Introduction to Laboratory Techniques

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"WARNINGS ABOUT SAFETY PRECAUTIONS

Some of the experiments contained in this Laboratory Manual involve a degree of risk on the part of the instructor and student. Although performing the experiments is generally safe for the college laboratory, unanticipated and potentially dangerous reactions are possible for a number of reasons, such as improper measurement or handling of chemicals, improper use of laboratory equipment, failure to follow laboratory safety procedures, and other causes. Neither the Publisher nor the Authors can accept any responsibility for personal injury or property damage resulting from the use of this publication."

Contents

LABORATORY GLASSWARE

Since 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, since cleaning problems and replacing broken glassware are time-consuming.

For those of you who are unfamiliar with the equipment found in an organic laboratory or who are uncertain about how such equipment should be treated, this section will provide some useful information. Topics such as cleaning glassware, caring for glassware when using corrosive or caustic reagents, and assembling components from your organic laboratory kit are included. At the end of this chapter are illustrations and names of most of the equipment you are likely to find in your drawer or locker.

CLEANING GLASSWARE

Glassware can be cleaned easily if you clean it immediately. It is good practice to do your "dish washing" right away. With time, the 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. Cleaning is then more difficult, because water will no longer wet the surface of the glass as effectively. If you are not able to wash your glassware immediately after use, you should soak the dirty pieces in soapy water. A half-gallon plastic container provides a convenient vessel in which to soak and wash your glassware. The use of a plastic container also helps to 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, since the residue remaining in dirty glassware is likely to be soluble in some organic solvent. After the solvent has been used, the flask probably will have to be washed with soap and water to remove the residual solvent. When you use solvents in cleaning glassware, use caution since the solvents are hazardous (see the chapter entitled "Laboratory Safety"). You should try to use fairly small amounts of a solvent for cleaning purposes. Usually less than 5 mL 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 directed by your instructor. If acetone does not work, other organic solvents such as methylene chloride or toluene can be used in the same way as acetone.

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

For troublesome stains and residues that insist on adhering to the glass in spite of your best efforts, a mixture of sulfuric acid and nitric acid can be used. Cautiously add about 20 drops of concentrated sulfuric acid and five drops of concentrated nitric acid to the flask.

Caution: You must wear safety glasses when you are using this cleaning solution. Do not allow the solution to come into contact with your skin or your clothing. It will cause severe burns and create holes in your clothing. It is also possible that the acids will 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 cautiously to accelerate the cleaning process. Continue heating 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 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.

DRYING GLASSWARE

The easiest way to dry glassware is to allow it to stand overnight. Vials, flasks, and beakers should be stored 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 a waste acetone 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, you should 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.

You should 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 performed in the equipment. 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.

GROUND-GLASS JOINTS

It is likely that the glassware in your organic kit has **standard-taper ground-glass joints.** Joints may be either inner (male) or outer (female). Each joint is ground to a precise size, which is designated by the symbol ℔ followed by two numbers. A common joint

size in most 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. 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 apparatus. One disadvantage of glassware with ground-glass joints, however, is that it is very expensive.

It is important to make sure no solid or liquid is on the joint surfaces. Such material will lessen the efficiency of the seal, and the joints may leak. 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 them with a cloth or lint-free paper towel before assembling.

Another disadvantage of glassware with ground-glass joints is that the joints have some tendency to stick together. To prevent this sticking, you can use a lubricant. Typical lubricants include a variety of hydrocarbon-based stopcock greases, such as Lubriseal and Apiezon. Silicone greases are also used. To apply the grease, coat the inner (male) joint with a *very thin* film of lubricant. You should be careful not to apply too much grease, since excess grease may contaminate the materials contained within the apparatus. A properly lubricated joint appears clear, with no striations. Contamination due to excess grease is a particular problem with silicone grease, which is much harder to remove than hydrocarbon-based greases. Because of this possible contamination, many chemists prefer to use grease only when necessary. The joints usually seal well without grease. In some situations, grease is necessary, including distillations under reduced pressure—when joints must be airtight—and in reactions involving strong caustic solutions (see below, "Etching Glassware"). Whenever there is doubt, it never hurts to use grease. Before lubricating the joints, always make sure that they are free of any adhering liquid or solid.

SEPARATING GROUND-GLASS JOINTS

The most important thing you can do to prevent ground-glass joints from becoming "frozen" or stuck together 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. Since smaller items of 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 this 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 breaks away from the inner section. Heat the joint very slowly and carefully, or it may break.

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, since 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 decreased. 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.

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. You should always clamp the glassware securely to a ring stand. Throughout this textbook, the illustrations of the various glassware arrangements include the clamps that attach the apparatus to a ring stand. You should assemble your apparatus using the clamps as shown in the illustrations.

ATTACHING RUBBER TUBING TO EQUIPMENT

When you attach rubber tubing to the glass apparatus or when you insert glass tubing into rubber stoppers, you should lubricate the rubber tubing or the rubber stopper with either water or glycerin beforehand. 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.

DESCRIPTION OF EQUIPMENT

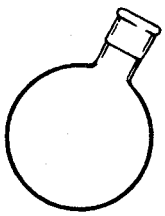
The figures that follow on pages 37–39 include glassware and equipment that are commonly used in the organic laboratory. Your glassware and equipment may vary slightly from the pieces shown.

The components of the organic kit recommended for use in this textbook are shown in the figure on page 37. Notice that most of the joints in these pieces of glassware are ₹ 19/22. The organic kits used in your laboratory may have different joint sizes, but these kits will work as well with the experiments in this book as the glassware recommended in the figure.

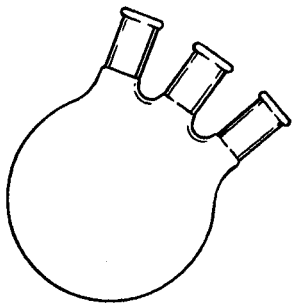
25-mL Round-bottom boiling flask

50-mL Round-bottom boiling flask

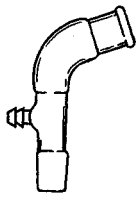
100-mL Round-bottom boiling flask



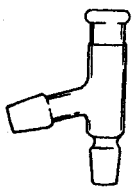
250-mL Round-bottom boiling flask



500-mL Three-necked round-bottom flask

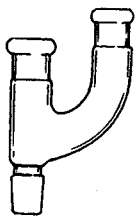


Vacuum adapter

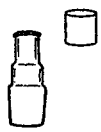


Distillation head

Stopper



Claisen head



Thermometer adapter (with rubber fitting)

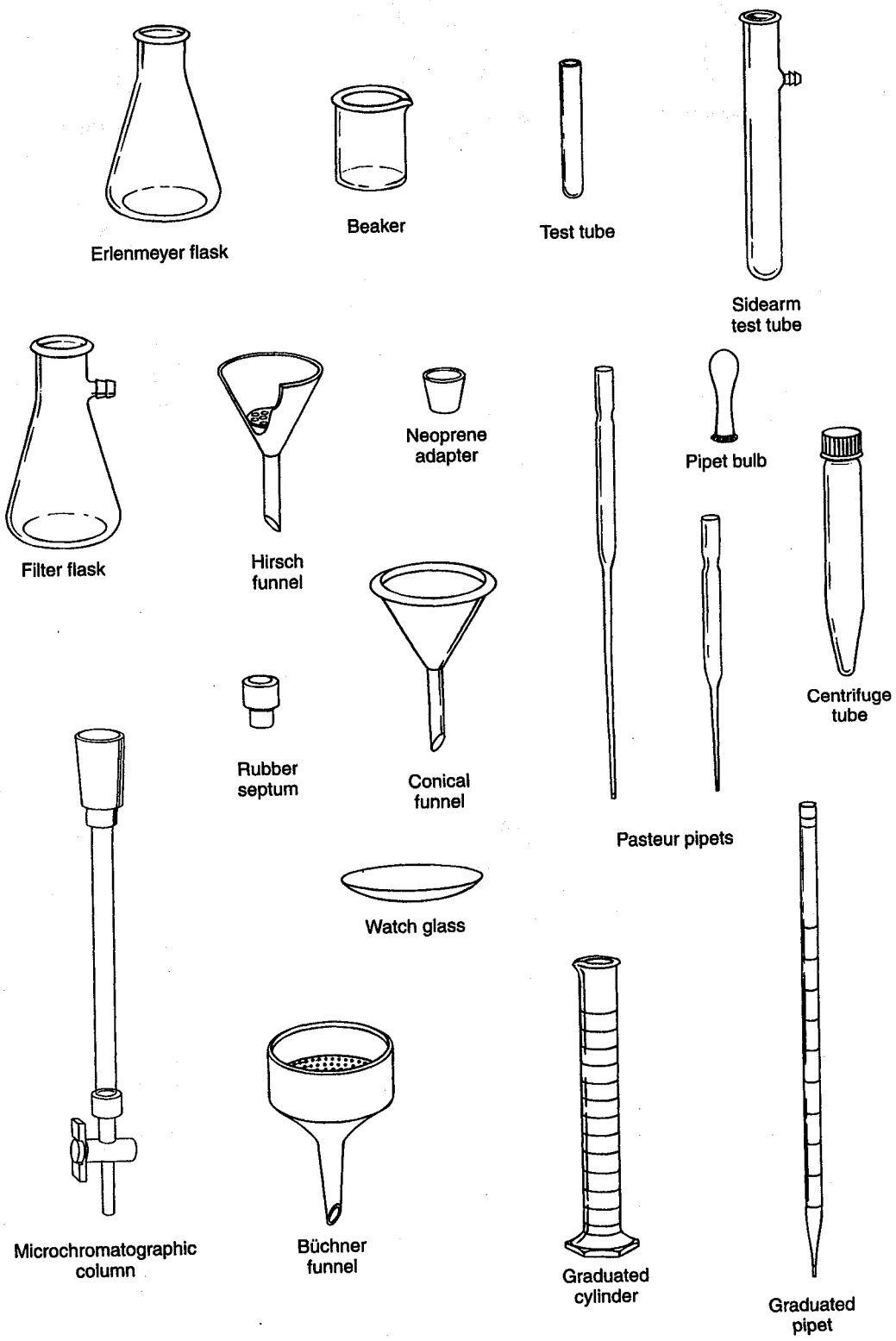
Ebulliator tube

Condenser (West)

125-mL Separatory funnel

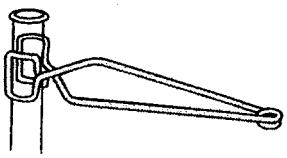
Fractionating column

Components of the organic laboratory kit.



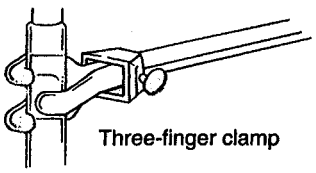
Equipment commonly used in the organic laboratory.

Test tube brush



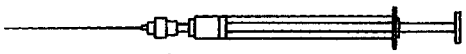
Test tube holder

Spin Bar

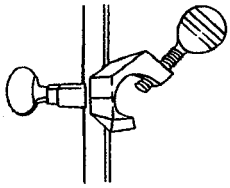


Three-finger clamp

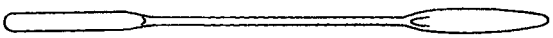
Forceps



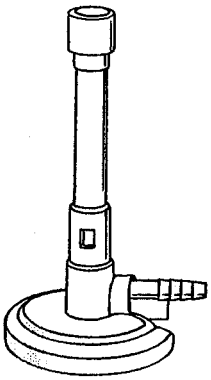
Syringe



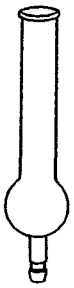
Clamp holder



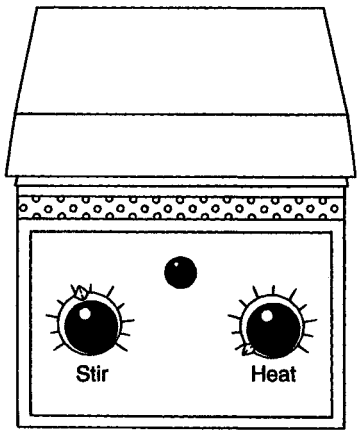
Spatula



Microburner



Drying tube



Hot plate / Stirrer

Equipment commonly used in the organic laboratory.

PART

TWO

The Techniques

TECHNIQUE 1

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 most of the experiments in this textbook, a graduated cylinder, a dispensing pump, or a graduated pipet will be used for measuring the volume of a liquid. You will usually transfer the required volume of liquid to a round-bottom flask or an Erlenmeyer flask.

In cases where the liquid is a limiting reagent, you should pre-weigh **(tare)** the container before dispensing the liquid into the container. When the container is reweighed, you obtain the actual weight for the volume of liquid you have dispensed. The laboratory procedure usually specifies when you should weigh the liquid. 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. It is also advisable to tare a glass stopper, along with the beaker and flask, so that you can stopper the flask immediately after dispensing the liquid and prevent vapors from escaping into the air.

In cases where the liquid is not the limiting reagent, you may calculate the weight of the liquid from the volume you have delivered and the density of the liquid. Usually, densities are provided in the experimental procedures. You may calculate the weight from the following relationship:

$$\text{Weight (g)} = \text{Density (g/mL)} \times \text{Volume (mL)}$$

When using a graduated cylinder to measure small volumes (< 3 mL) of a limiting reagent, it is important to transfer the liquid **quantitatively** from the cylinder to the reaction vessel. This means that all of the liquid should be transferred. When the reagent is poured from the graduated cylinder, a small amount of liquid will remain in the cylinder. This remaining liquid can be transferred by pouring a small amount of the solvent being used in the reaction into the cylinder and then pouring this solution into the reaction vessel. If no solvent is used in the reaction, most of the remaining liquid in the cylinder can be transferred by using a Pasteur pipet.

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 to be used for an experiment will usually be found near the balance. When an accurate measurement is required, solids must be weighed on a balance that reads at least to the nearest decigram (0.01 g). To weigh a solid, place your round-bottom flask or

Erlenmeyer flask in a small beaker and take these with you to the balance. Place a piece of paper that has been folded once on the balance pan. The folded paper will enable you to pour the solid into the flask without spilling. Use your spatula to aid the transfer of the solid to the paper. Never weigh directly into the 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 flask. The flask should be placed in a beaker while transferring the solid. The beaker acts as a trap for any material that fails to make it into the container. It also supports the round-bottom 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 1.52 g of a solid, rather than the 1.50 g specified in a procedure, the actual amount weighed should be recorded in your notebook. Use the 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.

1.1 GRADUATED CYLINDERS

Graduated cylinders are most often used to measure liquids for the experiments in this book (see Fig. 1.1). 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

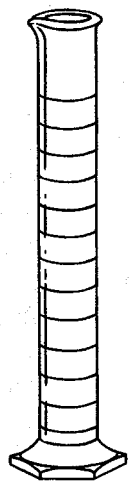


Figure 1.1 Graduated cylinder.

about 2 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 large 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 using a graduated cylinder 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.

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.

1.2 DISPENSING PUMPS

Dispensing pumps are simple to operate, chemically inert, and quite accurate. Since 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 1.2, 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.

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 are commonly observed when the pump has not been

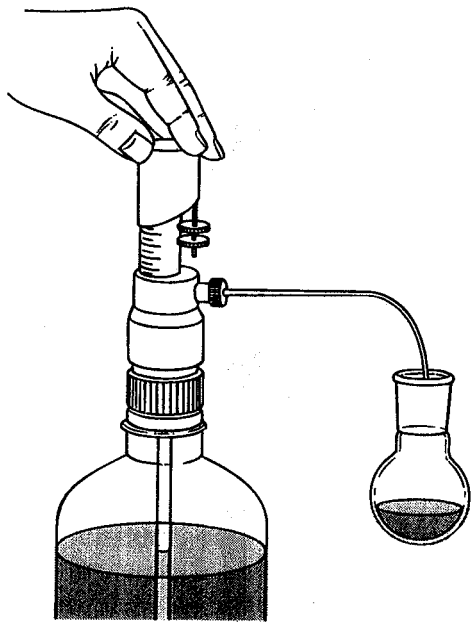


Figure 1.2 Use of a dispensing pump.

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.

1.3 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

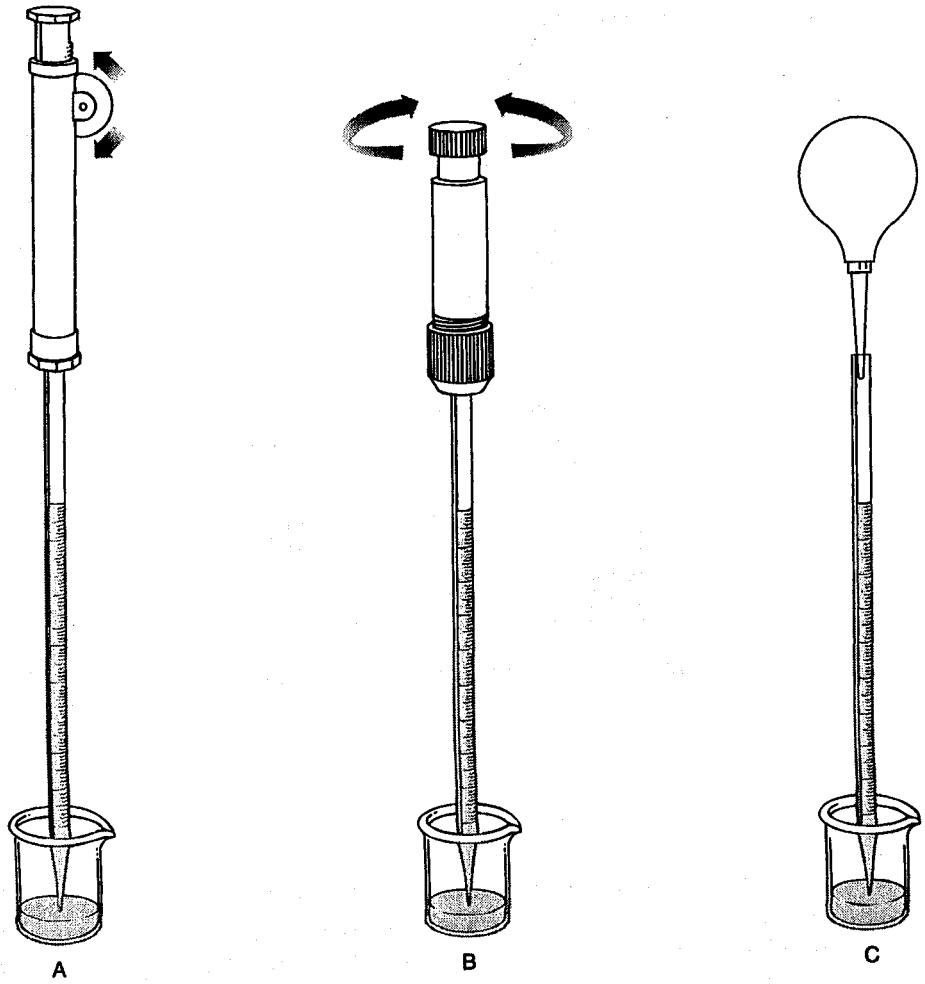


Figure 1.3 Pipet pumps and pipet bulb.

a pipet bulb are shown in Figure 1.3. 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, solutions.

The style of pipet pump shown in Figure 1.3A 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 1.3B 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 1.3C. 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.

The following description, along with Figure 1.4, 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 in order 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 (Figure 1.5). 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 1.5A, 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, one does not need to transfer the entire volume to a container. In order 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 1.5B. 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 1.5B 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 1.5A has its last graduation at 0.90 mL. The last 0.10-mL volume is blown out to give the 1.00-mL volume.

A nongraduated volumetric pipet is shown in Figure 1.5C. 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.

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

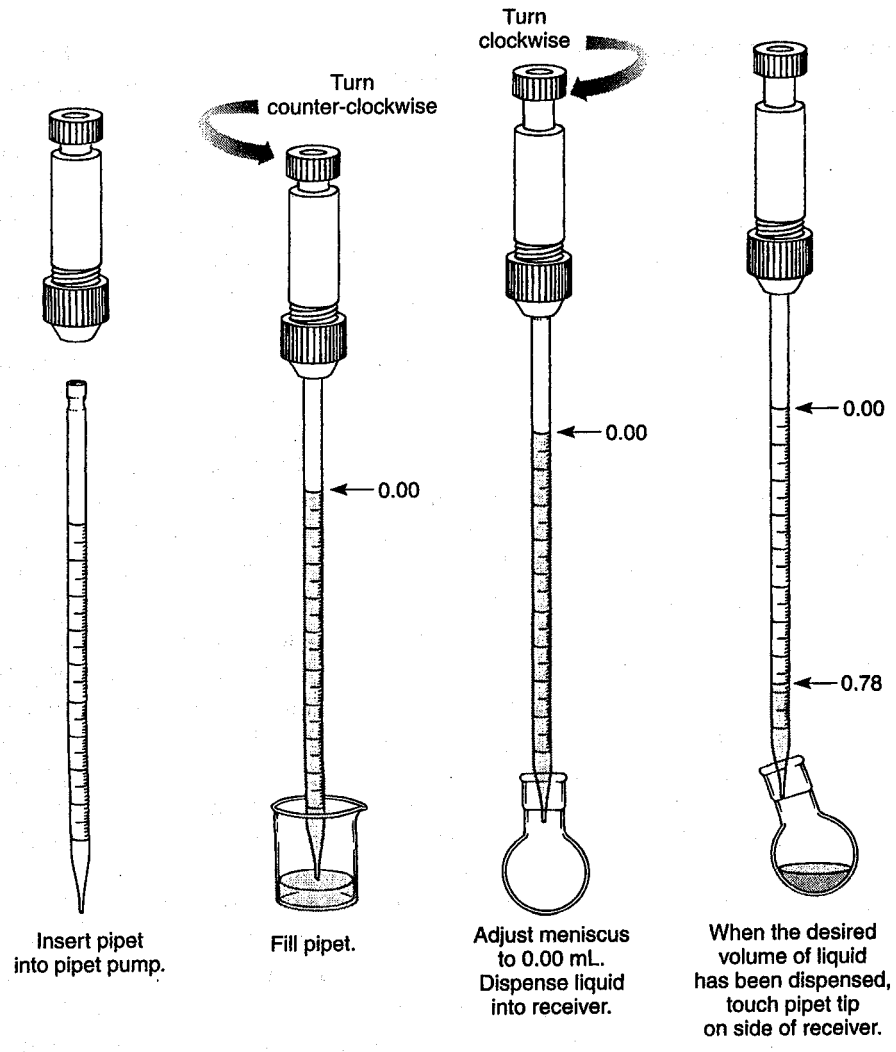

Figure 1.4 Use of a graduated pipet. (The figure shows, as an illustration, the technique required to deliver a volume of 0.78 mL from a 1.00-mL pipet.)

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.

1.4 PASTEUR PIPETS

The Pasteur pipet is shown in Figure 1.6A 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

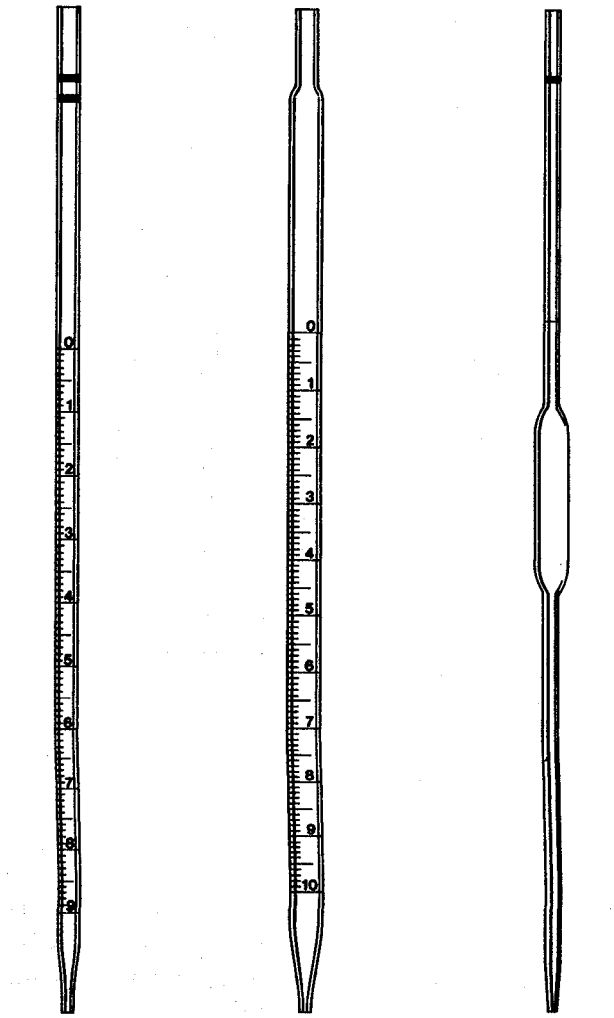

Figure 1.5 Pipets.

piece of equipment for the routine transfer of liquids. It is also used for separations (Technique 7). Pasteur pipets may be packed with cotton for use in gravity filtration (Technique 4) or packed with an adsorbent for small-scale column chromatography (Technique 12). Although they 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.

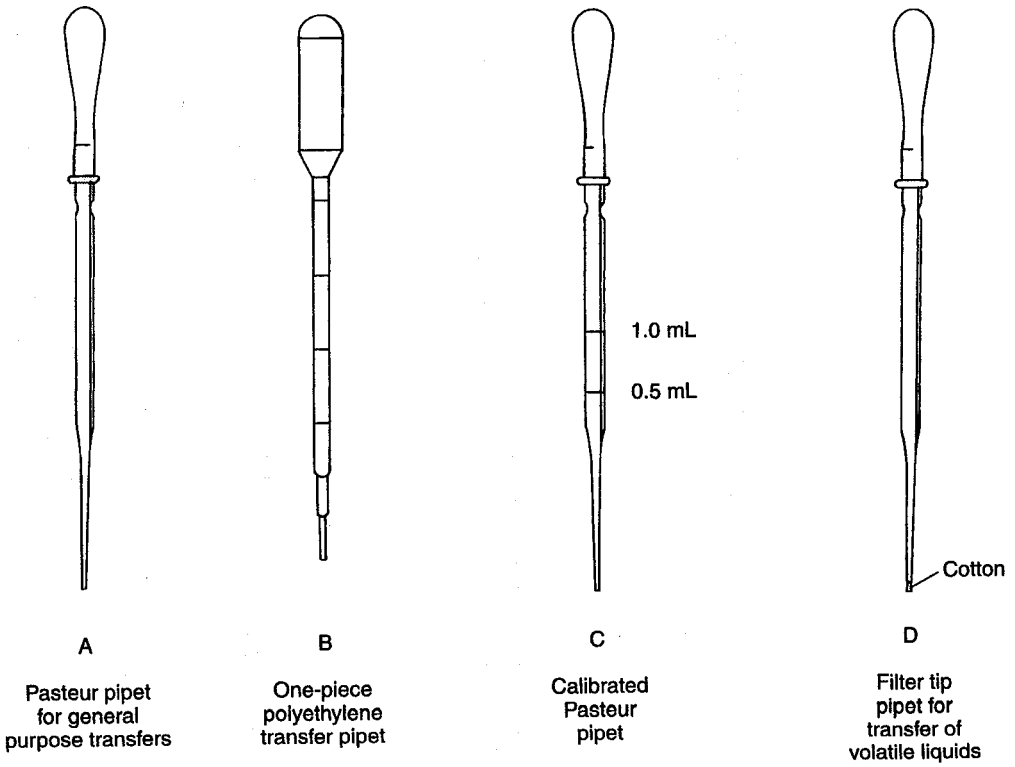

Figure 1.6 Pasteur and transfer pipets.

One may avoid the rubber dropper bulb entirely by using one-piece transfer pipets made entirely of polyethylene (Figure 1.6B). 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.

Pasteur pipets may be calibrated for use in operations where 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 1.6C. It is suggested that you calibrate several $5\frac{3}{4}$-inch pipets using the following procedure. On a balance, weigh 0.5 grams (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 gram 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.

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 1.6D. This pipet is prepared by the instructions given in Technique 4, Section 4.6, page 645. 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 NMR analysis.

1.5 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 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. 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.

1.6 AUTOMATIC PIPETS

Automatic pipets are commonly used in microscale organic laboratories and in biochemistry laboratories. One type of adjustable automatic pipet is shown in Figure 1.7. The automatic pipet is very accurate with aqueous solutions, but it is not as accurate with organic liquids. They are available in different sizes and can deliver accurate volumes ranging from 0.10 mL to 1.0 mL. These pipets are very expensive and must be shared by the entire laboratory. If they are used in your laboratory, your instructor will give directions for the correct use of the automatic pipet.

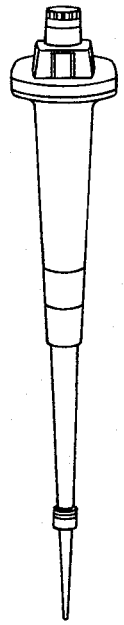

Figure 1.7 The adjustable automatic pipet.

1.7 MEASURING VOLUMES WITH BEAKERS AND ERLENMEYER FLASKS

Beakers and Erlenmeyer flasks both 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. You should use a graduated cylinder, dispensing pump, or graduated pipet for accurate measurement of liquids.

1.8 BALANCES

Solids and some liquids will need to be weighed on a balance that reads to at least the nearest decigram (0.01 g). A top-loading balance (see Fig. 1.8) 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 Fig. 1.9) 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 al-

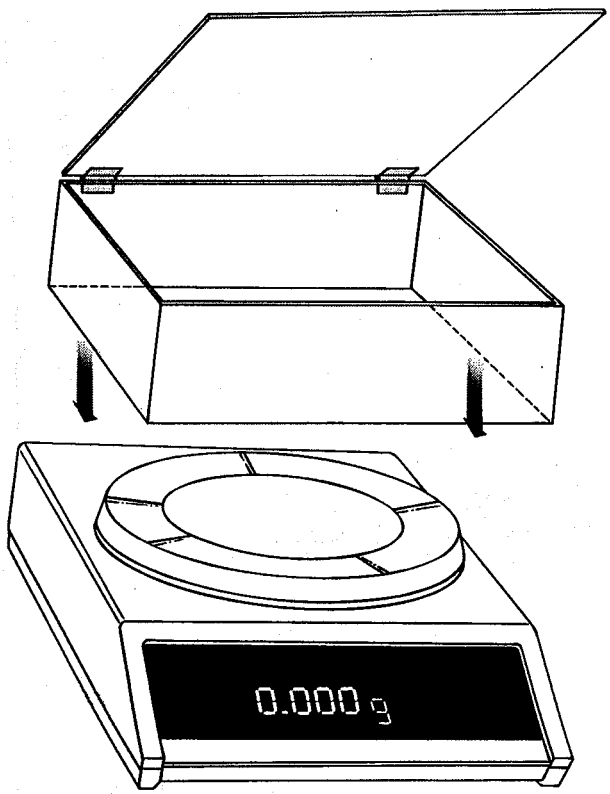

Figure 1.8 A top-loading balance with plastic draft shield.

ways 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.

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 answer to the question.

(a) 25 mL of a solvent needed for a crystallization

(b) 2.4 mL of a liquid needed for a reaction

(c) 1 mL of a solvent needed for an extraction

2. Assume that the liquid used in Question 1b is a limiting reagent for a reaction. What should you do after measuring the volume?

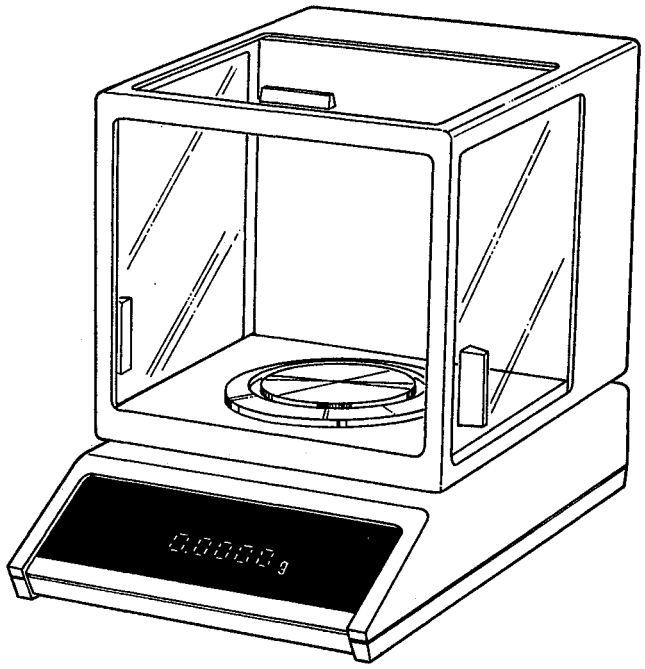

Figure 1.9 An analytical balance with glass draft shield.

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 1.46 g of acetic anhydride. Calculate the volume of this reagent needed in the reaction.

TECHNIQUE 2

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 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 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.

2.1 HEATING MANTLES

A useful source of heat for most experiments in this textbook is the heating mantle, illustrated in Figure 2.1. 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 (Section 2.3) or a steam bath (Section 2.8).

In the center of the heating mantle shown in Figure 2.1 is a well which can accomodate 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 2.2 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

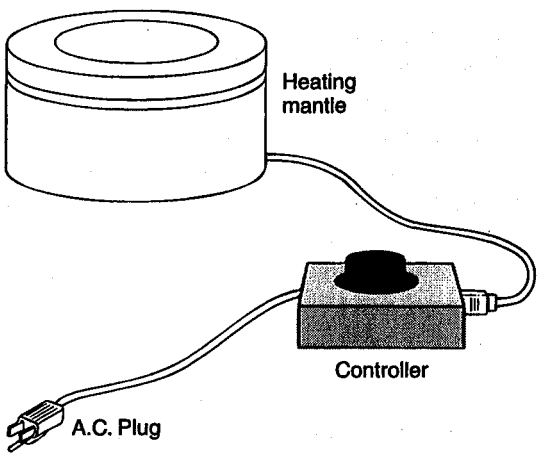

Figure 2.1 Heating mantle.

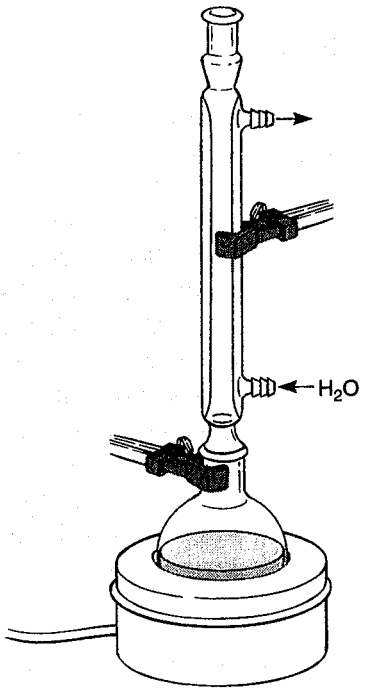

Figure 2.2 Heating with a heating mantle.

reason, the entire apparatus should be clamped above the heating mantle so that it can be raised quickly if overheating occurs. Some laboratories may provide a lab jack or blocks of wood which 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 situation from happening. The second situation occurs when one is first bringing the reaction mixture to a boil. In order 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.

2.2 HOTPLATES

Hotplates 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

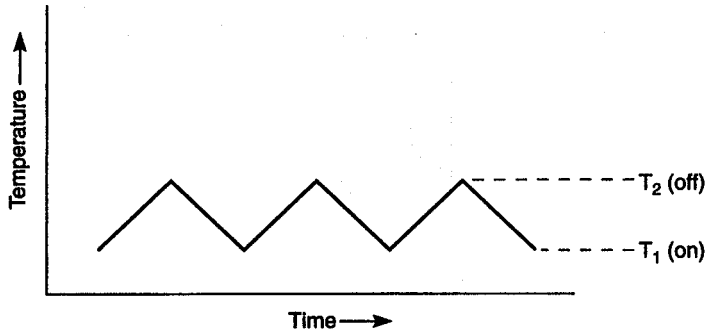

Figure 2.3 Temperature response for a hotplate with a thermostat.

taken with flammable solvents to ensure against fires caused by "flashing," when solvent vapors come into contact with the hotplate surface. One should never evaporate large quantities of a solvent by this method; the fire hazard is too large.

Some hotplates *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 hotplates have a thermostat to control the temperature. A good thermostat will maintain a very even temperature. With many hotplates, however, the temperature may vary greatly (>10°–20°C), depending upon whether the heater is in its "on" cycle or its "off" cycle. These hotplates will have a cycling (or oscillating) temperature, as shown in Figure 2.3. They too will have to be adjusted continually to maintain even heat.

Some hotplates 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 3.5, p. 621.

2.3 WATER BATH WITH HOTPLATE/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 Figure 2.4. A mixture can be stirred with a magnetic stir bar (Technique 3, Section 3.5, p. 621). 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.

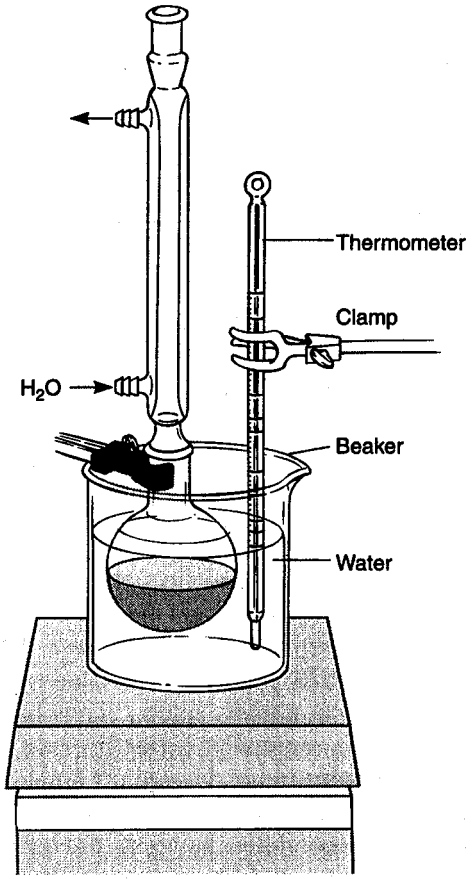

Figure 2.4 Water bath with hotplate/stirrer.

2.4 OIL BATH WITH HOTPLATE/STIRRER

In some laboratories oil baths may be available. An oil bath can be used when one is carrying out a distillation or is heating a reaction mixture that needs a temperature above 100°C. An oil bath can be heated most conveniently with a hotplate, and a *heavy-wall* beaker[1] provides a suitable container for the oil. 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.

An oil bath with ordinary mineral oil cannot be used above 200 to 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; dis-

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

continue heating. Old oil, which is dark, is more likely to flash than new oil is. Also, hot oil causes bad burns. Water should be kept away from a hot oil bath, since 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 there should be water 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 since it minimizes both storage and spillage problems. Vegetable shortening is occasionally used in heating baths.

2.5 ALUMINUM BLOCK WITH HOTPLATE/STIRRER

Although aluminum blocks are most commonly used in microscale organic laboratories, they can also be used with the smaller round-bottom flasks used in standard-scale experiments.[2] The aluminum block shown in Figure 2.5A 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 2.5B, 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 2.6 shows a reaction mixture being heated with an aluminum block on a hotplate/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.

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

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

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

Figure 2.5 Aluminum heating blocks.

As already mentioned, aluminum blocks are often used in the microscale organic laboratory. The use of an aluminum block to heat a microscale reflux apparatus is shown in Figure 2.7. The reaction vessel in the figure is a conical vial, which is used in many microscale experiments. Also shown in Figure 2.7 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.

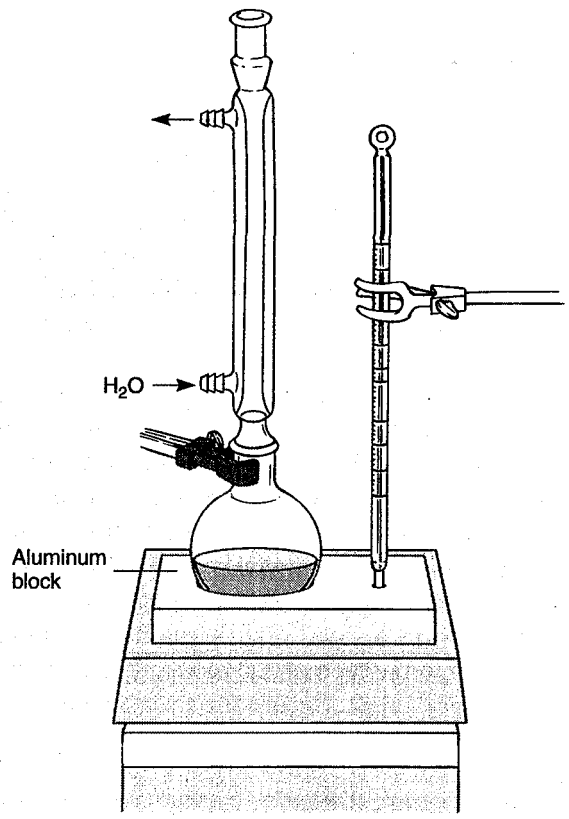


Figure 2.6 Heating with an aluminum block.

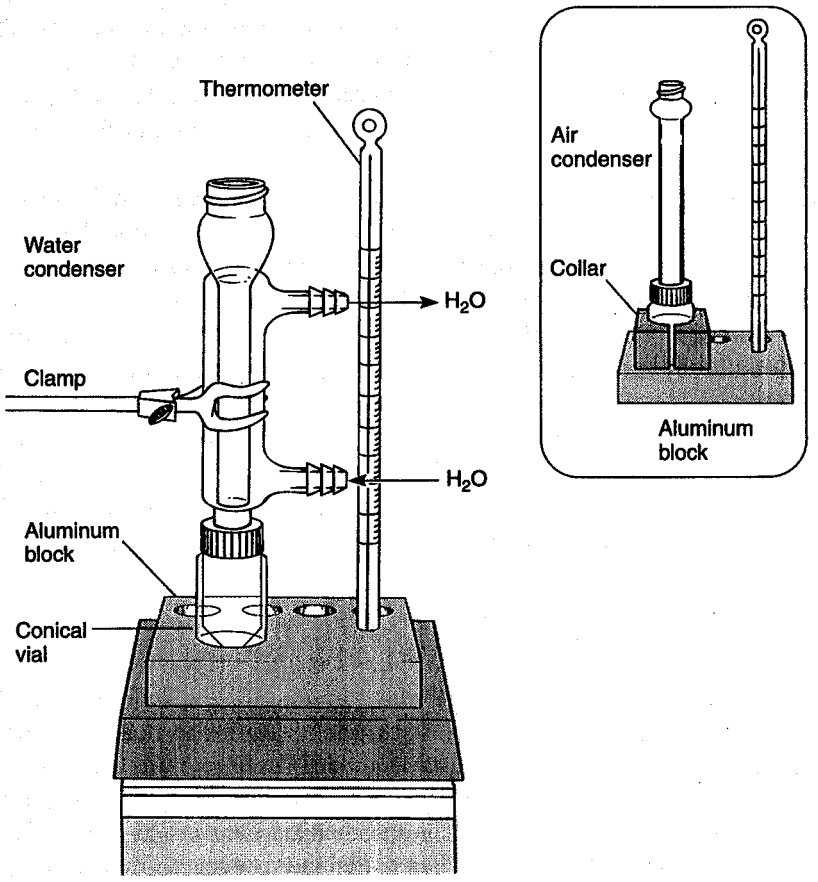


Figure 2.7 Heating with an aluminum block (microscale).

You should first calibrate the aluminum block so that you have an approximate idea where to set the control on the hotplate to achieve a desired temperature. Place the aluminum block on the hotplate 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 hotplate. 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 hotplate each time, as it is very likely that two hotplates of the same type may give different temperatures with identical settings. Record the identification number printed on the unit that you are using in your notebook to ensure that you always use the same hotplate.

[4]See, however, Technique 2, Section 2.2, p. 602.

For many experiments, you can determine what the approximate setting on the hotplate 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 (Technique 3, Fig. 3.10A, p. 621) in a round-bottom flask containing the reaction mixture as shown in Figure 2.8A. If the mixture is to be heated as well as stirred, attach a water condenser as shown in Figure 2.6. With the combination stirrer/hotplate unit, it is possible to stir and heat a mixture simultaneously. Many reactions in this textbook are stirred continuously during the course of the reaction. With conical vials, a magnetic spin vane must be used to stir mixtures (Fig. 3.10B, p. 621). This is shown in Figure 2.8B. More uniform stirring will be obtained if the flask or vial is placed in the aluminum block so that it is centered on the hotplate. Mixing may also be achieved by boiling the mixture. A boiling stone (Section 3.6, p. 621) should be added when a mixture is boiled without magnetic stirring.

2.6 SAND BATH WITH HOTPLATE/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 standard-scale experiments. Sand provides a clean way of distributing heat to a reaction mixture. To prepare a sand bath, place about a 1-cm depth of sand in a crystallizing dish and then set the dish on a hotplate/stirrer unit. The apparatus is shown in Figure 2.9. 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.

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 alu-

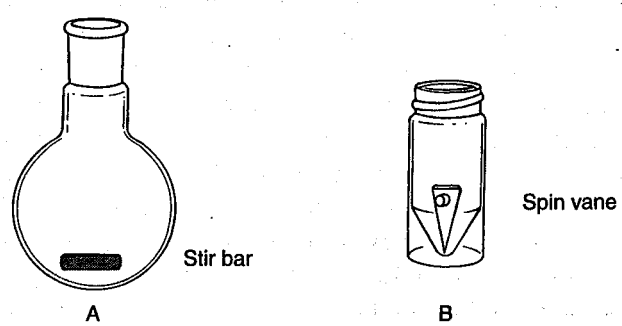


Figure 2.8 Methods of stirring in a round-bottom flask or conical vial.

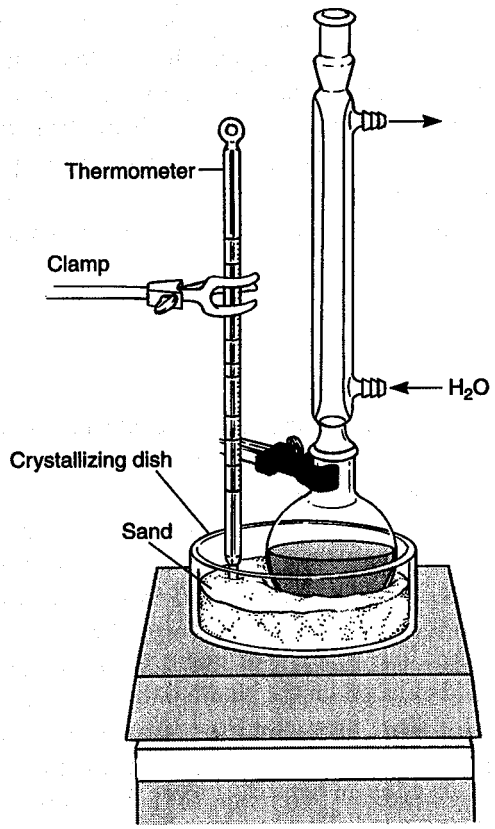


Figure 2.9 Heating with a sand bath.

minum 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 hotplate. 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 hotplate.

2.7 FLAMES

The simplest technique for heating mixtures is to use a Bunsen burner. Because of the high danger of fires, however, the use of the 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 in-

structor 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.

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.

2.8 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 2.10. 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

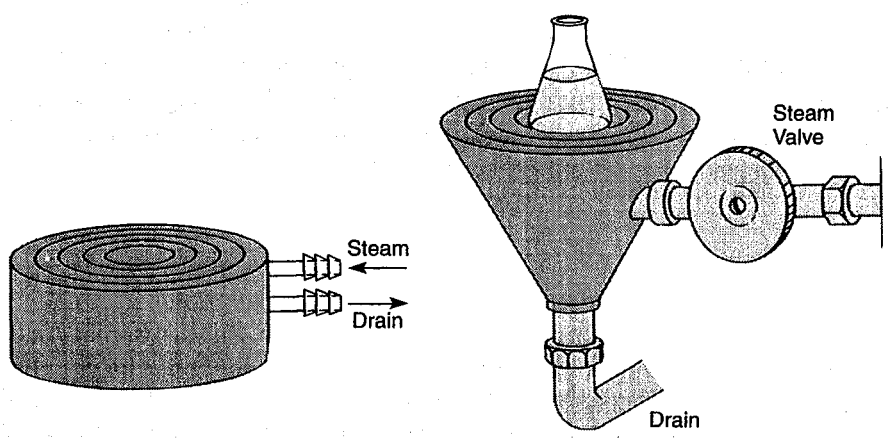


Figure 2.10 Steam bath and steam cone.

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.

2.9 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 temperatures. 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 since 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 (Technique 20, Section 20.1, p. 861). 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 (Technique 20, Section 20.1 p. 861) 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?

TECHNIQUE 3

Reaction Methods

The successful completion of an organic reaction requires the chemist to be familiar with a variety of laboratory methods. These methods include operating safely, choosing and handling solvents correctly, heating reaction mixtures, adding liquid reagents, maintaining anhydrous conditions in the reaction, and collecting gaseous products. Several techniques that are used in bringing a reaction to a successful conclusion are treated in this chapter.

3.1 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 the introductory chapter, "Laboratory Safety."

Read "Laboratory Safety," pages 5–22.

TABLE 3.1. Common Organic Solvents

Solvent	bp (°C)	Solvent	bp (°C)
Hydrocarbons		Ethers	
Pentane	36	**Ether** (Diethyl)	35
Hexane	69	**Dioxane***	101
Benzene*	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*	61	Dimethylformamide	153
Carbon tetrachloride*	77	Dimethylsulfoxide	189
Alcohols			
Methanol	65		
Ethanol	78		
Isopropyl alcohol	82		

NOTE: Boldface type indicates flammability.

*Suspect carcinogen (see p. 21).

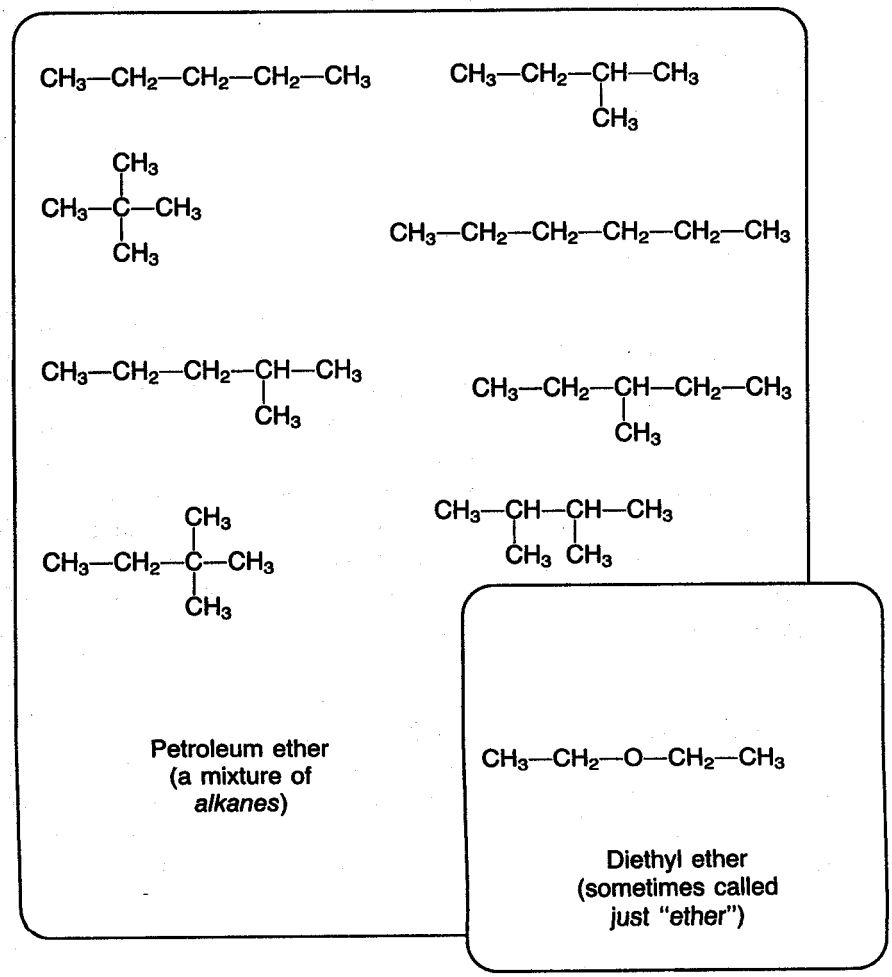


Figure 3.1 A comparison between "ether" (diethyl ether) and "petroleum ether."

The most common organic solvents are listed in Table 3.1 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 3.1 shows some of the hydrocarbons that appear commonly in petroleum 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.

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. While 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.

3.2 GROUND-GLASS JOINTS

The glassware in your organic kit has **standard-taper ground-glass joints.** For example, the Claisen head in Figure 3.2 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 ℑ followed by two numbers. A common joint size in standard-scale glassware is ℑ 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 Fig. 3.2). 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 apparatus. One disadvantage of glassware with ground-glass joints, however, is that it is very expensive.

It is important to make sure no solid is on the joint surfaces. Such material will lessen the efficiency of the seal, and the joints may leak. 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 them with a cloth or lint-free paper towel before assembling. It is sometimes advisable to lubricate joints lightly with stopcock grease before assembling them (see p. 34).

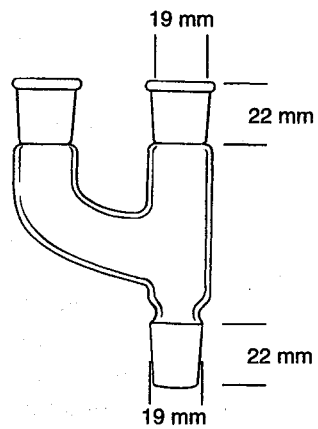


Figure 3.2 Illustration of ℑ 19/22 inner and outer joints showing dimensions.

The most important thing you can do to prevent ground-glass joints from becoming "frozen" or stuck together 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 flasks. 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, see page 34 for other options.

3.3 ASSEMBLING THE APPARATUS

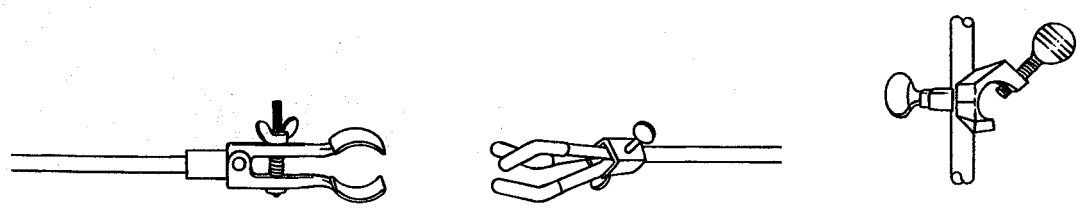
Care must be taken when assembling the glass components into the desired apparatus. You should always remember that Newtonian physics applies to chemical apparatus, and unsecured pieces of glassware are certain to respond to gravity.

Assembling an apparatus in the correct manner requires that the individual pieces of glassware are connected to each other securely and 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 3.3. 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 3.3C.

Securing Standard-Scale 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 3.4. It is held together securely



A. Extension clamp B. Three finger clamp C. Clamp holder

Figure 3.3 Adjustable metal clamps.

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 one must 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 3.5A. 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 3.5B. 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 3.6 shows the same distillation apparatus held in place with both adjustable metal clamps and plastic joint clips.

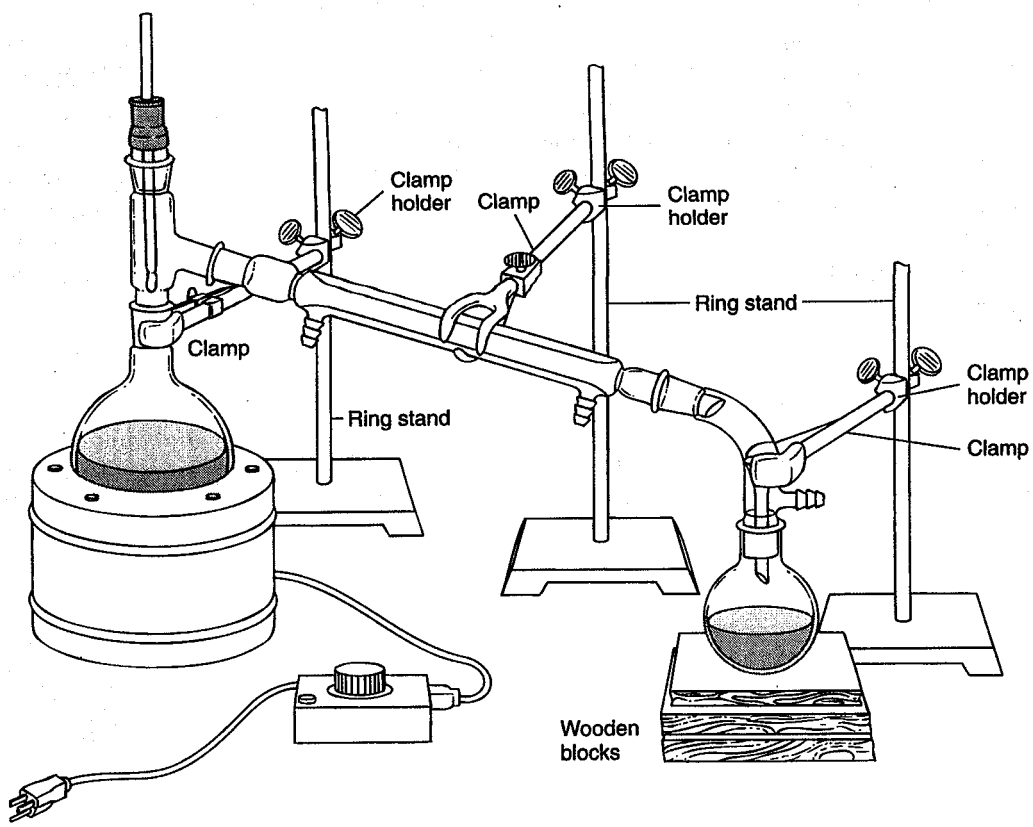


Figure 3.4 Distillation apparatus secured with metal clamps.

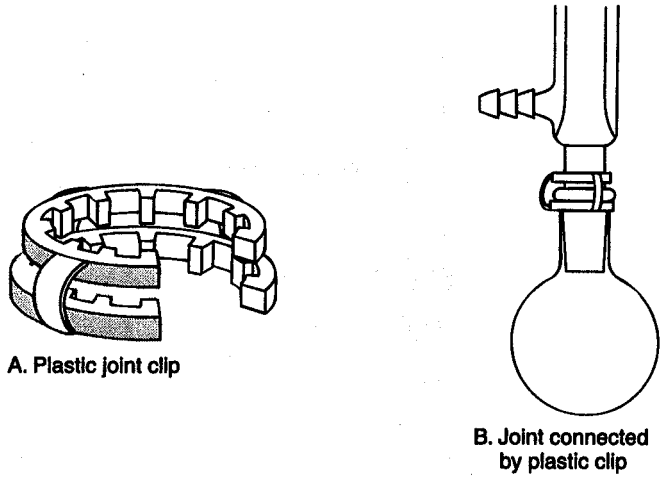


Figure 3.5 Plastic joint clip.

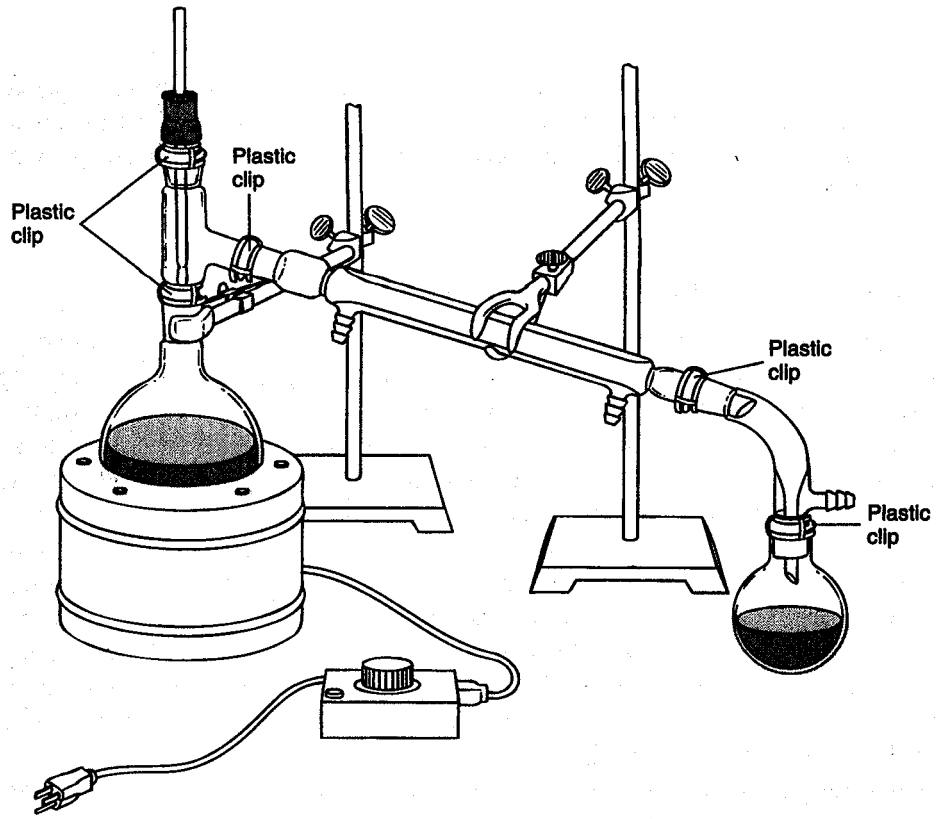


Figure 3.6 Distillation apparatus secured with metal clamps and plastic joint clips.

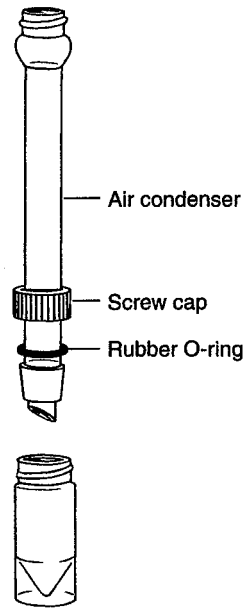


Figure 3.7 A microscale standard-taper joint assembly.

To assemble this apparatus, one would 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.

Securing Microscale Apparatus Assemblies

The glassware in most microscale kits is made with standard-taper ground joints. The most common joint size is ₹ 14/10. Some microscale glassware with ground-glass joints also has threads cast into the outside surface of the outer joints (see top of air condenser in Figure 3.7). 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 3.7). 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 air-tight. 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.

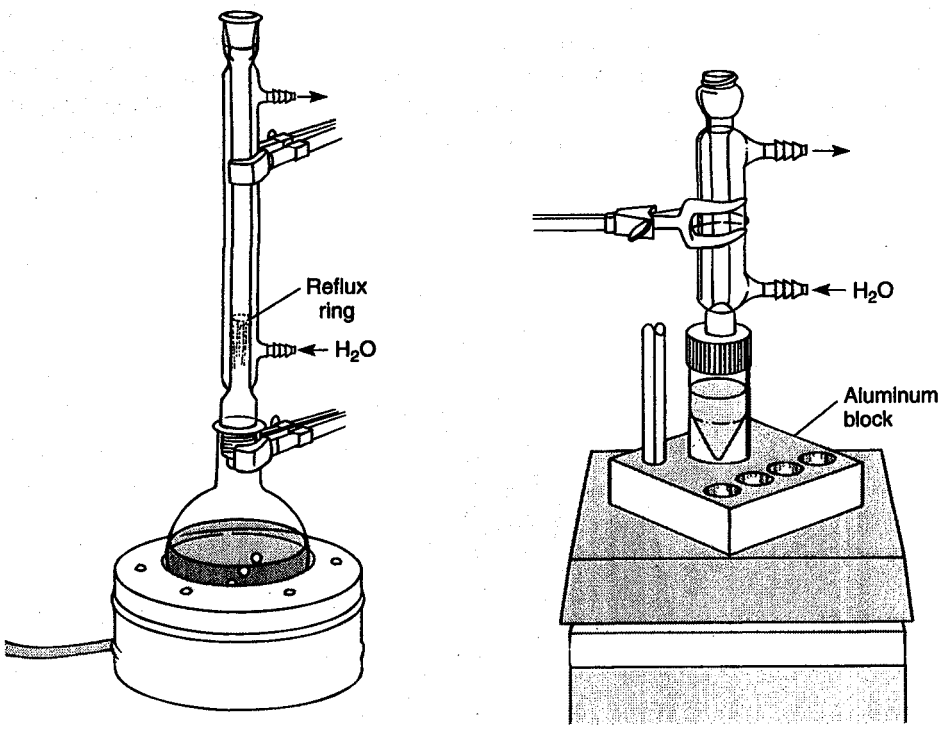
Microscale glassware connected together in this fashion can be assembled very easily. The entire apparatus is held together securely, and usually only one metal clamp is required to hold the apparatus onto a ring stand.

3.4 HEATING UNDER REFLUX

Often we wish to heat a mixture for a long time and to leave it untended. A **reflux apparatus** (see Fig. 3.8) allows such heating. It also keeps the solvent from being lost by evaporation. A condenser is attached to the boiling flask.

Condenser. The **water-jacketed condenser** shown in the figure 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. The figure also shows a typical microscale apparatus for heating small quantities of material under reflux (Fig. 3.8B).

When using a water-jacketed condenser, the direction of the water flow should be 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



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

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

Figure 3.8 Heating under reflux.

rubber tubing securely with wire to the condenser. If a flame is used as a source of heat (see Cautions, p. 609), 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 3.5 and 3.6) to keep the solution from "bumping" (see next section).

Rate of Heating. If the heating rate has been correctly adjusted, the liquid being heated under reflux will travel only part way 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 3.8A. In heating under reflux, the rate of heating should be adjusted so that the reflux ring is no higher than a third to a half 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 standard-scale 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 Fig. 3.9) 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.

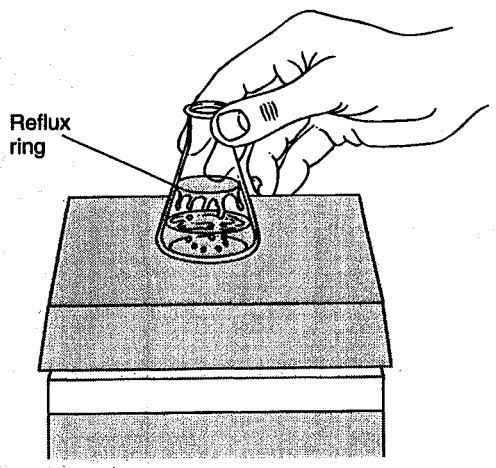


Figure 3.9 Tended reflux of small quantities on a hotplate.

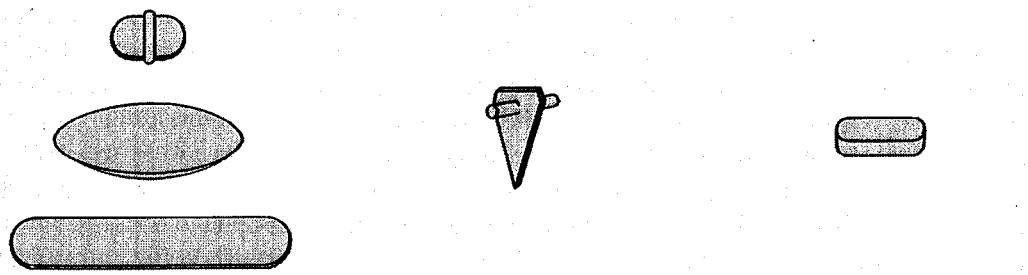
3.5 STIRRING METHODS

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 it brings with it the risk that material may be lost from the apparatus, that a fire might 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 hotplate. This type of hotplate-stirrer permits one to heat the reaction and stir it simultaneously.

Magnetic stirring bars are available in several sizes and shapes. For standard-scale 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 3.10.

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 3.10 Magnetic stirring bars.

3.6 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 breaks 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 chip. Carborundum boiling stones are more inert and the pieces are usually quite small, suitable for most small-scale 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.

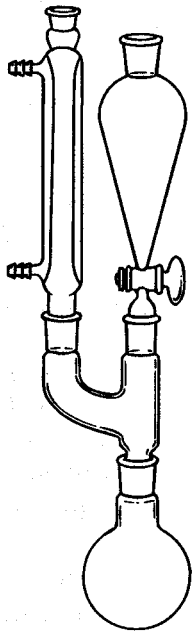
Because boiling stones act to promote the smooth boiling of liquids, you should always make certain that a boiling stone has been placed in a liquid *before* heating is begun. If you wait until the liquid is hot, it may have become superheated. Adding a boiling stone to a superheated liquid will cause 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.

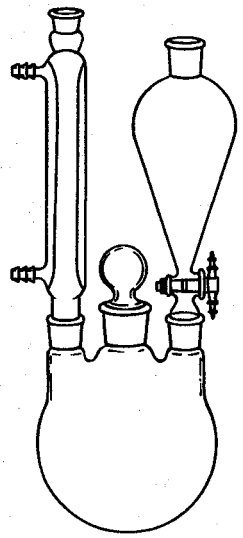
Wooden applicator sticks are used in some applications. They function in the same manner as boiling stones. Occasionally, glass beads are used. Their presence also causes sufficient turbulence in the liquid to prevent bumping.

3.7 ADDITION OF LIQUID REAGENTS

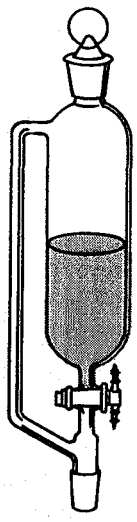
Liquid reagents and solutions are added to a reaction by several means, some of which are shown in Figure 3.11. The most common type of assembly for standard-scale experiments is shown in Figure 3.11A. In this apparatus, a separatory funnel is attached to the sidearm of a Claisen head adapter. The separatory 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 3.8) may be attached to the upper 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



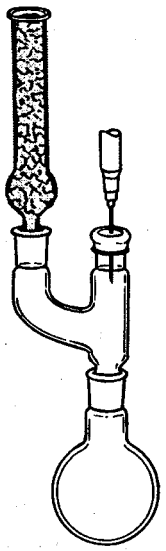
A. Standard-scale equipment, using a separatory funnel as an addition funnel.



B. Standard-scale, for larger amounts.



C. A pressure equalizing addition funnel.



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

Figure 3.11 Methods for adding liquid reagents to a reaction.

reactions that are particularly sensitive to moisture, it is also advisable to attach a second drying tube to the top of the condenser.

Another standard-scale assembly, suitable for larger amounts of material, is shown in Figure 3.11B. Drying tubes may also be used with this apparatus to prevent contamination from atmospheric moisture.

Figure 3.11C 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.

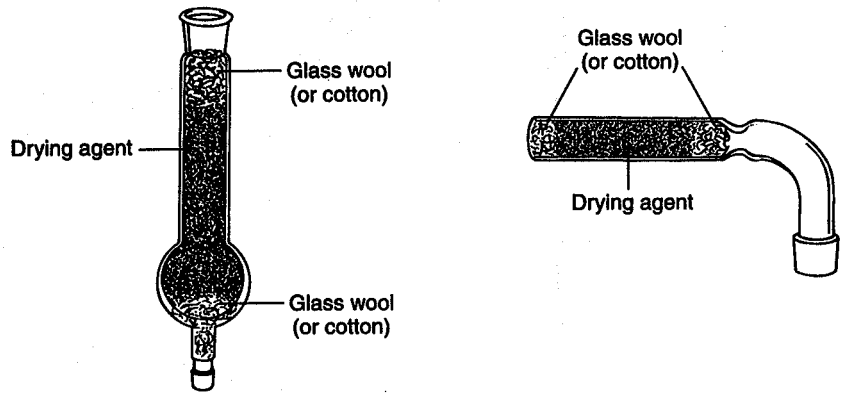
With either type of standard-scale addition funnel, you can control the rate of addition of the liquid by carefully adjusting the stopcock. Even after careful adjustment, changes in pressure can occur, causing the flow rate to change. In some cases, the stopcock can become clogged. It is important, therefore, 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 3.11D, is suitable for use in microscale and some standard-scale experiments where 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 where anhydrous conditions must be maintained. The drying tube is used to protect the reaction mixture from atmospheric moisture.

3.8 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 3.12. 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 7, Section 7.8, p. 696), is poured on top of the plug to the approximate depth shown in Figure 3.12. 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.



A. Standard-sized drying tube.

B. Microscale drying tube.

Figure 3.12 Drying tubes.

3.9 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 standard-scale 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 3.13.

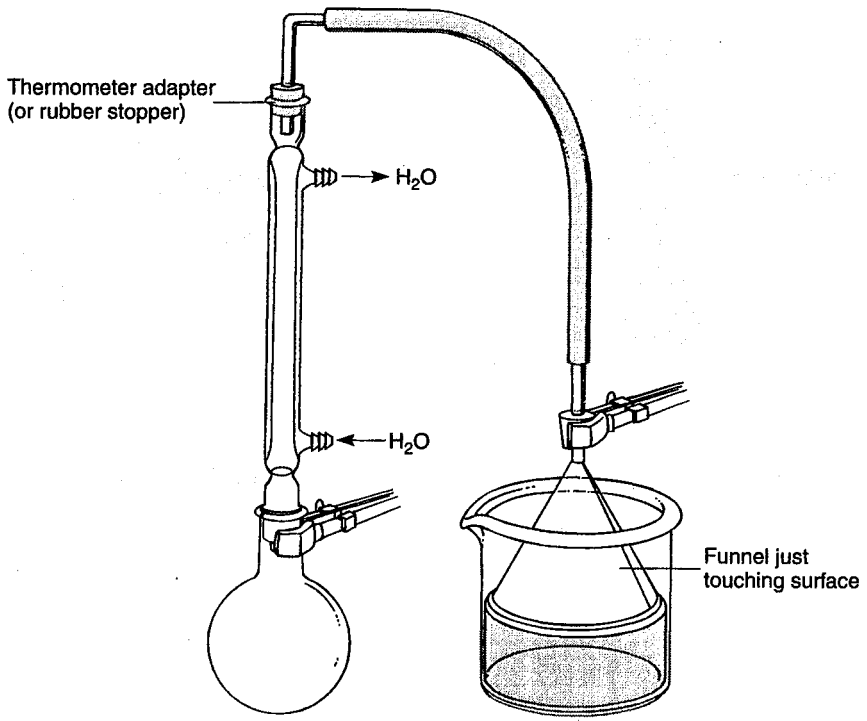


Figure 3.13 Inverted-funnel gas trap.

One method that works well for standard-scale 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 is 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 3.14.

B. DRYING-TUBE METHOD

Some standard-scale 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 water solubility of corrosive gases such as hydrogen chloride, hydrogen bromide, and sulfur dioxide. A simple technique is to attach the drying tube (see Fig. 3.12) 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

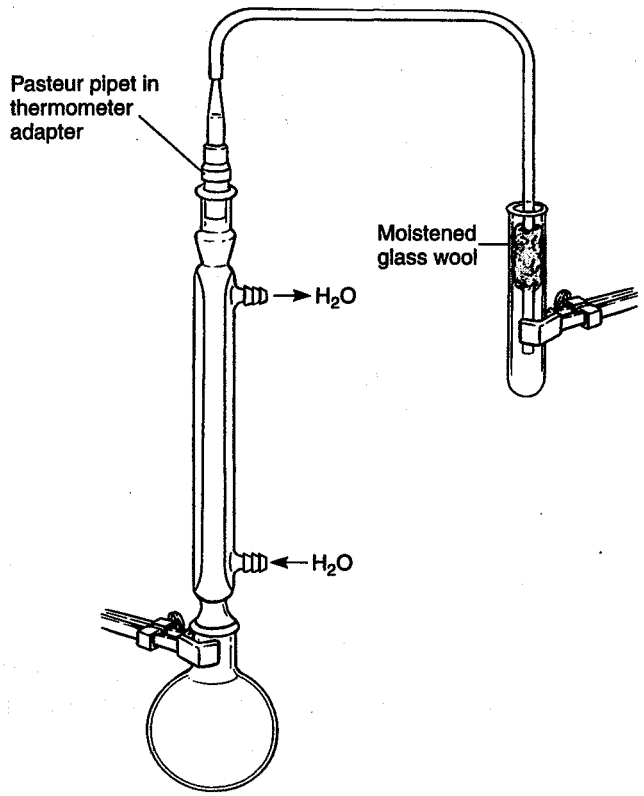


Figure 3.14 External gas trap.

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 Fig. 3.12B). 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 3.12A as a gas trap and it is essential that water not be allowed to enter the reaction flask, the modification shown in Figure 3.15 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

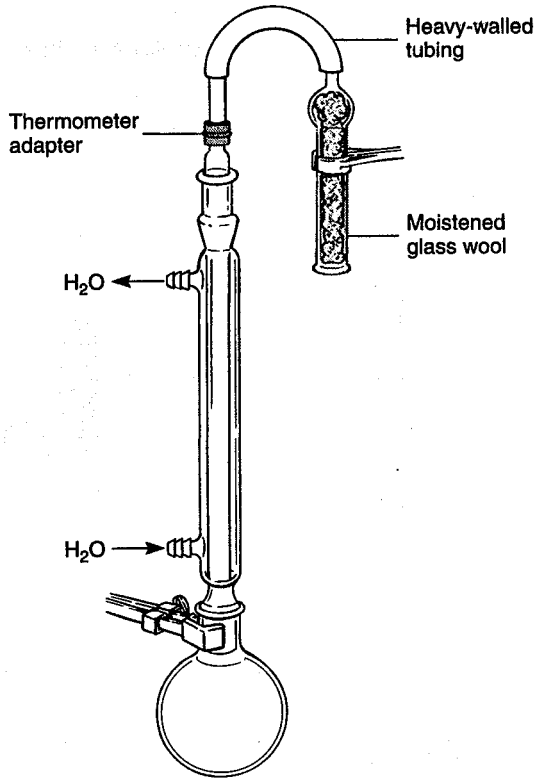


Figure 3.15 Drying tube used to capture evolved gases.

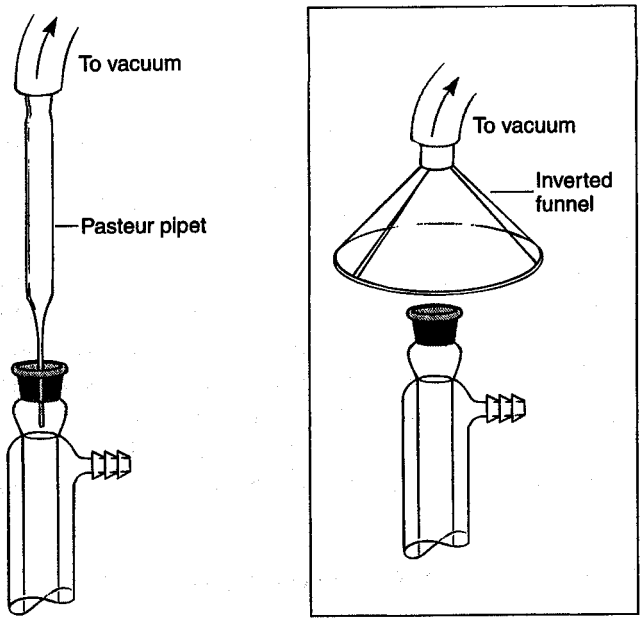


Figure 3.16 Removal of noxious gases under vacuum. (The inset shows an alternative assembly, using an inverted funnel in place of the Pasteur pipet.)

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 3.16. In the special case where 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.

3.10 COLLECTING GASEOUS PRODUCTS

In Section 3.9, means of 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 3.17. 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 14).

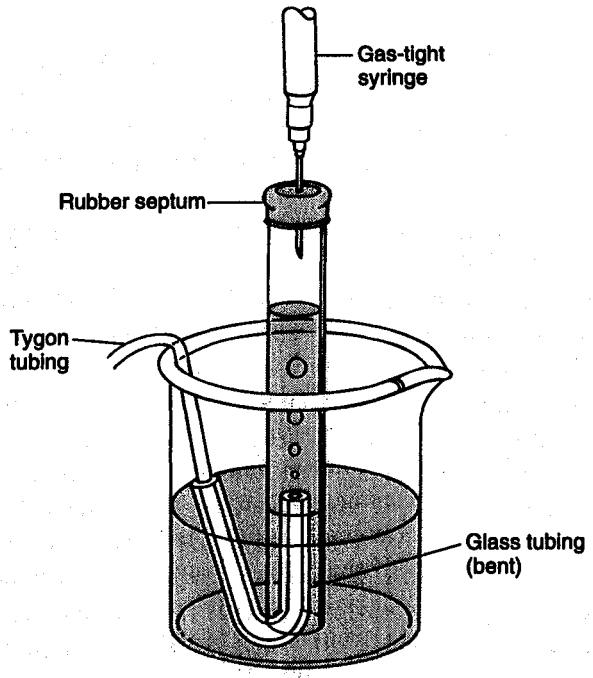


Figure 3.17 Gas collection tube, with rubber septum.

In Figure 3.17, 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.

3.11 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.

This can be done by evaporating the solvent from an open Erlenmeyer flask (Fig. 3.18A and B). Such an evaporation must be conducted in a hood, since many solvent vapors are toxic or flammable. A boiling 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 (Fig. 3.18A). A tube or an inverted funnel connected to an aspirator may also be used (Fig. 3.18B). In this case, vapors are removed by suction. It is better to use an Erlenmeyer flask than a beaker for this procedure, since 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 hotplate 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 hotplate surface.

It is also possible to remove low-boiling solvents under reduced pressure (Figure 3.18C). In this method, the solution is placed in a filter flask, along with a wooden applicator stick. The flask is stoppered, and the sidearm is connected to an aspirator (by a trap), as described in Technique 4, Section 4.3, p. 640. Under reduced pressure, the solvent begins to boil. The wooden stick serves the same function as a boiling stone. By this method, solvent 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. Since 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.

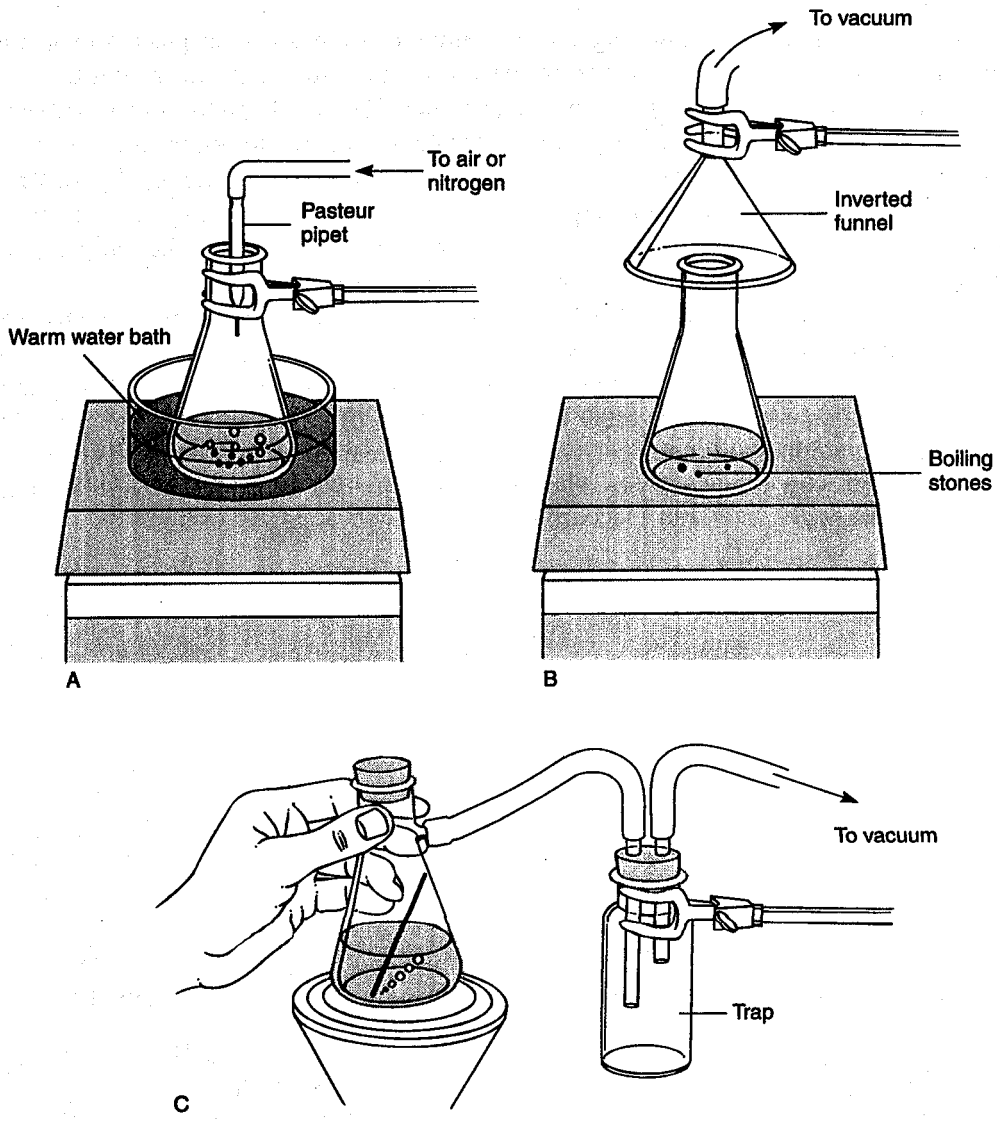


Figure 3.18 Evaporation of solvents (heat source can be varied among those shown.)

Large amounts of a solvent should be removed by distillation (see Technique 8). **One should 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.

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 (Fig. 3.19A). 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 (Fig. 3.19B). 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 hotplate for use in the evaporation of small amounts of solvent.

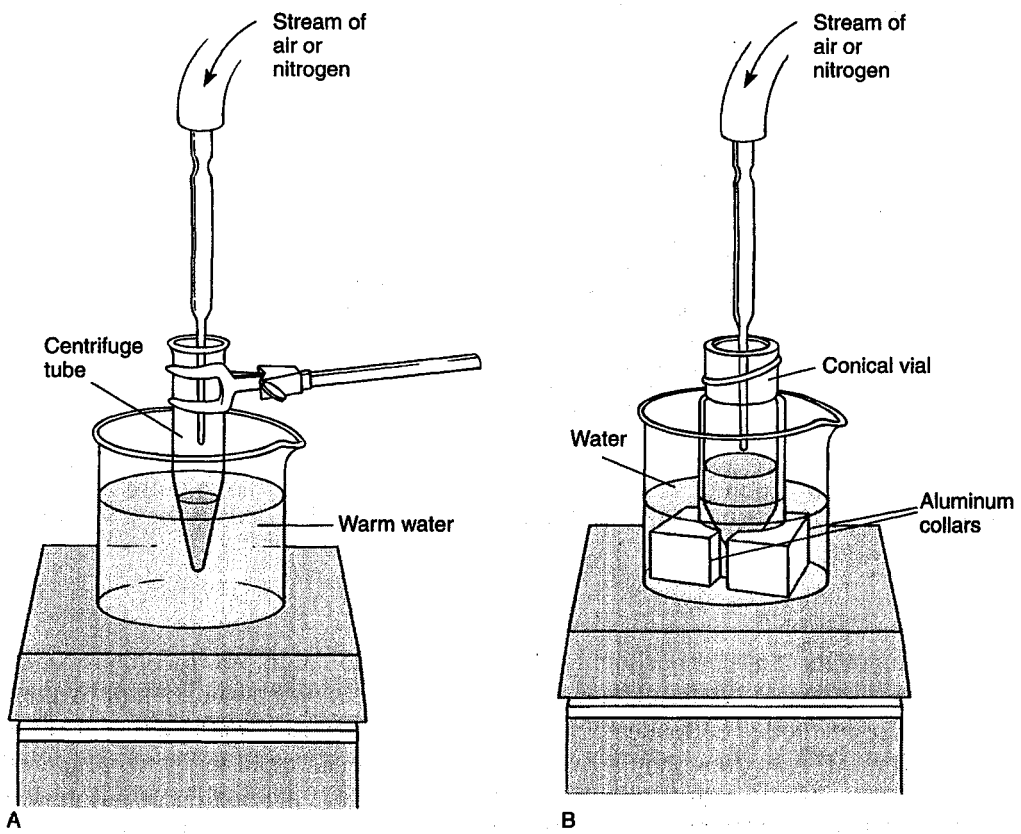


Figure 3.19 Evaporation of solvents (small-scale methods).

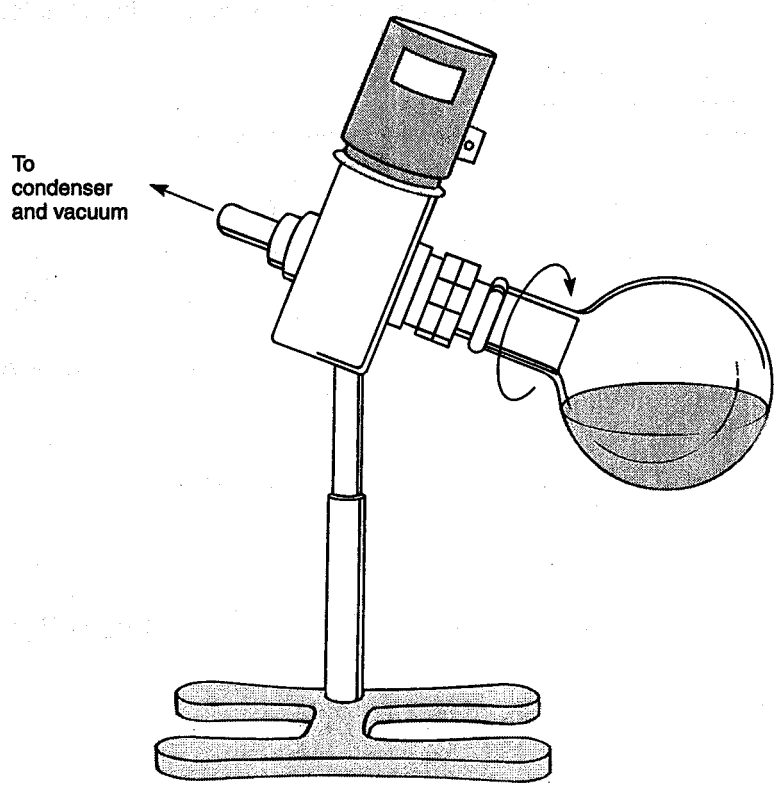


Figure 3.20 Rotary evaporator.

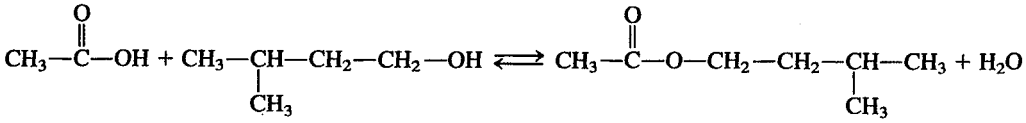
3.12 ROTARY EVAPORATOR

In the research laboratory, solvents are evaporated under reduced pressure using a **rotary evaporator.** This is a motor-driven device, which 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. This 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. A rotary evaporator is shown in Figure 3.20.

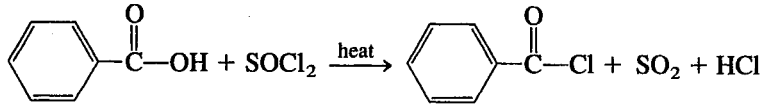
PROBLEMS

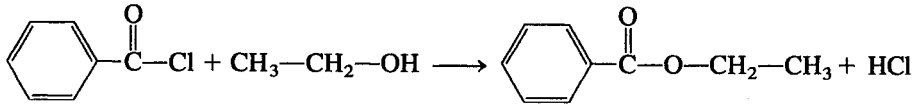
1. What is the difference between
   (a) ether and petroleum ether?
   (b) ether and diethyl ether?
   (c) ligroin and petroleum ether?

2. What is the best type of stirring device to use for stirring a reaction that takes place in
   (a) a conical vial?
   (b) a 10-mL round-bottom flask?
   (c) a 250-mL round-bottom flask?
3. Should you use a drying tube for the following reaction? Explain.

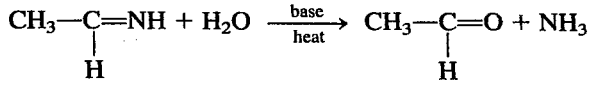


4. For which of the following reactions should you use a trap to collect noxious gases?

(a) 

(b) 

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

(d) 

TECHNIQUE 4

Filtration

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 are commonly used: two general methods include gravity filtration and vacuum (or suction) filtration. The various filtration techniques and their applications are summarized in Table 4.1. These techniques are discussed in more detail in the following sections.

4.1 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. This technique is useful only when the volume of mixture to be filtered is greater than 10 mL. For

TABLE 4.1. 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.	4.1A
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.	4.1B
Filtering pipets	Used with volumes less than about 10 mL to remove solid impurities from a liquid.	4.1C
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.	4.3
Hirsch funnels	Used in the same way as Büchner funnels, except the volume of liquid is usually smaller (1–10 mL)	4.3
FILTERING MEDIA	Used to remove finely divided impurities.	4.4
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.	4.6
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.	4.7
CENTRIFUGATION	Although not strictly a filtration technique, centrifugation may be used to remove suspended impurities from a liquid (1–25 mL).	4.8

some small-scale 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 only when a relatively large volume (greater than 10 mL) is being filtered and when a Büchner funnel (Section 4.3) is not appropriate.

The filter cone is prepared as indicated in Figure 4.1. 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 alter-

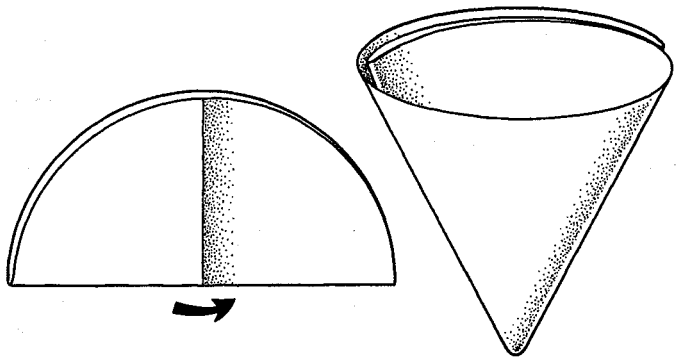


Figure 4.1 Folding a filter cone.

native, you can support the funnel by a clamp fixed *above* the flask, rather than by placing it on the neck of the flask. A gravity filtration using a filter cone is shown in Figure 4.2.

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 4.3. An advantage of a fluted filter is that it increases the speed of filtration, which occurs for two reasons.

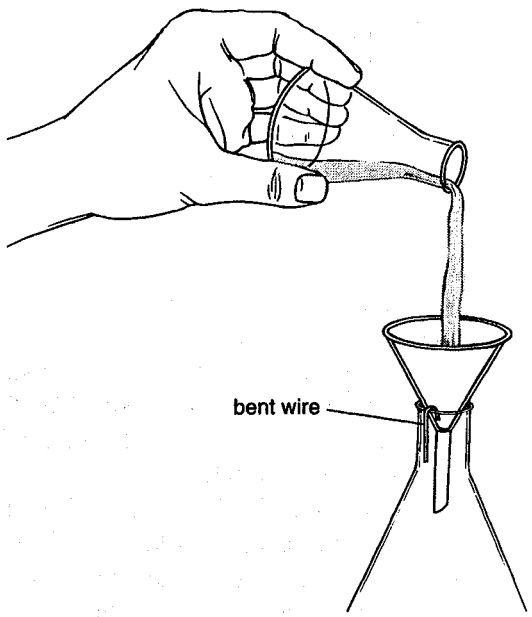


Figure 4.2 Gravity filtration with a filter cone.

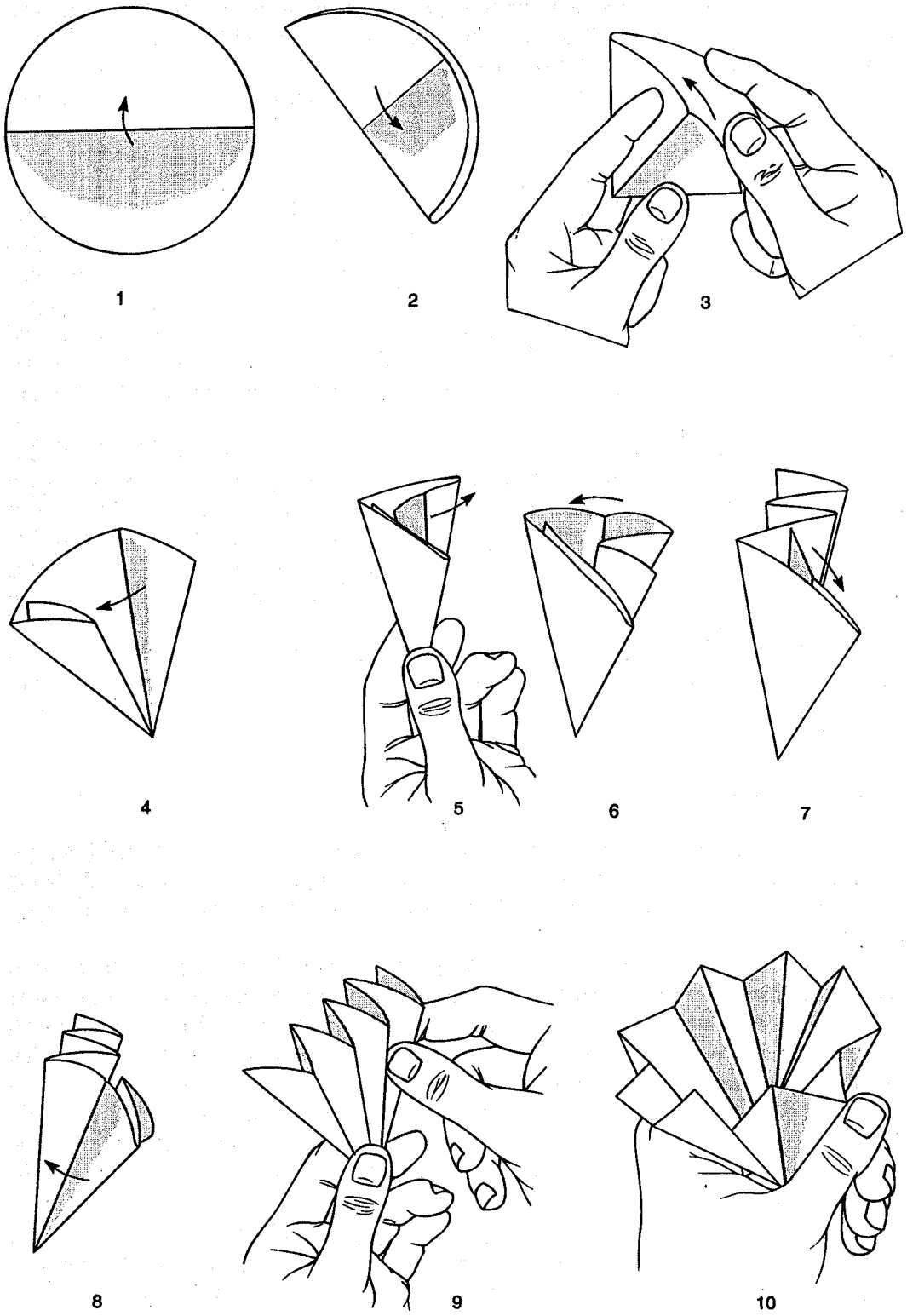


Figure 4.3 Folding a fluted filter paper, or origami at work in the organic lab.

First, 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 a 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 hotplate, 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.

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 4.4. It is important that enough cotton is used 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 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

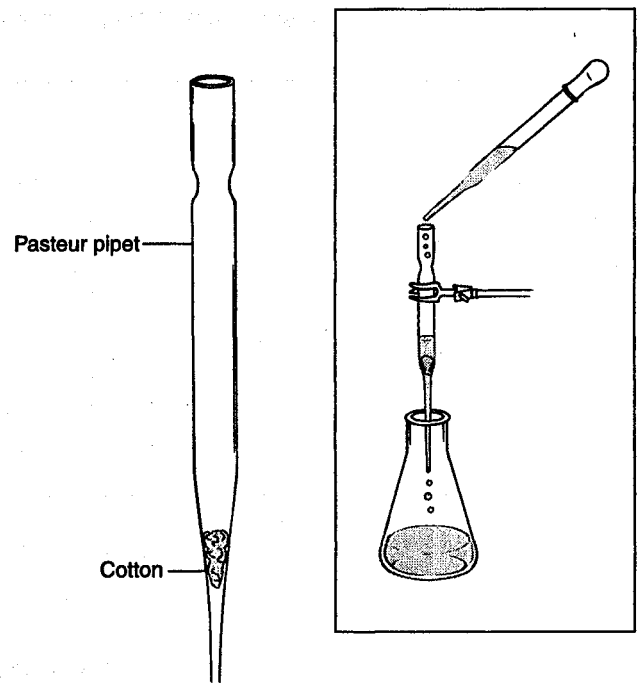


Figure 4.4 Filtering pipet.

wool is that the fibers do not pack together as tightly, and small particles will pass through the filter more easily.

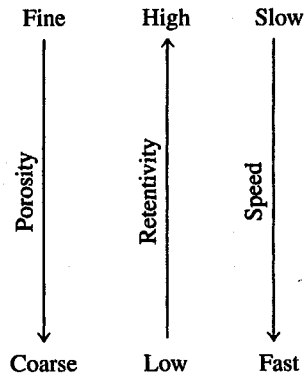
To conduct a filtration (with either a cotton or glass wool plug), the filtering pipet is clamped so that the filtrate will drain into an appropriate container. The mixture to be filtered is usually transferred to the filtering pipet with another Pasteur pipet. If a small volume of liquid is being filtered (less than 1 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 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 the one already used.

4.2 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.

TABLE 4.2. Some Common Qualitative Filter Paper Types and Approximate Relative Speeds and Retentivities



Speed	Type (by number)		
	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

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. Since 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 4.2 compares some commonly available qualitative filter paper types and ranks them according to porosity, retentivity, and speed. Eaton-Dikeman (E&D), 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.

4.3 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 (Section 4.7) is the preferred technique. In a vacuum filtration, a receiver flask with a sidearm, a **filter flask,** is used. For small-scale laboratory work, the most useful sizes of filter flasks range from 50 mL to 500 mL, depending on the volume of liquid being filtered. The sidearm is connected by *heavy-walled* rubber tubing (see Technique 9, Fig. 9.2, p. 720) 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 should be clamped, as shown in Figure 4.5.

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. Büchner funnels are usually made from polypropylene or porcelain. A Büchner funnel (see Fig. 4.5) is sealed 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 unfiltered mixture from passing around the edges of the filter paper.

The **Hirsch funnel,** which is shown in Figure 4.5B and C, operates on the same principle as the Büchner funnel, but it is usually smaller and its sides are sloped rather

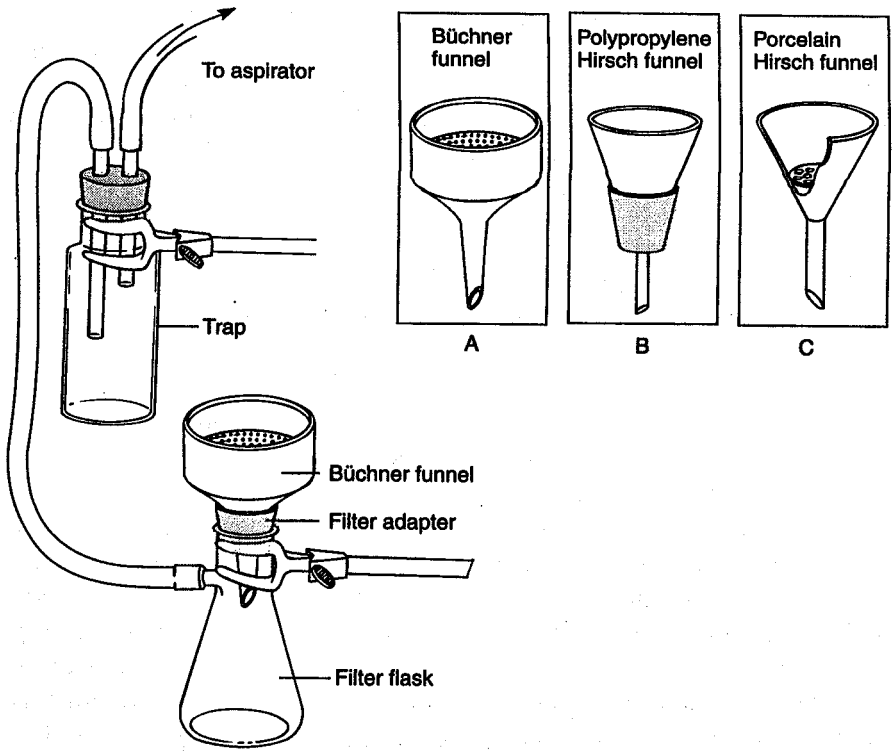


Figure 4.5 Vacuum filtration.

than vertical. The polypropylene Hirsch funnel (see Fig. 4.5B) is sealed to a 50-mL filter flask by a small section of Gooch tubing. 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, a vacuum filtration is generally not used to separate fine particles such as decolorizing charcoal, since 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 4.4).

4.4 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 they 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: 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.

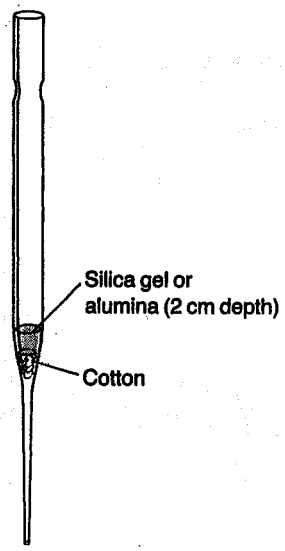


Figure 4.6 Pasteur pipet with filtering media.

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 4.6.

4.5 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 4.7. This device passes water rapidly past a small hole to which a sidearm is attached. The water pulls air in

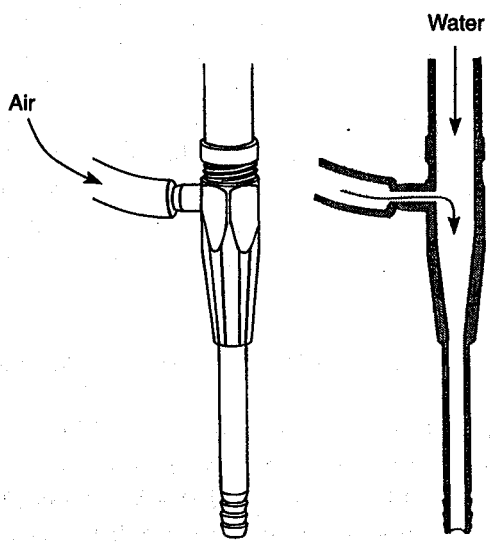


Figure 4.7 Aspirator.

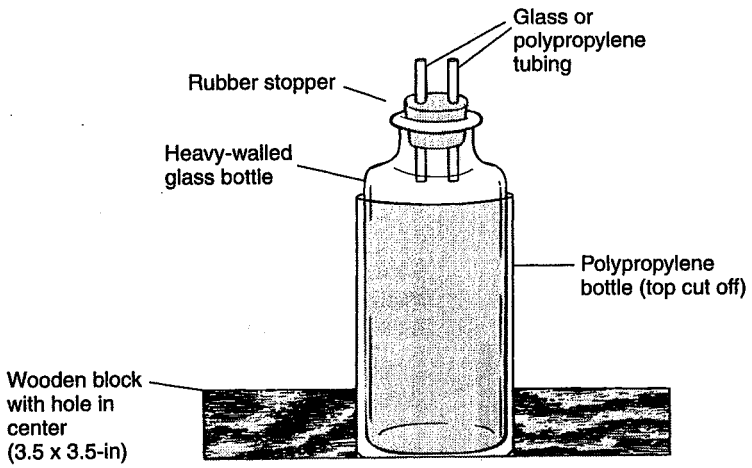


Figure 4.8 Simple aspirator trap and holder.

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.

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 4.5. Another method for securing this type of trap is shown in Figure 4.8. 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.

Always disconnect the tubing before stopping the aspirator.

If a "back-up" 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.

4.6 FILTER-TIP PIPET

The filter-tip pipet, illustrated in Figure 4.9, 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). A filter-tip pipet is very useful for removing small particles from solutions of samples prepared for NMR analysis. It can also be helpful when using a Pasteur pipet to transfer a highly volatile liquid, especially during an extraction procedure (see Technique 7, Section 7.6, p. 693).

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, the ball of cotton is pushed 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

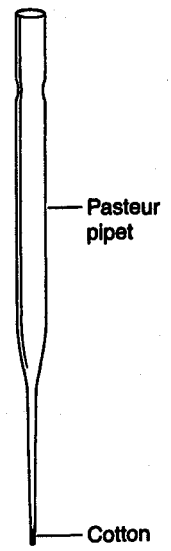


Figure 4.9 Filter-tip pipet.

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 that you can control the movement of liquid in the Pasteur pipet more easily.

4.7 CRAIG TUBES

The **Craig tube,** illustrated in Figure 4.10, is used primarily to separate crystals from a solution after a microscale crystallization procedure has been performed (Technique 5, Section 5.4, p. 658). 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 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 where the solution is separated from the crystals.

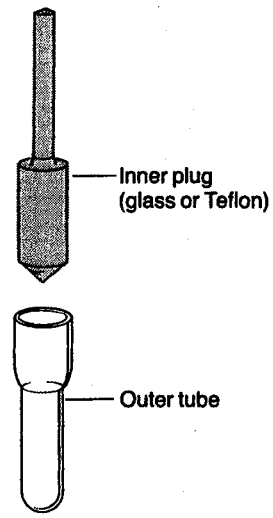


Figure 4.10 Craig tube (2 mL).

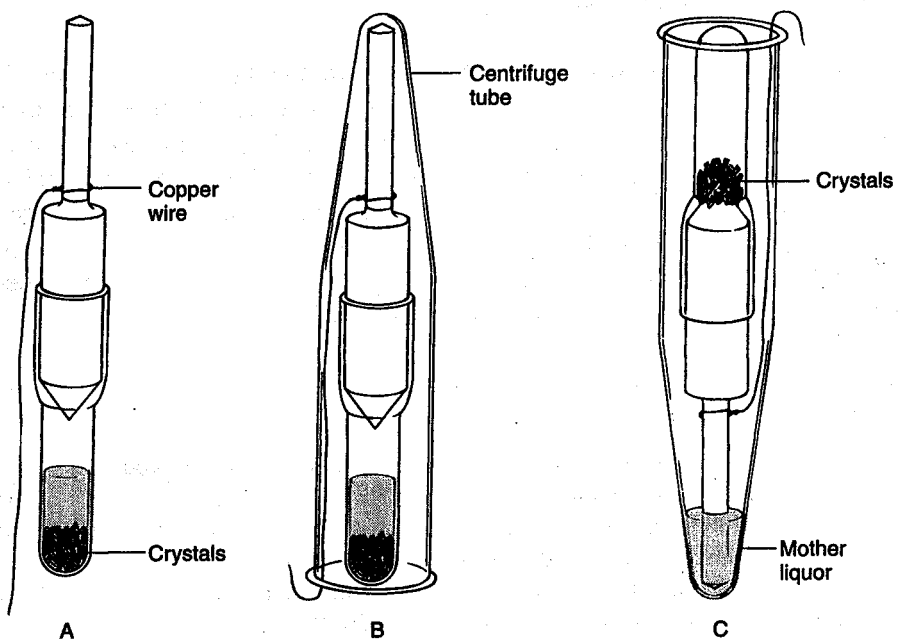


Figure 4.11 Separation with a Craig tube.

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 4.11A. While holding the Craig tube in an upright position, a plastic centrifuge tube is placed over the Craig tube so that the bottom of the centrifuge tube rests on top of the inner plug, as shown in Figure 4.11B. 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 Fig. 4.11C). 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. 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.

Using the copper wire, the Craig tube is then pulled out of the centrifuge tube. If the crystals 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.

4.8 CENTRIFUGATION

Sometimes centrifugation is more effective in removing solid impurities than are conventional filtration techniques. Centrifugation is particularly effective in removing suspended particles which are so small that the particles would pass through most filtering devices. Another situation in which centrifugation may be useful is 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.

PROBLEMS

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.

TECHNIQUE 5

Crystallization: Purification of Solids

Organic compounds that are solid at room temperature are usually purified by 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.

The method of crystallization described in detail in this chapter is called **standard-scale 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 5.4.

5.1 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 the 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 5.1. A curve with a low slope (line B, Fig. 5.1) 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, Fig. 5.1) 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 behavior shown in line A is an ideal crystallization solvent.

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 it is nonpolar, a nonpolar solvent is needed. Usually, compounds having functional groups that can form hydrogen bonds (for example, —OH, —NH—, —COOH, —CONH—) will be more soluble in hydroxylic solvents such as water or methanol than in hydrocarbon solvents such as toluene or hexane. However, if the functional group is not a major part of the molecules, this solubility behavior may be reversed. For instance, dodecyl alcohol $CH_3(CH_2)_{10}CH_2OH$ is almost insoluble in water; its 12-carbon chain causes it to behave more like a hydrocarbon than an alcohol. The list in Table 5.1 gives an approximate order for decreasing polarity of organic functional groups.

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.

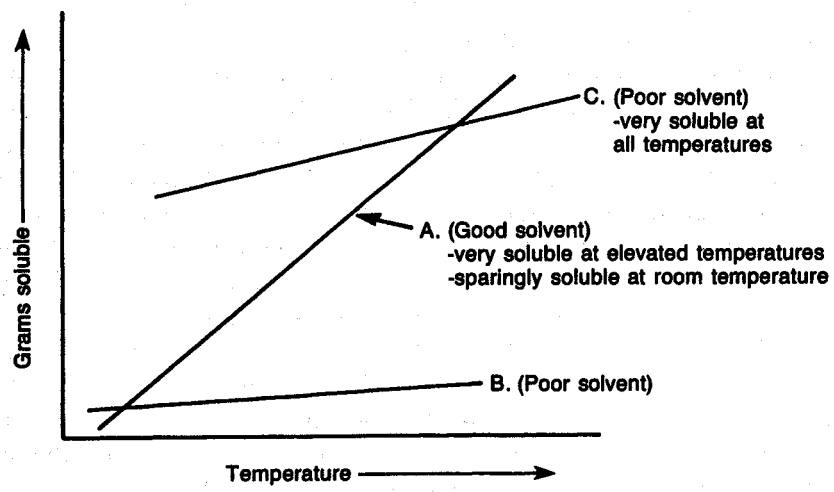


Figure 5.1 Graph of solubility vs. temperature.

TABLE 5.1. Solvents, in Decreasing Order of Polarity

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

5.2 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 an impure sample of A, the composition is given to be 9 g of A and 2 g of B for this particular example. 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. One hundred mL of solvent is used in each crystallization to make the calculations easier to understand. 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 5.2. 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 5.2. 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

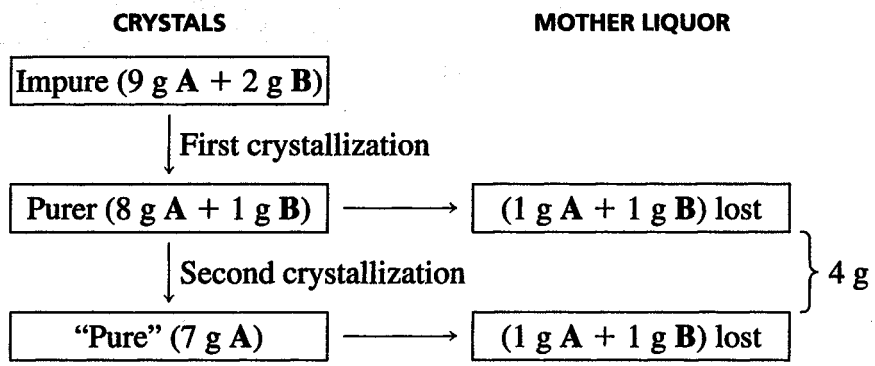


Figure 5.2 Purification of a mixture by crystallization.

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 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 in this book, 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.

5.3 STANDARD-SCALE CRYSTALLIZATION—BÜCHNER FUNNEL

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

1. Dissolving the solid
2. Removing insoluble impurities (when necessary)
3. Crystallization
4. Isolation of crystals

These steps are illustrated in Figure 5.3. 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 5.4).

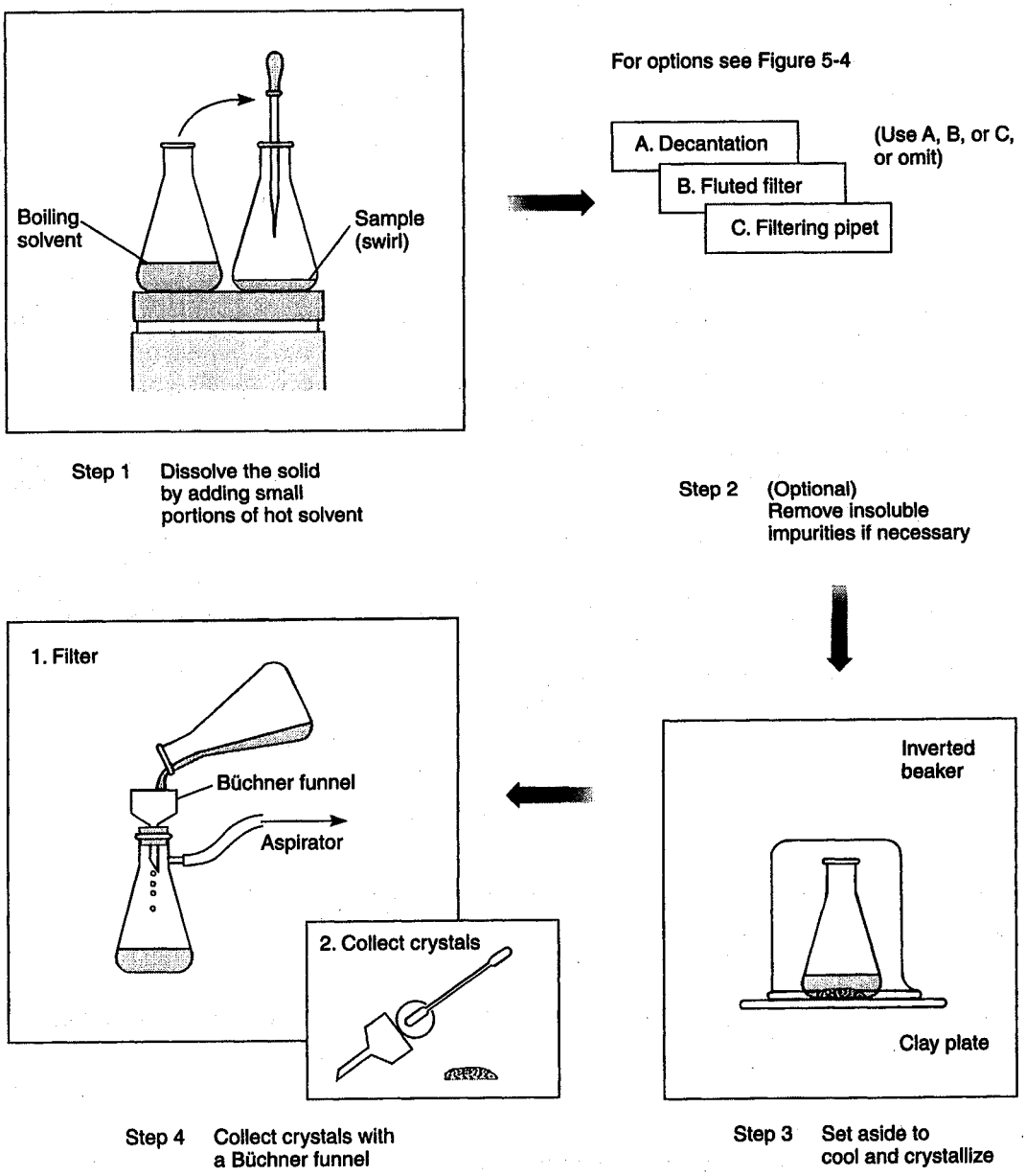


Figure 5.3 Steps in a standard-scale cystallization (no decolorization).

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 hotplate). 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. Do not heat the flask containing the solid until after you have added the first portion of solvent. 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 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 that 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 tell when saturation has been achieved.

In many of the experiments in this textbook, 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 for dissolving the solid. The amount of solvent recommended has been selected to provide the optimum conditions for good crystal formation.

Occasionally, you can 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, without realizing that they are not soluble. In such cases, you must be careful not to add too much solvent.

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 5.6, Parts A and B, and Technique 12, Section 12.14, p. 782). (Note: Often, there may be a small amount of colored material that will remain in solution during the crystallization step. When you believe that this may be the case, omit the decolorizing 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 4, Section 4.1, Part C, p. 638), and you should use gravity filtration through a fluted filter when the volume is 10 mL or greater (see Technique 4, Section 4.1, Part B, p. 636). These three methods are illustrated in Figure 5.4, and each one 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 4, Section 4.1, Part B, p. 636). You should first add a small amount of extra solvent to the hot mixture. This action helps to 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 hotplate (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.

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 3, Section 3.11, p. 630).

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

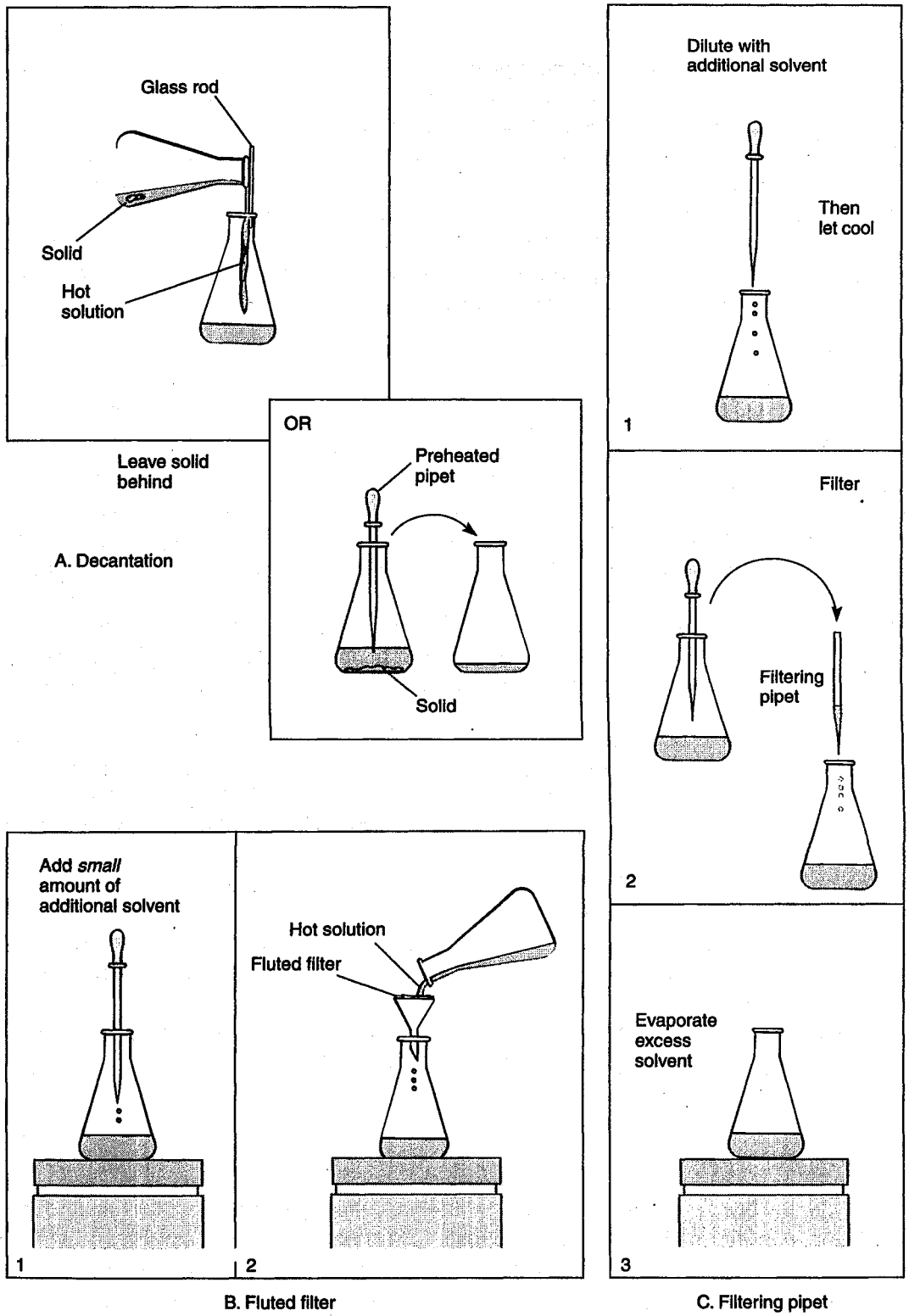


Figure 5.4 Methods for removing insoluble impurities in a semi-microscale crystallization.

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 4, Section 4.1, Part C, p. 638. After filtration, the excess solvent is evaporated by boiling until the solution is saturated at the boiling point of the mixture (see Technique 3, Section 3.11, p. 630). 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 else a fluted filter can be used.

C. CRYSTALLIZATION

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 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 hotplate 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 5.7, Part A.

D. ISOLATION OF CRYSTALS

After the flask has been cooled, the crystals are collected by vacuum filtration through a Büchner (or Hirsch) funnel (see Technique 4, Section 4.3, p. 640, and Fig. 4.5). 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 oversize 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 (so paper fibers are not removed with the crystals) the filter paper onto a watch glass or clay plate for further drying (see Section 5.8).

The four steps in a standard scale crystallization are summarized in Figure 5.5

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 silica gel or alumina column.

B. Removing Insoluble Impurities

1. Decant or remove the solution with a Pasteur pipet, or
2. 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.
   (a) Air-dry the crystals, or
   (b) Place the crystals in a drying oven, or
   (c) Dry the crystals *in vacuo.*

Figure 5.5 Steps in a crystallization.

5.4 MICROSCALE CRYSTALLIZATION—CRAIG TUBE

In most microscale experiments, the amount of solid to be crystallized is small enough (generally less than 0.1 g) that a **Craig tube** (see Technique 4, Fig. 4.10, p. 646) 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 4, Section 4.7, p. 646). 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 5.8).

5.5 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 the crystallization. With compounds that are well known, such as the compounds that are either isolated or prepared in this textbook, the correct crystallization solvent is already known 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 handbooks or tables frequently provide this information. Quite often, the correct crystallization solvents are indicated in the experimental procedures in this textbook.

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 one is trying to purify a solid material that has not been previously studied.

When choosing a crystallization solvent, take care not to pick one whose boiling point is higher than the melting point of the substance to be crystallized. If the boiling point of the solvent is high, the solid may melt in the solvent rather than dissolve. In such a case, the solid may **oil out.** Oiling out occurs when the solid substance melts and forms a liquid that is not soluble in the solvent. On cooling, the liquid refuses to crystallize; rather, it becomes a supercooled liquid, or oil. Oils may solidify if the temperature is lowered, but often they will not crystallize. A solidified oil becomes an amorphous solid or a hardened mass—a condition that does not result in the purification of the substance. 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 they will precipitate as crystals 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 sometimes helpful in working with difficult oils. Other methods of inducing crystallization are discussed in Section 5.7.

One additional criterion for selecting the correct crystallization solvent is the **volatility** of that solvent. Volatile solvents are those that 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.

Table 5.2 lists common crystallization solvents. The solvents used most commonly are listed first in the table.

5.6 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 to the color of the desired product, and if the color is significant. Small amounts of colored impurities will remain in solution during crystalliza-

TABLE 5.2 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.

†Suspected carcinogen.

tion, making the decolorizing step unnecessary. The use of activated charcoal is described separately for standard scale and microscale crystallizations, and the column technique, which can be used with both crystallization techniques, is also described.

PART A. STANDARD-SCALE—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, powdered Norit should be added because it has a larger surface area and can remove impurities more effectively. A reasonable amount of Norit would be what could be held on the end of a small spatula, or about 0.1–0.2 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 black 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 for several minutes and then filtered by gravity, using a fluted filter (see Section 5.3 and Technique 4, Section 4.1, Part B, p. 636), and the crystallization is carried forward as described in Section 5.3.

The Norit preferentially absorbs 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. DECOLORIZATION ON A COLUMN

Another 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 4, Fig. 4.6, p. 643, and Technique 12, Section 12.14, p. 782). 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 (Technique 3, Section 3.11, p. 630), and the crystallization procedure is continued as described in Section 5.3.

C. 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 carry out the subsequent filtration, 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 the color can be removed no matter how much is added. The decolorized solution is then removed with a preheated filter-tip pipet (see Section 5.4 and Technique 4, Section 4.6, p. 645) to filter the mixture and transferred to a Craig tube for crystallization as described in Section 5.4.

5.7 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 standard scale and microscale crystallizations.

A. STANDARD-SCALE

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 these measures fail to induce crystallization, it is likely that too much solvent was added. The excess solvent must then be evaporated (Technique 3, Section 3.11, p. 630) and the solution allowed to cool.

B. MICROSCALE

The strategy is basically the same as described for standard scale 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 spat-

ula 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 (Technique 3, Section 3.11, p. 630) and allow the solution to cool again.

5.8 DRYING CRYSTALS

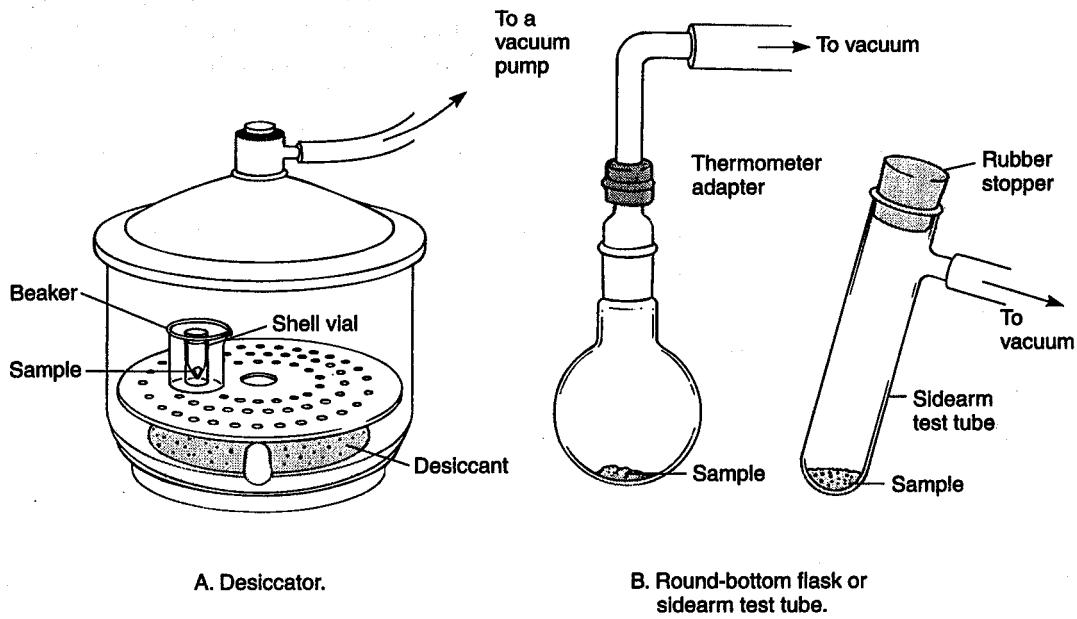
The most common method of drying crystals involves placing them on a watch glass, a clay plate, or a piece of paper and allowing them to dry in air. While the advantage of this method is that heat is not required, thus reducing the danger of decomposition or melting, exposure to atmospheric moisture may cause the hydration of strongly **hygroscopic** materials. A hygroscopic substance is one that absorbs moisture from the air. When crystals are allowed to air-dry, they should be covered with a watch glass or inverted beaker to protect them from air-borne dust particles.

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 5.6.

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 4, Fig. 4.5, p. 641).

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 5.6B. 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 5.6B. With either apparatus, install a water trap when an aspirator is used.



A. Desiccator.

B. Round-bottom flask or sidearm test tube.

Figure 5.6 Methods for drying crystals in a vacuum.

5.9 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 5.3.

TABLE 5.3. 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*–Water

*Suspected carcinogen.

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.

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
0	1.5 g
20	3.0 g
40	6.5 g
60	11.0 g
80	17.0 g

(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 the 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 be likely to 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 dissolving the substance 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 of 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 1 g/100 mL of water at 25°C and 10 g/100 mL of water at 100°C. You have a sample that contains 10 g of A and an impurity B.

(a) Assuming that 0.2 g of the impurity B is present along with 10 g of A, describe how you could purify A if B is completely insoluble in water.

(b) Assuming that 0.2 g of the impurity B is present along with 10 g of A, describe how you could purify A if B had the same solubility behavior as A. Would one crystallization produce absolutely pure A?

(c) Assume that 3 g of the impurity B is present along with 10 g of A. Describe how you would purify A if B had the same solubility behavior as A. Each time, use the correct amount of water to just dissolve the solid. Would one crystallization produce absolutely pure A? How many crystallizations would be needed to produce pure A? How much A would have been recovered when the crystallizations had been completed?

TECHNIQUE 6

Physical Constants: Melting Points, Boiling Points, Density

6.1 PHYSICAL PROPERTIES

The physical properties of a compound are those properties that are intrinsic to a given compound when it is pure. Often, a compound may 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. In this chapter, we look at methods of determining the melting point, boiling point, and density of compounds. Refractive index, optical rotation, and spectra are considered separately in their own technique chapters.

Many reference books list the physical properties of substances. Useful works for finding lists of values for the nonspectroscopic physical properties include:

The Merck Index

The CRC Handbook of Chemistry and Physics

The Dictionary of Organic Compounds

Lange's Handbook of Chemistry

CRC Handbook of Tables for Organic Compound Identification

Complete citations for these references may be found in Technique 20 (Guide to the Chemical Literature, p. 861). 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,* in your first attempt to locate information. *The Dictionary of Organic Compounds* is a multivolume work. A trip to the reference shelves of your library is required for you to use it, but it is a very complete source book.

PART A. MELTING POINTS

6.2 THE MELTING POINT

The melting point of a compound is used by the organic chemist not only to identify it, 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° 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 the 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 $\longrightarrow$ liquid) approached from the opposite direction (liquid $\longrightarrow$ solid).

Figure 6.1 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 temperatures) are shown for various mixtures of the two. The upper curves indicate the temperature 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

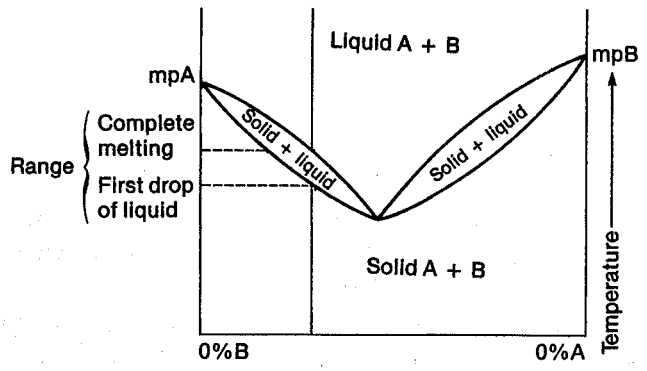


Figure 6.1 Melting point–composition curve.

are not close to the eutectic, the melting range increases as the sample becomes less pure. The range indicated by the lines in Figure 6.1 represents the typical behavior.

We can generalize the behavior shown in Figure 6.1. 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.

6.3 MELTING POINT THEORY

Figure 6.2 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 6.2, 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 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

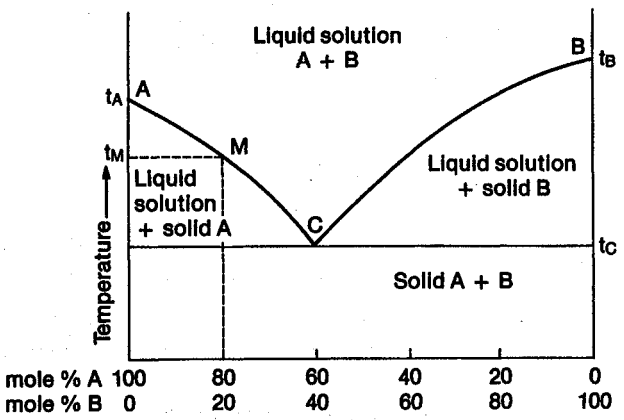


Figure 6.2 Phase diagram for melting in a two-component system.

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 6.2, 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 will be 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 6.1.

6.4 MIXED 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 **mixed melting point** may also be performed. The mixed 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 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.

6.5 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 desk top. When the capillary tube hits the desk top, the crystals will pack down into the bottom of the tube. This procedure is repeated if necessary. Tapping the capillary on the desk top 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.

6.6 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 6.3, is the simpler device. 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 throughout 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 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

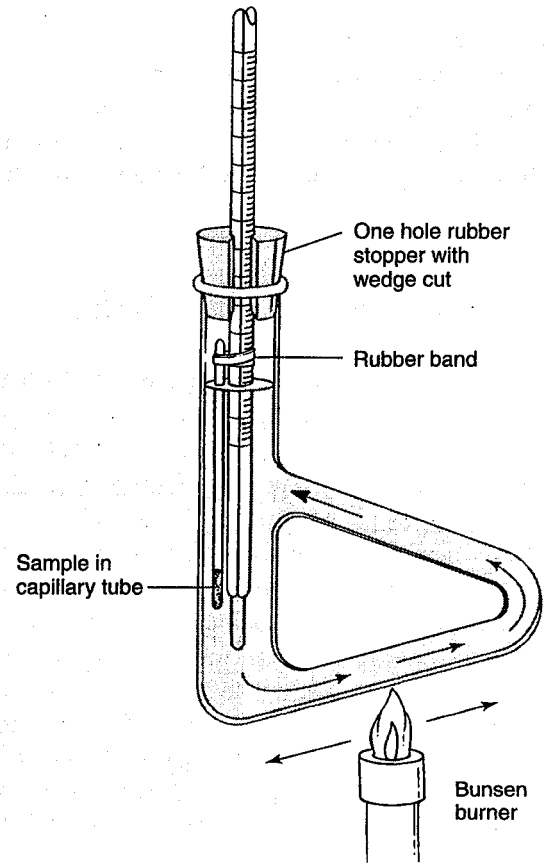


Figure 6.3 Thiele tube.

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 min.) 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.

6.7 DETERMINING THE MELTING POINT—ELECTRICAL INSTRUMENTS

Three types of electrically heated melting point instruments are illustrated in Figure 6.4. In each case, the melting-point tube is filled as described in Section 6.5 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 control dial for the

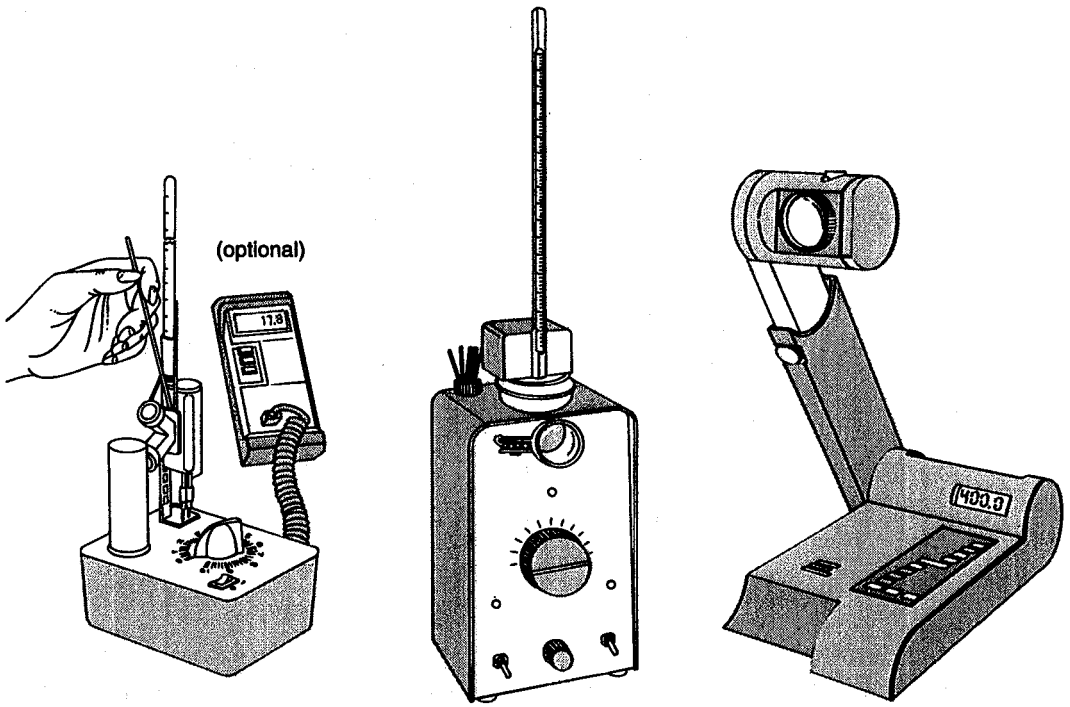


Figure 6.4 Melting-point apparatus.

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 6.5. 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.

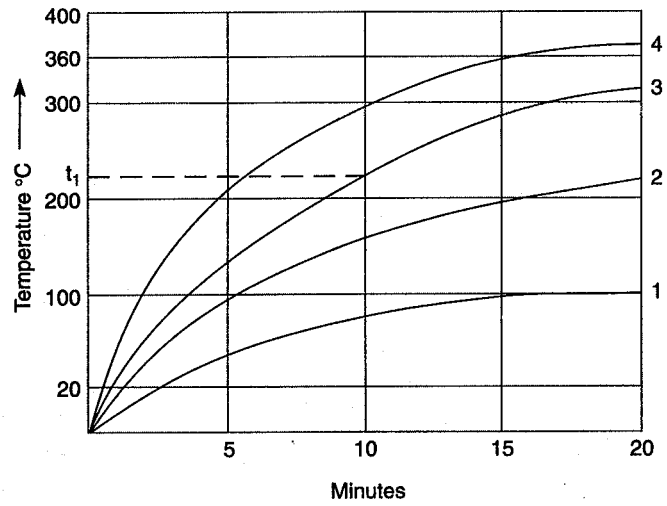


Figure 6.5 Heating-rate curves.

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 Section 6.13. An even better solution is to calibrate the thermometer as described in Section 6.12.

6.8 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 6.6 shows two simple methods of evacuating a packed tube. Method A uses an ordinary melting-point tube, while 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.

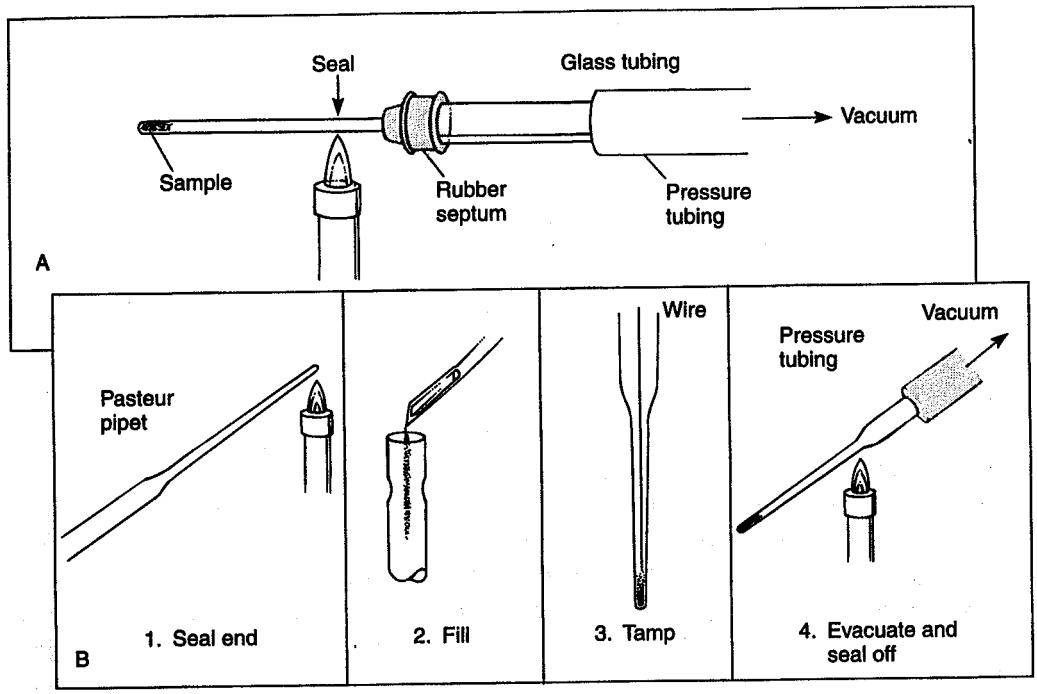


Figure 6.6 Evacuation and sealing of a melting-point capillary.

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 evacuating the tube, the upper end of the tube may be sealed by heating and pulling it closed.

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

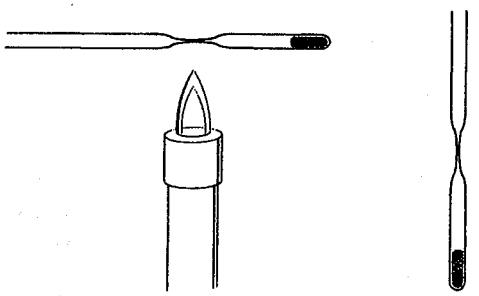


Figure 6.7 Sealing a tube for a substance that sublimes.

when the first drop of liquid becomes visible, and the melting range continues until the temperature 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 rage: 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 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 a 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, 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 6.7 illustrates the method.

PART B. BOILING POINTS

6.9 THE BOILING POINT

As a liquid is heated, the vapor pressure of the liquid increases to the point where 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 6.8 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

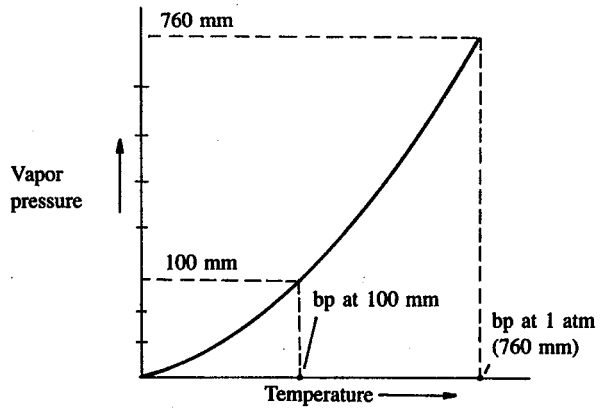


Figure 6.8 The vapor pressure–temperature curve for a typical liquid.

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 9) 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.

A more accurate estimate of the change in boiling point with a change of pressure can be made by using a **nomograph.** In Figure 6.9, 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.

6.10 DETERMINING BOILING POINTS—STANDARD-SCALE METHODS

Experimental methods of determining the boiling point of a liquid are easily available. When you have large quantities of material, you can simply record the boiling point (or boiling range) as indicated on a thermometer as the substance distills during a simple distillation (see Technique 8, Section 8.3, page 710). Alternatively, you may find it convenient to use a direct method, shown in Figure 6.10. 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.

The liquid can be brought to its boiling point very quickly when a test tube is used. Select a test tube that is long and narrow. You should avoid a large space between the sides of the test tube and the thermometer. Place the bulb of the thermometer as close as possible to the boiling liquid without actually touching it. You should use a small, inert

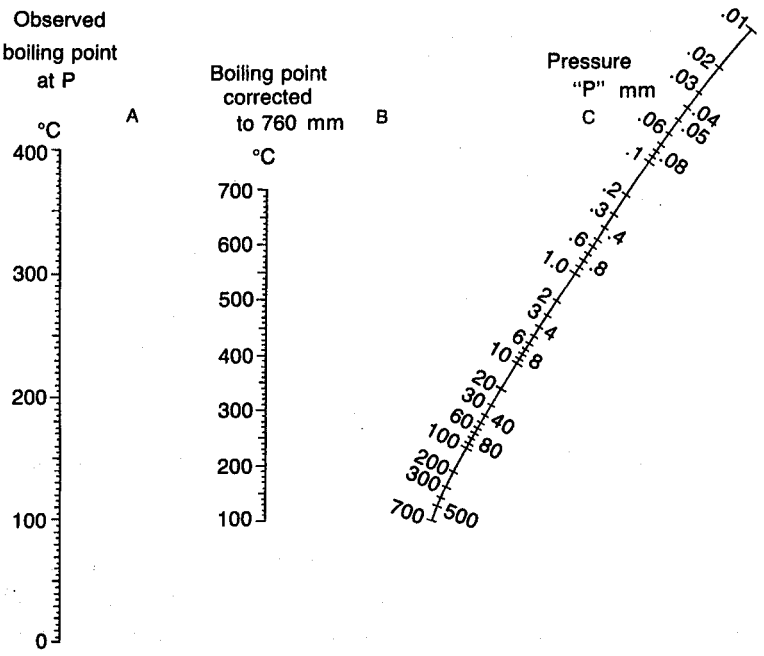


Figure 6.9 Pressure–temperature alignment nomograph. How to use the nomograph: Assume a reported boiling point of 100°C at 1 mm. To determine the boiling point at 18 mm, connect 100°C (column A) to 1 mm (column C) with a transparent plastic rule and observe where this line intersects column B (about 280°C). This value would correspond to the normal boiling point. Next, connect 280°C (column B) with 18 mm (column C) and observe where this intersects column A (151°C). The approximate boiling point will be 151°C at 18 mm. Reprinted by courtesy of MC/B Manufacturing Chemists, Inc.

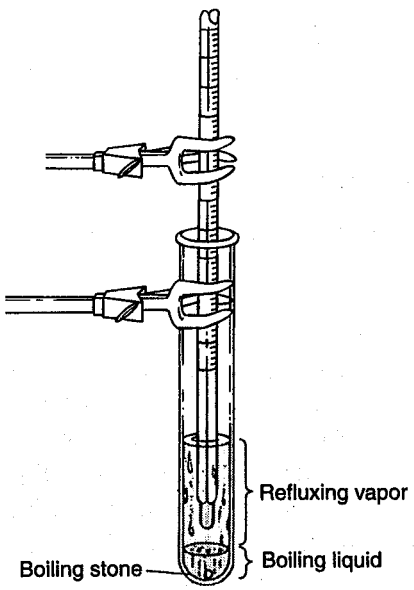


Figure 6.10 Standard-scale method of determining the boiling point.

carborundum (black) boiling stone. Do not use a marble or calcium carbonate (white) boiling chip. If safe operation permits, the best heating source is a small microburner. The flame will heat the liquid to boiling very quickly. The liquid must boil vigorously, such that you see a reflux ring and drops of liquid condensing on the sides of the test tube. You must, however, watch carefully so that you do not heat so much as to cause the liquid to boil out of the test tube, contact the flame, and cause a fire. The temperature reading on the thermometer must remain constant at its highest observed value. If the temperature continues to rise, the liquid has not yet reached its true boiling point.

6.11 DETERMINING BOILING POINTS—MICROSCALE METHODS

When you have smaller amounts of material, you can carry out a microscale or semimicroscale determination of the boiling point by using the apparatus shown in Figure 6.11.

Semi-Microscale Method. To carry out the semi-microscale determination, a piece of 5-mm glass tubing sealed at one end is attached to a thermometer with a rubber band

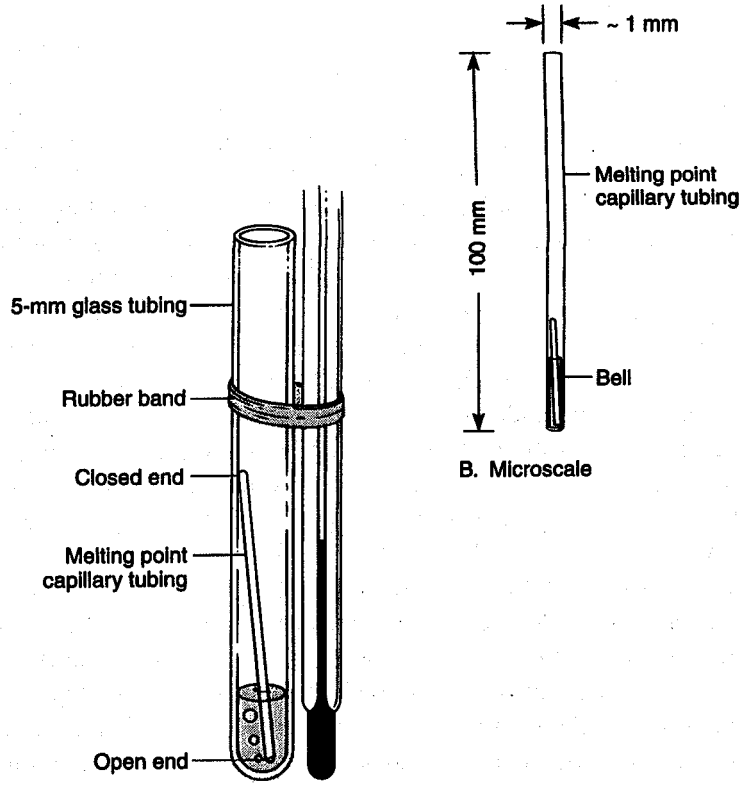


Figure 6.11 Boiling-point determinations.

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 Section 6.6 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 is often too little product available to use the semi-microscale method described above. 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 finger 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 6.12 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 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 that a continuous stream of bubbles, too fast for individual bubbles to be distinguished, is observed before lowering the temperature. Also, be sure that 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 be-

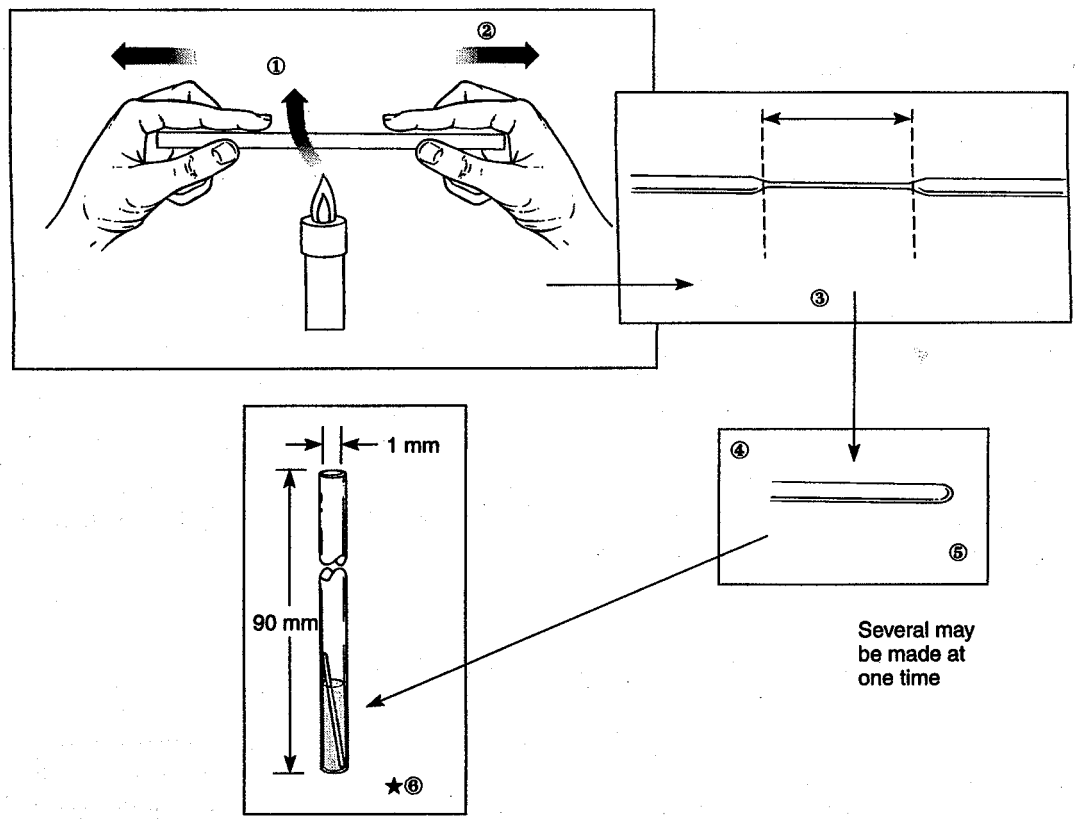


Figure 6.12 Construction of microcapillary bell for microscale boiling-point determination.

fore 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 6.13, or to calibrate the thermometer as described in Section 6.12.

PART C. THERMOMETER CALIBRATION AND CORRECTION

6.12 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 6.13. 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 6.1. The standard substances, of course, must be pure in order for the corrections to be valid.

6.13 THERMOMETER STEM CORRECTIONS

Three types of thermometers are available: bulb immersion, stem immersion (partial 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. **Stem immersion** thermometers are calibrated to give correct temperature readings when they are immersed to a specified depth in the medium to be measured. Stem immersion thermometers are easily rec-

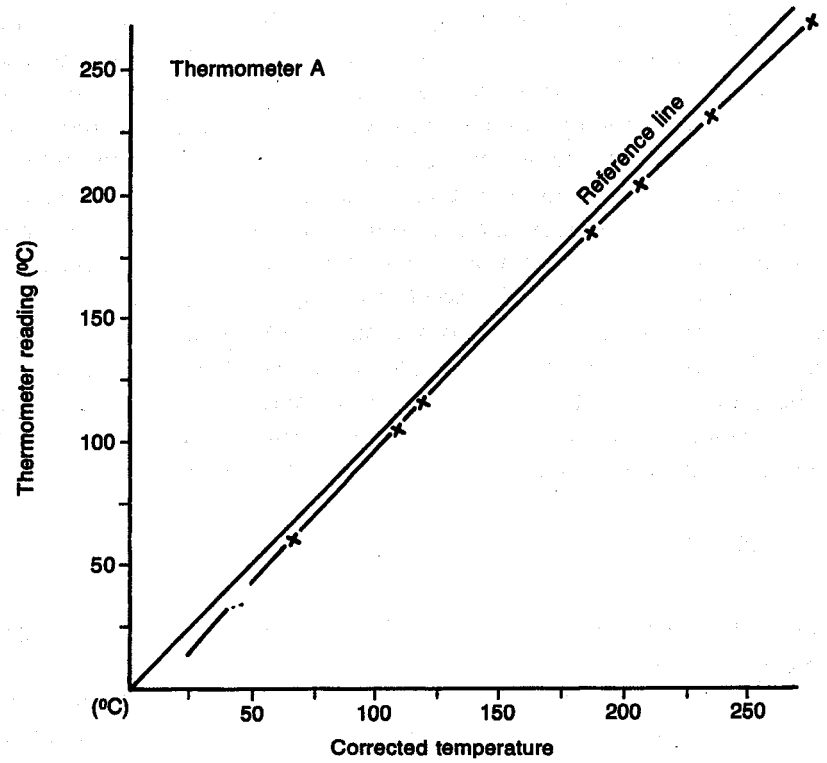


Figure 6.13 Thermometer calibration curve.

ognized 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 thermometer 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. Because total immersion thermometers are less expensive, they are the type you are most likely to find in the laboratory.

TABLE 6.1 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

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 Section 6.12 for a melting-point apparatus), a stem correction should not be 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 formula given below 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 0.00154 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. It is convenient to 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 that the bulb is close to the stem of the main thermometer.

Figure 6.14 shows how to apply this method for a distillation. By the formula given above, it can be shown that high temperatures are more likely to require a stem correction and that low temperatures need not be corrected. The calculations given below illustrate this point.

Example 1		**Example 2**	
$T = 200°C$		$T = 100°C$	
$t_1 = 0°C$		$t_1 = 0°C$	
$t_2 = 35°C$		$t_2 = 35°C$	
$(0.000154)(200)(165) = 5.1°$	stem correction	$(0.000154)(100)(65) = 1.0°C$	stem correction
$200°C + 5°C = 205°C$	corrected temp	$100°C + 1°C = 101°C$	corrected temp

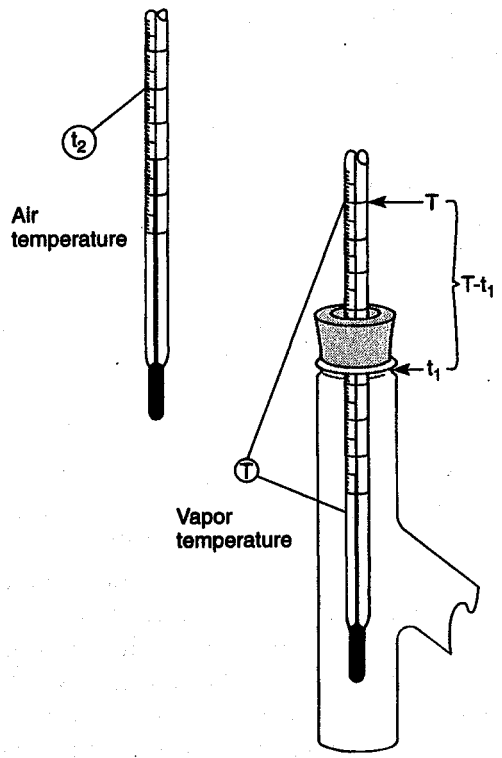


Figure 6.14 Measurement of a thermometer stem correction during distillation.

PART D. DENSITY

6.14 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.

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}} \quad \text{or} \quad D = \frac{M}{V}$$

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 measurement of the densities of liquids at the microscale level have been developed, they are often difficult to perform. An approx-

TABLE 6.2 Densities Determined by the Automatic Pipet Method (g/mL)

Substance	bp	lit	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

imate method for measuring densities can be found in using a 100-μL (0.100-mL) automatic pipet (Technique 1, Section 1.6, p. 597). Clean, dry, and pre-weigh one or more small vials (including their caps and liners) and record their weights. You should handle these vials with a tissue in order 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 6.2 compares some literature values with those that could be obtained by this method.

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 6.5, 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. Using the pressure–temperature alignment chart in Figure 6.9, 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?

5. Calculate the corrected boiling point for nitrobenzene by using the method given in Section 6.13. The boiling point was determined using an apparatus similar to that shown in Figure 6.10. 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.

6. 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.

7. 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?

8. 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.

9. 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. During the micro 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?

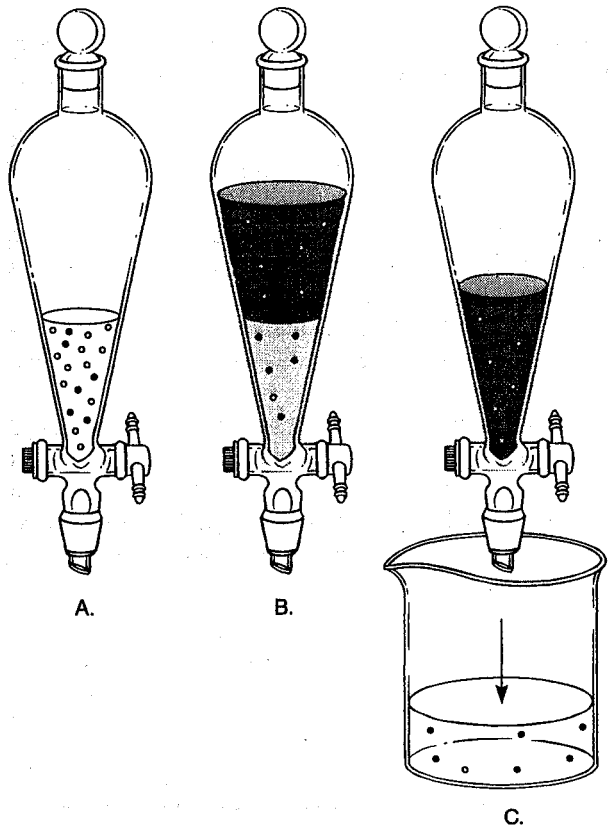
TECHNIQUE 7

Extractions, Separations, and Drying Agents

7.1 EXTRACTION

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 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 it 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 7.1. The first solvent contains a mixture of black and white molecules (Fig. 7.1A). 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 ex-



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, while 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 7.1 The extraction process.

ample the second solvent (shaded) is less dense than the first, so it becomes the top layer (Fig. 7.1B). Because of differences in physical properties, the white molecules are more soluble in the second solvent, while 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 (Fig. 7.1C). 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 from each other. A water wash removes highly polar and water-soluble materials, such as sulfuric acid, hydrochloric acid, or sodium hydroxide from the organic layer. The washing operation helps to purify the desired organic compound present in the original reaction mixture.

7.2 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 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 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.

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

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

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.

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

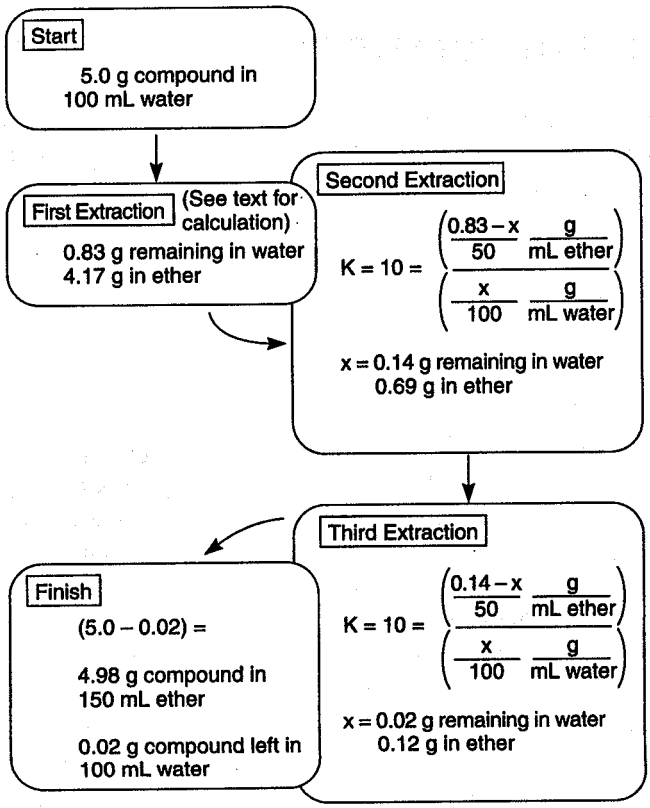


Figure 7.2 The result of extraction of 5.0 g of compound in 100 mL of water by three successive 50-mL portions of ether. Compare this result with that of Figure 7.3.

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 7.2. 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 7.3 shows the result of a *single* extraction with 150 mL of ether. As shown there, 4.69 g of solute was extracted into the ether layer, leaving 0.31 g of compound in the aqueous phase. One can see that three successive 50-mL ether extractions (Fig. 7.2) succeeded in removing 0.29 g more solute from the aqueous phase than using one 150-mL portion of either (Fig. 7.3). This differential represents 5.8% of the total material.

7.3 CHOOSING AN EXTRACTION METHOD AND A SOLVENT

Three types of apparatus are used for extractions: conical vials, centrifuge tubes, and separatory funnels. These are shown in Figure 7.4. Conical vials may be used with volumes

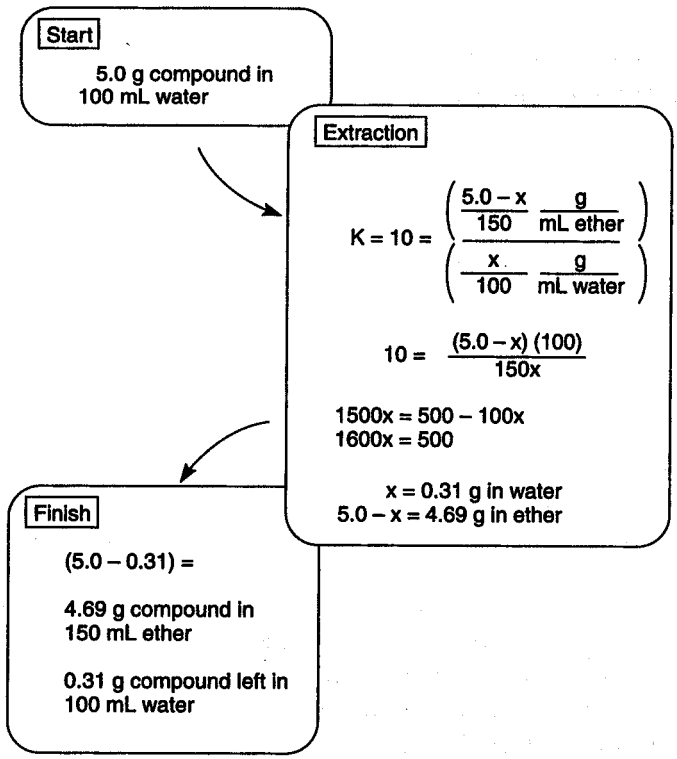


Figure 7.3 The result of extraction of 5.0 g of compound in 100 mL of water with one 150-mL portion of ether. Compare this result with that of Figure 7.2

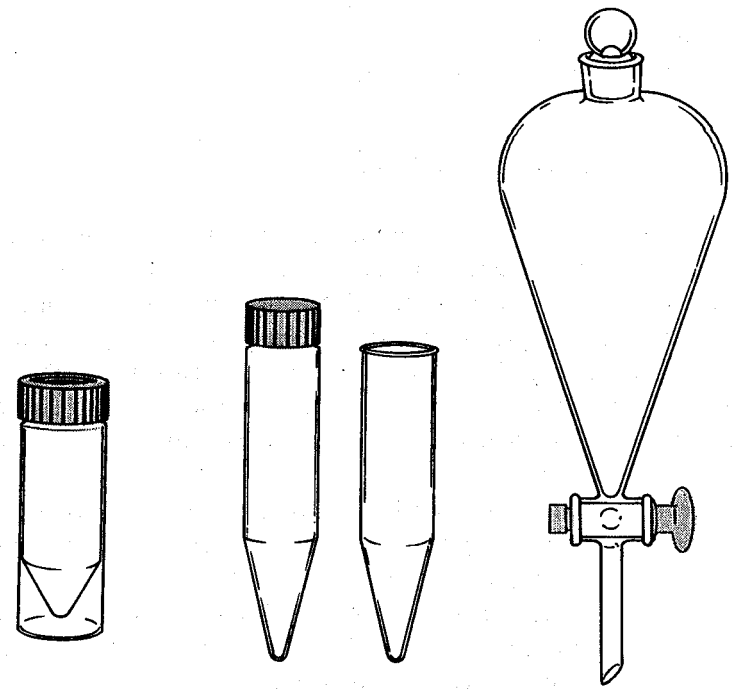


Figure 7.4 Apparatus used for extraction.

TABLE 7.1 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

of less than 4 mL; volumes of up to 10 mL may be handled in centrifuge tubes. A centrifuge tube equipped with a screwcap is particularly useful for extractions. The separatory funnel is used in large-scale reactions. Each type of equipment is discussed in a separate section.

Most extractions consist of an aqueous phase and an organic phase. In order to extract a substance from an aqueous phase, an organic solvent that is not miscible with water must be used. Table 7.1 lists a number of the common organic solvents that are not miscible with water and are used for extractions.

Those solvents that have a density less than that of water (1.00 g/mL) will separate as the top layer when shaken with water. Those solvents that have a greater density than 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 performing an extraction, slightly different methods are used when you wish to separate the lower layer (whether or not it is the aqueous layer or the organic layer) than when you wish to separate the upper layer.

7.4 THE SEPARATORY FUNNEL

A separatory funnel is illustrated in Figure 7.5. It is the piece of equipment used for carrying out extractions with medium to large quantities of material, and it will be used frequently in the procedures in this text. 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 7.5. 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, the first step is to close the stopcock. (Don't forget!) Using a powder funnel (wide bore) placed in the top of the separatory funnel, fill it with both the solution to be extracted and the extraction solvent. Swirl the funnel gently 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 7.6. Hold then 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 hold-

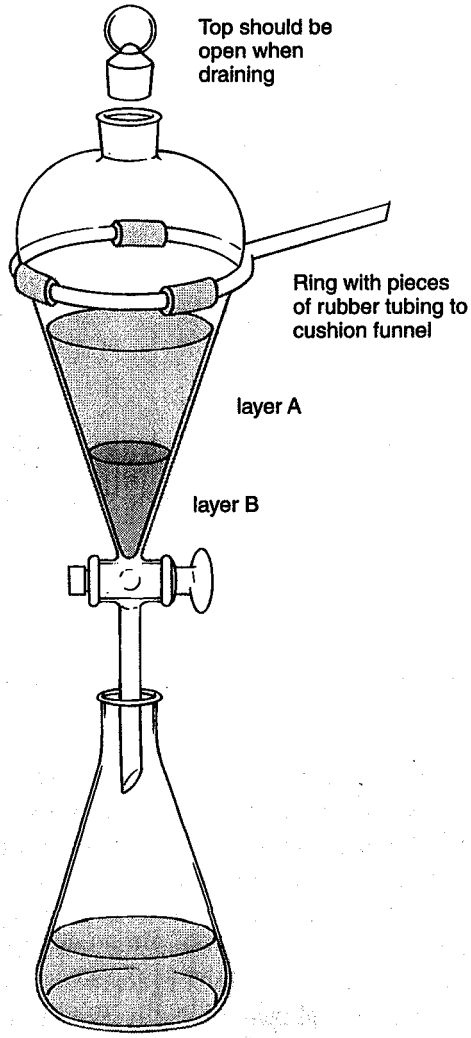


Figure 7.5 The separatory funnel.

ing 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 one 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 7.9, p. 699), by shaking the funnel more vigorously for less time.

There is an art to shaking and venting a separatory funnel correctly, and it 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.

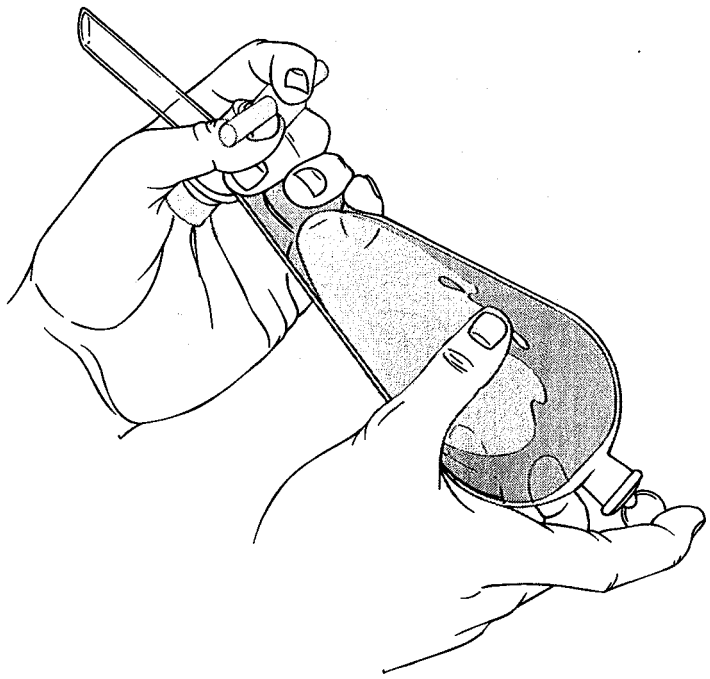


Figure 7.6 Correct way of shaking and venting the separatory funnel.

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.

> 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

[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 since a partial vacuum is created in the space above the liquid.

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 (Section 7.8) before the solvent is removed.

7.5 HOW DO YOU DETERMINE WHICH ONE IS THE ORGANIC LAYER?

A common problem that you might encounter 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 is 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 7.1). However, the aqueous layer will be on the top when you use methylene chloride as a solvent (again, see Table 7.1). Although the textbook frequently identifies the expected relative positions of the organic and aqueous layers, sometimes their actual positions are reversed. Surprises usually occur in situations where 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.

> 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 an 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.

7.6 THE CONICAL VIAL

The 5-mL conical vial is the most useful piece of equipment for carrying out extractions with small amounts of material. Before you begin you should check the capped conical vial for leaks. Leaks are especially serious with a conical vial since you are dealing with a small volume of liquid from the very beginning. To check for leaks, 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 used for extractions must not be chipped on the top edge of the vial. The cap and liner seal against this top edge and, if there are chips, the seal may not be adequate. If there is a leak, try tightening the cap or replacing the liner with a new one. The liners are a sandwich with two sides, a hard Teflon surface (thin) on one side and a softer rubber surface (thick) on the other. Sometimes the rubber surface will provide a better seal to the top edge than the Teflon surface. If all else fails, replace the glass vial.

As an alternative to shaking, the contents of a conical vial can be mixed by spinning your microspatula in the vial for several minutes (twirl it between your thumb and your index finger). Another mixing technique involves repeatedly drawing the mixture into a disposable Pasteur pipet and squirting it rapidly back into the vial for a period of several minutes.

The conical vial, with a capacity of 5 mL of liquid, is commonly used in microscale procedures. In this section, we consider explicitly the method whereby the lower layer is removed by a disposable Pasteur pipet. A concrete example would be the extraction of the desired product from an aqueous layer using methylene chloride (d = 1.33 g/mL) as the extraction solvent.

Always remember to place a conical vial in a small beaker when it is not being held. Although the vials have a flat bottom, they can tip easily and roll off the bench.

Figure 7.7 shows the steps in using a conical vial for a separation. Figure 7.7A shows the solution to be extracted. The extraction solvent is added, and the vial is capped and

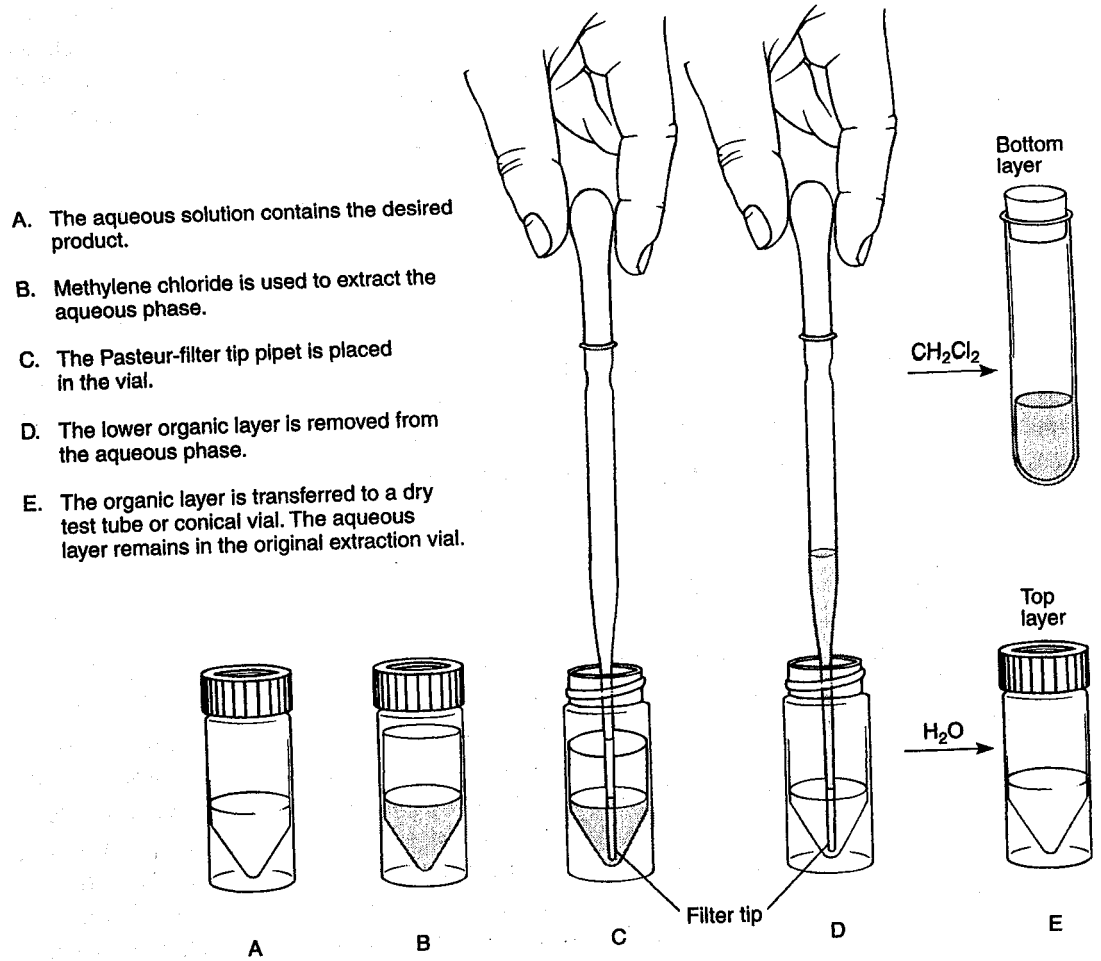


Figure 7.7 Extraction of an aqueous solution using a solvent more dense than water: Methylene chloride.

shaken (with occasional venting to relieve pressure). Figure 7.7B shows the mixture after the immiscible layers have reseparated. The lower layer is removed using a disposable Pasteur pipet (Fig. 7.7C) and transferred to a *dry* storage container such as a test tube. This operation requires a little practice. You must learn to depress the rubber bulb just the right amount to remove only the lower layer, and to leave the upper layer behind. To avoid spillage, it is best to have the storage test tube or another vial held in the same hand as the source vial as shown in Figure 7.8.

Many workers prefer to use a **filter tip pipet** when separating the layers. A filter tip pipet is a Pasteur pipet that has been modified to have a loose plug of cotton in the end. The filter tip pipet both fills and empties more slowly than an unmodified Pasteur pipet. This allows for better control when trying to separate the two layers in the conical vial. A *very small amount* of cotton or glass wool is used to make the filter plug, and it is pushed in place with a short length of copper wire. Care must be taken to avoid compressing the cotton or glass wool so tightly that liquid will not pass through the tip of the pipet.

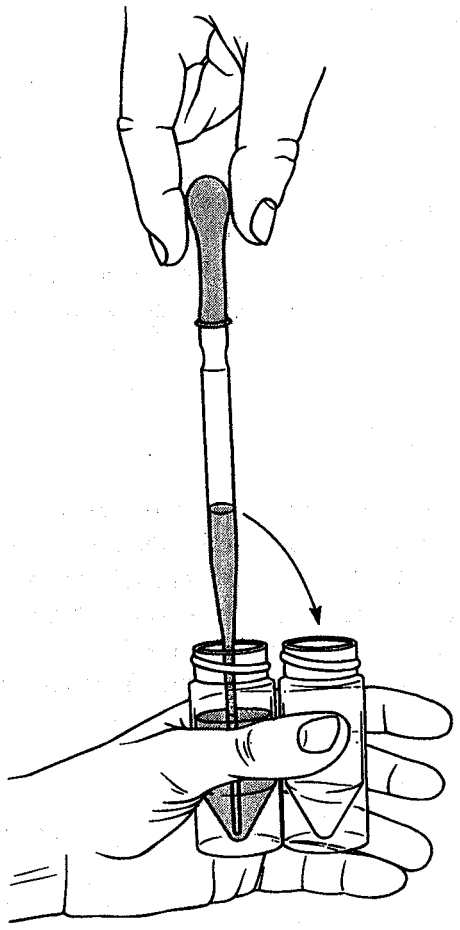


Figure 7.8 Method of holding vials while transferring liquids.

In Figure 7.7, methylene chloride, a solvent more dense than water, was illustrated. If you are extracting with a solvent less dense than water (for example, diethyl ether), you will want to save the upper layer. In that case, the extraction sequence shown in Figure 7.7 will have the positions of the water and the solvent reversed at stage E of the separation. The water layer will be in the test tube, and the ether in the conical vial.

7.7 THE SCREW-CAP CENTRIFUGE TUBE

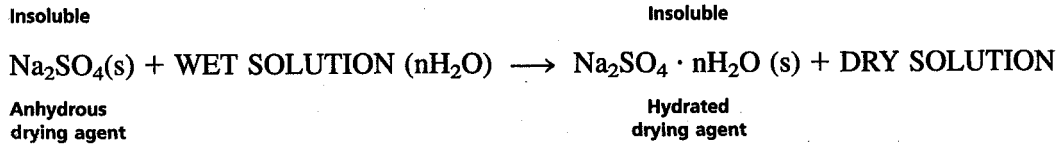
If you require an extraction that uses a larger volume than a conical vial can accommodate (5 mL), a centrifuge tube can often be used. A commonly available size of centrifuge tube has a volume of about 15 mL, and is supplied with a screw cap. In performing an extraction with a screwcapped centrifuge tube, the same procedures outlined for the conical vial (Section 7.6) are used. 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.

A centrifuge tube has a large advantage over other methods of extraction. If an emulsion (Section 7.9) 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.

7.8 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 miscibility 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 (about 1.5% by weight). To remove water from a wet ether solution obtained from an extraction, a **drying agent** is used. A drying agent is an insoluble, *anhydrous* inorganic salt that acquires waters of hydration when exposed to moist air or a wet 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 drying agents differ in their properties and applications. Two major properties are defined for a drying agent: capacity and completeness. **Capacity** refers to the amount of water a drying agent absorbs per unit weight (usually per gram). **Completeness** refers to a compound's effectiveness in removing all of the water from a solution by the time equilibrium has been reached with the solution. Sodium and magnesium sulfates both absorb a large amount of water (capacity), but magnesium sulfate usually leaves less water in the solution (completeness). You can equalize this difference by drying with several smaller portions of sodium sulfate, where you might use one large portion of magnesium sulfate. A third sulfate compound, calcium sulfate, dries a solution completely, but has a low capacity (you would have to use a lot more of it than of magnesium sulfate, but a single drying might suffice).

Many magnesium compounds are good drying agents, but magnesium ion is a strong Lewis acid, and it can sometimes cause rearrangements of sensitive 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 also useful for removing these solvents when they are present as impurities or they make a solution "wet." Potassium carbonate is a base and is used for drying solutions of basic substances. Potassium hydroxide is often used to dry solutions of aromatic amines.

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 (see p. 699). Sodium sulfate must be used at room temperature to be effective; it cannot be used with boiling solutions. Table 7.2 compares the various common drying agents.

Large-Scale Reactions. To dry a large amount of solution, you should add enough granular anhydrous sodium sulfate to give a 1–3 mm layer on the bottom of the flask, depending on the volume of the solution. Dry the solution for at least 15 minutes, occasionally swirling the flask. The mixture is dry if it appears clear and shows the common signs of a dry solution given in Table 7.3.

If the solution remains cloudy after treatment with the first batch of drying agent, add more drying agent and repeat the drying procedure. If the drying agent clumps badly, with no drying agent that will flow freely when the flask is swirled, you should transfer the solution to a clean, dry flask and add a fresh portion of drying agent. If droplets of water are present, you should also transfer the solution to a new container and add a fresh quantity of drying agent. You should not add more drying agent if a puddle (water layer) forms. Instead, separate the layers, using a separatory funnel if necessary, and then add fresh drying agent to the organic layer, placed in a new container. If the first batch of drying agent does not completely dry the solution, it is not at all unusual to have to transfer (decant) the solution to a clean, dry flask and add a fresh portion of drying agent.

TABLE 7.2 Common Drying Agents

	Acidity	Hydrated	Capacity*	Completeness†	Rate‡	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

*Amount of water removed per given weight of drying agent.

†Refers to amount of H_2O still in solution at equilibrium with drying agent.

‡Refers to rate of action (drying).

When the solution is dry, the drying agent should be removed by using decantation (pouring carefully to leave the drying agent behind). With granular sodium sulfate, decantation is quite 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 a gravity filtration (Technique 4, Section 4.1B, p. 636) to remove the drying agent. The solvent is removed by distillation (Technique 8, Section 8.3, p. 710) or evaporation (Technique 3, Section 3.11, p. 630)

Microscale Reactions. Before attempting to dry an organic layer, check closely to see that there are no visible signs of water. If you see droplets of water in the organic layer or water droplets clinging to the sides of the conical vial or test tube, transfer the organic layer

TABLE 7.3 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.

with a *dry* Pasteur pipet to a *dry* container before adding any drying agent. Now add one spatulaful of granular anhydrous sodium sulfate (or other drying agent) from the V-grooved end of a microspatula into a solution contained in a conical vial or test tube. If all the drying agent "clumps," add another spatulaful of sodium sulfate. Dry the solution for at least 15 minutes. Stir the mixture occasionally with a spatula during that period. The mixture is dry if there are no visible signs of water and the drying agent flows freely in the container when stirred with a microspatula. The solution should not be cloudy. Add more drying agent if necessary. You should not add more drying agent if a "puddle" (water layer) forms or if drops of water are visible. Instead, you should transfer the organic layer to a dry container before adding fresh drying agent. When dry, use a *dry* Pasteur pipet or a *dry* filter-tip pipet (Technique 4, Section 4.6, p. 645) to remove the solution from the drying agent and transfer the solution to a *dry* conical vial. Rinse the drying agent with a small amount of fresh solvent and transfer this solvent to the vial containing the solution. Remove the solvent by evaporation using heat and a stream of air or nitrogen (Technique 3, Section 3.11, p. 630).

An alternative method of drying an organic phase is to pass it through a filtering pipet (Technique 4, Section 4.1C, p. 638) that has been packed with a small amount (ca. 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 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 7.2.

7.9 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. This makes the aqueous and organic layers less compatible, thereby forcing separation.

3. With microscale and many small-scale experiments, 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 of the centrifuge to balance it.
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 4, Section 4.1, p. 634) may help to destroy an emulsion by removing a gummy polymeric substance. With large-scale reactions, you might try filtering the mixture through a fluted filter (Technique 4, Section 4.1B, p. 636) or a piece of cotton. With microscale reactions, a filtering pipet may work (Technique 4, Section 4.1C, p. 638). 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 that you use a longer extraction period if the more gentle techniques described in this paragraph are being employed. Otherwise, you will not transfer all the material from the first phase to the second one.

7.10 PURIFICATION AND SEPARATION METHODS

In nearly all the synthetic experiments undertaken in this textbook, 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, the desired product is separated 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 5 to 10% 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.

$$RNH_2 + HCl \longrightarrow \underset{\text{(Water-soluble salt)}}{RNH_3^+Cl^-}$$

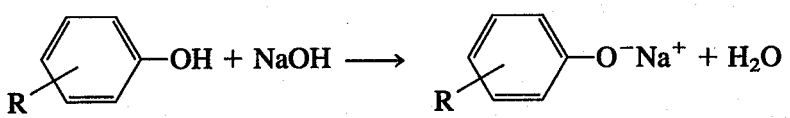
Cationic salts are usually soluble in the aqueous solution, and they are thus extracted from the organic material. A water extraction may be used immediately following the acid extraction to ensure that all traces of the acid have been removed from the organic material.

The third category is extraction of an organic mixture with a dilute base, usually 5% 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.

$$\underset{(pKa \sim 5)}{RCOOH} + NaHCO_3 \longrightarrow \underset{\text{(Water-soluble salt)}}{RCOO^-Na^+} + H_2O + CO_2$$

Anionic salts, being highly polar, are soluble in the aqueous phase. As a result, these acidic 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 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.



($pK_a \sim 10$) (Water-soluble salt)

It would be a useful exercise for you to examine the instructions for some of the preparative experiments given in the textbook. While you are examining these procedures, you should try to identify which impurities are being removed at each extraction step. Mixtures of acidic, basic, and neutral compounds are easily separated by extraction techniques. One such example is shown in Figure 7.9.

Materials that have been extracted can be regenerated by neutralizing the extraction reagent. If an acidic material has been extracted with aqueous base, the material can be

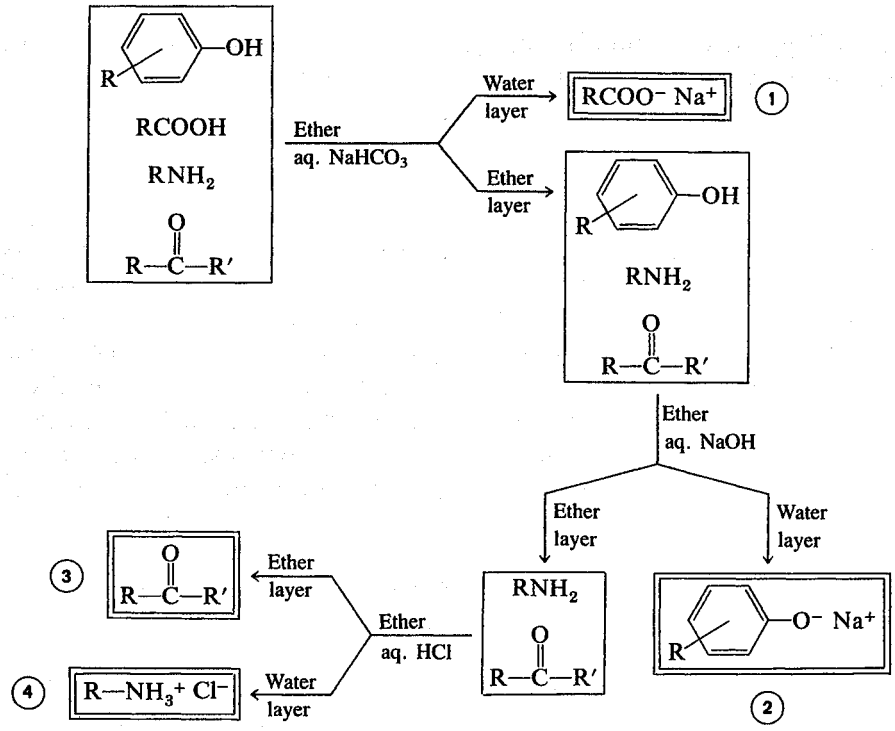


Figure 7.9 Separating a four-component mixture by extraction.

regenerated by acidifying the extract until the solution becomes acidic to blue litmus. The material will separate from the acidified solution. A basic material can be recovered from the acidic extract by adding base to the extract. These substances can then be removed from the neutralized aqueous solutions by extraction with an organic solvent such as ether. After the ether phase is dried with a drying agent, evaporation of the ether yields the isolated compounds.

7.11 CONTINUOUS SOLID–LIQUID EXTRACTION

The technique of liquid–liquid extraction was described in Sections 7.1–7.7. 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 that leaves behind the undesired insoluble solid. A continuous solid–liquid extraction apparatus, called a Soxhlet extractor, is commonly used in a research laboratory (Fig. 7.10).

As shown in Figure 7.10, 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 heated to reflux. The vapor rises through the left sidearm into the condenser where it liquefies. The con-

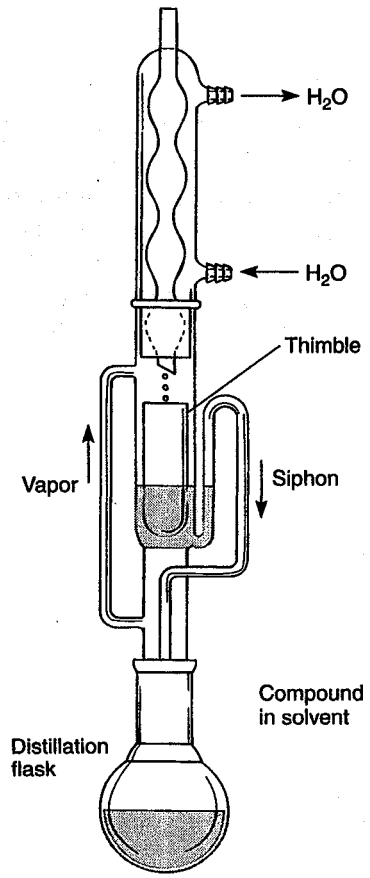


Figure 7.10 *Continuous solid–liquid extraction using a Soxhlet extractor.*

densate (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 it has a boiling point higher than that of the solvent or because it is a solid.

7.12 CONTINUOUS LIQUID–LIQUID EXTRACTION

When a product is very soluble in water, it is often difficult to extract using the techniques described in Sections 7.4–7.7, 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 7.11. Diethyl ether is usually the solvent of choice.

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.

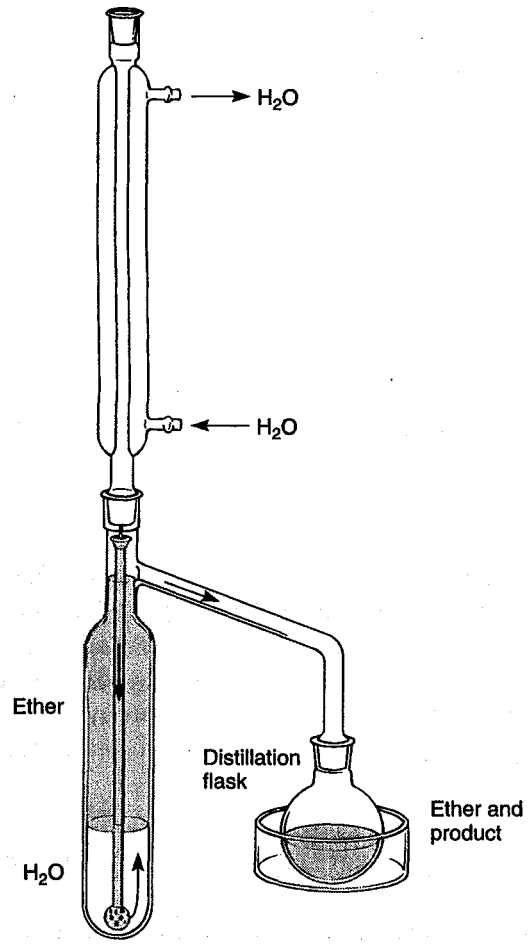


Figure 7.11 Continuous liquid–liquid extraction using a solvent less dense than water.

PROBLEMS

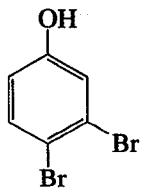
1. Suppose solute A has a distribution coefficient of 1.0 between water and diethyl ether. Demonstrate that if 100 mL of a solution of 5.0 g of A in water were extracted with two 25-mL portions of ether, a smaller amount of A would remain in the water than if the solution were extracted with one 50-mL 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 7.9.

3. Aqueous hydrochloric acid was used *after* the sodium bicarbonate and sodium hydroxide extractions in the separation scheme shown in Figure 7.9. Is it possible to use this reagent earlier in the separation scheme so as to achieve the same overall result? If so, explain where you would perform this extraction.

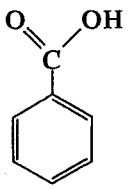
4. Using aqueous hydrochloric acid, sodium bicarbonate, or sodium hydroxide solutions, devise a separation scheme using the style shown in Figure 7.9 to separate the following two-component mixtures. All the substances are soluble in ether. Also indicate how you would recover each of the compounds from their respective salts.

(a) Give two different methods for separating this mixture.



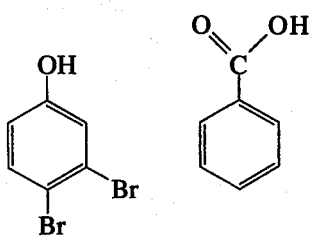
$(CH_3CH_2CH_2CH_2)_3N$

(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 7.1 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 (Technique 20. Section 20.1, p. 861).

(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 (Technique 20, Section 20.1, p. 861). 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 7.2.

8. Explain the following laboratory instructions in a procedure:
(a) "Wash the organic layer with 5.0 mL of 5% 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)

TECHNIQUE 8

Simple Distillation

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, vacuum distillation (distillation at reduced pressure), fractional distillation, and steam distillation. This technique chapter will discuss simple distillation. Vacuum distillation will be discussed in Technique 9. Fractional distillation will be discussed in Technique 10, and steam distillation will be discussed in Technique 11.

8.1 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** (Fig. 8.1). They were used by alchemists in the Middle Ages and the

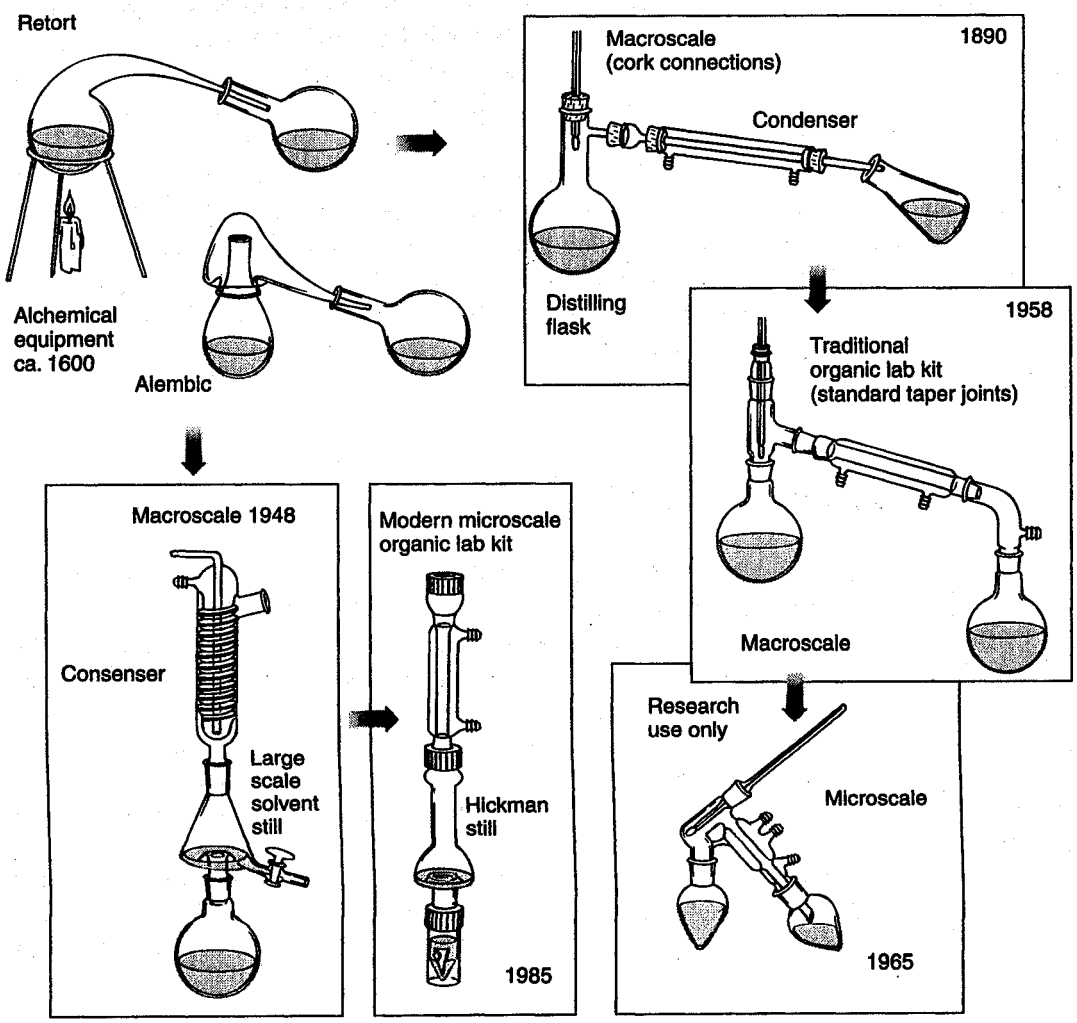


Figure 8.1 Some stages in the evolution of distillation equipment from alchemical equipment (dates represent approximate time of use).

Renaissance, and probably even earlier by Arabic chemists. Most other distillation equipment has evolved as variations on these designs.

Figure 8.1 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 common in the laboratory. Although the retort itself was still in use early in this 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 Fig. 8.1, see the box labeled 1965, 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 1985, Hickman still). This new microscale equipment has ₹ 14/10 standard-taper joints, threaded outer joints with screwcap 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.

8.2 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 Fig. 8.2A). 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 Fig. 8.2B).

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 8.3, which is a phase diagram of the typical vapor–liquid relation for a two-component system (A + B).

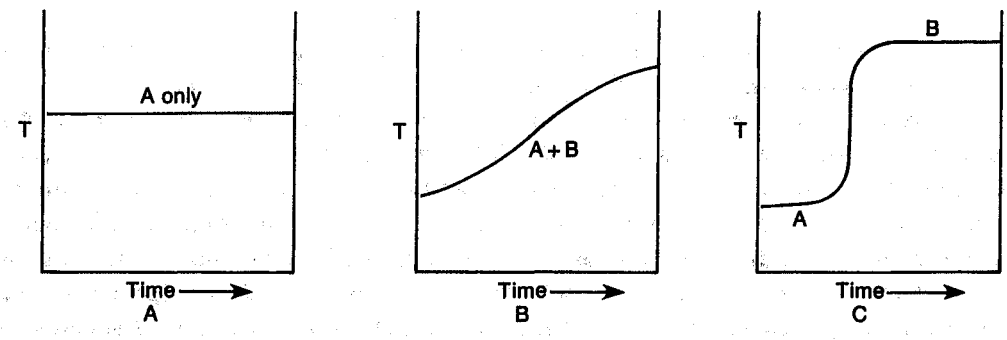


Figure 8.2 Three types of temperature behavior during a simple distillation. (A) A single pure component. (B) Two components of similar boiling points. (C) Two components with widely differing boiling points. Good separations are achieved in A and C.

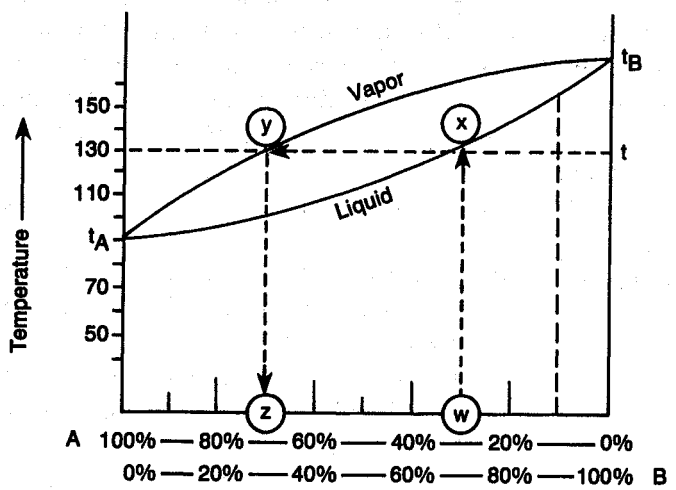


Figure 8.3 Phase diagram for a typical liquid mixture of two components.

On this diagram, horizontal lines represent constant temperatures. The upper curve represents vapor composition, and the lower curve represents liquid composition. For any horizontal line (constant temperature), like 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 on 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°), 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 distil-**

lation. Fractional distillation is described in Technique 10, where the behavior during a simple distillation is also considered in detail. Note only that as vapor distills from the mixture of composition *w* (Fig. 8.3), 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 Fig. 8.3) 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 Fig. 8.2B).

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 8.2C. 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 usually is left as a residue and not distilled. This separation is not difficult and represents a case where simple distillation might be used to advantage.

8.3 SIMPLE DISTILLATION—STANDARD APPARATUS

For a simple distillation, the apparatus shown in Figure 8.4 is used. Six pieces of specialized glassware are used:

1. Distilling flask
2. Distillation head
3. Thermometer adapter
4. Water condenser
5. Vacuum takeoff 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 3 (Fig. 3.4, page 616 and Fig. 3.6, page 617). 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 below, 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 sur-

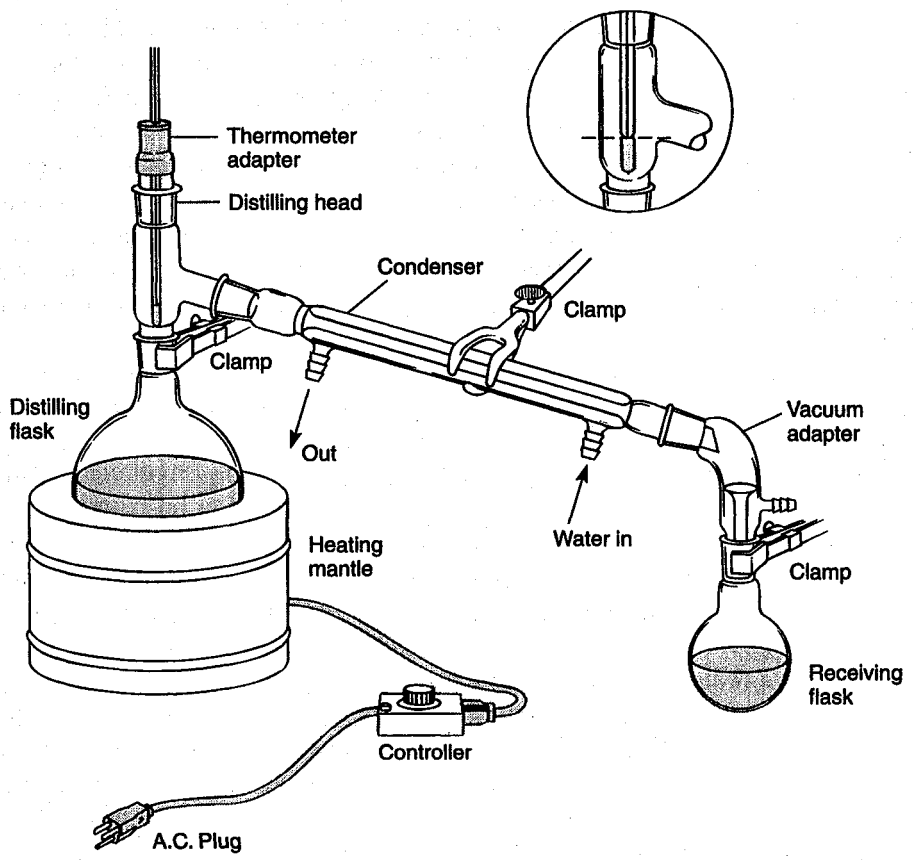


Figure 8.4 Distillation with the standard macroscale lab kit.

face 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 since 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 3, Section 3.6, page 622) 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 3, Section 3.5, page 621). 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 it is placed directly in the stream of va-

por that is distilling. This can be accomplished if the entire bulb of the thermometer is positioned *below* the side arm of the distilling head (see the circular inset in Fig. 8.4). 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 3, Section 3.4, page 619) positioned well above both the thermometer bulb and the bottom of the side arm.

Thermometer Adapter. The thermometer adapter connects to the top of the distillation head (see Fig. 8.4). 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 side arm.

Water Condenser. The joint between the distillation head and the water condenser is the joint most prone to leak in this entire apparatus. Since 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 3, Figure 3.5, page 617. 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 so that it can explode. 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 they are available, it is a good idea to use plastic joint clips 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 since the temperature recorded on the thermometer is not maintained by a constant vapor stream, thus leading to an inaccurately low observation of the boiling point.

Receiving Flask. The receiving flask collects the distilled liquid, and is usually a round-bottom flask. 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 clean ones 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!

8.4 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 from 5 to 15 mL. An example of such a "semimicroscale" apparatus is given in Figure 8.5. 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 not have a large amount of material and can cool the receiving flask in an ice-water bath as shown in the figure.

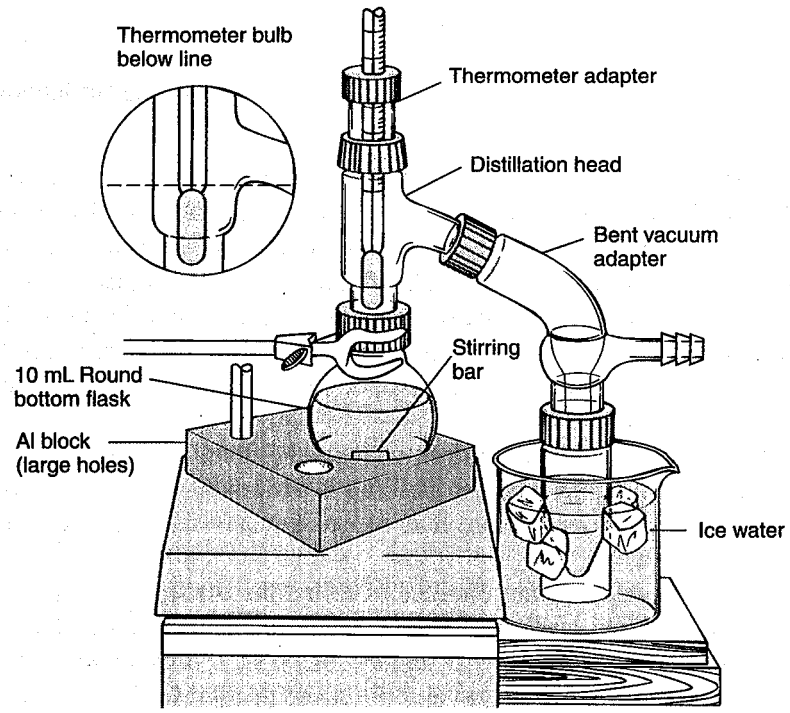


Figure 8.5 Semi-microscale distillation.

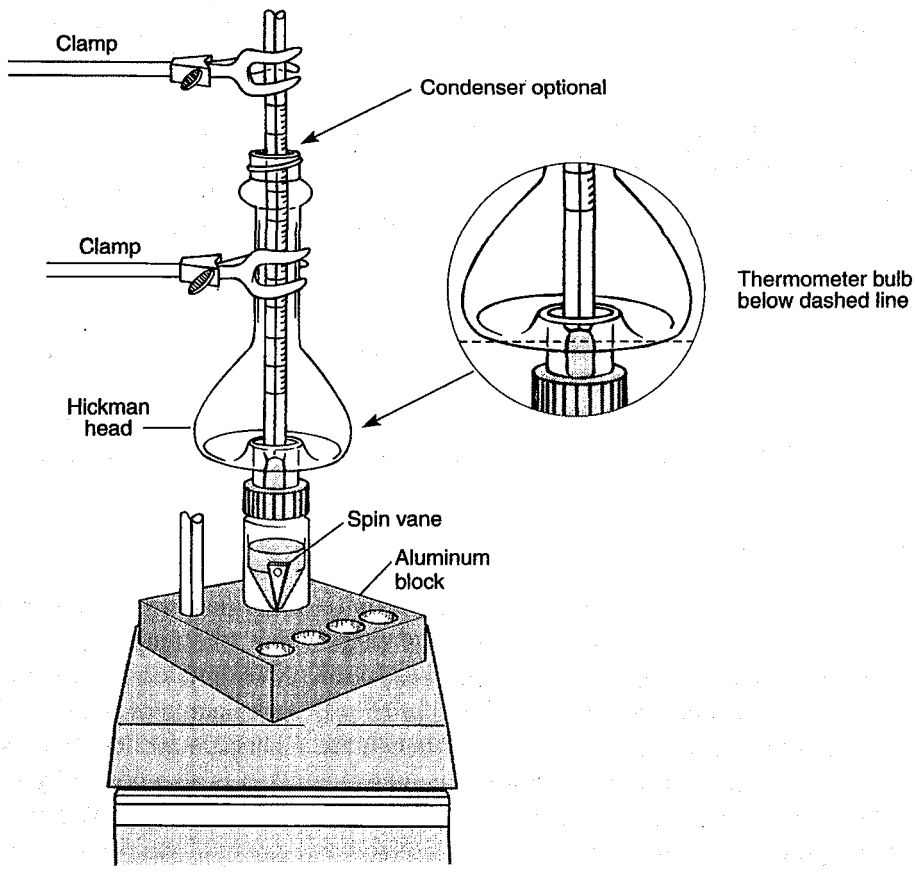


Figure 8.6 Basic microscale distillation.

B. MICROSCALE—STUDENT EQUIPMENT

Figure 8.6 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 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 from 1 to 3 mL of liquid. Unfortunately, the well in most Hickman heads holds only about 0.5–1.0 mL. That means the well must be emptied several times. This is done using a disposable Pasteur pipet as shown in Figure 8.7. The figure shows two different styles of Hickman head. The one with the side port makes removal of the distillate easier.

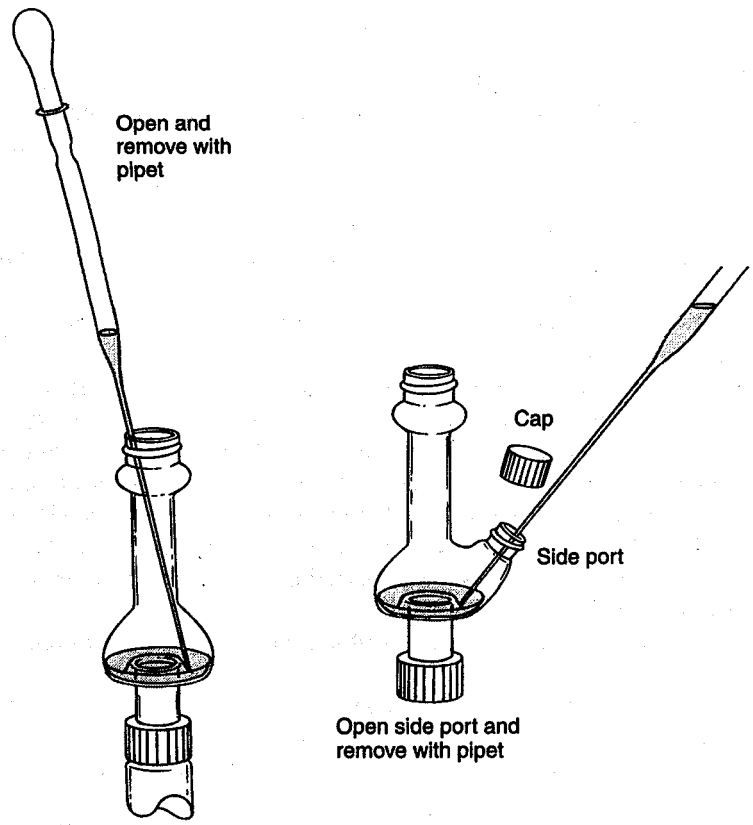


Figure 8.7 Two styles of Hickman head.

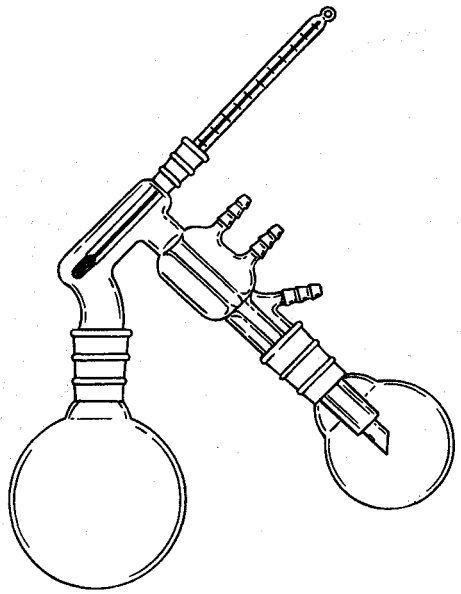


Figure 8.8 A research-style short-path distillation apparatus.

C. MICROSCALE—RESEARCH EQUIPMENT

Figure 8.8 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.

PROBLEMS

1. Using Figure 8.3, 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 8.4, 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 mm Hg) 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 8.3.

4. Using Figure 8.3, 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

(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?

TECHNIQUE 9

Vacuum Distillation, Manometers

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 6 (Section 6.9, p. 674). A nomograph is given (Fig. 6.9, p. 676) 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.

9.1 STANDARD SCALE 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 9.1 may be used for vacuum distillations. The major differences to be found when comparing this assembly to one for simple distillation (Fig. 8.4, p. 711) 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 (Technique 4, Section 4.5, p. 643), a mechanical vacuum pump (Section 9.6, p. 728), or a "house" vacuum system (one piped directly to the laboratory bench) may be used. The

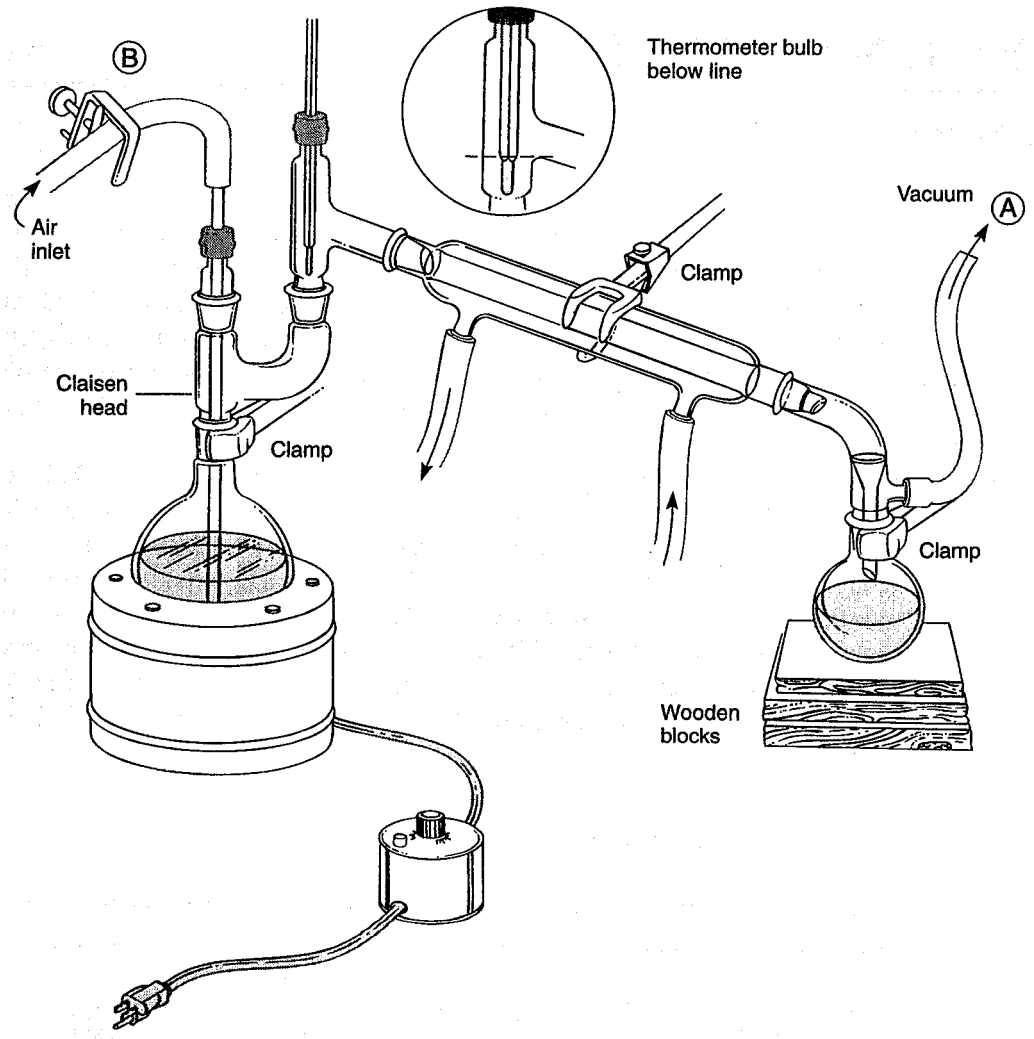


Figure 9.1 Macroscale vacuum distillation using the standard organic laboratory kit.

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.

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 air-tight and they will leak.

Greasing Joints. With standard scale 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-wall tubing (see pressure tubing below), the ebulliator is adjusted to admit a slow continuous stream of air bubbles into the distillation flask while you are distilling. Since 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 9.1, 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 Fig. 9.1). 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, it may not reach temperature equilibrium. As a result, the temperature reading would be incorrect (low).

Joint Clips. If plastic joint clips are available (Technique 3, Figure 3.5, p. 617), 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 9.2.

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 it or bend it, it may be old and leak air into the system. Replace any tubing that shows its age.

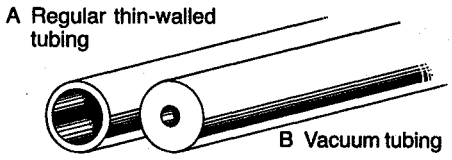


Figure 9.2 Comparison of tubing.

Rubber Stoppers. Always use soft rubber stoppers in a vacuum apparatus; corks will not give an air-tight 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 pre-weighed receiver flasks, including the original, available before the distillation begins. Such preparation permits the rapid changing of receiving flasks during the distillation. The pre-weighing 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 the next section.

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 9.3 and 9.4. 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 Fig. 9.8, p. 728). Variations in pressure are to be expected when using an aspiratory 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 take corrective action (i.e., 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.

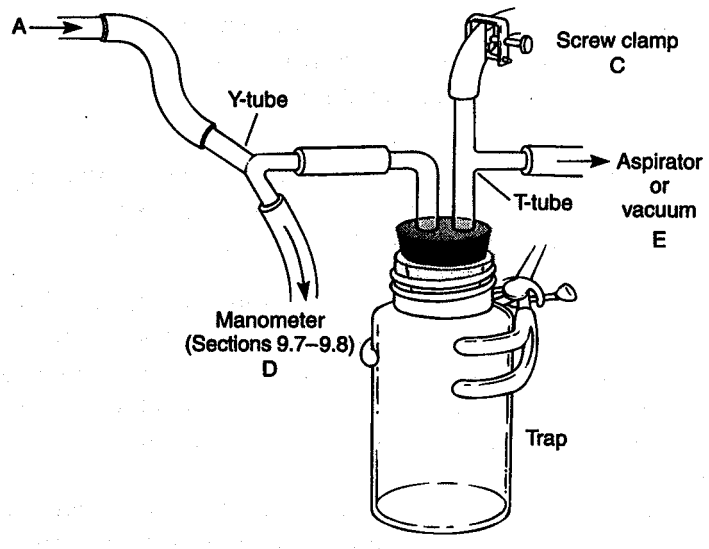


Figure 9.3 Vacuum trap using a gas bottle. The assembly connects to Figure 9.1 by joining the tubing at the point marked A. (The Y-tube connection to a manometer is optional.)

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

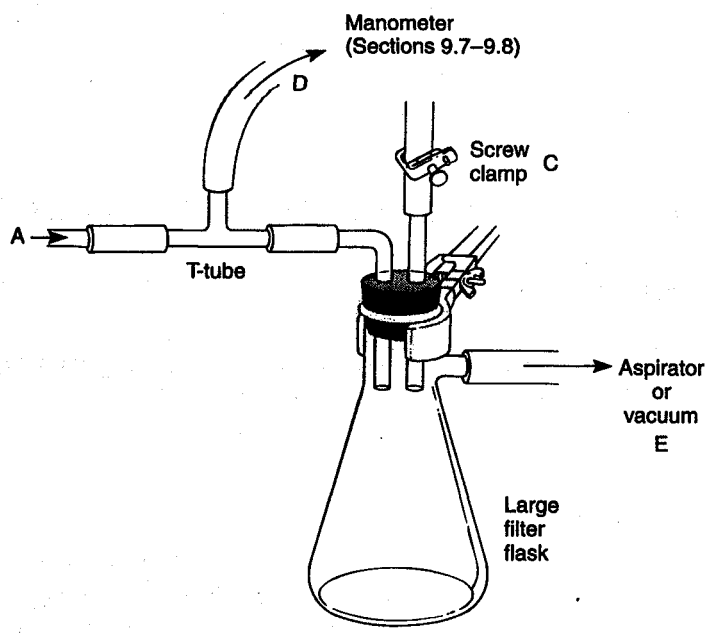


Figure 9.4 Vacuum trap using a heavy-wall filter flask. The assembly connects to Figure 9.1 by joining the tubing at the point A. (The T-tube connection to the manometer is optional.)

Sections 9.7 and 9.8. 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 the joints and connections to obtain the best working pressure *before* you begin to distill. Generally a working pressure of from 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 mm Hg at 25°C; 18 mm Hg at 20°C; 9 mm Hg 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.

9.2 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 9.1 as discussed in Section 9.1, and attach a trap (either Fig. 9.3 or 9.4). 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 (Figure 9.3 or 9.4) open the clamp at **C** and attach a manometer at point **D**.
6. Turn on the aspirator (or house vacuum) (Fig. 9.3) to the maximum extent.
7. Tighten the screw clamp at **B** (Fig. 9.1) until the tubing is nearly closed.
8. Going back to the trap (Fig. 9.3), 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.

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, and the manometer may 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 glass wool 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 it, 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.

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, pre-weighed 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.

Shutdown

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.

If you used grease, thoroughly clean all grease off the joints, or it will contaminate your samples in other procedures.

9.3 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, and it 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 9.5. 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.

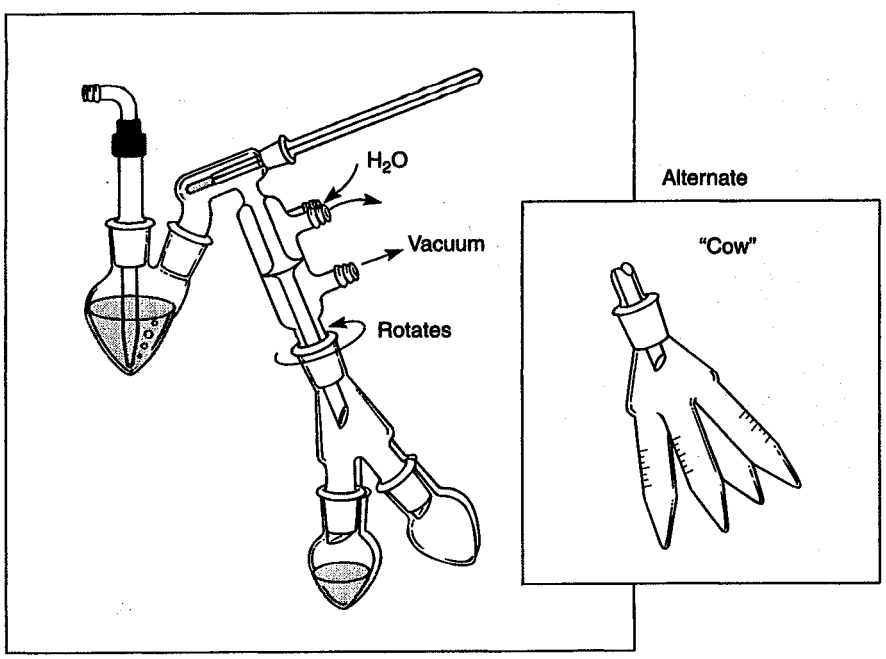


Figure 9.5 Rotary fraction collector.

9.4 MICROSCALE METHODS—STUDENT APPARATUS

Figure 9.6 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 to 3 mL of liquid. The Hickman head replaces the Claisen head, distilling head, condenser, and receiving flask with a single piece of glassware.

9.5 BULB-TO-BULB DISTILLATION

The ultimate in microscale methods is to use a bulb-to-bulb distillation apparatus. This apparatus is shown in Figure 9.7. The sample to be distilled is placed in the

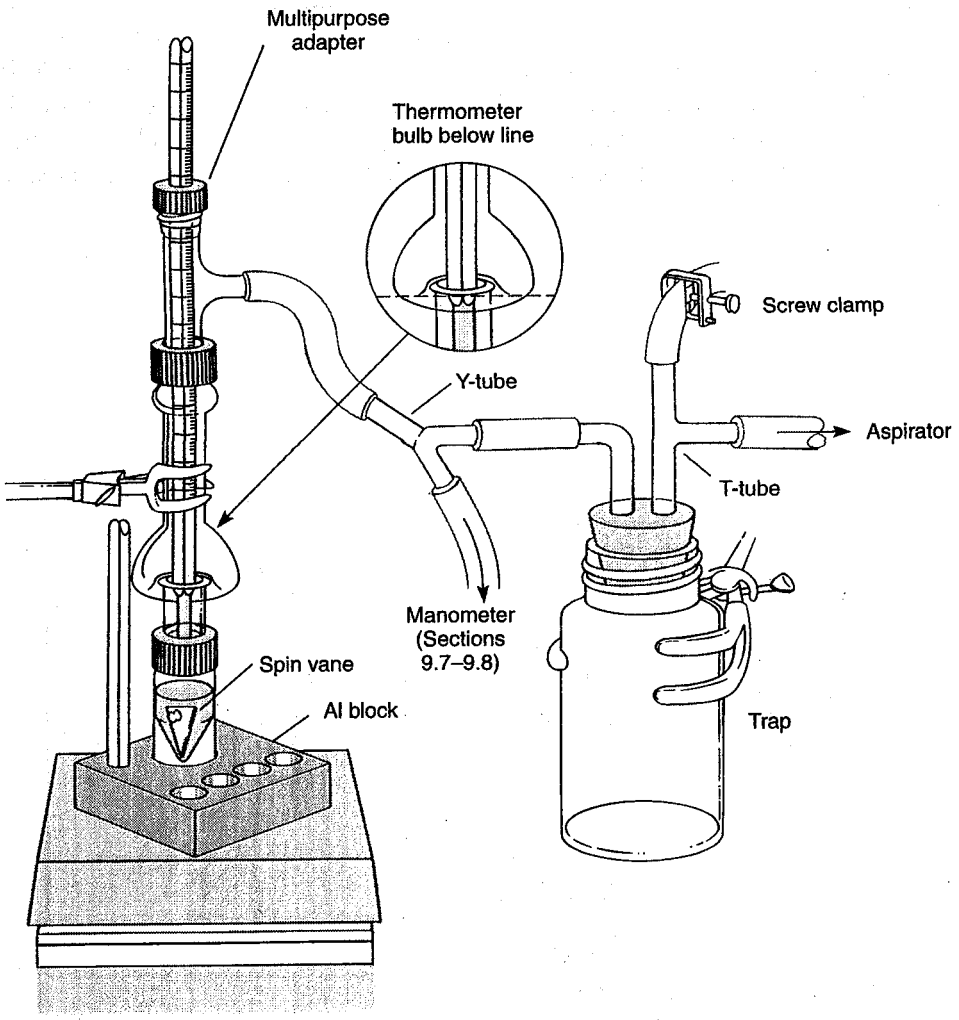


Figure 9.6 Reduced-pressure microscale distillation.

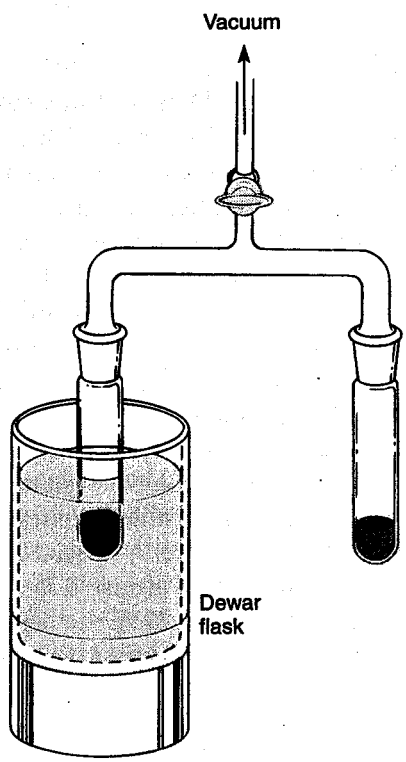


Figure 9.7 Bulb-to-bulb distillation.

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, the entire apparatus is evacuated 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.*

The bulb-to-bulb distillation is most effective when liquid nitrogen is used as 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.

9.6 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 9.8 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 discarding the oil as it is used, it is recycled continuously through the system.

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 9.8. 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

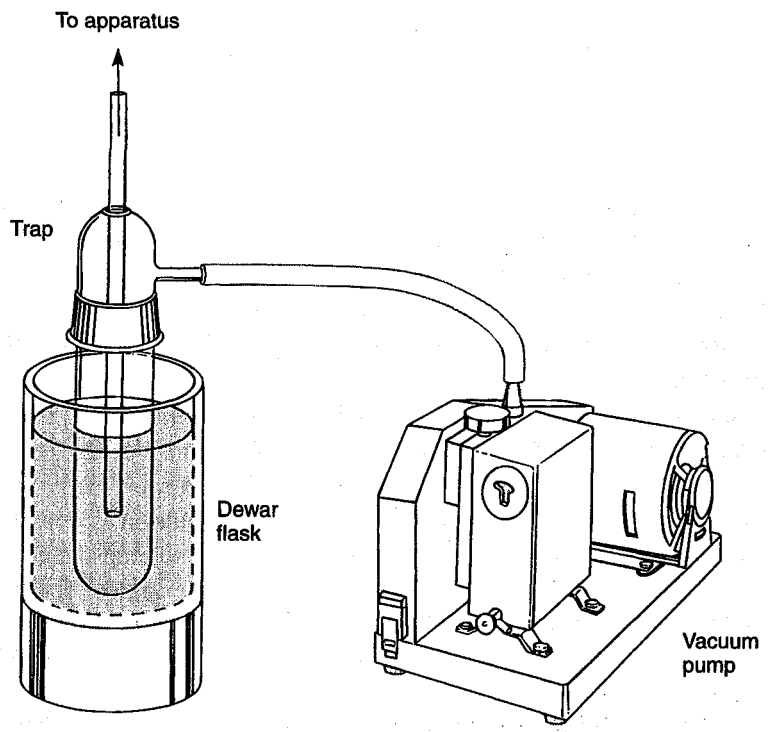


Figure 9.8 A vacuum pump and its trap.

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.

9.7 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 9.9 and 9.10. The manometer shown in Figure 9.9 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 9.11.

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 in case of a spill or if you break a manometer. Spills must be cleaned immediately.

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 mer-

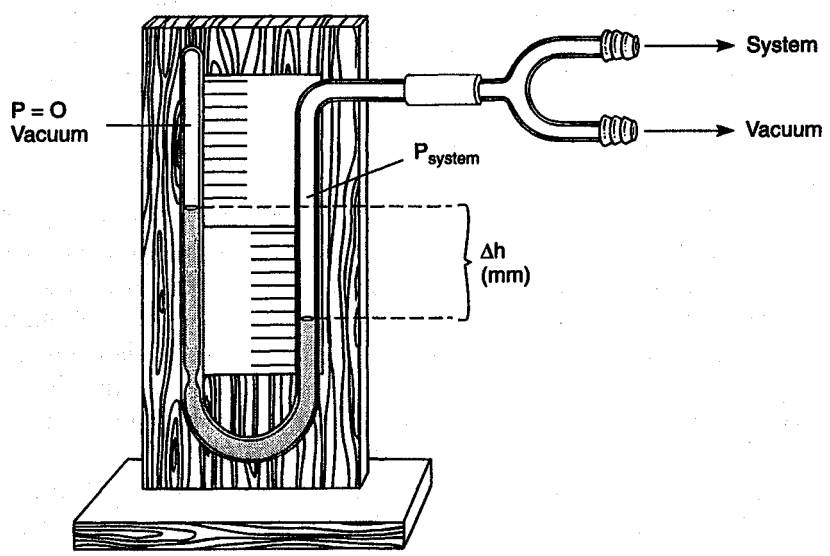


Figure 9.9 A simple U-tube manometer.

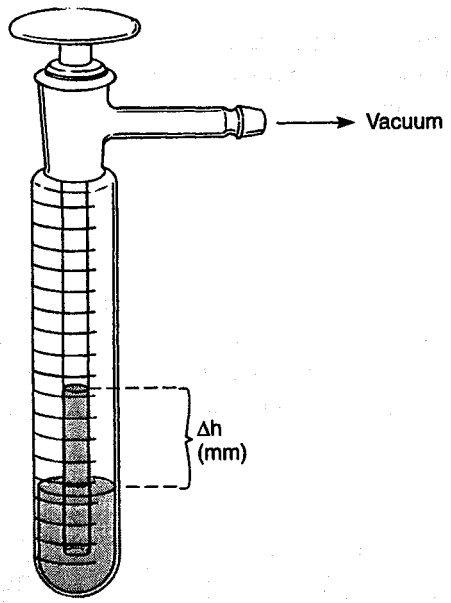


Figure 9.10 Commercial "stick" manometer.

cury 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 9.11 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.

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 Fig. 9.9).

$$\Delta h = (P_{\text{system}} - P_{\text{reference arm}}) = (P_{\text{system}} - 10^{-3}\ \text{mmHg}) \approx P_{\text{system}}$$

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 9.10. With this manometer, the pressure is given by the difference in the mercury levels in the inner and outer tubes.

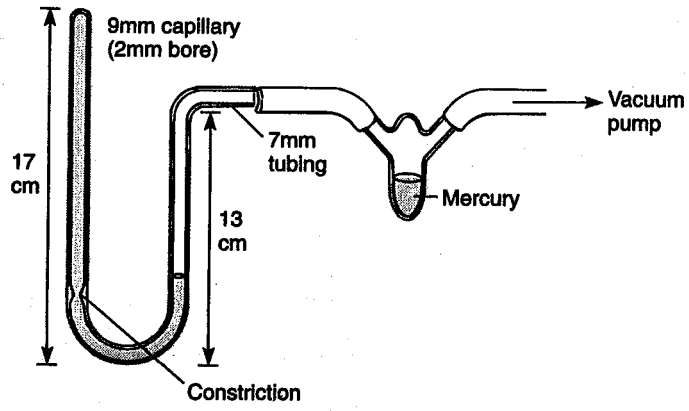


Figure 9.11 Filling a U-tube manometer.

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.

9.8 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 9.12. 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 9.12 appear in Figures 9.3 and 9.4. 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 into the room. In the closed-end manometer, if the system 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 9.12 if it is opened only a small amount. In those systems with a screw clamp on the trap (Figs. 9.3 and 9.4), 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.

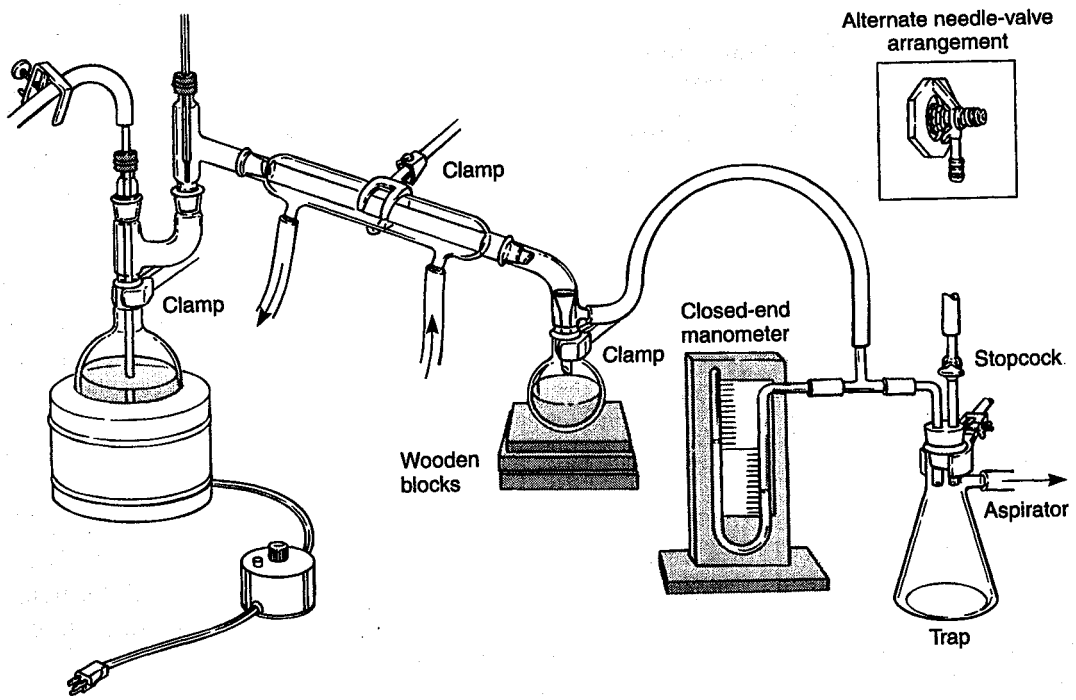


Figure 9.12 Connecting a manometer to the system. To construct a "bleed," the needle valve may replace the stopcock.

PROBLEMS

1. Give some reasons that would lead you to purify a liquid by using vacuum distillation rather than by using 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 was distilled under vacuum at 20 mmHg?
4. Boiling stones generally do not work when 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?

TECHNIQUE 10

Fractional Distillation, Azeotropes

Simple distillation, described in Technique 8, works well for most routine separation and purification procedures for organic compounds. When boiling-point differences of components to be separated are not large, however, **fractional distillation** must be used to achieve a good separation.

Part A. Fractional Distillation

10.1 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 8, Section 8.2 (pp. 708–710), and using the vapor-liquid composition curve given in Figure 10.1, you can see what would happen if you started with a 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 8.2B, p. 708), 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 10.1, we can see that this liquid would begin to boil at about 84°C and would give an initial distillate containing 90

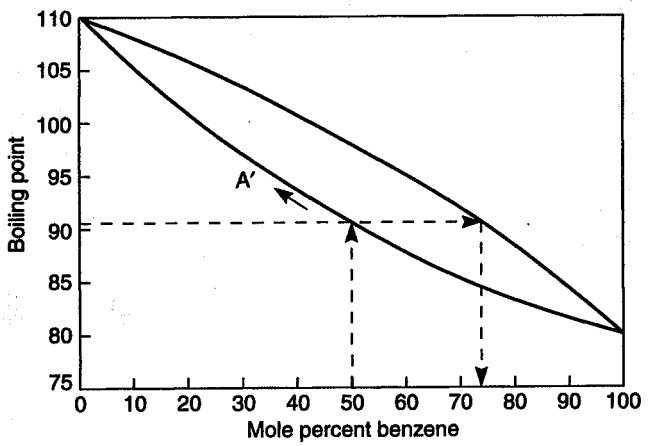


Figure 10.1 The vapor-liquid composition curve for mixtures of benzene and toluene.

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 per cent 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 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, while 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 10.2. 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).

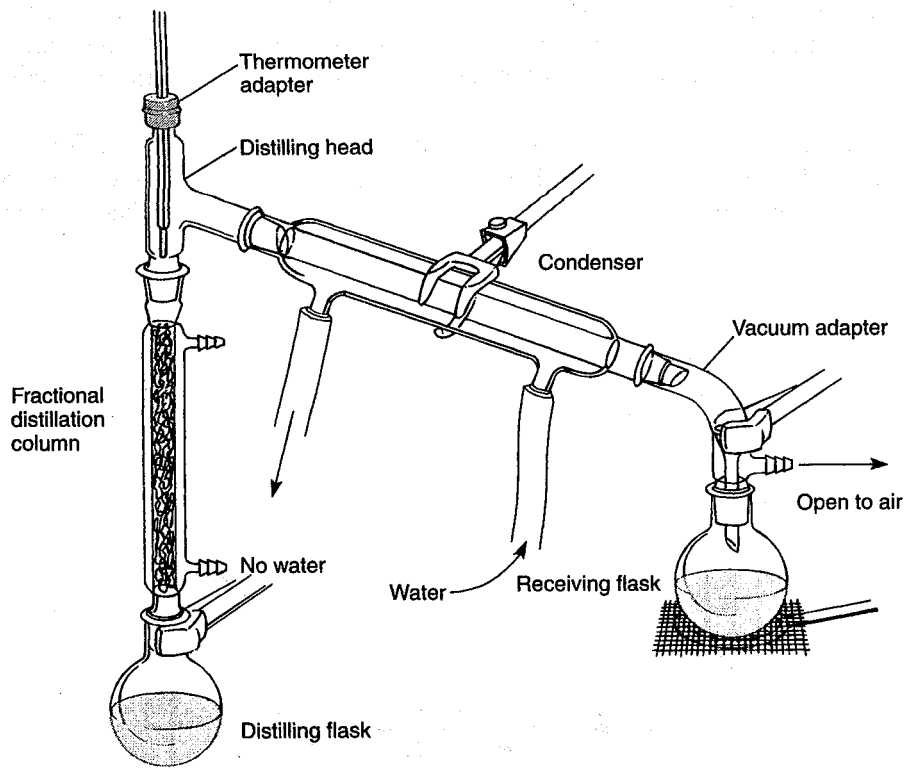


Figure 10.2 Fractional distillation apparatus.

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 the benzene is removed. The distillation must be carried out slowly to ensure that numerous vaporization–condensation cycles occur. When nearly all 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 8.2C (p. 708). This separation would be much better than that achieved by simple distillation (Figure 8.2B (p. 708).

10.2 VAPOR–LIQUID COMPOSITION DIAGRAMS

A vapor–liquid composition phase diagram like the one in Figure 10.3 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, 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 10.3.

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 pro-

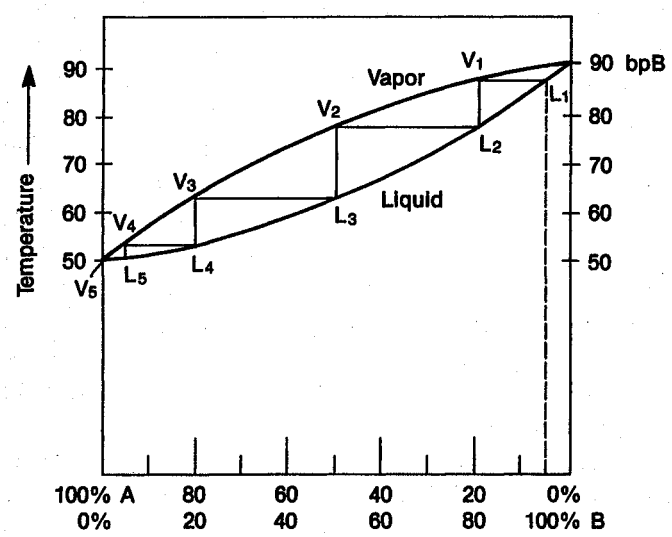


Figure 10.3 Phase diagram for a fractional distillation of an ideal two-component system.

duces that vapor. By convention, composition is expressed either in **mole fraction** or in **mole percentage.** The mole fraction is defined as follows:

$$\text{Mole fraction A} = N_A = \frac{\text{Moles A}}{\text{Moles A + Moles B}}$$

$$\text{Mole fraction B} = N_B = \frac{\text{Moles B}}{\text{Moles A + Moles B}}$$

$$N_A + N_B = 1$$

$$\text{Mole percentage A} = N_A \times 100$$

$$\text{Mole percentage B} = N_B \times 100$$

The horizontal and vertical lines shown in Figure 10.3 represents the processes that occur during a fractional distillation. Each of the **horizontal lines** (L_1V_1, L_2V_2, etc.) represents the **vaporization** step of a given vaporization–condensation cycle and represents 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.

Each of the **vertical lines** (V_1L_2, V_2L_3, etc.) 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 to 53°C.

In the example shown in Figure 10.3, 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, 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 10.4, where the composition of the liquids, their boiling points, and the composition of the vapors present are shown alongside the fractionating column.

10.3 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^0) times its mole frac-

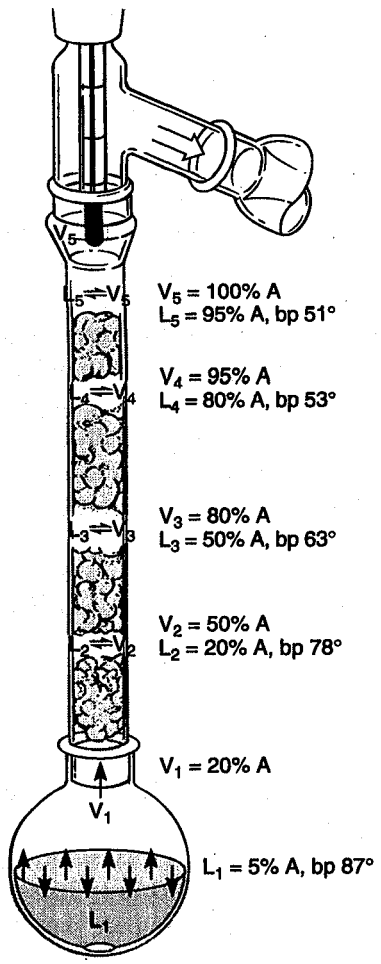


Figure 10.4 Vaporization-condensation in a fractionation column.

tion (N_A) (Eq.1). A similar expression can be written for component B (Eq. 2). The mole fractions N_A and N_B were defined in Section 10.2.

$$\text{Partial vapor pressure of A in solution} = P_A = (P_A^0)(N_A) \tag{1}$$

$$\text{Partial vapor pressure of B in solution} = P_B = (P_B^0)(N_B) \tag{2}$$

P_A^0 is the vapor pressure of pure A, independent of B. P_B^0 is the vapor pressure of 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 (Eq. 3). When the total pressure (sum of the partial pressures) equals the applied pressure, the solution boils.

$$P_{total} = P_A + P_B = P_A^0 N_A + P_B^0 N_B \tag{3}$$

The composition of A and B in the vapor produced is given by Equations 4 and 5.

$$N_A \text{ (vapor)} = \frac{P_A}{P_{total}} \tag{4}$$

$$N_B \text{ (vapor)} = \frac{P_B}{P_{total}} \tag{5}$$

Several exercises involving applications of Raoult's Law are illustrated in Figure 10.5. Note, particularly in the result from Equation 4, that the vapor is richer ($N_A = 0.67$) in the lower-boiling (higher vapor pressure) component A than it was before vaporization ($N_A = 0.50$). This proves mathematically what was described in Section 10.2.

The consequences of Raoult's Law for distillations are shown schematically in Figure 10.6. 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.

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.

$$P_{total} = P_{water}^0 N_{water} + P_{salt}^0 N_{salt}$$

$$P_{salt}^0 = 0$$

$$P_{total} = P_{water}^0 N_{water}$$

A solution whose mole fraction of water is 0.7 will not boil at 100°C, because P_{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_{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.)

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: $P_A = P°_A N_A = (1020)(0.5) = 510$ 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: $P_B = P°_B N_B = (500)(0.5) = 250$ 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

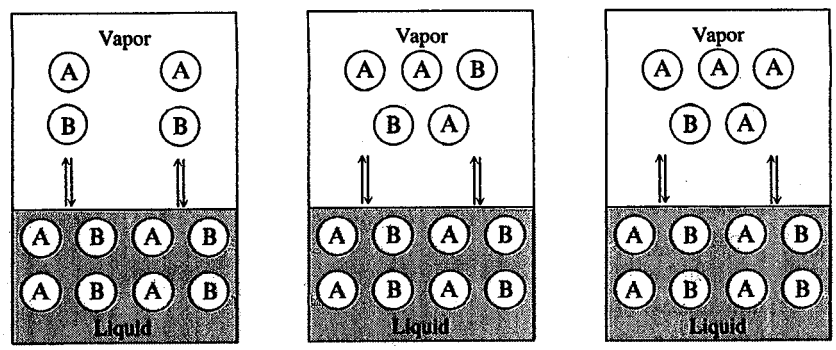
4. What is the composition of the vapor at the boiling point?

   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 10.5 Sample calculations with Raoult's Law.



$N_A = N_B$
$P_A° = P_B°$
$P_A°N_A = P_B°N_B$

Equal amounts of A and B in vapor—no separation

A

$N_A = N_B$
$P_A° > P_B°$ ($bp_A < bp_B$)
$P_A°N_A > P_B°N_B$

More A in vapor than B—some separation

B

$N_A = N_B$
$P_A° >>> P_B°$
$P_A°N_A >>> P_B°N_B$

Much more A in vapor than B—good separation

C

Figure 10.6 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.

10.4 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 10.3, 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 10.3, *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 10.3. 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 as long as it 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 10.1. 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.

TABLE 10.1 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

10.5 TYPES OF FRACTIONATING COLUMNS AND PACKINGS

Several types of fractionating columns are shown in Figure 10.7. The Vigreux column, shown in Part A, has indentations that incline downward at angles of 45° and are in pairs on opposites 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 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 a slightly greater efficiency yet. 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.

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 (Fig. 10.8). A spinning-band column that is available for microscale work is shown in Figure 10.9. This spinning-band column has a band about 2–3 cm in length and provides 4–5 theoretical

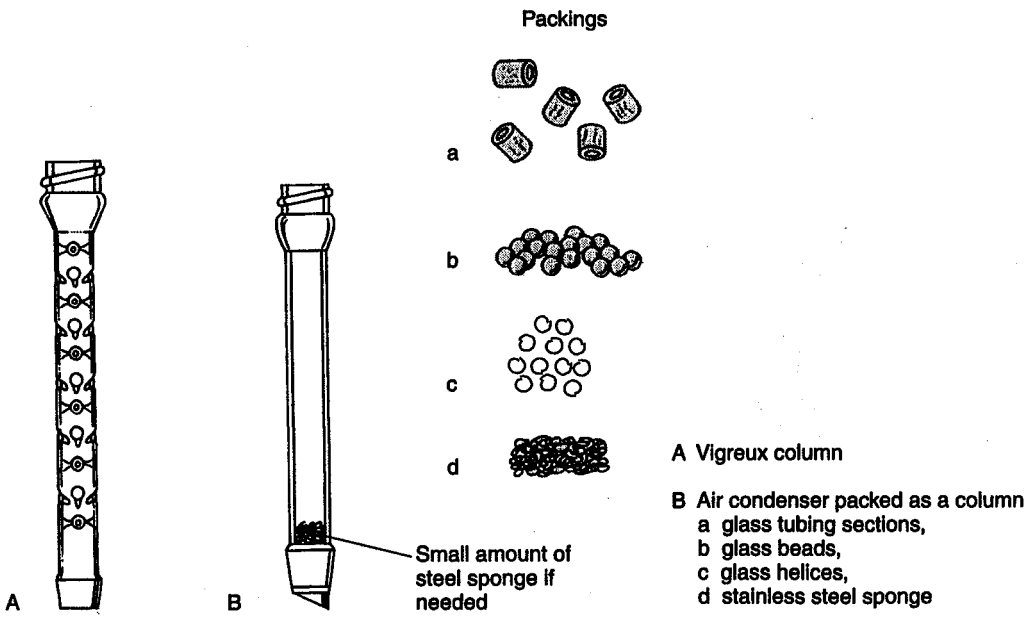


Figure 10.7 Columns for fractional distillation.

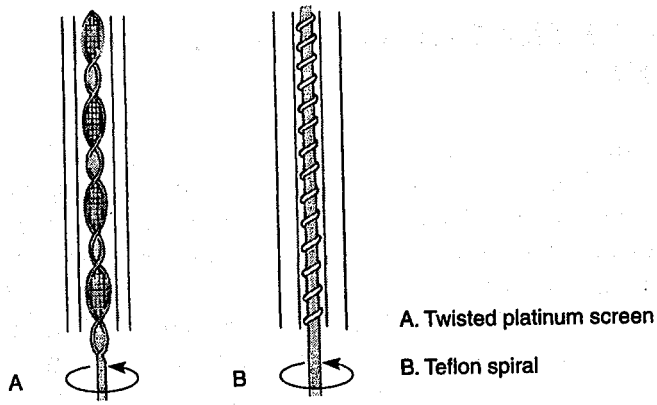


Figure 10.8 Bands for spinning-band columns.

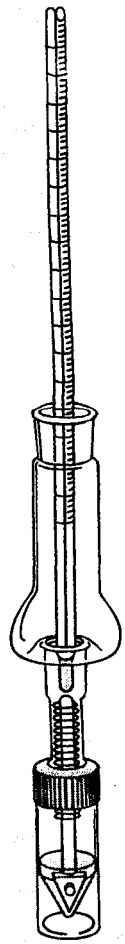


Figure 10.9 A commercially available microscale spinning-band column.

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. 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.

10.6 FRACTIONAL DISTILLATION: METHODS AND PRACTICE

In performing a fractional distillation, the column should be clamped in a vertical position. The distillation should be conducted as slowly as possible, but the rate of distillation should be steady enough to produce a constant temperature reading at the thermometer.

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 evacuated outer jacket, but those that do not can benefit from being wrapped in insulation.

Glass wool and aluminum foil (shiny side in) are often used for insulation. You can wrap the column with glass wool and then use a wrapping of the aluminum foil to keep it in place. An especially effective method is to make an insulation blanket by placing a layer of glass wool or 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.

Standard Scale Apparatus. Figure 10.2 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.

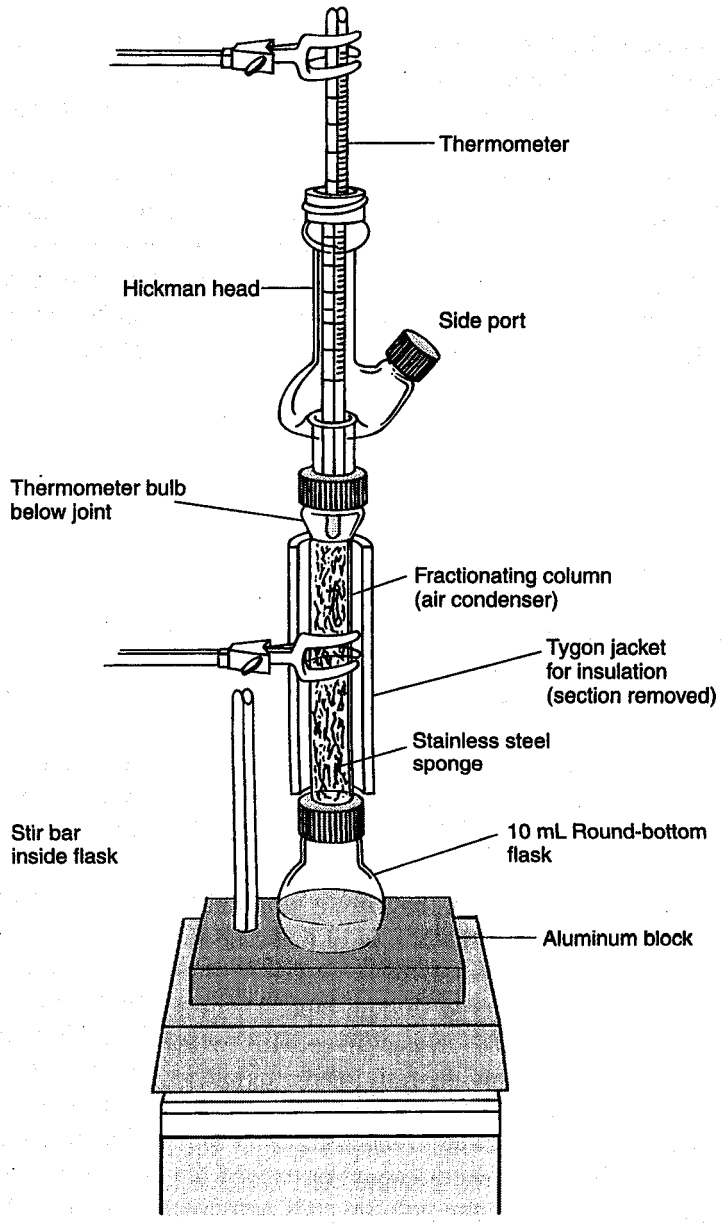


Figure 10.10 Microscale apparatus for fractional distillation.

Microscale Apparatus. The apparatus shown in Figure 10.10 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 those shown in Figure 10.9.

Part B. Azeotropes

10.7 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 10.11. The azeotrope at V_3 has a composition

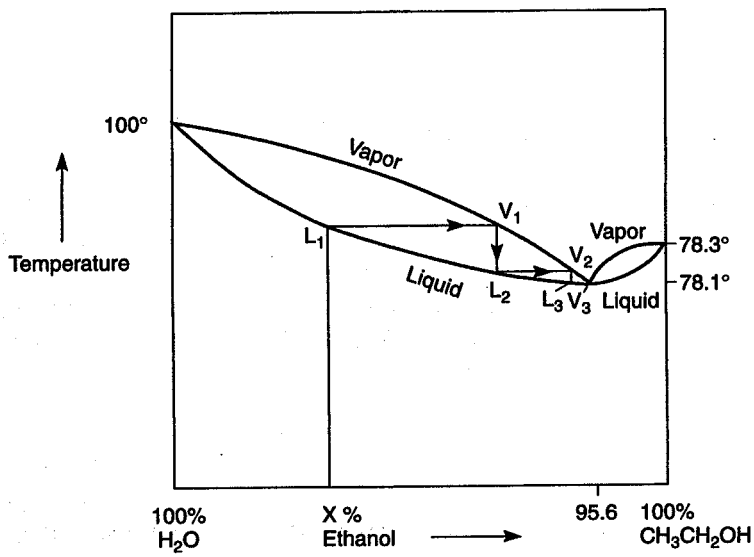


Figure 10.11 Ethanol–water minimum-boiling-point phase diagram.

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.

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.[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, 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 azeotropes are given in Table 10.2. 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 *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 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 10.12. Because the azeotrope has a higher boil-

[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: American Chemical Society, 1973).

TABLE 10.2 Common Minimum-Boiling 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

ing 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 10.12. 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 the material in the distillation flask has been exhausted.

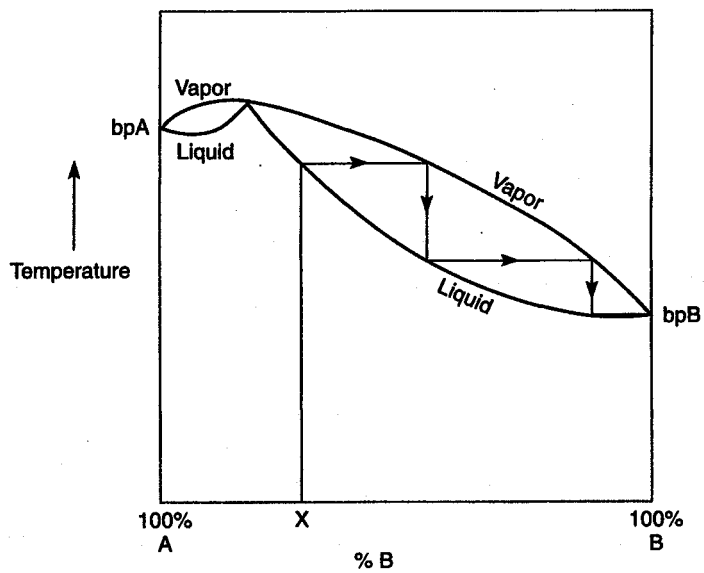


Figure 10.12 A maximum-boiling-point phase diagram.

TABLE 10.3 Maximum-Boiling 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 10.3. 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, while 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	unseparable
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	unseparable
to right of azeotrope	pure B distills first, azeotrope second

[3]See Footnote 2.

10.8 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:

$$R{-}\overset{\overset{O}{\|}}{C}{-}OH + R{-}O{-}H \overset{H^+}{\rightleftharpoons} R{-}\overset{\overset{O}{\|}}{C}{-}OR + H_2O$$

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 8) and methyl salicylate (Experiment 10) are examples of esters 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 above 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 10.13A. In this technique, an in-

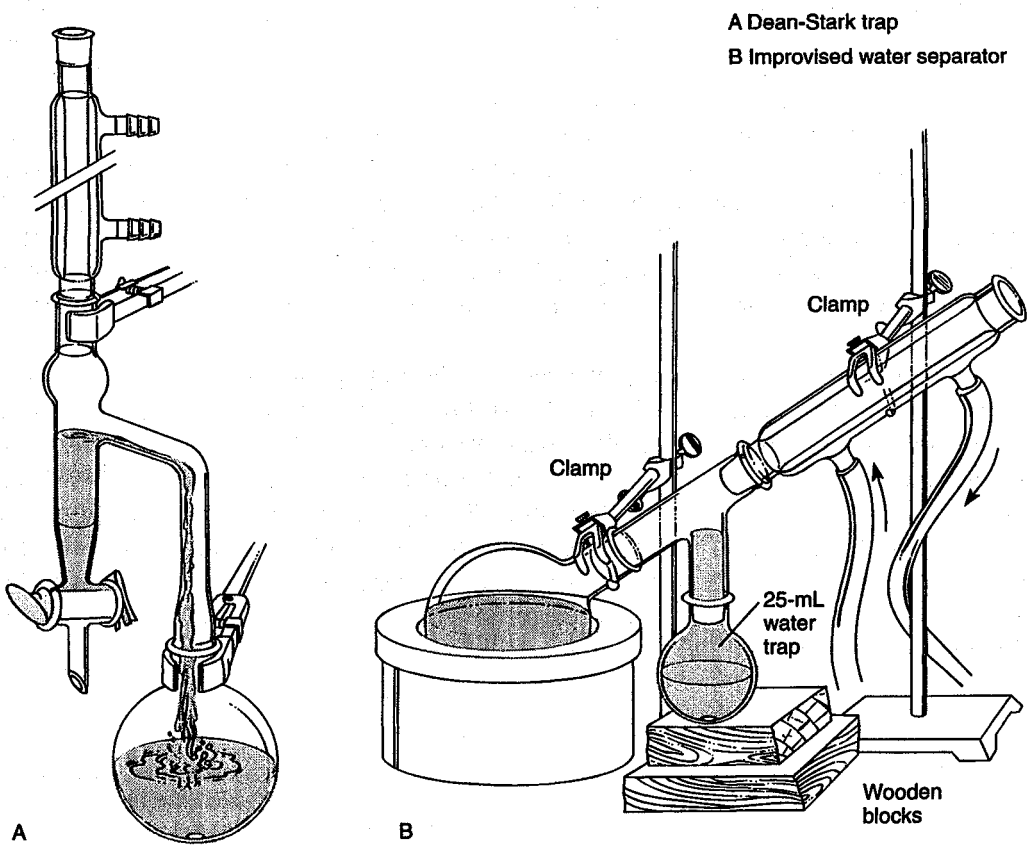


Figure 10.13 Large-scale water separators.

ert solvent, commonly benzene or toluene, is added to the reaction mixture contained in the round-bottom flask. The side-arm 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 10.2) distills out of the flask.[4] When the vapor condenses, it enters the side-arm 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 side-arm back into the flask. The cycle is repeated continuously until no more water forms in the side-arm. You may calculate the weight of water that should theoretically be produced and compare this value with the amount of water collected in the side-arm. 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 10.13B. 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 (Fig. 10.14). 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 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 8 (Fig. 8.7, p. 715). 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 p. 749) 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. For example, you can mix the carboxylic acid, methanol, the acid catalyst, and *1,2-dichloroethane* in a conventional reflux apparatus (Technique 3, Fig. 3.8, p. 619) without a water separator. During the reaction, water separates from the 1,2-dichloroethane 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.

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[4]Actually, with ethanol, a lower-boiling-point, three-component azeotrope distills at 64.9°C (see Table 10.2). 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.

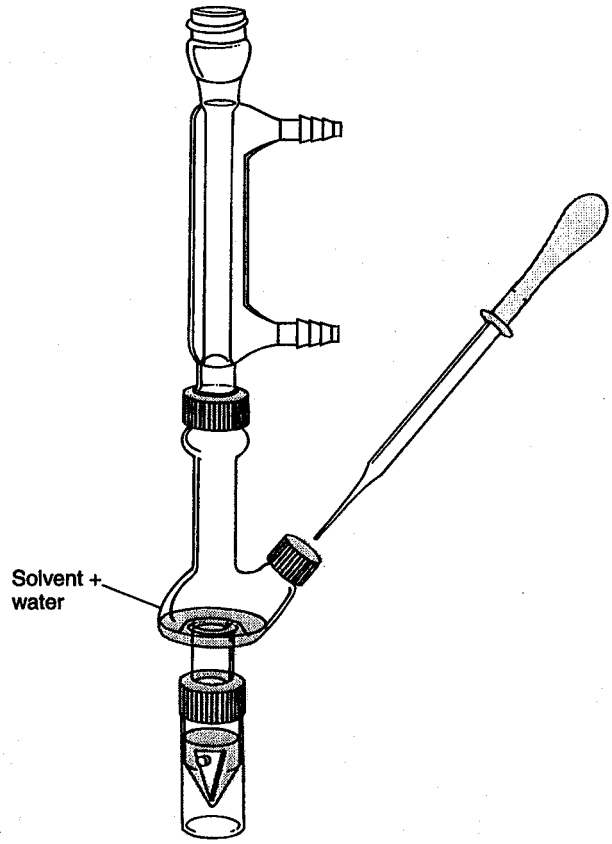
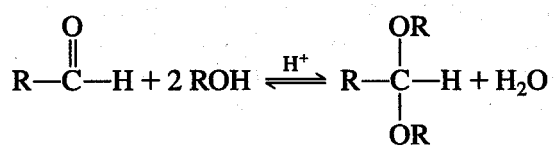


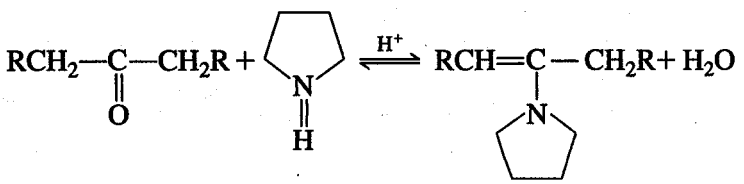
Figure 10.14 Microscale water separator (both layers are removed).

Azeotropic distillation is also used in other types of reactions, such as ketal or acetal formation, and in enamine formation.

Acetal Formation



Enamine Formation



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 10.3.

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^0 and P_B^0) 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 on distillation of a 98% ethanol solution through an efficient column. Refer to Figure 10.11.

7. Construct an approximate boiling-point-composition diagram for a benzene-methanol system. The mixture shows azeotropic behavior (see Table 10.2). 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 azeotrope (Table 10.3). Describe the behavior on distillation of a mixture that is initially rich in acetone (90%), then describe the behavior of a mixture that is initially rich in chloroform (90%).

9. Two components have boiling points of 130 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?

TECHNIQUE 11

Steam Distillation

The simple, vacuum, and fractional distillations described in Techniques 8, 9, and 10 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.

11.1 DIFFERENCES BETWEEN DISTILLATION OF MISCIBLE AND IMMISCIBLE MIXTURES

$$\text{MISCIBLE LIQUIDS} \quad P_{\text{total}} = P_{\text{A}}^{0} N_{\text{A}} + P_{\text{B}}^{0} N_{\text{B}} \tag{1}$$

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^0 and P_B^0 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^0 and P_B^0 and also N_A and N_B. Thus, the composition of the vapor will also depend on *both* the vapor pressures and the mole fractions of each component.

$$\text{IMMISCIBLE LIQUIDS} \quad P_{total} = P_A^0 + P_B^0 \tag{2}$$

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 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 11.2.

$$\frac{\text{Moles A}}{\text{Moles B}} = \frac{P_A^0}{P_B^0} \tag{3}$$

A mixture of two immiscible liquids boils at a lower temperature than the boiling points of either component. The explanation for this behavior is like that given for minimum-boiling-point azeotropes (Technique 10, Section 10.7). Immiscible liquids behave as they do because an extreme incompatibility between the two liquids leads to higher combined vapor pressures 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 11.1. Note that with miscible liquids, the composition of the vapor depends on the relative amounts of A and B present (Fig. 11.1A). 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 (Fig. 11.1B). 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 compartments, as shown in Figure 11.1B, 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.

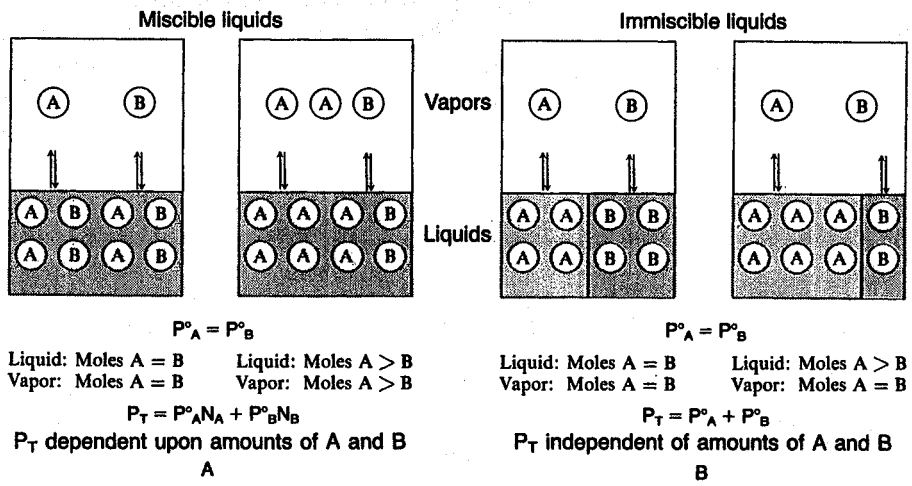


Figure 11.1 Total pressure behavior for miscible and immiscible liquids. (A) Ideal miscible liquids follow Raoult's Law: P_T depends on the mole fractions and vapor pressures of A and B. (B) Immiscible liquids do not follow Raoult's Law: P_T depends only on the vapor pressures of A and B.

11.2 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 11.1. 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.

TABLE 11.1 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%

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 relation 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 Figure 11.2. Notice that the result of this calculation is very close to the experimental value given in Table 11.1.

11.3 STEAM DISTILLATION: METHODS

Two methods for steam distillation are in general use 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.

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.

$$\text{1-octanol} = 1.55 \text{ g}/(10 \text{ g} + 1.55 \text{ g}) = 13.4\%$$
$$\text{water} = 10 \text{ g}/(10 \text{ g} + 1.55 \text{ g}) = 86.6\%$$

Figure 11.2 Sample calculations for a steam distillation.

A. DIRECT METHOD

Standard Scale. A large-scale direct method steam distillation is illustrated in Figure 11.3. 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 that all of the organic material codistills.

Microscale. The direct method of steam distillation is the only one suitable for microscale reactions. 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 11.4. 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

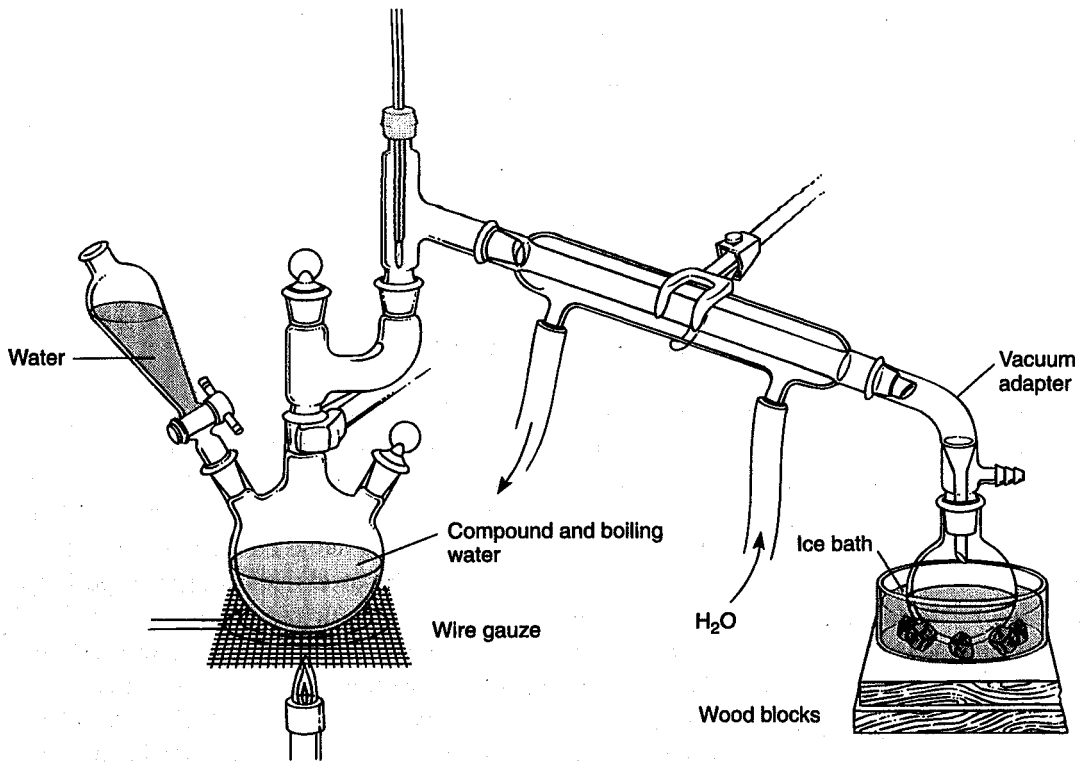


Figure 11.3 Macroscale direct steam distillation.

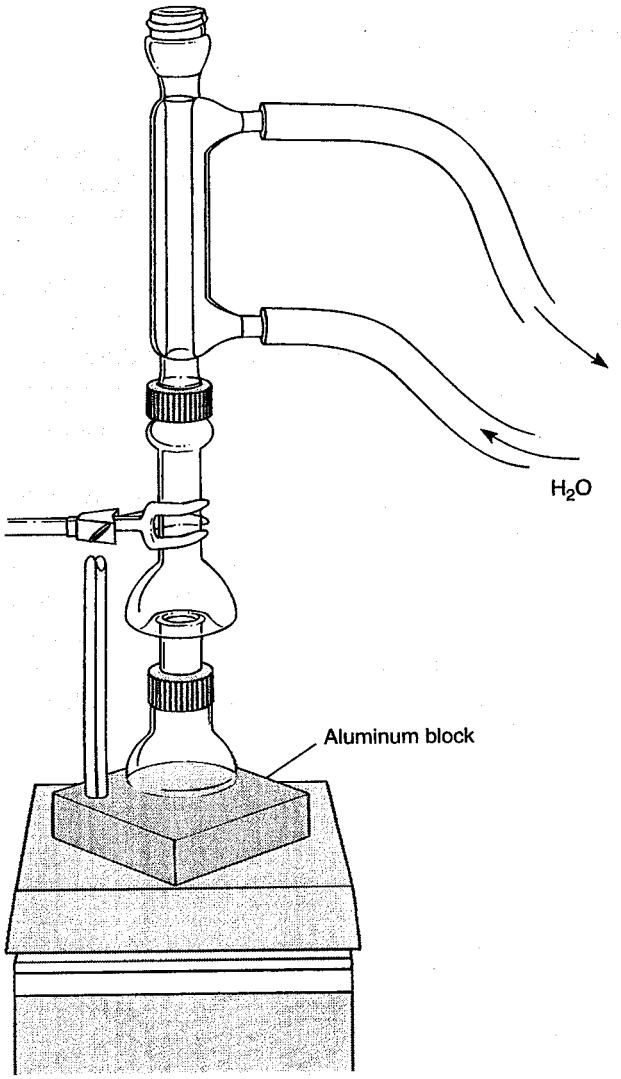


Figure 11.4 Microscale steam distillation.

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 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.

Semi-Microscale. The apparatus shown in Figure 8.5, page 714, 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.

B. LIVE STEAM METHOD

Standard Scale. A large-scale steam distillation using the live steam method is shown in Figure 11.5. 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

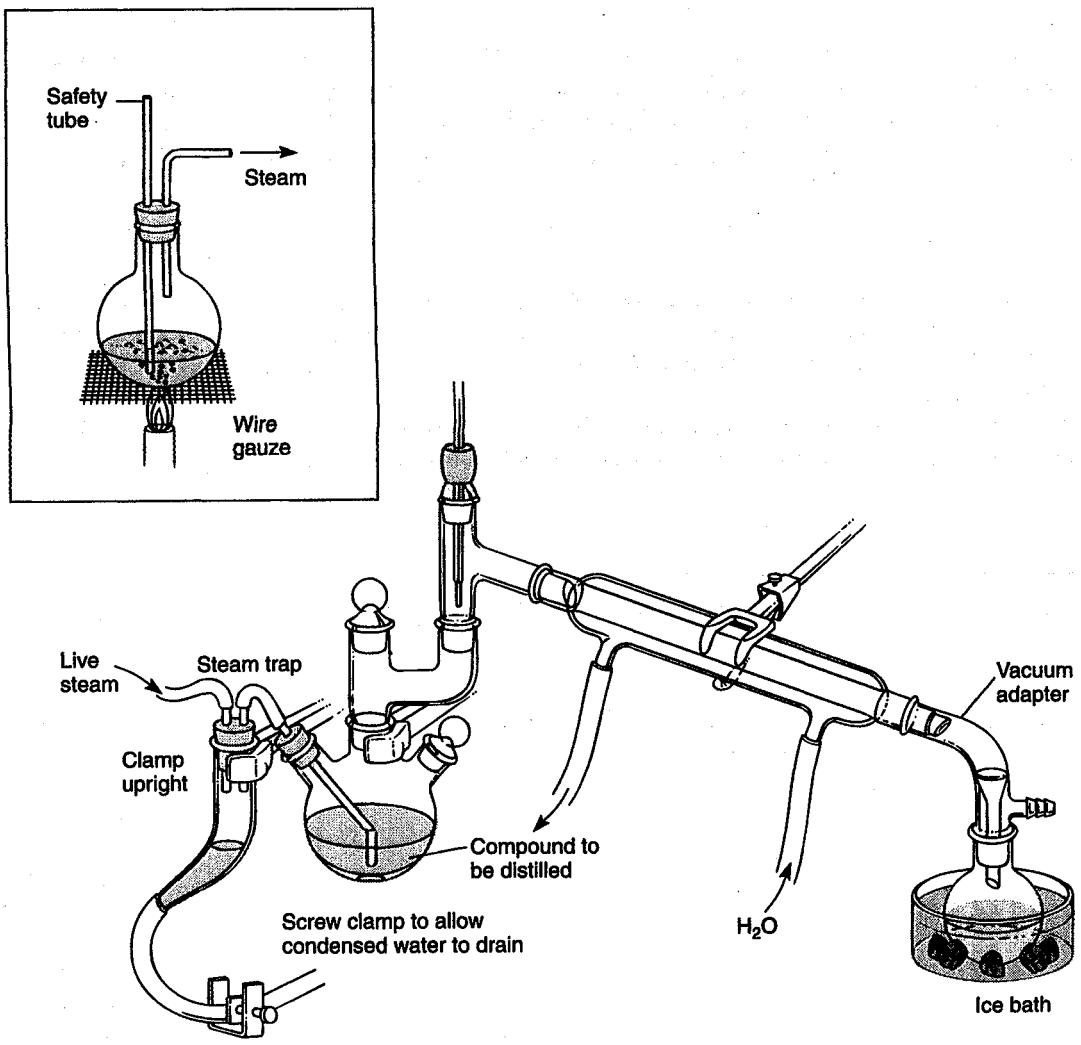


Figure 11.5 Macroscale steam distillation using live steam.

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.

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 11.1.

2. Calculate the approximate boiling point of a mixture of bromobenzene and water at atmospheric pressure. A table of vapor pressures 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.

TECHNIQUE 12

Column Chromatography

The most modern and sophisticated methods of separating mixtures that the organic chemist has available 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 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 (Technique 7). 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. In this chapter, column chromatography, a solid–liquid method, is considered. High-performance liquid chromatography is discussed in Technique 13. Thin-layer chromatography is examined in Technique 14; gas chromatography, a gas–liquid method, is discussed in Technique 15.

12.1 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- to 400-mesh).

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.

$$\text{Bauxite (crude)} \xrightarrow{\text{hot NaOH}} Al(OH)_4^-(aq) + Fe_2O_3\ \text{(insoluble)}$$

$$Al(OH)_4^-(aq) + CO_2 \longrightarrow Al(OH)_3 + HCO_3^-$$

$$2\ Al(OH)_3 \xrightarrow{\text{heat}} Al_2O_3(s) + 3\ H_2O$$

Alumnia 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 alumnia is being used for chromatography. Silica gel is not available in any form other than that suitable for chromatography.

12.2 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 alumnia. 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 12.1, 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 approximate order:

Salt formation > Coordination > Hydrogen-bonding > Dipole–dipole > van der Waals

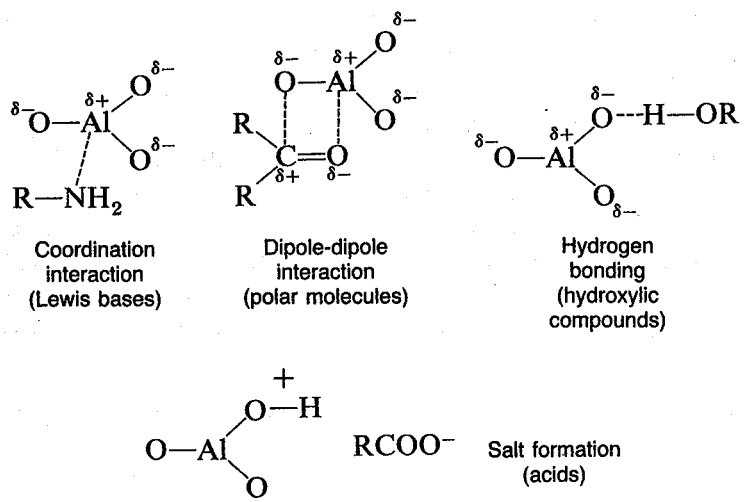


Figure 12.1 Possible interactions of organic compounds with alumina.

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:

> The more polar the functional group, the stronger the bond to alumina (or silica gel).

A similar rule holds for solubility. Polar solvents dissolve polar compounds more effectively than nonpolar solvents: 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 12.2.

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.

12.3 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

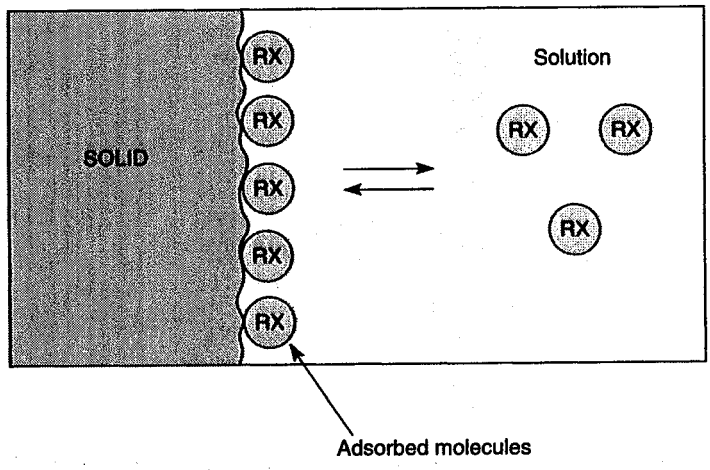


Figure 12.2 Dynamic adsorption equilibrium.

of compounds to be separated is introduced onto the top of a cylindrical glass column (Figure 12.3) **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.

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 between the adsorbent, the solutes, and the solvent. The constant equilibration means that different compounds will move down the column at differing rates depending on their relative affinity for the adsorbent on 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), 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 or bands of pure solvent in between. As each band (solvent and solute) passes out 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 at all is the result. A successful chromatographic separation is illustrated in Figure 12.4.

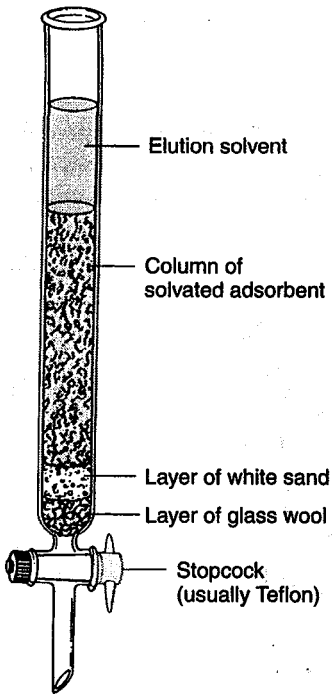


Figure 12.3 Chromatographic column.

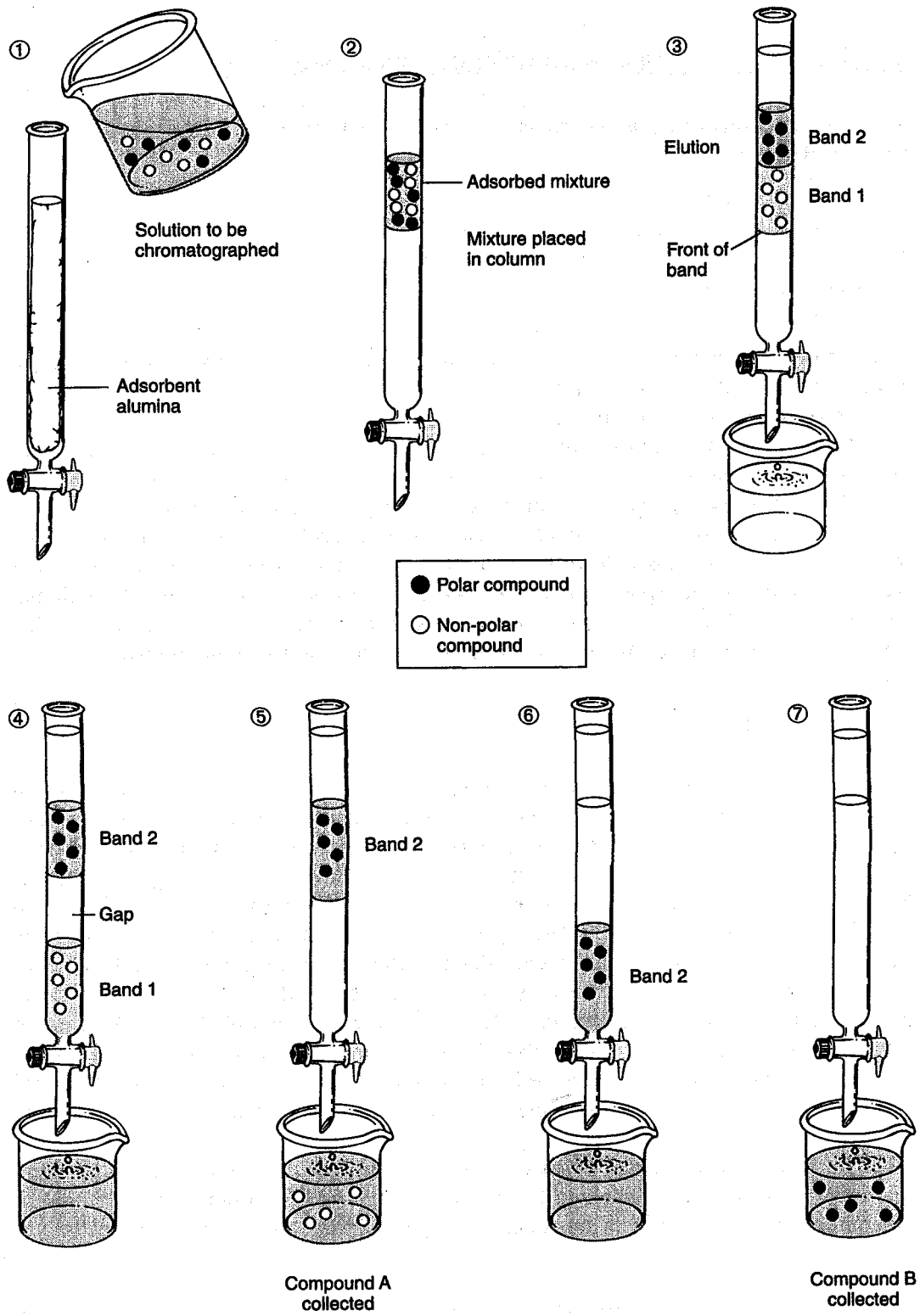


Figure 12.4 Sequence of steps in a chromatographic separation.

12.4 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 column or 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)

By carefully choosing the conditions, 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 other hand, if too polar a solvent is chosen, all 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.[1]

A. ADSORBENTS

In Table 12.1, 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, amines. Alumina is the most widely used adsorbent and is obtained in the three forms mentioned in Section 12.1: 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 12.1 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 depend on the amount of water pre-

[1]Often the chemist uses thin-layer chromatography (TLC), which is described in Technique 14, 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.

TABLE 12.1 Solid Adsorbents for Column Chromatography

Paper	
Cellulose	
Starch	
Sugars	
Magnesium silicate	
Calcium sulfate	**Increasing strength of**
Silicic acid	**binding interactions**
Silica gel	**toward polar compounds**
Florisil	
Magnesium oxide	
Aluminum oxide (Alumina)*	
Activated charcoal (Norit)	

*Basic, acid-washed, and neutral.

sent. Water binds very tightly to either adsorbent, taking up sites on the particles that could otherwise be used for equilibration with solute molecules. If one adds water to the adsorbent, it is said to have been **deactivated.** Anhydrous alumina or silica gel are 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.

B. SOLVENTS

In Table 12.2, 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 elute. The approximate order in which various classes of compounds elute by this procedure is given in Table 12.3. In general, nonpolar compounds travel through the column faster (elute first), and polar compounds travel more slowly (elute last). However, molecular weight is also 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.

TABLE 12.2 Solvents (Eluents) for Chromatography

Petroleum ether	
Cyclohexane	
Carbon tetrachloride*	
Toluene	
Chloroform*	
Methylene chloride	**Increasing polarity**
Diethyl ether	**and "solvent power"**
Ethyl acetate	**toward polar functional**
Acetone	**groups**
Pyridine	
Ethanol	
Methanol	
Water	
Acetic acid	

*Suspected carcinogens.

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.

$$\text{Solvent} + \text{Alumina} \longrightarrow (\text{Alumina} \cdot \text{Solvent}) + \text{Heat}$$

TABLE 12.3 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 (need a polar solvent)**

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.

That the solvent itself has a tendency to adsorb on the alumina is an important factor in how compounds move down the column. The solvent can displace the adsorbed compound if it is more polar than the compound and, hence, can move it down the column. Thus, a more polar solvent not only dissolves more compound but also is effective in removing the compound from the alumina, because it displaces the compound from its site of adsorption.

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 going to solvents more polar than diethyl ether or methylene chloride in the eluent series (Table 12.2).

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 12.4.

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 in the amount of adsorbent needed. Compounds that do not separate easily may require larger columns and more adsorbent than specified in Table 12.4. For easily separated compounds, a smaller column and less adsorbent may suffice.

TABLE 12.4 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.

12.5 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 12.5. There

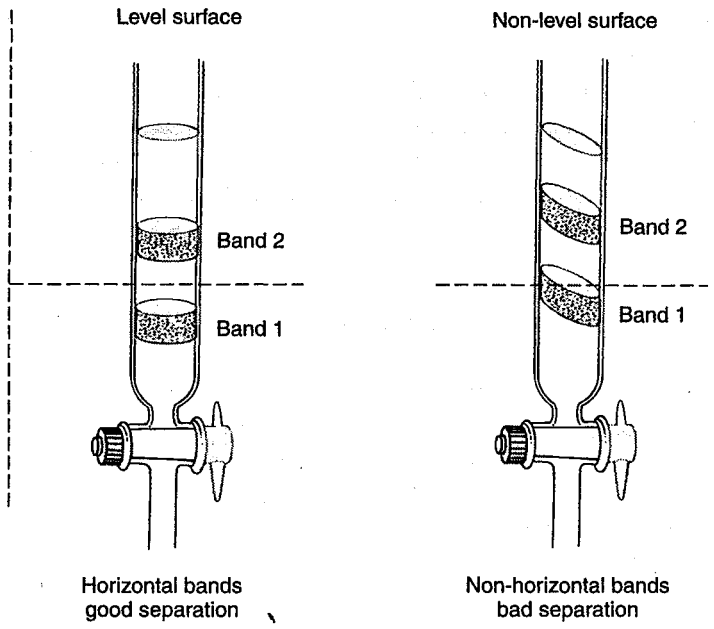


Figure 12.5 Comparison of horizontal and nonhorizontal band fronts.

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 you are preparing a column, you must watch both 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 12.6.

12.6 PACKING THE COLUMN: STANDARD-SCALE AND SEMI-MICROSCALE METHODS

The following methods 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 well affect the quality of the separation.

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.

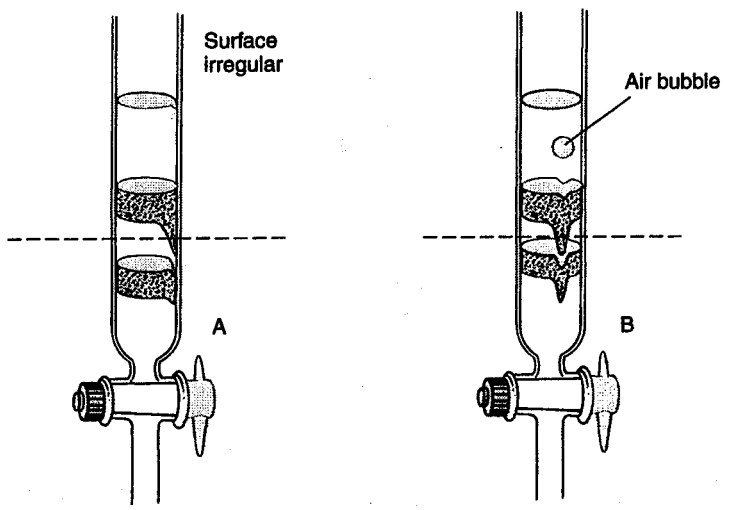


Figure 12.6 Channeling complications.

A. PREPARING THE SUPPORT BASE

Standard-Scale Columns. For large-scale applications, clamp a chromatography column upright (vertically). The column (Fig. 12.3) is a piece of cylindrical glass tubing with a stopcock attached at one end. The stopcock usually has a Teflon plug, because stopcock 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, attach a piece of flexible tubing to the bottom of the column, with a screw clamp used to stop or regulate the flow (Fig. 12.7). When a screw clamp is used, care must be taken that the tubing 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 like 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

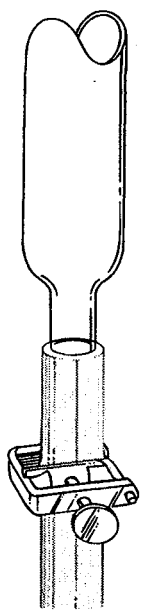


Figure 12.7 Tubing with screw clamp to regulate solvent flow on a chromatography column.

of adsorbent and prevents it from washing through the stopcock. The column is packed in one of two ways: by the slurry method or by the dry pack method.

Semi-Microscale Columns. An alternative apparatus for small-scale column chromatography is a commercial column, such as the one shown in Figure 12.8. This type of column is made of glass and has a solvent-resistant plastic stopcock at the bottom.[1] 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 12.8 is equipped with the solvent reservoir. This type of column is available in a variety of lengths, ranging from 100 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.

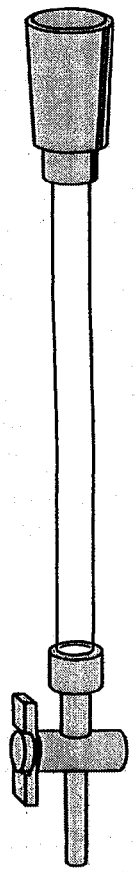


Figure 12.8 Commercial semi-microscale chromatography column. (The column is shown equipped with an optional solvent reservoir.)

[1]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 solvents that they intend to use before the beginning of the laboratory class.

B. DEPOSITING THE ADSORBENT

Slurry Method

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 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 homogenous and relatively free of entrapped air bubbles.

For standard-sized or semi-microscale columns, 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 re-added 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. You should take care never to let the column run dry during packing.

Dry Pack Method 1

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.

Standard-Scale Columns. A plug of cotton is placed at the base of the column, and an even layer of sand is formed on top (see p. 764). 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 in order to ensure that the column is packed evenly. When the column has the desired length, no more adsorbent is added. This method also produces an evenly packed column. Solvent should be cycled through this column

(for standard scale 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 (Section 12.7). 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 acts to prevent adsorbent from escaping from the column.

Dry Pack Method 2

Standard-Scale Columns. Standard-scale columns can also be packed by a dry pack method that is similar to the microscale methods described in Section 12.7. 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 is similar to that described for Pasteur pipets (Section 12.7), 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 Fig. 12.8).

12.7 PACKING THE COLUMN: MICROSCALE METHODS

As with standard-scale or semi-microscale columns, the procedures described in this section should be followed carefully in preparing a microscale chromatography column. Failure to pay close attention to the details of these procedures may adversely affect the quality of the separation.

Again, preparation of a column involves two distinct stages: preparation of the support base and filling the column with adsorbent.

A. PREPARING THE SUPPORT BASE

For microscale applications, select a Pasteur pipet ($5\frac{3}{4}$-inch) and clamp it upright (vertically). In order to reduce the amount of solvent needed to fill the column, break off most of the tip of the pipet. Place a small ball of cotton in the pipet and tamp it 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 12.9. A microscale chromatography column is packed by one of the dry pack methods described in Part B of this section.

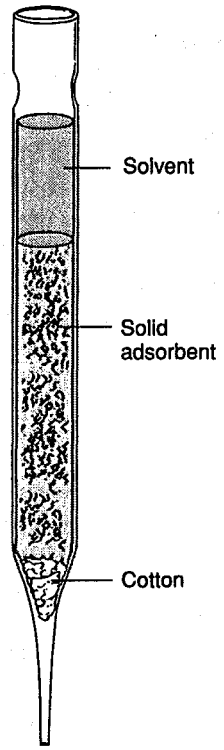


Figure 12.9 Microscale chromatography column.

B. DEPOSITING THE ADSORBENT

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 the one of the dry pack methods, as described in the following discussion.

Dry Pack Method 1

To fill a microscale column, fill the Pasteur pipet (with the cotton plug, prepared as described in Section A) 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 ap-

proach to controlling the flow rate is to use a finger over the top of the Pasteur pipet, much as you control the flow of liquid in a volumetric pipet. Continue adding the adsorbent slowly, with constant tapping, until the level of the adsorbent 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 12.9.

Dry Pack Method 2

An alternative dry pack method for microscale columns is to fill the Pasteur pipet with *dry* adsorbent, without any solvent. A plug of cotton is positioned in the bottom of the Pasteur pipet. The desired amount of adsorbent is added slowly, and the pipet tapped constantly, until the level of adsorbent has reached the desired height. Figure 12.9 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 not recommended for use with silica gel nor for experiments where a very careful separation is required.

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.

12.8 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 highly 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 adsor-

bent. 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 so as 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 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 so as 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 microscale chromatography, using Pasteur pipets, there is no stopcock, and it is not possible to stop the flow. In this case, it is not considered necessary to allow the column to stand.

12.9 ELUTION TECHNIQUES

Solvents for analytical and preparative chromatography should be pure reagents. Commercial-grade solvents often contain small amounts of residue, which remains when the solvent is evaporated. For normal 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. Most of the experiments in this laboratory manual have been designed to avoid this particular problem.

One usually begins elution of the products with a nonpolar solvent, like hexane or petroleum ether. The polarity of the elution solvent can be increased gradually by adding successively greater percentages of either ether or toluene (for instance, 1, 2, 5, 10, 15, 25, 50, 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 standard scale 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 semimicroscale 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.

12.10 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 (Figure 12.10A). 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 (Figure 12.10B). 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 12.10C. 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. Some semi-microscale columns, such as that shown in Figure 12.8, are equipped with a solvent reservoir that fits onto the top of the column. It functions just like the reservoirs 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. 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.

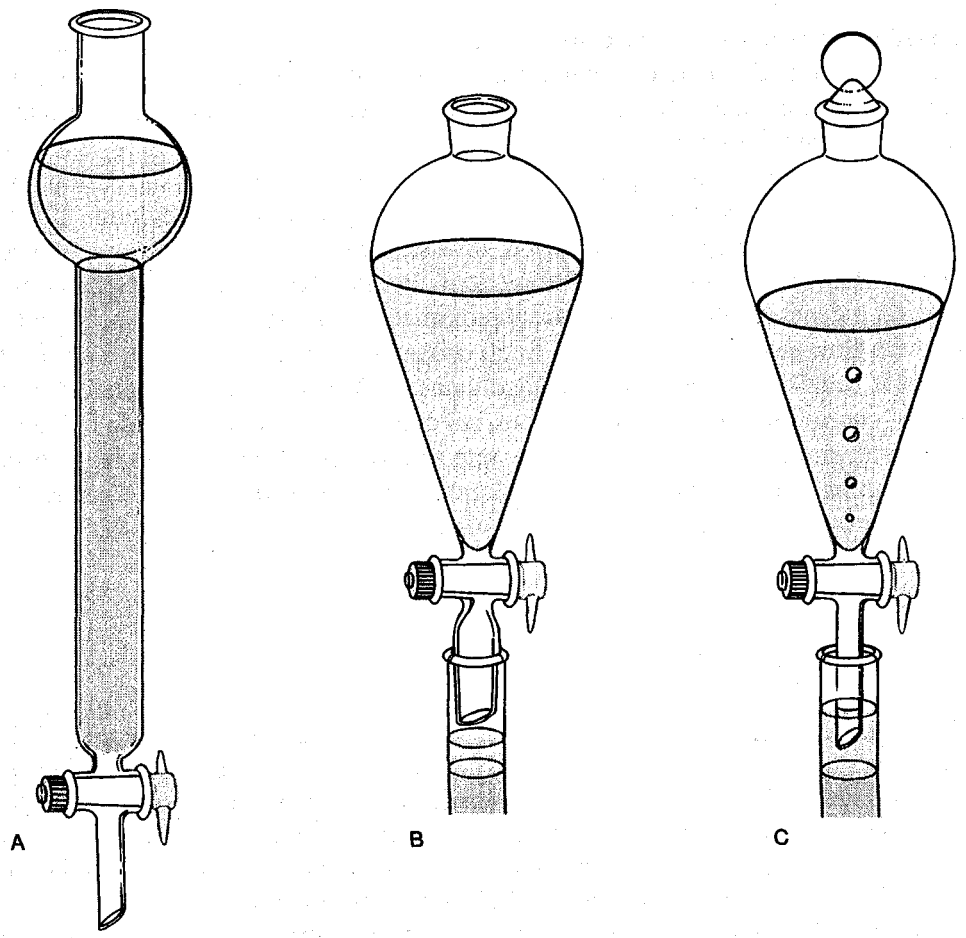


Figure 12.10 Various types of solvent-reservoir arrangements for chromatographic columns.

12.11 MONITORING THE COLUMN

It is a happy instance 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 pre-weighed flasks, to evaporate the solvent from each fraction, and to reweigh the flask plus any residue. A plot of fraction number *versus* the weight of the residues after evaporation of solvent gives a plot like that in Figure 12.11. 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.

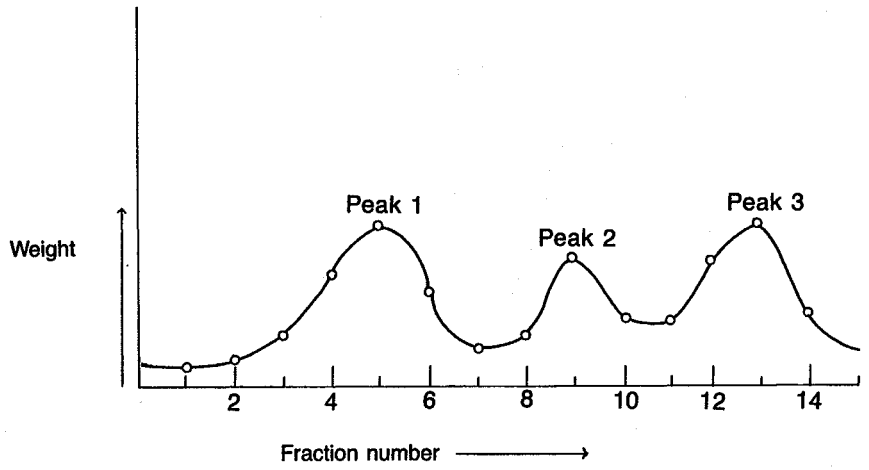


Figure 12.11 Typical elution graph.

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 14 (Section 14.10, p. 804). Several sophisticated instrumental and spectroscopic methods, which we shall not detail, can also monitor a chromatographic separation.

12.12 TAILING

Often, when a single solvent is used for elution, an elution curve (weight versus fraction) like that shown as a solid line in Figure 12.12 is 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.

12.13 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

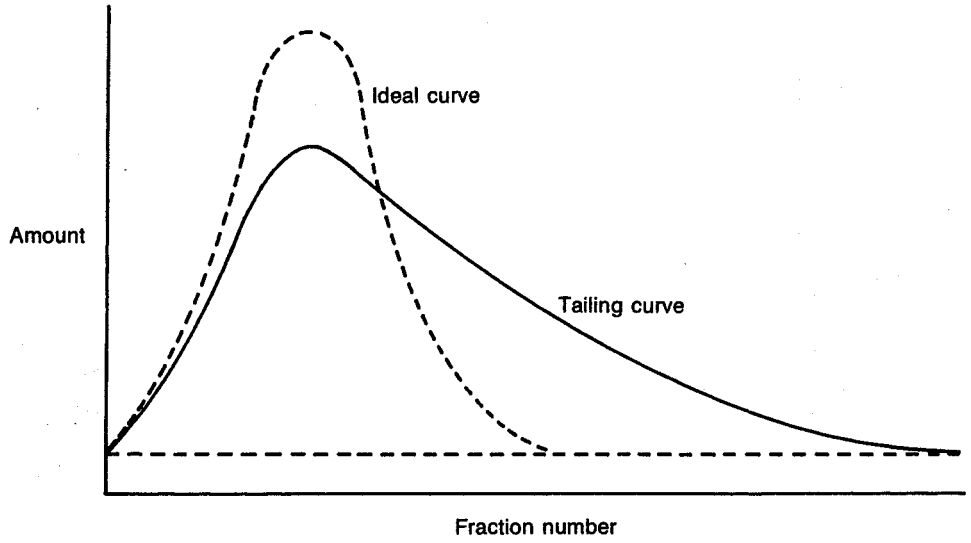


Figure 12.12 Elution curves: One ideal and one that "tails."

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.

12.14 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 5.6 of Technique 5 (pp. 659–661) details methods of decolorizing an organic product. In most cases, these methods involve the use of a form of activated charcoal, or Norit.

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 adsor-

bent (Section 12.6). 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 (Technique 3, Section 3.11, p. 630).

12.15 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 sieve-like 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 12.13. 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.

Equivalent terms used by chemists for the gel-chromatography technique are **gel filtration** (biochemistry term), **gel-permeation chromatography** (polymer chemistry term),

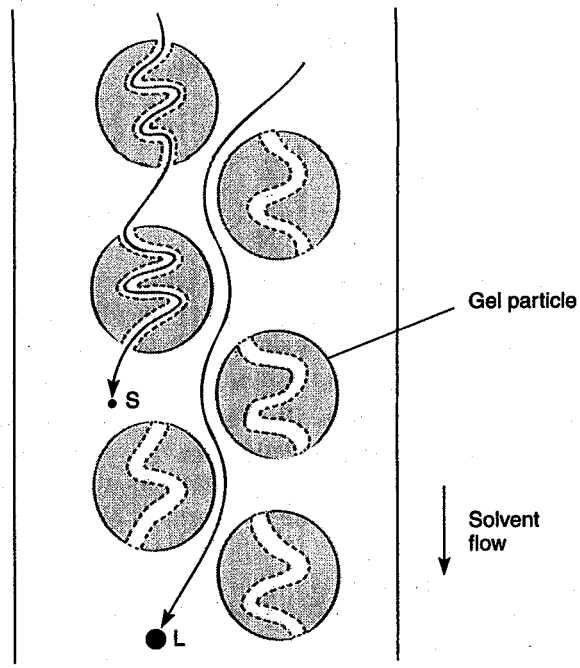


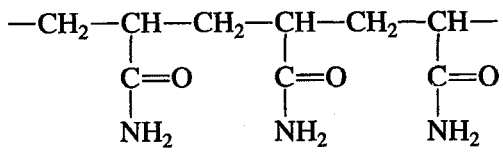
Figure 12.13 Gel chromatography: Comparison of the paths of large (L) and small (S) molecules through the column during the same interval of time.

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. Assume for the moment that one has 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 below.



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 divinyl benzene) 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.

12.16 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."

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 12.14. 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 to 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 in/min. This system would be appropriate to separate the components of a 250-mg sample.

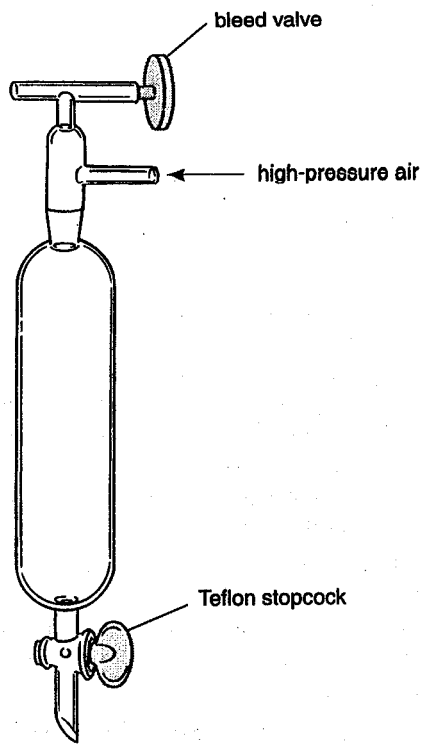


Figure 12.14 Apparatus for flash chromatography.

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 caused 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.

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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 in order 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 being added as a function of time.

4. An orange compound was added to the top of a chromatography column. Solvent was added immediately, with the result that 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.

TECHNIQUE 13

High-Performance Liquid Chromatography (HPLC)

The separation that can be achieved is greater if the column packing used in column chromatography is made more dense by using an adsorbent that has a small 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 more dense 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 modern 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 where 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 13.1. The instrument contains the following essential components:

1. Solvent reservoir
2. Solvent filter and degasser
3. Pump
4. Pressure gauge
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 in order to maintain the column at a specified temperature, fraction collectors, and microprocessor-controlled data-handling systems. Additional filters for the solvent and

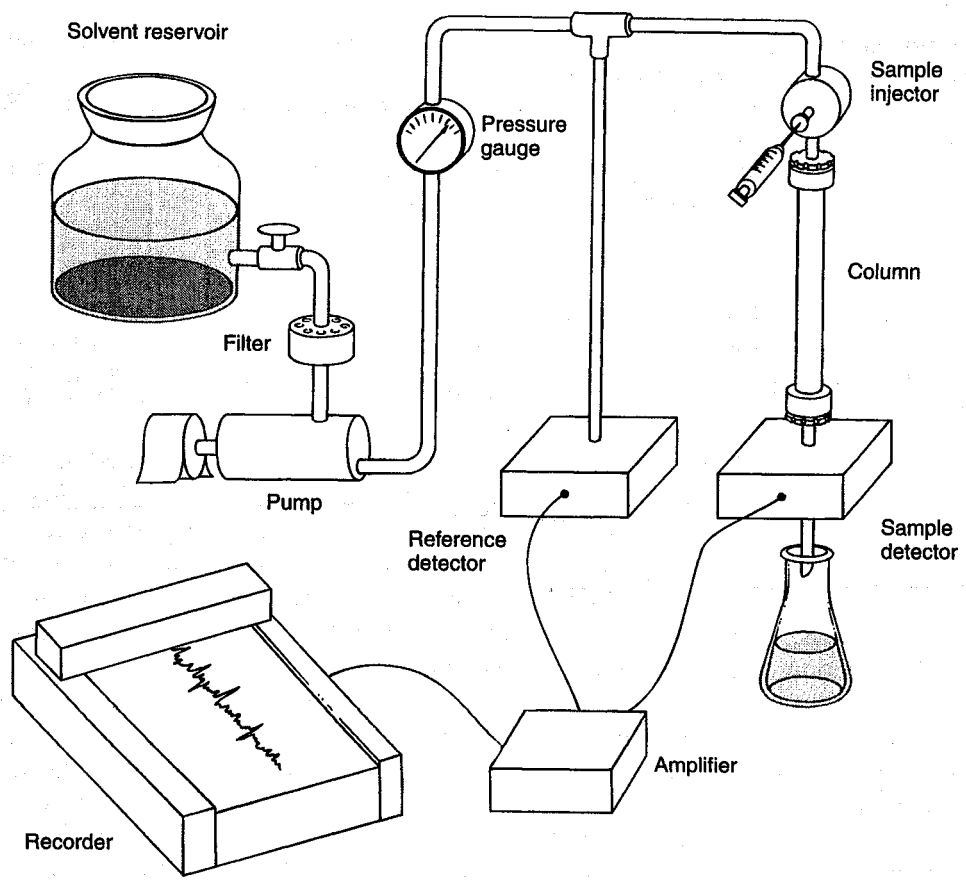

Figure 13.1 Schematic diagram of a high-performance liquid chromatography (HPLC).

sample may also be included. You may find it interesting to compare this schematic diagram with that shown in Technique 15 (Fig. 15.2, p. 809) for a gas chromatography instrument. Many of the essential components are common to both types of instruments.

13.1 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. Unlike column chromatography, however, the adsorbents used for HPLC have a much smaller particle size. Typically, particle size ranges from 5 to 20 μm in diameter for HPLC; it is 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, al-

though 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. In this chapter, 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, substances move faster 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. In this type of chromatography, known as **reversed-phase 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, where 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 that which 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 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, a column that is packed with an ion-exchange resin is used. 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 12, Section 12.15, page 783.

13.2 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 and 5 mm, although analytical columns with inside diameters of 1 or 2 mm are also available. A typical analytical column has a length of about 7.5 to 30 cm. This type of column is suitable for the separation of a 0.1- 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 to 100 mg can be separated on a **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-size 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 (e.g., for a subsequent chemical reaction or for spectroscopic analysis). A preparative column may be as large as 20 mm in inside diameter and 30 cm in length. A preparative column can handle samples as large as 1 g per injection.

13.3 SOLVENTS

The choice of solvent used for an HPLC run depends on the type of chromatographic separation selected. For a normal-phase separation, the solvent is selected based on its polarity. The criteria described in Technique 12, Section 12.4B, page 767, are used. A sol-

vent 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 12.2 on page 768.

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 upon the specific requirements of the separation.

13.4 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 (Technique 15, Section 15.6, p. 814).

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.

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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?

TECHNIQUE 14

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 small-scale and microscale experiments. The technique is closely related to column chromatography. In fact, TLC can be considered simply 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 12, on column chromatography, should be read before reading this one.

14.1 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 glass plate, 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 of glass is called a **thin-layer plate** or a **thin-layer slide.** (The reference to *slide* comes about because microscope slides are often used to prepare small thin-layer plates.) 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 12, Sections 12.2 and 12.3, pp. 762–765.) 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, substances that are the most polar travel slowly upward, or not at all, and nonpolar substances travel more rapidly if the solvent is sufficiently nonpolar.

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 be recovered from the plate when the iodine method is used. (Other methods of visualization are discussed in Section 14.7.)

14.2 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. The indicator renders the spots due to the presence of compounds in the sample visible under ultraviolet light (see Section 14.7). Although these plates are relatively expensive when compared with plates prepared in the laboratory, they are far more convenient to use, and they provide more consistent results. The plates are manufactured quite uniformly. Because the plastic backing is flexible, they have the additional advantage that the coating does not flake off the plates easily. The plastic sheets can also be cut with a pair of scissors to whatever size may be required.

14.3 PREPARATION OF THIN-LAYER SLIDES AND PLATES

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 like 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.

A. MICROSCOPE SLIDE TLC PLATES

For qualitative work such as identifying the number of components in a mixture or trying to establish that two compounds are identical, small TLC plates made from microscope slides are especially convenient. Coated microscope slides are easily made by dipping the slides into a container holding a slurry of the adsorbent material. Although numerous solvents can be used to prepare a slurry, methylene chloride is probably the best choice. It has the two advantages of low boiling point (40°C) and inability to cause the adsorbent to set or form lumps. The low boiling point means that it is not necessary to dry the coated slides in an oven. Its inability to cause the gypsum binder to set means that slurries made with it are stable for several days. The layer of adsorbent formed is fragile, however, and must be treated carefully. For this reason, some persons prefer to add a small amount of methanol to the methylene chloride to enable the gypsum to set more firmly.

The methanol solvates the calcium sulfate much as water does. More durable plates can be made by dipping plates into a slurry prepared from water. These plates must be oven-dried before use. Also, a slurry prepared from water must be used soon after its preparation. If it is not, it begins to set and form lumps. Thus, an aqueous slurry must be prepared immediately before use; it cannot be used after it has stood for any length of time. For microscope slides, a slurry of silica gel G in methylene chloride is not only convenient but also adequate for most purposes.

Preparing the Slurry. The slurry is most conveniently prepared in a 4-oz wide-mouthed screwcap jar. About 3 mL of methylene chloride is required for each gram of silica gel G. For a smooth slurry without lumps, the silica gel should be added to the solvent while the mixture is being either stirred or swirled. Adding solvent to the adsorbent usually causes lumps to form in the mixture. When the addition is complete, the cap should be placed on the jar tightly and the jar shaken vigorously to ensure thorough mixing (use protective gloves). The slurry may be stored in the tightly capped jar until it is to be used. More methylene chloride may have to be added to replace evaporation losses.

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. Use protective gloves.

Preparing the Slides. If new microscope slides are available, you can use them without any special treatment. However, it is more economical to reuse or recycle microscope slides. Wash the slides with soap and water, rinse with water, and then rinse with 50% aqueous methanol. Allow the plates to dry thoroughly on paper towels. They should be handled by the edges, because fingerprints on the plate surface will make it difficult for the adsorbent to bind to the glass.

Coating the Slides. The slides are coated with adsorbent by dipping them into the container of slurry. You can coat two slides simultaneously by sandwiching them together before dipping them in the slurry.

Perform the coating operation under a hood. Use gloves.

Shake the slurry vigorously just before dipping the slides. Because the slurry settles on standing, it should be mixed in this way before each set of slides is dipped. The depth of the slurry in the jar should be about 3 inches, and the plates should be dipped into the slurry until only about 0.25 inches at the top remains uncoated. The dipping operation should be performed smoothly. The plates may be held at the top (see Fig. 14.1), where they will not be coated. They are dipped into the slurry and withdrawn with a slow and steady motion. The dipping operation takes about 2 seconds. Some practice may be required to get the correct timing. After dipping, replace the cap on the jar, and hold the plates for a minute until most of the solvent has evaporated. Separate the plates and place them on paper towels to complete the drying.

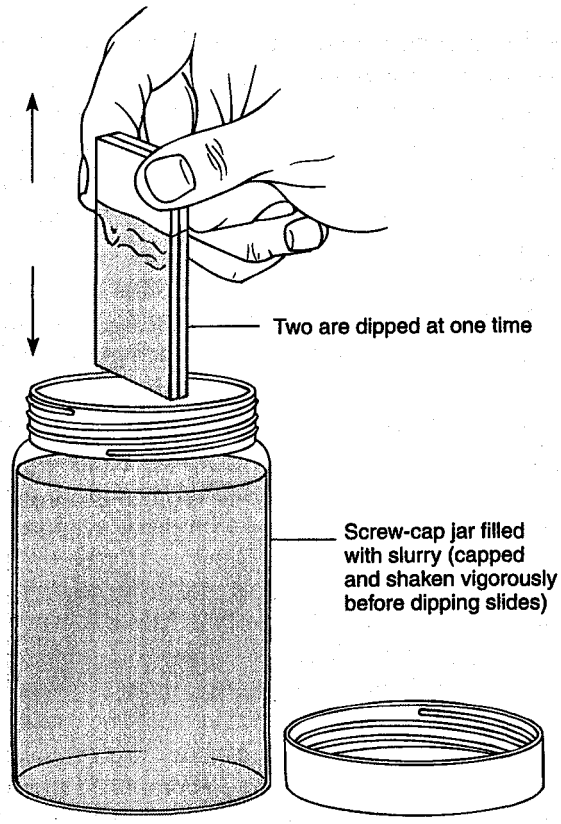


Figure 14.1 Dipping slides to coat them (gloves recommended).

The plates should have an even coating; there should be no streaks and no thin spots where glass shows through the adsorbent. The plates should not have a thick and lumpy coating.

Two conditions cause thin and streaked plates. First, the slurry may not have been mixed thoroughly before the dipping operation; the adsorbent might then have settled to the bottom of the jar, and the thin slurry at the top would not have coated the slides properly. Second, the slurry simply may not have been thick enough; more silica gel G must then be added to the slurry until the consistency is correct. If the slurry is too thick, the coating on the plates will be thick, uneven, and lumpy. To correct this, dilute the slurry with enough solvent to achieve the proper consistency.

Plates with an unsatisfactory coating may be wiped clean with a paper towel and redipped. Take care to handle the plates only from the top or by the sides, to avoid getting fingerprints on the glass surface.

B. LARGER THIN-LAYER PLATES

For separations involving large amounts of material, or for difficult separations, it may be necessary to use larger thin-layer plates. Plates with dimensions up to 20–25 cm^2

are common. With larger plates, it is desirable to have a more 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 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.

Observe the precautions stated on page 795.

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 14.2. 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 10–25 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.

14.4 SAMPLE APPLICATION: SPOTTING THE PLATES

Preparing a Micropipet

To apply the sample that is to be separated to the thin-layer plate, one uses a micropipet. A micropipet is easily made from a short length of thin-walled capillary tubing like that used for melting-point determinations. The capillary tubing is heated at its midpoint with a microburner and rotated until it is soft. When the tubing is soft, the heated

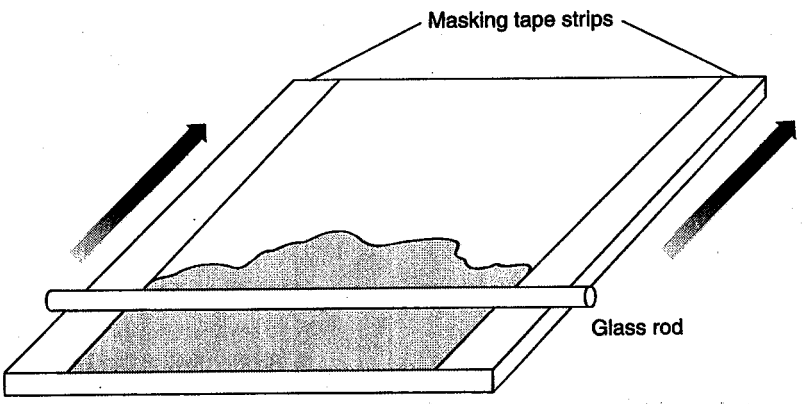
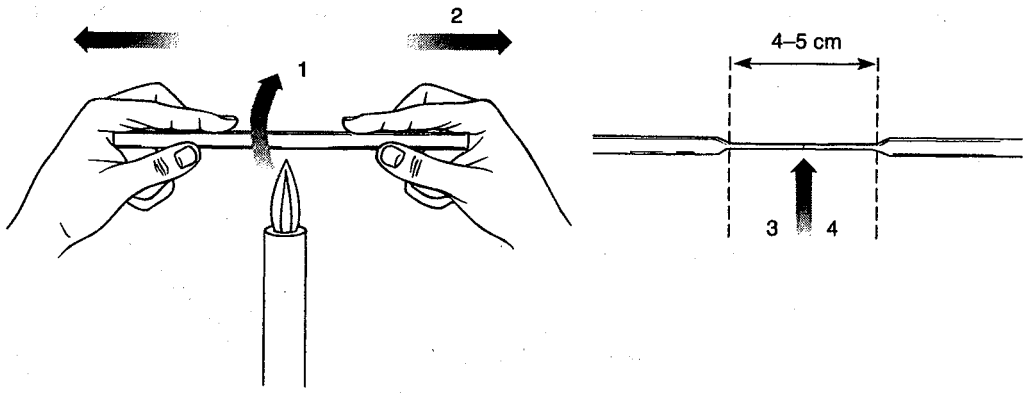


Figure 14.2 Preparing a large plate.

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. Figure 14.3 shows how to make such pipets.

Spotting the Plate

To apply a sample to the plate, begin by placing about 1 mg of a solid test substance, or one drop of a liquid test substance, in a small container like 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. 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 (Fig. 14.4). The spot must be high enough 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 to 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



① Rotate in flame until soft.
② Remove from flame and pull.
③ Score lightly in center of pulled section.
④ Break in half to give two pipets.

Figure 14.3 Construction of two capillary micropipets.

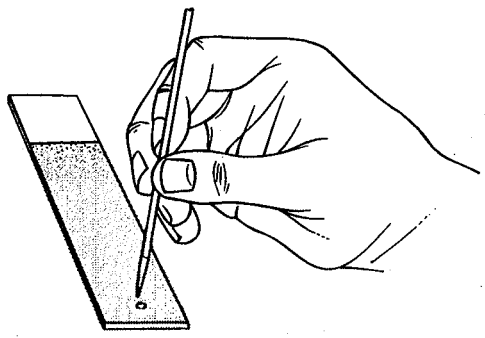


Figure 14.4 Spotting the plate with a drawn capillary pipet.

is repeatedly dipped into a small portion of solvent to rinse it and touched to a paper towel to empty it.

As many as three different spots may be applied to a microscope-slide 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.

14.5 DEVELOPING (RUNNING) TLC PLATES

Preparing a Development Chamber

A convenient development chamber for microscope-slide TLC plates can be made from a 4-oz wide-mouthed 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 for observing the development. 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 slide in place) is shown in Figure 14.5.

Developing the TLC Plate

Once the spot has been applied to the thin-layer plate and the solvent has been selected (see Sections 14.4–14.6), the plate is placed in the chamber for development. The

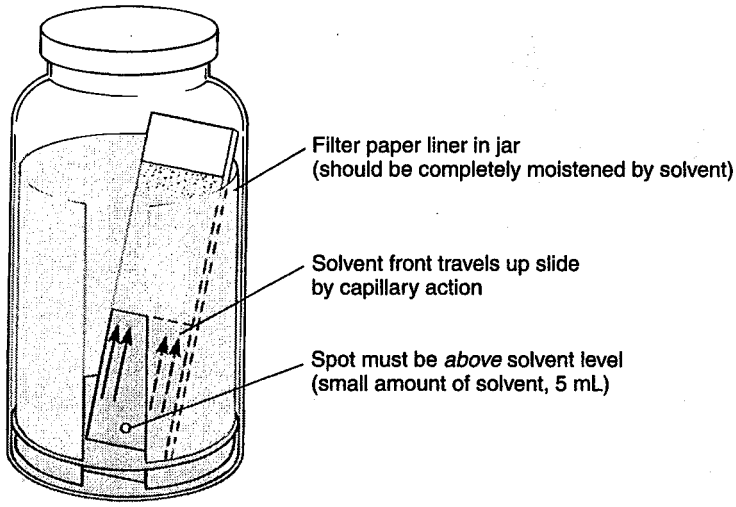


Figure 14.5 Development chamber with thin-layer plate undergoing development.

plate must be placed in the chamber carefully so that none of the coated portion 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 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 (Section 14.7) may be needed.

14.6 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 microscope slides can be prepared and developed rapidly, an empirical choice is usually not hard to make. A solvent that causes all 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 12.2 in Technique 12 (p. 768).

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 14.6.

14.7 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, the separated materials must be made visible by some reagent or some method that makes the separated compounds visible. Reagents that give rise to colored spots are called **visualization reagents.** Methods of viewing that make the spots apparent are **visualization methods.**

The visualization reagent used most often is iodine. 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-mouthed screwcap 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

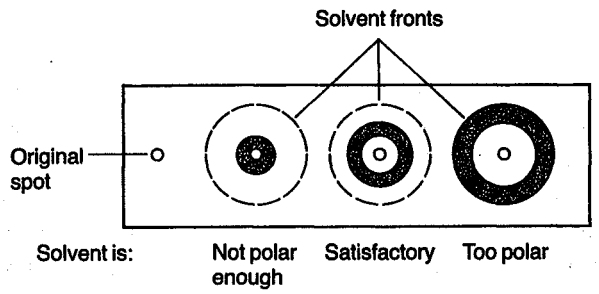


Figure 14.6 Concentric ring method of testing solvents.

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.

The second 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 because certain types of compounds shine very brightly under UV light because they fluoresce.

Another method that provides good results involves adding a fluorescent indicator to the adsorbent used to coat the plates. 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.

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 using ferric chloride for visualizing phenols and using bromocresol green for detecting carboxylic acids. Chromium trioxide, potassium dichromate, and potassium permanganate can be used for visualizing 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.

14.8 PREPARATIVE PLATES

If you use large plates (Section 14.3B), 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.

14.9 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 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:

$$R_f = \frac{\textit{Distance traveled by substance}}{\textit{Distance traveled by solvent front}}$$

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 is 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 mea-

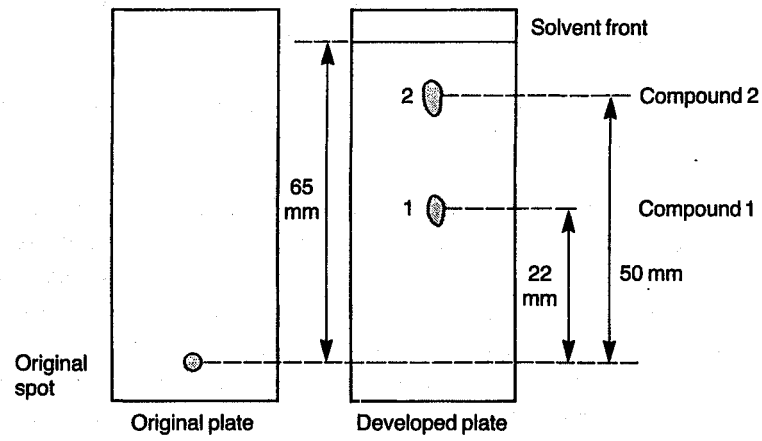
surement is made to the "center of gravity" of the spot. This first distance measurement is then divided by the distance the solvent front has traveled from the same original spot. A sample calculation of the R_f values of two compounds is illustrated in Figure 14.7.

14.10 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 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 in. on a side) and have a relatively thick coating of adsorbent (>500 μm), it is often possible to separate from 0.2 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.



R_f (compound 1) $= \frac{22}{65} = 0.34$ $\quad$ R_f (compound 2) $= \frac{50}{65} = 0.77$

Figure 14.7 Sample calculation of R_f values.

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), they are probably identical. If the spot positions are not the same, the compounds are definitely not identical. It is important to spot both compounds *on the same plate.* This is especially important with hand-dipped microscope slides. Because they vary widely from plate to plate, no two plates have exactly the same thickness of adsorbent. If you use commercial plates, this precaution is not necessary, although it is nevertheless a good idea.

Thin-layer chromatography can establish whether a sample is a single substance or a mixture. A single substance gives a single spot no matter what solvent is used to develop the plate. On the other hand, 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, isomers for example, 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 14.8. A solvent was found that

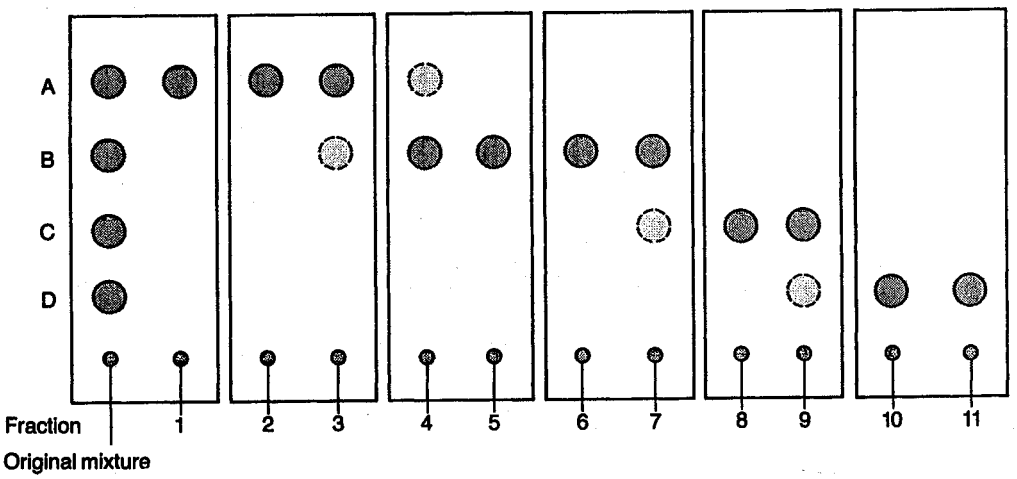


Figure 14.8 Monitoring a column.

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 slide. 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 14.9. In this case, the desired reaction was the conversion of A to B. At the beginning of the reaction (0 hr), a TLC slide was prepared that was spotted with pure A, pure B, and the reaction mixture. Similar slides were prepared at 0.5, 1, 2, and 3 hours after the start of the reaction. The slides 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.

14.11 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–

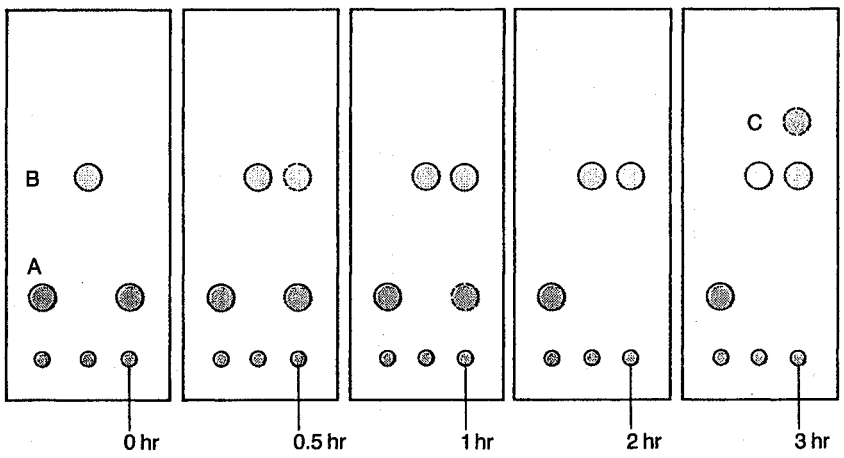


Figure 14.9 Monitoring a reaction.

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 those 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?

2. You and another student were each given an unknown compound. Both samples contained colorless material. You each prepared your own hand-dipped TLC plates and developed the plate using the same solvent. Each of you obtained a single spot of $R_f = 0.75$. Were the samples that you and the other student were assigned necessarily the same substance? How could you prove unambiguously that they were identical, using TLC?

3. 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 12.3.

4. Calculate the R_f value of a spot that travels 5.7 cm, with a solvent front that travels 13 cm.

5. 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?

6. 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 in order to visualize the spots if the compound is

(a) an alkyl halide
(b) a ketone
(c) an amino acid
(d) a sugar

TECHNIQUE 15

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.) A second difference is that 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, but GC is used most often.

15.1 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 15.1. A schematic block diagram of a basic gas chromatograph is shown in Figure 15.2. The basic elements of the apparatus are apparent. In short, 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 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.

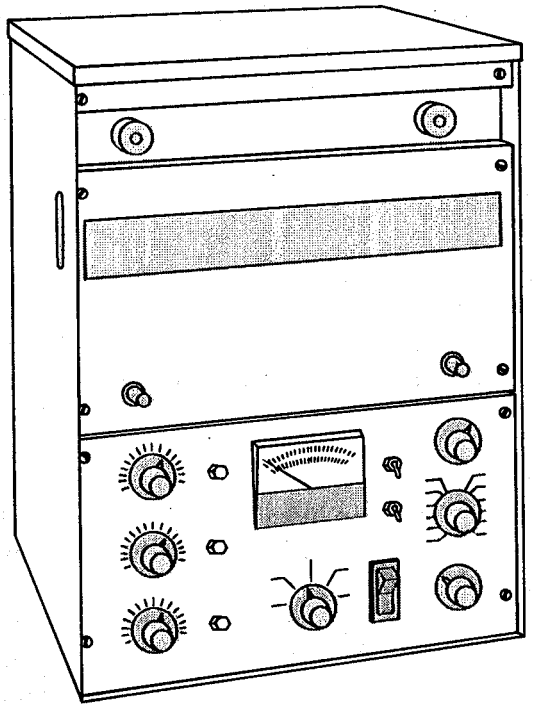


Figure 15.1 Gas chromatograph.

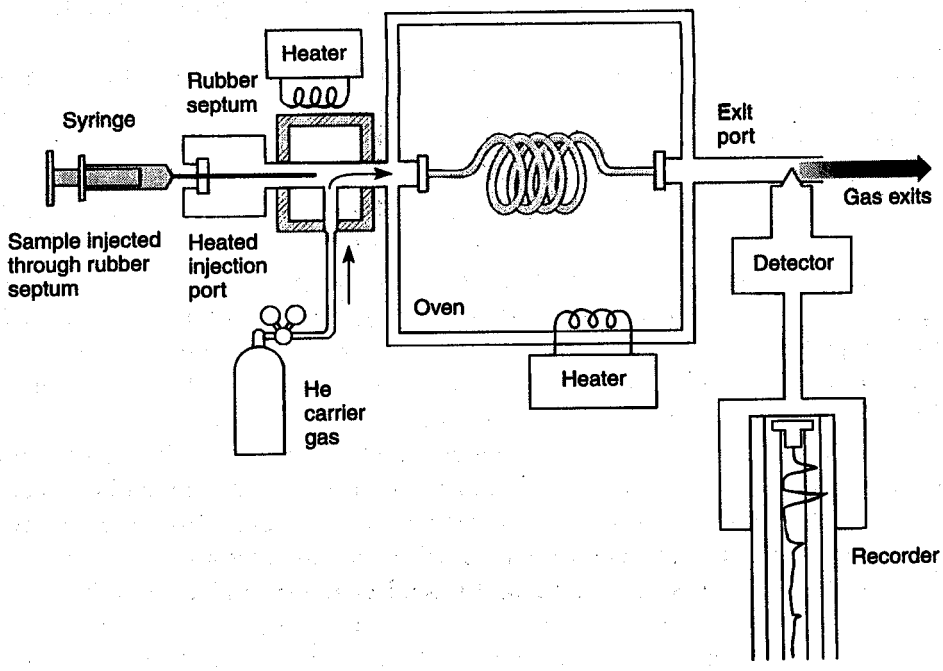


Figure 15.2 Schematic diagram of gas chromatograph.

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.

15.2 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 $\frac{1}{8}$ in. (3 mm) and $\frac{1}{4}$ in. (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 it to the apparatus. The most common length is 4–12 ft, but some columns may be up to 50 ft 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 15.1.

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 like 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 15.2.

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 about two factors. First, most of them 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 are 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).

TABLE 15.1 Typical Liquid Phases

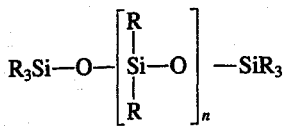
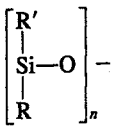
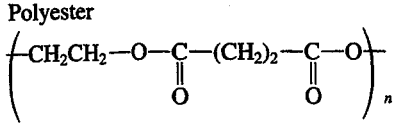
	Type	Composition	Maximum Temperature (°C)	Typical Use
Increasing polarity ↓				
Apiezons (L, M, N, etc.)	Hydrocarbon greases (varying MW)	Hydrocarbon mixtures	250–300	Hydrocarbons
SE–30	Methyl silicone rubber	Like silicone oil, but cross-linked	350	General applications
DC–200	Silicone oil ($R = CH_3$)		225	Aldehydes, ketones, halocarbons
DC–710	Silicone oil ($R = CH_3$) ($R' = C_6H_5$)		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 	200	General applications

TABLE 15.2 Typical Solid Supports

Crushed firebrick	Chromosorb T (Teflon beads)
Nylon beads	Chromosorb P (Pink diatomaceous earth, highly absorptive, 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	

The length of a capillary column is usually very long, typically 50–100 ft. 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 packed columns.

15.3 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 (Figure 15.3). 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. 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 it spends in the vapor phase and how much time it spends in the liquid phase. The more time it 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 their vapor pressure, and the more volatile component arrives at the end of the column first, as illustrated in Figure 15.3. By selecting the correct temperature of the oven and the correct liquid phase, the compounds in the injected mixture travel through the column at different rates and are separated.

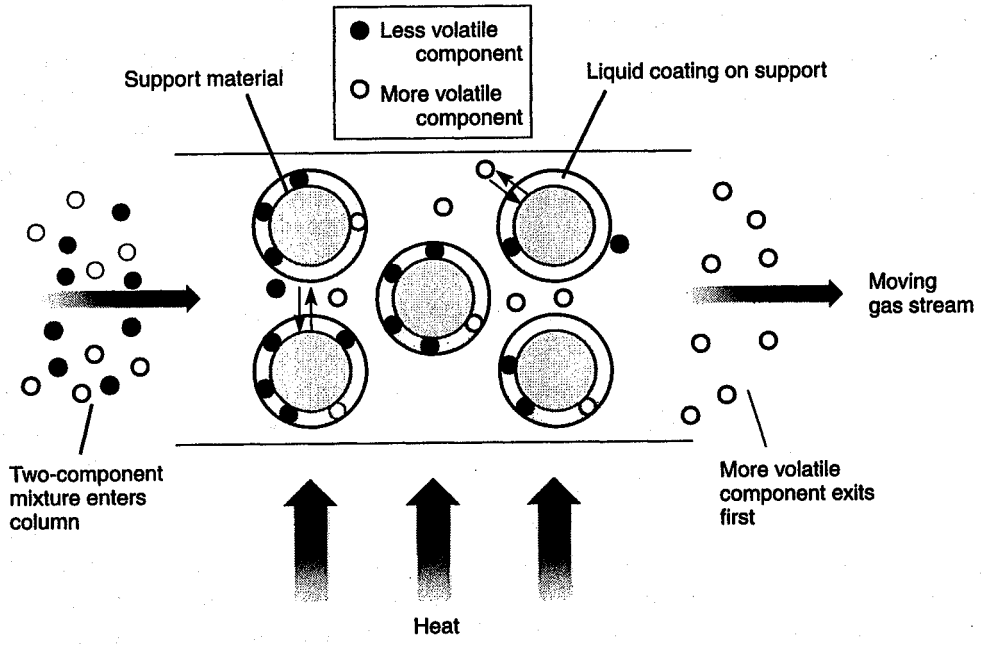


Figure 15.3 The separation process.

15.4 FACTORS AFFECTING SEPARATION

Several factors determine the rate at which a given compound travels through a gas chromatograph. First of all, compounds of low boiling point will generally travel through the gas chromatograph faster than compounds of higher boiling point. This is because the column is heated, and low-boiling compounds always have higher vapor pressures than compounds of higher boiling point. 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.

Second, the rate of flow of the carrier gas is important. 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 15.8).

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. One generally uses a different type of material 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.

Fourth, the length of the column is important. 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.

15.5 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 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.

15.6 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 higher thermal conductivity than 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 so as to form the arms of a Wheatstone bridge circuit, as shown in Figure 15.4. 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 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 15.5. 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 it 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.

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 15.6. As organic compounds burn in the fame, ion fragments are produced which collect on the ring above the flame. The resulting electrical signal is amplified and sent to a recorder in a similar manner to a TCD, except that a 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 a 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

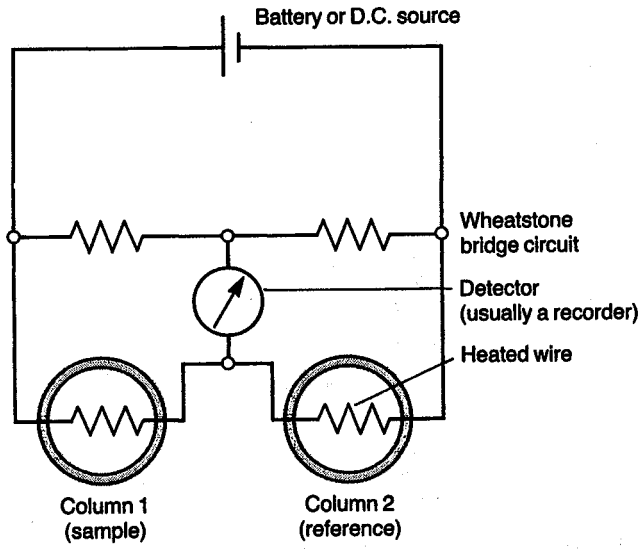


Figure 15.4 Typical thermal conductivity detector.

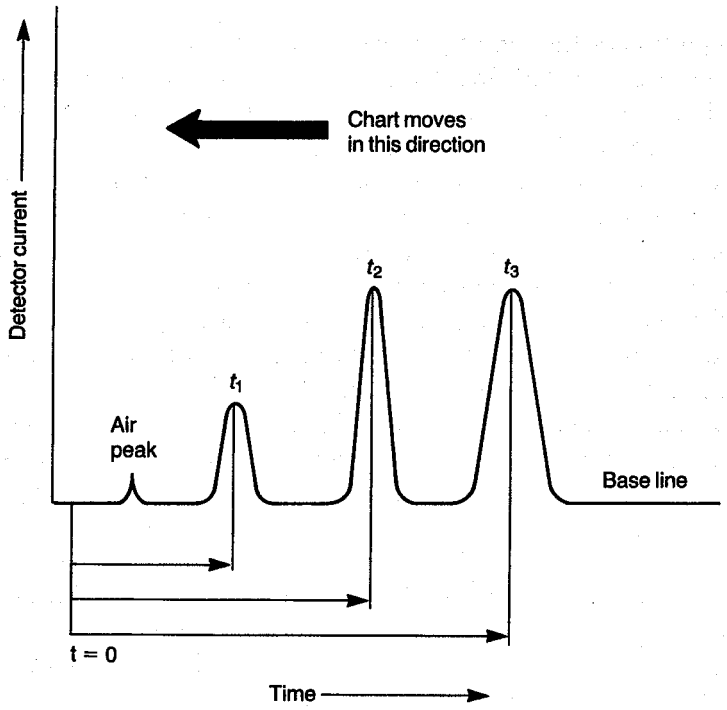


Figure 15.5 Typical chromatograph.

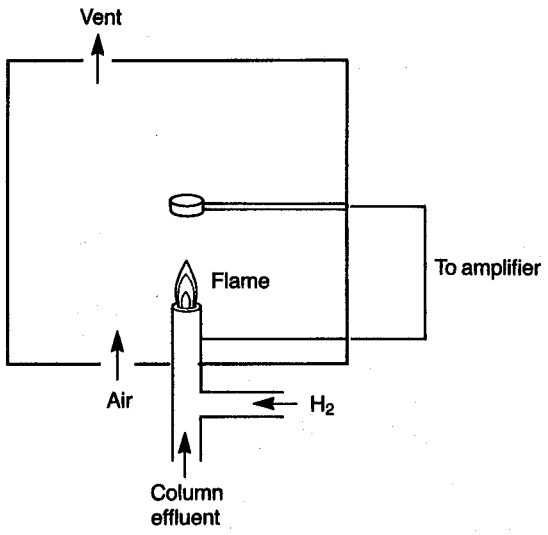


Figure 15.6 Flame ionization detector.

to operate and the detection process destroys the sample. Therefore, an FID gas chromatograph cannot be used to do preparative work, which is often desired in the microscale laboratory.

15.7 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 14, Section 14.9, p. 803). The retention time is measured from the time of injection to the time of maximum pen deflection (detector current) for the component being 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 15.5 for the three peaks illustrated.

15.8 POOR RESOLUTION AND TAILING

The peaks in Figure 15.5 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 15.7, the peaks overlap and the resolution is not good. Poor resolution is often caused by using too much sample, too high a column temperature, too short a column, a liquid phase that does not discriminate well between the two components, a column with too large a diameter, or, in short, 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 15.11.

Another desirable feature illustrated by the chromatogram in Figure 15.5 is that each peak is symmetrical. A common example of an unsymmetrical peak is one in which **tailing** has occurred, as shown in Figure 15.8. Tailing usually results from injecting too much sample into the gas chromatograph. Another cause of tailing occurs with polar compounds,

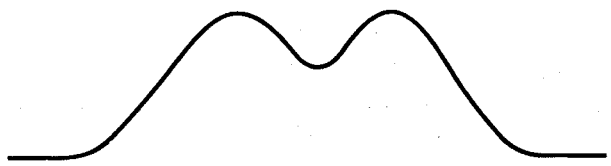


Figure 15.7 Poor resolution or peaks overlap.

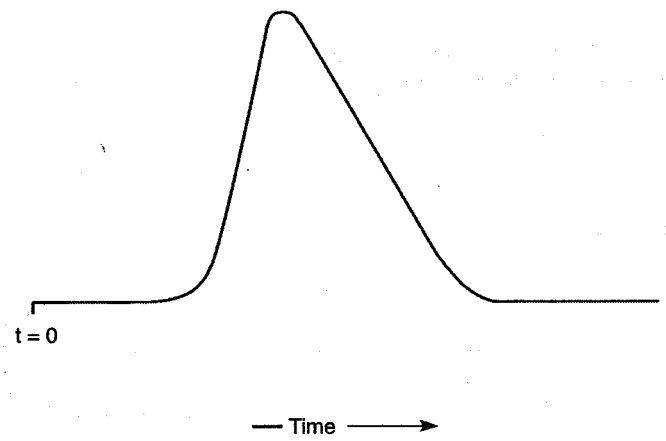


Figure 15.8 Tailing.

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.

15.9 QUALITATIVE ANALYSIS

A disadvantage of the gas chromatograph is that it gives no information whatever 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 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.

15.10 COLLECTING THE SAMPLE

For gas chromatographs with a thermal conductivity detector, it is possible to collect samples that have passed through the column. One uses a form of cooled trap connected to the outlet of the column as a collecting device. The simplest form of trap is just a U-shaped tube dipped into a bath of coolant (ice water, liquid nitrogen, or dry ice–acetone), as shown in Figure 15.9.

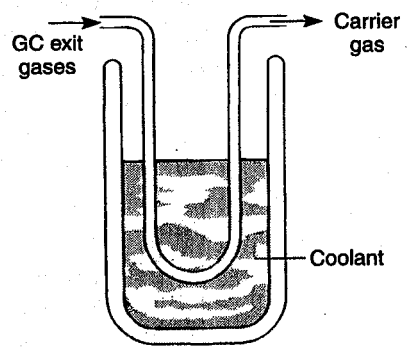


Figure 15.9 Collection trap.

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 at the bottom of the U-shaped tube, while the carrier gas continues to flow. However, if the compound leaving is frozen in the form of a fine mist, it may be carried through the trap even though it is frozen. When this happens, special trapping arrangements are required. To collect each component of the mixture, one must change the trap each time a new peak begins to appear on the chromatogram. Since even a gas chromatograph with large-diameter columns can rarely handle more than about 0.5 mL of a mixture at a time, a chemist or student having 50 mL of a mixture would have to make 50 to 100 separate injections, changing the trap for each component as it comes off the column. Fortunately, there are accessories that can be attached to a gas chromatograph to do this task automatically.

A microscale method uses a gas collection tube (see Fig. 15.10), which is included in most microscale glassware kits. A collection tube is joined to the exit port of the col-

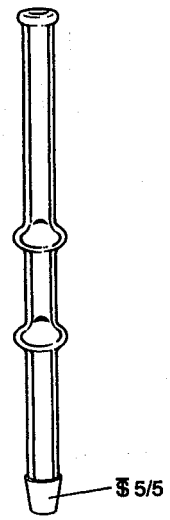


Figure 15.10 Gas chromatograph collection tube.

umn by inserting the T 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, the tapered joint of the collection tube is inserted into a 0.1-mL conical vial, which has a T 5/5 outer joint. The assembly is placed into a test tube, as illustrated in Figure 15.11. 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 in order to prevent contamination by water or other solvents used in cleaning this glassware.

15.11 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 de-

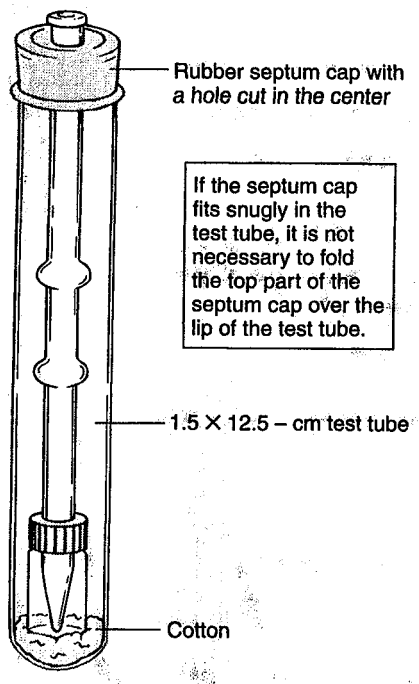


Figure 15.11 Gas chromatograph collection tube and 0.1-mL conical vial.

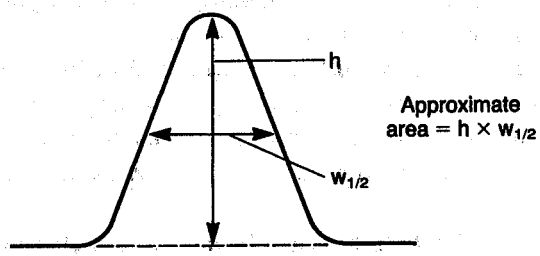


Figure 15.12 Triangulation of a peak.

tector 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 geometrical 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 15.12. The baseline is approximated by drawing a line between the two side-arms 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 15.13. If peaks overlap (see Fig. 15.7), either

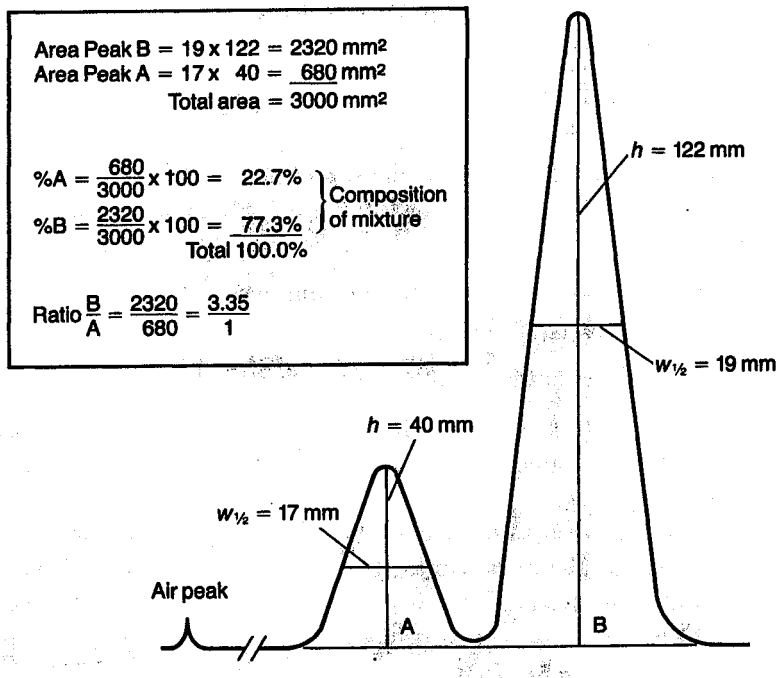


Figure 15.13 Sample percentage composition calculation.

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.

For the experiments in this textbook, we have assumed 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 and FID gas chromatographs. With a TCD, the responses are different because not all compounds have the same thermal conductivity. Different compounds analyzed with a 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.

Consider the following example, which illustrates how response factors are determined. In this 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:

Benzene	966463
Hexane	831158
Ethyl Acetate	1449695

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:

Benzene	966463/966463 = 1.00 (by definition)
Hexane	831158/966463 = 0.86
Ethyl Acetate	1449695/966463 = 1.50

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. For a quantitative analysis, it is likely that you will have to convert molar response factors into *weight* response factors. Next, the chromatography experiment us-

ing 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.

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 15.14.

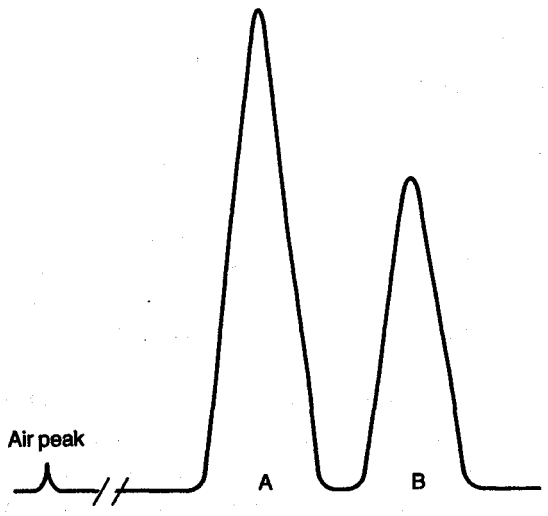


Figure 15.14 Chromatogram for Problem 2.

3. Make a photocopy of the chromatogram in Figure 15.14. 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

TECHNIQUE 16

Sublimation

In Technique 6, the influence of temperature on the change in vapor pressure of a liquid was considered (see Fig. 6.8, p. 675). 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.

16.1 VAPOR PRESSURE BEHAVIOR OF SOLIDS AND LIQUIDS

In Figure 16.1, 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 16.1.

In the first case (Fig. 16.1A), the substance shows normal change-of-state behavior on 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 16.1A. 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 (Fig. 16.1B), 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 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

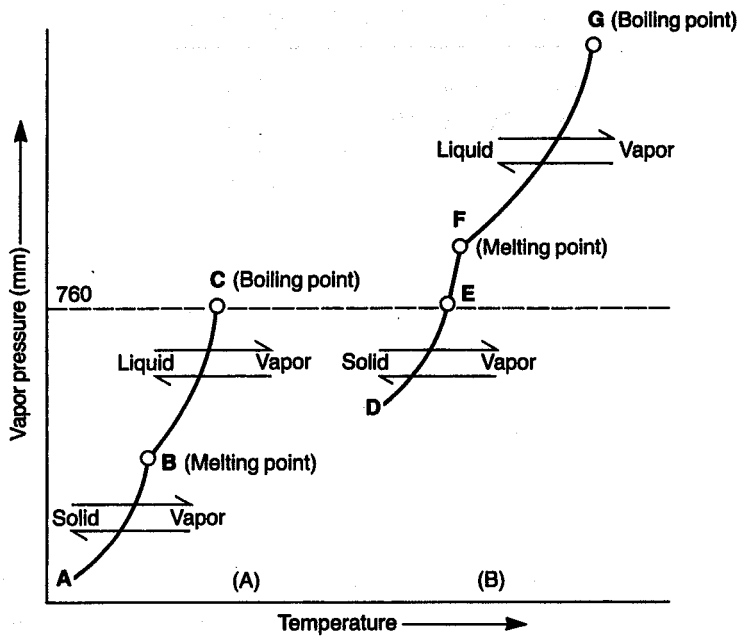


Figure 16.1 Vapor pressure curves for solids and liquids. (A) Substance shows normal solid to liquid to gas transitions at 760-mmHg pressure. (B) Substance shows a solid to gas transition at 760-mmHg pressure.

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 16.1. 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! With a sealed capillary tube, the melting point of 186°C is observed.

16.2 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.

TABLE 16.1 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

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 16.1. The first three entries in the table were discussed in Section 16.1. At atmospheric pressure they would sublime rather than melt, as shown in Figure 16.1B.

The next four entries in Table 16.1 (camphor, iodine, naphthalene, and benzoic acid) exhibit typical change-of-state behavior (solid, liquid, and gas) at atmospheric pressure, as shown in Figure 16.1A. These compounds sublime readily under reduced pressure, however. Vacuum sublimation is discussed in Section 16.3.

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, 39, 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, one seals the capillary tube or rapidly determines 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.

16.3 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 16.1B. The solid phase passes directly into the vapor phase. From the data given in Table 16.1, you should expect camphor, naphthalene, and benzoic acid to sublime at or below the respective applied pressures of 370, 7, 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.

16.4 SUBLIMATION METHODS

Sublimation can be used to purify solids. The 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 16.2. Since 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 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 or 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 16.2A and B. It is recommended that the laboratory instructor make available either one type or the other to be used on a communal basis. Each of the 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 16.2C can be constructed from a side-arm test tube, a neoprene adapter, and a piece of glass tubing sealed at one end. Alternatively, a 15 × 125-mm test tube may be used instead of the piece of glass tubing. The test tube is inserted into a #2 neoprene adapter using a little water as a lubricant. All pieces must fit securely in order to be able to obtain a good vacuum and to avoid water being drawn into the side-arm test tube around the rubber adapter. In order to achieve an adequate seal, the side-arm test tube may need to be flared somewhat. A complete description of the assembly of the apparatus, similar to that shown in Figure 16.2C, is given in Experiment 5A, p. 73. Detailed procedures for using this apparatus are also given in that experiment.

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

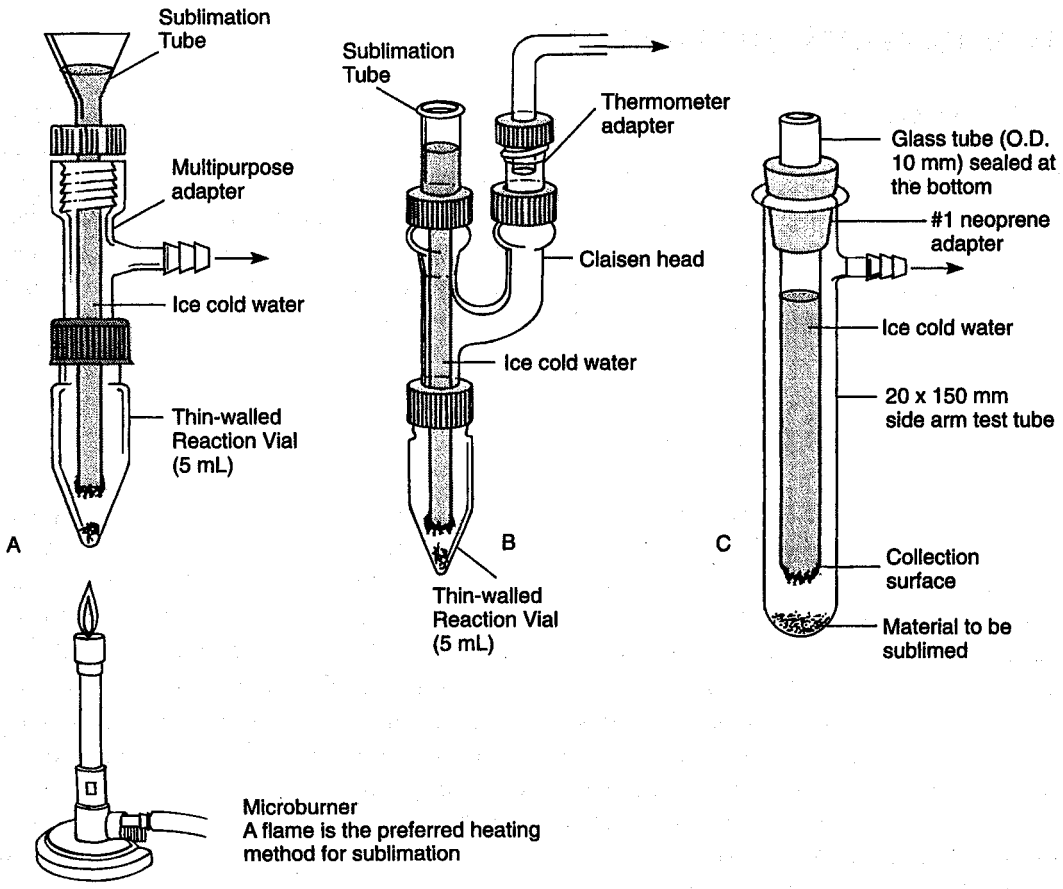


Figure 16.2 Sublimation apparatus.

on the sides toward the cold tube in the center. When using the apparatus shown in Figures 16.2A and B with a flame, you will need to use a thin-wall 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.

16.5 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, like 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, instead of becoming lost, it condenses on the cooled surface and thus interferes with the sublimation.

Sublimation is a faster method of purification than crystallization but 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, isoborneol, and camphor.

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 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.

TECHNIQUE 17

Polarimetry

17.1 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 fil-

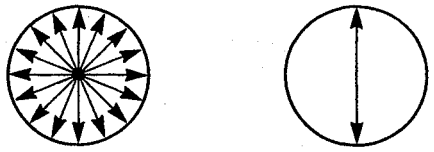


Figure 17.1 Ordinary versus plane-polarized light.

ters or special light sources. Frequently, a sodium lamp (sodium D line = 5893 Å) is used. Although the light from this lamp consists of waves of only 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 in the left part of Figure 17.1.

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 in the right portion of Figure 17.1.

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 Fig. 17.2) 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 ce-

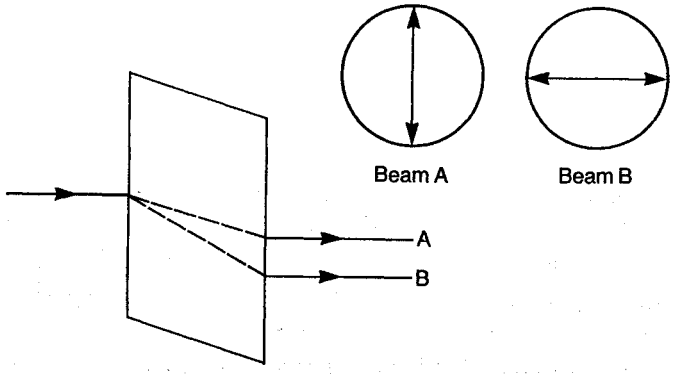


Figure 17.2 Double refraction.

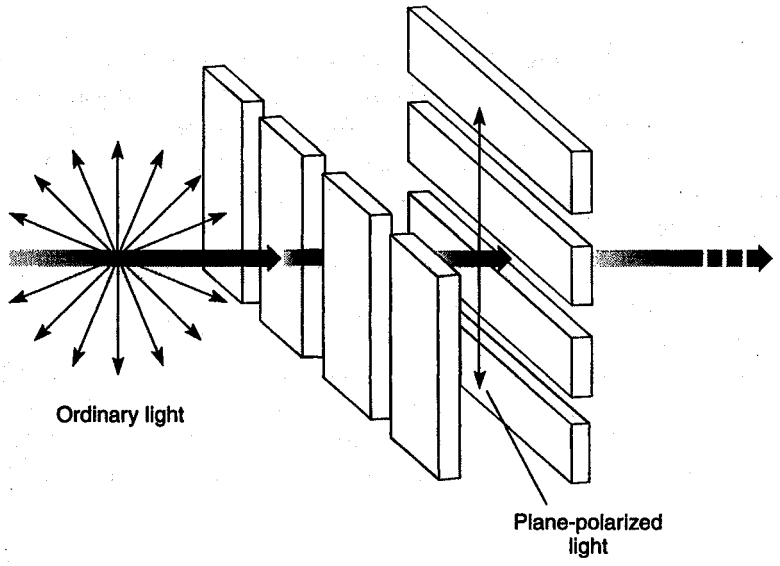


Figure 17.3 The picket-fence analogy.

mented by Canada balsam. This prism transmits one of the two 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 17.3. 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.

An **optically active substance** is one that interacts with polarized light to rotate the plane of polarization through some angle α. Figure 17.4 illustrates this phenomenon.

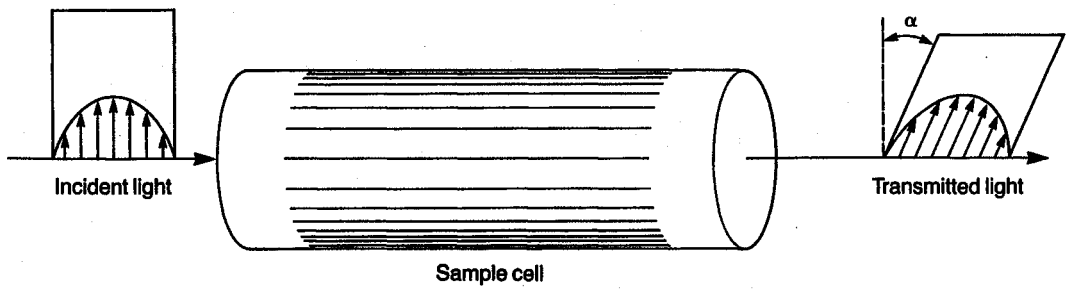


Figure 17.4 Optical activity.

17.2 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 17.5. 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** $[\alpha]_\lambda^t$, 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

$$[\alpha]_\lambda^t = \frac{\alpha}{cl}$$

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

$$M_\lambda^t = \frac{[\alpha_\lambda^t] \times \text{Molecular weight}}{100}$$

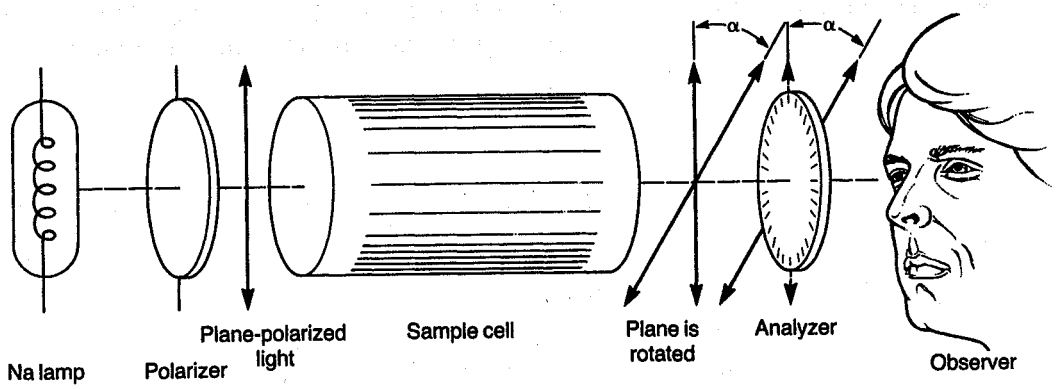


Figure 17.5 Schematic diagram of a polarimeter.

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 which 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 D line of sodium (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.

17.3 THE SAMPLE CELLS

It is important for the solution whose optical rotation is to be determined to contain no suspended particles of dust or dirt that might disperse the incident polarized light. Therefore, you must clean the sample cell carefully and make certain that there are no air bubbles trapped in the path of the light. The sample cells contain an enlarged ring near one end, in which the air bubbles may be trapped. Sample cells are available in various lengths, with 0.5 and 1.0 dm being the most common.

The sample is generally prepared by dissolving 0.1–0.5 g of the substance to be studied in 25 mL of solvent, usually water, ethanol, or methylene chloride (chloroform was used in the past). If the specific rotation of the substance is very high or very low, you may need to make the concentration of the solution respectively lower or higher, but usually this is determined after first trying a concentration range such as that suggested previously. The sample cell shown in Figure 17.6 is filled with solution. It is then tilted upward and tapped until the air bubbles move into the enlarged ring. It is important not to get fingerprints on the glass endplate in reassembling the cell.

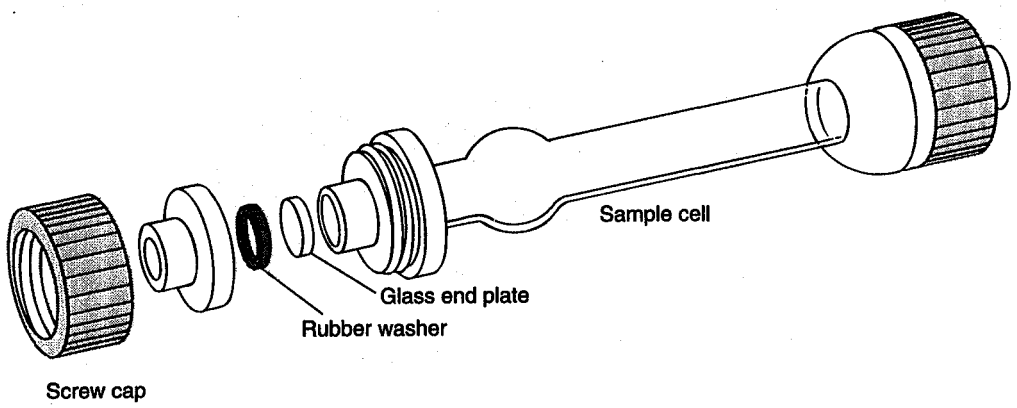


Figure 17.6 Polarimeter cell assembly.

17.4 OPERATION OF THE POLARIMETER

The procedures given here for preparing the cells and for operating the instrument are appropriate for the Zeiss polarimeter with the circular scale; other models of polarimeter are operated similarly. It is necessary before beginning the experiments to turn the power switch to the ON position and wait 5–10 minutes until the sodium lamp is properly warmed.

The instrument should be checked initially by making a zero reading with a sample cell filled only with solvent. If the zero reading does not correspond with the zero-degree calibration mark, then the difference in readings must be used to correct all subsequent readings. The reading is determined by laying the sample tube in the cradle, enlarged end up (making sure that there are no air bubbles in the light path), closing the cover, and turning the knob until the proper angle of the analyzer is reached. Most instruments, including the Zeiss polarimeter, are of the double-field type, in which the eye sees a split field whose sections must be matched in light intensity. The value of the angle through which the plane of polarized light has been rotated (if any) is read directly from the scale that can be seen through the eyepiece directly below the split-field image. Figure 17.7 shows how this split field might appear.

The cell containing the solution of the sample is then placed in the polarimeter, and the observed angle of rotation is measured in the same way. Be sure to record not only the numerical value of the angle of rotation in degrees but also the direction of rotation. 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 "−." It is best, in making a determination, to take several readings, including readings for which the actual value was approached from both sides. In other words, where the actual reading might be +75°, first approach this reading upward from a reading near zero; on the next measurement approach this reading downward from an angle greater than +75°. Duplicating readings and approaching the observed value from both sides reduce errors. The readings are then averaged to get the observed rotation α. This rotation is then corrected by the appropriate factors, according to the formulas in Section 17.2, to provide the specific rotation. The specific rotation is always reported as a function of temperature, indicating the wavelength by "D" if a sodium lamp is used and reporting the concentration and solvent used. For example $[\alpha]_D^{20} = +43.8°$ (c = 7.5 g/100 mL in absolute ethanol).

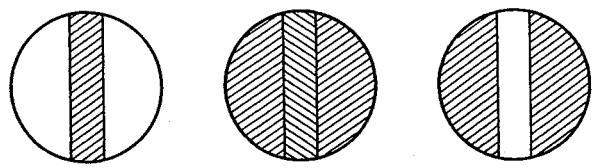


Figure 17.7 Split-field image in the polarimeter.

17.5 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 equation shown above because you do not know the exact amount of each enantiomer present in a mixture. It is far easier to calculate the optical purity (enantiomeric excess) 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 only holds true 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 the 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°.

$$\text{Optical purity} = \frac{+26.3°}{+43.8°} \times 100 = 60\% \text{ optically pure}$$

$$\%\ (+) \text{ enantiomer} = 60 + \left(\frac{100 - 60}{2}\right) = 80\%$$

$$\%\ (-) \text{ enantiomer} = \left(\frac{100 - 60}{2}\right) = 20\%$$

Notice that the difference between these two calculated values equals the optical purity or enantiomeric excess (ee).

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.

TECHNIQUE 18

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.

18.1 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 de-

fined as the ratio of the velocity of light in air to the velocity of light in the medium being measured:

$$n = \frac{V_{\text{air}}}{V_{\text{liquid}}} = \frac{\sin \theta}{\sin \phi}$$

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 18.1.

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

$$n_{\text{D}}^{20} = 1.4892$$

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 nm = 10^{-9} m).

Notice that the hypothetical value reported above 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

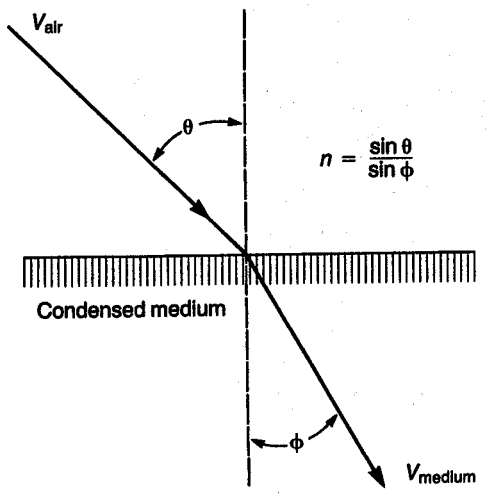


Figure 18.1 The refractive index.

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.

18.2 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.
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 18.2.

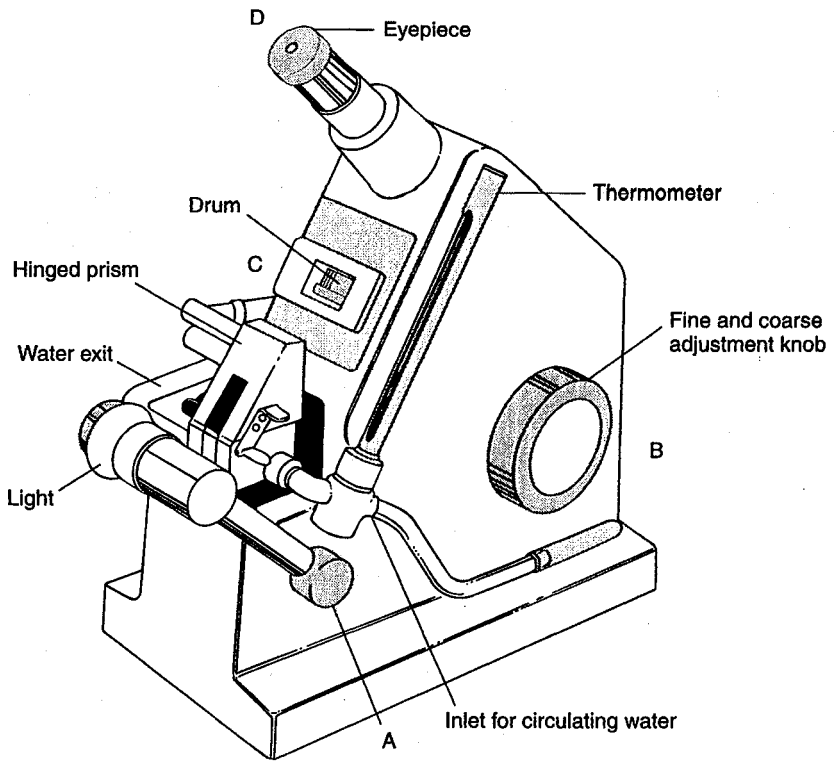


Figure 18.2 Abbé refractometer (Bausch and Lomb Abbé 3L).

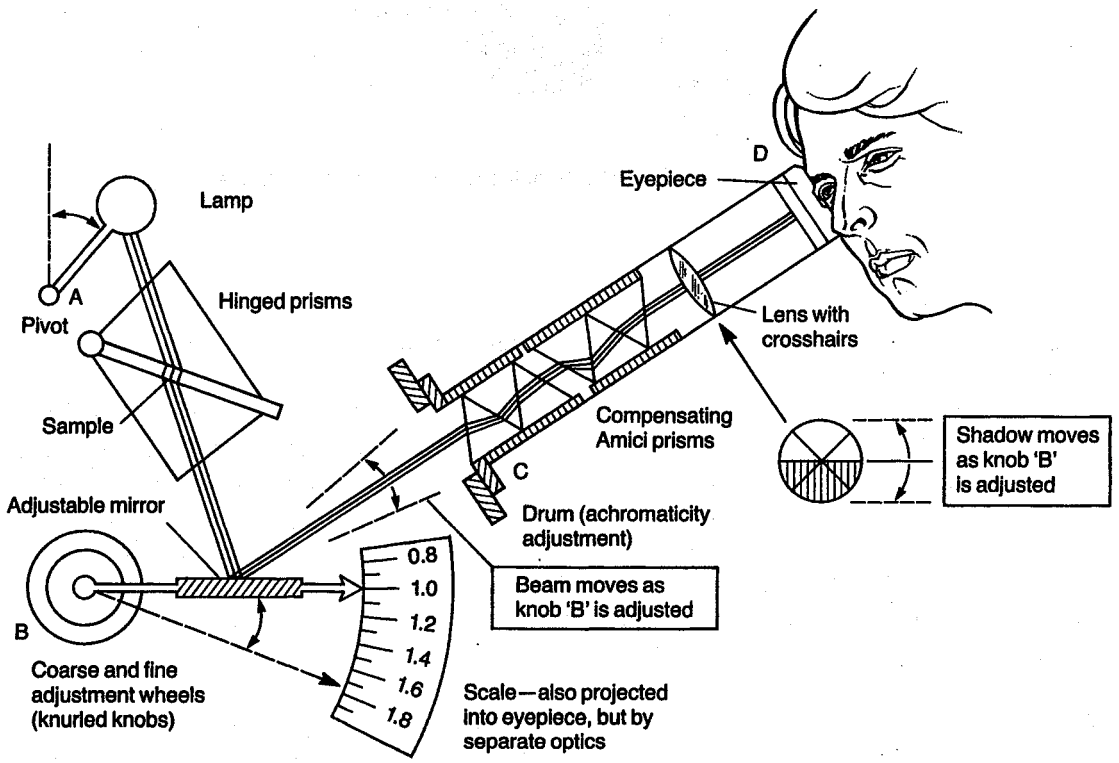


Figure 18.3 Simplified diagram of a refractometer.

The optical arrangement of the refractometer is very complex; a simplified diagram of the internal workings is given in Figure 18.3. The letters *A, B, C,* and *D* label corresponding parts in both Figures 18.2 and 18.3. A complete description of refractometer optics is too difficult to attempt here, but Figure 18.3 gives a simplified diagram of the essential operating principles.

Using the standard method, the sample to be measured is introduced 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, you 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*.

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 cross hairs

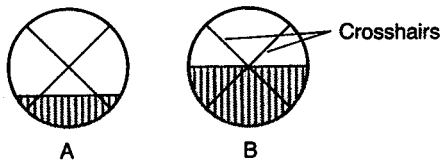


Figure 18.4 (A) Refractometer incorrectly adjusted. (B) Correct adjustment.

(Fig. 18.4). If the cross hairs 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 18.5, the refractometer shows **chromatic aberration** (color dispersion). This can be adjusted with the knob labeled *C* drum. This knurled knob rotates a series of prisms, called Amici prisms, that color-compensate the refractometer and cancel out dispersion. Adjust the knob to give a sharp, uncolored division between the light and dark segments. When you have adjusted everything correctly (as in Fig. 18.4B), 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.

There are many styles of refractometer, but most have adjustments similar to those described here.

In the procedure described above, 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, the sample is applied to a small piece of lens paper. The lens paper can be

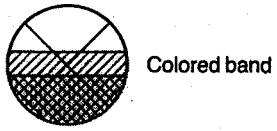


Figure 18.5 Refractometer showing chromatic aberration (color dispersion). The dispersion is incorrectly adjusted.

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, a forceps or tweezers with plastic tips should be used to handle the disc. About 5 μL of liquid is carefully placed on the lens paper using a microliter syringe. After closing the prisms, the refractometer is adjusted as described above and the refractive index is read. 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.

18.3 CLEANING THE REFRACTOMETER

In using the refractometer, you should always remember that if the prisms are scratched, the instrument will be ruined.

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. *Soft* tissues are moistened with the solvent, and the prisms are wiped *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.

18.4 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:

$$n_D^{20} = 1.5506 + 5(0.00045) = 1.5529$$

[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.

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.

TECHNIQUE 19

Preparation of Samples for Spectroscopy

Modern organic chemistry requires sophisticated scientific instruments. Most important among these instruments are the two spectroscopic instruments: the infrared (IR) and nuclear magnetic resonance (NMR) spectrometers. These instruments are indispensable to the modern organic chemist in proving the structures of unknown substances, in verifying that reaction products are indeed the predicted ones, and in characterizing organic compounds. The theory underlying these instruments can be found in most standard lecture textbooks in organic chemistry. Additional information, including correlation charts, to help in interpreting spectra are found in this textbook in Appendix 3 (Infrared Spectroscopy), Appendix 4 (Nuclear Magnetic Resonance Spectroscopy) and Appendix 5 (Carbon-13 Nuclear Magnetic Resonance Spectroscopy). This technique chapter concentrates on the preparation of samples for these spectroscopic methods. Part A covers techniques used in infrared spectroscopy, and Part B describes sample preparation for nuclear magnetic resonance spectroscopy.

Part A. Infrared Spectroscopy

19.1 INTRODUCTION

To determine the infrared spectrum of a compound, one must place it 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.

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, and they cannot be used with compounds that have an amino functional group. Amines react with silver chloride.

Solid Samples. A *solid* sample is usually 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.

19.2 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 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.

> The plates should be touched only on their edges. Be certain to use a sample that is dry or free from water.

Add a drop of the liquid to the surface of one plate, then place the second plate on top. 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 19.1, 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.

> Do not overtighten the nuts or the salt plates will cleave or split.

Tighten the nuts firmly, but do not use any force at all 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.

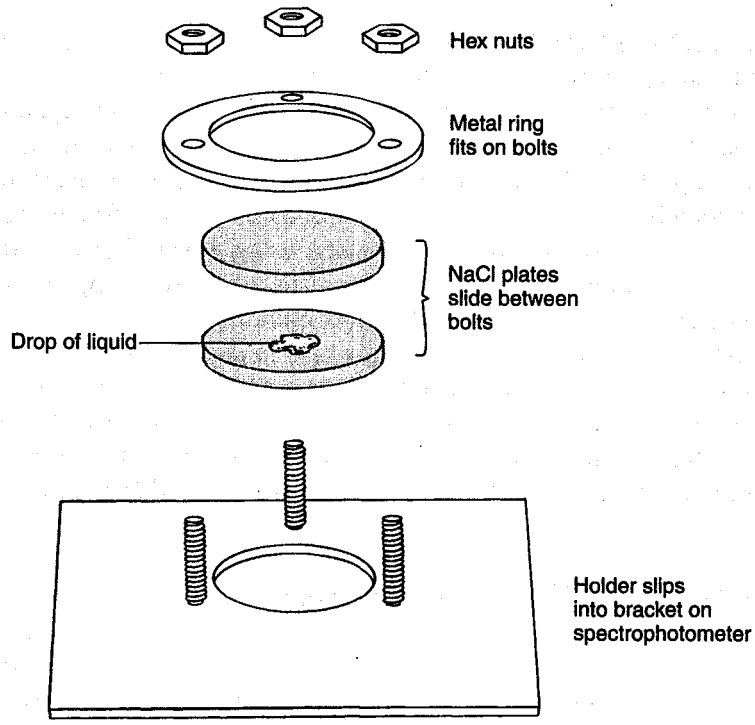


Figure 19.1 Salt plates and holder.

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 (one drop, two drops, etc.) and (2) the pressure used to hold the plates together. If more than one or two drops of liquid have been used, it 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, you may find that the capillary film is 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 19.3, or a solution cell described in Section 19.5. 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 19.8.

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. Use gloves.

19.3 LIQUID SAMPLES—AgCl PLATES

The mini-cell[1] shown in Figure 19.2 may also be used with liquids. 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. The advantages of using silver chloride plates are that they may be used with wet samples or solutions. A disadvantage is that silver chloride darkens when exposed to light for extended periods. They also scratch more easily than salt plates and react with amines.

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 to not 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. If you are going to determine the infrared spectrum of a pure liquid (neat

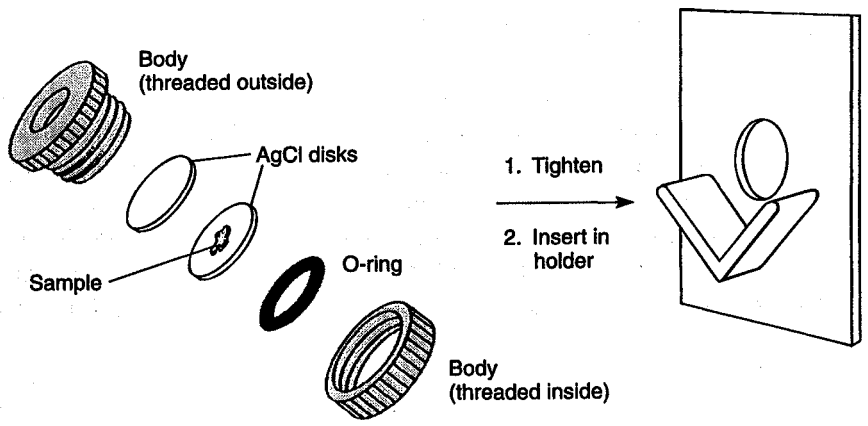


Figure 19.2 AgCl mini-liquid cell and V-mount holder.

[1]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 a 0.10-mm depression, rather than the 0.025-mm depression.

spectrum), you should select the flat side of each silver chloride plate. Insert the O-ring into the cell body as shown in Figure 19.2, place the plate into the cell body with the flat surface up, and add one drop or less of liquid to the plate.

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 19.3A. This arrangement is used to obtain a capillary film of your sample. Screw the top of the mini-cell 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 19.3B and 19.3C. If you add your sample to 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 (Fig. 19.3B). 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 (Fig. 19.3C). This orientation may be used for a solution of a solid (or liquid) in carbon tetrachloride (Section 19.5B).

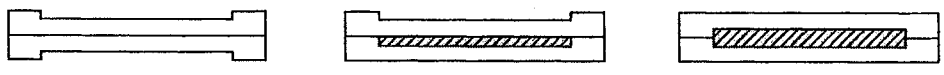
Determining the Spectrum. Slide the V-mount holder shown in Figure 19.2 into the slot on the infrared spectrophotometer. Set the cell assembly in the V-mount holder and determine the infrared spectrum of the liquid.

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 as they scratch easily. AgCl plates are light-sensitive. Store the plates in a light-tight container.

19.4 SOLID SAMPLES—KBr PELLETS

The easiest 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



A. Capillary film B. 0.10–mm path length C. 0.20–mm path length

Figure 19.3 Path length variations for AgCl plates.

size will become so small that the surface of the solid appears shiny. Add 80 mg (0.080 g) of *powdered* potassium bromide 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.

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 Hand Press. Two methods are commonly used to prepare KBr pellets. The first method uses the hand press apparatus shown in Figure 19.4.[2]

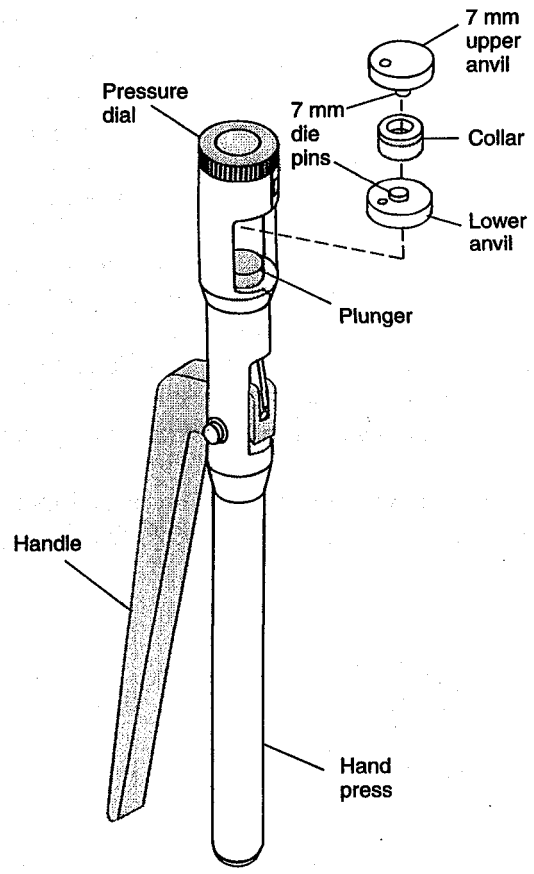


Figure 19.4 Making a KBr pellet with a hand press.

[2]KBr Quick Press unit is available from Wilmad Glass Company, Inc., Route 40 and Oak Road, Buena, NJ 08310.

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 19.4) 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 hand press slightly, tilt the press back a bit, and insert the die set into the press. Make sure that the die set is seated 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 hand press just touches the upper anvil of the die assembly. Tilt the unit back so that the die set does not fall out of the press. 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 hand press. 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.

Making a Pellet with a KBr Minipress. The second method of preparing a pellet uses the minipress apparatus shown in Figure 19.5. Obtain a ground KBr mixture as

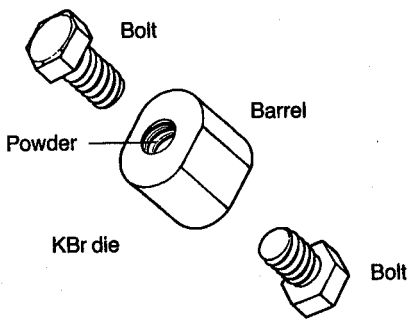


Figure 19.5 Making a KBr pellet with a minipress.

described above 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 19.5, 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 bench top 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 bench top. 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 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.

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 (Section 19.5).

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. Pull a piece of Kimwipe through the die unit to remove all the sample. Also wipe any surfaces with a Kimwipe. *Do not wash the dies with*

water. 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 and acetone, dry them carefully with paper towels, and return them to the desiccator. Return the KBr powder to its desiccator.

19.5 SOLID SAMPLES—SOLUTION SPECTRA

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 one or two drops of the solution between sodium chloride plates in precisely the same manner as that used for pure liquids (Section 19.2). The spectrum is determined as described for pure liquids using salt plates (Section 19.2). 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 Fig. 19.6), 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 Fig. 19.7).

Caution: Carbon tetrachloride is a hazardous solvent. Work under the hood! Use gloves.

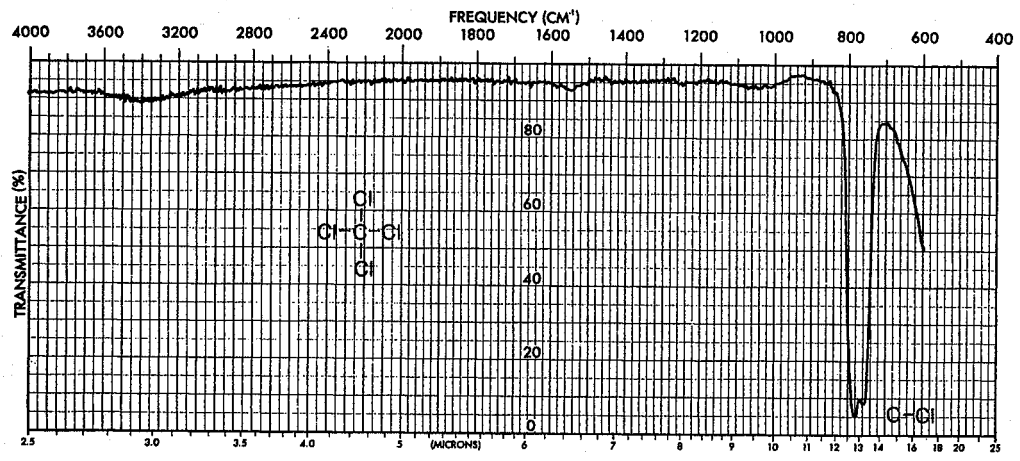


Figure 19.6 Infrared spectrum of carbon tetrachloride.

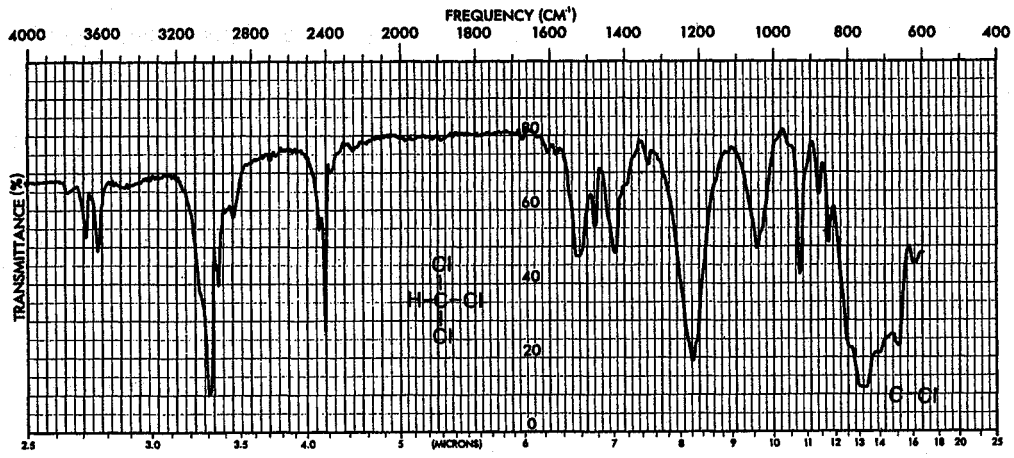


Figure 19.7 Infrared spectrum of chloroform.

Carbon tetrachloride, besides being toxic, is suspected of being a carcinogen. In spite of 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 very 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.

Method B—AgCl Mini-Cell

The AgCl mini-cell described in Section 19.3 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 19.3, position the AgCl plates as shown in Figure 19.3C to obtain the maximum possible path length of 0.20 mm. When the cell is tightened firmly, it 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 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.

> 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.

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 19.8, 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 very 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 so-

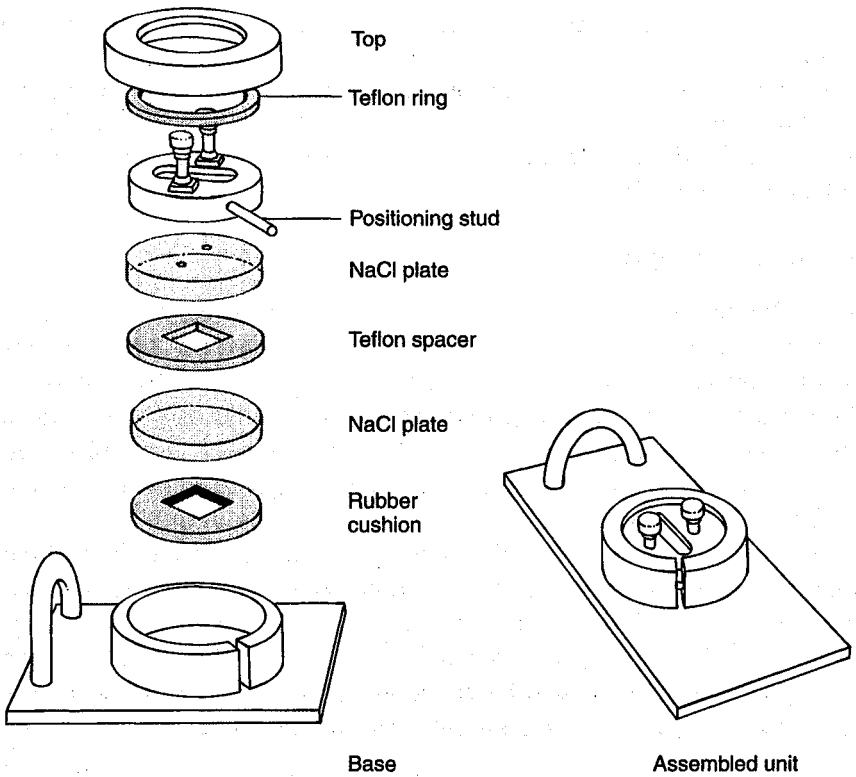


Figure 19.8 Solution cell.

lution (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 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, chloroform, and carbon disulfide. The spectra of these substances are shown in Figures 19.6, 19.7, and 19.9. 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 on page 851 for carbon tetrachloride should be followed. This procedure serves equally well for chloroform.

Before you use the solution cells, you must obtain the instructor's permission and instruction on how to fill and clean the cells.

19.6 SOLID SAMPLES—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 one or two 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 (Section 19.2).

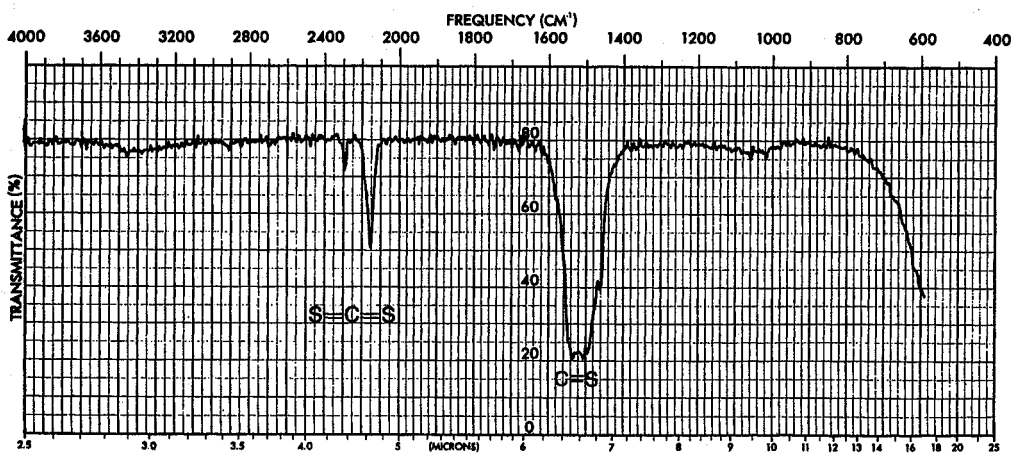


Figure 19.9 Infrared spectrum of carbon disulfide.

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 (Fig. 19.10). 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.

19.7 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, while 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 (Section 19.8).

19.8 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 19.11. The most important

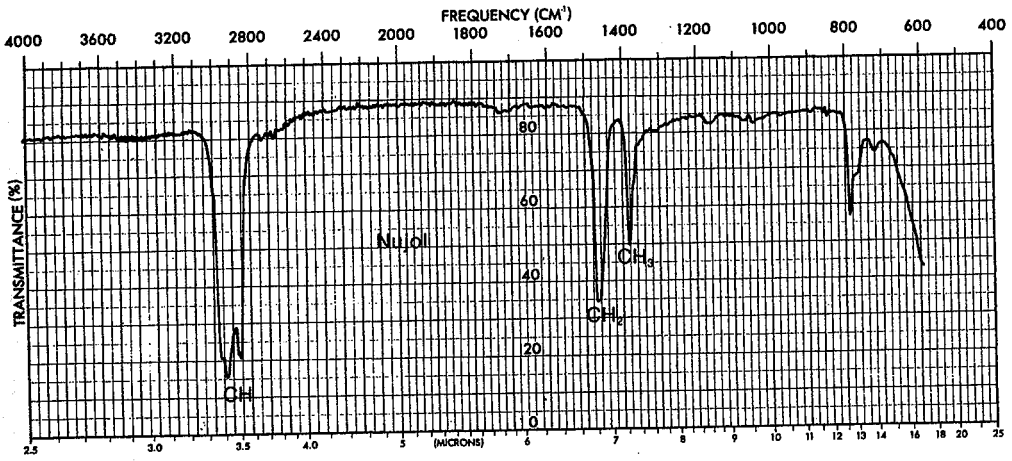


Figure 19.10 Infrared spectrum of Nujol (mineral oil).

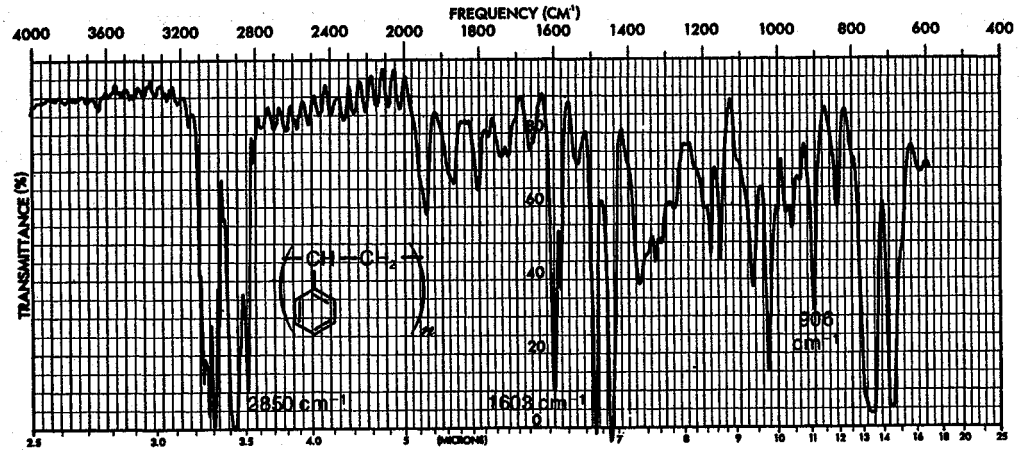


Figure 19.11 Infrared spectrum of polystyrene (thin film).

of these peaks is at 1603 cm^{-1}; other useful peaks are at 2850 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. Nuclear Magnetic Resonance (NMR)

19.9 PREPARING A SAMPLE FOR PROTON NMR

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.

To prepare the solution you must first choose the appropriate solvent. The solvent should not have NMR absorption peaks of its own, that is, no protons. Carbon tetrachloride CCl_4 fits this requirement and can be used in some instruments. However, because

Fourier transform (FT) NMR spectrometers require deuterium to stabilize (lock) the field (Section 19.10), 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 by your instructor to use another solvent, such as carbon tetrachloride CCl_4.

Routine Sample Preparation Using Deuterated Chloroform

1. Most organic liquids and low-melting solids will dissolve in deuterated chloroform. However, you should first determine if 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 alternate solvent, or consult the section entitled "Nonroutine Sample Preparation" later in this section.

Caution: Chloroform, deuterated chloroform, and carbon tetrachloride are all toxic solvents. In addition, they may be carcinogenic substances (see p. 21). Use protective gloves.

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. With the help of your instructor, transfer about 0.5 mL of the deuterated chloroform with a *clean and 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 and dry Pasteur pipet. Be careful when transferring the solution into the NMR tube so that you 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[1] to about 35 mm total (Fig. 19.12). In some cases, you will need to add a small amount of tetramethylsilane (TMS) as a reference substance (Section 19.11). 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 ppm. This impurity may also help you to "reference" your spectrum.

[1] Your instructor may recommend a different height than the one specified here (35 mm).

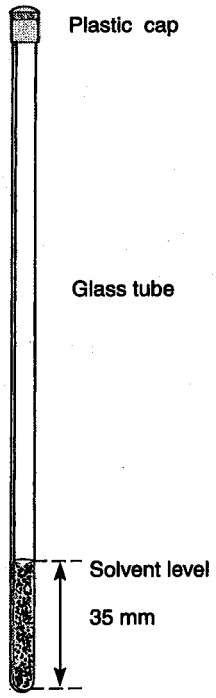


Figure 19.12 NMR sample tube.

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. See Section 19.12.

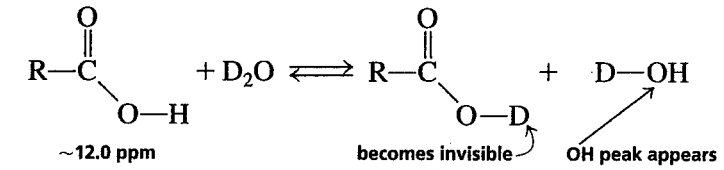
Cleaning the NMR Tube

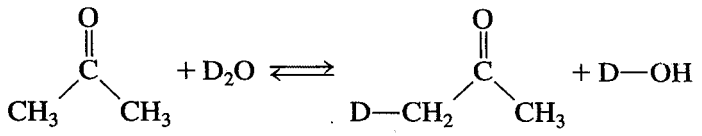
1. Carefully uncap the tube so that you do not break it. Turn the tube upside-down and hold it vertically over a beaker. Shake the tube up and down gently so that the contents of the tube empties into the beaker.
2. Partially refill the NMR tube with acetone using a Pasteur pipet. Carefully replace the 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.

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.

Nonroutine Sample Preparation. With highly polar substances you may find that your sample will not dissolve in deuterated chloroform. 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.





$$CH_3CH_2OH + D_2O \rightleftharpoons CH_3CH_2OD + D{-}OH$$

Most solid carboxylic acids do not dissolve in CCl_4, $CDCl_3$, or even D_2O. In such cases, a small piece of sodium metal is added 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.

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) analogues of these compounds are also used in special instances (for example, acetone-d_6, dimethylsulfoxide-d_6, dimethylformamide-d_7, and benzene-d_6).[2] 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 different chemical shift values 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

[2]Unisol, a commercial mixture of dimethylsulfoxide-d_6 and $CDCl_3$, dissolves most carboxylic acids.

to pyridine, benzene, acetone, or dimethylsulfoxide as solvents, to separate peaks that overlap when CCl_4 or $CDCl_3$ solutions are used.

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 also suspected carcinogens. In spite of these health problems, these solvents are commonly used in NMR spectroscopy, because there are no suitable alternatives. These solvents are used because they contain no protons and because they 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 screwcaps, 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.

19.10 PREPARING A SAMPLE FOR CARBON-13 NMR

Section 19.9 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.

Because of the low natural abundance of carbon-13 in a sample, you often need to acquire multiple scans over a long period (Appendix 5, Section CMR.1, p. 931). You can save considerable time by using a relatively concentrated sample.

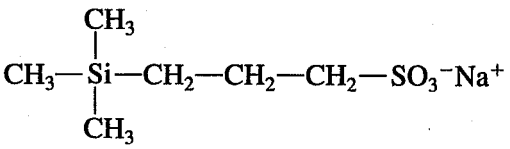
Modern FT-NMR spectrometers allow chemists to obtain both the proton and carbon NMR spectra of the same sample in the same NMR tube. After changing several parameters in the program operating the spectrometer, you can obtain both spectra without removing the sample from the probe. The only real difference is that a proton spectrum may be obtained after a few scans, whereas the carbon spectrum may require several thousand scans to obtain a suitable spectrum.

19.11 REFERENCE SUBSTANCES

Proton NMR. To provide the internal reference standard, tetramethylsilane (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 (0.00 δ). 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 to 3%. Some people prefer to add one to two 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 (0.00 δ).



Sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS)

Carbon NMR. 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 Appendix 5. (For example, see Fig. CMR.3 on p. 933).

In most instances, the instructor or some qualified laboratory assistant will actually record your NMR spectrum. If you are permitted to operate the NMR spectrometer, the instructor will provide instructions. Because the controls of NMR spectrometers vary, depending on the make or model of the instrument, we shall not try to describe these controls.

Do not operate the NMR spectrometer unless you have been properly instructed.

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 a 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. Describe the method that you should employ 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.
3. In order to save money, a student uses chloroform instead of deuterated chloroform to run a carbon-13 NMR spectrum. Is this a good idea?
4. 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)
5. What would happen if you ran a proton NMR spectrum without any TMS in the sample?

TECHNIQUE 20

Guide to the Chemical Literature

Often, it may be necessary to go beyond the information contained in the typical organic chemistry textbook and to 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.

20.1 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

S. Budavari, ed. *The Merck Index.* 12th ed. Whitehouse Station, NJ: Merck & Co., 1996.
J. A. Dean, ed. *Lange's Handbook of Chemistry.* 14th ed. New York: McGraw-Hill, 1992.
D. R. Lide, ed. *CRC Handbook of Chemistry and Physics.* 76th ed. Boca Raton, FL: CRC Press, 1993.

The *Handbook of Chemistry and Physics* is the handbook consulted most often. For organic chemistry, however, *The Merck Index* is probably better suited. *The Merck Index* also contains literature references on the isolation, structure determination, and synthesis of a substance, along with its molecular formula, elemental analysis, and certain properties of medicinal interest (e.g., toxicity and medicinal and veterinary uses).

A more complete handbook is

J. Buckingham, ed., *Dictionary of Organic Compounds.* New York: Chapman & Hall/Methuen, 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.

20.2 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.

W. H. Brown. *Organic Chemistry,* 2nd ed. Philadelphia: Saunders College Publishing, 1997.
F. A. Carey. *Organic Chemistry.* 3rd ed. New York: McGraw-Hill, 1996.
S. Ege. *Organic Chemistry.* 3rd ed. Lexington, MA: D. C. Heath, 1994.
R. J. Fessenden and J. S. Fessenden. *Organic Chemistry.* 5th ed. Pacific Grove, CA: Brooks/Cole, 1994.
M. A. Fox and J. K. Whitesell. *Organic Chemistry,* 2nd ed. Boston: Jones and Bartlett, 1997.
G. M. Loudon. *Organic Chemistry.* 3rd ed. Menlo Park, CA: Benjamin/Cummings, 1995.
J. March. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.* 4th ed. New York: John Wiley, 1992. Appendix B.
J. McMurry. *Organic Chemistry.* 4th ed. Pacific Grove, CA: Brooks/Cole, 1996.
R. T. Morrison and R. N. Boyd. *Organic Chemistry.* 6th ed. Englewood Cliffs, NJ: Prentice Hall, 1992.
S. H. Pine. *Organic Chemistry.* 5th ed. New York: McGraw-Hill, 1987.
T. W. G. Solomons. *Organic Chemistry.* 6th ed. New York: John Wiley, 1996.
A. Streitwieser, C. H. Heathcock, and E. M. Kosower. *Introduction to Organic Chemistry.* 4th ed. New York: Macmillan, 1992.
K. P. C. Vollhardt and N. E. Schore. *Organic Chemistry.* 2nd ed. New York: W. H. Freeman, 1994.
L. G. Wade, Jr. *Organic Chemistry.* 3rd ed. Englewood Cliffs, NJ: Prentice Hall, 1995.

20.3 SEARCHING THE CHEMICAL LITERATURE

If the information you are seeking is not available in any of the handbooks mentioned in Section 20.1 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 of this chapter outline how the various types of sources should be used and what sort of information can be obtained from them.

The methods for searching the literature discussed in this chapter use mainly printed materials. Modern search methods also make use of computerized databases and are discussed in Section 20.11. These are vast collections of data and bibliographic materials that can be scanned very rapidly from remote computer terminals. Although computerized searching is widely available, its use may not be readily accessible to undergraduate students. The following references provide excellent introductions to the literature of organic chemistry:

C. Carr. "Teaching and Using Chemical Information." *Journal of Chemical Education, 70* (September 1993): 719.
J. March. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.* 4th ed. New York: John Wiley, 1992. Appendix A.
A. N. Somerville. "Information Sources for Organic Chemistry, 1: Searching by Name Reaction and Reaction Type." *Journal of Chemical Education, 68* (July 1991): 553.
A. N. Somerville. "Information Sources for Organic Chemistry, 2: Searching by Functional Group." *Journal of Chemical Education, 68* (October 1991): 842.
A. N. Somerville. "Information Sources for Organic Chemistry, 3: Searching by Reagent." *Journal of Chemical Education, 69* (May 1992): 379.
G. Wiggins. *Chemical Information Sources.* New York: McGraw Hill, 1990. Integrates printed materials and computer sources of information.

20.4 COLLECTIONS OF SPECTRA

Collections of infrared, nuclear magnetic resonance, and mass spectra can be found in the following catalogs of spectra:

A. Cornu and R. Massot. *Compilation of Mass Spectral Data.* 2nd ed. London: Heyden and Sons, Ltd., 1975.
High-Resolution NMR Spectra Catalog. Palo Alto, CA: Varian Associates. Volume 1, 1962; Volume 2, 1963.
L. F. Johnson and W. C. Jankowski. *Carbon-13 NMR Spectra.* New York: John Wiley, 1972.
C. J. Pouchert. *Aldrich Library of Infrared Spectra.* 3rd ed. Milwaukee: Aldrich Chemical Co., 1981.
C. J. Pouchert. *Aldrich Library of FT-IR Spectra.* Milwaukee: Aldrich Chemical Co., 1985.
C. J. Pouchert. *Aldrich Library of NMR Spectra,* 2nd ed. Milwaukee: Aldrich Chemical Co., 1983.
C. J. Pouchert and J. Behnke. *Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra.* Milwaukee: Aldrich Chemical Co., 1993.
Sadtler Standard Spectra. Philadelphia: Sadtler Research Laboratories. Continuing collection.
E. Stenhagen, S. Abrahamsson, and F. W. McLafferty. *Registry of Mass Spectral Data.* New York: John Wiley-Interscience, 1974. Four-volume set.

The American Petroleum Institute has also published collections of infrared, nuclear magnetic resonance, and mass spectra.

20.5 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

F. A. Carey and R. J. Sundberg. *Advanced Organic Chemistry. Part A. Structure and Mechanisms; Part B. Reactions and Synthesis.* 3rd ed. New York: Plenum Press, 1990.

W. Carruthers. *Some Modern Methods of Organic Synthesis.* 3rd ed. Cambridge, U.K.: Cambridge University Press, 1986.
E. J. Corey and Xue-Min Cheng. *The Logic of Chemical Synthesis.* New York: John Wiley, 1989.
L. F. Fieser and M. Fieser. *Advanced Organic Chemistry.* New York: Reinhold, 1961.
I. L. Finar. *Organic Chemistry.* 6th ed. London: Longman Group, Ltd., 1986.
H. O. House. *Modern Synthetic Reactions.* 2nd ed. Menlo Park, CA: W. H. Benjamin, 1972.
J. March. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.* 4th ed. New York: John Wiley, 1992.
C. R. Noller. *Chemistry of Organic Compounds.* 3rd ed. Philadelphia: W. B. Saunders, 1965.
M. B. Smith. *Organic Synthesis.* New York: McGraw-Hill, 1994.
J. C. Stowell. *Intermediate Organic Chemistry.* 2nd ed. New York: John Wiley, 1993.
S. Warren. *Organic Synthesis: The Disconnection Approach.* New York: John Wiley, 1982.

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 March is particularly useful for this purpose.

20.6 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

N. Anand, J. S. Bindra, and S. Ranganathan. *Art in Organic Synthesis.* 2nd ed. New York: John Wiley, 1988.
D. Barton and W. D. Ollis, eds. *Comprehensive Organic Chemistry.* Oxford: Pergamon Press, 1979. Six-volume set.
C. A. Buehler and D. E. Pearson. *Survey of Organic Syntheses.* New York: John Wiley-Interscience, 1970 and 1977. Two-volume set.
F. A. Carey and R. J. Sundberg. *Advanced Organic Chemistry. Part B. Reactions and Synthesis.* 3rd ed. New York: Plenum Press, 1990.
Compendium of Organic Synthetic Methods. New York: John Wiley-Interscience, 1971–1995. This is a continuing series, now in eight volumes.
L. F. Fieser and M. Fieser. *Reagents for Organic Synthesis.* New York: John Wiley-Interscience, 1967–1994. This is a continuing series, now in 17 volumes.
T. W. Greene and P. G. M. Wuts. *Protective Groups in Organic Synthesis.* 2nd ed. New York: John Wiley, 1991.
H. O. House. *Modern Synthetic Reactions.* 2nd ed. Menlo Park, CA: W. H. Benjamin, 1972.
R. C. Larock. *Comprehensive Organic Transformations.* New York: VCH Press, 1989.
J. March. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.* 4th ed. New York: John Wiley, 1992.
B. P. Mundy and M. G. Ellerd. *Name Reactions and Reagents in Organic Synthesis.* New York: John Wiley, 1988.
S. Patai, ed. *The Chemistry of the Functional Groups.* London: Interscience, 1964–present. This series consists of many volumes, each one specializing in a particular functional group.

A. I. Vogel. Revised by members of the School of Chemistry, Thames Polytechnic. *Vogel's Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis.* 5th ed. London: Longman Group, Ltd., 1989.
R. B. Wagner and H. D. Zook. *Synthetic Organic Chemistry.* New York: John Wiley, 1956.

More specific information, including actual reaction conditions, exists in collections specializing in organic synthetic methods. The most important of these is

Organic Syntheses. New York: John Wiley, 1921–present. Published annually.
Organic Syntheses, Collective Volumes. New York: John Wiley, 1941–1993.
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

It is much more convenient to use the collective volumes where the earlier annual volumes of *Organic Syntheses* are combined in groups of nine or ten in the first six collective volumes (Vol. 1–6), and then in groups of five for the next two volumes (Vol. 7 and 8). 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 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. New York: John Wiley, 1960–present.
Annual Reports of the Chemical Society, Section B. London: Chemical Society, 1905–present. Specifically, the section on *Synthetic Methods.*
Annual Reports in Organic Synthesis. Orlando, FL: Academic Press, 1985–1995.
Progress in Organic Chemistry. New York: John Wiley, 1952–1973.
Organic Reactions. New York: John Wiley, 1942–present.

Each of these publications contains a great many citations to the appropriate articles in the original literature.

20.7 ADVANCED LABORATORY TECHNIQUES

The student who is interested in reading about more advanced techniques 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 also provide advice on purifying reagents and solvents. Useful sources of information on organic laboratory techniques include

R. B. Bates and J. P. Schaefer. *Research Techniques in Organic Chemistry.* Englewood Cliffs, NJ: Prentice-Hall, 1971.

A. J. Krubsack. *Experimental Organic Chemistry.* Boston: Allyn and Bacon, 1973.

J. Leonard, B. Lygo, and G. Procter. *Advanced Practical Organic Chemistry,* 2nd ed. London: Chapman and Hall, 1995.

R. S. Monson, *Advanced Organic Synthesis: Methods and Techniques.* New York: Academic Press, 1971.

Techniques of Chemistry. New York: John Wiley, 1970–present. Currently 21 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.

A. Weissberger, et al., eds. *Technique of Organic Chemistry.* 3rd ed. New York: John Wiley-Interscience, 1959–1969. This work is in 14 volumes.

K. B. Wiberg. *Laboratory Technique in Organic Chemistry.* New York: McGraw-Hill, 1960.

J. W. Zubrick. *The Organic Chem Lab Survival Manual: A Student's Guide to Techniques.* 4th ed. New York: John Wiley, 1997.

Numerous works and some general textbooks specialize in particular techniques. The above list is only representative of the most common books in this category. The following books deal specifically with micro and semi-microscale techniques.

N. D. Cheronis. "Micro and Semimicro Methods." In: A Weissberger, ed. *Technique of Organic Chemistry,* Volume 6. New York: John Wiley-Interscience, 1954.

N. D. Cheronis and T. S. Ma. *Organic Functional Group Analysis by Micro and Semimicro Methods.* New York: John Wiley-Interscience, 1964.

T. S. Ma and V. Horak. *Microscale Manipulations in Chemistry.* New York: John Wiley-Interscience, 1976.

20.8 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

A. Miller. *Writing Reaction Mechanisms in Organic Chemistry.* San Diego: Academic Press, 1992.

P. Sykes. *A Guidebook to Mechanism in Organic Chemistry.* 6th ed. London: Longman Group, Ltd., 1986.

More advanced textbooks include

F. A. Carey and R. J. Sundberg. *Advanced Organic Chemistry. Part A. Structure and Mechanisms.* 3rd ed. New York: Plenum Press, 1990.
L. P. Hammett. *Physical Organic Chemistry: Reaction Rates, Equilibria, and Mechanisms.* 2nd ed. New York: McGraw-Hill, 1970.
J. Hine. *Physical Organic Chemistry.* 2nd ed. New York: McGraw-Hill, 1962.
C. K. Ingold. *Structure and Mechanism in Organic Chemistry.* 2nd ed. Ithaca, NY: Cornell University Press, 1969.
N. S. Isaacs. *Physical Organic Chemistry.* 2nd ed. New York: John Wiley, 1995.
R. A. Y. Jones. *Physical and Mechanistic Organic Chemistry.* 2nd ed. Cambridge, U.K.: Cambridge University Press, 1984.
T. H. Lowry and K. S. Richardson. *Mechanism and Theory in Organic Chemistry.* 3rd ed. New York: Harper & Row, 1987.
J. March. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.* 4th ed. New York: John Wiley, 1992.
J. W. Moore and R. G. Pearson. *Kinetics and Mechanism.* 3rd ed. New York: John Wiley, 1981.

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. London: Academic Press, 1963–present.
Annual Reports of the Chemical Society. Section B. London: Chemical Society, 1905–present. Specifically, the section on *Reaction Mechanisms.*
Organic Reaction Mechanisms. Chichester, U.K.: John Wiley, 1965–present.
Progress in Physical Organic Chemistry. New York: Interscience, 1963–present.

These publications provide the reader with citations from the original literature that can be very useful in an extensive literature search.

20.9 ORGANIC QUALITATIVE ANALYSIS

Experiment 57 contains a procedure 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

N. D. Cheronis and J. B. Entriken. *Identification of Organic Compounds: A Student's Text Using Semimicro Techniques.* New York: Interscience, 1963.
D. J. Pasto and C. R. Johnson. *Laboratory Text for Organic Chemistry: A Source Book of Chemical and Physical Techniques.* Englewood Cliffs, NJ: Prentice-Hall, 1979.
Z. Rappoport, ed. *Handbook of Tables for Organic Compound Identification.* 3rd ed. Cleveland: Chemical Rubber Co., 1967.

R. L. Shriner, R. C. Fuson, D. Y. Curtin, and T. C. Morrill. *The Systematic Identification of Organic Compounds: A Laboratory Manual.* 6th ed. New York: John Wiley, 1980.

A. I. Vogel, *Elementary Practical Organic Chemistry. Part 2. Qualitative Organic Analysis.* 2nd ed. New York: John Wiley, 1966.

A. I. Vogel. Revised by members of the School of Chemistry, Thames Polytechnic. *Vogel's Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis.* 5th ed. London: Longman Group, Ltd., 1989.

20.10 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 covers completely 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 1910–1919; 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

A. M. Patterson. *German–English Dictionary for Chemists.* 3rd ed. New York: John Wiley, 1959.

Beilstein is organized according to a very sophisticated and complicated system. To locate a compound in *Beilstein,* you can learn all the intricacies of this 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. 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 us that *p*-nitroaniline is listed in the main edition (*Hauptwerk*) in volume 12, page 711. Locating this particular volume, which is devoted to isocyclic monoamines, we turn to page 711 and find the beginning of the section on *p*-nitroaniline. At the left side of the top of this page, we find "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/H 711." The information on *p*-nitroaniline is found on this page (p. 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

E. H. Huntress. *A Brief Introduction to the Use of Beilsteins Handbuch der Organischen Chemie.* 2nd ed. New York: John Wiley, 1938.

How to Use Beilstein. Beilstein Institute, Frankfurt am Main. Berlin: Springer-Verlag.
O. Weissbach. *The Beilstein Guide: A Manual for the Use of Beilsteins Handbuch der Organischen Chemie.* New York: Springer-Verlag, 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 Catalog 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 paper, 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. Washington, D.C.: Chemical Abstracts Service, American Chemical Society, 1977.
How to Search Printed CA. Washington, D.C.: Chemical Abstracts Service, American Chemical Society, 1989.

Chemical Abstracts Service maintains a computerized database that permits users to search through *Chemical Abstracts* very rapidly and thoroughly. This service, which is called *CA Online,* is described in Section 20.11. *Beilstein* is also available for online searching by computer.

20.11 COMPUTER ONLINE SEARCHING

You can search a number of chemistry databases online by using a computer and modem. 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 earlier than 1967 must be made with printed abstracts (Section 20.10). An online search 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 Substance Registry Number (CAS number) as part of the search routine. For the more common organic compounds, you can easily obtain CAS numbers from the catalogues 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 20.10, *Beilstein* is very useful to organic chemists. Currently, there are over 3.5 million compounds listed in the database. You can use the CAS Registry 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 Registry Numbers. Further information on *CA Online, Beilstein, CASREACTS,* and other databases can be obtained from the following references:

J. March. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.* 4th ed. New York: John Wiley, 1992. Appendix A contains a summary.

A. N. Somerville. "Information Sources for Organic Chemistry, 2: Searching by Functional Group." *Journal of Chemical Education, 68* (October 1991): 842.

A. N. Somerville. "Subject Searching of Chemical Abstracts Online." *Journal of Chemical Education, 70* (March 1993): 200.

G. Wiggins. *Chemical Information Sources.* New York: McGraw Hill, 1990. Integrates printed materials and computer sources of information.

20.12 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 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 might be mentioned here. These are

Canadian Journal of Chemistry
Chemische Berichte
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 Organic Chemistry
Journal of Organometallic Chemistry
Liebigs Annalen der Chemie
Organometallics
Synthesis
Tetrahedron
Tetrahedron Letters

20.13 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 in Britain

Chemistry and Industry
Chemtech
Discover
Journal of Chemical Education
Nature
New Scientist
Omni
Science
Science Digest
Scientific American
SciQuest (formerly *Chemistry*)

20.14 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 20.10) 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 they failed to cite that particular key reference in their 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 (Section 20.11) 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 further into this subject.

R. T. Bottle and J. F. B. Rowland, eds. *Information Sources in Chemistry,* 4th ed. New York: Bowker-Saur, 1992.

M. G. Mellon. *Chemical Publications.* 5th ed. New York: McGraw-Hill, 1982.

R. E. Maizell. *How to Find Chemical Information: A Guide for Practicing Chemists, Teachers, and Students,* 2nd ed. New York: John Wiley-Interscience, 1987.

G. Wiggins. *Chemical Information Sources.* New York: McGraw Hill, 1990. Integrates printed materials and computer sources of information.

PROBLEMS

1. Using the *Merck Index* discussed in Section 20.1, 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 *Handbook of Chemistry and Physics* or *Lange's Handbook of Chemistry* (Section 20.1):

(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 references given in Problem 2, give the specific rotations $[\alpha]_D$ 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.

7. Find the following compounds in the formula index for the *Second Supplement of Beilstein* (Section (20.10). (i) List the page numbers from the Main Work and the Supplements (First and Second). (ii) 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. (iii) 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)

8. Using the *Science Citation Index* (Section 20.14), 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 Cumulation 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

9. The reference book by J. March is listed in Section 20.2. Using Appendix B 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)

10. *Organic Synthesis* is described in Section 20.6. There are currently eight 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*-Δ^4-tetrahydrophthalic anhydride (listed as tetrahydrophthalic anhydride)

11. Provide four ways 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 (Section 20.6).

Appendices

APPENDIX 1

Tables of Unknowns and Derivatives

More extensive tables of unknowns may be found in Z. Rappoport, ed. *Handbook of Tables for Organic Compound Identification,* 3rd ed. Cleveland: Chemical Rubber Co., 1967

ALDEHYDES

Compound	BP	MP	Semi-carbazone*	2,4-Dinitro-phenyl-hydrazone*
Ethanal (acetaldehyde)	21	—	162	168
Propanal (propionaldehyde)	48	—	89	148
Propenal (acrolein)	52	—	171	165
2-Methylpropanal (isobutyraldehyde)	64	—	125	187
Butanal (butyraldehyde)	75	—	95	123
3-Methylbutanal (isovaleraldehyde)	92	—	107	123
Pentanal (valeraldehyde)	102	—	—	106
2-Butenal (crotonaldehyde)	104	—	199	190
2-Ethylbutanal (diethylacetaldehyde)	117	—	99	95
Hexanal (caproaldehyde)	130	—	106	104
Heptanal (heptaldehyde)	153	—	109	108
2-Furaldehyde (furfural)	162	—	202	212
2-Ethylhexanal	163	—	254	114
Octanal (caprylaldehyde)	171	—	101	106
Benzaldehyde	179	—	222	237
Phenylethanal (phenylacetaldehyde)	195	33	153	121
2-Hydroxybenzaldehyde (salicylaldehyde)	197	—	231	248
4-Methylbenzaldehyde (*p*-tolualdehyde)	204	—	234	234
3,7-Dimethyl-6-octenal (citronellal)	207	—	82	77
2-Chlorobenzaldehyde	213	11	229	213
4-Methoxybenzaldehyde (*p*-anisaldehyde)	248	2.5	210	253
trans-Cinnamaldehyde	250 d.	—	215	255
3,4-Methylenedioxybenzaldehyde (piperonal)	263	37	230	266 d.
2-Methoxybenzaldehyde (*o*-anisaldehyde)	245	38	215 d.	254
4-Chlorobenzaldehyde	214	48	230	254
3-Nitrobenzaldehyde	—	58	246	293
4-Dimethylaminobenzaldehyde	—	74	222	325
Vanillin	285 d.	82	230	271

ALDEHYDES *(Cont.)*

Compound	BP	MP	Semi-carbazone*	2,4-Dinitro-phenyl-hydrazone*
4-Nitrobenzaldehyde	—	106	221	320 d.
4-Hydroxybenzaldehyde	—	116	224	280 d.
(±)-Glyceraldehyde	—	142	160 d.	167

NOTE: "*d*" indicates "*decomposition.*"

*See Appendix 2, "Procedures for Preparing Derivatives."

KETONES

Compound	BP	MP	Semi-carbazone*	2,4-Dinitro-phenyl hydrazone*
2-Propanone (acetone)	56	—	187	126
2-Butanone (methyl ethyl ketone)	80	—	146	117
3-Methyl-2-butanone (isopropyl methyl ketone)	94	—	112	120
2-Pentanone (methyl propyl ketone)	101	—	112	143
3-Pentanone (diethyl ketone)	102	—	138	156
Pinacolone	106	—	157	125
4-Methyl-2-pentanone (isobutyl methyl ketone)	117	—	132	95
2,4-Dimethyl-3-pentanone (diisopropyl ketone)	124	—	160	95
2-Hexanone (methyl butyl ketone)	128	—	125	106
4-Methyl-3-penten-2-one (mesityl oxide)	130	—	164	205
Cyclopentanone	131	—	210	146
2,3-Pentanedione	134	—	122 (mono) 209 (di)	209
2,4-Pentanedione (acetylacetone)	139	—	—	122 (mono) 209 (di)
4-Heptanone (dipropyl ketone)	144	—	132	75
2-Heptanone (methyl amyl ketone)	151	—	123	89
Cyclohexanone	156	—	166	162
2,6-Dimethyl-4-heptanone (diisobutyl ketone)	168	—	122	92
2-Octanone	173	—	122	58
Cycloheptanone	181	—	163	148
2,5-Hexanedione (acetonylacetone)	191	−9	185 (mono) 224 (di)	257 (di)
Acetophenone (methyl phenyl ketone)	202	20	198	238

KETONES *(Cont.)*

Compound	BP	MP	Semi-carbazone*	2,4-Dinitro-phenyl hydrazone*
Phenyl-2-propanone (phenylacetone)	216	27	198	156
Propiophenone (ethyl phenyl ketone)	218	21	182	191
4-Methylacetophenone	226	—	205	258
2-Undecanone	231	12	122	63
4-Chloroacetophenone	232	12	204	236
4-Phenyl-2-butanone (benzylacetone)	235	—	142	127
4-Chloropropiophenone	—	36	176	223
4-Phenyl-3-buten-2-one	—	37	187	227
4-Methoxyacetophenone	258	38	198	228
Benzophenone	305	48	167	238
4-Bromoacetophenone	225	51	208	230
2-Acetonaphthone	—	54	235	262
Desoxybenzoin	320	60	148	204
3-Nitroacetophenone	202	80	257	228
9-Fluorenone	345	83	234	283
Benzoin	344	136	206	245
4-Hydroxypropiophenone	—	148	—	229
(±)-Camphor	205	179	237	177

*See Appendix 2, "Procedures for Preparing Derivatives."

CARBOXYLIC ACIDS

Compound	BP	MP	*p*-Toluidide*	Anilide*	Amide*
Formic acid	101	8	53	47	43
Acetic acid	118	17	148	114	82
Propenoic acid (acrylic acid)	139	13	141	104	85
Propanoic acid (propionic acid)	141	—	124	103	81
2-Methylpropanoic acid (isobutyric acid)	154	—	104	105	128
Butanoic acid (butyric acid)	162	—	72	95	115
2-Methylpropenoic acid (methacrylic acid)	163	16	—	87	102
Trimethylacetic acid (pivalic acid)	164	35	—	127	178
Pyruvic acid	165 d.	14	109	104	124
3-Methylbutanoic acid (isovaleric acid)	176	—	109	109	135

CARBOXYLIC ACIDS *(Cont.)*

Compound	BP	MP	*p*-Toluidide*	Anilide*	Amide*
Pentanoic acid (valeric acid)	186	—	70	63	106
2-Methylpentanoic acid	186	—	80	95	79
2-Chloropropanoic acid	186	—	124	92	80
Dichloroacetic acid	194	6	153	118	98
Hexanoic acid (caproic acid)	205	—	75	95	101
2-Bromopropanoic acid	205	24	125	99	123
Octanoic acid (caprylic acid)	237	16	70	57	107
Nonanoic acid	254	12	84	57	99
Decanoic acid (capric acid)	268	32	78	70	108
4-Oxopentanoic acid (levulinic acid)	246	33	108	102	108 d.
Dodecanoic acid (lauric acid)	299	43	87	78	100
3-Phenylpropanoic acid (hydrocinnamic acid)	279	48	135	98	105
Bromoacetic acid	208	50	—	131	91
Tetradecanoic acid (myristic acid)	—	54	93	84	103
Trichloroacetic acid	198	57	113	97	141
Hexadecanoic acid (palmitic acid)	—	62	98	90	106
Chloroacetic acid	189	63	162	137	121
Octadecanoic acid (stearic acid)	—	69	102	95	109
trans-2-Butenoic acid (crotonic acid)	—	72	132	118	158
Phenylacetic acid	—	77	136	118	156
2-Methoxybenzoic acid (*o*-anisic acid)	200	101	—	131	129
2-Methylbenzoic acid (*o*-toluic acid)	—	104	144	125	142
Nonanedioic acid (azelaic acid)	—	106	201 (di)	107 (mono) 186 (di)	93 (mono) 175 (di)
3-Methylbenzoic acid (*m*-toluic acid)	263 s.	110	118	126	94
(±)-Phenylhydroxyacetic acid (mandelic acid)	—	118	172	151	133
Benzoic acid	249	122	158	163	130
2-Benzoylbenzoic acid	—	127	—	195	165
Maleic acid	—	130	142 (di)	198 (mono) 187 (di)	172 (mono) 260 (di)
Decanedioic acid (sebacic acid)	—	133	201 (di)	122 (mono) 200 (di)	170 (mono) 210 (di)
Cinnamic acid	300	133	168	153	147

NOTE: "*s*" indicates "*sublimination*"; "*d*" indicates "*decomposition.*"

*See Appendix 2, "Procedures for Preparing Derivatives."

CARBOXYLIC ACIDS (*Cont.*)

Compound	BP	MP	*p*-Toluidide*	Anilide*	Amide*
2-Chlorobenzoic acid	—	140	131	118	139
3-Nitrobenzoic acid	—	140	162	155	143
2-Aminobenzoic acid (anthranilic acid)	—	146	151	131	109
Diphenylacetic acid	—	148	172	180	167
2-Bromobenzoic acid	—	150	—	141	155
Benzilic acid	—	150	190	175	154
Hexanedioic acid (adipic acid)	—	152	239	151 (mono)	125 (mono)
				241 (di)	220 (di)
Citric acid	—	153	189 (tri)	199 (tri)	210 (tri)
4-Chlorophenoxyacetic acid	—	158	—	125	133
2-Hydroxybenzoic acid (salicylic acid)	—	158	156	136	142
5-Bromo-2-hydroxybenzoic acid (5-bromosalicylic acid)	—	165	—	222	232
Methylenesuccinic acid (itaconic acid)	—	166 d.	—	152 (mono)	191 (di)
(+)-Tartaric acid	—	169	—	180 (mono)	171 (mono)
				264 (di)	196 (di)
4-Chloro-3-nitrobenzoic acid	—	180	—	131	156
4-Methylbenzoic acid (*p*-toluic acid)	—	180	160	145	160
4-Methoxybenzoic acid (*p*-anisic acid)	280	184	186	169	167
Butanedioic acid (succinic acid)	235 d.	188	180 (mono)	143 (mono)	157 (mono)
			255 (di)	230 (di)	260 (di)
3-Hydroxybenzoic acid	—	201	163	157	170
3,5-Dinitrobenzoic acid	—	202	—	234	183
Phthalic acid	—	210 d.	150 (mono)	169 (mono)	144 (mono)
			201 (di)	253 (di)	220 (di)
4-Hydroxybenzoic acid	—	214	204	197	162
Pyridine-3-carboxylic acid (nicotinic acid)	—	236	150	132	128
4-Nitrobenzoic acid	—	240	204	211	201
4-Chlorobenzoic acid	—	242	—	194	179
Fumaric acid	—	300	—	233 (mono)	270 (mono)
				314 (di)	266 (di)

NOTE: "*d*" indicates "*decomposition.*"

*See Appendix 2, "Procedures for Preparing Derivatives."

PHENOLS†

Compound	BP	MP	α-Naphthylurethane*	Bromo Derivative*			
				Mono	*Di*	*Tri*	*Tetra*
2-Chlorophenol	176	7	120	48	76	—	—
3-Methylphenol (*m*-cresol)	203	12	128	—	—	84	—
2-Methylphenol (*o*-cresol)	191	32	142	—	56	—	—
2-Methoxyphenol (guaiacol)	204	32	118	—	—	116	—
4-Methylphenol (*p*-cresol)	202	34	146	—	49	—	198
Phenol	181	42	133	—	—	95	—
4-Chlorophenol	217	43	166	33	90	—	—
2,4-Dichlorophenol	210	45	—	68	—	—	—
4-Ethylphenol	219	45	128	—	—	—	—
2-Nitrophenol	216	45	113	—	117	—	—
2-Isopropyl-5-methylphenol (thymol)	234	51	160	55	—	—	—
3,4-Dimethylphenol	225	64	141	—	—	171	—
4-Bromophenol	238	64	169	—	—	95	—
3,5-Dimethylphenol	220	68	109	—	—	166	—
2,5-Dimethylphenol	212	75	173	—	—	178	—
1-Naphthol (α-naphthol)	278	96	152	—	105	—	—
2-Hydroxyphenol (catechol)	245	104	175	—	—	—	192
3-Hydroxyphenol (resorcinol)	281	109	275	—	—	112	—
4-Nitrophenol	—	112	150	—	142	—	—
2-Naphthol (β-naphthol)	286	121	157	84	—	—	—
1,2,3-Trihydroxybenzene (pyrogallol)	309	133	—	—	158	—	—
4-Phenylphenol	305	164	—	—	—	—	—

*See Appendix 2, "Procedures for Preparing Derivatives."
†Also check:
Salicylic acid (2-hydroxybenzoic acid)
Esters of salicylic acid (salicylates)
Salicylaldehyde (2-hydroxybenzaldehyde)
4-Hydroxybenzaldehyde
4-Hydroxypropiophenone
3-Hydroxybenzoic acid
4-Hydroxybenzoic acid
4-Hydroxybenzophenone

PRIMARY AMINES†

Compound	BP	MP	Benzamide*	Picrate*	Acetamide*
t-Butylamine	46	—	134	198	101
Propylamine	48	—	84	135	—

PRIMARY AMINES† *(Cont.)*

Compound	BP	MP	Benzamide*	Picrate*	Acetamide*
Allylamine	56	—	—	140	—
sec-Butylamine	63	—	76	139	—
Isobutylamine	69	—	57	150	—
Butylamine	78	—	42	151	—
Cyclohexylamine	135	—	149	—	104
Furfurylamine	145	—	—	150	—
Benzylamine	184	—	105	194	60
Aniline	184	—	163	198	114
2-Methylaniline (*o*-toluidine)	200	—	144	213	110
3-Methylaniline (*m*-toluidine)	203	—	125	200	65
2-Chloroaniline	208	—	99	134	87
2,6-Dimethylaniline	216	11	168	180	177
2-Methoxyaniline (*o*-anisidine)	225	6	60	200	85
3-Chloroaniline	230	—	120	177	74
2-Ethoxyaniline (*o*-phenetidine)	231	—	104	—	79
4-Chloro-2-methylaniline	241	29	142	—	140
4-Ethoxyaniline (*p*-phenetidine)	250	2	173	69	137
4-Methylaniline (*p*-toluidine)	200	43	158	182	147
2-Ethylaniline	210	47	147	194	111
2,5-Dichloroaniline	251	50	120	86	132
4-Methoxyaniline (*p*-anisidine)	—	58	154	170	130
4-Bromoaniline	245	64	204	180	168
2,4,5-Trimethylaniline	—	64	167	—	162
4-Chloroaniline	—	70	192	178	179
2-Nitroaniline	—	72	110	73	92
Ethyl *p*-aminobenzoate	—	89	148	—	110
o-Phenylenediamine	258	102	301 (di)	208	185 (di)
2-Methyl-5-nitroaniline	—	106	186	—	151
2-Chloro-4-nitroaniline	—	108	161	—	139
3-Nitroaniline	—	114	157	143	155
4-Chloro-2-nitroaniline	—	118	—	—	104
2,4,6-Tribromoaniline	300	120	200	—	232 (mono) 127 (di)
2-Methyl-4-nitroaniline	—	130	—	—	202
2-Methoxy-4-nitroaniline	—	138	149	—	153
p-Phenylenediamine	267	140	128 (mono) 300 (di)	—	162 (mono) 304 (di)
4-Nitroaniline	—	148	199	100	215
4-Aminoacetanilide	—	162	—	—	304
2,4-Dinitroaniline	—	180	202	—	120

*See Appendix 2, "Procedures for Preparing Derivatives."

†Also check: 4-Aminobenzoic acid and its esters.

SECONDARY AMINES

Compound	BP	MP	Benzamide*	Picrate*	Acetamide*
Diethylamine	56	—	42	155	—
Diisopropylamine	84	—	—	140	—
Pyrrolidine	88	—	Oil	112	—
Piperidine	106	—	48	152	—
Dipropylamine	110	—	—	75	—
Morpholine	129	—	75	146	—
Diisobutylamine	139	—	—	121	86
N-Methylcyclohexylamine	148	—	85	170	—
Dibutylamine	159	—	—	59	—
Benzylmethylamine	184	—	—	117	—
N-Methylaniline	196	—	63	145	102
N-Ethylaniline	205	—	60	132	54
N-Ethyl-*m*-toluidine	221	—	72	—	—
Dicyclohexylamine	256	—	153	173	103
N-Benzylaniline	298	37	107	48	58
Indole	254	52	68	—	157
Diphenylamine	302	52	180	182	101
N-Phenyl-1-naphthylamine	335	62	152	—	115

*See Appendix 2, "Procedures for Preparing Derivatives."

TERTIARY AMINES†

Compound	BP	MP	Picrate*	Methiodide*
Triethylamine	89	—	173	280
Pyridine	115	—	167	117
2-Methylpyridine (α-picoline)	129	—	169	230
3-Methylpyridine (β-picoline)	144	—	150	92
Tripropylamine	157	—	116	207
N,N-Dimethylbenzylamine	183	—	93	179
N,N-Dimethylaniline	193	—	163	228 d.
Tributylamine	216	—	105	186
N,N-Diethylaniline	217	—	142	102
Quinoline	237	—	203	133

NOTE: "*d*" indicates "*decomposition.*"

*See Appendix 2, "Procedures for Preparing Derivatives."

†Also check: Nicotinic acid and its esters.

ALCOHOLS

Compound	BP	MP	3,5-Dinitrobenzoate*	Phenylurethane*
Methanol	65	—	108	47
Ethanol	78	—	93	52
2-Propanol (isopropyl alcohol)	82	—	123	88
2-Methyl-2-propanol (*t*-butyl alcohol)	83	26	142	136
2-Propen-1-ol (allyl alcohol)	97	—	49	70
1-Propanol	97	—	74	57
2-Butanol (*sec*-butyl alcohol)	99	—	76	65
2-Methyl-2-butanol (*t*-pentyl alcohol)	102	−8.5	116	42
2-Methyl-3-butyn-2-ol	104	—	112	—
2-Methyl-1-propanol (isobutyl alcohol)	108	—	87	86
2-Propyn-1-ol (propargyl alcohol)	114	—	—	—
3-Pentanol	115	—	101	48
1-Butanol	118	—	64	61
2-Pentanol	119	—	62	—
3-Methyl-3-pentanol	123	—	96	43
2-Methoxyethanol	124	—	—	(113)†
2-Chloroethanol	129	—	95	51
3-Methyl-1-butanol (isoamyl alcohol)	130	—	70	31
4-Methyl-2-pentanol	132	—	65	143
1-Pentanol	138	—	46	46
Cyclopentanol	140	—	115	132
2-Ethyl-1-butanol	146	—	51	—
2,2,2-Trichloroethanol	151	—	142	87
1-Hexanol	157	—	58	42
Cyclohexanol	160	—	113	82
(2-Furyl)-methanol (furfuryl alcohol)	170	—	80	45
1-Heptanol	176	—	47	60
2-Octanol	179	—	32	114
1-Octanol	195	—	61	74
3,7-Dimethyl-1,6-octadien-3-ol (linalool)	196	—	—	66
Benzyl alcohol	204	—	113	77
1-Phenylethanol	204	20	92	95
2-Phenylethanol	219	—	108	78
1-Decanol	231	7	57	59
3-Phenylpropanol	236	—	45	92
1-Dodecanol (lauryl alcohol)	—	24	60	74
3-Phenyl-2-propen-1-ol (cinnamyl alcohol)	250	34	121	90
1-Tetradecanol (myristyl alcohol)	—	39	67	74
(−)-Menthol	212	41	158	111
1-Hexadecanol (cetyl alcohol)	—	49	66	73

ALCOHOLS *(Cont.)*

Compound	BP	MP	3,5-Dinitrobenzoate*	Phenylurethane*
1-Octadecanol (stearyl alcohol)	—	59	77	79
Diphenylmethanol (benzhydrol)	288	68	141	139
Benzoin	—	133	—	165
Cholesterol	—	147	—	168
(+)-Borneol	—	208	154	138

*See Appendix 2, "Procedures for Preparing Derivatives."
†α-Naphthylurethane.

ESTERS

Compound	BP	MP	Compound	BP	MP
Methyl formate	34	—	Ethyl lactate	154	—
Ethyl formate	54	—	Ethyl hexanoate (ethyl caproate)	168	—
Vinyl acetate	72	—	Methyl acetoacetate	170	—
Ethyl acetate	77	—	Dimethyl malonate	180	—
Methyl propanoate (methyl propionate)	80	—	Ethyl acetoacetate	181	—
Methyl acrylate	80	—	Diethyl oxalate	185	—
2-Propyl acetate (isopropyl acetate)	85	—	Methyl benzoate	199	—
Ethyl chloroformate	93	—	Ethyl octanoate (ethyl caprylate)	207	—
Methyl 2-methylpropanoate	93	—	Ethyl cyanoacetate	210	—
(methyl isobutyrate)			Ethyl benzoate	212	—
2-Propenyl acetate (isopropenyl acetate)	94	—	Diethyl succinate	217	—
2-(2-Methylpropyl acetate	98	—	Methyl phenylacetate	218	—
(*t*-butyl acetate)			Diethyl fumarate	219	—
Ethyl acrylate	99	—	Methyl salicylate	222	—
Ethyl propanoate (ethyl propionate)	99	—	Diethyl maleate	225	—
Methyl methacrylate	100	—	Ethyl phenylacetate	229	—
Methyl trimethylacetate (methyl pivalate)	101	—	Ethyl salicylate	234	—
Propyl acetate	102	—	Dimethyl suberate	268	—
Methyl butanoate (methyl butyrate)	102	—	Ethyl cinnamate	271	—
2-Butyl acetate (*sec*-butyl acetate)	111	—	Diethyl phthalate	298	—
Methyl 3-methylbutanoate	117	—	Dibutyl phthalate	340	—
(methyl isovalerate)			Methyl cinnamate	—	36
Ethyl butanoate (ethyl butyrate)	120	—	Phenyl salicylate	—	42
Butyl acetate	127	—	Methyl *p*-chlorobenzoate	—	44
Methyl pentanoate (methyl valerate)	128	—	Ethyl *p*-nitrobenzoate	—	56
Methyl chloroacetate	130	—	Phenylbenzoate	314	69

ESTERS *(Cont.)*

Compound	BP	MP	Compound	BP	MP
Ethyl 3-methylbutanoate (ethyl isovalerate)	132	—	Methyl *m*-nitrobenzoate	—	78
Pentyl acetate (*n*-amyl acetate)	142	—	Methyl *p*-bromobenzoate	—	81
3-Methylbutyl acetate (isoamyl acetate)	142	—	Ethyl *p*-aminobenzoate	—	90
Ethyl chloroacetate	143	—	Methyl *p*-nitrobenzoate	—	94

APPENDIX 2

Procedures for Preparing Derivatives

Caution: Some of the chemicals used in preparing derivatives are suspected carcinogens. The list of suspected carcinogens on page 21 should be consulted before beginning any of these procedures. Care should be exercised in handling these substances.

ALDEHYDES AND KETONES

Semicarbazones. Place 0.5 mL of a 2*M* stock solution of semicarbazide hydrochloride (or 0.5 mL of a solution prepared by dissolving 1.11 g of semicarbazide hydrochloride [MW = 111.5] in 5 mL of water) in a small test tube. Add an estimated 1 millimole (mmol) of the unknown compound to the test tube. If the unknown does not dissolve in the solution, or if the solution becomes cloudy, add enough methanol (maximum of 10 mL) to dissolve the solid and produce a clear solution. If a solid or cloudiness remains after adding 10 mL of methanol, do not add any more methanol and continue this procedure with the solid present. Using a Pasteur pipet, add 10 drops of pyridine and heat the mixture in a hot-water bath (about 60°C) for about 10–15 minutes. By that time, the product should have begun to crystallize. Collect the product by vacuum filtration. The product can be recrystallized from ethanol if necessary.

Semicarbazones (Alternative Method). Dissolve 0.25 g of semicarbazide hydrochloride and 0.38 g of sodium acetate in 1.3 mL of water. Then dissolve 0.25 g of the unknown in 2.5 mL of ethanol. Mix the two solutions together in a 25-mL Erlenmeyer flask and heat the mixture to boiling for about 5 minutes. After heating, place the reaction flask in a beaker of ice and scratch the sides of the flask with a glass rod to induce crystallization of the derivative. Collect the derivative by vacuum filtration and recrystallize it from ethanol.

2,4-Dinitrophenylhydrazones. Place 10 mL of a solution of 2,4-dinitrophenylhydrazine (prepared as described for the classification test in Experiment 57D) in a test tube and add an estimated 1 mmol of the unknown compound. If the unknown is a solid, it should be dissolved in the minimum amount of 95% ethanol or 1,2-dimethoxyethane before it is added. If crystallization is not immediate, gently warm the solution for a minute in a hot-water bath (90°C) and then set it aside to crystallize. Collect the product by vacuum filtration.

CARBOXYLIC ACIDS

Working in a hood, place 0.5 g of the acid and 2 mL of thionyl chloride into a small round-bottom flask. Add a magnetic stir bar and attach a condenser and a drying tube packed with calcium chloride. While stirring, heat the reaction mixture almost to boiling with a heating mantle with a magnetic stirrer or a hotplate/stirrer. *If the mixture does not turn color,* heat the solution for 30 minutes. Allow the mixture to cool to room temperature. *If the mixture begins to turn color,* remove the heat source and stir the mixture for 45 minutes at room temperature. Use the mixture for one of the following three procedures.

Amides. Working in a hood, pour the reaction mixture into a beaker containing 10 mL of ice cold concentrated ammonium hydroxide and stir it vigorously. When the reaction is complete, collect the product by vacuum filtration and recrystallize it from water or from water–ethanol, using the mixed-solvents method (Technique 5, Section 5.9).

Anilides. Dissolve 1 g of aniline in 25 mL of methylene chloride in a 125-mL Erlenmeyer flask. Using a Pasteur pipet, carefully add the reaction mixture to this solution. Warm the mixture for an additional 5 minutes on a hotplate, unless a significant color change occurs. *If a color change occurs,* discontinue heating, add a magnetic stirring bar, and stir the mixture for 20 minutes at room temperature. Then transfer the methylene chloride solution to a small separatory funnel and wash it sequentially with 5 mL of water, 5 mL of 5% hydrochloric acid, 5 mL of 5% sodium hydroxide, and a second 5-mL portion of water (the methylene chloride solution should be the bottom layer). Dry the methylene chloride layer over a small amount of anhydrous sodium sulfate. Decant the methylene chloride layer away from the drying agent into a small flask and evaporate the methylene chloride on a warm hotplate in the hood. Use a stream of air or nitrogen to speed up the evaporation. Recrystallize the product from water or from ethanol–water, using the mixed-solvents method (Technique 5, Section 5.9).

***p*-Toluidides.** Use the same procedure as that described for the anilide but substitute *p*-toluidine for aniline.

PHENOLS

α-Naphthylurethanes. Follow the procedure given later for preparing phenylurethanes from alcohols but substitute α-naphthylisocyanate for phenylisocyanate.

Bromo Derivatives. First, if a stock brominating solution is not available, prepare one by dissolving 0.75 g of potassium bromide in 5 mL of water and adding 0.5 g of bromine. Dissolve 0.1 g of the phenol in 1 mL of methanol or 1,2-dimethoxyethane; then add 1 mL of water. Add 1 mL of the brominating mixture to the phenol solution and swirl the mixture vigorously. Then, continue adding the brominating solution dropwise while swirling, until the color of the bromine reagent persists. Finally, add 3–5 mL of water and shake the mixture vigorously. Collect the precipitated product by vacuum filtration and wash it well with water. Recrystallize the derivative from methanol–water, using the mixed-solvents method (Technique 5, Section 5.9).

AMINES

Acetamides. Place an estimated 1 mmol of the amine and 0.5 mL of acetic anhydride in a small Erlenmeyer flask. Heat the mixture for about 5 minutes; then add 5 mL of water and stir the solution vigorously to precipitate the product and hydrolyze the excess acetic anhydride. If the product does not crystallize, it may be necessary to scratch the walls of the flask with a glass rod. Collect the crystals by vacuum filtration and wash them with several portions of cold 5% hydrochloric acid. Recrystallize the derivative from methanol–water, using the mixed-solvents method (Technique 5, Section 5.9).

Aromatic amines, or those amines that are not very basic, may require pyridine (2 mL) as a solvent and a catalyst for the reaction. If pyridine is used, a longer period of heating is required (up to 1 hour), and the reaction should be carried out in an apparatus equipped with a reflux condenser. After reflux, the reaction mixture must be extracted with 5–10 mL of 5% sulfuric acid to remove the pyridine.

Benzamides. Using a centrifuge tube suspend an estimated 1 mmol of the amine in 1 mL of 10% sodium hydroxide solution and add 0.5 g of benzoyl chloride. Cap the tube and shake the mixture vigorously for about 10 minutes. After shaking, add enough dilute hydrochloric acid to bring the pH of the solution to pH 7 or 8. Collect the precipitate by vacuum filtration, wash it thoroughly with cold water, and recrystallize it from ethanol–water, using the mixed-solvents method (Technique 5, Section 5.9).

Benzamides (Alternative Method). Dissolve 0.5 g of the amine in a solution of 2.5 mL of pyridine and 5 mL of toluene. Add 0.5 mL of benzoyl chloride to the solution and heat the mixture under reflux about 30 minutes. Pour the cooled reaction mixture into 50 mL of water and stir the mixture vigorously to hydrolyze the excess benzoyl chloride. Separate the toluene layer and wash it, first with 3 mL of water and then with 3 mL of 5% sodium carbonate. Dry the toluene over anhydrous sodium sulfate, decant the toluene into a small flask, and remove the toluene by evaporation on a hotplate in the hood. Use a stream of air or nitrogen to speed up the evaporation. Recrystallize the benzamide from ethanol or ethanol–water, using the mixed-solvents method (Technique 5, Section 5.9).

Picrates. Dissolve 0.2 g of the unknown in about 5 mL of ethanol and add 5 mL of a saturated solution of picric acid in ethanol. Heat the solution to boiling and then allow it to cool slowly. Collect the product by vacuum filtration and rinse it with a small amount of cold ethanol.

Methiodides. Mix equal-volume quantities of the amine and methyl iodide in a test tube (about 0.25 mL is sufficient) and allow the mixture to stand for several minutes. Then heat the mixture gently under reflux for about 5 minutes. The methiodide should crystallize on cooling. If it does not, you can induce crystallization by scratching the walls of the test tube with a glass rod. Collect the product by vacuum filtration and recrystallize it from ethanol or ethyl acetate.

ALCOHOLS

3,5-Dinitrobenzoates. *Liquid Alcohols.* Dissolve 0.25 g of 3,5-dinitrobenzoyl chloride[1] in 0.25 mL of the alcohol and heat the mixture for about 5 minutes. Allow the mixture to cool and add 1.5 mL of a 5% sodium carbonate solution and 1 mL of water. Stir the mixture vigorously and crush any solid that forms. Collect the product by vacuum filtration and wash it with cold water. Recrystallize the derivative from ethanol–water, using the mixed-solvent method (Technique 5, Section 5.9).

Solid Alcohols. Dissolve 0.25 g of the alcohol in 1.5 mL of dry pyridine and add 0.25 g of 3,5-dinitrobenzoyl chloride.[2] Heat the mixture under reflux for 15 minutes. Pour the cooled reaction mixture into a cold mixture of 2.5 mL of 5% sodium carbonate and 2.5 mL of water. Keep the solution cooled in an ice bath until the product crystallizes and stir it vigorously during the entire period. Collect the product by vacuum filtration, wash it with cold water, and recrystallize it from ethanol–water, using the mixed-solvents method (Technique 5, Section 5.9).

Phenylurethanes. Place 0.25 g of the *anhydrous* alcohol in a dry test tube and add 0.25 mL of phenylisocyanate (α-naphthylisocyanate for a phenol). If the compound is a phenol, add one drop of pyridine to catalyze the reaction. If the reaction is not spontaneous, heat the mixture in a hot-water bath (90°C) for 5–10 minutes. Cool the test tube in a beaker of ice and scratch the tube with a glass rod to induce crystallization. Decant the liquid from the solid product or, if necessary, collect the product by vacuum filtration. Dissolve the product in 2.5–3 mL of hot ligroin or hexane and filter the mixture by gravity (preheat funnel) to remove any unwanted and insoluble diphenylurea present. Cool the filtrate to induce crystallization of the urethane. Collect the product by vacuum filtration.

ESTERS

We recommend that esters be characterized by spectroscopic methods whenever possible. A derivative of the alcohol part of an ester can be prepared with the procedure described below. For other derivatives, consult a comprehensive textbook. Several are listed in Experiment 57 (p. 485).

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[1]This is an acid chloride and undergoes hydrolysis readily. The purity of this reagent should be checked before its use by determining its melting point. When the carboxylic acid is present, the melting point will be high.

[2]See Footnote 1.

3,5-Dinitrobenzoates. Place 2.0 mL of the ester and 1.5 g of 3,5-dinitrobenzoic acid in a small round-bottom flask. Add 4 drops of concentrated sulfuric acid and a boiling stone to the flask and attach a condenser. If the boiling point of the ester is below 150°C, heat under reflux while stirring for 30–45 minutes. If the boiling point of the ester is above 150°C, heat the mixture at about 150°C for 30–45 minutes. Cool the mixture and transfer it to a small separatory funnel. Add 20 mL of ether. Extract the ether layer two times with 10 mL of 5% aqueous sodium carbonate (save the ether layer). Wash the organic layer with 10 mL of water and dry the ether solution over magnesium sulfate. Evaporate the ether in a hot-water bath in the hood. Use a stream of air or nitrogen to speed the evaporation. Dissolve the residue, usually an oil, in 4 mL of boiling ethanol and add water dropwise until the mixture becomes cloudy. Cool the solution to induce crystallization of the derivative.

APPENDIX 3

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 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 is defined as that which includes radiations with wavelengths (λ) between 2.5 and 15 μm (1 μm = 10^{-6} m). The relation of the infrared region to others included in the electromagnetic spectrum is illustrated in Figure IR.1.

As with other types of energy absorption, molecules are excited to a higher energy state when they absorb infrared radiation. The absorption of infrared radiation is, like other

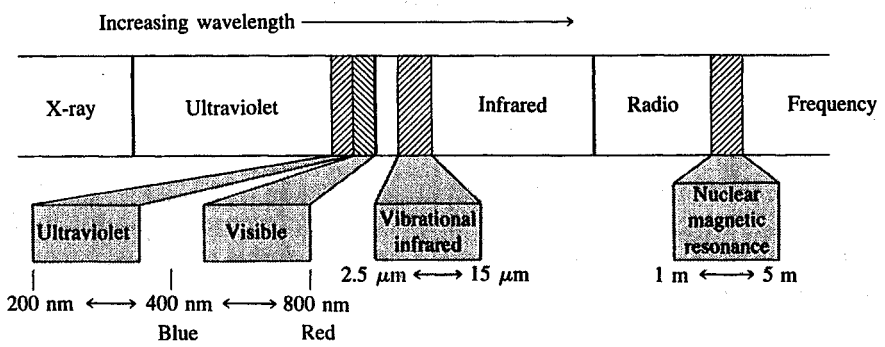


Figure IR.1 Portion of electromagnetic spectrum, showing relation of vibrational infrared to other types of radiation.

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** ***(ν)***. 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 to 650 cm^{-1} (or wavenumbers).

Wavelengths (μm) and wavenumbers (cm^{-1}) can be interconverted by the following relationships:

$$cm^{-1} = \frac{1}{(\mu m)} \times 10{,}000$$

$$\mu m = \frac{1}{(cm^{-1})} \times 10{,}000$$

IR.1 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 for molecules much as a fingerprint can be used for people. By comparing the infrared spectra of two substances thought to be identical, you can 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 $3000 \pm 150\ cm^{-1}$ will almost always be due to the presence of a CH bond in the molecule; an absorption in the range $1700 \pm 100\ cm^{-1}$ 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

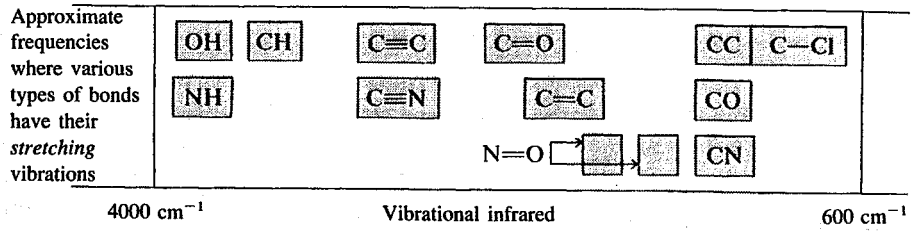
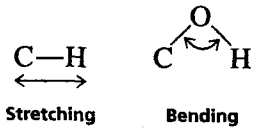


Figure IR.2 Approximate regions in which various common types of bonds absorb. (Bending and twisting and other types of bond vibration have been omitted for clarity).

way these are spread out over the vibrational infrared is illustrated schematically in Figure IR.2. It is a good idea to remember this general scheme for future convenience.

IR.2 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 on page 895.

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 the asymmetric mode. Examples of such groups 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.

IR.3 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 calibrated chart 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 IR.3.

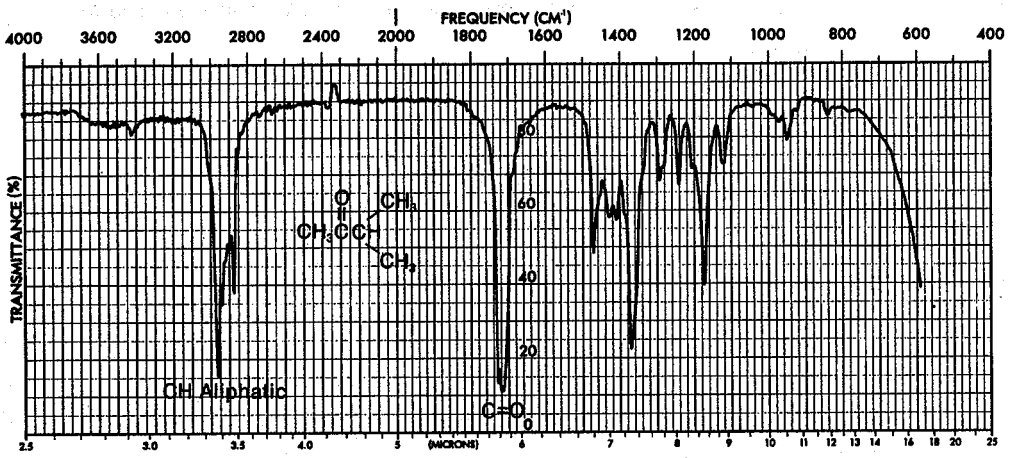
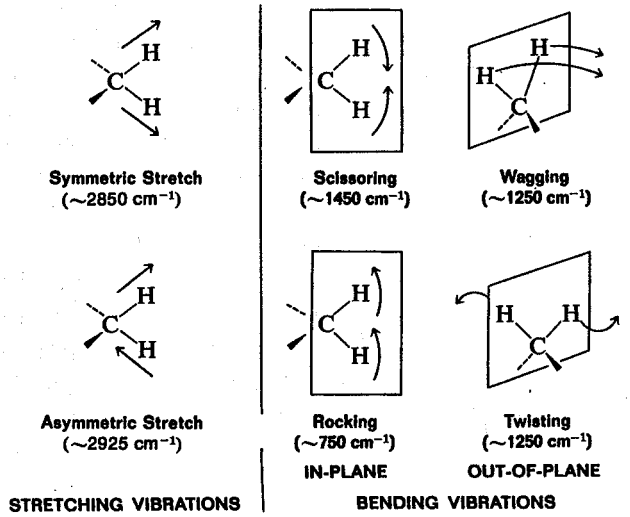


Figure IR.3 Infrared spectrum of methyl isopropyl ketone (neat liquid, salt plates.)

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:

$$\begin{array}{ll} C{=}O & 1850\text{–}1630\ cm^{-1} \\ C{=}C & 1680\text{–}1620\ cm^{-1} \end{array}$$

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 nor 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. Often, in the literature of organic chemistry, you will 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, you should be aware that the relative intensities of all 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.

IR.4 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 appendix present extensive lists of correlation tables (see page 911). Sometimes the absorption information is given in a chart, called a **correlation chart.** A simplified correlation table is given in Table IR.1.

Although you may think assimilating the mass of data in Table IR.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 IR.2 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 ± 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 IR.15, which gives typical val-

TABLE IR.1 A Simplified Correlation Table

Type of Vibration			Frequency (cm^{-1})	Intensity
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

NOTE: s, strong; m, medium; w, weak.

TABLE IR.2 Base Values for Absorptions of Bonds

OH	3600 cm^{-1}	C≡C	2150 cm^{-1}
NH	3500 cm^{-1}	C=O	1715 cm^{-1}
CH	3000 cm^{-1}	C=C	1650 cm^{-1}
C≡N	2250 cm^{-1}	C—O	1100 cm^{-1}

ues for carbonyl compounds. Also learn how factors like 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 IR.2 for this approach. Notice that there are only eight values.

IR.5 ANALYZING A SPECTRUM (OR WHAT YOU CAN TELL AT A GLANCE)

In trying to analyze the spectrum of an unknown, you should concentrate first on trying to establish the presence (or absence) of a few major functional groups. The most conspicuous peaks are C=O, C—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. 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 3.)

ACIDS	Is OH also present? **Broad** absorption near 3300–2500 cm^{-1} (usually overlaps C—H).
AMIDES	Is NH 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 CH present? Two weak absorptions near 2850 and 2750 cm^{-1} on the right side of CH absorptions.
KETONES	The above five choices have been eliminated.

3. If C=O is absent

ALCOHOLS or PHENOLS	Check for OH. **Broad** absorption near 3600–3300 cm^{-1}. Confirm this by finding C—O near 1300–1000 cm^{-1}.
AMINES	Check for NH. Medium absorption(s) near 3500 cm^{-1}.
ETHERS	Check for C—O (and absence of OH) 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 CH region.
Aromatic and vinyl CH occur to the left of 3000 cm^{-1} (aliphatic CH 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 CH near 3300 cm^{-1}.
6. Nitro Groups	*Two* strong absorptions 1600–1500 cm^{-1} and 1390–1300 cm^{-1}.
7. Hydrocarbons	None of the above is found. Main absorptions are in CH region near 3000 cm^{-1}. Very simple spectrum, only other absorptions 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.

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 description of peak positions. The meaning is clear, because all spectra are conventionally presented left to right from 4000 to 600 cm^{-1}.

IR.6 SURVEY OF THE IMPORTANT FUNCTIONAL GROUPS

Alkanes

Spectrum is usually simple with few peaks.

C—H Stretch occurs around 3000 cm^{-1}.
(a) In alkanes (except strained ring compounds), absorption always occurs to the right of 3000 cm^{-1}.
(b) 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 IR.4.

Alkenes

=C—H Stretch occurs to the left of 3000 cm^{-1}.

=C—H Out-of-plane ("oop") bending at 1000–650 cm^{-1}.
The C—H out-of-plane 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 IR.5 shows the positions of these bands.

C=C Stretch 1675–1600 cm^{-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.

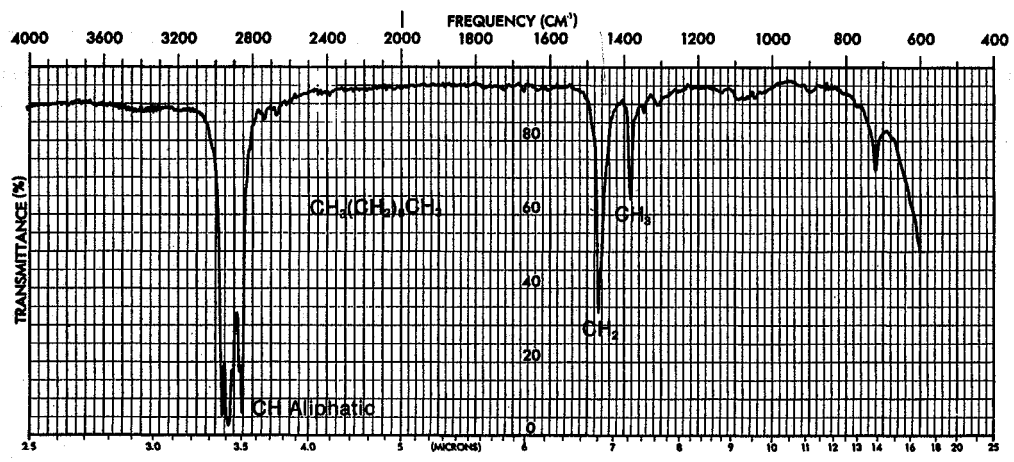


Figure IR.4 Infrared spectrum of decane (neat liquid, salt plates).

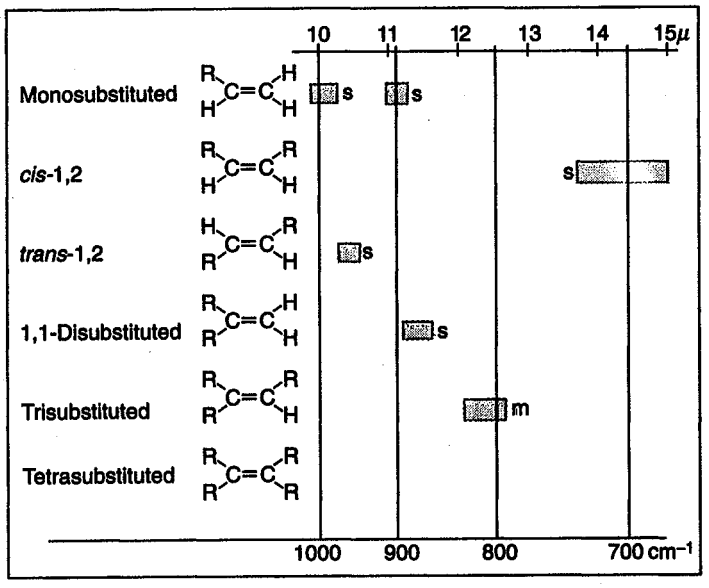


Figure IR.5 The C—H out-of-plane bending vibrations for substituted alkenes.

The spectrum of styrene is shown in Figure IR.6. The spectrum of 4-methylcyclohexene in shown in Experiment 27.

Aromatic Rings

=C—H Stretch is always to the left of 3000 cm^{-1}.

=C—H Out-of-plane (oop) bending at 900 to 690 cm^{-1}.

The CH out-of-plane absorptions often allow you to determine the type of ring substitution by their numbers, intensities, and positions. The correlation chart in Figure IR.7A indicates the positions of these bands.

The patterns are generally reliable—most particularly reliable for rings with alkyl substituents, least for polar substituents.

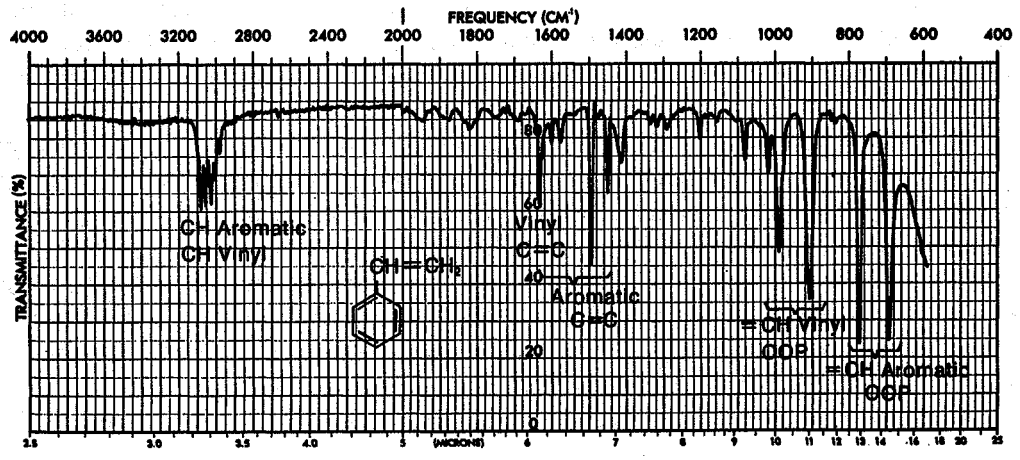


Figure IR.6 Infrared spectrum of styrene (neat liquid, salt plates).

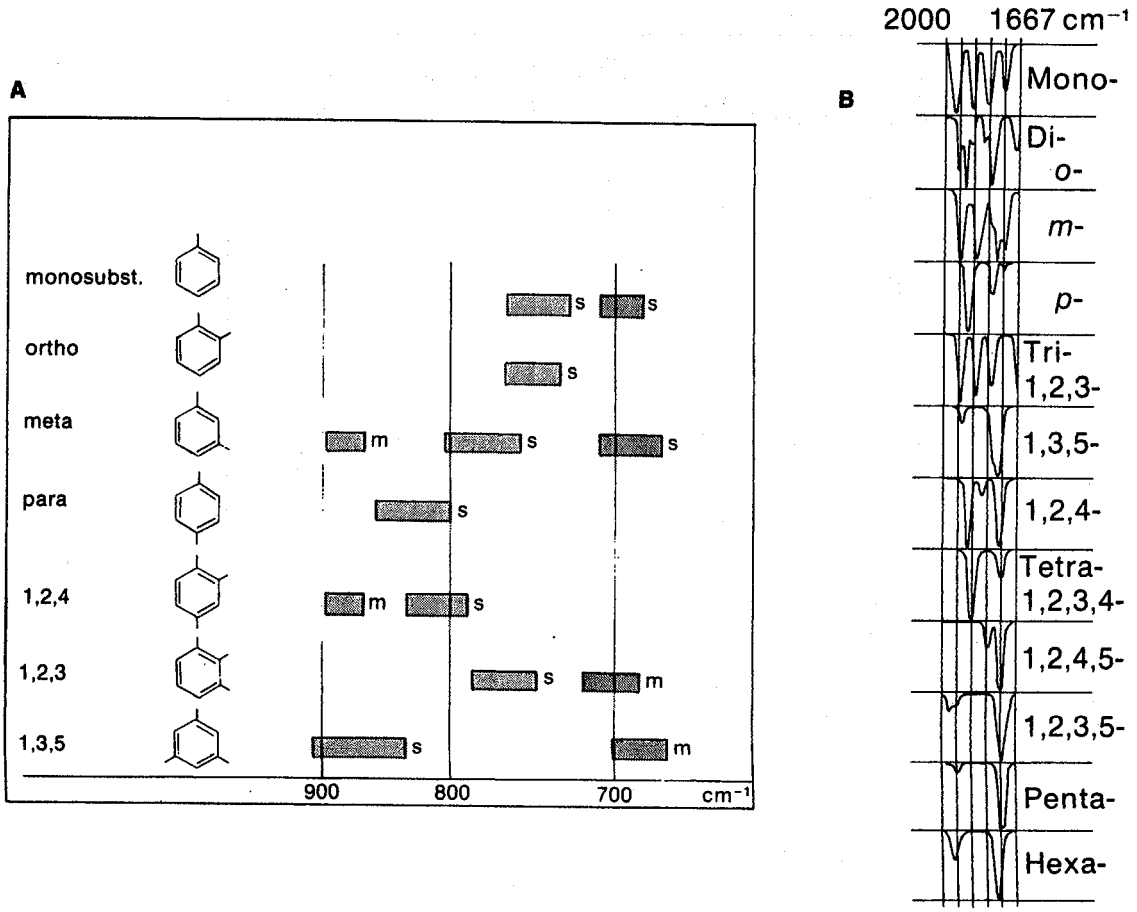


Figure IR.7 The C—H out-of-plane bending vibrations for substituted benzenoid compounds. (B) The 2000–1667 cm^{-1} region for substituted benzenoid compounds. (From John R. Dyer, *Applications of Absorption Spectroscopy of Organic Compounds.* Englewood Cliffs, NJ: Prentice-Hall, 1965.)

Ring Absorptions (C=C). There are often four sharp absorptions that occur in pairs at 1600 and 1450 cm^{-1} and are characteristic of an aromatic ring. See, for example, the spectra of anisole (Fig. IR.11), benzonitrile (Fig. IR.14), and methyl benzoate (Fig. IR.18).

There are many weak combination and overtone absorptions that appear between 2000 and 1667 cm^{-1}. The relative shapes and numbers of these peaks can be used to tell whether an aromatic ring is monosubstituted or di-, tri-, tetra-, penta-, or hexasubstituted. 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 that no useful information can be obtained from analyzing this region. The various patterns that are obtained in this region are shown in Figure IR.7B.

The spectra of styrene and *o*-dichlorobenzene are shown in Figures IR.6 and IR.8.

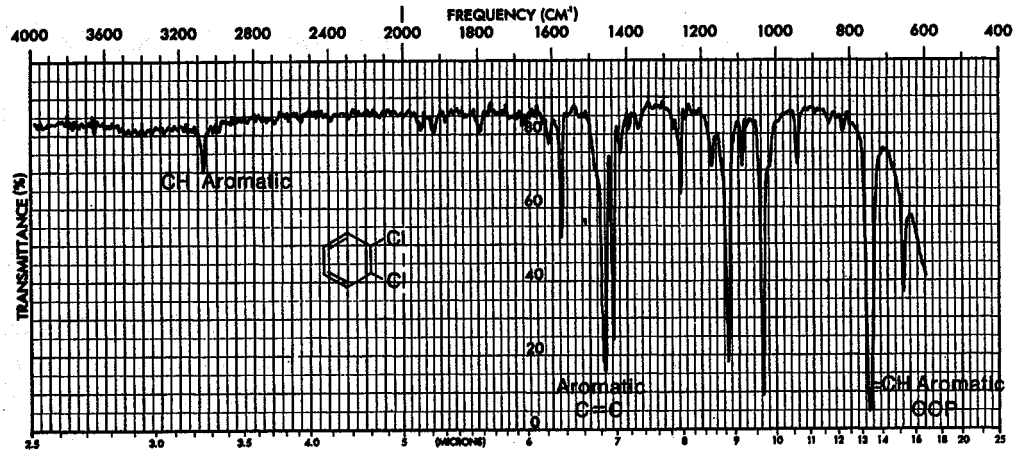


Figure IR.8 Infrared spectrum of *o*-dichlorobenzene (neat liquid, salt plates).

Alkynes

≡C—H Stretch is usually near 3300 cm^{-1}.

C≡C Stretch is near 2150 cm^{-1}.
Conjugation moves C≡C stretch to the right.
Disubstituted or symmetrically substituted triple bonds give either no absorption or weak absorption.

The spectrum of propargyl alcohol is shown in Figure IR.9.

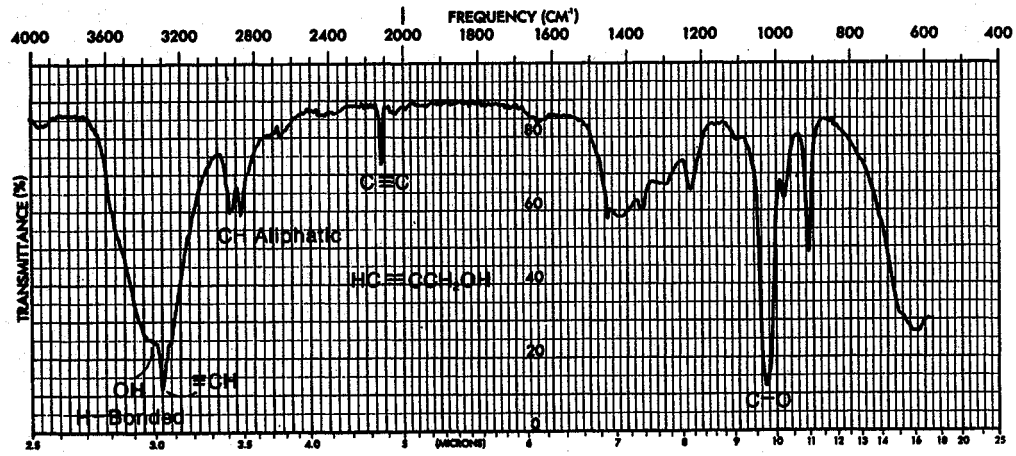


Figure IR.9 Infrared spectrum of propargyl alcohol (neat liquid, salt plates).

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 (usually 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 1300–1000 cm^{-1}.

Phenols are like alcohols. The 2-naphthol shown in Figure IR.10 has some molecules hydrogen-bonded and some free. The spectrum of 4-methylcyclohexanol is given in Experiment 27. This alcohol, which was determined neat, would also have had a free OH spike to the left of its hydrogen-bonded band if it had been determined in dilute solution. The solution spectra of borneol and isoborneol are shown in Experiment 20.

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 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 IR.11.

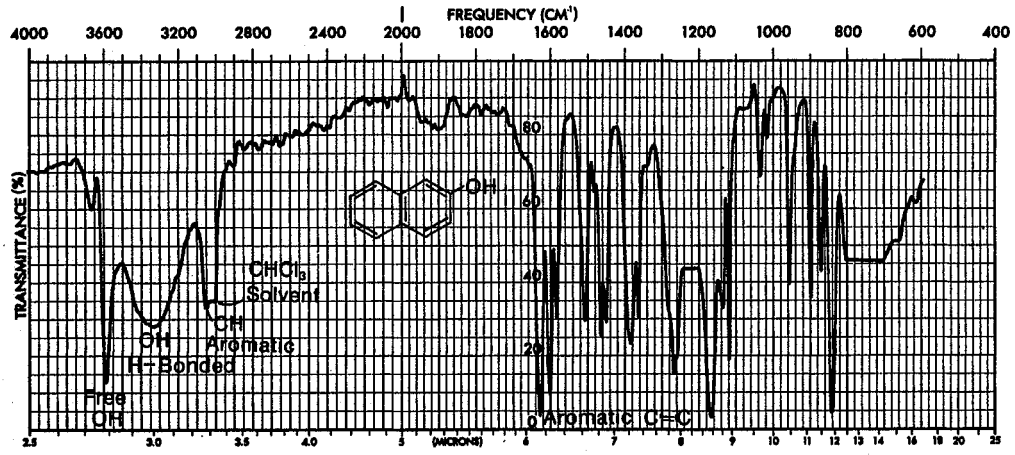


Figure IR.10 Infrared spectrum of 2-naphthol, showing both free and hydrogen-bonded OH ($CHCl_3$ solution).

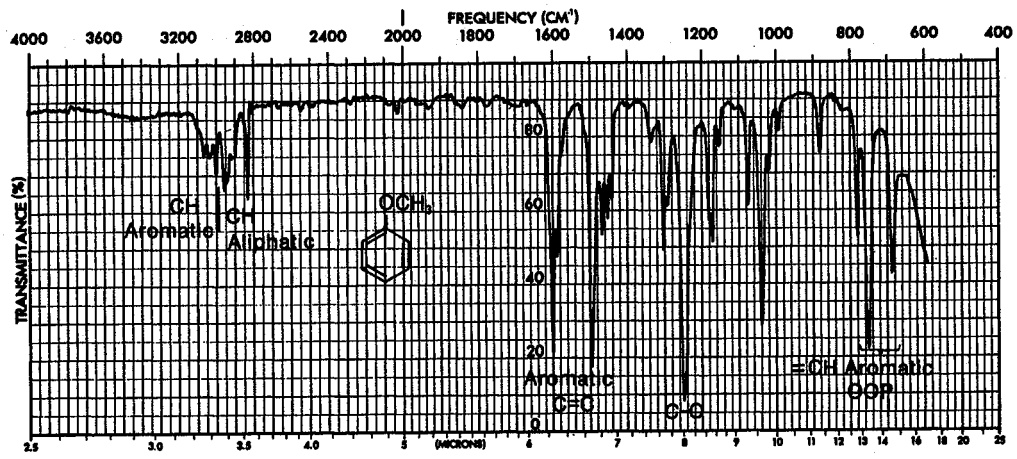


Figure IR.11 Infrared spectrum of anisole (neat liquid, salt plates).

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 mode occurs in the range of 1640–1560 cm^{-1} (broad).
An out-of-plane bending absorption can sometimes be observed at about 800 cm^{-1}.

The spectrum of *n*-butylamine is shown in Figure IR.12.

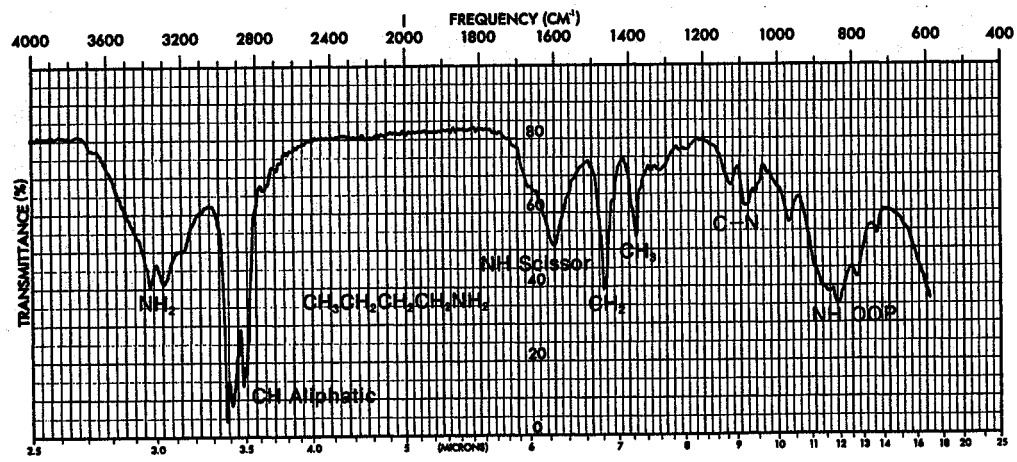


Figure IR.12 Infrared spectrum of *n*-butylamine (neat liquid, salt plates).

Nitro Compounds

N=O Stretch is usually two strong bonds at 1600–1500 cm^{-1} and 1390–1300 cm^{-1}.

The spectrum of nitrobenzene is shown in Figure IR.13.

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 IR.14.

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 so on) in the range of 1850–1650 cm^{-1}. In Figure IR.15 the normal values for the various types of carbonyl groups are compared. In the sections that follow, each type is examined separately.

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.

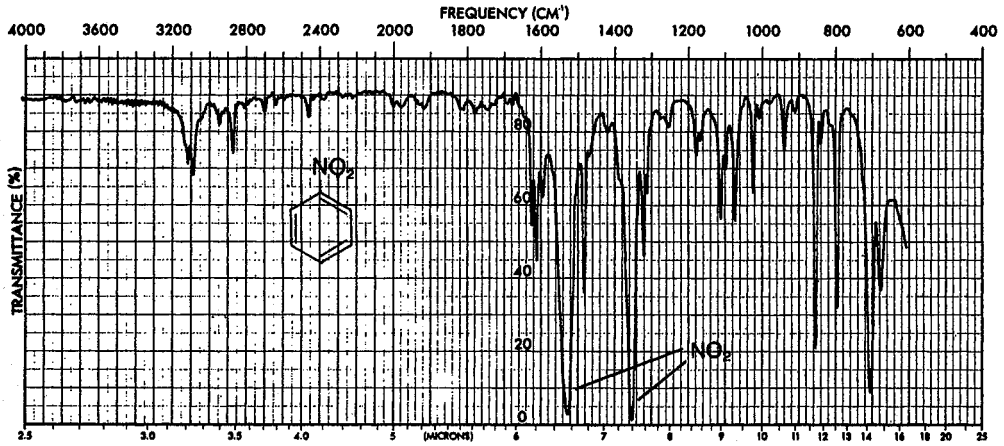


Figure IR.13 Infrared spectrum of nitrobenzene, neat.

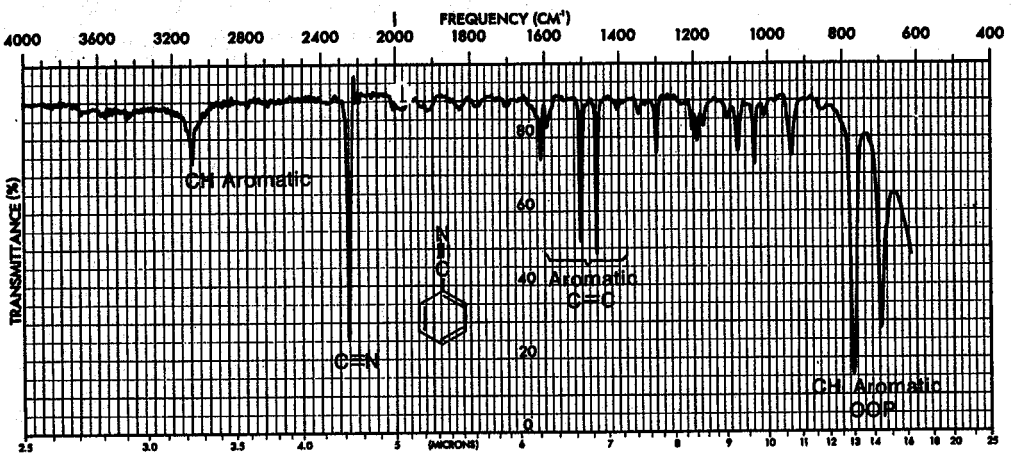


Figure IR.14 Infrared spectrum of benzonitrile (neat liquid, salt plates).

C—H Stretch, aldehyde hydrogen (—CHO), consists of *weak* bands at about 2750 and 2850 cm^{-1}. Note that the CH stretch in alkyl chains does not usually extend this far to the right.

The spectrum of nonanal is shown in Figure IR.16. In addition, the spectrum of benzaldehyde is shown in Experiment 40.

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.

The spectra of methyl isopropyl ketone and mesityl oxide are shown in Figure IR.3 and IR.17. The spectrum of camphor is shown in Experiment 20.

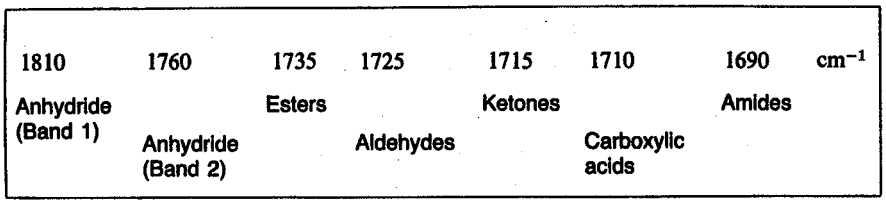


Figure IR.15 Normal values (± 10 cm^{-1}) for various types of carbonyl groups.

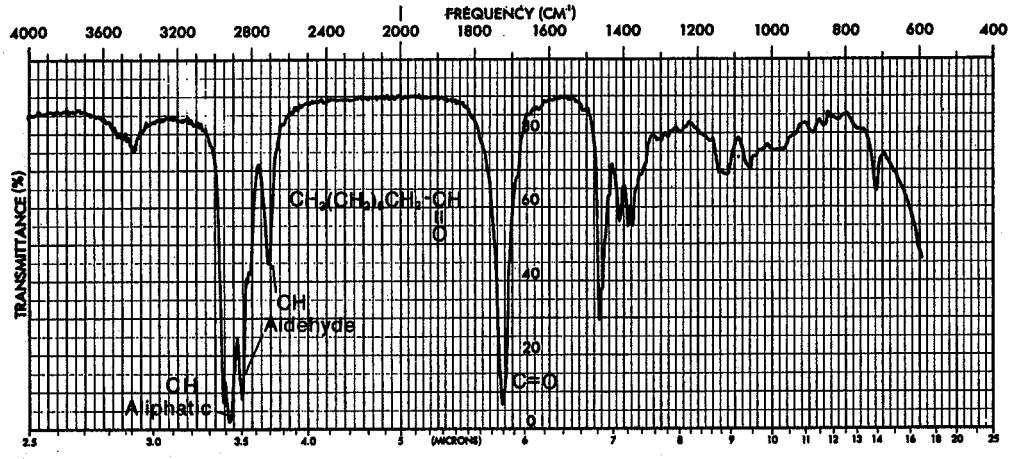
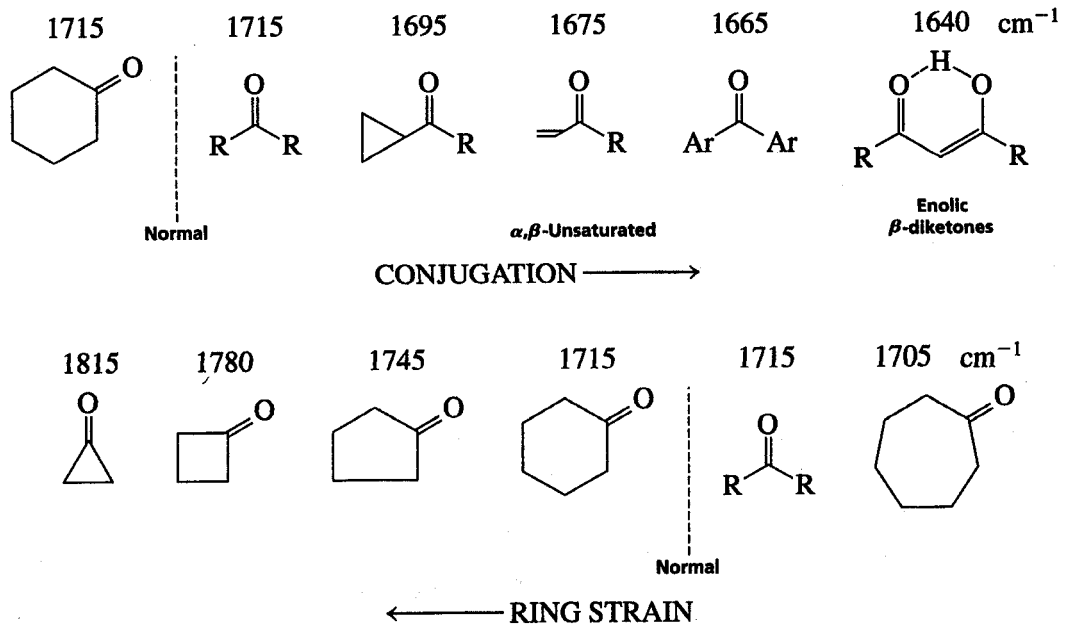


Figure IR.16 Infrared spectrum of nonanal (neat liquid, salt plates).



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 range of 1320–1210 cm^{-1}, strong.

The spectrum of benzoic acid is shown in Experiment 30B.

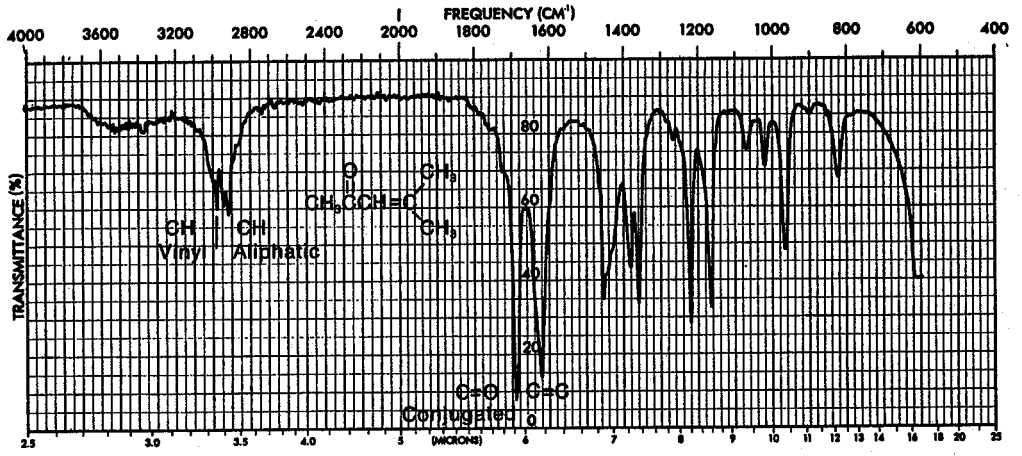


Figure IR.17 Infrared spectrum of mesityl oxide (neat liquid, salt plates).

Esters (R—C(=O)—OR′)

C=O Stretch occurs at about 1735 cm^{-1} in normal esters.
(a) Conjugation in the R part moves the absorption to the right.
(b) Conjugation with the O in the R′ part moves the absorption to the left.
(c) 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 methyl benzoate is shown in Figure IR.18. The spectra of isopentyl acetate and methyl salicylate are shown in Experiments 8 and 10.

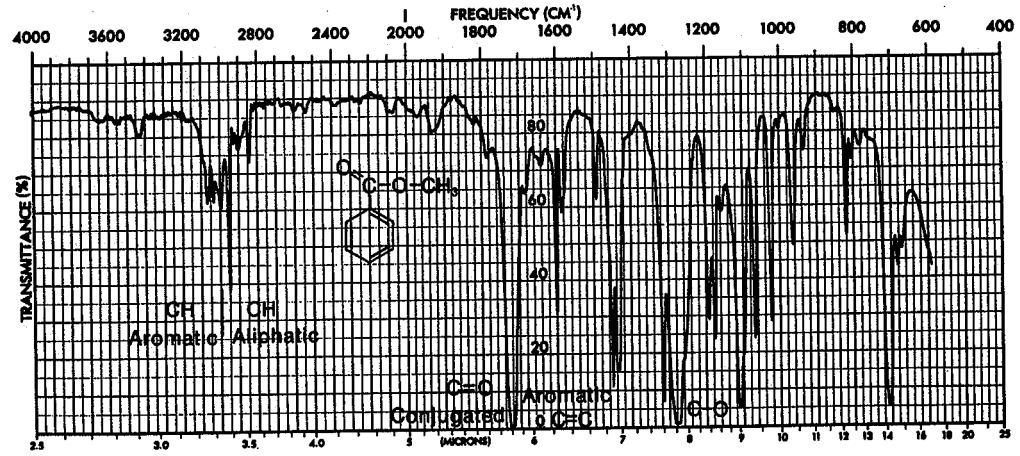


Figure IR.18 Infrared spectrum of methyl benzoate (neat liquid, salt plates).

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) 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 IR.19.

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*-norbornane-5,6-*endo*-dicarboxylic anhydride is shown in Experiment 51.

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 carbon tetrachloride and chloroform are shown in Technique 19, Figures 19.6 and 19.7, respectively (pp. 850–851).

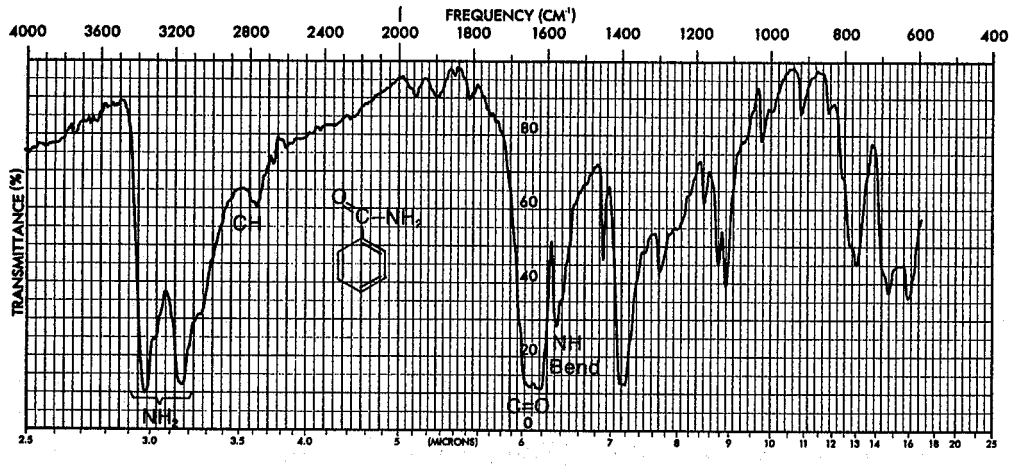


Figure IR.19 Infrared spectrum of benzamide (solid phase, KBr).

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APPENDIX 4

Nuclear Magnetic Resonance Spectroscopy

NMR.1 THE RESONANCE PHENOMENON

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 ($^{1}_{1}H$) and carbon atoms ($^{13}_{6}C$) are of the greatest interest to the organic chemist. Atoms of the ordinary isotopes of carbon ($^{12}_{6}C$) and oxygen ($^{16}_{8}O$) do not have nuclear magnetic moments, and ordinary nitrogen atoms ($^{14}_{7}N$), 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 ($^{19}_{9}F$), which does show active NMR behavior. The hydrogen nucleus is discussed in this appendix and carbon-13 NMR is described in Appendix 5.

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 ($+\frac{1}{2}$ and $-\frac{1}{2}$), either the nuclear magnets of individual atoms can be aligned with the magnetic field (spin $+\frac{1}{2}$), or they can be opposed to it (spin $-\frac{1}{2}$). A slight majority of the nuclei are aligned with the field, as this spin orientation constitutes a slightly lower-energy spin state. If radio-frequency 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 (Fig. NMR.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

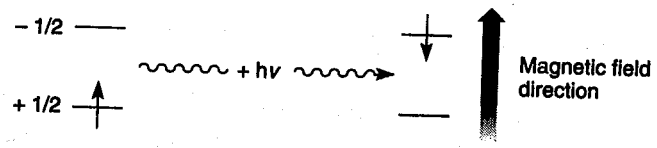


Figure NMR.1 The NMR absorption process.

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 NMR.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 induce spin conversion in a hydrogen nucleus of spin $+\frac{1}{2}$ 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 14,000 gauss is applied, radiofrequency radiation of 60 MHz (60,000,000 cycles per second) is required to induce a spin transition. 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 typical proton nuclear magnetic resonance spectrometer supplies a basic radiofrequency 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 NMR spectrum is shown in Figure NMR.3.

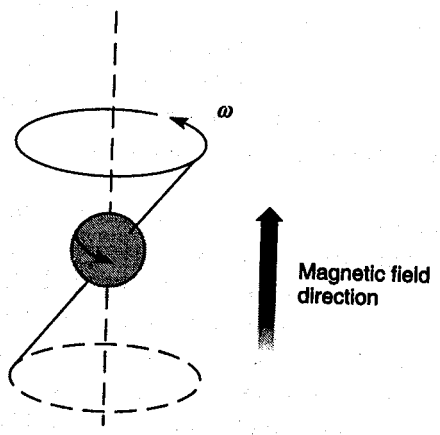


Figure NMR.2 Precessional motion of a spinning nucleus in an applied magnetic field.

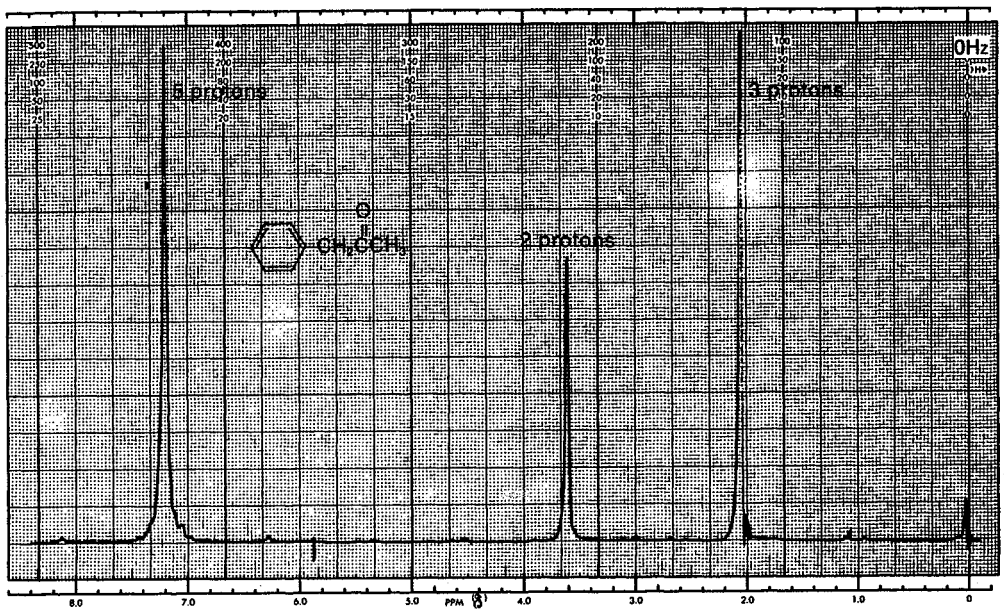


Figure NMR.3 NMR spectrum of phenylacetone (the absorption peak at the far right is caused by the added reference substance, TMS).

NMR.2 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. To achieve this measurement, a standard reference substance is used, 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 all other molecules do, 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 1-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 $\delta = 0$ 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 ($\delta = 0$ 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.

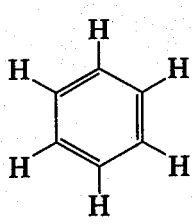
Because the frequency at which a proton precesses, and hence the frequency at which it absorbs radiation, is directly proportional to the strength of the applied magnetic field, a second method of measuring an NMR spectrum is possible. You could hold the magnetic field strength constant and vary the frequency of the radiofrequency radiation supplied. Thus, a given proton could be induced to absorb *either* by increasing the field strength, as described earlier, or alternatively, by decreasing the frequency of the radiofrequency oscillator. A 1-ppm decrease in the frequency of the oscillator would have the same effect as a 1-ppm increase in the magnetic field strength. For reasons of instrumental design, it is simpler to vary the strength of the magnetic field than to vary the frequency of the oscillator. Most instruments operate on the former principle. Nevertheless, the recording chart is calibrated not only in δ units but in Hertz (Hz) as well (1 ppm = 60 Hz when the frequency is 60 MHz), and the chemical shift is customarily defined and computed using Hertz rather than gauss:

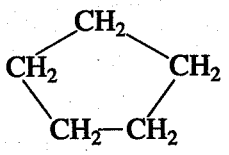
$$\delta = \text{Chemical shift} = \frac{\text{Observed shift from TMS (in Hz)}}{60 \text{ MHz}} = \frac{\text{Hz}}{\text{MHz}} = \text{ppm}$$

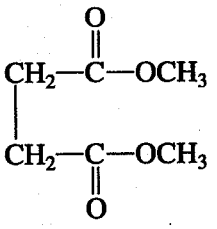
Although the equation defines the chemical shift for a spectrometer operating at 14,100 gauss and 60 MHz, the chemical shift value that is calculated is *independent* of the field strength. For instance, at 23,500 gauss the oscillator frequency would have to be 100 MHz. Although the observed shifts from TMS (in Hertz) would be larger at this field strength, the divisor of the equation would be 100 MHz, instead of 60 MHz, and δ would turn out to be identical under either set of conditions.

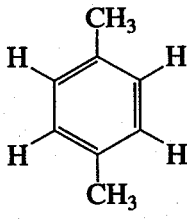
NMR.3 CHEMICAL EQUIVALENCE—INTEGRALS

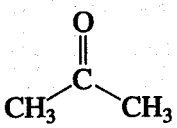
All the protons in a molecule that are in chemically identical environments often exhibit the same chemical shift. Thus, all the protons in tetramethylsilane (TMS) or all the protons in benzene, cyclopentane, or acetone have their own respective resonance values all at the same δ value. Each compound 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.





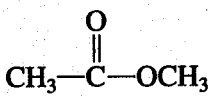






$(CH_3)_4Si$

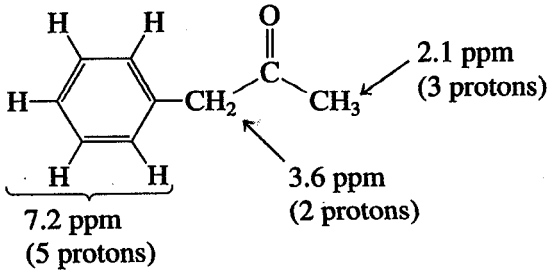
Molecules giving rise to one NMR absorption peak—all protons chemically equivalent



$CH_3—O—CH_2Cl$

Molecules giving rise to two NMR absorption peaks—two different sets of chemically equivalent protons

The NMR spectrum given in Figure NMR.3 is that of phenylacetone, a compound having *three* chemically distinct types of protons:



You can immediately see that the NMR spectrum furnishes valuable information on this basis alone. In fact, the NMR spectrum can not only 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 NMR.4 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 gives 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 num-

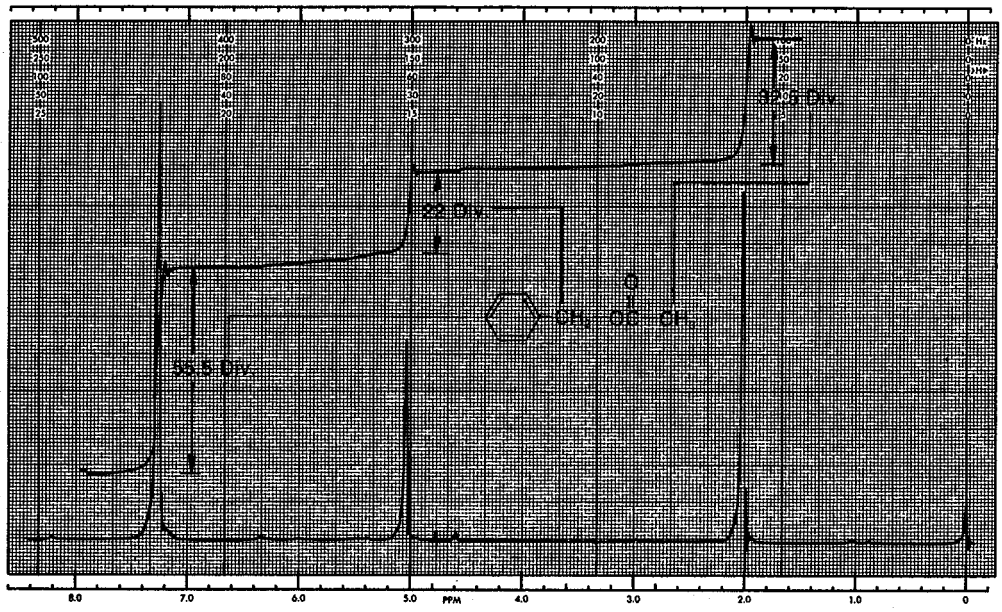


Figure NMR.4 Determination of the integral ratios for benzyl acetate.

bers 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 if you assume 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 two 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 protons. Notice then that the integrals give the simplest ratios, but not necessarily the true ratios, of the number of protons of each type.

NMR.4 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, 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. Notice, for instance, that the aromatic protons of both phenylacetone (Fig. NMR.3) and benzyl acetate (Fig. NMR.4) 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 NMR.5) 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 NMR.5 is a correlation chart that contains the most essential and frequently encountered types of protons. For the beginner, it is often difficult to memorize a large body of numbers relating to chemical shifts and proton types. You need actually do this only crudely. It is more important to "get a feel" for the regions and the types of protons than to know a string of factual numbers.

The values of chemical shift given in Figure NMR.5 can be easily understood in terms of two factors: local diamagnetic shielding and anisotropy. These two factors are discussed in Sections NMR.5 and NMR.6.

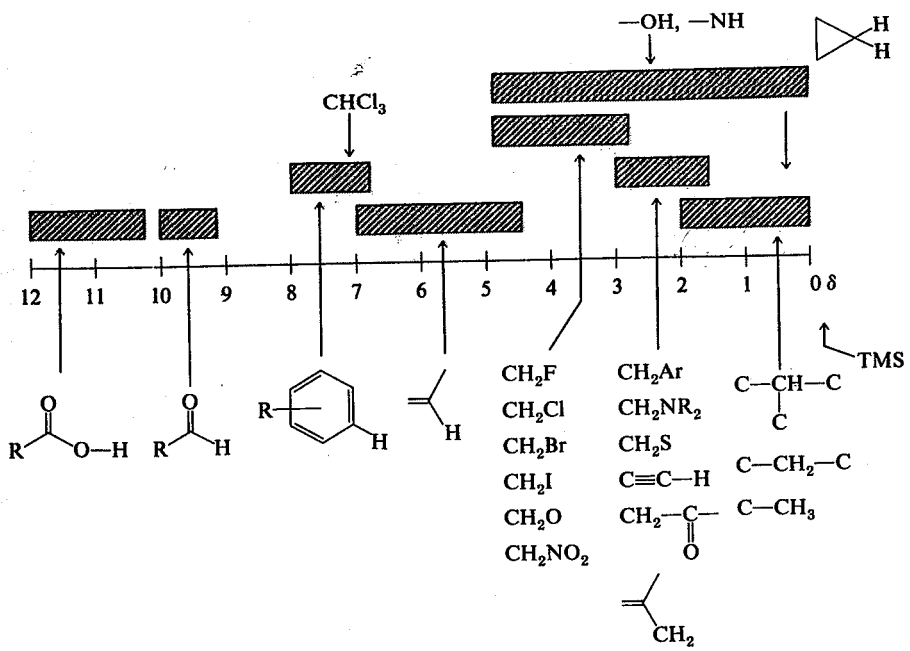


Figure NMR.5 Simplified correlation chart for proton chemical shift values.

NMR.5 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 NMR.1 for several compounds of the type CH_3X.

Multiple substituents have a stronger effect than a single substituent. The influence of the substituent, an electronegative element having little effect on protons that are more than three carbons away, drops off rapidly with distance. These effects are illustrated in Table NMR.2.

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 and thus to generate an induced magnetic field, which *opposes* the applied field. This is illustrated in Figure NMR.6. 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.

NMR.6 ANISOTROPY

Figure NMR.5 clearly shows that several types of protons have chemical shifts not easily explained by 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 mag-

TABLE NMR.1 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 NMR.2 Substitution Effects

	$CHCl_3$	CH_2Cl_2	CH_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	3.30	1.69	1.25

netic 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 NMR.7. The benzene hydrogens are deshielded by the **diamagnetic anisotropy** of the ring. An applied magnetic field is non-uniform (anisotropic) in the vicinity of a benzene molecule because of the labile 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 electromagnets 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.

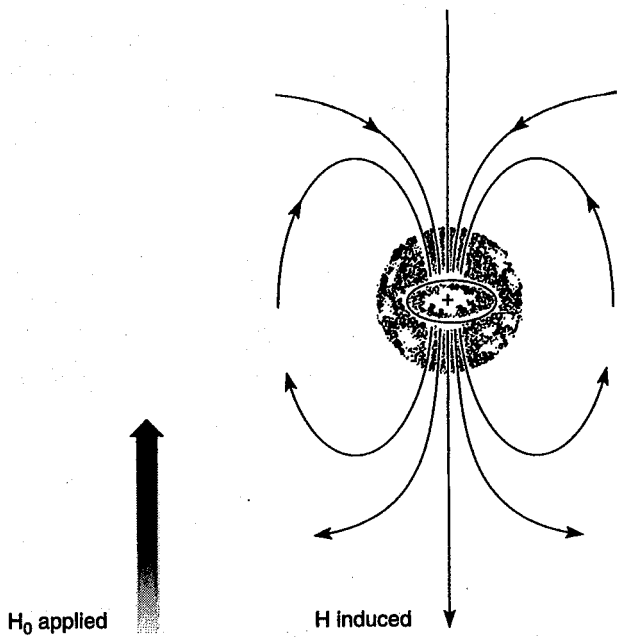


Figure NMR.6 Local diamagnetic shielding of a proton due to its valence electrons.

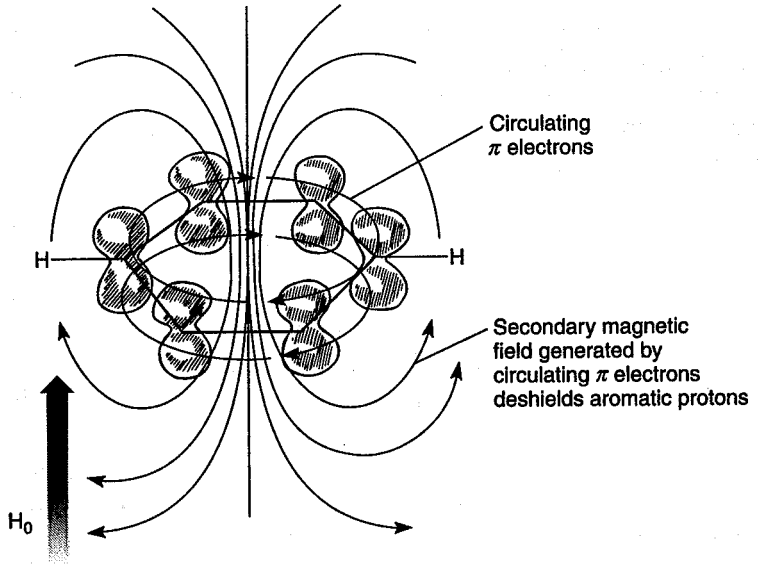


Figure NMR.7 Diamagnetic anisotropy in benzene.

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 NMR.8. 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.

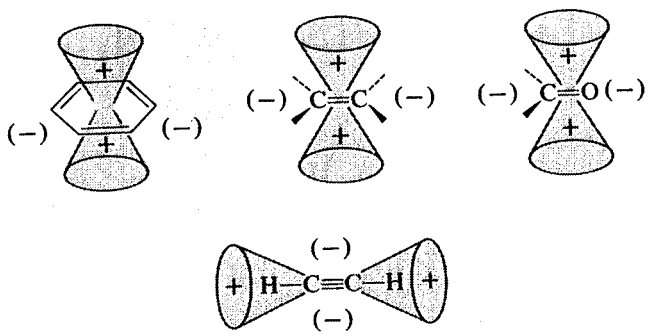
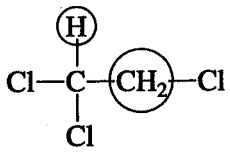


Figure NMR.8 Anisotropy caused by the presence of π electrons in some common multiple-bond systems.

NMR.7 SPIN–SPIN SPLITTING (*N* + 1 RULE)

We have already considered how the chemical shift and the integral (peak area) can give information about the number and type 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 this 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 NMR.9. The methine (CH) resonance (5.77 ppm) is split into a triplet, and the methylene resonance (3.95 ppm) is 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.

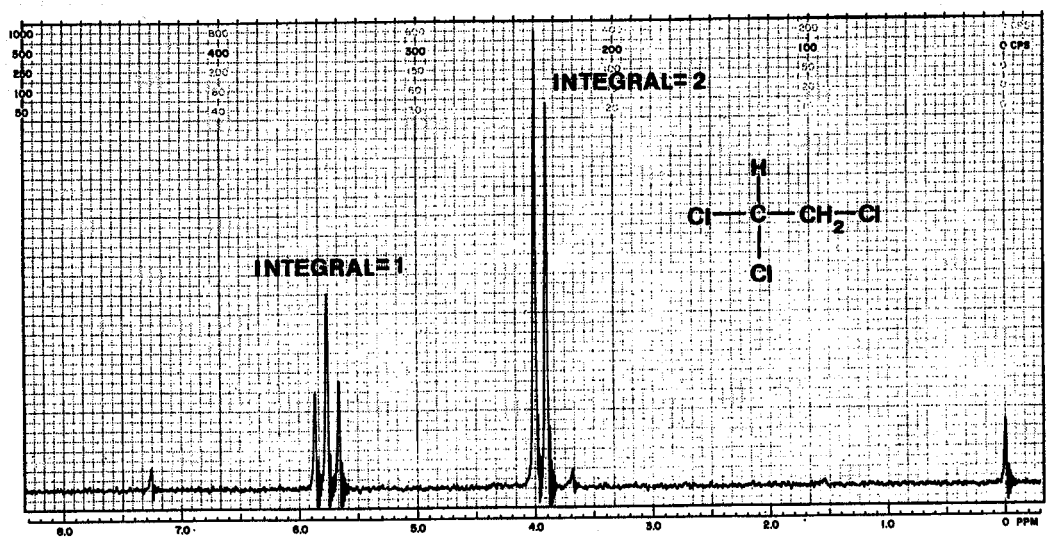
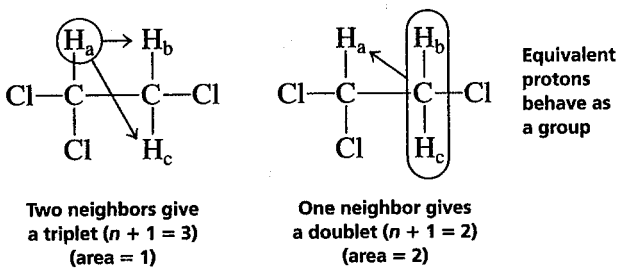


Figure NMR.9 NMR spectrum of 1,1,2-trochloroethane (courtesy of Varian Associates).

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 molecular solution will give *three* absorption peaks (a triplet) for H_a because H_b and H_c have three different possible spin combinations (Fig. NMR.10). 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 NMR.11. 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 ($6 + 1 = 7$).

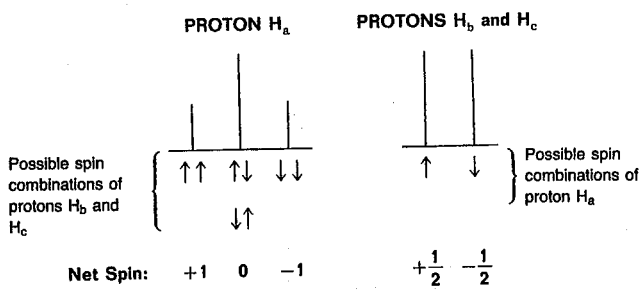


Figure NMR.10 Analysis of the spin–spin splitting pattern of 1,1,2-trichloroethane.

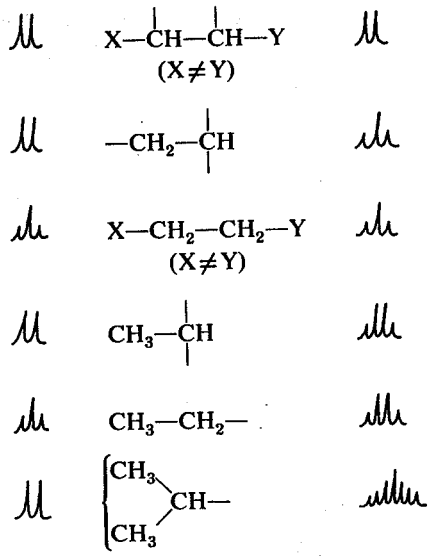


Figure NMR.11 Some common splitting patterns.

NMR.8 THE COUPLING CONSTANT

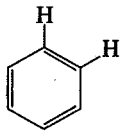
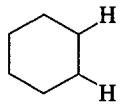
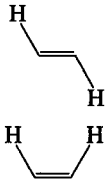
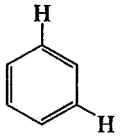
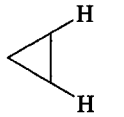
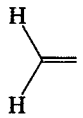
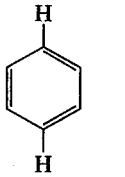
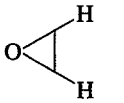
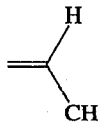
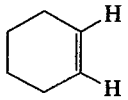
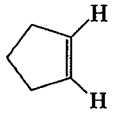
The quantitative amount of spin–spin interaction between two protons can be defined by the **coupling constant.** The spacing between the component peaks in a simple multiplet is called the coupling constant *J.* This distance is measured on the same scale as the chemical shift and is expressed in Hertz (Hz).

For the interaction of most aliphatic protons in acyclic systems, the magnitudes of the coupling constants are always near 7.5 Hz. See, for instance, the NMR spectrum of 1,1,2-trichloroethane in Figure NMR.9, where the coupling constant is approximately 6 Hz. Different magnitudes of J are found for different types of protons. For instance, the *cis* and *trans* protons substituted on a double bond commonly have values where $J_{trans} \cong 17$ Hz and $J_{cis} \cong 10$ Hz are typical coupling constants. In ordinary compounds, coupling constants may range anywhere from 0 to 18 Hz. The magnitude of J often provides structural clues. You can usually distinguish, for example, between a *cis* olefin and a *trans* olefin on the basis of the observed coupling constants for the vinyl protons. The approximate values of some representative coupling constants are given in Table NMR.3.

NMR.9 MAGNETIC EQUIVALENCE

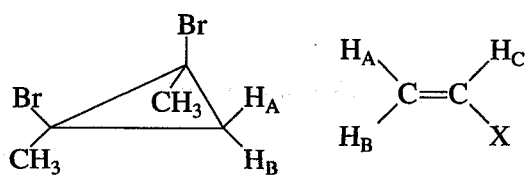
In the example of spin–spin splitting in 1,1,2-trichloroethane, notice that the two protons H_b and H_c, which are attached to the same carbon atom, do not split one another.

TABLE NMR.3 Representative Coupling Constants and Approximate Values (Hz)

	6–8		*ortho* 6–10		a,a 8–14 a,e 0–7 e,e 0–5
	11–18 6–15		*meta* 1–4		*cis* 6–12 *trans* 4–8
	0–5		*para* 0–2		*cis* 2–5 *trans* 1–3
	4–10		8–11		5–7
H—C≡C—CH	0–3				

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, 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.

It is important to differentiate magnetic equivalence and chemical equivalence. Note the following two compounds:



In the cyclopropane compound, the two geminal hydrogens 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, $J_{geminal}$ is usually around 5 Hz.

Another situation in which protons are chemically equivalent but not magnetically equivalent exists in the vinyl compound. In this example, protons A and B are chemically equivalent but not magnetically equivalent. H_A and H_B have different chemical shifts. In addition, a second distinction can be made between H_A and H_B in this type of compound. Each has a different coupling constant with H_C. The constant J_{AC} is a *cis* coupling constant, and J_{BC} is a *trans* coupling constant. Whenever two protons have different coupling constants relative to a third proton, they are not magnetically equivalent. In the vinyl compound, H_A and H_B do not act as a group to split proton H_C. Each proton acts independently. Thus, H_B splits H_C with coupling constant J_{BC} into a doublet, and then H_A splits each of the components of the doublet into doublets with coupling constant J_{AC}. In such a case, the NMR spectrum must be analyzed graphically, splitting by splitting. An NMR spectrum of a vinyl compound is shown in Figure NMR.12. The graphical analysis of the vinyl portion of the NMR spectrum is in Figure NMR.13.

NMR.10 AROMATIC COMPOUNDS

The NMR spectra of protons on aromatic rings are often too complex to explain by simple theories. However, some simple generalizations can be made that are useful in an-

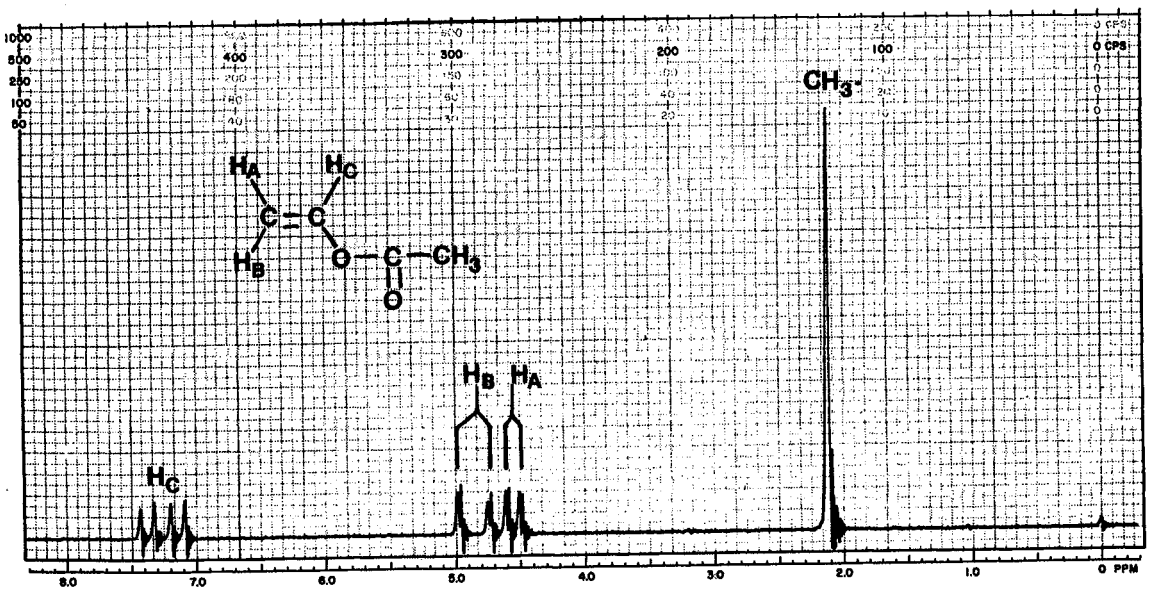


Figure NMR.12 NMR spectrum of vinyl acetate (courtesy of Varian Associates).

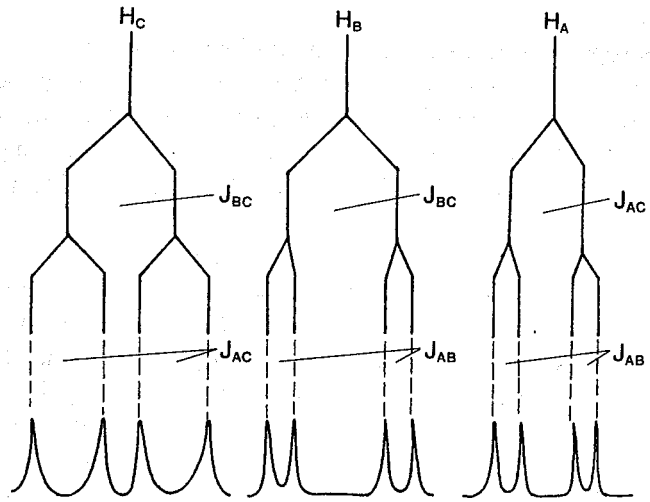


Figure NMR.13 Analysis of the splittings in vinyl acetate.

alyzing the aromatic region of the NMR spectrum. First of all, most aromatic protons have resonance near 7.0 ppm. In monosubstituted rings in which the ring substituent is an alkyl group, all the ring protons often have chemical shifts that are very nearly identical, and the five ring protons may appear as if they gave rise to an overly broad singlet (Fig. NMR.14A). If an electronegative group is attached to the ring, all the ring protons are

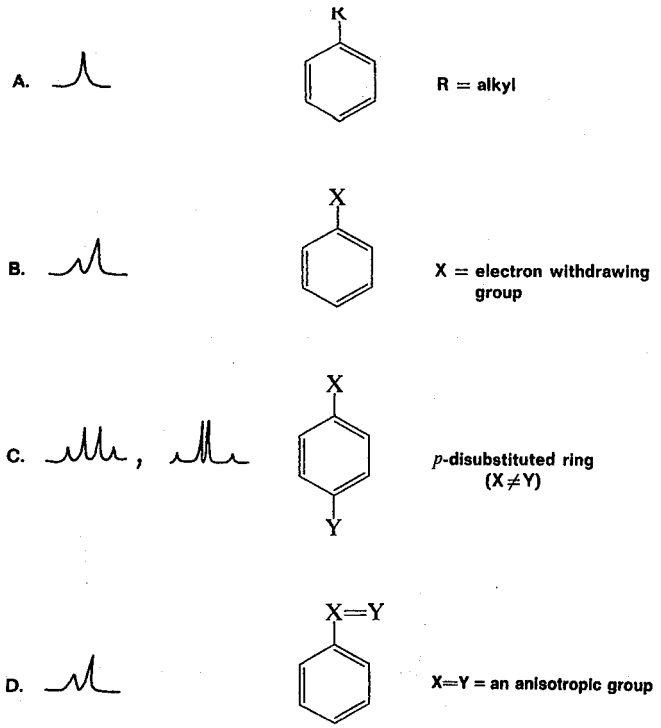


Figure NMR.14 Some common aromatic patterns.

shifted downfield from where they would appear in benzene. However, often the *ortho* protons are shifted more than the others, as they are more affected by the group. This often gives rise to an absorption pattern like that in Figure NMR.14B. In a *para*-disubstituted ring with two substituents X and Y that are identical, all the protons in the ring are chemically and magnetically equivalent, and a singlet is observed. If X is different from Y in electronegativity, however, a pattern like that shown in the left side of Figure NMR.14C is often observed, clearly identifying a *p*-disubstituted ring. If X and Y are more nearly similar, a pattern more like the one on the right is observed. In monosubstituted rings that have a carbonyl group or a double bond attached directly to the ring, a pattern like that in Figure NMR.14D is not uncommon. In this case, the *ortho* protons of the ring are influenced by the anisotropy of the π systems that make up the CO and CC double bonds and are deshielded by them. In other types of substitution, such as *ortho* or *meta,* or polysubstituted ring systems, the patterns may be much more complicated and require an advanced analysis.

NMR.11 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 NMR.4. 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. This is primarily because such protons often exchange very rapidly with those of the solvent medium. The absorption position is variable because these groups also undergo varying degrees of hydrogen bonding in solutions of different 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.

TABLE NMR.4 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

NMR.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 of the ways in which such a situation can be simplified is by using a spectrometer that operates at a higher frequency. Although both 60- and 90-MHz instruments are quite common, it is not unusual to find instruments with operating frequencies of 100, 220, 300 MHz, or even higher.

Although NMR coupling constants are not dependent on the frequency or the field strength of operation of the NMR spectrometer, chemical shifts in Hertz are dependent on these parameters. This circumstance can often be used to simplify an otherwise undecipherable spectrum. Suppose, for instance, that a compound contained three multiplets: a quartet and two triplets derived from groups of protons with very similar chemical shifts. At 60 MHz these peaks might overlap, as illustrated in Figure NMR.15, and simply give an unresolved envelope of absorption.

Figure NMR.15 also shows the spectrum of the same compound at two higher field strengths (frequencies). In redetermining the spectrum at higher field strengths, the coupling constants 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 should be noted that at 220 MHz the individual multiplets are cleanly separated and resolved.

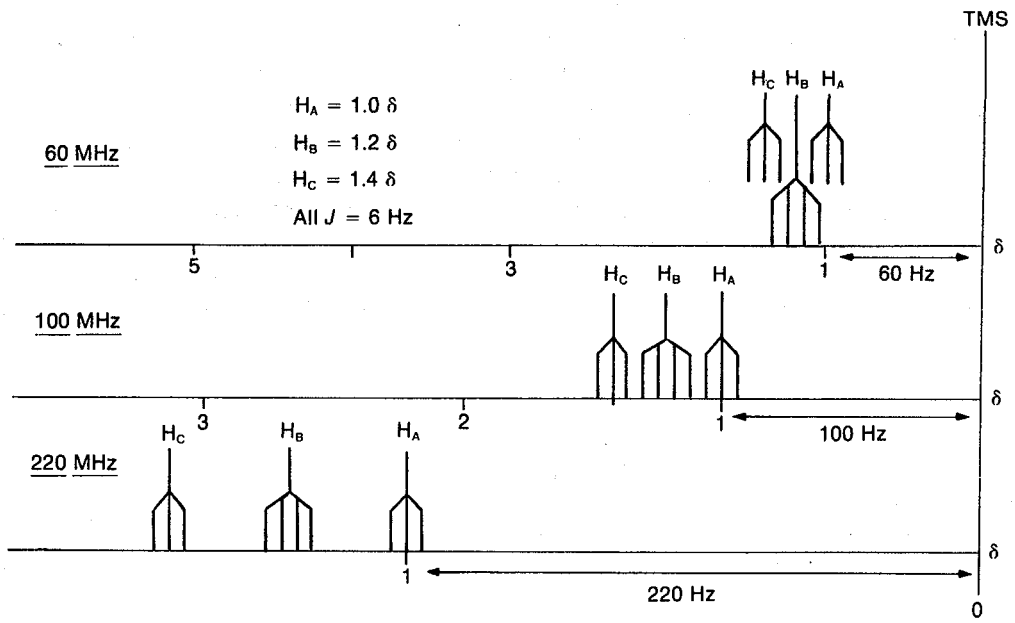
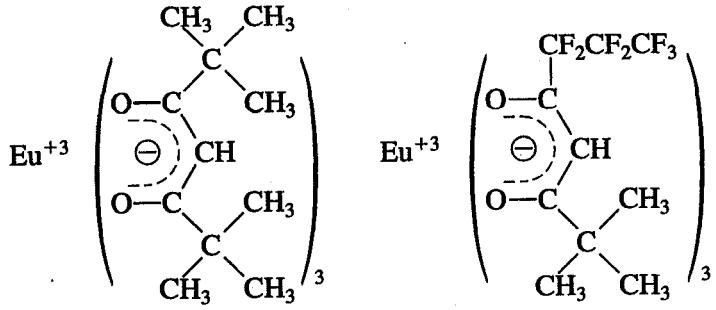


Figure NMR.15 A comparison of the spectrum of a compound with overlapping multiplets at 60 MHz with spectra of the same compound also determined at 100 MHz and 220 MHz. The drawing is to scale.

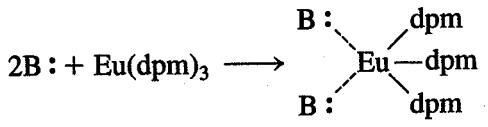
NMR.13 CHEMICAL SHIFT REAGENTS

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 (e.g., 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 like benzene, which impose local anisotropic effects on surrounding molecules. In many cases, it was possible to resolve partially overlapping multiplets by such a solvent change. However, 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.



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:



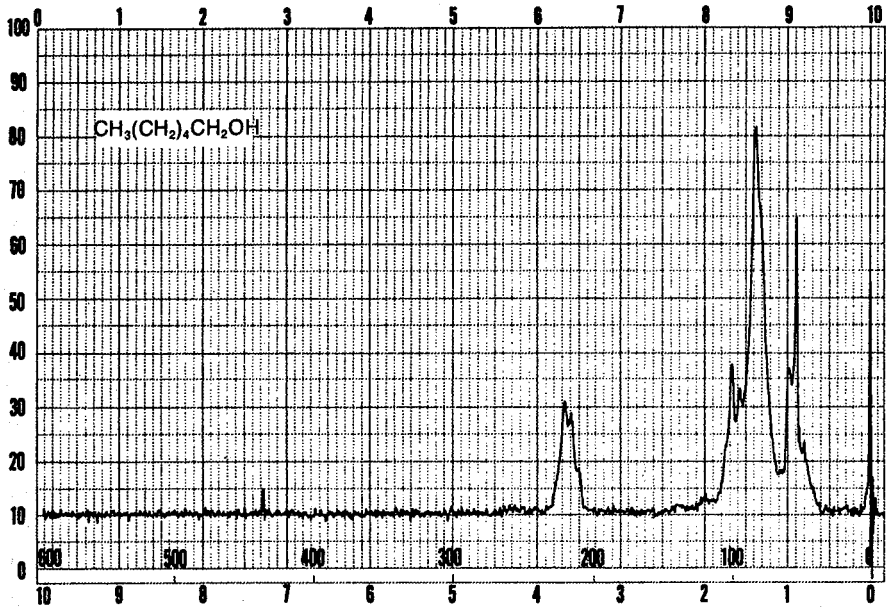


Figure NMR.16 The normal 60-MHz spectrum of hexanol (courtesy of Aldrich Chemical Co.).

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 NMR.16 and NMR.17. In the absence of shift reagent, the normal spectrum is obtained

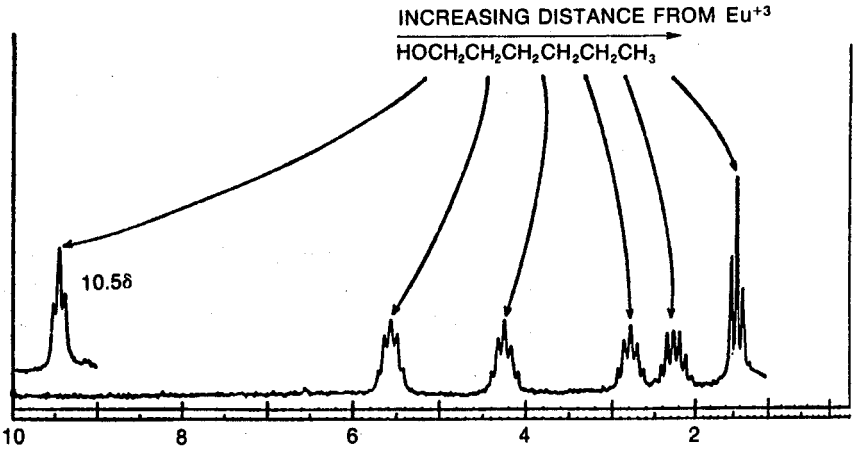


Figure NMR.17 The 100-MHz spectrum of hexanol with 0.29 mole equivalents of $Eu(dpm)_3$. (Reprinted with permission from J.K.M. Sanders and D.H. Williams, *Chem. Commun.*, 422[1970].)

(Figure NMR.16). 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 (Figure NMR.17), 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 NMR.17 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.

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APPENDIX 5

Carbon-13 Nuclear Magnetic Resonance Spectroscopy

CMR.1 CARBON-13 NUCLEAR MAGNETIC RESONANCE

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 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 its low natural abundance (0.0108), the probability of finding two ^{13}C atoms adjacent to one another is extremely low.

CMR.2 COMPLETELY COUPLED ^{13}C SPECTRA

Figure CMR.1 shows the carbon-13 spectrum of ethyl phenylacetate. Consider first the upper trace shown in the figure. Chemical shifts, just as in proton NMR, are reported by the number of ppm (δ units) that the peak is shifted downfield from TMS. Keep in mind, however, that it is a ^{13}C atom of the methyl group of TMS that is being observed, not the 12 methyl hydrogens. Notice the extent of the scale. Although the chemical shifts of protons encompass a range of only about 20 ppm, ^{13}C chemical shifts cover an extremely wide range of up to 200 ppm! Under these circumstances, even adjacent —CH_2— carbons in a long hydrocarbon chain generally have their own distinct resonance peaks, and these peaks are clearly resolved. It is unusual to find any two carbon atoms in a molecule having resonance at the same chemical shift unless these two carbon atoms are equivalent by symmetry.

Returning to the upper spectrum in Figure CMR.1, you can see that the first quartet downfield from TMS (14.2 ppm) corresponds to the carbon of the methyl group. It is

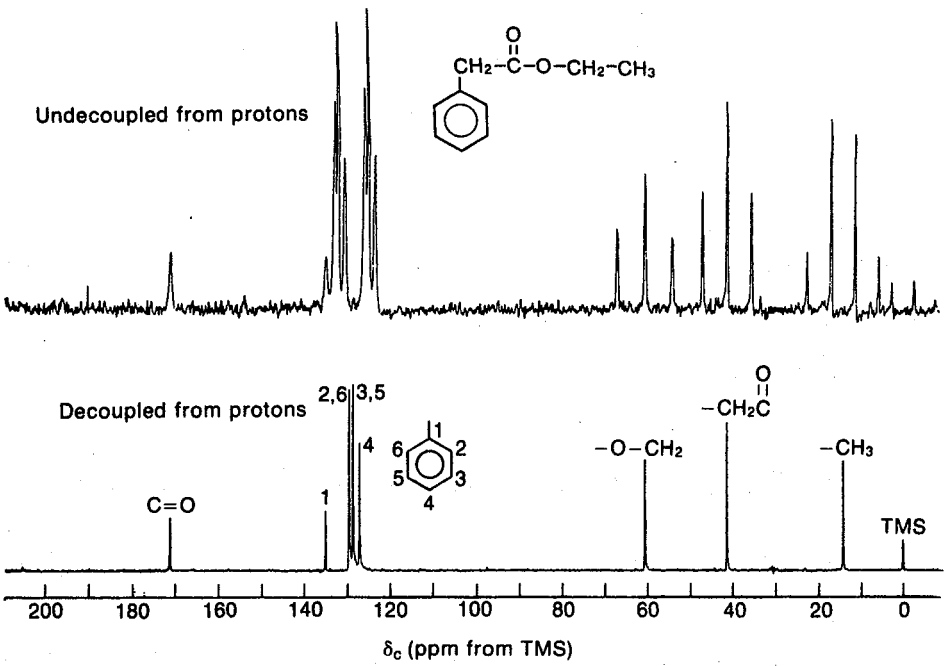

Figure CMR.1 Carbon-13 spectra of ethyl phenylacetate. (From Rodig, O.R., Bell, C.E., Jr., and Clark, A.K., *Organic Chemistry Laboratory; Standard and Microscale Experiments,* 1990 by Saunders College Publishing, Philadelphia, PA. Reprinted by permission of the publisher.)

split into a quartet (J = 127 Hz) by the three attached hydrogen atoms. In addition, although it cannot be seen on the scale of this spectrum, 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 geminal couplings (H—C—^{13}C) of a type that commonly occurs in carbon-13 spectra, with coupling constants that are generally small (J = 0–2 Hz). The quartet is caused by **direct coupling** (^{13}C—H). Direct coupling constants are larger, usually about 100–200 Hz and are more obvious on the scale in which the spectrum is presented.

There are two —CH_2— groups in ethyl phenylacetate. The one corresponding to the ethyl —CH_2— group is found further downfield (60.6 ppm), as this carbon is deshielded by the attached oxygen. It is a triplet because of the two attached hydrogens. Again, although it is not seen in this unexpanded spectrum, each of the triplet peaks is finely split into a quartet by the three hydrogens on the adjacent methyl group. The benzyl —CH_2— carbon is the intermediate triplet (41.4 ppm). Furthest downfield is the carbonyl group carbon (171.1 ppm). On the scale of 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 over the range from 127 ppm to 136 ppm.

CMR.3 BROAD-BAND DECOUPLED ^{13}C SPECTRA

Although the splittings in a simple molecule such as ethyl phenylacetate yield interesting structural information, namely the number of hydrogens attached to each carbon (as well as those adjacent if the spectrum is expanded), for large molecules the carbon-13 spectrum becomes very complex due to these splittings, and the splitting patterns often overlap. It is customary, therefore, to decouple *all* the protons in the molecule by irradiating them simultaneously with a broad spectrum of frequencies in the proper range. This type of spectrum is said to be **completely decoupled.** The completely decoupled spectrum is much simpler and, for larger molecules, much easier to interpret. The decoupled spectrum of ethyl phenylacetate is presented in the lower trace of Figure CMR.1.

In the completely decoupled carbon-13 spectrum, each peak represents a different carbon atom. If two carbons are represented by a single peak, they must be equivalent by symmetry. Thus, the carbons at positions 2 and 6 of the aromatic ring of ethyl phenylacetate give a single peak, and the carbons at positions 3 and 5 also give a single peak in the lower spectrum of Figure CMR.1.

CMR.4 CHEMICAL SHIFTS

Just as is the case for proton spectra, the chemical shift of each carbon indicates both its type and its structural environment. In fact, a correlation chart can be presented for ^{13}C chemical shift ranges, similar to the correlation chart for proton resonances shown in Figure NMR.5. Figure CMR.2 gives typical chemical shift ranges for the types of carbon resonances.

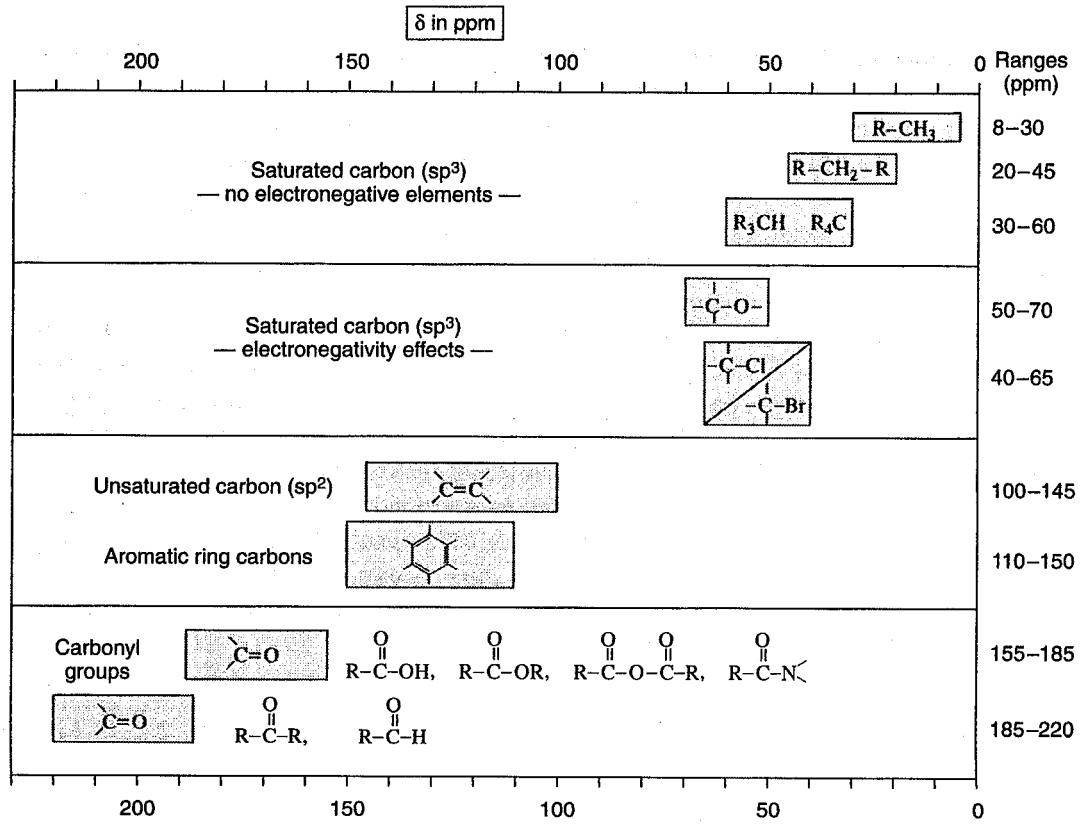

Figure CMR.2 A correlation chart for ^{13}C chemical shifts (ppm from TMS).

Electronegativity, hybridization, and anisotropy effects all influence ^{13}C chemical shifts, just as they do for protons, but in a more complex fashion. These factors are not discussed in any detail here, but note that the $—CH_2—$ group carbon attached to oxygen in ethyl phenylacetate has a larger chemical shift than the $—CH_2—$ carbon of the benzyl group. Note also that the carbonyl carbon appears relatively far downfield, probably due to an anisotropy effect.

CMR.5 SOME SAMPLE SPECTRA

The following spectra illustrate some of the effects that can be observed in carbon-13 spectra. The spectrum of 2,2-dimethylbutane is presented in Figure CMR.3. Notice that, although this compound has six total carbon atoms, 2,2-dimethylbutane shows only four peaks in the carbon-13 spectrum along with the solvent peaks ($CDCl_3$) and TMS. The carbon-13 atoms that are equivalent appear at the same chemical shift value. Thus, a single methyl carbon **a** appears at highest field (8.8 ppm), while the three equivalent methyl carbons **b** appear at 28.9 ppm. The quaternary carbon **c** gives rise to the small peak of 30.4 ppm, whereas the methylene carbon **d** appears at 36.5 ppm. The relative sizes of

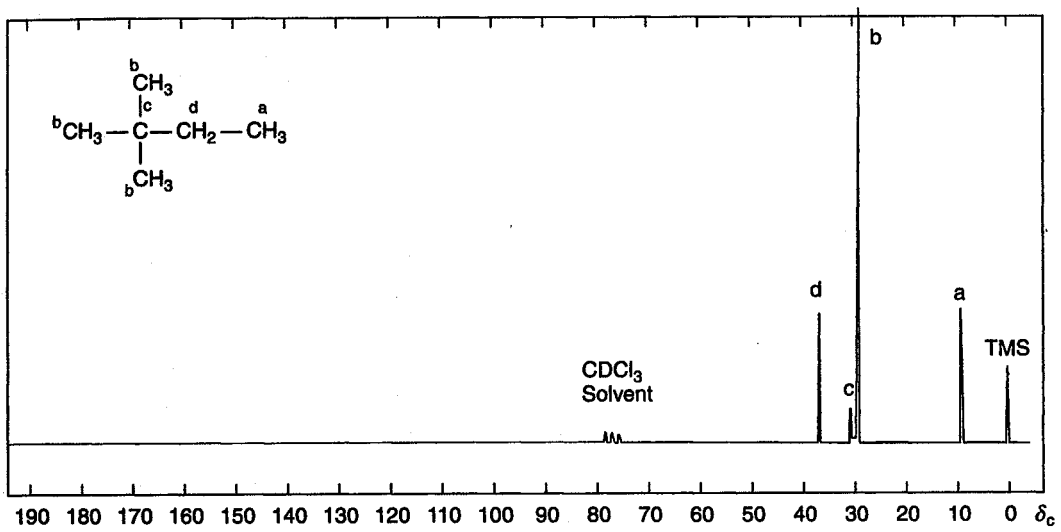

Figure CMR.3 Carbon-13 spectrum of 2,2-dimethylbutane. (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

peaks gives some idea of the numbers of each type of carbon atom present in the molecule. For example, in Figure CMR.3 notice that the peak at 28.9 ppm (**b**) is much larger than the other peaks. A characteristic of proton-decoupled ^{13}C NMR spectra is that carbon atoms that do not have hydrogens attached to them generally appear as weak peaks. Thus, the quaternary carbon at 30.4 ppm (**c**) is very weak (see Section CMR.6).

The presence of an electronegative element should deshield a carbon atom closest to it, as is illustrated in the cases of bromocyclohexane (Fig. CMR.4) and cyclohexanol

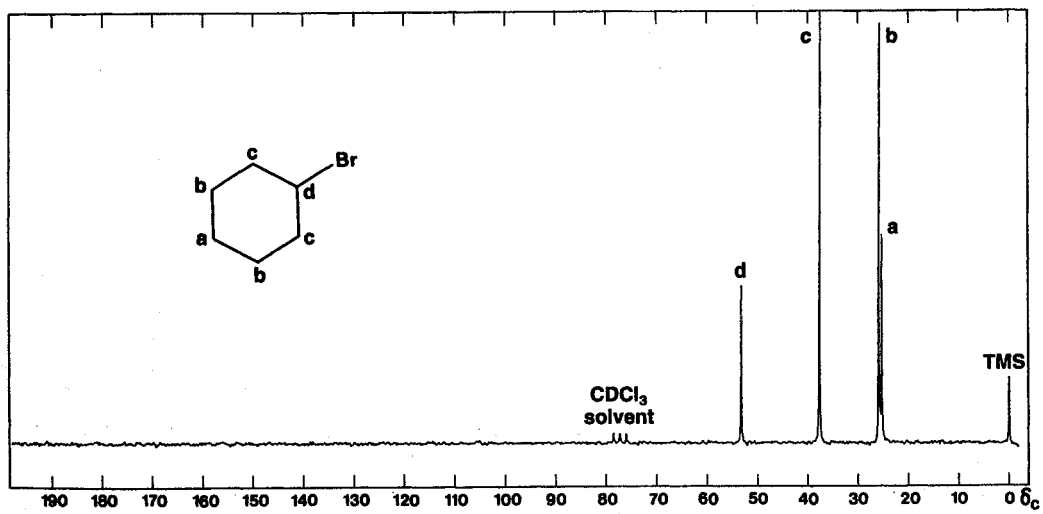

Figure CMR.4 Carbon-13 spectrum of bromocyclohexane. (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

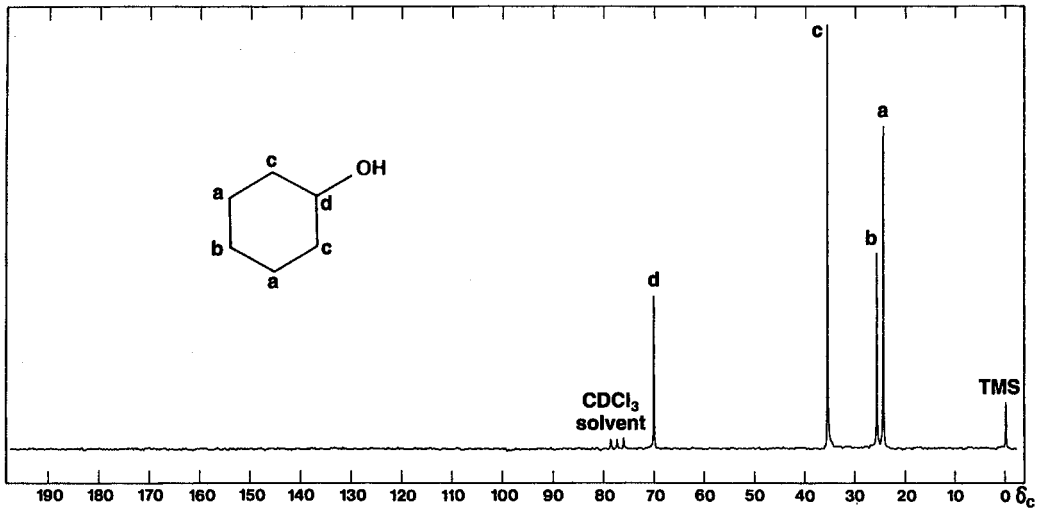

Figure CMR.5 Carbon-13 spectrum of cyclohexanol. (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

(Fig. CMR.5). The carbon bearing the bromine in bromocyclohexane appears at 53.0 ppm; the carbon bearing the hydroxyl group of cyclohexanol appears at 70.0 ppm. In each of these cases, note that as the ring carbons are located farther away from the electronegative element, their resonances appear at higher field. A carbon attached to a double bond appears deshielded, due to diamagnetic anisotropy. This effect can be seen in the spectrum of cyclohexene (Fig. CMR.6). The carbon atoms of the double bond appear at 127.2

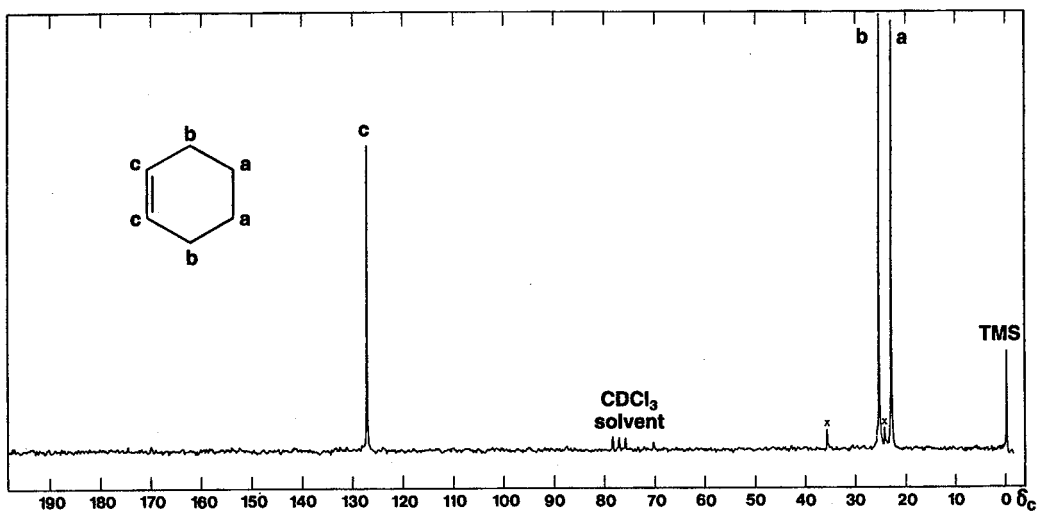

Figure CMR.6 Carbon-13 spectrum of cyclohexene. (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

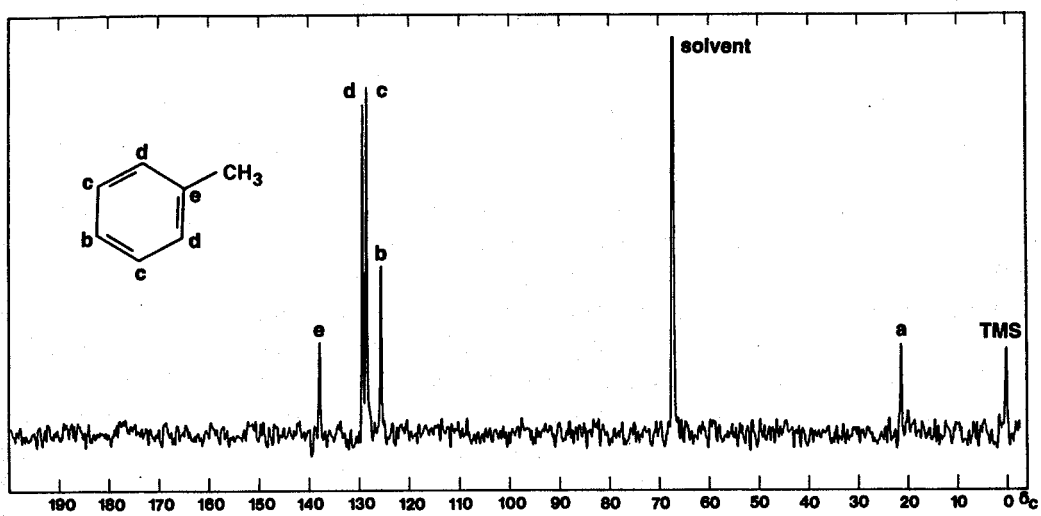

Figure CMR.7 Carbon-13 spectrum of toluene. (The peak at 67.4 is due to the solvent, dioxane.) (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

ppm. Again, it can be seen that as carbon atoms are located farther from the double bond, their resonances appear at higher field. The effect of diamagnetic anisotropy can be seen in the spectrum of toluene (Fig. CMR.7), where the carbon atoms of the aromatic ring appear at low field (125.5–137.7 ppm). Finally, the strong deshielding experienced by the carbon atom of a carbonyl group can be seen in the carbon-13 spectrum of cyclohexanone (Fig. CMR.8). The carbon atom appears at a chemical shift of 211.3 ppm.

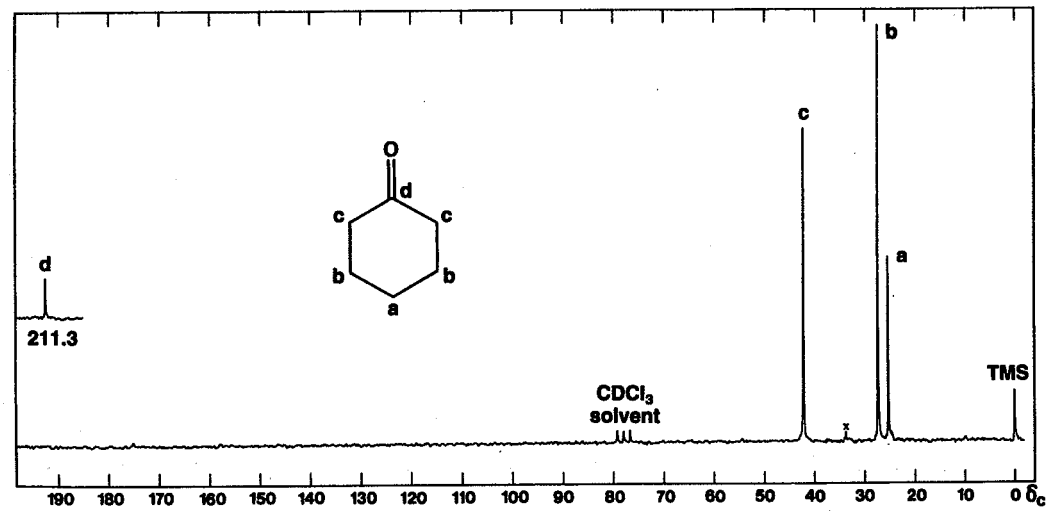

Figure CMR.8 Carbon-13 spectrum of cyclohexanone. (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

CMR.6 NUCLEAR OVERHAUSER EFFECT

As mentioned previously, integrals (areas under peaks) are not as reliable for carbon spectra as they are for hydrogen spectra. This is due in part to the **nuclear Overhauser effect.** This effect operates when two dissimilar adjacent atoms (in this case carbon and hydrogen) both exhibit spins and are NMR active. The atoms can influence the NMR absorption intensities of each other. The effect can be either positive or negative, but in the case of carbon-13 interacting with hydrogen, the effect is positive. As a result, carbon-13 NMR absorptions vary in intensity with respect to the number of hydrogen atoms that are directly attached to the carbon atom being observed. In general, the more hydrogens that are attached to a given carbon, the stronger its NMR absorption. Other factors also influence the absorption intensities (they are related to molecular relaxation phenomena), so the number of attached hydrogens can only be taken as a single factor influencing absorption intensity; this is often a very helpful factor in deciding which carbon to assign to a given absorption. In Figure CMR.1 note the low intensity of the carbonyl carbon (172 ppm), and in Figure CMR.7 note the low intensity of the ring carbon to which the methyl group is attached (138 ppm). The carbonyl peak in cyclohexanone (Fig. CMR.8) is also weak. None of these carbons has attached hydrogens.

CMR.7 AN EXAMPLE OF SYMMETRY

As one example of the utility of carbon-13 experiments, consider the cases of the isomers 1,2- and 1,3-dichlorobenzene. Although these isomers could be difficult to dis-

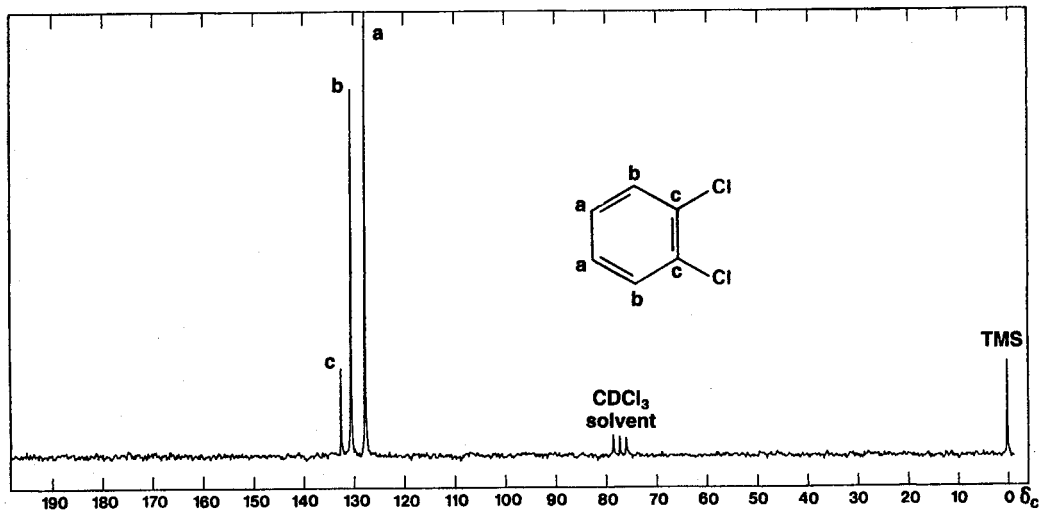

Figure CMR.9 Carbon-13 spectrum of 1,2-dichlorobenzene. (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

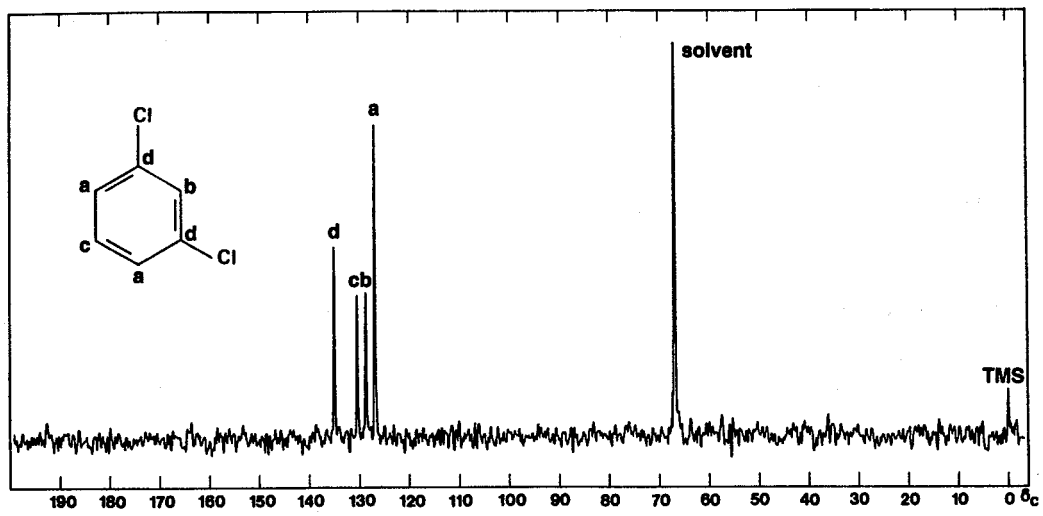

Figure CMR.10 Carbon-13 spectrum of 1,3-dichlorobenzene. (The peak at 67.4 ppm is due to the solvent, dioxane.) (From Johnson, L.F., and Jankowski, W.C., *Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra,* 1972 by John Wiley and Sons, New York. Reprinted by permission of the publisher.)

tinguish from one another on the basis of their boiling points or their infrared spectra, each can be identified clearly by their carbon-13 spectra. 1,2-Dichlorobenzene has a plane of symmetry that gives it only three different types of carbon atoms. 1,3-Dichlorobenzene has a plane of symmetry that gives it four different types of carbon atoms. The proton-decoupled carbon-13 spectra of these two compounds are shown in Figures CMR.9 and CMR.10, respectively. It is easy to see the differences in the carbon-13 spectra of these two isomers.

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APPENDIX 6

Index of Spectra

Infrared Spectra

^{1}H NMR Spectra

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Ultraviolet-Visible Spectra

Mixtures

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