PART 6

The Techniques

1 **TECHNIQUE 1**

Laboratory Safety

In any laboratory course, familiarity with the fundamentals of laboratory safety is critical. Any chemistry laboratory, particularly an organic chemistry laboratory, can be a dangerous place in which to work. Understanding potential hazards will serve you well in minimizing that danger. It is ultimately your responsibility, along with your laboratory instructor's, to make sure that all laboratory work is carried out in a safe manner.

1.1 Safety Guidelines

It is vital that you take necessary precautions in the organic chemistry laboratory. Your laboratory instructor will advise you of specific rules for the laboratory in which you work. The following list of safety guidelines should be observed in all organic chemistry laboratories.

A. Eye Safety

Always Wear Approved Safety Glasses or Goggles. It is essential to wear eye protection whenever you are in the laboratory. Even if you are not actually carrying out an experiment, a person near you might have an accident that could endanger your eyes. Even dishwashing can be hazardous. We know of cases in which a person has been cleaning glassware—only to have an undetected piece of reactive material explode, throwing fragments into the person's eyes. To avoid such accidents, wear your safety glasses or goggles at all times.

Learn the Location of Eyewash Facilities. If there are eyewash fountains in your laboratory, determine which one is nearest to you before you start to work. If any chemical enters your eyes, go immediately to the eyewash fountain and flush your eyes and face with large amounts of water. If an eyewash fountain is not available, the laboratory will usually have at least one sink fitted with a piece of flexible hose. When the water is turned on, this hose can be aimed upward, and the water can be directed into the face, working much as an eyewash fountain does. To avoid damaging the eyes, the water flow rate should not be set too high, and the water temperature should be slightly warm.

B. Fires

Use Care with Open Flames in the Laboratory. Because an organic chemistry laboratory course deals with flammable organic solvents, the danger of fire is frequently present. Because of this danger, DO NOT SMOKE IN THE LABORATORY. Furthermore, use extreme caution when you light matches or use any open flame. Always check to see whether your neighbors on either side, across the bench, and behind you are using flammable solvents. If so, either wait or move to a safe location, such as a fume hood, to use your open flame. Many flammable organic substances are the source of dense vapors that can travel for some distance down a bench. These vapors present a fire danger, and you should be careful, as the source of those vapors may be far away from you. Do not use the bench sinks

to dispose of flammable solvents. If your bench has a trough running along it, pour only *water* (no flammable solvents!) into it. The troughs and sinks are designed to carry water—not flammable materials—from the condenser hoses and aspirators.

Learn the Location of Fire Extinguishers, Fire Showers, and Fire Blankets. For your own protection in case of a fire, you should immediately determine the location of the nearest fire extinguisher, fire shower, and fire blanket. You should learn how to operate these safety devices, particularly the fire extinguisher. Your instructor can demonstrate this.

If there is a fire, the best advice is to get away from it and let the instructor or laboratory assistant take care of it. DON'T PANIC! Time spent thinking before acting is never wasted. If it is a small fire in a container, it can usually be extinguished quickly by placing a wire-gauze screen with a ceramic fiber center or, possibly, a watch glass over the mouth of the container. It is good practice to have a wire screen or watch glass handy whenever you are using a flame. If this method does not extinguish the fire and if help from an experienced person is not readily available, then extinguish the fire yourself with a fire extinguisher.

Should your clothing catch on fire, DO NOT RUN. Walk *purposefully* toward the fire shower station or the nearest fire blanket. Running will fan the flames and intensify them.

C. Organic Solvents: Their Hazards

Avoid Contact with Organic Solvents. It is essential to remember that most organic solvents are flammable and will burn if they are exposed to an open flame or a match. Remember also that on repeated or excessive exposure, some organic solvents may be toxic, carcinogenic (cancer causing), or both. For example, many chlorocarbon solvents, when accumulated in the body, result in liver deterioration similar to cirrhosis caused by excessive use of ethanol. The body does not easily rid itself of chlorocarbons nor does it detoxify them; they build up over time and may cause future illness. Some chlorocarbons are also suspected of being carcinogens. MINIMIZE YOUR EXPOSURE. Long-term exposure to benzene may cause a form of leukemia. Do not sniff benzene and avoid spilling it on yourself. Many other solvents, such as chloroform and ether, are good anesthetics and will put you to sleep if you breathe too much of them. They subsequently cause nausea. Many of these solvents have a synergistic effect with ethanol, meaning that they enhance its effect. Pyridine causes temporary impotence. In other words, organic solvents are just as dangerous as corrosive chemicals, such as sulfuric acid, but manifest their hazardous nature in other, more subtle ways.

If you are pregnant, you may want to consider taking this course at a later time. Some exposure to organic fumes is inevitable, and any possible risk to an unborn baby should be avoided.

Minimize any direct exposure to solvents and treat them with respect. The laboratory room should be well ventilated. Normal cautious handling of solvents should not result in any health problems. If you are trying to evaporate a solution in an open container, you must do the evaporation in the hood. Excess solvents should be discarded in a container specifically intended for waste solvents, rather than down the drain at the laboratory bench.

A sensible precaution is to wear gloves when working with solvents. Gloves made from polyethylene are inexpensive and provide good protection.

The disadvantage of polyethylene gloves is that they are slippery. Disposable surgical gloves provide a better grip on glassware and other equipment, but they do not offer as much protection as polyethylene gloves. Nitrile gloves offer better protection.

Do Not Breathe Solvent Vapors. In checking the odor of a substance, be careful not to inhale very much of the material. The technique for smelling flowers is not advisable here; you could inhale dangerous amounts of the compound. Rather, a technique for smelling minute amounts of a substance should be used. Pass a stopper or spatula moistened with the substance (if it is a liquid) under your nose. Or hold the substance away from you and waft the vapors toward you with your hand. But *never* hold your nose over the container and inhale deeply!

The hazards associated with organic solvents you are likely to encounter in the organic laboratory are discussed in detail in Section 1.3. If you use proper safety precautions, your exposure to harmful organic vapors will be minimized and should present no health risks.

Safe Transportation of Chemicals. When transporting chemicals from one location to another, particularly from one room to another, it is always best to use some form of **secondary containment**. This means that the bottle or flask is carried inside another, larger container. This outer container serves to contain the contents of the inner vessel in case a leak or breakage should occur. Scientific suppliers offer a variety of chemical-resistant carriers for this purpose.

D. Waste Disposal

Do Not Place Any Liquid or Solid Waste in Sinks; Use Appropriate Waste Containers. Many substances are toxic, flammable, and difficult to degrade; it is neither legal nor advisable to dispose of organic solvents or other liquid or solid reagents by pouring them down the sink.

The correct disposal method for wastes is to put them in appropriately labeled waste containers. These containers should be placed in the hoods in the laboratory. The waste containers will be disposed of safely by qualified persons using approved protocols.

Specific guidelines for disposing of waste will be determined by the people in charge of your particular laboratory and by local regulations. Two alternative systems for handling waste disposal are presented here. For each experiment that you are assigned, you will be instructed to dispose of all wastes according to the system that is in operation in your laboratory.

In one model of waste collection, a separate waste container for each experiment is placed in the laboratory. In some cases, more than one container, each labeled according to the type of waste that is anticipated, is set out. The containers will be labeled with a list that details each substance that is present in the container. In this model, it is common practice to use separate waste containers for aqueous solutions, organic halogenated solvents, and other organic nonhalogenated materials. At the end of the laboratory class period, the waste containers are transported to a central hazardous materials storage location. These wastes may be later consolidated and poured into large drums for shipping. Complete labeling, detailing each chemical contained in the waste, is required at each stage of this waste-handling process, even when the waste is consolidated into drums.

In a second model of waste collection, you will be instructed to dispose of all wastes in one of the following ways:

Nonhazardous solids. Nonhazardous solids such as paper and cork can be placed in an ordinary wastebasket.

Broken glassware. Broken glassware should be put into a container specifically designated for broken glassware.

Organic solids. Solid products that are not turned in or any other organic solids should be disposed of in the container designated for organic solids.

Inorganic solids. Solids such as alumina and silica gel should be put in a container specifically designated for them.

Nonhalogenated organic solvents. Organic solvents such as diethyl ether, hexane, and toluene, or any solvent that does not contain a halogen atom, should be disposed of in the container designated for nonhalogenated organic solvents.

Halogenated solvents. Methylene chloride (dichloromethane), chloroform, and carbon tetrachloride are examples of common halogenated organic solvents. Dispose of all halogenated solvents in the container designated for them.

Strong inorganic acids and bases. Strong acids such as hydrochloric, sulfuric, and nitric acid will be collected in specially marked containers. Strong bases such as sodium hydroxide and potassium hydroxide will also be collected in specially designated containers.

Aqueous solutions. Aqueous solutions will be collected in a specially marked waste container. It is not necessary to separate each type of aqueous solution (unless the solution contains heavy metals); rather, unless otherwise instructed, you may combine all aqueous solutions into the same waste container. Although many types of solutions (aqueous sodium bicarbonate, aqueous sodium chloride, and so on) may seem innocuous and it may seem that their disposal down the sink drain is not likely to cause harm, many communities are becoming increasingly restrictive about what substances they will permit to enter municipal sewage-treatment systems. In light of this trend toward greater caution, it is important to develop good laboratory habits regarding the disposal of *all* chemicals.

Heavy metals. Many heavy metal ions such as mercury and chromium are highly toxic and should be disposed of in specifically designated waste containers.

Whichever method is used, the waste containers must eventually be labeled with a complete list of each substance that is present in the waste. Individual waste containers are collected, and their contents are consolidated and placed into drums for transport to the waste-disposal site. Even these drums must bear labels that detail each of the substances contained in the waste.

In either waste-handling method, certain principles will always apply:

- Aqueous solutions should not be mixed with organic liquids.
- Concentrated acids should be stored in separate containers; certainly they must *never* be allowed to come into contact with organic waste.
- Organic materials that contain halogen atoms (fluorine, chlorine, bromine, or iodine) should be stored in separate containers from those used to store materials that do not contain halogen atoms.

In each experiment in this textbook, we have suggested a method of collecting and storing wastes. Your instructor may opt to use another method for collecting wastes.

E. Use of Flames

Even though organic solvents are frequently flammable (for example, hexane, diethyl ether, methanol, acetone, and petroleum ether), there are certain laboratory procedures for which a flame must be used. Most often, these procedures involve an aqueous solution. In fact, as a general rule, use a flame to heat only aqueous solutions. Heating methods that do not use a flame are discussed in detail in Technique 6. Most organic solvents boil below 100°C, and an aluminum block, heating mantle, sand bath, or water bath may be used to heat these solvents safely. Common organic solvents are listed in Technique 10, Table 10.3. Solvents marked in the table with boldface type will burn. Diethyl ether, pentane, and hexane are especially dangerous, because in combination with the correct amount of air, they may explode.

Some common-sense rules apply to using a flame in the presence of flammable solvents. Again, we stress that you should check to see whether anyone in your vicinity is using flammable solvents before you ignite any open flame. If someone is using a flammable solvent, move to a safer location before you light your flame. Your laboratory should have an area set aside for using a burner to prepare micropipets or other pieces of glassware.

The drainage troughs or sinks should never be used to dispose of flammable organic solvents. They will vaporize if they are low boiling and may encounter a flame farther down the bench on their way to the sink.

F. Inadvertently Mixed Chemicals

To avoid unnecessary hazards of fire and explosion, never pour any reagent back into a stock bottle. There is always the chance that you may accidentally pour back some foreign substance that will react explosively with the chemical in the stock bottle. Of course, by pouring reagents back into the stock bottles, you may also introduce impurities that could spoil the experiment for the person using the stock reagent after you. Pouring reagents back into bottles is not only a dangerous practice, but an inconsiderate one. Thus, you should not take more chemicals than you need.

G. Unauthorized Experiments

Never undertake any unauthorized experiments. The risk of an accident is high, particularly if the experiment has not been completely checked to reduce hazards. Never work alone in the laboratory. The laboratory instructor or supervisor must always be present.

H. Food in the Laboratory

Because all chemicals are potentially toxic, avoid accidentally ingesting any toxic substance; therefore, never eat or drink any food while in the laboratory. There is always the possibility that whatever you are eating or drinking may become contaminated with a potentially hazardous material.

I. Clothing

Always wear closed shoes in the laboratory; open-toed shoes or sandals offer inadequate protection against spilled chemicals or broken glass. Do not wear your best clothing in the laboratory because some chemicals can make holes in or permanent stains on your clothing. To protect yourself and your clothing, it is advisable to wear a full-length laboratory apron or coat.

When working with chemicals that are very toxic, wear some type of gloves. Disposable gloves are inexpensive, offer good protection, provide acceptable "feel," and can be bought in many departmental stockrooms and college bookstores. Disposable latex surgical or polyethylene gloves are the least expensive type of glove; they are satisfactory when working with inorganic reagents and solutions. Better protection is afforded by disposable nitrile gloves. This type of glove provides good protection against organic chemicals and solvents. Heavier nitrile gloves are also available.

Finally, hair that is shoulder length or longer should be tied back. This precaution is especially important if you are working with a burner.

J. First Aid: Cuts, Minor Burns, and Acid or Base Burns

If any chemical enters your eyes, immediately irrigate the eyes with copious quantities of water. Tempered (slightly warm) water, if available, is preferable. Be sure that the eyelids are kept open. Continue flushing the eyes in this way for 15 minutes.

In case of a cut, wash the wound well with water unless you are specifically instructed to do otherwise. If necessary, apply pressure to the wound to stop the flow of blood.

Minor burns caused by flames or contact with hot objects may be soothed by immediately immersing the burned area in cold water or cracked ice until you no longer feel a burning sensation. Applying salves to burns is discouraged. Severe burns must be examined and treated by a physician. For chemical acid or base burns, rinse the burned area with copious quantities of water for at least 15 minutes.

If you accidentally ingest a chemical, call the local poison control center for instructions. Do not drink anything until you have been told to do so. It is important that the examining physician be informed of the exact nature of the substance ingested.

1.2 Right-to-Know Laws

The federal government and most state governments now require that employers provide their employees with complete information about hazards in the workplace. These regulations are often referred to as **Right-to-Know Laws.** At the federal level, the Occupational Safety and Health Administration (OSHA) is charged with enforcing these regulations.

In 1990, the federal government extended the Hazard Communication Act, which established the Right-to-Know Laws, to include a provision that requires the establishment of a Chemical Hygiene Plan at all academic laboratories. Every college and university chemistry department should have a Chemical Hygiene Plan. Having this plan means that all of the safety regulations and laboratory safety procedures should be written in a manual. The plan also provides for the training of all employees in laboratory safety. Your laboratory instructor and assistants should have this training.

One of the components of Right-to-Know Laws is that employees and students have access to information about the hazards of any chemicals with which they are

working. Your instructor will alert you to dangers to which you need to pay particular attention. However, you may want to seek additional information. Two excellent sources of information are labels on the bottles that come from a chemical manufacturer and **Material Safety Data Sheets** (MSDSs). The MSDSs are also provided by the manufacturer and must be kept available for all chemicals used at educational institutions.

A. Material Safety Data Sheets

Reading an MSDS for a chemical can be a daunting experience, even for an experienced chemist. MSDSs contain a wealth of information, some of which must be decoded to understand. The MSDS for methanol is shown below. Only the information that might be of interest to you is described in the paragraphs that follow.

Section 1. The first part of Section 1 identifies the substance by name, formula, and various numbers and codes. Most organic compounds have more than one name. In this case, the systematic (or International Union of Pure and Applied Chemistry [IUPAC]) name is methanol, and the other names are common names or are from an older system of nomenclature. The Chemical Abstract Service Number (CAS No.) is often used to identify a substance, and it may be used to access extensive information about a substance found in many computer databases or in the library.

Section 3. The Baker SAF-T-DATA System is found on all MSDSs and bottle labels for chemicals supplied by J. T. Baker, Inc. For each category listed, the number indicates the degree of hazard. The lowest number is 0 (very low hazard), and the highest number is 4 (extreme hazard). The Health category refers to damage involved when the substance is inhaled, ingested, or absorbed. Flammability indicates the tendency of a substance to burn. Reactivity refers to how reactive a substance is with air, water, or other substances. The last category, Contact, refers to how hazardous a substance is when it comes in contact with external parts of the body. Note that this rating scale is applicable only to Baker MSDSs and labels; other rating scales with different meanings are also in common use.

Section 4. This section provides helpful information for emergency and first aid procedures.

Section 6. This part of the MSDS deals with procedures for handling spills and disposal. The information could be very helpful, particularly if a large amount of a chemical was spilled. More information about disposal is also given in Section 13.

Section 8. Much valuable information is found in Section 8. To help you understand this material, some of the more important terms used in this section are defined:

> ***Threshold Limit Value (TLV).*** The American Conference of Governmental Industrial Hygienists (ACGIH) developed the TLV: This is the maximum concentration of a substance in air that a person should be exposed to on a regular basis. It is usually expressed in ppm or mg/m^3. Note that this value assumes that a person is exposed to the substance 40 hours per week, on a long-term basis. This value may not be particularly applicable in the case of a student performing an experiment in a single laboratory period.
>
> ***Permissible Exposure Limit (PEL).*** This has the same meaning as TLV; however, PELs were developed by OSHA. Note that for methanol, the TLV and PEL are both 200 ppm.

MSDS Number: M2015 Effective Date: 12/8/96

MSDS Material Safety Data Sheet

From: Mallinckrodt Baker, Inc.
222 Red School Lane
Phillipsburg, NJ 08865

MALLINCKRODT J.T.Baker

24 Hour Emergency Telephone: 908-859-2151
CHEMTREC: 1-800-424-9300

National Response in Canada
CANUTEC: 613-996-6666

Outside U.S. and Canada
Chemtrec: 202-483-7616

NOTE: CHEMTREC, CANUTEC and National Response Center emergency numbers to be used only in the event of chemical emergencies involving a spill, leak, fire, exposure or accident involving chemicals.

All non-emergency questions should be directed to Customer Service (1-800-582-2537) for assistance.

METHYL ALCOHOL

1. Product Identification

Synonyms: Wood alcohol; methanol; carbinol
CAS No: 67-56-1
Molecular Weight: 32.04
Chemical Formula: CH_3OH
Product Codes: **J.T. Baker:**
5217, 5370, 5794, 5807, 5811, 5842, 5869, 9049, 9063, 9066, 9067, 9069, 9070, 9071, 9073, 9075, 9076, 9077, 9091, 9093, 9096, 9097, 9098, 9263, 9893
Mallinckrodt:
3004, 3006, 3016, 3017, 3018, 3024, 3041, 3701, 4295, 5160, 8814, H080, H488, H603, V079, V571

2. Composition/Information on Ingredients

Ingredient	CAS No.	Percent	Hazardous
Methyl Alcohol	67-56-1	100%	Yes

3. Hazards Identification

Emergency Overview

POISON! DANGER! VAPOR HARMFUL. MAY BE FATAL OR CAUSE BLINDNESS IF SWALLOWED. HARMFUL IF INHALED OR ABSORBED THROUGH SKIN. CANNOT BE MADE NONPOISONOUS. FLAMMABLE LIQUID AND VAPOR. CAUSES IRRITATION TO SKIN, EYES AND RESPIRATORY TRACT. AFFECTS THE LIVER.

J.T. Baker SAF-T-DATA(tm) Ratings

(Provided here for your convenience)

Health:	Flammability:	Reactivity:	Contact:
3 - Severe (Poison)	4 - Extreme (Flammable)	1 - Slight	1 - Slight

Lab Protection Equip: GOGGLES & SHIELD; LAB COAT & APRON; VENT HOOD; PROPER GLOVES; CLASS B EXTINGUISHER
Storage Color Code: Red (Flammable)

Potential Health Effects

Inhalation:

A slight irritant to the mucous membranes. Toxic effects exerted upon nervous system, particularly the optic nerve. Once absorbed into the body, it is very slowly eliminated. Symptoms of overexposure may include headache, drowsiness, nausea, vomiting, blurred vision, blindness, coma, and death. A person may get better but then worse again up to 30 hours later.

Ingestion:

Toxic. Symptoms parallel inhalation. Can intoxicate and cause blindness. Usual fatal dose: 100-125 milliliters.

Skin Contact:

Methyl alcohol is a defatting agent and may cause skin to become dry and cracked. Skin absorption can occur; symptoms may parallel inhalation exposure.

Eye Contact:

Irritant. Continued exposure may cause eye lesions.

Chronic Exposure:

Marked impairment of vision and enlargement of the liver has been reported. Repeated or prolonged exposure may cause skin irritation.

Aggravation of Pre-existing Conditions:

Persons with pre-existing skin disorders or eye problems or impaired liver or kidney function may be more susceptible to the effects of the substance.

4. First Aid Measures

Inhalation:

Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.

Ingestion:

Induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person.

Skin Contact:

Remove any contaminated clothing. Wash skin with soap or mild detergent and water for at least 15 minutes. Get medical attention if irritation develops or persists.

Eye Contact:

Immediately flush eyes with plenty of water for at least 15 minutes, lifting lower and upper eyelids occasionally. Get medical attention immediately.

5. Fire Fighting Measures

Fire:

Flash point: 12°C (54°F) CC
Autoignition temperature: 464°C (867°F)
Flammable limits in air % by volume:
lel: 7.3; uel: 36
Flammable.

Explosion:

Above flash point, vapor-air mixtures are explosive within flammable limits noted above. Moderate explosion hazard and dangerous fire hazard when exposed to heat, sparks or flames. Sensitive to static discharge.

Fire Extinguishing Media:

Water spray, dry chemical, alcohol foam, or carbon dioxide.

Special Information:

In the event of a fire, wear full protective clothing and NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode. Use water spray to blanket fire, cool fire exposed containers, and to flush non-ignited spills or vapors away from fire. Vapors can flow along surfaces to distant ignition source and flash back.

6. Accidental Release Measures

Ventilate area of leak or spill. Remove all sources of ignition. Wear appropriate personal protective equipment as specified in Section 8. Isolate hazard area. Keep unnecessary and unprotected personnel from entering. Contain and recover liquid when possible. Use non-sparking tools and equipment. Collect liquid in an appropriate container or absorb with an inert material (e. g., vermiculite, dry sand, earth), and place in a chemical waste container. Do not use combustible materials, such as saw dust. Do not flush to sewer! J. T. Baker SOLUSORB® solvent adsorbent is recommended for spills of this product.

7. Handling and Storage

Protect against physical damage. Store in a cool, dry well-ventilated location, away from any area where the fire hazard may be acute. Outside or detached storage is preferred. Separate from incompatibles. Containers should be bonded and grounded for transfers to avoid static sparks. Storage and use areas should be No Smoking areas. Use non-sparking type tools and equipment, including explosion proof ventilation. Containers of this material may be hazardous when empty since they retain product residues (vapors, liquid); observe all warnings and precautions listed for the product.

8. Exposure Controls/Personal Protection

Airborne Exposure Limits:

For Methyl Alcohol:
- OSHA Permissible Exposure Limit (PEL):
  200 ppm (TWA)
- ACGIH Threshold Limit Value (TLV):
  200 ppm (TWA), 250 ppm (STEL) skin

Ventilation System:

A system of local and/or general exhaust is recommended to keep employee exposures below the Airborne Exposure Limits. Local exhaust ventilation is generally preferred because it can control the emissions of the contaminant at its source, preventing dispersion of it into the general work area. Please refer to the ACGIH document, "Industrial Ventilation, A Manual of Recommended Practices", most recent edition, for details.

Personal Respirator (NIOSH Approved)

If the exposure limit is exceeded, wear a supplied air, full-facepiece respirator, airlined hood, or full-facepiece self-contained breathing apparatus.

Skin Protection:

Rubber or neoprene gloves and additional protection including impervious boots, apron, or coveralls, as needed in areas of unusual exposure.

Eye Protection:

Use chemical safety goggles. Maintain eye wash fountain and quick-drench facilities in work area.

9. Physical and Chemical Properties

Appearance:
Clear, colorless liquid.

Odor:
Characteristic odor.

Solubility:
Miscible in water.

Specific Gravity:
0.8

pH:
No information found.

% Volatiles by volume @ 21°C (70°F):
100

Boiling Point:
64.5°C (147°F)

Melting Point:
-98°C (-144°F)

Vapor Density (Air=1):
1.1

Vapor Pressure (mm Hg):
97 @ 20°C (68°F)

Evaporation Rate (BuAc=1):
5.9

10. Stability and Reactivity

Stability:
Stable under ordinary conditions of use and storage.
Hazardous Decomposition Products:
May form carbon dioxide, carbon monoxide, and formaldehyde when heated to decomposition.
Hazardous Polymerization:
Will not occur.
Incompatabilities:
Strong oxidizing agents such as nitrates, perchlorates or sulfuric acid. Will attack some forms of plastics, rubber, and coatings. May react with metallic aluminum and generate hydrogen gas.
Conditions to Avoid:
Heat, flames, ignition sources and incompatibles.

11. Toxicological Information

Methyl Alcohol (Methanol) Oral rat LD50: 5628 mg/kg; inhalation rat LC50: 64000 ppm/4H; skin rabbit LD50: 15800 mg/kg; Irritation data-standard Draize test: skin, rabbit: 20mg/24 hr. Moderate; eye, rabbit: 100 mg/24 hr. Moderate; Investigated as a mutagen, reproductive effector.

Cancer Lists

	---NTP Carcinogen---		
Ingredient	**Known**	**Anticipated**	**IARC Category**
Methyl Alcohol (67-56-1)	No	No	None

12. Ecological Information

Environmental Fate:
When released into the soil, this material is expected to readily biodegrade. When released into the soil, this material is expected to leach into groundwater. When released into the soil, this material is expected to quickly evaporate. When released into the water, this material is expected to have a half-life between 1 and 10 days. When released into water, this material is expected to readily biodegrade. When released into the air, this material is expected to exist in the aerosol phase with a short half-life. When released into the air, this material is expected to be readily degraded by reaction with photochemically produced hydroxyl radicals. When released into air, this material is expected to have a half-life between 10 and 30 days. When released into the air, this material is expected to be readily removed from the atmosphere by wet deposition.
Environmental Toxicity:
This material is expected to be slightly toxic to aquatic life.

13. Disposal Considerations

Whatever cannot be saved for recovery or recycling should be handled as hazardous waste and sent to a RCRA approved incinerator or disposed in a RCRA approved waste facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations.

Dispose of container and unused contents in accordance with federal, state and local requirements.

14. Transport Information

Domestic (Land, D.O.T.)

Proper Shipping Name:	METHANOL		
Hazard Class:	3		
UN/NA:	UN1230	**Packing Group:**	II

Information reported for product/size: 350LB

International (Water, I.M.O.)

Proper Shipping Name: METHANOL

Hazard Class: 3.2, 6.1

UN/NA: UN1230 **Packing Group:** II

Information reported for product/size: 350LB

15. Regulatory Information

Chemical Inventory Status

Ingredient	TSCA	EC	Japan	Australia	Korea	Canada DSL	Canada NDSL	Canada Phil.
Methyl Alcohol (67-56-1)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Federal, State & International Regulations

Ingredient	SARA 302 RQ	SARA 302 TPQ	SARA 313 List	SARA 313 Chemical Catg.	CERCLA	RCRA 261.33	TSCA 8(d)
Methyl Alcohol (67-56-1)	No	No	Yes	No	5000	U154	No

Chemical Weapons Convention: No **TSCA 12(b):** No **CDTA:** No

SARA 311/312: Acute: Yes Chronic: Yes Fire: Yes Pressure: No Reactivity: No (Pure / Liquid)

Australian Hazchem Code: 2PE **Australian Poison Schedule:** S6

WHMIS: This MSDS has been prepared according to the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

16. Other Information

NFPA Ratings:

Health: 1 Flammability: 3 Reactivity: 0

Label Hazard Warning:

POISON! DANGER! VAPOR HARMFUL. MAY BE FATAL OR CAUSE BLINDNESS IF SWALLOWED. HARMFUL IF INHALED OR ABSORBED THROUGH SKIN. CANNOT BE MADE NONPOISONOUS. FLAMMABLE LIQUID AND VAPOR. CAUSES IRRITATION TO SKIN, EYES AND RESPIRATORY TRACT. AFFECTS THE LIVER.

Label Precautions:

Keep away from heat, sparks and flame.
Keep container closed.
Use only with adequate ventilation.
Wash thoroughly after handling.
Avoid breathing vapor.
Avoid contact with eyes, skin and clothing.

Label First Aid:

If swallowed, induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Wash clothing before reuse. If inhaled, remove to fresh air. If not breathing give artificial respiration. If breathing is difficult, give oxygen. In all cases get medical attention immediately.

Product Use:

Laboratory Reagent.

Revision Information:

New 16 section MSDS format, all sections have been revised.

Disclaimer:

Mallinckrodt Baker, Inc. provides the information contained herein in good faith but makes no representation as to its comprehensiveness or accuracy. This document is intended only as a guide to the appropriate precautionary handling of the material by a properly trained person using this product. Individuals receiving the information must exercise their independent judgment in determining its appropriateness for a particular purpose. MALLINCKRODT BAKER, INC. MAKES NO REPRESENTATIONS OR WARRANTIES, EITHER EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY WARRANTIES OR MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE WITH RESPECT TO THE INFORMATION SET FORTH HEREIN OR THE PRODUCT TO WHICH THE INFORMATION REFERS. ACCORDINGLY, MALLINCKRODT BAKER, INC. WILL NOT BE RESPONSIBLE FOR DAMAGES RESULTING FROM USE OF OR RELIANCE UPON THIS INFORMATION.

Prepared By: Strategic Services Division
Phone Number: (314) 539-1600 (U.S.A.)

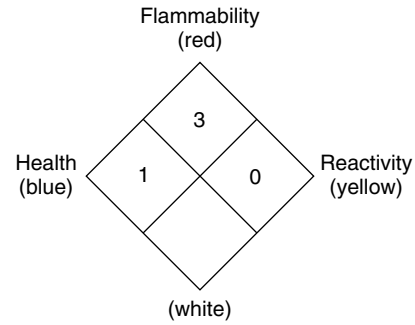
Section 10. The information contained in Section 10 refers to the stability of the compound and the hazards associated with mixing of chemicals. It is important to consider this information before carrying out an experiment not previously done.

Section 11. More information about the toxicity is given in this section. Another important term must first be defined:

> ***Lethal Dose, 50% Mortality (LD_{50})***. This is the dose of a substance that will kill 50% of the animals administered a single dose. Different means of administration are used, such as oral, intraperitoneal (injected into the lining of the abdominal cavity), subcutaneous (injected under the skin), and application to the surface of the skin. The LD_{50} is usually expressed in milligrams (mg) of substance per kilogram (kg) of animal weight. The lower the value of LD_{50}, the more toxic the substance. It is assumed that the toxicity in humans will be similar.

Unless you have considerably more knowledge about chemical toxicity, the information in Sections 8 and 11 is most useful for comparing the toxicity of one substance with another. For example, the TLV for methanol is 200 ppm, whereas the TLV for benzene is 10 ppm. Clearly, performing an experiment involving benzene would require much more stringent precautions than an experiment involving methanol. One of the LD_{50} values for methanol is 5628 mg/kg. The comparable LD_{50} value of aniline is 250 mg/kg. Clearly, aniline is much more toxic, and because it is easily absorbed through the skin, it presents a significant hazard. It should also be mentioned that both TLV and PEL ratings assume that the worker comes in contact with a substance on a repeated and long-term basis. Thus, even if a chemical has a relatively low TLV or PEL, it does not mean that using it for one experiment will present a danger to you. Furthermore, by performing experiments using small amounts of chemicals and with proper safety precautions, your exposure to organic chemicals in this course will be minimal.

Section 16. Section 16 contains the National Fire Protection Association (NFPA) rating. This is similar to the Baker SAF-T-DATA (discussed in Section 3), except that the number represents the hazards when a fire is present. The order here is Health, Flammability, and Reactivity. Often, this is presented in graphic form on a label (see figure). The small diamonds are often color coded: blue for Health, red for Flammability, and yellow for Reactivity. The bottom diamond (white) is sometimes used to display graphic symbols denoting unusual reactivity, hazards, or special precautions to be taken.



B. Bottle Labels

Reading the label on a bottle can be a very helpful way of learning about the hazards of a chemical. The amount of information varies greatly, depending on which company supplied the chemical.

Apply some common sense when you read MSDSs and bottle labels. Using these chemicals does not mean you will experience the consequences that can potentially result from exposure to each chemical. For example, an MSDS for sodium chloride states, "Exposure to this product may have serious adverse health effects." Despite the apparent severity of this cautionary statement, it would not be reasonable to expect people to stop using sodium chloride in a chemistry experiment or to stop sprinkling a small amount of it (as table salt) on eggs to enhance their flavor. In many cases, the consequences described in MSDSs from exposure to chemicals are somewhat overstated, particularly for students using these chemicals to perform a laboratory experiment.

1.3 Common Solvents

Most organic chemistry experiments involve an organic solvent at some step in the procedure. A list of common organic solvents follows, with a discussion of toxicity, possible carcinogenic properties, and precautions that you should use when handling these solvents. A tabulation of the compounds currently suspected of being carcinogens appears at the end of Technique 1.

Acetic Acid. Glacial acetic acid is corrosive enough to cause serious acid burns on the skin. Its vapors can irritate the eyes and nasal passages. Care should be exercised not to breathe the vapors and not to allow them to escape into the laboratory.

Acetone. Relative to other organic solvents, acetone is not very toxic. It is flammable, however. Do not use acetone near open flames.

Benzene. Benzene can damage bone marrow, it causes various blood disorders, and its effects may lead to leukemia. Benzene is considered a serious carcinogenic hazard. It is absorbed rapidly through the skin and also poisons the liver and kidneys. In addition, benzene is flammable. Because of its toxicity and its carcinogenic properties, benzene should not be used in the laboratory; you should use some less dangerous solvent instead. Toluene is considered a safer alternative solvent in procedures that specify benzene.

Carbon Tetrachloride. Carbon tetrachloride can cause serious liver and kidney damage, as well as skin irritation and other problems. It is absorbed rapidly through the skin. In high concentrations, it can cause death as a result of respiratory failure. Moreover, carbon tetrachloride is suspected of being a carcinogenic material. Although this solvent has the advantage of being nonflammable (in the past, it was used on occasion as a fire extinguisher), it can cause health problems, so it should not be used routinely in the laboratory. If no reasonable substitute exists, however, it must be used in small quantities, as in preparing samples for infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. In such cases, you must use it in a hood.

Chloroform. Chloroform is similar to carbon tetrachloride in its toxicity. It has been used as an anesthetic. However, chloroform is currently on the list of suspected

carcinogens. Because of this, do not use chloroform routinely as a solvent in the laboratory. If it is occasionally necessary to use chloroform as a solvent for special samples, then you must use it in a hood. Methylene chloride is usually found to be a safer substitute in procedures that specify chloroform as a solvent. Deuterochloroform, $CDCl_3$, is a common solvent for NMR spectroscopy. Caution dictates that you should treat it with the same respect as chloroform.

1,2-Dimethoxyethane (Ethylene Glycol Dimethyl Ether or Monoglyme). Because it is miscible with water, 1,2-dimethoxyethane is a useful alternative to solvents such as dioxane and tetrahydrofuran, which may be more hazardous. 1,2-Dimethoxyethane is flammable and should not be handled near an open flame. Upon long exposure of 1,2-dimethoxyethane to light and oxygen, explosive peroxides may form. 1,2-Dimethoxyethane is also a possible reproductive toxin.

Dioxane. Dioxane has been used widely because it is a convenient, water-miscible solvent. It is now suspected, however, of being carcinogenic. It is also toxic, affecting the central nervous system, liver, kidneys, skin, lungs, and mucous membranes. Dioxane is also flammable and tends to form explosive peroxides when it is exposed to light and air. Because of its carcinogenic properties, it is no longer used in the laboratory unless absolutely necessary. Either 1,2-dimethoxyethane or tetrahydrofuran is a suitable, water-miscible alternative solvent.

Ethanol. Ethanol has well-known properties as an intoxicant. In the laboratory, the principal danger arises from fires, because ethanol is a flammable solvent. When using ethanol, take care to work where there are no open flames.

Ether (diethyl ether). The principal hazard associated with diethyl ether is fire or explosion. Ether is probably the most flammable solvent found in the laboratory. Because ether vapors are much denser than air, they may travel along a laboratory bench for a considerable distance from their source before being ignited. Before using ether, it is very important to be sure that no one is working with matches or any open flame. Ether is not a particularly toxic solvent, although in high enough concentrations it can cause drowsiness and perhaps nausea. It has been used as a general anesthetic. Ether can form highly explosive peroxides when exposed to air. Consequently, you should never distill it to dryness.

Hexane. Hexane may be irritating to the respiratory tract. It can also act as an intoxicant and a depressant of the central nervous system. It can cause skin irritation because it is an excellent solvent for skin oils. The most serious hazard, however, comes from its flammability. The precautions recommended for using diethyl ether in the presence of open flames apply equally to hexane.

Ligroin. See Hexane.

Methanol. Much of the material outlining the hazards of ethanol applies to methanol. Methanol is more toxic than ethanol; ingestion can cause blindness and even death. Because methanol is more volatile, the danger of fires is more acute.

Methylene Chloride (Dichloromethane). Methylene chloride is not flammable. Unlike other members of the class of chlorocarbons, it is not currently considered a serious carcinogenic hazard. Recently, however, it has been the subject of much serious

investigation, and there have been proposals to regulate it in industrial situations in which workers have high levels of exposure on a day-to-day basis. Methylene chloride is less toxic than chloroform and carbon tetrachloride. It can cause liver damage when ingested, however, and its vapors may cause drowsiness or nausea.

Pentane. See Hexane.

Petroleum Ether. See Hexane.

Pyridine. Some fire hazard is associated with pyridine. However, the most serious hazard arises from its toxicity. Pyridine may depress the central nervous system; irritate the skin and respiratory tract; damage the liver, kidneys, and gastrointestinal system; and even cause temporary sterility. You should treat pyridine as a highly toxic solvent and handle it only in the fume hood.

Tetrahydrofuran. Tetrahydrofuran may cause irritation of the skin, eyes, and respiratory tract. It should never be distilled to dryness because it tends to form potentially explosive peroxides on exposure to air. Tetrahydrofuran does present a fire hazard.

Toluene. Unlike benzene, toluene is not considered a carcinogen. However, it is at least as toxic as benzene. It can act as an anesthetic and damage the central nervous system. If benzene is present as an impurity in toluene, expect the usual hazards associated with benzene. Toluene is also a flammable solvent, and the usual precautions about working near open flames should be applied.

You should not use certain solvents in the laboratory because of their carcinogenic properties. Benzene, carbon tetrachloride, chloroform, and dioxane are among these solvents. For certain applications, however, notably as solvents for infrared or NMR spectroscopy, there may be no suitable alternative. When it is necessary to use one of these solvents, use safety precautions and refer to the discussions in Techniques 25–28.

Because relatively large amounts of solvents may be used in a large organic laboratory class, your laboratory supervisor must take care to store these substances safely. Only the amount of solvent needed for a particular experiment should be kept in the laboratory. The preferred location for bottles of solvents being used during a class period is in a hood. When the solvents are not being used, they should be stored in a fireproof storage cabinet for solvents. If possible, this cabinet should be ventilated into the fume hood system.

1.4 Carcinogenic Substances

A **carcinogen** is a substance that causes cancer in living tissue. The usual procedures for determining whether a substance is carcinogenic is to expose laboratory animals to high dosages over a long period. It is not clear whether short-term exposure to these chemicals carries a comparable risk, but it is prudent to use these substances with special precautions.

Many regulatory agencies have compiled lists of carcinogenic substances or substances suspected of being carcinogenic. Because these lists are inconsistent,

compiling a definitive list of carcinogenic substances is difficult. The following common substances are included in many of these lists.

Acetamide	4-Methyl-2-oxetanone (β-butyrolactone)
Acrylonitrile	1-Naphthylamine
Asbestos	2-Naphthylamine
Benzene	*N*-Nitroso compounds
Benzidine	2-Oxetanone (β-propiolactone)
Carbon tetrachloride	Phenacetin
Chloroform	Phenylhydrazine and its salts
Chromic oxide	Polychlorinated biphenyl (PCB)
Coumarin	Progesterone
Diazomethane	Styrene oxide
1,2-Dibromoethane	Tannins
Dimethyl sulfate	Testosterone
p-Dioxane	Thioacetamide
Ethylene oxide	Thiourea
Formaldehyde	*o*-Toluidine
Hydrazine and its salts	Trichloroethylene
Lead (II) acetate	Vinyl chloride

REFERENCES

Aldrich Catalog and Handbook of Fine Chemicals. Aldrich Chemical Co.: Milwaukee, WI, current edition.

Armour, M. A., *Pollution Prevention and Waste Minimization in Laboratories.* Reinhardt, P. A., Leonard, K. L., Ashbrook P. C., Eds.; Lewis Publishers: Boca Raton, Florida, 1996.

Fire Protection Guide on Hazardous Materials, 10th ed. National Fire Protection Quincy, MA: Association 1991.

Flinn Chemical Catalog Reference Manual. Flinn Scientific: Batavia, IL, current edition.

Gosselin, R. E., Smith, R. P., Hodge, H. C. *Clinical Toxicology of Commercial Products,* 5th ed. Williams & Wilkins: Baltimore, MD 1984.

Lenga, R. E., ed. *The Sigma-Aldrich Library of Chemical Safety Data.* Sigma-Aldrich: Milwaukee, WI 1985.

Lewis, R. J. *Carcinogenically Active Chemicals: A Reference Guide*. Van Nostrand Reinhold: New York 1990.

Lewis, R. J., *Sax's Dangerous Properties of Industrial Materials,* 11th edition, Van Nostrand Reinhold: New York 2007.

The Merck Index, 14th ed. Merck and Co.: Rahway, NJ 2006.

Prudent Practices in the Laboratory: Handling and Disposal of Chemicals. Washington, DC: Committee on Prudent Practices for Handling, Storage, and Disposal of Chemicals in Laboratories; Board on Chemical Sciences and Technology; Commission on Physical Sciences, Mathematics, and Applications; National Research Council, National Academy Press, 1995.

Renfrew, M. M., ed. *Safety in the Chemical Laboratory.* Division of Chemical Education, American Chemical Society; Easton, PA 1967–1991.

Safety in Academic Chemistry Laboratories, 4th ed. Committee on Chemical Safety, American Chemical Society: Washington, DC 1985.

Sax, N. I., Lewis, R. J., eds. *Rapid Guide to Hazardous Chemicals in the Work Place*, 4th ed. Van Nostrand Reinhold: New York 2000.

Useful Safety-Related Internet Addresses

Interactive Learning Paradigms, Inc.
http://www.ilpi.com/msds/
This is an excellent general site for MSDS sheets. The site lists chemical manufacturers and suppliers. Selecting a company will take you directly to the appropriate place to obtain an MSDS sheet. Many of the sites listed require you to register in order to obtain an MSDS sheet for a particular chemical. Ask your departmental or college safety supervisor to obtain the information for you.

Acros chemicals and Fisher Scientific
https://www1.fishersci.com/

Alfa Aesar
http://www.alfa.com/alf/index.htm

Cornell University, Department of Environmental Health and Safety
http://msds.pdc.cornell.edu/msdssrch.asp
This is an excellent searchable database of more than 325,000 MSDS files. No registration is required.

Eastman Kodak
http://msds.kodak.com/ehswww/external/index.jsp

EMD Chemicals (formerly EM Science) and Merck
http://www.emdchemicals.com/corporate/emd_corporate.asp

J. T. Baker and Mallinckrodt Laboratory Chemicals
http://www.jtbaker.com/asp/Catalog.asp

National Institute for Occupational Safety and Health (NIOSH) has an excellent "Website" that includes databases and information resources, including links:
http://www.cdc.gov/niosh/topics/chemical-safety/default.html

Sigma, Aldrich and Fluka
http://www.sigmaaldrich.com/Area_of_Interest/The_Americas/United_States.html

VWR Scientific Products
http://www.vwrsp.com/search/index.cgi?tmpl=msds

2 TECHNIQUE 2

The Laboratory Notebook, Calculations, and Laboratory Records

In the Introduction to this book, we mentioned the importance of advance preparation for laboratory work. Presented here are some suggestions about what specific information you should try to obtain in your advance studying. Because much of this information must be obtained while preparing your laboratory notebook, the two subjects, advance study and notebook preparation, are developed simultaneously.

An important part of any laboratory experience is learning to maintain very complete records of every experiment undertaken and every item of data obtained. Far too often, careless recording of data and observations has resulted in mistakes, frustration, and lost time due to needless repetition of experiments. If reports are required, you will find that proper collection and recording of data can make your report writing much easier.

Because organic reactions are seldom quantitative, special problems result. Frequently, reagents must be used in large excess to increase the amount of product. Some reagents are expensive, and, therefore, care must be used in measuring the amounts of these substances. Very often, many more reactions take place than you desire. These extra reactions, or **side reactions**, may form products other than the desired product. These are called **side products**. For all of these reasons, you must plan your experimental procedure carefully before undertaking the actual experiment.

2.1 The Notebook

For recording data and observations during experiments, use a *bound notebook.* The notebook should have consecutively numbered pages. If it does not, number the pages immediately. A spiral-bound notebook or any other notebook from which the pages can be removed easily is not acceptable, because the possibility of losing the pages is great.

All data and observations must be recorded in the notebook. Paper towels, napkins, toilet tissue, or scratch paper tend to become lost or destroyed. It is bad laboratory practice to record information on such random and perishable pieces of paper. All entries must be recorded in *permanent ink.* It can be frustrating to have important information disappear from the notebook because it was recorded in washable ink or pencil and could not survive a flood caused by the student at the next position on the bench. Because you will be using your notebook in the laboratory, the book will probably become soiled or stained by chemicals, filled with scratched-out entries, or even slightly burned. That is expected and is a normal part of laboratory work.

Your instructor may check your notebook at any time, so you should always have it up to date. If your instructor requires reports, you can prepare them quickly from the material recorded in the laboratory notebook.

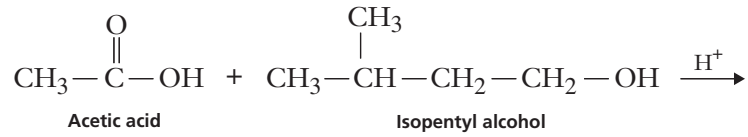
2.2 Notebook Format

A. Advance Preparation

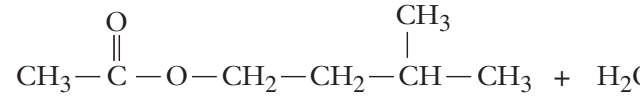
Individual instructors vary greatly in the type of notebook format they prefer; such variation stems from differences in philosophies and experience. You must obtain specific directions from your own instructor for preparing a notebook. Certain features, however, are common to most notebook formats. The following discussion indicates what might be included in a typical notebook.

It will be very helpful and you can save much time in the laboratory if for each experiment you know the main reactions, the potential side reactions, the mechanism, and the stoichiometry, and you understand fully the procedure and the theory underlying it before you come to the laboratory. Understanding the procedure by which the desired product is to be separated from undesired materials is also very important. If you examine each of these topics before coming to class, you will be prepared to do the experiment efficiently. You will have your equipment and reagents already prepared when they are to be used. Your reference material will be at hand when you need it. Finally, with your time efficiently organized, you will be able to take advantage of long reaction or reflux periods to perform other tasks, such as doing shorter experiments or finishing previous ones.

For experiments in which a compound is synthesized from other reagents, that is, **preparative experiments**, it is essential to know the main reaction. To perform stoichiometric calculations, you should balance the equation for the main reaction. Therefore, before you begin the experiment, your notebook should contain the balanced equation for the pertinent reaction. Using the preparation of isopentyl acetate, or banana oil, as an example, you should write the following:



Acetic acid — Isopentyl alcohol



Isopentyl acetate

Also, before beginning the experiment enter in the notebook the possible side reactions that divert reagents into contaminants (side products). You will have to separate these side products from the major product during purification.

You should list physical constants such as melting points, boiling points, densities, and molecular weights in the notebook when this information is needed to perform an experiment or to do calculations. These data are located in sources such as the *CRC Handbook of Chemistry and Physics, The Merck Index, Lange's Handbook of Chemistry,* or the *Aldrich Handbook of Fine Chemicals.* Write physical constants required for an experiment in your notebook before you come to class.

Advance preparation may also include examining some subjects, information not necessarily recorded in the notebook, that should prove useful in understanding the experiment. Included among these subjects are an understanding of the mechanism of the reaction, an examination of other methods by which the same compound might be prepared, and a detailed study of the experimental procedure. Many students find that an outline of the procedure, prepared *before* they come to class, helps them use their time more efficiently once they begin the experiment. Such an outline could very well be prepared on some loose sheet of paper rather than in the notebook itself.

Once the reaction has been completed, the desired product does not magically appear as purified material; it must be isolated from a frequently complex mixture of side products, unreacted starting materials, solvents, and catalysts. You should try to outline a **separation scheme** in your notebook for isolating the product from its contaminants. At each stage, you should try to understand the reason for the particular instruction given in the experimental procedure. This not only will familiarize you with the basic separation and purification techniques used in organic chemistry but also will help you understand when to use these techniques. Such an outline might take the form of a flowchart. For example, see the separation scheme for isopentyl acetate (see Figure 2.1). Careful attention to understanding the separation, besides familiarizing you with the procedure by which the desired product is separated from impurities in your particular experiments, may prepare you for original research in which no experimental procedure exists.

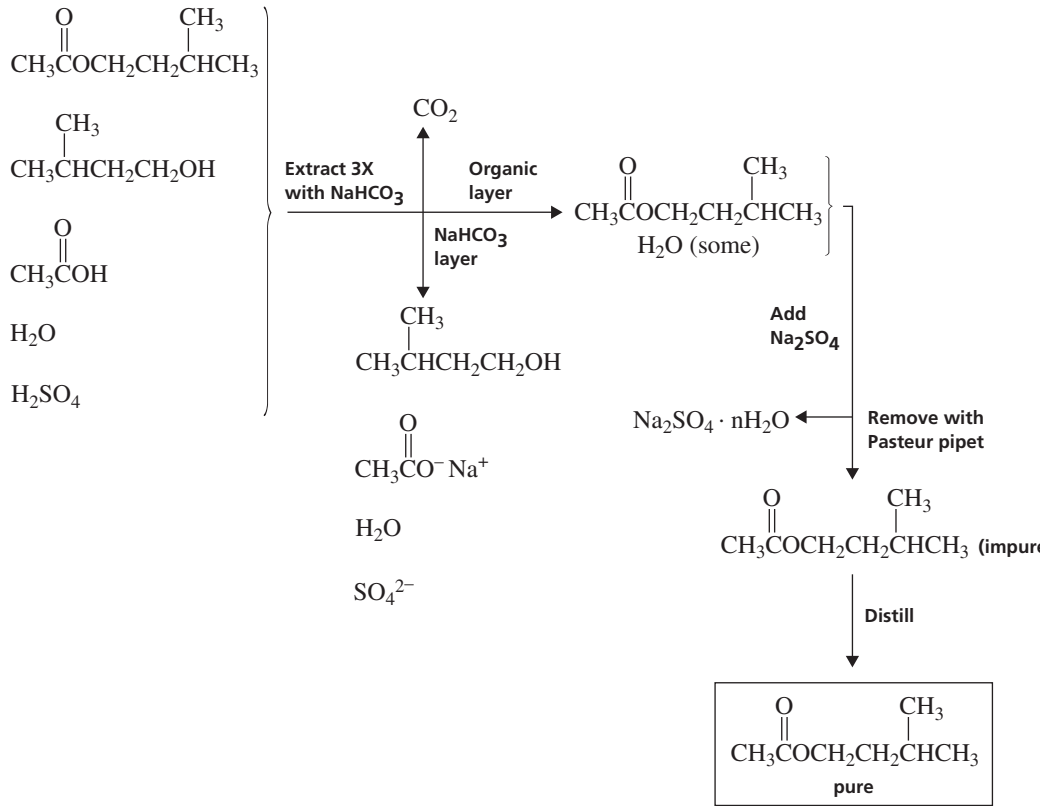


Figure 2.1 Separation scheme for isopentyl acetate.

In designing a separation scheme, note that the scheme outlines those steps undertaken once the reaction period has been concluded. For this reason, the represented scheme does not include steps such as the addition of the reactants (isopentyl alcohol and acetic acid) and the catalyst (sulfuric acid) or the heating of the reaction mixture.

For experiments in which a compound is isolated from a particular source and is not prepared from other reagents, some information described in this section will not be applicable. Such experiments are called **isolation experiments**. A typical isolation experiment involves isolating a pure compound from a natural source. Examples include isolating caffeine from tea or isolating cinnamaldehyde from cinnamon. Although isolation experiments require somewhat different advance preparation, this advance study may include looking up physical constants for the compound isolated and outlining the isolation procedure. A detailed examination of the separation scheme is very important here because it is the heart of such an experiment.

B. Laboratory Records

When you begin the actual experiment, keep your notebook nearby so you will be able to record those operations you perform. When working in the laboratory, your notebook serves as a place in which to record a rough transcript of your experimental method. Data from actual weighings, volume measurements, and determinations

of physical constants are also noted. This section of your notebook should *not* be prepared in advance. The purpose is not to write a recipe but rather to record what you *did* and what you *observed.* These observations will help you write reports without resorting to memory. They will also help you or other workers repeat the experiment in as nearly as possible the same way. The sample notebook pages found in Figures 2.2 and 2.3 illustrate the type of data and observations that should be written in your notebook.

When your product has been prepared and purified, or isolated if it is an isolation experiment, record pertinent data such as the melting point or boiling point of the substance, its density, its index of refraction, and the conditions under which spectra were determined.

C. Calculations

A chemical equation for the overall conversion of the starting materials to products is written on the assumption of simple ideal stoichiometry. Actually, this assumption is seldom realized. Side reactions or competing reactions will also occur, giving other products. For some synthetic reactions, an equilibrium state will be reached in which an appreciable amount of starting material is still present and can be recovered. Some of the reactant may also remain if it is present in excess or if the reaction was incomplete. A reaction involving an expensive reagent illustrates another reason for needing to know how far a particular type of reaction converts reactants to products. In such a case, it is preferable to use the most efficient method for this conversion. Thus, information about the efficiency of conversion for various reactions is of interest to the person contemplating the use of these reactions.

The quantitative expression for the efficiency of a reaction is found by calculating the **yield** for the reaction. The **theoretical yield** is the number of grams of the product expected from the reaction on the basis of ideal stoichiometry, with side reactions, reversibility, and losses ignored. To calculate the theoretical yield, it is first necessary to determine the **limiting reagent**. The limiting reagent is the reagent that is not present in excess and on which the overall yield of product depends. The method for determining the limiting reagent in the isopentyl acetate experiment is illustrated in the sample notebook pages shown in Figures 2.2 and 2.3. You should consult your general chemistry textbook for more complicated examples. The theoretical yield is then calculated from the expression:

Theoretical yield = (moles of limiting reagent)(ratio)(molecular weight of product)

The ratio here is the stoichiometric ratio of product to limiting reagent. In preparing isopentyl acetate, that ratio is 1:1. One mole of isopentyl alcohol, under ideal circumstances, should yield 1 mole of isopentyl acetate.

The **actual yield** is simply the number of grams of desired product obtained. The **percentage yield** describes the efficiency of the reaction and is determined by

$$\text{Percentage yield} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \times 100$$

THE PREPARATION OF ISOPENTYLACETATE (BANANA OIL)

Main Reaction

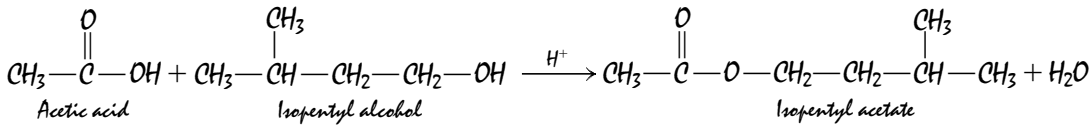


Table of Physical Constants

	MW	BP	Density
Isopentyl alcohol	88.2	132°C	0.813 g/ml
Acetic acid	60.1	118	1.06
Isopentyl acetate	130.2	142	0.876

Separation Scheme

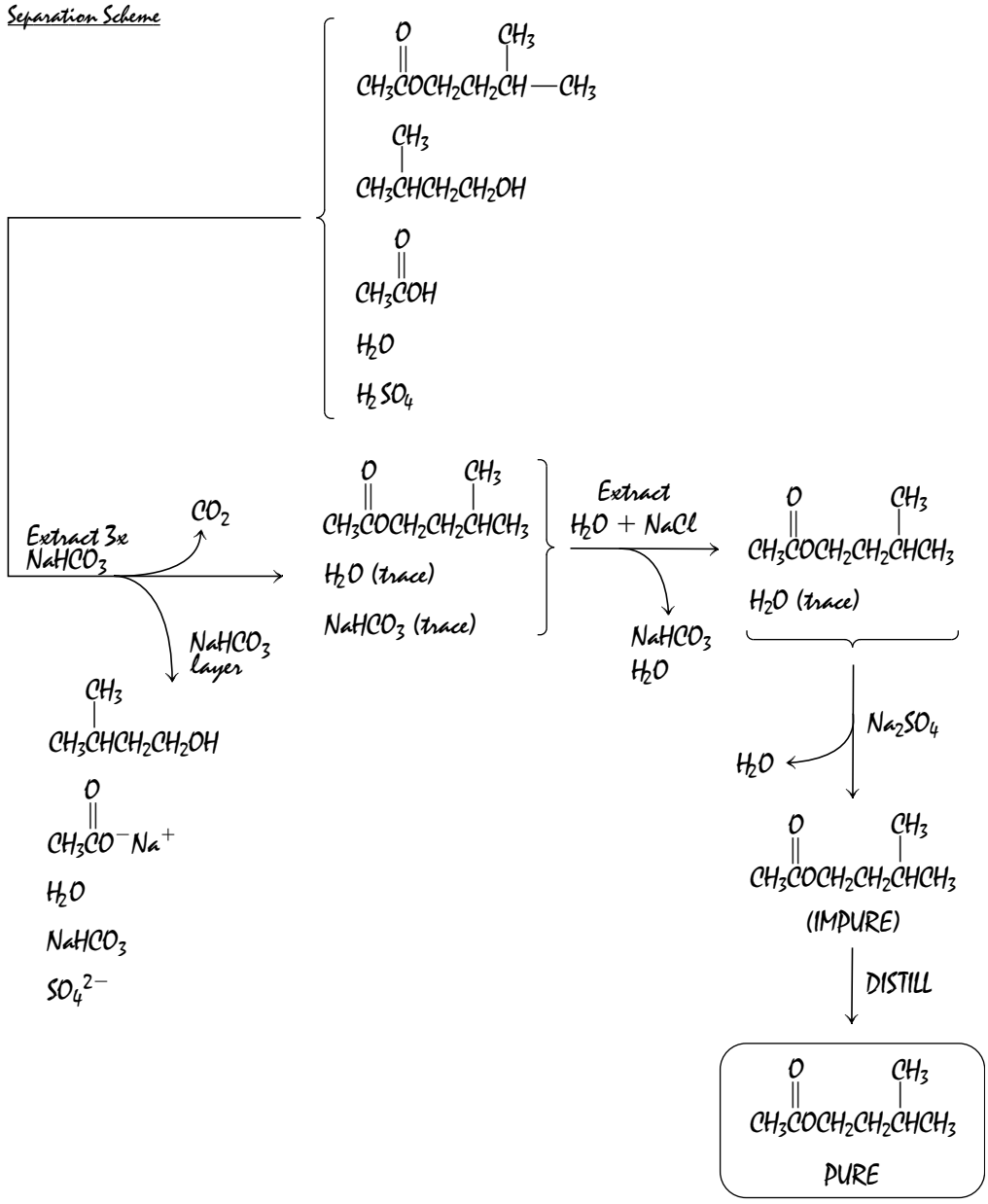


Figure 2.2 A sample notebook, page 1.

Data and Observations

7.5 mL of isopentyl alcohol was added to a pre-weighed 50-mL round-bottomed flask:

Flask + alcohol	139.75 g
Flask	133.63 g
	6.12 g isopentyl alcohol

Glacial acetic acid (10 mL) and 2 mL of concentrated sulfuric acid were also added to the flask, with swirling, along with several boiling stones. A water-cooled condenser was attached to the flask. The reaction was allowed to boil, using a heating mantle, for about one hour. The color of the reaction mixture was brownish-yellow.

After the reaction mixture had cooled to room temperature, the boiling stones were removed, and the reaction mixture was poured into a separatory funnel. About 30 mL of cold water was added to the separatory funnel. The reaction flask was rinsed with 5 mL of cold water, and the water was also added to the separatory funnel. The separatory funnel was shaken, and the lower aqueous layer was removed and discarded. The organic layer was extracted twice with two 10–15-mL portions of 5% aqueous sodium bicarbonate. During the first extraction, much CO_2 was given off, but the amount of gas evolved was markedly diminished during the second extraction. The organic layer was a light yellow in color. After the second extraction, the aqueous layer turned red litmus blue. The bicarbonate layers were discarded, and the organic layer was extracted with a 10–15-mL portion of water. A 2–3 mL portion of saturated sodium chloride solution was added during this extraction. When the aqueous layer had been removed, the upper, organic phase was transferred to a 15-mL Erlenmeyer flask. 2 g of anhydrous magnesium sulfate was added. The flask was stoppered, swirled gently, and allowed to stand for 15 mins.

The product was transferred to a 25-mL round-bottomed flask, and it was distilled by simple distillation. The distillation continued until no liquid could be observed dripping into the collection flask. After the distillation, the ester was transferred to a pre-weighed sample vial.

Sample vial + product	9.92 g
Sample vial	6.11 g
	3.81 g isopentyl acetate

The product was colorless and clear. The observed boiling point obtained during the distillation, was 140°C. An IR spectrum was obtained of the product.

Calculations

Determine limiting reagent:

$$\text{isopentyl alcohol } 6.12\text{ g}\left(\frac{1\text{ mol isopentyl alcohol}}{88.2\text{ g}}\right) = 6.94 \times 10^{-2}\text{mol}$$

$$\text{acetic acid: } (10\text{mL})\left(\frac{1.06\text{ g}}{\text{mL}}\right)\left(\frac{1\text{ mol acetic acid}}{60.1\text{ g}}\right) = 1.76 \times 10^{-1}\text{mol}$$

Since they react in a 1:1 ratio, isopentyl alcohol is the limiting reagent. Theoretical yield:

$$(6.94\ 3\ 10^{-2}\ \cancel{\text{mol isopentyl alcohol}})\left(\frac{\cancel{1\text{ mol isopentyl acetate}}}{\cancel{1\text{ mol isopentyl alcohol}}}\right)\left(\frac{\cancel{130.2\text{ g isopentyl acetate}}}{\cancel{1\text{ mol isopentyl acetate}}}\right)$$

$$= 9.03\text{ g isopentyl acetate}$$

$$\text{Percentage yield} = \frac{3.81\text{ g}}{9.03\text{ g}} \times 100 = 42.2\%$$

Figure 2.3 A sample notebook, page 2.

Calculation of the theoretical yield and percentage yield can be illustrated using hypothetical data for the isopentyl acetate preparation:

$$\text{Theoretical yield} = (6.94 \times 10^{-2}\ \cancel{\text{mol isopentyl alcohol}})\left(\frac{1\ \cancel{\text{mol isopentyl acetate}}}{1\ \cancel{\text{mol isopentyl alcohol}}}\right)$$

$$\times \left(\frac{130.2\ \text{g isopentyl acetate}}{\cancel{1\ \text{mol isopentyl acetate}}}\right) = 9.03\,\text{g isopentyl acetate}$$

$$\text{Actual yield} = 3.81\,\text{g isopentyl acetate}$$

$$\text{Percentage yield} = \frac{3.81\,\text{g}}{9.03\,\text{g}} \times 100 = 42.2\%$$

For experiments that have the principal objective of isolating a substance such as a natural product rather than preparing and purifying some reaction product, the **weight percentage recovery** and not the percentage yield is calculated. This value is determined by

$$\text{Weight percentage recovery} = \frac{\text{Weight of substance isolated}}{\text{Weight of original material}} \times 100$$

Thus, for instance, if 0.014 g of caffeine was obtained from 2.3 g of tea, the weight percentage recovery of caffeine would be

$$\text{Weight percentage recovery} = \frac{0.014\ \text{g caffeine}}{2.3\ \text{g tea}} \times 100 = 0.61\%$$

2.3 Laboratory Reports

Various formats for reporting the results of the laboratory experiments may be used. You may write the report directly in your notebook in a format similar to the sample notebook pages included in this section. Alternatively, your instructor may require a more formal report that is not written in your notebook. When you do original research, these reports should include a detailed description of all the experimental steps undertaken. Frequently, the style used in scientific periodicals such as *Journal of the American Chemical Society* is applied to writing laboratory reports. Your instructor is likely to have his or her own requirements for laboratory reports and should describe the requirements to you.

2.4 Submission of Samples

In all preparative experiments and in some isolation experiments, you will be required to submit to your instructor the sample of the substance you prepared or isolated. How this sample is labeled is very important. Again, learning a correct method of labeling bottles and vials can save time in the laboratory, because fewer mistakes will be made. More importantly, learning to label properly can decrease the danger inherent in having samples of material that cannot be identified correctly at a later date.

Solid materials should be stored and submitted in containers that permit the substance to be removed easily. For this reason, narrow-mouthed bottles or vials are not used for solid substances. Liquids should be stored in containers that will not let them escape through leakage. Be careful not to store volatile liquids in containers that have plastic caps, unless the cap is lined with an inert material such as Teflon. Otherwise, the vapors from the liquid are likely to contact the plastic and dissolve some of it, thus contaminating the substance being stored.

On the label, print the name of the substance, its melting or boiling point, the actual and percentage yields, and your name. An illustration of a properly prepared label follows:

Isopentyl Acetate
BP 140°C
Yield 3.81 g (42.2%)
Joe Schmedlock

3 TECHNIQUE 3

Laboratory Glassware: Care and Cleaning

Because your glassware is expensive and you are responsible for it, you will want to give it proper care and respect. If you read this section carefully and follow the procedures presented here, you may be able to avoid some unnecessary expense. You may also save time, because cleaning problems and replacing broken glassware are time consuming.

If you are unfamiliar with the equipment found in an organic chemistry laboratory or are uncertain about how such equipment should be treated, this section provides some useful information, such as how to clean and care for glassware when using corrosive or caustic reagents. At the end of this section are illustrations that show and name most of the equipment you are likely to find in your drawer or locker.

3.1 Cleaning Glassware

Glassware can be cleaned easily if you clean it immediately after use. It is good practice to do your "dishwashing" right away. With time, organic tarry materials left in a container begin to attack the surface of the glass. The longer you wait to clean glassware, the more extensively this interaction will have progressed. If you wait, cleaning is more difficult, because water will no longer wet the surface of the glass as effectively. If you cannot wash your glassware immediately after use, soak the dirty pieces of glassware in soapy water. A half-gallon plastic container is convenient for soaking and washing glassware. Using a plastic container also helps prevent the loss of small pieces of equipment.

Various soaps and detergents are available for washing glassware. They should be tried first when washing dirty glassware. Organic solvents can also be used, because the residue remaining in dirty glassware is likely to be soluble. After the solvent has been used, the glass item probably will have to be washed with soap and water to remove the residual solvent. When you use solvents to clean glassware, use caution, because the solvents are hazardous (see Technique 1). Use fairly small amounts of a solvent for cleaning purposes. Usually less than 5 mL (or 1–2 mL for microscale glassware) will be sufficient. Acetone is commonly used, but it is expensive. Your **wash acetone** can be used effectively several times before it is

"spent." Once your acetone is spent, dispose of it as your instructor directs. If acetone does not work, other organic solvents such as methylene chloride or toluene can be used.

CAUTION

Acetone is very flammable. Do not use it around flames.

For troublesome stains and residues that adhere to the glass despite your best efforts, use a mixture of sulfuric acid and nitric acid. Cautiously add about 20 drops of concentrated sulfuric acid and 5 drops of concentrated nitric acid to the flask or vial.

CAUTION

You must wear safety glasses when you are using a cleaning solution made from sulfuric acid and nitric acid. Do not allow the solution to come into contact with your skin or clothing. It will cause severe burns on your skin and create holes in your clothing. The acids may also react with the residue in the container.

Swirl the acid mixture in the container for a few minutes. If necessary, place the glassware in a warm water bath and heat it cautiously to accelerate the cleaning process. Continue heating the glassware until any sign of a reaction ceases. When the cleaning procedure is completed, decant the mixture into an appropriate waste container.

CAUTION

Do not pour the acid solution into a waste container that is intended for organic wastes.

Rinse the piece of glassware thoroughly with water and then wash it with soap and water. For most common organic chemistry applications, any stains that survive this treatment are not likely to cause difficulty in subsequent laboratory procedures.

If the glassware is contaminated with stopcock grease, rinse the glassware with a small amount (1–2 mL) of methylene chloride. Discard the rinse solution into an appropriate waste container. Once the grease is removed, wash the glassware with soap or detergent and water.

3.2 Drying Glassware

The easiest way to dry glassware is to let it stand overnight. Store vials, flasks, and beakers upside down on a piece of paper towel to permit the water to drain from them. Drying ovens can be used to dry glassware if they are available and if they are not being used for other purposes. Rapid drying can be achieved by rinsing the glassware with acetone and air drying it or placing it in an oven. First, thoroughly drain the glassware of water. Then rinse it with one or two *small* portions (1–2 mL) of acetone. Do not use any more acetone than is suggested here. Return the used acetone to an acetone waste container for recycling. After you rinse the glassware with acetone, dry it by placing it in a drying oven for a few minutes or allow it to air dry at room temperature. The acetone can also be removed by aspirator suction. In some laboratories, it may be possible to dry the glassware by blowing a *gentle* stream of dry air into the container. (Your laboratory instructor will indicate if you should do this.) Before drying the glassware with air, make sure that the air line is not filled with oil. Otherwise, the oil will be blown into the container, and you will

have to clean it again. It is not necessary to blast the acetone out of the glassware with a wide-open stream of air; a gentle stream of air is just as effective and will not startle other people in the room.

Do not dry your glassware with a paper towel unless the towel is lint-free. Most paper will leave lint on the glass that can interfere with subsequent procedures. Sometimes it is not necessary to dry a piece of equipment thoroughly. For example, if you are going to place water or an aqueous solution in a container, it does not need to be completely dry.

3.3 Ground-Glass Joints

It is likely that the glassware in your organic kit has **standard-taper ground-glass joints**. For example, the Claisen head in Figure 3.1 consists of an inner (male) ground-glass joint at the bottom and two outer (female) joints at the top. Each end is ground to a precise size, which is designated by the symbol ⧲ followed by two numbers. A common joint size in many macroscale organic glassware kits is ⧲ 19/22. The first number indicates the diameter (in millimeters) of the joint at its widest point, and the second number refers to its length (see Figure 3.1). One advantage of standard-taper joints is that the pieces fit together snugly and form a good seal. In addition, standard-taper joints allow all glassware components with the same joint size to be connected, thus permitting the assembly of a wide variety of apparatuses. One disadvantage of glassware with ground-glass joints, however, is that it is expensive.

3.4 Connecting Ground-Glass Joints

It is a simple matter to connect pieces of macroscale glassware using standard-taper ground-glass joints. Figure 3.2B illustrates the connection of a condenser to a round-bottom flask. At times, however, it may be difficult to secure the connection so that it does not come apart unexpectedly. Figure 3.2A shows a plastic clip that serves to secure the connection. Methods to secure ground-glass connections with macroscale apparatus, including the use of plastic clips, are covered in Technique 7.

It is important to make sure no solid or liquid is on the joint surfaces. Either of these will decrease the efficiency of the seal, and the joints may leak. With microscale glassware, the presence of solid particles could cause the ground-glass joints to break when the plastic cap is tightened. Also, if the apparatus is to be heated, material caught between the joint surfaces will increase the tendency for the joints to stick. If the joint surfaces are coated with liquid or adhering solid, you should wipe the surfaces with a cloth or a lint-free paper towel before assembling.

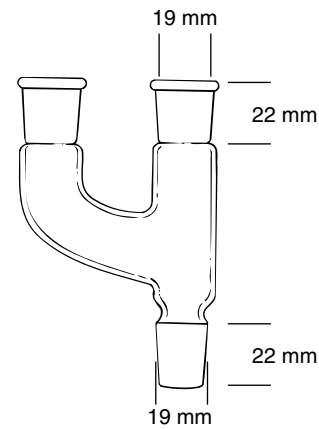


Figure 3.1 Illustration of inner and outer joints, showing dimensions. A Claisen head with ⧲ 19/22 joints.

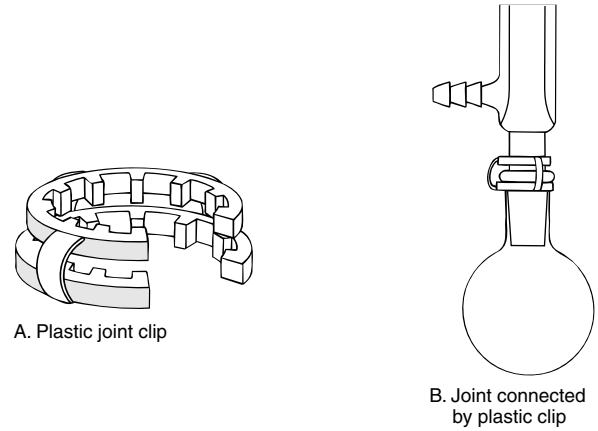


Figure 3.2 Connection of ground-glass joints. The use of a plastic clip (A) is also shown (B).

3.5 Capping Flasks, Conical Vials, and Openings

The sidearms in two-necked or three-necked round-bottom flasks can be capped using the ℱ 19/22 ground-glass stoppers that are part of a normal macroscale organic kit. Figure 3.3 shows such a stopper being used to cap the sidearm of a three-necked flask.

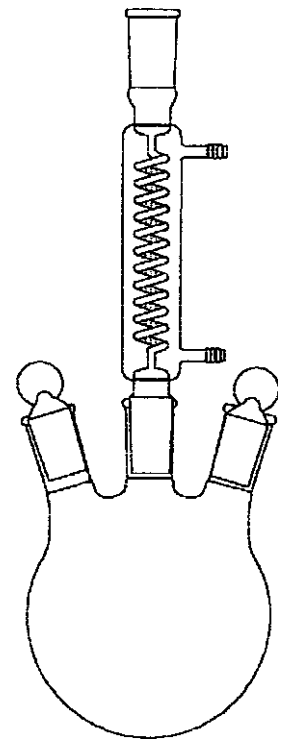


Figure 3.3 Capping a sidearm with a ℱ 19/22 stopper.

3.6 Separating Ground-Glass Joints

When ground-glass joints become "frozen" or stuck together, you are faced with the often vexing problem of separating them. The techniques for separating ground-glass joints, or for removing stoppers that are stuck in the openings of flasks and vials, are the same for both macroscale and microscale glassware.

The most important thing you can do to prevent ground-glass joints from becoming frozen is to disassemble the glassware as soon as possible after a procedure is completed. Even when this precaution is followed, ground-glass joints may become stuck tightly together. The same is true of glass stoppers in bottles or conical vials. Because certain items of microscale glassware may be small and very fragile, it is relatively easy to break a piece of glassware when trying to pull two pieces apart. If the pieces do not separate easily, you must be careful when you try to pull them apart. The best way is to hold the two pieces, with both hands touching, as close as possible to the joint. With a firm grasp, try to loosen the joint with a slight twisting motion (do not twist very hard). If this does not work, try to pull your hands apart without pushing sideways on the glassware.

If it is not possible to pull the pieces apart, the following methods may help. A frozen joint can sometimes be loosened if you tap it *gently* with the wooden handle of a spatula. Then try to pull it apart as already described. If this procedure fails, you may try heating the joint in hot water or a steam bath. If heating fails, the instructor may be able to advise you. As a last resort, you may try heating the joint in a flame. You should not try this unless the apparatus is hopelessly stuck, because heating by flame often causes the joint to expand rapidly and crack or break. If you use a flame, make sure the joint is clean and dry. Heat the outer part of the joint slowly, in the yellow portion of a low flame, until it expands and separates from the inner section. Heat the joint very slowly and carefully, or it may break.

3.7 Etching Glassware

Glassware that has been used for reactions involving strong bases such as sodium hydroxide or sodium alkoxides must be cleaned thoroughly *immediately* after use. If these caustic materials are allowed to remain in contact with the glass, they will etch the glass permanently. The etching makes later cleaning more difficult, because dirt particles may become trapped within the microscopic surface irregularities of the etched glass. Furthermore, the glass is weakened, so the lifetime of the glassware is shortened. If caustic materials are allowed to come into contact with ground-glass joints without being removed promptly, the joints will become fused or "frozen." It is extremely difficult to separate fused joints without breaking them.

3.8 Attaching Rubber Tubing to Equipment

When you attach rubber tubing to the glass apparatus or when you insert glass tubing into rubber stoppers, first lubricate the rubber tubing or the rubber stopper with either water or glycerin. Without such lubrication, it can be difficult to attach rubber tubing to the sidearms of items of glassware such as condensers and filter flasks. Furthermore, glass tubing may break when it is inserted into rubber stoppers. Water is a good lubricant for most purposes. Do not use water as a lubricant when it might contaminate the reaction. Glycerin is a better lubricant than water and should be used when there is considerable friction between the glass and rubber. If glycerin is the lubricant, be careful not to use too much.

3.9 Description of Equipment

Figures 3.4 and 3.5 include examples of glassware and equipment that are commonly used in the organic laboratory. Your glassware and equipment may vary slightly from the pieces shown.

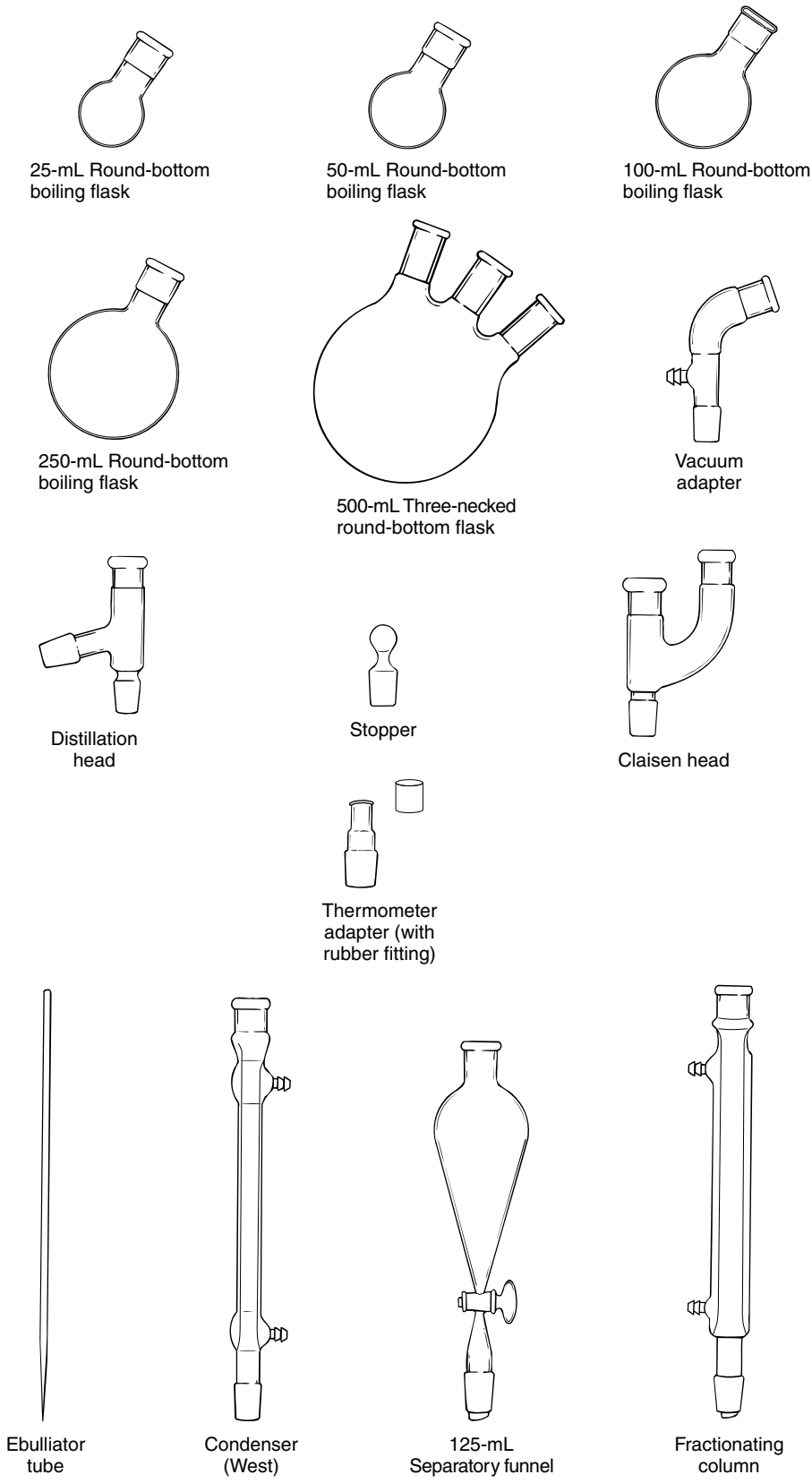


Figure 3.4 Components of the macroscale organic laboratory kit.

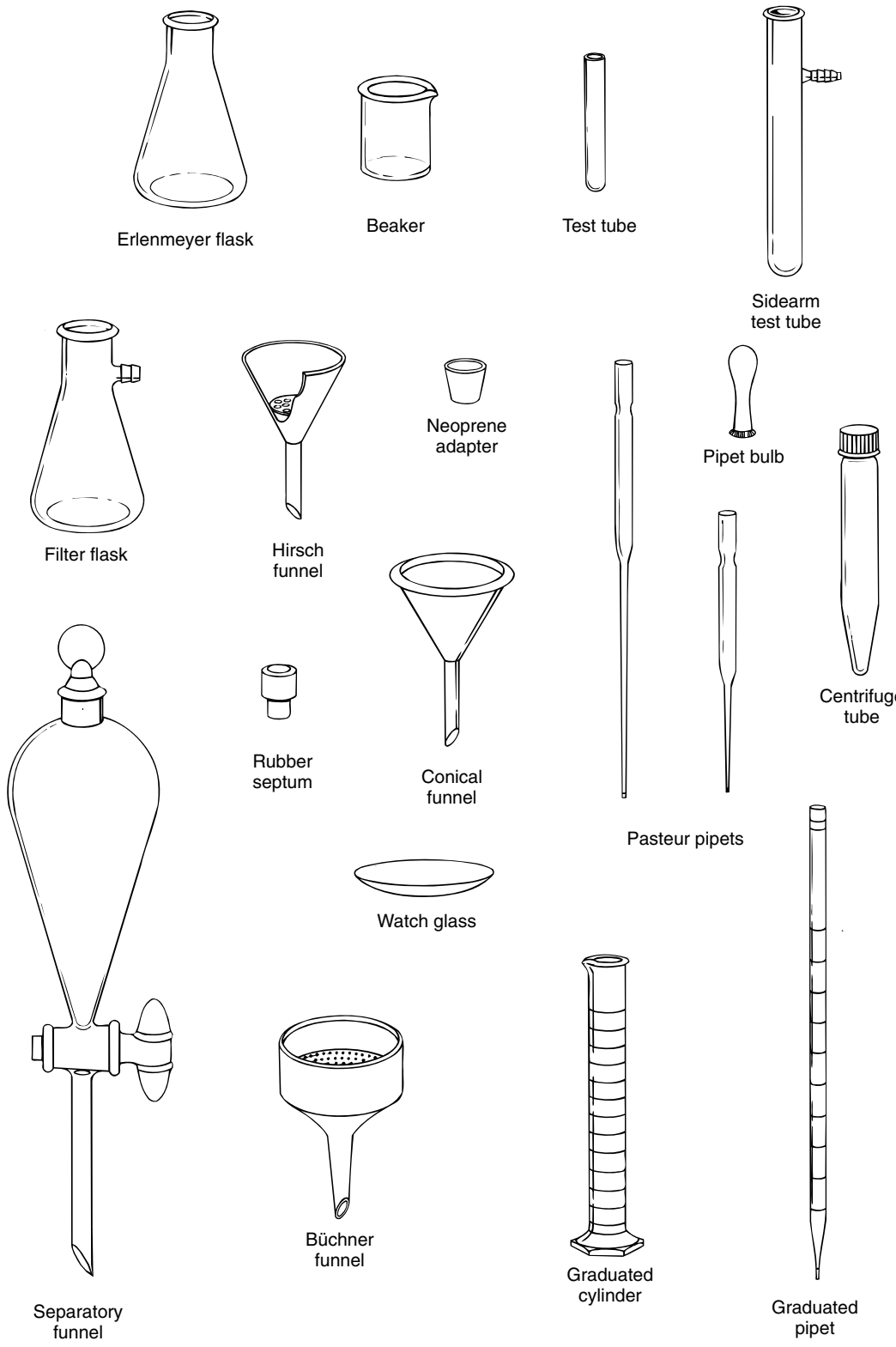
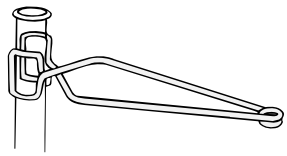
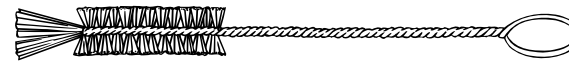


Figure 3.5 Equipment commonly used in the organic chemistry laboratory.

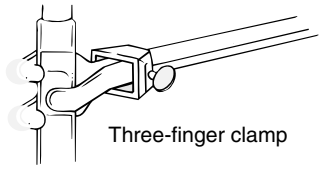


Test tube holder



Test tube brush

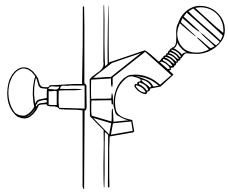
Spin Bar



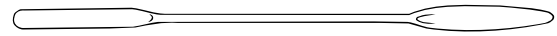
Three-finger clamp

Forceps

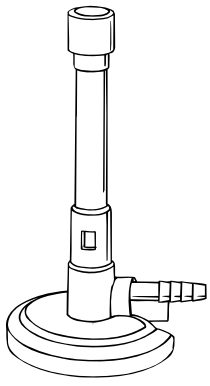
Syringe



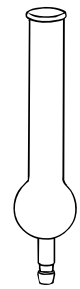
Clamp holder



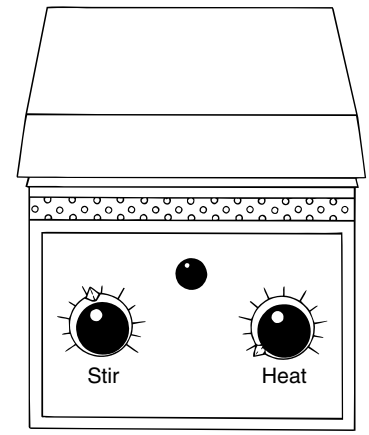
Spatula



Microburner



Drying tube



Hot plate / Stirrer

4 TECHNIQUE 4

How to Find Data for Compounds: Handbooks and Catalogs

The best way to find information quickly on organic compounds is to consult a handbook. We will discuss the use of the *CRC Handbook of Chemistry and Physics, Lange's Handbook of Chemistry, The Merck Index,* and the *Aldrich Handbook of Fine Chemicals.* Complete citations to these handbooks are provided in Technique 29. Depending on the type of handbook consulted, the following information may be found:

- Name and common synonyms
- Formula
- Molecular weight
- Boiling point for a liquid or melting point for a solid
- Beilstein reference
- Solubility data
- Density
- Refractive index
- Flash point
- Chemical Abstracts Service (CAS) Registry Number
- Toxicity data
- Uses and synthesis

4.1 CRC Handbook of Chemistry and Physics

This is the handbook that is most often consulted for data on organic compounds. Although a new edition of the handbook is published each year, the changes that are made are often minor. An older copy of the handbook will often suffice for most purposes. In addition to the extensive tables of properties of organic compounds, the *CRC Handbook* includes sections on nomenclature and ring structures, an index of synonyms, and an index of molecular formulas.

The nomenclature used in this book most closely follows the Chemical Abstracts system of naming organic compounds. This system differs, but only slightly, from standard IUPAC nomenclature. Table 4.1 lists some examples of how some commonly encountered compounds are named in this handbook. The first thing you will notice is that this handbook is not like a dictionary. Instead, you must first identify the *parent* name of the compound of interest. The parent names are found in alphabetical order. Once the parent name is identified and found, then you look for the particular substituent or substituents that may be attached to this parent.

For most compounds, it is easy to find what you are looking for as long as you know the parent name. Alcohols are, as expected, named by IUPAC nomenclature. Notice in Table 4.1 that the branched-chain alcohol, isopentyl alcohol, is listed as 1-butanol, 3-methyl.

TABLE 4.1 Examples of Names of Compounds in the *CRC Handbook*

Name of Organic Compound	Location in *CRC Handbook*
1-Chloropentane	Pentane, 1-chloro-
1,4-Dichlorobenzene	Benzene, 1,4-dichloro-
4-Chlorotoluene	Benzene, 1-chloro-4-methyl-
Ethanoic acid	Acetic acid
tert-Butyl acetate (ethanoate)	Acetic acid, 1,1-dimethylethyl ester
Ethyl propanoate	Propanoic acid, ethyl ester
Isopentyl alcohol	1-Butanol, 3-methyl-
Isopentyl acetate (banana oil)	1-Butanol, 3-methyl-, acetate
Salicylic acid	Benzoic acid, 2-hydroxy-
Acetylsalicylic acid (aspirin)	Benzoic acid, 2-acetyloxy-

Esters, amides, and acid halides are usually named as derivatives of the parent carboxylic acid. Thus, in Table 4.1, you find ethyl propanoate listed under the parent carboxylic acid, propanoic acid. If you have trouble finding a particular ester under the parent carboxylic acid, try looking under the alcohol part of the name. For example, isopentyl acetate is not listed under acetic acid, as expected, but instead is found under the alcohol part of the name (see Table 4.1). Fortunately, this handbook has a Synonym Index that nicely locates isopentyl acetate for you in the main part of the handbook.

Once you locate the compound by its name, you will find the following useful information:

CRC number	This is an identification number for the compound. You can use this number to find the molecular structure located elsewhere in the handbook. This is especially useful when the compound has a complicated structure.
Name and synonym	The Chemical Abstracts name and possible synonyms.
Mol. form.	Molecular formula for the compound.
Mol. wt.	Molecular weight.
CAS RN	Chemical Abstracts Service Registry Number. This number is useful for locating additional information on the compound in the primary chemical literature (see Technique 29, Section 29.11).
mp/°C	Melting point of the compound in degrees Celsius.
bp/°C	Boiling point of the compound in degrees Celsius. A number without a superscript indicates that the recorded boiling point was obtained at 760 mmHg pressure (atmospheric pressure). A number with a superscript indicates that the boiling point was obtained at reduced pressure. For example, for an entry of 234, 122^{16} would indicate that the compound boils at 234 °C at 760 mmHg and 122 °C at 16 mmHg pressure.

Den/g cm^{-3}	Density of a liquid. A superscript indicates the temperature in degrees Celsius at which the density was obtained.
n_D	Refractive index determined at a wavelength of 589 nm, the yellow line in a sodium lamp (D line). A superscript indicates the temperature at which the refractive index was obtained (see Technique 24).
Solubility	Solubility classification: 1 = insoluble; 2 = slightly soluble; 3 = soluble; 4 = very soluble; 5 = miscible; 6 = decomposes. Solvent abbreviations: ace = acetone; bz = benzene; chl = chloroform; EtOH = ethanol; eth = ether; hx = hexane
Beil. ref.	Beilstein reference. An entry of 4-02-00-00157 would indicate that the compound is found in the 4th supplement in Volume 2, with no subvolume, on page 157 (see Technique 29, Section 29.10 for details on the use of Beilstein).
Merck No.	*Merck Index* number in the 11th edition of the handbook. These numbers change each time a new edition of *The Merck Index* is issued.

Examples of sample handbook entries for isopentyl alcohol (1-butanol, 3-methyl) and isopentyl acetate (1-butanol, 3-methyl, acetate) are shown in Table 4.2.

4.2 Lange's Handbook of Chemistry

This handbook tends not to be as available as the *CRC Handbook,* but it has some interesting differences and advantages. *Lange's Handbook* has synonyms listed at the bottom of each page, along with structures of more complicated molecules. The most noticeable difference is in how compounds are named. For many compounds, the system lists names as they would appear in a dictionary. Table 4.3 lists examples of how some commonly encountered compounds are named in this handbook. Most often, you do not need to identify the *parent* name. Unfortunately, *Lange's Handbook* frequently uses common names that are becoming obsolete. For example, propionate is used rather than propanoate. Nevertheless, this handbook often names compounds as a practicing organic chemist would tend to name them. Notice how easy it is to find the entries for isopentyl acetate and acetylsalicylic acid (aspirin) in this handbook.

TABLE 4.2 Properties of Isopentyl Alcohol and Isopentyl Acetate as Listed in the *CRC Handbook*

No.	Name Synonym	Mol. Form. Mol. Wt.	CAS RN mp/°C	Merck No. bp/°C	Beil. Ref. den/g cm^{-3}	Solubility n_D
3627	1-Butanol, 3-methyl	$C_5H_{12}O$	123-51-3	5081	4-01-00-01677	ace 4; eth 4; EtOH 4
	Isopentyl alcohol	88.15	−117.2	131.1	0.8104^{20}	1.4053^{20}
3631	1-Butanol, 3-methyl, acetate	$C_7H_{14}O_2$	123-92-2	4993	4-02-00-00157	H_2O 2; EtOH 5; eth 5; ace 3
	Isopentyl acetate	130.19	−78.5	142.5	0.876^{15}	1.4000^{20}

TABLE 4.3 Examples of Names of Compounds in *Lange's Handbook*

Name of Organic Compound	Location in *Lange's Handbook*
1-Chloropentane	1-Chloropentane
1,4-Dichlorobenzene	1,4-Dichlorobenzene
4-Chlorotoluene	4-Chlorotoluene
Ethanoic acid	Acetic acid
tert-Butyl acetate (ethanoate)	*tert*-Butyl acetate
Ethyl propanoate	Ethyl propionate
Isopentyl alcohol	3-Methyl-1-butanol
Isopentyl acetate (banana oil)	Isopentyl acetate
Salicylic acid	2-Hydroxybenzoic acid
Acetylsalicylic acid (aspirin)	Acetylsalicylic acid

Once you locate the compound by its name, you will find the following useful information:

Lange's number	This is an identification number for the compound.
Name	See examples in Table 4.3.
Formula	Structures are drawn out. If they are complicated, then the structures are shown at the bottom of the page.
Formula weight	Molecular weight of the compound.
Beilstein reference	An entry of 2, 132 would indicate that the compound is found in Volume 2 of the main work on page 132. An entry of 3^2, 188 would indicate that the compound is found in Volume 3 of the second supplement on page 188 (see Technique 29, Section 29.10 for details on the use of *Beilstein*).
Density	Density is usually expressed in units of g/mL or g/cm^3. A superscript indicates the temperature at which the density was measured. If the density is also subscripted, usually 4°, it indicates that the density was measured at a certain temperature relative to water at its maximum density, 4°C. Most of the time you can simply ignore the subscripts and superscripts.
Refractive index	A superscript indicates the temperature at which the refractive index was determined (see Technique 24).
Melting point	Melting point of the compound in degrees Celsius. When a "d" or "dec" appears with the melting point, it indicates that the compound decomposes at the melting point. When decomposition occurs, you will often observe a change in color of the solid.
Boiling point	Boiling point of the compound in degrees Celsius. A number without a superscript indicates that the recorded boiling point was obtained at 760 mmHg pressure (atmospheric pressure). A number with a superscript indicates that the boiling point was

obtained at reduced pressure. For example, an entry of $102^{11\ mm}$ would indicate that the compound boils at 102 °C at 11 mmHg pressure.

Flash point — This number is the temperature in degrees Celsius at which the compound will ignite when heated in air and a spark is introduced into the vapor. There are a number of different methods that are used to measure this value, so this number varies considerably. It gives a crude indication of flammability. You may need this information when heating a substance with a hot plate. Hot plates can be a serious source of trouble because of the sparking action that can occur with switches and thermostats used in hot plates.

Solubility in 100 parts solvent — Parts by weight of a compound that can be dissolved in 100 parts by weight of solvent at room temperature. In some cases, the values given are expressed as the weight in grams that can be dissolved in 100 mL of solvent. This handbook is not consistent in describing solubility. Sometimes gram amounts are provided, but in other cases the description will be more vague, using terms such as *soluble, insoluble,* or *slightly soluble.*

Solvent abbreviations	Solubility characteristics
acet = acetone	i = insoluble
bz = benzene	s = soluble
chl = chloroform	sls = slightly soluble
aq = water	vs = very soluble
alc = ethanol	misc = miscible
eth = ether	
HOAc = acetic acid	

Examples of sample handbook entries for isopentyl alcohol (3-methyl-1-butanol) and isopentyl acetate are shown in Table 4.4.

4.3 The Merck index

The Merck Index is a very useful book because it has additional information not found in the other two handbooks. This handbook, however, tends to emphasize medicinally related compounds, such as drugs and biological compounds, although it also lists many other common organic compounds. It is not revised each year; new editions are published in five- or six-year cycles. It does not contain all of the compounds listed in *Lange's Handbook* or the *CRC Handbook.* However, for the compounds listed, it provides a wealth of useful information. The handbook will provide you with some or all of the following data for each entry.

Merck number, which changes each time a new edition is issued

Name, including synonyms and stereochemical designation

Molecular formula and structure

Molecular weight

Percentages of each of the elements in the compound

Uses

Source and synthesis, including references to the primary literature

Optical rotation for chiral molecules

Density, boiling point, and melting point

Solubility characteristics, including crystalline form

Pharmacology information

Toxicity data

One of the problems with looking up a compound in this handbook is trying to decide the name under which the compound will be listed. For example, isopentyl alcohol can also be named as 3-methyl-1-butanol or isoamyl alcohol. In the 12th edition of the handbook, it is listed under the name isopentyl alcohol (#5212) on page 886. Finding isopentyl acetate is an even more challenging task. It is located in the handbook under the name isoamyl acetate (#5125) on page 876. Often, it is easier to look up the name in the name index or to find it in the formula index.

The handbook has some useful appendices that include the CAS registry numbers, a biological activity index, a formula index, and a name index that also includes synonyms. When looking up a compound in one of the indexes, you need to remember that the numbers provided are compound numbers, rather than page numbers. There is also a very useful section on organic name reactions that includes references to the primary literature.

4.4 Aldrich Handbook of Fine Chemicals

The *Aldrich Handbook* is actually a catalog of chemicals sold by the Aldrich Chemical Company. The company includes in its catalog a large body of useful data on each compound that it sells. Because the catalog is reissued each year at no cost to the user, you should be able to find an old copy when the new one is issued. As you are mainly interested in the data on a particular compound and not the price, an old volume is perfectly fine. Isopentyl alcohol is listed as 3-methyl-1-butanol, and isopentyl acetate is listed as isoamyl acetate in the *Aldrich Handbook.* The following includes some of the properties and information listed for individual compounds.

Aldrich catalog number

Name: Aldrich uses a mixture of common and IUPAC names. It takes a bit of time to master the names. Fortunately, the catalog does a good job of cross-referencing compounds and has a very good molecular formula index.

CAS Registry Number

Structure

Synonym

Formula weight

Boiling point/melting point

Index of refraction

Density

TABLE 4.4 Properties of 3-Methyl-1-butanol and Isopentyl Acetate as Listed in *Lange's Handbook*

No.	Name	Formula	Formula Weight	Beilstein Reference	Density	Refractive Index	Melting Point	Boiling Point	Flash Point	Solubility in 100 Parts Solvent
m155	3-methyl-1-butanol	$(CH_3)_2CHCH_2CH_2OH$	88.15	1, 392	0.8129^{15}_{4}	1.4085^{15}	−117.2	132.0	45	2 aq; misc alc, bz, chl, eth, HOAc
i80	Isopentyl acetate	$CH_3COOCH_2CH_2CH(CH_3)_2$	130.19	2, 132	0.876^{15}_{4}	1.4007^{20}	−78.5	142.0	80	0.25 aq; misc alc, eth

Beilstein reference

Merck reference

Infrared spectrum reference to the Aldrich Library of FT-IR spectra

NMR spectrum reference to the Aldrich Library of ^{13}C and ^{1}H FT-NMR spectra

Literature references to the primary literature on the uses of the compound

Toxicity

Safety data and precautions

Flash point

Prices of chemicals

4.5 Strategy for Finding Information: Summary

Most students and professors find *The Merck Index* and *Lange's Handbook* easier and more "intuitive" to use than the *CRC Handbook.* You can go directly to a compound without rearranging the name according to the parent or base name followed by its substituents. Another great source of information is the *Aldrich Handbook*, which contains those compounds that are easily available from a commercial source. Many compounds are found in the *Aldrich Handbook* that you may never find in any of the other handbooks. The Sigma–Aldrich Web site (*http://www.sigmaaldrich.com/*) allows you to search by name, synonym, and catalog number.

PROBLEMS

1. Using *The Merck Index,* find and draw structures for the following compounds:
   - **a.** atropine
   - **b.** quinine
   - **c.** saccharin
   - **d.** benzo[*a*]pyrene (benzpyrene)
   - **e.** itaconic acid
   - **f.** adrenosterone
   - **g.** chrysanthemic acid (chrysanthemumic acid)
   - **h.** cholesterol
   - **i.** vitamin C (ascorbic acid)
2. Find the melting points for the following compounds in the *CRC Handbook, Lange's Handbook,* or the *Aldrich Handbook:*
   - **a.** biphenyl
   - **b.** 4-bromobenzoic acid
   - **c.** 3-nitrophenol

3. Find the boiling point for each compound in the references listed in problem 2:
   a. octanoic acid at reduced pressure
   b. 4-chloroacetophenone at atmosphere and reduced pressure
   c. 2-methyl-2-heptanol
4. Find the index of refraction n_D and density for the liquids listed in problem 3.
5. Using the *Aldrich Handbook,* report the specific rotations for the enantiomers of camphor.
6. Read the section on carbon tetrachloride in *The Merck Index* and list some of the health hazards for this compound.

5 TECHNIQUE 5

Measurement of Volume and Weight

Performing successful organic chemistry experiments requires the ability to measure solids and liquids accurately. This ability involves both selecting the proper measuring device and using this device correctly.

Liquids to be used for an experiment will usually be found in small containers in a hood. For *macroscale* experiments, a graduated cylinder, a dispensing pump, or a graduated pipet will be used for measuring the volume of a liquid. For **limiting reactants**, it is best to preweigh (**tare**) the container before adding the liquid to the container and then reweigh after adding the liquid. This gives an exact weight and avoids the experimental error involved in using densities to calculate weights when working with smaller amounts of a liquid. For **nonlimiting** liquid reactants, you may calculate the weight of the liquid from the volume you have delivered and the density of the liquid:

$$\text{Weight (g)} = \text{density (g/mL)} \times \text{volume (mL)}$$

For *microscale* experiments, an automatic pipet, dispensing pump, or calibrated Pasteur pipet will be used for measuring the volume of a liquid. It is even more critical that limiting reactants be weighed as described in the preceding paragraph. Measurement of a small volume of a liquid is subject to large experimental error when converted to a weight using a density of the liquid. Weights of nonlimiting liquid reactants, however, can be calculated using the previous expression.

You will usually transfer the required volume of liquid to a round-bottom flask or an Erlenmeyer flask in macroscale experiments, or to a conical vial or round-bottom flask in microscale experiments. When transferring the liquid to a round-bottom flask, place the flask in a beaker and tare both the flask and the beaker. The beaker keeps the round-bottom flask in an upright position and prevents spills from occurring. The same advice should be followed if a conical vial is being used.

When using a graduated cylinder to measure small volumes of a limiting reagent, it is important to preweigh the cylinder and transfer the required amount

of liquid reagent to it using a Pasteur pipet. Reweigh the cylinder to obtain the exact weight of liquid reagent. To *quantitatively* transfer the liquid from the graduated cylinder, pour as much of the liquid as possible into the reaction container. The remaining liquid in the graduated cylinder can be removed by rinsing the cylinder with small amounts of the solvent being used for the reaction. By this procedure, all of the limiting reagent will be transferred from the graduated cylinder to the reaction container.

Using a small amount of solvent to transfer a liquid quantitatively can also be applied in other situations. For example, if your product is dissolved in a solvent and the procedure instructs you to transfer the reaction mixture from a round-bottom flask to a separatory funnel, after pouring most of the liquid into the funnel, a small amount of solvent could be used to transfer the rest of the product quantitatively.

Solids are usually found near the balance. For *macroscale* experiments, it is usually sufficient to weigh solids on a balance that reads at least to the nearest decigram (0.01 g). For *microscale* experiments, solids must be weighed on a balance that reads to the nearest milligram (0.001 g) or tenth of a milligram (0.0001 g). To weigh a solid, place your conical vial or round-bottom flask in a small beaker and take these with you to the balance. Place a smooth piece of paper that has been folded once on the balance pan. The folded paper will enable you to pour the solid into the conical vial or flask without spilling. Use a spatula to aid the transfer of the solid to the paper. Never weigh directly into a conical vial or flask, and never pour, dump, or shake a material from a bottle. While still at the balance, carefully transfer the solid from the paper to your vial or flask. The vial or flask should be in a beaker while you transfer the solid. The beaker traps any material that fails to make it into the container. It also supports the vial or flask so that it does not fall over. It is not necessary to obtain the exact amount specified in the experimental procedure, and trying to be exact requires too much time at the balance. For example, if you obtained 0.140 g of a solid, rather than the 0.136 g specified in a procedure, you could use it, but the actual amount weighed should be recorded in your notebook. Use the actual amount you weighed to calculate the theoretical yield, if this solid is the limiting agent.

Careless dispensing of liquids and solids is a hazard in any laboratory. When reagents are spilled, you may be subjected to an unnecessary health or fire hazard. In addition, you may waste expensive chemicals, destroy balance pans and clothing, and damage the environment. Always clean up any spills immediately.

5.1 Graduated Cylinders

Graduated cylinders are most often used to measure liquids for macroscale experiments (see Figure 5.1). The most common sizes are 10 mL, 25 mL, 50 mL, and 100 mL, but it is possible that not all of these will be available in your laboratory. Volumes from about 2 mL to 100 mL can be measured with reasonably good accuracy provided that the correct cylinder is used. You should use the *smallest* cylinder available that can hold all of the liquid that is being measured. For example, if a procedure calls for 4.5 mL of a reagent, use a 10-mL graduated cylinder. Using a larger cylinder in this case will result in a less accurate measurement. Furthermore, using any cylinder to measure less than 10% of the total capacity of that cylinder will likely result in an inaccurate measurement. Always remember that whenever a graduated cylinder is used to measure the volume of a limiting reagent, you must weigh the liquid to determine the amount used accurately. You should use a graduated pipet, a dispensing pump, or an automatic pipet for accurate transfer of liquids with a volume of less than 2 mL.

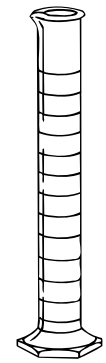


Figure 5.1 Graduated cylinder.

If the storage container is reasonably small (< 1.0 L) and has a narrow neck, you may pour most of the liquid into the graduated cylinder and use a Pasteur pipet to adjust to the final line. If the storage container is large (> 1.0 L) or has a wide mouth, two strategies are possible. First, you may use a pipet to transfer the liquid to the graduated cylinder. Alternatively, you may pour some of the liquid into a beaker first and then pour this liquid into a graduated cylinder. Use a Pasteur pipet to adjust to the final line. Remember that you should not take more than you need. Excess material should never be returned to the storage bottle. Unless you can convince someone else to take it, it must be poured into the appropriate waste container. You should be frugal in your estimation of amounts needed.

NOTE: Never return used reagents to the stock bottle.

5.2 Dispensing Pumps

Dispensing pumps are simple to operate, chemically inert, and quite accurate. Because the plunger assembly is made of Teflon, the dispensing pump may be used with most corrosive liquids and organic solvents. Dispensing pumps come in a variety of sizes, ranging from 1 mL to 300 mL. When used correctly, dispensing pumps can be used to deliver accurate volumes ranging from 0.1 mL to the maximum capacity of the pump. The pump is attached to a bottle containing the liquid being dispensed. The liquid is drawn up from this reservoir into the pump assembly through a piece of inert plastic tubing.

Dispensing pumps are somewhat difficult to adjust to the proper volume. Normally, the instructor or assistant will carefully adjust the unit to deliver the proper amount of liquid. As shown in Figure 5.2, the plunger is pulled up as far as it will travel to draw in the liquid from the glass reservoir. To expel the liquid from the spout into a container, you slowly guide the plunger down. With low-viscosity liquids, the weight of the plunger will expel the liquid. With more viscous liquids, however, you may need to push the plunger gently to deliver the liquid into a container. Remove the last drop of liquid on the end of the spout by touching the tip on the interior wall of the container. When the liquid being transferred is a limiting reagent or when you need to know the weight precisely, you should weigh the liquid to determine the amount accurately.

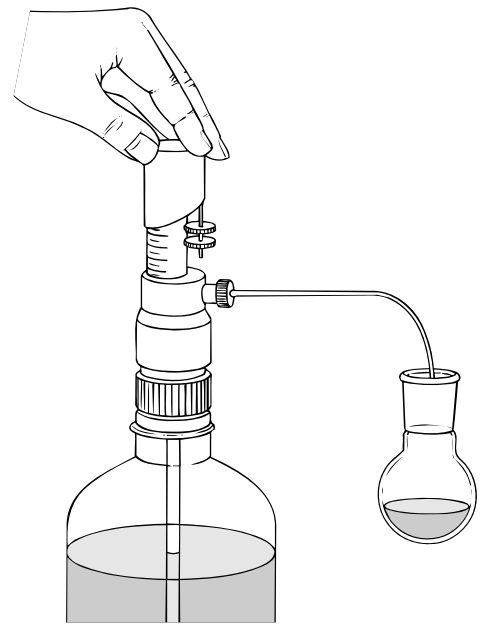


Figure 5.2 Use of a dispensing pump.

As you pull up the plunger, look to see if the liquid is being drawn up into the pump unit. Some volatile liquids may not be drawn up in the expected manner, and you will observe an air bubble. Air bubbles commonly occur when the pump has not been used for a while. The air bubble can be removed from the pump by dispensing, and discarding, several volumes of liquid to "reprime" the dispensing pump. Also check to see if the spout is filled completely with liquid. An accurate volume will not be dispensed unless the spout is filled with liquid before you lift up the plunger.

5.3 Graduated Pipets

A widely used measuring device is the graduated serological pipet. These *glass* pipets are available commercially in a number of sizes. "Disposable" graduated pipets may be used many times and discarded only when the graduations become too faint to be seen. A good assortment of these pipets consists of the following:

1.00-mL pipets calibrated in 0.01-mL divisions (1 in 1/100 mL)

2.00-mL pipets calibrated in 0.01-mL divisions (2 in 1/100 mL)

5.0-mL pipets calibrated in 0.1-mL divisions (5 in 1/10 mL)

Never draw liquids into the pipets using mouth suction. A pipet pump or a pipet bulb, not a rubber dropper bulb, must be used to fill pipets. Two types of pipet pumps and a pipet bulb are shown in Figure 5.3. A pipet fits snugly into the pipet pump, and the pump can be controlled to deliver precise volumes of liquids. Control of the pipet pump is accomplished by rotating a knob on the pump. Suction created when the knob is turned draws the liquid into the pipet. Liquid is expelled from the pipet by turning the knob in the opposite direction. The pump works satisfactorily with organic, as well as aqueous, liquids.

The style of pipet pump shown in Figure 5.3A is available in four sizes. The top of the pipet must be inserted securely into the pump and held there with one hand to obtain an adequate seal. The other hand is used to load and release the liquid.

The pipet pump shown in Figure 5.3B may also be used with graduated pipets. With this style of pipet, the top of the pipet is held securely by a rubber O-ring, and it is easily handled with one hand. You should be certain that the pipet is held securely by the O-ring before using it. Disposable pipets may not fit tightly in the O-ring because they often have smaller diameters than nondisposable pipets.

An alternative, and less expensive, approach is to use a rubber pipet bulb, shown in Figure 5.3C. Use of the pipet bulb is made more convenient by inserting a plastic automatic pipet tip into a rubber pipet bulb.[1] The tapered end of the pipet tip fits snugly into the end of a pipet. Drawing the liquid into the pipet is made easy, and it is also convenient to remove the pipet bulb and place a finger over the pipet opening to control the flow of liquid.

The calibrations printed on graduated pipets are reasonably accurate, but you should practice using the pipets in order to achieve this accuracy. When accurate quantities of liquids are required, the best technique is to weigh the reagent that has been delivered from the pipet.

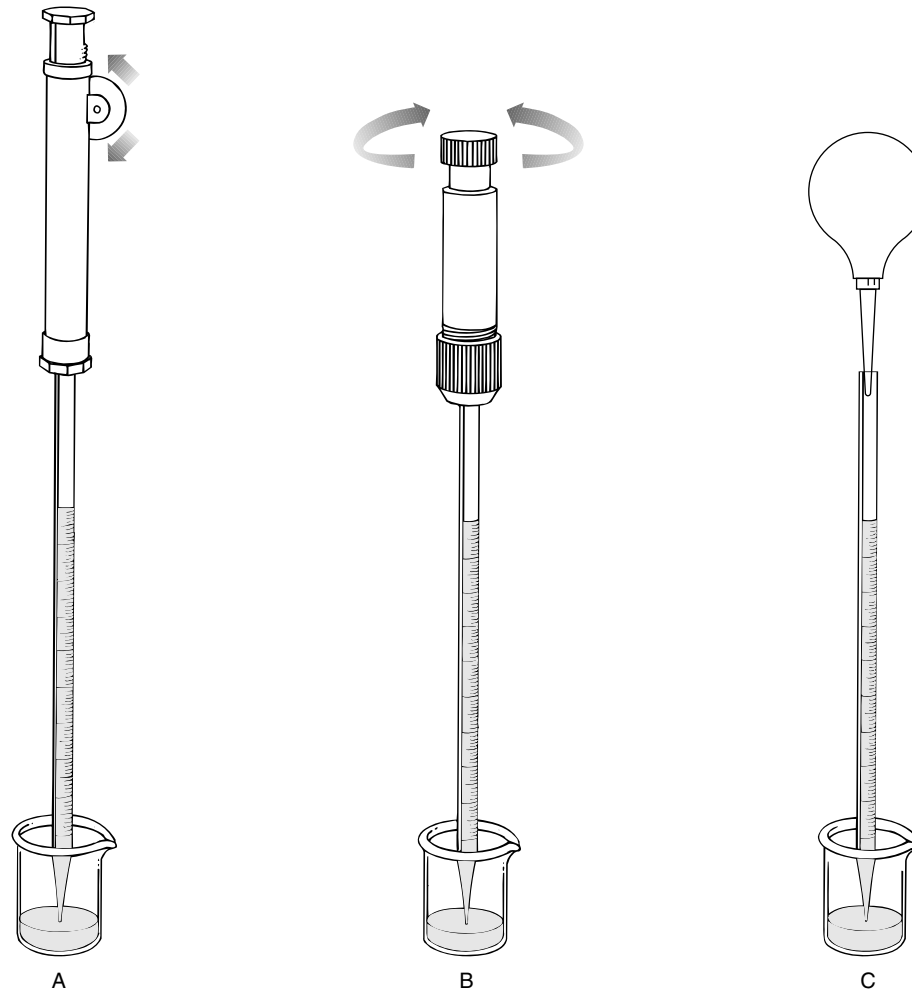


Figure 5.3 Pipet pumps (A, B) and a pipet bulb (C).

[1] This technique was described in G. Deckey, "A Versatile and Inexpensive Pipet Bulb," *Journal of Chemical Education, 57* (July 1980): 526.

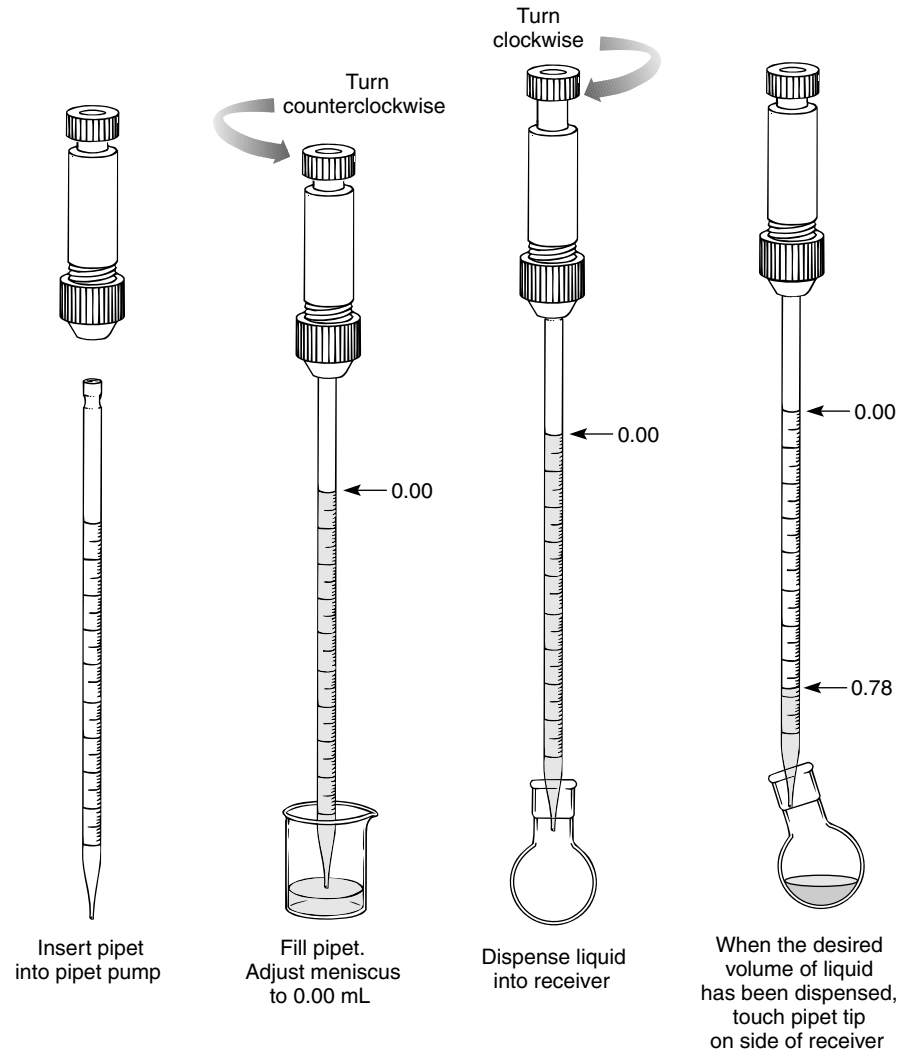


Figure 5.4 Use of a graduated pipet. (The figure shows, as an illustration, the technique required to deliver a volume of 0.78 mL from a 1.00-mL pipet.)

The following description, along with Figure 5.4, illustrates how to use a graduated pipet. Insert the end of the pipet firmly into the pipet pump. Rotate the knob of the pipet pump in the correct direction (counterclockwise or up) to fill the pipet. Fill the pipet to a point just above the uppermost mark and then reverse the direction of rotation of the knob to allow the liquid to drain from the pipet until the meniscus is adjusted to the 0.00-mL mark. Move the pipet to the receiving vessel. Rotate the knob of the pipet pump (clockwise or down) to force the liquid from the pipet. Allow the liquid to drain from the pipet until the meniscus arrives at the mark corresponding to the volume that you wish to dispense. Be sure to touch the tip of the pipet to the inside of the container before withdrawing the pipet. Remove the pipet and drain the remaining liquid into a waste receiver. Avoid transferring the entire contents of the pipet when measuring volumes with a pipet. Remember that to achieve the greatest possible accuracy with this method, you should deliver volumes as a *difference* between two marked calibrations.

Pipets may be obtained in a number of styles, but only three types will be described here (see Figure 5.5). One type of graduated pipet is calibrated "to deliver" (TD) its total capacity when the last drop is blown out. This style of pipet, shown in Figure 5.5A, is probably the most common type of graduated pipet in use in the laboratory; it is designated by two rings at the top. Of course, it is not necessary to transfer the entire volume to a container. To deliver a more accurate volume, you should transfer an amount less than the total capacity of the pipet using the graduations on the pipet as a guide.

Another type of graduated pipet is shown in Figure 5.5B. This pipet is calibrated to deliver its total capacity when the meniscus is located on the last graduation mark near the bottom of the pipet. For example, the pipet shown in the Figure 5.5B delivers 10.0 mL of liquid when it has been drained to the point where the meniscus is located on the 10.0-mL mark. With this type of pipet, you must not drain the entire pipet or blow it out. In contrast, notice that the pipet discussed in Figure 5.5A has its last graduation at 0.90 mL. The last 0.10-mL volume is blown out to give the 1.00-mL volume.

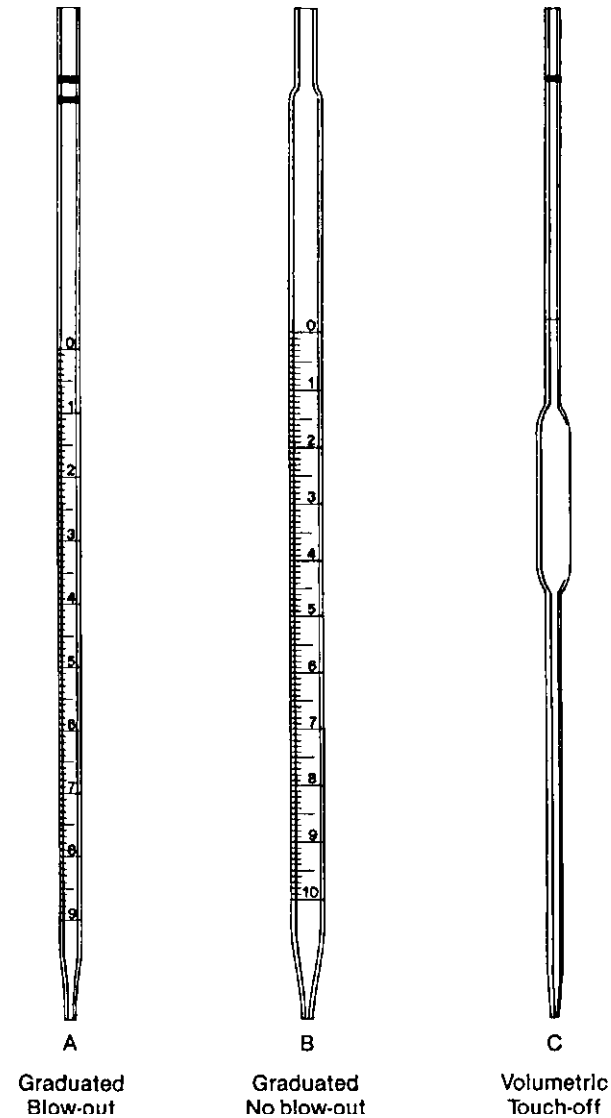


Figure 5.5 Pipets.

A nongraduated volumetric pipet is shown in Figure 5.5C. It is easily identified by the large bulb in the center of the pipet. This pipet is calibrated so that it will retain its last drop after the tip is touched on the side of the container. It must not be blown out. These pipets often have a single colored band at the top that identifies it as a "touch-off" pipet. The color of the band is keyed to its total volume. This type of pipet is commonly used in analytical chemistry.

5.4 Pasteur Pipets

The Pasteur pipet is shown in Figure 5.6A with a 2-mL rubber bulb attached. There are two sizes of Pasteur pipets: a short one ($5\frac{3}{4}$-inch), which is shown in the figure, and a long one (9-inch). It is important that the pipet bulb fit securely. You should not use a medicine dropper bulb because of its small capacity. A Pasteur pipet is an indispensable piece of equipment for the routine transfer of liquids. It is also used for separations (Technique 12). Pasteur pipets may be packed with cotton for use in gravity filtration (Technique 8) or packed with an adsorbent for small-scale column chromatography (Technique 19). Although Pasteur pipets are considered disposable, you should be able to clean them for reuse as long as the tip remains unchipped.

A Pasteur pipet may be supplied by your instructor for dropwise addition of a particular reagent to a reaction mixture. For example, concentrated sulfuric acid is often dispensed in this way. When sulfuric acid is transferred, you should take care to avoid getting the acid into the rubber or latex dropper bulb.

The rubber dropper bulb may be avoided entirely by using one-piece transfer pipets made entirely of polyethylene (see Figure 5.6B). These plastic pipets are available in 1- or 2-mL sizes. They come from the manufacturers with approximate calibration marks stamped on them. These pipets can be used with all aqueous solutions and most organic liquids. They cannot be used with a few organic solvents or with concentrated acids.

Pasteur pipets may be calibrated for use in operations in which the volume does not need to be known precisely. Examples include measurement of solvents needed for extraction and for washing a solid obtained following crystallization. A calibrated Pasteur pipet is shown in Figure 5.6C. It is suggested that you calibrate several $5\frac{3}{4}$-inch pipets using the following procedure. On a balance, weigh 0.5 g (0.5 mL) of water into a small test tube. Select a short Pasteur pipet and attach a rubber bulb. Squeeze the rubber bulb before inserting the tip of the pipet into the water. Try to control how much you depress the bulb so that when the pipet is placed into the water and the bulb is completely released, only the desired amount of liquid is drawn into the pipet. When the water has been drawn up, place a mark with an indelible marking pen at the position of the meniscus. A more durable mark can be made by scoring the pipet with a file. Repeat this procedure with 1.0 g of water, and make a 1-mL mark on the same pipet.

Your instructor may provide you with a calibrated Pasteur pipet and bulb for transferring liquids where an accurate volume is not required. The pipet may be used to transfer a volume of 1.5 mL or less. You may find that the instructor has taped a test tube to the side of the storage bottle. The pipet is stored in the test tube with that particular reagent.

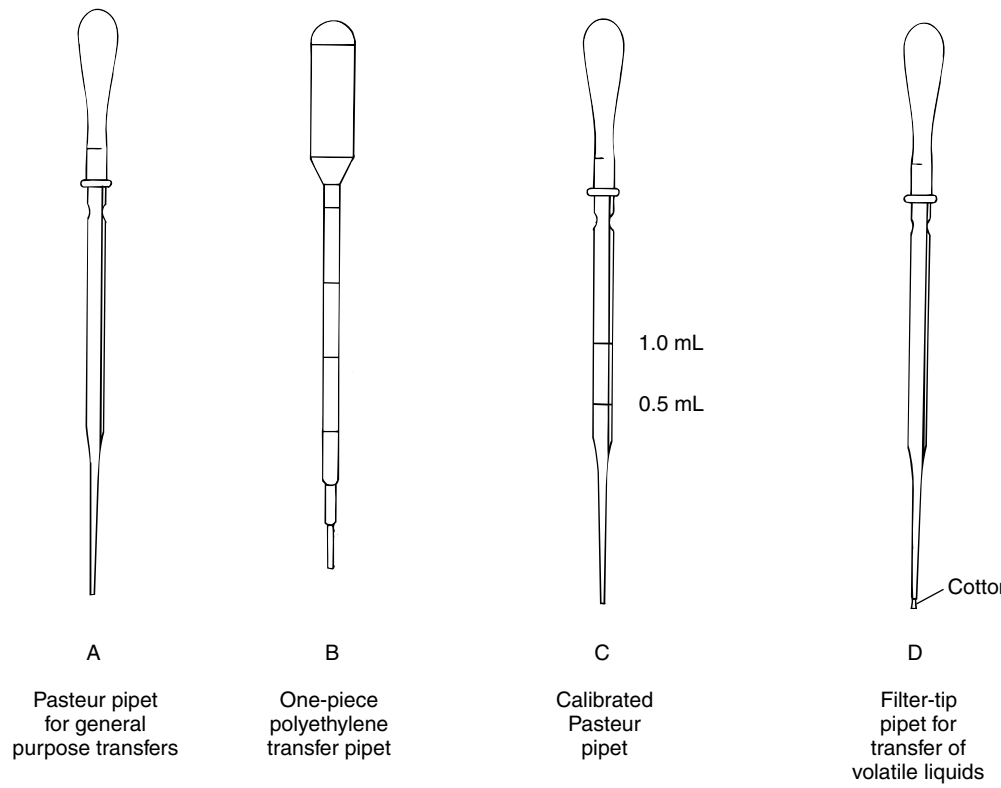


Figure 5.6 Pasteur (A, C, D) and transfer pipets (B).

NOTE: You should not assume that a certain number of drops equals a 1-mL volume. The common rule that 20 drops equal 1 mL, often used for a buret, does not hold true for a Pasteur pipet!

A Pasteur pipet may be packed with cotton to create a filter-tip pipet as shown in Figure 5.6D. This pipet is prepared by the instructions given in Technique 8, Section 8.6. Pipets of this type are very useful in transferring volatile solvents during extractions and in filtering small amounts of solid impurities from solutions. A filter-tip pipet is very useful for removing small particles from a solution of a sample prepared for nuclear magnetic resonance (NMR) analysis.

5.5 Syringes

Syringes may be used to add a pure liquid or a solution to a reaction mixture. They are especially useful when anhydrous conditions must be maintained. The needle is inserted through a septum, and the liquid is added to the reaction mixture. Caution should be used with some disposable syringes, as they often use solvent-soluble rubber gaskets on the plungers. A syringe should be cleaned carefully after each use by drawing acetone or another volatile solvent into it and expelling the solvent with the plunger. Repeat this procedure several times to clean the syringe thoroughly. Remove the plunger and draw air through the barrel with an aspirator to dry the syringe.

Syringes are usually supplied with volume graduations inscribed on the barrel. Large-volume syringes are not accurate enough to be used for measuring liquids in small-scale experiments. A small microliter syringe, such as that used in gas chromatography, delivers a very precise volume.

5.6 Automatic Pipets

Automatic pipets are commonly used in microscale organic laboratories and in biochemistry laboratories. Several types of adjustable automatic pipets are shown in Figure 5.7. The automatic pipet is very accurate with aqueous solutions, but it is not as accurate with organic liquids. These pipets are available in different sizes and can deliver accurate volumes ranging from 0.10 mL to 1.0 mL. They are very expensive and must be shared by the entire laboratory. Automatic pipets should never be used with corrosive liquids, such as sulfuric acid or hydrochloric acid. *Always use the pipet with a plastic tip.*

Automatic pipets may vary in design, according to the manufacturer. The following description, however, should apply to most models. The automatic pipet consists of a handle that contains a spring-loaded plunger and a micrometer dial. The dial controls the travel of the plunger and is the means used to select the amount of liquid that the pipet is intended to dispense. Automatic pipets are designed to deliver liquids within a particular range of volumes. For example, a pipet may be designed to cover the range 10–100 μL (0.010–0.100 mL) or 100–1000 μL (0.100–1.000 mL).

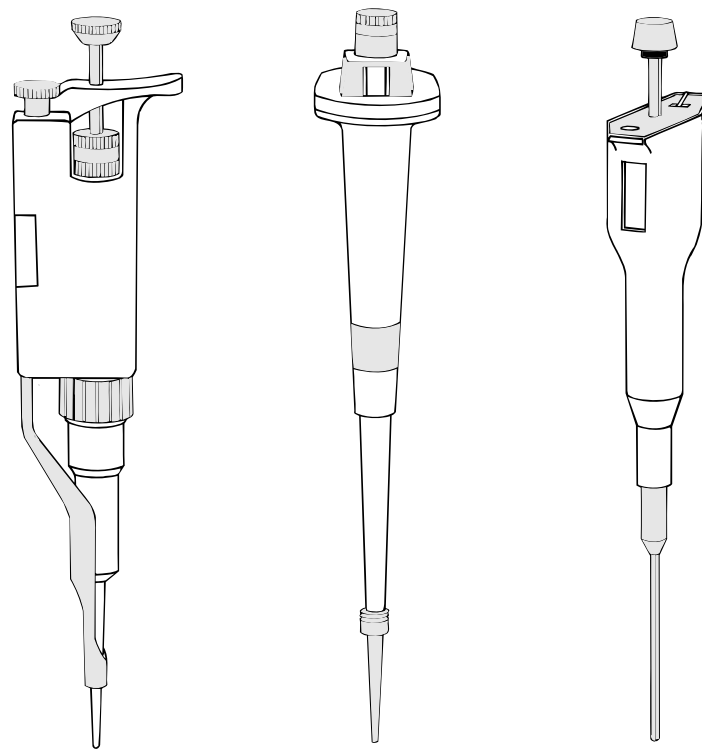


Figure 5.7 The adjustable automatic pipet.

5.7 Measuring Volumes with Conical Vials, Beakers, and Erlenmeyer Flasks

Conical vials, beakers, and Erlenmeyer flasks all have graduations inscribed on them. Beakers and flasks can be used to give only a crude approximation of the volume. They are much less precise than graduated cylinders for measuring volume. In some cases, a conical vial may be used to estimate volumes. For example, the graduations are sufficiently accurate for measuring a solvent needed to wash a solid obtained on a Hirsch funnel after a crystallization. You should use an automatic pipet, dispensing pump, or graduated transfer pipet for accurate measurement of liquids in microscale experiments.

5.8 Balances

Solids and some liquids will need to be weighed on a balance that reads to at least the nearest milligram (0.001 g) for microscale experiments or to at least the nearest decigram (0.01 g) for macroscale experiments. A top-loading balance (see Figure 5.8) works well if the balance pan is covered with a plastic draft shield. The shield has a flap that opens to allow access to the balance pan. An analytical balance (see Figure 5.9) may also be used. This type of balance will weigh to the nearest tenth of a milligram (0.0001 g) when provided with a glass draft shield.

Modern electronic balances have a tare device that automatically subtracts the weight of a container or a piece of paper from the combined weight to give the weight of the sample. With solids, it is easy to place a piece of paper on the balance pan, press the tare device so that the paper appears to have zero weight, and then add your solid until the balance gives the weight you desire. You can then transfer the weighed solid to a container. You should always use a spatula to transfer a solid and never pour material from a bottle. In addition, solids must be weighed on paper and not directly on the balance pan. Remember to clean any spills.

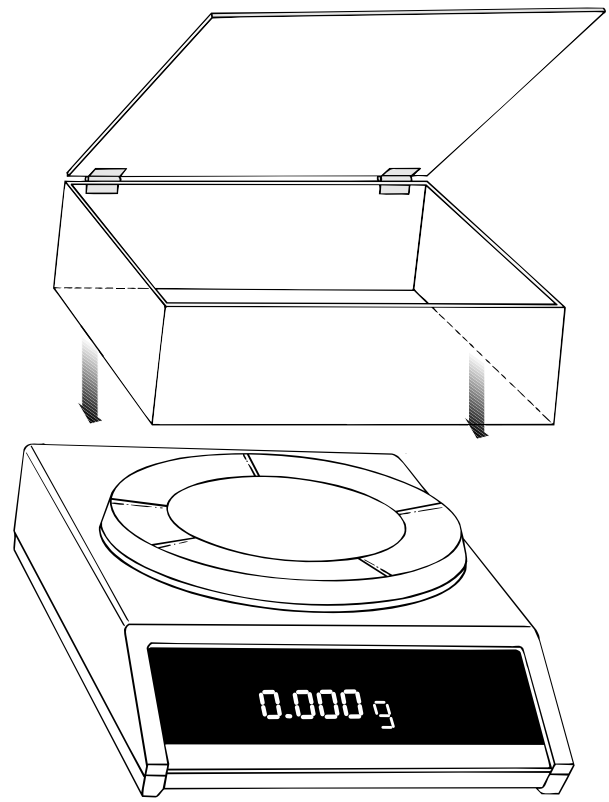


Figure 5.8 A top-loading balance with a plastic draft shield.

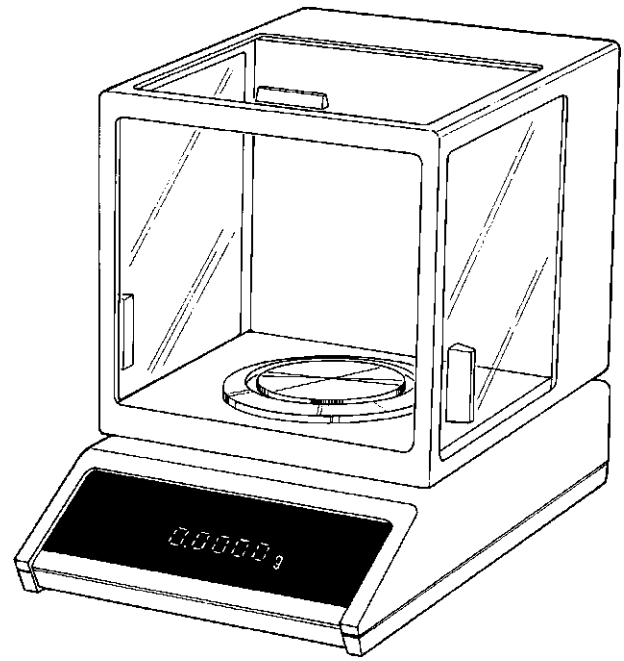


Figure 5.9 An analytical balance with a glass draft shield.

With liquids, you should weigh the flask to determine the tare weight; transfer the liquid with a graduated cylinder, dispensing pump, or graduated pipet into the flask; and then reweigh it. With liquids, it is usually necessary to weigh only the limiting reagent. The other liquids may be transferred using a graduated cylinder, dispensing pump, or graduated pipet. Their weights can be calculated by knowing the volumes and densities of the liquids.

PROBLEMS

1. What measuring device would you use to measure the volume under each of the conditions described below? In some cases, there may be more than one correct answer.
   - **a.** 25 mL of a solvent needed for a crystallization
   - **b.** 2.4 mL of a liquid needed for a reaction
   - **c.** 0.64 mL of a liquid needed for a reaction
   - **d.** 5 mL of a solvent needed for an extraction
2. Assume that the liquid used in problem 1b is a limiting reagent for a reaction. What should you do after measuring the volume?
3. Calculate the weight of a 2.5-mL sample of each of the following liquids:
   - **a.** Diethyl ether (ether)
   - **b.** Methylene chloride (dichloromethane)
   - **c.** Acetone
4. A laboratory procedure calls for 5.46 g of acetic anhydride. Calculate the volume of this reagent needed in the reaction.
5. Criticize the following techniques:
   - **a.** A 100-mL graduated cylinder is used to measure accurately a volume of 2.8 mL.

b. A one-piece polyethylene transfer pipet (see Figure 5.6B) is used to transfer precisely 0.75 mL of a liquid that is being used as the limiting reactant.

c. A calibrated Pasteur pipet (see Figure 5.6C) is used to transfer 25 mL of a solvent.

d. The volume markings on a 100-mL beaker are used to transfer accurately 5 mL of a liquid.

e. An automatic pipet is used to transfer 10 mL of a liquid.

f. A graduated cylinder is used to transfer 0.126 mL of a liquid.

g. For a small-scale reaction, the weight of a liquid limiting reactant is calculated from its density and volume.

6 **TECHNIQUE 6**

Heating and Cooling Methods

Most organic reaction mixtures need to be heated in order to complete the reaction. In general chemistry, you used a Bunsen burner for heating because nonflammable aqueous solutions were used. In an organic chemistry laboratory, however, the student must heat nonaqueous solutions that may contain *highly flammable* solvents. You *should not heat organic mixtures with a Bunsen burner* unless you are directed to do so by your laboratory instructor. Open flames present a potential fire hazard. Whenever possible you should use one of the alternative heating methods, as described in the following sections.

6.1 Heating Mantles

A useful source of heat for most macroscale experiments is the heating mantle, illustrated in Figure 6.1. The heating mantle shown here consists of a ceramic heating shell with electric heating coils embedded within the shell. The temperature of a heating mantle is regulated with the heat controller. Although it is difficult to monitor the actual temperature of the heating mantle, the controller is calibrated so that it is fairly easy to duplicate approximate heating levels after one has gained some experience with this apparatus. Reactions or distillations requiring relatively high temperatures can be easily performed with a heating mantle. For temperatures in the range of 50–80°C, you should use a water bath (see Section 6.3) or a steam bath (see Section 6.8).

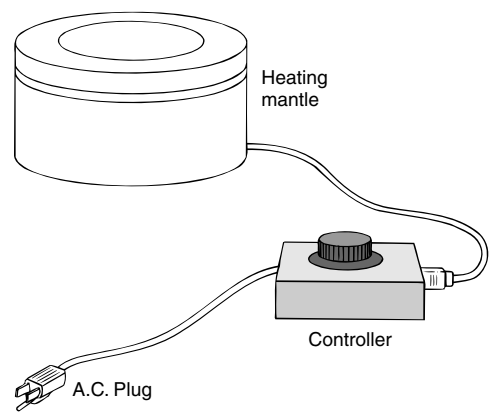


Figure 6.1 A heating mantle.

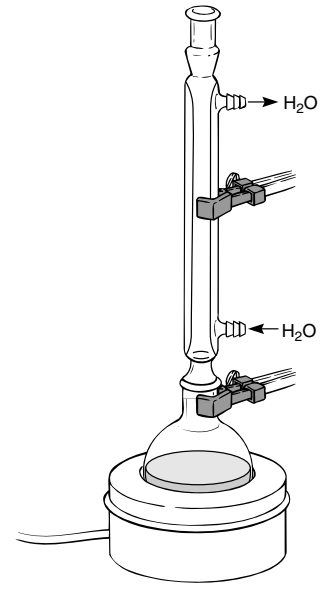


Figure 6.2 Heating with a heating mantle.

In the center of the heating mantle shown in Figure 6.1 is a well that can accommodate round-bottom flasks of several different sizes. Some heating mantles, however, are designed to fit only specific sizes of round-bottom flasks. Some heating mantles are also made to be used with a magnetic stirrer so that the reaction mixture can be heated and stirred at the same time. Figure 6.2 shows a reaction mixture being heated with a heating mantle.

Heating mantles are very easy to use and safe to operate. The metal housing is grounded to prevent electrical shock if liquid is spilled into the well; however, flammable liquids may ignite if spilled into the well of a hot heating mantle.

CAUTION

You should be very careful to avoid spilling liquids into the well of the heating mantle. The surface of the ceramic shell may be very hot and could cause the liquid to ignite.

Raising and lowering the apparatus is a much more rapid method of changing the temperature within the flask than changing the temperature with the controller. For this reason, the entire apparatus should be clamped above the heating mantle so that it can be raised if overheating occurs. Some laboratories may provide a lab jack or blocks of wood that can be placed under the heating mantle. In this case, the heating mantle itself is lowered and the apparatus remains clamped in the same position.

There are two situations in which it is relatively easy to overheat the reaction mixture. The first situation occurs when a larger heating mantle is used to heat a relatively small flask. You should be very careful when doing this. Many laboratories provide heating mantles of different sizes to prevent this from happening. The second situation occurs when the reaction mixture is first brought to a boil. To bring the mixture to a boil as rapidly as possible, the heat controller is often turned up higher than it will need to be set in order to keep the mixture boiling. When the mixture begins boiling very rapidly, turn the controller to a lower setting and raise the apparatus until the mixture boils less rapidly. As the temperature of the heating mantle cools down, lower the apparatus until the flask is resting on the bottom of the well.

6.2 Hot Plates

Hot plates are a very convenient source of heat; however, it is difficult to monitor the actual temperature, and changes in temperature occur somewhat slowly. Care must be taken with flammable solvents to ensure against fires caused by "flashing" when solvent vapors come into contact with the hot-plate surface. Never evaporate large quantities of a solvent by this method; the fire hazard is too great.

Some hot plates *heat constantly* at a given setting. They have no thermostat, and you will have to control the temperature manually, either by removing the container being heated or by adjusting the temperature up or down until a balance point is found. Some hot plates have a thermostat to control the temperature. A good thermostat will maintain a very even temperature. With many hot plates, however, the temperature may vary greatly (>10–20°C), depending upon whether the heater is in its "on" cycle or its "off" cycle. These hot plates will have a cycling (or oscillating) temperature, as shown in Figure 6.3. They, too, will have to be adjusted continually to maintain even heat.

Some hot plates also have built-in magnetic stirring motors that enable the reaction mixture to be stirred and heated at the same time. Their use is described in Section 6.5.

6.3 Water Bath with Hot Plate/Stirrer

A hot-water bath is a very effective heat source when a temperature below 80°C is required. A beaker (250-mL or 400-mL) is partially filled with water and heated on a hot plate. A thermometer is clamped into position in the water bath. You may need to cover the water bath with aluminum foil to prevent evaporation, especially at higher temperatures. The water bath is illustrated in Technique 6, Figure 6.4. A mixture can be stirred with a magnetic stir bar (see Technique 7, Section 7.3). A hot-water bath has some advantage over a heating mantle in that the temperature in the bath is uniform. In addition, it is sometimes easier to establish a lower temperature with a water bath than with other heating devices. Finally, the temperature of the reaction mixture will be closer to the temperature of the water, which allows for more precise control of the reaction conditions.

6.4 Oil Bath with Hot Plate/Stirrer

In some laboratories, oil baths may be available. An oil bath can be used when carrying out a distillation or heating a reaction mixture that needs a temperature above 100°C. An oil bath can be heated most conveniently with a hot plate, and a *heavy-walled* beaker provides a suitable container for the oil.[1] A thermometer is clamped into position in the oil bath. In some laboratories, the oil may be heated electrically by an immersion coil. Because oil baths have a high heat capacity and heat slowly, it is advisable to heat the oil bath partially before the actual time at which it is to be used.

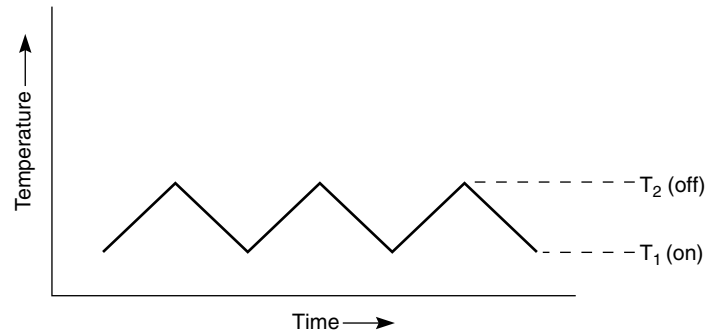


Figure 6.3 Temperature response for a hot plate with a thermostat.

[1]It is very dangerous to use a thin-walled beaker for an oil bath. Breakage due to heating can occur, spilling hot oil everywhere!

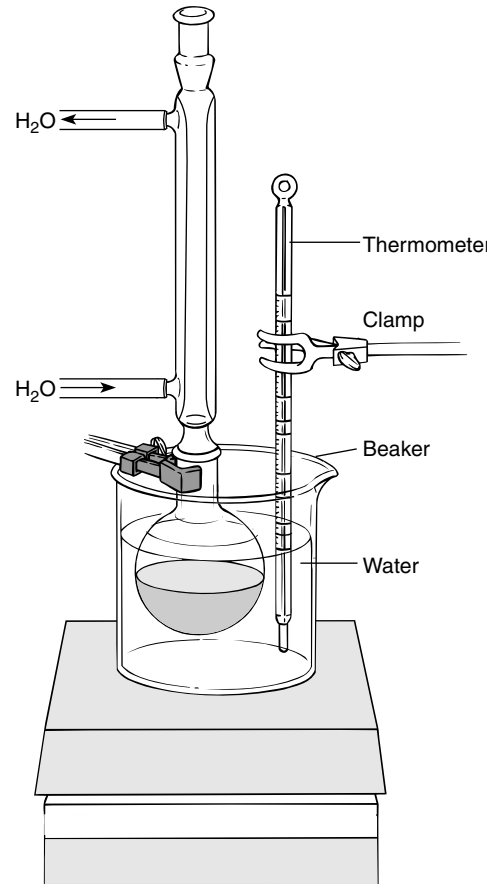


Figure 6.4 A water bath with a hot plate/stirrer.

An oil bath with ordinary mineral oil cannot be used above 200–220 °C. Above this temperature, the oil bath may "flash," or suddenly burst into flame. A hot oil fire is not extinguished easily. If the oil starts smoking, it may be near its flash temperature; discontinue heating. Old oil, which is dark, is more likely to flash than new oil. Also, hot oil causes bad burns. Water should be kept away from a hot oil bath, because water in the oil will cause it to splatter. Never use an oil bath when it is obvious that there is water in the oil. If water is present, replace the oil before using the heating bath. An oil bath has only a finite lifetime. New oil is clear and colorless but, after extended use, becomes dark brown and gummy from oxidation.

Besides ordinary mineral oil, a variety of other types of oils can be used in an oil bath. Silicone oil does not begin to decompose at as low a temperature as does mineral oil. When silicone oil is heated high enough to decompose, however, its vapors are far more hazardous than mineral oil vapors. The polyethylene glycols may be used in oil baths. They are water-soluble, which makes cleaning up after using an oil bath much easier than with mineral oil. One may select any one of a variety of polymer sizes of polyethylene glycol, depending on the temperature range required. The polymers of large molecular weight are often solid at room temperature. Wax may also be used for higher temperatures, but this material also becomes solid at room temperature. Some workers prefer to use a material that solidifies when not in use because it minimizes both storage and spillage problems.

6.5 Aluminum Block with a Hot Plate/Stirrer

Although aluminum blocks are most commonly used in microscale organic chemistry laboratories, they can also be used with the smaller round-bottom flasks used in macroscale experiments.[2] The aluminum block shown in Figure 6.5A can be used to hold 25-, 50-, or 100-mL round-bottom flasks, as well as a thermometer. Heating will occur more rapidly if the flask fits all the way into the hole; however, heating is also effective if the flask only partially fits into the hole. The aluminum block with smaller holes, as shown in Figure 6.5B, is designed for microscale glassware. It will hold a conical vial, a Craig tube or small test tubes, and a thermometer.

There are several advantages to heating with an aluminum block. The metal heats very quickly, high temperatures can be obtained, and you can cool the aluminum rapidly by removing it with crucible tongs and immersing it in cold water. Aluminum blocks are also inexpensive or can be fabricated readily in a machine shop.

Figure 6.6 shows a reaction mixture being heated with an aluminum block on a hot plate/stirrer unit. The thermometer in the figure is used to determine the temperature of the aluminum block. *Do not use a mercury thermometer:* use a thermometer containing a liquid other than mercury or use a metal dial thermometer that can be inserted into a smaller-diameter hole drilled into the side of the block.[3] Make sure that the thermometer fits loosely in the hole, or it may break. Secure the thermometer with a clamp.

To avoid the possibility of breaking a glass thermometer, your hot plate may have a hole drilled into the metal plate so that a metal dial thermometer can be inserted into the unit (see Figure 6.7A). These metal thermometers, such as the one shown in Figure 6.7B, can be obtained in a number of temperature ranges. For example, a 0–250°C thermometer with 2-degree divisions can be obtained at a reasonable price. Also shown in Figure 6.7 (inset) is an aluminum block with a small hole drilled into it so that a metal thermometer can be inserted. An alternative to the metal thermometer is a digital electronic temperature measuring device that can be inserted into the aluminum block or hot plate. It is strongly recommended that mercury thermometers be avoided when measuring the surface temperature of the hot plate or aluminum block. If a mercury thermometer is broken on a hot surface, you will introduce toxic mercury vapors into the laboratory. Nonmercury thermometers filled with high-boiling colored liquids are available as alternatives.

A. Large holes for 25-, 50-, or 100-mL round-bottom flasks

B. Small holes for Craig tube, 3-mL and 5-mL conical vials, and small test tubes

Figure 6.5 Aluminum heating blocks.

[2] The use of solid aluminum heating devices was developed by Siegfried Lodwig at Centralia College, Centralia, WA: Lodwig, S. N., *Journal of Chemical Education, 66* (1989): 77.

[3] C. M. Garner, "A Mercury-Free Alternative for Temperature Measurement in Aluminum Blocks," *Journal of Chemical Education, 68* (1991): A244.

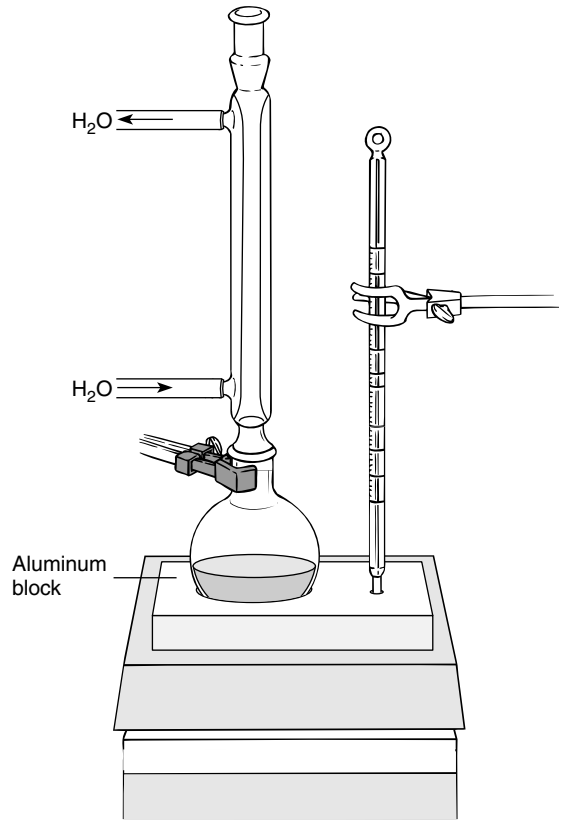


Figure 6.6 Heating with an aluminum block.

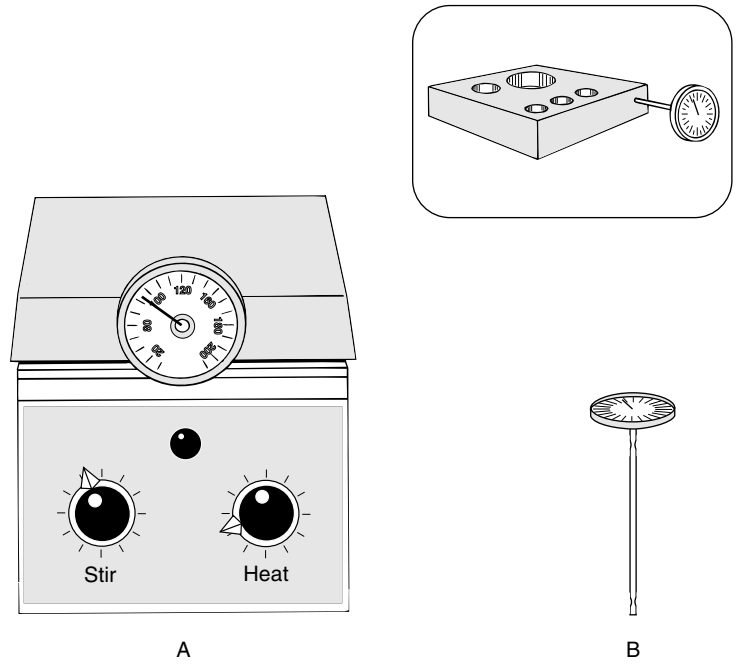


Figure 6.7 Dial thermometers.

As already mentioned, aluminum blocks are often used in the microscale organic chemistry laboratory. The use of an aluminum block to heat a microscale reflux apparatus is shown in Figure 6.8. The reaction vessel in the figure is a conical vial, which is used in many microscale experiments. Also shown in Figure 6.8 is a split aluminum collar that may be used when very high temperatures are required. The collar is split to facilitate easy placement around a 5-mL conical vial. The collar helps to distribute heat further up the wall of the vial.

You should first calibrate the aluminum block so that you have an approximate idea where to set the control on the hot plate to achieve a desired temperature. Place the aluminum block on the hot plate and insert a thermometer into the small hole in the block. Select five equally spaced temperature settings, including the lowest and highest settings, on the heating control of the hot plate. Set the dial to the first of these settings and monitor the temperature recorded on the thermometer. When the thermometer reading arrives at a constant value,[4] record this final temperature, along with the dial setting. Repeat this procedure with the remaining four settings. Using these data, prepare a calibration curve for future reference.

It is a good idea to use the same hot plate each time, as it is very likely that two hot plates of the same type may give different temperatures with identical settings. Record in your notebook the identification number printed on the unit that you are using to ensure that you always use the same hot plate.

For many experiments, you can determine what the approximate setting on the hot plate should be from the boiling point of the liquid being heated. Because the temperature inside the flask is lower than the aluminum block temperature, you should add at least 20°C to the boiling point of the liquid and set the aluminum block at this higher temperature. In fact, you may need to raise the temperature even higher than this value in order to bring the liquid to a boil.

Many organic mixtures need to be stirred as well as heated to achieve satisfactory results. To stir a mixture, place a magnetic stir bar (see Technique 7, Figure 7.8A) in a round-bottom flask containing the reaction mixture as shown in Figure 6.9A. If the mixture is to be heated as well as stirred, attach a water condenser as shown in Figure 6.6. With the combination hot plate/stirrer unit, it is possible to stir and heat a mixture simultaneously. With conical vials, a magnetic spin vane must be used to stir mixtures (see Technique 7, Figure 7.8B). This is shown in Figure 6.9B. More uniform stirring will be obtained if the flask or vial is placed in the aluminum block so that it is centered on the hot plate. Mixing may also be achieved by boiling the mixture. A boiling stone (see Technique 7, Section 7.4) must be added when a mixture is boiled without magnetic stirring.

6.6 Sand Bath with Hot Plate/Stirrer

The sand bath is used in some microscale laboratories to heat organic mixtures. It can also be used as a heat source in some macroscale experiments. Sand provides a clean way of distributing heat to a reaction mixture. To prepare a sand bath for microscale use, place about a 1-cm depth of sand in a crystallizing dish and then set the dish on a hot plate/stirrer unit. The apparatus is shown in Figure 6.10. Clamp the thermometer into position in the sand bath. You should calibrate the sand bath in a manner similar to that used with the aluminum block (see previous section). Because sand heats more slowly than an aluminum block, you will need to begin heating the sand bath well before using it.

[4] See, however, Section 6.2.

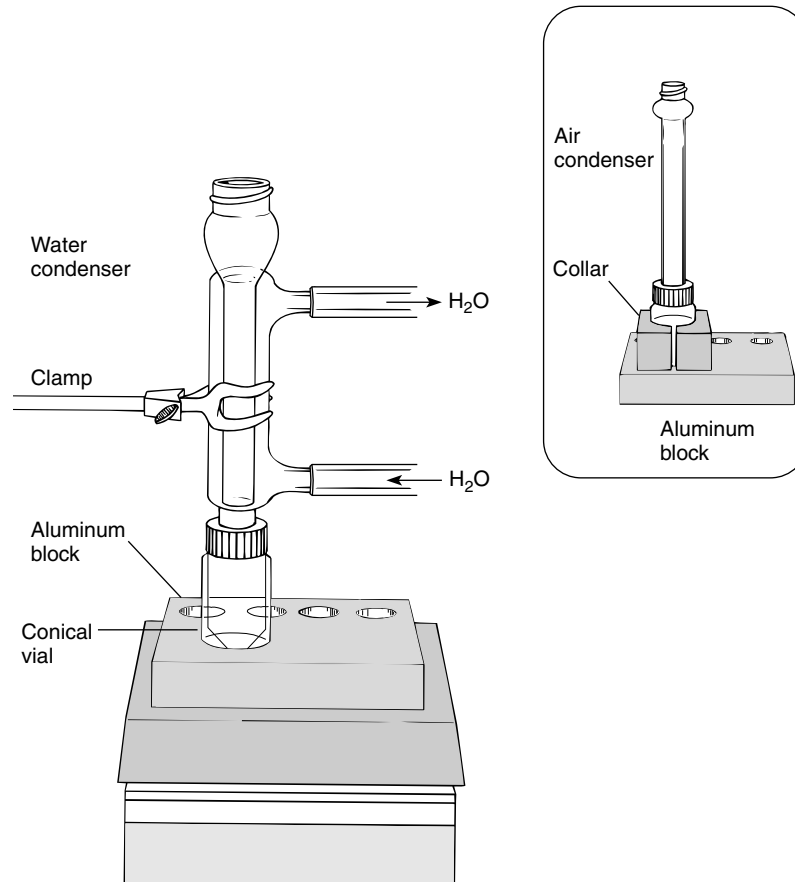


Figure 6.8 Heating with an aluminum block (microscale).

Do not heat the sand bath much above 200°C, or you may break the dish. If you need to heat at very high temperatures, you should use a heating mantle or an aluminum block rather than a sand bath. With sand baths, it may be necessary to cover the dish with aluminum foil to achieve a temperature near 200°C. Because of the relatively poor heat conductivity of sand, a temperature gradient is established within the sand bath. It is warmer near the bottom of the sand bath and cooler near the top for a given setting on the hot plate. To make use of this gradient, you may find it convenient to bury the flask or vial in the sand to heat a mixture more rapidly. Once the mixture is boiling, you can then slow the rate of heating by raising the flask or vial. These adjustments may be made easily and do not require a change in the setting on the hot plate.

6.7 Flames

The simplest technique for heating mixtures is to use a Bunsen burner. Because of the high danger of fires, however, the use of a Bunsen burner should be strictly limited to those cases for which the danger of fire is low or for which no reasonable alternative source of heat is available. A flame should generally be used only to heat aqueous solutions or solutions with very high boiling points. You should always check with your instructor about using a burner. If you use a burner at your bench, great care should be taken to ensure that others in the vicinity are not using flammable solvents.

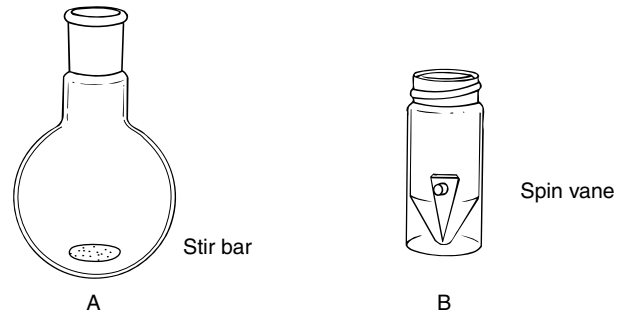


Figure 6.9 Methods of stirring in a round-bottom flask or conical vial.

In heating a flask with a Bunsen burner, you will find that using a wire gauze can produce more even heating over a broader area. The wire gauze, when placed under the object being heated, spreads the flame to keep the flask from being heated in one small area only.

Bunsen burners may be used to prepare capillary micropipets for thin-layer chromatography or to prepare other pieces of glassware requiring an open flame. For these purposes, burners should be used in designated areas in the laboratory and not at your laboratory bench.

6.8 Steam Baths

The steam cone or steam bath is a good source of heat when temperatures around 100°C are needed. Steam baths are used to heat reaction mixtures and solvents needed for crystallization. A steam cone and a portable steam bath are shown in

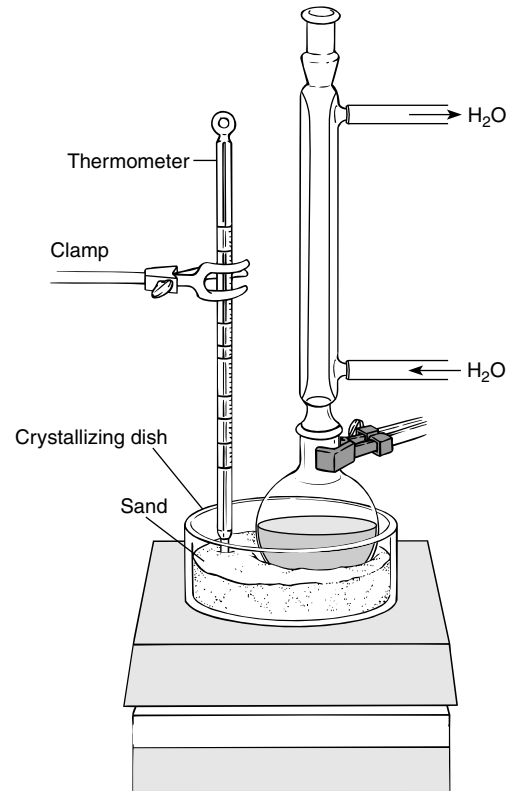


Figure 6.10 Heating with a sand bath.

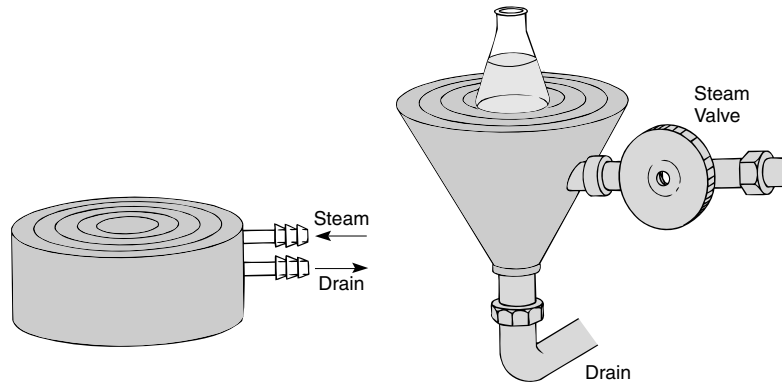


Figure 6.11 A steam bath and a steam cone.

Figure 6.11. These methods of heating have the disadvantage that water vapor may be introduced, through condensation of steam, into the mixture being heated. A slow flow of steam may minimize this difficulty.

Because water condenses in the steam line when it is not in use, it is necessary to purge the line of water before the steam will begin to flow. This purging should be accomplished before the flask is placed on the steam bath. The steam flow should be started with a high rate to purge the line; then the flow should be reduced to the desired rate. When using a portable steam bath, be certain that condensate (water) is drained into a sink. Once the steam bath or cone is heated, a slow steam flow will maintain the temperature of the mixture being heated. There is no advantage to having a Vesuvius on your desk! An excessive steam flow may cause problems with condensation in the flask. This condensation problem can often be avoided by selecting the correct place at which to locate the flask on top of the steam bath.

The top of the steam bath consists of several flat concentric rings. The amount of heat delivered to the flask being heated can be controlled by selecting the correct sizes of these rings. Heating is most efficient when the largest opening that will still support the flask is used. Heating large flasks on a steam bath while using the smallest opening leads to slow heating and wastes laboratory time.

6.9 Cold Baths

At times, you may need to cool an Erlenmeyer flask or round-bottom flask below room temperature. A cold bath is used for this purpose. The most common cold bath is an **ice bath**, which is a highly convenient source of 0°C temperature. An ice bath requires water along with ice to work well. If an ice bath is made up of only ice, it is not a very efficient cooler because the large pieces of ice do not make good contact with the flask. Enough water should be present with ice so that the flask is surrounded by water but not so much that the temperature is no longer maintained at 0°C. In addition, if too much water is present, the buoyancy of a flask resting in the ice bath may cause it to tip over. There should be enough ice in the bath to allow the flask to rest firmly.

For temperatures somewhat below 0°C, you may add some solid sodium chloride to the ice-water bath. The ionic salt lowers the freezing point of the ice so that temperatures in the range of 0 to −10°C can be reached. The lowest temperatures are reached with ice-water mixtures that contain relatively little water.

A temperature of −78.5°C can be obtained with solid carbon dioxide or dry ice. However, large chunks of dry ice do not provide uniform contact with a flask being cooled. A liquid such as isopropyl alcohol is mixed with small pieces of dry ice to provide an efficient cooling mixture. Acetone and ethanol can be used in place of

isopropyl alcohol. Be careful when handling dry ice because it can inflict severe frostbite. Extremely low temperatures can be obtained with liquid nitrogen (−195.8°C).

PROBLEMS

1. What would be the preferred heating device(s) in each of the following situations?
   - **a.** Reflux a solvent with a 56°C boiling point
   - **b.** Reflux a solvent with a 110°C boiling point
   - **c.** Distillation of a substance that boils at 220°C
2. Obtain the boiling points for the following compounds by using a handbook (see Technique 4). In each case, suggest a heating device(s) that should be used for refluxing the substance.
   - **a.** Butyl benzoate
   - **b.** 1-Pentanol
   - **c.** 1-Chloropropane
3. What type of bath would you use to get a temperature of −10°C?
4. Obtain the melting point and boiling point for benzene and ammonia from a handbook (see Technique 4) and answer the following questions.
   - **a.** A reaction was conducted in benzene as the solvent. Because the reaction was very exothermic, the mixture was cooled in a salt-ice bath. This was a bad choice. Why?
   - **b.** What bath should be used for a reaction that is conducted in liquid ammonia as the solvent?
5. Criticize the following techniques:
   - **a.** Refluxing a mixture that contains diethyl ether using a Bunsen burner
   - **b.** Refluxing a mixture that contains a large amount of toluene using a hot-water bath
   - **c.** Refluxing a mixture using the apparatus shown in Figure 6.6, but with an unclamped thermometer
   - **d.** Using a mercury thermometer that is inserted into an aluminum block on a hot plate
   - **e.** Running a reaction with *tert*-butyl alcohol (2-methyl-2-propanol) that is cooled to 0°C in an ice bath

7 **TECHNIQUE 7**

Reaction Methods

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

The successful completion of an organic reaction requires the chemist to be familiar with a variety of laboratory methods. These methods include operating safely, assembling the apparatus, heating and stirring reaction mixtures, adding liquid reagents, maintaining anhydrous and inert conditions in the reaction, and collecting gaseous products. Several techniques that are used in bringing a reaction to a successful conclusion are discussed here.

7.1 Assembling the Apparatus

Care must be taken when assembling the glass components into the desired apparatus. You should always remember that Newtonian physics applies to chemical apparatus, and unsecured pieces of glassware are certain to respond to gravity.

Assembling an apparatus in the correct manner requires that the individual pieces of glassware be connected to each other securely and that the entire apparatus is held in the correct position. This can be accomplished by using **adjustable metal clamps** or a combination of adjustable metal clamps and **plastic joint clips**.

Two types of adjustable metal clamps are shown in Figure 7.1. Although these two types of clamps can usually be interchanged, the extension clamp is more commonly used to hold round-bottom flasks in place, and the three-finger clamp is frequently used to clamp condensers. Both types of clamps must be attached to a ring stand using a clamp holder, shown in Figure 7.1C.

A. Securing Macroscale Apparatus Assemblies

It is possible to assemble an apparatus using only adjustable metal clamps. An apparatus used to perform a distillation is shown in Figure 7.2. It is held together securely with three metal clamps. Because of the size of the apparatus and its geometry, the various clamps would likely be attached to three different ring stands. This apparatus would be somewhat difficult to assemble, because it is necessary to ensure that the individual pieces stay together while securing and adjusting the clamps required to hold the entire apparatus in place. In addition, one must be very careful not to bump any part of the apparatus or the ring stands after the apparatus is assembled.

A more convenient alternative is to use a combination of metal clamps and plastic joint clips. A plastic joint clip is shown in Figure 7.3A. These clips are very easy to use (they just clip on), will withstand temperatures up to 140°C, and are quite durable. They hold together two pieces of glassware that are connected by ground-glass joints, as shown in Figure 7.3B. These clips come in different sizes to fit ground-glass joints of different sizes and they are color-coded for each size.

When used in combination with metal clamps, the plastic joint clips make it much easier to assemble most apparatus in a secure manner. There is less chance of dropping the glassware while assembling the apparatus, and once the apparatus is set up, it is more secure. Figure 7.4 shows the same distillation apparatus held in place with both adjustable metal clamps and plastic joint clips.

To assemble this apparatus, first connect all of the individual pieces together using the plastic clips. The entire apparatus is then connected to the ring stands using the adjustable metal clamps. Note that only two ring stands are required and the wooden blocks are not needed.

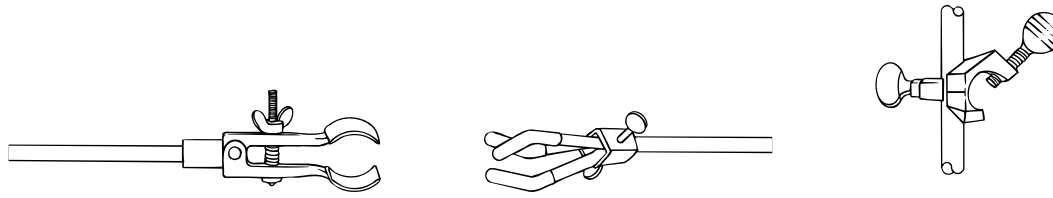


Figure 7.1 Adjustable metal clamps.

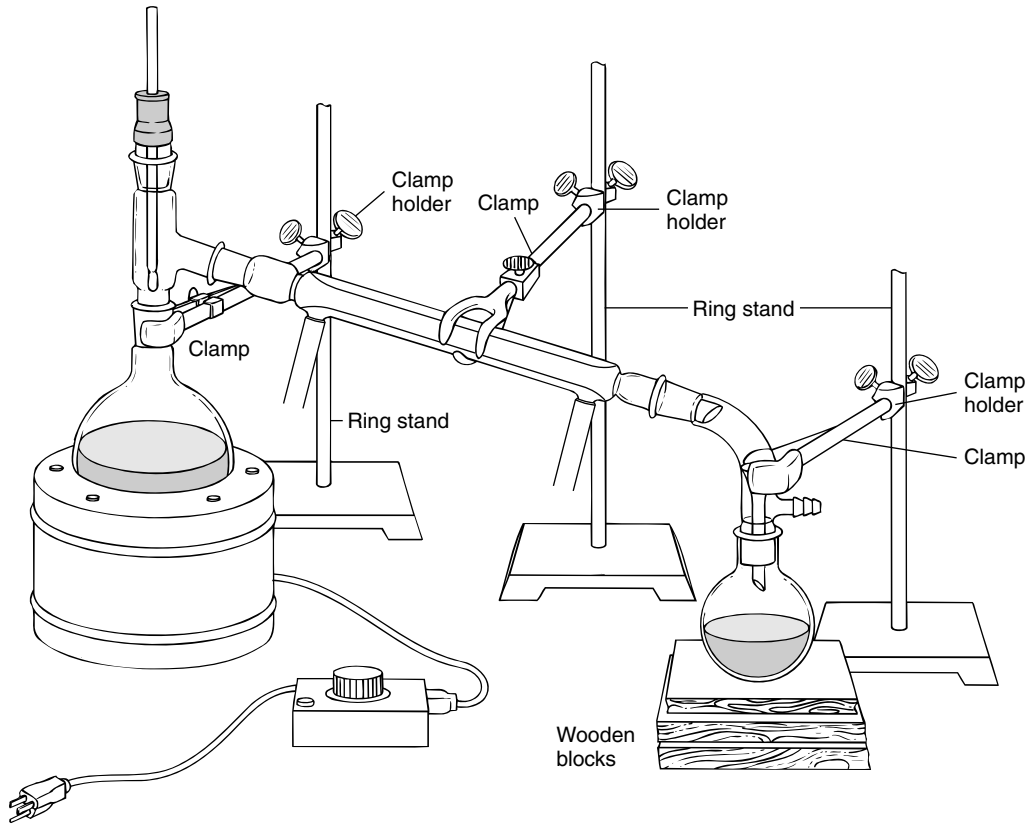


Figure 7.2 Distillation apparatus secured with metal clamps.

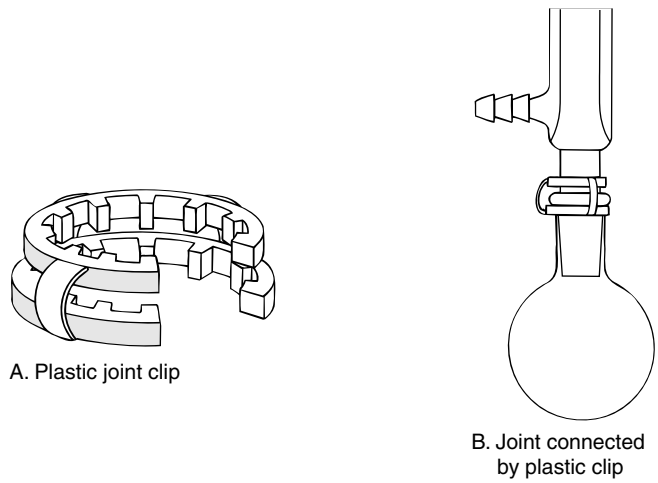


Figure 7.3 Plastic joint clip.

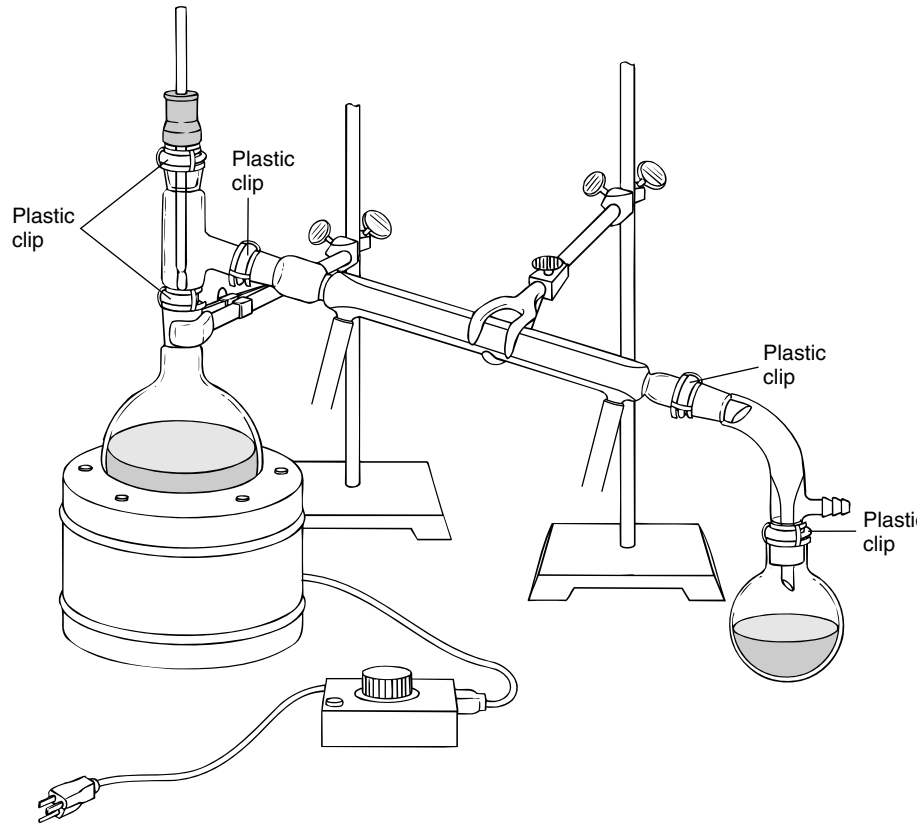


Figure 7.4 Distillation apparatus secured with metal clamps and plastic joint clips.

B. Securing Microscale Apparatus Assemblies

The glassware in most microscale kits is made with standard-taper ground joints. The most common joint size is ST 14/10. Some microscale glassware with ground-glass joints also has threads cast into the outside surface of the outer joints (see the top of the air condenser in Figure 7.5). The threaded joint allows the use of a plastic screw cap with a hole in the top to fasten two pieces of glassware together securely. The plastic cap is slipped over the inner joint of the upper piece of glassware, followed by a rubber O-ring (see Figure 7.5). The O-ring should be pushed down so that it fits snugly on top of the ground-glass joint. The inner ground-glass joint is then fitted into the outer joint of the bottom piece of glassware. The screw cap is tightened, without excessive force, to attach the entire apparatus firmly together. The O-ring provides an additional seal that makes this joint airtight. With this connecting system, it is unnecessary to use any type of grease to seal the joint. The O-ring *must be used* to obtain a good seal and to lessen the chances of breaking the glassware when you tighten the plastic cap.

Microscale glassware connected together in this fashion can be assembled very easily. The entire apparatus is held together securely, and usually only one metal clamp is required to hold the apparatus onto a ring stand.

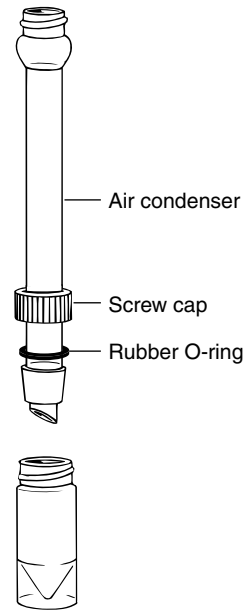


Figure 7.5 A microscale standard-taper joint assembly.

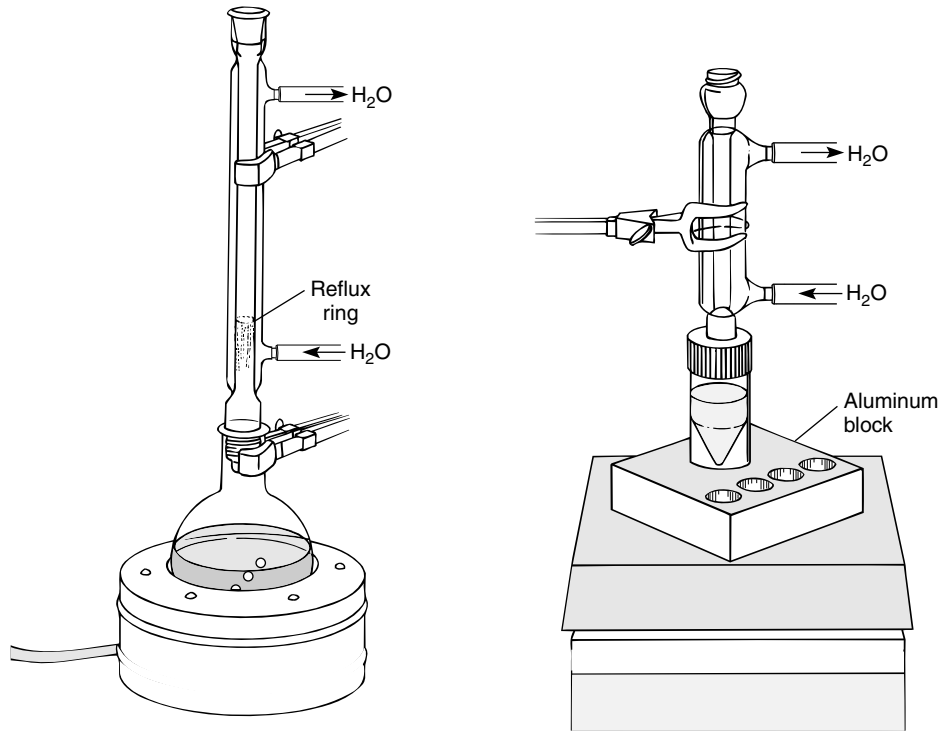
7.2 Heating Under Reflux

Often we wish to heat a mixture for a long time and to leave it untended. A **reflux apparatus** (see Figure 7.6) allows such heating. The liquid is heated to a boil, and the hot vapors are cooled and condensed as they rise into the water-jacketed condenser. Therefore, very little liquid is lost by evaporation, and the mixture is kept at a constant temperature, the boiling point of the liquid. The liquid mixture is said to be **heating under reflux**.

Condenser. The **water-jacketed condenser** shown in Figure 7.6 consists of two concentric tubes with the outer cooling tube sealed onto the inner tube. The vapors rise within the inner tube, and water circulates through the outer tube. The circulating water removes heat from the vapors and condenses them. Figure 7.6 also shows a typical microscale apparatus for heating small quantities of material under reflux (see Figure 7.6B).

When using a water-jacketed condenser, make sure that the direction of the water flow is such that the condenser will fill with cooling water. The water should enter the bottom of the condenser and leave from the top. The water should flow fast enough to withstand any changes in pressure in the water lines, but it should not flow any faster than absolutely necessary. An excessive flow rate greatly increases the chance of a flood, and high water pressure may force the hose from the condenser. Cooling water should be flowing before heating is begun! If the water is to remain flowing overnight, it is advisable to fasten the rubber tubing securely with wire to the condenser. If a flame is used as a source of heat, it is wise to use a wire gauze beneath the flask to provide an even distribution of heat from the flame. In most cases, a heating mantle, water bath, oil bath, aluminum block, sand bath, or steam bath is preferred over a flame.

Stirring. When heating a solution, always use a magnetic stirrer or a boiling stone (see Sections 7.3 and 7.4) to keep the solution from "bumping" (see next section).



A. Reflux apparatus for macroscale reactions, using a heating mantle and water-jacketed condenser.

B. Reflux apparatus for microscale reactions, using a hot plate, aluminum block, and water-jacketed condenser.

Figure 7.6 Heating under reflux.

Rate of Heating. If the heating rate has been correctly adjusted, the liquid being heated under reflux will travel only partway up the condenser tube before condensing. Below the condensation point, solvent will be seen running back into the flask; above it, the interior of the condenser will appear dry. The boundary between the two zones will be clearly demarcated, and a **reflux ring**, or a ring of liquid, will appear there. The reflux ring can be seen in Figure 7.6A. In heating under reflux, the rate of heating should be adjusted so that the reflux ring is no higher than a third to half of the distance to the top of the condenser. With microscale experiments, the quantities of vapor rising in the condenser frequently are so small that a clear reflux ring cannot be seen. In those cases, the heating rate must be adjusted so that the liquid boils smoothly but not so rapidly that solvent can escape the condenser. With such small volumes, the loss of even a small amount of solvent can affect the reaction. With macroscale reactions, the reflux ring is much easier to see, and one can adjust the heating rate more easily.

Tended Reflux. It is possible to heat small amounts of a solvent under reflux in an Erlenmeyer flask. By heating gently, the evaporated solvent will condense in the relatively cold neck of the flask and return to the solution. This technique (see Figure 7.7) requires constant attention. The flask must be swirled frequently and removed from the heating source for a short period if the boiling becomes too vigorous. When heating is in progress, the reflux ring should not be allowed to rise into the neck of the flask.

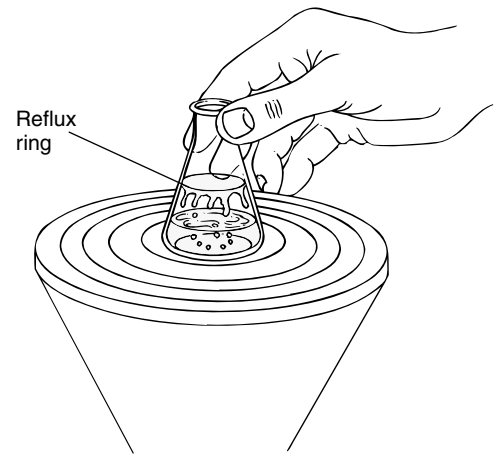


Figure 7.7 Tended reflux of small quantities on a steam cone (this can also be done with a hot plate).

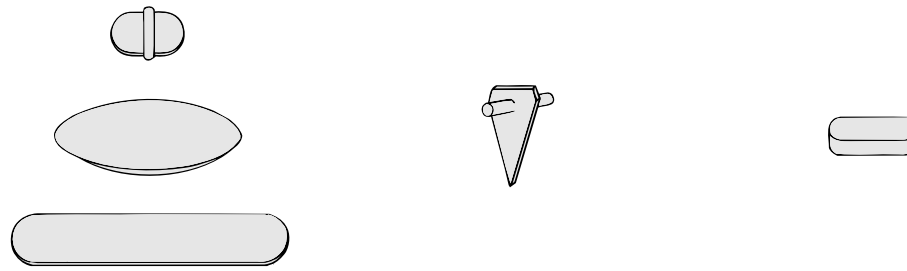
7.3 Stirring Methods

When a solution is heated, there is a danger that it may become superheated. When this happens, very large bubbles sometimes erupt violently from the solution; this is called **bumping**. Bumping must be avoided because of the risk that material may be lost from the apparatus, that a fire may start, or that the apparatus may break.

Magnetic stirrers are used to prevent bumping because they produce turbulence in the solution. The turbulence breaks up the large bubbles that form in boiling solutions. An additional purpose for using a magnetic stirrer is to stir the reaction to ensure that all the reagents are thoroughly mixed. A magnetic stirring system consists of a magnet that is rotated by an electric motor. The rate at which this magnet rotates can be adjusted by a potentiometric control. A small magnet, which is coated with a nonreactive material such as Teflon or glass, is placed in the flask. The magnet within the flask rotates in response to the rotating magnetic field caused by the motor-driven magnet. The result is that the inner magnet stirs the solution as it rotates. A very common type of magnetic stirrer includes the stirring system within a hot plate. This type of hot plate/stirrer permits one to heat the reaction and stir it simultaneously. In order for the magnetic stirrer to be effective, the contents of the flask being stirred should be placed as close to the center of the hot plate as possible and not offset.

For macroscale apparatus, magnetic stirring bars of various sizes and shapes are available. For microscale apparatus, a **magnetic spin vane** is often used. It is designed to contain a tiny bar magnet and to have a shape that conforms to the conical bottom of a reaction vial. A small Teflon-coated magnetic stirring bar works well with very small round-bottom boiling flasks. Small stirring bars of this type (often sold as "disposable" stirring bars) can be obtained very cheaply. A variety of magnetic stirring bars is illustrated in Figure 7.8.

There is also a variety of simple techniques that may be used to stir a liquid mixture in a centrifuge tube or conical vial. A thorough mixing of the components of a liquid can be achieved by repeatedly drawing the liquid into a Pasteur pipet and then ejecting the liquid back into the container by pressing sharply on the dropper bulb. Liquids can also be stirred effectively by placing the flattened end of a spatula into the container and twirling it rapidly.



A. Standard-sized magnetic stirring bars

B. Microscale magnetic spin vane

C. Small magnetic stirring bar ("disposable" type)

Figure 7.8 Magnetic stirring bars.

7.4 Boiling Stones

A **boiling stone**, also known as a **boiling chip** or **Boileezer**, is a small lump of porous material that produces a steady stream of fine air bubbles when it is heated in a solvent. This stream of bubbles and the turbulence that accompanies it break up the large bubbles of gases in the liquid. In this way, it reduces the tendency of the liquid to become superheated, and it promotes the smooth boiling of the liquid. The boiling stone decreases the chances for bumping.

Two common types of boiling stones are carborundum and marble chips. Carborundum boiling stones are more inert, and the pieces are usually quite small, suitable for most applications. If available, carborundum boiling stones are preferred for most purposes. Marble chips may dissolve in strong acid solutions, and the pieces are larger. The advantage of marble chips is that they are cheaper.

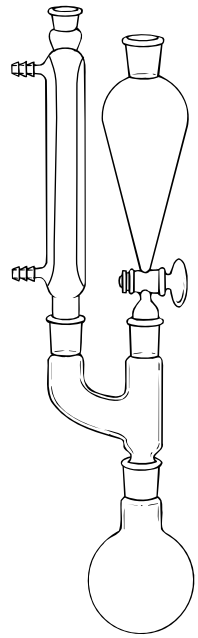
Because boiling stones act to promote the smooth boiling of liquids, you should always make certain that a boiling stone has been placed in a liquid *before* heating is begun. If you wait until the liquid is hot, it may have become superheated. Adding a boiling stone to a superheated liquid will cause all the liquid to try to boil at once. The liquid, as a result, would erupt entirely out of the flask or froth violently.

As soon as boiling ceases in a liquid containing a boiling stone, the liquid is drawn into the pores of the boiling stone. When this happens, the boiling stone no longer can produce a fine stream of bubbles; it is spent. You may have to add a new boiling stone if you have allowed boiling to stop for a long period.

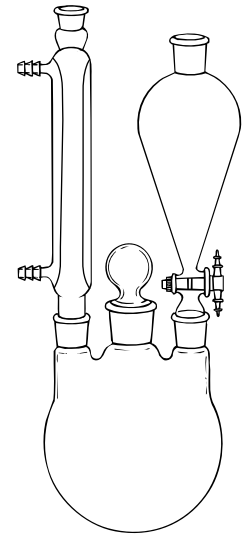
Wooden applicator sticks are used in some applications. They function in the same manner as boiling stones. Occasionally, glass beads are used. Their presence also causes sufficient turbulence in the liquid to prevent bumping.

7.5 Addition of Liquid Reagents

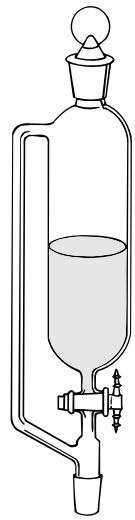
Liquid reagents and solutions are added to a reaction by several means, some of which are shown in Figure 7.9. The most common type of assembly for macroscale experiments is shown in Figure 7.9A. In this apparatus, a separatory funnel is attached to the sidearm of a Claisen head adapter. The separatory funnel must be equipped with a standard-taper, ground-glass joint to be used in this manner. The liquid is stored in the separatory funnel (which is called an **addition funnel** in this application) and is added to the reaction. The rate of addition is controlled by adjusting the stopcock. When it is being used as an addition funnel, the upper opening must be kept open to the atmosphere. If the upper hole is stoppered, a vacuum will develop in the funnel and will prevent the liquid from passing into the reaction vessel. Because the funnel is open to the atmosphere, there is a danger that atmospheric moisture can contaminate the liquid reagent as it is being added. To prevent this outcome, a drying tube (see Section 7.6) may be attached to the upper



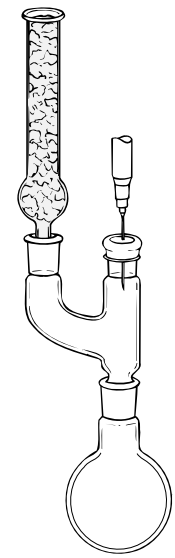
A. Macroscale equipment, using a separatory funnel as an addition funnel.



B. Macroscale, for larger amounts.



C. A pressure-equalizing addition funnel



D. Addition with a hypodermic syringe inserted through a rubber septum

Figure 7.9 Methods for adding liquid reagents to a reaction.

opening of the addition funnel. The drying tube allows the funnel to maintain atmospheric pressure without allowing the passage of water vapor into the reaction. For reactions that are particularly sensitive to moisture, it is also advisable to attach a second drying tube to the top of the condenser.

Another macroscale assembly, suitable for larger amounts of material, is shown in Figure 7.9B. Drying tubes may also be used with this apparatus to prevent contamination from atmospheric moisture.

Figure 7.9C shows an alternative type of addition funnel that is useful for reactions that must be maintained under an atmosphere of inert gas. This is the **pressure-equalizing addition funnel**. With this glassware, the upper opening is stoppered. The sidearm allows the pressure above the liquid in the funnel to be in equilibrium with the pressure in the rest of the apparatus, and it allows the inert gas to flow over the top of the liquid as it is being added.

With either type of macroscale addition funnel, you can control the rate of addition of the liquid by carefully adjusting the stopcock. Even after careful adjustment, changes in pressure can occur, causing the flow rate to change. In some cases, the stopcock can become clogged. It is important, therefore, to monitor the addition rate carefully and to refine the adjustment of the stopcock as needed to maintain the desired rate of addition.

A fourth method, shown in Figure 7.9D, is suitable for use in microscale and some macroscale experiments in which the reaction should be kept isolated from the atmosphere. In this approach, the liquid is kept in a hypodermic syringe. The syringe needle is inserted through a rubber septum, and the liquid is added dropwise from the syringe. The septum seals the apparatus from the atmosphere, which makes this technique useful for reactions that are conducted under an atmosphere of inert gas or in which anhydrous conditions must be maintained. The drying tube is used to protect the reaction mixture from atmospheric moisture.

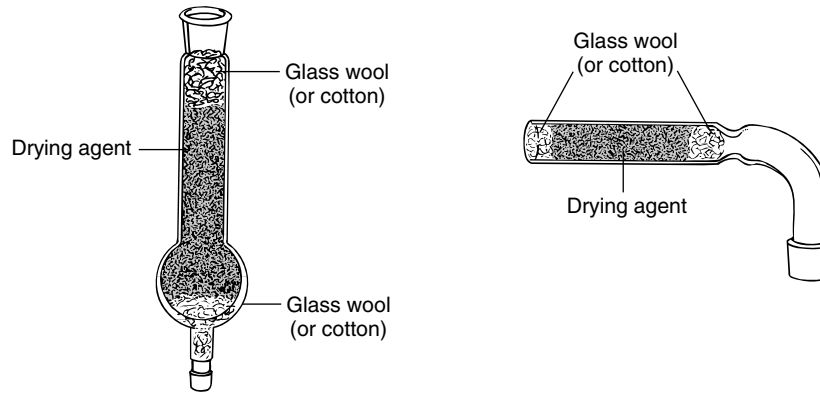
7.6 Drying Tubes

With certain reactions, atmospheric moisture must be prevented from entering the reaction vessel. A **drying tube** can be used to maintain anhydrous conditions within the apparatus. Two types of drying tubes are shown in Figure 7.10. The typical drying tube is prepared by placing a small, loose plug of glass wool or cotton into the constriction at the end of the tube nearest the ground-glass joint or hose connection. The plug is tamped gently with a glass rod or piece of wire to place it in the correct position. A drying agent, typically calcium sulfate ("Drierite") or calcium chloride (see Technique 12, Section 12.9), is poured on top of the plug to the approximate depth shown in Figure 7.10. Another loose plug of glass wool or cotton is placed on top of the drying agent to prevent the solid material from falling out of the drying tube. The drying tube is then attached to the flask or condenser.

Air that enters the apparatus must pass through the drying tube. The drying agent absorbs any moisture from air passing through it so that air entering the reaction vessel has had the water vapor removed from it.

7.7 Reactions Conducted under an Inert Atmosphere

Some reactions are very sensitive to oxygen and water vapor present in air and require an inert atmosphere in order to obtain satisfactory results. The usual reactions in which it is desirable to exclude air often include organometallic reagents, such as organomagnesium or organolithium reagents, where water vapor and oxygen (air) react with these compounds. The most common inert gases available in a laboratory are nitrogen and argon, which are available in gas cylinders. Nitrogen is probably the gas most often used to carry out reactions under an inert atmosphere, although argon has a distinct advantage because it is denser than air. This allows the argon to push air away from the reaction mixture.



A. Macroscale drying tube. B. Microscale drying tube.

Figure 7.10 Drying tubes.

When laboratories are not equipped with individual gas lines to benches or hoods, it is very useful to supply nitrogen or argon to the reaction apparatus using a balloon assembly (shown in Figure 7.11). Your instructor will provide you with the apparatus.

Construct the balloon assembly by cutting off the top of a 3-mL disposable plastic syringe. Attach a small balloon snugly to the top of the syringe, securing it with a small rubber band that has been doubled to hold the balloon securely to the body of the syringe. Attach a needle to the syringe. Fill the balloon with the inert gas through the needle using a piece of rubber tubing attached to the gas source. When the balloon has been inflated to 2–3 inches in diameter, quickly pinch off the neck of the balloon while removing the gas source. Now push the needle into a rubber stopper to keep the balloon inflated. It is possible to keep an assembly like this filled with inert gas for several days without the balloon deflating.

Before you start the reaction, you may need to dry your apparatus thoroughly in an oven. Add all reagents carefully to avoid water. The following instructions are based on the assumption that you are using an apparatus consisting of a round-bottom flask equipped with a condenser. Attach a rubber septum to the top of your condenser. Now flush the air out of the apparatus with the inert gas. It is best not to use the balloon assembly for this purpose, unless you are using argon (see next paragraph). Instead, remove the round-bottom flask from the apparatus and, with the help of your instructor, flush it with the inert gas using a Pasteur pipet to bubble the gas through the solvent and reaction mixture in the flask. In this way, you can remove air from the reaction assembly prior to attaching the balloon assembly. Quickly reattach the flask to the apparatus. Pinch off the neck of the balloon between your fingers, remove the rubber stopper, and insert the needle into the rubber septum. The reaction apparatus is now ready for use.

When argon is employed as an inert gas, you can use the balloon assembly to remove air from the reaction apparatus in the following way. Insert the balloon assembly into the rubber septum as previously described. Also insert a second needle (no syringe attached) through the septum. The pressure from the balloon will force argon down the reflux condenser (argon is denser than air) and push the less dense air out through the second syringe needle. When the apparatus has been thoroughly flushed with argon, remove the second needle. Nitrogen does not work as well with this method because it is less dense than air and it will be difficult to remove the air that is in contact with the reaction mixture in the round-bottom flask.

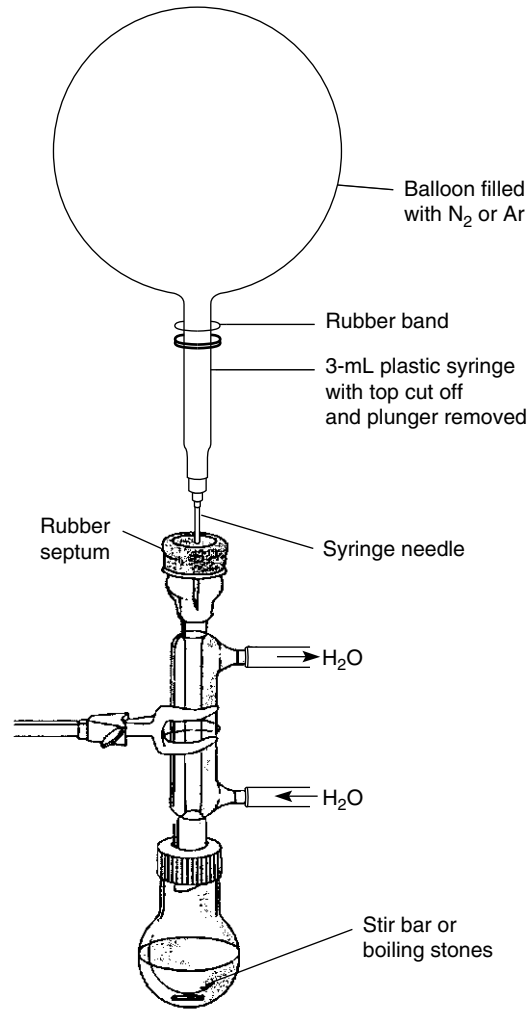


Figure 7.11 Conducting a reaction under an inert atmosphere using a balloon assembly.

For reactions conducted at room temperature, you can remove the condenser shown in Figure 7.11. Attach the rubber septum directly to the round-bottom flask and insert the needle of an argon-filled balloon assembly through the rubber septum. To flush the air out of the reaction flask, insert a second syringe needle into the rubber septum. Any air present in the flask will be flushed out through this second syringe needle, and the air will be replaced with argon. Now remove the second needle, and you have a reaction mixture free of air.

7.8 Capturing Noxious Gases

Many organic reactions involve the production of a noxious gaseous product. The gas may be corrosive, such as hydrogen chloride, hydrogen bromide, or sulfur dioxide, or it may be toxic, such as carbon monoxide. The safest way to avoid exposure to these gases is to conduct the reaction in a ventilated hood where the gases can be safely drawn away by the ventilation system.

In many instances, however, it is quite safe and efficient to conduct the experiment on the laboratory bench, away from the hood. This is particularly true when the gases are soluble in water. Some techniques for capturing noxious gases are presented in this section.

A. External Gas Traps

One approach to capturing gases is to prepare a trap that is separate from the reaction apparatus. The gases are carried from the reaction to the trap by means of tubing. There are several variations on this type of trap. With macroscale reactions, a trap using an inverted funnel placed in a beaker of water is used. A piece of glass tubing, inserted through a thermometer adapter attached to the reaction apparatus, is connected to flexible tubing. The tubing is attached to a conical funnel. The funnel is clamped in place inverted over a beaker of water. The funnel is clamped so that its lip *almost touches* the water surface, but is not placed below the surface of the water. With this arrangement, water cannot be sucked back into the reaction if the pressure in the reaction vessel changes suddenly. This type of trap can also be used in microscale applications. An example of the inverted-funnel type of gas trap is shown in Figure 7.12.

One method that works well for macroscale and microscale experiments is to place a thermometer adapter into the opening in the reaction apparatus. A Pasteur pipet is inserted upside down through the adapter, and a piece of flexible tubing is fitted over the narrow tip. It might be helpful to break the Pasteur pipet before using it for this purpose so that only the narrow tip and a short section of the barrel are used. The other end of the flexible tubing is placed through a large plug of moistened glass wool in a test tube. The water in the glass wool absorbs the water-soluble gases. This method is shown in Figure 7.13.

B. Drying-Tube Method

Some macroscale and most microscale experiments have the advantage that the amounts of gases produced are very small. Hence, it is easy to trap them and prevent them from escaping into the laboratory room. You can take advantage of the

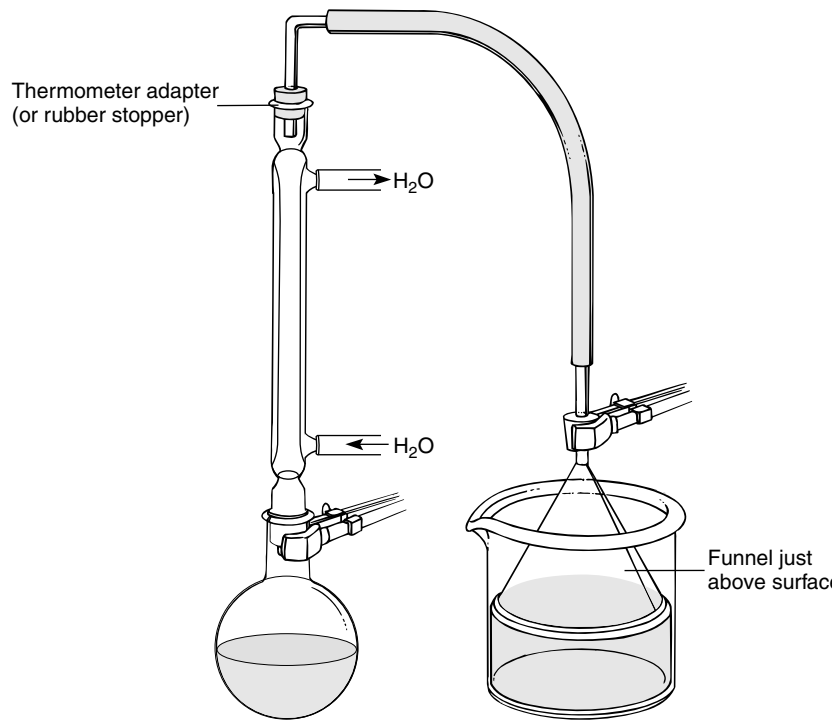


Figure 7.12 An inverted-funnel gas trap.

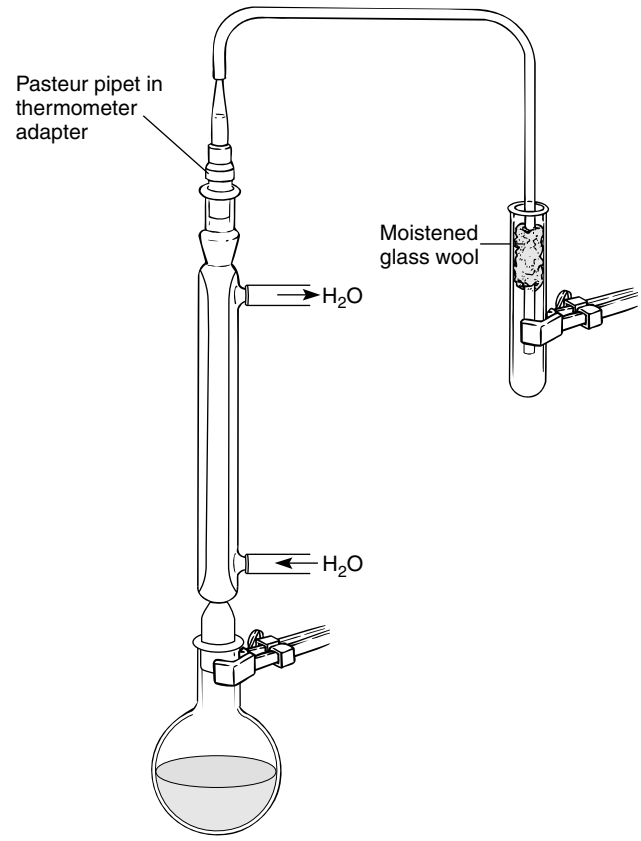


Figure 7.13 An external gas trap.

water solubility of corrosive gases such as hydrogen chloride, hydrogen bromide, and sulfur dioxide. A simple technique is to attach the drying tube (see Figure 7.10) to the top of the reaction flask or condenser. The drying tube is filled with moistened glass wool. The moisture in the glass wool absorbs the gas, preventing its escape. To prepare this type of gas trap, fill the drying tube with glass wool and then add water dropwise to the glass wool until it has been moistened to the desired degree. Moistened cotton can also be used, although cotton will absorb so much water that it is easy to plug the drying tube.

When using glass wool in a drying tube, moisture from the glass wool must not be allowed to drain from the drying tube into the reaction. It is best to use a drying tube that has a constriction between the part where the glass wool is placed and the neck, where the joint is attached (see Figure 7.10B). The constriction acts as a partial barrier preventing the water from leaking into the neck of the drying tube. Make certain not to make the glass wool too moist. When it is necessary to use the drying tube shown in Figure 7.10A as a gas trap and it is essential that water not be allowed to enter the reaction flask, the modification shown in Figure 7.14 should be used. The rubber tubing between the thermometer adapter and the drying tube should be heavy enough to prevent crimping.

C. Removal of Noxious Gases Using an Aspirator

An aspirator can be used to remove noxious gases from the reaction. The simplest approach is to clamp a disposable Pasteur pipet so that its tip is placed well into the

condenser atop the reaction flask. An inverted funnel clamped over the apparatus can also be used. The pipet or funnel is attached to an aspirator with flexible tubing. A trap should be placed between the pipet or funnel and the aspirator. As gases are liberated from the reaction, they rise into the condenser. The vacuum draws the gases away from the apparatus. Both types of systems are shown in Figure 7.15. In the special case in which the noxious gases are soluble in water, connecting a water aspirator to the pipet or funnel removes the gases from the reaction and traps them in the flowing water without the need for a separate gas trap.

7.9 Collecting Gaseous Products

In Section 7.8, means for removing unwanted gaseous products from the reaction system were examined. Some experiments produce gaseous products that you must collect and analyze. Methods to collect gaseous products are all based on the same principle. The gas is carried through tubing from the reaction to the opening of a flask or a test tube, which has been filled with water and is inverted in a container of water. The gas is allowed to bubble into the inverted collection tube (or flask). As the collection tube fills with gas, the water is displaced into the water container. If the collection tube is graduated, as in a graduated cylinder or a centrifuge tube, you can monitor the quantity of gas produced in the reaction.

If the inverted gas collection tube is constructed from a piece of glass tubing, a rubber septum can be used to close the upper end of the container. This type of collection tube is shown in Figure 7.16. A sample of the gas can be removed using a gas-tight syringe equipped with a needle. The gas that is removed can be analyzed by gas chromatography (see Technique 22).

In Figure 7.16, a piece of glass tubing is attached to the free end of the flexible hose. This piece of glass tubing sometimes makes it easier to fix the open end in the proper position in the opening of the collection tube or flask. The other end of the flexible tubing is attached to a piece of glass tubing or a Pasteur pipet that has been inserted into a thermometer adapter.

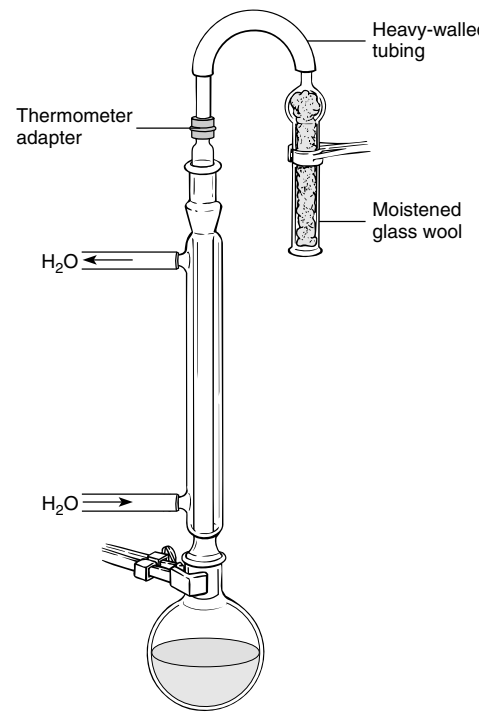


Figure 7.14 A drying tube used to capture evolved gases.

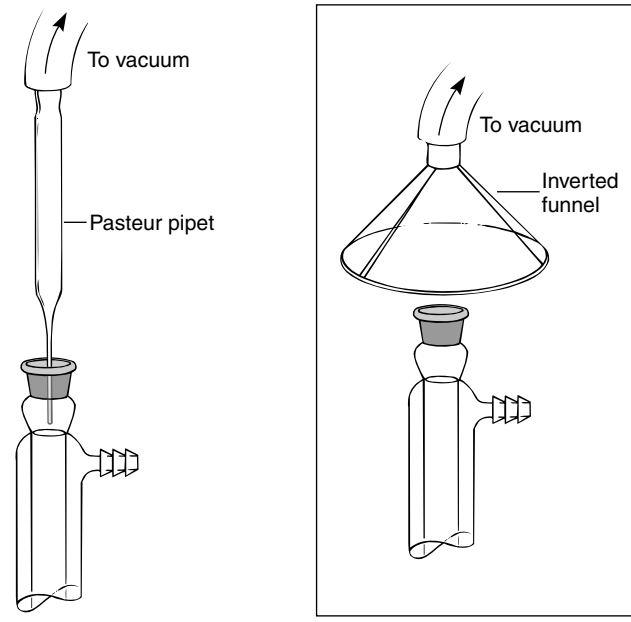


Figure 7.15 Removal of noxious gases under vacuum. (The inset shows an alternative assembly, using an inverted funnel in place of the Pasteur pipet.)

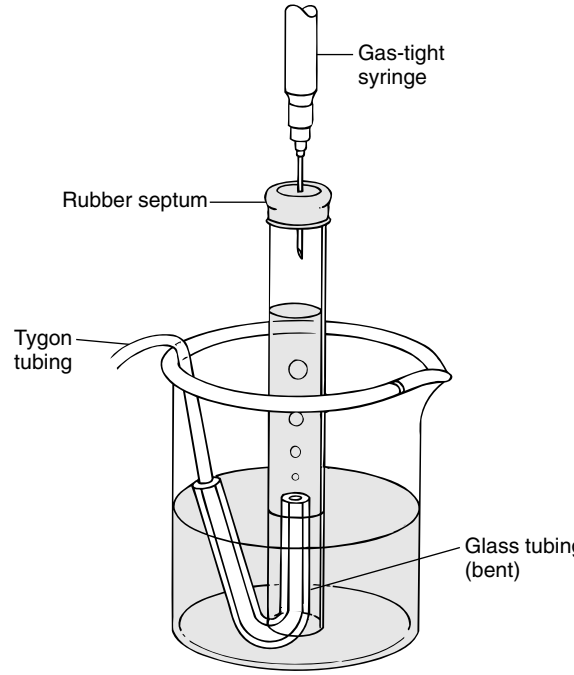


Figure 7.16 A gas collection tube, with rubber septum.

7.10 Evaporation of Solvents

In many experiments, it is necessary to remove excess solvent from a solution. An obvious approach is to allow the container to stand unstoppered in the hood for several hours until the solvent has evaporated. This method is generally not practical, however, and a quicker, more efficient means of evaporating solvents must be used.

CAUTION

You must always evaporate solvents in the hood.

A. Large-Scale Methods

A large-scale method to remove excess solvent is to evaporate the solvent from an open Erlenmeyer flask (Figures 7.17A and B). Such evaporation must be conducted in a hood, because many solvent vapors are toxic or flammable. A boiling

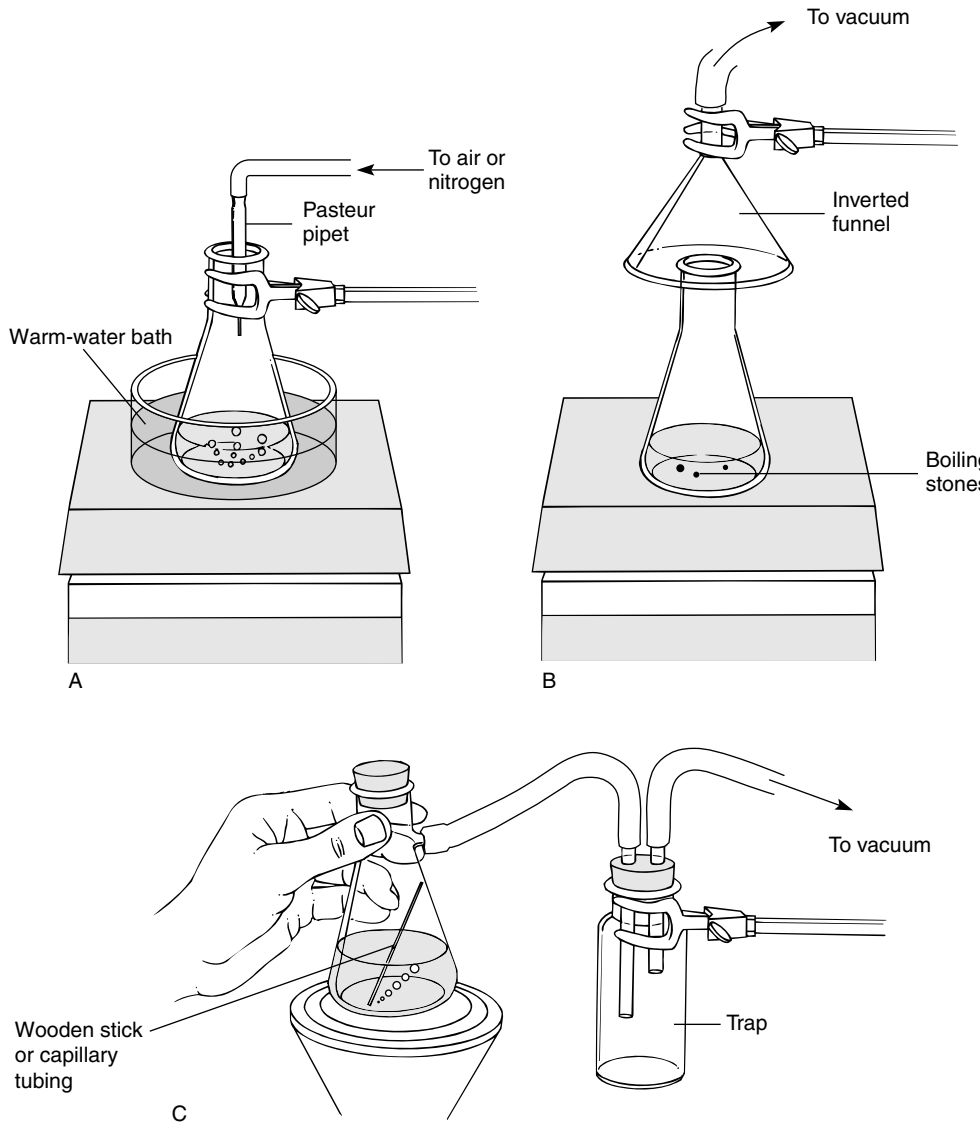


Figure 7.17 Evaporation of solvents (heat source can be varied among those shown).

stone must be used. A gentle stream of air directed toward the surface of the liquid will remove vapors that are in equilibrium with the solution and accelerate the evaporation. A Pasteur pipet connected by a short piece of rubber tubing to the compressed air line will act as a convenient air nozzle (see Figure 7.17A). A tube or an inverted funnel connected to an aspirator may also be used (see Figure 7.17B). In this case, vapors are removed by suction. It is better to use an Erlenmeyer flask than a beaker for this procedure because deposits of solid will usually build up on the sides of the beaker where the solvent evaporates. The refluxing action in an Erlenmeyer flask does not allow this buildup. If a hot plate is used as the heat source, care must be taken with flammable solvents to ensure against fires caused by "flashing," when solvent vapors come into contact with the hot-plate surface.

It is also possible to remove low-boiling solvents under reduced pressure (see Figure 7.17C). In this method, the solution is placed in a filter flask, along with a wooden applicator stick or a short length of capillary tubing. The flask is stoppered, and the sidearm is connected to an aspirator (by a trap), as described in Technique 8, Section 8.3. Under reduced pressure, the solvent begins to boil. The wooden stick or capillary tubing serves the same function as a boiling stone. By this method, solvents can be evaporated from a solution without using much heat. This technique is often used when heating the solution might decompose thermally-sensitive substances. The method has the disadvantage that when low-boiling solvents are used, solvent evaporation cools the flask below the freezing point of water. When this happens, a layer of frost forms on the outside of the flask. Because frost is insulating, it must be removed to keep evaporation proceeding at a reasonable rate. Frost is best removed by one of two methods: either the flask is placed in a bath of warm water (with constant swirling) or it is heated on the steam bath (again with swirling). Either method promotes efficient heat transfer.

Large amounts of a solvent should be removed by distillation (see Technique 14). *Never evaporate ether solutions to dryness,* except on a steam bath or by the reduced-pressure method. The tendency of ether to form explosive peroxides is a serious potential hazard. If peroxides should be present, the large and rapid temperature increase in the flask once the ether evaporates could bring about the detonation of any residual peroxides. The temperature of a steam bath is not high enough to cause such a detonation.

B. Small-Scale Methods

A simple means of evaporating a small amount of solvent is to place a centrifuge tube in a warm-water bath. The heat from the water bath will warm the solvent to a temperature at which it can evaporate within a short time. The heat from the water can be adjusted to provide the best rate of evaporation, but the liquid should not be allowed to boil vigorously. The evaporation rate can be increased by allowing a stream of dry air or nitrogen to be directed into the centrifuge tube (see Figure 7.18A). The moving gas stream will sweep the vapors from the tube and accelerate the evaporation. As an alternative, a vacuum can be applied above the tube to draw away solvent vapors.

A convenient water bath suitable for microscale methods can be constructed by placing the aluminum collars, which are generally used with aluminum heating blocks, into a 150-mL beaker (see Figure 7.18B). In some cases, it may be necessary to round off the sharp edges of the collars with a file in order to allow them to fit properly into the beaker. Held by the aluminum collars, the conical vial will stand securely in the beaker. This assembly can be filled with water and placed on a hot plate for use in the evaporation of small amounts of solvent.

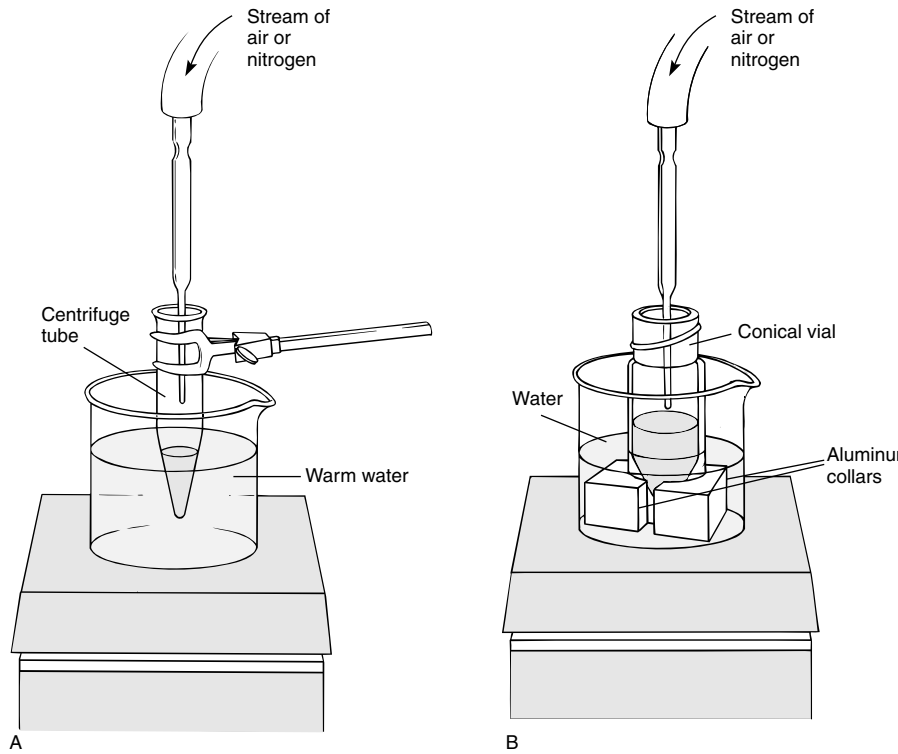


Figure 7.18 Evaporation of solvents (small-scale methods).

7.11 Rotary Evaporator

In some organic chemistry laboratories, solvents are evaporated under reduced pressure using a **rotary evaporator**. This is a motor-driven device that is designed for rapid evaporation of solvents, with heating, while minimizing the possibility of bumping. A vacuum is applied to the flask, and the motor spins the flask. The rotation of the flask spreads a thin film of the liquid over the surface of the glass, which accelerates evaporation. The rotation also agitates the solution sufficiently to reduce the problem of bumping. A water bath can be placed under the flask to warm the solution and increase the vapor pressure of the solvent. One can select the speed at which the flask is rotated and the temperature of the water bath to attain the desired evaporation rate. As the solvent evaporates from the rotating flask, the vapors are cooled by the condenser, and the resulting liquid collects in the flask. The product remains behind in the rotating flask. A complete rotary evaporator assembly is shown in Figure 7.19. If the coolant is sufficiently cold, virtually all of the solvent can be recovered and recycled. This is a good example of *Green Chemistry* (see the essay "Green Chemistry") that precedes Experiment 27.

7.12 Microwave-Assisted Organic Chemistry

We are all familiar with the use of a microwave oven in the kitchen and its particular advantages. Cooking food in a microwave oven is much faster than in a conventional oven. Microwave cooking is much simpler, does not require as much crockery, and energy is not wasted in heating the container.

All of these advantages can also be applied to the chemistry laboratory. It is possible to conduct chemical reactions in much less time than with ordinary laboratory methods. Since the mid-1980s, chemists have been working on developing methods to apply microwave heating to chemical synthesis. Microwave-assisted organic chemical methods, or **microwave chemistry**, have gained wide acceptance, especially in industrial and research laboratories. Microwave heating is able to heat

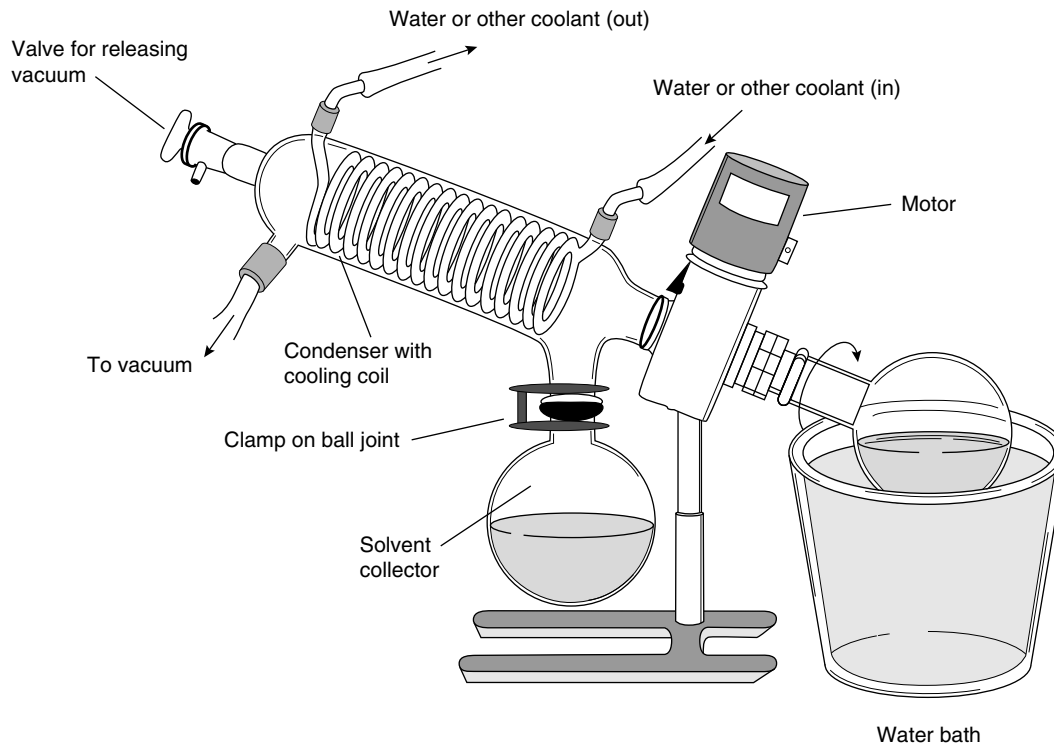


Figure 7.19 A rotary evaporator.

the chemical reagents without wasting energy in heating their container. In "green chemistry" applications, it allows the chemist to perform chemical reactions using less energy, in less time, often using water as a solvent, and often without using any solvent at all.

There does not seem to be general agreement as to the mechanism of microwave heating. The arguments are too complex to be included here. A basic understanding is possible, however. Microwave radiation is a form of *electromagnetic radiation*; this means that microwave radiation consists of oscillating electric and magnetic fields. When an oscillating electric field passes through a medium that contains polar or ionic substances, these molecules will attempt to orient themselves or oscillate in response to the electric field. Because these molecules are bound to surrounding molecules in the medium, however, their motions are restricted, and they cannot respond completely to the oscillations of the electric field. This causes a non-equilibrium condition that results in an elevated instantaneous temperature in the immediate microscopic region surrounding the molecules that are being affected. As this localized temperature increases, molecules are activated above the required energy-of-activation threshold. Rates of reactions are dependent upon temperature; as the localized temperature increases, the molecules in that microscopic region will react faster.

Chemists first tried using domestic kitchen microwave ovens to speed up chemical reactions. They found that they were able to accelerate reactions, increase yields, and initiate otherwise impossible reactions. The results were often unsatisfactory, however, owing to uneven heating, lack of reproducibility, and the possibility of explosions. The power output of a typical kitchen microwave oven cannot be adjusted. The oven cycles between periods of full power and periods of zero power.

Figure 7.20 A microwave reaction system. (Reprinted courtesy of CEM Corporation.)

This means that the amount of microwave energy being transmitted into an experiment cannot be controlled precisely.

In recent years, companies have developed state-of-the-art microwave reaction systems to overcome these deficiencies. A modern reaction system, such as the one shown in Figure 7.20, has a specially-designed vessel that focuses the microwave energy for efficient heating. Such systems are often equipped with automatic stirring and computer controls. Often a pressure control system may be included; this allows one to conduct a reaction at elevated temperature and pressure in the presence of volatile solvents or reagents. An automated sample changer is a useful accessory; this allows the chemist to conduct a series of repeated experiments without having to spend time watching the system.

Papers describing the advantages of microwave chemistry are appearing with increasing frequency in the chemical literature. Examples of experiments that can be conducted using microwave reaction systems include esterifications, condensation reactions, hydrogenations, cycloadditions, and even peptide syntheses. Besides offering a versatile method of chemical synthesis, microwave reaction systems also include the advantages that many of the reactions can be conducted in water, rather than in harmful organic solvents, or even in the complete absence of solvent. This capability makes microwave chemistry an important tool in "green chemistry."

PROBLEMS

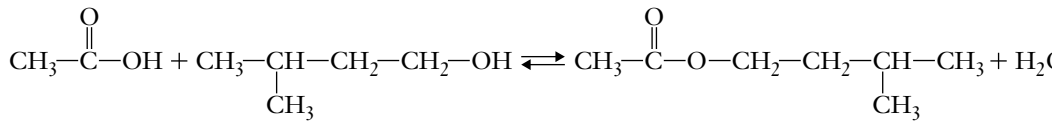
1. What is the best type of stirring device to use for stirring a reaction that takes place in the following type of glassware?

a. A conical vial

b. A 10-mL round-bottom flask

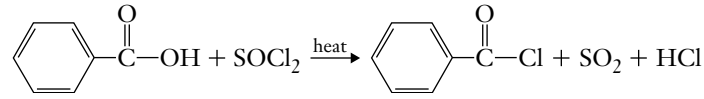
c. A 250-mL round-bottom flask

2. Should you use a drying tube for the following reaction? Explain.

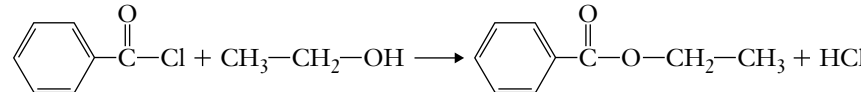


3. For which of the following reactions should you use a trap to collect noxious gases?

a.

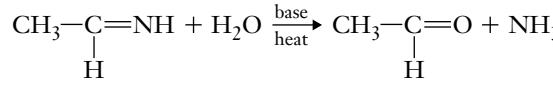


b.



c. $C_{12}H_{22}O_{11} + H_2O \longrightarrow 4\,CH_3{-}CH_2{-}OH + 4\,CO_2$
(Sucrose)

d.



4. Criticize the following techniques:

a. A reflux is conducted with a stopper in the top of the condenser.

b. Water is passed through the reflux condenser at the rate of 1 gallon per minute.

c. No water hoses are attached to the condenser during a reflux.

d. A boiling stone is not added to the round-bottom flask until the mixture is boiling vigorously.

e. To save money, you decide to save your boiling stones for another experiment.

f. The reflux ring is located near the top of the condenser in a reflux setup.

g. A rubber O-ring is omitted when the water condenser is attached to a conical vial.

h. A gas trap is assembled with the funnel in Figure 7.12 completely submerged in the water in the beaker.

i. Powdered drying agent is used rather than granular material.

j. A reaction involving hydrogen chloride is conducted on the laboratory bench and not in a hood.

k. An air-sensitive reaction apparatus is set up as shown in Figure 7.6.

l. Air is used to evaporate solvent from an air-sensitive compound.

8 **TECHNIQUE 8**

Filtration

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

Filtration is a technique used for two main purposes. The first is to remove solid impurities from a liquid. The second is to collect a desired solid from the solution from which it was precipitated or crystallized. Several different kinds of filtration techniques are commonly used: two general methods include gravity filtration and vacuum (or suction) filtration. Two techniques specific to the microscale laboratory are filtration with a filter-tip pipet and filtration with a Craig tube. The various filtration techniques and their applications are summarized in Table 8.1. These techniques are discussed in more detail in the following sections.

8.1 Gravity Filtration

The most familiar filtration technique is probably filtration of a solution through a paper filter held in a funnel, allowing gravity to draw the liquid through the paper. Because even a small piece of filter paper will absorb a significant volume of liquid, this technique is useful only when the volume of mixture to be filtered is greater than 10 mL. For many macroscale and microscale procedures, a more suitable technique, which also makes use of gravity, is to use a Pasteur (or disposable) pipet with a cotton or glass wool plug (called a filtering pipet).

A. Filter Cones

This filtration technique is most useful when the solid material being filtered from a mixture is to be collected and used later. The filter cone, because of its smooth sides, can easily be scraped free of collected solids. Because of the many folds, fluted filter paper, described in the next section, cannot be scraped easily. The filter cone is likely to be used in experiments only when a relatively large volume (greater than 10 mL) is being filtered and when a Büchner or Hirsch funnel (see Section 8.3) is not appropriate.

The filter cone is prepared as indicated in Figure 8.1. It is then placed into a funnel of an appropriate size. With filtrations using a simple filter cone, solvent may form seals between the filter and the funnel and between the funnel and the lip of the receiving flask. When a seal forms, the filtration stops because the displaced air has no possibility of escaping. To avoid the solvent seal, you can insert a small piece of paper, a paper clip, or some other bent wire between the funnel and the lip of the flask to let the displaced air escape. As an alternative, you can support the funnel by a clamp fixed *above* the flask rather than placed on the neck of the flask. A gravity filtration using a filter cone is shown in Figure 8.2.

B. Fluted Filters

This filtration method is also most useful when filtering a relatively large amount of liquid. Because a fluted filter is used when the desired material is expected to remain in solution, this filter is used to remove undesired solid materials, such as dirt particles, decolorizing charcoal, and undissolved impure crystals. A fluted filter is often used to filter a hot solution saturated with a solute during a crystallization procedure.

The technique for folding a fluted filter paper is shown in Figure 8.3. An advantage of a fluted filter is that it increases the speed of filtration in two ways. First,

TABLE 8.1 Filtration Methods

Method	Application	Section
Gravity filtration		
Filter cones	The volume of liquid to be filtered is about 10 mL or greater, and the solid collected in the filter is saved.	8.1A
Fluted filters	The volume of liquid to be filtered is greater than about 10 mL, and solid impurities are removed from a solution; often used in crystallization procedures.	8.1B
Filtering pipets	Used with volumes less than about 10 mL to remove solid impurities from a liquid.	8.1C
Decantation	Although not a filtration technique, decantation can be used to separate a liquid from large, insoluble particles.	8.1D
Vacuum filtration		
Büchner funnels	Primarily used to collect a desired solid from a liquid when the volume is greater than about 10 mL; used frequently to collect the crystals obtained from crystallization.	8.3
Hirsch funnels	Used in the same way as Büchner funnels, except the volume of liquid is usually smaller (1–10 mL).	8.3
Filtering media	Used to remove finely divided impurities.	8.4
Filter-tip pipets	May be used to remove a small amount of solid impurities from a small volume (1–2 mL) of liquid; also useful for pipetting volatile liquids, especially in extraction procedures.	8.6
Craig tubes	Used to collect a small amount of crystals resulting from crystallizations in which the volume of the solution is less than 2 mL.	8.7
Centrifugation	Although not strictly a filtration technique, centrifugation may be used to remove suspended impurities from a liquid (1–25 mL).	8.8

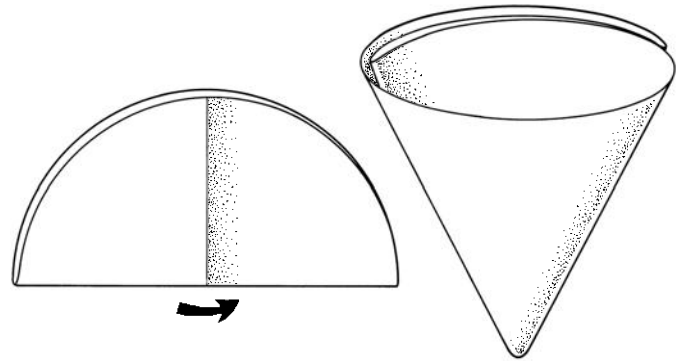


Figure 8.1 Folding a filter cone.

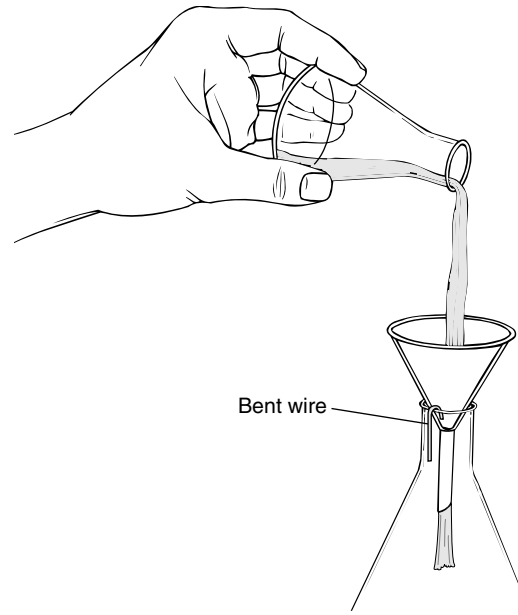


Figure 8.2 Gravity filtration with a filter cone.

it increases the surface area of the filter paper through which the solvent seeps; second, it allows air to enter the flask along its sides to permit rapid pressure equalization. If pressure builds up in the flask from hot vapors, filtering slows down. This problem is especially pronounced with filter cones. The fluted filter tends to reduce this problem considerably, but it may be a good idea to clamp the funnel above the receiving flask or to use a piece of paper, paper clip, or wire between the funnel and the lip of the flask as an added precaution against solvent seals.

Filtration with a fluted filter is relatively easy to perform when the mixture is at room temperature. However, when it is necessary to filter a hot solution saturated with a dissolved solute, a number of steps must be taken to ensure that the filter does not become clogged by solid material accumulated in the stem of the funnel or in the filter paper. When the hot, saturated solution comes in contact with a relatively cold funnel (or a cold flask, for that matter), the solution is cooled and may become supersaturated. If crystallization then occurs in the filter, either the crystals will fail to pass through the filter paper or they will clog the stem of the funnel.

To keep the filter from clogging, use one of the following four methods. The first is to use a short-stemmed or stemless funnel. With these funnels, it is less likely that the stem of the funnel will become clogged by solid material. The second method is to keep the liquid to be filtered at or near its boiling point at all times. The third way is to preheat the funnel by pouring hot solvent through it before the actual filtration. This keeps the cold glass from causing instantaneous crystallization. And fourth, it is helpful to keep the **filtrate** (filtered solution) in the receiver hot enough to continue boiling *slightly* (by setting it on a hot plate, for example). The refluxing solvent heats the receiving flask and the funnel stem and washes them clean of solids. This boiling of the filtrate also keeps the liquid in the funnel warm.

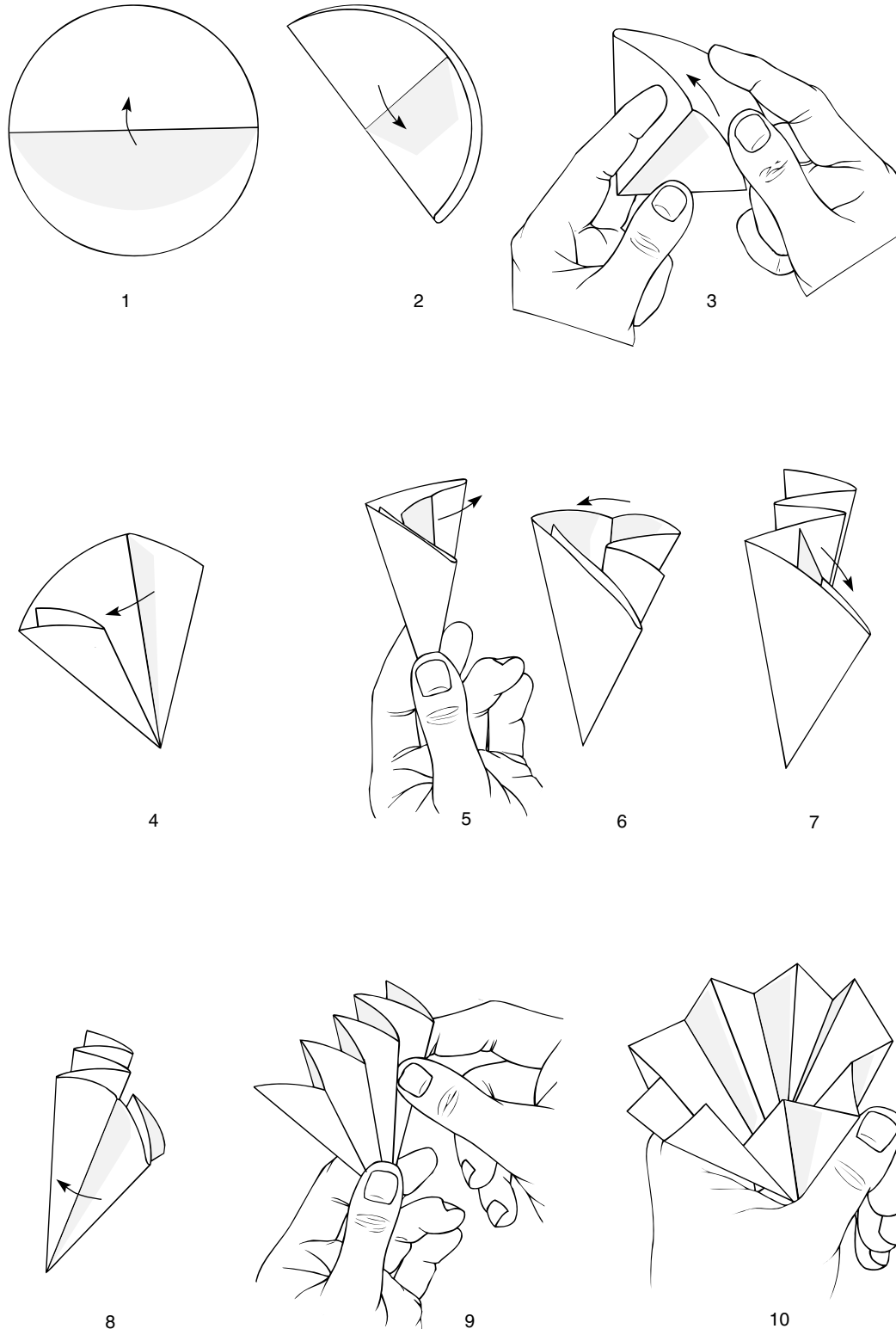


Figure 8.3 Folding a fluted filter paper, or origami at work in the organic chemistry laboratory.

C. Filtering Pipets

A filtering pipet is a microscale technique most often used to remove solid impurities from a liquid with a volume less than 10 mL. It is important that the mixture being filtered be at or near room temperature because it is difficult to prevent premature crystallization in a hot solution saturated with a solute.

To prepare this filtration device, a small piece of cotton is inserted into the top of a Pasteur (disposable) pipet and pushed down to the beginning of the lower constriction in the pipet, as shown in Figure 8.4. It is important to use enough cotton to collect all the solid being filtered; however, the amount of cotton used should not be so large that the flow rate through the pipet is significantly restricted. For the same reason, the cotton should not be packed too tightly. The cotton plug can be pushed down gently with a long thin object such as a glass stirring rod or a wooden applicator stick. It is advisable to wash the cotton plug by passing about 1 mL of solvent (usually the same solvent that is to be filtered) through the filter.

In some cases, such as when filtering a strongly acidic mixture or when performing a very rapid filtration to remove dirt or impurities of large particle size from a solution, it may be better to use glass wool in place of the cotton. The disadvantage in using glass wool is that the fibers do not pack together as tightly, and small particles will pass through the filter more easily.

To conduct a filtration (with either a cotton or glass wool plug), the filtering pipet is clamped so that the filtrate will drain into an appropriate container. The mixture to be filtered is usually transferred to the filtering pipet with another Pasteur pipet. If a small volume of liquid is being filtered (less than 1 mL or 2 mL), it is advisable to rinse the filter and plug with a small amount of solvent after the last of the filtrate has passed through the filter. The rinse solvent is then combined

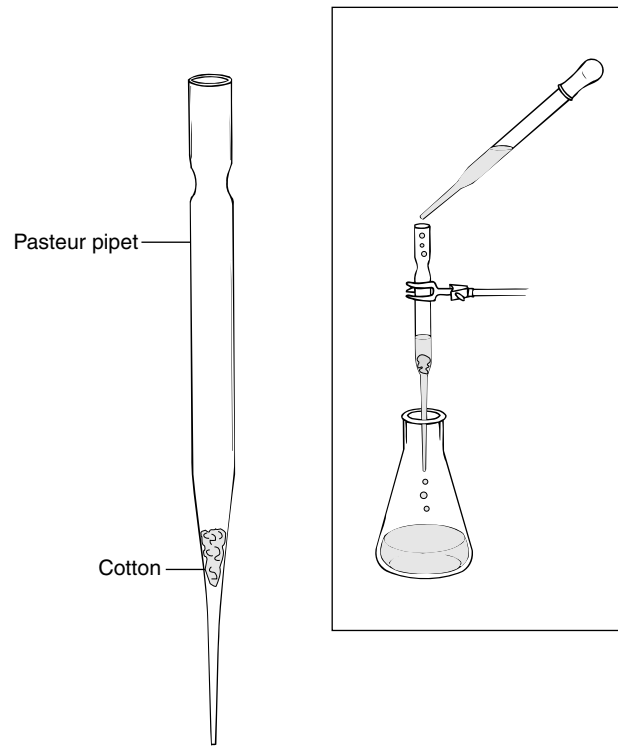


Figure 8.4 A filtering pipet.

with the original filtrate. If desired, the rate of filtration can be increased by gently applying pressure to the top of the pipet using a pipet bulb.

Depending on the amount of solid being filtered and the size of the particles (small particles are more difficult to remove by filtration), it may be necessary to put the filtrate through a second filtering pipet. This should be done with a new filtering pipet rather than with the one already used.

D. Decantation

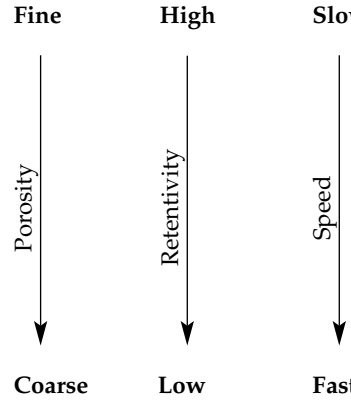
It is not always necessary to use filter paper to separate insoluble particles. If you have large, heavy, insoluble particles, with careful pouring you can decant the solution, leaving behind the solid particles that will settle to the bottom of the flask. The term *decant* means "to carefully pour out the liquid, leaving the insoluble particles behind." For example, boiling stones or sand granules in the bottom of an Erlenmeyer flask filled with a liquid can easily be separated in this way. This procedure is often preferred over filtration and usually results in a smaller loss of material. If there are a large number of particles and they retain a significant amount of the liquid, they can be rinsed with solvent and a second decantation performed. The term *decant* was coined in the wine industry, where it is often necessary to let the wine settle and then carefully pour it out of the original bottle into a clean one, leaving the "must" (insoluble particles) behind.

8.2 Filter Paper

Many kinds and grades of filter paper are available. The paper must be correct for a given application. In choosing filter paper, you should be aware of its various properties. **Porosity** is a measure of the size of the particles that can pass through the paper. Highly porous paper does not remove small particles from solution; paper with low porosity removes very small particles. **Retentivity** is a property that is the opposite of porosity. Paper with low retentivity does not remove small particles from the filtrate. The **speed** of filter paper is a measure of the time it takes a liquid to drain through the filter. Fast paper allows the liquid to drain quickly; with slow paper, it takes much longer to complete the filtration. Because all these properties are related, fast filter paper usually has a low retentivity and high porosity, and slow filter paper usually has high retentivity and low porosity.

Table 8.2 compares some commonly available qualitative filter paper types and ranks them according to porosity, retentivity, and speed. Eaton–Dikeman (E&D),

TABLE 8.2 Some Common Qualitative Filter Paper Types and Approximate Relative Speeds and Retentivities



	Type (by number)		
Speed	**E&D**	**S&S**	**Whatman**
Very slow	610	576	5
Slow	613	602	3
Medium	615	597	2
Fast	617	595	1
Very fast	—	604	4

Schleicher and Schuell (S&S), and Whatman are the most common brands of filter paper. The numbers in the table refer to the grades of paper used by each company.

8.3 Vacuum Filtration

Vacuum, or suction, filtration is more rapid than gravity filtration and is most often used to collect solid products resulting from precipitation or crystallization. This technique is used primarily when the volume of liquid being filtered is more than 1–2 mL. With smaller volumes, use of the Craig tube (see Section 8.7) is the preferred technique. In a vacuum filtration, a receiver flask with a sidearm, a **filter flask**, is used. For macroscale laboratory work, the most useful sizes of filter flasks range from 50 mL to 500 mL, depending on the volume of liquid being filtered. For microscale work, the most useful size is a 50-mL filter flask. The sidearm is connected by *heavy-walled* rubber tubing (see Technique 16, Figure 16.2) to a source of vacuum. Thin-walled tubing will collapse under vacuum, due to atmospheric pressure on its outside walls, and will seal the vacuum source from the flask. Because this apparatus is unstable and can tip over easily, it must be clamped, as shown in Figure 8.5.

CAUTION

It is essential that the filter flask be clamped.

Two types of funnels are useful for vacuum filtration, the Büchner funnel and the Hirsch funnel. The **Büchner funnel** is used for filtering larger amounts of solid from solution in macroscale applications. Büchner funnels are usually made from polypropylene or porcelain. A Büchner funnel (see Figures 8.5 and 8.5A) is sealed

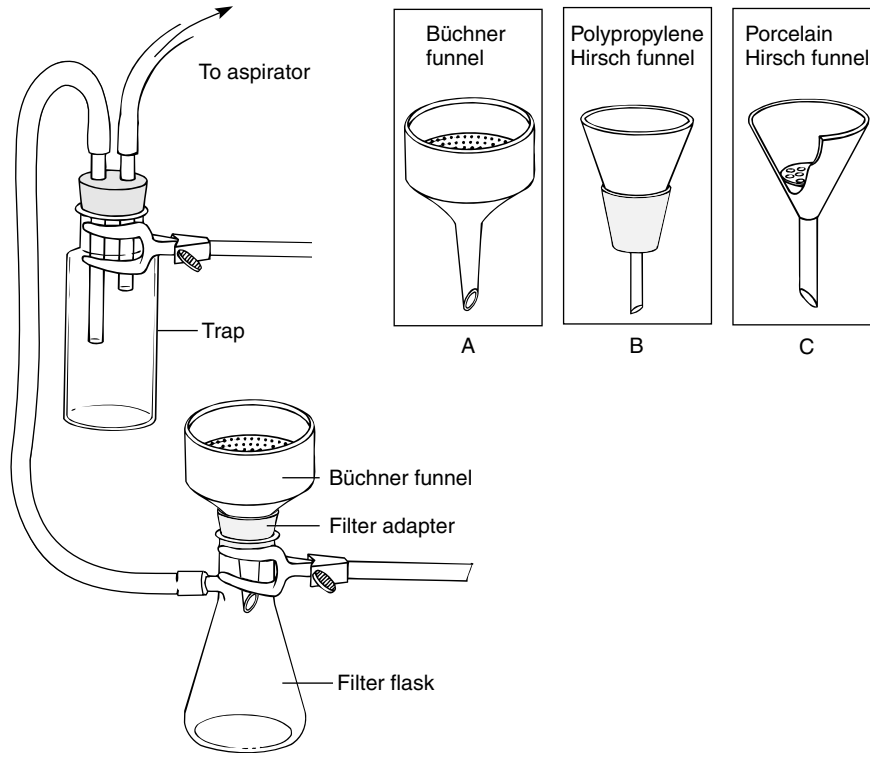


Figure 8.5 Vacuum filtration.

to the filter flask by a rubber stopper or a filter (neoprene) adapter. The flat bottom of the Büchner funnel is covered with an unfolded piece of circular filter paper. To prevent the escape of solid materials from the funnel, you must be certain that the filter paper fits the funnel exactly. It must cover all the holes in the bottom of the funnel, but not extend up the sides. Before beginning the filtration, it is advisable to moisten the paper with a small amount of solvent. The moistened filter paper adheres more strongly to the bottom of the funnel and prevents the unfiltered mixture from passing around the edges of the filter paper.

The **Hirsch funnel**, which is shown in Figures 8.5B and C, operates on the same principle as the Büchner funnel, but it is usually smaller, and its sides are sloped rather than vertical. The Hirsch funnel is used primarily in microscale experiments. The polypropylene Hirsch funnel (see Figure 8.5B) is sealed to a 50-mL filter flask by a small section of Gooch tubing or a one-hole rubber stopper. This Hirsch funnel has a built-in adapter that forms a tight seal with some 25-mL filter flasks without the Gooch tubing. A polyethylene fritted disk fits into the bottom of the funnel. To prevent the holes in this disk from becoming clogged with solid material, the funnel should always be used with a circular filter paper that has the same diameter (1.27 cm) as the polyethylene disk. With a polypropylene Hirsch funnel, it is also important to moisten the paper with a small amount of solvent before beginning the filtration.

The porcelain Hirsch funnel is sealed to the filter flask with a rubber stopper or a neoprene adapter. In this Hirsch funnel, the filter paper must also cover all the holes in the bottom but must not extend up the sides.

Because the filter flask is attached to a source of vacuum, a solution poured into a Büchner funnel or Hirsch funnel is literally "sucked" rapidly through the filter paper. For this reason, vacuum filtration is generally not used to separate fine particles such as decolorizing charcoal, because the small particles would likely be pulled through the filter paper. However, this problem can be alleviated, when desired, by the use of specially prepared filter beds (see Section 8.4).

8.4 Filtering Media

It is occasionally necessary to use specially prepared filter beds to separate fine particles when using vacuum filtration. Often, very fine particles either pass right through a paper filter or clog it so completely that the filtering stops. This is avoided by using a substance called Filter Aid, or Celite. This material is also called **diatomaceous earth** because of its source. It is a finely divided inert material derived from the microscopic shells of dead diatoms (a type of phytoplankton that grows in the sea).

CAUTION

Diatomaceous earth is a lung irritant. When using Filter Aid, take care not to breathe the dust.

Filter Aid will not clog the fiber pores of filter paper. It is **slurried**, mixed with a solvent to form a rather thin paste, and filtered through a Hirsch or Büchner funnel (with filter paper in place) until a layer of diatoms about 2–3 mm thick is formed on top of the filter paper. The solvent in which the diatoms were slurried is poured from the filter flask, and, if necessary, the filter flask is cleaned before the actual filtration is begun. Finely divided particles can now be suction-filtered through this layer and will be caught in the Filter Aid. This technique is used for removing impurities, not for collecting a product. The filtrate (filtered solution) is the desired material in this procedure. If the material caught in the filter were the desired material, you would have to try to separate the product from all those diatoms! Filtration

with Filter Aid is not appropriate when the desired substance is likely to precipitate or crystallize from solution.

In microscale work, it may sometimes be more convenient to use a column prepared with a Pasteur pipet to separate fine particles from a solution. The Pasteur pipet is packed with alumina or silica gel, as shown in Figure 8.6.

8.5 The Aspirator

The most common source of vacuum (approximately 10–20 mmHg) in the laboratory is the water aspirator, or "water pump," illustrated in Figure 8.7. This device passes water rapidly past a small hole to which a sidearm is attached. The water pulls air in through the sidearm. This phenomenon, called the Bernoulli effect, causes a reduced pressure along the side of the rapidly moving water stream and creates a partial vacuum in the sidearm.

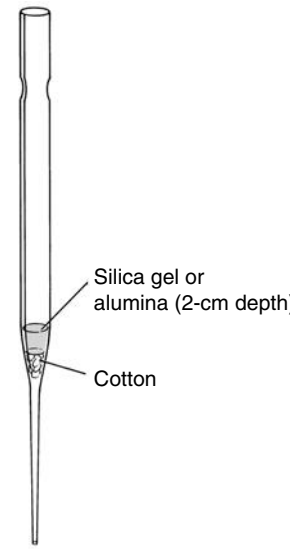


Figure 8.6 A Pasteur pipet with filtering media.

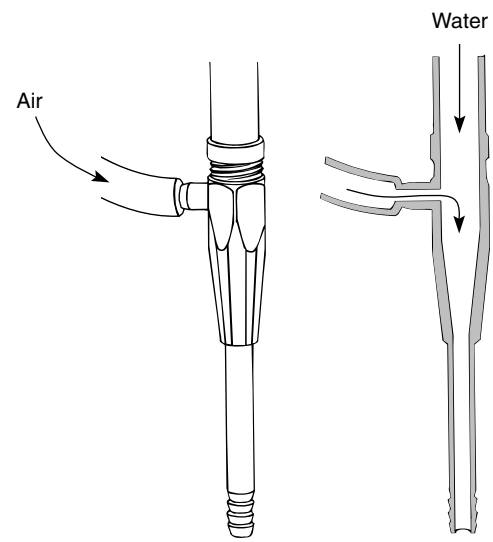


Figure 8.7 An aspirator.

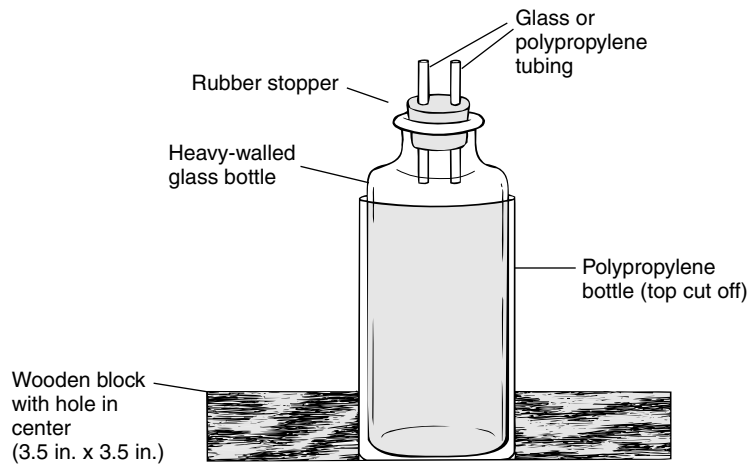


Figure 8.8 A simple aspirator trap and holder.

NOTE: The aspirator works most effectively when the water is turned on to the fullest extent.

A water aspirator can never lower the pressure beyond the vapor pressure of the water used to create the vacuum. Hence, there is a lower limit to the pressure (on cold days) of 9–10 mmHg. A water aspirator does not provide as high a vacuum in the summer as in the winter, due to this water-temperature effect.

A trap must be used with an aspirator. One type of trap is illustrated in Figure 8.5. Another method for securing this type of trap is shown in Figure 8.8. This simple holder can be constructed from readily available material and can be placed anywhere on the laboratory bench. Although not often needed, a trap can prevent water from contaminating your experiment. If the water pressure in the laboratory drops suddenly, the pressure in the filter flask may suddenly become lower than the pressure in the water aspirator. This would cause water to be drawn from the aspirator stream into the filter flask and contaminate the filtrate or even the material in the filter. The trap stops this reverse flow. A similar flow will occur if the water flow at the aspirator is stopped before the tubing connected to the aspirator sidearm is disconnected.

NOTE: Always disconnect the tubing before stopping the aspirator.

If a "backup" begins, disconnect the tubing as rapidly as possible before the trap fills with water. Some chemists like to fit a stopcock into the stopper on top of the trap. A three-hole stopper is required for this purpose. With a stopcock in the trap, the system can be vented before the aspirator is shut off. Then water cannot back up into the trap.

Aspirators do not work well if too many people use the water line at the same time because the water pressure is lowered. Also, the sinks at the ends of the lab benches or the lines that carry away the water flow may have a limited capacity for draining the resultant water flow from too many aspirators. Care must be taken to avoid floods.

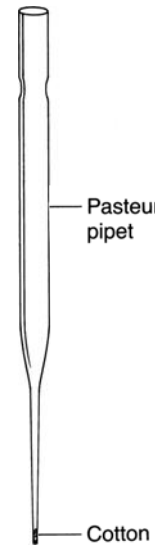


Figure 8.9 A filter-tip pipet.

8.6 Filter-Tip Pipet

The filter-tip pipet, illustrated in Figure 8.9, has two common uses. The first is to remove a small amount of solid, such as dirt or filter paper fibers, from a small volume of liquid (1–2 mL). It can also be helpful when using a Pasteur pipet to transfer a highly volatile liquid, especially during an extraction procedure (see Technique 12, Section 12.5).

Preparing a filter-tip pipet is similar to preparing a filtering pipet, except that a much smaller amount of cotton is used. A *very tiny* piece of cotton is loosely shaped into a ball and placed into the large end of a Pasteur pipet. Using a wire with a diameter slightly smaller than the inside diameter of the narrow end of the pipet, push the ball of cotton to the bottom of the pipet. If it becomes difficult to push the cotton, you have probably started with too much cotton; if the cotton slides through the narrow end with little resistance, you probably have not used enough.

To use a filter-tip pipet as a filter, the mixture is drawn up into the Pasteur pipet using a pipet bulb and then expelled. With this procedure, a small amount of solid will be captured by the cotton. However, very fine particles, such as activated charcoal, cannot be removed efficiently with a filter-tip pipet, and this technique is not effective in removing more than a trace amount of solid from a liquid.

Transferring many organic liquids with a Pasteur pipet can be a somewhat difficult procedure for two reasons. First, the liquid may not adhere well to the glass. Second, as you handle the Pasteur pipet, the temperature of the liquid in the pipet increases slightly, and the increased vapor pressure may tend to "squirt" the liquid out the end of the pipet. This problem can be particularly troublesome when separating two liquids during an extraction procedure. The purpose of the cotton plug in this situation is to slow the rate of flow through the end of the pipet so you can control the movement of liquid in the Pasteur pipet more easily.

8.7 Craig Tubes

The **Craig tube,** illustrated in Figure 8.10, is used primarily to separate crystals from a solution after a microscale crystallization procedure has been performed (see Technique 11, Section 11.4). Although it may not be a filtration procedure in the traditional sense, the outcome is similar. The outer part of the Craig tube is similar to a test tube, except that the diameter of the tube becomes wider part of the way up

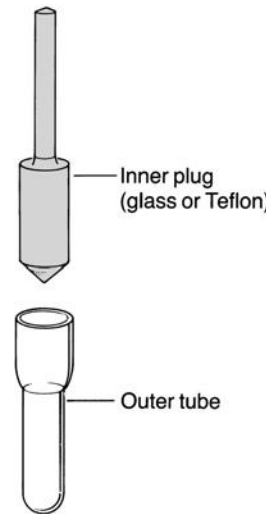


Figure 8.10 A Craig tube (2 mL).

the tube, and the glass is ground at this point so that the inside surface is rough. The inner part (plug) of the Craig tube may be made of Teflon or glass. If this part is glass, the end of the plug is also ground. With either a glass or a Teflon inner plug, there is only a partial seal where the plug and the outer tube come together. Liquid may pass through, but solid will not. This is the place where the solution is separated from the crystals.

After crystallization has been completed in the outer Craig tube, replace the inner plug (if necessary) and connect a thin copper wire or strong thread to the narrow part of the inner plug, as indicated in Figure 8.11A. While holding the Craig tube in an upright position, place a plastic centrifuge tube over the Craig tube so that the bottom of the centrifuge tube rests on top of the inner plug, as shown in Figure 8.11B. The copper wire should extend just below the lip of the centrifuge tube and is now bent upward around the lip of the centrifuge tube. This apparatus is then turned over so that the centrifuge tube is in an upright position. The Craig tube is spun in a centrifuge (be sure it is balanced by placing another tube filled with water on the opposite side of the centrifuge) for several minutes until the **mother liquor** (solution from which the crystals grew) goes to the bottom of the centrifuge tube and the crystals collect on the end of the inner plug (see Figure 8.11C). Depending on the consistency of the crystals and the speed of the centrifuge, the crystals may spin down to the inner plug, or (if you are unlucky) they may remain at the other end of the Craig tube.[1] If the latter situation occurs, it may be helpful to centrifuge the Craig tube longer or, if this problem is anticipated, to stir the crystal-and-solution mixture with a spatula or stirring rod before centrifugation.

[1]Note to the instructor: In some centrifuges, the bottom of the Craig tube may be very close to the center of the centrifuge when the Craig tube assembly is placed into the centrifuge. In this situation, very little centrifugal force will be applied to the crystals, and it is likely that the crystals will not spin down. It may then be helpful to use an inner plug with a shorter stem. The stem on a Teflon inner plug can be easily cut off about 0.5 inch with a pair of wire cutters. This will help to spin down the crystals to the inner plug and the centrifuge can also be run at a lower speed, which can help prevent breakage of the Craig tube.

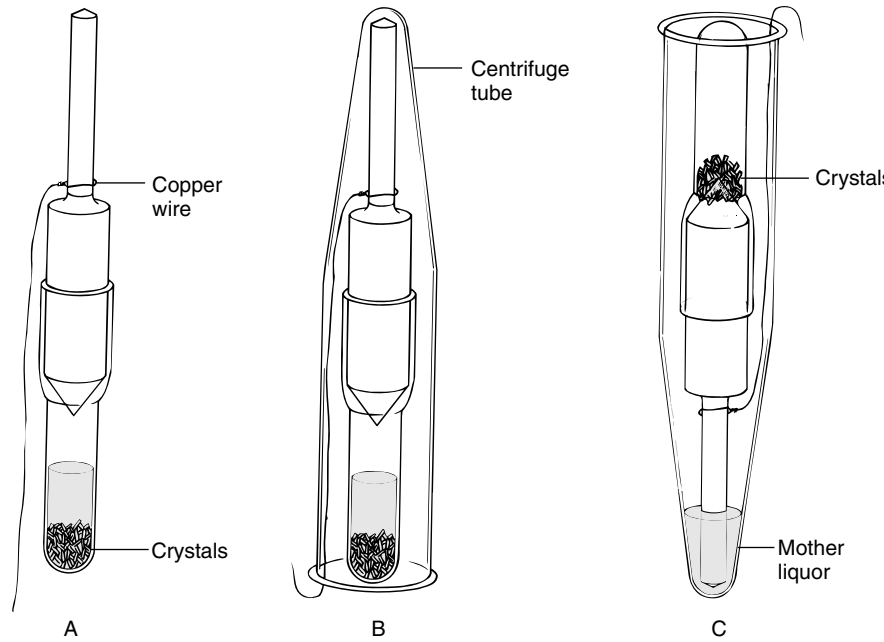


Figure 8.11 Separation with a Craig tube.

Using the copper wire, then pull the Craig tube out of the centrifuge tube. If the crystals are collected on the end of the inner plug, it is now a simple procedure to remove the plug and scrape the crystals with a spatula onto a watch glass, a clay plate, or a piece of smooth paper. Otherwise, it will be necessary to scrape the crystals from the inside surface of the outer part of the Craig tube.

8.8 Centrifugation

Sometimes, centrifugation is more effective than conventional filtration techniques in removing solid impurities. Centrifugation is particularly effective in removing suspended particles, which are so small that the particles would pass through most filtering devices. Centrifugation may also be useful when the mixture must be kept hot to prevent premature crystallization while the solid impurities are removed.

Centrifugation is performed by placing the mixture in one or two centrifuge tubes (be sure to balance the centrifuge) and centrifuging for several minutes. The supernatant liquid is then decanted (poured off) or removed with a Pasteur pipet.

PROBLEM

1. In each of the following situations, what type of filtration device would you use?

- **a.** Remove powdered decolorizing charcoal from 20 mL of solution.
- **b.** Collect crystals obtained from crystallizing a substance from about 1 mL of solution.
- **c.** Remove a very small amount of dirt from 1 mL of liquid.
- **d.** Isolate 2.0 g of crystals from about 50 mL of solution after performing a crystallization.
- **e.** Remove dissolved colored impurities from about 3 mL of solution.
- **f.** Remove solid impurities from 5 mL of liquid at room temperature.

9 TECHNIQUE 9

Physical Constants of Solids: The Melting Point

9.1 Physical Properties

The physical properties of a compound are those properties that are intrinsic to a given compound when it is pure. A compound may often be identified simply by determining a number of its physical properties. The most commonly recognized physical properties of a compound include its color, melting point, boiling point, density, refractive index, molecular weight, and optical rotation. Modern chemists would include the various types of spectra (infrared, nuclear magnetic resonance, mass, and ultraviolet-visible) among the physical properties of a compound. A compound's spectra do not vary from one pure sample to another. Here, we look at methods of determining the melting point. Boiling point and density of compounds are covered in Technique 13. Refractive index, optical rotation, and spectra are also considered separately.

Many reference books list the physical properties of substances. You should consult Technique 4 for a complete discussion on how to find data for specific compounds. The works most useful for finding lists of values for the nonspectroscopic physical properties include:

The Merck Index

The CRC Handbook of Chemistry and Physics

Lange's Handbook of Chemistry

Aldrich Handbook of Fine Chemicals

Complete citations for these references can be found in Technique 29. Although the *CRC Handbook* has very good tables, it adheres strictly to IUPAC nomenclature. For this reason, it may be easier to use one of the other references, particularly *The Merck Index* or the *Aldrich Handbook of Fine Chemicals,* in your first attempt to locate information (see Technique 4).

9.2 The Melting Point

The melting point of a compound is used by the organic chemist not only to identify the compound, but also to establish its purity. A small amount of material is heated *slowly* in a special apparatus equipped with a thermometer or thermocouple, a heating bath or heating coil, and a magnifying eyepiece for observing the sample. Two temperatures are noted. The first is the point at which the first drop of liquid forms among the crystals; the second is the point at which the whole mass of crystals turns to a *clear* liquid. The melting point is recorded by giving this range of melting. You might say, for example, that the melting point of a substance is 51–54°C. That is, the substance melted over a 3-degree range.

The melting point indicates purity in two ways. First, the purer the material, the higher its melting point. Second, the purer the material, the narrower its melting-point range. Adding successive amounts of an impurity to a pure substance generally causes its melting point to decrease in proportion to the amount of impurity. Looking at it another way, adding impurities lowers the freezing point. The freezing point, a colligative property, is simply the melting point (solid → liquid) approached from the opposite direction (liquid → solid).

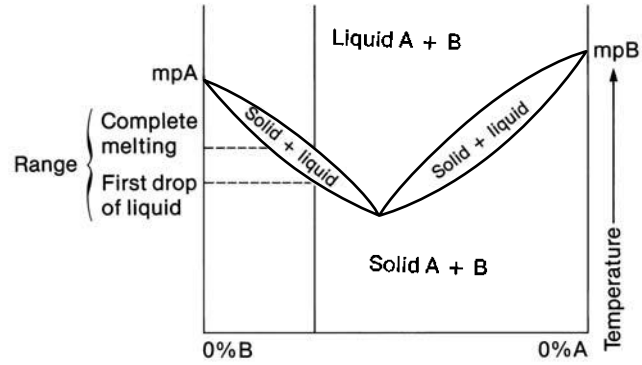


Figure 9.1 A melting-point–composition curve.

Figure 9.1 is a graph of the usual melting-point behavior of mixtures of two substances, A and B. The two extremes of the melting range (the low and high temperature) are shown for various mixtures of the two. The upper curves indicate the temperatures at which all the sample has melted. The lower curves indicate the temperature at which melting is observed to begin. With pure compounds, melting is sharp and without any range. This is shown at the left- and right-hand edges of the graph. If you begin with pure A, the melting point decreases as impurity B is added. At some point, a minimum temperature, or **eutectic**, is reached, and the melting point begins to increase to that of substance B. The vertical distance between the lower and upper curves represents the melting range. Notice that for mixtures that contain relatively small amounts of impurity (< 15%) and are not close to the eutectic, the melting range increases as the sample becomes less pure. The range indicated by the lines in Figure 9.1 represents the typical behavior.

We can generalize the behavior shown in Figure 9.1. Pure substances melt with a narrow range of melting. With impure substances, the melting range becomes wider, and the entire melting range is lowered. Be careful to note, however, that at the minimum point of the melting-point–composition curves, the mixture often forms a eutectic, which also melts sharply. Not all binary mixtures form eutectics, and some caution must be exercised in assuming that every binary mixture follows the previously described behavior. Some mixtures may form more than one eutectic; others might not form even one. In spite of these variations, both the melting point and its range are useful indications of purity, and they are easily determined by simple experimental methods.

9.3 Melting-Point Theory

Figure 9.2 is a phase diagram describing the usual behavior of a two-component mixture (A + B) on melting. The behavior on melting depends on the relative amounts of A and B in the mixture. If A is a pure substance (no B), then A melts sharply at its melting point t_A. This is represented by point A on the left side of the diagram. When B is a pure substance, it melts at t_B; its melting point is represented by point B on the right side of the diagram. At either point A or point B, the pure solid passes cleanly, with a narrow range, from solid to liquid.

In mixtures of A and B, the behavior is different. Using Figure 9.2, consider a mixture of 80% A and 20% B on a mole-per-mole basis (that is, mole percentage). The melting point of this mixture is given by t_M at point M on the diagram. That is, adding B to A has lowered the melting point of A from t_A to t_M. It has also expanded

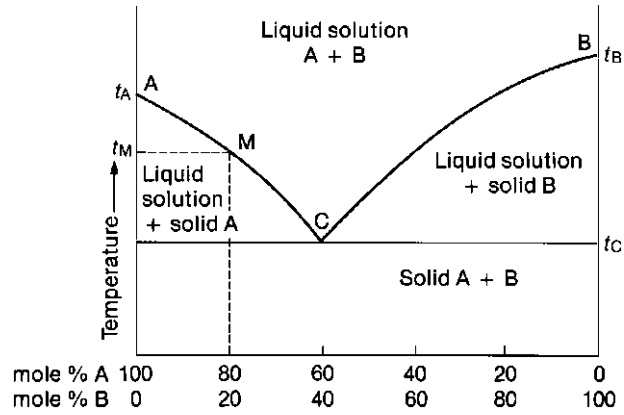


Figure 9.2 A phase diagram for melting in a two-component system.

the melting range. The temperature t_M corresponds to the **upper limit** of the melting range.

Lowering the melting point of A by adding impurity B comes about in the following way. Substance A has the lower melting point in the phase diagram shown, and if heated, it begins to melt first. As A begins to melt, solid B begins to dissolve in the liquid A that is formed. When solid B dissolves in liquid A, the melting point is depressed. To understand this, consider the melting point from the opposite direction. When a liquid at a high temperature cools, it reaches a point at which it solidifies, or "freezes." The temperature at which a liquid freezes is identical to its melting point. Recall that the freezing point of a liquid can be lowered by adding an impurity. Because the freezing point and the melting point are identical, lowering the freezing point corresponds to lowering the melting point. Therefore, as more impurity is added to a solid, its melting point becomes lower. There is, however, a limit to how far the melting point can be depressed. You cannot dissolve an infinite amount of the impurity substance in the liquid. At some point, the liquid will become saturated with the impurity substance. The solubility of B in A has an upper limit. In Figure 9.2, the solubility limit of B in liquid A is reached at point C, the **eutectic point**. The melting point of the mixture cannot be lowered below t_C, the melting temperature of the eutectic.

Now consider what happens when the melting point of a mixture of 80% A and 20% B is approached. As the temperature is increased, A begins to "melt." This is not really a visible phenomenon in the beginning stages; it happens before liquid is visible. It is a softening of the compound to a point at which it can begin to mix with the impurity. As A begins to soften, it dissolves B. As it dissolves B, the melting point is lowered. The lowering continues until all B is dissolved or until the eutectic composition (saturation) is reached. When the maximum possible amount of B has been dissolved, actual melting begins, and one can observe the first appearance of liquid. The initial temperature of melting will be below t_A. The amount below t_A at which melting begins is determined by the amount of B dissolved in A, but will never be below t_C. Once all B has been dissolved, the melting point of the mixture begins to rise as more A begins to melt. As more A melts, the semisolid solution is diluted by more A, and its melting point rises. While all this is happening, you can observe *both* solid and liquid in the melting-point capillary. Once all A has begun to melt, the composition of the mixture M becomes uniform and will reach 80% A and 20% B. At this point, the mixture finally melts sharply, giving a clear solution.

The maximum melting-point range will be $t_C - t_M$, because t_A is depressed by the impurity B that is present. The lower end of the melting range will always be t_C; however, melting will not always be observed at this temperature. An observable melting at t_C comes about only when a large amount of B is present. Otherwise, the amount of liquid formed at t_C will be too small to observe. Therefore, the melting behavior that is actually observed will have a smaller range, as shown in Figure 9.1.

9.4 Mixture Melting Points

The melting point can be used as supporting evidence in identifying a compound in two different ways. Not only may the melting points of the two individual compounds be compared, but a special procedure called a **mixture melting point** may also be performed. The mixture melting point requires that an authentic sample of the same compound be available from another source. In this procedure, the two compounds (authentic and suspected) are finely pulverized and mixed together in equal quantities. Then the melting point of the mixture is determined. If there is a melting-point depression or if the range of melting is expanded by a large amount compared to that of the individual substances, you may conclude that one compound has acted as an impurity toward the other and that they are not the same compound. If there is no lowering of the melting point for the mixture (the melting point is identical with those of pure A and pure B), then A and B are almost certainly the same compound.

9.5 Packing the Melting-Point Tube

Melting points are usually determined by heating the sample in a piece of thin-walled capillary tubing (1 mm × 100 mm) that has been sealed at one end. To pack the tube, press the open end gently into a *pulverized* sample of the crystalline material. Crystals will stick in the open end of the tube. The amount of solid pressed into the tube should correspond to a column no more than 1–2 mm high. To transfer the crystals to the closed end of the tube, drop the capillary tube, closed end first, down a $\frac{2}{3}$-m length of glass tubing, which is held upright on the desktop. When the capillary tube hits the desktop, the crystals will pack down into the bottom of the tube. This procedure is repeated if necessary. Tapping the capillary on the desktop with fingers is not recommended because it is easy to drive the small tubing into a finger if the tubing should break.

Some commercial melting-point instruments have a built-in vibrating device that is designed to pack capillary tubes. With these instruments, the sample is pressed into the open end of the capillary tube, and the tube is placed in the vibrator slot. The action of the vibrator will transfer the sample to the bottom of the tube and pack it tightly.

9.6 Determining the Melting Point—The Thiele Tube

There are two principal types of melting-point apparatus available: the Thiele tube and commercially available, electrically heated instruments. The Thiele tube, shown in Figure 9.3, is the simpler device and was once widely used. It is a glass tube designed to contain a heating oil (mineral oil or silicone oil) and a thermometer to which a capillary tube containing the sample is attached. The shape of the Thiele tube allows convection currents to form in the oil when it is heated. These currents maintain a uniform temperature distribution through the oil in the tube. The sidearm of the tube is designed to generate these convection currents and thus transfer the heat from the flame evenly and rapidly throughout the oil. The sample, which is in a capillary tube attached to the thermometer, is held by a rubber band or a thin slice of rubber tubing. It is important that this rubber band be above the level of the

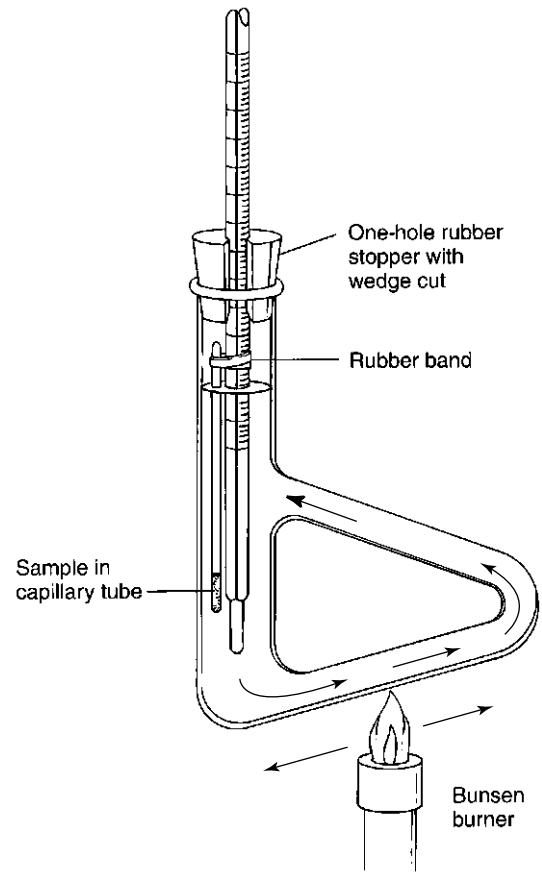


Figure 9.3 A Thiele tube.

oil (allowing for expansion of the oil on heating) so that the oil does not soften the rubber and allow the capillary tubing to fall into the oil. If a cork or a rubber stopper is used to hold the thermometer, a triangular wedge should be sliced in it to allow pressure equalization.

The Thiele tube is usually heated by a microburner. During the heating, the rate of temperature increase should be regulated. Hold the burner by its cool base and, using a low flame, move the burner slowly back and forth along the bottom of the arm of the Thiele tube. If the heating is too fast, remove the burner for a few seconds and then resume heating. The rate of heating should be *slow* near the melting point (about 1°C per minute) to ensure that the temperature increase is not faster than the rate at which heat can be transferred to the sample being observed. At the melting point, it is necessary that the mercury in the thermometer and the sample in the capillary tube be at temperature equilibrium.

9.7 Determining the Melting Point—Electrical Instruments

Three types of electrically heated melting-point instruments are illustrated in Figure 9.4. In each case, the melting-point tube is filled as described in Section 9.5 and placed in a holder located just behind the magnifying eyepiece. The apparatus is operated by moving the switch to the ON position, adjusting the potentiometric

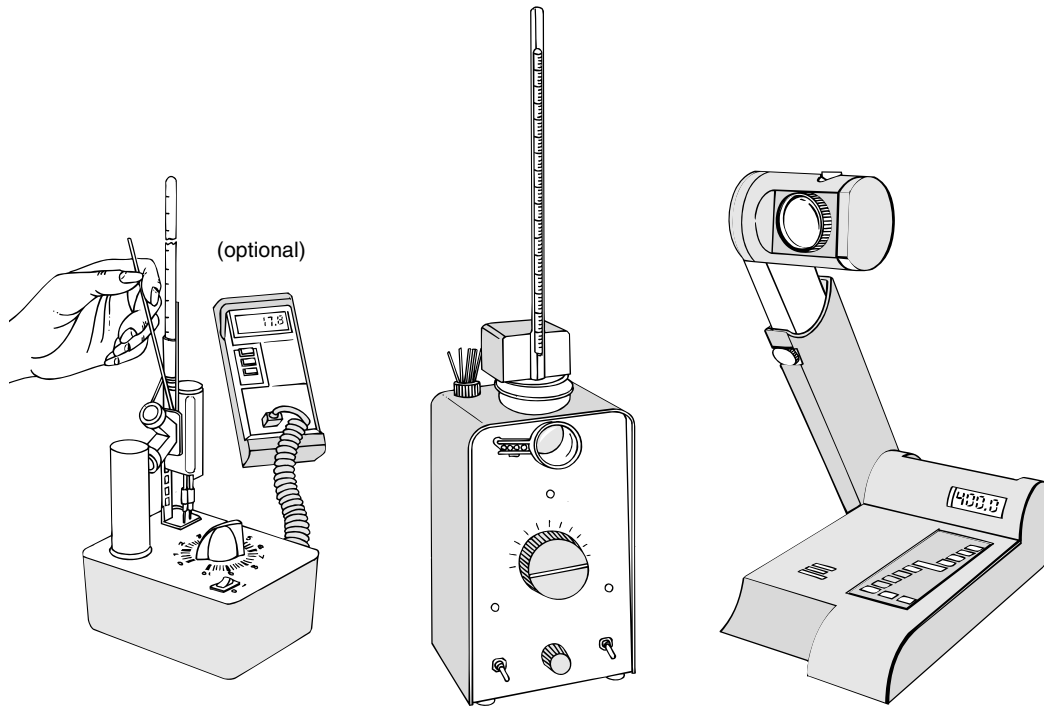


Figure 9.4 Melting-point apparatus.

control dial for the desired rate of heating, and observing the sample through the magnifying eyepiece. The temperature is read from a thermometer or, in the most modern instruments, from a digital display attached to a thermocouple. Your instructor will demonstrate and explain the type used in your laboratory.

Most electrically heated instruments do not heat or increase the temperature of the sample linearly. Although the rate of increase may be linear in the early stages of heating, it usually decreases and leads to a constant temperature at some upper limit. The upper-limit temperature is determined by the setting of the heating control. Thus, a family of heating curves is usually obtained for various control settings, as shown in Figure 9.5. The four hypothetical curves shown (1–4) might correspond to different control settings. For a compound melting at temperature t_1, the setting corresponding to curve 3 would be ideal. In the beginning of the curve, the temperature is increasing too rapidly to allow determination of an accurate melting point, but after the change in slope, the temperature increase will have slowed to a more usable rate.

If the melting point of the sample is unknown, you can often save time by preparing two samples for melting-point determination. With one sample, you can rapidly determine a crude melting-point value. Then repeat the experiment more carefully using the second sample. For the second determination, you already have an approximate idea of what the melting-point temperature should be, and a proper rate of heating can be chosen.

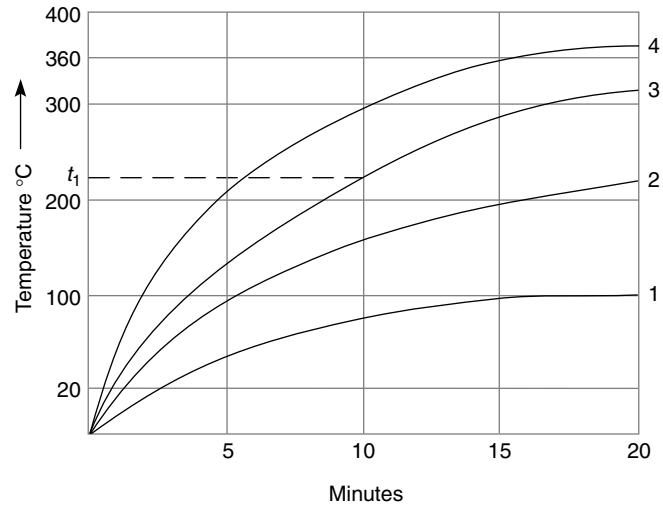


Figure 9.5 Heating-rate curves.

When measuring temperatures above 150°C, thermometer errors can become significant. For an accurate melting point with a high-melting solid, you may wish to apply a **stem correction** to the thermometer as described in Technique 13, Section 13.4. An even better solution is to calibrate the thermometer as described in Section 9.9.

9.8 Decomposition, Discoloration, Softening, Shrinkage, and Sublimation

Many solid substances undergo some degree of unusual behavior before melting. At times it may be difficult to distinguish these types of behavior from actual melting. You should learn, through experience, how to recognize melting and how to distinguish it from decomposition, discoloration, and, particularly, softening and shrinkage.

Some compounds decompose on melting. This decomposition is usually evidenced by discoloration of the sample. Frequently, this decomposition point is a reliable physical property to be used in lieu of an actual melting point. Such decomposition points are indicated in tables of melting points by placing the symbol *d* immediately after the listed temperature. An example of a decomposition point is thiamine hydrochloride, whose melting point would be listed as 248°d, indicating that this substance melts with decomposition at 248°C. When decomposition is a result of reaction with the oxygen in air, it may be avoided by determining the melting point in a sealed, evacuated melting-point tube.

Figure 9.6 shows two simple methods of evacuating a packed tube. Method A uses an ordinary melting-point tube, and method B constructs the melting-point tube from a disposable Pasteur pipet. Before using method B, be sure to determine that the tip of the pipet will fit into the sample holder in your melting-point instrument.

Method A

In method A, a hole is punched through a rubber septum using a large pin or a small nail, and the capillary tube is inserted from the inside, sealed end first. The septum is placed over a piece of glass tubing connected to a vacuum line. After the tube is evacuated, the upper end of the tube may be sealed by heating and pulling it closed.

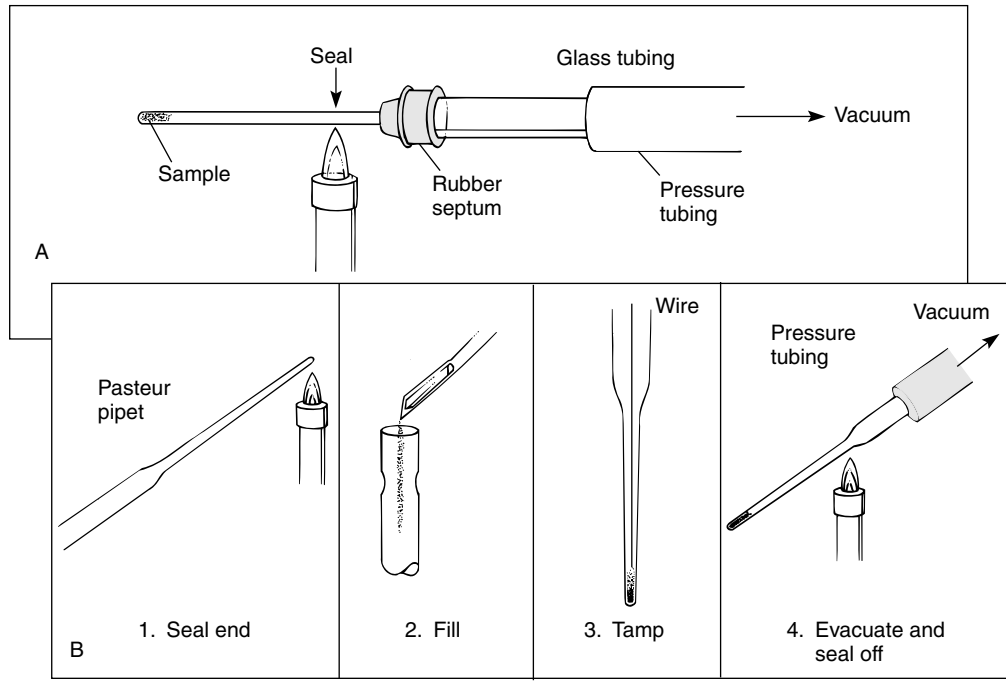


Figure 9.6 Evacuation and sealing of a melting-point capillary.

Method B

In method B, the thin section of a 9-inch Pasteur pipet is used to construct the melting-point tube. Carefully seal the tip of the pipet using a flame. Be sure to hold the tip *upward* as you seal it. This will prevent water vapor from condensing inside the pipet. When the sealed pipet has cooled, the sample may be added through the open end using a microspatula. A small wire may be used to compress the sample into the closed tip. (If your melting-point apparatus has a vibrator, it may be used in place of the wire to simplify the packing.) When the sample is in place, the pipet is connected to the vacuum line with tubing and evacuated. The evacuated sample tube is sealed by heating it with a flame and pulling it closed.

Some substances begin to decompose *below* their melting points. Thermally unstable substances may undergo elimination reactions or anhydride formation reactions during heating. The decomposition products formed represent impurities in the original sample, so the melting point of the substance may be lowered due to their presence.

It is normal for many compounds to soften or shrink immediately before melting. Such behavior represents not decomposition, but a change in the crystal structure or a mixing with impurities. Some substances "sweat," or release solvent of crystallization, before melting. These changes do not indicate the beginning of melting. Actual melting begins when the first drop of liquid becomes visible, and the melting range continues until the temperature is reached at which all the solid has been converted to the liquid state. With experience, you soon learn to distinguish between softening, or "sweating," and actual melting. If you wish, the temperature of the onset of softening or sweating may be reported as a part of your melting-point range: 211°C (softens), 223–225°C (melts).

Some solid substances have such a high vapor pressure that they sublime at or below their melting points. In many handbooks, the sublimation temperature is listed along with the melting point. The symbols *sub, subl,* and sometimes *s* are used

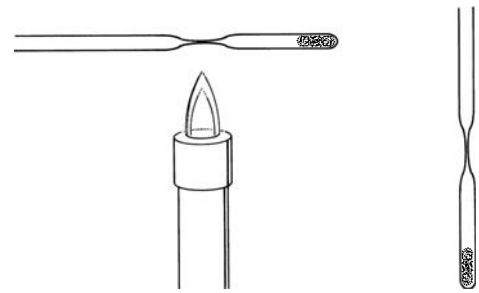


Figure 9.7 Sealing a tube for a substance that sublimes.

to designate a substance that sublimes. In such cases, the melting-point determination must be performed in a sealed capillary tube to avoid loss of the sample. The simplest way to accomplish sealing a packed tube is to heat the open end of the tube in a flame and pull it closed with tweezers or forceps. A better way, although more difficult to master, is to heat the center of the tube in a small flame, rotating it about its axis and keeping the tube straight until the center collapses. If this is not done quickly, the sample may melt or sublime while you are working. With the smaller chamber, the sample will not be able to migrate to the cool top of the tube that may be above the viewing area. Figure 9.7 illustrates the method.

9.9 Thermometer Calibration

When a melting-point or boiling-point determination has been completed, you expect to obtain a result that exactly duplicates the result recorded in a handbook or in the original literature. It is not unusual, however, to find a discrepancy of several degrees from the literature value. Such a discrepancy does not necessarily indicate that the experiment was incorrectly performed or that the material is impure; rather, it may indicate that the thermometer used for the determination was slightly in error. Most thermometers do not measure the temperature with perfect accuracy.

To determine accurate values, you must calibrate the thermometer that is used. This calibration is done by determining the melting points of a variety of standard substances with the thermometer. A plot is drawn of the observed temperature vs. the published value of each standard substance. A smooth line is drawn through the points to complete the chart. A correction chart prepared in this way is shown in Figure 9.8. This chart is used to correct any melting point determined with that particular thermometer. Each thermometer requires its own calibration curve. A list of suitable standard substances for calibrating thermometers is provided in Table 9.1. The standard substances, of course, must be pure in order for the corrections to be valid.

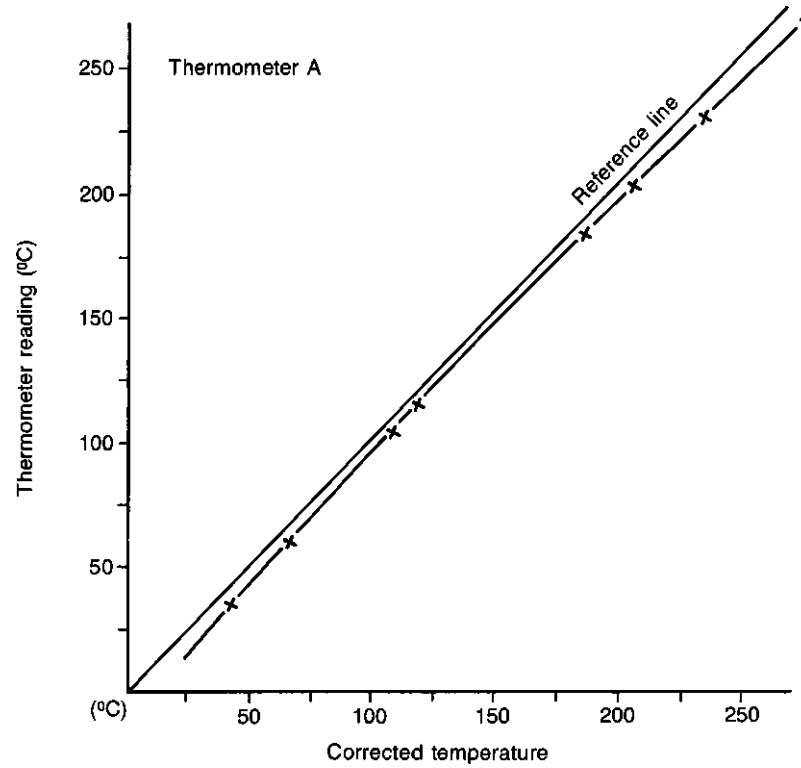


Figure 9.8 A thermometer-calibration curve.

TABLE 9.1 Melting-Point Standards

Compound	Melting Point (°C)
Ice (solid–liquid water)	0
Acetanilide	115
Benzamide	128
Urea	132
Succinic acid	189
3,5-Dinitrobenzoic acid	205

PROBLEMS

1. Two substances, A and B, have the same melting point. How can you determine if they are the same without using any form of spectroscopy? Explain in detail.
2. Using Figure 9.5, determine which heating curve would be most appropriate for a substance with a melting point of about 150°C.
3. What steps can you take to determine the melting point of a substance that sublimes before it melts?
4. A compound melting at 134°C was suspected to be either aspirin (mp 135°C) or urea (mp 133°C). Explain how you could determine whether one of these two suspected compounds was identical to the unknown compound without using any form of spectroscopy.
5. An unknown compound gave a melting point of 230°C. When the molten liquid solidified, the melting point was redetermined and found to be 131°C. Give a possible explanation for this discrepancy.

10 TECHNIQUE 10

Solubility

The solubility of a **solute** (a dissolved substance) in a **solvent** (the dissolving medium) is the most important chemical principle underlying three basic techniques you will study in the organic chemistry laboratory: crystallization, extraction, and chromatography. In this discussion of solubility, you will gain an understanding of the structural features of a substance that determine its solubility in various solvents. This understanding will help you to predict solubility behavior and to understand the techniques that are based on this property. Understanding solubility behavior will also help you understand what is going on during a reaction, especially when there is more than one liquid phase present or when a precipitate is formed.

10.1 Definition of Solubility

Although we often describe solubility behavior in terms of a substance being **soluble** (dissolved) or **insoluble** (not dissolved) in a solvent, solubility can be described more precisely in terms of the *extent* to which a substance is soluble. Solubility may be expressed in terms of grams of solute per liter (g/L) or milligrams of solute per milliliter (mg/mL) of solvent. Consider the solubilities at room temperature for the following three substances in water:

Cholesterol	0.002 mg/mL
Caffeine	22 mg/mL
Citric acid	620 mg/mL

In a typical test for solubility, 40 mg of solute is added to 1 mL of solvent. Therefore, if you were testing the solubility of these three substances, cholesterol would be insoluble, caffeine would be partially soluble, and citric acid would be soluble. Note that a small amount (0.002 mg) of cholesterol would dissolve. It is very unlikely, however, that you would be able to observe this small amount dissolving, and you would report that cholesterol is insoluble. On the other hand, 22 mg (55%) of the caffeine would dissolve. It is likely that you would be able to observe this, and you would state that caffeine is partially soluble.

When the solubility of a liquid solute in a solvent is described, it is sometimes helpful to use the terms **miscible** and **immiscible**. Two liquids that are miscible will mix homogeneously (one phase) in all proportions. For example, water and ethyl alcohol are miscible. When they are mixed in any proportion, only one layer will be observed. When two liquids are miscible, it is also true that either one of them will be completely soluble in the other one. Two immiscible liquids do not mix homogeneously in all proportions, and under some conditions they will form two layers. Water and diethyl ether are immiscible. When mixed in roughly equal amounts, they will form two layers. However, each liquid is slightly soluble in the other one. Even when two layers are present, a small amount of water will be soluble in the diethyl ether, and a small amount of diethyl ether will be soluble in the water. Furthermore, if only a small amount of either one is added to the other, it may dissolve completely, and only one layer will be observed. For example, if a small amount of water (less than 1.2% at 20°C) is added to diethyl ether, the water will dissolve completely in the diethyl ether, and only one layer will be observed. When more water

is added (more than 1.2%), some of the water will not dissolve, and two layers will be present.

Although the terms *solubility* and *miscibility* are related in meaning, it is important to understand that there is one essential difference. There can be different degrees of solubility, such as slightly, partially, very, and so on. Unlike solubility, miscibility does not have any degrees—a pair of liquids is either miscible, or it is not.

10.2 Predicting Solubility Behavior

A major goal of this section is to explain how to predict whether a substance will be soluble in a given solvent. This is not always easy, even for an experienced chemist. However, guidelines will help you make a good guess about the solubility of a compound in a specific solvent. In discussing these guidelines, it is helpful to separate the types of solutions we will be looking at into two categories: solutions in which both the solvent and the solute are covalent (molecular) and ionic solutions, in which the solute ionizes and dissociates.

A. Solutions in Which the Solvent and Solute Are Molecular

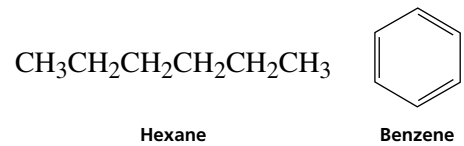
A useful generalization in predicting solubility is the widely used rule "Like dissolves like." This rule is most commonly applied to polar and nonpolar compounds. According to this rule, a polar solvent will dissolve polar (or ionic) compounds, and a nonpolar solvent will dissolve nonpolar compounds.

The reason for this behavior involves the nature of intermolecular forces of attraction. Although we will not be focusing on the nature of these forces, it is helpful to know what they are called. The force of attraction between polar molecules is called **dipole–dipole interaction**; between nonpolar molecules, forces of attraction are called **van der Waals forces** (also called **London** or **dispersion forces**). In both cases, these attractive forces can occur between molecules of the same compound or different compounds. Consult your lecture textbook for more information on these forces.

To apply the rule "Like dissolves like," you must first determine whether a substance is polar or nonpolar. The polarity of a compound is dependent on both the polarities of the individual bonds and the shape of the molecule. For most organic compounds, evaluating these factors can become quite complicated because of the complexities of the molecules. However, it is possible to make some reasonable predictions just by looking at the types of atoms that a compound possesses. As you read the following guidelines, it is important to understand that although we often describe compounds as being polar or nonpolar, polarity is a matter of degree, ranging from nonpolar to highly polar.

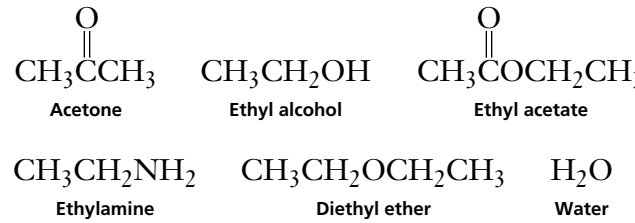
Guidelines for Predicting Polarity and Solubility

1. All hydrocarbons are nonpolar.
Examples:



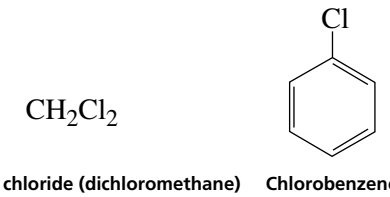
Hydrocarbons such as benzene are slightly more polar than hexane because of their pi (π) bonds, which allow for greater van der Waals or London attractive forces.

2. Compounds possessing the electronegative elements oxygen or nitrogen are polar.
   Examples:



   The polarity of these compounds depends on the presence of polar C—O, C═O, OH, NH, and CN bonds. The compounds that are most polar are capable of forming hydrogen bonds (see Guideline 6) and have NH or OH bonds. Although all of these compounds are polar, the degree of polarity ranges from slightly polar to highly polar. This is due to the effect on polarity of the shape of the molecule and size of the carbon chain, and whether the compound can form hydrogen bonds.

3. The presence of halogen atoms, even though their electronegativities are relatively high, does not alter the polarity of an organic compound in a significant way. Therefore, these compounds are only slightly polar. The polarities of these compounds are more similar to those of hydrocarbons, which are nonpolar, than to that of water, which is highly polar.
   Examples:



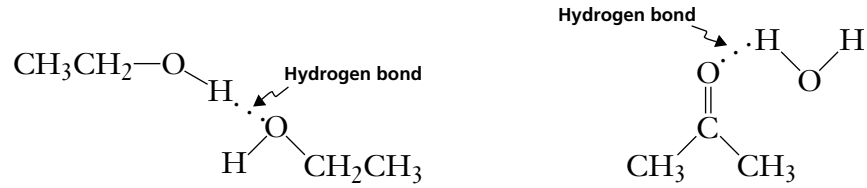
   Methylene chloride (dichloromethane) **Chlorobenzene**

4. When comparing organic compounds within the same family, note that adding carbon atoms to the chain decreases the polarity. For example, methyl alcohol (CH_3OH) is more polar than propyl alcohol ($CH_3CH_2CH_2OH$). The reason is that hydrocarbons are nonpolar, and increasing the length of a carbon chain makes the compound more hydrocarbon-like.

5. Compounds that contain four or fewer carbons and also contain oxygen or nitrogen are often soluble in water. Almost any functional group containing these elements will lead to water solubility for low-molecular-weight (up to C_4) compounds. Compounds having five or six carbons and containing one of these elements are often insoluble in water or have borderline solubility.

6. As mentioned earlier, the force of attraction between polar molecules is dipole–dipole interaction. A special case of dipole–dipole interaction is hydrogen bonding. Hydrogen bonding is a possibility when a compound possesses a hydrogen atom bonded to a nitrogen, oxygen, or fluorine atom. The bond is formed by the attraction between this hydrogen atom and a nitrogen, oxygen, or fluorine atom in another molecule. Hydrogen bonding may occur between

two molecules of the same compound or between molecules of different compounds:



Hydrogen bonding is the strongest type of dipole–dipole interaction. When hydrogen bonding between solute and solvent is possible, solubility is greater than one would expect for compounds of similar polarity that cannot form hydrogen bonds. Hydrogen bonding is very important in organic chemistry, and you should be alert for situations in which hydrogen bonding may occur.

7. Another factor that can affect solubility is the degree of branching of the alkyl chain in a compound. Branching of the alkyl chain in a compound lowers the intermolecular forces between the molecules. This is usually reflected in a greater solubility in water for the branched compound than for the corresponding straight-chain compound. This occurs simply because the molecules of the branched compounds are more easily separated from one another.
8. The solubility rule ("Like dissolves like") may be applied to organic compounds that belong to the same family. For example, 1-octanol (an alcohol) is soluble in the solvent ethyl alcohol. Most compounds within the same family have similar polarity. However, this generalization may not apply if there is a substantial difference in size between the two compounds. For example, cholesterol, an alcohol with a molecular weight (MW) of 386.64, is only slightly soluble in methanol (MW 32.04). The large hydrocarbon component of cholesterol negates the fact that they belong to the same family.
9. Almost all organic compounds that are in the ionic form are water soluble (see next section B - Solutions in Which the Solute Ionizes and Dissociates).
10. The stability of the crystal lattice also affects solubility. Other things being equal, the higher the melting point (the more stable the crystal), the less soluble the compound. For instance, *p*-nitrobenzoic acid (mp 242°C) is, by a factor of 10, less soluble in a fixed amount of ethanol than the *ortho* (mp 147°C) and *meta* (mp 141°C) isomers.

You can check your understanding of some of these guidelines by studying the list given in Table 10.1, which is given in order of increasing polarity. The structures of these compounds are given above.

This list can be used to make some predictions about solubility, based on the rule "Like dissolves like." Substances that are close to one another on this list will have similar polarities. Thus, you would expect hexane to be soluble in methylene chloride, but not in water. Acetone should be soluble in ethyl alcohol. On the other hand, you might predict that ethyl alcohol would be insoluble in hexane. However, ethyl alcohol is soluble in hexane because ethyl alcohol is somewhat less polar than methyl alcohol or water. This last example demonstrates that you must be careful in using the guidelines on polarity for predicting solubilities. Ultimately, solubility tests must be done to confirm predictions until you gain more experience.

The trend in polarities shown in Table 10.1 can be expanded by including more organic families. The list in Table 10.2 gives an approximate order for the increasing polarity of organic functional groups. It may appear that there are some discrepancies

TABLE 10.1 Compounds in Increasing Order of Polarity

Increasing Polarity ↓
Aliphatic hydrocarbons
Hexane (nonpolar)
Aromatic hydrocarbons (π bonds)
Benzene (nonpolar)
Halocarbons
Methylene chloride (slightly polar)
Compounds with polar bonds
Diethyl ether (slightly polar)
Ethyl acetate (intermediate polarity)
Acetone (intermediate polarity)
Compounds with polar bonds and hydrogen bonding
Ethyl alcohol (intermediate polarity)
Methyl alcohol (intermediate polarity)
Water (highly polar)

TABLE 10.2 Solvents in Increasing Order of Polarity

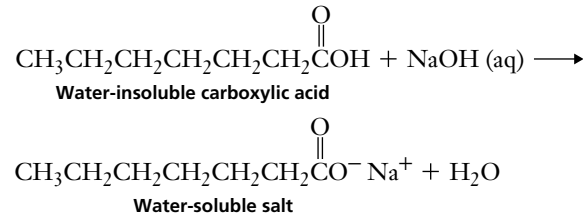
Increasing Polarity (Approximate) ↓	
RH	Alkanes (hexane, petroleum ether)
ArH	Aromatics (benzene, toluene)
ROR	Ethers (diethyl ether)
RX	Halides (CH_2Cl_2 > $CHCl_3$ > CCl_4)
RCOOR	Esters (ethyl acetate)
RCOR	Aldehydes, ketones (acetone)
RNH_2	Amines (triethylamine, pyridine)
ROH	Alcohols (methanol, ethanol)
$RCONH_2$	Amides (N,N-dimethylformamide)
RCOOH	Organic acids (acetic acid)
H_2O	Water

between the information provided in these two tables. The reason is that Table 10.1 provides information about specific compounds, whereas the trend shown in Table 10.2 is for major organic families and is approximate.

B. Solutions in Which the Solute Ionizes and Dissociates

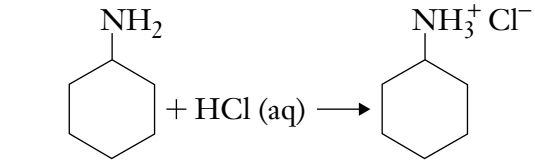
Many ionic compounds are highly soluble in water because of the strong attraction between ions and the highly polar water molecules. This also applies to organic compounds that can exist as ions. For example, sodium acetate consists of Na^+ and CH_3COO^- ions, which are highly soluble in water. Although there are some exceptions, you may assume that all organic compounds that are in the ionic form will be water soluble.

The most common way by which organic compounds become ions is in acid–base reactions. For example, carboxylic acids can be converted to water-soluble salts when they react with dilute aqueous NaOH:



The water-soluble salt can then be converted back to the original carboxylic acid (which is insoluble in water) by adding another acid (usually aqueous HCl) to the solution of the salt. The carboxylic acid precipitates out of solution.

Amines, which are organic bases, can also be converted to water-soluble salts when they react with dilute aqueous HCl:



This salt can be converted back to the original amine by adding a base (usually aqueous NaOH) to the solution of the salt.

TABLE 10.3 Common Organic Solvents

Solvent	Bp (°C)	Solvent	Bp (°C)
Hydrocarbons		Ethers	
Pentane	36	**Ether** (diethyl)	35
Hexane	69	**Dioxane**[a]	101
Benzene[a]	80	**1,2-Dimethoxyethane**	83
Toluene	111	Others	
Hydrocarbon mixtures		Acetic acid	118
Petroleum ether	30–60	Acetic anhydride	140
Ligroin	60–90	**Pyridine**	115
Chlorocarbons		**Acetone**	56
Methylene chloride	40	**Ethyl acetate**	77
Chloroform[a]	61	Dimethylformamide	153
Carbon tetrachloride[a]	77	Dimethylsulfoxide	189
Alcohols			
Methanol	65		
Ethanol	78		
Isopropyl alcohol	82		

Note: **Boldface type** indicates flammability.

[a]Suspect carcinogen.

10.3 Organic Solvents

Organic solvents must be handled safely. Always remember that organic solvents are all at least mildly toxic and that many are flammable. You should become thoroughly familiar with laboratory safety (see Technique 1).

The most common organic solvents are listed in Table 10.3 along with their boiling points. Solvents marked in boldface type will burn. Ether, pentane, and hexane are especially dangerous; if they are combined with the correct amount of air, they will explode.

The terms **petroleum ether** and **ligroin** are often confusing. Petroleum ether is a mixture of hydrocarbons with isomers of formulas C_5H_{12} and C_6H_{14} predominating. Petroleum ether is not an ether at all because there are no oxygen-bearing compounds in the mixture. In organic chemistry, an ether is usually a compound containing an oxygen atom to which two alkyl groups are attached. Figure 10.1 shows some of the hydrocarbons that commonly appear in petroleum ether. It also shows the structure of ether (diethyl ether). Use special care when instructions call for either **ether** or **petroleum ether**; the two must not become accidentally confused. Confusion is particularly easy when one is selecting a container of solvent from the supply shelf.

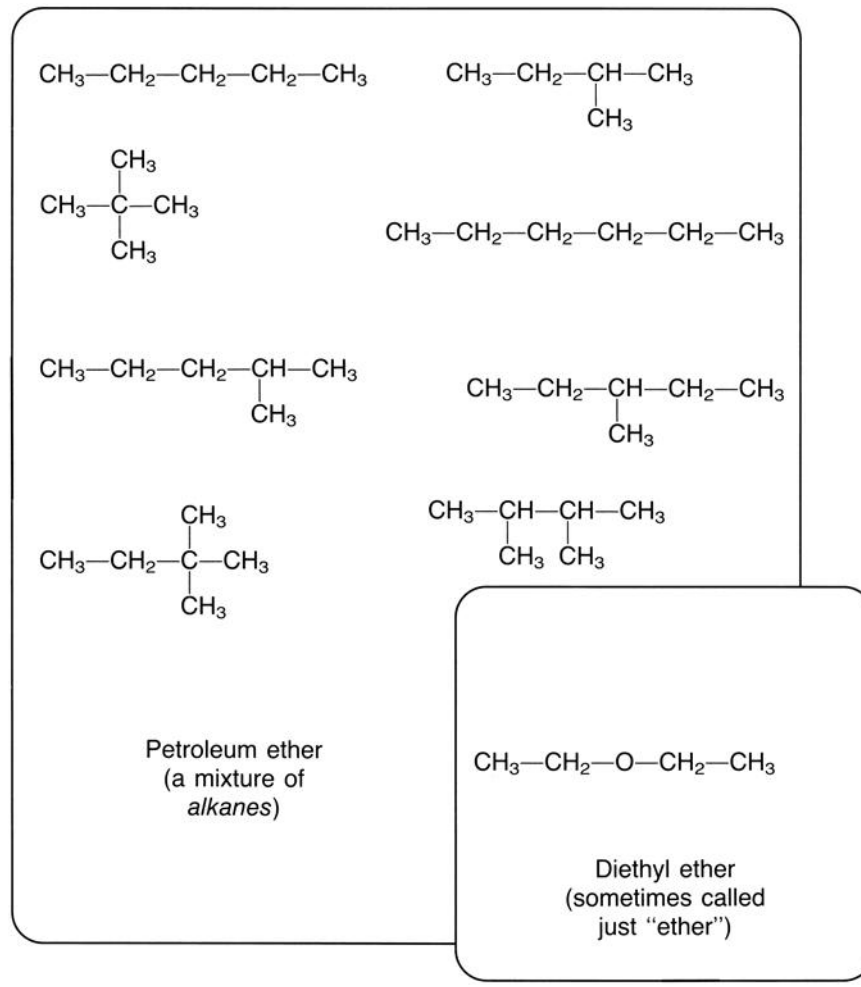


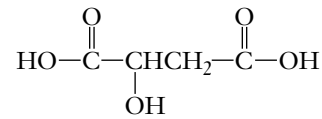
Figure 10.1 A comparison between "ether" (diethyl ether) and "petroleum ether."

Ligroin, or high-boiling petroleum ether, is like petroleum ether in composition except that compared with petroleum ether, ligroin generally includes higher-boiling alkane isomers. Depending on the supplier, ligroin may have different boiling ranges. Whereas some brands of ligroin have boiling points ranging from about 60°C to about 90°C, other brands have boiling points ranging from about 60°C to about 75°C. The boiling-point ranges of petroleum ether and ligroin are often included on the labels of the containers.

PROBLEMS

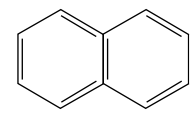
1. For each of the following pairs of solutes and solvent, predict whether the solute would be soluble or insoluble. After making your predictions, you can check your answers by looking up the compounds in *The Merck Index* or the *CRC Handbook of Chemistry and Physics*. Generally, *The Merck Index* is the easier reference book to use. If the substance has a solubility greater than 40 mg/mL, you may conclude that it is soluble.

a. Malic acid in water



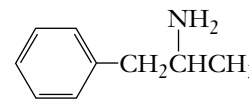
Malic acid

b. Naphthalene in water



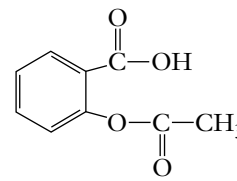
Naphthalene

c. Amphetamine in ethyl alcohol



Amphetamine

d. Aspirin in water

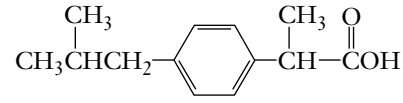


Aspirin

e. Succinic acid in hexane (*Note:* the polarity of hexane is similar to that of petroleum ether.)

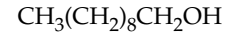
Succinic acid

f. Ibuprofen in diethyl ether



Ibuprofen

g. 1-Decanol (*n*-decyl alcohol) in water



1-Decanol

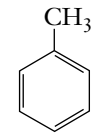
2. Predict whether the following pairs of liquids would be miscible or immiscible:

a. Water and methyl alcohol

b. Hexane and benzene

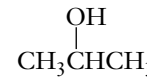
c. Methylene chloride and benzene

d. Water and toluene



Toluene

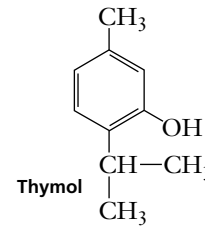
e. Ethyl alcohol and isopropyl alcohol



Isopropyl alcohol

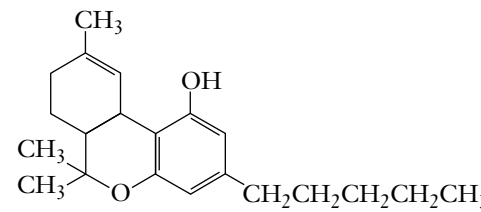
3. Would you expect ibuprofen (see problem 1f) to be soluble or insoluble in 1.0 M NaOH? Explain.

4. Thymol is very slightly soluble in water and very soluble in 1.0 M NaOH. Explain.



Thymol

5. Although cannabinol and methyl alcohol are both alcohols, cannabinol is very slightly soluble in methyl alcohol at room temperature. Explain.



Cannabinol

6. What is the difference between the compounds in each of the following pairs?

a. Ether and petroleum ether

b. Ether and diethyl ether

c. Ligroin and petroleum ether

11 TECHNIQUE 11

Crystallization: Purification of Solids

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

In most organic chemistry experiments, the desired product is first isolated in an impure form. If this product is a solid, the most common method of purification is crystallization. The general technique involves dissolving the material to be crystallized in a *hot* solvent (or solvent mixture) and cooling the solution slowly. The dissolved material has a decreased solubility at lower temperatures and will separate from the solution as it is cooled. This phenomenon is called either **crystallization**, if the crystal growth is relatively slow and selective, or **precipitation**, if the process is rapid and nonselective. Crystallization is an equilibrium process and produces very pure material. A small seed crystal is formed initially, and it then grows layer by layer in a reversible manner. In a sense, the crystal "selects" the correct molecules from the solution. In precipitation, the crystal lattice is formed so rapidly that impurities are trapped within the lattice. Therefore, any attempt at purification with too rapid a process should be avoided. Because the impurities are usually present in much smaller amounts than the compound being crystallized, most of the impurities will remain in the solvent even when it is cooled. The purified substance can then be separated from the solvent and from the impurities by filtration.

The method of crystallization described here is called **macroscale crystallization**. This technique, which is carried out with an Erlenmeyer flask to dissolve the material and a Büchner funnel to filter the crystals, is normally used when the weight of solid to be crystallized is more than 0.1 g. Another method, which is performed with a Craig tube, is used with smaller amounts of solid. Referred to as **microscale crystallization**, this technique is discussed briefly in Section 11.4.

When the macroscale crystallization procedure described in Section 11.3 is used with a Hirsch funnel, the procedure is sometimes referred to as a **semi-microscale crystallization**. This procedure is commonly used in microscale work when the amount of solid is greater than 0.1 g or in macroscale work when the amount of solid is less than about 0.5 g.

PART A. THEORY

11.1 Solubility

The first problem in performing a crystallization is selecting a solvent in which the material to be crystallized shows the desired solubility behavior. In an ideal case, the material should be sparingly soluble at room temperature and yet quite soluble at the boiling point of the solvent selected. The solubility curve should be steep, as can be seen in line A of Figure 11.1. A curve with a low slope (line B) would not cause significant crystallization when the temperature of the solution was lowered. A solvent in which the material is very soluble at all temperatures (line C) also would not be a suitable crystallization solvent. The basic problem in performing a crystallization is to select a solvent (or mixed solvent) that provides a steep solubility-vs.-temperature curve for the material to be crystallized. A solvent that allows the

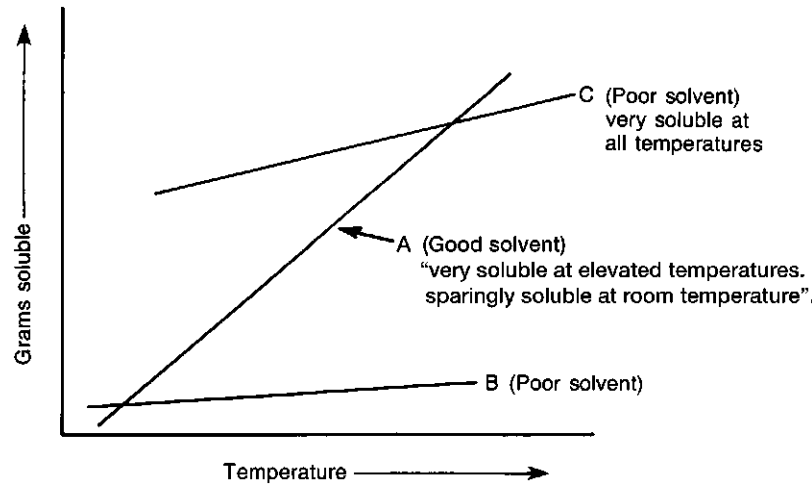


Figure 11.1 Graph of solubility vs. temperature.

behavior shown in line A is an ideal crystallization solvent. It should also be mentioned that solubility curves are not always linear, as they are depicted in Figure 11.1. This figure represents an idealized form of solubility behavior. The solubility curve for sulfanilamide in 95% ethyl alcohol, shown in Figure 11.2, is typical of many organic compounds and shows what solubility behavior might look like for a real substance.

The solubility of organic compounds is a function of the polarities of both the solvent and the **solute** (dissolved material). A general rule is "Like dissolves like." If the solute is very polar, a very polar solvent is needed to dissolve it; if the solute is nonpolar, a nonpolar solvent is needed. Applications of this rule are discussed extensively in Technique 10, Section 10.2, and in Technique 11, Section 11.5.

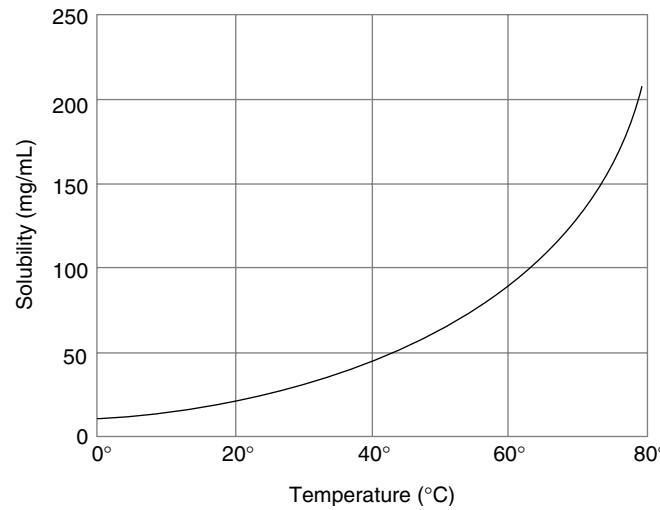


Figure 11.2 Solubility of sulfanilamide in 95% ethyl alcohol.

11.2 Theory Of Crystallization

A successful crystallization depends on a large difference between the solubility of a material in a hot solvent and its solubility in the same solvent when it is cold. When the impurities in a substance are equally soluble in both the hot and the cold solvent, an effective purification is not easily achieved through crystallization. A material can be purified by crystallization when both the desired substance and the impurity have similar solubilities, but only when the impurity represents a small fraction of the total solid. The desired substance will crystallize on cooling, but the impurities will not.

For example, consider a case in which the solubilities of substance A and its impurity B are both 1 g/100 mL of solvent at 20°C and 10 g/100 mL of solvent at 100°C. In the impure sample of A, the composition is 9 g of A and 2 g of B. In the calculations for this example, it is assumed that the solubilities of both A and B are unaffected by the presence of the other substance. To make the calculations easier to understand, 100 mL of solvent are used in each crystallization. Normally, the minimum amount of solvent required to dissolve the solid would be used.

At 20°C, this total amount of material will not dissolve in 100 mL of solvent. However, if the solvent is heated to 100°C, all 11 g dissolve. The solvent has the capacity to dissolve 10 g of A *and* 10 g of B at this temperature. If the solution is cooled to 20°C, only 1 g of each solute can remain dissolved, so 8 g of A and 1 g of B crystallize, leaving 2 g of material in the solution. This crystallization is shown in Figure 11.3. The solution that remains after a crystallization is called the **mother liquor**. If the process is now repeated by treating the crystals with 100 mL of fresh solvent, 7 g of A will crystallize again, leaving 1 g of A and 1 g of B in the mother liquor. As a result of these operations, 7 g of pure A are obtained, but with the loss of 4 g of material (2 g of A plus 2 g of B). Again, this second crystallization step is illustrated in Figure 11.3. The final result illustrates an important aspect of crystallization—it is wasteful. Nothing can be done to prevent this waste; some A must be lost along with the impurity B for the method to be successful. Of course, if the impurity B were *more* soluble than A in the solvent, the losses would be reduced. Losses could also be reduced if the impurity were present in *much smaller* amounts than the desired material.

Note that in the preceding case, the method operated successfully because A was present in substantially larger quantity than its impurity B. If there had been a

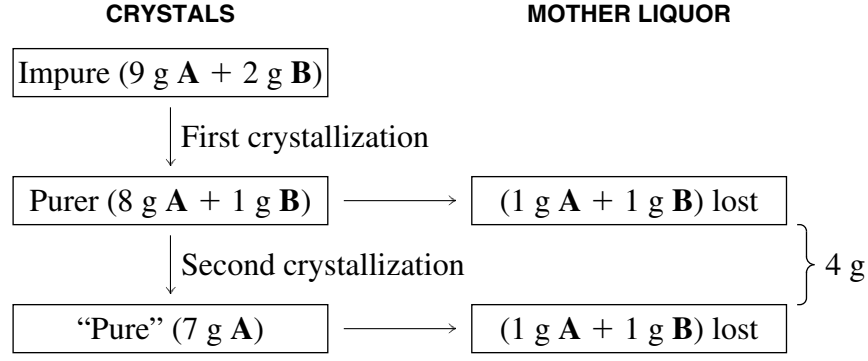


Figure 11.3 Purification of a mixture by crystallization.

50–50 mixture of A and B initially, no separation would have been achieved. In general, a crystallization is successful only if there is a *small* amount of impurity. As the amount of impurity increases, the loss of material must also increase. Two substances with nearly equal solubility behavior, present in equal amounts, cannot be separated. If the solubility behavior of two components present in equal amounts is different, however, a separation or purification is frequently possible.

In the preceding example, two crystallization procedures were performed. Normally, this is not necessary; however, when it is, the second crystallization is more appropriately called **recrystallization**. As illustrated in this example, a second crystallization results in purer crystals, but the yield is lower.

In some experiments, you will be instructed to cool the crystallizing mixture in an ice-water bath before collecting the crystals by filtration. Cooling the mixture increases the yield by decreasing the solubility of the substance; however, even at this reduced temperature, some of the product will be soluble in the solvent. It is not possible to recover all your product in a crystallization procedure even when the mixture is cooled in an ice-water bath. A good example of this is illustrated by the solubility curve for sulfanilamide shown in Figure 11.2. The solubility of sulfanilamide at 0°C is still significant, 14 mg/mL.

PART B. MACROSCALE CRYSTALLIZATION

11.3 Macroscale Crystallization

The crystallization technique described in this section is used when the weight of solid to be crystallized is more than 0.1 g. There are four main steps in a macroscale crystallization:

1. Dissolving the solid
2. Removing insoluble impurities (when necessary)
3. Crystallizing
4. Collecting and drying

These steps are illustrated in Figure 11.4. An Erlenmeyer flask of an appropriate size must be chosen. It should be pointed out that a microscale crystallization with a Craig tube involves the same four steps, although the apparatus and procedures are somewhat different (see Section 11.4).

A. Dissolving the Solid

To minimize losses of material to the mother liquor, it is desirable to *saturate* the boiling solvent with solute. This solution, when cooled, will return the maximum possible amount of solute as crystals. To achieve this high return, the solvent is brought to its boiling point, and the solute is dissolved in the *minimum amount* (!) *of boiling solvent.* For this procedure, it is advisable to maintain a container of boiling solvent (on a hot plate). From this container, a small portion (about 1–2 mL) of the solvent is added to the Erlenmeyer flask containing the solid to be crystallized, and this mixture is heated while swirling occasionally until it resumes boiling.

CAUTION

Do not heat the flask containing the solid until after you have added the first portion of solvent.

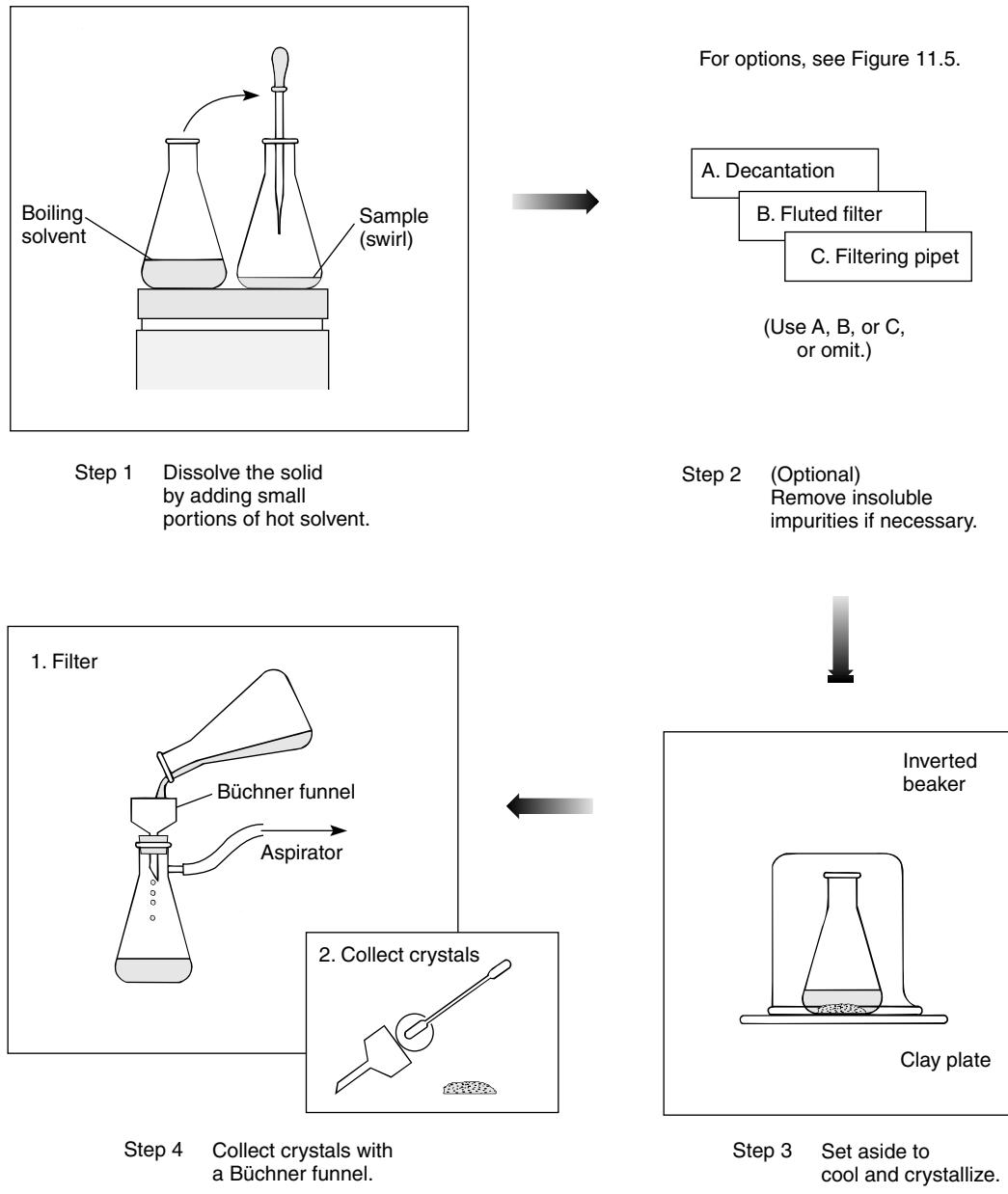


Figure 11.4 Steps in a macroscale crystallization (no decolorization).

If the solid does not dissolve in the first portion of boiling solvent, then another small portion of boiling solvent is added to the flask. The mixture is swirled and heated again until it resumes boiling. If the solid dissolves, no more solvent is added. But if the solid has not dissolved, another portion of boiling solvent is added, as before, and the process is repeated until the solid dissolves. It is important to stress that the portions of solvent added each time are small, so only the *minimum* amount of solvent necessary for dissolving the solid is added. It is also important to emphasize that the procedure requires the addition of solvent to solid.

You must never add portions of solid to a fixed quantity of boiling solvent. By this latter method, it may be impossible to determine when saturation has been achieved. This entire procedure should be performed fairly rapidly, or you may lose solvent through evaporation nearly as quickly as you are adding it, and this procedure will then take a very long time. This is most likely to happen when using highly volatile solvents such as methyl alcohol or ethyl alcohol. The time from the first addition of solvent until the solid dissolves completely should not be longer than 15–20 minutes.

Comments on This Procedure for Dissolving the Solid

1. One of the most common mistakes is to add too much solvent. This can happen most easily if the solvent is not hot enough or if the mixture is not stirred sufficiently. If too much solvent is added, the percentage recovery will be reduced; it is even possible that no crystals will form when the solution is cooled. If too much solvent is added, you must evaporate the excess by heating the mixture. A nitrogen or air stream directed into the container will accelerate the evaporation process (see Technique 7, Section 7.10).
2. It is very important not to heat the solid until you have added some solvent. Otherwise, the solid may melt and possibly form an oil or decompose, and it may not crystallize easily (see Section 11.5).
3. It is also important to use an Erlenmeyer flask rather than a beaker for performing the crystallization. A beaker should not be used because the large opening allows the solvent to evaporate too rapidly and allows dust particles to get in too easily.
4. In some experiments, a specified amount of solvent for a given weight of solid will be recommended. In these cases, you should use the amount specified rather than the minimum amount of solvent necessary to dissolve the solid. The amount of solvent recommended has been selected to provide the optimum conditions for good crystal formation.
5. Occasionally, you may encounter an impure solid that contains small particles of insoluble impurities, pieces of dust, or paper fibers that will not dissolve in the hot crystallizing solvent. A common error is to add too much of the hot solvent in an attempt to dissolve these small particles, not realizing that they are insoluble. In such cases, you must be careful not to add too much solvent.
6. It is sometimes necessary to decolorize the solution by adding activated charcoal or by passing the solution through a column containing alumina or silica gel (see Section 11.7 and Technique 19, Section 19.15). A decolorization step should be performed only if the mixture is *highly* colored and it is clear that the color is due to impurities and not due to the actual color of the substance being crystallized. If decolorization is necessary, it should be accomplished before the following filtration step.

B. Removing Insoluble Impurities

It is necessary to use one of the following three methods only if insoluble material remains in the hot solution or if decolorizing charcoal has been used.

CAUTION

Indiscriminate use of the procedure can lead to needless loss of your product.

Decantation is the easiest method of removing solid impurities and should be considered first. If filtration is required, a filtering pipet is used when the volume of liquid to be filtered is less than 10 mL (see Technique 8, Section 8.1C), and you should use gravity filtration through a fluted filter when the volume is 10 mL or greater (see Technique 8, Section 8.1B). These three methods are illustrated in Figure 11.5, and each is discussed below.

Decantation. If the solid particles are relatively large in size or they easily settle to the bottom of the flask, it may be possible to separate the hot solution from the impurities by carefully pouring off the liquid, leaving the solid behind. This is accomplished most easily by holding a glass stirring rod along the top of the flask and tilting the flask so that the liquid pours out along one end of the glass rod into another container. A technique similar in principle to decantation, which may be easier to perform with smaller amounts of liquid, is to use a **preheated Pasteur pipet** to remove the hot solution. With this method, it may be helpful to place the tip of the pipet against the bottom of the flask when removing the last portion of solution. The small space between the tip of the pipet and the inside surface of the flask prevents solid material from being drawn into the pipet. An easy way to preheat the pipet is to draw up a small portion of hot *solvent* (not the *solution* being transferred) into the pipet and expel the liquid. Repeat this process several times.

Fluted Filter. This method is the most effective way to remove solid impurities when the volume of liquid is greater than 10 mL or when decolorizing charcoal has been used (see Technique 8, Section 8.1B and Section 11.7). You should first add a small amount of extra solvent to the hot mixture. This action helps prevent crystal formation in the filter paper or the stem of the funnel during the filtration. The funnel is then fitted with a fluted filter and installed at the top of the Erlenmeyer flask to be used for the actual filtration. It is advisable to place a small piece of wire between the funnel and the mouth of the flask to relieve any increase in pressure caused by hot filtrate.

The Erlenmeyer flask containing the funnel and fluted paper is placed on top of a hot plate (low setting). The liquid to be filtered is brought to its boiling point and poured through the filter in portions. (If the volume of the mixture is less than 10 mL, it may be more convenient to transfer the mixture to the filter with a preheated Pasteur pipet.) It is necessary to keep the solutions in both flasks at their boiling temperatures to prevent premature crystallization. The refluxing action of the filtrate keeps the funnel warm and reduces the chance that the filter will clog with crystals that may have formed during the filtration. With low-boiling solvents, be aware that some solvent may be lost through evaporation. Consequently, extra solvent must be added to make up for this loss. If crystals begin to form in the filter during filtration, a minimum amount of boiling solvent is added to redissolve the crystals and to allow the solution to pass through the funnel. If the volume of liquid being filtered is less than 10 mL, a small amount of hot solvent should be used to rinse the filter after all the filtrate has been collected. The rinse solvent is then combined with the original filtrate.

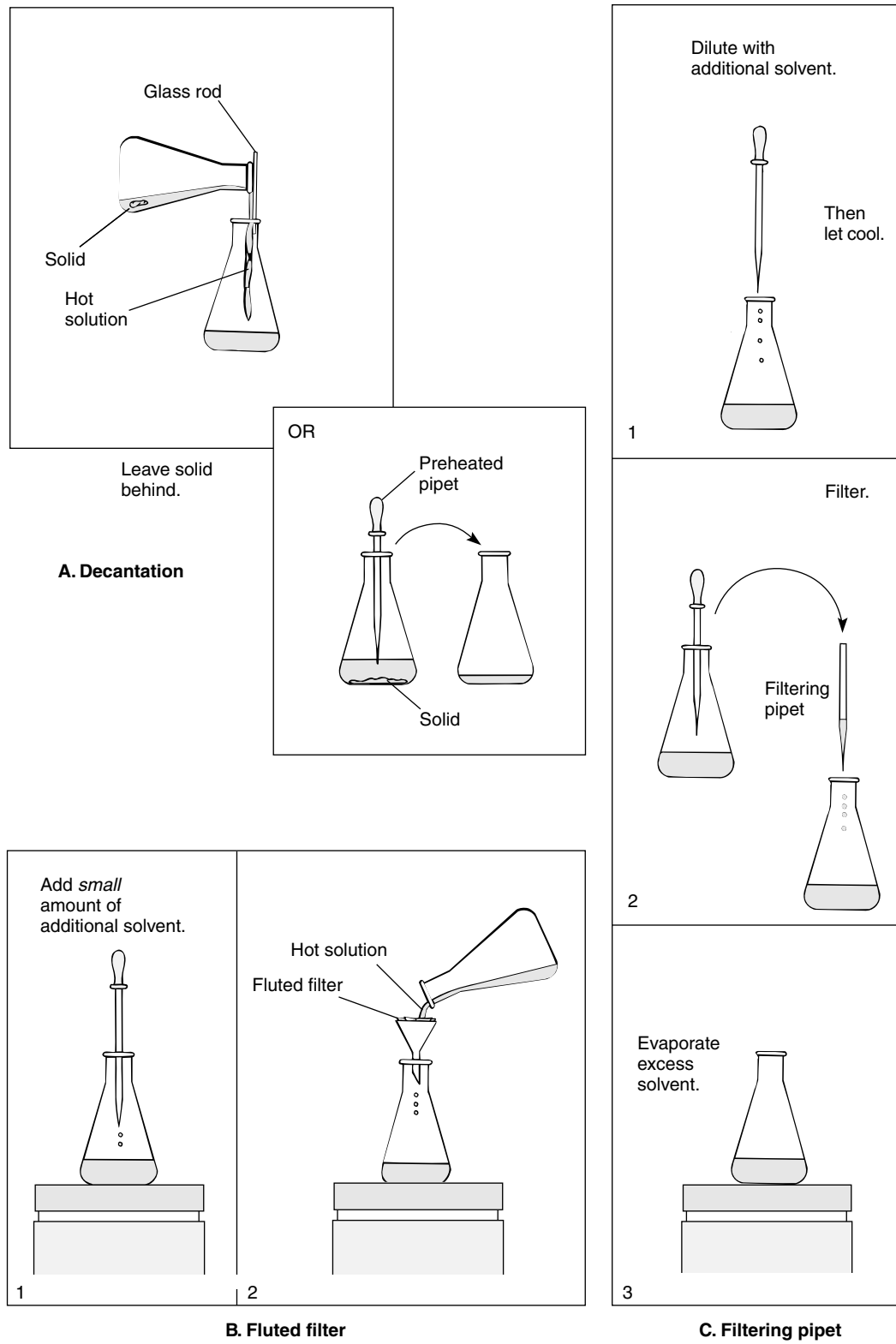


Figure 11.5 Methods for removing insoluble impurities in a macroscale crystallization.

After the filtration, it may be necessary to remove extra solvent by evaporation until the solution is once again saturated at the boiling point of the solvent (see Technique 7, Section 7.10).

Filtering Pipet. If the volume of solution after dissolving the solid in hot solvent is less than 10 mL, gravity filtration with a filtering pipet may be used to remove solid impurities. However, using a filtering pipet to filter a hot solution saturated with solute can be difficult without premature crystallization. The best way to prevent this from occurring is to add enough solvent to dissolve the desired product at room temperature (be sure not to add too much solvent) and perform the filtration at room temperature, as described in Technique 8, Section 8.1C. After filtration, the excess solvent is evaporated by boiling until the solution is saturated at the boiling point of the mixture (see Technique 7, Section 7.10). If powdered decolorizing charcoal was used, it will probably be necessary to perform two filtrations with a filtering pipet to remove all of the charcoal, or a fluted filter can be used.

C. Crystallizing

An Erlenmeyer flask, not a beaker, should be used for crystallization. The large open top of a beaker makes it an excellent dust catcher. The narrow opening of the Erlenmeyer flask reduces contamination by dust and allows the flask to be stoppered if it is to be set aside for a long period. Mixtures set aside for long periods must be stoppered after cooling to room temperature to prevent evaporation of solvent. If all of the solvent evaporates, no purification is achieved, and the crystals originally formed become coated with the dried contents of the mother liquor. Even if the time required for crystallization to occur is relatively short, it is advisable to cover the top of the Erlenmeyer flask with a small watch glass or inverted beaker to prevent evaporation of solvent while the solution is cooling to room temperature.

The chances of obtaining pure crystals are improved if the solution cools to room temperature slowly. When the volume of solution is 10 mL or less, the solution is likely to cool more rapidly than is desired. This can be prevented by placing the flask on a surface that is a poor heat conductor and covering the flask with a beaker to provide a layer of insulating air. Appropriate surfaces include a clay plate or several pieces of filter paper on top of the laboratory bench. It may also be helpful to use a clay plate that has been warmed slightly on a hot plate or in an oven.

After crystallization has occurred, it is sometimes desirable to cool the flask in an ice-water bath. Because the solute is less soluble at lower temperatures, this will increase the yield of crystals.

If a cooled solution does not crystallize, it will be necessary to induce crystallization. Several techniques are described in Section 11.8A.

D. Collecting and Drying

After the flask has been cooled, the crystals are collected by vacuum filtration through a Büchner (or Hirsch) funnel (see Technique 8, Section 8.3 and Figure 8.5). The crystals should be washed with a small amount of *cold* solvent to remove any

mother liquor adhering to their surface. Hot or warm solvent will dissolve some of the crystals. The crystals should then be left for a short time (usually 5–10 minutes) in the funnel, where air, as it passes, will dry them free of most of the solvent. It is often wise to cover the Büchner funnel with an oversized filter paper or towel during this air drying. This precaution prevents accumulation of dust in the crystals. When the crystals are nearly dry, they should be gently scraped off the filter paper (so paper fibers are not removed with the crystals) onto a watch glass or clay plate for further drying (see Section 11.9).

The four steps in a macroscale crystallization are summarized in Table 11.1.

TABLE 11.1 Steps in a Macroscale Crystallization

A. Dissolving the Solid

1. Find a solvent with a steep solubility-vs.-temperature characteristic (done by trial and error using small amounts of material or by consulting a handbook).
2. Heat the desired solvent to its boiling point.
3. Dissolve the solid in a **minimum** of boiling solvent in a flask.
4. If necessary, add decolorizing charcoal or decolorize the solution on a silicagel or alumina column.

B. Removing Insoluble Impurities

1. Decant or remove the solution with a Pasteur pipet.
2. Alternatively, filter the hot solution through a fluted filter, a filtering pipet, or a filter-tip pipet to remove insoluble impurities or charcoal.

NOTE: If no decolorizing charcoal has been added or if there are no undissolved particles, Part B should be omitted.

C. Crystallizing

1. Allow the solution to cool.
2. If crystals appear, cool the mixture in an ice-water bath (if desired) and go to Part D. If crystals do not appear, go to the next step.
3. Inducing crystallization.
   - **a.** Scratch the flask with a glass rod.
   - **b.** Seed the solution with original solid, if available.
   - **c.** Cool the solution in an ice-water bath.
   - **d.** Evaporate excess solvent and allow the solution to cool again.

D. Collecting and Drying

1. Collect crystals by vacuum filtration using a Büchner funnel.
2. Rinse crystals with a small portion of **cold** solvent.
3. Continue suction until crystals are nearly dry.
4. Drying (three options).
   - **a.** Air-dry the crystals.
   - **b.** Place the crystals in a drying oven.
   - **c.** Dry the crystals under a vacuum.

PART C. MICROSCALE CRYSTALLIZATION

11.4 Microscale Crystallization

In many microscale experiments, the amount of solid to be crystallized is small enough (generally less than 0.1 g) that a **Craig tube** (see Technique 8, Figure 8.10) is the preferred method for crystallization. The main advantage of the Craig tube is that it minimizes the number of transfers of solid material, thus resulting in a greater yield of crystals. Also, the separation of the crystals from the mother liquor with the Craig tube is very efficient, and little time is required for drying the crystals. The steps involved are, in principle, the same as those performed when a crystallization is accomplished with an Erlenmeyer flask and a Büchner funnel.

The solid is transferred to the Craig tube, and small portions of hot solvent are added to the tube while the mixture is stirred with a spatula and heated. If there are any insoluble impurities present, they can be removed with a filter-tip pipet. The inner plug is then inserted into the Craig tube and the hot solution is cooled slowly to room temperature. When the crystals have formed, the Craig tube is placed into a centrifuge tube, and the crystals are separated from the mother liquor by centrifugation (see Technique 8, Section 8.7). The crystals are then scraped off the end of the inner plug or from inside the Craig tube onto a watch glass or piece of paper. Minimal drying will be necessary (see Section 11.9).

PART D. ADDITIONAL EXPERIMENTAL CONSIDERATIONS: MACROSCALE AND MICROSCALE

11.5 Selecting a Solvent

A solvent that dissolves little of the material to be crystallized when it is cold but a great deal of the material when it is hot is a good solvent for crystallization. Quite often, correct crystallization solvents are indicated in the experimental procedures that you will be following. When a solvent is not specified in a procedure, you can determine a good crystallization solvent by consulting a handbook or making an educated guess based on polarities, both discussed in this section. A third approach, involving experimentation, is discussed in Section 11.6.

With compounds that are well known, the correct crystallization solvent has already been determined through the experiments of earlier researchers. In such cases, the chemical literature can be consulted to determine which solvent should be used. Sources such as *The Merck Index* or the *CRC Handbook of Chemistry and Physics* may provide this information.

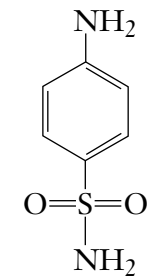
For example, consider naphthalene, which is found in *The Merck Index.* It states under the entry for naphthalene: "Monoclinic prismatic plates from ether." This statement means that naphthalene can be crystallized from ether. It also gives the type of crystal structure. Unfortunately, the crystal structure may be given without reference to the solvent. Another way to determine the best solvent is by looking at solubility-vs.-temperature data. When this is given, a good solvent is one in which the solubility of the compound increases significantly as the temperature increases. Sometimes, the solubility data will be given for only cold solvent and boiling solvent. This should provide enough information to determine whether this would be a good solvent for crystallization.

In most cases, however, the handbooks will state only whether a compound is soluble or not in a given solvent, usually at room temperature. Determining a good solvent for crystallization from this information can be somewhat difficult. The solvent in which the compound is soluble may or may not be an appropriate solvent

for crystallization. Sometimes, the compound may be too soluble in the solvent at all temperatures, and you would recover very little of your product if this solvent were used for crystallization. It is possible that an appropriate solvent would be the one in which the compound is nearly insoluble at room temperature because the solubility-vs.-temperature curve is very steep. Although the solubility information may give you some ideas about what solvents to try, you will most likely need to determine a good crystallizing solvent by experimentation as described in Section 11.6.

When using *The Merck Index* or *Handbook of Chemistry and Physics,* you should be aware that alcohol is frequently listed as a solvent. This generally refers to 95% or 100% ethyl alcohol. Because 100% (absolute) ethyl alcohol is more expensive than 95% ethyl alcohol, the cheaper grade is usually used in the chemistry laboratory. Another solvent frequently listed is benzene. Benzene is a known carcinogen, so it is rarely used in student laboratories. Toluene is a suitable substitute; the solubility behavior of a substance in benzene and toluene is so similar that you may assume any statement made about benzene also applies to toluene.

Another way to identify a solvent for crystallization is to consider the polarities of the compound and the solvents. Generally, you would look for a solvent that has a polarity somewhat similar to that of the compound to be crystallized. Consider the compound sulfanilamide, shown in the figure. There are several polar bonds in sulfanilamide, the NH and the SO bonds. In addition, the NH_2 groups and the oxygen



Sulfanilamide

atoms in sulfanilamide can form hydrogen bonds. Although the benzene ring portion of sulfanilamide is nonpolar, sulfanilamide has an intermediate polarity because of the polar groups. A common organic solvent of intermediate polarity is 95% ethyl alcohol. Therefore, it is likely that sulfanilamide would be soluble in 95% ethyl alcohol because they have similar polarities. (Note that the other 5% in 95% ethyl alcohol is usually a substance such as water or isopropyl alcohol, which does not alter the overall polarity of the solvent.) Although this kind of analysis is a good first step in determining an appropriate solvent for crystallization, without more information it is not enough to predict the shape of the solubility curve for the temperature-vs.-solubility data (see Figure 11.1). Therefore, knowing that sulfanilamide is soluble in 95% ethyl alcohol does not necessarily mean that this is a good solvent for crystallizing sulfanilamide. You would still need to test the solvent to see if it is appropriate. The solubility curve for sulfanilamide (see Figure 11.2) indicates that 95% ethyl alcohol is a good solvent for crystallizing this substance.

When choosing a crystallization solvent, do not select one whose boiling point is higher than the melting point of the substance (solute) to be crystallized. If the boiling point of the solvent is too high, the substance may come out of solution as a liquid rather than a crystalline solid. In such a case, the solid may **oil out**. oiling out occurs when upon cooling the solution to induce crystallization, the solute begins to come out of solution at a temperature above its melting point. The solute will then come out of solution as a liquid. Furthermore, as cooling continues, the substance may still not

TABLE 11.2 Common Solvents for Crystallization

	Boils (°C)	Freezes (°C)	Soluble in H_2O	Flammability
Water	100	0	+	−
Methanol	65	*	+	+
95% Ethanol	78	*	+	+
Ligroin	60–90	*	−	+
Toluene	111	*	−	+
Chloroform**	61	*	−	−
Acetic acid	118	17	+	+
Dioxane**	101	11	+	+
Acetone	56	*	+	+
Diethyl ether	35	*	Slightly	++
Petroleum ether	30–60	*	−	++
Methylene chloride	41	*	−	−
Carbon tetrachloride**	77	*	−	−

*Lower than 0°C (ice temperature).

**Suspected carcinogen.

crystallize; rather, it will become a supercooled liquid. Oils may eventually solidify if the temperature is lowered, but often they will not actually crystallize. Instead, the solidified oil will be an amorphous solid or a hardened mass. In this case, purification of the substance will not have occurred as it does when the solid is crystalline. It can be very difficult to deal with oils when trying to obtain a pure substance. You must try to redissolve them and hope that the substance will crystallize with slow, careful cooling. During the cooling period, it may be helpful to scratch the glass container where the oil is present with a glass stirring rod that has not been fire polished. Seeding the oil as it cools with a small sample of the original solid is another technique that is sometimes helpful in working with difficult oils. Other methods of inducing crystallization are discussed in Section 11.8.

One additional criterion for selecting the correct crystallization solvent is the **volatility** of that solvent. Volatile solvents have low boiling points or evaporate easily. A solvent with a low boiling point may be removed from the crystals through evaporation without much difficulty. It will be difficult to remove a solvent with a high boiling point from the crystals without heating them under vacuum. On the other hand, solvents with very low boiling points are not ideal for crystallizations. The recovery will not be as great with low-boiling solvents because they cannot be heated past the boiling point. Diethyl ether (bp = 35°C) and methylene chloride (bp = 41°C) are not often used as crystallization solvents.

Table 11.2 lists common crystallization solvents. The solvents used most commonly are listed in the table first.

11.6 Testing Solvents for Crystallization

When the appropriate solvent is not known, select a solvent for crystallization by experimenting with various solvents and a very small amount of the material to be crystallized. Experiments are conducted on a small test tube scale before the entire quantity of material is committed to a particular solvent. Such trial-and-error methods are common when trying to purify a solid material that has not been previously studied.

Procedure

1. Place about 0.05 g of the sample in a test tube.
2. Add about 0.5 mL of solvent at room temperature and stir the mixture by rapidly twirling a microspatula between your fingers. If all (or almost all) of the solid dissolves at room temperature, then your solid is ***probably*** too soluble in this solvent and little compound would be recovered if this solvent were used. Select another solvent.
3. If none (or very little) of the solid dissolves at room temperature, heat the tube carefully and stir with a spatula. (A hotwater bath is perhaps better than an aluminum block because you can more easily control the temperature of the hot-water bath. The temperature of the hot-water bath should be slightly higher than the boiling point of the solvent.) Add more solvent dropwise, while continuing to heat and stir. Continue adding solvent until the solid dissolves, but do not add more than about 1.5 mL (total) of solvent. If all of the solid dissolves, go to step 4. If all of the solid has not dissolved by the time you have added 1.5 mL of solvent, this is probably not a good solvent. However, if most of the solid has dissolved at this point, you might try adding a little more solvent. Remember to heat and stir at all times during this step.
4. If the solid dissolves in about 1.5 mL or less of boiling solvent, then remove the test tube from the heat source, stopper the tube, and allow it to cool to room temperature. Then place it in an ice-water bath. If a lot of crystals come out, this is most likely a good solvent. If crystals do not come out, scratch the sides of the tube with a glass stirring rod to induce crystallization. If crystals still do not form, this is probably not a good solvent.

Comments about This Procedure

1. Selecting a good solvent is something of an art. There is no perfect procedure that can be used in all cases. You must think about what you are doing and use some common sense in deciding whether to use a particular solvent.
2. Do not heat the mixture above the melting point of your solid. This can occur most easily when the boiling point of the solvent is higher than the melting point of the solid. Normally, do not select a solvent that has a higher boiling point than the melting point of the substance. If you do, make certain that you do not heat the mixture beyond the melting point of your solid.

11.7 Decolorization

Small amounts of highly colored impurities may make the original crystallization solution appear colored; this color can often be removed by **decolorization**, either by using activated charcoal (often called Norit) or by passing the solution through a column packed with alumina or silica gel. A decolorizing step should be performed only if the color is due to impurities, not due to the color of the desired product, and if the color is significant. Small amounts of colored impurities will remain in solution during crystallization, making the decolorizing step unnecessary. The use of activated charcoal is described separately for macroscale and microscale crystallizations, and the column technique, which can be used with both crystallization techniques, is then described.

A. Macroscale—Powdered Charcoal

As soon as the solute is dissolved in the minimum amount of boiling solvent, the solution is allowed to cool slightly, and a small amount of Norit (powdered charcoal)

is added to the mixture. The Norit adsorbs the impurities. When performing a crystallization in which the filtration is performed with a fluted filter, you should add powdered Norit because it has a larger surface area and can remove impurities more effectively. A reasonable amount of Norit is what could be held on the end of a microspatula, or about 0.01–0.02 g. If too much Norit is used, it will adsorb product as well as impurities. A small amount of Norit should be used, and its use should be repeated if necessary. (It is difficult to determine if the initial amount added is sufficient until after the solution is filtered, because the suspended particles of charcoal will obscure the color of the liquid.) Caution should be exercised so that the solution does not froth or erupt when the finely divided charcoal is added. The mixture is boiled with the Norit for several minutes and then filtered by gravity, using a fluted filter (see Section 11.3 and Technique 8, Section 8.1B), and the crystallization is carried forward as described in Section 11.3.

The Norit preferentially adsorbs the colored impurities and removes them from the solution. The technique seems to be most effective with hydroxylic solvents. In using Norit, be careful not to breathe the dust. Normally, small quantities are used so that little risk of lung irritation exists.

B. Microscale—Pelletized Norit

If the crystallization is being performed in a Craig tube, it is advisable to use pelletized Norit. Although this is not as effective in removing impurities as powdered Norit, it is easier to remove, and the amount of pelletized Norit required is more easily determined because you can see the solution as it is being decolorized. Again, the Norit is added to the hot solution (the solution should not be boiling) after the solid has dissolved. This should be performed in a test tube rather than in a Craig tube. About 0.02 g is added, and the mixture is boiled for a minute or so to see if more Norit is required. More Norit is added, if necessary, and the liquid is boiled again. It is important not to add too much pelletized Norit because the Norit will also adsorb some of the desired material, and it is possible that not all of the color can be removed no matter how much Norit is added. The decolorized solution is then removed with a preheated filter-tip pipet (see Technique 8, Section 8.6) to filter the mixture and transferred to a Craig tube for crystallization as described in Section 11.4.

C. Decolorization on a Column

The other method for decolorizing a solution is to pass the solution through a column containing alumina or silica gel. The adsorbent removes the colored impurities while allowing the desired material to pass through (see Technique 8, Figure 8.6, and Technique 19, Section 19.15). If this technique is used, it will be necessary to dilute the solution with additional solvent to prevent crystallization from occurring during the process. The excess solvent must be evaporated after the solution is passed through the column (see Technique 7, Section 7.10), and the crystallization procedure is continued as described in Sections 11.3 or 11.4.

11.8 Inducing Crystallization

If a cooled solution does not crystallize, several techniques may be used to induce crystallization. Although identical in principle, the actual procedures vary slightly when performing macroscale and microscale crystallizations.

A. Macroscale

In the first technique, you should try scratching the inside surface of the flask vigorously with a glass rod that *has not been* fire polished. The motion of the rod should

be vertical (in and out of the solution) and should be vigorous enough to produce an audible scratching. Such scratching often induces crystallization, although the effect is not well understood. The high-frequency vibrations may have something to do with initiating crystallization; or perhaps—a more likely possibility—small amounts of solution dry by evaporation on the side of the flask, and the dried solute is pushed into the solution. These small amounts of material provide "seed crystals," or nuclei, on which crystallization may begin.

A second technique that can be used to induce crystallization is to cool the solution in an ice bath. This method decreases the solubility of the solute.

A third technique is useful when small amounts of the original material to be crystallized are saved. The saved material can be used to "seed" the cooled solution. A small crystal dropped into the cooled flask often will start the crystallization—this is called **seeding**.

If all of these measures fail to induce crystallization, it is likely that too much solvent was added. The excess solvent must then be evaporated (see Technique 7, Section 7.10) and the solution allowed to cool.

B. Microscale

The strategy is basically the same as described for macroscale crystallizations. Scratching vigorously with a glass rod *should be avoided*, however, because the Craig tube is fragile and expensive. Scratching *gently* is allowed.

Another measure is to dip a spatula or glass stirring rod into the solution and allow the solvent to evaporate so that a small amount of solid will form on the surface of the spatula or glass rod. When placed back into the solution, the solid will seed the solution. A small amount of the original material, if some was saved, may also be used to seed the solution.

A third technique is to cool the Craig tube in an ice-water bath. This method may also be combined with either of the previous suggestions.

If none of these measures is successful, it is possible that too much solvent is present, and it may be necessary to evaporate some of the solvent (see Technique 7, Section 7.10) and allow the solution to cool again.

11.9 Drying Crystals

The most common method of drying crystals involves allowing them to dry in air. Several different methods are illustrated in Figure 11.6 below. In all three methods, the crystals must be covered to prevent accumulation of dust particles. Note that in each method, the spout on the beaker provides an opening so that solvent vapor can escape from the system. The advantage of this method is that heat is not required, thus reducing the danger of decomposition or melting; however, exposure to atmospheric moisture may cause the hydration of strongly hygroscopic materials. A **hygroscopic** substance is a substance that absorbs moisture from the air.

Another method of drying crystals is to place the crystals on a watch glass, a clay plate, or a piece of absorbent paper in an oven. Although this method is simple, some possible difficulties deserve mention. Crystals that sublime readily should not be dried in an oven because they might vaporize and disappear. Care should be taken that the temperature of the oven does not exceed the melting point of the crystals. Remember that the melting point of crystals is lowered by the presence of solvent; allow for this melting-point depression when selecting a suitable oven temperature. Some materials decompose on exposure to heat, and they should not be dried in an oven. Finally, when many different samples are being dried in the

same oven, crystals might be lost due to confusion or reaction with another person's sample. It is important to label the crystals when they are placed in the oven.

A third method, which requires neither heat nor exposure to atmospheric moisture, is drying *in vacuo.* Two procedures are illustrated in Figure 11.7.

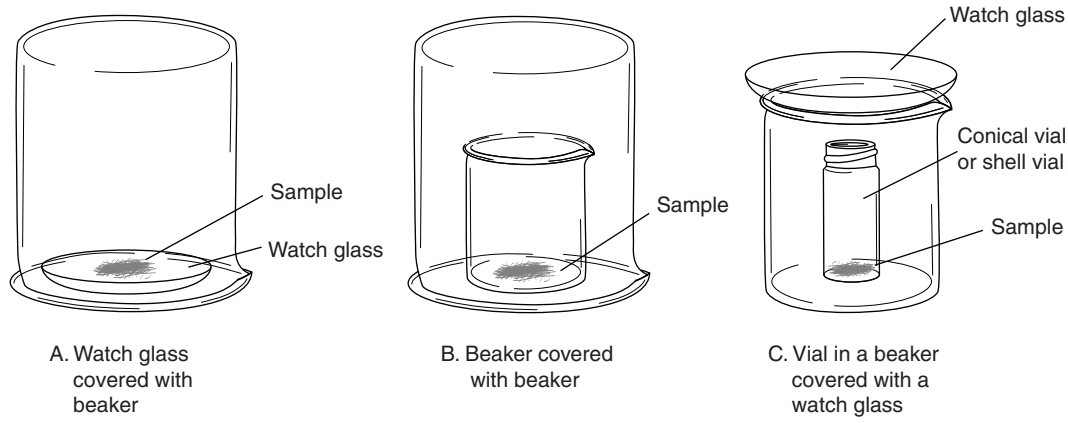


Figure 11.6 Methods for drying crystals in air.

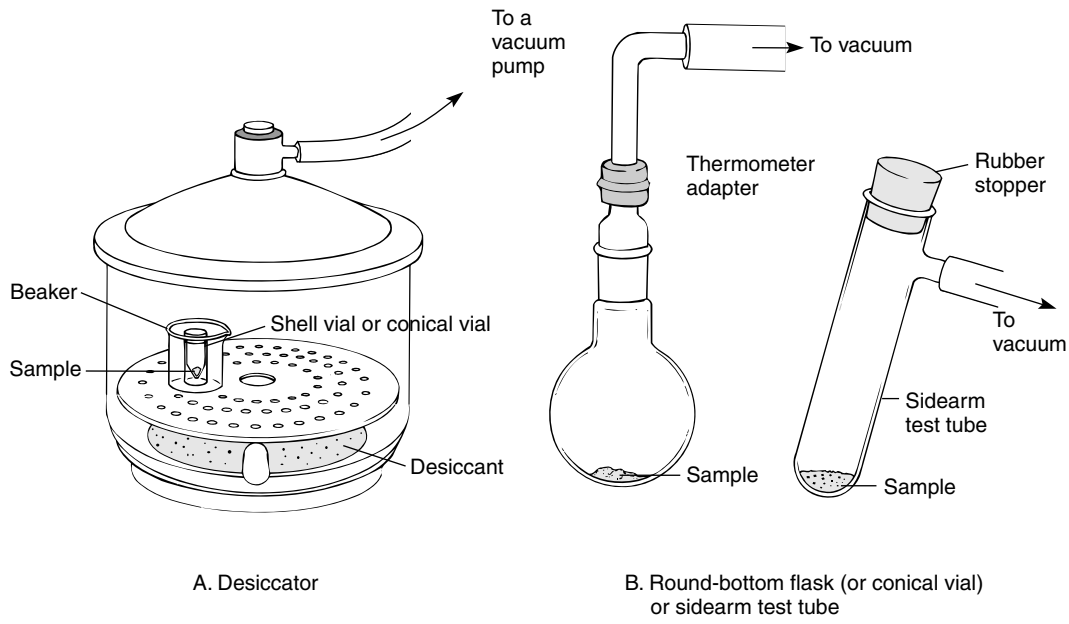


Figure 11.7 Methods for drying crystals in vacuum.

Procedure A

In this method, a desiccator is used. The sample is placed under vacuum in the presence of a drying agent. Two potential problems must be noted. The first deals with samples that sublime readily. Under vacuum, the likelihood of sublimation is increased. The second problem deals with the vacuum desiccator itself. Because the surface area of glass that is under vacuum is large, there is some danger that the desiccator could implode. A vacuum desiccator should never be used unless it has been placed within a protective metal container (cage). If a cage is not available, the

desiccator can be wrapped with electrical or duct tape. If you use an aspirator as a source of vacuum, you should use a water trap (see Technique 8, Figure 8.5).

Procedure B

This method can be accomplished with a round-bottom flask and a thermometer adapter equipped with a short piece of glass tubing, as illustrated in Figure 11.7B. In microscale work, the apparatus with the round-bottom flask can be modified by replacing the round-bottom flask with a conical vial. The glass tubing is connected by vacuum tubing to either an aspirator or a vacuum pump. A convenient alternative, using a sidearm test tube, is also shown in Figure 11.7B. With either apparatus, install a water trap when an aspirator is used.

11.10 Mixed Solvents

Often, the desired solubility characteristics for a particular compound are not found in a single solvent. In these cases, a mixed solvent may be used. You simply select a first solvent in which the solute is soluble and a second solvent, miscible with the first, in which the solute is relatively insoluble. The compound is dissolved in a minimum amount of the boiling solvent in which it is soluble. Following this, the second hot solvent is added to the boiling mixture, dropwise, until the mixture barely becomes cloudy. The cloudiness indicates precipitation. At this point, more of the first solvent should be added. Just enough is added to clear the cloudy mixture. At that point, the solution is saturated, and as it cools, crystals should separate. Common solvent mixtures are listed in Table 11.3.

It is important not to add an excess of the second solvent or to cool the solution too rapidly. Either of these actions may cause the solute to oil out, or separate as a viscous liquid. If this happens, reheat the solution and add more of the first solvent.

TABLE 11.3 Common Solvent Pairs for Crystallization

Methanol–water	Ether–acetone
Ethanol–water	Ether–petroleum ether
Acetic acid–water	Toluene–ligroin
Acetone–water	Methylene chloride–methanol
Ether–methanol	Dioxane[a]–water

[a]Suspected carcinogen.

PROBLEMS

1. Listed below are solubility-vs.-temperature data for an organic substance A dissolved in water.

Temperature (°C)	Solubility of A in 100 mL of Water (g)
0	1.5
20	3.0
40	6.5
60	11.0
80	17.0

a. Graph the solubility of A vs. temperature. Use the data given in the table. Connect the data points with a smooth curve.

b. Suppose 0.1 g of A and 1.0 mL of water were mixed and heated to 80°C. Would all of substance A dissolve?

c. The solution prepared in (b) is cooled. At what temperature will crystals of A appear?

d. Suppose the cooling described in (c) were continued to 0°C. How many grams of A would come out of solution? Explain how you obtained your answer.

2. What would likely happen if a hot saturated solution were filtered by vacuum filtration using a Büchner funnel? (*Hint:* The mixture will cool as it comes in contact with the Büchner funnel.)

3. A compound you have prepared is reported in the literature to have a pale yellow color. When the substance is dissolved in hot solvent to purify it by crystallization, the resulting solution is yellow. Should you use decolorizing charcoal before allowing the hot solution to cool? Explain your answer.

4. While performing a crystallization, you obtain a light tan solution after dissolving your crude product in hot solvent. A decolorizing step is determined to be unnecessary, and there are no solid impurities present. Should you perform a filtration to remove impurities before allowing the solution to cool? Why or why not?

5. a. Draw a graph of a cooling curve (temperature vs. time) for a solution of a solid substance that shows no supercooling effects. Assume that the solvent does not freeze.

b. Repeat the instructions in (a) for a solution for a solid substance that shows some supercooling behavior, but eventually yields crystals if the solution is cooled sufficiently.

6. A solid substance A is soluble in water to the extent of 10 mg/mL of water at 25°C and 100 mg/mL of water at 100°C. You have a sample that contains 100 mg of A and an impurity B.

a. Assuming that 2 mg of B are present along with 100 mg of A, describe how you can purify A if B is completely insoluble in water. Your description should include the volume of solvent required.

b. Assuming that 2 mg of the impurity B are present along with 100 mg of A, describe how you can purify A if B has the same solubility behavior as A. Will one crystallization produce pure A? (Assume that the solubilities of both A and B are unaffected by the presence of the other substance.)

c. Assume that 25 mg of the impurity B are present along with 100 mg of A. Describe how you can purify A if B has the same solubility behavior as A. Each time, use the minimum amount of water to just dissolve the solid. Will one crystallization produce absolutely pure A? How many crystallizations would be needed to produce pure A? How much A will have been recovered when the crystallizations have been completed?

7. Consider the crystallization of sulfanilamide from 95% ethyl alcohol. If impure sulfanilamide is dissolved in the minimum amount of 95% ethyl alcohol at 40°C rather than 78°C (the boiling point of ethyl alcohol), how would this affect the percent recovery of pure sulfanilamide? Explain your answer.

12 TECHNIQUE 12

Extractions, Separations, and Drying Agents

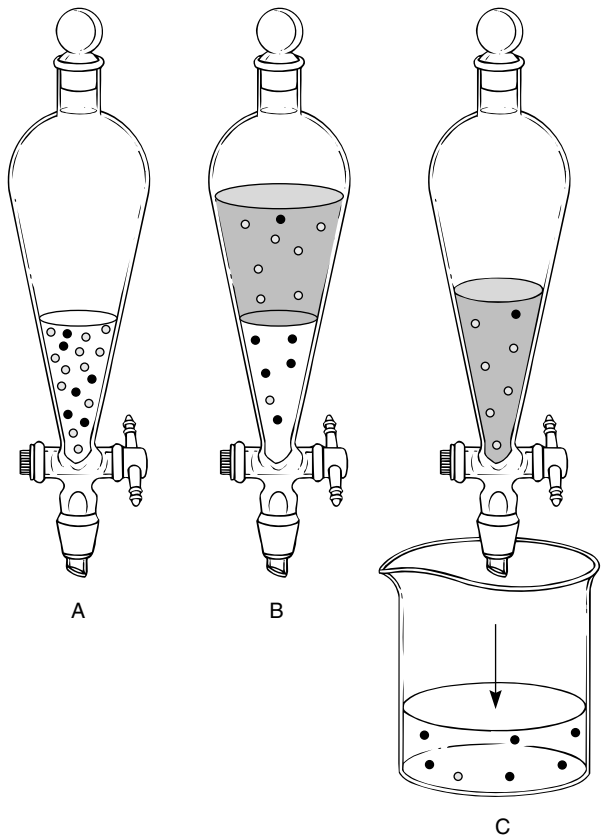
PART A. THEORY

12.1 Extraction

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

Transferring a solute from one solvent into another is called **extraction**, or, more precisely, liquid–liquid extraction. The solute is extracted from one solvent into the other because the solute is more soluble in the second solvent than in the first. The two solvents must not be **miscible** (mix freely), and they must form two separate **phases** or layers, in order for this procedure to work. Extraction is used in many ways in organic chemistry. Many **natural products** (organic chemicals that exist in nature) are present in animal and plant tissues having high water content. Extracting these tissues with a water-immiscible solvent is useful for isolating the natural products. Often, diethyl ether (commonly referred to as "ether") is used for this purpose. Sometimes, alternative water-immiscible solvents such as hexane, petroleum ether, ligroin, and methylene chloride are used. For instance, caffeine, a natural product, can be extracted from an aqueous tea solution by shaking the solution successively with several portions of methylene chloride.

A generalized extraction process, using a specialized piece of glassware called a **separatory funnel**, is illustrated in Figure 12.1. The first solvent contains a



A. Solvent 1 contains a mixture of molecules (black and white).

B. After shaking with solvent 2 (shaded), most of the white molecules have been extracted into the new solvent. The white molecules are more soluble in the second solvent, whereas the black molecules are more soluble in the original solvent.

C. With removal of the lower phase, the black and white molecules have been partially separated.

Figure 12.1 The extraction process.

mixture of black-and-white molecules (see Figure 12.1A). A second solvent that is not miscible with the first is added. After the separatory funnel is capped and shaken, the layers separate. In this example, the second solvent (shaded) is less dense than the first, so it becomes the top layer (see Figure 12.1B). Because of differences in physical properties, the white molecules are more soluble in the second solvent, whereas the black molecules are more soluble in the first solvent. Most of the white molecules are in the upper layer, but there are some black molecules there, too. Likewise, most of the black molecules are in the lower layer. However, there are still a few white molecules in this lower phase. The lower phase may be separated from the upper phase by opening the stopcock at the bottom of the separatory funnel and allowing the lower layer to drain into a beaker (see Figure 12.1C). In this example, notice that it was not possible to effect a complete separation of the two types of molecules with a single extraction. This is a common occurrence in organic chemistry.

Many substances are soluble in both water and organic solvents. Water can be used to extract, or "wash," water-soluble impurities from an organic reaction mixture. To carry out a "washing" operation, you add water and an immiscible organic solvent to the reaction mixture contained in a separatory funnel. After stoppering the funnel and shaking it, you allow the organic layer and the aqueous (water) layer to separate. A water wash removes highly polar and water-soluble materials, such as sulfuric acid, hydrochloric acid, and sodium hydroxide, from the organic layer. The washing operation helps to purify the desired organic compound present in the original reaction mixture.

12.2 Distribution Coefficient

When a solution (solute A in solvent 1) is shaken with a second solvent (solvent 2) with which it is not miscible, the solute distributes itself between the two liquid phases. When the two phases have separated again into two distinct solvent layers, an equilibrium will have been achieved such that the ratio of the concentrations of the solute in each layer defines a constant. The constant, called the **distribution coefficient** (or partition coefficient) K, is defined by

$$K = \frac{C_2}{C_1}$$

where C_1 and C_2 are the concentrations at equilibrium, in grams per liter or milligrams per milliliter of solute A in solvent 1 and in solvent 2, respectively. This relationship is a ratio of two concentrations and is independent of the actual amounts of the two solvents mixed. The distribution coefficient has a constant value for each solute considered and depends on the nature of the solvents used in each case.

Not all of the solute will be transferred to solvent 2 in a single extraction unless K is very large. Usually, it takes several extractions to remove all of the solute from solvent 1. In extracting a solute from a solution, it is always better to use several small portions of the second solvent than to make a single extraction with a large portion. Suppose, as an illustration, a particular extraction proceeds with a distribution coefficient of 10. The system consists of 5.0 g of organic compound dissolved in 100 mL of water (solvent 1). In this illustration, the effectiveness of three 50-mL extractions with ether (solvent 2) is compared with one 150-mL extraction with ether. In the first 50-mL extraction, the amount extracted into the ether layer is given by the following calculation. The amount of compound remaining in the aqueous phase is given by x.

$$K = 10 = \frac{C_2}{C_1} = \frac{\left(\dfrac{5.0 - x}{50}\dfrac{\text{g}}{\text{mL ether}}\right)}{\left(\dfrac{x}{100}\dfrac{\text{g}}{\text{mL H}_2\text{O}}\right)}; \qquad 10 = \frac{(5.0 - x)(100)}{50x}$$

$$\begin{aligned} 500x &= 500 - 100x \\ 600x &= 500 \\ x &= 0.83 \text{ g remaining in the aqueous phase} \\ 5.0 - x &= 4.17 \text{ g in the ether layer} \end{aligned}$$

As a check on the calculation, it is possible to substitute the value 0.83 g for x in the original equation and demonstrate that the concentration in the ether layer divided by the concentration in the water layer equals the distribution coefficient.

$$\frac{\left(\dfrac{5.0 - x}{50}\dfrac{\text{g}}{\text{mL ether}}\right)}{\left(\dfrac{x}{100}\dfrac{\text{g}}{\text{mL H}_2\text{O}}\right)} = \frac{\dfrac{4.17}{50}}{\dfrac{0.83}{100}} = \frac{0.083 \text{ g/mL}}{0.0083 \text{ g/mL}} = 10 = K$$

The second extraction with another 50-mL portion of fresh ether is performed on the aqueous phase, which now contains 0.83 g of the solute. The amount of solute extracted is given by the calculation shown in Figure 12.2. Also shown in the figure is a calculation for a third extraction with another 50-mL portion of ether. This third extraction will transfer 0.12 g of solute into the ether layer, leaving 0.02 g of solute remaining in the water layer. A total of 4.98 g of solute will be extracted into the combined ether layers, and 0.02 g will remain in the aqueous phase.

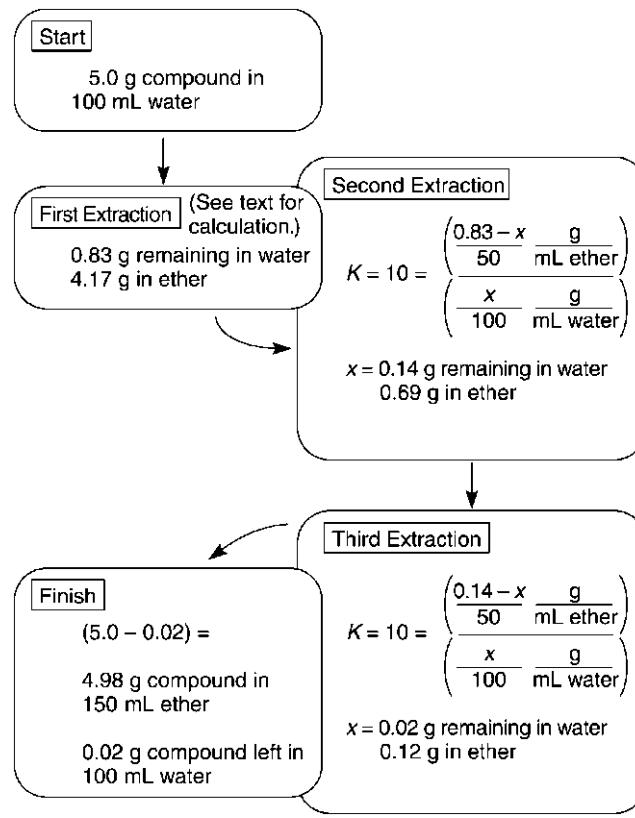


Figure 12.2 The result of extraction of 5.0 g of compound in 100 mL of water by three successive 50-mL portions of ether. Compare this result with that of Figure 12.3.

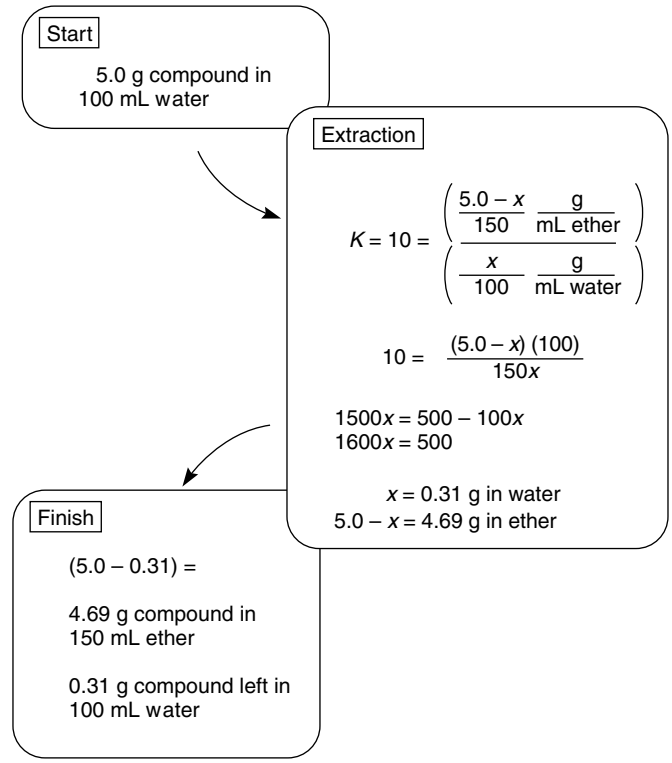


Figure 12.3 The result of extraction of 5.0 g of compound in 100 mL of water with one 150-mL portion of ether. Compare this result with that of Figure 12.2.

Figure 12.3 shows the result of a *single* extraction with 150 mL of ether. As shown there, 4.69 g of solute were extracted into the ether layer, leaving 0.31 g of compound in the aqueous phase. Three successive 50-mL ether extractions (see Figure 12.2) succeeded in removing 0.29 g more solute from the aqueous phase than using one 150-mL portion of ether (see Figure 12.3). This differential represents 5.8% of the total material.

NOTE: Several extractions with smaller amounts of solvent are more effective than one extraction with a larger amount of solvent.

12.3 Choosing an Extraction Method and a Solvent

Three types of apparatus are used for extractions: conical vials, centrifuge tubes, and separatory funnels (see Figure 12.4). Conical vials may be used with volumes of less than 4 mL; volumes of up to 10 mL may be handled in centrifuge tubes. A centrifuge tube equipped with a screw cap is particularly useful for extractions. Conical vials and centrifuge tubes are most often used in microscale experiments, although a centrifuge tube may also be used in some macroscale applications. The separatory funnel is used with larger volumes of liquid in macroscale experiments. The separatory funnel is discussed in Part B and the conical vial and centrifuge tube are discussed in Part C.

TABLE 12.1 Densities of Common Extraction Solvents

Solvent	Density (g/mL)
Ligroin	0.67–0.69
Diethyl ether	0.71
Toluene	0.87
Water	1.00
Methylene chloride	1.330

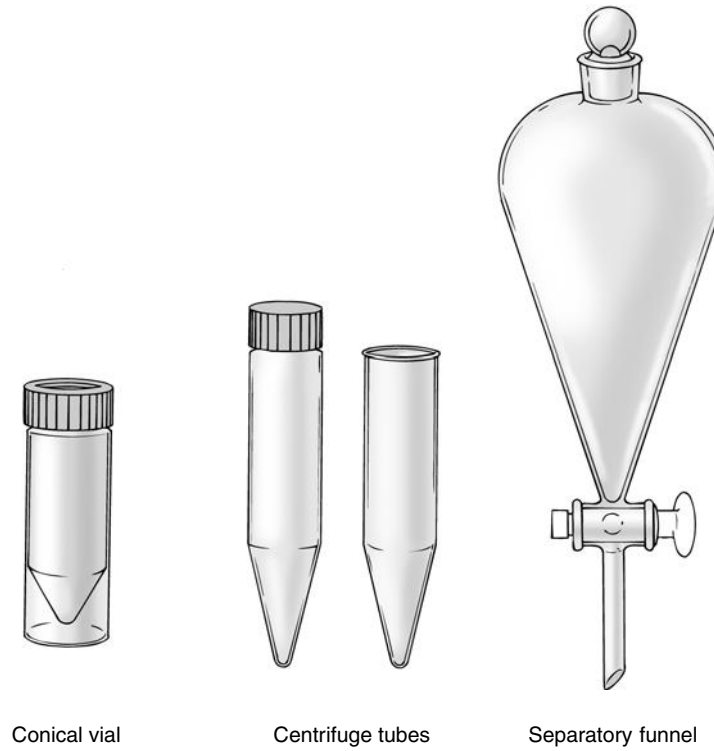


Figure 12.4 The apparatus used in extraction.

Most extractions consist of an aqueous phase and an organic phase. To extract a substance from an aqueous phase, you must use an organic solvent that is not miscible with water. Table 12.1 lists a number of the common organic solvents that are not miscible with water and are used for extractions.

Solvents that have a density less than that of water (1.00 g/mL) will separate as the top layer when shaken with water. Solvents that have a density greater than that of water will separate into the lower layer. For instance, diethyl ether (d = 0.71 g/mL) when shaken with water will form the upper layer, whereas methylene chloride (d = 1.33 g/mL) will form the lower layer. When an extraction is performed, slightly different methods are used to separate the lower layer (whether or not it is the aqueous layer or the organic layer) than to separate the upper layer.

PART B. MACROSCALE EXTRACTION

12.4 The Separatory Funnel

A separatory funnel is illustrated in Figure 12.5. It is the piece of equipment used for carrying out extractions with medium to large quantities of material. To fill the separatory funnel, support it in an iron ring attached to a ring stand. Since it is easy to break a separatory funnel by "clanking" it against the metal ring, pieces of rubber tubing are often attached to the ring to cushion the funnel, as shown in Figure 12.5. These are short pieces of tubing cut to a length of about 3 cm and slit open along their length. When slipped over the inside of the ring, they cushion the funnel in its resting place.

When beginning an extraction, first close the stopcock. (Don't forget!) Using a powder funnel (wide bore) placed in the top of the separatory funnel, fill the funnel with both the solution to be extracted and the extraction solvent. Swirl the funnel gently

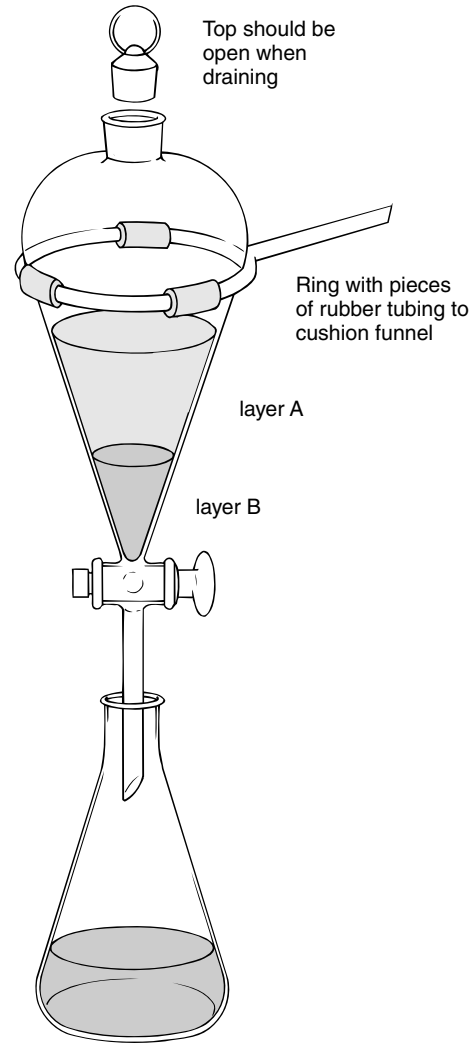


Figure 12.5 A separatory funnel.

by holding it by its upper neck and then stopper it. Pick up the separatory funnel with two hands and hold it as shown in Figure 12.6. Hold the stopper in place firmly because the two immiscible liquids will build pressure when they mix, and this pressure may force the stopper out of the separatory funnel. To release this pressure, vent the funnel by holding it upside down (hold the stopper securely) and slowly open the stopcock. Usually, the rush of vapors out of the opening can be heard. Continue shaking and venting until the "whoosh" is no longer audible. Now continue shaking the mixture gently for about 1 minute. This can be done by inverting the funnel in a rocking motion repeatedly or, if the formation of an emulsion is not a problem (see Section 12.10), by shaking the funnel more vigorously for less time.

NOTE: There is an art to shaking and venting a separatory funnel correctly, and this technique usually seems awkward to the beginner. The technique is best learned by observing a person, such as your instructor, who is thoroughly familiar with the separatory funnel's use.

When you have finished mixing the liquids, place the separatory funnel in the iron ring and remove the top stopper immediately. The two immiscible solvents separate into two layers after a short time, and they can be separated from one another by draining most of the lower layer through the stopcock.[1] Allow a few minutes to pass so that any of the lower phase adhering to the inner glass surfaces of the separatory funnel can drain down. Open the stopcock again and allow the remainder of the lower layer to drain until the interface between the upper and lower phases just begins to enter the bore of the stopcock. At this moment, close the stopcock and remove the remaining upper layer by pouring it from the top opening of the separatory funnel.

Figure 12.6 The correct way of shaking and venting a separatory funnel.

[1]A common error is to try to drain the separatory funnel without removing the top stopper. Under this circumstance, the funnel will not drain because a partial vacuum is in the space above the liquid.

NOTE: To minimize contamination of the two layers, the lower layer should always be drained from the bottom of the separatory funnel and the upper layer poured out from the top of the funnel.

When methylene chloride is used as the extracting solvent with an aqueous phase, it will settle to the bottom and be removed through the stopcock. The aqueous layer remains in the funnel. A second extraction of the remaining aqueous layer with fresh methylene chloride may be needed.

With a diethyl ether (ether) extraction of an aqueous phase, the organic layer will form on top. Remove the lower aqueous layer through the stopcock and pour the upper ether layer from the top of the separatory funnel. Pour the aqueous phase back into the separatory funnel and extract it a second time with fresh ether. The combined organic phases must be dried using a suitable drying agent (see Section 12.9) before the solvent is removed.

The usual macroscale procedure requires the use of a 125-mL or 250-mL separatory funnel. For microscale procedures, a 60-mL or 125-mL separatory funnel is recommended. Because of surface tension, water has a difficult time draining from the bore of smaller funnels.

PART C. MICROSCALE EXTRACTION

12.5 The Conical Vial—Separating the Lower Layer

Before using a conical vial for an extraction, make sure that the capped conical vial does not leak when shaken. To do this, place some water in the conical vial, place the Teflon liner in the cap, and screw the cap securely onto the conical vial. Shake the vial vigorously and check for leaks. Conical vials that are used for extractions must not be chipped on the edge of the vial or they will not seal adequately. If there is a leak, try tightening the cap or replacing the Teflon liner with another one. Sometimes it helps to use the silicone rubber side of the liner to seal the conical vial. Some laboratories are supplied with Teflon stoppers that fit into the 5-mL conical vials. You may find that this stopper eliminates leakage.

When shaking the conical vial, do it gently at first in a rocking motion. When it is clear that an emulsion will not form (see Section 12.10), you can shake it more vigorously.

In some cases, adequate mixing can be achieved by spinning your microspatula for at least 10 minutes in the conical vial. Another technique of mixing involves drawing the mixture up into a Pasteur pipet and squirting it rapidly back into the vial. Repeat this process for at least 5 minutes to obtain an adequate extraction.

The 5-mL conical vial is the most useful piece of equipment for carrying out extractions on a microscale level. In this section, we consider the method for removing the lower layer. A concrete example would be the extraction of a desired product from an aqueous layer using methylene chloride (d = 1.33 g/mL) as the extraction solvent. Methods for removal of the upper layer are discussed in the next section.

NOTE: Always place a conical vial in a small beaker to prevent the vial from falling over.

Removing the Lower Layer. Suppose that we extract an aqueous solution with methylene chloride. This solvent is denser than water and will settle to the bottom of the conical vial. Use the following procedure, which is illustrated in Figure 12.7, to remove the lower layer.

1. Place the aqueous phase containing the dissolved product into a 5-mL conical vial (see Figure 12.7A).
2. Add about 1 mL of methylene chloride, cap the vial, and shake the mixture gently at first in a rocking motion and then more vigorously when it is clear that an emulsion will not form. Vent or unscrew the cap slightly to release the pressure in the vial. Allow the phases to separate completely so that you can detect two distinct layers in the vial. The organic phase will be the lower layer in the vial (see Figure 12.7B). If necessary, tap the vial with your finger or stir the mixture gently if some of the organic phase is suspended in the aqueous layer.
3. Prepare a Pasteur filter-tip pipet (see Technique 8, Section 8.6) using a $5\frac{3}{4}$-inch pipet. Attach a 2-mL rubber bulb to the pipet, depress the bulb, and insert the pipet into the vial so that the tip touches the bottom (see Figure 12.7C). The filter-tip pipet gives you better control in removing the lower layer. In some cases, however, you may be able to use a Pasteur pipet (no filter tip), but considerably more care must be taken to avoid losing liquid from the pipet during the transfer operation. With experience, you should be able to judge how much to squeeze the bulb to draw in the desired volume of liquid.
4. Slowly draw the lower layer (methylene chloride) into the pipet in such a way that you exclude the aqueous layer and any emulsion (see Section 12.10) that might be at the interface between the layers (see Figure 12.7D). Be sure to keep the tip of the pipet squarely in the V at the bottom of the vial.
5. Transfer the withdrawn organic phase into a *dry* test tube or another *dry* conical vial if one is available. It is best to have the test tube or vial located next to the extraction vial. Hold the vials in the same hand between your index finger and thumb, as shown in Figure 12.8. This avoids messy and disastrous transfers. The aqueous layer (upper layer) is left in the original conical vial (see Figure 12.7E).

In performing an actual extraction in the laboratory, you would extract the aqueous phase with a second 1-mL portion of fresh methylene chloride to achieve a more complete extraction. Steps 2–5 would be repeated, and the organic layers from both extractions would be combined. In some cases, you may need to extract a third time with yet another 1-mL portion of methylene chloride. Again, the methylene chloride would be combined with the other extracts. The overall process would use three 1-mL portions of methylene chloride to transfer the product from the water layer into methylene chloride. Sometimes you will see the statement "extract the aqueous phase with three 1-mL portions of methylene chloride" in an experimental procedure. This statement describes in a shorter fashion the process described previously. Finally, the methylene chloride extracts will contain some water and must be dried with a drying agent as indicated in Section 12.9.

NOTE: If an organic solvent has been extracted with water, it should be dried with a drying agent (see Section 12.9) before proceeding.

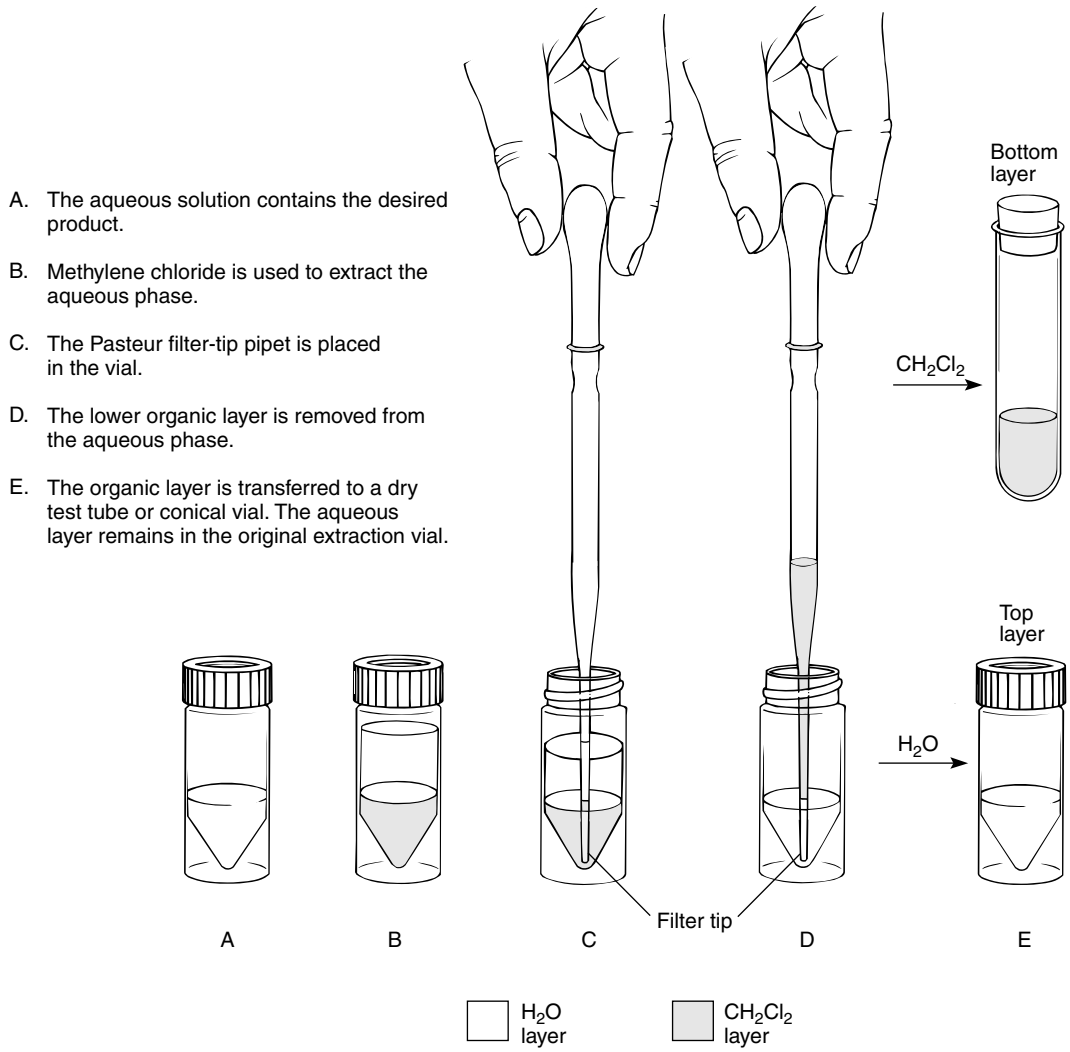


Figure 12.7 Extraction of an aqueous solution using a solvent denser than water: methylene chloride.

In this example, we extracted water with the heavy solvent methylene chloride and removed it as the lower layer. If you were extracting a light solvent (for instance, diethyl ether) with water and you wished to keep the water layer, the water would be the lower layer and would be removed using the same procedure. You would not dry the water layer, however.

12.6 The Conical Vial—Separating the Upper Layer

In this section, we consider the method used when you wish to remove the upper layer. A concrete example would be the extraction of a desired product from an aqueous layer using diethyl ether (d = 0.71 g/mL) as the extraction solvent. Methods for removing the lower layer were discussed previously.

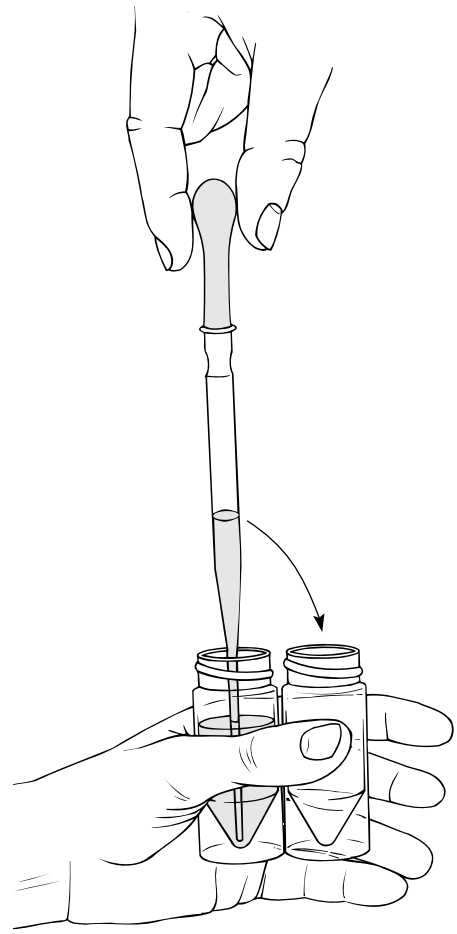


Figure 12.8 Method for holding vials while transferring liquids.

NOTE: Always place a conical vial in a small beaker to prevent the vial from falling over.

Removing the Upper Layer. Suppose we extract an aqueous solution with diethyl ether (ether). This solvent is less dense than water and will rise to the top of the conical vial. Use the following procedure, which is illustrated in Figure 12.9, to remove the upper layer.

1. Place the aqueous phase containing the dissolved product in a 5-mL conical vial (Figure 12.9A).
2. Add about 1 mL of ether, cap the vial, and shake the mixture vigorously. Vent or unscrew the cap slightly to release the pressure in the vial. Allow the phases to separate completely so that you can detect two distinct layers in the vial. The ether phase will be the upper layer in the vial (see Figure 12.9B).
3. Prepare a Pasteur filter-tip pipet (see Technique 8, Section 8.6) using a $5\frac{3}{4}$-inch pipet. Attach a 2-mL rubber bulb to the pipet, depress the bulb, and insert the pipet into the vial so that the tip touches the bottom. The filter-tip pipet gives you better control in removing the lower layer. In some cases, however, you may be able to use a Pasteur pipet (no filter tip), but considerably

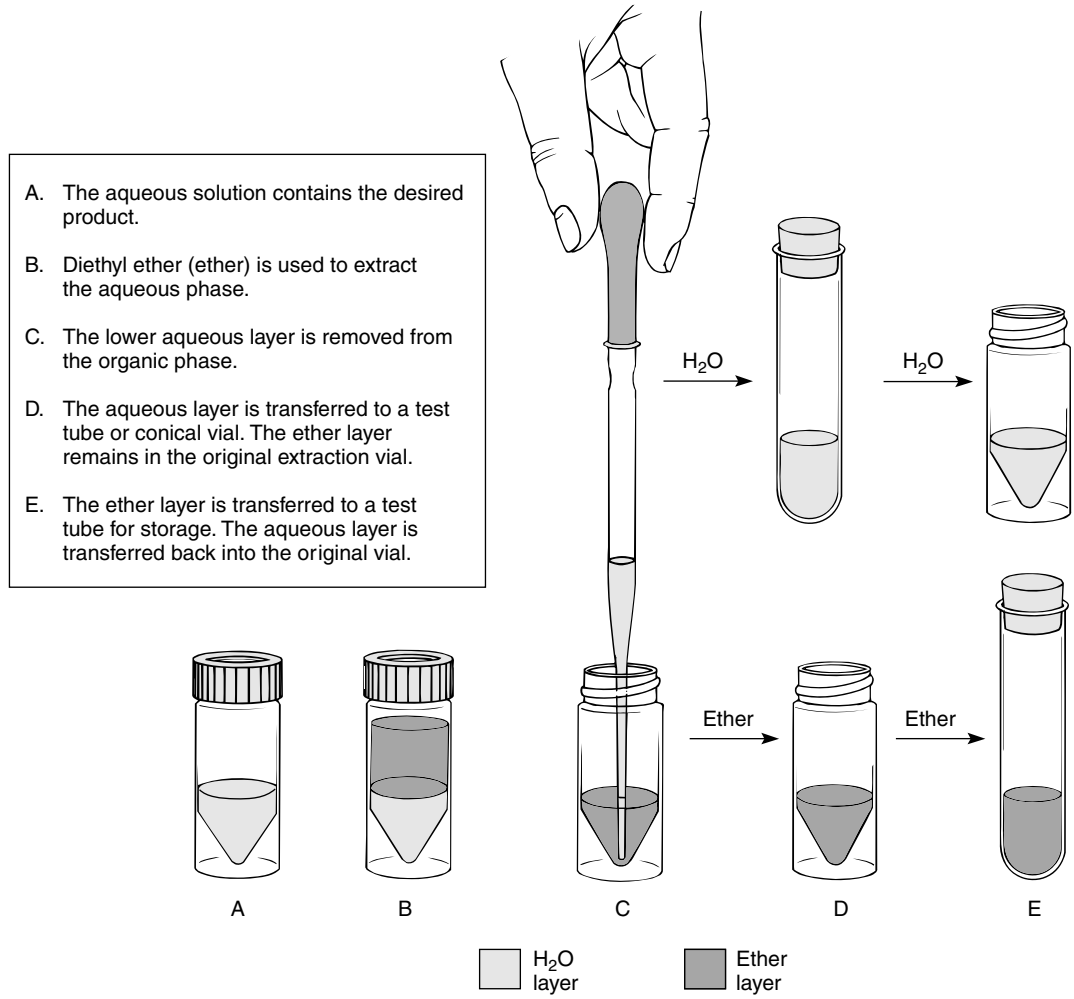


Figure 12.9 Extraction of an aqueous solution using a solvent less dense than water: diethyl ether.

more care must be taken to avoid losing liquid from the pipet during the transfer operation. With experience, you should be able to judge how much to squeeze the bulb to draw in the desired volume of liquid. Slowly draw the lower *aqueous* layer into the pipet. Be sure to keep the tip of the pipet squarely in the V at the bottom of the vial (see Figure 12.9C).

4. Transfer the withdrawn aqueous phase into a test tube or another conical vial for temporary storage. It is best to have the test tube or vial located next to the extraction vial. This avoids messy and disastrous transfers. Hold the vials in the same hand between your index finger and thumb, as shown in Figure 12.8. The ether layer is left behind in the conical vial (see Figure 12.9D).
5. The ether phase remaining in the original conical vial should be transferred with a Pasteur pipet into a test tube for storage and the aqueous phase returned to the original conical vial (see Figure 12.9E).

In performing an actual extraction, you would extract the aqueous phase with another 1-mL portion of fresh ether to achieve a more complete extraction. Steps 2–5 would be repeated, and the organic layers from both extractions would be

combined in the test tube. In some cases, you may need to extract the aqueous layer a third time with yet another 1-mL portion of ether. Again, the ether would be combined with the other two layers. This overall process uses three 1-mL portions of ether to transfer the product from the water layer into ether. The ether extracts contain some water and must be dried with a drying agent as indicated in Section 12.9.

12.7 The Screw-Cap Centrifuge Tube

If you require an extraction that uses a larger volume than a conical vial can accommodate (about 4 mL), a centrifuge tube can often be used. A centrifuge tube can also be used instead of a separatory funnel for some macroscale applications in which the total volume of liquid is less than about 12 mL. A commonly available size of centrifuge tube has a volume of about 15 mL and is supplied with a screw cap. In performing an extraction with a screw-cap centrifuge tube, use the same procedures outlined for the conical vial (see Sections 12.5 and 12.6). As is the case for a conical vial, the tapered bottom of the centrifuge tube makes it easy to withdraw the lower layer with a Pasteur pipet.

NOTE: A centrifuge tube has a great advantage over other methods of extraction. If an emulsion (Section 12.10) forms, you can use a centrifuge to aid in the separation of the layers.

You should check the capped centrifuge tube for leaks by filling it with water and shaking it vigorously. If it leaks, try replacing the cap with a different one. A **vortex mixer**, if available, provides an alternative to shaking the tube. In fact, a vortex mixer works well with a variety of containers, including small flasks, test tubes, conical vials, and centrifuge tubes. You start the mixing action on a vortex mixer by holding the test tube or other container on one of the neoprene pads. The unit mixes the sample by high-frequency vibration.

PART D. ADDITIONAL EXPERIMENTAL CONSIDERATIONS: MACROSCALE AND MICROSCALE

12.8 How Do You Determine Which One Is the Organic Layer?

A common problem encountered during an extraction is trying to determine which of the two layers is the organic layer and which is the aqueous (water) layer. The most common situation occurs when the aqueous layer is on the bottom in the presence of an upper organic layer consisting of ether, ligroin, petroleum ether, or hexane (see densities in Table 12.1). However, the aqueous layer will be on the top when you use methylene chloride as a solvent (again, see Table 12.1). Although a laboratory procedure may frequently identify the expected relative positions of the organic and aqueous layers, sometimes their actual positions are reversed. Surprises usually occur in situations in which the aqueous layer contains a high concentration of sulfuric acid or a dissolved ionic compound, such as sodium chloride. Dissolved substances greatly increase the density of the aqueous layer, which may lead to the aqueous layer being found on the bottom even when coexisting with a relatively dense organic layer such as methylene chloride.

NOTE: Always keep both layers until you have actually isolated the desired compound or until you are certain where your desired substance is located.

To determine if a particular layer is the aqueous one, add a few drops of water to the layer. Observe closely as you add the water to see where it goes. If the layer is water, then the drops of added water will dissolve in the aqueous layer and increase its volume. If the added water forms droplets or a new layer, however, you can assume that the suspected aqueous layer is actually organic. You can use a similar procedure to identify a suspected organic layer. This time, try adding more of the solvent, such as methylene chloride. The organic layer should increase in size, without separation of a new layer, if the tested layer is actually organic.

When performing an extraction procedure on the microscale level, you can use the following approach to identify the layers. When both layers are present, it is always a good idea to think carefully about the volumes of materials that you have added to the conical vial. You can use the graduations on the vial to help determine the volumes of the layers in the vial. If, for example, you have 1 mL of methylene chloride in a vial and you add 2 mL of water, you should expect the water to be on top because it is less dense than methylene chloride. As you add the water, *watch to see where it goes.* By noting the relative volumes of the two layers, you should be able to tell which is the aqueous layer and which is the organic layer. This approach can also be used when performing an extraction procedure using a centrifuge tube. Of course, you can always test to see which layer is the aqueous layer by adding one or two drops of water, as described previously.

12.9 Drying Agents

After an organic solvent has been shaken with an aqueous solution, it will be "wet"; that is, it will have dissolved some water even though its solubility with water is not great. The amount of water dissolved varies from solvent to solvent; diethyl ether represents a solvent in which a fairly large amount of water dissolves. To remove water from the organic layer, use a **drying agent**. A drying agent is an *anhydrous* inorganic salt that acquires waters of hydration when exposed to moist air or a wet solution:

$$\underset{\text{Anhydrous drying agent}}{\underset{\textbf{Insoluble}}{Na_2SO_4(s)}} + \text{Wet Solution } (nH_2O) \longrightarrow \underset{\text{Hydrated drying agent}}{\underset{\textbf{Insoluble}}{Na_2SO_4 \cdot nH_2O\,(s)}} + \text{Dry Solution}$$

The insoluble drying agent is placed directly into the solution, where it acquires water molecules and becomes hydrated. If enough drying agent is used, all of the water can be removed from a wet solution, making it "dry," or free of water.

The following anhydrous salts are commonly used: sodium sulfate, magnesium sulfate, calcium chloride, calcium sulfate (Drierite), and potassium carbonate. These salts vary in their properties and applications. For instance, not all will absorb the same amount of water for a given weight, nor will they dry the solution to the same extent. **Capacity** refers to the amount of water a drying agent absorbs per unit weight. Sodium and magnesium sulfates absorb a large amount of water (high capacity), but magnesium sulfate dries a solution more completely. **Completeness** refers to a compound's effectiveness in removing all the water from a solution by the time equilibrium has been reached. Magnesium ion, a strong Lewis acid, sometimes causes rearrangements of compounds such as epoxides. Calcium chloride is a good drying agent, but cannot be used with many compounds containing oxygen or nitrogen because it forms complexes. Calcium chloride absorbs methanol and ethanol in addition to water, so it is useful for removing these materials when they are present as impurities. Potassium carbonate is a base

and is used for drying solutions of basic substances, such as amines. Calcium sulfate dries a solution completely, but has a low capacity.

Anhydrous sodium sulfate is the most widely used drying agent. The granular variety is recommended because it is easier to remove the dried solution from it than from the powdered variety. Sodium sulfate is mild and effective. It will remove water from most common solvents, with the possible exception of diethyl ether, in which case a prior drying with saturated salt solution may be advised. Sodium sulfate must be used at room temperature to be effective; it cannot be used with boiling solutions. Table 12.2 compares the various common drying agents.

Drying Procedure with Snhydrous Sodium Sulfate. In experiments that require a drying step, the instructions are usually given in the following way: dry the organic layer (or phase) over granular anhydrous sodium sulfate (or some other drying agent). More specific instructions, such as the amount of drying agent to add, usually will not be given, and you will need to determine this each time that you perform a drying step. The drying procedure consists of four steps:

1. Remove the organic layer from any visible water.
2. Add the appropriate amount of granular anhydrous sodium sulfate (or other drying agent).
3. Allow a drying period during which dissolved water is removed from the organic layer by the drying agent.
4. Separate the dried organic layer from the drying agent.

More specific instructions are given below for both macroscale and microscale procedures. The only differences between these two procedures is that they are

TABLE 12.2 Common Drying Agents

	Acidity	Hydrated	Capacity[a]	Completeness[b]	Rate[c]	Use
Magnesium sulfate	Neutral	$MgSO_4 \cdot 7H_2O$	High	Medium	Rapid	General
Sodium sulfate	Neutral	$Na_2SO_4 \cdot 7H_2O$ $Na_2SO_4 \cdot 10H_2O$	High	Low	Medium	General
Calcium chloride	Neutral	$CaCl_2 \cdot 2H_2O$ $CaCl_2 \cdot 6H_2O$	Low	High	Rapid	Hydrocarbons Halides
Calcium sulfate (Drierite)	Neutral	$CaSO_4 \cdot \frac{1}{2}H_2O$ $CaSO_4 \cdot 2H_2O$	Low	High	Rapid	General
Potassium carbonate	Basic	$K_2CO_3 \cdot 1\frac{1}{2}H_2O$ $K_2CO_3 \cdot 2H_2O$	Medium	Medium	Medium	Amines, esters, bases, ketones
Potassium hydroxide	Basic	—	—	—	Rapid	Amines only
Molecular sieves (3 or 4 Å)	Neutral	—	High	Extremely high	—	General

[a]Amount of water removed per given weight of drying agent.

[b]Refers to amount of H_2O still in solution at equilibrium with drying agent.

[c]Refers to rate of action (drying).

intended for different volumes of liquid and they require different glassware. The microscale procedure is generally for volumes up to about 5 mL, and the macroscale procedure is usually appropriate for volumes of 5 mL or greater.

A. Macroscale Drying Procedure

Step 1. Removal of Visible Water. Before attempting to dry an organic layer, check closely to see that there are no visible signs of water. If there is a separate layer of water (top or bottom), droplets or a globule of water floating in the organic layer, or water droplets clinging to the sides of the container, then transfer the organic layer to a clean, dry Erlenmeyer flask before adding any drying agent. If there is a large amount of water, it may be best to separate the layers using a separatory funnel. Otherwise, you may use a dry Pasteur pipet to make the transfer. The size of the Erlenmeyer flask is not critical, but it's best that the flask not be filled more than half full with the solution and it is best to have a layer of liquid in the flask at least 1 cm deep. If there is any doubt whether water is present, it is advisable to make a transfer to a dry flask. Performing this step when necessary will save time later in the drying procedure and result in a greater recovery of the desired substance.

Step 2. Addition of Drying Agent. Each time a drying procedure is performed, it is necessary to determine how much granular anhydrous sodium sulfate (or other drying agent) should be added. This will depend on the total volume of the organic phase and how much water is dissolved in the solvent. Nonpolar organic solvents such as methylene chloride or hydrocarbons (hexane, pentane, etc.) can dissolve relatively small amounts of water and generally require less drying agent, whereas more polar organic solvents such as ether and ethyl acetate can dissolve more water, and more drying agent will be required. A common guideline is to add enough granular anhydrous sodium sulfate (or other drying agent) to give a 1- to 3-mm layer on the bottom of the flask, depending on the volume of the solution. However, it is best to add the drying agent in small portions in the following way. In this procedure, use the larger microspatula shown in Figure 12.10 to add the drying agent. Generally, an appropriate portion to add each time is about 0.5–1.0 g. (You should weigh this out the first time so that you will know how much to add.) Begin by adding one portion of granular anhydrous sodium sulfate (or other drying agent) into the solution. If all of the drying agent "clumps," add another portion of sodium sulfate. To determine if the drying agent has clumped, it is helpful to stir the mixture with a clean, dry spatula or to rapidly swirl the flask. If any portion of the drying agent flows freely (is not clumped) on the bottom of the container when stirred or swirled, then you can assume that enough of the drying agent has been added. Otherwise, you must continue adding one portion of drying agent at a time until it is clear that some of the drying agent has stopped clumping. Stir or swirl the mixture after adding each portion of the drying agent. It is likely that you will need to add at least several portions of drying agent. However, the actual amount must be determined by experimentation, as just described. It is best to use a slight excess of drying agent; but if too great an excess is used, the recovery may be poor because some of the solution always adheres to the solid drying agent after the liquid is separated from it (Step 4). Take care not to add so much drying agent that all of the liquid is absorbed (disappears). If you do this, you will have to add additional solvent to recover your product from the drying agent!

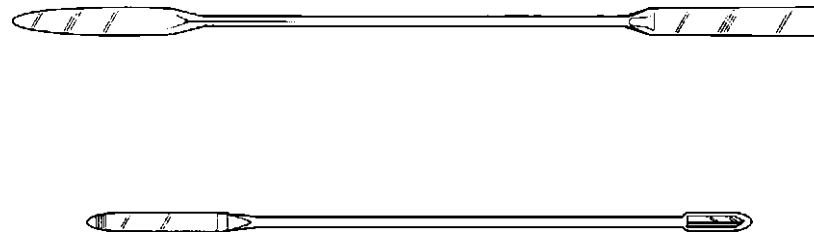


Figure 12.10 Microspatulas.

Step 3. Drying Period. Stopper or cap the container, and let the solution dry for at least 15 minutes.

NOTE: It is important that you stopper or cap the container to prevent evaporation and exposure to atmospheric moisture.

Swirl the mixture occasionally during the drying period. The mixture is dry if it appears clear (not cloudy) and shows the common signs of a dry solution given in Table 12.3. Note that a "clear" solution may be colorless or colored. If the solution remains cloudy after treatment with the first batch of drying agent, add more drying agent and repeat the drying procedure. However, if a water layer forms or if drops of water are visible, transfer the organic layer to a dry container before adding fresh drying agent, as described in Step 2. It will also be necessary to repeat the 15-minute drying step described in Step 3.

Step 4. Removal of Liquid from Drying Agent. When the solution is dry, the drying agent should be removed by using decantation (pouring carefully to leave the drying agent behind). Transfer the liquid to a dry Erlenmeyer flask. If the volume of liquid is relatively small (less than 10 mL), it may be easier to complete this step by using a dry Pasteur pipet or a dry filter-tip pipet (see Technique 8, Section 8.6) to remove the dried organic layer. With granular sodium sulfate, decantation is easy to perform because of the size of the drying-agent particles. If a powdered drying agent, such as magnesium sulfate, is used, it may be necessary to use gravity filtration (see Technique 8, Section 8.1B) to remove the drying agent. Finally, to isolate the desired material, remove the solvent by distillation (see Technique 14, Section 14.3) or evaporation (see Technique 7, Section 7.10).

B. Microscale Drying Procedure

To dry a small amount of organic liquid (less than about 5 mL), follow the same four steps just described for the "Macroscale Drying Procedure." The main differences

TABLE 12.3 Common Signs That Indicate a Solution Is Dry

1. There are no visible water droplets on the side of flask or suspended in solution.
2. There is not a separate layer of liquid or a "puddle."
3. The solution is clear, not cloudy. Cloudiness indicates water is present.
4. The drying agent (or a portion of it) flows freely on the bottom of the container when stirred or swirled and does not "clump" together as a solid mass.

are that a test tube or conical vial is used rather than an Erlenmeyer flask, and less drying agent will be required.

Step 1. Removal of visible water. Refer to Step 1 above for additional information. If there is a separate layer of water (top or bottom), droplets or a globule of water floating in the organic layer, or water droplets clinging to the sides of the container, then transfer the organic layer with a dry Pasteur pipet to a dry container, usually a conical vial or test tube, before adding any drying agent. If there is any doubt about whether water is present, it is advisable to make a transfer to a dry container.

Step 2. Addition of Drying Agent. Refer to Step 2 in the "Macroscale Drying Procedure" for the basic instructions. The only difference is that in this microscale procedure, less drying agent will be required. Begin by adding one spatulaful of granular anhydrous sodium sulfate (or other drying agent) from the V-grooved end of a microspatula (smaller microspatula in Figure 12.10) into the solution. If all of the drying agent "clumps," add another spatulaful of sodium sulfate. To determine if the drying agent has clumped, it is helpful to stir the mixture with a clean, dry spatula or to rapidly swirl the container. If any portion of the drying agent flows freely (does not clump) on the bottom of the container when stirred or swirled, then you can assume that enough of the drying agent has been added. Otherwise, you must continue adding one spatulaful of drying agent at a time until it is clear that the drying agent has stopped clumping. Stir or swirl the mixture after adding each spatulaful of the drying agent. For small amounts of liquid (less than 5 mL), about 1–6 microspatulafuls of drying agent will usually be required. However, the actual amount must be determined by experimentation, as just described. It is best to use a slight excess of drying agent; but if too great an excess is used, the recovery may be poor because some of the solution always adheres to the solid drying after the liquid is separated from the drying agent (Step 4). Take care not to add so much drying agent that all of the liquid is absorbed (disappears). If you do this, you will have to add additional solvent to recover your product from the drying agent!

Step 3. Drying Period. The instructions are the same as for Step 3 in the "Macroscale Drying Procedure."

Step 4. Removal of Liquid from Drying Agent. When the organic phase is dry, use a dry Pasteur pipet or a dry filter-tip pipet (see Technique 8, Section 8.6) to remove the dried organic layer from the drying agent and transfer the solution to a dry conical vial or test tube. Be careful not to transfer any of the drying agent when performing this step. Rinse the drying agent with a small amount of fresh solvent, and transfer this additional solvent to the vial containing the dried organic layer. To isolate the desired material, remove the solvent by evaporation using heat and a stream of air or nitrogen (see Technique 7, Section 7.10).

An alternative method of drying a small volume of organic phase is to pass it through a filtering pipet (see Technique 8, Section 8.1C) that has been packed with a small amount (about 2 cm) of drying agent. Again, the solvent is removed by evaporation.

Saturated Salt Solution. At room temperature, diethyl ether (ether) dissolves 1.5% by weight of water, and water dissolves 7.5% of ether. Ether, however, dissolves a much smaller amount of water from a saturated aqueous sodium chloride solution. Hence, the bulk of water in ether, or ether in water, can be removed by shaking it

with a saturated aqueous sodium chloride solution. A solution of high ionic strength is usually not compatible with an organic solvent and forces separation of it from the aqueous layer. The water migrates into the concentrated salt solution. The ether phase (organic layer) will be on top, and the saturated sodium chloride solution will be on the bottom (d =1.2 g/mL). After removing the organic phase from the aqueous sodium chloride, dry the organic layer completely with sodium sulfate or with one of the other drying agents listed in Table 12.2.

12.10 Emulsions

An **emulsion** is a colloidal suspension of one liquid in another. Minute droplets of an organic solvent are often held in suspension in an aqueous solution when the two are mixed or shaken vigorously; these droplets form an emulsion. This is especially true if any gummy or viscous material was present in the solution. Emulsions are often encountered in performing extractions. Emulsions may require a long time to separate into two layers and are a nuisance to the organic chemist.

Fortunately, several techniques may be used to break a difficult emulsion once it has formed.

1. Often an emulsion will break up if it is allowed to stand for some time. Patience is important here. Gently stirring with a stirring rod or spatula may also be useful.
2. If one of the solvents is water, adding a saturated aqueous sodium chloride solution will help destroy the emulsion. The water in the organic layer migrates into the concentrated salt solution.
3. If the total volume is less than 13 mL, the mixture may be transferred to a centrifuge tube. The emulsion will often break during centrifugation. Remember to place another tube filled with water on the opposite side of the centrifuge to balance it. Both tubes should weigh the same.
4. Adding a very small amount of a water-soluble detergent may also help. This method has been used in the past for combating oil spills. The detergent helps to solubilize the tightly-bound oil droplets.
5. Gravity filtration (see Technique 8, Section 8.1) may help to destroy an emulsion by removing gummy polymeric substances. With large volumes, you might try filtering the mixture through a fluted filter (see Technique 8, Section 8.1B) or a piece of cotton. With small-scale reactions, a filtering pipet may work (see Technique 8, Section 8.1C). In many cases, once the gum is removed, the emulsion breaks up rapidly.
6. If you are using a separatory funnel, you might try to use a gentle swirling action in the funnel to help break an emulsion. Gently stirring with a stirring rod may also be useful.

When you know through prior experience that a mixture may form a difficult emulsion, you should avoid shaking the mixture vigorously. When using conical vials for extractions, it may be better to use a magnetic spin vane for mixing and not shake the mixture at all. When using separatory funnels, extractions should be performed with gentle swirling instead of shaking, or with several gentle inversions of the separatory funnel. Do not shake the separatory funnel vigorously in these cases. It is important to use a longer extraction period if the more gentle techniques described in this paragraph are being employed. Otherwise, you will not transfer all of the material from the first phase to the second one.

12.11 Purification and Separation Methods

In nearly all synthetic experiments undertaken in the organic laboratory, a series of operations involving extractions is used after the actual reaction has been concluded. These extractions form an important part of the purification. Using them, you separate the desired product from unreacted starting materials or from undesired side products in the reaction mixture. These extractions may be grouped into three categories, depending on the nature of the impurities they are designed to remove.

The first category involves extracting or "washing" an organic mixture with water. Water washes are designed to remove highly polar materials, such as inorganic salts, strong acids or bases, and low-molecular-weight, polar substances including alcohols, carboxylic acids, and amines. Many organic compounds containing fewer than five carbons are water soluble. Water extractions are also used immediately following extractions of a mixture with either acid or base to ensure that all traces of acid or base have been removed.

The second category concerns extraction of an organic mixture with a dilute acid, usually 1–2 *M* hydrochloric acid. Acid extractions are intended to remove basic impurities, especially such basic impurities as organic amines. The bases are converted to their corresponding cationic salts by the acid used in the extraction. If an amine is one of the reactants or if pyridine or another amine is a solvent, such an extraction might be used to remove any excess amine present at the end of a reaction.

$$\underset{}{RNH_2} + HCl \longrightarrow \underset{\text{(water-soluble ammonium salt)}}{RNH_3^+Cl^-}$$

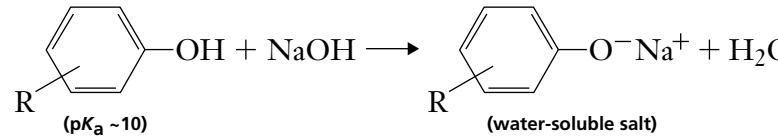
Cationic ammonium salts are usually soluble in the aqueous solution, and they are thus extracted from the organic material. A water extraction may be used immediately following the acid extraction to ensure that all traces of the acid have been removed from the organic material.

The third category is extraction of an organic mixture with a dilute base, usually 1 *M* sodium bicarbonate, although extractions with dilute sodium hydroxide can also be used. Such basic extractions are intended to convert acidic impurities, such as organic acids, to their corresponding anionic salts. For example, in the preparation of an ester, a sodium bicarbonate extraction might be used to remove any excess carboxylic acid that is present.

$$\underset{(pK_a \sim 5)}{RCOOH} + NaHCO_3 \longrightarrow \underset{\text{(water-soluble carboxylate salt)}}{RCOO^-Na^+} + H_2O + CO_2$$

Anionic carboxylate salts, being highly polar, are soluble in the aqueous phase. As a result, these acid impurities are extracted from the organic material into the basic solution. A water extraction may be used after the basic extraction to ensure that all of the base has been removed from the organic material.

Occasionally, phenols may be present in a reaction mixture as impurities, and removing them by extraction may be desired. Because phenols, although they are acidic, are about 10^5 times less acidic than carboxylic acids, basic extractions may be used to separate phenols from carboxylic acids by a careful selection of the base. If sodium bicarbonate is used as a base, carboxylic acids are extracted into the aqueous base, but phenols are not. Phenols are not sufficiently acidic to be deprotonated by the weak base bicarbonate. Extraction with sodium hydroxide, on the other hand, extracts both carboxylic acids and phenols into the aqueous basic solution, because hydroxide ion is a sufficiently strong base to deprotonate phenols.



Mixtures of acidic, basic, and neutral compounds are easily separated by extraction techniques. One such example is shown in Figure 12.10.

Organic acids or bases that have been extracted can be regenerated by neutralizing the extraction reagent. This would be done if the organic acid or base were a product of a reaction rather than an impurity. For example, if a carboxylic acid has been extracted with the aqueous base, the compound can be regenerated by acidifying the extract with 6 *M* HCl until the solution becomes *just* acidic, as indicated by litmus or pH paper. When the solution becomes acidic, the carboxylic acid will separate from the aqueous solution. If the acid is a solid at room temperature, it will precipitate and can be purified by filtration and crystallization. If the acid is a liquid, it will form a separate layer. In this case, it would usually be necessary to extract the mixture with ether or methylene chloride. After removing the organic layer and drying it, the solvent can be evaporated to yield the carboxylic acid.

In the example shown in Figure 12.10, you also need to perform a drying step at (3) before isolating the neutral compound. When the solvent is ether, you should first extract the ether solution with saturated aqueous sodium chloride to remove much of the water. The ether layer is then dried over a drying agent such as anhydrous sodium sulfate. If the solvent were methylene chloride, it would not be necessary to do the step with saturated sodium chloride.

When performing acid–base extractions, it is common practice to extract a mixture several times with the appropriate reagent. For example, if you were extracting a carboxylic acid from a mixture, you might extract the mixture three times with 2-mL portions of 1 *M* NaOH. In most published experiments, the procedure will specify the volume and concentration of extracting reagent and the number of times to do the extractions. If this information is not given, you must devise your own procedure. Using a carboxylic acid as an example, if you know the identity of the acid and the approximate amount present, you can actually calculate how much sodium hydroxide is needed. Because the carboxylic acid (assuming it is monoprotic) will react with sodium hydroxide in a 1:1 ratio, you would need the same number of moles of sodium hydroxide as there are moles of acid. To ensure that all the carboxylic acid is extracted, you should use about a *twofold* excess of the base. From this, you could calculate the number of milliliters of base needed. This should be divided into two or three equal portions, one portion for each extraction. In a similar fashion, you could calculate the amount of 5% sodium bicarbonate required to extract an acid or the amount of 1 *M* HCl required to extract a base. If the amount of organic acid or base is not known, then the situation is more difficult. A guideline that sometimes works is to do two or three extractions so that the total volume of the extracting reagent is approximately equal to the volume of the organic layer. To test this procedure, neutralize the aqueous layer from the last extraction. If a precipitate or cloudiness results, perform another extraction and test again. When no precipitate forms, you know that all the organic acid or base has been removed.

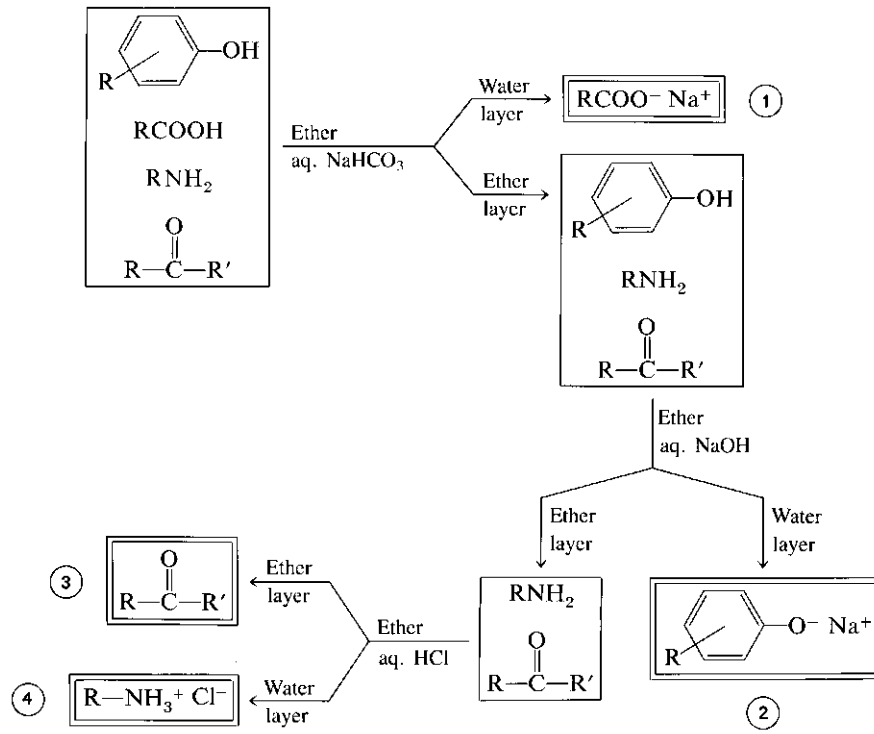


Figure 12.11 Separating a four-component mixture by extraction.

For some applications of acid base extraction, an additional step, called **backwashing** or **back extraction**, is added to the scheme shown in Figure 12.11. Consider the first step, in which the carboxylic acid is extracted by sodium bicarbonate. This aqueous layer may contain some unwanted neutral organic material from the original mixture. To remove this contamination, backwash the aqueous layer with an organic solvent such as ether or methylene chloride. After shaking the mixture and allowing the layers to separate, remove and discard the organic layer. This technique may also be used when an amine is extracted with hydrochloric acid. The resulting aqueous layer is backwashed with an organic solvent to remove unwanted neutral material.

PART E. OTHER EXTRACTION METHODS

12.12 Continuous Solid–Liquid Extraction

The technique of liquid–liquid extraction was described in Sections 12.1–12.8. In this section, solid–liquid extraction is described. Solid–liquid extraction is often used to extract a solid natural product from a natural source, such as a plant. A solvent is chosen that selectively dissolves the desired compound, but leaves behind the undesired insoluble solid. A continuous solid–liquid extraction apparatus, called a Soxhlet extractor, is commonly used in a research laboratory.

As shown in Figure 12.12, the solid to be extracted is placed in a thimble made from filter paper, and the thimble is inserted into the central chamber. A low-boiling solvent, such as diethyl ether, is placed in the round-bottom distilling flask and is

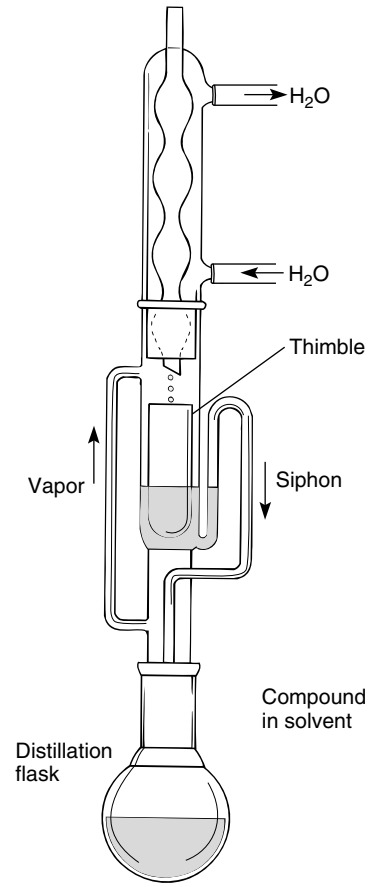


Figure 12.12 Continuous solid–liquid extraction using a Soxhlet extractor.

heated to reflux. The vapor rises through the left sidearm into the condenser where it liquefies. The condensate (liquid) drips into the thimble containing the solid. The hot solvent begins to fill the thimble and extracts the desired compound from the solid. Once the thimble is filled with solvent, the sidearm on the right acts as a siphon, and the solvent, which now contains the dissolved compound, drains back into the distillation flask. The vaporization–condensation–extraction–siphoning process is repeated hundreds of times, and the desired product is concentrated in the distillation flask. The product is concentrated in the flask because the product has a boiling point higher than that of the solvent or because it is a solid.

12.13 Continuous Liquid–Liquid Extraction

When a product is very soluble in water, it is often difficult to extract using the techniques described in Sections 12.4–12.7 because of an unfavorable distribution coefficient. In this case, you need to extract the aqueous solution numerous times with fresh batches of an immiscible organic solvent to remove the desired product from water. A less labor-intensive technique involves the use of a continuous liquid–liquid extraction apparatus. One type of extractor, used with solvents that are less dense than water, is shown in Figure 12.13. Diethyl ether is usually the solvent of choice.

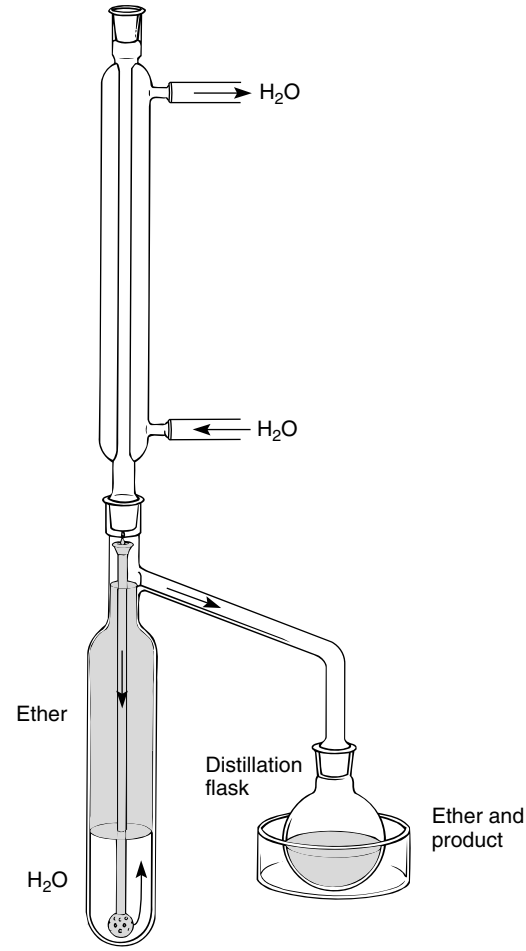


Figure 12.13 Continuous liquid–liquid extraction using a solvent less dense than water.

The aqueous phase is placed in the extractor, which is then filled with diethyl ether up to the sidearm. The round-bottom distillation flask is partially filled with ether. The ether is heated to reflux in the round-bottom flask, and the vapor is liquefied in the water-cooled condenser. The ether drips into the central tube, passes through the porous sintered glass tip, and flows through the aqueous layer. The solvent extracts the desired compound from the aqueous phase, and the ether is recycled back into the round-bottom flask. The product is concentrated in the flask. The extraction is rather inefficient and must be placed in operation for at least 24 hours to remove the compound from the aqueous phase.

12.14 Solid Phase Extraction

Solid phase extraction (SPE) is a relatively new technique, which is similar in appearance and function to column chromatography and high performance liquid chromatography (Techniques 19 and 21). In some applications, SPE is also similar to liquid-liquid extraction, discussed in this technique chapter. In addition to performing separation processes, SPE can also be used to carry out reactions in which new compounds are prepared.

A typical SPE column is constructed from the body of a plastic syringe, which is packed with a **sorbent**. The term *sorbent* is used by many manufactures as a

general term for materials that can both adsorb (attract to the surface of the sorbent by a physical attraction) or absorb (penetrate into the material like a sponge). A frit is inserted at the bottom of the column to support the sorbent. After the sorbent is added, another frit is inserted on top of the sorbent to hold it in place. The remainder of the tube serves as a reservoir for the solvent. Generally, the column comes packed with the sorbent from the manufacturer, but unpacked columns can also be purchased and packed by the user for specific applications. The Luer-lock tip at the bottom is connected to a vacuum source that pulls the solvents through the column.

SPE columns can be packed with many kinds of sorbents, depending on how the column will be used. Some common types are identified in the same way that column chromatography adsorbents are classified (see Technique 21, Section 21.1): normal-phase, reversed-phase, and ion exchange. Examples of normal-phase sorbents, which are polar, include silica and alumina. These columns are used to isolate polar compounds from a nonpolar solvent. Reversed-phase sorbents are made by alkylating silica. As a result, nonpolar alkyl groups are bonded to the silica surface, making the sorbet nonpolar. A common column of this type, known as a C_{18} column, is prepared by attaching an octadecyl (—C_8H_{18}) group to the silica surface (see Figure 12.14). C_{18} columns most likely function by an adsorption process. Reversed-phase sorbents are used to isolate relatively nonpolar compounds from polar solvents. Ion-exchange sorbents consist of charged or highly polar materials and are used to isolate charged compounds, either as anions or cations.

A major advantage of SPE columns is that they are fast and convenient to use compared to traditional column chromatography or liquid-liquid extraction. However, there are many other advantages that are of benefit to the environment, and their use is a good example of green chemistry (see the essay "Green Chemistry" that precedes Experiment 27). These advantages include the use of more environmentally friendly solvents, higher recovery, elimination of emulsions, enormous decrease in the use of solvents, and reduced toxic waste generation.

A good example of the use of SPE columns for performing a task that is normally done by liquid-liquid extraction is the isolation of caffeine from tea or coffee. In this application, a C_{18} column is used. As the tea or coffee flows through the column, caffeine is attracted to the sorbent, and the polar impurities come off with water. Ethyl acetate is then used to remove the caffeine from the column. The experimental setup is shown in Figure 12.15. The SPE column[2] is attached to the filter flask by using two neoprene adapters (sizes #1 and #2). The filter flask is connected to either a vacuum line or a water aspirator to provide the vacuum. After each step, the solvents with impurities or desired product are drawn through the column into the filter flask using the vacuum.

The following steps are used with an SPE tube to remove caffeine from tea or coffee (see Figure 12.16):

A. Condition the C_{18} reversed-phase silica column by passing methanol and water through the tube.

B. Apply the sample of caffeinated drink to the column.

C. Wash the polar impurities from the column with water.

D. Elute the caffeine from the tube with ethyl acetate.

---

[2]This is a Strata SPE column available from Phenomenex, 411 Madrid Ave, Torrance, CA 90501-1430; phone: (310)212-0555. Part number: 8B-S001-JCH-S, Strata C-18-E, 1000 mg sorbent/6-mL tube.

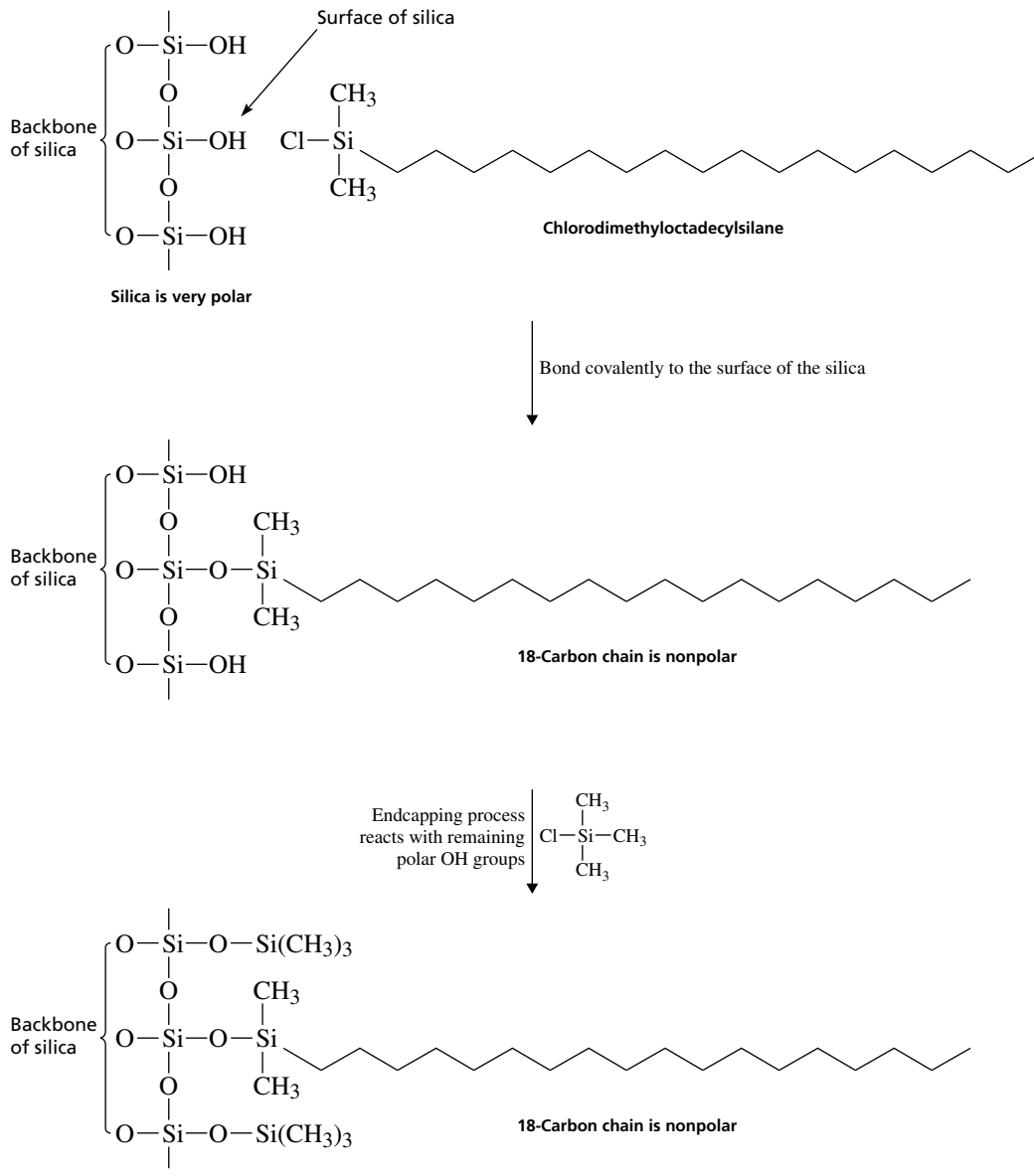


Figure 12.14 Preparation of C-18 silica for reversed-phase extractions using SPE tubes. The process changes polar silica (hydrophilic material) to nonpolar silica (hydrophobic material).

Even though Figure 12.16 is applied to the isolation of caffeine, the general scheme may be used in any application in which it is desired to separate polar substances, such as water, from a relatively nonpolar substance. Numerous applications are found in the medical field, in which analyzing body fluids is important.

There are many other diverse applications that SPE columns can be used for. By modifying the silica with specific chemical reagents, new compounds can be prepared in SPE columns. For example, oxidation reactions can be performed by mixing the silica with the appropriate oxidizing agents. Aldol condensation reactions can also be conducted in SPE columns. In another type of application, SPE has been adopted as an alternative to liquid–liquid extraction.

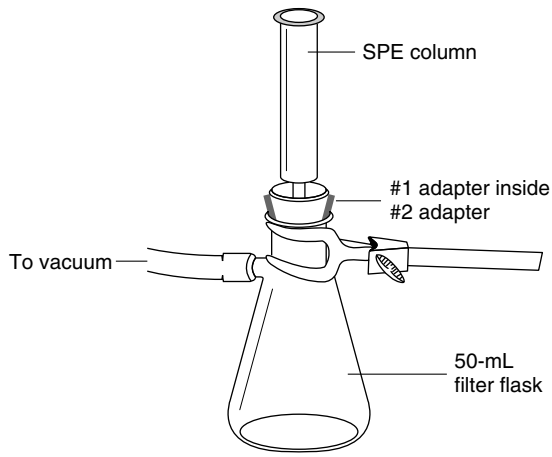


Figure 12.15 Experimental setup for SPE column.

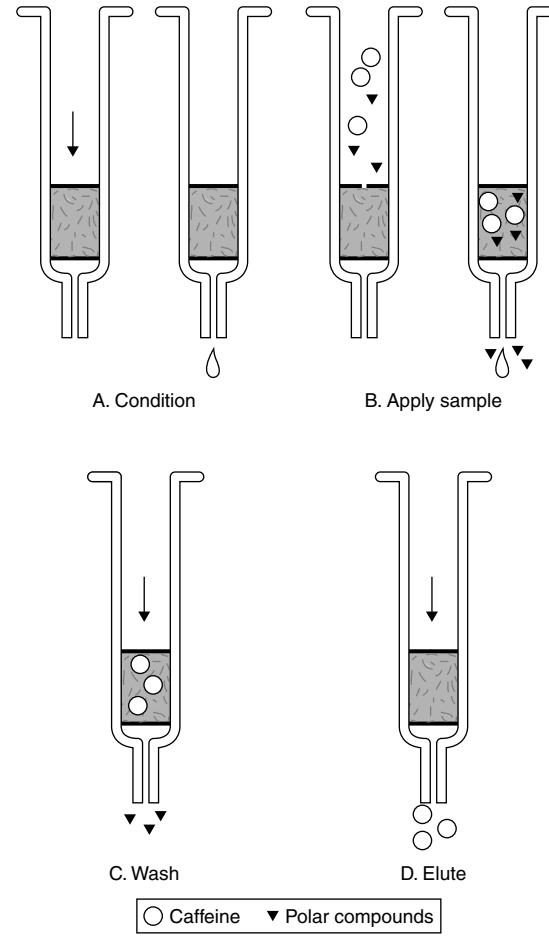
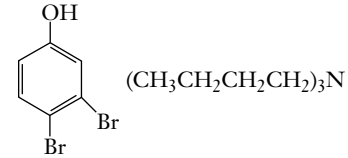


Figure 12.16 Steps to remove caffeine from tea or coffee.

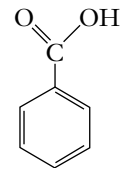
PROBLEMS

1. Suppose solute A has a distribution coefficient of 1.0 between water and diethyl ether. Demonstrate that if 100 mL of a solution of 5.0 g of A in water were extracted with two 25-mL portions of ether, a smaller amount of A would remain in the water than if the solution were extracted with one 50-mL portion of ether.
2. Write an equation to show how you could recover the parent compounds from their respective salts (1, 2, and 4) shown in Figure 12.11.
3. Aqueous hydrochloric acid was used *after* the sodium bicarbonate and sodium hydroxide extractions in the separation scheme shown in Figure 12.11. Is it possible to use this reagent earlier in the separation scheme to achieve the same overall result? If so, explain where you would perform this extraction.
4. Using aqueous hydrochloric acid, sodium bicarbonate, or sodium hydroxide solutions, devise a separation scheme using the style shown in Figure 12.11 to separate the following two-component mixtures. All the substances are soluble in ether. Also indicate how you would recover each of the compounds from its respective salts.

   a. Give two different methods for separating this mixture.

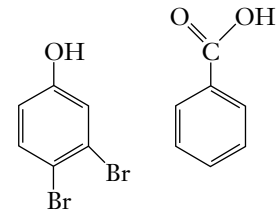


b. Give two different methods for separating this mixture.



$CH_3CH_2CH_2CH_2CH_2CH_2OH$

c. Give one method for separating this mixture.



5. Solvents other than those in Table 12.1 may be used for extractions. Determine the relative positions of the organic layer and the aqueous layer in a conical vial or separatory funnel after shaking each of the following solvents with an aqueous phase. Find the densities for each of these solvents in a handbook (see Technique 4).

a. 1,1,1-Trichloroethane

b. Hexane

6. A student prepares ethyl benzoate by the reaction of benzoic acid with ethanol using a sulfuric acid catalyst. The following compounds are found in the crude reaction mixture: ethyl benzoate (major component), benzoic acid, ethanol, and sulfuric acid. Using a handbook, obtain the solubility properties in water for each of these compounds (see Technique 4). Indicate how you would remove benzoic acid, ethanol, and sulfuric acid from ethyl benzoate. At some point in the purification, you should also use an aqueous sodium bicarbonate solution.

7. Calculate the weight of water that could be removed from a wet organic phase using 50.0 mg of magnesium sulfate. Assume that it gives the hydrate listed in Table 12.2.

8. Explain exactly how you would perform the following laboratory instructions:

a. "Wash the organic layer with 5.0 mL of 1 *M* aqueous sodium bicarbonate."

b. "Extract the aqueous layer three times with 2-mL portions of methylene chloride."

9. Just prior to drying an organic layer with a drying agent, you notice water droplets in the organic layer. What should you do next?

10. What should you do if there is some question about which layer is the organic one during an extraction procedure?

11. Saturated aqueous sodium chloride (d = 1.2 g/mL) is added to the following mixtures in order to dry the organic layer. Which layer is likely to be on the bottom in each case?

a. Sodium chloride layer or a layer containing a high-density organic compound dissolved in methylene chloride (d = 1.4 g/mL)

b. Sodium chloride layer or a layer containing a low-density organic compound dissolved in methylene chloride (d = 1.1 g/mL)

13 TECHNIQUE 13

Physical Constants of Liquids: The Boiling Point and Density

PART A. BOILING POINTS AND THERMOMETER CORRECTION

13.1 The Boiling Point

As a liquid is heated, its vapor pressure increases to the point at which it just equals the applied pressure (usually atmospheric pressure). At this point, the liquid is observed to boil. The normal boiling point is measured at 760 mmHg (760 torr) or 1 atm. At a lower applied pressure, the vapor pressure needed for boiling is also lowered, and the liquid boils at a lower temperature. The relation between applied pressure and temperature of boiling for a liquid is determined by its vapor pressure–temperature behavior. Figure 13.1 is an idealization of the typical vapor pressure–temperature behavior of a liquid.

Because the boiling point is sensitive to pressure, it is important to record the barometric pressure when determining a boiling point if the determination is being conducted at an elevation significantly above or below sea level. Normal atmospheric variations may affect the boiling point, but they are usually of minor importance. However, if a boiling point is being monitored during the course of a vacuum distillation (Technique 16) that is being performed with an aspirator or a vacuum pump, the variation from the atmospheric value will be especially marked. In these cases, it is quite important to know the pressure as accurately as possible.

As a rule of thumb, the boiling point of many liquids drops about 0.5°C for a 10-mm decrease in pressure when in the vicinity of 760 mmHg. At lower pressures, a 10°C drop in boiling point is observed for each halving of the pressure. For example, if the observed boiling point of a liquid is 150°C at 10 mm pressure, then the boiling point would be about 140°C at 5 mmHg.

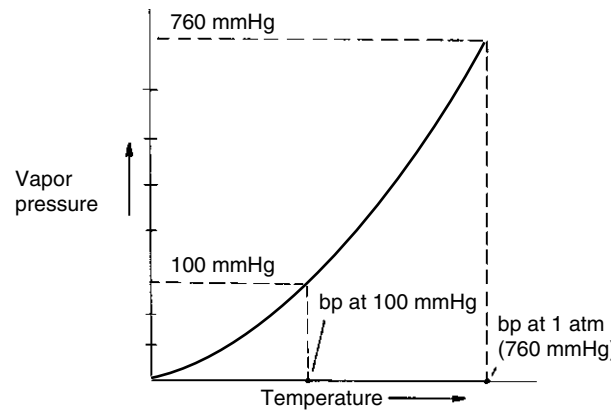


Figure 13.1 The vapor pressure–temperature curve for a typical liquid.

A more accurate estimate of the change in boiling point with a change of pressure can be made by using a nomograph. In Figure 13.2, a nomograph is given, and a method is described for using it to obtain boiling points at various pressures when the boiling point is known at some other pressure.

13.2 Determining the Boiling Point—Macroscale Methods

Two experimental methods of determining boiling points are easily available. When you have large quantities of material, you can simply record the boiling point (or boiling range) as viewed on a thermometer while you perform a simple distillation (see Technique 14).

Alternatively, you may find it convenient to use a direct method, shown in Figure 13.3. With this method, the bulb of the thermometer can be immersed in vapor from the boiling liquid for a period long enough to allow it to equilibrate and give a good temperature reading. A 13-mm × 100-mm test tube works well in this procedure. Use 0.3–0.5 mL of liquid and a small, inert carborundum (black) boiling stone. This method works best with a partial immersion (76 mm) mercury thermometer (see Section 13.4). It is not necessary to perform a stem correction with this type of thermometer. This method also works well with a temperature probe and computer interface (see Section 13.5).

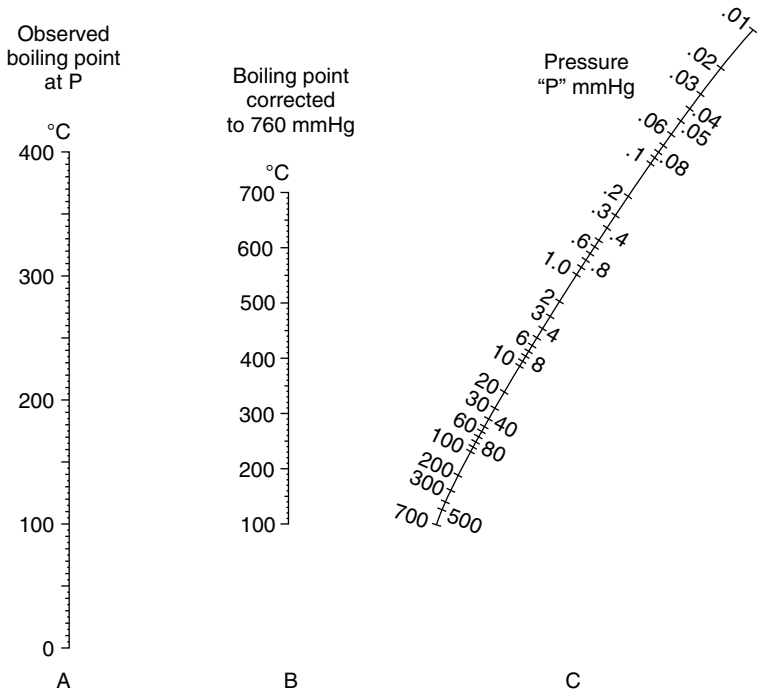


Figure 13.2 Pressure–temperature alignment nomograph. How to use the nomograph: Assume a reported boiling point of 100°C (column A) at 1 mmHg. To determine the boiling point at 18 mmHg, connect 100°C (column A) to 1 mmHg (column C) with a transparent plastic rule and observe where this line intersects column B (about 280°C). This value would correspond to the normal boiling point. Next, connect 280°C (column B) with 18 mmHg (column C) and observe where this intersects column A (151°C). The approximate boiling point will be 151°C at 18 mmHg. (Reprinted courtesy of EMD Chemicals, Inc.)

Place the bulb of the thermometer as close as possible to the boiling liquid without actually touching it. The best heating device is a hot plate with either an aluminum block or a sand bath.[1]

While you are heating the liquid, it is helpful to record the temperature at 1-minute intervals. This makes it easier to keep track of changes in the temperature and to know when you have reached the boiling point. The liquid must boil vigorously, such that you see a reflux ring above the bulb of the thermometer and drops of liquid condensing on the sides of the test tube. Note that with some liquids, the reflux ring will be very faint, and you must look closely to see it. The boiling point is reached when the temperature reading on the thermometer has remained constant at its highest observed value for 2–3 minutes. It is usually best to turn the heat control on the hot plate to a relatively high setting initially, especially if you are starting with a cold hot plate and aluminum block or sand bath. If the temperature begins to level off at a relatively low temperature (less than about 100°C) or if the reflux ring reaches the immersion ring on the thermometer, you should turn down the heat-control setting immediately.

Two problems can occur when you perform this boiling-point procedure. The first is much more common and occurs when the temperature appears to be leveling off at a temperature below the boiling point of the liquid. This is more likely to happen with a relatively high-boiling liquid (boiling points greater than about 150°C) or when the sample is not heated sufficiently. The best way to prevent this problem is to heat the sample more strongly. With high-boiling liquids, it may be helpful to wait for the temperature to remain constant for 3–4 minutes to make sure that you have reached the actual boiling point.

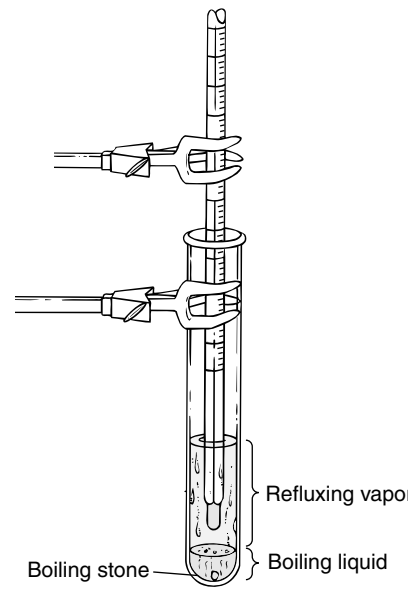


Figure 13.3 Macroscale method of determining the boiling point.

[1] Note to the instructor: The aluminum block should have a hole drilled in it that goes *all the way through* the block and is just slightly larger than the outside diameter of the test tube. A sand bath can be conveniently prepared by adding 40 mL of sand to a 150-mL beaker or by using a heating mantle partially filled with sand. For additional comments about these heating methods, see the Instructor's Manual, Experiment 7, "Infrared Spectroscopy and Boiling-Point Determination."

The second problem, which is rare, occurs when the liquid evaporates completely, and the temperature inside the dry test tube may rise higher than the actual boiling point of the liquid. This is more likely to happen with low-boiling liquids (boiling point less than 100°C), or if the temperature on the hot plate is set too high for too long. To check for this possibility, observe the amount of liquid remaining in the test tube as soon as you have finished the procedure. If there is no liquid remaining, it is possible that the highest temperature you observed is greater than the boiling point of the liquid. In this case, you should repeat the boiling-point determination, heating the sample less strongly or using more sample.

Depending on the skill of the person performing this technique, boiling points may be slightly inaccurate. When experimental boiling points are inaccurate, it is more common for them to be lower than the literature value, and inaccuracies are more likely to occur for higher-boiling liquids. With higher-boiling liquids, the difference may be as much as 5°C. Carefully following the previous instructions will make it more likely that your experimental value will be close to the literature value.

13.3 Determining the Boiling Point—Microscale Methods

With smaller amounts of material, you can carry out a microscale or semimicroscale determination of the boiling point by using the apparatus shown in Figure 13.4.

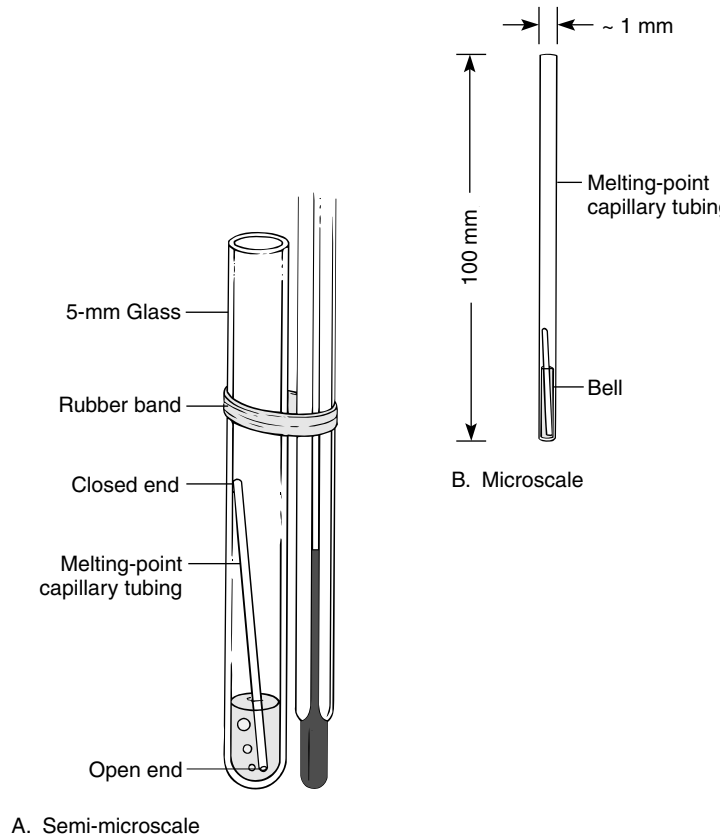


Figure 13.4 Boiling-point determinations.

Semi-microscale Method. To carry out the semi-microscale determination, attach a piece of 5-mm glass tubing (sealed at one end) to a thermometer with a rubber band or a thin slice of rubber tubing. The liquid whose boiling point is being determined is introduced with a Pasteur pipet into this piece of tubing, and a short piece of melting-point capillary (sealed at one end) is dropped in with the open end down. The whole unit is then placed in a Thiele tube. The rubber band should be placed above the level of the oil in the Thiele tube; otherwise the band may soften in the hot oil. When positioning the band, keep in mind that the oil will expand when heated. Next, the Thiele tube is heated in the same fashion as described in Technique 9, Section 9.6, for determining a melting point. Heating is continued until a rapid and continuous stream of bubbles emerges from the inverted capillary. At this point, you should stop heating. Soon, the stream of bubbles slows down and stops. When the bubbles stop, the liquid enters the capillary tube. The moment at which the liquid enters the capillary tube corresponds to the boiling point of the liquid, and the temperature is recorded.

Microscale Method. In microscale experiments, there often is too little product available to use the semi-microscale method just described. However, the method can be scaled down in the following manner. The liquid is placed in a 1-mm melting-point capillary tube to a depth of about 4–6 mm. Use a syringe or a Pasteur pipet that has had its tip drawn thinner to transfer the liquid into the capillary tube. It may be necessary to use a centrifuge to transfer the liquid to the bottom of the tube. Next, prepare an appropriately-sized inverted capillary, or **bell**.

The easiest way to prepare a bell is to use a commercial micropipet, such as a 10-μL Drummond "microcap." These are available in vials of 50 or 100 microcaps and are very inexpensive. To prepare the bell, cut the microcap in half with a file or scorer and then seal one end by inserting it a small distance into a flame, turning it on its axis until the opening closes.

If microcaps are not available, a piece of 1-mm open-end capillary tubing (same size as a melting-point capillary) can be rotated along its axis in a flame while being held horizontally. Use your index fingers and thumbs to rotate the tube; do not change the distance between your two hands while rotating. When the tubing is soft, remove it from the flame and pull it to a thinner diameter. When pulling, keep the tube straight by *moving both your hands and your elbows outward* by about 4 inches. Hold the pulled tube in place a few moments until it cools. Using the edge of a file or your fingernail, break out the thin center section. Seal one end of the thin section in the flame; then break it to a length that is about one and one-half times the height of your sample liquid (6–9 mm). Be sure the break is done squarely. Invert the bell (open end down), and place it in the capillary tube containing the sample liquid. Push the bell to the bottom with a fine copper wire if it adheres to the side of the capillary tube. A centrifuge may be used if you prefer. Figure 13.5 shows the construction method for the bell and the final assembly.

Place the microscale assembly in a standard melting-point apparatus (or a Thiele tube if an electrical apparatus is not available) to determine the boiling point. Heating is continued until a rapid and continuous stream of bubbles emerges from the inverted capillary. At this point, stop heating. Soon, the stream of bubbles slows down and stops. When the bubbles stop, the liquid enters the capillary tube. The moment at which the liquid enters the capillary tube corresponds to the boiling point of the liquid, and the temperature is recorded.

Explanation of the Method. During the initial heating, the air trapped in the inverted bell expands and leaves the tube, giving rise to a stream of bubbles. When the

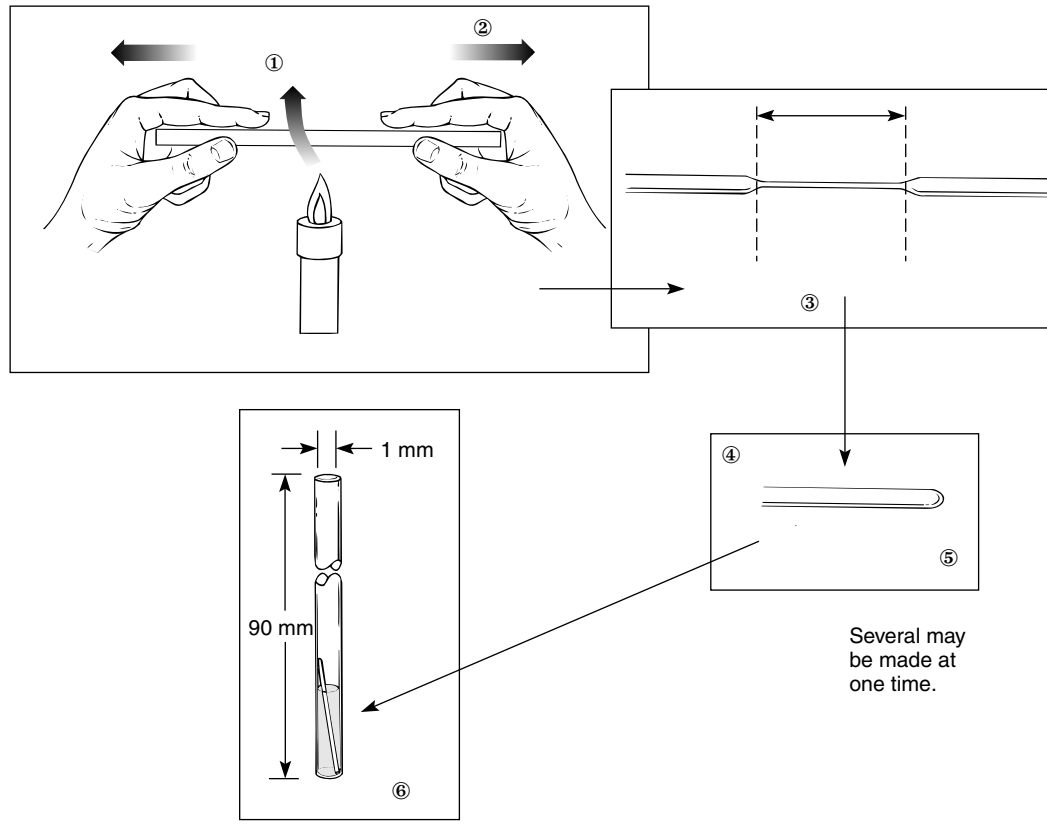


Figure 13.5 Construction of a microcapillary bell for microscale boiling-point determination.

liquid begins boiling, most of the air has been expelled; the bubbles of gas are due to the boiling action of the liquid. Once the heating is stopped, most of the vapor pressure left in the bell comes from the vapor of the heated liquid that seals its open end. There is always vapor in equilibrium with a heated liquid. If the temperature of the liquid is above its boiling point, the pressure of the trapped vapor will either exceed or equal the atmospheric pressure. As the liquid cools, its vapor pressure decreases. When the vapor pressure drops just below atmospheric pressure (just below the boiling point), the liquid is forced into the capillary tube.

Difficulties. Three problems are common to this method. The first arises when the liquid is heated so strongly that it evaporates or boils away. The second arises when the liquid is not heated above its boiling point before heating is discontinued. If the heating is stopped at any point below the actual boiling point of the sample, the liquid enters the bell *immediately,* giving an apparent boiling point that is too low. Be sure you observe a continuous stream of bubbles, too fast for individual bubbles to be distinguished, before lowering the temperature. Also be sure the bubbling action decreases slowly before the liquid enters the bell. If your melting-point apparatus

has fine enough control and fast response, you can actually begin heating again and force the liquid out of the bell before it becomes completely filled with the liquid. This allows a second determination to be performed on the same sample. The third problem is that the bell may be so light that the bubbling action of the liquid causes the bell to move up the capillary tube. This problem can sometimes be solved by using a longer (heavier) bell or by sealing the bell so that a larger section of solid glass is formed at the sealed end of the bell.

When measuring temperatures above 150°C, thermometer errors can become significant. For an accurate boiling point with a high-boiling liquid, you may wish to apply a *stem correction* to the thermometer, as described in Section 13.4, or to calibrate the thermometer, as described in Technique 9, Section 9.9.

13.4 Thermometers and Stem Corrections

Three types of thermometers are available: bulb immersion, partial immersion (stem immersion), and total immersion. Bulb immersion thermometers are calibrated by the manufacturer to give correct temperature readings when only the bulb (not the rest of the thermometer) is placed in the medium to be measured. Partial immersion thermometers are calibrated to give correct temperature readings when they are immersed to a specified depth in the medium to be measured. Partial immersion thermometers are easily recognized because the manufacturer always scores a mark, or immersion ring, completely around the stem at the specified depth of immersion. The immersion ring is normally found below any of the temperature calibrations. Total immersion thermometers are calibrated when the entire thermometer is immersed in the medium to be measured. The three types of thermometers are often marked on the back (opposite side from the calibrations) by the words *bulb, immersion,* or *total,* but this may vary from one manufacturer to another.

Boiling-point determination and distillation are two techniques in which an accurate temperature reading may be obtained most easily with a partial immersion thermometer. A common immersion length for this type of thermometer is 76 mm. This length works well for these two techniques because the hot vapors are likely to surround the bottom of the thermometer up to a point fairly close to the immersion line. If a total immersion thermometer is used in these applications, a stem correction, which is described later, must be used to obtain an accurate temperature reading.

The liquid used in thermometers may be either mercury or a colored organic liquid such as an alcohol. Because mercury is highly poisonous and is difficult to clean up completely when a thermometer is broken, many laboratories now use nonmercury thermometers. When a highly accurate temperature reading is required, such as in a boiling-point determination or in some distillations, mercury thermometers may have an advantage over nonmercury thermometers for two reasons. Mercury has a lower coefficient of expansion than the liquids used in nonmercury thermometers. Therefore, a partial immersion mercury thermometer will give a more accurate reading when the thermometer is not immersed in the hot vapors exactly to the immersion line. In other words, the mercury thermometer is more forgiving. Furthermore, because mercury is a better conductor of heat, a mercury thermometer will respond more quickly to changes in the temperature of the hot vapors. If the temperature is read before the thermometer reading has stabilized, which is more likely to occur with a nonmercury thermometer, the temperature reading will be inaccurate.

Manufacturers design total immersion thermometers to read correctly only when they are immersed totally in the medium to be measured. The entire mercury thread must be covered. Because this situation is rare, a **stem correction** should be added to the observed temperature. This correction, which is positive, can be fairly large when high temperatures are being measured. Keep in mind, however, that if your thermometer has been calibrated for its desired use (such as described in Technique 9, Section 9.9, for a melting-point apparatus), a stem correction is not necessary for any temperature within the calibration limits. You are most likely to want a stem correction when you are performing a distillation. If you determine a melting point or boiling point using an uncalibrated, total immersion thermometer, you will also want to use a stem correction.

When you wish to make a stem correction for a total immersion thermometer, the following formula may be used. It is based on the fact that the portion of the mercury thread in the stem is cooler than the portion immersed in the vapor or the heated area around the thermometer. The mercury will not have expanded in the cool stem to the same extent as in the warmed section of the thermometer. The equation used is

$$(0.000154)(T - t_1)(T - t_2) = \text{correction to be added to } T \text{ observed}$$

1. The factor 0.000154 is a constant, the coefficient of expansion for the mercury in the thermometer.
2. The term $T - t_1$ corresponds to the length of the mercury thread not immersed in the heated area. Use the temperature scale on the thermometer itself for this measurement, rather than an actual length unit. T is the observed temperature, and t_1 is the *approximate* place where the heated part of the stem ends and the cooler part begins.
3. The term $T - t_2$ corresponds to the difference between the temperature of the mercury in the vapor T and the temperature of the mercury in the air outside the heated area (room temperature). The term T is the observed temperature, and t_2 is measured by hanging another thermometer so the bulb is close to the stem of the main thermometer.

Figure 13.6 shows how to apply this method for a distillation. By the formula just given, it can be shown that high temperatures are more likely to require a stem correction and that low temperatures need not be corrected. The following sample calculations illustrate this point.

Example 1	**Example 2**
$T = 200$ °C	$T = 100$ °C
$t_1 = 0$ °C	$t_1 = 0$ °C
$t_2 = 35$ °C	$t_2 = 35$ °C
(0.000154)(200)(165) = 5.1 °C stem correction	(0.000154)(100)(165) = 1.0 °C stem correction
200 °C + 5 °C = 205 °C corrected temperature	100 °C + 1 °C = 101 °C corrected temperature

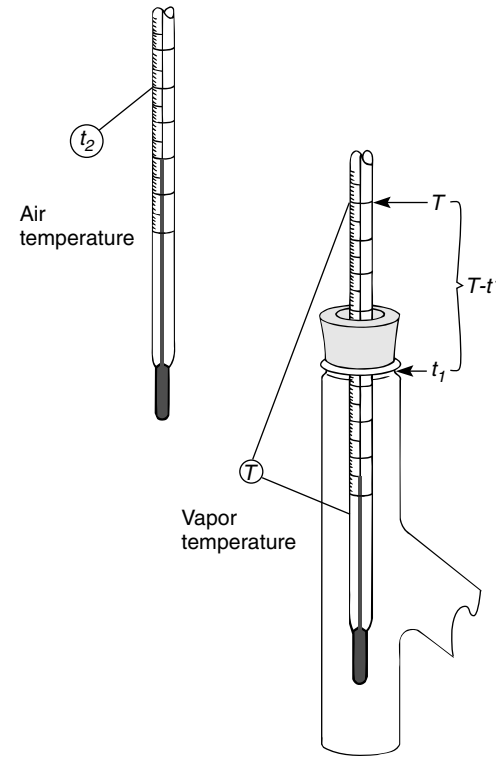


Figure 13.6 Measurement of a thermometer stem correction during distillation.

13.5 Computer Interface and Temperature Probe

Rather than using a thermometer to determine a boiling point or to monitor the temperature during a distillation, one can use a Vernier LabPro interface with a stainless-steel temperature probe and a laptop computer. This system provides a very accurate way of measuring the temperature. The data (temperature vs. time) is displayed on the monitor while it is being collected. When performing a boiling-point determination, the visual display of the temperature on the monitor makes it easy to know when the maximum temperature (the boiling point) has been reached. When a temperature probe is used with the macroscale method of determining a boiling point (see Section 13.2), the boiling point can usually be determined to within 2°C of the literature value. Being able to see a graph of temperature vs. time when performing a distillation gives students a better sense of when the different liquids are distilling.

The temperature probes (or thermocouples) work only in a given temperature range. It is therefore important to select a probe that has a maximum temperature that is somewhat higher than the boiling points of the liquids you will be working with. See the Instructor's Manual, Experiment 6, Simple and Fractional Distillation, for more specific information about selecting an appropriate temperature probe.

PART B. DENSITY

13.6 Density

Density is defined as mass per unit volume and is generally expressed in units of grams per milliliter (g/mL) for a liquid and grams per cubic centimeter (g/cm^3) for a solid.

$$\text{Density} = \frac{\text{mass}}{\text{volume}} \qquad \text{or} \qquad D = \frac{M}{V}$$

In organic chemistry, density is most commonly used in converting the weight of liquid to a corresponding volume, or vice versa. It is often easier to measure a volume of a liquid than to weigh it. As a physical property, density is also useful for identifying liquids in much the same way that boiling points are used.

Although precise methods that allow the measurements of the densities of liquids at the microscale level have been developed, they are often difficult to perform. An approximate method for measuring densities can be found in using a 100-μL (0.100-mL) automatic pipet (see Technique 5, Section 5.6). Clean, dry, and preweigh one or more conical vials (including their caps and liners) and record their weights. Handle these vials with a tissue to avoid getting your fingerprints on them. Adjust the automatic pipet to deliver 100 μL and fit it with a clean, new tip. Use the pipet to deliver 100 μL of the unknown liquid to each of your tared vials. Cap them so that the liquid does not evaporate. Reweigh the vials and use the weight of the 100 μL of liquid delivered to calculate a density for each case. It is recommended that from three to five determinations be performed, that the calculations be performed to three significant figures, and that all the calculations be averaged to obtain the final result. This determination of the density will be accurate to within two significant figures. Table 13.1 compares some literature values with those that could be obtained by this method.

TABLE 13.1 Densities determined by the automatic pipet method (g/mL)

Substance	BP	Literature	100 μL
Water	100	1.000	1.01
Hexane	69	0.660	0.66
Acetone	56	0.788	0.77
Dichloromethane	40	1.330	1.27
Diethyl ether	35	0.713	0.67

PROBLEMS

1. Using the pressure–temperature alignment chart in Figure 13.2, answer the following questions.
   a. What is the normal boiling point (at 760 mmHg) for a compound that boils at 150 °C at 10 mmHg pressure?
   b. At what temperature would the compound in (a) boil if the pressure were 40 mmHg?
   c. A compound was distilled at atmospheric pressure and had a boiling point of 285 °C. What would be the approximate boiling range for this compound at 15 mmHg?
2. Calculate the corrected boiling point for nitrobenzene by using the method given in Section 13.4. The boiling point was determined using an apparatus similar to that shown in Figure 13.3. Assume that a total immersion thermometer was used. The

observed boiling point was 205 °C. The reflux ring in the test tube just reached up to the 0 °C mark on the thermometer. A second thermometer suspended alongside the test tube, at a slightly higher level than the one inside, gave a reading of 35 °C.

3. Suppose that you had calibrated the thermometer in your melting-point apparatus against a series of melting-point standards. After reading the temperature and converting it using the calibration chart, should you also apply a stem correction? Explain.
4. The density of a liquid was determined by the automatic pipet method. A 100-μL automatic pipet was used. The liquid had a mass of 0.082 g. What was the density in grams per milliliter of the liquid?
5. During the microscale boiling-point determination of an unknown liquid, heating was discontinued at 154 °C and the liquid immediately began to enter the inverted bell. Heating was begun again at once, and the liquid was forced out of the bell. Heating was again discontinued at 165 °C, at which time a very rapid stream of bubbles emerged from the bell. On cooling, the rate of bubbling gradually diminished until the liquid reached a temperature of 161 °C and entered and filled the bell. Explain this sequence of events. What was the boiling point of the liquid?

14 TECHNIQUE 14

Simple Distillation

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

Distillation is the process of vaporizing a liquid, condensing the vapor, and collecting the condensate in another container. This technique is very useful for separating a liquid mixture when the components have different boiling points or when one of the components will not distill. It is one of the principal methods of purifying a liquid. Four basic distillation methods are available to the chemist: simple distillation, fractional distillation, vacuum distillation (distillation at reduced pressure), and steam distillation. Fractional distillation will be discussed in Technique 15; vacuum distillation in Technique 16; and steam distillation in Technique 18.

A typical modern distillation apparatus is shown in Figure 14.1. The liquid to be distilled is placed in the distilling flask and heated, usually by a heating mantle. The heated liquid vaporizes and is forced upward past the thermometer and into the condenser. The vapor is condensed to liquid in the cooling condenser, and the liquid flows downward through the vacuum adapter (no vacuum is used) and into the receiving flask.

14.1 The Evolution of Distillation Equipment

There are probably more types and styles of distillation apparatus than exist for any other technique in chemistry. Over the centuries, chemists have devised just about every conceivable design. The earliest known types of distillation apparatus were the **alembic** and the **retort** (see Figure 14.2). They were used by alchemists in the Middle Ages and the Renaissance, and probably even earlier by Arabic chemists. Most other distillation equipment has evolved as variations on these designs.

Figure 14.2 shows several stages in the evolution of distillation equipment as it relates to the organic laboratory. It is not intended to be a complete history; rather, it is representative. Up until recent years, equipment based on the retort design was

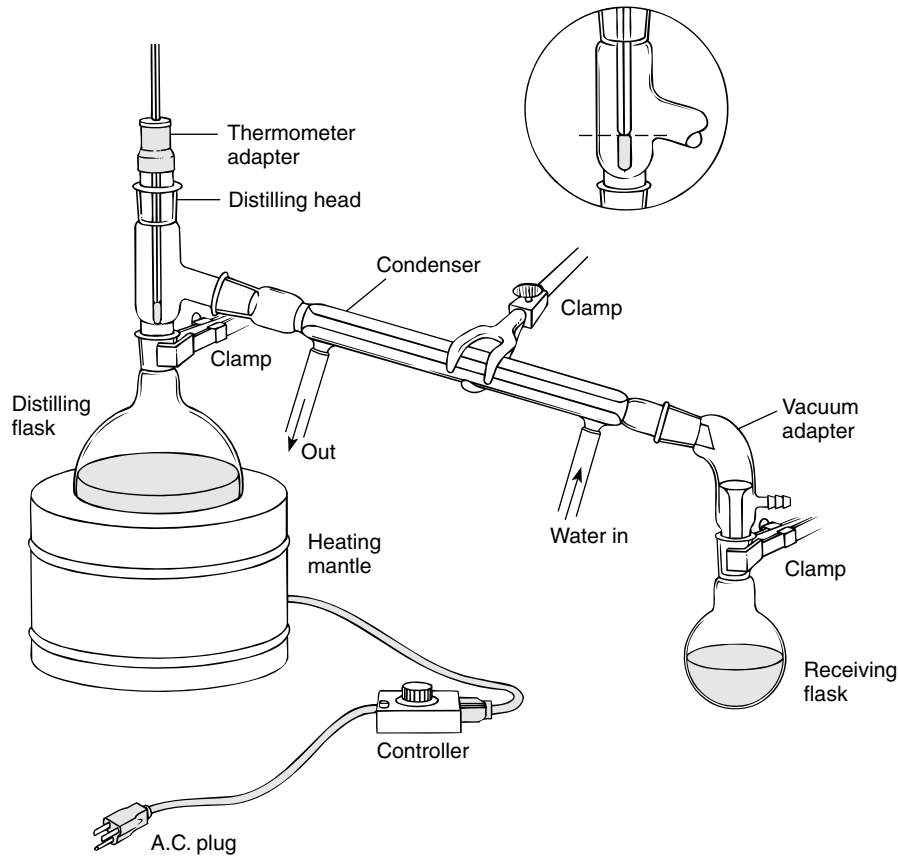


Figure 14.1 Distillation with the standard macroscale lab kit.

common in the laboratory. Although the retort itself was still in use early in the last century, it had evolved by that time into the distillation flask and water-cooled condenser combination. This early equipment was connected with drilled corks. By 1958, most introductory laboratories were beginning to use "organic lab kits" that included glassware connected by standard-taper glass joints. The original lab kits contained large ⏋ 24/40 joints. Within a short time, they became smaller with ⏋ 19/22 and even ⏋ 14/20 joints. These later kits are still being used today in many "macroscale" laboratory courses such as yours.

In the 1960s, researchers developed even smaller versions of these kits for working at the "microscale" level (in Figure 14.2, see the box labeled "Research use only"), but this glassware is generally too expensive to use in an introductory laboratory. However, in the mid-1980s, several groups developed a different style of microscale distillation equipment based on the alembic design (see the box labeled "Modern microscale organic lab kit"). This new microscale equipment has ⏋ 14/10 standard-taper joints, threaded outer joints with screw-cap connectors, and an internal O-ring for a compression seal. Microscale equipment similar to this is now used in many introductory courses. The advantages of this glassware are that there is less material used (lower cost), lower personal exposure to chemicals, and less waste generated. Because both types of equipment are in use today, after we describe macroscale equipment, we will also show the equivalent microscale distillation apparatus.

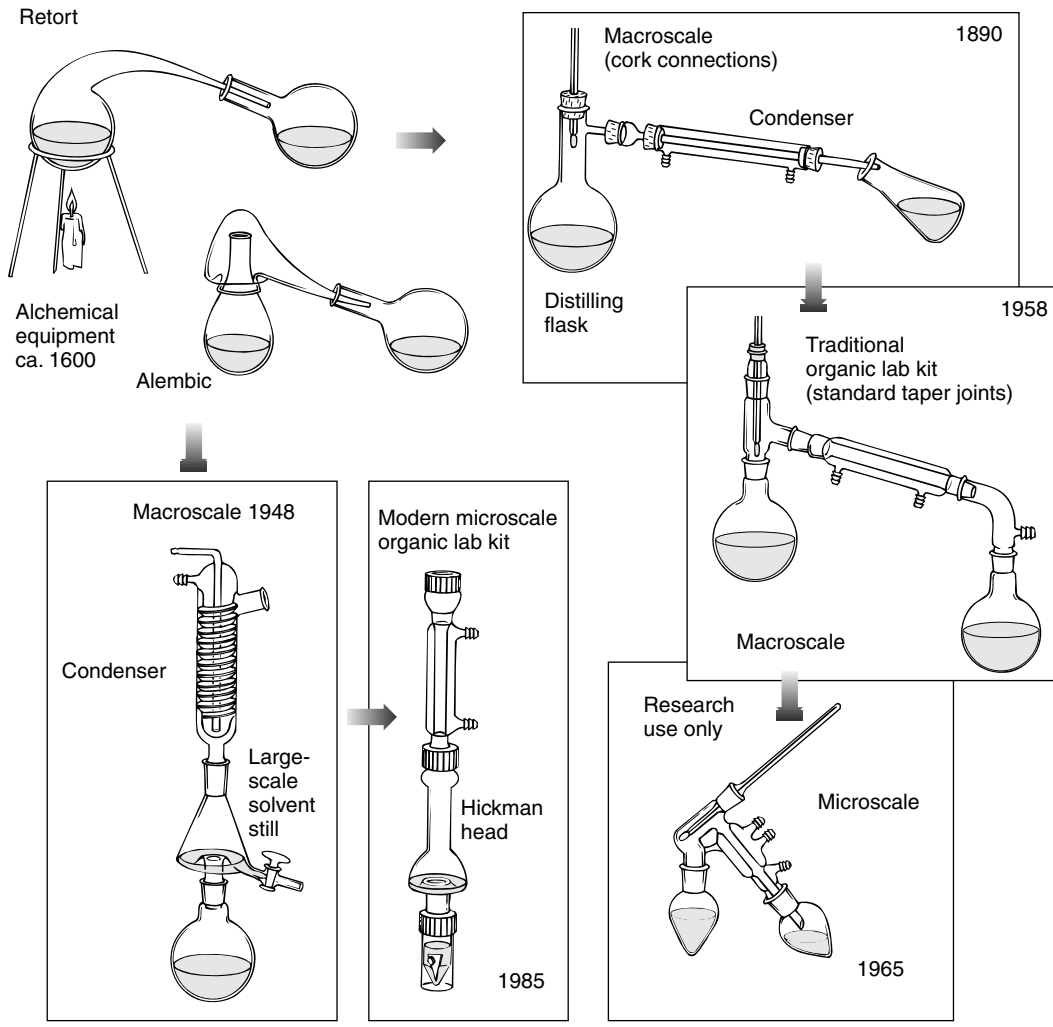


Figure 14.2 Some stages in the evolution of distillation equipment from alchemical equipment (dates represent approximate time of use).

14.2 Distillation Theory

In the traditional distillation of a pure substance, vapor rises from the distillation flask and comes into contact with a thermometer that records its temperature. The vapor then passes through a condenser, which reliquefies the vapor and passes it into the receiving flask. The temperature observed during the distillation of a **pure substance** remains constant throughout the distillation so long as both vapor *and* liquid are present in the system (see Figure 14.3A). When a **liquid mixture** is distilled, often the temperature does not remain constant but increases throughout the distillation. The reason for this is that the composition of the vapor that is distilling varies continuously during the distillation (see Figure 14.3B).

For a liquid mixture, the composition of the vapor in equilibrium with the heated solution is different from the composition of the solution itself. This is shown in Figure 14.4, which is a phase diagram of the typical vapor–liquid relation for a two-component system (A + B).

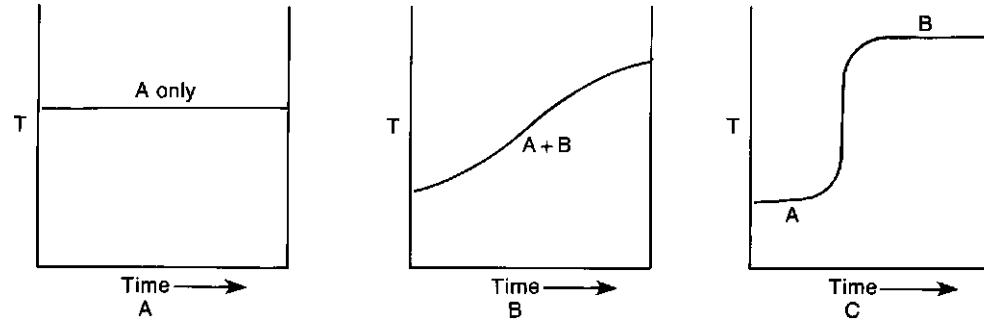


Figure 14.3 Three types of temperature behavior during a simple distillation. (A) A single pure component. (B) Two components of similar boiling points. (C) Two components with widely differing boiling points. Good separations are achieved in A and C.

In Figure 14.4, horizontal lines represent constant temperatures. The upper curve represents vapor composition, and the lower curve represents liquid composition. For any horizontal line (constant temperature), such as that shown at t, the intersections of the line with the curves give the compositions of the liquid and the vapor that are in equilibrium with each other at that temperature. In the diagram, at temperature t, the intersection of the curve at x indicates that liquid of composition w will be in equilibrium with vapor of composition z, which corresponds to the intersection at y. Composition is given as a mole percentage of A and B in the mixture. Pure A, which boils at temperature t_A, is represented at the left. Pure B, which boils at temperature t_B, is represented at the right. For either pure A or pure B, the vapor and liquid curves meet at the boiling point. Thus, either pure A or pure B will distill at a constant temperature (t_A or t_B). Both the vapor and the liquid must have the same composition in either of these cases. This is not the case for mixtures of A and B.

A mixture of A and B of composition w will have the following behavior when heated. The temperature of the liquid mixture will increase until the boiling point of the mixture is reached. This corresponds to following line wx from w to x, the boiling point of the mixture t. At temperature t the liquid begins to vaporize, which corresponds to line xy. The vapor has the composition corresponding to z. In other words, the first vapor obtained in distilling a mixture of A and B does not consist of pure A. It is richer in A than the original mixture but still contains a significant amount of the higher-boiling component B, *even from the very beginning of the distillation.* The result is that it is never possible to separate a mixture completely by a simple distillation. However, in two cases it is possible to get an acceptable separation into relatively pure components. In the first case, if the boiling points of A and B differ by a large amount (> 100°C) and if the distillation is carried out carefully, it will be possible to get a fair separation of A and B. In the second case, if A contains a fairly small amount of B (< 10%), a reasonable separation of A from B can be achieved. When the boiling-point differences are not large and when highly pure components are desired, it is necessary to perform a **fractional distillation**. Fractional distillation is described in Technique 15, where the behavior during a simple distillation is also considered in detail. Note only that as vapor distills from the mixture of composition w (see Figure 14.4) it is richer in A than is the solution. Thus, the composition of the material left behind in the distillation becomes richer in B (moves to the right from w toward pure B in the graph). A mixture of 90% B (dotted line on the right side in Figure 14.4) has a higher boiling point than at w. Hence, the temperature of the liquid in the distillation flask will increase during the distillation, and the composition of the distillate will change (as is shown in Figure 14.3B).

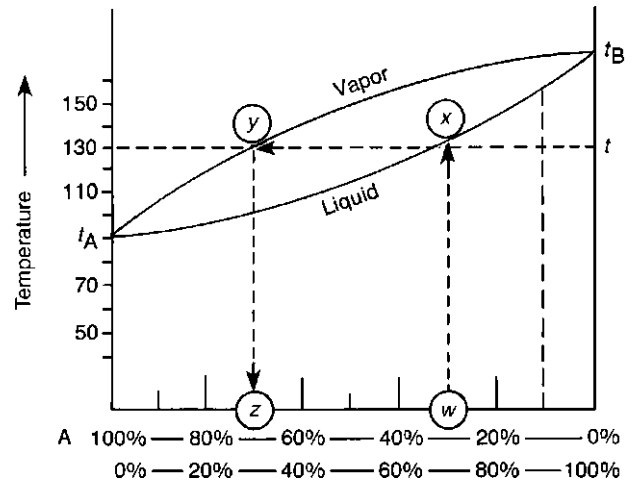


Figure 14.4 Phase diagram for a typical liquid mixture of two components.

When two components that have a large boiling-point difference are distilled, the temperature remains constant while the first component distills. If the temperature remains constant, a relatively pure substance is being distilled. After the first substance distills, the temperature of the vapors rises, and the second component distills, again at a constant temperature. This is shown in Figure 14.3C. A typical application of this type of distillation might be an instance of a reaction mixture containing the desired component A (bp 140°C) contaminated with a small amount of undesired component B (bp 250°C) and mixed with a solvent such as diethyl ether (bp 36°C). The ether is removed easily at low temperature. Pure A is removed at a higher temperature and collected in a separate receiver. Component B can then be distilled, but it is usually left as a residue and not distilled. The separation is not difficult and represents a case where simple distillation might be used to advantage.

14.3 Simple Distillation—Standard Apparatus

For a simple distillation, the apparatus shown in Figure 14.1 is used. Six pieces of specialized glassware are used:

1. Distilling flask
2. Distillation head
3. Thermometer adapter
4. Water condenser
5. Vacuum adapter
6. Receiving flask

The apparatus is usually heated electrically, using a heating mantle. The distilling flask, condenser, and vacuum adapter should be clamped. Two different methods of clamping this apparatus were shown in Technique 7 (Figure 7.2, p. 625 and Figure 7.4, p. 626). The receiving flask should be supported by removable wooden blocks or a wire gauze on an iron ring attached to a ring stand. The various components are each discussed in the following sections, along with some other important points.

Distilling Flask. The distilling flask should be a round-bottom flask. This type of flask is designed to withstand the required input of heat and to accommodate the boiling action. It gives a maximized heating surface. The size of the distilling flask should be chosen so that it is never filled more than two-thirds full. When the flask

is filled beyond this point, the neck constricts and "chokes" the boiling action, resulting in bumping. The surface area of the boiling liquid should be kept as large as possible. However, too large a distilling flask should also be avoided. With too large a flask, the **holdup** is excessive; the holdup is the amount of material that cannot distill because some vapor must fill the empty flask. When you cool the apparatus at the end, this material drops back into the distilling flask.

Boiling Stones. A boiling stone (Technique 7, Section 7.4, p. 631) should be used during distillation to prevent bumping. As an alternative, the liquid being distilled may be rapidly stirred using a magnetic stirrer and stir bar (Technique 7, Section 7.3, p. 630). If you forget a boiling stone, cool the mixture before adding it. If you add a boiling stone to a hot superheated liquid, it may "erupt" into vigorous boiling, breaking your apparatus and spilling hot solvent everywhere.

Grease. In most cases, it is unnecessary to grease standard-taper joints for a simple distillation. The grease makes cleanup more difficult, and it may contaminate your product.

Distillation Head. The distillation head directs the distilling vapors into the condenser and allows the connection of a thermometer via the thermometer adapter. The thermometer should be positioned in the distillation head so that the thermometer is directly in the stream of vapor that is distilling. This can be accomplished if the entire bulb of the thermometer is positioned *below* the sidearm of the distilling head (see the circular inset in Figure 14.1). The entire bulb must be immersed in the vapor to achieve an accurate temperature reading. When distilling, you should be able to see a reflux ring (Technique 7, Section 7.2, p. 628) positioned well above both the thermometer bulb and the bottom of the sidearm.

Thermometer Adapter. The thermometer adapter connects to the top of the distillation head (see Figure 14.1). There are two parts to the thermometer adapter: a glass joint with an open rolled edge on the top, and a rubber adapter that fits over the rolled edge and holds the thermometer. The thermometer fits in a hole in the top of the rubber adapter and can be adjusted upward and downward by sliding it in the hole. Adjust the bulb to a point below the sidearm. The distillation temperature can be monitored most accurately by using a partial immersion mercury thermometer (see Technique 13, Section 13.4).

Water Condenser. The joint between the distillation head and the water condenser is the joint most prone to leak in this entire apparatus. Because the distilling liquid is both hot and vaporized when it reaches this joint, it will leak out of any small opening between the two joint surfaces. The odd angle of the joint, neither vertical or horizontal, also makes a good connection more difficult. Be sure this joint is well sealed. If possible, use one of the plastic joint clips described in Technique 7, Figure 7.3. Otherwise, adjust your clamps to be sure that the joint surfaces are pressed together and not pulled apart.

The condenser will remain full of cooling water only if the water flows *upward,* not downward. The water input hose should be connected to the lower opening in the jacket, and the exit hose should be attached to the upper opening. Place the other end of the exit hose in a sink. A moderate water flow will perform a good deal of cooling. A high rate of water flow may cause the tubing to pop off the joints and cause a flood. If you hold the exit hose horizontally and point the end into a sink,

the flow rate is correct if the water stream continues horizontally for about two inches before bending downward.

If a distillation apparatus is to be left untended for a period of time, it is a good idea to wrap copper wire around the ends of the tubing and twist it tight. This will help to prevent the hoses from popping off of the connectors if there is an unexpected water-pressure change.

Vacuum Adapter. In a simple distillation, the vacuum adapter is not connected to a vacuum but is left open. It is merely an opening to the outside air so that pressure does not build up in the distillation system. If you plug this opening, you will have a **closed system** (no outlet). It is always dangerous to heat a closed system. Enough pressure can build up in the closed system to cause an explosion. The vacuum adapter, in this case, merely directs the distillate into the receiving, or collection, flask.

If the substance you are distilling is water sensitive, you can attach a calcium chloride drying tube to the vacuum connection to protect the freshly distilled liquid from atmospheric water vapor. Air that enters the apparatus will have to pass through the calcium chloride and be dried. Depending on the severity of the problem, drying agents other than calcium chloride may also be used.

The vacuum adapter has a disturbing tendency to obey the laws of Newtonian physics and fall off the slanted condenser onto the desk and break. If plastic joint clips are available, it is a good idea to use them on both ends of this piece. The top clip will secure the vacuum adapter to the condenser, and the bottom clip will secure the receiving flask, preventing it from falling.

Rate of Heating. The rate of heating for the distillation can be adjusted to the proper rate of **takeoff**, the rate at which distillate leaves the condenser, by watching drops of liquid emerge from the bottom of the vacuum adapter. A rate of from one to three drops per second is considered a proper rate of takeoff for most applications. At a greater rate, equilibrium is not established within the distillation apparatus, and the separation may be poor. A slower rate of takeoff is also unsatisfactory because the temperature recorded on the thermometer is not maintained by a constant vapor stream, thus leading to an inaccurate low boiling point.

Receiving Flask. The receiving flask, which is usually a round-bottom flask, collects the distilled liquid. If the liquid you are distilling is extremely volatile and there is danger of losing some of it to evaporation, it is sometimes advisable to cool the receiving flask in an ice-water bath.

Fractions. The material being distilled is called the **distillate**. Frequently, a distillate is collected in contiguous portions, called **fractions**. This is accomplished by replacing the collection flask with a clean one at regular intervals. If a small amount of liquid is collected at the beginning of a distillation and not saved or used further, it is called a **forerun**. Subsequent fractions will have higher boiling ranges, and each fraction should be labeled with its correct boiling range when the fraction is taken. For a simple distillation of a pure material, most of the material will be collected in a single, large **midrun** fraction, with only a small forerun. In some small-scale distillations, the volume of the forerun will be so small that you will not be able to collect it separately from the midrun fraction. The material left behind is called the **residue**. It is usually advised that you discontinue a distillation before the distilling flask becomes empty. Typically, the residue becomes increasingly dark in color during distillation, and it frequently contains thermal decomposition products.

In addition, a dry residue may explode on overheating, or the flask may melt or crack when it becomes dry. Don't distill until the distilling flask is completely dry!

14.4 Microscale and Semi-Microscale Equipment

When you wish to distill quantities that are smaller than 4–5 mL, different equipment is required. What you use depends on how small a quantity you wish to distill.

A. Semi-Microscale

One possibility is to use equipment identical in style to that used with conventional macroscale procedures, but to "downsize" it using ₹14/10 joints. The major manufacturers do make distillation heads and vacuum takeoff adapters with ₹14/10 joints. This equipment will allow you to handle quantities of 5–15 mL. An example of such a "semi-microscale" apparatus is given in Figure 14.5. Although the manufacturers make ₹14/10 condensers, the condenser has been left out in this example. This can be done if the material to be distilled is not extremely volatile or is high boiling. It is also possible to omit the condenser if you do not have a large amount of material and can cool the receiving flask in an ice-water bath as shown in the figure.

B. Microscale—Student Equipment

Figure 14.6 shows the typical distillation setup for those students who are taking a microscale laboratory course. Instead of a distillation head, condenser, and vacuum takeoff, this equipment uses a single piece of glassware called a **Hickman head**. The Hickman head provides a "short path" for the distilled liquid to travel

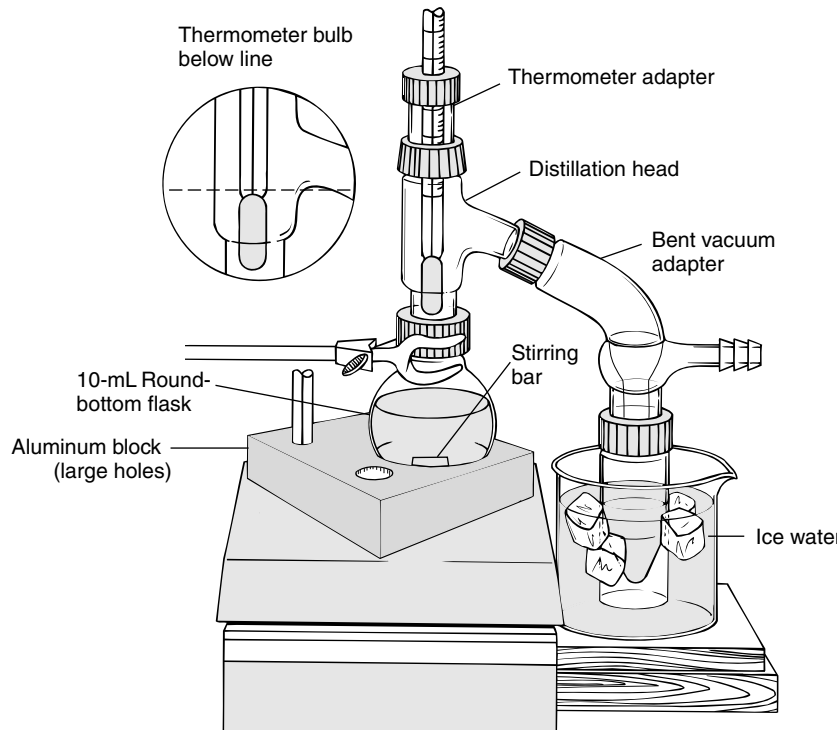


Figure 14.5 Semi-microscale distillation.

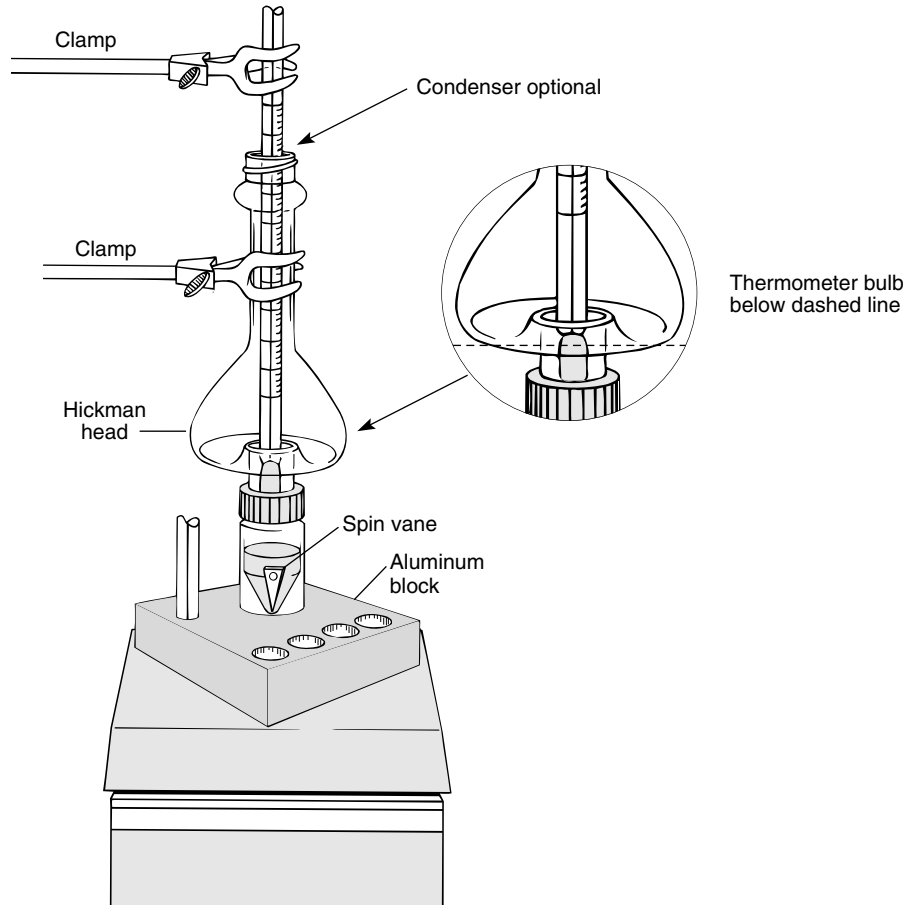


Figure 14.6 Basic microscale distillation.

before it is collected. The liquid is boiled, moves upward through the central stem of the Hickman head, condenses on the walls of the "chimney," and then runs down the sides into the circular well surrounding the stem. With very volatile liquids, a condenser can be placed on top of the Hickman head to improve its efficiency. The apparatus shown uses a 5-mL conical vial as the distilling flask, meaning that this apparatus can distill 1–3 mL of liquid. Unfortunately, the well in most Hickman heads holds only about 0.5–1.0 mL. Thus, the well must be emptied several times using a disposable Pasteur pipet, as shown in Figure 14.7. The figure shows two different styles of Hickman head. The one with the side port makes removal of the distillate easier.

C. Microscale—Research Equipment

Figure 14.8 shows a very well-designed research-style, short-path distillation head. Note how the equipment has been "unitized," eliminating several joints and decreasing the holdup.

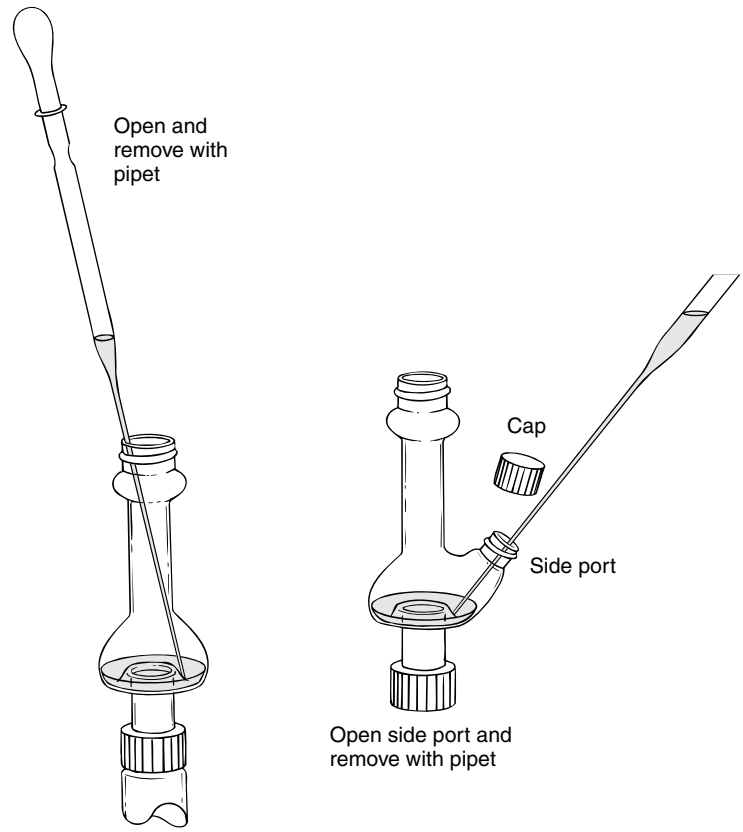


Figure 14.7 Two styles of Hickman head.

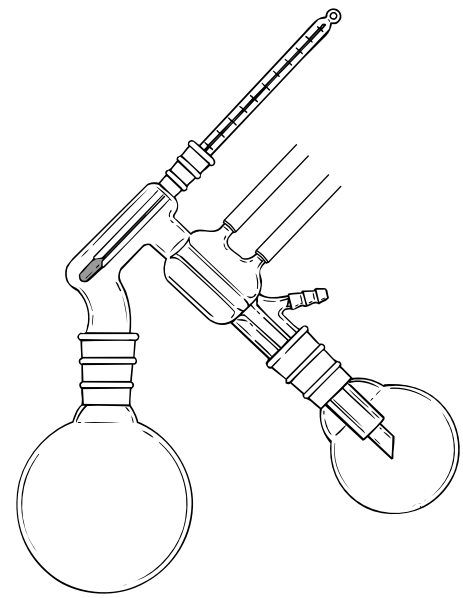


Figure 14.8 A research-style short-path distillation apparatus.

PROBLEMS

1. Using Figure 14.4, answer the following questions.
   a. What is the molar composition of the vapor in equilibrium with a boiling liquid that has a composition of 60% A and 40% B?
   b. A sample of vapor has the composition 50% A and 50% B. What is the composition of the boiling liquid that produced this vapor?
2. Use an apparatus similar to that shown in Figure 14.1 and assume that the round-bottom flask holds 100 mL and the distilling head has an internal volume of 12 mL in the vertical section. At the end of a distillation, vapor would fill this volume, but it could not be forced through the system. No liquid would remain in the distillation flask. Assuming this holdup volume of 112 mL, use the ideal gas law and assume a boiling point of 100 °C (760 mmHg) to calculate the number of milliliters of liquid ($d = 0.9$ g/mL, $MW = 200$) that would recondense into the distillation flask upon cooling.
3. Explain the significance of a horizontal line connecting a point on the lower curve with a point on the upper curve (such as line *xy*) in Figure 14.4.
4. Using Figure 14.4, determine the boiling point of a liquid having a molar composition of 50% A and 50% B.
5. Where should the thermometer bulb be located in the following setups:
   a. a microscale distillation apparatus using a Hickman head?
   b. a macroscale distillation apparatus using a distilling head, condenser, and vacuum takeoff adapter
6. Under what conditions can a good separation be achieved with a simple distillation?

15 TECHNIQUE 15

Fractional Distillation, Azeotropes

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

Simple distillation, described in Technique 14, works well for most routine separation and purification procedures for organic liquids. When the boiling-point differences of the components to be separated are not large, however, fractional distillation must be used to achieve a good separation.

A typical fractional distillation apparatus is shown in Figure 15.2 in Section 15.1, where the differences between simple and fractional distillation are discussed in detail. This apparatus differs from that for simple distillation by the insertion of a **fractionating column** between the distilling flask and the distillation head. The fractionating column is filled with a **packing**, a material that causes the liquid to condense and revaporize repeatedly as it passes through the column. With a good fractionating column, better separations are possible, and liquids with small boiling-point differences may be separated by using this technique.

PART A. FRACTIONAL DISTILLATION

15.1 Differences between Simple and Fractional Distillation

When an ideal solution of two liquids, such as benzene (bp 80°C) and toluene (bp 110°C), is distilled by simple distillation, the first vapor produced will be enriched in the lower-boiling component (benzene). However, when that initial vapor is condensed and analyzed, the distillate will not be pure benzene. The boiling point difference of benzene and toluene (30°C) is too small to achieve a complete separation by simple distillation. Following the principles outlined in Technique 14, Section 14.2 and using the vapor–liquid composition curve given in Figure 15.1, you can see what would happen if you started with an equimolar mixture of benzene and toluene.

Following the dashed lines shows that an equimolar mixture (50 mole percent benzene) would begin to boil at about 91°C and, far from being 100% benzene, the distillate would contain about 74 mole percent benzene and 26 mole percent toluene. As the distillation continued, the composition of the undistilled liquid would move in the direction of A′ (there would be increased toluene due to removal of more benzene than toluene), and the corresponding vapor would contain a progressively smaller amount of benzene. In effect, the temperature of the distillation would continue to increase throughout the distillation (as in Figure 14.3B), and it would be impossible to obtain any fraction that consisted of pure benzene.

Suppose, however, that we are able to collect a small quantity of the first distillate that was 74 mole percent benzene and redistill it. Using Figure 15.1, we can see that this liquid would begin to boil at about 84°C and would give an initial distillate containing 90 mole percent of benzene. If we were experimentally able to continue taking small fractions at the beginning of each distillation and redistill them, we would eventually reach a liquid with a composition of nearly 100 mole percent benzene. However, since we took only a small amount of material at the beginning of each distillation, we would have lost most of the material we started with. To recapture a reasonable amount of benzene, we would have to process each of the fractions

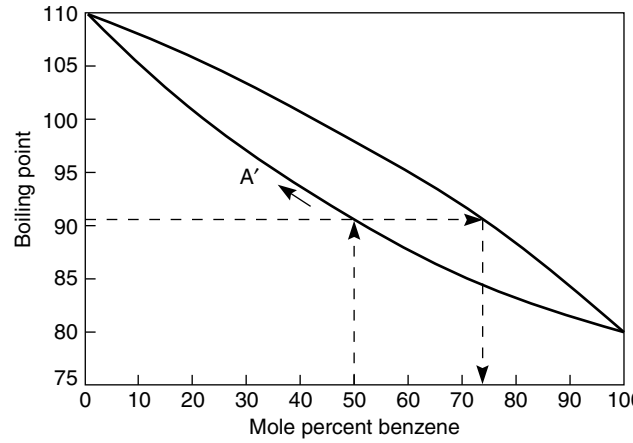


Figure 15.1 The vapor–liquid composition curve for mixtures of benzene and toluene.

left behind in the same way as our early fractions. As each of them was partially distilled, the material advanced would become progressively richer in benzene, and that left behind would become progressively richer in toluene. It would require thousands (maybe millions) of such microdistillations to separate benzene from toluene.

Obviously, the procedure just described would be very tedious; fortunately, it need not be performed in usual laboratory practice. **Fractional distillation** accomplishes the same result. You simply have to use a column inserted between the distillation flask and the distilling head, as shown in Figure 15.2. This **fractionating column** is filled, or **packed**, with a suitable material, such as a stainless-steel sponge. This packing allows a mixture of benzene and toluene to be subjected continuously to many vaporization–condensation cycles as the material moves up the column. With each cycle within the column, the composition of the vapor is progressively enriched in the lower-boiling component (benzene). Nearly pure benzene (bp 80°C) finally emerges from the top of the column, condenses, and passes into the receiving head or flask. This process continues until all of the benzene is removed. The distillation must be carried out slowly to ensure that numerous vaporization–condensation cycles occur. When nearly all of the benzene has been removed, the temperature begins to rise, and a small amount of a second fraction, which contains some benzene and toluene, may be collected. When the temperature reaches 110°C, the boiling point of pure toluene, the vapor is condensed and collected as the third fraction. A plot of boiling point versus volume of condensate (distillate) would resemble Figure 14.3C in Technique 14. This separation would be much better than that achieved by simple distillation (see Figure 14.3B).

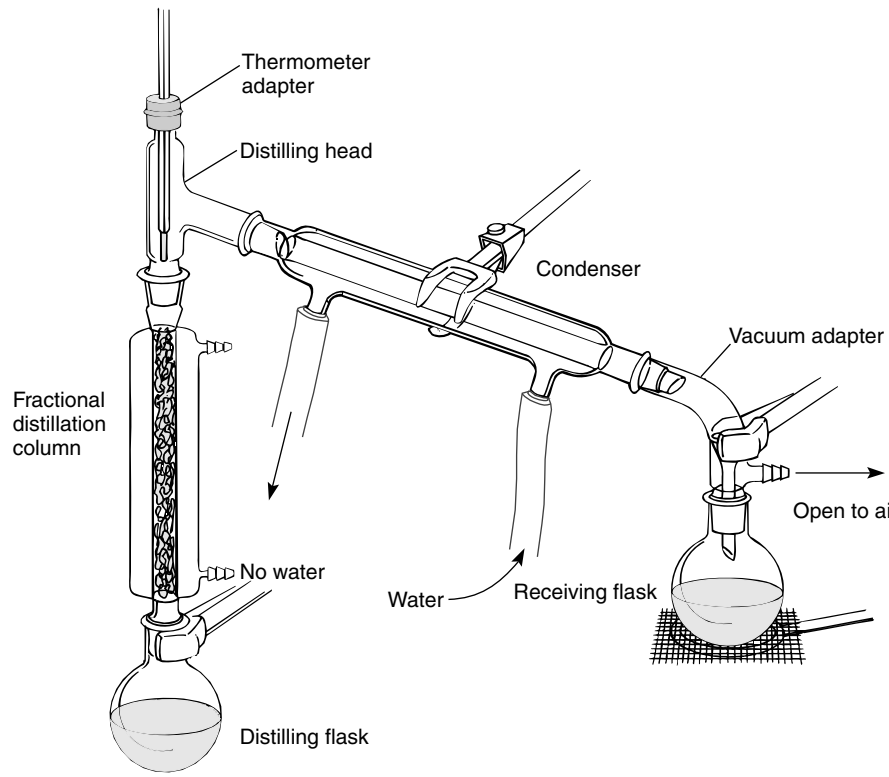


Figure 15.2 Fractional distillation apparatus.

15.2 Vapor–Liquid Composition Diagrams

A vapor–liquid composition phase diagram like the one in Figure 15.3 can be used to explain the operation of a fractionating column with an **ideal solution** of two liquids, A and B. An ideal solution is one in which the two liquids are chemically similar, are miscible (mutually soluble) in all proportions, and do not interact. Ideal solutions obey **Raoult's Law**. Raoult's Law is explained in detail in Section 15.3.

The phase diagram relates the compositions of the boiling liquid (lower curve) and its vapor (upper curve) as a function of temperature. Any horizontal line drawn across the diagram (a constant-temperature line) intersects the diagram in two places. These intersections relate the vapor composition to the composition of the boiling liquid that produces that vapor. By convention, composition is expressed either in **mole fraction** or in **mole percentage**. The mole fraction is defined as follows:

$$\text{Mole fraction A} = N_A = \frac{\text{Moles A}}{\text{Moles A} + \text{Moles B}}$$

$$\text{Mole fraction B} = N_B = \frac{\text{Moles B}}{\text{Moles A} + \text{Moles B}}$$

$$N_A + N_B = 1$$

$$\text{Mole percentage A} = N_A \times 100$$

$$\text{Mole percentage B} = N_B \times 100$$

The horizontal and vertical lines shown in Figure 15.3 represent the processes that occur during a fractional distillation. Each of the **horizontal lines** ($L_1\ V_1$, $L_2\ V_2$, and so on) represents both the **vaporization** step of a given vaporization–condensation cycle and the composition of the vapor in equilibrium with liquid at a given temperature. For example, at 63°C a liquid with a composition of 50% A (L_3 on the diagram) would yield vapor of composition 80% A (V_3 on diagram) at equilibrium. The vapor is richer in the lower-boiling component A than the original liquid was.

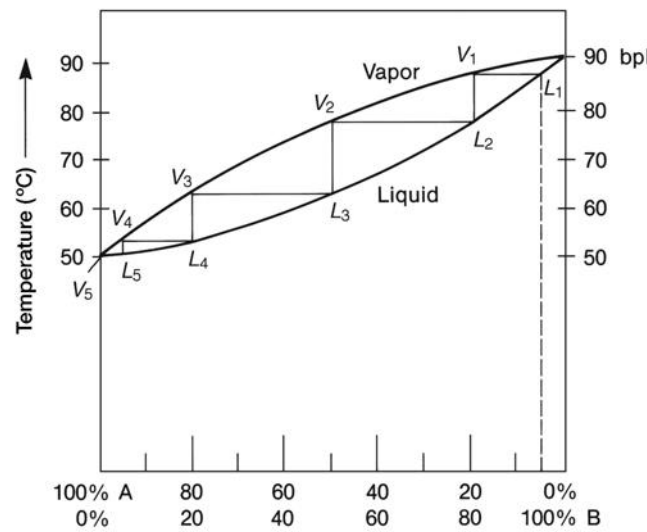


Figure 15.3 Phase diagram for a fractional distillation of an ideal two-component system.

Each of the **vertical lines** (V_1L_2, V_2L_3, and so on) represents the **condensation** step of a given vaporization–condensation cycle. The composition does not change as the temperature drops on condensation. The vapor at V_3, for example, condenses to give a liquid (L_4 on the diagram) of composition 80% A with a drop in temperature from 63°C to 53°C.

In the example shown in Figure 15.3, pure A boils at 50°C, and pure B boils at 90°C. These two boiling points are represented at the left- and right-hand edges of the diagram, respectively. Now consider a solution that contains only 5% of A but 95% of B. (Remember that these are *mole* percentages.) This solution is heated (following the dashed line) until it is observed to boil at L_1 (87°C). The resulting vapor has composition V_1 (20% A, 80% B). The vapor is richer in A than the original liquid was, but it is by no means pure A. In a simple distillation apparatus, this vapor would be condensed and passed into the receiver in a very impure state. However, with a fractionating column in place, the vapor is condensed in the **column** to give liquid L_2 (20% A, 80% B). Liquid L_2 is immediately revaporized (bp 78°C) to give a vapor of composition V_2 (50% A, 50% B), which is condensed to give liquid L_3. Liquid L_3 is revaporized (bp 63°C) to give vapor of composition V_3 (80% A, 20% B), which is condensed to give liquid L_4. Liquid L_4 is revaporized (bp 53°C) to give vapor of composition V_4 (95% A, 5% B). This process continues to V_5, which condenses to give nearly pure liquid A. The fractionating process follows the stepped lines in the figure downward and to the left.

As this process continues, all of liquid A is removed from the distillation flask or vial, leaving nearly pure B behind. If the temperature is raised, liquid B may be distilled as a nearly pure fraction. Fractional distillation will have achieved a separation of A and B, a separation that would have been nearly impossible with simple distillation. Notice that the boiling point of the liquid becomes lower each time it vaporizes. Because the temperature at the bottom of a column is normally higher than the temperature at the top, successive vaporizations occur higher and higher in the column as the composition of the distillate approaches that of pure A. This process is illustrated in Figure 15.4, where the composition of the liquids, their boiling points, and the composition of the vapors present are shown alongside the fractionating column.

15.3 Raoult's Law

Two liquids (A and B) that are miscible and that do not interact form an **ideal solution** and follow Raoult's Law. The law states that the partial vapor pressure of component A in the solution (P_A) equals the vapor pressure of pure A (P_A°) times its mole fraction (N_A) (equation 1). A similar expression can be written for component B (equation 2). The mole fractions N_A and N_B were defined in Section 15.2.

$$\text{Partial vapor pressure of A in solution} = P_A = (P_A^\circ)(N_A) \quad (1)$$

$$\text{Partial vapor pressure of B in solution} = P_B = (P_B^\circ)(N_B) \quad (2)$$

P_A° is the vapor pressure of pure A, independent of B. P_B° is the vapor pressure of pure B, independent of A. In a mixture of A and B, the partial vapor pressures are added to give the total vapor pressure above the solution (equation 3). When the total pressure (sum of the partial pressures) equals the applied pressure, the solution boils.

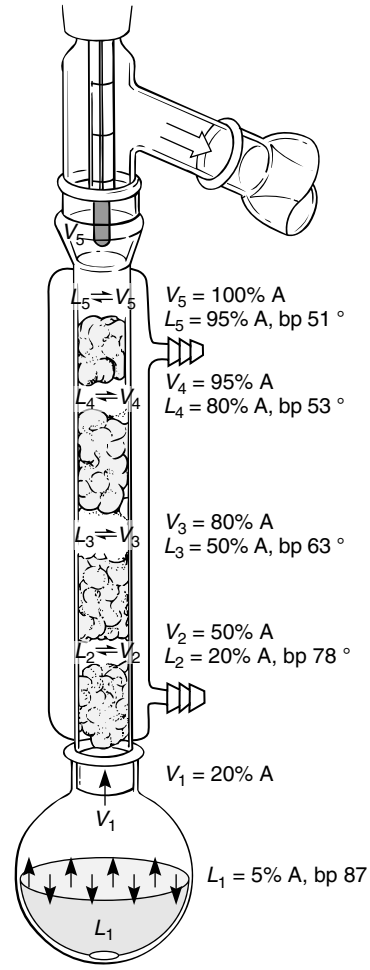


Figure 15.4 Vaporization–condensation in a fractionation column.

$$P_{\text{total}} = P_{\text{A}} + P_{\text{B}} = P_{\text{A}}^{\circ} N_{\text{A}} + P_{\text{B}}^{\circ} N_{\text{B}} \tag{3}$$

The composition of A and B in the vapor produced is given by equations 4 and 5.

$$N_A\,(\text{vapor}) = \frac{P_A}{P_{\text{total}}} \tag{4}$$

$$N_B\,(\text{vapor}) = \frac{P_B}{P_{\text{total}}} \tag{5}$$

Several exercises involving applications of Raoult's Law are illustrated in Table 15.1. Note, particularly in the result from equation 4, that the vapor is richer ($N_{\text{A}} = 0.67$) in the lower-boiling (higher vapor pressure) component A than it was before vaporization ($N_{\text{A}} = 0.50$). This proves mathematically what was described in Section 15.2.

The consequences of Raoult's Law for distillations are shown schematically in Figure 15.5. In Part A the boiling points are identical (vapor pressures the same), and no separation is attained regardless of how the distillation is conducted. In Part B a fractional distillation is required, while in Part C a simple distillation provides an adequate separation.

TABLE 15.1 Sample Calculations with Raoult's Law

Consider a solution at 100 °C where $N_A = 0.5$ and $N_B = 0.5$.

1. What is the partial vapor pressure of A in the solution if the vapor pressure of pure A at 100 °C is 1020 mmHg?
   Answer: $P_A = P_A^\circ N_A = (1020)(0.5) = 510$ mmHg
2. What is the partial vapor pressure of B in the solution if the vapor pressure of pure B at 100 °C is 500 mmHg?
   Answer: $P_B = P_B^\circ N_B = (500)(0.5) = 250$ mmHg
3. Would the solution boil at 100 °C if the applied pressure were 760 mmHg?
   Answer: Yes. $P_{total} = P_A + P_B = (510 + 250) = 760$ mmHg
4. What is the composition of the vapor at the boiling point?
   Answer: The boiling point is 100 °C.

$$N_A(\text{vapor}) = \frac{P_A}{P_{total}} = 510/760 = 0.67$$

$$N_B(\text{vapor}) = \frac{P_B}{P_{total}} = 250/760 = 0.33$$

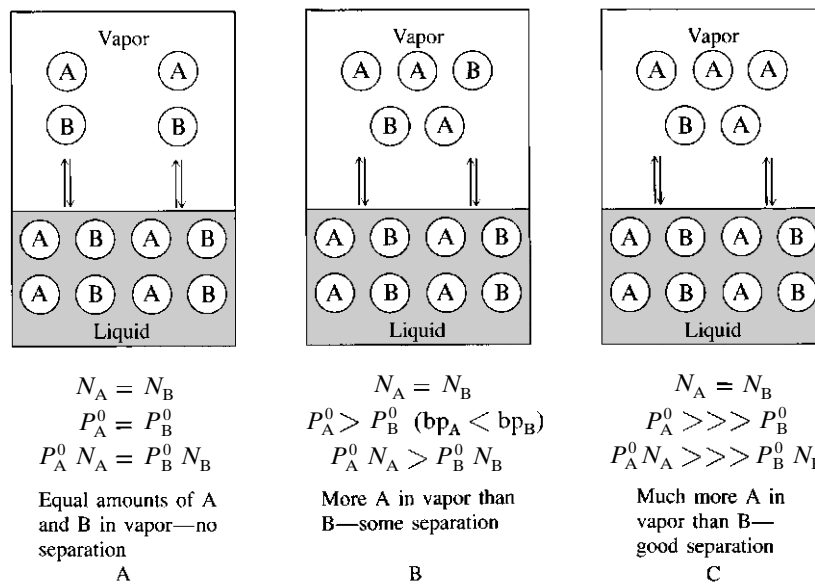


Figure 15.5 Consequences of Raoult's Law. (A) Boiling points (vapor pressures) are identical—no separation. (B) Boiling points somewhat less for A than for B—requires fractional distillation. (C) Boiling points much less for A than for B—simple distillation will suffice.

When a solid B (rather than another liquid) is dissolved in a liquid A, the boiling point is increased. In this extreme case, the vapor pressure of B is negligible, and the vapor will be pure A no matter how much solid B is added. Consider a solution of salt in water.

$$P_{\text{total}} = P^{\circ}_{\text{water}} N_{\text{water}} + P^{\circ}_{\text{salt}} N_{\text{salt}}$$

$$P^{\circ}_{\text{salt}} = 0$$

$$P_{\text{total}} = P^{\circ}_{\text{water}} N_{\text{water}}$$

A solution whose mole fraction of water is 0.7 will not boil at 100°C, because $P_{\text{total}} = (760)(0.7) = 532$ mmHg and is less than atmospheric pressure. If the solution is heated to 110°C, it will boil because $P_{\text{total}} = (1085)(0.7) = 760$ mmHg. Although the solution must be heated at 110°C to boil it, the vapor is pure water and has a boiling-point temperature of 100°C. (The vapor pressure of water at 110°C can be looked up in a handbook; it is 1085 mmHg.)

15.4 Column Efficiency

A common measure of the efficiency of a column is given by its number of **theoretical plates**. The number of theoretical plates in a column is related to the number of vaporization–condensation cycles that occur as a liquid mixture travels through it. Using the example mixture in Figure 15.3, if the first distillate (condensed vapor) had the composition at L_2 when starting with liquid of composition L_1, the column would be said to have *one theoretical plate.* This would correspond to a simple distillation, or one vaporization–condensation cycle. A column would have two theoretical plates if the first distillate had the composition at L_3. The two-theoretical-plate column essentially carries out "two simple distillations." According to Figure 15.3, *five theoretical plates* would be required to separate the mixture that started with composition L_1. Notice that this corresponds to the number of "steps" that need to be drawn in the figure to arrive at a composition of 100% A.

Most columns do not allow distillation in discrete steps, as indicated in Figure 15.3. Instead, the process is *continuous,* allowing the vapors to be continuously in contact with liquid of changing composition as they pass through the column. Any material can be used to pack the column as long as it can be wetted by the liquid and does not pack so tightly that vapor cannot pass.

The approximate relationship between the number of theoretical plates needed to separate an ideal two-component mixture and the difference in boiling points is given in Table 15.2. Notice that more theoretical plates are required as the boiling-point differences between the components decrease. For instance, a mixture of A (bp 130°C) and B (bp 166°C) with a boiling-point difference of 36°C would be expected to require a column with a minimum of five theoretical plates.

15.5 Types of Fractionating Columns and Packings

Several types of fractionating columns are shown in Figure 15.6. The Vigreux column (A) has indentations that incline downward at angles of 45° and are in pairs on opposite sides of the column. The projections into the column provide increased possibilities for condensation and for the vapor to equilibrate with the liquid. Vigreux columns are popular in cases where only a small number of theoretical plates are required. They are not very efficient (a 20-cm column might have only 2.5 theoretical plates), but they allow for rapid distillation and have a small **holdup** (the amount of liquid retained by the column). A column packed with a stainless-steel sponge is a

TABLE 15.2 Theoretical Plates Required to Separate Mixtures, Based on Boiling-Point Differences of Components

Boiling-Point Difference	Number of Theoretical Plates
108	1
72	2
54	3
43	4
36	5
20	10
10	20
7	30
4	50
2	100

more effective fractionating column than a Vigreux column, but not by a large margin. Glass beads or glass helices can also be used as a packing material, and they have even a slightly greater efficiency. The air condenser or the water condenser can be used as an improvised column if an actual fractionating column is unavailable. If a condenser is packed with glass beads, glass helices, or sections of glass tubing, the packing must be held in place by inserting a small plug of stainless steel sponge into the bottom of the condenser.

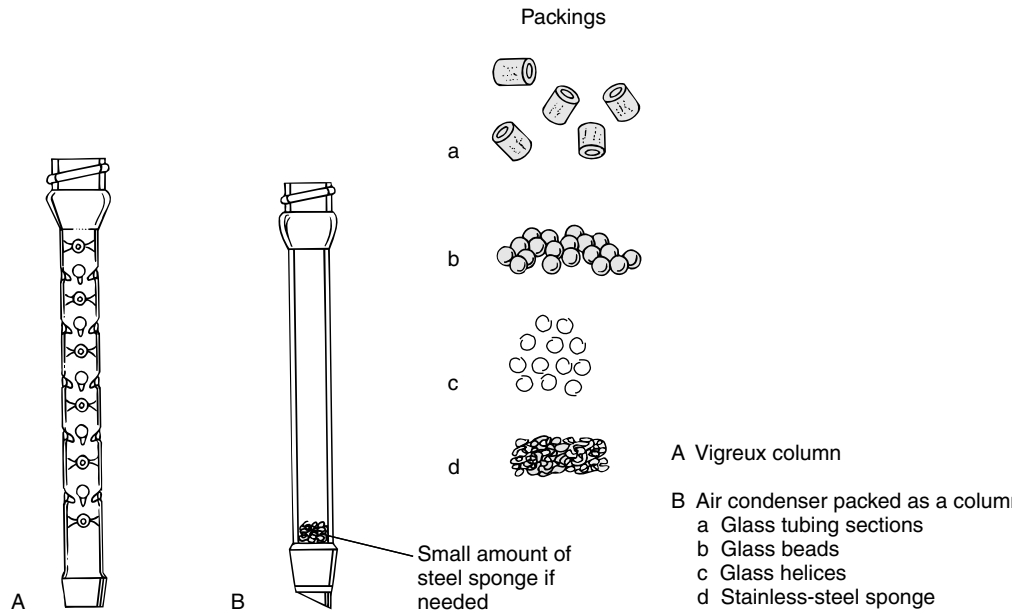


Figure 15.6 Columns for fractional distillation.

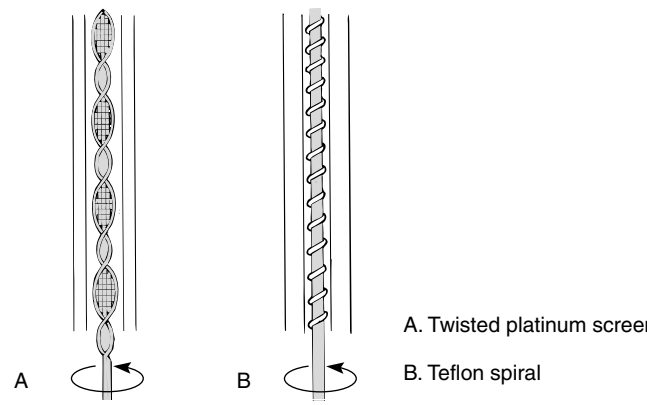


Figure 15.7 Bands for spinning-band columns.

The most effective type of column is the **spinning-band column**. In the most elegant form of this device, a tightly fitting, twisted platinum screen or a Teflon rod with helical threads is rotated rapidly inside the bore of the column (see Figure 15.7). A spinning-band column that is available for microscale work is shown in Figure 15.8. This spinning-band column has a band about 2–3 cm in length and provides four or five theoretical plates. It can separate 1–2 mL of a mixture with a 30°C boiling-point difference. Larger research models of this spinning-band column can provide as many as 20 or 30 theoretical plates and can separate mixtures with a boiling-point difference of as little as 5–10°C.

Manufacturers of fractionating columns often offer them in a variety of lengths. Because the efficiency of a column is a function of its length, longer columns have more theoretical plates than shorter ones do. It is common to express efficiency of a column in a unit called **HETP**, the **H**eight of a column that is **E**quivalent to one **T**heoretical **P**late. HETP is usually expressed in units of cm/plate. When the height of the column (in centimeters) is divided by this value, the total number of theoretical plates is specified.

Fractionating columns must be insulated so that temperature equilibrium is maintained at all times. External temperature fluctuations will interfere with a good separation. Many fractionating columns are jacketed as a condenser is, but instead of water passing through the outer jacket, the jacket is evacuated and sealed. A vacuum jacket provides very good insulation of the inner column from the outside air temperature. In most student macroscale kits, the fractionating column is not evacuated but does have a jacket for insulation. This jacket, even though not evacuated, is usually sufficient for the demands of the introductory laboratory. The fractionating column looks very much like a water condenser; however, it has a larger diameter both for the inner tube and for the jacket. Be sure to take care to distinguish the larger-diameter fractionating column from the smaller-diameter water condenser.

15.6 Fractional Distillation: Methods and Practice

Many fractionating columns must be insulated so that temperature equilibrium is maintained at all times. Additional insulation will not be required for columns that have an outer jacket, but those that do not can benefit from being wrapped in insulation.

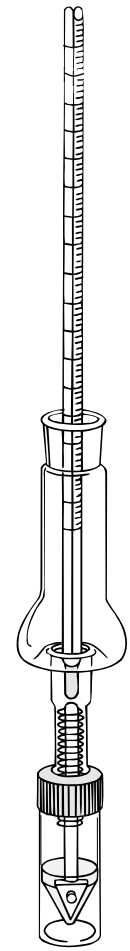


Figure 15.8 A commercially available microscale spinning-band column.

Cotton and aluminum foil (shiny side in) are often used for insulation. You can wrap the column with cotton and then use a wrapping of the aluminum foil to keep it in place. Another version of this method, which is especially effective, is to make an insulation blanket by placing a layer of cotton between two rectangles of aluminum foil, placed shiny side in. The sandwich is bound together with duct tape. This blanket, which is reusable, can be wrapped around the column and held in place with twist ties or tape.

The **reflux ratio** is defined as the ratio of the number of drops of distillate that return to the distillation flask compared to the number of drops of distillate collected. In an efficient column, the reflux ratio should equal or exceed the number of theoretical plates. A high reflux ratio ensures that the column will achieve temperature equilibrium and achieve its maximum efficiency. This ratio is not easy to determine; in fact, it is impossible to determine when using a Hickman head, and it should not concern a beginning student. In some cases, the **throughput**, or **rate of takeoff**, of a column may be specified. This is expressed as the number of milliliters of distillate that can be collected per unit of time, usually as mL/min.

Macroscale Apparatus. Figure 15.2 illustrates a fractional distillation assembly that can be used for larger-scale distillations. It has a glass-jacketed column that is packed with a stainless-steel sponge. This apparatus would be common in situations where quantities of liquid in excess of 10 mL were to be distilled.

In a fractional distillation, the column should be clamped in a vertical position. The distilling flask would normally be heated by a heating mantle, which allows a precise adjustment of the temperature. A proper rate of distillation is extremely important. The distillation should be conducted as slowly as possible to allow as many vaporization–condensation cycles as possible to occur as the vapor passes through the column. However, the rate of distillation must be steady enough to produce a constant temperature reading at the thermometer. A rate that is too fast will cause the column to "flood" or "choke." In this instance, there is so much condensing liquid flowing downward in the column that the vapor cannot rise upward, and the column fills with liquid. Flooding can also occur if the column is not well insulated and has a large temperature difference from bottom to top. This situation can be remedied by employing one of the insulation methods that uses cotton or aluminum foil, as described in Section 15.5. It may also be necessary to insulate the distilling head at the top of the column. If the distilling head is cold, it will stop the progress of the distilling vapor. The distillation temperature can be monitored most accurately by using a partial immersion mercury thermometer (see Technique 13, Section 13.4).

Microscale Apparatus. The apparatus shown in Figure 15.9 is the one you are most likely to use in the microscale laboratory. If your laboratory is one of the better equipped ones, you may have access to spinning-band columns like the one shown in Figure 15.8.

PART B. AZEOTROPES

15.7 Nonideal Solutions: Azeotropes

Some mixtures of liquids, because of attractions or repulsions between the molecules, do not behave ideally; they do not follow Raoult's Law. There are two types of vapor–liquid composition diagrams that result from this nonideal behavior: **minimum-boiling-point** and **maximum-boiling-point** diagrams. The minimum or maximum points in these diagrams correspond to a constant-boiling mixture called an **azeotrope**. An azeotrope is a mixture with a fixed composition that cannot be altered by either simple or fractional distillation. An azeotrope behaves as if it were a pure compound, and it distills from the beginning to the end of its distillation at a constant temperature, giving a distillate of constant (azeotropic) composition. The vapor in equilibrium with an azeotropic liquid has the same composition as the azeotrope. Because of this, an azeotrope is represented as a *point* on a vapor–liquid composition diagram.

A. Minimum-Boiling-Point Diagrams

A minimum-boiling-point azeotrope results from a slight incompatibility (repulsion) between the liquids being mixed. This incompatibility leads to a higher-than-expected combined vapor pressure from the solution. This higher combined vapor pressure brings about a lower boiling point for the mixture than is observed for the pure components. The most common two-component mixture that gives a minimum-boiling-point azeotrope is the ethanol–water system shown in Figure 15.10.

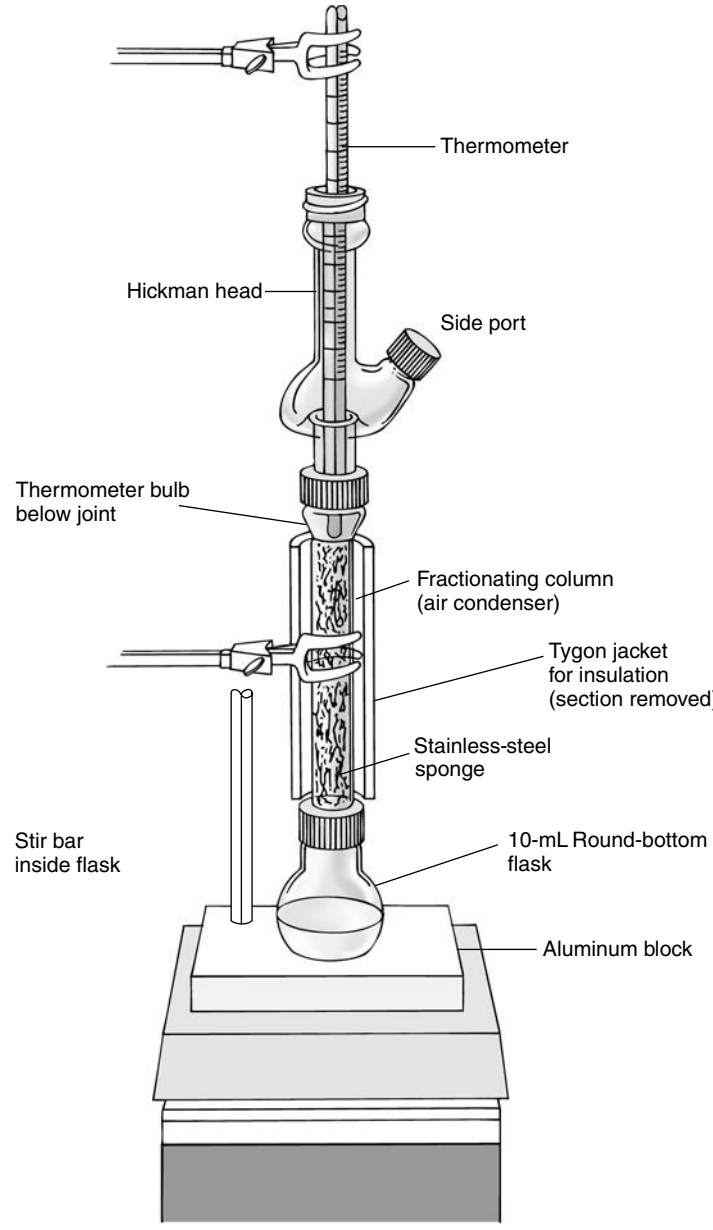


Figure 15.9 Microscale apparatus for fractional distillation.

The azeotrope at V_3 has a composition of 96% ethanol–4% water and a boiling point of 78.1°C. This boiling point is not much lower than that of pure ethanol (78.3°C), but it means that it is impossible to obtain pure ethanol from the distillation of any ethanol–water mixture that contains more than 4% water. Even with the best fractionating column, you cannot obtain 100% ethanol. The remaining 4% of water can be removed by adding benzene and removing a different azeotrope, the ternary benzene–water–ethanol azeotrope (bp 65°C). Once the water is removed, the excess benzene is removed as an ethanol–benzene azeotrope (bp 68°C). The resulting material is free of water and is called "absolute" ethanol.

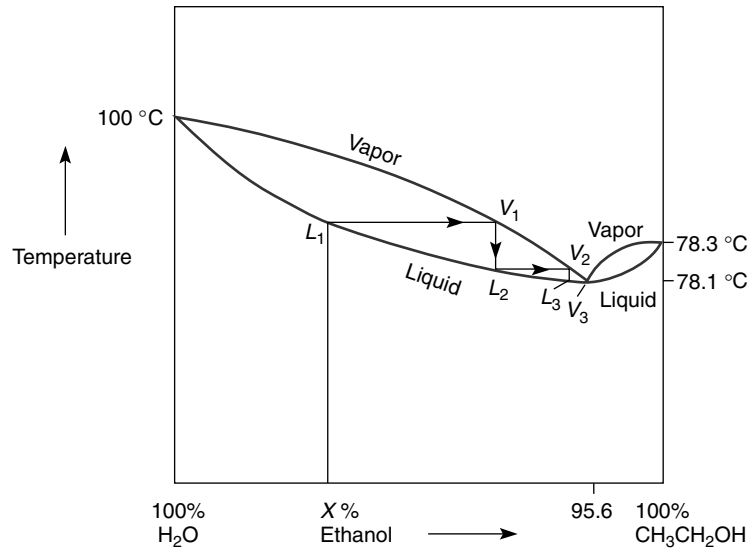


Figure 15.10 Ethanol–water minimum-boiling-point phase diagram.

The fractional distillation of an ethanol–water mixture of composition X can be described as follows. The mixture is heated (follow line XL_1) until it is observed to boil at L_1. The resulting vapor at V_1 will be richer in the lower-boiling component, ethanol, than the original mixture was.[1] The condensate at L_2 is vaporized to give V_2. The process continues, following the lines to the right, until the azeotrope is obtained at V_3. The liquid that distills is not pure ethanol, but it has the azeotropic composition of 96% ethanol and 4% water, and it distills at 78.1°C. The azeotrope, which is richer in ethanol than the original mixture was, continues to distill. As it distills, the percentage of water left behind in the distillation flask continues to increase. When all the ethanol has been distilled (as the azeotrope), pure water remains behind in the distillation flask, and it distills at 100°C.

If the azeotrope obtained by the preceding procedure is redistilled, it distills from the beginning to the end of the distillation at a constant temperature of 78.1°C as if it were a pure substance. There is no change in the composition of the vapor during the distillation.

Some common minimum-boiling-point azeotropes are given in Table 15.3. Numerous other azeotropes are formed in two- and three-component systems; such azeotropes are common. Water forms azeotropes with many substances; therefore, water must be carefully removed with **drying agents** whenever possible before compounds are distilled. Extensive azeotropic data are available in references such as the *CRC Handbook of Chemistry and Physics.*[2]

B. Maximum-Boiling-Point Diagrams

A maximum-boiling-point azeotrope results from a slight attraction between the component molecules. This attraction leads to lower combined vapor pressure

[1] Keep in mind that this distillate is not pure ethanol, but is an ethanol–water mixture.

[2] More examples of azeotropes, with their compositions and boiling points, can be found in the *CRC Handbook of Chemistry and Physics;* also in L. H. Horsley, ed., *Advances in Chemistry Series,* No. 116, Azeotropic Data, III (Washington, DC: American Chemical Society, 1973).

TABLE 15.3 Common Minimum-Boiling-Point Azeotropes

Azeotrope	Composition (Weight Percentage)	Boiling Point (°C)
Ethanol–water	95.6% C_2H_5OH, 4.4% H_2O	78.17
Benzene–water	91.1% C_6H_6, 8.9% H_2O	69.4
Benzene–water–ethanol	74.1% C_6H_6, 7.4% H_2O, 18.5% C_2H_5OH	64.9
Methanol–carbon tetrachloride	20.6% CH_3OH, 79.4% CCl_4	55.7
Ethanol–benzene	32.4% C_2H_5OH, 67.6% C_6H_6	67.8
Methanol–toluene	72.4% CH_3OH, 27.6% $C_6H_5CH_3$	63.7
Methanol–benzene	39.5% CH_3OH, 60.5% C_6H_6	58.3
Cyclohexane–ethanol	69.5% C_6H_{12}, 30.5% C_2H_5OH	64.9
2-Propanol–water	87.8% $(CH_3)_2CHOH$, 12.2% H_2O	80.4
Butyl acetate–water	72.9% $CH_3COOC_4H_9$, 27.1% H_2O	90.7
Phenol–water	9.2% C_6H_5OH, 90.8% H_2O	99.5

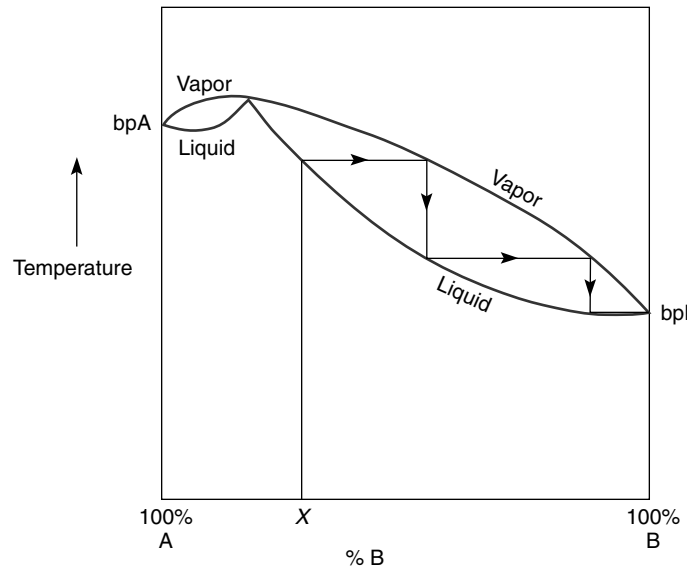


Figure 15.11 A maximum-boiling-point phase diagram.

than expected in the solution. The lower combined vapor pressures cause a higher boiling point than what would be characteristic for the components. A two-component maximum-boiling-point azeotrope is illustrated in Figure 15.11. Because the azeotrope has a higher boiling point than any of the components, it will be concentrated in the distillation flask as the distillate (pure B) is removed. The distillation of a solution of composition *X* would follow to the right along the lines in Figure 15.11. Once the composition of the material remaining in the flask has reached that of the azeotrope, the temperature will rise, and the azeotrope will begin to distill. The azeotrope will continue to distill until all of the material in the distillation flask has been exhausted.

TABLE 15.4 Maximum-Boiling-Point Azeotropes

Azeotrope	Composition (Weight Percentage)	Boiling Point (°C)
Acetone–chloroform	20.0% CH_3COCH_3, 80.0% $CHCl_3$	64.7
Chloroform–methyl ethyl ketone	17.0% $CHCl_3$, 83.0% $CH_3COCH_2CH_3$	79.9
Hydrochloric acid	20.2% HCl, 79.8% H_2O	108.6
Acetic acid–dioxane	77.0% CH_3COCH, 23.0% $C_4H_8O_2$	119.5
Benzaldehyde–phenol	49.0% C_6H_5CHO, 51.0% C_6H_5OH	185.6

Some maximum-boiling-point azeotropes are listed in Table 15.4. They are not nearly as common as minimum-boiling-point azeotropes.[3]

C. Generalizations

There are some generalizations that can be made about azeotropic behavior. They are presented here without explanation, but you should be able to verify them by thinking through each case using the phase diagrams given. (Note that pure A is always to the left of the azeotrope in these diagrams, and pure B is to the right of the azeotrope.)

Minimum-Boiling-Point Azeotropes

Initial Composition	Experimental Result
To left of azeotrope	Azeotrope distills first, pure A second
Azeotrope	Inseparable
To right of azeotrope	Azeotrope distills first, pure B second

Maximum-Boiling-Point Azeotropes

Initial Composition	Experimental Result
To left of azeotrope	Pure A distills first, azeotrope second
Azeotrope	Inseparable
To right of azeotrope	Pure B distills first, azeotrope second

15.8 Azeotropic Distillation: Applications

There are numerous examples of chemical reactions in which the amount of product is low because of an unfavorable equilibrium. An example is the direct acid-catalyzed esterification of a carboxylic acid with an alcohol:

$$R{-}\overset{\overset{O}{\|}}{C}{-}OH + R{-}O{-}H \overset{H^+}{\rightleftharpoons} R{-}\overset{\overset{O}{\|}}{C}{-}OR + H_2O$$

[3] See footnote 2.

Because the equilibrium does not favor formation of the ester, it must be shifted to the right, in favor of the product, by using an excess of one of the starting materials. In most cases, the alcohol is the least expensive reagent and is the material used in excess. Isopentyl acetate (Experiment 12) is an example of an ester prepared by using one of the starting materials in excess.

Another way of shifting the equilibrium to the right is to remove one of the products from the reaction mixture as it is formed. In the previous example, water can be removed as it is formed by **azeotropic distillation**. A common large-scale method is to use the Dean–Stark water separator shown in Figure 15.12A. In this technique, an inert solvent, commonly benzene or toluene, is added to the reaction mixture contained in the round-bottom flask. The sidearm of the water separator is also filled with this solvent. If benzene is used, as the mixture is heated under reflux, the benzene–water azeotrope (bp 69.4°C, Table 15.3) distills out of the flask.[4] When the vapor condenses, it enters the sidearm directly below the condenser, and water separates from the benzene–water condensate; benzene and water mix as vapors, but they are not miscible as cooled liquids. Once the water (lower phase) separates from the benzene (upper phase), liquid benzene overflows from the sidearm back into the flask. The cycle is repeated continuously until no more water forms in the sidearm. You may calculate the weight of water that should theoretically be produced and compare this value with the amount of water collected in the sidearm. Because the density of water is 1.0, the volume of water collected can be compared directly with the calculated amount, assuming 100% yield.

An improvised water separator, constructed from the components found in the traditional organic kit, is shown in Figure 15.12B. Although this requires the condenser to be placed in a nonvertical position, it works quite well.

At the microscale level, water separation can be achieved using a standard distillation assembly with a water condenser and a Hickman head (see Figure 15.13). The side-ported variation of the Hickman head is the most convenient one to use for this purpose, but it is not essential. In this variation, you simply remove all of the distillate (both solvent and water) several times during the course of the reaction. Use a Pasteur pipet to remove the distillate, as shown in Technique 14 (see Figure 14.7). Because both the solvent and water are removed in this procedure, it may be desirable to add more solvent from time to time, adding it through the condenser with a Pasteur pipet.

The most important consideration in using azeotropic distillation to prepare an ester (described on the previous page) is that the azeotrope containing water must have a **lower boiling point** than the alcohol used. With ethanol, the benzene–water azeotrope boils at a much lower temperature (69.4°C) than ethanol (78.3°C), and the technique previously described works well. With higher-boiling-point alcohols, azeotropic distillation works well because of the large boiling-point difference between the azeotrope and the alcohol.

With methanol (bp 65°C), however, the boiling point of the benzene–water azeotrope is actually *higher* by about 5°C, and methanol distills first. Thus, in esterifications involving methanol, a totally different approach must be taken.

---

[4] Actually, with ethanol, a lower-boiling-point, three-component azeotrope distills at 64.9°C (see Table 15.3). It consists of benzene–water–ethanol. Because some ethanol is lost in the azeotropic distillation, a large excess of ethanol is used in esterification reactions. The excess also helps to shift the equilibrium to the right.

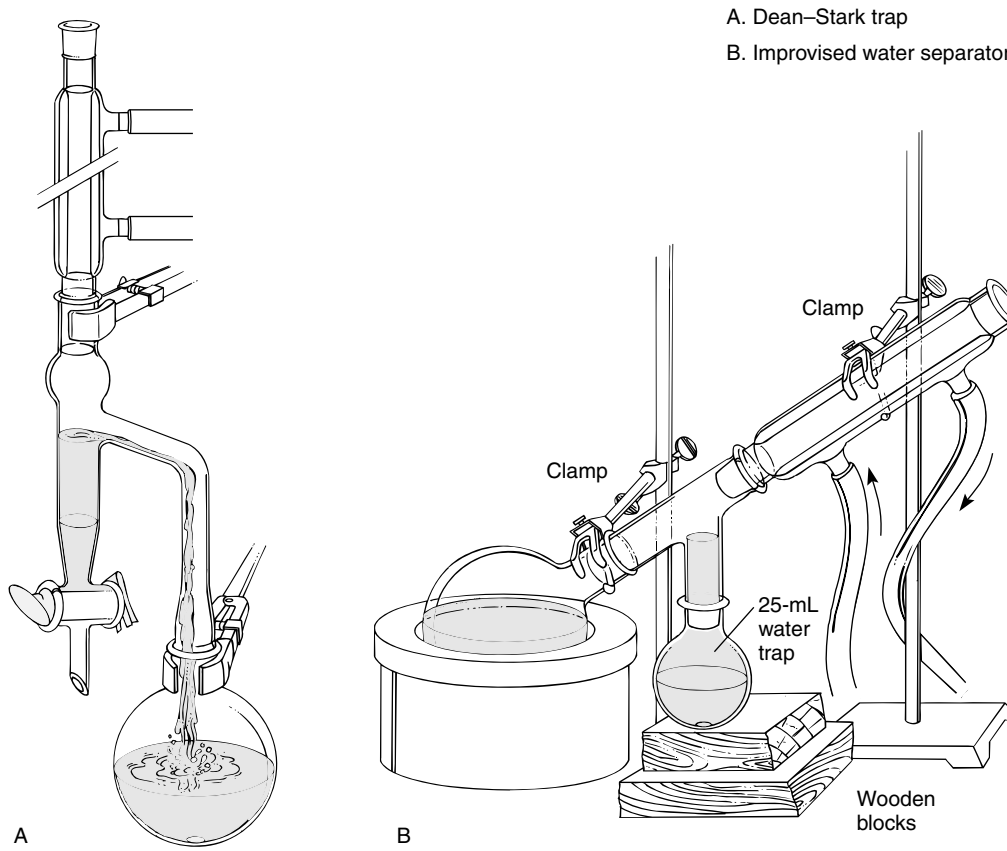


Figure 15.12 Large-scale water separators.

For example, you can mix the carboxylic acid, methanol, the acid catalyst, and *1,2-dichloroethane* in a conventional reflux apparatus (see Technique 7, Figure 7.6) without a water separator. During the reaction, water separates from the 1,2-dichlo-roethane because it is not miscible; however, the remainder of the components are soluble, so the reaction can continue. The equilibrium is shifted to the right by the "removal" of water from the reaction mixture.

Azeotropic distillation is also used in other types of reactions, such as ketal or acetal formation, and in enamine formation.

Acetal formation

$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}H + 2\ ROH \overset{H^+}{\rightleftharpoons} R{-}\overset{\displaystyle OR}{\overset{|}{C}}{-}H + H_2O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OR$$

Enamine formation

$$RCH_2{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_2R + \underset{\displaystyle H}{\overset{\displaystyle N}{\overset{\|}{\text{⬠}}}} \overset{H^+}{\rightleftharpoons} RCH{=}\overset{\displaystyle N}{\overset{|}{C}}{-}CH_2R + H_2O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{⬠}$$

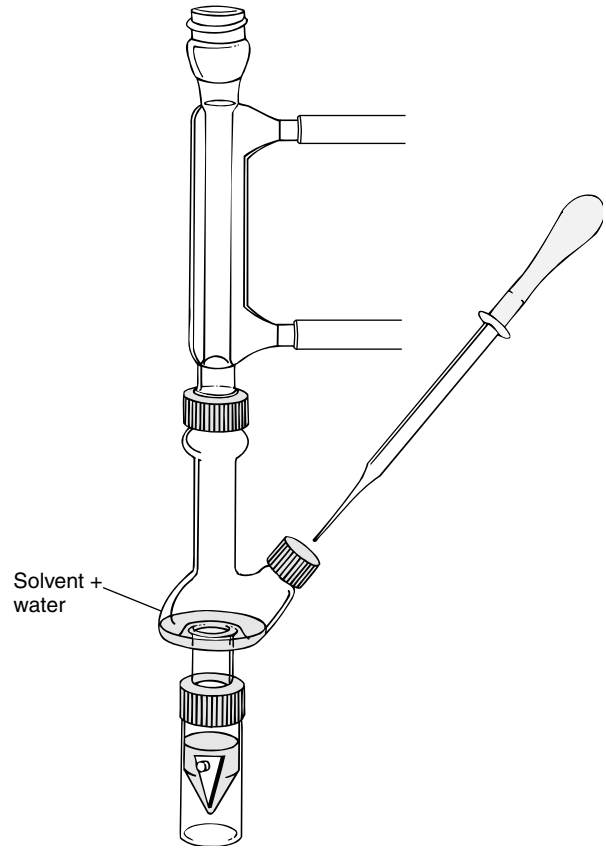


Figure 15.13 Microscale water separator (both layers are removed).

PROBLEMS

1. In the accompanying chart are approximate vapor pressures for benzene and toluene at various temperatures.

Temp (°C)	mmHg	Temp (°C)	mmHg
Benzene 30	120	Toluene 30	37
40	180	40	60
50	270	50	95
60	390	60	140
70	550	70	200
80	760	80	290
90	1010	90	405
100	1340	100	560
		110	760

a. What is the mole fraction of each component if 3.9 g of benzene (C_6H_6) is dissolved in 4.6 g of toluene (C_7H_8)?

b. Assuming that this mixture is ideal, that is, it follows Raoult's Law, what is the partial vapor pressure of benzene in this mixture at 50 °C?

c. Estimate to the nearest degree the temperature at which the vapor pressure of the solution equals 1 atm (bp of the solution).

d. Calculate the composition of the vapor (mole fraction of each component) that is in equilibrium in the solution at the boiling point of this solution.

e. Calculate the composition in weight percentage of the vapor that is in equilibrium with the solution.

2. Estimate how many theoretical plates are needed to separate a mixture that has a mole fraction of B equal to 0.70 (70% B) in Figure 15.3.

3. Two moles of sucrose are dissolved in 8 moles of water. Assume that the solution follows Raoult's Law and that the vapor pressure of sucrose is negligible. The boiling point of water is 100 °C. The distillation is carried out at 1 atm (760 mmHg).

a. Calculate the vapor pressure of the solution when the temperature reaches 100 °C.

b. What temperature would be observed during the entire distillation?

c. What would be the composition of the distillate?

d. If a thermometer were immersed below the surface of the liquid of the boiling flask, what temperature would be observed?

4. Explain why the boiling point of a two-component mixture rises slowly throughout a simple distillation when the boiling-point differences are not large.

5. Given the boiling points of several known mixtures of A and B (mole fractions are known) and the vapor pressures of A and B in the pure state (P°_{A} and P°_{B}) at these same temperatures, how would you construct a boiling-point-composition phase diagram for A and B? Give a stepwise explanation.

6. Describe the behavior upon distillation of a 98% ethanol solution through an efficient column. Refer to Figure 15.10.

7. Construct an approximate boiling-point-composition diagram for a benzene-methanol system. The mixture shows azeotropic behavior (see Table 15.3). Include on the graph the boiling points of pure benzene and pure methanol and the boiling point of the azeotrope. Describe the behavior for a mixture that is initially rich in benzene (90%) and then for a mixture that is initially rich in methanol (90%).

8. Construct an approximate boiling-point-composition diagram for an acetone–chloroform system, which forms a maximum-boiling-point azeotrope (see Table 15.4). Describe the behavior upon distillation of a mixture that is initially rich in acetone (90%), and then describe the behavior of a mixture that is initially rich in chloroform (90%).

9. Two components have boiling points of 130 °C and 150 °C. Estimate the number of theoretical plates needed to separate these substances in a fractional distillation.

10. A spinning-band column has an HETP of 0.25 in./plate. If the column has 12 theoretical plates, how long is it?

16 TECHNIQUE 16

Vacuum Distillation, Manometers

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

Vacuum distillation (distillation at reduced pressure) is used for compounds that have high boiling points (above 200°C). Such compounds often undergo thermal decomposition at the temperatures required for their distillation at atmospheric pressure. The boiling point of a compound is lowered substantially by reducing the applied pressure. Vacuum distillation is also used for compounds that, when heated, might react with the oxygen present in air. It is also used when it is more convenient to distill at a lower temperature because of experimental limitations. For instance, a heating device may have difficulty heating to a temperature in excess of 250°C.

The effect of pressure on the boiling point is discussed more thoroughly in Technique 13 (see Section 13.1). A nomograph is given (see Figure 13.2) that allows you to estimate the boiling point of a liquid at a pressure different from the one at which it is reported. For example, a liquid reported to boil at 200°C at 760 mmHg would be expected to boil at 90°C at 20 mmHg. This is a significant decrease in temperature, and it would be advantageous to use a vacuum distillation if any problems were to be expected. Counterbalancing this advantage, however, is the fact that separations of liquids of different boiling points may not be as effective with a vacuum distillation as with a simple distillation.

16.1 Macroscale Methods

When working with glassware that is to be evacuated, you should wear safety glasses at all times. There is always danger of an implosion.

CAUTION

Safety glasses must be worn at all times during vacuum distillation.

It is a good idea to work in a hood when performing a vacuum distillation. If the experiment will involve high temperatures (> 220°C) for distillation or an extremely low pressure (< 0.1 mmHg), for your own safety you should definitely work in a hood, behind a shield.

A basic apparatus similar to the one shown in Figure 16.1 may be used for vacuum distillations. The major differences to be found when comparing this assembly to one for simple distillation (see Technique 14, Figure 14.1) are that a Claisen head has been inserted between the distillation flask and the distilling head and that the opening to the atmosphere has been replaced by a connection (A) to a vacuum source. In addition, an air inlet tube (B) has been added to the top of the Claisen head. When connecting to a vacuum source, an aspirator (see Technique 8, Section 8.5), a mechanical vacuum pump (see Section 16.6), or a "house" vacuum system (one piped directly to the laboratory bench) may be used. The aspirator is probably the simplest of these sources and the vacuum source most likely to be available. However, if pressures below 10–20 mmHg are required, a mechanical vacuum pump must be used.

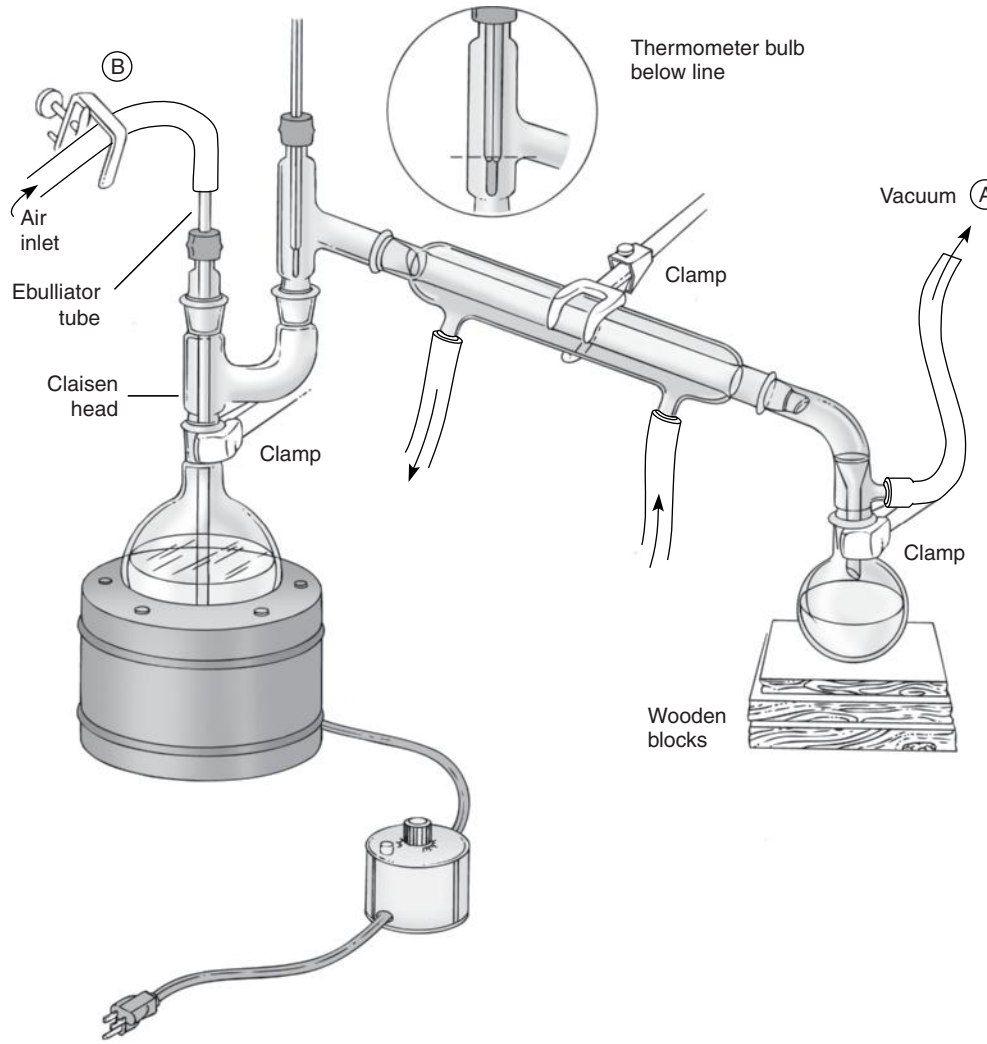


Figure 16.1 Macroscale vacuum distillation using the standing organic laboratory kit.

Assembling the Apparatus

When assembling an apparatus for vacuum distillation, it is important to check the following points.

Glassware. Before assembly, check all glassware to be sure there are no cracks and that there are no chips in the standard-taper joints. Cracked glassware may break when evacuated. Joints that have chips may not be airtight and they will leak.

Greasing Joints. With macroscale equipment, it is necessary to grease all standard-taper joints lightly. Take care not to use too much grease. Grease can become a very serious contaminant if it oozes out the bottom of the joints into your system. Apply a small amount of grease (thin film) completely around the top of the *inner* joint; then mate the joints and press or turn them slightly to spread the grease evenly. If you have used the correct amount of grease, it will not ooze out the bottom of the joint; rather, the entire joint will appear clear and without striations or uncovered areas.

Claisen Head. The Claisen head is placed between the distilling flask and the distilling head to help prevent material from "bumping over" into the condenser.

Ebulliator Tube. The air inlet tube on top of the Claisen head is called an ebulliator (*EBB-u-lay-tor*) tube. Using the screw clamp (B) on the attached heavy-walled tubing (see the following discussion on pressure tubing), the ebulliator is adjusted to admit a slow continuous stream of air bubbles into the distillation flask while you are distilling. Because boiling stones will not work in a vacuum, these bubbles keep the solution stirred and help to prevent bumping. The ebulliator tube is drawn to a point at its lower end. The end of the tube should be adjusted so that it is just above the bottom of the distilling flask.

Most standard ground-glass kits contain an ebulliator tube. If one is not available, an ebulliator can be prepared easily by heating a section of glass tubing and drawing it out about 3 cm. The glass is then scored in the middle of this drawn-out section and broken, making two tubes at once. In Figure 16.1, the ebulliator is inserted into a thermometer adapter. If you do not have a second thermometer adapter, a one-hole rubber stopper may be used, placing the stopper directly into the joint on top of the Claisen head.

Wooden Applicator Sticks. An alternative to an ebulliator tube that is sometimes used is the wooden pine splint or wooden applicator stick. Air is trapped in the pores of the wood. Under vacuum, the stick will emit a slow stream of bubbles to stir the solution. The disadvantage is that each time you open the system, you must use a new stick.

Thermometer Placement. Be sure that the thermometer is positioned so that the entire mercury bulb is below the sidearm in the distilling head (see the circular insert in Figure 16.1). If it is placed higher, it may not be surrounded by a constant stream of vapor from the material being distilled. If the thermometer is not exposed to a continuous stream of vapor, the thermometer may not reach temperature equilibrium. As a result, the temperature reading would be incorrect (low).

Joint Clips. If plastic joint clips are available (see Technique 7, Figure 7.3), they should be used to secure the greased joints, particularly those on either side of the condenser and the one at the bottom of the vacuum adapter where the receiving flask is attached.

Pressure Tubing. The connection to the vacuum source (A) is made using pressure tubing. Pressure tubing (also called vacuum tubing), unlike the more common thin-walled tubing used to carry water or gas, has heavy walls and will not collapse inward when it is evacuated. A comparison of the two types of tubing is shown in Figure 16.2.

Make doubly sure that any connections to pressure tubing are tight. If a tight connection cannot be made, you may have the wrong size of tubing (either the rubber tubing or the glass tubing to which it is attached). Keep the lengths of pressure tubing relatively short. The pressure tubing should be relatively new and without cracks. If the tubing shows cracks when you stretch or bend it, it may be old and leak air into the system. Replace any tubing that shows its age.

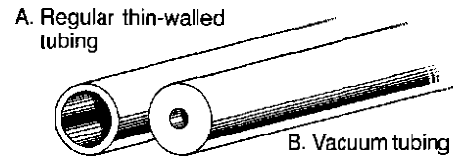


Figure 16.2 Comparison of tubing.

Rubber Stoppers. Always use soft rubber stoppers in a vacuum apparatus; corks will not give an airtight seal. Rubber stoppers harden with age and use. If a rubber stopper is not soft (will not squeeze), discard it. Glass tubing should fit securely into any rubber stoppers. If you can move the tubing up and down with only gentle force, it is too loose, and you should obtain a larger size.

Receiving Flask. When more than one fraction is expected from a vacuum distillation, it is considered good practice to have several preweighed receiver flasks, including the original, available before the distillation begins. Such preparation permits the rapid changing of receiving flasks during the distillation. The preweighing allows easy calculation of the weight of distillate in each fraction without the need to transfer the distillate to yet another flask.

To change receiving flasks, heating must be stopped and the system vented at both ends before replacing a flask. Complete directions for this procedure are given in Section 16.2.

Vacuum Traps. When performing a vacuum distillation, it is customary to place a "trap" in the line that connects to the vacuum source. Two common trap arrangements are shown in Figures 16.3 and 16.4. This type of trap is essential if an aspirator or a house vacuum is used as the source of vacuum. A mechanical vacuum pump requires a different type of trap (see Figure 16.8). Variations in pressure are to be expected when using an aspirator or a house vacuum. With an aspirator, if the pressure drops low enough, the vacuum in the system will draw water from the aspirator into the connecting line. The trap allows you to see this happening and

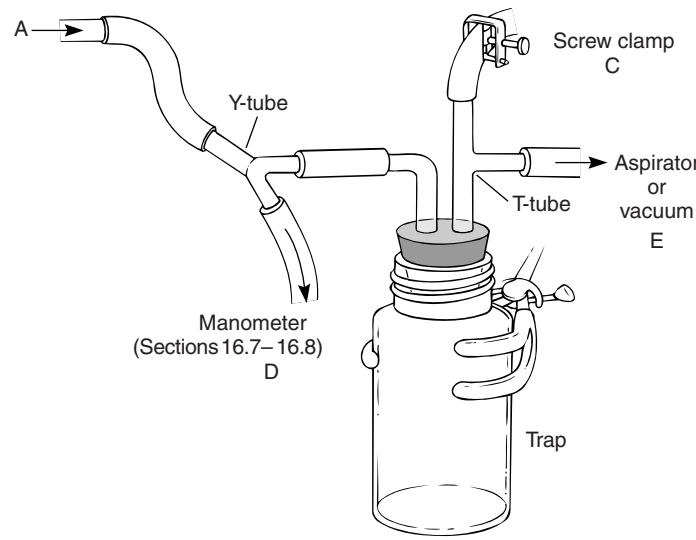


Figure 16.3 Vacuum trap using a gas bottle. The assembly connects to Figure 16.1 by joining the tubing at point A. (The Y-tube connection to a manometer is optional.)

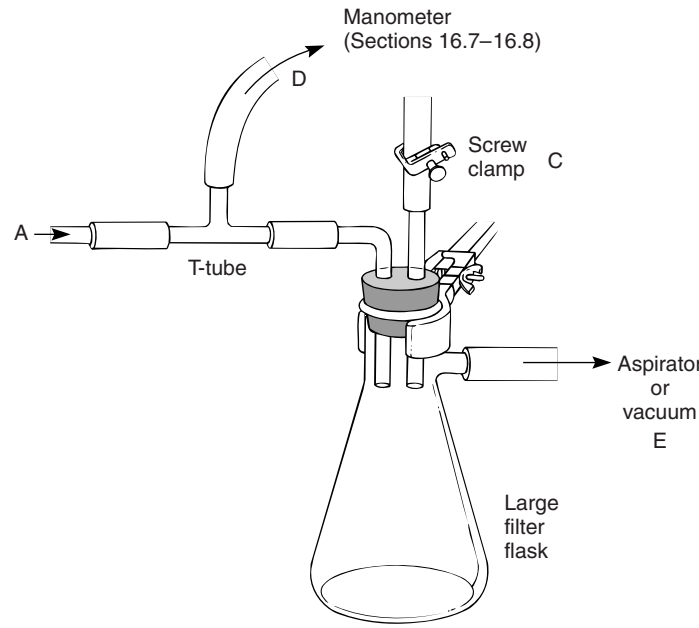


Figure 16.4 Vacuum trap using a heavy-walled filter flask. The assembly connects to Figure 16.1 by joining the tubing at point A. (The T-tube connection to the manometer is optional.)

take corrective action (that is, prevent water from entering the distillation apparatus). The correct action for anything but a small amount of water is to "vent" the system. This can be accomplished by opening the screw clamp (C) at the top of the trap to let air into the system. This is also the way air is admitted into the system at the end of the distillation.

CAUTION

Note also that it is always necessary to vent the system *before* the aspirator is stopped. If you fail to vent the system, water may be drawn into it, contaminating your product. Be sure, however, that you vent *both ends* of the system. After venting the vacuum trap, you should immediately open the screw clamp on top of the ebulliator tube.

The trap, which contains a large volume, also acts as a buffer to pressure changes, evening out small variations in the line. In the house vacuum system, it prevents oil and water (often present in house lines) from entering your system.

Manometer Connection. A manometer allows measurement of pressure. A Y-tube (or T-tube) connection (D) is shown in the line from the apparatus to the trap. This branching connection is optional, but is required if you wish to monitor the actual pressure of your system when using a manometer. The operation of manometers is discussed in Sections 16.7 and 16.8. A suitable manometer should be included in the system at least part of the time during the distillation to measure the pressure at which the distillation is being conducted. A boiling point is of little value if the pressure is not known! After use, the manometer can be removed if a screw clamp is used to close the connection.

CAUTION

The manometer must be vented very slowly to prevent a rush of mercury from breaking out the end of the tubing.

A manometer is also very useful in troubleshooting your system. It can be attached to the aspirator or house vacuum to determine the working pressure. In this way, a defective aspirator (not uncommon) can be spotted and replaced. When you connect your apparatus, you can adjust all of the joints and connections to obtain the best working pressure *before* you begin to distill. Generally, a working pressure of 25–50 mmHg is adequate for the procedures in this text.

Aspirators. In many labs, the most convenient source of vacuum for a reduced-pressure distillation is the aspirator. The aspirator, or other vacuum source, is attached to the trap. The aspirator can theoretically pull a vacuum equal to the vapor pressure of the water flowing through it. The vapor pressure of flowing water depends on its temperature (24 mmHg at 25°C; 18 mmHg at 20°C; 9 mmHg at 10°C). However, in the typical laboratory, the pressures attained are higher than expected due to reduced water pressure when many students are using their aspirators simultaneously. Good laboratory practice requires that only a few students on a given bench use the aspirator at the same time. It may be necessary to establish a schedule for aspirator use, or at least to have some students wait until others are finished.

House Vacuum. As stated for aspirators, depending on the capacity of the system, it may not be possible for everyone to use the vacuum system at once. Students may have to take turns or work in rotation. A typical house vacuum system will have a base pressure of about 35–100 mmHg when it is not overloaded.

16.2 Vacuum Distillation: Stepwise Directions

The procedures in applying vacuum distillation are described in this section.

CAUTION

Safety glasses must be worn at all times during vacuum distillation.

Evacuating the Apparatus

1. Assemble the apparatus shown in Figure 16.1 as discussed in Section 16.1 and attach a trap (see either Figure 16.3 or 16.4). The connection is made at the points labeled A. Next, attach the trap to either an aspirator or a house vacuum system at point E. Do not close any clamps at this time.
2. Weigh each empty receiving flask to be used in collecting the various fractions during the distillation.
3. Concentrate the material to be distilled in an Erlenmeyer flask or beaker by removing all volatile solvents, such as ether, using a steam bath or a water bath in the hood. Use boiling stones and a stream of air to help the solvent removal.
4. Remove the distilling flask from the vacuum distillation apparatus, remove the grease by wiping with a towel, and transfer the concentrate to the flask, using a funnel. Complete the transfer by rinsing with a *small* amount of solvent. Again, concentrate the material until no additional volatile solvent can be removed

(boiling will cease). The flask should be no more than half-full after concentration. Regrease the joint and reattach the flask to the distilling apparatus. Make sure all joints are tight.

5. On the trap assembly (see Figure 16.3 or 16.4), open the clamp at C and attach a manometer at point D.
6. Turn on the aspirator (or house vacuum) (see Figure 16.3) to the maximum extent.
7. Tighten the screw clamp at B (see Figure 16.1) until the tubing is nearly closed.
8. Going back to the trap (see Figure 16.3), slowly tighten the screw clamp at point C. Watch the bubbling action of the ebulliator tube to see that it is not too vigorous or too slow. Any volatile solvents you could not remove during concentration will be removed now. Once the loss of volatiles slows down, close screw clamp C to the fullest extent.
9. Adjust the ebulliator tube at B until a fine, steady stream of bubbles is formed.
10. Wait a few minutes and then record the pressure obtained.
11. If the pressure is not satisfactory, check all connections to see that they are tight. Gently twist any hoses to snug them down. Press down on any rubber stoppers. Check the fit of all glass tubing. Press any joints together until they appear evenly greased and well joined. If you crimp the rubber tubing between the apparatus and the trap with your hand and the pressure decreases, you will know that there is a leak in the glassware assembly. If there is no change, the problem may be with the aspirator or the trap. Readjust the ebulliator screw clamp at B if necessary.

NOTE: Do not proceed until you have a good vacuum. Ask your instructor for help if necessary.

---

12. Once your vacuum has been established, record the pressure. The manometer may then be removed for use by another student if necessary. Place a screw clamp ahead of the manometer at D and tighten it. With careful venting, the manometer may now be removed.

Beginning Distillation

13. Raise the heat source into position with wooden blocks, or other means, and begin to heat.
14. Increase the temperature. Eventually, a reflux ring will contact the thermometer bulb, and distillation will begin.
15. Record the temperature range and the pressure range (if the manometer is still connected) during the distillation. The distillate should be collected at a rate of about 1 drop per second.
16. If the reflux ring is in the Claisen head but will not rise into the distilling head, it may be necessary to insulate these pieces by wrapping them with cotton and aluminum foil (shiny side in). The insulation should aid the distillate to pass into the condenser.
17. The boiling point should be relatively constant so long as the pressure is constant. A rapid increase in pressure may be due to increased use of the aspirators in the lab (or additional connections to the house vacuum). It could also be due to decomposition of the material being distilled. Decomposition will produce a dense white fog in the distilling flask. If this happens, reduce the

temperature of the heat source or remove the source, and *stand back* until the system cools. When the fog subsides, you can investigate the cause.

Changing Receiving Flasks

18. To change receiving flasks during distillation when a new component begins to distill (higher boiling point at the same pressure), carefully open the clamp on top of the trap assembly at C and immediately lower the heat source.

CAUTION

Watch the ebulliator for excessive backup! It may also be necessary to open the clamp at B.

19. Remove the wooden blocks or other support under the receiving flask, release the clamp, and replace the flask with a clean, preweighed receiver. Use a small amount of grease, if necessary, to reestablish a good seal.
20. Reclose the clamp at C and allow several minutes for the system to reestablish the reduced pressure. If you opened the ebulliator screw clamp at B, you will have to close and readjust it. Bubbling will not recommence until any liquid is drawn back out of the ebulliator. This liquid may have been forced into the ebulliator when the vacuum was interrupted.
21. Raise the heating source back into position under the distilling flask and continue with the distillation.
22. When the temperature falls at the thermometer, this usually indicates that distillation is complete. If a significant amount of liquid remains, however, the bubbling may have stopped, the pressure may have risen, the heating source may not be hot enough, or perhaps insulation of the distillation head is required. Adjust accordingly.

Shutting Down

23. At the end of the distillation, remove the heat source and slowly open the screw clamps at C and B. When the system is vented, you may shut off the aspirator or house vacuum and disconnect the tubing.
24. Remove the receiving flask and clean all glassware as soon as possible after disassembly (let it cool a bit) to keep the ground-glass joints from sticking.

NOTE: If you used grease, thoroughly clean all grease off the joints, or it will contaminate your samples in other procedures.

16.3 Rotary Fraction Collectors

With the types of apparatus we have discussed previously, the vacuum must be stopped to remove fractions when a new substance (fraction) begins to distill. Quite a few steps are required to perform this change, which is quite inconvenient when there are several fractions to be collected. Two pieces of semi-microscale apparatus that are designed to alleviate the difficulty of collecting fractions while working under vacuum are shown in Figure 16.5. The collector, which is shown to the right, is sometimes called a "cow" because of its appearance. With these rotary fraction collecting devices, all you need to do is rotate the device to collect fractions.

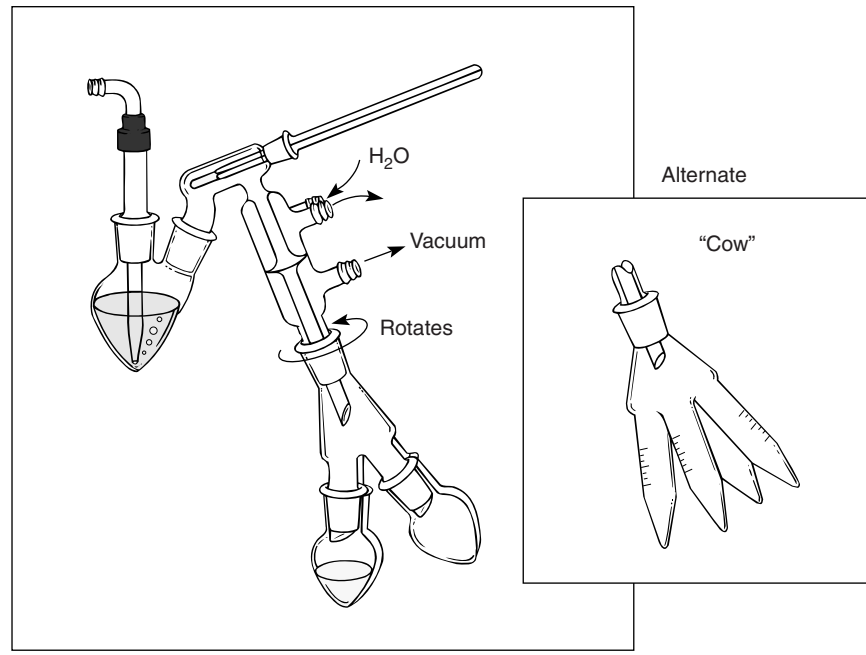


Figure 16.5 Rotary fraction collector.

16.4 Microscale Methods—Student Apparatus

Figure 16.6 shows the type of vacuum distillation equipment that would be used by a student enrolled in a microscale laboratory program. This apparatus, which uses a 5-mL conical vial as a distilling flask, can distill from 1 mL to 3 mL of liquid. The Hickman head replaces the Claisen head, distilling head, condenser, and receiving flask with a single piece of glassware.

16.5 Bulb-to-Bulb Distillation

The ultimate in microscale methods is to use a bulb-to-bulb distillation apparatus. This apparatus is shown in Figure 16.7. The sample to be distilled is placed in the glass container attached to one of the arms of the apparatus. The sample is frozen solid, usually by using liquid nitrogen, but dry ice in 2-propanol or an ice–salt–water mixture may also be used. The coolant container shown in the figure is a **Dewar flask**. The Dewar flask has a double wall with the space between the walls evacuated and sealed. A vacuum is a very good thermal insulator, and there is little heat loss from the cooling solution.

After freezing the sample, evacuate the entire apparatus by opening the stopcock. When the evacuation is complete, the stopcock is closed, and the Dewar flask is removed. The sample is allowed to thaw and then it is frozen again. This freeze–thaw–freeze cycle removes any air or gases that were trapped in the frozen sample. Next, the stopcock is opened to evacuate the system again. When the second evacuation is complete, the stopcock is closed, and the Dewar flask is moved to the other arm to cool the empty container. As the sample warms, it will vaporize, travel to the other side, and be frozen or liquefied by the cooling solution. This transfer of the liquid from one arm to the other may take quite a while, but *no heating is required.*

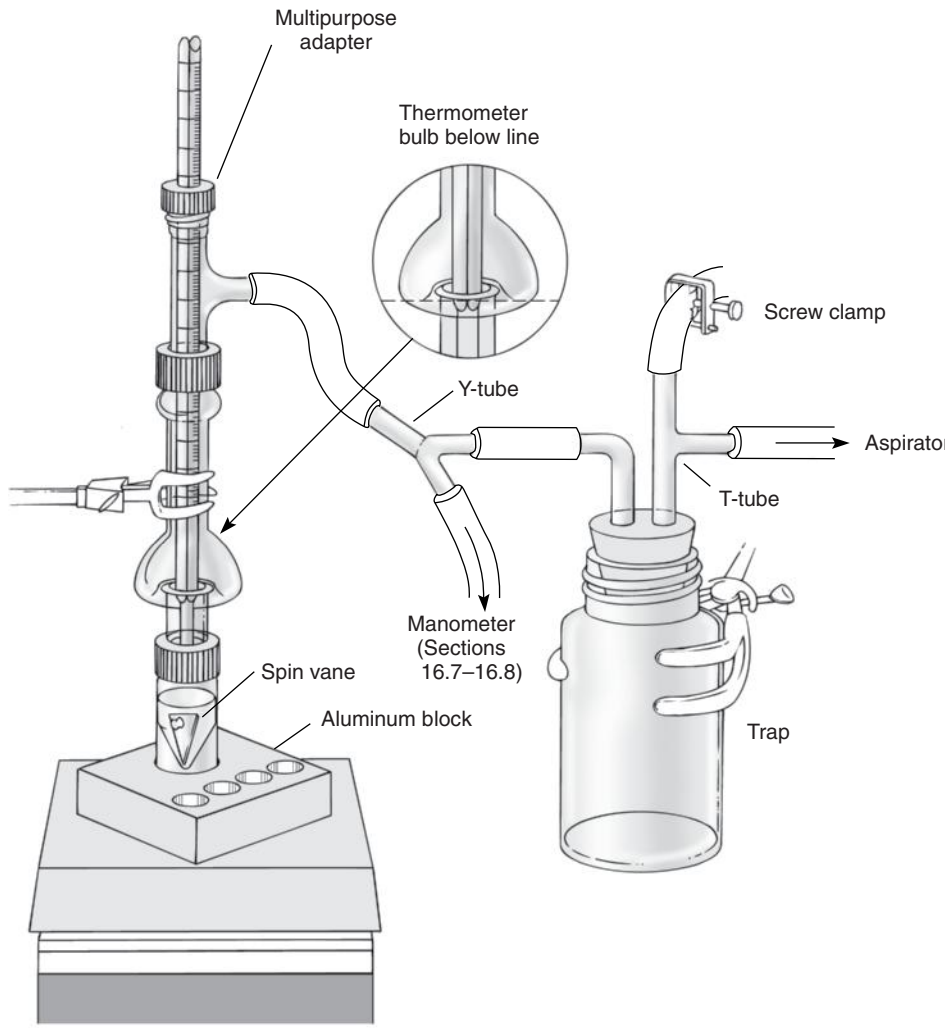


Figure 16.6 Reduced-pressure microscale distillation.

The bulb-to-bulb distillation is most effective when liquid nitrogen is used as the coolant and when the vacuum system can achieve a pressure of 10^{-3} mmHg or lower. This requires a vacuum pump; an aspirator cannot be used.

16.6 The Mechanical Vacuum Pump

The aspirator is not capable of yielding pressures below about 5 mmHg. This is the vapor pressure of water at 0°C, and water freezes at this temperature. A more realistic value of pressure for an aspirator is about 20 mmHg. When pressures below 20 mmHg are required, a vacuum pump will have to be employed. Figure 16.8 illustrates a mechanical vacuum pump and its associated glassware. The vacuum pump operates on a principle similar to that of the aspirator, but the vacuum pump uses a high-boiling oil, rather than water, to remove air from the attached system. The oil used in a vacuum pump, a silicone oil or a high-molecular-weight, hydrocarbon-based oil, has a very low vapor pressure, and very low system pressures can be achieved. A good vacuum pump with new oil can achieve pressures of 10^{-3} or 10^{-4} mmHg. Instead of the oil being discarded as it is used, it is recycled continuously through the system.

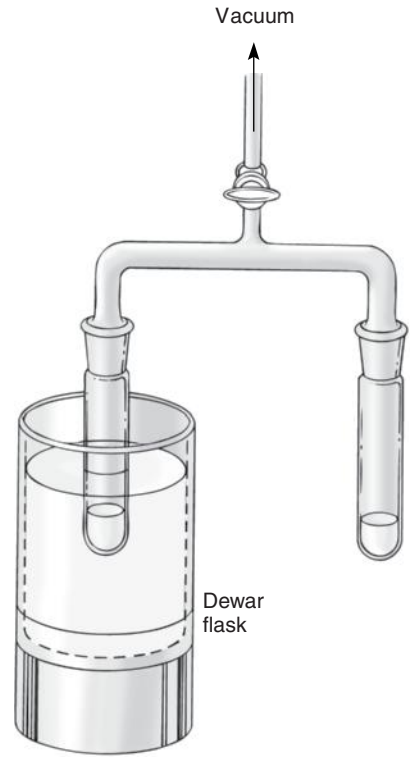


Figure 16.7 Bulb-to-bulb distillation.

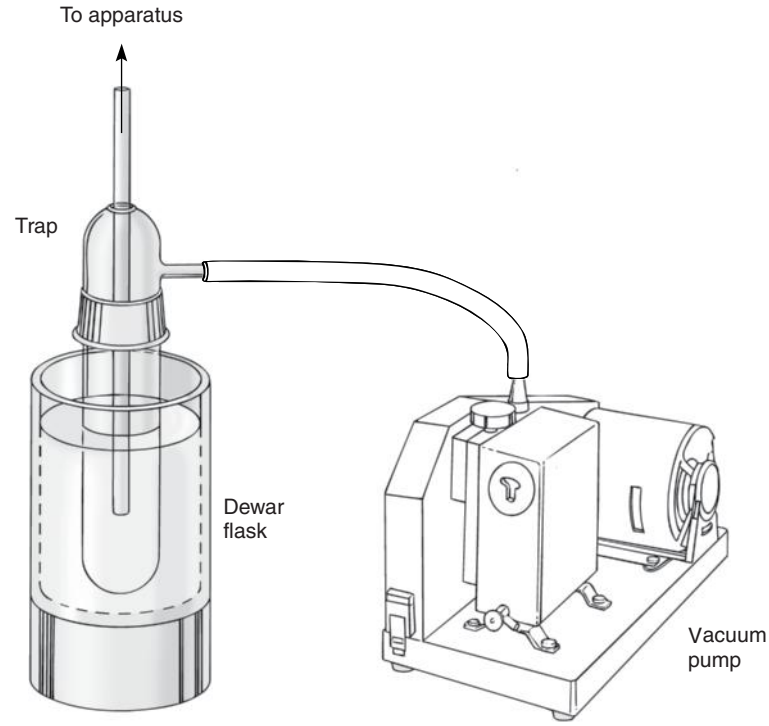


Figure 16.8 A vacuum pump and its trap.

A cooled trap is required when using a vacuum pump. This trap protects the oil in the pump from any vapors that may be present in the system. If vapors from organic solvents or from the organic compounds being distilled dissolve in the oil, the oil's vapor pressure will increase, rendering it less effective. A special type of vacuum trap is illustrated in Figure 16.8. It is designed to fit into an insulated Dewar flask so that the coolant will last for a long period. At a minimum, this flask should be filled with ice water, but a dry ice–acetone mixture or liquid nitrogen is required to achieve lower temperatures and better protect the oil. Often two traps are used: the first trap contains ice water and the second trap, dry ice–acetone or liquid nitrogen. The first trap liquefies low-boiling vapors that might freeze or solidify in the second trap and block it.

16.7 The Closed-End Manometer

The principal device used to measure pressures in a vacuum distillation is the **closed end manometer**. Two basic types are shown in Figures 16.9 and 16.10. The manometer shown in Figure 16.9 is widely used because it is relatively easy to construct. It consists of a U-tube that is closed at one end and mounted on a wooden support. You can construct the manometer from 9-mm glass capillary tubing and fill it, as shown in Figure 16.11.

A small filling device is connected to the U-tube with pressure tubing. The U-tube is evacuated with a good vacuum pump; then the mercury is introduced by tilting the mercury reservoir. The entire filling operation should be conducted in a shallow pan in order to contain any spills that might occur. Enough mercury should be added to form a column about 20 cm in total length. When the vacuum is interrupted by admitting air, the mercury is forced by atmospheric pressure to the end of the evacuated tube. The manometer is then ready for use. The constriction shown in Figure 16.11 helps to protect the manometer against breakage when the pressure is released. Be sure that the column of mercury is long enough to pass through this constriction.

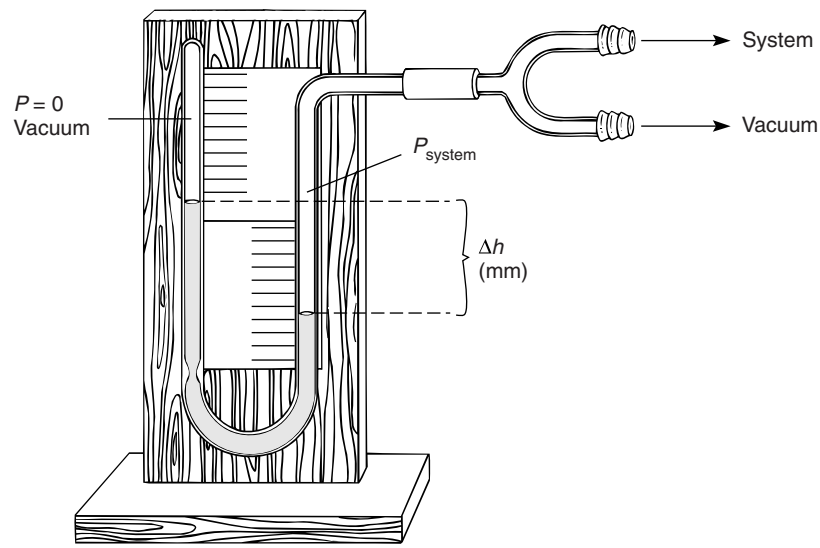


Figure 16.9 A simple U-tube manometer.

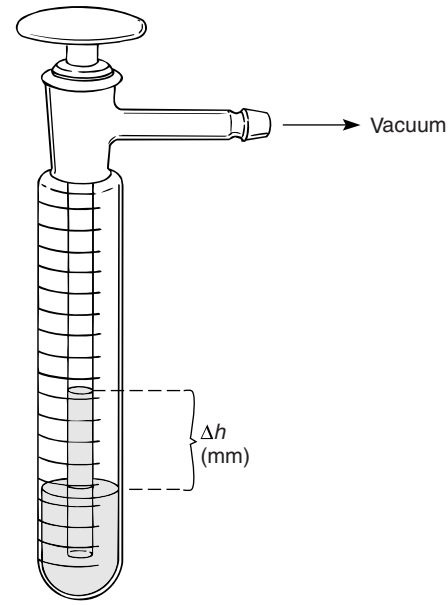


Figure 16.10 Commercial "stick" manometer.

CAUTION

Mercury is a very toxic metal with cumulative effects. Because mercury has a high vapor pressure, it must not be spilled in the laboratory. You must not touch it with your skin. Seek immediate help from an instructor if there is a spill or if you break a manometer. Spills must be cleaned up immediately.

When an aspirator or any other vacuum source is used, a manometer can be connected into the system. As the pressure is lowered, the mercury rises in the right tube and drops in the left tube until Δh corresponds to the approximate pressure of the system (see Figure 16.9).

$$\Delta h = (P_{\text{system}} - P_{\text{reference arm}}) = (P_{\text{system}} - 10^{-3}\ \text{mmHg}) \approx P_{\text{system}}$$

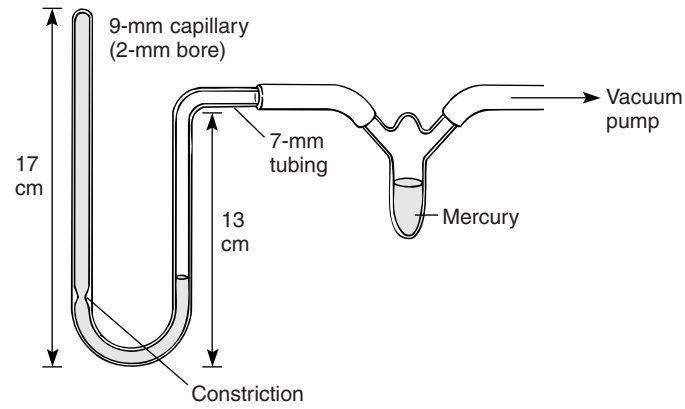


Figure 16.11 Filling a U-tube manometer.

A short piece of metric ruler or a piece of graph paper ruled in millimeter squares is mounted on the support board to allow Δh to be read. No addition or subtraction is necessary because the reference pressure (created by the initial evacuation when filling) is approximately zero (10^{-3} mmHg) when referred to readings in the 10–50 mmHg range. To determine the pressure, count the number of millimeter squares beginning at the top of the mercury column on the left and continuing downward to the top of the mercury column on the right. This is the height difference Δh, and it gives the pressure in the system directly.

A commercial counterpart to the U-tube manometer is shown in Figure 16.10. With this manometer, the pressure is given by the difference in the mercury levels in the inner and outer tubes.

The manometers described here have a range of about 1–150 mmHg in pressure. They are convenient to use when an aspirator is the source of vacuum. For high-vacuum systems (pressures below 1 mmHg), a more elaborate manometer or an electronic measuring device must be used. These devices will not be discussed here.

16.8 Connecting and Using a Manometer

The most common use of a closed-end manometer is to monitor pressure during a reduced-pressure distillation. The manometer is placed in a vacuum distillation system, as shown in Figure 16.12. Generally, an aspirator is the source of vacuum. Both the manometer and the distillation apparatus should be protected by a trap from possible backups in the water line. Alternatives to the trap arrangements shown in Figure 16.12 appear in Figures 16.3 and 16.4. Notice in each case that the trap has a device (screw clamp or stopcock) for opening the system to the atmosphere. This is especially important in using a manometer because you should always make pressure changes slowly. If this is not done, there is a danger of spraying mercury throughout the system, breaking the manometer, or spurting mercury

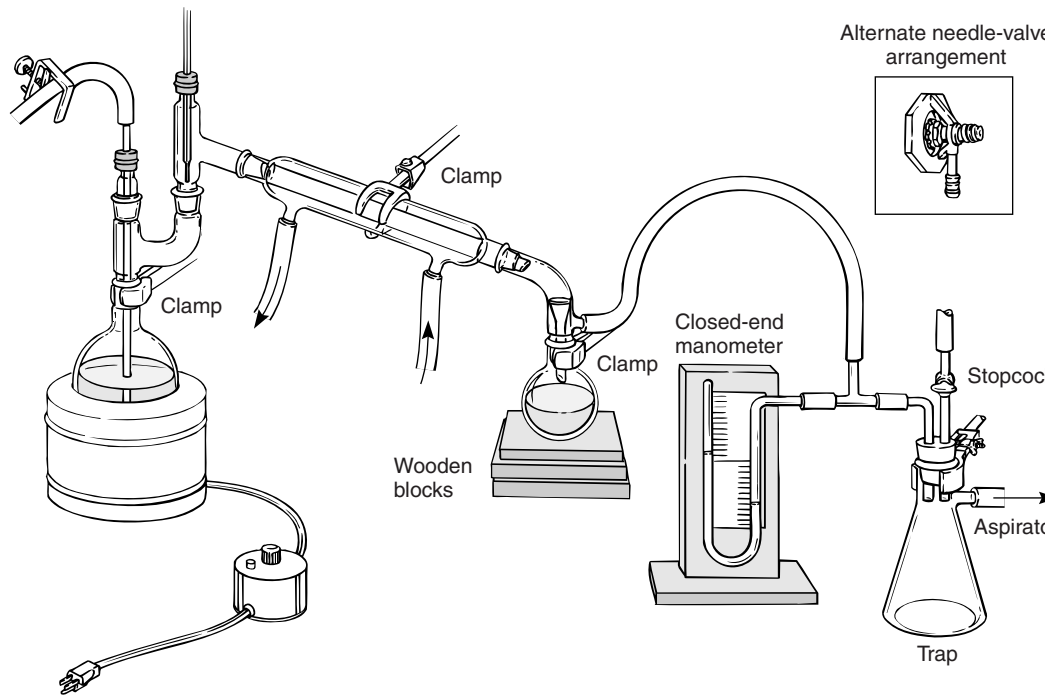


Figure 16.12 Connecting a manometer to the system. In construction of a "bleed," the needle valve may replace the stopcock.

into the room. If a system using a closed-end manometer is opened suddenly, the mercury rushes to the closed end of the U-tube. The mercury rushes with such speed and force that the end will be broken out of the manometer. Air should be admitted *slowly* by opening the valve cautiously. In a similar fashion, the valve should be closed slowly when the vacuum is being started, or mercury may be forcefully drawn into the system through the open end of the manometer.

If the pressure in a reduced-pressure distillation is lower than desired, it is possible to adjust it by means of a **bleed valve**. The stopcock can serve this function in Figure 16.12 if it is opened only a small amount. In those systems with a screw clamp on the trap (see Figures 16.3 and 16.4), remove the screw clamp from the trap valve and attach the base of a Tirrill-style Bunsen burner. The needle valve in the base of the burner can be used to adjust precisely the amount of air that is admitted (bled) to the system and, hence, control the pressure.

PROBLEMS

1. Give some reasons that would lead you to purify a liquid by using vacuum distillation rather than simple distillation.
2. When using an aspirator as a source of vacuum in a vacuum distillation, do you turn off the aspirator before venting the system? Explain.
3. A compound was distilled at atmospheric pressure and had a boiling range of 310–325 °C. What would be the approximate boiling range of this liquid if it were distilled under vacuum at 20 mmHg?
4. Boiling stones generally do not work when you are performing a vacuum distillation. What substitutes may be used?
5. What is the purpose of the trap that is used during a vacuum distillation performed with an aspirator?

17 TECHNIQUE 17

Sublimation

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

In Technique 13, the influence of temperature on the change in vapor pressure of a liquid was considered (see Figure 13.1). It was shown that the vapor pressure of a liquid increases with temperature. Because the boiling point of a liquid occurs when its vapor pressure is equal to the applied pressure (normally atmospheric pressure), the vapor pressure of a liquid equals 760 mmHg at its boiling point. The vapor pressure of a solid also varies with temperature. Because of this behavior, some solids can pass directly into the vapor phase without going through a liquid phase. This process is called **sublimation**. Because the vapor can be resolidified, the overall vaporization–solidification cycle can be used as a purification method. The purification can be successful only if the impurities have significantly lower vapor pressures than the material being sublimed.

PART A. THEORY

17.1 Vapor Pressure Behavior of Solids and Liquids

In Figure 17.1, vapor pressure curves for solid and liquid phases for two different substances are shown. Along lines *AB* and *DF,* the sublimation curves, the solid and vapor are at equilibrium. To the left of these lines, the solid phase exists, and to the right of these lines, the vapor phase is present. Along lines *BC* and *FG,* the liquid and vapor are at equilibrium. To the left of these lines, the liquid phase exists, and to the right, the vapor is present. The two substances vary greatly in their physical properties, as shown in Figure 17.1.

In the first case (see Figure 17.1A), the substance shows normal change-of-state behavior upon being heated, going from solid to liquid to gas. The dashed line, which represents an atmospheric pressure of 760 mmHg, is located *above* the melting point *B* in Figure 17.1A. Thus, the applied pressure (760 mmHg) is *greater* than the vapor pressure of the solid–liquid phase at the melting point. Starting at *A,* as the temperature of the solid is raised, the vapor pressure increases along *AB* until the solid is observed to melt at *B.* At *B,* the vapor pressures of *both* the solid and liquid are identical. As the temperature continues to rise, the vapor pressure will increase along *BC* until the liquid is observed to boil at *C.* The description given is for the "normal" behavior expected for a solid substance. All three states (solid, liquid, and gas) are observed sequentially during the change in temperature.

In the second case (see Figure 17.1B), the substance develops enough vapor pressure to vaporize completely at a temperature below its melting point. The substance shows a solid-to-gas transition only. The dashed line is now located *below* the melting point *F* of this substance. Thus, the applied pressure (760 mmHg) is *less* than the

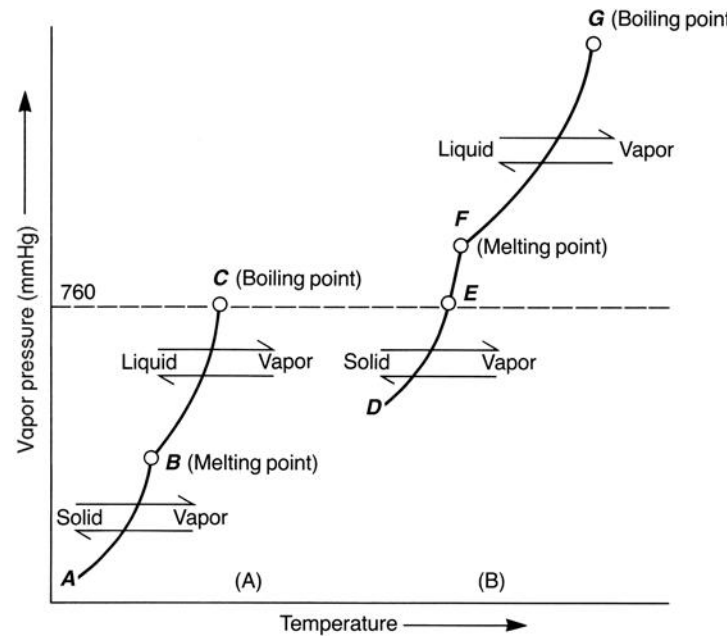


Figure 17.1 Vapor pressure curves for solids and liquids. (A) This substance shows normal solid-to-liquid-to-gas transitions at 760 mmHg pressure. (B) This substance shows a solid-to-gas transition at 760 mmHg pressure.

vapor pressure of the solid–liquid phase at the melting point. Starting at *D,* the vapor pressure of the solid rises as the temperature increases along line *DF.* However, the vapor pressure of the solid reaches atmospheric pressure (point *E*) *before* the melting point at *F* is attained. Therefore, sublimation occurs at *E.* No melting behavior will be observed at atmospheric pressure for this substance. For a melting point to be reached and the behavior along line *FG* to be observed, an applied pressure greater than the vapor pressure of the substance at point *F* would be required. This could be achieved by using a sealed pressure apparatus.

The sublimation behavior just described is relatively rare for substances at atmospheric pressure. Several compounds exhibiting this behavior—carbon dioxide, perfluorocyclohexane, and hexachloroethane—are listed in Table 17.1. Notice that these compounds have vapor pressures *above* 760 mmHg at their melting points. In other words, their vapor pressures reach 760 mmHg below their melting points, and they sublime rather than melt. Anyone trying to determine the melting point of hexachloroethane at atmospheric pressure will see vapor pouring from the end of the melting-point tube! Using a sealed capillary tube, you will observe the melting point of 186°C.

17.2 Sublimation Behavior of Solids

Sublimation is usually a property of relatively nonpolar substances that also have highly symmetrical structures. Symmetrical compounds have relatively high melting points and high vapor pressures. The ease with which a substance can escape from the solid state is determined by the strength of intermolecular forces. Symmetrical molecular structures have a relatively uniform distribution of electron density and a small dipole moment. A smaller dipole moment means a higher vapor pressure because of lower electrostatic attractive forces in the crystal.

Solids sublime if their vapor pressures are greater than atmospheric pressure at their melting points. Some compounds with the vapor pressures at their melting points are listed in Table 17.1. The first three entries in the table were discussed in Section 17.1. At atmospheric pressure, they would sublime rather than melt, as shown in Figure 17.1B.

The next four entries in Table 17.1 (camphor, iodine, naphthalene, and benzoic acid) exhibit typical change-of-state behavior (solid, liquid, and gas) at atmospheric pressure, as shown in Figure 17.1A. These compounds sublime readily under reduced pressure, however. Vacuum sublimation is discussed in Section 17.3.

TABLE 17.1 Vapor Pressures of Solids at Their Melting Points

Compound	Vapor Pressure of Solid at MP (mmHg)	Melting Point (°C)
Carbon dioxide	3876 (5.1 atm)	−57
Perfluorocyclohexane	950	59
Hexachloroethane	780	186
Camphor	370	179
Iodine	90	114
Naphthalene	7	80
Benzoic acid	6	122
p-Nitrobenzaldehyde	0.009	106

Compared with many other organic compounds, camphor, iodine, and naphthalene have relatively high vapor pressures at relatively low temperatures. For example, they have a vapor pressure of 1 mmHg at 42°C, 39°C, and 53°C, respectively. Although this vapor pressure does not seem very large, it is high enough to lead, after a time, to **evaporation** of the solid from an open container. Mothballs (naphthalene and 1,4-dichlorobenzene) show this behavior. When iodine stands in a closed container over a period of time, you can observe movement of crystals from one part of the container to another.

Although chemists often refer to any solid–vapor transition as sublimation, the process described for camphor, iodine, and naphthalene is really an **evaporation** of a solid. Strictly speaking, a sublimation point is like a melting point or a boiling point. It is defined as the point at which the vapor pressure of the solid *equals* the applied pressure. Many liquids readily evaporate at temperatures far below their boiling points. It is, however, much less common for solids to evaporate. Solids that readily sublime (evaporate) must be stored in sealed containers. When the melting point of such a solid is being determined, some of the solid may sublime and collect toward the open end of the melting-point tube while the rest of the sample melts. To solve the sublimation problem, seal the capillary tube or rapidly determine the melting point. It is possible to use the sublimation behavior to purify a substance. For example, at atmospheric pressure, camphor can be readily sublimed just below its melting point at 175°C. At 175°C, the vapor pressure of camphor is 320 mmHg. The vapor solidifies on a cool surface.

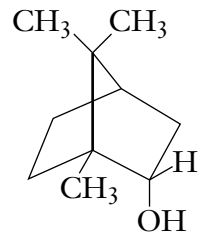
17.3 Vacuum Sublimation

Many organic compounds sublime readily under reduced pressure. When the vapor pressure of the solid equals the applied pressure, sublimation occurs, and the behavior is identical to that shown in Figure 17.1B. The solid phase passes directly into the vapor phase. From the data given in Table 17.1, you should expect camphor, naphthalene, and benzoic acid to sublime at or below the respective applied pressures of 370 mmHg, 7 mmHg, and 6 mmHg. In principle, you can sublime *p*-nitrobenzaldehyde (last entry in the table), but it would not be practical because of the low applied pressure required.

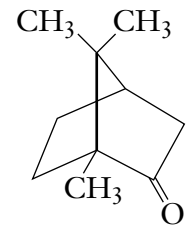
17.4 Advantages of Sublimation

One advantage of sublimation is that no solvent is used, and therefore none needs to be removed later. Sublimation also removes occluded material, such as molecules of solvent, from the sublimed substance. For instance, caffeine (sublimes at 178°C, melts at 236°C) absorbs water gradually from the atmosphere to form a hydrate. During sublimation, this water is lost, and anhydrous caffeine is obtained. If too much solvent is present in a sample to be sublimed, however, it condenses on the cooled surface instead of becoming lost and thus interferes with the sublimation.

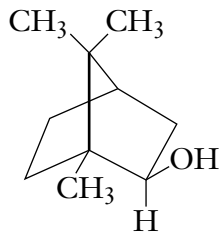
Sublimation is a faster method of purification than crystallization, but is not as selective. Similar vapor pressures are often a factor in dealing with solids that sublime; consequently, little separation can be achieved. For this reason, solids are far more often purified by crystallization. Sublimation is most effective in removing a volatile substance from a nonvolatile compound, particularly a salt or other inorganic material. Sublimation is also effective in removing highly volatile bicyclic or other symmetrical molecules from less-volatile reaction products. Examples of volatile bicyclic compounds are borneol, camphor, and isoborneol.



Borneol



Camphor



Isoborneol

PART B. MACROSCALE AND MICROSCALE SUBLIMATION

17.5 Sublimation—Methods

Sublimation can be used to purify solids. A solid is warmed until its vapor pressure becomes high enough for it to vaporize and condense as a solid on a cooled surface placed closely above. Three types of apparatus are illustrated in Figure 17.2. Because all of the parts fit securely, they are all capable of holding a vacuum. Chemists usually perform vacuum sublimations because most solids undergo the solid-to-gas transition only at low pressures. Reduction of pressure also helps to

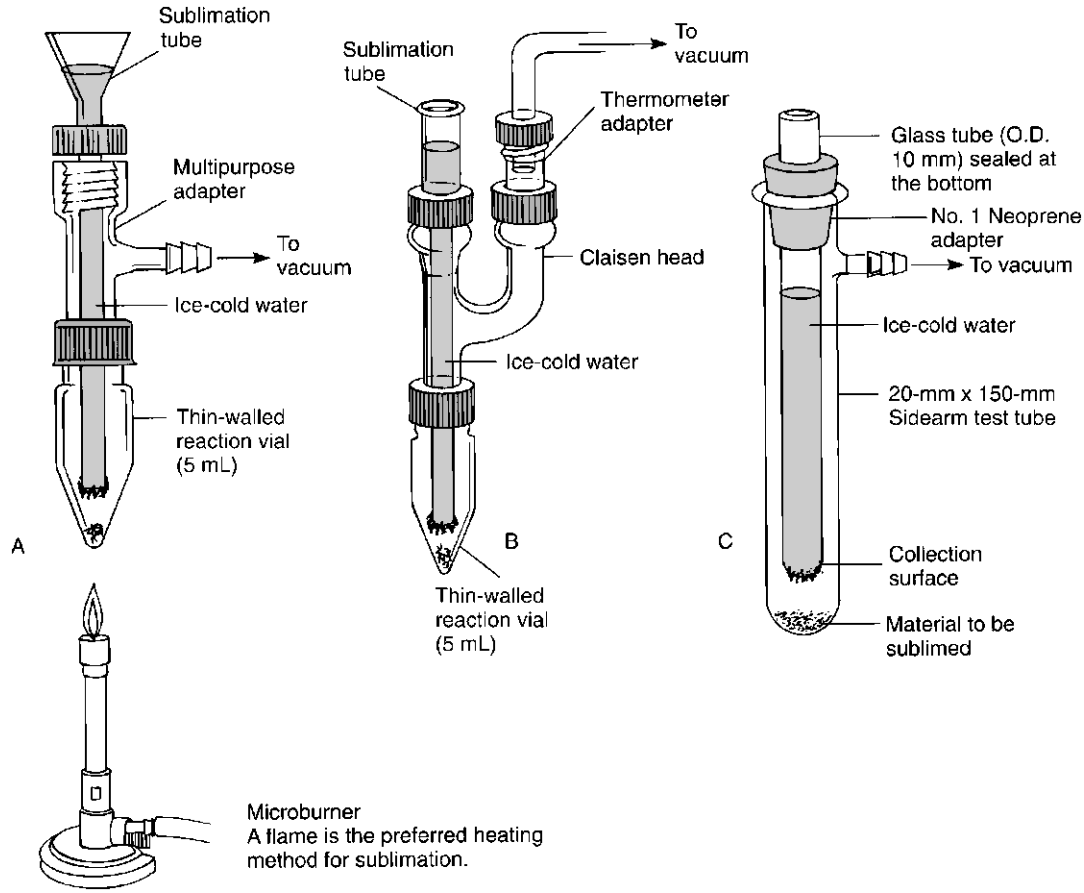


Figure 17.2 A sublimation apparatus.

prevent thermal decomposition of substances that would require high temperatures to sublime at ordinary pressures. One end of a piece of rubber pressure tubing is attached to the apparatus, and the other end is attached to an aspirator, to the house vacuum system, or to a vacuum pump.

A sublimation is probably best carried out using one of the pieces of microscale equipment shown in Figures 17.2A and 17.2B. It is recommended that the laboratory instructor make available either one type or the other to be used on a communal basis. Each apparatus shown employs a central tube (closed on one end) filled with ice-cold water that serves as a condensing surface. The tube is filled with ice chips and a minimum of water. If the cooling water becomes warm before the sublimation is completed, a Pasteur pipet can be used to remove the warm water. The tube is then refilled with more ice-cold water. Warm water is undesirable because the vapor will not condense efficiently to form a solid as readily on a warm surface as it would on a cold surface. A poor recovery of solid results.

The apparatus shown in Figure 17.2C can be constructed from a sidearm test tube, a neoprene adapter, and a piece of glass tubing sealed at one end. Alternatively, a 15-mm × 125-mm test tube may be used instead of the piece of glass tubing. The test tube is inserted into a No. 1 neoprene adapter using a little water as a lubricant. All pieces must fit securely to obtain a good vacuum and to avoid water being drawn into the sidearm test tube around the rubber adapter. To achieve an adequate seal, you may need to flare the sidearm test tube somewhat.

A flame is the preferred heating device because the sublimation will occur more quickly than with other heating devices. The sublimation will be finished before the ice water warms significantly. The burner can be held by its cool base (not the hot barrel!) and moved up and down the sides of the outer tube to "chase" any solid that has formed on the sides toward the cold tube in the center. When using the apparatus shown in Figures 17.2A and 17.2B with a flame, you will need to use a thin-walled vial. Thicker glass can shatter when heated with a flame.

Remember that while performing a sublimation, it is important to keep the temperature below the melting point of the solid. After sublimation, the material that has collected on the cooled surface is recovered by removing the central tube (cold finger) from the apparatus. Take care in removing this tube to avoid dislodging the crystals that have collected. The deposit of crystals is scraped from the inner tube with a spatula. If reduced pressure has been used, the pressure must be released carefully to keep a blast of air from dislodging the crystals.

17.6 Sublimation—Specific Directions

A. Microscale Apparatus

Assemble a sublimation apparatus as shown in Figure 17.2A.[1] Place your impure compound in a small Erlenmeyer flask. Add approximately 0.5 mL of methylene chloride to the Erlenmeyer flask, swirl to dissolve the solid, and transfer the solution of your compound to a clean 5-mL, thin-walled, conical vial, using a clean, dry Pasteur pipet.[2] Add a few more drops of methylene chloride to the flask in order to rinse the compound out completely. Transfer this liquid to the conical vial. Evaporate the methylene chloride from the conical vial by gentle heating in a warm-water bath under a stream of dry air or nitrogen.

---

[1] If you are using another type of sublimation apparatus, your instructor will provide you with specific instructions on how to assemble it correctly.

[2] If your compound does not dissolve freely in methylene chloride, use some other appropriate low-boiling solvent, such as ether, acetone, or pentane.

Insert the cold finger into the sublimation apparatus. If you are using the sublimator with the multipurpose adapter, adjust it so that the tip of the cold finger will be positioned about 1 cm above the bottom of the conical vial. Be sure that the inside of the assembled apparatus is clean and dry. If you are using an aspirator, install a trap between the aspirator and the sublimation apparatus. Turn on the vacuum and check to make sure that all joints in the apparatus are sealed tightly. Place *ice-cold* water in the inner tube of the apparatus. Heat the sample gently and carefully with a microburner to sublime your compound. Hold the burner in your hand (hold it at its base, *not* by the hot barrel) and apply the heat by moving the flame back and forth under the conical vial and up the sides. If the sample begins to melt, remove the flame for a few seconds before you resume heating. When sublimation is complete, discontinue heating. Remove the cold water and remaining ice from the inner tube and allow the apparatus to cool while continuing to apply the vacuum.

When the apparatus is at room temperature, slowly vent the vacuum and *carefully* remove the inner tube. If this operation is done carelessly, the sublimed crystals may be dislodged from the inner tube and fall back into the conical vial. Scrape the sublimed compound onto a tared piece of smooth paper and determine the weight of your compound recovered.

B. Sidearm Test Tube Apparatus

Assemble a sublimation apparatus as shown in Figure 17.2C. Insert a 15-mm × 125-mm test tube into a No. 1 neoprene adapter, using a *little* water as a lubricant, until the tube is fully inserted. Place the crude compound into a 20-mm × 150-mm sidearm test tube. Next, place the 15-mm × 120-mm test tube into the sidearm test tube, making sure they fit together tightly. Turn on the aspirator or house vacuum and make sure a good seal is obtained. At the point at which a good seal has been achieved, you should hear or observe a change in the water velocity in the aspirator. At this time, also make sure that the central tube is centered in the sidearm test tube; this will allow for optimal collection of the purified compound. Once the vacuum has been established, place small chips of ice in the test tube to fill it.[3] When a good vacuum seal has been obtained and ice has been added to the inner test tube, heat the sample gently and carefully with a microburner to sublime your compound. Hold the burner in your hand (hold it at the *base*, not by the hot barrel) and apply heat by moving the flame back and forth under the outer tube and up the sides. If the sample begins to melt, remove the flame for a few seconds before you resume heating. When sublimation is complete, remove the burner and allow the apparatus to cool. As the apparatus is cooling and before you disconnect the vacuum, remove the water and ice from the inner tube using a Pasteur pipet.

When the apparatus has cooled and the water has been removed from the tube, you may disconnect the vacuum. The vacuum should be removed carefully to avoid dislodging the crystals from the inner tube by the sudden rush of air into the apparatus. *Carefully* remove the inner tube of the sublimation apparatus. If this operation is done carelessly, the sublimed crystals may be dislodged from the inner tube and fall back into the residue. Scrape the sublimed compound onto tared weighing paper, using a small spatula. Determine the weight of this purified compound.

---

[3] It is very important that ice not be added to the inner test tube until the vacuum has been established. If the ice is added before the vacuum is turned on, condensation on the outer walls of the inner tube will contaminate the sublimed compound.

PROBLEMS

1. Why is solid carbon dioxide called dry ice? How does it differ from solid water in behavior?
2. Under what conditions can you have *liquid* carbon dioxide?
3. A solid substance has a vapor pressure of 800 mmHg at its melting point (80 °C). Describe how the solid behaves as the temperature is raised from room temperature to 80 °C while as the atmospheric pressure is held constant at 760 mmHg.
4. A solid substance has a vapor pressure of 100 mmHg at the melting point (100 °C). Assuming an atmospheric pressure of 760 mmHg, describe the behavior of this solid as the temperature is raised from room temperature to its melting point.
5. A substance has a vapor pressure of 50 mmHg at the melting point (100 °C). Describe how you would experimentally sublime this substance.

18 TECHNIQUE 18

Steam Distillation

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

The simple, fractional, and vacuum distillations described in Techniques 14, 15, and 16 are applicable to completely soluble (miscible) mixtures only. When liquids are *not* mutually soluble (immiscible), they can also be distilled but with a somewhat different result. A mixture of immiscible liquids will boil at a lower temperature than the boiling points of any of the separate components as pure compounds. When steam is used to provide one of the immiscible phases, the process is called **steam distillation**. The advantage of this technique is that the desired material distills at a temperature below 100°C. Thus, if unstable or very high-boiling substances are to be removed from a mixture, decomposition is avoided. Because all gases mix, the two substances can mix in the vapor and codistill. Once the distillate is cooled, the desired component, which is not miscible, separates from the water. Steam distillation is used widely in isolating liquids from natural sources. It is also used in removing a reaction product from a tarry reaction mixture.

PART A. THEORY

18.1 Differences Between Distillation of Miscible and Immiscible Mixtures

$$\text{Miscible liquids} \qquad P_{\text{total}} = P_{\text{A}}^{0} N_{\text{A}} + P_{\text{B}}^{0} N_{\text{B}} \tag{1}$$

Two liquids A and B that are mutually soluble (miscible) and that do not interact form an ideal solution and follow Raoult's Law, as shown in equation 1. Note that the vapor pressures of pure liquids P_{A}° and P_{B}° are not added directly to give the total pressure P_{total}, but are reduced by the respective mole fractions N_{A} and N_{B}. The total pressure above a miscible or homogeneous solution will depend on P_{A}° and P_{B}° and also on N_{A} and N_{B}. Thus, the composition of the vapor will depend on *both* the vapor pressures and the mole fractions of each component.

$$\text{Immiscible liquids} \qquad P_{\text{total}} = P_{\text{A}}^{0} + P_{\text{B}}^{0} \tag{2}$$

In contrast, when two mutually insoluble (immiscible) liquids are "mixed" to give a heterogeneous mixture, each exerts its own vapor pressure, independently of

the other, as shown in equation 2. The mole fraction term does not appear in this equation, because the compounds are not miscible. You simply add the vapor pressures of the pure liquids P_A^0 and P_B^0 at a given temperature to obtain the total pressure above the mixture. When the total pressure equals 760 mmHg, the mixture boils. The composition of the vapor from an immiscible mixture, in contrast to that of the miscible mixture, is determined only by the vapor pressures of the two substances codistilling. Equation 3 defines the composition of the vapor from an immiscible mixture. Calculations involving this equation are given in Section 18.2.

$$\frac{\text{Moles A}}{\text{Moles B}} = \frac{P_A^0}{P_B^0} \tag{3}$$

A mixture of two immiscible liquids boils at a lower temperature than the boiling points of either component. The explanation for this behavior is similar to that given for minimum-boiling-point azeotropes (see Technique 15, Section 15.7). Immiscible liquids behave as they do because an extreme incompatibility between the two liquids leads to higher combined vapor pressure than Raoult's Law would predict. The higher combined vapor pressures cause a lower boiling point for the mixture than for either single component. Thus, you may think of steam distillation as a special type of azeotropic distillation in which the substance is completely insoluble in water.

The differences in behavior of miscible and immiscible liquids, where it is assumed that P_A^0 equals P_B^0, are shown in Figure 18.1. Note that with miscible liquids, the composition of the vapor depends on the relative amounts of A and B present (see Figure 18.1A). Thus, the composition of the vapor must change during a distillation. In contrast, the composition of the vapor with immiscible liquids is independent of the amounts of A and B present (see Figure 18.1B). Hence, the vapor composition must remain *constant* during the distillation of such liquids, as predicted by equation 3. Immiscible liquids act as if they were being distilled simultaneously from separate

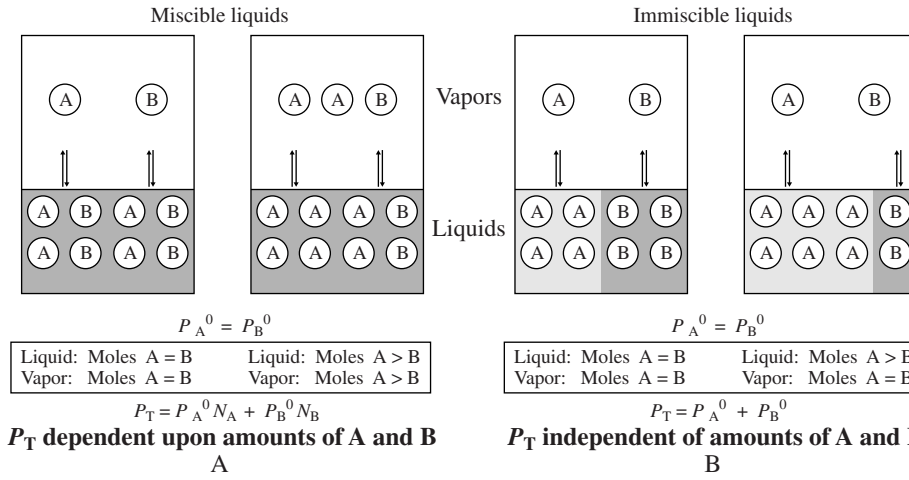


Figure 18.1 Total pressure behavior for miscible and immiscible liquids. (A) Ideal miscible liquids follow Raoult's Law: P_T depends on the mole fractions and vapor pressures of A and B. (B) Immiscible liquids do not follow Raoult's Law: P_T depends only on the vapor pressures of A and B.

compartments, as shown in Figure 18.1B, even though in practice they are "mixed" during a steam distillation. Because all gases mix, they do give rise to a homogeneous vapor and codistill.

18.2 Immiscible Mixtures: Calculations

The composition of the distillate is constant during a steam distillation, as is the boiling point of the mixture. The boiling points of steam-distilled mixtures will always be below the boiling point of water (bp 100°C), as well as the boiling point of any of the other substances distilled. Some representative boiling points and compositions of steam distillates are given in Table 18.1. Note that the higher the boiling point of a pure substance, the more closely the temperature of the steam distillate approaches, but does not exceed, 100°C. This is a reasonably low temperature, and it avoids the decomposition that might result at high temperatures with a simple distillation.

For immiscible liquids, the molar proportions of two components in a distillate equal the ratio of their vapor pressures in the boiling mixture, as given in equation 3. When equation 3 is rewritten for an immiscible mixture involving water, equation 4 results. Equation 4 can be modified by substituting the relationship moles = (weight/molecular weight) to give equation 5.

$$\frac{\text{Moles substance}}{\text{Moles water}} = \frac{P^0_{\text{substance}}}{P^0_{\text{water}}} \tag{4}$$

$$\frac{\text{Wt substance}}{\text{Wt water}} = \frac{(P^0_{\text{substance}})(\text{Molecular weight}_{\text{substance}})}{(P^0_{\text{water}})(\text{Molecular weight}_{\text{water}})} \tag{5}$$

A sample calculation using this equation is given in Table 18.2. Notice that the result of this calculation is very close to the experimental value given in Table 18.1.

TABLE 18.1 Boiling Points and Compositions of Steam Distillates

Mixture	Boiling Point of Pure Substance (°C)	Boiling Point of Mixture (°C)	Composition (% water)
Benzene–water	80.1	69.4	8.9%
Toluene–water	110.6	85.0	20.2%
Hexane–water	69.0	61.6	5.6%
Heptane–water	98.4	79.2	12.9%
Octane–water	125.7	89.6	25.5%
Nonane–water	150.8	95.0	39.8%
1-Octanol–water	195.0	99.4	90.0%

TABLE 18.2 Sample Calculations for a Steam Distillation

Problem How many grams of water must be distilled to steam distill 1.55 g of 1-octanol from an aqueous solution? What will be the composition (wt%) of the distillate? The mixture distills at 99.4°C.

Answer The vapor pressure of water at 99.4°C must be obtained from the CRC Handbook (= 744 mmHg).

a. Obtain the partial pressure of 1-octanol.

$$P^{\circ}_{\text{1-octanol}} = P_{\text{total}} - P^{\circ}_{\text{water}}$$

$$P^{\circ}_{\text{1-octanol}} = (760 - 744) = 16 \text{ mmHg}$$

b. Obtain the composition of the distillate.

$$\frac{\text{wt 1-octanol}}{\text{wt water}} = \frac{(16)(130)}{(744)(18)} = 0.155 \text{ g/g-water}$$

c. Clearly, 10 g of water must be distilled.

$$(0.155 \text{ g/g-water})(10 \text{ g-water}) = 1.55 \text{ g 1-octanol}$$

d. Calculate the weight percentages.

$$\text{1-octanol} = 1.55 \text{ g}/(10 \text{ g} + 1.55 \text{ g}) = 13.4\cdots$$

$$\text{water} = 10 \text{ g}/(10 \text{ g} + 1.55 \text{ g}) = 86.6\cdots$$

PART B. MACROSCALE DISTILLATION

18.3 Steam Distillation—Macroscale Methods

Two methods for steam distillation are generally used in the laboratory: the **direct method** and the **live steam method**. In the first method, steam is generated *in situ* (in place) by heating a distillation flask containing the compound and water. In the second method, steam is generated outside and is passed into the distillation flask using an inlet tube.

A. Direct Method

A macroscale direct method steam distillation is illustrated in Figure 18.2. Although a heating mantle may be used, it is probably best to use a flame with this method, because a large volume of water must be heated rapidly. A boiling stone must be used to prevent bumping. The separatory funnel allows more water to be added during the course of the distillation.

Distillate is collected as long as it is either cloudy or milky white in appearance. Cloudiness indicates that an immiscible liquid is separating. When the distillate runs clear in the distillation, it is usually a sign that only water is distilling. However, there are some steam distillations where the distillate is never cloudy, even though material has codistilled. You must observe carefully, and be sure to collect enough distillate so that all of the organic material codistills.

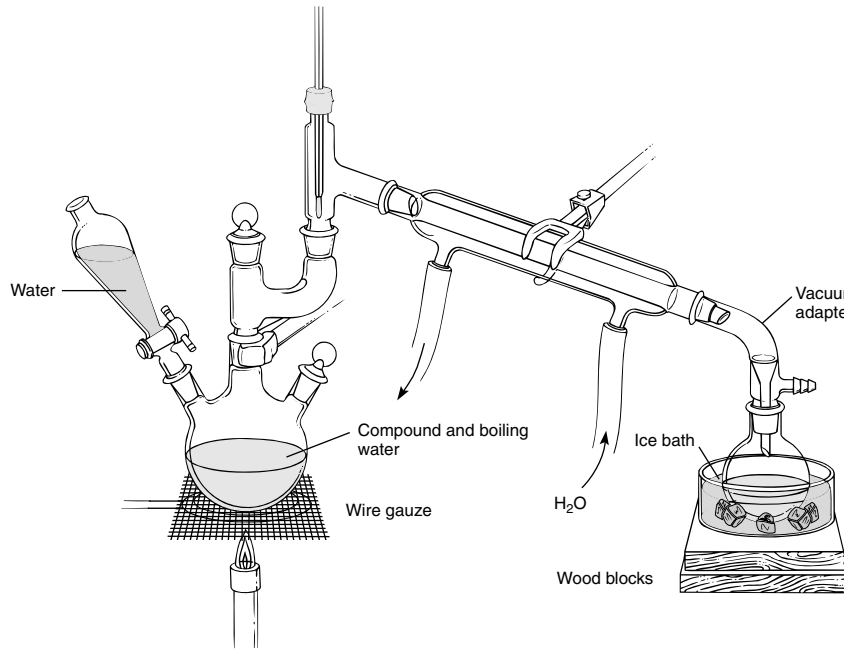


Figure 18.2 A macroscale direct method steam distillation.

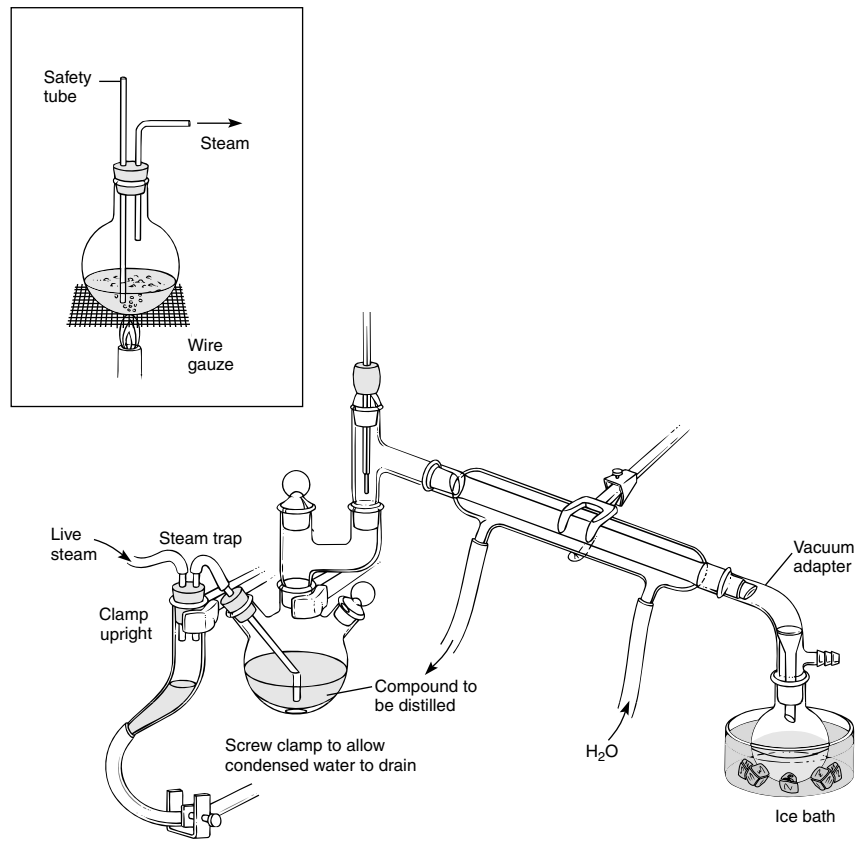


Figure 18.3 A macroscale steam distillation using live steam.

B. Live Steam Method

A macroscale steam distillation using the live steam method is shown in Figure 18.3. If steam lines are available in the laboratory, they may be attached directly to the steam trap (purge them first to drain water). If steam lines are not available, an external steam generator (see inset) must be prepared. The external generator usually will require a flame to produce steam at a rate fast enough for the distillation. When the distillation is first started, the clamp at the bottom of the steam trap is left open. The steam lines will have a large quantity of condensed water in them until they are well heated. When the lines become hot and condensation of steam ceases, the clamp may be closed. Occasionally, the clamp will have to be reopened to remove condensate. In this method, the steam agitates the mixture as it enters the bottom of the flask, and a stirrer or boiling stone is not required.

CAUTION

Hot steam can produce very severe burns.

Sometimes it is helpful to heat the three-necked distilling flask with a heating mantle (or flame) to prevent excessive condensation at that point. Steam must be admitted at a fast enough rate for you to see the distillate condensing as a milky white fluid in the condenser. The vapors that codistill will separate on cooling to give this cloudiness. When the condensate becomes clear, the distillation is near the end. The flow of water through the condenser should be faster than in other types of distillation to help cool the vapors. Make sure the vacuum adapter remains cool to the touch. An ice bath may be used to cool the receiving flask if desired. When the distillation is to be stopped, the screw clamp on the steam trap should be opened, and the steam inlet tube must be removed from the three-necked flask. If this is not done, liquid will back up into the tube and steam trap.

PART C. MICROSCALE DISTILLATION

18.4 Steam Distillation—Microscale Methods

The direct method of steam distillation is the only one suitable for microscale experiments. Steam is produced in the conical vial or distillation flask (*in situ*) by heating water to its boiling point in the presence of the compound to be distilled. This method works well for small amounts of materials. A microscale steam distillation apparatus is shown in Figure 18.4. Water and the compound to be distilled are placed in the flask and heated. A stirring bar or a boiling stone should be used to prevent bumping. The vapors of the water and the desired compound codistill when they are heated. They are condensed and collect in the Hickman head. When the Hickman head fills, the distillate is removed with a Pasteur pipet and placed in another vial for storage. For the typical microscale experiment, it will be necessary to fill the well and remove the distillate three or four times. All of these distillate fractions are placed in the same storage container. The efficiency in collecting the distillate can sometimes be improved if the inside walls of the Hickman head are rinsed several times into the well. A Pasteur pipet is used to perform the rinsing. Distillate is withdrawn from the well, and then it is used to wash the walls of the Hickman head all the way around the head. After the walls have been washed and

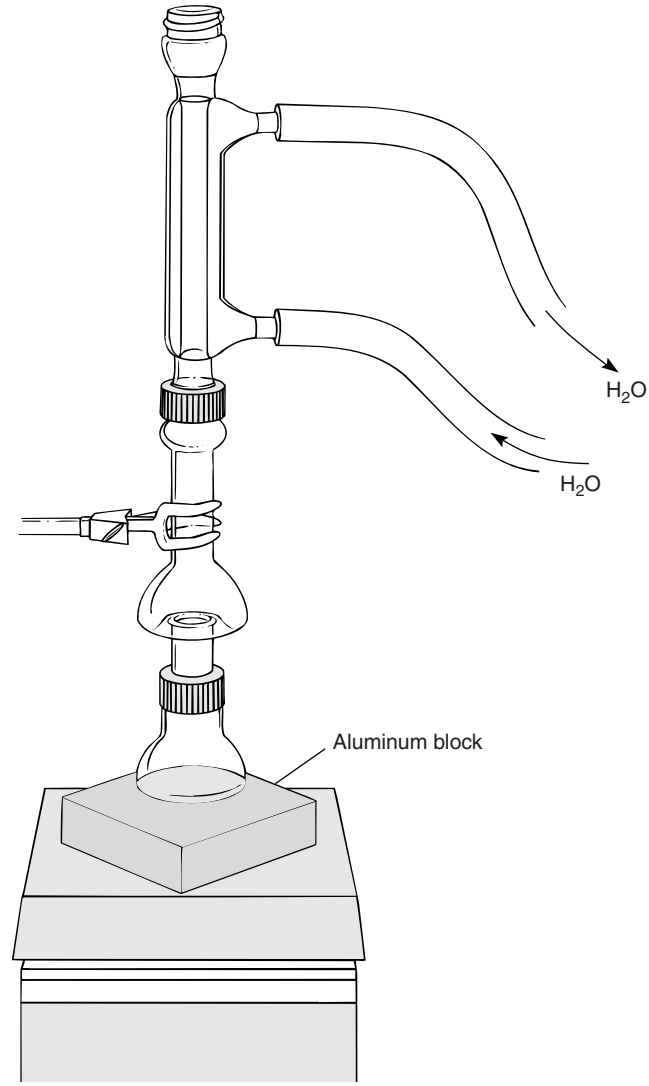


Figure 18.4 Microscale steam distillation.

when the well is full, the distillate can be withdrawn and transferred to the storage container. It may be necessary to add more water during the course of the distillation. More water is added (remove the condenser if used) through the center of the Hickman head by using a Pasteur pipet.

PART D. SEMI-MICROSCALE DISTILLATION

18.5 Steam Distillation—Semi-Microscale Methods

The apparatus shown in Technique 14, Figure 14.5, may also be used to perform a steam distillation at the microscale level or slightly above. This apparatus avoids the need to empty the collected distillate during the course of the distillation, as is required when a Hickman head is used.

PROBLEMS

1. Calculate the weight of benzene codistilled with each gram of water and the percentage composition of the vapor produced during a steam distillation. The boiling point of the mixture is 69.4°C. The vapor pressure of water at 69.4°C is 227.7 mmHg. Compare the result with the data in Table 18.1.
2. Calculate the approximate boiling point of a mixture of bromobenzene and water at atmospheric pressure. A table of vapor pressure of water and bromobenzene at various temperatures is given.

	Vapor Pressures (mmHg)	
Temperature (°C)	**Water**	**Bromobenzene**
93	588	110
94	611	114
95	634	118
96	657	122
97	682	127
98	707	131
99	733	136

3. Calculate the weight of nitrobenzene that codistills (bp 99°C of mixture) with each gram of water during a steam distillation. You may need the data given in problem 2.
4. A mixture of *p*-nitrophenol and *o*-nitrophenol can be separated by steam distillation. The *o*-nitrophenol is steam volatile, and the *para* isomer is not volatile. Explain. Base your answer on the ability of the isomers to form hydrogen bonds internally.

19 TECHNIQUE 19

Column Chromatography

Sign in at www.cengage.com/login to access the Pre-Lab Video Exercise for this technique.

The most modern and sophisticated methods of separating mixtures available to the organic chemist all involve **chromatography**. Chromatography is defined as the separation of a mixture of two or more different compounds or ions by distribution between two phases, one of which is stationary and the other is moving. Various types of chromatography are possible, depending on the nature of the two phases involved: **solid–liquid** (column, thin-layer, and paper), **liquid–liquid** (high-performance liquid), and **gas–liquid** (vapor-phase) chromatographic methods are common.

All chromatography works on much the same principle as solvent extraction (see Technique 12). Basically, the methods depend on the differential solubilities or adsorptivities of the substances to be separated relative to the two phases between which they are to be partitioned. Here, column chromatography, a solid–liquid method, is considered. Thin-layer chromatography is examined in Technique 20;

high-performance liquid chromatography is discussed in Technique 21; and gas chromatography, a gas–liquid method, is discussed in Technique 22.

19.1 Adsorbents

Column chromatography is a technique based on both adsorptivity and solubility. It is a solid–liquid phase-partitioning technique. The solid may be almost any material that does not dissolve in the associated liquid phase; the solids used most commonly are silica gel $SiO_2 \cdot xH_2O$, also called silicic acid, and alumina $Al_2O_3 \cdot xH_2O$. These compounds are used in their powdered or finely ground forms (usually 200–400 mesh).[1]

Most alumina used for chromatography is prepared from the impure ore bauxite $Al_2O_3 \cdot xH_2O{+}Fe_2O_3$. The bauxite is dissolved in hot sodium hydroxide and filtered to remove the insoluble iron oxides; the alumina in the ore forms the soluble amphoteric hydroxide $Al(OH)_4^-$. The hydroxide is precipitated by CO_2, which reduces the pH, as $Al(OH)_3$. When heated, the $Al(OH)_3$ loses water to form pure alumina Al_2O_3.

$$\text{Bauxite (crude)} \xrightarrow{\text{hot NaOH}} AL(OH)_4^- \text{ (aq)} + Fe_2O_3 \text{ (insoluble)}$$

$$Al(OH)_4^-(aq) + CO_2 \longrightarrow Al(OH)_3 + HCO_3^-$$

$$2Al(OH)_3 \xrightarrow{\text{heat}} Al_2O_3(s) + 3H_2O$$

Alumina prepared in this way is called **basic alumina** because it still contains some hydroxides. Basic alumina cannot be used for chromatography of compounds that are base sensitive. Therefore, it is washed with acid to neutralize the base, giving **acid-washed alumina**. This material is unsatisfactory unless it has been washed with enough water to remove *all* the acid; on being so washed, it becomes the best chromatographic material, called **neutral alumina**. If a compound is acid sensitive, either basic or neutral alumina must be used. You should be careful to ascertain what type of alumina is being used for chromatography. Silica gel is not available in any form other than that suitable for chromatography.

19.2 Interactions

If powdered or finely ground alumina (or silica gel) is added to a solution containing an organic compound, some of the organic compound will **adsorb** onto or adhere to the fine particles of alumina. Many kinds of intermolecular forces cause organic molecules to bind to alumina. These forces vary in strength according to their type. Nonpolar compounds bind to the alumina using only van der Waals forces. These are weak forces, and nonpolar molecules do not bind strongly unless they have extremely high molecular weights. The most important interactions are those typical of polar organic compounds. Either these forces are of the dipole–dipole type or they involve some direct interaction (coordination, hydrogen bonding, or salt formation). These types of interactions are illustrated in Figure 19.1, which for convenience shows only a portion of the alumina structure. Similar interactions occur with silica gel. The strengths of such interactions vary in the following approximate order:

Salt formation > coordination > hydrogen bonding > dipole–dipole > van der Waals

[1] The term "mesh" refers to the number of openings per linear inch found in a screen. A large number refers to a fine screen (finer wires more closely spaced). When particles are sieved through a series of these screens, they are classified by the smallest mesh screen that they will pass through. Mesh 5 would represent a coarse gravel, and mesh 800 would be a fine powder.

The more polar the functional group, the stringer the bond to alumina (or silica gel).

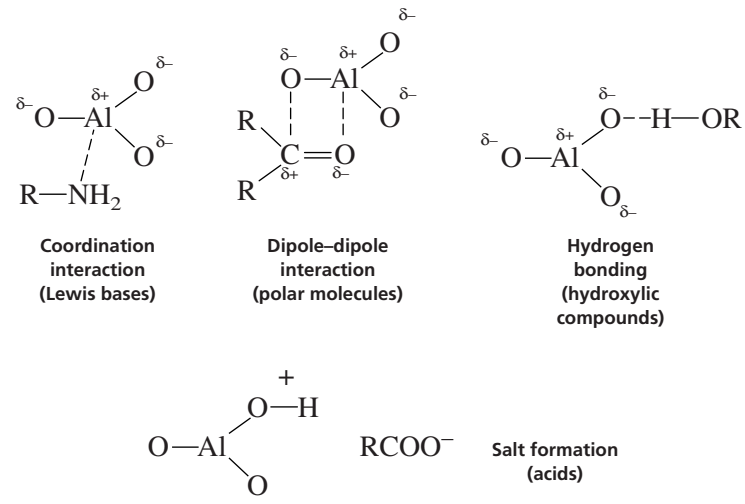


Figure 19.1 Possible interactions of organic compounds with alumina.

Strength of interaction varies among compounds. For instance, a strongly basic amine would bind more strongly than a weakly basic one (by coordination). In fact, strong bases and strong acids often interact so strongly that they **dissolve** alumina to some extent. You can use the following rule of thumb.

A similar rule holds for solubility. Polar solvents dissolve polar compounds more effectively than nonpolar solvents do; nonpolar compounds are dissolved best by nonpolar solvents. Thus, the extent to which any given solvent can wash an adsorbed compound from alumina depends almost directly on the relative polarity of the solvent. For example, although a ketone adsorbed on alumina might not be removed by hexane, it might be removed completely by chloroform. For any adsorbed material, a kind of **distribution** equilibrium can be envisioned between the adsorbent material and the solvent. This is illustrated in Figure 19.2.

The distribution equilibrium is **dynamic**, with molecules constantly **adsorbing** from the solution and **desorbing** into it. The average number of molecules remaining adsorbed on the solid particles at equilibrium depends both on the particular molecule (**RX**) involved and the dissolving power of the solvent with which the adsorbent must compete.

19.3 Principle of Column Chromatographic Separation

The dynamic equilibrium mentioned previously and the variations in the extent to which different compounds adsorb on alumina or silica gel underlie a versatile and ingenious method for **separating** mixtures of organic compounds. In this method, the mixture of compounds to be separated is introduced onto the top of a cylindrical glass column (see Figure 19.3) **packed** or filled with fine alumina particles (stationary solid phase). The adsorbent is continuously washed by a flow of solvent (moving phase) passing through the column.

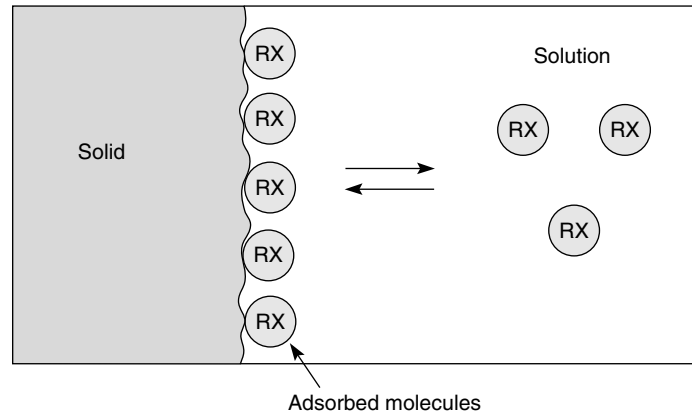


Figure 19.2 Dynamic adsorption equilibrium.

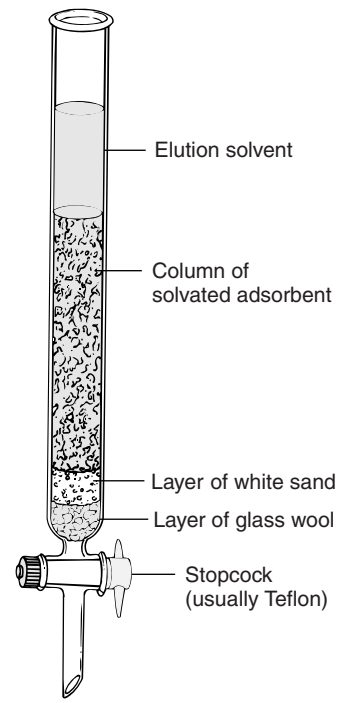


Figure 19.3 A chromatographic column.

Initially, the components of the mixture adsorb onto the alumina particles at the top of the column. The continuous flow of solvent through the column **elutes**, or washes, the solutes off the alumina and sweeps them down the column. The solutes (or materials to be separated) are called **eluates** or **elutants**, and the solvents are called **eluents**. As the solutes pass down the column to fresh alumina, new equilibria are established among the adsorbent, the solutes, and the solvent. The

constant equilibration means that different compounds will move down at differing rates depending on their relative affinity for the adsorbent on the one hand, and for the solvent on the other. Because the number of alumina particles is large, because they are closely packed, and because fresh solvent is being added continuously, the number of equilibrations between adsorbent and solvent that the solutes experience is enormous.

As the components of the mixture are separated, they begin to form moving bands (or zones), with each band containing a single component. If the column is long enough and the other parameters (column diameter, adsorbent, solvent, and flow rate) are correctly chosen, the bands separate from one another, leaving gaps of pure solvent in between. As each band (solvent and solute) passes out from the bottom of the column, it can be collected before the next band arrives. If the parameters mentioned are poorly chosen, the various bands either overlap or coincide, in which case either a poor separation or no separation is the result. A successful chromatographic separation is illustrated in Figure 19.4.

19.4 Parameters Affecting Separation

The versatility of column chromatography results from the many factors that can be adjusted. These include

1. Adsorbent chosen
2. Polarity of the solvents chosen
3. Size of the column (both length and diameter) relative to the amount of material to be chromatographed
4. Rate of elution (or flow)

If the conditions are carefully chosen, almost any mixture can be separated. This technique has even been used to separate optical isomers. An optically active solid-phase adsorbent was used to separate the enantiomers.

Two fundamental choices for anyone attempting a chromatographic separation are the kind of adsorbent and the solvent system. In general, nonpolar compounds pass through the column faster than polar compounds, because they have a smaller affinity for the adsorbent. If the adsorbent chosen binds all the solute molecules (both polar and nonpolar) strongly, they will not move down the column. On the contrary, if too polar a solvent is chosen, all of the solutes (polar and nonpolar) may simply be washed through the column, with no separation taking place. The adsorbent and the solvent should be chosen so that neither is favored excessively in the equilibrium competition for solute molecules.[2]

[2] Often, the chemist uses thin-layer chromatography (TLC), which is described in Technique 20, to arrive at the best choices of solvents and adsorbents for the best separation. The TLC experimentation can be performed quickly and with extremely small amounts (microgram quantities) of the mixture to be separated. This saves significant time and materials. Technique 20, Section 20.10, describes this use of TLC.

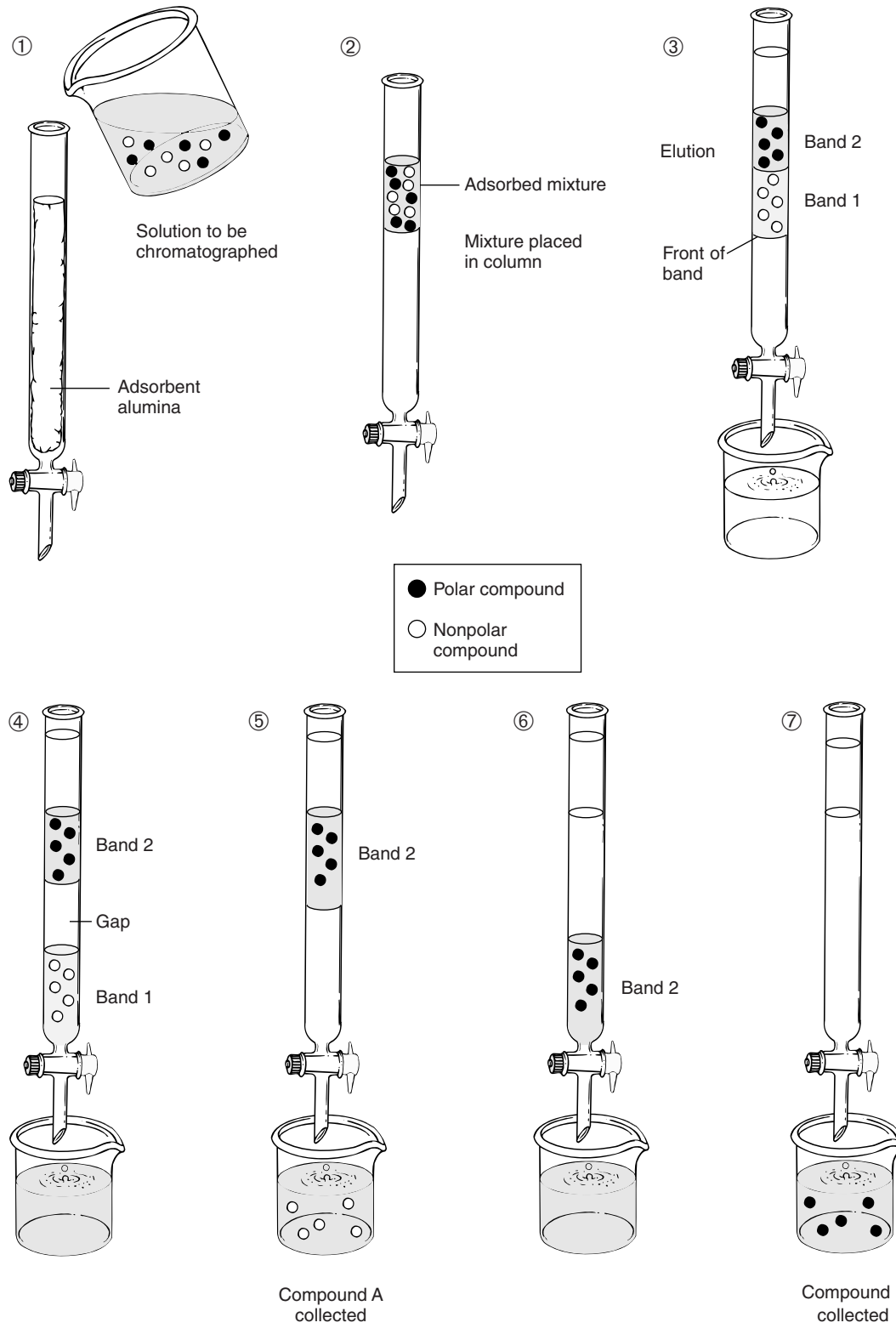


Figure 19.4 Sequence of steps in a chromatographic separation.

A. Adsorbents

In Table 19.1, various kinds of adsorbents (solid phases) used in column chromatography are listed. The choice of adsorbent often depends on the types of compounds to be separated. Cellulose, starch, and sugars are used for polyfunctional plant and animal materials (natural products) that are very sensitive to acid–base interactions. Magnesium silicate is often used for separating acetylated sugars, steroids, and essential oils. Silica gel and Florisil are relatively mild toward most compounds and are widely used for a variety of functional groups—hydrocarbons, alcohols, ketones, esters, acids, azo compounds, and amines. Alumina is the most widely used adsorbent and is obtained in the three forms mentioned in Section 19.1: acidic, basic, and neutral. The pH of acidic or acid-washed alumina is approximately 4. This adsorbent is particularly useful for separating acidic materials such as carboxylic acids and amino acids. Basic alumina has a pH of 10 and is useful in separating amines. Neutral alumina can be used to separate a variety of nonacidic and nonbasic materials.

The approximate strength of the various adsorbents listed in Table 19.1 is also given. The order is only approximate, and therefore it may vary. For instance, the strength, or separating abilities, of alumina and silica gel largely depends on the amount of water present. Water binds very tightly to either adsorbent, taking up sites on the particles that could otherwise be used for equilibration with solute molecules. If water is added to the adsorbent, it is said to have been **deactivated**. Anhydrous alumina or silica gel is said to be highly **activated**. High activity is usually avoided with these adsorbents. Use of the highly active forms of either alumina or silica gel, or of the acidic or basic forms of alumina, can often lead to molecular rearrangement or decomposition in certain types of solute compounds.

The chemist can select the degree of activity that is appropriate to carry out a particular separation. To accomplish this, highly activated alumina is mixed thoroughly with a precisely measured quantity of water. The water partially hydrates the alumina and thus reduces its activity. By carefully determining the amount of water required, the chemist can have available an entire spectrum of possible activities.

TABLE 19.1 Solid Adsorbents for Column Chromatography

Paper	
Cellulose	
Starch	
Sugars	
Magnesium silicate	Increasing strength of
Calcium sulfate	binding interactions
Silicic acid	toward polar compounds
Florisil	
Magnesium oxide	
Aluminum oxide (alumina)[a]	
Activated charcoal (Norit)	

[a]Basic, acid washed, and neutral.

B. Solvents

In Table 19.2, some common chromatographic solvents are listed along with their relative ability to dissolve polar compounds. Sometimes a single solvent can be found that will separate all the components of a mixture. Sometimes a mixture of solvents can be found that will achieve separation. More often you must start elution with a nonpolar solvent to remove relatively nonpolar compounds from the column and then gradually increase the solvent polarity to force compounds of greater polarity to come down the column, or to elute. The approximate order in which various classes of compounds elute by this procedure is given in Table 19.3. In general, nonpolar compounds travel through the column faster (elute first), and polar compounds travel more slowly (elute last). However, molecular weight is also

TABLE 19.2 Solvents (Eluents) for Chromatography

Petroleum ether	
Cyclohexane	
Carbon tetrachloride[a]	
Toluene	
Chloroform[a]	
Methylene chloride	Increasing polarity and
Diethyl ether	"solvent power" toward
Ethyl acetate	polar functional groups
Acetone	
Pyridine	
Ethanol	
Methanol	
Water	
Acetic acid	

[a]Suspected carcinogens.

TABLE 19.3 Elution Sequence for Compounds

Hydrocarbons	Fastest (will elute with nonpolar solvent)
Olefins	
Ethers	
Halocarbons	
Aromatics	
Ketones	Order of elution
Aldehydes	
Esters	
Alcohols	
Amines	
Acids, strong bases	Slowest (needs a polar solvent)

a factor in determining the order of elution. A nonpolar compound of high molecular weight travels more slowly than a nonpolar compound of low molecular weight, and it may even be passed by some polar compounds.

Solvent polarity functions in two ways in column chromatography. First, a polar solvent will better dissolve a polar compound and move it down the column faster. Therefore, as already mentioned, the polarity of the solvent is usually increased during column chromatography to wash down compounds of increasing polarity. Second, as the polarity of the solvent increases, the solvent itself will displace adsorbed molecules from the alumina or silica and take their place on the column. Because of this second effect, a polar solvent will move **all types of compounds**, both polar and nonpolar, down the column at a faster rate than a nonpolar solvent will.

When the polarity of the solvent has to be changed during a chromatographic separation, some precautions must be taken. Rapid changes from one solvent to another are to be avoided (especially when silica gel or alumina is involved). Usually, small percentages of a new solvent are mixed slowly into the one in use until the percentage reaches the desired level. If this is not done, the column packing often "cracks" as a result of the heat liberated when alumina or silica gel is mixed with a solvent. The solvent solvates the adsorbent, and the formation of a weak bond generates heat.

$$\text{Solvent} + \text{alumina} \longrightarrow (\text{alumina} \cdot \text{solvent}) + \text{heat}$$

Often, enough heat is generated locally to evaporate the solvent. The formation of vapor creates bubbles, which forces a separation of the column packing; this is called **cracking**. A cracked column does not produce a good separation because it has discontinuities in the packing. The way in which a column is packed or filled is also very important in preventing cracking.

Certain solvents should be avoided with alumina or silica gel, especially with the acidic, basic, and highly active forms. For instance, with any of these adsorbents, acetone dimerizes via an aldol condensation to give diacetone alcohol. Mixtures of esters **transesterify** (exchange their alcoholic portions) when ethyl acetate or an alcohol is the eluent. Finally, the most active solvents (pyridine, methanol, water, and acetic acid) dissolve and elute some of the adsorbent itself. Generally, try to avoid solvents more polar than diethyl ether or methylene chloride in the eluent series (see Table 19.2).

C. Column Size and Adsorbent Quantity

The column size and the amount of adsorbent must also be selected correctly to separate a given amount of sample well. As a rule of thumb, the amount of adsorbent should be 25 to 30 times, by weight, the amount of material to be separated by chromatography. Furthermore, the column should have a height-to-diameter ratio of about 8:1. Some typical relations of this sort are given in Table 19.4.

Note, as a caution, that the difficulty of the separation is also a factor in determining the size and length of the column to be used and the amount of adsorbent needed. Compounds that do not separate easily may require longer columns and more adsorbent than specified in Table 19.4. For easily separated compounds, a shorter column and less adsorbent may suffice.

TABLE 19.4 Size of Column and Amount of Adsorbent for Typical Sample Sizes

Amount of Sample (g)	Amount of Adsorbent (g)	Column Diameter (mm)	Column Height (mm)
0.01	0.3	3.5	30
0.10	3.0	7.5	60
1.00	30.0	16.0	130
10.00	300.0	35.0	280

D. Flow Rate

The rate at which solvent flows through the column is also significant in the effectiveness of a separation. In general, the time the mixture to be separated remains on the column is directly proportional to the extent of equilibration between stationary and moving phases. Thus, similar compounds eventually separate if they remain on the column long enough. The time a material remains on the column depends on the flow rate of the solvent. If the flow is too slow, however, the dissolved substances in the mixture may diffuse faster than the rate at which they move down the column. Then the bands grow wider and more diffuse, and the separation becomes poor.

19.5 Packing the Column: Typical Problems

The most critical operation in column chromatography is packing (filling) the column with adsorbent. The **column packing** must be evenly packed and free of irregularities, air bubbles, and gaps. As a compound travels down the column, it moves in an advancing zone, or **band**. It is important that the leading edge, or **front**, of this band be horizontal, or perpendicular to the long axis of the column. If two bands are close together and do not have horizontal band fronts, it is impossible to collect one band while completely excluding the other. The leading edge of the second band begins to elute before the first band has finished eluting. This condition can be seen in Figure 19.5. There are two main reasons for this problem. First, if the top surface edge of the adsorbent packing is not level, nonhorizontal bands result. Second, bands may be nonhorizontal if the column is not held in an exactly vertical position in both planes (front to back and side to side). When preparing a column, you must watch both of these factors carefully.

Another phenomenon, called **streaming** or **channeling**, occurs when part of the band front advances ahead of the major part of the band. Channeling occurs if there are any cracks or irregularities in the adsorbent surface or any irregularities caused by air bubbles in the packing. A part of the advancing front moves ahead of the rest of the band by flowing through the channel. Two examples of channeling are shown in Figure 19.6.

The methods outlined in Sections 19.6–19.8 are used to avoid problems resulting from uneven packing and column irregularities. These procedures should be followed carefully in preparing a chromatography column. Failure to pay close attention to the preparation of the column may affect the quality of the separation.

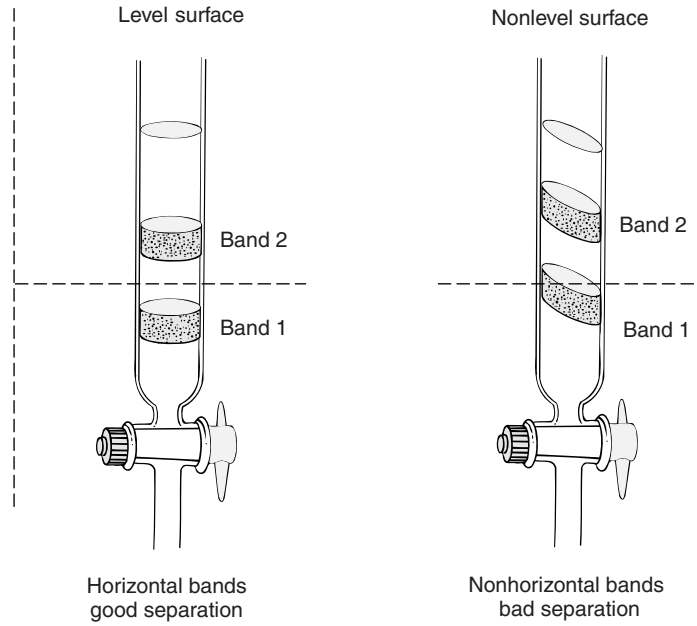


Figure 19.5 Comparison of horizontal and nonhorizontal band fronts.

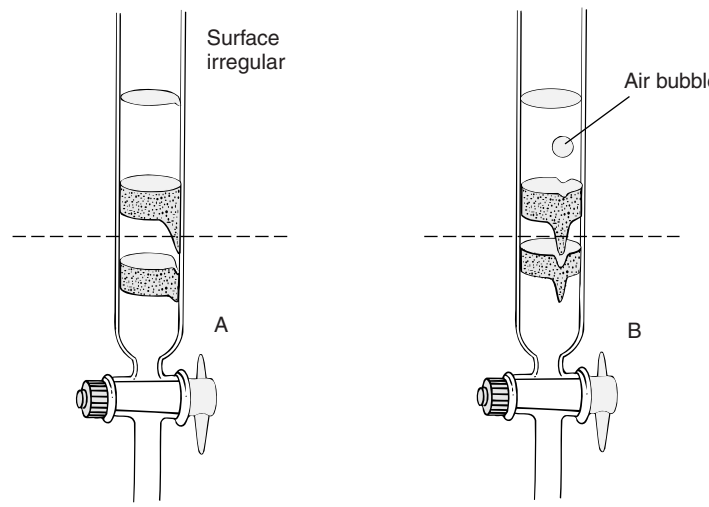


Figure 19.6 Channeling complications.

19.6 Packing the Column: Preparing the Support Base

Preparation of a column involves two distinct stages. In the first stage, a support base on which the packing will rest is prepared. This must be done so that the packing, a finely divided material, does not wash out of the bottom of the column. In the second stage, the column of adsorbent is deposited on top of the supporting base.

A. Macroscale Columns

For large-scale applications, a chromatography column is clamped upright (vertically). The column (see Figure 19.3) is a piece of cylindrical glass tubing with a stopcock attached at one end. The stopcock usually has a Teflon plug, because stopcock

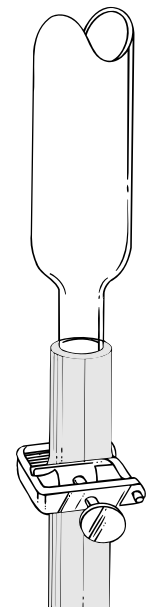


Figure 19.7 Tubing with screw clamp to regulate solvent flow on a chromatography column.

grease (used on glass plugs) dissolves in many of the organic solvents used as eluents. Stopcock grease in the eluent will contaminate the eluates.

Instead of a stopcock, a piece of flexible tubing may be attached to the bottom of the column, with a screw clamp used to stop or regulate the flow (See Figure 19.7). When a screw clamp is used, care must be taken that the tubing used is not dissolved by the solvents that will pass through the column during the experiment. Rubber, for instance, dissolves in chloroform, benzene, methylene chloride, toluene, or tetrahydrofuran (THF). Tygon tubing dissolves (actually, the plasticizer is removed) in many solvents, including benzene, methylene chloride, chloroform, ether, ethyl acetate, toluene, and THF. Polyethylene tubing is the best choice for use at the end of a column because it is inert with most solvents.

Next, the column is partially filled with a quantity of solvent, usually a nonpolar solvent such as hexane, and a support for the finely divided adsorbent is prepared in the following way. A loose plug of glass wool is tamped down into the bottom of the column with a long glass rod until all entrapped air is forced out as bubbles. Take care not to plug the column totally by tamping the glass wool too hard. A small layer of clean, white sand is formed on top of the glass wool by pouring sand into the column. The column is tapped to level the surface of the sand. Any sand adhering to the side of the column is washed down with a small quantity of solvent. The sand forms a base that supports the column of adsorbent and prevents it from washing through the stopcock. The column is packed in one of two ways: by the slurry method (see Section 9.8) or by the dry pack method (see Section 9.7).

B. Semi-microscale Columns

An alternative apparatus for macroscale column chromatography on a smaller scale is a commercial column, such as the one shown in Figure 19.8. This type of column is made of glass and has a solvent-resistant plastic stopcock at the

bottom.[3] The stopcock assembly contains a filter disc to support the adsorbent column. An optional upper fitting, also made of solvent-resistant plastic, serves as a solvent reservoir. The column shown in Figure 19.8 is equipped with the solvent reservoir. This type of column is available in a variety of lengths, ranging from 100 mm to 300 mm. Because the column has a built-in filter disc, it is not necessary to prepare a support base before the adsorbent is added.

C. Microscale Columns

For microscale applications, a Pasteur pipet ($5\frac{3}{4}$-inch) is used; it is clamped upright (vertically). To reduce the amount of solvent needed to fill the column, you may break off most of the tip of the pipet. A small ball of cotton is placed in the pipet and tamped into position using a glass rod or a piece of wire. Take care not to plug the column totally by tamping the cotton too hard. The correct position of the cotton is shown in Figure 19.9. A microscale chromatography column is packed by one of the dry pack methods described in Section 19.7.

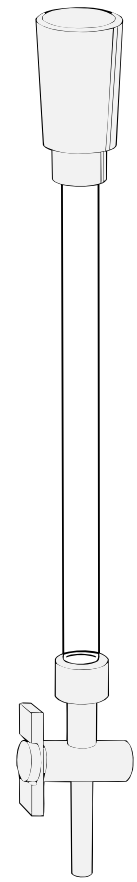


Figure 19.8 A commercial semi-microscale chromatography column. (The column shown is equipped with an optional solvent reservoir.)

[3] Note to the instructor: With certain organic solvents, we have found that the "solvent-resistant" plastic stopcock may tend to dissolve! We recommend that instructors test their equipment with the solvent that they intend to use before the start of the laboratory class.

Figure 19.9 A microscale chromatography column.

19.7 Packing the Column: Depositing the Adsorbent—Dry Pack Methods

A. Dry Pack Method 1

Macroscale Columns. In the first of the dry pack methods introduced here, the column is filled with solvent and allowed to drain *slowly*. The dry adsorbent is added, a little at a time, while the column is tapped gently with a pencil, finger, or glass rod.

A plug of cotton is placed at the base of the column, and an even layer of sand is formed on top (see Section 19.6, A. Macroscale Columns). The column is filled about half-full with solvent, and the solid adsorbent is added carefully from a beaker while the solvent is allowed to flow slowly from the column. As the solid is added, the column is tapped as described for the slurry method (see Section 19.8) to ensure that the column is packed evenly. When the column has the desired length, no more adsorbent is added. This method produces an evenly packed column. Solvent should be cycled through this column (for macroscale applications) several times before each use. The same portion of solvent that has drained from the column during the packing is used to cycle through the column.

Semi-microscale Columns. The procedure to fill a commercial semi-microscale column is essentially the same as that used to fill a Pasteur pipet (see the following paragraph). The commercial column has the advantage that it is much easier to control the flow of solvent from the column during the filling process, because the stopcock can be adjusted appropriately. It is not necessary to use a cotton plug or to deposit a layer of sand before adding the adsorbent. The presence of the fritted disc at the base of the column prevents adsorbent from escaping from the column.

Microscale Columns. To fill a microscale column, fill the Pasteur pipet (with the cotton plug, prepared as described in Section 19.6) about half full with solvent. Using a microspatula, add the solid adsorbent slowly to the solvent in the column. As you add the solid, tap the column *gently* with a pencil, a finger, or a glass rod. The tapping promotes even settling and mixing and gives an evenly packed column free of air bubbles. As the adsorbent is added, solvent flows out of the Pasteur pipet. Because the adsorbent must not be allowed to dry during the packing process, you must use a means of controlling the solvent flow. If a piece of small-diameter plastic tubing is available, it can be fitted over the narrow tip of the Pasteur pipet. The flow rate can then be controlled using a screw clamp. A simple approach to controlling the flow rate is to use a finger over the top of the Pasteur pipet, much as you would control the flow of liquid in a volumetric pipet. Continue adding the adsorbent slowly, with constant tapping, until it has reached the desired level. As you pack the column, be careful not to let the column run dry. The final column should appear as shown in Figure 19.9.

B. Dry Pack Method 2

Macroscale Columns. Macroscale columns can also be packed by a dry pack method that is commonly used in the packing of microscale columns (see "Microscale Columns" below). In this method, the column is filled with dry adsorbent without any solvent. When the desired amount of adsorbent has been added, solvent is allowed to percolate through the column. The disadvantages described for the microscale method also apply to the macroscale method. This method is not recommended for use with silica gel or alumina because the combination leads to uneven packing, air bubbles, and cracking, especially if a solvent that has a highly exothermic heat of solvation is used.

Semi-microscale Columns. The dry pack method 2 for semi-microscale columns is similar to that described for Pasteur pipets (see next paragraph), except that the plug of cotton is not required. The flow rate of solvent through the column can be controlled using the stopcock, which is part of the column assembly (see Figure 19.8).

Microscale Columns. An alternative dry pack method for microscale columns is to fill the Pasteur pipet with *dry* adsorbent, without any solvent. Position a plug of cotton in the bottom of the Pasteur pipet. The desired amount of adsorbent is added slowly, and the pipet is tapped constantly until the level of adsorbent has reached the desired height. Figure 19.9 can be used as a guide to judge the correct height of the column of adsorbent. When the column is packed, added solvent is allowed to percolate through the adsorbent until the entire column is moistened. The solvent is not added until just before the column is to be used.

This method is useful when the adsorbent is alumina, but it does not produce satisfactory results with silica gel. Even with alumina, poor separations can arise due to uneven packing, air bubbles, and cracking, especially if a solvent that has a highly exothermic heat of solvation is used.

19.8 Packing the Column: Depositing the Adsorbent—the Slurry Method

The slurry method is not recommended as a microscale method for use with Pasteur pipets. On a very small scale, it is too difficult to pack the column with the slurry without losing the solvent before the packing has been completed. Microscale columns should be packed by one of the dry pack methods, as described in Section 19.7.

In the slurry method, the adsorbent is packed into the column as a mixture of a solvent and an undissolved solid. The slurry is prepared in a separate container (Erlenmeyer flask) by adding the solid adsorbent, a little at a time, to a quantity of the solvent. This order of addition (adsorbent added to solvent) should be followed strictly, because the adsorbent solvates and liberates heat. If the solvent is added to the adsorbent, it may boil away almost as fast as it is added due to heat evolved. This will be especially true if ether or another low-boiling solvent is used. When this happens, the final mixture will be uneven and lumpy. Enough adsorbent is added to the solvent, and mixed by swirling the container, to form a thick, but flowing, slurry. The container should be swirled until the mixture is homogeneous and relatively free of entrapped air bubbles.

For a macroscale column, the procedure is as follows. When the slurry has been prepared, the column is filled about half full with solvent, and the stopcock is opened to allow solvent to drain slowly into a large beaker. The slurry is mixed by swirling and is then poured in portions into the top of the draining column (a wide-necked funnel may be useful here). Be sure to swirl the slurry thoroughly before each addition to the column. The column is tapped constantly and *gently* on the side during the pouring operation, with the fingers or with a pencil fitted with a rubber stopper. A short piece of large-diameter pressure tubing may also be used for tapping. The tapping promotes even settling and mixing and gives an evenly packed column free of air bubbles. Tapping is continued until all the material has settled, showing a well-defined level at the top of the column. Solvent from the collecting beaker may be readded to the slurry if it becomes too thick to be poured into the column at one time. In fact, the collected solvent should be cycled through the column several times to ensure that settling is complete and that the column is firmly packed. The downward flow of solvent tends to compact the adsorbent. Take care never to let the column "run dry" during packing. There should always be solvent on top of the absorbent column.

19.9 Applying the Sample to the Column

The solvent (or solvent mixture) used to pack the column is normally the least polar elution solvent that can be used during chromatography. The compounds to be chromatographed are not highly soluble in the solvent. If they were, they would probably have a greater affinity for the solvent than for the adsorbent and would pass right through the column without equilibrating with the stationary phase.

The first elution solvent, however, is generally not a good solvent to use in preparing the sample to be placed on the column. Because the compounds are not highly soluble in nonpolar solvents, it takes a large amount of the initial solvent to dissolve the compounds, and it is difficult to get the mixture to form a narrow band on top of the column. A narrow band is ideal for an optimum separation of components. For the best separation, therefore, the compound is applied to the top of the column undiluted if it is a liquid, or in a *very small* amount of polar solvent if it is a solid. Water must not be used to dissolve the initial sample being chromatographed because it reacts with the column packing.

In adding the sample to the column, use the following procedure. Lower the solvent level to the top of the adsorbent column by draining the solvent from the column. Add the sample (either a pure liquid or a solution) to form a small layer on top of the adsorbent. A Pasteur pipet is convenient for adding the sample to the column. Take care not to disturb the surface of the adsorbent. This is best accomplished by touching the pipet to the inside of the glass column and slowly draining it to allow the sample to spread into a thin film, which slowly descends to cover the entire adsorbent surface. Drain the pipet close to the surface of the adsorbent. When

all of the sample has been added, drain this small layer of liquid into the column until the top surface of the column *just begins* to dry. Then add a small layer of the chromatographic solvent carefully with a Pasteur pipet, again being careful not to disturb the surface. Drain this small layer of solvent into the column until the top surface of the column just dries. Add another small layer of fresh solvent, if necessary, and repeat the process until it is clear that the sample is strongly adsorbed on the top of the column. If the sample is colored and the fresh layer of solvent acquires some of this color, the sample has not been properly adsorbed. Once the sample has been properly applied, you can protect the level surface of the adsorbent by carefully filling the top of the column with solvent and sprinkling clean, white sand into the column to form a small protective layer on top of the adsorbent. For microscale applications, this layer of sand is not required.

Separations are often better if the sample is allowed to stand a short time on the column before elution. This allows a true equilibrium to be established. In columns that stand for too long, however, the adsorbent often compacts or even swells, and the flow can become annoyingly slow. Diffusion of the sample to widen the bands also becomes a problem if a column is allowed to stand over an extended period. For small-scale chromatography using Pasteur pipets, there is no stopcock, and it is not possible to stop the flow. In this case, it is not necessary to allow the column to stand.

19.10 Elution Techniques

Solvents for analytical and preparative chromatography should be pure reagents. Commercial-grade solvents often contain small amounts of residue, which remain when the solvent is evaporated. For routine work and for relatively easy separations that take only small amounts of solvent, the residue usually presents few problems. For large-scale work, commercial-grade solvents may have to be redistilled before use. This is especially true for hydrocarbon solvents, which tend to have more residue than other solvent types.

Elution of the products is usually begun with a nonpolar solvent, such as hexane or petroleum ether. The polarity of the elution solvent can be increased gradually by adding successively greater percentages of ether or toluene (for instance, 1, 2, 5, 10, 15, 25, 50, or 100%) or some other solvent of greater solvent power (polarity) than hexane. The transition from one solvent to another should not be too rapid in most solvent changes. If the two solvents to be changed differ greatly in their heats of solvation in binding to the adsorbent, enough heat can be generated to crack the column. Ether is especially troublesome in this respect, as it has both a low boiling point and a relatively high heat of solvation. Most organic compounds can be separated on silica gel or alumina using hexane–ether or hexane–toluene combinations for elution, and following these by pure methylene chloride. Solvents of greater polarity are usually avoided for the various reasons mentioned previously. In microscale work, the usual procedure is to use only one solvent for the chromatography.

The flow of solvent through the column should not be too rapid, or the solutes will not have time to equilibrate with the adsorbent as they pass down the column. If the rate of flow is too low or stopped for a period, diffusion can become a problem—the solute band will diffuse, or spread out, in all directions. In either of these cases, separation will be poor. As a general rule (and only an approximate one), most macroscale columns are run with flow rates ranging from 5 to 50 drops of effluent per minute; a steady flow of solvent is usually avoided. Microscale columns made from Pasteur pipets do not have a means of controlling the solvent flow rate, but commercial microscale columns are equipped with stopcocks. The solvent flow rate in this type of column can be adjusted in a manner similar to that used with larger columns. To avoid diffusion of the bands, do not stop the column, and do not set it aside overnight.

In some cases, the chromatography may proceed too slowly; the rate of solvent flow can be accelerated by attaching a rubber dropper bulb to the top of the Pasteur pipet column and squeezing *gently.* The additional air pressure forces the solvent through the column more rapidly. If this technique is used, however, care must be taken to remove the rubber bulb from the column before releasing it. Otherwise, air may be drawn up through the bottom of the column, destroying the column packing.

19.11 Reservoirs

When large quantities of solvent are used in a chromatographic separation, it is often convenient to use a solvent reservoir to forestall having to add small portions of fresh solvent continually. The simplest type of reservoir, a feature of many columns, is created by fusing the top of the column to a round-bottom flask (see Figure 19.10A). If the column has a standard-taper joint at its top, a reservoir can be created by joining a standard-taper separatory funnel to the column (see Figure 19.10B). In this arrangement, the stopcock is left open, and no stopper is placed in the top of the separatory funnel. A third common arrangement is shown in Figure 19.10C. A separatory funnel is filled with solvent; its stopper is wetted with solvent and put *firmly* in place. The funnel is inserted into the empty filling space at the top of the chromatographic column, and the stopcock is opened. Solvent flows out of the funnel, filling the space at the top of the column until the solvent level is well above the outlet of the separatory funnel. As solvent drains from the column, this arrangement automatically refills the space at the top of the column by allowing air to enter through the stem of the separatory funnel.

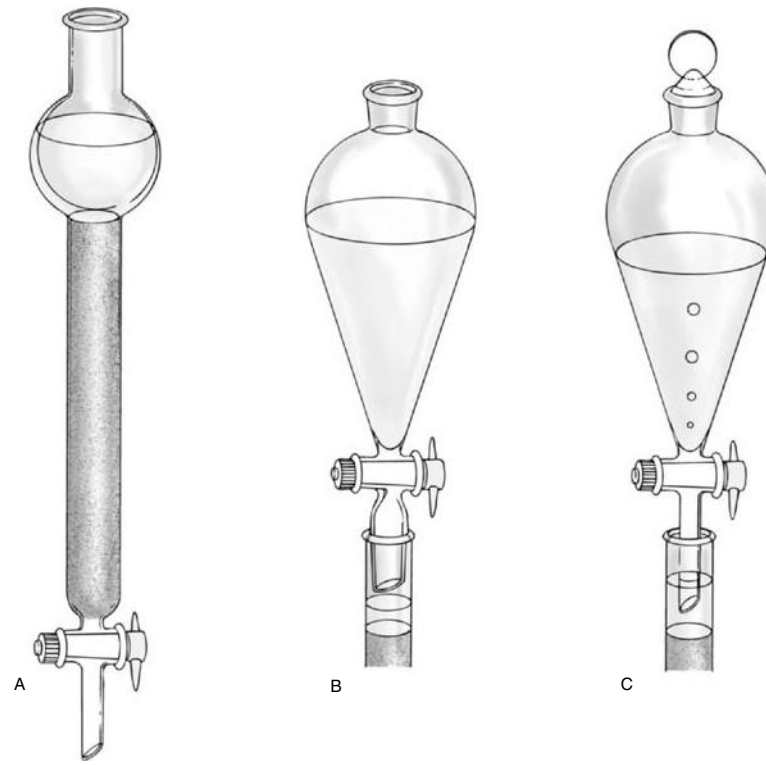


Figure 19.10 Various types of solvent-reservoir arrangements for chromatographic columns.

Some semi-microscale columns, such as that shown in Figure 19.8, are equipped with a solvent reservoir that fits onto the top of the column. It functions just as the reservoirs do that are described in this section.

For a microscale chromatography, the portion of the Pasteur pipet above the adsorbent is used as a reservoir of solvent. Fresh solvent, as needed, is added by means of another Pasteur pipet. When it is necessary to change solvent, the new solvent is also added in this manner.

19.12 Monitoring the Column

It is a lucky circumstance when the compounds to be separated are colored. The separation can then be followed visually and the various bands collected separately as they elute from the column. For the majority of organic compounds, however, this lucky circumstance does not exist, and other methods must be used to determine the positions of the bands. The most common method of following a separation of colorless compounds is to collect *fractions* of constant volume in preweighed flasks or test tubes, to evaporate the solvent from each fraction, and to reweigh the container plus any residue. A plot of fraction number versus the weight of the residues after evaporation of solvent gives a plot similar to that in Figure 19.11. Clearly, fractions 2 through 7 (peak 1) may be combined as a single compound, and so can fractions 8 through 11 (peak 2) and 12 through 15 (peak 3). The size of the fractions collected (1, 10, 100, or 500 mL) depends on the size of the column and the ease of separation.

Another common method of monitoring the column is to mix an inorganic phosphor into the adsorbent used to pack the column. When the column is illuminated with an ultraviolet light, the adsorbent treated in this way fluoresces. However, many solutes have the ability to **quench** the fluorescence of the indicator phosphor. In areas in which solutes are present, the adsorbent does not fluoresce and a dark band is visible. In this type of column, the separation can also be followed visually.

Thin-layer chromatography is often used to monitor a column. This method is described in Technique 20 (see Section 20.10). Several sophisticated instrumental and spectroscopic methods, which we shall not detail, can also monitor a chromatographic separation.

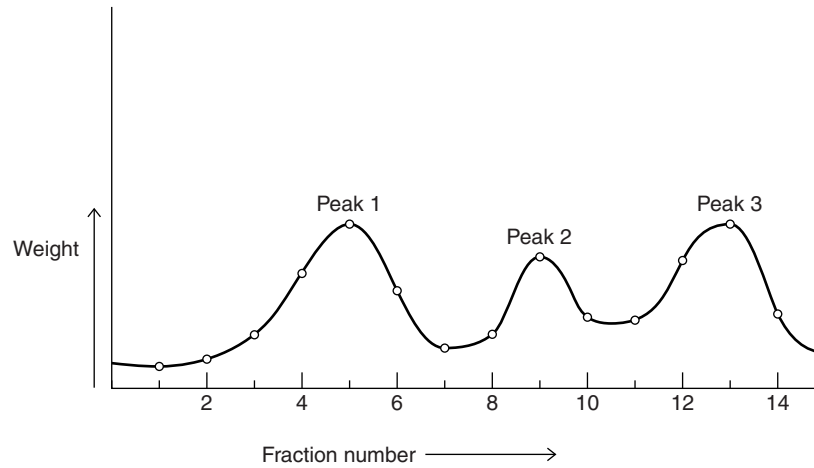


Figure 19.11 A typical elution graph.

19.13 Tailing

When a single solvent is used for elution, an elution curve (weight versus fraction) such as that shown as a solid line in Figure 19.12 is often observed. An ideal elution curve is shown by dashed lines. In the nonideal curve, the compound is said to be **tailing**. Tailing can interfere with the beginning of a curve or a peak of a second component and lead to a poor separation. One way to avoid this is to increase the polarity of the solvent constantly while eluting. In this way, at the tail of the peak, where the solvent polarity is increasing, the compound will move slightly faster than at the front and allow the tail to squeeze forward, forming a more nearly ideal band.

19.14 Recovering the Separated Compounds

In recovering each of the separated compounds of a chromatographic separation when they are solids, the various correct fractions are combined and evaporated. If the combined fractions contain sufficient material, they may be purified by recrystallization. If the compounds are liquids, the correct fractions are combined and the solvent is evaporated. If sufficient material has been collected, liquid samples can be purified by distillation. The combination of chromatography–crystallization or chromatography–distillation usually yields very pure compounds. For microscale applications, the amount of sample collected is too small to allow a purification by crystallization or distillation. The samples that are obtained after the solvent has been evaporated are considered to be sufficiently pure, and no additional purification is attempted.

19.15 Decolorization by Column Chromatography

A common outcome of organic reactions is the formation of a product that is contaminated by highly colored impurities. Very often, these impurities are highly polar, and they have a high molecular weight as well as being colored. The purification of the desired product requires that these impurities be removed. Section 11.7 of Technique 11 details methods of decolorizing an organic product. In most cases, these methods involve the use of a form of activated charcoal, or Norit.

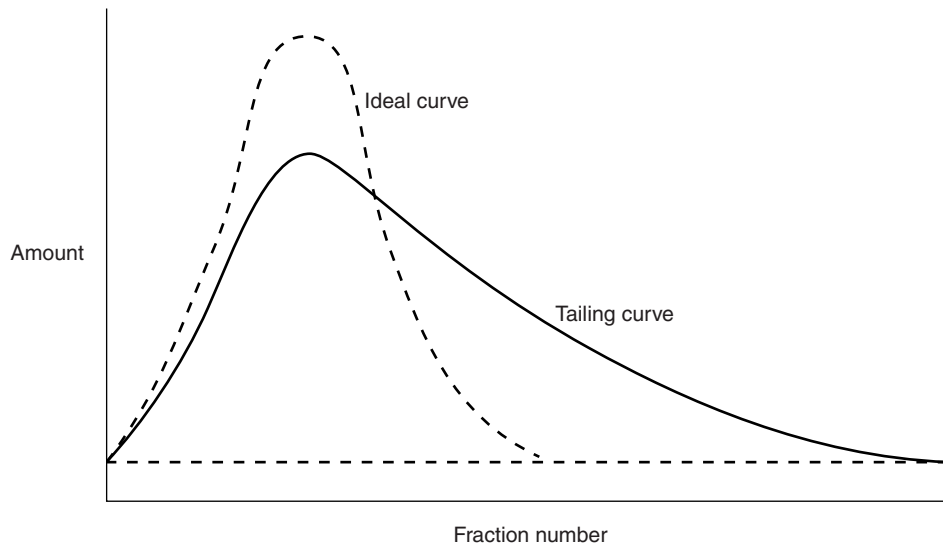


Figure 19.12 Elution curves: one ideal and one that "tails."

An alternative, which is applied conveniently in microscale experiments, is to remove the colored impurity by column chromatography. Because of the polarity of the impurities, the colored components are strongly adsorbed on the stationary phase of the column, and the less polar desired product passes through the column and is collected.

Microscale decolorization of a solution on a chromatography column requires that a column be prepared in a Pasteur pipet, using either alumina or silica gel as the adsorbent (See Sections 19.6 and 19.7). The sample to be decolorized is diluted to the point where crystallization within the column will not take place, and it is then passed through the column in the usual manner. The desired compound is collected as it exits the column, and the excess solvent is removed by evaporation (see Technique 7, Section 7.10).

19.16 Gel Chromatography

The stationary phase in gel chromatography consists of a cross-linked polymeric material. Molecules are separated according to their *size* by their ability to penetrate a sievelike structure. Molecules permeate the porous stationary phase as they move down the column. Small molecules penetrate the porous structure more easily than large ones. Thus, the large molecules move through the column faster than the smaller ones and elute first. The separation of molecules by gel chromatography is depicted in Figure 19.13. With adsorption chromatography using materials such as alumina or silica, the order is usually the reverse. Small molecules (of low molecular weight) pass through the column *faster* than large molecules (of high molecular weight) because large molecules are more strongly attracted to the polar stationary phase.

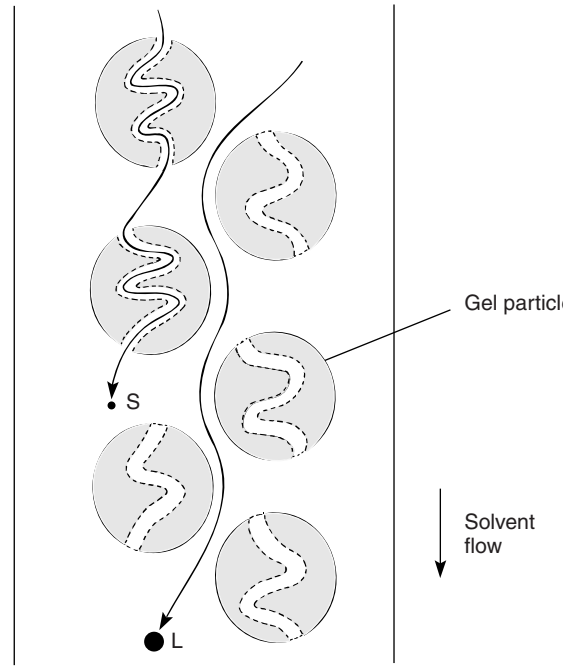


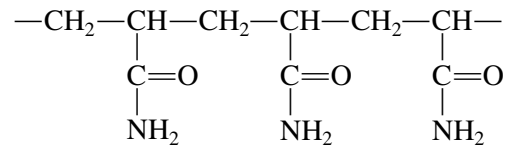
Figure 19.13 Gel chromatography. Comparison of the paths of large (L) and small (S) molecules through the column during the same interval of time.

Equivalent terms used by chemists for the gel chromatography technique are **gel-filtration chromatography** (biochemistry term), **gel-permeation chromatography** (polymer chemistry term), and **molecular-sieve chromatography. Size-exclusion chromatography** is a general term for the technique, and it is perhaps the most descriptive term for what occurs on a molecular level.

Sephadex is one of the most popular materials for gel chromatography. It is widely used by biochemists for separating proteins, nucleic acids, enzymes, and carbohydrates. Most often, water or aqueous solutions of buffers are used as the moving phase. Chemically, Sephadex is a polymeric carbohydrate that has been cross-linked. The degree of cross-linking determines the size of the "holes" in the polymer matrix. In addition, the hydroxyl groups on the polymer can adsorb water, which causes the material to swell. As it expands, "holes" are created in the matrix. Several different gels are available from manufacturers, each with its own set of characteristics. For example, a typical Sephadex gel, such as G-75, can separate molecules in the molecular weight (MW) range 3000 to 70,000. Consider a four-component mixture containing compounds with molecular weights of 10,000, 20,000, 50,000, and 100,000. The 100,000-MW compound would pass through the column first, because it cannot penetrate the polymer matrix. The 50,000-, 20,000-, and 10,000-MW compounds penetrate the matrix to varying degrees and would be separated. The molecules would elute in the order given (decreasing order of molecular weights). The gel separates on the basis of molecular size and configuration rather than molecular weight.

Sephadex LH-20 has been developed for nonaqueous solvents. Some of the hydroxyl groups have been alkylated, and thus the material can swell under both aqueous and nonaqueous conditions (it now has "organic" character). This material can be used with several organic solvents, such as alcohol, acetone, methylene chloride, and aromatic hydrocarbons.

Another type of gel is based on a polyacrylamide structure (Bio-Gel P and Poly-Sep AA). A portion of a polyacrylamide chain is shown here:



Gels of this type can also be used in water and some polar organic solvents. They tend to be more stable than Sephadex, especially under acidic conditions. Polyacrylamides can be used for many biochemical applications involving macromolecules. For separating synthetic polymers, cross-linked polystyrene beads (copolymer of styrene and divinylbenzene) find common application. Again, the beads are swollen before use. Common organic solvents can be used to elute the polymers. As with other gels, the higher-molecular-weight compounds elute before the lower-molecular-weight compounds.

19.17 Flash Chromatography

One of the drawbacks to column chromatography is that for large-scale preparative separations, the time required to complete a separation may be very long. Furthermore, the resolution that is possible for a particular experiment tends to deteriorate as the time for the experiment grows longer. This latter effect arises because the bands of compounds that move very slowly through a column tend to "tail."

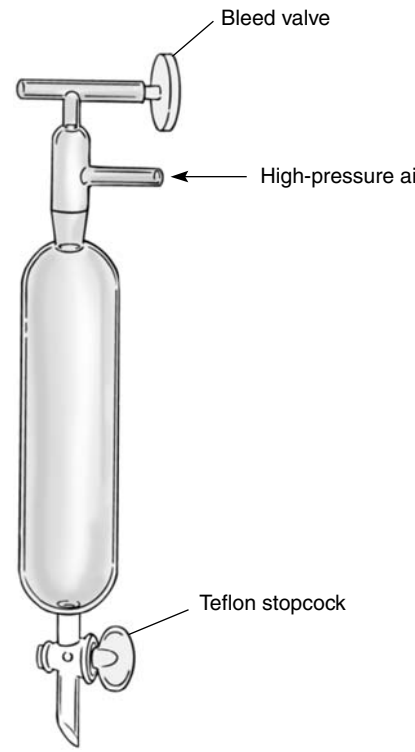


Figure 19.14 Apparatus for flash chromatography.

A technique that can be useful in overcoming these problems has been developed.This technique, called **flash chromatography**, is actually a very simple modification of an ordinary column chromatography. In flash chromatography, the adsorbent is packed into a relatively short glass column, and air pressure is used to force the solvent through the adsorbent.

The apparatus used for flash chromatography is shown in Figure 19.14. The glass column is fitted with a Teflon stopcock at the bottom to control the flow rate of solvent. A plug of glass wool is placed in the bottom of the column to act as a support for the adsorbent. A layer of sand may also be added on top of the glass wool. The column is filled with adsorbent using the dry pack method. When the column has been filled, a fitting is attached to the top of the column, and the entire apparatus is connected to a source of high-pressure air or nitrogen. The fitting is designed so that the pressure applied to the top of the column can be adjusted precisely. The source of the high-pressure air is often a specially adapted air pump.

A typical column would use silica gel adsorbent (particle size = 40–63 μm) packed to a height of 5 inches in a glass column of 20-mm diameter. The pressure applied to the column would be adjusted to achieve a solvent flow rate such that the solvent level in the column would decrease by about 2 inches/minute. This system would be appropriate to separate the components of a 250-mg sample.

The high-pressure air forces the solvent through the column of adsorbent at a rate that is much greater than what would be achieved if the solvent flowed through the column under the force of gravity. Because the solvent is made to flow faster, the time required for substances to pass through the column is reduced. By itself, simply applying air pressure to the column might reduce the clarity of the separation, because the components of the mixture would not have time to establish themselves

into distinctly separate bands. However, in flash chromatography, you can use a much finer adsorbent than would be used in ordinary chromatography. With a much smaller particle size for the adsorbent, the surface area is increased and the resolution possible thereby improves.

A simple variation on this idea does not use air pressure. Instead, the lower end of the column is inserted into a stopper, which is fitted into the top of a suction flask. Vacuum is applied to the system, and the vacuum acts to draw the solvent through the adsorbent column. The overall effect of this variation is similar to that obtained when air pressure is applied to the top of the column.

REFERENCES

Deyl, Z., Macek, K., and Janák, J. *Liquid Column Chromatography.* Amsterdam: Elsevier, 1975.

Heftmann, E. *Chromatography,* 3rd ed. New York: Van Nostrand Reinhold, 1975.

Jacobson, B. M. "An Inexpensive Way to Do Flash Chromatography." *Journal of Chemical Education, 65* (May 1988): 459.

Still, W. C., Kahn, M., and Mitra, A. "Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution." *Journal of Organic Chemistry, 43* (1978): 2923.

PROBLEMS

1. A sample was placed on a chromatography column. Methylene chloride was used as the eluting solvent. All of the components eluted off the column, but no separation was observed. What must have been happening during this experiment? How would you change the experiment to overcome this problem?

2. You are about to purify an impure sample of naphthalene by column chromatography. What solvent should you use to elute the sample?

3. Consider a sample that is a mixture composed of biphenyl, benzoic acid, and benzyl alcohol. Predict the order of elution of the components in this mixture. Assume that the chromatography uses a silica column and the solvent system is based on cyclohexane, with an increasing proportion of methylene chloride added as a function of time.

4. An orange compound was added to the top of a chromatography column. Solvent was added immediately, and the entire volume of solvent in the solvent reservoir turned orange. No separation could be obtained from the chromatography experiment. What went wrong?

5. A yellow compound dissolved in methylene chloride is added to a chromatography column. The elution is begun using petroleum ether as the solvent. After 6 L of solvent had passed through the column, the yellow band still had not traveled down the column appreciably. What should be done to make this experiment work better?

6. You have 0.50 g of a mixture that you wish to purify by column chromatography. How much adsorbent should you use to pack the column? Estimate the appropriate column diameter and height.

7. In a particular sample, you wish to collect the component with the *highest* molecular weight as the *first* fraction. What chromatographic technique should you use?

8. A colored band shows an excessive amount of tailing as it passes through the column. What can you do to rectify this problem?

9. How would you monitor the progress of a column chromatography when the sample is colorless? Describe at least two methods.

20 TECHNIQUE 20

Thin-Layer Chromatography

Thin-layer chromatography (TLC) is a very important technique for the rapid separation and qualitative analysis of small amounts of material. It is ideally suited for the analysis of mixtures and reaction products in both macroscale and microscale experiments. The technique is closely related to column chromatography. In fact, TLC can be considered column chromatography *in reverse*, with the solvent ascending the adsorbent rather than descending. Because of this close relationship to column chromatography and because the principles governing the two techniques are similar, Technique 19, on column chromatography, should be read first.

20.1 Principles of Thin-Layer Chromatography

Like column chromatography, TLC is a solid–liquid partitioning technique. However, the moving liquid phase is not allowed to percolate down the adsorbent; it is caused to *ascend* a thin layer of adsorbent coated onto a backing support. The most typical backing is a plastic material, but other materials are also used. A thin layer of the adsorbent is spread onto the plate and allowed to dry. A coated and dried plate is called a **thin-layer plate** or a **thin-layer slide**. (Microscope slides were often used to prepare small thin-layer plates, thus the reference to *slide*.) When a thin-layer plate is placed upright in a vessel that contains a shallow layer of solvent, the solvent ascends the layer of adsorbent on the plate by capillary action.

In TLC, the sample is applied to the plate before the solvent is allowed to ascend the adsorbent layer. The sample is usually applied as a small spot near the base of the plate; this technique is often referred to as **spotting**. The plate is spotted by repeated applications of a sample solution from a small capillary pipet. When the filled pipet touches the plate, capillary action delivers its contents to the plate and a small spot is formed.

As the solvent ascends the plate, the sample is partitioned between the moving liquid phase and the stationary solid phase. During this process, you are **developing**, or **running**, the thin-layer plate. In development, the various components in the applied mixture are separated. The separation is based on the many equilibrations the solutes experience between the moving and the stationary phases. (The nature of these equilibrations was thoroughly discussed in Technique 19, Sections 19.2 and 19.3.) As in column chromatography, the least polar substances advance faster than the most polar substances. A separation results from the differences in the rates at which the individual components of the mixture advance upward on the plate. When many substances are present in a mixture, each has its own characteristic solubility and adsorptivity properties, depending on the functional groups in its structure. In general, the stationary phase is strongly polar and strongly binds polar substances. The moving liquid phase is usually less polar than the adsorbent and most easily dissolves substances that are less polar or even nonpolar. Thus, the most polar substances travel slowly upward, or not at all, and nonpolar substances travel more rapidly.

When the thin-layer plate has been developed, it is removed from the developing tank and allowed to dry until it is free of solvent. If the mixture that was originally spotted on the plate was separated, there will be a vertical series of spots on the plate. Each spot corresponds to a separate component or compound from the

original mixture. If the components of the mixture are colored substances, the various spots will be clearly visible after development. More often, however, the "spots" will not be visible because they correspond to colorless substances. If spots are not apparent, they can be made visible only if a **visualization method** is used. Often, spots can be seen when the thin-layer plate is held under ultraviolet light; the ultraviolet lamp is a common visualization method. Also common is the use of iodine vapor. The plates are placed in a chamber containing iodine crystals and left to stand for a short time. The iodine reacts with the various compounds adsorbed on the plate to give colored complexes that are clearly visible. Because iodine often changes the compounds by reaction, the components of the mixture cannot usually be recovered from the plate when the iodine method is used. (Other methods of visualization are discussed in Section 20.7.)

20.2 Commercially Prepared TLC Plates

The most convenient type of TLC plate is prepared commercially and sold in a ready-to-use form. Many manufacturers supply glass plates precoated with a durable layer of silica gel or alumina. More conveniently, plates are also available that have either a flexible plastic backing or an aluminum backing. The most common types of commercial TLC plates are composed of plastic sheets that are coated with silica gel and polyacrylic acid, which serves as a binder. A fluorescent indicator may be mixed with the silica gel. Due to the presence of compounds in the sample, the indicator renders the spots visible under ultraviolet light (see Section 20.7). Although these plates are relatively expensive compared with plates prepared in the laboratory, they are far more convenient to use and provide more consistent results. The plates are manufactured quite uniformly. Because the plastic backing is flexible, an additional advantage is that the coating does not flake off the plates easily. The plastic sheets (usually 8 in. × 8 in. square) can also be cut with a pair of scissors or paper cutter to whatever size may be required.

If the package of commercially prepared TLC plates has been opened previously or if the plates have not been purchased recently, they should be dried before use. Dry the plates by placing them in an oven at 100°C for 30 minutes and store them in a desiccator until they are to be used.

20.3 Preparation of Thin-Layer Slides And Plates

Commercially prepared plates (see Section 20.2) are the most convenient to use, and we recommend their use for most applications. If you must prepare your own slides or plates, this section provides directions for doing so. The two adsorbent materials used most often for TLC are alumina G (aluminum oxide) and silica gel G (silicic acid). The G designation stands for gypsum (calcium sulfate). Calcined gypsum $CaSO_4 \cdot \frac{1}{2}H_2O$ is better known as plaster of paris. When exposed to water or moisture, gypsum sets in a rigid mass $CaSO_4 \cdot 2H_2O$, which binds the adsorbent together and to the glass plates used as a backing support. In the adsorbents used for TLC, about 10–13% by weight of gypsum is added as a binder. The adsorbent materials are otherwise similar to those used in column chromatography; the adsorbents used in column chromatography have a larger particle size, however. The material for thin-layer work is a fine powder. The small particle size, along with the added gypsum, makes it impossible to use silica gel G or alumina G for column work. In a column, these adsorbents generally set so rigidly that solvent virtually stops flowing through the column.

For separations involving large amounts of material or for difficult separations, it may be necessary to use larger thin-layer plates. Under these circumstances, you may have to prepare your own plates. Plates with dimensions up to 200–250 cm^2

are common. With larger plates, it is desirable to have a somewhat durable coating, and a water slurry of the adsorbent should be used to prepare them. If silica gel is used, the slurry should be prepared in the ratio of about 1 g silica gel G to each 2 mL of water. The glass plate used for the thin-layer plate should be washed, dried, and placed on a sheet of newspaper. Place two strips of masking tape along two edges of the plate. Use more than one layer of masking tape if a thicker coating is desired on the plate. A slurry is prepared, shaken well, and poured along one of the untaped edges of the plate.

CAUTION

Avoid breathing silica dust or methylene chloride, prepare and use the slurry in a hood, and avoid getting methylene chloride or the slurry mixture on your skin. Perform the coating operation under a hood.

A heavy piece of glass rod, long enough to span the taped edges, is used to level and spread the slurry over the plate. While the rod is resting on the tape, it is pushed along the plate from the end at which the slurry was poured toward the opposite end of the plate. This is illustrated in Figure 20.1. After the slurry is spread, the masking tape strips are removed, and the plates are dried in a 110°C oven for about 1 hour. Plates of 200–250 cm^2 are easily prepared by this method. Larger plates present more difficulties. Many laboratories have a commercially manufactured spreading machine that makes the entire operation simpler.

20.4 Sample Application: Spotting The Plates

A. Preparing a Micropipet

To apply the sample that is to be separated to the thin-layer plate, use a micropipet. A micropipet is easily made from a short length of thin-walled capillary tubing such as that used for melting-point determinations, but open at both ends. The capillary tubing is heated at its midpoint with a microburner and rotated until it is soft. When the tubing is soft, the heated portion of the tubing is drawn out until a constricted portion of tubing 4–5 cm long is formed. After cooling, the constricted portion of tubing is scored at its center with a file or scorer and broken. The two halves yield two capillary micropipets. Try to make a clean break without jagged or sharp edges. Figure 20.2 shows how to make such pipets.

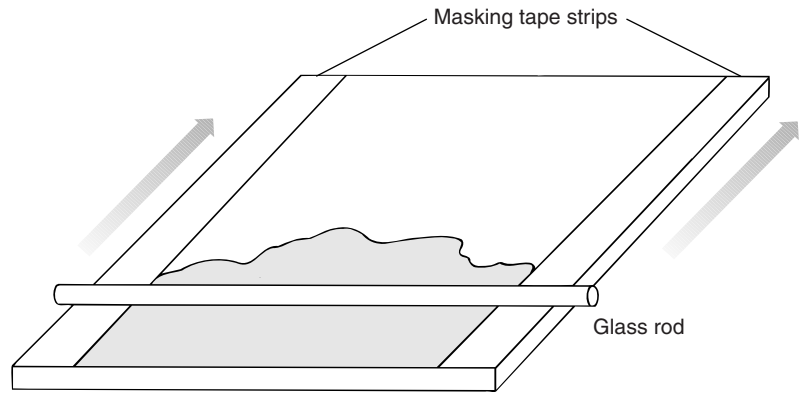


Figure 20.1 Preparing a large thin-layer chromatography plate.

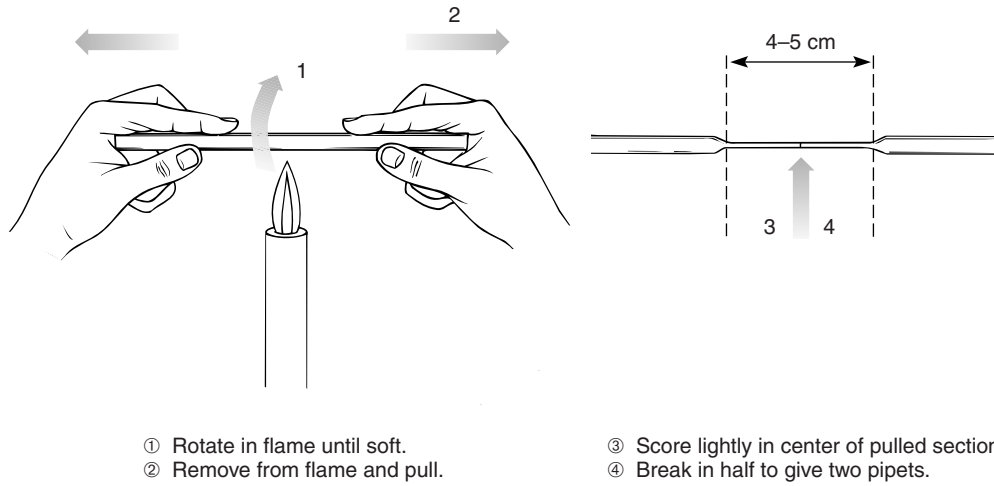


Figure 20.2 The construction of two capillary micropipets.

B. Spotting the Plate

To apply a sample to the plate, begin by placing about 1 mg of a solid test substance or 1 drop of a liquid test substance in a small container such as a watch glass or a test tube. Dissolve the sample in a few drops of a volatile solvent. Acetone or methylene chloride is usually a suitable solvent. If a solution is to be tested, it can often be used directly (undiluted).The small capillary pipet, prepared as described, is filled by dipping the pulled end into the solution to be examined. Capillary action fills the pipet. Empty the pipet by touching it lightly to the thin-layer plate at a point about 1 cm from the bottom (see Figure 20.3). The spot must be high enough so that it does not dissolve in the developing solvent. It is important to touch the plate very lightly and not to gouge a hole in the adsorbent. When the pipet touches the plate, the solution is transferred to the plate as a small spot. The pipet should be touched to the plate very briefly and then removed. If the pipet is held to the plate, its entire contents will be delivered to the plate. Only a small amount of material is needed. It is often helpful to blow gently on the plate as the sample is applied. This helps keep the spot small by evaporating the solvent before it can spread out on the plate. The smaller the spot formed, the better the separation obtainable. If needed, additional material can be applied to the plate by repeating the spotting procedure. You should repeat the procedure with several small amounts rather than apply one large amount. The solvent should be allowed to evaporate between applications. If the spot is not small (about 2 mm in diameter), a new plate should be prepared. The capillary pipet may be used several times if it is rinsed between uses. It is repeatedly dipped into a small portion of solvent to rinse it and touched to a paper towel to empty it.

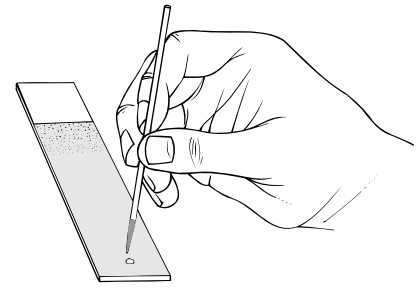


Figure 20.3 Spotting the thin-layer chromatography plate with a drawn capillary pipet.

As many as three different spots may be applied to a 1-inch-wide TLC plate. Each spot should be about 1 cm from the bottom of the plate, and all spots should be evenly spaced, with one spot in the center of the plate. Due to diffusion, spots often increase in diameter as the plate is developed. To keep spots containing different materials from merging and to avoid confusing the samples, do not place more than three spots on a single plate. Larger plates can accommodate many more samples.

20.5 Developing (Running) TLC Plates

A. Preparing a Development Chamber

A convenient development chamber for TLC plates can be made from a 4-oz wide-mouth jar. An alternative development chamber can be constructed from a beaker, using aluminum foil to cover the opening. The inside of the jar or beaker should be lined with a piece of filter paper, cut so that it does not quite extend around the inside of the jar. A small vertical opening (2–3 cm) should be left in the filter paper so the development can be observed. Before development, the filter paper inside the jar or beaker should be thoroughly moistened with the development solvent. The solvent-saturated liner helps to keep the chamber saturated with solvent vapors, thereby speeding the development. Once the liner is saturated, the level of solvent in the bottom of the development chamber is adjusted to a depth of about 5 mm, and the chamber is capped (or covered with aluminum foil) and set aside until it is to be used. A correctly prepared development chamber (with TLC plate in place) is shown in Figure 20.4.

B. Developing the TLC Plate

Once the spot has been applied to the thin-layer plate and the solvent has been selected (see Section 20.6), the plate is placed in the chamber for development. The plate must be placed in the chamber carefully so that no part of the plate touches the filter paper liner. In addition, the solvent level in the bottom of the chamber must not be above the spot that was applied to the plate, or the spotted material will dissolve in the pool of solvent instead of undergoing chromatography. Once the plate has been placed correctly, replace the cap on the developing chamber and wait for the solvent to advance up the plate by capillary action. This generally occurs rapidly, and you should watch carefully. As the solvent rises, the plate becomes visibly moist. When the solvent has advanced to within 5 mm of the end of the coated

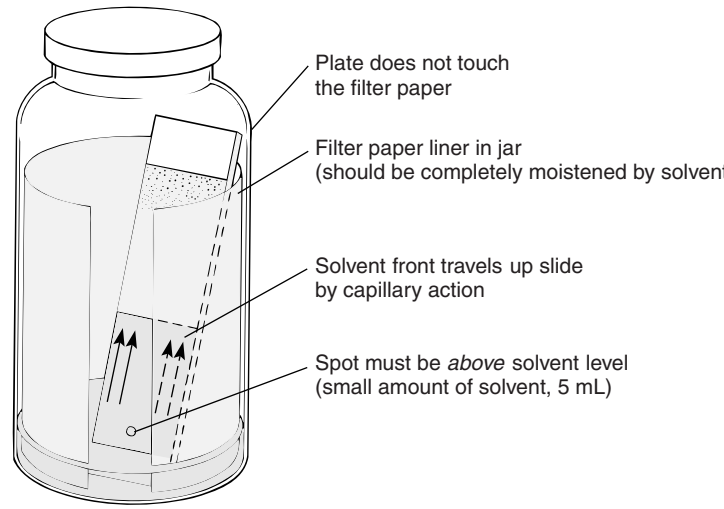


Figure 20.4 A development chamber with a thin-layer chromatography plate undergoing development.

surface, the plate should be removed and the position of the solvent front should be marked immediately by scoring the plate along the solvent line with a pencil. The solvent front must not be allowed to travel beyond the end of the coated surface. The plate should be removed before this happens. The solvent will not actually advance beyond the end of the plate, but spots allowed to stand on a completely moistened plate on which the solvent is not in motion expand by diffusion. Once the plate has dried, any visible spots should be outlined on the plate with a pencil. If no spots are apparent, a visualization method (see Section 20.7) may be needed.

20.6 Choosing A Solvent for Development

The development solvent used depends on the materials to be separated. You may have to try several solvents before a satisfactory separation is achieved. Because small TLC plates can be prepared and developed rapidly, an empirical choice is usually not hard to make. A solvent that causes all of the spotted material to move with the solvent front is too polar. One that does not cause any of the material in the spot to move is not polar enough. As a guide to the relative polarity of solvents, consult Table 19.2 in Technique 19.

Methylene chloride and toluene are solvents of intermediate polarity and good choices for a wide variety of functional groups to be separated. For hydrocarbon materials, good first choices are hexane, petroleum ether (ligroin), or toluene. Hexane or petroleum ether with varying proportions of toluene or ether gives solvent mixtures of moderate polarity that are useful for many common functional groups. Polar materials may require ethyl acetate, acetone, or methanol.

A rapid way to determine a good solvent is to apply several sample spots to a single plate. The spots should be placed a minimum of 1 cm apart. A capillary pipet is filled with a solvent and gently touched to one of the spots. The solvent expands outward in a circle. The solvent front should be marked with a pencil. A different solvent is applied to each spot. As the solvents expand outward, the spots expand as concentric rings. From the appearance of the rings, you can judge approximately the suitability of the solvent. Several types of behavior experienced with this method of testing are shown in Figure 20.5.

20.7 Visualization Methods

It is fortunate when the compounds separated by TLC are colored because the separation can be followed visually. More often than not, however, the compounds are colorless. In that case, some reagent or some method must be used to make the separated materials visible. Reagents that give rise to colored spots are called **visualization reagents**. Methods of viewing that make the spots apparent are **visualization methods**.

The most common method of visualization is by an ultraviolet (UV) lamp. Under UV light, compounds often look like bright spots on the plate. This often suggests the structure of the compound. Certain types of compounds shine very brightly under UV light because they fluoresce.

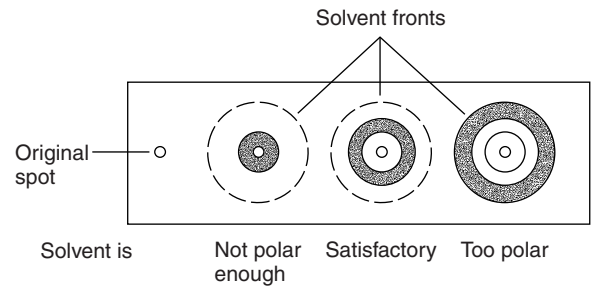


Figure 20.5 The concentric ring method of testing solvents.

Plates can be purchased with a fluorescent indicator added to the adsorbent. A mixture of zinc and cadmium sulfides is often used. When treated in this way and held under UV light, the entire plate fluoresces. However, dark spots appear on the plate where the separated compounds are seen to quench this fluorescence.

Iodine is also used to visualize plates. Iodine reacts with many organic materials to form complexes that are either brown or yellow. In this visualization method, the developed and dried TLC plate is placed in a 4-oz wide-mouth, screw-cap jar along with a few crystals of iodine. The jar is capped and gently warmed on a steam bath or a hot plate at low heat. The jar fills with iodine vapors, and the spots begin to appear. When the spots are sufficiently intense, the plate is removed from the jar and the spots are outlined with a pencil. The spots are not permanent. Their appearance results from the formation of complexes the iodine makes with the organic substances. As the iodine sublimes off the plate, the spots fade. Hence, they should be marked immediately. Nearly all compounds except saturated hydrocarbons and alkyl halides form complexes with iodine. The intensities of the spots do not accurately indicate the amount of material present, except in the crudest way.

In addition to the preceding methods, several chemical methods are available that either destroy or permanently alter the separated compounds through reaction. Many of these methods are specific for particular functional groups.

Alkyl halides can be visualized if a dilute solution of silver nitrate is sprayed on the plates. Silver halides are formed. These halides decompose if exposed to light, giving rise to dark spots (free silver) on the TLC plate.

Most organic functional groups can be made visible if they are charred with sulfuric acid. Concentrated sulfuric acid is sprayed on the plate, which is then heated in an oven at 110°C to complete the charring. Permanent spots are thus created.

Colored compounds can be prepared from colorless compounds by making derivatives before spotting them on the plate. An example of this is the preparation of 2,4-dinitrophenylhydrazones from aldehydes and ketones to produce yellow and orange compounds. You may also spray the 2,4-dinitrophenylhydrazine reagent on the plate after the ketones or aldehydes have separated. Red and yellow spots form where the compounds are located. Other examples of this method are the use of ferric chloride to visualize phenols and the use of bromocresol green to detect carboxylic acids. Chromium trioxide, potassium dichromate, and potassium permanganate can be used to visualize compounds that are easily oxidized. *p*-Dimethylaminobenzaldehyde easily detects amines. Ninhydrin reacts with amino acids to make them visible. Numerous other methods and reagents available from various supply outlets are specific for certain types of functional groups. These visualize only the class of compounds of interest.

20.8 Preparative Plates

If you use large plates (see Section 20.3), materials can be separated and the separated components can be recovered individually from the plates. Plates used in this way are called **preparative plates**. For preparative plates, a thick layer of adsorbent is generally used. Instead of being applied as a spot or a series of spots, the mixture to be separated is applied as a line of material about 1 cm from the bottom of the plate. As the plate is developed, the separated materials form bands. After development, you can observe the separated bands, usually by UV light, and outline the zones in pencil. If the method of visualization is destructive, most of the plate is

covered with paper to protect it, and the reagent is applied only at the extreme edge of the plate.

Once the zones have been identified, the adsorbent in those bands is scraped from the plate and extracted with solvent to remove the adsorbed material. Filtration removes the adsorbent, and evaporation of the solvent gives the recovered component from the mixture.

20.9 The R_f Value

Thin-layer chromatography conditions include:

1. Solvent system
2. Adsorbent
3. Thickness of the adsorbent layer
4. Relative amount of material spotted

Under an established set of such conditions, a given compound always travels a fixed distance relative to the distance the solvent front travels. This ratio of the distance the compound travels to the distance the solvent front travels is called the **R_f value**. The symbol R_f stands for "retardation factor," or "ratio to front," and it is expressed as a decimal fraction:

$$R_f = \frac{\text{distance traveled by substance}}{\text{distance traveled by solvent front}}$$

When the conditions of measurement are completely specified, the R_f value is constant for any given compound, and it corresponds to a physical property of that compound.

The R_f value can be used to identify an unknown compound, but like any other identification based on a single piece of data, the R_f value is best confirmed with some additional data. Many compounds can have the same R_f value, just as many compounds have the same melting point.

It is not always possible, in measuring an R_f value, to duplicate exactly the conditions of measurement another researcher has used. Therefore, R_f values tend to be of more use to a single researcher in one laboratory than they are to researchers in different laboratories. The only exception to this occurs when two researchers use TLC plates from the same source, as in commercial plates, or know the exact details of how the plates were prepared. Nevertheless, the R_f value can be a useful guide. If exact values cannot be relied on, the relative values can provide another researcher with useful information about what to expect. Anyone using published R_f values will find it a good idea to check them by comparing them with standard substances whose identity and R_f values are known.

To calculate the R_f value for a given compound, measure the distance that the compound has traveled from the point at which it was originally spotted. For spots that are not too large, measure to the center of the migrated spot. For large spots, the measurement should be repeated on a new plate, using less material. For spots that show tailing, the measurement is made to the "center of gravity" of the spot. This first distance measurement is then divided by the distance the solvent front has traveled from the same original spot. A sample calculation of the R_f values of two compounds is illustrated in Figure 20.6.

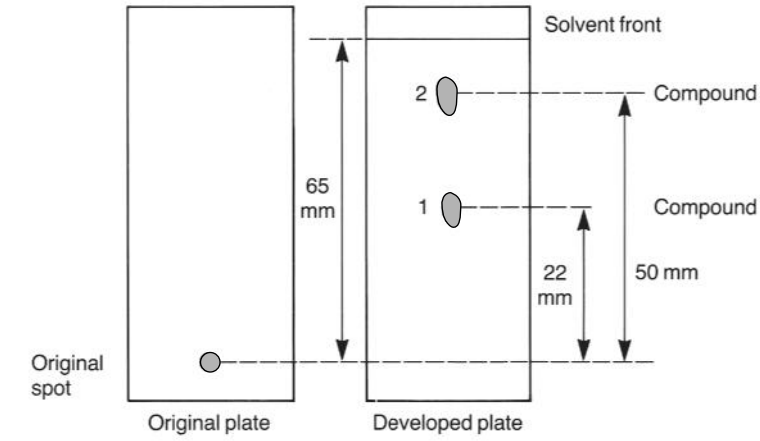


Figure 20.6 Sample calculation of R_f values.

20.10 Thin-Layer Chromatography Applied in Organic Chemistry

Thin-layer chromatography has several important uses in organic chemistry. It can be used in the following applications:

1. To establish that two compounds are identical
2. To determine the number of components in a mixture
3. To determine the appropriate solvent for a column-chromatographic separation
4. To monitor a column-chromatographic separation
5. To check the effectiveness of a separation achieved on a column, by crystallization or by extraction
6. To monitor the progress of a reaction

In all of these applications, TLC has the advantage that only small amounts of material are necessary. Material is not wasted. With many of the visualization methods, less than a tenth of a microgram (10^{-7} g) of material can be detected. On the other hand, samples as large as a milligram may be used. With preparative plates that are large (about 9 inches on a side) and have a relatively thick coating of adsorbent (>500 μm), it is often possible to separate from 0.2 g to 0.5 g of material at one time. The main disadvantage of TLC is that volatile materials cannot be used because they evaporate from the plates.

Thin-layer chromatography can establish that two compounds suspected to be identical are in fact identical. Simply spot both compounds side by side on a single plate and develop the plate. If both compounds travel the same distance on the plate (have the same R_f value), they are probably identical. If the spot positions are not the same, the compounds are definitely not identical. It is important to spot compounds *on the same plate.* This is especially important with slides and plates that you prepare yourself. Because plates vary widely from one sample to another, no two plates have exactly the same thickness of adsorbent. If you use commercial plates, this precaution is not necessary, although it is nevertheless strongly recommended.

Thin-layer chromatography can establish whether a sample is a single substance or a mixture. A single substance gives a single spot no matter which solvent is used to develop the plate. However, the number of components in a mixture can be established by trying various solvents on a mixture. A word of caution should be given.

It may be difficult, in dealing with compounds of very similar properties, such as isomers, to find a solvent that will separate the mixture. Inability to achieve a separation is not absolute proof that a sample is a single pure substance. Many compounds can be separated only by *multiple developments* of the TLC slide with a fairly nonpolar solvent. In this method, you remove the plate after the first development and allow it to dry. After being dried, it is placed in the chamber again and developed once more. This effectively doubles the length of the slide. At times, several developments may be necessary.

When a mixture is to be separated, you can use TLC to choose the best solvent to separate it if column chromatography is contemplated. You can try various solvents on a plate coated with the same adsorbent as will be used in the column. The solvent that resolves the components best will probably work well on the column. These small-scale experiments are quick, use very little material, and save time that would be wasted by attempting to separate the entire mixture on the column. Similarly, TLC plates can *monitor* a column. A hypothetical situation is shown in Figure 20.7. A solvent was found that would separate the mixture into four components (A–D). A column was run using this solvent, and 11 fractions of 15 mL each were collected. Thin-layer analysis of the various fractions showed that fractions 1–3 contained component A; fractions 4–7, component B; fractions 8–9, component C; and fractions 10–11, component D. A small amount of cross-contamination was observed in fractions 3, 4, 7, and 9.

In another TLC example, a researcher found a product from a reaction to be a mixture. It gave two spots, A and B, on a TLC plate. After the product was crystallized, the crystals were found by TLC to be pure A, whereas the mother liquor was found to have a mixture of A and B. The crystallization was judged to have purified A satisfactorily.

Finally, it is often possible to monitor the progress of a reaction by TLC. At various points during a reaction, samples of the reaction mixture are taken and subjected to TLC analysis. An example is given in Figure 20.8. In this case, the desired reaction was the conversion of A to B. At the beginning of the reaction (0 hour), a TLC plate was prepared that was spotted with pure A, pure B, and the reaction mixture. Similar plates were prepared at 0.5, 1, 2, and 3 hours after the start of the reaction. The plates showed that the reaction was complete in 2 hours. When the reaction was run longer than 2 hours, a new compound, side product C, began to appear. Thus, the optimum reaction time was judged to be 2 hours.

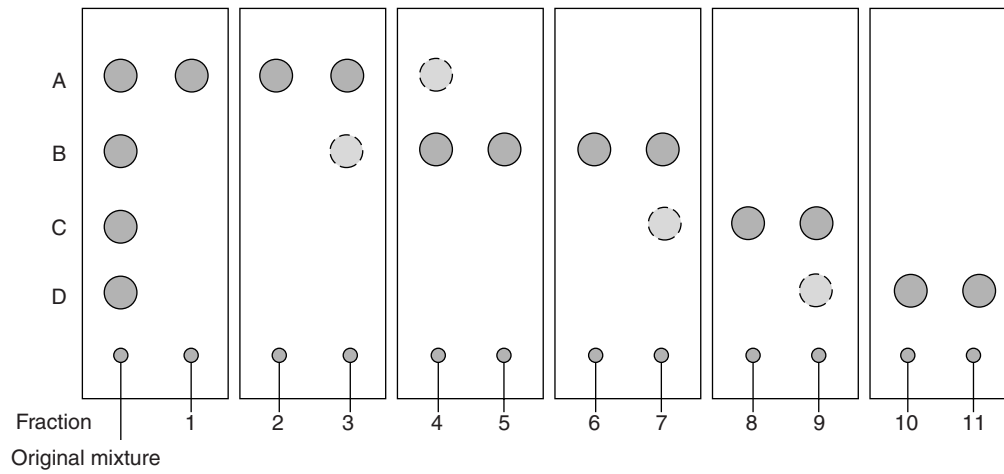


Figure 20.7 Monitoring column chromatography with TLC plates.

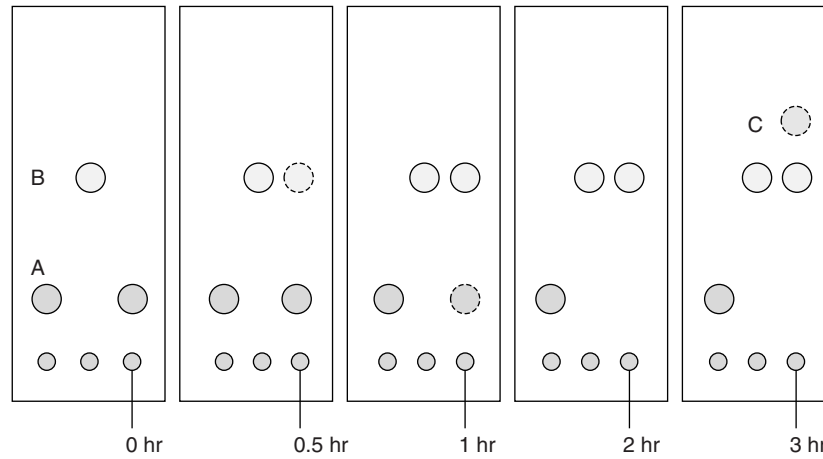


Figure 20.8 Monitoring a reaction with TLC plates.

20.11 Paper Chromatography

Paper chromatography is often considered to be related to thin-layer chromatography. The experimental techniques are somewhat like those of TLC, but the principles are more closely related to those of extraction. Paper chromatography is actually a liquid–liquid partitioning technique rather than a solid–liquid technique. For paper chromatography, a spot is placed near the bottom of a piece of high-grade filter paper (Whatman No. 1 is often used). Then the paper is placed in a developing chamber. The development solvent ascends the paper by capillary action and moves the components of the spotted mixture upward at differing rates. Although paper consists mainly of pure cellulose, the cellulose itself does not function as the stationary phase. Rather, the cellulose absorbs water from the atmosphere, especially from an atmosphere saturated with water vapor. Cellulose can absorb up to about 22% of water. It is this water adsorbed on the cellulose that functions as the stationary phase. To ensure that the cellulose is kept saturated with water, many development solvents used in paper chromatography contain water as a component. As the solvent ascends the paper, the compounds are partitioned between the stationary water phase and the moving solvent. Because the water phase is stationary, the components in a mixture that are most highly water soluble, or those that have the greatest hydrogen-bonding capacity, are the ones that are held back and move most slowly. Paper chromatography applies mostly to highly polar compounds or to compounds that are polyfunctional. The most common use of paper chromatography is for sugars, amino acids, and natural pigments. Because filter paper is manufactured consistently, R_f values can often be relied on in paper chromatographic work. However, R_f values are customarily measured from the leading edge (top) of the spot—not from its center, as is customary in TLC.

PROBLEMS

1. A student spots an unknown sample on a TLC plate and develops it in dichloromethane solvent. Only one spot, for which the R_f value is 0.95, is observed. Does this indicate that the unknown material is a pure compound? What can be done to verify the purity of the sample using thin-layer chromatography?
2. You and another student were each given an unknown compound. Both samples contained colorless material. You each used the same brand of commercially

prepared TLC plate and developed the plates using the same solvent. Each of you obtained a single spot of R_f = 0.75. Were the two samples necessarily the same substances? How could you prove unambiguously that they were identical using TLC?

3. Each of the solvents given should effectively separate one of the following mixtures by TLC. Match the appropriate solvent with the mixture that you would expect to separate well with that solvent. Select your solvent from the following: hexane, methylene chloride, or acetone. You may need to look up the structures of the solvents and compounds in a handbook.
   - **a.** 2-Phenylethanol and acetophenone
   - **b.** Bromobenzene and *p*-xylene
   - **c.** Benzoic acid, 2,4-dinitrobenzoic acid, and 2,4,6-trinitrobenzoic acid
4. Consider a sample that is a mixture composed of biphenyl, benzoic acid, and benzyl alcohol. The sample is spotted on a TLC plate and developed in a dichloromethane–cyclohexane solvent mixture. Predict the relative R_f values for the three components in the sample. (*Hint:* See Table 19.3.)
5. Consider the following errors that could be made when running TLC. Indicate what should be done to correct the error.
   - **a.** A two-component mixture containing 1-octene and 1,4-dimethylbenzene gave only one spot with an R_f value of 0.95. The solvent used was acetone.
   - **b.** A two-component mixture containing a dicarboxylic acid and a tricarboxylic acid gave only one spot with an R_f value of 0.05. The solvent used was hexane.
   - **c.** When a TLC plate was developed, the solvent front ran off the top of the plate.
6. Calculate the R_f value of a spot that travels 5.7 cm, with a solvent front that travels 13 cm.
7. A student spots an unknown sample on a TLC plate and develops it in pentane solvent. Only one spot, for which the R_f value is 0.05, is observed. Is the unknown material a pure compound? What can be done to verify the purity of the sample using thin-layer chromatography?
8. A colorless unknown substance is spotted on a TLC plate and developed in the correct solvent. The spots do not appear when visualization with a UV lamp or iodine vapors is attempted. What could you do to visualize the spots if the compound is the following?
   - **a.** An alkyl halide
   - **b.** A ketone
   - **c.** An amino acid
   - **d.** A sugar

21 TECHNIQUE 21

High-Performance Liquid Chromatography (HPLC)

The separation that can be achieved is greater if the column packing used in column chromatography is made denser by using an adsorbent that has a smaller particle size. The solute molecules encounter a much larger surface area on which they can be adsorbed as they pass through the column packing. At the same time, the solvent spaces between the particles are reduced in size. As a result of this tight packing,

equilibrium between the liquid and solid phases can be established very rapidly with a fairly short column, and the degree of separation is markedly improved. The disadvantage of making the column packing denser is that the solvent flow rate becomes very slow or even stops. Gravity is not strong enough to pull the solvent through a tightly packed column.

A recently developed technique can be applied to obtain much better separations with tightly packed columns. A pump forces the solvent through the column packing. As a result, solvent flow rate is increased, and the advantage of better separation is retained. This technique, called **high-performance liquid chromatography (HPLC)**, is becoming widely applied to problems in which separations by ordinary column chromatography are unsatisfactory. Because the pump often provides pressures in excess of 1000 pounds per square inch (psi), this method is also known as **high-pressure liquid chromatography**. High pressures are not required, however, and satisfactory separations can be achieved with pressures as low as 100 psi.

The basic design of an HPLC instrument is shown in Figure 21.1. The instrument contains the following essential components:

1. Solvent reservoir
2. Solvent filter and degasser
3. Pump
4. Pressure gauge

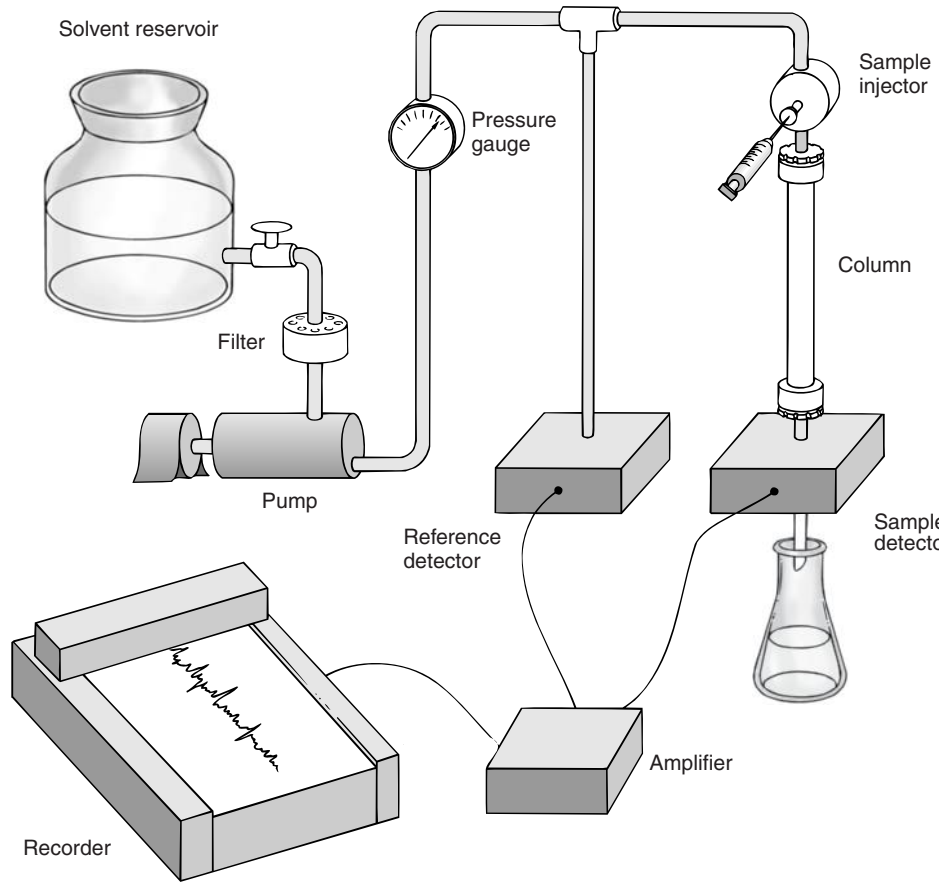


Figure 21.1 A schematic diagram of a high-performance liquid chromatograph.

5. Sample injection system
6. Column
7. Detector
8. Amplifier and electronic controls
9. Chart recorder

There may be other variations on this simple design. Some instruments have heated ovens to maintain the column at a specified temperature, fraction collectors, and microprocessor-controlled data-handling systems. Additional filters for the solvent and sample may also be included. You may find it interesting to compare this schematic diagram with Figure 22.2 in Technique 22 for a gas chromatography instrument. Many of the essential components are common to both types of instruments.

21.1 Adsorbents and Columns

The most important factor to consider when choosing a set of experimental conditions is the nature of the material packed into the column. You must also consider the size of the column that will be selected. The chromatography column is generally packed with silica or alumina adsorbents. However, the adsorbents used for HPLC have a much smaller particle size than those used in column chromatography. Typically, particle size ranges from 5 μm to 20 μm in diameter for HPLC and on the order of 100 μm for column chromatography.

The adsorbent is packed into a column that can withstand the elevated pressures typical of this type of experiment. Generally, the column is constructed of stainless steel, although some columns that are constructed of a rigid polymeric material ("PEEK"—Poly Ether Ether Ketone) are available commercially. A strong column is required to withstand the high pressures that may be used. The columns are fitted with stainless-steel connectors, which ensure a pressure-tight fit between the column and the tubing that connects the column to the other components of the instrument.

Columns that fulfill a large number of specialized purposes are available. Here, we consider only the four most important types of columns:

1. Normal-phase chromatography
2. Reversed-phase chromatography
3. Ion-exchange chromatography
4. Size-exclusion chromatography

In most types of chromatography, the adsorbent is more polar than the mobile phase. For example, the solid packing material, which may be either silica or alumina, has a stronger affinity for polar molecules than does the solvent. As a result, the molecules in the sample adhere strongly to the solid phase, and their progress down the column is much slower than the rate at which solvent moves through the column. The time required for a substance to move through the column can be altered by changing the polarity of the solvent. In general, as the solvent becomes more polar, the faster substances move through the column. This type of behavior is known as **normal-phase chromatography**. In HPLC, you inject a sample onto a normal-phase column and elute it by varying the polarity of the solvent, much as you do with ordinary column chromatography. Disadvantages of normal phase chromatography are that retention times tend to be long and bands have a tendency to "tail."

These disadvantages can be ameliorated by selecting a column in which the solid support is *less polar* than the moving solvent phase. This type of chromatography is known as **reversed-phase chromatography**. In this type of chromatography, the silica column packing is treated with alkylating agents. As a result, nonpolar

alkyl groups are bonded to the silica surface, making the adsorbent nonpolar. The alkylating agents that are used most commonly can attach methyl (—CH_3), octyl (—C_8H_{17}), or octadecyl (—$C_{18}H_{37}$) groups to the silica surface. The latter variation, in which an 18-carbon chain is attached to the silica, is the most popular. This type of column is known as a **C_{18} column**. The bonded alkyl groups have an effect similar to what would be produced by an extremely thin organic solvent layer coating the surface of the silica particles. The interactions that take place between the substances dissolved in the solvent and the stationary phase thus become more like those observed in a liquid–liquid extraction. The solute particles distribute themselves between the two "solvents"—that is, between the moving solvent and the organic coating on the silica. The longer the chains of the alkyl groups that are bonded to the silica, the more effective the alkyl groups are as they interact with solute molecules.

Reversed-phase chromatography is widely used because the rate at which solute molecules exchange between moving phase and stationary phase is very rapid, which means that substances pass through the column relatively quickly. Furthermore, problems arising from the "tailing" of peaks are reduced. A disadvantage of this type of column, however, is that the chemically bonded solid phases tend to decompose. The organic groups are slowly hydrolyzed from the surface of the silica, which leaves a normal silica surface exposed. Thus, the chromatographic process that takes place on the column slowly shifts from a reversed-phase to a normal-phase separation mechanism.

Another type of solid support that is sometimes used in reversed-phase chromatography is organic polymer beads. These beads present a surface to the moving phase that is largely organic in nature.

For solutions of ions, select a column that is packed with an ion-exchange resin. This type of chromatography is known as **ion-exchange chromatography**. The ion-exchange resin that is chosen can be either an anion-exchange resin or a cation-exchange resin, depending upon the nature of the sample being examined.

A fourth type of column is known as a **size-exclusion column** or a **gel-filtration column**. The interaction that takes place on this type of column is similar to that described in Technique 19, Section 19.16.

21.2 Column Dimensions

The dimensions of the column that you use depend upon the application. For analytical applications, a typical column is constructed of tubing that has an inside diameter of between 4 mm and 5 mm, although analytical columns with inside diameters of 1 mm or 2 mm are also available. A typical analytical column has a length of about 7.5 cm to 30 cm. This type of column is suitable for the separation of a 0.1-mg to 5-mg sample. With columns of smaller diameter, it is possible to perform an analysis with samples smaller than 1 *micro*gram.

High-performance liquid chromatography is an excellent analytical technique, but the separated compounds may also be isolated. The technique can be used for preparative experiments. Just as in column chromatography, the fractions can be collected into individual receiving containers as they pass through the column. The solvents can be evaporated from these fractions, allowing you to isolate separated components of the original mixture. Samples that range in size from 5 mg to 100 mg can be separated on a semipreparative, or **semiprep column**. The dimensions of a semiprep column are typically 8 mm inside diameter and 10 cm in length. A semiprep column is a practical choice when you wish to use the same column for both analytical and preparative separations. A semiprep column is small enough to provide reasonable sensitivity in analyses, but it is also capable of handling moderate-sized samples when you need to isolate the components of a mixture. Even larger samples

can be separated using a **preparative column**. This type of column is useful when you wish to collect the components of a mixture and then use the pure samples for additional study (for example, for a subsequent chemical reaction or for spectroscopic analysis). A preparative column may be as large as 20 mm inside diameter and 30 cm in length. A preparative column can handle samples as large as 1 g per injection.

21.3 Solvents

The choice of solvent used for an HPLC separation depends on the type of chromatographic process selected. For a normal-phase separation, the solvent is selected based on its polarity. The criteria described in Technique 19, Section 19.4B, are used. A solvent of very low polarity might be pentane, petroleum ether, hexane, or carbon tetrachloride; a solvent of very high polarity might be water, acetic acid, methanol, or 1-propanol.

For a reversed-phase experiment, a less polar solvent causes solutes to migrate *faster.* For example, for a mixed methanol–water solvent, as the percentage of methanol in the solvent increases (solvent becomes less polar), the time required to elute the components of a mixture from a column decreases. The behavior of solvents as eluents in a reversed-phase chromatography would be the reverse of the order shown in Table 19.2 in Technique 19, Section 19.4B.

If a single solvent (or solvent mixture) is used for the entire separation, the chromatogram is said to be **isochratic**. Special electronic devices are available with HPLC instruments that allow you to program changes in the solvent composition from the beginning to the end of the chromatography. These are called **gradient elution systems**. With gradient elution, the time required for a separation may be shortened considerably.

The need for pure solvents is especially acute with HPLC. The narrow bore of the column and the very small particle size of the column packing require that solvents be particularly pure and free of insoluble residue. In most cases, the solvents must be filtered through ultrafine filters and **degassed** (have dissolved gases removed) before they can be used.

The solvent gradient is chosen so that the eluting power of the solvent increases over the duration of the experiment. The result is that components of the mixture that tend to move very slowly through the column are caused to move faster as the eluting power of the solvent gradually increases. The instrument can be programmed to change the composition of the solvent following a linear gradient or a nonlinear gradient, depending on the specific requirements of the separation.

21.4 Detectors

A flow-through **detector** must be provided to determine when a substance has passed through the column. In most applications, the detector detects either the change in index of refraction of the liquid as its composition changes or the presence of solute by its absorption of ultraviolet or visible light. The signal generated by the detector is amplified and treated electronically in a manner similar to that found in gas chromatography (see Technique 22, Section 22.6).

A detector that responds to changes in the index of refraction of the solution may be considered the most universal of the HPLC detectors. The refractive index of the liquid passing through the detector changes slightly, but significantly, as the liquid changes from pure solvent to a liquid where the solvent contains some type of organic solute. This change in refractive index can be detected and compared to the refractive index of pure solvent. The difference in index values is then recorded as a peak on a chart. A disadvantage of this type of detector is that it must respond to very small changes in refractive index. As a result, the detector tends to be unstable and difficult to balance.

When the components of the mixture have some type of absorption in the ultraviolet or visible regions of the spectrum, a detector that is adjusted to detect absorption at a particular wavelength of light can be used. This type of detector is much more stable, and the readings tend to be more reliable. Unfortunately, many organic compounds do not absorb ultraviolet light, and this type of detector cannot be used.

21.5 Presentation of Data

The data produced by an HPLC instrument appear in the form of a chart, where detector response is the vertical axis and time is represented on the horizontal axis. These are recorded on a continuously moving strip of chart paper, although they may also be observed in graphic form on a computer display. In virtually all respects, the form of the data is identical to that produced by a gas chromatograph; in fact, in many cases, the data-handling system for the two types of instruments is essentially identical. To understand how to analyze the data from an HPLC instrument, read Sections 22.11 and 22.12 in Technique 22.

REFERENCES

Bidlingmeyer, B. A. *Practical HPLC Methodology and Applications*, New York: Wiley, 1992.

Katz, E., editor. *Handbook of HPLC.* Volume 78 in Chromatographic Science Series, New York: M. Dekker, 1998.

Lough, W. J., and Wainer, I. W., editors. *High Performance Liquid Chromatography: Fundamental Principles and Practice.* London and New York: Blackie Academic & Professional, 1996.

Rubinson, K. A. "Liquid Chromatography." Chap. 14 in *Chemical Analysis.* Boston: Little, Brown and Co., 1987.

PROBLEMS

1. For a mixture of biphenyl, benzoic acid, and benzyl alcohol, predict the order of elution and describe any differences that you would expect for a normal-phase HPLC experiment (in hexane solvent) compared with a reversed-phase experiment (in tetrahydrofuran–water solvent).
2. How would the gradient elution program differ between normal-phase and reversed-phase chromatography?

22 TECHNIQUE 22

Gas Chromatography

Gas chromatography is one of the most useful instrumental tools for separating and analyzing organic compounds that can be vaporized without decomposition. Common uses include testing the purity of a substance and separating the components of a mixture. The relative amounts of the components in a mixture may also be determined. In some cases, gas chromatography can be used to identify a compound. In microscale work, it can also be used as a preparative method to isolate pure compounds from a small amount of a mixture.

Gas chromatography resembles column chromatography in principle, but it differs in three respects. First, the partitioning processes for the compounds to be separated are carried out between a **moving gas phase** and a **stationary liquid phase**. (Recall that in column chromatography, the moving phase is a liquid, and the stationary phase is a solid adsorbent.) Second, the temperature of the gas system can be controlled, because the column is contained in an insulated oven. And third, the concentration of any given compound in the gas phase is a function of its vapor pressure only. Because gas chromatography separates the components of a mixture primarily on the basis of their vapor pressures (or boiling points), this technique is also similar in principle to fractional distillation. In microscale work, it is sometimes used to separate and isolate compounds from a mixture; fractional distillation would normally be used with larger amounts of material.

Gas chromatography (GC) is also known as vapor-phase chromatography (VPC) and as gas–liquid partition chromatography (GLPC). All three names, as well as their indicated abbreviations, are often found in the literature of organic chemistry. In reference to the technique, the last term, GLPC, is the most strictly correct and is preferred by most authors.

22.1 The Gas Chromatograph

The apparatus used to carry out a gas–liquid chromatographic separation is generally called a **gas chromatograph**. A typical student-model gas chromatograph, the GOW-MAC model 69-350, is illustrated in Figure 22.1. A schematic block diagram of a basic gas chromatograph is shown in Figure 22.2. The basic elements of the apparatus are apparent. The sample is injected into the chromatograph, and it is immediately vaporized in a heated injection chamber and introduced into a moving stream of gas, called the **carrier gas**. The vaporized sample is then swept into a column filled with particles coated with a liquid adsorbent. The column is contained in a

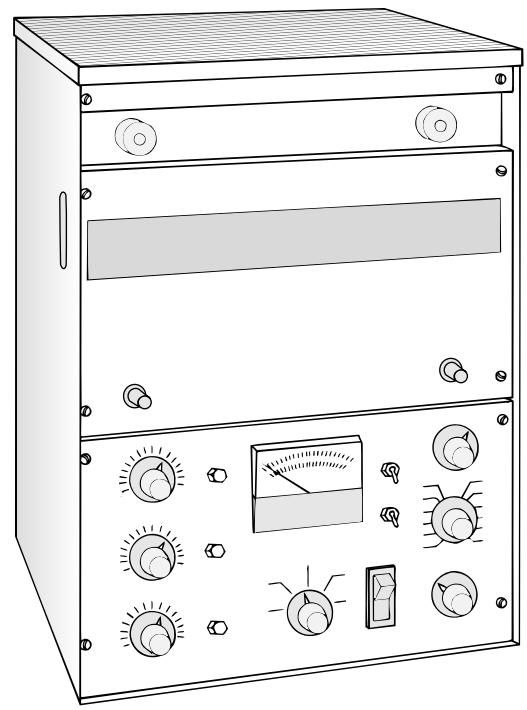


Figure 22.1 A gas chromatograph.

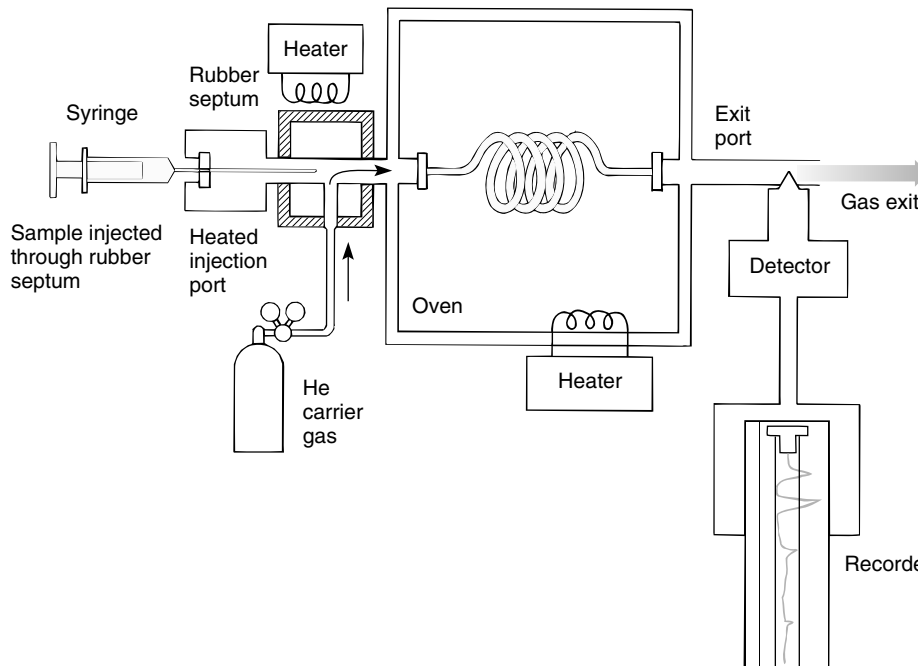


Figure 22.2 A schematic diagram of a gas chromatograph.

temperature-controlled oven. As the sample passes through the column, it is subjected to many gas–liquid partitioning processes, and the components are separated. As each component leaves the column, its presence is detected by an electrical detector that generates a signal that is recorded on a strip chart recorder.

Many modern instruments are also equipped with a microprocessor, which can be programmed to change parameters, such as the temperature of the oven, while a mixture is being separated on a column. With this capability, it is possible to optimize the separation of components and to complete a run in a relatively short time.

22.2 The Column

The heart of the gas chromatograph is the packed column. This column is usually made of copper or stainless steel tubing, but sometimes glass is used. The most common diameters of tubing are $\frac{1}{8}$ inch (3 mm) and $\frac{1}{4}$ inch (6 mm). To construct a column, cut a piece of tubing to the desired length and attach the proper fittings on each of the two ends to connect to the apparatus. The most common length is 4–12 feet, but some columns may be up to 50 feet in length.

The tubing (column) is then packed with the **stationary phase**. The material chosen for the stationary phase is usually a liquid, a wax, or a low-melting solid. This material should be relatively nonvolatile; that is, it should have a low vapor pressure and a high boiling point. Liquids commonly used are high-boiling hydrocarbons, silicone oils, waxes, and polymeric esters, ethers, and amides. Some typical substances are listed in Table 22.1.

The liquid phase is usually coated onto a **support material**. A common support material is crushed firebrick. Many methods exist for coating the high-boiling liquid phase onto the support particles. The easiest is to dissolve the liquid (or low-melting wax or solid) in a volatile solvent such as methylene chloride (bp 40°C). The firebrick (or other support) is added to this solution, which is then slowly evaporated (rotary evaporator) so as to leave each particle of support material evenly coated. Other support materials are listed in Table 22.2.

TABLE 22.1 Typical Liquid Phases

		Type	Composition	Maximum Temperature (°C)	Typical Use
Increasing polarity	Apiezons (L, M, N, etc.)	Hydrocarbon greases (varying MW)	Hydrocarbon mixtures	250–300	Hydrocarbons
	SE-30	Methyl silicone rubber	Like silicone oil, but cross-linked	350	General applications
	DC-200	Silicone oil (R = CH_3)	$R_3Si-O-\left[\begin{matrix}R\\|\\Si-O\\|\\R\end{matrix}\right]_n-SiR_3$	225	Aldehydes, ketones, halocarbons
	DC-710	Silicone oil (R = CH_3) (R′ = C_6H_5)	$\left[\begin{matrix}R'\\|\\Si-O\\|\\R\end{matrix}\right]_n$	300	General applications
	Carbowaxes (400–20M)	Polyethylene glycols (varying chain lengths)	Polyether $HO-(CH_2CH_2-O)n-CH_2CH_2OH$	Up to 250	Alcohols, ethers, halocarbons
	DEGS	Diethylene glycol succinate	Polyester $\left(-CH_2CH_2-O-\overset{\overset{O}{\|}}{C}-(CH_2)_2-\overset{\overset{C}{\|}}{C}-O-\right)_n$	200	General applications

TABLE 22.2 Typical Solid Supports

Crushed firebrick	Chromosorb T (Teflon beads)
Nylon beads	Chromosorb P (pink diatomaceous earth, high absorptivity, pH 6–7)
Glass beads	Chromosorb W (white diatomaceous earth, medium absorptivity, pH 8–10)
Silica	Chromosorb G (like the above, low absorptivity, pH 8.5)
Alumina	
Charcoal	
Molecular sieves	

In the final step, the liquid-phase-coated support material is packed into the tubing as evenly as possible. The tubing is bent or coiled so that it fits into the oven of the gas chromatograph with its two ends connected to the gas entrance and exit ports.

Selection of a liquid phase usually revolves around two factors. First, most liquid phases have an upper temperature limit above which they cannot be used. Above the specified limit of temperature, the liquid phase itself will begin to "bleed" off the column. Second, the materials to be separated must be considered. For polar samples, it is usually best to use a polar liquid phase; for nonpolar samples, a nonpolar liquid phase is indicated. The liquid phase performs best when the substances to be separated *dissolve* in it.

Most researchers today buy packed columns from commercial sources rather than pack their own. A wide variety of types and lengths is available.

Alternatives to packed columns are Golay or glass capillary columns of diameters 0.1–0.2 mm. With these columns, no solid support is required, and the liquid is coated directly on the inner walls of the tubing. Liquid phases commonly used in glass capillary columns are similar in composition to those used in packed columns. They include DB-1 (similar to SE-30), DB-17 (similar to DC-710), and DB-WAX (similar to Carbowax 20M). The length of a capillary column is usually very long, typically 50–100 feet. Because of the length and small diameter, there is increased interaction between the sample and the stationary phase. Gas chromatographs equipped with these small-diameter columns are able to separate components more effectively than instruments using larger packed columns.

22.3 Principles of Separation

After a column is selected, packed, and installed, the **carrier gas** (usually helium, argon, or nitrogen) is allowed to flow through the column supporting the liquid phase. The mixture of compounds to be separated is introduced into the carrier gas stream, where its components are equilibrated (or partitioned) between the moving gas phase and the stationary liquid phase (see Figure 22.3). The latter is held stationary because it is adsorbed onto the surfaces of the support material.

The sample is introduced into the gas chromatograph by a microliter syringe. It is injected as a liquid or as a solution through a rubber septum into a heated chamber, called the **injection port**, where it is vaporized and mixed with the carrier gas.

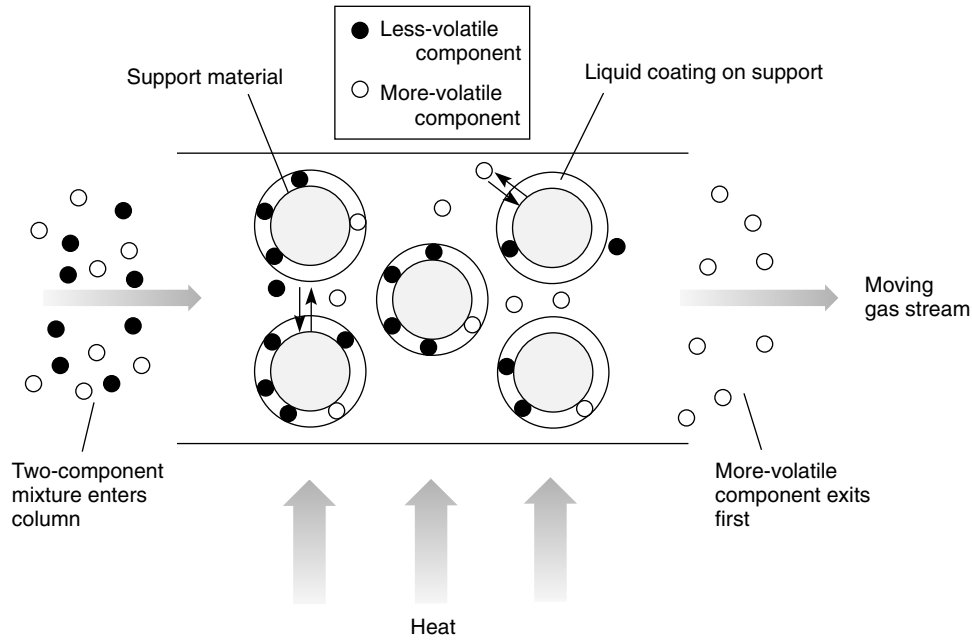


Figure 22.3 The separation process.

As this mixture reaches the column, which is heated in a controlled oven, it begins to equilibrate between the liquid and gas phases. The length of time required for a sample to move through the column is a function of how much time the sample spends in the vapor phase and how much time it spends in the liquid phase. The more time the sample spends in the vapor phase, the faster it gets to the end of the column. In most separations, the components of a sample have similar solubilities in the liquid phase. Therefore, the time the different compounds spend in the vapor phase is primarily a function of the vapor pressure of the compounds, and the more-volatile component arrives at the end of the column first, as illustrated in Figure 22.3. When the correct temperature of the oven and the correct liquid phase have been selected, the compounds in the injected mixture travel through the column at different rates and are separated.

22.4 Factors Affecting Separation

Several factors determine the rate at which a given compound travels through a gas chromatograph. First, compounds with low boiling points will generally travel through the gas chromatograph faster than compounds with higher boiling points. The reason is that the column is heated, and low-boiling compounds always have higher vapor pressures than higher-boiling compounds. In general, therefore, for compounds with the same functional group, the higher the molecular weight, the longer the retention time. For most molecules, the boiling point increases as the molecular weight increases. If the column is heated to a temperature that is too high, however, the entire mixture to be separated is flushed through the column at the same rate as the carrier gas, and no equilibration takes place with the liquid phase. On the other hand, at too low a temperature, the mixture dissolves in the liquid phase and never revaporizes. Thus, it is retained on the column.

The second factor is the rate of flow of the carrier gas. The carrier gas must not move so rapidly that molecules of the sample in the vapor phase cannot equilibrate with those dissolved in the liquid phase. This may result in poor separation between components in the injected mixture. If the rate of flow is too slow, however, the bands broaden significantly, leading to poor resolution (see Section 22.8).

The third factor is the choice of liquid phase used in the column. The molecular weights, functional groups, and polarities of the component molecules in the mixture to be separated must be considered when a liquid phase is being chosen. A different type of material is generally used for hydrocarbons, for instance, than for esters. The materials to be separated should dissolve in the liquid. The useful temperature limit of the liquid phase selected must also be considered.

The fourth factor is the length of the column. Compounds that resemble one another closely, in general, require longer columns than dissimilar compounds. Many kinds of isomeric mixtures fit into the "difficult" category. The components of isomeric mixtures are so much alike that they travel through the column at very similar rates. You need a longer column, therefore, to take advantage of any differences that may exist.

22.5 Advantages of Gas Chromatography

All factors that have been mentioned must be adjusted by the chemist for any mixture to be separated. Considerable preliminary investigation is often required before a mixture can be separated successfully into its components by gas chromatography. Nevertheless, the advantages of the technique are many.

First, many mixtures can be separated by this technique when no other method is adequate. Second, as little as 1–10 μL (1 μL = 10^{-6} L) of a mixture can be separated by this technique. This advantage is particularly important when working at the microscale level. Third, when gas chromatography is coupled with an electronic

recording device (see the following discussion), the amount of each component present in the separated mixture can be estimated quantitatively.

The range of compounds that can be separated by gas chromatography extends from gases, such as oxygen (bp –183°C) and nitrogen (bp –196°C), to organic compounds with boiling points over 400°C. The only requirement for the compounds to be separated is that they have an appreciable vapor pressure at a temperature at which they can be separated and that they be thermally stable at this temperature.

22.6 Monitoring The Column (The Detector)

To follow the separation of the mixture injected into the gas chromatograph, it is necessary to use an electrical device called a **detector**. Two types of detectors in common use are the **thermal conductivity detector (TCD)** and the **flame-ionization detector (FID)**.

The thermal conductivity detector is simply a hot wire placed in the gas stream at the column exit. The wire is heated by constant electrical voltage. When a steady stream of carrier gas passes over this wire, the rate at which it loses heat and its electrical conductance have constant values. When the composition of the vapor stream changes, the rate of heat flow from the wire, and hence its resistance, changes. Helium, which has a thermal conductivity higher than that of most organic substances, is a common carrier gas. Thus, when a substance elutes in the vapor stream, the thermal conductivity of the moving gases will be lower than with helium alone. The wire then heats up, and its resistance decreases.

A typical TCD operates by difference. Two detectors are used: one exposed to the actual effluent gas and the other exposed to a reference flow of carrier gas only. To achieve this situation, a portion of the carrier gas stream is diverted before it enters the injection port. The diverted gas is routed through a reference column into which no sample has been admitted. The detectors mounted in the sample and reference columns are arranged to form the arms of a Wheatstone bridge circuit, as shown in Figure 22.4. As long as the carrier gas alone flows over both detectors, the circuit is in balance. However, when a sample elutes from the sample column, the bridge circuit becomes unbalanced, creating an electrical signal. This signal can be amplified and used to activate a strip chart recorder. The recorder is an instrument that plots, by means of a moving pen, the unbalanced bridge current versus time on a

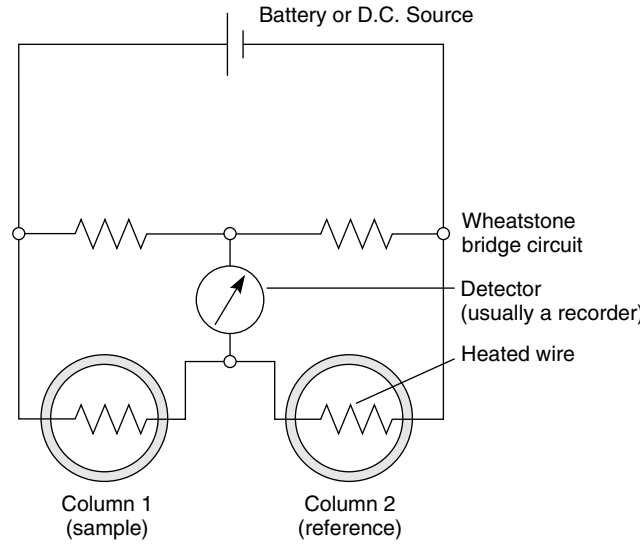


Figure 22.4 A typical thermal conductivity detector.

continuously moving roll of chart paper. This record of detector response (current) versus time is called a **chromatogram**. A typical gas chromatogram is illustrated in Figure 22.5. Deflections of the pen are called **peaks**.

When a sample is injected, some air (CO_2, H_2O, N_2, and O_2) is introduced along with the sample. The air travels through the column almost as rapidly as the carrier gas; as air passes the detector, it causes a small pen response, thereby giving a peak, called the **air peak**. At later times (t_1, t_2, t_3), the components also give rise to peaks on the chromatogram as they pass out of the column and past the detector.

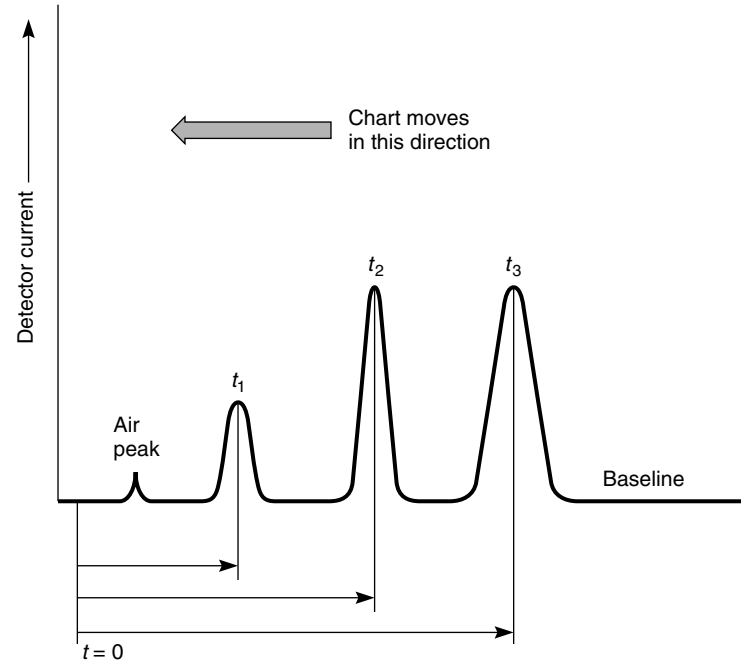


Figure 22.5 A typical gas chromatograph.

In a flame-ionization detector, the effluent from the column is directed into a flame produced by the combustion of hydrogen, as illustrated in Figure 22.6. As organic compounds burn in the flame, ion fragments are produced and collect on the ring above the flame. The resulting electrical signal is amplified and sent to a recorder in a manner similar to that for a TCD, except that an FID does not produce an air peak. The main advantage of the FID is that it is more sensitive and can be used to analyze smaller quantities of sample. Also, because an FID does not respond to water, a gas chromatograph with this detector can be used to analyze aqueous solutions. Two disadvantages are that it is more difficult to operate and the detection process destroys the sample. Therefore, an FID gas chromatograph cannot be used to do preparative work.

22.7 Retention Time

The period following injection that is required for a compound to pass through the column is called the **retention time** of that compound. For a given set of constant conditions (flow rate of carrier gas, column temperature, column length, liquid phase, injection port temperature, carrier), the retention time of any compound is always constant (much like the R_f value in thin-layer chromatography, as described in Technique 20, Section 20.9). The retention time is measured from the time of injection to the time of maximum pen deflection (detector current) for the component being

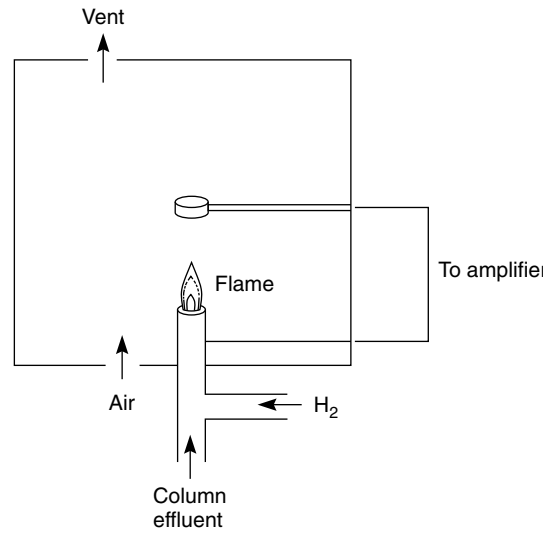


Figure 22.6 A flame-ionization detector.

observed. This value, when obtained under controlled conditions, can identify a compound by a direct comparison of it with values for known compounds determined under the same conditions. For easier measurement of retention times, most strip chart recorders are adjusted to move the paper at a rate that corresponds to time divisions calibrated on the chart paper. The retention times (t_1, t_2, t_3) are indicated in Figure 22.5 for the three peaks illustrated.

Most modern gas chromatographs are attached to a "data station," which uses a computer or a microprocessor to process the data. With these instruments, the chart often does not have divisions. Instead, the computer prints the retention time, usually to the nearest 0.01 minute, above each peak. A more complete discussion of the results obtained from a modern data station and how these data are treated may be found in Section 22.13.

22.8 Chiral Stationary Phases

A recent innovation in gas chromatography is to use chiral adsorbent materials to achieve separations of stereoisomers. The interaction between a particular stereoisomers and the chiral adsorbent may be different from the interaction between the opposite stereoisomer and the same chiral adsorbent. As a result, retention times for the two stereoisomers are likely to be sufficiently different to allow for a clean separation. The interactions between a chiral substance and the chiral adsorbent will include hydrogen-bonding and dipole-dipole attraction forces, although other properties may also be involved. One enantiomer should interact more strongly with the adsorbent than its opposite form. Thus, one enantiomer should pass through the gas chromatography column more slowly than its opposite form.

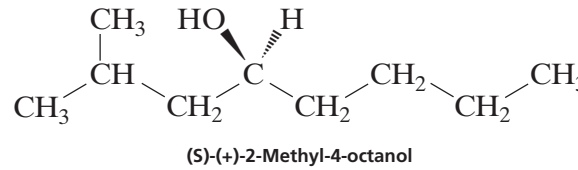
The ability of chiral adsorbents to separate stereoisomers is rapidly finding many useful applications, particularly in the synthesis of pharmaceutical agents. The biological activity of chiral substances often depends upon their stereochemistry because the living body is a highly chiral environment. A large number of pharmaceutical compounds have two enantiomeric forms that in many cases show significant differences in their behavior and activity. The ability to prepare enantiomerically pure drugs is very important because these pure substances are much more potent (and often have fewer side effects) than their racemic analogues.

Another type of stationary phase in gas chromatography is based on molecules such as the **cyclodextrins**. With these materials, the discrimination between enantiomers depends on the interactions between the stereoisomers and the chiral cavity that

is formed within these materials. Because enantiomers differ in shape, they will fit differently within the chiral cavity. The result will be that the enantiomers will pass through the cyclodextrin stationary phase at different rates, thus leading to a separation.

The cyclodextrins owe their specificity to their structure, which is based on polymers of D-(+)- glucose. The hydroxyl groups of the glucose have been alkylated, so that the cavity is relatively nonpolar. The exterior hydroxyl groups of the cyclodextrins have also been substituted with *tert*-butyldimethylsilyl groups. The result is a material that can also utilize differences in hydrogen-bonding and dipole-dipole interactions to separate stereoisomers.

The structure of one important cyclodextrin-based chiral adsorbent is shown in Figure 22.7. Gas chromatography using this chiral adsorbent as a stationary phase has been used to separate a wide variety of stereoisomers. In one recent publication, this method was used to isolate a pure sample of (S)-(+)-2-methyl-4-octanol, a male-specific compound released by the sugarcane weevil, *Sphenophorus levis.*[1]



(S)-(+)-2-Methyl-4-octanol

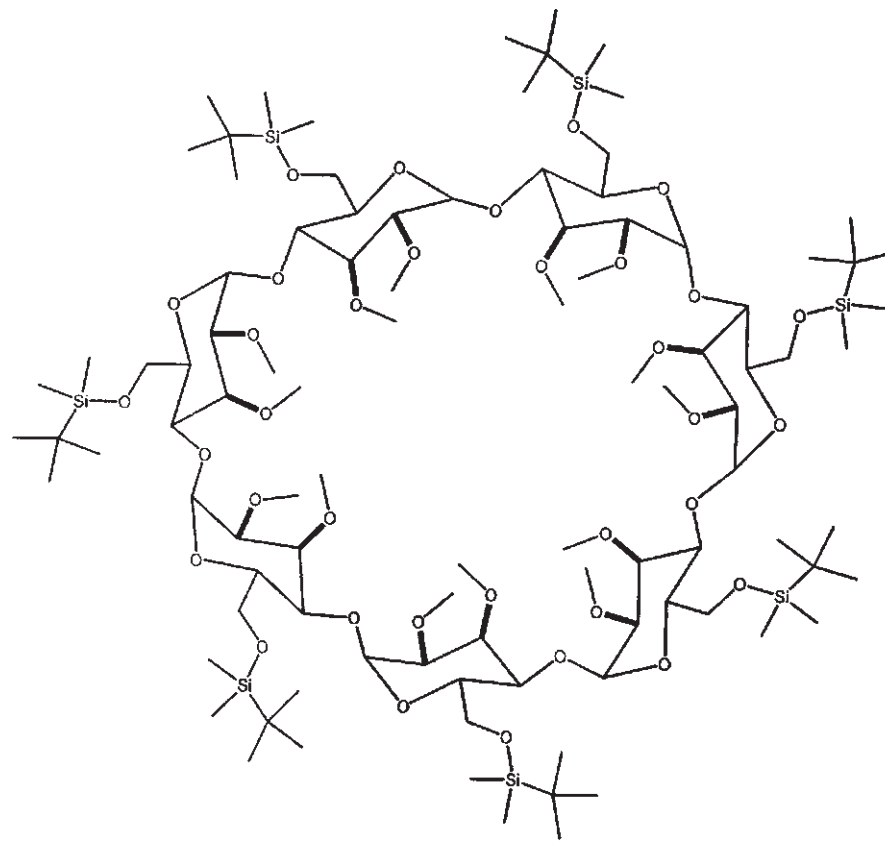


Figure 22.7 Cyclodextrin derivative used as a chiral adsorbent in gas chromatography.

[1]Zarbin, P. H. G., Princival, J. L., dos Santos, A. A., and de Oliveira, A. R. M. "Synthesis of (S)-()-2-Methyl-4-octanol: Male-Specific Compound Released by Sugarcane Weevil *Sphenophorus levis.*" *Journal of the Brazilian Chemical Society*, *15* (2004): 331–334.

22.9 Poor Resolution and Tailing

The peaks in Figure 22.5 are well **resolved**. That is, the peaks are separated from one another, and between each pair of adjacent peaks the tracing returns to the baseline. In Figure 22.8, the peaks overlap and the resolution is not good. Poor resolution is often caused by using too much sample; by a column that is too short, has too high a temperature, or has too large a diameter; by a liquid phase that does not discriminate well between the two components; or, in short, by almost any wrongly adjusted parameter. When peaks are poorly resolved, it is more difficult to determine the relative amount of each component. Methods for determining the relative percentages of each component are given in Section 22.12.

Another desirable feature illustrated by the chromatogram in Figure 22.5 is that each peak is symmetrical. A common example of an unsymmetrical peak is one in which **tailing** has occurred, as shown in Figure 22.9. Tailing usually results from injecting too much sample into the gas chromatograph. Another cause of tailing occurs with polar compounds, such as alcohols and aldehydes. These compounds may be temporarily adsorbed on column walls or areas of the support material that are not adequately coated by the liquid phase. Therefore, they do not leave in a band, and tailing results.

22.10 Qualitative Analysis

A disadvantage of the gas chromatograph is that it gives no information about the identities of the substances it has separated. The little information it does provide is given by the retention time. It is hard to reproduce this quantity from day to day, however, and exact duplications of separations performed last month may be difficult to make this month. It is usually necessary to **calibrate** the column each time it is used. That is, you must run pure samples of all known and suspected components of a mixture individually, just before chromatographing the mixture, to obtain the retention time of each known compound. As an alternative, each suspected

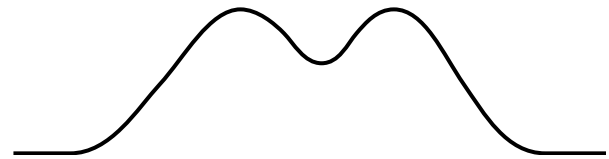


Figure 22.8 Poor resolution, or peaks overlap.

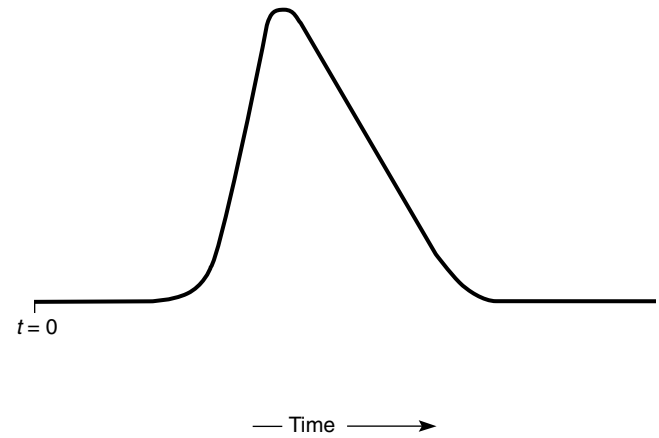


Figure 22.9 Tailing.

component can be added, one by one, to the unknown mixture while the operator looks to see which peak has its intensity increased relative to the unmodified mixture. Another solution is to collect the components individually as they emerge from the gas chromatograph. Each component can then be identified by other means, such as by infrared or nuclear magnetic resonance spectroscopy or by mass spectrometry.

22.11 Collecting the Sample

For gas chromatographs with a thermal conductivity detector, it is possible to collect samples that have passed through the column. One method uses a gas collection tube (see Figure 22.10), which is included in most microscale glassware kits. A collection tube is joined to the exit port of the column by inserting the 5/5 inner joint into a metal adapter, which is connected to the exit port. When a sample is eluted from the column in the vapor state, it is cooled by the connecting adapter and the gas collection tube and condenses in the collection tube. The gas collection tube is removed from the adapter when the recorder indicates that the desired sample has completely passed through the column. After the first sample has been collected, the process can be repeated with another gas collection tube.

To isolate the liquid, insert the tapered joint of the collection tube into a 0.1-mL conical vial, which has a 5/5 outer joint. Place the assembly into a test tube, as illustrated in Figure 22.11. During centrifugation, the sample is forced into the bottom of the conical vial. After disassembling the apparatus, the liquid can be removed from the vial with a syringe for a boiling-point determination or analysis by infrared spectroscopy. If a determination of the sample weight is desired, the empty conical vial and cap should be tared and reweighed after the liquid has been collected. It is advisable to dry the gas collection tube and the conical vial in an oven before use to prevent contamination by water or other solvents used in cleaning this glassware.

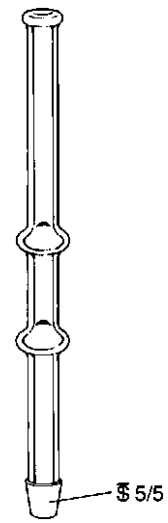


Figure 22.10 A gas chromatography collection tube.

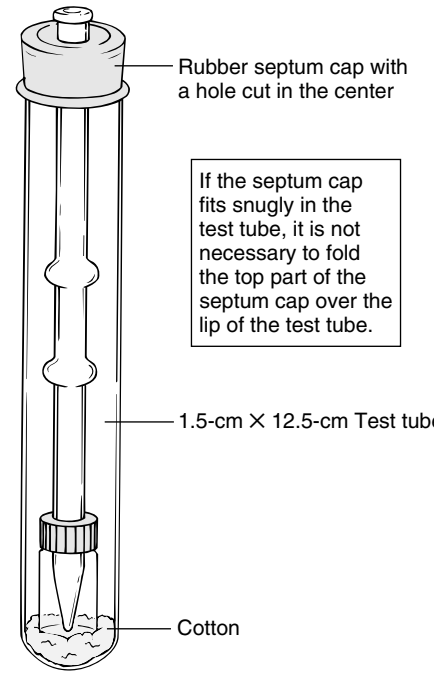


Figure 22.11 A gas chromatography collection tube and a 0.1-mL conical vial.

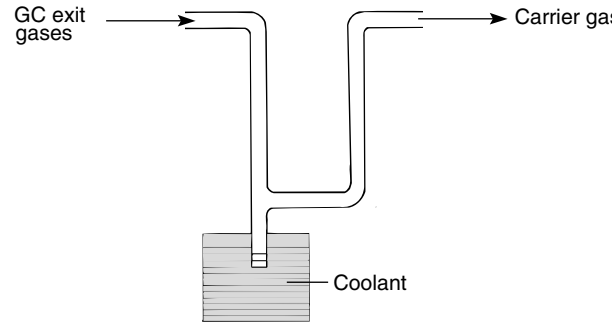


Figure 22.12 A collection trap.

Another method for collecting samples is to connect a cooled trap to the exit port of the column. A simple trap, suitable for microscale work, is illustrated in Figure 22.12. Suitable coolants include ice water, liquid nitrogen, or dry ice–acetone. For instance, if the coolant is liquid nitrogen (bp –196°C) and the carrier gas is helium (bp –269°C), compounds boiling above the temperature of liquid nitrogen generally are condensed or trapped in the small tube at the bottom of the U-shaped tube. The small tube is scored with a file just below the point at which it is connected to the larger tube, the tube is broken off, and the sample is removed for analysis. To collect each component of the mixture, you must change the trap after each sample is collected.

22.12 Quantitative Analysis

The area under a gas chromatograph peak is proportional to the amount (moles) of compound eluted. Hence, the molar percentage composition of a mixture can be approximated by comparing relative peak areas. This method of analysis assumes that the detector is equally sensitive to all compounds eluted and that it gives a linear response with respect to amount. Nevertheless, it gives reasonably accurate results.

The simplest method of measuring the area of a peak is by geometric approximation, or triangulation. In this method, you multiply the height h of the peak above the baseline of the chromatogram by the width of the peak at half of its height $w_{1/2}$. This is illustrated in Figure 22.13. The baseline is approximated by drawing a line between the two sidearms of the peak. This method works well only if the peak is symmetrical. If the peak has tailed or is unsymmetrical, it is best to cut out the peaks with scissors and weigh the pieces of paper on an **analytical balance**. Because the weight per area of a piece of good chart paper is reasonably constant from place to place, the ratio of the areas is the same as the ratio of the weights. To obtain a percentage composition for the mixture, first add all the peak areas (weights). Then, to calculate the percentage of any component in the mixture, divide its individual area by the total area and multiply the result by 100. A sample calculation is illustrated in Figure 22.14. If peaks overlap (see Figure 22.8), either the gas chromatographic conditions must be readjusted to achieve better resolution of the peaks or the peak shape must be estimated.

There are various instrumental means, which are built into recorders, of detecting the amounts of each sample automatically. One method uses a separate pen that produces a trace that integrates the area under each peak. Another method employs an electronic device that automatically prints out the area under each peak and the percentage composition of the sample.

Most modern data stations (see Section 22.13) label the top of each peak with its retention time in minutes. When the trace is completed, the computer prints a table of all the peaks with their retention times, areas, and the percentage of the total area (sum of all the peaks) that each peak represents. Some caution should be used with these results because the computer often does not include smaller peaks and occasionally does not resolve narrow peaks that are so close together that they overlap. If the trace has several peaks and you would like the ratio of only two of them, you will have to determine their percentages yourself using only their two areas or instruct the instrument to integrate only these two peaks.

For many applications, one assumes that the detector is equally sensitive to all compounds eluted. Compounds with different functional groups or with widely varying molecular weights, however, produce different responses with both TCD

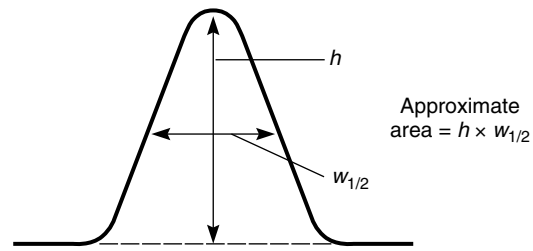


Figure 22.13 Triangulation of a peak.

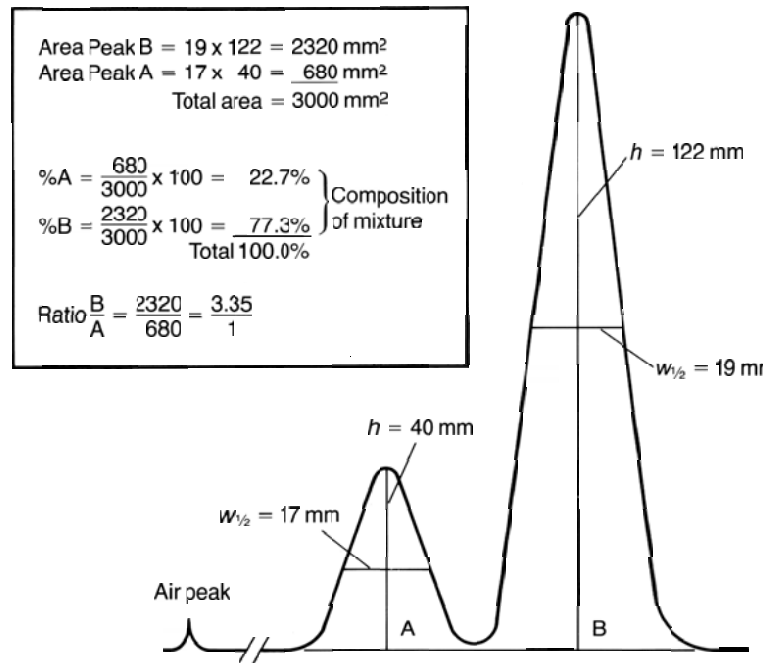


Figure 22.14 Sample percentage composition calculation.

and FID gas chromatographs. With a TCD, the responses are different because not all compounds have the same thermal conductivity. Different compounds analyzed with an FID gas chromatograph also give different responses because the detector response varies with the type of ions produced. For both types of detectors, it is possible to calculate a **response factor** for each compound in a mixture. Response factors are usually determined by making up an equimolar mixture of two compounds, one of which is considered to be the reference. The mixture is separated on a gas chromatograph, and the relative percentages are calculated using one of the methods described previously. From these percentages, you can determine a response factor for the compound being compared to the reference. If you do this for all the components in a mixture, you can then use these correction factors to make more accurate calculations of the relative percentages for the compounds in the mixture.

To illustrate how response factors are determined, consider the following example. An equimolar mixture of benzene, hexane, and ethyl acetate is prepared and analyzed using a flame-ionization gas chromatograph. The peak areas obtained are

Hexane	831158
Ethyl acetate	1449695
Benzene	966463

In most cases, benzene is taken as the standard, and its response factor is defined to be equal to 1.00. Calculation of the response factors for the other components of the test mixture proceeds as follows:

Hexane	831158/966463 = 0.86
Ethyl acetate	1449695/966463 = 1.50
Benzene	966463/966463 = 1.00 (by definition)

Notice that the response factors calculated in this example are molar response factors. It is necessary to correct these values by the relative molecular weights of each substance to obtain weight response factors.

When you use a flame-ionization gas chromatograph for quantitative analysis, it is first necessary to determine the response factors for each component of the mixture being analyzed, as just shown. For a quantitative analysis, it is likely that you will have to convert molar response factors into weight response factors. Next, the chromatography experiment using the unknown samples is performed. The observed peak areas for each component are corrected using the response factors in order to arrive at the correct weight percentage of each component in the sample. The application of response factors to correct the original results of a quantitative analysis will be illustrated in the following section.

22.13 Treatment of Data: Chromatograms Produced by Modern Data Stations

A. Gas Chromatograms and Data Tables

Most modern gas chromatography instruments are equipped with computer-based data stations. Interfacing the instrument with a computer allows the operator to display and manipulate the results in whatever manner might be desired. The operator thus can view the output in a convenient form. The computer can both display the actual gas chromatogram and display the integration results. It can even display the result of two experiments simultaneously, making a comparison of parallel experiments convenient.

Figure 22.15 shows a gas chromatogram of a mixture of hexane, ethyl acetate, and benzene. The peaks corresponding to each peak can be seen; the peaks are labeled with their respective retention times:

	Retention Time (minutes)
Hexane	2.959
Ethyl acetate	3.160
Benzene	3.960

We can also see that there is a very small amount of an unspecified impurity, with a retention time of about 3.4 minutes.

Figure 22.16 shows part of the printed output that accompanies the gas chromatogram. It is this information that is used in the quantitative analysis of the mixture. According to the printout, the first peak has a retention time of 2.954 minutes (the difference between the retention times that appear as labels on the graph and those that appear in the data table are not significant). The computer has also determined the area under this peak (422373 counts). Finally, the computer has calculated the percentage of the first substance (hexane) by determining the total area of all the peaks in the chromatogram (1227054 counts) and dividing that into the area for the hexane peak. The result is displayed as 34.4217%. In a similar manner, the data table shows the retention times and peak areas for the other two peaks in the sample, along with a determination of the percentage of each substance in the mixture.

B. Application of Response Factors

If the detector responded with equal sensitivity to each of the components of the mixture, the data table shown in Figure 22.16 would contain the complete quantitative analysis of the sample. Unfortunately, as we have seen (see Section 22.12), gas

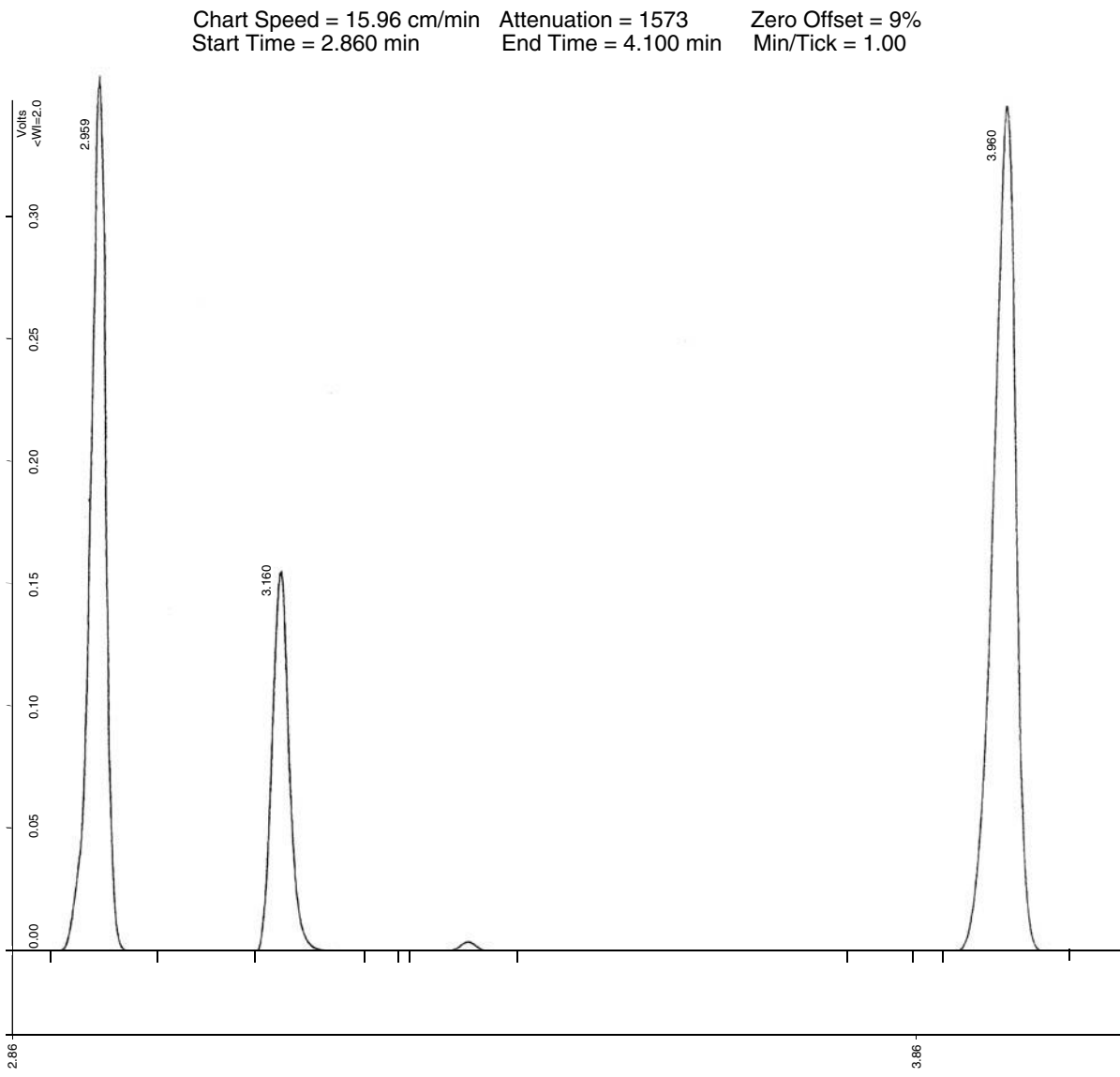


Figure 22.15 A sample gas chromatogram obtained from a data station.

chromatography detectors respond more sensitively to some substances than they do to others. To correct for this discrepancy, it is necessary to apply corrections that are based on the **response factors** for each component of the mixture.

The method for determining the response factors was introduced in Section 22.12. In this section, we will see how this information is applied in order to obtain a correct analysis. This example should serve to demonstrate the procedure for correcting raw gas chromatography results when response factors are known. According to the data table, the reported peak area for the first (hexane) peak is 422373 counts. The response factor for hexane was previously determined to be 0.86. The area of the hexane peak is thus corrected as follows:

$$422373/0.86 = 491000$$

Notice that the calculated result has been adjusted to reflect a reasonable number of significant figures.

The areas for the other peaks in the gas chromatogram are corrected in a similar manner:

Hexane	422373/0.86 =	491000
Ethyl acetate	204426/1.50 =	136000
Benzene	600255/1.00 =	600000
Total peak area		1227000

Using these corrected areas, the true percentages of each component can be easily determined:

		Composition
Hexane	491000/1227000	40.0%
Ethyl acetate	136000/1227000	11.1%
Benzene	600000/1227000	48.9%
Total		100.0%

C. Determination of Relative Percentages of Components in a Complex Mixture

In some circumstances, one may wish to determine the relative percentages of two components when the mixture being analyzed may be more complex and may contain more than two components. Examples of this situation might include the analysis of a reaction product where the laboratory worker might be interested in the relative percentages of two isomeric products when the sample might also contain peaks arising from the solvent, unreacted starting material, or some other product or impurity.

The example provided in Figures 22.15 and 22.16 can be used to illustrate the method of determining the relative percentages of some, but not all, of the components

```
Run Mode        : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

                                 Ret.    Time                        Width
 Peak      Peak        Result    Time   Offset      Area    Sep.  1/2   Status
  No.      Name          ()     (min)   (min)    (counts)  Code (sec)  Codes
 ---- ------------ ---------- ------- ------- ---------- ---- -----  ------
    1                  34.4217   2.954   0.000     422373   BB   1.0
    2                  16.6599   3.155   0.000     204426   BB   1.2
    3                  48.9184   3.954   0.000     600255   BB   1.6
 ---- ------------ ========== ======= ======= ========== ---- -----  ------
      Totals:         100.0000           0.000    1227054

Total Unidentified Counts:     1227054 counts

Detected Peaks: 8           Rejected Peaks: 5      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 1 microVolts

Noise (used): 28 microVolts — monitored before this run

Manual injection

********************************************************************************
```

Figure 22.16 A data table to accompany the gas chromatogram shown in Figure 22.14.

in the sample. Assume we are interested in the relative percentages of hexane and ethyl acetate in the sample but not in the percentage of benzene, which may be a solvent or an impurity. We know from the previous discussion that the *corrected* relative areas of the two peaks of interest are as follows:

	Relative Area
Hexane	491000
Ethyl acetate	136000
Total	627000

We can determine the relative percentages of the two components simply by dividing the area of each peak by the total area of the two peaks:

		Percentage
Hexane	491000/627000	78.3%
Ethyl acetate	136000/627000	21.7%
Total		100.0%

22.14 Gas Chromatography-Mass Spectrometry (GC-MS)

A recently developed variation on gas chromatography is **gas chromatography-mass spectrometry**, also known as **GC-MS**. In this technique, a gas chromatograph is coupled to a mass spectrometer (see Technique 28). In effect, the mass spectrometer acts as a detector. The gas stream emerging from the gas chromatograph is admitted through a valve into a tube, where it passes over the sample inlet system of the mass spectrometer. Some of the gas stream is thus admitted into the ionization chamber of the mass spectrometer.

The molecules in the gas stream are converted into ions in the ionization chamber, and thus the gas chromatogram is actually a plot of time versus **ion current**, a measure of the number of ions produced. At the same time that the molecules are converted into ions, they are also accelerated and passed through the **mass analyzer** of the instrument. The instrument, therefore, determines the mass spectrum of each fraction eluting from the gas chromatography column.

A drawback of this method involves the need for rapid scanning by the mass spectrometer. The instrument must determine the mass spectrum of each component in the mixture before the next component exits from the column so that the spectrum of one substance is not contaminated by the spectrum of the next fraction.

Because high-efficiency capillary columns are used in the gas chromatograph, in most cases compounds are completely separated before the gas stream is analyzed. The typical GC-MS instrument has the capability of obtaining at least one scan per second in the range of 10–300 amu. Even more scans are possible if a narrow range of masses is analyzed. Using capillary columns, however, requires the user to take particular care to ensure that the sample does not contain any particles that might obstruct the flow of gases through the column. For this reason, the sample is carefully filtered through a very fine filter before the sample is injected into the chromatograph.

With a GC-MS system, a mixture can be analyzed and results obtained that resemble very closely those shown in Figures 22.14 and 22.15. A library search on each component of the mixture can also be conducted. The data stations of most instruments contain a library of standard mass spectra in their computer memory. If the components are known compounds, they can be identified tentatively by a comparison of their mass spectrum with the spectra of compounds found in the

computer library. In this way, a "hit list" can be generated that reports on the probability that the compound in the library matches the known substance. A typical printout from a GC-MS instrument will list probable compounds that fit the mass spectrum of the component, the names of the compounds, their CAS Nos. (see Technique 29, Section 29.11), and a "quality" or "confidence" number. This last number provides an estimate of how closely the mass spectrum of the component matches the mass spectrum of the substance in the computer library.

A variation on the GC-MS technique includes coupling a Fourier-transform infrared spectrometer (FT–IR) to a gas chromatograph. The substances that elute from the gas chromatograph are detected by determining their infrared spectra rather than their mass spectra. A new technique that also resembles GC-MS is **high-performance liquid chromatography–mass spectrometry (HPLC–MS)**. An HPLC instrument is coupled through a special interface to a mass spectrometer. The substances that elute from the HPLC column are detected by the mass spectrometer, and their mass spectra can be displayed, analyzed, and compared with standard spectra found in the computer library built into the instrument.

PROBLEMS

1. a. A sample consisting of 1-bromopropane and 1-chloropropane is injected into a gas chromatograph equipped with a nonpolar column. Which compound has the shorter retention time? Explain your answer.

b. If the same sample were run several days later with the conditions as nearly the same as possible, would you expect the retention times to be identical to those obtained the first time? Explain.

2. Using triangulation, calculate the percentage of each component in a mixture composed of two substances, A and B. The chromatogram is shown in Figure 22.17.

3. Make a photocopy of the chromatogram in Figure 22.17. Cut out the peaks and weigh them on an analytical balance. Use the weights to calculate the percentage of each component in the mixture. Compare your answer to what you calculated in problem 2.

4. What would happen to the retention time of a compound if the following changes were made?

a. Decrease the flow rate of the carrier gas

b. Increase the temperature of the column

c. Increase the length of the column

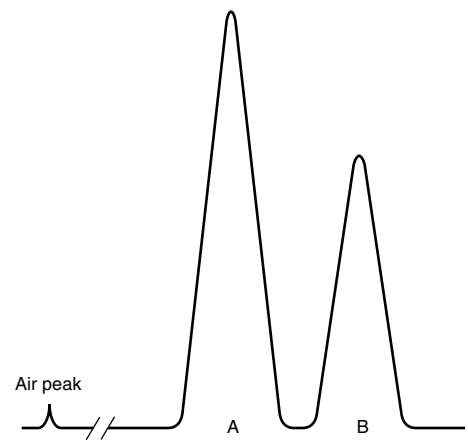


Figure 22.17 A chromatogram for problem 2.

23 TECHNIQUE 23

Polarimetry

23.1 Nature of Polarized Light

Light has a dual nature because it shows properties of both waves and particles. The wave nature of light can be demonstrated by two experiments: polarization and interference. Of the two, polarization is the more interesting to organic chemists, because they can take advantage of polarization experiments to learn something about the structure of an unknown molecule.

Ordinary white light consists of wave motion in which the waves have a variety of wavelengths and vibrate in all possible planes perpendicular to the direction of propagation. Light can be made to be **monochromatic** (of one wavelength or color) by using filters or special light sources. Frequently, a sodium lamp (sodium D line = 5893 Å) is used.[1] Although the light from this lamp consists of waves of essentially one wavelength, the individual light waves still vibrate in all possible planes perpendicular to the beam. If we imagine that the beam of light is aimed directly at the viewer, ordinary light can be represented by showing the edges of the planes oriented randomly around the path of the beam, as on the left side of Figure 23.1.

A Nicol prism, which consists of a specially prepared crystal of Iceland spar (or calcite), has the property of serving as a screen that can restrict the passage of light waves. Waves that are vibrating in one plane are transmitted; those in all other planes are rejected (either refracted in another direction or absorbed). The light that passes through the prism is called **plane-polarized light**, and it consists of waves that vibrate in only one plane. A beam of plane-polarized light aimed directly at the viewer can be represented by showing the edges of the plane oriented in one particular direction, as on the right side of Figure 23.1.

Iceland spar has the property of **double refraction**; that is, it can split, or doubly refract, an entering beam of ordinary light into two separate emerging beams of light. Each of the two emerging beams (labeled A and B in Figure 23.2) has only a single plane of vibration, and the plane of vibration in beam A is perpendicular to the plane of beam B. In other words, the crystal has separated the incident beam of ordinary light into two beams of plane-polarized light, with the plane of polarization of beam A perpendicular to the plane of beam B.

To generate a single beam of plane-polarized light, one can take advantage of the double-refracting property of Iceland spar. A Nicol prism, invented by the Scottish physicist William Nicol, consists of two crystals of Iceland spar cut to specified angles and cemented by Canada balsam. This prism transmits one of the two

Figure 23.1 Ordinary versus plane-polarized light.

[1]A sodium emission lamp actually emits *two* yellow lines near 5893Å, but they are closely spaced and only separated by high-resolution monochrometers.

beams of plane-polarized light while reflecting the other at a sharp angle so that it does not interfere with the transmitted beam. Plane-polarized light can also be generated by a Polaroid filter, a device invented by E. H. Land, an American physicist. Polaroid filters consist of certain types of crystals embedded in transparent plastic and capable of producing plane-polarized light.

After passing through a first Nicol prism, plane-polarized light can pass through a second Nicol prism, but only if the second prism has its axis oriented so that it is *parallel* to the incident light's plane of polarization. Plane-polarized light is *absorbed* by a Nicol prism that is oriented so that its axis is *perpendicular* to the incident light's plane of polarization. These situations can be illustrated by the picket-fence analogy, as shown in Figure 23.3. Plane-polarized light can pass through a fence whose slats are oriented in the proper direction, but is blocked out by a fence whose slats are oriented perpendicularly.

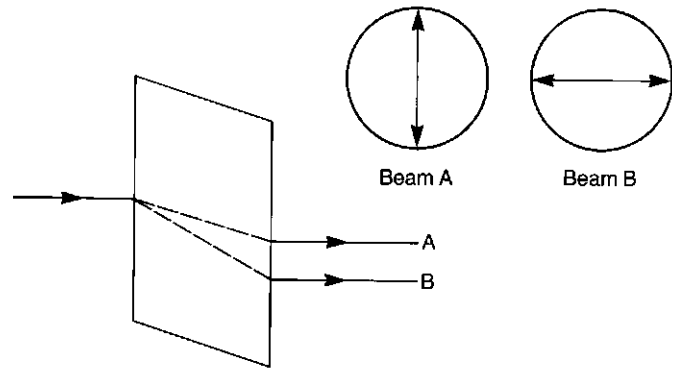


Figure 23.2 Double refraction.

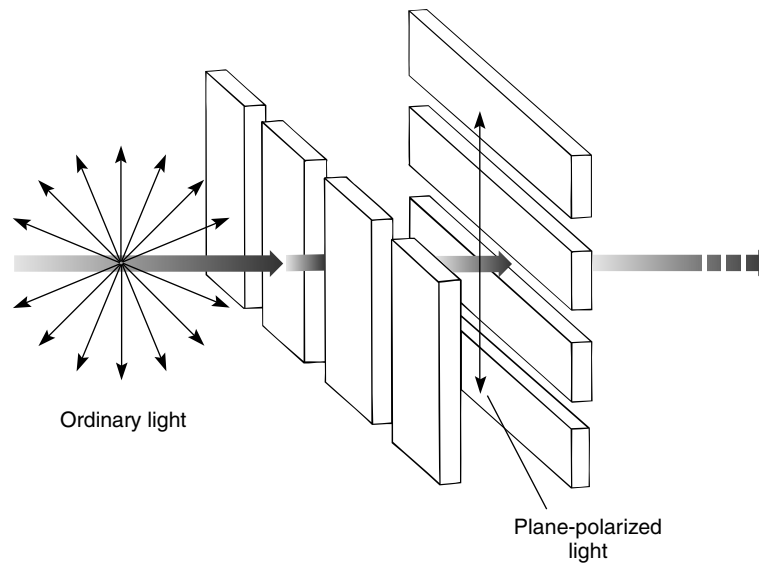


Figure 23.3 The picket-fence analogy.

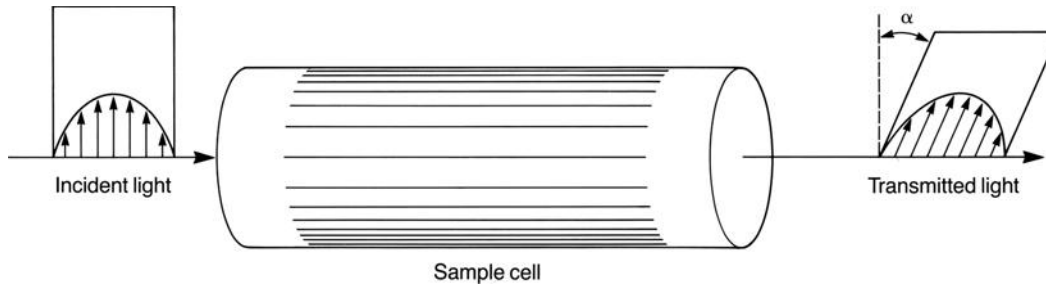


Figure 23.4 Optical activity.

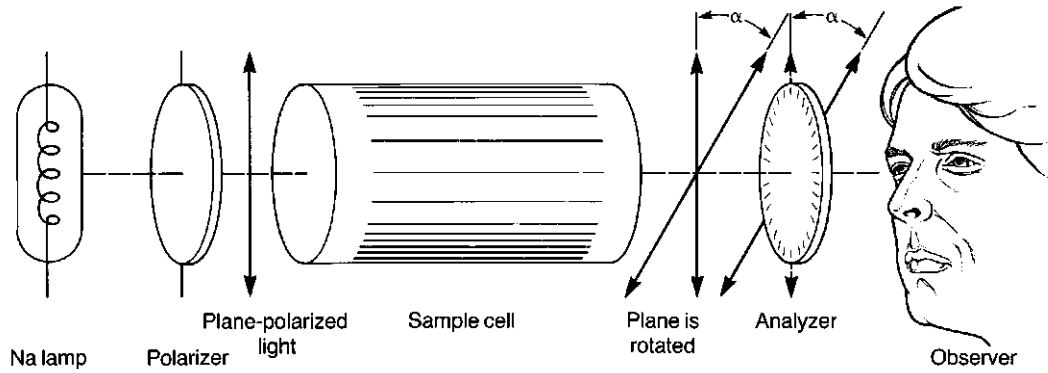


Figure 23.5 Schematic diagram of a polarimeter.

An **optically active substance** is one that interacts with polarized light to rotate the plane of polarization through some angle α. Figure 23.4 illustrates this phenomenon.

23.2 The Polarimeter

An instrument called a **polarimeter** is used to measure the extent to which a substance interacts with polarized light. A schematic diagram of a polarimeter is shown in Figure 23.5. The light from the source lamp is polarized by being passed through a fixed Nicol prism, called a **polarizer**. This light passes through the sample with which it may or may not interact to have its plane of polarization rotated in one direction or the other. A second, rotatable Nicol prism, called the **analyzer**, is adjusted to allow the maximum amount of light to pass through. The number of degrees and the direction of rotation required for this adjustment are measured to give the **observed rotation** α.

So that data determined by several persons under different conditions can be compared, a standardized means of presenting optical rotation data is necessary. The most common way of presenting such data is by recording the **specific rotation** $[\alpha]^t_\gamma$, which has been corrected for differences in concentration, cell path length, temperature, solvent, and wavelength of the light source. The equation defining the specific rotation of a compound in solution is

$$[\alpha]^t_\lambda = \frac{\alpha}{cl}$$

where α = observed rotation in degrees, c = concentration in grams per milliliter of solution, l = length of sample tube in decimeters, λ = wavelength of light (usually indicated as "D," for the sodium D line), and t = temperature in degrees Celsius. For pure liquids, the density d of the liquid in grams per milliliter replaces c in the preceding formula. You may occasionally want to compare compounds of different

molecular weights, so a **molecular rotation**, based on moles instead of grams, is more convenient than a specific rotation. The molecular rotation M_λ^t is derived from the specific rotation $[\alpha]_\lambda^t$, by

$$M_\lambda^t = \frac{[\alpha]_\lambda^t \times \text{Molecular weight}}{100}$$

Usually, measurements are made at 25°C with the sodium D line as a light source; consequently, specific rotations are reported as $[\alpha]_D^{25}$.

Polarimeters that are now available incorporate electronics to determine the angle of rotation of chiral molecules. These instruments are essentially automatic. The only real difference between an automatic polarimeter and a manual one is that a light detector replaces the eye. No visual observation of any kind is made with an automatic instrument. A microprocessor adjusts the analyzer until the light reaching the detector is at a minimum. The angle of rotation is displayed digitally in an LCD window, including the sign of rotation. The simplest instrument is equipped with a sodium lamp that gives rotations based on the sodium D line (589 nm). More expensive instruments use a tungsten lamp and filters so that wavelengths can be varied over a range of values. Using the latter instrument, a chemist can observe rotations at different wavelengths.

23.3 Sample Preparation, The Sample Cell

It is important that the solution whose optical rotation is to be determined contain no suspended particles of dust, dirt, or undissolved material that might disperse the incident polarized light. Therefore, you must clean the sample cell carefully, and your sample must be free of suspended particles. You must also prevent the presence of any air bubbles in the bore when you fill the cell. Most cells have a stem in the center or an area at one end of the cell where the diameter of the tube is increased. These features are designed to help you catch any bubbles in an area that is above the path that the light takes through the main bore.

Two modern **polarimetry cells** are shown in Figure 23.6. In the first case, the cell is filled until the liquid completely fills the bore and a small portion of the center stem. Then, if one gently rocks the cell back and forth along its axis, bubbles will rise and collect in the stem where they are above the light path. A stopper is placed in the stem when you are finished. In the second case, the cell is filled vertically, and the end is screwed on. Bubbles are trapped at the raised end when the cell is turned horizontally.

Sample cells are available in various lengths, with 0.5 dm and 1.0 dm being the most common. A typical 0.5-dm cell holds about 3–5 mL of solution, but many companies sell **microcells** that have a very narrow diameter bore and require much less solution. Polarimeter cells are quite expensive because the windows must be made out of quartz rather than ordinary glass. Be sure to handle them carefully and to avoid getting fingerprints on the end windows, as this will also disperse the polarized light.

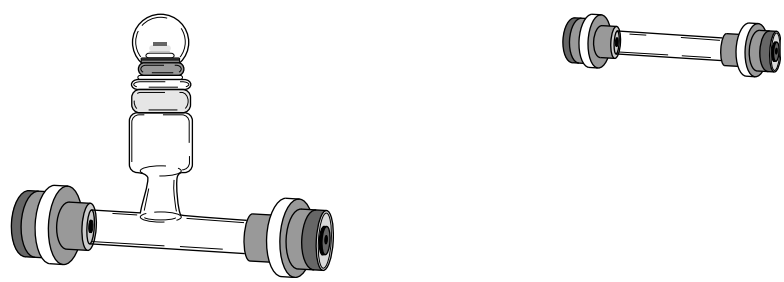


Figure 23.6 Two modern polarimetry cells (Rudolph Research).

With liquid samples, it is often quite possible to use the **neat** (undiluted) liquid as your sample. In this case, the concentration of the sample is just the density of the liquid (g/mL). If you have a solid sample or if you have too little of a liquid to fill the cell, you will have to either dissolve or dilute the sample with a solvent. In this case, you must weigh (grams) the amount of material you use and divide by the total volume (mL) to obtain the concentration in g/mL. Water, methanol, and ethanol are the best solvents to use because they are unlikely to attack the cell you are using. Many cells have rubber parts or use a cement to attach the windows to the ends of the bore. Rubber and cements will often dissolve in stronger solvents such as acetone or methylene chloride, thereby damaging the cell. Check with your instructor before using any solvent stronger than water, methanol, or ethanol. These are also the preferred solvents to use for cleaning the cells.

23.4 Operation of the Polarimeter

A. The Zeiss Polarimeter, a Classic Instrument

The procedures given here are for the operation of the Zeiss polarimeter (see Figure 23.7), a classic analog instrument with a circular scale and a sodium lamp. Many other older polarimeters models are operated in a similar fashion.

Before taking any measurements, turn on the sodium lamp and wait 5–10 minutes for the lamp to warm up and stabilize. After the warm-up period is complete, you should make an initial check of the instrument by taking a zero reading with a sample cell filled only with solvent. If the zero reading does not correspond with the zero-degree (0°) calibration mark, then the difference in readings must be used to correct all subsequent readings.

To take the zero measurement, place the polarimeter cell with the sample in the sloped cradle or rack inside the instrument. If you are using a cell with an enlarged end, that end must be placed at the high end of the cradle, making sure that no bubbles are in the bore of the cell. After closing the cover and while watching through the eyepiece, turn the analyzer knob or ring until the proper angle of the analyzer is reached (the angle that allows no light to pass through the instrument). Most analog instruments, including the Zeiss polarimeter, are of the split-field type. When you look upward through the eyepiece, you see a circle split into three sectors (see Figure 23.8), with the center sector either lighter or darker than those on either side. The analyzer prism is rotated until all of the sectors are matched in intensity, usually the darker color (see Figure 23.8). This is called the **null** reading.

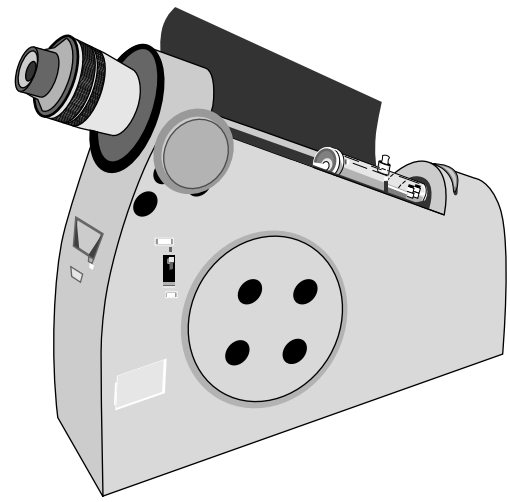


Figure 23.7 The Zeiss polarimeter.

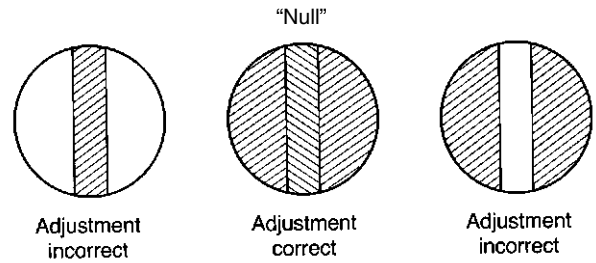


Figure 23.8 Image field sectiors in the polarimeter.

When you look downward in the eyepiece, you see the value of the angle through which the plane of the polarized light has been rotated (if any) indicated on a vernier degree scale (see Figure 23.9). Some polarimeters, such as the original Rudolph polarimeter, have instead a large circular scale, like a halo, attached directly to the knob you turn.

After determining the zero setting on the blank solution, place the polarimeter cell containing your sample into the polarimeter and measure the observed angle of rotation in the same way as described for the zero measurement. Be sure to record not only the numerical value of the reading but also the direction of rotation. Also record the solvent, temperature, and concentration, as these are also critical to the measurement. Rotations clockwise are due to dextrorotatory substances and are indicated by the "+" sign. Rotations counterclockwise are due to levorotatory substances and are indicated by the "–" sign. You should take several readings, including readings for which the value was approached from both sides. In other words, where the actual reading might be +75°, first approach this reading upward from somewhere between 0° and 75°; on the next measurement, approach the null from an angle greater than 75°. Duplicating readings, approaching the observed rotation from both sides, and averaging the readings reduce the error.

If you are not sure if you have a dextrorotatory or a levorotatory substance, you can make this determination by halving the concentration of your compound, reducing the length of the cell by half, or reducing the intensity of the light. The confusion between dextrorotatory and levorotatory arises because you are reading a circular scale. The null reading can be approached from either direction (clockwise or counterclockwise), starting from zero (see Figure 23.10). For instance, is your null at +120°, or is it at –240°? Both readings are at the same point on the scale. Figure 23.10 shows that by reducing the concentration, the cell length, or the light intensity in half (any one of these), the reading will change, and it will move in a different direction for levorotatory substances than for dextrorotatory substances. The direction of rotation is most often determined by making measurements at different dilutions.

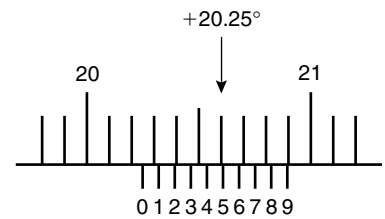


Figure 23.9 The vernier degree scale seen in the lower field of the Zeiss polarimeter.

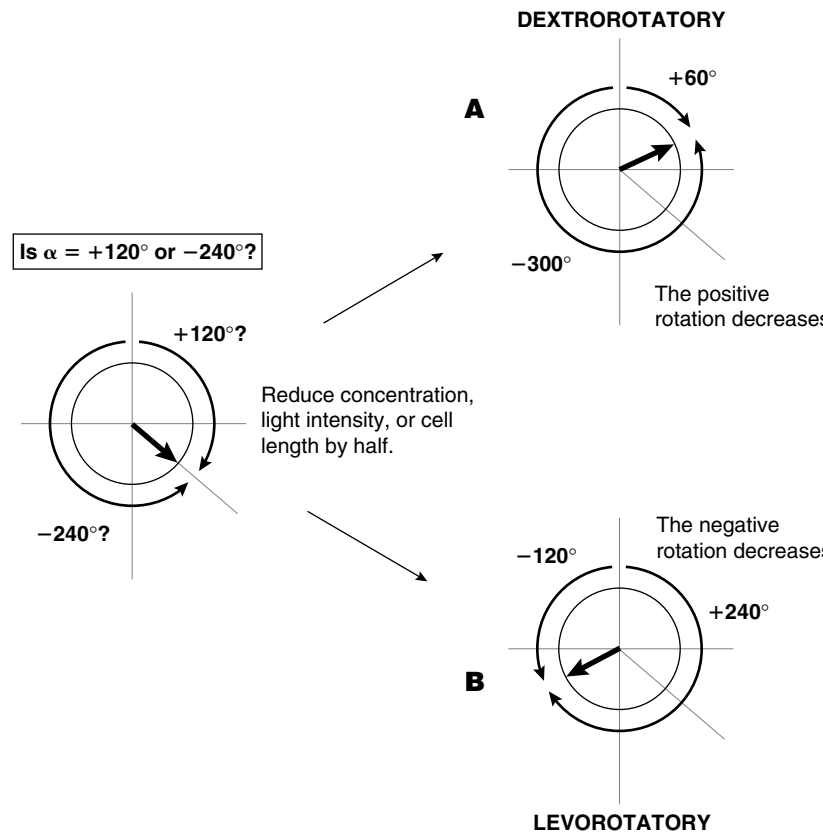


Figure 23.10 How to determine the direction of rotation. This diagram shows the effect on observed rotation if you reduce by half the concentration of the compound, the light intensity, or the length of the cell. By this method, it is easy to determine if the compound is dextrorotatory (A) or levorotatory (B).

Once you have determined the value and direction of the observed rotation α, you must correct it by the zero value and then use the formulas in Section 23.2 to convert it to the specific rotation $[\alpha]_D$. The specific rotation is always reported as a function of temperature, indicating the wavelength by "D" if a sodium lamp was used, and the solvent and concentration used are also reported. For example:

$$[\alpha]_D = +43.8 \ (c = 7.5 \text{ g}/100 \text{ mL, in absolute ethanol})$$

B. The Modern Digital Polarimeter

A modern digital polarimeter, such as the one shown in Figure 23.11, is much easier to operate than the older analog instruments. The modern instrument will store the zero reading for you, subtract it from every subsequent reading automatically, determine the direction of rotation, and calculate the specific rotation from the reading obtained on your sample. When finished, it can print everything out on a sheet of paper for you to take with you. In a typical instrument, you first determine the zero reading and then store it in electronic memory. Once the zero reading is determined, you place your sample in the instrument. The instrument automatically finds the null angle and the direction of rotation and displays it on an LED readout. The instrument approaches the null several times to be sure of its reading and determines the direction of rotation by reducing the intensity of the light. It can do

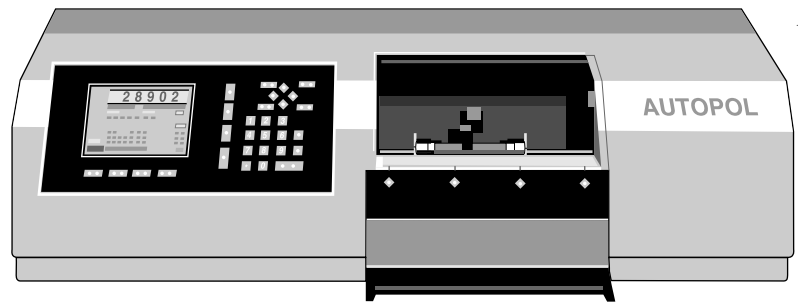


Figure 23.11 The Autopol IV (Rudolph Research), a modern digital polarimeter.

this in several different ways. One common method is to attenuate (reduce) the incident light intensity of the beam of polarized light and see what effect this has on the angle of rotation. Even a digital polarimeter, however, cannot extract a reading from a poor sample, such as one that is cloudy, has a bubble, or has suspended solid material. A good sample is still your responsibility.

23.5 Optical Purity

When you prepare a sample of an enantiomer by a resolution method, the sample is not always 100% of a single enantiomer. It frequently is contaminated by residual amounts of the opposite stereoisomer. If you know the amount of each enantiomer in a mixture, you can calculate the **optical purity**. Some chemists prefer to use the term **enantiomeric excess (ee)** rather than optical purity. The two terms can be used interchangeably. The percentage enantiomeric excess or optical purity is calculated as follows:

$$\%\ \text{Optical purity} = \frac{\text{moles one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

$$\%\ \text{Optical purity} = \%\ \text{enantiomeric excess (ee)}$$

Often, it is difficult to apply the previous equation because you do not know the exact amount of each enantiomer present in a mixture. It is far easier to calculate the optical purity (ee) by using the observed specific rotation of the mixture and dividing it by the specific rotation of the pure enantiomer. Values for the pure enantiomers can sometimes be found in literature sources.

$$\%\ \text{Optical purity} = \%\ \text{enantiomeric excess} = \frac{\text{observed specific rotation}}{\text{specific rotation of pure enantiomer}} \times 100$$

This latter equation holds true only for mixtures of two chiral molecules that are mirror images of each other (enantiomers). If some other chiral substance is present in the mixture as an impurity, then the actual optical purity will deviate from the value calculated.

In a racemic (±) mixture, there is no excess enantiomer and the optical purity (enantiomeric excess) is zero; in a completely resolved material, the optical purity (enantiomeric excess) is 100%. A compound that is x% optically pure contains x% of one enantiomer and $(100 - x)$% of a racemic mixture.

Once the optical purity (enantiomeric excess) is known, the relative percentages of each of the enantiomers can be calculated easily. If the predominant form in the impure, optically active mixture is assumed to be the (+) enantiomer, the percentage of the (+) enantiomer is

$$\left[x + \left(\frac{100 - x}{2}\right)\right]\%$$

and the percentage of the (−) enantiomer is [(100 − x)/2]%. The relative percentages of (+) and (−) forms in a partially resolved mixture of enantiomers can be calculated as shown next. Consider a partially resolved mixture of camphor enantiomers. The specific rotation for pure (+)-camphor is +43.8° in absolute ethanol, but the mixture shows a specific rotation of +26.3°.

$$\text{Optical purity} = \frac{+26.3^\circ}{+43.8^\circ} \times 100 = 60\% \text{ optically pure}$$

$$\%\,(+)\text{ enantiomer} = 60 + \left(\frac{100-60}{2}\right) = 80\%$$

$$\%\,(-)\text{ enantiomer} = \left(\frac{100-60}{2}\right) = 20\%$$

Notice that the difference between these two calculated values equals the optical purity or enantiomeric excess.

PROBLEMS

1. Calculate the specific rotation of a substance that is dissolved in a solvent (0.4 g/mL) and that has an observed rotation of −10° as determined with a 0.5-dm cell.
2. Calculate the observed rotation for a solution of a substance (2.0 g/mL) that is 80% optically pure. A 2-dm cell is used. The specific rotation for the optically pure substance is +20°.
3. What is the optical purity of a partially racemized product if the calculated specific rotation is −8° and the pure enantiomer has a specific rotation of −10°? Calculate the percentage of each of the enantiomers in the partially racemized product.

24 TECHNIQUE 24

Refractometry

The **refractive index** is a useful physical property of liquids. Often, a liquid can be identified from a measurement of its refractive index. The refractive index can also provide a measure of the purity of the sample being examined. This is accomplished by comparing the experimentally measured refractive index with the value reported in the literature for an ultrapure sample of the compound. The closer the measured sample's value to the literature value, the purer the sample.

24.1 The Refractive Index

The refractive index has as its basis the fact that light travels at a different velocity in condensed phases (liquids, solids) than in air. The refractive index n is defined as the ratio of the velocity of light in air to the velocity of light in the medium being measured:

$$n = \frac{V_{\text{air}}}{V_{\text{liquid}}} = \frac{\sin\theta}{\sin\phi}$$

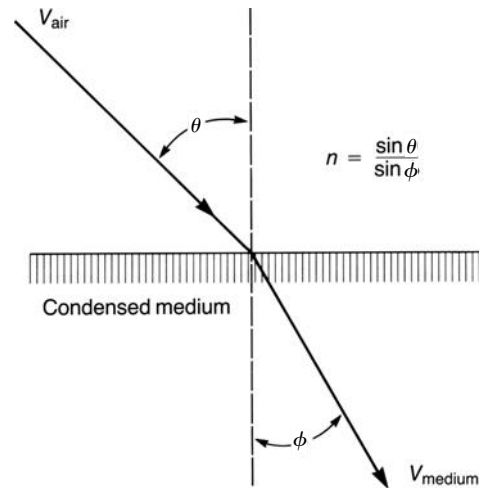


Figure 24.1 The refractive index.

It is not difficult to measure the ratio of the velocities experimentally. It corresponds to ($\sin\theta/\sin\phi$), where θ is the angle of incidence for a beam of light striking the surface of the medium and ϕ is the angle of refraction of the beam of light *within* the medium. This is illustrated in Figure 24.1.

The refractive index for a given medium depends on two variable factors. First, it is *temperature* dependent. The density of the medium changes with temperature; hence, the speed of light in the medium also changes. Second, the refractive index is *wavelength* dependent. Beams of light with different wavelengths are refracted to different extents in the same medium and give different refractive indices for that medium. It is usual to report refractive indices measured at 20°C, with a sodium discharge lamp as the source of illumination. The sodium lamp gives off yellow light of 589-nm wavelength, the so-called sodium D line. Under these conditions, the refractive index is reported in the following form:

$$n_{\mathrm{D}}^{20} = 1.4892$$

The superscript indicates the temperature, and the subscript indicates that the sodium D line was used for the measurement. If another wavelength is used for the determination, the D is replaced by the appropriate value, usually in nanometers ($1\ \mathrm{nm} = 10^{-9}\ \mathrm{m}$).

Notice that the hypothetical value reported has four decimal places. It is easy to determine the refractive index to within several parts in 10,000. Therefore, n_{D} is a very accurate physical constant for a given substance and can be used for identification. However, it is sensitive to even small amounts of impurity in the substance measured. Unless the substance is purified *extensively*, you will not usually be able to reproduce the last two decimal places given in a handbook or other literature source. Typical organic liquids have refractive index values between 1.3400 and 1.5600.

24.2 The Abbé Refractometer

The instrument used to measure the refractive index is called a **refractometer**. Although many styles of refractometer are available, by far the most common instrument is the Abbé refractometer. This style of refractometer has the following advantages:

1. White light may be used for illumination; the instrument is compensated, however, so that the index of refraction obtained is actually that for the sodium D line.

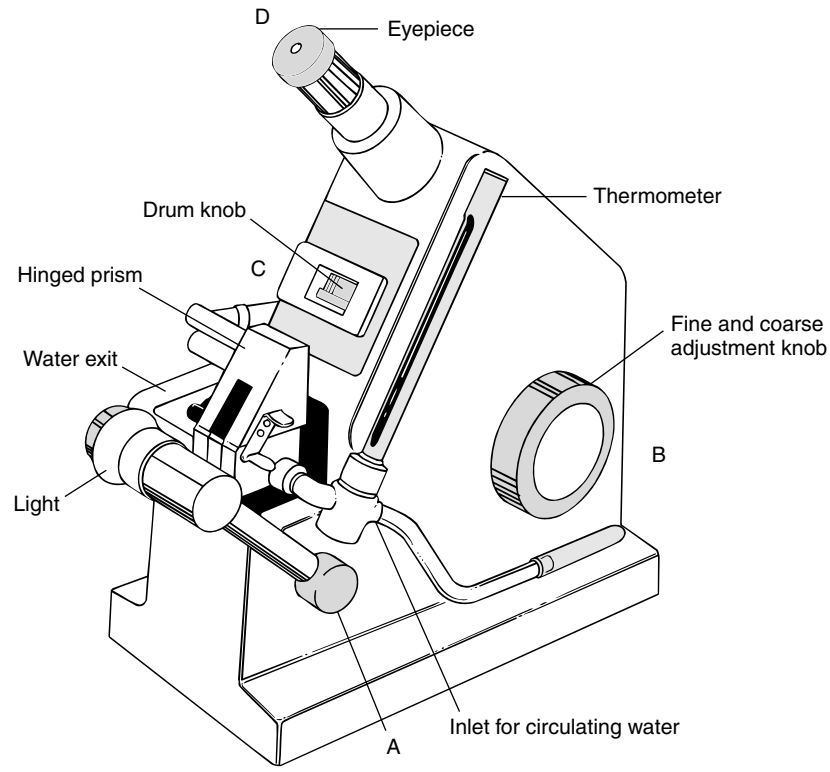


Figure 24.2 Abbé refractometer (Bausch and Lomb Abbé 3L).

2. The prisms can be temperature controlled.
3. Only a small sample is required (a few drops of liquid using the standard method, or about 5 μL using a modified technique).

A common type of Abbé refractometer is shown in Figure 24.2.

The optical arrangement of the refractometer is very complex; a simplified diagram of the internal workings is given in Figure 24.3. The letters *A*, *B*, *C*, and *D* label corresponding parts in both Figures 24.2 and 24.3. A complete description of refractometer optics is too difficult to attempt here, but Figure 24.3 gives a simplified diagram of the essential operating principles.

Using the standard method, introduce the sample to be measured between the two prisms. If it is a free-flowing liquid, it may be introduced into a channel along the side of the prisms, injected from a Pasteur pipet. If it is a viscous sample, the prisms must be opened (they are hinged) by lifting the upper one; a few drops of liquid are applied to the lower prism with a Pasteur pipet or a wooden applicator. If a Pasteur pipet is used, take care not to touch the prisms because they become scratched easily. When the prisms are closed, the liquid should spread evenly to make a thin film. With highly volatile samples, the remaining operations must be performed rapidly. Even when the prisms are closed, evaporation of volatile liquids can readily occur.

Next, turn on the light and look into the eyepiece (D). The hinged lamp is adjusted to give the maximum illumination to the visible field in the eyepiece. The light rotates at pivot (A).

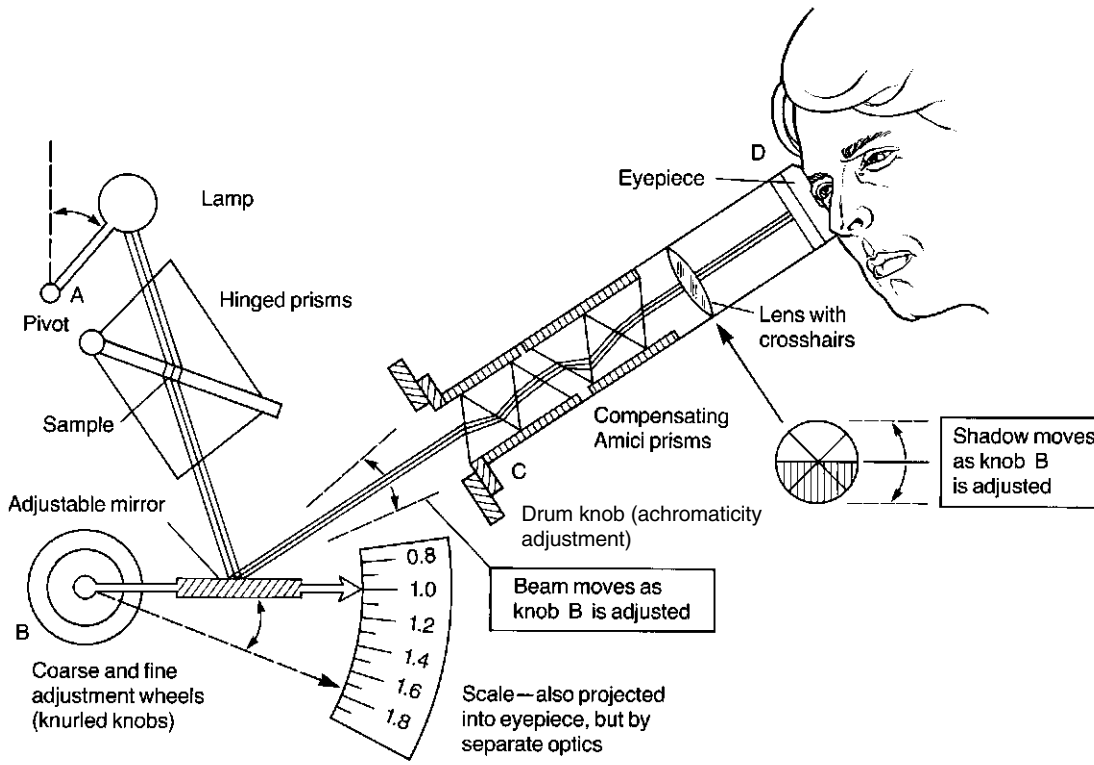


Figure 24.3 Simplified diagram of a refractometer.

Rotate the coarse and fine adjustment knobs at (B) until the dividing line between the light and dark halves of the visual field coincide with the center of the crosshairs (see Figure 24.4). If the crosshairs are not in sharp focus, adjust the eyepiece to focus them. If the horizontal line dividing the light and dark areas appears as a colored band, as in Figure 24.5, the refractometer shows **chromatic aberration** (color dispersion). This can be adjusted with the drum knob (C) (see Figure 24.3). This knurled knob rotates a series of prisms, called Amici prisms, that color-compensate the refractometer and cancel out dispersion. Adjust the drum knob to give a sharp, uncolored division between the light and dark segments. When you have adjusted everything correctly (as in Figure 24.4B), read the refractive index. In the instrument described here, press a small button on the left side of the housing to make the scale visible in the eyepiece. In other refractometers, the scale is visible at all times, frequently through a separate eyepiece.

Occasionally, the refractometer will be so far out of adjustment that it may be difficult to measure the refractive index of an unknown. When this happens, it is wise to place a pure sample of known refractive index in the instrument, set the scale to the correct value of refractive index, and adjust the controls for the sharpest line possible. Once this is done, it is easier to measure an unknown sample. It is especially helpful to perform this procedure prior to measuring the refractive index of a highly volatile sample.

NOTE: There are many styles of refractometer, but most have adjustments similar to those described here.

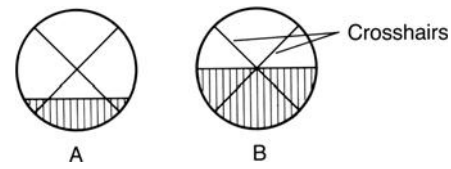


Figure 24.4 (A) Refractometer incorrectly adjusted. (B) Correct adjustment.

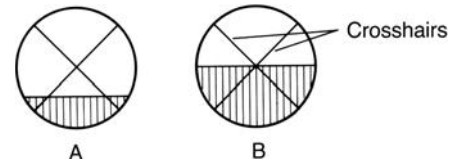


Figure 24.5 Refractometer showing chromatic aberration (color dispersion). The dispersion is incorrectly adjusted.

In the procedure just described, several drops of liquid are required to obtain the refractive index. In some experiments, you may not have enough sample to use this standard method. It is possible to modify the procedure so that a reasonably accurate refractive index can be obtained on about 5 μL of liquid. Instead of placing the sample directly onto the prism, you apply the sample to a small piece of lens paper. The lens paper can be conveniently cut with a hand-held paper punch,[1] and the paper disc (0.6-cm diameter) is placed in the center of the bottom prism of the refractometer. To avoid scratching the prism, use forceps or tweezers with plastic tips to handle the disc. About 5 μL of liquid is carefully placed on the lens paper using a microliter syringe. After closing the prisms, adjust the refractometer as described previously and read the refractive index. With this method, the horizontal line dividing the light and dark areas may not be as sharp as it is in the absence of the lens paper. It may also be impossible to eliminate color dispersion completely. Nonetheless, the refractive index values determined by this method are usually within 10 parts in 10,000 of the values determined by the standard procedure.

24.3 Cleaning the Refractometer

In using the refractometer, you should always remember that if the prisms are scratched, the instrument will be ruined.

NOTE: Do not touch the prisms with any hard object.

This admonition includes Pasteur pipets and glass rods.

When measurements are completed, the prisms should be cleaned with ethanol or petroleum ether. Moisten *soft* tissues with the solvent and wipe the prisms *gently*. When the solvent has evaporated from the prism surfaces, the prisms should be locked together. The refractometer should be left with the prisms closed to avoid collection of dust in the space between them. The instrument should also be turned off when it is no longer in use.

24.4 The Digital Refractometer

Today, there are modern digital refractometers available that determine the refractive index of a liquid electronically (see Figure 24.6). Once the instrument has been calibrated, it is only necessary to place a drop of your liquid between the prisms

[1] In order to cut the lens paper more easily, place several sheets between two pieces of heavier paper, such as that used for file folders.

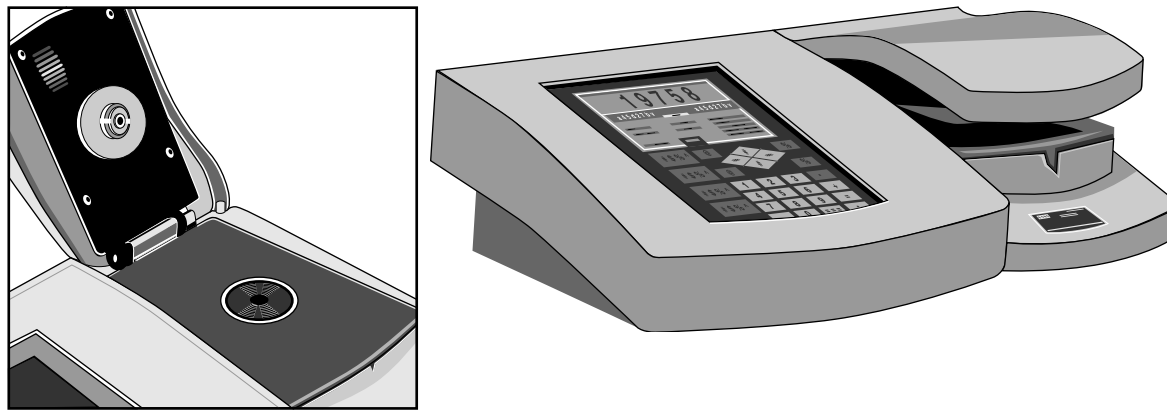


Figure 24.6 The Rudolph J-series, a modern digital refractometer. To make a measurement, place the sample on the lower prism (see the insert) and close the lid.

(see the inset in Figure 24.6), close the lid, and read the display. The instrument can make temperature corrections and store the values of your readings in its microprocessor memory. Once again, these instruments must be treated with respect, taking care not to scratch the prisms and to clean them after use.

24.5 Temperature Corrections

Most refractometers are designed so that circulating water at a constant temperature can maintain the prisms at 20°C. If this temperature-control system is not used or if the water is not at 20°C, a temperature correction must be made. Although the magnitude of the temperature correction may vary from one class of compound to another, a value of 0.00045 per degree Celsius is a useful approximation for most substances. The index of refraction of a substance *decreases* with *increasing* temperature. Therefore, add the correction to the observed n_D value for temperatures higher than 20°C and subtract it for temperatures lower than 20°C. For example, the reported n_D value for nitrobenzene is 1.5529. One would observe a value at 25°C of 1.5506. The temperature correction would be made as follows:

$$n_D^{20} = 1.5506 + 5(0.00045) = 1.5529$$

PROBLEMS

1. A solution consisting of isobutyl bromide and isobutyl chloride is found to have a refractive index of 1.3931 at 20°C. The refractive indices at 20°C of isobutyl bromide and isobutyl chloride are 1.4368 and 1.3785, respectively. Determine the molar composition (in percent) of the mixture by assuming a linear relation between the refractive index and the molar composition of the mixture.
2. The refractive index of a compound at 16°C is found to be 1.3982. Correct this refractive index to 20°C.

25 TECHNIQUE 25

Infrared Spectroscopy

Almost any compound having covalent bonds, whether organic or inorganic, will be found to absorb frequencies of electromagnetic radiation in the infrared region of the spectrum. The infrared region of the electromagnetic spectrum lies at wavelengths longer than those associated with visible light, which includes wavelengths from approximately 400 nm to 800 nm (1 nm = 10^{-9} m), but at wavelengths shorter than those associated with radio waves, which have wavelengths longer than 1 cm. For chemical purposes, we are interested in the *vibrational* portion of the infrared region. This portion includes radiations with wavelengths (λ) between 2.5 μm and 15 μm (1 μm = 10^{-6} m). The relation of the infrared region to other regions included in the electromagnetic spectrum is illustrated in Figure 25.1.

As with other types of energy absorption, molecules are excited to a higher energy state when they absorb infrared radiation. The absorption of the infrared radiation is, like other absorption processes, a quantized process. Only selected frequencies (energies) of infrared radiation are absorbed by a molecule. The absorption of infrared radiation corresponds to energy changes on the order of 8–40 kJ/mole (2–10 kcal/mole). Radiation in this energy range corresponds to the range encompassing the stretching and bending vibrational frequencies of the bonds in most covalent molecules. In the absorption process, those frequencies of infrared radiation that match the natural vibrational frequencies of the molecule in question are absorbed, and the energy absorbed increases the *amplitude* of the vibrational motions of the bonds in the molecule.

Most chemists refer to the radiation in the vibrational infrared region of the electromagnetic spectrum by units called **wavenumbers** ($\bar{\nu}$). Wavenumbers are expressed in reciprocal centimeters (cm^{-1}) and are easily computed by taking the reciprocal of the wavelength (λ) expressed in centimeters. This unit has the advantage, for those performing calculations, of being directly proportional to energy. Thus, the vibrational infrared region of the spectrum extends from about 4000 cm^{-1} to 650 cm^{-1} (or wavenumbers).

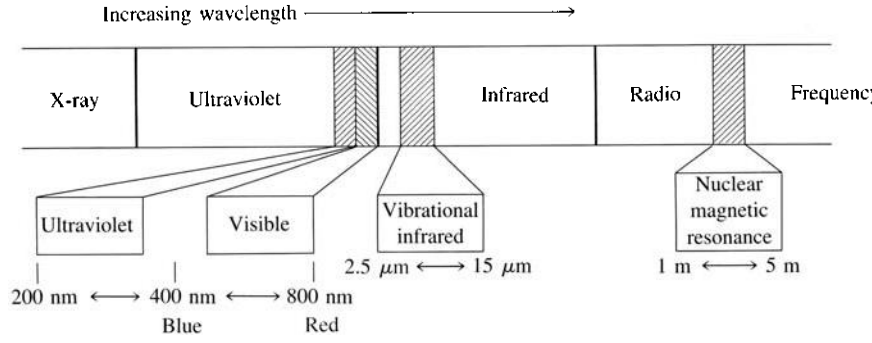


Figure 25.1 A portion of the electromagnetic spectrum showing the relation of vibrational infrared radiation to other types of radiation.

Wavelengths (μm) and wavenumbers (cm^{-1}) can be interconverted by the following relationships:

$$cm^{-1} = \frac{1}{(\mu m)} \times 10{,}000$$

$$\mu m = \frac{1}{(cm)^{-1}} \times 10{,}000$$

PART A. SAMPLE PREPARATION AND RECORDING THE SPECTRUM

25.1 Introduction

To determine the infrared spectrum of the compound, one must place the compound in a sample holder or cell. In infrared spectroscopy, this immediately poses a problem. Glass, quartz, and plastics absorb strongly throughout the infrared region of the spectrum (any compound with covalent bonds usually absorbs) and cannot be used to construct sample cells. Ionic substances must be used in cell construction. Metal halides (sodium chloride, potassium bromide, silver chloride) are commonly used for this purpose.

Sodium Chloride Cells. Single crystals of sodium chloride are cut and polished to give plates that are transparent throughout the infrared region. These plates are then used to fabricate cells that can be used to hold *liquid* samples. Because sodium chloride is water soluble, samples must be *dry* before a spectrum can be obtained. In general, sodium chloride plates are preferred for most applications involving liquid samples. Potassium bromide plates may also be used in place of sodium chloride.

Silver Chloride Cells. Cells may be constructed of silver chloride. These plates may be used for *liquid* samples that contain small amounts of water, because silver chloride is water insoluble. However, because water absorbs in the infrared region, as much water as possible should be removed, even when using silver chloride. Silver chloride plates must be stored in the dark. They darken when exposed to light, and they cannot be used with compounds that have an amino functional group. Amines react with silver chloride.

Solid Samples. The easiest way to hold a *solid* sample in place is to dissolve the sample in a volatile organic solvent, place several drops of this solution on a salt plate, and allow the solvent to evaporate. This dry film method can be used only with modern FT-IR spectrometers. The other methods described here can be used with both FT-IR and dispersion spectrometers. A solid sample can also be held in place by making a potassium bromide pellet that contains a small amount of dispersed compound. A solid sample may also be suspended in mineral oil, which absorbs only in specific regions of the infrared spectrum. Another method is to dissolve the solid compound in an appropriate solvent and place the solution between two sodium chloride or silver chloride plates.

25.2 Liquid Samples—NaCl Plates

The simplest method of preparing the sample, if it is a liquid, is to place a thin layer of the liquid between two sodium chloride plates that have been ground flat and polished. This is the method of choice when you need to determine the infrared

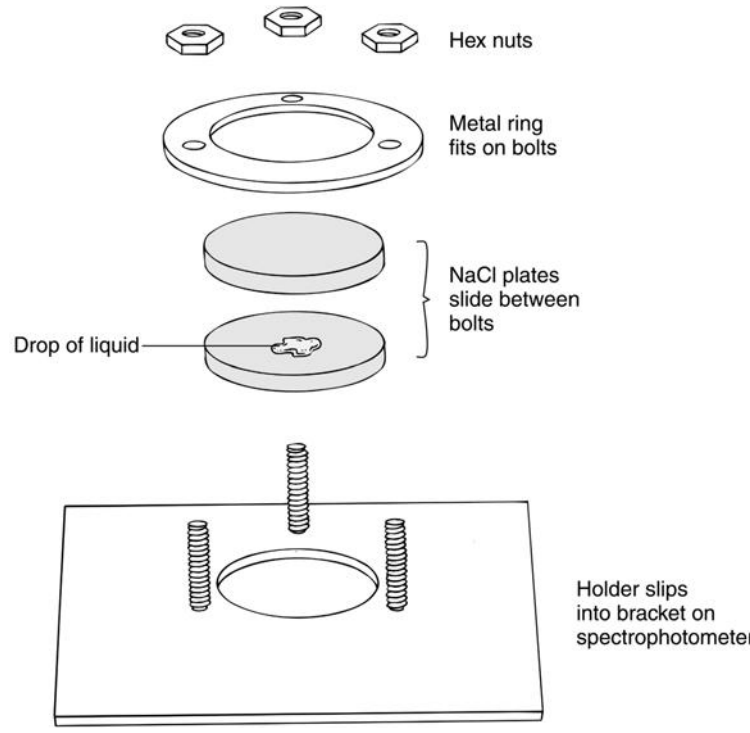


Figure 25.2 Salt plates and holder.

spectrum of a pure liquid. A spectrum determined by this method is referred to as a **neat** spectrum. No solvent is used. The polished plates are expensive because they are cut from a large, single crystal of sodium chloride. Salt plates break easily, and they are water soluble.

Preparing the Sample. Obtain two sodium chloride plates and a holder from the desiccator where they are stored. Moisture from fingers will mar and occlude the polished surfaces. Samples that contain water will destroy the plates.

NOTE: The plates should be touched only on their edges. Be certain to use a sample that is dry or free from water.

Add 1 or 2 drops of the liquid to the surface of one plate and then place the second plate on top.[1] The pressure of this second plate causes the liquid to spread out and form a thin capillary film between the two plates. As shown in Figure 25.2, set the plates between the bolts in a holder and place the metal ring carefully on the salt plates. Use the hex nuts to hold the salt plates in place.

NOTE: Do not overtighten the nuts or the salt plates will cleave or split.

---

[1] Use a Pasteur pipet or a short length of microcapillary tubing. If you use the microcapillary tubing, it can be filled by touching it into the liquid sample. When you touch it (lightly) to the salt plate, it will empty. Be careful not to scratch the plate.

Tighten the nuts firmly, but do not use any force to turn them. Spin them with the fingers until they stop; then turn them just another fraction of a full turn, and they will be tight enough. If the nuts have been tightened carefully, you should observe a *transparent film of sample* (a uniform wetting of the surface). If a thin film has not been obtained, either loosen one or more of the hex nuts and adjust them so that a uniform film is obtained or add more sample.

The thickness of the film obtained between the two plates is a function of two factors: (1) the amount of liquid placed on the first plate (1 drop, 2 drops, and so on), and (2) the pressure used to hold the plates together. If more than 1 or 2 drops of liquid have been used, the amount will probably be too much, and the resulting spectrum will show strong absorptions that are off the scale of the chart paper. Only enough liquid to wet both surfaces is needed.

If the sample has a very low viscosity, the capillary film may be too thin to produce a good spectrum. Another problem you may find is that the liquid is so volatile that the sample evaporates before the spectrum can be determined. In these cases, you may need to use the silver chloride plates discussed in Section 25.3 or a solution cell described in Section 25.6. Often, you can obtain a reasonable spectrum by assembling the cell quickly and running the spectrum before the sample runs out of the salt plates or evaporates.

Determining the Infrared Spectrum. Slide the holder into the slot in the sample beam of the spectrophotometer. Determine the spectrum according to the instructions provided by your instructor. In some cases, your instructor may ask you to calibrate your spectrum. If this is the case, refer to Section 25.8.

Cleaning and Storing the Salt Plates. Once the spectrum has been determined, demount the holder and rinse the salt plates with methylene chloride (or *dry* acetone). (Keep the plates away from water!) Use a soft tissue, moistened with the solvent, to wipe the plates. If some of your compound remains on the plates, you may observe a shiny surface. Continue to clean the plates with solvent until no more compound remains on the surfaces of the plates.

CAUTION

Avoid direct contact with methylene chloride. Return the salt plates and holder to the desiccator for storage.

25.3 Liquid Samples—AgCl Plates

The minicell shown in Figure 25.3 may also be used with liquids.[2] The cell assembly consists of a two-piece threaded body, an O-ring, and two silver chloride plates. The plates are flat on one side, and there is a circular depression (0.025 mm or 0.10 mm deep) on the other side of the plate. An advantage of using silver chloride plates is that they may be used with wet samples or solutions. A disadvantage is that silver chloride darkens when exposed to light for extended periods. Silver chloride plates also scratch more easily than salt plates and react with amines.

[2] The Wilks Mini-Cell liquid sample holder is available from the Foxboro Company, 151 Woodward Avenue, South Norwalk, CT 06856. We recommend the AgCl cell windows with 0.10-mm depression rather than the 0.025-mm depression.

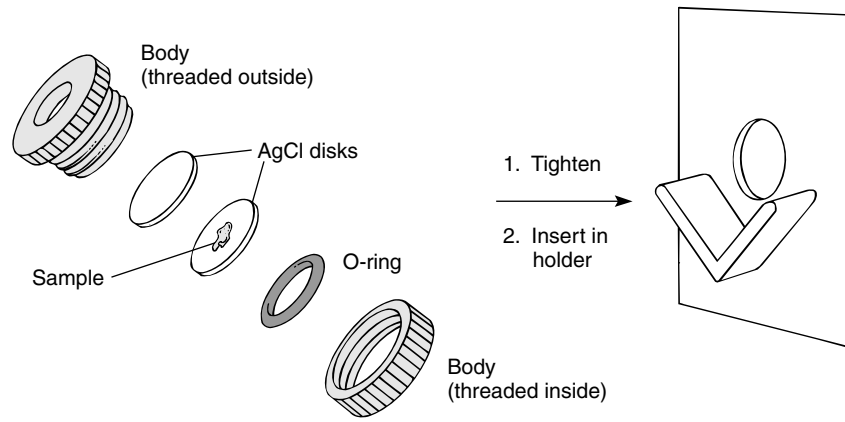
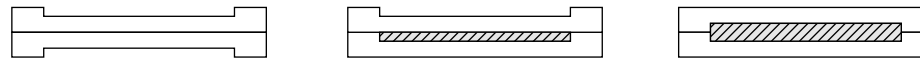


Figure 25.3 AgCl minicell liquid sample cell and V-mount holder.



A. Capillary film B. 0.10-mm Path length C. 0.20-mm Path length

Figure 25.4 Path-length variations for AgCl plates.

Preparing the Sample. Silver chloride plates should be handled in the same way as salt plates. Unfortunately, they are smaller and thinner (about like a contact lens) than salt plates, and care must be taken not to lose them! Remove them from the light-tight container with care. It is difficult to tell which side of the plate has the slight circular depression. Your instructor may have etched a letter on each plate to indicate which side is the flat one. To determine the infrared spectrum of a pure liquid (neat spectrum), select the flat side of each silver chloride plate. Insert the O-ring into the cell body as shown in Figure 25.3, place the plate into the cell body with the flat surface up, and add 1 drop or less of liquid to the plate.

NOTE: Do not use amines with AgCl plates.

Place the second plate on top of the first with the flat side down. The orientation of the silver chloride plates is shown in Figure 25.4A. This arrangement is used to obtain a capillary film of your sample. Screw the top of the minicell into the body of the cell so that the silver chloride plates are held firmly together. A tight seal forms because AgCl deforms under pressure.

Other combinations may be used with these plates. For example, you may vary the sample path length by using the orientations shown in Figures 25.4B and C. If you add your sample and the 0.10-mm depression of one plate and cover it with the flat side of the other one, you obtain a path length of 0.10 mm (see Figure 25.4B). This arrangement is useful for analyzing volatile or low-viscosity liquids. Placement of the two plates with their depressions toward each other gives a path length of 0.20 mm (see Figure 25.4C). This orientation may be used for a solution of a solid (or liquid) in carbon tetrachloride (see Section 25.6B).

Determining the Spectrum. Slide the V-mount holder shown in Figure 25.3 into the slot on the infrared spectrophotometer. Set the cell assembly in the V-mount holder, and determine the infrared spectrum of the liquid.

Cleaning and Storing the AgCl Plates. Once the spectrum has been determined, the cell assembly holder should be demounted and the AgCl plates rinsed with methylene chloride or acetone. Do not use tissue to wipe the plates, because they scratch easily. AgCl plates are light sensitive. Store the plates in a light-tight container.

25.4 Solid Samples—Dry Film

A simple method for determining the infrared spectrum of a solid sample is the **dry film** method. This method is easier than the other methods described here, it does not require any specialized equipment, and the spectra are excellent.[3] The disadvantage is that the dry film method can be used only with modern FT-IR spectrometers.

To use this method, place about 5 mg of your solid sample in a small, clean test tube. Add about 5 drops of methylene chloride (or diethyl ether, pentane, or dry acetone), and stir the mixture to dissolve the solid. Using a Pasteur pipet (not a capillary tube), place several drops of the solution on the face of a salt plate. Allow the solvent to evaporate; a uniform deposit of your product will remain as a dry film coating the salt plate. Mount the salt plate on a V-shaped holder in the infrared beam. Note that only one salt plate is used; the second salt plate is not used to cover the first. Once the salt plate is positioned properly, you may determine the spectrum in the normal manner. With this method, it is *very important* that you clean your material off the salt plate. When you are finished, use methylene chloride or dry acetone to clean the salt plate.

25.5 Solid Samples—KBr Pellets and Nujol Mulls

The methods described in this section can be used with both FT-IR and dispersion spectrometers.

A. KBr Pellets

One method of preparing a solid sample is to make a **potassium bromide (KBr) pellet**. When KBr is placed under pressure, it melts, flows, and seals the sample into a solid solution, or matrix. Because potassium bromide does not absorb in the infrared spectrum, a spectrum can be obtained on a sample without interference.

Preparing the Sample. Remove the agate mortar and pestle from the desiccator for use in preparing the sample. (Take care of them; they are expensive.) Grind 1 mg (0.001 g) of the solid sample for 1 minute in the agate mortar. At this point, the particle size will become so small that the surface of the solid appears shiny. Add 80 mg (0.080 g) of *powdered* KBr and grind the mixture for about 30 seconds with the pestle. Scrape the mixture into the middle with a spatula and grind the mixture again for about 15 seconds. This grinding operation helps to mix the sample thoroughly with the KBr. You should work as rapidly as possible because KBr absorbs water. The sample and KBr must be finely ground, or the mixture will scatter the infrared radiation excessively. Using your spatula, heap the mixture in the center of the mortar. Return the bottle of potassium bromide to the desiccator where it is stored when it is not in use.

---

[3] Feist, P. L. "Sampling Techniques for Organic Solids in IR Spectroscopy: Thin Solid Films as the Method of Choice in Teaching Laboratories." *Journal of Chemical Education,* 78 (2001): 351.

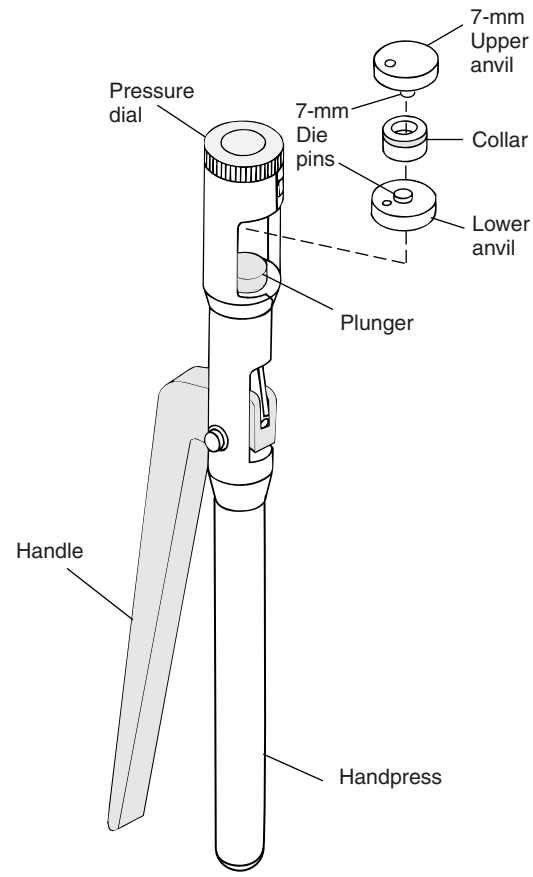


Figure 25.5 Making a KBr pellet with a handpress.

The sample and potassium bromide should be weighed on an analytical balance the first few times that a pellet is prepared. After some experience, you can estimate these quantities quite accurately by eye.

Making a Pellet Using a KBr Handpress. Two methods are commonly used to prepare KBr pellets. The first method uses the handpress apparatus shown in Figure 25.5.[4] Remove the die set from the storage container. Take extreme care to avoid scratching the polished surfaces of the die set. Place the anvil with the shorter die pin (lower anvil in Figure 25.5) on a bench. Slip the collar over the pin. Remove about one fourth of your KBr mixture with a spatula and transfer it into the collar. The powder may not cover the head of the pin completely, but do not be concerned about this. Place the anvil with the longer die pin into the collar so that the die pin comes into contact with the sample. Never press the die set unless it contains a sample.

Lift the die set carefully by holding onto the lower anvil so that the collar stays in place. If you are careless with this operation, the collar may move enough to allow the powder to escape. Open the handle of the handpress slightly, tilt the press back a bit, and insert the die set into the press. Make sure that the die set is seated

[4] KBr Quick Press unit is available from Wilmad Glass Company, Inc., Route 40 and Oak Road, Buena, NJ 08310.

against the side wall of the chamber. Close the handle. It is imperative that the die set be seated against the side wall of the chamber so that the die is centered in the chamber. Pressing the die in an off-centered position can bend the anvil pins.

With the handle in the closed position, rotate the pressure dial so that the upper ram of the handpress just touches the upper anvil of the die assembly. Tilt the unit back so that the die set does not fall out of the handpress. Open the handle and rotate the pressure dial clockwise about one-half turn. Slowly compress the KBr mixture by closing the handle. The pressure should be no greater than that exerted by a very firm handshake. Do not apply excessive pressure or the dies may be damaged. If in doubt, rotate the pressure dial counterclockwise to lower the pressure. If the handle closes too easily, open the handle, rotate the pressure dial clockwise, and compress the sample again. Compress the sample for about 60 seconds.

After this time, tilt the unit back so that the die set does not fall out of the handpress. Open the handle and carefully remove the die set from the unit. Turn the pressure dial counterclockwise about one full turn. Pull the die set apart and inspect the KBr pellet. Ideally, the pellet should appear clear like a piece of glass, but usually it will be translucent or somewhat opaque. There may be some cracks or holes in the pellet. The pellet will produce a good spectrum, even with imperfections, as long as light can travel through the pellet. Clean the dies using the procedure outlined below, in "Cleaning and Storing the Equipment."

Making a Pellet with a KBr Minipress. The second method of preparing a pellet uses the minipress apparatus shown in Figure 25.6. Obtain a ground KBr mixture as described in "Preparing the Sample" and transfer a portion of the finely ground powder (usually not more than half) into a die that compresses it into a translucent pellet. As shown in Figure 25.6, the die consists of two stainless steel bolts and a threaded barrel. The bolts have their ends ground flat. To use this die, screw one of the bolts into the barrel, but not all the way; leave one or two turns. Carefully add the powder with a spatula into the open end of the partly assembled die and tap it lightly on the benchtop to give an even layer on the face of the bolt. While keeping the barrel upright, carefully screw the second bolt into the barrel until it is finger tight. Insert the head of the bottom bolt into the hexagonal hole in a plate bolted to the benchtop. This plate keeps the head of one bolt from turning. The top bolt is tightened with a torque wrench to compress the KBr mixture. Continue to turn the torque wrench until you hear a loud click (the ratchet mechanism makes softer clicks) or until you reach the appropriate torque value (20 ft-lb). If you tighten the bolt beyond this point, you may twist the head off one of the bolts. Leave the die under pressure for about 60 seconds; then reverse the ratchet on the torque wrench or pull the torque wrench in the opposite

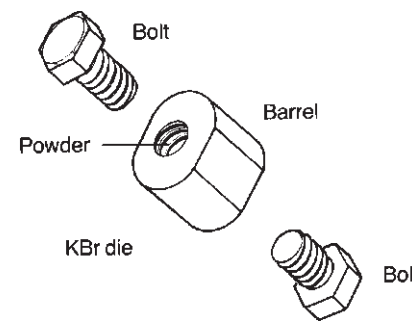


Figure 25.6 Making a KBr pellet with a minipress.

direction to open the assembly. When the two bolts are loose, hold the barrel horizontally and carefully remove the two bolts. You should observe a clear or translucent KBr pellet in the center of the barrel. Even if the pellet is not totally transparent, you should be able to obtain a satisfactory spectrum as long as light passes through the pellet.

Determining the Infrared Spectrum. To obtain the spectrum, slide the holder appropriate for the type of die that you are using into the slot on the infrared spectrophotometer. Set the die containing the pellet in the holder so that the sample is centered in the optical path. Obtain the infrared spectrum. If you are using a double-beam instrument, you may be able to compensate (at least partially) for a marginal pellet by placing a wire screen or attenuator in the reference beam, thereby balancing the lowered transmittance of the pellet. An FT-IR instrument will automatically deal with the low intensity if you select the "autoscale" option.

Problems with an Unsatisfactory Pellet. If the pellet is unsatisfactory (too cloudy to pass light), one of several things may have been wrong:

1. The KBr mixture may not have been ground finely enough, and the particle size may be too big. The large particle size creates too much light scattering.
2. The sample may not be dry.
3. Too much sample may have been used for the amount of KBr taken.
4. The pellet may be too thick; that is, too much of the powdered mixture was put into the die.
5. The KBr may have been "wet" or have acquired moisture from the air while the mixture was being ground in the mortar.
6. The sample may have a low melting point. Low-melting solids not only are difficult to dry, but also melt under pressure. You may need to dissolve the compound in a solvent and run the spectrum in solution (see Section 25.6).

Cleaning and Storing the Equipment. After you have determined the spectrum, punch the pellet out of the die with a wooden applicator stick (a spatula should not be used as it may scratch the dies). Remember that the polished faces of the die set must not be scratched, or they become useless. After the pellet has been punched out, wash all parts of the die set or minipress with warm water. Then rinse the parts with acetone and dry them using a Kimwipe. Check with your instructor to see if there are additional instructions for cleaning the die set. Return the dies to the storage container. Wash the mortar and pestle with water, dry them carefully with paper towels, and return them to the desiccator. Return the KBr powder to its desiccator.

B. Nujol Mulls

If an adequate KBr pellet cannot be obtained or if the solid is insoluble in a suitable solvent, the spectrum of a solid may be determined as a **Nujol mull**. In this method, finely grind about 5 mg of the solid sample in an agate mortar with a pestle. Then add 1 or 2 drops of Nujol mineral oil (white) and grind the mixture to a very fine dispersion. The solid is not dissolved in the Nujol; it is actually

a suspension. This mull is then placed between two salt plates using a rubber policeman. Mount the salt plates in the holder in the same way as for liquid samples (see Section 25.2).

Nujol is a mixture of high-molecular-weight hydrocarbons. Hence, it has absorptions in the C—H stretch and CH_2 and CH_3 bending regions of the spectrum (see Figure 25.7). Clearly, if Nujol is used, no information can be obtained in these portions of the spectrum. In interpreting the spectrum, you must ignore these Nujol peaks. It is important to label the spectrum immediately after it was determined, noting that it was determined as a Nujol mull. Otherwise, you might forget that the C—H peaks belong to Nujol and not to the dispersed solid.

25.6 Solid Samples—Solution Spectra

A. Method A—Solution Between Salt (NaCl) Plates

For substances that are soluble in carbon tetrachloride, a quick and easy method for determining the spectra of solids is available. Dissolve as much solid as possible in 0.1 mL of carbon tetrachloride. Place 1 or 2 drops of the solution between sodium chloride plates in precisely the same manner as used for pure liquids (see Section 25.2). The spectrum is determined as described for pure liquids using salt plates (see Section 25.2). You should work as quickly as possible. If there is a delay, the solvent will evaporate from between the plates before the spectrum is recorded. Because the spectrum contains the absorptions of the solute superimposed on the absorptions of carbon tetrachloride, it is important to remember that any absorption that appears near 800 cm^{-1} may be due to the stretching of the C—Cl bond of the solvent. Information contained to the right of about 900 cm^{-1} is not usable in this method. There are no other interfering bands for this solvent (see Figure 25.8), and any other absorptions can be attributed to your sample. Chloroform solutions should not be studied by this method because the solvent has too many interfering absorptions (see Figure 25.9).

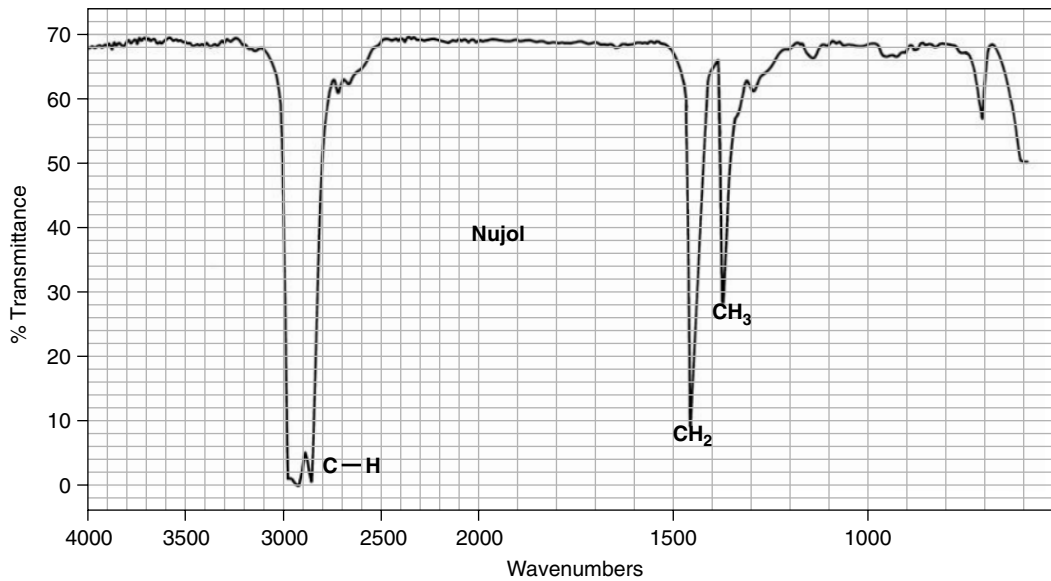


Figure 25.7 Infrared spectrum of Nujol (mineral oil).

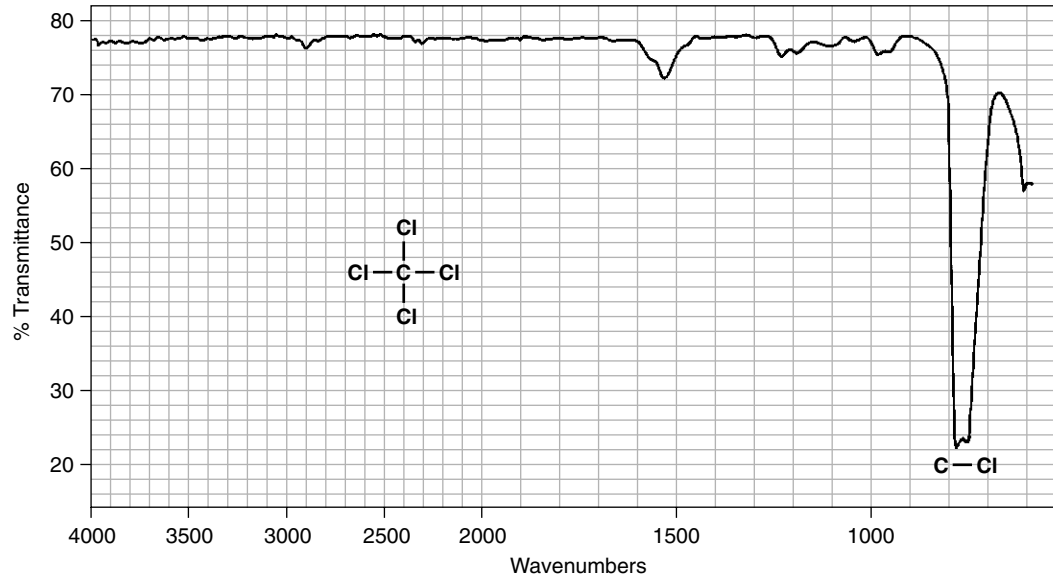


Figure 25.8 Infrared spectrum of carbon tetrachloride.

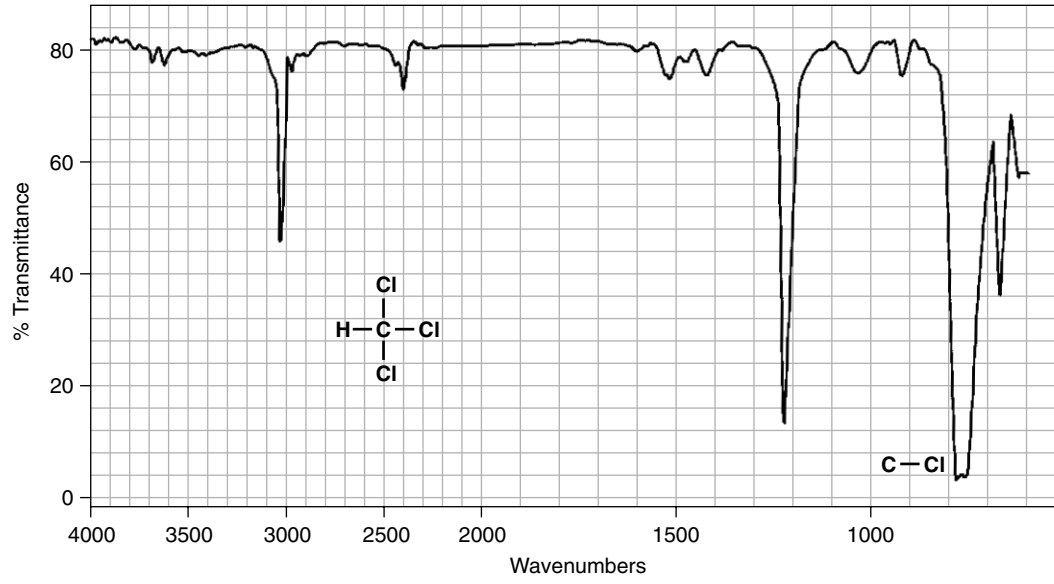


Figure 25.9 Infrared spectrum of chloroform.

CAUTION

Carbon tetrachloride is a hazardous solvent. Work under the hood!

Carbon tetrachloride, besides being toxic, is suspected of being a carcinogen. Despite the health problems associated with its use, there is no suitable alternative solvent for infrared spectroscopy. Other solvents have too many interfering infrared absorption bands. Handle carbon tetrachloride carefully to minimize the adverse

health effects. The spectroscopic-grade carbon tetrachloride should be stored in a glass-stoppered bottle in a hood. A Pasteur pipet should be attached to the bottle, possibly by storing it in a test tube taped to the side of the bottle. All sample preparation should be conducted in a hood. Rubber or plastic gloves should be worn. The cells should also be cleaned in the hood. All carbon tetrachloride used in preparing samples should be disposed of in an appropriately marked waste container.

B. Method B—AgCl Minicell

The AgCl minicell described in Section 25.3 may be used to determine the infrared spectrum of a solid dissolved in carbon tetrachloride. Prepare a 5–10% solution (5–10 mg in 0.1 mL) in carbon tetrachloride. If it is not possible to prepare a solution of this concentration because of low solubility, dissolve as much solid as possible in the solvent. Following the instructions given in Section 25.3, position the AgCl plates as shown in Figure 25.4C to obtain the maximum possible path length of 0.20 mm. When the cell is tightened firmly, the cell will not leak.

As indicated in method A, the spectrum will contain the absorptions of the dissolved solid superimposed on the absorptions of carbon tetrachloride. A strong absorption appears near 800 cm^{-1} for the C—Cl stretch in the solvent. No useful information may be obtained for the sample to the right of about 900 cm^{-1}, but other bands that appear in the spectrum will belong to your sample. Read the safety material provided in method A. Carbon tetrachloride is toxic, and it should be used under a hood.

NOTE: Care should be taken in cleaning the AgCl plates. Because AgCl plates scratch easily, they should not be wiped with tissue. Rinse them with methylene chloride and keep them in a dark place. Amines will destroy the plates.

C. Method C—Solution Cells (NaCl)

The spectra of solids may also be determined in a type of permanent sample cell called a **solution cell**. (The infrared spectra of liquids may also be determined in this cell.) The solution cell, shown in Figure 25.10, is made from two salt plates, mounted with a Teflon spacer between them to control the thickness of the sample. The top sodium chloride plate has two holes drilled in it so that the sample can be introduced into the cavity between the two plates. These holes are extended through the face plate by two tubular extensions designed to hold Teflon plugs, which seal the internal chamber and prevent evaporation. The tubular extensions are tapered so that a syringe body (Luer lock without a needle) will fit snugly into them from the outside. The cells are thus filled from a syringe; usually, they are held upright and filled from the bottom entrance port.

These cells are expensive, and you should try either method A or B before using solution cells. If you do need them, obtain your instructor's permission and receive instruction before using the cells. The cells are purchased in matched pairs, with identical path lengths. Dissolve a solid in a suitable solvent, usually carbon tetrachloride, and add the solution to one of the cells (**sample cell**) as described in the previous paragraph. The pure solvent, identical to that used to dissolve the solid, is placed in the other cell (**reference cell**). The spectrum of the solvent is subtracted from the spectrum of the solution (not always completely), and a spectrum of the solute is thus provided. For the solvent compensation to be as exact as possible and to avoid contamination of the reference cell, it is essential that one cell be used as

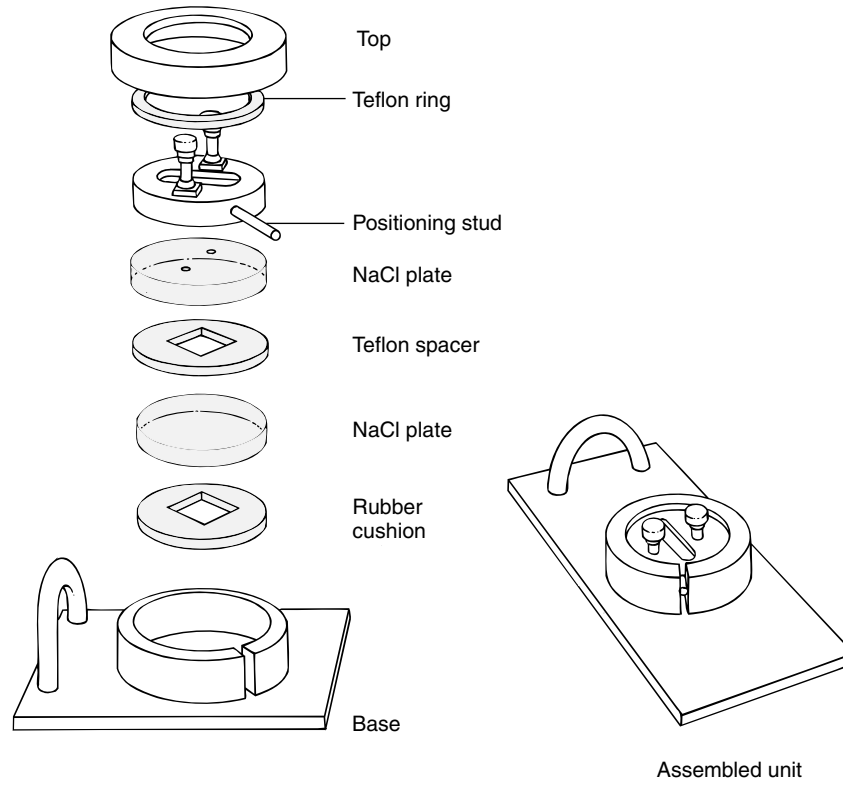


Figure 25.10 A solution cell.

a reference and that the other cell be used as a sample cell without ever being interchanged. After the spectrum is determined, it is important to clean the cells by flushing them with clean solvent. They should be dried by passing dry air through the cell.

Solvents most often used in determining infrared spectra are carbon tetrachloride (see Figure 25.8), chloroform (see Figure 25.9), and carbon disulfide (see Figure 25.11). A 5–10% solution of solid in one of these solvents usually gives a good spectrum. Carbon tetrachloride and chloroform are suspected carcinogens; however, because there are no suitable alternative solvents, these compounds must be used in infrared spectroscopy. The procedure outlined above for carbon tetrachloride should be followed. This procedure serves equally well for chloroform.

NOTE: Before you use the solution cells, you must obtain the instructor's permission and instruction on how to fill and clean the cells.

25.7 Recording the Spectrum

The instructor will describe how to operate the infrared spectrophotometer, because the controls vary considerably, depending on the manufacturer, model of the instrument, and type. For example, some instruments involve pushing only a few buttons, whereas others use a more complicated computer interface system.

In all cases, it is important that the sample, the solvent, the type of cell or method used, and any other pertinent information be written on the spectrum immediately after the determination. This information may be important, and it is easily forgotten if not recorded. You may also need to calibrate the instrument (see Section 25.8).

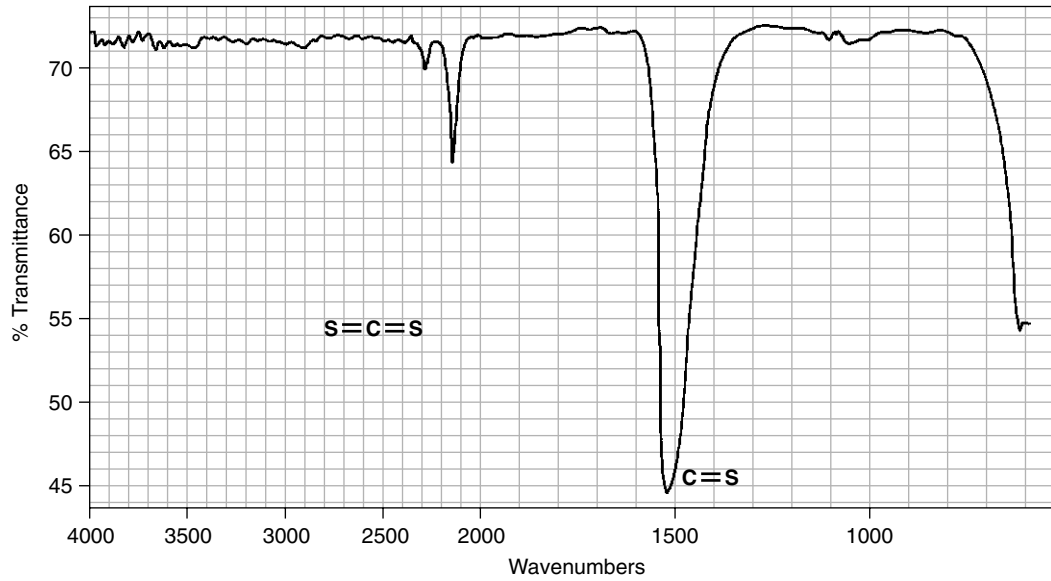


Figure 25.11 Infrared spectrum of carbon disulfide.

25.8 Calibration

For some instruments, the frequency scale of the spectrum must be calibrated so that you know the position of each absorption peak precisely. You can recalibrate by recording a very small portion of the spectrum of polystyrene over the spectrum of your sample. The complete spectrum of polystyrene is shown in Figure 25.12. The most important of these peaks is at 1603 cm^{-1}; other useful peaks are at

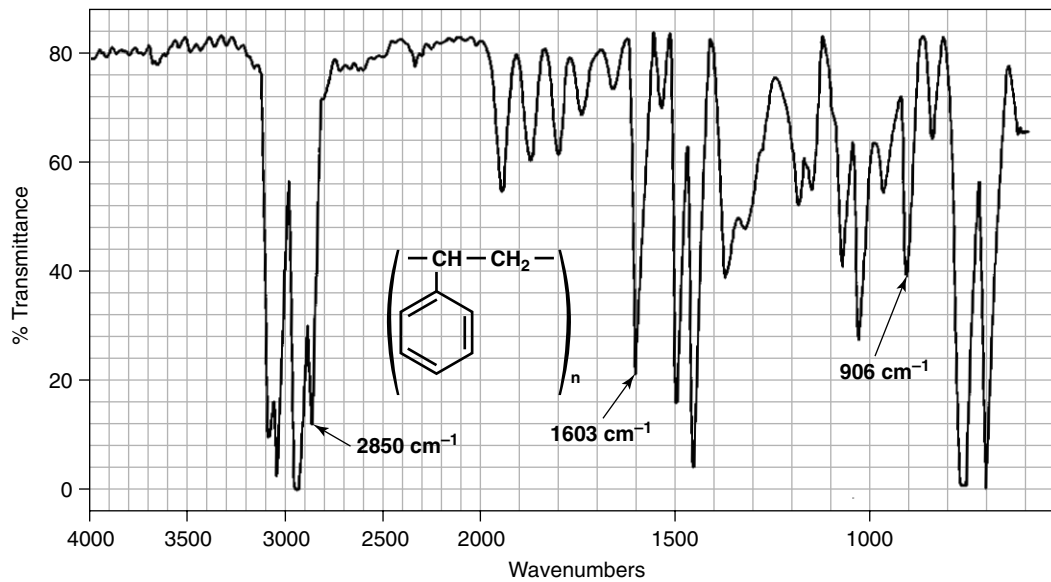


Figure 25.12 Infrared spectrum of polystyrene (thin film).

2850 cm^{-1} and 906 cm^{-1}. After you record the spectrum of your sample, substitute a thin film of polystyrene for the sample cell and record the tips (not the entire spectrum) of the most important peaks over the sample spectrum.

It is always a good idea to calibrate a spectrum when the instrument uses chart paper with a preprinted scale. It is difficult to align the paper properly so that the scale matches the absorption lines precisely. You often need to know the precise values for certain functional groups (for example, the carbonyl group). Calibration is essential in these cases.

With computer-interfaced instruments, the instrument does not need to be calibrated. With this type of instrument, the spectrum and scale are printed on blank paper at the same time. The instrument has an internal calibration that ensures that the positions of the absorptions are known precisely and that they are placed at the proper positions on the scale. With this type of instrument, it is often possible to print a list of the locations of the major peaks as well as to obtain the complete spectrum of your compound.

PART B. INFRARED SPECTROSCOPY

25.9 Uses of the Infrared Spectrum

Because every type of bond has a different natural frequency of vibration and because the same type of bond in two different compounds is in a slightly different environment, no two molecules of different structure have exactly the same infrared absorption pattern, or **infrared spectrum**. Although some of the frequencies absorbed in the two cases might be the same, in no case of two different molecules will their infrared spectra (the patterns of absorption) be identical. Thus, the infrared spectrum can be used to identify molecules much as a fingerprint can be used to identify people. Comparing the infrared spectra of two substances thought to be identical will establish whether or not they are in fact identical. If the infrared spectra of two substances coincide peak for peak (absorption for absorption), in most cases, the substances are identical.

A second and more important use of the infrared spectrum is that it gives structural information about a molecule. The absorptions of each type of bond (N—H, C—H, O—H, C—X, C═O, C—O, C—C, C═C, C≡C, C≡N, and so on) are regularly found only in certain small portions of the vibrational infrared region. A small range of absorption can be defined for each type of bond. Outside this range, absorptions will normally be due to some other type of bond. Thus, for instance, any absorption in the range 3000 ± 150 cm^{-1} will almost always be due to the presence of a CH bond in the molecule; an absorption in the range 1700 ± 100 cm^{-1} will normally be due to the presence of a C═O bond (carbonyl group) in the molecule. The same type of range applies to each type of bond. The way these are spread out over the vibrational infrared is illustrated schematically in Figure 25.13. It is a good idea to remember this general scheme for future convenience.

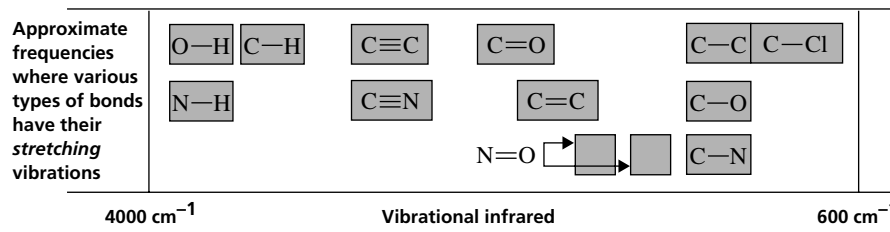
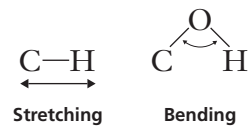


Figure 25.13 Approximate regions in which various common types of bonds absorb. (Bending, twisting, and other types of bond vibration have been omitted for clarity.)

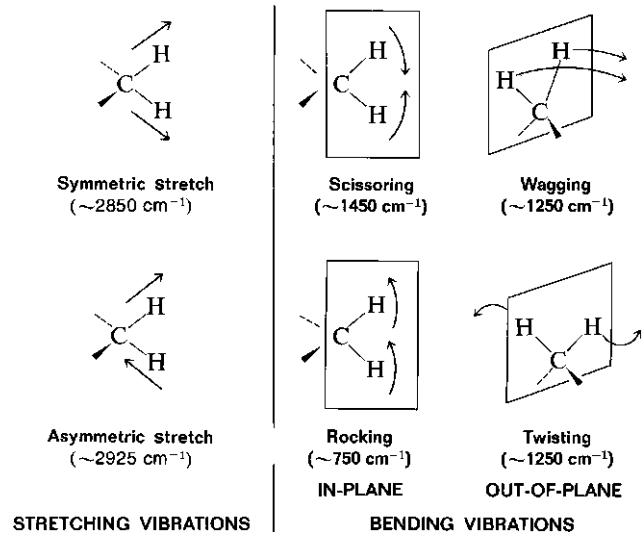
25.10 Modes of Vibration

The simplest types, or **modes**, of vibrational motion in a molecule that are **infrared active**, that is, give rise to absorptions, are the stretching and bending modes.



Other, more complex types of stretching and bending are also active, however. To introduce several words of terminology, the normal modes of vibration for a methylene group are shown below.

In any group of three or more atoms—at least two of which are identical—there are *two* modes of stretching or bending: the symmetric mode and asymmetric mode. Examples of such groupings are $—CH_3$, $—CH_2—$, $—NO_2$, $—NH_2$, and anhydrides $(CO)_2O$. For the anhydride, owing to asymmetric and symmetric modes of stretch, this functional group gives *two* absorptions in the C=O region. A similar phenomenon is seen for amino groups, where primary amines usually have *two* absorptions in the NH stretch region, whereas secondary amines R_2NH have only one absorption peak. Amides show similar bands. There are two strong N=O stretch peaks for a nitro group, which are caused by asymmetric and symmetric stretching modes.



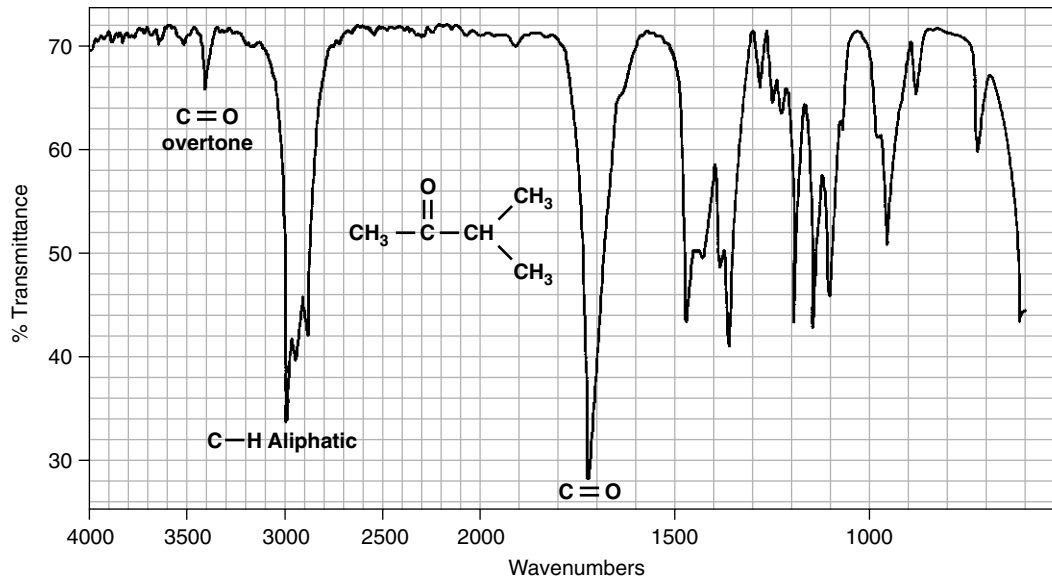


Figure 25.14 Infrared spectrum of methyl isopropyl ketone (neat liquid, salt plates).

25.11 What to Look for in Examining Infrared Spectra

The instrument that determines the absorption spectrum for a compound is called an **infrared spectrophotometer**. The spectrophotometer determines the relative strengths and positions of all the absorptions in the infrared region and plots this information on a piece of paper. This plot of absorption intensity versus wavenumber or wavelength is referred to as the **infrared spectrum** of the compound. A typical infrared spectrum, that of methyl isopropyl ketone, is shown in Figure 25.14.

The strong absorption in the middle of the spectrum corresponds to C═O, the carbonyl group. Note that the C═O peak is quite intense. In addition to the characteristic position of absorption, the **shape** and **intensity** of this peak are also unique to the C═O bond. This is true for almost every type of absorption peak; both shape and intensity characteristics can be described, and these characteristics often make it possible to distinguish the peak in a confusing situation. For instance, to some extent both C═O and C═C bonds absorb in the same region of the infrared spectrum:

C═O 1850–1630 cm^{-1}

C═C 1680–1620 cm^{-1}

However, the C═O bond is a strong absorber, whereas the C═C bond generally absorbs only weakly. Hence, a trained observer would not normally interpret a strong peak at 1670 cm^{-1} to be a carbon–carbon double bond or a weak absorption at this frequency to be due to a carbonyl group.

The shape of a peak often gives a clue to its identity as well. Thus, although the NH and OH regions of the infrared overlap,

OH 3650–3200 cm^{-1}

NH 3500–3300 cm^{-1}

NH usually gives a **sharp** absorption peak (absorbs a very narrow range of frequencies), and OH, when it is in the NH region, usually gives a **broad** absorption peak. Primary amines give *two* absorptions in this region, whereas alcohols give only one.

Therefore, while you are studying the sample spectra in the pages that follow, you should also notice shapes and intensities. They are as important as the frequency at which an absorption occurs, and you must train your eye to recognize these features. In the literature of organic chemistry, you will often find absorptions referred to as strong (s), medium (m), weak (w), broad, or sharp. The author is trying to convey some idea of what the peak looks like without actually drawing the spectrum. Although the intensity of an absorption often provides useful information about the identity of a peak, be aware that the relative intensities of all of the peaks in the spectrum are dependent on the amount of sample that is used and the sensitivity setting of the instrument. Therefore, the *actual* intensity of a particular peak may vary from spectrum to spectrum, and you must pay attention to *relative* intensities.

25.12 Correlation Charts and Tables

To extract structural information from infrared spectra, you must know the frequencies or wavelengths at which various functional groups absorb. Infrared **correlation tables** present as much information as is known about where the various functional groups absorb. The books listed at the end of this chapter present extensive lists of correlation tables. Sometimes, the absorption information is given in a chart, called a **correlation chart**. A simplified correlation table is given in Table 25.1.

Although you may think assimilating the mass of data in Table 25.1 will be difficult, it is not if you make a modest start and then gradually increase your familiarity with the data. An ability to interpret the fine details of an infrared spectrum will follow. This is most easily accomplished by first establishing the broad visual patterns of Figure 25.13 firmly in mind. Then, as a second step, a "typical absorption value" can be memorized for each of the functional groups in this pattern. This value will be a single number that can be used as a pivot value for the memory. For instance, start with a simple aliphatic ketone as a model for all typical carbonyl compounds. The typical aliphatic ketone has a carbonyl absorption of $1715 \pm 10\ cm^{-1}$. Without worrying about the variation, memorize $1715\ cm^{-1}$ as the base value for carbonyl absorption. Then learn the extent of the carbonyl range and the visual pattern of how the different kinds of carbonyl groups are arranged throughout this region. See, for instance, Figure 25.27, which gives typical values for carbonyl compounds. Also learn how factors such as ring size (when the functional group is contained in a ring) and conjugation affect the base values (that is, in which direction the values are shifted). Learn the trends—always remembering the base value ($1715\ cm^{-1}$). It might prove useful as a beginning to memorize the base values in Table 25.2 for this approach. Notice that there are only eight values.

25.13 Analyzing a Spectrum (Or What You Can Tell at a Glance)

In analyzing the spectrum of an unknown, concentrate first on establishing the presence (or absence) of a few major functional groups. The most conspicuous peaks are C═O, O—H, N—H, C—O, C═C, C≡C, C≡N, and NO_2. If they are present, they give immediate structural information. Do not try to analyze in detail the CH absorptions near $3000\ cm^{-1}$; almost all compounds have these absorptions.

TABLE 25.1 A Simplified Correlation Table

	Type of Vibration		Frequency (cm^{-1})	Intensity[a]
C—H	Alkanes	(stretch)	3000–2850	s
	—CH_3	(bend)	1450 and 1375	m
	—CH_2—	(bend)	1465	m
	Alkenes	(stretch)	3100–3000	m
		(bend)	1700–1000	s
	Aromatics	(stretch)	3150–3050	s
		(out-of-plane bend)	1000–700	s
	Alkyne	(stretch)	ca. 3300	s
	Aldehyde		2900–2800	w
			2800–2700	w
C—C	Alkane	Not interpretatively useful		
C=C	Alkene		1680–1600	m–w
	Aromatic		1600–1400	m–w
C≡C	Alkyne		2250–2100	m–w
C=O	Aldehyde		1740–1720	s
	Ketone (acyclic)		1725–1705	s
	Carboxylic acid		1725–1700	s
	Ester		1750–1730	s
	Amide		1700–1640	s
	Anhydride		ca. 1810	s
			ca. 1760	s
C—O	Alcohols, ethers, esters, carboxylic acids		1300–1000	s
O—H	Alcohol, phenols			
	Free		3650–3600	m
	H-Bonded		3400–3200	m
	Carboxylic acids		3300–2500	m
N—H	Primary and secondary amines		ca. 3500	m
C≡N	Nitriles		2260–2240	m
N=O	Nitro (R—NO_2)		1600–1500	s
			1400–1300	s
C—X	Fluoride		1400–1000	s
	Chloride		800–600	s
	Bromide, iodide		<600	s

[a] s, strong; m, medium; w, weak.

TABLE 25.2 Base Values for Absorptions of Bonds

O—H	3400 cm^{-1}	C≡C	2150 cm^{-1}
N—H	3500 cm^{-1}	C=O	1715 cm^{-1}
C—H	3000 cm^{-1}	C=C	1650 cm^{-1}
C≡N	2250 cm^{-1}	C—O	1100 cm^{-1}

Do not worry about subtleties of the exact type of environment in which the functional group is found. A checklist of the important gross features follows:

1. Is a carbonyl group present?
The C═O group gives rise to a strong absorption in the region 1820–1600 cm^{-1}. The peak is often the strongest in the spectrum and of medium width. You can't miss it.

2. If C═O is present, check the following types. (If it is absent, go to item 3.)

Acids	Is O—H also present? **Broad** absorption near 3300–2500 cm^{-1} (usually overlaps C—H).
Amides	Is N—H also present? Medium absorption near 3500 cm^{-1}, sometimes a double peak, equivalent halves.
Esters	Is C—O also present? Medium intensity absorptions near 1300–1000 cm^{-1}.
Anhydrides	Have *two* C═O absorptions near 1810 and 1760 cm^{-1}.
Aldehydes	Is aldehyde C—H present? Two weak absorptions near 2850 cm^{-1} and 2750 cm^{-1} on the right side of C—H absorptions.
Ketones	The preceding five choices have been eliminated.

3. If C═O is absent

Alcohols or Phenols	Check for O—H. **Broad** absorption near 3600–3300 cm^{-1}. Confirm this by finding C—O near 1300–1000 cm^{-1}.
Amines	Check for N—H. Medium absorption(s) near 3500 cm^{-1}.
Ethers	Check for C—O (and absence of O—H) near 1300–1000 cm^{-1}.

4. Double bonds or aromatic rings or both
C═C is a **weak** absorption near 1650 cm^{-1}.
Medium to strong absorptions in the region 1650–1450 cm^{-1} often imply an aromatic ring.
Confirm the above by consulting the C—H region.
Aromatic and vinyl C—H occur to the left of 3000 cm^{-1} (aliphatic C—H occurs to the right of this value).

5. Triple bonds
C≡N is a medium, sharp absorption near 2250 cm^{-1}.
C≡C is a weak but sharp absorption near 2150 cm^{-1}.
Check also for acetylenic C—H near 3300 cm^{-1}.

6. Nitro groups
Two strong absorptions near 1600–1500 cm^{-1} and 1390–1300 cm^{-1}.

7. Hydrocarbons
None of the above is found.
Main absorptions are in the C—H region near 3000 cm^{-1}.
Very simple spectrum, only other absorptions are near 1450 cm^{-1} and 1375 cm^{-1}.

The beginning student should resist the idea of trying to assign or interpret *every* peak in the spectrum. You simply will not be able to do this. Concentrate first on learning the principal peaks and recognizing their presence or absence. This is best done by carefully studying the illustrative spectra in the section that follows.

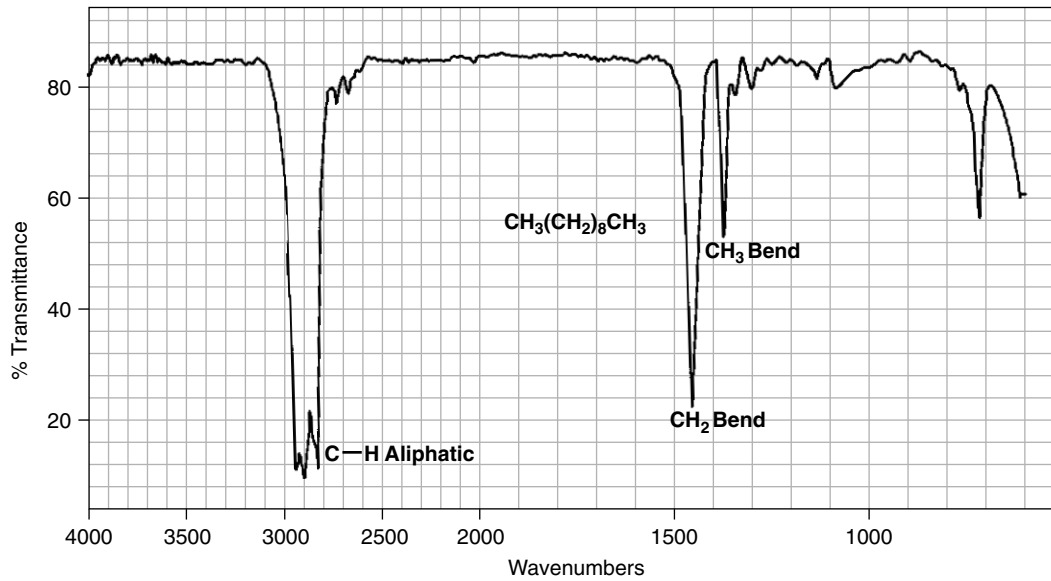


Figure 25.15 Infrared spectrum of decane (neat liquid, salt plates).

NOTE: In describing the shifts of absorption peaks or their relative positions, we have used the phrases "to the left" and "to the right." This was done to simplify descriptions of peak positions. The meaning is clear because all spectra are conventionally presented left to right from 4000–600 cm^{-1}.

25.14 Survey of the Important Functional Groups

A. Alkanes

The spectrum is usually simple, with a few peaks.

C—H Stretch occurs around 3000 cm^{-1}.
1. In alkanes (except strained ring compounds), absorption always occurs to the right of 3000 cm^{-1}.
2. If a compound has vinylic, aromatic, acetylenic, or cyclopropyl hydrogens, the CH absorption is to the left of 3000 cm^{-1}.

CH_2 Methylene groups have a characteristic absorption at approximately 1450 cm^{-1}.

CH_3 Methyl groups have a characteristic absorption at approximately 1375 cm^{-1}.

C—C Stretch—not interpretatively useful—has many peaks.

The spectrum of decane is shown in Figure 25.15.

B. Alkenes

=C—H Stretch occurs to the left of 3000 cm^{-1}.

=C—H Out-of-plane (oop) bending occurs at 1000–650 cm^{-1}.
The C—H oop absorptions often allow you to determine the type of substitution pattern on the double bond, according to the number of absorptions and their positions. The correlation chart in Figure 25.16 shows the positions of these bands.

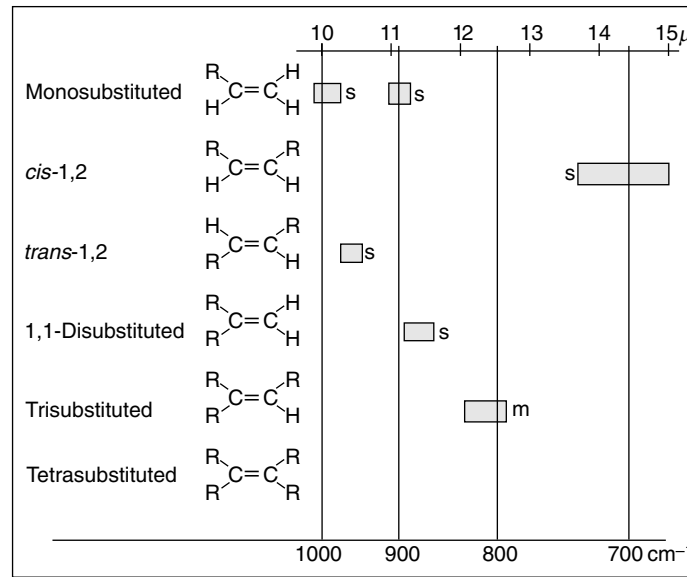


Figure 25.16 The C—H out-of-plane bending vibrations for substituted alkenes.

C═C Stretch 1675–1600cm^{-1}, often weak.
Conjugation moves C═C stretch to the right.
Symmetrically substituted bonds, as in 2,3-dimethyl-2-butene, do not absorb in the infrared region (no dipole change). Highly substituted double bonds are often vanishingly weak in absorption.

The spectra of 4-methylcyclohexene and styrene are shown in Figures 25.17 and 25.18.

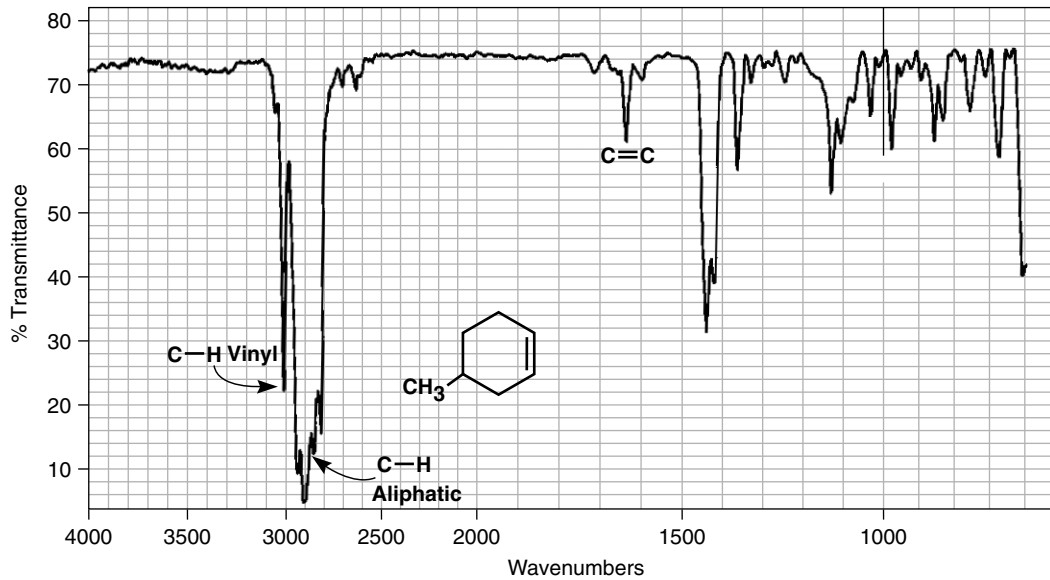


Figure 25.17 Infrared spectrum of 4-methylcyclohexene (neat liquid, salt plates).

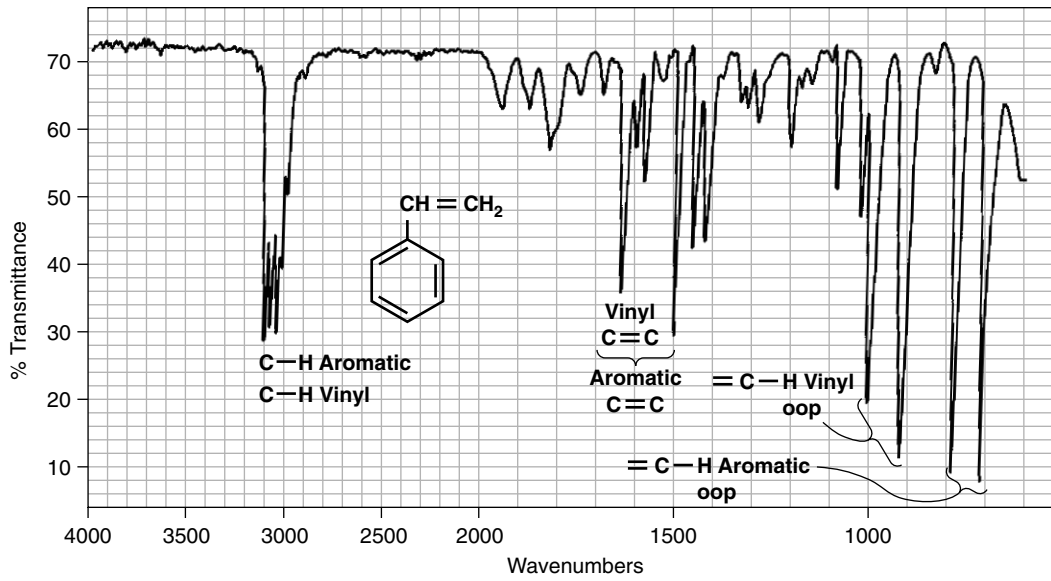


Figure 25.18 Infrared spectrum of styrene (neat liquid, salt plates).

C. Aromatic Rings

═C—H Stretch is always to the left of 3000 cm^{-1}.

═C—H Out-of-plane oop bending occurs at 900 to 690 cm^{-1}.

The C—H oop absorptions often allow you to determine the type of ring substitution by their numbers, intensities, and positions. The correlation chart in Figure 25.19A indicates the positions of these bands.

The patterns are generally reliable—they are most reliable for rings with alkyl substituents and least reliable for polar substituents.

Ring Absorptions (C═C). There are often four sharp absorptions that occur in pairs at 1600 cm^{-1} and 1450 cm^{-1} and are characteristic of an aromatic ring. See, for example, the spectra of anisole (Figure 25.23), benzonitrile (Figure 25.26), and methyl benzoate (Figure 25.35).

There are many weak combination and overtone absorptions that appear between 2000 cm^{-1} and 1667 cm^{-1}. The relative shapes and numbers of these peaks can be used to determine whether an aromatic ring is monosubstituted or di-, tri-, tetra-, penta-, or hexa-substituted. Positional isomers can also be distinguished. Because the absorptions are weak, these bands are best observed by using neat liquids or concentrated solutions. If the compound has a high-frequency carbonyl group, this absorption overlaps the weak overtone bands, so no useful information can be obtained from analyzing this region. The various patterns that are obtained in this region are shown in Figure 25.19B.

The spectra of styrene and *o*-dichlorobenzene are shown in Figures 25.18 and 25.20.

D. Alkynes

≡C—H Stretch is usually near 3300 cm^{-1}, sharp peak.

C≡C Stretch is near 2150 cm^{-1}, sharp peak.

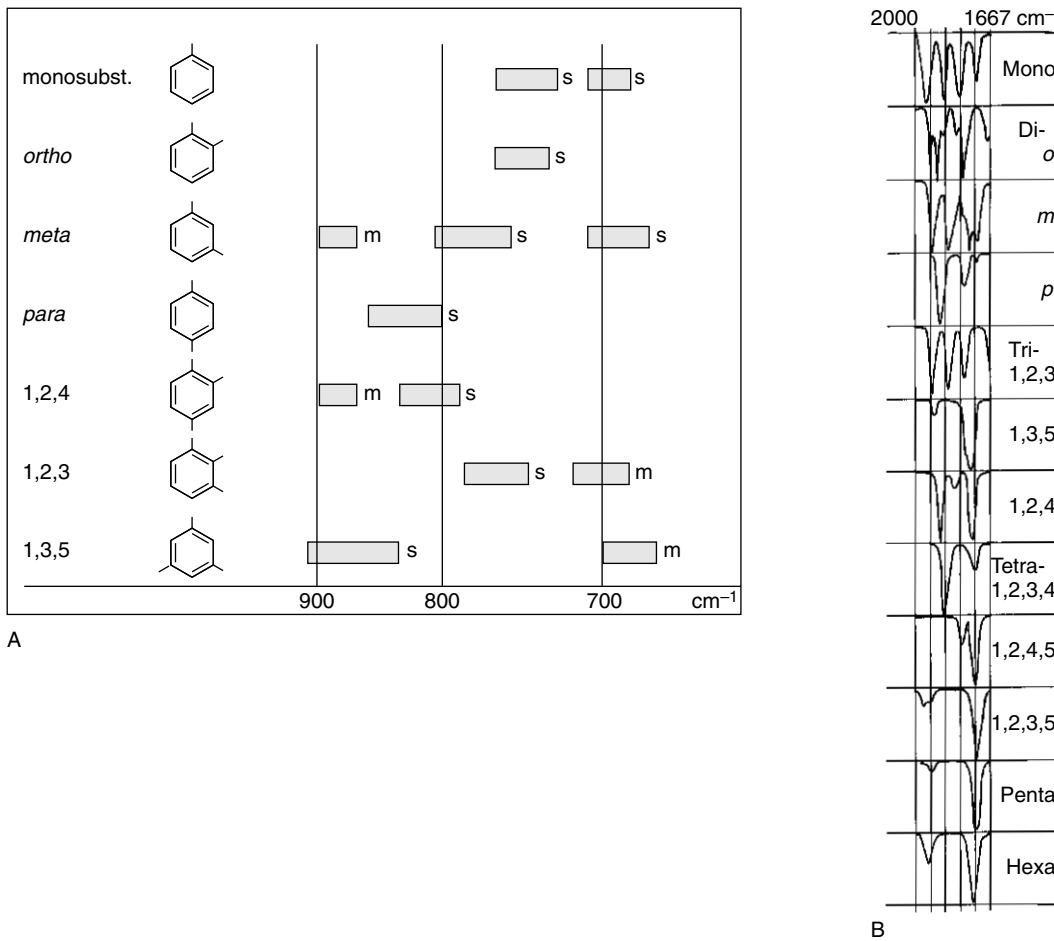


Figure 25.19 (**A**) The C—H out-of-plane bending vibrations for substituted benzenoid compounds. (**B**) The 2000–1667 cm^{-1} region for substituted benzenoid compounds. (From Dyer, J.R., *Applications of Absorption Spectroscopy of Organic Compounds,* Englewood Cliffs, NJ: Prentice Hall, 1965.)

Conjugation moves C≡C stretch to the right.
Disubstituted or symmetrically substituted triple bonds give either no absorption or weak absorption.

E. Alcohols and Phenols

O—H Stretch is a sharp peak at 3650–3600 cm^{-1} if no hydrogen bonding takes place. (This is usually observed only in dilute solutions.)
If there is hydrogen bonding (usual in neat or concentrated solutions), the absorption is *broad* and occurs more to the right at 3500–3200 cm^{-1}, sometimes overlapping C—H stretch absorptions.

C—O Stretch is usually in the range of 1300–1000 cm^{-1}.
Phenols are like alcohols. The 2-naphthol shown in Figure 25.21 has some molecules hydrogen bonded and some free. The spectrum of 4-methylcyclohexanol is shown in Figure 25.22. This alcohol, which was determined neat, would also have had a free OH spike to the left of this hydrogen-bonded band if it had been determined in dilute solution.

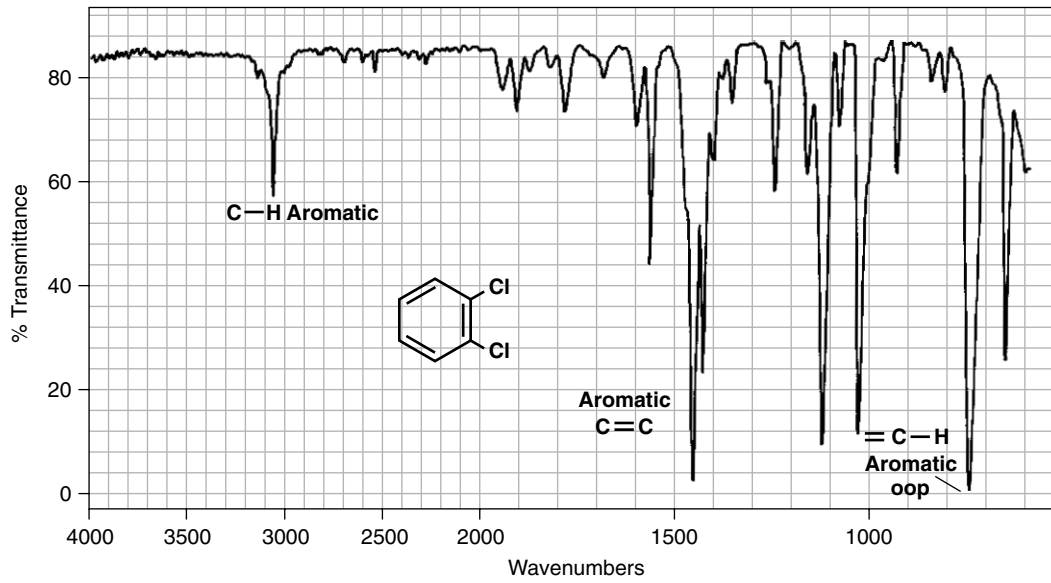


Figure 25.20 Infrared spectrum of o-dichlorobenzene (neat liquid, salt plates).

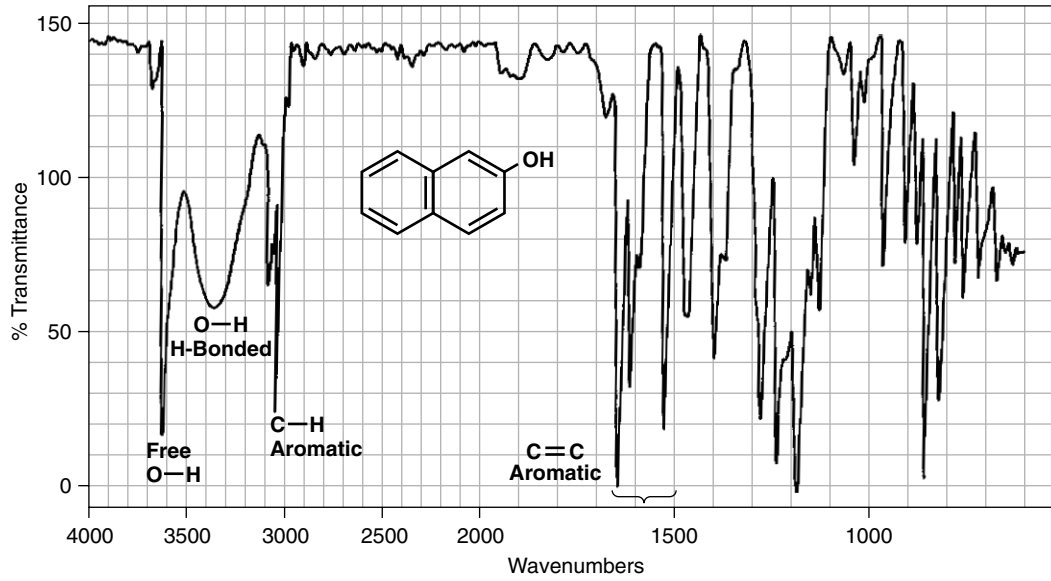


Figure 25.21 Infrared spectrum of 2-naphthol showing both free and hydrogen-bonded OH ($CHCl_3$ solution).

F. Ethers

C—O The most prominent band is due to C—O stretch at 1300–1000 cm^{-1}. Absence of C=O and O—H bands is required to be sure the C—O stretch is not due to an alcohol or ester. Phenyl and vinyl ethers are found in the left portion of the range, aliphatic ethers in the right. (Conjugation with the oxygen moves the absorption to the left.)

The spectrum of anisole is shown in Figure 25.23.

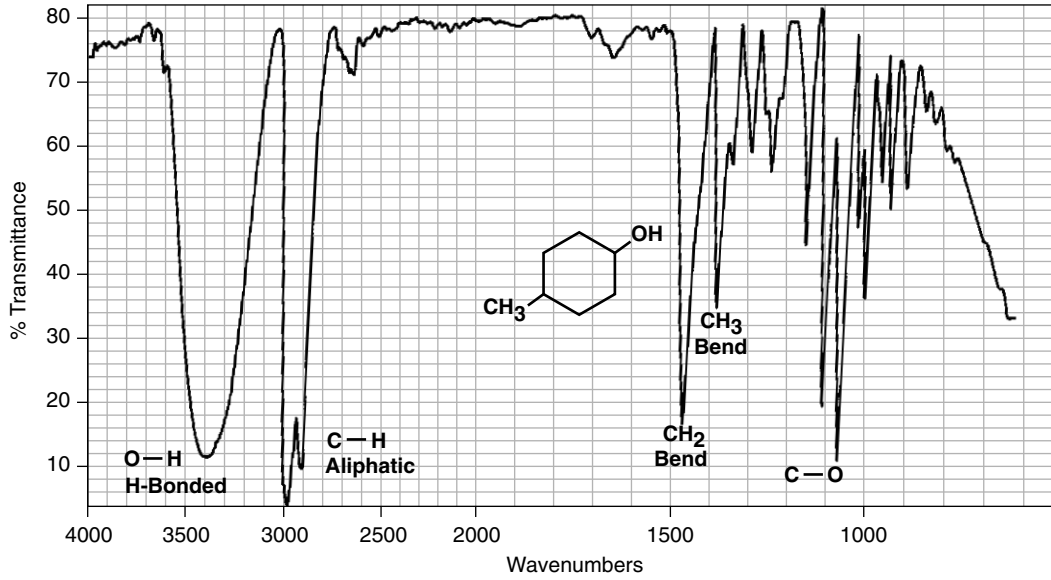


Figure 25.22 Infrared spectrum of 4-methylcyclohexanol (neat liquid, salt plates).

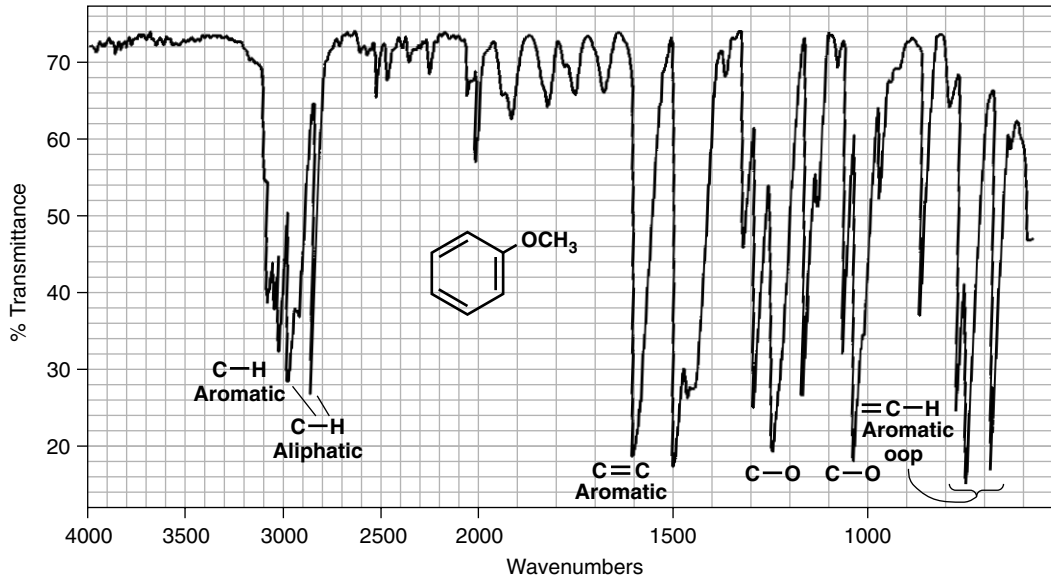


Figure 25.23 Infrared spectrum of anisole (neat liquid, salt plates).

G. Amines

N—H Stretch occurs in the range of 3500–3300 cm^{-1}.
Primary amines have *two* bands typically 30 cm^{-1} apart.
Secondary amines have one band, often vanishingly weak.
Tertiary amines have no NH stretch.

C—N Stretch is weak and occurs in the range of 1350–1000 cm^{-1}.

N—H Scissoring bending mode occurs in the range of 1640–1560 cm^{-1} (broad).
An oop bending absorption can sometimes be observed at about 800 cm^{-1}.

The spectrum of *n*-butylamine is shown in Figure 25.24.

H. Nitro Compounds

N═O Stretch is usually two strong bands at 1600–1500 cm^{-1} and 1390–1300 cm^{-1}.

The spectrum of nitrobenzene is shown in Figure 25.25.

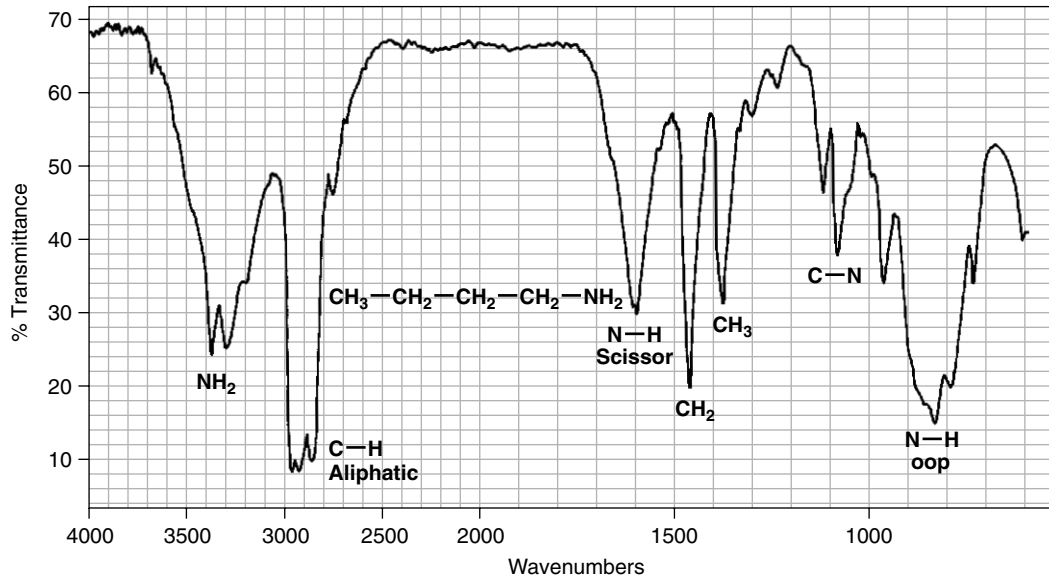


Figure 25.24 Infrared spectrum of *n*-butylamine (neat liquid, salt plates).

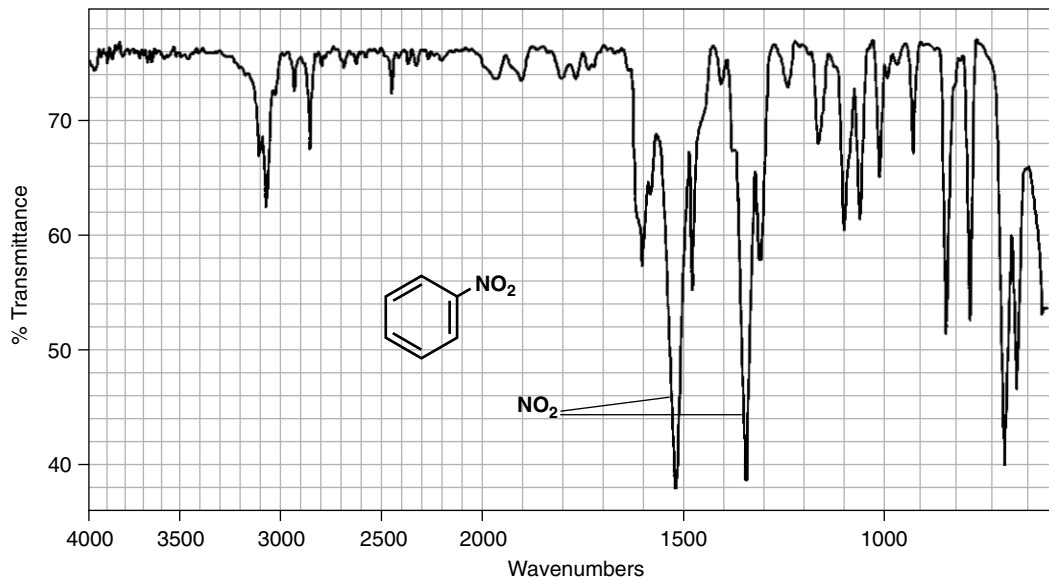


Figure 25.25 Infrared spectrum of nitrobenzene (neat liquid, salt plates).

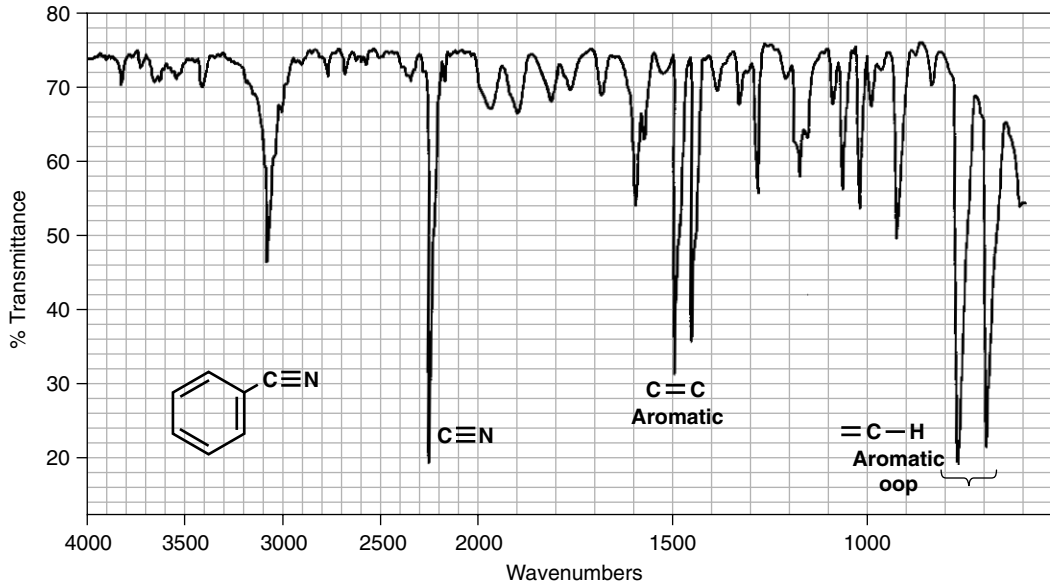


Figure 25.26 Infrared spectrum of benzonitrile (neat liquid, salt plates).

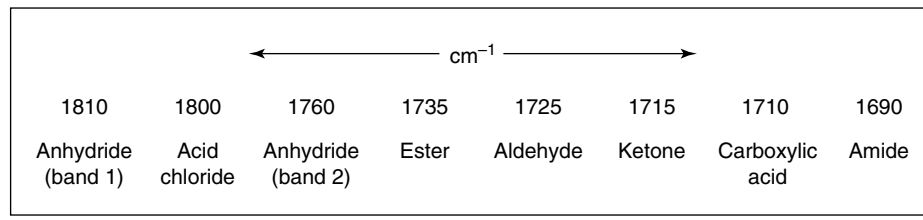


Figure 25.27 Normal base values for the C═O stretching vibrations for carbonyl groups.

I. Nitriles

C≡N Stretch is a sharp absorption near 2250 cm^{-1}.
Conjugation with double bonds or aromatic rings moves the absorption to the right.

The spectrum of benzonitrile is shown in Figure 25.26.

J. Carbonyl Compounds

The carbonyl group is one of the most strongly absorbing groups in the infrared region of the spectrum. This is mainly due to its large dipole moment. It absorbs in a variety of compounds (aldehydes, ketones, acids, esters, amides, anhydrides, and acid chlorides) in the range of 1850–1650 cm^{-1}. In Figure 25.27, the normal values for the various types of carbonyl groups are compared. In the sections that follow, each type is examined separately.

K. Aldehydes

C═O Stretch at approximately 1725 cm^{-1} is normal.
Aldehydes *seldom* absorb to the left of this value.
Conjugation moves the absorption to the right.

C—H Stretch, aldehyde hydrogen (—CHO), consists of *weak* bands at about 2750 cm^{-1} and 2850 cm^{-1}. Note that the CH stretch in alkyl chains does not usually extend this far to the right.

The spectrum of an unconjugated aldehyde, nonanal, is shown in Figure 25.28, and the conjugated aldehyde, benzaldehyde, is shown in Figure 25.29.

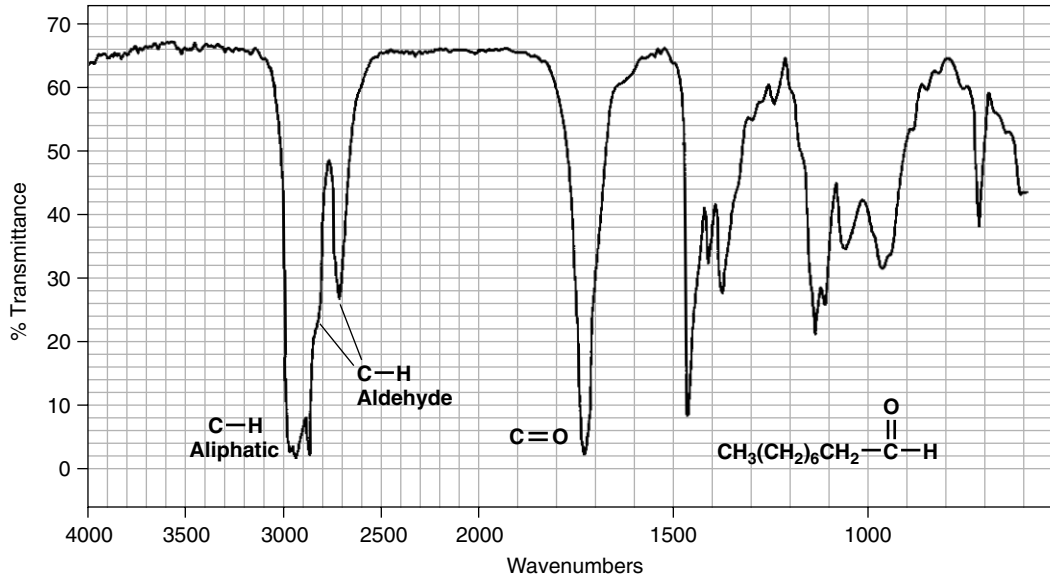


Figure 25.28 Infrared spectrum of nonanal (neat liquid, salt plates).

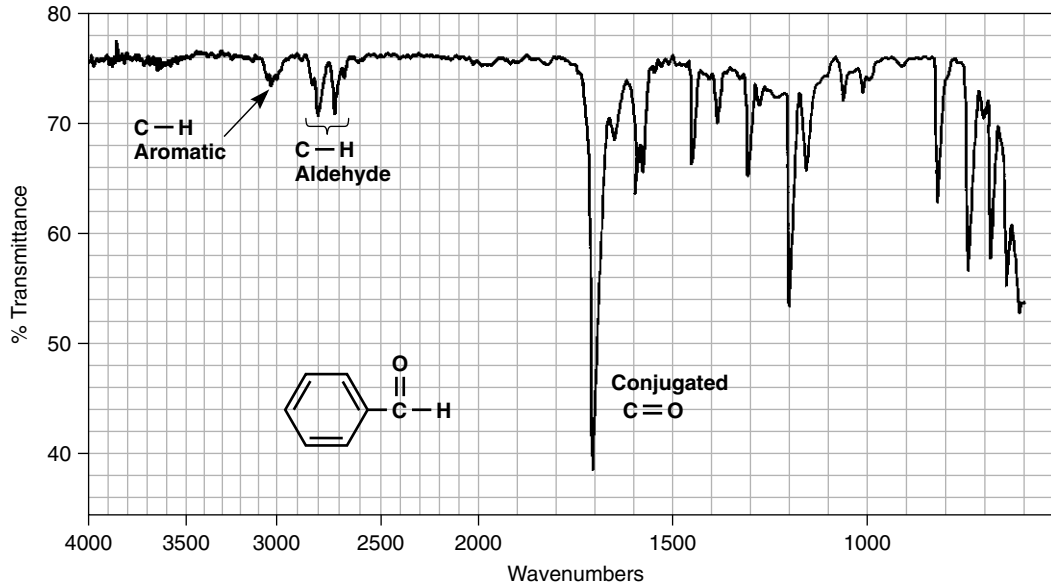


Figure 25.29 Infrared spectrum of benzaldehyde (neat liquid, salt plates).

L. Ketones

C═O Stretch at approximately 1715 cm^{-1} is normal.
Conjugation moves the absorption to the right.
Ring strain moves the absorption to the left in cyclic ketones (see Figure 25.30).

The spectra of methyl isopropyl ketone and mesityl oxide are shown in Figures 25.14 and 25.31. The spectrum of camphor, shown in Figure 25.32, has a carbonyl group that has been shifted to a higher frequency because of ring strain (1745 cm^{-1}).

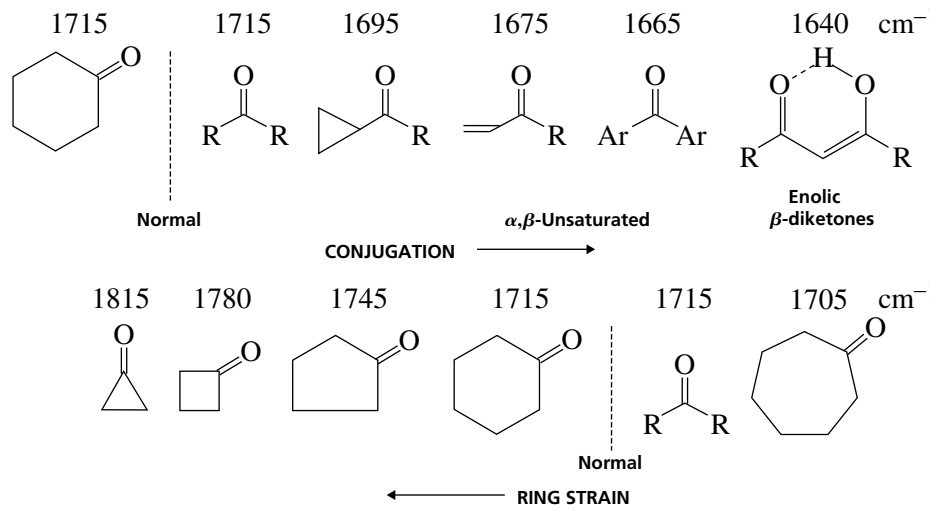


Figure 25.30 Effects of conjugation and ring strain on carbonyl frequencies in ketones.

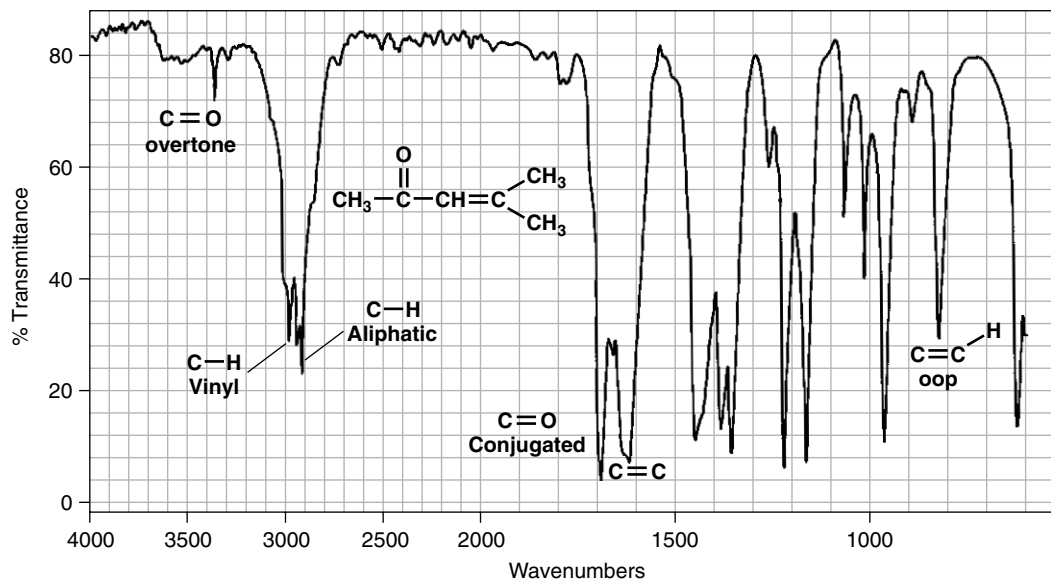


Figure 25.31 Infrared spectrum of mesityl oxide (neat liquid, salt plates).

M. Acids

O—H Stretch, usually *very broad* (strongly hydrogen-bonded) at 3300–2500 cm^{-1}, often interferes with C—H absorptions.

C═O Stretch, broad, 1730–1700 cm^{-1}. Conjugation moves the absorption to the right.

C—O Stretch, in the range of 1320–1210 cm^{-1}, is strong.

The spectrum of benzoic acid is shown in Figure 25.33.

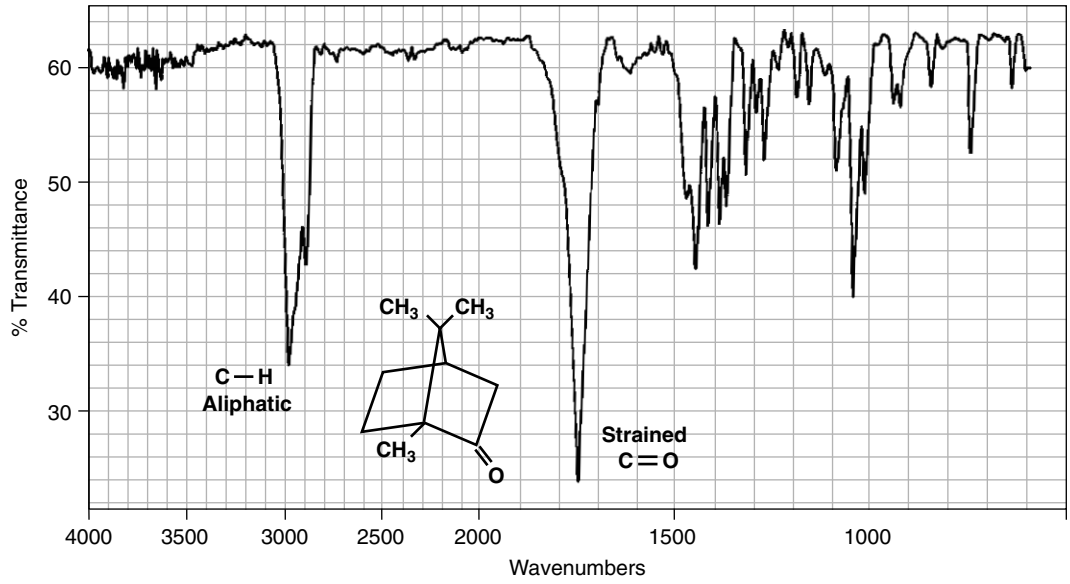


Figure 25.32 Infrared spectrum of camphor (KBr pellet).

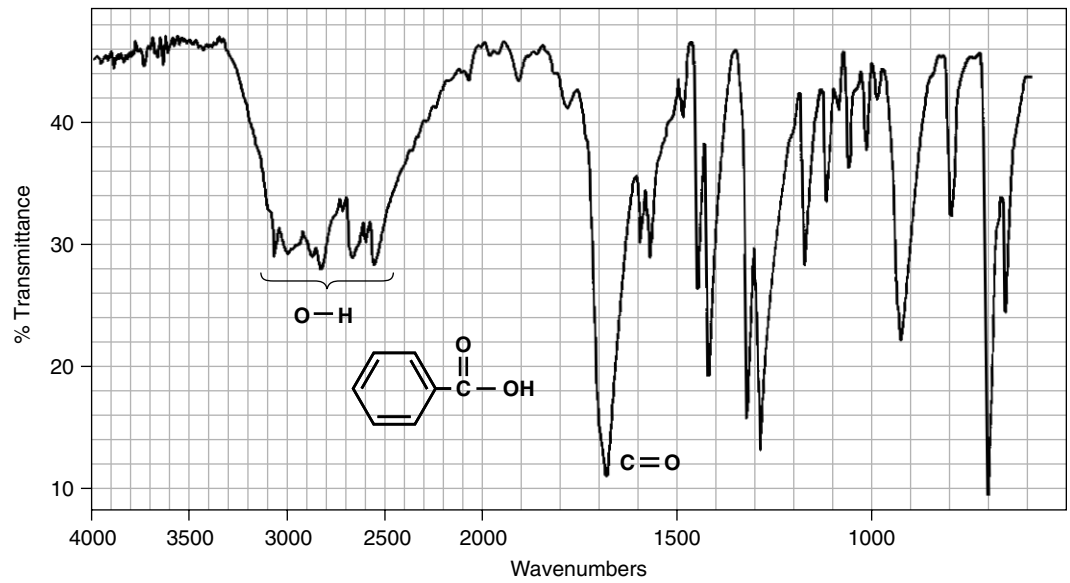


Figure 25.33 Infrared spectrum of benzoic acid (KBr pellet).

N. Esters (R—C(=O)—OR′)

C=O Stretch occurs at about 1735 cm^{-1} in normal esters.

1. Conjugation in the R part moves the absorption to the right.
2. Conjugation with the O in the R′ part moves the absorption to the left.
3. Ring strain (lactones) moves the absorption to the left.

C—O Stretch, two bands or more, one stronger than the others, is in the range of 1300–1000 cm^{-1}.

The spectrum of an unconjugated ester, isopentyl acetate, is shown in Figure 25.34 (C=O appears at 1740 cm^{-1}). A conjugated ester, methyl benzoate, is shown in Figure 25.35 (C=O appears at 1720 cm^{-1}).

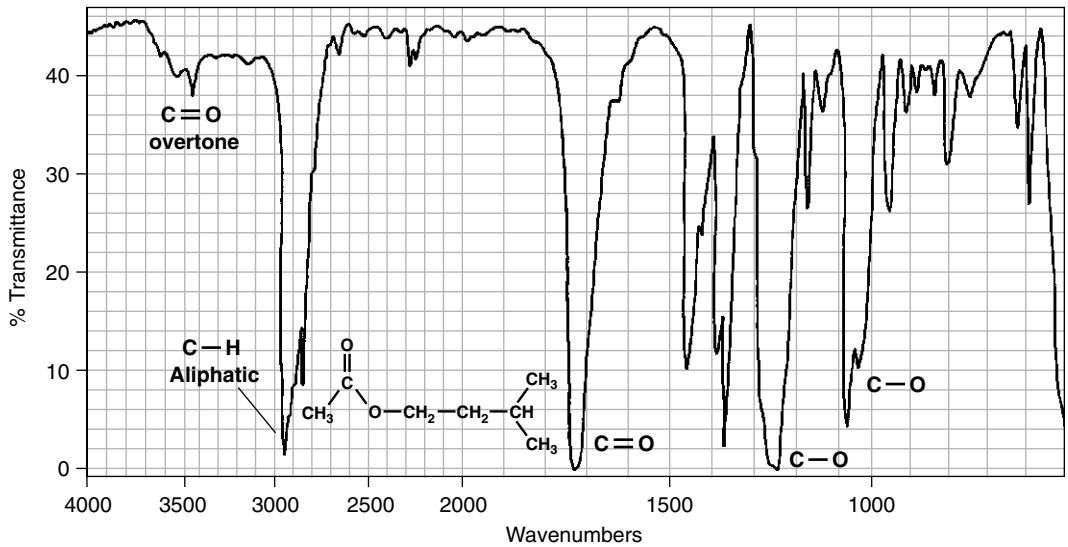


Figure 25.34 Infrared spectrum of isopentyl acetate (neat liquid, salt plates).

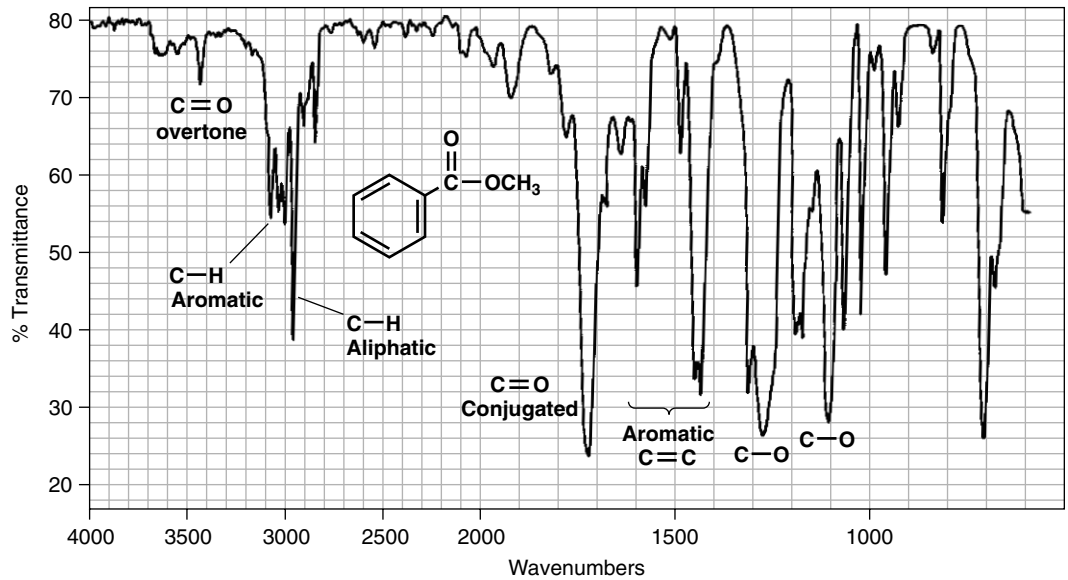


Figure 25.35 Infrared spectrum of methyl benzoate (neat liquid, salt plates).

O. Amides

C═O	Stretch is at approximately 1670–1640 cm^{-1}. Conjugation and ring size (lactams) have the usual effects.
N—H	Stretch (if monosubstituted or unsubstituted) is at 3500–3100 cm^{-1}. Unsubstituted amides have two bands (—NH_2) in this region.
N—H	Bending around 1640–1550 cm^{-1}.

The spectrum of benzamide is shown in Figure 25.36.

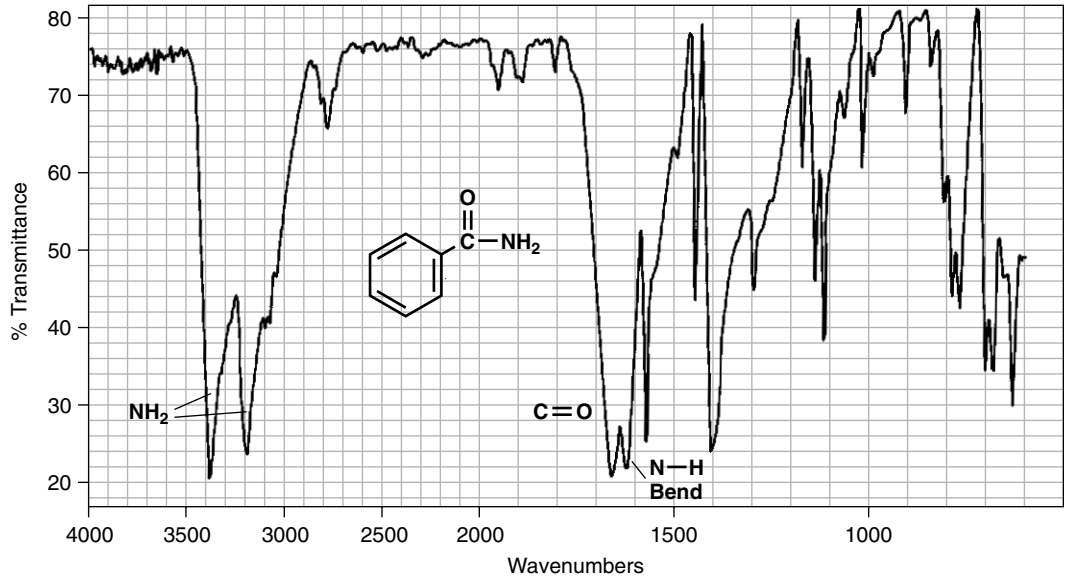


Figure 25.36 Infrared spectrum of benzamide (solid phase, KBr).

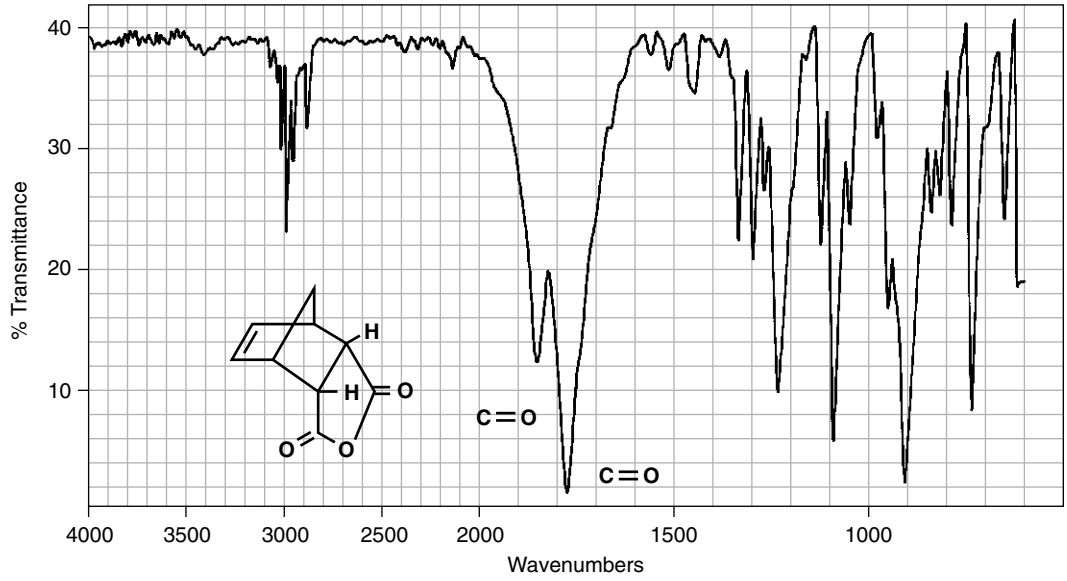


Figure 25.37 Infrared spectrum of cis-norbornene-5,6-endo-dicarboxylic anhydride (KBr pellet).

P. Anhydrides

C═O Stretch always has *two* bands: 1830–1800 cm^{-1} and 1775–1740 cm^{-1}.
Unsaturation moves the absorptions to the right.
Ring strain (cyclic anhydrides) moves the absorptions to the left.

C—O Stretch is at 1300–900 cm^{-1}. The spectrum of *cis*-norbornene-5,6-*endo*-dicarboxylic anhydride is shown in Figure 25.37.

Q. Acid Chlorides

C═O Stretch occurs in the range 1810–1775 cm^{-1} in unconjugated chlorides. Conjugation lowers the frequency to 1780–1760 cm^{-1}.

C—O Stretch occurs in the range 730–550 cm^{-1}.

R. Halides

It is often difficult to determine either the presence or the absence of a halide in a compound by infrared spectroscopy. The absorption bands cannot be relied on, especially if the spectrum is being determined with the compound dissolved in CCl_4 or $CHCl_3$ solution.

C—F Stretch, 1350–960 cm^{-1}.
C—Cl Stretch, 850–500 cm^{-1}.
C—Br Stretch, to the right of 667 cm^{-1}.
C—I Stretch, to the right of 667 cm^{-1}.

The spectra of the solvents, carbon tetrachloride and chloroform, are shown in Figures 25.8 and 25.9, respectively.

REFERENCES

Bellamy, L. J. *The Infra-Red Spectra of Complex Molecules*, 3rd ed.; New York: Methuen, 1975.

Colthup, N. B.; Daly, L. H.; Wiberly, S. E. *Introduction to Infrared and Raman Spectroscopy,* 3rd ed.; San Diego, CA: Academic Press, 1990.

Dyer, J. R. *Applications of Absorption Spectroscopy of Organic Compounds*; Englewood Cliffs, NJ: Prentice Hall, 1965.

Lin-Vien, D.; Colthup, N. B.; Fateley, W. G.; Grasselli, J. G. *Infrared and Raman Characteristic Frequencies of Organic Molecules*; San Diego, CA: Academic Press, 1991.

Nakanishi, K.; Soloman, P. H. *Infrared Absorption Spectroscopy,* 2nd ed.; San Francisco: Holden-Day, 1977.

Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Vyryan, J. R. *Introduction to Spectroscopy: A Guide for Students of Organic Chemistry,* 4th ed. Brooks/Cole, 2008.

Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrometric Identification of Organic Compounds,* 7th ed.; New York: Wiley & Sons, 2005.

PROBLEMS

1. Comment on the suitability of running the infrared spectrum under each of the following conditions. If there is a problem with the conditions given, provide a suitable alternative method.

a. A neat spectrum of liquid with a boiling point of 150 °C is determined using salt plates.

b. A neat spectrum of a liquid with a boiling point of 35 °C is determined using salt plates.

c. A KBr pellet is prepared with a compound that melts at 200 °C.

d. A KBr pellet is prepared with a compound that melts at 30 °C.

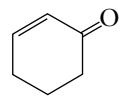
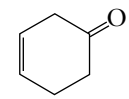
e. A solid aliphatic hydrocarbon compound is determined as a Nujol mull.

f. Silver chloride plates are used to determine the spectrum of aniline.

g. Sodium chloride plates are selected to run the spectrum of a compound that contains some water.

2. Indicate how you could distinguish between the following pairs of compounds by using infrared spectroscopy.

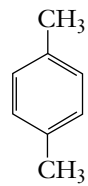
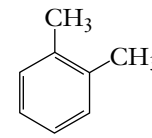
a. $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}-H$ $\qquad$ $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_3$

b.  $\qquad$ 

c. $CH_3CH_2\overset{\overset{H}{|}}{N}CH_2CH_3$ $\qquad$ $CH_3CH_2CH_2CH_2NH_2$

d. $CH_3CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$ $\qquad$ $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2OCH_3$

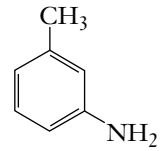
e. $CH_3CH_2\overset{\overset{O}{\|}}{C}OH$ $\qquad$ $CH_3CH_2CH_2OH$

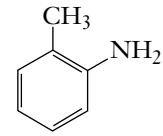
f.  $\qquad$ 

g. $CH_3CH_2CH{=}CH_2$ $\qquad$ $CH_3CH{=}CHCH_3$ (trans)

h. $CH_3CH_2CH_2C{\equiv}CH$ $\qquad$ $CH_3CH_2CH_2CH{=}CH_2$

i.





j. $CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}-OH$ $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_3$

k. $CH_3CH_2CH_2CH_2CH_3$ $CH_2{=}CHCH_2CH_2CH_2CH_3$

l. $CH_3CH_2CH_2CH_2C{\equiv}CH$ $CH_3CH_2CH_2C{\equiv}CCH_3$

26 TECHNIQUE 26

Nuclear Magnetic Resonance Spectroscopy (Proton NMR)

Nuclear magnetic resonance (NMR) spectroscopy is an instrumental technique that allows the number, type, and relative positions of certain atoms in a molecule to be determined. This type of spectroscopy applies only to those atoms that have nuclear magnetic moments because of their nuclear spin properties. Although many atoms meet this requirement, hydrogen atoms (^1_1H) are of the greatest interest to the organic chemist. Atoms of the ordinary isotopes of carbon ($^{12}_6C$) and oxygen ($^{16}_8O$) do not have nuclear magnetic moments, and ordinary nitrogen atoms ($^{14}_7N$), although they do have magnetic moments, generally fail to show typical NMR behavior for other reasons. The same is true of the halogen atoms, except for fluorine ($^{19}_9F$), which does show active NMR behavior. Of the atoms mentioned here, the hydrogen nucleus (^1_1H) and carbon-13 nucles ($^{13}_6C$) are the most important to organic chemists. Proton (^1H) NMR is discussed here and carbon (^{13}C) NMR is described in Technique 27.

Nuclei of NMR-active atoms placed in a magnetic field can be thought of as tiny bar magnets. In hydrogen, which has two allowed nuclear spin states ($+½$ and $-½$), either the nuclear magnets of individual atoms can be aligned with the magnetic field (spin $+½$) or they can be opposed to it (spin $-½$). A slight majority of the nuclei are aligned with the field, because this spin orientation constitutes a slightly lower-energy spin state. If radiofrequency waves of the appropriate energy are supplied, nuclei aligned with the field can absorb this radiation and reverse their direction of spin or become reoriented so that the nuclear magnet opposes the applied magnetic field (see Figure 26.1).

The frequency of radiation required to induce spin conversion is a direct function of the strength of the applied magnetic field. When a spinning hydrogen nucleus is placed in a magnetic field, the nucleus begins to precess with angular frequency ω, much like a child's toy top. This precessional motion is depicted in Figure 26.2. The angular frequency of nuclear precession ω increases as the strength of the applied magnetic field is increased. The radiation that must be supplied to

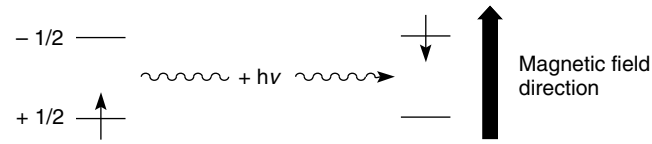


Figure 26.1 The NMR absorption process.

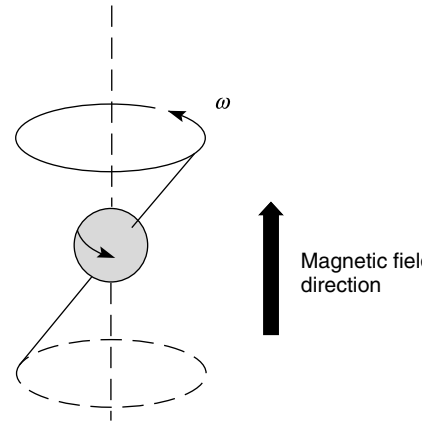


Figure 26.2 Precessional motion of a spinning nucleus in an applied magnetic field.

induce spin conversion in a hydrogen nucleus of spin +½ must have a frequency that just matches the angular precessional frequency ω. This is called the resonance condition, and spin conversion is said to be a resonance process.

For the average proton (hydrogen atom), if a magnetic field of approximately 1.4 tesla is applied, radio-frequency radiation of 60 MHz is required to induce a spin transition.[1] Fortunately, the magnetic field strength required to induce the various protons in a molecule to absorb 60-MHz radiation varies from proton to proton within the molecule and is a sensitive function of the immediate *electronic* environment of each proton. The proton nuclear magnetic resonance spectrometer supplies a basic radio-frequency radiation of 60 MHz to the sample being measured and *increases* the strength of the applied magnetic field over a range of several parts per million from the basic field strength. As the field increases, various protons come into resonance (absorb 60-MHz energy), and a resonance signal is generated for each proton. An NMR spectrum is a plot of the strength of the magnetic field versus the intensity of the absorptions. A typical 60-MHz NMR spectrum is shown in Figure 26.3.

Modern FT–NMR instruments produce the same type of NMR spectrum just described, even though they do it by a different method. See your lecture textbook for a discussion of the differences between classic CW instruments and modern FT–NMR instruments. Fourier transform spectrometers operating at magnetic field strengths of at least 7.1 tesla and at spectrometer frequencies of 300 MHz and above allow chemists to obtain both the proton and carbon NMR spectra on the same sample.

[1] Most modern instruments (FT-NMR instruments) use higher fields than described here and operate differently. The classical 60-MHz continous wave (CW) instrument is used here as a simple example.

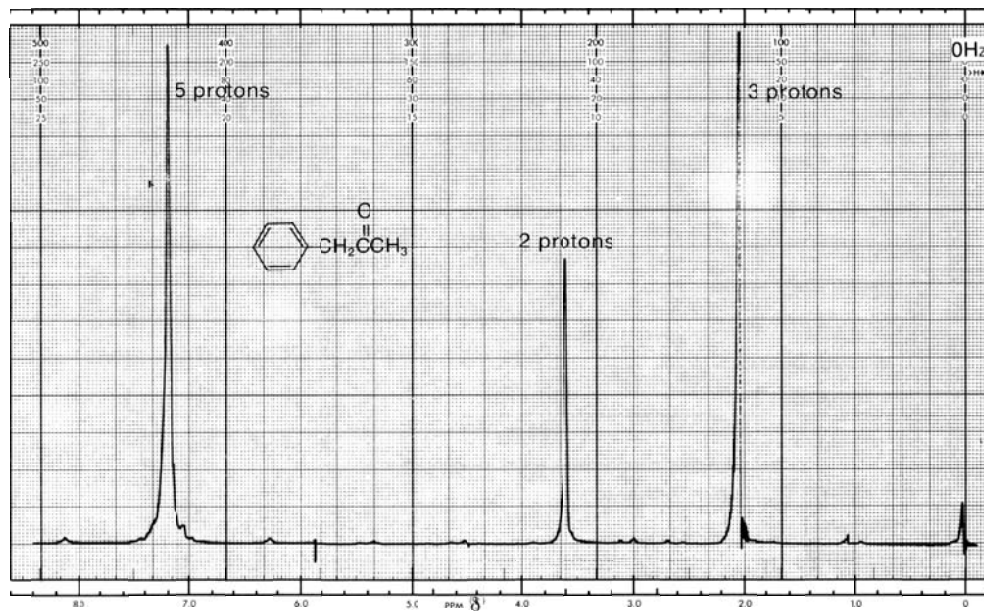


Figure 26.3 Nuclear magnetic resonance spectrum of phenylacetone (the absorption peak at the far right is caused by the added reference substance tetramethylsilane).

PART A. PREPARING A SAMPLE FOR NMR SPECTROSCOPY

The NMR sample tubes used in most instruments are approximately 0.5 cm × 18 cm in overall dimension and are fabricated of uniformly thin glass tubing. These tubes are very fragile and expensive, so care must be taken to avoid breaking the tubes.

CAUTION

NMR tubes are made out of very thin glass and break easily.Never place the cap on tightly, and take special care when removing it.

To prepare the solution, you must first choose the appropriate solvent. The solvent should not have NMR absorption peaks of its own, that is, it should contain no protons. Carbon tetrachloride (CCl_4) fits this requirement and can be used in some instruments. However, because FT–NMR spectrometers require deuterium to stabilize (lock) the field, organic chemists usually use deuterated chloroform ($CDCl_3$) as a solvent. This solvent dissolves most organic compounds and is relatively inexpensive. You can use this solvent with any NMR instrument. You should not use normal chloroform $CHCl_3$, because the solvent contains a proton. Deuterium ^2H does not absorb in the proton region and is thus "invisible," or not seen, in the proton NMR spectrum. Use deuterated chloroform to dissolve your sample, unless you are instructed to use another solvent, such as deuterated derivatives of water, acetone, or dimethylsulfoxide.

26.1 Routine Sample Preparation Using Deuterated Chloroform

1. Most organic liquids and low-melting solids will dissolve in deuterated chloroform. However, you should first determine whether your sample will dissolve in ordinary $CHCl_3$ before using the deuterated solvent. If your sample does not dissolve in chloroform, consult your instructor about a possible alternative solvent, or consult Section 26.2.

CAUTION

Chloroform, deuterated chloroform, and carbon tetrachloride are all toxic solvents. In addition, they may be carcinogenic substances.

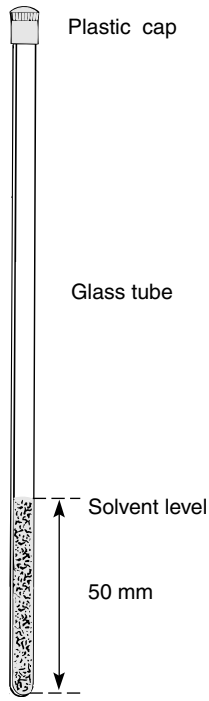


Figure 26.4 An NMR sample tube.

2. If you are using an FT–NMR spectrometer, add 30 mg (0.030 g) of your liquid or solid sample to a tared conical vial or test tube. Use a Pasteur pipet to transfer a liquid or a spatula to transfer a solid. Non-FT instruments usually require a more concentrated solution in order to obtain an adequate spectrum. Typically, a 10–30% sample concentration (weight/weight) is used.
3. Transfer about 0.5 mL of the deuterated chloroform with a clean, dry Pasteur pipet to your sample. Swirl the test tube or conical vial to help dissolve the sample. At this point, the sample should have completely dissolved. Add a little more solvent, if necessary, to dissolve the sample fully.
4. Transfer the solution to the NMR tube using a clean, dry Pasteur pipet. Be careful when transferring the solution to avoid breaking the edge of the fragile NMR tube. It is best to hold the NMR tube and the container with the solution in the same hand when making the transfer.
5. Once the solution has been transferred to the NMR tube, use a clean pipet to add enough deuterated chloroform to bring the total solution height to about 50 mm (see Figure 26.4). In some cases, you will need to add a small amount of tetramethylsilane (TMS) as a reference substance (see Section 26.3). Check with your instructor to see if you need to add TMS to your sample. Deuterated chloroform has a small amount of $CHCl_3$ impurity, which gives rise to a low-intensity peak in the NMR spectrum at 7.27 parts per million (ppm). This impurity may also help you to "reference" your spectrum.
6. Cap the NMR tube. Do this firmly but not too tightly. If you jam the cap on, you may have trouble removing it later without breaking the end off of the very thin glass tube. Make sure that the cap is on straight. Invert the NMR tube several times to mix the contents.
7. You are now ready to record the NMR spectrum of your sample. Insert the NMR tube into its holder and adjust its depth by using the gauge provided to you.

Cleaning the NMR Tube

1. Carefully uncap the tube so that you do not break it. Turn the tube upside down and hold it vertically over a beaker. Shake the tube up and down gently so that its contents empty into the beaker.
2. Partially refill the NMR tube with acetone using a Pasteur pipet. Carefully replace the cap and invert the tube several times to rinse it.
3. Remove the cap and drain the tube as before. Place the open tube upside down in a beaker with a Kimwipe or paper towel placed in the bottom of the beaker.

Leave the tube standing in this position for at least one laboratory period so that the acetone completely evaporates. Alternatively, you may place the beaker and NMR tube in an oven for at least 2 hours. If you need to use the NMR tube before the acetone has fully evaporated, attach a piece of pressure tubing to the tube and pull a vacuum with an aspirator. After several minutes, the acetone should have fully evaporated. Because acetone contains protons, you must not use the NMR tube until the acetone has evaporated completely[2].

4. Once the acetone is evaporated, place the clean tube and its cap (do not cap the tube) in its storage container and place it in your desk. The storage container will prevent the tube from being crushed.

Health Hazards Associated With NMR Solvents

Carbon tetrachloride, chloroform (and chloroform-d), and benzene (and benzene-d_6) are hazardous solvents. Besides being highly toxic, they are suspected carcinogens. In spite of these health problems, these solvents are commonly used in NMR spectroscopy. Deuterated acetone may be a safer alternative. These solvents are used because they contain no protons and are excellent solvents for most organic compounds. Therefore, you must learn to handle these solvents with great care to minimize the hazard. These solvents should be stored either under a hood or in septum-capped bottles. If the bottles have screw caps, a pipet should be attached to each bottle. A recommended way of attaching the pipet is to store it in a test tube taped to the side of the bottle. Septum-capped bottles can be used only by withdrawing the solvent with a hypodermic syringe that has been designated solely for this use. All samples should be prepared under a hood, and solutions should be disposed of in an appropriately designated waste container that is stored under the hood. Wear rubber or plastic gloves when preparing or discarding samples.

26.2 Nonroutine Sample Preparation

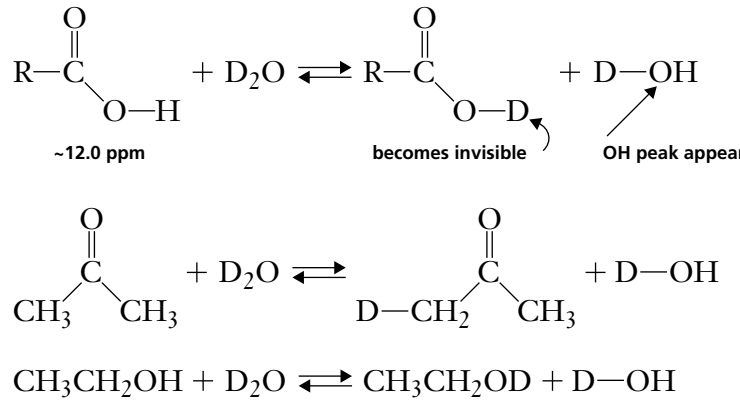
Some compounds do not dissolve readily in $CDCl_3$. A commercial solvent called Unisol will often dissolve the difficult cases. Unisol is a mixture of $CDCl_3$ and DMSO-d_6. Deuterated acetone may also dissolve more polar substances.

With highly polar substances, you may find that your sample will not dissolve in deuterated chloroform or Unisol. If this is the case, you may be able to dissolve the sample in deuterium oxide D_2O. Spectra determined in D_2O often show a small peak at about 5 ppm because of OH impurity. If the sample compound has acidic hydrogens, they may *exchange* with D_2O, leading to the appearance of an OH peak in the spectrum and the *loss* of the original absorption from the acidic proton, owing to the exchanged hydrogen. In many cases, this will also alter the splitting patterns of a compound.

Many solid carboxylic acids do not dissolve in $CDCl_3$ or even D_2O. In such cases, add a small piece of sodium metal to about 1 mL of D_2O. The acid is then dissolved in this solution. The resulting basic solution enhances the solubility of the carboxylic acid. In such a case, the hydroxyl proton of the carboxylic acid cannot be observed in the NMR spectrum because it exchanges with the solvent. A large DOH peak is observed, however, due to the exchange and the H_2O impurity in the D_2O solvent.

---

[2] If you can't wait to be sure all of the acetone has evaporated, you may rinse the tube once or twice with a *very small* amount of $CDCl_3$ before using it.



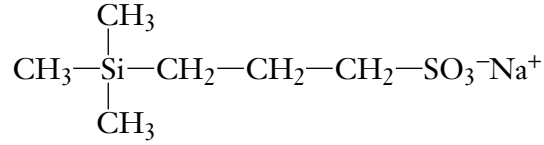
When the above solvents fail, other special solvents can be used. Acetone, acetonitrile, dimethylsulfoxide, pyridine, benzene, and dimethylformamide can be used if you are not interested in the region or regions of the NMR spectrum in which they give rise to absorption. The deuterated (but expensive) analogs of these compounds are also used in special instances (for example, acetone-d_6, dimethylsulfoxide-d_6, dimethylformamide-d_7, and benzene-d_6). If the sample is not sensitive to acid, trifluoroacetic acid (which has no protons with $\delta < 12$) can be used. You must be aware that these solvents often lead to chemical shift values different from those determined in CCl_4 or $CDCl_3$. Variations of as much as 0.5–1.0 ppm have been observed. In fact, it is sometimes possible, by switching to pyridine, benzene, acetone, or dimethylsulfoxide as solvents, to separate peaks that overlap when CCl_4 or $CDCl_3$ solutions are used.

26.3 Reference Substances

To provide the internal reference standard, TMS must be added to the sample solution. This substance has the formula $(CH_3)_4Si$. By universal convention, the chemical shifts of the protons in this substance are defined as 0.00 ppm. The spectrum should be shifted so that the TMS signal appears at this position on precalibrated paper.

The concentration of TMS in the sample should range from 1%–3%. Some people prefer to add 1 to 2 drops of TMS to the sample just before determining the spectrum. Because TMS has 12 equivalent protons, not much of it needs to be added. A Pasteur pipet or a syringe may be used for the addition. It is far easier to have available in the laboratory a prepared solvent that already contains TMS. Deuterated chloroform and carbon tetrachloride often have TMS added to them. Because TMS is highly volatile (bp 26.5°C), such solutions should be stored, tightly stoppered, in a refrigerator. Tetramethylsilane itself is best stored in a refrigerator as well.

Tetramethylsilane does not dissolve in D_2O. For spectra determined in D_2O, a different internal standard, sodium 2,2-dimethyl-2-silapentane-5-sulfonate, must be used. This standard is water soluble and gives a resonance peak at 0.00 ppm.



Sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS)

PART B. NUCLEAR MAGNETIC RESONANCE (^{1}H NMR)

26.4 The Chemical Shift

The differences in the applied field strengths at which the various protons in a molecule absorb 60-MHz radiation are extremely small. The different absorption positions amount to a difference of only a few parts per million (ppm) in the magnetic field strength. Because it is experimentally difficult to measure the precise field strength at which each proton absorbs to less than one part in a million, a technique has been developed whereby the *difference* between two absorption positions is measured directly. A standard reference substance is used to achieve this measurement, and the positions of the absorptions of all other protons are measured relative to the values for the reference substance. The reference substance that has been universally accepted is **tetramethylsilane** $(CH_3)_4Si$, which is also called **TMS**. the proton resonances in this molecule appear at a higher field strength than the proton resonances in most other molecules, and all the protons of TMS have resonance at the same field strength.

To give the position of absorption of a proton, a quantitative measurement, a parameter called the **chemical shift** (δ), has been defined. One δ unit corresponds to a one-ppm change in the magnetic field strength. To determine the chemical shift value for the various protons in a molecule, the operator determines an NMR spectrum of the molecule with a small quantity of TMS added directly to the sample. That is, both spectra are determined *simultaneously*. The TMS absorption is adjusted to correspond to the δ=0 ppm position on the recording chart, which is calibrated in δ units, and the δ values of the absorption peaks for all other protons can be read directly from the chart.

Because the NMR spectrometer increases the magnetic field as the pen moves from left to right on the chart, the TMS absorption appears at the extreme right edge of the spectrum (δ= 0 ppm) or at the *upfield* end of the spectrum. The chart is calibrated in δ units (or ppm), and most other protons absorb at a lower field strength (or *downfield*) from TMS.

The shift from TMS for a given proton depends on the strength of the applied magnetic field. In an applied field of 1.41 tesla, the resonance of a proton is approximately 60 MHz, whereas in an applied field of 2.35 tesla, (23,500 gauss), the resonance appears at approximately 100 MHz. The ratio of the resonance frequencies is the same as the ratio of the two field strengths:

$$\frac{100\text{ MHz}}{60\text{ MHz}} = \frac{2.35\text{ Tesla}}{1.41\text{ Tesla}} = \frac{23{,}500\text{ Gauss}}{14{,}100\text{ Gauss}} = \frac{5}{3}$$

Hence, for a given proton, the shift (in hertz) from TMS is five-thirds larger in the 100-MHz range than in the 60-MHz range. This can be confusing for workers trying to compare data if they have spectrometers that differ in the strength of the applied magnetic field. The confusion is easily overcome by defining a new parameter that is independent of field strength—for instance, by dividing the shift in hertz of a given proton by the frequency in megahertz of the spectrometer with which the shift value was obtained. In this manner, a field-independent measure called the **chemical shift** (δ) is obtained:

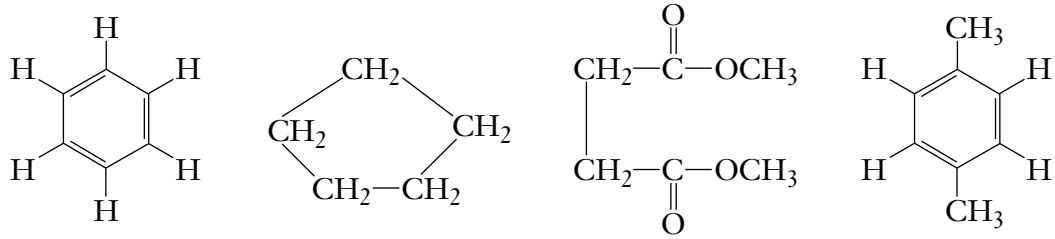
$$\delta = \frac{(\text{shift in Hz})}{(\text{spectrometer frequency in MHz})} \qquad (1)$$

The chemical shift in δ units expresses the amount by which a proton resonance is shifted from TMS, in parts per million (ppm), of the spectrometer's basic operating frequency. Values of δ for a given proton are always the same, irrespective of whether the measurement was made at 60 MHz, 100 MHz, or 300 MHz. For instance, at 60 MHz, the shift of the protons in CH_3Br is 162 Hz from TMS; at 100 MHz, the shift is 270 Hz; and at 300 MHz, the shift is 810 Hz. However, all three correspond to the same value of $\delta = 2.70$ ppm:

$$\delta = \frac{162 \text{ Hz}}{60 \text{ MHz}} = \frac{270 \text{ Hz}}{100 \text{ MHz}} = \frac{810 \text{ Hz}}{300 \text{ MHz}} = 2.70 \text{ ppm}$$

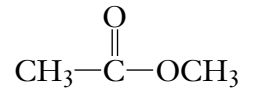
26.5 Chemical Equivalence—Integrals

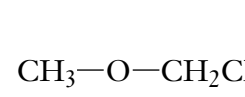
All of the protons in a molecule that are in chemically identical environments often exhibit the same chemical shift. Thus, all of the protons in TMS or all of the protons in benzene, cyclopentane, or acetone have their own respective resonance values all at the same δ value. Each compound gives rise to a single absorption peak in its NMR spectrum. The protons are said to be **chemically equivalent**. On the other hand, molecules that have sets of protons that are chemically distinct from one another may give rise to an absorption peak from each set.



$(CH_3)_4Si$

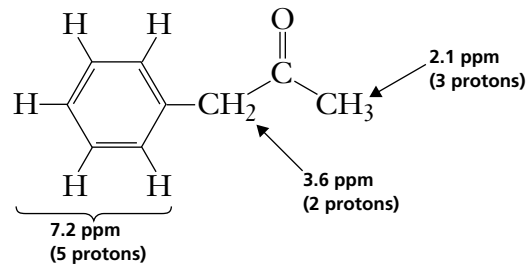
Molecules giving rise to one NMR absorption peak—all protons chemically equivalent





Molecules giving rise to two NMR absorption peaks—two different sets of chemically equivalent protons

The NMR spectrum given in Figure 26.3 is that of phenylacetone, a compound having *three* chemically distinct types of protons:



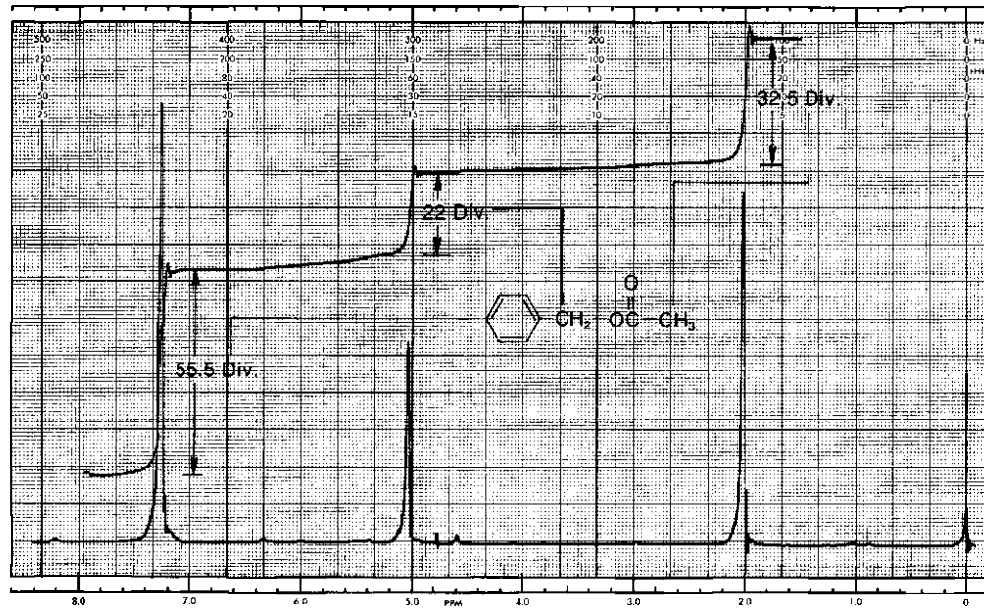


Figure 26.5 Determination of the integral ratios for benzyl acetate.

You can immediately see that the NMR spectrum furnishes valuable information on this basis alone. In fact, the NMR spectrum not only can distinguish how many types of protons a molecule has, but also can reveal *how many* of each type are contained within the molecule.

In the NMR spectrum, the area under each peak is proportional to the number of hydrogens generating that peak. Hence, in the case of phenylacetone, the area ratio of the three peaks is 5:2:3, the same as the ratio of the numbers of each type of hydrogen. The NMR spectrometer can electronically "integrate" the area under each peak. It does this by tracing over each peak a vertically rising line, which rises in height by an amount proportional to the area under the peak. Shown in Figure 26.5 is an NMR spectrum of benzyl acetate, with each of the peaks integrated in this way.

It is important to note that the height of the integral line does not give the absolute number of hydrogens; it gives the *relative* numbers of each type of hydrogen. For a given integral to be of any use, there must be a second integral to which it is referred. The benzyl acetate case provides a good example of this. The first integral rises for 55.5 divisions on the chart paper, the second for 22.0 divisions, and the third for 32.5 divisions. These numbers are relative and give the *ratios* of the various types of protons. You can find these ratios by dividing each of the larger numbers by the smallest number:

$$\frac{55.5 \text{ div}}{22.0 \text{ div}} = 2.52 \qquad \frac{22.0 \text{ div}}{22.0 \text{ div}} = 1.00 \qquad \frac{32.5 \text{ div}}{22.0 \text{ div}} = 1.48$$

Thus, the number ratio of the protons of each type is 2.52:1.00:1.48. If you assume that the peak at 5.1 ppm is really caused by two hydrogens and that the integrals are slightly in error (this can be as much as 10%), then you can arrive at the true ratios by multiplying each figure by 2 and rounding off; we then get 5:2:3. Clearly, the peak at 7.3 ppm, which integrates for 5, arises from the resonance of the aromatic ring protons, and the peak at 2.0 ppm, which integrates for 3, is caused by the methyl protons. The two-proton resonance at 5.1 ppm arises from the benzyl

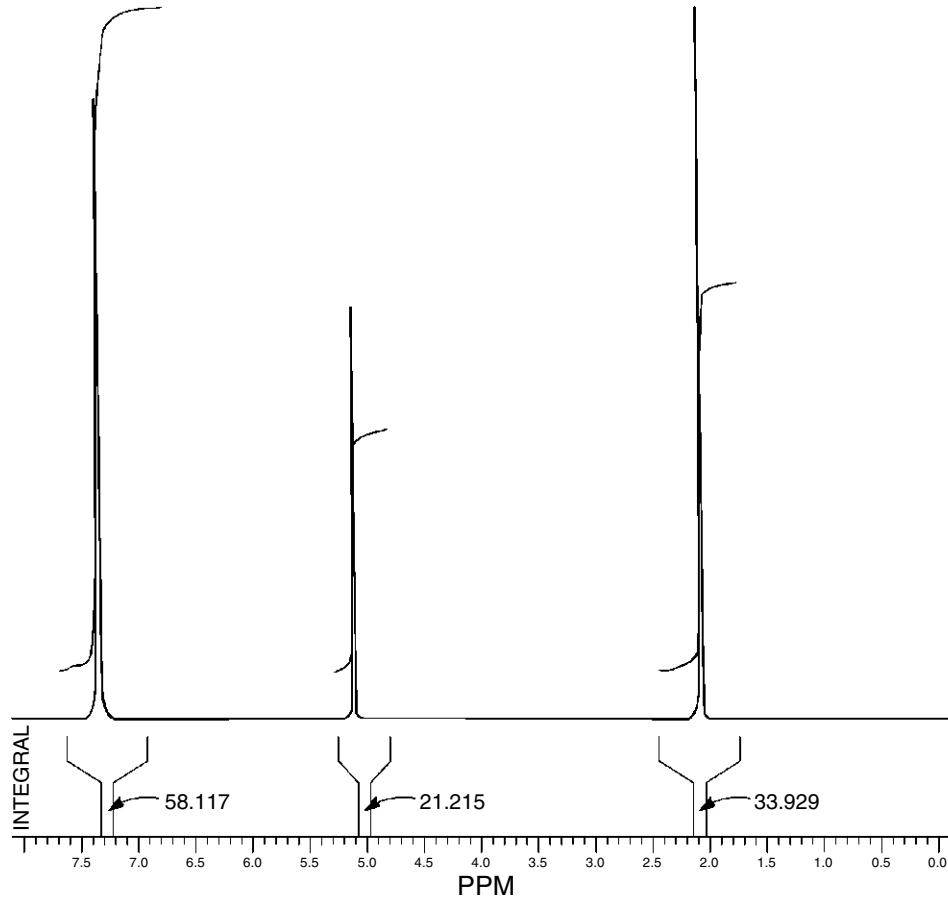


Figure 26.6 An integrated spectrum of benzyl acetate determined on a 300-MHzFT-NMR.

protons. Notice then that the integrals give the simplest ratios, but not necessarily the true ratios, of the number of protons in each type.

In addition to the rising integral line, modern instruments usually give digitized numerical values for the integrals. Like the heights of the integral lines, these digitized integral values are not absolute but relative, and they should be treated as explained in the preceding paragraph. These digital values are also not exact; like the integral lines, they have the potential for a small degree of error (up to 10%). Figure 26.6 is an example of an integrated spectrum of benzyl acetate determined on a 300-MHz pulsed FT–NMR instrument. The digitized values of the integrals appear under the peaks.

26.6 Chemical Environment and Chemical Shift

If the resonance frequencies of all protons in a molecule were the same, NMR would be of little use to the organic chemist. However, not only do different types of protons have different chemical shifts but they also have a value of chemical shift that characterizes the type of proton they represent. Every type of proton has only a limited range of δ values over which it gives resonance. Hence, the numerical value of the chemical shift for a proton indicates the *type of proton* originating the signal, just as the infrared frequency suggests the type of bond or functional group.

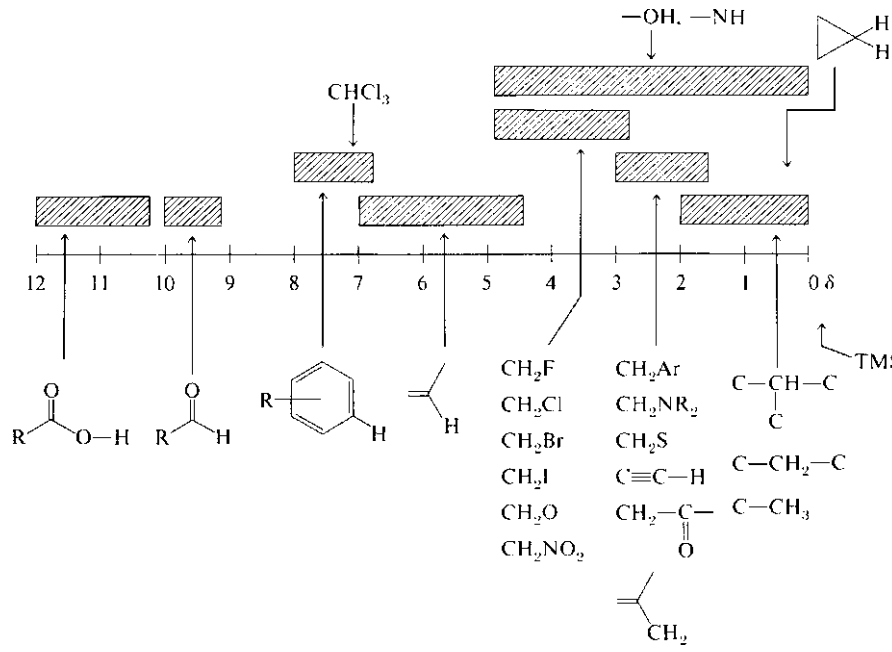


Figure 26.7 A simplified correlation chart for proton chemical shift values.

Notice, for instance, that the aromatic protons of both phenylacetone (See Figure 26.3) and benzyl acetate (See Figure 26.5) have resonance near 7.3 ppm and that both methyl groups attached directly to a carbonyl group have a resonance of approximately 2.1 ppm. Aromatic protons characteristically have resonance near 7–8 ppm, and acetyl groups (the methyl protons) have their resonance near 2 ppm. These values of chemical shift are diagnostic. Notice also how the resonance of the benzyl (—CH_2—) protons comes at a higher value of chemical shift (5.1 ppm) in benzyl acetate than in phenylacetone (3.6 ppm). Being attached to the electronegative element, oxygen, these protons are more deshielded (see Section 26.7) than the protons in phenylacetone. A trained chemist would have readily recognized the probable presence of the oxygen by the chemical shift shown by these protons.

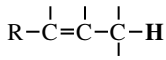
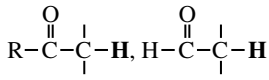
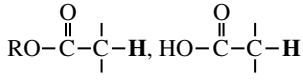
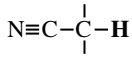
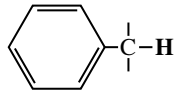
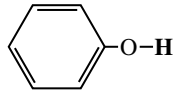
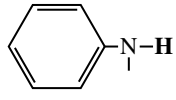
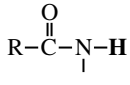
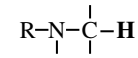
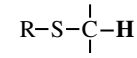
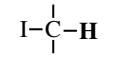
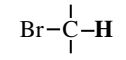
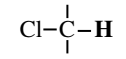
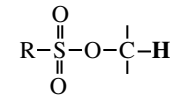
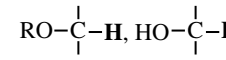
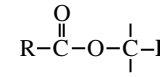
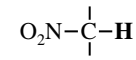
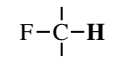
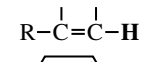
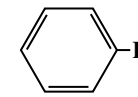
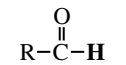
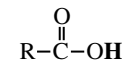
It is important to learn the ranges of chemical shifts over which the most common types of protons have resonance. Figure 26.7 is a correlation chart that contains the most essential and frequently encountered types of protons. Table 26.1 lists the chemical shift ranges for selected types of protons. For the beginner, it is often difficult to memorize a large body of numbers relating to chemical shifts and proton types. However, this needs to be done only crudely. It is more important to "get a feel" for the regions and the types of protons than to know a string of actual numbers. To do this, study Figure 26.7 carefully.

The values of chemical shift given in Figure 26.7 and in Table 26.1 can be easily understood in terms of two factors: local diamagnetic shielding and anisotropy. These two factors are discussed in Sections 26.7 and 26.8.

26.7 Local Diamagnetic Shielding

The trend of chemical shifts that is easiest to explain is that involving electronegative elements substituted on the same carbon to which the protons of interest are attached. The chemical shift simply increases as the electronegativity of the attached element increases. This is illustrated in Table 26.2 for several compounds of the type CH_3X.

TABLE 26.1 Approximate Chemical Shift Ranges (ppm) for Selected Types of Protons

$R-CH_3$		0.7–1.3
$R-CH_2-R$		1.2–1.4
R_3CH		1.4–1.7
		1.6 – 2.6
		2.1 – 2.4
		2.1 – 2.5
		2.1 – 3.0
		2.3 – 2.7
$R-C\equiv C-H$		1.7 – 2.7
$R-S-H$	var	1.0 – 4.0[a]
	var	0.5 – 4.0[a]
$R-O-H$	var	0.5 – 5.0[a]
	var	4.0 – 7.0[a]
	var	3.0 – 5.0[a]
	var	5.0 – 9.0[a]
		2.2–2.9
		2.0–3.0
		2.0–4.0
		2.7–4.1
		3.1–4.1
		ca. 3.0
		3.2–3.8
		3.5–4.8
		4.1–4.3
		4.2–4.8
		4.5–6.5
		6.5–8.0
		9.0–10.0
		11.0–12.0

Note: For those hydrogens shown as  , if that hydrogen is part of a methyl group (CH_3), the shift is generally at the low end of the range given; if the hydrogen is in a methylene group ($—CH_2—$), the shift is intermediate; and if the hydrogen is in a methine group (—CH—), the shift is typically at the high end of the range given.

[a]The chemical shift of these groups is variable, depending on the chemical environment in the molecule and on concentration, temperature, and solvent.

TABLE 26.2 Dependence of Chemical Shift of CH_3X on the Element X

Compound CH_3X	CH_3F	CH_3OH	CH_3Cl	CH_3Br	CH_3I	CH_4	$(CH_3)_4Si$
Element X	F	O	Cl	Br	I	H	Si
Electronegativity of X	4.0	3.5	3.1	2.8	2.5	2.1	1.8
Chemical shift (ppm)	4.26	3.40	3.05	2.68	2.16	0.23	0

TABLE 26.3 Substitution Effects

	$C\underline{H}Cl_3$	$C\underline{H}_2Cl_2$	$C\underline{H}_3Cl$	$—C\underline{H}_2Br$	$—C\underline{H}_2—CH_2Br$	$—C\underline{H}_2—CH_2CH_2Br$
δ (ppm)	7.27	5.30	3.05	3.3	1.69	1.25

Note: Values apply to underlined hydrogens.

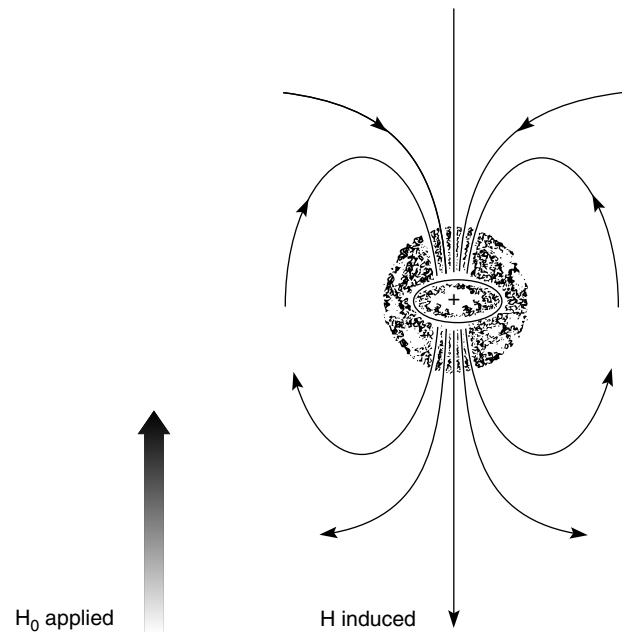


Figure 26.8 Local diamagnetic shielding of a photon due to its valence electrons.

Multiple substituents have a stronger effect than a single substituent. The influence of the substituent drops off rapidly with distance. An electronegative element has little effect on protons that are more than three carbons away from it. These effects are illustrated in Table 26.3.

Electronegative substituents attached to a carbon atom, because of their electron withdrawing effects, reduce the valence electron density around the protons attached to that carbon. These electrons *shield* the proton from the applied magnetic

field. This effect, called **local diamagnetic shielding**, occurs because the applied magnetic field induces the valence electrons to circulate. This circulation generates an induced magnetic field, which *opposes* the applied field. This is illustrated in Figure 26.8. Electronegative substituents on carbon reduce the local diamagnetic shielding in the vicinity of the attached protons because they reduce the electron density around those protons. Substituents that produce this effect are said to *deshield* the proton. The greater the electronegativity of the substituent, the more the deshielding of the protons and, hence, the greater the chemical shift of those protons.

26.8 Anisotropy

Figure 26.7 clearly shows that several types of protons have chemical shifts not easily explained by a simple consideration of the electronegativity of the attached groups. Consider, for instance, the protons of benzene or other aromatic systems. Aryl protons generally have a chemical shift that is as large as that for the proton of chloroform. Alkenes, alkynes, and aldehydes also have protons whose resonance values are not in line with the expected magnitude of any electron-withdrawing effects. In each of these cases, the effect is due to the presence of an unsaturated system (π electrons) in the vicinity of the proton in question. In benzene, for example, when the π electrons in the aromatic ring system are placed in a magnetic field, they are induced to circulate around the ring. This circulation is called a **ring current**. Moving electrons (the ring current) generate a magnetic field much like that generated in a loop of wire through which a current is induced to flow. The magnetic field covers a spatial volume large enough to influence the shielding of the benzene hydrogens. This is illustrated in Figure 26.9. The benzene hydrogens are deshielded by the **diamagnetic anisotropy** of the ring. An applied magnetic field is nonuniform (anisotropic) in the vicinity of a benzene molecule because of the labile

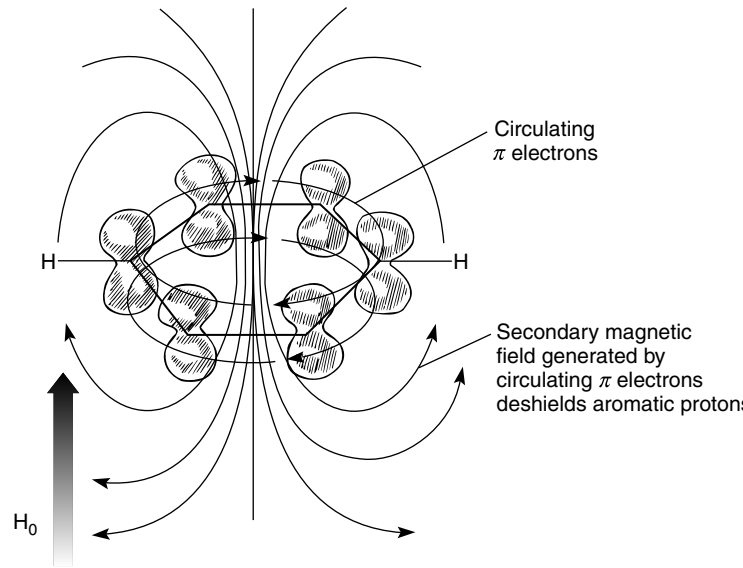


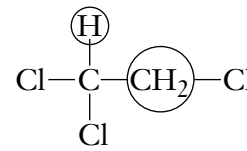
Figure 26.9 Diamagnetic anisotropy in benzene.

electrons in the ring that interact with the applied field. Thus, a proton attached to a benzene ring is influenced by *three* magnetic fields: the strong magnetic field applied by the magnets of the NMR spectrometer and two weaker fields, one due to the usual shielding by the valence electrons around the proton and the other due to the anisotropy generated by the ring system electrons. It is this anisotropic effect that gives the benzene protons a greater chemical shift than is expected. These protons just happen to lie in a **deshielding** region of this anisotropic field. If a proton were placed in the center of the ring rather than on its periphery, the proton would be shielded because the field lines would have the opposite direction.

All groups in a molecule that have π electrons generate secondary anisotropic fields. In acetylene, the magnetic field generated by induced circulation of π electrons has a geometry such that the acetylene hydrogens are **shielded**. Hence, acetylenic hydrogens come at a higher field than expected. The shielding and deshielding regions due to the various π electron functional groups have characteristic shapes and directions; they are illustrated in Figure 26.10. Protons falling within the cones are shielded, and those falling outside the conical areas are deshielded. Because the magnitude of the anisotropic field diminishes with distance, beyond a certain distance anisotropy has essentially no effect.

26.9 Spin–Spin Splitting (n + 1 Rule)

We have already considered how the chemical shift and the integral (peak area) can give information about the numbers and types of hydrogens contained in a molecule. A third type of information available from the NMR spectrum is derived from spin-spin splitting. Even in simple molecules, each type of proton rarely gives a single resonance peak. For instance, in 1,1,2-trichloroethane there are two chemically distinct types of hydrogen:



From information given thus far, you would predict *two* resonance peaks in the NMR spectrum of 1,1,2-trichloroethane with an area ratio (integral ratio) of 2:1. In fact, the NMR spectrum of this compound has *five* peaks. A group of three peaks (called a *triplet*) exists at 5.77 ppm, and a group of two peaks (called a *doublet*) is found at 3.95 ppm. The spectrum is shown in Figure 26.11. The methine (CH) resonance (5.77 ppm) is split into a triplet, and the methylene resonance (3.95 ppm) is

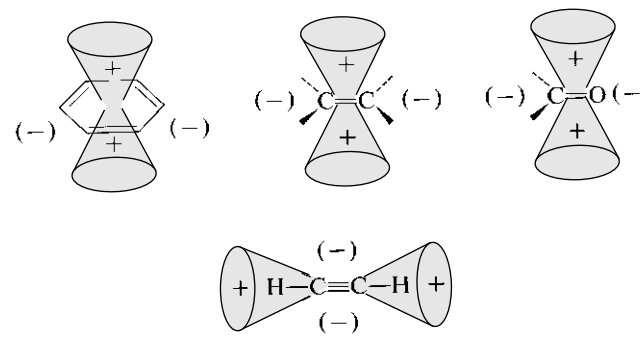


Figure 26.10 Anisotropy caused by the presence of π electrons in some common multiple-bond systems.

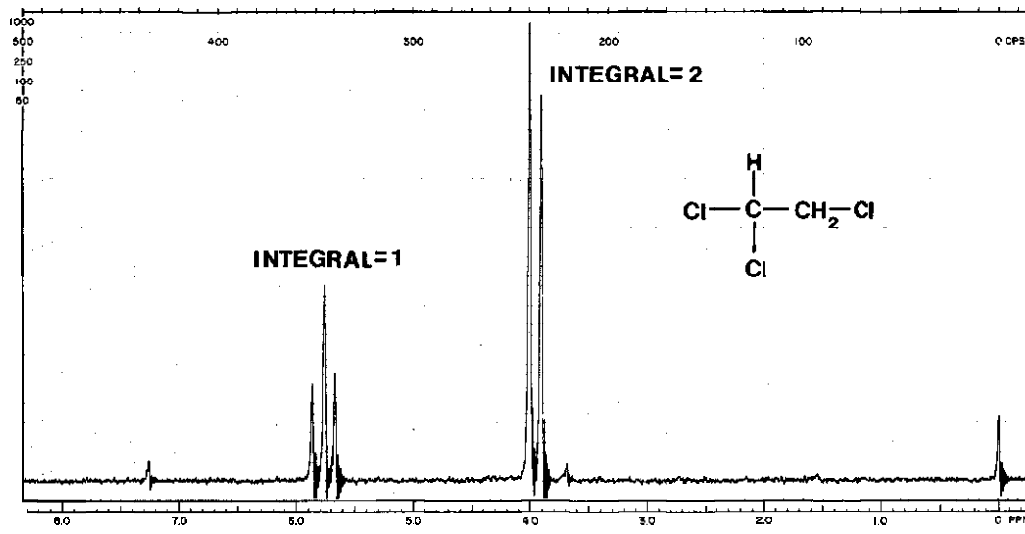
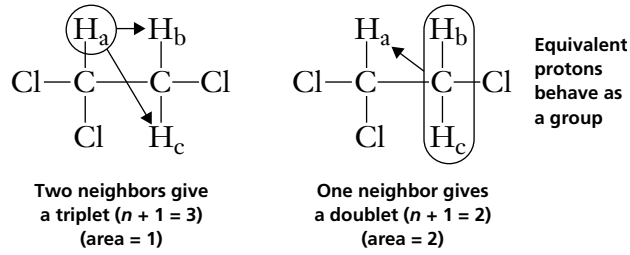


Figure 26.11 NMR spectrum of 1,1,2-trichloroethane. (Courtesy of Varian Associates.)

split into a doublet. The area under the three triplet peaks is *one*, relative to an area of *two* under the two doublet peaks.

This phenomenon is called **spin–spin splitting**. Empirically, spin–spin splitting can be explained by the "$n + 1$ rule." Each type of proton "senses" the number of equivalent protons (n) on the carbon atom or atoms next to the one to which it is bonded, and its resonance peak is split into $n + 1$ components.

Let's examine the case at hand, 1,1,2-trichloroethane, using the $n + 1$ rule. First, the lone methine hydrogen is situated next to a carbon bearing two methylene protons. According to the rule, it has two equivalent neighbors ($n = 2$) and is split into $n + 1 = 3$ peaks (a triplet). The methylene protons are situated next to a carbon bearing only one methine hydrogen. According to the rule, they have one neighbor ($n = 1$) and are split into $n + 1 = 2$ peaks (a doublet).



The spectrum of 1,1,2-trichloroethane can be explained easily by the interaction, or coupling, of the spins of protons on adjacent carbon atoms. The position of absorption of proton H_a is affected by the spins of protons H_b and H_c attached to the neighboring (adjacent) carbon atom. If the spins of these protons are aligned with the applied magnetic field, the small magnetic field generated by their nuclear spin properties will augment the strength of the field experienced by the first-mentioned proton H_a. The proton H_a will thus be *deshielded*. If the spins of H_b and H_c are opposed to the applied field, they will decrease the field experienced by proton H_a. It will then be *shielded*. In each of these situations, the absorption position of H_a will be altered. Among the many molecules in the solution, you will find all the various possible spin combinations for H_b and H_c; hence, the NMR spectrum of the

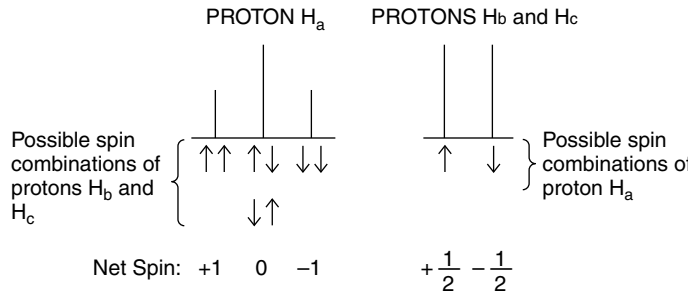


Figure 26.12 Analysis of spin–spin splitting pattern for 1,1,2-trichloroethane.

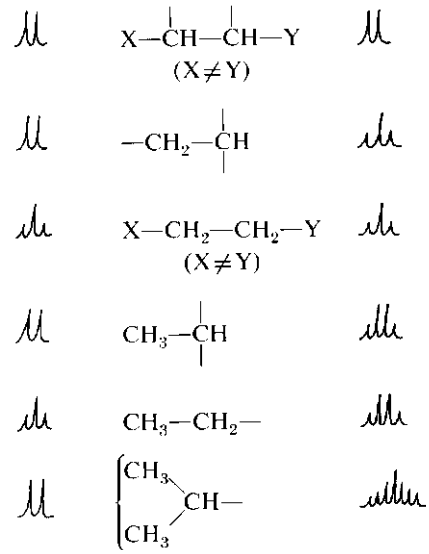


Figure 26.13 Some common splitting patterns.

molecular solution will give *three* absorption peaks (a triplet) for H_a because H_b and H_c have three different possible spin combinations (Figure 26.12). By a similar analysis, it can be seen that protons H_b and H_c should appear as a doublet.

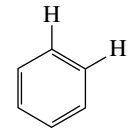
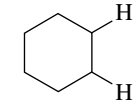
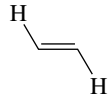
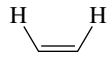
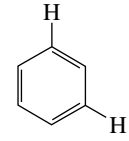
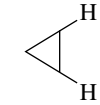
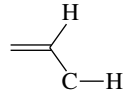
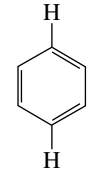
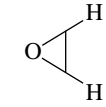
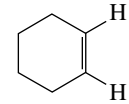
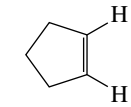
Some common splitting patterns that can be predicted by the n + 1 rule and that are frequently observed in a number of molecules are shown in Figure 26.13. Notice particularly the last entry, where *both* methyl groups (six protons in all) function as a unit and split the methine proton into a septet (6 + 1 = 7).

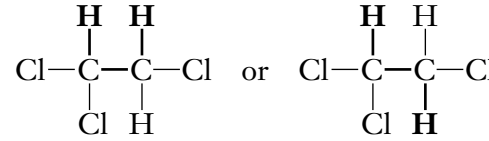
26.10 The Coupling Constant

The quantitative amount of spin–spin interaction between two protons can be defined by the **coupling constant**. The spacing between the component peaks in a single multiplet is called the coupling constant *J*. This distance is measured on the same scale as the chemical shift and is expressed in hertz (Hz).

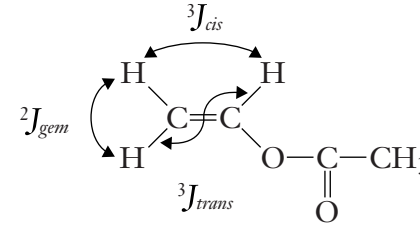
Coupling constants for protons on adjacent carbon atoms have magnitudes of from about 6 Hz to 8 Hz (see Table 26.4). You should expect to see a coupling constant in this range for compounds where there is free rotation about a single bond. Because three bonds separate protons from each other on adjacent carbon atoms, we label these coupling constants as ^3J. For example, the coupling constant for the compound shown in Figure 26.11 would be written as $^3J = 6$ Hz. The boldfaced lines in the following diagram show how the protons on adjacent carbon atoms are three bonds away from each other.

TABLE 26.4 Representative Coupling Constants and Approximate Values (Hz)

	^3J	6 – 8			*ortho*			a,a 8 – 14
	$^3J_{trans}$	11 – 18		^3J	6 – 10		^3J	a,e 0 – 7
	$^3J_{cis}$	6 – 15			*meta*			e,e 0 – 5
	$^2J_{gem}$	0 – 5		^4J	1 – 4		^3J	*cis* 6 – 12
	^3J	4 – 10			*para*			*trans* 4 – 8
H—C═C—C—H	^4J	0 – 3		^5J	≈ 0		^3J	*cis* 2 – 5
								*trans* 1 – 3
				^3J	8 – 11		^3J	5 – 7



In compounds where there is a C═C double bond, free rotation is restricted. In compounds of this kind, we often find two types of ^3J coupling constants; $^3J_{trans}$ and $^3J_{cis}$. These coupling constants vary in value as shown in Table 26.4, but $^3J_{trans}$ is almost always larger than $^3J_{cis}$. The magnitudes of these ^3J_s often provide important structural clues. You can distinguish, for example, between a *cis* alkene and a *trans* alkene on the basis of the observed coupling constants for the two vinyl protons on disubstituted alkenes. Most of the coupling constants shown in the first column of Table 26.4 are three bond couplings, but you will notice that there is a two-bond (^2J) coupling constant listed. These protons that are bonded to a common carbon atom are often referred to as *geminal* protons and can be labeled as $^2J_{gem}$. Notice that the coupling constants for *geminal* protons are quite small for alkenes. The ^2J couplings are observed only when the protons on a methylene group are in a different environment (see Section 26.11). The following structure shows the various types of couplings that you observe for protons on a C═C double bond in a typical alkene, vinyl acetate. The spectrum for this compound is described in detail in Section 26.11.



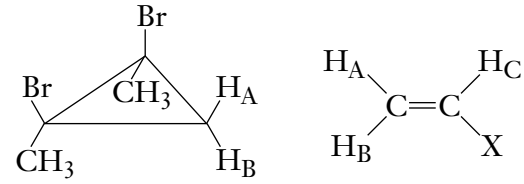
Vinyl acetate

Longer-range couplings that occur over four or more bonds are observed in some alkenes and also in aromatic compounds. Thus, in Table 26.4, we see that it is possible to observe a small H—H coupling (^4J = 0–3 Hz) occurring over four bonds in an alkene. In an aromatic compound, you often observe a small but measurable coupling between *meta* protons that are four bonds away from each other (^4J = 1–4 Hz). Couplings over five bonds are usually quite small, with values close to 0 Hz. The long-range couplings are usually observed only in *unsaturated* compounds. The spectra of saturated compounds are often more easily interpreted because they usually have only three bond couplings. Aromatic compounds are discussed in detail in Section 26.13.

26.11 Magnetic Equivalence

In the example of spin–spin splitting in 1,1,2-trichloroethane (see Figure 26.11), notice that the two protons H_b and H_c, which are attached to the same carbon atom, do not split one another. They behave as an integral group. Actually, the two protons H_b and H_c *are* coupled to one another; however, for reasons we cannot explain fully here, protons that are attached to the same carbon and both of which have the same chemical shift do not show spin–spin splitting. Another way of stating this is that protons coupled to the same extent to *all* other protons in a molecule do not show spin–spin splitting. Protons that have the same chemical shift and are coupled equivalently to all other protons are magnetically equivalent and do not show spin–spin splitting. Thus, in 1,1,2-trichloroethane in (see Figure 26.11), protons H_b and H_c have the same value of δ and are coupled by the same value of J to proton H_a. They are magnetically equivalent, and $^2J_{gem} = 0$.

It is important to differentiate magnetic equivalence and chemical equivalence. Note the following two compounds.



In the cycloproprane compound, the two geminal hydrogens H_A and H_B are chemically equivalent; however, they are not magnetically equivalent. Proton H_A is on the same side of the ring as the two halogens. Proton H_B is on the same side of the ring as the two methyl groups. Protons H_A and H_B will have different chemical shifts, will couple to one another, and will show spin–spin splitting. Two doublets will be seen for H_A and H_B. For cyclopropane rings, $^2J_{gem}$ is usually around 5 Hz.

The general vinyl structure (alkene) shown in the previous figure and the specific example of vinyl acetate shown in Figure 26.14 are examples of cases in which the methylene protons H_A and H_B are nonequivalent. They appear at different chemical shift values and will split each other. This coupling constant, $^2J_{gem}$, is usually small with vinyl compounds (about 2 Hz).

The spectrum of vinyl acetate is shown in Figure 26.14. H_C appears downfield at about 7.3 ppm because of the electronegativity of the attached oxygen atom. This proton is split by H_B into a doublet ($^3J_{trans} = {}^3J_{BC}$ = 15 Hz), and then each leg of the doublet is split by H_A into a doublet ($^3J_{cis} = {}^3J_{AC}$ =7 Hz). Notice that then $n + 1$ rule is applied individually to each adjacent proton. The pattern that results is usually referred to as a doublet of doublets (dd). The graphic analysis shown in Figure 26.15 should help you understand the pattern obtained for proton H_C.

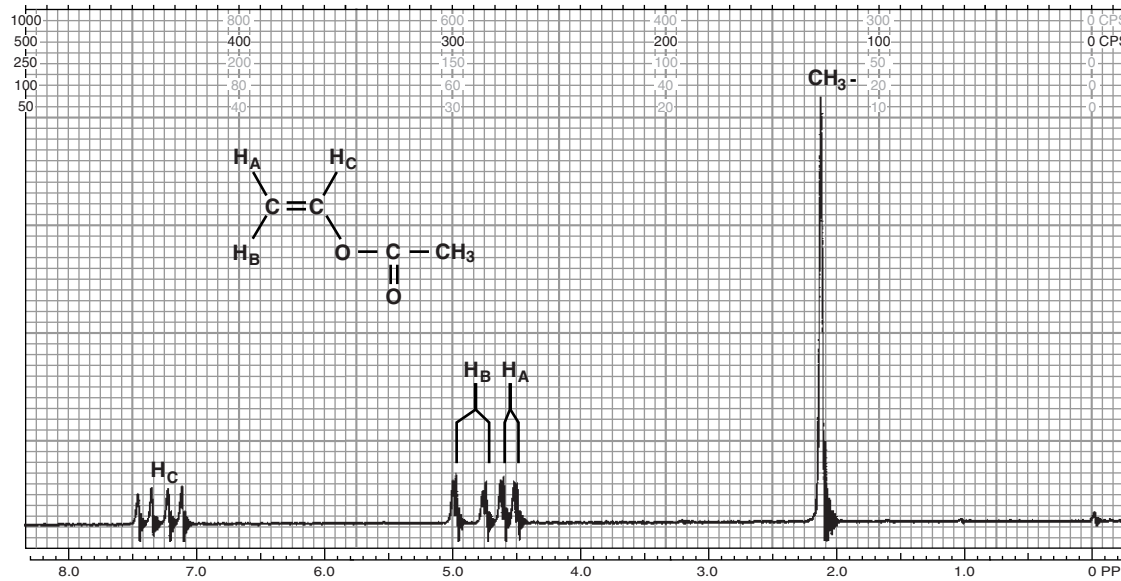


Figure 26.14 NMR spectrum of vinyl acetate. (Courtesy of Varian Associates.)

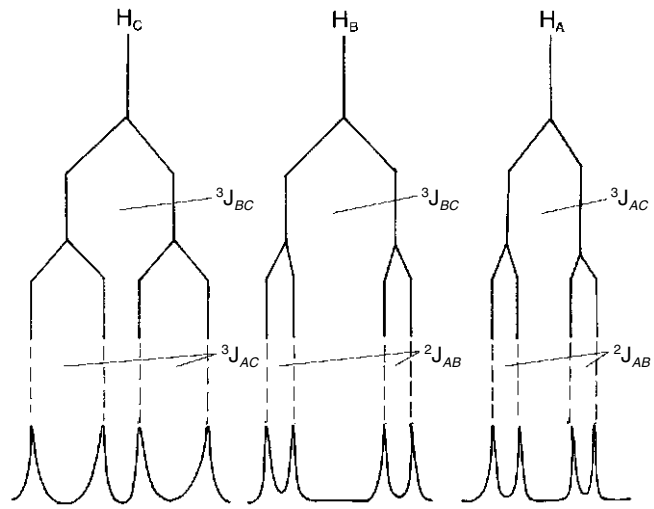


Figure 26.15 Analysis of the splittings in vinyl acetate.

Now look at the pattern shown in Figure 26.14 for proton H_B at 4.85 ppm. It is also a doublet of doublets. Proton H_B is split by proton H_C into a doublet ($^3J_{trans} = {}^3J_{BC} = 15$ Hz), and then each leg of the doublet is split by the geminal proton H_A into doublets ($^2J_{gem} = {}^2J_{AB} = 2H_Z$).

Proton H_A shown in Figure 26.14 appears at 4.55 ppm. This pattern is also a doublet of doublets. Proton H_A is split by proton H_C into a doublet ($^3J_{cis} = 3J_{AB} = 7$ Hz), and then each leg of the doublet is split by the geminal proton H_B into doublets ($^2J_{gem} = {}^2J_{AB} = 2$ Hz). For each proton shown in Figure 26.14, the NMR spectrum must be analyzed graphically, splitting by splitting. This complete graphic analysis is shown in Figure 26.15.

26.12 Spectra at Higher Field Strength

Occasionally, the 60-MHz spectrum of an organic compound, or a portion of it, is almost undecipherable because the chemical shifts of several groups of protons are all very similar. In these cases, all the proton resonances occur in the same area of the spectrum, and peaks often overlap so extensively that individual peaks and splittings cannot be extracted. One way to simplify such a situation is to use a spectrometer that operates at a higher frequency. Although both 60-MHz and 100-MHz instruments are still in use, it is becoming increasingly common to find instruments operating at much higher fields and with spectrometer frequencies 300, 400, or 500 MHz.

Although NMR coupling constants do not depend on the frequency or the field strength of operation of the NMR spectrometer, chemical shifts in hertz depend on these parameters. This circumstance can often be used to simplify an otherwise undecipherable spectrum. Suppose, for instance, that a compound contained three multiplets derived from groups of protons with very similar chemical shifts. At 60 MHz, these peaks might overlap, as illustrated in Figure 26.16, and simply give an unresolved envelope of absorption. It turns out that the $n + 1$ rule fails to make the proper predictions when chemical shifts are similar for the protons in a molecule. The spectral patterns that result are said to be **second order**, and what you end up seeing is an amorphous blob of unrecognizable patterns!

Figure 26.16 also shows the spectrum of the same compound at two higher frequencies (100 MHz and 300 MHz). When the spectrum is redetermined at a higher frequency, the coupling constants (J) do not change, but the chemical shifts in *hertz* (not ppm) of the proton groups (H_A, H_B, H_C) responsible for the multiplets do increase. It is important to realize, however, that the chemical shift in *ppm* is a constant, and it will not change when the frequency of the spectrometer is increased (see equation 1 in Section 26.4).

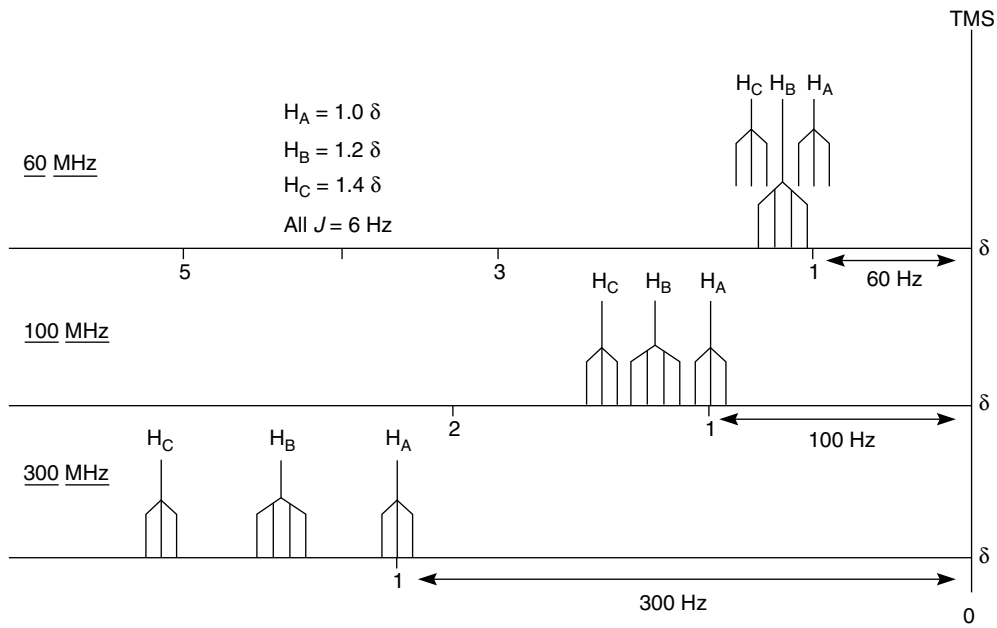


Figure 26.16 A comparison of the spectrum of a compound with overlapping multiplets at 60 MHz, with spectra of the same compound also determined at 100 MHz and 300 MHz.

Notice that at 300 MHz, the individual multiplets are cleanly separated and resolved. At high frequency, the chemical shift differences of each proton increase, resulting in more clearly recognizable patterns (that is, triplets, quartets, and so on) and less overlap of proton patterns in the spectrum. At high frequency, the chemical shift differences are large, and the $n + 1$ rule will more likely correctly predict the patterns. Thus, it is a clear advantage to use NMR spectrometers operating at high frequency (300 MHz or above) because the resulting spectra are more likely to provide nonoverlapped and well-resolved peaks. When the protons in a spectrum follow the $n + 1$ rule, the spectrum is said to be **first order**. The result is that you will obtain a spectrum with much more recognizable patterns, as shown in Figure 26.16.

26.13 Aromatic Compounds—Substituted Benzene Rings

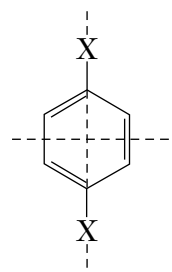
Phenyl rings are so common in organic compounds that it is important to know a few facts about NMR absorptions in compounds that contain them. In general, the ring protons of a benzenoid system have resonance near 7.3 ppm; however, electron-withdrawing ring substituents (for example, nitro, cyano, carboxyl, or carbonyl) move the resonance of these protons downfield (larger ppm values), and electron-donating ring substituents (for example, methoxy or amino) move the resonance of these protons upfield (smaller ppm values). Table 26.5 shows these trends for a series of symmetrically *p*-disubstituted benzene compounds. The *p*-disubstituted compounds were chosen because their two planes of symmetry render all of the hydrogens equivalent. Each compound gives only one aromatic peak (a singlet) in the proton NMR spectrum. Later, you will see that some positions are affected more strongly than others in systems with substitution patterns different from this one.

In the sections that follow, we will attempt to cover some of the most important types of benzene ring substitution. In some cases, it will be necessary to examine sample spectra taken at both 60 MHz and 300 MHz. Many benzenoid rings show second-order splittings at 60 MHz, but are essentially first order at 300 MHz.

A. Monosubstituted Rings

Alkylbenzenes. In monosubstituted benzenes in which the substituent is neither a strongly electron-withdrawing nor a strongly electron-donating group, all the ring protons give rise to what appears to be a *single resonance* when the spectrum is determined at 60 MHz. This is a particularly common occurrence in alkyl-substituted benzenes. Although the protons *ortho*, *meta*, and *para* to the substituent are

TABLE 26.5 Proton Chemical Shifts in p-disubstituted Benzene Compounds

Substituent X		δ (ppm)	
	—OCH_3	6.80	Electron donating (shielding)
	—OH	6.60	
	—NH_2	6.36	
	—CH_3	7.05	
	—H	7.32	
	—COOH	8.20	Electron withdrawing (deshielding)
	—NO_2	8.48	

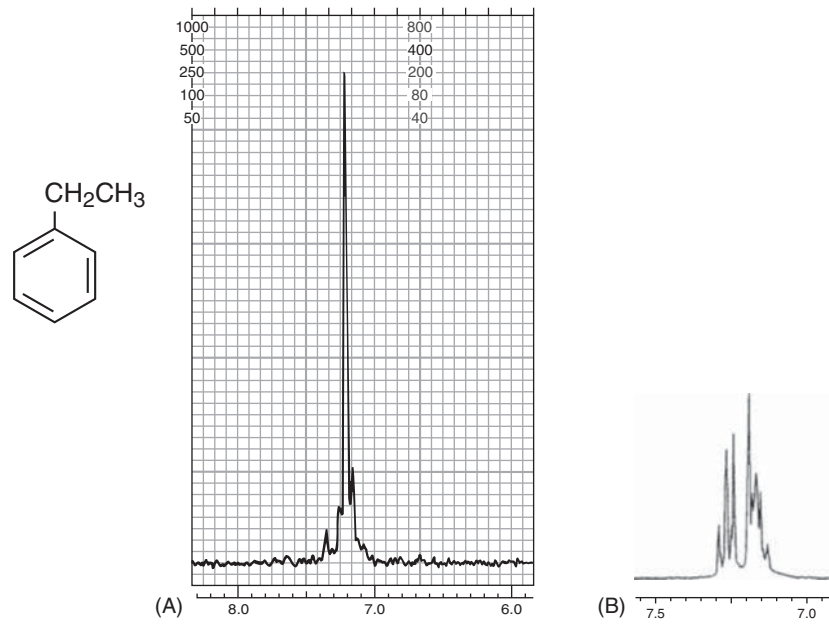
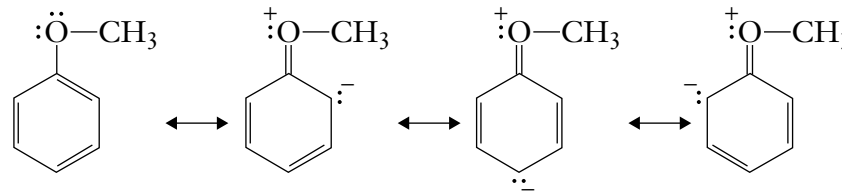


Figure 26.17 The aromatic ring portions of the ^{1}H NMR spectra of ethylbenzene at (A) 60 MHz and (B) 300 MHz.

not chemically equivalent, they generally give rise to a single unresolved absorption peak. A possible explanation is that the chemical shift differences, which should be small in any event, are somehow eliminated by the presence of the ring current, which tends to equalize them. All of the protons are nearly equivalent under these conditions. The NMR spectra of the aromatic portions of alkylbenzene compounds are good examples of this type of circumstance. Figure 26.17A is the 60-MHz ^{1}H spectrum of ethylbenzene.

The 300-MHz spectrum of ethylbenzene, shown in Figure 26.17B, presents quite a different picture. With the increased frequency shifts at 300 MHz, the nearly equivalent (at 60 MHz) protons are neatly separated into two groups. The *ortho* and *para* protons appear upfield from the *meta* protons. The splitting pattern is clearly second order.

Electron-Donating Groups. When electron-donating groups are attached to the ring, the ring protons are not equivalent, even at 60 MHz. A highly activating substituent such as methoxy clearly increases the electron density at the *ortho* and *para* positions of the ring (by resonance) and helps to give these protons greater shielding than those in the *meta* positions and, thus, a substantially different chemical shift.



At 60 MHz, this chemical shift difference results in a complicated second-order splitting pattern for anisole (methoxybenzene), but the protons do fall clearly into two groups, the *ortho/para* protons and the *meta* protons. The 60-MHz NMR spectrum of the aromatic portion of anisole (see Figure 26.18A) has a complex multiplet

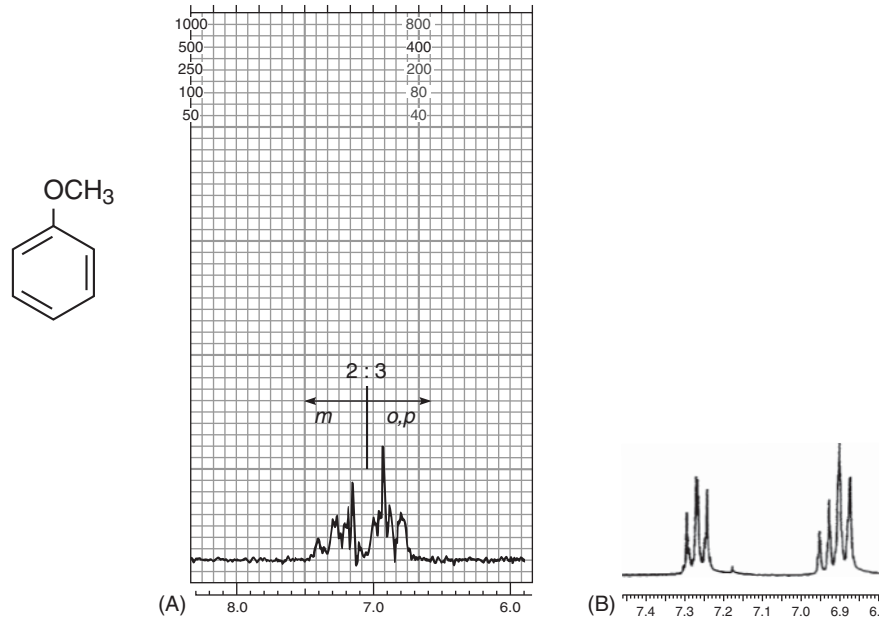


Figure 26.18 The aromatic ring portions of the 1H NMR spectra of anisole at (A) 60 MHz and (B) 300 MHz.

for the *o,p,* protons (integrating for three protons) that is upfield from the *meta* protons (integrating for two protons), with a clear distinction (gap) between the two types. Aniline (aminobenzene) provides a similar spectrum, also with a 3:2 split, owing to the electron-releasing effect of the amino group.

The 300-MHz spectrum of anisole (see Figure 26.18B) shows the same separation between the *ortho/para* hydrogens (upfield) and the *meta* hydrogens (downfield). However, because the actual shift in Hertz between the two types of hydrogens is greater, there is less second-order interaction and the lines in the pattern are sharper at 300 MHz. In fact, it might be tempting to try to interpret the observed pattern as if it were first order, a triplet at 7.25 ppm (*meta*, 2 H) and an overlapping triplet (para, 1 H) with a doublet (*ortho*, 2 H) at about 6.9 ppm.

Anisotropy—Electron-Withdrawing Groups. A carbonyl or a nitro group would be expected to show (aside from anisotropy effects) a reverse effect, because these groups are electron withdrawing. It would be expected that the group would act to decrease the electron density around the *ortho* and *para* positions, thus deshielding the *ortho* and *para* hydrogens and providing a pattern exactly the reverse of the one shown for anisole (3:2 ratio, downfield:upfield). Convince yourself of this by drawing resonance structures. Nevertheless, the actual NMR spectra of nitrobenzene and benzaldehyde do not have the appearances that would be predicted on the basis of resonance structures. Instead, the *ortho* protons are much more deshielded than the *meta* and *para* protons, due to the magnetic anisotropy of the π bonds in these groups.

Anisotropy is observed when a substituent group bonds a carbonyl group directly to the benzene ring (see Figure 26.19). Once again, the ring protons fall into two groups, with the *ortho* protons downfield from the *meta/para* protons. Benzaldehyde (see Figure 26.20) and acetophenone both show this effect in their NMR spectra. A similar effect is sometimes observed when a carbon–carbon double bond is attached to the ring. The 300-MHz spectrum of benzaldehyde (see Figure 26.20B) is a nearly first-order spectrum and shows a doublet (H_C, 2 H), a triplet (H_B, 1 H), and a triplet (H_A, 2 H). It can be analyzed by the n + 1 rule.

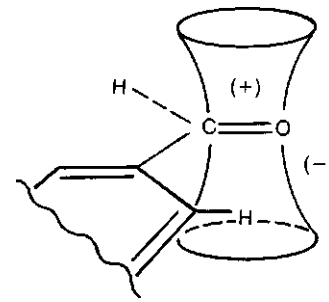


Figure 26.19 Anisotropic deshielding of the ortho protons of benzaldehyde.

B. *para*-Disubstituted Rings

Of the possible substitution patterns of a benzene ring, some are easily recognized. One of these is the para-disubstituted benzene ring. Examine anethole (see Figure 26.21) as a first example.

On one side of the anethole ring shown in Figure 26.21, proton H_a is coupled to H_b, ^3J = 8 Hz resulting in a doublet at about 6.80 ppm in the spectrum. Proton H_a appears upfield (smaller ppm value) relative to H_b because of shielding by the electron-releasing effect of the methoxy group. Likewise, H_b is coupled to H_a, ^3J = 8 Hz, producing another doublet at 7.25 ppm for this proton. Because of the plane of symmetry, both halves of the ring are equivalent. Thus, H_a and H_b on the other side of the ring also appear at 6.80 ppm and 7.25 ppm, respectively. Each doublet, therefore, integrates for two protons each. A *para*-disubstituted ring, with two different substituents attached, is easily recognized by the appearance of two doublets, each integrating for two protons each.

As the chemical shifts of H_a and H_b approach each other in value, the *para*-disubstituted pattern becomes similar to that of 4-allyloxyanisole (see Figure 26.22). The inner peaks move closer together, and the outer ones become smaller or even disappear. Ultimately, when H_a and H_b approach each other closely enough in chemical shift, the outer peaks disappear, and the two inner peaks merge into a *singlet;* 1,4-dimethylbenzene (*para*-xylene), for instance, gives a singlet at 7.05 ppm.

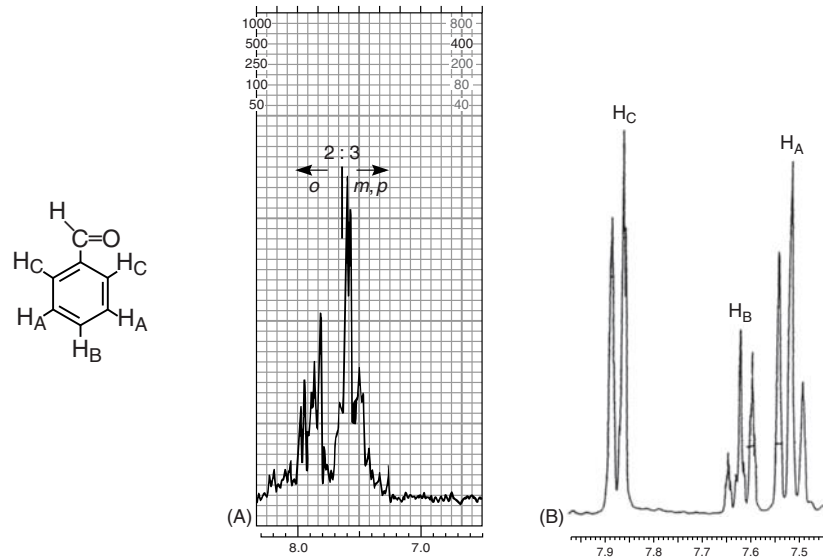


Figure 26.20 The aromatic ring portions of the ^{1}H NMR spactra of benzaldehyde at (A) 60 MHZ and (B) 300 MHZ.

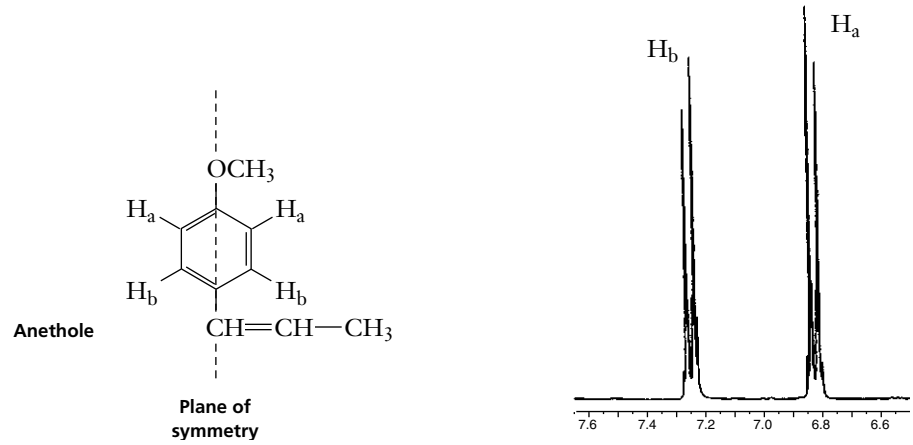


Figure 26.21 The aromatic ring protons of the 300-MHz ^{1}H NMR spectrum of anethole showing a para-disubstituted pattern.

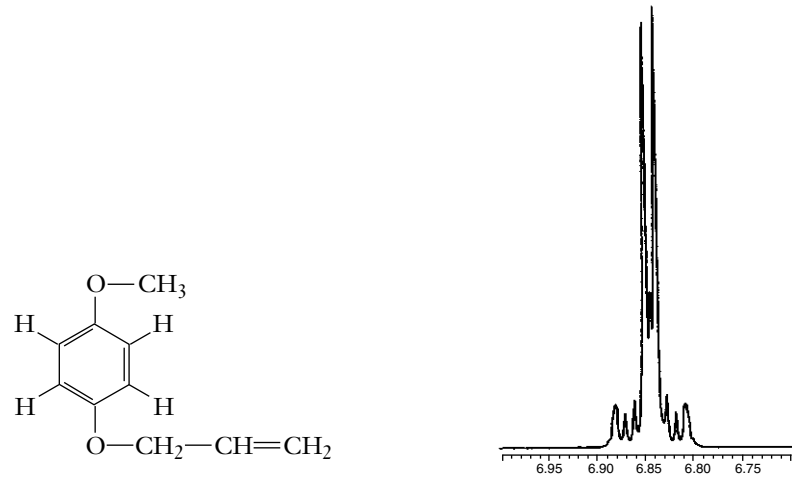


Figure 26.22 The aromatic ring protons of the 300-MHz ^{1}H NMR spectrum of 4-allyloxyanisole.

Hence, a single aromatic resonance integrating for four protons could easily represent a *para*-disubstituted ring, but the substituents would obviously be either identical or very similar.

C. Other Substitution

Figure 26.23 shows the 300-MHz ^{1}H spectra of the aromatic ring portions of 2-, 3-, and 4-nitroaniline (the *ortho*, *meta*, and *para* isomers). The characteristic pattern of a *para*-disubstituted ring, with its pair of doublets, makes it easy to recognize 4-nitroaniline. The splitting patterns for 2- and 3-nitroaniline are first order, and they can be analyzed by the $n + 1$ rule. As an exercise, see if you can analyze these patterns, assigning the multiplets to specific protons on the ring. Use the indicated multiplicities (s, d, t) and expected chemical shifts to help your assignments. Remember that the amino group releases electrons by resonance, and the nitro group shows a significant anisotropy toward ortho protons. You may ignore any *meta* and *para* couplings, remembering that these long-range couplings will be too small in magnitude to be observed on the scale on which these figures are presented. If the spectra were expanded, you would be able to observe ^4J couplings.

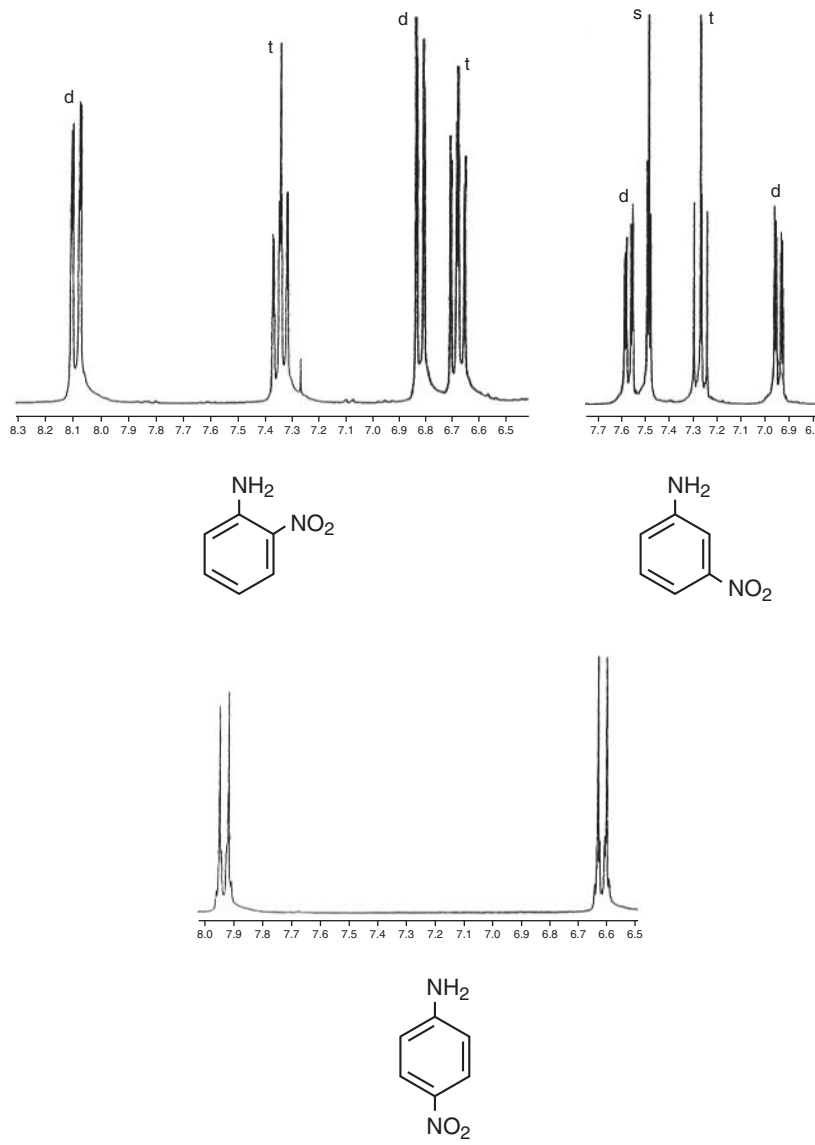


Figure 26.23 The 300-MHz ^{1}H NMR spectra of the aromatic ring portions of 2-, 3-, and 4-nitroaniline (s, singlet; d, doublet; t, triplet).The NH_2 group is not shown.

The spectrum shown in Figure 26.24 is of 2-nitrophenol. It is helpful to look also at the coupling constants for the benzene ring found in Table 26.4. Because the spectrum is expanded, it is now possible to see ^3J couplings (about 8 Hz) as well as ^4J couplings (about 1.5 Hz). ^5J couplings are not observed ($^5J \approx 0$). Each of the protons on this compound is assigned on the spectrum. Proton H_d appears downfield at 8.11 ppm as a doublet of doublets ($^3J_{ad}$ = 8 Hz and $^4J_{cd}$ = 1.5 Hz); H_c appears at 7.6 ppm as a triplet of doublets ($^3J_{ac} = {}^3J_{bc}$ = 8 Hz and $^4J_{cd}$ = 1.5 Hz); H_b appears at 7.17 ppm as a doublet of doublets ($^3J_{bc}$ = 8 Hz and $^4J_{ab}$ = 1.5 Hz); and H_a appears at 7.0 ppm as a triplet of doublets ($^3J_{ac} = {}^3J_{ad}$ = 8 Hz and $^4J_{ab}$ = 1.5 Hz). H_d appears the furthest downfield because of the anisotropy of the nitro group. H_a and H_b are relatively shielded because of the resonance-releasing effect of the hydroxyl group, which shields these two protons. H_c is assigned by a process of elimination in the absence of these two effects.

26.14 Protons Attached to Atoms Other Than Carbon

Protons attached to atoms other than carbon often have a widely variable range of absorptions. Several of these groups are tabulated in Table 26.6. In addition, under the usual conditions of determining an NMR spectrum, protons on heteroelements normally do not couple with protons on adjacent carbon atoms to give spin–spin splitting. The primary reason is that such protons often exchange rapidly with those of the solvent medium. The absorption position is variable because these groups also undergo various degrees of hydrogen bonding in solutions of different

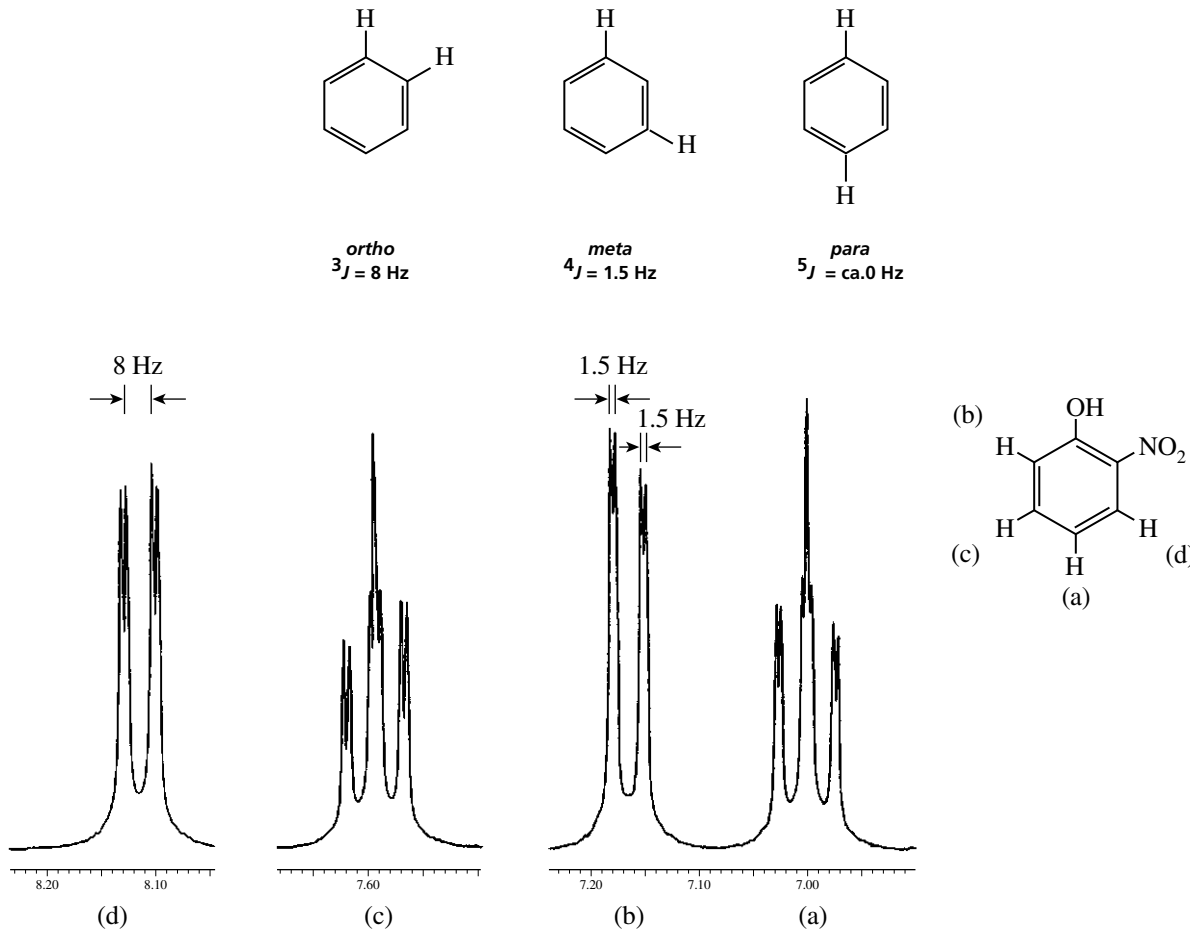


Figure 26.24 Expansions of the aromatic ring proton multiplets from the 300-MHz ^{1}H spectrum of 2-nitrophenol. The accompanying hydroxyl absorption (OH) is not shown. Coupling constants are indicated on some of the peaks of the spectrum to give an idea of scale.

TABLE 26.6 Typical Ranges for Groups with Variable Chemical Shift

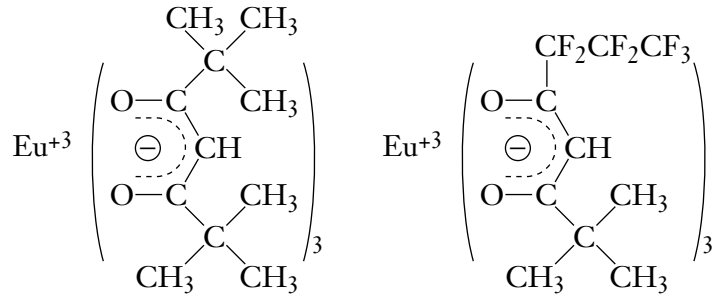
Acids	RCOOH	10.5–12.0 ppm
Phenols	ArOH	4.0–7.0
Alcohols	ROH	0.5–5.0
Amines	RNH_2	0.5–5.0
Amides	$RCONH_2$	5.0–8.0
Enols	CH═CH—OH	≥15

concentrations. The amount of hydrogen bonding that occurs with a proton radically affects the valence electron density around that proton and produces correspondingly large changes in the chemical shift. The absorption peaks for protons that have hydrogen bonding or are undergoing exchange are frequently broad relative to other singlets and can often be recognized on that basis. For a different reason, called **quadrupole broadening**, protons attached to nitrogen atoms often show an extremely broad resonance peak, often almost indistinguishable from the baseline.

26.15 Chemical Shift Reagents

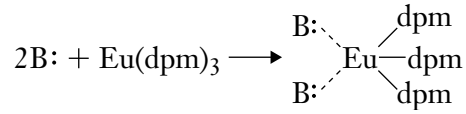
Researchers have known for some time that interactions between molecules and solvents, such as those due to hydrogen bonding, can cause large changes in the resonance positions of certain types of protons (for example, hydroxyl and amino). They have also known that the resonance positions of some groups of protons can be greatly affected by changing from the usual NMR solvents such as CCl_4 and $CDCl_3$ to solvents such as benzene, which impose local anisotropic effects on surrounding molecules. In many cases, it is possible to resolve partially overlapping multiplets by such a solvent change. The use of **chemical shift reagents** for this purpose dates from about 1969. Most of these chemical shift reagents are organic complexes of paramagnetic rare earth metals from the lanthanide series of elements. When these metal complexes are added to the compound whose spectrum is being determined, profound shifts in the resonance positions of the various groups of protons are observed. The direction of the shift (upfield or downfield) depends primarily on which metal is being used. Complexes of europium, erbium, thulium, and ytterbium shift resonances to lower field; complexes of cerium, praseodymium, neodymium, samarium, terbium, and holmium generally shift resonances to higher field. The advantage of using such reagents is that shifts similar to those observed at higher field can be induced without the purchase of an expensive higher-field instrument.

Of the lanthanides, europium is probably the most commonly used metal. Two of its widely used complexes are *tris*-(dipivalomethanato)europium and *tris*-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium. These are frequently abbreviated $Eu(dpm)_3$ and $Eu(fod)_3$, respectively.



$Eu(dpm)_3$ or $Eu(thd)_3$ **$Eu(fod)_3$**

These lanthanide complexes produce spectral simplifications in the NMR spectrum of any compound that has a relatively basic pair of electrons (unshared pair) that can coordinate with Eu^{3+}. Typically, aldehydes, ketones, alcohols, thiols, ethers, and amines will all interact:



The amount of shift that a given group of protons will experience depends (1) on the distance separating the metal (Eu^{3+}) and that group of protons, and (2) on the concentration of the shift reagent in the solution. Because of the latter dependence, it is necessary when reporting a lanthanide-shifted spectrum to report the number of mole equivalents of shift reagent used or its molar concentration.

The distance factor is illustrated in the spectra of hexanol, which are given in Figures 26.25 and 26.26. In the absence of shift reagent, the normal spectrum is obtained (see Figure 26.25). Only the triplet of the terminal methyl group and the triplet of the methylene group next to the hydroxyl are resolved in the spectrum. The other protons (aside from OH) are found together in a broad unresolved group. With shift reagent added (see Figure 26.26), each of the methylene groups is clearly separated and resolved into the proper multiplet structure. The spectrum is first-order and simplified; all the splittings are explained by the $n + 1$ rule.

One final consequence of using a shift reagent should be noted. Notice in Figure 26.26 that the multiplets are not as nicely resolved into sharp peaks as you might expect. This is due to the fact that shift reagents cause a small amount of peak broadening. At high-shift reagent concentrations, this problem becomes serious, but at most useful concentrations the amount of broadening experienced is tolerable.

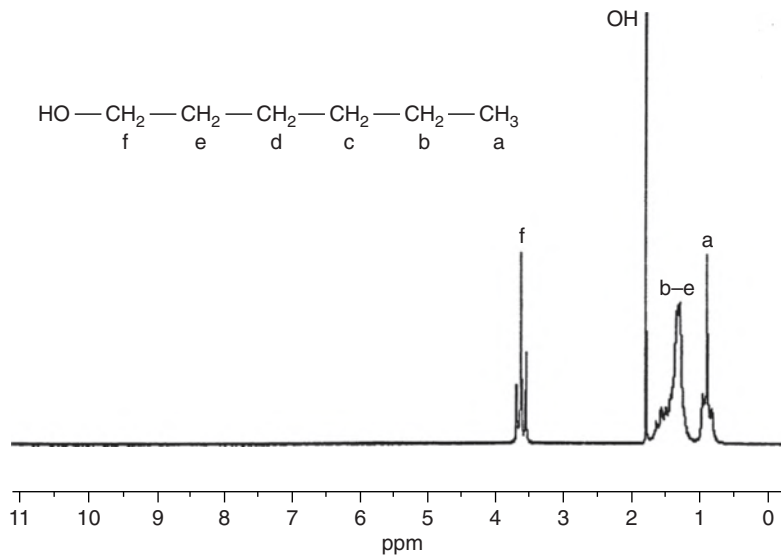


Figure 26.25 90-MHz ^{1}H NMR spectrum of hexanol determined without $Eu(dpm)_3$

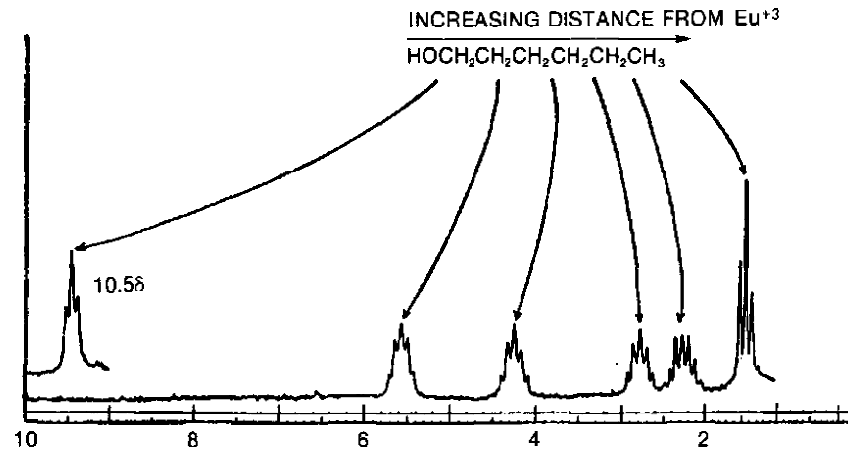


Figure 26.26 The 100-MHz ^{1}H NMR spectrum of hexanol with 0.29 mole equivalents of Eu(dpm)$_3$ added. From Sanders J. K. M. and Williams, D. H. Chemical Communications, (1970): 422. Reproduced by permission of The Royal Society of Chemistry.

REFERENCES

Textbooks

Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*, 3rd ed. New York: VCH Publishers, 1998.

Gunther, H. *NMR Spectroscopy*, 2nd ed. New York: John Wiley & Sons, 1995.

Jackman, L. M., and Sternhell, S. *Nuclear Magnetic Resonance Spectroscopy* in *Organic Chemistry*, 2nd ed. New York: Pergamon Press, 1969.

Macomber, R. S. *A Complete Introduction to Modern NMR Spectroscopy*. NewYork: John Wiley & Sons, 1997.

Macomber, R. S. *NMR Spectroscopy: Essential Theory and Practice*. New York: College Outline Series, Harcourt Brace Jovanovich, 1988.

Pavia, D. L., Lampman, G. M., and vyvyan, J. R. Kriz, G. S. Brooks Cole 2008. *Introduction to Spectroscopy*, 4th ed.

Sanders, J. K. M., and Hunter, B. K. *Modern NMR Spectroscopy—A Guide for Chemists*, 2nd ed. Oxford: Oxford University Press, 1993.

Silverstein, R. M., and Webster, F. X. and Kiemle, D. *Spectrometric Identification of Organic Compound*s, 7th ed. New York: John Wiley & Sons, 2005.

Compilations of Spectra

Pouchert, C. J. *The Aldrich Library of* NMR *Spectra, 60 MHz*, 2nd ed. Milwaukee, WI: Aldrich Chemical Company, 1983.

Pouchert, C. J., and Behnke, J. *The Aldrich Library of ^{13}C and ^1H FT–NMR Spectra, 300 MHz*. Milwaukee, WI: Aldrich Chemical Company, 1993.

Pretsch, E., Clerc, T., Seibl, J., and Simon,W. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed. Berlin and New York: Springer-Verlag, 1989. Translated from the German by K. Biemann.

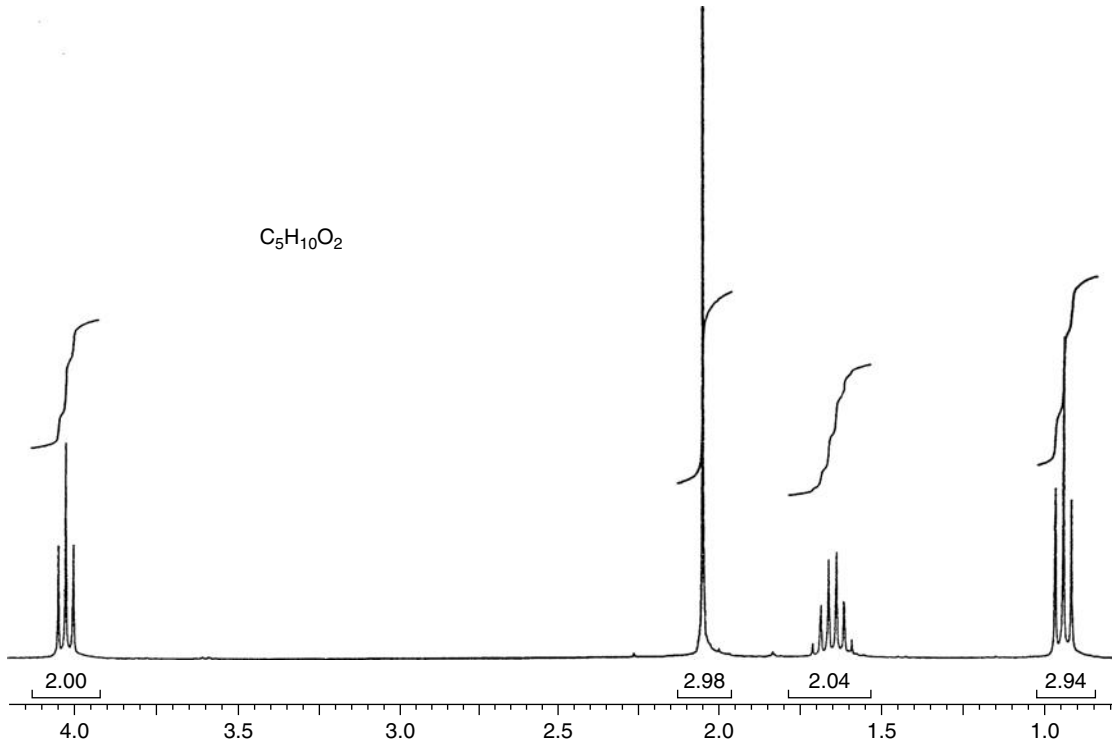
Web Sites

http://www.aist.go.jp/RIODB/SDBS/menu-e.html
Integrated Spectral DataBase System for Organic Compounds, National Institute of Materials and Chemical Research, Tsukuba, Ibaraki 305-8565, Japan. This database includes infrared, mass spectra, and NMR data (proton and carbon-13) for a large number of compounds.

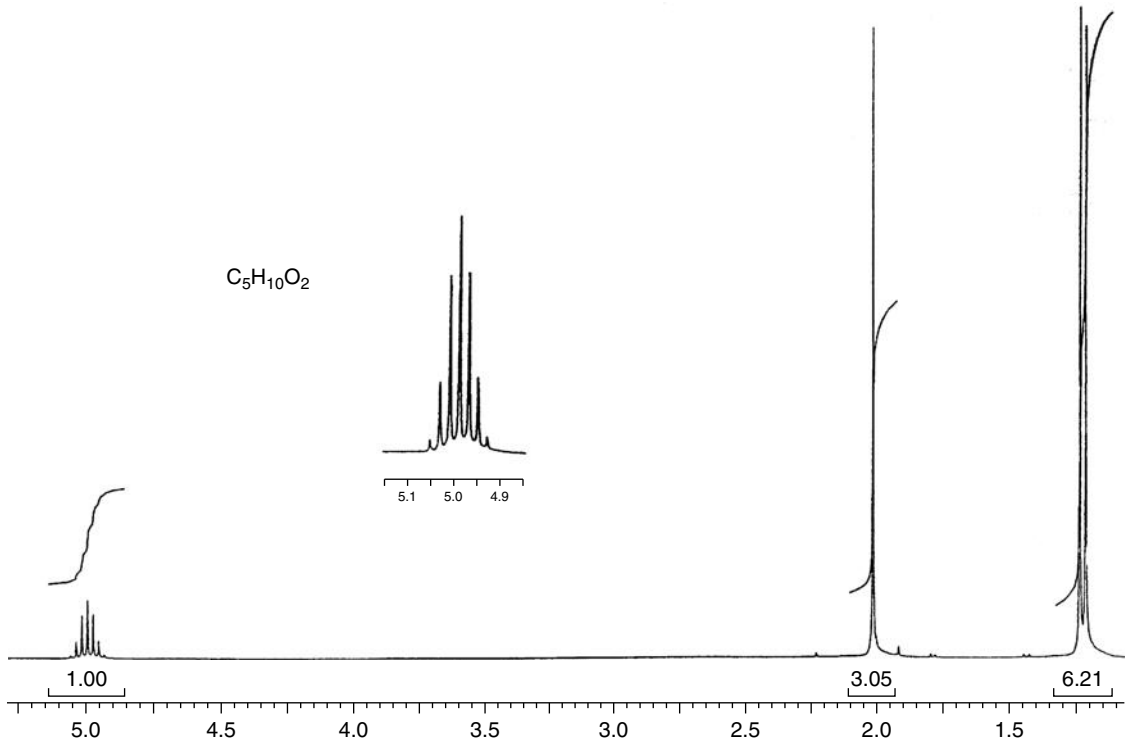
http://www.chem.ucla.edu/~webspectra/
UCLA Department of Chemistry and Biochemistry in connection with Cambridge University Isotope Laboratories maintains a Web site,WebSpectra, that provides NMR and IR spectroscopy problems for students to interpret. They provide links to other sites with problems for students to solve.

PROBLEMS

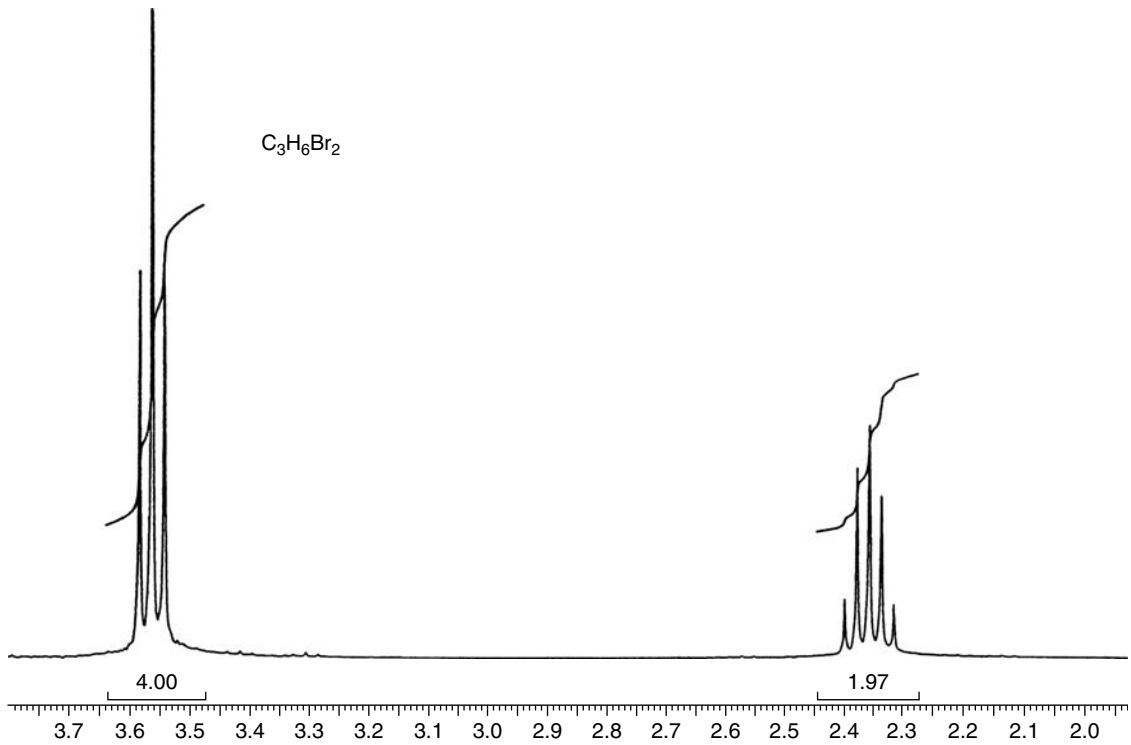
1. Describe the method that you should use to determine the proton NMR spectrum of a carboxylic acid, which is insoluble in *all* the common organic solvents that your instructor is likely to make available.
2. To save money, a student uses chloroform instead of deuterated chloroform to run a proton NMR spectrum. Is this a good idea?
3. Look up the solubilities for the following compounds and decide whether you would select deuterated chloroform or deuterated water to dissolve the substances for NMR spectroscopy.
   a. Glycerol (1,2,3-propanetriol)
   b. 1,4-Diethoxybenzene
   c. Propyl pentanoate (propyl ester of pentanoic acid)
4. Assign each of the proton patterns in the spectra of 2-, 3-, and 4-nitroaniline as shown in Figure 26.23.
5. The following two compounds are isomeric esters derived from acetic acid, each with formula $C_5H_{10}O_2$. These expanded spectra clearly show the splitting patterns: singlet, doublet, triplet, quartet, etc. Integral curves are drawn on the spectra, along with relative integration values provided just above the scale and under each set of peaks. These numbers indicate the number of protons assigned to each pattern. Remember that these integral values are approximate. You will need to round the values off to the nearest whole number. Draw the structure of each compound.



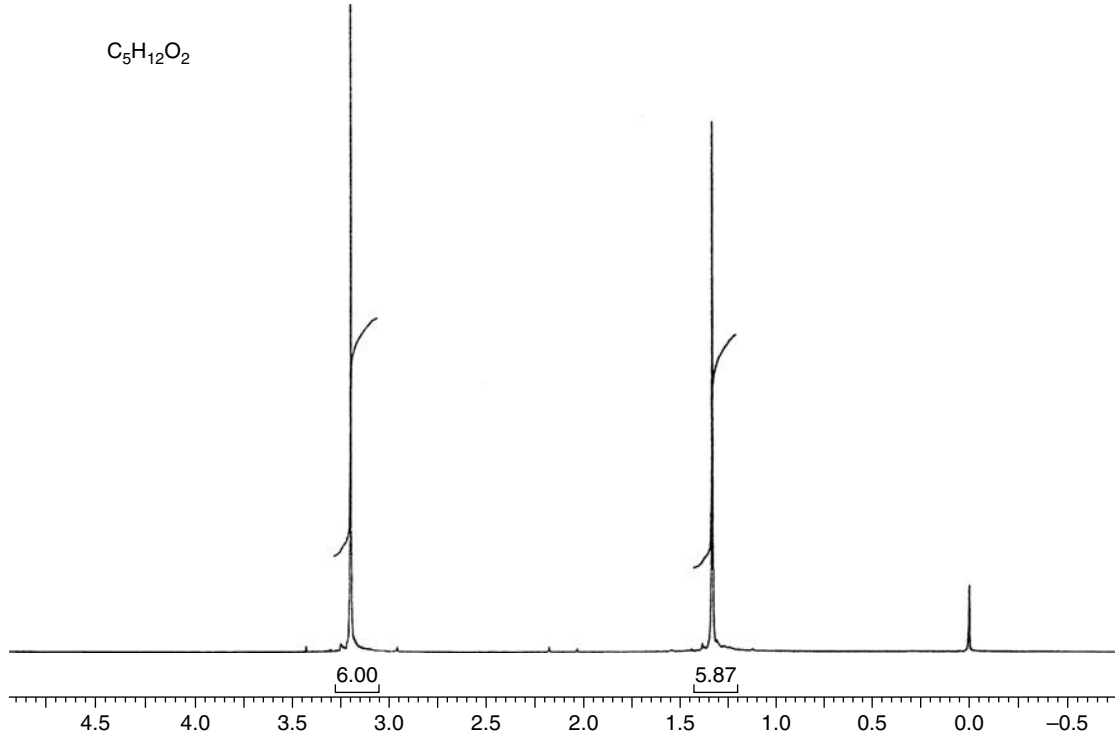
b. The set of peaks centering on 5 ppm is expanded in both the *x* and *y* directions in order to show the pattern more clearly. This expanded pattern is shown as an inset on the full spectrum.



6. The compound that gives the following NMR spectrum has the formula $C_3H_6Br_2$. Draw the structure.

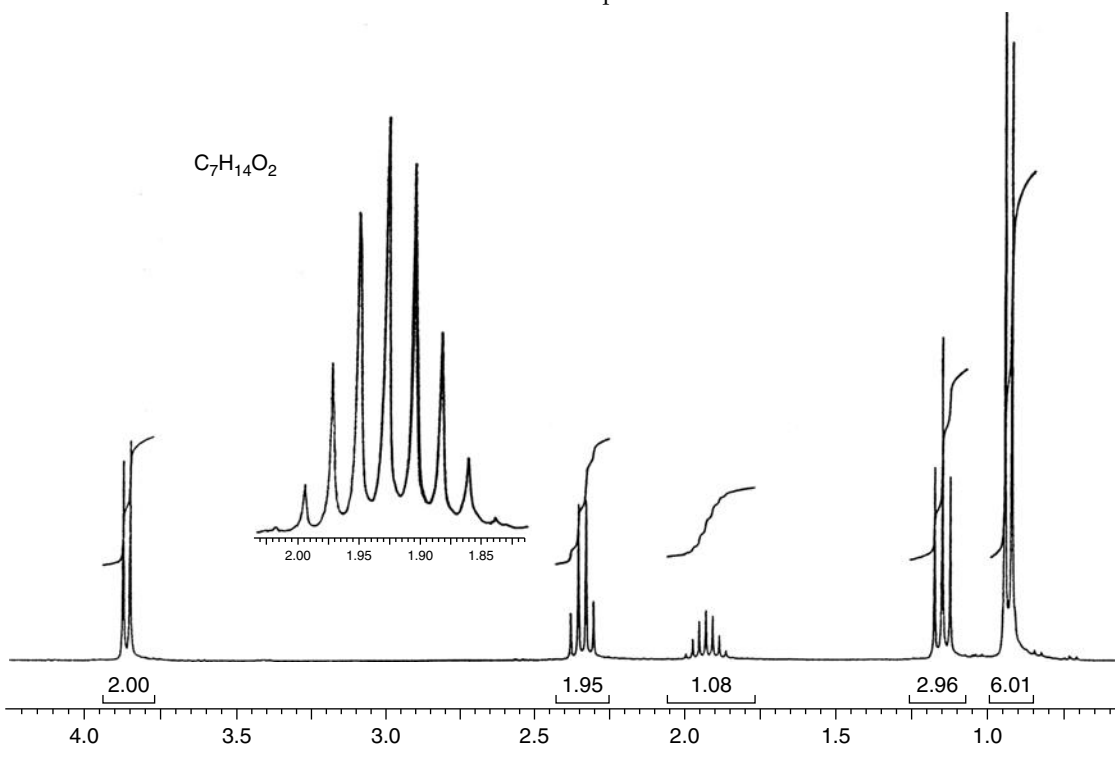


7. Draw the structure of an ether with formula $C_5H_{12}O_2$ that fits the following NMR spectrum.

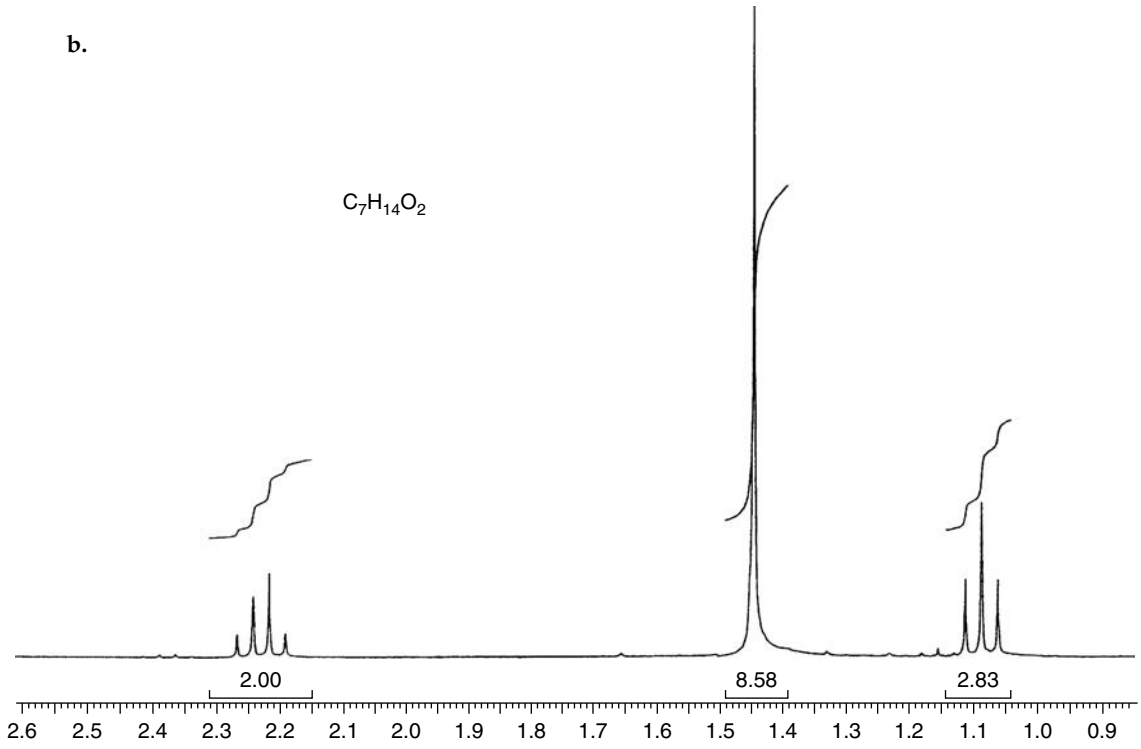


8. Following are the NMR spectra of three isomeric esters with the formula $C_7H_{14}O_2$, all derived from propanoic acid. Provide a structure for each.

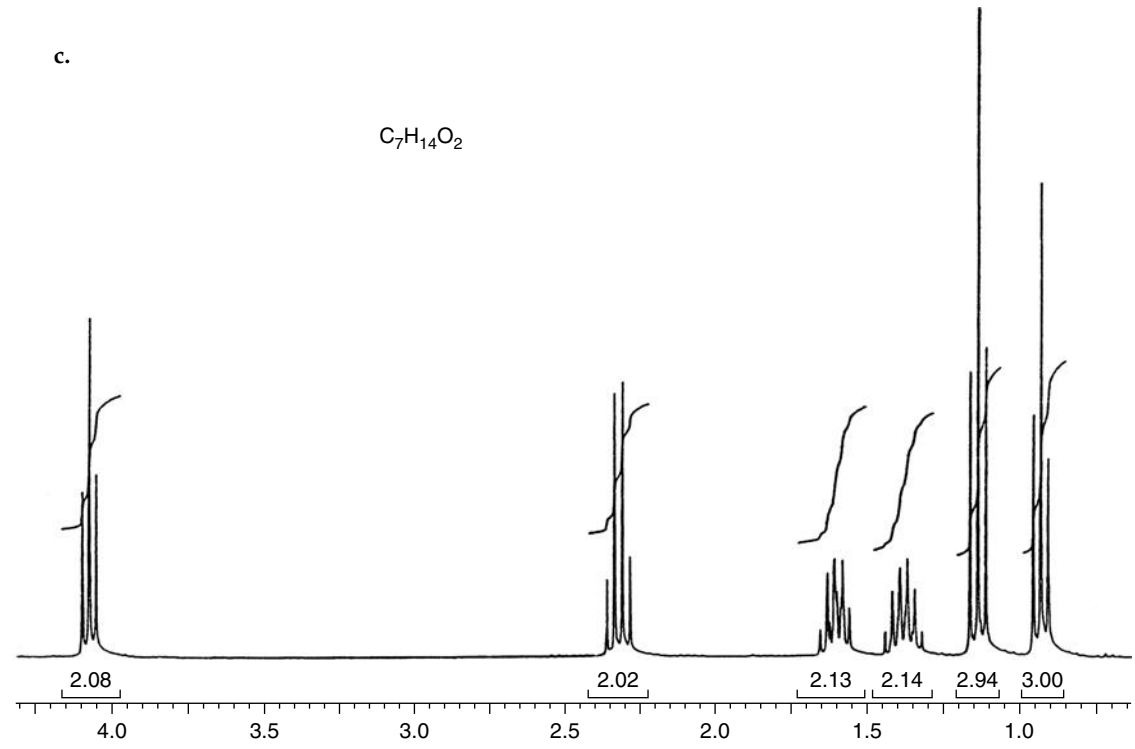
a. The set of peaks centering on about 1.9 ppm is expanded in both the *x* and *y* directions in order to show the pattern more clearly. This expanded pattern is shown as an inset on the full spectrum.



b.

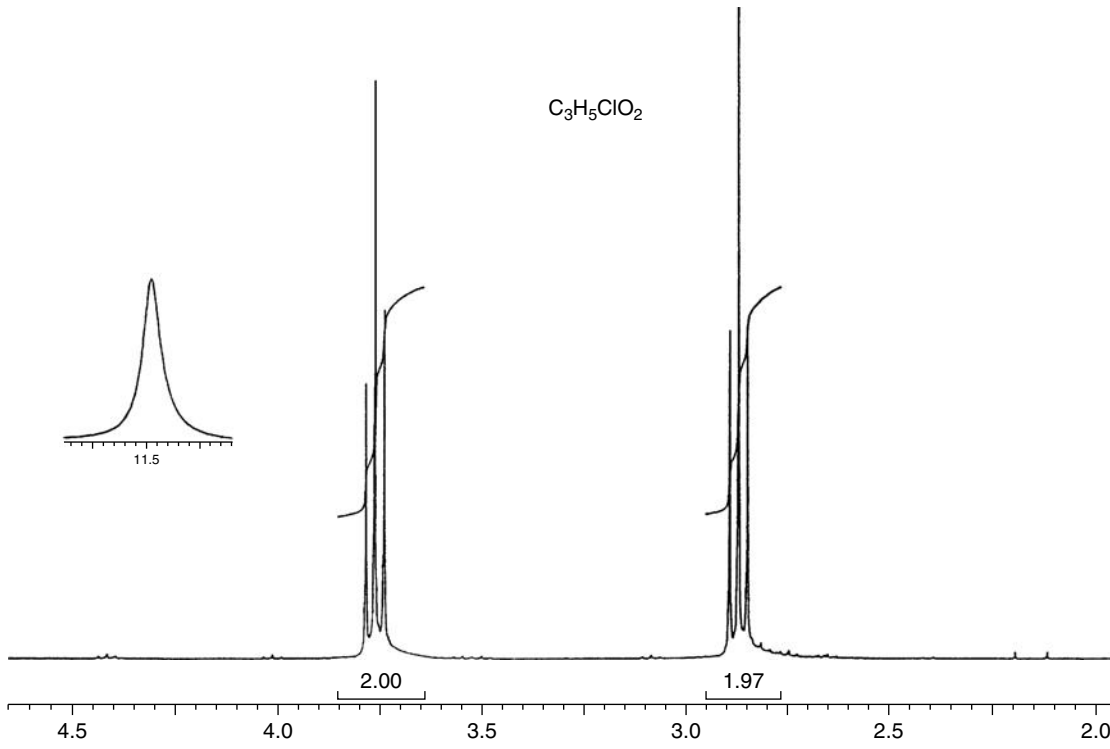

$C_7H_{14}O_2$
2.00
8.58
2.83
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9

c.

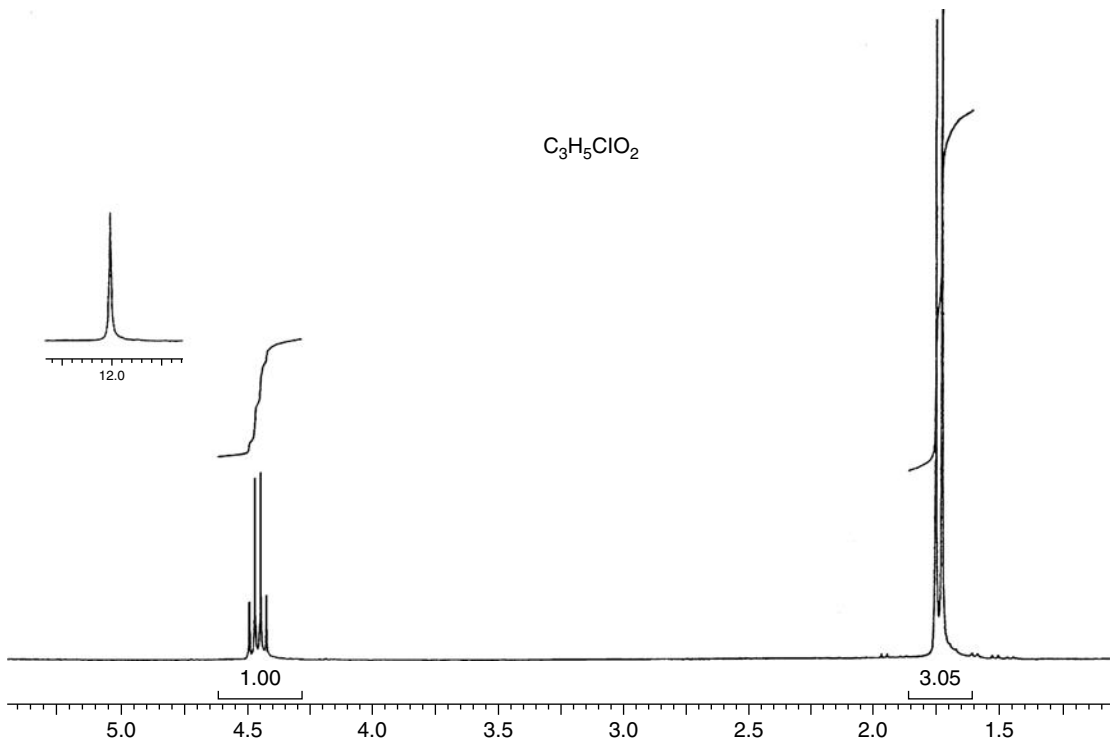

$C_7H_{14}O_2$
2.08
2.02
2.13
2.14
2.94
3.00
4.0 3.5 3.0 2.5 2.0 1.5 1.0

9. The two isomeric carboxylic acids that give the following NMR spectra both have the formula $C_3H_5ClO_2$. Draw their structures.

a. The broad singlet integrating for one proton that is shown as an inset on the spectrum appears downfield at 11.5 ppm.

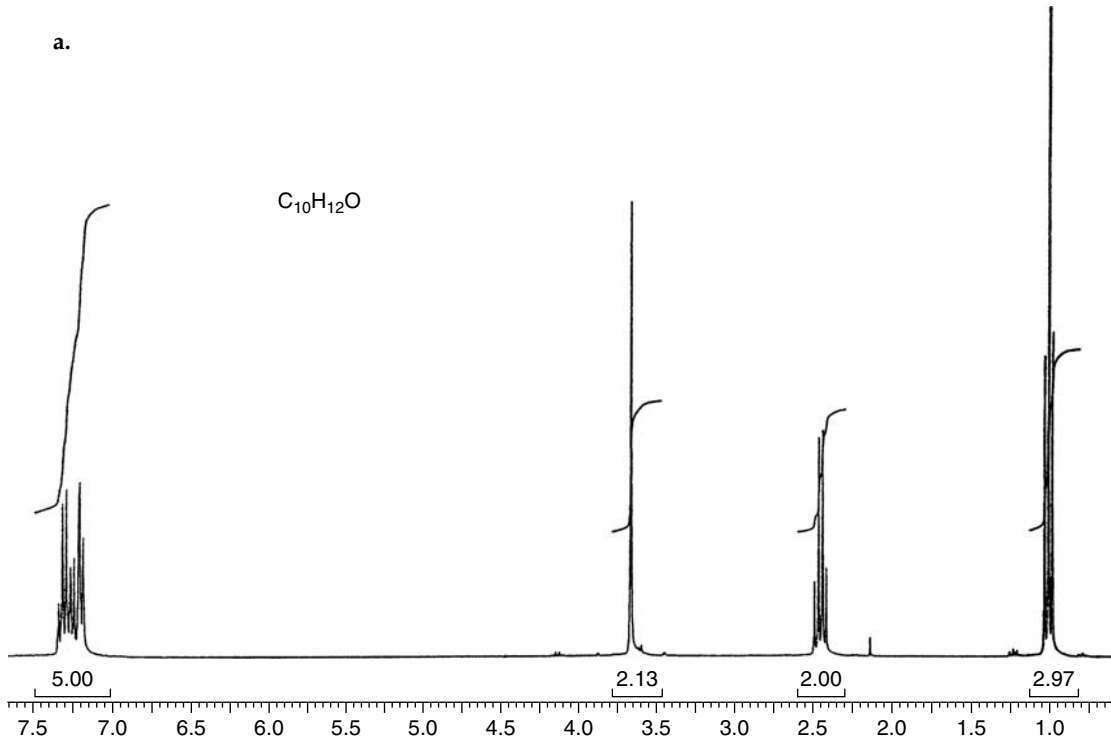


b. The singlet integrating for one proton that is shown as an inset on the spectrum appears downfield at 12.0 ppm.

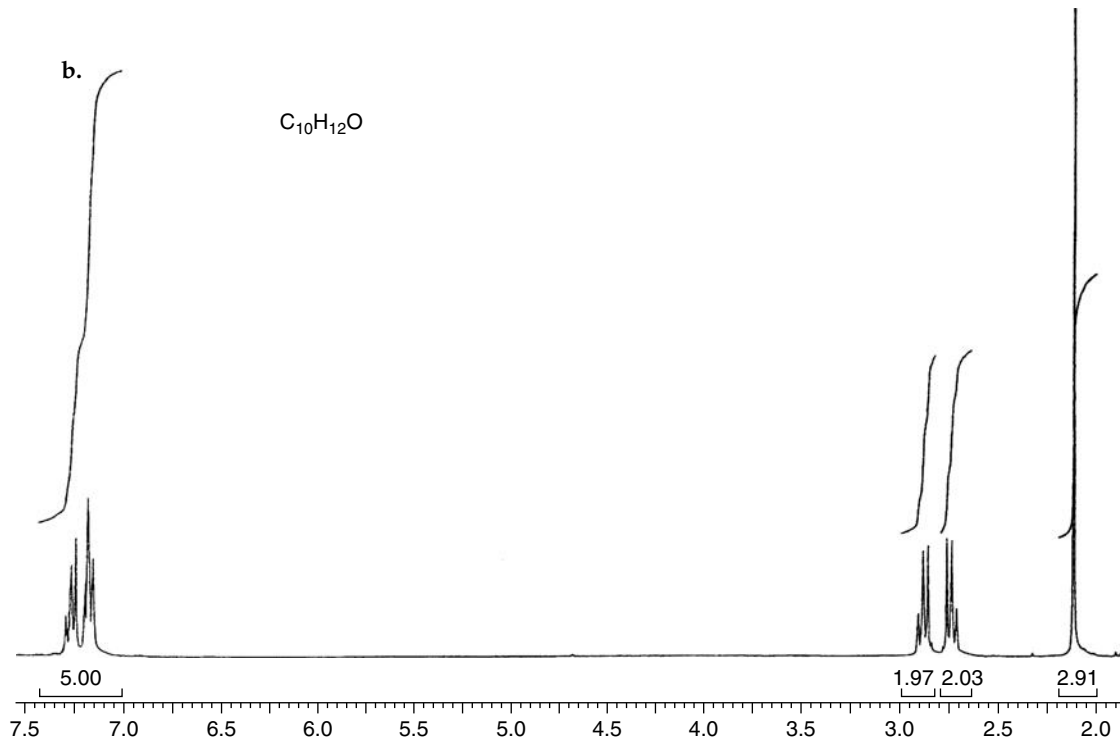


10. The following compounds are isomers with formula $C_{10}H_{12}O$. Their infrared spectra show strong bands near 1715 cm^{-1} and in the range from 1600 cm^{-1} to 1450 cm^{-1}. Draw their structures.

a.



b.



27 TECHNIQUE 27

Carbon-13 Nuclear Magnetic Resonance Spectroscopy

Carbon-12, the most abundant isotope of carbon, does not possess spin ($I = 0$); it has both an even atomic number and an even atomic weight. The second principal isotope of carbon, ^{13}C, however, does have the nuclear spin property ($I = \frac{1}{2}$). ^{13}C atom resonances are not easy to observe, due to a combination of two factors. First, the natural abundance of ^{13}C is low; only 1.08% of all carbon atoms are ^{13}C. Second, the magnetic moment μ of ^{13}C is low. For these two reasons, the resonances of ^{13}C are about 6000 times weaker than those of hydrogen. With special Fourier transform (FT) instrumental techniques, which are not discussed here, it is possible to observe ^{13}C nuclear magnetic resonance (carbon-13) spectra on samples that contain only the natural abundance of ^{13}C.

The most useful parameter derived from carbon-13 spectra is the chemical shift. Integrals are unreliable and are not necessarily related to the relative numbers of ^{13}C atoms present in the sample. Hydrogens that are attached to ^{13}C atoms cause spin–spin splitting, but spin–spin interaction between adjacent carbon atoms is rare. With the low natural abundance carbon-13 (0.0108), the probability of finding two ^{13}C atoms adjacent to one another is extremely low.

Carbon spectra can be used to determine the number of nonequivalent carbons and to identify the types of carbon atoms (methyl, methylene, aromatic, carbonyl, and so on) that may be present in a compound. Thus, carbon NMR provides direct information about the carbon skeleton of a molecule. Because of the low natural abundance of carbon-13 in a sample, it is often necessary to acquire multiple scans over what is needed for proton NMR.

For a given magnetic field strength, the resonance frequency of a ^{13}C nucleus is about one-fourth the frequency required to observe proton resonances. For example, in a 7.05-tesla applied magnetic field, protons are observed at 300 MHz, and ^{13}C nuclei are observed at about 75 MHz.

27.1 Preparing a Sample for Carbon-13 NMR

Technique 26, Section 26.1, describes the technique for preparing samples for proton NMR. Much of what is described there also applies to carbon NMR. There are some differences, however, in determining a carbon spectrum. Fourier transform instruments require a deuterium signal to stabilize (lock) the field. Therefore, the solvents must contain deuterium. Deuterated chloroform, $CDCl_3$, is used most commonly for this purpose because of its relatively low cost. Other deuterated solvents may also be used.

Modern FT–NMR spectrometers allow chemists to obtain both the proton and carbon NMR spectra of the same sample in the same NMR tube. After changing several parameters in the program operating the spectrometer, you can obtain both spectra without removing the sample from the probe. The only real difference is that a proton spectrum may be obtained after a few scans, whereas the carbon spectrum may require 10–100 times more scans.

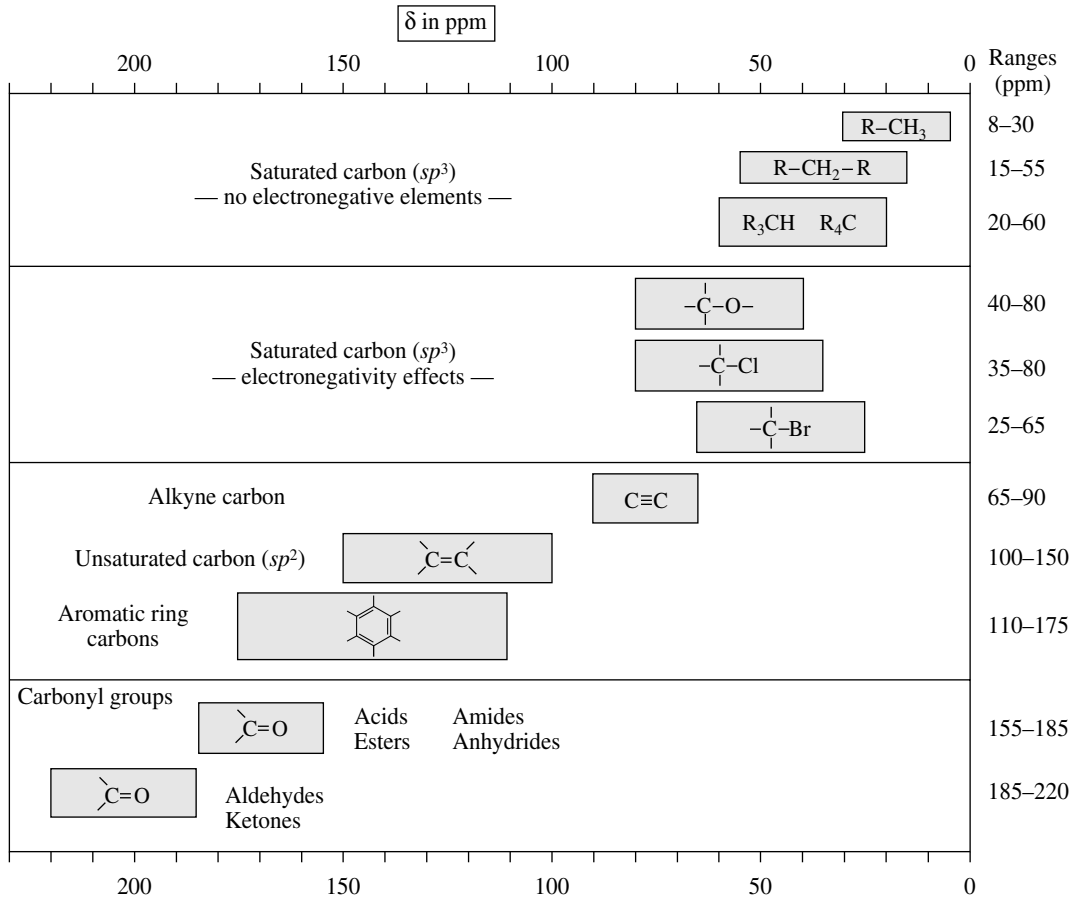


Figure 27.1 A correlation chart for ^{13}C chemical shifts (chemical shifts are listed in parts per million from tetramethylsilane).

Tetramethylsilane (TMS) may be added as an internal reference standard, where the chemical shift of the methyl carbon is defined as 0.00 ppm. Alternatively, you may use the center peak of the $CDCl_3$ pattern, which is found at 77.0 ppm. This pattern can be observed as a small "triplet" near 77.0 ppm in a number of the spectra given in this chapter.

27.2 Carbon-13 Chemical Shifts

An important parameter derived from carbon-13 spectra is the chemical shift. The correlation chart in Figure 27.1 shows typical ^{13}C chemical shifts, listed in parts per million (ppm) from TMS, where the carbons of the methyl groups of TMS (not the hydrogens) are used for reference. Notice that the chemical shifts appear over a range (0–220 ppm) much larger than that observed for protons (0–12 ppm). Because of the very large range of values, nearly every nonequivalent carbon atom in an organic molecule gives rise to a peak with a different chemical shift. Peaks rarely overlap as they often do in proton NMR.

The correlation chart is divided into four sections. Saturated carbon atoms appear at the highest field, nearest to TMS (8–60 ppm). The next section of the chart demonstrates the effect of electronegative atoms (40–80 ppm). The third section includes alkene and aromatic- ring carbon atoms (100–175 ppm). Finally, the fourth section contains carbonyl carbons, which appear at the lowest field values (155–220 ppm).

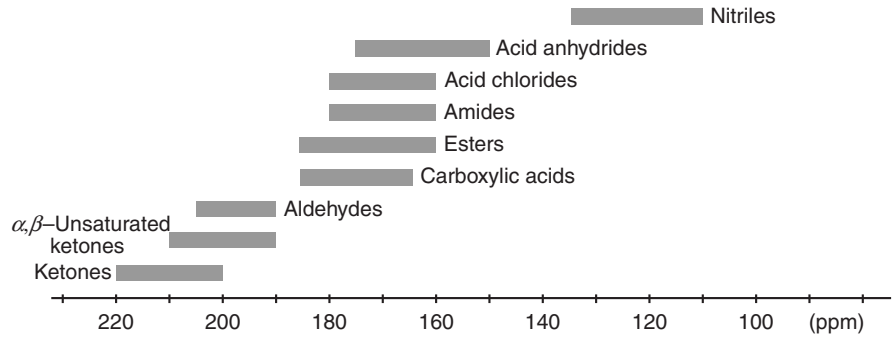


Figure 27.2 A ^{13}C correlation chart for carbonyl and nitrile functional groups.

Electronegativity, hybridization, and anisotropy all affect ^{13}C chemical shifts in nearly the same fashion as they affect ^{1}H chemical shifts; however ^{13}C chemical shifts are about 20 times larger. Electronegativity (see Section 26.7) produces the same deshielding effect in carbon NMR as in proton NMR—the electronegative element produces a large downfield shift. The shift is greater for a ^{13}C atom than for a proton because the electronegative atom is directly attached to the ^{13}C atom and the effect occurs through only a single bond, C—X. With protons, the electronegative atoms are attached to carbon, not hydrogen; the effect occurs through two bonds, H—C—X, rather than one.

Analogous with ^{1}H shifts, changes in hybridization also produce larger shifts for the carbon-13 that is *directly involved* (no bonds) than they do for the hydrogens attached to that carbon (one bond). In ^{13}C NMR, the carbons of carbonyl groups have the largest chemical shifts, due both to sp^2 hybridization and to the fact that an electronegative oxygen is directly attached to the carbonyl carbon, deshielding it even further. Anisotropy (see Section 26.8) is responsible for the large chemical shifts of the carbons in aromatic rings and alkenes.

Notice that the range of chemical shifts is larger for carbon atoms than for hydrogen atoms. Because the factors affecting carbon shifts operate either through one bond or directly on carbon, they are greater than those for hydrogen, which operate through more bonds. As a result, the entire range of chemical shifts becomes larger for ^{13}C (0–220 ppm) than for ^{1}H (0–12 ppm).

Many of the important functional groups of organic chemistry contain a carbonyl group. In determining the structure of a compound containing a carbonyl group, it is frequently helpful to have some idea of the type of carbonyl group in the unknown. Figure 27.2 illustrates the typical ranges of ^{13}C chemical shifts for some carbonyl-containing functional groups. Although there is some overlap in the ranges, ketones and aldehydes are easy to distinguish from the other types. Chemical shift data for carbonyl carbons are particularly powerful when combined with data from an infrared spectrum.

27.3 Proton-Coupled ^{13}C Spectra—Spin–Spin Splitting of Carbon-13 Signals

Unless a molecule is artificially enriched by synthesis, the probability of finding two ^{13}C atoms in the same molecule is low. The probability of finding two ^{13}C atoms adjacent to each other in the same molecule is even lower. Therefore, we rarely observe **homonuclear** (carbon–carbon) spin–spin splitting patterns where the interaction occurs between two ^{13}C atoms. However, the spins of protons attached directly to ^{13}C atoms do interact with the spin of carbon and cause the

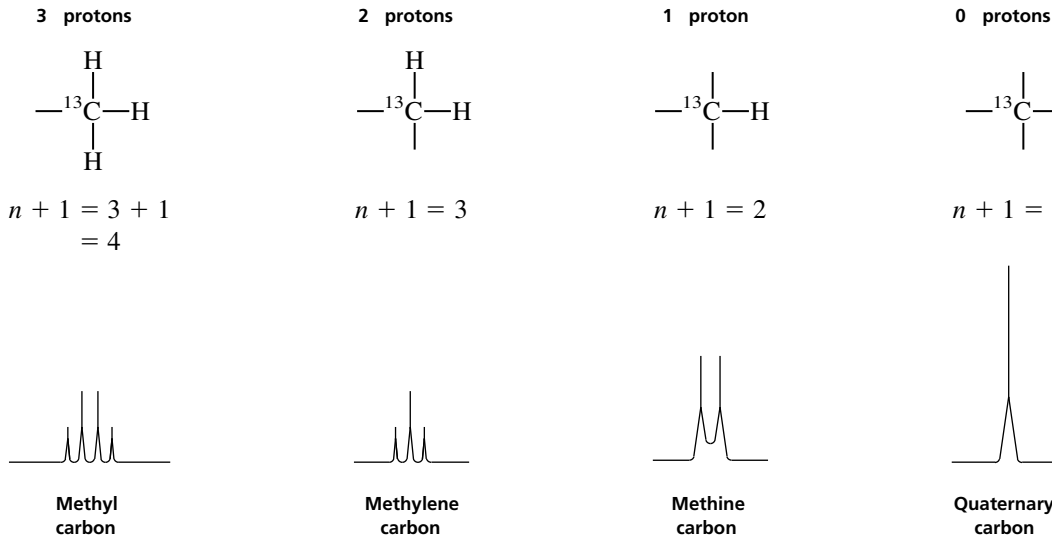


Figure 27.3 The effect of attached protons on ^{13}C resonances.

carbon signal to be split according to the $n + 1$ rule. This is **heteronuclear** (carbon–hydrogen) coupling involving two different types of atoms. With ^{13}C NMR, we generally examine splitting that arises from the protons *directly attached* to the carbon atom being studied. This is a one-bond coupling. In proton NMR, the most common splittings are *homonuclear* (hydrogen–hydrogen), which occur between protons attached to *adjacent* carbon atoms. In these cases, the interaction is a three-bond coupling, H—C—C—H.

Figure 27.3 illustrates the effect of protons directly attached to a ^{13}C atom. The $n + 1$ rule predicts the degree of splitting in each case. The resonance of a ^{13}C atom with three attached protons, for instance, is split into a quartet ($n + 1 = 3 + 1 = 4$). Because the hydrogens are directly attached to the carbon-13 (one-bond couplings), the coupling constants for this interaction are quite large, with J values of about 100 Hz to 250 Hz. Compare the typical three-bond H—C—C—H couplings that are common in NMR spectra, which have J values of about 4 Hz to 18 Hz.

It is important to note while examining Figure 27.3 that you are not "seeing" protons directly when looking at a ^{13}C spectrum (proton resonances occur at frequencies outside the range used to obtain ^{13}C spectra); you are observing only the effect of the protons on ^{13}C atoms. Also remember that we cannot observe ^{12}C, because it is NMR inactive.

Spectra that show the spin–spin splitting, or coupling, between carbon-13 and the protons directly attached to it are called **proton-coupled spectra**. Figure 27.4 A is the proton-coupled ^{13}C NMR spectrum of ethyl phenylacetate. In this spectrum, the first quartet downfield from TMS (14.2 ppm) corresponds to the carbon of the methyl group. It is split into a quartet (J = 127 Hz) by the three attached hydrogen atoms (^{13}C—H, one-bond couplings). In addition, although it cannot be seen on the scale of this spectrum (an expansion must be used), each of the quartet lines is split into a closely spaced triplet (J = ca. 1 Hz). This additional fine splitting is caused by the two protons on the adjacent —CH_2— group. These are two-bond couplings (H—C—^{13}C) of a type that occurs commonly in ^{13}C spectra, with coupling constants that are generally quite small (J = 0–2 Hz) for systems with carbon atoms in

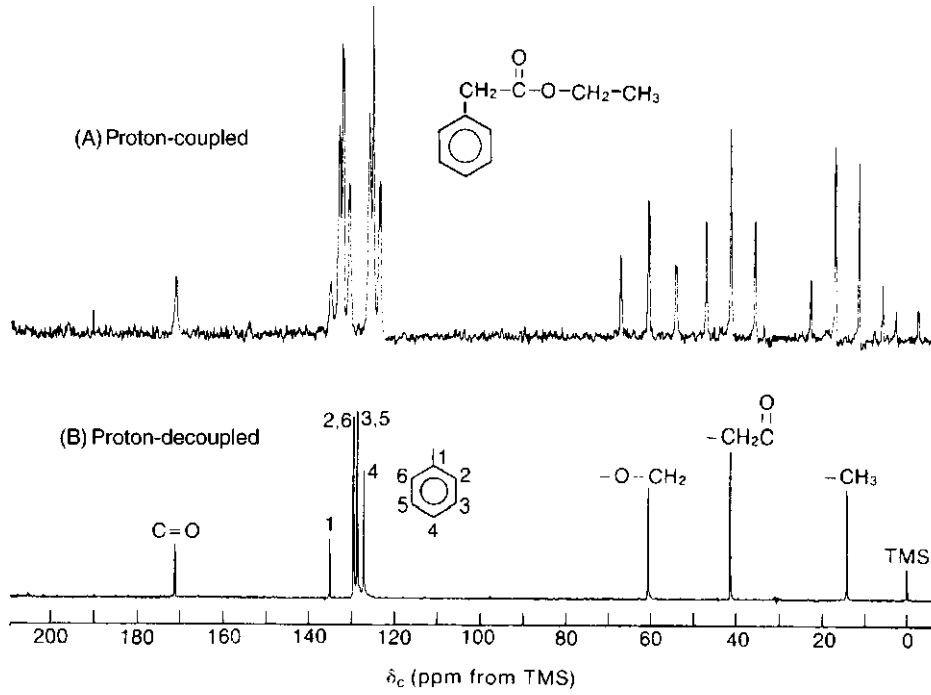


Figure 27.4 Ethyl phenylacetate. (A) The proton-coupled ^{13}C NMR spectrum (20 MHz). (B) The proton-decoupled ^{13}C spectrum (20 MHz). (From Moore, J. A., Dalrymple, D. L., and Rodig, O. R. Experimental Methods in Organic Chemistry, 3rd ed. [Philadelphia: W. B. Saunders, 1982].)

an aliphatic chain. Because of their small size, these couplings are frequently ignored in the routine analysis of spectra, with greater attention being given to the larger one-bond splittings seen in the quartet itself.

There are two —CH_2— groups in ethyl phenylacetate. The one corresponding to the ethyl —CH_2— group is found farther downfield (60.6 ppm), as this carbon is deshielded by the attached oxygen. It is a triplet because of the two attached hydrogens (one-bond couplings). Again, although it is not seen in this unexpanded spectrum, the three hydrogens on the adjacent methyl group finely split each of the triplet peaks into a quartet. The benzyl —CH_2— carbon is the intermediate triplet (41.4 ppm). Farthest downfield is the carbonyl-group carbon (171.1 ppm). On the scale of this presentation, it is a singlet (no directly attached hydrogens), but because of the adjacent benzyl —CH_2 — group, it is actually split finely into a triplet. The aromatic ring carbons also appear in the spectrum, and they have resonances in the range from 127 ppm to 136 ppm. Section 27.7 will discuss aromatic ring ^{13}C resonances.

Proton-coupled spectra for large molecules are often difficult to interpret. The multiplets from different carbons commonly overlap because the ^{13}C—H coupling constants are frequently larger than the chemical shift differences of the carbons in the spectrum. Sometimes, even simple molecules such as ethyl phenylacetate (see Figure 27.4A) are difficult to interpret. Proton decoupling, which is discussed in the next section, avoids this problem.

27.4 Proton-Decoupled ^{13}C Spectra

By far, the great majority of ^{13}C NMR spectra are obtained as **proton-decoupled spectra**. The decoupling technique obliterates all interactions between protons and ^{13}C nuclei; therefore, only **singlets** are observed in a decoupled ^{13}C NMR spectrum.

Although this technique simplifies the spectrum and avoids overlapping multiplets, it has the disadvantage that the information on attached hydrogens is lost.

Proton **decoupling** is accomplished in the process of determining a ^{13}C NMR spectrum by simultaneously irradiating all of the protons in the molecule with a broad spectrum of frequencies in the proper range for protons. Modern NMR spectrometers provide a second, tunable radio-frequency generator, the **decoupler**, for this purpose. Irradiation causes the protons to become saturated, and they undergo rapid upward and downward transitions, among all their possible spin states. These rapid transitions decouple any spin–spin interactions between the hydrogens and the ^{13}C nuclei being observed. In effect, all spin interactions are averaged to zero by the rapid changes. The carbon nucleus "senses" only one average spin state for the attached hydrogens rather than two or more distinct spin states.

Figure 27.4B is a proton-decoupled spectrum of ethyl phenylacetate. The proton coupled spectrum (see Figure 27.4A) was discussed in Section 27.3. It is interesting to compare the two spectra to see how the proton-decoupling technique simplifies the spectrum. Every chemically and magnetically distinct carbon gives only a single peak. Notice, however, that the two *ortho* ring carbons (carbons 2 and 6) and the two *meta* ring carbons (carbons 3 and 5) are equivalent by symmetry and that each pair gives only a single peak.

Figure 27.5 is a second example of a proton-decoupled spectrum. Notice that the spectrum shows three peaks corresponding to the exact number of

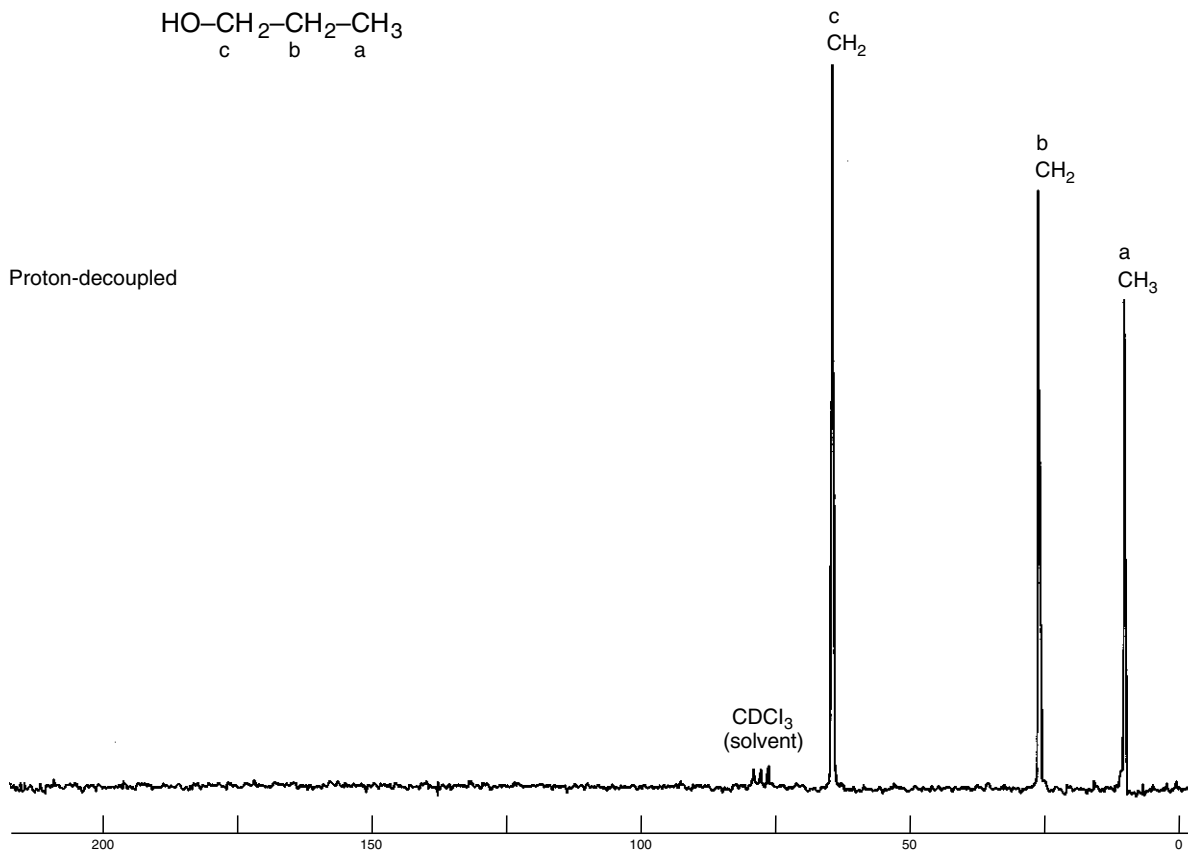


Figure 27.5 The proton-decoupled ^{13}C NMR spectrum of 1-propanol (22.5 MHz).

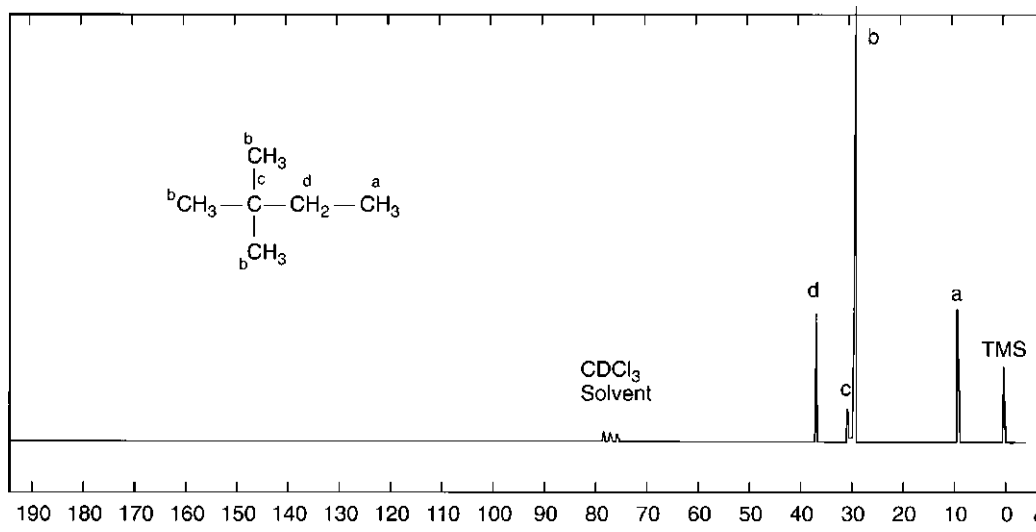


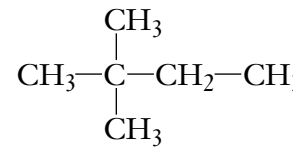
Figure 27.6 The proton-decoupled ^{13}C NMR spectrum of 2,2-dimethylbutane.

carbon atoms in 1-propanol. If there are no equivalent carbon atoms in a molecule, a ^{13}C peak will be observed for *each* carbon. Notice also that the assignments given in Figure 27.5 are consistent with the values in the chemical shift chart (see Figure 27.1). The carbon atom closest to the electronegative oxygen is farthest downfield, and the methyl carbon is at highest field.

The three-peak pattern centered at $\delta = 77$ ppm is due to the solvent $CDCl_3$. This pattern results from the coupling of a deuterium (^2H) nucleus to the ^{13}C nucleus. Often, the $CDCl_3$ pattern is used as an internal reference in place of TMS.

27.5 Some Sample Spectra—Equivalent Carbons

Equivalent ^{13}C atoms appear at the same chemical shift value. Figure 27.6 shows the proton-decoupled carbon spectrum for 2,2-dimethylbutane. The three methyl groups at the left side of the molecule are equivalent by symmetry.



Although this compound has a total of six carbons, there are only four peaks in the ^{13}C NMR spectrum. The ^{13}C atoms that are equivalent appear at the same chemical shift. The single methyl carbon, a, appears at highest field (9 ppm), and the three equivalent methyl carbons, b, appear at 29 ppm. The quaternary carbon, c, gives rise to the small peak at 30 ppm, and the methylene carbon, d, appears at 37 ppm. The relative sizes of the peaks are related, in part, to the number of each type of carbon atom present in the molecule. For example, notice in Figure 27.6 that the peak at 29 ppm (b) is much larger than the others. This peak is generated by three carbons. The quaternary carbon at 30 ppm (c) is very weak. Because no hydrogens are attached to this carbon, there is very little nuclear Overhauser enhancement (NOE) (see Section 27.6). Without attached hydrogen atoms, relaxation times are also

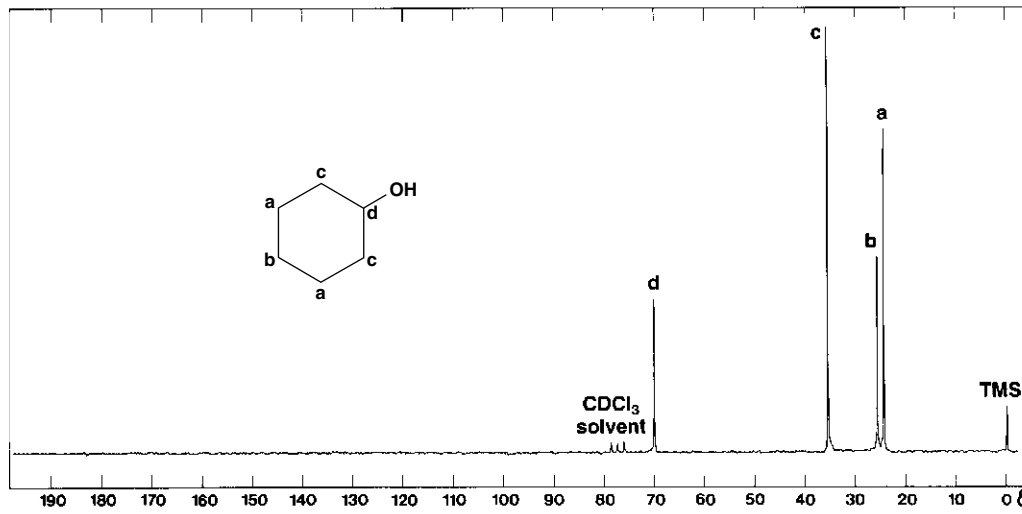


Figure 27.7 The proton-decoupled ^{13}C NMR spectrum of cyclohexanol.

longer than for other carbon atoms. Quaternary carbons, those with no hydrogens attached, frequently appear as weak peaks in proton-decoupled ^{13}C NMR spectra (see Section 27.6).

Figure 27.7 is a proton-decoupled ^{13}C spectrum of cyclohexanol. This compound has a plane of symmetry passing through its hydroxyl group, and it shows only four carbon resonances. Carbons a and c are doubled due to symmetry and give rise to larger peaks than carbons b and d. Carbon d, bearing the hydroxyl group, is deshielded by oxygen and has its peak at 70.0 ppm. Notice that this peak has the lowest intensity of all of the peaks. Its intensity is lower than that of carbon b in part because the carbon d peak receives the least amount of NOE; there is only one hydrogen attached to the hydroxyl carbon, whereas each of the other carbons has two hydrogens.

A carbon attached to a double bond is deshielded due to its sp^2 hybridization and some diamagnetic anisotropy. This effect can be seen in the ^{13}C NMR spectrum of cyclohexene (see Figure 27.8). Cyclohexene has a plane of symmetry that runs perpendicular to the double bond. As a result, we observe only three absorption peaks. There are two of each type of sp^3 carbon. Each of the double-bond carbons c has only one hydrogen, whereas each of the remaining carbons has two. As a result of a reduced NOE, the double-bond carbons (127 ppm) have a lower-intensity peak in the spectrum.

In Figure 27.9, the spectrum of cyclohexanone, the carbonyl carbon has the lowest intensity. This is due not only to reduced NOE (no hydrogen attached) but also to the long relaxation time of the carbonyl carbon (see Section 27.6). Notice also that Figure 27.2 predicts the large chemical shift for this carbonyl carbon (211 ppm).

27.6 Nuclear Overhauser Enhancement (NOE)

When we obtain a proton-decoupled ^{13}C spectrum, the intensities of many of the carbon resonances increase significantly above those observed in a proton-coupled experiment. Carbon atoms with hydrogen atoms directly attached are enhanced the most, and the enhancement increases (but not always linearly) as more hydrogens are attached. This effect is known as the nuclear Overhauser effect, and the degree of increase in the signal is called the **nuclear Overhauser enhancement (NOE)**. Thus,

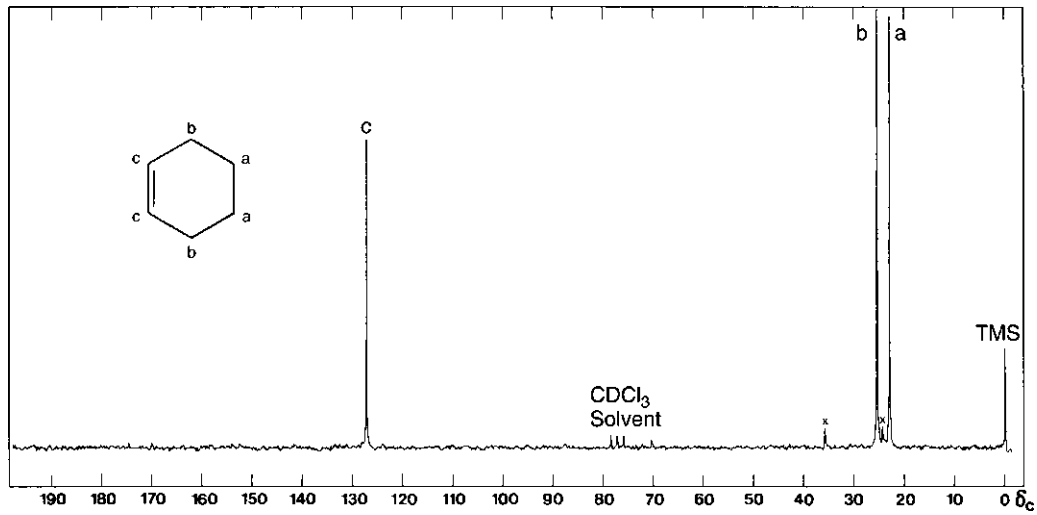


Figure 27.8 The proton-decoupled ^{13}C NMR spectrum of cyclohexanone. (The peak marked with an x are impurities.)

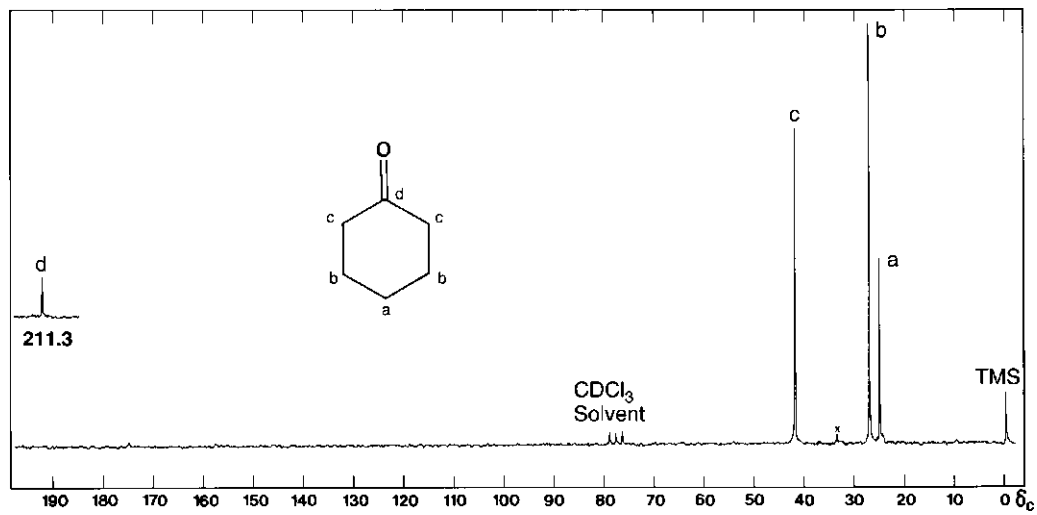


Figure 27.9 The proton-decoupled ^{13}C NMR spectrum of cyclohexanone. (The peak marked with an x is an impurity.)

we expect that the intensity of the carbon peaks should increase in the following order in a typical carbon-13 NMR spectrum:

$$\mathbf{CH_3 > CH_2 > CH > C}$$

Carbon atom relaxation times influence the intensity of peaks in a spectrum. When more protons are attached to a carbon atom, relaxation times become shorter, resulting in more intense peaks. Thus, we expect methyl and methylene groups to be relatively more intense than the intensity observed for quaternary carbon atoms where there are no attached protons. Thus, a weak-intensity peak is observed for the quaternary carbon atom at 30 ppm in 2,2-dimethylbutane (see Figure 27.6).

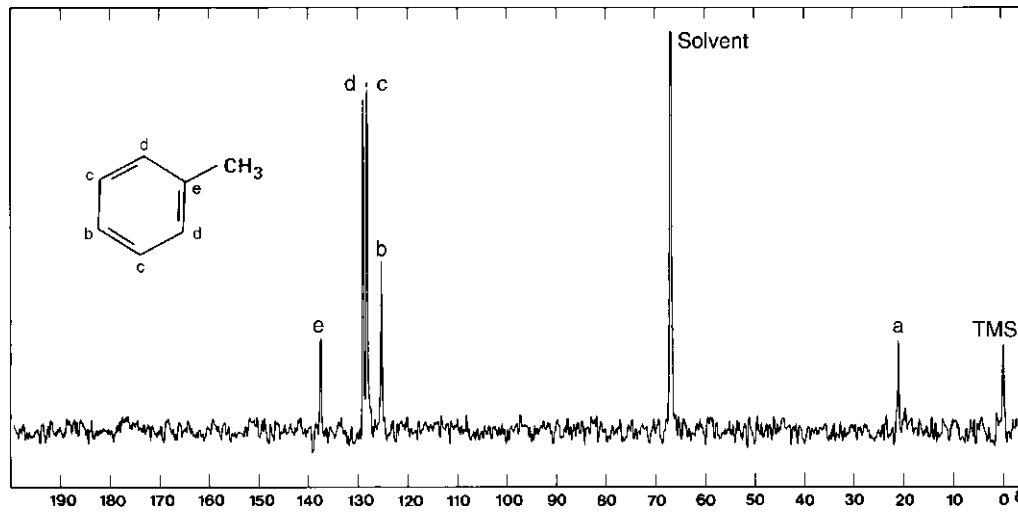


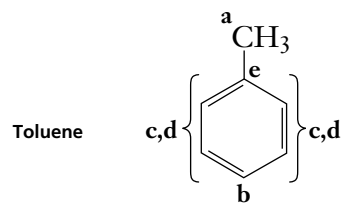
Figure 27.10 The proton-decoupled ^{13}C NMR spectrum of toluene.

In addition, weak carbonyl carbon peaks are observed at 171 ppm in ethyl phenylacetate (see Figure 27.4) and at 211 ppm in cyclohexanone (see Figure 27.9).

27.7 Compounds with Aromatic Rings

Compounds with carbon–carbon double bonds or aromatic rings give rise to chemical shifts from 100 ppm to 175 ppm. Because relatively few other peaks appear in this range, a great deal of useful information is available when peaks appear here.

A **monosubstituted** benzene ring shows *four* peaks in the aromatic carbon area of a proton-decoupled ^{13}C spectrum, because the *ortho* and *meta* carbons are doubled by symmetry. Often the carbon with no protons attached, the *ipso* carbon, has a very weak peak due to a long relaxation time and a weak NOE. In addition, there are two larger peaks for the doubled *ortho* and *meta* carbons and a medium-sized peak for the *para* carbon. In many cases, it is not important to be able to assign all of the peaks precisely. In the example of toluene, shown in Figure 27.10, notice that carbons c and d are not easy to assign by inspection of the spectrum.



Toluene — Difficult to assign

In a proton-coupled ^{13}C spectrum, a monosubstituted benzene ring shows three doublets and one singlet. The singlet arises from the *ipso* carbon, which has no attached hydrogen. Each of the other carbons in the ring (*ortho*, *meta*, and *para*) has one attached hydrogen and yields a doublet.

Figure 27.4B is the proton-decoupled spectrum of ethyl phenylacetate, with the assignments noted next to the peaks. Notice that the aromatic ring region shows

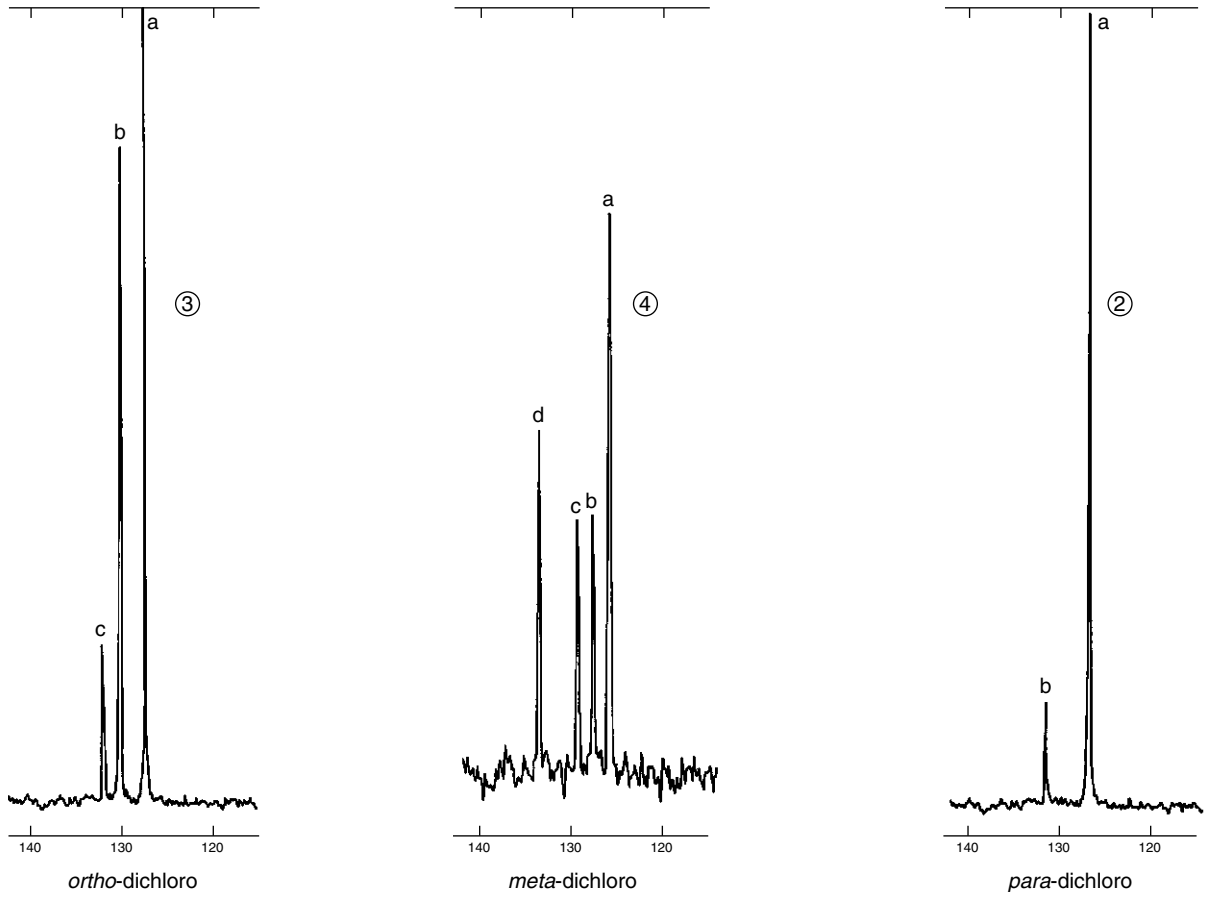


Figure 27.11 The proton-decoupled ^{13}C NMR spectra of the three isomers of dichlorobenzene (25 MHz).

four peaks between 125 ppm and 135 ppm, consistent with a monosubstituted ring. There is one peak for the methyl carbon (13 ppm), and there are two peaks for the methylene carbons. One of the methylene carbons is directly attached to an electronegative oxygen atom and appears at 61 ppm, and the other is more shielded (41 ppm). The carbonyl carbon (an ester) has resonance at 171 ppm. All of the carbon chemical shifts agree with the values in the correlation chart (see Figure 27.1).

Depending on the mode of substitution, a symmetrically **disubstituted** benzene ring can show two, three, or four peaks in the proton-decoupled ^{13}C spectrum. The following drawings illustrate this for the isomers of dichlorobenzene.

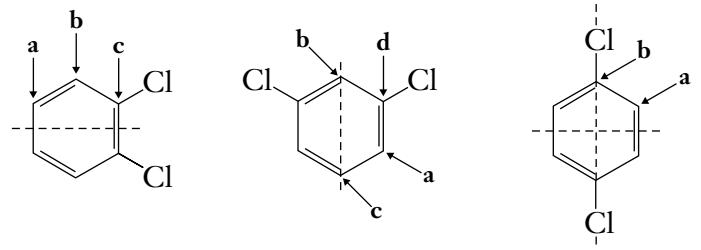


Figure 27.11 shows the spectra of all three dichlorobenzenes, each of which has the number of peaks consistent with the analysis just given. You can see that ^{13}C NMR spectroscopy is very useful in the identification of isomers.

Most other polysubstitution patterns on a benzene ring yield six peaks in the proton-decoupled ^{13}C NMR spectrum, one for each carbon. However, when identical substituents are present, watch carefully for planes of symmetry that may reduce the number of peaks.

REFERENCES

Textbooks

Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy,* 3rd ed. New York: VCH Publishers, 1998.

Gunther, H. *NMR Spectroscopy,* 2nd ed. New York: John Wiley & Sons, 1995.

Levy, G. C. *Topics in Carbon-13 Spectroscopy.* New York: John Wiley & Sons, 1984.

Levy, G. C., Lichter, R. L., and Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy,* 2nd ed. NewYork: John Wiley & Sons, 1980.

Macomber, R. S. *A Complete Introduction to Modern NMR Spectroscopy*. New York: John Wiley & Sons, 1997.

Macomber, R. S. *NMR Spectroscopy—Essential Theory and Practice.* New York: College Outline Series, Harcourt Brace Jovanovich, 1988.

Pavia, D. L., Lampman, G. M., and Kriz, G. S. *Introduction to Spectroscopy,* 4th ed. and vyvyan, J. R. Brooks/Cole 2008.

Sander, J. K. M., and Hunter, B. K. *Modern NMR Spectroscopy—A Guide for Chemists,* 2d ed. Oxford, England: Oxford University Press, 1993.

Silverstein, R. M., Webster, F. X., and Kiemle, D. *Spectrometric Identification of Organic Compounds,* 7th ed. New York: John Wiley & Sons, 2005.

Compilations of Spectra

Johnson, L. F., and Jankowski, W. C. *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra, 25 MHz.* New York: Wiley-Interscience, 1972.

Pouchert, C. J., and Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT–NMR Spectra, 75 and 300 MHz*. Milwaukee, WI: Aldrich Chemical Company, 1993.

Pretsch, E., Clerc, T., Seibl, J., and Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds,* 2nd ed. Berlin and New York: Springer-Verlag, 1989. Translated from the German by K. Biemann.

Web Sites

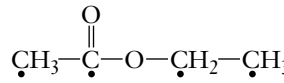
http://www.aist.go.jp/RIODB/SDBS/menu-e.html
Integrated Spectral DataBase System for Organic Compounds, National Institute of Materials and Chemical Research, Tsukuba, Ibaraki 305-8565, Japan. This database includes infrared, mass spectra, and NMR data (proton and carbon-13) for a number of compounds.

http://www.chem.ucla.edu/~webspectra
UCLA Department of Chemistry and Biochemistry in connection with Cambridge University Isotope Laboratories maintains a Web site, WebSpectra, that provides NMR and IR spectroscopy problems for students to interpret. They provide links to other sites with problems for students to solve.

PROBLEMS

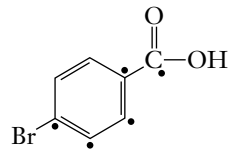
1. Predict the number of peaks that you would expect in the proton-decoupled ^{13}C spectrum of each of the following compounds. Problems 1a and 1b are provided as examples. Dots are used to show the nonequivalent carbon atoms in these two examples.

a.



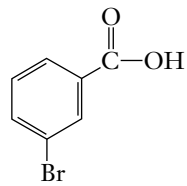
Four peaks

b.

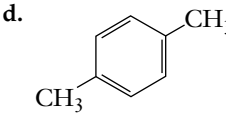


Five peaks

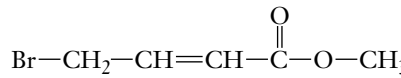
c.



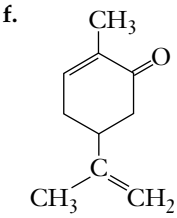
d.



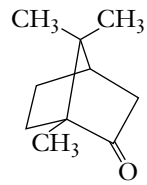
e.



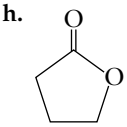
f.



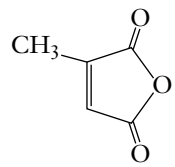
g.



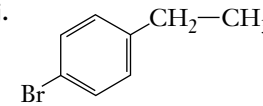
h.



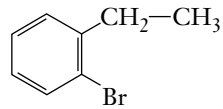
i.



j.



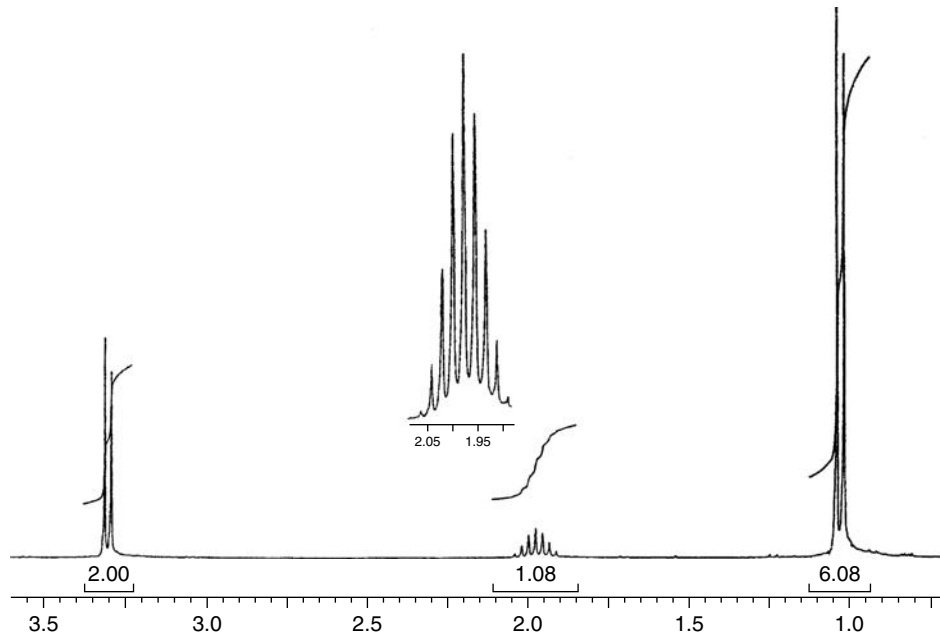
k.



2. Following are the ^{1}H and ^{13}C spectra for two isomeric bromoalkanes (**A** and **B**) with formula C_4H_9Br. Integral curves are drawn on the spectra, along with relative integral values provided just above the scale and under each set of peaks. These numbers indicate the relative number of protons assigned to each pattern. Remember that these integral values are approximate. You will need to round the values off to the nearest whole number. Also, in some cases, the lowest whole-number ratios are given. In such cases, the values provided may need to be multiplied by two or three in order to obtain the actual number of protons in each pattern.

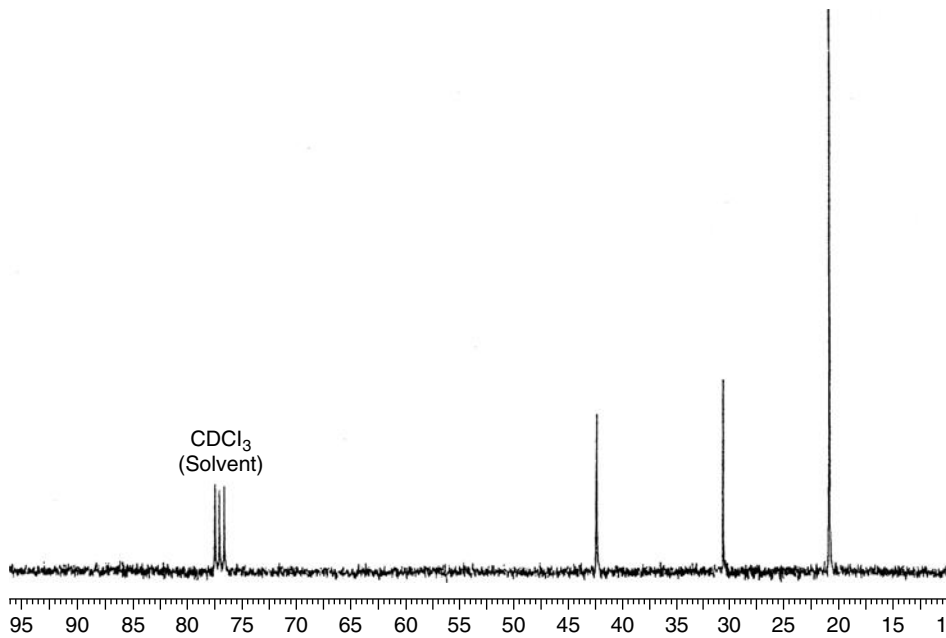
^{1}H

A



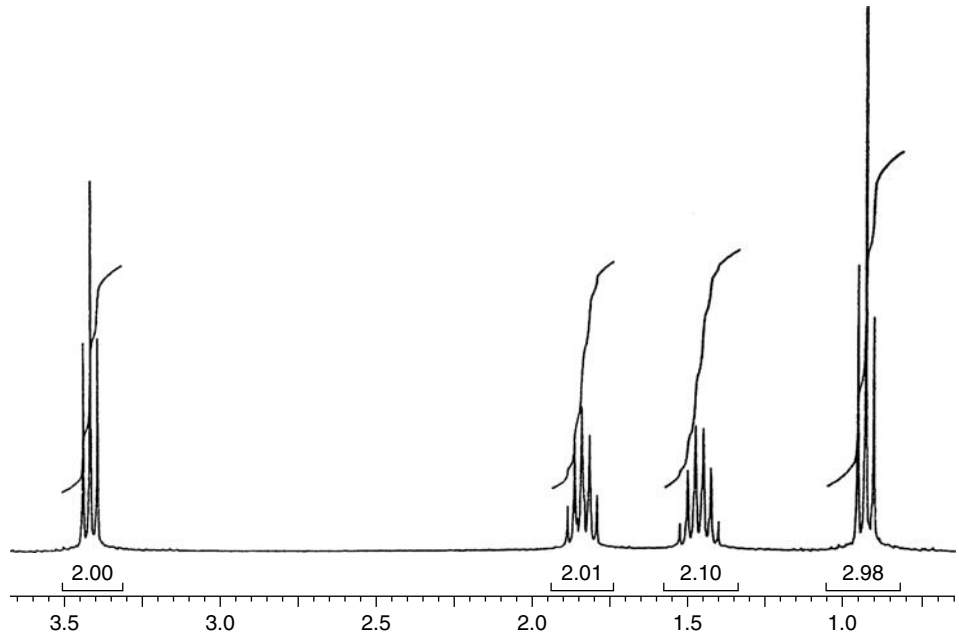
^{13}C

A



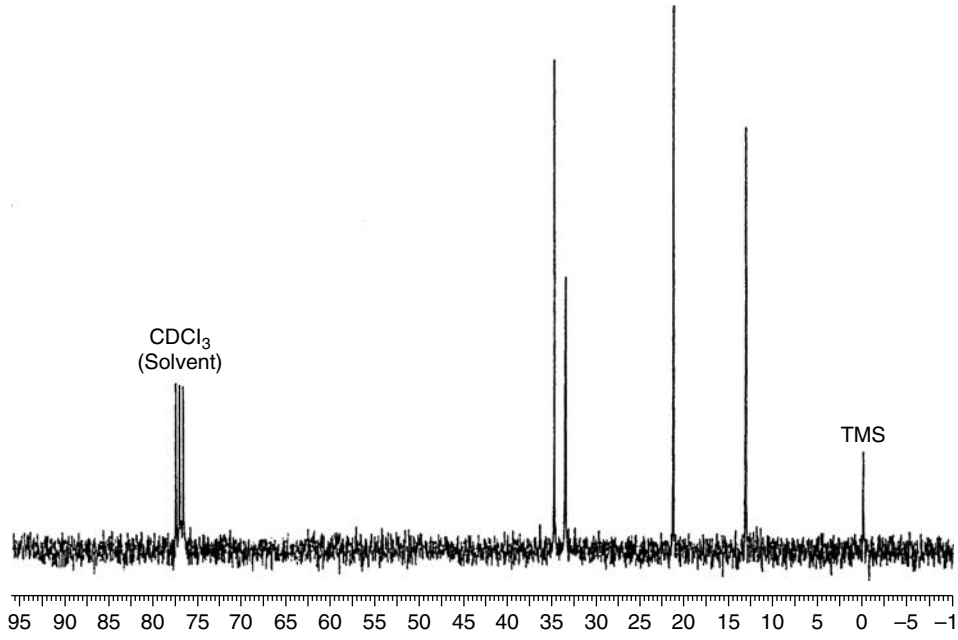
^{1}H

B


2.00
2.01
2.10
2.98
3.5
3.0
2.5
2.0
1.5
1.0

^{13}C

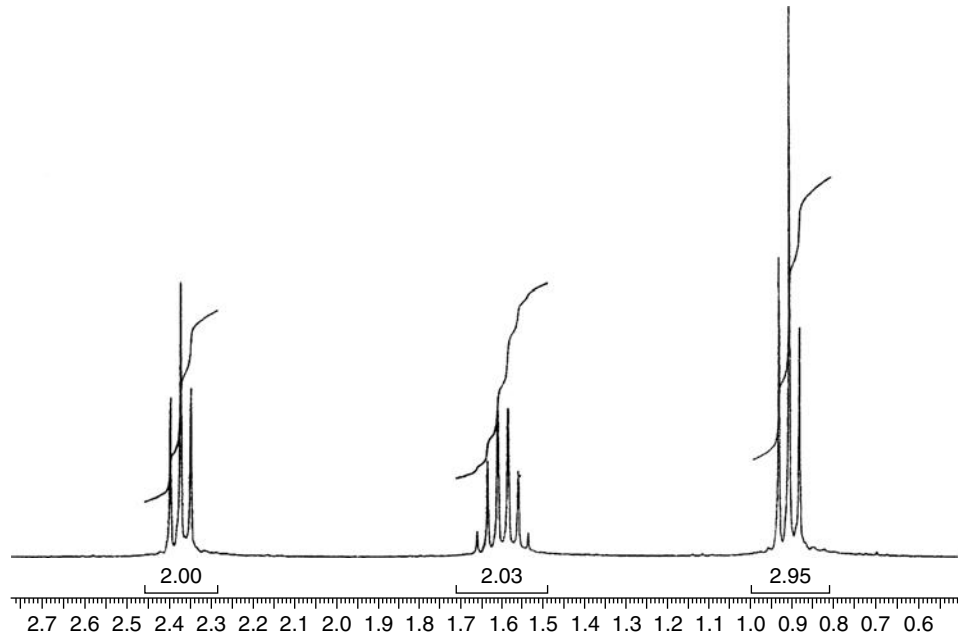
B


CDCl3
(Solvent)
TMS
95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 –5 –10

3. Following are the ^{1}H and ^{13}C spectra for each of three isomeric ketones (**A**, **B**, and **C**) with formula $C_7H_{14}O$. Integral curves are drawn on the spectra, along with relative integral values provided just above the scale and under each set of peaks. These numbers indicate the relative number of protons assigned to each pattern. Remember that these integral values are approximate. You will need to round the values off to the nearest whole number. Also, in some cases, the lowest whole-number ratios are given. In such cases, the values provided may need to be multiplied by two or three in order to obtain the actual number of protons in each pattern.

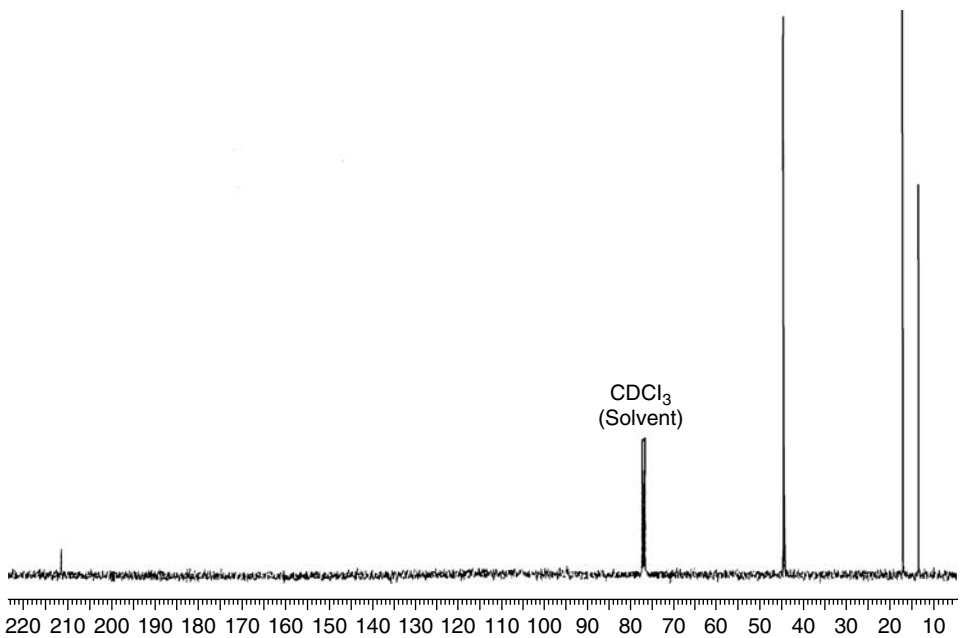
^{1}H

A



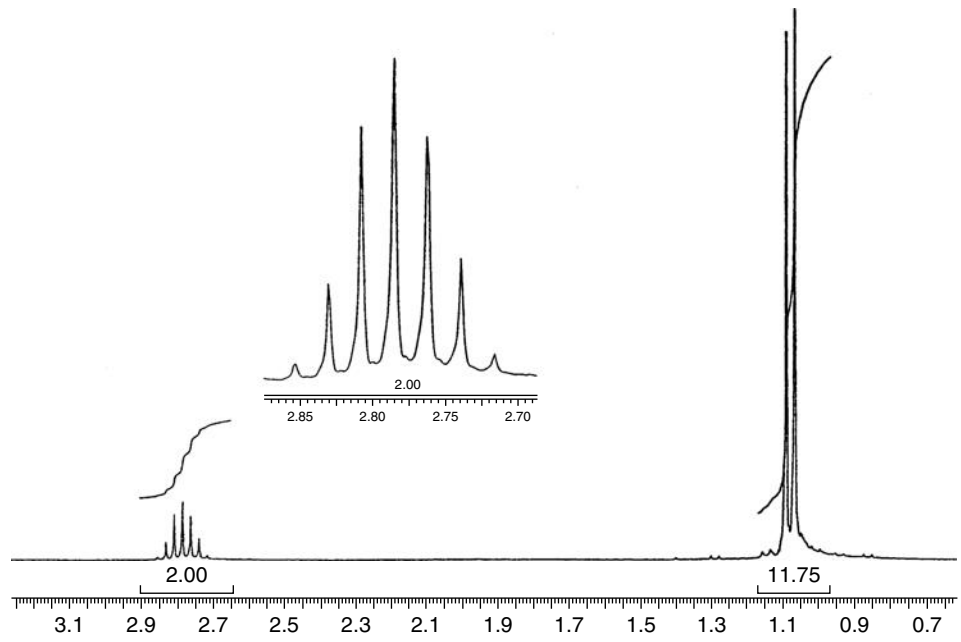
^{13}C

A



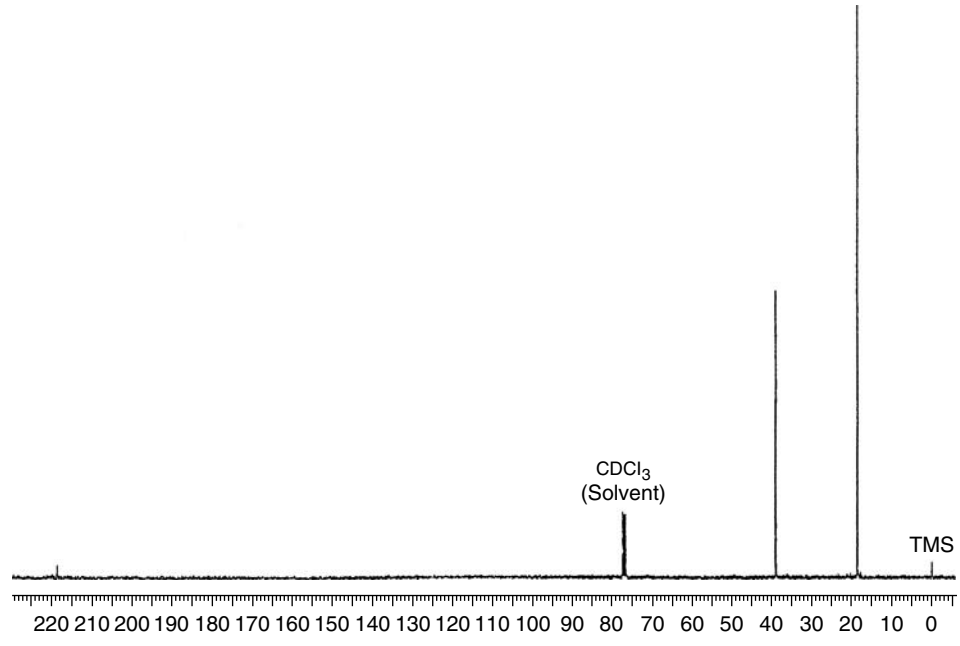
^{1}H

B


2.00
2.85
2.80
2.75
2.70
2.00
11.75
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7

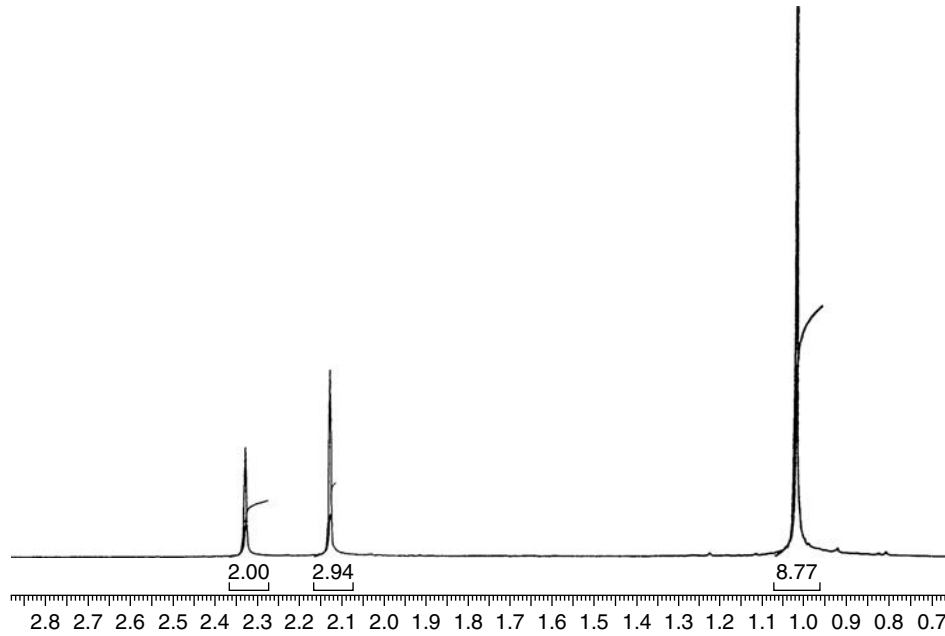
^{13}C

B


CDCl3
(Solvent)
TMS
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

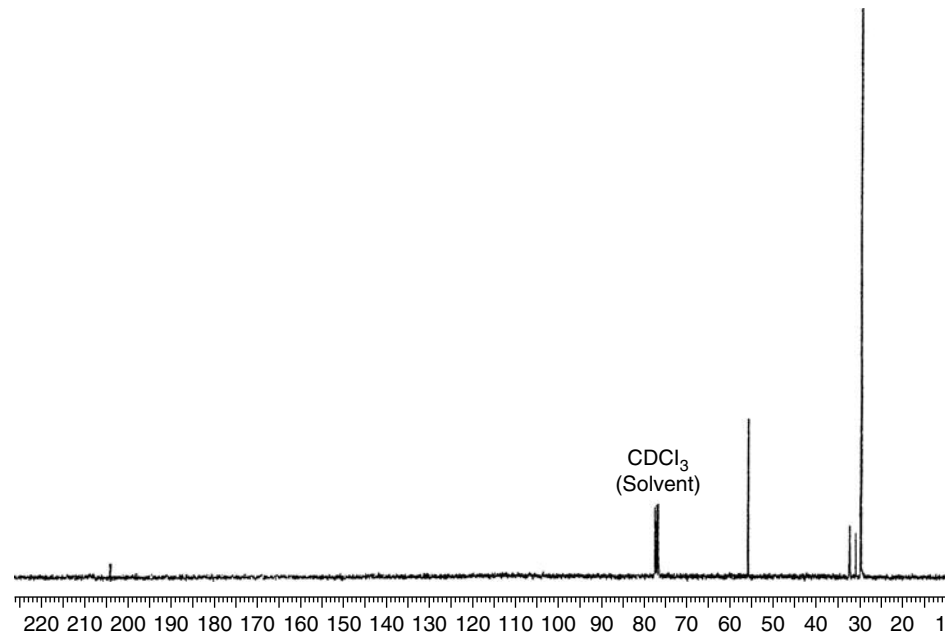
^{1}H

C


2.00
2.94
8.77
2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7

^{13}C

C


$CDCl_3$
(Solvent)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

28 **TECHNIQUE 28**

Mass Spectrometry

In its simplest form, the mass spectrometer performs three essential functions. First, molecules are bombarded by a stream of high-energy electrons, converting some of the molecules to positive ions. Because of their high energy, some of these ions **fragment**, or break apart into smaller ions. All of these ions are accelerated in an electric field. Second, the accelerated ions are separated according to their mass-to-charge ratio in a magnetic or electric field. Finally, the ions with a particular mass-to-charge ratio are detected by a device that is able to count the number of ions that strike it. The output of the detector is amplified and fed to a recorder. The trace from the recorder is a **mass spectrum**—a graph of the number of particles detected as a function of mass-to-charge ratio.

Ions are formed in an **ionization chamber**. The sample is introduced into the ionization chamber using a sample inlet system. In the ionization chamber, a heated **filament** emits a beam of high-energy electrons. The filament is heated to several thousand degrees Celsius. In normal operation, the electrons have an energy of about 70 electron-volts. These high-energy electrons strike a stream of molecules that has been admitted from the sample system and ionize the molecules in the sample stream by removing electrons from them. The molecules are thus converted into **radical-cations**.

$$e^- + M \longrightarrow 2e^- + M^{\bullet +}$$

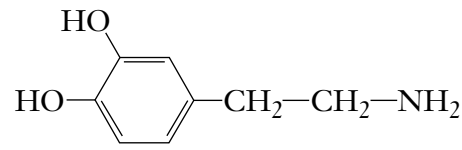
The energy required to remove an electron from an atom or molecule is its **ionization potential**. The ionized molecules are accelerated and focused into a beam of rapidly moving ions by means of charged plates.

From the ionization chamber, the beam of ions passes through a short field-free region. From there, the beam enters the **mass analyzer**, where the ions are separated according to their mass-to-charge ratio.

The detector of most instruments consists of a counter that produces a current proportional to the number of ions that strike it. Electron multiplier circuits allow accurate measurement of the current from even a single ion striking the detector. The signal from the detector is fed to **a recorder**, which produces the actual mass spectrum.

28.1 The Mass Spectrum

The **mass spectrum** is a plot of ion abundance versus mass-to-charge (*m/e*) ratio. A typical mass spectrum is shown in Figure 28.1. The spectrum shown is that of dopamine, a substance that acts as a neurotransmitter in the central nervous system. The spectrum is displayed as a bar graph of percentage ion abundance (relative abundance) plotted against *m/e.*



Dopamine

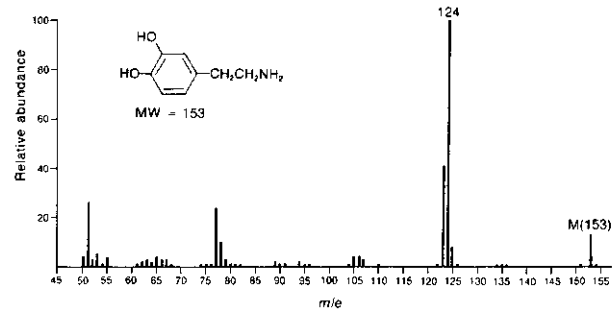


Figure 28.1 The mass spectrum of dopamine.

The most abundant ion formed in the ionization chamber gives rise to the tallest peak in the mass spectrum, called the **base peak**. For dopamine, the base peak appears at *m/e* = 124. The relative abundances of all the other peaks in the spectrum are reported as percentages of the abundance of the base peak.

The beam of electrons in the ionization chamber converts some of the sample molecules into positive ions. Removal of a single electron from a molecule yields an ion whose weight is the actual molecular weight of the original molecule. This ion is the **molecular ion**, frequently symbolized as M^+. The value of *m/e* at which the molecular ion appears on the mass spectrum, assuming that the ion has only one electron removed, gives the molecular weight of the original molecule. In the mass spectrum of dopamine, the molecular ion appears at *m/e* = 153, the molecular weight of dopamine. If you can identify the molecular ion peak in the mass spectrum, you can use the spectrum to determine the molecular weight of an unknown substance. If the presence of heavy isotopes is ignored for the moment, the molecular ion peak corresponds to the heaviest particle observed in the mass spectrum.

Molecules do not occur in nature as isotopically pure species. Virtually all atoms have heavier isotopes that occur in varying natural abundances. Hydrogen occurs largely as ^1H, but a small percent of hydrogen atoms occur as the isotope ^2H. Further, carbon normally occurs as ^{12}C, but a small percent of carbon atoms are the heavier isotope, ^{13}C. With the exception of fluorine, most other elements have a certain percentage of heavier isotopes that occur naturally. Peaks caused by ions bearing these heavier isotopes are also found in the mass spectrum. The relative abundances of these isotopic peaks are proportional to the abundances of the isotopes in nature. Most often, the isotopes occur at one or two mass units above the mass of the "normal" atom. Therefore, besides looking for the molecular ion (M^+) peak, you should also attempt to locate the M + 1 and M + 2 peaks. As will be demonstrated later, you can use the relative abundances of these M + 1 and M + 2 peaks to determine the molecular formula of the substance being studied.

The beam of electrons in the ionization chamber can produce the molecular ion. This beam also has sufficient energy to break some of the bonds in the molecule, producing a series of molecular fragments. Fragments that are positively charged are also accelerated in the ionization chamber, sent through the analyzer, detected, and recorded on the mass spectrum. These **fragment ion peaks** appear at *m/e* values corresponding to their individual masses. Very often, a fragment ion rather than the molecular ion will be the most abundant ion produced in the mass spectrum (the base peak). A second means of producing fragment ions occurs with the molecular ion, which, once it is formed, is so unstable that it disintegrates before it can pass into the accelerating region of the ionization chamber. Lifetimes shorter

than 10^{-5} seconds are typical in this type of fragmentation. Those fragments that are charged then appear as fragment ions in the mass spectrum. As a result of these fragmentation processes, the typical mass spectrum can be quite complex, containing many more peaks than the molecular ion and M+1 and M+2 peaks. Structural information about a substance can be determined by examining the fragmentation pattern in the mass spectrum. Fragmentation patterns are discussed further in Section 28.3.

28.2 Molecular Formula Determination

Mass spectrometry can be used to determine the molecular formulas of molecules that provide reasonably abundant molecular ions. Although there are at least two principal techniques for determining a molecular formula, only one will be described here.

The molecular formula of a substance can be determined through the use of **precise atomic masses**. High-resolution mass spectrometers are required for this method. Atoms are normally thought of as having integral atomic masses; for example, H = 1, C = 12, and O = 16. If you can determine atomic masses with sufficient precision, however, you find that the masses do not have values that are exactly integral. The mass of each atom actually differs from a whole mass number by a small fraction of a mass unit. The actual masses of some atoms are given in Table 28.1.

TABLE 28.1 Precise Masses of Some Common Elements

Element	Atomic Weight	Nuclide	Precise Mass
Hydrogen	1.00797	^{1}H	1.00783
		^{2}H	2.01410
Carbon	12.01115	^{12}C	12.0000
		^{13}C	13.00336
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	28.086	^{28}Si	27.9769
		^{29}Si	28.9765
		^{30}Si	29.9738
Phosphorus	30.974	^{31}P	30.9738
Sulfur	32.064	^{32}S	31.9721
		^{33}S	32.9715
		^{34}S	33.9679
Chlorine	35.453	^{35}Cl	34.9689
		^{37}Cl	36.9659
Bromine	79.909	^{79}Br	78.9183
		^{81}Br	80.9163
Iodine	126.904	^{127}I	126.9045

Depending on the atoms that are contained within a molecule, it is possible for particles of the same nominal mass to have slightly different measured masses when precise mass determinations can be made. To illustrate, a molecule whose molecular weight is 60 could be C_3H_8O, $C_2H_8N_2$, $C_2H_4O_2$, or CH_4N_2O. The species have the following precise masses:

C_3H_8O	60.05754
$C_2H_8N_2$	60.06884
$C_2H_4O_2$	60.02112
CH_4N_2O	60.03242

Observing a molecular ion with a mass of 60.058 would establish that the unknown molecule was C_3H_8O. Distinguishing among these possibilities is well within the capability of a modern high-resolution instrument.

In another method, these four compounds may also be distinguished by differences in the relative intensities of their M, M+1, and M+2 peaks. The predicted intensities are either calculated by formula or looked up in tables. Details of this method may be found in the References at the end of this Technique Chapter.

28.3 Detecting Halogens

When chlorine or bromine is present in a molecule, the isotope peak that is two mass units heavier than the molecular ion (the M+2 peak) becomes very significant. The heavy isotope of each of these elements is two mass units heavier than the lighter isotope. The natural abundance of ^{37}Cl is 32.5% that of ^{35}Cl; the natural abundance of ^{81}Br is 98.0% that of ^{79}Br. When these elements are present, the M+2 peak becomes quite intense, and the pattern is characteristic of the particular halogen present. If a compound contains two chlorine or bromine atoms, a quite distinct M+4 peak should be observed, as well as an intense M+2 peak. In these cases, you should exercise caution in identifying the molecular ion peak in a mass spectrum, but the pattern of peaks is characteristic of the nature of the halogen substitution in the molecule. Table 28.2 gives the relative intensities of isotope peaks for various combinations of bromine and chlorine atoms. The patterns of molecular ion and isotopic peaks observed with halogen substitution are shown in Figure 28.2. Examples of these patterns can be seen in the mass spectra of chloroethane (see Figure 28.3) and bromoethane (see Figure 28.4).

TABLE 28.2 Relative Intensities of Isotope Peaks for Various Combinations of Bromine and Chlorine

Halogen	M	M+2	M+4	M+6
Br	100	97.7	—	—
Br_2	100	195.0	95.4	—
Br_3	100	293.0	286.0	93.4
Cl	100	32.6	—	—
Cl_2	100	65.3	10.6	—
Cl_3	100	97.8	31.9	3.47
BrCl	100	130.0	31.9	—
Br_2Cl	100	228.0	159.0	31.2
$BrCl_2$	100	163.0	74.4	10.4

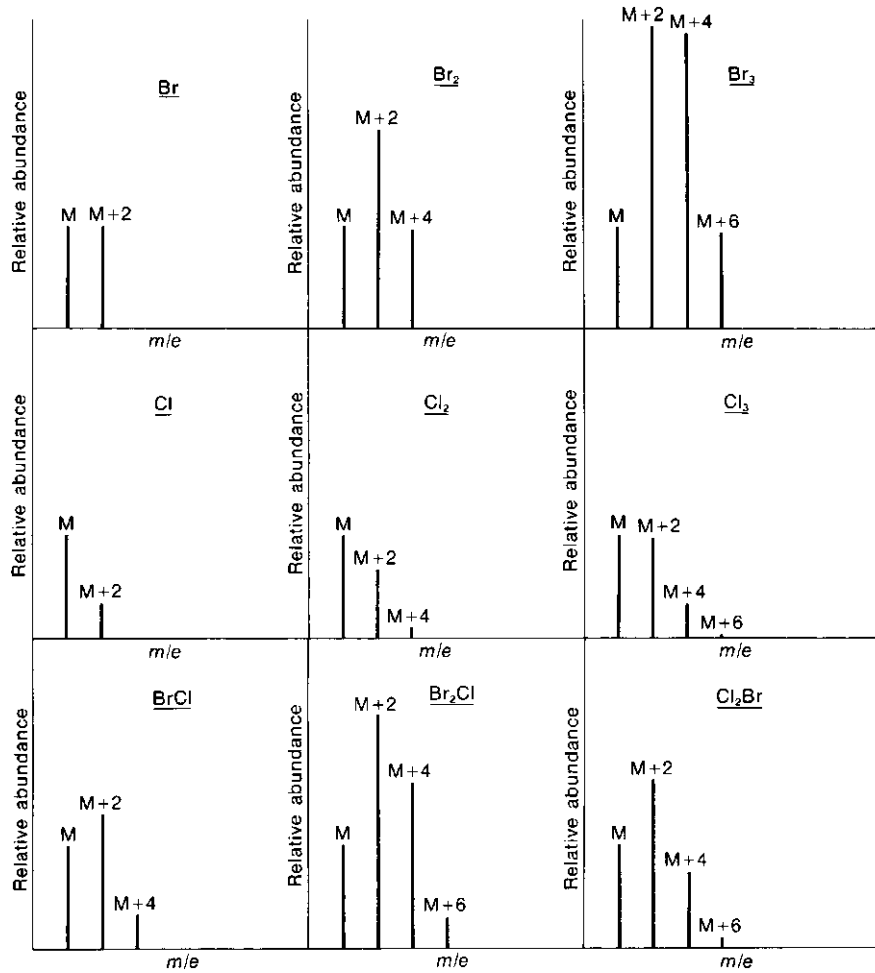


Figure 28.2 Mass spectra expected for various combinations of bromine and chlorine.

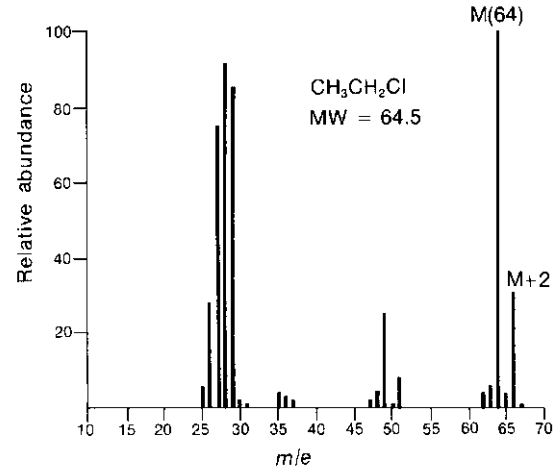


Figure 28.3 The mass spectrum of chloroethane.

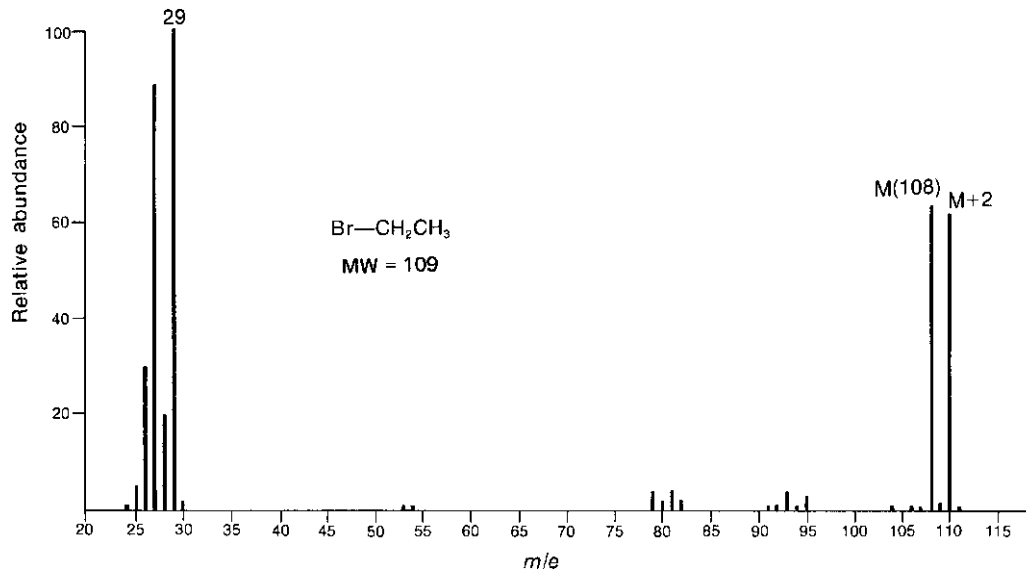


Figure 28.4 The mass spectrum of bromoethane.

28.4 Fragmentation Patterns

When the molecule has been bombarded by high-energy electrons in the ionization chamber of a mass spectrometer, besides losing one electron to form an ion, the molecule also absorbs some of the energy transferred in the collision between the molecule and the incident electrons. This extra energy puts the molecular ion in an excited vibrational state. The vibrationally excited molecular ion is often unstable and may lose some of this extra energy by breaking apart into fragments. If the lifetime of an individual molecular ion is longer than 10^{-5} seconds, a peak corresponding to the molecular ion will be observed in the mass spectrum. Those molecular ions with lifetimes shorter than 10^{-5} seconds will break apart into fragments before they are accelerated within the ionization chamber. In such cases, peaks corresponding to the mass-to-charge ratios for these fragments will also appear in the mass spectrum. For a given compound, not all the molecular ions formed by ionization have precisely the same lifetime. The ions have a range of lifetimes; some individual ions may have shorter lifetimes than others. As a result, peaks are usually observed arising from both the molecular ion and the fragment ions in a typical mass spectrum.

For most classes of compounds, the mode of fragmentation is somewhat characteristic. In many cases, it is possible to predict how a molecule will fragment. Remember that the ionization of the sample molecule forms a molecular ion that not only carries a positive charge but also has an unpaired electron. The molecular ion, then, is actually a **radical–cation**, and it contains an odd number of electrons. In the structural formulas that follow, the radical–cation is indicated by enclosing the structure in square brackets. The positive charge and the unshared electron are shown as superscripts.

$$[\mathrm{R{-}CH_3}]^{+\cdot}$$

When fragment ions form in the mass spectrometer, they almost always form by means of unimolecular processes. The pressure of the sample in the ionization chamber is too low to permit a significant number of bimolecular collisions. Those

unimolecular processes that require the least energy will give rise to the most abundant fragment ions.

Fragment ions are cations. Much of the chemistry of these fragment ions can be explained in terms of what is known about carbocations in solution. For example, alkyl substitution stabilizes fragment ions (and promotes their formation) in much the same way that it stabilizes carbocations. Those fragmentation processes that lead to more stable ions will be favored over processes that lead to the formation of less-stable ions.

Fragmentation often involves the loss of an electrically neutral fragment. The neutral fragment does not appear in the mass spectrum, but you can deduce its existence by noting the difference in masses of the fragment ion and the original molecular ion. Again, processes that lead to the formation of a more stable neutral fragment will be favored over those that lead to the formation of a less-stable neutral fragment. The loss of a stable neutral molecule, such as water, is commonly observed in the mass spectrometer.

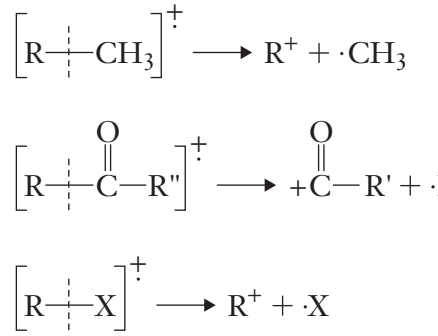
A. Cleavage of One Bond

The most common mode of fragmentation involves the cleavage of one bond. In this process, the odd-electron molecular ion yields an odd-electron neutral fragment and an even-electron fragment. The neutral fragment that is lost is a **free radical**, whereas the ionic fragment is of the carbocation type. Cleavages that lead to the formation of more stable carbocations will be favored. Thus, the ease of fragmentation to form ions increases in the following order:

$$CH_3^+ < RCH_2^+ < R_2CH^+ < R_3C^+ < CH_2{=}CH{-}CH_2^+ < C_6H_5{-}CH_2^+$$

Increasing ease of formation →

The following reactions show examples of fragmentation that take place with the cleavage of one bond:

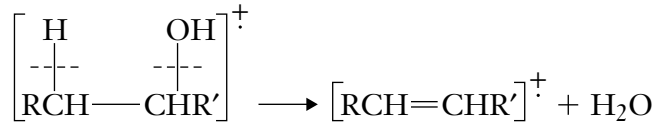


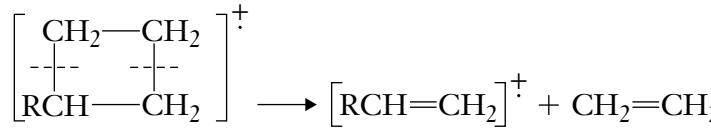
where X = halogen, OR, SR, or NR_2, and where R = H, alkyl, or aryl

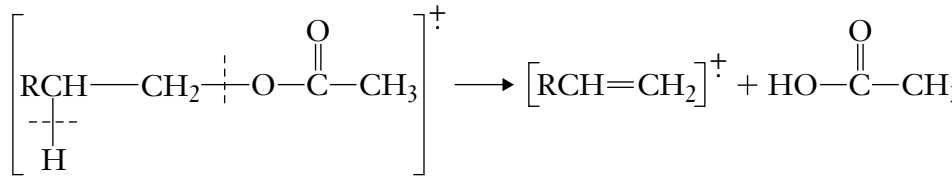
B. Cleavage of Two Bonds

The next most important type of fragmentation involves the cleavage of two bonds. In this type of process, the odd-electron molecular ion yields an odd-electron

fragment ion and an even-electron neutral fragment, usually a small, stable molecule. Examples of this type of cleavage are shown next:







C. Other Cleavage Processes

In addition to the processes just mentioned, fragmentation reactions involving rearrangements, migrations of groups, and secondary fragmentations of fragment ions are also possible. These processes occur less often than the types of processes just described. Nevertheless, the pattern of molecular ion and fragment ion peaks observed in the typical mass spectrum is quite complex and unique for each particular molecule. As a result, the mass spectral pattern observed for a given substance can be compared with the mass spectra of known compounds as a means of identification. The mass spectrum is like a fingerprint. For a treatment of the specific modes of fragmentation characteristic of particular classes of compounds, refer to more advanced textbooks (see References at the end of this chapter). The unique appearance of the mass spectrum for a given compound is the basis for identifying the components of a mixture in the **gas chromatography–mass spectrometry** (GC–MS) technique (see Technique 22, Section 22.14). The mass spectrum of every component in a mixture is compared with standard spectra stored in the computer memory of the instrument. The printed output produced by a GC–MS instrument includes an identification based on the results of the computer matching of mass spectra.

28.5 Interpreted Mass Spectra

In this section, the mass spectra of some representative organic compounds are presented. The important fragment ion peaks in each mass spectrum are identified. In some of the examples, identification of the fragments is presented without explanation, although some interpretation is provided where an unusual or interesting process takes place. In the first example, that of butane, a more complete explanation of the symbolism used is offered.

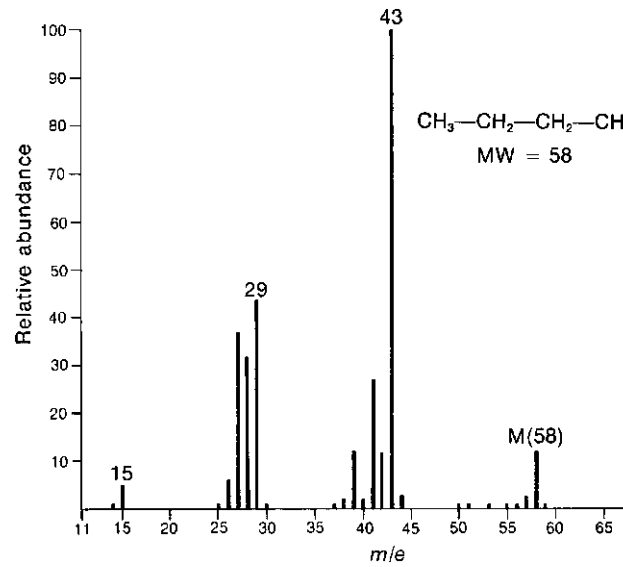


Figure 28.5 The mass spectrum of butane.

Butane; C_4H_{10}, MW = 58 (see Figure 28.5)

$$CH_3\overset{15}{\leftarrow}CH_2\overset{29}{\leftarrow}CH_2\overset{43}{\leftarrow}CH_3$$

In the structural formula of butane, the dashed lines represent the location of bond-breaking processes that occur during fragmentation. In each case, the fragmentation process involves the breaking of one bond to yield a neutral radical and a cation. The arrows point toward the fragment that bears the positive charge. This positive fragment is the ion that appears in the mass spectrum. The mass of the fragment ion is indicated beneath the arrow.

The mass spectrum shows the molecular ion at *m/e* = 58. Breaking of the C1—C2 bond yields a three-carbon fragment with a mass of 43.

$$CH_3—CH_2—CH_2\text{┆}CH_3 \longrightarrow \underset{m/e = 43}{CH_3—CH_2—CH_2^+} + \cdot CH_3$$

Cleavage of the central bond yields an ethyl cation, with a mass of 29.

$$CH_3—CH_2\text{┆}CH_2—CH_3 \longrightarrow \underset{m/e = 29}{CH_3—CH_2^+} + \cdot CH_2—CH_3$$

The terminal bond can also break to yield a methyl cation, which has a mass of 15.

$$CH_3\text{┆}CH_2—CH_2—CH_3 \longrightarrow \underset{m/e = 15}{CH_3^+} + \cdot CH_2—CH_2—CH_3$$

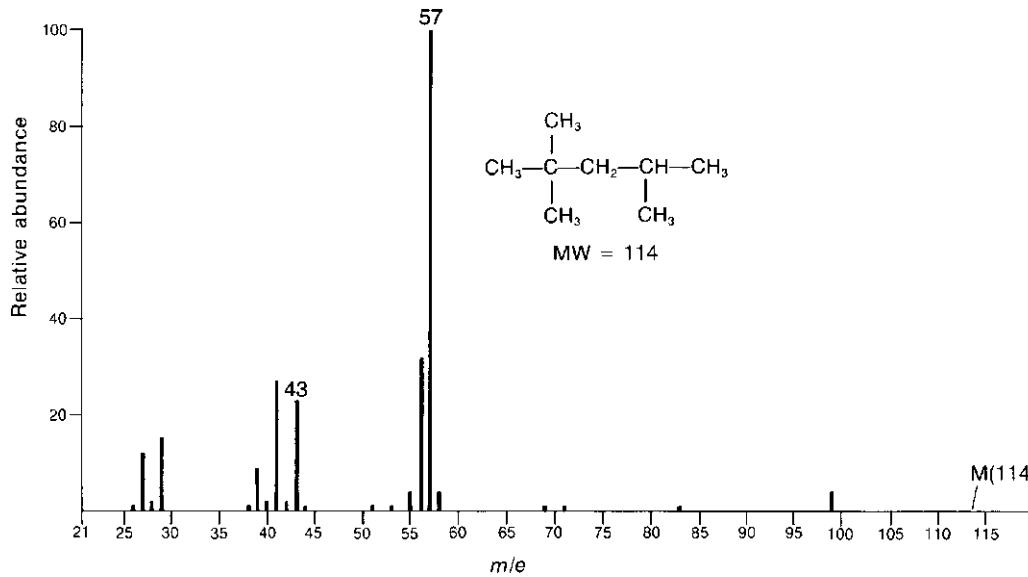
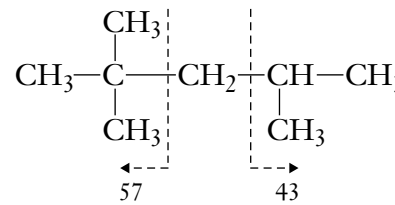


Figure 28.6 The mass spectrum of 2,2,4-trimethylpentane ("isooctane").

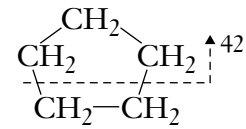
Each of these fragments appears in the mass spectrum of butane and has been identified.

2,2,4-Trimethylpentane; C_8H_{18}, MW = 114 (see Figure 28.6)



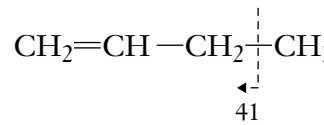
Notice that in the case of 2,2,4-trimethylpentane, by far the most abundant fragment is the *tert*-butyl cation (*m/e* = 57). This result is not surprising when one considers that the *tert*-butyl cation is a particularly stable carbocation.

Cyclopentane; C_5H_{10}, MW = 70 (see Figure 28.7)



In the case of cyclopentane, the most abundant fragment results from the simultaneous cleavage of two bonds. This mode of fragmentation eliminates a neutral molecule of ethene (MW = 28), and results in the formation of a cation at *m/e* = 42.

1-Butene; C_4H_8, MW = 56 (see Figure 28.8)



An important fragment in the mass spectra of alkenes is the allyl cation (*m/e* = 41). This cation is particularly stable due to resonance.

$$[^{+}CH_2{-}CH{=}CH_2 \longleftrightarrow CH_2{=}CH{-}CH_2{}^{+}]$$

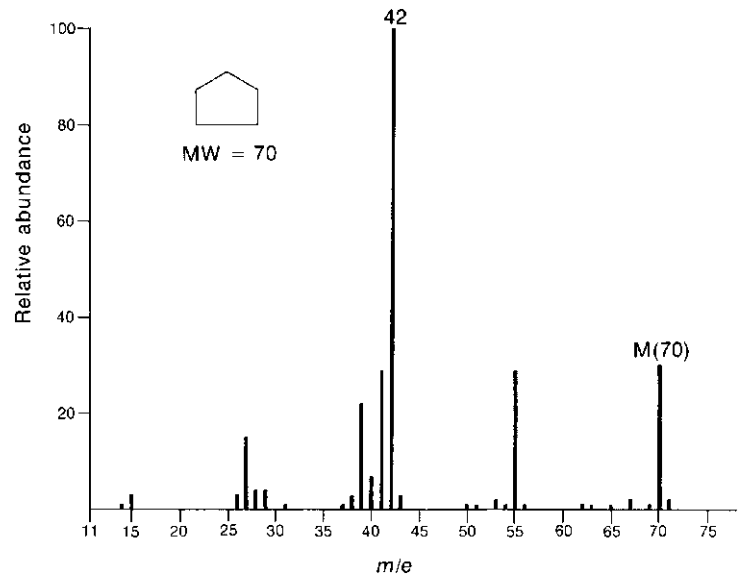


Figure 28.7 The mass spectrum of cyclopentane.

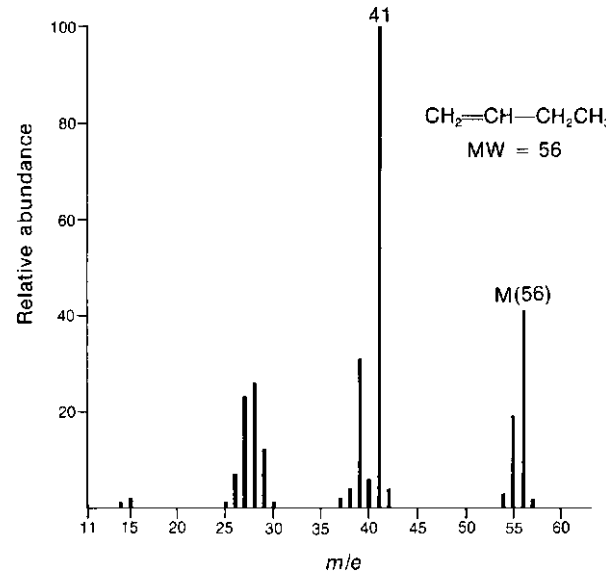
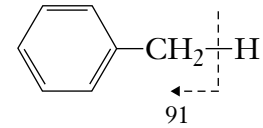


Figure 28.8 The mass spectrum of 1-butene.

Toluene; C_7H_8, MW = 92 (see Figure 28.9)



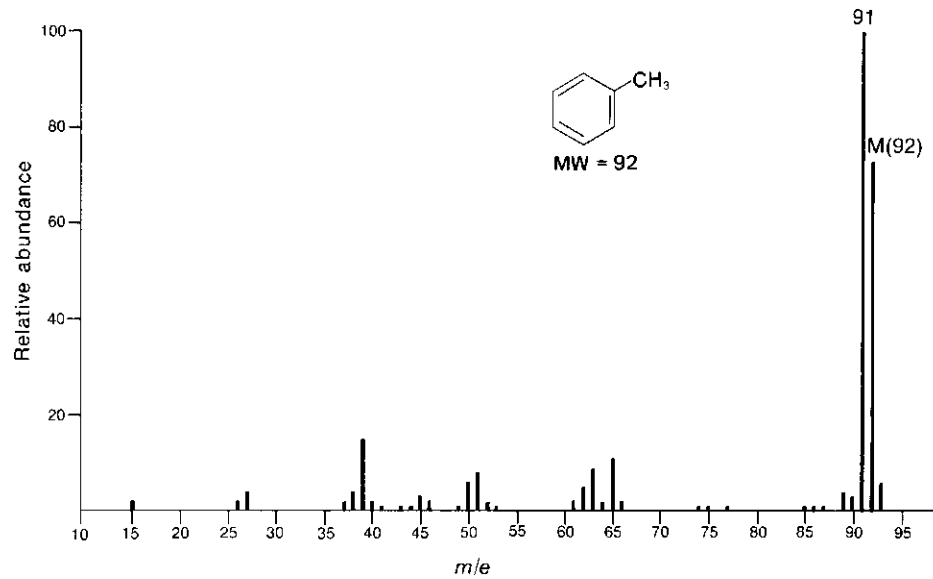
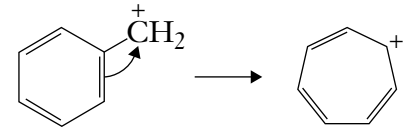


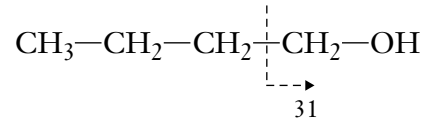
Figure 28.9 The mass spectrum of toluene.

When an alkyl group is attached to a benzene ring, preferential fragmentation occurs at a benzylic position to form a fragment ion of the formula $C_7H_7^+$ ($m/e = 91$). In the mass spectrum of toluene, loss of hydrogen from the molecule ion gives a strong peak at $m/e = 91$. Although it may be expected that this fragment ion peak is due to the benzyl carbocation, evidence suggests the benzyl carbocation actually rearranges to form the **tropylium ion.** Isotope-labeling experiments tend to confirm the formation of the tropylium ion. The tropylium ion is a seven-carbon ring system that contains six electrons in π-molecular orbitals and hence is resonance-stabilized in a manner similar to that observed in benzene.

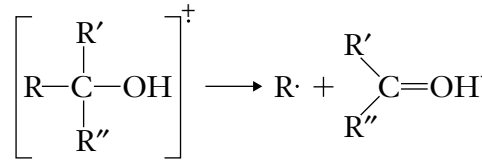


Benzyl cation **Tropylium ion**

1-Butanol; $C_4H_{10}O$, MW = 74 (see Figure 28.10)



The most important fragmentation reaction for alcohols is loss of an alkyl group:



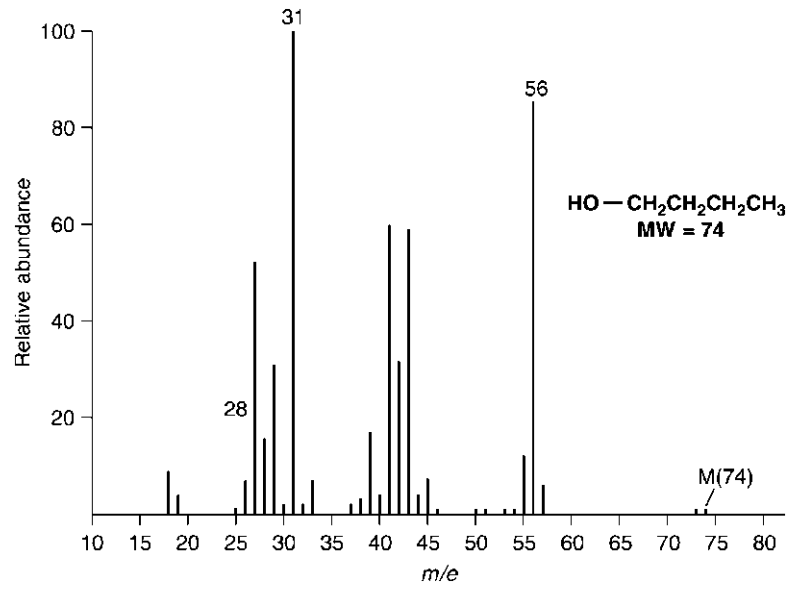
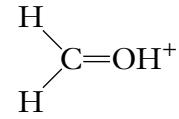
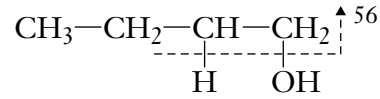


Figure 28.10 The mass spectrum of 1-butanol.

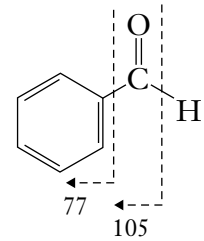
The largest alkyl group is the one that is lost most readily. In the spectrum of 1-butanol, the intense peak at *m/e* = 31 is due to the loss of a propyl group to form



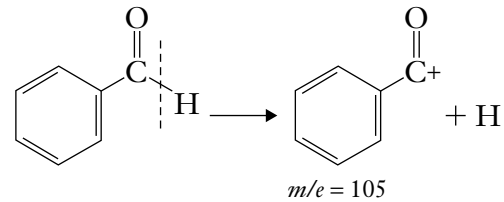
A second common mode of fragmentation involves dehydration. Loss of a molecule of water from 1-butanol leaves a cation of mass 56.



Benzaldehyde; C_7H_6O, MW = 106 (see Figure 28.11)



The loss of a hydrogen atom from an aldehyde is a favorable process. The resulting fragment ion is a benzoyl cation, a particularly stable type of carbocation.



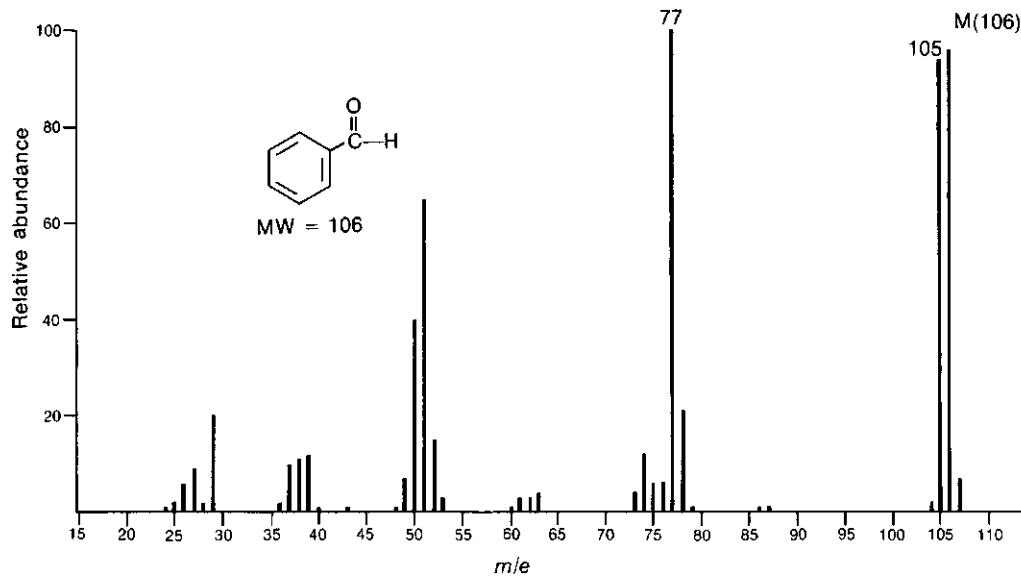
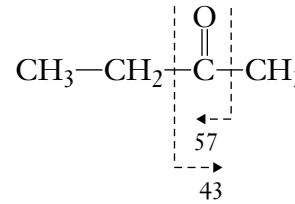


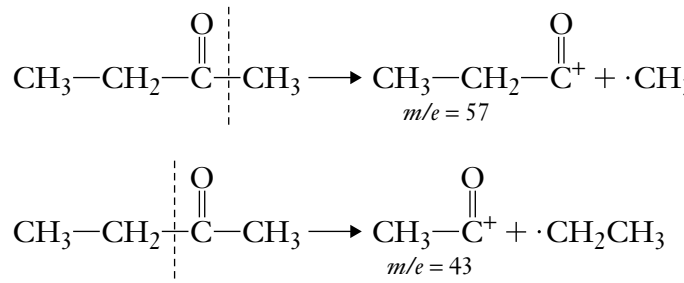
Figure 28.11 The mass spectrum of benzaldehyde.

Loss of the entire aldehyde functional group leaves a phenyl cation. This ion can be seen in the spectrum of an *m/e* value of 77.

2-Butanone; C_4H_8O, MW = 72 (see Figure 28.12)



If the methyl group is lost as a neutral fragment, the resulting cation, an **acylium ion**, has an *m/e* value of 57. If the ethyl group is lost, the resulting acylium ion appears at an *m/e* value of 43.



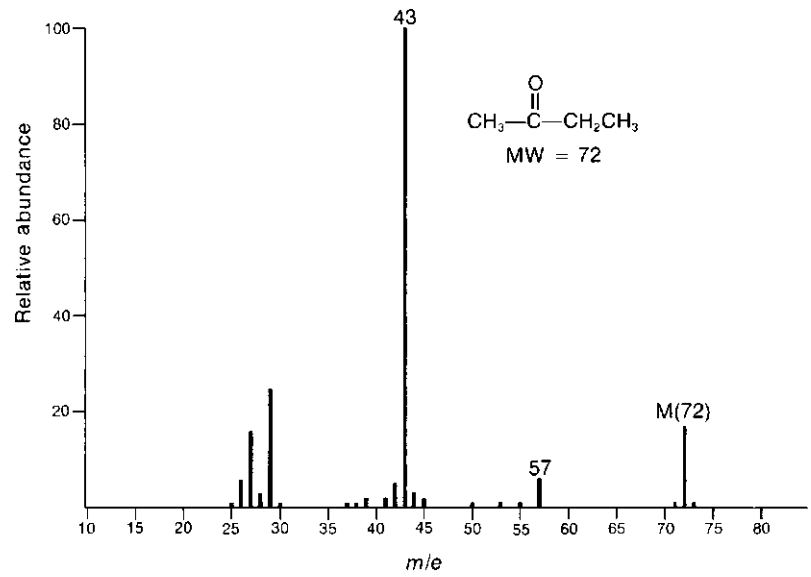


Figure 28.12 The mass spectrum of 2-butanone.

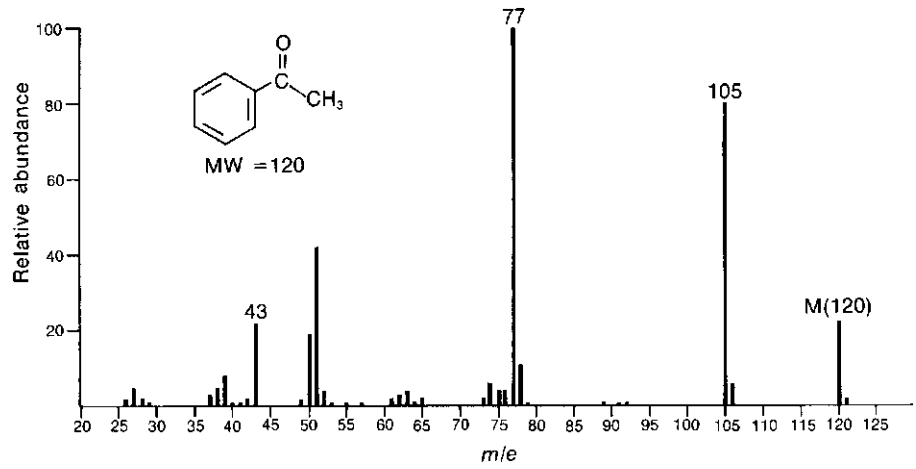
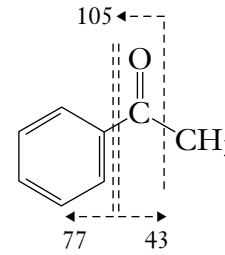


Figure 28.13 The mass spectrum of acetophenone.

Acetophenone; C_8H_8O, MW = 120 (see Figure 28.13)



Aromatic ketones undergo α-cleavage to lose the alkyl group and form the benzoyl cation (*m/e* = 105). This ion subsequently loses carbon monoxide to form the

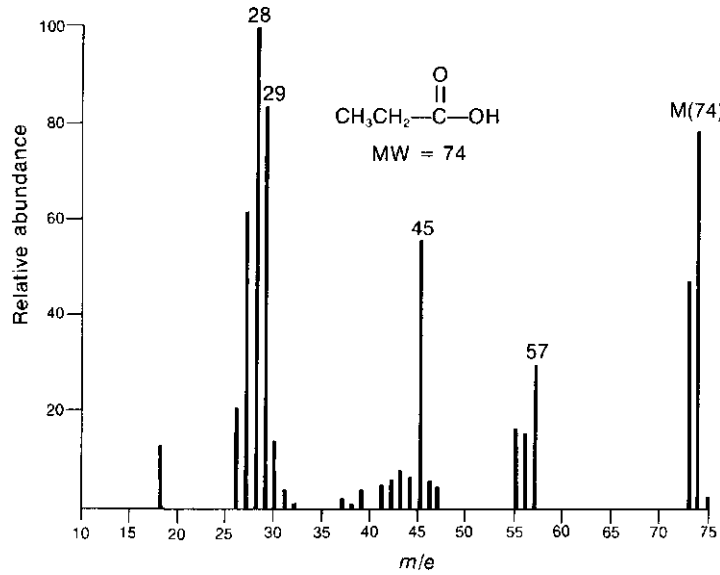
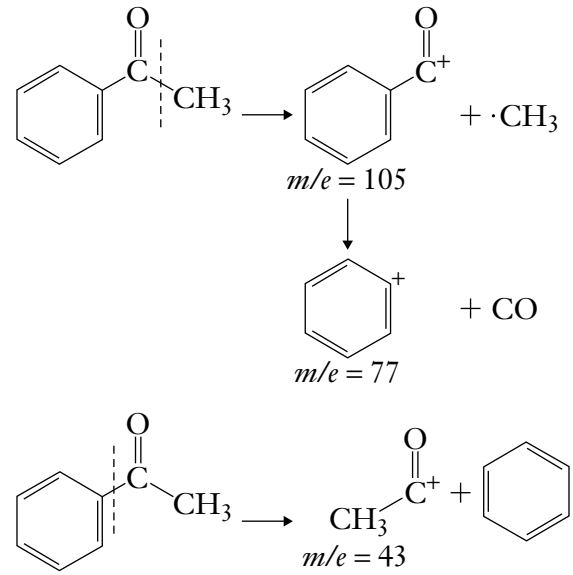
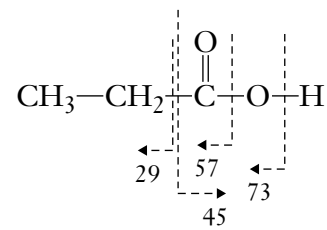


Figure 28.14 The mass spectrum of propanoic acid.

phenyl cation (*m/e* = 77). Aromatic ketones also undergo α-cleavage on the other side of the carbonyl group, forming an alkyl acylium ion. In the case of acetophenone, this ion appears at an *m/e* value of 43.



Propanoic acid; $C_3H_6O_2$, MW = 74 (see Figure 28.14)



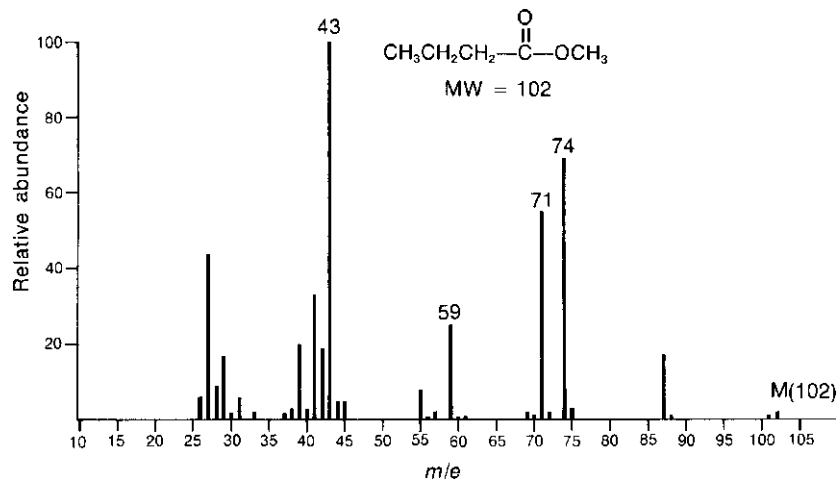
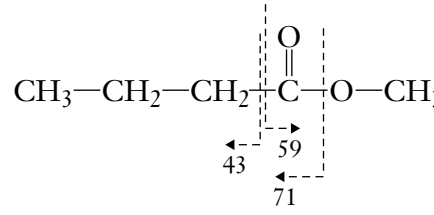


Figure 28.15 The mass spectrum of methyl butanoate.

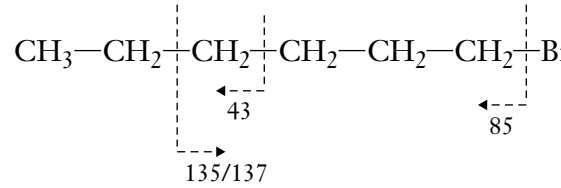
With short-chain carboxylic acids, the loss of OH and COOH through α-cleavage on either side of the C═O group may be observed. In the mass spectrum of propanoic acid, loss of OH gives rise to a peak at *m/e* = 57. Loss of COOH gives rise to a peak at *m/e* = 29. Loss of the alkyl group as a free radical, leaving the $COOH^+$ ion (*m/e* = 45), also occurs. The intense peak at *m/e* = 28 is due to additional fragmentation of the ethyl portion of the acid molecule.

Methyl butanoate; $C_5H_{10}O_2$, MW = 102 (see Figure 28.15)



The most important of the α-cleavage reactions involves the loss of the alkoxy group from the ester to form the corresponding acylium ion, RCO^+. The acylium ion peak appears at *m/e* = 71 in the mass spectrum of methyl butanoate. A second important peak results from the loss of the alkyl group from the acyl portion of the ester molecule, leaving a fragment $CH_3—O—C═O^+$ that appears at *m/e* = 59. Loss of the carboxylate function group to leave the alkyl group as a cation gives rise to a peak at *m/e* = 43. The intense peak at *m/e* = 74 results from a rearrangement process (see Section 28.6).

1-Bromohexane; $C_6H_{13}Br$, MW = 165 (see Figure 28.16)



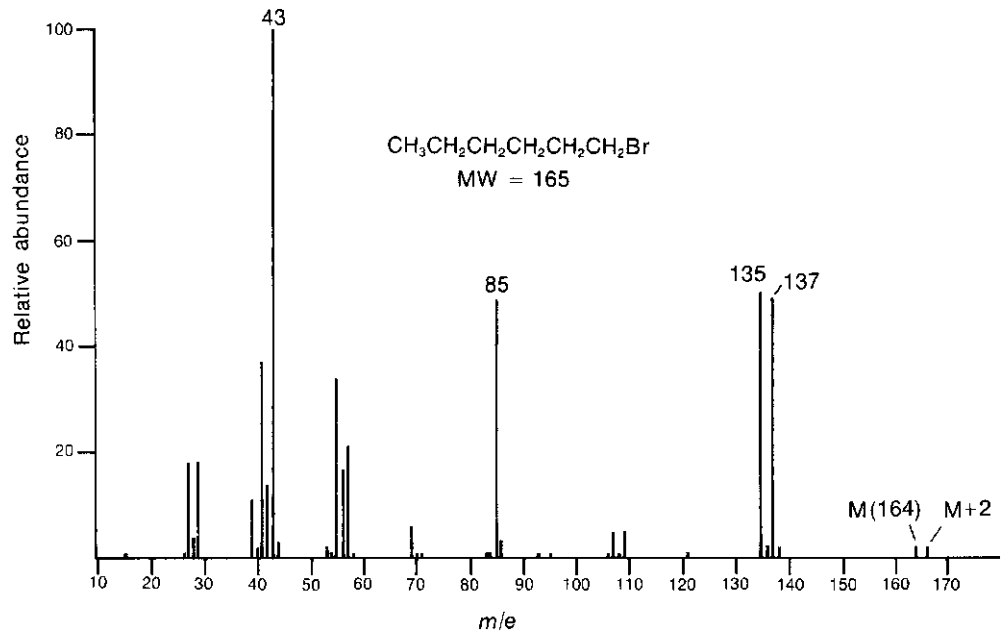


Figure 28.16 The mass spectrum of 1-bromohexane.

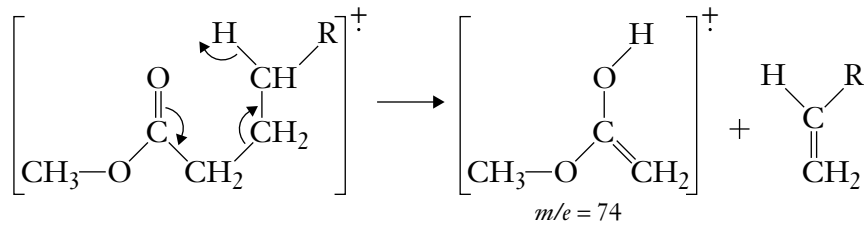
The most interesting characteristic of the mass spectrum of 1-bromohexane is the presence of the doublet in the molecular ion. These two peaks, of equal height and separated by two mass units, are strong evidence that bromine is present in the substance. Notice also that loss of the terminal ethyl group yields a fragment ion that still contains bromine (*m/e* = 135 and 137). The presence of the doublet demonstrates that this fragment contains bromine.

28.6 Rearrangement Reactions

Because the fragment ions that are detected in a mass spectrum are cations, we can expect that these ions will exhibit behavior we are accustomed to associate with carbocations. It is well known that carbocations are prone to rearrangement reactions, converting a less-stable carbocation into a more stable one. These types of rearrangements are also observed in the mass spectrum. If the abundance of a cation is especially high, it is assumed that a rearrangement to yield a longer-lived cation must have occurred.

Other types of rearrangements are also known. An example of a rearrangement that is not normally observed in solution chemistry is the rearrangement of a benzyl cation to a tropylium ion. This rearrangement is seen in the mass spectrum of toluene (see Figure 28.9).

A particular type of rearrangement process that is unique to mass spectrometry is the **McLafferty rearrangement**. This type of rearrangement occurs when an alkyl chain of at least three carbons in length is attached to an energy-absorbing structure such as a phenyl or carbonyl group that can accept the transfer of a hydrogen ion. The mass spectrum of methyl butanoate (see Figure 28.15) contains a prominent peak at *m/e* = 74. This peak arises from a McLafferty rearrangement of the molecular ion.



REFERENCES

Beynon, J. H. Mass *Spectrometry and Its Applications to Organic Chemistry. Elsevier*: Amsterdam, 1960.

Biemann, K. *Mass Spectrometry: Organic Chemical Applications*. McGraw-Hill: New York, 1962.

Budzikiewicz, H.; Djerassi, C; Williams, D. H. *Mass Spectrometry of Organic Compounds.* Holden-Day: San Francisco, 1967.

McLafferty, F. W.; Turecȼek, F. *Interpretation of Mass Spectra,* 4th ed. University Science Books: Mill Valley, CA, 1993.

Pavia, D. L.; Lampman, G. M.; Kriz, G. S., *Introduction to Spectroscopy, A Guide for Students of Organic Chemistry,* 4th ed., and vyvya., J.R. Brooks/Cole 2008.

Silverstein, R. M.; Webster, F. X. and Kiemele, D, J. *Spectrometric Identification of Organic Compounds,* 7th ed. John Wiley & Sons: New York, 2005.

29 TECHNIQUE 29

Guide to the Chemical Literature

Often, you may need to go beyond the information contained in the typical organic chemistry textbook and use reference material in the library. At first glance, using library materials may seem formidable because of the numerous sources the library contains. If, however, you adopt a systematic approach, the task can prove rather useful. This description of various popular sources and an outline of logical steps to follow in the typical literature search should be helpful.

29.1 Locating Physical Constants: Handbooks

To find information on routine physical constants, such as melting points, boiling points, indices of refraction, and densities, you should first consider a handbook. Examples of suitable handbooks are

Aldrich Handbook of Fine Chemicals. Sigma-Aldrich: Milwaukee WI, 2009–2010.

Budavari, S., ed. *The Merck Index,* 14th ed. Merck: Whitehouse Station, NJ, 2006.

Dean, J. A., ed. *Lange's Handbook of Chemistry,* 14th ed. McGraw-Hill: New York, 1999.

Lide, D. R., ed. *CRC Handbook of Chemistry and Physics,* 89th ed. CRC Press: Boca Raton, FL, 2008–2009.

Each of these references is discussed in detail in Technique 4. The *CRC Handbook* is the reference consulted most often because the book is so widely available. There

are, however, distinct advantages to using the other handbooks. The *CRC Handbook* uses the *Chemical Abstracts* system of nomenclature that requires you to identify the parent name; 3-methyl-1-butanol is listed as 1-butanol, 3-methyl.

The Merck Index lists fewer compounds, but there is far more information provided for the ones listed. If the compound is a medicinal or natural product, this is the reference of choice. This handbook contains literature references for the isolation and synthesis of a compound, along with certain properties of medicinal interest, such as toxicity. *Lange's Handbook* and the *Aldrich Handbook* list compounds in alphabetical order; 3-methyl-1-butanol is listed as 3-methyl-1-butanol.

A more complete handbook that is usually housed in the library is

Buckingham, J., ed. *Dictionary of Organic Compounds.* Chapman & Hall/Methuen: New York, 1982–1992.

This is a revised version of an earlier four-volume handbook edited by I. M. Heilbron and H. M. Bunbury. In its present form, it consists of seven volumes with 10 supplements.

29.2 General Synthetic Methods

Many standard introductory textbooks in organic chemistry provide tables that summarize most of the common reactions, including side reactions, for a given class of compounds. These books also describe alternative methods of preparing compounds.

Brown, W. H.; Foote, C. S.; Iverson, B. L.; Anslyn, E. *Organic Chemistry,* 5th ed. Brooks/Cole: Pacific Grove, CA, 2009.
Bruice, P. Y. *Organic Chemistry*, 5th ed. Prentice-Hall: New York, 2007.
Carey, F. A. *Organic Chemistry,* 7th ed. McGraw-Hill: New York, 2008.
Ege, S. *Organic Chemistry,* 5th ed. Boston: Houghton-Mifflin, 2004.
Fessenden, R. J.; Fessenden, J. S. *Organic Chemistry,* 6th ed. Brooks/Cole: Pacific Grove, CA, 1998.
Fox, M. A.; Whitesell, J. K. *Organic Chemistry,* 3rd ed. Jones & Bartlett: Boston, 2004.
Hornback, J. *Organic Chemistry,* 2nd ed. Brooks/Cole: Pacific Grove, CA, 2006.
Jones, M., Jr. *Organic Chemistry,* 3rd ed. W. W. Norton: New York, 2003.
Loudon, G. M. *Organic Chemistry,* 4th ed. Benjamin/Cummings: Menlo Park, CA, 2004.
McMurry, J. *Organic Chemistry,* 7th ed. Brooks/Cole: Pacific Grove, CA, 2008.
Morrison, R. T.; Boyd, R. N. *Organic Chemistry,* 7th ed. Prentice-Hall: Englewood Cliffs, NJ, 1999.
Smith, M. B.; March, J. *Advanced Organic Chemistry,* 6th ed. John Wiley & Sons: New York, 2007.
Solomons, T. W. G.; Fryhle, C. *Organic Chemistry,* 8th ed. John Wiley & Sons: New York, 2003.
Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry,* 4th ed. Prentice-Hall: New York, 1992.
Vollhardt, K. P. C.; Schore, N. E. *Organic Chemistry,* 5th ed. W. H. Freeman: New York, 2007.
Wade, L. G., Jr. *Organic Chemistry,* 7th ed. Prentice-Hall: Englewood Cliffs, NJ, 2009.

29.3 Searching the Chemical Literature

If the information you are seeking is not available in any of the handbooks mentioned in Section 29.1 or if you are searching for more detailed information than they can provide, then a proper literature search is in order. Although an examination of standard textbooks can provide some help, you often must use all the resources of the library, including journals, reference collections, and abstracts. The following sections outline how the various types of sources should be used and what sort of information can be obtained from them.

The methods discussed for searching the literature use mainly printed materials. Modern search methods also make use of computerized databases and are discussed in Section 29.11. These are vast collections of data and bibliographic materials that can be scanned rapidly from remote computer terminals. Although computerized searching is widely available, it may not be readily accessible to undergraduate students. The following references provide excellent introductions to the literature of organic chemistry:

Carr, C. Teaching and Using Chemical Information. *Journal of Chemical Education,* **1993**, 719.

Maizell, R. E. *How to Find Chemical Information,* 3rd ed. John Wiley & Sons: *New York*, 1998.

Smith, M. B.; March, J. *Advanced Organic Chemistry,* 6th ed. John Wiley & Sons: New York, 2007.

Somerville, A. N. Information Sources for Organic Chemistry, 1: Searching by Name Reaction and Reaction Type. *Journal of Chemical Education*, **1991**, 553.

Somerville, A. N. Information Sources for Organic Chemistry, 2: Searching by Functional Group. *Journal of Chemical Education,* **1991**, 842.

Somerville, A. N. Information Sources for Organic Chemistry, 3: Searching by Reagent. *Journal of Chemical Education*, **1992**, 379.

Wiggins, G. *Chemical Information Sources.* McGraw-Hill: NewYork, 1991. Integrates printed materials and computer sources of information.

29.4 Collections of Spectra

Collections of infrared, nuclear magnetic resonance, and mass spectra can be found in the following catalogs of spectra:

Cornu, A.; Massot, R. *Compilation of Mass Spectral Data,* 2nd ed. Heyden and Sons: London, 1975.

High-Resolution NMR Spectra Catalog. Palo Alto, CA: Varian Associates. Vol. 1, 1962; Vol. 2, 1963.

Johnson, L. F.; Jankowski, W. C. *Carbon-13 NMR Spectra.* John Wiley & Sons: New York, 1972.

Pouchert, C. J. *Aldrich Library of Infrared Spectra,* 3rd ed. Aldrich Chemical Co.: Milwaukee, 1981.

Pouchert, C. J. *Aldrich Library of FT-IR Spectra,* 2nd ed. Aldrich Chemical Co.: Milwaukee, 1997.

Pouchert, C. J. *Aldrich Library of NMR Spectra,* 2nd ed. Aldrich Chemical Co.: Milwaukee, 1983.

Pouchert, C. J.; Behnke, J. *Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra.* Aldrich Chemical Co.: Milwaukee, 1993.

Sadtler Standard Spectra. Philadelphia: Sadtler Research Laboratories. Continuing collection.

Stenhagen, E.; Abrahamsson, S.; McLafferty, F. W. *Registry of Mass Spectral Data,* 4 vols. Wiley-Interscience: New York, 1974.

The American Petroleum Institute has also published collections of infrared, nuclear magnetic resonance, and mass spectra.

29.5 Advanced Textbooks

Much information about synthetic methods, reaction mechanisms, and reactions of organic compounds is available in any of the many current advanced textbooks in organic chemistry. Examples of such books are

Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry. Part A. Structure and Mechanisms; Part B. Reactions and Synthesis*, 4th ed. Kluwer Academic: New York, 2000.

Carruthers, W. *Some Modern Methods of Organic Synthesis*, 4th ed. Cambridge University Press: Cambridge, UK, 2004.

Corey, E. J.; Cheng, X. -M. *The Logic of Chemical Synthesis.* John Wiley & Sons: New York, 1995.
Fieser, L. F.; Fieser, M. *Advanced Organic Chemistry.* Reinhold: New York, 1961.
Finar, I. L. *Organic Chemistry,* 6th ed. Longman Group: London, 1986.
House, H. O. *Modern Synthetic Reactions,* 2nd ed. W. H. Benjamin: Menlo Park, CA, 1972.
Noller, C. R. *Chemistry of Organic Compounds,* 3rd ed. W. B. Saunders: Philadelphia, 1965.
Smith, M. B. *Organic Synthesis,* 2nd ed. McGraw-Hill: New York, 2002.
Smith, M. B.; March, J. *Advanced Organic Chemistry,* 6th ed. John Wiley & Sons: New York, 2007.
Stowell, J. C. *Intermediate Organic Chemistry,* 2nd ed. John Wiley & Sons: New York, 1993.
Warren, S.; Wyatt, P. *Organic Synthesis: The Disconnection Approach,* 2nd ed. John Wiley & Sons: New York, 2009.
Zweifel, G. S.; Nantz, M. H. *Modern Organic Synthesis*. W. H. Freeman and Company: New York, 2007.

These books often contain references to original papers in the literature for students wanting to follow the subject further. Consequently, you obtain not only a review of the subject from such a textbook but also a key reference that is helpful toward a more extensive literature search. The textbook by Smith and March is particularly useful for this purpose.

29.6 Specific Synthetic Methods

Anyone interested in locating information about a particular method of synthesizing a compound should first consult one of the many general textbooks on the subject. Useful ones are

Anand, N.; Bindra, J. S.; Ranganathan, S. *Art in Organic Synthesis,* 2nd ed. John Wiley & Sons: New York, 1988.
Barton, D.; Ollis, W. D., eds. *Comprehensive Organic Chemistry,* 6 vols. Pergamon Press: Oxford, 1979.
Buehler, C. A.; Pearson, D. E. *Survey of Organic Syntheses.* Wiley-Interscience: New York, 1970, 2 vols., 1977.
Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry. Part B. Reactions and Synthesis,* 4th ed. Kluwer: New York, 2000.
Compendium of Organic Synthetic Methods. Wiley-Interscience: New York, 1971–2002. This is a continuing series, now in 10 volumes.
Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis.* Wiley-Interscience: New York, 1967–2008. This is a continuing series, now in 24 volumes.
Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis,* 4th ed. John Wiley & Sons: New York, 2007.
House, H. O. *Modern Synthetic Reactions,* 2nd ed. W. H. Benjamin: Menlo Park, CA, 1972.
Larock, R. C. *Comprehensive Organic Transformations,* 2nd ed. Wiley-VCH: New York, 1999.
Mundy, B. P.; Ellerd, M. G. *Name Reactions and Reagents in Organic Synthesis.* 2nd ed. John Wiley & Sons: New York, 2005.
Patai, S., ed. *The Chemistry of the Functional Groups.* Interscience, 1964–present: London, 2005. This series consists of many volumes, each one specializing in a particular functional group.
Smith, M. B.; March, J. *Advanced Organic Chemistry,* 6th ed. John Wiley & Sons: New York, 2007.
Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis.* Pergamon/Elsevier Science: Amsterdam, 1992. This series consists of 9 volumes plus supplements.
Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis,* 5th ed. Longman Group: London, 1989. Revised by members of the School of Chemistry, Thames Polytechnic.
Wagner, R. B.; Zook, H. D. *Synthetic Organic Chemistry.* John Wiley & Sons: New York, 1956.

Wang, Z. *Comprehensive Organic Name Reactions and Reagents,* John Wiley: New York, 2009.

More specific information, including actual reaction conditions, exists in collections specializing in organic synthetic methods. The most important of these are

Organic Syntheses. John Wiley & Sons: New York, 1921–present. Published annually.
Organic Syntheses, Collective Volumes. John Wiley & Sons: New York, 1941–2004.
Vol. 1, 1941, Annual Volumes 1–9
Vol. 2, 1943, Annual Volumes 10–19
Vol. 3, 1955, Annual Volumes 20–29
Vol. 4, 1963, Annual Volumes 30–39
Vol. 5, 1973, Annual Volumes 40–49
Vol. 6, 1988, Annual Volumes 50–59
Vol. 7, 1990, Annual Volumes 60–64
Vol. 8, 1993, Annual Volumes 65–69
Vol. 9, 1998, Annual Volumes 70–74
Vol. 10, 2004, Annual Volumes 75–79

It is much more convenient to use the collective volumes where the earlier annual volumes of *Organic Syntheses* are combined in groups of 9 or 10 in the first six collective volumes (Volumes 1–6), and then in groups of 5 for the next three volumes (Volumes 7, 8, 9, and 10). Useful indices are included at the end of each of the collective volumes that classify methods according to the type of reaction, type of compound prepared, formula of compound prepared, preparation or purification of solvents and reagents, and use of various types of specialized apparatus.

The main advantage of using one of the *Organic Syntheses* procedures is that they have been tested to make sure that they work as written. Often, an organic chemist will adapt one of these tested procedures to the preparation of another compound. One of the features of the advanced organic textbook by Smith and March is that it includes references to specific preparative methods contained in *Organic Syntheses.*

More advanced material on organic chemical reactions and synthetic methods may be found in any one of a number of annual publications that review the original literature and summarize it. Examples include

Advances in Organic Chemistry: Methods and Results. John Wiley & Sons: New York, 1960–present.
Annual Reports in Organic Synthesis. Academic Press: Orlando, FL, 1985–1995.
Annual Reports of the Chemical Society, Section B. Chemical Society: London, 1905–present. Specifically, the section "Synthetic Methods."
Organic Reactions. John Wiley & Sons: New York, 1942–present.
Progress in Organic Chemistry. John Wiley & Sons: New York, 1952–1973.

Each of these publications contains a great many citations to the appropriate articles in the original literature.

29.7 Advanced Laboratory Techniques

The student who is interested in reading about techniques more advanced than those described in this textbook, or in more complete descriptions of techniques, should consult one of the advanced textbooks specializing in organic laboratory techniques. Besides focusing on apparatus construction and the performance of complex reactions, these books provide advice on purifying reagents and solvents. Useful sources of information on organic laboratory techniques include

Bates, R. B.; Schaefer, J. P. *Research Techniques in Organic Chemistry.* Prentice-Hall: Englewood Cliffs, NJ, 1971.

Krubsack, A. J. *Experimental Organic Chemistry.* Allyn & Bacon: Boston, 1973.
Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry,* 2nd ed. Chapman & Hall: London, 1995.
Monson, R. S. *Advanced Organic Synthesis: Methods and Techniques*. Academic Press: New York, 1971.
Pirrung, M. C. *The Synthetic Organic Chemist's Companion*, John Wiley: New York, 2009.
Techniques of Chemistry. John Wiley & Sons: New York, 1970–present. Currently 23 volumes. The successor to *Technique of Organic Chemistry,* this series covers experimental methods of chemistry, such as purification of solvents, spectral methods, and kinetic methods.
Weissberger, A., et al., eds. *Technique of Organic Chemistry,* 3rd ed., 14 vols. Wiley-Interscience: New York, 1959–1969.
Wiberg, K. B. *Laboratory Technique in Organic Chemistry.* McGraw-Hill: New York, 1960.

Numerous works and some general textbooks specialize in particular techniques. The preceding list is representative only of the most common books in this category. The following books deal specifically with microscale and semimicroscale techniques.

Cheronis, N. D. "Micro and Semimicro Methods." In A. Weissberger, ed., *Technique of Organic Chemistry,* Vol. 6. Wiley-Interscience: New York, 1954.
Cheronis, N. D.; Ma, T. S. *Organic Functional Group Analysis by Micro and Semimicro Methods*. Wiley-Interscience: New York, 1964.
Ma, T. S.; Horak, V. *Microscale Manipulations in Chemistry.* Wiley-Interscience: New York, 1976.

29.8 Reaction Mechanisms

As with the case of locating information on synthetic methods, you can obtain a great deal of information about reaction mechanisms by consulting one of the common textbooks on physical organic chemistry. The textbooks listed here provide a general description of mechanisms, but they do not contain specific literature citations. Very general textbooks include

Bruckner, R. *Advanced Organic Chemistry: Reaction Mechanisms*. Academic Press: New York, 2001.
Miller, A.; Solomon, P. *Writing Reaction Mechanisms in Organic Chemistry,* 2nd ed. Academic Press: San Diego, CA, 1999.
Sykes, P. *A Primer to Mechanisms in Organic Chemistry.* Benjamin/Cummings: Menlo Park, CA, 1995.

More advanced textbooks include

Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry. Part A. Structure and Mechanisms*, 4th ed. Kluwer: New York, 2000.
Hammett, L. P. *Physical Organic Chemistry: Reaction Rates, Equilibria, and Mechanisms*, 2nd ed. McGraw-Hill: New York, 1970.
Hine, J. *Physical Organic Chemistry,* 2nd ed. McGraw-Hill: New York, 1962.
Ingold, C. K. *Structure and Mechanism in Organic Chemistry,* 2nd ed. Cornell University Press: Ithaca, NY, 1969.
Isaacs, N. S. *Physical Organic Chemistry,* 2nd ed. John Wiley & Sons: New York, 1995.
Jones, R. A. Y. *Physical and Mechanistic Organic Chemistry,* 2nd ed. Cambridge University Press: Cambridge, 1984.
Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry,* 3rd ed. Harper & Row: New York, 1987.
Moore, J. W.; Pearson, R. G. *Kinetics and Mechanism,* 3rd ed. John Wiley & Sons: New York, 1981.
Smith, M. B.; March, J. *Advanced Organic Chemistry,* 6th ed. John Wiley & Sons: New York, 2007.

These books include extensive bibliographies that permit the reader to delve more deeply into the subject.

Most libraries also subscribe to annual series of publications that specialize in articles dealing with reaction mechanisms. Among these are

Advances in Physical Organic Chemistry. Academic Press: London, 1963–present.
Annual Reports of the Chemical Society. Section B. Chemical Society: London, 1905–present. Specifically, the section "Reaction Mechanisms."
Organic Reaction Mechanisms. John Wiley & Sons: Chichester, 1965–present.
Progress in Physical Organic Chemistry. Interscience: New York, 1963–present.

These publications provide the reader with citations from the original literature that can be very useful in an extensive literature search.

29.9 Organic Qualitative Analysis

Many laboratory manuals provide basic procedures for identifying organic compounds through a series of chemical tests and reactions. Occasionally, you might require a more complete description of analytical methods or a more complete set of tables of derivatives. Textbooks specializing in organic qualitative analysis should fill this need. Examples of sources for such information include

Cheronis, N. D.; Entriken, J. B. *Identification of Organic Compounds:* A *Student's Text Using Semimicro Techniques*. Interscience: New York, 1963.
Pasto, D. J.; Johnson, C. R. *Laboratory Text for Organic Chemistry*: *A Source Book of Chemical and Physical Techniques.* Prentice-Hall: Englewood Cliffs, NJ, 1979.
Rappoport, Z. ed. *Handbook of Tables for Organic Compound Identification,* 3rd ed. CRC Press: Boca Raton, FL, 1967.
Shriner, R. L.; Hermann, C. K. F.; Merrill, T. C.; Curtin, D. Y.; Fuson, R. C. *The Systematic Identification of Organic Compounds,* 7th ed. John Wiley & Sons: New York, 1998.
Vogel, A. I. *Elementary Practical Organic Chemistry. Part 2. Qualitative Organic Analysis,* 2nd ed. John Wiley & Sons: New York, 1966.
Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis,* 5th ed. Longman Group: London, 1989. Revised by members of the School of Chemistry, Thames Polytechnic.

29.10 *Beilstein* and *Chemical Abstracts*

One of the most useful sources of information about the physical properties, synthesis, and reactions of organic compounds is *Beilsteins Handbuch der Organischen Chemie.* This is a monumental work, initially edited by Friedrich Konrad Beilstein and updated through several revisions by the Beilstein Institute in Frankfurt am Main, Germany. The original edition (the *Hauptwerk,* abbreviated H) was published in 1918 and completely covers the literature to 1909. Five supplementary series (*Ergänzungswerken*) have been published since that time. The first supplement (*Erstes Ergänzungswerk,* abbreviated E I) covers the literature from 1910 to 1919; the second supplement (*Zweites Ergänzungswerk,* E II) covers 1920–1929; the third supplement (*Drittes Ergänzungswerk,* E III) covers 1930–1949; the fourth supplement (*Viertes Ergänzungswerk,* E IV) covers 1950–1959; and the fifth supplement (in English) covers 1960–1979. Volumes 17–27 of supplementary series III and IV, covering heterocyclic compounds, are combined in a joint issue, E III/IV. Supplementary series III, IV, and V are not complete, so the coverage of *Handbuch der Organischen Chemie* can be considered complete to 1929, with partial coverage to 1979.

Beilsteins Handbuch der Organischen Chemie, usually referred to simply as *Beilstein*, also contains two types of cumulative indices. The first of these is a name index (*Sachregister*), and the second is a formula index (*Formelregister*). These indices are particularly useful for a person wishing to locate a compound in *Beilstein.*

The principal difficulty in using *Beilstein* is that it is written in German through the fourth supplement. The fifth supplement is in English. Although some reading knowledge of German is useful, you can obtain information from the work by learning a few key phrases. For example, *Bildung* is "formation" or "structure." *Darst* or *Darstellung* is "preparation," K_p or *Siedepunkt* is "boiling point," and *F* or *Schmelzpunkt* is "melting point." Furthermore, the names of some compounds in German are not cognates of the English names. Some examples are *Apfelsäure* for "malic acid" (*säure* means "acid"), *Harnstoff* for "urea," *Jod* for "iodine," and *Zimtsäure* for "cinnamic acid." If you have access to a German–English dictionary for chemists, many of these difficulties can be overcome. The best such dictionary is

Patterson, A. M. *German–English Dictionary for Chemists,* 4th ed. John Wiley & Sons: New York, 1991.

Beilstein is organized according to a very sophisticated and complicated system. However, most students do not wish to become experts on *Beilstein* to this extent. A simpler, though slightly less reliable, method is to look for the compound in the formula index that accompanies the second supplement. By looking under the molecular formula, you will find the names of compounds that have that formula. After that name will be a series of numbers that indicate the pages and volume in which that compound is listed. Suppose, as an example, that you are searching for information on *p*-nitroaniline. This compound has the molecular formula $C_6H_6N_2O_2$. Searching for this formula in the formula index to the second supplement, you find

4-Nitro-anilin **12** 711, **I** 349, **II** 383

This information tells you that *p*-nitroaniline is listed in the main edition, *Hauptwerk,* in Volume 12, page 711. Locate this particular volume, which is devoted to isocyclic monoamines and turn to page 711 to find the beginning of the section on *p*-nitroaniline. At the left side of the top of this page is "Syst. No. 1671." This is the system number given to compounds in this part of Volume 12. The system number is useful, as it can help you find entries for this compound in subsequent supplements. The organization of *Beilstein* is such that all entries on *p*-nitroaniline in each of the supplements will be found in Volume 12. The entry in the formula index also indicates that material on this compound may be found in the first supplement on page 349 and in the second supplement on page 383. On page 349 of Volume 12 of the first supplement, there is a heading, "XII, 710–712," and on the left is "Syst. No. 1671." Material on *p*-nitroaniline is found in each supplement on a page that is headed with the volume and page of the *Hauptwerk* in which the same compound is found. On page 383 of Volume 12 of the second supplement, the heading in the center of the top of the page is "H12, 710–712." On the left, you find "Syst. No. 1671." Again, because *p*-nitroaniline appeared in Volume 12, page 711, of the main edition, you can locate it by searching through Volume 12 of any supplement until you find a page with the heading corresponding to Volume 12, page 711.

Because the third and fourth supplements are not complete, there is no comprehensive formula index for these supplements. However, you can still find material on *p*-nitroaniline by using the system number and the volume and page in the main work. In the third supplement, because the amount of information available has grown so much since the early days of Beilstein's work, Volume 12 has now expanded so that it is found in several bound parts. However, you select the part that includes system number 1671. In this part of Volume 12, you look through the

pages until you find a page headed "Syst. No. 1671/H711." The information on *p*-nitroaniline is found on this page (page 1580). If Volume 12 of the fourth supplement were available, you would go on in the same way to locate more recent data on *p*-nitroaniline. This example is meant to illustrate how you can locate information on particular compounds without having to learn the *Beilstein* system of classification. You might do well to test your ability at finding compounds in *Beilstein* as we have described here.

Guidebooks to using *Beilstein,* which include a description of the *Beilstein* system, are recommended for anyone who wants to work extensively with *Beilstein.* Among such sources are

Heller, S. R. *The Beilstein System: Strategies for Effective Searching.* Oxford University Press: New York, 1997.

How to Use Beilstein. Beilstein Institute, Frankfurt am Main. Springer-Verlag: Berlin,

Huntress, E. H. *A Brief Introduction to the Use of* Beilsteins Handbuch der Organischen Chemie, 2nd ed. John Wiley & Sons: New York, 1938.

Weissbach, O. *The Beilstein Guide: A Manual for the Use of* Beilsteins Handbuch der Organischen Chemie. Springer-Verlag: New York, 1976.

Beilstein reference numbers are listed in such handbooks as *CRC Handbook of Chemistry and Physics* and *Lange's Handbook of Chemistry.* Additionally, *Beilstein* numbers are included in the *Aldrich Handbook of Fine Chemicals,* issued by the Aldrich Chemical Company. If the compound you are seeking is listed in one of these handbooks, you will find that using *Beilstein* is simplified.

Another very useful publication for finding references for research on a particular topic is *Chemical Abstracts,* published by the Chemical Abstracts Service of the American Chemical Society. *Chemical Abstracts* contains abstracts of articles appearing in more than 10,000 journals from virtually every country conducting scientific research. These abstracts list the authors, the journal in which the article appeared, the title of the article, and a short summary of the contents of the article. Abstracts of articles that appeared originally in a foreign language are provided in English, with a notation indicating the original language.

To use *Chemical Abstracts,* you must know how to use the various indices that accompany it. At the end of each volume, there appears a set of indices, including a formula index, a general subject index, a chemical substances index, an author index, and a patent index. The listings in each index refer the reader to the appropriate abstract according to the number assigned to it. There are also collective indices that combine all the indexed material appearing in a 5-year period (10-year period before 1956). In the collective indices, the listings include the volume number as well as the abstract number.

For material after 1929, *Chemical Abstracts* provides the most complete coverage of the literature. For material before 1929, use *Beilstein* before consulting *Chemical Abstracts. Chemical Abstracts* has the advantage that it is written entirely in English. Nevertheless, most students perform a literature search to find a relatively simple compound. Finding the desired entry for a simple compound is much easier in *Beilstein* than in *Chemical Abstracts.* For simple compounds, the indices in *Chemical Abstracts* are likely to contain very many entries. To locate the desired information, you must comb through this multitude of listings—potentially a very time-consuming task.

The opening pages of each index in *Chemical Abstracts* contain a brief set of instructions on using that index. If you want a more complete guide to *Chemical*

Abstracts, consult a textbook designed to familiarize you with these abstracts and indices. Two such books are

CAS Printed Access Tools: A Workbook. Chemical Abstracts Service, American Chemical Society: Washington, DC, 1977.

How to Search Printed CA. Chemical Abstracts Service, American Chemical Society: Washington, DC, 1989.

Chemical Abstracts Service maintains a computerized database that permits users to search through *Chemical Abstracts* rapidly and thoroughly. This service, which is called *CA Online,* is described in Section 29.11. *Beilstein* is also available for online searching by computer.

29.11 Computer Online Searching

You can search a number of chemistry databases online by using a computer and modem or a direct Internet connection. Many academic and industrial libraries can access these databases through their computers. One organization that maintains a large number of databases is the Scientific and Technical Information Network (STN International). The fee charged to the library for this service depends on the total time used in making the search, the type of information being asked for, the time of day when the search is being conducted, and the type of database being searched.

The Chemical Abstracts Service database (*CA Online*) is one of many databases available on STN. It is particularly useful to chemists. Unfortunately, this database extends back only to about 1967, although some earlier references are available. Searches for references earlier than 1967 must be made with printed abstracts (see Section 29.10). Searching online is much faster than searching in the printed abstracts. In addition, you can tailor the search in a number of ways by using keywords and the Chemical Abstracts Service Registry Number (CAS Number) as part of the search routine. The CAS Number is a specific number assigned to every compound listed in the *Chemical Abstracts* database. The CAS Number is used as a key in an online search to locate information about the compound. For the more common organic compounds, you can easily obtain CAS Numbers from the catalogs of most of the companies that supply chemicals. Another advantage of performing an online search is that the *Chemical Abstracts* files are updated much more quickly than the printed versions of abstracts. This means that your search is more likely to reveal the most current information available.

Other useful databases available from STN include *Beilstein* and *CASREACTS.* As described in Section 29.10, *Beilstein* is very useful to organic chemists. Currently, there are more than 3.5 million compounds listed in the database. You can use the CAS Numbers to help in a search that has the potential of going back to 1830. *CASREACTS* is a chemical reactions database derived from over 100 journals covered by *Chemical Abstracts,* starting in 1985. With this database, you can specify a starting material and a product using the CAS Numbers. Further information on *CA Online, Beilstein, CASREACTS,* and other databases can be obtained from the following references:

Heller, S. R., ed. *The Beilstein Online Database: Implementation, Content and Retrival.* American Chemical Society: Washington, DC, 1990.

Smith, M. B.; March, J. *Advanced Organic Chemistry,* 5th ed. John Wiley & Sons: New York, 2001.

Somerville, A. N. Information Sources for Organic Chemistry, 2: Searching by Functional Group. *Journal of Chemical Education*, **1991**, 842.

Somerville, A. N. Subject Searching of Chemical Abstracts Online. *Journal of Chemical Education,* **1993**, 200.

Wiggins, G. *Chemical Information Sources.* McGraw-Hill: New York, 1990. Integrates printed materials and computer sources of information.

SciFinder and SciFinder Scholar

The newest tools for online searching are SciFinder and SciFinder Scholar, the latter being the academic version of the software. This online service requires a yearly subscription and is available for use at many colleges and universities. SciFinder allows you to search several multidisciplinary CAS databases that contain information from as far back as 1907 to the present. The database may be searched in a variety of ways: by name, chemical substance, reaction, research topic, CAS number, or author. The program has drawing tools similar to ChemDraw, and what makes the program extremely useful is the ability to draw a structure on the screen and search for it. This avoids the need to name the structure first. In addition, substructure searching is allowed, which means that you may enter a partial structure and the program will find all references having compounds with the features you have indicated. Once you retrieve literature references, hyperlinks allow you to view abstracts of the papers or retrieve physical property information. SciFinder is easy to use and requires minimal training. A recent book explains the program thoroughly:

Ridley, D. D. *Information Retrieval: SciFinder and SciFinder Scholar*. Wiley: New York, 2002.

For these who are at a university that subscribes to the service, there is an online tutorial at www.cas.org/SCIFINDER/SCHOLAR.

29.12 Scientific Journals

Ultimately, someone wanting information about a particular area of research will be required to read articles from the scientific journals. These journals are of two basic types: review journals and primary scientific journals. Journals that specialize in review articles summarize all of the work that bears on the particular topic. These articles may focus on the contributions of one particular researcher, but often consider the contributions of many researchers to the subject. These articles also contain extensive bibliographies, which refer you to the original research articles. Among the important journals devoted, at least partly, to review articles are

Accounts of Chemical Research
Angewandte Chemie (International Edition, in English)
Chemical Reviews
Chemical Society Reviews (formerly known as *Quarterly Reviews*)
Nature
Science

The details of the research of interest appear in the primary scientific journals. Although there are thousands of journals published in the world, a few important journals specializing in articles dealing with organic chemistry include

Canadian Journal of Chemistry
European Journal of Organic Chemistry (formerly known as *Chemische Berichte*)
Journal of Organic Chemistry
Journal of the American Chemical Society
Journal of the Chemical Society, Chemical Communications
Journal of the Chemical Society, Perkin Transactions (Parts I and II)
Journal of Organometallic Chemistry
Organic Letters
Organometallics
Synlett
Synthesis
Tetrahedron
Tetrahedron Letters

29.13 Topics of Current Interest

The following journals and magazines are good sources for topics of educational and current interest. They specialize in news articles and focus on current events in chemistry or in science in general. Articles in these journals (magazines) can be useful in keeping you abreast of developments in science that are not part of your normal specialized scientific reading.

American Scientist
Chemical and Engineering News
Chemistry and Industry
Chemistry in Britain
Chemtech
Discover
Journal of Chemical Education
Nature
Omni
Science
Scientific American

Other sources for topics of current interest include the following:

Encyclopedia of Chemical Technology, 4th ed., 25 vols. plus index and supplements, 1992. Also called *Kirk-Othmer Encyclopedia of Chemical Technology.*
McGraw-Hill Encyclopedia of Science and Technology, 20 volumes and supplements, 1997.

29.14 How to Conduct a Literature Search

The easiest method to follow in searching the literature is to begin with secondary sources and then go to the primary sources. In other words, you would try to locate material in a textbook, *Beilstein,* or *Chemical Abstracts.* From the results of that search, you would then consult one of the primary scientific journals.

A literature search that ultimately requires you to read one or more papers in the scientific journals is best conducted if you can identify a particular paper central to the study. Often, you can obtain this reference from a textbook or a review article on the subject. If this is not available, a search through *Beilstein* is required. A search through one of the handbooks that provides *Beilstein* reference numbers (see Section 29.10) may be helpful. Searching through *Chemical Abstracts* would be considered the next logical step. From these sources, you should be able to identify citations from the original literature on the subject.

Additional citations may be found in the references cited in the journal article. In this way, the background leading to the research can be examined. It is also possible to conduct a search forward in time from the date of the journal article through the *Science Citation Index.* This publication provides the service of listing articles and the papers in which these articles were cited. Although the *Science Citation Index* consists of several types of indices, the *Citation Index* is most useful for the purposes described here. A person who knows of a particular key reference on a subject can examine the *Science Citation Index* to obtain a list of papers that have used that seminal reference in support of the work described. The *Citation Index* lists papers by their senior author, journal, volume, page, and date, followed by citations of papers that have referred to that article, author, journal, volume, page, and date of each. The *Citation Index* is published in annual volumes, with quarterly supplements issued during the current year. Each volume contains a complete list of the citations of the key articles made during that year. A disadvantage is that *Science Citation Index* has been available only since 1961. An additional disadvantage is that you may miss journal articles on the subject of interest if *Citation Index* failed to cite that particular key reference in its bibliographies—a reasonably likely possibility.

You can, of course, conduct a literature search by a "brute force" method, by beginning the search with *Beilstein* or even with the indices in *Chemical Abstracts.*

However, the task can be made much easier by performing a computer search (see Section 29.11) or by starting with a book or an article of general and broad coverage, which can provide a few citations for starting points in the search.

The following guides to using the chemical literature are provided for the reader who is interested in going farther into this subject.

Bottle, R. T.; Rowland, J. F. B., eds. *Information Sources in Chemistry,* 4th ed. Bowker-Saur: New York, 1992.

Maizell, R. E. *How to Find Chemical Information: A Guide for Practicing Chemists, Educators, and Students,* 3rd ed. John Wiley & Sons: New York, 1998.

Mellon, M. G. *Chemical Publications,* 5th ed. McGraw-Hill: New York, 1982.

Wiggins, G. *Chemical Information Sources.* McGraw-Hill: New York, 1991. Integrates printed materials and computer sources of information.

PROBLEMS

1. Find the following compounds in the formula index for the *Second Supplement of Beilstein* (see Section 29.10). (1) List the page numbers from the main work and the supplements (first and second). (2) Using these page numbers, look up the system number (Syst. No.) and the main work number (*Hauptwerk* number, H) for each compound in the main work and the first and second supplements. In some cases, a compound may not be found in all three places. (3) Now use the system number and main work number to find each of these compounds in the third and fourth supplements. List the page numbers where these compounds are found.

a. 2,5-hexanedione (acetonylacetone)

b. 3-nitroacetophenone

c. 4-*tert*-butylcyclohexanone

d. 4-phenylbutanoic acid (4-phenylbutyric acid, γ-phenylbuttersäure)

2. Using the *Science Citation Index* (see Section 29.14), list five research papers by complete title and journal citation for each of the following chemists who have been awarded the Nobel Prize. Use the *Five-Year Cumulative Source Index* for the years 1980–1984 as your source.

a. H. C. Brown

b. R. B. Woodward

c. D. J. Cram

d. G. Olah

3. The reference book by Smith and March is listed in Section 29.2. Using Appendix 2 in this book, give two methods for preparing the following functional groups. You will need to provide equations.

a. carboxylic acids

b. aldehydes

c. esters (carboxylic esters)

4. *Organic Syntheses* is described in Section 29.6. There are currently nine collective volumes in the series, each with its own index. Find the compounds listed below and provide the equations for preparing each compound.

a. 2-methylcyclopentane-1,3-dione

b. *cis*-$\triangle^4$-tetrahydrophthalic anhydride (listed as tetrahydrophthalic anhydride)

5. Provide four methods that may be used to oxidize an alcohol to an aldehyde. Give complete literature references for each method, as well as equations. Use the *Compendium of Organic Synthetic Methods* or *Survey of Organic Syntheses* by Buehler and Pearson (see Section 29.6).

This page intentionally left blank