Contents

CHAPTER

1 Introduction

Prelab Exercise: Study the glassware diagrams and be prepared to identify the reaction tube, fractionating column, distilling head, addition port, and Hirsch funnel.

Welcome to the organic chemistry laboratory! This laboratory manual presents a unique approach for carrying out organic experiments—they can be conducted on either a microscale or a macroscale. The latter is the traditional way of teaching the principles of experimental organic chemistry and is the basis for all the experiments in this book, a book which traces its history to 1934 when Louis Fieser was its author. Most teaching institutions are equipped to carry out macroscale experiments. Instructors are familiar with these techniques and experiments, and much research in industry and academe is carried out on this scale. These experiments typically involve the use of about 10 g of *starting material*, the chief reagent used in the reaction.

For reasons primarily of safety and cost, there is a growing trend toward carrying out work in the laboratory on a microscale, a scale one-tenth to one-thousandth of that previously used. Using smaller quantities of chemicals exposes the laboratory worker to smaller amounts of toxic, flammable, explosive, carcinogenic, and teratogenic material. Microscale experiments can be carried out much more rapidly than macroscale experiments because of rapid heat transfer, rapid filtration, and rapid drying. Since the apparatus advocated by the author is inexpensive, more than one reaction can be set up at once. The cost of chemicals is, of course, greatly reduced. A principal advantage of microscale experimentation is that the quantity of waste is reduced by one-tenth to one-thousandth that formerly produced.

To allow maximum flexibility in the conduct of organic experiments, this book presents procedures for the vast majority of the experiments on both the microscale and the macroscale. As will be seen, some of the equipment and techniques are different. A careful reading of the two procedures will indicate what changes and precautions must be employed in going from one scale to the other.

Synthesis and structure determination

Synthesis and structure determination are two major concerns of the organic chemist, and both are dealt with in this book. The rational synthesis of an organic compound, whether it involves the transformation of one functional group into another or a carbon-carbon bond-forming reaction, starts with a *reaction*.

Organic reactions usually take place in the liquid phase and are *homogeneous*, in that the reactants are all in one phase. The reactants can be solids and/or liquids dissolved in an appropriate solvent to mediate the reaction. Some reactions are *heterogeneous*—one of the reactants is in the solid phase—and thus

require stirring or shaking to bring the reactants in contact with one another. A few heterogeneous reactions involve the reaction of a gas, such as oxygen, carbon dioxide, or hydrogen, with material in solution. Examples of all these will be found among the experiments in this book.

Effect of temperature

In an *exothermic* organic reaction, simply mixing the reactants will produce the products; the reaction evolves heat. If it is highly exothermic, one reactant is added slowly to the other, and heat is removed by external cooling. Most organic reactions are, however, mildly *endothermic,* which means the reaction mixture must be heated to increase the rate of the reaction. A very useful rule of thumb is that *the rate of an organic reaction doubles with a 10°C rise of temperature*. The late Louis Fieser, an outstanding organic chemist and professor at Harvard University, introduced the idea of changing the traditional solvents of many reactions to high-boiling solvents in order to reduce reaction times. Throughout this book we will use solvents such as triethylene glycol, with a boiling point (bp) of 290°C, to replace ethanol (bp 78°C) and triethylene glycol dimethyl ether (bp 222°C) to replace dimethoxyethane (bp 85°C). The use of these high-boiling solvents can greatly increase the rates of many reactions.

Running an organic reaction is usually the easiest part of a synthesis. The challenge comes in isolating and purifying the product from the reaction because organic reactions seldom give quantitative yields of one pure substance.

"Working up the reaction"
Chapter 3: Crystallization
Chapter 7: Vacuum Distillation and Sublimation
Chapter 8: Extraction of Acids and Bases

In some cases the solvent and concentrations of reactants are chosen so that, after the reaction mixture has been cooled, the product will *crystallize*. It is then collected by *filtration,* and the crystals are washed with an appropriate solvent. If sufficiently pure at that point, the product is dried and collected; otherwise, it is purified by the process of recrystallization, *column chromatography,* or less commonly, *sublimation*.

If the product of reaction does not crystallize from the reaction mixture, it is often isolated by the process of *extraction*. This involves adding a solvent to the reaction mixture that will dissolve the product and will be immiscible with the solvent used in the reaction. Shaking the mixture will cause the product to dissolve in the extracting solvent, after which the two layers of liquid are separated and the product isolated from the extraction solvent.

Chapter 5: Distillation
Chapter 6: Steam Distillation

If the product is a liquid, it is isolated by *distillation,* usually after extraction. Occasionally, the product can be isolated by the process of *steam distillation* from the reaction mixture.

Organic reactions are usually carried out by dissolving the reactants in a solvent and then heating the mixture to boiling. To keep the solvent from boiling away, the vapor is condensed to a liquid which is allowed to run back into the boiling solvent.

On a microscale, reactions are carried out in a *reaction tube* (Fig. 1.1a). The mass of the reaction tube is so small that a milliliter of nitrobenzene (bp 210°C) will boil in 10 s and a milliliter of benzene (mp 5°C) will crystallize in the same period of time. Cooling is effected by simply shaking the tube in a small beaker of ice water and heating by immersing the reaction tube to the appropriate depth in an electrically heated sand bath. On a larger scale, heat transfer is not so fast because of the smaller ratio of surface area to volume in a round-bottomed flask. Cooling is again conducted using an ice bath, but heating

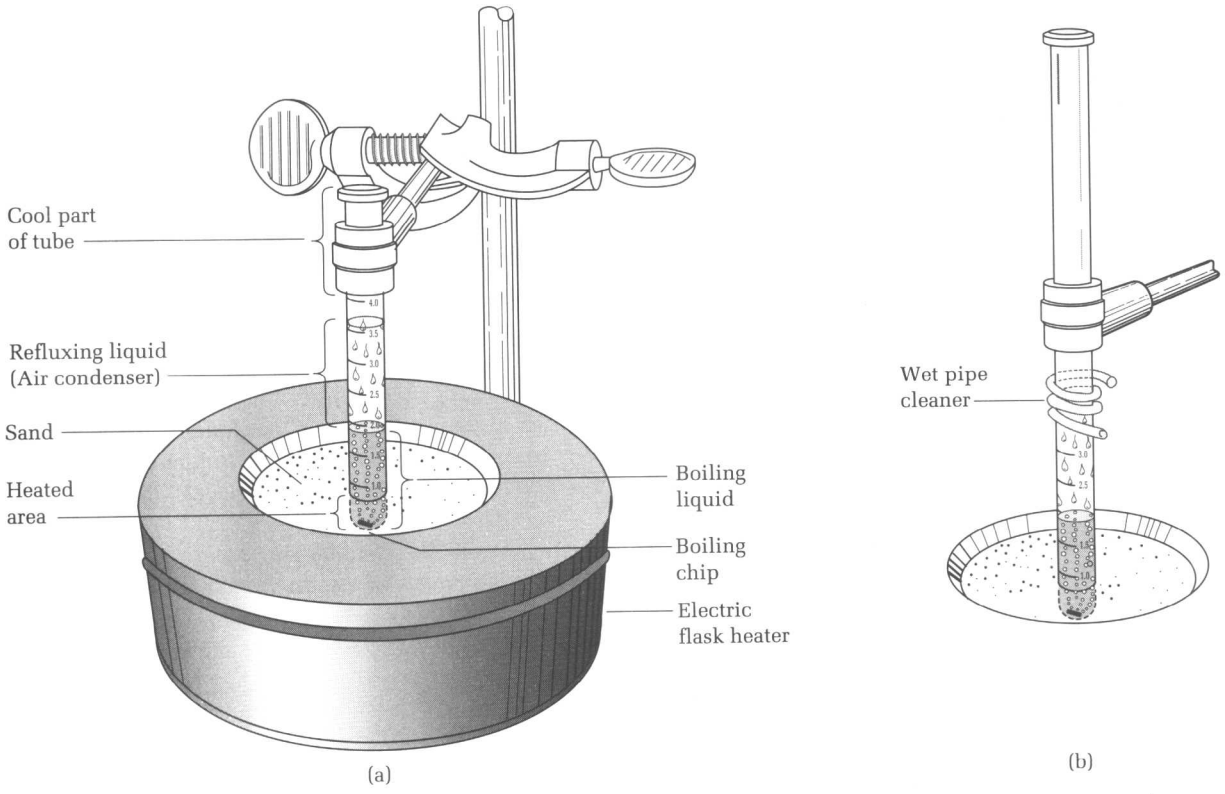

FIG. 1.1 (a) Reaction tube being heated on hot sand bath in a flask heater. The area of the tube exposed to heat is small. The liquid boils and condenses on the cool upper portion of the tube, which functions as an air condenser. (b) The condensing area can be increased by adding the distilling column as an air condenser.

is sometimes done on a steam bath for low-boiling liquids. Higher temperatures require electric *heating mantles* or *flask heaters*.

For microscale heating, a *sand bath* in an electric 100-mL flask heater filled with sand is a versatile heat source (Fig. 1.1a). The relatively poor heat conduction of sand results in a very large temperature difference between the top of the sand and the bottom. Thus, depending on the immersion depth in the sand, a similarly wide temperature range will be found in the reaction tube. Because the area of the tube exposed to heat is fairly small, it is difficult to transfer enough heat to the contents of the tube to cause solvents to boil away. The reaction tube is 100 mm long so that the upper part of the tube can function as an efficient *air condenser* (Fig. 1.1a), since the area of glass is large and the volume of vapor is comparatively small. The air condenser can be made even longer by attaching the empty *distilling column* to the reaction tube using the *connector with support rod* (Fig. 1.1b). The black connector is made of Viton, which is resistant to high-boiling aromatic solvents. The cream-colored connector is made of Santoprene, which is resistant to all but high-boiling aromatic solvents.

Solvents, such as water and ethanol, are boiled, and as the hot vapor ascends to the upper part of the tube, it condenses and runs back down the tube. This process is called *refluxing* and is the most common method for conducting a reaction at a constant temperature, the boiling point of the solvent. For very low-boiling solvents such as ether (bp 35°C), a pipe cleaner dampened with water makes an efficient cooling device. A water-cooled condenser is also available (Fig. 1.2) but is seldom needed.

On a larger scale, the same electric flask heater or a sand bath on a hot plate can be used to heat a flask which is connected via a *standard-taper ground glass joint* to a water-cooled *reflux condenser*, where the water flows in a jacket around the central tube. The high heat capacity of water makes it possible to remove the large amount of heat put into the larger volume of refluxing vapor (Fig. 1.3).

It is worth noting that the reaction tube (Fig. 1.1a) functions as both flask and reflux condenser and is completely equivalent in function to the macroscale standard-taper flask and reflux condenser of Fig. 1.3 but costs about 1/40th as much money.

Chapter 10: Thin-Layer Chromatography

The progress of a reaction can be followed by withdrawing tiny samples at intervals and analyzing them by *thin-layer chromatography*. If the product of a

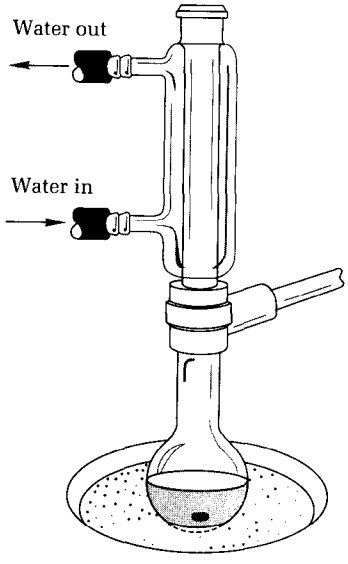

FIG. 1.2 Refluxing solvent in 5-mL round-bottomed flask fitted with water-cooled condenser.

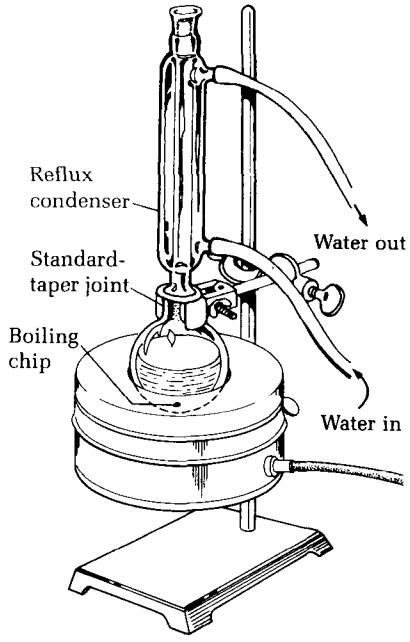

FIG. 1.3 Reflux apparatus for larger reactions. Liquid boils in flask and condenses on cold inner surface of water-cooled condenser.

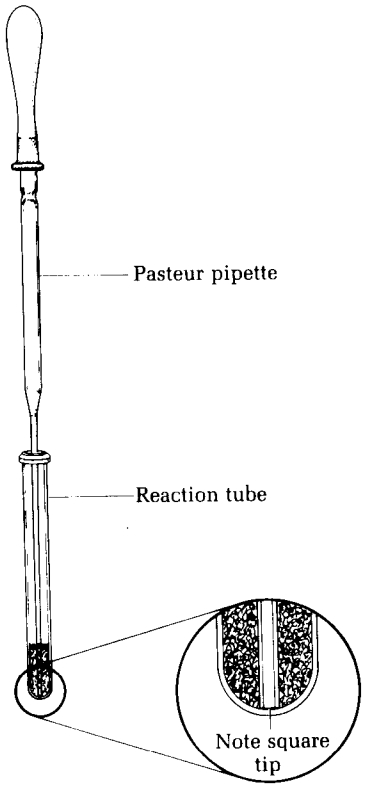

FIG. 1.4 Filtration using the Pasteur pipette and reaction tube.

reaction crystallizes from the reaction mixture on cooling, it is isolated by *filtration*. On a microscale, this can be done in several ways. If the crystals are large enough and in the reaction tube, this is accomplished by inserting a *Pasteur pipette* to the bottom of the tube while expelling the air and withdrawing the solvent (Fig. 1.4). Very effective filtration occurs between the square tip of the pipette and the bottom of the tube. This method of filtration has several advantages over the alternatives. The mixture of crystals and solvent can be kept on ice during the entire process. This minimizes the solubility of the crystals in the solvent. There are no transfer losses of material because an external filtration device is not used. This technique allows several recrystallizations to be carried out in the same tube with final drying of the product under vacuum. Knowing the *tare* of the tube (the weight of the empty tube) allows the weight of the product to be determined without removing it from the tube. In this manner a compound can be synthesized, purified by crystallization, and dried without ever leaving the reaction tube. After removal of material for analysis, the compound in the tube can then be used for the next reaction. This technique is used in many of the microscale experiments in this book. When the crystals are dry, they are easily removed from the reaction tube. When they are wet, it is difficult to scrape them out. If the crystals are in more than about 2 mL of solvent, they can be isolated by filtration on the *Hirsch funnel*. The one that is in the microscale kit of apparatus is particularly easy to use because the funnel fits into the *filter flask* with no adapter, and it is equipped with a *polyethylene frit* for removal of the crystals (Fig. 1.5).

Macroscale quantities of material are crystallized in *Erlenmeyer flasks* (Fig. 1.6); the crystals are collected in porcelain or plastic *Büchner funnels* fitted with

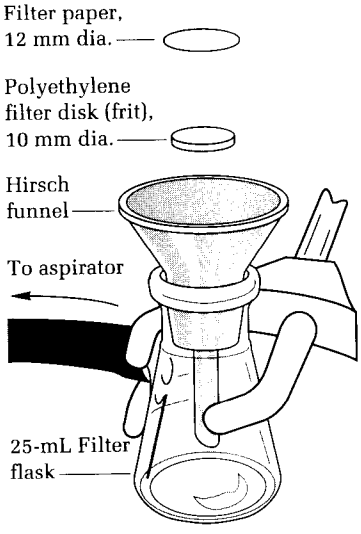

FIG. 1.5 Hirsch funnel with integral adapter, polyethylene frit, and 25-mL filter flask.

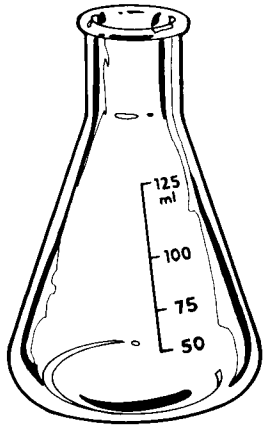

FIG. 1.6 Erlenmeyer flask with approximate volume graduations.

pieces of filter paper in the bottom of the funnel. A *filter adapter* (*Filtervac*) is used to form a vacuum-tight seal between the flask and funnel (Fig. 1.7).

Many solids can be purified by the process of *sublimation*. The solid is heated, and the vapor of the solid condenses on a cold surface to form crystals in an apparatus constructed from a *centrifuge tube* fitted with a rubber adapter (a *Pluro stopper*) and pushed into a *filter flask* (Fig. 1.8). Caffeine can be purified in this manner. This is primarily a microscale technique, although sublimers holding several grams of solid are available.

Chapter 11: Column Chromatography

Mixtures of solids and, occasionally, of liquids can be separated and purified by *column chromatography*. The *chromatography column* for both microscale and macroscale work is very similar (Fig. 1.9).

Chapter 8: Extraction of Acids and Bases

Often the product of a reaction will not crystallize. It may be a liquid, it may be a mixture of compounds, or it may be too soluble in the solvent being used. In this case, an immiscible solvent is added, the two layers are shaken to effect *extraction*, and after the layers separate, one layer is removed. On a microscale, this can be done with a Pasteur pipette, and the process is repeated if necessary. A tall, thin column of liquid such as that produced in the reaction tube makes it easy to remove one layer selectively. This is much more difficult to do in the usual test tube because the height/diameter ratio is too small.

The chromatography column in the apparatus kit is also a *micro separatory funnel* (Fig. 1.10b). Remember to remove the frit at the column base of the micro Büchner funnel and to close the valve before adding liquid.

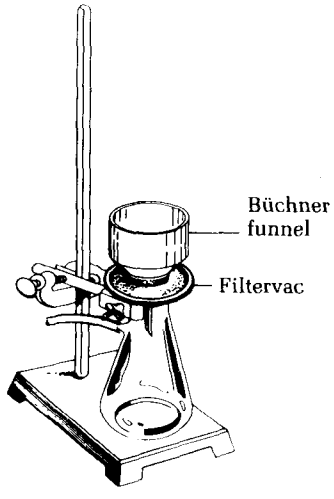

FIG. 1.7 Suction filter assembly.

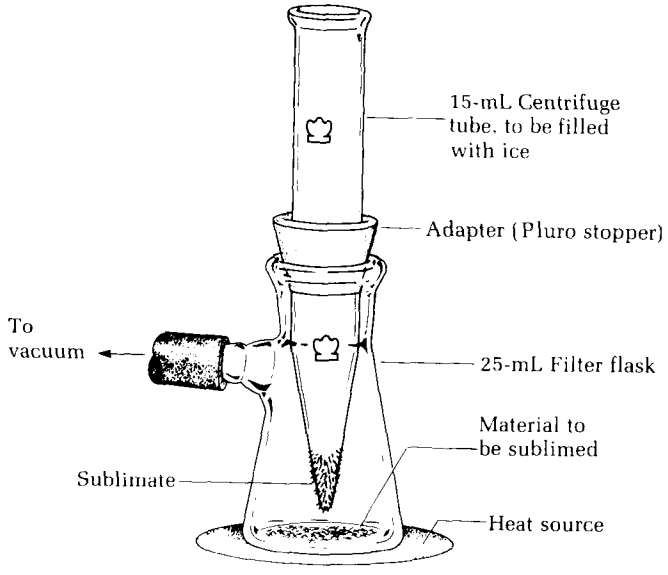

FIG. 1.8 Small-scale sublimation apparatus.

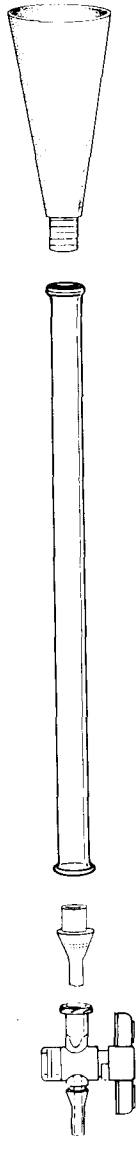

FIG. 1.9 Chromatography column consisting of funnel, tube, base fitted with polyethylene frit, and Leur valve.

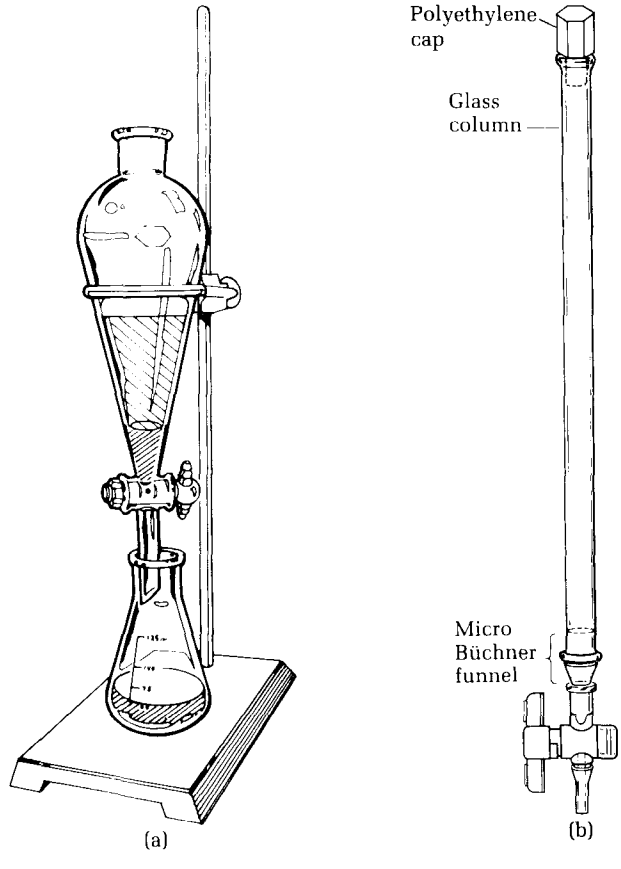

FIG. 1.10 (a) Separatory funnel with Teflon stopcock. (b) Microscale separatory funnel. Remove polyethylene frit from micro Büchner funnel before using.

On a larger scale, a *separatory funnel* is used for extraction (Fig. 1.10a). The mixture can be shaken in the funnel and then the lower layer removed through the stopcock after the stopper is removed. These funnels are available in sizes from 10 to 5000 mL. The microscale version is seen in Fig. 1.10(b).

Some of the compounds to be synthesized in these experiments are liquids. On a very small scale, the best way to separate and purify a mixture of liquids is by *gas chromatography*, but this technique is limited to less than 100 mg of material on the usual gas chromatograph. For larger quantities of material, *distillation* is used. For this purpose, small distilling flasks are used. These flasks

Chapter 12: Liquid Chromatography
Chapter 5: Distillation

have a large surface area to allow sufficient heat input to cause the liquid to vaporize rapidly so that it can be distilled and then condensed for collection in a *receiver*. The apparatus (Fig. 1.11) consists of a *distilling flask, distilling adapter* (which also functions as an air condenser on a microscale), a *thermometer adapter, thermometer,* and on a macroscale a water-cooled *condenser* and *distilling adapter* (Fig. 1.12). *Fractional distillation* is carried out using a small packed *fractionating column* (Fig. 1.13). The apparatus is very similar on both a microscale and macroscale. On a microscale, 2 to 4 mL of a liquid can be fractionally distilled, and 1 mL or more can be simply distilled. The usual scale in these experiments for macroscale distillation is about 25 mL. The individual components for microscale experimentation are shown in Fig. 1.14.

Chapter 6: Steam Distillation

Some liquids with a relatively high vapor pressure can be isolated and purified by *steam distillation,* a process in which the organic compound codistills with water at a temperature below the boiling point of water. The microscale

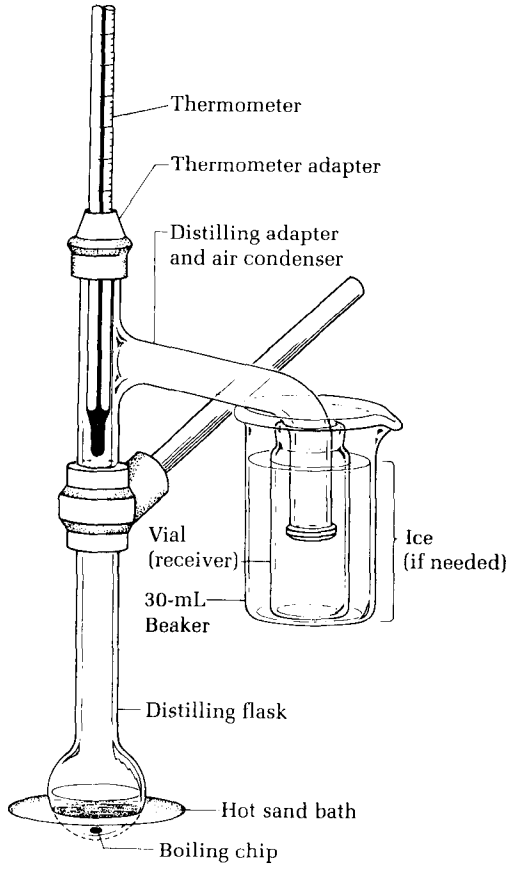

FIG. 1.11 Small-scale simple distillation apparatus.

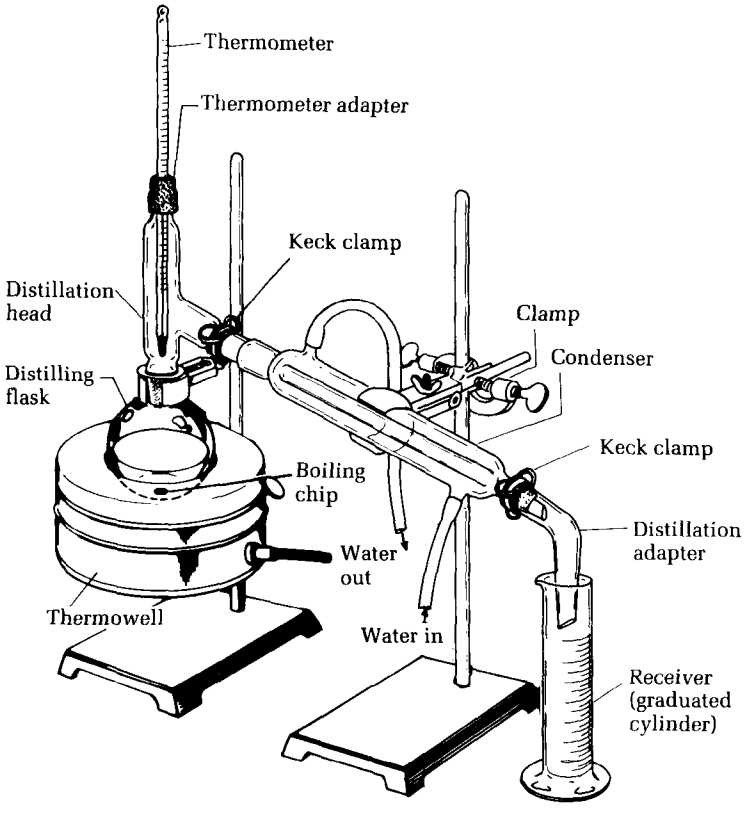

FIG. 1.12 Apparatus for simple distillation.

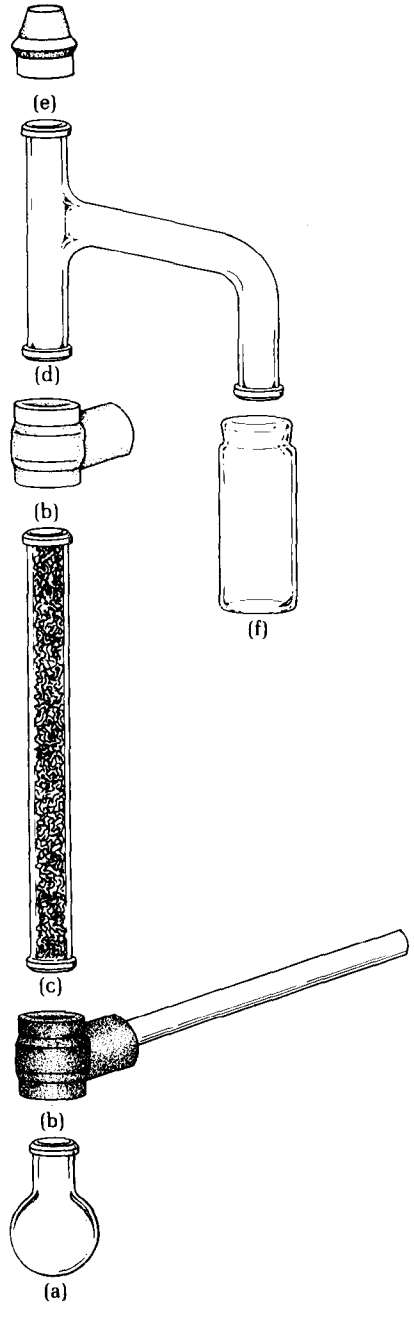

FIG. 1.13 Microscale fractional distillation apparatus. (a) 5-mL round-bottomed flask. (b) Elastomeric connector [Santoprene (white) or Viton (black)]. (c) Fractionating column packed with copper sponge. (d) Distilling head and air condenser. (e) Thermometer adapter (Santoprene). (f) Receiver (1-dram vial).

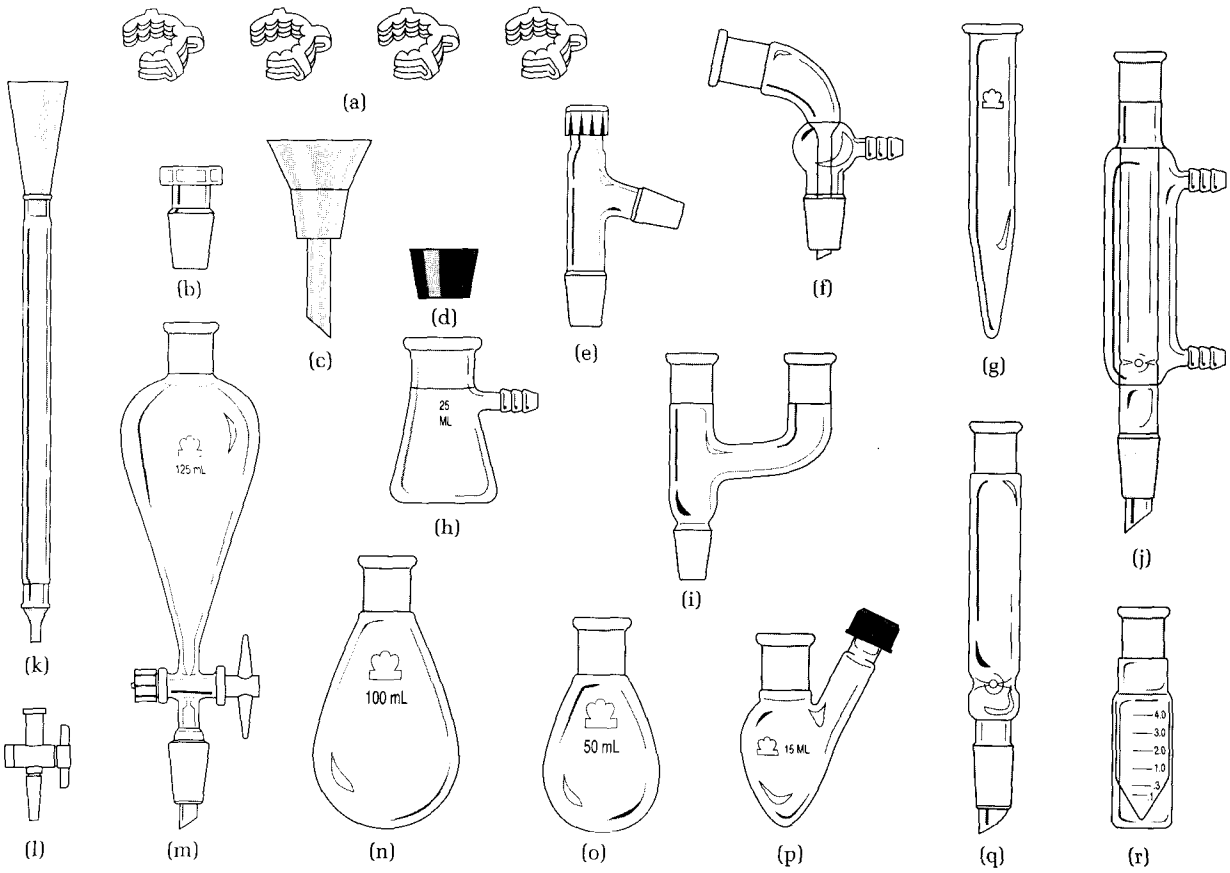

FIG. 1.14 Macroscale apparatus kit with 14/20 standard-taper ground-glass joints.

(a) Polyacetal Keck clamps, size 14
(b) Hex-head glass stopper, 14/20 standard taper
(c) Hirsch funnel (polypropylene) with 20-μm fritted polyethylene disk
(d) Filter adapter (Santoprene) for sublimation apparatus
(e) Distilling head with O-ring thermometer adapter
(f) Vacuum adapter
(g) Centrifuge tube (15 mL)/ sublimation receiver
(h) Filter flask, 25 mL
(i) Claisen adapter
(j) Water-jacketed condenser
(k) Chromatography column (glass) with polypropylene funnel and 20-μm polyethylene fritted base in micro Büchner funnel
(l) Stopcock for chromatography column
(m) Separatory funnel, 125 mL
(n) Pear-shaped flask, 100 mL
(o) Pear-shaped flask, 50 mL
(p) Conical flask (15 mL) with side arm for inlet tube
(q) Distilling column/air condenser
(r) Conical reaction vial (5 mL)/ distillation receiver

and macroscale apparatus for this process is shown in the chapter on steam distillation.

Other apparatus commonly used in the organic laboratory is shown in Fig. 1.15 on pages 12–13.

Check In

Your first duty will be to check in to your assigned desk. The identity of much of the equipment should already be apparent from the preceding outline of the experimental processes used in the organic laboratory. The complete kit of microscale apparatus is illustrated in Fig. 1.16 on page 14.

CAUTION: Notify your instructor immediately if you break a thermometer. Mercury is very toxic.

Check to see that your thermometer reads about 22 to 25°C (20°C = 68°F), normal room temperature. Examine the mercury column to see if the thread is broken—i.e., that the mercury column is continuous from the bulb up. Replace any flasks that have star-shaped cracks. Remember that porcelain apparatus with graduations and standard-taper joints are expensive; small-scale apparatus, Erlenmeyer flasks, beakers, test-tubes, and reaction tubes are, by comparison, fairly cheap.

Washing and Drying Laboratory Equipment

Clean apparatus immediately

Considerable time can be saved by cleaning each piece of equipment soon after use, for you will know at that point what contaminant is present and be able to select the proper method for removal. A residue is easier to remove before it has dried and hardened. A small amount of organic residue usually can be dissolved with a few milliliters of an appropriate organic solvent. Ethanol is a good solvent to try first. Acetone (bp 56.1°C) has greater solvent power and is often effective but is more expensive than ethanol. Because they are miscible with water and vaporize readily, they are easy to remove from the vessel. Cleaning after an operation often can be carried out while another experiment is in process.

Both ethanol and acetone are very flammable

A *polyethylene bottle* (Fig. 1.15l) is a convenient wash bottle for acetone. The name, symbol, or formula of a solvent can be written on a bottle with a Magic Marker or wax pencil. For large-scale crystallizations, extractions, and reaction solvents, it is convenient to have a bottle for each frequently used solvent—95% ethanol, ligroin [hexane(s)], dichloromethane, and *tert*-butyl methyl ether. A pinhole opposite the spout, which is covered with the finger in use, will prevent the spout from dribbling the solvent. For microscale work, these solvents are best dispensed from 25- or 50-mL bottles with an attached test tube containing a graduated (1-mL) polyethylene pipette (Fig. 1.17 on page 15).

Pasteur pipettes (see Figs. 1.4 and 1.15d) are very useful for transferring small quantities of liquid, adding reagents dropwise, and carrying out crystallizations. Surprisingly, the cost of the solvent used to clean a Pasteur pipette is often more than the cost of the pipette! Used pipettes should be disposed of in