17 Alcohols and Phenols

Organic KNOWLEDGE TOOLS

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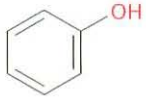
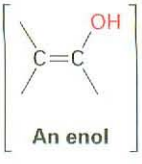
Alcohols and **phenols** can be thought of as organic derivatives of water in which one of the water hydrogens is replaced by an organic group: H–O–H versus R–O–H and Ar–O–H. In practice, the group name *alcohol* is restricted to compounds that have their –OH group bonded to a saturated, sp^3-hybridized carbon atom, while compounds with their –OH group bonded to a vinylic, sp^2-hybridized carbon are called *enols*. We'll look at enols in Chapter 22.

An alcohol



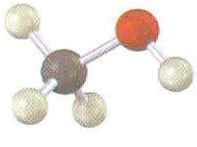
A phenol



An enol

Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Methanol, for instance, is one of the most important of all industrial chemicals. Historically, methanol was prepared by heating wood in the absence of air and thus came to be called *wood alcohol*. Today, approximately 1.3 billion gallons of methanol is manufactured each year in the United States by catalytic reduction of carbon monoxide with hydrogen gas. Methanol is toxic to humans, causing blindness in small doses (15 mL) and death in larger amounts (100–250 mL). Industrially, it is used both as a solvent and as a starting material for production of formaldehyde (CH_2O) and acetic acid (CH_3CO_2H).

$$CO + 2\,H_2 \xrightarrow[\text{Zinc oxide/chromia catalyst}]{400\ ^\circ C} CH_3OH$$

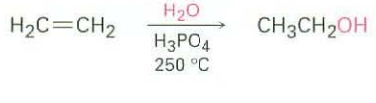


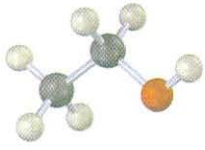
Ethanol was one of the first organic chemicals to be prepared and purified. Its production by fermentation of grains and sugars has been carried out for perhaps 9000 years, and its purification by distillation goes back at least as far as the 12th century. Today, approximately 4 billion gallons of ethanol is produced

Sean Dugan

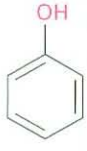
annually in the United States by fermentation of corn, barley, and sorghum, and production is expected to double by 2012. Essentially the entire amount is used to make E85 automobile fuel, a blend of 85% ethanol and 15% gasoline.

Ethanol for nonbeverage use is obtained by acid-catalyzed hydration of ethylene. Approximately 110 million gallons of ethanol a year is produced in the United States for use as a solvent or as a chemical intermediate in other industrial reactions.

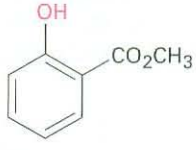




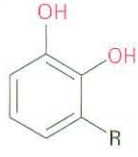
Phenols occur widely throughout nature and also serve as intermediates in the industrial synthesis of products as diverse as adhesives and antiseptics. Phenol itself is a general disinfectant found in coal tar; methyl salicylate is a flavoring agent found in oil of wintergreen; and the urushiols are the allergenic constituents of poison oak and poison ivy. Note that the word *phenol* is the name both of the specific compound hydroxybenzene and of a class of compounds.



Phenol (also known as carbolic acid)



Methyl salicylate



Urushiols (R = different C_{15} alkyl and alkenyl chains)

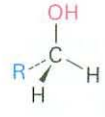
WHY THIS CHAPTER?

Up to this point, we've focused on developing some general ideas of organic reactivity, on looking at the chemistry of hydrocarbons, and on seeing some of the tools used in structural studies. With that background, it's now time to begin a study of the oxygen-containing functional groups that lie at the heart of biological chemistry. We'll look at alcohols in this chapter and then move on to carbonyl compounds in Chapters 19 through 23.

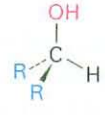
17.1 Naming Alcohols and Phenols

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to draw structures of alcohols based on their IUPAC names.**

Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol



A secondary (2°) alcohol

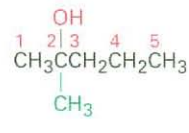
A tertiary (3°) alcohol

Simple alcohols are named by the IUPAC system as derivatives of the parent alkane, using the suffix *-ol*.

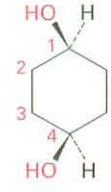
Rule 1 Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the *-e* ending of the corresponding alkane with *-ol*. The *-e* is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.

Rule 2 Number the alkane chain beginning at the end nearer the hydroxyl group.

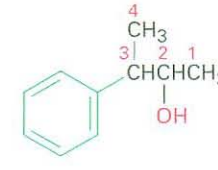
Rule 3 Number the substituents according to their position on the chain, and write the name listing the substituents in alphabetical order and identifying the position to which the —OH is bonded. Note that in naming *cis*-1,4-cyclohexanediol, the final *-e* of cyclohexane is not deleted because the next letter, *d*, is not a vowel, that is, cyclohexanediol rather than cyclohexandiol. Also, as with alkenes (Section 6.3), newer IUPAC naming recommendations place the locant immediately before the suffix rather than before the parent.



2-Methyl-2-pentanol
(New: 2-Methylpentan-2-ol)

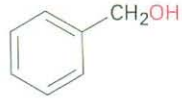


***cis*-1,4-Cyclohexanediol**
(New: *cis*-Cyclohexane-1,4-diol)

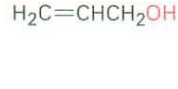


3-Phenyl-2-butanol
(New: 3-Phenylbutan-2-ol)

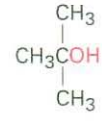
Some simple and widely occurring alcohols have common names that are accepted by IUPAC. For example:



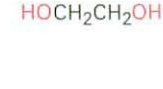
Benzyl alcohol
(phenylmethanol)



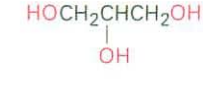
Allyl alcohol
(2-propen-1-ol)



***tert*-Butyl alcohol**
(2-methyl-2-propanol)

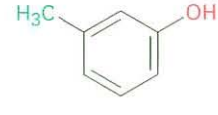


Ethylene glycol
(1,2-ethanediol)

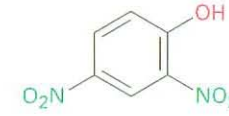


Glycerol
(1,2,3-propanetriol)

Phenols are named as described previously for aromatic compounds according to the rules discussed in Section 15.1. Note that *-phenol* is used as the parent name rather than *-benzene*.

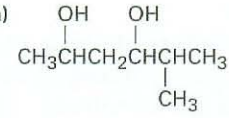


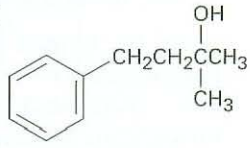
***m*-Methylphenol**
(*m*-Cresol)

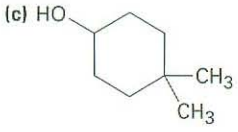


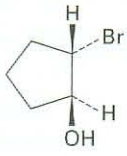
2,4-Dinitrophenol

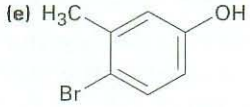
Problem 17.1 Give IUPAC names for the following compounds:

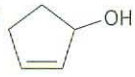
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Problem 17.2 Draw structures corresponding to the following IUPAC names:

(a) (*Z*)-2-Ethyl-2-buten-1-ol
(b) 3-Cyclohexen-1-ol
(c) *trans*-3-Chlorocycloheptanol
(d) 1,4-Pentanediol
(e) 2,6-Dimethylphenol
(f) *o*-(2-Hydroxyethyl)phenol

17.2 Properties of Alcohols and Phenols

Alcohols and phenols have nearly the same geometry around the oxygen atom as water. The R–O–H bond angle has an approximately tetrahedral value (109° in methanol, for example), and the oxygen atom is sp^3-hybridized.

Also like water, alcohols and phenols have higher boiling points than might be expected because of hydrogen-bonding (Section 2.13). A positively polarized –OH hydrogen atom from one molecule is attracted to a lone pair of electrons on the electronegative oxygen atom of another molecule, resulting in a weak force that holds the molecules together (Figure 17.1). These intermolecular attractions must be overcome for a molecule to break free from the liquid and enter the vapor state, so the boiling temperature is raised. For example, 1-propanol (MW = 60), butane (MW = 58), and chloroethane (MW = 65) have similar molecular weights, yet 1-propanol boils at 97 °C, compared with −0.5 °C for the alkane and 12.5 °C for the chloroalkane.

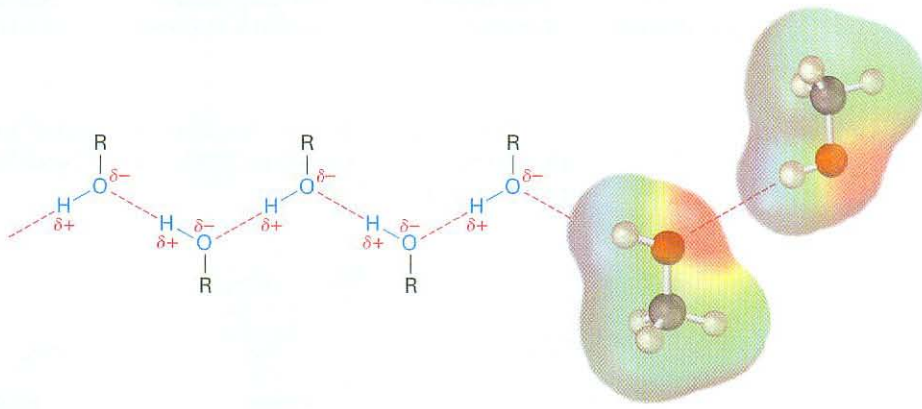
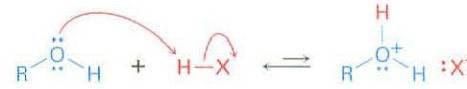


Figure 17.1 Hydrogen-bonding in alcohols and phenols. A weak attraction between a positively polarized OH hydrogen and a negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the positively polarized O–H hydrogen (blue) and the negatively polarized oxygen (red).

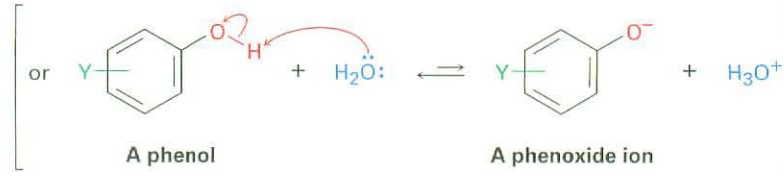
Another similarity with water is that alcohols and phenols are both weakly basic and weakly acidic. As weak bases, they are reversibly protonated by strong acids to yield oxonium ions, ROH_2^+.



An alcohol An oxonium ion

As weak acids, they dissociate slightly in dilute aqueous solution by donating a proton to water, generating H_3O^+ and an **alkoxide ion**, RO^-, or a **phenoxide ion**, ArO^-.

An alcohol An alkoxide ion



A phenol A phenoxide ion

Recall from the earlier discussion of acidity in Sections 2.7 through 2.11 that the strength of any acid HA in water can be expressed by an acidity constant, K_a.

$$K_a = \frac{[A^-]\,[H_3O^+]}{[HA]} \qquad pK_a = -\log K_a$$

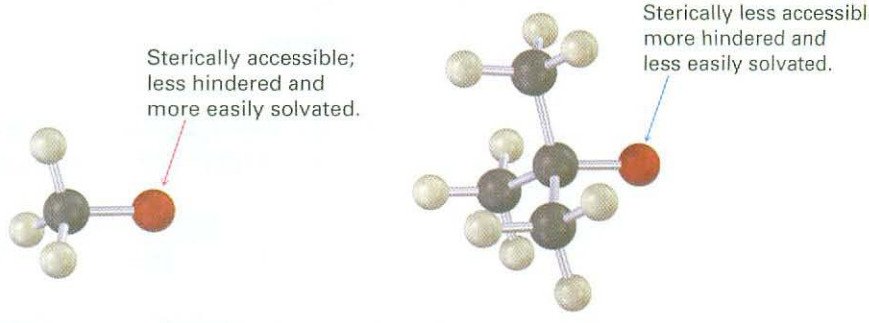
Compounds with a smaller K_a and larger pK_a are less acidic, whereas compounds with a larger K_a and smaller pK_a are more acidic. As shown by the data in Table 17.1, simple alcohols like methanol and ethanol are about as acidic as water but substituent groups can have a significant effect. *tert*-Butyl alcohol is a weaker acid, for instance, and 2,2,2-trifluoroethanol is stronger. Phenols and *thiols,* the sulfur analogs of alcohols, are substantially more acidic than water.

The effect of alkyl substitution on alcohol acidity is due primarily to solvation of the alkoxide ion that results from dissociation. The more readily the alkoxide ion is solvated by water, the more stable it is, the more its formation is energetically favored, and the greater the acidity of the parent alcohol. For example, the oxygen atom of an unhindered alkoxide ion, such as that from methanol, is sterically accessible and is easily solvated by water. The oxygen

Table 17.1 Acidity Constants of Some Alcohols and Phenols

Compound	pK_a	
$(CH_3)_3COH$	18.00	Weaker acid
CH_3CH_2OH	16.00	
H_2O	15.74	
CH_3OH	15.54	
CF_3CH_2OH	12.43	
p-Aminophenol	10.46	
CH_3SH	10.3	
p-Methylphenol	10.17	
Phenol	9.89	
p-Chlorophenol	9.38	
p-Nitrophenol	7.15	Stronger acid

atom of a hindered alkoxide ion, however, such as that from *tert*-butyl alcohol, is less easily solvated and is therefore less stabilized.



Methoxide ion, CH_3O^- (pK_a = 15.54) **_tert_-Butoxide ion, $(CH_3)_3CO^-$ (pK_a = 18.00)**

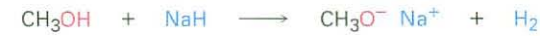
Inductive effects (Section 16.4) are also important in determining alcohol acidities. Electron-withdrawing halogen substituents, for example, stabilize an alkoxide ion by spreading out the charge over a larger volume, thus making the alcohol more acidic. Compare, for example, the acidities of ethanol (pK_a = 16.00) and 2,2,2-trifluoroethanol (pK_a = 12.43), or of *tert*-butyl alcohol (pK_a = 18.0) and nonafluoro-*tert*-butyl alcohol (pK_a = 5.4).

Electron-withdrawing groups stabilize the alkoxide ion and lower the *p*Ka.

*p*Ka = 5.4 *p*Ka = 18.0

Because alcohols are weak acids, they don't react with weak bases such as amines or bicarbonate ion, and they react to only a limited extent with metal hydroxides such as NaOH. Alcohols do, however, react with alkali metals and with strong bases such as sodium hydride (NaH), sodium amide ($NaNH_2$), and Grignard reagents (RMgX). Alkoxides are themselves bases that are frequently used as reagents in organic chemistry. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance.

tert-Butyl alcohol (2-methyl-2-propanol) — **Potassium tert-butoxide (potassium 2-methyl-2-propanolate)**

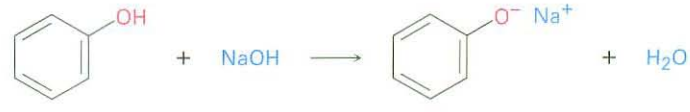


Methanol — **Sodium methoxide (sodium methanolate)**

Ethanol — **Sodium ethoxide (sodium ethanolate)**

Cyclohexanol — **Bromomagnesium cyclohexanolate**

Phenols are about a million times more acidic than alcohols (Table 17.1). They are therefore soluble in dilute aqueous NaOH and can often be separated from a mixture simply by basic extraction into aqueous solution, followed by reacidification.



Phenol — **Sodium phenoxide (sodium phenolate)**

Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized. Delocalization of the negative charge over the ortho and para positions of the aromatic ring results in increased stability of the phenoxide anion relative to undissociated phenol and in a consequently lower $\Delta G°$ for dissociation. Figure 17.2 compares electrostatic potential maps of an alkoxide ion (CH_3O^-) with phenoxide ion and shows how the negative charge in phenoxide ion is delocalized from oxygen to the ring.

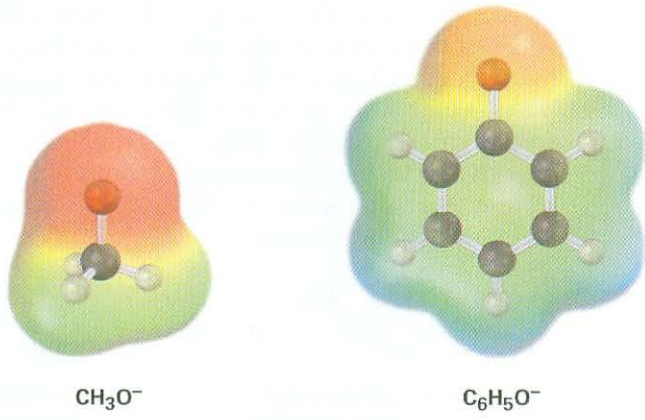
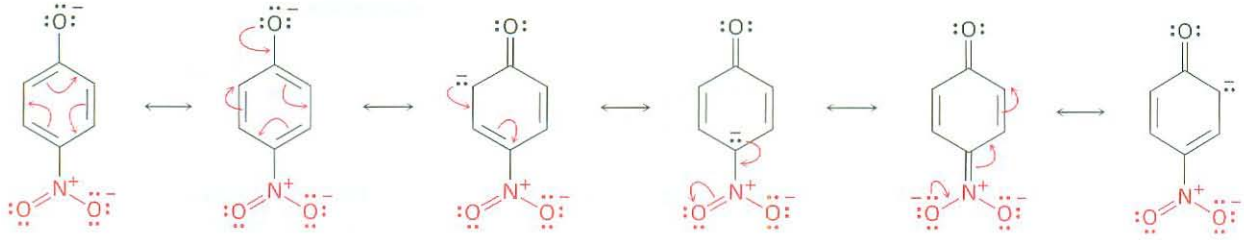


Figure 17.2 The resonance-stabilized phenoxide ion is more stable than an alkoxide ion. Electrostatic potential maps show how the negative charge is concentrated on oxygen in the methoxide ion but is spread over the aromatic ring in the phenoxide ion.

Substituted phenols can be either more acidic or less acidic than phenol itself, depending on whether the substituent is electron-withdrawing or electron-donating (Section 16.4). Phenols with an electron-withdrawing substituent are more acidic because these substituents delocalize the negative charge; phenols with an electron-donating substituent are less acidic because these substituents concentrate the charge. The acidifying effect of an electron-withdrawing substituent is particularly noticeable in phenols with a nitro group at the ortho or para position.

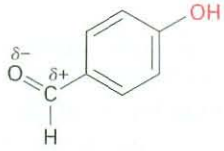


WORKED EXAMPLE 17.1 ***Predicting the Relative Acidity of a Substituted Phenol***

Is *p*-hydroxybenzaldehyde more acidic or less acidic than phenol?

Strategy Identify the substituent on the aromatic ring, and decide whether it is electron-donating or electron-withdrawing. Electron-withdrawing substituents make the phenol more acidic by stabilizing the phenoxide anion, and electron-donating substituents make the phenol less acidic by destabilizing the anion.

Solution We saw in Section 16.4 that a carbonyl group is electron-withdrawing. Thus, *p*-hydroxybenzaldehyde is more acidic ($pK_a = 7.9$) than phenol ($pK_a = 9.89$).



***p*-Hydroxybenzaldehyde**
($pK_a = 7.9$)

Problem 17.3 The following data for isomeric four-carbon alcohols show that there is a decrease in boiling point with increasing substitution of the OH-bearing carbon. How might you account for this trend?

1-Butanol, bp 117.5 °C
2-Butanol, bp 99.5 °C
2-Methyl-2-propanol, bp 82.2 °C

Problem 17.4 Rank the following substances in order of increasing acidity:

(a) $(CH_3)_2CHOH$, $HC{\equiv}CH$, $(CF_3)_2CHOH$, CH_3OH
(b) Phenol, *p*-methylphenol, *p*-(trifluoromethyl)phenol
(c) Benzyl alcohol, phenol, *p*-hydroxybenzoic acid

Problem 17.5 *p*-Nitrobenzyl alcohol is more acidic than benzyl alcohol but *p*-methoxybenzyl alcohol is less acidic. Explain.

17.3 Preparation of Alcohols: A Review

Alcohols occupy a central position in organic chemistry. They can be prepared from many other kinds of compounds (alkenes, alkyl halides, ketones, esters, and aldehydes, among others), and they can be transformed into an equally wide assortment of compounds (Figure 17.3).

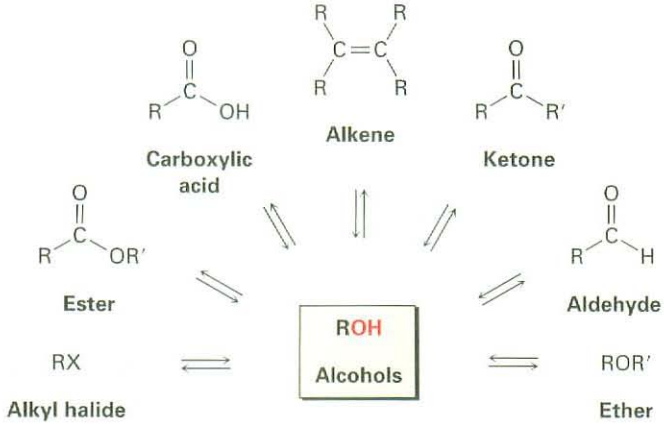
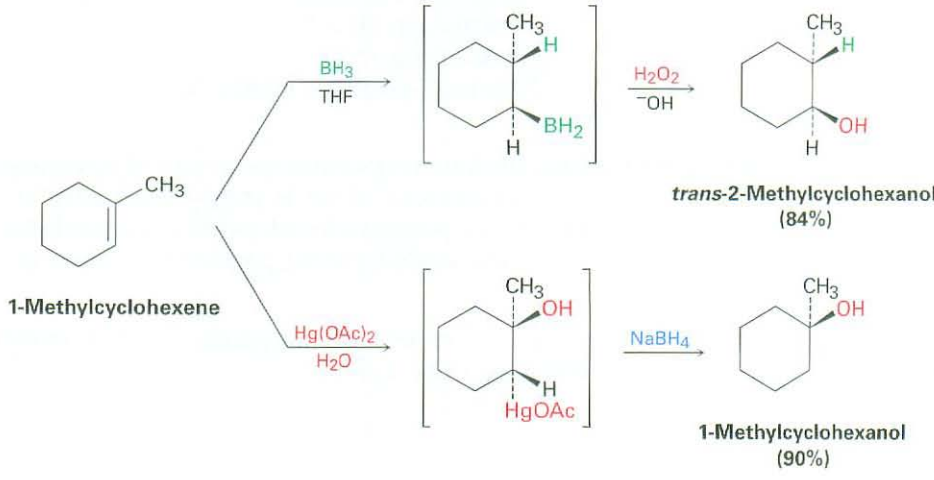


Figure 17.3 The central position of alcohols in organic chemistry. Alcohols can be prepared from, and converted into, many other kinds of compounds.

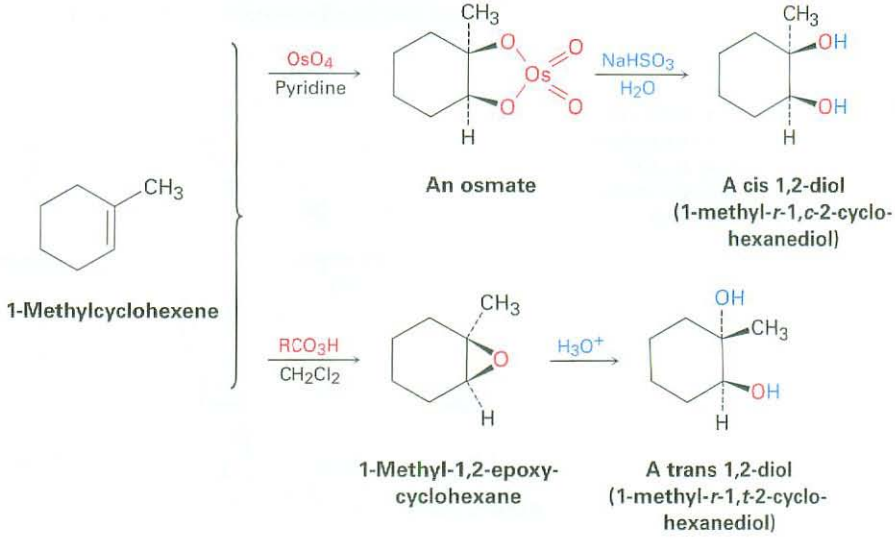
We've already seen several methods of alcohol synthesis:

- Alcohols can be prepared by hydration of alkenes. Because the direct hydration of alkenes with aqueous acid is generally a poor reaction in the laboratory, two indirect methods are commonly used. Hydroboration/oxidation yields the product of syn, non-Markovnikov hydration (Section 7.5), whereas

oxymercuration/reduction yields the product of Markovnikov hydration (Section 7.4).

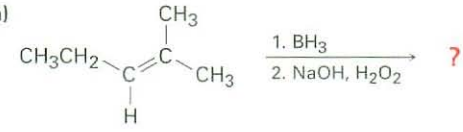


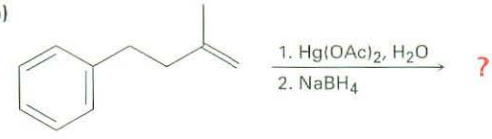
- 1,2-Diols can be prepared either by direct hydroxylation of an alkene with OsO_4 followed by reduction with $NaHSO_3$ or by acid-catalyzed hydrolysis of an epoxide (Section 7.8). The OsO_4 reaction occurs with syn stereochemistry to give a cis diol, and epoxide opening occurs with anti stereochemistry to give a trans diol.

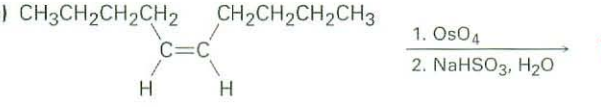


As noted at the end of Section 7.8, the prefixes *cis-* and *trans-* would be ambiguous when naming the diols derived from 1-methylcyclohexene because the ring has three substituents. Instead, a reference substituent *r* is chosen and other substituents are either cis (*c*) or trans (*t*) to that reference. For the two 1-methyl-1,2-cyclohexanediol isomers, the −OH group at C1 is the reference (*r*-1), and the −OH at C2 is either cis (*c*-2) or trans (*t*-2) to that reference. Thus, the diol isomer derived by cis hydroxylation is named 1-methyl-*r*-1,*c*-2-cyclohexanediol, and the isomer derived by trans hydroxylation is named 1-methyl-*r*-1,*t*-2-cyclohexanediol.

Problem 17.6 Predict the products of the following reactions:

(a) 

(b) 

(c) 

17.4 Alcohols from Reduction of Carbonyl Compounds

The most general method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of a carbonyl compound. Just as reduction of an alkene adds hydrogen to a C=C bond to give an alkane (Section 7.7), reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. All kinds of carbonyl compounds can be reduced, including aldehydes, ketones, carboxylic acids, and esters.

where [H] is a reducing agent

A carbonyl compound **An alcohol**

Reduction of Aldehydes and Ketones

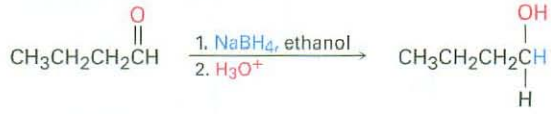
Aldehydes are easily reduced to give primary alcohols, and ketones are reduced to give secondary alcohols.

An aldehyde **A primary alcohol** **A ketone** **A secondary alcohol**

Literally dozens of reagents are used in the laboratory to reduce aldehydes and ketones, depending on the circumstances, but sodium borohydride, $NaBH_4$, is usually chosen because of its safety and ease of handling. Sodium borohydride

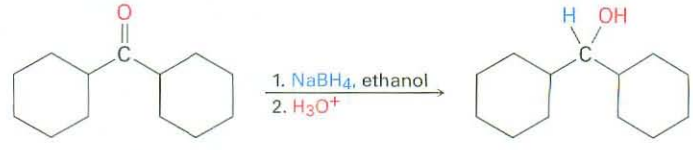
is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution to give high yields of products.

Aldehyde reduction



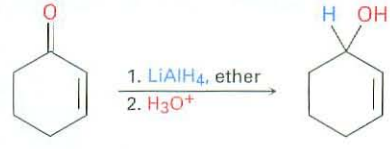
Butanal **1-Butanol (85%) (a 1° alcohol)**

Ketone reduction



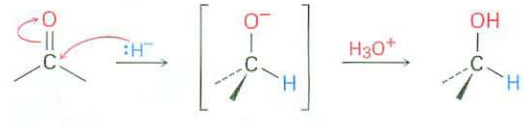
Dicyclohexyl ketone **Dicyclohexylmethanol (88%) (a 2° alcohol)**

Lithium aluminum hydride, $LiAlH_4$, is another reducing agent often used for reduction of aldehydes and ketones. A grayish powder that is soluble in ether and tetrahydrofuran, $LiAlH_4$ is much more reactive than $NaBH_4$ but also more dangerous. It reacts violently with water and decomposes explosively when heated above 120 °C.



2-Cyclohexenone **2-Cyclohexenol (94%)**

We'll defer a detailed discussion of the mechanisms of these reductions until Chapter 19. For the moment, we'll simply note that they involve the addition of a nucleophilic hydride ion ($:H^-$) to the positively polarized, electrophilic carbon atom of the carbonyl group. The initial product is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step to yield the alcohol product.



A carbonyl compound **An alkoxide ion intermediate** **An alcohol**

In living organisms, aldehyde and ketone reductions are carried out by either of the coenzymes NADH (reduced nicotinamide adenine dinucleotide) or NADPH (reduced nicotinamide adenine dinucleotide phosphate). Although

these biological "reagents" are much more complex structurally than $NaBH_4$ or $LiAlH_4$, the mechanisms of laboratory and biological reactions are similar. The coenzyme acts as a hydride-ion donor, and the intermediate anion is then protonated by acid. An example is the reduction of acetoacetyl ACP to β-hydroxybutyryl ACP, a step in the biological synthesis of fats (Figure 17.4). Note that the *pro-R* hydrogen of NADPH is the one transferred in this example. Enzyme-catalyzed reactions usually occur with high specificity, although it's not usually possible to predict the stereochemical result before the fact.

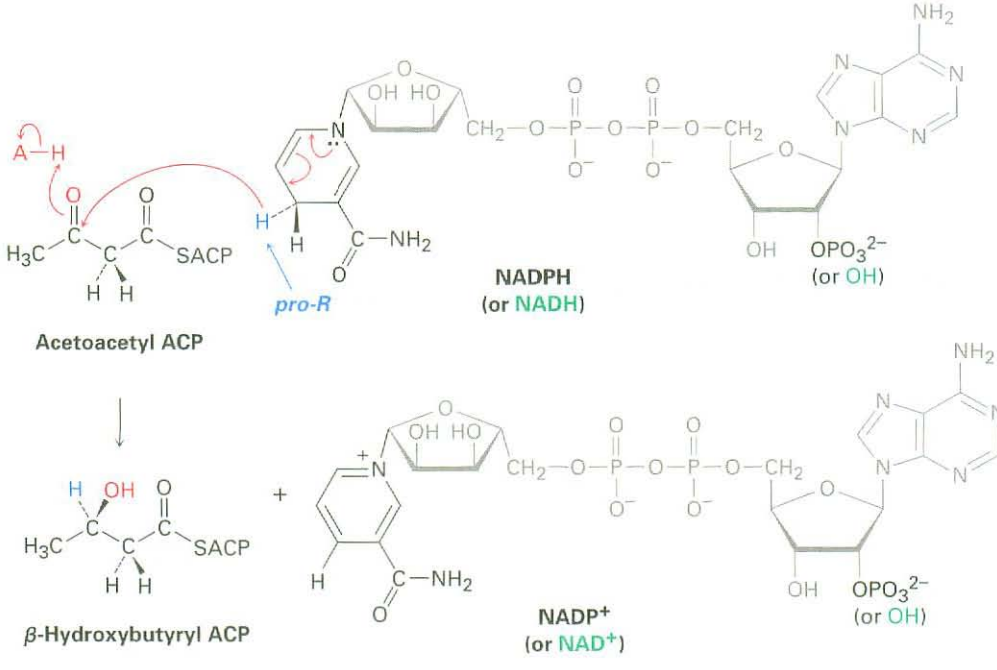
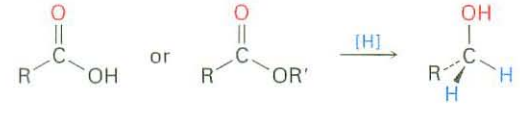


Figure 17.4 The biological reduction of a ketone (acetoacetyl ACP) to an alcohol (β-hydroxybutyryl ACP) by NADPH.

Reduction of Carboxylic Acids and Esters

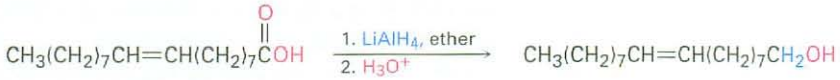
Carboxylic acids and esters are reduced to give primary alcohols.



These reactions aren't as rapid as the reductions of aldehydes and ketones. $NaBH_4$ reduces esters very slowly and does not reduce carboxylic acids at all. Instead, carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent $LiAlH_4$. All carbonyl groups, including acids, esters, ketones, and aldehydes, are reduced by $LiAlH_4$. Note that one hydrogen atom is delivered to the carbonyl carbon atom during aldehyde and ketone reductions but that two hydrogens become bonded to the former carbonyl

carbon during carboxylic acid and ester reductions. We'll defer a discussion of the mechanisms of these reactions until Chapter 21.

Carboxylic acid reduction



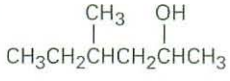
9-Octadecenoic acid (oleic acid) — **9-Octadecen-1-ol (87%)**

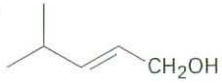
Ester reduction

Methyl 2-pentenoate — **2-Penten-1-ol (91%)**

WORKED EXAMPLE 17.2 *Predicting the Structure of a Reactant, Given the Product*

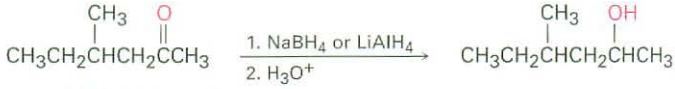
What carbonyl compounds would you reduce to obtain the following alcohols?

(a) 

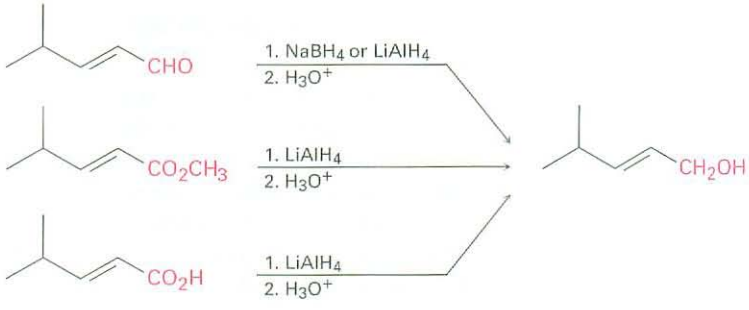
(b) 

Strategy Identify the target alcohol as primary, secondary, or tertiary. A primary alcohol can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid; a secondary alcohol can be prepared by reduction of a ketone; and a tertiary alcohol can't be prepared by reduction.

Solution (a) The target molecule is a secondary alcohol, which can be prepared only by reduction of a ketone. Either $NaBH_4$ or $LiAlH_4$ can be used.



(b) The target molecule is a primary alcohol, which can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid. $LiAlH_4$ is needed for the ester and carboxylic acid reductions.

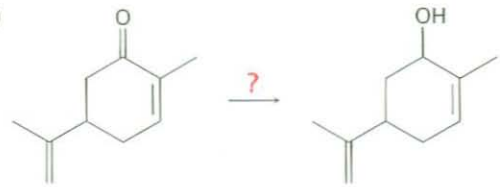


Problem 17.7 What reagent would you use to accomplish each of the following reactions?

(a) $CH_3CCH_2CH_2COCH_3 \xrightarrow{?} CH_3CHCH_2CH_2COCH_3$ (OH, O)

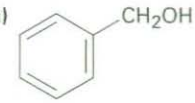
(b) $CH_3CCH_2CH_2COCH_3 \xrightarrow{?} CH_3CHCH_2CH_2CH_2OH$ (OH)

(c)

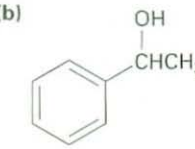


Problem 17.8 What carbonyl compounds give the following alcohols on reduction with $LiAlH_4$? Show all possibilities.

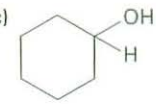
(a)



(b)



(c)



(d) $(CH_3)_2CHCH_2OH$

17.5 Alcohols from Reaction of Carbonyl Compounds with Grignard Reagents

ThomsonNOW Click *Organic Interactive* to **find supplemental problems and stepwise solutions to the design of Grignard syntheses.**

We saw in Section 10.7 that alkyl, aryl, and vinylic halides react with magnesium in ether or tetrahydrofuran to generate Grignard reagents, RMgX, which act as carbon-based nucleophiles. These Grignard reagents react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do.

$$R{-}X + Mg \longrightarrow \overset{\delta-\ \ \delta+}{R{-}MgX}$$

A Grignard reagent

R = 1°, 2°, or 3° alkyl, aryl, or vinylic
X = Cl, Br, I

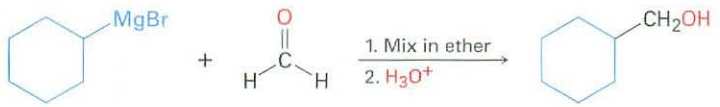
$$\text{C=O} \xrightarrow[2.\ H_3O^+]{1.\ RMgX,\ \text{ether}} \text{C(OH)(R)} + HOMgX$$

The reaction of Grignard reagents with carbonyl compounds has no direct biological counterpart, because organomagnesium compounds are too

strongly basic to exist in an aqueous medium. The reaction *does* have an indirect biological counterpart, however, for we'll see in Chapter 23 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon–carbon bonds.

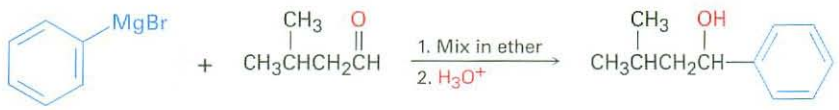
As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $H_2C{=}O$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.

Formaldehyde reaction



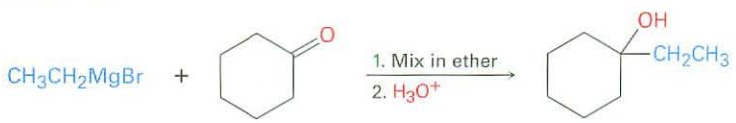
Cyclohexylmagnesium bromide + **Formaldehyde** → **Cyclohexylmethanol (65%) (a 1° alcohol)**

Aldehyde reaction



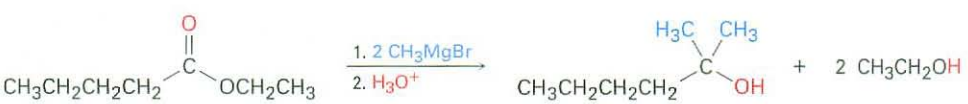
Phenylmagnesium bromide + **3-Methylbutanal** → **3-Methyl-1-phenyl-1-butanol (73%) (a 2° alcohol)**

Ketone reaction



Ethylmagnesium bromide + **Cyclohexanone** → **1-Ethylcyclohexanol (89%) (a 3° alcohol)**

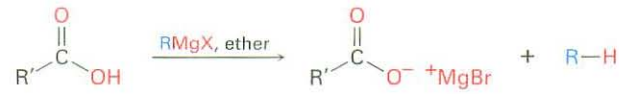
Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as $LiAlH_4$ reduction of an ester adds two hydrogens.



Ethyl pentanoate → **2-Methyl-2-hexanol (85%) (a 2° alcohol)**

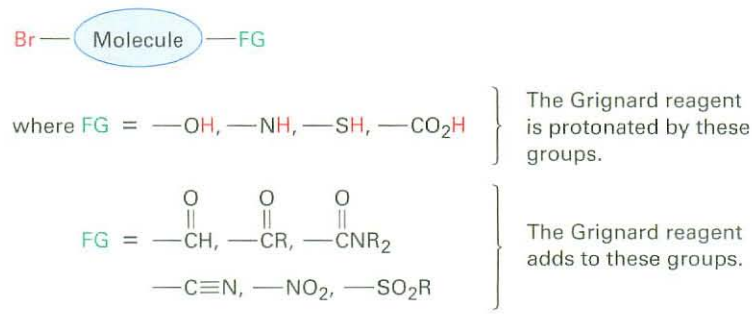
Carboxylic acids don't give addition products with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to

yield a hydrocarbon and the magnesium salt of the acid. We saw this reaction in Section 10.7 as a means of reducing an alkyl halide to an alkane.

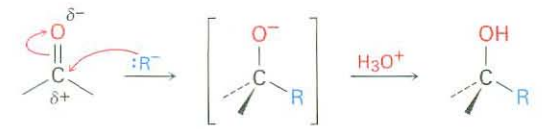


A carboxylic acid **A carboxylic acid salt**

The Grignard reaction, although useful, also has limitations. One major problem is that a Grignard reagent can't be prepared from an organohalide if other reactive functional groups are in the same molecule. For example, a compound that is both an alkyl halide and a ketone can't form a Grignard reagent because it would react with itself. Similarly, a compound that is both an alkyl halide and a carboxylic acid, an alcohol, or an amine can't form a Grignard reagent because the acidic RCO_2H, ROH, or RNH_2 hydrogen present in the same molecule would react with the basic Grignard reagent as rapidly as it forms. In general, Grignard reagents can't be prepared from alkyl halides that contain the following functional groups (FG):



As with the reduction of carbonyl compounds discussed in the previous section, we'll defer a detailed treatment of the mechanism of Grignard reactions until Chapter 19. For the moment, it's sufficient to note that Grignard reagents act as nucleophilic carbon anions, or *carbanions* ($:R^-$), and that the addition of a Grignard reagent to a carbonyl compound is analogous to the addition of hydride ion. The intermediate is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step.



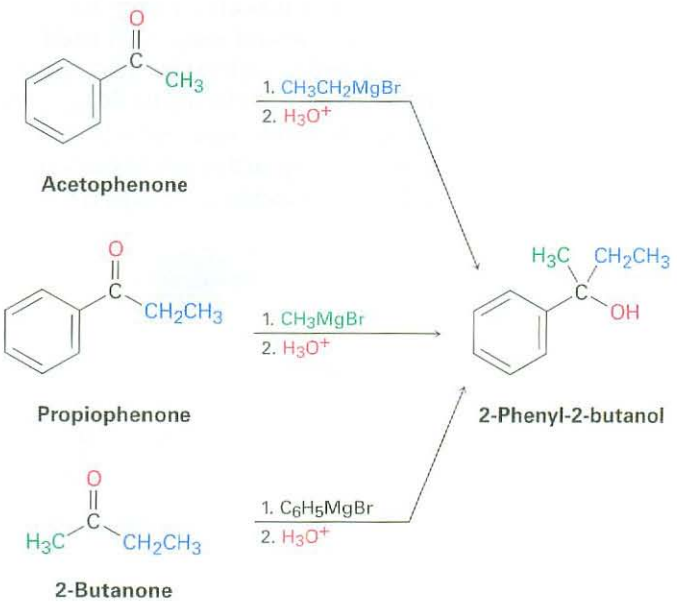
A carbonyl compound **An alkoxide ion intermediate** **An alcohol**

WORKED EXAMPLE 17.3 *Using a Grignard Reaction to Synthesize an Alcohol*

How could you use the addition of a Grignard reagent to a ketone to synthesize 2-phenyl-2-butanol?

Strategy Draw the product, and identify the three groups bonded to the alcohol carbon atom. One of the three will have come from the Grignard reagent, and the remaining two will have come from the ketone.

Solution 2-Phenyl-2-butanol has a methyl group, an ethyl group, and a phenyl group ($-C_6H_5$) attached to the alcohol carbon atom. Thus, the possibilities are addition of ethylmagnesium bromide to acetophenone, addition of methylmagnesium bromide to propiophenone, and addition of phenylmagnesium bromide to 2-butanone.

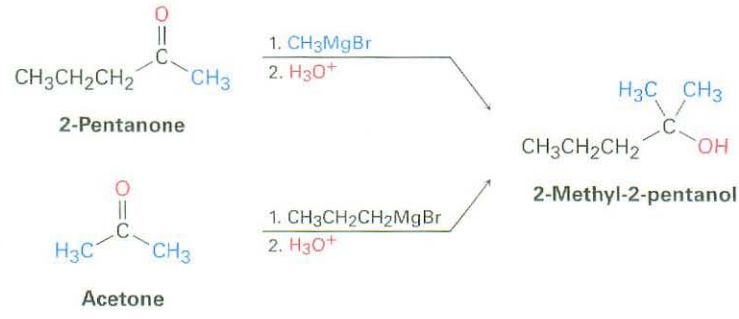


WORKED EXAMPLE 17.4 *Using a Grignard Reaction to Synthesize an Alcohol*

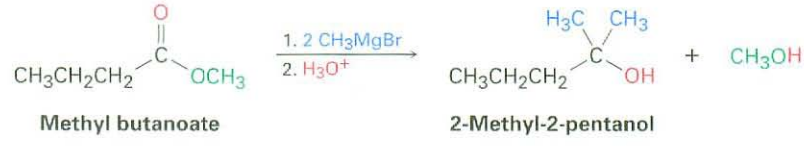
How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methyl-2-pentanol?

Strategy Draw the product, and identify the three groups bonded to the alcohol carbon atom. If the three groups are all different, the starting carbonyl compound must be a ketone. If two of the three groups are identical, the starting carbonyl compound might be either a ketone or an ester.

Solution In the present instance, the product is a tertiary alcohol with two methyl groups and one propyl group. Starting from a ketone, the possibilities are addition of methylmagnesium bromide to 2-pentanone and addition of propylmagnesium bromide to acetone.



Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate.



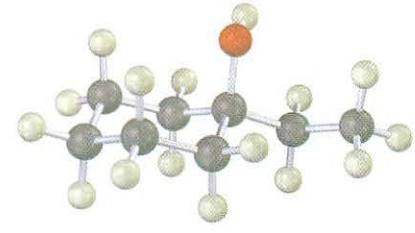
Problem 17.9 Show the products obtained from addition of methylmagnesium bromide to the following compounds:

(a) Cyclopentanone (b) Benzophenone (diphenyl ketone)
(c) 3-Hexanone

Problem 17.10 Use a Grignard reaction to prepare the following alcohols:

(a) 2-Methyl-2-propanol (b) 1-Methylcyclohexanol (c) 3-Methyl-3-pentanol
(d) 2-Phenyl-2-butanol (e) Benzyl alcohol (f) 4-Methyl-1-pentanol

Problem 17.11 Use the reaction of a Grignard reagent with a carbonyl compound to synthesize the following compound:



17.6 Reactions of Alcohols

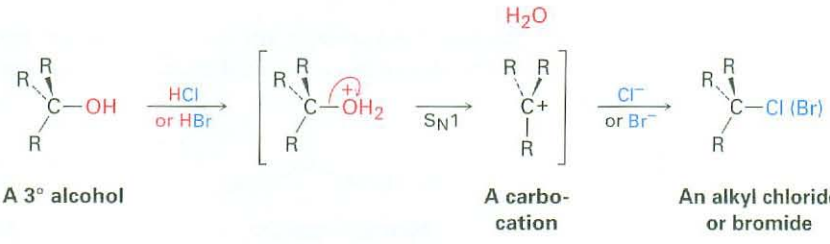
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from a variety of *reactions* involving alcohols.**

We've already seen several reactions of alcohols—their conversion into alkyl halides and tosylates in Section 10.6 and their dehydration to give alkenes in Section 7.1—although without mechanistic details. Let's now look at those details.

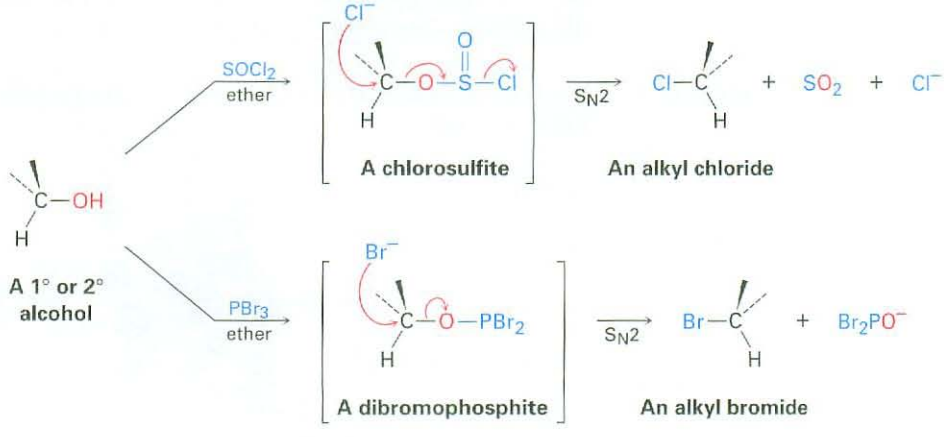
Conversion of Alcohols into Alkyl Halides

Tertiary alcohols react with either HCl or HBr at 0 °C by an S_N1 mechanism through a carbocation intermediate. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into halides by treatment with either $SOCl_2$ or PBr_3 through an S_N2 mechanism.

The reaction of a tertiary alcohol with HX takes place by an S_N1 mechanism when acid protonates the hydroxyl oxygen atom, water is expelled to generate a carbocation, and the cation reacts with nucleophilic halide ion to give the alkyl halide product.

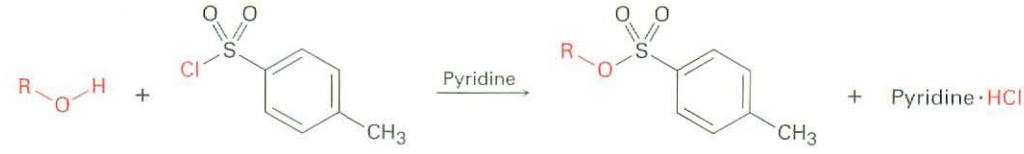


The reactions of primary and secondary alcohols with $SOCl_2$ and PBr_3 take place by S_N2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_N2 reactions, but reaction of an alcohol with $SOCl_2$ or PBr_3 converts the $-OH$ into a much better leaving group, either a chlorosulfite ($-OSOCl$) or a dibromophosphite ($-OPBr_2$), that is readily expelled by backside nucleophilic substitution.



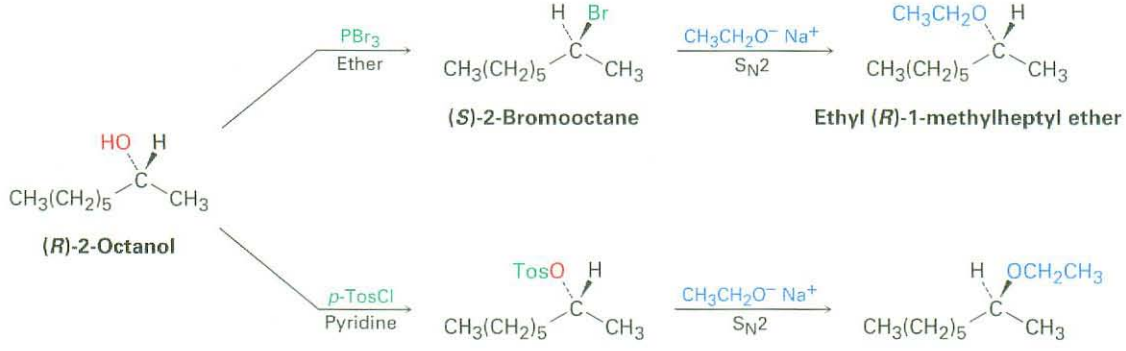
Conversion of Alcohols into Tosylates

Alcohols react with *p*-toluenesulfonyl chloride (tosyl chloride, *p*-TosCl) in pyridine solution to yield alkyl tosylates, ROTos (Section 11.1). Only the O–H bond of the alcohol is broken in this reaction; the C–O bond remains intact, so no change of configuration occurs if the oxygen is attached to a chirality center. The resultant alkyl tosylates behave much like alkyl halides, undergoing both S_N1 and S_N2 substitution reactions.



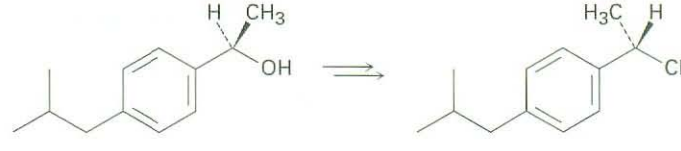
An alcohol **p-Toluenesulfonyl chloride** **A tosylate (ROTos)**

One of the most important reasons for using tosylates in S_N2 reactions is stereochemical. The S_N2 reaction of an alcohol via an alkyl halide proceeds with *two* inversions of configuration—one to make the halide from the alcohol and one to substitute the halide—and yields a product with the same stereochemistry as the starting alcohol. The S_N2 reaction of an alcohol via a tosylate, however, proceeds with only *one* inversion and yields a product of opposite stereochemistry to the starting alcohol. Figure 17.5 shows a series of reactions on the *R* enantiomer of 2-octanol that illustrates these stereochemical relationships.



Active Figure 17.5 Stereochemical consequences of S_N2 reactions on derivatives of (*R*)-2-octanol. Substitution through the halide gives a product with the same stereochemistry as the starting alcohol; substitution through the tosylate gives a product with opposite stereochemistry to the starting alcohol. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

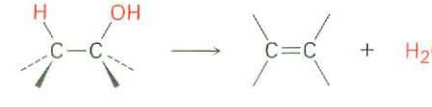
Problem 17.12 How would you carry out the following transformation, a step used in the commercial synthesis of (*S*)-ibuprofen?



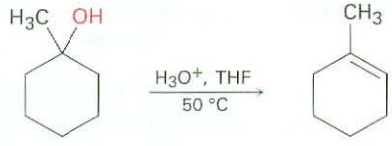
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. The C–O bond and a neighboring C–H are broken, and an alkene π bond is formed.

A dehydration reaction

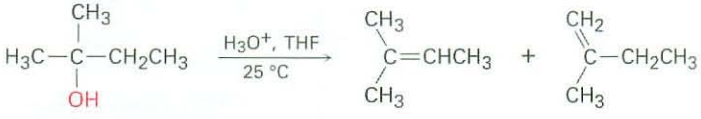


Because of the usefulness of the reaction, a number of ways have been devised for carrying out dehydrations. One method that works particularly well for tertiary alcohols is the acid-catalyzed reaction discussed in Section 7.1. For example, treatment of 1-methylcyclohexanol with warm aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.



1-Methylcyclohexanol **1-Methylcyclohexene (91%)**

Acid-catalyzed dehydrations usually follow Zaitsev's rule (Section 11.7) and yield the more stable alkene as the major product. Thus, 2-methyl-2-butanol gives primarily 2-methyl-2-butene (trisubstituted double bond) rather than 2-methyl-1-butene (disubstituted double bond).

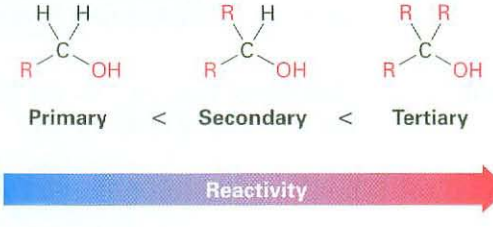


2-Methyl-2-butanol

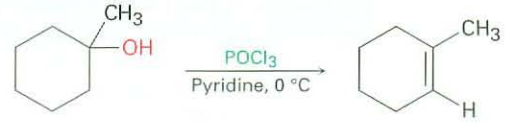
2-Methyl-2-butene (trisubstituted) — **Major product**

2-Methyl-1-butene (disubstituted) — **Minor product**

The reaction is an E1 process and occurs through the three-step mechanism shown in Figure 17.6). As usual for E1 reactions (Section 11.10), only tertiary alcohols are readily dehydrated with acid. Secondary alcohols can be made to react, but the conditions are severe (75% H_2SO_4, 100 °C) and sensitive molecules don't survive. Primary alcohols are even less reactive than secondary ones, and very harsh conditions are necessary to cause dehydration (95% H_2SO_4, 150 °C). Thus, the reactivity order for acid-catalyzed dehydrations is



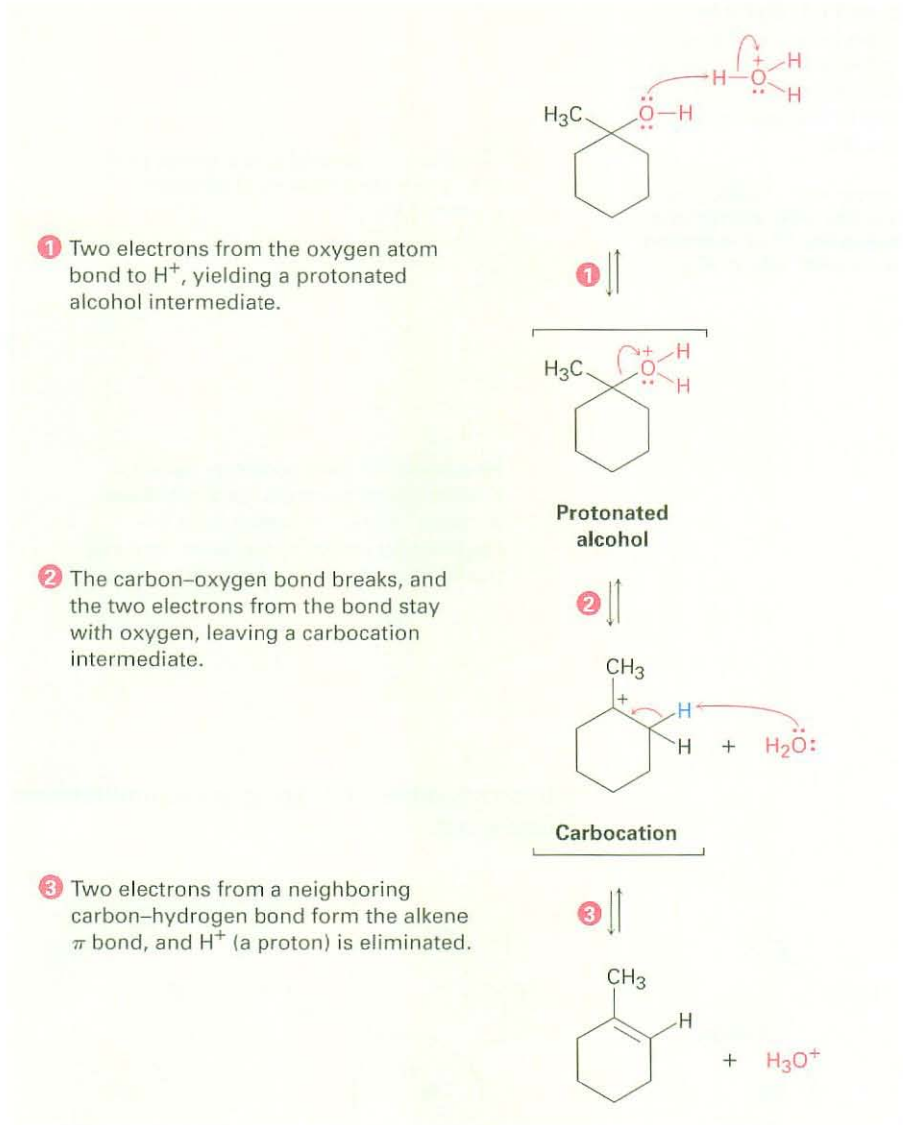
To circumvent the need for strong acid and allow the dehydration of secondary alcohols, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride ($POCl_3$) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0 °C.



1-Methylcyclohexanol **1-Methylcyclohexene (96%)**

Figure 17.6 MECHANISM: Mechanism of the acid-catalyzed dehydration of an alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.

ThomsonNOW Click *Organic Process* to **view animations showing the E1 acid-catalyzed dehydration of an alcohol.**

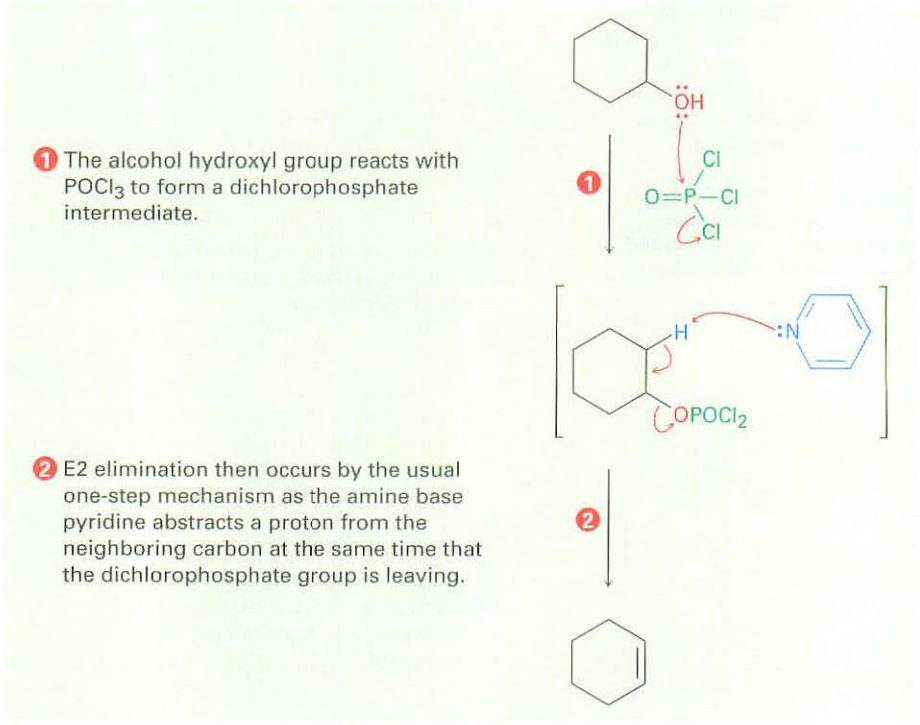


Alcohol dehydrations carried out with $POCl_3$ in pyridine take place by an E2 mechanism, as shown in Figure 17.7. Because hydroxide ion is a poor leaving group, direct E2 elimination of water from an alcohol does not occur. On reaction with $POCl_3$, however, the $-OH$ group is converted into a dichlorophosphate ($-OPOCl_2$), which is a good leaving group and is readily eliminated. Pyridine is both the reaction solvent and the base that removes a neighboring proton in the E2 elimination step.

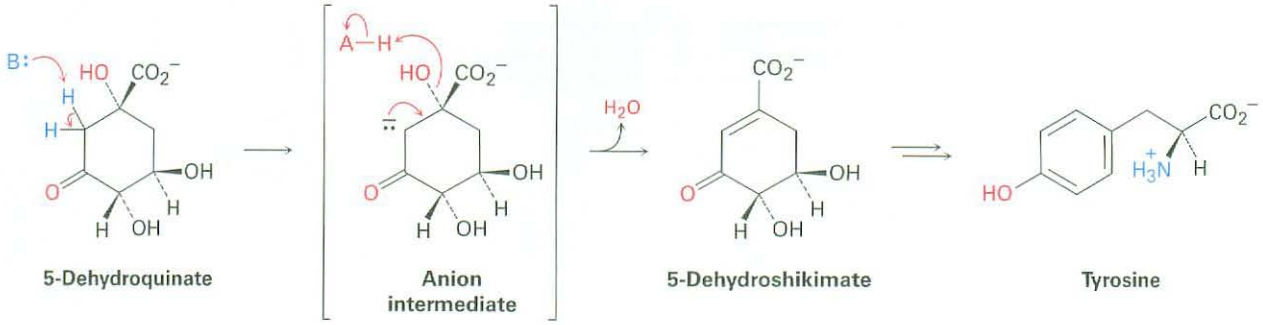
As noted previously in Section 11.10, biological dehydrations are also common and usually occur by an E1cB mechanism on a substrate in which the $-OH$ group is two carbons away from a carbonyl group. An example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base first abstracts a proton from the carbon adjacent to the carbonyl group, and the anion intermediate

Figure 17.7 MECHANISM: Mechanism of the dehydration of secondary and tertiary alcohols by reaction with $POCl_3$ in pyridine. The reaction is an E2 process.

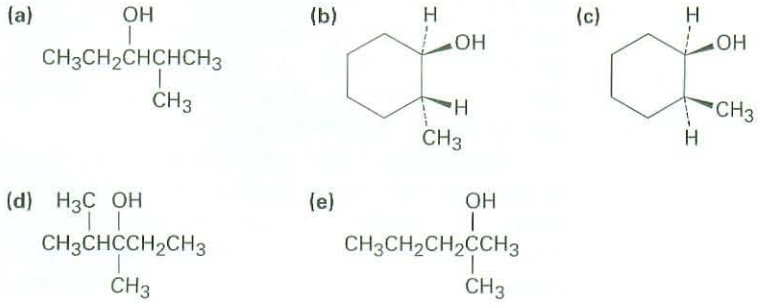
ThomsonNOW Click *Organic Process* to **view animations showing the E2 dehydration of an alcohol with $POCl_3$.**



then expels the –OH group with simultaneous protonation by an acid (HA) to form water.

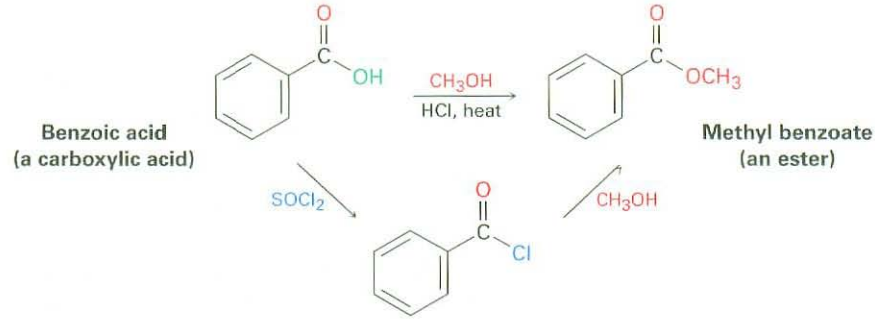


Problem 17.13 What product(s) would you expect from dehydration of the following alcohols with $POCl_3$ in pyridine? Indicate the major product in each case.

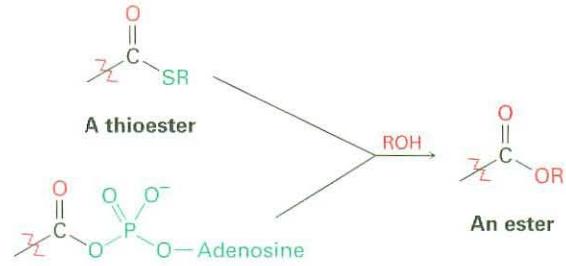


Conversion of Alcohols into Esters

Alcohols react with carboxylic acids to give esters, a reaction that is common in both the laboratory and living organisms. In the laboratory, the reaction can be carried out in a single step if a strong acid is used as catalyst. More frequently, though, the reactivity of the carboxylic acid is enhanced by first converting it into a carboxylic acid chloride, which then reacts with the alcohol. We'll look in detail at the mechanisms of these reactions in Chapter 21.

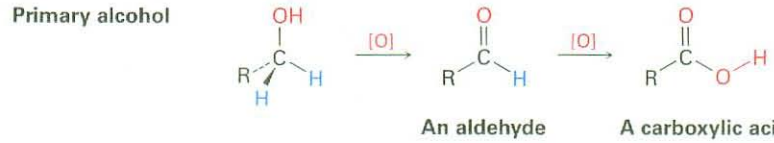


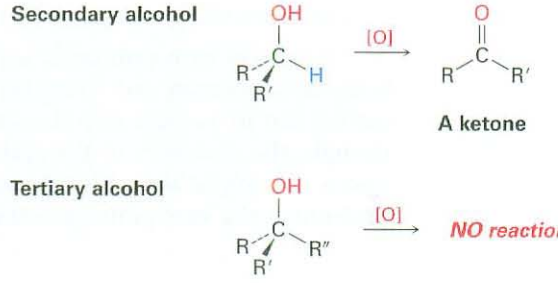
In living organisms, a similar process occurs, although a thioester or acyl adenosyl phosphate is the substrate rather than a carboxylic acid chloride.



17.7 Oxidation of Alcohols

Perhaps the most valuable reaction of alcohols is their oxidation to yield carbonyl compounds—the opposite of the reduction of carbonyl compounds to yield alcohols. Primary alcohols yield aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols don't normally react with most oxidizing agents.

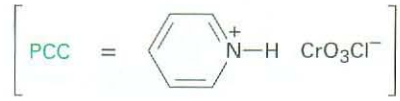




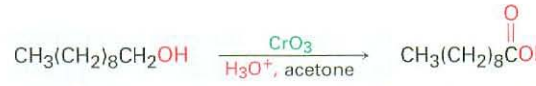
The oxidation of a primary or secondary alcohol can be accomplished by any of a large number of reagents, including $KMnO_4$, CrO_3, and $Na_2Cr_2O_7$. Which reagent is used in a specific case depends on such factors as cost, convenience, reaction yield, and alcohol sensitivity. For example, the large-scale oxidation of a simple, inexpensive alcohol such as cyclohexanol might best be done with a cheap oxidant such as $Na_2Cr_2O_7$. On the other hand, the small-scale oxidation of a delicate and expensive polyfunctional alcohol might best be done with one of several mild and high-yielding reagents, regardless of cost.

Primary alcohols are oxidized to either aldehydes or carboxylic acids, depending on the reagents chosen and the conditions used. One of the best methods for preparing an aldehyde from a primary alcohol on a small laboratory scale, as opposed to a large industrial scale, is to use pyridinium chlorochromate (PCC, $C_5H_6NCrO_3Cl$) in dichloromethane solvent.

Citronellol (from rose oil) **Citronellal (82%)**

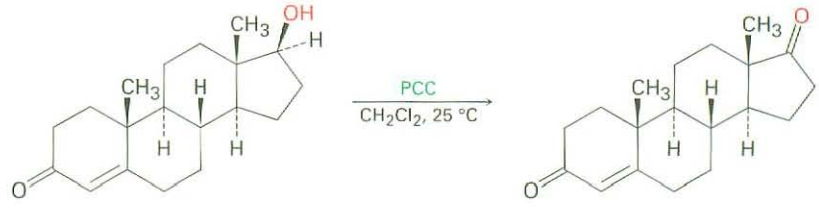


Most other oxidizing agents, such as chromium trioxide (CrO_3) in aqueous acid, oxidize primary alcohols directly to carboxylic acids. An aldehyde is involved as an intermediate in this reaction but can't usually be isolated because it is further oxidized too rapidly.



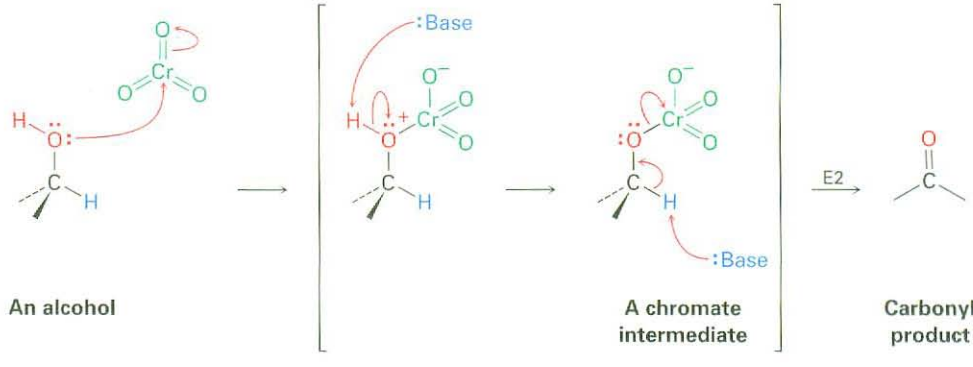
1-Decanol **Decanoic acid (93%)**

Secondary alcohols are oxidized easily and in high yield to give ketones. For large-scale oxidations, an inexpensive reagent such as $Na_2Cr_2O_7$ in aqueous acetic acid might be used. For a more sensitive or costly alcohol, however, pyridinium chlorochromate is often used because the reaction is milder and occurs at lower temperatures.



Testosterone (male sex hormone) **4-Androstene-3,17-dione (82%)**

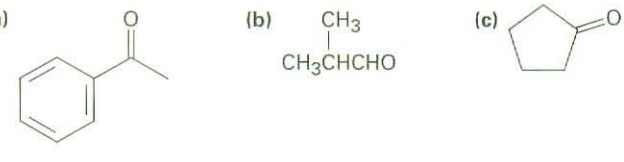
All these oxidations occur by a pathway that is closely related to the E2 reaction (Section 11.8). The first step involves reaction between the alcohol and a Cr(VI) reagent to form a *chromate* intermediate, followed by expulsion of chromium as the leaving group to yield the carbonyl product. Although we usually think of the E2 reaction as a means of generating a carbon–*carbon* double bond by elimination of a halide leaving group, the reaction is also useful for generating a carbon–*oxygen* double bond by elimination of a reduced metal as the leaving group.



An alcohol **A chromate intermediate** **Carbonyl product**

Biological alcohol oxidations are the exact opposite of biological carbonyl reductions and are carried by the coenzymes NAD^+ and $NADP^+$. A base removes the −OH proton, and the alkoxide ion transfers a hydride ion to the coenzyme. An example is the oxidation of *sn*-glycerol 3-phosphate to dihydroxyacetone phosphate, a step in the biological metabolism of fats (Figure 17.8). Note that addition occurs exclusively on the *Re* face of the NAD^+ ring, adding a hydrogen with *pro-R* stereochemistry.

Problem 17.14 What alcohols would give the following products on oxidation?



Problem 17.15 What products would you expect from oxidation of the following compounds with CrO_3 in aqueous acid? With pyridinium chlorochromate?

(a) 1-Hexanol (b) 2-Hexanol (c) Hexanal

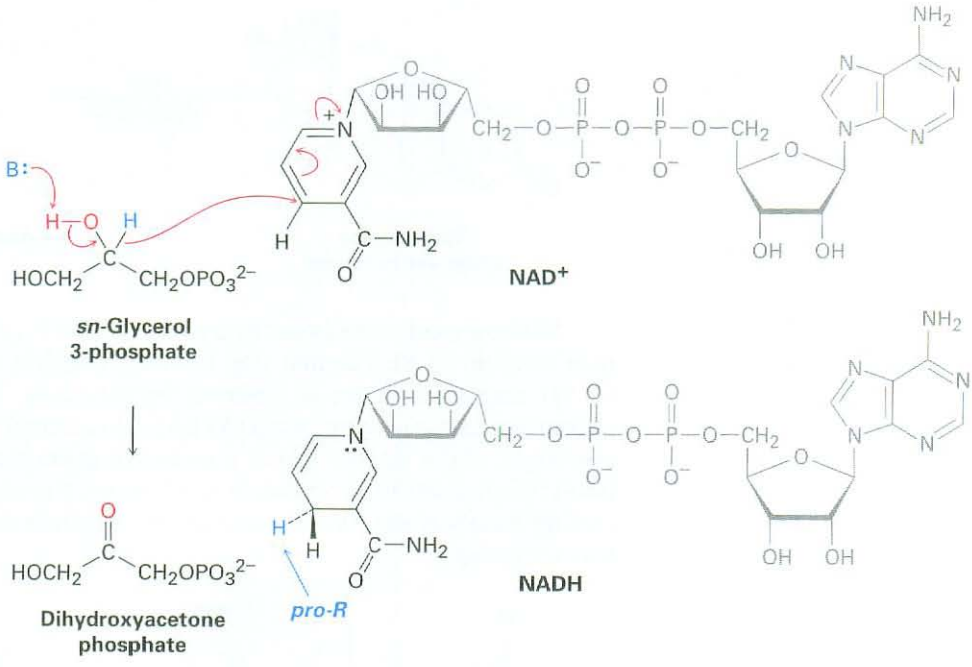
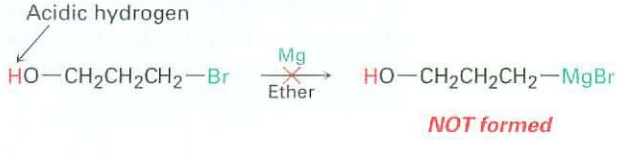


Figure 17.8 The biological oxidation of an alcohol (*sn*-glycerol 3-phosphate) to give a ketone (dihydroxyacetone phosphate). This mechanism is the exact opposite of the ketone reduction shown previously in Figure 17.4.

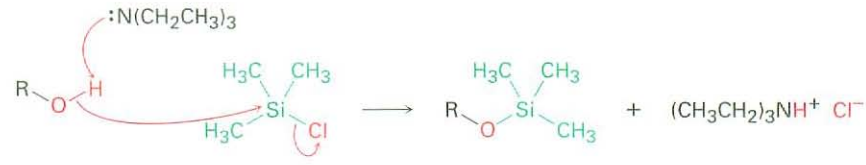
17.8 Protection of Alcohols

It often happens, particularly during the synthesis of complex molecules, that one functional group in a molecule interferes with an intended reaction on a second functional group elsewhere in the same molecule. For example, we saw earlier in this chapter that a Grignard reagent can't be prepared from a halo alcohol because the C–Mg bond is not compatible with the presence of an acidic –OH group in the same molecule.



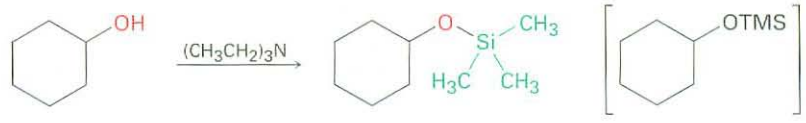
When this kind of incompatibility arises, it's sometimes possible to circumvent the problem by *protecting* the interfering functional group. Protection involves three steps: (1) introducing a **protecting group** to block the interfering function, (2) carrying out the desired reaction, and (3) removing the protecting group.

One of the more common methods of alcohol protection is by reaction with a chlorotrialkylsilane, $Cl-SiR_3$, to yield a trialkylsilyl ether, $R'-O-SiR_3$. Chlorotrimethylsilane is often used, and the reaction is carried out in the presence of a base, such as triethylamine, to help form the alkoxide anion from the alcohol and to remove the HCl by-product from the reaction.



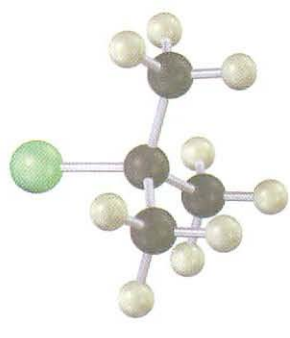
An alcohol | **Chlorotrimethylsilane** | **A trimethylsilyl (TMS) ether**

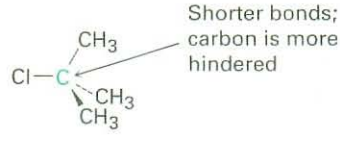
For example:



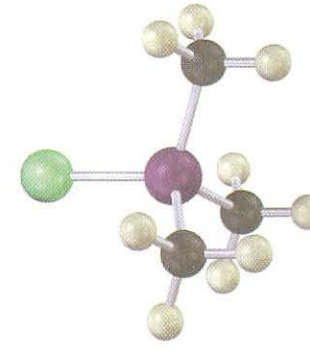
Cyclohexanol | **Cyclohexyl trimethylsilyl ether (94%)**

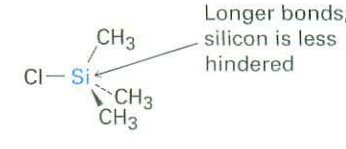
The ether-forming step is an S_N2-like reaction of the alkoxide ion on the silicon atom, with concurrent loss of the leaving chloride anion. Unlike most S_N2 reactions, though, this reaction takes place at a *tertiary* center—a trialkyl-substituted silicon atom. The reaction occurs because silicon, a third-row atom, is larger than carbon and forms longer bonds. The three methyl substituents attached to silicon thus offer less steric hindrance to reaction than they do in the analogous *tert*-butyl chloride.





C–C bond length: 154 pm

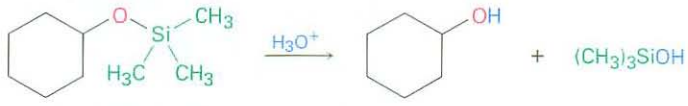




C–Si bond length: 195 pm

Like most other ethers, which we'll study in the next chapter, TMS ethers are relatively unreactive. They have no acidic hydrogens and don't react with

oxidizing agents, reducing agents, or Grignard reagents. They do, however, react with aqueous acid or with fluoride ion to regenerate the alcohol.



Cyclohexyl trimethylsilyl ether **Cyclohexanol**

To now solve the problem posed at the beginning of this section, it's possible to use a halo alcohol in a Grignard reaction by employing a protection sequence. For example, we can add 3-bromo-1-propanol to acetaldehyde by the route shown in Figure 17.9.

Figure 17.9 Use of a TMS-protected alcohol during a Grignard reaction.

Step 1 Protect alcohol:

$$HOCH_2CH_2CH_2Br + (CH_3)_3SiCl \xrightarrow{(CH_3CH_2)_3N} (CH_3)_3SiOCH_2CH_2CH_2Br$$

Step 2a Form Grignard reagent:

$$(CH_3)_3SiOCH_2CH_2CH_2Br \xrightarrow[\text{Ether}]{Mg} (CH_3)_3SiOCH_2CH_2CH_2MgBr$$

Step 2b Do Grignard reaction:

$$(CH_3)_3SiOCH_2CH_2CH_2MgBr \xrightarrow[2.\ H_3O^+]{1.\ CH_3\overset{\overset{O}{\|}}{C}H} (CH_3)_3SiOCH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3$$

Step 3 Remove protecting group:

$$(CH_3)_3SiOCH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3 \xrightarrow{H_3O^+} HOCH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3 + (CH_3)_3SiOH$$

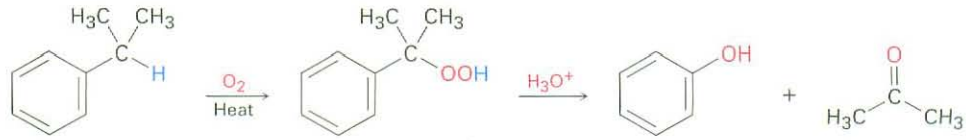
Problem 17.16 TMS ethers can be removed by treatment with fluoride ion as well as by acid-catalyzed hydrolysis. Propose a mechanism for the reaction of cyclohexyl TMS ether with LiF. Fluorotrimethylsilane is a product.

17.9 Phenols and Their Uses

Historically, the outbreak of the first World War provided a stimulus for the industrial preparation of large amounts of synthetic phenol, which was needed as a raw material to manufacture the explosive picric acid (2,4,6-trinitrophenol). Today, more than 2 million tons of phenol is manufactured each year in the United States for use in such products as Bakelite resin and adhesives for binding plywood.

Phenol was manufactured for many years by the Dow process, in which chlorobenzene reacts with NaOH at high temperature and pressure (Section 16.8). Now, however, an alternative synthesis from isopropylbenzene, commonly called

cumene, is used. Cumene reacts with air at high temperature by benzylic oxidation through a radical mechanism to form cumene hydroperoxide, which is converted into phenol and acetone by treatment with acid. This is a particularly efficient process because two valuable chemicals are prepared at the same time.



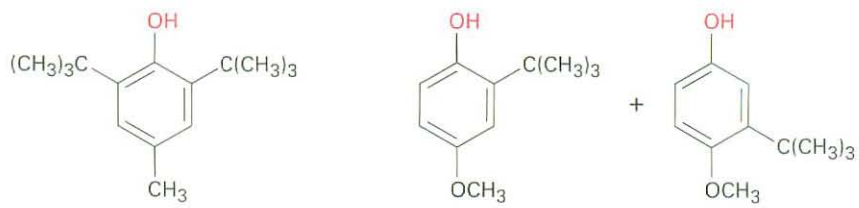
Cumene (isopropylbenzene) | **Cumene hydroperoxide** | **Phenol** | **Acetone**

The reaction occurs by protonation of oxygen, followed by rearrangement of the phenyl group from carbon to oxygen with simultaneous loss of water. Readdition of water then yields an intermediate called a *hemiacetal*—a compound that contains one −OR group and one −OH group bonded to the same carbon atom—which breaks down to phenol and acetone (Figure 17.10).

In addition to its use in making resins and adhesives, phenol is also the starting material for the synthesis of chlorinated phenols and the food preservatives BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole). Pentachlorophenol, a widely used wood preservative, is prepared by reaction of phenol with excess Cl_2. The herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) is prepared from 2,4-dichlorophenol, and the hospital antiseptic agent hexachlorophene is prepared from 2,4,5-trichlorophenol.

Pentachlorophenol (wood preservative) | **2,4-Dichlorophenoxyacetic acid, 2,4-D (herbicide)** | **Hexachlorophene (antiseptic)**

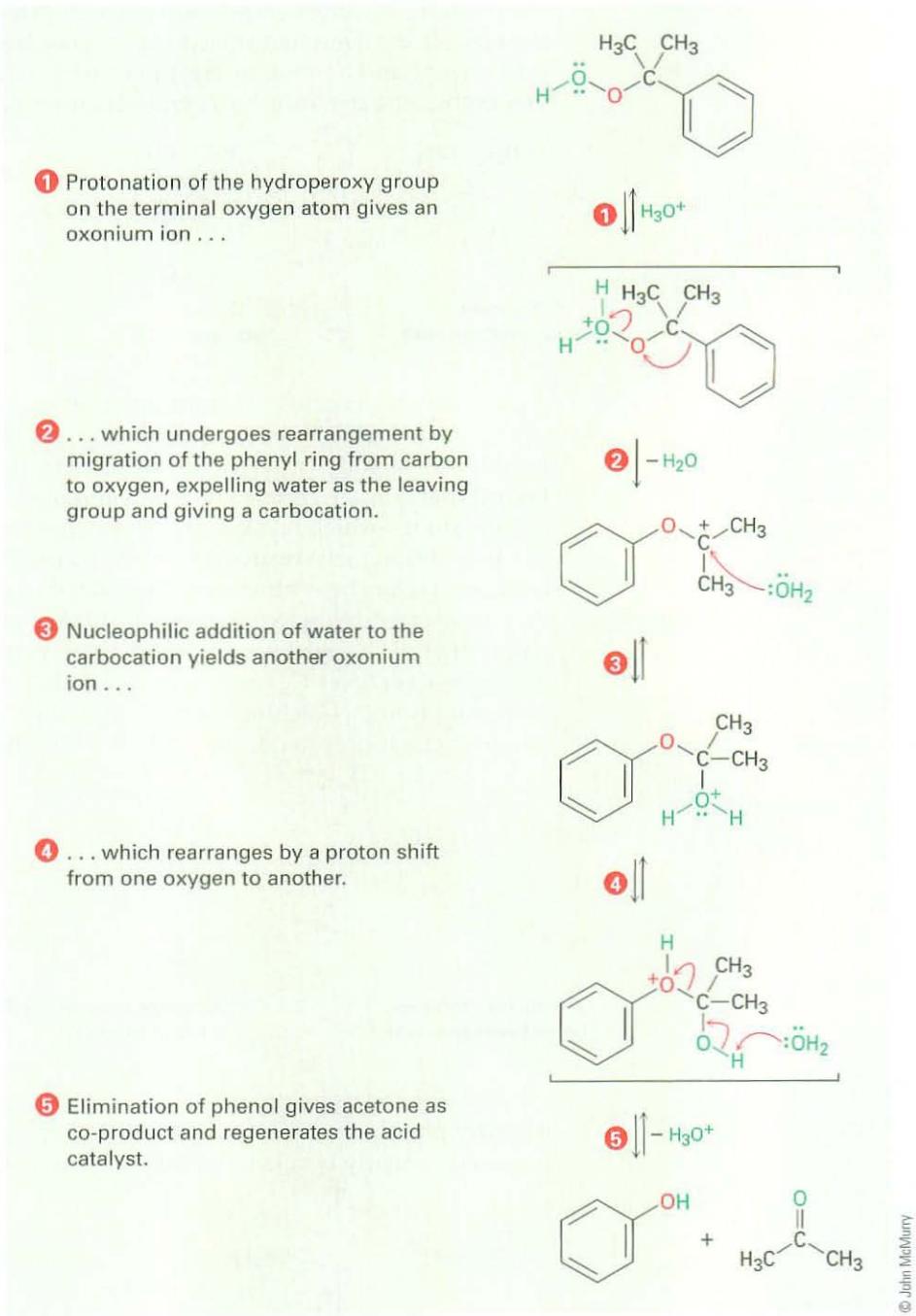
The food preservative BHT is prepared by Friedel–Crafts alkylation of *p*-methylphenol (*p*-cresol) with 2-methylpropene in the presence of acid; BHA is prepared similarly by alkylation of *p*-methoxyphenol.



BHT | **BHA**

Problem 17.17 | Show the mechanism of the reaction of *p*-methylphenol with 2-methylpropene and H_3PO_4 catalyst to yield the food additive BHT.

Figure 17.10 MECHANISM: Mechanism of the formation of phenol by acid-catalyzed rearrangement of cumene hydroperoxide.

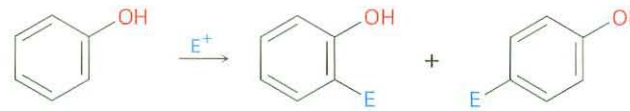


17.10 Reactions of Phenols

Electrophilic Aromatic Substitution Reactions

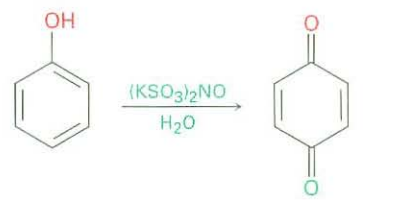
ThomsonNOW Click *Organic Interactive* to **use a web-based palette to predict products from a variety of reactions involving phenols.**

The hydroxyl group is a strongly activating, ortho- and para-directing substituent in electrophilic aromatic substitution reactions (Section 16.4). As a result, phenols are highly reactive substrates for electrophilic halogenation, nitration, sulfonation, and Friedel–Crafts reactions.

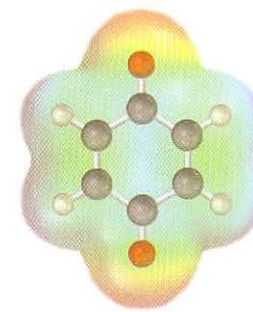


Oxidation of Phenols: Quinones

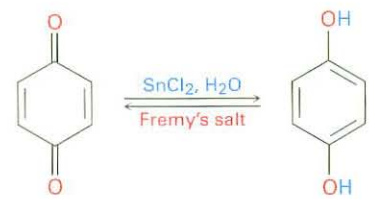
Phenols don't undergo oxidation in the same way that alcohols do because they don't have a hydrogen atom on the hydroxyl-bearing carbon. Instead, reaction of a phenol with a strong oxidizing agent yields a 2,5-cyclohexadiene-1,4-dione, or **quinone**. Older procedures employed $Na_2Cr_2O_7$ as oxidant, but Fremy's salt [potassium nitrosodisulfonate, $(KSO_3)_2NO$] is now preferred. The reaction takes place under mild conditions through a radical mechanism.



Phenol **Benzoquinone (79%)**

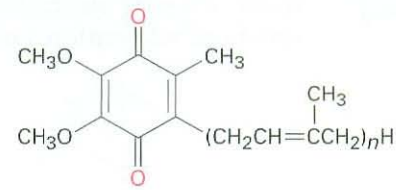


Quinones are an interesting and valuable class of compounds because of their oxidation–reduction, or *redox*, properties. They can be easily reduced to **hydroquinones** (*p*-dihydroxybenzenes) by reagents such as $NaBH_4$ and $SnCl_2$, and hydroquinones can be easily reoxidized back to quinones by Fremy's salt.



Benzoquinone **Hydroquinone**

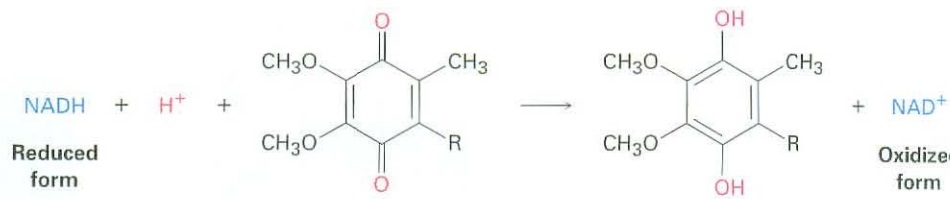
The redox properties of quinones are crucial to the functioning of living cells, where compounds called *ubiquinones* act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production. Ubiquinones, also called *coenzymes Q*, are components of the cells of all aerobic organisms, from the simplest bacterium to humans. They are so named because of their ubiquitous occurrence in nature.



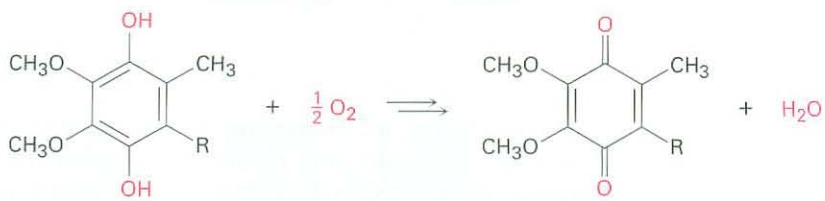
Ubiquinones (n = 1–10)

Ubiquinones function within the mitochondria of cells to mediate the respiration process in which electrons are transported from the biological reducing agent NADH to molecular oxygen. Through a complex series of steps, the ultimate result is a cycle whereby NADH is oxidized to NAD^+, O_2 is reduced to water, and energy is produced. Ubiquinone acts only as an intermediary and is itself unchanged.

Step 1



Step 2



Net change: $NADH + \frac{1}{2}O_2 + H^+ \longrightarrow NAD^+ + H_2O$

17.11 Spectroscopy of Alcohols and Phenols

Infrared Spectroscopy

Alcohols have a strong C–O stretching absorption near 1050 cm^{-1} and a characteristic O–H stretching absorption at 3300 to 3600 cm^{-1}. The exact position of the O–H stretch depends on the extent of hydrogen bonding in the molecule.

Unassociated alcohols show a fairly sharp absorption near 3600 cm^{-1}, whereas hydrogen-bonded alcohols show a broader absorption in the 3300 to 3400 cm^{-1} range. The hydrogen-bonded hydroxyl absorption appears at 3350 cm^{-1} in the IR spectrum of cyclohexanol (Figure 17.11).

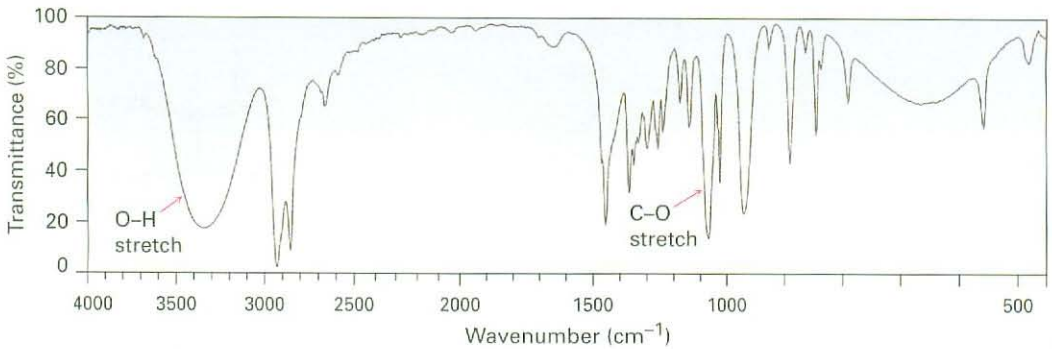


Figure 17.11 Infrared spectrum of cyclohexanol. Characteristic O–H and C–O stretching absorptions are indicated.

Phenols also show a characteristic broad IR absorption at 3500 cm^{-1} due to the –OH group, as well as the usual 1500 and 1600 cm^{-1} aromatic bands (Figure 17.12). In phenol itself, the monosubstituted aromatic-ring peaks at 690 and 760 cm^{-1} are visible.

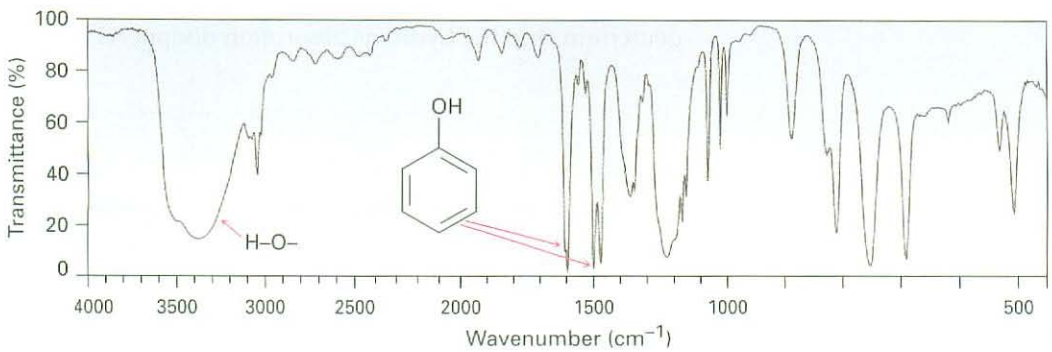
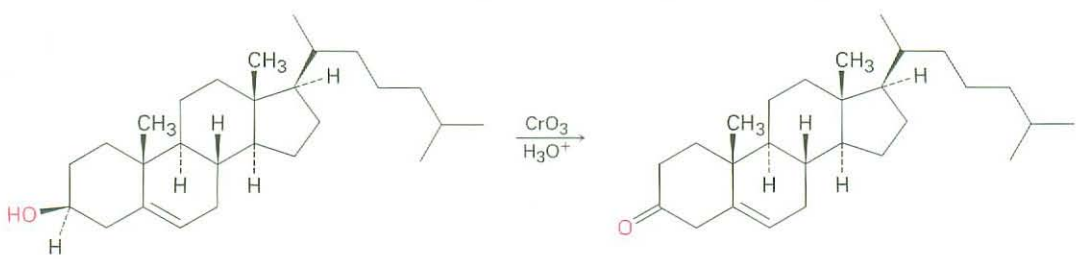


Figure 17.12 Infrared spectrum of phenol.

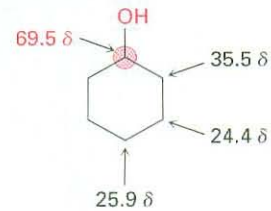
Problem 17.18 Assume that you need to prepare 5-cholesten-3-one from cholesterol. How could you use IR spectroscopy to tell whether the reaction was successful? What differences would you look for in the IR spectra of starting material and product?



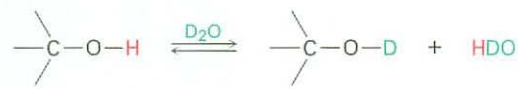
Cholesterol **5-Cholestene-3-one**

Nuclear Magnetic Resonance Spectroscopy

Carbon atoms bonded to electron-withdrawing —OH groups are deshielded and absorb at a lower field in the ^{13}C NMR spectrum than do typical alkane carbons. Most alcohol carbon absorptions fall in the range 50 to 80 δ, as the following data illustrate for cyclohexanol:



Alcohols also show characteristic absorptions in the ^1H NMR spectrum. Hydrogens on the oxygen-bearing carbon atom are deshielded by the electron-withdrawing effect of the nearby oxygen, and their absorptions occur in the range 3.4 to 4.5 δ. Spin–spin splitting, however, is not usually observed between the O—H proton of an alcohol and the neighboring protons on carbon. Most samples contain small amounts of acidic impurities, which catalyze an exchange of the O—H proton on a timescale so rapid that the effect of spin–spin splitting is removed. It's often possible to take advantage of this rapid proton exchange to identify the position of the O—H absorption. If a small amount of deuterated water, D_2O, is added to the NMR sample tube, the O—H proton is rapidly exchanged for deuterium, and the hydroxyl absorption disappears from the spectrum.



Typical spin–spin splitting *is* observed between protons on the oxygen-bearing carbon and other neighbors. For example, the signal of the two $-CH_2O-$ protons in 1-propanol is split into a triplet by coupling with the neighboring $-CH_2-$ protons (Figure 17.13).

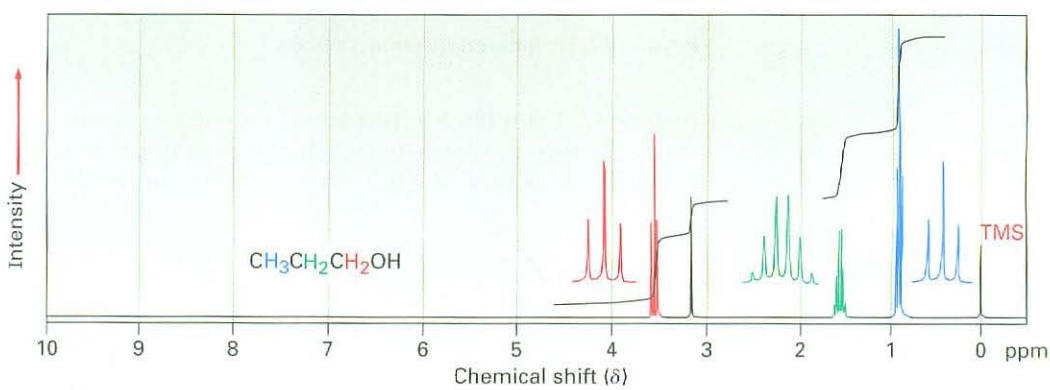


Figure 17.13 ^1H NMR spectrum of 1-propanol. The protons on the oxygen-bearing carbon are split into a triplet at 3.58 δ.

Phenols, like all aromatic compounds, show ^1H NMR absorptions near 7 to 8 δ, the expected position for aromatic-ring protons (Section 15.8). In addition, phenol O—H protons absorb at 3 to 8 δ. In neither case are these

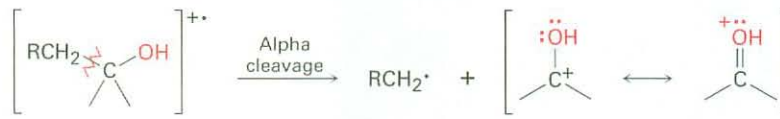
absorptions uniquely diagnostic for phenols, since other kinds of protons absorb in the same range.

Problem 17.19 When the ^1H NMR spectrum of an alcohol is run in dimethyl sulfoxide (DMSO) solvent rather than in chloroform, exchange of the O–H proton is slow and spin–spin splitting is seen between the O–H proton and C–H protons on the adjacent carbon. What spin multiplicities would you expect for the hydroxyl protons in the following alcohols?

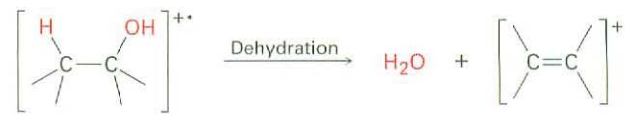
(a) 2-Methyl-2-propanol (b) Cyclohexanol (c) Ethanol
(d) 2-Propanol (e) Cholesterol (f) 1-Methylcyclohexanol

Mass Spectrometry

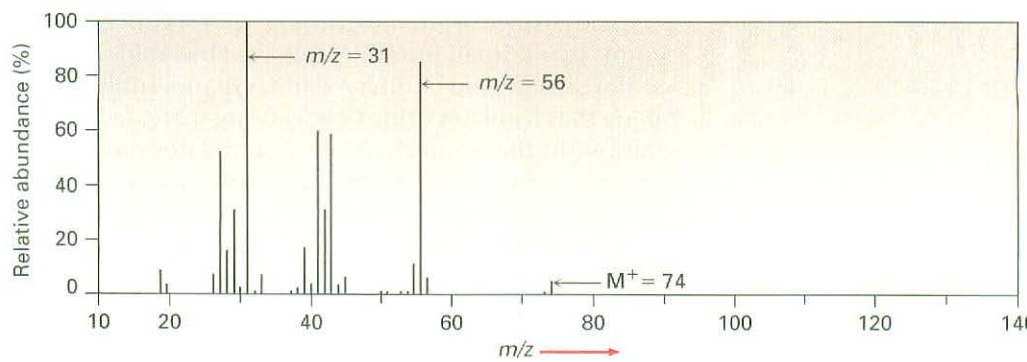
As noted previously in Section 12.3, alcohols undergo fragmentation in the mass spectrometer by two characteristic pathways, *alpha cleavage* and *dehydration*. In the alpha-cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a resonance-stabilized, oxygen-containing cation.



In the dehydration pathway, water is eliminated, yielding an alkene radical cation.



Both fragmentation modes are apparent in the mass spectrum of 1-butanol (Figure 17.14). The peak at $m/z = 56$ is due to loss of water from the molecular ion, and the peak at $m/z = 31$ is due to an alpha cleavage.



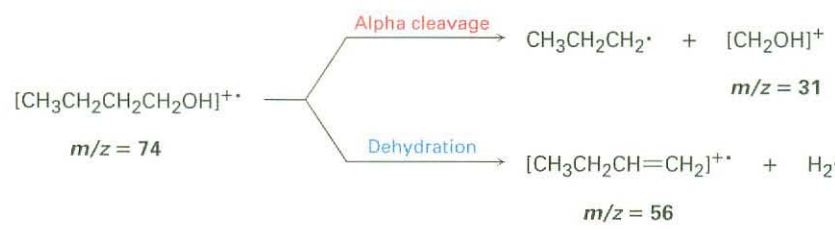
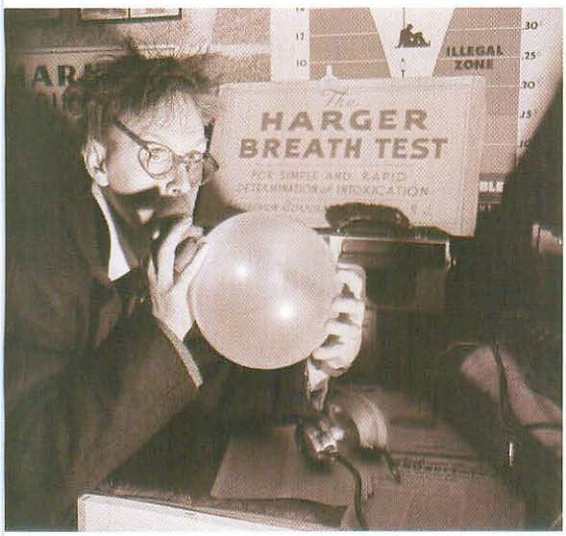


Figure 17.14 Mass spectrum of 1-butanol ($M^+ = 74$). Dehydration gives a peak at $m/z = 56$, and fragmentation by alpha cleavage gives a peak at $m/z = 31$.

Focus On . . .

Ethanol: Chemical, Drug, and Poison



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The Harger Drunkometer was introduced in 1938 to help convict drunk drivers.

The production of ethanol by fermentation of grains and sugars is one of the oldest known organic reactions, going back at least 8000 years in the Middle East and perhaps as many as 9000 years in China. Fermentation is carried out by adding yeast to an aqueous sugar solution, where enzymes break down carbohydrates into ethanol and CO_2. As noted in the chapter introduction, approximately 4 billion gallons of ethanol is produced each year in the United States by fermentation, with essentially the entire amount used to make E85 automobile fuel.

$$C_6H_{12}O_6 \xrightarrow{\text{Yeast}} 2\ CH_3CH_2OH + 2\ CO_2$$

A carbohydrate

Ethanol is classified for medical purposes as a central nervous system (CNS) depressant. Its effects—that is, being drunk—resemble the human response to anesthetics. There is an initial excitability and increase in sociable behavior, but this results from depression of inhibition rather than from stimulation. At a blood alcohol concentration of 0.1% to 0.3%, motor coordination is affected, accompanied by loss of balance, slurred speech, and amnesia. When blood alcohol concentration rises to 0.3% to 0.4%, nausea and loss of consciousness occur. Above 0.6%, spontaneous respiration and cardiovascular regulation are affected, ultimately leading to death. The LD_{50} of ethanol is 10.6 g/kg (Chapter 1 *Focus On*).

The passage of ethanol through the body begins with its absorption in the stomach and small intestine, followed by rapid distribution to all body fluids and organs. In the pituitary gland, ethanol inhibits the production of a hormone that regulates urine flow, causing increased urine production and dehydration. In the stomach, ethanol stimulates production of acid. Throughout the body, ethanol causes blood vessels to dilate, resulting in flushing of the skin and a sensation of warmth as blood moves into capillaries beneath the surface. The result is not a warming of the body, but an increased loss of heat at the surface.

Ethanol metabolism occurs mainly in the liver and proceeds by oxidation in two steps, first to acetaldehyde (CH_3CHO) and then to acetic acid (CH_3CO_2H). When continuously present in the body, ethanol and acetaldehyde are toxic, leading to the devastating physical and metabolic deterioration

(continued)

seen in chronic alcoholics. The liver usually suffers the worst damage since it is the major site of alcohol metabolism.

Approximately 17,000 people are killed each year in the United States in alcohol-related automobile accidents. Thus, all 50 states—Massachusetts was the last holdout—have made it illegal to drive with a blood alcohol concentration (BAC) above 0.08%. Fortunately, simple tests have been devised for measuring blood alcohol concentration. The *Breathalyzer test* measures alcohol concentration in expired air by the color change that occurs when the bright orange oxidizing agent potassium dichromate ($K_2Cr_2O_7$) is reduced to blue-green chromium(III). The *Intoxilyzer* test uses IR spectroscopy to measure blood alcohol levels in expired air. Just breathe into the machine, and let the spectrum tell the tale.

SUMMARY AND KEY WORDS

alcohol (ROH), 599
alkoxide ion (RO^-), 603
hydroquinone, 631
phenol (ArOH), 599
phenoxide ion (ArO^-), 603
protecting group, 626
quinone, 631

Alcohols are among the most versatile of all organic compounds. They occur widely in nature, are important industrially, and have an unusually rich chemistry. The most widely used methods of alcohol synthesis start with carbonyl compounds. Aldehydes, ketones, esters, and carboxylic acids are reduced by reaction with $LiAlH_4$. Aldehydes, esters, and carboxylic acids yield primary alcohols (RCH_2OH) on reduction; ketones yield secondary alcohols (R_2CHOH).

Alcohols are also prepared by reaction of carbonyl compounds with Grignard reagents, RMgX. Addition of a Grignard reagent to formaldehyde yields a primary alcohol, addition to an aldehyde yields a secondary alcohol, and addition to a ketone or an ester yields a tertiary alcohol. The Grignard reaction is limited by the fact that Grignard reagents can't be prepared from alkyl halides that contain reactive functional groups in the same molecule. This problem can sometimes be avoided by **protecting** the interfering functional group. Alcohols are often protected by formation of trimethylsilyl (TMS) ethers.

Alcohols undergo many reactions and can be converted into many other functional groups. They can be dehydrated to give alkenes by treatment with $POCl_3$ and can be transformed into alkyl halides by treatment with PBr_3 or $SOCl_2$. Furthermore, alcohols are weakly acidic ($pK_a \approx 16$–18) and react with strong bases and with alkali metals to form **alkoxide anions**, which are used frequently in organic synthesis.

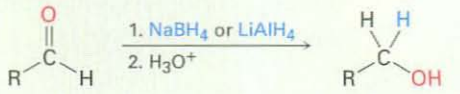
Perhaps the most important reaction of alcohols is their oxidation to carbonyl compounds. Primary alcohols yield either aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols are not normally oxidized. Pyridinium chlorochromate (PCC) in dichloromethane is often used for oxidizing primary alcohols to aldehydes and secondary alcohols to ketones. A solution of CrO_3 in aqueous acid is frequently used for oxidizing primary alcohols to carboxylic acids and secondary alcohols to ketones.

Phenols are aromatic counterparts of alcohols but are more acidic ($pK_a \approx 10$) because the corresponding **phenoxide anions** are resonance stabilized by delocalization of the negative charge into the aromatic ring. Substitution of the aromatic ring by an electron-withdrawing group increases phenol acidity, and substitution by an electron-donating group decreases acidity. Phenols

can be oxidized to **quinones** by reaction with Fremy's salt (potassium nitrosodisulfonate), and quinones can be reduced to **hydroquinones** by reaction with $NaBH_4$.

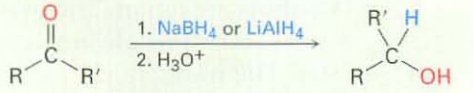
SUMMARY OF REACTIONS

1. Synthesis of alcohols
   (a) Reduction of carbonyl compounds (Section 17.4)
      (1) Aldehydes



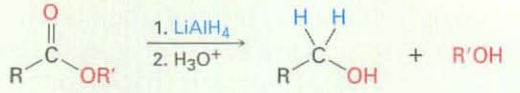
Primary alcohol

      (2) Ketones



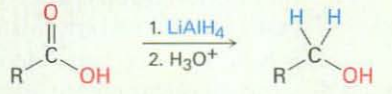
Secondary alcohol

      (3) Esters



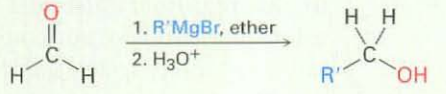
Primary alcohol

      (4) Carboxylic acids



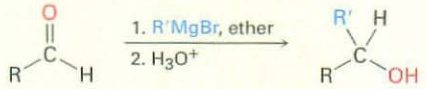
Primary alcohol

   (b) Grignard addition to carbonyl compounds (Section 17.5)
      (1) Formaldehyde



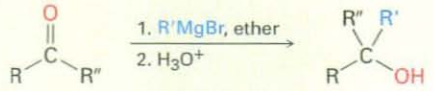
Primary alcohol

(2) Aldehydes



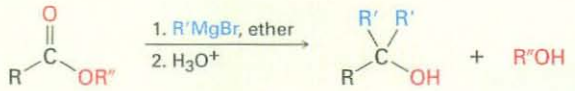
Secondary alcohol

(3) Ketones



Tertiary alcohol

(4) Esters

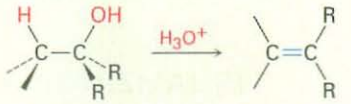


Tertiary alcohol

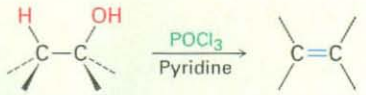
2. Reactions of alcohols

(a) Dehydration (Section 17.6)

(1) Tertiary alcohols

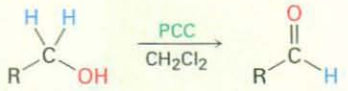


(2) Secondary and tertiary alcohols

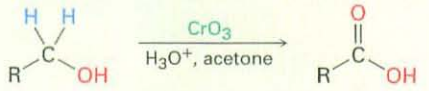


(b) Oxidation (Section 17.7)

(1) Primary alcohols

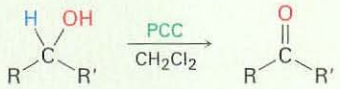


Aldehyde



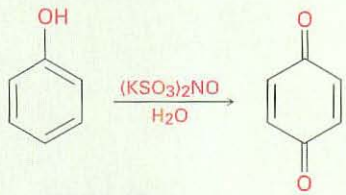
Carboxylic acid

(2) Secondary alcohols



Ketone

3. Oxidation of phenols to quinones (Section 17.10)



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

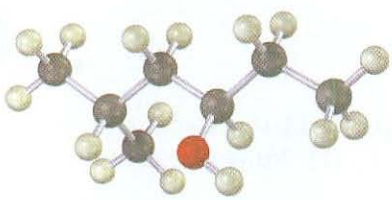
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

(Problems 17.1–17.19 appear within the chapter.)

17.20 ■ Give IUPAC names for the following compounds:

(a)



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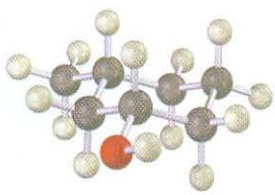

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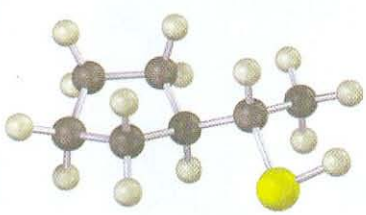

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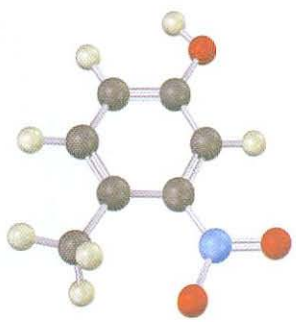
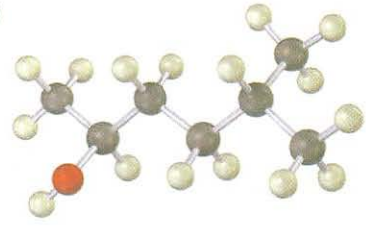


■ Assignable in OWL

17.21 ■ Draw the structure of the carbonyl compound(s) from which each of the following alcohols might have been prepared, and show the products you would obtain by treatment of each alcohol with (i) Na metal, (ii) $SOCl_2$, and (iii) pyridinium chlorochromate.

(a)



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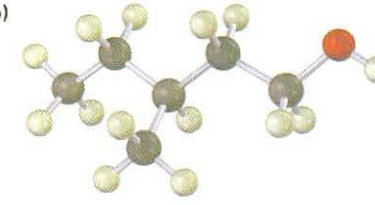
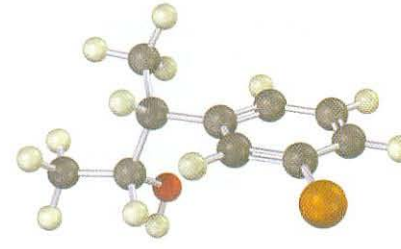


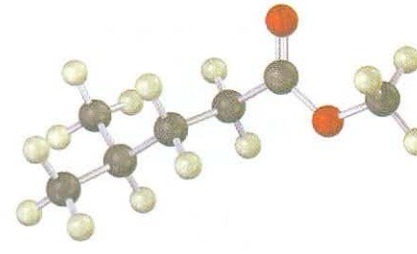
17.22 ■ Predict the product from reaction of the following substance (reddish brown = Br) with:

(a) PBr_3 (b) Aqueous H_2SO_4 (c) $SOCl_2$
(d) PCC (e) Br_2, $FeBr_3$

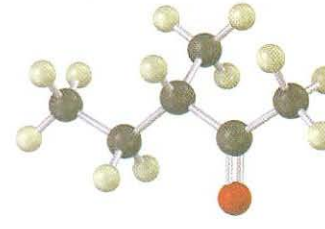


17.23 ■ Predict the product from reaction of the following substance with:

(a) $NaBH_4$; then H_3O^+ (b) $LiAlH_4$; then H_3O^+
(c) CH_3CH_2MgBr; then H_3O^+



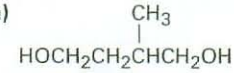
17.24 Name and assign *R* or *S* stereochemistry to the product(s) you would obtain by reaction of the following substance with ethylmagnesium bromide. Is the product chiral? Is it optically active? Explain.

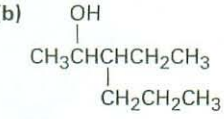


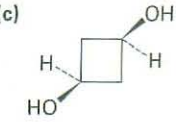
■ Assignable in OWL

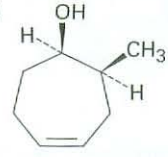
ADDITIONAL PROBLEMS

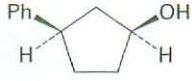
17.25 ■ Give IUPAC names for the following compounds:

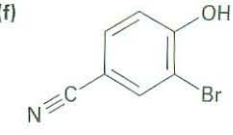
(a) 

(b) 

(c) 

(d) 

(e) 

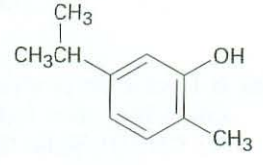
(f) 

17.26 Draw and name the eight isomeric alcohols with formula $C_5H_{12}O$.

17.27 Which of the eight alcohols you identified in Problem 17.26 react with CrO_3 in aqueous acid? Show the products you would expect from each reaction.

17.28 Named *bombykol*, the sex pheromone secreted by the female silkworm moth has the formula $C_{16}H_{28}O$ and the systematic name (10*E*,12*Z*)-10,12-hexadecadien-1-ol. Draw bombykol showing correct geometry for the two double bonds.

17.29 *Carvacrol* is a naturally occurring substance isolated from oregano, thyme, and marjoram. What is its IUPAC name?



Carvacrol

17.30 ■ What products would you obtain from reaction of 1-pentanol with the following reagents?

(a) PBr_3 (b) $SOCl_2$ (c) CrO_3, H_2O, H_2SO_4 (d) PCC

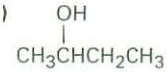
17.31 ■ How would you prepare the following compounds from 2-phenylethanol? More than one step may be required.

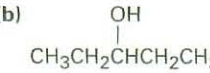
(a) Styrene ($PhCH{=}CH_2$)
(b) Phenylacetaldehyde ($PhCH_2CHO$)
(c) Phenylacetic acid ($PhCH_2CO_2H$)
(d) Benzoic acid
(e) Ethylbenzene
(f) Benzaldehyde
(g) 1-Phenylethanol
(h) 1-Bromo-2-phenylethane

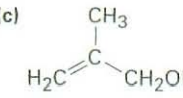
17.32 ■ How would you prepare the following compounds from 1-phenylethanol? More than one step may be required.

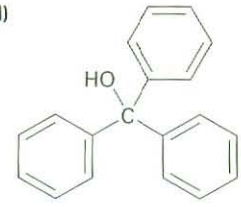
(a) Acetophenone ($PhCOCH_3$)
(b) Benzyl alcohol
(c) *m*-Bromobenzoic acid
(d) 2-Phenyl-2-propanol

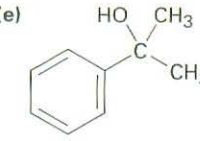
17.33 ■ What Grignard reagent and what carbonyl compound might you start wit to prepare the following alcohols?

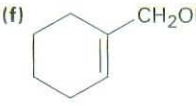
(a) 

(b) 

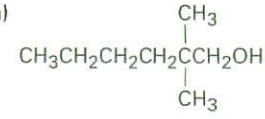
(c) 

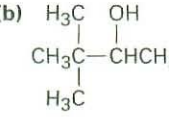
(d) 

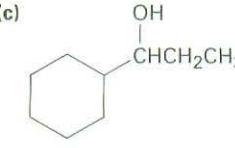
(e) 

(f) 

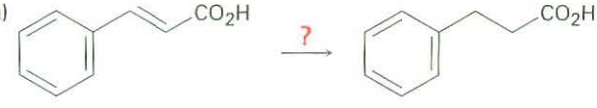
17.34 What carbonyl compounds would you reduce to prepare the following alcohols? List all possibilities.

(a) 

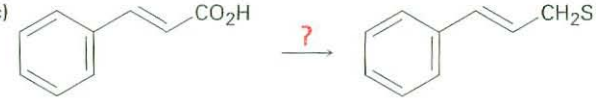
(b) 

(c) 

17.35 ■ How would you carry out the following transformations?

(a) 

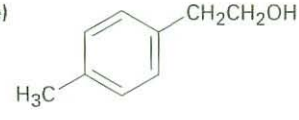
(b) 

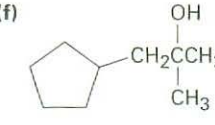
(c) 

17.36 ■ What carbonyl compounds might you start with to prepare the following compounds by Grignard reaction? List all possibilities.

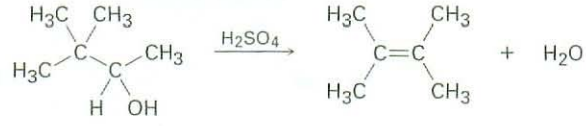
(a) 2-Methyl-2-propanol **(b)** 1-Ethylcyclohexanol

(c) 3-Phenyl-3-pentanol **(d)** 2-Phenyl-2-pentanol

(e) 

(f) 

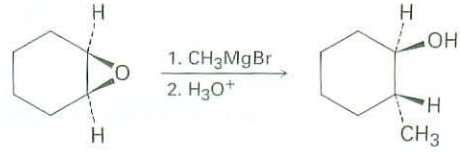
17.37 ■ Evidence for the intermediate carbocations in the acid-catalyzed dehydration of alcohols comes from the observation that rearrangements sometimes occur. Propose a mechanism to account for the formation of 2,3-dimethyl-2-butene from 3,3-dimethyl-2-butanol.



17.38 ■ Acid-catalyzed dehydration of 2,2-dimethylcyclohexanol yields a mixture of 1,2-dimethylcyclohexene and isopropylidenecyclopentane. Propose a mechanism to account for the formation of both products.

Isopropylidenecyclopentane

17.39 Epoxides react with Grignard reagents to yield alcohols. Propose a mechanism.



17.40 ■ How would you prepare the following substances from cyclopentanol? More than one step may be required.

(a) Cyclopentanone **(b)** Cyclopentene
(c) 1-Methylcyclopentanol **(d)** *trans*-2-Methylcyclopentanol

17.41 ■ What products would you expect to obtain from reaction of 1-methylcyclohexanol with the following reagents?

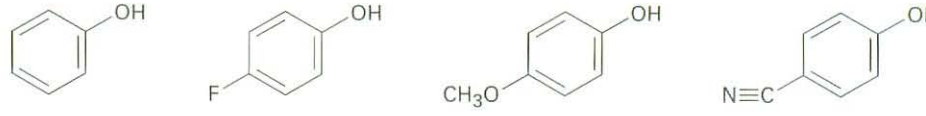
(a) HBr **(b)** NaH **(c)** H_2SO_4 **(d)** $Na_2Cr_2O_7$

17.42 Treatment of the following epoxide with aqueous acid produces a carbocation intermediate that reacts with water to give a diol product. Show the structure of the carbocation, and propose a mechanism for the second step.

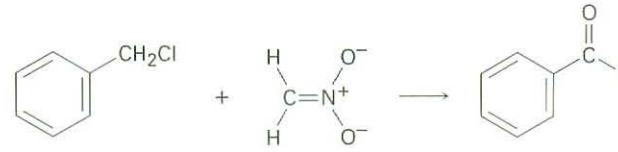
■ Assignable in OWL

17.43 Benzoquinone is an excellent dienophile in the Diels–Alder reaction. What product would you expect from reaction of benzoquinone with 1 equivalent of 1,3-butadiene? From reaction with 2 equivalents of 1,3-butadiene?

17.44 ■ Rank the following substituted phenols in order of increasing acidity, and explain your answer:



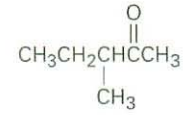
17.45 Benzyl chloride can be converted into benzaldehyde by treatment with nitromethane and base. The reaction involves initial conversion of nitromethane into its anion, followed by S_N2 reaction of the anion with benzyl chloride and subsequent E2 reaction. Write the mechanism in detail, using curved arrows to indicate the electron flow in each step.



Benzyl chloride **Nitromethane anion** **Benzaldehyde**

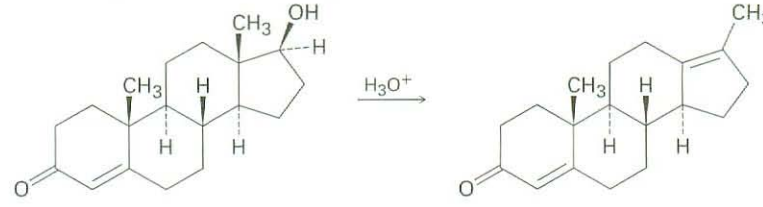
17.46 Reduction of 2-butanone with $NaBH_4$ yields 2-butanol. Is the product chiral? Is it optically active? Explain.

17.47 Reaction of (*S*)-3-methyl-2-pentanone with methylmagnesium bromide followed by acidification yields 2,3-dimethyl-2-pentanol. What is the stereochemistry of the product? Is the product optically active?



3-Methyl-2-pentanone

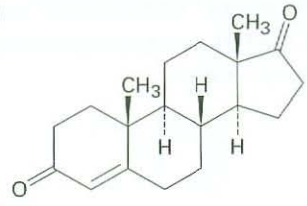
17.48 ■ Testosterone is one of the most important male steroid hormones. When testosterone is dehydrated by treatment with acid, rearrangement occurs to yield the product shown. Propose a mechanism to account for this reaction.



Testosterone

17.49 Starting from testosterone (Problem 17.48), how would you prepare the following substances?

(a)



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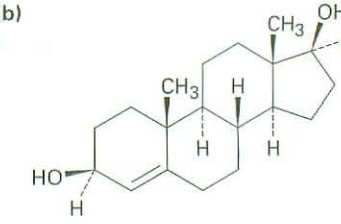

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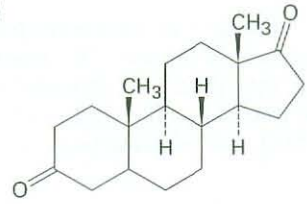
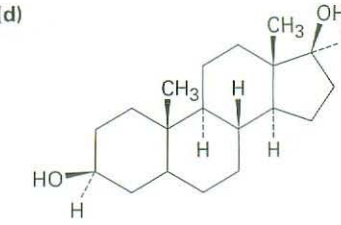


(d)

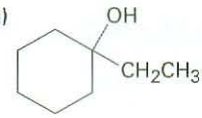


17.50 Compound A, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at 25 °C to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, **B**, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Write the reactions involved, and identify A and B.

17.51 Dehydration of *trans*-2-methylcyclopentanol with $POCl_3$ in pyridine yields predominantly 3-methylcyclopentene. Is the stereochemistry of this dehydration syn or anti? Can you suggest a reason for formation of the observed product? (Make molecular models!)

17.52 How would you synthesize the following alcohols, starting with benzene and other alcohols of six or fewer carbons as your only organic reagents?

(a)



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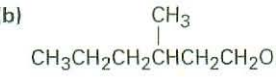
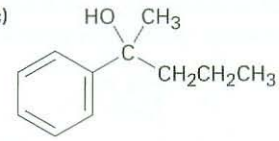
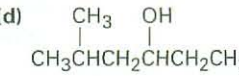


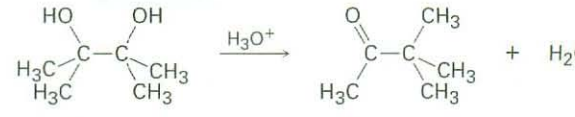
(c)



(d)



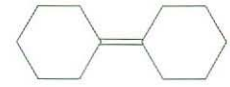
17.53 ■ 2,3-Dimethyl-2,3-butanediol has the common name *pinacol*. On heating with aqueous acid, pinacol rearranges to *pinacolone*, 3,3-dimethyl-2-butanone. Suggest a mechanism for this reaction.



Pinacol **Pinacolone**

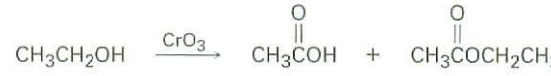
17.54 As a rule, axial alcohols oxidize somewhat faster than equatorial alcohols. Which would you expect to oxidize faster, *cis*-4-*tert*-butylcyclohexanol or *trans*-4-*tert*-butylcyclohexanol? Draw the more stable chair conformation of each molecule.

17.55 Propose a synthesis of bicyclohexylidene, starting from cyclohexanone as the only source of carbon.

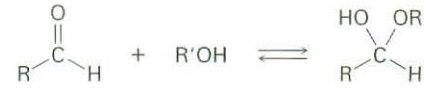


Bicyclohexylidene

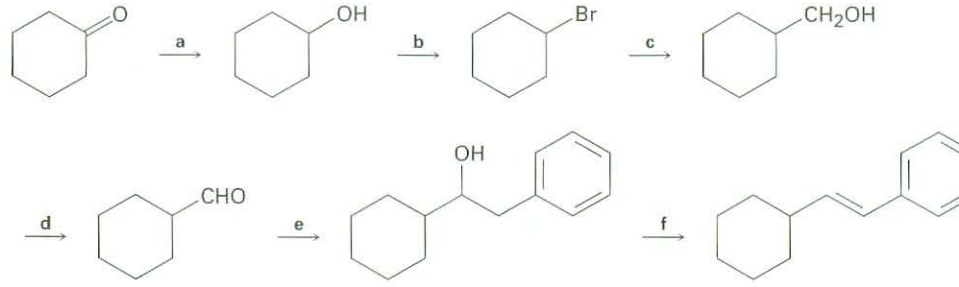
17.56 A problem often encountered in the oxidation of primary alcohols to acids is that esters are sometimes produced as by-products. For example, oxidation of ethanol yields acetic acid and ethyl acetate:



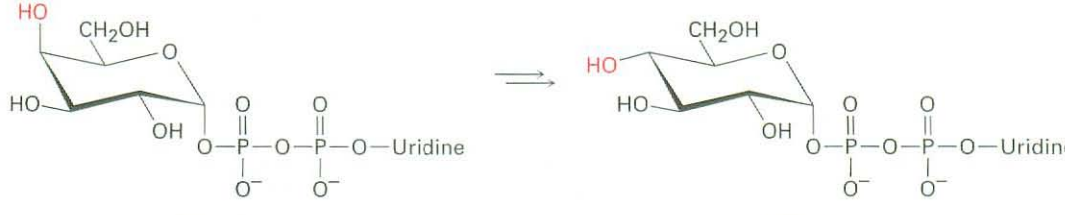
Propose a mechanism to account for the formation of ethyl acetate. Take into account the reversible reaction between aldehydes and alcohols:



17.57 Identify the reagents **a**–**f** in the following scheme:



17.58 Galactose, a constituent of the disaccharide lactose found in dairy products, is metabolized by a pathway that includes the isomerization of UDP-galactose to UDP-glucose, where UDP = uridylyl diphosphate. The enzyme responsible for the transformation uses NAD^+ as cofactor. Propose a mechanism.



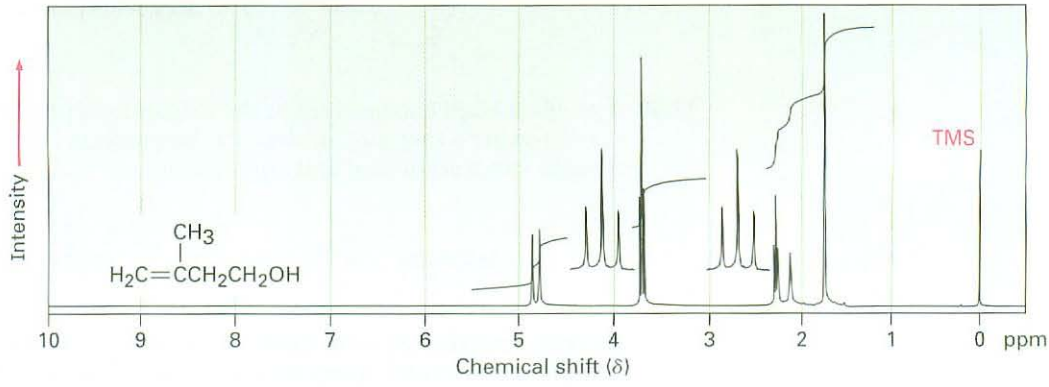
UDP-galactose **UDP-glucose**

17.59 ■ Propose a structure consistent with the following spectral data for a compound $C_8H_{18}O_2$:

IR: 3350 cm^{-1}

^1H NMR: 1.24 δ (12 H, singlet); 1.56 δ (4 H, singlet); 1.95 δ (2 H, singlet)

17.60 The ^1H NMR spectrum shown is that of 3-methyl-3-buten-1-ol. Assign all the observed resonance peaks to specific protons, and account for the splitting patterns.



17.61 ■ Compound A, $C_5H_{10}O$, is one of the basic building blocks of nature. All steroids and many other naturally occurring compounds are built from compound A. Spectroscopic analysis of A yields the following information:

IR: 3400 cm^{-1}; 1640 cm^{-1}

^1H NMR: 1.63 δ (3 H, singlet); 1.70 δ (3 H, singlet); 3.83 δ (1 H, broad singlet); 4.15 δ (2 H, doublet, J = 7 Hz); 5.70 δ (1 H, triplet, J = 7 Hz)

(a) How many double bonds and/or rings does A have?
(b) From the IR spectrum, what is the identity of the oxygen-containing functional group?
(c) What kinds of protons are responsible for the NMR absorptions listed?
(d) Propose a structure for A.

17.62 ■ A compound of unknown structure gave the following spectroscopic data:

Mass spectrum: M^+ = 88.1

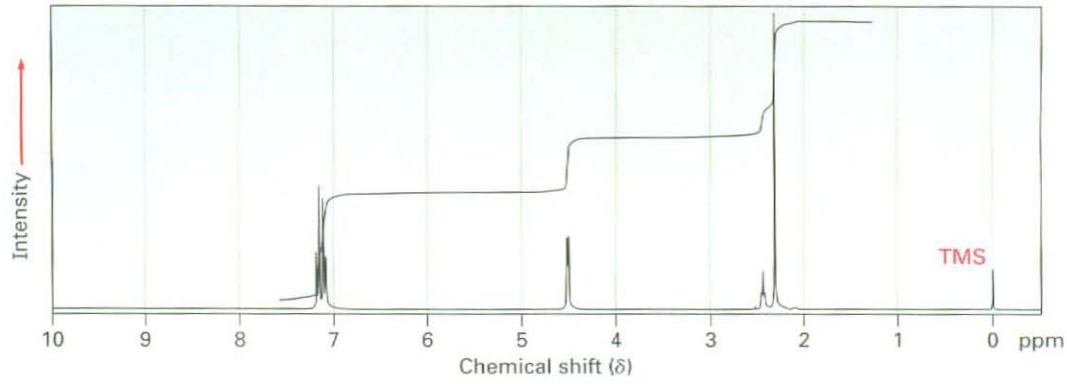
IR: 3600 cm^{-1}

^1H NMR: 1.4 δ (2 H, quartet, J = 7 Hz); 1.2 δ (6 H, singlet); 1.0 δ (1 H, singlet); 0.9 δ (3 H, triplet, J = 7 Hz)

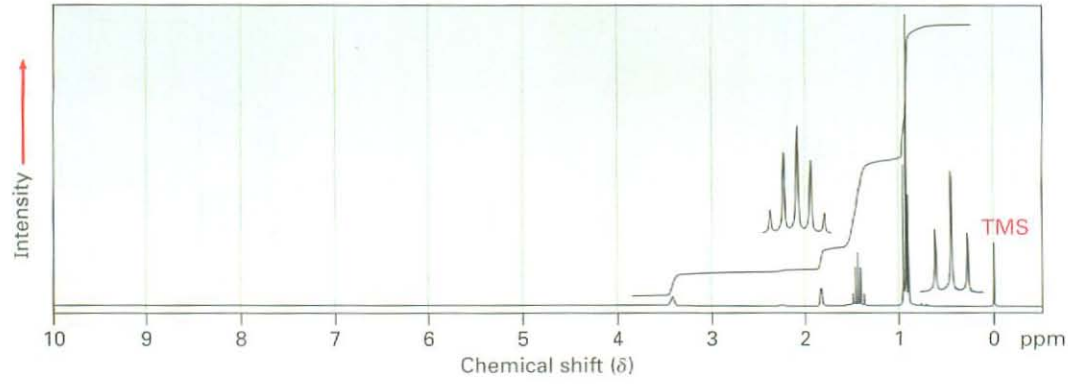
^{13}C NMR: 74, 35, 27, 25 δ

(a) Assuming that the compound contains C and H but may or may not contain O, give three possible molecular formulas.
(b) How many protons (H) does the compound contain?
(c) What functional group(s) does the compound contain?
(d) How many carbons does the compound contain?
(e) What is the molecular formula of the compound?
(f) What is the structure of the compound?
(g) Assign the peaks in the ^1H NMR spectrum of the molecule to specific protons.

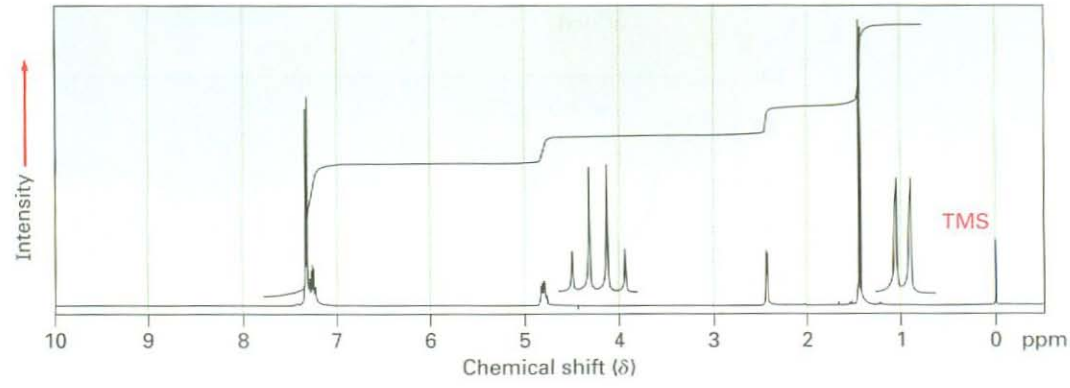
17.63 ■ The following ^{1}H NMR spectrum is that of an alcohol, $C_8H_{10}O$. Propose a structure.



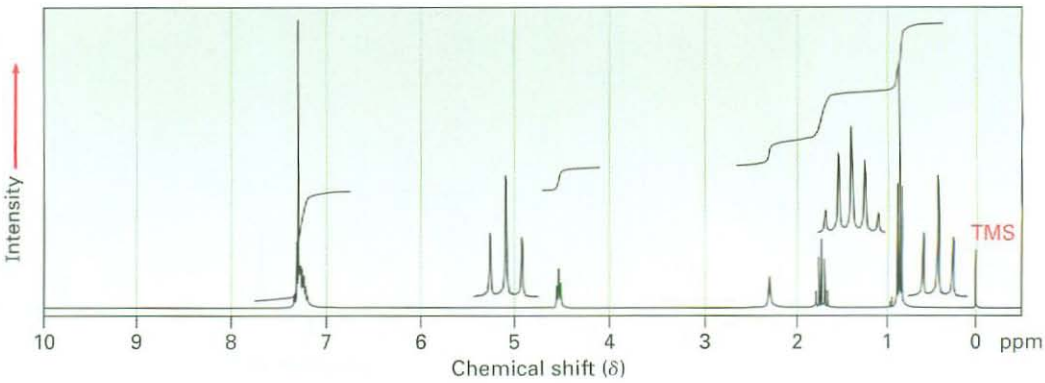
17.64 ■ Propose structures for alcohols that have the following ^{1}H NMR spectra:
(a) $C_5H_{12}O$



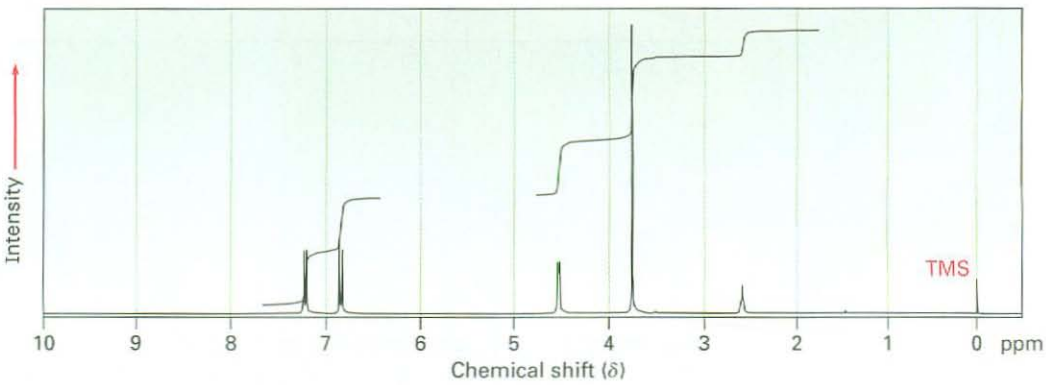
(b) $C_8H_{10}O$



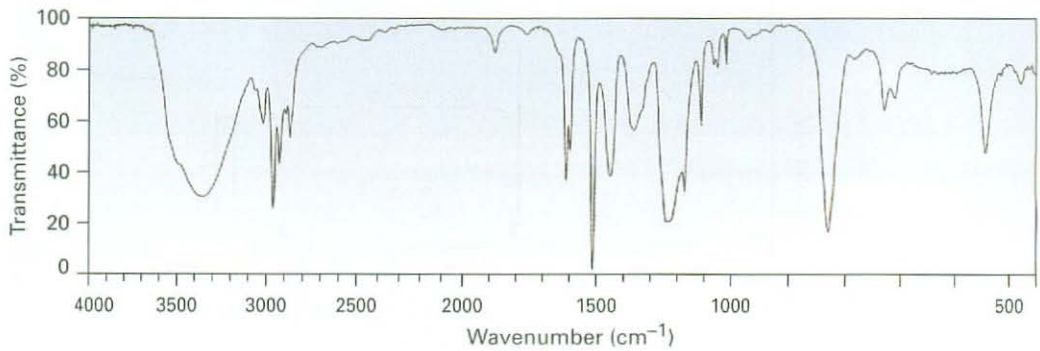
17.65 ■ Propose structures for alcohols that have the following ^{1}H NMR spectra:
(a) $C_9H_{12}O$



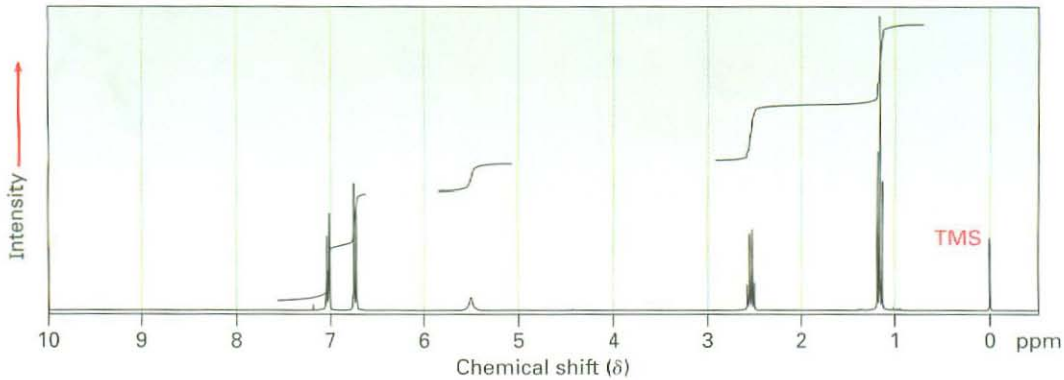
(b) $C_8H_{10}O_2$



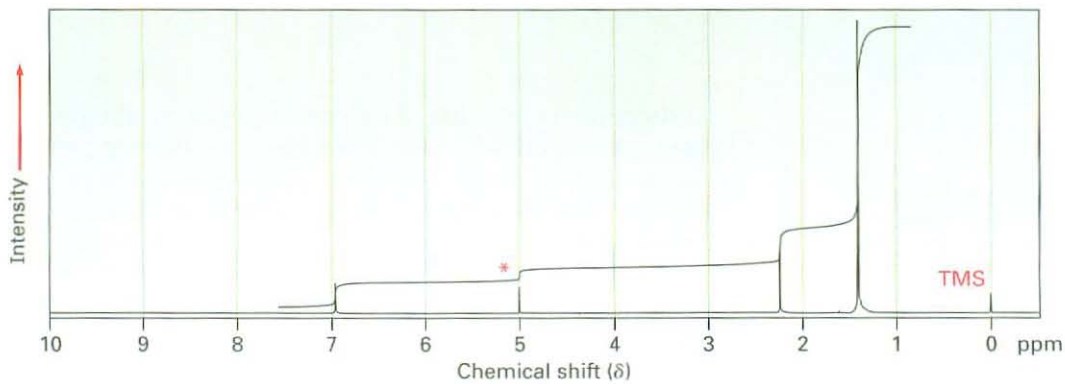
17.66 ■ Compound A, $C_8H_{10}O$, has the IR and ^{1}H NMR spectra shown. Propose a structure consistent with the observed spectra, and assign each peak in the NMR spectrum. Note that the absorption at 5.5 δ disappears when D_2O is added.



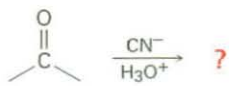
■ Assignable in OWL



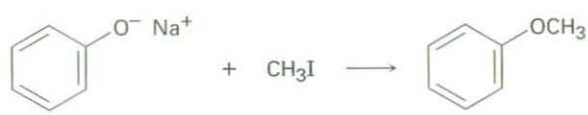
17.67 ■ Propose a structure for a compound $C_{15}H_{24}O$ that has the following ^1H NMR spectrum. The peak marked by an asterisk disappears when D_2O is added to the sample.



17.68 The reduction of carbonyl compounds by reaction with hydride reagents ($H:^-$) and the Grignard addition by reaction with organomagnesium halides ($R:^-\ ^+MgBr$) are examples of *nucleophilic carbonyl addition reactions*. What analogous product do you think might result from reaction of cyanide ion with a ketone?



17.69 Ethers can be prepared by reaction of an alkoxide or phenoxide ion with a primary alkyl halide. Anisole, for instance, results from reaction of sodium phenoxide with iodomethane. What kind of reaction is occurring? Show the mechanism.



Sodium phenoxide **Anisole**

■ Assignable in OWL