrile, such as the signal at 2230 cm^{-1} in the spectrum of benzonitrile (Figure 20.20). The difference in electronegativity between carbon and nitrogen leads to a highly polarized C≡N bond and thus a strong absorption. Alkynes have weak- to medium-intensity absorption bands in this region. The C≡C bond stretch in phenylacetylene is the small peak at 2100 cm^{-1} (see Figure 20.18).

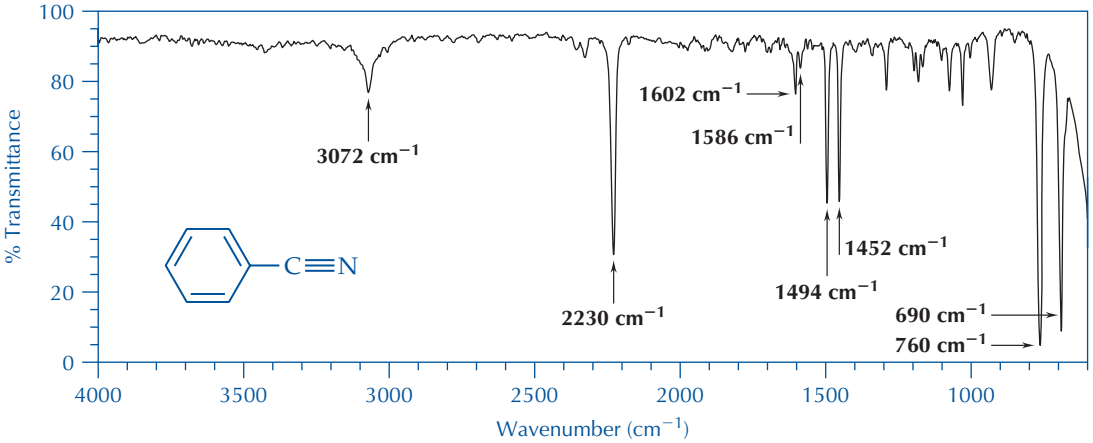
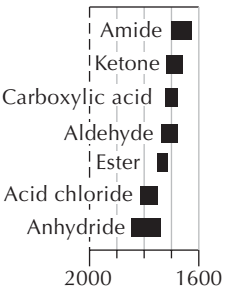


FIGURE 20.20 IR spectrum of benzonitrile (thin film).

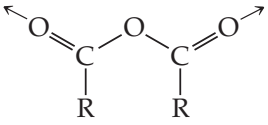
C═O stretch (1850–1630 cm^{-1})



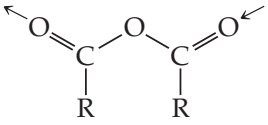
The carbonyl group is one of the most important functional groups in organic compounds. If there is a C═O present in the molecule, there will be a strong, sharp absorption band in the 1850–1630 cm^{-1} region. Good examples of C═O stretching are the strong band at 1747 cm^{-1} in the spectrum of cyclopentanone (see Figure 20.1) and the strong band at 1722 cm^{-1} in the spectrum of propanoic acid (see Figure 20.17). If there is no strong band in the 1850–1630 cm^{-1} region, there is no C═O in the molecule. The exact position of the signal within this region, however, depends on what type of functional group contains the C═O group.

Functional group	Example	C═O stretch, cm^{-1}
Amides	Acetamide	1681
Ketones	Acetone	1715
Carboxylic acids	Propanoic acid	1722
Aldehydes	Acetaldehyde	1727
Esters	Methyl acetate	1745
Acid chlorides	Acetyl chloride	1806
Acid anhydrides	Propanoic anhydride	1827 and 1766

Notice that acid anhydrides are characterized by the presence of two peaks in the C═O stretching region. These peaks arise from symmetric and asymmetric C═O stretching vibrations.



Symmetric C═O stretch



Asymmetric C═O stretch

Effect of ring strain and conjugation. Factors such as ring strain and conjugation cause deviations from the position of the C═O band for saturated acyclic compounds. Ring strain causes the position of the absorption band to move to a higher frequency, indicating that the strength of the bond has increased. Compare the absorption bands of acetone (1715 cm^{-1}) and methyl acetate (1745 cm^{-1}) to the carbonyl absorption bands of the cyclic compounds listed here.

Ketone	C═O stretch, cm^{-1}	Ester	C═O stretch, cm^{-1}
Cyclopropanone	1818	—	—
Cyclobutanone	1783	Propanolactone	1840
Cyclopentanone	1747	4-Butanolactone	1770
Cyclohexanone	1716	5-Pentanolactone	1730
Cycloheptanone	1702	6-Hexanolactone	1732

Conjugation with a C═C double bond or with an aromatic ring decreases the bond order of the C═O slightly and causes the position of absorption to move to a lower frequency by 20–30 cm^{-1}. Compare the position of the C═O absorption band of 4-methylpentan-2-one (Figure 20.21) to that of the conjugated compound 4-methyl-3-penten-2-one (Figure 20.22). The absorption band is shifted from 1719 cm^{-1} to 1695 cm^{-1}. A similar shift is observed when the C═O group is conjugated with a benzene ring. The C═O absorption band in

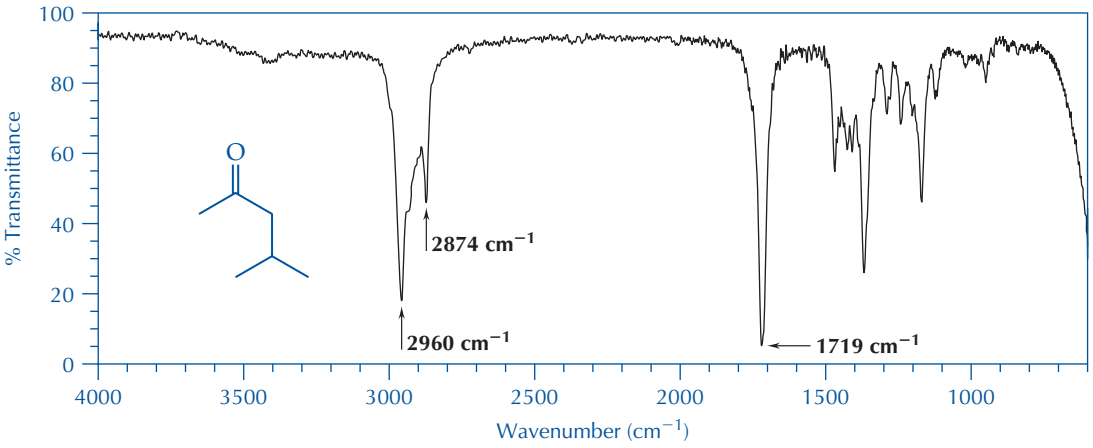


FIGURE 20.21 IR spectrum of 4-methylpentan-2-one (thin film).

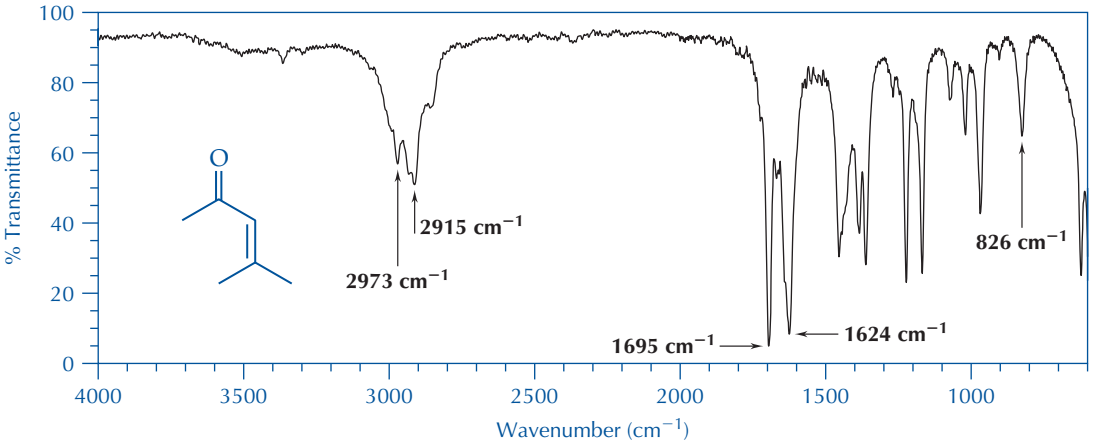


FIGURE 20.22 IR spectrum of 4-methyl-3-penten-2-one (thin film).

acetophenone appears at 1690 cm^{-1}, whereas the C═O absorption band in acetone appears at 1715 cm^{-1}.

Corroborating IR peaks. Because the C═O bond is present in many functional groups and the position of the stretching vibration is affected by many variables, it can be difficult to differentiate between carbonyl-containing functional groups by the C═O stretching frequency alone. It is usually necessary to identify other absorption bands in the IR spectrum to ascertain the identity of the functional group exhibiting the C═O stretch.

Primary and secondary amides exhibit N—H stretching absorption bands in the 3500–3150 cm^{-1} region, two bands for primary amides and one band for secondary amides.

Carboxylic acids exhibit an extremely broad absorption band between 3200 and 2500 cm^{-1} because of hydrogen-bonded O—H stretching vibrations (see Figure 20.17).

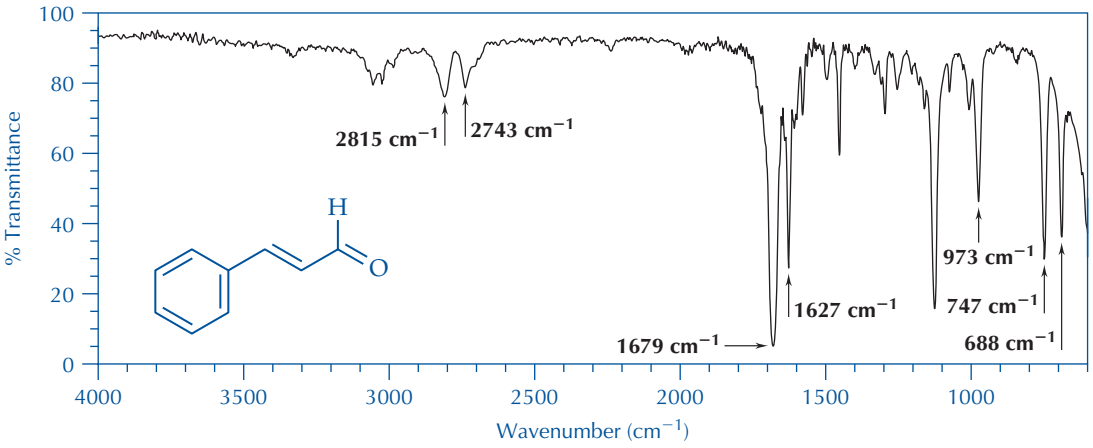


FIGURE 20.23 IR spectrum of cinnamaldehyde (thin film).

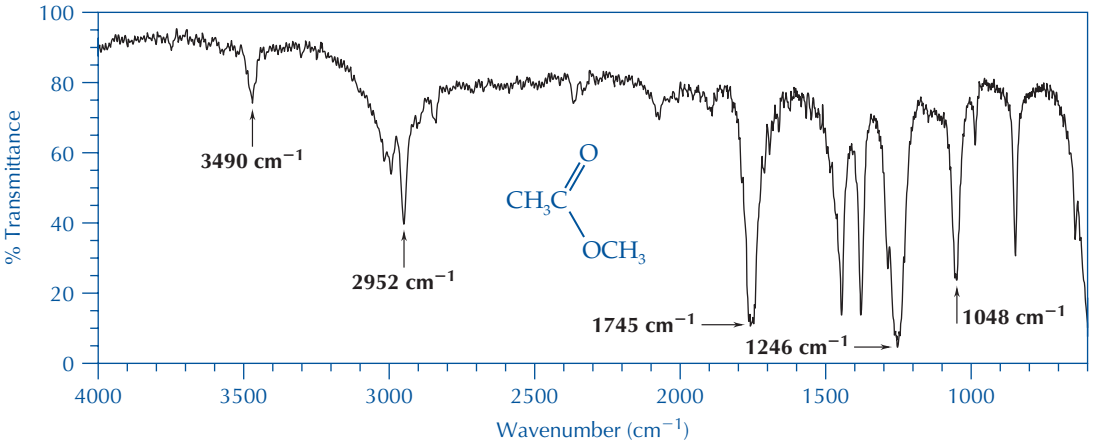
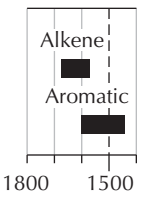


FIGURE 20.24 IR spectrum of methyl acetate (thin film).



Aldehydes exhibit two weak but very distinct absorption bands in the C—H stretching region (2900–2800 cm^{-1} and 2800–2700 cm^{-1}). The two bands are an example of a Fermi doublet as a result of the interaction of the fundamental stretching vibration of the aldehyde C—H bond with an overtone band. The characteristic aldehyde C—H bands at 2815 cm^{-1} and 2743 cm^{-1} are evident in the spectrum of cinnamaldehyde shown in Figure 20.23.

Esters exhibit a very strong band in the C—O stretching region (1300–1000 cm^{-1}). In the spectrum of methyl acetate, shown in Figure 20.24, a C—O stretching vibration appears at 1246 cm^{-1}.

C═C Stretch (1680–1440 cm^{-1})

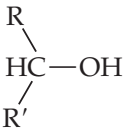
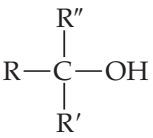
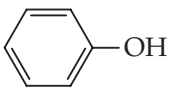
Absorptions in the 1680–1440 cm^{-1} region occur because of C═C bonds in alkenes as well as C═C bonds in aromatic compounds. Their intensities vary from weak to medium. A typical absorption of this type is the band at 1648 cm^{-1} in the spectrum of 1-hexene (see Figure 20.19). The position of the band and its intensity are affected by conjugation. The position of the C═C stretching absorption in

4-methyl-3-penten-2-one (see Figure 20.22) appears at 1624 cm^{-1}, and its intensity is significantly stronger than the intensity of the band in 1-hexene.

Aromatic compounds have four bands in this region near 1600, 1580, 1500, and 1450 cm^{-1}. The first two bands are generally weak and the second two are generally moderate in intensity. The band at 1450 cm^{-1} can be obscured by CH_2 bending vibrations if an alkyl group is present. These bands are evident in the spectra of phenylacetylene (see Figure 20.18) and benzonitrile (see Figure 20.20).

C—O Stretch (1300–1000 cm^{-1})

Because C—O bonds are highly polarized, their absorption bands are generally very strong. However, the assignment can sometimes be ambiguous because the peaks occur in the fingerprint region (1500–900 cm^{-1}), which is cluttered with many absorption bands due to bending vibrations, overtone bands, and combination bands. Esters, ethers, and alcohols show useful bands in this region. In the spectrum of 2-propanol (see Figure 20.15), the signal at 1131 cm^{-1} is attributed to the C—O stretching vibration. Esters often exhibit two C—O stretching vibrations, one for the C—O bond to the carbonyl carbon and one for the C—O bond to the carbon of the alcohol group. In the spectrum of methyl acetate (see Figure 20.24), the bands appear at 1246 cm^{-1} and 1048 cm^{-1}. Strong absorptions within this region have been correlated with the degree and type of substitution of alcohols.

Type of alcohol	C—O stretch, cm^{-1}
$RCH_2—OH$ Primary	1080–1000
 Secondary	1130–1000
 Tertiary	1210–1100
 Phenol	1260–1180

NO_2 Stretches (1570–1490 cm^{-1} and 1390–1300 cm^{-1})

Aromatic nitro groups have two very distinctive absorptions due to symmetric and asymmetric O—N—O stretches. The bands are usually the most intense peaks in the spectrum. In the spectrum of

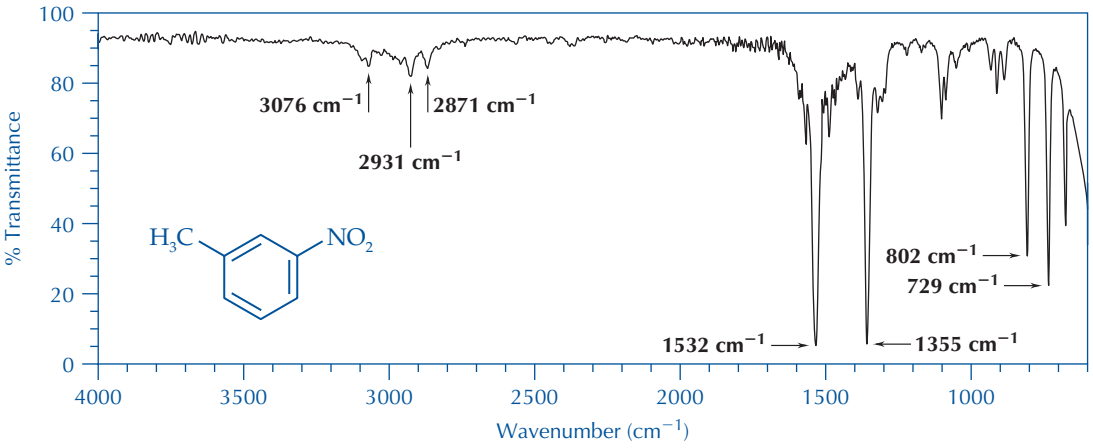
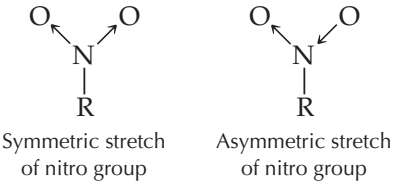


FIGURE 20.25 IR spectrum of 3-nitrotoluene (thin film).

3-nitrotoluene, shown in Figure 20.25, the signals appear at 1532 cm^{-1} and 1355 cm^{-1}.



Useful Diagnostic Peaks (1000–600 cm^{-1})

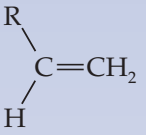
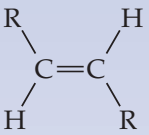
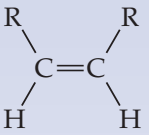
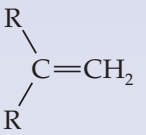
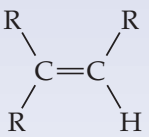
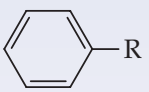
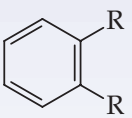
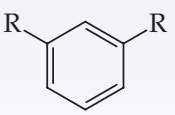
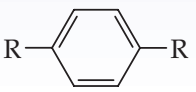
An infrared spectrum can be highly cluttered with peaks, and not every one can be easily or directly correlated to a specific vibration. However, there are some absorption bands, in addition to the fundamental IR stretching vibrations, that can provide structural information. The number and arrangement of substituents on a C═C bond can often be determined from the presence of strong signals below 1000 cm^{-1}; these occur because of C—H bending vibrations. Table 20.3 summarizes these diagnostic peaks in the region 1000–600 cm^{-1}.

Absorptions at 997 and 914 cm^{-1} in the spectrum of 1-hexene (see Figure 20.19) are characteristic of a monosubstituted alkene. In the spectrum of cinnamaldehyde (see Figure 20.23), the *trans*-disubstituted C═C bond is indicated by the absorption at 973 cm^{-1}. The trisubstituted alkene in 4-methyl-3-penten-2-one is indicated by the absorption appearing at 826 cm^{-1} in its IR spectrum (see Figure 20.22). Absorptions at 760 and 690 cm^{-1} in the spectrum of benzonitrile (see Figure 20.20) are characteristic of a monosubstituted benzene ring.

20.8 Procedure for Interpreting an IR Spectrum

IR spectroscopy is an important tool for determining which functional groups are in a molecule. For most organic compounds, this information alone is not sufficient to unequivocally determine the

TABLE 20.3 Out-of-plane C—H bending vibrations of alkenes and aromatic compounds

Structure	Position (cm^{-1})
	997–985 and 915–905
	980–960
	730–665
	895–885
	840–790
	770–730 and 720–680
	770–735
	810–750 and 725–680
	860–800

structure. However, the inventory of functional groups coupled with other data, particularly NMR and mass spectra, usually leads to a definitive elucidation of a compound's structure.

After you have interpreted numerous IR spectra, the need for a structured approach in compiling an inventory of functional groups will not be very great. But in the beginning, a general method that provides a structured and logical approach may be helpful in learning to interpret an IR spectrum.

Step 1. Check 1850–1630 cm^{-1} Region

A strong signal in this region indicates the presence of a carbonyl group. If there are no strong signals, no C═O group is present, and you should proceed to Step 2. If a C═O group is present, use signals in other regions of the IR spectrum to identify the specific type of carbonyl functional group:

- Two strong bands centered near 1800 cm^{-1} indicate an acid anhydride group.
- Two weak absorption bands in the region 2900–2700 cm^{-1} indicate an aldehyde group.
- An extremely broad band extending from 3200 to 2500 cm^{-1} indicates a carboxylic acid group.
- Two strong absorption bands in the region 1300–1000 cm^{-1} indicate an ester group.
- One or two medium-intensity bands in the 3500–3150 cm^{-1} region indicate an amide group.

In the absence of any of the preceding conditions, a single strong C═O stretching absorption near 1700 cm^{-1} probably indicates a ketone. A single strong absorption near 1800 cm^{-1} is probably the result of an acid chloride.

Step 2. Check 3550–3200 cm^{-1} Region

The presence of a strong, broad signal indicates the hydroxyl group of an alcohol. There should be an accompanying strong band due to C—O stretching in the region 1300–1000 cm^{-1}. The presence of medium-intensity bands indicates an amine group. Primary amines have two bands and secondary amines have one.

Step 3. Check C—H Stretching Region at 3310–2850 cm^{-1}

A strong, sharp band near 3300 cm^{-1} indicates a terminal alkyne group. There should be an accompanying weak- to medium-intensity band due to C≡C stretching near 2200 cm^{-1}. Bands in the region 3100–3000 cm^{-1} are a result of C—H stretching in alkenes or aromatic compounds. Corroborating bands can narrow the choices.

- A medium-intensity band near 1650 cm^{-1} indicates a C═C bond.
- Several weak- to medium-intensity bands in the region 1620–1450 cm^{-1} may suggest an aromatic ring.
- If an alkene or an aromatic ring is indicated, the region 1000–600 cm^{-1} may determine the substitution pattern (see Table 20.3).

Signals in the region 2990–2850 cm^{-1} are caused by C—H stretching in alkyl groups.

Step 4. Check 2280–2100 cm^{-1} Region

A strong signal near 2250 cm^{-1} indicates a nitrile group. A medium- to weak-intensity band near 2170 cm^{-1} indicates a C≡C group.

Step 5. Check 1300–1000 cm^{-1} Region

If there are one or two strong absorptions in this region and no signals in the O—H or C═O stretching regions, an ether group may be present.

Step 6. Prepare an Inventory of Functional Groups

Assemble a list of the functional groups indicated by the IR spectrum. If NMR data or a molecular formula are available, coordinate them with the results from IR spectroscopy. Fit the pieces together into likely chemical structures that are consistent with the data and with the rules of chemical bonding.

20.9 Case Study

In this section you will see how the information derived from an IR spectrum of an organic compound can help you to determine its molecular structure. The molecular formula of the compound is $C_9H_{10}O$, and its IR spectrum, run using an ATR attachment, is shown in Figure 20.26.

Begin by surveying the 4000–1500 cm^{-1} functional group region. The general approach presented in Technique 20.8 can then lead you to the creation of an inventory of bond types present in the molecule. This inventory allows you to get a good idea of which functional groups are and are not present in the compound.

The absence of a strong signal in the region 1850–1630 cm^{-1} indicates that no C═O groups are present. Prominent in the region 3650–3200 cm^{-1} is the intense, broad band at 3327 cm^{-1}. Its intensity and position indicate the presence of a hydroxyl group. There are also strong bands in the 1300–1000 cm^{-1} region, consistent with the C—O stretching vibration of an alcohol, although the cluttered nature of this region makes a definitive assignment of the signals difficult.

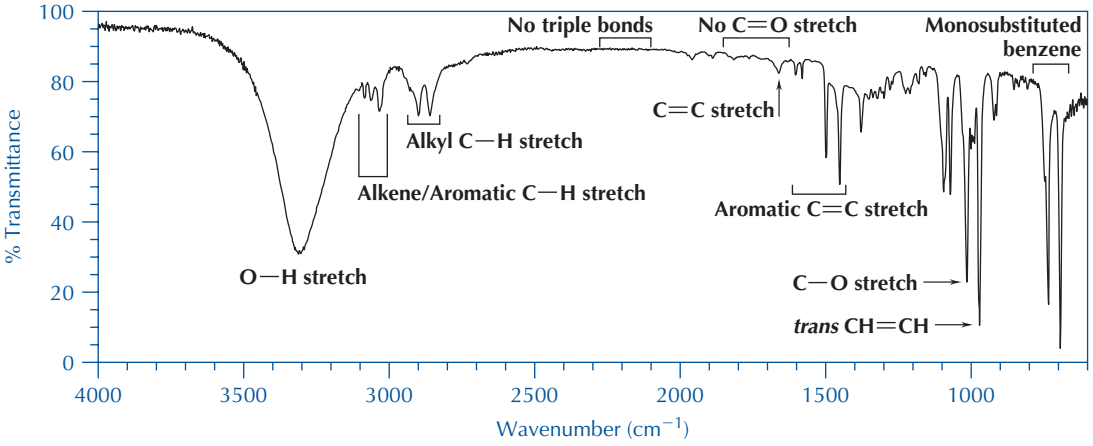


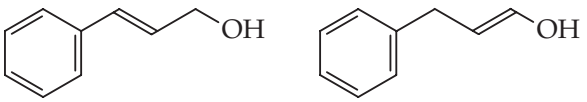
FIGURE 20.26 IR spectrum of $C_9H_{10}O$ (ATR-corrected).

In the C—H stretching region, 3310–2850 cm^{-1}, there are signals from 3100 to 3000 cm^{-1} superimposed on the shoulder of the broad and intense O—H stretching signal. The signals in the region 3100–3000 cm^{-1} signify C—H stretching in alkenes or aromatic compounds. The presence of a C═C bond is confirmed by a weak-intensity band at 1668 cm^{-1}. The signals at 1599, 1578, 1494, and 1449 cm^{-1} are consistent with the presence of an aromatic ring. There are also two signals of medium intensity at about 2900 cm^{-1}, which signify C—H stretching vibrations of at least one alkyl group.

An absence of any signals in the region 2250–2100 cm^{-1} rules out the presence of a C≡C bond.

Because the presence of a C═C bond and the presence of an aromatic ring are indicated, a check of the region 1000–600 cm^{-1} is warranted. The signal at 967 cm^{-1} indicates that the double bond is *trans*-disubstituted. The signals at 740 and 692 cm^{-1} indicate that the aromatic ring is monosubstituted (see Table 20.3).

In summary, our inventory of functional groups consists of a monosubstituted benzene ring (C_6H_5—), a *trans*-disubstituted double bond (—CH═CH—), a hydroxyl group (—OH), and at least one sp^3 carbon atom. The molecular formula of the compound is $C_9H_{10}O$. If the alkyl carbon atom is part of a methylene group, we have accounted for all the necessary atoms. There are two ways to put these pieces together:



The structure on the right can be eliminated because it is the unstable enol isomer of an aldehyde. The compound that produced the IR spectrum shown in Figure 20.26 is the structure on the left, (*E*)-3-phenyl-2-propen-1-ol, commonly called cinnamyl alcohol.

This case study was carefully chosen to show the power of infrared spectroscopy. In most cases it would be difficult if not impossible to reach a definitive structure for a compound given only a molecular formula and an IR spectrum unless one successfully searched a database for a match with the spectrum of the compound. However, even if a complete structure doesn't result from the assembly of an inventory of functional groups, the knowledge of which functional groups are present can be a great help in understanding the compound and its properties.

20.10 Sources of Confusion

The three major sources of confusion in infrared spectroscopy arise from faulty sample preparation, incorrect use of the FTIR spectrometer, and the inherent complexity of IR spectra.

Problems with Sample Preparation

Careful sample preparation is essential to producing a useful IR spectrum.

Water. If the sample is not scrupulously dry, the suspended or dissolved water will result in bands in the O—H stretching region near 3500 cm^{-1} and in the O—H bending region near 1650 cm^{-1}. In addition to producing a spectrum with misleading absorptions, the water will also etch sodium chloride disks used to contain a sample. Etched disks absorb and scatter infrared radiation and future spectra will have less resolved IR signals.

Intense signals. If the sample is too thick in the case of thin films or too concentrated, the large bands will "bottom out" at 0% transmittance, producing wide absorption bands from which it is impossible to determine an exact absorption frequency. Small signals will appear to have larger significance than they deserve, often leading to erroneous assignments of the IR peaks. The remedy is to prepare a less concentrated KBr or Nujol dispersion or a thinner film.

Broad, indistinct signals. If you are working with a thin film, it is likely that the sample has evaporated or migrated away from the sampling region of the infrared beam. With mulls and KBr pellets, the solid sample probably has not been ground finely enough.

Sloping baseline. A sloping baseline, as shown in the spectrum of fluorenone in Figure 20.27, is a problem with Nujol mulls that is difficult to avoid. Often a severely sloping baseline is the result of a poorly ground solid, but even with careful grinding, some samples still produce spectra with sloping baselines. With the availability of digitized data on an FTIR spectrometer, the baseline can be adjusted with the instrument's software.

Missing peaks. At times, you may encounter spectra that seem internally inconsistent. For example, you may be working with the Nujol mull spectrum of a compound that you strongly suspect contains one or more functional groups, yet there are no signals in its IR spectrum

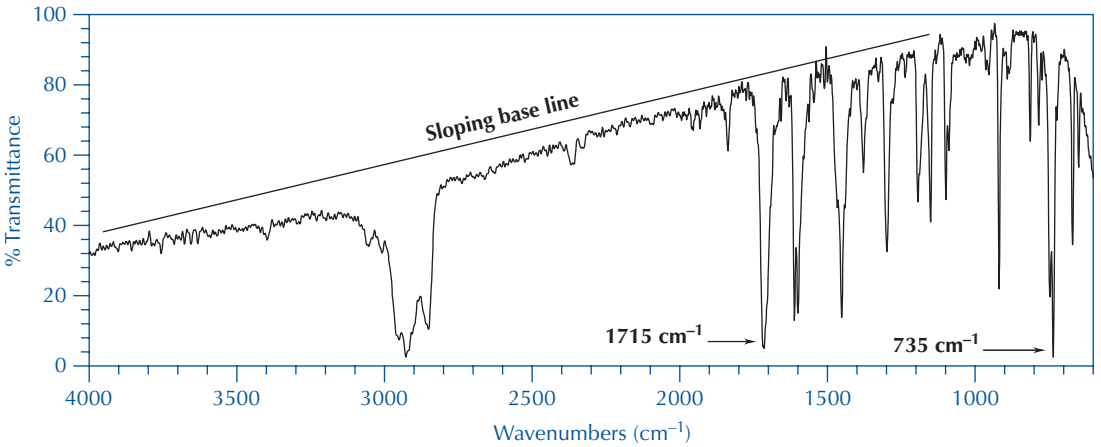


FIGURE 20.27 IR spectrum of fluorenone (Nujol mull).

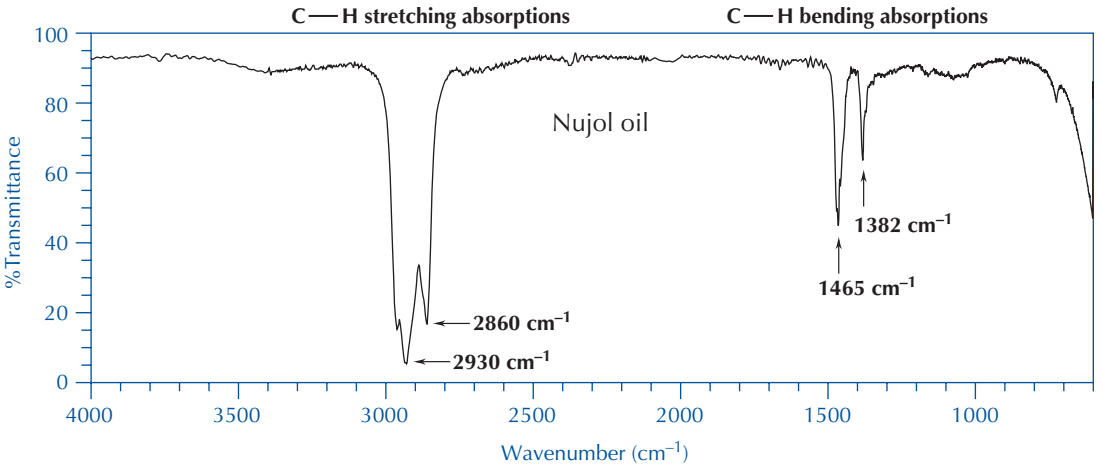


FIGURE 20.28 IR spectrum of Nujol (thin film).

indicating their presence. A common mistake made when preparing Nujol mulls is the addition of too much mineral oil, leading to a spectrum that is virtually indistinguishable from the spectrum of Nujol itself, shown in Figure 20.28.

Problems Using the Spectrometer

Although FTIR spectrometers are not especially difficult to use, two confusing situations are encountered from time to time.

No spectrum. What if the IR spectrum you obtain consists of a flat line at 100% transmittance? The easy explanation is that you forgot to put the sample into the IR beam. But what if you did put the sample into the beam? In all likelihood, you placed the sample in the IR beam before you ran a background scan and then left the sample in the beam and ran a sample scan. In that case, the background scan and the sample scan are the same. The result of subtracting the background scan from the sample scan is equivalent to 100% transmittance over the entire wavelength range.

Unexpected peaks near 2350 cm^{-1}. You may see a pair of signals near 2350 cm^{-1} on your IR spectrum, which may be either up or down in direction. These signals are absorption bands of carbon dioxide. If the sample compartment is left open for long periods, the ambient atmosphere, which contains CO_2, infiltrates the compartment. If the signals are down, the sample compartment was left open before running the sample scan. If the signals are up (greater than 100% transmittance), the sample compartment was left open before running the background scan. The remedy for this problem is to keep the sample compartment closed except when installing or removing a sample and to allow enough time for the closed sample compartment to be purged with purified air or nitrogen before obtaining the IR spectrum.

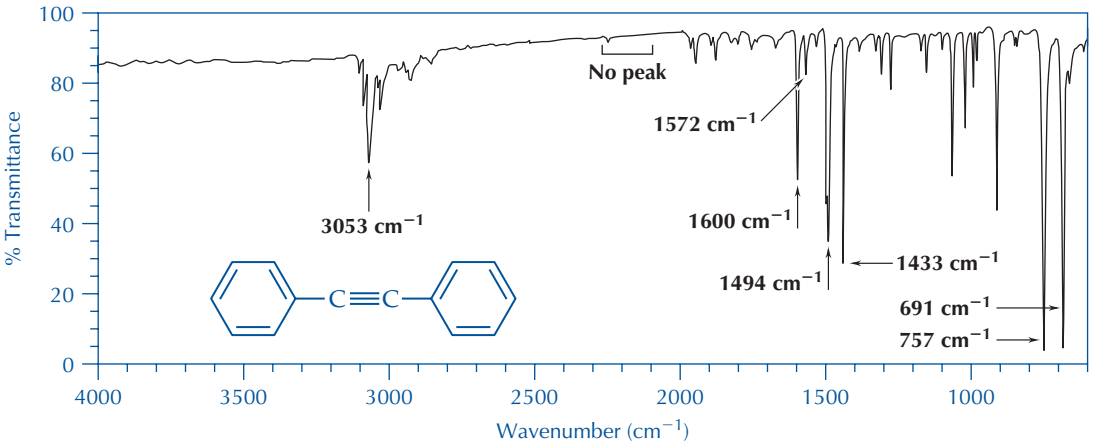


FIGURE 20.29 IR spectrum of diphenylethyne (KBr disk).

Inherent Complexity of IR Spectra

The number of observed absorption bands is generally different from the total number of possible fundamental molecular vibrations. Some vibrations are not IR active and do not absorb energy. Some absorption bands result from overtone vibrations, combination vibrations, and the coupling of vibrations.

Missing peaks. When the IR spectrum of a symmetric or nearly symmetric compound is taken, an expected absorption peak may be missing from the spectrum. For example, the spectrum of diphenylethyne, shown in Figure 20.29, displays no characteristic C≡C stretch near 2200 cm^{-1}. The absence of the C≡C absorption is the result of symmetry; the C≡C bond does not have a dipole bond moment and its stretching vibration is not IR active.

Extra peaks. Extra peaks in unexpected positions can lead to confusion. In most cases, the extraneous signals are overtones of very strong peaks in the spectrum. A good example is seen in the spectrum of methyl acetate (see Figure 20.24). The signal at 3490 cm^{-1} is in the region where O—H stretching absorptions appear, but the peak is clearly not an OH stretch because of its weak intensity and the shape of the absorption. It is an overtone of the intense C═O peak at 1745 cm^{-1}.

Further Reading

The Aldrich Library of FT-IR Spectra; 2nd ed.; Aldrich Chemical Company: Milwaukee, WI, 1992; 3 volumes.

Colthup, N. B.; Daly, L. H.; Wiberly, S. E. *Introduction to Infrared and Raman Spectroscopy*, 3rd. ed.; Academic: Boston, 1990.

Crews, P.; Rodríguez, J.; Jaspars, M. *Organic Structure Analysis;* Oxford University Press: Oxford, 1998.

Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrometric Identification of Organic Compounds;* 7th ed.; Wiley: New York, 2005.

Questions

1. In each of the sets that follow, match the proper compound with the appropriate set of IR bands and give the rationale for your assignment.
   a. dodecane, 1-decene, 1-hexyne, 1,2-dimethylbenzene
   3311(s), 2961(s), 2119(m) cm^{-1}
   3020(s), 2940(s), 1606(s), 1495(s), 741(s) cm^{-1}
   3049(w), 2951(m), 1642(m) cm^{-1}
   2924(s), 1467(m) cm^{-1}
   b. phenol, benzyl alcohol, methoxybenzene
   3060(m), 2835(m), 1498(s), 1247(s), 1040(s) cm^{-1}
   3370(s), 3045(m), 1595(s), 1224(s) cm^{-1}
   3330(br, s), 3030(m), 2950(m), 1454(m), 1223(s) cm^{-1}
   c. 2-pentanone, acetophenone, 2-phenylpropanal, heptanoic acid, 2-methylpropanamide, phenyl acetate, 1-aminooctane
   3070(m), 2978(m), 2825(s), 2720(m), 1724(s) cm^{-1}
   3372(m), 3290(m), 2925(s) cm^{-1}
   3070(w), 1765(s), 1215(s), 1193(s) cm^{-1}
   3300—2500(br, s), 2950(m), 1711(s) cm^{-1}
   3060(m), 2985(w), 1690(s) cm^{-1}
   3352(s), 3170(s), 2960(m), 1640(s) cm^{-1}
   2964(s), 1717(s) cm^{-1}
2. Treatment of cyclohexanone with sodium borohydride results in a product that can be isolated using distillation. The IR spectrum of this product is shown in Figure 20.30. Identify the product and assign the major IR bands.

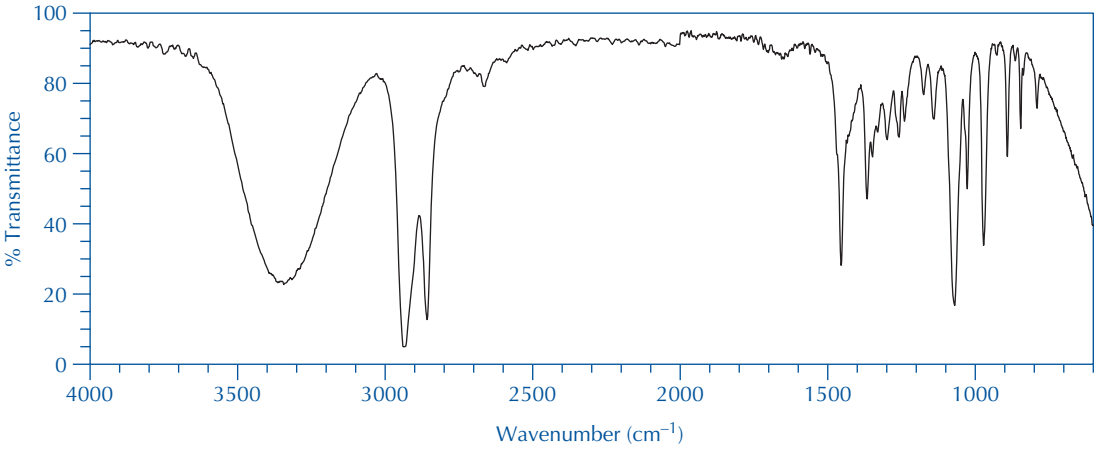


FIGURE 20.30 IR spectrum for question 2 (thin film).

3. In an attempt to prepare diphenylacetylene, 1,2-dibromo-1,2-diphenylethane is refluxed with potassium hydroxide. A hydrocarbon with the chemical formula $C_{14}H_{10}$ is isolated. The infrared spectrum exhibits signals at 3100–3000 cm^{-1} but no signals in the region 2300–2100 cm^{-1}. Is this spectrum consistent with a compound containing a carbon-carbon triple bond? Explain the absence of a signal in the 2300–2100 cm^{-1} region.
4. When benzene is treated with chloroethane in the presence of aluminum chloride, the product is expected to be ethylbenzene (bp 136°C). During the isolation of this product by distillation, some liquid of bp 80°C was obtained. Identify this product, using its boiling point and the IR spectrum in Figure 20.31.

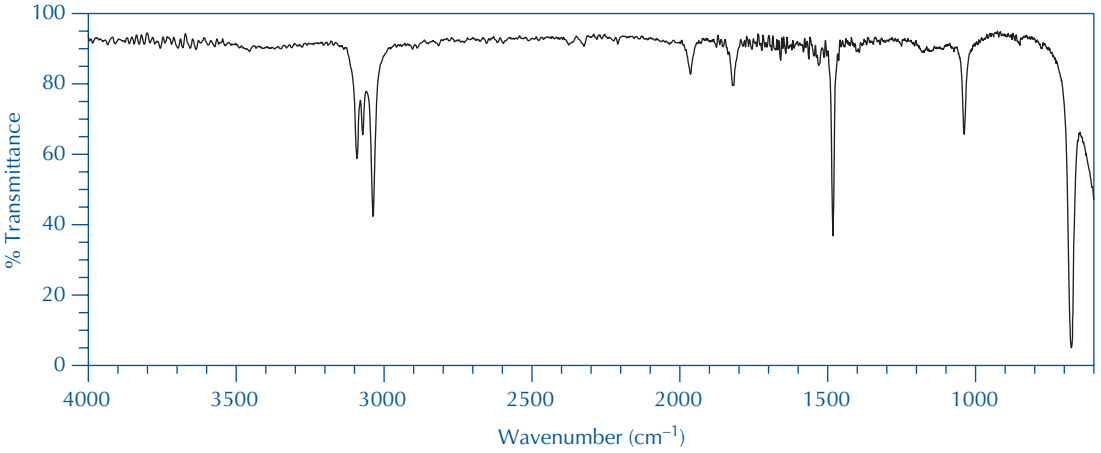


FIGURE 20.31 IR spectrum for question 4 (thin film).

5. Consider the IR spectra shown in Figures 20.32 through 20.39 and match them to the following compounds: biphenyl, 4-isopropyl-1-methylbenzene, 1-butanol, phenol, 4-methylbenzaldehyde, ethyl propanoate, benzophenone, acetanilide. (**Note:** Some samples were prepared as thin films and others were prepared as Nujol mulls or by using an ATR accessory.)

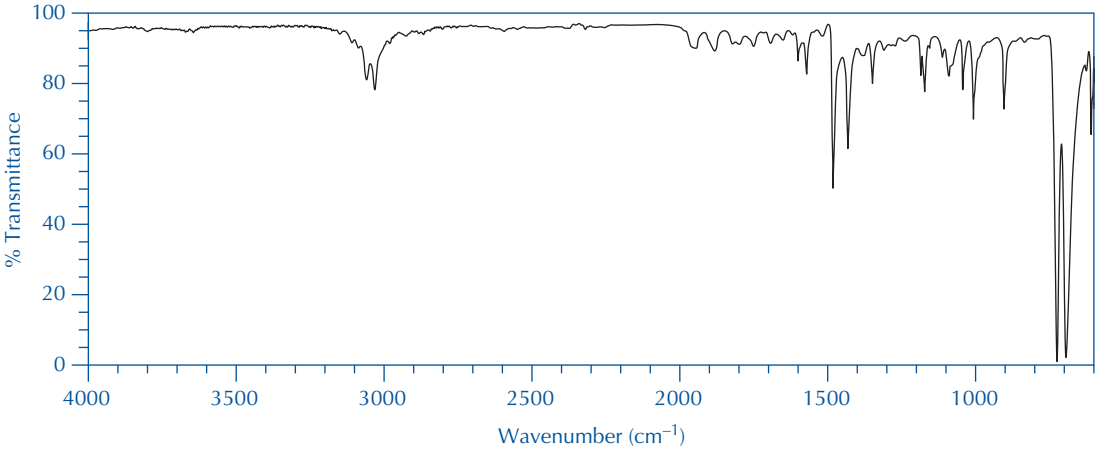


FIGURE 20.32 IR spectrum for question 5 (ATR).

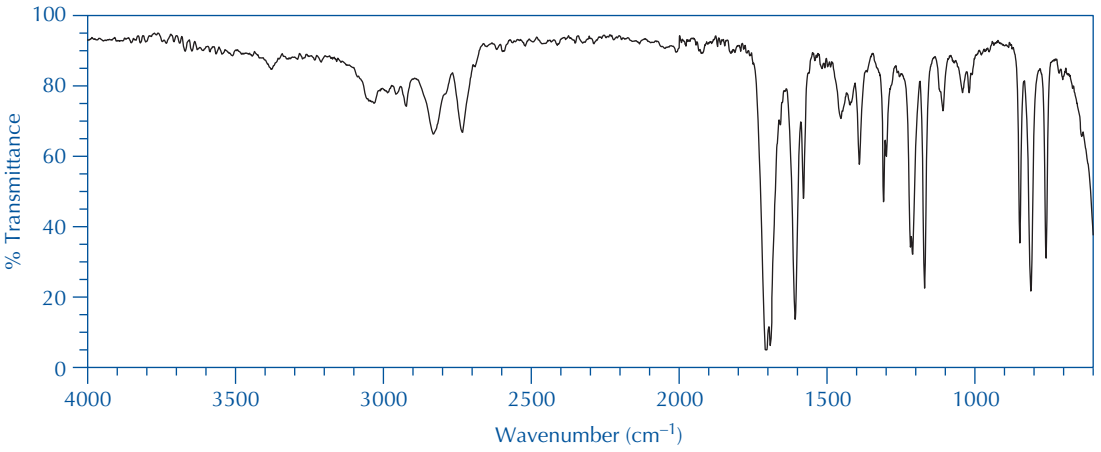


FIGURE 20.33 IR spectrum for question 5 (thin film).

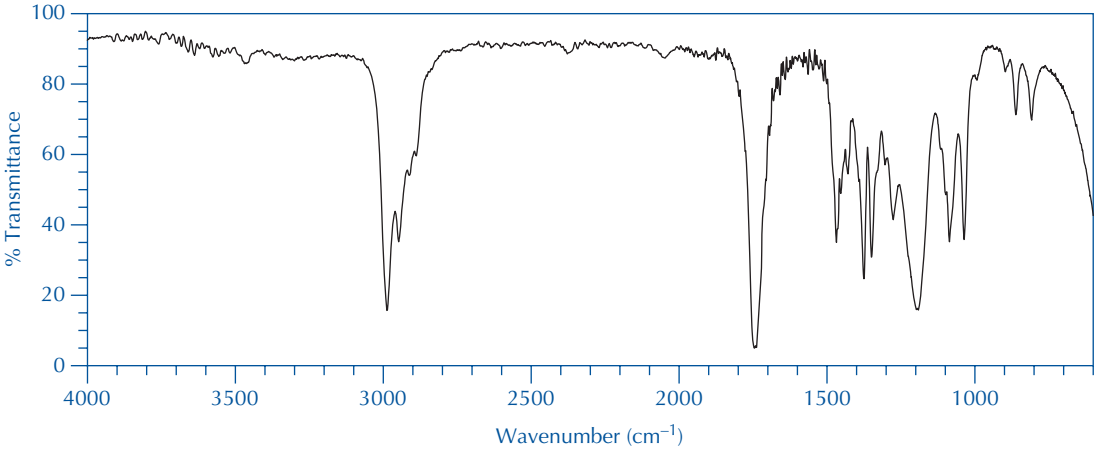


FIGURE 20.34 IR spectrum for question 5 (thin film).

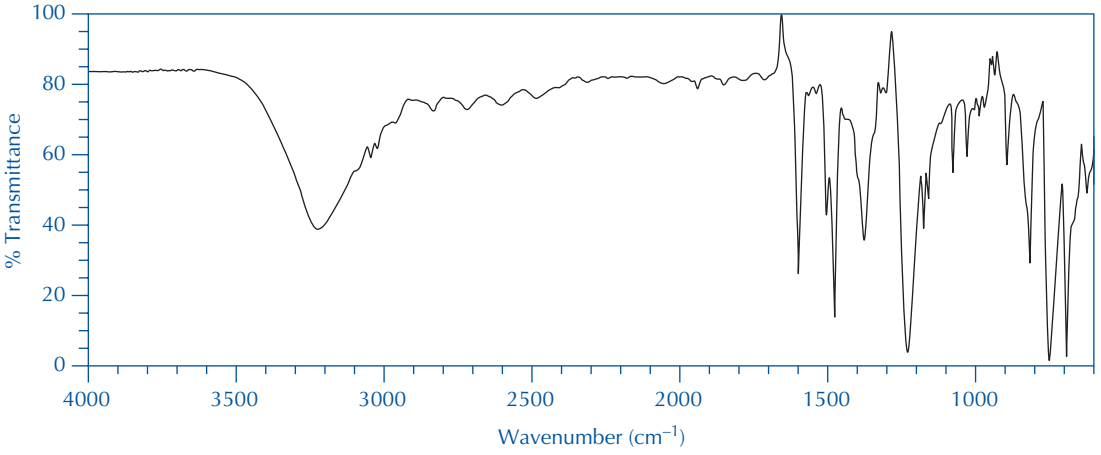


FIGURE 20.35 IR spectrum for question 5 (ATR).

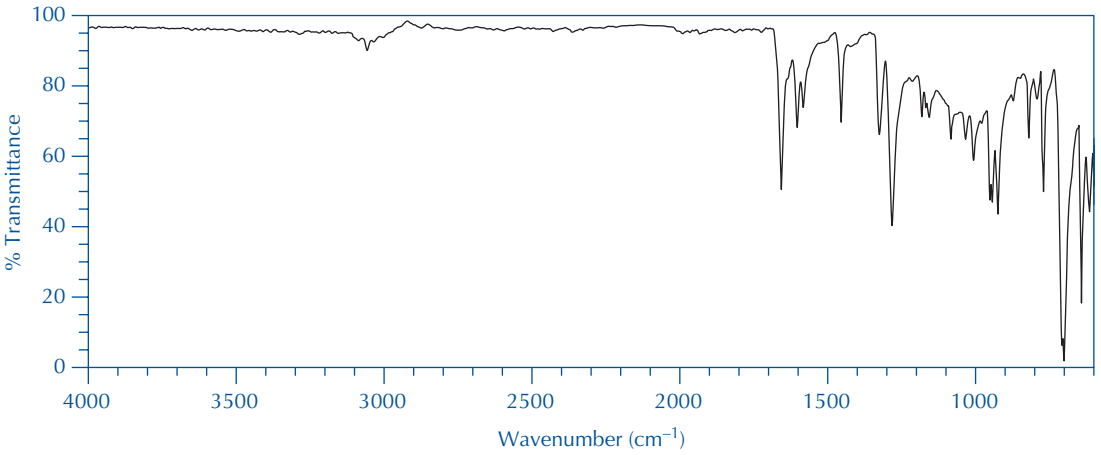


FIGURE 20.36 IR spectrum for question 5 (ATR).

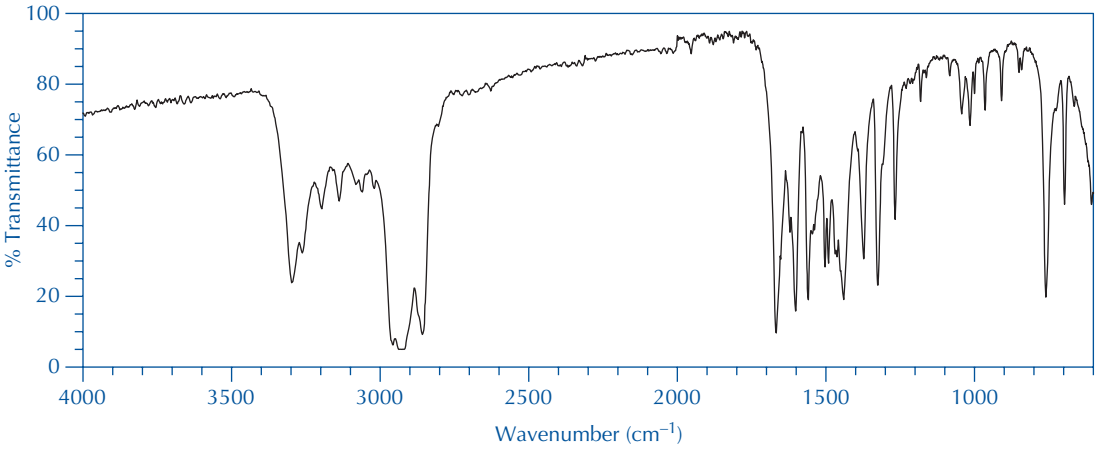


FIGURE 20.37 IR spectrum for question 5 (Nujol mull).

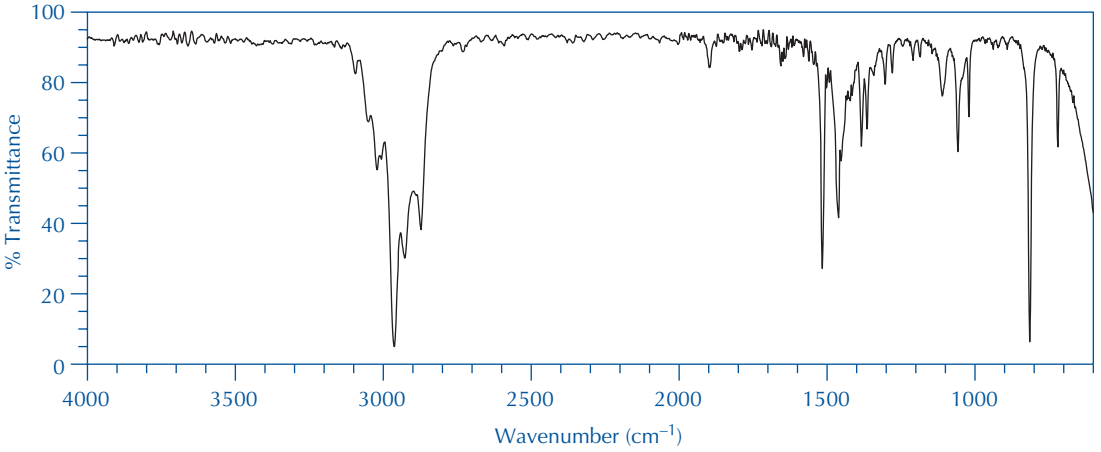


FIGURE 20.38 IR spectrum for question 5 (thin film).

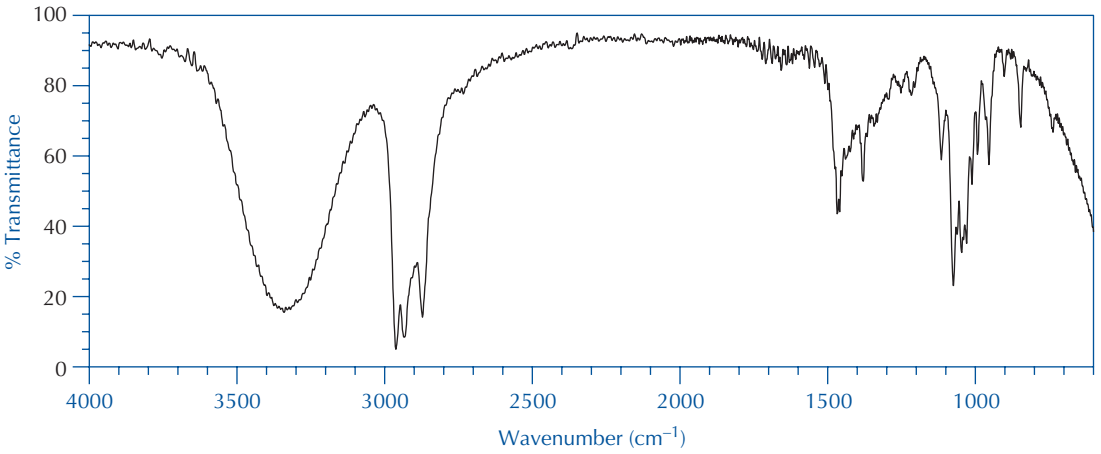


FIGURE 20.39 IR spectrum for question 5 (thin film).

TECHNIQUE

21 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

If Technique 21 is your introduction to spectroscopic analysis, read the Essay "The Spectroscopic Revolution" on pages 275–276 before you read Technique 21.

Nuclear magnetic resonance (NMR) spectroscopy is one of the most important modern instrumental techniques used in the determination of molecular structure. For the past fifty years, nuclear magnetic resonance has been in the forefront of the spectroscopic techniques that have completely revolutionized organic structure determination. Like other spectroscopic techniques, NMR depends on quantized energy changes that are induced in molecules when they interact with electromagnetic radiation. The energy needed for NMR is in the radio frequency range of the electromagnetic spectrum and is much lower energy than that needed by other spectroscopic techniques.

Nuclear Spin

The theoretical foundation for nuclear magnetic resonance arises from the ***spin, I,*** of an atomic nucleus. The value of I is related to the atomic number and the mass number and may be 0, ½, 1, ³⁄₂, 2, and so forth. Any isotope whose nucleus has a nonzero magnetic moment ($I > 0$) is in theory detectable by NMR spectroscopy. Readily observable nuclei include ^{1}H, ^{2}H, ^{13}C, ^{15}N, ^{19}F, and ^{31}P. The most important nuclei for organic structure determination are ^{1}H and ^{13}C, both of which have spin of ½. ^{1}H NMR is the focus of this technique and ^{13}C NMR is the focus of Technique 22. The basic principles of NMR, which apply both to ^{1}H and ^{13}C NMR, are discussed in this technique.

Any nucleus with both an even atomic number and an even mass number has a nuclear spin of 0. Because ^{12}C and ^{16}O have nuclear spins of 0, they do not produce NMR signals and do not interfere with or complicate the signals from ^{1}H and ^{13}C. In addition, ^{12}C is the major isotope of carbon and is present in almost 99% natural abundance. Therefore, the small amount of NMR-active ^{13}C does not complicate ^{1}H NMR spectra to any great extent.

Nuclear Energy Levels

There are $(2I + 1)$ energy levels allowed for a nucleus with spin of I. Because ^{1}H and ^{13}C have spins of ½, there are two possible energy levels for these nuclei $(2I + 1 = 2)$. In the absence of an external magnetic field, the two levels are ***degenerate***—they have the same energy. However, in the presence of an applied magnetic field, the energy levels move apart. The separation of degenerate nuclear spin energy levels by an external applied magnetic field is illustrated in Figure 21.1. One energy level, designated α, decreases in energy and the other level, designated β, increases in energy. The difference in energy between the levels, ΔE, is directly related to the strength of the externally applied magnetic field, B_0.

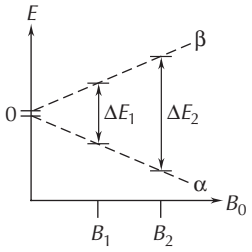


FIGURE 21.1
Influence of an external magnetic field on spin state energy levels.

In spectroscopy, the usual convention for expressing energy changes is frequency (ν), as described by Planck's law:

$$\Delta E = h\nu$$

The change in energy of an NMR transition is extremely small by chemical standards—only about 10^{-6} kJ · mol^{-1}, which corresponds to energy in the radio frequency region. With a magnetic field strength of 1.41 tesla, the resonance frequency for ^{1}H nuclei is 60 MHz. If the magnetic field strength is 7.05 tesla, the resonance frequency is 300 MHz.

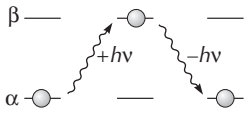


FIGURE 21.2
Excitation of a nucleus from low-energy state to high-energy state and emission of energy on relaxation of the nucleus.

As shown in Figure 21.2, the absorption of energy can cause excitation of a nucleus from the α to the β energy level. When a nucleus in the higher-energy state drops to the lower-energy state, a process called ***relaxation,*** it gives up a quantum of energy. The emitted energy, in the radio frequency region, produces an NMR signal.

Magnetic Resonance

We can think of any nucleus with a spin number greater than 0 as a spinning, charged body. The principles of physics tell us that a magnetic field is associated with this moving charge. When placed in an external magnetic field, a spinning nucleus precesses about an axis aligned in the direction of the magnetic field. The precession of a child's top about a vertical axis as it spins can be used as a mechanical model for this process. The magnetic dipole of the spinning nucleus shown in Figure 21.3a is aligned with the external magnetic field, whereas the magnetic dipole of the spinning nucleus shown in Figure 21.3b is opposed to the external magnetic field. To flip the magnetic dipole from the aligned position to the opposed position requires a quantized addition of energy to the system. Absorption of energy can occur only if the system is in resonance.

For ***resonance*** to occur, the applied frequency (ν) must be precisely tuned to the rotational frequency of the precessing nucleus. Then the nucleus can absorb a quantum of energy and flip from the lower-energy spin state (α) to the higher-energy spin state (β). The energy difference between the two spin states is very small and the number of nuclei in each spin state is nearly equal, but in the large magnetic field of a modern NMR spectrometer there are a few more nuclei, approximately 0.001%, in the lower-energy spin state than in the higher-energy spin state. Because the spin states are not equally populated, a nuclear magnetic resonance effect can be observed.

If all the ^{1}H nuclei in a molecule had the same resonance frequency, ^{1}H NMR spectroscopy would be of little use to organic chemists. However, in an NMR spectrometer, energies of the ^{1}H nuclei in an organic compound differ slightly because of their different structural environments, and a typical ^{1}H NMR spectrum is an array of many different frequencies. The same is true for ^{13}C NMR spectra.

21.1 NMR Instrumentation

The first NMR spectrometers were continuous wave (cw) instruments. The sample was irradiated with radio frequency energy as the applied magnetic field was varied. When a match between the radio frequency energy and the energy difference between the two spin states of the nucleus—($h\nu$) in Figure 21.2—occurred, a signal was detected. The energy required reflected the environment of the nucleus. A radio frequency receiver was used to monitor the energy changes.

Fourier Transform NMR

More recent instruments use a technique known as ***pulsed Fourier transform NMR (FT NMR).*** In this technique, a broad pulse of electromagnetic radiation excites all the ^{1}H or ^{13}C nuclei simultaneously, resulting in a continuously decreasing oscillation caused by the decay of excited nuclei back to their stable energy distribution. The oscillating, or decaying, sine curve is called a ***free-induction decay (FID).*** The FID, often referred to as a time domain signal, is converted to a set of frequencies, or a "normal" spectrum, by the mathematical treatment of a Fourier transform. The relatively simple FID of a compound with only a single frequency is shown in Figure 21.4a. In Figure 21.4b, you can see that the FID from a compound with two frequencies is more complex. Constructive combinations of the two frequencies produce enhanced signals and destructive combinations give little or no signal. The Fourier transform of the FID in Figure 21.4b produces two signals.

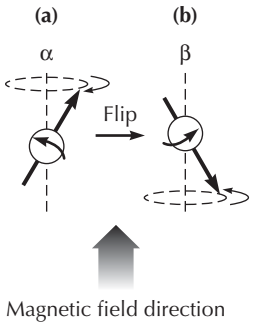


FIGURE 21.3
Nuclear magnetic dipole **(a)** aligned with an external magnetic field (α) and **(b)** opposed to an external magnetic field (β).

Most organic compounds are much more complex and the FID can be made up of the contributions from hundreds of frequencies. A computer program using Fourier transform mathematics is required to convert the FID to the "normal" spectrum. When the sample size is small, the acquisition of the signal from more than one pulse (or "scan") is necessary to obtain NMR signals with the desired signal-to-noise ratio. Modern FT NMR spectrometers "lock" on a signal from deuterium in the NMR solvent, assuring

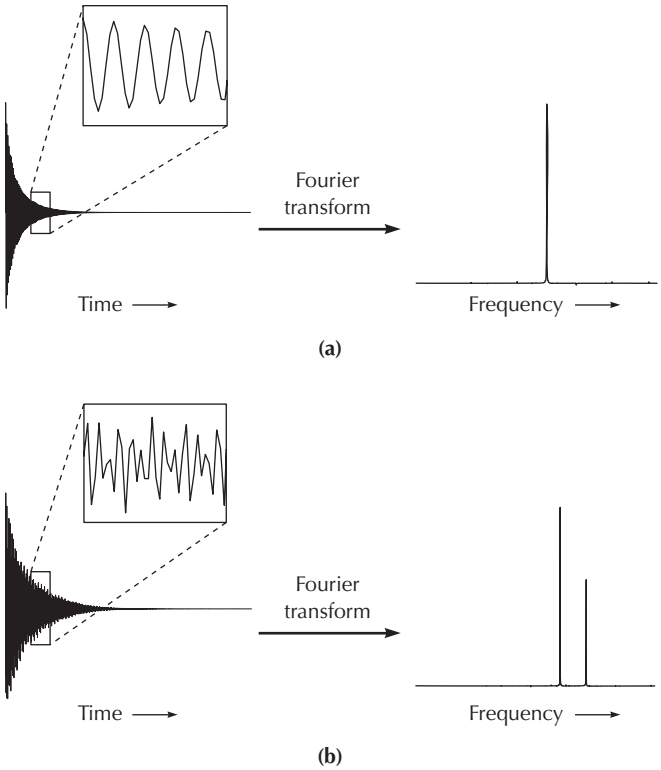


FIGURE 21.4 FID and Fourier transform of the FID of **(a)** one signal and **(b)** two signals.

that multiple acquisition scans are synchronized. The NMR computer programs the multiple pulses and collects the data from them. The components of an FT NMR spectrometer are illustrated in Figure 21.5.

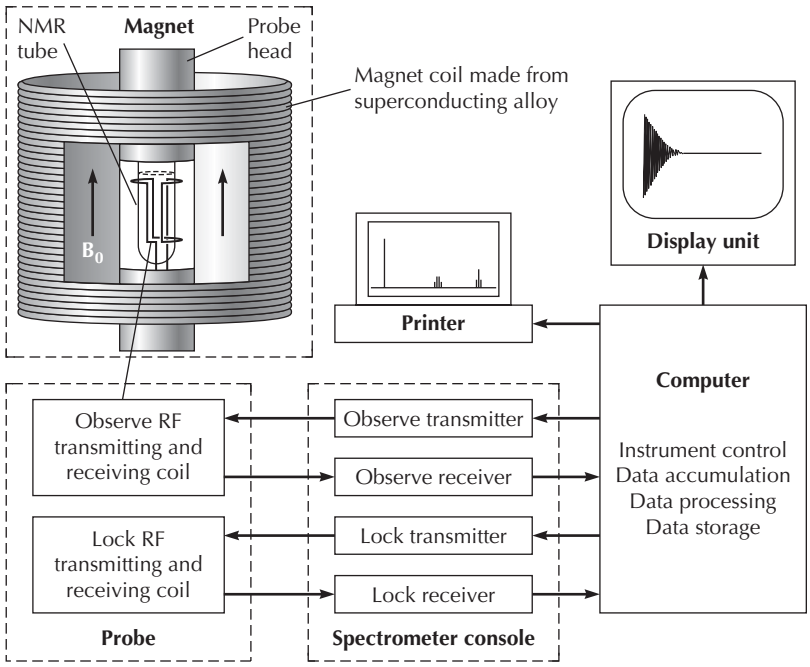


FIGURE 21.5 Block diagram of a basic FT NMR spectrometer.

NMR Spectrometers

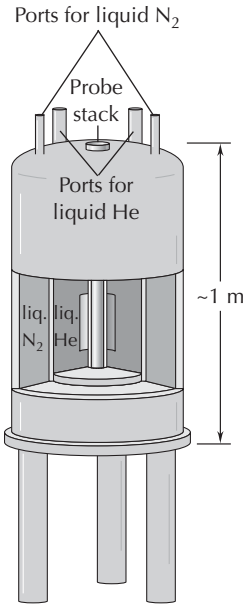


FIGURE 21.6
Typical superconducting electromagnet for a 200- to 400-MHz NMR spectrometer, showing the vacuum-jacketed Dewar vessels for the liquid nitrogen and liquid helium coolants.

There are many different models of NMR spectrometers, and it is common practice to refer to them by their nominal operating frequency. Modern NMR instruments operate at substantially higher frequencies than the 60-MHz instruments that were once the standard. Research instruments routinely operate at 300–500 MHz, and many laboratories have instruments with operating frequencies of 600 and even 800 MHz. The high magnetic fields necessary for these instruments can be achieved only by using superconducting electromagnets. Because the materials used to build the magnets are superconducting only at very low temperatures, these magnets are maintained in double-jacketed Dewar vessels cooled by liquid helium and liquid nitrogen (Figure 21.6).

There are numerous benefits in using higher frequency and field strength. High-field instruments have greater sensitivity because of a greater difference in spin state populations, which translates into stronger sample signals relative to background noise. The higher field strength also means larger energy differences between different nuclei and thus greater signal separation. The advantage of greater signal separation is evident by comparing the spectra of ethyl propanoate, $C_5H_{10}O_2$, shown in Figure 21.7. The NMR spectrum in Figure 21.7a was obtained on a 60-MHz continuous wave (cw) NMR spectrometer. The spectrum in Figure 21.7b was obtained with a 200-MHz FT NMR spectrometer. In the 60-MHz spectrum, a group of signals is centered at 1.15, which in the 200-MHz spectrum separates into two groups of signals, one centered at 1.15 and one centered at 1.26.

21.2 Preparing Samples for NMR Analysis

Almost all NMR analysis is done using dilute solutions, whether the sample is a solid or a liquid. Concentrated solutions, undiluted liquids, and solids usually exhibit broad peaks that are not easy to interpret. Spectra with sharp, well-differentiated signals are obtained only with dissolved samples. It is important to use the required minimum amount of sample for an NMR spectrum but not much more.

NMR Solvents

The choice of solvent for an NMR sample is important. Most of the material in an NMR tube is solvent, so ideally we want a chemically inert solvent that does not absorb energy in the magnetic field. Thus, for ^1H NMR we want a solvent with no protons. Most of the solvents used for preparation of NMR samples are deuterated forms of common solvents, such as chloroform ($CHCl_3$), acetone, and water. Although deuterium does have a magnetic moment, its signal is well removed from the region where protons absorb.

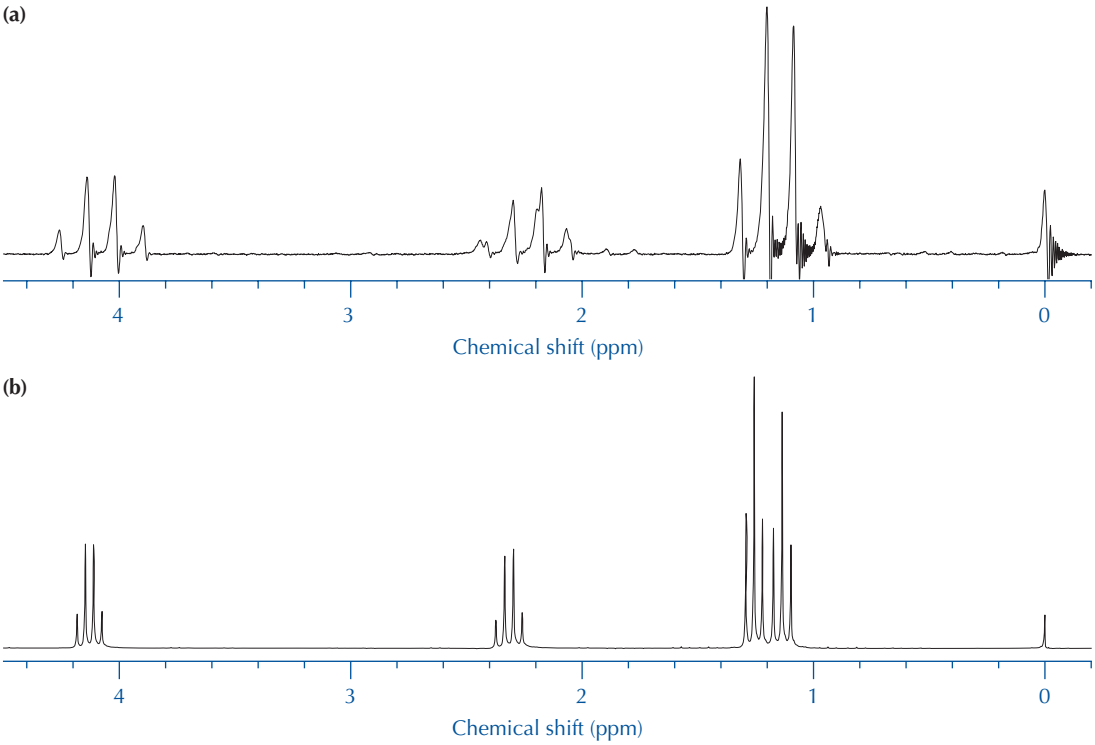


FIGURE 21.7 ^{1}H NMR spectra of ethyl propanoate at **(a)** 60 MHz and **(b)** 200 MHz.

Deuterated chloroform ($CDCl_3$) is the most commonly used NMR solvent because it dissolves a wide range of organic compounds and is not prohibitively expensive. Deuterated acetone is another commonly used solvent, but it is quite a bit more expensive. Table 21.1 lists several standard NMR solvents.

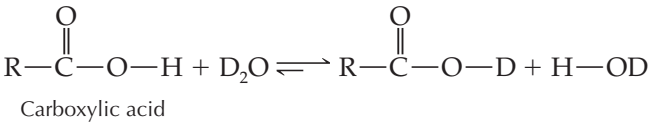
Deuterated solvents are never 100% deuterated. For example, the commercial $CDCl_3$ that is commonly used for NMR samples has 99.8% deuterium and 0.2% protium in its molecules. The residual protons give a small peak ($CHCl_3$) at 7.26 ppm. The residual proton signals for the various solvents are listed in Table 21.1. **It is important to be aware of the position of these residual signals because you do not want to confuse solvent signals with the signals of your sample compound.**

TABLE 21.1 Deuterated solvents for NMR spectroscopy

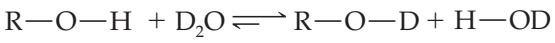
Solvent	Structure	Residual ^{1}H signal (ppm)	^{13}C chemical shift (ppm)
Chloroform-d	$CDCl_3$	7.26 (singlet)	77.0 (triplet)
Acetone-d_6	$CD_3(C{=}O)CD_3$	2.04 (quintet)	29.8 (septet), 206.5 (singlet)
Deuterium oxide	D_2O	4.6 (broad singlet)	—
Dimethyl sulfoxide-d_6	$CD_3(S{=}O)CD_3$	2.49 (quintet)	39.7 (septet)

Polar compounds. Polar chemicals, such as carboxylic acids and polyhydroxyl compounds, are usually not soluble in $CDCl_3$. However, in most cases these compounds are soluble in deuterium oxide (D_2O). If a carboxylic acid is not soluble in D_2O, it is probably soluble in D_2O containing sodium hydroxide. Adding a drop or two of concentrated sodium hydroxide solution to the sample in D_2O is usually enough to dissolve it.

Problems with the use of D_2O. The use of D_2O presents several problems. There is always a broad peak at approximately 4.6 ppm because of a small amount of HOD present in the original D_2O solvent. This solvent peak can hide important signals from the compound being analyzed. Also, D_2O may exchange with protons in the sample compound, producing HOD. Consider, for example, what happens when a carboxylic acid or alcohol dissolves in D_2O:



Carboxylic acid



Alcohol

Deuterium nuclei are "invisible" in ^1H NMR spectra, and in an NMR solution there are many more molecules of solvent D_2O than of the sample. The equilibrium positions in these reactions lie well to the right, and the hydroxyl protons do not appear as separate signals but instead merge into the HOD signal.

NMR Reference Calibration

Solvents used for preparing NMR samples often have a small amount of a standard reference substance dissolved in them. However, a reference compound is not really necessary because the residual proton signal of partially deuterated solvent can be used for reference calibration unless sample signals obscure it (see Table 21.1).

Tetramethylsilane. The most common added reference compound is tetramethylsilane, $(CH_3)_4Si$. **Tetramethylsilane, usually referred to as TMS, has been so important as a reference substance in the past that the position of its signal is used to define the 0.0 point on an NMR spectrum.** TMS was chosen because all its protons are equivalent, and they absorb at a magnetic field in which very few other protons in typical organic compounds absorb. TMS is also chemically inert and is soluble in most organic solvents. The amount of TMS in the solvent depends on the type of instrument being used. For a cw NMR spectrometer, the typical concentration of TMS is 1–2%. With a modern FT NMR instrument, the typical concentration of TMS is 0.1%; often TMS is not even added to the NMR solution.

NMR reference for D_2O. Tetramethylsilane is not soluble in deuterium oxide (D_2O), so it cannot be used as a standard with this solvent, and the HOD peak is too broad and variable to be a useful reference standard. The reference substance used for D_2O solutions

is the ionic compound sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS), $(CH_3)_3SiCH_2CH_2CH_2SO_3^-Na^+$. Its major signal appears at nearly the same position as the TMS absorption. Acetone can also be used as a reference in D_2O solutions as long as its signal does not interfere with signals from the sample. In D_2O solutions, the signal for acetone appears at 2.22 ppm.

Preparing an NMR Sample Solution

The appropriate concentration of the sample solution depends on the type of NMR instrumentation available. A sample mass of 4–20 mg of compound dissolved in approximately 0.5–0.7 mL of solvent is used to prepare a modern high-frequency FT NMR sample solution.

NMR tubes. NMR tubes are delicate, precision pieces of equipment. The most commonly used NMR tubes are made of thin glass and their rims are easily chipped if not handled carefully. **Caution:** Chipping occurs most often during pipetting of the sample into the tube and when trying to remove the plastic cap from the top of the tube.

Check solubility in deuterium-free solvent first. Before using an expensive deuterated solvent for an NMR analysis, be sure that your compound dissolves in the deuterium-free solvent. Prepare a preliminary sample using the necessary amount of solvent in a small vial or test tube. If the preliminary test is satisfactory, place the necessary amount of your sample in another vial or small test tube and add approximately 0.7 mL of deuterated solvent. Agitate the mixture to facilitate dissolution of the sample. If a clear, homogeneous solution is obtained, transfer the sample to the NMR tube with a glass Pasteur pipet.

Particulate matter in the sample solution. If a clear, homogeneous solution is not obtained, the particulate material must be removed before the sample is transferred to the NMR tube. Particulate material may contain paramagnetic metallic impurities that will produce extensive line broadening and poor signal intensity in the NMR spectrum. A convenient filter can be prepared by inserting a small wad of glass wool into the neck of a glass Pasteur pipet [see Technique 10.3]. The narrow end of the filter pipet is placed in the NMR tube and the sample to be filtered is transferred into the filter with a second Pasteur pipet. Pressure from a pipet bulb can be used to force any solution trapped in the filter into the NMR tube.

Height of the NMR solution in the tube. Only a small part of an NMR tube is in the effective probe area of the instrument. Typically, the height of the sample in the tube should be 25–30 mm (Figure 21.8). However, the required height can be 50–55 mm in some NMR instruments. You need to ascertain the required minimum for the instrument you are using. Often a gauge is available in the lab for checking the solution height in the sample tube. If the solution height is slightly short, add a few drops of solvent to bring it to the required level. Too much solution may also produce a poor-quality spectrum. Agitate the NMR tube to thoroughly mix the solution. Cap the tube, and wipe off any material on the outside.

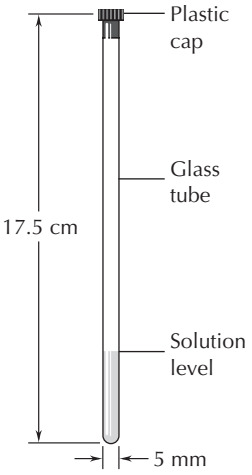


FIGURE 21.8
NMR sample tube filled to the correct height.

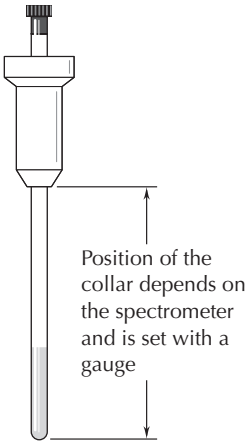


FIGURE 21.9
NMR sample tube fitted with collar.

Recovery of the sample. Because none of the sample is destroyed when taking an NMR spectrum, the sample can be recovered if necessary by evaporating the solvent.

Obtaining the NMR Spectrum

Before the NMR sample tube is placed into the magnet of the spectrometer, it is fitted with a collar that is made of a nonmagnetic plastic or ceramic material (Figure 21.9). The collar positions the sample at a precise location within the magnetic field where the RF transmitter/receiver coil is located. A depth gauge provided with the instrument is used to set the position of the collar on the NMR sample tube. A second purpose of the collar can be to enable the sample to spin around its vertical axis once it has been placed in the magnet.

The magnetic field in the RF transmitter/receiver coil region must be homogeneous; that is, the strength and direction of the magnetic field must be exactly the same at every point. A homogeneous magnetic field is achieved through a complex adjustment called ***shimming.*** Even after shimming, some small magnetic field inhomogeneities may be present. Spinning the sample serves to average out these inhomogeneities, which allows acquisition of spectra with sharp, well-defined peaks. NMR tubes are selected for uniform wall thickness and minimum wobble. Too much sample in the tube is not only a waste of material, it also tends to make the tube top-heavy, often resulting in poor spinning performance and thus poor-quality spectra. With some of the latest NMR spectrometers, the magnet technology has advanced to the point that spinning the sample is not recommended.

Cleaning the NMR Sample Tube

After the spectrum has been obtained, the NMR tube should be cleaned, usually by rinsing with a solvent such as acetone, and then allowing the tube to dry. Solvents cling tenaciously to the inside surface of the long, thin NMR tubes, and a long drying period or passing a stream of dry nitrogen gas through the tube is required to remove all residual solvent. If NMR tubes are not cleaned soon after use, the solvent usually evaporates and leaves a caked or gummy residue that can be difficult to dissolve.

21.3 Summary of Steps for Preparing an NMR Sample

1. Test the solubility of the sample in ordinary, nondeuterated solvents. Select a solvent that dissolves the sample completely.
2. Place 4–20 mg of the sample in a clean, small vial or test tube.
3. Add 0.5–0.7 mL of the appropriate deuterated solvent.
4. Agitate the mixture in the vial to produce dissolution of the sample.
5. Transfer the sample solution into a clean NMR tube using a glass Pasteur pipet. If there are any solids present, filter the solution through a small plug of glass wool.
6. Check the level of the sample in the tube. If needed, add drops of solvent to bring the solution to the recommended level for the instrument and agitate the mixture to produce a homogeneous solution.
7. Cap the NMR tube.
8. Wipe the outside of the tube to remove any material that may impede smooth spinning of the sample in the NMR instrument.

21.4 Interpreting ^{1}H NMR Spectra

Typically, four types of information can be extracted from a ^{1}H NMR spectrum. All of them are important in determining the structure of a compound, and all are discussed in the following sections.

- ***Number of different kinds of protons*** in the molecules of the sample, given by the number of groups of signals [see Technique 21.5]
- Relative number of protons contributing to each group of signals in the spectrum, called ***integration*** [see Technique 21.6]
- Positions of the groups of signals along the horizontal axis, called the ***chemical shift*** [see Techniques 21.7 and 21.8]
- Patterns within groups of signals, called ***spin-spin coupling*** [see Technique 21.9]

21.5 How Many Types of Protons Are Present?

As the first step in analyzing an NMR spectrum, examine the entire spectrum. A common mistake is to focus on some detail in the spectrum, often a prominent signal, and develop an analysis from an assumption that is consistent with only that detail. Sometimes this method works, but many times it does not. A general method for analysis starts by looking at the entire spectrum and counting the number of groups of signals. A structure consistent with the spectrum is required to have at least this many different kinds of protons. This number is a minimum requirement, and often, as the analysis is refined, it is possible to divide a group of signals into

subsets of protons that are subtly different from each other. If you examine the 200-MHz NMR spectrum of ethyl propanoate (Figure 21.10), you will see that four groups of signals are centered at 1.15, 1.26, 2.32, and 4.13 ppm along the horizontal scale. **Note that the horizontal scale is read from right to left, with 0.0 ppm at the far right.**

21.6 Counting Protons (Integration)

Above each group of signals in the 200-MHz NMR spectrum of ethyl propanoate in Figure 21.10 is what looks like a set of steps with a number over it. **The height of each set of steps corresponds to the total signal intensity encompassed by the set.** The numbers correspond to the heights normalized to one of the signals. Software on modern digital NMR spectrometers makes normalization an easy task. Reading from right to left, the normalized integration values for the groups of signals are 3.00, 3.03, 1.97, and 2.00, respectively.

Integration values represent the relative number of each kind of proton in the molecule. If the normalization is not done correctly, the integration values will be a multiple of the true values. Also, integration values are usually not neat, whole-number ratios. Deviations from whole numbers can be as much as 10% and are usually attributed to differences in the amount of time it takes different types of excited hydrogen nuclei to relax back to their lower energy spin states. In acquiring NMR data, it is important to allow enough time for the nuclei to relax. Otherwise, the measured integrals will not accurately reflect the relative number of protons responsible for the signals. In addition, if the integration is done manually, you must use good judgment about where to start and stop each set of steps.

The integrals for the spectrum in Figure 21.10 are interpreted as 3:3:2:2. The two groups of signals at 1.15 ppm and 1.26 ppm, with

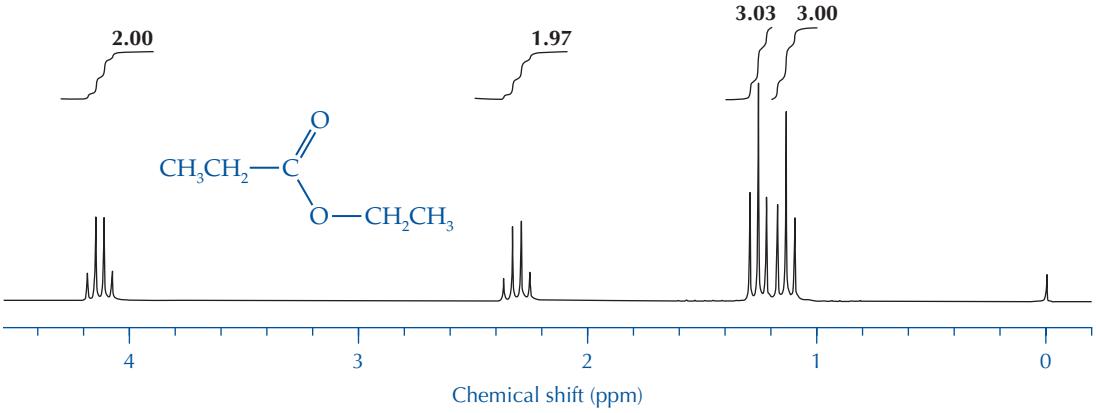


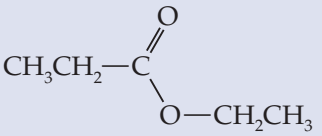
FIGURE 21.10 ^{1}H NMR spectrum of ethyl propanoate at 200 MHz.

three protons each, are produced by two groups of nearly equivalent kinds of protons. The group of signals at 2.32 ppm and the group at 4.13 ppm are each produced by a group of two equivalent protons.

- Primary hydrogens, those on a carbon atom with three hydrogens attached, are called ***methyl*** protons.
- Secondary hydrogens, on a carbon atom with two hydrogens attached, are called ***methylene*** protons.
- A tertiary hydrogen, on a carbon atom with only one hydrogen attached, is called a ***methine*** proton.

EXERCISE

Refer to the structure of ethyl propanoate and identify the set of protons that is responsible for each of the four groups of signals in its NMR spectrum.



Ethyl propanoate

Answer: Because there are two groups of two protons and two groups of three protons, we cannot unambiguously assign the signals without more information. But help is on the way. In the next section you will find out how to use the positions of the signals along the horizontal scale to make the necessary assignments.

21.7 Chemical Shift

An NMR spectrum is a plot of the intensity of the NMR signals versus the magnetic field or frequency. Nuclei that are chemically equivalent, such as the four protons in methane (CH_4) or the two protons in dichloromethane (CH_2Cl_2), show only one peak in the NMR spectrum. However, protons that are not chemically equivalent absorb at different frequencies. The local magnetic field experienced by the different protons in a molecule varies with different magnetic environments within the molecule. At 300 MHz, the typical range of these frequencies is about 3500 Hz.

Most important, the positions of the signals along the horizontal scale of an NMR spectrum, called the ***chemical shifts,*** can be correlated with a molecule's structure. The goal of Techniques 21.7 and 21.8 is to show how the chemical shifts can be used to determine the structures of organic compounds. Arguably, **the chemical shifts are the most powerful of all the information available in NMR spectroscopy.**

Chemical Shift Units (Parts per Million, ppm)

Because it is difficult to reproduce magnetic fields exact enough for NMR spectroscopy, an internal standard is used as a reference point. The position of an NMR signal is measured relative to the absorption of the standard. Tetramethylsilane, $(CH_3)_4Si$, is the standard for

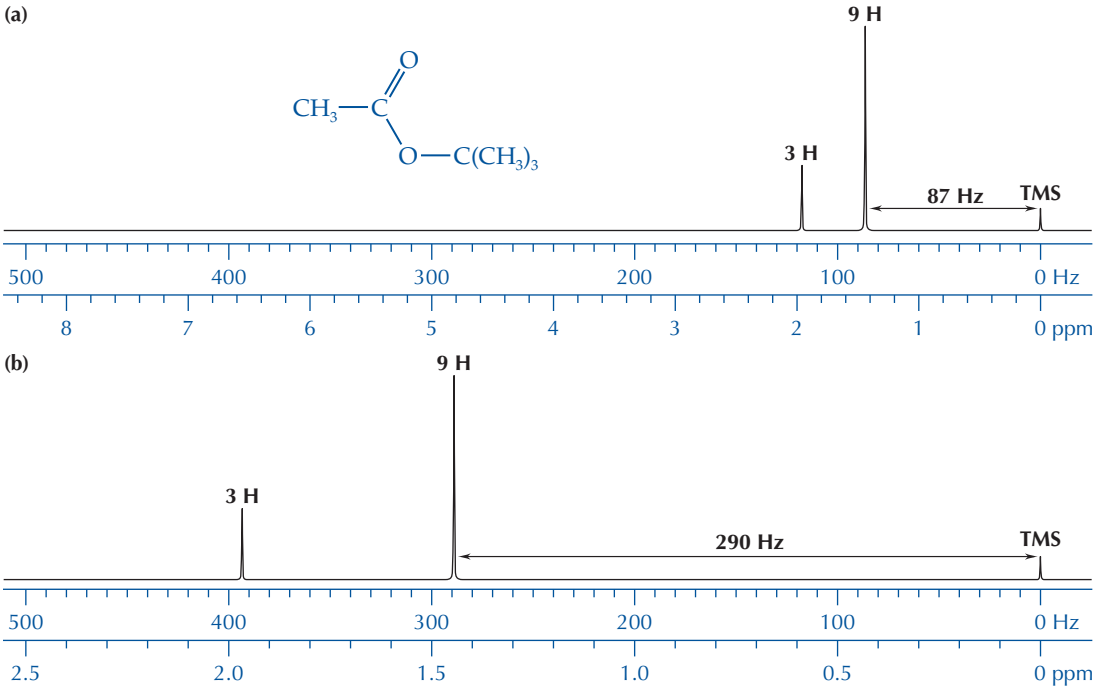


FIGURE 21.11 ^{1}H NMR spectra of *tert*-butyl acetate in the region from 0 to 500 Hz at **(a)** 60 MHz and **(b)** 200 MHz. The chemical shift of each signal is the same regardless of the spectrometer frequency.

^{1}H and ^{13}C NMR. Chemical shifts are measured at a frequency (Hz) corresponding to a signal's position relative to tetramethylsilane, usually referred to as TMS. It is conventional, however, to convert frequency to a value ***δ (ppm)*** by dividing the chemical shift frequency by the operating frequency of the spectrometer. This conversion produces an important result; **the chemical shift (δ) is independent of the frequency of the spectrometer.**

M = mega = million

$$\delta(\text{ppm}) = \frac{\text{frequency of the signal (in Hz, from TMS)}}{\text{applied spectrometer frequency (in MHz)}}$$

Because the frequency of an NMR spectrometer is given in megahertz (MHz), the δ values are always given in parts per million (ppm). On the chemical shift scale of an NMR spectrum, the position of the TMS absorption is at the far right and is set at 0.0 ppm. The δ values increase to the left of the TMS peak.*

Consider the two NMR spectra of *tert*-butyl acetate shown in Figure 21.11. The *tert*-butyl group, which has nine equivalent protons, and the methyl group, which has three equivalent protons, give a relative integration of 3:1. In the 60-MHz spectrum (Figure 21.11a), the difference between the signals of TMS and the *tert*-butyl

* In the older NMR literature a τ (tau) scale for chemical shifts was used, in which the TMS absorption signal was given the value of 10.0 ppm and the chemical shift values decreased to the left of TMS on an NMR spectrum. With the τ system, a chemical shift of 2.0 ppm (δ), for example, would be 8.0 ppm.

group is 87 Hz. In the 200-MHz spectrum (Figure 21.11b), the difference between these same signals is 290 Hz. Dividing each signal's frequency by the operating frequency of the instrument, we find that the chemical shift (δ) of the *tert*-butyl protons is 1.45 ppm.

$$1.45 \text{ ppm} = 87 \text{ Hz}/60 \text{ MHz} = 290 \text{ Hz}/200 \text{ MHz}$$

The position of the signal in terms of its chemical shift (δ) is the same, regardless of the magnetic field strength. To be able to compare NMR spectra from different instruments, the chemical shift scales for all NMR spectra are plotted using ppm units.

EXERCISE

On an NMR instrument operating at 60 MHz, the signal for the methyl group of *tert*-butyl acetate is shifted 118 Hz relative to the signal for TMS (see Figure 21.11a).

(a) What is the chemical shift (δ) of the methyl group signal?
(b) What is the frequency difference (in Hz) between the signal for the methyl group and the signal for TMS on an NMR instrument operating at 200 MHz (see Figure 21.11b)?

Answer: (a) δ = 118 Hz/60 MHz = 1.97 ppm
(b) ΔHz = 1.97 ppm × 200 MHz = 394 Hz

Figure 21.12 shows the approximate chemical shift regions of signals for different types of protons attached to carbon, oxygen, and nitrogen atoms. A list of chemical shifts for different types of protons is given in Table 21.2.

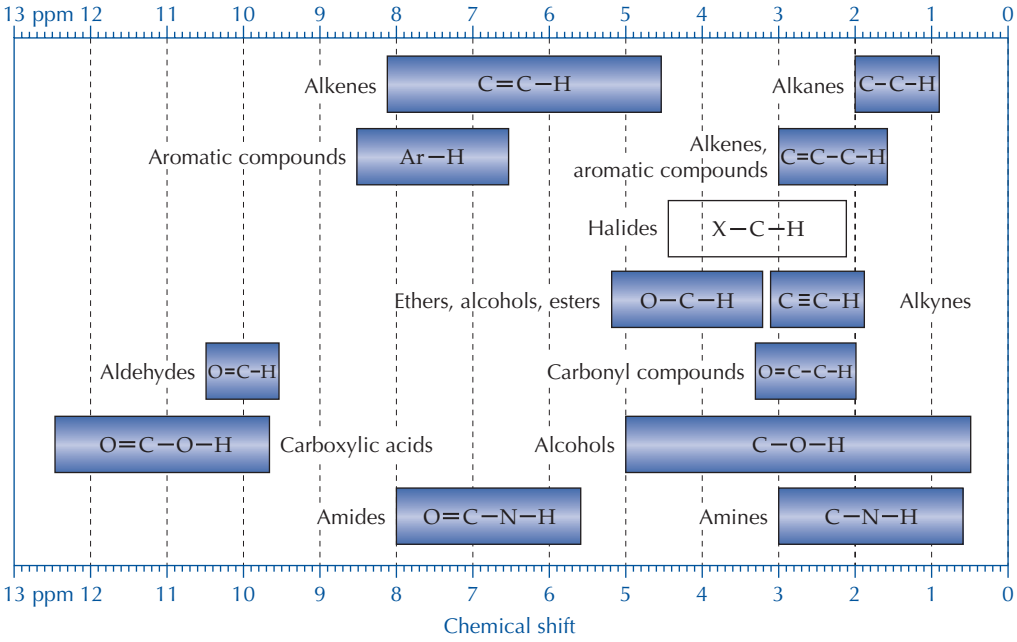


FIGURE 21.12 Approximate regions of chemical shifts for different types of protons in organic compounds.

TABLE 21.2 Characteristic ^{1}H NMR chemical shifts in $CDCl_3$

Compound	Chemical shift (δ, ppm)
TMS	0.0
Alkanes (C—C—**H**)	0.9–1.9
Amines (C—N—**H**)	0.6–3.0
Alcohols (C—O—**H**)	0.5–5.0
Alkenes[a] (C═C—C—**H**)	1.6–2.5
Alkynes (C≡C—**H**)	1.7–3.1
Carbonyl compounds (O═C—C—**H**)	1.9–3.3
Halides (X—C—**H**)	2.1–4.5
Aromatic compounds[b] (Ar—C—**H**)	2.2–3.0
Alcohols, esters, ethers (O—C—**H**)	3.2–5.2
Alkenes (C═C—**H**)	4.5–8.1
Phenols (Ar—O—**H**)	4.0–8.0
Amides (O═C—N—**H**)	5.5–8.0
Aromatic compounds (Ar—**H**)	6.5–8.5
Aldehydes (O═C—**H**)	9.5–10.5
Carboxylic acids (O═C—O—**H**)	9.7–12.5

a. Allylic protons.
b. Benzylic protons.

Diamagnetic Shielding

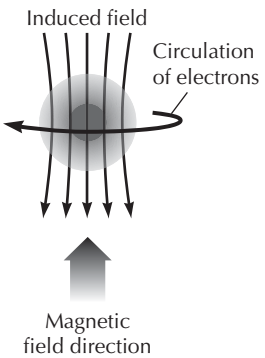


FIGURE 21.13
The opposing magnetic field induced by circulation of electrons around a nucleus in an applied magnetic field. The nucleus is partially shielded from the applied magnetic field by the opposing magnetic field.

The chemical shift of a hydrogen nucleus is strongly influenced by the electron density surrounding it. Under the influence of an applied magnetic field, circulating electrons in the spherical electron cloud induce a small magnetic field opposed to the applied field, as illustrated in Figure 21.13. Thus, the effective magnetic field that a proton feels is a little less than the applied field. The electron cloud is said to shield the nucleus from the applied magnetic field, and the effect is called ***local diamagnetic shielding.***

If the electron density around a proton is decreased, the opposing induced magnetic field will be smaller. Therefore, the nucleus is less shielded from the applied magnetic field, and the proton is said to be ***deshielded.*** With greater deshielding, the effective magnetic field felt by the proton increases, and the chemical shift of its signal increases. For example, the protons of methane resonate at 0.23 ppm. Attaching an electron-withdrawing chlorine atom to the carbon atom pulls electron density away from the electron cloud surrounding the nearby protons. Thus, the chlorine deshields the protons. The protons of chloromethane resonate at 3.1 ppm.

Magnitude of the deshielding effect. The magnitude of the deshielding effect decreases rapidly as the distance from the electron-withdrawing substituent increases. This effect is demonstrated by the decrease in the chemical shifts of methyl protons as their distance from a bromine atom increases.

CH_3Br	CH_3CH_2Br	$CH_3CH_2CH_2Br$	$CH_3CH_2CH_2CH_2Br$
2.69 ppm	1.66 ppm	1.06 ppm	0.93 ppm

Deshielding and shielding effects are additive. For instance, the chemical shift of the protons in substituted methane derivatives increases as the number of attached electron-withdrawing bromine atoms increases.

CH_4	CH_3Br	CH_2Br_2	$CHBr_3$
0.23 ppm	2.69 ppm	4.94 ppm	6.82 ppm

The additive nature of the deshielding effect is also seen as the carbon atom bearing the proton becomes more highly substituted. With the same electron-withdrawing groups nearby, tertiary hydrogen atoms have a greater chemical shift than do secondary hydrogens. Likewise, secondary hydrogen atoms have a greater chemical shift than do primary hydrogens with the same electron-withdrawing groups nearby. This trend is illustrated by the chemical shifts of the proton(s) attached to the carbon atom adjacent to a bromine atom in bromomethane, bromoethane, and 2-bromopropane.

CH_3Br	CH_3CH_2Br	$(CH_3)_2CHBr$
2.69 ppm	3.37 ppm	4.21 ppm

Deshielding effects and electronegativity. The position of the signal for a proton attached to a carbon atom also depends on the electronegativity (χ) of the other atoms attached to carbon. The periodic trends seen in the electronegativities of elements are mirrored in the chemical shifts of methyl groups attached to these elements.

	$CH_3—I$	$CH_3—Br$	$CH_3—Cl$	$CH_3—F$
δ	2.2 ppm	2.7 ppm	3.1 ppm	4.3 ppm
χ	2.66	2.96	3.16	3.98

Similarly, as you move from left to right along a row of elements in the periodic table, the electronegativities increase and the chemical shifts of attached methyl groups also increase.

	$(CH_3)_4C$	$(CH_3)_3N$	$(CH_3)_2O$	CH_3F
δ	0.9 ppm	2.2 ppm	3.2 ppm	4.3 ppm
χ	2.50	3.04	3.44	3.98

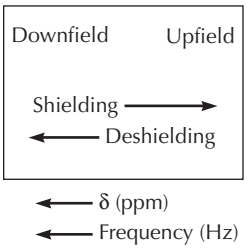


FIGURE 21.14
When the opposing induced magnetic field decreases, the effective magnetic field felt by the nucleus increases. Thus, as a nucleus becomes more deshielded, the chemical shift of its NMR signal increases.

Summary of shielding and deshielding effects. Let's briefly summarize the effect of shielding and deshielding on the chemical shift of protons and introduce some commonly used terms (Figure 21.14). Increasing the electron density around a nucleus shields it from the applied field, making the effective field experienced by the nucleus smaller. The value of the observed chemical shift of the signal therefore decreases, and, on a typical NMR spectrum, the signal moves to the **right,** which is called an ***upfield*** shift because at a constant frequency, a slightly higher applied magnetic field is needed for resonance to occur. Decreasing the electron density around a nucleus deshields it, causing the chemical shift to increase and moving the signal to the **left,** resulting in a ***downfield*** shift.

Anisotropy

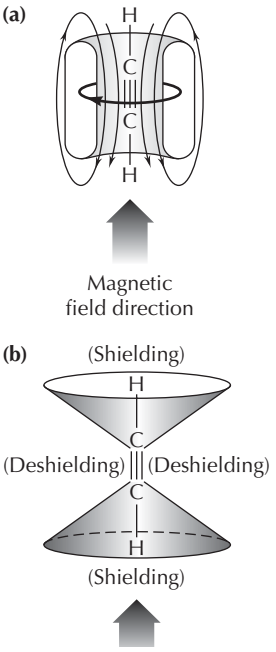


FIGURE 21.15
(a) Circulation of π-electrons in an applied magnetic field induces an opposing magnetic field that shields the acetylenic proton. **(b)** Regions of shielding and deshielding for acetylene.

In molecules with π-orbitals, local diamagnetic shielding does not completely account for the chemical shifts observed for different protons. The shielding effect on a proton depends in part on the location of the proton relative to the induced magnetic field because a π-orbital is not spherically symmetrical. This effect is called ***anisotropy,*** a term that means "having a different effect along a different axis."

Consider acetylene, H—C≡C—H, for example. Although acetylene molecules are oriented more or less randomly because of rapid tumbling in solution, at any one time some of these linear molecules are lined up with the applied magnetic field. In the aligned molecules, the circulation of the electrons in the cylindrical π-orbital system of the triple bond induces a diamagnetic field, as illustrated in Figure 21.15a. This induced magnetic field opposes the applied magnetic field, shielding the acetylene proton and moving its NMR signal upfield. Regions of shielding are often represented by cones, as shown in Figure 21.15b. The chemical shift of the protons in acetylene is 1.80 ppm; it is affected by both local diamagnetic shielding effects and anisotropic shielding.

Alkenes and aldehydes also exhibit strong anisotropic effects. When a π-orbital of a double bond is aligned with an applied magnetic field, the circulation of the two π-electrons induces a diamagnetic field perpendicular to the plane of the double bond. Anything in the region above the π-orbital is shielded. However, at the sides of the double bond the flux lines of the induced magnetic field add to the applied magnetic field, which creates a deshielding region in the plane perpendicular to the π-orbital. The shielding and deshielding regions of ethylene and formaldehyde are shown in Figures 21.16a and b. Strong anisotropic effects are demonstrated by the strongly deshielded protons of ethylene and formaldehyde.

$H_2C{=}CH_2$	$H_2C{=}O$
5.28 ppm	9.60 ppm

Because of anisotropic deshielding, protons of methyl groups attached to the carbon atoms of C═C or C═O bonds appear near 2.0 ppm, whereas protons of methyl groups attached to carbon atoms of C—C or C—O bonds appear closer to 1.0 ppm.

Protons attached to benzene rings absorb at a position even farther downfield from that of the vinyl protons in alkenes. The

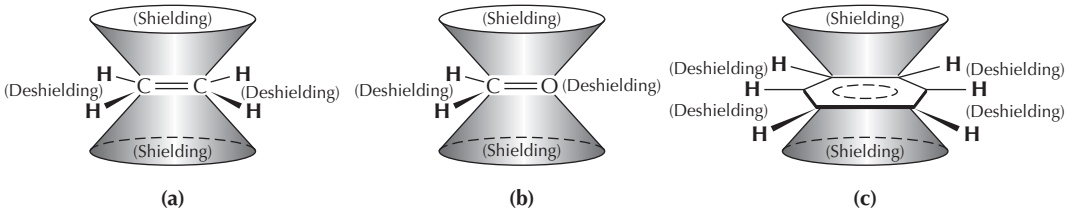


FIGURE 21.16 Regions of shielding and deshielding for **(a)** ethylene, **(b)** formaldehyde, and **(c)** benzene.

interactions of the six π-electrons of the aromatic ring produce a stronger anisotropic effect than that found with simple alkenes. The ring current created by the movement of these electrons induces a magnetic field, as illustrated in Figure 21.16c. The regions above and below the aromatic ring are shielded, whereas the protons at the edge of the ring are deshielded. The signal for the protons in benzene appears at 7.36 ppm, about 2 ppm downfield from the signal produced by the protons in ethylene.

21.8 Quantitative Estimation of Chemical Shifts

Much of the power of NMR spectroscopy comes from the correlation of molecular structure with positions of signals along the chemical shift scale. As you have already seen, the type of bonding and the proximity of electronegative atoms influence the chemical shift position of protons.

Signals for different types of protons attached to carbon appear in well-defined regions. Tables cataloging these relationships, constructed by compiling large numbers of NMR signals from many organic compounds, contain much data, too much to memorize. However, to master the use of NMR spectroscopy for determining molecular structures, you must be able to use Tables 21.3–21.5, which allow you to calculate estimated chemical shifts. The calculated chemical shifts can then be compared to the signals in the spectrum you are analyzing.

From the empirical correlations in Tables 21.3–21.5, it is possible to calculate the chemical shift of a hydrogen nucleus in a straightforward, additive way. The ability to add the individual effects of nearby functional groups is extremely useful because it allows an estimation of the chemical shifts for most of the protons in organic compounds.

Chemical Shifts of Alkyl Protons

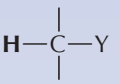
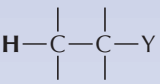
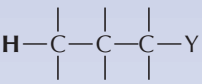
The aggregate effect of multiple functional groups on the chemical shift of the proton(s) of an alkyl group can be determined from Table 21.3.

Base values. To use Table 21.3, begin with the base values at the top of the table. In any proposed molecular structure, primary hydrogen atoms (methyl groups) have a base value of 0.9 ppm. Secondary hydrogen atoms (methylene groups) are somewhat more deshielded, as shown by their chemical shift base value of 1.2 ppm. Tertiary (methine) hydrogen atoms have an even greater chemical shift; their base value is 1.5 ppm.

Effects of nearby substituents. The effect of each nearby substituent is added to the base value to arrive at the chemical shift of a particular proton in a molecule. If the substituent is directly attached to the carbon atom to which the proton is attached, it is called an ***α (alpha) substituent***. If the group is attached to a carbon atom once

TABLE 21.3 Additive parameters for predicting NMR chemical shifts of alkyl protons in $CDCl_3$[a]

Base values	
Methyl	0.9 ppm
Methylene	1.2 ppm
Methine	1.5 ppm

Group (Y)	Alpha (α) substituent 	Beta (β) substituent 	Gamma (γ) substituent 
—R	0.0	0.0	0.0
—C═C	0.8	0.2	0.1
—C═C—Ar[b]	0.9	0.1	0.0
—C═C(C═O)OR	1.0	0.3	0.1
—C≡C—R	0.9	0.3	0.1
—C≡C—Ar	1.2	0.4	0.2
—Ar	1.4	0.4	0.1
—(C═O)OH	1.1	0.3	0.1
—(C═O)OR	1.1	0.3	0.1
—(C═O)H	1.1	0.4	0.1
—(C═O)R	1.2	0.3	0.0
—(C═O)Ar	1.7	0.3	0.1
—(C═O)NH_2	1.0	0.3	0.1
—(C═O)Cl	1.8	0.4	0.1
—C≡N	1.1	0.4	0.2
—Br	2.1	0.7	0.2
—Cl	2.2	0.5	0.2
—OH	2.3	0.3	0.1
—OR	2.1	0.3	0.1
—OAr	2.8	0.5	0.3
—O(C═O)R	2.8	0.5	0.1
—O(C═O)Ar	3.1	0.5	0.2
—NH_2	1.5	0.2	0.1
—NH(C═O)R	2.1	0.3	0.1
—NH(C═O)Ar	2.3	0.4	0.1

a. There may be differences of 0.1–0.5 ppm in the chemical shift values calculated from this table and those measured from individual spectra.
b. Ar = aromatic group.

removed, it is a ***β (beta) substituent.*** And if the group is attached to a carbon atom twice removed, it is a ***γ (gamma) substituent.***

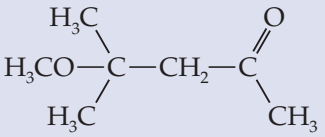
The effect of an α substituent on the chemical shift of the proton is found by using a value from the first column in Table 21.3, and the effects of β and γ groups are found in the second and third columns, respectively. Notice that the topmost group, —R, an alkyl group, has no effect on the chemical shift other than changing the base values. When the carbon atom bearing the proton is farther away from the functional group, its effect on the chemical shift of the proton is smaller. The effect of a group more than three carbon atoms away from the carbon bearing the proton of interest is small enough to be safely ignored. There may be a difference of

0.1–0.5 ppm between the chemical shift value calculated from Table 21.3 and the measured value, but the difference is usually no greater than 0.2–0.3 ppm, close enough to figure out if a proposed structure fits the spectrum.

Identifying α, β, and γ substituents. It is important in calculating estimated chemical shifts to use a systematic methodology. A good way not to forget to include all α, β, and γ substituents for each type of proton in a target molecule is to **write down all the α groups first, then all the β groups, and last the γ groups**. **Only then go to Table 21.3,** look up the base value and the value for each α, β, and γ substituent from the correct column, and do the necessary addition.

EXERCISE

Identify the α, β, and γ substituents for the two methylene protons and for the methyl group attached to C—4 of 4-methoxy-4-methyl-2-pentanone.



4-Methoxy-4-methyl-2-pentanone

Answer: The methylene protons have one α substituent, a —(C═O)CH_3 group, listed in Table 21.3 as —(C═O)R. The methylene group also has one β substituent, a methoxy group, listed in Table 21.3 as —OR. The C—4 methyl groups have no α substituents other than an alkyl group, but they do have a β substituent, the methoxy group, as well as a γ substituent, the —(C═O)CH_3 group.

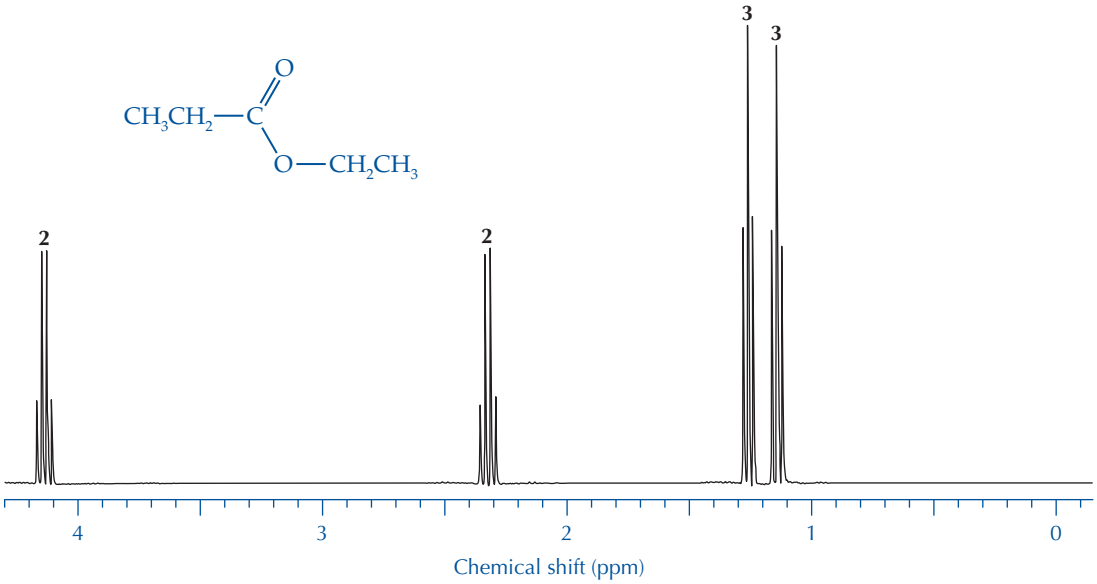


FIGURE 21.17 ^{1}H NMR spectrum of ethyl propanoate at 360 MHz.

FOLLOW-UP ASSIGNMENT

Identify the α and β substituents for the *tert*-butyl protons of the compound $(CH_3)_3C(C{=}O)OCH_3$.

Calculating estimated chemical shifts. Table 21.3 is laid out with carbon substituents at the top, followed by the heteroatoms—halogens, and oxygen and nitrogen substituents. To illustrate its use, let us return to the example of ethyl propanoate, whose 360-MHz NMR spectrum is shown in Figure 21.17.

WORKED EXAMPLE

The integration in Figure 21.17 shows that the signal at 4.13 ppm comes from a methylene group. Referring to Figure 21.12 or Table 21.2, the best correlation is with a methylene group directly attached (α) to the oxygen atom of the ester group. Using Table 21.3, we can determine with more accuracy if this correlation is valid. Scan down the table to the entry fifth from the bottom to find the —O(C═O)R group. Here is the calculation:

Base value for a methylene group	1.2 ppm
Presence of the α—O(C═O)R group	2.8 ppm
Calculated chemical shift of the methylene protons	4.0 ppm

The calculated value is within 0.13 ppm of the methylene group attached to the oxygen atom, close enough to be consistent with the assignment.

The second methylene group at 2.32 ppm must be attached to the carbonyl carbon. Repeat the calculation for that methylene group, again using Table 21.3 and scanning down to the ninth entry.

Base value for a methylene group	1.2 ppm
Presence of the α—(C═O)OR group	1.1 ppm
Calculated chemical shift of the methylene protons	2.3 ppm

The estimated value of the chemical shift of the second methylene group is within 0.02 ppm of the measured value.

EXERCISE

Estimate the chemical shifts of the two different methyl groups in ethyl propanoate. Are these values consistent with the observed chemical shifts of 1.13 ppm and 1.26 ppm?

Answer: From Table 21.3, the value of the chemical shift for the methyl protons β to the —(C═O)OR group is 0.9 + 0.3 = 1.2 ppm. The chemical shift of the methyl protons β to the oxygen atom of the —O(C═O)R group is 0.9 + 0.5 = 1.4 ppm. These calculated values compare reasonably well with the measured chemical shifts of 1.13 and 1.26 ppm. Even though the estimates of the chemical shifts differ by 0.07 and 0.14 ppm from the measured values, their relative order of increasing chemical shift adds to our confidence in the assignments.

FOLLOW-UP ASSIGNMENT

A compound, $C_7H_{14}O_2$, has the structure $CH_3(C{=}O)CH_2C(OCH_3)(CH_3)_2$. In its NMR spectrum are four separate signals, at 1.21 ppm, 2.08 ppm, 2.46 ppm, and 3.16 ppm, with the relative integrations of 6:3:2:3. This integration pattern is consistent with the structure of the compound having three kinds of methyl groups, one of which is duplicated, and one methylene group. Calculate the chemical shifts for each of the four kinds of protons in $C_7H_{14}O_2$ using Table 21.3 and assign them to their correct NMR signals.

Chemical Shifts of Aromatic Protons

The chemical shifts of protons on substituted benzene rings can also be calculated. To estimate the chemical shifts, the contributions of substituents shown in Table 21.4 are added to a base value of 7.36 ppm, the chemical shift for the protons of benzene dissolved in $CDCl_3$.

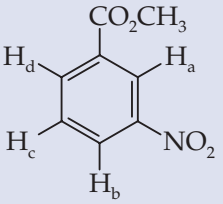
TABLE 21.4 Additive parameters for predicting NMR chemical shifts of aromatic protons in $CDCl_3$

	Base value	7.36 ppm[a]	
Group	***ortho***	***meta***	***para***
—CH_3	−0.18	−0.11	−0.21
—$CH(CH_3)_2$	−0.14	−0.08	−0.20
—CH_2Cl	0.02	−0.01	−0.04
—$CH{=}CH_2$	0.04	−0.04	−0.12
—$CH{=}CHAr$	0.14	−0.02	−0.11
—$CH{=}CHCO_2H$	0.19	0.04	0.05
—$CH{=}CH(C{=}O)Ar$	0.28	0.06	0.05
—Ar	0.23	0.07	−0.02
—$(C{=}O)H$	0.53	0.18	0.28
—$(C{=}O)R$	0.60	0.10	0.20
—$(C{=}O)Ar$	0.45	0.12	0.23
—$(C{=}O)CH{=}CHAr$	0.67	0.14	0.21
—$(C{=}O)OCH_3$	0.68	0.08	0.19
—$(C{=}O)OCH_2CH_3$	0.69	0.06	0.17
—$(C{=}O)OH$	0.77	0.11	0.25
—$(C{=}O)Cl$	0.76	0.16	0.33
—$(C{=}O)NH_2$	0.46	0.09	0.17
—$C{\equiv}N$	0.29	0.12	0.25
—F	−0.32	−0.05	−0.25
—Cl	−0.02	−0.07	−0.13
—Br	0.13	−0.13	−0.08
—OH	−0.53	−0.14	−0.43
—OR	−0.45	−0.07	−0.41
—OAr	−0.36	−0.04	−0.28
—$O(C{=}O)R$	−0.27	0.02	−0.13
—$O(C{=}O)Ar$	−0.14	0.07	−0.09
—NH_2	−0.71	−0.22	−0.62
—$N(CH_3)_2$	−0.68	−0.15	−0.73
—$NH(C{=}O)R$	0.14	−0.07	−0.27
—NO_2	0.87	0.20	0.35

a. Base value is the measured chemical shift of benzene in $CDCl_3$ (1% solution).

WORKED EXAMPLE

Using Table 21.4, estimate the chemical shift of H_a in the structure of methyl 3-nitrobenzoate.



Methyl 3-nitrobenzoate

There are two functional groups that affect the chemical shift of H_a, an *ortho*-(C═O)OCH_3 group and an *ortho*-nitro group. The contribution of the *ortho*-(C═O)OCH_3 group to the chemical shift of H_a is the 13th item of Table 21.4; it is 0.68 ppm. The contribution of the *ortho*-NO_2 group, at the end of the table, is an additional 0.87 ppm. Adding these values to the base value of 7.36 ppm gives an estimated chemical shift of 8.91 ppm for H_a, compared to a measured value of 8.87 ppm.

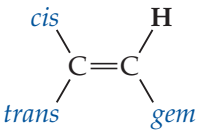
Base value for a benzene ring	7.36 ppm
Presence of the *ortho*-(C═O)OCH_3 group	0.68 ppm
Presence of the *ortho*-NO_2 group	0.87 ppm
Calculated chemical shift for H_a	8.91 ppm
Measured chemical shift for H_a	8.87 ppm

FOLLOW-UP ASSIGNMENT

The measured chemical shifts for the remaining three aromatic protons of methyl 3-nitrobenzoate are 7.67 ppm, 8.38 ppm, and 8.42 ppm. The chemical shifts have been assigned to H_c, H_d, and H_b, respectively. Using Table 21.4, calculate the estimated chemical shifts of these three aromatic protons and justify their assignments.

Chemical Shifts of Vinyl Protons

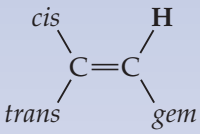
Chemical shifts of protons attached to C═C bonds, called ***vinyl*** protons, can be estimated using Table 21.5. The estimated chemical shift for a vinyl proton is the sum of the base value of 5.28 ppm, the chemical shift for $H_2C{=}CH_2$, and the contributions for all *cis*, *trans*, and *geminal (gem)* substituents. A ***geminal group*** is the one that is attached to the same carbon atom as the vinyl proton whose estimated chemical shift is being calculated.



WORKED EXAMPLE

Styrene, the monomer from which polystyrene is made, has the formula $C_6H_5CH{=}CH_2$. In addition to the three signals of the protons attached directly to the benzene ring, there are separate NMR signals for the three vinyl

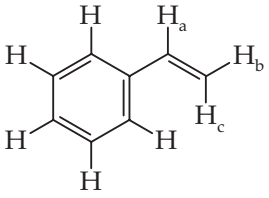
TABLE 21.5 Additive Parameters for Predicting NMR Chemical Shifts of Vinyl Protons in $CDCl_3$[a]



Base value 5.28 ppm

Group	*gem*	*cis*	*trans*
—R	0.45	−0.22	−0.28
—CH=CH_2	1.26	0.08	−0.01
—CH_2OH	0.64	−0.01	−0.02
—CH_2X (X=F, Cl, Br)	0.70	–0.11	−0.04
—(C=O)OH	0.97	1.41	0.71
—(C=O)OR	0.80	1.18	0.55
—(C=O)H	1.02	0.95	1.17
—(C=O)R	1.10	1.12	0.87
—(C=O)Ar	1.82	1.13	0.63
—Ar	1.38	0.36	−0.07
—Br	1.07	0.45	0.55
—Cl	1.08	0.18	0.13
—OR	1.22	−1.07	−1.21
—OAr	1.21	−0.60	−1.00
—O(C=O)R	2.11	−0.35	−0.64
—NH_2, —NHR, —NR_2	0.80	−1.26	1.21
—NH(C=O)R	2.08	−0.57	−0.72

a. There may be small differences in the chemical-shift values calculated from this table and those measured from individual spectra.



Styrene

protons at 5.25 ppm, 5.75 ppm, and 6.70 ppm. Calculate the expected chemical shifts for H_a, H_b, and H_c of styrene and assign the three measured signals to the correct protons.

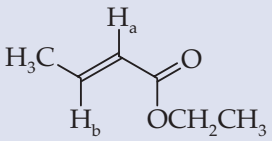
Table 21.5 has a base value of 5.28 ppm, which will be part of the calculation for all three vinyl protons. H_a has the phenyl group (C_6H_5—) on the same carbon atom; it is a *geminal* group. The phenyl (Ar) group is about halfway down Table 21.5 and its *gem* parameter is 1.38 ppm. Here is the calculation for the chemical shift of H_a.

Base value for a vinyl proton	5.28 ppm
Presence of the *gem* C_6H_5— group	1.38 ppm
Calculated chemical shift of H_a	6.66 ppm
Measured chemical shift of H_a	6.70 ppm

In the same manner, we can calculate the chemical shifts for H_b and H_c. The phenyl group is *trans* to H_b, so −0.07 ppm must be added to the base value: 5.28 + (−0.07) = 5.21 ppm. This value fits well with the signal at 5.25 ppm in the NMR spectrum of styrene. The phenyl group is *cis* to H_c, so 0.36 ppm must be added to the base value: 5.28 + 0.36 = 5.64 ppm. It seems clear that the 5.75-ppm signal must be H_c

EXERCISE

Consider the structure of ethyl *trans*-2-butenoate, $C_6H_{10}O_2$. Estimate the chemical shift for each of the two different vinyl protons in the molecule using Table 21.5 and then assign H_a and H_b. The measured chemical shift values are 5.80 ppm and 6.90 ppm.



Ethyl *trans*-2-butenoate

Answer: Calculating the estimated chemical shift of H_a, we find

Base value for a vinyl proton	5.28 ppm
Presence of the *gem* —(C═O)OR group	0.80 ppm
Presence of the *cis* R group	−0.22 ppm
Calculated chemical shift of H_a	5.86 ppm
Measured chemical shift of H_a	5.80 ppm

For the estimated chemical shift of H_b, we find

Base value for a vinyl proton	5.28 ppm
Presence of the *cis* —(C═O)OR group	1.18 ppm
Presence of the *gem* R group	0.45 ppm
Calculated chemical shift of H_b	6.91 ppm
Measured chemical shift of H_b	6.90 ppm

Using Tables 21.3–21.5 in Combination

Now you can test your skills in the use of Tables 21.3–21.5, as well as Figure 21.12.

PROBLEM ONE

Figure 21.18 is the ^{1}H NMR spectrum of a compound with the molecular formula $C_6H_{12}O_2$. It is an ester, which is one of the two isomers

$$(CH_3)_3C(C{=}O)OCH_3 \quad \text{or} \quad CH_3(C{=}O)OC(CH_3)_3$$

Calculate the chemical shifts for the two different kinds of methyl groups in each structure and then assign the NMR signals in Figure 21.18 to the appropriate methyl groups in the correct isomer.

Hint: Look first at the whole spectrum, paying attention to the integrals that are associated with the two signals. Use the spectrum to measure each of the chemical shift values. Consider each isomer and think about the proximity of the two kinds of protons to electronegative atoms. Make a hypothesis as to which isomer seems correct. Then calculate the estimated chemical shifts for each of the two possible isomers using Table 21.3. Decide which molecular structure is correct and assign the NMR signals to the appropriate protons.

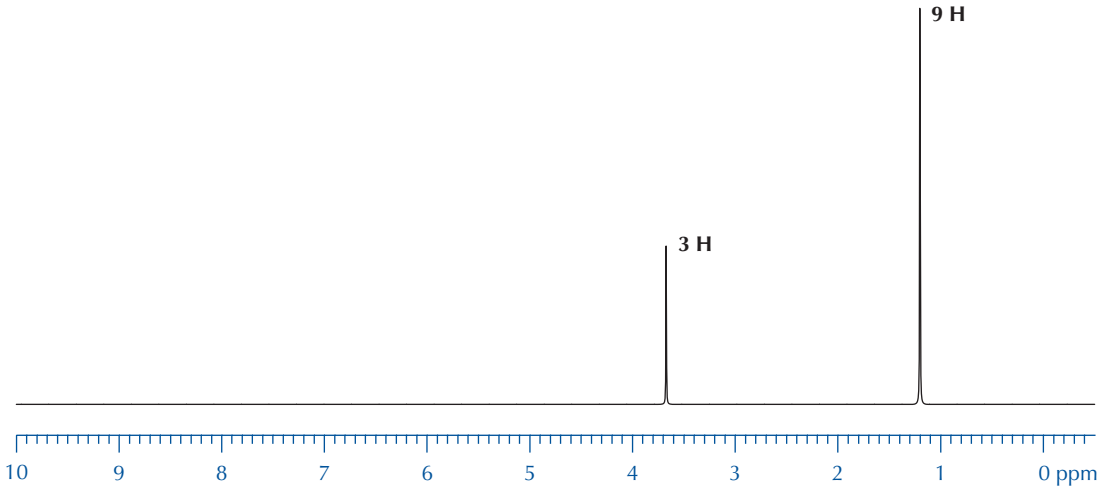
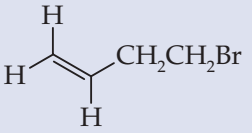


FIGURE 21.18 ^{1}H NMR spectrum of compound with the molecular formula $C_6H_{12}O_2$ at 300 MHz.

PROBLEM TWO

Calculate the estimated chemical shifts of each of the five types of protons in 4-bromo-1-butene and assign each of them to their respective NMR signals. Briefly discuss any ambiguities in your assignments. The observed chemical shift values are 2.62 ppm, 3.41 ppm, 5.10 ppm, 5.15 ppm, and 5.80 ppm.

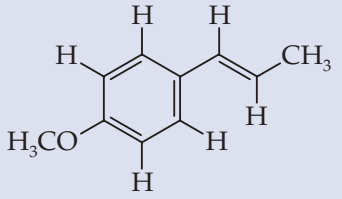


4-Bromo-1-butene

Hint: Decide which of the protons are alkyl protons and which are vinyl protons and then use Tables 21.3 and 21.5 to calculate the estimated chemical shifts. Assign each observed NMR signal to the appropriate proton(s).

PROBLEM THREE

trans-1-(*para*-Methoxyphenyl)propene has the following structure:



trans-1-(*para*-Methoxyphenyl)propene

Its measured NMR signals are observed at 1.83 ppm, 3.75 ppm, 6.07 ppm, 6.33 ppm, 6.80 ppm, and 7.23 ppm. Their respective integrations are 3:3:1:1:2:2. Which NMR signals are produced by alkyl protons, aromatic protons, and vinyl protons? Using Tables 21.3–21.5, calculate the estimated chemical shift for each type of proton in *trans*-1-(*para*-methoxyphenyl)propene and assign the observed chemical shifts to the correct protons.

Final Words on Calculating Estimated Chemical Shifts

In general, Tables 21.3–21.5 provide good estimates. However, a word of caution is in order. It is important to remember that the simple acyclic compounds used to generate the tables incorporate some structural features that may not be present in every situation. Anisotropic effects of rings, multiple deshielding groups, and hindered rotation can lead to estimated chemical shifts that are different from the actual chemical shifts.

Rings. The signals produced by methylene protons in rings are slightly deshielded compared to the signals produced by methylene protons in acyclic compounds. Signals produced by methylene protons in cyclopentanes and cyclohexanes typically appear near 1.5 ppm compared to 1.2 ppm for open-chain compounds.

Cyclopropanes and oxiranes are unique in that the σ-bonding in three-membered rings has some π-orbital character, which produces an anisotropic effect and shielding above and below the plane of the ring. Chemical shifts of protons on cyclopropane and epoxide rings are approximately 1.0 ppm upfield from their acyclic counterparts.

Multiple deshielding groups. If there are multiple deshielding α substituents, especially alkoxy groups and halogen atoms, the calculated chemical shift values can sometimes differ from the measured chemical shifts by more than 1 ppm. The divergence between the actual chemical shifts and the estimates can be seen in the following series, as more methoxy groups are attached to the carbon atom of methane.

	CH_3OCH_3	$CH_2(OCH_3)_2$	$CH(OCH_3)_3$
Measured	3.24 ppm	4.58 ppm	4.97 ppm
Estimation	3.0 ppm	5.4 ppm	7.8 ppm

Hindered rotation. The estimates of chemical shifts of protons *ortho* to bulky groups on benzene rings can differ considerably from the measured values. This difference is evident in the calculation of chemical shift values for acetanilides (Ar—NH—(C═O)CH_3) that are substituted in the *ortho* position with substituents such as bromine, chlorine, or a nitro group. In these compounds, the chemical shift of the *ortho* proton is nearly 1 ppm downfield from the estimated chemical shift calculated from Table 21.4. Hydrogen bonding between the amide hydrogen and the *ortho* substituent impedes rotation about the C—N bond, freezing the conformation of the molecule so that the carbonyl group is located in the vicinity of the *ortho* hydrogen.

Computer Programs for Estimating ^1H NMR Chemical Shifts

Computer programs have been developed that use additivity parameters for calculating the NMR spectrum of any molecule of interest. The ChemDraw Ultra program in ChemBioOffice from CambridgeSoft includes a module called ChemNMR, which estimates ^1H chemical shifts and displays the calculated NMR spectrum after the structure of a molecule is drawn. The logic of the program

is a rule-based calculation of chemical shifts on structural fragments, similar to the method presented in this technique. The Chem NMR module uses 700 base values and about 2000 increments; the calculated chemical shifts are stated to be within 0.2–0.3 ppm, roughly comparable to the use of the additivity parameters presented in this chapter.

Alternative methods for estimating chemical shifts are the Advanced Chemical Development/NMR Predictor (from Advanced Chemistry Development) and HyperChem/HyperNMR. The predicted chemical shifts are based on a large database of structures and the database can be expanded as new compounds become available. The display can be interrogated by clicking on either the structure or the spectrum to highlight their co-relationships.

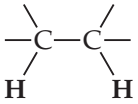
These programs are sophisticated, research quality tools and are priced accordingly. Some institutions have negotiated site licenses making the programs accessible to all their members.

21.9 Spin-Spin Coupling (Splitting)

The chemical shifts and integrals of NMR signals provide a great deal of information about the structure of a molecule. However, this information is often not enough to determine the structure. Closer examination of NMR signals reveals that they are generally not shapeless blobs but highly structured patterns with a multiplicity of lines. Reexamine the spectrum of ethyl propanoate shown in Figure 21.17 (page 334). The signal at 4.1 ppm is actually a group of four peaks, as is the signal at 2.3 ppm. The signals at 1.2 and 1.1 ppm are groups of three peaks. The fine structure of these patterns is caused by interactions between the proton(s) producing the signals and neighboring nuclei, particularly other protons. The effects are small compared with those of shielding and deshielding, but analysis of the patterns provides valuable information about the local environments of protons in a molecule.

Vicinal Coupling ($^3J_{HH}$)

The interactions that cause the fine structure of NMR signals are transmitted through the bonding framework of the molecules. They are usually observable only when the interacting nuclei are near one another. The most commonly observed effects are produced by the interaction between protons attached to adjacent carbon atoms. These protons, which are separated by three bonds, are called ***vicinal,*** or nearby, protons.



Vicinal protons

A proton that is affected by the spin states of another nucleus is ***coupled*** to that nucleus and its signal is split into multiple signals. A simple example of coupling between two vicinal hydrogen atoms can be seen in the NMR spectrum of 1,1,2-tribromo-2-phenylethane shown in Figure 21.19. Both H_a and H_b have a spin of ½ and therefore have two spin states, one aligned with the applied magnetic field and one opposed to it. In the absence of H_b, H_a would exhibit a single peak at 5.97 ppm. However, in the presence of the neighboring H_b, H_a is affected by the spin state of H_b.

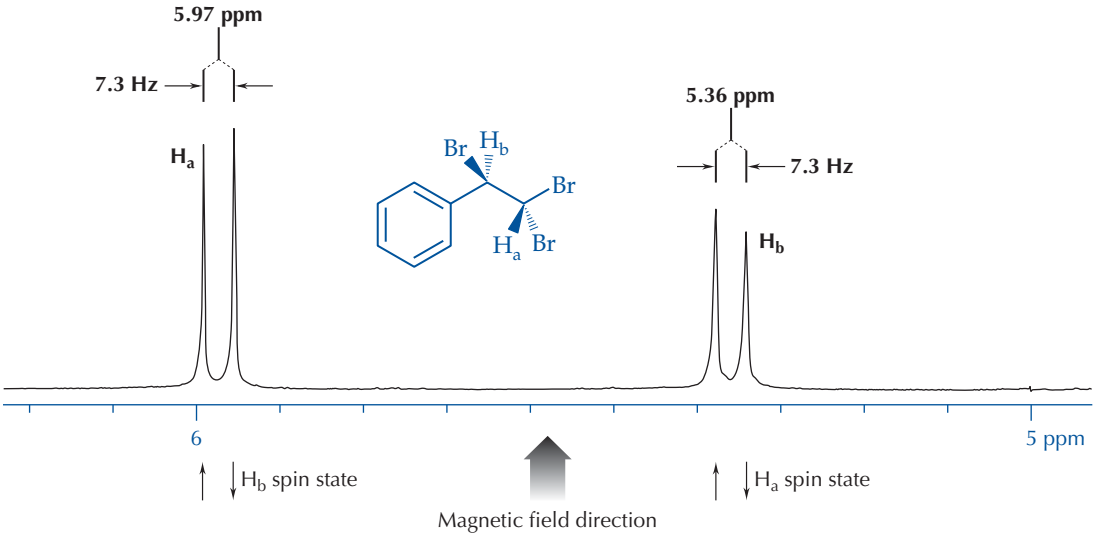


FIGURE 21.19 Section of the ^{1}H NMR spectrum of 1,1,2-tribromo-2-phenylethane at 360 MHz.

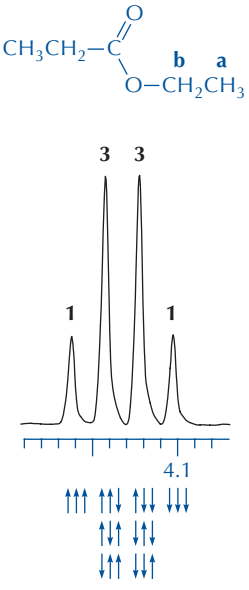


FIGURE 21.20 Signal at 4.13 ppm in the ^{1}H NMR spectrum of ethyl propanoate at 360 MHz.

The effective magnetic field felt by H_a increases a little when the magnetic field of H_b is aligned with the applied magnetic field. The aligned orientation leads to a slight deshielding effect, and the position of the H_a signal moves slightly downfield. The magnetic field of the spin state of H_b opposed to the applied magnetic field decreases the effective magnetic field felt by H_a, moving the H_a position slightly upfield. Thus, the signal for H_a is split into a ***doublet.*** Because the number of H_b nuclei in each spin state is nearly equal, two peaks of nearly equal intensity are observed.

The distance between the signals of the doublet is called the ***coupling constant (J).*** When it is a vicinal (three-bond) coupling constant that involves two protons, the notation is $^3J_{HH}$. Coupling constants are measured in Hz (cycles per second), and their values are independent of the spectrometer operating frequency. In Figure 21.19, the value of the coupling constant is 7.3 Hz. In an analogous manner, proton H_a interacts with proton H_b, and H_b also appears as a doublet with the same coupling constant. The fact that interacting protons have coupling constants of exactly the same value is very useful for identifying which protons are coupled to each other.

Now consider a slightly more complicated pattern. An expanded section of the 360-MHz NMR spectrum of ethyl propanoate near 4.1 ppm is shown in Figure 21.20. This set of NMR signals is produced by the methylene group **b**, which has a relative integration of two protons. The protons of the methylene group are coupled to the protons of the adjacent methyl group, and they split into a four-peak pattern called a ***quartet.*** The four peaks are produced by the three adjacent protons of the methyl group, which have the four spin states shown in Figure 21.20:

1. The three spins of the methyl protons aligned with the applied magnetic field produce the left peak.

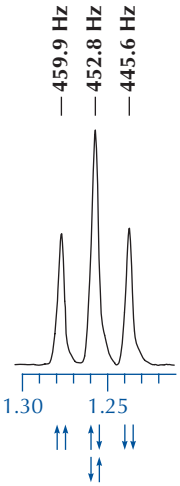


FIGURE 21.21
Signal at 1.26 ppm in the ^{1}H NMR spectrum of ethyl propanoate at 360 MHz.

2. The two spins of the methyl protons aligned with and the one opposed to the applied magnetic field produce the middle-left peak.
3. The one spin aligned with and the two spins of the methyl protons opposed to the applied magnetic field produce the middle-right peak.
4. The three spins of the methyl protons opposed to the applied magnetic field produce the right peak.

Statistically, there are three possible combinations that lead to spin states 2 and 3. Because every combination of spins has the same probability of occurring, the relative intensities of the four peaks in the pattern are 1:3:3:1. The measured coupling constant is 7.1 Hz.

EXERCISE

Analyze the ***triplet*** (three-peak) pattern of methyl group **a** of ethyl propanoate at 1.26 ppm, shown in Figure 21.21. The protons of this methyl group are coupled to the protons of methylene group **b** (see Figure 21.20).

Answer: The key to the splitting pattern of the methyl group is the number of spin states of the methylene group to which it is coupled. As usual, the spins of the two methylene protons have an equal probability of being aligned or opposed to the applied magnetic field. Three combinations are possible. The two spins can be aligned, one can be aligned and the other opposed, or the two spins can be opposed to the applied magnetic field. There is twice the probability of one spin aligned and one opposed. This produces a triplet pattern for the nearby methyl group, with the relative intensities 1:2:1.

We can check to make sure that methyl group **a** is coupling with methylene group **b** by calculating the coupling constant, *J*, between them. If they are coupled, both groups of peaks must have the same *J* value. Figure 21.21 gives the positions of the peaks for the methyl group in Hz. The distance between the individual peaks must be the same.

$$459.9\ \text{Hz} - 452.8\ \text{Hz} = 7.1\ \text{Hz}$$
$$452.8\ \text{Hz} - 445.6\ \text{Hz} = 7.2\ \text{Hz}$$

Within experimental error, the coupling constants are the same.

Singlet	One peak
Doublet	Two peaks
Triplet	Three peaks
Quartet	Four peaks

Splitting Trees and the N + 1 Rule

A common device for predicting and analyzing the fine structure of coupling patterns is a ***splitting tree,*** constructed by mapping the effect of each spin-spin coupling on a signal. The splitting tree for the methylene group **b** of ethyl propanoate is shown in Figure 21.22. Notice that there are three branching sites in the tree—one set of branches for each proton in methyl group **a**, whose coupling produces the splitting tree.

Splitting of signals. Because the three adjacent methyl protons are equivalent to one another, the methylene signal can be thought of as splitting into doublets three times. The signal is split into a doublet by the first methyl proton. The coupling with a second methyl proton

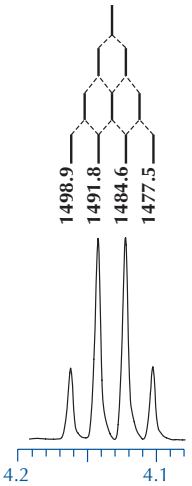


FIGURE 21.22
Splitting tree for the signal at 4.13 ppm in the ^{1}H NMR spectrum of ethyl propanoate at 360 MHz.

splits each signal of the doublet into two signals. Because the coupling constants of these two interactions are exactly the same, the position of the high-field signal of one doublet reinforces the position of the low-field signal of the second doublet. If no more splitting occurred, the pattern would consist of three equally spaced signals, the center signal having twice the intensity of the two outer ones. Coupling with the third methyl proton, however, again splits each of the signals of the triplet into two signals. Because the coupling constant is the same, the signals again reinforce each other. As seen in the splitting tree in Figure 21.22, the resulting pattern is a ***quartet,*** a group of four equally spaced signals. The ratio of the intensities is 1:3:3:1.

The presence of doublets, triplets, and quartets in NMR spectra has led to the ***N + 1 rule*** for multiplicity: **A proton that has N equivalent protons on adjacent carbon atoms will be split into N + 1 signals.**

Pascal's triangle. The ratio of the intensities of the multiplet signals can be obtained from Pascal's triangle (Figure 21.23), a triangular arrangement of the mathematical coefficients obtained by a binomial expansion. The N + 1 rule assumes that all N protons are equivalent, with equal coupling constants. If the protons are not all equivalent, the coupling constants will probably not all be equal.

N	N+1	Relative intensities of peaks	Typical pattern
0	1	1	Singlet
1	2	1 1	Doublet
2	3	1 2 1	Triplet
3	4	1 3 3 1	Quartet
4	5	1 4 6 4 1	Quintet
5	6	1 5 10 10 5 1	Sextet
6	7	1 6 15 20 15 6 1	Septet

FIGURE 21.23 Pascal's triangle can be used to predict the multiplicity and relative intensities of the signal of any magnetically active nucleus coupled to N equivalent nuclei of spin 1/2. It applies to both ^{1}H and ^{13}C spectra.

In that case, the total number of peaks will be greater than N + 1. Multiple couplings are discussed below.

Returning to the 360-MHz NMR spectrum of ethyl propanoate (see Figure 21.17), you will see that the methylene signal at 4.13 ppm appears as a quartet because of the splitting by the three hydrogen nuclei of the adjacent methyl group (N = 3; N + 1 = 4). In turn, the three-proton signal at 1.26 ppm appears as a triplet because of the two hydrogen nuclei of the adjacent methylene group (N = 2, N + 1 = 3). **This triplet-quartet pattern is seen quite often and is diagnostic for an ethyl group.** A second triplet-quartet pattern occurs in the NMR spectrum of ethyl propanoate, indicative of the presence of a second ethyl group. In this case, the quartet is located at 2.32 ppm because the methylene component of the ethyl group is attached to a carbonyl group rather than to an oxygen atom.

Multiple Couplings

In most organic compounds there will be coupling constants that are similar in magnitude as well as coupling constants that are quite different. This situation creates patterns that are more complicated than the ones shown in Figures 21.17 and 21.19. The 360-MHz spectrum of ethyl *trans*-2-butenoate shown in Figure 21.24 is an example. The spectrum shows five groups of signals at 1.2 ppm, 1.8 ppm, 4.1 ppm, 5.8 ppm, and 6.9 ppm, with integral values of 3:3:2:1:1, respectively. Notice that Figure 21.24 has an expanded inset near every set of peaks. It is often necessary to expand regions in an NMR spectrum to more clearly reveal the detail of the splitting patterns.

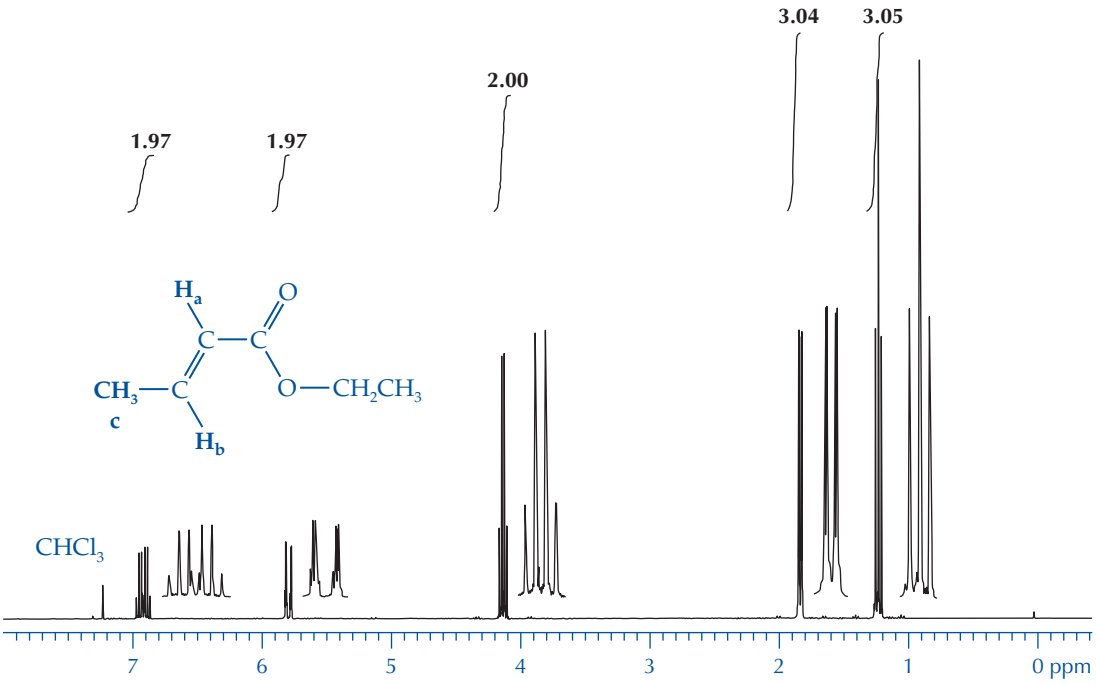


FIGURE 21.24 ^{1}H NMR spectrum of ethyl *trans*-2-butenoate at 360 MHz, with superimposed expanded (4×) insets adjacent to the signals.

The quartet pattern at 4.1 ppm, which integrates to two protons, and the triplet pattern at 1.2 ppm, which integrates to three protons, indicates that an ethyl group is incorporated into the structure of the molecule. The chemical shift of the methylene group suggests that the ethyl group is bonded to an oxygen atom. Taken together, the partial structure producing the signals at 4.1 ppm and 1.2 ppm must be —OCH_2CH_3.

The three-proton signal at 1.8 ppm is the result of a second methyl group. Its position is consistent with the chemical shift of a methyl group attached to a C═C bond (see Figure 21.12). The signal appears to be a doublet, indicating that there is only one proton on the adjacent carbon atom, which confirms CH_3—CH═C— as a component part of the molecule. From Table 21.2, we know that the two signals at 5.8 ppm and 6.9 ppm are produced by protons attached to the carbon atoms of a C═C bond. Because the signal at 5.8 ppm is a doublet, there is only one other proton on an adjacent carbon. Therefore, we can assign it to the vinyl proton (H_a) next to the carbonyl group. Taking all these observations into consideration leads us to the conclusion that the partial structure that produces the signals at 5.8 ppm, 6.9 ppm, and 1.8 ppm must be —(C═O)—CH═CH—CH_3.

EXERCISE

What coupling pattern accounts for the complex set of peaks centered at 6.93 ppm in Figure 21.25, which is an expanded section of the H_b signal in the NMR spectrum of ethyl *trans*-2-butenoate in Figure 21.24?

Answer: The signal at 6.93 ppm is produced by the CH_3—C**H**═CH— proton. This set of peaks is a good deal more complex than the simple N + 1 pattern we have seen previously. It seems to have eight peaks. If the coupling constants between the vinyl proton and the four protons on adjacent carbon atoms were the same, the signal should appear as a quintet (N = 4, N + 1 = 5); however, it clearly is not a five-peak pattern. If there were only coupling with the other vinyl proton (H_a) signal at 5.8 ppm, the N + 1 rule predicts that the signal at 6.93 ppm would appear as a doublet. However, because there is also coupling with the adjacent methyl group (H_c), each peak of the doublet is split into a quartet. Two overlapping quartets produce the observed eight-peak pattern in Figure 21.25.

By accurately measuring the distances between the signals, it is possible to determine the coupling constants. One coupling constant can be determined by measuring the distance from the outermost signal of the pattern to the adjacent signal. Using the leftmost signals, we can calculate this coupling constant to be 6.9 Hz:

$$2513.5\ \text{Hz} - 2506.6\ \text{Hz} = 6.9\ \text{Hz}$$

This value is the coupling constant between the three hydrogen atoms of the methyl group at 1.8 ppm and the vinyl proton at 6.93 ppm.

The distance in Hz between the outermost signals of the pattern (2513.5 Hz − 2477.3 Hz = 36.2 Hz) is the sum of all the coupling constants. The coupling constant between the two vinyl protons can be calculated by

subtracting the coupling constants of each proton in the methyl group from this sum:

$$36.2 \text{ Hz} - (3 \times 6.9 \text{ Hz}) = 15.5 \text{ Hz}$$

The splitting tree for the proton appearing at 6.93 ppm is shown at the top of Figure 21.25.

Other Types of Coupling

Most of the observed coupling in NMR spectroscopy is a result of vicinal coupling through three bonds, $\mathbf{H}_a$—C—C—$\mathbf{H}_b$, called $^3J_{HH}$ coupling. However, coupling through one, two, and four bonds can also be observed. One-bond coupling occurs between ^{13}C and ^1H ($^1J_{CH}$). Because the relative abundance of ^{13}C is so small, the signals produced by this splitting are usually negligible in a ^1H NMR spectrum. With concentrated samples, it is possible to observe this splitting

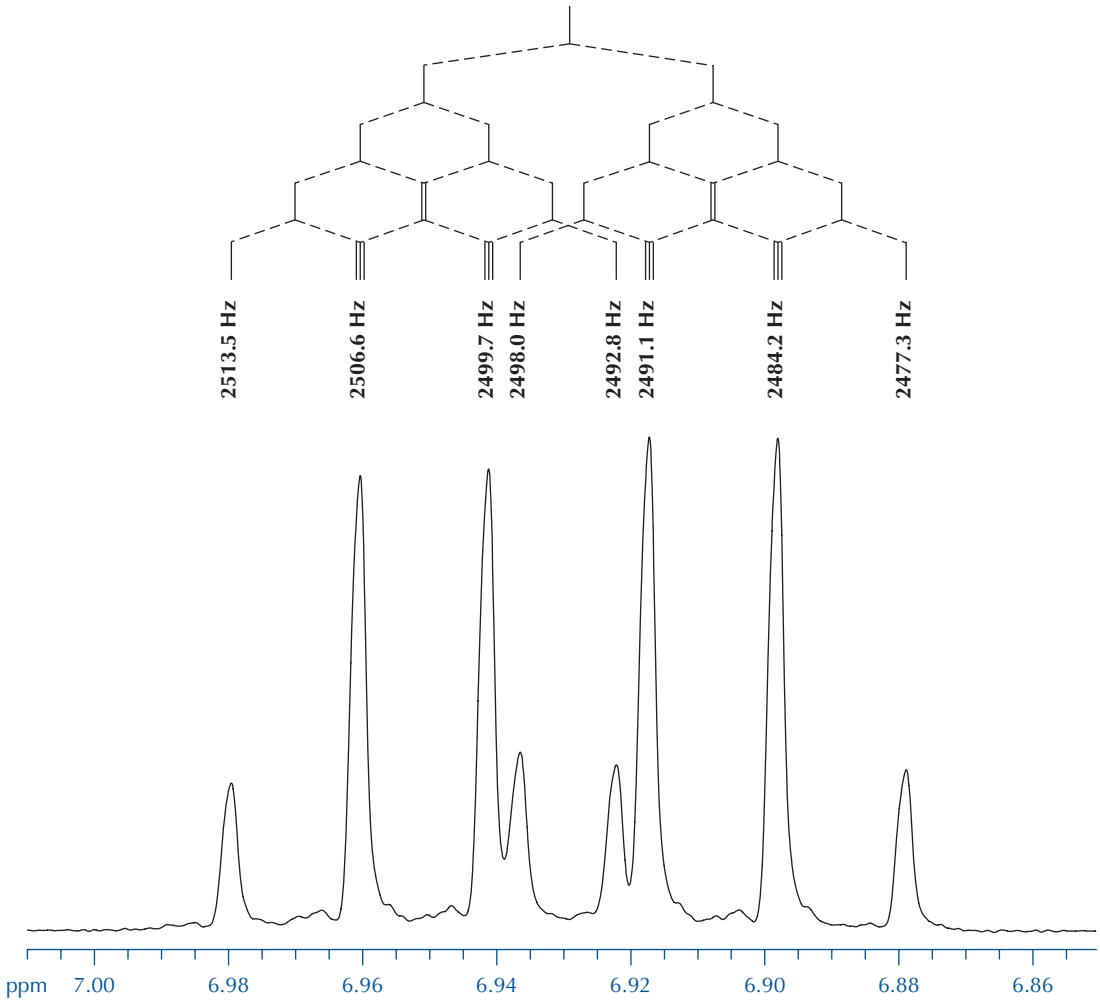


FIGURE 21.25 Splitting tree for the vinyl proton signal at 6.93 ppm in the ^1H NMR spectrum of ethyl *trans*-2-butenoate.

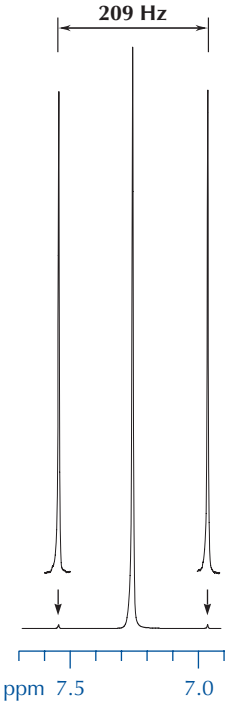


FIGURE 21.26
Expanded and amplified section of the ^{1}H NMR spectrum of chloroform at 360 MHz, showing ^{13}C splitting.

by turning up the amplitude, as demonstrated by the ^{1}H NMR spectrum of chloroform shown in Figure 21.26. This type of coupling is a major consideration when observing ^{13}C signals, as you will see in Technique 22 on ^{13}C NMR spectroscopy.

Geminal coupling. Coupling through two bonds ($^{2}J_{HH}$), or geminal coupling, occurs between two protons attached to the same carbon atom, $\mathbf{H}_a$—C—$\mathbf{H}_b$. In many molecules, these two protons are equivalent and coupling is not observed. However, geminal coupling is frequently observed in compounds with vinyl methylene groups, $H_2C{=}C{-}$, where the two geminal protons can be nonequivalent. Other examples where methylene protons are not equivalent are discussed in the advanced NMR topics section [see Technique 21.12].

Allylic coupling. Coupling through four bonds ($^{4}J_{HH}$) is often observed in compounds containing carbon-carbon double bonds ($\mathbf{H}_a$—C=C—C—$\mathbf{H}_c$) and is called ***allylic coupling.*** When the NMR spectrum of ethyl *trans*-2-butenoate is expanded, its allylic coupling can be seen. Expansion of the signals at 5.8 ppm and 1.84 ppm (H_a and H_c in Figure 21.24) reveals further fine structure (Figures 21.27a and b). At 5.8 ppm, the pattern of the NMR signal is a doublet of quartets and the signal at 1.84 ppm is a doublet of doublets. The coupling constant for this $^{4}J_{HH}$ coupling is quite small, only 1.7 Hz. Until the signals are expanded, it is hardly noticeable.

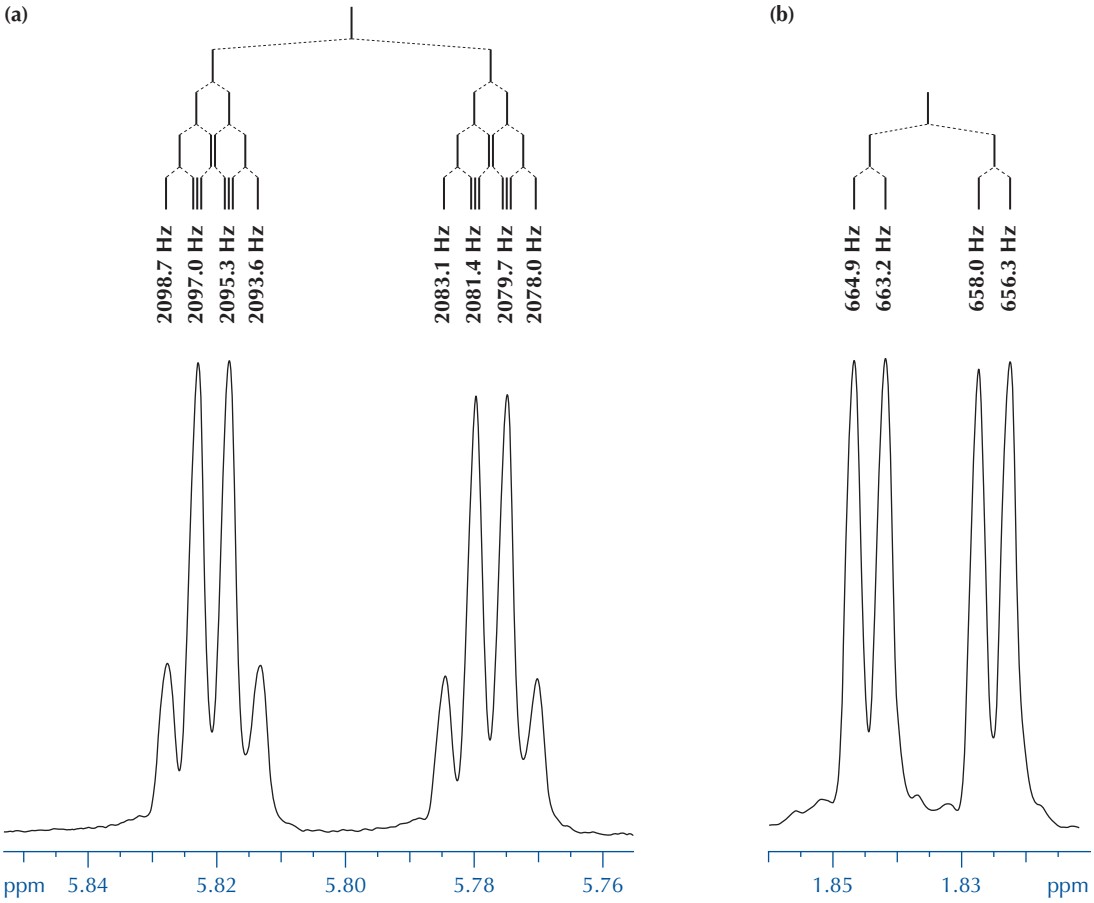


FIGURE 21.27 Expansions of signals at **(a)** 5.8 ppm and **(b)** 1.8 ppm in the ^{1}H NMR spectrum of ethyl *trans*-2-butenoate.

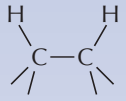
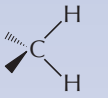
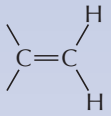
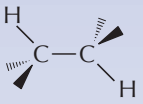
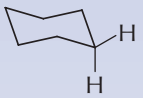
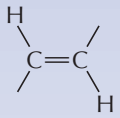
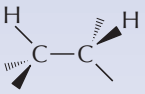
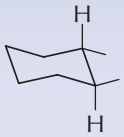
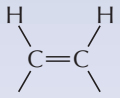
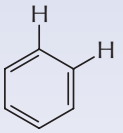
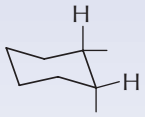
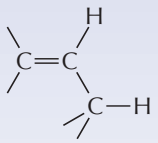
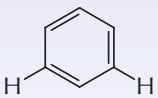
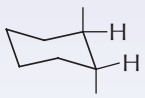
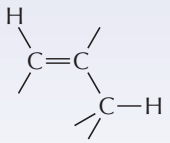
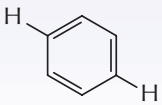
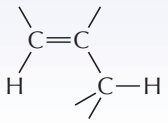
Magnitude of Coupling Constants

The magnitude of coupling constants can reveal valuable information about the structure of a molecule. The magnitude is related to the number of bonds between the interacting protons; the more bonds, the smaller the coupling constant. The size of vicinal coupling for alkyl protons ranges from about 2 to 13 Hz. The size of geminal coupling depends on bond angles and hybridization; for alkyl protons it is generally on the order of 10–16 Hz. The geminal coupling of vinyl protons is much smaller (0–3 Hz). Coupling through four or more bonds is also very small, 0–3 Hz. Typical coupling constants for various arrangements of protons are listed in Table 21.6.

Our analysis of Figure 21.25 showed that the coupling constant for the splitting of the two vinyl protons is 15.5 Hz. This large coupling constant indicates that the protons are *trans* to one another; therefore, the molecule must be a *trans* (E) alkene.

If there is free rotation about a carbon-carbon single bond connecting the coupled protons, the vicinal or three-bond coupling

TABLE 21.6 Typical proton-proton coupling constants

Arrangment of protons	J(Hz)	Arrangement of protons	J(Hz)	Arrangement of protons	J(Hz)
 Free rotation	7		10 to 16		0 to 3
 Anti	8 to 13		11 to 14		12 to 18
 Gauche	2 to 4		8 to 13		6 to 12
	6 to 9		2 to 6		4 to 10
	1 to 3		2 to 5		0.5 to 2
	0 to 1				0

constants are usually about 7 Hz. If rotation about the carbon-carbon bond is restricted, the coupling constant can range from 0 to 13 Hz. The size of a vicinal coupling constant is related to the angle ϕ on a Newman projection of the interacting protons (Figure 21.28). This angle is called the ***dihedral angle.***

In the early days of NMR spectroscopy, Martin Karplus at Harvard studied the relationship between the size of a coupling constant and the dihedral angle. His conclusions are now widely accepted and are often presented as a plot of the coupling constant versus dihedral angle. This plot is called a ***Karplus curve*** and is shown in Figure 21.28. The important characteristics of the Karplus relationship are the minimum value of the coupling constant at a dihedral angle of 90° and the large values of the vicinal coupling constant at dihedral angles of 0° and 180°.

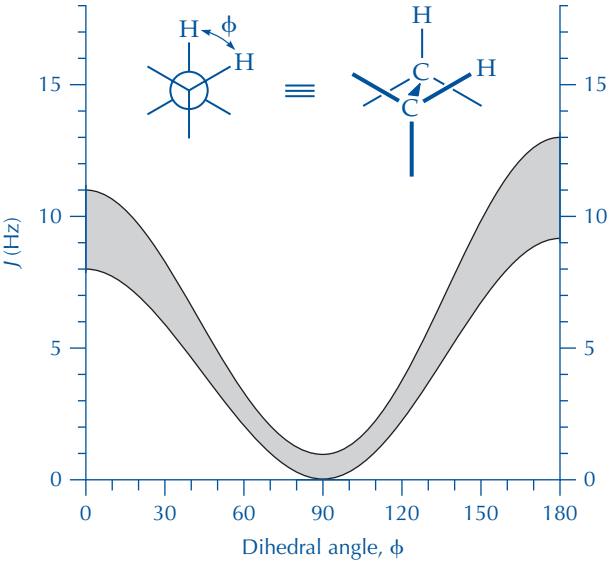


FIGURE 21.28
Dependence of the coupling constant on dihedral angle, ϕ, formed by two vicinal C—H bonds (Karplus relationship). Coupling constants usually fall between the two curves, which are calculated using different assumptions.

21.10 Sources of Confusion

Using NMR spectroscopy to analyze the structures of organic compounds is a logical process. However, sometimes the process of interpreting a spectrum becomes complicated beyond the factors of chemical shift and spin-spin splitting that we have discussed. It is important to be aware of some of the complicating factors so that you can make rational choices when confronted with unexpected, confusing, or poorly defined signals in a spectrum.

In this section we will briefly discuss four common, potentially confusing areas in the interpretation of NMR spectra:

- History of the NMR sample: Mixtures of compounds
- Overlap of NMR signals
- NMR sample preparation and data acquisition
- O—H and N—H protons

History of the NMR Sample: Mixtures of Compounds

Extra signals in an NMR spectrum are often a product of a mixture of the compound whose structure you want to ascertain with solvents, starting materials, reaction side products, and residual proton signals from the deuterated solvent. Much puzzlement and frustration can be avoided by careful consideration of what might be present in the NMR tube.

Sources of extra signals. To determine the source of extra signals, it is important to know the history of the NMR sample. If you prepared it, you already know the solvents and reagents that could be present. What solvent did you use for the reaction mixture? If you purified your compounds by extraction, recrystallization, or chromatography,

TABLE 21.7 ^{1}H NMR signals of common solvents

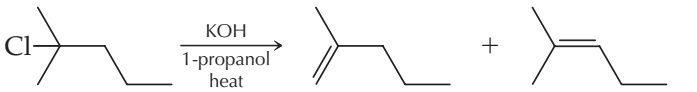
Solvent	NMR signals (ppm)[a]
Acetone	2.1 (s)
Benzene	7.4 (s)
Chloroform	7.3 (s)
Cyclohexane	1.4 (s)
Dichloromethane	5.3 (s)
Diethyl ether	1.2 (t), 3.5 (q)
Dimethyl sulfoxide	2.5 (s)
Ethanol (anhydrous)	1.2 (t), 3.0 (t) or (s), 3.7 (m) or (q)
Ethyl acetate	1.3 (t), 2.0 (s), 4.1 (q)
Hexane	0.9 (t), 1.3 (m)
2-Propanol	1.2 (d), 2.6 (d) or (s), 4.0 (m)
Methanol (anhydrous)	2.3 (q) or (s), 3.4 (d) or (s)
Tetrahydrofuran	1.9 (m), 3.8 (m)
Toluene	2.3 (s), 7.2 (m) or (s)
Water (dissolved)	1.6 (s)
Water (bulk)	4.6 (br s)

a. In $CDCl_3$. Multiplicity of signal is shown in parentheses.

what solvents did you use? What does the NMR spectrum of the starting material look like? What solvent did you use to clean the NMR sample tube?

Table 21.7 lists some organic solvents that are common impurities in NMR samples and the chemical shift positions and multiplicity of their NMR signals.*

Example of a typical mixture. The NMR spectrum shown in Figure 21.29 is a typical example of a mixture encountered in the laboratory. The material for the sample was obtained from the base-catalyzed dehydrochlorination of 2-chloro-2-methylpentane.



2-Methyl-1-pentene 2-Methyl-2-pentene

The expected products of the reaction are 2-methyl-1-pentene and 2-methyl-2-pentene, and it is quite possible that they will be contaminated with a small amount of 1-propanol, the solvent used in the reaction. The singlet at 2.2 ppm and the triplet at 3.6 ppm are produced by the hydroxyl proton of 1-propanol and the methylene group attached to the hydroxyl group. The other signals of 1-propanol, at 1.55 ppm and 0.92 ppm, are obscured by signals of the two alkenes.

Even though every signal in the spectrum is not distinct, much useful information can be obtained because each component of the

* An extensive, useful list of impurity peaks has been collected by Gottlieb, Kotlyar, and Nudelman (*J. Org. Chem.* **1997,** *62,* 7512–7515).

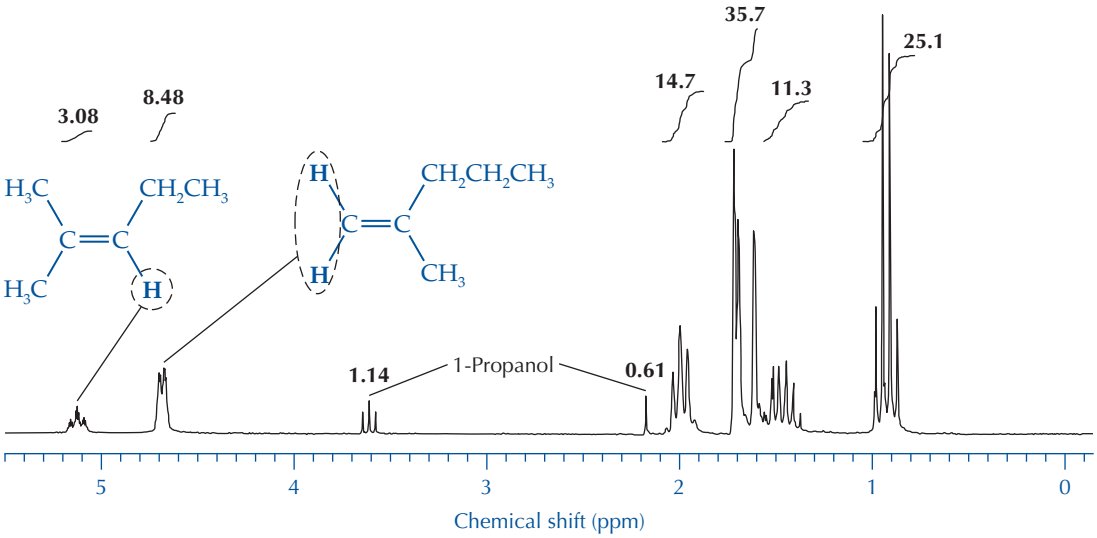


FIGURE 21.29 200-MHz ^{1}H NMR spectrum of the reaction product from dehydrochlorination of 2-chloro-2-methylpentane, a mixture of 2-methyl-1-pentene and 2-methyl-2-pentene.

mixture exhibits unique features. For example, the ability of NMR to count each of the protons in every component of a mixture can be put to good use. This information allows you to tell which sets of NMR peaks relate to the same compound, because each set must have integral proton ratios. It also allows you to determine the molar composition of the mixture.

Calculating the ratio of products. The integrals of the vinyl proton signals at 5.1 ppm and 4.7 ppm can be used to determine the ratio of 2-methyl-2-pentene to 2-methyl-1-pentene in the mixture. The broad triplet at 5.1 ppm is caused by the vinyl proton attached to C-3 in 2-methyl-2-pentene. The two broad signals at 4.7 ppm are produced by the two protons attached to C-1 in 2-methyl-1-pentene. To calculate the molar ratio of the two alkenes in the product mixture, the integrals need to be normalized by dividing them by the number of protons causing the signals.

$$\frac{\text{moles of 2-methyl-1-pentene}}{\text{moles of 2-methyl-2-pentene}} = \frac{8.48/2}{3.08/1} = \frac{1.38}{1}$$

The calculation shows that the dehydrochlorination of 2-chloro-2-methylpentane produces 58% 2-methyl-1-pentene and 42% 2-methyl-2-pentene.

Overlap of NMR Signals

Signals from protons with similar chemical shifts may overlap with one another, leading to broad and poorly defined patterns. Often these patterns are so poorly defined that analyzing the coupling is not even tempting. An example of poorly defined peaks is shown in the 60-MHz NMR spectrum of 1-butanol (Figure 21.30a). The region

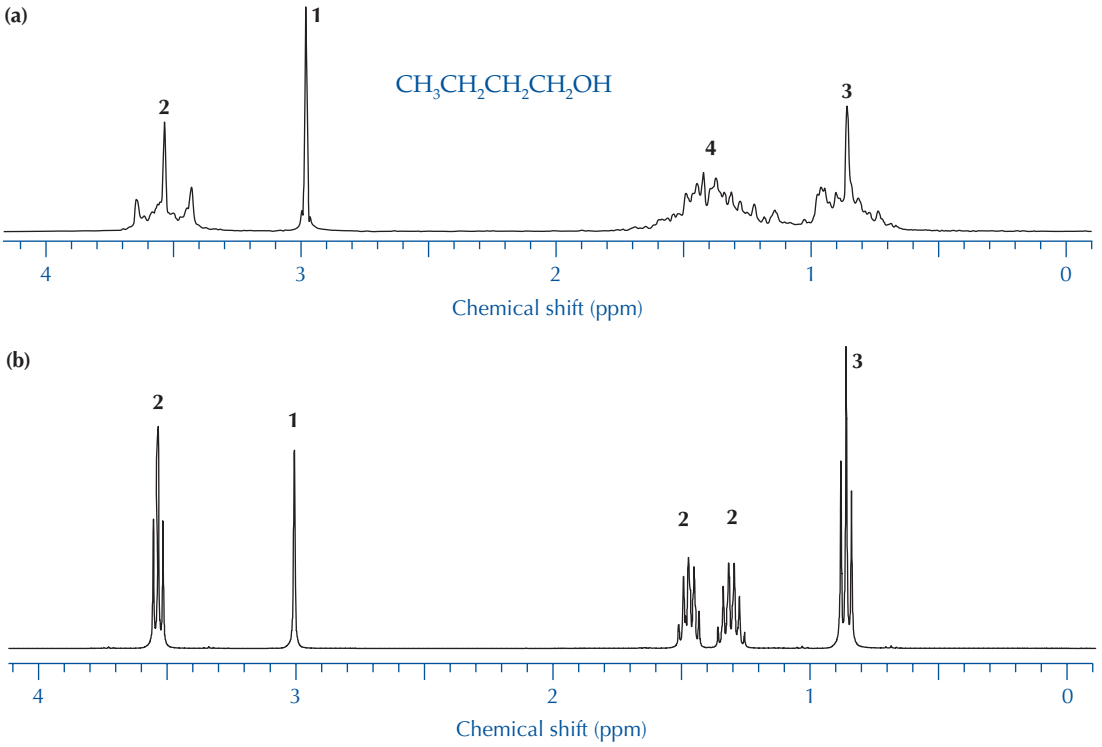


FIGURE 21.30 ^{1}H NMR spectra of 1-butanol at **(a)** 60 MHz and **(b)** 360 MHz.

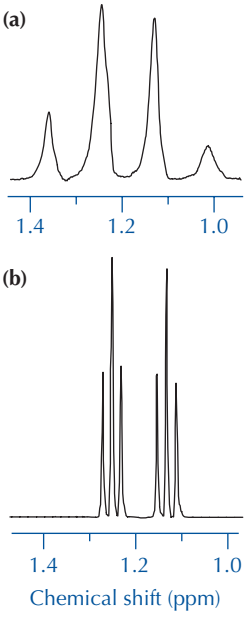


FIGURE 21.31 ^{1}H NMR spectra of the methyl group signals of ethyl propanoate at **(a)** 60 MHz and **(b)** 360 MHz.

from 1–2 ppm exhibits a complex multiplet integrating to four protons, which includes both of the two similar methylene groups of 1-butanol. In addition, little can be learned from the methyl protons that appear at 0.7–1.0 ppm.

Sometimes it is possible to unravel complex multiplets with an NMR spectrum obtained using a higher-field instrument. The 360-MHz NMR spectrum of 1-butanol is shown in Figure 21.30b. In this spectrum, the chemical shifts of the two methylene groups are different enough so that their signals are separated into two well-defined multiplets; one signal at 1.3 ppm is a six-peak multiplet and the other signal at 1.47 ppm is a quintet. Also, notice that the methyl group at 0.86 ppm is a well-defined triplet.

There are also cases where two or more well-defined patterns overlap, producing what at first glance may resemble a single pattern but which, on closer examination, has coupling constants and/or signal intensities that do not correlate with a single pattern. A good example of such a deceptive pattern is the apparent quartet at 1.2 ppm in the 60-MHz NMR spectrum of ethyl propanoate. An expanded section of this 60-MHz spectrum, containing the four-line pattern, is shown in Figure 21.31a. Figure 21.31b shows the same section of the spectrum obtained on a 360-MHz NMR instrument; at the higher magnetic field the pattern separates into two triplets, one centered at 1.13 ppm and the other centered at 1.26 ppm.

NMR Sample Preparation and Data Acquisition

Broad and distorted signals are often the result of either poor sample preparation or improper operation or adjustment of the NMR instrument.

Spinning sidebands. Reflections of a signal, called spinning sidebands, that appear symmetrically around the signal are evidence of problems with NMR instrument settings, especially those that control the homogeneity of the magnetic field. Sometimes the spinning sidebands are large enough that a quick glance suggests that a singlet peak may be a triplet. However, it is rare that the sidebands are large enough to approach the 1:2:1 peak heights necessary for a triplet pattern that is caused by spin-spin coupling. You can always tell if the set of peaks is a real triplet by examining the relative heights of the three peaks. In addition, spinning sidebands will appear around all the peaks in the NMR spectrum, not just one or two of them.

Poor sample preparation. Following are typical examples of poor sample preparation:

- The sample is not completely dissolved or there are insoluble impurities present.
- The sample solution is too concentrated.
- The height of the solution in the NMR tube is not correct.

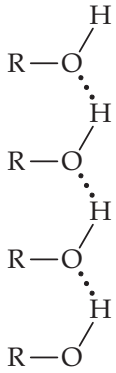
Problems during data acquisition. Following are examples of problems that occur during data acquisition:

- The sample tube is not positioned properly in the spin collar.
- The sample is not spinning evenly during data acquisition.
- The NMR sample tube is spinning too rapidly during the data acquisition, leading to a vortex in the sample solution.
- The spectrometer is not tuned properly.

Some of these sources of confusion cannot be avoided, but many of them can be minimized with careful sample preparation and conscientious data acquisition.

O—H and N—H Protons

Hydrogen bonding. Hydrogen bonding involving oxygen or nitrogen atoms draws electron density away from the O—H and N—H protons, deshielding them and shifting their signals downfield. Because concentration and temperature affect the extent of intermolecular hydrogen bonding, the chemical shift of protons attached to oxygen and nitrogen atoms in alcohols, amines, and carboxylic acids can appear over a wide range. In fact, O—H and N—H signals often vary in two NMR spectra of the same compound in the same solvent because the concentration differs. In dilute samples, there is little or no intermolecular hydrogen bonding and the signals may have small chemical shift values. Intermolecular hydrogen bonding in concentrated samples shifts O—H or N—H peaks downfield. The extreme case where hydrogen bonding causes deshielding occurs with carboxylic acids, which have a chemical shift of 10–13 ppm for the O—H proton.



Intermolecular hydrogen bonding

Proton exchange. Another potential source of confusion is the chemical exchange of O—H and N—H protons, which has two

consequences for NMR spectroscopy. First, a proton may not be attached to the heteroatom long enough for coupling to occur with nearby protons. Second, the signal for the exchangeable protons can merge into a single peak with an unpredictable chemical shift.

If a proton on the oxygen atom of an alcohol exchanges rapidly, which it usually does in $CDCl_3$ that contains a small amount of water or acid, no coupling between the hydroxyl proton and protons on the adjacent carbon is observed. The hydroxyl proton signal becomes a broadened singlet. However, if the sample solution used to obtain the NMR spectrum is anhydrous and acid-free, splitting is often observed because exchange of the O—H proton is relatively slow under these conditions, and the hydroxyl proton signal is split by the protons attached to the adjacent carbon atom. The choice of solvent can affect the likelihood of proton exchange. Samples of alcohols prepared in deuterated chloroform almost always show proton exchange, whereas the use of dimethyl sulfoxide-d_6 suppresses it.

The NMR spectrum of methanol dissolved in $CDCl_3$ is shown in Figure 21.32a. Proton exchange is evident because both the signal produced by the methyl protons and the signal produced by the hydroxyl proton appear as singlets. In the NMR spectrum of methanol dissolved in CD_3SOCD_3, shown in Figure 21.32b, the signal produced by the methyl protons appears as a doublet and the signal produced by the hydroxyl proton appears as a quartet, as predicted by the N + 1 rule. The protons are coupled because there is no chemical exchange of the hydroxyl proton in DMSO-d_6. Notice also that the differing amounts of intermolecular hydrogen bonding in the two solvents cause very different chemical shifts for the O—H proton of methanol.

The second consequence of chemical exchange is that O—H and N—H protons can exchange so quickly that they merge into a common environment and become combined into a single "averaged" NMR peak, whose chemical shift depends on concentration, solvent, temperature, and the presence of water or acid. When NMR samples are dissolved in D_2O, all O—H and N—H protons in the compounds merge into a broadened peak at the chemical shift of H—O—D.

Using chemical exchange as a diagnostic probe. Chemical exchange can be used as a diagnostic probe for protons of alcohols and amines

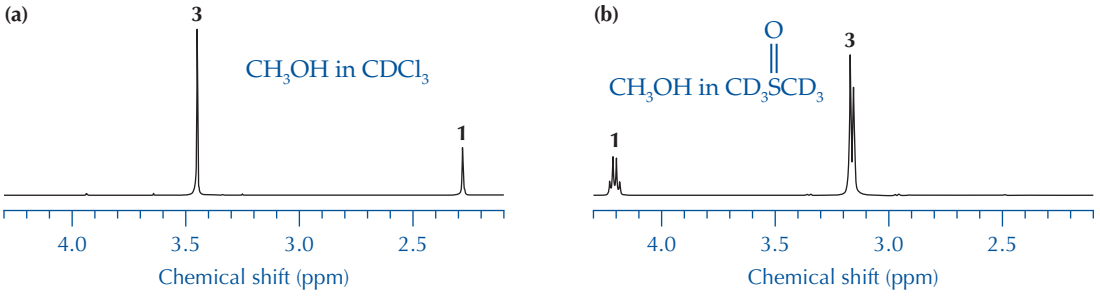


FIGURE 21.32 360-MHz ^1H NMR spectra of methanol in **(a)** deuterochloroform and **(b)** dimethyl sulfoxide-d_6.

dissolved in a deuterated organic solvent. The experiment is carried out by obtaining a second NMR spectrum after addition of a drop of D_2O to the solution. Hydroxyl and amine protons in the molecule are replaced by deuterons through chemical exchange. If the compound is an alcohol or amine, the signal resulting from the exchangeable proton disappears and a new signal produced by HOD appears at approximately 4.6 ppm.

21.11 Two Case Studies

NMR spectroscopy is the principal tool used by organic chemists for determining the structures of organic compounds. In this section we look at the ^{1}H NMR spectra of two organic molecules and show how the information derived from their spectra can help determine their molecular structures.

Four Major Pieces of Information from an NMR Spectrum

To start, it may be useful to recap the four major pieces of information that are used in the interpretation of a ^{1}H NMR spectrum of a pure compound:

- ***Number of signals*** tells us how many kinds of nonequivalent protons are in the molecule.
- ***Integration*** determines the relative number of non-equivalent protons in a ^{1}H NMR spectrum.
- ***Chemical shift*** provides important information on the environment of a proton. Downfield signals (larger ppm values) suggest nearby deshielding oxygen atoms, halogen atoms, or π-systems. Tables 21.2–21.5 and Figure 21.12 are useful aids for correlating chemical shifts with molecular structure.
- ***Splitting of signals,*** caused by spin-spin coupling of protons to other protons, reveals the presence of nearby protons that produce the coupling. Values of coupling constants can establish coupling connections between protons and can reveal stereochemical relationships (see Table 21.6).

Analysis of the Spectrum

First you should examine the entire spectrum without being too eager to focus on a prominent signal or splitting pattern. To ensure success, a structured and logical approach to the interpretation of an NMR spectrum is necessary. In time, after you have interpreted numerous spectra, you can replace the structured approach with a less formal one. The following approach will assist you in learning this skill:

1. Make inferences and deductions based on the spectral information.
2. Build up a collection of structure fragments.
3. Put the pieces together into a molecular structure that is consistent with the data and with the rules of chemical bonding.
4. Confirm the chemical shift assignments with calculated chemical shifts based on Tables 21.3–21.5. Any inconsistencies between the values should be examined and resolved. Explanations of minor inconsistencies usually hinge on subtle structural features of the molecule.

Double-Bond Equivalents

In NMR problem sets, the molecular formula of a pure compound is often provided. If it is available, the molecular formula can be used to determine the ***double-bond equivalents (DBE),*** which provide the number of double bonds and/or rings present in the molecule.

$$\text{double-bond equivalents (DBE)} = C + \frac{N - H - X}{2} + 1$$

where C is the number of carbon atoms, H is the number of hydrogen atoms, X is the number of halogen atoms, and N is the number of nitrogen atoms. Other names for double-bond equivalents are ***degree of unsaturation*** and ***index of unsaturation.***

Organizing the Spectral Information

We suggest the following method for organizing information from an NMR spectrum. First, prepare an informal table with the following headings:

- Chemical Shift (ppm)
- ^{1}H Type
- Integration
- Splitting Pattern
- Possible Structure Fragment(s)

Chemical Shift. In the Chemical Shift column, list the positions (or ranges) of all the signals in the spectrum.

^{1}H Type. Based on the chemical shifts, use Figure 21.12 and Table 21.2 as guides for entering likely structural assignments in the ^{1}H Type column for each NMR signal, for example, Ar—H, ═C—H, —O—C—H, and so on. Consider any reasonable structure within the chemical shift range. A few types of protons can appear over a wide range of chemical shifts, but at this early juncture it is better to err on the side of being too inclusive. As the analysis is refined the possibilities can usually be narrowed down.

Integration. Enter the value of each integral, rounded to whole numbers, in the Integration column. Remember that the integrals must add up to the total number of hydrogen atoms in the molecular formula.

Splitting Pattern. In the Splitting Pattern column, enter a description of the splitting pattern. Be as precise as possible, using standard descriptive terms, such as doublet, triplet, quartet, and combinations of these terms, such as doublet of triplets. If you have processed the FID to obtain the NMR spectrum or if you have access to the actual NMR data collected on the spectrometer, rather than just being given the spectrum, you should consider expanding regions in your NMR spectrum to reveal the detail of important splitting patterns. Later in the NMR analysis, when you have a complete structure proposal to consider, you may also wish to measure some of the coupling constants. Coupling constants can be used to determine which

signals are coupled to one another and in some cases to assign stereochemistry.

Possible Structure Fragment(s). The Possible Structure Fragment(s) column is where you pull the information together and enter all of the structural fragments that are consistent with the data for each NMR signal. Be flexible and consider all reasonable possibilities. For example, in the spectrum you may have a quartet that integrates to two protons. The quartet is probably the result of coupling to three protons with equal coupling constants. Two arrangements are consistent with this pattern, —C**H**$_2$—CH$_3$ and perhaps —CH—C**H**$_2$—CH$_2$ (boldface indicates the protons exhibiting the quartet).

Proposed Structure

Once you have constructed the table, the analysis is a matter of eliminating proposed structure fragments that are inconsistent and then putting the remaining structure fragments together into reasonable proposals for the structure of the compound. The final structure must be consistent with all the NMR data. Of particular importance is calculating the quantitative estimation of the chemical shifts (Tables 21.3–21.5). In all but the simplest cases, it is important to estimate the chemical shift for each type of proton. The estimated chemical shifts allow you to eliminate proposed structures inconsistent with the chemical shift data.

PROBLEM ONE

An organic compound has a molecular formula of $C_5H_{12}O$. Its 200-MHz ^1H NMR spectrum is shown in Figure 21.33. Determine its structure.

Double-bond equivalents. First, determine the compound's double-bond equivalents (DBE).

$$\text{DBE} = \text{C} + \frac{\text{N} - \text{H} - \text{X}}{2} + 1 = 5 + \frac{0 - 12 - 0}{2} + 1 = 0$$

Because DBE = 0, we know that the compound contains no rings or double bonds. Because the molecule has no double bonds and contains an oxygen atom, it must be either an alcohol or an ether.

Table of data from the spectrum. The data from the spectrum are summarized in Table 21.8. An assignment for the signal at 2.36 ppm is tentative because that region is normally where protons on carbons adjacent to alkenes and carbonyl groups appear, and we know from the DBE calculation that there are no double bonds in the molecule. However, the proton on the oxygen atom of an alcohol could also appear in this chemical shift region.

Assembling structure fragments. Two possible fragments could explain the splitting of the signal at 1.46 ppm:

$$\text{CH}_3\text{—C}\mathbf{H}_2\text{—} \qquad \text{or} \qquad \text{—CH}_2\text{—C}\mathbf{H}_2\text{—CH—}$$

The ethyl fragment has to be eliminated because there is no signal exhibiting a pattern consistent with the methyl portion of that fragment—a three-proton triplet at approximately 1.0 ppm.

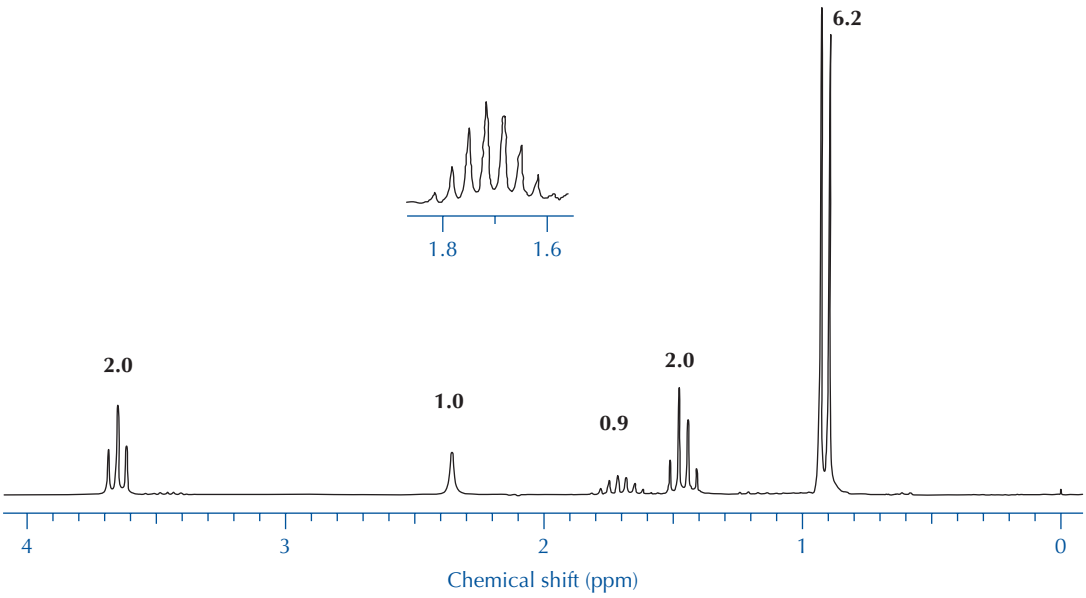


FIGURE 21.33 200-MHz ^{1}H NMR spectrum of $C_5H_{12}O$.

The splitting pattern at 1.71 ppm is difficult to know with certainty. Because the outermost signals of highly split patterns are very small relative to the other signals, the multiplet could be either an octet or a nonet. In either case, there must be two methyl groups attached to a methine group. The downfield triplet signal at 3.65 ppm is the result of a methylene group attached to an oxygen atom.

From the analysis so far, we can propose that the compound $C_5H_{12}O$ is an alcohol with an isopropyl group ($(CH_3)_2CH$—), as well as a methylene group flanked by methine and methylene groups (—CH—CH_2—CH_2—). In addition, there seems to be a methylene group attached to an oxygen atom and a second methylene group (—CH_2—CH_2—O—). This array of fragments consists of eight carbon atoms, sixteen hydrogen atoms, and one oxygen atom. Obviously, there are some atoms common to more than one fragment.

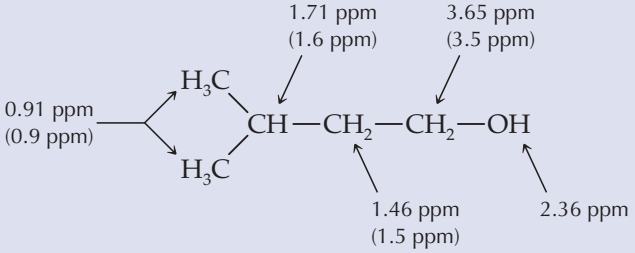
TABLE 21.8 Interpreted data from ^{1}H NMR spectrum (200 MHz) of $C_5H_{12}O$

Chemical shift (ppm)	^{1}H type	Integration	Splitting pattern	Possible structure fragment(s)
0.91	C—C—**H**	6	Doublet	—CH($C\mathbf{H}_3$)$_2$
1.46	C—C—**H**	2	Quartet	$CH_3C\mathbf{H}_2$— or —$CH_2C\mathbf{H}_2$CH—
1.71	C—C—**H**	1	Multiplet	—$CH_2C\mathbf{H}(CH_3)_2$ or —CH$C\mathbf{H}(CH_3)_2$
2.36	Perhaps C—O—**H**	1	Broad singlet	R—O—**H**
3.65	O—C—**H**	2	Triplet	—$CH_2C\mathbf{H}_2$O—

To solve this puzzle, set out the three structure fragments side-by-side to look for possible overlap:

$(CH_3)_2CH—$ **1** $—HC—CH_2—CH_2—$ **2** $—CH_2—CH_2—O—H$ **3**

Possible structures. It looks as if fragment 2 overlaps both fragment 1 and fragment 3. Combining fragments 1 and 3 produces a five-carbon alcohol, $(CH_3)_2CH—CH_2—CH_2—OH$, 3-methyl-1-butanol. The estimated chemical shifts from Table 21.3 are shown in the following structure; as you can see, the correspondence is very good.



Observed chemical shifts of 3-methyl-1-butanol
(calculated estimates of chemical shifts)

FOLLOW-UP ASSIGNMENT

Using Table 21.3, calculate the chemical shifts for each of the four kinds of protons attached to carbon atoms in 3-methyl-1-butanol. Do your answers correspond to the shifts shown in the structure at the end of the problem?

PROBLEM TWO

An organic compound has a molecular formula of $C_{10}H_{12}O$. Its 200-MHz ^1H NMR spectrum is shown in Figure 21.34. Determine the structure of this compound.

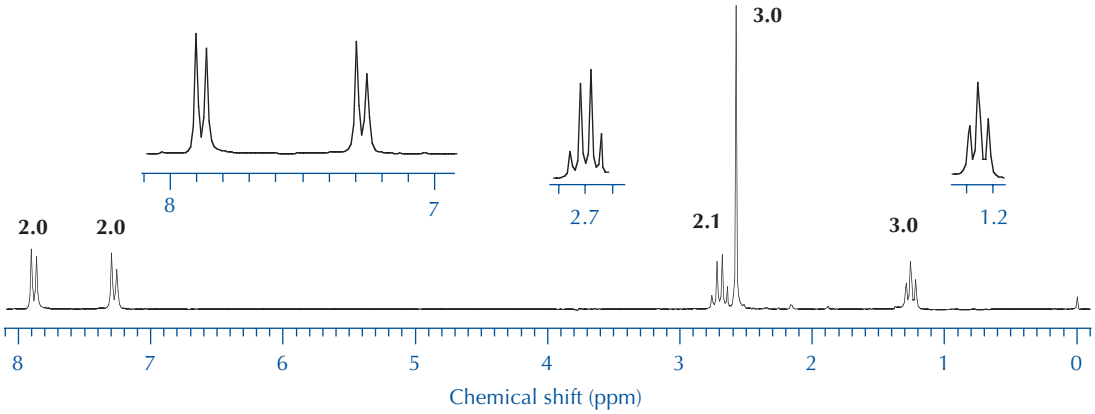


FIGURE 21.34 200-MHz ^1H NMR spectrum of $C_{10}H_{12}O$.

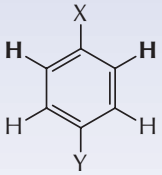
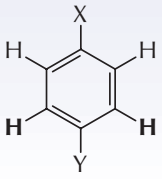
Table of data from the spectrum. The NMR data from Figure 21.34 are summarized in Table 21.9.

Double-bond equivalents. The double-bond equivalent calculation indicates that the compound contains a combination of five double bonds and/or rings.

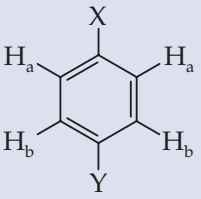
$$\text{DBE} = \text{C} + \frac{\text{N} - \text{H} - \text{X}}{2} + 1 = 10 + \frac{0 - 12 - 0}{2} + 1 = 5$$

Whenever there is a large DBE value, it is likely that the molecular structure of the compound incorporates one or more benzene rings, because each benzene ring accounts for four DBEs (three double bonds and one ring). The NMR spectrum confirms this assumption by the presence of signals in the aromatic proton region (6.5–8.5 ppm). The total integration of the aromatic protons is four, implying that the benzene ring is disubstituted. Moreover, the symmetry of the two signals in the aromatic region, a pair of doublets, indicates two groups of equivalent protons. This pattern is possible only if the two substituents are attached to the 1- and 4-positions of the

TABLE 21.9 Interpreted data from ^{1}H NMR spectrum (200 MHz) of $C_{10}H_{12}O$

Chemical shift (ppm)	^{1}H type	Integration	Splitting pattern	Possible structure fragment(s)
1.25	C—C—**H**	3	Triplet	CH_3CH_2—
2.58	O=C—C—**H** or Ar—C—**H** or C=C—C—**H**	3	Singlet	CH_3—C=O or CH_3—Ar or CH_3—C=C
2.70	O=C—C—**H** or Ar—C—**H** or C=C—C—**H**	2	Quartet	CH_3CH_2C=O or CH_3CH_2—Ar or CH_3CH_2—C=C
7.28	Ar—**H**	2	Doublet	
7.88	Ar—**H**	2	Doublet	

benzene ring (*para* substitution). Several ***signature patterns*** are observed in NMR spectra, and a pair of symmetrical doublets in the aromatic region is one of the more frequently encountered ones.



1,4 disubstitution with two types of aromatic protons

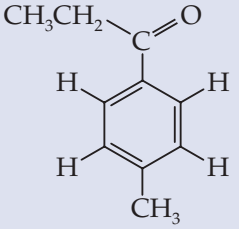
Possible structure fragments. The three-proton triplet at 1.25 ppm and two-proton quartet at 2.70 ppm are a signature pattern, which indicates an ethyl group. The 2.70-ppm chemical shift of the two-proton quartet indicates the environment of the methylene protons, suggesting that the ethyl group could be a part of three possible structure fragments:

$$CH_3CH_2C{=}O \quad CH_3CH_2Ar \quad CH_3CH_2C{=}C$$

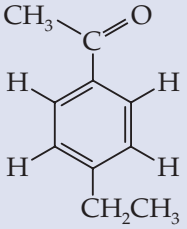
A decision to eliminate one of these possibilities can be made reasonably easily. The compound has the molecular formula $C_{10}H_{12}O$. The benzene ring has six carbons, and the third structure fragment has four carbon atoms. It leaves no room for the methyl group appearing at 2.58 ppm, and there is no indication how the oxygen atom could be incorporated in the structure. Therefore, the only viable structure fragment options for the ethyl group are $CH_3CH_2C{=}O$ and $CH_3CH_2{-}Ar$.

The only NMR signal left to analyze is the methyl group at 2.58 ppm, which must be in one of two possible structure fragments, $CH_3C{=}O$ or CH_3Ar. To summarize, $C_{10}H_{12}O$ includes a methyl group ($CH_3{-}$), an ethyl group ($CH_3CH_2{-}$), and a *para*-disubstituted benzene ring (C_6H_4). The atom count in the fragments is nine carbon atoms and twelve hydrogen atoms, leaving only one carbon atom and one oxygen atom to be accounted for. Because one more double-bond equivalent is required, the last fragment for the molecule is a carbonyl group, which is also consistent with the possible structure fragments.

Possible structures. Two possible structures are consistent with the data: 4′-methylphenyl-1-propanone and 4′-ethylphenyl-1-ethanone.



4′-Methylphenyl-1-propanone



4′-Ethylphenyl-1-ethanone

FOLLOW-UP ASSIGNMENT

To discover which of the two structures is more likely, it is necessary to calculate the estimated chemical shifts for both structures, using Tables 21.3 and 21.4. Carry out these calculations and decide which structure is more likely for the compound.

21.12 Advanced Topics in ^{1}H NMR

Second-Order Effects

Observed splitting patterns may differ from patterns predicted by simple coupling rules as a result of ***second-order effects.*** As the chemical shifts of the coupled protons become closer to one another, second-order effects become more pronounced. The usual rule of thumb is that they become apparent in a spectrum when the difference in chemical shifts ($\Delta\nu$, measured in Hz) is less than five times the coupling constant ($\Delta\nu < 5J$).

Consequences of second-order effects. Large second-order effects produce the following:

- Signal intensities that are different from predicted values
- Additional signals beyond those predicted by simple splitting rules
- Coupling constants that cannot be directly measured from differences in signal positions

When the second-order effects are small, they can be useful, such as when the differences in signal intensities produce "leaning" peaks, which indicate the relative position of a coupling partner. Look back at the quartet signal at 2.32 ppm in the 200-MHz NMR spectrum of ethyl propanoate (Figure 21.10, page 325) for an example of "leaning" peaks. The pattern is not perfectly symmetrical. The right-hand peaks are slightly higher than those on the left, an indication that these protons are coupled with protons whose signals appear to the right of that pattern. In this case, the coupling partner appears at 1.15 ppm. Notice that the signal at 1.15 ppm is "leaning" to the left because its coupling partner appears downfield.

Complexities produced by second-order effects. Examine the expanded sections of the 60-MHz and 360-MHz spectra of cinnamyl alcohol, which show the vinyl proton regions (Figure 21.35). On the 360-MHz NMR spectrum (Figure 21.35b), the individual vinyl protons appear as well-defined signals at 6.3 ppm and 6.6 ppm, separated by 100 Hz (0.28 ppm $\times$ 360 MHz); the coupling constant is 15.9 Hz. On a 60-MHz instrument these signals are separated by only 17 Hz (0.28 ppm $\times$ 60 MHz) and the coupling constant is again 15.9 Hz. When the difference in chemical shifts is nearly the same as the coupling constant between two protons, the NMR spectrum is almost useless for any analysis of NMR splitting.

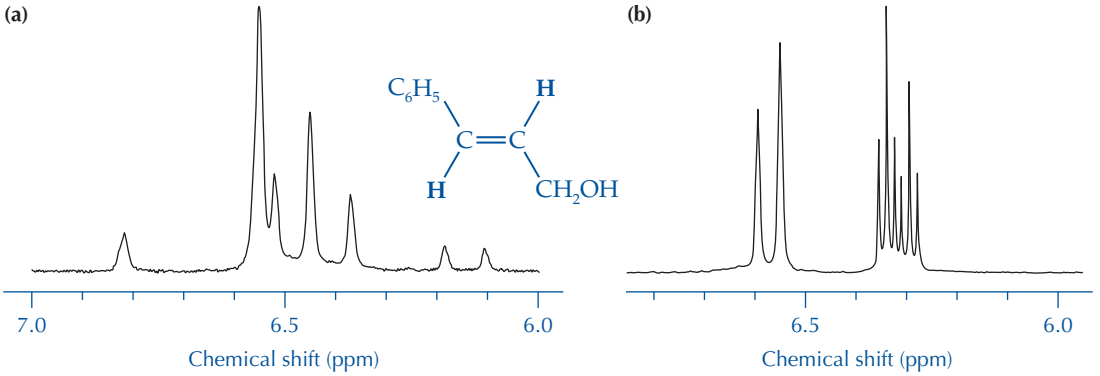


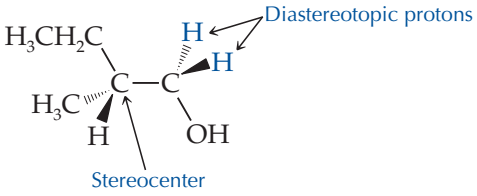
FIGURE 21.35 ^{1}H NMR spectra of the vinyl protons of cinnamyl alcohol at **(a)** 60 MHz and **(b)** 360 MHz

Even the 360-MHz spectrum exhibits small second-order effects. The patterns at 6.3 ppm and 6.6 ppm lean toward each other. In other words, the upfield portion of the 6.6-ppm signal and the downfield portion of the 6.3-ppm signal are larger than the other parts of the two patterns. On higher-field instruments, the frequency difference between signals is even larger, so that second-order effects, in many cases, become negligible.

Diastereotopic Protons

Subtle structural differences between protons in a molecule may not be obvious at first glance, which can be a source of confusion. For example, it is easy to assume that the two protons of a methylene group are always equivalent, and in most cases they are. However, if the methylene group is next to a stereocenter, such as an asymmetric carbon atom, the two protons of the methylene group become nonequivalent. They cannot be interchanged with one another by any bond rotation or symmetry operation, and they are said to be ***diastereotopic.*** They have different chemical shifts, and they also couple with each other. The appearance of diastereotopic protons is common in the NMR spectra of chiral molecules, those with stereocenters.

Consider the compound 2-methyl-1-butanol:



2-Methyl-1-butanol

If there is no coupling to the hydroxyl proton, you might expect the NMR signal for the adjacent methylene protons to appear as a doublet because of coupling with the vicinal methine proton. However, the protons of the methylene group are diastereotopic, which makes the NMR spectrum of 2-methyl-1-butanol much more complex.

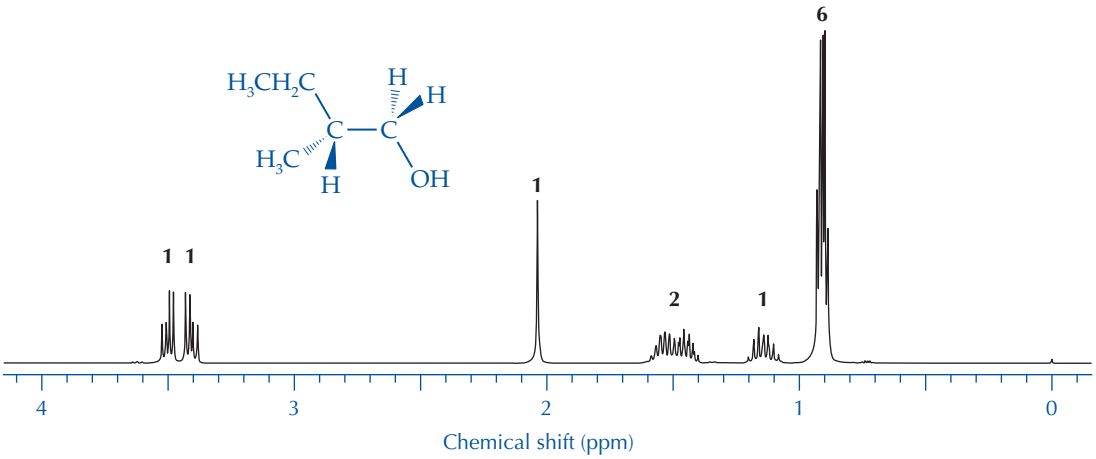


FIGURE 21.36 ^{1}H NMR spectrum of 2-methyl-1-butanol at 360 MHz.

The spectrum shown in Figure 21.36 reveals an eight-line pattern for the methylene group of 2-methyl-1-butanol. The chemical shifts of the C-1 methylene protons are 3.4 ppm and 3.5 ppm. Because these two protons are not identical, they couple with each other, and each of the diastereotopic protons becomes a doublet of doublets. An expanded view of the C-1 methylene signals is shown in Figure 21.37. The coupling constants in one four-line set are

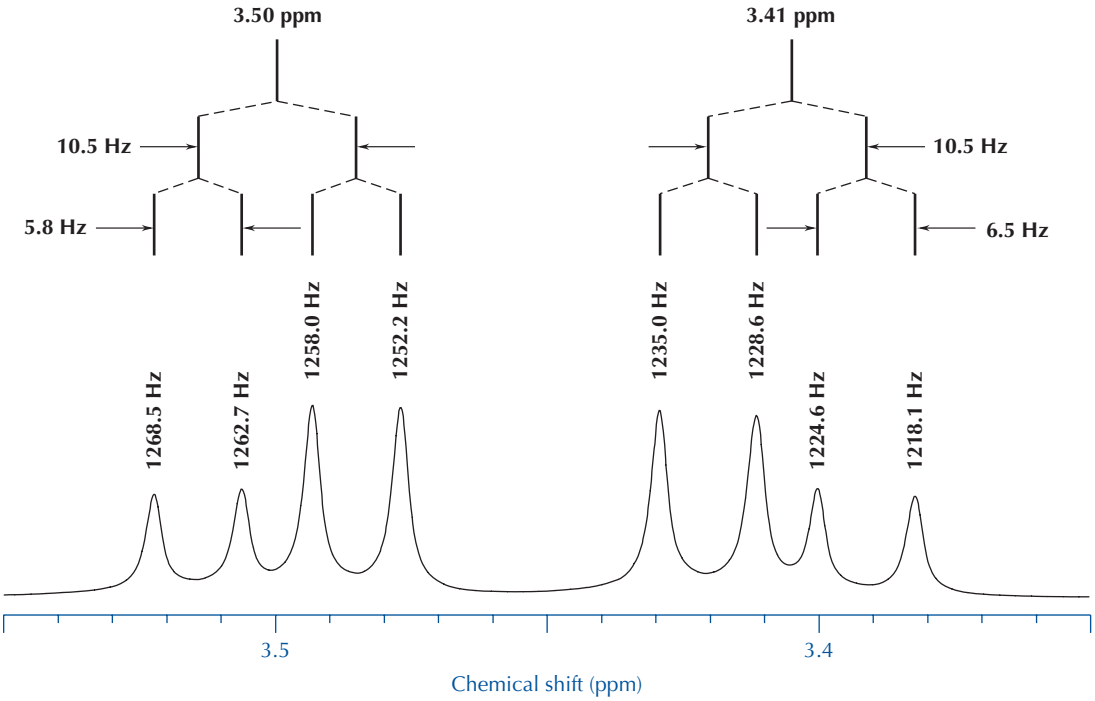


FIGURE 21.37 Splitting tree for the diastereotopic protons of 2-methyl-1-butanol.

6.5 Hz and 10.5 Hz, and the coupling constants for the other set are 5.8 Hz and 10.5 Hz. Notice that the two halves of the eight-line pattern in Figure 21.37 lean into each other. This leaning makes the central lines more intense than the outside lines, even though the splitting tree for this pattern shows equal intensities for all the lines. Use of a higher field NMR instrument for the spectrum would make all eight lines closer to equal intensity. The methylene protons of the ethyl group attached to the stereocenter are also diastereotopic, but the pattern is not distinct enough to analyze accurately.

Further Reading

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Questions

1. Given the ^{1}H NMR spectrum and molecular formula for each of the following compounds, deduce the structure of the compound, estimate the chemical shifts of all its protons using the parameters in Tables 21.3–21.5, and assign the NMR signals to their respective protons.
   a. $C_5H_{11}Cl$; ^{1}H NMR ($CDCl_3$): δ 3.33 (2H, s); 1.10 (9H, s)
   b. $C_5H_{10}O_2$; ^{1}H NMR ($CDCl_3$): δ 3.88 (1H, s); 2.25 (3H, s); 1.40 (6H, s)
   c. $C_6H_{12}O_2$; ^{1}H NMR ($CDCl_3$): δ 3.83 (1H, s); 2.63 (2H, s); 2.18 (3H, s); 1.26 (6H, s)
   d. $C_5H_{10}O$; ^{1}H NMR ($CDCl_3$): δ 9.77 (1H, t, J = 2 Hz); 2.31 (2H, dd, J = 2 Hz, J = 7 Hz); 2.21 (1H, m); 0.98 (6H, d, J = 7 Hz)
   e. C_4H_8O; ^{1}H NMR ($CDCl_3$): δ 5.90 (1H, ddd, J = 6, 10, 17 Hz); 5.19 (1H, d, J = 17 Hz); 5.06 (1H, d, J = 10 Hz); 4.30 (1 H, quintet); 2.50 (1H, bs); 1.27 (3H, d, J = 6 Hz)
2. The ^{1}H NMR spectrum of a compound of molecular formula $C_5H_8O_2$ is shown in Figure 21.38. Deduce the structure of the compound and assign its NMR signals.
3. A compound of molecular formula C_3H_8O produces the ^{1}H NMR spectrum shown in Figure 21.39. In addition, when this compound is treated with D_2O, the ^{1}H NMR signal at 2.0 disappears and another signal at 4.6 ppm appears. Moreover, when the C_3H_8O compound is highly purified and care is taken to remove all traces of acid in the NMR solvent, the singlet at 2.0 ppm is replaced by a doublet. Finally, the chemical shift of the 2.0-ppm signal is highly concentration dependent; an increase in the concentration of C_3H_8O in the NMR sample results in a downfield shift of this signal. Deduce the structure of C_3H_8O, assign its NMR signals, and explain the changes observed for the 2.0-ppm signal. Estimate the chemical shifts of the different types of protons using the parameters in Figure 21.12 and Table 21.3; compare them with those measured from the spectrum.

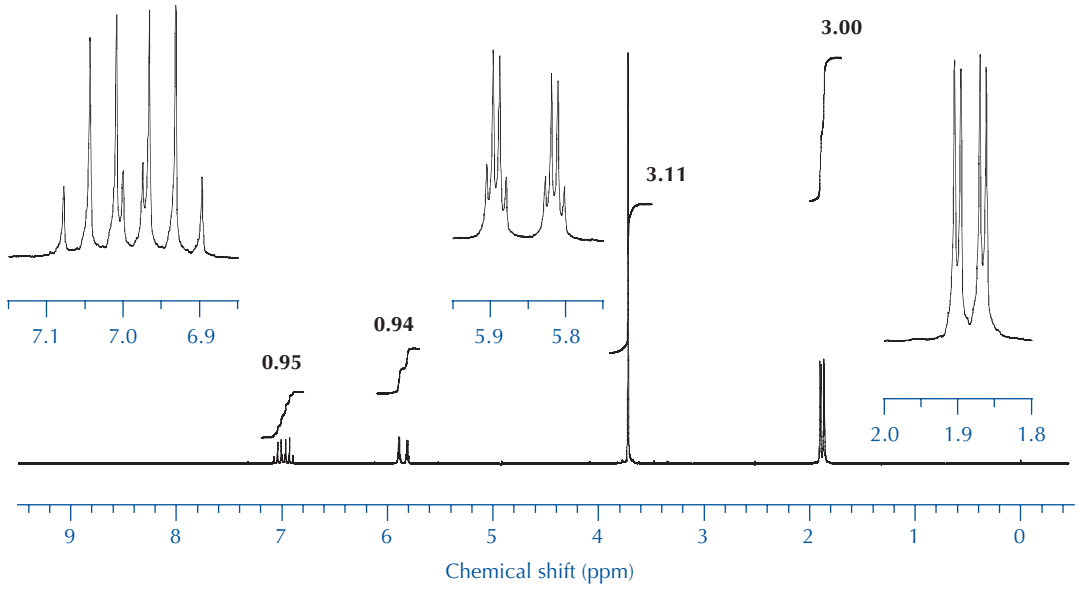


FIGURE 21.38 200-MHz ^{1}H NMR spectrum of a compound of molecular formula $C_5H_8O_2$.

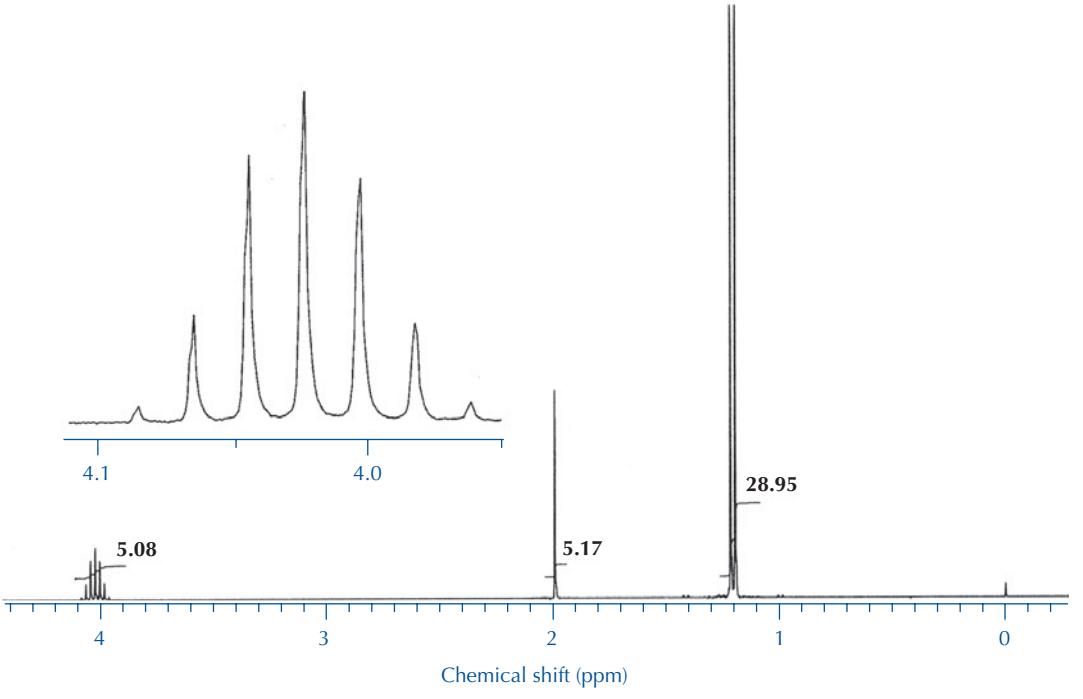


FIGURE 21.39 300-MHz ^{1}H NMR spectrum of a compound of molecular formula C_3H_8O.

4. In solution, dimedone (5,5-dimethylcyclohexan-1,3-dione) is a mixture of keto and enol isomers. The ^{1}H NMR spectrum of a solution of dimedone in $CDCl_3$ is shown in Figure 21.40. In the sample, the two enol isomers are equilibrating very fast compared with the NMR time scale. Assign all the NMR signals and use NMR

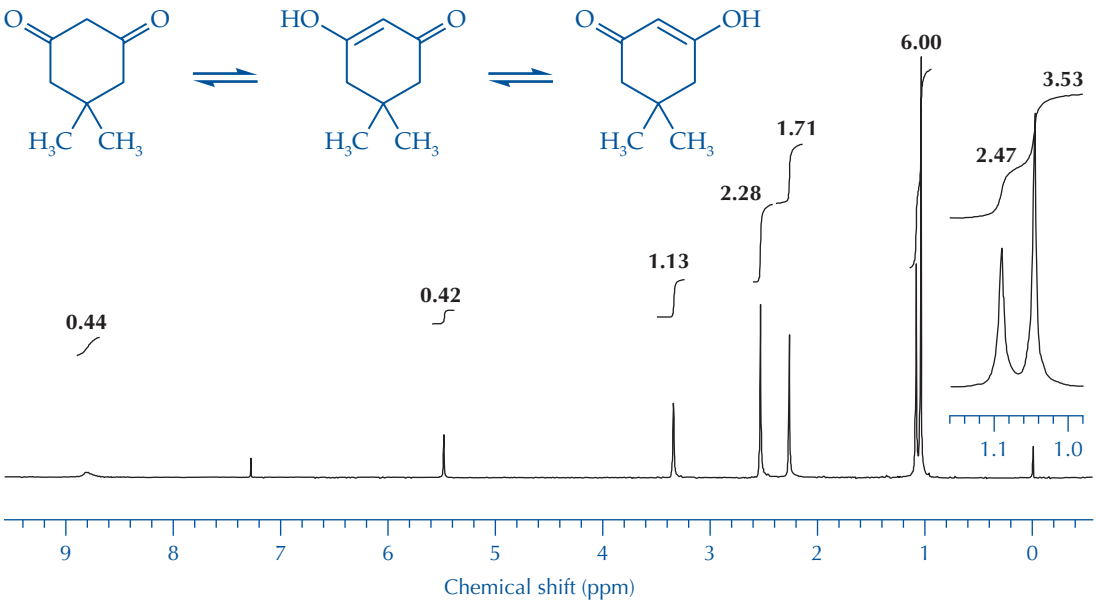


FIGURE 21.40 200-MHz ^{1}H NMR spectrum of 5,5-dimethylcyclohexan-1,3-dione.

integrations to determine the composition of the keto/enol mixture.

5. A compound of molecular formula $C_8H_{14}O$ produces the ^{1}H NMR spectrum shown in Figure 21.41. Its infrared spectrum shows a strong carbonyl stretching peak, which indicates that $C_8H_{14}O$ is either an aldehyde or a ketone. Deduce the structure of the compound, estimate the chemical shifts of the different types of protons using the parameters in Tables 21.3–21.5, and assign all the NMR signals.

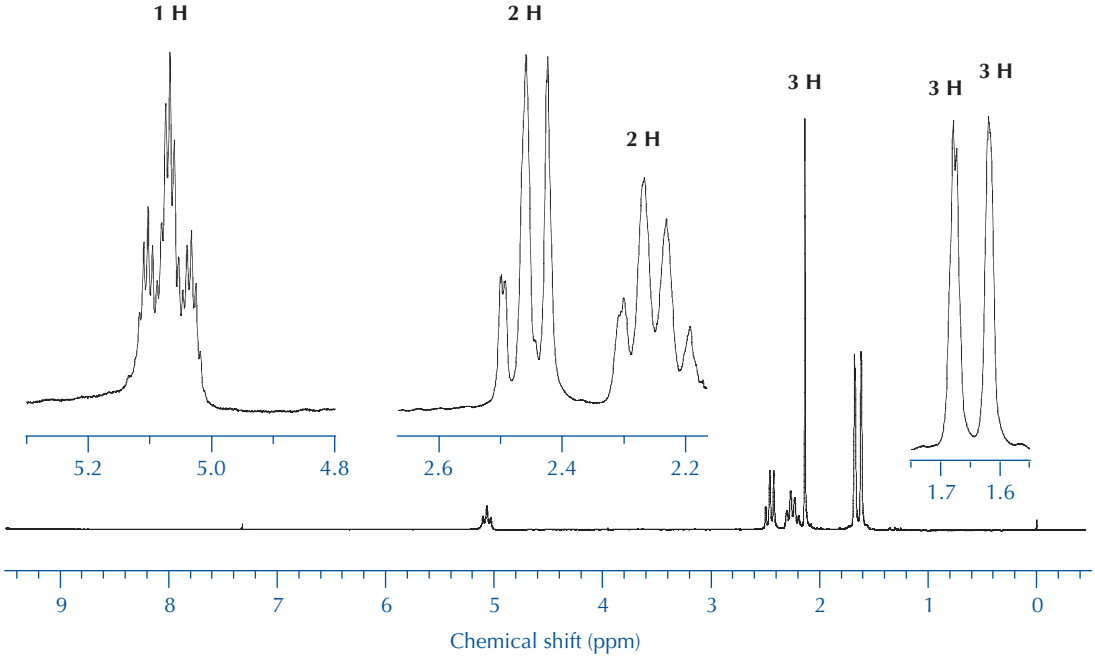


FIGURE 21.41 200-MHz ^{1}H NMR spectrum of a compound of molecular formula $C_8H_{14}O$.

TECHNIQUE

22 ^{13}C AND TWO-DIMENSIONAL NMR SPECTROSCOPY

If Technique 22 is your introduction to spectroscopic analysis, read the Essay "The Spectroscopic Revolution" on pages 275–276 before you read Technique 22.

NMR topics have already been discussed in some detail in Technique 21, which focused on ^{1}H NMR. A brief summary of NMR information that can be gleaned from a ^{1}H NMR spectrum can be found in Technique 21.4. ^{13}C NMR has many similarities to ^{1}H NMR, but there are a few important differences.

^{13}C NMR gives direct evidence about the carbon skeleton of an organic molecule, so you might think that it would be the favored NMR technique for determination of molecular structures. In part, the reason ^{1}H NMR receives more attention in organic chemistry textbooks is historical. ^{1}H NMR spectroscopy was developed first. Carbon NMR became a useful and routine tool only when pulsed Fourier transform (FT) instrumentation was developed in the 1970s and 1980s. Most modern NMR spectrometers are equipped with both ^{1}H and ^{13}C probes, and chemists routinely obtain both types of spectra. The ^{13}C NMR technique is becoming much more important.

The magnetically active isotope of carbon, ^{13}C, is only 1.1% as abundant in nature as ^{12}C. Thus, the signal from carbon is extremely weak because very few of the carbon atoms present in a compound provide a signal. In addition, ^{13}C nuclei are much less sensitive than ^{1}H nuclei. An inherent property of the ^{13}C nucleus, called the ***gyromagnetic ratio***, is only one-fourth the gyromagnetic ratio for ^{1}H. Because the inherent NMR sensitivity depends on the cube of the gyromagnetic ratio, the sensitivity of ^{13}C NMR relative to ^{1}H NMR is only $(0.25)^3$, or 0.016. This difference in the gyromagnetic ratio also explains why an instrument built to analyze protons at 300 MHz operates at 75 MHz, or one-fourth the frequency, for ^{13}C nuclei. The lower frequency in ^{13}C NMR usually presents no problems, however, since carbon shifts occur over a 200-ppm range. Overlapping signals are not a significant problem.

The use of pulsed FT NMR spectrometers allows NMR spectra to be acquired rapidly. By pulsing many times and adding together the NMR signals, the signals from the sample accumulate in a constructive fashion. The signal-to-noise ratio is proportional to the square root of the number of pulse sequences. Very good ^{13}C NMR spectra with a high signal-to-noise ratio can be obtained routinely with 25–50 mg of compound, using a modern high-field FT NMR instrument and a suitable number of pulses.

22.1 ^{13}C NMR Spectra

Samples are prepared for ^{13}C NMR much as they are for ^{1}H NMR [see Technique 21.2]. Table 21.1 (page 320) lists the suitable solvents and their ^{13}C chemical shifts. As is the case for ^{1}H NMR, the primary

standard for the ^{13}C NMR chemical shift scale is tetramethylsilane ($(CH_3)_4Si$, TMS), which is set at 0.0 ppm. TMS absorbs at a magnetic field in which few other carbon atoms in typical organic compounds absorb.

Solvent Peaks and Multiplicities

Deuterated chloroform ($CDCl_3$) has been the solvent of choice because it dissolves most organic compounds and is relatively inexpensive. Of course, each molecule of $CDCl_3$ has a carbon atom. **The solvent signal for $CDCl_3$ always appears at 77.0 ppm in a ^{13}C NMR spectrum.** The triplet signal of $CDCl_3$ can be used as an internal reference point for the chemical shifts of the sample signals, and it is often unnecessary to add a reference material, such as TMS, to the sample.

The spin multiplicity of ^{13}C is the same as that of hydrogen (^1H); thus the same splitting rules apply. For example, the ^{13}C signal of a methine group (C—H) will be split into a doublet by the attached proton. Unlike ^1H, however, a deuterium nucleus (^2H) has a spin of 1. Therefore, the ^{13}C signal of $CDCl_3$ is always a characteristic triplet in which the three lines have equal height.

Recently, in an effort to reduce the use of halogenated solvents in the organic chemistry laboratory, deuterated acetone has become more common as an NMR solvent. Each molecule of acetone has two different carbons, a carbonyl carbon that appears at 206 ppm and a methyl carbon at 29.8 ppm. The carbonyl carbon is well removed from most signals, except other ketone carbonyl carbon atoms, and appears as a singlet. Because each methyl carbon of deuterated acetone has three deuterium atoms attached, it appears as a seven-line pattern.

Spin-Spin Splitting

As with ^1H NMR, spin interactions in ^{13}C NMR are transmitted through the bonding framework of molecules. They are usually observable only when the interacting nuclei are near each other. When protons are directly attached to a ^{13}C atom, the ^{13}C—H coupling constants are very large—on the order of 150 Hz. Coupling between adjacent carbon nuclei is not observed because the probability that two attached carbons will both be ^{13}C is extremely small, about 1 in 10,000. The splitting of signals in a ^{13}C NMR spectrum can be used to identify the number of protons attached to a carbon atom. A methyl carbon signal appears as a quartet, a methylene signal appears as a triplet, a methine signal appears as a doublet, and a quaternary-carbon signal appears as a singlet.

The ^{13}C spectrum of ethyl *trans*-2-butenoate shown in Figure 22.1 demonstrates these splitting patterns clearly. The carbonyl carbon at 166 ppm is a singlet because it has no attached protons. The alkene carbons at 144 ppm and 123 ppm are doublets because each one has only one attached proton. The signal at 60 ppm, produced by the methylene group attached to oxygen, appears as a triplet because it has two attached protons. The complex pattern of signals between 12 and 20 ppm is two overlapping quartets due to the two methyl groups.

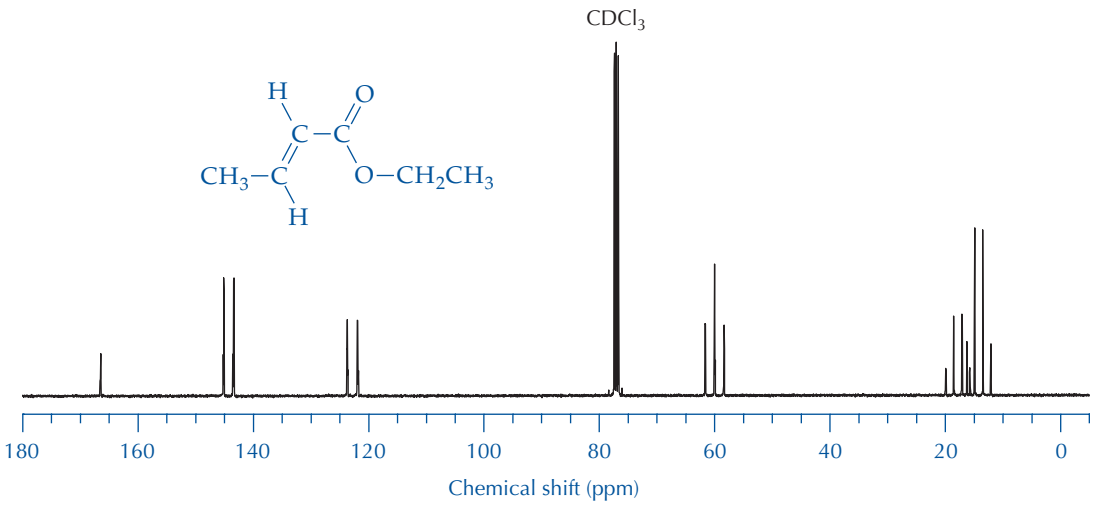


FIGURE 22.1 90-MHz ^{13}C NMR spectrum of ethyl *trans*-2-butenoate in $CDCl_3$.

Broadband Decoupling

In molecules containing many carbon atoms, the coupled ^{13}C spectrum can become extremely complex because of multiple overlapping splitting patterns and are often almost impossible to interpret. The usual practice is to avoid this complexity by a technique called ***broadband decoupling.*** Irradiation of the sample with a broad band of energy during data acquisition decouples ^{13}C from ^{1}H nuclei and collapses the ^{13}C multiplets to singlets. The decoupled spectrum of ethyl *trans*-2-butenoate shown in Figure 22.2 consists of six sharp signals at 14, 18, 60, 123, 144, and 166 ppm, corresponding to the six different carbon nuclei in the molecule.

In addition to simplifying the spectrum, broadband decoupling enhances the signal-to-noise ratio and reduces the acquisition time

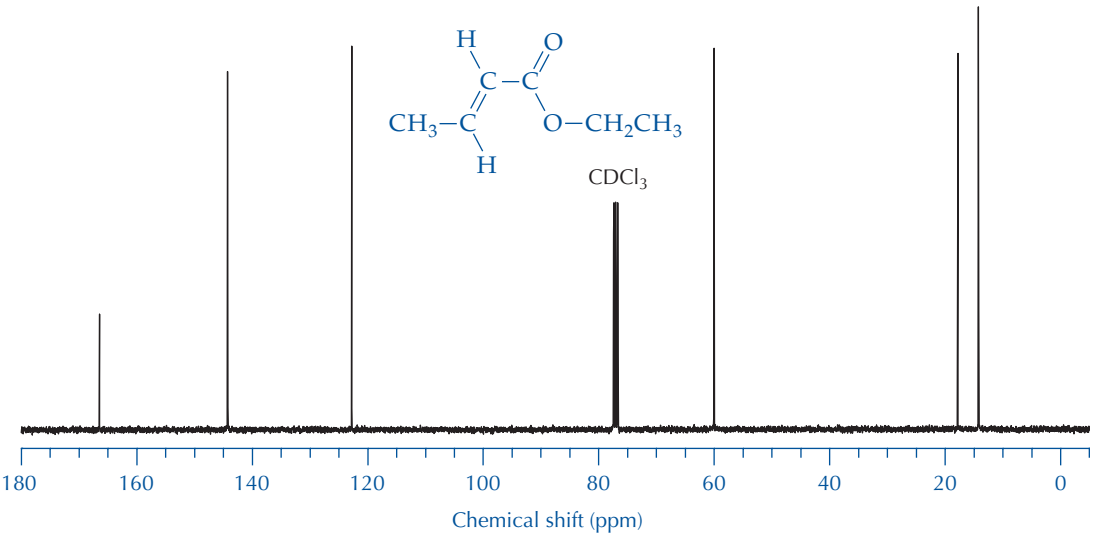


FIGURE 22.2 Broadband-decoupled 90-MHz ^{13}C NMR spectrum of ethyl *trans*-2-butenoate in $CDCl_3$.

dramatically. The coupled spectrum of ethyl *trans*-2-butenoate (Figure 22.1) was acquired in 15,000 scans (overnight); the decoupled spectrum of the same sample (Figure 22.2) was acquired in 450 scans (approximately 20 min).

In both Figure 22.1 and Figure 22.2, the signal at 166 ppm is much smaller than the other five signals for ethyl *trans*-2-butenoate. This is a general phenomenon. Peak areas for different carbon signals vary greatly, and quantitative ^{13}C integration is not easily accomplished. Excited ^{13}C NMR nuclei relax back to lower-energy spin states at a slow rate. Because many scans are necessary to produce adequate signal-to-noise ratios in ^{13}C spectra, the time between scans is generally set at too short a time for complete relaxation to occur. In addition, the sizes of ^{13}C signals also vary due to the nuclear Overhauser enhancement. Integrals of routine ^{13}C spectra are generally unreliable.

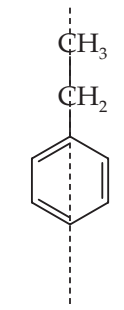
Nuclear Overhauser Enhancement

The size of a ^{13}C signal is influenced significantly by its close proximity to protons, a phenomenon termed the ***nuclear Overhauser enhancement (NOE).*** The NOE effect can produce up to a fourfold increase in the NMR signal intensity of a ^{13}C nucleus when the resonance of nearby coupled protons is perturbed by broadband decoupling. This effect helps to explain why the signals of different types of carbon atoms, such as methyl, methylene, and methine carbons, can have much greater signal amplitudes than the relatively low intensity observed for quaternary carbons.

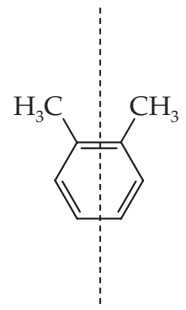
Symmetry and the Number of ^{13}C Signals

The number of signals in a ^{13}C NMR spectrum of a pure compound indicates the number of different types of carbon atoms in the molecule. If the number of signals is less than the number of carbon atoms in the molecule, there is probably some element of symmetry, which makes some of the carbon atoms equivalent to one another. Symmetry elements, which include mirror planes and axes of rotation, can be used advantageously to select a structure from several possibilities.

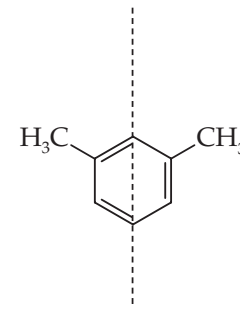
Consider an aromatic compound with the molecular formula C_8H_{10}. There are four possible structures that are consistent with this formula: ethylbenzene, 1,2-dimethylbenzene, 1,3-dimethylbenzene, and 1,4-dimethylbenzene. Each structure possesses at least one plane of symmetry, and 1,4-dimethylbenzene has two planes of symmetry.



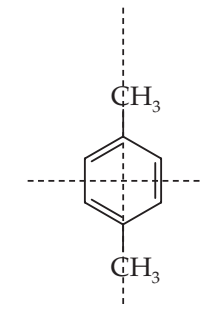
Ethylbenzene



1,2-Dimethylbenzene



1,3-Dimethylbenzene



1,4-Dimethylbenzene

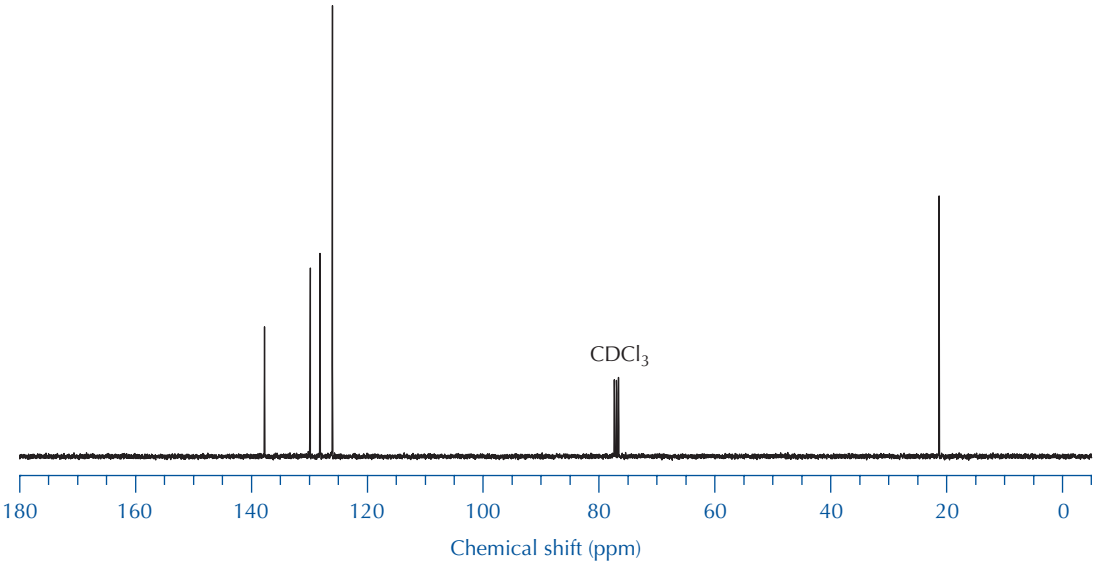


FIGURE 22.3 Broadband-decoupled 90-MHz ^{13}C NMR spectrum of an aromatic compound with molecular formula C_8H_{10} in $CDCl_3$.

Each of these compounds contains a different number of nonequivalent carbon atoms: ethylbenzene has six, 1,2-dimethylbenzene has four, 1,3-dimethylbenzene has five, and 1,4-dimethylbenzene has three. Ethylbenzene is unique because it has two ^{13}C signals in the alkyl region, whereas each of the dimethylbenzenes has only one signal upfield. Obtaining the ^{13}C NMR spectrum and counting the number of signals can determine the structure of the compound.

EXERCISE

The ^{13}C NMR spectrum of an aromatic compound with the molecular formula C_8H_{10} is shown in Figure 22.3. What is the structure of the compound?

Answer: The ^{13}C NMR spectrum shows one upfield signal due to the carbon atoms of two identical methyl groups and four signals due to the carbon atoms in the aromatic ring. The compound that produces these five signals in the ^{13}C spectrum is 1,3-dimethylbenzene.

Summary and a Look Ahead

A typical interpretation of a simple ^{13}C NMR spectrum relies on only two kinds of information—the number of different carbon signals in the spectrum and the positions of these signals along the horizontal axis (chemical shifts). Integration of ^{13}C signals and spin-spin coupling have little importance in the interpretation. However, the use of complex pulse sequences for ^{13}C NMR allows the determination of the number of protons on carbon atoms [Technique 22.4] as well as the use of spin-spin coupling to establish the connectivity of carbon atoms within a molecule [Technique 22.6]. Techniques 22.2 and 22.3 explore the topic of ^{13}C chemical shifts in some detail.

22.2 ^{13}C Chemical Shifts

The chemical shifts for carbon atoms are affected by electronegativity and anisotropy in ways similar to ^{1}H NMR [see Technique 21, Introduction and section 21.7]. Figure 22.4 and Table 22.1 reveal the same kind of chemical shift trends that occur in ^{1}H NMR spectroscopy. In addition, sp^2 and sp hybridization of a ^{13}C carbon nucleus have a strong deshielding effect.

Alkyl Substitution Effects

Carbon atoms of alkanes appear in the upfield region of the NMR spectrum, from approximately 5–40 ppm. This upfield region can be further refined into regions for methyl, methylene, methine, and quaternary carbons, but considerable overlap occurs. In similarly substituted molecules, increasing the substitution decreases shielding and causes the chemical shift of a carbon atom to increase.

$\mathbf{C}H_4$	$CH_3\mathbf{C}H_3$	$(CH_3)_2\mathbf{C}H_2$	$(CH_3)_3\mathbf{C}H$	$(CH_3)_4\mathbf{C}$
−2.3 ppm	7.3 ppm	15.9 ppm	25.0 ppm	27.7 ppm

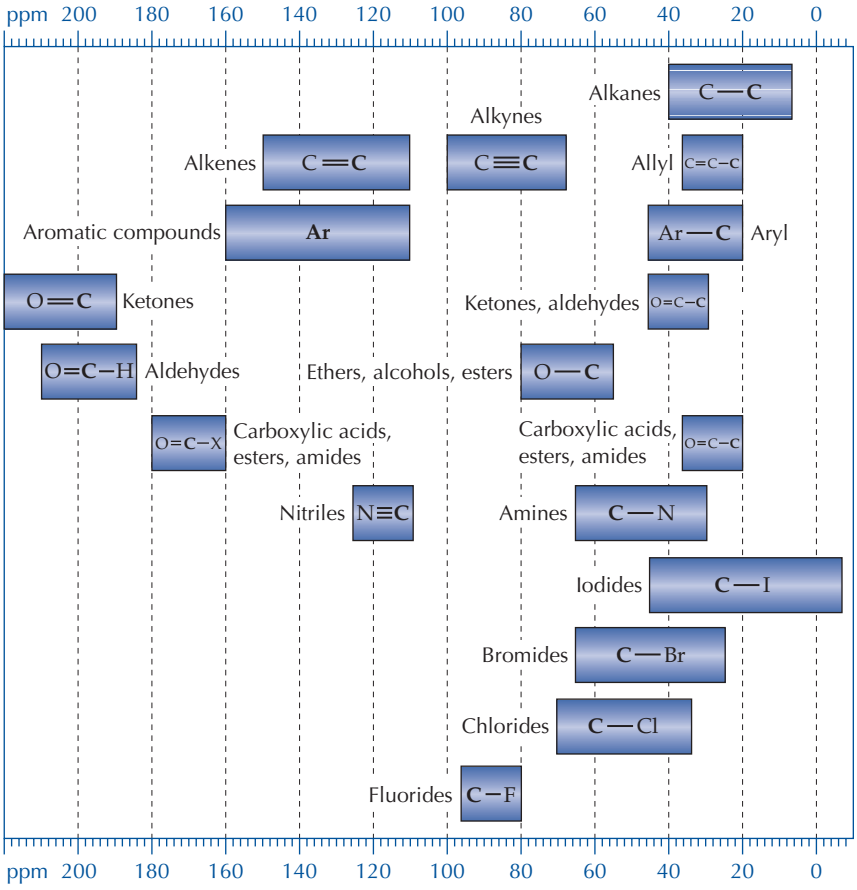


FIGURE 22.4 Approximate regions of ^{13}C chemical shifts for different types of carbon atoms in organic compounds.

TABLE 22.1 Characteristic ^{13}C NMR chemical shifts in $CDCl_3$

Compound	Chemical shift (ppm)
TMS	0.0
CDCl_3 (t)	77
Alkane (C—**C**H_3)	7–30
Alkane (C—**C**H_2)	15–40
Alkane (C—**C**H) and (C—**C**)	15–40
Carboxylic acids, esters, and amides (**C**—C═O)	20–35
Allyl (**C**—C═C)	20–35
Arene (**C**—Ar)	20–45
Ketones, aldehydes (**C**—C═O)	30–45
Amines (**C**—N)	30–65
Iodides (**C**—I)	−5–45
Bromides (**C**—Br)	25–65
Chlorides (**C**—Cl)	35–70
Fluorides (**C**—F)	80–95
Alcohols (**C**—OH), ethers (**C**—OR), esters (**C**—O[C═O]R)	55–80
Alkyne (**C**≡C)	70–100
Alkene (**C**═C)	110–150
Aromatic	110–160
Nitriles (**C**≡N)	110–125
Carboxylic acids, esters, and amides (**C**═O)	160–180
Aldehydes (**C**═O)	185–210
Ketones (**C**═O)	190–220

Electronegativity. Signals of ^{13}C atoms that are in close proximity to electronegative atoms are moved downfield by diamagnetic deshielding [see Technique 21.7]. Carbon atoms attached to electronegative atoms usually appear in the region 30–90 ppm. If the carbon is attached to an oxygen atom of an alcohol, ether, or ester, the typical range of the chemical shift is 55–80 ppm.

The periodic trends seen in the electronegativities (χ) of elements are mirrored in the chemical shifts of the carbons attached to these elements. Strongly electronegative halogens deshield carbon, but as the halogen atoms increase in atomic number, the deshielding of nearby carbon atoms is attenuated considerably.

	CH_3—I	**C**H_3—Br	**C**H_3—Cl	**C**H_3—F
δ	−24.0 ppm	9.6 ppm	25.6 ppm	71.6 ppm
χ	2.66	2.96	3.16	3.98

Iodomethane has a ^{13}C chemical shift of −24 ppm, which is more than 20 ppm *upfield* of methane. This shielding effect has been attributed to "steric compression;" steric factors apparently cause the electrons in the orbitals of the carbon atom to become compacted into a smaller volume closer to the nucleus, thus making the nucleus more highly shielded.

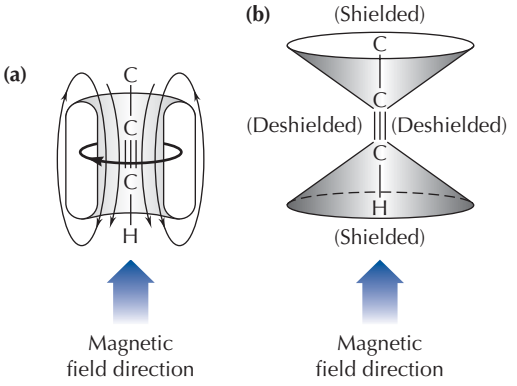


FIGURE 22.5
Two representations of the regions of shielding and deshielding for an alkyne.

Anisotropy. As with ^{1}H NMR, anisotropic effects influence the chemical shifts of alkyl ^{13}C nuclei adjacent to multiple bonds [see Technique 21.7]. Consider a comparison of the chemical shifts of a C-3 of pentane with those of 1-pentene and 1-pentyne.

$CH_3CH_2\mathbf{C}H_2CH_2CH_3$	$CH_2{=}CH\mathbf{C}H_2CH_2CH_3$	$HC{\equiv}C\mathbf{C}H_2CH_2CH_3$
34.6 ppm	36.2 ppm	20.1 ppm

C-3 is in the shielding cone of the C≡C of 1-pentyne and its chemical shift is decreased by approximately 15 ppm (Figure 22.5).

By contrast, the C-3 of an alkene is in the plane of the double bond, a deshielded region of the molecule (Figure 22.6). The chemical shift is increased slightly relative to the alkane. The six π-electrons of an aromatic ring produce a stronger anisotropic effect than that found with simple alkenes.

The anisotropic effect can also be seen with alkyl carbon atoms adjacent to carbonyl groups, which are deshielded somewhat compared to carbons attached to the carbon of a C—O bond. The carbon atom α to the carbonyl group in 4-heptanone appears at 45.0 ppm, 5 ppm downfield from the carbon α to the C—OH group in 4-heptanol.

$CH_3CH_2\mathbf{C}H_2CH(OH)CH_2CH_2CH_3$	$CH_3CH_2\mathbf{C}H_2C(=O)CH_2CH_2CH_3$
40.0 ppm	45.0 ppm

Hybridization. The hybridization of a carbon atom has a dramatic effect on its chemical shift. Whereas sp^3 carbons of alkanes appear in

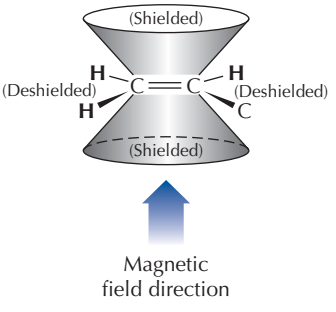


FIGURE 22.6
Regions of shielding and deshielding in an alkene.

the region 5–40 ppm, the *sp* carbon atoms of alkynes appear in the range 70–100 ppm, and the sp^2 carbon atoms of alkenes appear in the range 110–150 ppm. The chemical shift region for aromatic carbon atoms overlaps the alkene region, extending from 125 to 160 ppm.

Additivity of Hybridization and Electronegativity Effects. The sp^2 carbon atom of a carbonyl (C═O) group is strongly deshielded because of its hybridization and because the carbon atom is directly attached to a strongly electronegative oxygen atom. Signals from carbonyl carbon atoms appear in the range 160–220 ppm. There are distinct differences in the shifts of carboxylic acids and their derivatives (amides and esters), which are in the range 160–180 ppm, compared with those of aldehydes and ketones, whose signals appear at 185–220 ppm. The difference is ascribed to the electron releasing effect of an additional heteroatom (O or N) attached to the carbonyl group. The chemical shift of a ketone is shifted approximately 5 ppm downfield relative to the chemical shift of a similar aldehyde. The chemical shifts of the carbonyl carbon atoms in butanal, 2-pentanone, and methyl butanoate are found in Table 22.2.

Conjugation. In conjugated systems, the π-electron density is distributed unevenly over an extended framework. The sp^2 carbons in the middle of a conjugated system are generally shielded more than the sp^2 carbons at its extremities.

Table 22.2 shows that with α,β-unsaturated carbonyl compounds, carbonyl carbon atoms are shielded more than is the case with their saturated analogs. Carbonyl carbon atoms attached to aromatic rings are shielded to approximately the same extent. The magnitude of the shielding is approximately 10 ppm.

The β-carbon atoms of α,β-unsaturated carbonyl compounds are more deshielded than the α-carbon atoms, as shown by the following resonance structures:

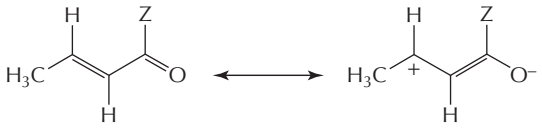
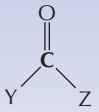


TABLE 22.2 The effects of carbonyl type and conjugation on ^{13}C chemical shifts of carbonyl carbon atoms



Group (Y)	Group (Z)	ppm
$CH_3CH_2CH_2$	H	203
CH_3CH═CH	H	193
$CH_3CH_2CH_2$	CH_3	207
CH_3CH═CH	CH_3	197
$CH_3CH_2CH_2$	OCH_3	174
CH_3CH═CH	OCH_3	167

Rings. The signals due to methylene carbons in saturated carbon rings are slightly shielded compared to the signals due to methylene carbons in acyclic compounds. In cyclopentanes and cyclohexanes, methylene carbons typically appear near 26–27 ppm, compared to 29–30 ppm for acyclic compounds.

Cyclopropanes are unique in that the σ-bonding in three-membered rings has some π-orbital character, which produces an anisotropic effect and shielding above and below the plane of the ring. Chemical shifts of carbons in cyclopropane rings are approximately 32–33 ppm upfield from their acyclic counterparts.

Recognition of trends and characteristic regions enables one to glean a great deal of information about a compound's structure from its ^{13}C NMR spectrum. In general, however, only chemical shifts greater than 40 ppm can be correlated unambiguously to a specific functional group.

WORKED EXAMPLE

Using Table 22.1, the signals in the broadband-decoupled ^{13}C spectrum of ethyl *trans*-2-butenoate (Figure 22.2) can be assigned. The upfield signals at 14 and 18 ppm are due to the sp^3 carbons atoms of the two methyl groups The methylene group attached to the electronegative oxygen atom, whose signal is at 60 ppm, is more deshielded than the corresponding carbon atoms attached only to other carbon atoms. The signals due to the two alkene carbon atoms appear at 123 ppm and 144 ppm. C-2 is responsible for the 123-ppm signal and C-3 for the 144-ppm signal. Finally, the ^{13}C signal due to the carbonyl carbon of the ester functional group appears at 166 ppm.

Compilations of ^{13}C NMR signals from a vast number of compounds have been used to develop systematic methods for estimating chemical shifts. These methods take into account functional groups, types of bonding, and steric constraints, as well as more subtle factors. Technique 22.3 provides a condensed version of some of these methods.

22.3 Quantitative Estimation of ^{13}C Chemical Shifts

Signals for different types of ^{13}C atoms in a molecule appear in well-defined chemical shift regions, depending on their type of bonding and the proximity of nearby electronegative atoms (Table 22.1). However, you may have noticed in Technique 22.2 that the chemical shifts can cover a wide spectral range for apparently similar types of carbon atoms. This uncertainty produces an undesirable degree of ambiguity in assigning peaks in ^{13}C NMR spectra.

The estimated chemical shift of a ^{13}C nucleus can be calculated in a straightforward, additive way from the empirical correlations in Tables 22.3–22.7. Being able to add the individual effects of nearby

functional groups is extremely useful because it allows a reasonably accurate estimation of the chemical shifts for many of the carbon atoms in organic compounds. In general, calculations using these tables are accurate to within ±3%.

Chemical Shifts of Alkyl Carbons

As shown in Table 22.3, the chemical shift of methane (–2.3 ppm), with reference to TMS at 0.0 ppm, is used as the base value for alkyl ^{13}C atoms. Additive parameters are then added to this value to account for shielding effects of nearby substituents in the molecule.

Effects of nearby substituents. The effect of each nearby substituent is added to the base value to arrive at the chemical shift of a particular ^{13}C atom in a molecule. If the group is directly attached to the carbon atom, it is called an ***α (alpha) substituent.*** If the group is attached to a carbon atom once removed, it is a ***β (beta) substituent***. And if the group is attached to a carbon atom twice removed, it is a ***γ (gamma) substituent***.

The effect of an α substituent on the chemical shift of the proton is found by using a value from the first numerical column in Table 22.3, and the effect of β and γ groups are found in the second and third columns, respectively. When the substituent (Y) is farther away from the ^{13}C atom, its influence becomes smaller. The effect of a group

TABLE 22.3 Additive parameters for predicting NMR chemical shifts of alkyl carbon atoms in $CDCl_3$

Base value: $CH_4 = -2.3$ ppm

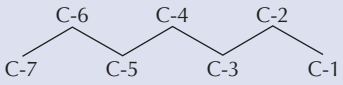
Group (Y)	alpha (α) C–Y	beta (β) C–C–Y	gamma (γ) C–C–C–Y
—C—(sp^3)	9.1	9.4	−2.5
—CH═CH_2	20.3	6.8	−2.6
—CH═CHR (*cis*)	13.4	6.9	−0.3
—CH═CHR (*trans*)	19.3	7.0	−0.3
—CH═CR_2	14.4	6.9	−0.3
—C_6H_5	22.5	8.9	−2.6
—C≡C—H	5.7	7.4	−2.0
—C≡C—R	4.7	7.7	−0.2
—OH	49.4	10.1	−6.3
—O(C═O)CH_3	50.9	5.9	−6.2
—OR	57.4	7.2	−5.9
—I	–6.8	10.9	−1.6
—Br	20.1	10.2	−3.9
—Cl	30.0	10.0	−4.6
—F	70.5	7.8	−6.9
—(C═O)OR	20.5	2.3	−2.9
—(C═O)OH	20.5	2.0	−2.9
—(C═O)H	30.3	4.8	−2.9
—(C═O)R	30.0	1.3	−2.7
—(C═O)C_6H_5	24.9	−0.4	−2.7

more than three carbon atoms away from the ^{13}C nucleus is small enough to be safely ignored.

Identifying α, β, and γ substituents. It is important in calculations of estimated chemical shifts to be systematic in methodology. A good way not to forget to include all α, β, and γ substituents for each type of carbon in a target molecule is to write down all the α groups first, then all the β groups, and finally the γ groups. Only then should you go to Table 22.3, look up the base value and the value for each α, β , and γ substituent from the correct column, and do the necessary addition.

EXERCISE

Identify the α, β , and γ substituents for carbon-4 of heptane.



Heptane

Answer: Carbon-4 has two α substituents, the methylene groups at C-3 and C-5. Carbon-4 also has two β substituents, the methylene groups at C-2 and C-6. In addition, carbon C-4 has two γ substituents, the two methyl groups C-1 and C-7.

Calculating estimated chemical shifts. Table 22.3 is laid out with carbon substituents at the top, followed by heteroatoms, the halogens and oxygen, and then by carbonyl substituents. To illustrate its use, let us assign the four peaks in the ^{13}C NMR spectrum of heptane, shown in Figure 22.7.

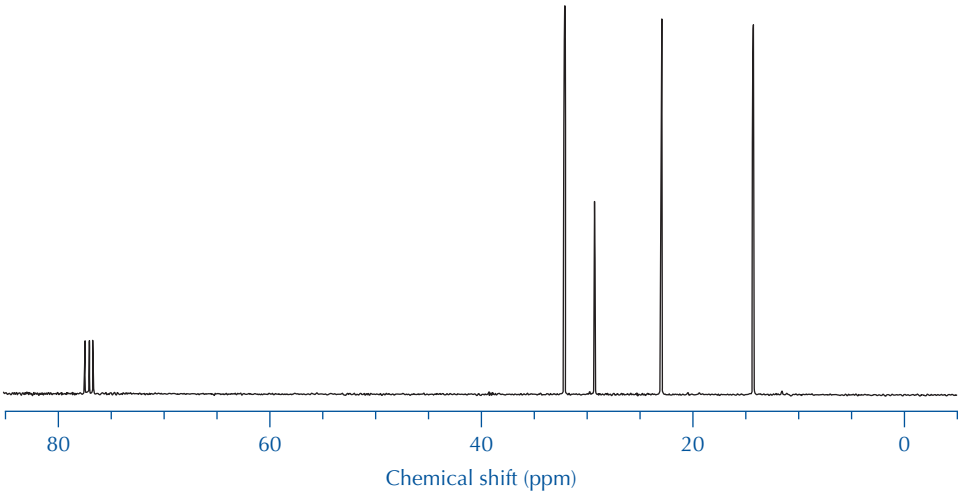


FIGURE 22.7 Broadband-decoupled 90-MHz ^{13}C NMR spectrum of heptane in $CDCl_3$.

WORKED EXAMPLE

In addition to the $CDCl_3$ triplet signal at 77.0 ppm, Figure 22.7 shows four nonequivalent kinds of carbon atoms, which fits with the symmetry of a heptane molecule. The four signals appear at 14.1 ppm, 22.8 ppm, 29.1 ppm, and 32.0 ppm. The two methyl carbons (C-1 and C-7) are affected by one α carbon, one β carbon, and one γ carbon. An sp^3 carbon substituent is the first entry in Table 22.3. Therefore, the calculated chemical shift for each methyl carbon is $-2.3 + 9.1 + 9.4 - 2.5 = 13.7$ ppm. This estimate compares to the measured chemical shift of 14.1 ppm, and we can be quite confident that the signal at 14.1 ppm is due to the methyl groups of heptane.

C-4 of heptane has two α carbon substituents, two β carbon substituents, and two γ carbon substituents. The calculated chemical shift for this carbon is $-2.3 + (2 \times 9.1) + (2 \times 9.4) + (2 \times -2.5) = 29.7$ ppm. This estimate compares favorably with the signal at 29.1 ppm in Figure 22.7.

FOLLOW-UP ASSIGNMENT

Two signals in Figure 22.7 remain to be assigned. Calculate the estimated chemical shifts for C-2 and C-3 of heptane and assign the 22.8-ppm and 32.0-ppm signals.

Effect of Alkyl Branching on ^{13}C Chemical Shifts

To calculate the estimated ^{13}C chemical shifts of branched chain alkanes, a further correction has to be taken into account. Table 22.4 shows that although these corrections are not necessary for linear alkanes, "steric" corrections become increasingly important with increased carbon branching. The steric effect can be attributed to intramolecular van der Waals repulsion between hydrogen atoms that are close together, which causes the electrons of the C—H bond to move away from the proton toward carbon. Nearby branching in a carbon chain always shields a ^{13}C nucleus.

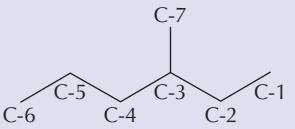
These steric additivity parameters always have negative values. Note that a separate parameter must be used for each α carbon atom, and their sum is the total steric correction for the ^{13}C carbon atom whose estimated chemical shift is being calculated.

TABLE 22.4 Steric additivity parameters in ppm for predicting NMR chemical shifts of alkyl carbon atoms in $CDCl_3$

	Type of α carbon atom			
Type of ^{13}C nucleus	Methyl	Methylene	Methine	Quaternary
Primary	0.0	0.0	−1.1	−3.4
Secondary	0.0	0.0	−2.5	−6.0
Tertiary	0.0	−3.7	−8.5	−10.0
Quaternary	−1.5	−8.0	−10.0	−12.5

WORKED EXAMPLE

The application of the steric correction for branched alkanes can be demonstrated with the calculation for the chemical shift of carbon-2 of 3-methylhexane, whose ^{13}C NMR spectrum is shown in Figure 22.8.



3-Methylhexane

The branch point in the carbon chain of 3-methylhexane is C-3, which is α to the carbon whose chemical shift is being calculated. The other α substituent of C-2 is a methyl group, and Table 22.4 shows this has a steric parameter of 0.0 (secondary carbon with an α methyl group).

Calculation of the estimated chemical shift for C-2:

Base value	= −2.3
Two α carbon substituents (2 × 9.1)	= 18.2
Two β carbon substituents (2 × 9.4)	= 18.8
One γ carbon substituent	= −2.5
Secondary carbon atom with an α methine group (Table 23.4)	= −2.5
Total	= 29.7 ppm

The application of the steric correction to the chemical shift of a carbon atom that is the branch point itself can be shown by calculating the chemical shift for C-3 of 3-methylhexane. Here there are three α substituents to consider, one for methylene C-2, one for methylene C-4, one for the α methyl group. For the tertiary carbon atom the steric parameters are −3.7, −3.7, and 0.0, respectively.

Calculation of the estimated chemical shift for C-3:

Base value	= −2.3
Three α carbon substituents (3 × 9.1)	= 27.3
Two β carbon substituents (2 × 9.4)	= 18.8
One γ carbon substituent	= −2.5
Tertiary carbon atom with two α methylene groups (2 × –3.7)	= −7.4
Total	= 33.9 ppm

The measured chemical shifts of the carbon signals of 3-methylhexane shown in Figure 22.8 are 11.4 ppm, 14.4 ppm, 19.2 ppm, 20.3 ppm, 29.6 ppm, 34.4 ppm, and 39.1 ppm. We have already calculated the estimated chemical shifts for C-2 and C-3; they are 29.7 ppm and 33.9 ppm, respectively. We can be reasonably confident that the 29.6-ppm signal can be assigned to C-2 and that the 34.4-ppm signal can be assigned to C-3.

EXERCISE

Calculate the estimated chemical shifts of C-1, C-4, C-5, C-6, and C-7 of 3-methylhexane and assign the remaining signals in Figure 22.8. How good is the correspondence?

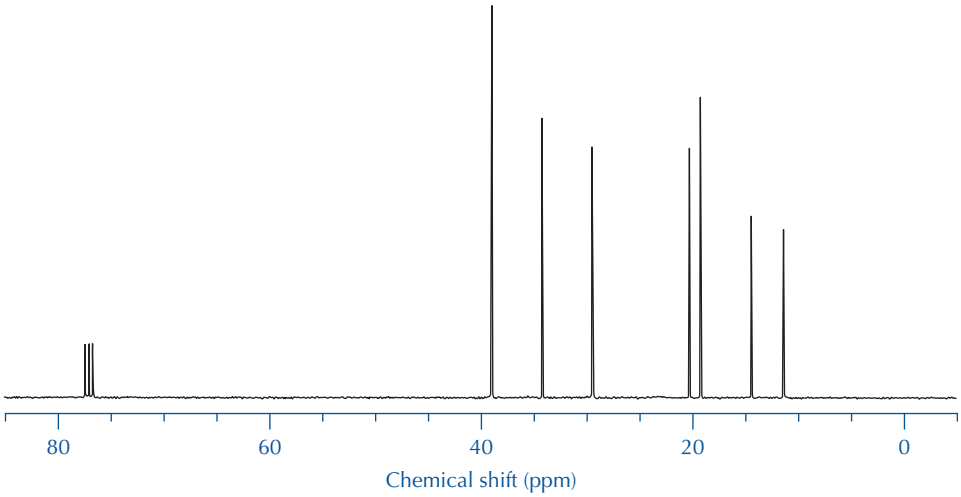


FIGURE 22.8 Broadband-decoupled 90-MHz ^{13}C NMR spectrum of 3-methylhexane in $CDCl_3$.

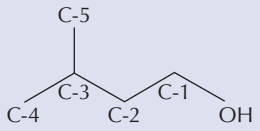
Answer: Calculation of the estimated chemical shifts using Tables 22.3 and 22.4 gives C-1 = 11.2 ppm, C-4 = 39.1 ppm, C-5 = 20.3 ppm, C-6 = 13.7 ppm, and C-7 = 19.5 ppm. The assignments are C-1 = 11.4 ppm, C-4 = 39.1 ppm, C-5 = 20.3 ppm, C-6 = 14.4 ppm, and C-7 = 19.2 ppm. The correspondence is excellent.

^{13}C Chemical Shifts for Functional Groups Other Than sp^3 Carbon

Additive parameters for a wide range of functional groups have been determined and are listed in Table 22.3. They are used in the same manner as the additive parameters for alkyl substituents. Again, the steric additivity parameters in Table 22.4 must also be part of the calculation of the estimated ^{13}C chemical shifts, which are usually within 5 ppm of measured chemical shifts. This discussion will be limited to using these additive parameters to calculate chemical shifts in simple alkyl molecules. A comprehensive discussion of additive parameters for a wide variety of functional groups and structural types can be found in *Carbon-13 NMR Spectroscopy: High-Resolution Methods and Applications in Organic Chemistry and Biochemistry* by Brietmaier and Voelter (VCH: New York, 1987).

WORKED EXAMPLE

We have already seen how the ^{13}C chemical shifts of linear and branched alkanes can be estimated using Tables 22.3 and 22.4. In this example we will show how this approach can be extended to 3-methyl-1-butanol, whose ^{13}C NMR spectrum is shown in Figure 22.9. We will assign the signals at 60.2 ppm and 41.8 ppm in Figure 22.9. The hydroxyl substituent is about half way down in Table 22.3.



3-Methyl-1-butanol

Calculation of the estimated chemical shift for C-1:

Base value	= −2.3
One α hydroxyl substituent	= 49.4
One α carbon substituent	= 9.1
One β carbon substituent	= 9.4
Two γ carbon substituents (2 × −2.5)	= −5.0
Total	= 60.6 ppm

Calculation of the estimated chemical shift for C-2:

Base value	= −2.3
One β hydroxyl substituent	= 10.1
Two α carbon substituents (2 × 9.1)	= 18.2
Two β carbon substituents (2 × 9.4)	= 18.8
Secondary carbon atom with an α methine group	= −2.5
Total	= 42.3 ppm

We are quite safe in assigning C-1 to the 60.2-ppm signal and C-2 to the 41.8-ppm signal. Each of these calculated chemical shifts is within 3% of the measured value. In the case of 3-methyl-1-butanol, we could actually make the assignments of C-1 and C-2 using Table 22.1, knowing that the influence of an electronegative substituent is smaller the farther away it is. With a more complex molecule, however, the sole use of Table 22.1 would be problematic. Using additive substituent parameters is a much safer method.

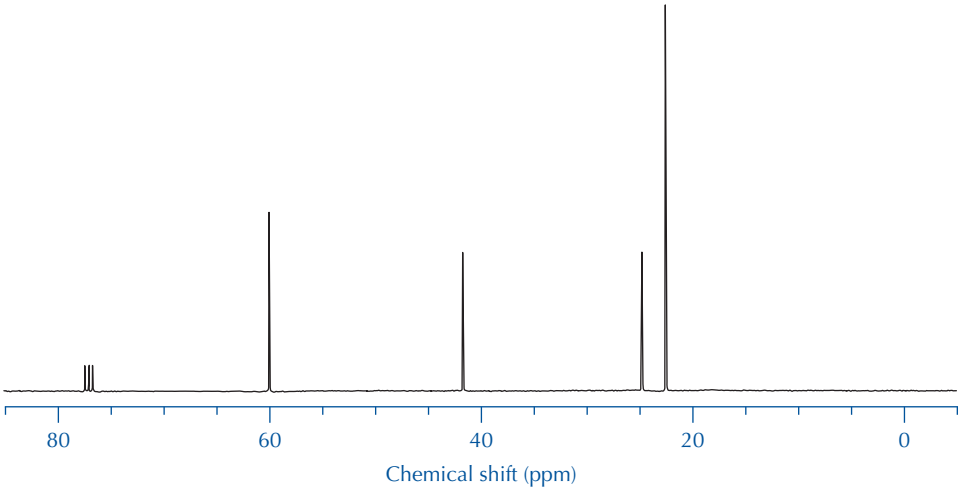


FIGURE 22.9 Broadband-decoupled 90-MHz ^{13}C NMR spectrum of 3-methyl-1-butanol in $CDCl_3$.

FOLLOW-UP ASSIGNMENT

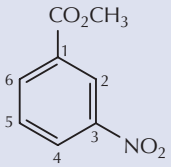
Calculate the estimated chemical shifts of C-3 and C-4 (C-5) of 3-methyl-1-butanol.

Chemical Shifts of Aromatic and Alkene Carbon Atoms

The chemical shifts of carbon atoms in substituted benzene rings can be estimated using the parameters listed in Table 22.5. Aromatic carbon atoms have sp^2 hybridization and therefore are significantly deshielded. The base value for the calculations is the ^{13}C chemical shift for benzene, which is 128.5 ppm.

WORKED EXAMPLE

Using methyl 3-nitrobenzoate as an example, the estimates of the chemical shifts calculated from Table 22.5 provide a useful guide for assigning the signals in the spectrum to the appropriate carbons.



	C-1	C-2	C-3	C-4	C-5	C-6
Base value	128.5	128.5	128.5	128.5	128.5	128.5
—(C═O)OCH_3	2.0	1.2	−0.1	4.3	−0.1	1.2
—NO_2	0.9	−4.9	19.9	−4.9	0.9	6.1
Estimated (ppm)	131.4	124.8	148.3	127.9	129.3	135.8
Measured (ppm)	131.9	124.5	148.3	127.3	129.6	135.2

TABLE 22.5 Additive parameters for predicting NMR chemical shifts of aromatic carbons atoms in $CDCl_3$

Base value: benzene = 128.5 ppm

Group	C-1	*ortho*	*meta*	*para*
—I	–34.1	8.9	1.6	–1.1
—Br	–5.8	3.2	1.6	–1.6
—Cl	6.3	0.4	1.4	–1.9
—F	34.8	–13.0	1.6	–1.1
—H	0.0	0.0	0.0	0.0
—(C═O)OCH_3	2.0	1.2	–0.1	4.3
—(C═O)OH	2.1	1.6	–0.1	5.2
—(C═O)H	8.2	1.2	0.5	5.8
—(C═O)CH_3	8.9	0.1	–0.1	4.4
—$CH{=}CH_2$	8.9	–2.3	–0.1	–0.8
—CH_3	9.2	0.7	–0.1	–3.0
—CH_2Cl	9.3	0.3	0.2	0.0
—C_6H_5	13.1	–1.1	0.5	–1.1
—CH_2CH_3	15.7	–0.6	–0.1	–2.8
—$CH(CH_3)_2$	20.2	–2.2	–0.3	–2.8
—$C(CH_3)_3$	22.4	–3.3	–0.4	–3.1
—NH(C═O)CH_3	9.7	–8.1	0.2	–4.4
—NH_2	18.2	–13.4	0.8	–10.0
—NO_2	19.9	–4.9	0.9	6.1
—O(C═O)CH_3	22.4	–7.1	0.4	–3.2
—OH	26.9	–12.8	1.4	–7.4
—OC_6H_5	27.6	–11.2	–0.3	–6.9
—OCH_3	31.4	–14.4	1.0	–7.7

Additive parameters for sp^2 alkene carbon atoms are added to a base value of 123.3 ppm, the chemical shift of the carbon atoms in ethylene. There are two general types of shielding/deshielding effects of an alkene carbon atom, those that are transferred solely through the σ bond network, described as α, β, and γ, and those that are transferred through the π bond network, which can be called α′, β′, and γ′.

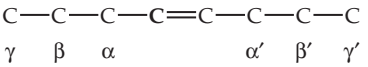
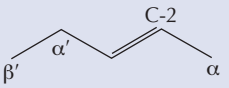


Table 22.6 lists additive parameters for the effect of a variety of functional groups on the chemical shift of alkene carbon atoms.

WORKED EXAMPLE

Determine the substituents that must be used to calculate the estimated chemical shift of the sp^2 C-2 carbon atom in *E*-2-pentene and use Table 22.6 to calculate it.



E-2-pentene

In this case the only substituents that must be considered are sp^3 α, α′, and β′ carbon atoms, which appear at the top of Table 22.6. The chemical shift of C-2 is estimated to be 123.3 + 10.1 − 7.7 − 2.5 = 123.2 ppm. The measured chemical shift is 123.5 ppm

TABLE 22.6 Additive parameters for predicting NMR chemical shifts of alkene carbon atoms in $CDCl_3$

Base value: CH_2═CH_2 = 123.3 ppm

	Y—**C**═C—Y′		Y—C—**C**═C—C—Y′		Y—C—C—**C**═C—C—C—Y′		
	α	α′	β	β′	γ		γ′
Group (Y)	**α**		**β**	**γ**	**α′**	**β′**	**γ′**
—C—(sp^3)	10.1		7.1	−1.5	−7.7	−2.5	1.0
—CH═CH_2	14.5		2.9	−2.4	−5.8	−0.5	1.2
—C_6H_5	13.6		4.9	−2.5	−9.6	0.7	1.1
—OH			3.9	−6.1		−0.8	3.8
—O(C═O)CH_3	17.9		−1.1	−6.7	−25.8	2.3	3.3
—OR	28.5		1.7	−4.9	−37.0	0.7	2.9
—Br	−9.4		1.0	−5.1	−1.5	2.4	4.2
—Cl	2.8		0.5		−6.1	2.7	
—(C═O)OR	3.0		−2.7	−3.4	7.3	2.2	1.9
—(C═O)OH	4.7		−2.9	−4.3	9.9	3.2	3.2
—(C═O)H	14.7			−4.1	16.2		2.0
—(C═O)R	14.1		−2.9	−3.5	5.5	3.0	1.7

Blank entries are due to lack of data.

EXERCISE

Calculate the chemical shift of the carbon atom at position 3 of *E*-2-pentene. The measured chemical shift is 133.2 ppm.

Answer: The estimated chemical shift of C-3 is calculated to be 123.3 + 10.1 + 7.1 − 7.7 = 132.8 ppm.

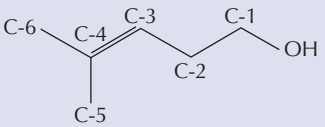
A set of correction factors to account for the steric contributions can be found in Table 22.7.

TABLE 22.7 Steric additivity parameters for predicting NMR chemical shifts of alkene carbon atoms in $CDCl_3$

Each pair of αα′ *cis* substituents	−1.1 ppm
Each pair of αα *geminal* substituents	−4.8 ppm
Each pair of α′α′ *geminal* substituents	2.5 ppm
Each α methine substituent	2.3 ppm
Each α quaternary substituent	4.6 ppm

WORKED EXAMPLE

The estimation of the ^{13}C chemical shift for C-4 of 4-methyl-3-penten-1-ol provides a useful demonstration of the utility of the additive parameters in Tables 22.6 and 22.7.



4-Methyl-3-penten-1-ol

Calculation of the estimated chemical shift for C-4:

Base value	= 123.3
Two α carbon substituents (2 × 10.1)	= 20.2
One α′ carbon substituent	= −7.7
One β′ carbon substituent	= −2.5
One γ′ hydroxyl substituent	= 3.8
One pair of αα′ *cis* substituents	= −1.1
One pair of αα *geminal* substituents	= −4.8
Total	= 131.2 ppm
Measured chemical shift	= 134.8 ppm

EXERCISE

Using the additive parameters for alkyl carbon atoms in Table 22.3 and the parameters for alkene carbon atoms in Tables 22.6 and 22.7, calculate the estimated chemical shifts of the remaining carbons of 4-methyl-3-penten-1-ol

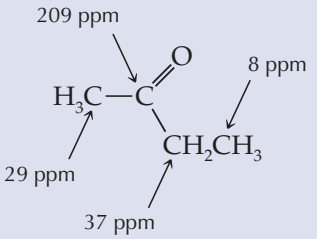
and assign them to the correct carbon atoms. How confident are you of your estimated chemical shifts? The measured chemical shifts of the four remaining carbon atoms are 17.9 ppm, 25.8 ppm, 31.6 ppm, and 120.1 ppm.

Answer: Calculation of the estimated chemical shifts using Tables 22.3, 22.6, and 22.7 gives C-2 = −2.3 + 9.1 + 14.4 + 10.1 = 31.3 ppm, C-3 = 123.3 + 10.1 + 7.1 − 6.1 − 15.4 − 1.1 + 2.5 = 120.4 ppm, C-5 = −2.3 + 13.4 + 9.4 = 20.5 ppm, and C-6 = −2.3 + 19.3 + 9.4 = 26.4 ppm. The C-2 signal appears at 31.6 ppm, the C-3 signal appears at 120.1 ppm, the C-5 signal appears at 17.9 ppm, and the C-6 signal appears at 25.8 ppm in the ^{13}C NMR spectrum. Note that the *cis*-methyl group is farther upfield than the *trans*-methyl group.

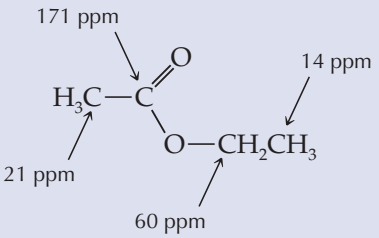
EXERCISE

The ^{13}C NMR spectrum of 2-butanone shows signals at 8 ppm, 29 ppm, 37 ppm, and 209 ppm. The ^{13}C NMR spectrum of ethyl acetate shows signals at 14 ppm, 21 ppm, 60 ppm, and 171 ppm. Assign the NMR signals to the carbon atoms in each structure.

Answer:



2-Butanone



Ethyl acetate

In general, the additive parameters in Tables 22.3–22.7 provide good estimates for ^{13}C chemical shifts. However, it is important to remember that they are estimates, not precision calculations. The estimates are usually within 3% of measured values (6 ppm over a 200-ppm range) and the relative positions of the signals are correct.

Computer Programs for Estimating ^{13}C NMR Chemical Shifts

Computer programs have been developed that use additivity parameters for calculating the NMR spectrum of any molecule of interest. ChemDraw Ultra and ChemBioDraw Ultra (from CambridgeSoft) include a module, called ChemNMR, which estimates ^{13}C chemical shifts and displays the calculated NMR spectrum as well as the assigned ^{13}C chemical shifts after the structure of

a molecule is drawn. Moving the cursor to a peak on the spectrum highlights the carbon atom in the molecule responsible for the peak, and vice versa. The logic of the program is rule-based calculation of chemical shifts on structural fragments, similar to the method presented in this technique. To improve the accuracy of the estimates, some 4000 parameters are used.

An alternative method for estimating chemical shifts is the ACD/CNMR Predictor (from Advanced Chemistry Development). The predicted chemical shifts are based on a large database of structures (almost 200,000) with 2.5 million assigned ^{13}C chemical shifts. The display can be interrogated by clicking on either the structure or the spectrum to highlight their corelationships, and the database can be expanded as new compounds become available.

These programs are sophisticated, research-quality tools and are priced accordingly. Some institutions have negotiated site licenses making the programs accessible to all their members. Estimated ^{13}C chemical shifts from these computer programs are usually within 3–4 ppm of the measured values, roughly comparable to the use of the additivity parameters used in Technique 22.3.

22.4 Determining Numbers of Protons on Carbon Atoms

Typically, ^{13}C NMR spectra are obtained using broadband decoupling so that the carbon signals are collapsed into singlets. The cost of this simplification is the loss of information regarding the number of protons attached to carbon atoms. Numerous techniques have been developed to supply this important information. Two commonly used experiments provided with most modern FT NMR spectrometers are APT (**A**ttached **P**roton **T**est) and DEPT (**D**istortionless **E**nhancement by **P**olarization **T**ransfer). These experiments use complex pulse sequences at observation frequencies for both ^{1}H and ^{13}C nuclei.

APT

In a typical broadband-decoupled ^{13}C NMR spectrum, each different carbon atom in the sample appears as a single positive peak. In APT spectra, CH and CH_3 carbon nuclei give positive signals, whereas quaternary and CH_2 carbon nuclei give negative signals.

In the APT spectrum of ethyl *trans*-2-butenoate, shown in Figure 22.10, positive signals at 14, 18, 123, and 144 ppm are due to the carbons of the methyl groups and the vinyl carbons. The negative signals at 60 and 166 ppm are due to the carbon of the methylene group and the carbonyl carbon. With concentrated samples, an APT spectrum can be acquired in a short time. The APT method is limited, however, because it is normally impossible to distinguish between the signals of quaternary and CH_2 carbon nuclei, or between signals of CH and CH_3 carbon nuclei.

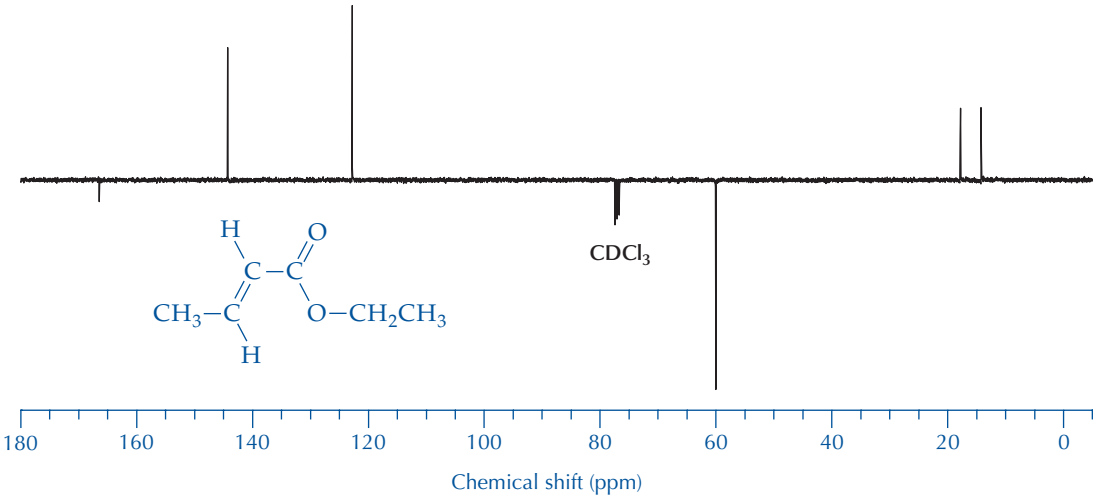


FIGURE 22.10 90-MHz ^{13}C NMR spectrum of ethyl *trans*-2-butenoate in $CDCl_3$ using an APT pulse sequence.

DEPT

In a DEPT experiment, signals in the ^{13}C NMR spectrum may be suppressed or inverted depending on the number of protons attached to the carbon and the conditions set in the pulse program. The DEPT(45) version of the experiment provides a ^{13}C spectrum in which only carbon atoms that have protons attached to them appear. Signals due to quaternary carbons are not observed. The spectrum produced by the DEPT(90) pulse program exhibits only signals from carbon atoms that have one hydrogen attached (methine carbons). Signals due to all carbon atoms with attached protons are observed in the ^{13}C NMR spectrum from a DEPT(135) experiment; however, the signals due to carbon atoms with two protons attached (methylene carbons) are inverted. Comparing the spectra from a set of DEPT experiments allows you to determine the number of protons attached to every carbon atom in a molecule. Table 22.8 summarizes the information that can be obtained from a broadband-decoupled ^{13}C spectrum and the three DEPT experimental spectra.

TABLE 22.8 Orientation of ^{13}C signals in DEPT NMR experiments

Type of ^{13}C spectrum \ Type of carbon and peak direction	CH_3	CH_2	CH	C
Broadband-decoupled ^{13}C	+	+	+	+
DEPT(45)	+	+	+	0
DEPT(90)	0	0	+	0
DEPT(135)	+	−	+	0

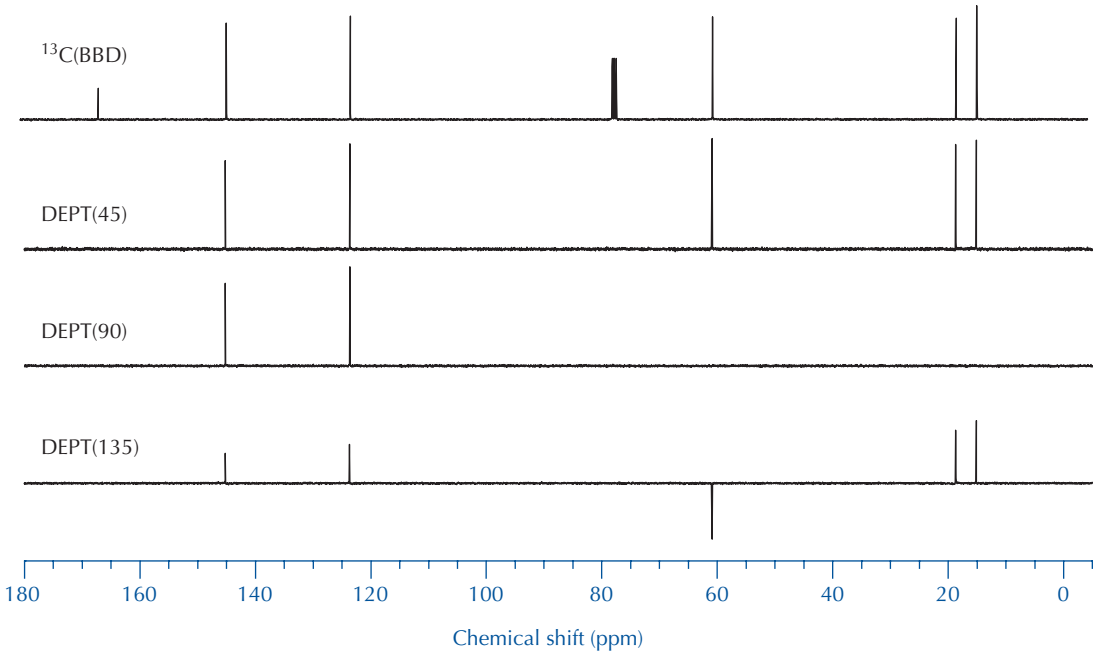


FIGURE 22.11 DEPT spectra of ethyl *trans*-2-butenoate in $CDCl_3$. The broadband-decoupled 90-MHz ^{13}C NMR spectrum is shown at the top.

The broadband-decoupled ^{13}C, DEPT(45), DEPT(90), and DEPT(135) spectra of ethyl *trans*-2-butenoate are shown in Figure 22.11. The six signals in the ^{13}C spectrum were assigned earlier in the discussion at the end of Section 22.2. There is no $CDCl_3$ signal at 77 ppm in DEPT spectra because the carbon nucleus in $CDCl_3$ is attached to ^{2}H, not ^{1}H.

22.5 Case Study

Figure 22.12 shows the DEPT(135) and ^{13}C NMR spectra for an acyclic compound whose molecular formula is $C_8H_{14}O$. The ^{13}C chemical shifts are 17.6 ppm, 22.7 ppm, 25.6 ppm, 29.8 ppm, 43.7 ppm, 122.6 ppm, 132.6 ppm, and 208.4 ppm. What is the structure of $C_8H_{14}O$?

We have three pieces of experimental data with which to work, the molecular formula, the ^{13}C NMR spectrum, and the DEPT spectrum. An approach to this kind of problem solving was described in Technique 21.11 in the context of ^{1}H NMR. There are differences between ^{1}H and ^{13}C NMR, to be sure. For example, there are no integration and splitting patterns to go by in ^{13}C NMR. However, the number of ^{13}C signals can easily be counted, and the DEPT(135) spectrum yields information about the numbers of protons on the carbon atoms.

As with ^{1}H NMR, a good place to start the analysis is with a look at the molecular formula, $C_8H_{14}O$. If the acyclic unknown compound

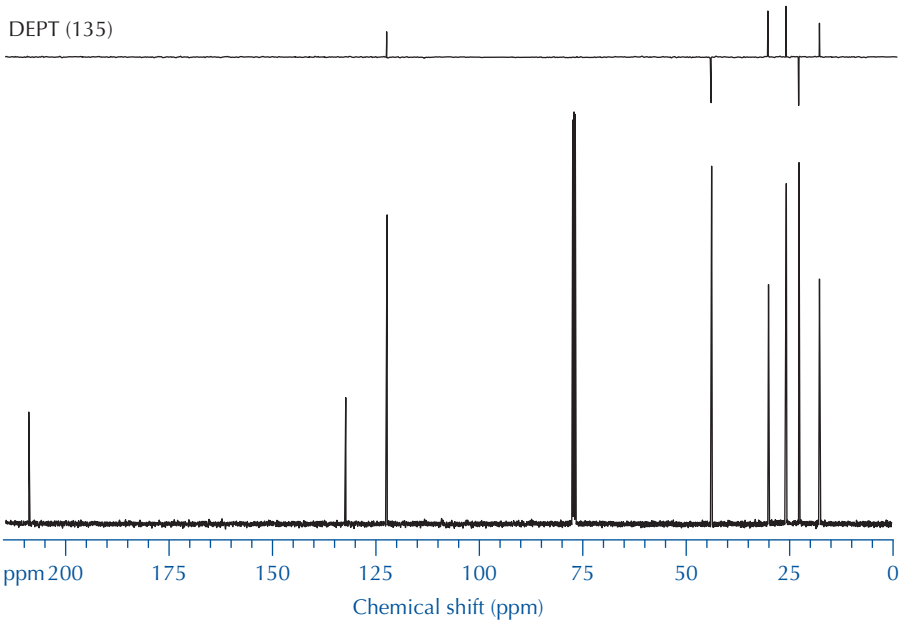


FIGURE 22.12 The 90-MHz DEPT(135) and ^{13}C NMR spectra of $C_8H_{14}O$ in $CDCl_3$.

were fully saturated, the molecular formula would be $C_8H_{18}O$. Therefore, the compound has two double-bond equivalents (DBEs). This suggests that it may have a C═O and a C═C group or two C═C groups and an OH or OR group.

In scanning the ^{13}C NMR spectrum, the first thing to notice is that the spectrum contains eight different carbon signals plus the $CDCl_3$ triplet at 77.0 ppm. There is a different signal for each carbon atom in the molecule. With the ^{13}C spectrum spread out over 200 ppm, it's easy to see that three of the carbon signals are highly deshielded compared to the other five. They appear at 122.6 ppm, 132.6 ppm, and 208.4 ppm. Table 22.1 shows that the 208.4 peak must be due to a carbonyl group, and the 122.6- and 132.6-ppm signals are most likely due to a C═C group. It is also likely that the signal at 43.7 ppm is due to a carbon atom α to the carbonyl group, because the signals of most alkyl and allyl carbon atoms don't appear at chemical shifts greater than 40 ppm. We will delay an analysis of the four upfield ^{13}C signals until later, when we have a better idea what the environments of these four alkyl signals might be.

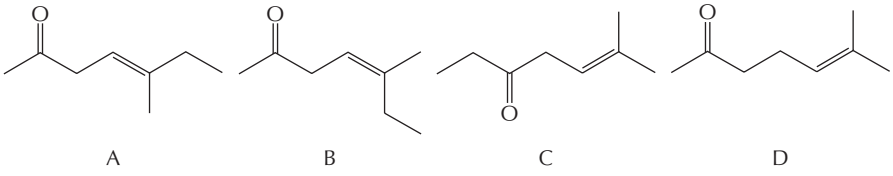
The third piece of data is the DEPT(135) spectrum. Using the data in Figure 22.12 the following points can be inferred:

- The 17.6-ppm, 25.6-ppm, and 29.8-ppm signals are due to methyl groups.
- The 22.7-ppm and 43.7-ppm signals are methylene groups.
- The alkene carbon atom at 122.6 ppm is a methine carbon atom.
- The signals at 132.6 ppm and 208.4 ppm are quaternary carbon atoms.

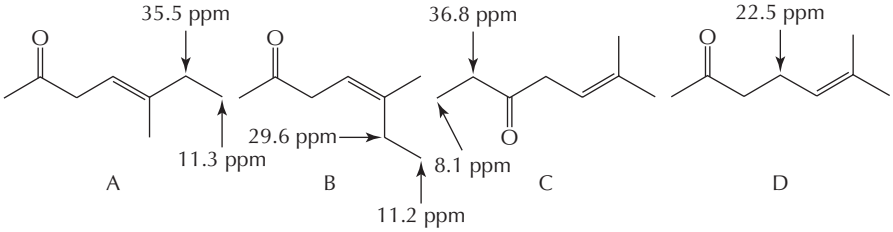
The DEPT spectrum indicates these possible structural fragments, accounting for eight carbon atoms in all:

$CH_3—(C{=}O)—CH_2—$ —CH=CR— $—CH_2—$ $—CH_3$ $—CH_3$

Now we need to establish the relationship of the C=O and C=C bonds, whether they are conjugated or nonconjugated. Table 22.2 offers an insight. A conjugated carbonyl group would have its chemical shift in the 190-ppm region, whereas this one is at 208.4 ppm. It's likely that the carbonyl group is not conjugated. There are four structures that fit this data:

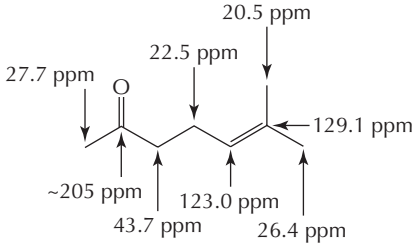


We can use Tables 22.3, 22.6, and 22.7 to calculate the estimated ^{13}C chemical shifts to determine which of these four structures is the correct one. Begin with structures A, B, and C, which have ethyl substituents in which the methyl and methylene groups would be the most upfield signals in the ^{13}C spectrum.

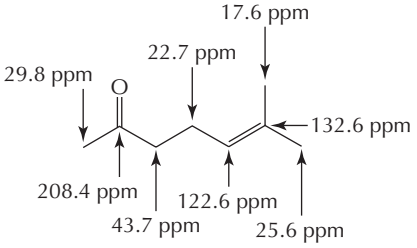


The measured chemical shifts of the methyl and methylene groups in Figure 22.12 are 17.6 ppm and 22.7 ppm. As you can see, the fit is rather poor for A, B, and C. However, you will see that the estimated chemical shift of the methylene group in D is an excellent fit.

Carrying out the calculations for every carbon atom in D gives the following result:



Estimated ^{13}C chemical shifts



Measured ^{13}C chemical shifts

A complete calculation for the carbon atoms of structures A, B, and C could be done to confirm this answer, but it seems unnecessary. $C_8H_{14}O$ is 6-methyl-5-hepten-2-one.

22.6 Two-Dimensional Correlated Spectroscopy (2D COSY)

The spin-spin coupling between nuclei affords a great deal of structural information. In Technique 21.9, the coupling between hydrogen nuclei was discussed and its usefulness in determining the ***connectivity*** within a molecule was demonstrated. Connectivity can be described as the covalent bonding network of nearby atoms within a molecule.

An alternative method of analyzing coupling within a molecule is provided by two-dimensional (2D) NMR spectroscopy. In a typical ^1H or ^{13}C NMR spectrum, the positions of signals along the abscissa (*x*-axis) of the spectrum correspond to the frequencies of the signals, which are measured as chemical shifts. The intensities of the signals are measured along the ordinate (*y*-axis). This typical spectrum is referred to as a one-dimensional (1D) spectrum because only one axis is a frequency axis. The most basic pulse sequence (or program) for producing a 1D NMR spectrum consists of an excitation pulse followed by a data acquisition period.

A 2D NMR spectrum is created from a series of 1D NMR spectra. The basic pulse program for producing each 1D spectrum consists of an excitation pulse, a time delay called the evolution period, a mixing period in which one or more pulses are required to create an observable signal, and finally a data acquisition period. More detailed information about pulse programs can be found in *200 and More NMR Experiments: A Practical Course,* 3rd ed., by Berger and Braun (Wiley-VCH: Weinheim, 2004). During the evolution period the magnetization from one nucleus is transferred to other nearby coupled nuclei. The time delay is increased by a small amount for each 1D spectrum. Since the data is time-based along both axes, it can be Fourier transformed along both axes, so both the *x*-axis and the *y*-axis are frequency axes. The signal intensities in a 2D NMR spectrum are usually represented on the graph as a series of closely spaced contour lines, similar to a topographical map.

The most commonly utilized 2D spectroscopy experiments are (H,H) COSY (**CO**rrelated **S**pectroscop**Y**) spectra, in which both axes correspond to ^1H chemical shifts, and (C,H) COSY spectra, in which one axis corresponds to ^{13}C chemical shifts and the other axis corresponds to ^1H chemical shifts.

2D COSY spectra indicate which nearby nuclei are coupling with one another. They correlate the nuclei that are coupling partners. The correlations are shown by the presence of cross peaks, the contour line signals in 2D spectra that appear at the crossing of implicit vertical and horizontal lines connecting to the peaks on the *x*- and *y*-axes.

Two-Dimensional Homonuclear (H,H)-Correlated NMR Spectroscopy—(H,H) COSY

The 2D (H,H) COSY spectrum of ethyl *trans*-2-butenoate is shown in Figure 22.13. Here the ^1H NMR spectrum is displayed along both the *x*-axis and the *y*-axis. For each signal in the ^1H NMR spectrum of ethyl *trans*-2-butenoate there is a corresponding peak on the diagonal that runs from the lower left corner to the upper right corner. The presence of peaks on the diagonal of an (H,H) COSY spectrum is not useful in determining coupling patterns. They appear because the magnetization is not completely transferred between the nuclei. It is the ***off-diagonal cross peaks*** that are useful in (H,H) COSY; they appear where there is coupling between ^1H nuclei.

The off-diagonal cross peak that comes at the intersection of the 1.2-ppm signal in the ^1H spectrum on the *x*-axis and the 4.1-ppm signal in the ^1H spectrum on the *y*-axis indicates that these two ^1H nuclei are coupled. Due to the symmetry of the 2D (H,H)COSY spectrum, there is another off-diagonal cross peak at the intersection of the 1.2-ppm signal in the ^1H spectrum on the *y*-axis and the 4.1-ppm signal in the ^1H spectrum on the *x*-axis. There are no other off-diagonal cross peaks involving the 1.2-ppm and 4.1-ppm signals, so the protons they represent are not coupled to any additional protons.

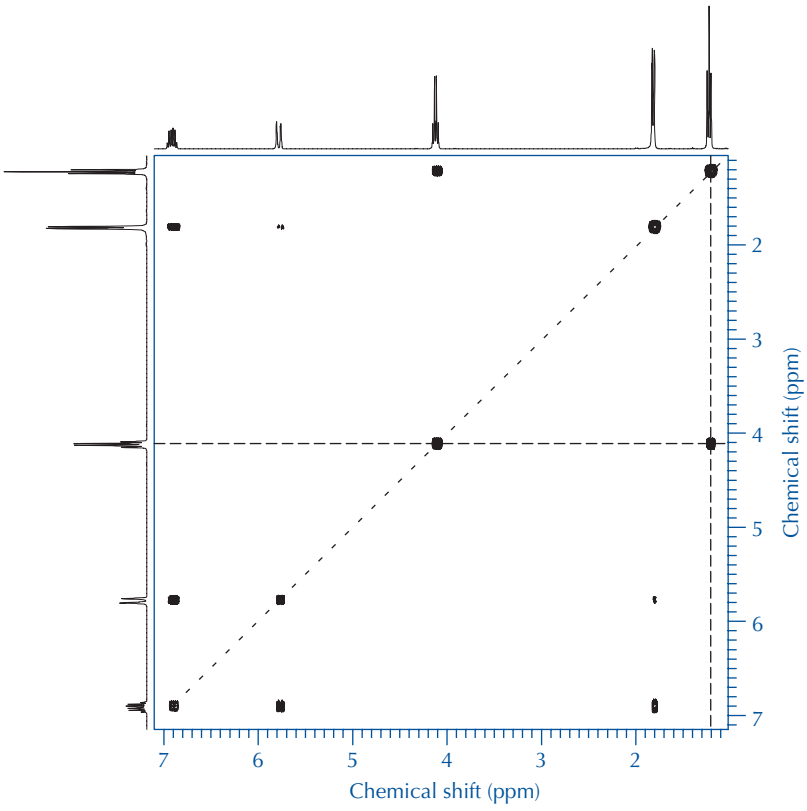


FIGURE 22.13 2D (H,H) COSY spectrum of ethyl *trans*-2-butenoate in $CDCl_3$. The 1D 360-MHz ^1H NMR spectra are shown at the top and left edges.

Figure 22.13 also shows two off-diagonal cross peaks involving the 1.8-ppm ^{1}H signals on the two axes. The most intense cross peak intersects with the 6.9-ppm signal. Thus, the ^{1}H nucleus at 1.8 ppm is coupled to the ^{1}H nucleus at 6.9 ppm. In addition, there is a less intense pair of off-diagonal cross peaks between the 1.8-ppm ^{1}H signal and the 5.8-ppm ^{1}H signal. Therefore, the proton at 1.8 ppm is also coupled to the proton at 5.8 ppm. The lesser intensity of the latter 2D peak suggests that the coupling constant is smaller; it is due to long-range allylic coupling. Lastly, the two off-diagonal peaks involving the 5.8-ppm signal and the 6.9-ppm signal show that these protons are coupled. In total, there are four pairs of off-diagonal cross peaks in Figure 22.13, showing four different ^{1}H-^{1}H couplings.

Other variations of the 2D (H,H) COSY experiment give basically the same information as the experiment described. All these data confirm our original interpretation of the 1D ^{1}H NMR spectrum of ethyl *trans*-2-butenoate in Technique 21.9, which came in part from a detailed analysis of the spin-spin splitting patterns in the spectrum.

Two-Dimensional Heteronuclear (C,H)-Correlated NMR Spectroscopy (C,H) COSY

An example of a 2D (C,H) COSY spectrum of ethyl *trans*-2-butenoate is shown in Figure 22.14. The *x*-axis of the 2D spectrum displays the ^{1}H NMR spectrum, and the *y*-axis displays the broadband-decoupled ^{13}C spectrum. Each signal in the ^{1}H spectrum can be correlated to a

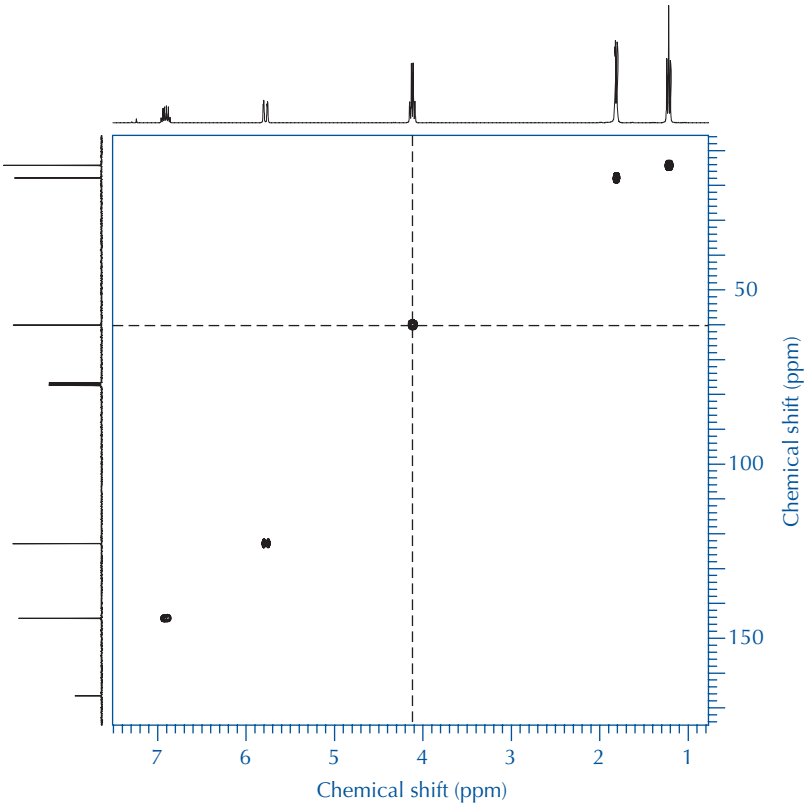


FIGURE 22.14 2D (C,H) COSY spectrum of ethyl *trans*-2-butenoate in $CDCl_3$. The 1D 360-MHz ^{1}H NMR spectrum is shown at the top edge and the 90-MHz ^{13}C NMR spectrum is shown at the left edge.

signal in the ^{13}C spectrum. The cross peaks are the result of coupling between a ^{1}H nucleus and the ^{13}C nucleus to which it is attached, where the one-bond coupling constant ($^{1}J_{CH}$) is very large.

The cross peak at 4.1 ppm along the chemical shift axis of the ^{1}H spectrum (*x*-axis) in the 2D (C,H) COSY spectrum is located at 60 ppm along the chemical shift axis of the ^{13}C spectrum (*y*-axis). This cross peak shows that the protons giving rise to the 4.1-ppm signal are attached to the carbon atom appearing at 60 ppm. The chemical shift of the ^{1}H spectrum thus correlates with the chemical shift of the ^{13}C spectrum. There are no cross peaks for quaternary carbon nuclei because they have no attached protons. Therefore, in Figure 22.14 there is no cross peak on the 2D spectrum for the 166-ppm peak in the ^{13}C spectrum, which is due to the carbonyl carbon atom.

There are several 2D (C,H) COSY experiments that give basically the same information. They are identified by a variety of abbreviations: HETCOR (**HET**eronuclear **COR**relation), HMQC (**H**eteronuclear **M**ultiple **Q**uantum **C**oherence), HSQC (**H**eteronuclear **S**ingle **Q**uantum **C**oherence), and others. While there are differences between the experiments, they are of little consequence when it comes to the interpretation of signals. The rationale for choosing particular NMR methods in many cases depends on the personal preferences of the people who obtain the spectra.

Long-Range (C,H) and (H,H) Coupling

By adjusting the evolution-period time delay in 2D NMR experiments it is also possible to identify long-range couplings over four or more bonds. Long-range couplings have proven to be a powerful tool for determining the structures of organic compounds. These methods are discussed in advanced texts, such as *200 and More NMR Experiments: A Practical Course,* 3rd edition, by Berger and Braun (Wiley-VCH: Weinheim, 2004).

Further Reading

Berger, S.; Braun, S. *200 and More NMR Experiments: A Practical Course*; 3rd ed.; Wiley-VCH: Weinheim, 2004.

Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy: High-Resolution Methods and Applications in Organic Chemistry and Biochemistry*; 3rd ed.; VCH: New York, 1987.

Crews, P.; Rodríguez, J.; Jaspars, M. *Organic Structure Analysis*; Oxford University Press: Oxford, 1998.

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Pouchert, C. J.; Behnke, J. (Eds.) *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra;* Aldrich Chemical Co.: Milwaukee, WI, 1993; 3 volumes.

Pretsch, E; Seibl, J.; Clerc, T; Simon, W., Biemann, K. (Trans.) *Tables of Spectral Data for Structure Determination of Organic Compounds;* 2nd English ed.; Springer-Verlag: New York, 1989.

Sanders, J. K.; Hunter, B. K. *Modern NMR Spectroscopy*; 2nd ed.; Oxford University Press: Oxford, 1993.

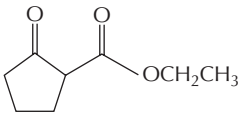
Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrometric Identification of Organic Compounds;* 7th ed.; Wiley: New York, 2005.

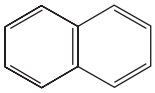
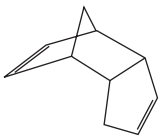
Questions

1. How many signals would you expect to see in the ^{13}C NMR spectrum of each of the following compounds? Show your logic.
   a. 2-pentanol, 2,2-dimethylbutane, isopropyl acetate, 2-acetoxybutane
   b. *para*-aminobenzoic acid, methyl

2-hydroxybenzoate, 1-phenyl-2-methylpropane, 1,3-cyclopentadiene

c. cyclohexane, *trans*-1,4-dimethylcyclohexane, *trans*-1,2-dimethylcyclohexane

d. 

2. Broadband-decoupled ^{13}C NMR spectra for three compounds with the molecular formula C_3H_8O are shown in Figure 22.15. Deduce the structure of each compound, estimate the chemical shift of each of its carbon atoms using the additive parameters in Tables 22.3 and 22.4, and assign the NMR signals to their respective carbon atoms. The measured chemical shifts of the carbon atoms follow.
   a. 64.4, 25.8, and 10.2 ppm
   b. 64.2 and 25.3 ppm
   c. 67.9, 58.2, and 15.0 ppm
3. The broadband-decoupled ^{13}C NMR spectrum, DEPT(90) spectrum, and DEPT(135) spectrum of a compound with the molecular formula C_8H_{10} are shown in Figure 22.16. Determine the structure of the compound and assign its signals in the ^{13}C NMR spectra. Estimate the chemical shifts of all carbon atoms using Tables 22.1, 22.3, and 22.5 and compare them with those measured from the spectrum.

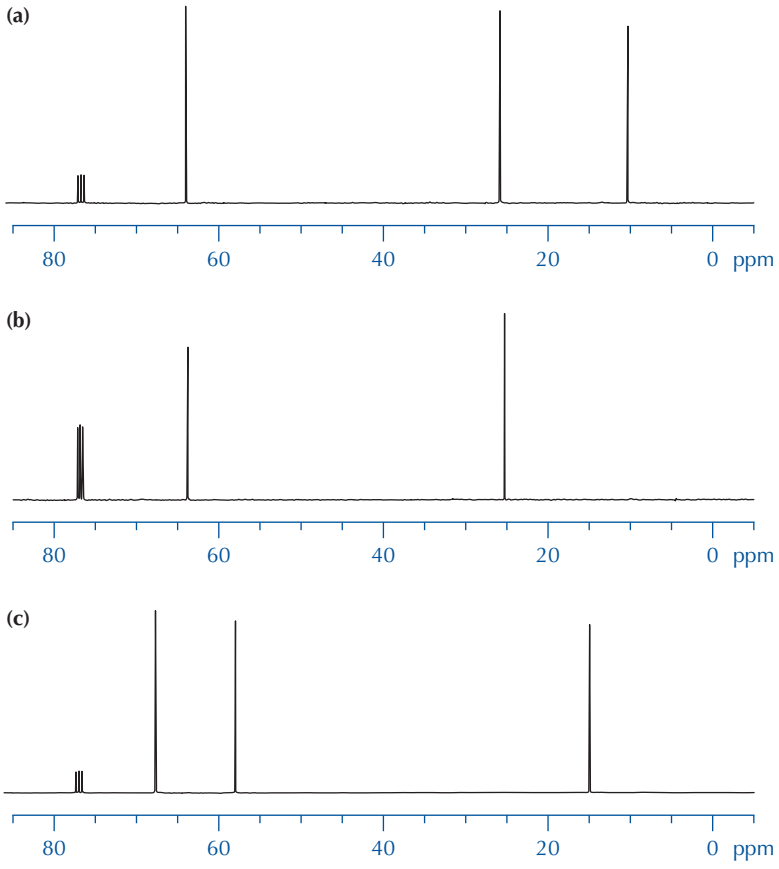


FIGURE 22.15 90-MHz ^{13}C NMR spectra of compounds with molecular formula C_3H_8O.

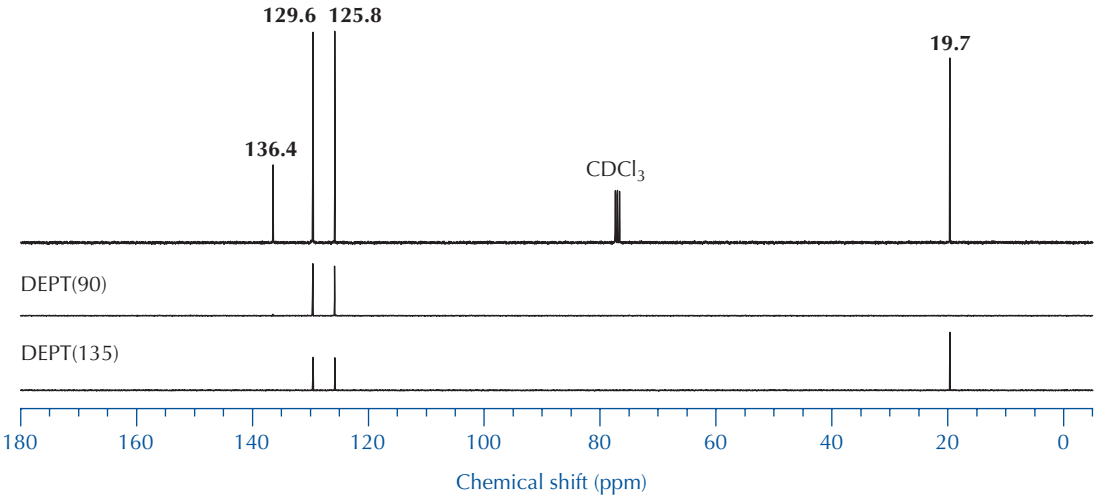


FIGURE 22.16 90-MHz ^{13}C NMR, DEPT(90), and DEPT(135) spectra of a compound with molecular formula C_8H_{10}.

4. A compound of molecular formula $C_{10}H_{14}$ produces a broadband-decoupled ^{13}C NMR spectrum, which has signals at 145.8, 135.1, 129.0, 126.3, 33.7, 24.1, and 20.9 ppm. The ^{13}C NMR spectrum, the DEPT(90) spectrum, and the DEPT(135) spectrum are shown in Figure 22.17. Deduce the structure of $C_{10}H_{14}$, estimate the chemical shifts of all carbon atoms using the parameters in Tables 22.1–22.5, and assign all the ^{13}C NMR signals.
5. Broadband-decoupled ^{13}C NMR and DEPT(135) spectra for all the compounds with the molecular formula $C_4H_{10}O$ are shown in Figure 22.18. Deduce the structure of each compound, estimate the

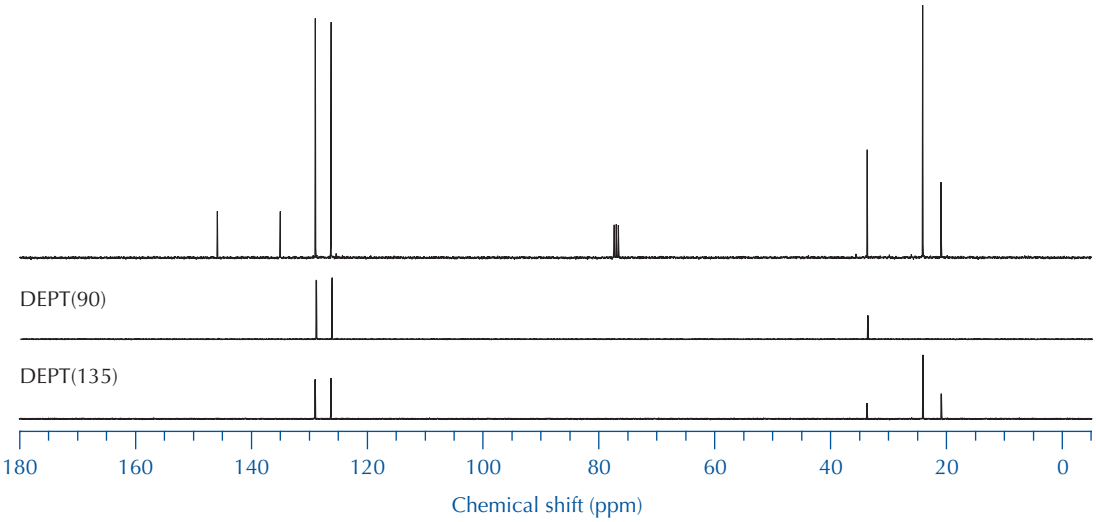


FIGURE 22.17 90-MHz ^{13}C NMR, DEPT(90), and DEPT(135) spectra of a compound with molecular formula $C_{10}H_{14}$.

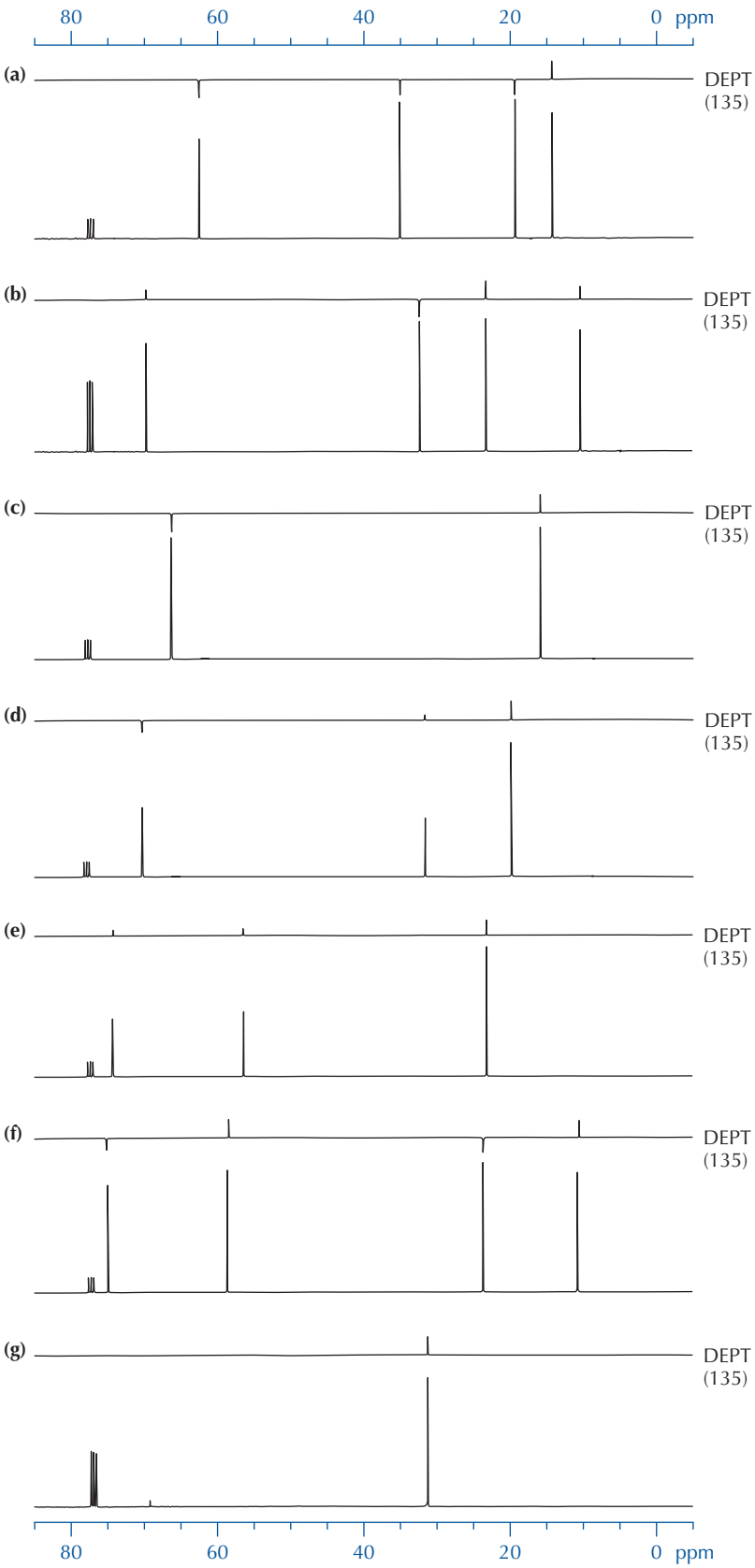


FIGURE 22.18
90-MHz ^{13}C NMR and DEPT(135) spectra of compounds with molecular formula $C_4H_{10}O$.

chemical shift of each of its carbon atoms using the additive parameters in Tables 22.3 and 22.4, and assign the NMR signals to their respective carbon atoms. The measured chemical shifts of the carbon atoms follow.

a. 62.4, 34.9, 19.0, and 13.9 ppm
b. 68.3, 32.0, 22.9, and 10.0 ppm
c. 65.9 and 15.4 ppm
d. 69.6, 30.8, and 18.9 ppm
e. 74.1, 56.4, and 22.9 ppm
f. 75.4, 59.1, 24.0, and 11.3 ppm
g. 69.1 and 31.2 ppm

6. Ibuprofen is the active ingredient in several nonsteroid anti-inflammatory drugs (NSAIDs). The molecular formula of the methyl ester of ibuprofen is $C_{14}H_{20}O_2$. The broadband-decoupled ^{13}C NMR spectrum, the DEPT(90) spectrum, and the DEPT(135) spectrum for the methyl ester of ibuprofen are shown in Figure 22.19. **Hint**: The ^{13}C signal at 45 ppm is broader than the other signals in the ^{13}C spectrum and resolves into two separate signals at higher resolution. Pay careful attention to the pattern of signals at 45 ppm in the DEPT(135) spectrum. The ^{1}H NMR spectrum of the methyl ester of ibuprofen is shown in Figure 22.20.

   The 2D (H,H) COSY spectrum of the methyl ester of ibuprofen is shown in Figure 22.21, and its 2D (C,H) COSY spectrum is shown in Figure 22.22. Deduce the structure of the methyl ester of ibuprofen using the parameters in Tables 22.1 and 22.3–22.5, and estimate the chemical shifts of all carbon atoms. Assign all the ^{13}C NMR signals. Show your reasoning.

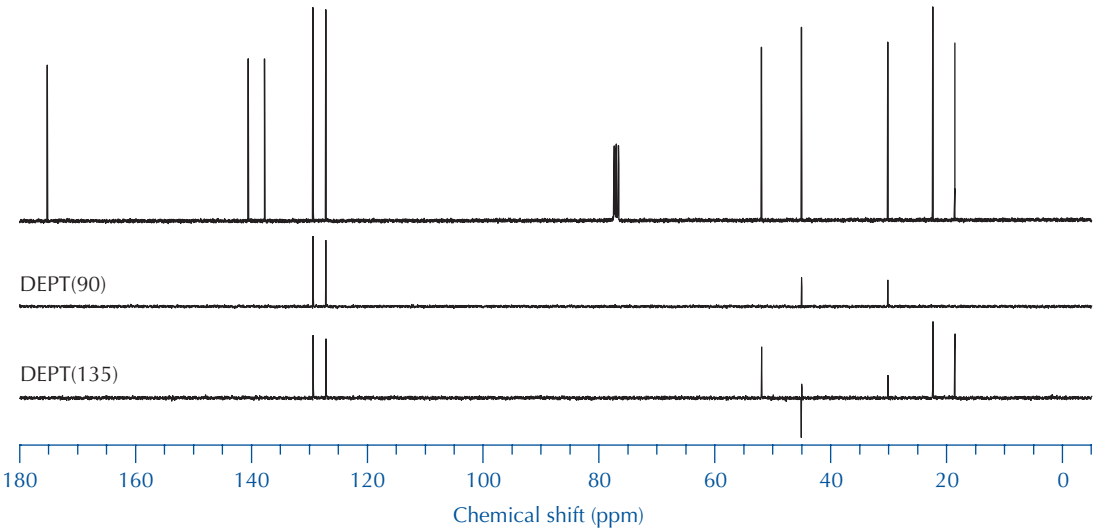


FIGURE 22.19 90-MHz ^{13}C NMR, DEPT(90), and DEPT(135) spectra of the methyl ester of ibuprofen.

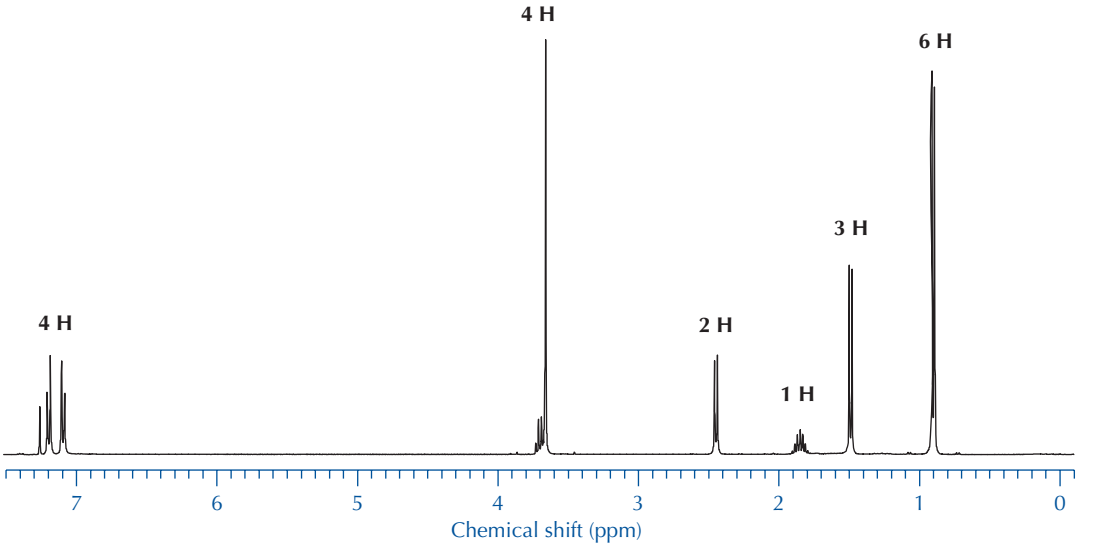


FIGURE 22.20 360-MHz ^{1}H NMR spectrum of the methyl ester of ibuprofen.

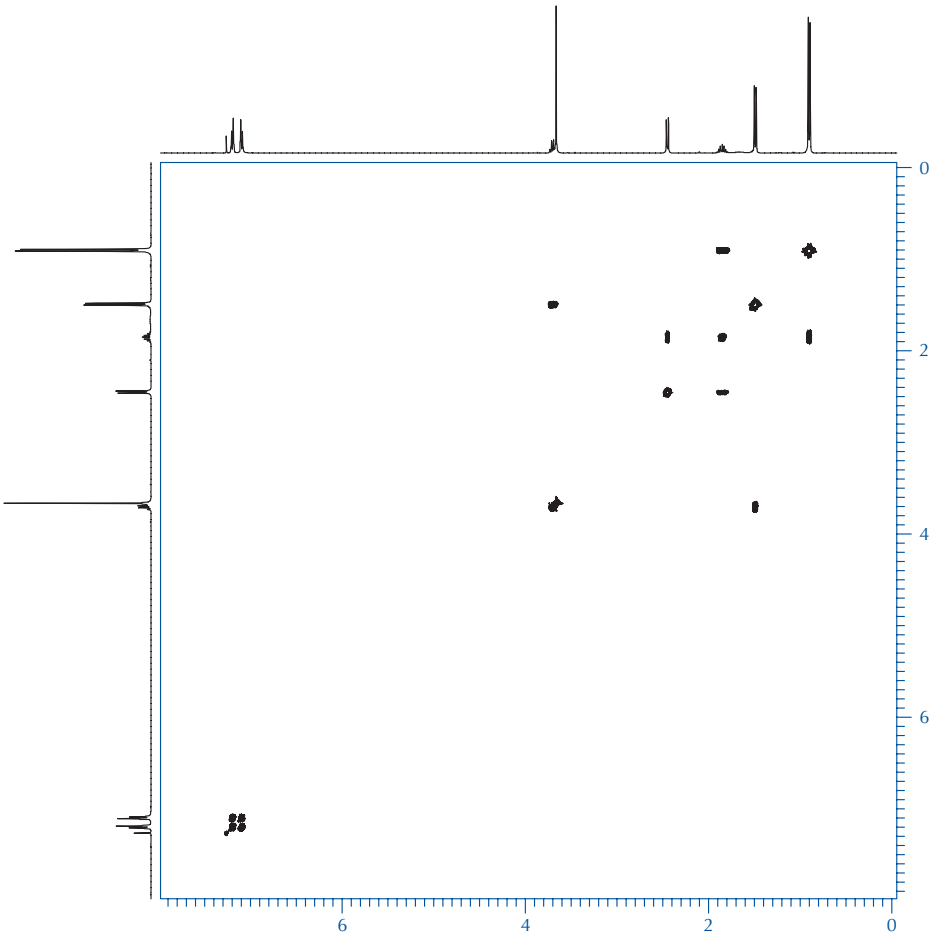


FIGURE 22.21 2D (H,H) COSY spectrum of the methyl ester of ibuprofen.

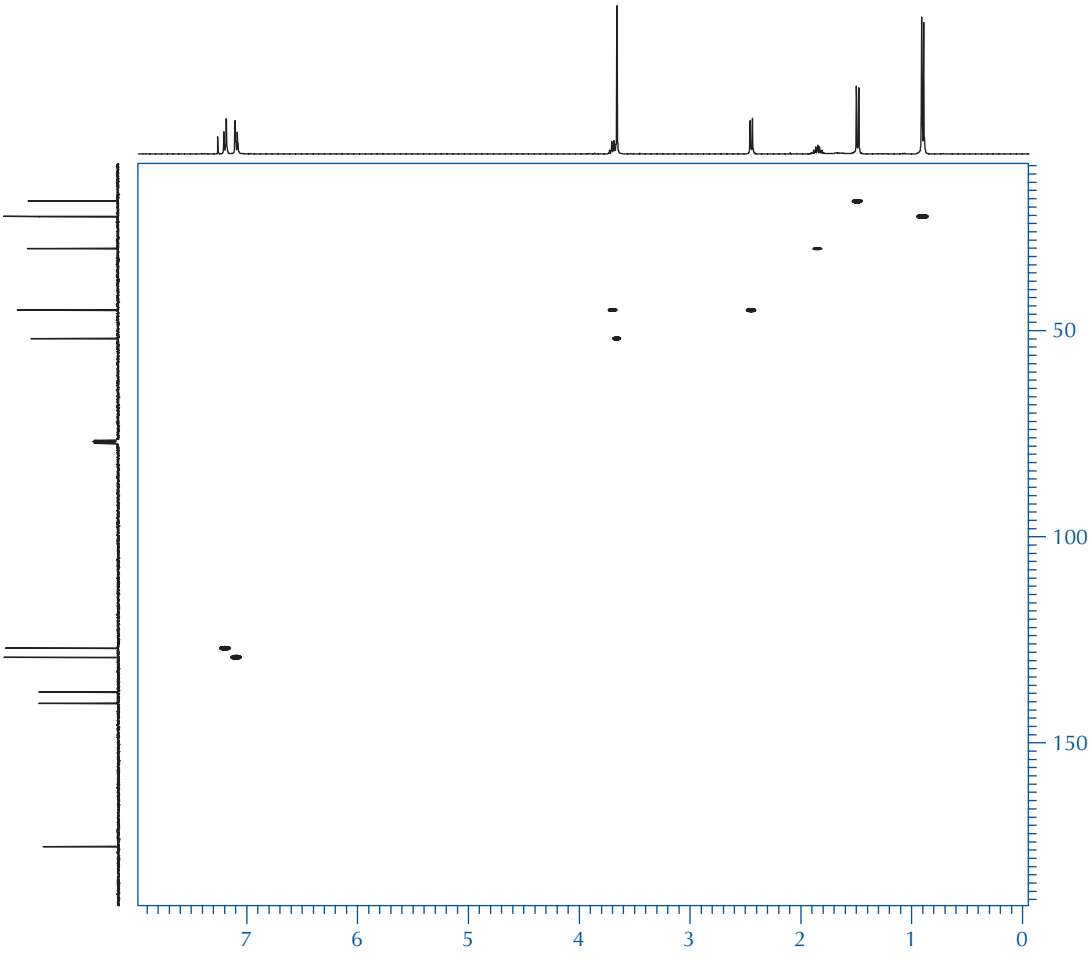


FIGURE 22.22 2D (C,H) COSY spectrum of the methyl ester of ibuprofen.

TECHNIQUE

23 MASS SPECTROMETRY

If Technique 23 is your introduction to spectroscopic analysis, read the Essay "The Spectroscopic Revolution" on pages 275–276 before you read Technique 23.

Most spectrometric techniques used by organic chemists involve the ability of molecules to absorb light of various energies. Mass spectrometry (MS) is different: rather than the absorption of light, it normally involves energy transfer from energetic electrons. This energy causes ionization of the molecules, and mass spectrometry measures the masses of these ions. It is a very sensitive technique that can be carried out with microgram quantities of compounds. Mass spectrometry is used to determine the molecular weights and molecular

formulas of compounds. Fragmentation of the initially formed ions in the mass spectrometer provides additional information that can be used to identify a compound or determine its structure.

23.1 Mass Spectrometers

In recent years, great strides have been made in instrumentation for mass spectrometry, and numerous types of mass spectrometers are now available. Even though they have functional differences, the basic components outlined in Figure 23.1 are common to all mass spectrometers. A sample is introduced into the mass spectrometer, where it is converted into a gas-phase ion through one of a variety of ionization techniques. The gas-phase ions are then sorted by their ***mass-to-charge (m/z) ratios*** in the mass analyzer. The sorted ions generate an electric current at the detector and a mass spectrum is created. Because the charge on the ions is typically +1, the m/z value for the molecular ion corresponds to the molecular weight of the compound.

Electron Impact (EI) Mass Spectrometry

The classic mass spectrometer ionizes the sample by electron impact and sorts the ions with a magnetic sector mass analyzer. To gain an appreciation of how all mass spectrometers work, it is worthwhile to examine this type of spectrometer in more detail. In the ionization chamber, shown in Figure 23.2, a stream of electrons with 70 electron volts (eV) of energy is created by heating a metal filament. The stream of electrons bombards the vaporized sample as it enters through a small hole in the vacuum chamber. A molecule struck by an external electron can become charged by either losing or gaining an electron; with electrons possessing 70 eV, the ionization produces many more positive than negative ions. The negative ions are attracted to the anode (electron trap), removing them from the ionization chamber. The positive ions are propelled toward the analyzer by the positively charged (+10,000 volts) repeller plate. Additional charged plates accelerate the ions to a constant velocity and focus the ion stream into the analyzer.

Molecules of the vast majority of organic compounds have only paired electrons, so when a single electron is lost from a molecule, a free radical is formed. Thus, the molecular ion formed by loss of an electron is a ***radical cation;*** it has an unpaired electron as well as a positive charge. The cation formed from an intact molecule is called the ***molecular ion*** ($M^{+\bullet}$)***.*** Once formed, the highly energetic molecular ion often breaks apart, forming both charged and uncharged fragments.

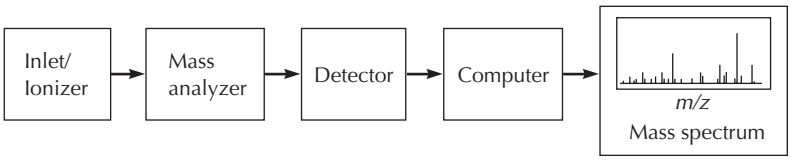


FIGURE 23.1
Basic components of a mass spectrometer.

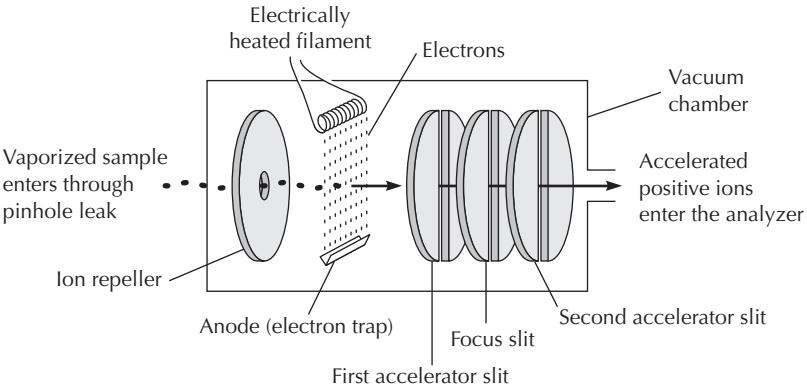
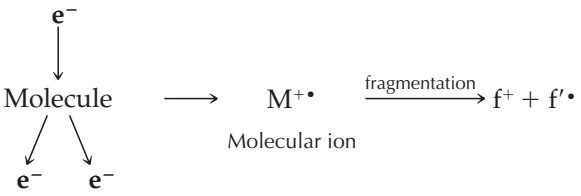


FIGURE 23.2
Electron impact (EI) ionization chamber.

Uncharged molecules and fragments are removed by the vacuum system. Usually, only the positively charged ions are analyzed.



As shown in Figure 23.3, the application of a magnetic field perpendicular to the flight path of the ions (perpendicular to the page) allows us to separate ions by their masses. The magnetic field causes the pathway of each ion to be curved. The amount of curvature is a function of the mass of the ion and the strength of the magnetic field. For an ion to strike the detector, it must follow a particular path consistent with the radius of the mass analyzer portion of the mass spectrometer. By adjusting the magnetic field strength, a beam of

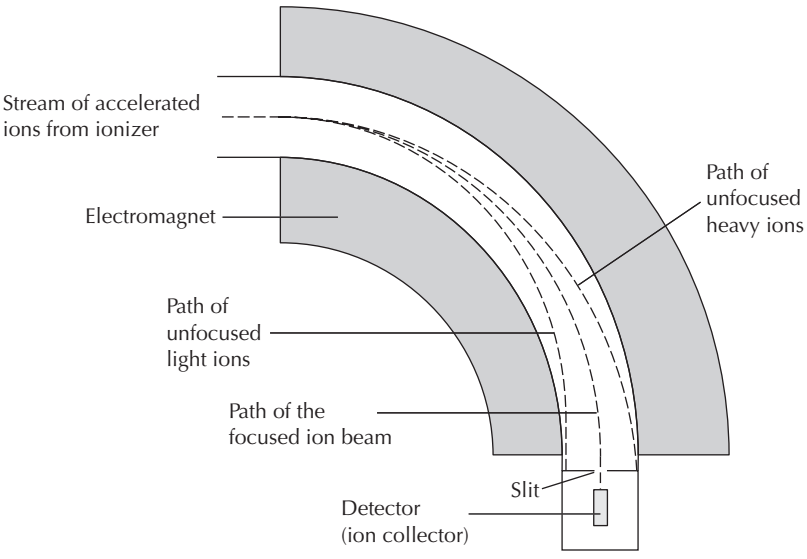


FIGURE 23.3
Magnetic sector mass analyzer.

ions with a specific mass-to-charge ratio can be focused on the detector. Ions with a larger *m/z* ratio do not bend enough to reach the detector, and ions with a smaller *m/z* ratio bend too much to hit the detector. The signal at the detector is recorded as a function of magnetic field strength. By varying the strength of the magnetic field, a scan over a range of *m/z* values can be collected. Because each ion usually bears a single positive charge, *m/z* simplifies to *m*, the mass of the ion.

GC-MS

If you are not familiar with gas chromatography, read "Overview of Gas Chromatography" on pages 257–258, plus Sections 19.1 and 19.2.

Many research and teaching laboratories have acquired hybrid instruments combining a ***gas chromatograph and a mass spectrometer (GC-MS).*** In these instruments, small samples of the effluent stream from a gas chromatograph are directed into a mass spectrometer. The molecules in the sample are then ionized by electron impact, and the resulting ions are accelerated and passed into the mass analyzer. The result is a mass spectrum for every compound eluting from the gas chromatograph. This technique is very efficient for analyzing mixtures of compounds because it provides the number of components in the mixture, a rough measure of their relative amounts, and the possible identities of the components.

The mass analyzer in most GC-MS instruments is a ***quadrupole mass filter,*** diagrammed in Figure 23.4. The quadrupole filter consists of four parallel stainless steel rods. Each pair of rods has opposing direct current (DC) voltages. Superimposed on the DC potential is a high-frequency alternating current (AC) voltage. As the stream of ions passes through the central space parallel to the rods, the combined DC and AC fields affect the ion trajectories, causing them to oscillate. For given DC and AC voltages and frequencies, only ions of a specific mass-to-charge ratio achieve a stable oscillation. These ions pass through the filter and strike the detector. Ions with different mass-to-charge ratios acquire unstable oscillations, tracing paths that collide with the rods or otherwise miss the detector. Although this mass sorting method is very different from the mass analyzer in magnetic sector instruments, the resulting mass spectra are comparable. Quadrupole mass filters are compact and fast, making them ideally suited for interfacing with other instruments, such as gas chromatographs. These systems have excellent resolution in the mass range of typical organic compounds. The GC-MS has become a major workhorse in modern organic and analytical chemistry laboratories.

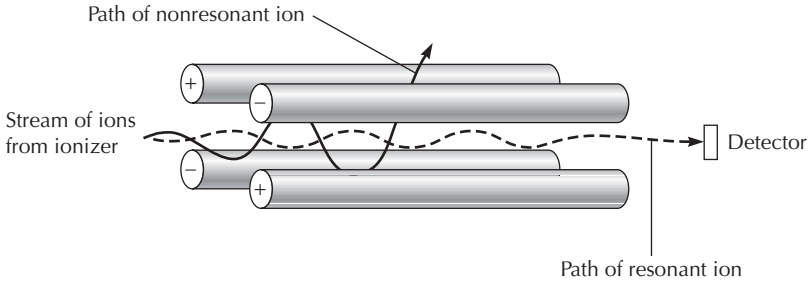


FIGURE 23.4
Quadrupole mass filter.

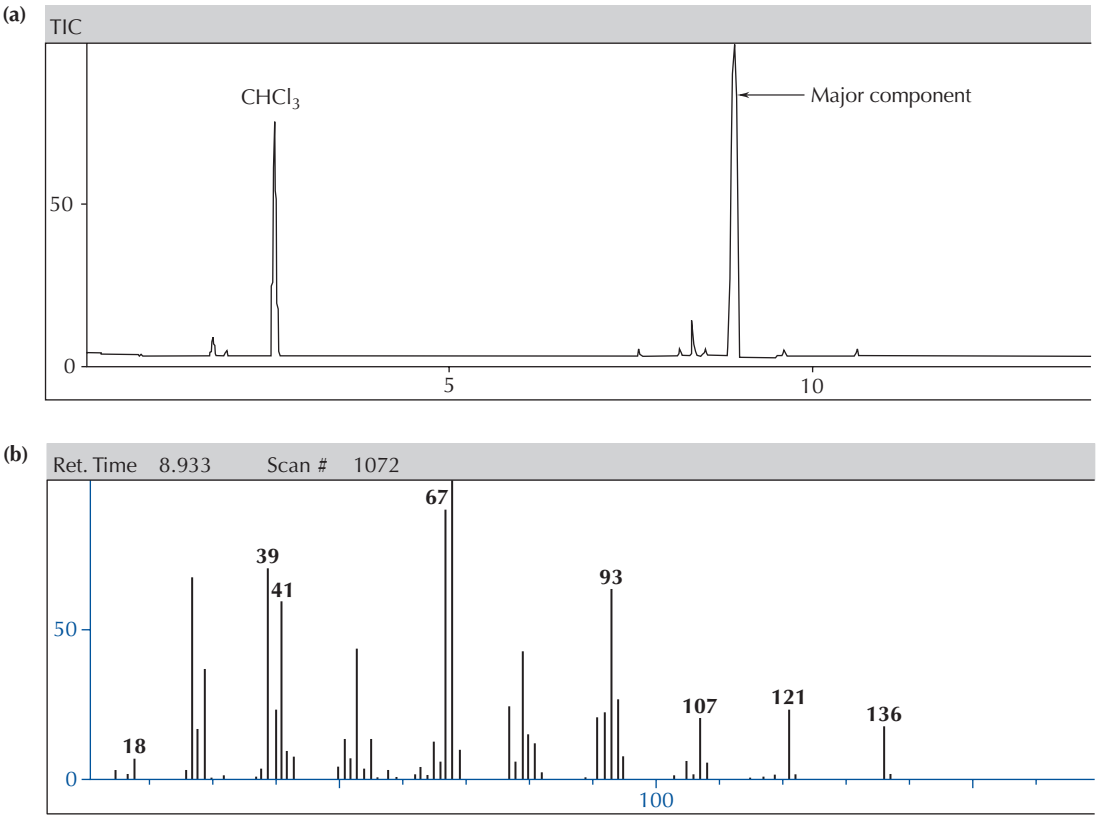


FIGURE 23.5 **(a)** Total ion current gas chromatogram of orange oil. **(b)** Mass spectrum of the major component.

An example of the data from a GC-MS is shown in Figure 23.5. The sample injected was orange oil purchased at a natural foods store. Figure 23.5a is a record of the total ion current (TIC) arriving at the detector of the mass spectrometer. This ion current corresponds to the gas chromatogram of the sample. The peak at approximately 2.5 min was caused by some residual chloroform that was used to clean the injection syringe. The peak at 8.9 min, designated with the arrow, is the major and virtually only compound in the sample. The mass spectrum of this major component of orange oil is shown in Figure 23.5b.

Advances in MS Instrumentation

Normally, samples are vaporized for simple mass spectrometric analysis. Thus, the electron impact technique is limited to compounds with significant vapor pressures. However, special ionization techniques can be used to ionize samples directly from the solid state or from solution. These techniques make it possible to study samples that have high molecular weights and very low vapor pressures, such as proteins and peptides. Special "softer" ionization techniques have also been developed that limit the amount of

energy transferred to the molecules, thereby minimizing the amount of fragmentation the molecular ions undergo and providing a more precise molecular weight of the compound.

23.2 Mass Spectra and the Molecular Ion

Mass spectral data are usually presented in graphical form as a histogram of ion intensity (*y*-axis) versus *m/z* (*x*-axis). For example, in the mass spectrum of 2-butanone shown in Figure 23.6, the molecular ion peak appears at *m/z* 72. Because the highly energized radical cation breaks into fragments, peaks also appear at smaller *m/z* values. The intensities are represented as percentages of the most intense peak of the spectrum, called the ***base peak.*** In this spectrum, the base peak is at *m/z* 43.

When interpreting a mass spectrum, the first area of interest is the molecular ion region. If the molecular ion does not completely fragment before being detected, its *m/z* provides the molecular weight of the compound, a valuable piece of information about any unknown.

Rule of Thirteen

A method known as the ***Rule of Thirteen*** can be used to generate the chemical formula of a hydrocarbon, C_nH_m, using the *m/z* of the molecular ion. The integer obtained by dividing *m/z* by 13 (atomic weight of carbon + atomic weight of hydrogen) corresponds to the number of carbon atoms in the formula. The remainder from the division is added to the integer to give the number of hydrogen atoms. For example, if the molecular ion of a hydrocarbon appears at *m/z* 92 in its mass spectrum, we can find the number of carbon atoms in the molecule by dividing *m/z* by 13: n = 92/13 = 7 with a remainder of 1. The value of *m* is 7 + 1 = 8, and the molecular formula for the hydrocarbon is C_7H_8. If the compound contains oxygen or nitrogen as well, some carbon atoms must be subtracted and the number of hydrogen atoms must be adjusted to give the appropriate *m/z* value. One oxygen atom is the equivalent of CH_4; that is, each oxygen and

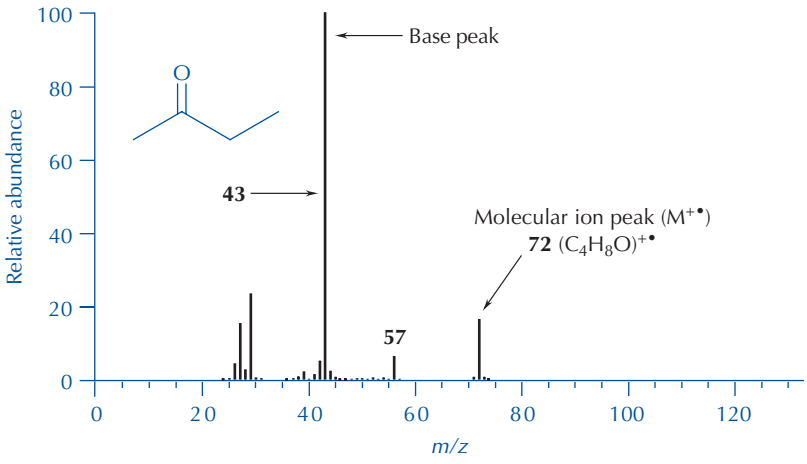


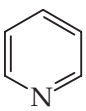
FIGURE 23.6
Mass spectrum of 2-butanone.

CH_4 unit accounts for 16 atomic mass units. One nitrogen atom is the equivalent of CH_2, 14 atomic mass units.

To apply the Rule of Thirteen to 2-butanone, the *m/z* of 72 is divided by 13, which gives the value of n in the formula C_nH_m. The remainder from the division is added to n to get the value of m. This calculation would provide the correct molecular formula if 2-butanone were a hydrocarbon. Because 2-butanone also contains an oxygen atom, an oxygen atom must be added to the formula and CH_4 subtracted. Dividing *m/z* by 13 yields 72/13 = 5 (with a remainder of 7); C_nH_m would be C_5H_{12}. Including the presence of oxygen, the correct molecular formula of 2-butanone is $C_5H_{12}O - CH_4 = C_4H_8O$. If the number of oxygen or nitrogen atoms is unknown, a number of candidate molecular formulas would have to be considered. All heteroatoms in the periodic table can be set equal to a C_nH_m equivalent. If the molecular ion has an odd *m/z* value, the first heteroatom to consider is nitrogen. Excellent tables that list formula masses of various combinations of C, H, O, and N can be found in *Spectrometric Identification of Organic Compounds*, 7th ed., by Silverstein, Webster, and Kiemle (Wiley: New York, 2005).

Fundamental Nitrogen Rule

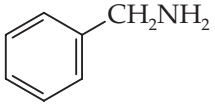
The fundamental nitrogen rule states that a compound whose molecular ion contains nothing other than C, H, N, or O atoms and that has an even *m/z* value must contain either no nitrogen atoms or an even number of nitrogen atoms. A compound whose molecular ion has an odd *m/z* value must contain an odd number of nitrogen atoms. The following compounds support the nitrogen rule:



Pyridine
MW 79

$(CH_3CH_2)_3N$

Triethylamine
MW 101



Benzylamine
MW 107

$H_2NCH_2CH_2NH_2$

Ethylenediamine
MW 60

M+1 and M+2 Peaks

Most elements occur in nature as a mixture of isotopes. Table 23.1 provides a list of isotopes for elements commonly found in organic compounds. If the molecular ion (M) is reasonably intense, signals for M+1 and M+2 ions can also be observed. The ratios of the intensities of the M+1 and M+2 peaks to that of the M peak depend on the isotopic abundances of the atoms in a molecule and the number of each kind of atom. Isotopes of carbon, hydrogen, oxygen, and nitrogen, the elements that make up most organic compounds, make small contributions to the M+1 and M+2 peaks, and the resulting intensities can sometimes reveal the molecular formulas of organic compounds. For example, the intensity of the M+1 peak relative to the intensity of the M peak in 2-butanone (molecular formula C_4H_8O) should be $(4 \times 1.08\%) + (8 \times 0.012\%) + (1 \times 0.038\%) = 4.45\%$. Useful tables listing molecular formulas and the ratios expected for these formulas can be found in *Mass and Abundance Tables for Use in Mass Spectrometry* by Beynon and Williams (Elsevier: New York, 1963).

Unfortunately, practical experience has shown that for many C, H, N, and O compounds, the expected ratios can be in error, which

TABLE 23.1 Relative isotope abundances of elements common in organic compounds

Elements	Isotope	Relative abundance	Isotope	Relative abundance	Isotope	Relative abundance
Hydrogen	^{1}H	100	^{2}H	0.012		
Carbon	^{12}C	100	^{13}C	1.08		
Nitrogen	^{14}N	100	^{15}N	0.37		
Oxygen	^{16}O	100	^{17}O	0.038	^{18}O	0.205
Fluorine	^{19}F	100				
Silicon	^{28}Si	100	^{29}Si	5.08	^{30}Si	3.35
Phosphorus	^{31}P	100				
Sulfur	^{32}S	100	^{33}S	0.79	^{34}S	4.47
Chlorine	^{35}Cl	100			^{37}Cl	32.0
Bromine	^{79}Br	100			^{81}Br	97.3
Iodine	^{127}I	100				

Adapted from J. R. de Laeter, J. K. Bohlke, P. de Bievre, H. Hidaka, H. S. Peiser, K. J. R. Rosman, and P. D. P. Taylor for the International Union of Pure and Applied Chemistry in "Atomic Weights of the Elements, Review 2000," *Pure and Applied Chemistry,* **2003,** 75, 683–800.

can occur for many reasons. For example, in the mass spectrometer the molecular ion may undergo ion/molecule collisions that provide additional intensity to the M+1 peak.

$$M^{+\bullet} + RH \longrightarrow MH^{+} + R^{\bullet}$$

In addition, if the molecular ion has a low relative abundance, the precision of the M+1 data is insufficient to give reliable ratios.

Although it can be difficult to use M+1 and M+2 data to determine accurate molecular formulas, MS is highly valuable for qualitative elemental analysis. In particular, it is fairly easy to use the M+2 peak to identify the presence of bromine and chlorine in organic compounds. The appearance of a large M+2 peak in a mass spectrum is evidence for the presence of one of these elements. The relative intensities tell you which one. A good example is seen in the mass spectrum of 1-bromopropane (Figure 23.7). The two major

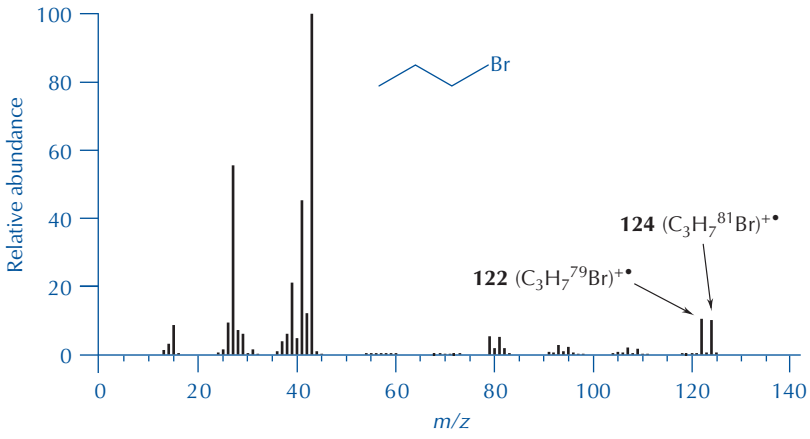


FIGURE 23.7 Mass spectrum of 1-bromopropane.

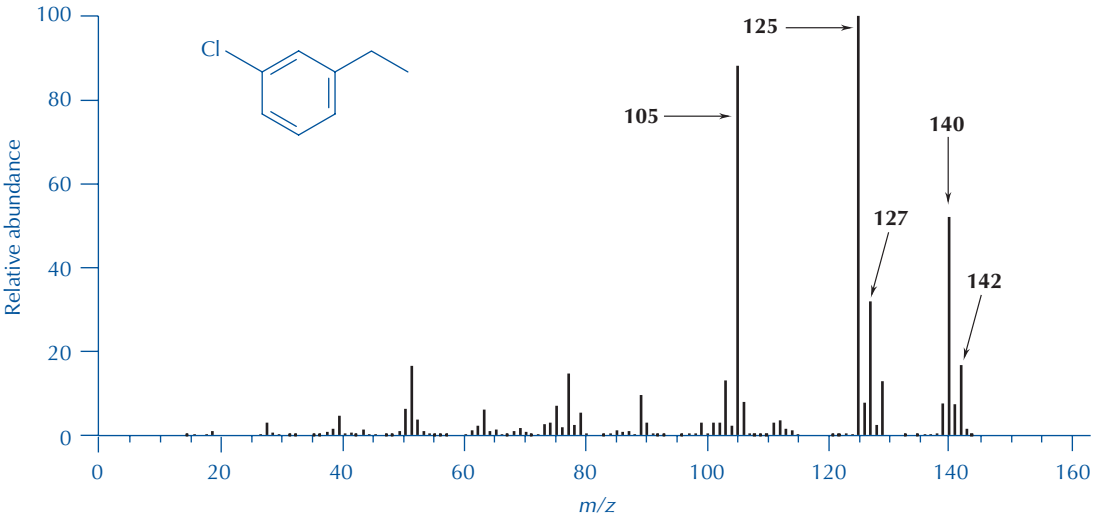


FIGURE 23.8 Mass spectrum of 3-chloroethylbenzene.

peaks in the molecular ion region are *m/z* 122 and 124 with an approximately 1:1 ratio. You can see from Table 23.1 that bromine exists in nature as a mixture of ^{79}Br and ^{81}Br in a ratio very close to 1:1. The peak at *m/z* 122, where the bromine atom has a mass of 79, is by convention defined as the molecular ion peak (M). Although the *m/z* 124 peak also corresponds to an intact molecule of +1 charge, it is referred to as the M+2 peak. Isotopic contributions of carbon, hydrogen, nitrogen, and oxygen to the M+1 and M+2 peaks are comparatively small. Thus a ratio of M/(M+2) that is very close to 1:1 is a clear indication that the molecule contains a bromine atom.

A monochloro compound is expected to have an M+2 peak that is 32.0% as intense as the M peak. For example, the mass spectrum of 3-chloroethylbenzene, shown in Figure 23.8, has a peak at *m/z* 142 that is approximately one-third the intensity of the molecular ion peak at *m/z* 140. A small contribution of ^{13}C is shown in the M+1 peak at *m/z* 141. The Rule of Thirteen can be used to calculate the molecular formula; the carbon equivalent of ^{35}Cl is C_2H_{11}. Dividing 140 by 13 yields 140/13 = 10 (with a remainder of 10); C_nH_m would be $C_{10}H_{20}$. Including the presence of a chlorine atom, the correct molecular formula of 3-chloroethylbenzene is shown to be $C_{10}H_{20}Cl - C_2H_{11} = C_8H_9Cl$.

23.3 High-Resolution Mass Spectrometry

In modern research laboratories, molecular formulas are usually determined by ***high-resolution mass spectrometry***. The expensive high-resolution instruments used for this purpose have both electric

and magnetic fields for focusing the ion pathways. These double-resolution instruments measure masses to four figures beyond the decimal point. Table 23.2 provides the masses that should be used for this approach. The exact mass of an isotope is established using carbon-12 as the standard. The exact mass of a molecule is determined by summing the masses of all the isotopes in the molecule. For example, the exact mass of the molecular ion of 2-butanone is $(4 \times 12.00000) + (8 \times 1.00783) + (1 \times 15.9949) = 72.0575$. By looking at the exact masses of molecules whose nominal molecular weight is 72, it is obvious that the correct molecular formula can be determined from the masses measured to four decimal places.

Formula	Exact Mass
$C_2H_4N_2O$	72.0324
$C_3H_4O_2$	72.0211
$C_3H_8N_2$	72.0688
C_4H_8O	72.0575
C_5H_{12}	72.0940

TABLE 23.2 Atomic weights and exact isotope masses for elements common in organic compounds

Element	Atomic weight	Nuclide	Mass
Hydrogen	1.00794	^{1}H	1.00783
		D(^{2}H)	2.01410
Carbon	12.0107	^{12}C	12.00000 (std)
		^{13}C	13.00335
Nitrogen	14.0067	^{14}N	14.0031
		^{15}N	15.0001
Oxygen	15.9994	^{16}O	15.9949
		^{17}O	16.9991
		^{18}O	17.9992
Fluorine	18.9984	^{19}F	18.9984
Silicon	28.0855	^{28}Si	27.9769
		^{29}Si	28.9765
		^{30}Si	29.9738
Phosphorus	30.9738	^{31}P	30.9738
Sulfur	32.065	^{32}S	31.9721
		^{33}S	32.9715
		^{34}S	33.9679
Chlorine	35.453	^{35}Cl	34.9689
		^{37}Cl	36.9659
Bromine	79.904	^{79}Br	78.9183
		^{81}Br	80.9163
Iodine	126.9045	^{127}I	126.9045

Adapted from J. R. de Laeter, J. K. Bohlke, P. de Bievre, H. Hidaka, H. S. Peiser, K. J. R. Rosman, and P. D. P. Taylor for the International Union of Pure and Applied Chemistry in "Atomic Weights of the Elements, Review 2000," *Pure and Applied Chemistry,* **2003,** *75,* 683–800.

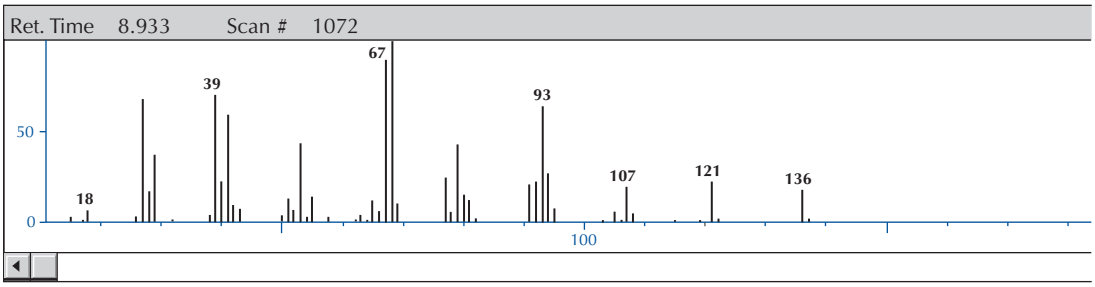
23.4 Mass Spectral Libraries

When a molecular ion breaks into fragments, the resulting mass spectrum can be complex because any one of a number of covalent bonds might be broken during fragmentation. Examination of Figures 23.5–23.8 shows that a large number of peaks arise even with relatively low-molecular-weight organic compounds. **The array of fragmentation peaks constitutes a fingerprint that can be used for identification.** Modern mass spectrometers are routinely equipped with computer libraries of mass spectra (some contain hundreds of thousands of spectra) for matching purposes. Typically, a computer program compares the experimental spectrum with spectra in the library and produces a ranked ***"hit list"*** of compounds with similar mass spectra. The ranking is based on how close the match is in terms of the presence of peaks and their intensities. At this point, the chemist intervenes. Mass spectra of highly ranked compounds on the hit list are compared with the acquired mass spectrum to determine the closest match.

The closest match does not necessarily prove the structure of a compound. Impurities that result from bleeding from the GC column can produce extra peaks in the mass spectrum and provide false hit-list candidates. In addition, the compound must be in the database, which is not always the case with research samples. Two comprehensive libraries of mass spectra are a collection of electron impact mass spectra of over 192,000 compounds from the National Institute of Standards and Technology (*NIST 08, NIST/EPA/NIH Mass Spectral Library*) and the *Wiley Registry 8th Ed/NIST 2008 Mass Spectral Library,* a collection of 562,000 EI mass spectra. There are also a number of specialized mass spectral libraries available that are limited and targeted to specific types of compounds, such as drug metabolites or steroids.

The hit list for the major component of orange oil is shown in Figure 23.9. The second column, labeled ***SI*** (for ***similarity index***), corresponds to how well the mass spectra that are stored in the computer library match the acquired spectrum of the compound from the GC-MS. Notice that several compounds appear more than once in the list; there are several spectra for these compounds in the library because many laboratories contribute spectra to the collection. Slight differences in instrument conditions and/or configurations can lead to subtle differences in the acquired spectra—another reason to examine the hit list with a critical eye.

A computer screen printout for comparing spectra of the hit list candidates is shown in Figure 23.10. The spectrum of hit 1 (Figure 23.10b) is virtually identical to the mass spectrum of the sample (Figure 23.10a). The spectrum of hit 2 (Figure 23.10c) is also similar, even though the compound's structure is different. However, on close examination some subtle differences can be discerned. A



Hit No.	SI	Name	Mol.Wgt.	Mol.Form.	Library
1	94	Limonene $$ Cyclohexene, 1-methyl-4-(1-n	136	C10H16	NIST62
2	90	1,5-Cyclooctadiene, 1,5-dimethyl-	136	C10H16	NIST12
3	90	Cyclohexene, 1-methyl-4-(1-methylethenyl)	136	C10H16	NIST12
4	87	Camphene $$ Bicyclo 2.2.1 heptane, 2,2-di	136	C10H16	NIST62
5	86	Cyclohexanol, 1-methyl-4-(1-methylethenyl	196	C12H20O2	NIST62
6	86	Limonene	136	C10H16	NIST12
7	86	Cyclohexene, 1-methyl-4-(1-methylethenyl)	136	C10H16	NIST62
8	85	D-Limonene	136	C10H16	NIST12
9	85	Bicyclo 2.2.1 hept-2-ene, 1,7,7-trimethyl- $$	136	C10H16	NIST62
10	85	D-Limonene $$ Cyclohexene, 1-methyl-4-(1	136	C10H16	NIST62
11	84	Limonene	136	C10H16	NIST12
12	83	D-Limonene	136	C10H16	NIST12
13	83	Cyclohexanol, 1-methyl-4-(1-methylethenyl	196	C12H20O2	NIST12
14	83	1,5-Cyclooctadiene, 1,5-dimethyl- $$ 1,5-Di	136	C10H16	NIST62
15	83	Cyclohexene, 1-methyl-4-(1-methylethenyl)	136	C10H16	NIST62
16	83	Limonene	136	C10H16	NIST12
17	82	Cyclohexene, 4-ethenyl-1,4-dimethyl- $$ 1,	136	C10H16	NIST62
18	82	Camphene	136	C10H16	NIST12
19	82	Cyclohexene, 1-methyl-5-(1-methylethenyl)	136	C10H16	NIST62
20	81	2,6-Octadien-1-ol, 3,7-dimethyl-, [Z]-	154	C10H18O	NIST12
21	80	4-Tridecen-6-yne, [Z]-	178	C13H22	NIST62
22	80	.alpha.-Myrcene	136	C10H16	NIST62
23	80	Bicyclo 2.2.1 heptane, 2,2-dimethyl-3-meth	136	C10H16	NIST62
24	80	2,6-Octadien-1-ol, 3,7-dimethyl-, [E]-	154	C10H18O	NIST12
25	80	D-Limonene	136	C10H16	NIST12

FIGURE 23.9 Hit list from a mass spectral library search for the major component of orange oil. The symbol $$ in the name denotes the start of a second name for the same compound.

significant signal at *m/z* 108 is present in Figure 23.10c but not in Figure 23.10a. Also, the signal at *m/z* 92 in Figure 23.10a is missing in Figure 23.10c. By these observations, hit 2 can be ruled out as a match, and a tentative conclusion can be reached that the major component of orange oil is limonene. The hit list is more reliable in confirming a structural option if it is combined with other spectroscopic evidence. Infrared or NMR evidence and the history of the sample—for example, if it came from a chemical reaction—can help to ascertain the correct molecular structure.

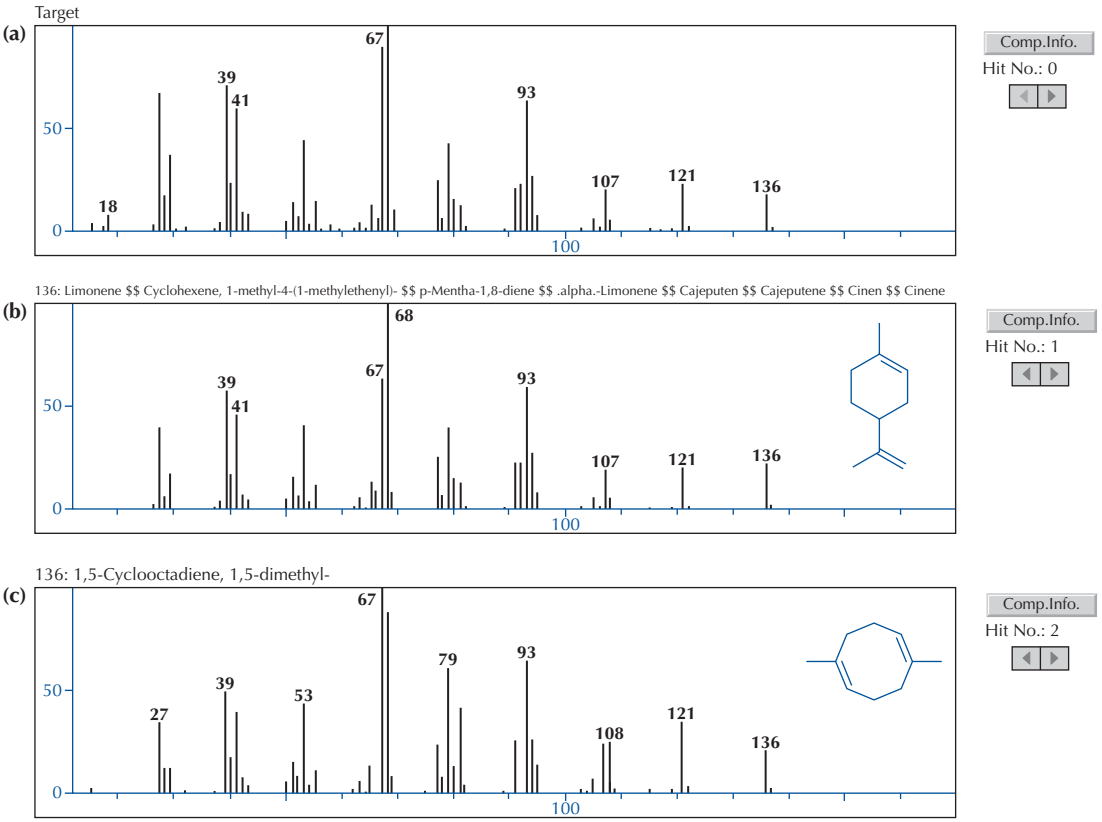


FIGURE 23.10 Computer comparison of two hit-list compounds for orange oil. **(a)** MS of the compound from GC-MS run. **(b)** MS of hit 1. **(c)** MS of hit 2.

23.5 Fragmentation of the Molecule

In cases where you are working with a compound not included in a library or the hit list of which does not lead to a satisfactory structure candidate, fragmentation pathways can provide important clues to the molecular structure. Numerous fragmentation rules have been established, but the topic is too wide in scope to be adequately covered in this book. However, a few of the most useful fragmentation patterns for common functional groups are described in the following paragraphs. **As a general rule, ions or free radicals that are more stable have a greater probability of forming from mass spectral fragmentation reactions.**

Mechanisms of fragmentation processes are sometimes easier to understand if ***"fishhooks"*** (curved arrows with half-heads) are used to represent the migration of single electrons. This notation is similar to that used in free-radical or photochemical processes:

$$\text{Molecule} \longrightarrow \underbrace{M^{+\bullet} = [f\overset{\frown}{-}f']^{+\bullet}}_{\text{Molecular cation radical}} \longrightarrow \underbrace{f^{+} + f'^{\bullet}}_{\text{Fragments}}$$

Forces that contribute to the ease with which fragmentation processes occur include the strength of bonds in the molecule (for example, the f—f′ bond) and the stability of the carbocations (f^+) and free radicals (f′·) produced by fragmentation. Although these fragments are formed in the gas phase, we can still apply our "chemical intuition," based on reactions in solution.

The carbocation fragment is often an even-electron species; the odd electron in the molecular cation radical ends up on the free-radical fragment. Of course, only ions are actually observed in the mass spectrum. When a molecular ion with an even *m/z* value gives a fragment ion that has an odd *m/z* value, a loss of a free radical by cleavage of just one covalent bond has occurred.

$$[H_3C\text{-}CH_3]^{+\cdot} \longrightarrow CH_3^+ + CH_3\cdot$$

m/z 30 *m/z* 15

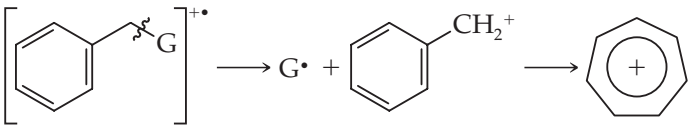
Simple cleavage of a molecular ion that has an odd *m/z* value gives a fragment ion with an even *m/z* value:

$$(CH_3CH_2)_2\overset{+\cdot}{N}\text{—}CH_2\text{-}CH_3 \longrightarrow (CH_3CH_2)_2\overset{+}{N}{=}CH_2 + CH_3\cdot$$

m/z 101 *m/z* 86

Aromatic Hydrocarbons

Aromatic hydrocarbons are prone to fragmentation at the bond β to the aromatic ring, yielding a benzylic cation that rearranges to a stable C_7H_7 aromatic carbocation called a tropylium ion.

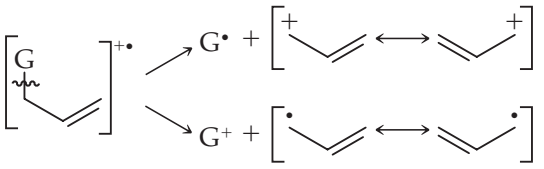


m/z 91

For mono-alkylbenzenes, the peak at *m/z* 91 is a very large signal, often the base peak. In the mass spectrum of ethylbenzene shown in Figure 23.11, the base peak of 91 (the tropylium ion) is the result of loss of a methyl group G· = ·CH_3.

Alkenes

Alkenes are similarly prone to fragmentation at the bond β to the double bond to give a stabilized allylic cation or allylic radical.



In the mass spectrum of 1-hexene shown in Figure 23.12, the allylic cation fragment ($CH_2{=}CH\text{—}CH_2^+$) is observed at *m/z* 41 and the propyl cation ($CH_3CH_2CH_2^+$) is observed at *m/z* 43.

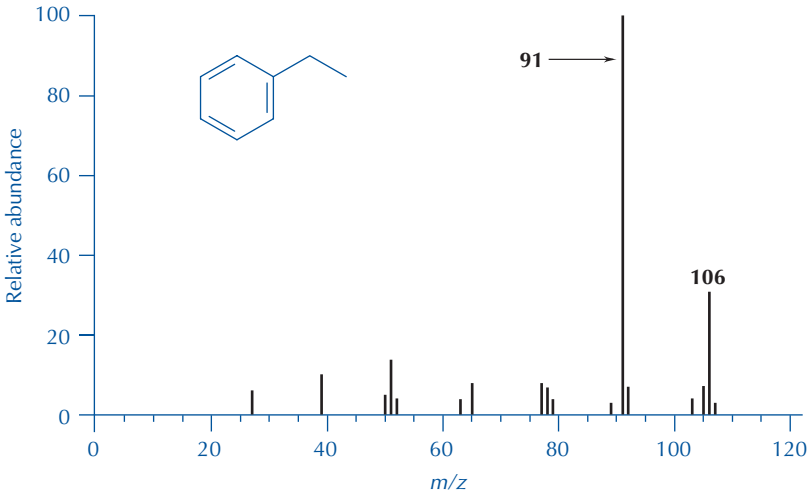


FIGURE 23.11 Mass spectrum of ethylbenzene.

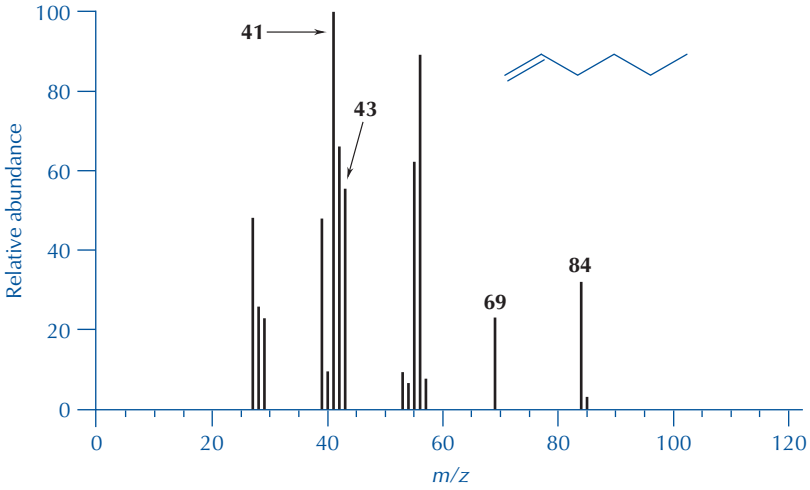
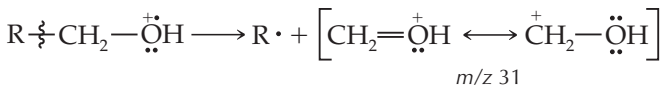


FIGURE 23.12 Mass spectrum of 1-hexene.

Alcohols

Alcohols fragment easily, and as a result, the molecular ion peak is often very small. In many cases, the molecular ion is not even apparent in the mass spectrum. One fragmentation pathway is the loss of hydroxyl radical (·OH) to produce a carbocation. However, the most important fragmentation pathway is the loss of an alkyl group from the molecular ion to form a resonance-stabilized oxonium ion. Primary alcohols show an intense *m/z* 31 peak resulting from this type of fragmentation.



The mass spectrum of 2-methyl-2-butanol shown in Figure 23.13 provides examples of the various fragmentation pathways available

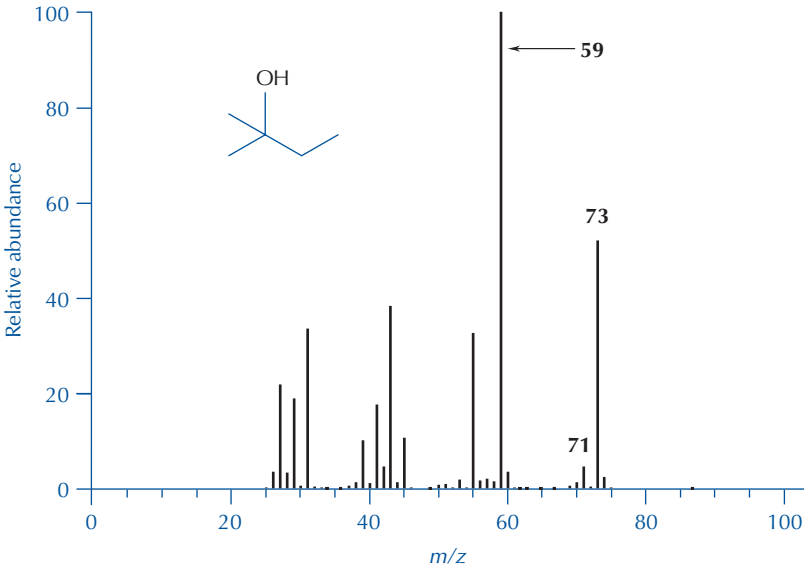
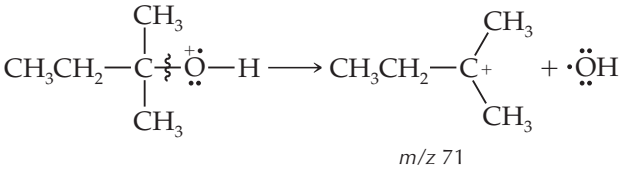
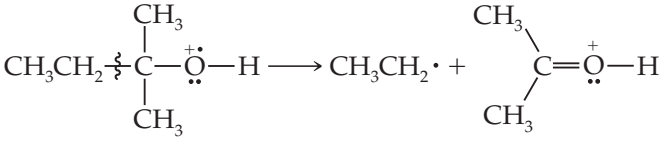


FIGURE 23.13
Mass spectrum of 2-methyl-2-butanol.

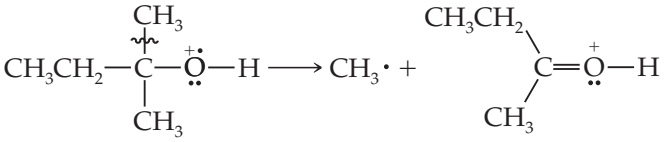
to alcohols. Notice that the molecular ion peak (*m/z* 88) is not present in the spectrum.



m/z 71

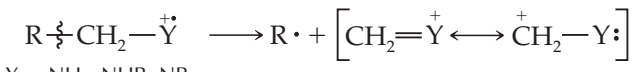


m/z 59



m/z 73

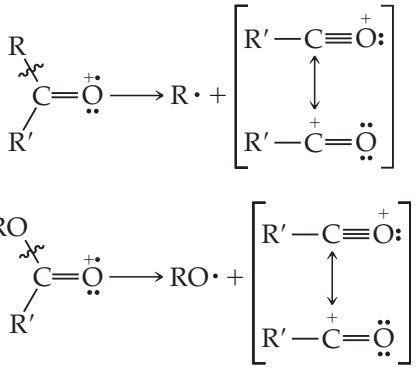
Other heteroatom-containing molecules undergo similar types of cleavage. Amines, ethers, and sulfur compounds can undergo fragmentations analogous to those exhibited by alcohols.



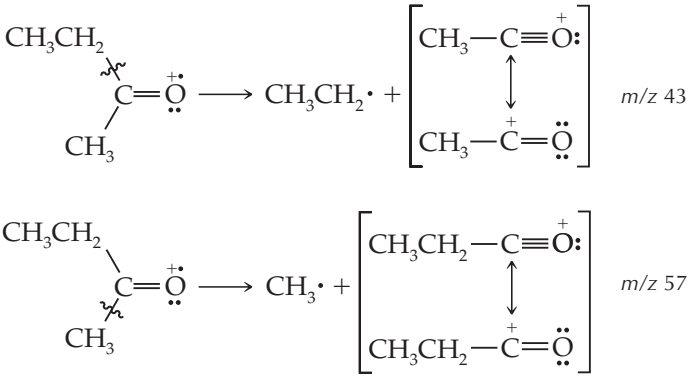
Y = NH_2, NHR, NR_2, OR, SH, or SR

Carbonyl Compounds

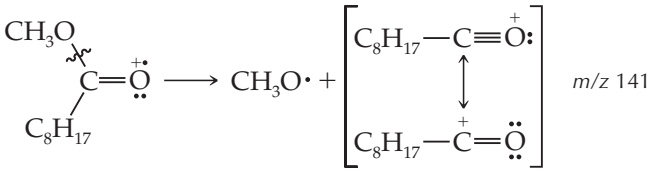
Ketones and other carbonyl compounds, such as esters, fragment by cleavage of bonds α to the carbonyl group to form a resonance-stabilized acylium ion.



In the spectrum of 2-butanone shown earlier in Figure 23.6, we see fragmentations on both sides of the carbonyl group.



In the mass spectrum of the ester methyl nonanoate (MW 172), shown in Figure 23.14, there is a significant peak at *m/z* 141. This peak results from formation of an acylium ion by loss of a fragment with a mass of 31, corresponding to a methoxyl radical.



The base peak at *m/z* 74 in Figure 23.14 occurs through the loss of a fragment with a mass of 98—a mass that corresponds to the loss of a neutral molecule with a molecular formula C_7H_{14}. That a neutral molecule (not a free radical) is lost by fragmentation is apparent because the molecular ion has an even *m/z* value and gives a fragment ion that also has an even *m/z* value. Carbonyl compounds with alkyl groups containing a chain of three or more carbon atoms can

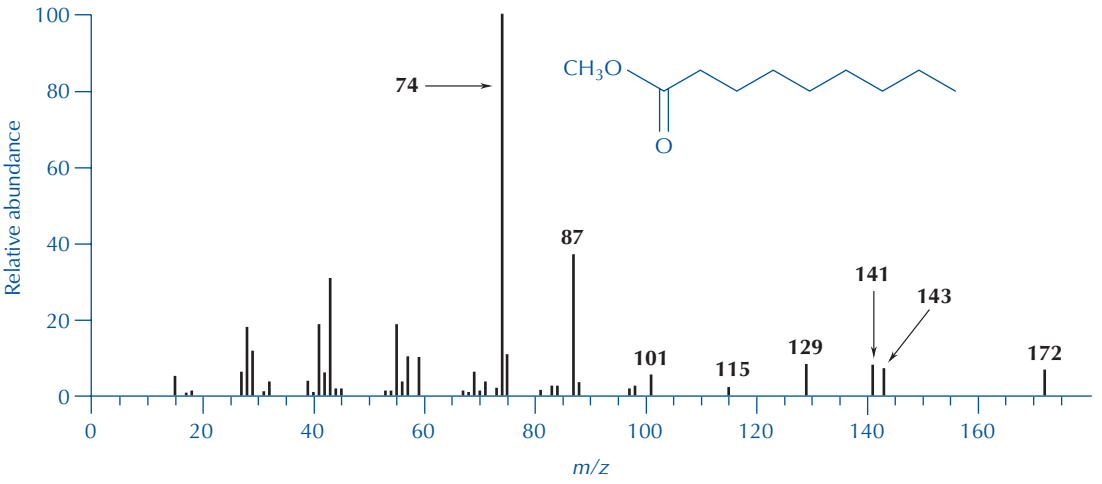
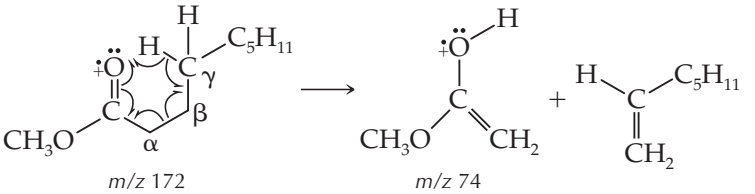


FIGURE 23.14 Mass spectrum of methyl nonanoate.

cleave at the β bond. This pathway, called the ***McLafferty rearrangement,*** requires the presence of a hydrogen atom on the γ (gamma) carbon atom.



The mass spectrum of methyl nonanoate demonstrates fragmentations also characteristic of other organic compounds with straight-chain alkyl groups. Carbon-carbon bonds can break at any point along the chain, leading to the loss of alkyl radicals.

m/z	Radical fragment lost from the molecular ion
143 (M–29)	$CH_3CH_2\cdot$
129 (M–43)	$CH_3CH_2CH_2\cdot$
115 (M–57)	$CH_3(CH_2)_2CH_2\cdot$
101 (M–71)	$CH_3(CH_2)_3CH_2\cdot$
87 (M–85)	$CH_3(CH_2)_4CH_2\cdot$

23.6 Case Study

We have seen that if a molecular ion does not fragment completely before being detected, its *m/z* value provides the molecular weight of the compound, which is a significant clue to its structure. Moreover, the profile for the fragmentation of the molecular ion can establish its identity, particularly if the compound is listed in the instrument's mass spectral library. Determining a structure from a

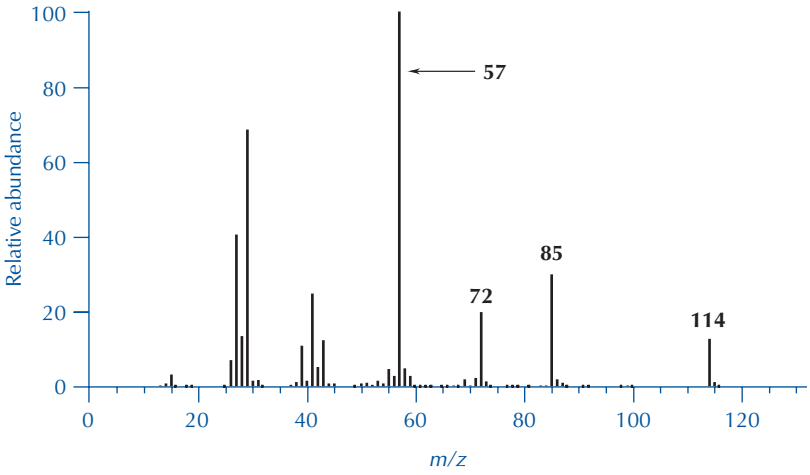
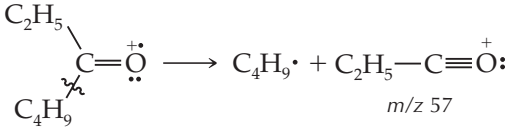


FIGURE 23.15 Mass spectrum of unknown for case study.

mass spectrum alone, however, is challenging and in most cases requires supplementary spectroscopic information.

As an example of how to approach mass spectrometric analysis, consider the mass spectrum shown in Figure 23.15. The molecular ion peak appears at *m/z* 114. The even value of *m/z* suggests that the compound does not contain nitrogen, unless it contains more than one nitrogen atom per molecule. The absence of a significant M+2 peak rules out the presence of chlorine or bromine. The IR spectrum of the compound has an intense peak at 1715 cm^{-1}, which indicates the presence of a C═O group. Knowing that we are working with a carbonyl compound suggests that the base peak at *m/z* 57 may be a stabilized oxonium-ion fragment, formed by α cleavage and loss of a C_4H_9 radical (M–57).

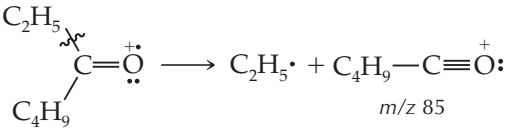


Application of the Rule of Thirteen can generate one or more candidate molecular formulas for the compound. Dividing 114 by 13, we have 114/13 = 8 (with a remainder of 10); if the compound were a hydrocarbon, its formula C_nH_m would be C_8H_{18}. Including the presence of an oxygen atom, we would have $C_8H_{18}O - CH_4 = C_7H_{14}O$. Our short list of possible molecular formulas is $C_7H_{14}O$ and perhaps $C_6H_{10}O_2$.

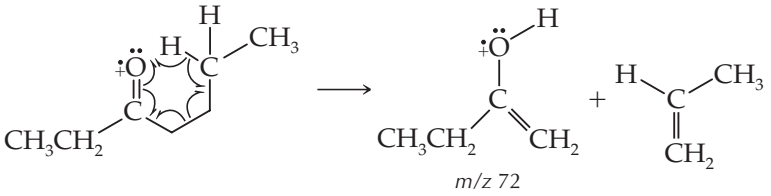
Next, an inventory of the significant MS peaks is put together, along with the masses lost on fragmentation.

m/z	Mass	Possible fragments
114	M	
85	M–29	C_2H_5·
72	M–42	C_3H_6
57	M–57	C_4H_9·

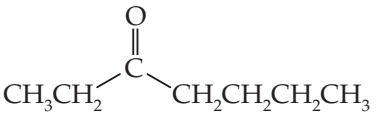
The mass spectral evidence gives no support for having more than one oxygen atom per molecule of the compound. It is likely that this carbonyl compound is a ketone, because the peak at *m/z* 85 is consistent with an α cleavage, with loss of an ethyl radical to give a stabilized oxonium ion.



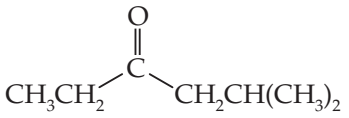
Another important clue in the mass spectrum shown in Figure 23.15 is the loss of a neutral molecule, C_3H_6, producing the peak at *m/z* 72. Loss of a neutral molecule results from a McLafferty rearrangement, which requires the presence of a carbonyl group and a γ hydrogen atom. This fact is also consistent with the presence of a C_4H_9 group, shown by the *m/z* 57 fragment ion.



Propene could be lost if a methyl group were attached to the β or the γ carbon atom. There are two compounds consistent with all the evidence, 3-heptanone and 5-methyl-3-hexanone.



3-Heptanone



5-Methyl-3-hexanone

Referring to spectra in the *Wiley Registry of Mass Spectral Data*, the spectrum of the unknown is very similar to the spectra of both 3-heptanone and 5-methyl-3-hexanone. However, the spectrum of 5-methyl-3-hexanone has a signal at *m/z* 99 that is missing in the spectra of 3-heptanone and the unknown. The identity of the unknown is probably 3-heptanone. A ^{1}H NMR spectrum of the compound would establish the structure unambiguously.

23.7 Sources of Confusion

As with IR and NMR spectroscopy, it is important to be aware of factors that can lead to unexpected, confusing, or poorly defined peaks in a mass spectrum. Some of the problems can be avoided by proper sample preparation or modification of sampling conditions. Some "problems" are inherent features of the technique.

Presence of Impurities

Small amounts of impurities can produce MS peaks in regions of the mass spectrum that should be blank. This is particularly important when you are trying to determine the *m/z* of the molecular ion. In

GC-MS the impurities may be residual material from a previous sample or from degradation of the GC column itself. Impurities can also produce small peaks at *m/z* values higher than the molecular weight of any compound in your sample. Thus it is necessary to be judicious in your assignment of a molecular ion peak. It is also important to allow enough time between GC injections to clear the previous sample from the GC column. A background scan can be used to identify peaks due to residual materials in the mass spectrometer.

Absence of a Molecular Ion

Many compounds fragment so easily that there is no discernible molecular ion in the mass spectrum. Examples of these types of compounds include tertiary alcohols, which dehydrate easily, and many alkyl bromides and chlorides, from which bromine or chlorine atoms are easily lost by fragmentation. Even without a usable molecular ion peak, use of the mass spectrometer's spectral library may provide a useful list of candidate molecular structures.

Complex Fragmentation Patterns

Sometimes a mass spectrum of a pure compound exhibits significant peaks that are difficult to rationalize. These fragments may be the result of multiple-step fragmentations or they may have been formed by complex rearrangements. Do not dwell on these peaks.

Further Reading

Crews, P.; Rodríguez, J.; Jaspars, M. *Organic Structure Analysis;* Oxford University Press: Oxford, 1998.

Lee, T. L. *A Beginner's Guide to Mass Spectral Interpretation;* Wiley: New York, 1998.

McLafferty, F. W.; Tureček, F. *Interpretation of Mass Spectra;* 4th ed.; University Science Books: Mill Valley, CA, 1993.

McMaster, M. C. GC/MS: *A Practical User's Guide;* 2nd ed.; Wiley: New York, 2008.

Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrometric Identification of Organic Compounds;* 7th ed.; Wiley: New York, 2005.

Useful Web Sites

NIST Standard Reference Database: http://webbook.nist.gov/chemistry

Spectral Database for Organic Compounds, National Institute of Advanced Industrial Science and Technology (AIST), Japan: http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng

Questions

1. Match the compounds azobenzene, ethanol, and pyridine with their molecular weights: 46, 79, and 182. How does the fact that in one case the molecular weight is odd and in the other two cases the molecular weight is even help in the selection process?
2. The mass spectrum of 1-bromopropane is shown in Figure 23.7. Propose a structure for the base peak at *m/z* 43.
3. The base peak of 1-pentanol is at *m/z* 31, whereas that for 2-pentanol is at *m/z* 45. Explain briefly.
4. Similar types of cleavages give rise to two peaks for 4-chlorobenzophenone, one at *m/z* 105 (the base peak) and one at *m/z* 139 (70% of base). A clue to their identities is the fact that the *m/z* 139 peak is accompanied by a peak at *m/z* 141 that is about one-third of the *m/z* 139 peak intensity.

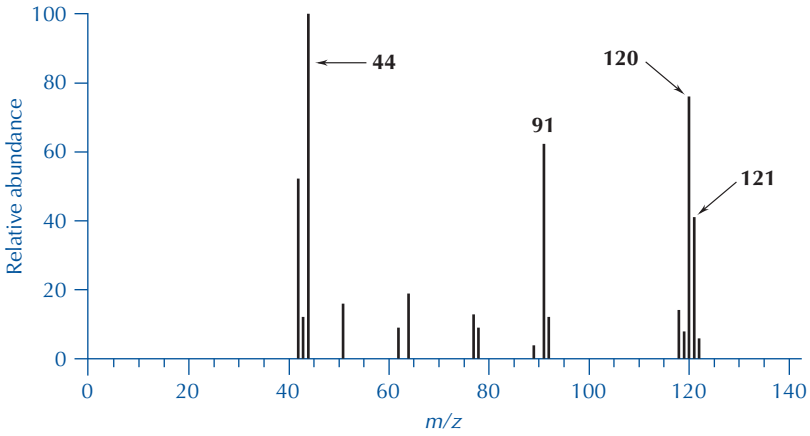
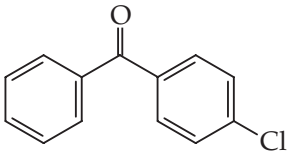


FIGURE 23.16 Mass spectrum of unknown for question 6.

The *m/z* 105 peak has no such partner. What structures correspond to these peaks? Show your reasoning.



4-Chlorobenzophenone

5. What fragmentations lead to the peaks at *m/z* 127, 125, and 105 in Figure 23.8?
6. An unknown compound has the mass spectrum shown in Figure 23.16. The molecular ion peak is at *m/z* 121. The infrared spectrum of the unknown shows a broad band of medium intensity at 3300 cm^{-1}. Determine the structure of the unknown. What fragmentations lead to the peaks at *m/z* 120, 91, and 44?

Hit No.	SI	Name	Mol.Wgt.	Mol.Form.	Library
1	89	Phenol, 2-methoxy-4-(1-propenyl)- $$ Phen	164	C10H12O2	NIST62
2	88	Phenol, 2-methoxy-5-(1-propenyl)-, [E]-	164	C10H12O2	NIST12
3	87	Phenol, 2-methoxy-5-(1-propenyl)-, [E]- $$	164	C10H12O2	NIST62
4	86	Phenol, 2-methoxy-4-(1-propenyl)-, [E]- $$	164	C10H12O2	NIST62
5	86	Phenol, 2-methoxy-4-(1-propenyl)-, acetate	206	C12H14O3	NIST62
6	85	Eugenol	164	C10H12O2	NIST12
7	84	Eugenol	164	C10H12O2	NIST12
8	83	7-Benzofuranol, 2,3-dihydro-2,2-dimethyl- $	164	C10H12O2	NIST62
9	82	Phenol, 2-methoxy-4-(1-propenyl)-	164	C10H12O2	NIST12
10	82	Phenol, 2-methoxy-4-(1-propenyl)-	164	C10H12O2	NIST12
11	81	Eugenol $$ Phenol, 2-methoxy-4-(2-propen	164	C10H12O2	NIST62
12	81	Eugenol	164	C10H12O2	NIST12
13	80	Phenol, 2-methoxy-4-(2-propenyl)-, acetate	206	C12H14O3	NIST12
14	78	Phenol, 2-methoxy-6-(2-propenyl)- $$ o-All	164	C10H12O2	NIST62
15	77	3-Allyl-6-methoxyphenol $$ Phenol, 2-meth	164	C10H12O2	NIST62
16	76	Phenol, 2-methoxy-6-(1-propenyl)- $$ Phen	164	C10H12O2	NIST62
17	76	Eugenol	164	C10H12O2	NIST12
18	75	Carbofuran	221	C12H15NO3	NIST12
19	74	Phenol, 2-methoxy-4-(1-propenyl)-	164	C10H12O2	NIST12
20	73	Phenol, 2-methoxy-4-(1-propenyl)-	164	C10H12O2	NIST12
21	71	7-Benzofuranol, 2,3-dihydro-2,2-dimethyl-	164	C10H12O2	NIST12
22	71	3-Octen-5-yne, 2,2,7,7-tetramethyl-, [E]-	164	C10H12O2	NIST62
23	71	Benzene, 4-ethenyl-1,2-dimethoxy- $$ 3,4-D	164	C10H12O2	NIST62
24	71	5-Decen-3-yne, 2,2-dimethyl-, [Z]-	164	C10H12O2	NIST62
25	71	3-Octen-5-yne, 2,2,7,7-tetramethyl-	164	C10H12O2	NIST62

FIGURE 23.17 Hit list from a mass spectral library search of a major clove oil component.

7. The exact *m/z* of a sample of aspirin was determined to be 180.0422. What is the molecular formula that corresponds to this exact mass?
8. A sample of clove oil was analyzed using a GC-MS. A search of the mass spectral library for a match to the mass spectrum of the major component of clove oil produced the hit list shown in Figure 23.17. A computer screen printout comparing the mass spectra of hit 1, hit 2, and hit 6 with the mass spectrum of the major component of clove oil is shown in Figure 23.18. Which of the three hit-list candidates is the best match with the MS of the major component of clove oil? Show your reasoning.

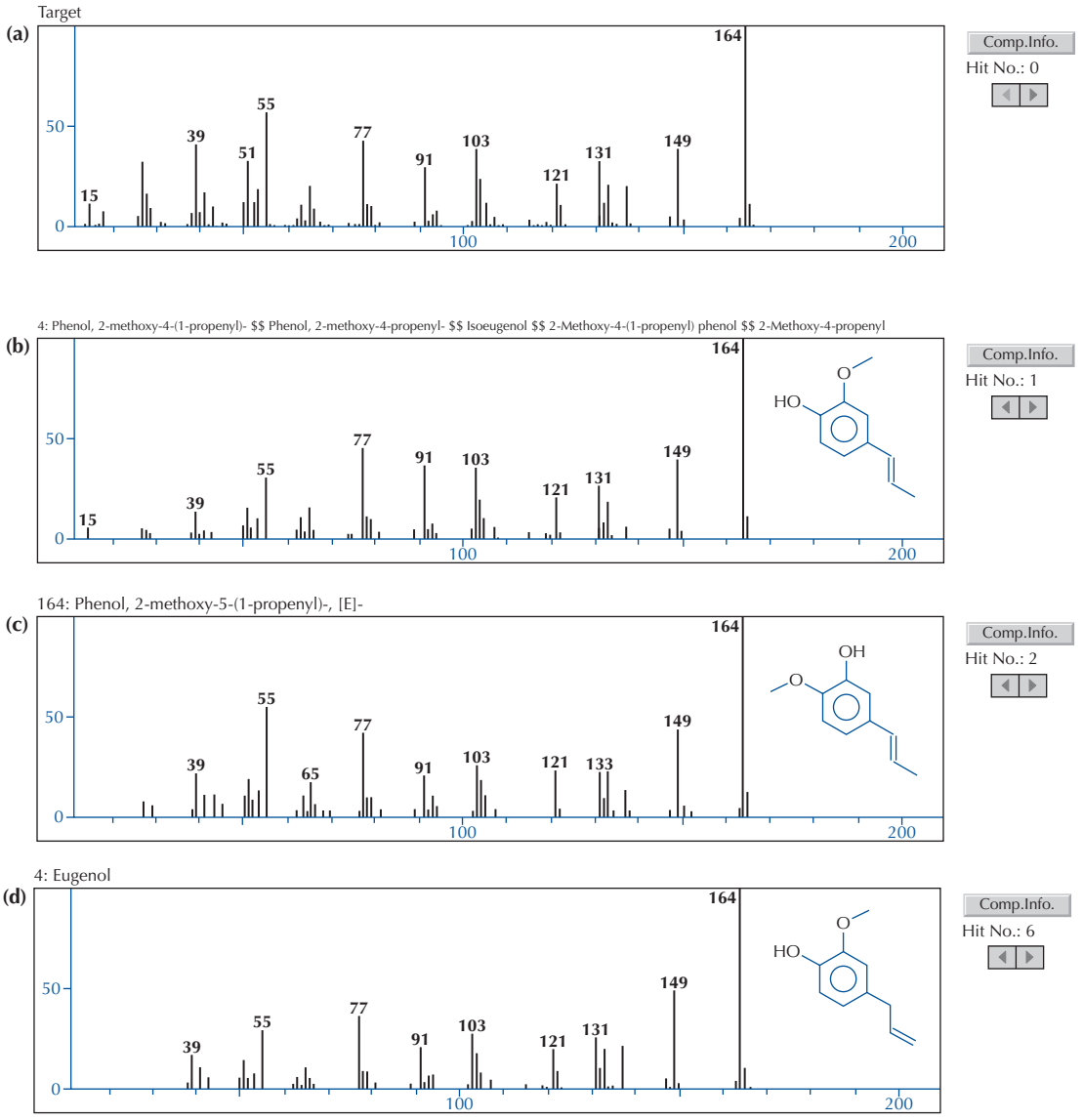
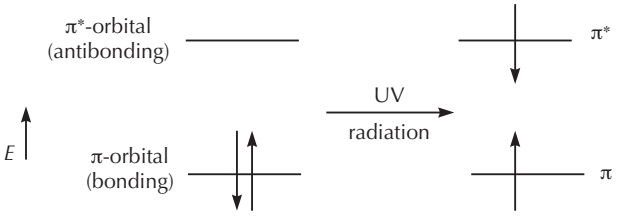


FIGURE 23.18 Computer comparison of three hit list compounds for clove oil. **(a)** MS of the compound from the GC-MS run. **(b)** MS of hit 1. **(c)** MS of hit 2. **(d)** MS of hit 6.

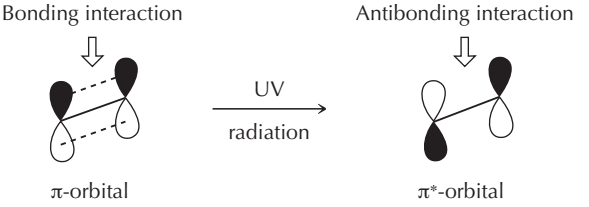
TECHNIQUE

24 ULTRAVIOLET AND VISIBLE SPECTROSCOPY

The absorption of ultraviolet (UV) or visible (VIS) light by organic compounds occurs by the excitation of an electron from a bonding or nonbonding molecular π-orbital to an antibonding molecular π*-orbital.

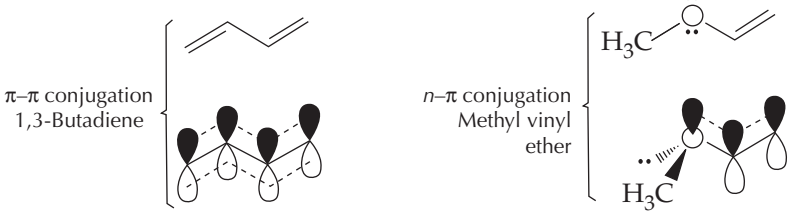


The bonding and antibonding molecular orbitals of a π-system can be depicted as follows:



This excitation process requires a substantial energy, comparable to the strength of a chemical bond. All organic compounds absorb UV light, but few commercial spectrometers can effectively scan the wavelengths where C—H, C—C, and nonconjugated C═C bonds absorb, due to interference from strong UV absorption by O_2 and CO_2 in the atmosphere.

The electronic transitions useful in UV spectroscopy involve the absorption of radiation between wavelengths of 200 and 400 ***nanometers (nm)*** or $200-400 \times 10^{-9}$ meters. In visible spectroscopy light between 400 and 800 nm is used. In either case, an electron from a π-bonding orbital or a nonbonding *n*-orbital is excited to an antibonding π*-orbital. We will be concerned only with $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions in conjugated organic compounds because these are the electronic transitions most likely to occur in the 200–800-nm region. Conjugated compounds can have either one or more pairs of alternating double bonds or else a double bond conjugated to a nonbonding pair of electrons on a heteroatom, such as oxygen, nitrogen, or halogen.



Until the 1950s the only physical method readily available for the determination of the structures of organic compounds was ultraviolet spectroscopy, but with the advent of NMR and mass spectrometry, few organic chemists now rely on UV as a primary tool for structure determination. However, UV and visible spectroscopy are important analytical tools for quantifying and characterizing organic compounds and are of vital importance in biochemistry. In fact, the Beckman DU spectrophotometer, which became commercially available in 1940, has been cited as one of the most important instruments ever developed for the advancement of the biosciences. It has also been estimated that more than 90% of the analyses performed in clinical laboratories are based on UV and visible spectroscopy.

Chromatographic analyses constitute the major application of UV spectroscopy in modern organic chemistry. High-performance liquid chromatographs (HPLCs) that are equipped with diode-array UV detectors are found in virtually all organic chemistry research labs. UV light is also utilized for the visualization of thin-layer chromatography (TLC) plates when silica plates with a fluorescent indicator are used. Currently, students of organic chemistry encounter UV spectroscopy less often than NMR, IR, and MS, but it is important to understand the basic principles and practice of ultraviolet spectroscopy.

24.1 UV/VIS Spectra and Electronic Excitation

UV and visible spectra are plots of absorbance (A) against the wavelength in nanometers. The absorbance is related to concentration by the ***Beer-Lambert law***:

$$A = \log (I°/I) = \varepsilon lc$$

where

$I°$ is the intensity of the incident light
I is the intensity of the transmitted light
ε is the molar extinction coefficient in $M^{-1}cm^{-1}$
l is the length of the cell path in centimeters
c is the sample concentration in moles/liter (M)

Notice that in UV/VIS spectroscopy the absorbance is plotted, not the percent transmission as in IR spectroscopy. Most important, the proportionality of the absorbance and the concentration is linear over a wide range of concentrations, making UV/VIS spectroscopy ideal for determining the concentration of a compound. Values of ε, the molar extinction coefficient, can vary from 10 to greater than 10^5. Thus, some ***chromophores***, the organic functional groups that absorb UV or visible light, can absorb far more efficiently than others, by factors of 10^4 or greater.

WORKED EXAMPLE

The principal photoreceptor of most green plants is chlorophyll a, which has a molar extinction coefficient of $1.11 \times 10^5\ cm^{-1} \cdot M^{-1}$ at 428 nm in ether. If the absorbance of pure chlorophyll a in a 1.00 cm cell is 0.884 at 428 nm, what is the concentration of chlorophyll in the ether solution?

Use of the Beer-Lambert Law provides the answer.

$A = \varepsilon lc$ or $c = A/\varepsilon l$

$c = 0.884/(1.11 \times 10^5\ cm^{-1} \cdot M^{-1} \times 1.00\ cm)$

$c = 7.96 \times 10^{-4}\ M$

π–π* and n–π* Electronic Transitions

As with IR and NMR spectroscopy, the relationship of the frequency of the absorbed radiation to the energy gap (ΔE) in UV spectroscopy is given by Planck's law:

$$\Delta E = h\nu = hc(1/\lambda)$$

where

h = Planck's constant
c = the speed of light
λ = the wavelength of the radiation that is being absorbed
$\nu = c/\lambda$

The energy gap has an inverse dependence on the wavelength of absorbed light; therefore, the smaller the gap, the longer the wavelength of light.

Energy gaps (ΔE) for electronic transitions that occur when UV radiation is absorbed are much greater for π–π* than *n*–π* transitions. Therefore, π–π* transitions occur at shorter wavelengths than *n*–π* transitions. Figure 24.1(a) shows the relative energy gaps

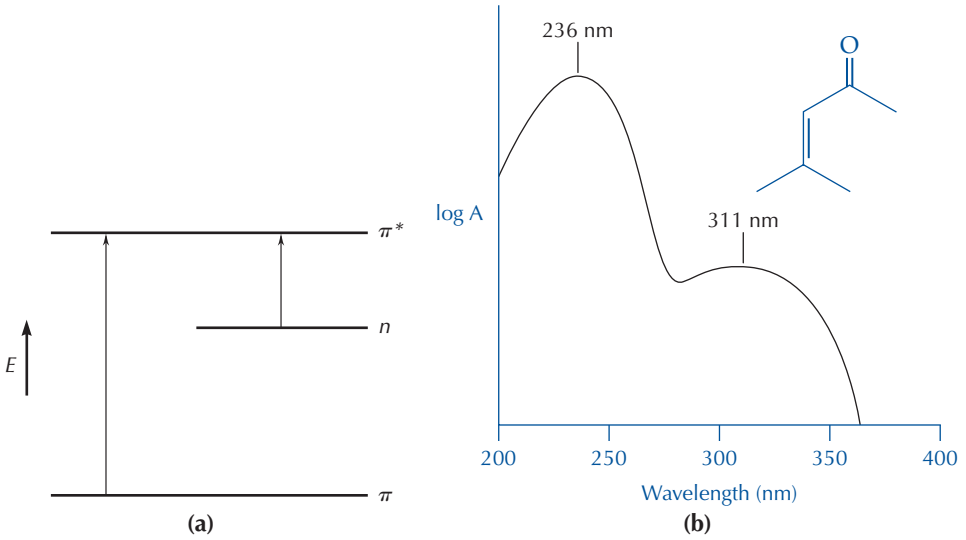


FIGURE 24.1 **(a)** Electronic transitions between orbital energy levels, illustrating a π–π* transition and a lower-energy *n*–π* transition. **(b)** UV spectrum of 4-methyl-3-penten-2-one in ethanol, showing a π–π* transition at λ_{max} = 236 nm and an *n*–π* transition at λ_{max} = 311 nm.

for π–π* and *n*–π* transitions and Figure 24.1(b) shows a UV spectrum that has absorbance for both types of transitions.

Electronic transitions occur much faster than the time necessary for a molecule to vibrate or rotate. Therefore, electronic excitation occurs from a range of vibrational and rotational energy levels. For this reason, when UV radiation interacts with a large population of molecules having a variety of vibrational and rotational states, it is absorbed at numerous wavelengths. In general, UV and visible radiation is absorbed in absorption bands rather than at discrete wavelengths. The absorption bands often have a width of 10 nm or more. The wavelength of a UV absorption band is given by λ_{max}, the wavelength of maximum absorbance.

The π–π* transition at λ_{max} 236 nm in Figure 24.1(b) has a molar extinction coefficient (ε) of 12,800, whereas the *n*–π* transition at λ_{max} 311 nm has an ε value of only 59. The intensity of π–π* transitions is virtually always greater than the intensity of *n*–π* transitions. The *n*–π* absorbances are much weaker because of the unfavorable spatial orientation of orbitals containing nonbonding electrons relative to the π-orbital, which does not allow much overlap between a nonbonding orbital and the π-orbital. In a quantum mechanical sense, π–π* transitions are "allowed" and *n*–π* transitions are "forbidden."

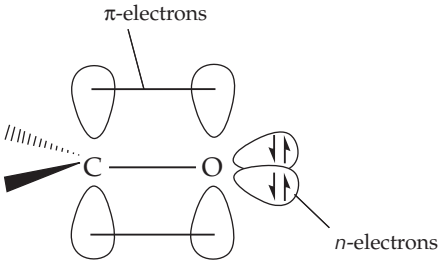


Table 24.1 shows the λ_{max} and the ε values for a variety of organic compounds.

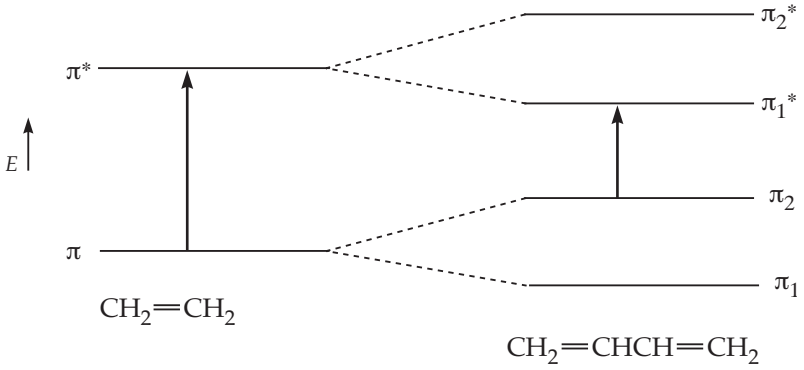
TABLE 24.1 UV data for various functional groups in organic compounds

Compound	Name	λ_{max}[a]	ε_{max}
$CH_2{=}CH_2$	Ethylene	171	15,500
$CH_2{=}CH{-}CH{=}CH_2$	1,3-Butadiene	217	21,000
$CH_2{=}CH{-}C(CH_3){=}CH_2$	2-Methyl-1,3-butadiene	222	10,800
C_5H_6	1,3-Cyclopentadiene	239	4,200
$CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2$	1,3,5-Hexatriene	268	36,300
CH_3COCH_3	Acetone	279	13
$CH_3COCH{=}CH_2$	3-Buten-2-one	217	7,100
		320	21
CH_3CONH_2	Acetamide	220	63
C_6H_6	Benzene	204	7,900
		256	200
$C_6H_5CO_2H$	Benzoic Acid	226	9,800
		272	850

a. All transitions are π–π* except for acetone, acetamide, and the longer wavelength absorption of 3-buten-2-one, which are *n*–π* transitions.

Conjugated Compounds

Consideration of a molecular orbital diagram shows why conjugated organic compounds absorb UV radiation of longer wavelengths than nonconjugated compounds. Ethylene has two π-orbitals, whereas 1,3-butadiene has four, two bonding π-orbitals and two antibonding π*-orbitals. The energy gap between the highest energy π-orbital of 1,3-butadiene and its lowest energy π*-orbital is much smaller than the corresponding gap for the ethylene orbitals.



This energy difference produces a shift of the λ_{max} from 171 nm for ethylene to 217 nm for butadiene.

When a molecule contains a benzene ring, with a total of six π- and π*-orbitals, a number of electronic transitions involving similar energy changes can occur. Figure 24.2 shows the complexity of the UV spectrum of toluene ($C_6H_5CH_3$) in the 240–265-nm region.

Visible Spectroscopy

Compounds that absorb visible light are colored. Organic compounds with eight or more conjugated double bonds absorb in the visible region (400–800 nm). One example is chlorophyll a, the principal photoreceptor of most green plants. Figure 24.3 shows the visible spectrum of chlorophyll a, which has two major absorption peaks, one in the 430-nm region (violet) and the other around 660-nm (red); the exact λ_{max} values depend on the solvent in which the chlorophyll is dissolved. A complementary relationship exists

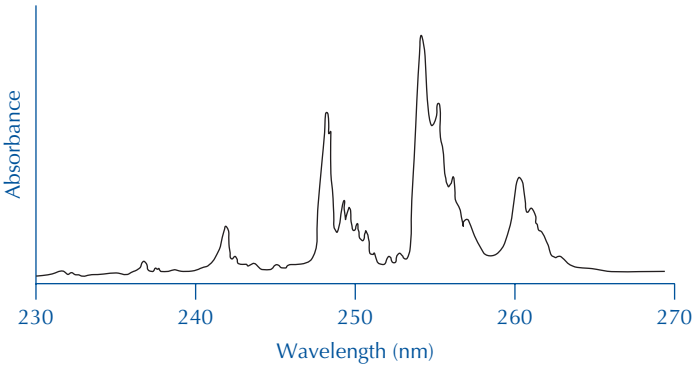


FIGURE 24.2
UV absorption spectrum of toluene.

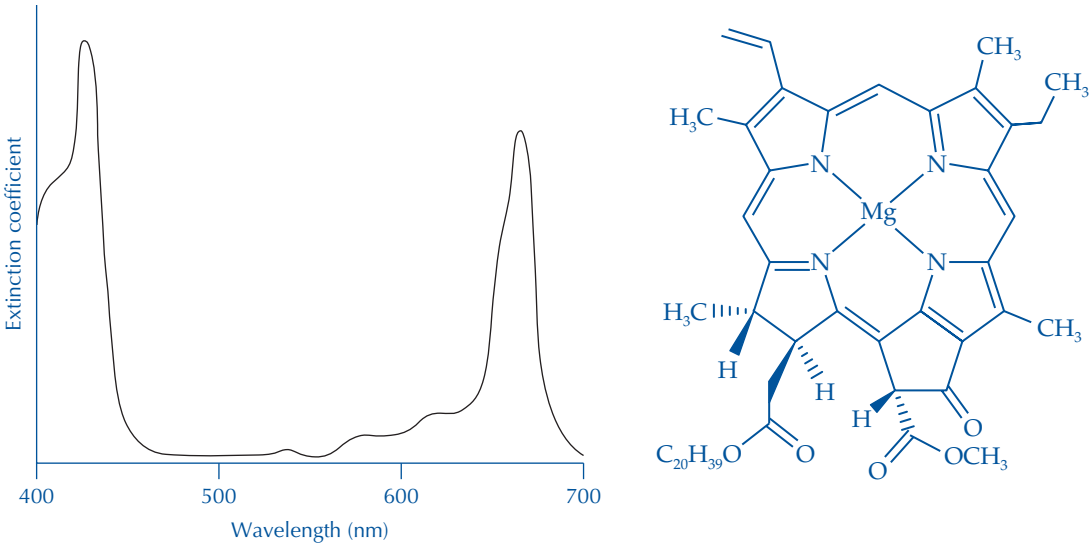
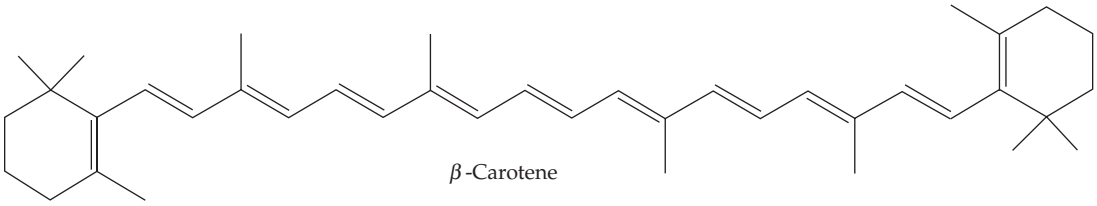


FIGURE 24.3 Visible spectrum and structure of chlorophyll a.

between the color of a compound and the color (or wavelength) of the light it absorbs. The green light waves that are not absorbed effectively by chlorophyll are reflected back to our eyes.

Another way of understanding the color of compounds is the color wheel in Figure 24.4. For example, β-carotene, the compound that gives carrots their color, has an intense absorption in the blue-green portion of the visible spectrum (λ_{max} 483 nm, $\varepsilon = 1.3 \times 10^5$).



The color wheel reveals that β-carotene is expected to reflect (transmit) the color on the opposite side of the wheel, that is, red-orange.

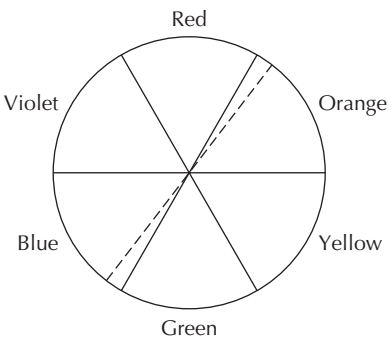


FIGURE 24.4 Color wheel. A compound that absorbs blue-green light transmits red-orange light.

24.2 UV/VIS Instrumentation

There are two major classes of UV/VIS spectrometers: ***dispersive*** and ***multiplex diode-array*** spectrometers. Dispersive spectrometers were the standard UV/VIS instruments for many years. More recently, diode-array spectrometers have become increasingly popular.

The light source in both dispersive and diode-array spectrometers is either a deuterium (D_2) discharge lamp, used for the 190−350-nm region of the spectrum, or a tungsten-halogen filament lamp, used for the 330−800-nm region of the spectrum. In the deuterium lamp, an electric discharge is passed through D_2, which is under pressure; the gas is excited and continuous UV radiation is emitted. Often, UV/VIS spectrophotometers are equipped with both deuterium and tungsten lamps, which can be turned on or off by the flick of a switch.

Dispersive UV Spectrometers

There are a number of instrumental designs for dispersive UV spectrometers, involving mirrors, slits, and detectors. Instrumental analysis textbooks treat these designs in considerable detail. Dispersive instruments use either a single-beam or a double-beam light pathway. In both types the light passes through a monochromator, which scans through narrow bands of separate light frequencies. In a double-beam spectrometer (Figure 24.5), after passing through the monochromator, the radiation is split into two beams and then directed by mirrors through sample and reference cells. The two beams are recombined later in the optical path. Double-beam instruments can compensate for fluctuations in the radiant output of the light source. They work well for the continuous recording of spectra.

Detectors for dispersive UV/VIS spectrometers are either photocells or photomultipliers. A photocell is the simplest kind of detector. It has a metal surface that is sensitive to light, and when radiation hits it, electrons are ejected and can be converted into a signal. The Spectronic 20 is a single-beam instrument with a tungsten lamp and a photocell detector. When radiation strikes a

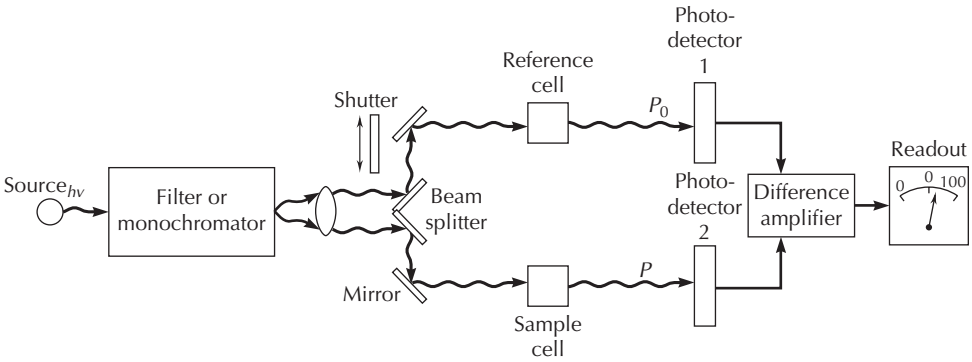


FIGURE 24.5 Schematic diagram of a double-beam spectrometer.

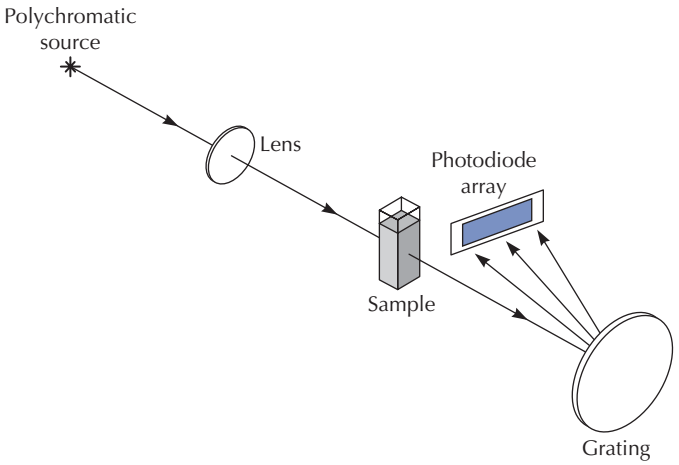


FIGURE 24.6
Diagram of a multichannel spectrophotometer based on a grating and a diode-array transducer.

photoreactive metal surface in a photomultiplier tube, electrons are ejected and directed to positively charged electrodes, called dynodes, which cause several more electrons to be emitted. This cascading process can be repeated several times and can lead to a great enhancement in sensitivity, up to 10^9 electrons per photon of radiation hitting the detector.

Sample concentrations obtained from UV measurements on dispersive spectrometers are often more accurate when they are obtained at the wavelength of the maximum absorbance. There is usually a small flat portion at maximum absorbance that reduces experimental error. In addition, the change in absorbance with concentration is greatest at λ_{max}.

Diode-Array UV/VIS Spectrometers

Diode-array spectrometers do not use a monochromator to scan the radiation before it passes through the sample cell. Instead, all the light passes through the sample. Diode-array spectrometers are single-beam instruments, which use a diffraction grating to disperse the different wavelengths of light after the light has passed through the sample. All the wavelengths are detected simultaneously on a linear array of photoreactive diodes. An electrical potential at each diode element can be converted into a digital signal. Usually, a diode-array detector has 1000–2000 elements, and each element covers a small wavelength region of the UV/VIS spectrum. Figure 24.6 is a diagram of a diode-array spectrophotometer.

24.3 Preparing Samples and Operating the Spectrometer

UV/VIS spectroscopy is often sensitive to concentrations of 10^{-4}–10^{-5} M with good accuracy. Relative errors are ~1–3%; with precautions, they can be reduced to a few tenths of a percent. To obtain accurate quantitative results in UV spectroscopy, careful sample preparation is vital. The samples must be accurately weighed on an

analytical balance and made up to volume in a volumetric flask. Dilutions are made by removing aliquots with volumetric pipets and diluting them in separate volumetric flasks.

After preparing your sample solution, you should obtain a complete spectrum in order to determine the wavelengths of maximum absorbance. Consult your instructor about specific operating procedures for the UV/VIS spectrometer in your laboratory.

Calibration Standards

It is important to run a set of calibration standards to ensure that the concentrations of the compounds you are working with adhere to the Beer-Lambert law. These calibrations should be carried out under conditions where the measured absorbance is less than 1.0 and definitely no greater than $A = 2.0$. The molar absorptivity (ε) should be determined experimentally in the solvent you choose to use. The best accuracy is obtained with dilute solutions, with concentrations less than 0.01 M.

Solvents

The solvents used in preparing solutions to be analyzed must be spectral grade. Even very small quantities of organic impurities that have high molar absorptivities can produce erroneous results.

Polar solvents stabilize antibonding π^*-orbitals more than π ground states, so the energy gap in π–π^* transitions is decreased and λ_{max} occurs at a longer wavelength in polar solvents. For n–π^* transitions the effect of hydrogen-bonding polar solvents is just the opposite. The energy levels of n electrons are stabilized more by hydrogen bonding than π^*-orbitals are, so the gap between n and π^* becomes greater and λ_{max} occurs at a shorter wavelength in polar hydrogen-bonding solvents. Figure 24.7 summarizes these solvent effects on the shifts of λ_{max} for π–π^* and n–π^* transitions.

Table 24.2 provides the cutoff wavelengths for standard UV solvents; below these wavelengths the solvent absorption interferes with the measurements. For example, cyclohexane can be used as a solvent from 400 nm down to 210 nm, whereas dichloromethane is not useful below 235 nm.

UV Cells

Good-quality UV transparent cells, or cuvettes, are generally made from quartz glass or fused silica and are 1.0 cm square. These cells are transparent above 200 nm and require about 3 mL of solution. Usually they come with fitted caps.

Clean cells are crucial. Before using cells with your samples, they should be rinsed several times with solvent and checked for absorption. Fingerprints or grease on the transparent cell surfaces must be avoided. UV cells should never be dried in an oven, as the heat may warp them. In addition, they should never experience solutions of strong bases, as these may etch the glass. If a double-beam spectrophotometer is being used, the reference and sample cells should be a matched pair, which allows any small solvent absorption to be erased so that it doesn't interfere with the spectral measurements. After the spectrum has been obtained, quartz cells should be cleaned immediately, usually by repeated rinsing with the

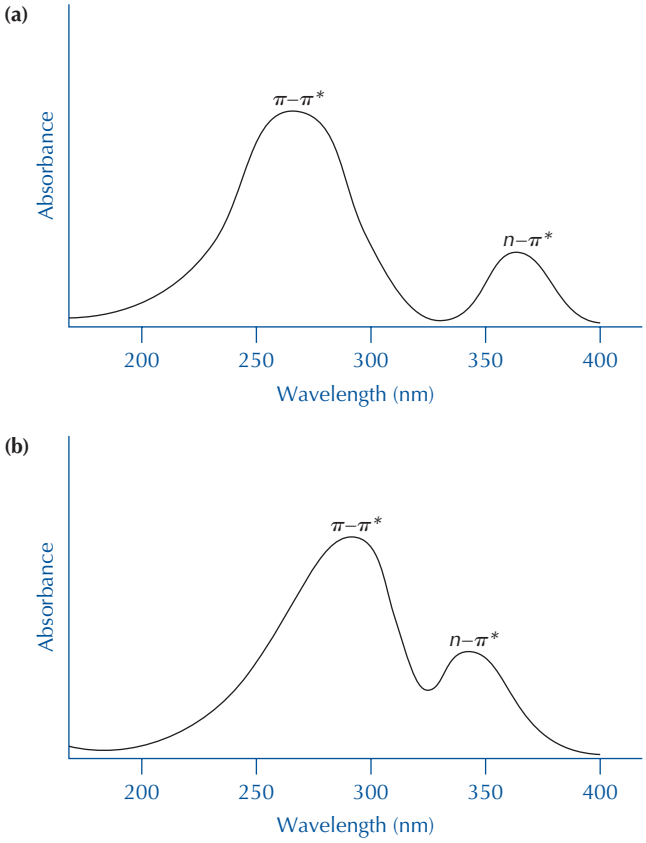


FIGURE 24.7
(a) UV spectrum of a compound undergoing π–π* and *n*–π* transitions in a nonpolar solvent. **(b)** UV spectrum of the same compound in a polar hydrogen-bonding solvent.

TABLE 24.2 Minimum wavelengths possible for use of standard UV solvents[a]

Solvent	Low-end cutoff (nm)
Acetonitrile	210
Cyclohexane	210
Dichloromethane	235
1,4-Dioxane	220
Ethanol	210
Hexane	220
Methanol	210
Isooctane	220
Water	205

a. These solvents can be used from the low-end cutoff up to 800 nm.

solvent used for the spectrum. After rinsing, the cells should be set upside down to dry on a clean cloth or tissue.

If the wavelength region being utilized is 300–800 nm, disposable acrylic cells can be used. Below 300 nm these disposable cells absorb too strongly to be useful.

24.4 Sources of Confusion

Major sources of confusion arise from faulty sample preparation and from incorrect use of the UV/VIS spectrometer.

Dirty cells. Cells that have traces of UV-absorbing substances on their surfaces, including grease and fingerprints, can produce confusing results.

Impure solvents. If solvents are not of spectral quality or if dirty volumetric glassware is used, poor-quality spectra will be obtained.

Nonlinear Beer-Lambert law plot. The nonlinearity will probably be caused by using a concentration above 0.01 M for the compounds under investigation. In addition, the relationship of absorbance to concentration can become nonlinear if the measured absorbance is too high, above $A = 1.0–2.0$.

The molar absorptivity ε does not confirm the published value. The exact value for the molar absorptivity can depend on a number of environmental factors, including the solvent used, the temperature, and other substances that may also be present in the sample solution.

Further Reading

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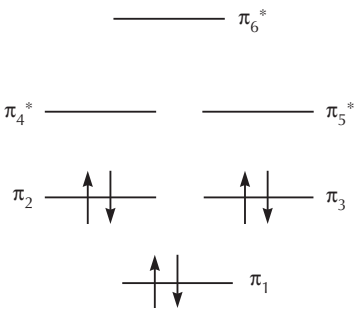
Scott, A. I. *Interpretation of the Ultraviolet Spectra of Natural Products*; Pergamon (Macmillan): New York, 1964.

Skoog, D. A.; Holler, F. J.; Crouch, S. R. *Principles of Instrumental Analysis;* 6th ed.; Brooks Cole: 2007.

Questions

1. Acetaldehyde shows two UV bands, one with a λ_{max} of 289 nm ($\varepsilon = 12$) and one with a λ_{max} of 182 nm ($\varepsilon = 10{,}000$). Which is the $n \rightarrow \pi^*$ transition and which is the $\pi \rightarrow \pi^*$ transition? Explain your reasoning.
2. It should not be surprising to find that cyclohexane and ethanol are reasonable UV solvents, whereas toluene is not. Why?
3. An ethanol solution of 3.50 mg/100 mL of compound X (150 g/mol) in a 1.00-cm quartz cell has an absorbance (A) of 0.972 at λ_{max} of 235 nm. Calculate its molar extinction coefficient.
4. Benzene shows more than one UV maximum. Use the orbital energy levels shown here to explain this observation.



TECHNIQUE

25 INTEGRATED SPECTROSCOPY PROBLEMS

The three major spectroscopic methods presented in Techniques 20–23 have revolutionized structure determinations of organic compounds. Although for the most part these methods were considered separately, the connections were made apparent from time to time. In practice, organic chemists generally solve structural problems by using an integrated spectroscopic approach. The mass spectrum is usually a good starting point because it can provide the molecular weight of the compound. Next comes the IR spectrum, which provides data for the identification of the functional groups present. Finally, interpretation of the ^{1}H and ^{13}C NMR spectra usually allows the structural analysis to be completed.

Many chemists believe that NMR is the most versatile source of structural data, and we have emphasized it more than infrared spectroscopy and mass spectrometry. However, to be efficient in tackling structure determinations, organic chemists need to be proficient in all three spectroscopic methods. One method may reveal features about a compound that are not clear from another. Researchers are alert to when extra emphasis should be placed on a few pieces of data chosen from a large data set, a skill that comes from experience. The following problems highlight the use of an integrated approach to using spectroscopy for organic structure determination.

1. A compound shows a molecular ion peak in its mass spectrum at *m/z* 72 and the base peak at *m/z* 43. An infrared spectrum of this compound shows, among other absorptions, four bands in the 2990–2850-cm^{-1} range and a strongband at 1715 cm^{-1}. There are no IR peaks at greater than 3000 cm^{-1}. The ^{1}H NMR spectrum contains a triplet at 1.08 ppm (3H), a singlet at 2.15 ppm (3H), and a quartet at 2.45 ppm (2H). The magnitudes of the splitting of both the quartet and triplet are identical. Deduce the structure of this compound and assign all the MS, IR, and NMR peaks.
2. The infrared spectrum of a compound is shown in Figure 25.1. Its ^{1}H NMR spectrum contains a somewhat broadened singlet at 7.3 ppm (5H), a singlet at 4.65 ppm (2H), and a broadened singlet at 2.5 ppm (1H). Deduce the structure of this compound and assign the NMR and important IR peaks.
3. A compound shows a molecular ion peak in its mass spectrum at *m/z* 92 and a satellite peak at *m/z* 94 that is 32% the intensity of the *m/z* 92 peak. The ^{1}H NMR spectrum contains only one signal, a singlet at 1.65 ppm. The proton-decoupled ^{13}C NMR spectrum reveals a strong peak at 35 ppm and a weaker peak at 67 ppm. Deduce the structure of this compound and assign all MS and NMR peaks.

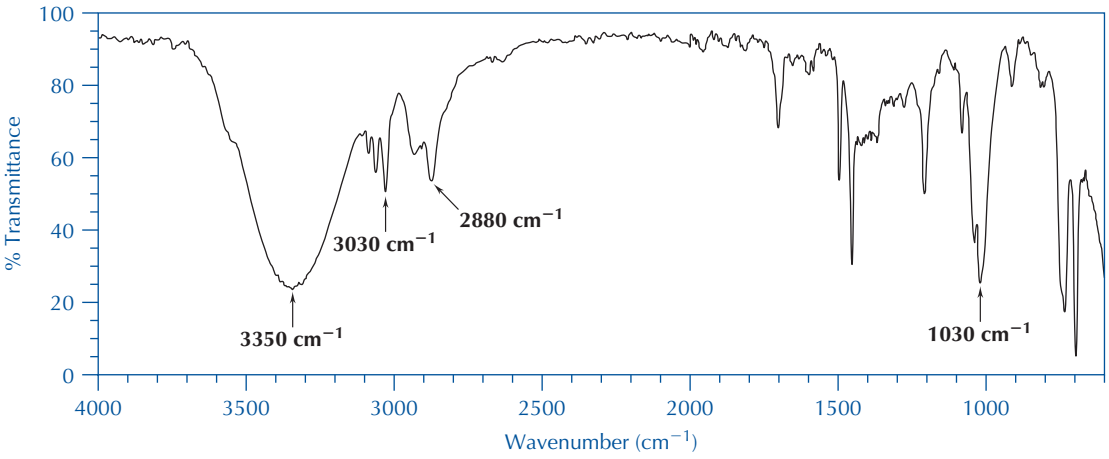


FIGURE 25.1 Infrared spectrum (thin film) of unknown compound for problem 2.

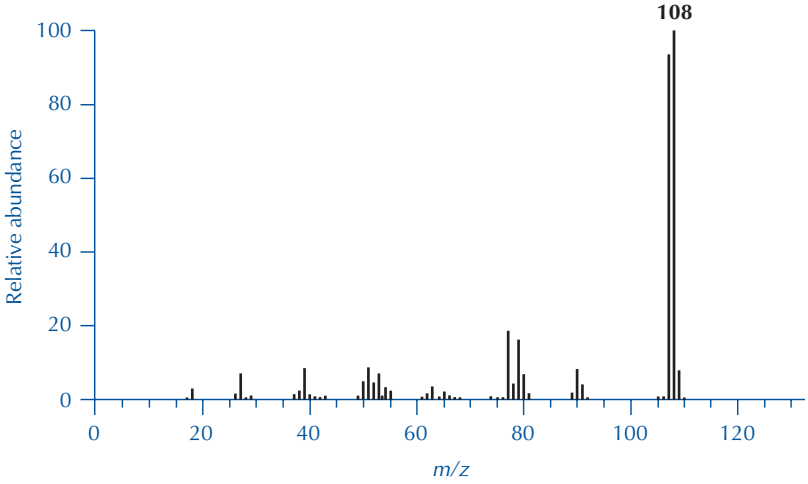


FIGURE 25.2 Mass spectrum of unknown compound for problem 4.

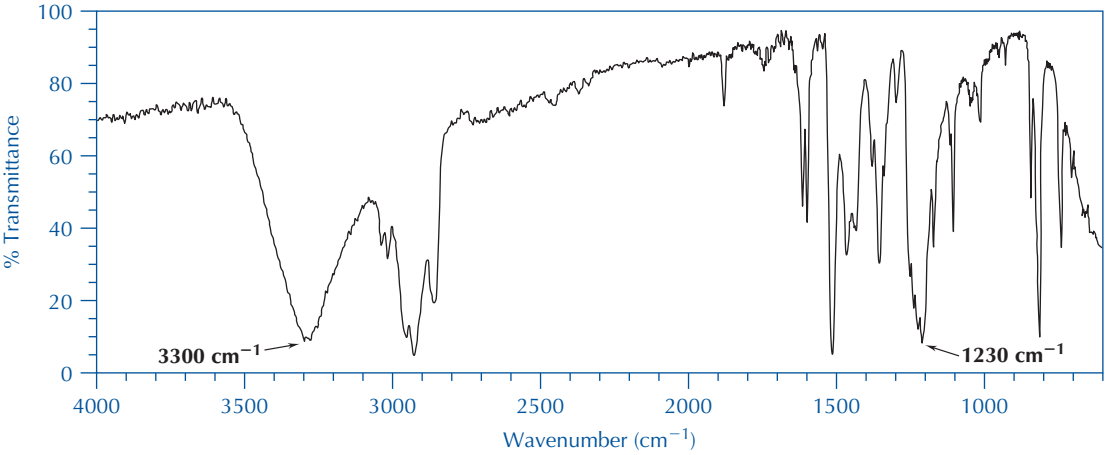


FIGURE 25.3 Infrared spectrum (KBr pellet) of unknown compound for problem 4.

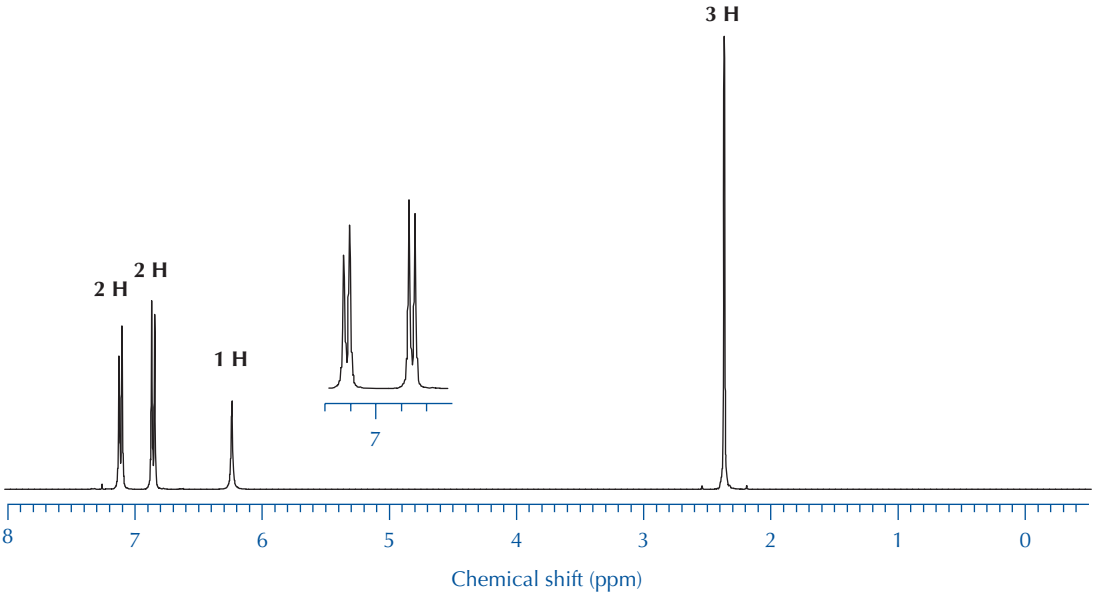


FIGURE 25.4 360-MHz ^{1}H NMR spectrum of unknown compound for problem 4.

4. The mass spectrum, infrared spectrum, and ^{1}H NMR spectrum of a compound are shown in Figures 25.2–25.4. Deduce the structure of this compound from the spectral data and show your reasoning.
5. Figure 25.5 shows the ^{1}H NMR spectrum of a compound of molecular formula $C_3H_6Cl_2$. The proton-decoupled ^{13}C NMR spectrum, which has signals at 56, 49, and 23 ppm, as well as the DEPT(90) and DEPT(135) spectra, are shown in Figure 25.6. Deduce the structure of this compound and assign all NMR peaks.

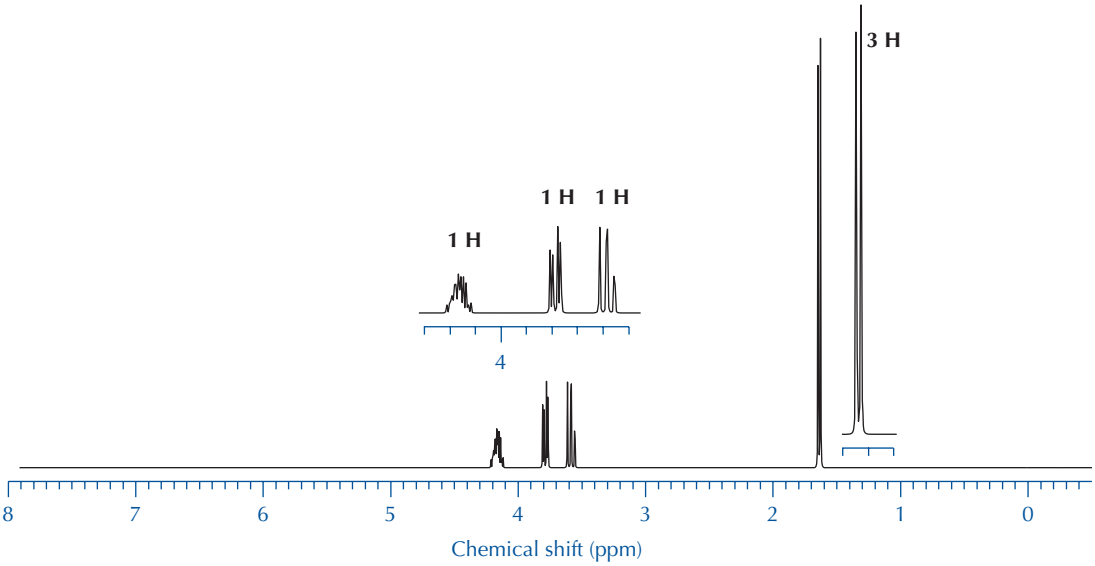


FIGURE 25.5 360-MHz ^{1}H NMR spectrum of unknown compound for problem 5.

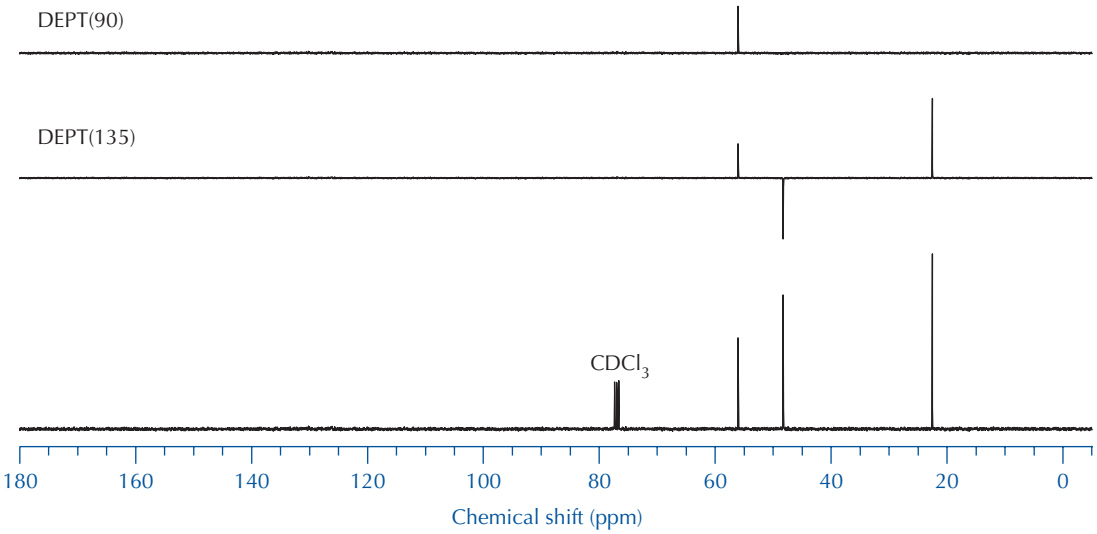


FIGURE 25.6 90-MHz ^{13}C NMR, DEPT(90), and DEPT(135) spectra of unknown compound for problem 5.

6. The infrared spectrum of a compound of molecular formula $C_7H_{16}O$ is shown in Figure 25.7. Its 360-MHz ^1H NMR spectrum is shown in Figure 25.8, and its proton-decoupled ^{13}C NMR and DEPT(135) spectra are shown in Figure 25.9. The ^{13}C NMR spectrum has signals at 63, 33, 32, 29, 26, 23, and 14 ppm. Deduce the structure of this compound, assign all the NMR and important IR peaks, and explain your reasoning. Estimate the chemical shifts of all protons and carbon atoms using Tables 21.3 and 22.3 and compare them with the chemical shifts measured from the NMR spectra.

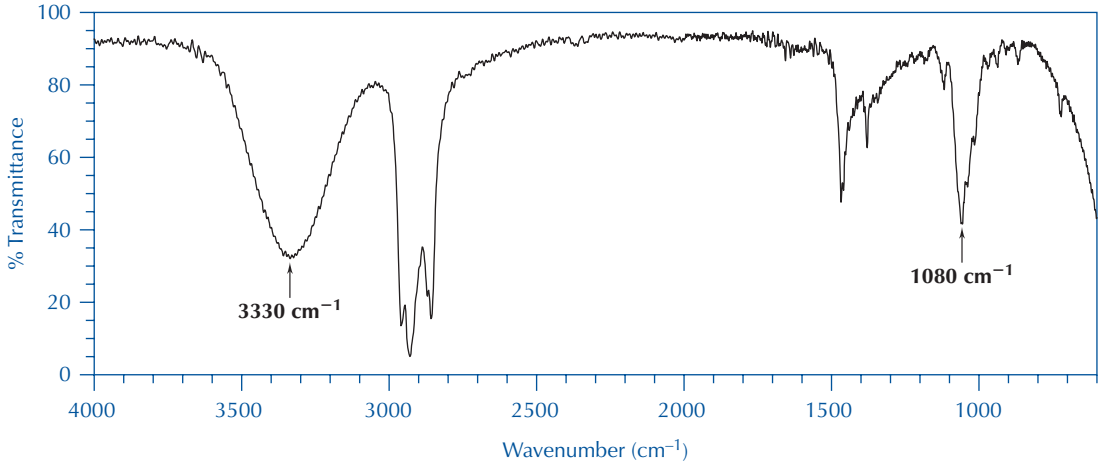


FIGURE 25.7 Infrared spectrum (thin film) of unknown compound for problem 6.

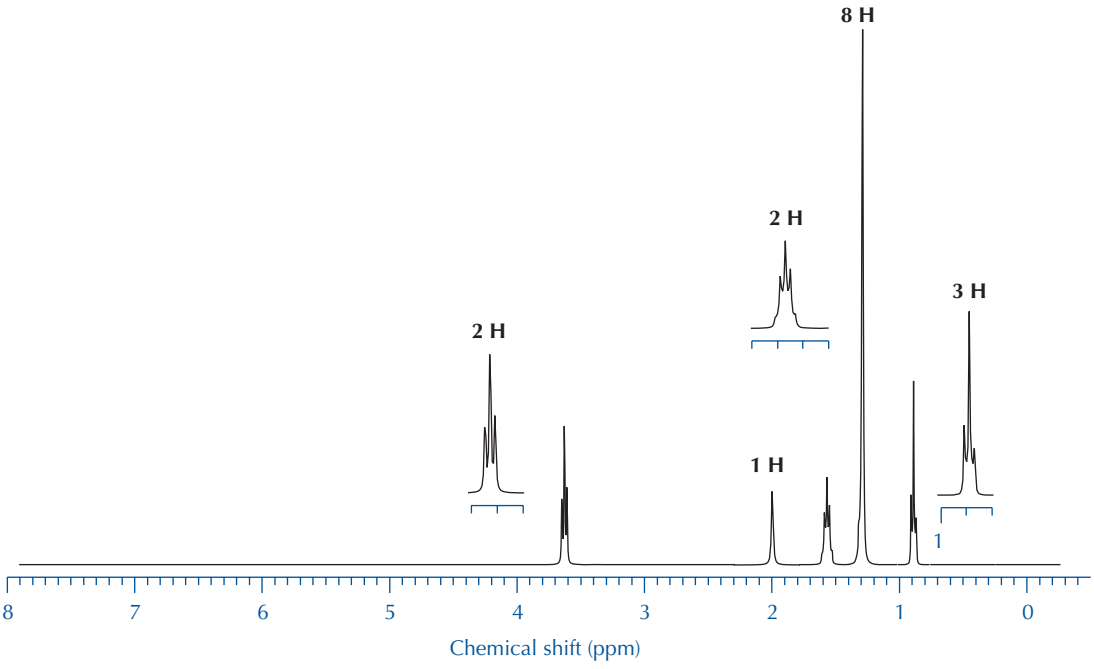


FIGURE 25.8 360-MHz ^{1}H NMR spectrum of $C_7H_{16}O$ for problem 6.

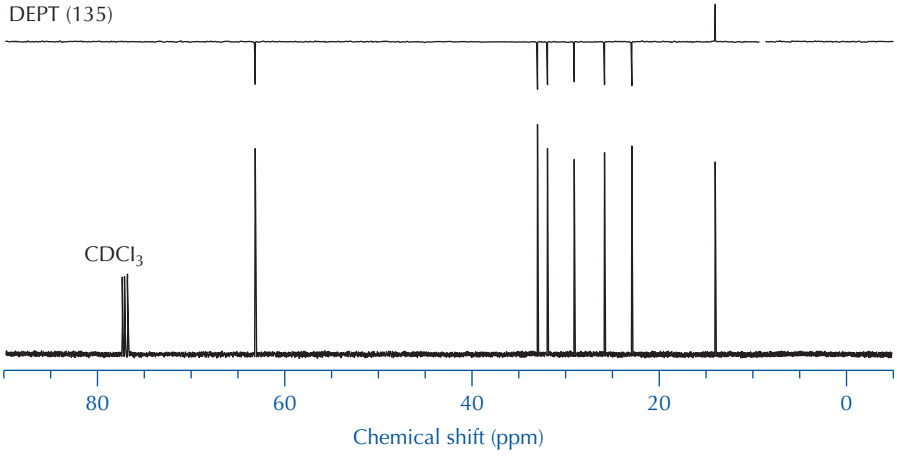


FIGURE 25.9 90-MHz ^{13}C NMR and DEPT(135) spectra of $C_7H_{16}O$ for problem 6.

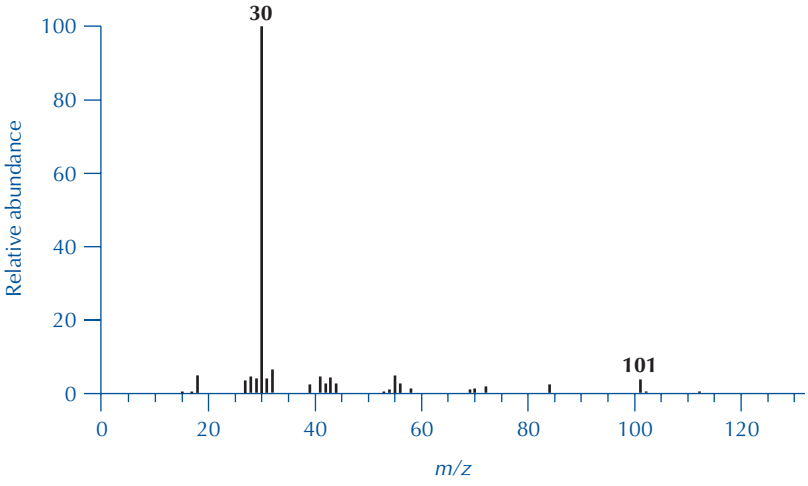


FIGURE 25.10
Mass spectrum of unknown compound for problem 7.

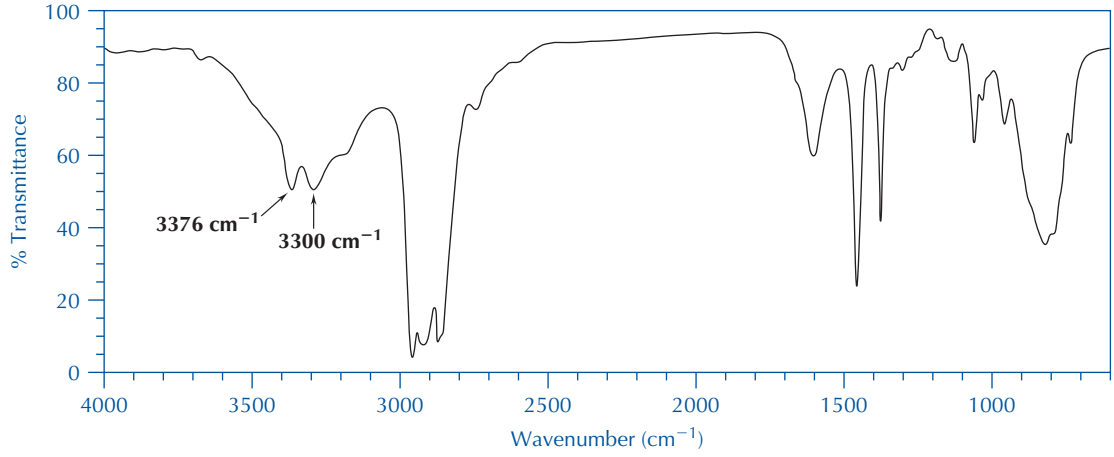


FIGURE 25.11 Infrared spectrum (thin film) of unknown compound for problem 7.

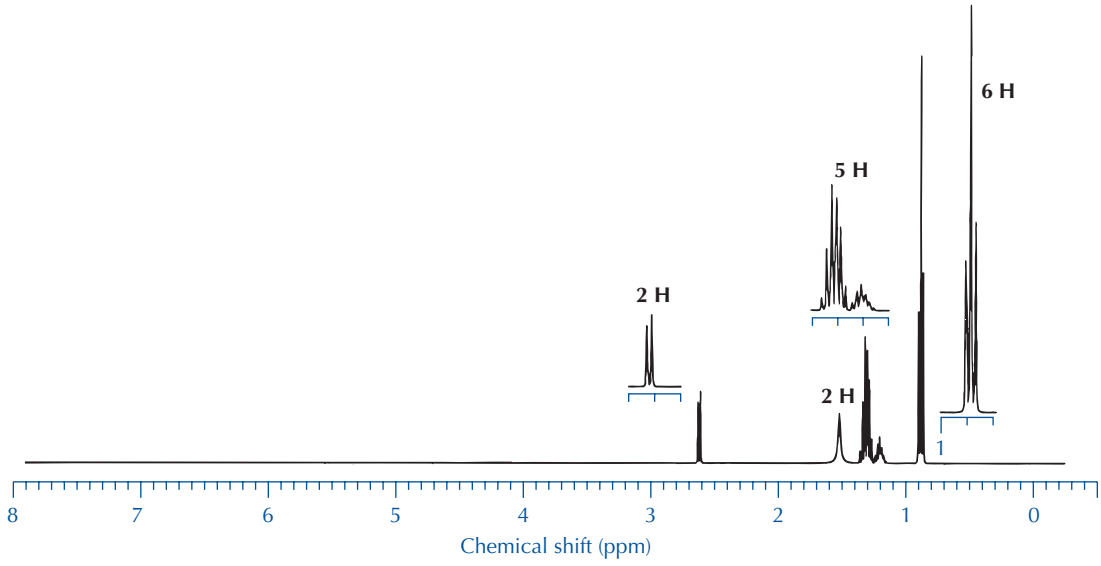


FIGURE 25.12 360-MHz ^{1}H NMR spectrum of unknown compound for problem 7.

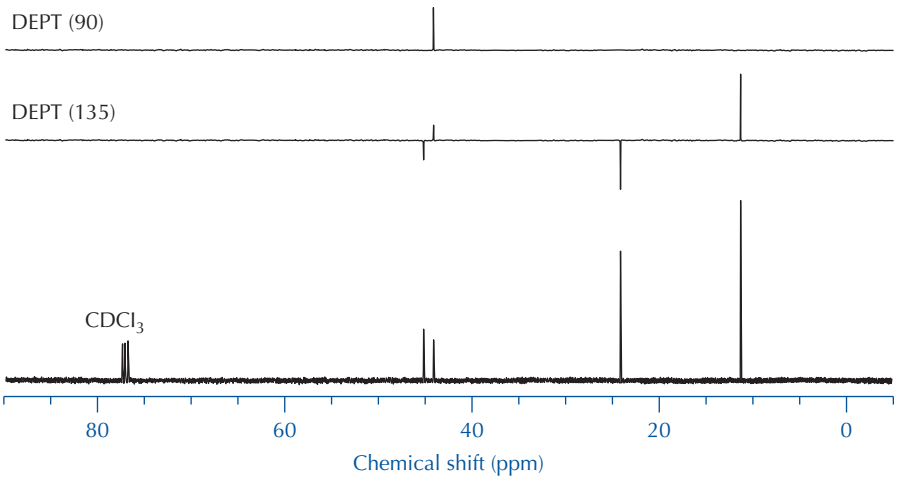


FIGURE 25.13 90-MHz ^{13}C NMR, DEPT(90), and DEPT(135) spectra of unknown compound for problem 7.

7. The mass spectrum, infrared spectrum, 360-MHz ^{1}H NMR spectrum, and proton-decoupled ^{13}C NMR and DEPT(90) and DEPT(135) spectra of a compound are shown in Figures 25.10–25.13. The ^{13}C NMR spectrum has signals at 45, 44, 24, and 11 ppm. Deduce the structure of this compound and show your reasoning. Assign all the NMR peaks and all important MS and IR peaks. Estimate the chemical shifts of all of the compound's protons and carbon atoms using Tables 21.3 and 22.3–22.4 and compare them with the chemical shifts measured from the NMR spectra.
8. The mass spectrum, infrared spectrum, 360-MHz ^{1}H NMR spectrum, and proton-decoupled ^{13}C NMR and DEPT(90) and DEPT(135) spectra of a compound are shown in Figures 25.14–25.17. The ^{13}C NMR spectrum has signals at 173, 132, 118, 65, 36, 19, and 14 ppm. The molecular ion is not discernible in the mass spectrum. Deduce the structure of this compound and show your reasoning. Assign all the NMR peaks and all important MS and IR peaks.

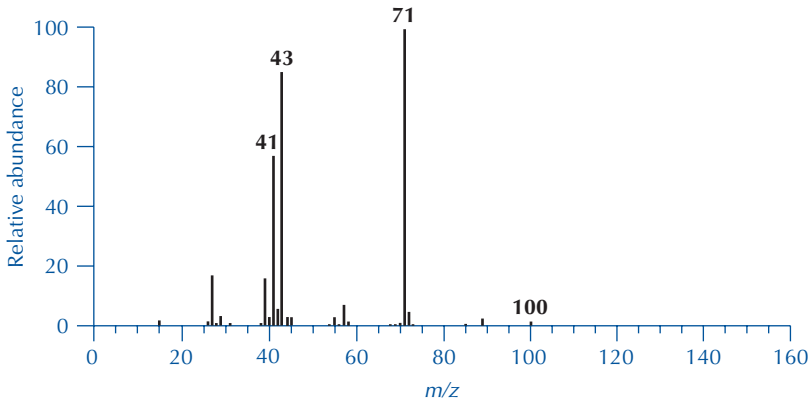


FIGURE 25.14 Mass spectrum of unknown compound for problem 8.

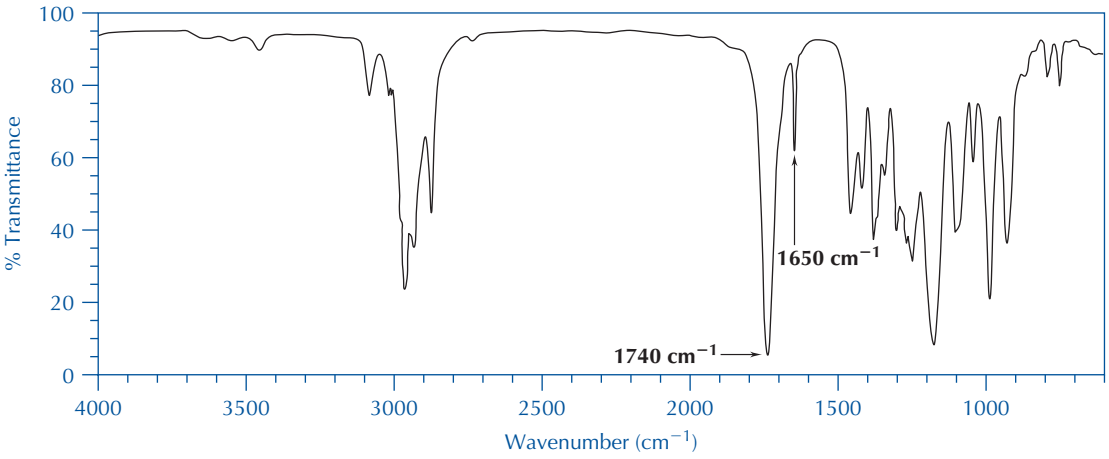


FIGURE 25.15 Infrared spectrum (thin film) of unknown compound for problem 8.

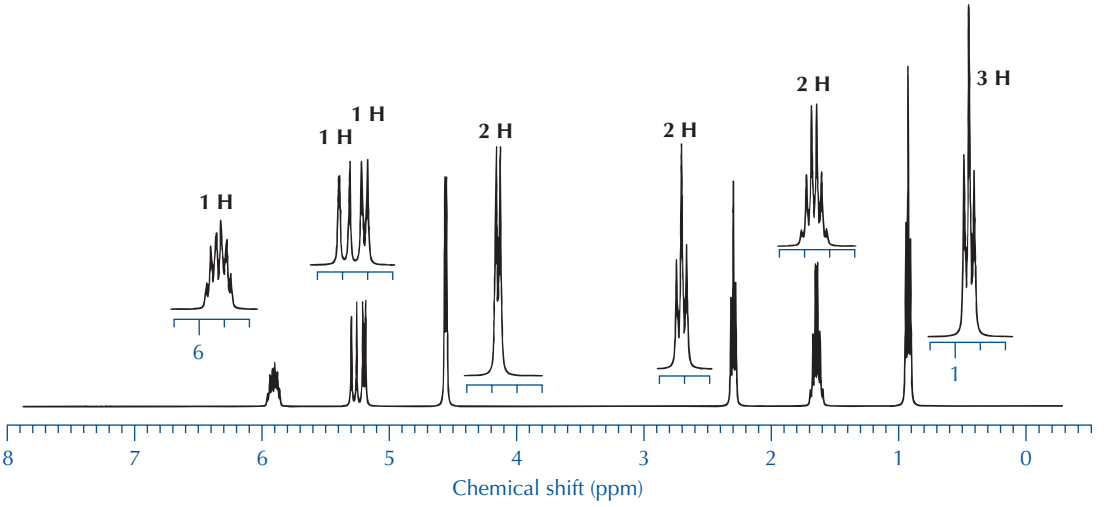


FIGURE 25.16 360-MHz ^{1}H NMR spectrum of unknown compound for problem 8.

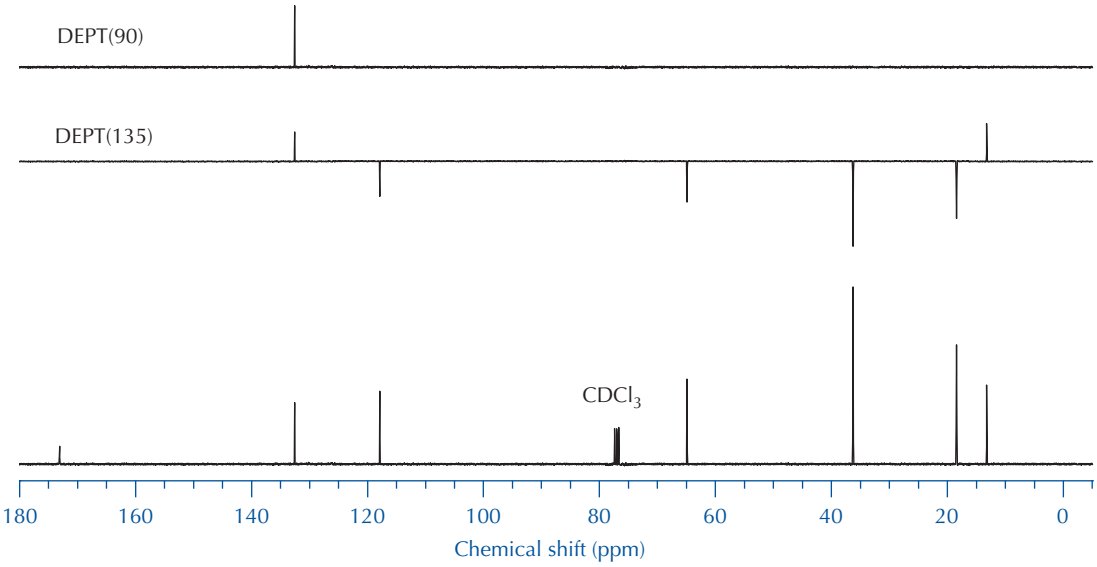


FIGURE 25.17 90-MHz ^{13}C NMR, DEPT(90), and DEPT(135) spectra of unknown compound for problem 8.

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INDEX

Note: Page numbers followed by f indicate figures; those followed by t indicate tables.

F

N

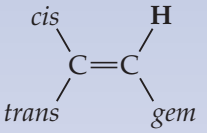
T

Additive parameters for predicting NMR chemical shifts of aromatic protons in $CDCl_3$

	Base value	7.36 ppm[a]	
Group	***ortho***	***meta***	***para***
—CH_3	−0.18	−0.11	−0.21
—$CH(CH_3)_2$	−0.14	−0.08	−0.20
—CH_2Cl	0.02	−0.01	−0.04
—$CH{=}CH_2$	0.04	−0.04	−0.12
—$CH{=}CHAr$	0.14	−0.02	−0.11
—$CH{=}CHCO_2H$	0.19	0.04	0.05
—$CH{=}CH(C{=}O)Ar$	0.28	0.06	0.05
—Ar	0.23	0.07	−0.02
—$(C{=}O)H$	0.53	0.18	0.28
—$(C{=}O)R$	0.60	0.10	0.20
—$(C{=}O)Ar$	0.45	0.12	0.23
—$(C{=}O)CH{=}CHAr$	0.67	0.14	0.21
—$(C{=}O)OCH_3$	0.68	0.08	0.19
—$(C{=}O)OCH_2CH_3$	0.69	0.06	0.17
—$(C{=}O)OH$	0.77	0.11	0.25
—$(C{=}O)Cl$	0.76	0.16	0.33
—$(C{=}O)NH_2$	0.46	0.09	0.17
—$C{\equiv}N$	0.29	0.12	0.25
—F	−0.32	−0.05	−0.25
—Cl	−0.02	−0.07	−0.13
—Br	0.13	−0.13	−0.08
—OH	−0.53	−0.14	−0.43
—OR	−0.45	−0.07	−0.41
—OAr	−0.36	−0.04	−0.28
—$O(C{=}O)R$	−0.27	0.02	−0.13
—$O(C{=}O)Ar$	−0.14	0.07	−0.09
—NH_2	−0.71	−0.22	−0.62
—$N(CH_3)_2$	−0.68	−0.15	−0.73
—$NH(C{=}O)R$	0.14	−0.07	−0.27
—NO_2	0.87	0.20	0.35

a. Base value is the measured chemical shift of benzene in $CDCl_3$ (1% solution).

Additive parameters for predicting NMR chemical shifts of vinyl protons in $CDCl_3$[a]

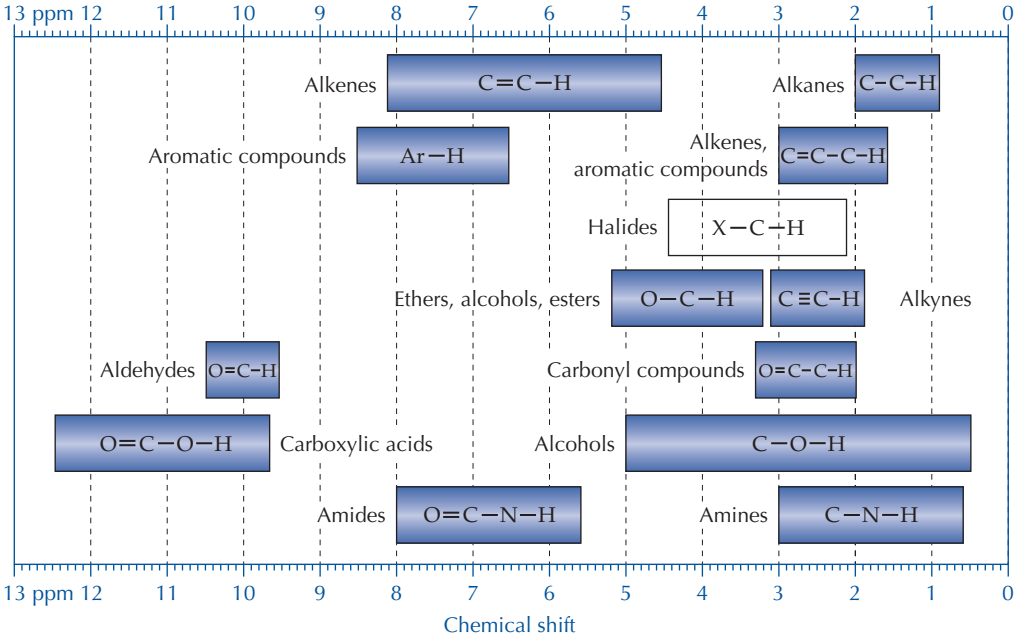


Base value 5.28 ppm

Group	*gem*	*cis*	*trans*
—R	0.45	−0.22	−0.28
—CH=CH_2	1.26	0.08	−0.01
—CH_2OH	0.64	−0.01	−0.02
—CH_2X (X=F, Cl, Br)	0.70	–0.11	−0.04
—(C=O)OH	0.97	1.41	0.71
—(C=O)OR	0.80	1.18	0.55
—(C=O)H	1.02	0.95	1.17
—(C=O)R	1.10	1.12	0.87
—(C=O)Ar	1.82	1.13	0.63
—Ar	1.38	0.36	−0.07
—Br	1.07	0.45	0.55
—Cl	1.08	0.18	0.13
—OR	1.22	−1.07	−1.21
—OAr	1.21	−0.60	−1.00
—O(C=O)R	2.11	−0.35	−0.64
—NH_2, —NHR, —NR_2	0.80	−1.26	1.21
—NH(C=O)R	2.08	−0.57	−0.72

a. There may be small differences in the chemical-shift values calculated from this table and those measured from individual spectra.

Approximate regions of chemical shifts for different types of protons in organic compounds



Characteristic ^{1}H NMR chemical shifts in $CDCl_3$

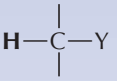
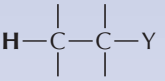
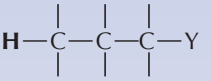
Compound	Chemical shift (δ, ppm)
TMS	0.0
Alkanes (C—C—**H**)	0.9–1.9
Amines (C—N—**H**)	0.6–3.0
Alcohols (C—O—**H**)	0.5–5.0
Alkenes[a] (C═C—C—**H**)	1.6–2.5
Alkynes (C≡C—**H**)	1.7–3.1
Carbonyl compounds (O═C—C—**H**)	1.9–3.3
Halides (X—C—**H**)	2.1–4.5
Aromatic compounds[b] (Ar—C—**H**)	2.2–3.0
Alcohols, esters, ethers (O—C—**H**)	3.2–5.2
Alkenes (C═C—**H**)	4.5–8.1
Phenols (Ar—O—**H**)	4.0–8.0
Amides (O═C—N—**H**)	5.5–8.0
Aromatic compounds (Ar—**H**)	6.5–8.5
Aldehydes (O═C—**H**)	9.5–10.5
Carboxylic acids (O═C—O—**H**)	9.7–12.5

a. Allylic protons.
b. Benzylic protons.

Additive parameters for predicting NMR chemical shifts of alkyl protons in $CDCl_3$[a]

Base values

Methyl	0.9 ppm
Methylene	1.2 ppm
Methine	1.5 ppm

Group (Y)	Alpha (α) substituent 	Beta (β) substituent 	Gamma (γ) substituent 
—R	0.0	0.0	0.0
—C═C	0.8	0.2	0.1
—C═C—Ar[b]	0.9	0.1	0.0
—C═C(C═O)OR	1.0	0.3	0.1
—C≡C—R	0.9	0.3	0.1
—C≡C—Ar	1.2	0.4	0.2
—Ar	1.4	0.4	0.1
—(C═O)OH	1.1	0.3	0.1
—(C═O)OR	1.1	0.3	0.1
—(C═O)H	1.1	0.4	0.1
—(C═O)R	1.2	0.3	0.0
—(C═O)Ar	1.7	0.3	0.1
—(C═O)NH_2	1.0	0.3	0.1
—(C═O)Cl	1.8	0.4	0.1
—C≡N	1.1	0.4	0.2
—Br	2.1	0.7	0.2
—Cl	2.2	0.5	0.2
—OH	2.3	0.3	0.1
—OR	2.1	0.3	0.1
—OAr	2.8	0.5	0.3
—O(C═O)R	2.8	0.5	0.1
—O(C═O)Ar	3.1	0.5	0.2
—NH_2	1.5	0.2	0.1
—NH(C═O)R	2.1	0.3	0.1
—NH(C═O)Ar	2.3	0.4	0.1

a. There may be differences of 0.1−0.5 ppm in the chemical shift values calculated from this table and those measured from individual spectra.
b. Ar = aromatic group.

Characteristic infrared absorption peaks of functional groups

Vibration	Position (cm^{-1})	Intensity[a]	
Alkanes			
C—H stretch	2990–2850	m to s	
C—H bend	1480–1430 and 1395–1340	m to w	
Alkenes			
═C—H stretch	3100–3000	m	
C═C stretch	1680–1620 (sat.)[b], 1650–1600 (conj.)[b]	w to m	
═C—H bend	995–685	s	See Table 20.3 for detail
Alkynes			
≡C—H stretch	3310–3200	s	
C≡C stretch	2250–2100	m to w	
Aromatic Compounds			
C—H stretch	3100–3000	m to w	
C═C stretch	1620–1440	m to w	
C—H bend	900–680	s	See Table 20.3 for detail
Alcohols			
O—H stretch	3650–3550	m	Non-hydrogen bonded
	3550–3200	br, s	Hydrogen bonded
C—O stretch	1300–1000	s	
Amines			
N—H stretch	3550–3250	br, m	1° (two bands), 2° (one band)
Nitriles			
C≡N stretch	2280–2200	s	
Aldehydes			
C—H stretch	2900–2800 and 2800–2700	w	H—C═O, Fermi doublet
C═O stretch	1740–1720 (sat.), 1715–1680 (conj.)		
Ketones			
C═O stretch	1750–1705 (sat.), 1700–1650 (conj.)	s	
Esters			
C═O stretch	1765–1735 (sat.), 1730–1715 (conj.)	s	
C—O stretch	1300–1000	s	
Carboxylic Acids			
O—H stretch	3200–2500	br, m to w	
C═O stretch	1725–1700 (sat.), 1715–1680 (conj.)	s	
C—O stretch	1300–1000	s	
Amides			
N—H stretch	3500–3150	m	1° (two bands), 2° (one band)
C═O stretch	1700–1630	s	
Anhydrides			
C═O stretch	1850–1800 and 1790–1740	s	
C—O stretch	1300–1000	s	
Acid chlorides			
C═O stretch	1815–1770	s	
Nitro compounds			
NO_2 stretch	1570–1490 and 1390–1300	s	

a. s = strong, m = medium, w = weak, br = broad b. sat. = saturated, conj. = conjugated

PERIODIC TABLE OF THE ELEMENTS

	1 I IA	2 II IIA	3 IIIB	4 IVB	5 VB	6 VIB	7 VIIB	8	9 VIIIB	10	11 IB	12 IIB	13 III IIIA	14 IV IVA	15 V VA	16 VI VIA	17 VII VIIA	18 VIII VIIIA
1	1 **H** 1.0079																	2 **He** 4.00
2	3 **Li** 6.94	4 **Be** 9.01											5 **B** 10.81	6 **C** 12.01	7 **N** 14.01	8 **O** 16.00	9 **F** 19.00	10 **Ne** 20.18
3	11 **Na** 22.99	12 **Mg** 24.31											13 **Al** 26.98	14 **Si** 28.09	15 **P** 30.97	16 **S** 32.06	17 **Cl** 35.45	18 **Ar** 39.95
4	19 **K** 39.10	20 **Ca** 40.08	21 **Sc** 44.96	22 **Ti** 47.88	23 **V** 50.94	24 **Cr** 52.00	25 **Mn** 54.94	26 **Fe** 55.85	27 **Co** 58.93	28 **Ni** 58.71	29 **Cu** 63.54	30 **Zn** 65.37	31 **Ga** 69.72	32 **Ge** 72.59	33 **As** 74.92	34 **Se** 78.96	35 **Br** 79.91	36 **Kr** 83.80
5	37 **Rb** 85.47	38 **Sr** 87.62	39 **Y** 88.91	40 **Zr** 91.22	41 **Nb** 92.91	42 **Mo** 95.94	43 **Tc** 98.91	44 **Ru** 101.07	45 **Rh** 102.91	46 **Pd** 106.4	47 **Ag** 107.87	48 **Cd** 112.40	49 **In** 114.82	50 **Sn** 118.69	51 **Sb** 121.75	52 **Te** 127.60	53 **I** 126.90	54 **Xe** 131.30
6	55 **Cs** 132.91	56 **Ba** 137.34	71 **Lu** 174.97	72 **Hf** 178.49	73 **Ta** 180.95	74 **W** 183.85	75 **Re** 186.2	76 **Os** 190.2	77 **Ir** 192.2	78 **Pt** 195.09	79 **Au** 196.97	80 **Hg** 200.59	81 **Tl** 204.37	82 **Pb** 207.19	83 **Bi** 208.98	84 **Po** 210	85 **At** 210	86 **Rn** 222
7	87 **Fr** 223	88 **Ra** 226.03	103 **Lr** 262.1	104 **Rf**	105 **Db**	106 **Sg**	107 **Bh**	108 **Hs**	109 **Mt**	110 **Uun**	111 **Uuu**	112 **Uub**	113 **Uut**					

← Metals | Nonmetals →

Metalloids

57 **La** 138.91	58 **Ce** 140.12	59 **Pr** 140.91	60 **Nd** 144.24	61 **Pm** 146.92	62 **Sm** 150.35	63 **Eu** 151.96	64 **Gd** 157.25	65 **Tb** 158.92	66 **Dy** 162.50	67 **Ho** 164.93	68 **Er** 167.26	69 **Tm** 168.93	70 **Yb** 173.04
89 **Ac** 227.03	90 **Th** 232.04	91 **Pa** 231.04	92 **U** 238.03	93 **Np** 237.05	94 **Pu** 239.05	95 **Am** 241.06	96 **Cm** 247.07	97 **Bk** 249.08	98 **Cf** 251.08	99 **Es** 254.09	100 **Fm** 257.10	101 **Md** 258.10	102 **No** 255

Lanthanides

Actinides

*Molar masses quoted to the number of significant figures given here can be regarded as typical of most naturally occurring samples.