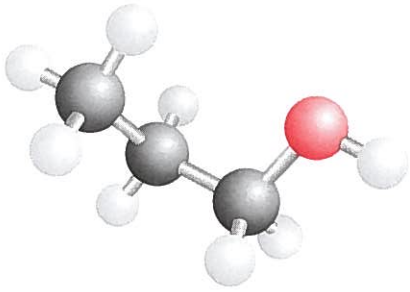
CHAPTER

7



Extraction

Online Study Center

This icon will direct you to techniques, equipment setups, and online resources at http://college.hmco.com/PIC/williamsonMMOE5e.

PRELAB EXERCISE: Describe how to separate a mixture of 3-toluic acid and 4'-aminoacetophenone using acid-base liquid/liquid extraction. What species will end up in the aqueous layer if you mix a solution of benzoic acid and aniline in ether with a solution of $NaHCO_3$ (aq)? Draw the structure of this species.

Extraction is one of the oldest chemical operations known to humankind. The preparation of a cup of coffee or tea involves the extraction of flavor and odor components from dried vegetable matter with hot water. Aqueous extracts of bay leaves, stick cinnamon, peppercorns, and cloves, along with alcoholic extracts of vanilla and almond, are used as food flavorings. For the past 150 years or so, organic chemists have extracted, isolated, purified, and characterized the myriad compounds produced by plants that for centuries have been used as drugs and perfumes—substances such as quinine from cinchona bark, morphine from the opium poppy, cocaine from coca leaves, and menthol from peppermint oil. The extraction of compounds from these natural products is an example of solid/liquid extraction—the solid being the natural product and the liquid being the solvent into which the compounds are extracted. In research, a Soxhlet extractor (Fig. 7.1) is often used for solid/liquid extraction.

Although solid/liquid extraction is the most common technique for brewing beverages and isolating compounds from natural products, liquid/liquid extraction is a very common method used in the organic laboratory, specifically when isolating reaction products. Reactions are typically homogeneous liquid mixtures and can therefore be extracted with either an organic or aqueous solvent. Organic reactions often yield a number of byproducts—some inorganic and some organic. Also, because some organic reactions do not go to 100% completion, a small amount of starting material is present at the end of the reaction. When a reaction is complete, it is necessary to do a *workup*, that is, separate and purify the desired product from the mixture of byproducts and residual starting material. Liquid/liquid extraction is a common separation step in this workup, which is then followed by

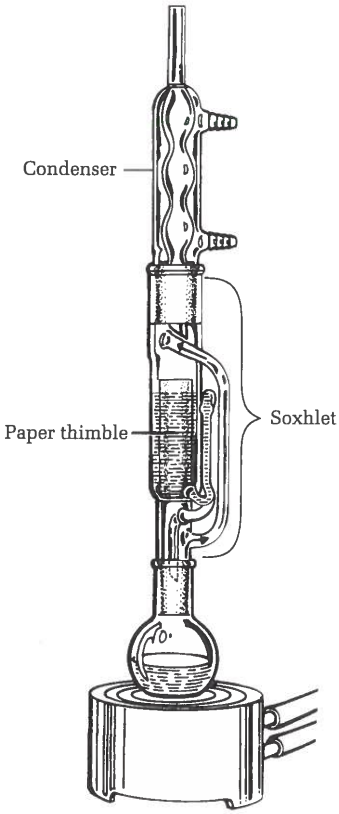
purification of the product. There are two types of liquid/liquid extraction: neutral and acid/base. The experiments in this chapter demonstrate solid/liquid extraction and the two types of liquid/liquid extraction.

Organic products are often separated from inorganic substances in a reaction mixture by liquid/liquid extraction with an organic solvent. For example, in the synthesis of 1-bromobutane (*see* Chapter 16), 1-butanol, also a liquid, is heated with an aqueous solution of sodium bromide and sulfuric acid to produce the product and sodium sulfate.

$$2\ CH_3CH_2CH_2CH_2OH + 2\ NaBr + H_2SO_4 \rightarrow 2\ CH_3CH_2CH_2CH_2Br + 2\ H_2O + Na_2SO_4$$

The 1-bromobutane is isolated from the reaction mixture by extraction with *t*-butyl methyl ether, an organic solvent in which 1-bromobutane is soluble and in which water and sodium sulfate are insoluble. The extraction is accomplished by simply adding *t*-butyl methyl ether to the aqueous mixture and shaking it. Two layers will result: an organic layer and an aqueous layer. The *t*-butyl methyl ether is less dense than water and floats on top; it is easily removed/drained away from the water layer and evaporated to leave the bromo product free of inorganic substances, which reside in the aqueous layer.

■ FIG. 7.1
The Soxhlet extractor for the extraction of solids such as dried leaves or seeds. The solid is put in a filter paper thimble. Solvent vapor rises in the tube on the right; condensate drops onto the solid in the thimble, leaches out soluble material, and, after initiating an automatic siphon, carries it to the flask where nonvolatile extracted material accumulates. Substances of low solubility can be extracted by prolonged operation.



Partition Coefficient

The extraction of a compound such as 1-butanol, which is slightly soluble in water as well as very soluble in ether, is an equilibrium process governed by the solubilities of the alcohol in the two solvents. The ratio of the solubilities is known as the *distribution coefficient*, also called the *partition coefficient* (k), and is an equilibrium constant with a certain value for a given substance, pair of solvents, and temperature.

The *concentration* of the solute in each solvent can be well correlated with the *solubility* of the solute in the pure solvent, a figure that is readily found in solubility tables in reference books. For substance C

$$k = \frac{\text{concentration of C in } t\text{-butyl methyl ether}}{\text{concentration of C in water}}$$

$$> \frac{\text{solubility of C in } t\text{-butyl methyl ether (g/100 mL)}}{\text{solubility of C in water (g/100 mL)}}$$

Consider compound A that dissolves in *t*-butyl methyl ether to the extent of 12 g/100 mL and dissolves in water to the extent of 6 g/100 mL.

$$k = \frac{12\text{ g/100 mL } t\text{-butyl methyl ether}}{6\text{ g/100 mL water}} = 2$$

If a solution of 6 g of A in 100 mL of water is shaken with 100 mL of *t*-butyl methyl ether, then

$$k = \frac{x \text{ g of A/100 mL } t\text{-butyl methyl ether}}{6 - x \text{ g of A/100 mL water}}$$

from which

$$x = 4.0 \text{ g of A in the ether layer}$$
$$6 - x = 2.0 \text{ g of A left in the water layer}$$

It is, however, more efficient to extract the 100 mL of aqueous solution twice with 50-mL portions of *t*-butyl methyl ether rather than once with a 100-mL portion.

$$k = \frac{x \text{ g of A/50 mL}}{6 - x \text{ g of A/100 mL}} = 2$$

from which

$$x = 3.0 \text{ g of A in the } t\text{-butyl methyl ether layer}$$
$$6 - x = 3.0 \text{ g of A in the water layer}$$

If this 3.0 g/100 mL of water is extracted again with 50 mL of *t*-butyl methyl ether, we can calculate that 1.5 g of A will be in the ether layer, leaving 1.5 g in the water layer. So two extractions with 50-mL portions of ether will extract 3.0 g + 1.5 g = 4.5 g of A, whereas one extraction with a 100-mL portion of *t*-butyl methyl ether removes only 4.0 g of A. Three extractions with 33-mL portions of *t*-butyl methyl ether would extract 4.7 g. Obviously, there is a point at which the increased amount of A extracted does not repay the effort of multiple extractions, but remember that several small-scale extractions are more effective than one large-scale extraction.

Properties of Extraction Solvents

Liquid/liquid extraction involves two layers: the organic layer and the aqueous layer. The solvent used for extraction should possess many properties, including the following:

- It should readily dissolve the substance to be extracted at room temperature.
- It should have a low boiling point so that it can be removed readily.
- It should not react with the solute or the other solvent.
- It should not be highly flammable or toxic.
- It should be relatively inexpensive.

In addition, it should not be miscible with water (the usual second phase). No solvent meets every criterion, but several come close. Some common liquid/liquid

TABLE 7.1 • Common Solvents Listed by Density

Solvent	Density (g/mL)
Hexane	0.695
Diethyl ether	0.708
t-Butyl methyl ether	0.740
Toluene	0.867
Water	1.000
Dichloromethane	1.325
Chloroform	1.492

extraction solvent pairs are water-ether, water-dichloromethane, and water-hexane. Notice that each combination includes water because most organic compounds are immiscible in water and therefore can be separated from inorganic compounds. Organic solvents such as methanol and ethanol are not good extraction solvents because they are soluble in water.

Identifying the Layers

One common mistake when performing an extraction is to misidentify the layers and discard the wrong one. It is good practice to save all layers until the desired product is in hand. The densities of the solvents will predict the identities of the top and bottom layers. In general, the densities of nonhalogenated organic solvents are less than 1.0 g/mL and those of halogenated solvents are greater than 1.0 g/mL. Table 7.1 lists the densities of common solvents used in extraction.

Although density is the physical property that determines which layer is on top or on bottom, a very concentrated amount of solute dissolved in either layer can reverse the order. The best method to avoid a misidentification is to perform a drop test. Add a few drops of water to the layer in question and watch the drop carefully. If the layer is water, then the drop will mix with the solution. If the solvent is the organic layer, then the water drop will create a second layer.

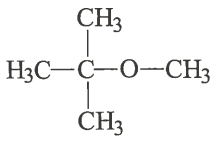
Identify layers by a drop test.

Ethereal Extraction Solvents

$CH_3CH_2—O—CH_2CH_3$

Diethyl ether
"Ether"
MW 74.12, den. 0.708
bp 34.6°C, n_D^{20} 1.3530

In the past, diethyl ether was the most common solvent for extraction in the laboratory. It has high solvent power for hydrocarbons and oxygen-containing compounds. It is highly volatile (bp 34.6°C) and is therefore easily removed from an extract. However, diethyl ether has two big disadvantages: it is highly flammable and poses a great fire threat, and it easily forms peroxides. The reaction of diethyl ether with air is catalyzed by light. The resulting peroxides are higher boiling than the ether and are left as a residue when the ether evaporates. If the residue is heated, it will explode because ether peroxides are treacherously high explosives. In recent years, a new solvent has come on the scene—*tert*-butyl methyl ether.



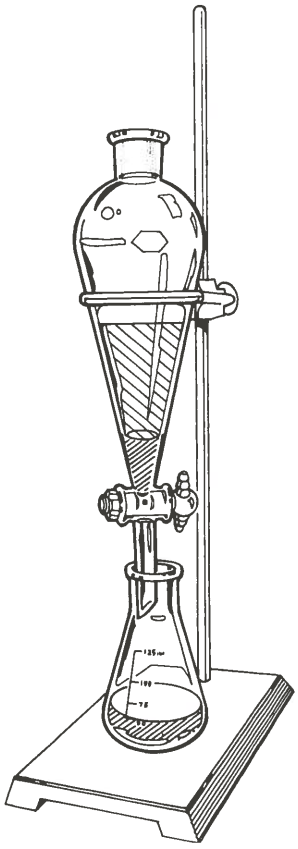
***tert*-Butyl methyl ether**
MW 88.14, den. 0.741
bp 55.2°C, n_D^{20} 1.369

tert-Butyl methyl ether, called methyl *tert*-butyl ether (MTBE) in industry, has many advantages over diethyl ether as an extraction solvent. Most important, it does not easily form peroxides, so it can be stored for much longer periods than diethyl ether. And, in the United States, it is less than two-thirds the price of diethyl ether. It is slightly less volatile (bp 55°C), so it does not pose the same fire threat as diethyl ether, although one must be as careful in handling this solvent as in handling any other highly volatile, flammable substance. The explosion limits for *t*-butyl methyl ether mixed with air are much narrower than for diethyl ether, the toxicity is less (it is not a carcinogen), the solvent power is the same, and the ignition temperature is higher (224°C versus 180°C).

The weight percent solubility of diethyl ether dissolved in water is 7.2%, whereas that of *t*-butyl methyl ether is 4.8%. The solubility of water in diethyl ether is 1.2%, while in *t*-butyl methyl ether it is 1.5%. Unlike diethyl ether, *t*-butyl methyl ether forms an azeotrope with water (4% water) that boils at 52.6°C. This means that evaporation of any *t*-butyl methyl ether solution that is saturated with water should leave no water residue, unlike diethyl ether.

The low price and ready availability of *t*-butyl methyl ether came about because it replaced tetraethyl lead as the antiknock additive for high-octane gasoline and as a fuel oxygenate, which helps reduce air pollution, but its water solubility has allowed it to contaminate drinking water supplies in states where leaking underground fuel storage tanks are not well regulated. Consequently, it is being replaced with the much more expensive ethanol. In this text, *t*-butyl methyl ether is *strongly* suggested wherever diethyl ether formerly would have been used in an extraction. It will not, however, work as the only solvent in the Grignard reaction, probably because of steric hindrance. So whenever the word *ether* appears in this text as an extraction solvent, it is suggested that *t*-butyl methyl ether be used and not diethyl ether.

■ FIG. 7.2
A separatory funnel with Teflon stopcock.



Mixing and Separating the Layers

For microscale separations, mixing and separating the layers with a pipette normally incurs very little product loss. Because the two solvents are typically in a reaction tube for microscale extraction, the two layers can be mixed by drawing up and rapidly expelling them with a pipette. Then the layers are allowed to separate, and the bottom layer is separated by drawing it up into a pipette and transferring it to a different container.

For macroscale separations, a separatory funnel (Fig. 7.2) is used to mix and separate the organic and aqueous layers. In macroscale experiments, a frequently used method of working up a reaction mixture is to dilute the mixture with water and extract it with an organic solvent, such as ether, in a separatory funnel. When the stoppered funnel is shaken to distribute the components between the immiscible solvents *t*-butyl methyl ether and water, pressure always develops through volatilization of ether from the heat of the hands, and liberation of a gas (CO_2) (in acid/base extractions) can increase the pressure. Consequently, the funnel is grasped so that the stopper is held in place by one hand



FIG. 7.3
The correct position for holding a separatory funnel when shaking. Point outlet away from yourself and your neighbors.

and the stopcock by the other, as illustrated in Figure 7.3. After a brief shake or two, the funnel is held in the inverted position shown, and the stopcock is opened cautiously (with the funnel stem pointed away from nearby persons) to release pressure. The mixture can then be shaken more vigorously, with pressure released as necessary. When equilibration is judged to be complete, the slight, constant terminal pressure due to ether is released, the stopper is rinsed with a few drops of ether delivered by a Pasteur pipette, and the layers are allowed to separate. The organic reaction product is distributed wholly or largely into the upper ether layer, whereas inorganic salts, acids, and bases pass into the water layer, which can be drawn off. If the reaction was conducted in alcohol or some other water-soluble solvent, the bulk of the solvent is removed in the water layer, and the remainder can be eliminated in two or three washings with 1–2 volumes of water conducted with the techniques used in the first equilibration. The separatory funnel should be supported in a ring stand, as shown in Figure 7.2.

Before adding a liquid to the separatory funnel, check the stopcock. If it is glass, see that it is properly greased, bearing in mind that too much grease will clog the hole in the stopcock and also contaminate the extract. If the stopcock is Teflon, see that it is adjusted to a tight fit in the bore. Store the separatory funnel with the Teflon stopcock loosened to prevent sticking. Because Teflon has a much larger temperature coefficient of expansion than glass, a stuck stopcock can be loosened by cooling the stopcock in ice or dry ice. Do not store liquids in the separatory funnel; they often leak or cause the stopper or stopcock to freeze. To have sufficient room for mixing the layers, fill the separatory funnel no more than three-fourths full. Withdraw the lower layer from the separatory funnel through the stopcock and pour the upper layer out through the neck.

All too often the inexperienced chemist discards the wrong layer when using a separatory funnel. Through incomplete neutralization, a desired component may still remain in the aqueous layer, or the densities of the layers may change. Cautious workers save all layers until the desired product has been isolated. The organic layer is not always the top layer. If in doubt, perform a drop test by adding a few drops of each to water in a test tube.

Practical Considerations When Mixing Layers

Pressure Buildup

The heat of one's hand or heat from acid/base reactions will cause pressure buildup in an extraction mixture that contains a very volatile solvent such as dichloromethane. The extraction container—whether a test tube or a separatory funnel—must be opened carefully to vent this pressure.

Sodium bicarbonate solution is often used to neutralize acids when carrying out acid/base extractions. The result is the formation of carbon dioxide, which can cause foaming and high pressure buildup. Whenever bicarbonate is used, add it very gradually with thorough mixing and frequent venting of the extraction device. If a large amount of acid is to be neutralized with bicarbonate, the process should be carried out in a beaker.

Emulsions

Imagine trying to extract a soap solution (e.g., a nonfoaming dishwashing detergent) into an organic solvent. After a few shakes with an organic solvent, you would have an absolutely intractable emulsion. An emulsion is a suspension of one liquid as droplets in another. Detergents stabilize emulsions, and so any time a detergent-like molecule is in the material being extracted, there is the danger that emulsions will form. Substances of this type are commonly found in nature, so one must be particularly wary of emulsion formation when creating organic extracts of aqueous plant material, such as caffeine from tea. Emulsions, once formed, can be quite stable. You would be quite surprised to open your refrigerator one morning and see a layer of clarified butter floating on the top of a perfectly clear aqueous solution that had once been milk, but milk is the classic example of an emulsion.

Prevention is the best cure for emulsions. This means shaking the solution to be extracted *very gently* until you see that the two layers will separate readily. If a bit of emulsion forms, it may break simply on standing for a sufficient length of time. Making the aqueous layer highly ionic will help. Add as much sodium chloride as will dissolve and shake the mixture gently. Vacuum filtration sometimes works and, when the organic layer is the lower layer, filtration through silicone-impregnated filter paper is helpful. Centrifugation works very well for breaking emulsions. This is easy on a small scale, but often the equipment is not available for large-scale centrifugation of organic liquids.

Shake gently to avoid emulsions.

Drying Agents

The organic solvents used for extraction dissolve not only the compound being extracted but also water. Evaporation of the solvent then leaves the desired compound contaminated with water. At room temperature water dissolves 4.8% of *t*-butyl methyl ether by weight, and the ether dissolves 1.5% of water. But ether is virtually insoluble in water saturated with sodium chloride (36.7 g/100 mL). If ether that contains dissolved water is shaken with a saturated aqueous solution of sodium chloride, water will be transferred from the *t*-butyl methyl ether to the aqueous layer. So, strange as it may seem, ethereal extracts are routinely dried by shaking them with an aqueous saturated sodium chloride solution.

Solvents such as dichloromethane do not dissolve nearly as much water and are therefore dried over a chemical drying agent. Many choices of chemical drying agents are available for this purpose, and the choice of which one to use is governed by four factors: (1) the possibility of reaction with the substance being extracted, (2) the speed with which it removes water from the solvent, (3) the efficiency of the process, and (4) the ease of recovery from the drying agent.

Some very good but specialized and reactive drying agents are potassium hydroxide, anhydrous potassium carbonate, sodium metal, calcium hydride, lithium aluminum hydride, and phosphorus pentoxide. Substances that are essentially neutral and unreactive and are widely used as drying agents include anhydrous calcium sulfate (Drierite), magnesium sulfate, molecular sieves, calcium chloride, and sodium sulfate.

Drierite, $CaSO_4$

Drierite, a specially prepared form of calcium sulfate, is a fast and effective drying agent. However, it is difficult to ascertain whether enough has been used.

An indicating type of Drierite is impregnated with cobalt chloride, which turns from blue to red when it is saturated with water. This works well when gases are being dried, but it should not be used for liquid extractions because the cobalt chloride dissolves in many protic solvents.

Magnesium sulfate, $MgSO_4$

Magnesium sulfate is also a fast and fairly effective drying agent, but it is so finely powdered that it always requires careful filtration for removal.

Molecular sieves, zeolites

Molecular sieves are sodium alumino-silicates (zeolites) that have well-defined pore sizes. The 4 Å size adsorbs water to the exclusion of almost all organic substances, making them a fast and effective drying agent. Like Drierite, however, it is impossible to ascertain by appearance whether enough has been used. Molecular sieves in the form of 1/16-in. pellets are often used to dry solvents by simply adding them to the container.

Calcium chloride ($CaCl_2$) pellets are the drying agent of choice for small-scale experiments.

Calcium chloride, recently available in the preferred form of pellets (4 to 80 mesh[1]), is a very fast and effective drying agent. It has the advantage that it clumps together when excess water is present, which makes it possible to know how much to add by observing its behavior. Unlike the older granular form, the pellets do not disintegrate into a fine powder. These pellets are admirably suited to microscale experiments where the solvent is removed from the drying agent with a Pasteur pipette. Calcium chloride is much faster and far more effective than anhydrous sodium sulfate; after much experimentation, we have decided that this is the agent of choice, particularly for microscale experiments. These pellets are used for most of the drying operations in this text. Note, however, that calcium chloride reacts with some alcohols, phenols, amides, and some carbonyl-containing compounds. Advantage is sometimes taken of this property to remove not only water from a solvent but also, for example, a contaminating alcohol (*see* Chapter 16—the synthesis of 1-bromobutane from 1-butanol). Because *t*-butyl methyl ether forms an azeotrope with water, its solutions should, theoretically, not need to be dried; evaporation carries away the water. Drying these ether solutions with calcium chloride pellets removes water droplets that get carried into the ether solution.

Sodium sulfate, Na_2SO_4

Sodium sulfate is a very poor drying agent. It has a very high capacity for water but is slow and not very efficient in the removal of water. Like calcium chloride pellets, it clumps together when wet, and solutions are easily removed from it using a Pasteur pipette. Sodium sulfate has been used extensively in the past and should still be used for compounds that react with calcium chloride.

PART 1: The Technique of Neutral Liquid/Liquid Extraction

The workup technique of liquid/liquid extraction has four steps: (1) mixing the layers, (2) separating the layers, (3) drying the organic layer, and (4) removing the solvent. The microscale neutral liquid/liquid extraction technique is described in the following sections.

1. These pellets are available from Fisher Scientific, Cat. No. C614–3.

Step 1. Mixing the Layers

Once the organic and aqueous layers are in contact with one another, mixing is required to ensure that the desired compound(s) get extracted into the desired layer. First, place 1–2 mL of an aqueous solution of the compound to be extracted in a reaction tube. Add about 1 mL of extraction solvent, for example, dichloromethane. Note, as you add the dichloromethane, whether it is the top or the bottom layer. (Since dichloromethane is more dense than water, predict what layer it will be.) An effective way to mix the two layers is to flick the tube with a finger. Grasp the tube firmly at the very top between the thumb and forefinger and flick it vigorously at the bottom (Fig. 7.4). You will find that this violent motion mixes the two layers well, but nothing comes out the top. Another good mixing technique is to pull the contents of the reaction tube into a Pasteur pipette and then expel the mixture back into the tube with force. Doing this several times will effect good mixing of the two layers. A stopper can be placed in the top of the tube, and the contents can be mixed by shaking the tube, but the problem with this technique is that the high vapor pressure of the solvent will often force liquid out around the cork or stopper.

Step 2. Separating the Layers

Always draw out the lower layer and place it in another container.

After thoroughly mixing the two layers, allow them to separate. Tap the tube if droplets of one layer are in the other layer or on the side of the tube. After the layers separate completely, draw up the lower dichloromethane layer into a Pasteur pipette. Leave behind any middle emulsion layer. The easiest way to do this is to attach the pipette to a pipette pump (Fig. 7.5). This allows very precise control of the liquid being removed. It takes more skill and practice to remove the lower layer cleanly with a 2-mL rubber bulb attached to a pipette because the high vapor pressure of the solvent tends to make it dribble out. To avoid losing any of the solution, it is best to hold a clean, dry, empty tube in the same hand as the full tube to receive the organic layer (Fig. 7.6).

From the discussion of the partition coefficient, you know that several small extractions are better than one large one, so repeat the extraction process with two further 1-mL portions of dichloromethane. An experienced chemist might summarize all the preceding with the following notebook entry, "Aqueous layer extracted 3 × 1-mL portions CH_2Cl_2," and in a formal report would write, "The aqueous layer was extracted three times with 1-mL portions of dichloromethane."

If you are working on a larger microscale, a microscale separatory funnel (Fig. 7.7) should be used. A separatory funnel, regardless of size, should be filled to only about two-thirds of its capacity so the layers can be mixed by shaking. The microscale separatory funnel has a capacity of 8.5 mL when full, so it is useful for an extraction with a total volume of about 6 mL.

Use a wood boiling stick to poke out the polyethylene frit from the bottom part of the separatory funnel. Store it for later replacement. Close the valve, add up to 5 mL of the solution to be extracted to the separatory funnel, then add the extraction solvent so that the total volume does not exceed 6 mL.

FIG. 7.4
Mixing the contents of a reaction tube by flicking it. Grasp the tube firmly at the very top and flick it vigorously at the bottom. The contents will mix without coming out of the tube.

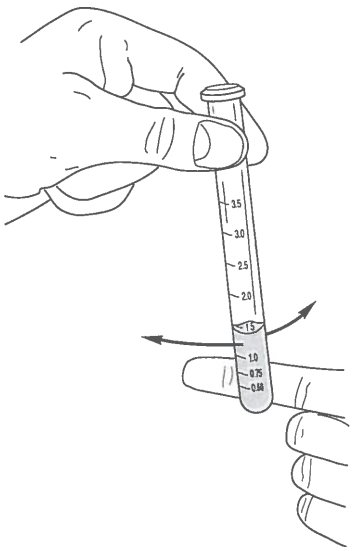


FIG. 7.5
The removal of a solvent from a reaction tube with a pipette and pipette pump.

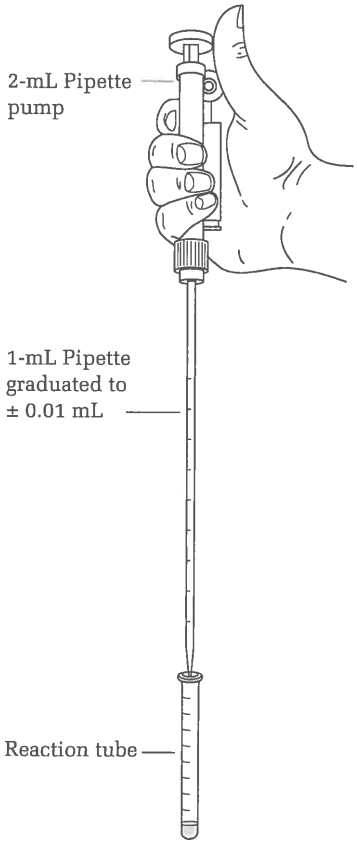
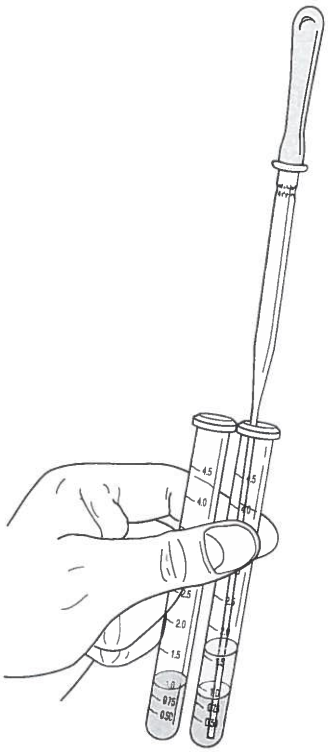


FIG. 7.6
Grasp both reaction tubes in one hand when transferring material from one tube to another with a Pasteur pipette.



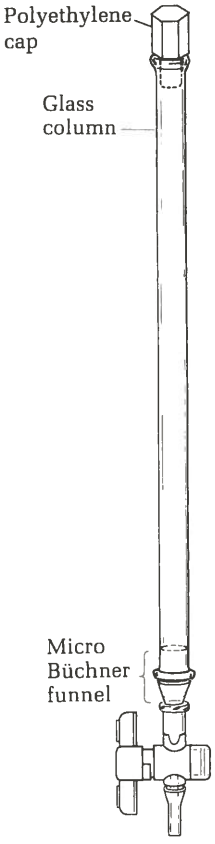
Cap the separatory funnel and mix the contents by inverting the funnel several times. If the two layers separate fairly easily, then the contents can be shaken more thoroughly. If the layers do not separate easily, be careful not to shake the funnel too vigorously because intractable emulsions could form.

Remove the stopper from the funnel, clamp it, and then, grasping the valve with two hands, empty the bottom layer into an Erlenmeyer flask or other container. If the top layer is desired, pour it out through the top of the separatory funnel—don't drain it through the valve, which may have a drop of the lower layer remaining in it.

Step 3. Drying the Organic Layer

Dichloromethane dissolves a very small quantity of water, and microscopic droplets of water are suspended in the organic layer, often making it cloudy. To remove the water, a drying agent, for example, anhydrous calcium chloride pellets, is added to the dichloromethane solution.

■ **FIG. 7.7**
A microscale separatory funnel. Remove the polyethylene frit from the micro Büchner funnel before using.



Record the tare of the final container.

How Much Drying Agent Should Be Used?

When a small quantity of the drying agent is added, the crystals or pellets become sticky with water, clump together, and fall rapidly as a lump to the bottom of the reaction tube. There will come a point when a new small quantity of drying agent no longer clumps together, but the individual particles settle slowly throughout the solution. As they say in Scandinavia, "Add drying agent until it begins to snow." The drying process takes about 10–15 min, during which time the tube contents should be mixed occasionally by flicking the tube. The solution should no longer be cloudy but clear (although it may be colored).

Once drying is judged complete, the solvent is removed by forcing a Pasteur pipette to the bottom of the reaction tube and pulling the solvent in. Air is expelled from the pipette as it is being pushed through the crystals or pellets so that no drying agent will enter the pipette. It is very important to wash the drying agent left in the reaction tube with several small quantities of pure solvent to transfer all the extract.

Step 4. Removing the Solvent

If the quantity of extract is relatively small, say 3 mL or less, then the easiest way to remove the solvent is to blow a stream of air (or nitrogen) onto the surface of the solution from a Pasteur pipette (Fig. 7.8). Be sure that the stream of air is very gentle before inserting it into the reaction tube. The heat of vaporization of the solvent will cause the tube to become rather cold during the evaporation and, of course, slow down the process. The easiest way to add heat is to hold the tube in your hand.

Another way to remove the solvent is to attach the Pasteur pipette to an aspirator and pull air over the surface of the liquid. This is not quite as fast as blowing air onto the surface of the liquid and runs the danger of sucking up the liquid into the aspirator.

If the volume of liquid is more than about 3 mL, put it into a 25-mL filter flask, put a plastic Hirsch funnel in place, and attach the flask to the aspirator. By placing your thumb in the Hirsch funnel, the vacuum can be controlled, and heat can be applied by holding the flask in the other hand while swirling the contents (Fig. 7.9).

The reaction tube or filter flask in which the solvent is evaporated should be tared (weighed empty), and this weight recorded in your notebook. In this way, the weight of material extracted can be determined by again weighing the container.

EXPERIMENT



Partition Coefficient of Benzoic Acid

IN THIS EXPERIMENT you will shake a solution of benzoic acid in water with the immiscible solvent dichloromethane. The benzoic acid will distribute (partition) itself between the two layers. By removing the organic layer, drying, and evaporating it, the weight of benzoic acid in the dichloromethane can be determined and thus the ratio in the two layers. This ratio is a constant known as the partition coefficient.

FIG. 7.8
An aspirator tube being used to remove solvent vapors.

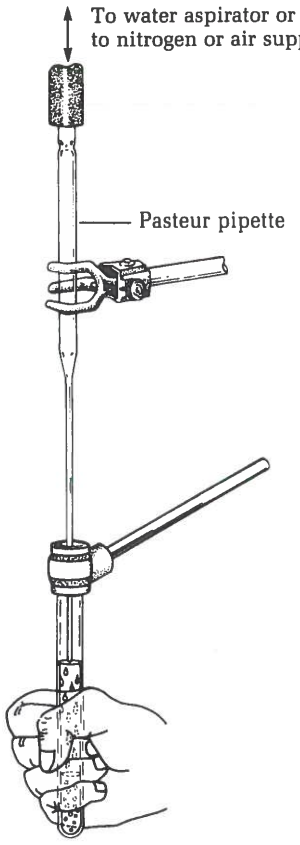
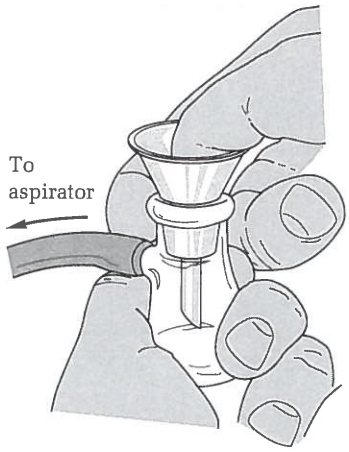


FIG. 7.9
The apparatus for removing a solvent under vacuum.



In a reaction tube, place about 100 mg of benzoic acid (weighed to the nearest milligram) and add exactly equal volumes of water followed by dichloromethane (about 1.6 mL each). While making this addition, note which layer is organic and which is aqueous. Put a septum on the tube and shake the contents vigorously for at least 2 min. Allow the tube to stand undisturbed until the layers separate and then carefully draw off, using a Pasteur pipette, *all* of the aqueous layer without removing any of the organic layer. It may be helpful to draw out the tip of the pipette to a fine point in a flame and, using this, to tilt the reaction tube on its side to make this separation as clean as possible.

Add anhydrous calcium chloride pellets to the dichloromethane in very small quantities until it no longer clumps together. Mix the contents of the tube by flicking it and allow it to stand for about 5 min to complete the drying process. Using a dry Pasteur pipette, transfer the dichloromethane to a tared dry reaction tube or a 10-mL Erlenmeyer flask containing a boiling chip. Complete the transfer by washing the drying agent with two more portions of solvent that are added to the original solution and then evaporate the solvent. This can be done by boiling off the solvent while removing solvent vapors with an aspirator tube or by blowing a

stream of air or nitrogen into the container while warming it in one's hand (*see* Fig. 7.8). This operation should be performed in a hood.

From the weight of the benzoic acid in the dichloromethane layer, the weight in the water layer can be obtained by difference. The ratio of the weight in dichloromethane to the weight in water is the distribution coefficient because the volumes of the two solvents were equal. Report the value of the distribution coefficient in your notebook.

Cleaning Up. The aqueous layer can be flushed down the drain. Dichloromethane goes into the halogenated organic solvents container. After allowing the solvent to evaporate from the sodium sulfate in the hood, place the sodium sulfate in the nonhazardous solid waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container.

Part 2: Acid/Base Liquid/Liquid Extraction

Acid/base liquid/liquid extraction involves carrying out simple acid/base reactions to separate strong organic acids, weak organic acids, neutral organic compounds, and basic organic substances. The chemistry involved is given in the following equations, using benzoic acid, phenol, naphthalene, and aniline as examples of the four types of compounds.

Here is the strategy (refer to the flow sheet in Fig. 7.10): The four organic compounds are dissolved in *t*-butyl methyl ether. The ether solution is shaken with a saturated aqueous solution of sodium bicarbonate, a weak base. This will react only with the strong acid, benzoic acid (**1**), to form the ionic salt, sodium benzoate (**5**), which dissolves in the aqueous layer and is removed. The ether solution now contains just phenol (**2**), naphthalene (**4**), and aniline (**3**). A 3 *M* aqueous solution of sodium hydroxide is added, and the mixture is shaken. The hydroxide, a strong base, will react only with the phenol (**2**), a weak acid, to form sodium phenoxide (**6**), an ionic compound that dissolves in the aqueous layer and is removed. The ether now contains only naphthalene (**4**) and aniline (**3**). Shaking it with dilute hydrochloric acid removes the aniline, a base, as the ionic anilinium chloride (**7**). The aqueous layer is removed. Evaporation of the *t*-butyl methyl ether now leaves naphthalene (**4**), the neutral compound. The other three compounds are recovered by adding acid to the sodium benzoate (**5**) and sodium phenoxide (**6**) and base to the anilinium chloride (**7**) to regenerate the covalent compounds benzoic acid (**1**), phenol (**2**), and aniline (**3**).

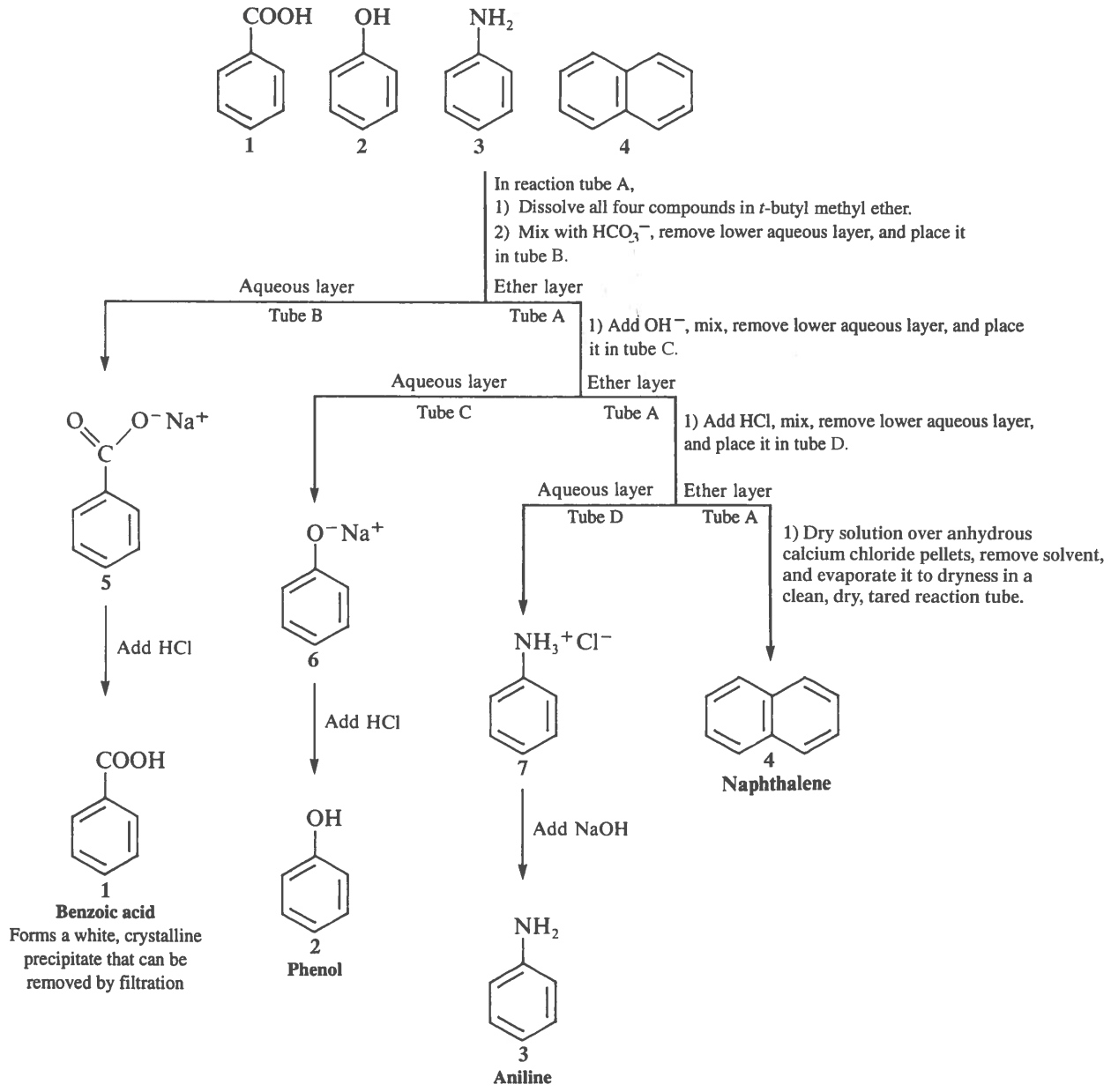
The pK_a of carbonic acid, H_2CO_3, is 6.35.

The ability to separate strong acids from weak acids depends on the acidity constants of the acids and the basicity constants of the bases. In the first equation consider the ionization of benzoic acid, which has an equilibrium constant (K_a) of 6.8×10^{25}. The conversion of benzoic acid to the benzoate anion in equation 4 is governed by the equilibrium constant, K (equation 5), obtained by combining equations 3 and 4.

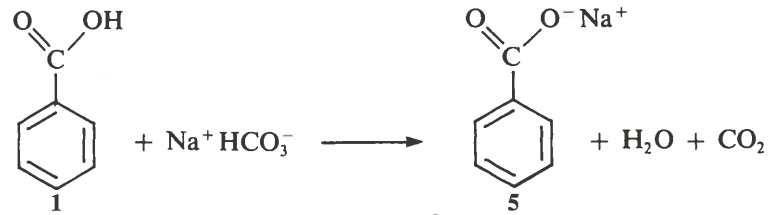
$$C_6H_5COOH + H_2O \rightleftharpoons C_6H_5COO^- + H_3O^+ \quad (1)$$

$$K_a = \frac{[C_6H_5COO^-][H_3O^+]}{[C_6H_5COOH]} = 6.8 \times 10^{-5},\ pK_a = 4.17 \quad (2)$$

■ FIG. 7.10
A flow sheet for the separation of a strong acid, a weak acid, a neutral compound, and a base: benzoic acid, phenol, naphthalene, and aniline (this page). Acid/base reactions of the acidic and basic compounds (opposite page).

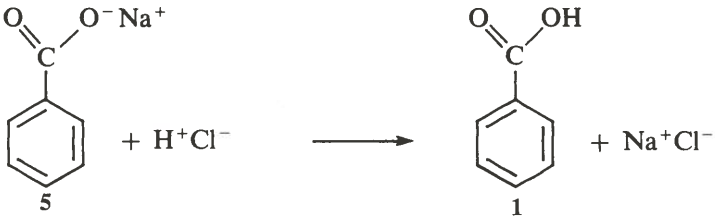


Phenol and aniline each form oily layers on top of the aqueous layer. Extract each with *t*-butyl methyl ether: Add ether to the tube, mix, separate layers, dry the ether layer over anhydrous calcium chloride pellets, remove solution from drying agent, and evaporate the solvent.

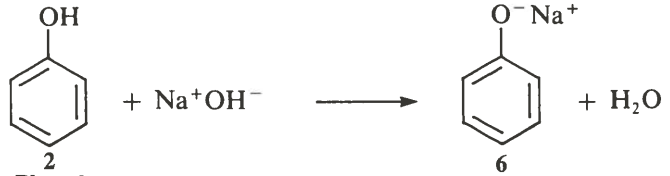


1
Benzoic acid
pK_a = 4.17
Covalent, sol. in org. solvents

5
Sodium benzoate
Ionic, sol. in water



5 1

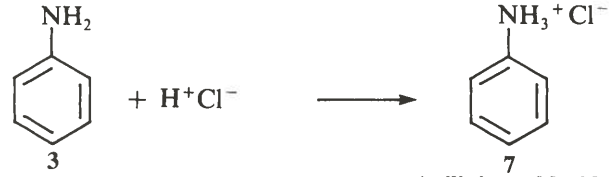


2
Phenol
pK_a = 10
Covalent, sol. in org. solvents

6
Sodium phenoxide
Ionic, sol. in water



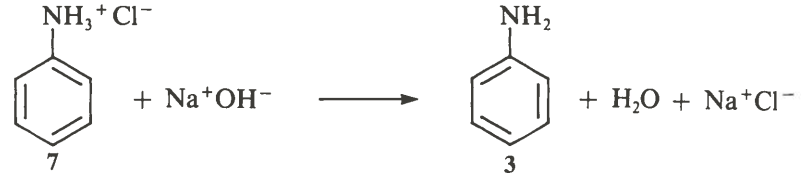
6 2



3 7

3
Aniline
pK_b = 9.30
Covalent, sol. in org. solvents

7
Anilinium chloride
Ionic, sol. in water



7 3

$$K_w = [H_3O^+][OH^-] = 10^{-14} \quad (3)$$

$$C_6H_5COOH + OH^- \rightleftharpoons C_6H_5COO^- + H_2O \quad (4)$$

$$K = \frac{[C_6H_5COO^-]}{[C_6H_5COOH][OH^-]} = \frac{K_a}{K_w} = \frac{6.8 \times 10^{-5}}{10^{-14}} = 3.2 \times 10^8 \quad (5)$$

If 99% of the benzoic acid is converted to $C_6H_5COO^-$,

$$\frac{[C_6H_5COO^-]}{[C_6H_5COOH]} = \frac{99}{1} \quad (6)$$

then from equation 5 the hydroxide ion concentration would need to be 6.8×10^{-7} *M*. Because saturated $NaHCO_3$ has $[OH^- = 3 \times 10^{-4}$ *M*, the hydroxide ion concentration is high enough to convert benzoic acid completely to sodium benzoate.

For phenol, with a K_a of 10^{-10}, the minimum hydroxide ion concentration that will produce the phenoxide anion in 99% conversion is 10^{-2} *M*. The concentration of hydroxide in 10% sodium hydroxide solution is 10^{-1} *M*, and so phenol in strong base is entirely converted to the water-soluble salt.

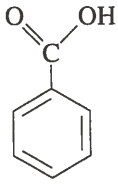
General Considerations

If acetic acid was used as the reaction solvent, it would also be distributed largely into the aqueous phase; if the reaction product is a neutral substance, however, the residual acetic acid in the ether can be removed by one washing with excess 5% sodium bicarbonate solution. If the reaction product is a higher molecular weight acid, for example, benzoic acid (C_6H_5COOH), it will stay in the ether layer, while acetic acid is being removed by repeated washing with water; the benzoic acid can then be separated from neutral byproducts by extraction with sodium bicarbonate or sodium hydroxide solution and acidification of the extract. Acids of high molecular weight are extracted only slowly by sodium bicarbonate, so sodium carbonate is used in its place; however, carbonate is more prone than bicarbonate to produce emulsions. Sometimes an emulsion in the lower layer can be settled by twirling the separatory funnel by its stem. An emulsion in the upper layer can be broken by grasping the funnel by the neck and swirling it. Because the tendency to emulsify increases with the removal of electrolytes and solvents, a little sodium chloride solution is added with each portion of wash water. If the layers are largely clear but an emulsion persists at the interface, the clear part of the water layer can be drawn off, and the emulsion run into a second funnel and shaken with fresh ether.

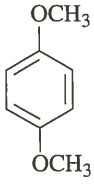
Liquid/liquid extraction and acid/base extraction are employed in the majority of organic reactions because it is unusual to have the product crystallize from the reaction mixture or to be able to distill the reaction product directly from the reaction mixture. In the research literature, one will often see the statement "the reaction mixture was worked up in the usual way," which implies an extraction process of the type described here. Good laboratory practice dictates, however, that the details of the process be written out.

EXPERIMENTS

1. Separation of a Carboxylic Acid, a Phenol, and a Neutral Substance

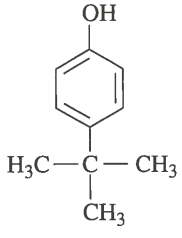


Benzoic acid
mp 123°C, pK_a 4.17



1,4-Dimethoxybenzene (Hydroquinone dimethyl ether)
mp 57°C

Online Study Center
Photo: Extraction with Ether;
Video: Extraction with Ether



4-*tert*-Butylphenol
mp 101°C, pK_a 10.17

A mixture of equal parts of a carboxylic acid, a phenol, and a neutral substance is to be separated by extraction from an ether solvent. Note carefully the procedure for this extraction. In the next experiment you are to work out your own extraction procedure. Your unknown will consist of either benzoic acid or 2-chlorobenzoic acid (the carboxylic acid), 4-*t*-butyl phenol or 4-bromophenol, and biphenyl or 1,4-dimethoxybenzene (the neutral substance). The object of this experiment is to identify the three substances in the mixture and to determine the percent recovery of each from the mixture.

Procedure

IN THIS EXPERIMENT three organic solids are separated by reaction with base followed by extraction. Bicarbonate converts carboxylic acids (but not phenols) to ions. Hydroxide ion converts phenols (as well as carboxylic acids) to ions. Ionic substances are soluble in water. The addition of hydrochloric acid to the aqueous ionic solutions regenerates nonionic substances. At each step you should ask yourself, "Have I converted a nonionic substance to an ionic one?" (or vice versa). The ionic substances will be in the aqueous layer; the nonionic ones will be in the organic layer.

Dissolve about 0.18 g of the mixture (record the exact weight) in 2 mL of *t*-butyl methyl ether or diethyl ether in a reaction tube (tube 1). Then add 1 mL of a saturated aqueous solution of sodium bicarbonate to the tube. Use the graduations on the side of the tube to measure the amounts because they do not need to be exact. Mix the contents of the tube thoroughly by pulling the two layers into a Pasteur pipette and expelling them forcefully into the reaction tube. Do this for about 3 min. Allow the layers to separate completely and then draw off the lower layer into another reaction tube (tube 2). Add another 0.15 mL of sodium bicarbonate solution to the tube, mix the contents as before, and add the lower layer to tube 2. Exactly which chemical species is in tube 2? Add 0.2 mL of ether to tube 2, mix it thoroughly, remove the ether layer, and discard it. This is called *backwashing* and serves to remove any organic material that might contaminate the contents of tube 2.

Add 1.0 mL of 3 *M* aqueous sodium hydroxide to tube 1, shake the mixture thoroughly, allow the layers to separate, draw off the lower layer using a clean Pasteur pipette, and place it in tube 3. Extract tube 1 with two 0.15-mL portions of water, and add these to tube 3. Backwash the contents of tube 3 with 0.15 mL of ether and discard the ether wash just as was done for tube 2. Exactly which chemical species is in tube 3?

To tube 1 add saturated sodium chloride solution, mix, remove the aqueous layer, and then add to the ether anhydrous calcium chloride pellets until the drying

agent no longer clumps together. Wash it off with ether after the drying process is finished. Allow 5–10 min for the drying of the ether solution.

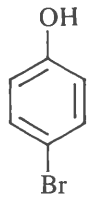
Using the concentration information given in the inside back cover of this book, calculate exactly how much concentrated hydrochloric acid is needed to neutralize the contents of tube 2. Then, by dropwise addition of concentrated hydrochloric acid, carry out this neutralization while testing the solution with litmus paper. An excess of hydrochloric acid does no harm. This reaction must be carried out with *extreme care* because much carbon dioxide is released in the neutralization. Add a boiling stick to the tube and very cautiously heat the tube to bring most of the solid carboxylic acid into solution. Allow the tube to cool slowly to room temperature and then cool it in ice. Remove the solvent with a Pasteur pipette and recrystallize the residue from boiling water. Again, allow the tube to cool slowly to room temperature and then cool it in ice. At the appropriate time, stir the crystals and collect them on a Hirsch funnel using the procedures detailed in Chapter 4. The crystals can be transferred and washed on the funnel using a small quantity of ice water. The solubility of benzoic acid in water is 1.9 g/L at 0°C and 68 g/L at 95°C. The solubility of chlorobenzoic acid is similar. Turn the crystals out onto a tared piece of paper, allow them to dry thoroughly, and determine the percent recovery of the acid. Assess the purity of the product by checking its melting point.



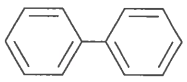
Add HCl with care; CO_2 is released.



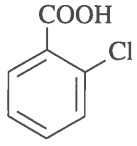
Videos: Filtration of Crystals Using the Pasteur Pipette, Microscale Filtration on the Hirsch Funnel



4-Bromophenol
mp 66°C, pK_a 10.2



Biphenyl
mp 71°C



2-Chlorobenzoic acid
mp 141°C, pK_a 2.92

In exactly the same way, neutralize the contents of tube 3 with concentrated hydrochloric acid. This time, of course, there will be no carbon dioxide evolution. Again, heat the tube to bring most of the material into solution, allow it to cool slowly, remove the solvent, and recrystallize the phenol from boiling water. At the appropriate time, after the product has cooled slowly to room temperature and then in ice, it is also collected on a Hirsch funnel, washed with a very small quantity of ice water, and allowed to dry. The percent recovery and melting point are determined.

The neutral compound is recovered using the Pasteur pipette to remove the ether from the drying agent and to transfer it to a tared reaction tube. The drying agent is washed two or three times with additional ether to ensure complete transfer of the product.

Evaporate the solvent by placing the tube in a warm water bath and directing a stream of nitrogen or air onto the surface of the ether in the hood (*see* Fig. 7.8 on page 146). An aspirator tube can also be used for this purpose. Determine the weight of the crude product and then recrystallize it from methanol-water if it is the low-melting compound. Reread Chapter 4 for detailed instructions on carrying out the process of recrystallization from a mixed solvent. The product is dissolved in about 0.5–1 mL of methanol, and water is added until the solution gets cloudy, which indicates that the solution is saturated. This process is best carried out while heating the tube in a hot water bath at 50°C. Allow the tube to cool slowly to room temperature and then cool it thoroughly in ice. If you have the high-melting compound, recrystallize it from ethanol (8 mL/g).

The best way to remove the solvent: under a gentle stream of air or nitrogen.

The products are best isolated by collection on a Hirsch funnel using an ice-cold alcohol–water mixture to transfer and wash the compounds. Determine the percent recovery and the melting point. Turn in the products in neatly labeled $1\frac{1}{2}$-in. × $1\frac{1}{2}$-in. (4 cm × 4 cm) ziplock plastic bags attached to the laboratory

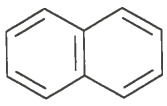
report. If the yield on recrystallization is low, concentrate the filtrate (the mother liquor) and obtain a second crop of crystals.

2. Separation of Neutral and Basic Substances

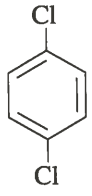
IN THIS EXPERIMENT remember that hydrochloric acid will convert a nonionic amine to an ionic substance and that base will regenerate the nonionic substance from the ionic form. The nonionic and neutral substances are ether soluble, and the ionic substances will be found in the aqueous layer.

Ether vapors are heavier than air and can travel along bench tops, run down drain troughs, and collect in sinks. Be extremely careful to avoid flames when working with volatile ethers.

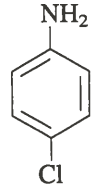
A mixture of equal parts of a neutral substance (naphthalene or 1,4-dichlorobenzene) and a basic substance (4-chloroaniline or ethyl 4-aminobenzoate) is to be separated by extraction from an ether solution. Naphthalene and 1,4-dichlorobenzene are completely insoluble in water. The bases will dissolve in hydrochloric acid, while the neutral compounds will remain in ether solution. The bases are insoluble in cold water but will dissolve to some extent in hot water and are soluble in ethanol. Naphthalene and 1,4-dichlorobenzene can be purified as described in Chapter 4. They also sublime very easily. Keep the samples covered.



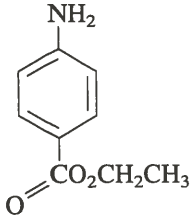
Naphthalene
mp 82°C



1,4-Dichlorobenzene
mp 56°C



4-Chloroaniline
mp 68–71°C, pK_b 4.15



Ethyl 4-aminobenzoate
mp 90°C, pK_b 4.92

Plan a step-by-step procedure for separating 200 mg of the mixture into its components and have the plan checked by your instructor before proceeding. A flow sheet is a convenient way to present the plan. Select the correct solvent or mixture of solvents for the recrystallization of the bases on the basis of solubility tests. Determine the weights and melting points of the isolated and purified products and calculate the percent recovery of each. Turn in the products in neatly labeled vials or 1 1/2-in. × 1 1/2-in. ziplock plastic bags attached to the report.

Cleaning Up. Combine all aqueous filtrates and solutions, neutralize them, and flush the resulting solution down the drain. Used ether should be placed in the organic solvents container, and the drying agent, once the solvent has evaporated from it, can be placed in the nonhazardous solid waste container. If local regulations

do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container. Any 4-chloroaniline or 1,4-dichlorobenzene should be placed in the halogenated waste container.

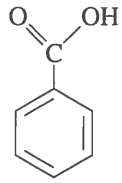
3. Separation of Acidic and Neutral Substances

pH = $-\log [H^+]$
pK_a = acidity constant
pK_b = basicity constant

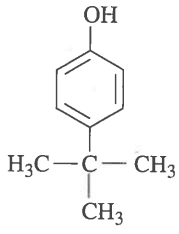
A mixture of equal proportions of benzoic acid, 4-*t*-butylphenol, and 1,4-dimethoxybenzene is to be separated by extraction from *t*-butyl methyl ether. Note the detailed directions for extraction carefully. Prepare a flow sheet (*see* Fig. 7.10 on page 148) for this sequence of operations. In the next experiment you will work out your own extraction procedure.

Procedure

Extinguish all flames when working with *t*-butyl methyl ether! The best method for removing the ether is by simple distillation. Dispose of waste ether in the container provided.



Benzoic acid
mp 123°C, pK_a 4.17



4-*tert*-Butylphenol
mp 101°C, pK_a 10.17

Dissolve 3 g of the mixture in 30 mL of *t*-butyl methyl ether and transfer the mixture to a 125-mL separatory funnel (*see* Fig. 7.2 on page 139) using a little *t*-butyl methyl ether to complete the transfer. Add 10 mL of water and note which layer is organic and which is aqueous. Add 10 mL of a 3 *M* aqueous solution of sodium bicarbonate to the funnel. Swirl or stir the mixture to allow carbon dioxide to escape. Stopper the funnel and cautiously mix the contents. Vent the liberated carbon dioxide and then shake the mixture thoroughly with frequent venting of the funnel. Repeat the process with another 10 mL of bicarbonate solution. Allow the layers to separate completely and then draw off the lower layer into a 50-mL Erlenmeyer flask (labeled flask 1). What does this layer contain?

Add 10 mL of 1.5 *M* aqueous sodium hydroxide to the separatory funnel, shake the mixture thoroughly, allow the layers to separate, and draw off the lower layer into a 50-mL Erlenmeyer flask (labeled flask 2). Repeat the process with another 10 mL of base. Then add an additional 5 mL of water to the separatory funnel, shake the mixture as before, and add this to flask 2. What does flask 2 contain?

Add 15 mL of a saturated aqueous solution of sodium chloride to the separatory funnel, shake the mixture thoroughly, allow the layers to separate, and draw off the lower layer, which can be discarded. What is the purpose of adding saturated sodium chloride solution? Carefully pour the ether layer into a 50-mL Erlenmeyer flask (labeled flask 3) from the top of the separatory funnel, taking great care not to allow any water droplets to be transferred. Add about 4 g of anhydrous calcium chloride pellets to the ether extract and set it aside.

Acidify the contents of flask 2 by dropwise addition of concentrated hydrochloric acid while testing with litmus paper. Cool the flask in an ice bath.

Cautiously add concentrated hydrochloric acid dropwise to flask 1 until the contents are acidic to litmus and then cool the flask in ice.

Decant (pour off) the ether from flask 3 into a tared flask, making sure to leave all of the drying agent behind. Wash the drying agent with additional ether to ensure complete transfer of the product. If decantation is difficult, then remove the drying agent by gravity filtration (*see* Fig. 4.6 on page 69). Put a boiling stick in the flask and evaporate the ether in the hood. An aspirator tube can be used for

Online Study Center
Video: Macroscale Crystallization

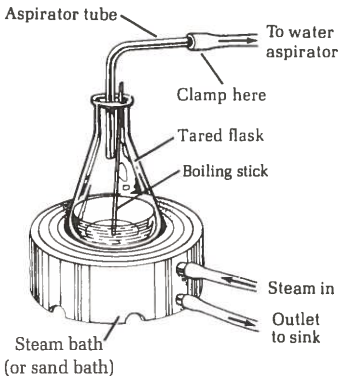


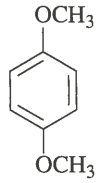
FIG. 7.11
An aspirator tube in use.

this purpose (Fig. 7.11). Determine the weight of the crude *p*-dimethoxybenzene and then recrystallize it from methanol. See Chapter 4 for detailed instructions on how to carry out recrystallization.

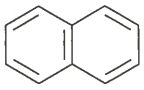
Isolate the *t*-butylphenol from flask 2, employing vacuum filtration on a Hirsch funnel, and wash it on the filter with a small quantity of ice water. Determine the weight of the crude product and then recrystallize it from ethanol. Similarly isolate, weigh, and recrystallize from boiling water the benzoic acid in flask 1. The solubility of benzoic acid in water is 1.9 g/L at 0°C and 68 g/L at 95°C.

Dry the purified products, determine their melting points and weights, and calculate the percent recovery of each substance, bearing in mind that the original mixture contained 1 g of each compound. Hand in the three products in neatly labeled vials.

Online Study Center
Video: Microscale Filtration on the Hirsch Funnel



1,4-Dimethoxybenzene
(Hydroquinone dimethyl ether)
mp 57°C



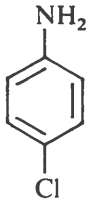
Naphthalene
mp 82°C

Cleaning Up. Combine all aqueous layers, washes, and filtrates. Dilute with water, neutralize using either sodium carbonate or dilute hydrochloric acid. This material can then be flushed down the drain with excess water. Methanol filtrate and any ether go in the organic solvents container. Allow ether to evaporate from the calcium chloride in the hood. Then place the calcium chloride in the nonhazardous solid waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container.

4. Separation of Neutral and Basic Substances

A mixture of equal parts of a neutral substance (naphthalene) and a basic substance (4-chloroaniline) is to be separated by extraction from *t*-butyl methyl ether solution. The base will dissolve in hydrochloric acid, whereas the neutral naphthalene will remain in the *t*-butyl methyl ether solution. 4-Chloroaniline is insoluble in cold water but will dissolve to some extent in hot water and is soluble in ethanol. Naphthalene can be purified as described in Chapter 4.

Plan a procedure for separating 2.0 g of the mixture into its components and have the plan checked by your instructor before proceeding. A flow sheet is a convenient way to present the plan. Using solubility tests, select the correct solvent or



4-Chloroaniline
mp 68–71°C, pK_b 10.0

mixture of solvents to recrystallize 4-chloroaniline. Determine the weights and melting points of the isolated and purified products and calculate the percent recovery of each. Turn in the products in neatly labeled vials.

Cleaning Up. Combine all aqueous filtrates and solutions, neutralize them, and flush the resulting solution down the drain with a large excess of water. Used *t*-butyl methyl ether should be placed in the organic solvents container, and the drying agent, once the solvent has evaporated from it, can be placed in the nonhazardous solid waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container. Any 4-chloroaniline should be placed in the chlorinated organic compounds container.

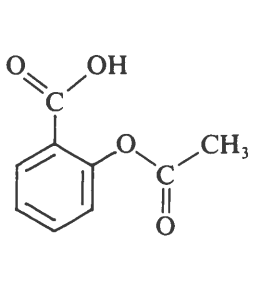


Handle aromatic amines with care. Most are toxic, and some are carcinogenic. Avoid breathing the dust and vapor from the solid and keep the compounds off the skin, which is best done by wearing nitrile gloves.

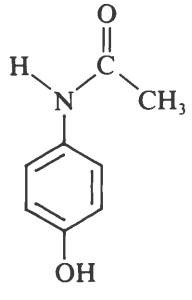
5. Extraction and Purification of Components in an Analgesic Tablet

IN THIS EXPERIMENT a powdered analgesic tablet, Excedrin, is boiled with dichloromethane and filtered. The solid on the filter is boiled with ethanol, which dissolves everything but the binder. The ethanol is evaporated and from the hot solution acetaminophen recrystallizes. The dichloromethane solution is shaken with base that converts aspirin to the water-soluble carboxylate anion. The dichloromethane is then evaporated to give caffeine that is purified by sublimation. The aqueous carboxylate anion solution is made acidic, which frees aspirin; warming the mixture and allowing it to cool allows aspirin to recrystallize. It is isolated by filtration.

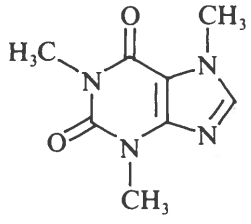
Excedrin contains aspirin, caffeine, and acetaminophen as determined by thin-layer chromatography (TLC; *see* Chapter 8) or high performance liquid chromatography. A tablet is held together with a binder to prevent the components from crumbling when stored or while being swallowed. A close reading of the contents on the package will disclose the nature of the binder. Starch is commonly used, as is microcrystalline cellulose or silica gel. All of these have one property in common: They are insoluble in water and common organic solvents.



Aspirin
(Acetylsalicylic acid)
mp 135°C



Acetaminophen
(*p*-Hydroxyacetanilide)
mp 169–170.5°C



Caffeine
mp 238°C

TABLE 7.2 • **Solubilities**

	Water	Ethanol	Chloroform	Diethyl ether	Ligroin
Aspirin	0.33 g/100 mL at 25°C; 1 g/100 mL at 37°C	1 g/5 mL	1 g/17 mL	1 g/13 mL	
Acetaminophen	v. sl. sol. cold; sol. hot	sol.	ins.	sl. sol.	ins.
Caffeine	1 g/46 mL at 25°C; 1 g/5.5 mL at 80°C; 1 g/1.5 mL at 100°C	1 g/66 mL at 25°C; 1 g/22 mL at 60°C	1 g/5.5 mL	1 g/530 mL	sl. sol.

Inspection of the structures of caffeine, acetylsalicylic acid, and acetaminophen reveals that one is a base, one is a strong organic acid, and one is a weak organic acid. It might be tempting to separate this mixture using exactly the same procedure employed in separating benzoic acid, 4-*t*-butylphenol, and 1,4-dimethoxybenzene (experiment 3)—that is, dissolve the mixture in dichloromethane; separate the strongly acidic component by reaction with bicarbonate ion, a weak base; then remove the weakly acidic component by reaction with hydroxide, a strong base. This process would leave the neutral compound in the dichloromethane solution.

In the present experiment the solubility data (see Table 7.2) reveal that the weak acid, acetaminophen, is not soluble in ether, chloroform, or dichloromethane, so it cannot be extracted by a strong base. We can take advantage of this lack of solubility by dissolving the other two components, caffeine and aspirin, in dichloromethane and removing the acetaminophen by filtration. The binder is also insoluble in dichloromethane, but treatment of the solid mixture with ethanol will dissolve the acetaminophen and not the binder. These can then be separated by filtration, with the acetaminophen isolated by evaporation of the ethanol.

This experiment is a test of technique. It is not easy to separate and recrystallize a few milligrams of a compound that occurs in a mixture.



Microscale Procedure



Handle dichloromethane in the hood. It is a suspected carcinogen.



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Photos: Micro Büchner Funnel, Vacuum Filtration into Reaction Tube through Hirsch Funnel, Use of the Wilfilter

The binder can be starch, microcrystalline cellulose, or silica gel.

In a mortar, grind an Extra Strength Excedrin tablet to a very fine powder. The label states that this analgesic contains 250 mg of aspirin, 250 mg of acetaminophen, and 65 mg of caffeine per tablet. Place 300 mg of this powder in a reaction tube and add 2 mL of dichloromethane. Warm the mixture briefly and note that a large part of the material does not dissolve. Filter the mixture on a microscale Büchner funnel (the base of a chromatography column; Fig. 7.12) into another reaction tube. This is done by transferring the slurry to the funnel with a Pasteur pipette and completing the transfer with a small portion of dichloromethane. This filtrate is solution 1. A Hirsch funnel (Fig. 7.13) or a Wilfilter (Fig. 7.14) can also be used for this procedure. Pressure filtration is another alternative.

Transfer the powder on the filter to a reaction tube, add 1 mL of ethanol, and heat the mixture to boiling on the sand bath (with a boiling stick). Not all the material will go into solution. That which does not is the binder. Filter the mixture on

FIG. 7.12
A microscale Büchner funnel assembly.

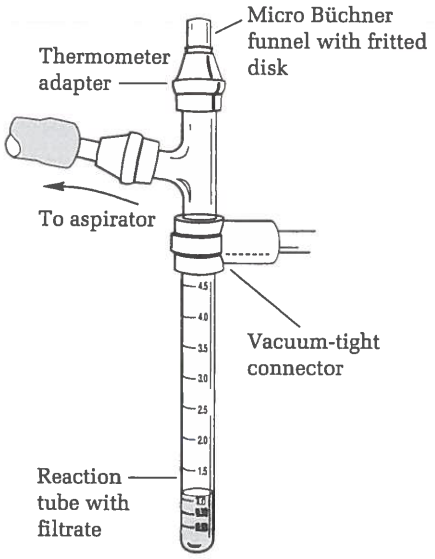


FIG. 7.13
A Hirsch funnel with an integral adapter, a polyethylene frit, and a 25-mL filter flask.

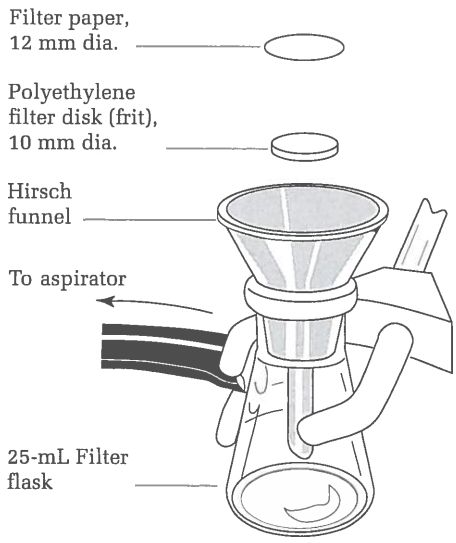
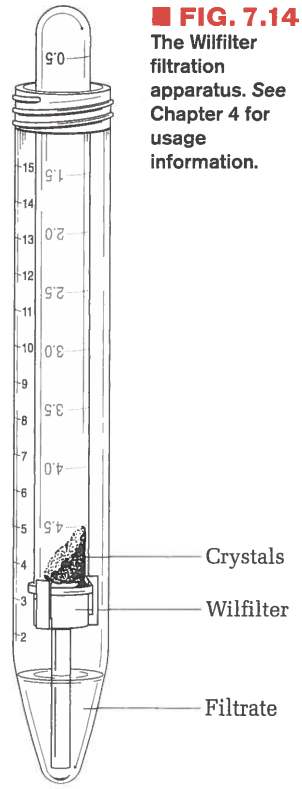


FIG. 7.14
The Wilfilter filtration apparatus. *See* Chapter 4 for usage information.



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Photos: Vacuum Filtration into Reaction Tube through Hirsch Funnel, Micro Büchner Funnel

Acetaminophen

Online Study Center
Video: Filtration of Crystals Using the Pasteur Pipette

Check product purity by TLC (Chapter 8) using 25:1 ethyl acetate–acetic acid to elute the silica gel plates.

the same microscale Büchner funnel into a tared reaction tube and complete the transfer and washing using a few drops of hot ethanol.

Evaporate about two-thirds of the filtrate by boiling off the ethanol or, better, by warming the solution and blowing a stream of air into the reaction tube. Heat the residue to boiling (add a boiling stick to prevent bumping) and, if necessary, add more ethanol to bring the solid into solution. Allow the saturated solution to cool slowly to room temperature to deposit crystals of acetaminophen, which is reported to melt at 169°C–170.5°C. After the mixture has cooled to room temperature, cool it in ice for several minutes, remove the solvent with a Pasteur pipette, wash the crystals once with 2 drops of ice-cold ethanol, remove the ethanol, and dry the crystals under aspirator vacuum while heating the tube on a steam or sand bath.

Alternatively, the original ethanol solution can be evaporated to dryness, and the residue recrystallized from boiling water. The crystals can be collected on a Hirsch funnel (Fig. 7.13) or by use of a Wilfilter (Fig. 7.14). Once the crystals are dry, determine their weight and melting point. TLC analysis (see Chapter 8) and a determination of the melting points of these crystals and the two other components of this mixture will indicate their purity.

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Video: Recrystallization; Photos: Vacuum Filtration into Reaction Tube through Hirsch Funnel, Use of the Wilfilter

Video: Extraction with Dichloromethane

Photos: Sublimation Apparatus, Filtration Using a Pasteur Pipette; Videos: Recrystallization, Filtration Using a Pasteur Pipette

Caffeine

See Figure 4.13 on page 73 for drying crystals under vacuum.

Online Study Center

Photos: Filtration Using a Pasteur Pipette, Use of the Wilfilter; Videos: Recrystallization, Filtration of Crystals Using the Pasteur Pipette

Aspirin

Alternative procedure: Use a Hirsch funnel or a Wilfilter to isolate the aspirin.

The dichloromethane filtered from the binder and acetaminophen mixture (solution 1) should contain caffeine and aspirin. These can be separated by extraction either with acid (which will remove the caffeine as a water-soluble salt) or with base (which will remove the aspirin as a water-soluble salt). We shall use the latter procedure.

To the dichloromethane solution in a reaction tube, add 1 mL of 3 *M* sodium hydroxide solution and shake the mixture thoroughly. Remove the aqueous layer, add 0.2 mL more water, shake the mixture thoroughly, and again remove the aqueous layer, which is combined with the first aqueous extract.

To the dichloromethane, add calcium chloride pellets until the drying agent no longer clumps together. Shake the mixture over a 5-min to 10-min period to complete the drying process; then remove the solvent, wash the drying agent with more solvent, and evaporate the combined extracts to dryness under a stream of air to leave crude caffeine.

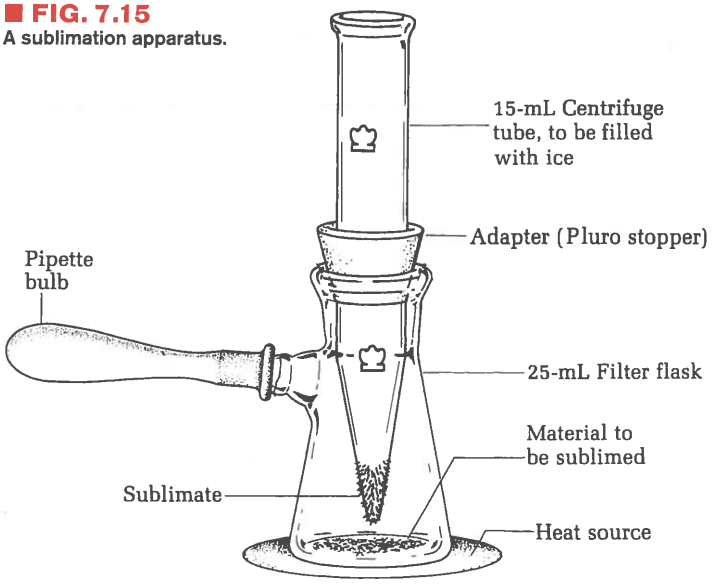
The caffeine can be purified by sublimation (Fig. 7.15) or by recrystallization. Recrystallize the caffeine by dissolving it in the minimum quantity of 30% ethanol in tetrahydrofuran. It also can be recrystallized by dissolving the product in a minimum quantity of hot toluene or acetone and adding to this solution ligroin (hexanes) until the solution is cloudy while at the boiling point. In any case, allow the solution to cool slowly to room temperature; then cool the mixture in ice and remove the solvent from the crystals with a Pasteur pipette. Remove the remainder of the solvent under aspirator vacuum and determine the weight of the caffeine and its melting point.

The aqueous hydroxide extract contains aspirin as the sodium salt of the carboxylic acid. To the aqueous solution, add 3 *M* hydrochloric acid dropwise until the solution tests strongly acid with indicator paper; then add 2 more drops of acid. This will give a suspension of white acetylsalicylic acid in the aqueous solution. It could be filtered off and recrystallized from boiling water, but this would cause transfer losses. An easier procedure is to heat the aqueous solution that contains the precipitated aspirin.

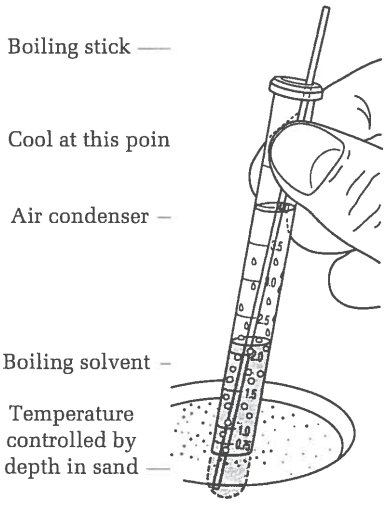
Add a boiling stick and heat the mixture to boiling (Fig. 7.16), at which time the aspirin should dissolve completely. If it does not, add more water. Long boiling will hydrolyze the aspirin to salicylic acid (mp 157°C–159°C). Once completely dissolved, the aspirin should be allowed to recrystallize slowly as the solution cools to room temperature in an insulated container. Once the tube has reached room temperature, it should be cooled in ice for several minutes, and then the solvent is removed with a Pasteur pipette. Wash the crystals with a few drops of ice-cold water and isolate them with a Wilfilter or scrape them out onto a piece of filter paper. Squeezing the crystals between sheets of filter paper will hasten drying. Once these crystals are completely dry, determine the weight of the acetylsalicylic acid and its melting point.

Cleaning Up. Place any dichloromethane-containing solutions in the halogenated organic waste container and the other organic liquids in the organic solvents container. The aqueous layers should be diluted and neutralized with sodium carbonate before being flushed down the drain. After it is free of solvent, the calcium

■ FIG. 7.15
A sublimation apparatus.



■ FIG. 7.16
Rerystallization in a reaction tube.



chloride can be placed in the nonhazardous solid waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container.

Macroscale Procedure

Handle dichloromethane in the hood. It is a suspected carcinogen.

In a mortar, grind two Extra Strength Excedrin tablets to a very fine powder. The label states that this analgesic contains 250 mg of aspirin, 250 mg of acetaminophen, and 65 mg of caffeine per tablet. Place this powder in a test tube and add 7.5 mL of dichloromethane. Warm the mixture briefly and note that a large part of the material does not dissolve. Filter the mixture into another test tube. This can be done by transferring the slurry to a funnel equipped with a piece of filter paper. Use a Pasteur pipette and complete the transfer with a small portion of dichloromethane. This filtrate is solution 1.

The binder can be starch, microcrystalline cellulose, or silica gel.

Transfer the powder on the filter to a test tube, add 4 mL of ethanol, and heat the mixture to boiling (with a boiling stick). Not all of the material will go into solution. That which does not is the binder. Filter the mixture into a tared test tube and complete the transfer and washing by using a few drops of hot ethanol. This is solution 2.

Acetaminophen

Evaporate about two-thirds of solution 2 by boiling off the ethanol (with a boiling stick) or, better, by warming the solution and blowing a stream of air into the test tube. Heat the residue to boiling (add a boiling stick to prevent bumping) and add more ethanol, if necessary, to bring the solid into solution. Allow the saturated solution to cool slowly to room temperature to deposit crystals of acetaminophen, which is reported to melt at 169°C–170.5°C. After the mixture has

Online Study Center
Photo: Filtration Using a Pasteur Pipette; Video: Filtration of Crystals Using the Pasteur Pipette

removed with a Pasteur pipette. The crystals are to be washed with a few drops of ice-cold water and then scraped out onto a piece of filter paper. Squeezing the crystals between sheets of the filter paper will hasten drying. Once these crystals are completely dry, determine the weight of the acetylsalicylic acid and its melting point.

Cleaning Up. Place any dichloromethane-containing solutions in the halogenated organic waste container and the other organic liquids in the organic solvents container. The aqueous layers should be diluted and neutralized with sodium carbonate before being flushed down the drain. After it is free of solvent, the calcium chloride can be placed in the nonhazardous solid waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container.

Extractions from Common Items

6. Extraction of Caffeine from Tea

Tea and coffee have been popular beverages for centuries, primarily because they contain caffeine, a stimulant. Caffeine stimulates respiration, the heart, and the central nervous system, and it is a diuretic (i.e., it promotes urination). It can cause nervousness and insomnia and, like many drugs, can be addictive, making it difficult to reduce the daily dose. A regular coffee drinker who consumes just 4 cups per day can experience headache, insomnia, and even nausea upon withdrawal from the drug. On the other hand, it helps people to pay attention and can sharpen moderately complex mental skills as well as prolong the ability to exercise.

Caffeine may be the most widely abused drug in the United States. During the course of a day, an average person may unwittingly consume up to 1 g of caffeine. The caffeine content of some common foods and drugs is given in Table 7.3.

Caffeine belongs to a large class of compounds known as alkaloids. These are of plant origin, contain basic nitrogen, often have a bitter taste and a complex structure, and usually have physiological activity. Their names usually end in *-ine*; many are quite familiar by name if not chemical structure—for example, nicotine, cocaine, morphine, and strychnine.

Tea leaves contain tannins, which are acidic, as well as a number of colored compounds and a small amount of undecomposed chlorophyll (soluble in dichloromethane). To ensure that the acidic substances remain water soluble and that the caffeine will be present as the free base, sodium carbonate is added to the extraction medium.

The solubility of caffeine in water is 2.2 mg/mL at 25°C, 180 mg/mL at 80°C, and 670 mg/mL at 100°C. It is quite soluble in dichloromethane, the solvent used in this experiment to extract the caffeine from water.

Caffeine can be easily extracted from tea bags. The procedure one would use to make a cup of tea—simply "steeping" the tea with very hot water for about 7 min—extracts most of the caffeine. There is no advantage to boiling the tea leaves with water for 20 min. Because caffeine is a white, slightly bitter, odorless,

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Photo: Filtration Using a Pasteur Pipette; Video: Filtration of Crystals Using the Pasteur Pipette

cooled to room temperature, cool it in ice for several minutes, remove the solvent with a Pasteur pipette, wash the crystals once with 2 drops of ice-cold ethanol, remove the ethanol, and dry the crystals under aspirator vacuum while heating the tube on a steam or sand bath.

Alternatively, the original ethanol solution is evaporated to dryness, and the residue is recrystallized from boiling water. The crystals are best collected and dried on a Hirsch funnel (*see* Fig. 7.13 on page 158). Once the crystals are dry, determine their weight and melting point. TLC analysis (*see* Chapter 8) and a determination of the melting points of these crystals and the two other components of this mixture will indicate their purity.

Check product purity by TLC using 25:1 ethyl acetate–acetic acid to elute the silica gel plates.

The dichloromethane filtered from the binder and acetaminophen mixture (solution 1) should contain caffeine and aspirin. These can be separated by extraction either with acid (which will remove the caffeine as a water-soluble salt) or with base (which will remove the aspirin as a water-soluble salt). We shall use the latter procedure.

Online Study Center
Video: Extraction with Dichloromethane

To the dichloromethane solution in a test tube, add 4 mL of 3 *M* sodium hydroxide solution and shake the mixture thoroughly. Remove the aqueous layer, add 1 mL more water, shake the mixture thoroughly, and again remove the aqueous layer, which is combined with the first aqueous extract.

An alternative to shaking is pipette mixing or using a vortex stirrer, if available.

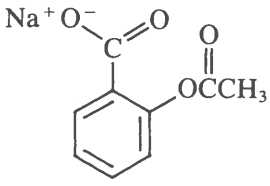
To the dichloromethane add anhydrous calcium chloride pellets until the drying agent no longer clumps together. Shake the mixture over a 5–10-min period to complete the drying process, then remove the solvent, wash the drying agent with more solvent, and evaporate the combined extracts to dryness under a stream of air to leave crude caffeine.

Online Study Center
Photo: Sublimation Apparatus

The caffeine can be purified by sublimation or by recrystallization. Recrystallize the caffeine by dissolving it in the minimum quantity of 30% ethanol in tetrahydrofuran. It can also be recrystallized by dissolving the product in a minimum quantity of hot toluene or acetone and adding hexanes to this solution until the solution is cloudy while at the boiling point. In any case, allow the solution to cool slowly to room temperature; then cool the mixture in ice and remove the solvent from the crystals with a Pasteur pipette. Remove the remainder of the solvent under aspirator vacuum and determine the weight of the caffeine and its melting point.

Caffeine

The aqueous hydroxide extract contains aspirin as the sodium salt of the carboxylic acid. To the aqueous solution add 3 *M* hydrochloric acid dropwise until the solution tests strongly acid with indicator paper; then add 2 more drops of acid. This will give a suspension of white acetylsalicylic acid in the aqueous solution. It could be filtered off and recrystallized from boiling water, but this would cause transfer losses. An easier procedure is to simply heat the aqueous solution that contains the precipitated aspirin and allow it to recrystallize on slow cooling.



Sodium acetylsalicylate (soluble in water)

Aspirin

Add a boiling stick and heat the mixture to boiling, at which time the aspirin should dissolve completely. If it does not, add more water. Long boiling will hydrolyze the aspirin to salicylic acid (mp 157°C–159°C). Once completely dissolved, the aspirin should be allowed to recrystallize slowly as the solution cools to room temperature in an insulated container. Once the tube has reached room temperature, it should be cooled in ice for several minutes, and then the solvent is

Alternative procedure: Use a Hirsch funnel (*see* Fig. 4.14 on page 74) to isolate the aspirin.

TABLE 7.3 • Caffeine Content of Common Foods and Drugs

Espresso	120 mg per 2 oz
Coffee, regular, brewed	103 mg per cup
Instant coffee	57 mg per cup
Coffee, decaffeinated	2–4 mg per cup
Tea	30–75 mg per cup
Cocoa	5–40 mg per cup
Milk chocolate	6 mg per oz
Baking chocolate	35 mg per oz
Coca-Cola, Classic	46 mg per 12 oz
Jolt Cola	72 mg per 12 oz
Anacin, Bromo-Seltzer, Midol	32 mg per pill
Excedrin, Extra Strength	65 mg per pill
Dexatrim, Dietac, Vivarin	200 mg per pill
Dristan	16 mg per pill
No-Doz	100 mg per pill

crystalline solid, it is obvious that water extracts more than just caffeine. When the brown aqueous solution is subsequently extracted with dichloromethane, caffeine primarily dissolves in the organic solvent. Evaporation of the solvent leaves crude caffeine, which on sublimation yields a relatively pure product. When the concentrated tea solution is extracted with dichloromethane, emulsions can form very easily. There are substances in tea that cause small droplets of the organic layer to remain suspended in the aqueous layer. This emulsion formation results from vigorous shaking. To avoid this problem, it might seem that one could boil the tea leaves with dichloromethane first and then extract the caffeine from the dichloromethane solution with water. In fact, this does not work. Boiling 25 g of tea leaves with 50 mL of dichloromethane gives only 0.05 g of residue after evaporation of the solvent. Subsequent extractions yield even less material. Hot water causes the tea leaves to swell and is obviously a far more efficient extraction solvent. An attempt to sublime caffeine directly from tea leaves is also unsuccessful.



Microscale Procedure



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Video: Caffeine from Tea

In a 30-mL beaker place 15 mL of water, 2 g of sodium carbonate, and a wooden boiling stick. Bring the water to a boil on the sand bath, remove the boiling stick, and brew a very concentrated tea solution by immersing a tea bag (2.4 g tea) in the very hot water for 5 min. After the tea bag cools enough to handle, and being careful not to break the bag, squeeze as much water from the bag as possible. Again bring the water to a boil and add a new tea bag to the hot solution. After 5 min, remove the tea bag and squeeze out as much water as possible. This can be done easily on a Hirsch funnel. Rinse the bag with a few mL of very hot water but be

sure the total volume of aqueous extract does not exceed 12 mL. Pour the extract into a 15-mL centrifuge tube and cool the solution in ice to below 40°C (the boiling point of dichloromethane).



CAUTION: Do not breathe the vapors of dichloromethane and, if possible, work with this solvent in the hood.

Using three 2-mL portions of dichloromethane, extract the caffeine from the tea. Cork the tube and use a gentle rocking motion to carry out the extraction. Vigorous shaking will produce an intractable emulsion, whereas extremely gentle mixing will fail to extract the caffeine. If you have ready access to a centrifuge, the shaking can be very vigorous because any emulsions formed can be broken fairly well by centrifugation for about 90 s. After each extraction, remove the lower organic layer into a reaction tube, leaving any emulsion layer behind. Dry the combined extracts over anhydrous calcium chloride pellets for 5–10 min in an Erlenmeyer flask. Add the drying agent in portions with shaking until it no longer clumps together. Transfer the dry solution to a tared 25-mL filter flask, wash the drying agent twice with 2-mL portions of dichloromethane, and evaporate it to dryness (*see* Fig. 7.9 on page 146). The residue will be crude caffeine (determine its weight), which is to be purified by sublimation.

Balance the centrifuge tubes.

Fit the filter flask with a Pluro stopper or no. 2 neoprene adapter through which is thrust a 15-mL centrifuge tube. Put a pipette bulb on the side arm. Clamp the flask with a large three-prong clamp, fill the centrifuge tube with ice and water, and heat the flask on a hot sand bath (*see* Fig. 7.15 on page 160). Caffeine is reported to sublime at about 170°C. Tilt the filter flask and rotate it in a hot sand bath to drive more caffeine onto the centrifuge tube. Use a heat gun to heat the upper walls of the filter flask. When sublimation ceases, remove the ice water from the centrifuge tube and allow the flask to cool somewhat before removing the centrifuge tube. Scrape the caffeine onto a tared weighing paper, weigh and, using a plastic funnel, transfer it to a small vial or a plastic bag. At the discretion of your instructor, determine the melting point with a sealed capillary. The melting point of caffeine is 238°C. Using the centrifugation technique to separate the extracts; about 30 mg of crude caffeine can be obtained. This will give you 10–15 mg of sublimed material, depending on the caffeine content of the particular tea being used. The isolated caffeine can be used to prepare caffeine salicylate (experiment 9).

Cleaning Up. Discard the tea bags in the nonhazardous solid waste container. Allow the solvent to evaporate from the drying agent and discard in the same container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container. Place any unused and unrecovered dichloromethane in the chlorinated organic compounds container. The apparatus can be cleaned with soap and hot water. Caffeine can be flushed down the drain because it is biodegradable.

Macroscale Procedure



To an Erlenmeyer flask containing 25 g of tea leaves (or 10 tea bags) and 20 g of sodium carbonate, add 225 mL of vigorously boiling water. Allow the mixture to stand for 7 min and then decant into another Erlenmeyer flask. To the hot tea leaves,

add another 50 mL of hot water and then immediately decant and combine with the first extract. Very little, if any, additional caffeine is extracted by boiling the tea leaves for 20 min. Decantation works nearly as well as vacuum filtration and is much faster.

CAUTION: Carry out work with dichloromethane in the hood.

Rock the separatory funnel very gently to avoid emulsions.

Dispose of used dichloromethane in the container provided.

Cool the aqueous solution to near room temperature and extract it twice with 30-mL portions of dichloromethane. Do not shake the separatory funnel so vigorously as to cause emulsion formation, bearing in mind that if it is not shaken vigorously enough the caffeine will not be extracted into the organic layer. Use a gentle rocking motion of the separatory funnel. Drain off the dichloromethane layer on the first extraction; include the emulsion layer on the second extraction. Dry the combined dichloromethane solutions and any emulsion layer with anhydrous calcium chloride pellets. Add sufficient drying agent until it no longer clumps together on the bottom of the flask. Carefully decant or filter the dichloromethane solution into a tared Erlenmeyer or distilling flask. Silicone-impregnated filter paper passes dichloromethane and retains water. Wash the drying agent with a further portion of solvent and evaporate or distill the solvent. A wood applicator stick is better than a boiling chip to promote smooth boiling because it is easily removed once the solvent is gone. The residue of greenish-white crystalline caffeine should weigh about 0.25 g.

Recrystallization of Caffeine

Online Study Center
Video: Recrystallization

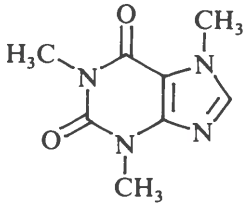
To recrystallize the caffeine, dissolve it in 5 mL of hot acetone, transfer it with a Pasteur pipette to a small Erlenmeyer flask and, while it is hot, add ligroin to the solution until a faint cloudiness appears. Set the flask aside and allow it to cool slowly to room temperature. This mixed-solvent method of recrystallization depends on the fact that caffeine is far more soluble in acetone than ligroin, so a combination of the two solvents can be found where the solution is saturated in caffeine and will appear cloudy. Cool the solution containing the crystals and remove them by vacuum filtration, employing a Hirsch funnel or a very small Büchner funnel. Use a few drops of ligroin to transfer and wash the crystals. If you wish to obtain a second crop of crystals, collect the filtrate in a test tube, concentrate it to the cloud point using an aspirator tube (*see* Fig. 7.11 on page 155), and repeat the recrystallization process.

Cleaning Up. The filtrate can be diluted with water and washed down the drain. Any dichloromethane collected goes into the halogenated organic waste container. After the solvent is allowed to evaporate from the drying agent in the hood, the drying agent can be placed in the nonhazardous solid waste container; otherwise it goes in the hazardous waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container. The tea leaves go in the nonhazardous solid waste container.

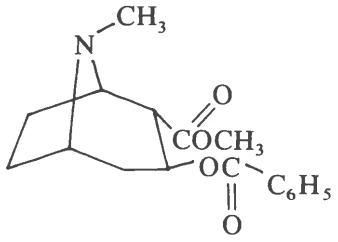
7. Extraction of Caffeine from Cola Syrup

Coca-Cola was originally flavored with extracts from the leaves of the coca plant and the kola nut. Coca is grown in northern South America; the Indians of Peru and Bolivia have for centuries chewed the leaves to relieve the pangs of hunger and

sensitivity to high mountain cold. The cocaine from the leaves causes local anesthesia of the stomach. It has limited use as a local anesthetic for surgery on the eye, nose, and throat. Unfortunately, it is now a widely abused and illicit drug. Kola nuts contain about 3% caffeine as well as a number of other alkaloids. The kola tree is in the same family as the cacao tree from which cocoa and chocolate are obtained. Modern cola drinks do not contain cocaine; however, Coca-Cola contains 46 mg of caffeine per 12-oz serving. The acidic taste of many soft drinks comes from citric, tartaric, phosphoric, and benzoic acids.



Caffeine
mp 238°C



Cocaine

Automatic soft drink dispensing machines mix a syrup with carbonated water. In the following experiment caffeine is extracted from concentrated cola syrup.

Microscale Procedure

Add 1 mL of concentrated ammonium hydroxide to a mixture of 5 mL of commercial cola syrup and 5 mL of water in a 15-mL centrifuge tube. Add 1 mL of dichloromethane and tip the tube gently back and forth for 5 min. Do not shake the mixture as in a normal extraction because an emulsion will form, and the layers will not separate. After the layers have separated as much as possible, remove the clear lower layer, leaving the emulsion behind. Using 1.5 mL of dichloromethane, repeat the extraction in the same way two more times. At the final separation, include the emulsion layer with the dichloromethane. If a centrifuge is available, the mixture can be shaken vigorously, and the emulsion broken by centrifugation for 90 s. Combine the extracts in a reaction tube and dry the solution with anhydrous calcium chloride pellets. Add the drying agent with shaking until it no longer clumps together. After 5–10 min, remove the solution with a Pasteur pipette and place it in a tared filter flask. Wash off the drying agent with more dichloromethane and evaporate the mixture to dryness. Determine the crude weight of caffeine; then sublime it as described in the preceding experiment.

CAUTION: Do not breathe the vapor of dichloromethane. Work with this solvent in the hood.

Macroscale Procedure

Add 10 mL of concentrated ammonium hydroxide to a mixture of 50 mL of commercial cola syrup and 50 mL of water. Place the mixture in a separatory funnel, add 50 mL of dichloromethane, and swirl the mixture and tip the funnel back and

forth for at least 5 min. Do not shake the solutions together as in a normal extraction because an emulsion will form, and the layers will not separate. An emulsion is made up of droplets of one phase suspended in the other. (Milk is an emulsion.) Separate the layers. Repeat the extraction with a second 50-mL portion of dichloromethane. From your knowledge of the density of dichloromethane and water, you should be able to predict which is the top layer and which is the bottom layer. If in doubt, add a few drops of each layer to water. The aqueous layer will be soluble; the organic layer will not. Combine the dichloromethane extracts and any emulsion that has formed in a 125-mL Erlenmeyer flask; then add anhydrous calcium chloride pellets to remove water from the solution. Add the drying agent until it no longer clumps together at the bottom of the flask but swirls freely in solution. Swirl the flask with the drying agent from time to time over a 10-min period. Carefully decant (pour off) the dichloromethane or remove it by filtration through a fluted filter paper, add about 5 mL more solvent to the drying agent to wash it, and decant this also. Combine the dried dichloromethane solutions in a tared flask and remove the dichloromethane by distillation or evaporation on a steam or sand bath. Remember to add a wood applicator stick to the solution to promote even boiling. Determine the weight of the crude product.



Chlorinated solvents are toxic, insoluble in water, and expensive and should never be poured down the drain.

Recrystallization of Caffeine

To recrystallize the caffeine, dissolve it in 5 mL of hot acetone, transfer it with a Pasteur pipette to a small Erlenmeyer flask, and, while it is hot, add ligroin to the solution until a faint cloudiness appears. Set the flask aside and allow it to cool slowly to room temperature. This mixed-solvent method of recrystallization depends on the fact that caffeine is far more soluble in acetone than ligroin, so a combination of the two solvents can be found where the solution is saturated in caffeine (the cloud point). Cool the solution containing the crystals and remove them by vacuum filtration, employing a Hirsch funnel or a very small Büchner funnel. Use a few drops of ligroin to transfer and wash the crystals. If you wish to obtain a second crop of crystals, collect the filtrate in a test tube, concentrate it to the cloud point using an aspirator tube (*see* Fig. 7.11 on page 155), and repeat the recrystallization process.

Cleaning Up. Combine all aqueous filtrates and solutions, neutralize them, and flush the resulting solution down the drain. Used dichloromethane should be placed in the halogenated waste container, and the drying agent, once the solvent has evaporated from it, can be placed in the nonhazardous solid waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container. The ligroin-acetone filtrates should be placed in the organic solvents container.

Sublimation of Caffeine. Sublimation is a fast and easy way to purify caffeine. Using the apparatus depicted in Figure 7.15 (on page 160), sublime the crude caffeine at atmospheric pressure following the procedure in part 3 of Chapter 6.

Online Study Center
Photos of Extraction Procedure

8. Isolation of Caffeine from Instant Coffee

Instant coffee, according to manufacturers, contains between 55 mg and 62 mg of caffeine per 6-oz cup, and a cup is presumably made from a teaspoon of the powder, which weighs 1.3 g; so 2 g of the powder should contain 85–95 mg of caffeine. Unlike tea, however, coffee contains other compounds that are soluble in dichloromethane, so obtaining pure caffeine from coffee is not easy. The objective of this experiment is to extract instant coffee with dichloromethane (the easy part) and then to try to devise a procedure for obtaining pure caffeine from the extract.

From TLC analysis (*see* Chapter 8), you may deduce that certain impurities have a high R_f value in hydrocarbons (in which caffeine is insoluble). Consult reference books (see especially the *Merck Index*[2]) to determine the solubility (and lack of solubility) of caffeine in various solvents. You might try trituration (grinding the crude solid with a solvent) to dissolve impurities preferentially. Column chromatography is another possible means of purifying the product. Or you might convert all of it to the salicylate and then regenerate the caffeine from the salicylate. Experiment! Or you can simply use the following procedure.

Procedure

IN THIS EXPERIMENT a very concentrated aqueous solution of coffee is prepared and shaken vigorously with an organic solvent to make an intractable emulsion that can be broken (separated into two layers) by centrifugation. Caffeine is isolated by recrystallization.

In a 10-mL Erlenmeyer flask, place 2 g of sodium carbonate and 2 g of instant coffee powder. Add 9 mL of boiling water, stir the mixture well, bring it to a boil again with stirring, cool it to room temperature, and then pour it into a 15-mL plastic centrifuge tube fitted with a screw cap. Add 2 mL of dichloromethane, cap the tube, shake it vigorously for 60 s; then centrifuge it at high speed for 90 s. Remove the clear yellow dichloromethane layer and place it in a 10-mL Erlenmeyer flask. Repeat this process twice more. To the combined extracts add anhydrous calcium chloride pellets until they no longer clump together, allow the solution to dry for a few minutes; then transfer it to a tared 25-mL filter flask and wash the drying agent with more solvent. Remove the solvent as was done in the tea extraction experiment and determine the weight of the crude caffeine. You should obtain about 60 mg of crude product. Sublimation of this orange powder gives an impure orange sublimate that smells strongly of coffee, so sublimation is not a good way to purify this material.

Caffeine has no odor.

Dissolve a very small quantity of the product in a drop of dichloromethane and perform a TLC analysis of the crude material. Dissolve the remainder of the material in 1 mL of boiling 95% ethanol; then dilute the mixture with 1 mL of

2. O'Neill, M. J.; Smith, A.; Heckelman, P. E.; Budavari, S., eds. *The Merck Index*, 13th ed.; Merck and Co., Inc.: Rahway, NJ, 2001.

Online Study Center
Video: Recrystallization

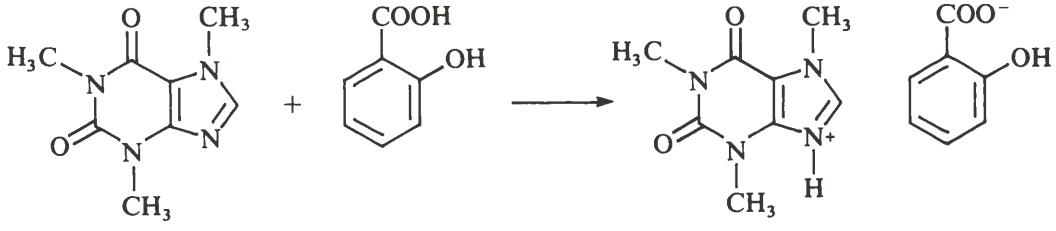
t-butyl methyl ether, heat to boiling, and allow to cool slowly to room temperature. Long, needlelike crystals should form in the orange solution. Alternatively, recrystallize the product from a 1:1 mixture of ligroin (hexanes) and 2-propanol, using about 2 mL. Cool the mixture in ice for at least 10 min and then collect the product on a Hirsch funnel. Complete the transfer with the filtrate and then wash the crystals twice with cold 50/50 ethanol/*t*-butyl methyl ether. The yield of white fluffy needles of caffeine should be more than 30 mg.

Cleaning Up. Allow the solvent to evaporate from the drying agent and discard it in the nonhazardous waste container. If local regulations do not allow for the evaporation of solvents in a hood, dispose of the wet sodium sulfate in a special container. Place any unused and unrecovered dichloromethane in the chlorinated organic solvents container.

9. Caffeine Salicylate

Preparation of a derivative of caffeine.

One way to confirm the identity of an organic compound is to prepare a derivative of it. Caffeine melts and sublimes at 238°C. It is an organic base and can therefore accept a proton from an acid to form a salt. The salt formed when caffeine combines with hydrochloric acid, like many amine salts, does not have a sharp melting point; it merely decomposes when heated. But the salt formed from salicylic acid, even though ionic, has a sharp melting point and can thus be used to help characterize caffeine. Figure 7.17 is the ^{1}H NMR spectrum of caffeine.



Caffeine **Salicylic acid** **Caffeine salicylate**

CAUTION: Petroleum ether is very flammable. Extinguish all flames.

Recrystallization from mixed solvents

Online Study Center
Video: Filtration of Crystals Using the Pasteur Pipette; Photo: Drying Crystals Under Vacuum

Procedure

The quantities given can be multiplied by 5 or 10, if necessary. To 10 mg of sublimed caffeine in a tared reaction tube, add 7.5 mg of salicylic acid and 0.5 mL of dichloromethane. Heat the mixture to boiling and add petroleum ether (a poor solvent for the product) dropwise until the mixture just turns cloudy, indicating that the solution is saturated. If too much petroleum ether is added, then clarify it by adding a very small quantity of dichloromethane. Insulate the tube to allow it to cool slowly to room temperature; then cool it in ice. The needlelike crystals are isolated by removing the solvent with a Pasteur pipette while the reaction tube is in the ice bath. Evaporate the last traces of solvent under vacuum (Fig. 7.18) and

FIG. 7.17
The ^{1}H NMR spectrum of caffeine (250 MHz).

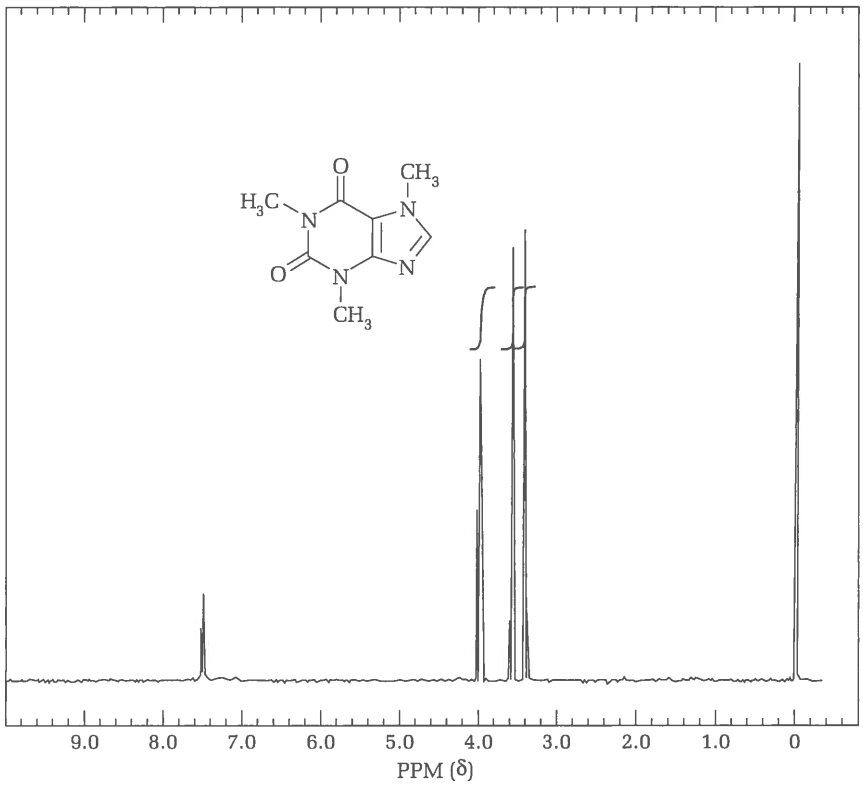
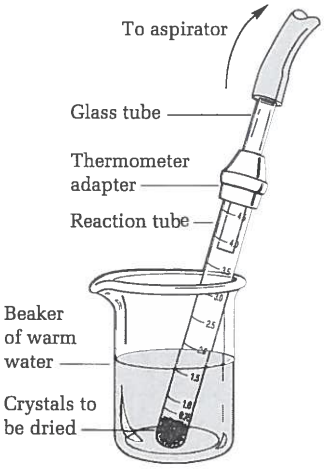


FIG. 7.18
The drying of crystals under vacuum in beaker of warm water.



determine the weight of the derivative and its melting point. Caffeine salicylate is reported to melt at 137°C.

Cleaning Up. Place the filtrate in the halogenated organic solvents container.

QUESTIONS

1. Suppose a reaction mixture, when diluted with water, afforded 300 mL of an aqueous solution of 30 g of the reaction product malononitrile [$CH_2(CN)_2$], which is to be isolated by extraction with ether. The solubility of malononitrile in ether at room temperature is 20.0 g/100 mL and in water is 13.3 g/100 mL. What weight of malononitrile would be recovered by extraction with (a) three 100-mL portions of ether and (b) one 300-mL portion of ether? *Suggestion*: For each extraction let x equal the weight extracted into the ether layer. In part (a) the concentration in the ether layer is $x/100$ and in the water layer is $(30 - x)/300$; the ratio of these quantities is equal to $k = 20/13.3$.

2. Why is it necessary to remove the stopper from a separatory funnel when liquid is being drained from it through the stopcock?
3. The pK_a of *p*-nitrophenol is 7.15. Would you expect this to dissolve in sodium bicarbonate solution? The pK_a of 2,5-dinitrophenol is 5.15. Will it dissolve in bicarbonate solution?
4. The distribution coefficient, k = conc. in ligroin ÷ conc. in water, between ligroin and water for solute A is 7.5. What weight of A would be removed from a solution of 10 g of A in 100 mL of water by a single extraction with 100 mL of ligroin? What weight of A would be removed by four successive extractions with 25-mL portions of ligroin? How much ligroin would be required to remove 98.5% of A in a single extraction?
5. In experiment 1, how many moles of benzoic acid are present? How many moles of sodium bicarbonate are contained in 1 mL of a 10% aqueous solution? (A 10% solution has 1 g of solute in 9 mL of solvent.) Is the amount of sodium bicarbonate sufficient to react with all of the benzoic acid?
6. To isolate benzoic acid from a bicarbonate solution, it is acidified with concentrated hydrochloric acid, as in experiment 1. What volume of acid is needed to neutralize the bicarbonate? The concentration of hydrochloric acid is expressed in various ways on the inside back cover of this laboratory manual.
7. How many moles of 4-*t*-butylphenol are in the mixture to be separated in experiment 1? How many moles of sodium hydroxide are contained in 1 mL of 5% sodium hydroxide solution? (Assume the density of the solution is 1.0.) What volume of concentrated hydrochloric acid is needed to neutralize this amount of sodium hydroxide solution?
8. Draw a flow sheet to show how you would separate the components of a mixture containing an acid substance, toluic acid, a basic substance, *p*-bromo-aniline, and anthracene, a neutral substance.
9. Write equations showing how caffeine could be extracted from an organic solvent and subsequently isolated.
10. Write equations showing how acetaminophen might be extracted from an organic solvent such as an ether, if it were soluble.
11. Write detailed equations showing the mechanism by which aspirin is hydrolyzed in boiling, slightly acidic water.



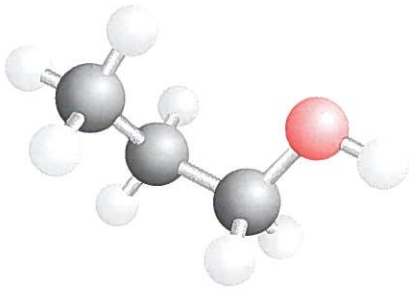
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General Resources

Web Links

CHAPTER

8



Thin-Layer Chromatography: Analyzing Analgesics and Isolating Lycopene from Tomato Paste

Online Study Center

This icon will direct you to techniques, equipment setups, and online resources at http://college.hmco.com/PIC/williamsonMMOE5e.

PRELAB EXERCISE: Based on the number and polarity of the functional groups in aspirin, acetaminophen, ibuprofen, and caffeine, whose structures are shown on page 184, predict which of these four compounds has the highest R_f value and which has the lowest.

Chromatography is the separation of two or more compounds or ions caused by their molecular interactions with two phases—one moving and one stationary. These two phases can be a solid and a liquid, a liquid and a liquid, a gas and a solid, or a gas and a liquid. You very likely have seen chromatography carried out on paper towels or coffee filters to separate inks and food dyes. The cellulose paper is the stationary or solid phase, and a propanol-water mixture is the mobile or liquid phase. The samples are spotted near one edge of the paper, and this edge is dipped into the liquid phase. The solvent is drawn through the paper by capillary action, and the molecules are separated based on how they interact with the paper. Although there are several different forms of chromatography, the principles are essentially the same.

Thin-layer chromatography (*TLC*) is a sensitive, fast, simple, and inexpensive analytical technique that you will use repeatedly while carrying out organic experiments. It is a micro technique; as little as 10^{-9} g of material can be detected, although the usual sample size is from 1×10^{-6} g to 1×10^{-8} g. The stationary phase is normally a polar solid adsorbent, and the mobile phase can be a single solvent or a combination of solvents.

TLC requires micrograms of material.

Uses of Thin-Layer Chromatography

1. **To determine the number of components in a mixture.** TLC affords a quick and easy method for analyzing such things as a crude reaction mixture, an extract from a plant substance, or the ingredients in a pill. Knowing the