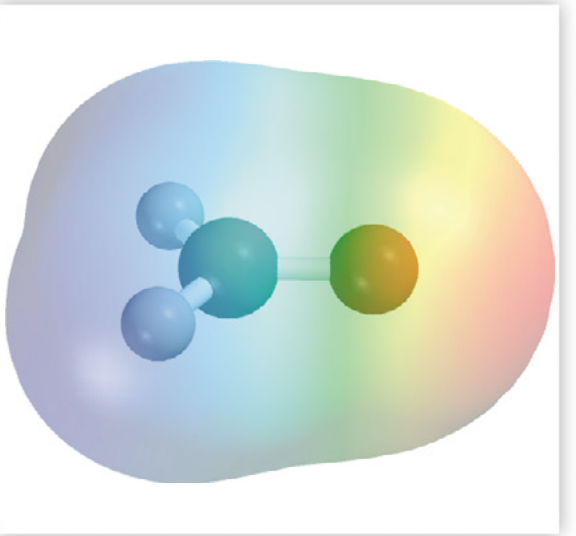


CHAPTER 17

ALDEHYDES AND KETONES: NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP

Aldehydes and ketones contain an acyl group $RC(=O)-$ bonded either to hydrogen or to another carbon.

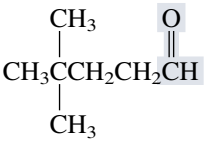
$HC(=O)H$	$RC(=O)H$	$RC(=O)R'$
Formaldehyde	Aldehyde	Ketone

Although the present chapter includes the usual collection of topics designed to acquaint us with a particular class of compounds, its central theme is a fundamental reaction type, *nucleophilic addition to carbonyl groups.* The principles of nucleophilic addition to aldehydes and ketones developed here will be seen to have broad applicability in later chapters when transformations of various derivatives of carboxylic acids are discussed.

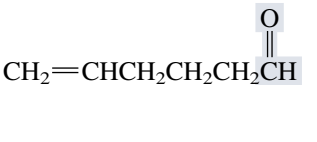
17.1 NOMENCLATURE

The longest continuous chain that contains the $-C(=O)H$ group provides the base name for aldehydes. The *-e* ending of the corresponding alkane name is replaced by *-al,* and substituents are specified in the usual way. It is not necessary to specify the location of the $-C(=O)H$ group in the name, since the chain must be numbered by starting with this group as C-1. The suffix *-dial* is added to the appropriate alkane name when the compound contains two aldehyde functions.*

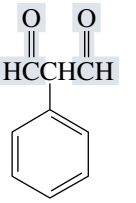
* The *-e* ending of an alkane name is dropped before a suffix beginning with a vowel *(-al)* and retained before one beginning with a consonant *(-dial).*



4,4-Dimethylpentanal

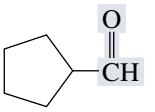


5-Hexenal

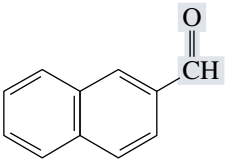


2-Phenylpropanedial

When a formyl group (—CH═O) is attached to a ring, the ring name is followed by the suffix *-carbaldehyde.*



Cyclopentanecarbaldehyde

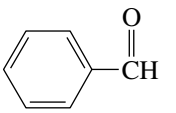


2-Naphthalenecarbaldehyde

Certain common names of familiar aldehydes are acceptable as IUPAC names. A few examples include

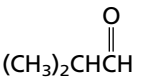
Formaldehyde
(methanal)

Acetaldehyde
(ethanal)

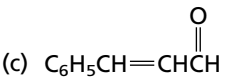


Benzaldehyde
(benzenecarbaldehyde)

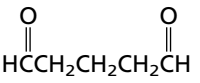
PROBLEM 17.1 The common names and structural formulas of a few aldehydes follow. Provide an IUPAC name.

(a) 

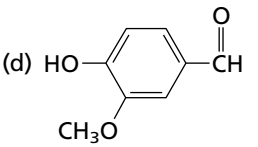
(isobutyraldehyde)

(c) 

(cinnamaldehyde)

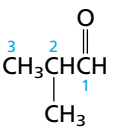
(b) 

(glutaraldehyde)

(d) 

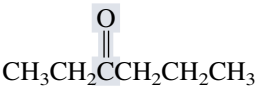
(vanillin)

SAMPLE SOLUTION (a) Don't be fooled by the fact that the common name is isobutyraldehyde. The longest continuous chain has three carbons, and so the base name is *propanal.* There is a methyl group at C-2; thus the compound is 2-methylpropanal.

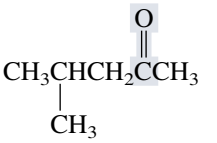


2-Methylpropanal
(isobutyraldehyde)

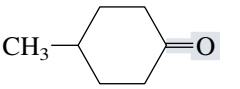
With ketones, the *-e* ending of an alkane is replaced by *-one* in the longest continuous chain containing the carbonyl group. The chain is numbered in the direction that provides the lower number for this group.



3-Hexanone

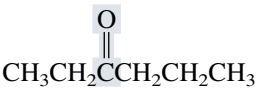


4-Methyl-2-pentanone

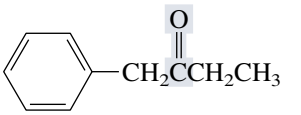


4-Methylcyclohexanone

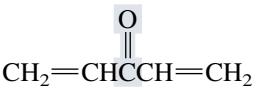
Although substitutive names of the type just described are preferred, the IUPAC rules also permit ketones to be named by functional class nomenclature. The groups attached to the carbonyl group are named as separate words followed by the word "ketone." The groups are listed alphabetically.



Ethyl propyl ketone



Benzyl ethyl ketone

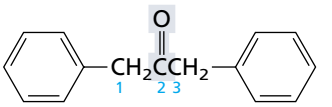


Divinyl ketone

PROBLEM 17.2 Convert each of the following functional class IUPAC names to a substitutive name.

(a) Dibenzyl ketone
(b) Ethyl isopropyl ketone
(c) Methyl 2,2-dimethylpropyl ketone
(d) Allyl methyl ketone

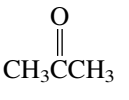
SAMPLE SOLUTION (a) First write the structure corresponding to the name. Dibenzyl ketone has two benzyl groups attached to a carbonyl.



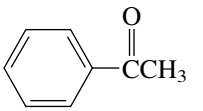
Dibenzyl ketone

The longest continuous chain contains three carbons, and C-2 is the carbon of the carbonyl group. The substitutive IUPAC name for this ketone is *1,3-diphenyl-2-propanone.*

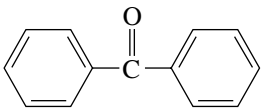
A few of the common names acceptable for ketones in the IUPAC system are



Acetone



Acetophenone

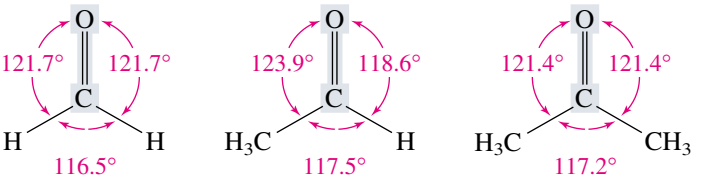


Benzophenone

(The suffix *-phenone* indicates that the acyl group is attached to a benzene ring.)

17.2 STRUCTURE AND BONDING: THE CARBONYL GROUP

Two notable aspects of the carbonyl group are its geometry and its polarity. The carbonyl group and the atoms directly attached to it lie in the same plane. Formaldehyde, for example, is planar. The bond angles involving the carbonyl group of aldehydes and ketones are close to 120°.



Formaldehyde Acetaldehyde Acetone

Verify their geometries by making models of formaldehyde, acetaldehyde, and acetone. Make sure you execute the minimization routine.

At 122 pm, the carbon–oxygen double bond distance in aldehydes and ketones is significantly shorter than the typical carbon–oxygen single bond distance of 141 pm in alcohols and ethers.

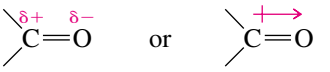
The carbonyl group makes aldehydes and ketones rather polar, with molecular dipole moments that are substantially larger than those of comparable compounds that contain carbon–carbon double bonds.

$CH_3CH_2CH{=}CH_2$	$CH_3CH_2CH{=}O$
1-Butene	Propanal
Dipole moment: 0.3 D	Dipole moment: 2.5 D

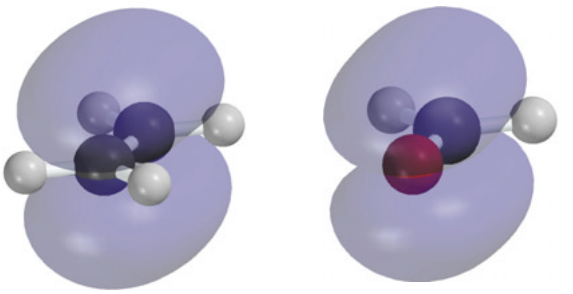
Compare the dipole moments and electrostatic potential maps of 1-butene and propanal on *Learning By Modeling.*

Bonding in formaldehyde can be described according to an sp^2 hybridization model analogous to that of ethylene, as shown in Figure 17.1.

Figure 17.2 compares the electrostatic potential surfaces of ethylene and formaldehyde and vividly demonstrates how oxygen affects the electron distribution in formaldehyde. The electron density in both the σ and π components of the carbon–oxygen double bond is displaced toward oxygen. The carbonyl group is polarized so that carbon is partially positive and oxygen is partially negative.



In resonance terms, electron delocalization in the carbonyl group is represented by contributions from two principal resonance structures:



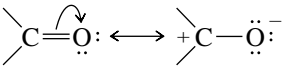
(*a*) Ethylene (*b*) Formaldehyde

FIGURE 17.1 Similarities between the orbital hybridization models of bonding in (*a*) ethylene and (*b*) formaldehyde. Both molecules have the same number of electrons, and carbon is sp^2-hybridized in both. In formaldehyde, one of the carbons is replaced by an sp^2-hybridized oxygen *(shown in red).* Oxygen has two unshared electron pairs; each pair occupies an sp^2-hybridized orbital. Like the carbon–carbon double bond of ethylene, the carbon–oxygen double bond of formaldehyde is composed of a two-electron σ component and a two-electron π component.

(*a*) Ethylene (*b*) Formaldehyde

FIGURE 17.2 Differences in the electron distribution of (*a*) ethylene and (*b*) formaldehyde. The region of highest electrostatic potential (*red*) in ethylene lies above and below the plane of the atoms and is associated with the π electrons. The region close to oxygen is the site of highest electrostatic potential in formaldehyde.

The chemistry of the carbonyl group is considerably simplified if you remember that carbon is partially positive (has carbocation character) and oxygen is partially negative (weakly basic).



A B

Of these two, A, having one more covalent bond and avoiding the separation of positive and negative charges that characterizes B, better approximates the bonding in a carbonyl group.

Alkyl substituents stabilize a carbonyl group in much the same way that they stabilize carbon–carbon double bonds and carbocations—by releasing electrons to sp^2-hybridized carbon. Thus, as their heats of combustion reveal, the ketone 2-butanone is more stable than its aldehyde isomer butanal.

	$CH_3CH_2CH_2CH(=O)$	$CH_3CH_2C(=O)CH_3$
	Butanal	2-Butanone
Heat of combustion:	2475 kJ/mol (592 kcal/mol)	2442 kJ/mol (584 kcal/mol)

The carbonyl carbon of a ketone bears two electron-releasing alkyl groups; an aldehyde carbonyl group has only one. Just as a disubstituted double bond in an alkene is more stable than a monosubstituted double bond, a ketone carbonyl is more stable than an aldehyde carbonyl. We'll see later in this chapter that structural effects on the relative *stability* of carbonyl groups in aldehydes and ketones are an important factor in their relative *reactivity*.

17.3 PHYSICAL PROPERTIES

Physical constants such as melting point, boiling point, and solubility in water are collected for a variety of aldehydes and ketones in Appendix 1.

In general, aldehydes and ketones have higher boiling points than alkenes because they are more polar and the dipole–dipole attractive forces between molecules are stronger. But they have lower boiling points than alcohols because, unlike alcohols, two carbonyl groups can't form hydrogen bonds to each other.

	$CH_3CH_2CH=CH_2$	$CH_3CH_2CH=O$	$CH_3CH_2CH_2OH$
	1-Butene	Propanal	1-Propanol
bp (1 atm)	−6°C	49°C	97°C
Solubility in water (g/100 mL)	Negligible	20	Miscible in all proportions

Aldehydes and ketones can form hydrogen bonds with the protons of OH groups. This makes them more soluble in water than alkenes, but less soluble than alcohols.

17.4 SOURCES OF ALDEHYDES AND KETONES

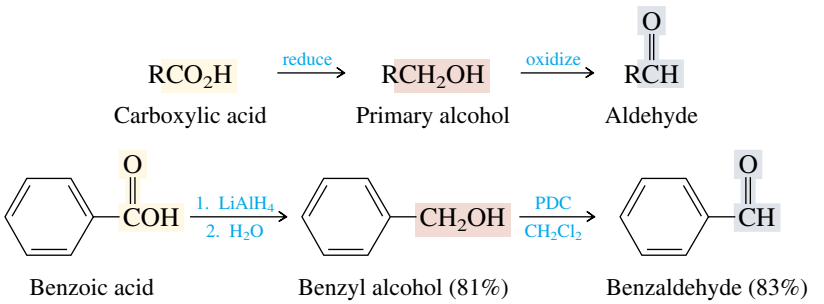
As we'll see later in this chapter and the next, aldehydes and ketones are involved in many of the most used reactions in synthetic organic chemistry. Where do aldehydes and ketones come from?

Many occur naturally. In terms of both variety and quantity, aldehydes and ketones rank among the most common and familiar natural products. Several are shown in Figure 17.3.

Many are made in the laboratory from alkenes, alkynes, arenes, and alcohols by reactions that you already know about and are summarized in Table 17.1.

To the synthetic chemist, the most important of the reactions in Table 17.1 are the last two: the oxidation of primary alcohols to aldehydes and secondary alcohols to ketones. *Indeed, when combined with reactions that yield alcohols, the oxidation methods are so versatile that it will not be necessary to introduce any new methods for preparing aldehydes and ketones in this chapter.* A few examples will illustrate this point.

Let's first consider how to prepare an aldehyde from a carboxylic acid. There are no good methods for going from RCO_2H to RCHO directly. Instead, we do it indirectly by first reducing the carboxylic acid to the corresponding primary alcohol, then oxidizing the primary alcohol to the aldehyde.



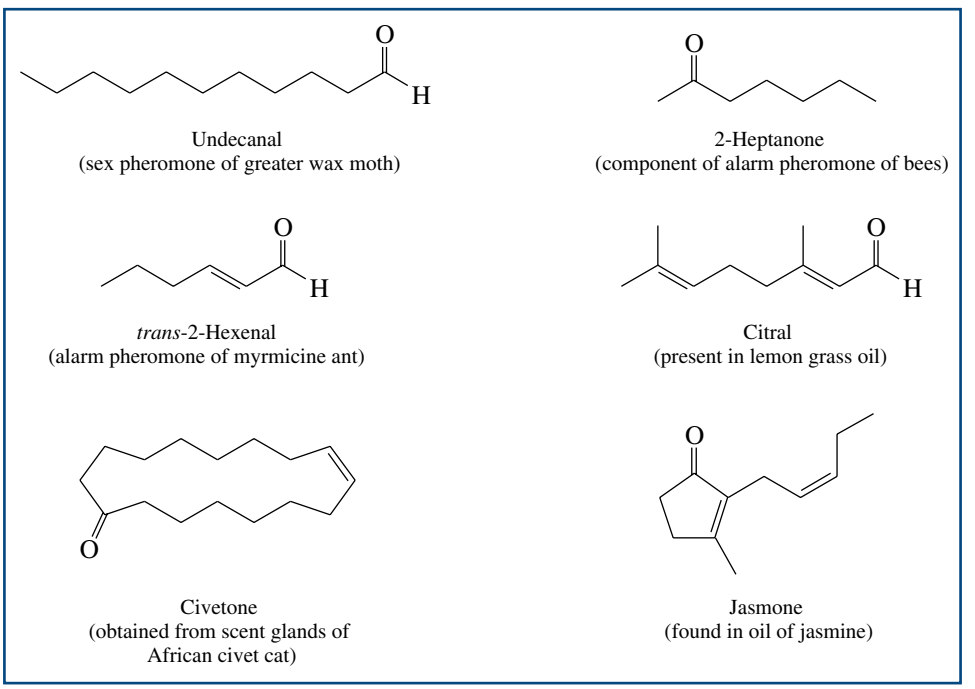
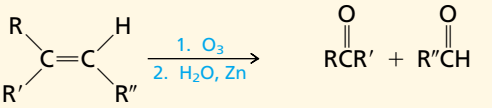
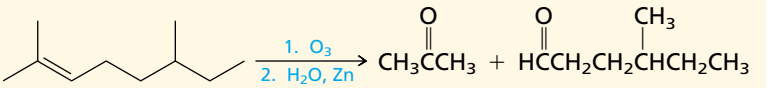
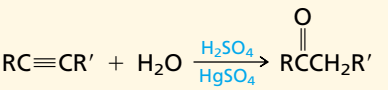
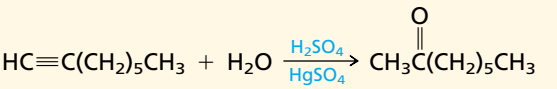
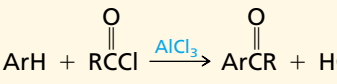
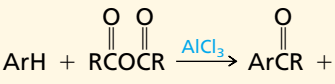
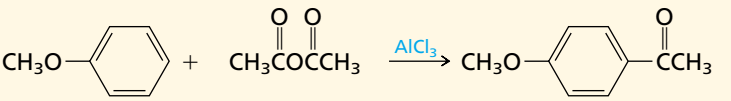
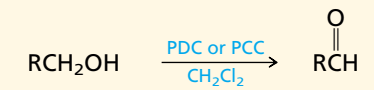
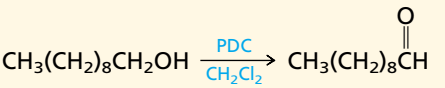
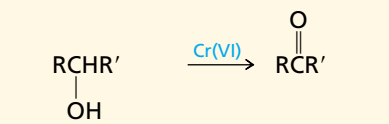
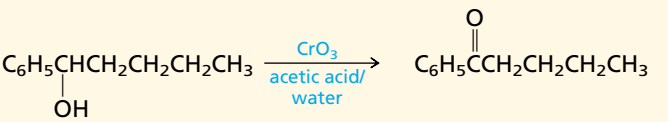


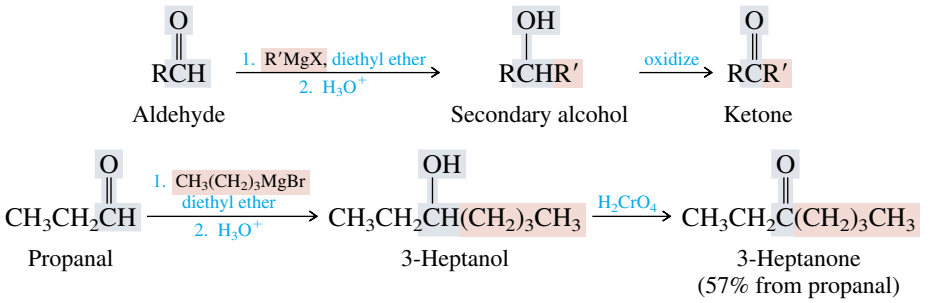
FIGURE 17.3 Some naturally occurring aldehydes and ketones.

TABLE 17.1 Summary of Reactions Discussed in Earlier Chapters That Yield Aldehydes and Ketones

Reaction (section) and comments	General equation and specific example
Ozonolysis of alkenes (Section 6.19) This cleavage reaction is more often seen in structural analysis than in synthesis. The substitution pattern around a double bond is revealed by identifying the carbonyl-containing compounds that make up the product. Hydrolysis of the ozonide intermediate in the presence of zinc (reductive workup) permits aldehyde products to be isolated without further oxidation.	 Alkene — Two carbonyl compounds  2,6-Dimethyl-2-octene — Acetone — 4-Methylhexanal (91%)
Hydration of alkynes (Section 9.12) Reaction occurs by way of an enol intermediate formed by Markovnikov addition of water to the triple bond.	 Alkyne — Ketone  1-Octyne — 2-Octanone (91%)
Friedel–Crafts acylation of aromatic compounds (Section 12.7) Acyl chlorides and carboxylic acid anhydrides acylate aromatic rings in the presence of aluminum chloride. The reaction is electrophilic aromatic substitution in which acylium ions are generated and attack the ring.	 or   Anisole — Acetic anhydride — *p*-Methoxyacetophenone (90–94%)
Oxidation of primary alcohols to aldehydes (Section 15.10) Pyridinium dichromate (PDC) or pyridinium chlorochromate (PCC) in anhydrous media such as dichloromethane oxidizes primary alcohols to aldehydes while avoiding overoxidation to carboxylic acids.	 Primary alcohol — Aldehyde  1-Decanol — Decanal (98%)
Oxidation of secondary alcohols to ketones (Section 15.10) Many oxidizing agents are available for converting secondary alcohols to ketones. PDC or PCC may be used, as well as other Cr(VI)-based agents such as chromic acid or potassium dichromate and sulfuric acid.	 Secondary alcohol — Ketone  1-Phenyl-1-pentanol — 1-Phenyl-1-pentanone (93%)

PROBLEM 17.3 Can catalytic hydrogenation be used to reduce a carboxylic acid to a primary alcohol in the first step of this sequence?

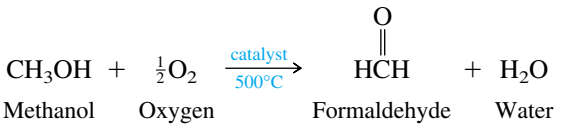
It is often necessary to prepare ketones by processes involving carbon–carbon bond formation. In such cases the standard method combines addition of a Grignard reagent to an aldehyde with oxidation of the resulting secondary alcohol:



PROBLEM 17.4 Show how 2-butanone could be prepared by a procedure in which all of the carbons originate in acetic acid (CH_3CO_2H).

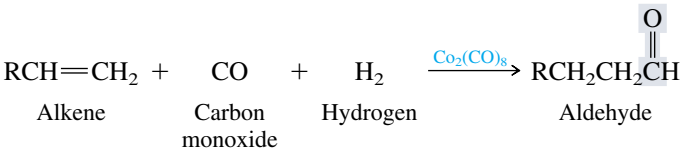
Many low-molecular-weight aldehydes and ketones are important industrial chemicals. Formaldehyde, a starting material for a number of plastics, is prepared by oxidation of methanol over a silver or iron oxide/molybdenum oxide catalyst at elevated temperature.

The name *aldehyde* was invented to stand for *al*cohol *dehyd*rogenatum, indicating that aldehydes are related to alcohols by loss of hydrogen.



Similar processes are used to convert ethanol to acetaldehyde and isopropyl alcohol to acetone.

The "linear α-olefins" described in Section 14.15 are starting materials for the preparation of a variety of aldehydes by reaction with carbon monoxide. The process is called **hydroformylation.**



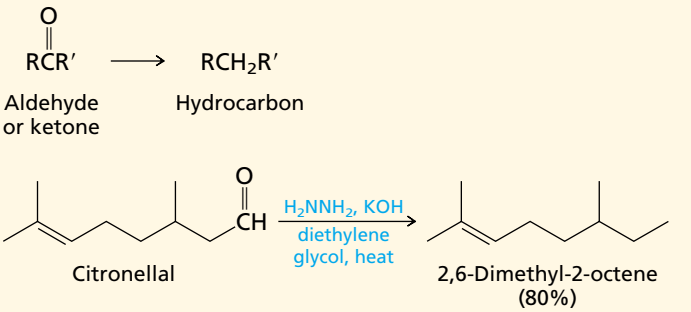
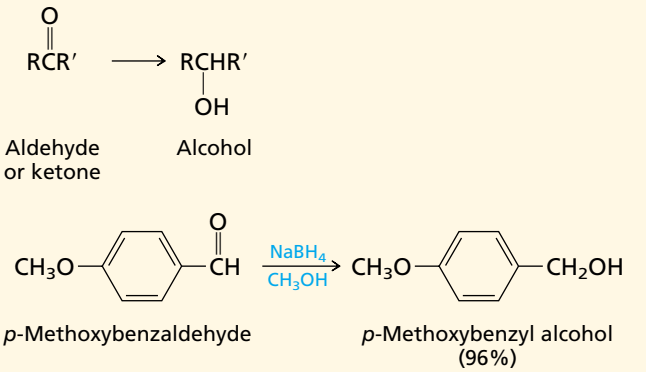
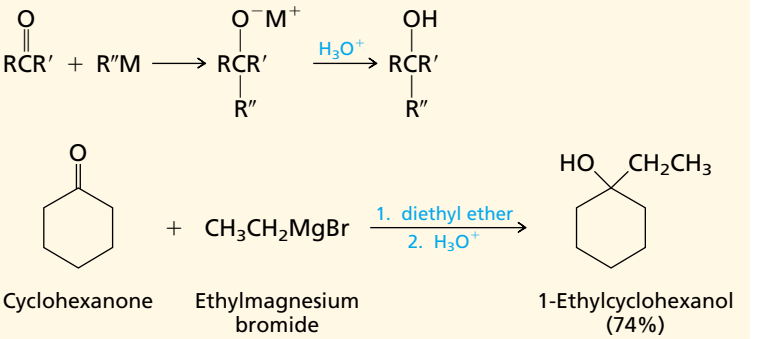
Excess hydrogen brings about the hydrogenation of the aldehyde and allows the process to be adapted to the preparation of primary alcohols. Over 2×10^9 lb/year of a variety of aldehydes and alcohols is prepared in the United States by hydroformylation.

A number of aldehydes and ketones are prepared both in industry and in the laboratory by a reaction known as the *aldol condensation,* which will be discussed in detail in Chapter 18.

17.5 REACTIONS OF ALDEHYDES AND KETONES: A REVIEW AND A PREVIEW

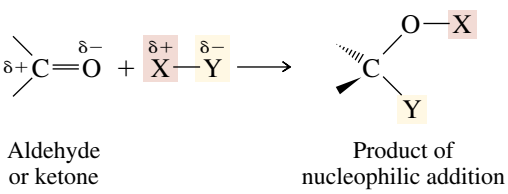
Table 17.2 summarizes the reactions of aldehydes and ketones that you've seen in earlier chapters. All are valuable tools to the synthetic chemist. Carbonyl groups provide access to hydrocarbons by Clemmensen of Wolff–Kishner reduction (Section 12.8), to

TABLE 17.2 Summary of Reactions of Aldehydes and Ketones Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Reduction to hydrocarbons (Section 12.8) Two methods for converting carbonyl groups to methylene units are the Clemmensen reduction (zinc amalgam and concentrated hydrochloric acid) and the Wolff–Kishner reduction (heat with hydrazine and potassium hydroxide in a high-boiling alcohol).	
Reduction to alcohols (Section 15.2) Aldehydes are reduced to primary alcohols, and ketones are reduced to secondary alcohols by a variety of reducing agents. Catalytic hydrogenation over a metal catalyst and reduction with sodium borohydride or lithium aluminum hydride are general methods.	
Addition of Grignard reagents and organolithium compounds (Sections 14.6–14.7) Aldehydes are converted to secondary alcohols and ketones to tertiary alcohols.	

alcohols by reduction (Section 15.2) or by reaction with Grignard or organolithium reagents (Sections 14.6 and 14.7).

The most important chemical property of the carbonyl group is its tendency to undergo *nucleophilic addition* reactions of the type represented in the general equation:

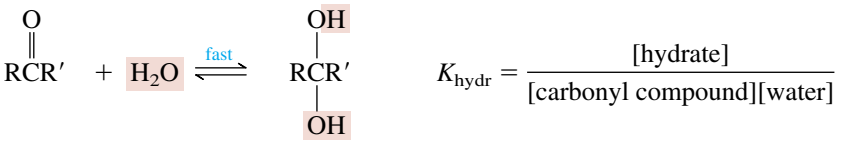


A negatively polarized atom or group attacks the positively polarized carbon of the carbonyl group in the rate-determining step of these reactions. Grignard reagents, organolithium reagents, lithium aluminum hydride, and sodium borohydride, for example, all react with carbonyl compounds by nucleophilic addition.

The next section explores the mechanism of nucleophilic addition to aldehydes and ketones. There we'll discuss their *hydration,* a reaction in which water adds to the C=O group. After we use this reaction to develop some general principles, we'll then survey a number of related reactions of synthetic, mechanistic, or biological interest.

17.6 PRINCIPLES OF NUCLEOPHILIC ADDITION: HYDRATION OF ALDEHYDES AND KETONES

Effects of Structure on Equilibrium: Aldehydes and ketones react with water in a rapid equilibrium:



$$K_{hydr} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}][\text{water}]}$$

Overall, the reaction is classified as an *addition.* The elements of water add to the carbonyl group. Hydrogen becomes bonded to the negatively polarized carbonyl oxygen, hydroxyl to the positively polarized carbon.

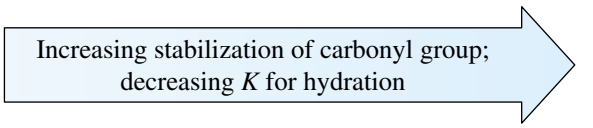
Table 17.3 compares the equilibrium constants K_{hydr} for hydration of some simple aldehydes and ketones. The position of equilibrium depends on what groups are attached to C=O and how they affect its *steric* and *electronic* environment. Both effects contribute, but the electronic effect controls K_{hydr} more than the steric effect.

TABLE 17.3 Equilibrium Constants (K_{hydr}) for Hydration of Some Aldehydes and Ketones

Carbonyl compound	Hydrate	K_{hydr}*	Percent conversion to hydrate†
HCH=O	$CH_2(OH)_2$	41	99.96
CH_3CH=O	$CH_3CH(OH)_2$	1.8×10^{-2}	50
$(CH_3)_3CCH$=O	$(CH_3)_3CCH(OH)_2$	4.1×10^{-3}	19
CH_3CCH_3=O	$(CH_3)_2C(OH)_2$	2.5×10^{-5}	0.14

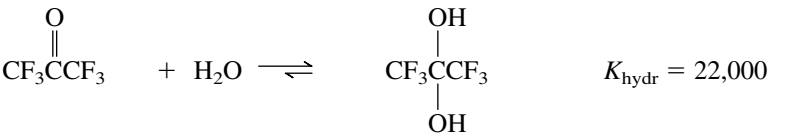
*$K_{hydr} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}][\text{water}]}$. Units of K_{hydr} are M^{-1}.
†Total concentration (hydrate plus carbonyl compound) assumed to be 1 M. Water concentration is 55.5 M.

Consider first the electronic effect of alkyl groups versus hydrogen atoms attached to C═O. Recall from Section 17.2 that alkyl substituents stabilize C═O, making a ketone carbonyl more stable than an aldehyde carbonyl. As with all equilibria, factors that stabilize the reactants decrease the equilibrium constant. Thus, the extent of hydration decreases as the number of alkyl groups on the carbonyl increase.



Formaldehyde	Acetaldehyde	Acetone
(almost completely hydrated in water)	(comparable amounts of aldehyde and hydrate present in water)	(hardly any hydrate present in water)

A striking example of an electronic effect on carbonyl group stability and its relation to the equilibrium constant for hydration is seen in the case of hexafluoroacetone. In contrast to the almost negligible hydration of acetone, hexafluoroacetone is completely hydrated.

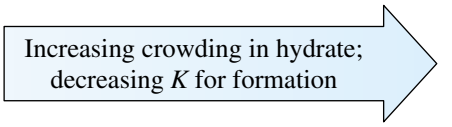


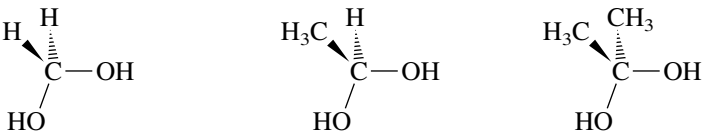
Hexafluoroacetone Water 1,1,1,3,3,3-Hexafluoro-2,2-propanediol

Instead of stabilizing the carbonyl group by electron donation as alkyl substituents do, trifluoromethyl groups destabilize it by withdrawing electrons. A less stabilized carbonyl group is associated with a greater equilibrium constant for addition.

PROBLEM 17.5 *Chloral* is one of the common names for trichloroethanal. A solution of chloral in water is called *chloral hydrate;* this material has featured prominently in countless detective stories as the notorious "Mickey Finn" knockout drops. Write a structural formula for chloral hydrate.

Now let's turn our attention to steric effects by looking at how the size of the groups that were attached to C═O affect K_{hydr}. The bond angles at carbon shrink from ≈120° to ≈109.5° as the hybridization changes from sp^2 in the reactant (aldehyde or ketone) to sp^3 in the product (hydrate). The increased crowding this produces in the hydrate is better tolerated, and K_{hydr} is greater when the groups are small (hydrogen) than when they are large (alkyl).





Hydrate of formaldehyde Hydrate of acetaldehyde Hydrate of acetone

Electronic and steric effects operate in the same direction. Both cause the equilibrium constants for hydration of aldehydes to be greater than those of ketones.

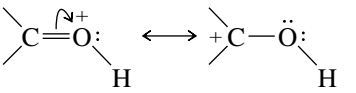
Mechanism of Hydration: Hydration of aldehydes and ketones is a rapid reaction, quickly reaching equilibrium, but faster in acid or base than in neutral solution. Thus instead of a single mechanism for hydration, we'll look at two mechanisms, one for basic and the other for acidic solution.

The base-catalyzed mechanism (Figure 17.4) is a two-step process in which the first step is rate-determining. In it, the nucleophile, a hydroxide ion, attacks the carbon of the carbonyl group and bonds to it. The product of this step is an alkoxide ion, which abstracts a proton from water in the second step, yielding the geminal diol. The second step, like all the other proton transfers between oxygens that we have seen, is fast.

The role of the basic catalyst (HO^-) is to increase the rate of the nucleophilic addition step. Hydroxide ion, the nucleophile in the base-catalyzed reaction, is much more reactive than a water molecule, the nucleophile in neutral media.

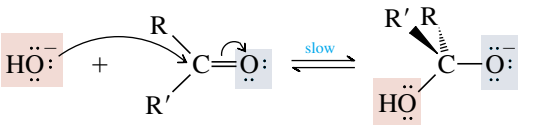
Aldehydes react faster than ketones for almost the same reasons that their equilibrium constants for hydration are more favorable. The $sp^2 \rightarrow sp^3$ hybridization change that the carbonyl carbon undergoes on hydration is partially developed in the transition state for the rate-determining nucleophilic addition step (Figure 17.5). Alkyl groups at the reaction site increase the activation energy by simultaneously lowering the energy of the starting state (ketones have a more stabilized carbonyl group than aldehydes) and raising the energy of the transition state (a steric crowding effect).

Three steps are involved in the acid-catalyzed hydration reaction, as shown in Figure 17.6. The first and last are rapid proton-transfer processes. The second is the nucleophilic addition step. The acid catalyst activates the carbonyl group toward attack by a weakly nucleophilic water molecule. Protonation of oxygen makes the carbonyl carbon of an aldehyde or a ketone much more electrophilic. Expressed in resonance terms, the protonated carbonyl has a greater degree of carbocation character than an unprotonated carbonyl.



Learning By Modeling includes models of formaldehyde ($H_2C{=}O$) and its protonated form ($H_2C{=}OH^+$). Compare the two with respect to their electrostatic potential maps and the degree of positive charge at carbon.

Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group



Step 2: Proton transfer from water to the intermediate formed in the first step

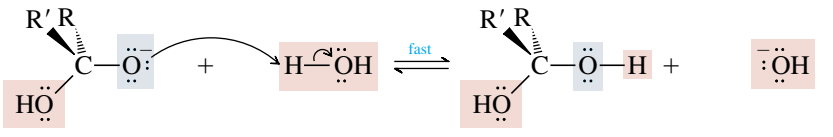


FIGURE 17.4 The mechanism of hydration of an aldehyde or ketone in basic solution. Hydroxide ion is a catalyst; it is consumed in the first step, and regenerated in the second.

FIGURE 17.5 Potential energy diagram for base-catalyzed hydration of an aldehyde or ketone.

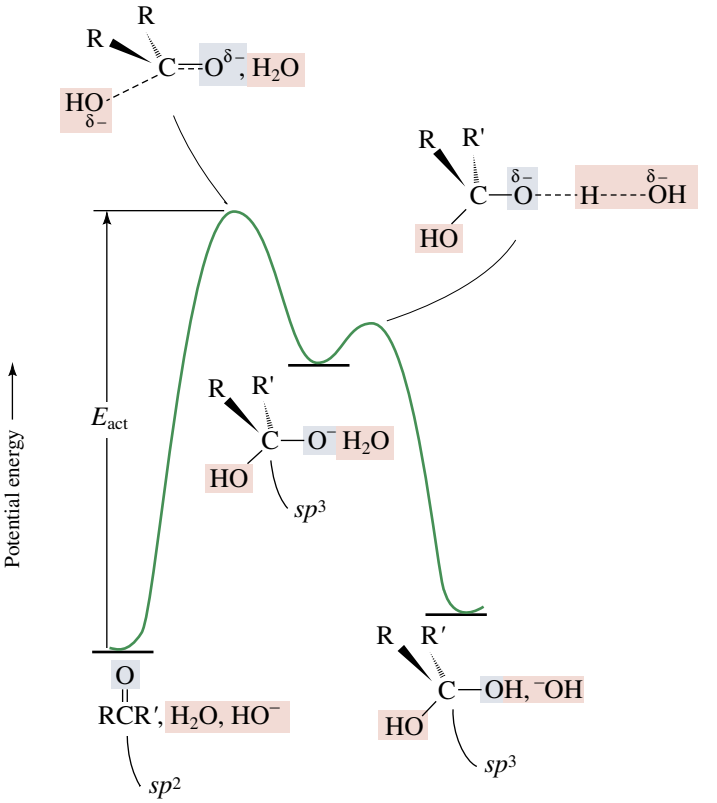
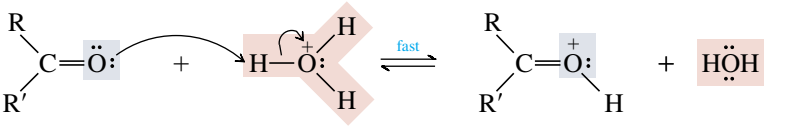


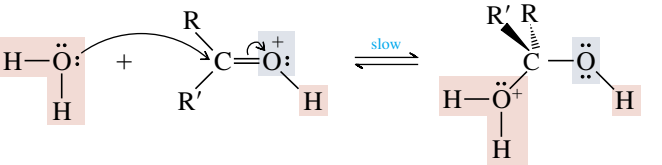
FIGURE 17.6 The mechanism of hydration of an aldehyde or ketone in acidic solution. Hydronium ion is a catalyst; it is consumed in the first step, and regenerated in the third.

Step 1: Protonation of the carbonyl oxgyen



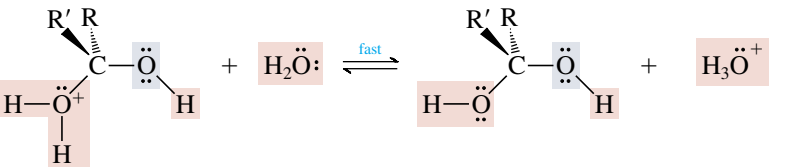
Aldehyde or ketone | Hydronium ion | Conjugate acid of carbonyl compound | Water

Step 2: Nucleophilic addition to the protonated aldehyde or ketone



Water | Conjugate acid of carbonyl compound | Conjugate acid of geminal diol

Step 3: Proton transfer from the conjugate acid of the geminal diol to a water molecule



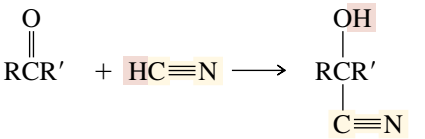
Conjugate acid of geminal diol | Water | Geminal diol | Hydronium ion

Steric and electronic effects influence the rate of nucleophilic addition to a protonated carbonyl group in much the same way as they do for the case of a neutral one, and protonated aldehydes react faster than protonated ketones.

With this as background, let us now examine how the principles of nucleophilic addition apply to the characteristic reactions of aldehydes and ketones. We'll begin with the addition of hydrogen cyanide.

17.7 CYANOHYDRIN FORMATION

The product of addition of hydrogen cyanide to an aldehyde or a ketone contains both a hydroxyl group and a cyano group bonded to the same carbon. Compounds of this type are called **cyanohydrins.**



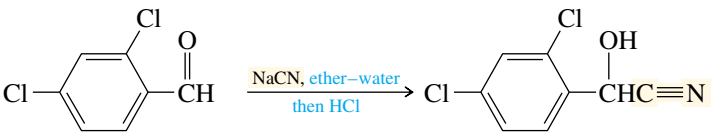
Aldehyde or ketone — Hydrogen cyanide — Cyanohydrin

The mechanism of this reaction is outlined in Figure 17.7. It is analogous to the mechanism of base-catalyzed hydration in that the nucleophile (cyanide ion) attacks the carbonyl carbon in the first step of the reaction, followed by proton transfer to the carbonyl oxygen in the second step.

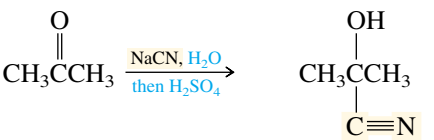
The addition of hydrogen cyanide is catalyzed by cyanide ion, but HCN is too weak an acid to provide enough $:\bar{C}{\equiv}N:$ for the reaction to proceed at a reasonable rate. Cyanohydrins are therefore normally prepared by adding an acid to a solution containing the carbonyl compound and sodium or potassium cyanide. This procedure ensures that free cyanide ion is always present in amounts sufficient to increase the rate of the reaction.

Cyanohydrin formation is reversible, and the position of equilibrium depends on the steric and electronic factors governing nucleophilic addition to carbonyl groups described in the preceding section. Aldehydes and unhindered ketones give good yields of cyanohydrins.

In substitutive IUPAC nomenclature, cyanohydrins are named as hydroxy derivatives of nitriles. Since nitrile nomenclature will not be discussed until Section 20.1, we will refer to cyanohydrins as derivatives of the parent aldehyde or ketone as shown in the examples. This conforms to the practice of most chemists.



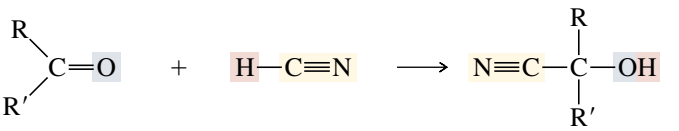
2,4-Dichlorobenzaldehyde — 2,4-Dichlorobenzaldehyde cyanohydrin (100%)



Acetone — Acetone cyanohydrin (77–78%)

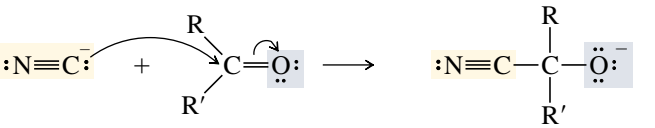
Converting aldehydes and ketones to cyanohydrins is of synthetic value for two reasons: (1) a new carbon–carbon bond is formed, and (2) the cyano group in the product can be converted to a carboxylic acid function (CO_2H) by hydrolysis (to be discussed in Section 19.12) or to an amine of the type CH_2NH_2 by reduction (to be discussed in Section 22.10).

The overall reaction:



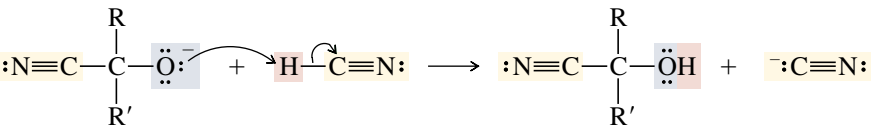
Aldehyde or ketone | Hydrogen cyanide | Cyanohydrin

Step 1: Nucleophilic attack by the negatively charged carbon of cyanide ion at the carbonyl carbon of the aldehyde or ketone. Hydrogen cyanide itself is not very nucleophilic and does not ionize to form cyanide ion to a significant extent. Thus, a source of cyanide ion such as NaCN or KCN is used.



Cyanide ion | Aldehyde or ketone | Conjugate base of cyanohydrin

Step 2: The alkoxide ion formed in the first step abstracts a proton from hydrogen cyanide. This step yields the cyanohydrin product and regenerates cyanide ion.



Conjugate base of cyanohydrin | Hydrogen cyanide | Cyanohydrin | Cyanide ion

FIGURE 17.7 The mechanism of cyanohydrin formation from an aldehyde or a ketone. Cyanide ion is a catalyst; it is consumed in the first step, and regenerated in the second.

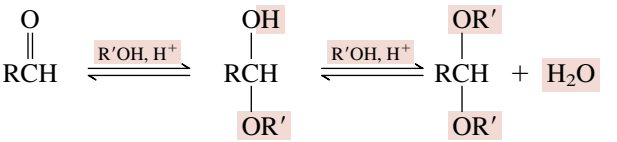
PROBLEM 17.6 The hydroxyl group of a cyanohydrin is also a potentially reactive site. *Methacrylonitrile* is an industrial chemical used in the production of plastics and fibers. One method for its preparation is the acid-catalyzed dehydration of acetone cyanohydrin. Deduce the structure of *methacrylonitrile.*

A few cyanohydrins and ethers of cyanohydrins occur naturally. One species of millipede stores benzaldehyde cyanohydrin, along with an enzyme that catalyzes its cleavage to benzaldehyde and hydrogen cyanide, in separate compartments above its legs. When attacked, the insect ejects a mixture of the cyanohydrin and the enzyme, repelling the invader by spraying it with hydrogen cyanide.

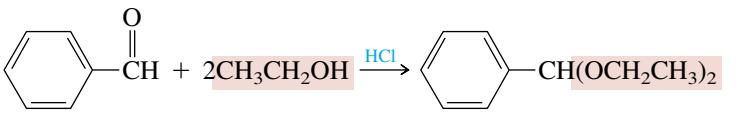
17.8 ACETAL FORMATION

Many of the most interesting and useful reactions of aldehydes and ketones involve transformation of the initial product of nucleophilic addition to some other substance under the reaction conditions. An example is the reaction of aldehydes with alcohols under con-

ditions of acid catalysis. The expected product of nucleophilic addition of the alcohol to the carbonyl group is called a **hemiacetal.** The product actually isolated, however, corresponds to reaction of one mole of the aldehyde with *two* moles of alcohol to give *geminal diethers* known as **acetals:**

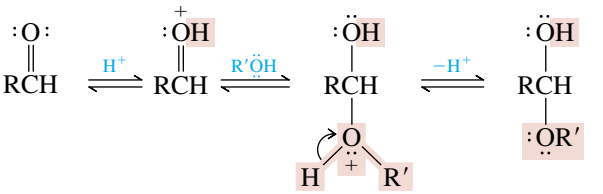


Aldehyde Hemiacetal Acetal Water



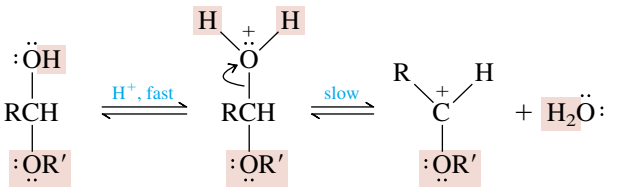
Benzaldehyde Ethanol Benzaldehyde diethyl acetal (66%)

The overall reaction proceeds in two stages. The hemiacetal is formed in the first stage by nucleophilic addition of the alcohol to the carbonyl group. The mechanism of hemiacetal formation is exactly analogous to that of acid-catalyzed hydration of aldehydes and ketones (Section 17.6):



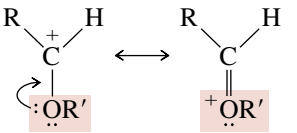
Aldehyde Hemiacetal

Under the acidic conditions of its formation, the hemiacetal is converted to an acetal by way of a carbocation intermediate:



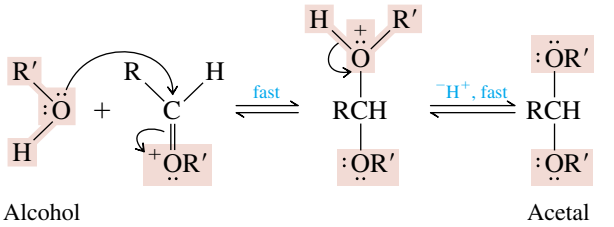
Hemiacetal Carbocation Water

This carbocation is stabilized by electron release from its oxygen substituent:



A particularly stable resonance form; both carbon and oxygen have octets of electrons.

Nucleophilic capture of the carbocation intermediate by an alcohol molecule leads to an acetal:



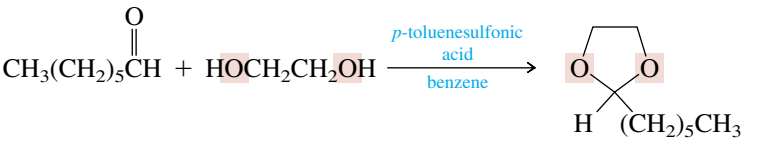
Alcohol Acetal

PROBLEM 17.7 Write a stepwise mechanism for the formation of benzaldehyde diethyl acetal from benzaldehyde and ethanol under conditions of acid catalysis.

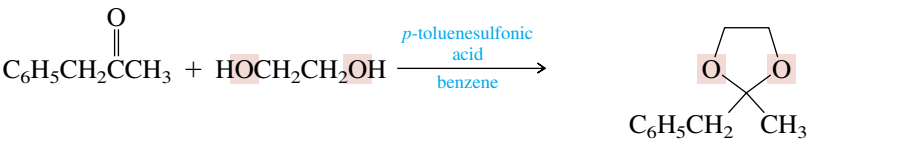
At one time it was customary to designate the products of addition of alcohols to ketones as *ketals*. This term has been dropped from the IUPAC system of nomenclature, and the term *acetal* is now applied to the adducts of both aldehydes and ketones.

Acetal formation is reversible in acid. An equilibrium is established between the reactants, that is, the carbonyl compound and the alcohol, and the acetal product. The position of equilibrium is favorable for acetal formation from most aldehydes, especially when excess alcohol is present as the reaction solvent. For most ketones the position of equilibrium is unfavorable, and other methods must be used for the preparation of acetals from ketones.

Diols that bear two hydroxyl groups in a 1,2 or 1,3 relationship to each other yield *cyclic acetals* on reaction with either aldehydes or ketones. The five-membered cyclic acetals derived from ethylene glycol are the most commonly encountered examples. Often the position of equilibrium is made more favorable by removing the water formed in the reaction by azeotropic distillation with benzene or toluene:



Heptanal Ethylene glycol (1,2-ethanediol) 2-Hexyl-1,3-dioxolane (81%)

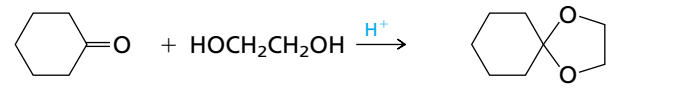


Benzyl methyl ketone Ethylene glycol (1,2-ethanediol) 2-Benzyl-2-methyl-1,3-dioxolane (78%)

PROBLEM 17.8 Write the structures of the cyclic acetals derived from each of the following.

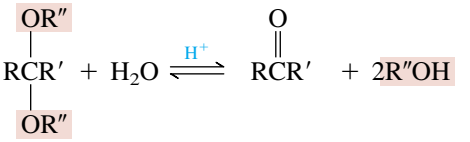
(a) Cyclohexanone and ethylene glycol
(b) Benzaldehyde and 1,3-propanediol
(c) Isobutyl methyl ketone and ethylene glycol
(d) Isobutyl methyl ketone and 2,2-dimethyl-1,3-propanediol

SAMPLE SOLUTION (a) The cyclic acetals derived from ethylene glycol contain a five-membered 1,3-dioxolane ring.



Cyclohexanone Ethylene glycol Acetal of cyclohexanone and ethylene glycol

Acetals are susceptible to hydrolysis in aqueous acid:



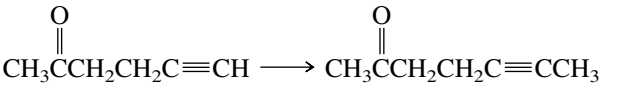
Acetal Aldehyde or ketone Alcohol

This reaction is simply the reverse of the reaction by which acetals are formed—acetal formation is favored by excess alcohol, acetal hydrolysis by excess water. Acetal formation and acetal hydrolysis share the same mechanistic pathway but travel along that pathway in opposite directions. In the following section you'll see a clever way in which acetal formation and hydrolysis have been applied to synthetic organic chemistry.

PROBLEM 17.9 Problem 17.7 asked you to write a mechanism describing formation of benzaldehyde diethyl acetal from benzaldehyde and ethanol. Write a stepwise mechanism for the acid hydrolysis of this acetal.

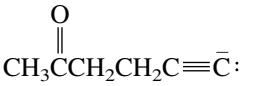
17.9 ACETALS AS PROTECTING GROUPS

In an organic synthesis, it sometimes happens that one of the reactants contains a functional group that is incompatible with the reaction conditions. Consider, for example, the conversion



5-Hexyn-2-one 5-Heptyn-2-one

It looks as though all that is needed is to prepare the acetylenic anion, then alkylate it with methyl iodide (Section 9.6). There is a complication, however. The carbonyl group in the starting alkyne will neither tolerate the strongly basic conditions required for anion formation nor survive in a solution containing carbanions. Acetylide ions add to carbonyl groups (Section 14.8). Thus, the necessary anion

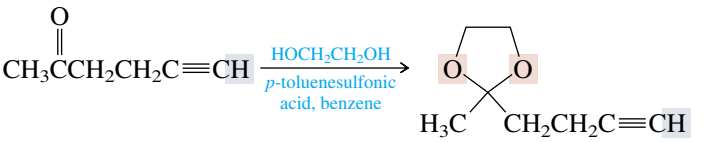


is inaccessible.

The strategy that is routinely followed is to *protect* the carbonyl group during the reactions with which it is incompatible and then to *remove* the protecting group in a subsequent step. Acetals, especially those derived from ethylene glycol, are among the most

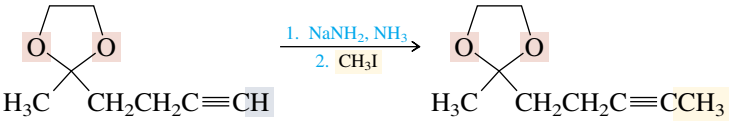
useful groups for carbonyl protection, because they can be introduced and removed readily. A key fact is that acetals resemble ethers in being inert to many of the reagents, such as hydride reducing agents and organometallic compounds, that react readily with carbonyl groups. The following sequence is the one that was actually used to bring about the desired transformation.

(a) Protection of carbonyl group



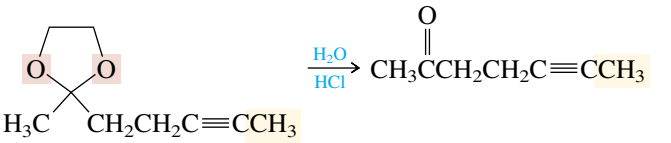
5-Hexyn-2-one Acetal of reactant

(b) Alkylation of alkyne



Acetal of product

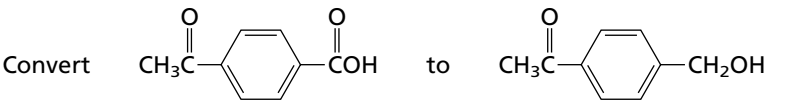
(c) Unmasking of the carbonyl group by hydrolysis



5-Heptyn-2-one (96%)

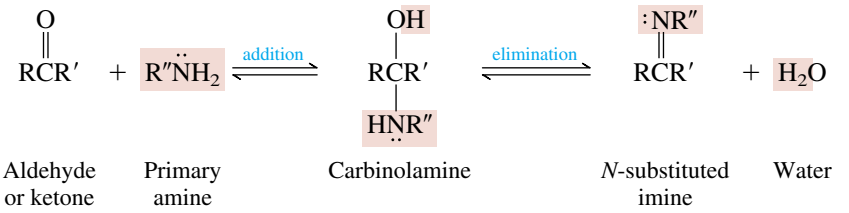
Although protecting and unmasking the carbonyl group add two steps to the synthetic procedure, both steps are essential to its success. The tactic of functional group protection is frequently encountered in preparative organic chemistry, and considerable attention has been paid to the design of effective protecting groups for a variety of functionalities.

PROBLEM 17.10 Acetal formation is a characteristic reaction of aldehydes and ketones, but not of carboxylic acids. Show how you could advantageously use a cyclic acetal protecting group in the following synthesis:

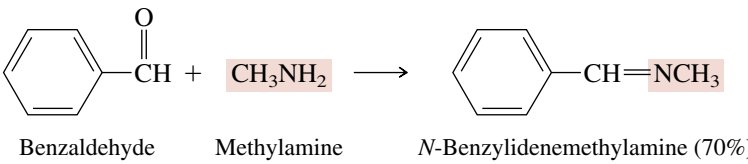


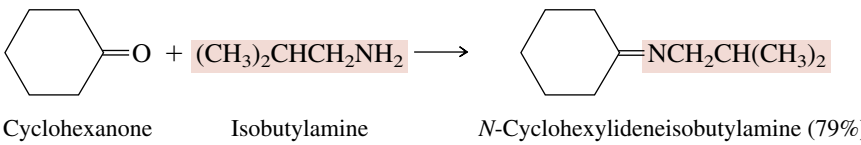
17.10 REACTION WITH PRIMARY AMINES: IMINES

A second two-stage reaction that begins with nucleophilic addition to aldehydes and ketones is their reaction with primary amines, compounds of the type RNH_2 or $ArNH_2$. In the first stage of the reaction the amine adds to the carbonyl group to give a species known as a **carbinolamine.** Once formed, the carbinolamine undergoes dehydration to yield the product of the reaction, an *N*-alkyl- or *N*-aryl-substituted **imine:**



N-substituted imines are sometimes called **Schiff's bases,** after Hugo Schiff, a German chemist who described their formation in 1864.





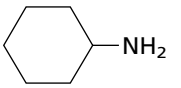
Both the addition and the elimination phase of the reaction are accelerated by acid catalysis. Careful control of pH is essential, since sufficient acid must be present to give a reasonable equilibrium concentration of the protonated form of the aldehyde or ketone. Too acidic a reaction medium, however, converts the amine to its protonated form, a form that is not nucleophilic, and retards reaction.

PROBLEM 17.11 Write the structure of the carbinolamine intermediate and the imine product formed in the reaction of each of the following:

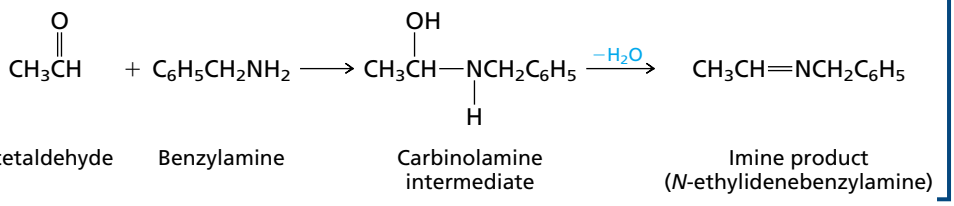
(a) Acetaldehyde and benzylamine, $C_6H_5CH_2NH_2$

(b) Benzaldehyde and butylamine, $CH_3CH_2CH_2CH_2NH_2$

(c) Cyclohexanone and *tert*-butylamine, $(CH_3)_3CNH_2$

(d) Acetophenone and cyclohexylamine, 

SAMPLE SOLUTION The carbinolamine is formed by nucleophilic addition of the amine to the carbonyl group. Its dehydration gives the imine product.



A number of compounds of the general type H_2NZ react with aldehydes and ketones in a manner analogous to that of primary amines. The carbonyl group (C═O) is converted to C═NZ, and a molecule of water is formed. Table 17.4 presents examples of some of these reactions. The mechanism by which each proceeds is similar to the nucleophilic addition–elimination mechanism described for the reaction of primary amines with aldehydes and ketones.

The reactions listed in Table 17.4 are reversible and have been extensively studied from a mechanistic perspective because of their relevance to biological processes.

TABLE 17.4 Reaction of Aldehydes and Ketones with Derivatives of Ammonia: $RCR' + H_2NZ \longrightarrow RCR' + H_2O$

Reagent (H_2NZ)	Name of reagent	Type of product	Example
H_2NOH	Hydroxylamine	Oxime	$CH_3(CH_2)_5CH \xrightarrow{H_2NOH} CH_3(CH_2)_5CH$ (Heptanal → Heptanal oxime (81–93%))
$H_2NNHC_6H_5$*	Phenylhydrazine	Phenylhydrazone	$C_6H_5CCH_3 \xrightarrow{H_2NNHC_6H_5} C_6H_5CCH_3$ (Acetophenone → Acetophenone phenylhydrazone (87–91%))
$H_2NNHCNH_2$	Semicarbazide	Semicarbazone	$CH_3C(CH_2)_9CH_3 \xrightarrow{H_2NNHCNH_2} CH_3C(CH_2)_9CH_3$ (2-Dodecanone → 2-Dodecanone semicarbazone (93%))

*Compounds related to phenylhydrazine react in an analogous way. *p*-Nitrophenylhydrazine yields *p*-nitrophenylhydrazones; 2,4-dinitrophenylhydrazine yields 2,4-dinitrophenylhydrazones.

Many biological reactions involve initial binding of a carbonyl compound to an enzyme or coenzyme via imine formation. The boxed essay "Imines in Biological Chemistry" gives some important examples.

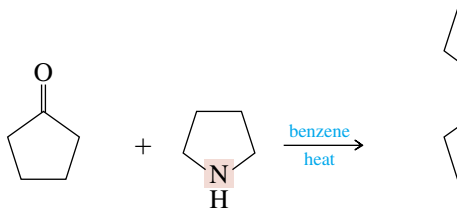
17.11 REACTION WITH SECONDARY AMINES: ENAMINES

Secondary amines are compounds of the type R_2NH. They add to aldehydes and ketones to form carbinolamines, but their carbinolamine intermediates can dehydrate to a stable product only in the direction that leads to a carbon–carbon double bond:

$$RCH_2CR' + R''_2\ddot{N}H \rightleftharpoons RCH_2C(OH)(NR''_2)R' \xrightleftharpoons{-H_2O} RCH{=}CR'(NR''_2)$$

Aldehyde or ketone — Secondary amine — Carbinolamine — Enamine

The product of this dehydration is an alkenyl-substituted amine, or **enamine.**



Cyclopentanone + Pyrrolidine → *N*-(1-Cyclopentenyl)-pyrrolidine (80–90%) + Water

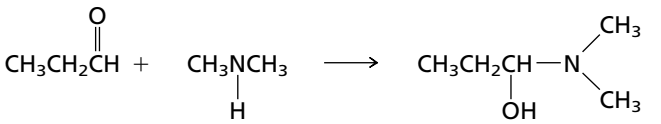
PROBLEM 17.12 Write the structure of the carbinolamine intermediate and the enamine product formed in the reaction of each of the following:

(a) Propanal and dimethylamine, CH_3NHCH_3

(b) 3-Pentanone and pyrrolidine

(c) Acetophenone and HN⟨⟩

SAMPLE SOLUTION (a) Nucleophilic addition of dimethylamine to the carbonyl group of propanal produces a carbinolamine:



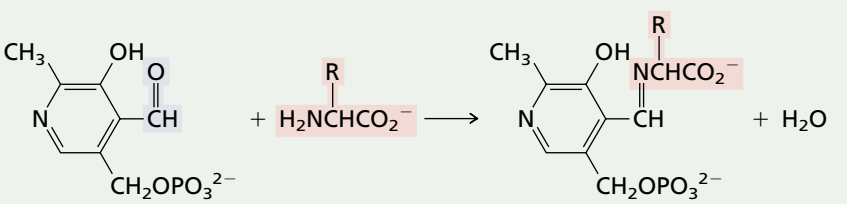
Propanal Dimethylamine Carbinolamine intermediate

IMINES IN BIOLOGICAL CHEMISTRY

Many biological processes involve an "association" between two species in a step prior to some subsequent transformation. This association can take many forms. It can be a weak association of the attractive van der Waals type, or a stronger interaction such as a hydrogen bond. It can be an electrostatic attraction between a positively charged atom of one molecule and a negatively charged atom of another. Covalent bond formation between two species of complementary chemical reactivity represents an extreme kind of "association." It often occurs in biological processes in which aldehydes or ketones react with amines via imine intermediates.

An example of a biologically important aldehyde is *pyridoxal phosphate.* Pyridoxal phosphate is the active form of *vitamin* B_6 and is a coenzyme for many of the reactions of α-amino acids. In these reactions the amino acid binds to the coenzyme by reacting with it to form an imine of the kind shown in the equation. Reactions then take place at the amino acid portion of the imine, modifying the amino acid. In the last step, enzyme-catalyzed hydrolysis cleaves the imine to pyridoxal and the modified amino acid.

A key step in the chemistry of vision is binding of an aldehyde to an enzyme via an imine. An outline of the steps involved is presented in Figure 17.8. It starts with *β-carotene,* a pigment that occurs naturally in several fruits and vegetables, including carrots. β-Carotene undergoes oxidative cleavage in the liver to give an alcohol known as *retinol* or *vitamin A.* Oxidation of vitamin A, followed by isomerization of one of its double bonds, gives the aldehyde 11-*cis*-retinal. In the eye, the aldehyde function of 11-*cis*-retinal combines with an amino group of the protein *opsin* to form an imine called *rhodopsin.* When rhodopsin absorbs a photon of visible light, the cis double bond of the retinal unit undergoes a photochemical cis-to-trans isomerization, which is attended by a dramatic change in its shape and a change in the conformation of rhodopsin. This conformational change is translated into a nerve impulse perceived by the brain as a visual image. Enzyme-promoted hydrolysis of the photochemically isomerized rhodopsin regenerates opsin and a molecule of all-*trans*-retinal. Once all-*trans*-retinal has been enzymatically converted to its 11-cis isomer, it and opsin reenter the cycle.



Pyridoxal phosphate α-Amino acid Imine

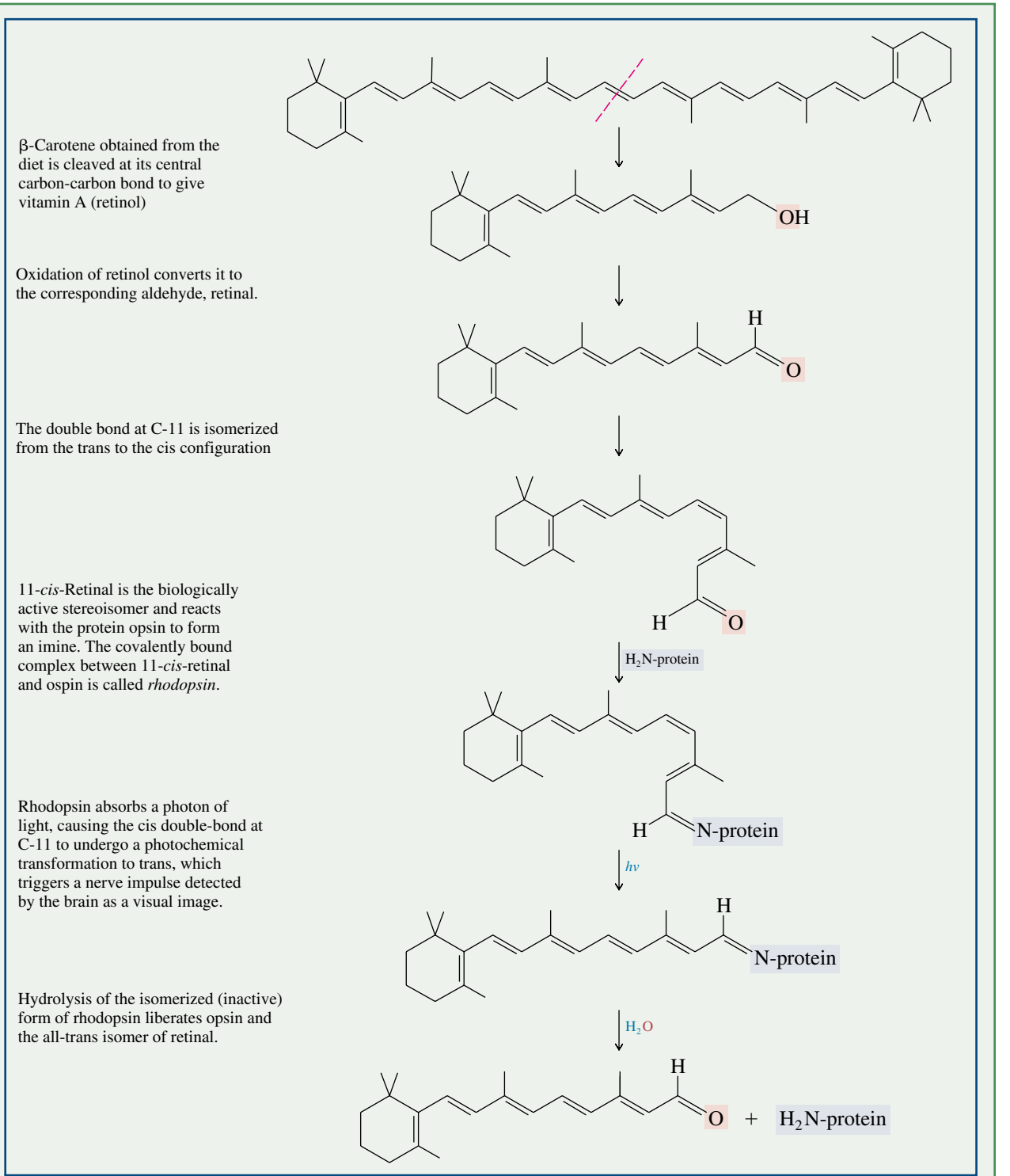
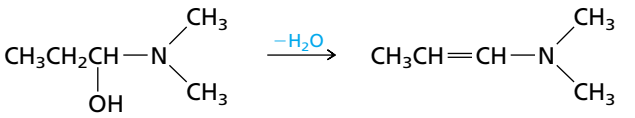


FIGURE 17.8 Imine formation between the aldehyde function of 11-*cis*-retinal and an amino group of a protein (opsin) is involved in the chemistry of vision. The numbering scheme used in retinal is based on one specifically developed for carotenes and compounds derived from them.

Dehydration of this carbinolamine yields the enamine:



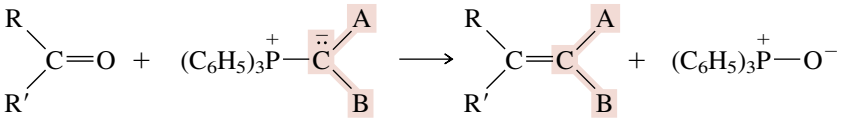
Carbinolamine intermediate — *N*-(1-Propenyl)dimethylamine

Enamines are used as reagents in synthetic organic chemistry and are involved in certain biochemical transformations.

17.12 THE WITTIG REACTION

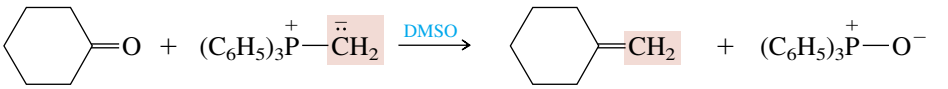
The **Wittig reaction** uses *phosphorus ylides* (called *Wittig reagents*) to convert aldehydes and ketones to alkenes.

The reaction is named after Georg Wittig, a German chemist who shared the 1979 Nobel Prize in chemistry for demonstrating its synthetic potential.



Aldehyde or ketone — Triphenylphosphonium ylide — Alkene — Triphenylphosphine oxide

Wittig reactions may be carried out in a number of different solvents; normally tetrahydrofuran (THF) or dimethyl sulfoxide (DMSO) is used.



Cyclohexanone — Methylenetriphenylphosphorane — Methylenecyclohexane (86%) — Triphenylphosphine oxide

The most attractive feature of the Wittig reaction is its regiospecificity. The location of the double bond is never in doubt. The double bond connects the carbon of the original C═O group of the aldehyde or ketone and the negatively charged carbon of the ylide.

PROBLEM 17.13 Identify the alkene product in each of the following Wittig reactions:

(a) Benzaldehyde + $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}$ (cyclopentylidene)

(b) Butanal + $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH=CH_2$

(c) Cyclohexyl methyl ketone + $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}H_2$

SAMPLE SOLUTION (a) In a Wittig reaction the negatively charged substituent attached to phosphorus is transferred to the aldehyde or ketone, replacing the carbonyl oxygen. The reaction shown has been used to prepare the indicated alkene in 65% yield.

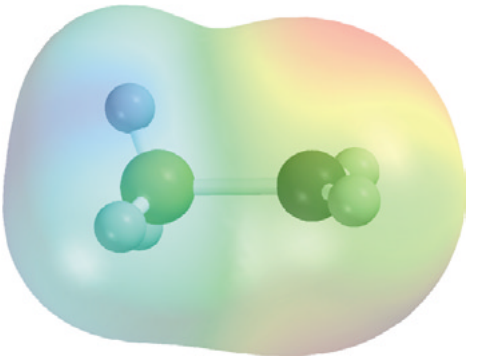
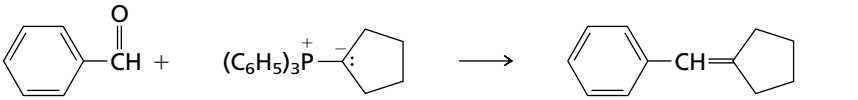


FIGURE 17.9 An electrostatic potential map of the ylide $H_3\overset{+}{P}-\overset{-}{\ddot{C}}H_2$. The region of greatest negative charge is concentrated at carbon.



In order to understand the mechanism of the Wittig reaction, we need to examine the structure and properties of ylides. **Ylides** are neutral molecules that have two oppositely charged atoms, each with an octet of electrons, directly bonded to each other. In an ylide such as $(C_6H_5)_3\overset{+}{P}-\overset{-}{\ddot{C}}H_2$, phosphorus has eight electrons and is positively charged; its attached carbon has eight electrons and is negatively charged.

PROBLEM 17.14 Can you write a resonance structure for $(C_6H_5)_3\overset{+}{P}-\overset{-}{\ddot{C}}H_2$ in which neither phosphorus nor carbon has a formal charge? (*Hint:* Remember phosphorus can have more than eight electrons in its valence shell.)

We can focus on the charge distribution in an ylide by replacing the phenyl groups in $(C_6H_5)_3\overset{+}{P}-\overset{-}{\ddot{C}}H_2$ by hydrogens. Figure 17.9 shows the electrostatic potential map of $H_3\overset{+}{P}-\overset{-}{\ddot{C}}H_2$, where it can be seen that the electron distribution is highly polarized in the direction that makes carbon electron-rich. The carbon has much of the character of a carbanion and can act as a nucleophile toward C=O.

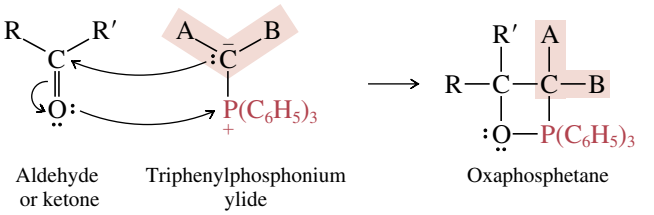
The Wittig reaction is one that is still undergoing mechanistic investigation. Another possibility is that the oxaphosphetane intermediate is formed by a two-step process, rather than the one-step process shown in Figure 17.10.

Figure 17.10 outlines a mechanism for the Wittig reaction. The first stage is a cycloaddition in which the ylide reacts with the carbonyl group to give an intermediate containing a four-membered ring called an **oxaphosphetane.** This oxaphosphetane then dissociates to give an alkene and triphenylphosphine oxide. Presumably the direction of dissociation of the oxaphosphetane is dictated by the strong phosphorus–oxygen bond that results. The P—O bond strength in triphenylphosphine oxide has been estimated to be greater than 540 kJ/mol (130 kcal/mol).

17.13 PLANNING AN ALKENE SYNTHESIS VIA THE WITTIG REACTION

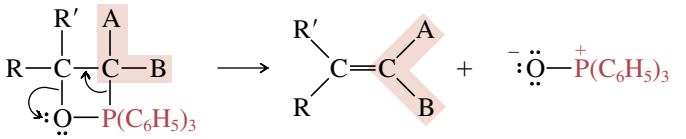
In order to identify the carbonyl compound and the ylide required to produce a given alkene, mentally disconnect the double bond so that one of its carbons is derived from a carbonyl group and the other is derived from an ylide. Taking styrene as a representative example, we see that two such disconnections are possible; either benzaldehyde or formaldehyde is an appropriate precursor.

Step 1: The ylide and the aldehyde or ketone combine to form an oxaphosphetane.



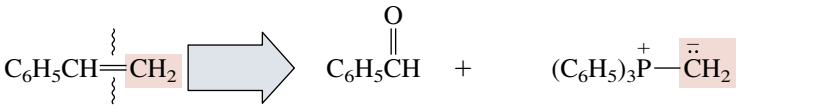
Aldehyde or ketone | Triphenylphosphonium ylide | Oxaphosphetane

Step 2: The oxaphosphetane dissociates to an alkene and triphenylphosphine oxide.

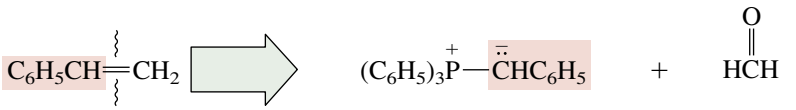


Oxaphosphetane | Alkene | Triphenylphosphine oxide

FIGURE 17.10 The mechanism of the Wittig reaction.



Styrene | Benzaldehyde | Methylenetriphenylphosphorane



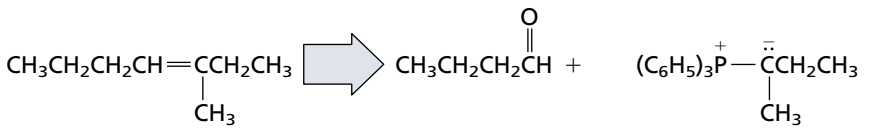
Styrene | Benzylidenetriphenylphosphorane | Formaldehyde

Either route is a feasible one, and indeed styrene has been prepared from both combinations of reactants. Typically there will be two Wittig routes to an alkene, and any choice between them is made on the basis of availability of the particular starting materials.

PROBLEM 17.15 What combinations of carbonyl compound and ylide could you use to prepare each of the following alkenes?

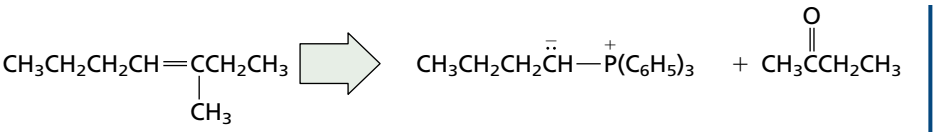
(a) $CH_3CH_2CH_2CH{=}C(CH_3)CH_2CH_3$ (b) $CH_3CH_2CH_2CH{=}CH_2$

SAMPLE SOLUTION (a) Two Wittig reaction routes lead to the target molecule.



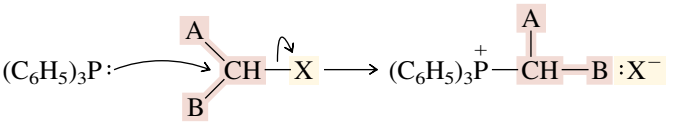
3-Methyl-3-heptene | Butanal | 1-Methylpropylidenetriphenylphosphorane

and



3-Methyl-3-heptene | Butylidenetriphenylphosphorane | 2-Butanone

Phosphorus ylides are prepared from alkyl halides by a two-step sequence. The first step is a nucleophilic substitution of the S_N2 type by triphenylphosphine on an alkyl halide to give an alkyltriphenylphosphonium salt:

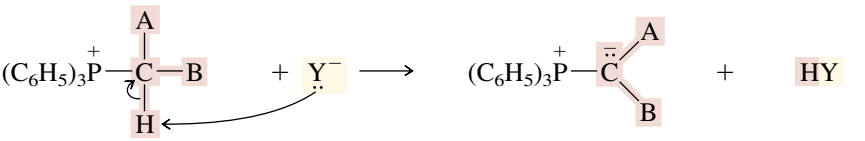


Triphenylphosphine | Alkyl halide | Alkyltriphenylphosphonium halide

Triphenylphosphine is a very powerful nucleophile, yet is not strongly basic. Methyl, primary, and secondary alkyl halides are all suitable substrates.

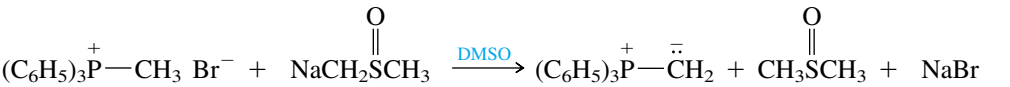
Triphenylphosphine | Bromomethane | Methyltriphenylphosphonium bromide (99%)

The alkyltriphenylphosphonium salt products are ionic and crystallize in high yield from the nonpolar solvents in which they are prepared. After isolation, the alkyltriphenylphosphonium halide is converted to the desired ylide by deprotonation with a strong base:



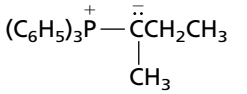
Alkyltriphenylphosphonium salt | Base | Triphenylphosphonium ylide | Conjugate acid of base used

Suitable strong bases include the sodium salt of dimethyl sulfoxide (in dimethyl sulfoxide as the solvent) and organolithium reagents (in diethyl ether or tetrahydrofuran).



Methyltriphenylphosphonium bromide | Sodiomethyl methyl sulfoxide | Methylenetriphenylphosphorane | Dimethyl sulfoxide | Sodium bromide

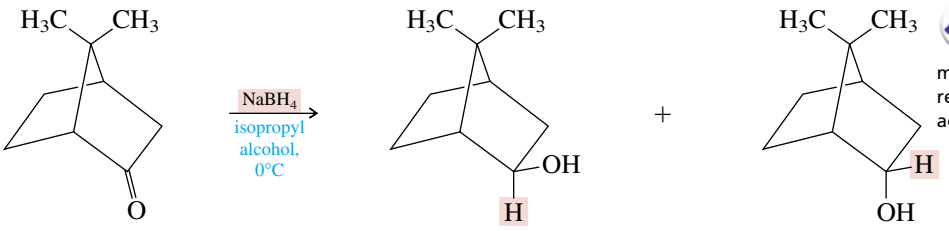
PROBLEM 17.16 The sample solution to Problem 17.15(a) showed the preparation of 3-methyl-3-heptene by a Wittig reaction involving the ylide shown. Write equations showing the formation of this ylide beginning with 2-bromobutane.



Normally the ylides are not isolated. Instead, the appropriate aldehyde or ketone is added directly to the solution in which the ylide was generated.

17.14 STEREOSELECTIVE ADDITION TO CARBONYL GROUPS

Nucleophilic addition to carbonyl groups sometimes leads to a mixture of stereoisomeric products. The direction of attack is often controlled by steric factors, with the nucleophile approaching the carbonyl group at its less hindered face. Sodium borohydride reduction of 7,7-dimethylbicyclo[2.2.1]heptan-2-one illustrates this point:



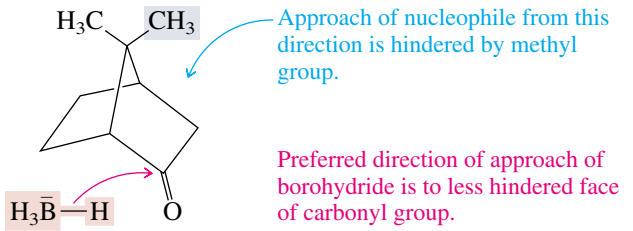
7,7-Dimethylbicyclo[2.2.1]-heptan-2-one

exo-7,7-Dimethylbicyclo[2.2.1]-heptan-2-ol (80%)

endo-7,7-Dimethylbicyclo[2.2.1]-heptan-2-ol (20%)

You may find it helpful to make molecular models of the reactant and products in the reaction shown.

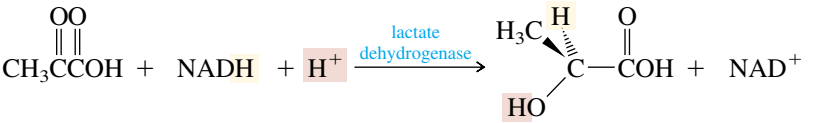
Approach of borohydride to the top face of the carbonyl group is sterically hindered by one of the methyl groups. The bottom face of the carbonyl group is less congested, and the major product is formed by hydride transfer from this direction.



The reduction is *stereoselective*. A single starting material can form two stereoisomers of the product but yields one of them preferentially.

It is possible to predict the preferred stereochemical path of nucleophilic addition if one face of a carbonyl group is significantly more hindered to the approach of the reagent than the other. When no clear distinction between the two faces is evident, other, more subtle effects, which are still incompletely understood, come into play.

Enzyme-catalyzed reductions of carbonyl groups are, more often than not, completely stereoselective. Pyruvic acid is converted exclusively to (*S*)-(+)-lactic acid by the lactate dehydrogenase-NADH system (Section 15.11). The enantiomer (*R*)-(−)-lactic acid is not formed.



Pyruvic acid

Reduced form of coenzyme

(*S*)-(+)-Lactic acid

Oxidized form of coenzyme

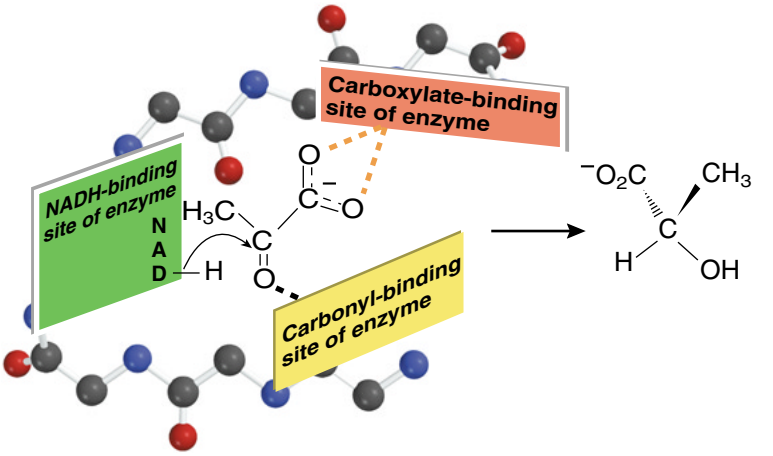


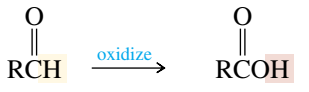
FIGURE 17.11 Enzyme-catalyzed reduction of pyruvate to (*S*)-(+)-lactate. A preferred orientation of binding of pyruvate to the enzyme, coupled with a prescribed location of the reducing agent, the coenzyme NADH, leads to hydrogen transfer exclusively to a single face of the carbonyl group.

Here the enzyme, a chiral molecule, binds the coenzyme and substrate in such a way that hydrogen is transferred exclusively to the face of the carbonyl group that leads to (*S*)-(+)-lactic acid (Figure 17.11).

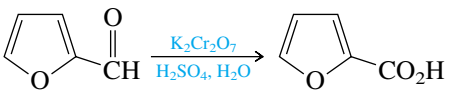
The stereochemical outcome of enzyme-mediated reactions depends heavily on the way the protein chain is folded. Aspects of protein conformation will be discussed in Chapter 27.

17.15 OXIDATION OF ALDEHYDES

Aldehydes are readily oxidized to carboxylic acids by a number of reagents, including those based on Cr(VI) in aqueous media.

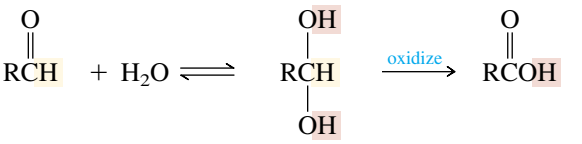


Aldehyde Carboxylic acid



Furfural Furoic acid (75%)

Mechanistically, these reactions probably proceed through the hydrate of the aldehyde and follow a course similar to that of alcohol oxidation.

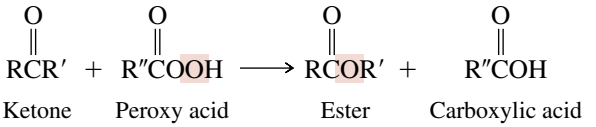


Aldehyde Geminal diol (hydrate) Carboxylic acid

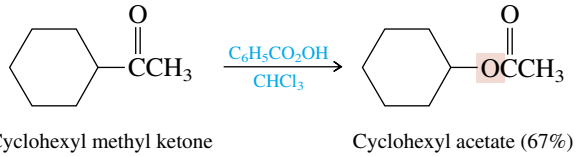
17.16 BAEYER–VILLIGER OXIDATION OF KETONES

The reaction of ketones with peroxy acids is both novel and synthetically useful. An oxygen from the peroxy acid is inserted between the carbonyl group and one of the attached carbons of the ketone to give an *ester*. Reactions of this type were first described by Adolf von Baeyer and Victor Villiger in 1899 and are known as **Baeyer–Villiger oxidations.**

Peroxy acids have been seen before as reagents for the epoxidation of alkenes (Section 6.18).

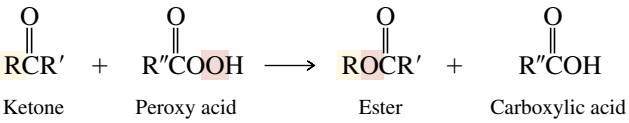


Methyl ketones give esters of acetic acid; that is, oxygen insertion occurs between the carbonyl carbon and the larger of the two groups attached to it.

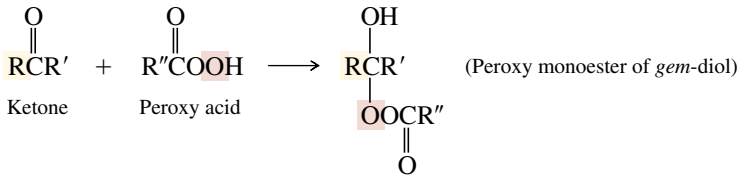


The mechanism of the Baeyer–Villiger oxidation is shown in Figure 17.12. It begins with nucleophilic addition of the peroxy acid to the carbonyl group of the ketone, which is followed by migration of an alkyl group from the carbonyl group to oxygen.

The overall reaction:



Step 1: The peroxy acid adds to the carbonyl group of the ketone. This step is a nucleophilic addition analogous to *gem*-diol and hemiacetal formation.



Step 2: The intermediate from step 1 undergoes rearrangement. Cleavage of the weak O—O bond of the peroxy ester is assisted by migration of one of the substituents from the carbonyl group to oxygen. The group R migrates with its pair of electrons in much the same way as alkyl groups migrate in carbocation rearrangements.

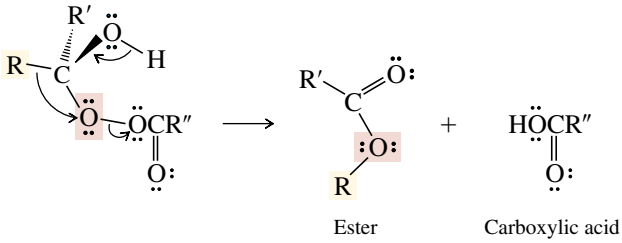


FIGURE 17.12 Mechanism of the Baeyer–Villiger oxidation of a ketone.

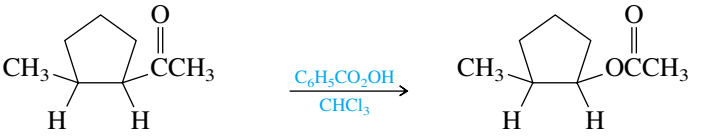
In general, it is the more substituted group that migrates. The *migratory aptitude* of the various alkyl groups is:

Tertiary alkyl > secondary alkyl > primary alkyl > methyl

PROBLEM 17.17 Using Figure 17.12 as a guide, write a mechanism for the Baeyer–Villiger oxidation of cyclohexyl methyl ketone by peroxybenzoic acid.

PROBLEM 17.18 Baeyer–Villiger oxidation of aldehydes yields carboxylic acids (e.g., *m*-nitrobenzaldehyde yields *m*-nitrobenzoic acid). What group migrates to oxygen?

The reaction is stereospecific; the alkyl group migrates with retention of configuration.

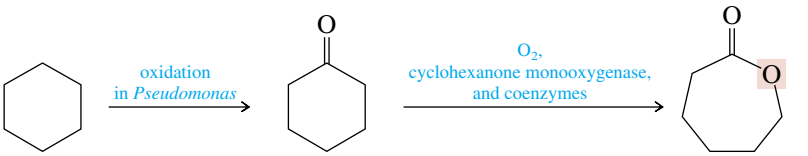


cis-1-Acetyl-2-methylcyclopentane

cis-2-Methylcyclopentyl acetate
(only product; 66% yield)

In the companion experiment carried out on the trans stereoisomer of the ketone, only the trans acetate was formed.

As unusual as the Baeyer–Villiger reaction may seem, what is even more remarkable is that an analogous reaction occurs in living systems. Certain bacteria, including those of the *Pseudomonas* and *Acinetobacter* type, can use a variety of organic compounds, even hydrocarbons, as a carbon source. With cyclohexane, for example, the early stages proceed by oxidation to cyclohexanone, which then undergoes the "biological Baeyer–Villiger reaction."



Cyclohexane Cyclohexanone 6-Hexanolide

The product (6-hexanolide) is a cyclic ester or *lactone* (Section 19.15). Like the Baeyer–Villiger oxidation, an oxygen atom is inserted between the carbonyl group and the carbon attached to it. But peroxy acids are not involved in any way; the oxidation of cyclohexanone is catalyzed by an enzyme called *cyclohexanone monooxygenase* with the aid of certain coenzymes.

17.17 SPECTROSCOPIC ANALYSIS OF ALDEHYDES AND KETONES

Infrared: Carbonyl groups are among the easiest functional groups to detect by infrared spectroscopy. The C=O stretching vibration of aldehydes and ketones gives rise to strong absorption in the region 1710–1750 cm^{-1} as illustrated for butanal in Figure 17.13. In addition to a peak for C=O stretching, the CH=O group of an aldehyde exhibits two weak bands for C—H stretching near 2720 and 2820 cm^{-1}.

^{1}H NMR: Aldehydes are readily identified by the presence of a signal for the hydrogen of CH=O at δ 9–10 ppm. This is a region where very few other protons ever appear. Figure 17.14 shows the ^{1}H NMR spectrum of 2-methylpropanal [$(CH_3)_2CHCH{=}O$)],

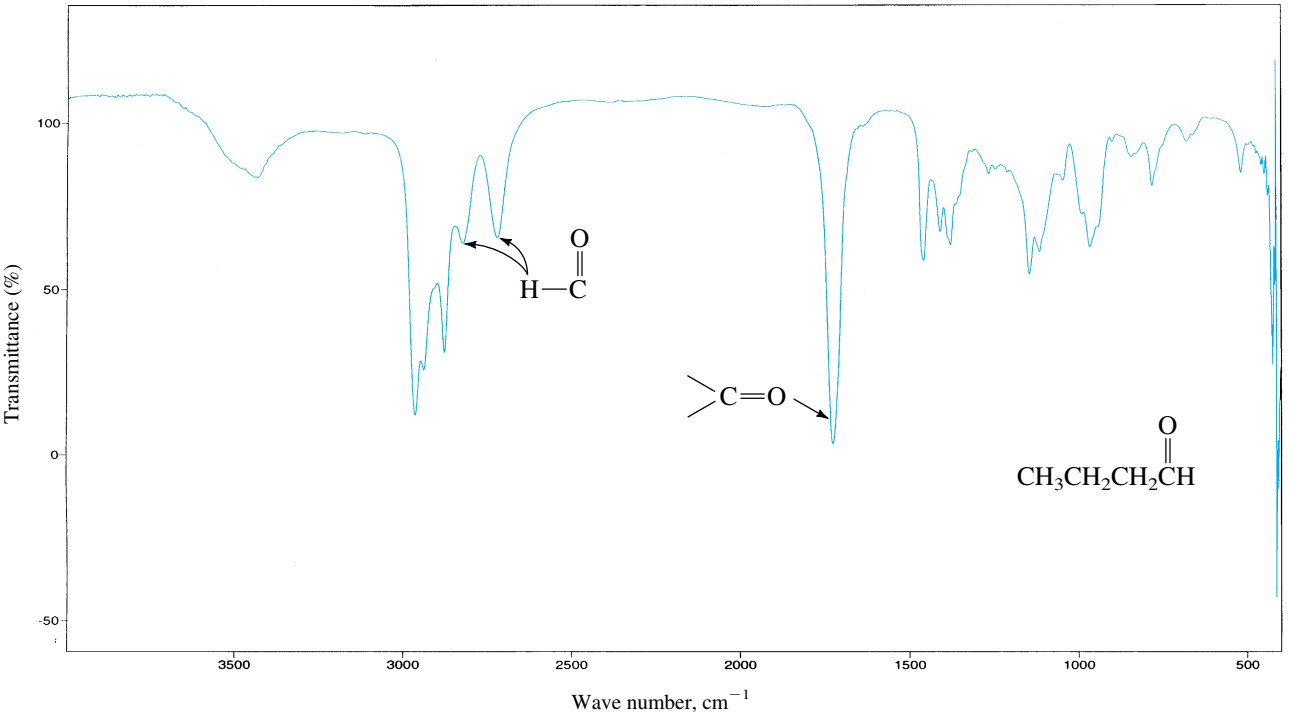


FIGURE 17.13 Infrared spectrum of butanal showing peaks characteristic of the CH═O unit at 2720 and 2820 cm^{-1} (C—H) and at 1720 cm^{-1} (C═O).

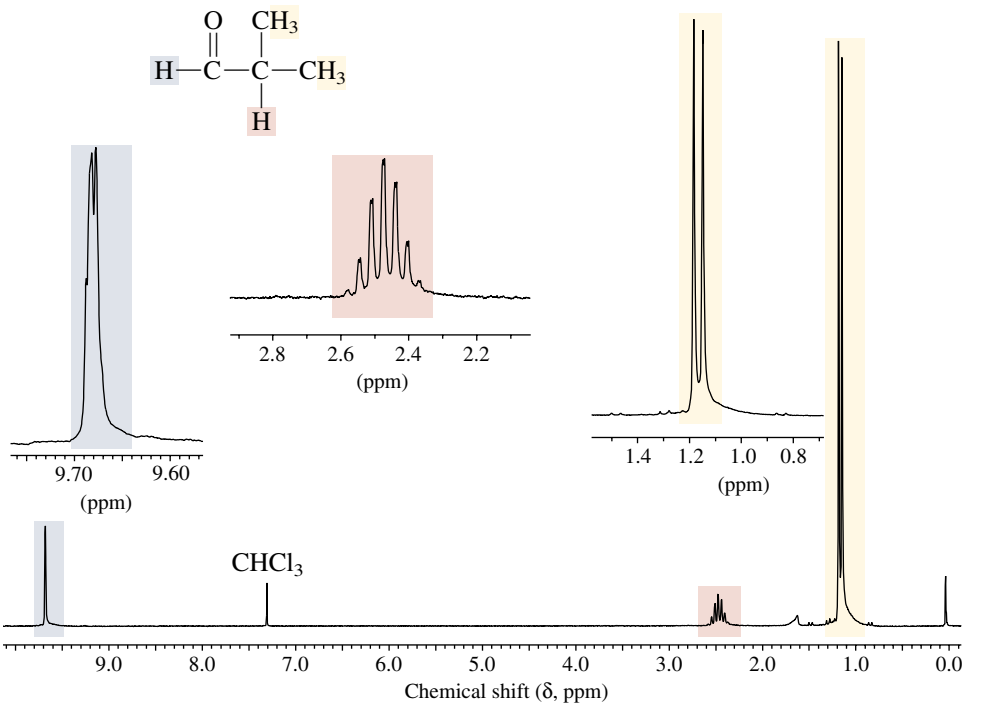


FIGURE 17.14 The 200-MHz ^{1}H NMR spectrum of 2-methylpropanal, showing the aldehyde proton as a doublet at low field strength (9.7 ppm).

where the large chemical shift difference between the aldehyde proton and the other protons in the molecule is clearly evident. As seen in the expanded-scale inset, the aldehyde proton is a doublet, split by the proton as C-2. Coupling between the protons in HC—CH=O is much smaller than typical vicinal couplings, making the multiplicity of the aldehyde peak difficult to see without expanding the scale.

Methyl ketones, such as 2-butanone in Figure 17.15, are characterized by sharp singlets near δ 2 ppm for the protons of $CH_3C{=}O$. Similarly, the deshielding effect of the carbonyl causes the protons of $CH_2C{=}O$ to appear at lower field (δ 2.4 ppm) than in a CH_2 group of an alkane.

^{13}C NMR: The signal for the carbon of C=O in aldehydes and ketones appears at very low field, some 190–220 ppm downfield from tetramethylsilane. Figure 17.16 illustrates this for 3-heptanone, in which separate signals appear for each of the seven carbons. The six sp^3-hybridized carbons appear in the range δ 8–42 ppm, while the carbon of the C=O group is at δ 210 ppm. Note, too, that the intensity of the peak for the C=O carbon is much less than all the others, even though each peak corresponds to a single carbon. This decreased intensity is a characteristic of Fourier transform (FT) spectra for carbons that don't have attached hydrogens.

UV-VIS: Aldehydes and ketones have two absorption bands in the ultraviolet region. Both involve excitation of an electron to an antibonding π*. In one, called a π→π*

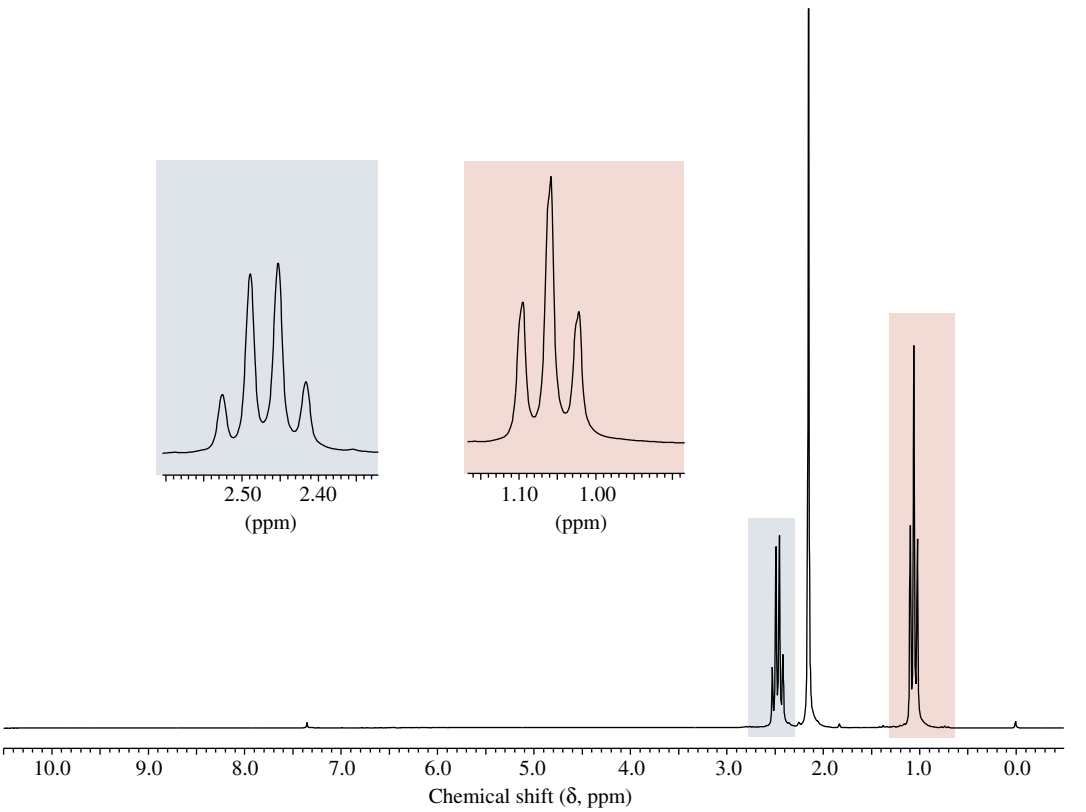
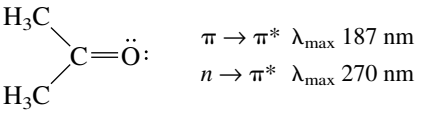


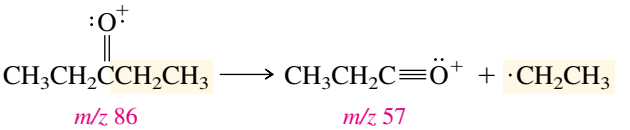
FIGURE 17.15 The 200-MHz ^{1}H NMR spectrum of 2-butanone. The triplet–quartet pattern of the ethyl group is more clearly seen in the scale-expanded insets.

transition, the electron is one of the π electrons of the C═O group. In the other, called an $n \rightarrow \pi^*$ transition, it is one of the oxygen lone-pair electrons. Since the π electrons are more strongly held than the lone-pair electrons, the $\pi \rightarrow \pi^*$ transition is of higher energy and shorter wavelength than the $n \rightarrow \pi^*$ transition. For simple aldehydes and ketones, the $\pi \rightarrow \pi^*$ transition is below 200 nm and of little use in structure determination. The $n \rightarrow \pi^*$ transition, although weak, is of more diagnostic value.



Acetone

Mass Spectrometry: Aldehydes and ketones typically give a prominent molecular ion peak in their mass spectra. Aldehydes also exhibit an M-1 peak. A major fragmentation pathway for both aldehydes and ketones leads to formation of acyl cations (acylium ions) by cleavage of an alkyl group from the carbonyl. The most intense peak in the mass spectrum of diethyl ketone, for example, is *m/z* 57, corresponding to loss of ethyl radical from the molecular ion.



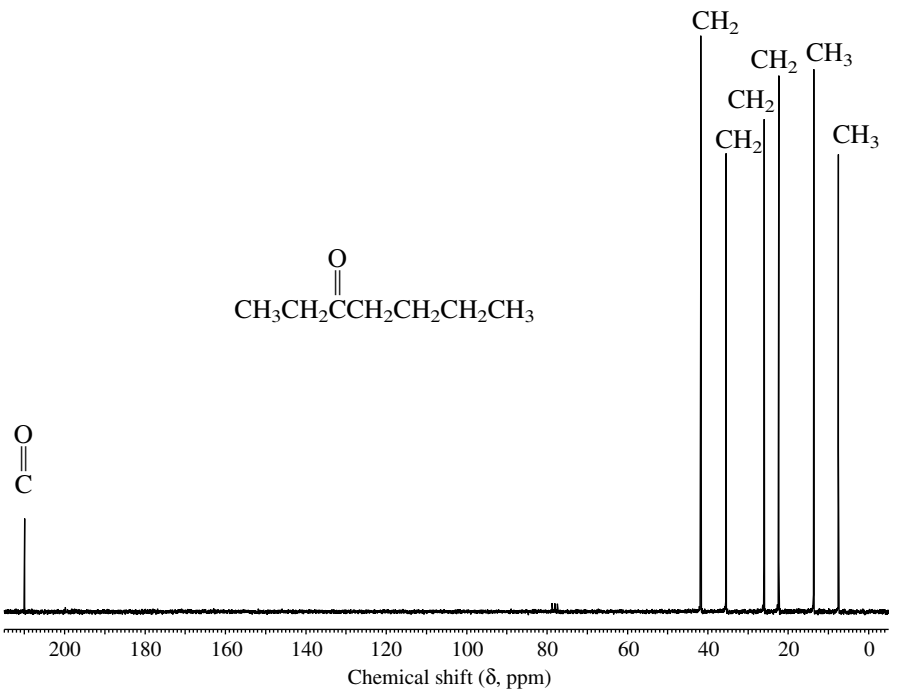
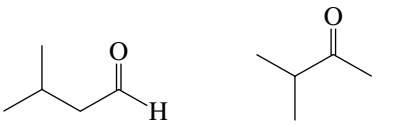


FIGURE 17.16 The ^{13}C NMR spectrum of 3-heptanone. Each signal corresponds to a single carbon. The carbonyl carbon is the least shielded and appears at δ 210 ppm.

17.18 SUMMARY

The chemistry of the carbonyl group is probably the single most important aspect of organic chemical reactivity. Classes of compounds that contain the carbonyl group include many derived from carboxylic acids (acyl chlorides, acid anhydrides, esters, and amides) as well as the two related classes discussed in this chapter—*aldehydes* and *ketones.*

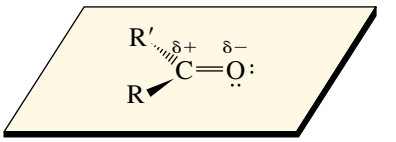
Section 17.1 The substitutive IUPAC names of aldehydes and ketones are developed by identifying the longest continuous chain that contains the carbonyl group and replacing the final *-e* of the corresponding alkane by *-al* for aldehydes and *-one* for ketones. The chain is numbered in the direction that gives the lowest locant to the carbon of the carbonyl group.



3-Methylbutanal 3-Methyl-2-butanone

Ketones are named using functional class IUPAC nomenclature by citing the two groups attached to the carbonyl in alphabetical order followed by the word "ketone." Thus, 3-methyl-2-butanone (substitutive) becomes isopropyl methyl ketone (functional class).

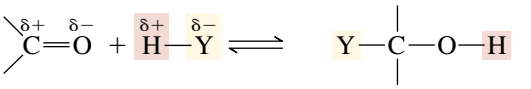
Section 17.2 The carbonyl carbon is sp^2-hybridized, and it and the atoms attached to it are coplanar (Section 17.2).



Section 17.3 Aldehydes and ketones are polar molecules. Nucleophiles attack C═O at carbon (positively polarized) and electrophiles, especially protons, attack oxygen (negatively polarized).

Section 17.4 The numerous reactions that yield aldehydes and ketones discussed in earlier chapters and reviewed in Table 17.1 are sufficient for most syntheses.

Sections 17.5–17.13 The characteristic reactions of aldehydes and ketones involve *nucleophilic addition* to the carbonyl group and are summarized in Table 17.5. Reagents of the type HY react according to the general equation

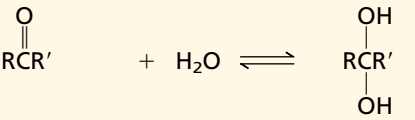
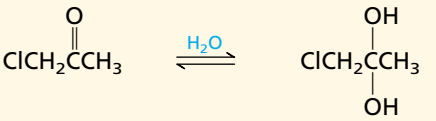
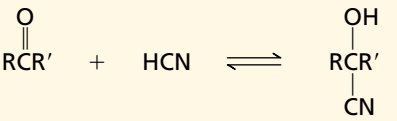
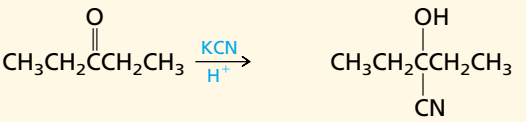
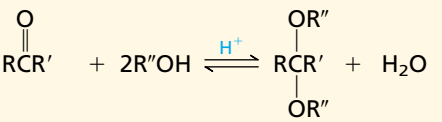
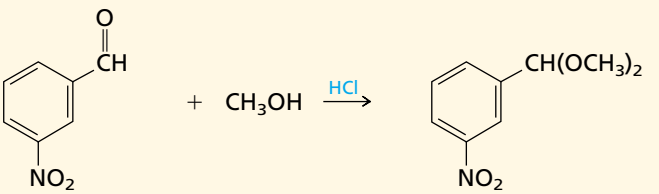
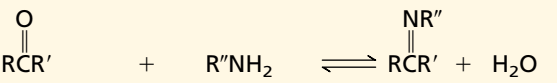
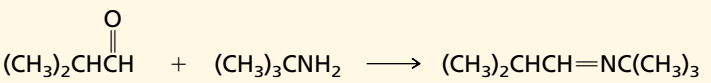


Aldehyde or ketone Product of nucleophilic addition to carbonyl group

Aldehydes undergo nucleophilic addition more readily and have more favorable equilibrium constants for addition than do ketones.

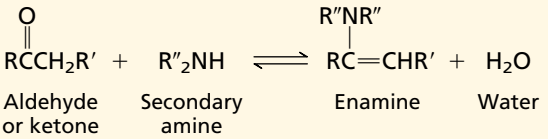
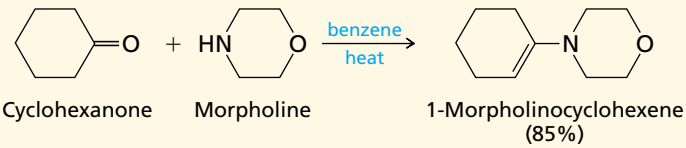
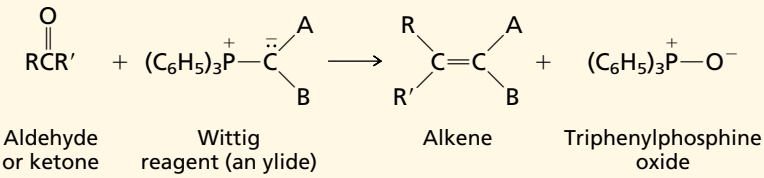
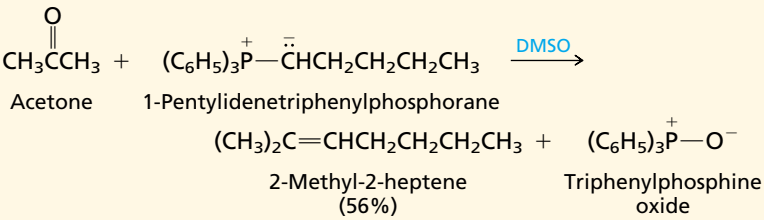
The step in which the nucleophile attacks the carbonyl carbon is

TABLE 17.5 Nucleophilic Addition to Aldehydes and Ketones

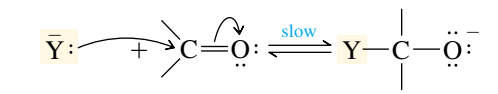
Reaction (section) and comments	General equation and typical example
Hydration (Section 17.6) Can be either acid- or base-catalyzed. Equilibrium constant is normally unfavorable for hydration of ketones unless R, R′, or both are strongly electron-withdrawing.	 Aldehyde or ketone Water Geminal diol  Chloroacetone (90% at equilibrium) Chloroacetone hydrate (10% at equilibrium)
Cyanohydrin formation (Section 17.7) Reaction is catalyzed by cyanide ion. Cyanohydrins are useful synthetic intermediates; cyano group can be hydrolyzed to $-CO_2H$ or reduced to $-CH_2NH_2$.	 Aldehyde or ketone Hydrogen cyanide Cyanohydrin  3-Pentanone 3-Pentanone cyanohydrin (75%)
Acetal formation (Sections 17.8–17.9) Reaction is acid-catalyzed. Equilibrium constant normally favorable for aldehydes, unfavorable for ketones. Cyclic acetals from vicinal diols form readily.	 Aldehyde or ketone Alcohol Acetal Water  *m*-Nitrobenzaldehyde Methanol *m*-Nitrobenzaldehyde dimethyl acetal (76–85%)
Reaction with primary amines (Section 17.10) Isolated product is an imine (Schiff's base). A carbinolamine intermediate is formed, which undergoes dehydration to an imine.	 Aldehyde or ketone Primary amine Imine Water  2-Methylpropanal *tert*-Butylamine *N*-(2-Methyl-1-propylidene)-*tert*-butylamine (50%)

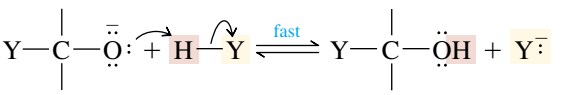
(Continued)

TABLE 17.5 Nucleophilic Addition to Aldehydes and Ketones *(Continued)*

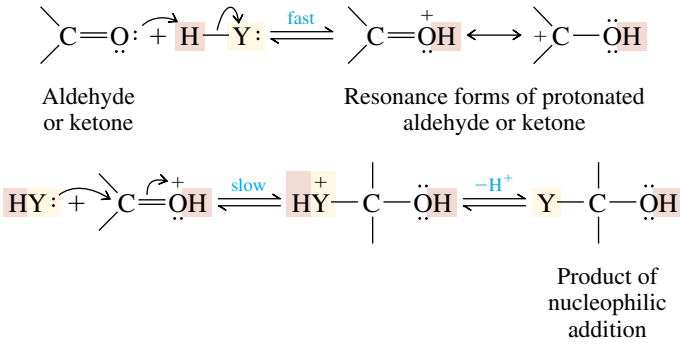
Reaction (section) and comments	General equation and typical example
Reaction with secondary amines (Section 17.11) Isolated product is an enamine. Carbinolamine intermediate cannot dehydrate to a stable imine.	 
The Wittig reaction (Sections 17.12–17.13) Reaction of a phosphorus ylide with aldehydes and ketones leads to the formation of an alkene. A versatile method for the preparation of alkenes.	 

rate-determining in both base-catalyzed and acid-catalyzed nucleophilic addition. In the base-catalyzed mechanism this is the first step.



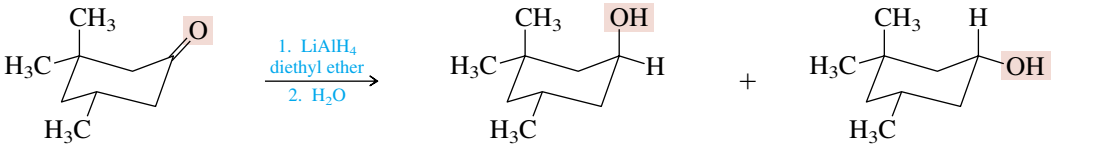


Under conditions of acid catalysis, the nucleophilic addition step follows protonation of the carbonyl oxygen. Protonation increases the carbocation character of a carbonyl group and makes it more electrophilic.



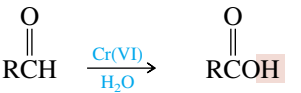
Often the product of nucleophilic addition is not isolated but is an intermediate leading to the ultimate product. Most of the reactions in Table 17.5 are of this type.

Section 17.14 Nucleophilic addition to the carbonyl group is *stereoselective*. When one direction of approach to the carbonyl group is less hindered than the other, the nucleophile normally attacks at the less hindered face.



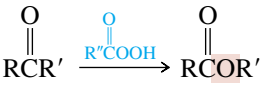
3,3,5-Trimethylcyclohexanone → *trans*-3,3,5-Trimethylcyclohexanol (83%) + *cis*-3,3,5-Trimethylcyclohexanol (17%)

Section 17.15 Aldehydes are easily oxidized to carboxylic acids.



Aldehyde → Carboxylic acid

Section 17.16 The oxidation of ketones with peroxy acids is called the *Baeyer–Villiger oxidation* and is a useful method for preparing esters.



Ketone → Ester

Section 17.17 A strong peak near 1700 cm^{-1} in the infrared is characteristic of compounds that bear a C═O group. The ^{1}H and ^{13}C NMR spectra of aldehydes and ketones are affected by the deshielding of a C═O group. The proton of an H—C═O group appears in the δ 8–10 ppm range. The carbon of a C═O group is at δ 190–210 ppm.

PROBLEMS

17.19 (a) Write structural formulas and provide IUPAC names for all the isomeric aldehydes and ketones that have the molecular formula $C_5H_{10}O$. Include stereoisomers.

(b) Which of the isomers in part (a) yield chiral alcohols on reaction with sodium borohydride?

(c) Which of the isomers in part (a) yield chiral alcohols on reaction with methylmagnesium iodide?

17.20 Each of the following aldehydes or ketones is known by a common name. Its substitutive IUPAC name is provided in parentheses. Write a structural formula for each one.

(a) Chloral (2,2,2-trichloroethanal)

(b) Pivaldehyde (2,2-dimethylpropanal)

(c) Acrolein (2-propenal)

(d) Crotonaldehyde [(*E*)-2-butenal]

(e) Citral [(*E*)-3,7-dimethyl-2,6-octadienal]

(f) Diacetone alcohol (4-hydroxy-4-methyl-2-pentanone)

(g) Carvone (5-isopropenyl-2-methyl-2-cyclohexenone)

(h) Biacetyl (2,3-butanedione)

17.21 Predict the product of the reaction of propanal with each of the following:

(a) Lithium aluminum hydride

(b) Sodium borohydride

(c) Hydrogen (nickel catalyst)

(d) Methylmagnesium iodide, followed by dilute acid

(e) Sodium acetylide, followed by dilute acid

(f) Phenyllithium, followed by dilute acid

(g) Methanol containing dissolved hydrogen chloride

(h) Ethylene glycol, *p*-toluenesulfonic acid, benzene

(i) Aniline ($C_6H_5NH_2$)

(j) Dimethylamine, *p*-toluenesulfonic acid, benzene

(k) Hydroxylamine

(l) Hydrazine

(m) Product of part (l) heated in triethylene glycol with sodium hydroxide

(n) *p*-Nitrophenylhydrazine

(o) Semicarbazide

(p) Ethylidenetriphenylphosphorane $[(C_6H_5)_3\overset{+}{P}-\ddot{\overset{-}{C}}HCH_3]$

(q) Sodium cyanide with addition of sulfuric acid

(r) Chromic acid

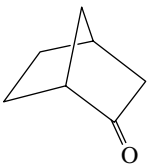
17.22 Repeat the preceding problem for cyclopentanone instead of propanal.

17.23 Hydride reduction (with $LiAlH_4$ or $NaBH_4$) of each of the following ketones has been reported in the chemical literature and gives a mixture of two diastereomeric alcohols in each case. Give the structures or build molecular models of both alcohol products for each ketone.

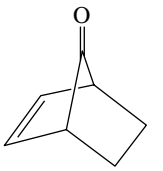
(a) (*S*)-3-Phenyl-2-butanone

(b) 4-*tert*-Butylcyclohexanone

(c)



(d)



17.24 Choose which member in each of the following pairs reacts faster or has the more favorable equilibrium constant for reaction with the indicated reagent. Explain your reasoning.

(a) C_6H_5CH (O) or $C_6H_5CCH_3$ (O) (rate of reduction with sodium borohydride)

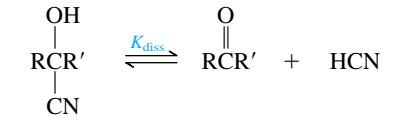
(b) Cl_3CCH (O) or CH_3CH (O) (equilibrium constant for hydration)

(c) Acetone or 3,3-dimethyl-2-butanone (equilibrium constant for cyanohydrin formation)

(d) Acetone or 3,3-dimethyl-2-butanone (rate of reduction with sodium borohydride)

(e) $CH_2(OCH_2CH_3)_2$ or $(CH_3)_2C(OCH_2CH_3)_2$ (rate of acid-catalyzed hydrolysis)

17.25 Equilibrium constants for the dissociation (K_{diss}) of cyanohydrins according to the equation



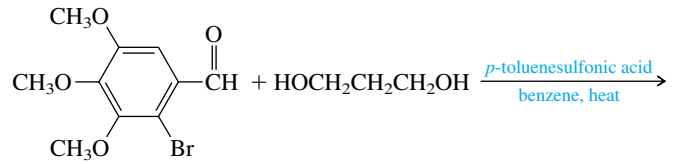
Cyanohydrin — Aldehyde or ketone — Hydrogen cyanide

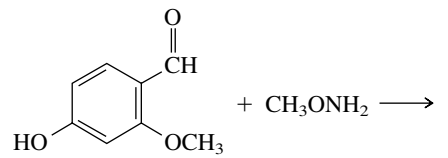
have been measured for a number of cyanohydrins. Which cyanohydrin in each of the following pairs has the greater dissociation constant?

(a) $CH_3CH_2CH(OH)CN$ or $(CH_3)_2C(OH)CN$

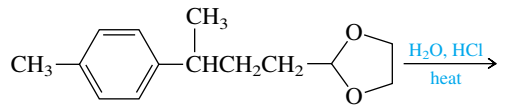
(b) $C_6H_5CH(OH)CN$ or $C_6H_5C(OH)(CH_3)CN$

17.26 Each of the following reactions has been reported in the chemical literature and gives a single organic product in good yield. What is the principal product in each reaction?

(a) 

(b) 

(c) $CH_3CH_2CH(=O) + (CH_3)_2NNH_2 \longrightarrow$

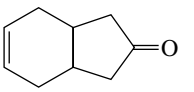
(d) 

(e) $C_6H_5CCH_3$ (O) $\xrightarrow[HCl]{NaCN}$

(f) $C_6H_5CCH_3$ (O) + HN O $\xrightarrow[\text{benzene, heat}]{p\text{-toluenesulfonic acid}}$

(g) $CH_3CH_2C(CH_3)(C_6H_5)CCH_3$ (O) + C_6H_5COOH (O) $\xrightarrow{CHCl_3}$

17.27 Wolff–Kishner reduction (hydrazine, KOH, ethylene glycol, 130°C) of the compound shown gave compound A. Treatment of compound A with *m*-chloroperoxybenzoic acid gave compound B, which on reduction with lithium aluminum hydride gave compound C. Oxidation of compound C with chromic acid gave compound D ($C_9H_{14}O$). Identify compounds A through D in this sequence.

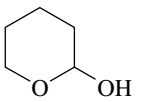


17.28 On standing in ^{17}O-labeled water, both formaldehyde and its hydrate are found to have incorporated the ^{17}O isotope of oxygen. Suggest a reasonable explanation for this observation.

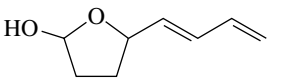
17.29 Reaction of benzaldehyde with 1,2-octanediol in benzene containing a small amount of *p*-toluenesulfonic acid yields almost equal quantities of two products in a combined yield of 94%. Both products have the molecular formula $C_{15}H_{22}O_2$. Suggest reasonable structures for these products.

17.30 Compounds that contain both carbonyl and alcohol functional groups are often more stable as cyclic hemiacetals or cyclic acetals than as open-chain compounds. Examples of several of these are shown. Deduce the structure of the open-chain form of each.

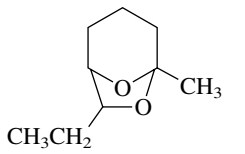
(a)



(b)

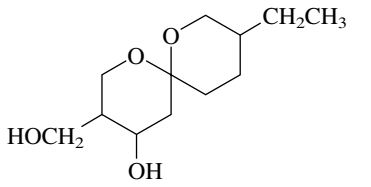


(c)



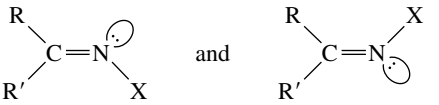
Brevicomin (sex attractant of Western pine beetle)

(d)



Talaromycin A (a toxic substance produced by a fungus that grows on poultry house litter)

17.31 Compounds that contain a carbon–nitrogen double bond are capable of stereoisomerism much like that seen in alkenes. The structures



are stereoisomeric. Specifying stereochemistry in these systems is best done by using *E*–*Z* descriptors and considering the nitrogen lone pair to be the lowest priority group. Write the structures or build molecular models, clearly showing stereochemistry, of the following:

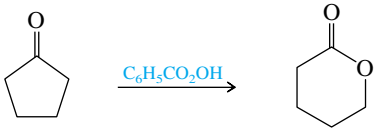
(a) (*Z*)-$CH_3CH{=}NCH_3$

(b) (*E*)-Acetaldehyde oxime

(c) (*Z*)-2-Butanone hydrazone

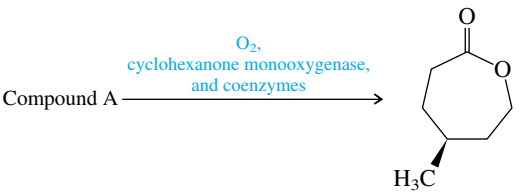
(d) (*E*)-Acetophenone semicarbazone

17.32 Compounds known as *lactones*, which are cyclic esters, are formed on Baeyer–Villiger oxidation of cyclic ketones. Suggest a mechanism for the Baeyer–Villiger oxidation shown.



Cyclopentanone 5-Pentanolide (78%)

17.33 Organic chemists often use enantiomerically homogeneous starting materials for the synthesis of complex molecules (see *Chiral Drugs,* p. 273). A novel preparation of the *S* enantiomer of compound B has been described using a bacterial cyclohexanone monooxygenase enzyme system.

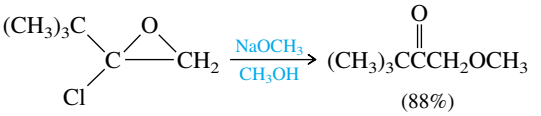


Compound B

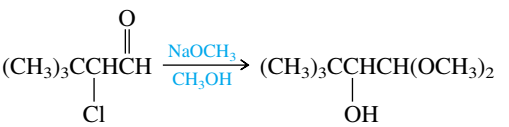
(a) What is compound A?

(b) How would the product obtained by treatment of compound A with peroxyacetic acid differ from that shown in the equation?

17.34 Suggest reasonable mechanism for each of the following reactions:

(a) 

(88%)

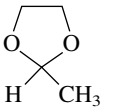
(b) 

(72%)

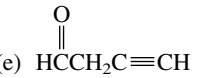
17.35 *Amygdalin,* a substance present in peach, plum, and almond pits, is a derivative of the *R* enantiomer of benzaldehyde cyanohydrin. Give the structure of (*R*)-benzaldehyde cyanohydrin.

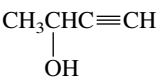
17.36 Using ethanol as the source of all the carbon atoms, describe efficient syntheses of each of the following, using any necessary organic or inorganic reagents:

(a) $CH_3CH(OCH_2CH_3)_2$

(b) 

(c) 

(e) 

(d) 

(f) $CH_3CH_2CH_2CH_2OH$

17.37 Describe reasonable syntheses of benzophenone,  from each of the following starting materials and any necessary inorganic reagents.

(a) Benzoyl chloride and benzene

(b) Benzyl alcohol and bromobenzene

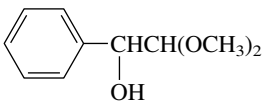
(c) Bromodiphenylmethane, $(C_6H_5)_2CHBr$

(d) Dimethoxydiphenylmethane, $(C_6H_5)_2C(OCH_3)_2$

(e) 1,1,2,2-Tetraphenylethene, $(C_6H_5)_2C{=}C(C_6H_5)_2$

17.38 The sex attractant of the female winter moth has been identified as the tetraene $CH_3(CH_2)_8CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH{=}CH_2$. Devise a synthesis of this material from 3,6-hexadecadien-1-ol and allyl alcohol.

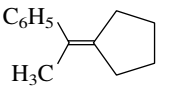
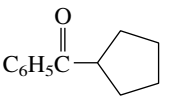
17.39 Hydrolysis of a compound A in dilute aqueous hydrochloric acid gave (along with methanol) a compound B, mp 164–165°C. Compound B had the molecular formula $C_{16}H_{16}O_4$; it exhibited hydroxyl absorption in its infrared spectrum at 3550 cm^{-1} but had no peaks in the carbonyl region. What is a reasonable structure for compound B?

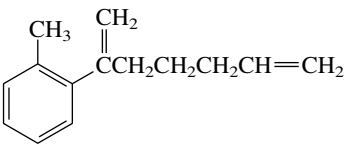


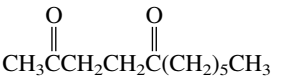
Compound A

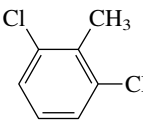
17.40 Syntheses of each of the following compounds have been reported in the chemical literature. Using the indicated starting material and any necessary organic or inorganic reagents, describe short sequences of reactions that would be appropriate for each transformation.

(a) 1,1,5-Trimethylcyclononane from 5,5-dimethylcyclononanone

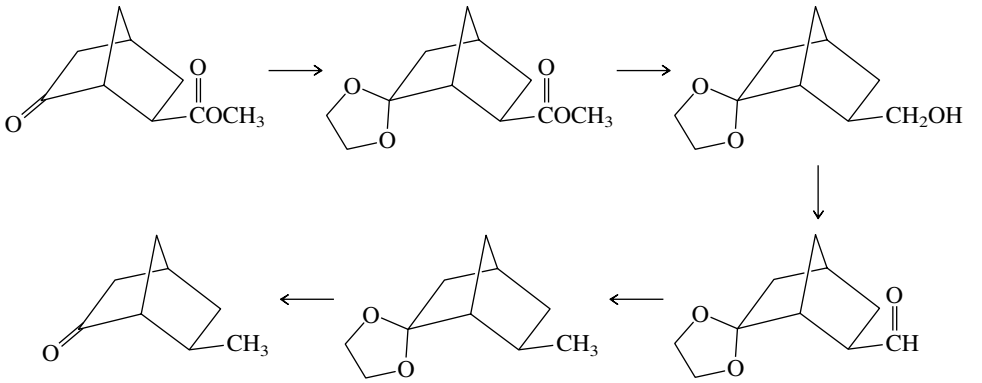
(b)  from 

(c)  from *o*-bromotoluene and 5-hexenal

(d)  from $HC{\equiv}CCH_2CH_2CH_2OH$

(e)  from 3-chloro-2-methylbenzaldehyde

17.41 The following five-step synthesis has been reported in the chemical literature. Suggest reagents appropriate for each step.



17.42 Increased "single-bond character" in a carbonyl group is associated with a decreased carbon–oxygen stretching frequency. Among the three compounds benzaldehyde, 2,4,6-trimethoxybenzaldehyde, and 2,4,6-trinitrobenzaldehyde, which one will have the lowest frequency carbonyl absorption? Which one will have the highest?

17.43 A compound has the molecular formula C_4H_8O and contains a carbonyl group. Identify the compound on the basis of its ^1H NMR spectrum shown in Figure 17.17.

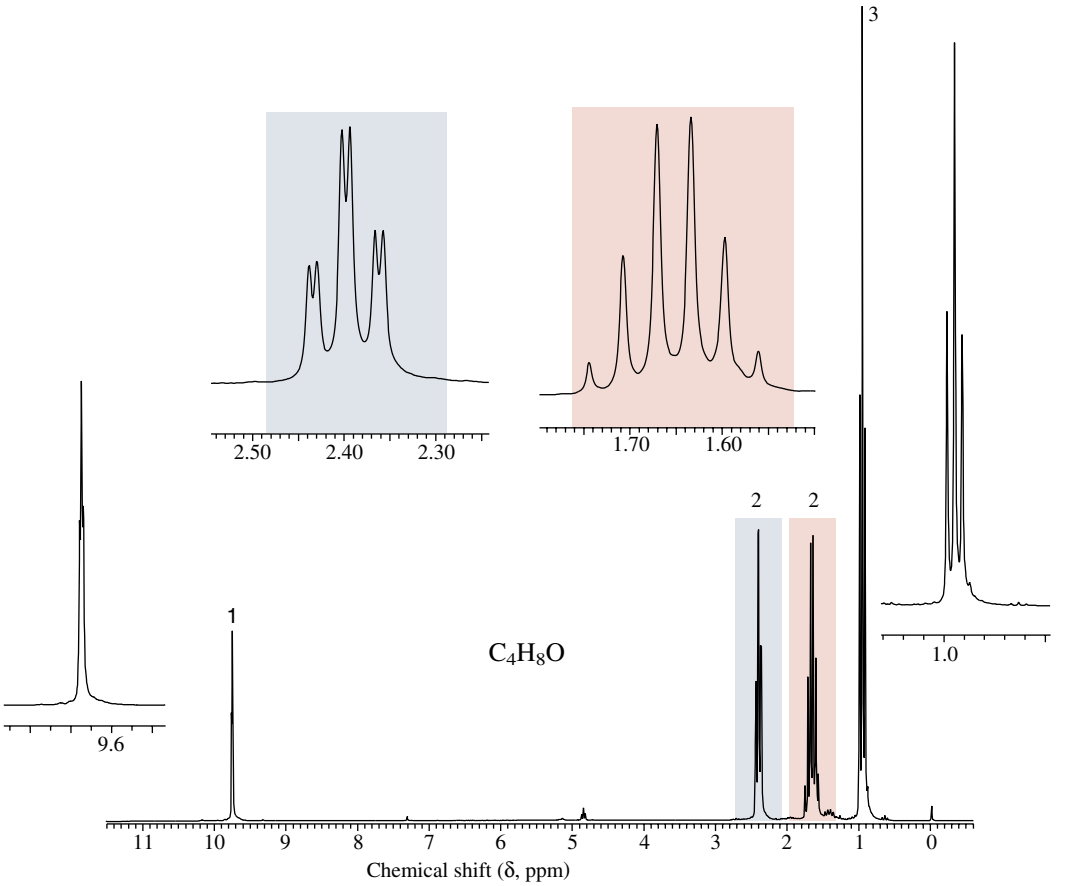


FIGURE 17.17 The 200-MHz ^1H NMR spectrum of a compound (C_4H_8O) (Problem 17.43).

17.44 A compound ($C_7H_{14}O$) has a strong peak in its infrared spectrum at 1710 cm^{-1}. Its ^1H NMR spectrum consists of three singlets in the ratio 9:3:2 at δ 1.0, 2.1, and 2.3 ppm, respectively. Identify the compound.

17.45 Compounds A and B are isomeric diketones of molecular formula $C_6H_{10}O_2$. The ^1H NMR spectrum of compound A contains two signals, both singlets, at δ 2.2 (6 protons) and 2.8 ppm (4 protons). The ^1H NMR spectrum of compound B contains two signals, one at δ 1.3 ppm (triplet, 6 protons) and the other at δ 2.8 ppm (quartet, 4 protons). What are the structures of compounds A and B?

17.46 A compound ($C_{11}H_{14}O$) has a strong peak in its infrared spectrum near 1700 cm^{-1}. Its 200-MHz ^1H NMR spectrum is shown in Figure 17.18. What is the structure of the compound?

17.47 A compound is a ketone of molecular formula $C_7H_{14}O$. Its ^{13}C NMR spectrum is shown in Figure 17.19. What is the structure of the compound?

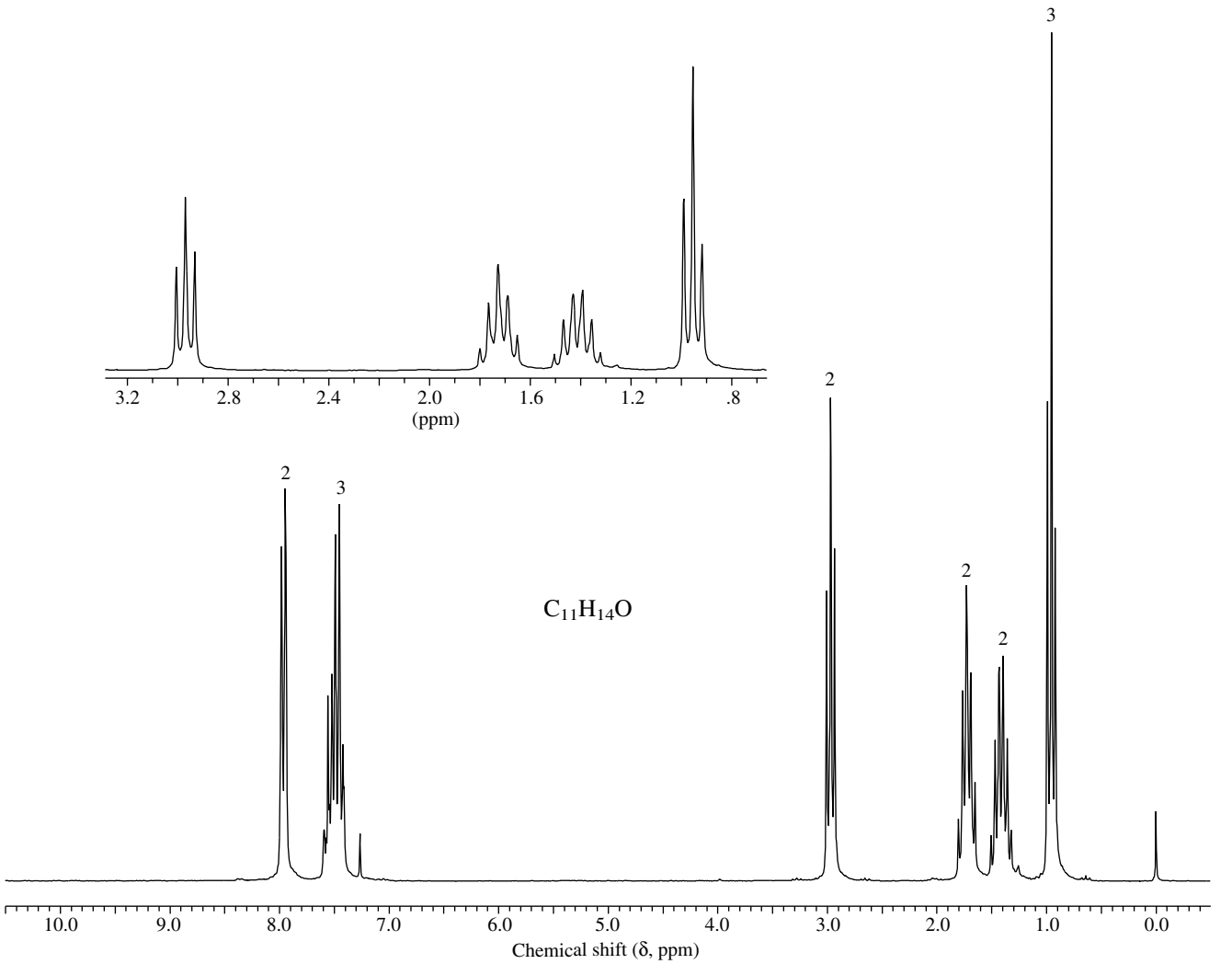


FIGURE 17.18 The 200-MHz ^1H NMR spectrum of a compound ($C_{11}H_{14}O$) (Problem 17.46).

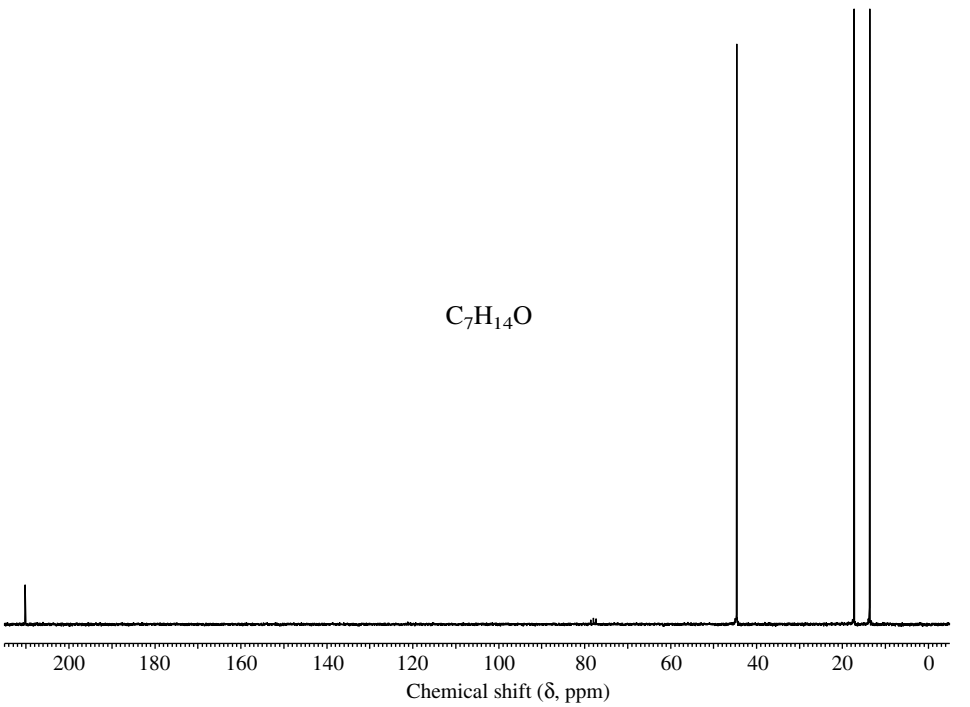


FIGURE 17.19 The ^{13}C NMR spectrum of an unknown compound ($C_7H_{14}O$) (Problem 17.47).

17.48 Compound A and compound B are isomers having the molecular formula $C_{10}H_{12}O$. The mass spectrum of each compound contains an abundant peak at *m/z* 105. The ^{13}C NMR spectra of compound A (Figure 17.20) and compound B (Figure 17.21) are shown. Identify these two isomers.

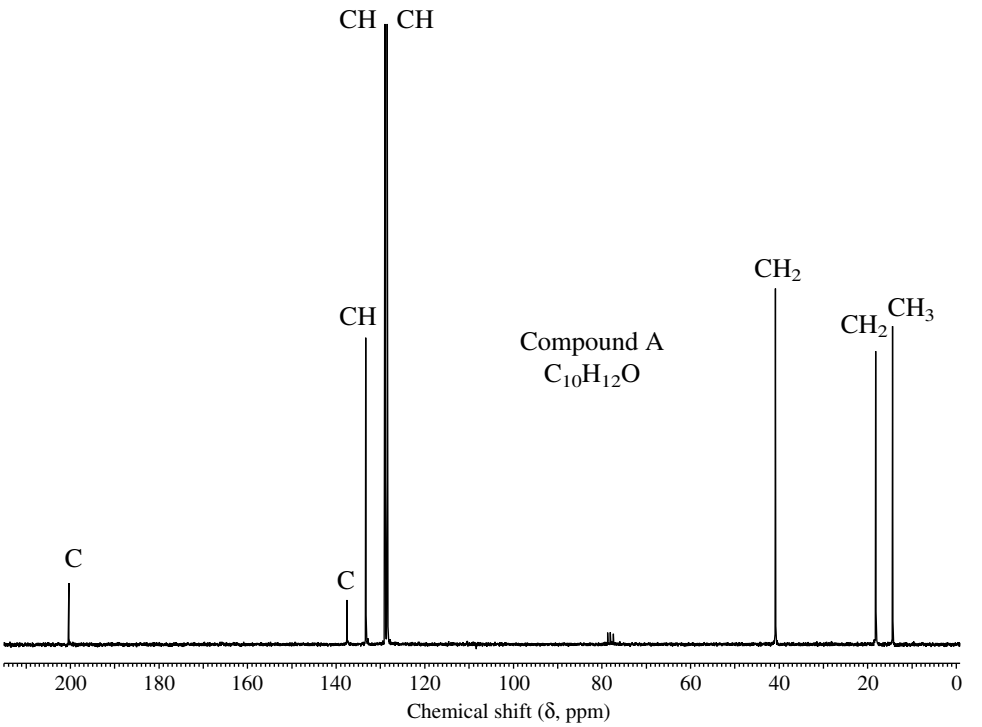


FIGURE 17.20 The ^{13}C NMR spectrum of compound A ($C_{10}H_{12}O$) (Problem 17.48).

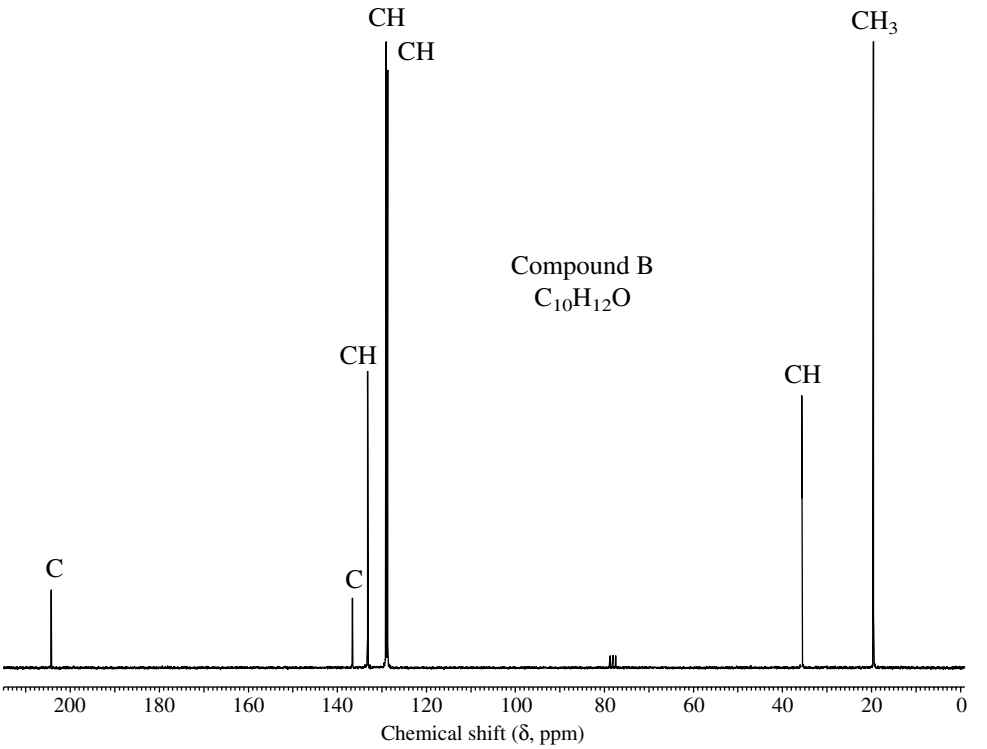


FIGURE 17.21 The ^{13}C NMR spectrum of compound B ($C_{10}H_{12}O$) (Problem 17.48).

17.49 The most stable conformation of acetone has one of the hydrogens of each methyl group eclipsed with the carbonyl oxygen. Construct a model of this conformation.

17.50 Construct a molecular model of cyclohexanone. Do either of the hydrogens of C-2 eclipse the carbonyl oxygen?