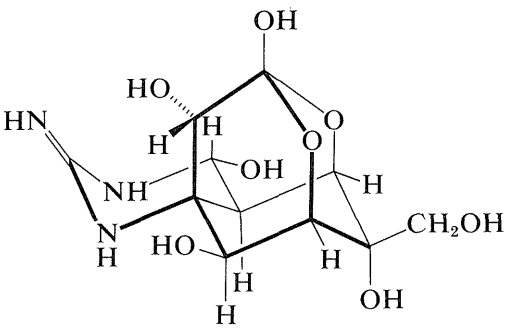
15

ALCOHOLS AND ETHERS

The hydroxyl group is one of the most important functional groups of naturally occurring organic molecules. All carbohydrates and their derivatives, including nucleic acids, have hydroxyl groups. Some amino acids, most steroids, many terpenes, and plant pigments have hydroxyl groups. These substances serve many diverse purposes for the support and maintenance of life. One extreme example is the potent toxin tetrodotoxin, which is isolated from puffer fish and has obvious use for defense against predators. This compound has special biochemical interest, having six different hydroxylic functions arranged on a cagelike structure:



tetrodotoxin

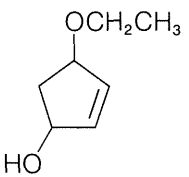
On the more practical side, vast quantities of simple alcohols—methanol, ethanol, 2-propanol, 1-butanol—and many ethers are made from petroleum-derived hydrocarbons. These alcohols are widely used as solvents and as intermediates for the synthesis of more complex substances.

The reactions involving the hydrogens of alcoholic OH groups are expected to be similar to those of water, HOH, the simplest hydroxylic compound. Alcohols, ROH, can be regarded in this respect as substitution products of water. However, with alcohols we shall be interested not only in reactions that proceed at the O–H bond but also with processes that result in cleavage of the C–O bond, or changes in the organic group R.

The simple ethers, ROR, do not have O–H bonds, and most of their reactions are limited to the substituent groups. The chemistry of ethers, therefore, is less varied than that of alcohols. This fact is turned to advantage in the widespread use of ethers as solvents for a variety of organic reactions, as we already have seen for Grignard reagents (Section 14-10). Nonetheless, cyclic ethers with small rings show enhanced reactivity because of ring strain and, for this reason, are valuable intermediates in organic synthesis.

Before turning to the specific chemistry of alcohols and ethers, we remind you that the naming of these compounds is summarized in Sections 7-2 and 7-3. The special problems encountered in naming cyclic ethers are discussed in Section 15-11A.

Exercise 15-1 **a.** Draw the structure of 4-methoxy-1-penten-3-ol.
b. Name the following structure by the IUPAC system:



15-1 PHYSICAL PROPERTIES OF ALCOHOLS; HYDROGEN BONDING

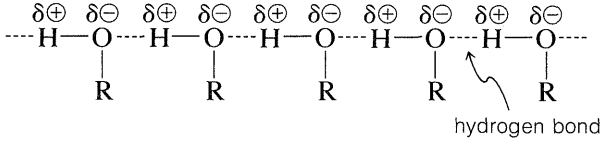
Comparison of the physical properties of alcohols with those of hydrocarbons of comparable molecular weight shows several striking differences, especially for those with just a few carbons. Alcohols are substantially less volatile, have higher melting points, and greater water solubility than the corresponding hydrocarbons (see Table 15-1), although the differences become progessively smaller as molecular weight increases.

The reason for these differences in physical properties is related to the high polarity of the hydroxyl group which, when substituted on a hydrocarbon chain, confers a measure of polar character to the molecule. As a result, there is a significant attraction of one molecule for another that is particularly pronounced in the solid and liquid states. This polar character leads to association

Table 15-1
Comparison of Physical Properties of Alcohols and Hydrocarbons

Alcohol	Hydrocarbon	Molecular weight	Bp, °C	Mp, °C
CH_3OH		32	65	−98
	CH_3CH_3	30	−89	−172
CH_3CH_2OH		46	78.5	−117.3
	$CH_3CH_2CH_3$	44	−42.2	−189.9
$CH_3CH_2CH_2OH$		60	97.2	−127
	$CH_3CH_2CH_2CH_3$	58	−0.6	−135
$CH_3(CH_2)_3CH_2OH$		88	138	−79
	$CH_3(CH_2)_4CH_3$	86	69	−95
$CH_3(CH_2)_8CH_2OH$		158	228	6
	$CH_3(CH_2)_9CH_3$	156	196	−26

of alcohol molecules through the rather positive hydrogen of one hydroxyl group with a correspondingly negative oxygen of another hydroxyl group:



This type of association is called "hydrogen bonding," and, although the strengths of such bonds are much less than those of most conventional chemical bonds, they are still significant (about 5 to 10 kcal per bond). Clearly then, the reason alcohols have higher boiling points than corresponding alkyl halides, ethers, or hydrocarbons is because, for the molecules to vaporize, additional energy is required to break the hydrogen bonds. Alternatively, association through hydrogen bonds may be regarded as effectively raising the molecular weight, thereby reducing volatility. (Also see Section 1-3.)

Exercise 15-2 Explain how hydrogen bonding makes *cis*-cyclopentane-1,2-diol substantially more volatile (bp 119° at 22 mm of Hg) than *trans*-cyclopentane-1,2-diol (bp 136° at 22 mm of Hg).

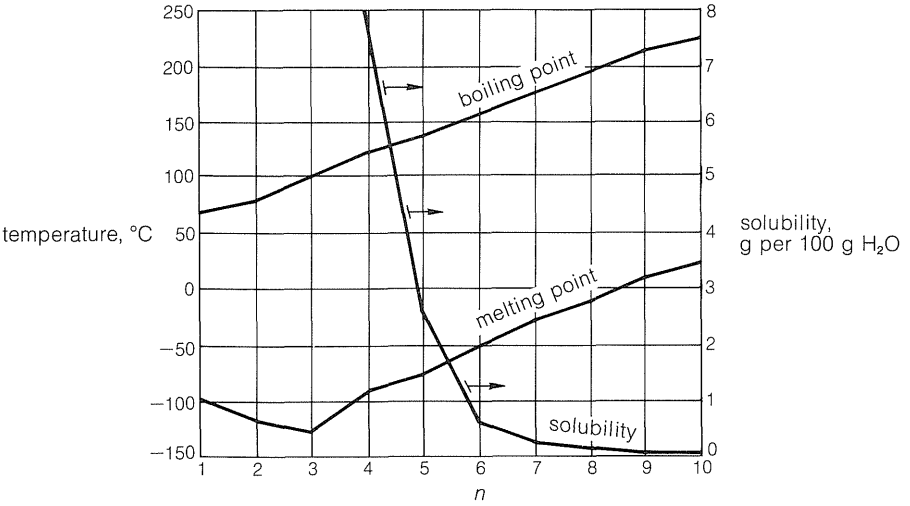
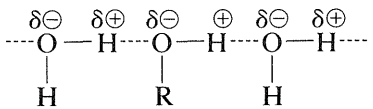


Figure 15-1 Dependence of melting points, boiling points, and water solubilities of straight-chain primary alcohols $H\text{-}(\text{-}CH_2\text{-})_n OH$ on *n*. The arrows on the solubility graph indicate that the scale is on the right ordinate.

The water solubility of the lower-molecular-weight alcohols is pronounced and is understood readily as the result of hydrogen bonding with water molecules:



In methanol, the hydroxyl group accounts for almost half of the weight of the molecule, and it is not surprising that the substance is completely soluble in water. As the size of the hydrocarbon groups of alcohols increases, the hydroxyl group accounts for progressively less of the molecular weight, hence water solubility decreases (Figure 15-1). Indeed, the physical properties of higher-molecular-weight alcohols are very similar to those of the corresponding hydrocarbons (Table 15-1). The importance of hydrogen bonding in the solvation of ions was discussed in Section 8-7F.

15-2 SPECTROSCOPIC PROPERTIES OF ALCOHOLS

The hydrogen–oxygen bond of a hydroxyl group gives a characteristic absorption band in the *infrared* but, as we may expect, this absorption is considerably influenced by hydrogen bonding. For example, in the vapor state (in which

there is essentially no hydrogen bonding), ethanol gives an infrared spectrum with a fairly sharp absorption band at 3700 cm^{-1}, owing to a free or unassociated hydroxyl group (Figure 15-2a). In contrast, this band is barely visible at

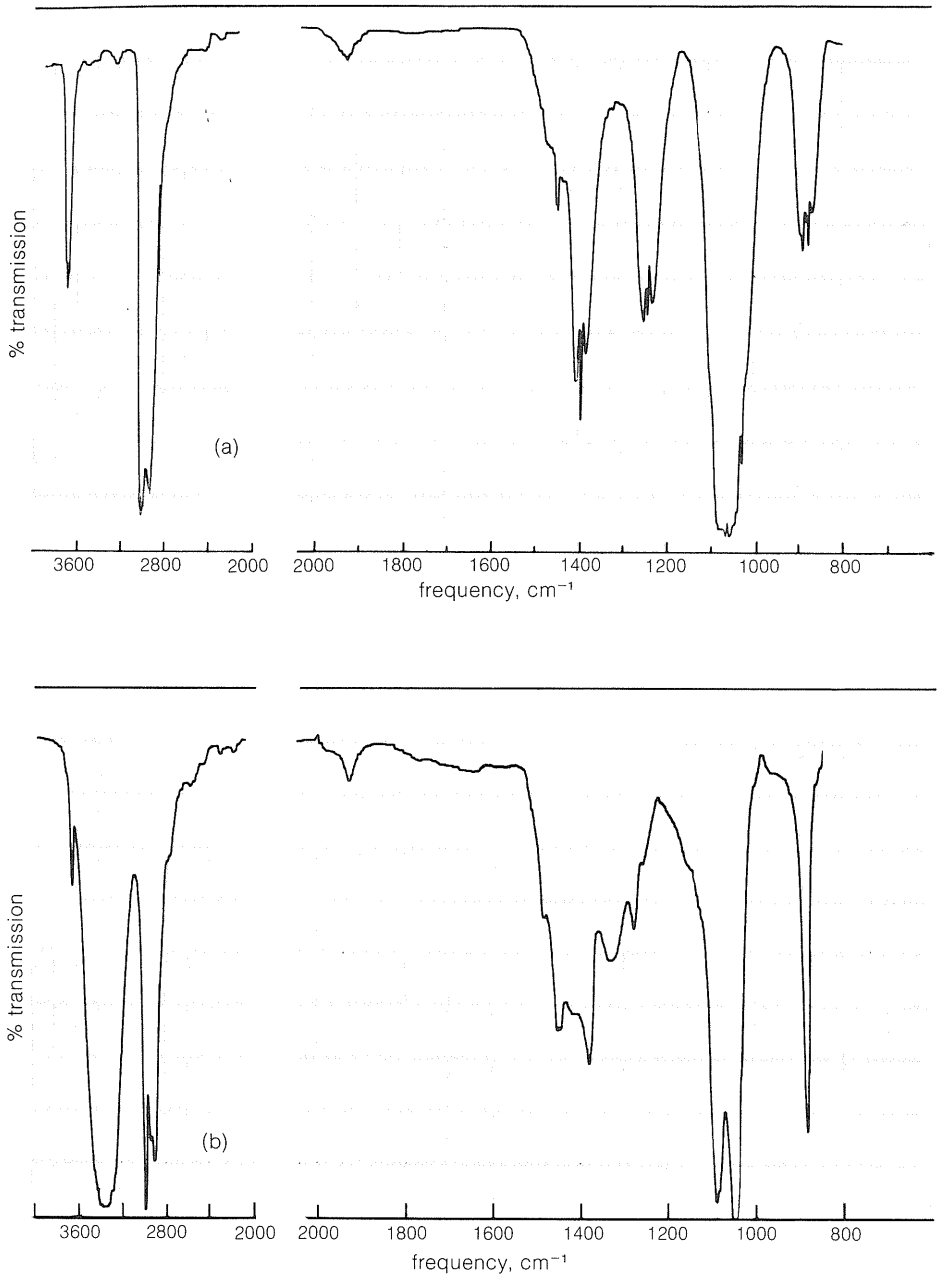
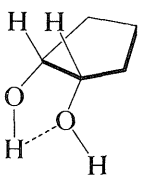


Figure 15-2 Infrared spectrum of ethanol (a) in the vapor phase and (b) as a 10% solution in carbon tetrachloride

3640 cm^{-1} in the spectrum of a 10% solution of ethanol in carbon tetrachloride (Figure 15-2b). However, there is a relatively broad band around 3350 cm^{-1}, which is characteristic of hydrogen-bonded hydroxyl groups. The shift in frequency of about 300 cm^{-1} arises because hydrogen bonding weakens the O–H bond; its absorption frequency then will be lower. The association band is broad because the hydroxyl groups are associated in aggregates of various sizes and shapes. This produces a variety of different kinds of hydrogen bonds and therefore a spectrum of closely spaced O–H absorption frequencies.

In very dilute solutions of alcohols in nonpolar solvents, hydrogen bonding is minimized. However, as the concentration is increased, more and more of the molecules become associated and the intensity of the infrared absorption band due to associated hydroxyl groups increases at the expense of the free-hydroxyl band. Furthermore, the frequency of the association band is a measure of the strength of the hydrogen bond. The lower the frequency relative to the position of the free hydroxyl group, the stronger is the hydrogen bond. As we shall see in Chapter 18 the hydroxyl group in carboxylic acids (RCO_2H) forms stronger hydrogen bonds than alcohols and accordingly absorbs at lower frequencies (lower by about 400 cm^{-1}, see Table 9-2).

The infrared spectra of certain 1,2-diols (glycols) are interesting in that they show absorption due to *intramolecular* hydrogen bonding. These usually are fairly sharp bands in the region 3450 to 3570 cm^{-1}, and, in contrast to bands due to intermolecular hydrogen bonding, they do not change in intensity with concentration. A typical example is afforded by *cis*-1,2-cyclopentanediol:



cis-cyclopentane-1,2-diol

Besides the O—H stretching vibrations of alcohols, there is a bending O—H vibration normally observed in the region 1410–1260 cm^{-1}. There also is a strong C—O stretching vibration between 1210 cm^{-1} and 1050 cm^{-1}. Both these bands are sensitive to structure as indicated below:

	—O—H bend, cm^{-1}	C—O stretch, cm^{-1}
primary alcohol:	1260–1350	1053–1085 (s)
secondary alcohol:	1260–1350	1087–1125 (s)
tertiary alcohol:	1310–1410	1124–1205 (s)

Exercise 15-3 What type of infrared absorption bands due to hydroxyl groups would you expect for *trans*-cyclobutane-1,2-diol and butane-1,2-diol (a) in very dilute solution, (b) in moderately concentrated solution, and (c) as pure liquids? Give your reasoning.

The influence of hydrogen bonding on the *proton nmr spectra* of alcohols has been discussed previously (Section 9-10E). You may recall that the chemical shift of the OH proton is variable and depends on the extent of association through hydrogen bonding; generally, the stronger the association, the lower the field strength required to induce resonance. Alcohols also undergo intermolecular OH proton exchange, and the rate of this exchange can influence the line-shape of the OH resonance, the chemical shift, and the incidence of spin-spin splitting, as discussed in more detail in Sections 9-10E and 9-10I. Concerning the protons on carbon bearing the hydroxyl group, that is, $-\overset{|}{C}H-OH$, they are deshielded by the electron-attracting oxygen atom and accordingly have chemical shifts some 2.5–3.0 ppm to *lower* fields than alkyl protons.

> Perhaps you are curious as to why absorptions are observed in the infrared spectrum of alcohols that correspond *both* to free and hydrogen-bonded hydroxyl groups, whereas only *one* OH resonance is observed in their proton nmr spectra. The explanation is that the lifetime of any molecule in either the free or the associated state is long enough to be detected by infrared absorption but much too short to be detected by nmr. Consequently, in the nmr one sees only the average OH resonance of the nonhydrogen-bonded and hydrogen-bonded species present. The situation here is very much like that observed for conformational equilibration (Section 9-10C).

The longest-wavelength *ultraviolet absorption* maxima of methanol and methoxymethane (dimethyl ether) are noted in Table 9-3. In each case the absorption maximum, which probably involves an $n \longrightarrow \sigma^*$ transition, occurs about 184 nm, well below the cut-off of the commonly available spectrometers.

Exercise 15-4 Suggest a likely structure for the compound of molecular formula C_4H_6O whose proton nmr and infrared spectra are shown in Figure 15-3a. Show your reasoning. Do the same for the compound of formula $C_3H_8O_2$, whose spectra are shown in Figure 15-3b.

Exercise 15-5 Pure, dry ethanol has a triplet nmr resonance for its OH proton and a quintet resonance for its CH_2 protons. If 5% by weight of water is added to the ethanol, a new single peak is observed about 0.8 ppm upfield of the ethanol OH triplet. If 30% by weight of water is added, there is only a single large OH resonance, and the CH_2 resonance becomes a quartet. Explain the changes produced in the nmr spectrum by adding water.

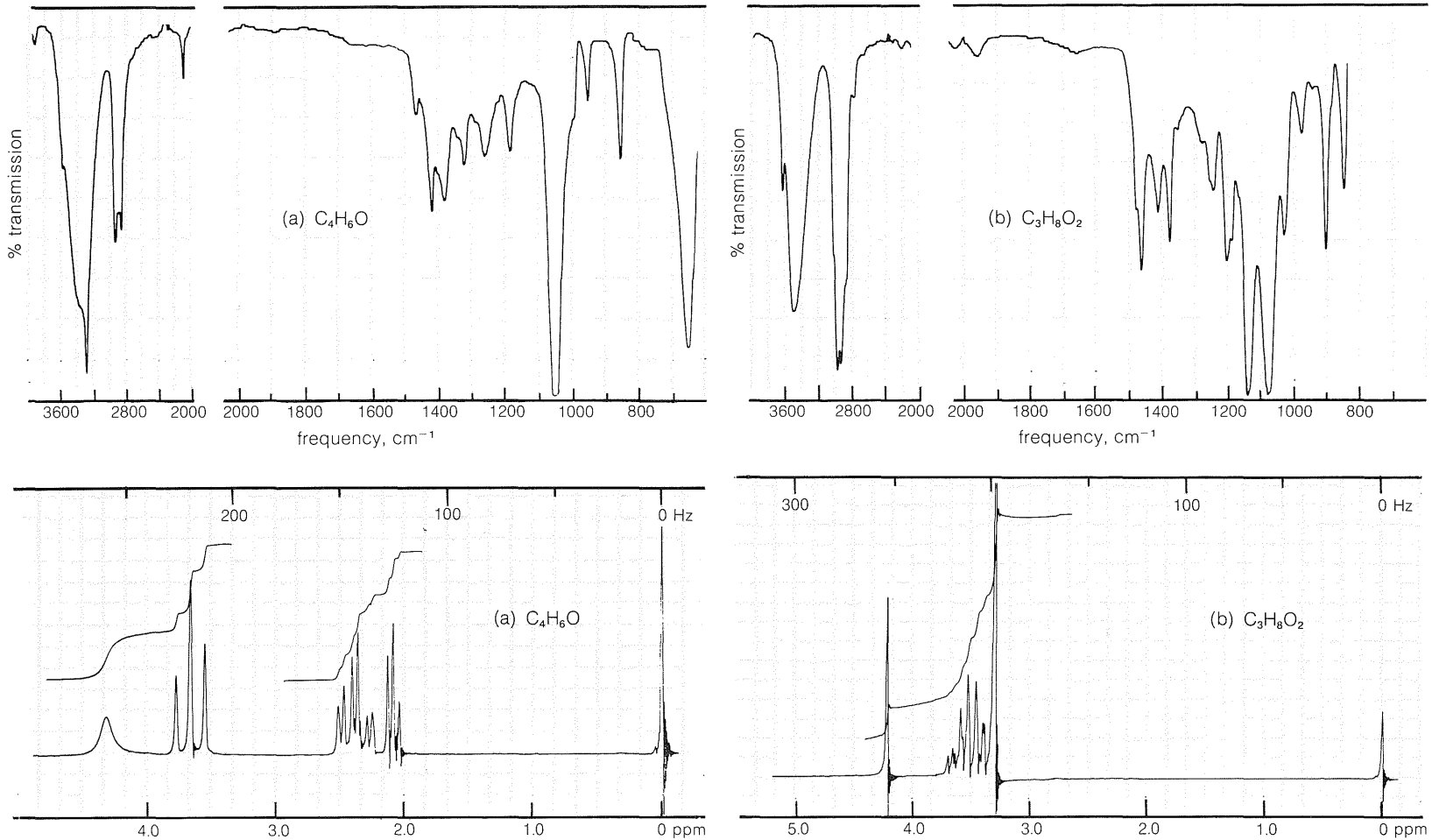
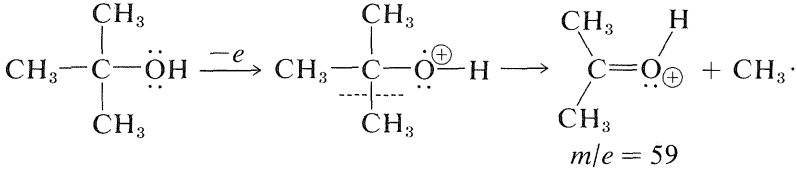
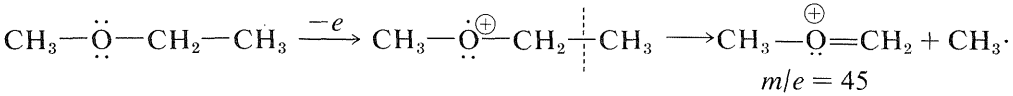


Figure 15-3 Proton nmr and infrared spectra (a) of C_4H_6O and (b) of $C_3H_8O_2$; *see* Exercise 15-4.

The *mass spectra* of alcohols may not always show strong molecular ions. The reason is that the M^+ ions readily fragment by α cleavage. The fragment ions are relatively stable and are the gaseous counterparts of protonated aldehydes and ketones:



Ethers also fragment by α cleavage:



15-3 PREPARATION OF ALCOHOLS

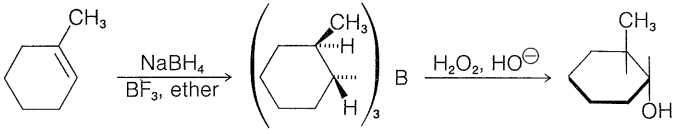
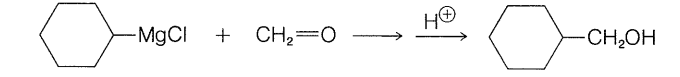
Many of the common laboratory methods for the preparation of alcohols have been discussed in previous chapters or will be considered later; thus to avoid undue repetition we shall not consider them in detail at this time. Included among these methods are hydration (Section 10-3E) and hydroboration (Section 11-6D), addition of hypohalous acids to alkenes (Section 10-4B), S_N1 and S_N2 hydrolysis of alkyl halides (Sections 8-4 to 8-7) and of allylic and benzylic halides (Sections 14-3B and 14-3C), addition of Grignard reagents to carbonyl compounds (Section 14-12), and the reduction of carbonyl compounds (Sections 16-4E and 16-5). These methods are summarized in Table 15-2.

Some of the reactions we have mentioned are used for large-scale industrial production. For example, ethanol is made in quantity by the hydration of ethene, using an excess of steam under pressure at temperatures around 300° in the presence of phosphoric acid:

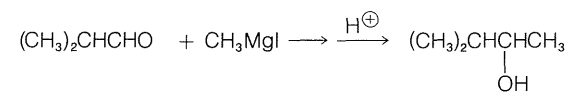
$$CH_2{=}CH_2 + H_2O \xrightleftharpoons{300^\circ,\ H_3PO_4} CH_3CH_2OH$$

A dilute solution of ethanol is obtained, which can be concentrated by distillation to a constant-boiling point mixture that contains 95.6% ethanol by weight. Dehydration of the remaining few percent of water to give "absolute alcohol" is achieved either by chemical means or by distillation with benzene, which results in preferential separation of the water. Ethanol also is made in large quantities by fermentation, but this route is not competitive for industrial uses with the hydration of ethene. Isopropyl alcohol and *tert*-butyl alcohol also are manufactured by hydration of the corresponding alkenes.

Table 15-2
General Methods of Preparation of Alcohols

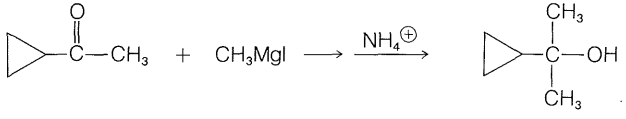
Reaction	Comment
1. *Hydration of alkenes* $RCH{=}CH_2 \xrightarrow{H^{\oplus},\ H_2O} RCHCH_3$ (OH) $CH_3CH{=}C(CH_3)_2 \xrightarrow{H_2SO_4,\ H_2O} CH_3CH_2C(CH_3)_2$ (OH) 2-methyl-2-butene → 2-methyl-2-butanol, 74%	Ease of preparation is *tert.* > *sec.* > *prim.* alcohol; ease of dehydration follows same sequence. Rearrangement is a frequent complication. See Sections 8-9B and 10-3E.
2. *Hydroboration of alkenes* $RCH{=}CH_2 \xrightarrow[2.\ H_2O_2,\ HO^{\ominus}]{1.\ B_2H_6} RCH_2CH_2OH$  *trans*-2-methylcyclohexanol, 90%	Diborane is best made *in situ* from $NaBH_4$ and BF_3 (Section 11-6E). The trialkylborane can be oxidized (without isolation) by H_2O_2. Reaction is stereospecific—suprafacial addition occurs to the less-hindered side of the double bond, and oxidation with hydrogen peroxide occurs with retention of configuration.
3. *Reaction of organometallic compounds with carbonyl compounds* a. *primary alcohols from methanal (formaldehyde)*  cyclohexylmagnesium chloride + methanal → cyclohexylcarbinol 69%	See Section 14-12A. Methanal and RMgX give primary alcohols.

b. *secondary alcohols from aldehydes*



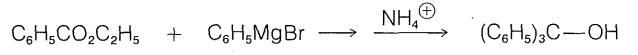
2-methylpropanal — 3-methyl-2-butanol, 56%

c. *tertiary alcohols from ketones*



cyclopropylethanone — 2-cyclopropyl-2-propanol, 68%

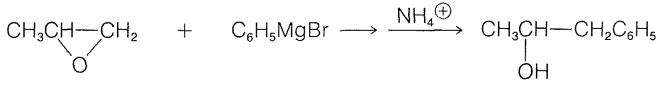
d. *tertiary alcohols from esters, acid halides, and anhydrides*



ethyl benzoate — phenylmagnesium bromide — triphenylmethanol, 93%

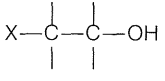
In Methods 3a to 3d, enolization of carbonyl compound and reduction of RMgX are side reactions that become important for hindered ketones and bulky Grignard reagents (Section 14-12A). Ammonium chloride is used to hydrolyze the reaction mixtures in preparation of tertiary alcohols to avoid dehydration. Organolithium compounds are superior to RMgX for preparation of bulky tertiary alcohols.

4. *Reaction of Grignard reagents with cyclic ethers*



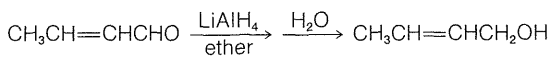
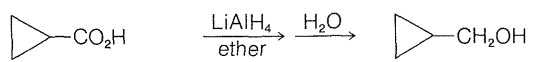
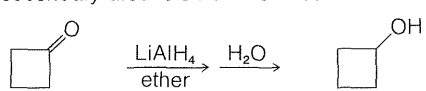
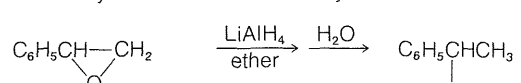
2-methyloxacyclopropane (2-methyloxirane) — 1-phenyl-2-propanol, 60%

Limited to three- and four-membered rings. Reaction is an S_N2-type displacement (Section 14-12A). Oxacyclopropanes often are used as a means of increasing chain length by two carbons in one step. A major side product is a haloalcohol,

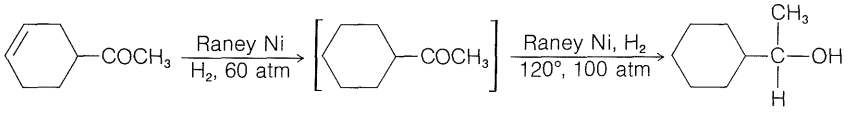


(Continued next page)

Table 15-2 (*continued*)
General Methods of Preparation of Alcohols

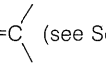
Reaction	Comment
5. *Reduction of carbonyl compounds with metal hydrides or boranes* a. *primary alcohols from aldehydes, acids, acid halides, and esters*  2-butenal → 2-butenol, 85%  cyclopropanecarboxylic acid → cyclopropylmethanol, 77%  hexanoic acid → 1-hexanol, 100% b. *secondary alcohols from ketones*  cyclobutanone → cyclobutanol, 90%	Excellent results are obtained with $LiAlH_4$ (see Section 16-4E), which is fairly selective and normally does not reduce C=C. Sodium borohydride, $NaBH_4$, is more selective and does not reduce carbonyl groups of acids and derivatives; it also may be used in aqueous and alcoholic solution, whereas $LiAlH_4$ may not. Borane (BH_3) in oxacyclopentane readily reduces aldehydes and acids to primary alcohols (Section 16-4E).
6. *Reduction of cyclic ethers with metal hydrides*  2-phenyloxacyclopropane (2-phenyloxirane) → 1-phenylethanol	Most used in the case of oxacyclopropanes. Orientation is such that $H:^{\ominus}$ from $LiAlH_4$ attacks *least*-hindered position. In the presence of $AlCl_3$, 2-phenylethanol is formed.

7. *Catalytic hydrogenation of carbonyl compounds*

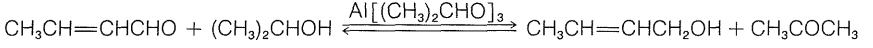


3-cyclohexenylethanone

1-cyclohexylethanol, 96%

Catalytic reduction is nonselective and reduces  (see Section 11-2B and compare with method 5).

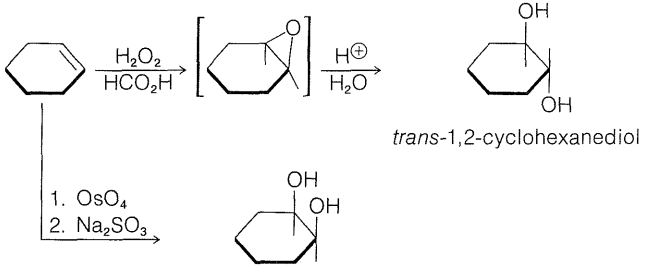
8. *Meerwein-Ponndorf-Oppenauer-Verley reduction of aldehydes and ketones*



2-butenal 2-propanol 2-buten-1-ol, 60%

See Section 16-4E. Reducing agent is usually aluminum isopropoxide; 2-propanone is formed and is removed by distillation, which shifts equilibrium to right. Carbon–carbon double bonds are unaffected.

9. *1,2-Glycols from alkenes*



trans-1,2-cyclohexanediol

cis-1,2-cyclohexanediol

An epoxide is formed from alkene and peroxymethanoic acid ($H_2O_2 + HCO_2H$) but is cleaved by the HCO_2H present to a *trans*-diol. Alternatively, osmium tetroxide may be used in *tert*-butyl alcohol and leads to the *cis*-diol. Potassium permanganate in neutral can be useful for preparation of *cis*-glycols. (See Section 11-7D.)

10. *Hydrolysis of alkyl and allylic halides*

See Sections 8-4 to 8-7.

11. *Hydrolysis of esters*

Of limited use because the ester often is prepared from the alcohol.

12. *Aldol condensation*

Gives β-hydroxy carbonyl compounds (see Section 17-3A).

13. *Cleavage of ethers*

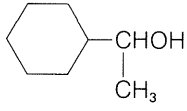
See Section 15-10 and Exercise 15-40.

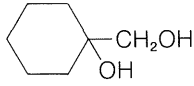
The industrial synthesis of methyl alcohol involves hydrogenation of carbon monoxide. Although this reaction has the favorable ΔH^0 value of -28.4 kcal mole^{-1}, it requires high pressures and high temperatures and a suitable catalyst; excellent conversions are achieved using zinc oxide-chromic oxide as a catalyst:

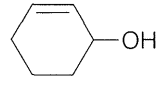
$$CO + 2H_2 \xrightarrow[ZnO\text{–}CrO_3]{400°,\ 200\ atm} CH_3OH$$

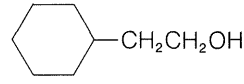
Various methods of synthesis of other alcohols by reduction of carbonyl compounds are discussed in Section 16-4E.

Exercise 15-6 Show how the following alcohols may be prepared from cyclohexene and any other needed reagents. Several steps may be necessary.

a. 

b. 

c. 

d. 

15-4 CHEMICAL REACTIONS OF ALCOHOLS. REACTIONS INVOLVING THE O—H BOND

15-4A Acidic Properties

Several important reactions of alcohols involve only the oxygen–hydrogen bond and leave the carbon–oxygen bond intact. An important example is salt formation with acids and bases. Alcohols, like water, are both weak bases and weak acids. The acid ionization constant (K_a) of ethanol is about 10^{-18}, slightly less than that of water. Ethanol can be converted to its conjugate base by the conjugate base of a weaker acid such as ammonia ($K_a \sim 10^{-35}$), or hydrogen ($K_a \sim 10^{-38}$). It is convenient to employ sodium metal or sodium hydride, which react vigorously but controllably with alcohols:

$$C_2H_5OH + Na^{\oplus}NH_2^{\ominus} \rightleftharpoons C_2H_5O^{\ominus}Na^{\oplus} + NH_3$$

sodium amide (sodamide) — sodium ethoxide

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

$$C_2H_5OH + Na^{\oplus}H^{\ominus} \longrightarrow C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

The order of acidity of various liquid alcohols generally is water > *primary* > *secondary* > *tertiary* ROH. By this we mean that the equilibrium position for the proton-transfer reaction (Equation 15-1) lies more on the side of ROH and $OH^{\ominus}$ as R is changed from *primary* to *secondary* to *tertiary;* therefore, *tert*-butyl alcohol is considered less acidic than ethanol:

$$ROH + {}^{\ominus}OH \rightleftharpoons RO^{\ominus} + HOH \qquad (15\text{-}1)$$

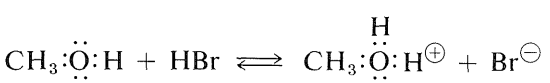
However, in the gas phase the order of acidity is reversed, and the equilibrium position for Equation 15-1 lies increasingly on the side of $RO^{\ominus}$ as R is changed from *primary* to *secondary* to *tertiary*. *tert*-Butyl alcohol is therefore *more* acidic than ethanol in the gas phase. This seeming contradiction appears more reasonable when one considers what effect solvation (or the lack of it) has on equilibria expressed by Equation 15-1. In solution, the larger anions of alcohols, known as **alkoxide ions,** probably are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions:

$CH_3O^{\ominus}$	$C_2H_5O^{\ominus}$	$(CH_3)_2CHO^{\ominus}$	$(CH_3)_3CO^{\ominus}$
methoxide	ethoxide	isopropoxide	*tert*-butoxide

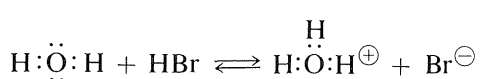
Acidity of alcohols therefore decreases as the size of the conjugate base increases. However, "naked" gaseous ions are more stable the larger the associated R groups, probably because the larger R groups can stabilize the charge on the oxygen atom better than the smaller R groups. They do this by polarization of their bonding electrons, and the bigger the group, the more polarizable it is. (Also see Section 11-8A, which deals with the somewhat similar situation encountered with respect to the relative acidities of ethyne and water.)

15-4B Basic Properties

Alcohols are bases similar in strength to water and accept protons from strong acids. An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen bromide and water:



methyloxonium bromide



hydroxonium bromide

Formation of a 1:1 reaction product from methanol and hydrogen bromide is shown by the change in melting point with composition of various mixtures (Figure 15-4). The melting point reaches a maximum at 50-50 mole percent of each component.

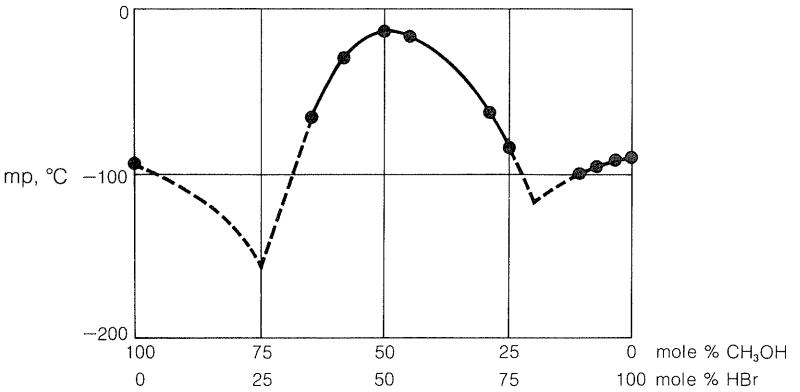


Figure 15-4 Melting points of mixtures of methanol and hydrogen bromide

Exercise 15-7 What order of *basicity* would you predict for water, methanol, isopropyl alcohol and *tert*-butyl alcohol *in the gas phase?* Give your reasoning.

15-4C Nucleophilic Properties. Ether Formation

Alkoxide ion formation is important as a means of generating a strong nucleophile that will readily form C–O bonds in S_N2 reactions. Thus ethanol reacts very slowly with methyl iodide to give methyl ethyl ether, but sodium ethoxide in ethanol solution reacts quite rapidly:

$$CH_3I + C_2H_5OH \overset{\text{slow}}{\rightleftharpoons} CH_3OC_2H_5 + HI$$

$$CH_3I + C_2H_5O^{\ominus}Na^{\oplus} \xrightarrow{\text{fast}} CH_3OC_2H_5 + \overset{\oplus\ \ominus}{NaI}$$

In fact, the reaction of alkoxides with alkyl halides or alkyl sulfates is an important general method for the preparation of ethers, and is known as the **Williamson synthesis.** Complications can occur because the increase of nucleophilicity associated with the conversion of an alcohol to an alkoxide ion always is accompanied by an even greater increase in eliminating power by the E2 mechanism. The reaction of an alkyl halide with alkoxide then may be one of elimination rather than substitution, depending on the temperature, the structure of the halide, and the alkoxide (Section 8-8). For example, if we wish to prepare isopropyl methyl ether, better yields would be obtained if we were to

use methyl iodide and isopropoxide ion rather than isopropyl iodide and methoxide ion because of the prevalence of E2 elimination with the latter combination:

$$CH_3I + (CH_3)_2CHO^{\ominus} \xrightarrow{S_N2} (CH_3)_2CHOCH_3 + I^{\ominus}$$

$$(CH_3)_2CHI + CH_3O^{\ominus} \xrightarrow{E2} CH_3CH{=}CH_2 + CH_3OH + I^{\ominus}$$

Potassium *tert*-butoxide is an excellent reagent to achieve E2 elimination because it is strongly basic and so bulky as to not undergo S_N2 reactions readily.

Exercise 15-8 Suggest a practical method for preparation of the following ethers. Show the reaction conditions as closely as possible.

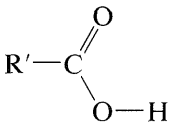
a. methoxyethane

b. 3-ethoxy-1-butene

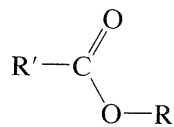
c. methoxycyclohexane

15-4D Nucleophilic Properties. Ester Formation

An ester may be thought of as a carboxylic acid in which the acidic proton has been replaced by some organic group, R,

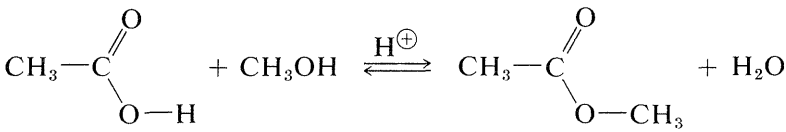


carboxylic acid



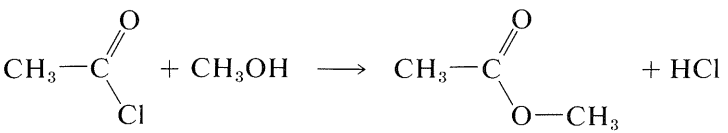
carboxylic ester

Esters can be prepared from carboxylic acids and alcohols provided an acidic catalyst is present,

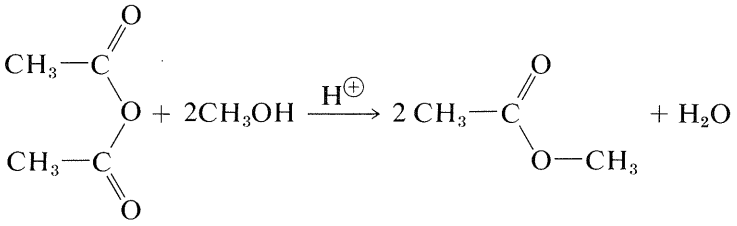


$$\Delta H^0 \text{ (gas)} = -4 \text{ kcal}$$
$$\Delta G^0 \text{ (gas)} \sim -4 \text{ kcal}$$

or they can be prepared from acyl halides and alcohols or carboxylic anhydrides and alcohols:



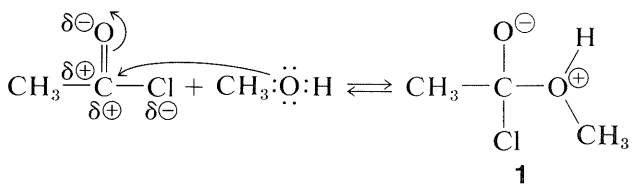
$$\Delta H^0 \text{ (gas)} = -14 \text{ kcal}$$
$$\Delta G^0 \text{ (gas)} = -14 \text{ kcal}$$



These reactions generally can be expressed by the equation $R'-\overset{\overset{O}{\|}}{C}-X + ROH \longrightarrow R'-\overset{\overset{O}{\|}}{C}-OR + HX$, which overall is a nucleophilic displacement of the X group by the nucleophile ROH. However, the mechanism of displacement is quite different from the S_N2 displacements of alkyl derivatives, $R'X + ROH \longrightarrow R'OR + HX$, and closely resembles the nucleophilic displacements of activated aryl halides (Section 14-6B) in being an *addition-elimination* process.

Acyl halides have a rather positive carbonyl carbon because of the polarization of the carbon–oxygen and carbon–halogen bonds. Addition of a nucleophilic group such as the oxygen of an alcohol occurs rather easily.

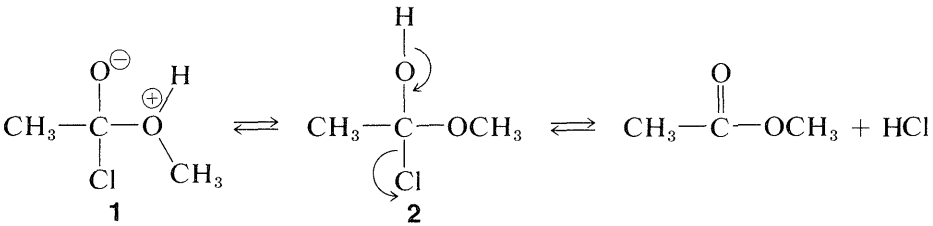
addition



1

The complex **1** contains both an acidic group ($CH_3—\overset{\oplus}{O}—H$) and a basic group ($—\overset{\ominus O}{C}—$), so that a proton shifts from one oxygen to the other to give **2**, which then rapidly loses hydrogen chloride by either an E1- or E2-type elimination to form the ester.

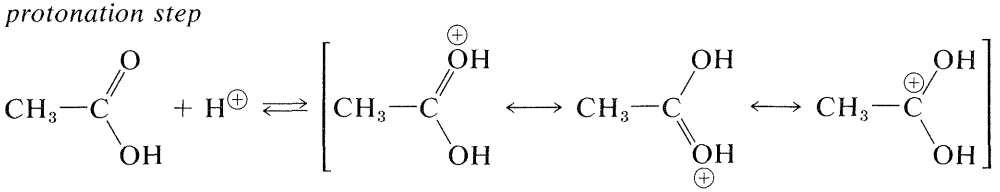
elimination



1 **2**

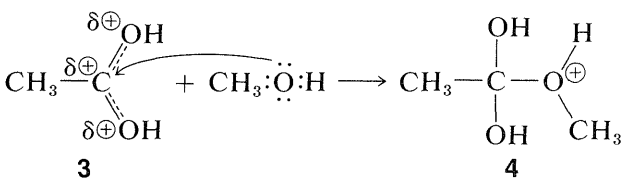
A similar but easily reversible reaction occurs between alcohols and carboxylic acids, which is slow in either direction in the absence of a strong mineral acid. The catalytic effect of acids, such as H_2SO_4, HCl, and H_3PO_4 is produced by protonation of the carbonyl oxygen of the carboxylic acid, thereby giving **3**. This protonation greatly enhances the affinity of the carbonyl carbon for an electron pair on the oxygen of the alcohol (i.e., **3** ⟶ **4**).

protonation step



3a **3b** **3c**

addition step

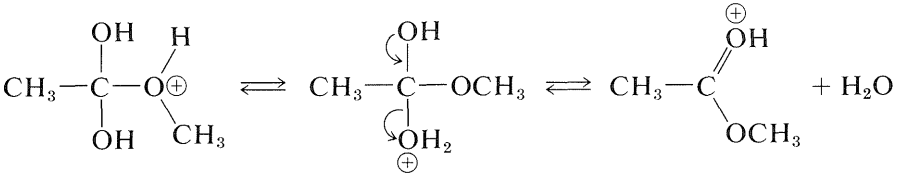


3 **4**

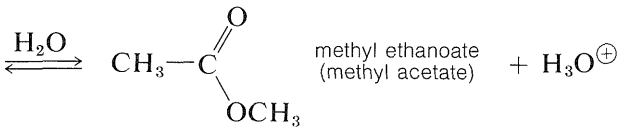
Subsequently, a proton is transferred from the OCH_3 to an OH group of **4** to give **5**. This process converts the OH into a good leaving group (H_2O). When H_2O leaves, the product, **6**, is the conjugate acid of the ester. Transfer

of a proton from **6** to a base such as H_2O or $HSO_4^{\ominus}$ completes the reaction, giving the neutral ester and regenerating the acid catalyst.

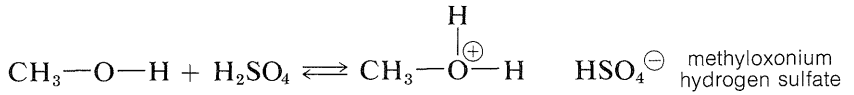
proton transfer and elimination



4 **5** **6**



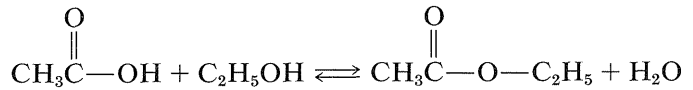
Although a small amount of strong acid catalyst is essential in the preparation of esters from acids and alcohols, the amount of acid catalyst added must not be too large. The reason for the "too much of a good thing" behavior of the catalyst can be understood from the basic properties of alcohols (Section 15-4B). If too much acid is present, then too much of the alcohol is converted to the oxonium salt:



Clearly, formation of the methyloxonium ion can operate only to *reduce* the nucleophilic reactivity of methanol toward the carbonyl carbon of the carboxylic acid.

Another practical limitation of esterification reactions is *steric hindrance*. If either the acid or the alcohol participants possesses highly branched groups, the positions of equilibrium are less favorable and the rates of esterification are slow. In general, the ease of esterification for alcohols, ROH, by the mechanism described is *primary* R > *secondary* R > *tertiary* R with a given carboxylic acid.

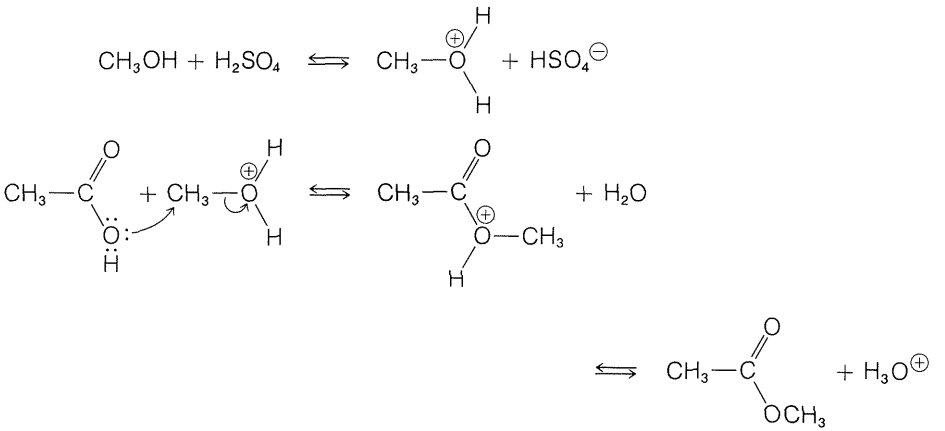
As mentioned, esterification is reversible, and with ethanol and ethanoic acid the equilibrium constant for the liquid phase is about 4 ($\Delta G^0 = -0.8$ kcal) at room temperature, which corresponds to 66% conversion to ester:



$$K = \frac{[CH_3CO_2C_2H_5][H_2O]}{[CH_3CO_2H][C_2H_5OH]} \cong 4$$

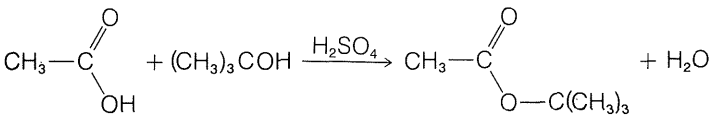
The reaction may be driven to completion by removing the ester or water or both as they are formed.

Exercise 15-9 An alternative and plausible mechanism for esterification of carboxylic acids is shown by the following steps:



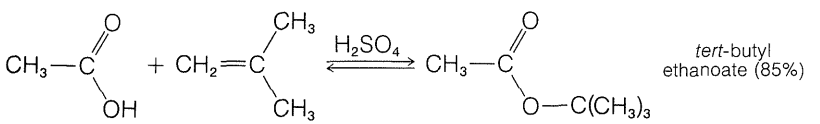
This mechanism corresponds to an S_N2 displacement of water from the methyloxonium ion by the acid. How could you distinguish between this mechanism and the addition-elimination mechanism using heavy oxygen (^{18}O) as a tracer?

Exercise 15-10 Formation of *tert*-butyl ethanoate by direct esterification goes very poorly:



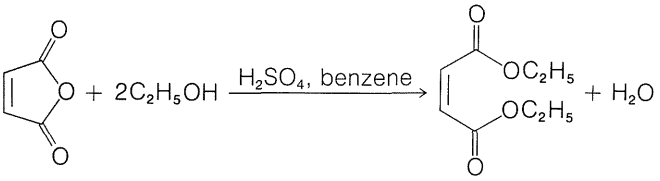
Explain why the reaction fails, and indicate the products you actually expect to form on heating a mixture of ethanoic acid and *tert*-butyl alcohol with sulfuric acid as a catalyst.

Exercise 15-11 A suitable method of preparing *tert*-butyl esters is to add the carboxylic acid to 2-methylpropene. Good yields can be obtained if a strong acid catalyst is used, if water is excluded, and if the temperature is kept low:



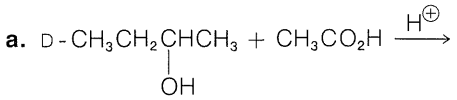
Write a mechanism for the reaction that accounts for the need for a strong acid catalyst, and why anhydrous conditions and low temperatures are necessary.

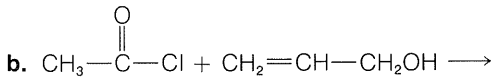
Exercise 15-12 The diethyl ester of *cis*-butenedioic acid can be prepared by heating the corresponding anhydride with ethanol and concentrated H_2SO_4 in benzene in a *mole* ratio of perhaps 1:2.5:0.25.

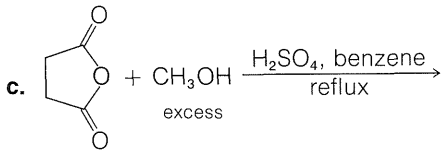


Write the steps that occur in this reaction and explain how the use of benzene and *more* than a catalytic amount of H_2SO_4 makes the formation of the diethyl ester thermodynamically more favorable than with just a catalytic amount of H_2SO_4.

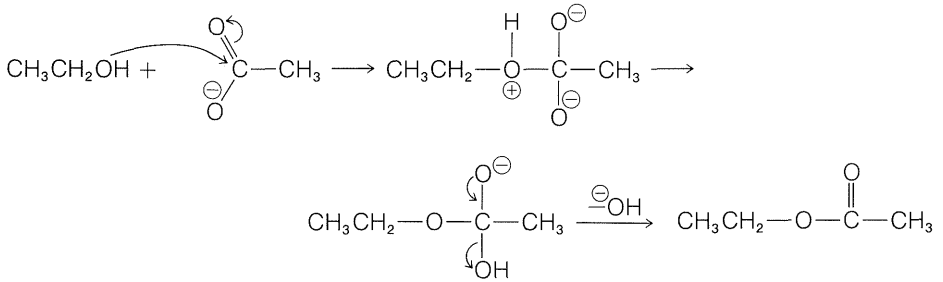
Exercise 15-13 Complete the following reactions by drawing structures for the major organic products expected.

a. 

b. 

c. 

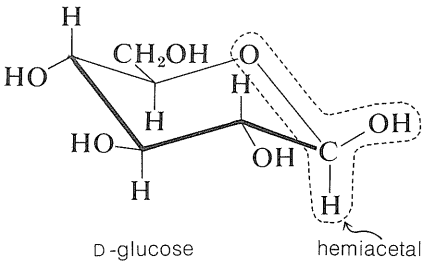
Exercise 15-14 One can conceive of an esterification procedure involving the reaction of ethanol with ethanoate ion in accord with the following mechanism:



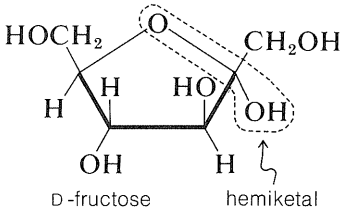
Assess the likelihood of the occurrence of this reaction at a reasonable rate *and* the favorableness of its overall equilibrium constant.

15-4E Nucleophilic Properties. RO—C—OH and RO—C—OR Formation

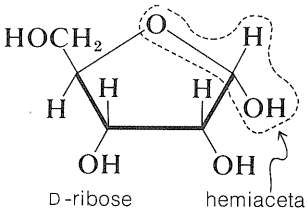
The structural unit, R—O—C—OH, possesses both an alkoxyl (OR) and a hydroxyl (OH) group on the *same* carbon. This arrangement, although often unstable, is an important feature of carbohydrates such as glucose, fructose, and ribose. When the grouping is of the type RO—CH—OH, it is called a **hemiacetal,** and if it is RO—C—OH, with no hydrogen attached to the carbon, it is called a **hemiketal:**



D-glucose hemiacetal



D-fructose hemiketal



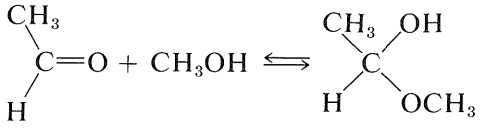
D-ribose hemiacetal

Each of these compounds has several other hydroxyl groups, but only *one* of them is a hemiacetal or hemiketal hydroxyl. Be sure you can identify which one.

The **acetal function** has two alkoxy (OR) groups and a hydrogen on the same carbon, RO—CH—OR, whereas the ketal function has the same structure but with no hydrogen on the carbon. These groupings also are found in carbohydrates and in carbohydrate derivatives, and are called **glycosido functions** (see Chapter 20).

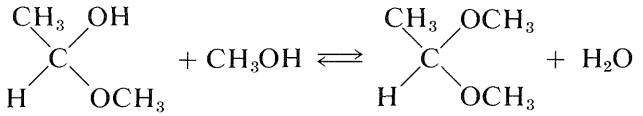
For our present purposes, we are interested in the ways in which hemiacetals, acetals, hemiketals, and ketals are formed. Hemiacetals and hemiketals can be regarded as products of the addition of alcohols to the carbonyl

groups of aldehydes and ketones. Thus methanol adds to ethanal to give a hemiacetal, 1-methoxyethanol:



ethanal methanol 1-methoxyethanol (a hemiacetal)

Acetals and ketals result from substitution of an alkoxy group for the OH group of a hemiacetal or hemiketal. Thus methanol can react with 1-methoxyethanol to form the acetal, 1,1-dimethoxyethane, and water:

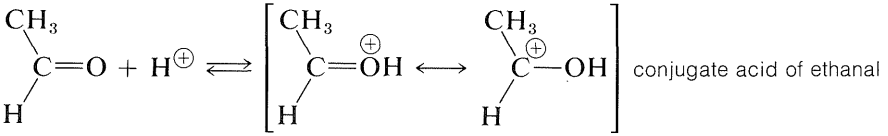


1,1-dimethoxyethane (an acetal)

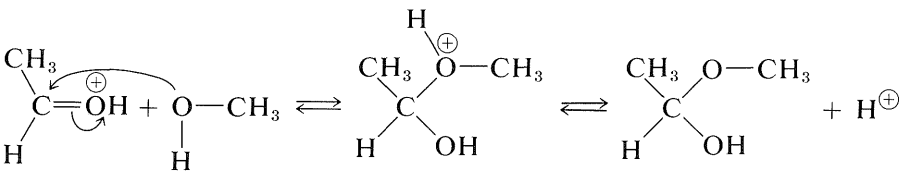
Exercise 15-15 How can D-glucose, D-fructose, and D-ribose be considered products of the addition of an alcohol to the carbonyl group of an aldehyde or ketone? Name each of the carbonyl compounds by the IUPAC system. For the ribose carbonyl structure, determine the configuration at each chiral center, using the D,L system.

The reactions of alcohols with aldehydes and ketones are related to the reactions of alcohols with acids (esterification) discussed in the preceding section. Both types involve addition of alcohols to carbonyl groups, and both are acid-catalyzed.

Acid catalysis of RO—C(—)—OH formation, like ester formation, depends on formation of the conjugate acid of the carbonyl compound. This is expected to enhance the positive (*electrophilic*) character of the carbonyl carbon so that the nucleophilic alcohol can add readily to it:

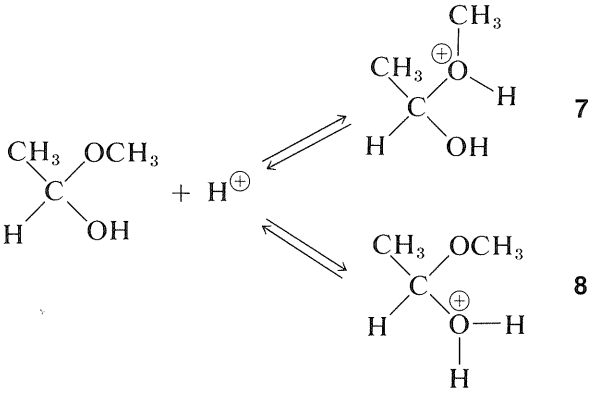


conjugate acid of ethanal

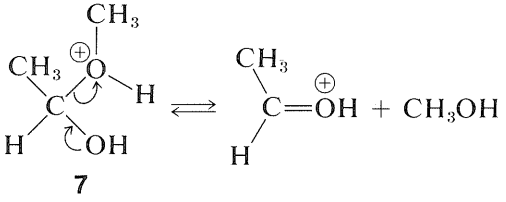


hemiacetal

The hemiacetal can react further, also with the aid of an acidic catalyst. Addition of a proton can occur in two ways, to give **7** or **8**:

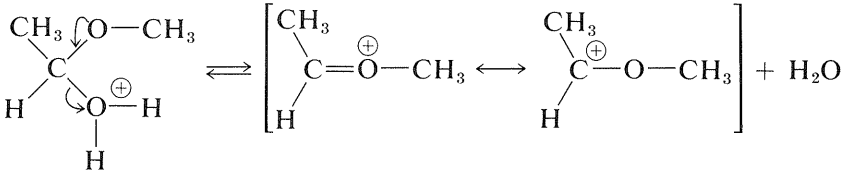


The first of these, **7**, has CH_3OH as a leaving group and reverts back to the conjugate acid of ethanal. This is the reverse of acid-catalyzed hemiacetal formation:



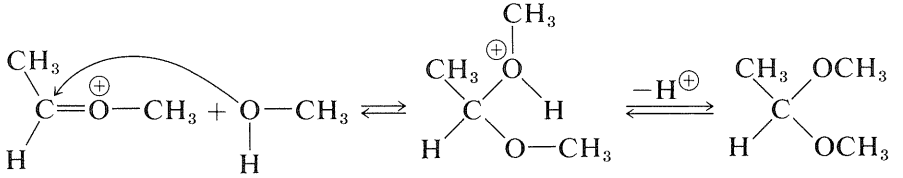
7

The second of these, **8**, has H_2O as a leaving group and can form a new entity, the methoxyethyl cation, **9**:



8 **9**

The ion **9** resembles $CH_3CH{=}\overset{\oplus}{O}H$ and can be expected to behave similarly by adding a second molecule of alcohol to the electrophilic carbon. The product, **10**, is then the conjugate acid of the acetal and loses a proton to give the acetal:

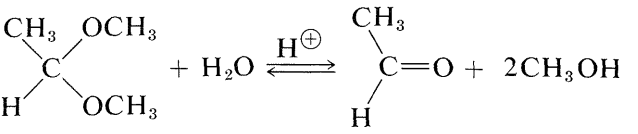


9 **10** acetal

Table 15-3
Conversion of Aldehydes to Acetals with Various Alcohols (1 Mole of Aldehyde to 5 Moles of Alcohol)

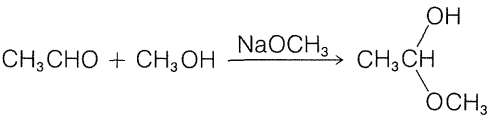
	Percent conversion to acetal			
Aldehyde	Ethanol	Cyclohexanol	2-Propanol	*tert*-Butyl alcohol
CH_3CHO	78	56	43	23
$(CH_3)_2CHCHO$	71	–	23	–
$(CH_3)_3CCHO$	56	16	11	–
C_6H_5CHO	39	23	13	–

Formation of hemiacetals and acetals, as well as of hemiketals and ketals, is reversible under acidic conditions, as we already have noted for acid-catalyzed esterification. The reverse reaction is *hydrolysis* and the equilibrium for this reaction can be made favorable by having an excess of water present:



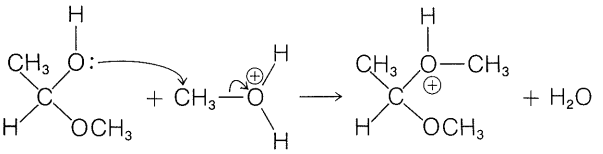
The position of equilibrium in acetal and hemiacetal formation is rather sensitive to steric hindrance. Large groups in either the aldehyde or the alcohol tend to make the reaction less favorable. Table 15-3 shows some typical conversions in acetal formation when 1 mole of aldehyde is allowed to come to equilibrium with 5 moles of alcohol. For ketones, the equilibria are still less favorable than for aldehydes, and to obtain reasonable conversion the water must be removed as it is formed.

Exercise 15-16 Hemiacetal formation is catalyzed by both acids *and* bases, but acetal formation is catalyzed only by acids. Write the steps involved in the formation of 1-methoxyethanol from ethanal in methanol containing sodium methoxide:



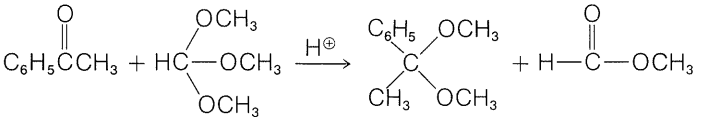
Explain why 1,1-dimethoxymethane cannot be prepared from ethanal and methanol with a basic catalyst.

Exercise 15-17 The slow step in an alternative mechanism for acetal formation may be as follows:



How could this mechanism be distinguished experimentally from the one given in Section 15-4E?

Exercise 15-18 Ketals are not always capable of being made in practical yields by the direct reaction of alcohols with ketones because of unfavorable equilibria. Satisfactory preparations of RO—C(—)—OR with R = methyl or ethyl are possible through the reactions of ketones with trimethoxy- or triethoxymethane. This process requires an acid catalyst:



Write the mechanistic steps involved in this acid-induced methoxy exchange reaction.

Exercise 15-19 Look at the structure of tetrodotoxin on p. 599. What would you expect to happen to the hydroxyl at the bridgehead position in dilute base?

15-5 REACTIONS INVOLVING THE C–O BOND OF ALCOHOLS

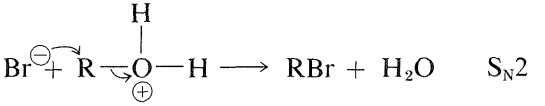
15-5A Electrophilic Properties of Alcohols

Alkyl halide formation from an alcohol and a hydrogen halide affords an important example of a reaction wherein the C–O bond of the alcohol is broken:

$$R\text{—}OH + HBr \rightleftharpoons RBr + H_2O$$

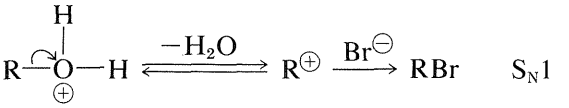
The reaction is reversible and the favored direction depends on the water concentration. Primary bromides often are prepared best by passing dry hydrogen bromide into the alcohol heated to just slightly below its boiling point.

Halide formation proceeds at a useful rate only in the presence of strong acid, which can be furnished by excess hydrogen bromide or, usually and more economically, by sulfuric acid. The alcohol accepts a proton from the acid to give an alkyloxonium ion, which is more reactive in subsequent displacement with bromide ion than the alcohol (by either S_N2 or S_N1 mechanisms) because H_2O is a better leaving group than $^{\ominus}OH$:



S_N2

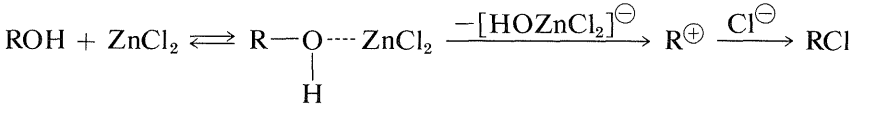
or



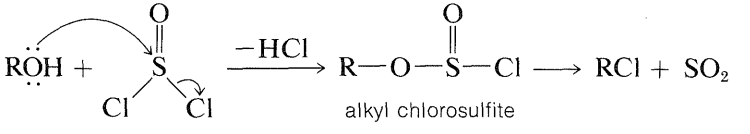
S_N1

Whether the displacement reaction is an S_N1 or S_N2 process depends on the structure of the alcohol. In general, the primary alcohols are considered to react by S_N2 and the secondary and tertiary alcohols by S_N1 mechanisms.

Hydrogen chloride is less reactive than hydrogen bromide toward primary alcohols, and a catalyst (zinc chloride) may be required. A solution of zinc chloride in concentrated hydrochloric acid (Lucas reagent) is a convenient reagent to differentiate between primary, secondary, and tertiary alcohols with less than eight or so carbons. Tertiary alcohols react very rapidly to give an insoluble layer of alkyl chloride at room temperature. Secondary alcohols react in several minutes, whereas primary alcohols form chlorides only on heating. The order of reactivity is typical of S_N1 reactions. Zinc chloride probably assists in the breaking of the C–O bond of the alcohol much as silver ion aids ionization of RCl (Section 8-7D):



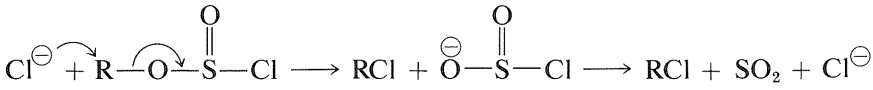
Thionyl chloride, $O{=}SCl_2$, is useful for the preparation of alkyl chlorides, especially when the use of strongly acidic reagents, such as zinc chloride and hydrochloric acid, is undesirable. Thionyl chloride can be regarded as the acid chloride of sulfurous acid, $O{=}S(OH)_2$, and like most acid chlorides the halogen is displaced readily by alcohols. Addition of 1 mole of an alcohol to 1 mole of thionyl chloride gives an unstable alkyl chlorosulfite, which generally decomposes on mild heating to yield the alkyl chloride and sulfur dioxide:



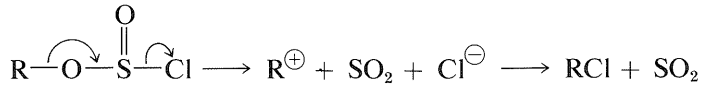
alkyl chlorosulfite

Chlorides can be prepared in this way from primary and secondary, but not tertiary, alcohols. In practice, an equivalent of a weak base, such as pyridine (azabenzene), is added to neutralize the hydrogen chloride that is formed. If the acid is not removed, undesirable degradation, elimination, and rearrangement reactions may occur.

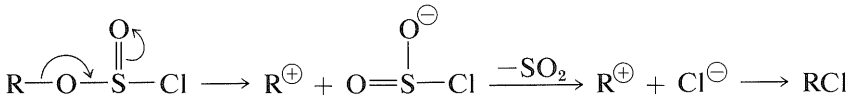
The thionyl chloride reaction apparently can proceed from the alkyl chlorosulfite stage by more than one mechanism: an ionic S_N2 chain reaction with chloride ion,



or an S_N1-like ionization and collapse of the resulting $R^{\oplus}Cl^{\ominus}$ ion pair to give RCl:

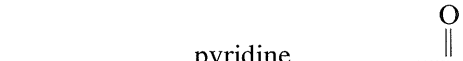


or



Obviously, the greater the S_N2 reactivity associated with $ROS(=O)-Cl$, the better the S_N2 reaction will go and, conversely, if $R^{\oplus}$ is formed easily from $ROS(=O)-Cl$, the S_N1 reaction is likely to be favored.

Other halides that are useful in converting alcohols to alkyl halides are PCl_5, PCl_3, PBr_3, and PI_3, which are acid halides of phosphorus oxyacids. As with thionyl chloride, a weak base often is used to facilitate the reaction. The base acts to neutralize the acid formed, and also to generate bromide ion for S_N reactions:



Exercise 15-20 If you wished to convert D-1-phenylethanol to L-1-chloro-1-phenylethane, which of the following reagents and conditions would you use? Give reasons for your choice.

a. HCl and $ZnCl_2$ **b.** $SOCl_2$ alone **c.** $SOCl_2$ with pyridine

Exercise 15-21 Write the steps that could plausibly take place in the reaction of a primary alcohol with phosphorus tribromide in the presence of the weak base pyridine to give an alkyl bromide.

15-5B Sulfate and Sulfonate Esters

It is possible to prepare esters of sulfuric acid by the reaction of an alcohol with the acid:

$$ROH + HOSO_3H \longrightarrow RO{-}SO_3H + H_2O$$

alkyl hydrogen sulfate

The reaction is closely related to alkyl halide formation under strongly acidic conditions, whereby conversion of the alcohol to an oxonium salt is a first step:

$$ROH + H_2SO_4 \rightleftharpoons \overset{\oplus}{R}OH_2 + \overset{\ominus}{O}{-}\overset{\displaystyle O}{\overset{\|}{S}}{-}OH \quad (\overset{\displaystyle O}{\|})$$

Conversion of the oxonium hydrogen sulfate to the ester probably proceeds by an S_N2 mechanism with primary alcohols and an S_N1 mechanism with tertiary alcohols:

$$\overset{\oplus}{R}OH_2 + \overset{\ominus}{O}SO_3H \xrightarrow[-H_2O]{S_N1} R^{\oplus} + \overset{\ominus}{O}SO_3H \longrightarrow RO{-}\overset{\displaystyle O}{\overset{\|}{S}}{-}OH \quad (\overset{\displaystyle O}{\|})$$

$$\overset{\oplus}{R}OH_2 + \overset{\ominus}{O}SO_3H \xrightarrow[-H_2O]{S_N2} RO{-}\overset{\displaystyle O}{\overset{\|}{S}}{-}OH \quad (\overset{\displaystyle O}{\|})$$

alkyl hydrogen sulfate

An alternative mechanism, which operates either in 100%, or in fuming sulfuric acid (which contains dissolved SO_3), is addition of sulfur trioxide to the OH group:

$$ROH + SO_3 \longrightarrow \left[R{-}\overset{\displaystyle H}{\overset{|}{\overset{\oplus}{O}}}{-}SO_3^{\ominus} \right] \longrightarrow R{-}O{-}SO_3H$$

The sodium salts of alkyl hydrogen sulfate esters have useful properties as detergents if the alkyl group is large, C_{12} or so:

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2{-}\overset{\ominus}{O}SO_3\overset{\oplus}{N}a$$

sodium dodecyl sulfate (a detergent)

The mechanism of detergent action will be considered in more detail in Chapter 18.

In principle, dialkyl sulfates could be formed by an S_N2 reaction between an alkyloxonium salt and an alkyl sulfate ion:

$$ROH + ROSO_3H \rightleftharpoons \overset{\oplus}{R}OH_2 + ROSO_3^{\ominus} \longrightarrow \underset{\text{dialkyl sulfate}}{RO(SO_2)OR} + H_2O$$

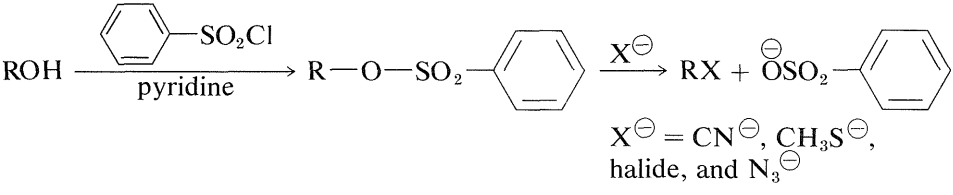
Indeed, if methanol is heated with fuming sulfuric acid, dimethyl sulfate, $CH_3O(SO_2)OCH_3$, is obtained; but other alcohols are better converted to dialkyl sulfates by oxidation of the corresponding dialkyl *sulfites* formed by the reaction of 1 mole of thionyl chloride ($SOCl_2$) with 2 moles of the alcohol:

$$2CH_3(CH_2)_3OH + SOCl_2 \longrightarrow \underset{\text{dibutyl sulfite}}{[CH_3(CH_2)_3O]_2SO} \xrightarrow{KMnO_4} \underset{\text{dibutyl sulfate}}{[CH_3(CH_2)_3O]_2SO_2}$$

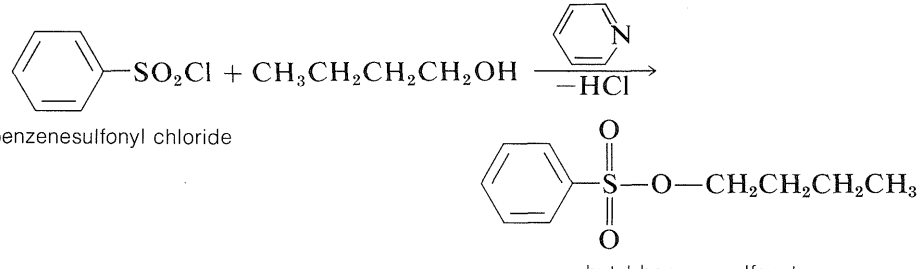
The reason that dialkyl sulfates seldom are prepared by direct reaction of the alcohol with H_2SO_4 is that the mono esters react rapidly on heating to eliminate sulfuric acid and form alkenes, as explained in Section 15-5C.

Sulfonic acids, R—SO_2—OH or Ar—SO_2—OH, are oxyacids of sulfur that resemble sulfuric acid, HO—SO_2—OH, but in which sulfur is in a lower oxidation state.

Sulfonate esters are useful intermediates in displacement reactions (Section 8-7C) and provide a route for the conversion of an alcohol, ROH, to RX by the sequence:



Sulfonate esters usually are prepared through treatment of the alcohol with the acid chloride (sulfonyl chloride) in the presence of pyridine (azabenzene):



15-5C Dehydration of Alcohols with Strong Acids

In the reaction of an alcohol with hot concentrated sulfuric acid, the alcohol is dehydrated to an alkene:

$$CH_3CH_2OH \xrightarrow[150^\circ]{H_2SO_4} CH_2{=}CH_2 + H_2O$$

This is the reverse of acid-catalyzed hydration of alkenes discussed previously (Section 10-3E) and goes to completion if the alkene is allowed to distill out of the reaction mixture as it is formed. One mechanism of dehydration involves proton transfer from sulfuric acid to the alcohol, followed by an E2 reaction of hydrogen sulfate ion or water with the oxonium salt of the alcohol:

$$H_2SO_4 + CH_3CH_2OH \rightleftharpoons HSO_4^{\ominus} + CH_3CH_2\overset{\oplus}{O}H_2$$

$$HSO_4^{\ominus} + CH_2(H)\text{—}CH_2\text{—}\overset{\oplus}{O}H_2 \longrightarrow H_2SO_4 + CH_2{=}CH_2 + H_2O$$

Alternatively, the alkyl hydrogen sulfate could be formed and eliminate sulfuric acid by an E2 reaction:

$$\begin{matrix} HSO_4^{\ominus} + CH_3CH_2\text{—}\overset{\oplus}{O}H_2 \\ \text{or} \\ CH_3CH_2OH + SO_3 \end{matrix} \longrightarrow CH_3CH_2\text{—}OSO_3H + H_2O$$

$$\longrightarrow CH_2{=}CH_2 + H_3O^{\oplus} + HSO_4^{\ominus}$$

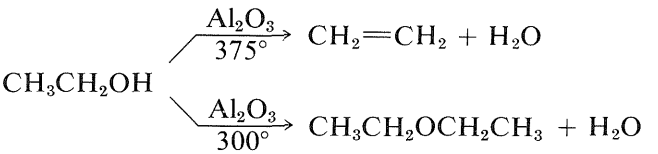
At lower temperatures the oxonium salt or the alkyl hydrogen sulfate may react by an S_N displacement mechanism with excess alcohol in the reaction mixture, thereby forming a dialkyl ether. Although each step in the reaction is reversible, ether formation can be enhanced by distilling away the ether as fast as it forms. Diethyl ether is made commercially by this process:

$$\begin{matrix} CH_3CH_2OSO_3H + CH_3CH_2OH \xrightarrow[-HSO_4^{\ominus}]{130^\circ} \\ CH_3CH_2\overset{\oplus}{O}H_2 + CH_3CH_2OH \xrightarrow[-H_2O]{130^\circ} \end{matrix} CH_3CH_2\text{—}\overset{H}{\underset{\oplus}{O}}\text{—}CH_2CH_3$$

$$\xrightleftharpoons{-H^{\oplus}} CH_3CH_2OCH_2CH_3$$

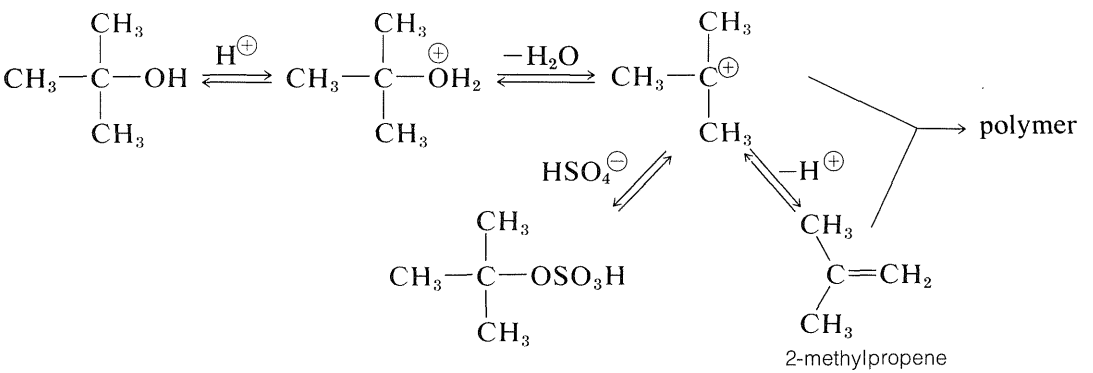
ethoxyethane
(diethyl ether)

Most alcohols also will dehydrate at fairly high temperatures in the presence of solid catalysts such as silica gel or aluminum oxide to give alkenes or ethers. The behavior of ethanol is reasonably typical of primary alcohols and is summarized in the following equations:



15-5D C–O Bond Cleavage of Tertiary Alcohols

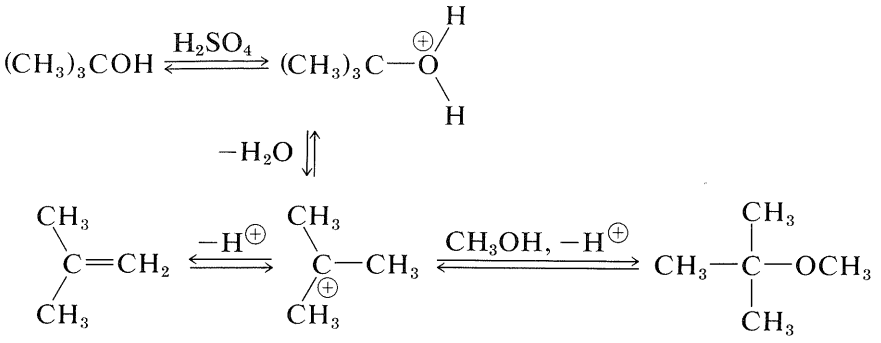
Tertiary alcohols react with sulfuric acid at much lower temperatures than do most primary or secondary alcohols. The reactions typically are S_N1 and E1 by way of a tertiary carbocation, as shown here for *tert*-butyl alcohol and sulfuric acid:



2-Methylpropene can be removed from the reaction mixture by distillation and easily is made the principal product by appropriate adjustment of the reaction conditions. If the 2-methylpropene is not removed as it is formed, polymer and oxidation products become important. Sulfuric acid often is an unduly strenuous reagent for dehydration of tertiary alcohols. Potassium hydrogen sulfate, copper sulfate, iodine, phosphoric acid, or phosphorus pentoxide may give better results by causing less polymerization and less oxidative degradation which, with sulfuric acid, results in the formation of sulfur dioxide.

The S_N1–E1 behavior of tertiary alcohols in strong acids can be used to advantage in the preparation of *tert*-butyl ethers. If, for example, a mixture of *tert*-butyl alcohol and methanol is heated in the presence of sulfuric acid, the tertiary alcohol reacts rapidly *but reversibly* to produce 2-methylpropene by

way of the *tert*-butyl cation. This cation can be trapped by the methanol to form *tert*-butyl methyl ether. High yields of ethers can be obtained in this way:



Exercise 15-22 Methylmagnesium iodide with 2-butenal gives an addition product that, when hydrolyzed with dilute sulfuric acid and extracted with ether, yields an ether solution of impure 3-penten-2-ol. Attempted purification by distillation of the ether extract gives only 1,3-pentadiene and di(1-methyl-2-butenyl) ether. Write equations for each of the reactions involved. How could you avoid ether and diene formation in the preparation of 3-penten-2-ol by this method?

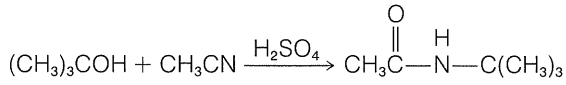
Exercise 15-23 What are the expected products on heating the following alcohols with strong sulfuric acid? Give your reasoning.

a. cyclohexanol

b. a mixture of methanol and 1-methylcyclohexanol

c. $(CH_3)_2C{=}CHCH_2OH$

Exercise 15-24* It is possible to prepare amides from tertiary alcohols and alkanenitriles, RCN, in concentrated sulfuric acid as the catalyst (Ritter reaction), as illustrated in the equation for the synthesis of *N-tert*-butylethanamide:

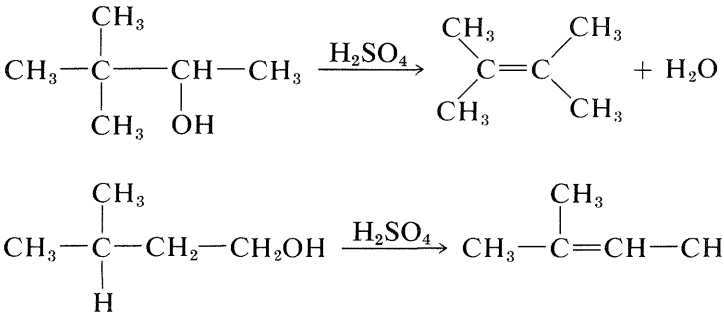


Show the steps in the mechanism of this reaction, given the fact that nitrilium ions of structure $R{-}C{\equiv}\overset{\oplus}{N}{-}R$ are likely to be intermediates.

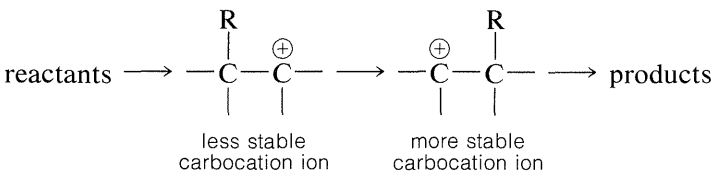
15-5E Carbocation Rearrangements

Rearrangement of the alkyl groups of alcohols is very common in dehydration, particularly in the presence of strong acids, which are conducive to carbocation

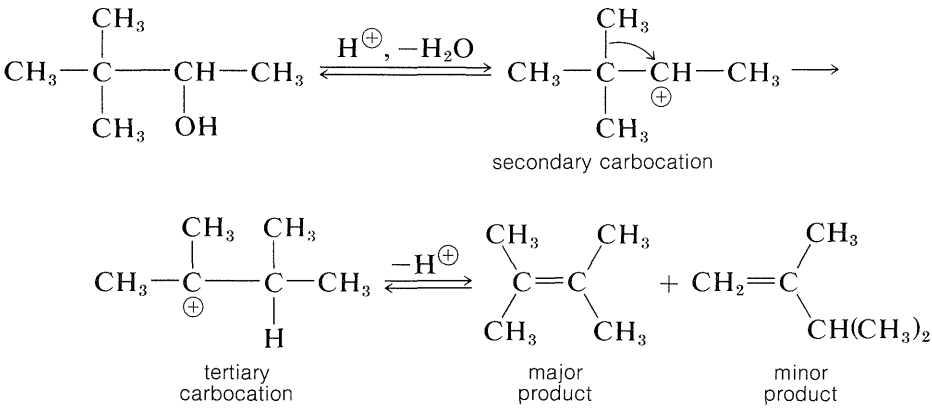
formation. Typical examples showing both methyl and hydrogen migration follow:



The key step in each such rearrangement is isomerization of a carbocation, as discussed in Section 8-9B. Under kinetic control, the final products always correspond to rearrangement of a less stable carbocation to a more stable carbocation. (Thermodynamic control may lead to quite different results, Section 10-4A.)

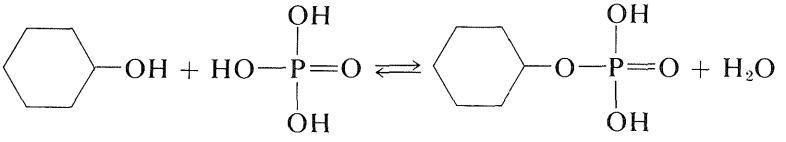


In the dehydration of 3,3-dimethyl-2-butanol, a secondary carbocation is formed initially, which rearranges to a tertiary carbocation when a neighboring methyl group *with* its bonding electron pair migrates to the positive carbon. The charge is thereby transferred to the tertiary carbon:



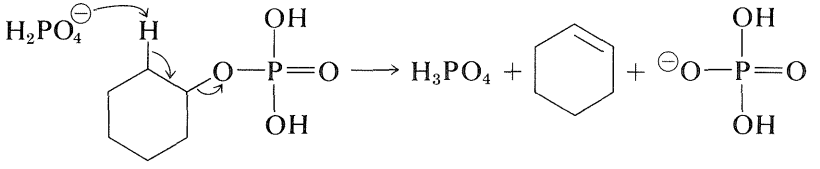
15-5F Phosphate Esters

Phosphoric acid (H_3PO_4) often is used in place of sulfuric acid to dehydrate alcohols. This is because phosphoric acid is less destructive; it is both a weaker acid and a less powerful oxidizing agent than sulfuric acid. Dehydration probably proceeds by mechanisms similar to those described for sulfuric acid (Section 15-5C) and very likely through intermediate formation of a *phosphate ester:*

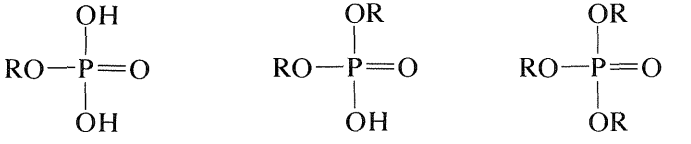


cyclohexyl dihydrogen phosphate

The ester can eliminate H_3PO_4, as sulfate esters eliminate H_2SO_4, to give alkenes:

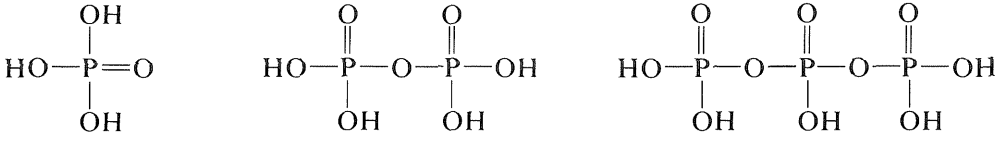


The chemistry of phosphate esters is more complicated than that of sulfate esters because it is possible to have one, two, or three alkyl groups substituted for the acidic hydrogens of phosphoric acid:



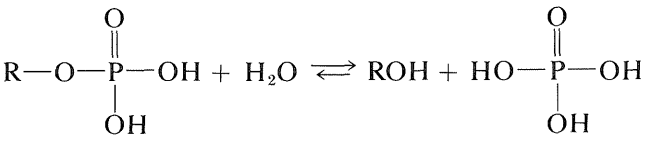
monoalkyl phosphate | dialkyl phosphate | trialkyl phosphate

Also, phosphoric acid forms an extensive series of anhydrides (with P—O—P bonds), which further diversify the number and kind of phosphate esters. The most important phosphate esters are derivatives of mono-, di-, and triphosphoric acid (sometimes classified as ortho-, pyro-, and meta-phosphoric acids, respectively):



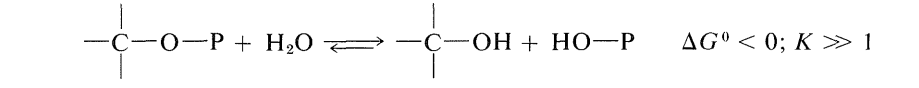
*mono*phosphoric acid (ortho) | *di*phosphoric acid (pyro) | *tri*phosphoric acid (meta)

The equilibrium between the esters of any of these phosphoric acids and water favors hydrolysis:

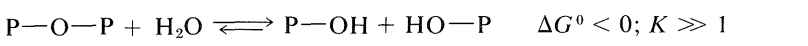


However, phosphate esters are *slow* to hydrolyze in water (unless a catalyst is present). The difference in kinetic and thermodynamic stability of phosphate esters toward hydrolysis is used to great effect in biological systems.

Of particular importance is the conversion of much of the energy that results from photosynthesis, or from the oxidation of fats, carbohydrates, and proteins in cells into formation of phosphate ester bonds (C—O—P) or phosphate anhydride bonds (P—O—P). The energy so stored is used in other reactions, the net result of which is hydrolysis:

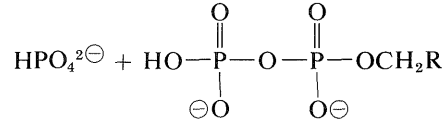


$\Delta G^0 < 0;\ K \gg 1$

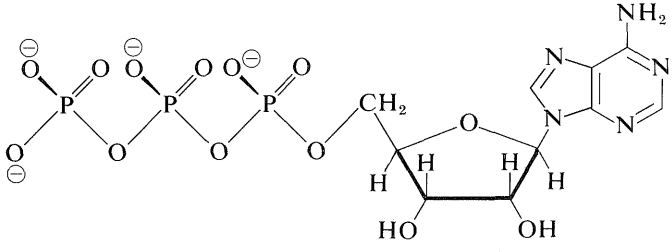


$\Delta G^0 < 0;\ K \gg 1$

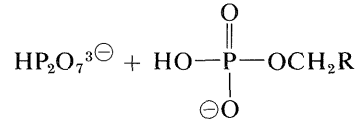
The substance that is the immediate source of energy for many biological reactions is adenosine triphosphate (ATP). Although this is a rather large and complex molecule, the business end for the purpose of this discussion is the *triphosphate* group. Hydrolysis of this group can occur to give adenosine diphosphate (ADP), adenosine monophosphate (AMP), or adenosine itself:



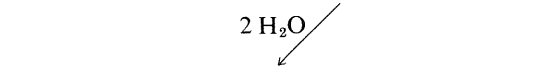
adenosine diphosphate (ADP) $\Delta G^0 = -7$ kcal



adenosine triphosphate (A + TP) = ATP



adenosine monophosphate (AMP) $\Delta G^0 = -7$ kcal



(The phosphate groups are repesented here as the major ionized form present at pH ≅7 in solutions of ATP.)

All of these hydrolysis reactions are energetically favorable ($\Delta G^0 < 0$), but they do not occur directly because ATP reacts slowly with water. However, hydrolysis of ATP is the indirect result of other reactions in which it participates. For example, as we showed in Section 15-4D, equilibrium for the direct formation of an ester from a carboxylic acid and an alcohol in the liquid phase is not very favorable (Equation 15-2). However, if esterification can be coupled with ATP hydrolysis (Equation 15-3), the overall reaction (Equation 15-4) becomes much more favorable thermodynamically than is direct esterification.

$$CH_3CH_2OH + CH_3CO_2H \rightleftharpoons CH_3CH_2O_2CCH_3 + H_2O$$

$$\Delta G^0 \cong -0.8 \text{ kcal} \quad (15\text{-}2)$$

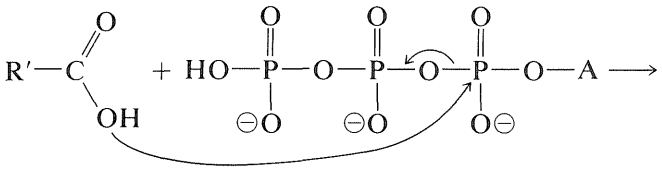
$$ATP + H_2O \rightleftharpoons AMP + HP_2O_7^{3\ominus}$$

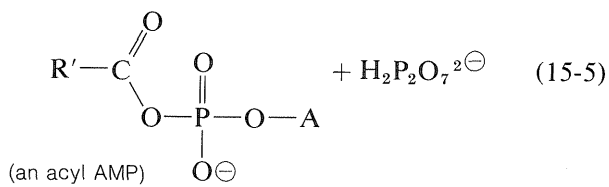
$$\Delta G^0 = -7 \text{ kcal} \quad (15\text{-}3)$$

$$CH_3CH_2OH + CH_3CO_2H + ATP \rightleftharpoons CH_3CH_2O_2CCH_3 + AMP + HP_2O_7^{3\ominus}$$

$$\Delta G^0 = -8 \text{ kcal} \quad (15\text{-}4)$$

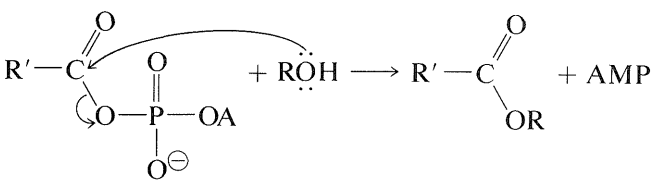
The ATP hydrolysis could be coupled to esterification (or other reactions) in a number of ways. The simplest would be to have the ATP convert one of the participants to a more reactive intermediate. For esterification, the reactive intermediate is an acyl derivative of AMP formed by the displacement of diphosphate from ATP:





(15-5)

The acyl AMP is like an acyl chloride, RCOCl, in having a leaving group (AMP) that can be displaced with an alcohol:

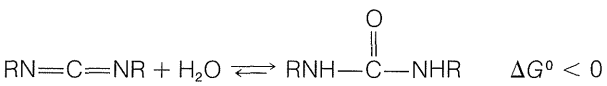


(15-6)

The net result of the sequence in Equations 15-5 and 15-6 is esterification in accord with Equation 15-4. It is not a catalyzed esterification because in the process one molecule of ATP is converted to AMP and diphosphate for each molecule of ester formed. The AMP has to be reconverted to ATP to participate again. These reactions are carried on by cells under the catalytic influence of enzymes. The adenosine part of the molecule is critical for the specificity of action by these enzymes. Just how these enzymes function obviously is of great interest and importance.

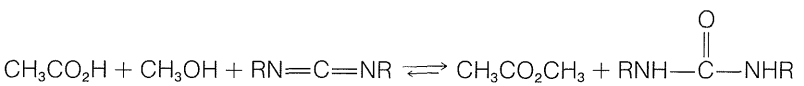
If the role of phosphate esters, such as ATP, in carrying out reactions such as esterification in aqueous media under the influence of enzymes in cells is not clear to you, think about how you would try to carry out an esterification of ethanol in dilute water solution. Remember that, with water in great excess, the equilibrium will be quite unfavorable for the esterification reaction of Equation 15-2. You might consider adding CH_3COCl, for which the equilibrium for ester formation is much more favorable (Section 15-4D). However, CH_3COCl reacts violently with water to form CH_3CO_2H, and this reaction destroys the CH_3COCl before it has much chance to react with ethanol to give the ester. Clearly, what you would need is a reagent that will convert CH_3CO_2H into something that will react with ethanol in water to give the ester with a favorable equilibrium constant and yet not react very fast with water. The phosphate esters provide this function in biochemical systems by being quite unreactive to water but able to react with carboxylic acids under the influence of enzymes to give acyl phosphates. These acyl phosphates then can react with alcohols under the influence of other enzymes to form esters in the presence of water. Many organic reagents can provide similar functions in organic synthesis. Examples of two reagents that can be coupled, respectively, to ester and acetal formation to give more favorable overall reactions are given in Exercises 15-25 and 15-26.

Exercise 15-25* The equilibrium for the formation of urea compounds from the hydrolysis of substances called "carbodiimides" is a thermodynamically favorable reaction:



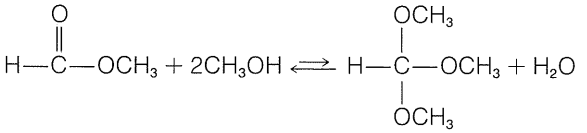
(1,3-diazapropadiene, a carbodiimide)

When coupled with an esterification involving an acid and an alcohol this reaction gives excellent conversions, although *not* in aqueous solution because the nucleophilic reactivities of water and alcohols are rather similar. Show the possible steps by which carbodiimides can achieve this conversion:



(In Chapter 25 we shall encounter reactions of amines and amino acids in which carbodiimides can be used in the presence of water. The difference is that amine nitrogen generally is more nucleophilic than water.)

Exercise 15-26* Trialkoxyalkanes, $R'C(OR)_3$, sometimes are called "orthoesters." They may be regarded as derived from alcohols and esters, although they seldom are prepared by this direct route because the following equilibrium is quite unfavorable:

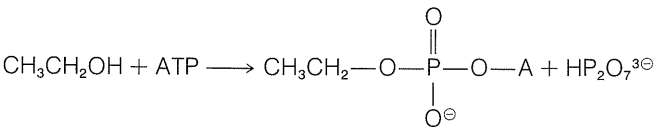


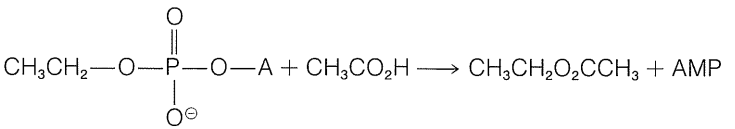
a. On the basis of the resonance theory, why should we expect the equilibrium for orthoester formation to be unfavorable?

b. Explain why trimethoxymethane and methanol together give a higher conversion of a ketone to the corresponding ketal than methanol alone does in the presence of an acid catalyst.

c. How may one synthesize $HC(OC_2H_5)_3$ from $CHCl_3$? (Review Section 14-7B.)

Exercise 15-27 A *possible* mechanism for producing esterification of an alcohol coupled with ATP hydrolysis would be the following:



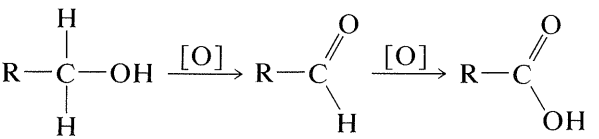


Work out possible mechanisms for each of these steps and decide whether this sequence is likely to be as feasible as the one described by Equations 15-5 and 15-6. Give your reasoning. How could you determine experimentally which mechanistic path was being followed?

15-6 OXIDATION OF ALCOHOLS

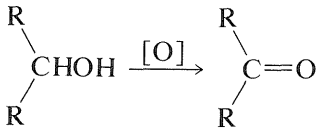
According to the scale of oxidation levels established for carbon (see Table 11-1), primary alcohols (RCH_2OH) are at a lower oxidation level than either aldehydes (RCHO) or carboxylic acids (RCO_2H). With suitable oxidizing agents, primary alcohols in fact can be oxidized first to aldehydes and then to carboxylic acids.

primary alcohols

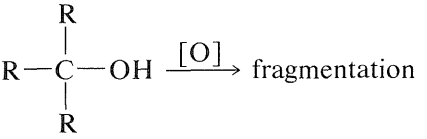


Unlike the reactions discussed previously in this chapter, oxidation of alcohols involves the *alkyl* portion of the molecule, or more specifically, the C–H bonds of the hydroxyl-bearing carbon (the α carbon). Secondary alcohols, which have only one such C–H bond, are oxidized to ketones, whereas tertiary alcohols, which have no C–H bonds to the hydroxylic carbon, are oxidized only with accompanying degradation into smaller fragments by cleavage of carbon–carbon bonds.

secondary alcohols



tertiary alcohols



15-6A Industrial Oxidation of Alcohols

Conversion of ethanol to ethanal is carried out on a commercial scale by passing gaseous ethanol over a copper catalyst at 300°:

$$CH_3CH_2OH \xrightarrow[300^\circ]{Cu} CH_3CH{=}O + H_2 \qquad \Delta H^0(25^\circ) = +15 \text{ kcal}$$

At room temperature this reaction is endothermic with an equilibrium constant of about 10^{-22}. At 300° conversions of 20%–50% per pass can be realized and, by recycling the unreacted alcohol, the yield can be greater than 90%.

Another commercial process uses a silver catalyst and oxygen to combine with the hydrogen, which makes the net reaction substantially exothermic:

$$CH_3CH_2OH + \tfrac{1}{2}O_2 \xrightarrow{Ag} CH_3CH{=}O + H_2O \qquad \Delta H^0 = -43 \text{ kcal}$$

In effect, this is a partial combustion reaction and requires very careful control to prevent overoxidation. In fact, by modifying the reaction conditions (alcohol-to-oxygen ratio, temperature, pressure, and reaction time), the oxidation proceeds smoothly to ethanoic acid:

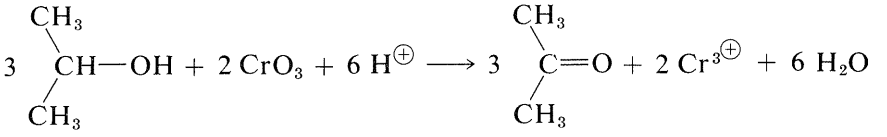
$$CH_3CH_2OH + O_2 \xrightarrow[550^\circ]{Ag} CH_3CO_2H + H_2O$$

Reactions of this type are particularly suitable as industrial processes because they generally can be run in continuous-flow reactors, and can utilize a cheap oxidizing agent, usually supplied directly as air.

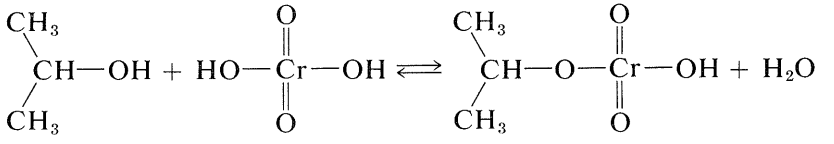
15-6B Laboratory Oxidation of Alcohols

Chromic Acid Oxidation

Laboratory oxidation of alcohols most often is carried out with chromic acid (H_2CrO_4), which usually is prepared as required from chromic oxide (CrO_3) or from sodium dichromate ($Na_2Cr_2O_7$) in combination with sulfuric acid. Ethanoic (acetic) acid is a useful solvent for such reactions:

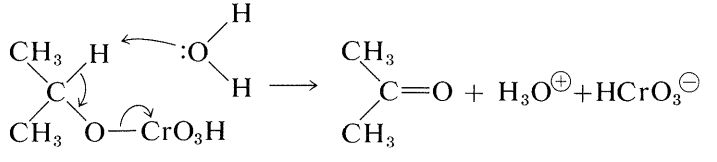


The mechanism of the chromic acid oxidation of 2-propanol to 2-propanone (acetone) has been investigated very thoroughly. It is a highly interesting reaction in that it reveals how changes of oxidation state can occur in a reaction involving a typical inorganic and a typical organic compound. The initial step is reversible formation of an isopropyl ester of chromic acid. This ester is unstable and is not isolated:



isopropyl hydrogen chromate

The subsequent step is the slowest in the sequence and appears to involve attack of a base (water) at the alpha hydrogen of the chromate ester concurrent with elimination of the $HCrO_3^{\ominus}$ group. There is an obvious analogy between this step and an E2 reaction (Section 8-8A):



The transformation of chromic acid (H_2CrO_4) to H_2CrO_3 amounts to the reduction of chromium from an oxidation state of +6 to +4. Disproportionation of Cr(IV) occurs rapidly to give compounds of Cr(III) and Cr(VI):

$$3Cr(IV) \longrightarrow Cr(VI) + 2Cr(III)$$

or

$$3H_2CrO_3 + 6H^{\oplus} \longrightarrow CrO_3 + 2Cr^{3\oplus} + 6H_2O$$

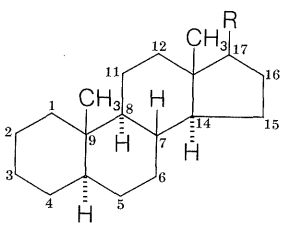
The E2 character of the ketone-forming step has been demonstrated in two ways. First, the rate of decomposition of isopropyl hydrogen chromate to 2-propanone and H_2CrO_3 is strongly accelerated by efficient proton-removing substances. Second, the hydrogen on the α carbon clearly is removed in a slow reaction because *the overall oxidation rate is diminished sevenfold by having a deuterium in place of the α hydrogen.* No significant slowing of oxidation is noted for 2-propanol having deuterium in the methyl groups:

	$(CH_3)_2CH-OH$	$(CH_3)_2CD-OH$	$(CD_3)_2CH-OH$
relative rate of oxidation with chromic acid:	1.0	0.16	1.0

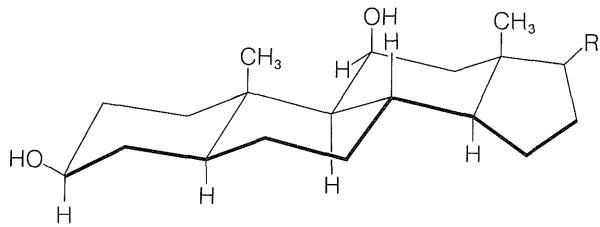
Carbon–deuterium bonds normally are broken more slowly than carbon–hydrogen bonds. This so-called **kinetic isotope effect** provides a general method for determining whether particular carbon–hydrogen bonds are broken in slow reaction steps.

Exercise 15-28 In the conversion of 2-propanol to 2-propanone with chromic acid, which is the redox step, esterification or elimination? What is the change in oxidation level of carbon in this reaction?

Exercise 15-29* The ring system, **11**, is found in many naturally occurring compounds known as **steroids.** Several important representatives of this class of compound have secondary hydroxyl groups at C3 and C11, with configurations represented by the sawhorse drawing, **12**:



11



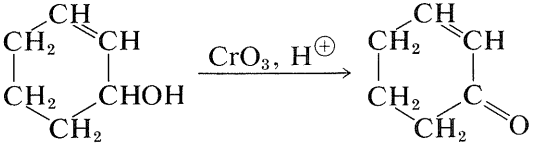
12

Explain in detail how steric hindrance would lead you to expect that the relative reactivity of these two hydroxyl groups in esterification is C3 > C11 and in chromic acid oxidation is C11 > C3.

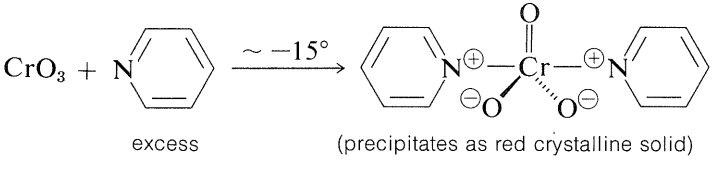
Primary alcohols are oxidized by chromic acid in sulfuric acid solution to aldehydes, but to stop the reaction at the aldehyde stage, it usually is necessary to remove the aldehyde from the reaction mixture as it forms. This can be done by distillation if the aldehyde is reasonably volatile:

$$\underset{\text{1-propanol}}{CH_3CH_2CH_2OH} \xrightarrow[H_2SO_4]{K_2Cr_2O_7} \underset{\substack{\text{propanal (49\%)}\\ \text{bp } 49^\circ}}{CH_3CH_2CHO}$$

Unsaturated alcohols can be oxidized to unsaturated ketones by chromic acid because chromic acid usually attacks double bonds relatively slowly:



However, complications are to be expected when the double bond of an unsaturated alcohol is particularly reactive or when the alcohol rearranges readily under strongly acidic conditions. It is possible to avoid the use of strong acid through the combination of chromic oxide with the weak base azabenzene (pyridine). A crystalline solid of composition $(C_5H_5N)_2 \cdot CrO_3$ is formed when CrO_3 is added to excess pyridine at low temperatures. (Addition of pyridine to CrO_3 is likely to give an uncontrollable reaction resulting in a fire.)



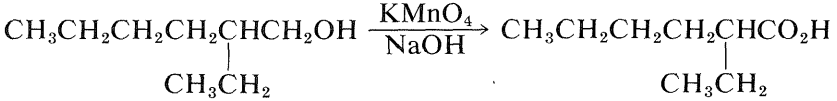
The pyridine–CrO_3 reagent is soluble in chlorinated solvents such as dichloromethane, and the resulting solutions rapidly oxidize $\diagup\!\!\diagdown CHOH$ to $\diagup\!\!\diagdown C{=}O$ at ordinary temperatures:

$$CH_3(CH_2)_5\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \xrightarrow[CH_2Cl_2,\ 25^\circ]{(C_5H_5N)_2 \cdot CrO_3} CH_3(CH_2)_5\underset{\displaystyle O}{\overset{\|}{C}}CH_3 \qquad 97\%$$

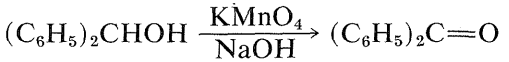
The yields usually are good, partly because the absence of strong acid minimizes degradation and rearrangement, and partly because the product can be isolated easily. The inorganic products are insoluble and can be separated by filtration, thereby leaving the oxidized product in dichloromethane from which it can be easily recovered.

Permanganate Oxidation

Permanganate ion, $MnO_4^{\ominus}$, oxidizes both primary and secondary alcohols in either basic or acidic solution. With primary alcohols the product normally is the carboxylic acid because the intermediate aldehyde is oxidized rapidly by permanganate:

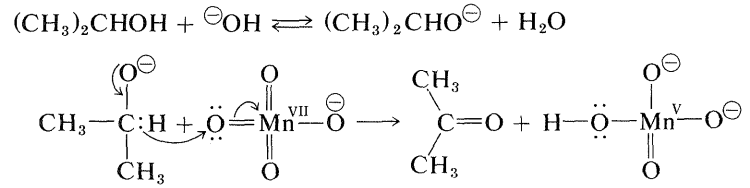


2-ethyl-1-hexanol — 2-ethylhexanoic acid (74%)



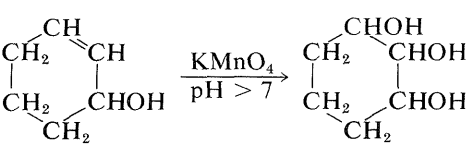
diphenylmethanol — diphenylmethanone (benzophenone, 65%)

Oxidation under *basic* conditions evidently involves the alkoxide ion rather than the neutral alcohol. The oxidizing agent, $MnO_4^{\ominus}$, abstracts the alpha hydrogen from the alkoxide ion either as an atom (one-electron transfer) or as hydride, $H:^{\ominus}$ (two-electron transfer). The steps for the two-electron sequence are:



In the second step, permanganate ion is reduced from Mn(VII) to Mn(V). However, the stable oxidation states of manganese are +2, +4, and +7; thus the Mn(V) ion formed disproportionates to Mn(VII) and Mn(IV). The normal manganese end product from oxidations in basic solution is manganese dioxide, MnO_2, in which Mn has an oxidation state of +4 corresponding to Mn(IV).

In Section 11-7C we described the use of permanganate for the oxidation of alkenes to 1,2-diols. How is it possible to control this reaction so that it will stop at the diol stage when permanganate also can oxidize $\diagdown\!\!\diagup CHOH$ to $\diagdown\!\!\diagup C{=}O$? Overoxidation with permanganate is always a problem, but the relative reaction rates are very much a function of the pH of the reaction mixture and, in basic solution, potassium permanganate oxidizes unsaturated groups more rapidly than it oxidizes alcohols:



Exercise 15-30 How many moles of permanganate would be required to oxidize (a) one mole of cyclohexanol to cyclohexanone and (b) one mole of phenylmethanol (benzyl alcohol) to benzenecarboxylic acid in basic solution? (Review Section 11-1 if you have difficulty.)

Exercise 15-31 Show the mechanistic steps you expect to be involved in the oxidation of benzenecarbaldehyde (benzaldehyde) to benzenecarboxylic (benzoic) acid in an alkaline solution of potassium permanganate.

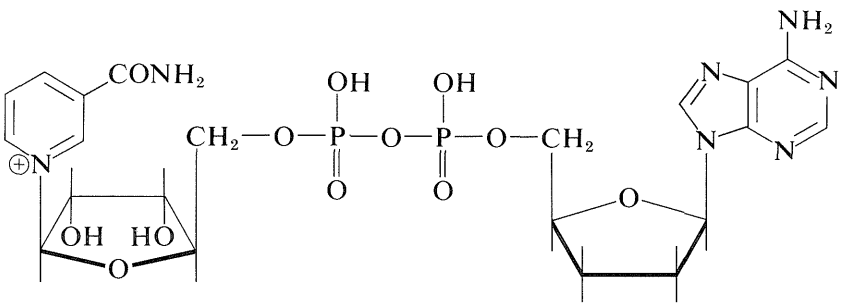
Exercise 15-32 Explain why oxidation of secondary alcohols with ^{18}O-labeled potassium permanganate produces an ^{18}O-containing ketone in *acidic* solution, but not in *basic* solution.

Exercise 15-33 The oxidation of $(CH_3)_2CDOH$ is one seventh as fast as the oxidation of $(CH_3)_2CHOH$ using potassium permanganate in acidic solution. What does this tell us about the mechanism of the reaction in acidic solution?

15-6C Biological Oxidations

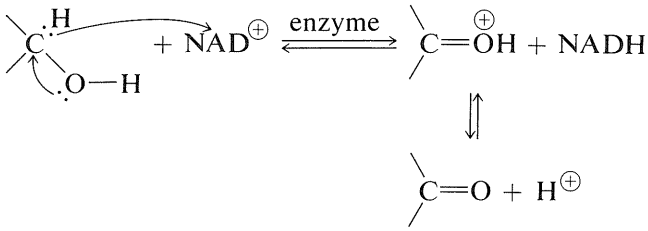
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all require enzymes as catalysts, which for these reactions usually are called *dehydrogenases*.

An important group of biological oxidizing agents includes the pyridine nucleotides, of which nicotinamide adenine dinucleotide ($NAD^{\oplus}$, **13**) is an example:

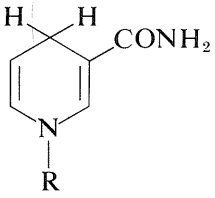


13

This very complex molecule functions to accept hydride ($H:^{\ominus}$) or the equivalent ($H^{\oplus} + 2e^{\ominus}$) from the α carbon of an alcohol:

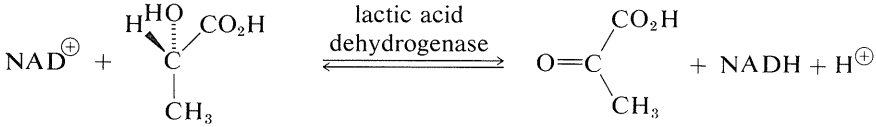


The reduced form of $NAD^{\oplus}$ is abbreviated as NADH and the $H:^{\ominus}$ is added at the 4-position of the pyridine ring:



NADH

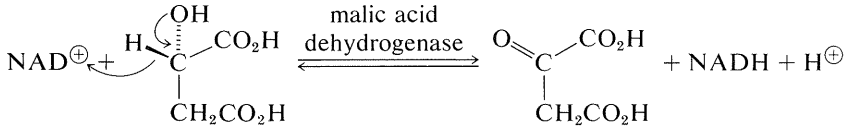
Some examples follow that illustrate the remarkable specificity of this kind of redox system. One of the last steps in the metabolic breakdown of glucose (glycolysis; Section 20-10A) is the reduction of 2-oxopropanoic (pyruvic) acid to L-2-hydroxypropanoic (lactic) acid. The reverse process is oxidation of L-lactic acid. The enzyme *lactic acid dehydrogenase* catalyses this reaction, and it functions only with the L-enantiomer of lactic acid:



L-2-hydroxypropanoic acid (L-lactic acid)

2-oxopropanoic acid (pyruvic acid)

A second example, provided by one of the steps in metabolism by way of the Krebs citric acid cycle (see Section 20-10B), is the oxidation of L-2-hydroxybutanedioic (L-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with L-malic acid:

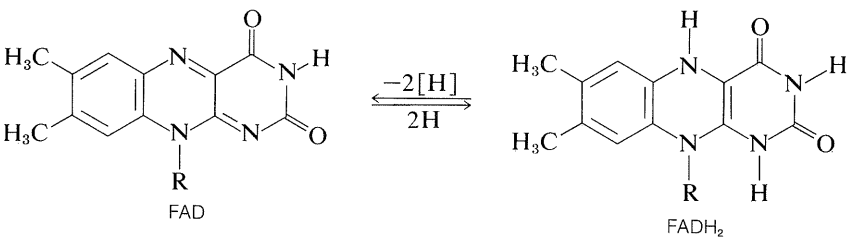


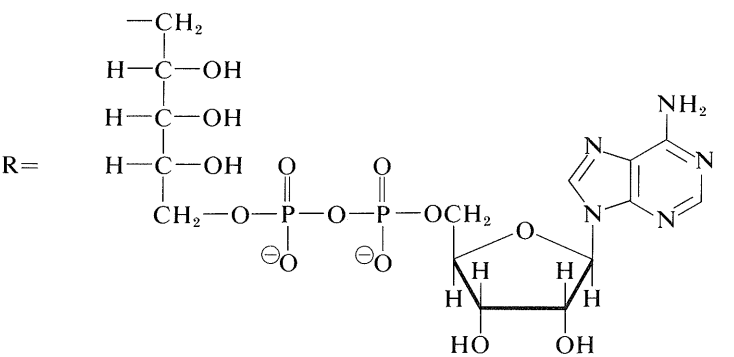
L-2-hydroxybutanedioic acid (L-malic acid)

2-oxobutanedioic acid (oxaloacetic acid)

All of these reactions release energy. In biological oxidations much of the energy is utilized to form ATP from ADP and inorganic phosphate (Section 15-5F). That is to say, electron-transfer reactions are coupled with ATP formation. The overall process is called **oxidative phosphorylation.**

Another important oxidizing agent in biological systems is flavin adenine dinucleotide, FAD. Like $NAD^{\oplus}$, it is a two-electron acceptor, but unlike $NAD^{\oplus}$, it accepts two electrons as 2H· rather than as $H:^{\ominus}$. The reduced form, $FADH_2$, has the hydrogens at ring nitrogens:





Exercise 15-34* For the transformations $NAD^{\oplus} + H^{\oplus} + 2e^{\ominus} \rightleftharpoons$ NADH and FAD + $2H^{\oplus} + 2e^{\ominus} \longrightarrow FADH_2$, determine which atoms undergo a change in oxidation level, and by how much, according to the rules set up in Section 11-1.

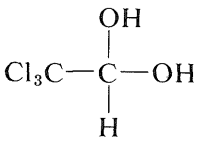
15-7 POLYHYDRIC ALCOHOLS

The simplest example of an alcohol with more than one hydroxyl group is methanediol or methylene glycol, $HOCH_2OH$. The term "glycol" indicates a *diol,* which is a substance with two alcoholic hydroxyl groups. Methylene

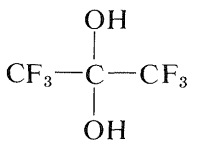
glycol is reasonably stable in water solution, but attempts to isolate it lead only to its dehydration product, methanal (formaldehyde):

$$HO{-}CH_2{-}OH \rightleftharpoons H_2C{=}O + H_2O$$

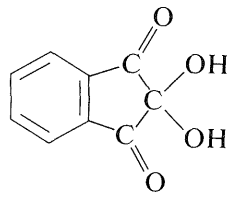
This behavior is rather typical of *gem*-diols (*gem* = geminal, that is, with both hydroxyl groups on the *same* carbon atom). The few *gem*-diols of this kind that can be isolated are those that carry strongly electron-attracting substituents such as the following:



2,2,2-trichloro-1,1-ethanediol (chloral hydrate)

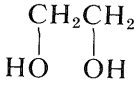


1,1,1,3,3,3-hexafluoro-2,2-propanediol (hexafluoroacetone hydrate)

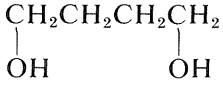


2,2-dihydroxy-4,5-benzocyclopentene-1,3-dione (ninhydrin)

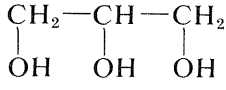
Polyhydric alcohols in which the hydroxyl groups are situated on different carbons are relatively stable, and, as we might expect for substances with multiple polar groups, they have high boiling points and considerable water solubility, but low solubility in nonpolar solvents:



1,2-ethanediol (ethylene glycol) bp 197°



1,4-butanediol (tetramethylene glycol) bp 230°



1,2,3-propanetriol (glycerol) bp 290°

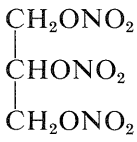
1,2-Diols are prepared from alkenes by oxidation with reagents such as osmium tetroxide, potassium permanganate, or hydrogen peroxide (Section 11-7C). However, ethylene glycol is made on a commercial scale from oxacyclopropane, which in turn is made by air oxidation of ethene at high temperatures over a silver oxide catalyst (Section 11-7D).

Exercise 15-35 How would you synthesize (a) *meso*-2,3-butanediol and (b) D,L-2,3-butanediol from *cis*-2-butene?

Ethylene glycol has important commercial uses. It is an excellent permanent antifreeze for automotive cooling systems because it is miscible with water in all proportions and a 50% solution freezes at −34° (−29°F). It also

is used as a solvent and as an intermediate in the production of polymers (polyesters) and other products (Chapter 29).

The trihydric alcohol, 1,2,3-propanetriol (glycerol), is a nontoxic, water-soluble, viscous, hygroscopic liquid that is used widely as a humectant (moistening agent). It is an important component of many food, cosmetic, and pharmaceutical preparations. At one time, glycerol was obtained on a commercial scale only as a by-product of soap manufacture through hydrolysis of fats, which are glyceryl esters of long-chain alkanoic acids (page 790). The major present source is by synthesis from propene (Section 14-3A). The trinitrate ester of glycerol (nitroglycerin) is an important but shock-sensitive explosive:



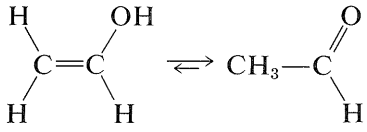
1,2,3-propanetriol trinitrate
(nitroglycerin)

Dynamite is a much safer and more controllable explosive, and is made by absorbing nitroglycerin in porous material such as sawdust or diatomaceous earth. Dynamite has largely been replaced by cheaper explosives containing ammonium nitrate as the principal ingredient.

Glycerol, as a constituent of fats and lipids, plays an important role in animal metabolism.

15-8 UNSATURATED ALCOHOLS—ALKENOLS

The simplest unsaturated alcohol, ethenol (vinyl alcohol), is unstable with respect to ethanal and has never been isolated (see Sections 10-5A and 13-5B):

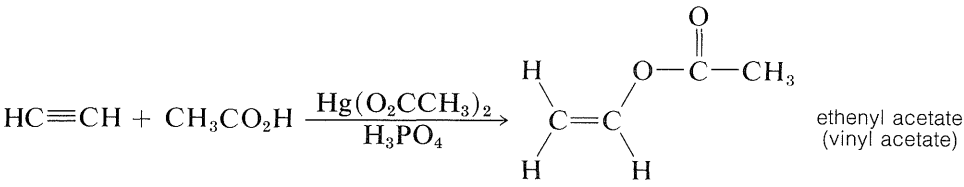


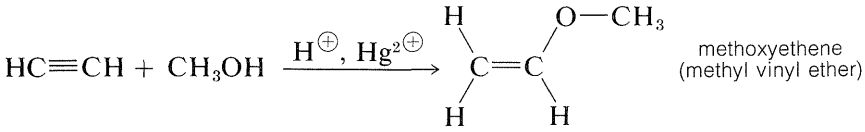
ethenol
(vinyl alcohol)

ethanal
(acetaldehyde)

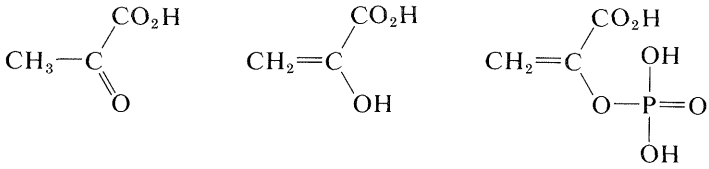
Other simple alkenols (enols) also rearrange to carbonyl compounds. However, ether and ester derivatives of enols are known and can be prepared by

the addition of alcohols and carboxylic acids to alkynes. The esters are used to make many commercially important polymers (Chapter 29):





The enol of 2-oxopropanoic acid (pyruvic acid) is of special biological interest because the phosphate ester of this compound is, like ATP (Section 15-5F), a reservoir of chemical energy that can be utilized by coupling its hydrolysis ($\Delta G^0 = -13$ kcal) to thermodynamically less favorable reactions:

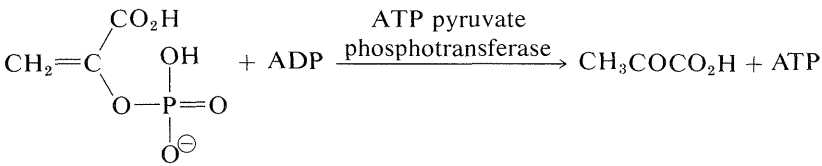


pyruvic acid

enol of pyruvic acid

1-carboxy-1-ethenylphosphoric acid ("phosphoenolpyruvic acid")

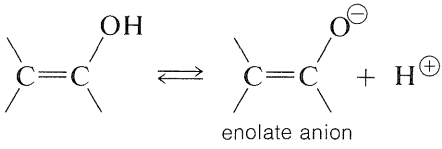
In fact, the ester can be utilized to synthesize ATP from ADP; that is, it is a phosphorylating agent, and a more powerful one than ATP:



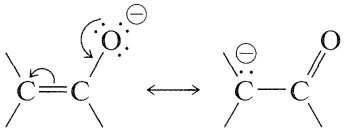
15-8A Acidity of Enols

Enols usually are unstable and are considerably more acidic than saturated alcohols. This means that the conjugate bases of the enols (the *enolate anions*) are more stable relative to the enols themselves than are alkoxide ions relative

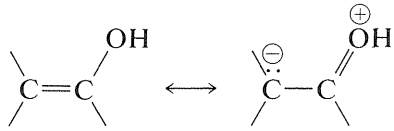
to alcohols. (Enolate anions are important reagents in the chemistry of carbonyl compounds and will be discussed in detail in Chapter 17.)



The important factor here is delocalization of the negative charge on oxygen of enolate anions, as represented by the valence-bond structures **14a** and **14b**:

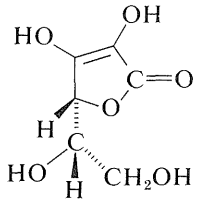


Because acidity depends on the *difference* in energy of the acid and its conjugate base, we must be sure that the stabilization of the enolate anion by electron delocalization represented by **14a** and **14b** is greater than the analogous stabilization of the neutral enol represented by **15a** and **15b**:



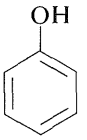
The rules for evaluating valence-bond structures (Section 6-5B) tell us that the stabilization will be greatest when there are two or more nearly equivalent low-energy electron-pairing schemes. Inspection of **14a** and **14b** suggests that they will be more nearly equivalent than **15a** and **15b** because, although **14b** and **15b** have a negative charge on the carbon, in **15b** the oxygen has a positive charge. Another way of putting it is that **15b** represents an electron-pairing scheme with a **charge separation,** which intuitively is of higher energy than **15a** with no charge separation. Structures corresponding to **14b** and **15b** are not possible for saturated alkanols or their anions, hence we can see that enols should be more acidic than alcohols.

Ascorbic acid (Vitamin C) is an example of a stable and quite acidic enol, or rather an enediol. It is a di-acid with pK_a values of 4.17 and 11.57:

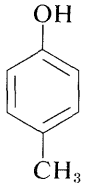


L-ascorbic acid (Vitamin C)

Other important examples of stable enol-type compounds are the aromatic alcohols, or *phenols*. The K_a's of these compounds are about 10^{-10}, some 10^8 times larger than the K_a's for alcohols.



benzenol
(phenol)



4-methylbenzenol

The chemistry of these compounds, including their stability as enols, is discussed in Chapter 26.

Exercise 15-36* Write equations for the dissociation of ascorbic acid to give progressively a monoanion and a dianion. Assign a pK_a to each dissociation and make your structures clear as to which are the acidic protons. Why is ascorbic acid a stronger diacid than cyclopentane-1,2-diol?

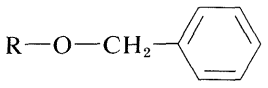
15-9 PROTECTION OF HYDROXYL GROUPS

By now it should be apparent that hydroxyl groups are very reactive to many reagents. This is both an advantage and a disadvantage in synthesis. To avoid interference by hydroxyl groups, it often is necessary to protect (or mask) them by conversion to less reactive functions. The general principles of how functional groups are protected were outlined and illustrated in Section 13-9. In the case of alcohols the hydroxyl group may be protected by formation of an ether, an ester, or an acetal.

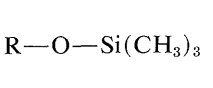
15-9A Ether Formation

A good protecting group is one that does everything you want it to do *when* you want it to. It must be easily put into place, stable to the reagents from which protection is required, *and* easily removed when desired. For this reason simple ethers such as methyl or ethyl ethers usually are not suitable protecting groups because they cannot be removed except under rather drastic conditions (Section 15-10).

More suitable ethers are phenylmethyl and trimethylsilyl ethers:

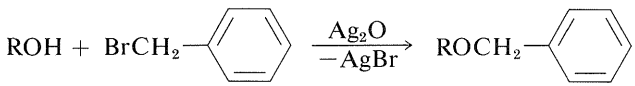


alkyl phenylmethyl ether

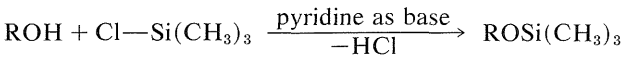


alkyl trimethylsilyl ether

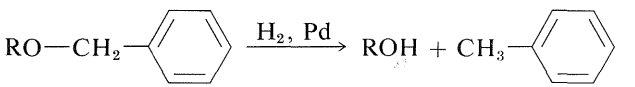
Both of these ethers are prepared easily by nucleophilic displacements (Equations 15-7 and 15-8) and can be converted back to the parent alcohol under mild conditions, by catalytic hydrogenation for phenylmethyl ethers (Equation 15-9), or by mild acid hydrolysis for trimethylsilyl ethers (Equation 15-10):



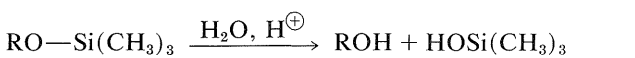
$$\text{ROH} + \text{BrCH}_2\text{C}_6\text{H}_5 \xrightarrow[-\text{AgBr}]{\text{Ag}_2\text{O}} \text{ROCH}_2\text{C}_6\text{H}_5 \qquad (15\text{-}7)$$



$$\text{ROH} + \text{Cl—Si(CH}_3)_3 \xrightarrow[-\text{HCl}]{\text{pyridine as base}} \text{ROSi(CH}_3)_3 \qquad (15\text{-}8)$$



$$\text{RO—CH}_2\text{C}_6\text{H}_5 \xrightarrow{\text{H}_2,\ \text{Pd}} \text{ROH} + \text{CH}_3\text{C}_6\text{H}_5 \qquad (15\text{-}9)$$

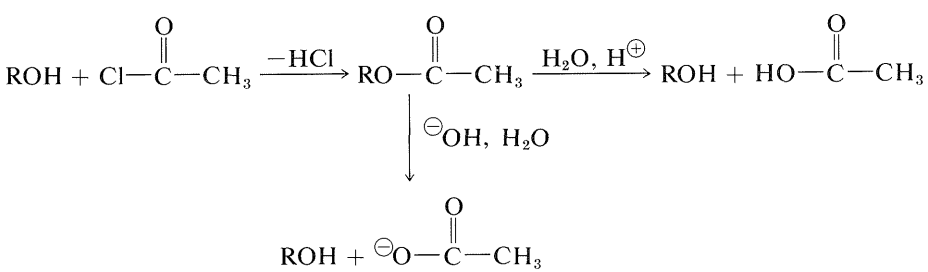


$$\text{RO—Si(CH}_3)_3 \xrightarrow{\text{H}_2\text{O},\ \text{H}^{\oplus}} \text{ROH} + \text{HOSi(CH}_3)_3 \qquad (15\text{-}10)$$

Exercise 15-37 The O–C bond of phenylmethyl ethers is reduced more readily by hydrogen over a metal catalyst than the O–C bond of methyl or ethyl ethers. How do you account for this?

15-9B Ester Formation

Esters are formed from the alcohol and acyl halide, anhydride, or acid (Section 15-4D). The alcohol can be regenerated easily by either acid or base hydrolysis of the ester:



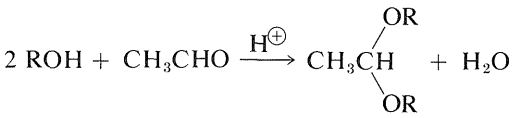
$$\text{ROH} + \text{Cl—C(=O)—CH}_3 \xrightarrow{-\text{HCl}} \text{RO—C(=O)—CH}_3 \xrightarrow{\text{H}_2\text{O},\ \text{H}^{\oplus}} \text{ROH} + \text{HO—C(=O)—CH}_3$$

$$\text{RO—C(=O)—CH}_3 \xrightarrow{{}^{\ominus}\text{OH},\ \text{H}_2\text{O}} \text{ROH} + {}^{\ominus}\text{O—C(=O)—CH}_3$$

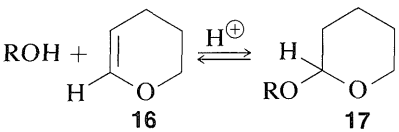
15-9C Acetal Formation

We have seen that alcohols can be converted *reversibly* to acetals under acidic conditions (Section 15-4E). The acetal function is a very suitable protecting

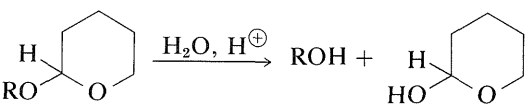
group for alcohols under basic conditions, but is not useful under acidic conditions because acetals are not stable to acids:



An excellent reagent to form acetals is the unsaturated cyclic ether, **16**. This ether adds alcohols in the presence of an acid catalyst to give the acetal **17**:

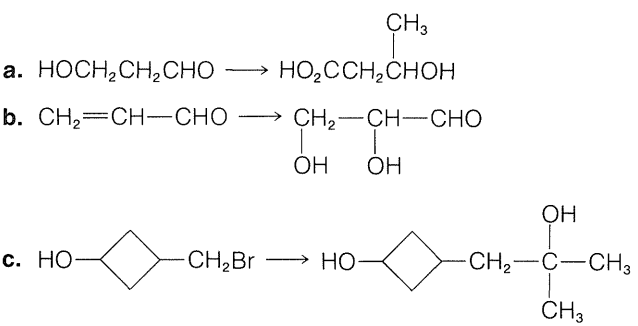


The 3-oxacyclohexene (dihydropyran) protecting group can be removed readily by treating the acetal, **17**, with aqueous acid:



An example of the use of **16** to protect an OH function is given in Section 13-10.

Exercise 15-38 Devise suitable reactions for the following conversions. (Indicate the specific protecting groups for the OH function appropriate for the reactions that you use.)



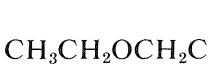
Exercise 15-39 Write the mechanistic steps involved in the acid-catalyzed addition of alcohols to the cyclic ether **16**. Why does cyclohexene react far less readily than **16** with alcohols under acidic conditions? Write equations for the steps involved in the hydrolysis of **17** with aqueous acid.

Would you anticipate ethoxyethene to be a comparably useful reagent for the protection of hydroxyl groups? Explain.

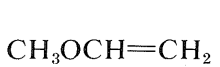
Ethers

15-10 TYPES AND REACTIONS OF SIMPLE ETHERS

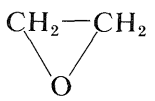
Substitution of the hydroxyl hydrogens of alcohols by hydrocarbon groups gives compounds known as ethers. These compounds may be classified further as open-chain, cyclic, saturated, unsaturated, aromatic, and so on. For the naming of ethers, see Sections 7-3 and 15-11A.



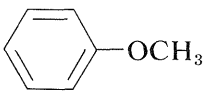
ethoxyethane
(diethyl ether)
bp 35°



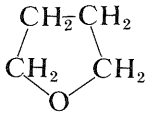
methoxyethene
(methyl ethenyl ether)
bp ~ 12°



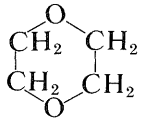
oxacyclopropane
(oxirane, ethylene oxide)
bp 11°



methoxybenzene
(methyl phenyl ether, anisole)
bp 155°



oxacyclopentane
(tetrahydrofuran, oxolane)
bp 65°



1,4-dioxacyclohexane
(1,4-dioxane)
bp 101.5°

The most generally useful methods of preparing ethers already have been discussed (Sections 8-7C, 8-7E, 15-4C, and 15-5C). These and some additional special procedures are summarized in Table 15-4.

In general, ethers are low on the scale of chemical reactivity because the carbon–oxygen bond is not cleaved readily. For this reason ethers frequently are employed as inert solvents in organic synthesis. Particularly important in this connection are diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane. The mono- and dialkyl ethers of 1,2-ethanediol, 3-oxa-1,5-pentanediol, and related substances are useful high-boiling solvents. Unfortunately, their trade names are not very rational. Abbreviated names are in

Table 15-4
General Methods of Preparation of Ethers

Reaction	Comment
1. *Reaction of alkoxides and alkyl compounds (Williamson synthesis)* $R'O^{\ominus} + RX \longrightarrow ROR' + X^{\ominus}$ $CH_3CH_2CH_2CH_2O^{\ominus} + CH_3I \longrightarrow CH_3CH_2CH_2CH_2OCH_3 + I^{\ominus}$ 1-methoxybutane, methyl butyl ether (70%)	S_N2 reaction and suitable only for primary RX (Sections 8-7A and 8-7C); *tert*-alkoxides are too bulky. Alkyl halides, alkyloxonium salts, sulfates, and sulfonates can be employed as RX component.
2. *Dehydration of alcohols* $ROH + H^{\oplus} \rightleftharpoons \overset{\oplus}{R}OH_2 \xrightarrow{ROH} ROR + H_3O^{\oplus}$ $(CH_3)_3COH + CH_3CH_2OH \xrightarrow{15\%\ H_2SO_4} (CH_3)_3COCH_2CH_3$ 2-ethoxy-2-methylpropane, ethyl *tert*-butyl ether (95%)	S_N1 or S_N2 reaction, depending on structure (Section 15-5C); excellent procedure for preparation of mixed ethers, ROR', where one R group is tertiary and the other primary (Section 15-5D).
$CH_2{=}CH{-}CH_2OH + C_2H_5OH \xrightarrow{H_2PtCl_4} CH_2{=}CH{-}CH_2{-}OC_2H_5 + H_2O$ 3-ethoxy-1-propene, 2-propenyl ethyl ether	Chloroplatinic acid is a specific catalyst for ether formation from allylic alcohols. Rearrangements may be observed (Section 14-3B).
3. *Methylation of alcohols with diazomethane* $ROH + CH_2N_2 \xrightarrow{H^{\oplus}} ROCH_3 + N_2$ $CH_3(CH_2)_6CH_2OH + CH_2N_2 \xrightarrow{HBF_4} CH_3(CH_2)_6CH_2OCH_3 + N_2$ 1-methoxyoctane, methyl octyl ether (87%)	Best with unhindered *prim.* and *sec.* alcohols. An acid catalyst is necessary (HBF_4 or BF_3), but acids with nucleophilic anions are unsatisfactory. Reaction probably involves intermediate formation of methyldiazonium ion, $CH_3N_2^{\oplus}$.
4. *Addition of alcohols to alkenes* $ROH + \diagdown C{=}C \diagup \xrightarrow{H^{\oplus}} RO{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}H$	See Method 1, Table 15-2.

common use, such as "polyglymes," "Cellosolves," and "Carbitols." For reference, **Cellosolves** are monoalkyl ethers of 1,2-ethanediol; **Carbitols** are monoalkyl ethers of 3-oxa-1,5-pentanediol; **polyglymes** are dimethyl ethers of 3-oxa-1,5-pentanediol or 3,6-dioxa-1,8-octanediol and are called **diglyme** and **triglyme,** respectively.

$CH_3OCH_2CH_2OH$
2-methoxyethanol
(Methyl Cellosolve)
bp 124°

$C_4H_9OCH_2CH_2OCH_2CH_2OH$
2-(2-butoxyethoxy)ethanol
(Butyl Carbitol)
bp 231°

$CH_3OCH_2CH_2OCH_2CH_2OCH_3$
bis-(2-methoxyethyl) ether, 2,5,8-trioxanonane
(diglyme) bp 161°

The spectroscopic properties of ethers are unexceptional. Like alcohols, they have no electronic absorption beyond 185 nm; the important infrared bands are the C—O stretching vibrations in the region 1000–1230 cm^{-1}; their proton nmr spectra show deshielding of the *alpha* hydrogens by the ether oxygen ($\delta_{HC_\alpha OC} \sim 3.4$ ppm). The mass spectra of ethers and alcohols are very similar and give abundant ions of the type $R-\overset{\oplus}{O}=C\diagup\diagdown$ (R = H or alkyl) by α-cleavage (see Section 15-2).

Unlike alcohols, ethers are not acidic and usually do not react with bases. However, exceptionally strong basic reagents, particularly certain alkali-metal alkyls, will react destructively with many ethers:

$$CH_3^{\ominus}Na^{\oplus} + H{:}CH_2{-}CH_2{-}O{-}CH_2CH_3 \longrightarrow CH_4 + CH_2{=}CH_2 + CH_3CH_2O^{\ominus}Na^{\oplus}$$

Ethers, like alcohols, are weakly basic and are converted to highly reactive salts by strong acids (e.g., H_2SO_4, $HClO_4$, and HBr) and to relatively stable coordination complexes with Lewis acids (e.g., BF_3 and RMgX):

$$C_2H_5\ddot{O}C_2H_5 + HBr \rightleftharpoons C_2H_5\overset{H^{\oplus}}{\ddot{O}}C_2H_5 + Br^{\ominus}$$

diethyloxonium bromide

$$C_2H_5\ddot{O}C_2H_5 + BF_3 \longrightarrow C_2H_5\overset{\oplus}{\underset{\ddot{}}{O}}(C_2H_5)\,B(F)_3^{\ominus}$$

boron trifluoride etherate, bp 126°

Dimethyl ether is converted to trimethyloxonium fluoroborate by the combination of boron trifluoride and methyl fluoride:

$$CH_3OCH_3 + CH_3F + BF_3 \longrightarrow CH_3-\overset{\oplus}{O}(CH_3)-CH_3\ BF_4^{\ominus}$$

trimethyloxonium fluoroborate, mp 141–143°

Both trimethyl- and triethyloxonium salts are fairly stable and can be isolated as crystalline solids. They are prepared more conveniently from the appropriate boron trifluoride etherate and chloromethyloxacyclopropane (epichlorohydrin, see Exercise 15-56).

Trialkyloxonium ions are much more susceptible to nucleophilic displacement reactions than are neutral ether molecules. The reason is that $RO^{\ominus}$ is a better leaving group than $RO^{\ominus}$. In fact, trimethyloxonium salts are among the most effective methylating reagents known:

$$CH_3-\overset{\oplus}{O}(CH_3)-CH_3 + R\ddot{O}H \xrightarrow{-H^{\oplus}} CH_3-\ddot{O}-CH_3 + R\ddot{O}CH_3$$

Ethers can be cleaved under strongly acidic conditions by intermediate formation of dialkyloxonium salts. Hydrobromic and hydroiodic acids are especially useful for ether cleavage because both are strong acids and their anions are good nucleophiles. Tertiary alkyl ethers are very easily cleaved by acid reagents:

$$C_2H_5-O-C_2H_5 + H^{\oplus} \rightleftharpoons C_2H_5-\overset{\oplus}{O}(H)-C_2H_5 \xrightarrow[S_N2]{Br^{\ominus}} C_2H_5Br + C_2H_5OH$$

$$(CH_3)_3C-O-C(CH_3)_3 + H^{\oplus} \rightleftharpoons (CH_3)_3C-\overset{\oplus}{O}(H)-C(CH_3)_3$$

$$\xrightarrow{E1} (CH_3)_2C{=}CH_2 + (CH_3)_3COH + H^{\oplus}$$

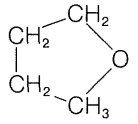
Exercise 15-40 Predict the products likely to be formed on cleavage of the following ethers with hydroiodic acid:

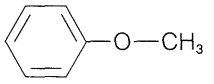
a. $CH_2{=}CH-CH_2-O-CH_3$

b. $CH_3CH_2-O-CH{=}CH_2$

c. $(CH_3)_3CCH_2-O-CH_3$

d. $(CH_3)_3COCH_3$

e. 

f. 

Exercise 15-41 **a.** Explain why trimethyloxonium salts will convert alcohols to methyl ethers at neutral or acidic pH, whereas either methyl iodide or dimethyl sulfate requires strongly basic reaction conditions.

b. What products would you expect from the reactions of trimethyloxonium fluoroborate with (1) ethanethiol, C_2H_5SH, (2) diethylamine, $(C_2H_5)_2NH$, and (3) hydrogen bromide.

Exercise 15-42 The amino acid methionine is a methyl donor in biological methylation of hydroxyl groups. However, direct methylation has an unfavorable free energy change:

$$\underset{\text{methionine}}{HO_2CCHCH_2CH_2SCH_3}\,|\,NH_2 + ROH \longrightarrow \underset{\text{homocysteine}}{HO_2CCHCH_2CH_2SH}\,|\,NH_2 + ROCH_3 \qquad \Delta G^0 \sim +8 \text{ kcal}$$

When coupled with hydrolysis of ATP (Section 15-5F) methylation becomes favorable as the result of the overall process:

$$\text{methionine} + ROH + ATP + H_2O \xrightarrow{\text{enzymes}} \text{homocysteine} + ROCH_3 + \text{adenosine} + (\text{triphosphate} \longrightarrow \text{phosphate} + \text{diphosphate})$$

Suggest a sequence of reasonable steps for this process on the basis that sulfides, RSR, are both excellent nucleophiles and good leaving groups. It is implicit that all steps will be enzyme-catalyzed, although the way the enzymes function is unknown. Each step must be energetically reasonable because enzymes, like other catalysts, cannot induce thermodynamically unfavorable reactions.

Ethers are susceptible to attack by halogen atoms and radicals, and for this reason they are not good solvents for radical reactions. In fact, ethers are potentially hazardous chemicals, because in the presence of atmospheric oxygen radical-chain formation of peroxides occurs, and peroxides are unstable, explosion-prone compounds. This process is called **autoxidation** and occurs not only with ethers but with many aldehydes and hydrocarbons. The reaction may be generalized in terms of the following steps involving initiation (1), propagation (2 and 3), and termination (4).

(1) $RH \longrightarrow R\cdot$ ($H\cdot$ is removed by the initiating agent)
(2) $R\cdot + O_2 \longrightarrow ROO\cdot$ } propagation
(3) $ROO\cdot + RH \longrightarrow ROOH + R\cdot$ }
(4) $R\cdot + R\cdot \longrightarrow RR$ (or disproportionation, Section 10-8C)

The initiation and termination steps can occur in a variety of ways but it is the chain-carrying steps, 2 and 3, that effect the overall destruction of the compound. Commonly used ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane often become seriously contaminated with peroxides formed by autoxidation on prolonged storage and exposure to air and light. Purification of ethers frequently is necessary before use, and caution always should be exercised in the last stages of distilling them, because the distillation residues may contain dangerously high concentrations of explosive peroxides.

15-11 CYCLIC ETHERS

15-11A Nomenclature

Ring compounds containing nitrogen, oxygen, sulfur, or other elements as ring atoms generally are known as *heterocyclic* compounds, and the ring atoms other than carbon are the *hetero* atoms. Over the years, the more common heterocyclic compounds have acquired a hodge-podge of trivial names, such as ethylene oxide, tetrahydrofuran, and dioxane. Systematic naming of ring compounds is necessary but, unfortunately, several competing systems have been developed. We prefer the simplest procedure, which is to name the simple heterocycles as *oxa, aza,* and *thia*-derivatives of cycloalkanes. However, this procedure has not been accepted (or adopted) universally and we are obliged to deal with the usages in existing literature. Having lived through at least two cycles of drastic changes in these matters, the authors hope that the simple procedure will prevail in the long run, but the long run is still ahead.

> We summarize here the rules of the so-called Hantzsch–Widman nomenclature system for heterocycles, which currently is the fashionable procedure, although relegated to second-class status by a recent, very practical approach to organic nomenclature.[1]
>
> 1. Ring size is denoted by the stem, *ir, et, ol, in, ep, oc, on,* or *ec* for 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered rings, respectively.
>
> 2. The kind of hetero atom present is indicated by the prefix, *oxa, thia,* or *aza* for oxygen, sulfur, or nitrogen, respectively; the prefixes *dioxa, dithia,* or *diaza* denote two oxygen, sulfur, or nitrogen atoms. When two or more different hetero atoms are present, they are cited in order of preference: oxygen before sulfur before nitrogen, as in the prefixes *oxaza* for one oxygen and one nitrogen, and *thiaza* for one sulfur and one nitrogen.
>
> 3. The degree of unsaturation is specified in the suffix. A list of appropriate suffixes and their stems according to ring sizes is given in Table 15-5. Notice that the suffix changes slightly according to whether the ring contains nitrogen.

[1]J. H. Fletcher, O. C. Dermer, and R. B. Fox (Editors), "Nomenclature of Organic Compounds, Principles and Practice," *Advances in Chemistry Series, No. 126,* American Chemical Society, Washington, D.C., 1974.

Table 15-5
Stems, Suffix, and Ring Size of Heterocyclic Compounds

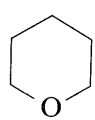
		Stem + suffix			
		Ring contains nitrogen		Ring contains no nitrogen	
Ring size	Stem	Unsaturated[a]	Saturated	Unsaturated[a]	Saturated
3	-ir-	-irine	-iridine	-irene	-irane
4	-et-	-ete	-etidine	-ete	-etane
5	-ol-	-ole	-olidine	-ole	-olane
6	-in-	-ine	*b*	-in	-ane
7	-ep-	-epine	*b*	-epin	-epane
8	-oc-	-ocine	*b*	-ocin	-ocane
9	-on-	-onine	*b*	-onin	-onane
10	-ec-	-ecine	*b*	-ecin	-ecane

[a]Corresponding to maximum number of double bonds, excluding cumulative double bonds.
[b]The prefix "perhydro" is attached to the stem and suffix of the parent unsaturated compound.

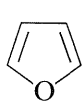
4. *Numbering of the ring starts with the hetero atom* and proceeds around the ring so as to give substituents (or other hetero atoms) the lowest numbered positions. When two or more *different* hetero atoms are present, oxygen takes precedence over sulfur and sulfur over nitrogen for the number one position. Examples follow to illustrate both the heterocycloalkane and the Hantzsch–Widman systems. Trivial names also are included.

oxacyclopropane
oxirane
(ethylene oxide)

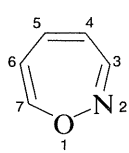
oxacyclopentane
oxolane
(tetrahydrofuran)



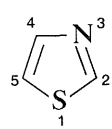
oxacyclohexane
oxane
(tetrahydropyran)



1-oxa-2,4-cyclopentadiene
oxole (furan)

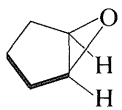


1,2-oxazacycloheptatriene
1,2-oxazepine

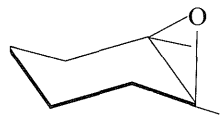


1,3-thiazacyclopentadiene
1,3-thiazole

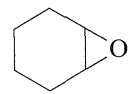
Although Hantzsch–Widman system works satisfactorily (if you can remember the rules) for monocyclic compounds, it is cumbersome for polycyclic compounds. In the case of oxiranes it is simplest for *conversational* purposes to name them as oxides of the cycloalkenes or *epoxy* derivatives of the corresponding cycloalkanes. The oxabicycloalkane names seem preferable for indexing purposes, particularly because the word "oxide" is used in many other connections.



cyclopentene oxide,
1,2-epoxycyclopentane,
6-oxa[3.1.0]bicyclohexane



or



cyclohexene oxide, 1,2-epoxycyclohexane,
7-oxa[4.1.0]bicycloheptane

Exercise 15-43 Draw structures for the following compounds and name each as an oxa-, aza-, or thiacycloalkane (cycloalkene, cycloalkadiene, and so on, as appropriate).

a. aziridine
b. thiirane
c. oxetan-2-one
d. 1,3-diazole
e. 1,3,5-trioxane
f. 3-phenyloxolane
g. perhydroazepine

15-11B Reactivity of Cyclic Ethers—Oxacyclopropanes (Oxiranes)

Oxacyclopropane (oxirane), the simplest cyclic ether, is an outstanding exception to the generalization that most ethers are resistant to cleavage. Like cyclopropane, the three-membered ring is highly strained and readily opens under mild conditions. Indeed, the importance of oxacyclopropane as an industrial chemical lies in its readiness to form other important compounds. The major products derived from it are shown in Figure 15-5.

The lesser known four-membered cyclic ether, oxacyclobutane (oxetane), $(CH_2)_3O$, also is cleaved readily, but less so than oxacyclopropane. Oxacyclopentane (oxolane, tetrahydrofuran) is a relatively unreactive water-miscible compound with desirable properties as an organic solvent. It often is used in place of diethyl ether in Grignard reactions and reductions with lithium aluminum hydride.

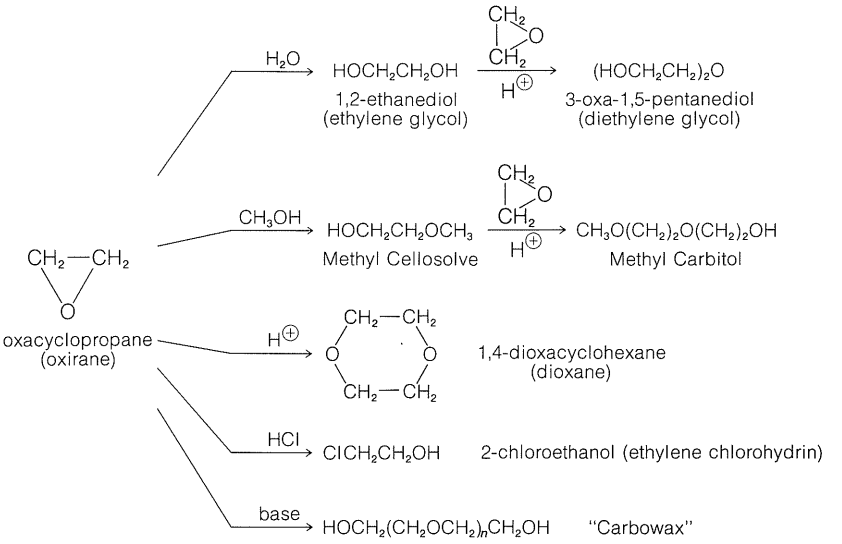
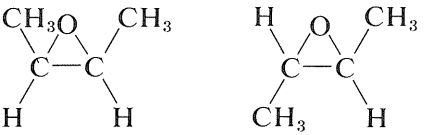


Figure 15-5 Important commercial reactions of oxacyclopropane (oxirane, ethylene oxide)

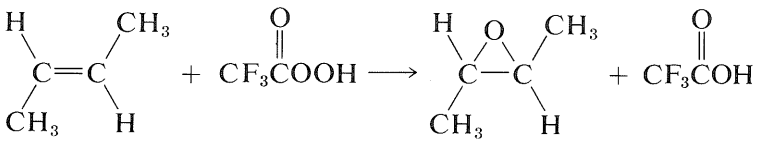
15-11C Preparation of Oxacyclopropanes

Three-membered cyclic ethers are important as reactive intermediates in organic synthesis. Like the cyclopropanes, the vicinal[2] disubstituted compounds have cis and trans isomers:



cis- and *trans*-2,3-dimethyloxacyclopropane
(*cis*- and *trans*-2,3-dimethyloxirane, *cis*- and *trans*-2-butene oxide)

The most important method of preparation involves oxidation, or "epoxidation," of an alkene with a peroxycarboxylic acid, RCO_3H. This reaction achieves suprafacial addition of oxygen across the double bond, and is a type of electrophilic addition to alkenes (see Exercise 15-53):

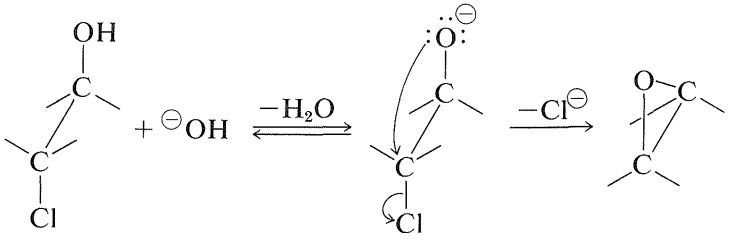


trans-2-butene

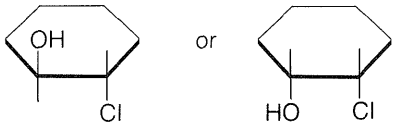
trans-2,3-dimethyl oxacyclopropane

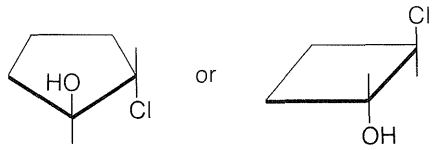
[2] *Vicinal* means substituted on adjacent carbons.

Oxacyclopropanes also can be prepared from vicinal chloro- or bromoalcohols and a base. This is an *internal* S_N2 reaction and, if the stereochemistry is correct, proceeds quite rapidly, even if a strained ring is formed:



Exercise 15-44 Which member of the following pairs of compounds would you expect to react faster with hydroxide ion?

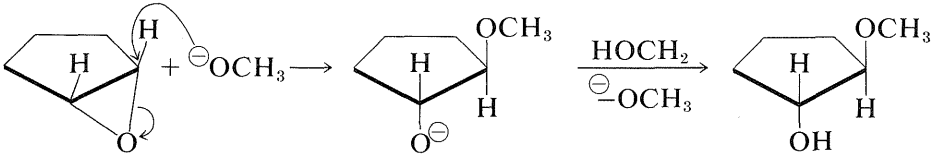
a. 

b. 

c. $HOCH_2CH_2Cl$ or $HOCH_2\underset{\displaystyle Cl}{\underset{|}{C}}H-CH=CH_2$

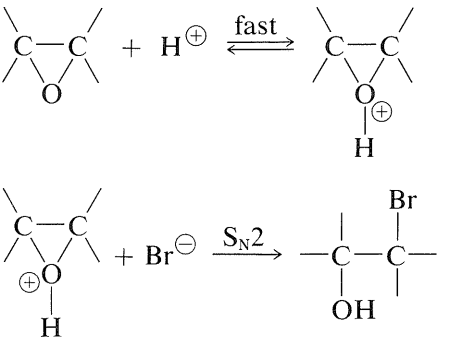
15-11D Ring-Opening Reactions of Oxacyclopropanes

Unlike most ethers, oxacyclopropanes react readily with nucleophilic reagents. These reactions are no different from the nucleophilic displacements previously encountered in Chapter 8, except that the leaving group, which is the oxygen of the oxide ring, remains a part of the original molecule. The stereochemistry is consistent with an S_N2 mechanism because inversion of configuration at the site of attack occurs. Thus cyclopentene oxide yields products with the trans configuration:

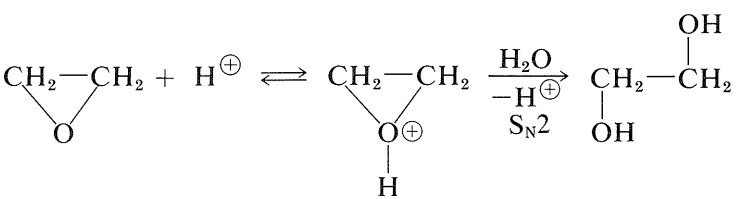


cyclopentene oxide

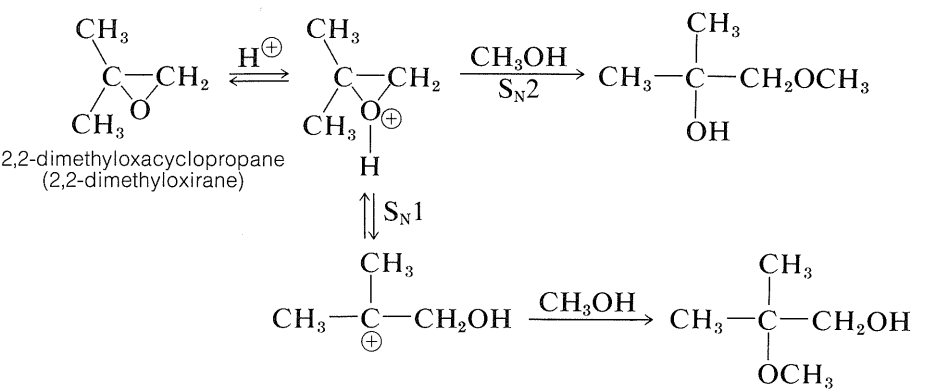
Acidic conditions also can be used for the cleavage of oxacyclopropane rings. An oxonium ion is formed first, which subsequently is attacked by the nucleophile in an S_N2 displacement or forms a carbocation in an S_N1 reaction. Evidence for the S_N2 mechanism, which produces inversion, comes not only from the stereochemistry but also from the fact that the rate is dependent on the concentration of the nucleophile. An example is ring opening with hydrogen bromide:



The same kind of mechanism can operate in the formation of 1,2-diols by acid-catalyzed ring-opening with water as the nucleophile:



Some acid-catalyzed solvolysis reactions of oxacyclopropanes appear to proceed by S_N1 mechanisms involving carbocation intermediates. Evidence for the S_N1 mechanism is available from the reactions of unsymmetrically substituted oxacyclopropanes. For example, we would expect the conjugate acid of 2,2-dimethyloxacyclopropane to be attacked by methanol at the primary carbon by an S_N2 reaction and at the tertiary carbon by an S_N1 reaction:

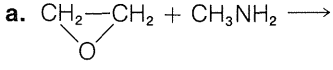


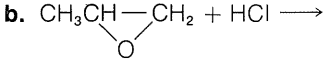
2,2-dimethyloxacyclopropane
(2,2-dimethyloxirane)

Because both products actually are obtained, we can conclude that both the S_N1 and S_N2 mechanisms occur. The S_N1 product, the tertiary ether, is the major product.

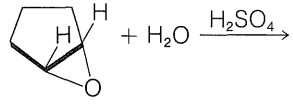
Exercise 15-45 Oxacyclopropanes tend to polymerize under basic conditions. Draw the structure of the polyether obtained on polymerization of D-2-methyloxacyclopropane catalyzed by $Na^{\oplus}{}^{\ominus}OCH_3$. Would you expect it to be formed with all D, all L, alternating D and L, or with random configurations of the chiral atoms in the chain?

Exercise 15-46 Draw the structures, showing the stereochemistry where necessary, for the products you would expect from the following reactions:

a. 

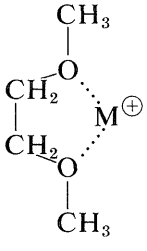
b. 

c. *meso*-dimethyloxacyclopropane + $(CH_3)_3O^{\oplus}BF_4^{\ominus}$ + CH_3OH ⟶

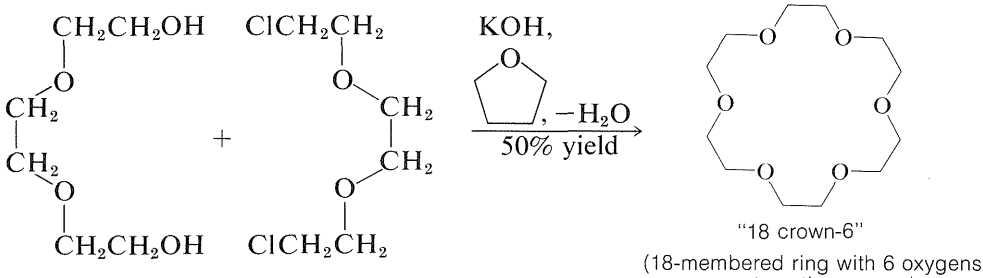
d. 

15-11E Metal Complexes of Cyclic Polyethers

We have emphasized the contrasts in properties between the ionic compounds, such as sodium chloride, and the nonpolar organic compounds, such as the alkanes and arenes. There are great difficulties in dissolving the extreme types of these substances in a mutually compatible medium for carrying on chemical reactions, as, for example, in S_N reactions of organic halides with alkali-metal salts (Sections 8-3 and 8-7F). The essence of the problem is that electrostatic forces in ionic crystals of inorganic salts are strong, and nonpolar solvents simply do not have the solvating power for ions to make dissolution of the crystals a favorable process. However, it has long been known that polyethers, such as the "glymes" (Section 15-10), are able to assist in the dissolution of ionic compounds through their ability to solvate metal cations by providing multiple complexing sites:



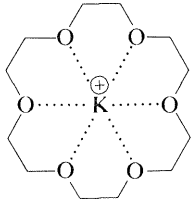
In 1967, C. J. Pedersen reported the synthesis of a series of cyclic polyethers, which he called "crown ethers," that have shown great promise for bringing together what traditionally have been regarded as wholly incompatible substances—even achieving measurable solubilities of salts such as NaCl, KOH, and $KMnO_4$ in benzene. The crown ethers can be regarded as cyclic "glymes" and are available by S_N2-type cyclization reactions:



"18 crown-6"
(18-membered ring with 6 oxygens; more systematic nomenclature is 1,4,7,10,13,16-hexaoxacyclooctadecane)

The crown ethers and many modifications of them (especially with nitrogen replacing one or more of the oxygens) function by coordinating with metal cations and converting them into less polar entities that are more stable in solution, even in a nonpolar solvent, than they are in the crystal.

Many of the crown ethers have considerable specificity with regard to the metal with which they complex. Ring size as well as the number and kind of hetero atoms are very important in this connection. 18-Crown-6 is especially effective for potassium:



An important application for the crown ethers in synthetic work is for solubilization of salts such as KCN in nonpolar solvents for use in S_N2 displacements. If the solvent has a low anion-solvating capability, then the reactivity of the anion is enhanced greatly. Consequently many displacement reactions that proceed slowly at elevated temperatures will proceed at useful rates at room temperatures, because the energy of "desolvating" the anion before it undergoes S_N2 displacement is low (Section 8-7F). For example, potassium fluoride becomes a potent nucleophilic reagent in nonpolar solvents when complexed with 18-crown-6:

$$CH_3(CH_2)_6CH_2Br + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} \underset{92\%}{CH_3(CH_2)_6CH_2F} + KBr$$

15-11F Acetals and Ketals as Ethers

The grouping C—O—C—O—C is characteristic of an acetal or a ketal (see Section 15-4E), but it also can be regarded as an ether with two ether links to one carbon. Compared to other ethers (except for the oxacyclopropanes), substances with the C—O—C—O—C group are very active toward acidic reagents, as pointed out in connection with their formation from alcohols (Section 15-4E) and their use as protecting groups for the OH function (Section 15-9C).

Additional Reading

G. A. Olah, *Carbocations and Electrophilic Reactions,* John Wiley and Sons, New York, 1974.

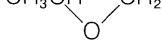
"Macrocyclic Polyethers Complex Alkali Metal Ions," *Chem. and Eng. News,* March 2, 1970, p. 26.

D. J. Cram and J. M. Cram, "Host-Guest Chemistry," *Science* **183,** 803 (1974).

Supplementary Exercises

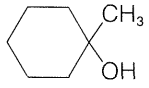
15-47 Show how you would synthesize each of the following alcohols, ethers, or acetals from the given organic starting materials and other necessary organic or inorganic reagents. Specify reagents and conditions as closely as possible.

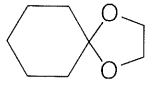
a. $CH_3OCH_2CH_2OCH_3$ from ethene

b.  from 1-propanol

c. $(CH_2{=}CHCH_2)_2O$ from $CH_2{=}CHCH_2Cl$

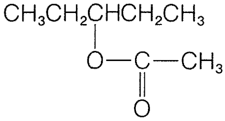
d. *trans*-1,2-cyclohexanediol from cyclohexene

e.  from cyclohexanol

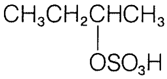
f.  from cyclohexanol and 1,2-ethanediol

15-48 Show how you would convert each of the following alcohols to the indicated products. Specify necessary reagents and conditions.

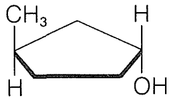
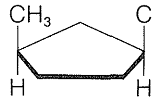
a. 1-propanol to $CH_3CH_2CH_2CH(CH_3)Cl$

b. ethanol to 

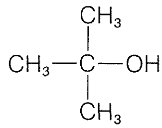
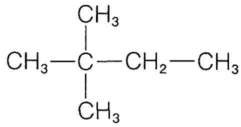
c. $(CH_3)_3COH$ to $(CH_3)_2CHCH_2Br$

d. 1-butanol to 

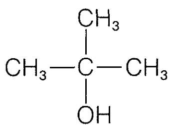
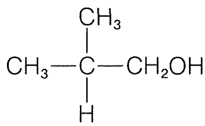
e. $(CH_3)_2C(OH)CH_2CH_3$ to $CH_3CH_2C(CH_3)_2CHO$

f.  to 

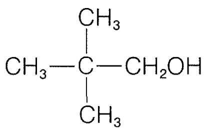
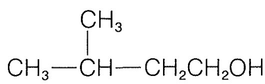
(*trans*) (*cis*)

g.  to 

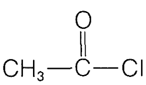
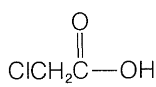
15-49 Give for each of the following pairs of compounds a chemical test, preferably a test-tube reaction, that will distinguish between the two substances. Describe the observation by which the distinction is made and write an equation for each reaction.

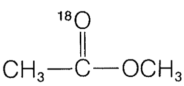
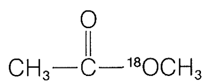
a.  and 

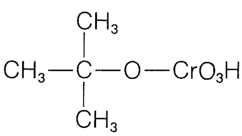
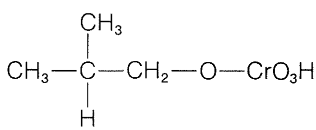
b. $CH_2{=}CH{-}CH_2CH_2OH$ and $CH_3CH{=}CH{-}CH_2OH$

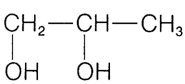
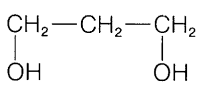
c.  and 

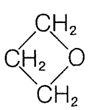
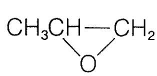
d. $CH_3CH_2{-}O{-}SO_2{-}O{-}CH_2CH_3$ and $CH_3CH_2CH_2CH_2{-}O{-}SO_3H$

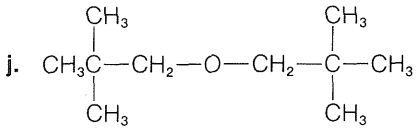
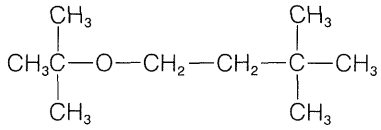
e.  and 

f.  and 

g.  and 

h.  and 

i.  and 

j.  and 

15-50 Suppose you were given unlabeled bottles, each of which is known to contain one of the following compounds: 1-pentanol, 2-pentanol, 2-methyl-2-butanol, 3-penten-1-ol, 4-pentyn-1-ol, 1-butoxybutane, and 1-pentyl acetate. Explain how you could use simple chemical tests (test-tube reactions only) to identify the contents of each bottle.

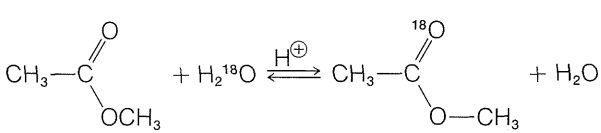
15-51 Either *tert*-butyl alcohol or 2-methylpropene treated with strong sulfuric acid and hydrogen peroxide (H_2O_2) gives a mixture of two reasonably stable liquid compounds (*A* and *B*), the ratio of which depends on whether the hydrogen peroxide or organic starting material is in excess. The molecular formula of *A* is $C_4H_{10}O_2$, whereas *B* is $C_8H_{18}O_2$.

Treatment of *A* and *B* with hydrogen over a nickel catalyst results in quantitative conversion of each compound to *tert*-butyl alcohol. *A* reacts with acyl halides and anhydrides, whereas *B* is unaffected by these reagents. Treatment of 1 mole of *A* with excess methylmagnesium iodide in diethyl ether solution produces 1 mole of methane and 1 mole each of *tert*-butyl alcohol and methanol. One mole of *B* with excess methylmagnesium iodide produces 1 mole of 2-methoxy-2-methylpropene and 1 mole of *tert*-butyl alcohol.

When *B* is heated with chloroethene, it causes chloroethene to polymerize. When *B* is heated *alone,* it yields 2-propanone and ethane, and if heated in the presence of *oxygen,* it forms methanol, 2-propanone, methanal, and water.

Determine the structure of *A* and *B* and write equations for all reactions involved, showing the mechanisms and intermediates that are important for each. Write at least one structure for *A* and for *B* that is isomeric with your preferred structures and show how these substances would behave in each of the given reactions.

15-52 The reaction of methyl ethanoate with water to give methanol and ethanoic acid is catalyzed by strong mineral acids such as sulfuric acid. Furthermore, when hydrolysis is carried out in water enriched in the rare oxygen isotope, ^{18}O, the following exchange takes place *faster* than formation of methanol:



No methanol-^{18}O ($CH_3{}^{18}OH$) is formed in hydrolysis under these conditions.

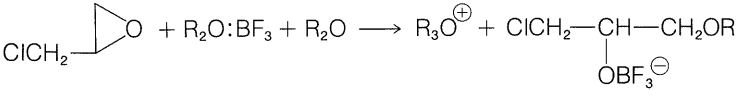
a. Write a stepwise mechanism that is in harmony with the acid catalysis and with the results obtained in ^{18}O water. Mark the steps of the reaction that are indicated to be fast or slow.
b. The reaction depends on methyl ethanoate having a proton-accepting ability comparable to that of water. Why? Consider different ways of adding a proton to methyl ethanoate and decide which is most favorable on the basis of structural theory. Give your reasoning.
c. Explain why the reaction is slowed down in the presence of very high concentrations of sulfuric acid.

15-53 Write a mechanism for the reaction of *trans*-2-butene with trifluoroperoxoethanoic acid to give *trans*-2,3-dimethyloxacyclopropane that is consistent with the fact that the reaction is first order in each participant and gives suprafacial addition.

15-54 2,2,4,4-Tetramethyl-3-oxapentane (di-*tert*-butyl ether) is very unstable to acidic reagents. Devise a synthesis of the compound that you think might have a reasonable chance for success. Give your reasoning.

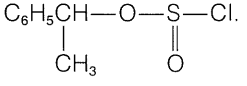
15-55 How would you expect the fraction of elimination toward the methyl groups, as opposed to elimination toward the methylene group, to compare in E1 and E2 reactions of 2-chloro-2-methylbutane and the corresponding deuterium-labeled chloride, 2-chloro-2-methylbutane-3-D_2? Give your reasoning. (Review Sections 8-8 and 15-6B.)

15-56 Triethyloxonium fluoroborate can be prepared from 1-chloromethyloxacyclopropane and a BF_3-etherate according to the equation



The boron in the complex boron anion ends up as $BF_4^{\ominus}$, but the details of this reaction need not concern you. Write the steps that you expect to be involved in the reaction to form $R_3O^{\oplus}$ and that you can support by analogy with other reactions discussed in this chapter.

15-57 Support your explanation of each of the following facts by reasoning based on mechanistic considerations:
a. D-1-Phenylethanol reacts with thionyl chloride, $SOCl_2$, in pyridine to give L-1-phenylethyl chloride by way of an intermediate chlorosulfite ester,



b. 2-Buten-1-ol and $SOCl_2$ in ether and a one-molar equivalent of tributylamine gives 1-chloro-2-butene. In the absence of the base, the rearrangement product, 3-chloro-1-butene, is obtained.

15-58 1,2-Ethanediol (ethylene glycol) is a familiar "antifreeze." However, it also is used in automotive cooling systems in climates that rarely, if ever, reach temperatures at which water would freeze. What other function, as important as lowering the freezing point, does the diol serve when added to automotive cooling systems?