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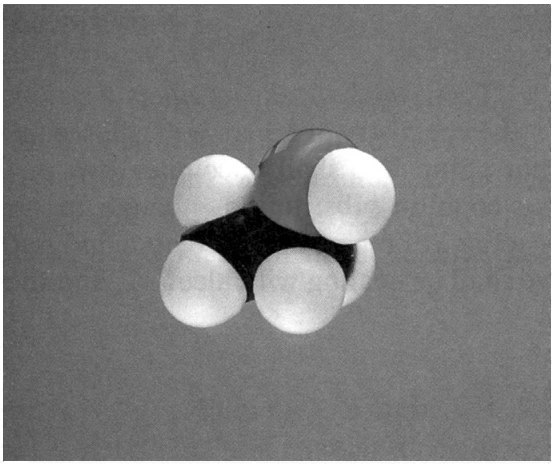


Alcohols and Ethers

10.1 Introduction

If, as an organic chemist, you were allowed to choose the ten aliphatic compounds with which to be stranded on a desert island, you would almost certainly pick alcohols. From them you could make nearly every other kind of aliphatic compound: alkyl halides, alkenes, ethers, aldehydes, ketones, acids, esters, and a host of others. From the alkyl halides, you could make Grignard reagents, and from the reaction between these and the aldehydes and ketones obtain more complicated alcohols and so on. On your desert island you would use your alcohols not only as raw materials, but frequently as the solvents in which reactions are carried out and from which products are recrystallized. Finally, hot and tired after a long day in the laboratory, you could refresh yourself with an (isopropyl) alcohol rub and perhaps relax over a cool (ethyl) alcoholic drink.

We cannot go very far into organic chemistry of almost any kind without encountering alcohols. In this chapter, we shall treat alcohols systematically, and try to understand the properties that give rise to their chemical behavior. We shall examine their acidity and basicity, properties that are involved in nearly everything they do. We shall see how alcohols take part in nucleophilic substitution, both as substrates and as nucleophiles. In this connection, we shall learn about the most important—and simplest—catalytic effect known to the organic chemist: an effect that plays a key role in the chemistry of compounds of all kinds, in the test tube and in the living organism. We shall begin our study of alcohols as the starting point for organic synthesis: how they are converted into alkyl halides and other compounds that undergo nucleophilic substitution—substitution that permits the introduction into a molecule of a host of functional groups. We shall see how alcohols give us access to oxygen compounds of higher oxidation states: aldehydes and ketones, and carboxylic acids.

Then, we shall take up *ethers*, a family of compounds closely related to alcohols. In the chemistry of ethers we shall see applications of what we have learned up to that point. We shall encounter two methods of making ethers, *both* involving nucleophilic substitution—though in quite different ways. We shall study the reactions of ethers and here, too, find nucleophilic substitution. And with all this, we shall be dealing with alcohols, and their rich and varied chemistry.

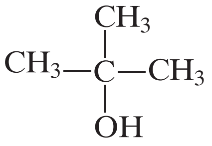
10.2 Structure of alcohols

Alcohols are compounds of the general formula ROH, where R is any alkyl or substituted alkyl group. The group may be primary, secondary, or tertiary; it may be

$$R{-}OH$$

An alcohol

open chain or cyclic; it may contain a halogen atom, additional hydroxyls, or one of the many, groups that are still unfamiliar to us: a double bond, for example, or an aromatic ring. For example:

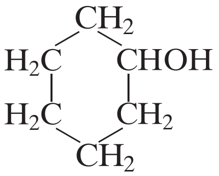


$$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}{-}CH_3$$

2-Methyl-2-propanol
tert-butyl alcohol

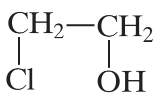
$CH_2{=}CH{-}CH_2OH$

2-Propen-1-ol
allyl alcohol



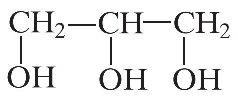
Cyclohexanol

Benzyl alcohol



$$\underset{\displaystyle Cl}{CH_2}{-}\underset{\displaystyle OH}{CH_2}$$

2-Chloroethanol
ethylene chlorohydrin



$$\underset{\displaystyle OH}{CH_2}{-}\underset{\displaystyle OH}{CH}{-}\underset{\displaystyle OH}{CH_2}$$

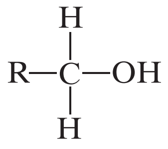
1,2,3-Propanetriol
glycerol

All alcohols contain the hydroxyl (—OH) group, which, as the functional group, determines the properties characteristic of this family. Variations in structure of the R group may affect the rate at which the alcohol undergoes certain reactions, and even, in a few cases, may affect the kind of reaction.

(Compounds in which the hydroxyl group is attached directly to an aromatic ring are not alcohols; they are *phenols*, and differ so markedly from the alcohols that we shall consider them in a separate chapter.)

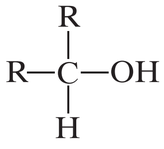
10.3 Classification of alcohols

An alcohol is classified as *primary*, *secondary*, or *tertiary* according to the kind of carbon that bears the —OH group;



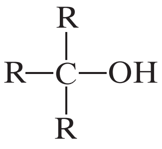
$$R-\overset{\displaystyle H}{\underset{\displaystyle H}{C}}-OH$$

Primary
(1°)



$$R-\overset{\displaystyle R}{\underset{\displaystyle H}{C}}-OH$$

Secondary
(2°)



$$R-\overset{\displaystyle R}{\underset{\displaystyle R}{C}}-OH$$

Tertiary
(3°)

One reaction, oxidation, which directly involves the hydrogen atoms attached to the carbon bearing the —OH group, takes an entirely different course for each class of alcohol. Usually, however, alcohols of different classes differ only in *rate* or *mechanism* of reaction, and in a way consistent with their structures. Certain substituents may affect reactivity in such a way as to make an alcohol of one class resemble the members of a different class.

Alcohols containing more than one —OH group are classified as:

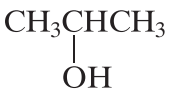
1. Dihydric alcohol, for example, glycol ($CH_2OH—CH_2OH$)
2. Trihydric alcohol, for example, glycerol ($CH_2OH\ CHOH—CH_2OH$)
3. Polyhydric alcohol, for example, sorbitol ($CH_2OH\ (CHOH)_4\ CH_2OH$)

10.4 Nomenclature of alcohols

Alcohols are named by two principal systems. For the simpler alcohols the **common names** are most often used. A common name consists simply of the name of the alkyl group followed by the word *alcohol*. For example:

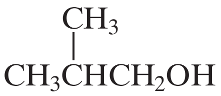
CH_3CH_2OH

Ethyl alcohol
(1°)



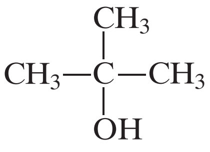
$$CH_3\underset{\displaystyle OH}{C}HCH_3$$

Isopropyl alcohol
(2°)



$$CH_3\overset{\displaystyle CH_3}{C}HCH_2OH$$

Isobutyl alcohol
(1°)



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}-CH_3$$

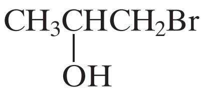
tert-Butyl alcohol
(3°)

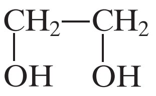
The most versatile system is, of course, the **IUPAC**. The rules are:

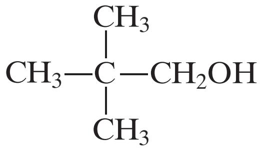
1. Select as the parent structure the longest continuous carbon chain *that contains the —OH group*; then consider the compound to have been derived from this structure by replacement of hydrogen by various groups. The parent structure is known as *ethanol, propanol, butanol*, etc., depending upon the number of carbon atoms; each name is derived by replacing the terminal *-e* of the corresponding alkane name by **-ol**.
2. Indicate by a number the position of the —OH group in the parent chain, generally using the lowest possible number for this purpose.
3. Indicate by numbers the positions of other groups attached to the parent chain.

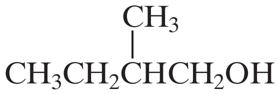
CH_3OH
Methanol

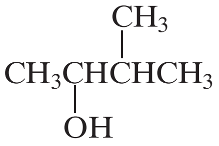
$CH_3CH_2CH_2OH$
1-Propanol


$CH_3\underset{OH}{\underset{|}{C}}HCH_2Br$
1-Bromo-2-propanol


$\underset{OH}{\underset{|}{CH_2}}-\underset{OH}{\underset{|}{CH_2}}$
1,2-Ethanediol


$CH_3-\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_2OH$
2,2-Dimethyl-1-propanol


$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2OH$
2-Methyl-1-butanol


$CH_3\underset{OH}{\underset{|}{C}}H\overset{CH_3}{\overset{|}{C}}HCH_3$
3-Methyl-2-butanol

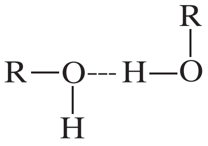
10.5 Physical properties of alcohols

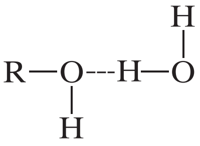
The physical properties of an alcohol are best understood if we recognize this simple fact: structurally, an alcohol is a composite of an alkane and water. It contains

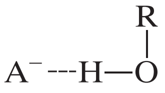
$R—H$	$H—OH$	$R—OH$
An alkane	Water	An alcohol

an alkane-like alkyl group and a water-like hydroxyl group. Of these two structural units, it is the —OH group that gives the alcohol its characteristic physical properties, and the alkyl group that, depending upon its size and shape, modifies these properties.

The hydroxyl group is quite polar and, most important, contains hydrogen bonded to the highly electronegative element oxygen. Through the hydroxyl group, an alcohol is capable of hydrogen bonding: hydrogen bonding to its fellow alcohol molecules and to other neutral molecules and to anions.


$R-\underset{H}{\underset{|}{O}}\cdots H-\overset{R}{\overset{|}{O}}$


$R-\underset{H}{\underset{|}{O}}\cdots H-\overset{H}{\overset{|}{O}}$


$A^-\cdots H-\overset{R}{\overset{|}{O}}$

Let us look first at **boiling points**. Among hydrocarbons the factors that determine boiling point seem to be chiefly molecular weight and shape; this is to be expected of molecules that are held together chiefly by van der Waals forces. Alcohols, too, show increase in boiling point with increasing carbon number, and decrease in boiling point with branching. But the unusual thing about alcohols is that they boil so *high*: as Table 10.1 shows, much higher than hydrocarbons of the same molecular weight, and higher, even, than many other compounds of considerable polarity. How are we to account for this?

The answer is, of course, that alcohols, like water, are *associated liquids*: their abnormally high boiling points are due to the greater energy needed to break the hydrogen bonds that hold the molecules together. Although ethers and aldehydes contain oxygen, they contain hydrogen that is bonded only to carbon; these hydrogens are not positive enough to bond appreciably with oxygen.

Infrared spectroscopy has played a key role in the study of hydrogen bonding. In dilute solution in a non-polar solvent like carbon tetrachloride (or in the gas phase), where association between molecules is minimal, ethanol, for example, shows an O—H stretching band at 3640 cm^{-1}. As the concentration of ethanol is increased, this band is gradually replaced by a broader band at 3350 cm^{-1}. The bonding of hydrogen to the second oxygen weakens the O—H bond, and lowers the energy and hence the frequency of vibration.

The behavior of alcohols as **solutes** also reflects their ability to form hydrogen bonds. In sharp contrast to hydrocarbons, the lower alcohols are miscible with water. Since alcohol molecules are held together by the same sort of intermolecular forces as water molecules, there can be mixing of the two kinds of molecules: the energy required to break a hydrogen bond between two water molecules or two alcohol molecules is provided by formation of a hydrogen bond between a water molecule and an alcohol molecule.

But this is true only for the lower alcohols, where the —OH group constitutes a large part of the molecule. As the alkane-like alkyl group becomes larger, water solubility decreases. For practical purposes we consider that the borderline between solubility and insolubility in water occurs at about four to five carbon atoms for normal primary alcohols.

Table 10.1 STRUCTURE AND BOILING POINT

Name	Structure	Mol. wt.	Dipole moment,D	B.p., °C
n-Pentane	$CH_3CH_2CH_2CH_2CH_3$	72	0	36
Diethyl ether	CH_3CH_2—O—CH_2CH_3	74	1.18	35
n-Propyl chloride	$CH_3CH_2CH_2Cl$	79	2.10	47
n-Butyraldehyde	$CH_3CH_2CH_2CHO$	72	2.72	76
n-Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	74	1.63	118

Polyhydroxy alcohols provide more than one site per molecule for hydrogen bonding, and their properties reflect this. The simplest diol, 1,2-ethanediol (ethylene glycol), boils at 197 °C. The lower diols are miscible with water, and those containing as many as seven carbon atoms show appreciable solubility in water. (Ethylene glycol owes its use as an antifreeze—for example, Prestone—to its high boiling point, low freezing point, and high solubility in water.)

Problem 10.1 The disaccharide *sucrose*, $C_{12}H_{22}O_{11}$, is a big molecule and yet (it is ordinary table sugar) is extremely soluble in water. What might you guess about its structure?

Problem 10.2 How do you account for the fact that, although diethyl ether has a much lower boiling point than *n*-butyl alcohol, it has the same solubility (8 g per 100 g) in water?

10.6 Industrial source of alcohols

For alcohols to be such important starting materials in aliphatic chemistry, they must be not only versatile in their reactions but also available in large amounts and at low prices. There are three principal ways to get the simple alcohols that are the backbone of aliphatic organic synthesis, ways that can utilize all our sources of organic raw material—petroleum, natural gas, coal, and the biomass. These methods are:

(a) by *hydration of alkenes* obtained from the cracking of petroleum; (b) by the *oxo process* from alkenes, carbon monoxide, and hydrogen; and (c) by *fermentation of carbohydrates*. In addition to these three chief methods, there are others that have more limited application (see Fig. 10.1). Methanol, for example, is made by the catalytic hydrogenation of carbon monoxide; the necessary mixture of hydrogen and carbon monoxide is obtained from the high-temperature reaction of water with methane, higher alkanes, or coal.

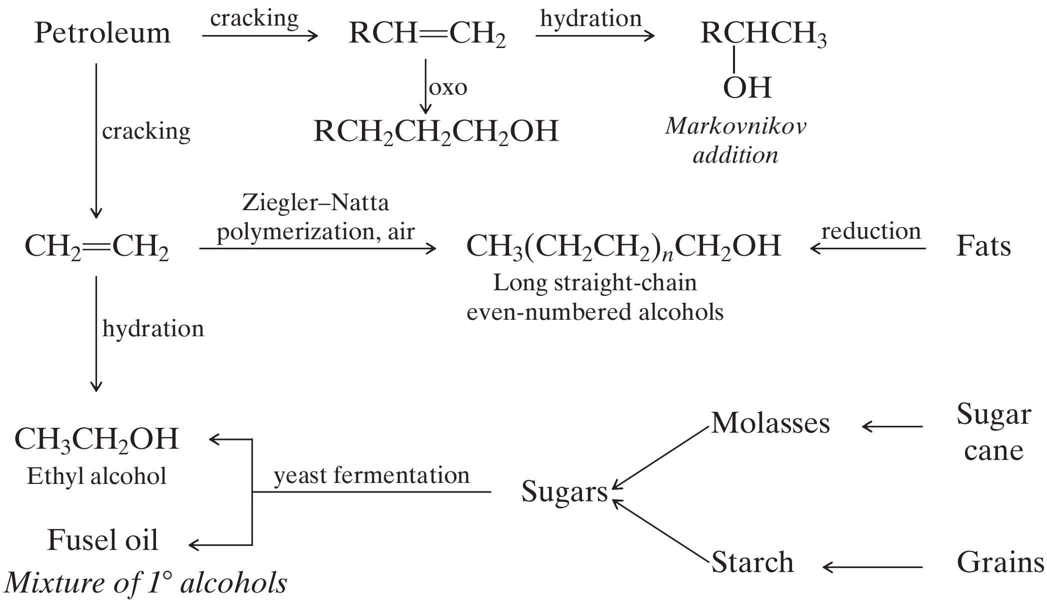


Figure 10.1 Industrial sources of alcohols.

Most of these methods we shall discuss later. But let us look now at one of them, important today and almost certainly of even greater importance in the decades to come.

10.7 Fermentation of carbohydrates

Fermentation of sugars by yeast, the oldest synthetic chemical process used by man, is still of enormous importance for the preparation of **ethanol** and certain other alcohols. The sugars come from a variety of sources, mostly molasses from sugar cane, or starch obtained from various grains; the name "grain alcohol" has been given to ethanol for this reason.

When starch is the starting material, there is obtained, in addition to ethanol, a smaller amount of *fusel oil* (German: *Fusel*, inferior liquor), a mixture of primary alcohols: mostly isopentyl alcohol with smaller amounts of *n*-propyl alcohol, isobutyl alcohol, and 2-methyl-1-butanol, known *as active amyl alcohol* (*amy*l = *pentyl*).

In the future there will undoubtedly be a shift toward carbohydrates as our source of carbon: carbon for organic chemicals and carbon in the form of fuels. With this shift, fermentation processes will take on greater and greater importance.

Problem 10.3 The isopentyl and active amyl alcohols are formed by enzymatic transformation of the amino acids *leucine* and *isoleucine*, which come from hydrolysis of protein material in the starch.

$(CH_3)_2CHCH_2CH(NH_3^+)COO^-$

Leucine

$CH_3CH_2CH(CH_3)CH(NH_3^+)COO^-$

Isoleucine

(a) Which amino acid gives which alcohol? (b) Although both amino acids are optically active, and the transformation processes are analogous, only one gives an alcohol that is optically active. Why is this?

10.8 Fuel from carbohydrates. Carbon dioxide balance

In petroleum we have a fuel reserve on which we can draw for energy—for as long as it lasts. We burn it, and either use the heat produced directly to warm ourselves or convert it into other forms of energy: mechanical energy to move things about; electrical energy, which is itself transformed—at a more convenient place than where the original burning happened—into light or mechanical energy, or back into heat.

With petroleum as fuel, we face two big problems. First, there is only a limited supply of this fossil fuel, and it is rapidly being used up. Second, burning it produces carbon dioxide which, as we have seen, is the most abundant of the "greenhouse gases" that threaten the earth with steadily rising temperatures.

But there is an alternative to petroleum as the source of much of the fuel we use: *carbohydrates*. The ethanol produced by fermentation has been found to serve admirably as transportation fuel—fuel to fill the tanks of our cars and trucks and trains. And transportation fuel now consumes over half of the petroleum used in the United States, and produces more than a quarter of the carbon dioxide emitted from fossil fuels in this country.

Carbohydrates have two enormous advantages over petroleum as a source of fuel. First, the supply of carbohydrates is not a limited one that we steadily deplete; rather, it is constantly replenished by the growing of plants. It has been calculated that our needs for transportation fuel could be fully met by ethanol from fermentation of cellulose: cellulose from wood and grasses grown on marginal croplands, and from municipal waste.

The second advantage of carbohydrates has to do with the production of carbon dioxide. The burning of ethanol, like the burning of petroleum, produces carbon dioxide—but there is a difference. To see what this difference is, let us look at how carbohydrates are formed.

In the leaf of a plant, carbon dioxide and water combine to form a carbohydrate: the sugar glucose. This process is photosynthesis; it requires the catalyst chlorophyll, and it requires *energy* in the form of light. This energy is, of course, supplied by the sun. Thousands of glucose molecules are then combined to form one or the other of two giant carbohydrate molecules: *cellulose*, which makes up the framework of the plant; and *starch*, which is stored in seeds.

$$CO_2 + H_2O + \text{energy} \longrightarrow \text{carbohydrates} + O_2\uparrow \qquad \textbf{In plants}$$

Energy from carbohydrates is nothing new; it has always been a (literally) vital part of our lives. Carbohydrates are the food reserve from which our bodies obtain the energy they need to keep warm, move about, and build new tissue. (We eat animals, too, but ultimately the chain goes back to a carbohydrate-eater.) When eaten by an animal, starch—and in some cases cellulose, too—is broken down into the original glucose units. Some of the glucose is converted into fats and proteins. Much is oxidized, ultimately to carbon dioxide and water, with the release of the energy originally supplied by sunlight.

$$\text{carbohydrates} + O_2 \longrightarrow H_2O + CO_2\uparrow + \text{energy} \qquad \textbf{In animals}$$

Now, there is a marvelous balance in this relationship between plants and animals—a balance that has permitted life to persist on this planet for hundreds of millions of years. Plants give off the oxygen needed for animals to breathe; plants absorb the carbon dioxide produced in animals by oxidation. In the oxidation of a carbohydrate the *carbon dioxide produced is exactly balanced by the carbon dioxide consumed* by the plant in making the carbohydrate. This balance holds *no matter how* the oxidation takes place. Like the metabolism of glucose in the body, the burning of fermentation alcohol in an engine causes *no* net increase in carbon dioxide in the atmosphere.

Contrast this with the burning of petroleum.True, the fossil fuels came from carbohydrates, too—once. But the carbon dioxide they produce is not balanced by carbon dioxide consumed; that consumption took place long, long ago, and extended over millions of years. Little wonder that burning up all that petroleum in a century or so has upset the carbon dioxide balance on our planet.

Using fuel from carbohydrates is a step toward doing as a society what our bodies already do individually: get energy from the sun by way of growing plants.

10.9 Ethanol

Ethanol is not only the oldest synthetic organic chemical used by man, but it is also one of the most important.

In industry ethanol is widely used as a solvent for lacquers, varnishes, perfumes, and flavorings; as a medium for chemical reactions; and in recrystallizations. In addition, it is an important raw material for synthesis; after we have learned more about the reactions of alcohols, we can better appreciate the role played by the leading member of the family. For these industrial purposes ethanol is prepared both by hydration of ethylene and by fermentation of sugar from molasses (or sometimes starch); thus its ultimate sources are petroleum, sugar cane, and various grains.

Ethanol is the alcohol of “alcoholic” beverages. For this purpose it is prepared by fermentation of sugar from a truly amazing variety of vegetable sources. The particular beverage obtained depends upon what is fermented (rye or corn, grapes or elderberries, cactus pulp or dandelions), how it is fermented (whether carbon dioxide is allowed to escape or is bottled up, for example), and what is done after fermentation (whether or not it is distilled). The special flavor of a beverage is not due to the ethanol but to other substances, either characteristic of the particular source, or deliberately added.

Medically, ethanol is classified as a *hypnotic* (sleep producer); it is less toxic than other alcohols. (Methanol, for example, is quite *poisonous*: drinking it, breathing it for prolonged periods, or allowing it to remain long on the skin can lead to blindness or death.)

Because of its unique position as both a highly taxed beverage and an important industrial chemical, ethanol poses a special problem: it must be made available to the chemical industry in a form that is unfit to drink. This problem is solved by addition of a *denaturant*, a substance that makes it unpalatable or even poisonous. Two of the eighty-odd legal denaturants, for example, are methanol and high-test gasoline. When necessary, pure undenatured ethanol is available for chemical purposes, but its use is strictly controlled by the Government.

Except for alcoholic beverages, nearly all the ethanol used is a mixture of 95% alcohol and 5% water, known simply as *95% alcohol*. What is so special about the concentration of 95%? Whatever the method of preparation, ethanol is obtained first mixed with water; this mixture is then concentrated by fractional distillation. But it happens that the component of lowest boiling point is not ethanol (b.p. 78.3 °C) but a *binary azeotrope* containing 95% alcohol and 5% water (b.p. 78.15 °C). As an azeotrope, it of course gives a vapor of the same composition, and hence cannot be further concentrated by distillation no matter how efficient the fractionating column used.

Pure ethanol is known as *absolute alcohol*. Although more expensive than 95% alcohol, it is available for use when specifically required. It is obtained by taking advantage of the existence of another azeotrope, this time a *ternary* one of b.p. 64.9 °C; this contains 7.5% water, 18.5% ethyl alcohol, and 74% benzene.

Problem 10.4 Describe exactly what will happen if one distills a mixture of 150 g of 95% alcohol and 74 g of benzene.

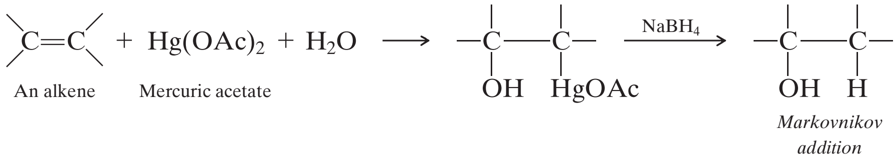
For certain special purposes even the slight trace of water found in commercial absolute alcohol must be removed. This can be accomplished by treatment of the alcohol with metallic magnesium; water is converted into insoluble $Mg(OH)_2$, from which the alcohol is then distilled.

10.10 Preparation of alcohols

Most of the simple alcohols and a few of the complicated ones are available from the industrial sources. Other alcohols must be prepared by one of the methods outlined below.

PREPARATION OF ALCOHOLS

1. Oxymercuration–demercuration.



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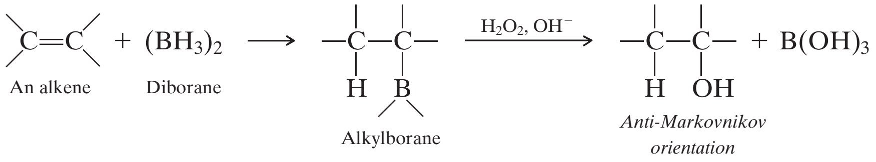
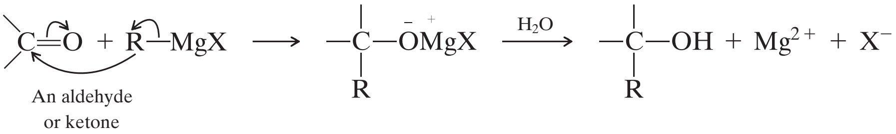
2. Hydroboration–oxidation.



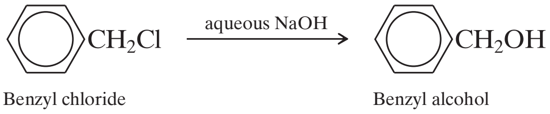
3. Grignard synthesis.

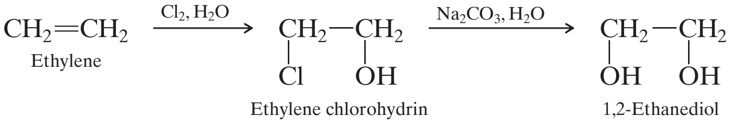


4. Hydrolysis of alkyl halides.

$$R{-}X + OH^- \text{ (or } H_2O) \longrightarrow R{-}OH + X^- \text{ (or HX)}$$

Examples:



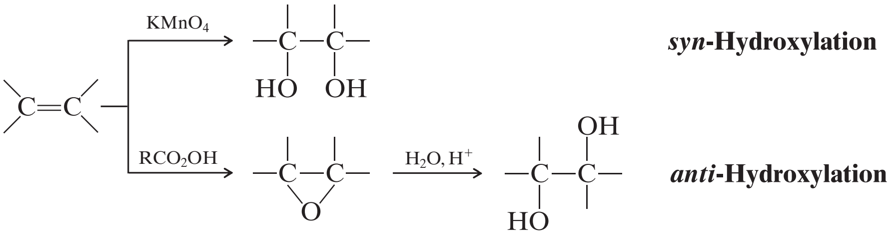


5. Aldol condensation.

6. Reduction of carbonyl compounds.

7. Reduction of acids and esters.

8. Hydroxylation of alkenes.



We can follow either of two approaches to the synthesis of alcohols—or, for that matter, of most other kinds of compounds, (a) We can retain the original carbon skeleton, and simply convert one functional group into another until we arrive at an alcohol; or (b) we can generate a new, bigger carbon skeleton and at the same time produce an alcohol.

By far the most important method of preparing alcohols is the **Grignard synthesis**. This is an example of the second approach, since it leads to the formation of carbon–carbon bonds. In the laboratory a chemist is chiefly concerned with preparing the more complicated alcohols that cannot be bought. These are prepared by the Grignard synthesis from rather simple starting materials: Grignard reagents, which we have already met; and *aldehydes* and *ketones*, which we shall meet later in this chapter. The alkyl halides from which the Grignard reagents are made, as well as the aldehydes and ketones themselves, are most conveniently prepared from alcohols; thus the method ultimately involves the synthesis of alcohols from less complicated alcohols.

Alcohols can be conveniently made from compounds containing carbon–carbon double bonds in two ways: by **oxymercuration–demercuration** and by **hydroboration–oxidation**. Both amount to addition of water to the double bond, but with *opposite orientation*, and hence the two methods neatly complement each other. Hydrolysis of alkyl halides is severely limited as a method of synthesizing alcohols, since alcohols are usually more available than the corresponding halides; indeed, the best general preparation of halides is from alcohols. There are, however, some useful applications of this method.

10.11 Reactions of alcohols

The chemical properties of an alcohol, ROH, are determined by its functional group, —OH, the hydroxyl group. When we have learned the chemistry of the alcohols, we shall have learned much of the chemistry of the hydroxyl group in whatever compound it may occur; we shall know, in part at least, what to expect of hydroxy halides, hydroxy acids, hydroxy aldehydes, etc.

Reactions of an alcohol can involve the breaking of either of two bonds: the C—OH bond, with removal of the —OH group; or the O—H bond, with removal of —H. Either kind of reaction can involve substitution, in which a group replaces the —OH or —H, or elimination, in which a double bond is formed.

Differences in the structure of the group R cause differences in reactivity, and in a few cases even profoundly alter the course of reaction. We shall see what these effects of structure on reactivity are, and how they can be accounted for.

Some of the more important reactions of alcohols are listed below, and are discussed in following sections.

REACTIONS OF ALCOHOLS

C---OH Bond Cleavage

$$C \nmid OH$$

1. **Reaction with hydrogen halides.**

$$R{-}OH + HX \longrightarrow R{-}X + H_2O \qquad R\ \textit{may rearrange}$$

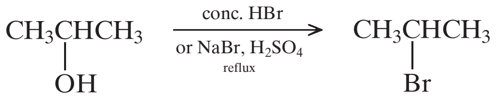
Reactivity of HX: HI > HBr > HCl

Reactivity of ROH: allyl, benzyl > 3° > 2° > 1°

CONTINUED

CONTINUED

Examples:



$$\underset{\displaystyle OH}{CH_3\overset{}{C}HCH_3} \xrightarrow[\text{or NaBr, } H_2SO_4 \text{ reflux}]{\text{conc. HBr}} \underset{\displaystyle Br}{CH_3\overset{}{C}HCH_3}$$

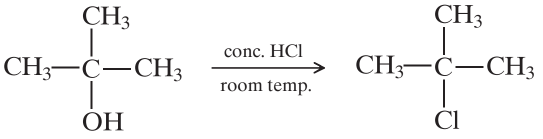
Isopropyl alcohol

Isopropyl bromide

$$CH_3CH_2CH_2CH_2CH_2OH \xrightarrow[\text{heat}]{HCl,\ ZnCl_2} CH_3CH_2CH_2CH_2CH_2Cl$$

n-Pentyl alcohol

n-Pentyl chloride



$$CH_3-\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{C}}-CH_3 \xrightarrow[\text{room temp.}]{\text{conc. HCl}} CH_3-\underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{C}}-CH_3$$

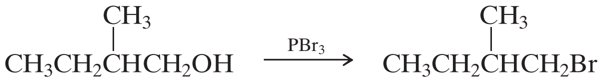
tert-Butyl alcohol

tert-Butyl chloride

2. Reaction with phosphorus trihalides.

$$3R-OH + PX_3 \longrightarrow 3R-X + H_3PO_3$$
$$(PX_3 = PBr_3, PI_3)$$

Examples:



$$CH_3CH_2\overset{\displaystyle CH_3}{C}HCH_2OH \xrightarrow{PBr_3} CH_3CH_2\overset{\displaystyle CH_3}{C}HCH_2Br$$

2-Methyl-1-butanol

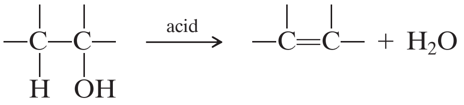
2-Methyl-1-bromobutane

$$CH_3CH_2OH \xrightarrow{P\ +\ I_2} CH_3CH_2I$$

Ethyl alcohol

Ethyl iodide

3. Dehydration.



$$-\underset{\displaystyle H}{\overset{|}{C}}-\underset{\displaystyle OH}{\overset{|}{C}}- \xrightarrow{\text{acid}} -\overset{|}{C}=\overset{|}{C}- + H_2O$$

Rearrangement may occur

Reactivity of ROH: 3° > 2° > 1°

O---H Bond Cleavage

$RO{+}H$

4. Reaction as acids: reaction with active metals.

$$RO-H + M \longrightarrow RO^-M^+ + \tfrac{1}{2}H_2 \qquad M = Na, K, Mg, Al, \text{etc.}$$

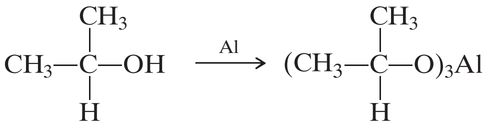
Reactivity of ROH: $CH_3OH > 1° > 2° > 3°$

CONTINUED

Examples:

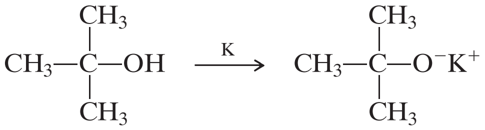
$$CH_3CH_2OH \xrightarrow{Na} CH_3CH_2O^-Na^+ + \tfrac{1}{2}H_2$$

Ethyl alcohol — Sodium ethoxide



$$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle H}{C}}{-}OH \xrightarrow{Al} (CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle H}{C}}{-}O)_3Al$$

Isopropyl alcohol — Aluminum isopropoxide

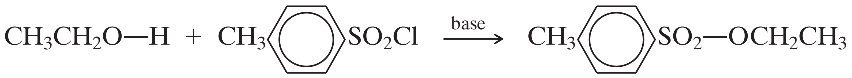


$$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}OH \xrightarrow{K} CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}O^-K^+$$

tert-Butyl alcohol — Potassium *tert*-butoxide

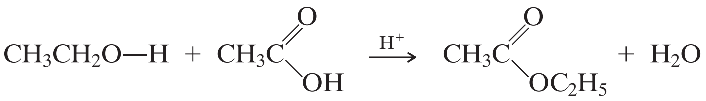
5. Ester formation.

Examples:



Tosyl chloride
(*p*-Toluenesulfonyl chloride)

Ethyl tosylate

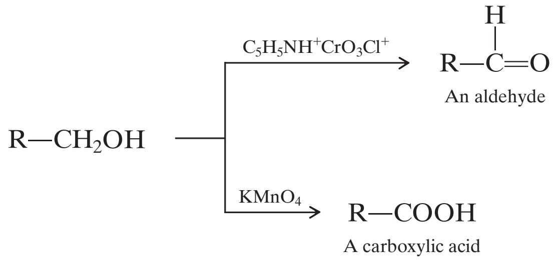


Acetic acid

Ethyl acetate

6. Oxidation.

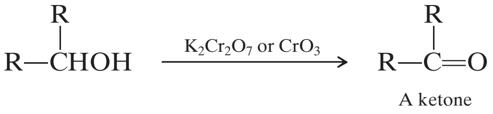
Primary



An aldehyde

A carboxylic acid

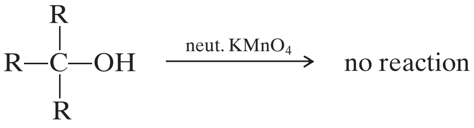
Secondary



$$R{-}\overset{\displaystyle R}{C}HOH \xrightarrow{K_2Cr_2O_7 \text{ or } CrO_3} R{-}\overset{\displaystyle R}{C}{=}O$$

A ketone

Tertiary



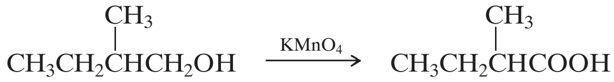
$$R{-}\overset{\displaystyle R}{\underset{\displaystyle R}{C}}{-}OH \xrightarrow{\text{neut. } KMnO_4} \text{no reaction}$$

CONTINUED

Examples:

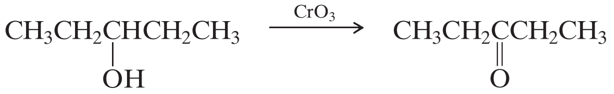
$$\mathrm{CH_3CH_2CH_2OH} \xrightarrow{\mathrm{C_5H_5NH^+CrO_3Cl^-}} \mathrm{CH_3CH_2}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}\mathrm{{=}O}$$

n-Propyl alcohol (1°) — Propionaldehyde



$$\mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCH_2OH} \xrightarrow{\mathrm{KMnO_4}} \mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCOOH}$$

2-Methyl-1-butanol (1°) — 2-Methylbutanoic acid



$$\mathrm{CH_3CH_2}\underset{\mathrm{OH}}{\underset{|}{\mathrm{C}}}\mathrm{HCH_2CH_3} \xrightarrow{\mathrm{CrO_3}} \mathrm{CH_3CH_2}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{CH_2CH_3}$$

3-Pentanol (2°) — 3-Pentanone

■

We can see that alcohols undergo many kinds of reactions, to yield many kinds of products. Because of the availability of alcohols, each of these reactions is one of the best ways to make the particular kind of product. Some of these reactions we shall discuss in this chapter; others we shall take up in later chapters, where we need them for the synthesis of other kinds of compounds.

10.12 Alcohols as acids and bases

Of the varied chemical properties of alcohols, there is one pair that underlies all the others; their *acidity* and *basicity*. These properties reside, of course, in the functional group of alcohols: the hydroxyl group, —OH. This group is like the hydroxyl group of water, a compound with which we are already familiar. Like water, alcohols are weak acids and weak bases—roughly, about as acidic and as basic as water.

It is oxygen, with its unshared electron pairs, that makes an alcohol basic. Like water, alcohols are basic enough to accept a proton from strong acids like hydrogen chloride and hydrogen sulfate, and thus bring about complete dissociation of these acids. For example:

$$\underset{\substack{\text{Alcohol}\\ \textit{Stronger}\\ \textit{base}}}{\mathrm{ROH}} + \mathrm{H_2SO_4} \rightleftharpoons \underset{\substack{\text{Protonated}\\ \text{alcohol}}}{\mathrm{ROH_2^+}} + \underset{\substack{\textit{Weaker}\\ \textit{base}}}{\mathrm{HSO_4^-}}$$

In alcohols, hydrogen is bonded to the very electronegative element oxygen. The polarity of the O—H bond facilitates the departure of a proton; viewed differently, electronegative oxygen readily accommodates the negative charge of electrons left behind.

The acidity of alcohols is shown by their reaction with active metals to liberate hydrogen gas.

$$\underset{\substack{\text{An}\\ \text{alcohol}\\ \textit{A weak acid}}}{\mathrm{ROH}} + \mathrm{Na} \longrightarrow \underset{\substack{\text{A sodium}\\ \text{alkoxide}\\ \textit{A stronger base}}}{\mathrm{RONa}} + \tfrac{1}{2}\mathrm{H_2}$$

The products are called *alkoxides*: sodium ethoxide, for example, or potassium isopropoxide.

Just how acidic are alcohols? With the possible exception of methanol, they are somewhat weaker acids than water. When water is added to an alkoxide, there is obtained sodium hydroxide and the parent alcohol. The weaker acid, RO—H, is displaced from its salt by the stronger acid, HO—H. In other language, the stronger base, RO^-, pulls the proton away from the weaker base, HO^-; if RO^- holds the proton more tightly than HO^-, then RO—H must be a weaker acid than HO—H.

$$\underset{\substack{\text{Stronger}\\ \text{base}}}{\mathrm{RO^-Na^+}} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\mathrm{H{-}OH}} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{base}}}{\mathrm{Na^+OH^-}} + \underset{\substack{\text{Weaker}\\ \text{acid}}}{\mathrm{RO{-}H}}$$

Like water and ammonia, alcohols are enormously stronger acids than alkanes, and readily displace them from their "salts": from Grignard reagents, for example.

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{\mathrm{ROH}} + \mathrm{R'MgX} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\mathrm{R'H}} + \mathrm{Mg(OR)X}$$

We can thus place alcohols in a sequence of acidity relative to other familiar compounds. And when we do this, we necessarily arrive at an order of relative basicity for the corresponding conjugate bases.

Relative acidities $H_2O > ROH > NH_3 > RH$

Relative basicities $OH^- < OR^- < NH_2^- < R^-$

The method we have just described for comparing acidities is a general one, and has been used to determine the relative acidities of a number of extremely weak acids. *One compound is shown to be a stronger acid than another by its ability to displace the second compound from salts.*

$$\underset{\substack{\text{Stronger}\\ \text{acid}}}{\mathrm{A{-}H}} + \mathrm{B^-M^+} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\mathrm{B{-}H}} + \mathrm{A^-M^+}$$

Let us look more closely at the relative acidities of alcohols and water. The difference between an alcohol and water is, of course, the alkyl group. Not only does the alkyl group make an alcohol less acidic than water, but the *bigger* the alkyl group, the less acidic the alcohol; methanol is the strongest and tertiary alcohols are the weakest. For a long time, this acid-weakening effect in alcohols was believed to be a polar effect: electron release by alkyl groups intensifies the negative charge of alkoxide ions and makes them stronger bases. But then it was found that in the gas phase the relative acidities of the various alcohols and of alcohols and water are reversed; evidently here the easily polarized alkyl groups are helping to accommodate the negative charge, just as they help to accommodate the positive charge in carbocations . Alcohols *are* weaker acids than water *in solution*—which is where we are normally concerned with acidity—and this is a solvation effect; a bulky group interferes with ion-dipole interactions that stabilize the anion.

Since an alcohol is a weaker acid than water, an alkoxide is not prepared by the reaction of the alcohol with sodium hydroxide, but rather by reaction of the alcohol with the active metal itself.

Alkoxides are extremely useful reagents. They are powerful bases—stronger than hydroxide—and, by varying the alkyl group, we can vary their degree of basicity, their steric requirements, and their solubility properties. As nucleophiles, they can be used to introduce the alkoxy group into molecules, as we shall see later in this chapter.

Problem 10.5 Which would you expect to be the stronger acid:

(a) β-chloroethyl alcohol or ethyl alcohol?
(b) isopropyl alcohol or hexafluoroisopropyl alcohol?
(c) *n*-propyl alcohol or glycerol, $HOCH_2CHOHCH_2OH$?
(d) Which alcohol of each pair would you expect to be the stronger nucleophile?

Problem 10.6 Sodium metal was added to *tert*-butyl alcohol and allowed to react. When the metal was consumed, ethyl bromide was added to the resulting mixture. Work-up of the reaction mixture yielded a compound of formula $C_6H_{14}O$.

(a) Write equations for all reactions. (b) What familiar reaction type is involved?

10.13 Reaction of alcohols with hydrogen halides. Acid catalysis

The acidity of alcohols clearly involves cleavage of the CO—H bond. Now let us turn to a reaction that just as clearly involves cleavage of the C—OH bond.

One method of making alkyl halides, we saw, is by the reaction of alcohols with hydrogen halides. Let us look more closely at this reaction, not just as an important synthetic method, but as an example of nucleophilic substitution, with alcohols

$$\underset{\text{Alcohol}}{\text{R—OH}} + \text{HX} \longrightarrow \underset{\text{Alkyl halide}}{\text{R—X}} + \text{H}_2\text{O}$$

as the substrate. In doing this, we shall see something completely new to us: how we can change a very poor leaving group into a very good leaving group *instantaneously*, and with no more effort than it takes to pour a solution from a bottle into a flask.

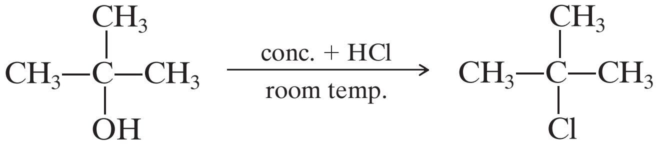
Alcohols react readily with hydrogen halides to yield alkyl halides and water.

The reaction is carried out either by passing the dry halogen halide gas into the alcohol, or by heating the alcohol with the concentrated aqueous acid. Sometimes hydrogen bromide is generated in the presence of the alcohol by reaction between sulfuric acid and sodium bromide.

The least reactive of the hydrogen halides, HCl, generally requires the presence of zinc chloride for reaction with primary and secondary alcohols; on the other hand, the very reactive *tert*-butyl alcohol is converted to the chloride by simply being shaken with concentrated hydrochloric acid at room temperature. For example:

$$\underset{n\text{-Butyl alcohol}}{CH_3CH_2CH_2CH_2OH} \xrightarrow[\text{NaBr, } H_2SO_4\text{, heat}]{\text{dry HBr or}} \underset{n\text{-Butyl bromide}}{CH_3CH_2CH_2CH_2Br}$$

$$\underset{n\text{-Propyl alcohol}}{CH_3CH_2CH_2OH} \xrightarrow[\text{heat}]{HCl + ZnCl_2} \underset{n\text{-Propyl chloride}}{CH_3CH_2CH_2Cl}$$



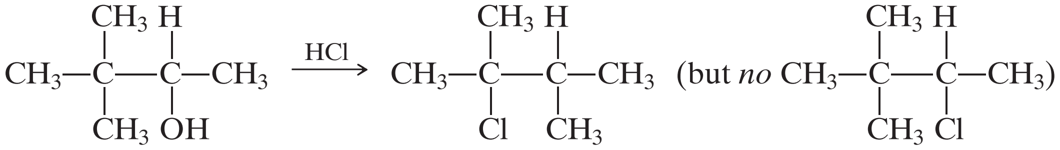
$$CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_3 \xrightarrow[\text{room temp.}]{\text{conc. + HCl}} CH_3-\underset{Cl}{\overset{CH_3}{C}}-CH_3$$

tert-Butyl alcohol *tert*-Butyl chloride

Let us list some of the facts that are known about the reaction between alcohols and hydrogen halides.

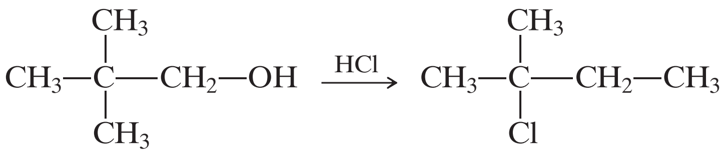
(a) The reaction is catalysed by acids. Even though the aqueous hydrogen halides are themselves strong acids, the presence of additional sulfuric acid speeds up the formation of alkyl halides.

(b) Rearrangement of the alkyl group occurs, except with most primary alcohols. The alkyl group in the halide does not always have the same structure as the alkyl group in the parent alcohol. For example:



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\underset{OH}{\overset{H}{C}}-CH_3 \xrightarrow{HCl} CH_3-\underset{Cl}{\overset{CH_3}{C}}-\underset{CH_3}{\overset{H}{C}}-CH_3 \quad (\text{but } no\ CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\underset{Cl}{\overset{H}{C}}-CH_3)$$

3,3-Dimethyl-2-butanol 2-Chloro-2,3-dimethylbutane



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-OH \xrightarrow{HCl} CH_3-\underset{Cl}{\overset{CH_3}{C}}-CH_2-CH_3$$

Neopentyl alcohol *tert*-Pentyl chloride

We see that the halogen does not always become attached to the carbon that originally held the hydroxyl (the first example); even the carbon skeleton may be different from that of the starting material (the second example).

On the other hand, as shown above for *n*-propyl *n*-butyl alcohols, most primary alcohols give high yields of primary halides *without* rearrangement.

(c) The order of reactivity of alcohols toward HX is 3° > 2° > 1° < CH_3. Reactivity decreases through most of the series (and this order is the basis of the *Lucas test*), passes through a *minimum* at 1°, and rises again at CH_3.

What do the facts that we have just listed suggest to us about the mechanism of reaction between alcohols and hydrogen halides?

Catalysis by *acid* suggests that the protonated alcohol ROH_2^+ is involved. The occurrence of *rearrangement* suggests that carbocations are intermediates— although *not* with primary alcohols. The idea of carbocations is strongly supported by the *order of reactivity* of alcohols, which parallels the stability of carbocations— *except* for methyl.

On the basis of this evidence, we formulate the following mechanism. The alcohol accepts

$$(1) \qquad R{-}OH + HX \rightleftharpoons R{-}OH_2^+ + :X^-$$

$$(2) \qquad R{-}OH_2^+ \rightleftharpoons R^+ + H_2O:$$

$$(3) \qquad R^+ + :X^- \longrightarrow R{-}X$$

S_N1:
all except methanol and most 1° alcohols

(step 1) the hydrogen ion to form the protonated alcohol, which dissociates (step 2) into water and a carbocation; the carbocation then combines (step 3) with a halide ion (not necessarily the one from step 1) to form the alkyl halide.

Looking at the mechanism we have written, we recognize the reaction for what it is: *nucleophilic substitution*, with the protonated alcohol as substrate and halide ion as the nucleophile. Once the reaction type is recognized, the other pieces of evidence fall into place.

The particular set of equations written above is, of course, the S_N1 mechanism for substitution. Primary alcohols do not undergo rearrangement simply because they do not react by this mechanism. Instead, they react by the alternative S_N2 mechanism:

$$:X^- + R{-}OH_2^+ \longrightarrow \left[\overset{\delta-}{X}\text{---}R\text{---}\overset{\delta+}{OH_2}\right] \longrightarrow X{-}R + H_2O:$$

S_N2:
most 1° alcohols and methanol

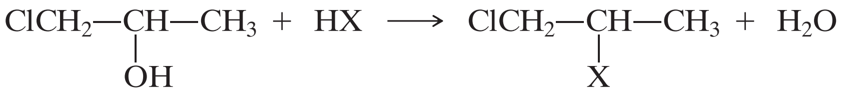
What we see here is another example of that characteristic of nucleophilic substitution: a shift in the molecularity of reaction, in this particular case occurring between 2° and 1°. This shift is confirmed by the fact that reactivity passes through a minimum at 1° and rises again at methyl.

Let us review what is probably happening here, beginning at the methyl end of the series. The methyl substrate is least capable of heterolysis and most open to nucleophilic attack; it reacts by a full-fledged S_N2 reaction. So do primary substrates but, because of greater steric hindrance, they react less rapidly than the methyl. Secondary substrates give still more steric hindrance, but are more capable of forming carbocations. For them heterolysis is faster than nucleophilic attack by a halide ion, and the mechanism change's here to S_N1. With the change in mechanism, the rate begins to rise. Tertiary substrates, too, react by an S_N1 mechanism; they react faster than secondary substrates because of the greater dispersal of charge in the incipient carbocations.

So far, we have discussed this reaction in terms of the very useful classification of substrates as 1°, 2°, or 3°. But we must always keep in mind that it is not this classification—*as such*—that is important. It is the factors actually at work: in this reaction, *steric hindrance* to nucleophilic attack, and *dispersal of charge* in the incipient carbocation. These factors give rise—*among other things*—to the relationship between 1°, 2°, 3° and the S_N2–S_N1 competition. But they do more than that. They can make a substrate of one class act like a substrate of another class; and yet such behavior is understandable if we simply examine the structures involved. Let us look at two such examples.

As shown above, neopentyl alcohol reacts with almost complete rearrangement, showing that, although primary, it follows the carbocation mechanism. This is contrary to our generalization, but readily accounted for. Although neopentyl is a primary group, it is a very bulky one and, as we have seen, neopentyl substrates undergo S_N2 reactions very slowly. Formation of the neopentyl cation here is slow, too. but is nevertheless much faster than the alternative bimolecular reaction.

Our second example involves 1-chloro-2-propanol. Although technically a secondary alcohol, it reacts with hydrogen halides "abnormally" slowly, and at about the rate of a primary alcohol. This time we are dealing, not with a steric effect, but



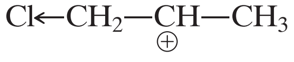
$$\mathrm{ClCH_2{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}CH_3} + \mathrm{HX} \longrightarrow \mathrm{ClCH_2{-}\underset{\underset{\displaystyle X}{|}}{CH}{-}CH_3} + \mathrm{H_2O}$$

1-Chloro-2-propanol 1-Chloro-2-halopropane

with a polar effect. The rate of an S_N1 reaction, we have seen, depends upon the stability of the carbocation being formed. Let us compare, then, the 1-chloro-2-propyl cation with a simple secondary cation, the isopropyl cation, say. Electronegative chlorine has an electron-withdrawing inductive effect. As we have seen, this intensifies the positive charge on the electron-deficient carbon and makes the carbocation

$$\mathrm{CH_3{-}\underset{\oplus}{CH}{-}CH_3}$$

Isopropyl cation



$$\mathrm{Cl{\leftarrow}CH_2{-}\underset{\oplus}{CH}{-}CH_3}$$

1-Chloro-2-propyl cation
Chlorine withdraws electrons:
intensifies charge,
destabilizes cation

less stable. This same electron withdrawal destabilizes the incipient cation in the transition state, raises E_{act}, and slows down the reaction.

Now let us turn to what is to us the most important aspect of the reaction between alcohol and hydrogen halides: the *acid catalysis*. What does acid do? In the first step, it converts the alcohol into the protonated alcohol, which is the substrate actually undergoing substitution. In the absence of acid, substitution—by either mechanism—would require loss of the hydroxide ion: strongly basic, and an extremely poor leaving group. Substitution with the protonated alcohol as substrate,

$$\text{R—OH}_2^{\oplus} \longrightarrow \underset{\substack{\text{Weak base:}\\ \textit{good leaving group}}}{\text{R}^{\oplus} + \text{H}_2\text{O}} \qquad \textbf{Easy}$$

$$\text{R—OH} \longrightarrow \underset{\substack{\text{Strong base:}\\ \textit{poor leaving group}}}{\text{R}^{\oplus} + \text{OH}^-} \qquad \textbf{Difficult}$$

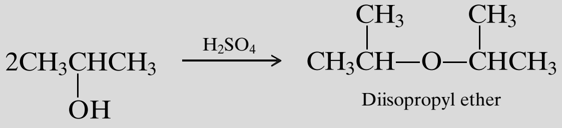
on the other hand, involves loss of water: weakly basic, and a very good leaving group. Protonation of the alcohol involves a simple acid–base equilibrium, and takes place instantaneously on mixing of the reagents. Yet it changes a very poor leaving group into a very good one and permits reaction to occur. The evidence indicates that separation of a hydroxide ion from an alcohol almost never occurs; reactions involving cleavage of the C—O bond of an alcohol seem in nearly every case to require an acidic catalyst, the purpose of which, as here, is to form the protonated alcohol.

Thus alcohols, like alkyl halides, undergo nucleophilic substitution by both S_N2 and S_N1 mechanisms, but alcohols lean more toward the unimolecular mechanism. We can see, in a general way, why this is so. To undergo substitution an alcohol must be protonated, and this requires an acidic medium. An S_N2 reaction, we have seen, is favored by the use of a strong nucleophile, something that is quite feasible in reactions of alkyl halides. But we cannot have a strong nucleophile—a strong *base*—present in the acidic medium required for protonation of an alcohol; any base much stronger than the alcohol itself would become protonated at the expense of the alcohol. Restricted, then, to reaction with weakly basic, weakly nucleophilic reagents, alcohols react chiefly by the carbocation mechanism.

In the introduction to this chapter it was, of course, protonation that was referred to as the most important—and simplest—catalytic effect in organic chemistry. In the presence of acid many kinds of atoms found in organic compounds are protonated to a significant degree: oxygen, nitrogen, sulfur, often even carbon. And, as we shall see in nearly every chapter of this book, this protonation exerts powerful effects on reactions of many kinds involving nearly every class of compound.

Problem 10.7 Because of the great tendency of the neopentyl cation to rearrange, neopentyl chloride cannot be prepared from the alcohol. How might neopentyl chloride be prepared?

Problem 10.8 When ispropyl alcohol is heated in the presence of H_2SO_4, there can be obtained diisopropyl ether (i-Pr_2O).



$$2\,\text{CH}_3\underset{\text{OH}}{\underset{|}{\text{C}}}\text{HCH}_3 \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3\overset{\text{CH}_3}{\overset{|}{\text{C}}}\text{H—O—}\overset{\text{CH}_3}{\overset{|}{\text{C}}}\text{HCH}_3$$

Isopropyl alcohol

Diisopropyl ether

(a) Show all steps in a likely mechanism or mechanisms for the formation of this product.
(b) To what class of reactions does this belong?

10.14 Formation of alkyl sulfonates

Alcohols are the precursors of a wide variety of compounds in which the —OH group has been lost: replaced by some group, like halide; or eliminated with formation of a double bond. But this loss of —OH is not brought about directly, in a single step: it must be brought about indirectly by first converting the alcohol into something else; the very poor leaving group must be converted into a good leaving group. The simplest way to do this is through protonation. But, as we have just seen, the acidic medium needed for protonation severely limits our choice of reagents to weak nucleophiles and weak bases; and under these conditions reaction tends to take place via carbocations, and hence with the likelihood of rearrangement.

There is another way, however, to change the —OH into a good leaving group; more elaborate than protonation, but with certain important advantages. It involves conversion of alcohols into certain esters, the alkyl sulfonates, $\mathrm{ArSO_2OR}$.

Sulfonic acids, $\mathrm{ArSO_3H}$, are related to sulfuric acid and, like sulfuric, are *strong* acids. Their anions, the sulfonates, are weak bases and hence good leaving groups.

$$\mathrm{ArSO_3H} \rightleftharpoons \mathrm{ArSO_3^-} + \mathrm{H^+}$$

A sulfonic acid
Strong acid

A sulfonate anion
Weak base

As a result, alkyl sulfonates undergo nucleophilic substitution (and elimination) in much the same manner as alkyl halides. They are most often used in the study of mechanisms, but frequently in synthesis, too.

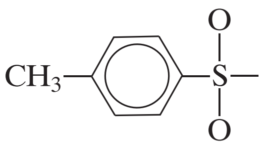
$$\mathrm{ArSO_2O{-}R} + :\mathrm{Z} \longrightarrow \mathrm{R{-}Z} + \mathrm{ArSO_3^-}$$

An alkyl sulfonate

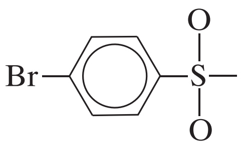
Nucleophile

A sulfonate anion
Weak base:
good leaving group

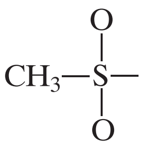
Most commonly used are esters of *p*-toluenesulfonic acid: the *p*-toluenesulfon-ates. The name of the *p*-toluenesulfonyl group is often shortened to *tosyl* (Ts) and *p*-toluenesulfonates become *tosylates* (TsOR).



Tosyl or *Ts*

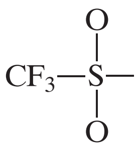


Brosyl or *Bs*



$$\mathrm{CH_3{-}SO_2{-}}$$

Mesyl or *Ms*

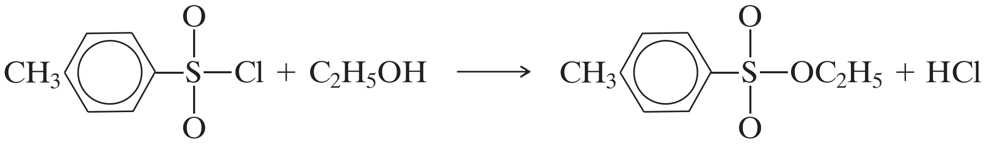


$$\mathrm{CF_3{-}SO_2{-}}$$

Trifyl or *Tf*

The tosyl and brosyl groups contain an aromatic ring. We shall understand the chemistry of this ring later; for now, we need know only that it is unreactive to the reagents used here. Two of the groups shown are simple aliphatic ones, derived from methanesulfonic acid ($\mathrm{CH_3SO_2OH}$) and trifluoromethanesulfonic acid ($\mathrm{CF_3SO_2OH}$).

Like alkyl halides, alkyl sulfonates are readily made from alcohols. For example:



TsCl
p-Toluenesulfonyl chloride
Tosyl chloride

$TsOC_2H_5$
Ethyl *p*-toluenesulfonate

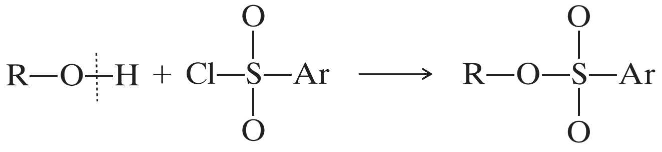
Ethyl tosylate

Alkyl sulfonates offer a very real advantage over alkyl halides in reactions where stereochemistry is important; this advantage lies not so much in the reactions of alkyl sulfonates as in their *preparation*. Whether we use an alkyl halide or sulfonate, and whether we let it undergo substitution or elimination, our starting point for the study is almost certainly the alcohol. The sulfonate *must* be prepared from the alcohol; the halide nearly always *will* be. It is at the alcohol stage that any resolution will be carried out, or any diastereomers separated; the alcohol is then converted into the halide or sulfonate, the reaction we are studying is carried out, and the products are examined.

Now, any preparation of a halide from an alcohol must involve breaking of the carbon–oxygen bond, and hence is accompanied by the likelihood of stereochemical

$$\mathrm{R}\vdots\mathrm{O{-}H} \xrightarrow{\mathrm{HX\ or\ PX_3}} \mathrm{R{-}X}$$

inversion and the possibility of racemization. Preparation of a sulfonate, on the other hand, does not involve the breaking of the carbon–oxygen bond, and hence proceeds with complete retention; when we carry out a reaction with this sulfonate, we know exactly what we are starting with.



$$\mathrm{R{-}O}\vdots\mathrm{H} + \mathrm{Cl{-}}\overset{\mathrm{O}}{\underset{\mathrm{O}}{\mathrm{S}}}\mathrm{{-}Ar} \longrightarrow \mathrm{R{-}O{-}}\overset{\mathrm{O}}{\underset{\mathrm{O}}{\mathrm{S}}}\mathrm{{-}Ar}$$

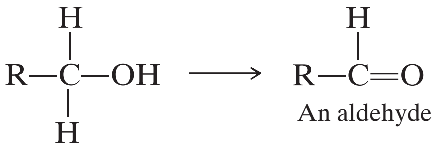
As a way of changing the —OH group of an alcohol into a good leaving group, conversion into sulfonates is just about ideal. We do not disturb the stereochemistry of the alkyl group. We can vary the structure of the sulfonate group and thus vary its leaving ability over a tremendous range. Although protonation of alcohols also generates a good leaving group, it limits our choice of reagents to those compatible with an acidic medium; but we can allow these alkyl sulfonates to react with just about any nucleophile or base we care to use.

Problem 10.9 You prepare *sec*-butyl tosylate from alcohol of $[\alpha]$ +6.9°. On hydrolysis with aqueous base, this ester gives *sec*-butyl alcohol of $[\alpha]$ −6.9°. Without knowing the configuration or optical purity of the starting alcohol, what (if anything) can you say about the stereochemistry of the hydrolysis step?

10.15 Oxidation of alcohols

The oxidation of an alcohol involves the loss of one or more hydrogens (*α-hydrogens*) from the carbon bearing the —OH group. The kind of product that is formed depends upon how many of these α-hydrogens the alcohol contains, that is, upon whether the alcohol is primary, secondary, or tertiary.

A **primary alcohol** contains two α-hydrogens, and can either lose one of them to form an *aldehyde*,

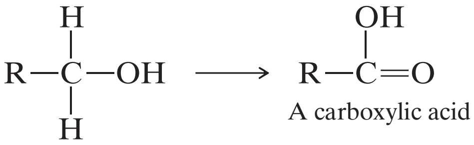


$$\mathrm{R{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}OH \longrightarrow R{-}\overset{\displaystyle H}{C}{=}O}$$

A 1° alcohol

An aldehyde

or both of them of form a *carboxylic acid*.



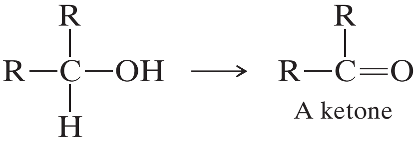
$$\mathrm{R{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}OH \longrightarrow R{-}\overset{\displaystyle OH}{C}{=}O}$$

A 1° alcohol

A carboxylic acid

(Under the proper conditions, as we shall find, an aldehyde can itself be oxidized to a carboxylic acid.)

A **secondary alcohol** can lose its only α-hydrogen to form a *ketone*.

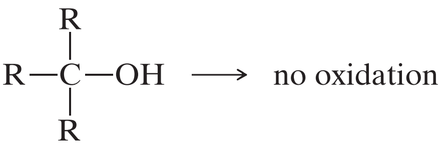


$$\mathrm{R{-}\overset{\displaystyle R}{\underset{\displaystyle H}{C}}{-}OH \longrightarrow R{-}\overset{\displaystyle R}{C}{=}O}$$

A 2° alcohol

A ketone

A **tertiary alcohol** contains no α-hydrogens and is *not oxidized*. (An acidic oxidizing agent can, however, dehydrate the alcohol to an alkene and then oxidize *this*.)



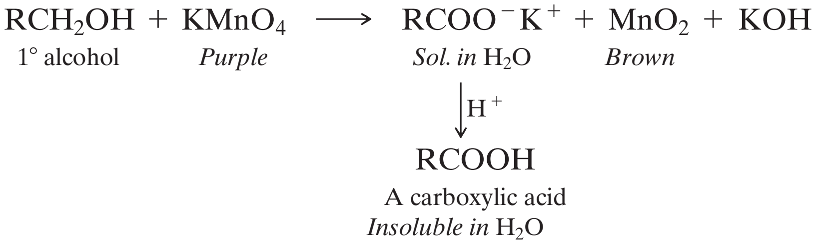
$$\mathrm{R{-}\overset{\displaystyle R}{\underset{\displaystyle R}{C}}{-}OH} \longrightarrow \text{no oxidation}$$

A 3° alcohol

These oxidation products—aldehydes, ketones, and carboxylic acids—are new to us, and at this point we need only learn to recognize their structures. As we shall find, they are extremely important compounds, and their preparation by the oxidation of alcohols is an essential part of organic synthesis.

The number of oxidizing agents available to the organic chemist is growing at a tremendous rate. As with all synthetic methods, emphasis is on the development of highly *selective* reagents, which will operate on only one functional group in a complex molecule, and leave the other functional groups untouched. Of the many reagents that can be used to oxidize alcohols, we can consider only the most common ones, those containing Mn(VII) or Cr(VI). Heptavalent manganese is used in the form of potassium permanganate, $KMnO_4$. Also widely used is hexavalent chromium, chromic acid essentially, in a form selected for the job at hand: acidic aqueous $K_2Cr_2O_7$, CrO_3 in glacial acetic acid, CrO_3 in pyridine, etc.

Oxidation of primary alcohols to carboxylic acids is usually accomplished by use of potassium permanganate. (Best yields are obtained if the permanganate and the alcohol are brought together in a non-polar solvent by use of phase-transfer catalysis. When reaction is complete, an aqueous solution of the soluble potassium salt of the carboxylic acid is filtered from MnO_2, and the acid is liberated by the addition of a stronger mineral acid.



$$\underset{1^\circ\text{ alcohol}}{RCH_2OH} + \underset{\textit{Purple}}{KMnO_4} \longrightarrow \underset{\textit{Sol. in } H_2O}{RCOO^-K^+} + \underset{\textit{Brown}}{MnO_2} + KOH$$

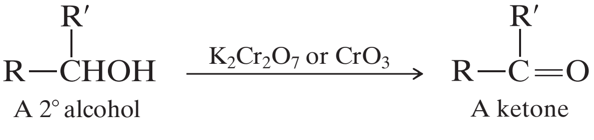
$$\downarrow H^+$$

$$\underset{\substack{\text{A carboxylic acid}\\ \textit{Insoluble in } H_2O}}{RCOOH}$$

10.16 Chemoselective oxidants for alcohols

The chemoselective oxidation reactions such as Oppenauer's oxidation, Moffatt–Pfitzner oxidation, Des–Martin oxidation, Fetizon oxidation, and oxidation with TPAP have been discussed in the chapter of oxidation reaction.

Oxidation of alcohols to the aldehyde or ketone stage is usually accomplished by the use of Cr(VI) in one of the forms described above. Oxidation of secondary alcohols to ketones is generally straightforward.



$$\underset{\text{A 2° alcohol}}{R{-}\overset{\overset{\displaystyle R'}{|}}{C}HOH} \xrightarrow{K_2Cr_2O_7\text{ or }CrO_3} \underset{\text{A ketone}}{R{-}\overset{\overset{\displaystyle R'}{|}}{C}{=}O}$$

Because aldehydes are susceptible to further oxidation, the conversion of primary alcohols to aldehydes can be troublesome. One of the best and most convenient reagents for this purpose is pyridinium chlorochromate ($C_5H_5NH^+ CrO_3Cl^-$) formed by the reaction between chromic acid and pyridinium chloride.

$$RCH_2OH \xrightarrow[\text{in } CH_2Cl_2]{C_5H_5NHCrO_3Cl} RCHO + Cr^{3+}$$

Later on, we shall encounter two reagents used to oxidize alcohols of special kinds: (a) *hypohalite*, and (b) *periodic acid*.

ETHERS

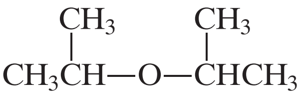
10.17 Structure and nomenclature of ethers

Ethers are compounds of the general formula R—O—R, Ar—O—R, or Ar—O—Ar. (Ar is phenyl or some other aromatic group.)

To name ethers we usually name the two groups that are attached to oxygen, and follow these names by the word *ether*:

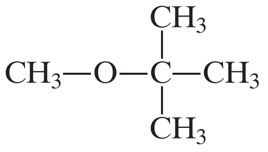
$C_2H_5OC_2H_5$

Diethyl ether



$$\overset{CH_3}{\overset{|}{CH_3CH}}—O—\overset{CH_3}{\overset{|}{CHCH_3}}$$

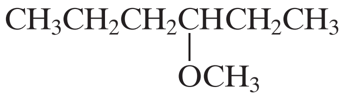
Diisopropyl ether



$$CH_3—O—\overset{CH_3}{\underset{CH_3}{C}}—CH_3$$

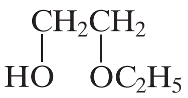
tert-Butyl methyl ether

If one group has no simple name, the compound may be named as an *alkoxy* derivative:



$$CH_3CH_2CH_2\underset{OCH_3}{CH}CH_2CH_3$$

3-Methoxyhexane



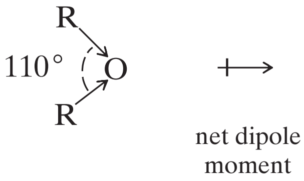
$$\underset{HO}{CH_2}\underset{OC_2H_5}{CH_2}$$

2-Ethoxyethanol

If the two groups are identical, the ether is said to be *symmetrical* (e.g., *diethyl ether, diisopropyl ether*); if different, *unsymmetrical* (e.g., *tert-butyl methyl ether*).

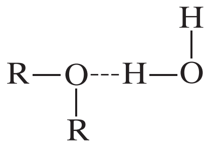
10.18 Physical properties of ethers

Since the C—O—C bond angle is not 180°, the dipole moments of the two C—O bonds do not cancel each other; consequently, ethers possess a small net dipole moment (for example, 1.18 D for diethyl ether).



This weak polarity does not appreciably affect the boiling points of ethers, which are about the same as those of alkanes having comparable molecular weights, and much lower than those of isomeric alcohols. Compare, for example, the boiling points of *n*-heptane (98 °C), methyl *n*-pentyl ether (100 °C), and *n*-hexyl alcohol (157 °C). The hydrogen bonding that holds alcohol molecules strongly together is not possible for ethers, since they contain hydrogen bonded only to carbon.

On the other hand, ethers show a solubility in water comparable to that of the alcohols, both diethyl ether and *n*-butyl alcohol, for example, being soluble to the extent of about 8 g per 100 g water. We attributed the water solubility of the lower alcohols to hydrogen bonding between water molecules and alcohol molecules. The water solubility of ethers arises in the same way: through the unshared electron pairs on oxygen, ethers can accept hydrogen bonds provided by water.



$$\mathrm{R{-}\underset{\displaystyle R}{\underset{|}{O}}{\cdots}H{-}\overset{\displaystyle H}{\overset{|}{O}}}$$

10.19 Industrial sources of ethers. Dehydration of alcohols

A number of symmetrical ethers containing the lower alkyl groups are prepared on a large scale, chiefly for use as solvents. The physical properties of a few common ethers are listed in Table 10.2. The most important of these is **diethyl ether**, the familiar solvent we use in extractions and in the preparation of Grignard reagents; others include diisopropyl ether and di-*n*-butyl ether.

Table 10.2 ETHERS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Dimethyl ether	−140	−24	Anisole	−37	154
Diethyl ether	−116	34.6	(Methyl phenyl ether)		
Di-*n*-propyl ether	−122	91	Phenetole	−33	172
Diisopropyl ether	−60	69	(Ethyl phenyl ether)		
Di-*n*-butyl ether	−95	142	Diphenyl ether	27	259
Divinyl ether		35	1,4-Dioxane	11	101
Diallyl ether		94	Tetrahydrofuran	−108	66

These ethers are prepared by reactions of the corresponding alcohols with sulfuric acid. Since a molecule of water is lost for every pair of alcohol molecules, the reaction is a kind of *dehydration*. As we shall soon see, alcohols can undergo another

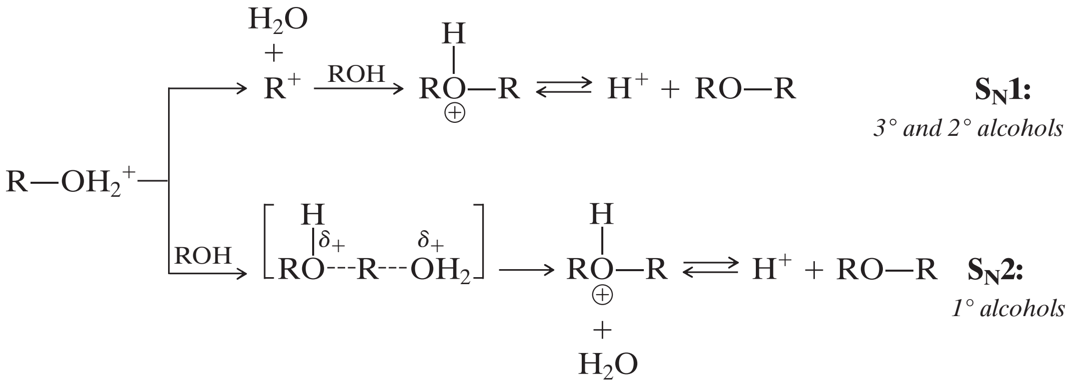
$$2\mathrm{R{-}O{-}H} \xrightarrow{\mathrm{H_2SO_4,\ heat}} \mathrm{R{-}O{-}R} + \mathrm{H_2O}$$

kind of dehydration, involving *elimination*, to give alkenes. Dehydration to ethers rather than to alkenes is controlled by the choice of reaction conditions. For example, ethylene is prepared by heating ethyl alcohol with concentrated sulfuric acid to 180 °C; diethyl ether is prepared by heating a mixture of ethyl alcohol and concentrated sulfuric acid to 140 °C, alcohol being continuously added to keep it in excess.

Dehydration is generally limited to the preparation of symmetrical ethers, because, as we might expect, a combination of two alcohols usually yields a mixture of three ethers.

Ether formation by dehydration is an example of nucleophilic substitution with the alcohol playing two roles: the protonated alcohol is the substrate, and the second molecule of alcohol is the nucleophile. Reaction could be either S_N1 or S_N2, depending upon whether the protonated alcohol loses water before, or simultaneously with,

$$\text{R—OH} + \text{H}^+ \rightleftharpoons \text{R—OH}_2{}^+$$



attack by the second alcohol molecule. It is probable that 2° and 3° alcohols follow the $\text{S}_\text{N}1$ pattern. On the other hand, *n*-butyl alcohol gives di-*n*-butyl ether without rearrangement and hence, presumably, without intermediate carbocations; evidently 1° alcohols, the least able to form carbocations but the most prone to back-side attack, follow the $\text{S}_\text{N}2$ path.

Problem 10.10 (a) Upon treatment with sulfuric acid, a mixture of ethyl and *n*-propyl alcohols yields a mixture of three ethers. What are they? (b) On the other hand, a mixture of *tert*-butyl alcohol and ethyl alcohol gives a good yield of a single ether. What ether is this likely to be? How do you account for the good yield?

In contact with air, most of the aliphatic ethers are converted to their unstable peroxides. These peroxides are dangerous even in small concentration since they decompose with explosive violence.

The presence of peroxides is indicated by formation of a red color when the ether is shaken with an aqueous solution of ferrous ammonium sulfate and potassium thiocyanate; the peroxide oxidizes ferrous ion to ferric ion, which reacts with thiocyanate ion to give the characteristic blood-red color of the complex.

$$\text{Peroxide} + \text{Fe}^{2+} \longrightarrow \text{Fe}^{3+} \xrightarrow{\text{SCN}^-} \underset{\textit{Red}}{\text{Fe(SCN)}_n{}^{(3-n)-}} \quad (n=1 \text{ to } 6)$$

Peroxides can be removed from ethers in a number of ways, including washing with solutions of ferrous ion (which reduces peroxides), or distillation from concentrated H_2SO_4 (which oxidizes peroxides).

For use in the preparation of Grignard reagents, the ether (usually diethyl) must be free from traces of water and alcohol. This so-called **absolute ether** can be prepared by distillation of ordinary ether from concentrated H_2SO_4 (which removes not only water and alcohol but also peroxides), and subsequent storing over metallic sodium. There is available today commercial anhydrous ether of such high quality that only the treatment with sodium is needed to make it ready for the Grignard reaction.

It is hard to overemphasize the hazards met in using diethyl ether, even when it is free of peroxides: it is highly volatile, and the flammability of its vapors makes explosions and fires ever-present dangers unless proper precautions are observed.

10.20 Preparation of ethers

The following methods are generally used for the laboratory preparation of ethers. (The Williamson synthesis is used for the preparation of alkyl aryl ethers industrially, as well.)

PREPARATION OF ETHERS

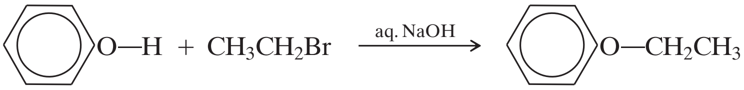
1. Williamson synthesis.

$$\mathrm{RX} + \begin{array}{c}\mathrm{R'O^-Na^+}\\ \text{or}\\ \mathrm{ArO^-Na^+}\end{array} \longrightarrow \begin{array}{c}\mathrm{R{-}OR'}\\ \text{or}\\ \mathrm{R{-}OAr}\end{array} \qquad \begin{array}{c}\textit{Yield from RX:}\\ \mathrm{CH_3} > 1° > 2° \ (>3°)\end{array}$$

Examples:

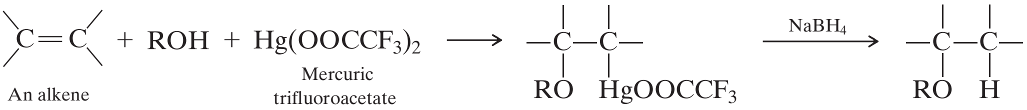
$$\left[(\mathrm{CH_3})_2\mathrm{CHO{-}H} \xrightarrow{\mathrm{Na}}\right] \underset{\text{Sodium isopropoxide}}{(\mathrm{CH_3})_2\mathrm{CHO^-Na^+}} + \underset{n\text{-Propyl bromide}}{\mathrm{CH_3CH_2CH_2Br}}$$

$$\longrightarrow \underset{\text{Isopropyl } n\text{-propyl ether}}{\mathrm{CH_3CH_2CH_2O{-}CH(CH_3)_2}}$$



Phenol Ethyl bromide Ethyl phenyl ether

2. Alkoxymercuration–demercuration.



$$>\!C{=}C\!< + \mathrm{ROH} + \mathrm{Hg(OOCCF_3)_2} \longrightarrow -\underset{\mathrm{RO}}{\overset{|}{\underset{|}{C}}}-\underset{\mathrm{HgOOCCF_3}}{\overset{|}{\underset{|}{C}}}- \xrightarrow{\mathrm{NaBH_4}} -\underset{\mathrm{RO}}{\overset{|}{\underset{|}{C}}}-\underset{\mathrm{H}}{\overset{|}{\underset{|}{C}}}-$$

An alkene Mercuric trifluoroacetate *Markovnikov orientation*

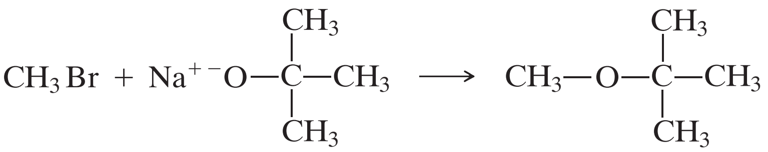
10.20.1 Williamson synthesis

In the laboratory, the Williamson synthesis of ethers is important because of its versatility: it can be used to make unsymmetrical ethers as well as symmetrical ethers.

In the Williamson synthesis an alkyl halide (or substituted alkyl halide) is allowed to react with a sodium alkoxide.

$$\mathrm{R{-}X} + \mathrm{Na^+\,{}^-O{-}R'} \longrightarrow \mathrm{R{-}O{-}R'} + \mathrm{Na^+X^-}$$

For example:

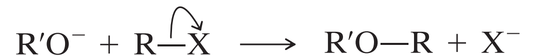


$$CH_3Br + Na^{+}\,{}^{-}O-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 \longrightarrow CH_3-O-\underset{CH_3}{\overset{CH_3}{C}}-CH_3$$

Sodium *tert*-butoxide

tert-Butyl methyl ether

Reaction involves nucleophilic substitution of alkoxide ion for halide ion; it is strictly analogous to the formation of alcohols by treatment of alkyl halides with aqueous hydroxide.

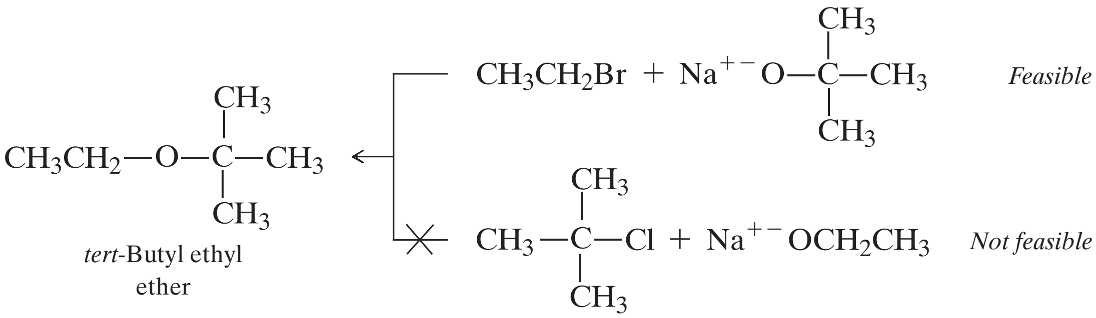


$$R'O^{-} + R-X \longrightarrow R'O-R + X^{-}$$

Nucleophile Substrate Leaving group

Since alkoxides and alkyl halides are both prepared from alcohols, the Williamson method ultimately involves the synthesis of an ether from two alcohols.

If we wish to make an unsymmetrical dialkyl ether, we have a choice of two combinations of reagents; one of these is nearly always better than the other. In the preparation of *tert*-butyl ethyl ether, for example, the following combinations are conceivable:



$$CH_3CH_2-O-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 \longleftarrow CH_3CH_2Br + Na^{+}\,{}^{-}O-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 \quad \textit{Feasible}$$

$$CH_3CH_2-O-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 \not\longleftarrow CH_3-\underset{CH_3}{\overset{CH_3}{C}}-Cl + Na^{+}\,{}^{-}OCH_2CH_3 \quad \textit{Not feasible}$$

tert-Butyl ethyl ether

Which do we choose? Alkoxides are not only nucleophiles, but also strong bases; bases, as we shall find tend to react with alkyl halides by *elimination*, to yield alkenes. Whenever we are trying to carry out nucleophilic substitution, we must be aware of the danger of a competing elimination reaction. We should keep in mind that the tendency of alkyl halides to undergo elimination is 3°< 2°< 1°.

In our present example, we reject the use of the tertiary halide, which would be expected to yield mostly—or all—elimination product; we must use the other combination.

Problem 10.11 When optically active 2-octanol of specific rotation −8.24° is converted into its sodium salt, and the salt is then treated with ethyl bromide, there is obtained the optically active ether, 2-ethoxyoctane, with specific rotation −15.6°. Making use of the configuration and maximum rotation of 2-octanol, what, if anything, can you say about: (a) the configuration of (−)-2-ethoxyoctane? (b) the maximum rotation of 2-ethoxyoctane?

Problem 10.12 (*Work this after Problem 10.11*) When (−)-2-bromooctane of specific rotation −30.3° is treated with ethoxide ion in ethyl alcohol, there is obtained 2-ethoxyoctane of specific rotation +15.3°. Using the configuration and maximum rotation of the bromide answer the following questions. (a) Does this reaction involve complete retention of configuration, complete inversion, or inversion plus racemization? (b) By what mechanism does this reaction appear to proceed? (c) In view of the reagents involved, is this the mechanism you would have expected to operate? (d) What mechanism do you suppose is involved in the alternative synthesis of 2-ethoxyoctane from the salt of 2-octanol and ethyl bromide? (e) Why, then, do the products of the two syntheses have *opposite* rotations?

10.21 Reactions of ethers. Cleavage by acids

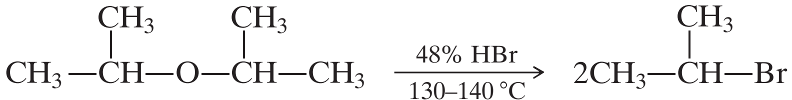
Ethers are comparatively unreactive compounds. The ether linkage is quite stable toward bases, oxidizing agents, and reducing agents. In so far as the ether linkage itself is concerned, ethers undergo just one kind of reaction, **cleavage by acids**:

$$\text{R—O—R}' + \text{HX} \longrightarrow \text{R—X} + \text{R}'\text{—OH} \xrightarrow{\text{HX}} \text{R}'\text{—X}$$

Reactivity of HX: HI > HBr > HCl

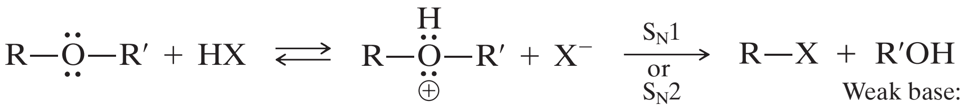
Cleavage takes place only under quite vigorous conditions: concentrated acids (usually HI or HBr) and high temperatures.

A dialkyl ether yields initially an alkyl halide and an alcohol; the alcohol may react further to form a second mole of alkyl halide. For example:



$$\underset{\text{Diisopropyl ether}}{CH_3\text{—}\overset{\overset{\displaystyle CH_3}{|}}{C}H\text{—O—}\overset{\overset{\displaystyle CH_3}{|}}{C}H\text{—}CH_3} \xrightarrow[130\text{–}140\ °C]{48\%\ HBr} \underset{\text{Isopropyl bromide}}{2CH_3\text{—}\overset{\overset{\displaystyle CH_3}{|}}{C}H\text{—Br}}$$

The oxygen of an ether is basic, like the oxygen of an alcohol. The initial reaction between an ether and an acid is undoubtedly formation of the *protonated ether*. Cleavage then involves nucleophilic attack by halide ion on this protonated ether, with displacement of the weakly basic alcohol molecule:

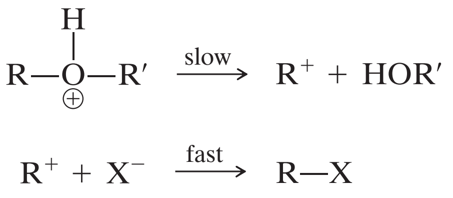


$$\text{R—}\ddot{\underset{\cdot\cdot}{O}}\text{—R}' + \text{HX} \rightleftarrows \underset{\text{Protonated ether}}{\text{R—}\overset{H}{\underset{\oplus}{\ddot{O}}}\text{—R}'} + \text{X}^- \xrightarrow[\text{or } S_N2]{S_N1} \text{R—X} + \underset{\substack{\text{Weak base:}\\ \textit{good leaving group}}}{\text{R}'\text{OH}}$$

Such a reaction occurs much more readily than displacement of the strongly basic alkoxide ion from the neutral ether.

$$\text{R—O—R}' + \text{X}^- \cancel{\longrightarrow} \text{R—X} + \underset{\substack{\text{Strong base:}\\ \textit{poor leaving group}}}{\text{R}'\text{O}^-}$$

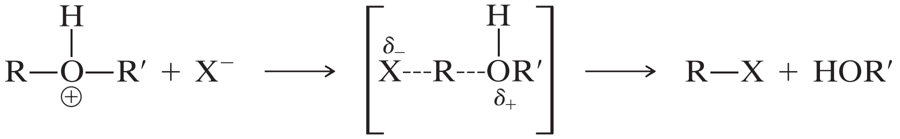
Reaction of a protonated ether with halide ion, like the corresponding reaction of protonated alcohol, can proceed either by an S_N1 mechanism,



$$(1)\qquad R-\underset{\oplus}{\overset{\overset{H}{|}}{O}}-R' \xrightarrow{\text{slow}} R^+ + HOR' \qquad \mathbf{S_N1}$$

$$(2)\qquad R^+ + X^- \xrightarrow{\text{fast}} R-X$$

or by an S_N2 mechanism,



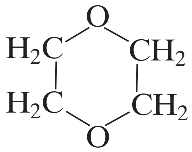
$$R-\underset{\oplus}{\overset{\overset{H}{|}}{O}}-R' + X^- \longrightarrow \left[\overset{\delta_-}{X}\text{---}R\text{---}\underset{\delta_+}{\overset{\overset{H}{|}}{O}}R'\right] \longrightarrow R-X + HOR' \qquad \mathbf{S_N2}$$

depending upon conditions and the structure of the ether. As we might expect, a primary alkyl group tends to undergo S_N2 displacement, whereas a tertiary alkyl group tends to undergo S_N1 displacement.

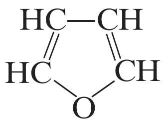
Problem 10.13 Cleavage of optically active *sec*-butyl methyl ether by anhydrous HBr yields chiefly methyl bromide and *sec*-butyl alcohol; the *sec*-butyl alcohol has the same configuration and optical purity as the starting material. How do you interpret these results?

10.22 Cyclic ethers

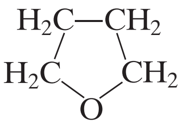
In their preparation and properties, most cyclic ethers are just like the ethers we have already studied: the chemistry of the ether linkage is essentially the same whether it forms part of an open chain or part of an aliphatic ring.



1,4-Dioxane



Furan



Tetrahydrofuran

Problem 10.14 1,4-*Dioxane* is prepared industrially (for use as a water-soluble solvent) by dehydration of an alcohol. What alcohol is used?

Problem 10.15 The unsaturated cyclic ether *furan* can readily be made from substances isolated from oat hulls and corncobs; one of its important uses involves its conversion into (a) *tetrahydrofuran*, and (b) 1,4-dichlorobutane. Using your knowledge of alkene chemistry and ether chemistry, show how these conversions can be carried out.

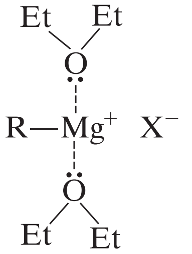
The rings contain more than one kind of atom, and hence are *heterocyclic* rings (Greek: *hetero*, different). Since divalent oxygen has bond angles not very different from those of carbon, the rings of cyclic ethers can exist in much the same conformations as the cycloalkane rings we have already discussed: they can be puckered and, if they are small, can be strained.

Cyclic ethers of two particular kinds deserve special attention because of their unusual properties: the *crown ethers* and the *epoxides*.

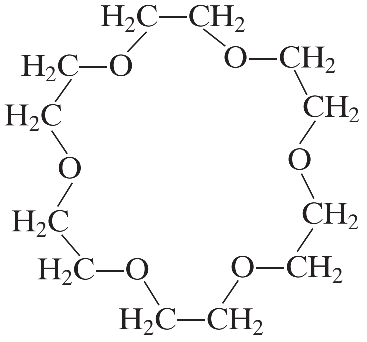
10.23 Crown ethers. Host–guest relationship

As we have seen, ethers cannot furnish an acidic proton for hydrogen bonding. They are thus aprotic solvents, but—the simple ones, at least—not very polar, and are essentially insoluble in water. Diethyl ether is very commonly used to extract organic materials from an aqueous solution, leaving ionic compounds behind in the water layer.

But the oxygen of ethers carries unshared electrons, and through these unshared pairs ethers can solvate cations. Diethyl ether and tetrahydrofuran are, for example, the solvents in which Grignard reagents are usually prepared and used. They are able to dissolve these important reagents because they strongly solvate the magnesium of the RMg^+ cation.



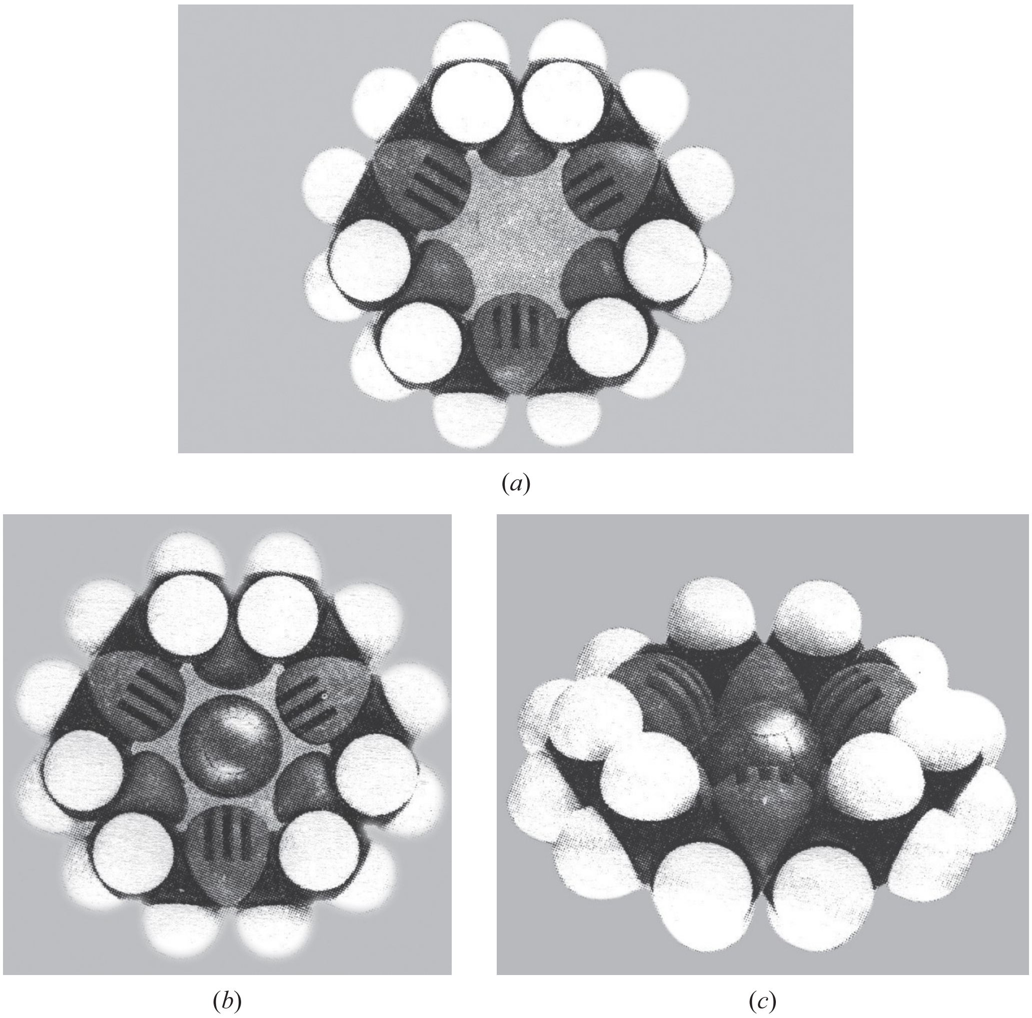
Now, crown ethers are cyclic ethers containing several—four, five, six, or more—oxygen atoms. Let us take as our example the crown ether I, which is one of the most effective and widely used of these catalysts. It is called 18-crown-6, to show



I

that there are 18 atoms in the ring, of which 6 are oxygen. As we would expect for a ring of this size, it is puckered. The name of "crown" was given to the first of these because, as its discoverer Charles J. Pedersen (E. I. Du Pont De Nemours) has said, "its molecular model looks like one and, with it, cations could be crowned and uncrowned without physical damage to either . . .".

This brings us to the function of these crown ethers. They are phase-transfer catalysts, and very powerful ones. They are used to transfer ionic compounds into an organic phase either from a water phase or, more commonly, from the solid crystal. Unlike the quat ions we studied earlier, crown ethers are neutral molecules; yet they do the same job. Now, how do they work?


(*a*)

(*b*) (*c*)

Figure 10.2 Host–guest relationship: crown ether–cation, (*a*) 18-Crown-6, unfolded. The hole is lined with oxygens, and has a diameter of 2.7 Å. (*b*) and (*c*) 18-Crown-6 holding a potassium ion through ion–dipole bonds to the oxygens. Diameter of K^+, 2.66 Å. The outside of the crown ether is carbon and hydrogen, and lipophilic.

Let us examine the structure of 18-crown-6 (Fig. 10.2). Unfolded, the molecule is shaped like a doughnut, and has a hole in the middle. Facing into the hole are the oxygen atoms; facing outward are the twelve CH_2 groups. There is thus a hydrophilic interior and a lipophilic exterior. The hole has a diameter of 2.7 Å.

Now, to this crown ether let us add a potassium ion, K^+. It has a diameter of 2.66 Å and *just fits* into the hole in the crown, where it is held by unshared pairs of electrons on the six oxygen atoms. Because of the close fit and because there are six oxygens, K^+ is bound very tightly. The crown ether is not a solvent, but it holds K^+ by the same forces that a solvent uses; the forces are simply much stronger here.

Together, K^+ and the crown ether make up a new cation. This new cation is much like a quat ion, except that it is held together by ion–dipole bonds instead of covalent bonds. Like a quat ion, it is lipophilic on the outside, and has the positive charge buried within the molecule. The lipophilicity makes it soluble in organic solvents of low polarity. When it enters such solvents, it takes an anion with it. This anion is shielded from the positive charge on K^+ by the bulky crown, thus forming only loose ion pairs, and is highly reactive.

Crown ethers have been made in a wide variety of shapes and sizes, and their ability to hold cations has been extensively studied. The hole in the ether can be larger than the cation and still bind it: Na^+, for example, is smaller than K^+, but is still bound by 18-crown-6, although less strongly than K^+. (The best size of hole for sodium is provided by 15–crown-5.) The hole can be smaller than the cation; in this case, the cation is simply seated in the cavity on one face or the other of the crown.

What we are seeing here is an example of the **host–guest relationship**.The crown ether is the *host*; the cation is the *guest*. This kind of relationship is of intense interest to the organic chemist, and is the subject of much research: for the practical purpose of designing new and better reagents; and for theoretical reasons, to understand better a wide range of interactions that extends all the way to that ultimate host–guest relationship, the one between enzyme and substrate.

Let us look at one example of a host–guest relationship involving hosts that are made, not by organic chemists, but by microorganisms. For various enzyme systems to function properly, cells must maintain certain concentrations of cations like K^+ and Na^+. Such maintenance is made feasible by the normally slow passage of these hydrated inorganic ions through the fatty (lipophilic) core of the cell membranes. A large number of antibiotics (*gramicidin, valinomycin, nonactin*, for example) upset this ionic balance: in their presence cations escape rapidly through the membrane, and the enzyme system must expend its energy forcing them back. It seems clear that these antibiotics exert their effect by *transporting* the cations through the membrane. Like crown ethers they wrap around the cation, holding it through ion–dipole bonds; then, with their lipophilic parts turned outward and the cation hidden within, they pass easily through the membrane. See, for example, nonactin in Fig. 10.3.

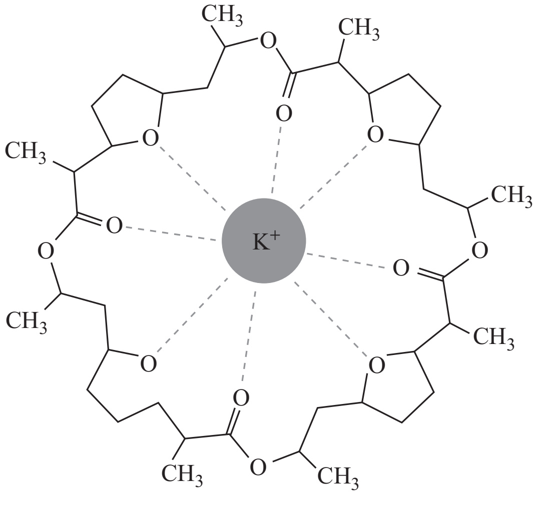


Figure 10.3 Host–guest relationship: the antibiotic nonactin holding a K^+ ion. The cation is held by ion–dipole bonds to inward-turning oxygens. The lipophilic parts of nonactin are turned outward.

Problem 10.16 Describe simple chemical tests (if any) that would distinguish between an ether and (a) an alkane; (b) an alkyl halide; (c) a primary or secondary alcohol; (d) a tertiary alcohol.

Tell exactly what you would *do* and *see*.

EXERCISE

1. (a) Ignoring enantiomerism, draw the structures of the eight isomeric pentyl alcohols, $C_5H_{11}OH$. (b) Name each by the IUPAC system. (c) Label each as primary, secondary, or tertiary. (d) Which one is isopentyl alcohol? *n*-Pentyl alcohol? *tert*-Pentyl alcohol? (e) Give the structure of a primary, a secondary, and a tertiary alcohol of the formula $C_6H_{13}OH$.

2. Write structural formulas for:

(a) dimethyl ether
(b) diisopropyl ether
(c) *n*-butyl methyl ether
(d) *tert*-butyl isobutyl ether
(e) 2-methoxypentane
(f) 1-methoxy-2-propanol

3. Name the following structures:

(a) $(CH_3)_2CHCH_2—O—CH_2CH(CH_3)_2$
(b) $CH_3—O—CH(CH_3)_2$
(c) $(CH_3)_3C—O—CH_2CH_3$
(d) $CH_3CH_2CH_2CH(OCH_3)CH_2CH_2CH_3$

4. Without referring to tables, arrange the following compounds in order of decreasing boiling point:

(a) 3-hexanol
(b) *n*-hexane
(c) 2-methyl-2-pentanol
(d) *n*-octyl alcohol
(e) *n*-hexyl alcohol

5. Looking at the beginning of each chapter for the structure involved, tell which families of compounds discussed in this book can: (a) form hydrogen bonds with other molecules of the same kind; (b) form hydrogen bonds with water.

6. Give structures and names of the chief products expected from the reaction (if any) of isopropyl alcohol with:

(a) cold conc. H_2SO_4
(b) cold dilute $KMnO_4$
(c) CrO_3,H_2SO_4
(d) Br_2/CCl_4
(e) conc. aqueous HBr
(f) product (e) + Mg
(g) $P + I_2$
(h) Na
(i) H_2,Ni
(j) CH_3MgBr
(k) NaOH(aq)
(l) tosyl chloride, OH^-

7. Write a balanced equation for each of the following. (If no reaction occurs, indicate "no reaction".)

(a) potassium *tert*-butoxide + ethyl iodide
(b) *tert*-butyl iodide + potassium ethoxide
(c) ethyl alcohol + H_2SO_4 (140 °C)
(d) di-*n*-butyl ether + boiling aqueous NaOH
(e) ethyl methyl ether + excess HI (hot)
(f) dimethyl ether + Na
(g) diethyl ether + cold conc. H_2SO_4
(h) diethyl ether + hot conc. H_2SO_4

8. Arrange the alcohols of each set in order of reactivity toward gaseous HBr:

(a) The isomeric pentyl alcohols of Problem 1(a). (*Note*: It may be necessary to list these in groups of about the same reactivity.)
(b) 2-butanol, 2-methyl-1-propanol, 2-methyl-2-propanol
(c) 3-pentanol, 2-fluoro-3-pentanol, 2,2-difluoro-3-pentanol, 1-fluoro-3-pentanol

9. Account for the fact that *either* 2-pentanol *or* 3-pentanol reacts with HCl to give *both* 2-chloropentane and 3-chloropentane.

10. In Great Britain during the past years, thousands of motorists have been (politely) stopped by the police and asked to blow into a "breathalyser": a glass tube containing silica gel impregnated with certain chemicals, and leading into a plastic bag. If, for more than half the length of the tube, the original yellow color turns green, the motorist looks very unhappy and often turns red. What chemicals are impregnated on the silica gel, why does the tube turn green, and why does the motorist turn red?

11. Triflate (trifluoromethanesulfonate) is a "super" leaving group: alkyl triflates are as much as a *billion times as reactive* as alkyl chlorides or bromides toward nucleophilic substitution. How do you account for this?

12. Describe simple chemical tests that would serve to distinguish between:

(a) *n*-butyl alcohol and *n*-octane
(b) *n*-butyl alcohol and *n*-pentyl bromide
(c) di-*n*-butyl ether and *n*-pentyl alcohol
(d) 3-pentanol and 1-pentanol
(e) diethyl ether and methyl iodide
(f) *n*-butyl alcohol and *tert*-pentyl alcohol
(g) *n*-butyl *tert*-butyl ether and *n*-octane
(h) 2-bromoethanol and *n*-butyl alcohol

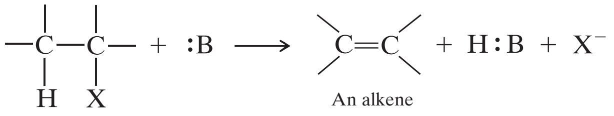
Tell exactly what you would *do* and *see*.

13. Starting from (*R*)-*sec*-butyl alcohol, and using any optically inactive reagents, show all steps in the synthesis of:

(a) (*R*)-*sec*-butyl ethyl ether ($CH_3CH_2CH(CH_3)OC_2H_5$)
(b) (*S*)-*sec*-butyl ethyl ether

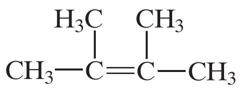
14. Optically active *sec*-butyl alcohol retains its activity indefinitely in contact with aqueous base, but is rapidly converted into optically inactive (racemic) *sec*-butyl alcohol by dilute sulfuric acid. How do you account for these facts? Suggest a detailed mechanism or mechanisms for the racemization by dilute acid.

15. The most important way to make *alkenes* is through *base-promoted* 1, 2-*elimination*:



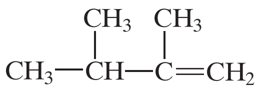
$$-\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{X}{\overset{|}{\underset{|}{C}}}- \;+\; :B \longrightarrow \underset{\text{An alkene}}{>C=C<} \;+\; H:B \;+\; X^-$$

(a) When 3-bromo-2,2-dimethylbutane is heated with a dilute solution of C_2H_5ONa in C_2H_5OH, or with C_2H_5OH alone, reaction follows first-order kinetics; along with substitution, there also occurs elimination, to yield alkenes I and II. What does the formation of these particular alkenes suggest to you? Propose a likely mechanism for the reaction by which they are formed.



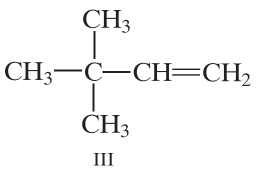
$$CH_3-\overset{H_3C}{\overset{|}{C}}=\overset{CH_3}{\overset{|}{C}}-CH_3$$

I



$$CH_3-\overset{CH_3}{\overset{|}{CH}}-\overset{CH_3}{\overset{|}{C}}=CH_2$$

II



$$CH_3-\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}-CH=CH_2$$

III

(b) When the same halide is allowed to react with a concentrated solution of C_2H_5ONa in C_2H_5OH, reaction follows second-order kinetics; again elimination accompanies substitution, this time to yield, not alkenes I and II, but alkene III. Propose a likely mechanism or mechanisms for the elimination taking place under these conditions.

(c) How do you account for the shift in mechanism between (a) and (b)?
(d) What substitution product or products would you expect in each case?

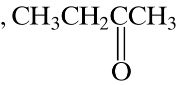
16. For many 2-substituted ethanols, GCH_2CH_2OH, the *gauche* conformation is more stable than the *anti*:

G = $—OH$, $—NH_2$, $—F$, $—Cl$, $—Br$, $—OCH_3$, $—NHCH_3$, $—N(CH_3)_2$, and $—NO_2$
How might this be accounted for?

17. Outline all steps in a possible laboratory synthesis of each of the following from *n*-butyl alcohol, using any inorganic reagents. Follow the general instructions in the box below.

(a) *n*-butyl bromide
(b) *n*-butyl iodide
(c) *n*-butyl hydrogen sulfate
(d) sodium *n*-butoxide
(e) butanenitrile, $CH_3CH_2CH_2CH_2CN$
(f) *n*-butyraldehyde, $CH_3CH_2CH_2CHO$
(g) *n*-butyric acid, $CH_3CH_2CH_2COOH$
(h) *n*-butane
(i) *n*-butane-1-*d*, $CH_3CH_2CH_2CH_2D$
(j) *n*-octane

18. Starting *from alcohols of four carbons or fewer*, and making use of any necessary solvents or reagents, outline a possible synthesis for each of the following compounds:

(a) 2-chloropropane
(b) ethyl tosylate
(c) potassium *tert*-butoxide
(d) propanenitrile, CH_3CH_2CN
(e) isobutane
(f) ethyl *n*-propyl ether
(g) butane-2-*d*, $CH_3CH_2CHDCH_3$
(h) 3-methylhexane
(i) isobutyric acid, $(CH_3)_2CHCOOH$
(j) acetaldehyde, CH_3CHO
(k) 2-butanone,  $CH_3CH_2\underset{\overset{\|}{O}}{C}CH_3$

About Synthesis

Each synthesis should be the one that gives a reasonably pure product in reasonably good yield.

It is not necessary to complete and balance each equation. Simply draw the structure of the organic compounds, and write on the arrow the necessary reagents and any critical conditions. For example:

$$CH_3CH_2OH \xrightarrow{HBr} CH_3CH_2Br \xrightarrow{CN^-} CH_3CH_2CN$$

At this stage you may be asked to make a particular compound that can readily be bought, or that might better be made by another method: the synthesis of *n*-butane, for example. But if you can work out a way to make *n*-butane from *n*-butyl alcohol, then, when the need arises, you will also know how to make a complicated alkane from a complicated alcohol, and, in fact, how to replace an —OH group by —H in just about any compound you encounter. Furthermore, you will have gained practice in putting together what you have learned about several different kinds of compounds.

Remember: Alkyl halides are *almost never* prepared by direct halogenation of alkanes. *From the standpoint of synthesis in the laboratory, an alkane is a dead-end.*