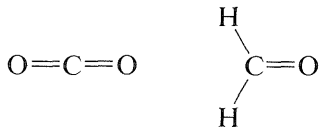
16

CARBONYL COMPOUNDS I. ALDEHYDES AND KETONES. ADDITION REACTIONS OF THE CARBONYL GROUP

The carbonyl group,  is a structural feature of many different types of compounds. It is present in carbon dioxide and in methanal, which represent respectively the high and low extremes in the level of oxidation of a carbonyl carbon:

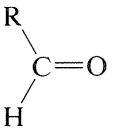


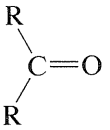
carbon dioxide

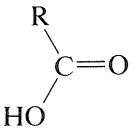
methanal

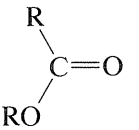
In between, there are carbonyl compounds ranging from aldehydes and ketones to carboxylic acids and their derivatives (esters, amides, anhydrides, and acyl

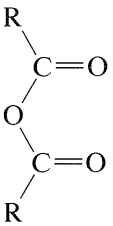
halides). The naming of these compounds is described in Sections 7-4 to 7-7.

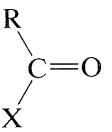

aldehyde

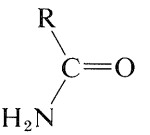

ketone


carboxylic acid

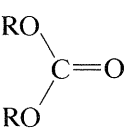

carboxylic ester

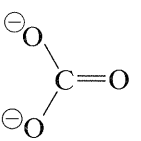

carboxylic anhydride

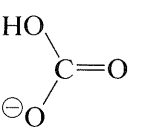

X = F, Cl, Br, I acyl halide

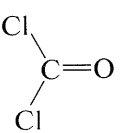

amide

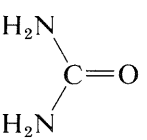
At the upper end of the oxidation scale, along with CO_2, are the carbonic acid derivatives such as carbonic esters, amides, halides, and carbonate salts, and isocyanates:

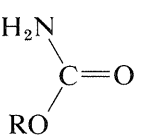

carbonic ester

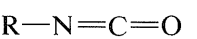

carbonate


bicarbonate


carbonyl chloride (phosgene)


carbonyl diamide (urea)

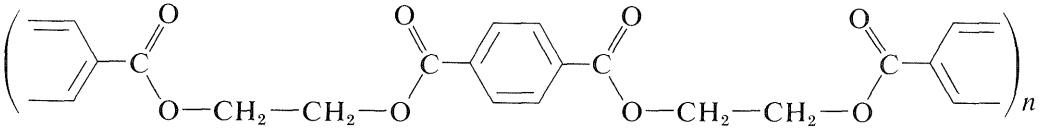

carbamic ester


isocyanate

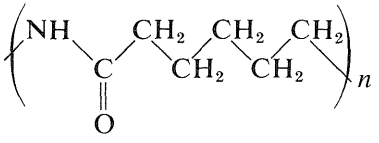
In this and succeeding chapters we describe the chemistry of these compounds with the intent of emphasizing the similarities that exist between them. The differences turn out to be more in degree than in kind. Even so, it is convenient to discuss aldehydes and ketones separately from carboxylic acids and, following some general observations about the carbonyl group, this chapter mainly is concerned with aldehydes and ketones.

Apart from CO_2 and metal carbonates, the most abundant carbonyl compounds of natural origin are carboxylic esters and amides. These occur as fats and lipids, which are esters of long-chain alkanoic acids (pp. 789–791), and as proteins, which are polyamides of natural amino acids. The same struc-

tural features are found in certain synthetic polymers, in particular the polyesters (e.g., Dacron) and the polyamides (e.g., nylon 6):



Dacron (polyester)



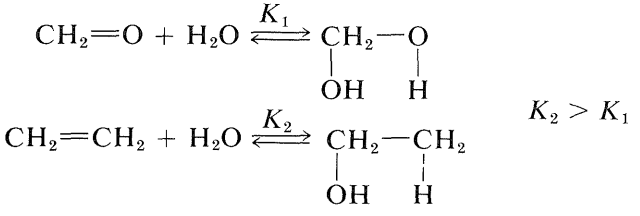
nylon 6 (polyamide)

Compared to carboxylic and carbonic acid derivatives, the less highly oxidized carbonyl compounds such as aldehydes and ketones are not so widespread in nature. That is not to say that they are unimportant. To the contrary. Aldehydes and ketones are of great importance both in biological chemistry and in synthetic organic chemistry. However, the high reactivity of the carbonyl group in these compounds enables them to function more as intermediates in metabolism or in synthesis than as end products. This fact will become evident as we discuss the chemistry of aldehydes and ketones. Especially important are the *addition* reactions of carbonyl groups, and this chapter is mostly concerned with this kind of reaction of aldehydes and ketones.

16-1 THE CARBONYL BOND

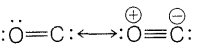
16-1A Comparison with Carbon–Carbon Double Bonds

The carbonyl bond is both a strong bond and a reactive bond. The bond energy varies widely with structure, as we can see from the carbonyl bond energies in Table 16-1. Methanal has the weakest bond (166 kcal) and carbon monoxide the strongest (257.3 kcal). Irrespective of these variations, the carbonyl bond not only is significantly *stronger* but also is *more reactive* than a carbon–carbon double bond. A typical difference in stability and reactivity is seen in hydration:



$K_2 > K_1$

Table 16-1
Carbonyl Bond Energies

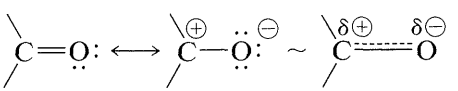
Compounds	Bond energy (kcal mole^{-1})
	257.3
O=C=O	192.0[a]
H_2C=O	166.0
H_2C=C=O	184.8
RCH=O (aldehydes)	176
R_2C=O (ketones)	179
 (alkenes)	146

[a]Average of ΔH^0 for breaking both of the C=O bonds.

The equilibrium constant for ethene hydration is considerably greater than for methanal hydration, largely because the carbon–carbon double bond is *weaker*. Even so, methanal adds water rapidly and reversibly at room temperature without need for a catalyst. The corresponding addition of water to ethene occurs only in the presence of strongly acidic catalysts (Section 10-3E, Table 15-2).

16-1B Structure and Reactivity

The reactivity of the carbonyl bond is primarily due to the difference in electronegativity between carbon and oxygen, which leads to a considerable contribution of the dipolar resonance form with oxygen negative and carbon positive:



In terms of an atomic-orbital description, the carbonyl bond can be represented as shown in Figure 16-1. The carbon is sp^2-hybridized so that its σ bonds (one of which is to oxygen) lie in one plane. The remaining p orbital on carbon is utilized to form a π bond to oxygen. The polarity of the carbon–

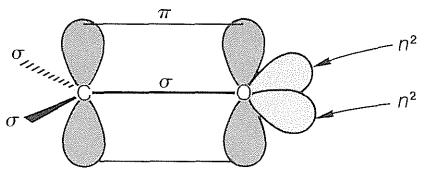


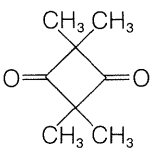
Figure 16-1 Atomic-orbital description of the carbonyl group. The σ bonds to carbon are coplanar, at angles near to 120°; the two pairs of unshared electrons on oxygen are shown as occupying orbitals *n*.

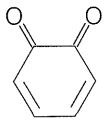
oxygen double bond implies that the electrons of the π bond (and also the σ bond) are associated more with oxygen than with carbon. This is supported by the dipole moments[1] of aldehydes and ketones, which indicate the degree of the polarization of the C=O bonds; the dipole moments are in the neighborhood of 2.7 D, which corresponds to 40–50% ionic character for the carbonyl bond.

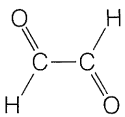
Exercise 16-1 Draw valence-bond structures and an atomic-orbital model for carbon monoxide. Why can the bond energy of this molecule be expected to be higher than for other carbonyl compounds (see Table 16-1)? Explain why the dipole moment of CO is very small (0.13 debye)..

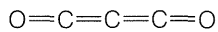
[1]An electrical dipole results when unlike charges are separated. The magnitude of the dipole, its **dipole moment,** is given by $e \times r$, where e is the magnitude of the charges and r is the distance the charges are separated. Molecular dipole moments are measured in debye units (D). A pair of ions, $\overset{\oplus}{C}$ and $\overset{\ominus}{O}$, as *point charges* at the C=O distance of 1.22 A, would have a dipole moment of 5.9 D. Thus, if the dipole moment of a carbonyl compound is 2.7 D, we can estimate the "% ionic character" of the bond to be (2.7/5.9) $\times$ 100 = 46%. The analysis is oversimplified in that the charges on the atom are not point charges and we have assumed that all of the ionic character of the molecule is associated with the C=O bond. One should be cautious in interpreting dipole moments in terms of the ionic character of bonds. Carbon dioxide has *no* dipole moment, but certainly has polar C=O bonds. The problem is that the dipoles associated with the C=O bonds of CO_2 are equal and *opposite in direction* to each other and, as a result, cancel. Thus, $\overset{\delta\ominus}{O}\!\!-\!\!-\overset{2\delta\oplus}{C}\!\!-\!\!-\overset{\delta\ominus}{O}$ has no *net* dipole moment, even though it has highly polar bonds.

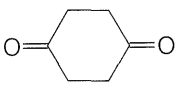
Exercise 16-2 Which of the following compounds would you expect to have zero or nearly zero dipole moments? Give your reasoning and don't forget possible conformational equilibria. (Models will be helpful.)

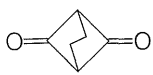




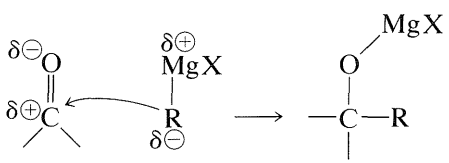








The polarity of the carbonyl bond facilitates addition of water and other polar reagents relative to addition of the same reagents to alkene double bonds. This we have seen previously in the addition of organometallic compounds $R{-}MgX$ and $R{-}Li$ to carbonyl compounds (Section 14-12A). Alkene double bonds are normally untouched by these reagents:



Likewise, alcohols add readily to carbonyl compounds, as described in Section 15-4E. However, we must keep in mind the possibility that, whereas additions to carbonyl groups may be rapid, the equilibrium constants may be small because of the strength of the carbonyl bond.

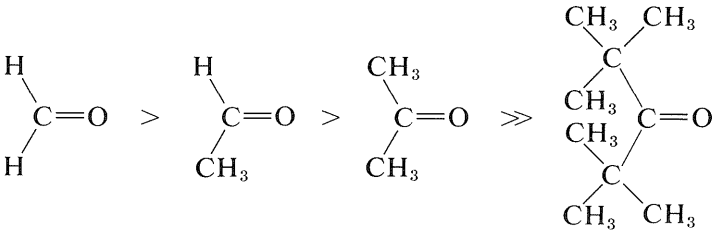
Exercise 16-3 The foregoing discussion explicitly refers to addition of *polar* reagents to carbonyl groups. Therefore an ionic mechanism is implied. Consider whether the same reactivity differences would be expected for ethene and methanal in the *radical-chain* addition of hydrogen bromide to methanal and ethene initiated by peroxides. What about the relative equilibrium constants? Show your reasoning. (Review Section 10-7.)

$H_2C{=}O + HBr \longrightarrow BrCH_2{-}OH$

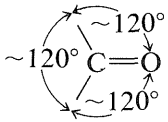
$H_2C{=}CH_2 + HBr \longrightarrow BrCH_2{-}CH_3$

16-1C Further Considerations of Reactivity

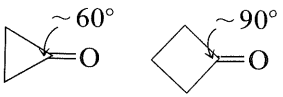
The important reactions of carbonyl groups characteristically involve addition at one step or another. For the reactions of organometallic reagents and alcohols with carbonyl compounds (Chapters 14 and 15), you may recall that steric hindrance plays an important role in determining the ratio between addition and other, competing reactions. Similar effects are observed in a wide variety of other reactions. We expect the reactivity of carbonyl groups in addition processes to be influenced by the size of the substituents thereon, because when addition occurs the substituent groups are pushed back closer to one another. In fact, reactivity and equilibrium constant decrease with increasing bulkiness of substituents, as in the following series (also see Table 15-3):



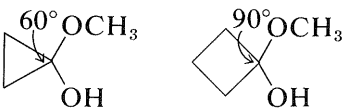
Strain effects also contribute to reactivity of cyclic carbonyl compounds. The normal bond angles around a carbonyl group are about 120°:



Consequently if the carbonyl group is on a small carbocyclic ring, there will be substantial angle strain and this will amount to about 120° − 60° = 60° of strain for cyclopropanone,

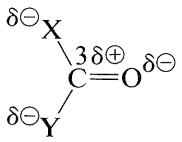


and 120° − 90° = 30° of strain for cyclobutanone (both values being for the ∠C—C—C at the carbonyl group). Addition of a nucleophile such as CH_3OH (cf. Section 15-4E) to these carbonyl bonds creates a tetrahedral center with less strain in the ring bonds to C1:



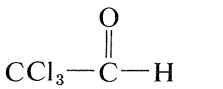
Thus the hemiketal from cyclopropanone will have $109.5° - 60° = 49.5°$, and that from cyclobutanone $109.5° - 90° = 19.5°$ of strain at C1. This change in the angle strain means that a sizable enhancement of *both* the reactivity and equilibrium constant for addition is expected. In practice, the strain effect is so large that cyclopropanone reacts rapidly with methanol to give a stable hemiketal from which the ketone cannot be recovered. Cyclobutanone is less reactive than cyclopropanone but more reactive than cyclohexanone or cyclopentanone.

Electrical effects also are important in influencing the ease of addition to carbonyl groups. Electron-attracting groups facilitate the addition of nucleophilic reagents to carbon by increasing its positive character:

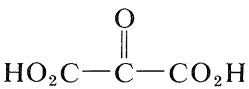


(X, Y, and O represent atoms that are electronegative relative to carbon in a hydrocarbon, Section 10-4B)

Thus compounds such as the following add nucleophilic reagents readily:



trichloroethanal (chloral)



oxopropanedioic acid (oxomalonic acid)

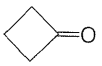
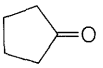
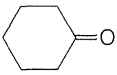
Exercise 16-4 Which compound in each of the following pairs would you expect to be more reactive toward addition of a common nucleophilic agent such as hydroxide ion to the carbonyl bond? Indicate your reasoning.

a. 2-propanone and 1,1,1-trichloro-2-propanone
b. 2,2-dimethylpropanal and 2-propanone
c. methyl 2-oxopropanoate and methyl 3-oxobutanoate
d. 2-propanone and 2,3-butanedione
e. 2-oxopropanenitrile and 2-propanone
f. ketene ($CH_2{=}C{=}O$) and cyclobutanone
g. bicyclo[2.1.1]-5-hexanone and cyclobutanone

16-2 PHYSICAL PROPERTIES

The polarity of the carbonyl group is manifest in the physical properties of carbonyl compounds. Boiling points for the lower members of a series of aldehydes and ketones are 50–80° *higher* than for hydrocarbons of the same molecular weight; this may be seen by comparing the data of Table 16-2 (physical

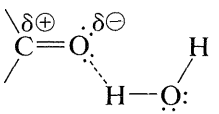
Table 16-2
Physical Properties of Aldehydes and Ketones

Compound	Formula	Mp, °C	Bp, °C	d_4^t, g ml^{-1}	Solubility in water[a]
methanal	CH_2O	−92	−21	0.815^{-20}	+
ethanal	CH_3CHO	−121	21	0.7951^{10}	+
propanal	CH_3CH_2CHO	−81	49	0.7966^{25}	+
2-propenal	$CH_2{=}CHCHO$	−87	52	0.8410^{20}	+
2-butenal	$CH_3CH{=}CHCHO$	−69	105	0.8575^{15}	+
butanal	$CH_3CH_2CH_2CHO$	−99	76	0.8170^{20}	sl.
2-methylpropanal	$(CH_3)_2CHCHO$	−66	64	0.7938^{20}	+
benzenecarbaldehyde (benzaldehyde)	C_6H_5CHO	−26	179	1.0504^{15}	v. sl.
2-propanone	CH_3COCH_3	−94	56	0.7899^{20}	+
2-butanone	$CH_3COCH_2CH_3$	−86	80	0.8054^{20}	+
3-buten-2-one	$CH_3COCH{=}CH_2$		80	0.8636^{20}	+
cyclobutanone			99	0.9548^{0}	+
cyclopentanone		−58.2	130	0.9480^{20}	+
cyclohexanone		−45	155	0.9478^{20}	+
4-methyl-3-penten-2-one	$(CH_3)_2C{=}CHCOCH_3$	−59	130	0.8653^{20}	+
phenylethanone (acetophenone)	$C_6H_5COCH_3$	20.5	202	1.0236^{25}	v. sl.
2,3-butanedione	$CH_3COCOCH_3$		88	0.9904^{15}	+
2,4-pentanedione	$CH_3COCH_2COCH_3$	−23	139^{746}	0.9721	+

[a]A plus sign means the compound is soluble; however, it may not be soluble in all proportions—*sl* means slightly soluble.

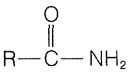
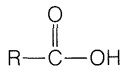
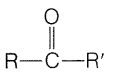
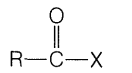
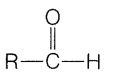
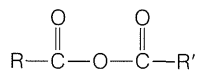
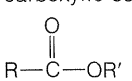
properties of aldehydes and ketones) with those in Table 4-1 (physical properties of alkanes).

The water solubility of the lower-molecular-weight aldehydes and ketones is pronounced (see Table 16-2). This is to be expected for most carbonyl compounds of low molecular weight and is the consequence of hydrogen-bonding between the water and the electronegative oxygen of the carbonyl group:



solvation of carbonyl compounds through hydrogen bonding

Table 16-3
Characteristic Infrared Absorption Frequencies of Carbonyl Compounds[a]

Functional group	Frequency (C=O stretch), cm^{-1}	Functional group	Frequency (C=O stretch), cm^{-1}
amides 	1680	carboxylic acids 	1710
ketones 	1715	acyl halides 	1800
aldehydes 	1725	carboxylic anhydrides 	1820 1760
carboxylic esters 	1735		

[a]The quoted frequencies are for typical open-chain saturated hydrocarbon chains (R). Conjugation and cyclic structures will influence the absorption frequency.

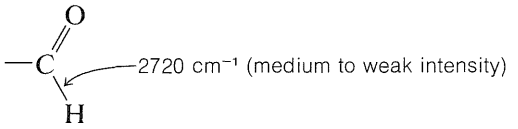
16-3 SPECTROSCOPIC PROPERTIES

16-3A Infrared Spectra

A carbonyl group in a compound can be positively identified by the strong infrared absorption band in the region 1650–1850 cm^{-1}, which corresponds to the stretching vibration of the carbon–oxygen double bond. The position of the band within this frequency range depends on the molecular environment of the carbonyl group. As a result, we frequently can tell from the band position whether the structure is an aldehyde, ketone, carboxylic acid, ester, amide, or anhydride. The data of Table 16-3 show typical infrared absorption

frequencies for specific types of carbonyl compounds. Thus aldehydes and ketones absorb at slightly lower frequencies (longer wavelengths) than carboxylic esters and anhydrides. We usually find that absorption shifts to lower frequencies ($\sim$20 cm^{-1}) when the carbonyl group is conjugated with other multiple bonds, as in aromatic ketones, $C_6H_5COCH_3$.

Aldehydes can be distinguished from ketones by a band at 2720 cm^{-1} which is characteristic of the C—H stretching vibration of an aldehyde function:



This band is unusually low in frequency for a C—H stretching vibration; although the band is rather weak, it occurs in a region of the spectrum where other absorptions generally are absent so it can be identified with no special difficulty.

Exercise 16-5 Use the infrared spectra given in Figure 16-2 (pp. 682–683) and the data of Tables 9-2 and 16-3 to deduce the type of carbonyl compound giving rise to each spectrum.

16-3B Electronic Absorption Spectra

Aldehydes and ketones absorb ultraviolet light in the region 275–295 nm, and the result is excitation of an unshared electron on oxygen to a higher energy level. This is the $n \longrightarrow \pi^*$ transition discussed in Section 9-9. A more intense $\pi \longrightarrow \pi^*$ transition occurs about 180–190 nm, which corresponds to excitation of an electron from a π-bonding orbital to a π-antibonding orbital. Neither of these absorptions is especially useful for specific identification unless the carbonyl group is conjugated, in which case the $n \longrightarrow \pi^*$ and $\pi \longrightarrow \pi^*$ bands occur at longer wavelengths (by 30–40 nm). For example, if you suspect that a compound is an *alkenone* from its infrared spectrum, you easily could tell from the λ_{max} of the $n \longrightarrow \pi^*$ and $\pi \longrightarrow \pi^*$ absorptions of the compound whether it is a conjugated alkenone. The absorption frequency would be expected around 320 nm and 220 nm (see Figure 9-20).

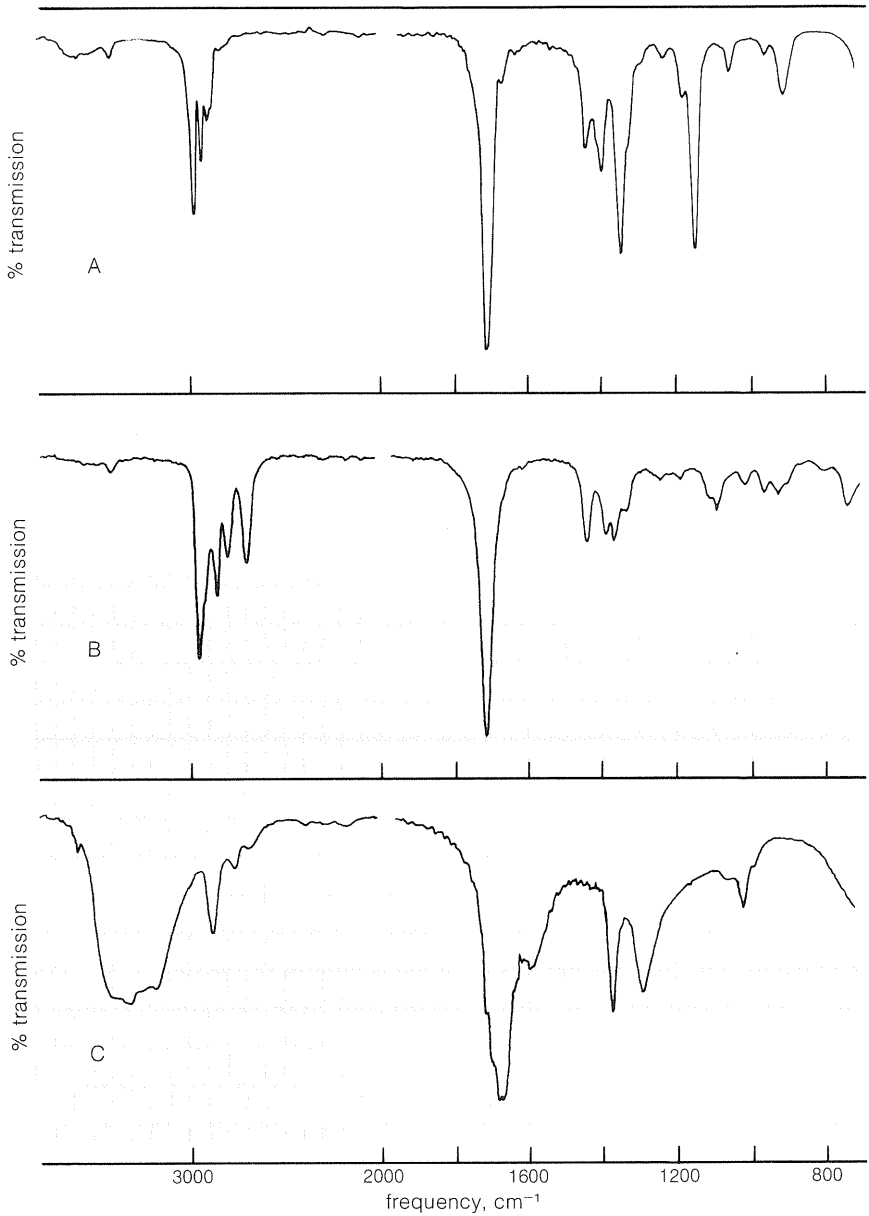
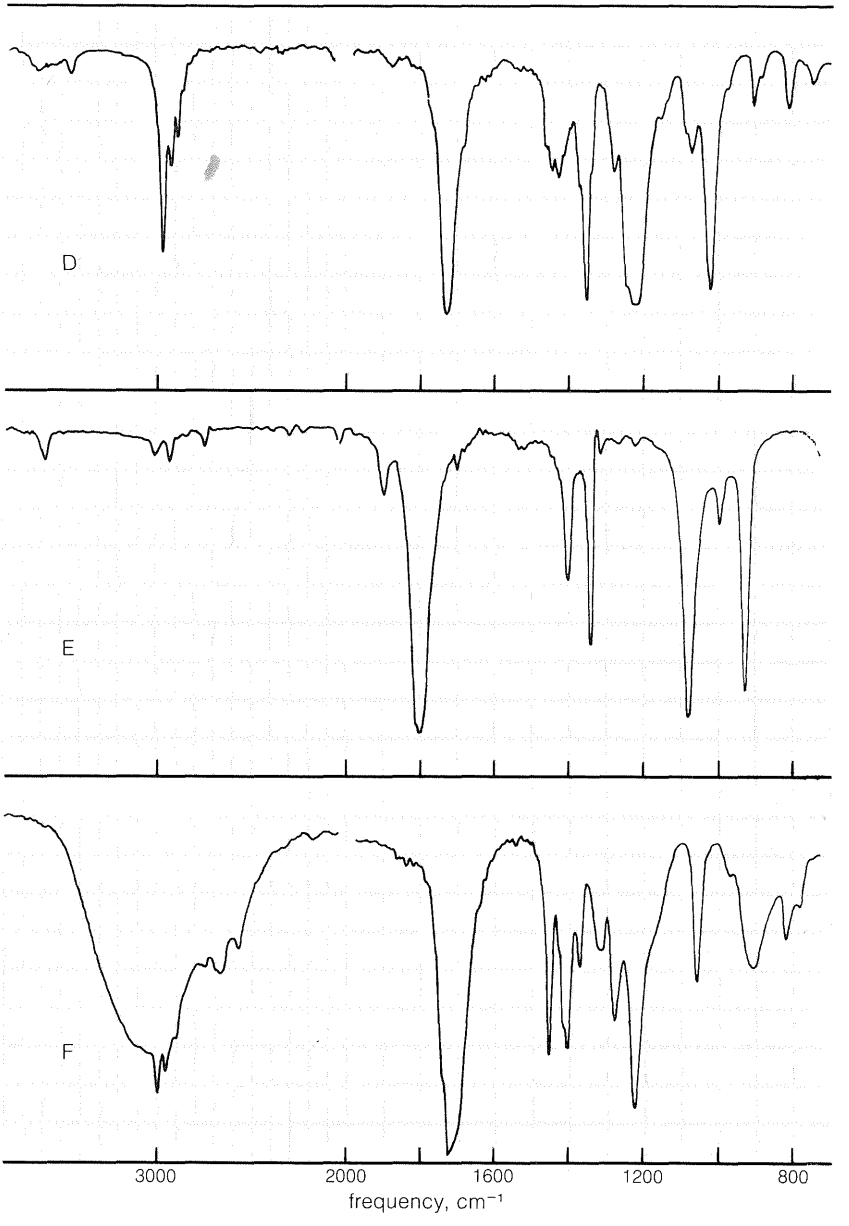


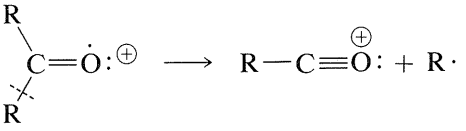
Figure 16-2 Infrared spectra for Exercise 16-5


D
E
F
3000
2000
1600
1200
800
frequency, cm⁻¹

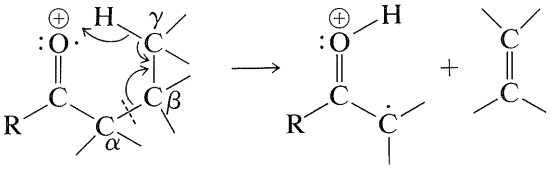
16-3C Mass Spectra

Aldehydes and ketones generally give moderately intense signals due to their molecular ions, M^+. Thus the determination of the molecular weight of a ketone by mass spectroscopy usually is not difficult. Furthermore, there are some characteristic fragmentation patterns that aid in structural identification. These are:

α cleavage



transfer of γ hydrogen with *β* cleavage (**McLafferty rearrangement**)



Exercise 16-6 A hydrocarbon isolated from a plant extract was treated with ozone, and the ozonide decomposed with zinc to give two ketones, A and B, which were readily separated by gas chromatography. Ketone A gave a mass spectrum identical with that of Figure 9-52c while ketone B gave mass spectral peaks at $m/e = 100$ (M^+), 85, 58, and 43. With this information, suggest possible structures for these ions and the parent hydrocarbon. Give your reasoning.

16-3D NMR Spectra

The character of the carbonyl bond gives rise to very low-field nmr absorptions for the proton of an aldehyde group (—CH=O). As Table 9-4 (pp. 308–309) shows, these absorptions are some 4 ppm to lower fields than alkenyl hydrogens (—CH=C<). Some of this difference in shift can be ascribed to the polarity of the carbonyl group $\overset{\delta\oplus\ \ \delta\ominus}{C{=}O}$, which reduces electron density around the aldehyde hydrogen (see Section 9-10E). The effect appears to carry over in much smaller degree to hydrogens in the α positions, and protons of the type $CH_3{-}\overset{|}{C}{=}O$ are about 0.3 ppm to lower fields than those of $CH_3{-}\overset{|}{C}{=}C<$.

Exercise 16-7 Show how structures can be deduced for the four substances with the infrared and nmr spectra shown in Figure 16-3 (pp. 686–687).

Exercise 16-8 Assuming that you had ready access to ultraviolet, infrared, nmr, and mass spectrometers, which spectral technique would you select to differentiate as unambiguously as possible between the following pairs of compounds? Give your reasoning in enough detail to show that you understand how well each technique is capable of distinguishing between the members of each pair. (D = hydrogen of mass 2)

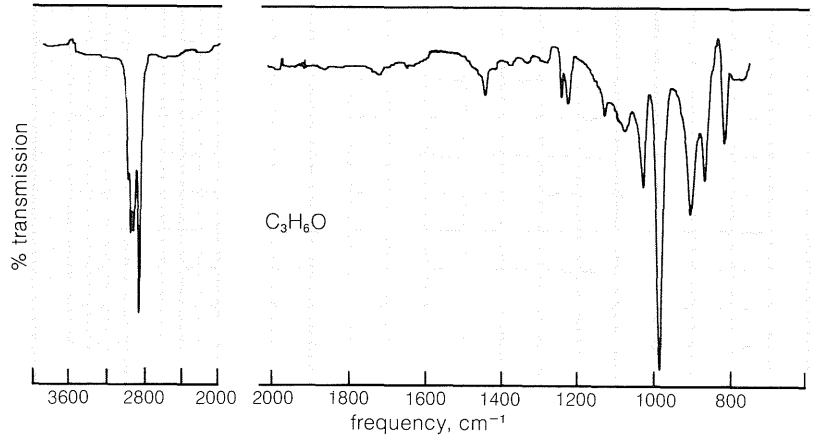
a. 2-butanone and 2-butanone-1-D_3
b. 3-cyclohexenone and 2-cyclohexenone
c. 4-penten-2-one and 4,4-dichloro-1-pentene
d. propanal and 2-butanone
e. 3-hexanone-6-D_3 and 3-hexanone-1-D_3

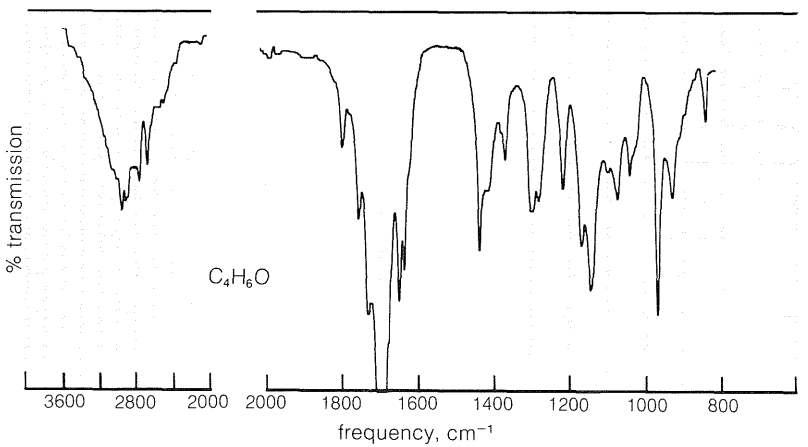
16-4 SOME TYPICAL CARBONYL-ADDITION REACTIONS

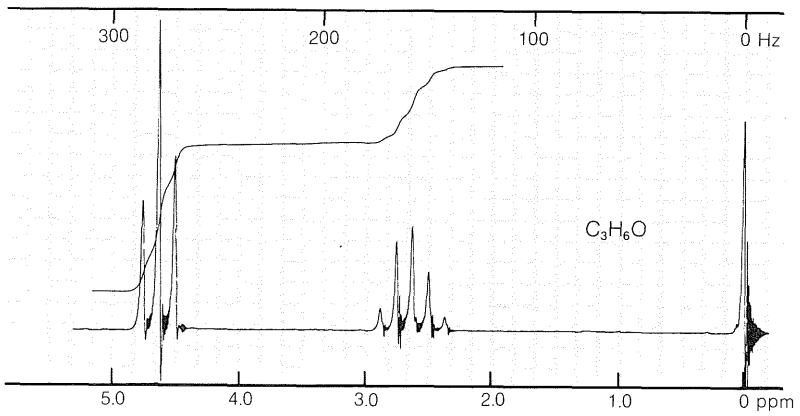
We turn now to discuss a few specific addition reactions of the carbonyl groups of aldehydes and ketones. We shall not attempt to provide an extensive catalog of reactions, but will try to emphasize the principles involved with especially important reactions that are useful in synthesis.

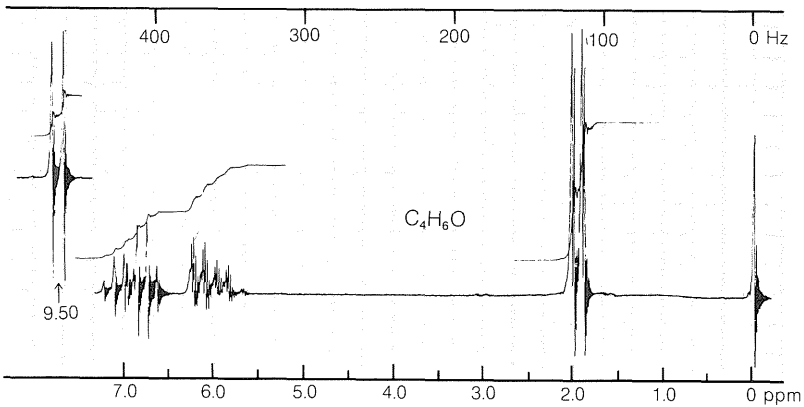
Grignard reagents, organolithium compounds, and the like generally add to aldehydes and ketones rapidly and irreversibly, but the same is not true of many other reagents; their addition reactions may require acidic or basic catalysts; the adducts may be formed reversibly and with relatively unfavorable equilibrium constants. Also, the initial adducts may be unstable and react further by elimination. (We recommend that you work Exercise 16-9 to see examples of these points, or review Section 15-4E.) To organize this very large number of addition reactions, we have arranged the reactions according to the nucleophile that adds to the carbonyl carbon. The types of nucleophiles considered here form C–C, C–O, C–N, C–halogen, C–S, and C–H bonds. A summary is given in Table 16-4 (pp. 688–689).

Exercise 16-9 Write equations to show the steps involved in the following carbonyl-addition reactions: (a) base-catalyzed addition of ethanol to ethanal to form the corresponding hemiacetal, 1-ethoxyethanol; (b) formation of 1-ethoxyethanol from ethanol and ethanal, but under conditions of acid catalysis; (c) formation of 1,1-diethoxyethane from 1-ethoxyethanol and ethanol with an acid catalyst; and (d) formation of diethyl carbonate $(CH_3CH_2O)_2C{=}O$ from ethanol and carbonyl dichloride.


% transmission
C_3H_6O
3600
2800
2000
2000
1800
1600
1400
1200
1000
800
frequency, cm⁻¹


% transmission
C_4H_6O
3600
2800
2000
2000
1800
1600
1400
1200
1000
800
frequency, cm⁻¹


300
200
100
0 Hz
C_3H_6O
5.0
4.0
3.0
2.0
1.0
0 ppm


400
300
200
100
0 Hz
C_4H_6O
9.50
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 ppm

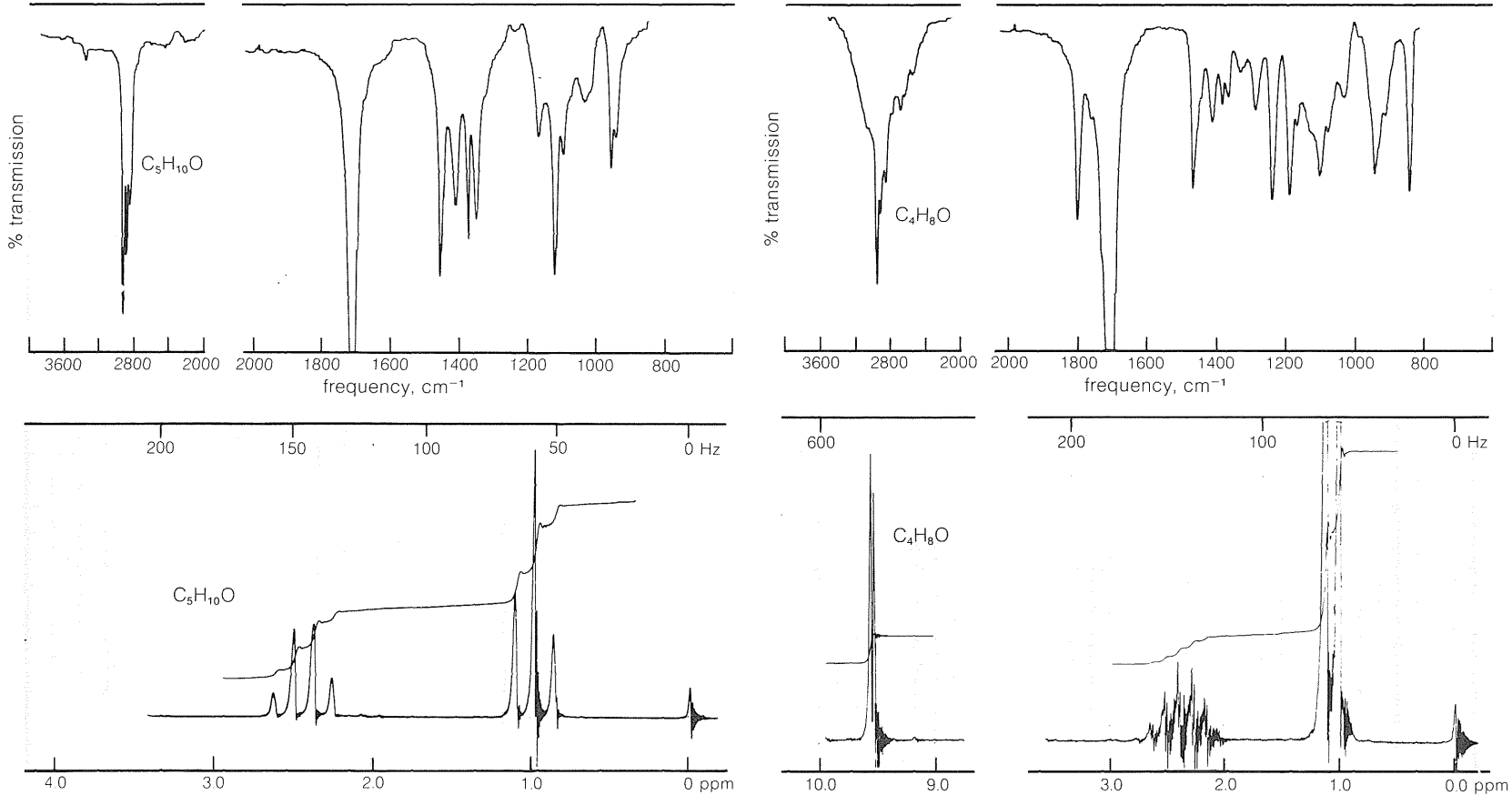


Figure 16-3 Infrared and proton nmr spectra of four organic compounds. See Exercise 16-7.

Table 16-4
Addition Reactions of Aldehydes and Ketones

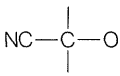
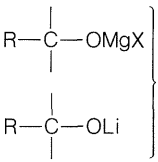
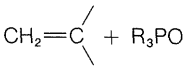
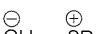
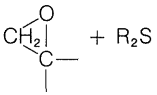
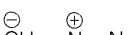
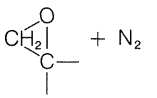
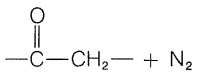
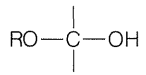
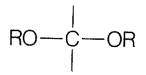
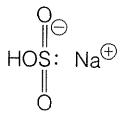
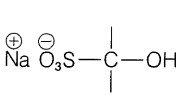
Reagent (Nu—E)	Adduct (to $\rangle C{=}O$)	Conditions	Comments
NC—H		basic catalysts	synthesis of cyanoalkenes, carboxylic acids, Section 16-4A
R—MgX R—Li		ether solvent, no catalyst needed	synthesis of alcohols, Section 14-12A
		acidic or basic catalysts	synthesis of hydroxyketones, hydroxyaldehydes, and their dehydration products (see Section 17-3)
		strongly basic medium	synthesis of alkenes, Section 16-4A
		strongly basic medium	oxacyclopropane synthesis, Section 16-4A
			oxacyclopropanes, Section 16-4A
			ketones, Section 16-4A
RO—H		acidic or basic catalysts	Section 15-4E
RO—H		acidic catalysts	useful to protect carbonyl and alcohol functions (see Sections 16-8 and 15-9)
		aqueous $NaHSO_3$ solution	purification, Section 16-4B
RNH_2	 (imine)	acidic catalysts	Section 16-4C, Table 16-5

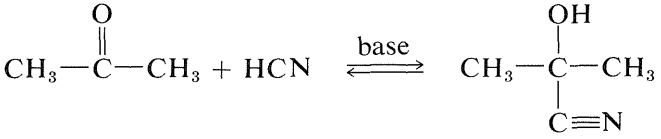
Table 16-4 (continued)
Addition Reactions of Aldehydes and Ketones

Reagent (Nu—E)	Adduct (to $\backslash C{=}O/$)	Conditions	Comments
R_2NH	$R_2N{-}\overset{|}{C}{=}$ (enamine)	acidic catalysts	Section 16-4C
Cl—H, ROH	Cl—C—OR	acidic catalysts	Section 16-4D, synthesis of α-halo ethers
$H{-}\overset{\ominus}{A}lH_3$, $Li^{\oplus}$	$H{-}C{-}O\overset{\ominus}{A}lH_3 + Li^{\oplus}$	ether solution	Section 16-4E, synthesis of alcohols
$H{-}\overset{\ominus}{B}H_3$, $Na^{\oplus}$	$H{-}C{-}O\overset{\ominus}{B}H_3 + Na^{\oplus}$	alcohols or aqueous solutions	Section 16-4E, synthesis of alcohols
$H{-}CR_2OH$	H—C—OH	strongly basic catalysts or $H{-}CR_2{-}O{-}Al\backslash$	Section 16-4E, synthesis of alcohols

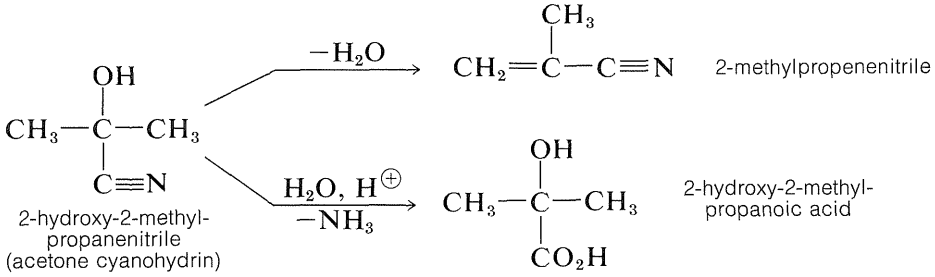
16-4A Addition of Carbon Nucleophiles

Cyanohydrin Formation

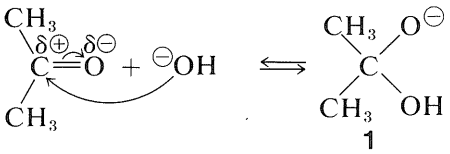
Hydrogen cyanide adds to many aldehydes and ketones to give hydroxynitriles, usually called "cyanohydrins":



The products are useful in synthesis—for example, in the preparation of cyanoalkenes and hydroxy acids:



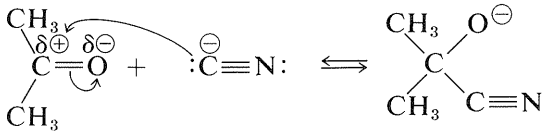
An important feature of cyanohydrin formation is that it requires a basic catalyst. In the absence of base, the reaction does not proceed, or is at best very slow. In principle, the basic catalyst may activate either the carbonyl group or hydrogen cyanide. With hydroxide ion as the base, one reaction to be expected is a reversible addition of hydroxide to the carbonyl group:

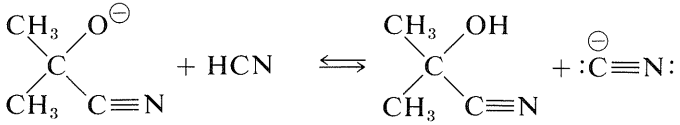


1

However, such addition is not likely to facilitate formation of cyanohydrin because it represents a *competitive* saturation of the carbonyl double bond. Indeed, if the equilibrium constant for this addition were large, an excess of hydroxide ion could inhibit cyanohydrin formation by tying up the ketone as the adduct **1**.

Hydrogen cyanide itself has no unshared electron pair on carbon and does not form a *carbon–carbon* bond to a carbonyl carbon. However, a small amount of a strong base can activate hydrogen cyanide by converting it to cyanide ion, which can function as a carbon nucleophile. A complete sequence for cyanohydrin formation follows:





The second step regenerates the cyanide ion. Each step of the reaction is reversible but, with aldehydes and most nonhindered ketones, formation of the cyanohydrin is reasonably favorable. In practical syntheses of cyanohydrins, it is convenient to add a strong acid to a mixture of sodium cyanide and the carbonyl compound, so that hydrogen cyanide is generated *in situ*. The amount of acid added should be insufficient to consume all the cyanide ion, therefore sufficiently alkaline conditions are maintained for rapid addition.

Exercise 16-10 One possible way of carrying out the cyanohydrin reaction would be to dispense with hydrogen cyanide and just use the carbonyl compound and sodium cyanide. Would the *equilibrium constant* for cyanohydrin formation be more

favorable, or less favorable, with 2-propanone and sodium cyanide in water compared to 2-propanone and hydrogen cyanide in water? Give your reasoning.

Exercise 16-11 What should be the equation for the rate of formation of 2-propanone cyanohydrin by the mechanism given above, (a) if the first step is slow and the second fast? (b) If the second step is slow and the first fast? (Review Sections 4-4C and 8-4A.)

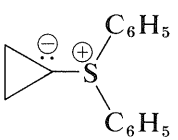
Exercise 16-12 Explain what factors would operate to make the equilibrium constant for cyanohydrin formation 1000 times greater for cyclohexanone than for cyclopentanone. Why? What would you expect for cyclobutanone relative to cyclopentanone? Why?

Addition of Organometallic Reagents (See Section 14-12A.)

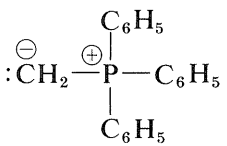
Addition of Enolate Anions (See Section 17-3.)

Addition of Ylide Reagents

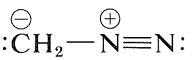
There are a number of rather interesting substances for which we can write important dipolar valence-bond structures of the type $-\overset{\ominus}{\underset{|}{\overset{\cdot\cdot}{C}}}-\overset{\oplus}{X}$. The important factor with these structures is that the negative end of the dipole is *carbon with an unshared electron pair.* The positive end of the dipole can be several kinds of atoms or groups, the most usual being sulfur, phosphorus, or nitrogen. Some examples (each written here as a single dipolar valence-bond structure) are:



cyclopropylidene-diphenylsulfurane (a sulfur ylide)



methylidenetriphenylphosphorane (a phosphorus ylide)

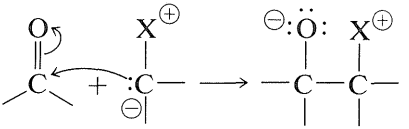


diazomethane (a nitrogen ylide)

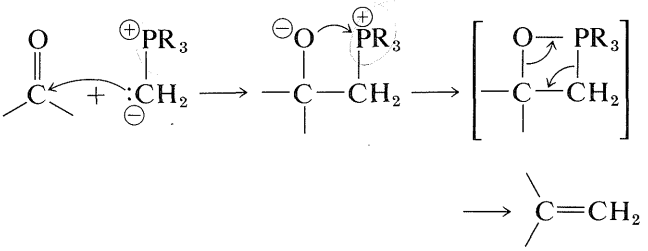
The systematic naming of these substances is cumbersome, but they have come to be known as **ylides.** The genesis of this name may seem obscure, but it is an attempt to reconcile the presence of a C–X σ bond, which is covalent and nonpolar as in alk*yl* derivatives, as well as an ionic bond as in metal hal*ides*. Hence, the combination *yl-ide.*[2]

[2]Pronounced variously as *ill/id, yill/id, ill/ide, yill/ide.* The dipolar structures usually written for ylides are an oversimplified representation of the bonding in these substances, as you will see if you work Exercise 16-15.

As we might expect from the dipolar structure, ylides can behave as carbon nucleophiles to form carbon–carbon bonds by addition to the carbonyl groups of aldehydes and ketones:

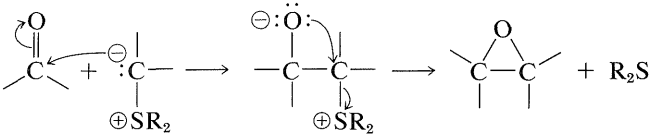


However, the further course of reaction depends on the type of ylide used. In the case of phosphorus ylides, the overall reaction amounts to a very useful *synthesis of alkenes* by the transfer of oxygen to phosphorus and carbon to carbon, as summarized in Equation 16-1. This is called the **Wittig reaction:**

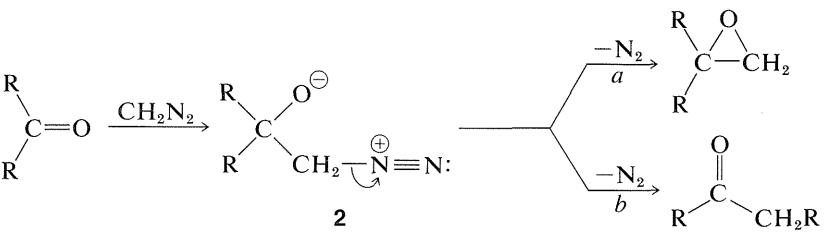


(16-1)

Reactions with sulfur ylides proceed differently. The products are oxacyclopropanes (oxiranes)—not alkenes. The addition step proceeds as with the phosphorus ylides, but the negatively charged oxygen of the dipolar adduct then displaces the sulfonium group as a neutral sulfide. This is an intramolecular S_N2 reaction similar to the formation of oxacyclopropanes from vicinal chloroalcohols (Section 15-11C):

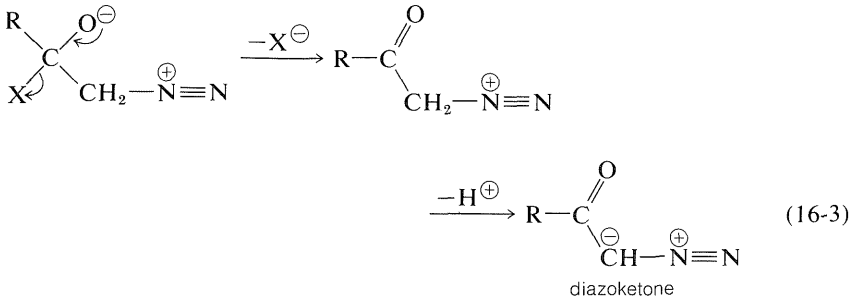


As for the nitrogen ylides, a useful reagent of this type is diazomethane, CH_2N_2. Diazomethane can react with carbonyl compounds in different ways, depending on what happens to the initial adduct **2**. Oxacyclopropanes are formed if the nitrogen is simply displaced (as N_2) by oxygen (Path *a*, Equation 16-2). Ketones of rearranged carbon framework result if nitrogen is displaced (as N_2) by $R:^{\ominus}$ which moves over to the CH_2 group (Path *b*, Equation 16-2):



(16-2)

Diazoketones, $RCOCHN_2$, are formed if there is a good leaving group, such as halogen, on the carbonyl (Equation 16-3). Under these circumstances the reactant is an acid halide, not an aldehyde or ketone:



diazoketone (16-3)

Exercise 16-13 **a.** Phosphorus ylides can be prepared by heating triphenylphosphine, $(C_6H_5)_3P$, with a primary alkyl halide, RCH_2X, in a solvent such as benzene. The initial product then is mixed with an equivalent quantity of a very strong base, such as phenyllithium in ether. Write equations for the reactions and probable mechanisms involved, using ethyl bromide as the alkyl halide.

b. Using the phosphorus ylide prepared according to Part a, draw structures for the products you would expect it to form with 2-pentanone.

Exercise 16-14 Show the structures of the reaction products to be expected in each of the steps listed.

a. $ClCH_2OCH_3 \xrightarrow[\text{benzene, 60 hr, 50°}]{\text{1. } (C_6H_5)_3P} \xrightarrow[\text{ether}]{\text{2. } C_6H_5Li} \xrightarrow[\text{ether, } -30°\text{, 15 hr}]{\text{3. cyclohexanone}}$

b. $BrCH_2CH_2CH_2CH_2Br \xrightarrow[\text{30 min., 250°}]{\text{1. } (C_6H_5)_3P \text{ (excess)}} \xrightarrow[\text{ether}]{\text{2. } C_6H_5Li \text{ (2 moles)}}$

$\xrightarrow{\text{3. } C_6H_5CHO \text{ (2 moles)}}$

Exercise 16-15* **a.** Write valence-bond structures for diazomethane, CH_2N_2, that accord with the fact that the actual molecule is a gas at room temperature and has a much smaller dipole moment (see Section 16-1B) than is suggested by the dipolar structure, $\overset{\ominus}{C}H_2—\overset{\oplus}{N}\equiv N$.

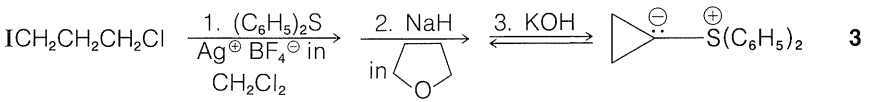
b. 1,2-Diazacyclopropene, CH_2N_2, is a stable isomer of diazomethane. Would you expect this substance to act as an ylide? Give your reasoning.

c. Phosphorus and sulfur ylides of the type $—\overset{\ominus}{\ddot{C}}—\overset{\oplus}{X}—$, but not the corresponding nitrogen ylides, $\overset{\ominus}{\ddot{C}}H_2—\overset{\oplus}{N}(CH_3)_3$, are not to be regarded as being strictly dipolar, but

rather to possess C–X bonds with considerable double-bond character, as expressed by the valence-bond structures

Use Figure 6-4 (Section 6-1) to explain why phosphorus and sulfur ylides are more stable than corresponding nitrogen ylides.

Exercise 16-16* **a.** Show the intermediate substances and indicate the probable mechanisms involved in the synthesis of the sulfur ylide **3** by the following sequence:

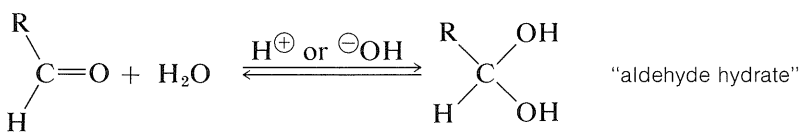


b. Draw structures for the products expected from the reaction of **3** with cyclopentanone.

16-4B Addition of Oxygen and Sulfur Nucleophiles

Alcohols, Thiols, Water

We already have discussed additions of alcohols and, by analogy, thiols (RSH) to carbonyl compounds (see Section 15-4E). We will not repeat this discussion here except to point out that addition of *water* to the carbonyl group of an aldehyde is analogous to hemiacetal formation (Section 15-4E) and is catalyzed both by acids and bases:

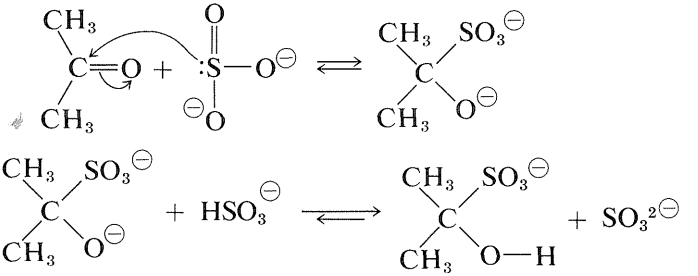


The equilibrium for hydrate formation depends both on steric and electrical factors. Methanal is 99.99 % hydrated in aqueous solution, ethanal is 58 % hydrated, and 2-propanone is not hydrated significantly. The hydrates seldom can be isolated because they readily revert to the parent aldehyde. The only stable crystalline hydrates known are those having strongly electronegative groups associated with the carbonyl (see Section 15-7).

Exercise 16-17 The equilibrium constants for hydration are especially large for methanal, trichloroethanal, cyclopropanone, and compounds with the grouping —COCOCO—. Explain.

Hydrogen Sulfite (Bisulfite) Addition to Carbonyl Compounds

Several carbonyl additions have characteristics similar to those of cyanohydrin formation. A typical example is the addition of sodium hydrogen sulfite, which proceeds readily with good conversion in aqueous solution with most aldehydes, methyl ketones, and unhindered cyclic ketones to form a carbon–sulfur bond. No catalyst is required because sulfite is an efficient nucleophilic agent. The addition step evidently involves the sulfite ion—not hydrogen sulfite ion:



2-propanone hydrogen sulfite addition product, 1-methyl-1-hydroxyethanesulfonate (isolated as sodium salt)

The addition products often are nicely crystalline solids that are insoluble in excess concentrated sodium hydrogen sulfite solution. Whether soluble or insoluble, the addition products are useful for separating carbonyl compounds from substances that do not react with sodium hydrogen sulfite.

Exercise 16-18 Sodium hydrogen sulfite addition products are decomposed to the parent carbonyl compounds when treated with mild acid or mild alkali. Write equations for the reactions involved and explain why the substances are unstable both in acid and base.

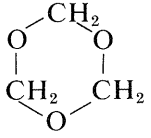
Exercise 16-19 Explain how sodium hydrogen sulfite might be used to separate cyclohexanone (bp 156°) from cyclohexanol (bp 161°).

Polymerization of Aldehydes

A reaction closely related to acetal formation is the polymerization of aldehydes. Both linear and cyclic polymers are obtained. For example, methanal in water solution polymerizes to a solid long-chain polymer called paraformaldehyde or "polyoxymethylene":

$$n(CH_2{=}O) + H_2O \longrightarrow \underset{\text{paraformaldehyde}}{H{-}O{-}CH_2{-}(O{-}CH_2)_{n-2}{-}O{-}CH_2{-}O{-}H}$$

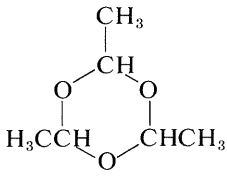
This material, when strongly heated, reverts to methanal; it therefore is a convenient source of gaseous methanal. When heated with dilute acid, paraformaldehyde yields the solid trimer, 1,3,5-trioxacyclohexane (mp 61°). The cyclic tetramer is also known.



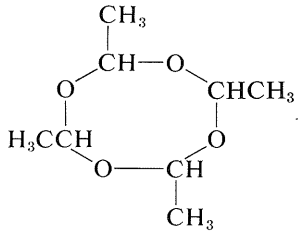
1,3,5-trioxacyclohexane
(1,3,5-trioxane)

Long-chain methanal polymers have become very important as plastics in recent years. The low cost of paraformaldehyde is highly favorable in this connection, but the instability of the material to elevated temperatures and dilute acids precludes its use in plastics. However, the "end-capping" of polyoxymethylene chains through formation of esters or acetals produces a remarkable increase in stability, and such modified polymers have excellent properties as plastics. Delrin (DuPont) is a stabilized methanal polymer with exceptional strength and ease of molding.

Ethanal (acetaldehyde) polymerizes under the influence of acids to the cyclic trimer, "paraldehyde," and a cyclic tetramer, "metaldehyde." Paraldehyde has been used as a relatively nontoxic sleep-producing drug (hypnotic). Metaldehyde is used as a poison for snails and slugs, "Snarol." Ketones do not appear to form stable polymers like those of aldehydes.



2,4,6-trimethyl-1,3,5-trioxacyclohexane
(paraldehyde)



2,4,6,8-tetramethyl-1,3,5,7-tetraoxacyclooctane
(metaldehyde)

Exercise 16-20 Write a reasonable mechanism for the polymerization of methanal in water solution under the influence of a basic catalyst. Would you expect base catalysis to produce any 1,3,5-trioxacyclohexane? Why?

Exercise 16-21 How many different configurational isomers are there for paraldehyde? Draw the conformation expected to be most stable for each. Review Section 12-3D

Exercise 16-22* What kind of reagents might be used to convert paraformaldehyde into a more thermally stable material? Give your reasoning.

16-4C Nitrogen Nucleophiles

Reactions of RNH_2 Derivatives with Carbonyl Compounds

A wide variety of substances with $-NH_2$ groups react with aldehydes and ketones by an addition-elimination sequence to give $\diagdown C{=}N- \diagup$ compounds and water. These reactions usually require acid catalysts:

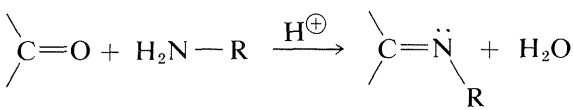


Table 16-5 summarizes several important reactions of this type and the nomenclature of the reactants and products.

The dependence of the rates of these reactions on acid concentration is revealing with respect to mechanism and illustrates several important points relating to acid catalysis. Typically, relative to pH 7, *the reaction rate goes through a maximum as pH decreases.* Figure 16-4 shows schematically the type of behavior observed. We can understand the maximum in rate by considering the rates and equilibria involving RNH_2 and the carbonyl compound as well as the rate of dehydration, Equations 16-4 through 16-6.

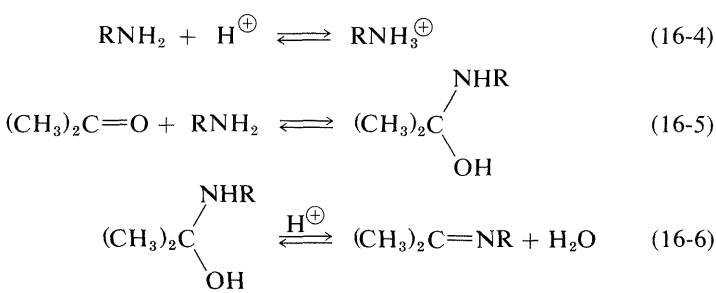
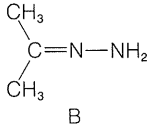
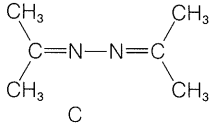
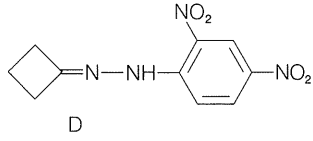
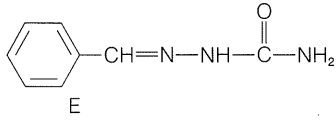


Table 16-5
Products from Reactions of Carbonyl Compounds with RNH_2 Derivatives

Reactant	Typical product[a]	Class of product
$H_2N—R$ (R = alkyl, aryl, or hydrogen) amine	$CH_3CH=N—CH_3$ A	imine[b] (Schiff's base)
$H_2N—NH_2$ hydrazine	 B	hydrazone
	 C	azine
$H_2N—NHR$ (R = alkyl, aryl) substituted hydrazine	 D	hydrazone[c]
$H_2NNHCNH_2$ semicarbazide	 E	semicarbazone[c]
$HO—NH_2$ hydroxylamine	$CH_2=N—OH$ F	oxime[c]

[a]The nomenclature of these substances is at best difficult. The first-choice names used here are those recommended by J. H. Fletcher, O. C. Dermer, and R. B. Fox, Eds. "Nomenclature of Organic Compounds," *Advances in Chemistry Series, No. 126,* American Chemical Society, Washington, D.C., 1974. These are far from common usage names as yet and, for conversational purposes, you will find it best to say the name of the compound along with the class of product formed, as in the italicized names below.

A. ethylidenemethanamine, 2-aza-2-butene, *methylimine of ethanal;*
B. 1-methylethylidenediazane, 1-methylethylidenehydrazine, 1,2-diaza-3-methyl-2-butene, *hydrazone of 2-propanone;*
C. bis(1-methylethylidene)diazine, bis(1-methylethylidene)hydrazine, 2,5-dimethyl-3,4-diaza-2,4-hexadiene, *azine of 2-propanone:*
D. 1-cyclobutylidene-2-(2,4-dinitrophenyl)diazane, cyclobutylidene-2,4-dinitrophenylhydrazine, *2,4-dinitrophenylhydrazone of cyclobutanone;*
E. 2-phenylmethylidenediazanecarboxamide, *semicarbazone of benzenecarbaldehyde;*
F. methylideneazanol, *oxime of methanal.*

[b]These are either ketimines or aldimines, according to whether the carbonyl compound is a ketone or an aldehyde. For R = H, the imine product generally is unstable and polymerizes.

[c]Usually these derivatives are solids and are excellent for the isolation and characterization of aldehydes and ketones.

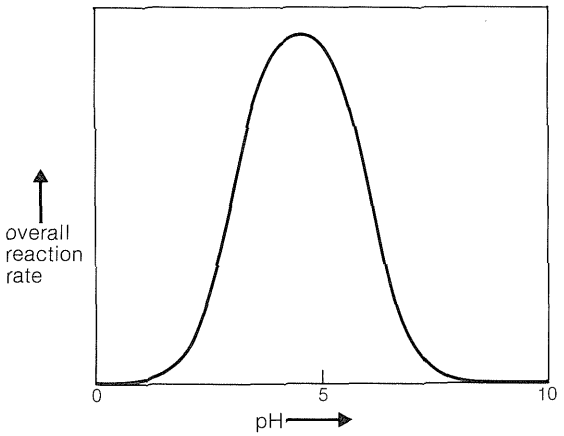
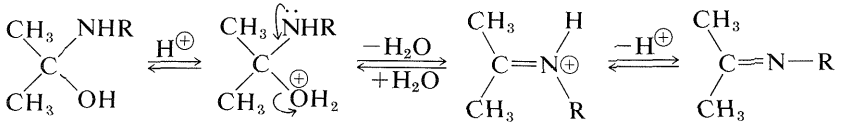


Figure 16-4 Schematic variation of the rate of condensation of RNH_2 with a carbonyl compound as a function of pH

Clearly, if the unshared electron pair on the nitrogen of RNH_2 is combined with a proton, Equation 16-4, it cannot attack the carbonyl carbon to give the aminoalkanol as in Equation 16-5. So at high acid concentration (low pH) we expect the rate and the equilibrium for the overall reaction to be unfavorable. In more dilute acid, the rate picks up because there is more free RNH_2 in solution. Dehydration of the aminoalkanol (Equation 16-6) is acid catalyzed; this reaction normally is fast at pH values smaller than 3–4. Therefore, the slow step at pH < 4 is addition of RNH_2 to the carbonyl group as per Equation 16-5. As the pH is increased above 4, the addition becomes progressively faster because less RNH_2 is tied up as $RNH_3^{\oplus}$. However, then the dehydration step, Equation 16-6, decreases in rate because it requires an acid catalyst. At pH 6 (remember that going from pH 4 to pH 6 is a 100-fold decrease in $H^{\oplus}$ concentration), dehydration is the slow step, and at higher pH values it finally becomes too slow to give a useful overall rate of reaction. This sequence of changes in rate and equilibria has been shown to account precisely for rate *vs.* pH curves such as in Figure 16-4.

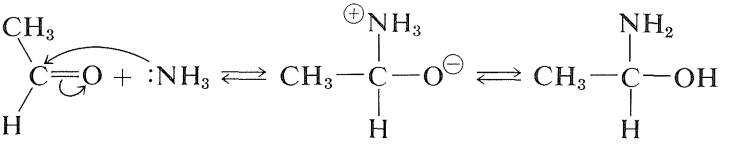
Dehydration of $(CH_3)_2CNHR(OH)$ to $(CH_3)_2C{=}NR$ involves acid catalysis in very much the same way as in acetal formation (Section 15-4E):



Exercise 16-23* Why should the equilibrium for formation of $(CH_3)_2C{=}NR$ from $(CH_3)_2C{=}O$ and RNH_2 be less favorable in strong acid than in neutral water solution? Be sure you consider the equilibria for the interaction of the acid with *all* of the participants. Give your reasoning.

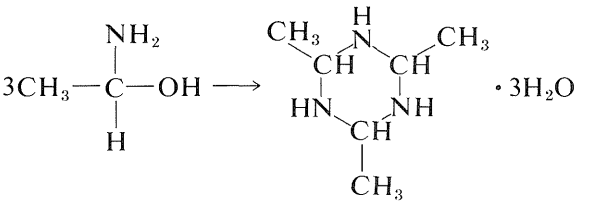
Addition of Ammonia to Aldehydes

Ammonia adds readily to many aldehydes. For example,



1-aminoethanol
(acetaldehyde ammonia)

The aldehyde–ammonia adducts usually are not very stable. They readily undergo dehydration and polymerization. 1-Aminoethanol, for example, gives a cyclic trimer of composition $C_6H_{15}N_3 \cdot 3H_2O$, mp 97°, with structure **4**:

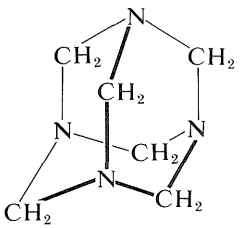


4

Methanal and ammonia react by a different course with the formation of a substance known as "hexamethylenetetramine":

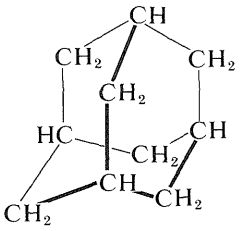
$$6CH_2{=}O + 4NH_3 \longrightarrow \underset{\text{"hexamethylene-tetramine"}}{C_6H_{12}N_4} + 6H_2O$$

The product is a high-melting solid (mp > 230° d.) and its structure has been established by x-ray diffraction (Section 9-3). In fact, it was the first organic substance whose structure was determined in this way. The high melting point is clearly associated with the considerable symmetry and rigidity of the cage structure:



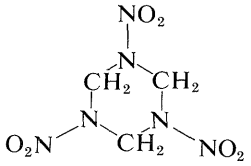
1,3,5,8-tetrazatricyclo[3.3.1.1^{3,7}]decane
(hexamethylenetetramine)

The corresponding all-carbon compound, adamantane (Section 12-8), also has a high melting point (268°):



adamantane

Treatment of hexamethylenetetramine with nitric acid gives the high explosive "cyclonite," which often is designated as RDX and was widely used in World War II:



cyclonite

The methanal and ammonia that split off the cage structure during the reaction with nitric acid need not be wasted. In the large-scale manufacture of cyclonite, a combination of nitric acid, ammonium nitrate, and ethanoic anhydride is used, which results in full utilization of the methanal and ammonia:

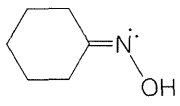
Exercise 16-24 **a.** How many different positional and stereoisomers are possible of a monomethyl-substituted hexamethylenetetramine?

b. How many stereoisomers are possible for structure **4**?

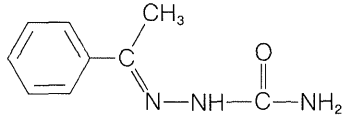
c. Name compound **4** as an azacycloalkane in accord with the systematic rules for cyclic compounds (Sections 12-8 and 15-11A).

Exercise 16-25 Suggest a method of synthesis of each of the following compounds, starting with an appropriate aldehyde or ketone. Indicate which of the products you expect to be mixtures of configurational isomers.

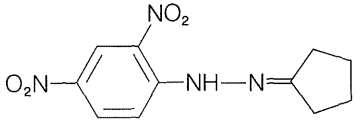
a.



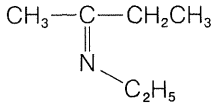
b.



c.

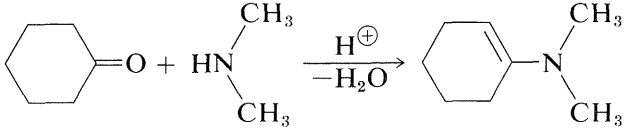


d.



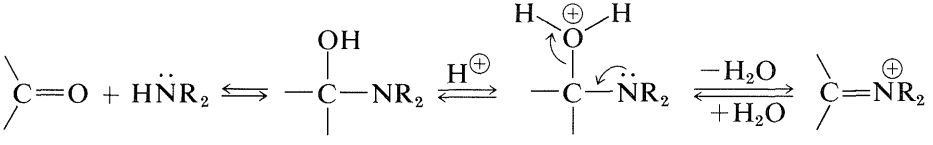
Enamines

Secondary amino compounds of the type $R_2N—H$ add to aldehyde and ketone carbonyl groups in an acid-catalyzed reaction in much the same way as do RNH_2 compounds—with one important difference. The product contains the structural unit C=C—N rather than C—C=N; and because there is a carbon–carbon double bond, such a substance is called an enamine (alk*ene* + *amine*). An example is:



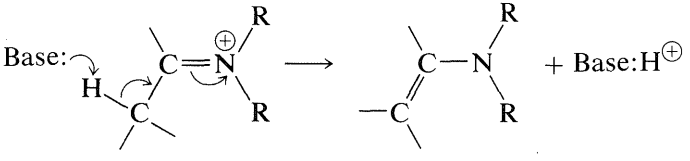
N,N-dimethyl-1-cyclohexenamine

The course of this reaction can be understood if we notice that loss of OH from the initial product leads to an immonium ion, **5**, that cannot lose a proton and form a C=N bond:



5

However, if there is a hydrogen on a carbon attached to the immonium carbon, it is possible for such a hydrogen to be lost as a proton with concurrent formation of the neutral enamine:

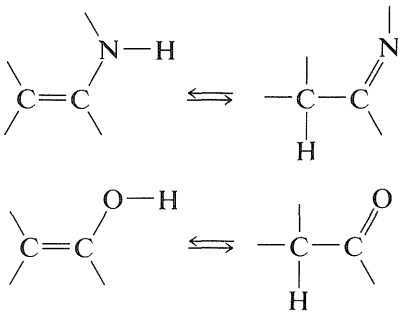


5 an enamine

Enamine formation, like many other carbonyl addition reactions, is readily reversible, and the carbonyl compound can be recovered by hydrolysis with aqueous acids. For this reason, to obtain a good conversion of carbonyl compound to enamine, it usually is necessary to remove the water that is formed by distilling it away from the reaction mixture.

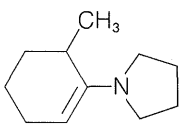
Enamines are useful synthetic intermediates for the formation of carbon–carbon bonds, as we will discuss in greater detail in Section 17-4B.

Enamines generally are unstable if there is a hydrogen on nitrogen. They rearrange to the corresponding imine. This behavior is analogous to the rearrangement of alkenols to carbonyl compounds (Section 10-5A):



Exercise 16-26 Write an equation to show the rearrangement of ethylidenemethanamine to *N*-methylethenamine ($CH_2{=}CH{-}NHCH_3$). Use bond energies to calculate the ΔH^0 of the rearrangement. Assuming $\Delta S^0 = 0$, which would be the more stable isomer? Would you expect that corrections for electron delocalization may be necessary for either of these compounds? Give your reasoning.

Exercise 16-27 How could you prepare the enamine **6** from suitable ketone and amine starting materials?

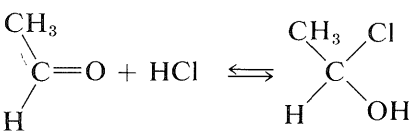


6

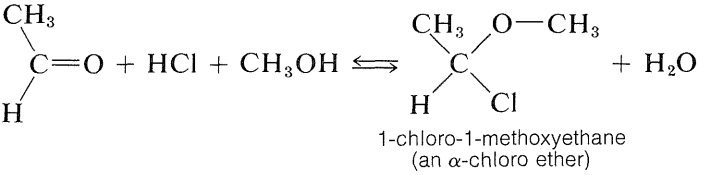
Specify the catalyst required and draw the structure of any by-products that you may expect to form in the reaction.

16-4D Hydrogen-Halide Addition to Carbonyl Groups and Replacement of Carbonyl by Halogen

Addition of hydrogen halides to carbonyl groups usually is so easily reversible as to preclude isolation of the addition products:



However, many aldehydes react with alcohols in the presence of an excess of hydrogen chloride to give α-chloro ethers:



(16-7)

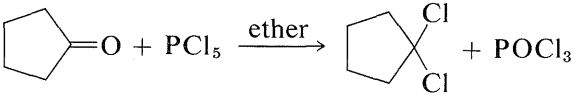
1-chloro-1-methoxyethane
(an α-chloro ether)

In carrying out laboratory syntheses of α-chloro ethers, gaseous hydrogen chloride is passed into a mixture of the alcohol and aldehyde. Aqueous HCl is not useful because the excess water gives an unfavorable equilibrium. α-Chloro ethers are highly reactive compounds that very readily undergo S_N2 as well as S_N1 and E1 reactions. Two simple examples, methoxychloromethane (chloromethyl methyl ether) and chloromethoxychloromethane (bis-chloromethyl ether), have been put under severe restrictions as the result of tests that show they have strong chemical carcinogenic properties.

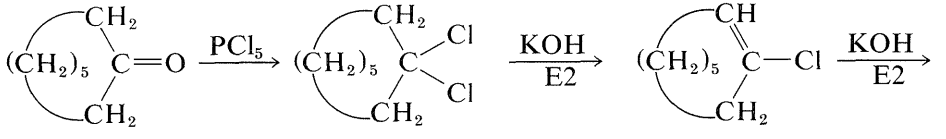
Exercise 16-28 Write equations to show how you would convert 2-butanone to 2-methoxy-2-methylthiobutane by way of the corresponding α-chloro ether.

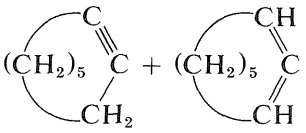
Exercise 16-29 Write a reasonable mechanism for the reaction of hydrogen chloride and methanol with methanal to give methoxychloromethane (methyl chloromethyl ether), Equation 16-7, that is consistent with the fact that the reaction occurs under conditions where neither dichloromethane nor chloromethane is formed.

Replacement of the carbonyl function by two chlorines occurs with phosphorus pentachloride in ether:

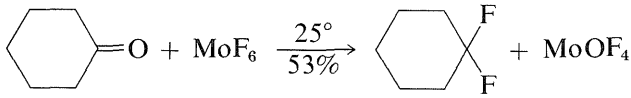


This reaction is useful in conjunction with E2 elimination to prepare alkenyl halides, allenes, and alkynes. Cycloalkenyl halides are easily prepared, but because of angle strain the cycloalkynes and cycloallenes with fewer than eight atoms in the ring cannot be isolated (see Section 12-7):





Replacement of a carbonyl group by *gem*-fluorines[3] can be achieved with molybdenum hexafluoride or sulfur tetrafluoride. Sulfur tetrafluoride converts carboxyl functions to trifluoromethyl groups:



$$CH_3CH_2CH_2CO_2H + 2SF_4 \longrightarrow CH_3CH_2CH_2CF_3 + 2SOF_2 + HF$$

Exercise 16-30 Cyclopentanone-1-^{14}C treated successively with phosphorus pentachloride and alkali gives 1-chlorocyclopentene-1-^{14}C. This substance on treatment with phenyllithium at 120° affords ^{14}C-labeled 1-phenylcyclopentene, which on vigorous oxidation gives benzoic acid ($C_6H_5CO_2H$) containing in its carboxyl carbon just half of the total ^{14}C of the 1-phenylcyclopentene. Write equations for all the reactions involved and write a mechanism for the phenyllithium substitution that accounts for the ^{14}C distribution.

Exercise 16-31* Work out reasonable mechanisms for the reactions of phosphorus pentachloride and sulfur tetrafluoride with carbonyl groups. Both phosphorus and sulfur can accommodate five (or more) bonded atoms, and the structure of phosphorus pentachloride in the solid state is $[PCl_4^{\oplus}][PCl_6^{\ominus}]$.

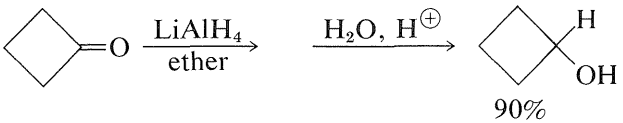
16-4E Hydride as a Nucleophile. Reduction of Carbonyl Compounds

Metal and Boron Hydrides

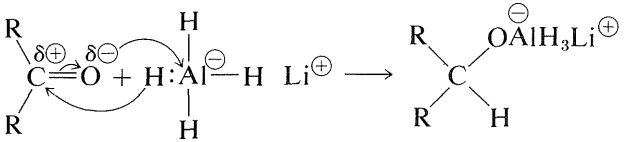
In recent years, inorganic hydrides such as lithium aluminum hydride, $LiAlH_4$, and sodium borohydride, $NaBH_4$, have become extremely important as reducing agents of carbonyl compounds. These reagents have considerable utility, especially with sensitive and expensive carbonyl compounds. The reduction of cyclobutanone to cyclobutanol is a good example, and you will

[3]*Gem* is an abbreviation for *geminal* (twinned) and is a common *conversational* designation for arrangements having two identical substituents on one carbon.

notice that the net reaction is the addition of hydrogen across the carbonyl double bond, $\text{C=O} \xrightarrow{2[H]} \text{CH—OH}$,

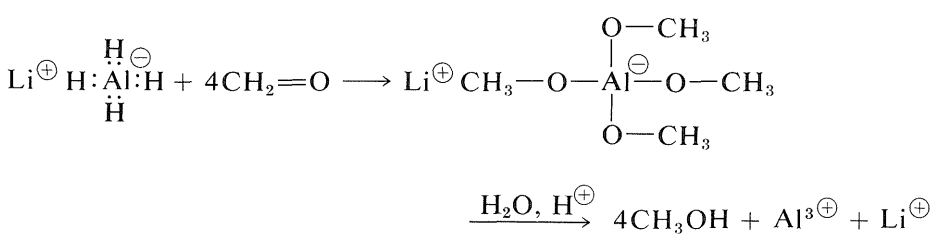


With the metal hydrides, the key step is transfer of a hydride ion to the carbonyl carbon of the substance being reduced.



The hydride transfer is analogous to the transfer of $R:^{\ominus}$ from organometallic compounds to carbonyl groups (Section 14-12A).

Lithium aluminum hydride is best handled like a Grignard reagent, because it is soluble in ether and is sensitive to both oxygen and moisture. (Lithium hydride is insoluble in organic solvents and is not an effective reducing agent for organic compounds.) All four hydrogens on aluminum can be utilized:



The reaction products must be decomposed with water and acid as with the Grignard complexes. Any excess lithium aluminum hydride is decomposed by water and acid with evolution of hydrogen:

$$LiAlH_4 + 2H_2SO_4 \longrightarrow \tfrac{1}{2}Li_2SO_4 + \tfrac{1}{2}Al_2(SO_4)_3 + 4H_2$$

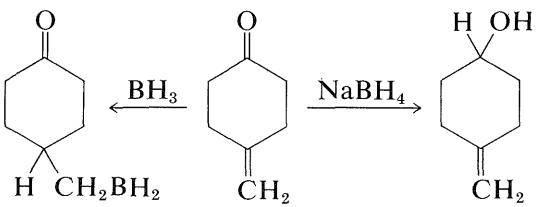
Lithium aluminum hydride usually reduces carbonyl groups without affecting carbon–carbon double bonds. It is, in addition, a good reducing agent for carbonyl groups of carboxylic acids, esters, and other acid derivatives, as will be described in Chapter 18.

Sodium borohydride is a milder reducing agent than lithium aluminum hydride and will reduce aldehydes and ketones, but not acids or esters. It

reacts sufficiently slowly with water in neutral or alkaline solution that reductions which are reasonably rapid can be carried out in water solution without appreciable hydrolysis of the reagent:

$$NaBH_4 + 4CH_2{=}O + 3H_2O \longrightarrow 4CH_3OH + NaOB(OH)_2$$

Borane (as BH_3 in tetrahydrofuran or dimethyl sulfide) is an even milder reducing agent than $BH_4^{\ominus}$ for the carbonyl group of aldehydes and ketones. This difference in reactivity can be used to advantage when selective reduction is necessary. For example, borohydride reduces a ketone carbonyl more rapidly than a carbon–carbon double bond, whereas borane reduces the carbon–carbon double bond more rapidly than carbonyl:



A useful comparison of the reactivities of boranes and metal hydrides toward various types of multiple bonds is given in Table 16-6.

Exercise 16-32 Show how you could prepare the following substances from the indicated starting materials:

a. 4-methylcyclohexanone from 4-methylenecyclohexanone
b. 4-(hydroxymethyl)cyclohexanone from 4-oxocyclohexanecarboxylic acid
c. 4-hydroxybutanoic acid from 4-oxobutanoic acid
d. 2,2,2-trichloroethanol from 2,2,2-trichloroethanal

The Cannizzaro Reaction

A characteristic reaction of aldehydes without α hydrogens is the self oxidation–reduction they undergo in the presence of strong base. With methanal as an example,

$$2CH_2{=}O + {}^{\ominus}OH \xrightarrow[H_2O]{\text{heat}} CH_3OH + H{-}C(=O){-}O^{\ominus}$$

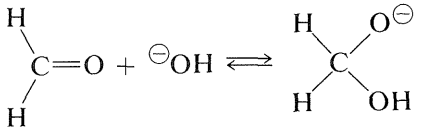
If the aldehyde has α hydrogens, other reactions usually occur more rapidly.

Table 16-6
Comparison of Products and Reactivities of Functional Groups for Reduction with Borane and Metal Hydrides[a,b]

Functional group	Reduction product[c]		
	$LiAlH_4$	$NaBH_4$	BH_3
$-CO_2H$	$-CH_2OH$ (6)		$-CH_2OH$ (1)
$\backslash C{=}C /$			$\backslash CH{-}CH / $ (2)
$-CHO$	$-CH_2OH$ (1)	$-CH_2OH$ (1)	$-CH_2OH$ (3)
$\backslash C{=}O /$	$\backslash CHOH / $ (2)	$\backslash CHOH / $ (2)	$\backslash CHOH / $ (4)
$-COCl$	$-CH_2OH$ (3)	$-CH_2OH$ (3)	
$-C(-)-C(-)-$ (O)	$\backslash CH{-}C(-)-OH / $ (4)	$\backslash CH{-}C(-)-OH / $ (4)	
$-CO_2R$	$-CH_2OH$ (5)		
$-CONR_2$	$-CH_2NR_2$ (6) or $-CHO$		
$-C{\equiv}N$	$-CH_2NH_2$ (7) or $-CHO$		
$\backslash C{=}NOH /$	$\backslash CHNH_2 / $ (8)		
$-C(-)-NO_2$	$-C(-)-NH_2$ (9)		
$-CH_2X$[d]	$-CH_3$ (10)		

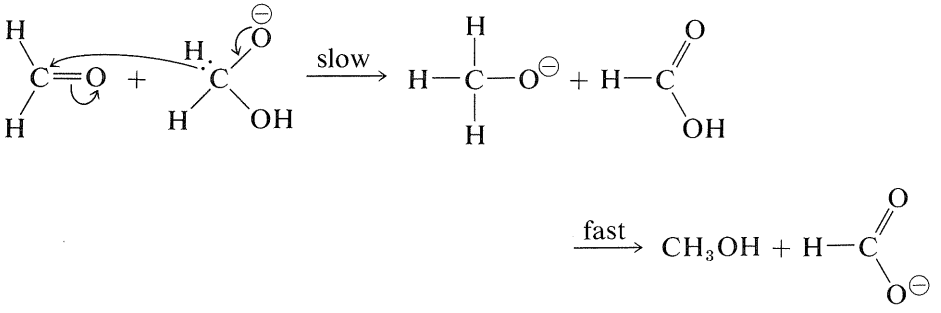
[a]Numbers in parenthesis indicate order of reactivity in the vertical column with (1) as the most reactive. [b]No product is listed where reaction normally is too slow to be of practical value. [c]After hydrolysis. [d]X is halogen or sulfonate, $-O-SO_2-Ar$.

The mechanism of this reaction, usually called the **Cannizzaro reaction,**[4] combines many features of other processes studied in this chapter. The first step is reversible addition of hydroxide ion to the carbonyl group:



[4]Named after its discoverer, the same Cannizzaro who, in 1860, made an enormous contribution to the problem of obtaining self-consistent atomic weights (Section 1-1).

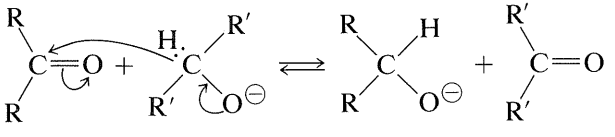
A hydrogen can be transferred as hydride ion to methanal from the hydroxyalkoxide ion, thereby reducing the methanal to methanol:



Exercise 16-33 Assume that an equimolar mixture of methanal and 2,2-dimethylpropanal (each undergoes the Cannizzaro reaction by itself) is heated with sodium hydroxide solution. Write equations for the various possible combinations of Cannizzaro reactions which may occur. Would you expect methanal used in excess to reduce, or oxidize, 2,2-dimethylpropanal? Give your reasoning?

Reduction with Aluminum Alkoxides

Hydride transfer similar to that of the Cannizzaro reaction also may be achieved from a C—H grouping in an alkoxide ion corresponding to a primary or secondary, but not a tertiary, alcohol. This is expected to be a reversible reaction, because the products are another alkoxide and another carbonyl compound:



To utilize this equilibrium process as a practical reduction method requires rather special conditions. It is preferable to use an aluminum alkoxide, $Al(OR)_3$, rather than a sodium alkoxide, $\overset{\oplus}{Na}\overset{\ominus}{O}R$, to ensure that the reaction mixture is not too strongly basic. (Carbonyl compounds, particularly aldehydes, are sensitive to strong bases.) The overall reaction may be written

$$3R_2C{=}O + Al(-O-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3)_3 \rightleftharpoons (R_2CH-O)_3Al + 3CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3$$

for which the alkoxide is derived from 2-propanol. The advantage of this

method is that the reaction can be driven essentially to completion by distilling out the 2-propanone as it is formed. The reduction product subsequently can be obtained by acid hydrolysis of the aluminum alkoxide:

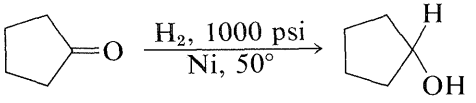
$$(R_2CHO)_3Al \xrightarrow{H_2O,\ H^{\oplus}} 3R_2CHOH + Al^{3\oplus}$$

Biological Reductions

These have been discussed already in the context of the reverse reactions—oxidation of alcohols (Section 15-6C).

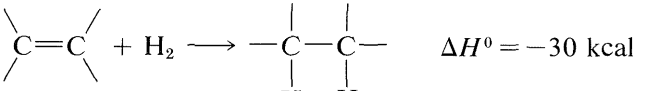
16-5 CATALYTIC HYDROGENATION

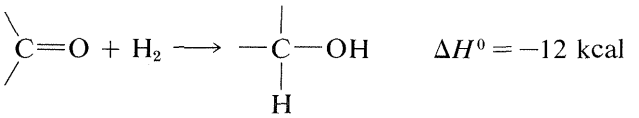
The simplest large-scale procedure for reduction of aldehydes and ketones to alcohols is by catalytic hydrogenation:



95–100%

The advantage over most other kinds of reduction is that usually the product can be obtained simply by filtration from the catalyst, then distillation. The common catalysts are nickel, palladium, copper chromite, or platinum activated with ferrous iron. Hydrogenation of aldehyde and ketone carbonyl groups is much slower than of carbon–carbon double bonds so more strenuous conditions are required. This is not surprising, because hydrogenation of carbonyl groups is calculated to be less exothermic than that of carbon–carbon double bonds:

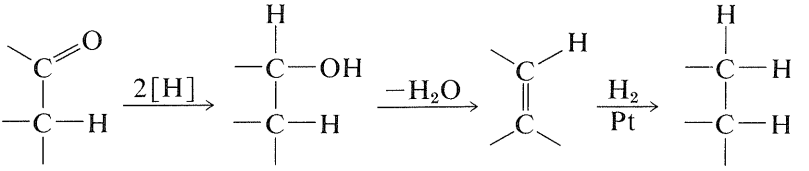




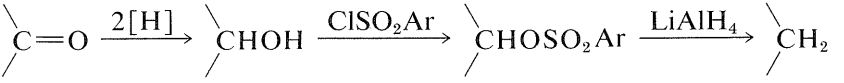
It follows that it is generally difficult to reduce a carbonyl group in the presence of a carbon–carbon double bond by hydrogenation without also saturating the double bond. Other reducing agents are more selective (Section 16-4E).

16-6 REDUCTION OF CARBONYL COMPOUNDS TO HYDROCARBONS

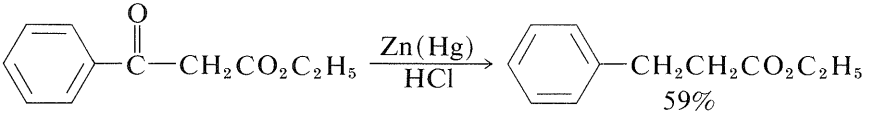
There are several methods of transforming $\rangle C{=}O$ to $\rangle CH_2$. In some cases, the following three-step sequence of conventional reactions may be useful:



This route requires a hydrogen α to the carbonyl function and may give rearrangement in the dehydration step (Sections 8-9B and 15-5E). Alternatively, the hydroxyl can be converted to a better leaving group (halogen or sulfonate ester), which then may be displaced by $H:^{\ominus}$ (as $LiAlH_4$; see Table 16-6):

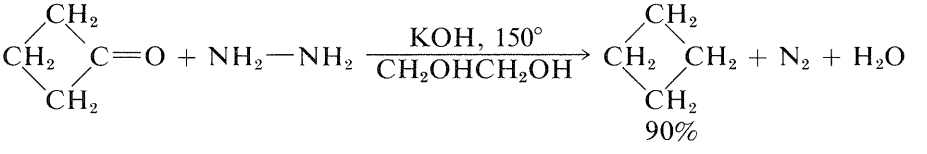


More direct methods may be used, depending on the character of the R groups of the carbonyl compound. If the R groups are stable to a variety of reagents there is no problem, but with sensitive R groups not all methods are equally applicable. When the R groups are stable to acid but unstable to base, the **Clemmensen** reduction with amalgamated zinc and hydrochloric acid is often very useful.

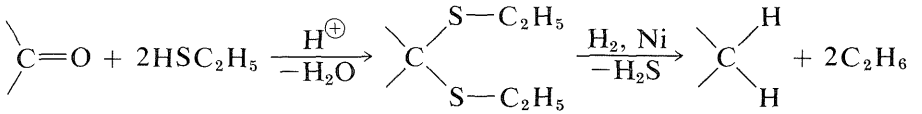


The mechanism of the Clemmensen reduction is not well understood. It is clear that in most cases the alcohol is *not* an intermediate, because the Clemmensen conditions do not suffice to reduce most alcohols to hydrocarbons.

When the R groups of the carbonyl compound are stable to base but not to acid, the **Huang-Minlon modification of the Wolff-Kishner reduction** usually gives good results. This procedure involves heating the carbonyl compound in a high-boiling polar solvent, such as 1,2-ethanediol, with hydrazine and potassium hydroxide and driving the reaction to completion by distilling out the water formed:



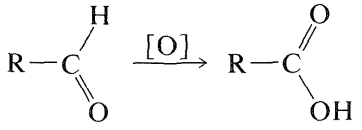
When the carbonyl compound is sensitive to both acids and bases, or for other reasons gives poor yields in both the Clemmensen and Wolff–Kishner reductions, a recourse may be reduction of the corresponding thioacetal or thioketal with hydrogen-saturated Raney nickel (Section 11-2B):



Thioketals, unlike ordinary ketals, are formed readily from ketones and thiols (RSH) in the presence of acid catalysts. The desulfurization procedure usually goes well, but the product is rather difficult to separate by extraction from the large excess of Raney nickel required for optimum yields.

16-7 OXIDATION OF CARBONYL COMPOUNDS

Aldehydes are oxidized easily by moist silver oxide or by potassium permanganate solution to the corresponding acids. The mechanism of the permanganate oxidation has some resemblance to the chromic acid oxidation of alcohols (Section 15-6B):

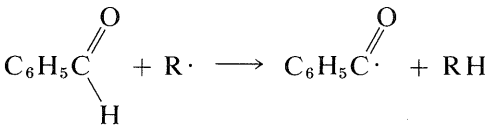


Exercise 16-34 Benzenecarbaldehyde (benzaldehyde, C_6H_5CHO) is oxidized to benzenecarboxylic acid (benzoic acid, $C_6H_5CO_2H$) by acid permanganate. The rate of the oxidation is proportional to the concentrations of $H^{\oplus}$, aldehyde, and $MnO_4^{\ominus}$. The reaction is much slower with C_6H_5CDO than with C_6H_5CHO. When the reaction is carried out in $H_2{}^{18}O$ with C_6H_5CHO and $MnO_4^{\ominus}$, the product is $C_6H_5CO_2H$. With C_6H_5CHO, H_2O, and $Mn^{18}O_4^{\ominus}$, the $C_6H_5CO_2H$ contains ^{18}O. Write a mechanism for the reaction that is consistent with all the above facts. (Notice that the C_6H_5 group is not involved.) Give your reasoning.

Many aldehydes are oxidized easily by atmospheric oxygen in a radical-chain mechanism. Oxidation of benzenecarbaldehyde to benzenecarboxylic acid has been studied particularly well and involves formation of a peroxy

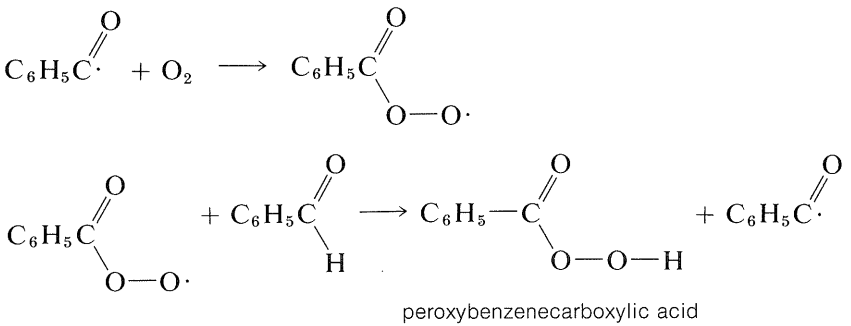
acid as an intermediate. Reaction is initiated by a radical R· which breaks the relatively weak aldehyde C–H bond (86 kcal).

initiation



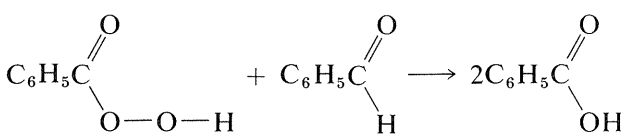
The benzenecarbonyl radical, $C_6H_5\dot{C}O$, then propagates a chain reaction.

propagation



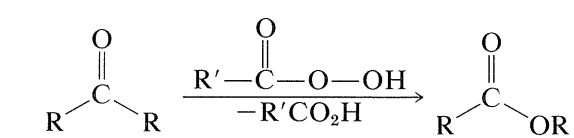
peroxybenzenecarboxylic acid

The peroxy acid formed then reacts with benzenecarbaldehyde to give two molecules of carboxylic acid:



(16-8)

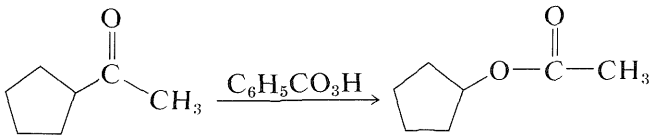
The oxidation of benzenecarbaldehyde with peroxybenzenecarboxylic acid (Equation 16-8) is an example of a reaction of wide applicability in which aldehydes are oxidized to carboxylic acids, and ketones are oxidized to esters.

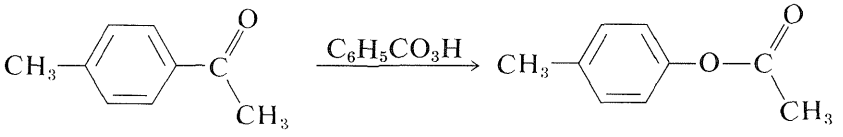


R = H, alkyl, or aryl

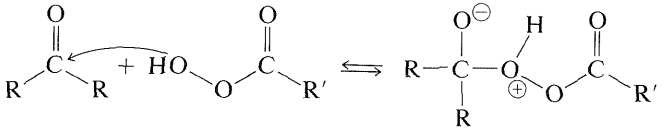
The reaction, which is known as the **Baeyer–Villiger oxidation,** has synthetic utility, particularly for the oxidation of ketones to esters because ketones

normally are difficult to oxidize without degrading the structure to smaller fragments. Two examples of the Baeyer–Villiger reaction follow:

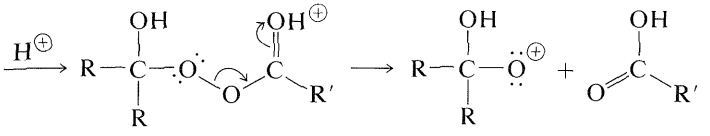




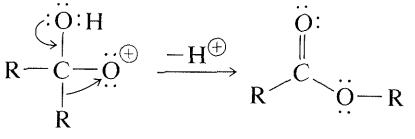
The mechanism of the Baeyer–Villiger oxidation has been studied extensively and is of interest because it involves a rearrangement step in which a substituent group (R) moves from carbon to oxygen. The reaction sequence is shown in Equations 16-9 through 16-11:



(16-9)



(16-10)



(16-11)

In the first step, Equation 16-9, the peroxy acid adds to the carbonyl group. The adduct has several oxygen atoms on which protons can reside, and there will be rapid shifts of protons between these oxygens. However, at some stage the structure will be appropriate to allow elimination of a molecule of carboxylic acid, $R'CO_2H$, Equation 16-10. The resulting intermediate has an electron-deficient oxygen atom with only six valence electrons. As with carbocations and borane complexes (Sections 8-9B, 15-5E, 11-6E, and 16-9 D, G), a neighboring R group can move over with its bonding electron-pair to the electron-deficient (oxygen) atom, Equation 16-11. You will notice that for aldehydes, the aldehyde hydrogen migrates in preference to the alkyl or aryl group. In the other examples given, a cycloalkyl migrates in preference to a methyl group, and aryl in preference to methyl.

Exercise 16-35 A radical-chain reaction similar to that described for the air oxidation of benzaldehyde occurs in the peroxide-initiated addition of aldehydes to alkenes (see Table 10-3). Write a mechanism for the peroxide-induced addition of ethanal to propene to give 2-pentanone.

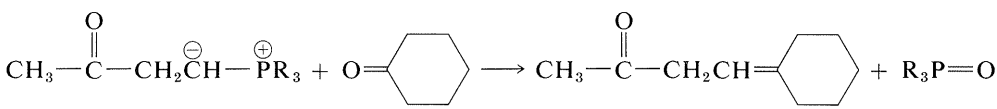
Exercise 16-36* Certain aldehydes decompose to hydrocarbons and carbon monoxide when *heated* in the presence of peroxides:

$$(CH_3)_2CHCH_2CHO \xrightarrow{ROOR} (CH_3)_2CHCH_3 + CO$$

Write a reasonable chain mechanism for such reactions that is supported by calculations of the ΔH^0 values for the propagation steps. Use needed data from Table 4-3 and Table 4-6. Your answer should reflect the fact that this reaction does not proceed well with most aldehydes unless the reactants are heated (above about 120°).

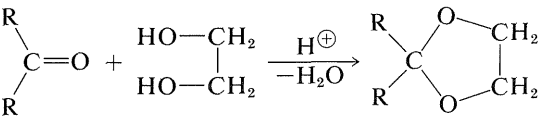
16-8 PROTECTION OF CARBONYL GROUPS

There are few reactions of aldehydes and ketones that do not in some way affect the carbonyl function. For this reason, it may be necessary to protect the carbonyl function when it is desirable to avoid reaction at this function. For example, you may plan to synthesize 4-cyclohexylidene-2-butanone by way of a Wittig reaction (Section 16-4A), which would involve the following sequence:

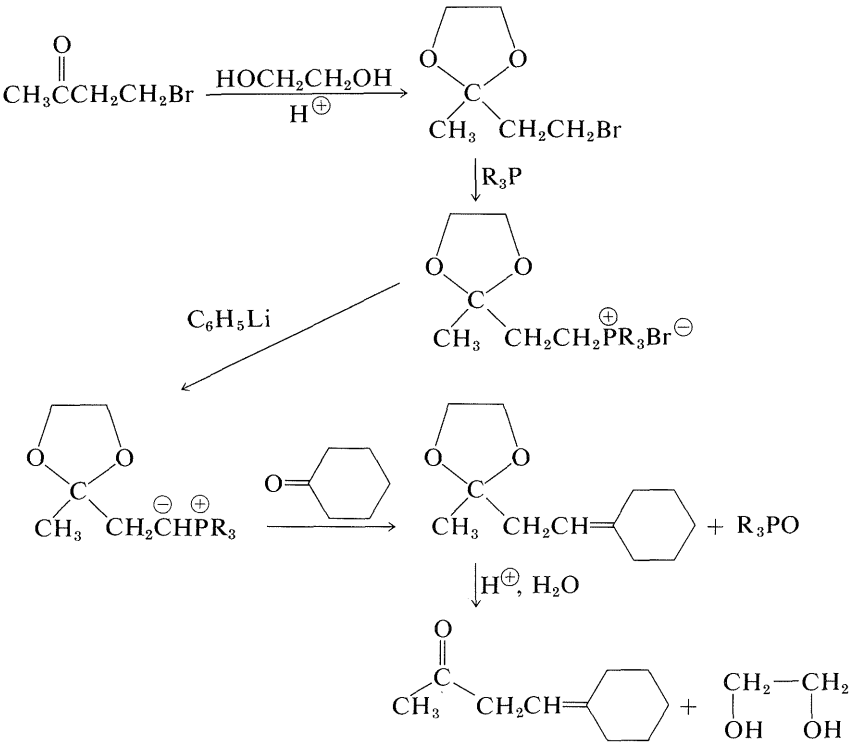


This synthesis would *fail* in the second step because the phenyllithium would add irreversibly to the carbonyl group. To avoid this, the carbonyl group would have to be protected or blocked, and the most generally useful method of

blocking is to convert the carbonyl group to a ketal, usually a cyclic ketal:



With the carbonyl group suitably protected, the proposed synthesis would have a much better chance of success:



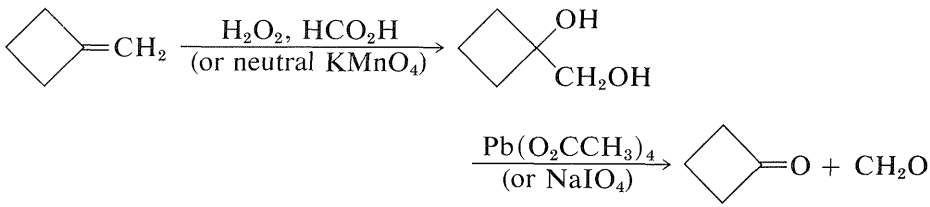
Notice that the carbonyl group is regenerated by acid hydrolysis in the last step.

16-9 PREPARATIVE METHODS FOR ALDEHYDES AND KETONES

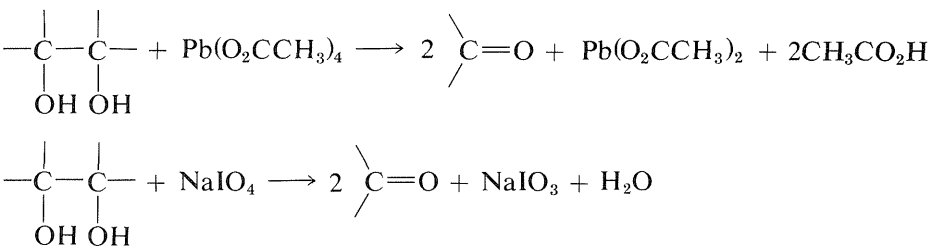
A number of useful reactions for the preparation of aldehydes and ketones, such as ozonization of alkenes and hydration of alkynes, have been considered in previous chapters. These and other methods of preparation are summarized in Tables 16-7 and 16-8 at the end of the chapter. Only a few rather general methods that we have not discussed will be taken up here.

16-9A Oxidation of 1,2-Diols and Alkenes

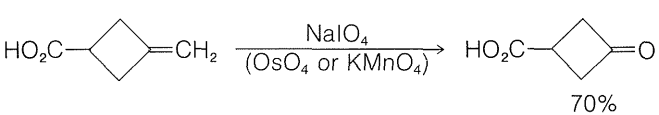
Aldehydes and ketones often can be prepared by oxidation of alkenes to 1,2-diols (Sections 11-7C and 11-7D), followed by oxidative cleavage of the 1,2-diols with lead tetraethanoate or sodium periodate. For example,



Cleavage of glycols with these reagents proceeds according to the following stoichiometry:



Exercise 16-37 An elegant modification of the two-step procedure to prepare ketones from alkenes by hydroxylation and oxidative cleavage of the diol formed uses a small amount of potassium permanganate (or osmium tetroxide, OsO_4) as the catalyst and sodium periodate as the oxidizing agent:

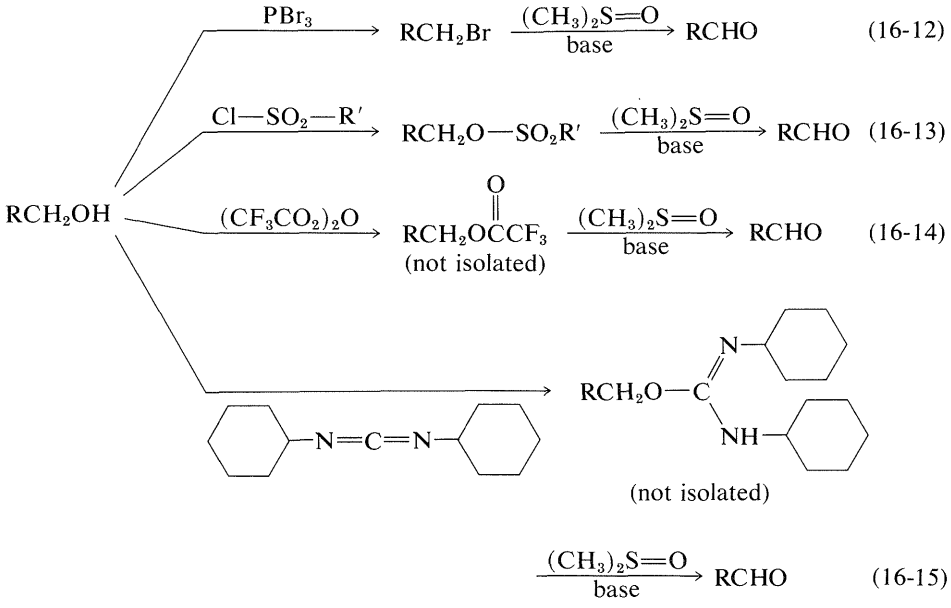


Explain how the reaction sequence could operate to enable $KMnO_4$ (or OsO_4) to function overall as a *catalyst* rather than as a *reagent.*

Exercise 16-38 Write mechanisms for the oxidative cleavage of 1,2-diols by lead tetraethanoate and sodium periodate based on consideration of the mechanism of chromic acid oxidation (Section 15-6B).

16-9B Oxidation of Primary Alcohols and Related Compounds

In Chapter 15 primary alcohols, RCH_2OH, were shown to be readily oxidized to aldehydes, RCHO, and secondary alcohols, R_2CHOH, to ketones, R_2CO, by inorganic reagents such as CrO_3 and $KMnO_4$. However, it is a problem to avoid overoxidation with primary alcohols because of the ease with which aldehydes are oxidized to acids, $RCHO \longrightarrow RCO_2H$. A milder oxidant is methylsulfinylmethane [dimethyl sulfoxide, $(CH_3)_2S{=}O$], and this reagent can be used to prepare aldehydes from alcohols by way of an intermediate such as the ester or halide in which the OH group is converted to a better leaving group:



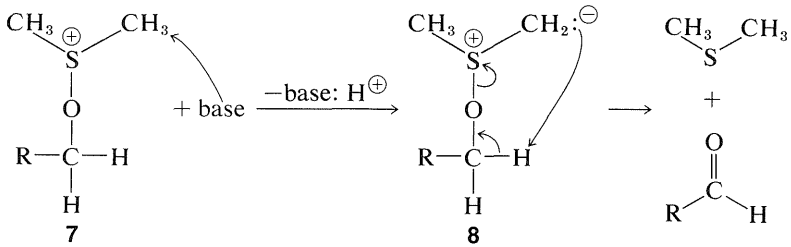
Whichever method is employed, the key step is the formation of an alkoxysulfonium salt, **7**, by a displacement reaction involving dimethyl sulfoxide as an oxygen nucleophile. (Notice that the S=O bond, like the C=O bond, is strongly polarized as $\overset{\oplus}{S}—\overset{\ominus}{O}$.)

$$RCH_2X + \overset{\ominus}{O}—\overset{\oplus}{S}(CH_3)_2 \xrightarrow{S_N2} RCH_2—O—\overset{\oplus}{S}(CH_3)_2 + X^{\ominus}$$

7

In the examples listed in Equations 16-12 through 16-15, the X group is Br, $—OSO_2R'$, $—O_2CCF_3$, and $C_6H_{11}NHC(=O)NC_6H_{11}$, respectively. In the next step a sulfur ylide, **8**, is formed from the reaction of a base with **7**, but the ylide

evidently is unstable and fragments by an internal E2 reaction to form an aldehyde:



7 8

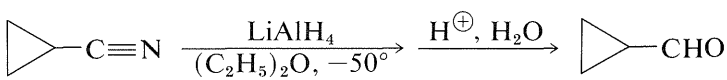
16-9C Reduction of Carboxylic Acids to Aldehydes

Conversion of a carboxylic acid to an aldehyde by direct reduction is not easy to achieve, because acids generally are difficult to reduce, whereas aldehydes are easily reduced. Thus the problem is to keep the reaction from going too far.

The most useful procedures involve conversion of the acid to a derivative that either is more easily reduced than an aldehyde, or else is reduced to a substance from which the aldehyde can be generated. The so-called **Rosenmund reduction** involves the first of these schemes; in this procedure, the acid is converted to an acyl chloride, which is reduced with hydrogen over a palladium catalyst to the aldehyde in yields up to 90%. The rate of reduction of the aldehyde to the corresponding alcohol is kept at a low level by poisoning the catalyst with sulfur:

$$R{-}CO_2H \xrightarrow{SOCl_2} RCOCl \xrightarrow[Pd(S)]{H_2} RCHO + HCl$$

Metal hydrides, such as lithium aluminum hydride, also can be used to reduce derivatives of carboxylic acids (such as amides and nitriles see Table 16-6) to aldehydes. An example follows:



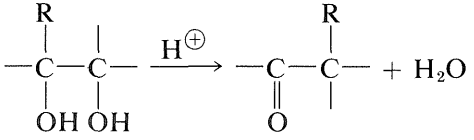
cyclopropanecarbonitrile cyclopropanecarboxaldehyde

The reduction step usually is successful only if **inverse addition** is used, that is, adding a solution of lithium aluminum hydride to a solution of the nitrile in ether, preferably at low temperatures. If the nitrile is added to the hydride, the reduction product is a primary amine, RCH_2NH_2 (see Section 18-7C).

Exercise 16-39 Explain how resonance can be used to account for the fact that the ΔH^0 for reduction of CH_3CO_2H to CH_3CHO is about 18 kcal mole^{-1} more positive than calculated from bond energies, whereas ΔH^0 for the corresponding reduction of CH_3COCl to CH_3CHO is about as expected from bond energies. Would you expect ΔH^0 for reduction of CH_3CONH_2 to be as expected from the pertinent bond energies? Why?

16-9D Rearrangements of 1,2-Diols

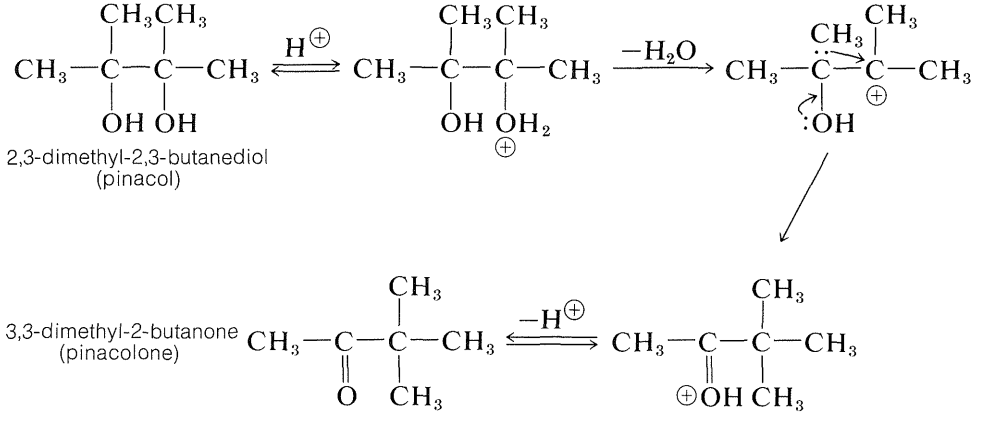
Many carbonyl compounds can be synthesized by acid-catalyzed rearrangements of 1,2-diols (a type of reaction often called the "pinacol–pinacolone" rearrangement).



R = alkyl, aryl, or hydrogen

The general characteristics of the reaction are similar to those of carbocation rearrangements (Section 8-9B). The acid assists the reaction by protonating one of the —OH groups to make it a better leaving group. The carbocation that results then can undergo rearrangement by shift of the neighboring R group with its pair of bonding electrons to give a new, thermodynamically more stable species with a carbon–oxygen double bond (see Section 16-7).

The prototype of this rearrangement is the conversion of pinacol to pinacolone as follows:



Exercise 16-40 Write a sequence of reactions whereby 2-methylpropene may be converted to 2-methylpropanal by way of a pinacol-type rearrangement. Would you expect any concomitant formation of 2-butanone? Explain.

Exercise 16-41 Predict the products to be expected from acid-catalyzed rearrangements of 1,2-propanediol and 2-methyl-2,3-butanediol.

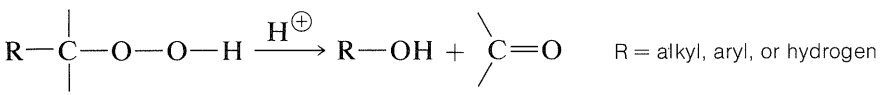
Exercise 16-42 Treatment of tetramethyloxacyclopropane, $(CH_3)_2C—C(CH_3)_2$ (O), with acid produces pinacolone. Explain.

Exercise 16-43 How could one dehydrate 2,3-dimethyl-2,3-butanediol to 2,3-dimethyl-1,3-butadiene without forming excessive amounts of 3,3-dimethyl-2-butanone in the process?

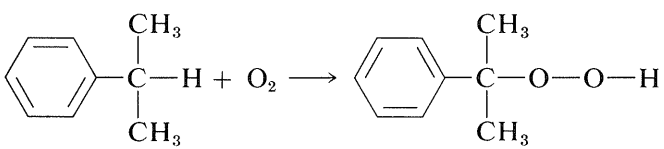
Exercise 16-44 Strong acid converts 1,1-diphenyl-1,2-ethanediol first to diphenylethanal and then more slowly to 1,2-diphenylethanone (benzyl phenyl ketone). Explain how and why kinetic and equilibrium control may be expected in this case to give different products.

16-9E Rearrangements of Hydroperoxides

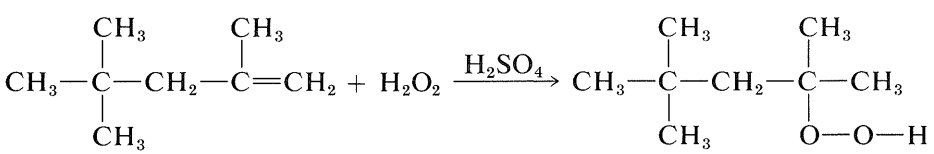
An important method of preparing carbonyl (and hydroxy) compounds, especially on an industrial scale, is through rearrangements of alkyl hydroperoxides:



The peroxides can be made in some cases by direct air oxidation of hydrocarbons,

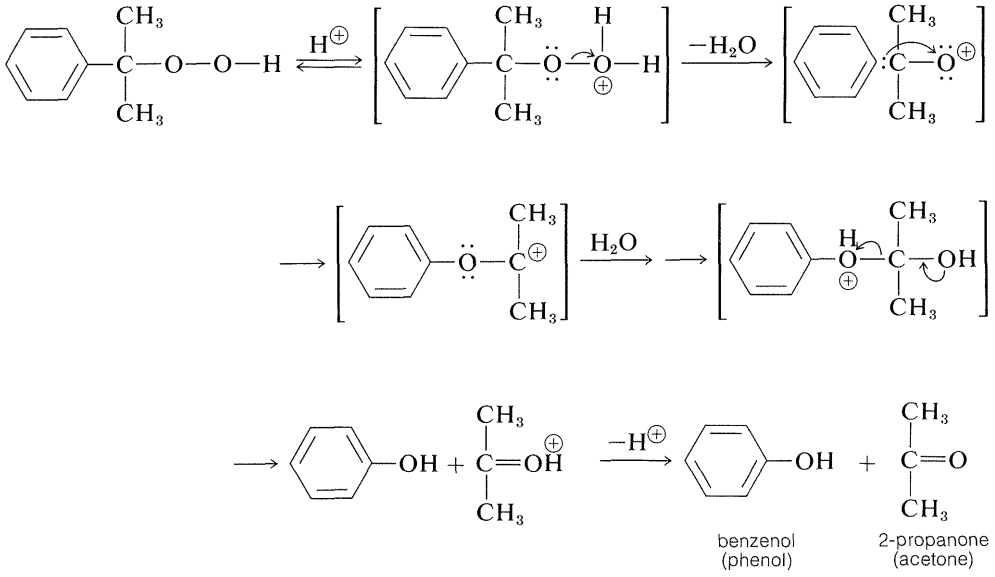


and in others by sulfuric acid-induced addition of hydrogen peroxide (as $H—O_2H$) to double bonds:



(Notice that hydrogen peroxide in methanoic acid behaves differently toward alkenes in producing addition of HO—OH, Section 11-7D.) The direct air oxidation of hydrocarbons is mechanistically similar to that of benzenecarbaldehyde (Section 16-7).

The rearrangements of hydroperoxides are acid-catalyzed and are analogous to carbocation rearrangements except that positive oxygen (with only *six* valence electrons) instead of positive carbon is involved in the intermediate stage:



In principle, either phenyl or methyl could migrate to the positive oxygen, but only phenyl migration occurs in this case. The rearrangement reaction is closely related to the Baeyer–Villiger reaction (Section 16-7).

Exercise 16-45 Write equations for the acid-catalyzed rearrangement of 1,3,3-trimethylbutyl hydroperoxide and predict the favored product therefrom.

16-9F Aldehydes by Hydroformylation of Alkenes

This reaction is important for a number of reasons. It is an industrial synthesis of aldehydes from alkenes by the addition of carbon monoxide and hydrogen in the presence of a cobalt catalyst. A prime example is the synthesis

of butanal from propene, in which 2-methylpropanal also is formed:

$$CH_3CH{=}CH_2 + CO + H_2 \xrightarrow[170°,\ 250\ atm]{Co_2(CO)_8} \underset{\text{butanal (75\%)}}{CH_3CH_2CH_2CHO} + \underset{\text{2-methylpropanal (25\%)}}{CH_3CH(CHO)CH_3}$$

As you can see, the reaction formally amounts to the addition of methanal as H—CHO to the alkene double bond. Because one additional carbon atom is introduced as a "formyl" CHO group, the reaction often is called *hydroformylation,* although the older name, *oxo reaction,* is widely used.

Hydroformylation to produce aldehydes is the first step in an important industrial route to alcohols. The intermediate aldehydes are reduced to alcohols by catalytic hydrogenation. Large quantities of C_4–C_8 alcohols are prepared by this sequence:

$$\underset{\text{CH}_3}{\overset{\text{CH}_3}{\diagdown}}\!\!>\!C{=}CH_2 \xrightarrow[Co_2(CO)_8]{CO,\ H_2} \underset{\text{CH}_3}{\overset{\text{CH}_3}{\diagdown}}\!\!>\!CHCH_2CHO \xrightarrow{H_2,\ Ni} \underset{\text{CH}_3}{\overset{\text{CH}_3}{\diagdown}}\!\!>\!CHCH_2CH_2OH$$

3-methylbutanal (90%)

The history of the oxo reaction is also noteworthy. It was developed originally in Germany in the years following World War I. At that time, the German chemical industry was faced with inadequate supplies of petroleum. Many German chemists therefore turned to research on ways by which hydrocarbons could be synthesized from smaller building blocks, particularly carbon monoxide and hydrogen derived from coal. The success achieved was remarkable and led to alkane and alkene syntheses known as the **Fischer–Tropsch process:**

$$n\,CO + (2n+1)H_2 \xrightarrow[\text{catalyst}]{\text{cobalt}} C_nH_{2n+2} + n\,H_2O$$

$$n\,CO + 2n\,H_2 \longrightarrow C_nH_{2n} + n\,H_2O$$

This reaction in turn led to the discovery that aldehydes were formed by the further addition of carbon monoxide and hydrogen to alkenes, and was further developed as the oxo process for production of alcohols. The combination $CO + H_2$ often is called "synthesis gas." It is prepared by the reduction of water under pressure and at elevated temperatures by carbon (usually coke), methane, or higher-molecular-weight hydrocarbons:

$$C + H_2O \longrightarrow CO + H_2$$

$$CH_4 + H_2O \longrightarrow CO + 3H_2$$

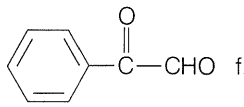
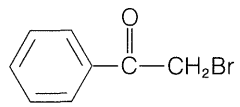
When carbon monoxide is produced from hydrocarbons, the process amounts to the reverse of the Fischer–Tropsch synthesis.

The mechanism of hydroformylation is in many respects related to the mechanism of homogeneous hydrogenation and is discussed further in Chapter 31.

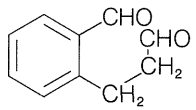
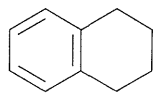
Exercise 16-46 Propose a possible synthesis of each of the following compounds from the indicated reagents and conditions where specified. Assume that any additional needed reagents are available. Reactions from other parts of Section 16-9 may be used.

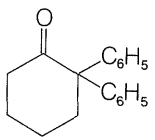
a. cyclohexanecarbaldehyde from cyclohexane by way of a hydroformylation reaction

b. cyclopentylmethanol from cyclopentene

c.  from 

d. heptanal from 1-heptene and $(CH_3)_2S{=}O$

e.  from  (two ways)

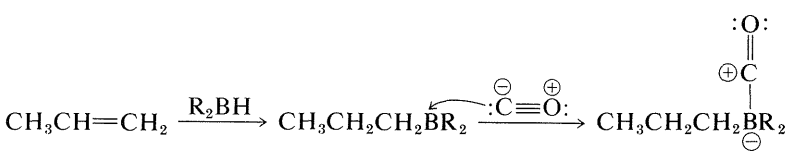
f.  from $(C_6H_5)_2C{=}O$ and cyclopentane by way of a Wittig reaction (Section 16-4A)

16-9G Carbonylation of Alkylboranes

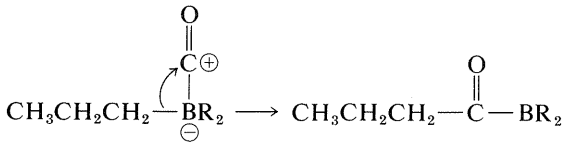
The aldehyde synthesis by hydroformylation of alkenes described in the preceding section can be achieved indirectly using boron hydrides. An oversimplified expression of this reaction is

$$CH_3CH{=}CH_2 \xrightarrow{R_2BH,\ CO} CH_3CH_2CH_2CHO$$

The overall reaction is quite complex but involves a rearrangement similar to that described for the hydroboration–oxidation of alkenes (Section 11-6E). The first step is hydroboration of the alkene to a trialkylborane. When the trialkylborane is exposed to carbon monoxide, it reacts (carbonylates) to form a tetracovalent boron, **9**:

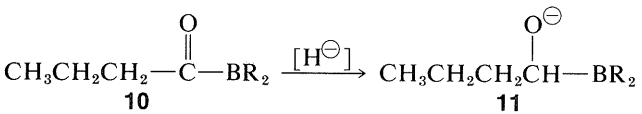


The complex **9** is unstable and rearranges by transfer of an alkyl group from boron to the electron-deficient carbonyl carbon to give **10**:



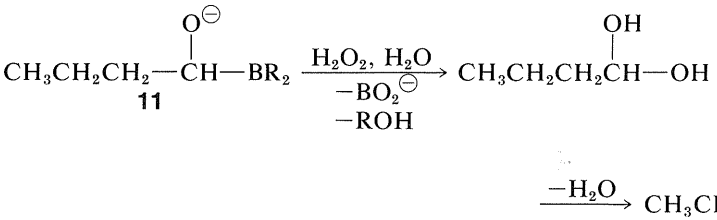
9 **10**

Now, if a metal-hydride reducing agent, such as $LiAlH_4$, is present, the carbonyl group of **10** is reduced and **11** is formed:

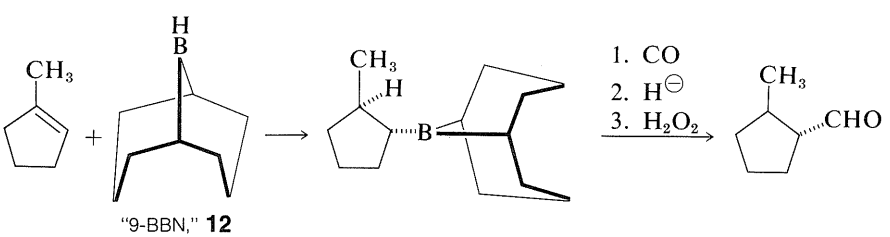


10 **11**

The reduction product, **11**, can be converted to an aldehyde by oxidation with aqueous hydrogen peroxide, provided the pH is carefully controlled. (Remember, aldehydes are unstable in strong base.)



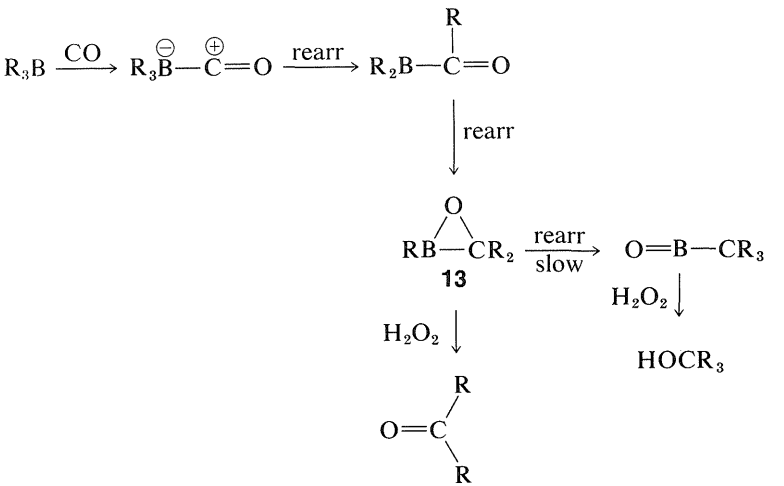
You may have noticed that only *one* of the three alkyl groups of a trialkylborane is converted to an aldehyde by the carbonylation–reduction–oxidation sequence. To ensure that carbonylation takes the desired course without wasting the starting alkene, hydroboration is achieved conveniently with a hindered borane, such as "9-BBN," **12**. With **12**, only the least-hindered alkyl group rearranges in the carbonylation step:



"9-BBN," **12**

Carbonylation of alkylboranes also can produce ketones. The conditions are similar to those in the aldehyde synthesis except that the hydride reducing

agent is omitted. By omitting the reducing agent, a second boron-to-carbon rearrangement can occur. Oxidation then produces a ketone:



Rearrangement will continue a third time (ultimately to produce a tertiary alcohol) unless movement of the alkyl group remaining on boron in **13** is prevented by steric hindrance.

Exercise 16-47* a. Show the steps and reaction conditions by which 2-methyl-1,3-butadiene can be converted to 3-methylcyclopentanone by an alkylborane, RBH_2, when R is a large alkyl group.

b. Suggest a route to each of the following compounds from the indicated starting materials: (1) 2-methyl-4-heptanone from propene and 2-methylpropene, and (2) octanedial from 1,5-hexadiene.

Additional Reading

H. C. Brown, "Organoborane–Carbon Monoxide Reactions. A New Versatile Approach to the Synthesis of Carbon Structures," *Accounts of Chemical Research* **2,** 65 (1969).

A. Maercker, "The Wittig Reaction," *Organic Reactions* **14,** 270 (1965).

G. Wittig, "From Diyls over Ylides to My Idyll," *Accounts of Chemical Research* **7,** 6 (1974).

C. H. Hassall, "The Baeyer–Villiger Oxidation of Aldehydes and Ketones," *Organic Reactions* **9,** 73 (1957).

E. Vedejs, "Clemmensen Reduction of Ketones in Anhydrous Organic Solvents," *Organic Reactions* **22,** 401 (1975).

Table 16-7
General Methods for the Preparation of Aldehydes[a]

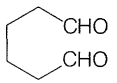
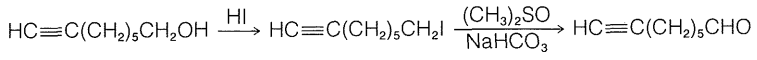
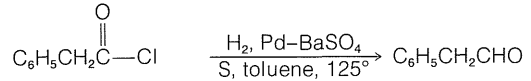
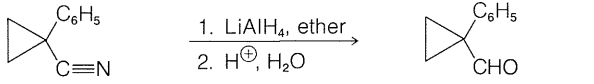
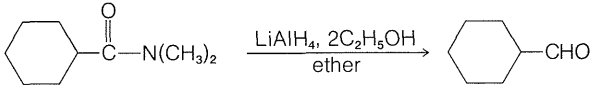
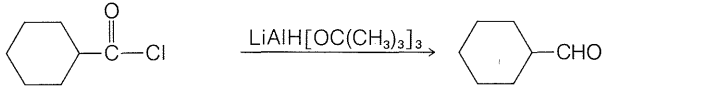
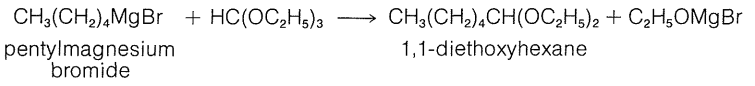
Reaction	Comment
1. *oxidation of alkenes with ozone,* $RCH{=}CH_2 \xrightarrow[2.\ H_2,\ Pd]{1.\ O_3} RCHO + H_2C{=}O$	See Section 11-7A; of limited preparative use; mainly used to locate position of double bonds in structure determinations.
 $\xrightarrow[2.\ H_2,\ Pd]{1.\ O_3,\ CH_3CO_2C_2H_5,\ -20°}$  hexanedial	
cyclohexene	
2. *oxidative cleavage of 1,2-diols,* $RCHCH_2$ (HO, OH) $\xrightarrow[\text{or } Pb(OCOCH_3)_4]{NaIO_4} RCHO + H_2C{=}O$	The 1,2-diols may be generated from alkenes *in situ* (see discussion in Section 16-9A and Method 2b, Table 16-8).
$C_6H_5CH_2CHCH_2$ (HO, OH) $\xrightarrow{Pb(OCOCH_3)_4} C_6H_5CH_2CHO + H_2C{=}O$	
3-phenylpropane-1,2-diol — phenylethanal	
3. *oxidation of primary alcohols,* $RCH_2OH \xrightarrow{[O]} RCHO$	See Section 15-6B; useful for the preparation of volatile aldehydes because with these, further oxidation usually can be prevented by distilling the product out of the reaction mixture.
a. chromic acid:	
$CH_3CH_2CH_2OH \xrightarrow[H_2SO_4]{Na_2Cr_2O_7} CH_3CH_2CHO$	
1-propanol — propanal	
b. aluminum alkoxides (Oppenauer oxidation):	See Section 16-4E; often useful for low-boiling aldehydes that can be distilled out of mixture as formed, thereby preventing condensation reactions; aluminum isopropoxide or *tert*-butoxide commonly are used as catalysts; carbon–carbon double bonds are not attacked.
$(CH_3)_2C{=}CHCH_2CH_2CH_2OH + C_6H_5CH{=}CHCHO \xrightarrow{Al(OC_3H_7\text{-iso})_3}$	
5-methyl-4-hexen-1-ol — 3-phenylpropenal	
$(CH_3)_2C{=}CHCH_2CH_2CHO + C_6H_5CH{=}CHCH_2OH$	
5-methyl-4-hexenal — 3-phenyl-2-propen-1-ol	

Table 16-7 (continued)

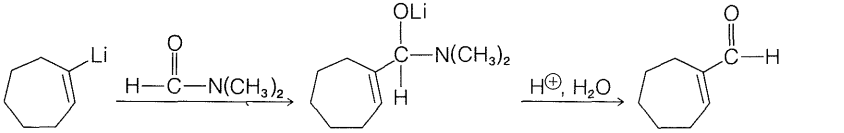
Reaction	Comment
c. dimethyl sulfoxide:  7-octyn-1-ol 7-octynal	See Sections 16-9B and 18-7C
4. *Rosenmund reduction of acyl chlorides,* ROCl $\xrightarrow{H_2}$ RCHO  phenylethanoyl chloride phenylethanal	See Section 16-9C; palladium on $BaSO_4$ is used as the catalyst in presence of sulfur.
5. *reductions with lithium aluminum hydride* a. nitriles:  1-phenylcyclopropane-carbonitrile 1-phenylcyclopropane-carbaldehyde	See Section 16-9C.
b. amides:  *N,N*-dimethylcyclohexane-carboxamide cyclohexane-carbaldehyde	Ethanol and $LiAlH_4$ produce $Li[AlH_2(OC_2H_5)_2]$, which is milder than $LiAlH_4$; the amide must be tertiary ($—CONR_2$, where $R \neq H$).
c. acyl chlorides:  cyclohexanecarbonyl chloride cyclohexanecarbaldehyde	The reducing agent is prepared from $LiAlH_4$ and *tert*-butyl alcohol—it is milder than $LiAlH_4$ (see Method 5b); the preferred solvent is diglyme, $(CH_3OCH_2CH_2)_2O$.

6. *addition of Grignard reagents to 1,1,1-triethoxymethane (ethyl orthoformate)*



The addition product is an acetal, which can be hydrolyzed in dilute acid to the aldehyde.

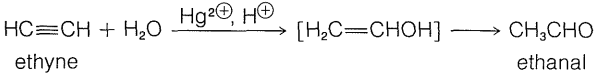
7. *addition of organometallic compounds to* N,N-*dimethylmethanamide*



1-cycloheptenecarbaldehyde

The tertiary amine, $R_2CHN(CH_3)_2$, often is a major product with RMgX and $HCON(CH_3)_2$. See Section 14-12C.

8. *hydration of alkynes*



A commercial synthesis of ethanal; see Section 10-5A.

9. *hydrolysis of aldehyde derivatives*—includes hydrogen sulfite addition compounds, acetals, oximes, Schiff's bases, hydrazones, and semicarbazones

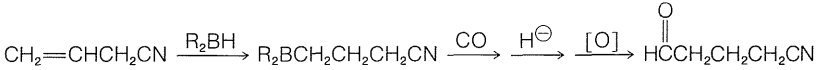
More useful for the purification than for preparation of aldehydes.

10. *addition of carbon monoxide and hydrogen to alkenes*

cyclopentene — cyclopentanecarbaldehyde (65%)

See Section 16-9F.

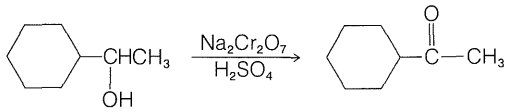
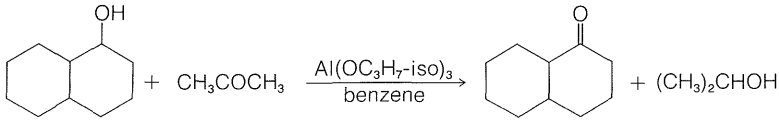
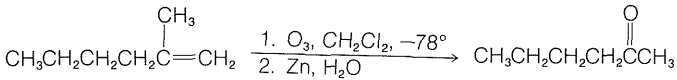
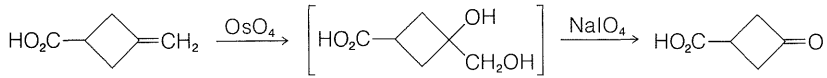
11. *hydroboration of alkenes and carbonylation of alkylboranes*



See Section 16-9G; R_2BH = "9-BBN"

[a]Preparations of aromatic aldehydes are described in Chapters 22 and 26.

Table 16-8
General Methods for the Preparation of Ketones[a]

Reaction	Comment
1. *oxidation of secondary alcohols*, $R_2CHOH \xrightarrow{[O]} R_2C{=}O$	See Section 15-6.
a. with chromic acid:  1-cyclohexylethanol 1-cyclohexylethanone	
b. Oppenauer oxidation:  α-decalol 2-propanone α-decalone	See Section 16-4E.
2. *oxidation of alkenes*, $R_2C{=}CR_2 \xrightarrow{[O]} 2R_2C{=}O$	See Section 11-7A and Method 1, Table 16-7.
a. with ozone: 	
b. via 1,2-diols:  3-methylenecyclobutanecarboxylic acid 3-oxocyclobutanecarboxylic acid	See Section 16-9A and Method 2, Table 16-7.

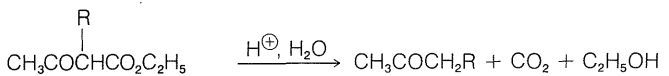
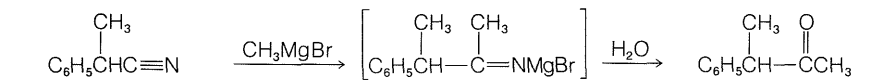
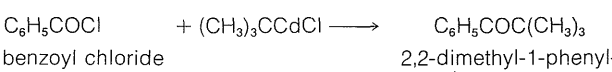
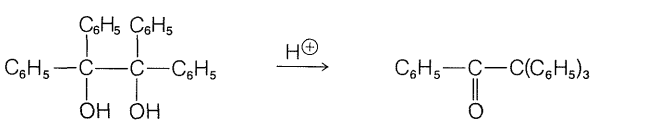
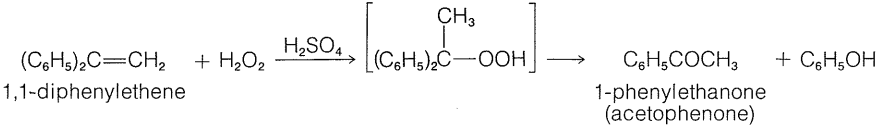
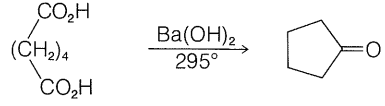
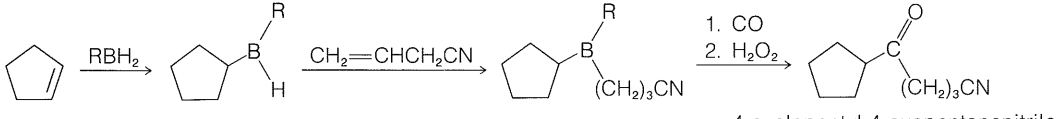
Reaction	Comment
3. *cleavage of β-keto esters*  ethyl 2-alkyl-3-oxobutanoate (alkylacetoacetic ester)	This is an important method based on ketonic cleavage of β-keto esters; see Chapter 18.
4. *addition of organometallic compounds to multiple bonds* a. nitriles:  2-phenylpropanenitrile 3-phenyl-2-butanone	For discussion of these reactions see Section 14-12C.
b. acyl chlorides:  benzoyl chloride 2,2-dimethyl-1-phenyl-1-propanone (phenyl *tert*-butyl ketone)	See Section 14-12C.
5. *rearrangement of 1,2-diols*  1,1,2,2-tetraphenylethane-1,2-diol (benzopinacol) 1,2,2,2-tetraphenylethanone (phenyl triphenylmethyl ketone)	See Section 16-9D.

Table 16-8 (continued)

Reaction	Comment
6. *rearrangements of hydroperoxides,* $R_3COOH \xrightarrow{H^{\oplus}} R_2C{=}O + ROH$  1,1-diphenylethene; 1-phenylethanone (acetophenone)	See Section 16-9E.
7. *thermal decarboxylation of carboxylic acids*  hexanedioic acid (adipic acid); cyclopentanone	The method is applicable to mono- and dibasic acids, as their calcium, barium, or thorium salts (Section 18-10B).
8. *hydroboration of alkenes and carbonylation of alkylboranes*  4-cyclopentyl-4-oxopentanenitrile	See Section 16-9G.

[a]Preparations of aromatic ketones are described in Chapters 22 and 26.

Supplementary Exercises

16-48 Write equations for the synthesis of the following substances based on the indicated starting materials. Give the reaction conditions as accurately as possible.

a. 2-methylpropanal from 3-methylbutanol
b. 1-cyclobutylethanone from cyclobutanecarboxylic acid
c. pentanedial from cyclopentanone
d. cyclobutane from methylenecyclobutane
e. 2,2,2-trichloroethyl trichloroethanoate from 2,2,2-trichloroethanal
f. cyclopentene-1-carboxylic acid from cyçlopentanone

16-49 Write reasonable mechanisms for each of the following reactions. Support your formulations with detailed analogies insofar as possible.

a. $$\mathrm{H{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}H + NaOH \xrightarrow{H_2O} HOCH_2CO_2Na}$$

b. $$CH_3COCH_3 + NH_2OH \xrightarrow[H_2O]{Na_2CO_3} CH_3C(NOH)CH_3 + H_2O$$

(Notice that this is a *base*-catalyzed reaction.)

c. $$\mathrm{CH_3{-}\overset{\overset{H}{|}}{\underset{\underset{Br}{|}}{C}}{-}\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{C}}{-}CH_3 \xrightarrow[H_2O]{Ag^{\oplus}} CH_3{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}CH_3}$$

d. Hexamethylenetetramine from methanal and ammonia. (Consider the possibility of $CH_2{=}NH$ as an intermediate for the stepwise formation of *N*,*N*′,*N*″-tris(hydroxymethyl)-1,3,5-triazacyclohexane as an intermediate followed by acid-induced condensation of the latter with ammonia.)

16-50 It is important to be able to decide whether a plausible-looking reaction actually will proceed as written. The following equations represent "possible" synthetic reactions. Consider each carefully and decide whether it will proceed as written. Show your reasoning. If you think another reaction would occur, write an equation for it.

a. $$CH_3CH(OC_2H_5)_2 + 2NaOCH_3 \xrightarrow[50^\circ]{\text{excess } CH_3OH} CH_3CH(OCH_3)_2 + 2NaOC_2H_5$$

b. $$(CH_3)_3CCOCH_2CH_3 + KMnO_4 \xrightarrow[KOH]{H_2O} (CH_3)_3COH + CH_3CH_2CO_2K$$

c. $$CH_3CCl(CH_3)CH_2Cl + 2NaOCH_3 \xrightarrow[50^\circ]{CH_3OH} CH_3C(CH_3)(OCH_3)CH_2OCH_3 + 2NaCl$$

d. $$\mathrm{CH_3CH_2CH{=}O + C_6H_5CO_3H \longrightarrow CH_3CH_2O{-}\overset{\overset{O}{\|}}{C}H + C_6H_5CO_2H}$$

e. $O{=}CH{-}CO_2H + NaBH_4 \xrightarrow{CH_3OH} O{=}CH{-}CH_2OH$

f. $CH_2{=}O + (CH_3)_2C{=}O + NaOH \longrightarrow HCO_2Na + (CH_3)_2CHOH$

16-51 Write a mechanism for the oxidation of sodium methanoate (formate) to carbon dioxide by potassium permanganate which is consistent with the following facts:

(a) $v = k[HCO_2^{\ominus}][MnO_4^{\ominus}]$

(b) the CO_2 has no ^{18}O in it if oxidized with $Mn^{18}O_4^{\ominus}$

(c) $DCO_2^{\ominus}$ is oxidized at one seventh the rate of $HCO_2^{\ominus}$

Compare your mechanism with that generally accepted for the Cannizzaro reaction.

16-52 2-Propanone reacts with trichloromethane in the presence of potassium hydroxide to give 1,1,1-trichloro-2-methyl-2-propanol. What is likely to be the mechanism of this reaction? What further evidence could be gained to establish the mechanism? (If you do not see a possible answer, refer to Section 14-7B for helpful information.)

16-53 The structure of the sex attractant of the silkworm, "bombykol," is given in Section 5-6 as structure **30**. The compound has been synthesized by the route given below. Write the structures of each of the synthetic intermediates A–F.

$$CH_3CH_2CH_2Br \xrightarrow{NaC{\equiv}CH} A \xrightarrow[2.\ HCHO]{1.\ CH_3MgCl} B \xrightarrow{PBr_3} C$$

$$C \xrightarrow{(C_6H_5)_3P} D \xrightarrow[2.\ O{=}CH(CH_2)_8CO_2C_2H_5]{1.\ base\ (C_2H_5\overset{\ominus\ \oplus}{O}Na)} E \xrightarrow[(Lindlar)]{H_2,\ Pd} F$$

$$F \xrightarrow{LiAlH_4} \text{"bombykol"}$$