CHAPTER

9

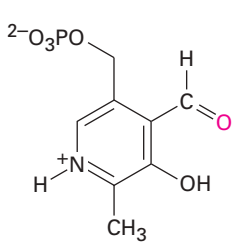
Few flowers are more beautiful or more fragrant than roses. Their perfumed odor is due to several simple organic compounds, including the ketone β-damascenone.

Aldehydes and Ketones: Nucleophilic Addition Reactions

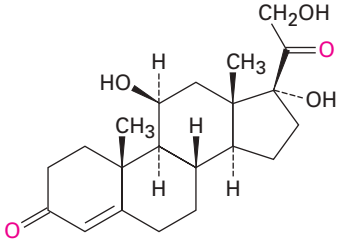
OWL

Online homework for this chapter can be assigned in OWL, an online homework assessment tool.

In this and the next two chapters, we'll discuss the most important functional group in both organic and biological chemistry—the carbonyl group, C=O. There are many different kinds of carbonyl compounds, but we'll begin our coverage by looking at just two: **aldehydes (RCHO)** and **ketones (R_2CO).** In nature, many substances found in living organisms are aldehydes or ketones. The aldehyde pyridoxal phosphate, for instance, is a coenzyme involved in a large number of metabolic reactions, and the ketone hydrocortisone is a steroid hormone secreted by the adrenal glands to regulate fat, protein, and carbohydrate metabolism.



Pyridoxal phosphate (PLP)



Hydrocortisone

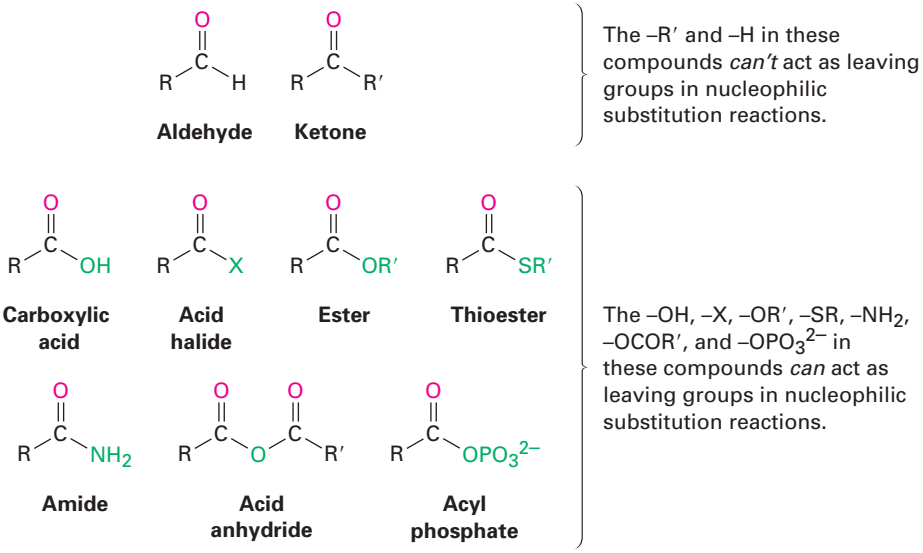
In the chemical industry, simple aldehydes and ketones are produced in large amounts for use as solvents and as starting materials to prepare a host of other compounds. More than 23 million tons per year of formaldehyde, $H_2C{=}O$, are produced worldwide for use in building insulation materials and in the adhesive resins that bind particle board and plywood. Acetone, $(CH_3)_2C{=}O$, is widely used as an industrial solvent, with approximately 3.3 million tons per year produced worldwide.

WHY THIS CHAPTER?

Much of organic chemistry is the chemistry of carbonyl compounds. Aldehydes and ketones, in particular, are intermediates in the synthesis of many pharmaceutical agents, in almost all biological pathways, and in numerous industrial processes. We'll look in this chapter at some of their most important reactions.

9.1 The Nature of Carbonyl Compounds

It's useful to classify carbonyl compounds into two general categories based on the kinds of chemistry they undergo. In one category are aldehydes and ketones; in the other are carboxylic acids and their derivatives. The C=O groups in aldehydes and ketones are bonded to atoms (H and C) that aren't electronegative enough to stabilize a negative charge and therefore can't act as leaving groups in nucleophilic substitution reactions. The C=O groups in carboxylic acids and their derivatives are bonded to atoms (oxygen, halogen, nitrogen, and so forth) that *can* stabilize a negative charge and therefore can act as leaving groups in substitution reactions.



The carbon–oxygen double bond of carbonyl groups is similar in some respects to the carbon–carbon double bond of alkenes (Figure 9.1). The carbonyl carbon atom is sp^2-hybridized and forms three σ bonds. The fourth

valence electron remains in a carbon *p* orbital and forms a π bond to oxygen by overlap with an oxygen *p* orbital. The oxygen also has two nonbonding pairs of electrons, which occupy its remaining two orbitals. Like alkenes, carbonyl compounds are planar about the double bond and have bond angles of approximately 120°.

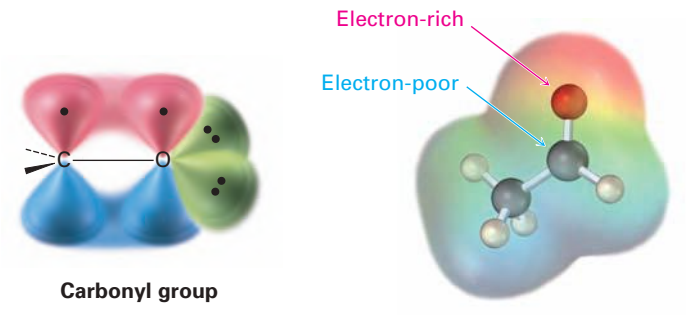


Figure 9.1 Electronic structure of the carbonyl group.

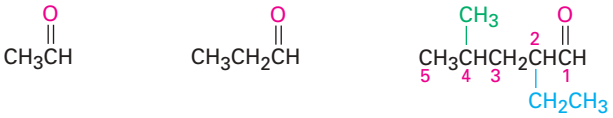
As indicated by the electrostatic potential map in Figure 9.1, the carbon–oxygen double bond is polarized because of the high electronegativity of oxygen relative to carbon. Thus, the carbonyl carbon is positively polarized and electrophilic (Lewis acidic), while the carbonyl oxygen is negatively polarized and nucleophilic (Lewis basic). We'll see in this and the next two chapters that most carbonyl-group reactions are the result of this bond polarity.

Problem 9.1 Propose structures for molecules that meet the following descriptions:

(a) A ketone, $C_5H_{10}O$ **(b)** An aldehyde, $C_6H_{10}O$
(c) A keto aldehyde, $C_6H_{10}O_2$ **(d)** A cyclic ketone, C_5H_8O

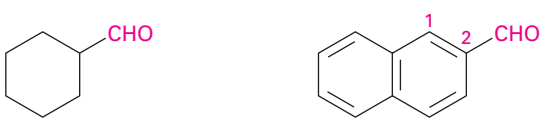
9.2 Naming Aldehydes and Ketones

Aldehydes are named by replacing the terminal *-e* of the corresponding alkane name with *-al*. The parent chain must contain the –CHO group, and numbering begins at the –CHO carbon, which is always C1. In the following examples, note that the longest chain in 2-ethyl-4-methylpentanal is actually a hexane, but this chain does not include the –CHO group and thus is not the parent.



Ethanal (acetaldehyde) **Propanal** (propionaldehyde) **2-Ethyl-4-methylpentanal**

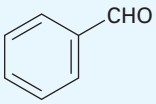
For more complex aldehydes in which the –CHO group is attached to a ring, the suffix *-carbaldehyde* is used.



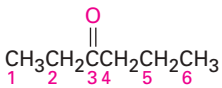
Cyclohexanecarbaldehyde **Naphthalene-2-carbaldehyde**

A few simple and well-known aldehydes have common names that are recognized by IUPAC. Several that you might encounter are listed in Table 9.1.

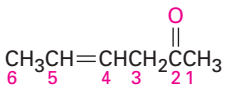
Table 9.1 Common Names of Some Simple Aldehydes

Formula	Common name	Systematic name
HCHO	Formaldehyde	Methanal
CH_3CHO	Acetaldehyde	Ethanal
$H_2C{=}CHCHO$	Acrolein	Propenal
$CH_3CH{=}CHCHO$	Crotonaldehyde	But-2-enal
	Benzaldehyde	Benzenecarbaldehyde

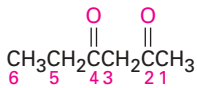
Ketones are named by replacing the terminal *-e* of the corresponding alkane name with *-one*. The parent chain is the longest one that contains the ketone group, and numbering begins at the end nearer the carbonyl carbon. As with alkenes (Section 3.1) and alcohols (Section 8.1), the numerical locant is placed immediately before the *-one* suffix in newer IUPAC recommendations. For example:



Hexan-3-one

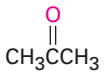


Hex-4-en-2-one

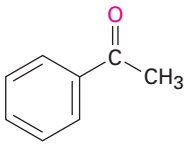


Hexane-2,4-dione

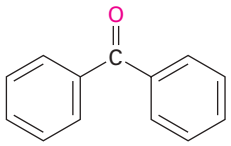
A few ketones also have common names.



Acetone



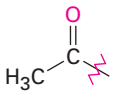
Acetophenone



Benzophenone

When it's necessary to refer to the –COR group as a substituent, the general term **acyl group** is used. More specifically, $-COCH_3$ is an *acetyl* group, –CHO is a *formyl* group, –COAr is an *aroyl* group, and $-COC_6H_5$ is a *benzoyl* group.

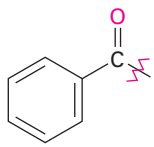
An acyl group (R = alkyl, alkenyl)



Acetyl

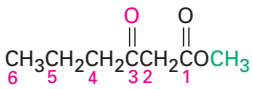
Formyl

Aroyl (Ar = aromatic)



Benzoyl

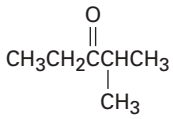
Occasionally, the doubly bonded oxygen is considered a substituent, and the prefix *oxo-* is used. For example:



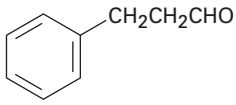
Methyl 3-oxohexanoate

Problem 9.2 Name the following aldehydes and ketones:

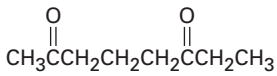
(a)



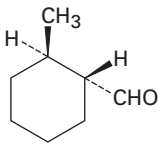
(b)



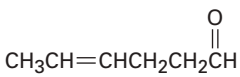
(c)



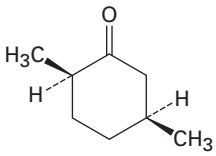
(d)



(e)



(f)

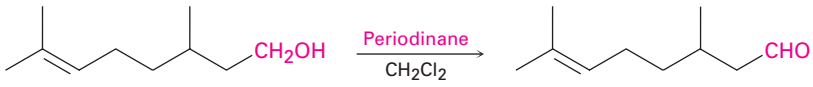


Problem 9.3 Draw structures corresponding to the following IUPAC names:

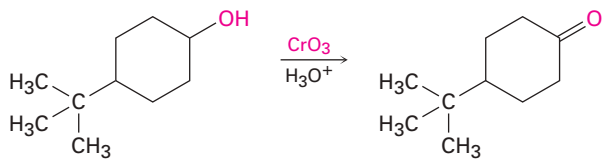
(a) 3-Methylbutanal
(b) 3-Methylbut-3-enal
(c) 4-Chloropentan-2-one
(d) Phenylacetaldehyde
(e) 2,2-Dimethylcyclohexanecarbaldehyde
(f) Cyclohexane-1,3-dione

9.3 Synthesis of Aldehydes and Ketones

We've already discussed one of the best methods for preparing aldehydes and ketones—the oxidation of alcohols (Section 8.4). Primary alcohols are oxidized to give aldehydes, and secondary alcohols are oxidized to give ketones. A periodinane oxidizing agent in dichloromethane is often chosen for making aldehydes, while CrO_3 and $Na_2Cr_2O_7$ in aqueous acid are frequently used for making ketones.

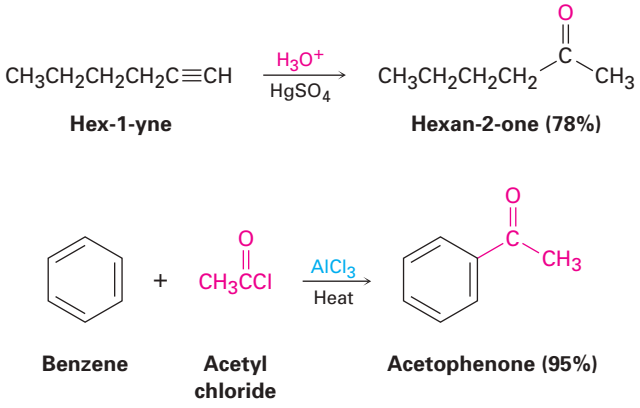


Citronellol **Citronellal (82%)**



4-*tert*-Butylcyclohexanol **4-*tert*-Butylcyclohexanone (90%)**

Other methods we've seen for preparing ketones include the hydration of a terminal alkyne to yield a methyl ketone (Section 4.11) and the Friedel–Crafts acylation of an aromatic ring (Section 5.5).

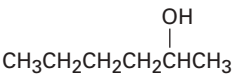


Problem 9.4 How could you prepare pentanal from the following starting materials?

(a) Pentan-1-ol **(b)** $CH_3CH_2CH_2CH_2CO_2H$ **(c)** Dec-5-ene

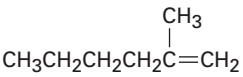
Problem 9.5 How could you prepare hexan-2-one from the following starting materials?

(a)



(b) $CH_3CH_2CH_2CH_2C{\equiv}CH$

(c)

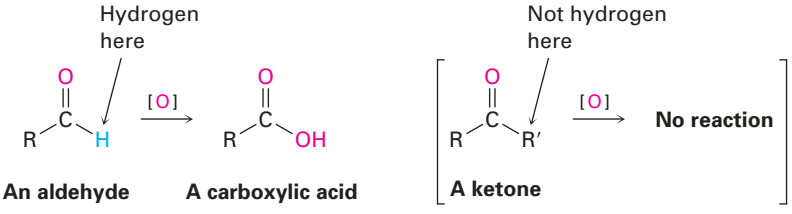


Problem 9.6 How would you carry out the following transformations? More than one step may be required.

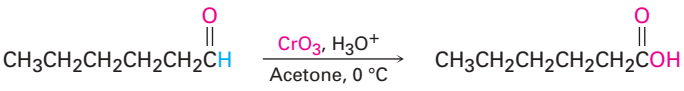
(a) Hex-3-ene → Hexan-3-one **(b)** Benzene → 1-Phenylethanol

9.4 Oxidation of Aldehydes

Aldehydes are easily oxidized to yield carboxylic acids, $RCHO \rightarrow RCO_2H$, but ketones are unreactive toward oxidation. This reactivity difference is a consequence of structure: aldehydes have a –C**H**O proton that can be removed during oxidation, but ketones do not.

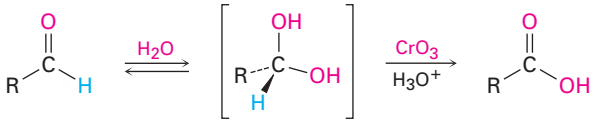


Many oxidizing agents convert aldehydes into carboxylic acids, but CrO_3 in aqueous acid is a common choice. The oxidation takes place rapidly at room temperature.



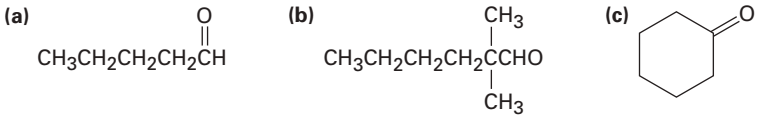
Hexanal **Hexanoic acid (85%)**

Aldehyde oxidations occur through intermediate *hydrates,* which are formed by a reversible addition of water to the carbonyl group. The hydrate reacts like any typical primary or secondary alcohol and is rapidly oxidized to a carbonyl compound.



An aldehyde **A hydrate** **A carboxylic acid**

Problem 9.7 Predict the products of the reaction of the following substances with CrO_3 in aqueous acid:



9.5 Nucleophilic Addition Reactions

The most common reaction of aldehydes and ketones is the **nucleophilic addition reaction**, in which a nucleophile adds to the electrophilic carbon of the carbonyl group. As shown in Figure 9.2, the reaction can take place under either basic or acidic conditions.

Under basic conditions (Figure 9.2a), the nucleophile is negatively charged ($:Nu^-$) and uses a pair of its electrons to form a bond to the electrophilic carbon atom of the C=O group. At the same time, the C=O carbon atom rehybridizes from sp^2 to sp^3 and two electrons from the C=O π bond are pushed onto the oxygen atom, giving an alkoxide ion. Addition of H^+ to the alkoxide ion then yields a neutral alcohol product.

Under acidic conditions (Figure 9.2b), the carbonyl oxygen atom is first protonated to make the carbonyl group more strongly electrophilic. A neutral

nucleophile (:Nu—H) then uses a pair of electrons to bond to the carbon atom of the C=O group, and two electrons from the C=O π bond move onto the oxygen atom. The positive charge on oxygen is thereby neutralized, while the nucleophile gains a positive charge. Finally, a deprotonation gives the neutral alcohol addition product and regenerates the acid catalyst.

MECHANISM

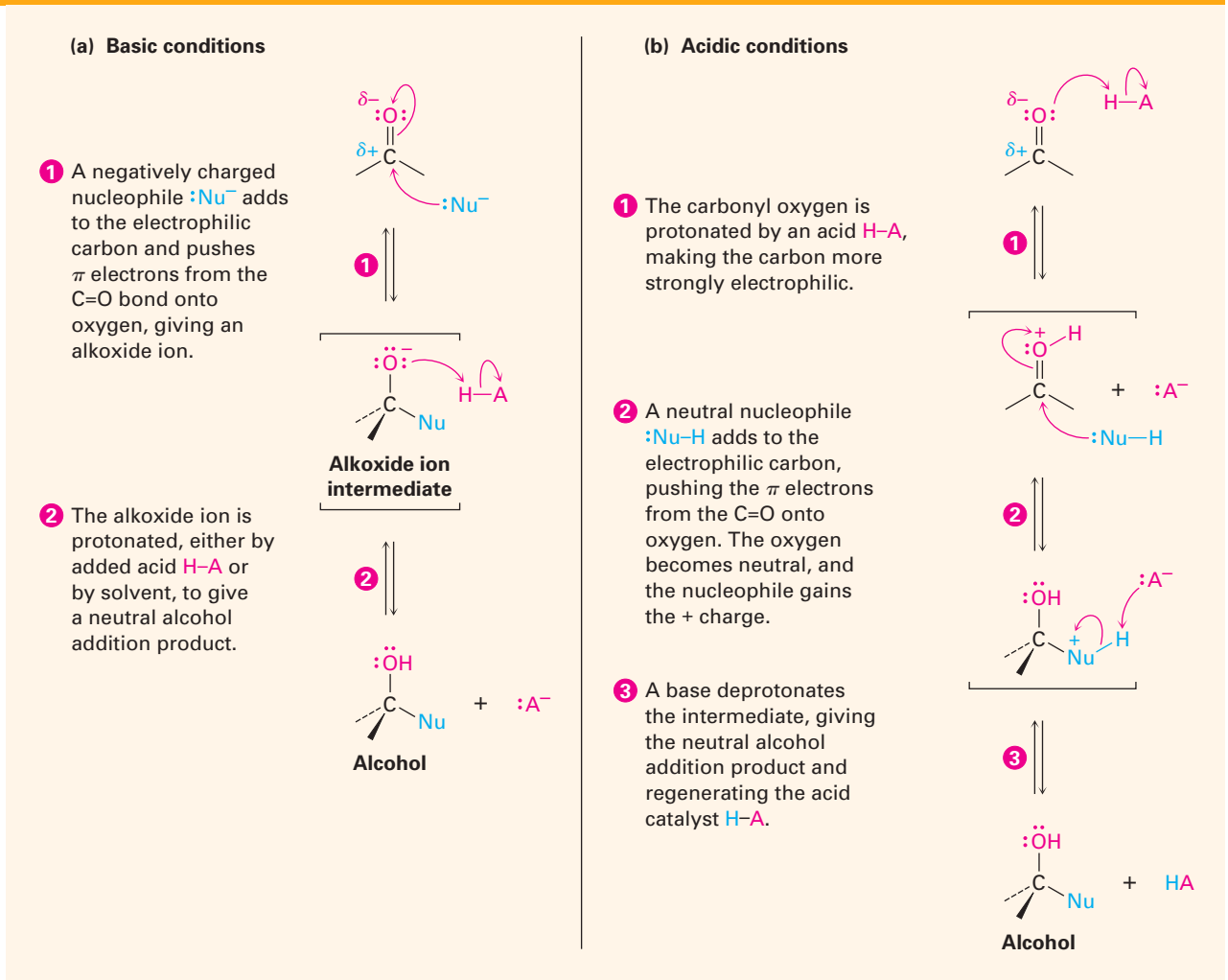


Figure 9.2 General mechanism of a nucleophilic addition reaction of aldehydes and ketones under both basic and acidic conditions. **(a)** Under basic conditions, a negatively charged nucleophile adds to the carbonyl group to give an alkoxide ion intermediate, which is subsequently protonated. **(b)** Under acidic conditions, protonation of the carbonyl group occurs first, followed by addition of a neutral nucleophile and subsequent deprotonation.

Note that the main difference between the basic and acidic reactions is in the timing of the protonation. Under basic conditions, the nucleophile is negatively charged and protonation occurs last. Under acidic conditions, the

nucleophile is neutral and protonation occurs first. Examples of some common nucleophiles are

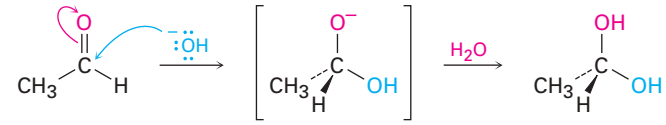
Some negatively charged nucleophiles (basic conditions)		Some neutral nucleophiles (acidic conditions)	
HO^-	(hydroxide ion)	H_2O	(water)
H^-	(hydride ion)	ROH	(alcohol)
R_3C^-	(carbanion)	NH_3	(ammonia)
RO^-	(alkoxide ion)	RNH_2	(amine)
$N{\equiv}C^-$	(cyanide ion)		

Worked Example 9.1 **Predicting the Product of a Nucleophilic Addition Reaction**

What product would you expect from nucleophilic addition of aqueous hydroxide ion to acetaldehyde?

Strategy The negatively charged hydroxide ion is a nucleophile, which can add to the C=O carbon atom and give an alkoxide ion intermediate. Protonation will then yield a hydrate.

Solution



Acetaldehyde

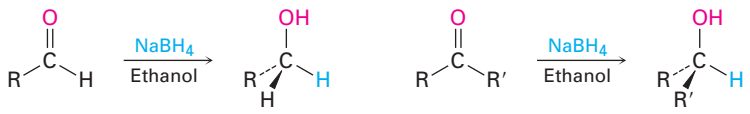
Problem 9.8 What product would you expect from nucleophilic addition of cyanide ion, CN^-, to acetone, followed by protonation?

Problem 9.9 What product would you expect from nucleophilic addition of methanol, CH_3OH, to benzaldehyde under acidic conditions?

9.6 Nucleophilic Addition of Hydride and Grignard Reagents: Alcohol Formation

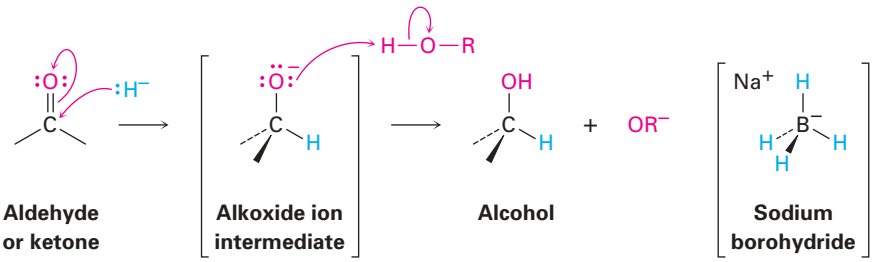
Addition of Hydride Reagents: Reduction

As we saw in Section 8.3, the most common method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of carbonyl compounds. Aldehydes are reduced with sodium borohydride ($NaBH_4$) to give primary alcohols, and ketones are similarly reduced to give secondary alcohols.



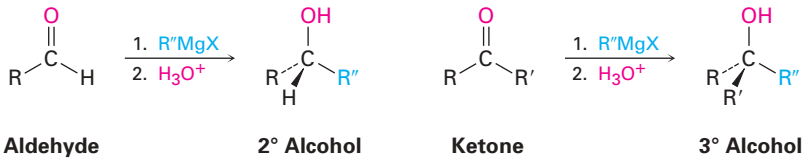
Aldehyde 1° Alcohol Ketone 2° Alcohol

Carbonyl reduction occurs by a typical nucleophilic addition mechanism under basic conditions, as shown previously in Figure 9.2a. The nucleophile is a negatively charged hydride ion (:H$^-$) supplied by $NaBH_4$, and the initially formed alkoxide ion intermediate is protonated by ethanol solvent. The reaction is irreversible because the reverse process would require expulsion of a very poor leaving group.

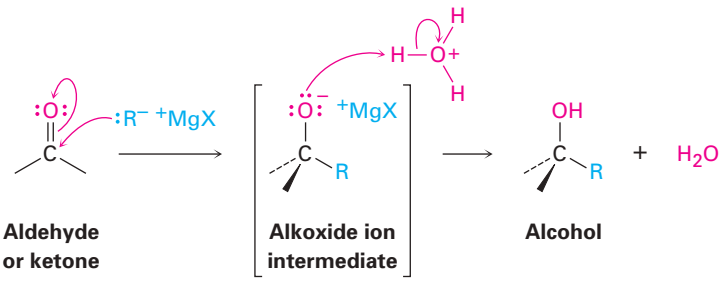


Addition of Grignard Reagents

Just as aldehydes and ketones undergo nucleophilic addition with hydride ion to give alcohols, they undergo a similar addition with Grignard reagents, R:$^-$ $^+$MgX (Section 8.3). Aldehydes give secondary alcohols on reaction with Grignard reagents in ether solution, and ketones give tertiary alcohols.



Like the reaction with hydride ion, a Grignard reaction takes place by a typical nucleophilic addition mechanism under basic conditions. The nucleophile is a carbanion (R:$^-$) from the Grignard reagent, which adds to the C=O bond and produces a tetrahedrally hybridized magnesium alkoxide intermediate. Protonation by addition of aqueous acid in a separate step then gives the neutral alcohol. Like reduction, the Grignard reaction is irreversible.



Although widely applicable, the Grignard reaction also has limitations. For example, a Grignard reagent can't be prepared from an organohalide that has other reactive functional groups in the same molecule. Some functional groups—carbonyls, for instance—cause the Grignard reagent to add to itself. Other groups—alcohols, for instance—destroy the Grignard reagent by

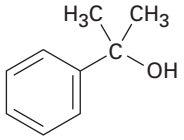
protonation (Section 7.3). In general, Grignard reagents can't be prepared from compounds that contain the following functional groups:

$-CHO$, $-COR$, $-CONR_2$, $-C{\equiv}N$, $-NO_2$, $-SO_2R$ } A Grignard reagent reacts with these groups.

$-OH$, $-NH_2$, $-NHR$, $-SH$, $-CO_2H$ } A Grignard reagent is protonated by these groups.

Worked Example 9.2 Using a Grignard Reaction to Prepare an Alcohol

How can you use the addition of a Grignard reagent to a ketone to synthesize 2-phenylpropan-2-ol?

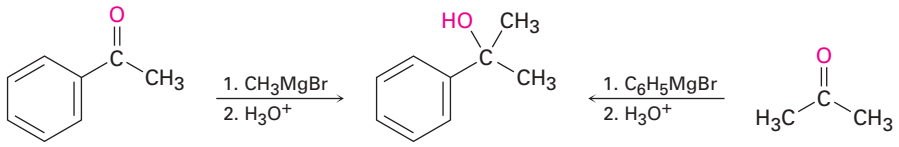


2-Phenylpropan-2-ol

Strategy

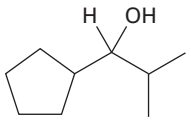
Look at the product, and identify the groups bonded to the alcohol carbon atom. In this instance, there are two methyl groups ($-CH_3$) and one phenyl ($-C_6H_5$). One of the three must come from a Grignard reagent, and the remaining two must come from a ketone. Thus, the possibilities are addition of CH_3MgBr to acetophenone and addition of C_6H_5MgBr to acetone.

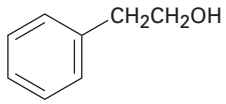
Solution

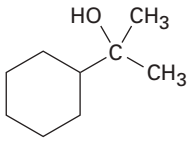


Acetophenone **2-Phenylpropan-2-ol** **Acetone**

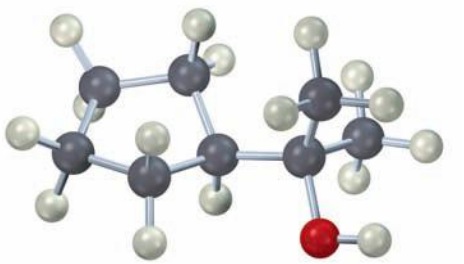
Problem 9.10 How might you prepare the following alcohols from an aldehyde or ketone? Show all possibilities.

(a) 

(b) 

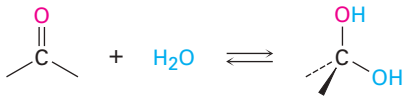
(c) 

Problem 9.11 How might you use a Grignard reaction of an aldehyde or ketone to prepare the following molecule (red = O)?



9.7 Nucleophilic Addition of Water: Hydrate Formation

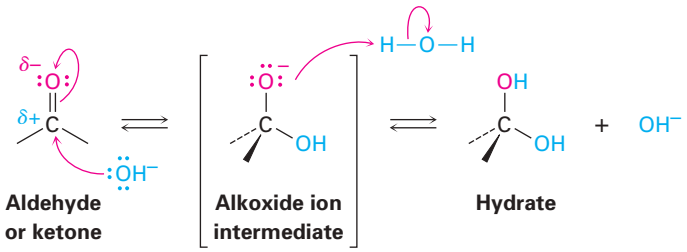
Aldehydes and ketones undergo a nucleophilic addition reaction with water to yield the corresponding carbonyl hydrates, sometimes called **geminal (gem) diols** from the Latin *geminus,* meaning "twin." The reaction is reversible, and the gem diol product can eliminate water to regenerate a ketone or aldehyde.



Aldehyde or ketone **Carbonyl hydrate (gem diol)**

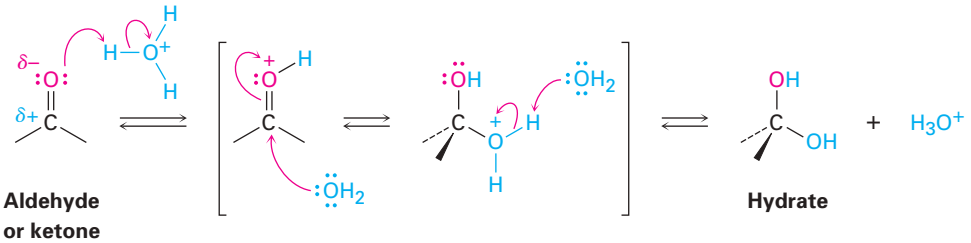
The position of the equilibrium between hydrate and aldehyde/ketone depends on the structure of the carbonyl compound. The equilibrium strongly favors the carbonyl compound in most cases, with the hydrate favored only for a few simple aldehydes. An aqueous solution of acetone, for instance, consists of about 0.1% hydrate and 99.9% ketone, whereas an aqueous solution of formaldehyde (CH_2O) consists of 99.9% hydrate and 0.1% aldehyde.

The nucleophilic addition of water to aldehydes and ketones is slow in pure water but is catalyzed by both base and acid. The base-catalyzed addition reaction takes place by the mechanism shown previously in Figure 9.2a, with the negatively charged hydroxide ion as the nucleophile and water as the proton source in the final step.



Aldehyde or ketone **Alkoxide ion intermediate** **Hydrate**

The acid-catalyzed reaction takes place by the mechanism shown previously in Figure 9.2b. The acid catalyst first protonates the basic oxygen atom of the carbonyl group to increase its reactivity, water adds as the nucleophile, and deprotonation gives the gem diol product.



Aldehyde or ketone **Hydrate**

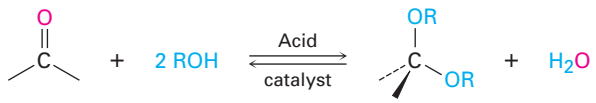
Note the crucial difference between the base-catalyzed and acid-catalyzed processes: the *base*-catalyzed reaction takes place rapidly because hydroxide ion is a much better *nucleophile* than neutral water. The *acid*-catalyzed

reaction takes place rapidly because the protonated carbonyl compound is a much better *electrophile* than the neutral compound.

Problem 9.12 The oxygen in water is primarily (99.8%) ^{16}O, but water enriched with the heavy isotope ^{18}O is also available. When a ketone or aldehyde is dissolved in $H_2{}^{18}O$, the isotopic label becomes incorporated into the carbonyl group: $R_2C{=}O + H_2{}^{18}O \rightarrow R_2C{=}{}^{18}O + H_2O$. Explain.

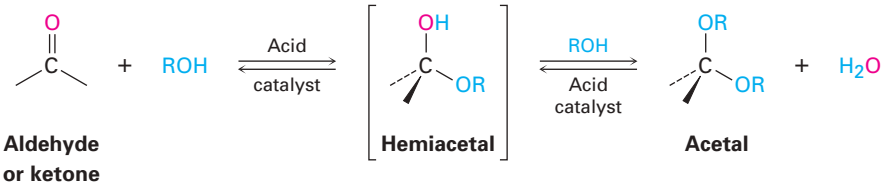
9.8 Nucleophilic Addition of Alcohols: Acetal Formation

Aldehydes and ketones undergo a reversible reaction with alcohols in the presence of an acid catalyst to yield **acetals, $R_2C(OR')_2$**, compounds that have two ether-like –OR groups bonded to the same carbon.



Aldehyde or ketone **Acetal**

Acetal formation involves the acid-catalyzed nucleophilic addition of an alcohol to an aldehyde or ketone in a process analogous to that of the acid-catalyzed addition of water discussed in the previous section. The initial nucleophilic addition step occurs by the usual mechanism (Figure 9.2b) and yields an intermediate hydroxy ether called a **hemiacetal**. The hemiacetal then reacts further with a second equivalent of alcohol and gives the acetal plus water.



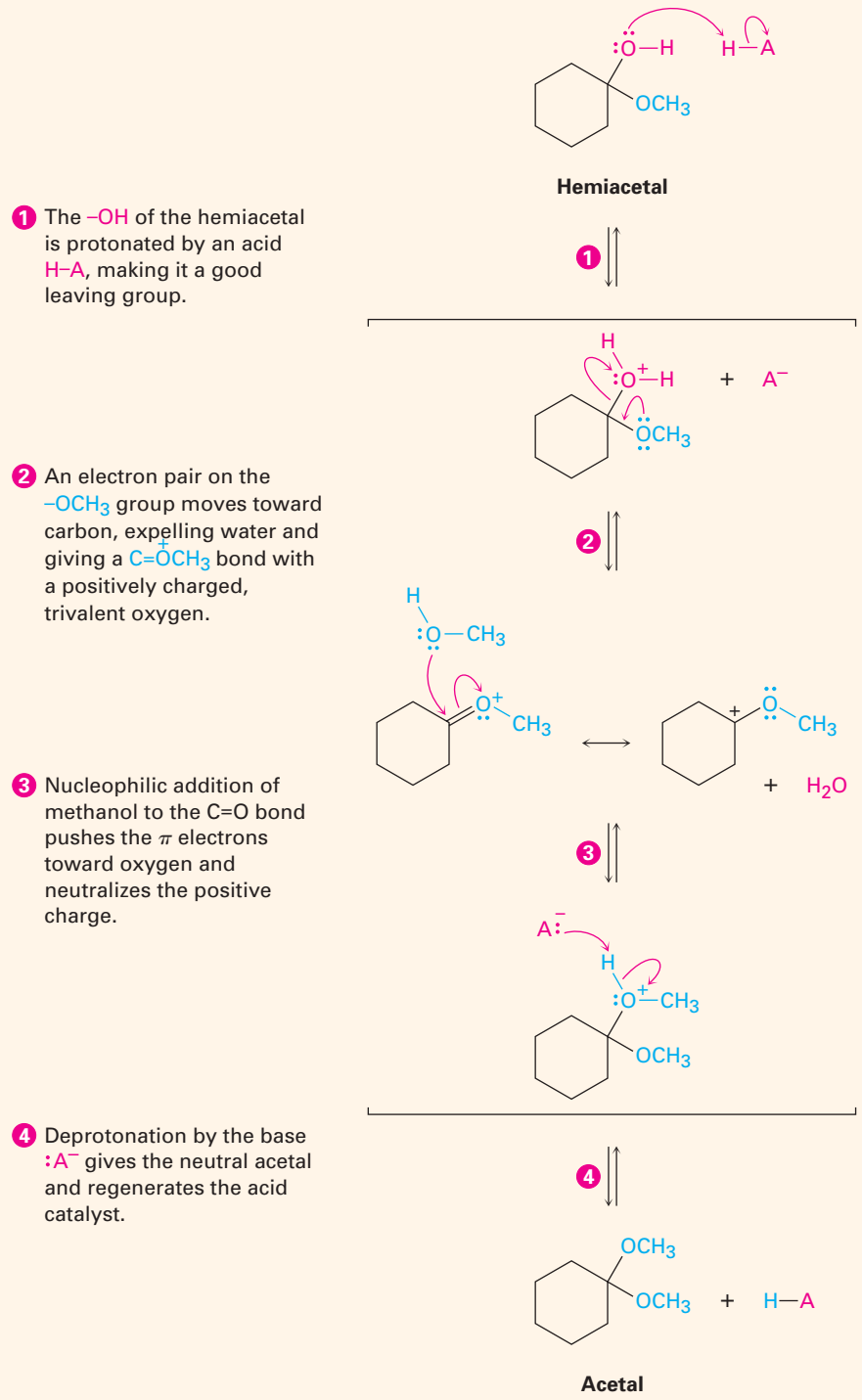
Aldehyde or ketone **Hemiacetal** **Acetal**

As with hydrate formation, all the steps during acetal formation are reversible, and the reaction can be made to go either forward (from carbonyl compound to acetal) or backward (from acetal to carbonyl compound), depending on the reaction conditions. The forward reaction is favored by conditions that remove water from the medium and thus drive the equilibrium to the right. The backward reaction is favored in the presence of a large excess of water, which drives the equilibrium to the left.

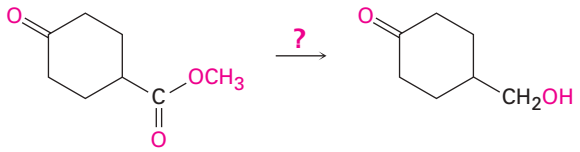
The mechanism of acetal formation from the hemiacetal is shown in Figure 9.3 for the reaction of cyclohexanone with methanol. Protonation of the hemiacetal –OH occurs first, making it a good leaving group and facilitating a spontaneous loss of water, much like what happens during the E1 reaction of an alcohol (Section 7.8). The resonance-stabilized cation that results then undergoes nucleophilic addition of alcohol to the C=O bond, followed by deprotonation to give the acetal.

MECHANISM

Figure 9.3 Mechanism of formation of an acetal from a hemiacetal. Protonation and loss of water give an intermediate cation, which undergoes a nucleophilic addition reaction with methanol.

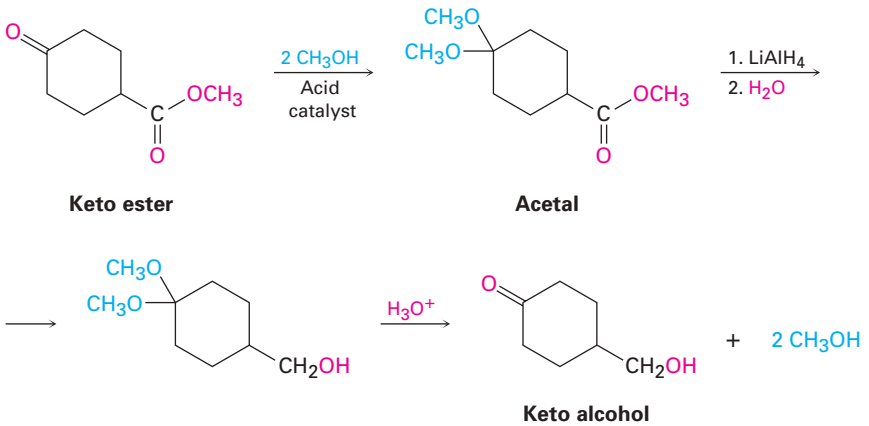


Acetals are valuable to organic chemists because they can serve as **protecting groups** for aldehydes and ketones. To see what this means, imagine that you need to reduce an ester group selectively in the presence of a keto group. The reaction can't be done in a single step because treating a keto ester with $LiAlH_4$ (Section 8.3) would reduce both groups.



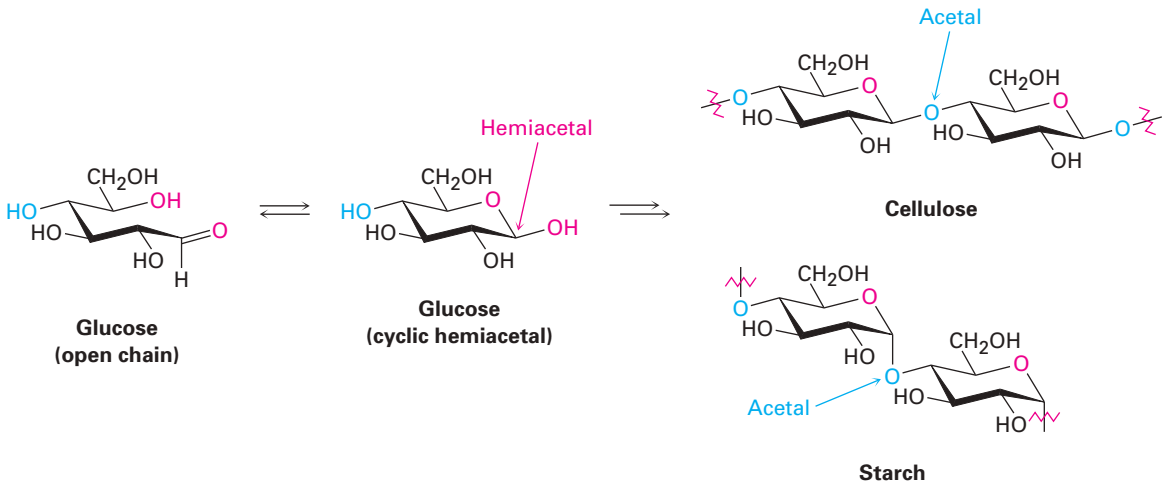
This situation isn't unusual; it often happens that one functional group in a complex molecule interferes with intended chemistry on another functional group elsewhere in the molecule. In such situations, it's often possible to circumvent the problem by *protecting* the interfering functional group to render it unreactive, then carrying out the desired reaction, and then removing the protecting group.

Aldehydes and ketones are usually protected by converting them into acetals. Acetals, like other ethers, are stable to bases, reducing agents, and various nucleophiles, but they can be cleaved by treatment with acid (Section 8.6). Thus, you can selectively reduce the ester group in a keto ester by converting the keto group into an acetal, reducing the ester with $LiAlH_4$ in ether, and removing the acetal protecting group by treatment with aqueous acid.



In nature, acetal and hemiacetal groups are particularly common in carbohydrate chemistry. Glucose, for instance, is a polyhydroxy aldehyde that undergoes a spontaneous *internal* nucleophilic addition reaction and exists primarily as a cyclic hemiacetal. Numerous glucose molecules then join

together with acetal links to form either cellulose or starch. We'll study this and other reactions of carbohydrates in Chapter 14.

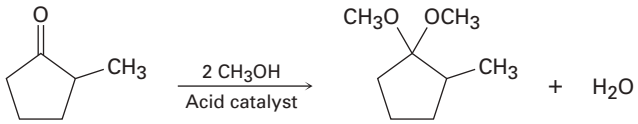


Worked Example 9.3 Predicting the Structure of an Acetal

What product would you obtain from the acid-catalyzed reaction of 2-methylcyclopentanone with methanol?

Strategy A ketone reacts with an alcohol in the presence of acid to yield an acetal. To find the product, replace the oxygen of the ketone with two $-OCH_3$ groups from the alcohol.

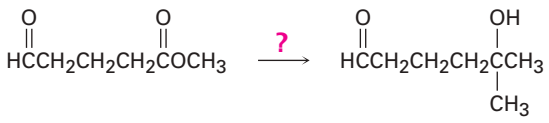
Solution



Problem 9.13 Write the mechanism of the acid-catalyzed reaction of methanol with cyclohexanone to give a hemiacetal.

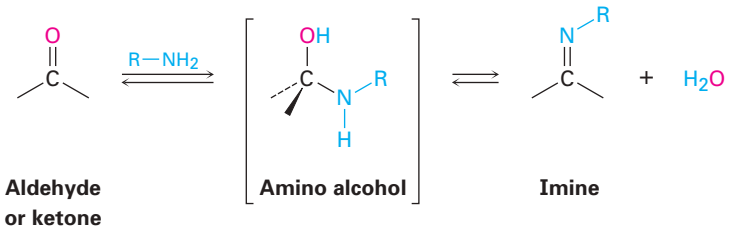
Problem 9.14 When an aldehyde or ketone is treated with a diol such as ethylene glycol (ethane-1,2-diol) and an acid catalyst, a *cyclic* acetal is formed. Draw the structure of the product you would obtain from benzaldehyde and ethylene glycol.

Problem 9.15 Show how you might carry out the following transformation. (A protection step is needed.)

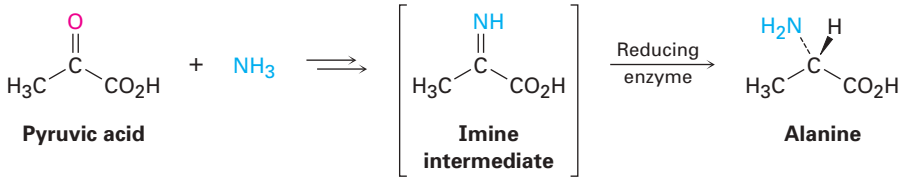


9.9 Nucleophilic Addition of Amines: Imine Formation

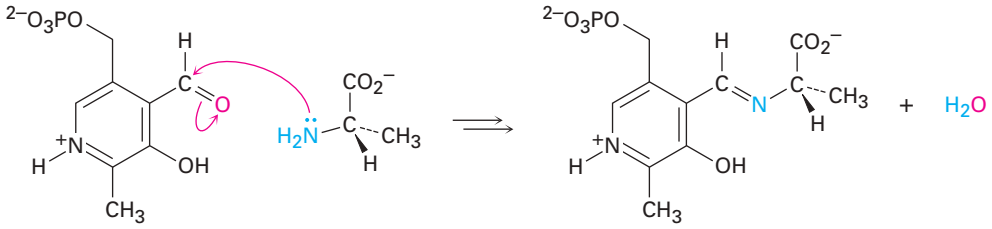
Ammonia and primary amines, R′NH_2, add to aldehydes and ketones to yield **imines, $R_2C{=}NR'$**. The reaction occurs by nucleophilic addition of the amine to the carbonyl group, followed by loss of water from the amino alcohol addition product.



Imines are common intermediates in numerous biological pathways and processes, including the route by which amino acids are synthesized and degraded in the body. One biological pathway for synthesis of the amino acid alanine, for instance, is by formation of an imine between pyruvic acid and ammonia, followed by reduction.



The pathway for biological degradation of alanine involves reaction with the aldehyde pyridoxal phosphate, a derivative of vitamin B_6, to yield an imine that is then further degraded.



Worked Example 9.4

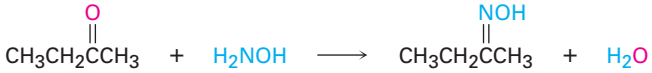
Predicting the Product of Imine Formation

What product do you expect from the reaction of butan-2-one with hydroxylamine, NH_2OH?

Strategy

Take oxygen from the ketone and two hydrogens from the amine to form water, and then join the fragments that remain.

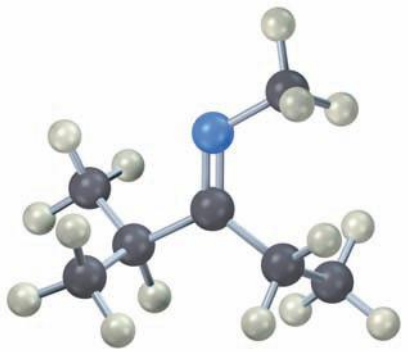
Solution



Problem 9.16 Write the products you would obtain from treatment of cyclohexanone with the following:

(a) CH_3NH_2 **(b)** CH_3CH_2OH, H^+ **(c)** $NaBH_4$

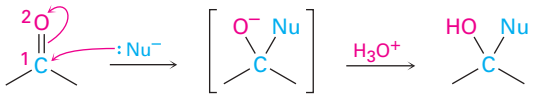
Problem 9.17 Show how the following molecule can be prepared from a carbonyl compound and an amine (blue = N):



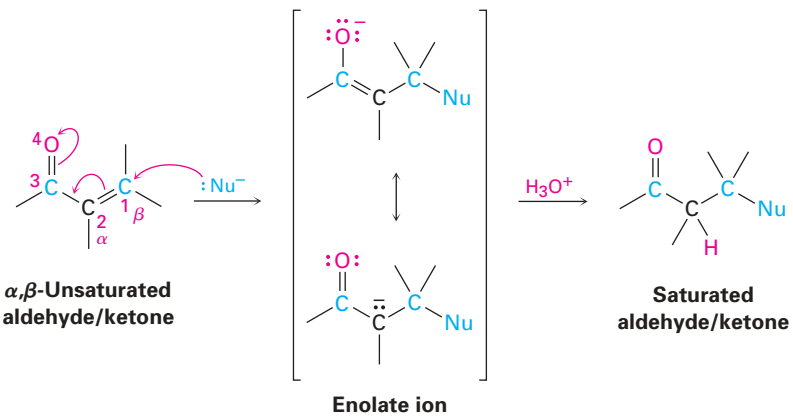
9.10 Conjugate Nucleophilic Addition Reactions

The reactions we've seen to this point have involved addition of a nucleophile directly to the carbonyl group in what is called a **1,2-addition**. Closely related to this direct addition is the *conjugate addition,* or **1,4-addition**, of a nucleophile to the C=C bond of an α,β-unsaturated aldehyde or ketone. (The carbon atom next to a carbonyl group is often called the α carbon, the next one is the β carbon, and so on.) Thus, an α,β-unsaturated aldehyde or ketone has its C=C and C=O bonds conjugated, much as a conjugated diene does (Section 4.8).

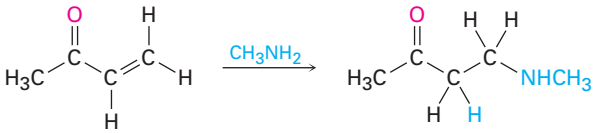
Direct (1,2) addition



Conjugate (1,4) addition

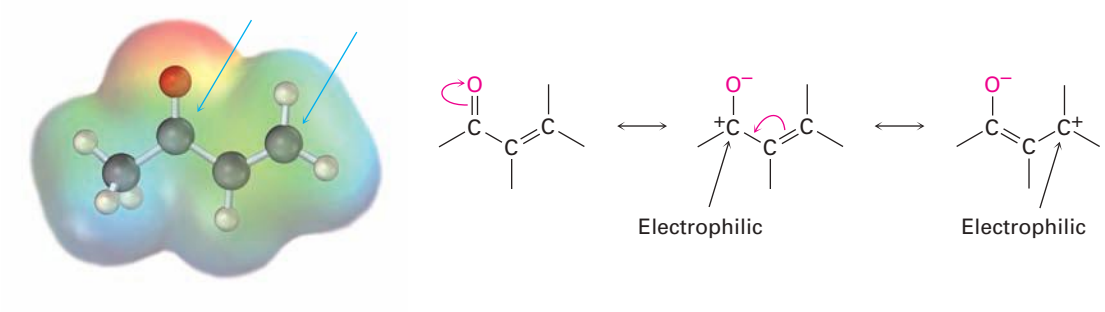


The initial product of conjugate addition is a resonance-stabilized **enolate ion**, which typically undergoes protonation on the α carbon to give a saturated aldehyde or ketone product. For example, methylamine reacts with but-3-en-2-one to give an amino ketone addition product.

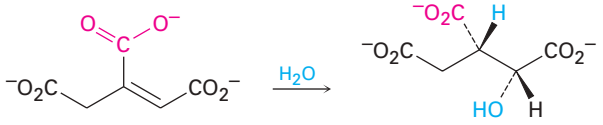


But-3-en-2-one **Conjugate addition product**

Conjugate addition occurs because the electronegative oxygen atom of the α,β-unsaturated carbonyl compound withdraws electrons from the β carbon, thereby making it more electron-poor and more electrophilic than a typical alkene C=C bond.

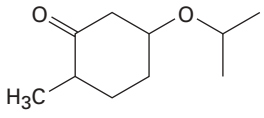


Conjugate additions are particularly common with amine nucleophiles and with water and occur in many biological pathways. An example is the addition of water to the C=C bond in *cis*-aconitate to give isocitrate, a step in the citric acid cycle of food metabolism.



***cis*-Aconitate** **Isocitrate**

Problem 9.18 The following compound was prepared by a conjugate addition reaction between an α,β-unsaturated ketone and an alcohol. Identify the two reactants.



INTERLUDE

Vitamin C

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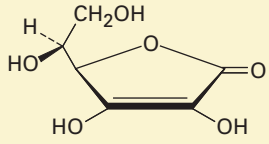
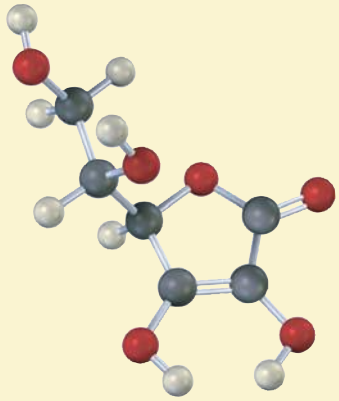
John Franklin's expedition in 1845 to chart the Northwest Passage between Atlantic and Pacific oceans resulted in the death of all 129 men aboard his two ships *Terror* and *Erebus*. Many of the men died of scurvy, a bleeding disease caused by a vitamin C deficiency.

Vitamin C, or ascorbic acid, is surely the best known of all vitamins. It was the first vitamin to be discovered (1928), the first to be structurally characterized (1933), and the first to be synthesized in the laboratory (1933). Over 200 million pounds of vitamin C are synthesized worldwide each year—more than the total amount of all other vitamins combined. In addition to its use as a vitamin supplement, vitamin C is used as a food preservative, a "flour improver" in bakeries, and an animal food additive.



Vitamin C (ascorbic acid)



Vitamin C is perhaps most famous for its antiscorbutic properties, meaning that it prevents the onset of scurvy, a bleeding disease affecting those with a deficiency of fresh vegetables and citrus fruits in their diet. Sailors in the Age of Exploration were particularly susceptible to scurvy, and the death toll was high. The Portuguese explorer Vasco da Gama lost more than half his crew to scurvy during his 2-year voyage around the Cape of Good Hope in 1497–1499. Even as late as 1845, all 129 men aboard John Franklin's expedition to find a Northwest Passage died, many of scurvy.

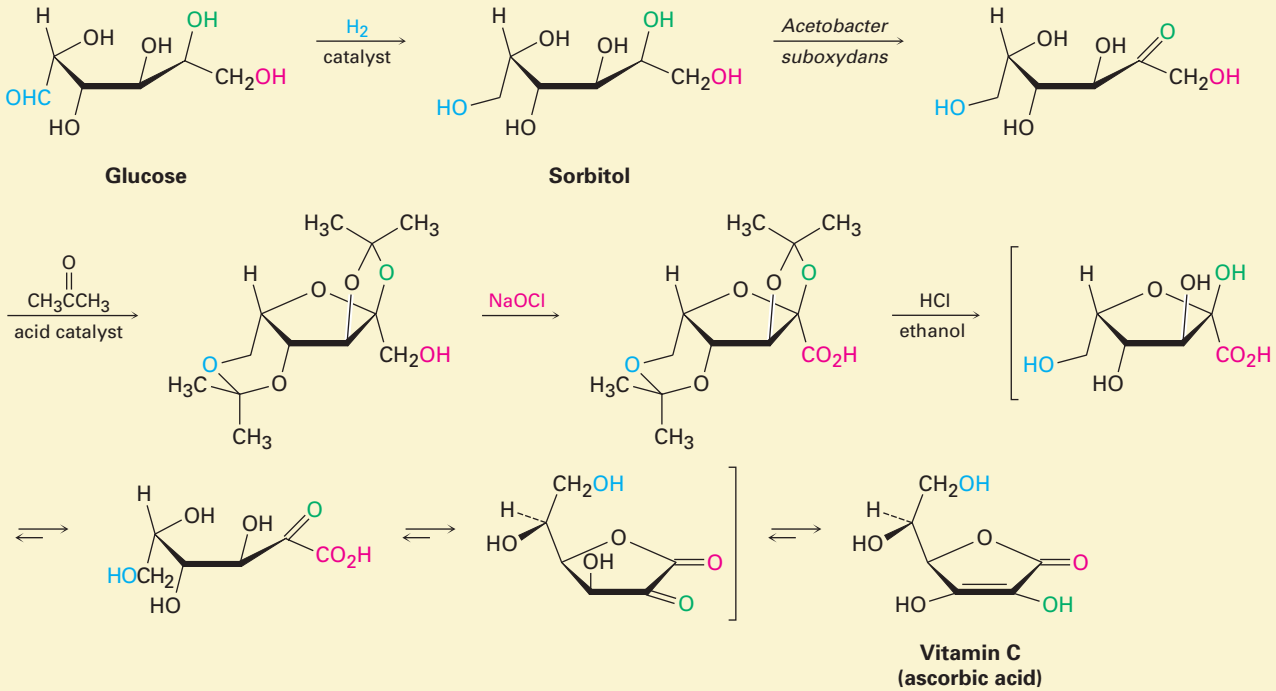
In more recent times, large doses of vitamin C have been claimed to prevent the common cold, cure infertility, delay the onset of symptoms in AIDS, and inhibit the development of gastric and cervical cancers. None of these claims have been backed by medical evidence, however. In the largest study yet done of the effect of vitamin C on the common cold, a meta-analysis of more than 100 separate trials covering 40,000 people found no difference in the incidence of colds between those who took supplemental vitamin C regularly and those who did not. When taken *during* a cold, however, vitamin C does appear to decrease the cold's duration by 8%.

The industrial preparation of vitamin C involves an unusual blend of biological and laboratory organic chemistry. The Hoffmann-La Roche company synthesizes ascorbic acid from glucose through the five-step route shown in Figure 9.4. Glucose, a pentahydroxy aldehyde, is first reduced to sorbitol, which is then oxidized by the microorganism *Acetobacter suboxydans*. No chemical reagent is known that is selective enough to oxidize

continued

INTERLUDE

only one of the six alcohol groups in sorbitol, so an enzymatic reaction is used. Treatment with acetone and an acid catalyst then converts four of the other hydroxyl groups into acetal linkages, and the remaining hydroxyl group is chemically oxidized to a carboxylic acid by reaction with aqueous NaOCl (household bleach). Hydrolysis with acid then removes the two acetal groups and causes an internal ester-forming reaction to take place to give ascorbic acid. Each of the five steps takes place in better than 90% yield.



Summary and Key Words

acetal 306
acyl group 297
1,2-addition reaction 311
1,4-addition reaction 311
aldehyde (RCHO) 294
carbonyl group 294
enolate ion 312
geminal (gem) diol 305
hemiacetal 306
imine 310
ketone ($R_2C{=}O$) 294
nucleophilic addition reaction 300
protecting group 308

Aldehydes and ketones are among the most important of all compounds, both in the chemical industry and in biological chemistry. In this chapter, we've looked at some of their typical reactions.

A carbon–oxygen double bond is structurally similar to a carbon–carbon double bond. The carbonyl carbon atom is sp^2-hybridized and forms both an sp^2 σ bond and a p π bond to oxygen. Carbonyl groups are strongly polarized because of the electronegativity of oxygen.

Aldehydes are usually prepared by oxidation of primary alcohols, and ketones are often prepared by oxidation of secondary alcohols. Aldehydes and ketones behave similarly in much of their chemistry. Both undergo **nucleophilic addition reactions**, which are useful for preparing a variety of products. For example, aldehydes and ketones undergo addition of hydride ion ($H{:}^-$) to give alcohol reduction products. Similarly, addition of the carbanion from Grignard reagents ($R{:}^{-}{}^{+}MgX$) gives alcohol products.

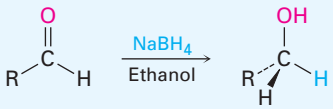
Reversible addition of an aldehyde or ketone with water yields a hydrate, also called a **gem diol**. Similarly, aldehydes and ketones react reversibly with alcohols to yield first **hemiacetals** and then **acetals**. Acetals are particularly useful as carbonyl **protecting groups**. Ammonia and primary amines add to aldehydes and ketones to give **imines**, **$R_2C{=}NR'$**.

Closely related to the direct 1,2-addition of nucleophiles to aldehydes and ketones is the conjugate **1,4-addition** of nucleophiles to the C=C double bond of α,β-unsaturated aldehydes and ketones. Both direct and conjugate addition reactions are common in biological pathways.

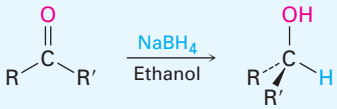
Summary of Reactions

Nucleophilic addition reactions of aldehydes and ketones

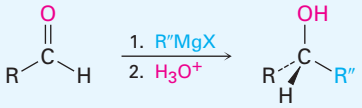
1. Reaction with hydride reagents to yield alcohols (Section 9.6)
   (a) Reaction of aldehydes to yield primary alcohols



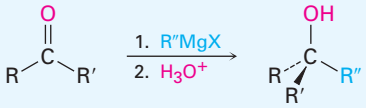
   (b) Reaction of ketones to yield secondary alcohols



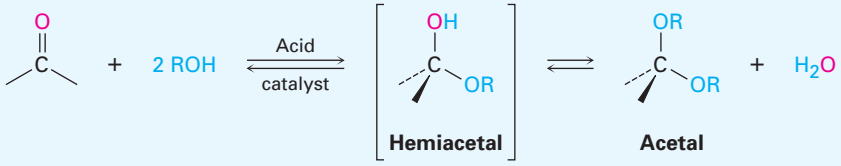
2. Reaction with Grignard reagents to yield alcohols (Section 9.6)
   (a) Reaction of aldehydes to yield secondary alcohols



   (b) Reaction of ketones to yield tertiary alcohols

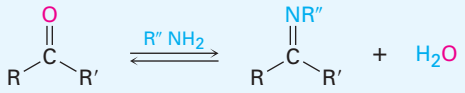


3. Reaction with alcohols to yield acetals (Section 9.8)

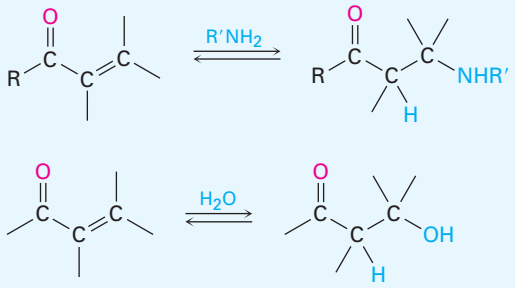


continued

4. Reaction with amines to yield imines (Section 9.9)



5. Conjugate (1,4) nucleophilic addition reaction (Section 9.10)



Exercises

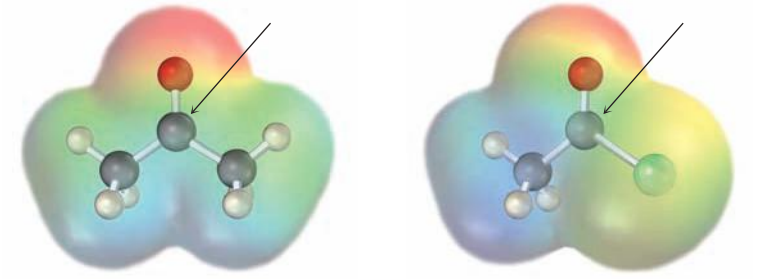
Visualizing Chemistry

(Problems 9.1–9.18 appear within the chapter.)

OWL

Interactive versions of these problems are assignable in OWL.

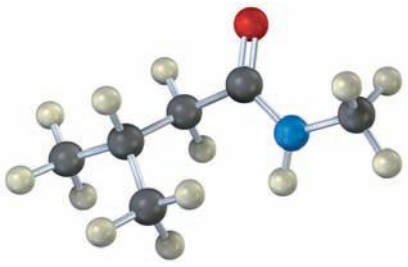
9.19 Judging from the following electrostatic potential maps, which kind of carbonyl compound has the more electrophilic carbonyl carbon atom, a ketone or an acid chloride? Which has the more nucleophilic carbonyl oxygen atom? Explain.



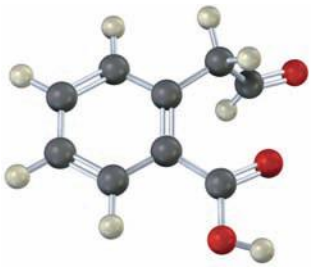
Acetone (ketone) **Acetyl chloride (acid chloride)**

9.20 Identify the kinds of carbonyl groups in the following molecules (red = O, blue = N):

(a)

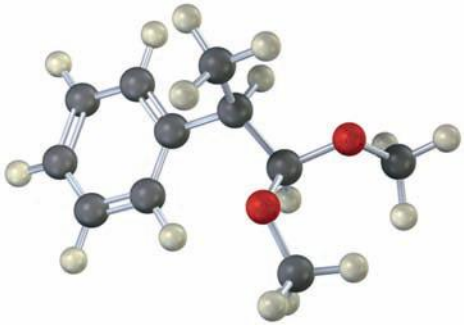


(b)

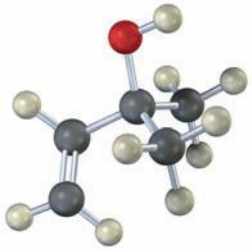


9.21 Identify the reactants from which the following molecules were prepared. If an acetal, identify the carbonyl compound and the alcohol; if an imine, identify the carbonyl compound and the amine; if an alcohol, identify the carbonyl compound and the Grignard reagent (red = O, blue = N):

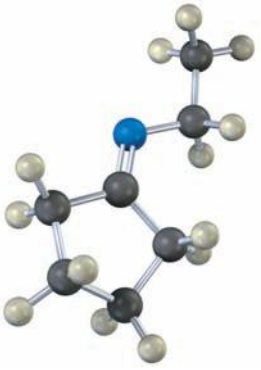
(a)



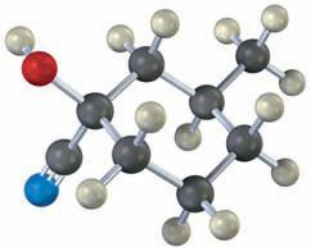
(b)



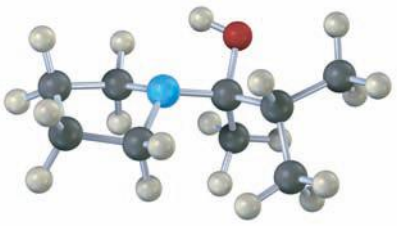
(c)



9.22 Compounds called *cyanohydrins* result from the nucleophilic addition of HCN to an aldehyde or ketone. Draw and name the carbonyl compound that the following cyanohydrin was prepared from (red = O, blue = N):



9.23 The following model represents the product resulting from addition of a nucleophile to an aldehyde or ketone. Identify the reactants, and write the reaction (red = O, blue = N).

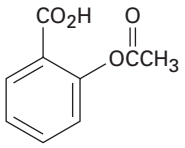


Additional Problems

Identifying and Naming Carbonyl Compounds

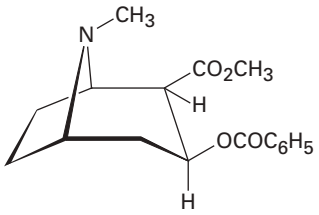
9.24 Identify the different kinds of carbonyl functional groups in the following molecules:

(a)



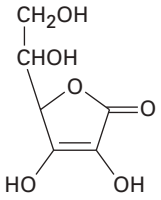
Aspirin

(b)



Cocaine

(c)



Ascorbic acid (vitamin C)

9.25 Draw structures corresponding to the following names:

(a) Bromoacetone
(b) 3-Methylbutan-2-one
(c) 3,5-Dinitrobenzaldehyde
(d) 3,5-Dimethylcyclohexanone
(e) 2,2,4,4-Tetramethylpentan-3-one
(f) Butanedial
(g) (*S*)-2-Hydroxypropanal
(h) 3-Phenylprop-2-enal

9.26 Draw and name the seven aldehydes and ketones with the formula $C_5H_{10}O$.

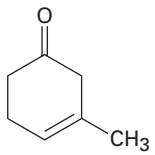
9.27 Which of the compounds you identified in Problem 9.26 are chiral?

9.28 Draw structures of molecules that meet the following descriptions:

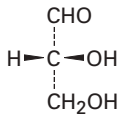
(a) A cyclic ketone, C_6H_8O
(b) A diketone, $C_6H_{10}O_2$
(c) An aryl ketone, $C_9H_{10}O$
(d) A 2-bromo aldehyde, C_5H_9BrO

9.29 Give IUPAC names for the following structures:

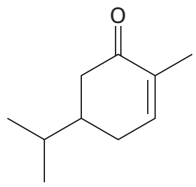
(a)



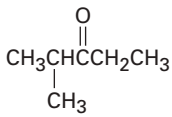
(b)



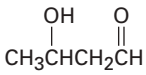
(c)



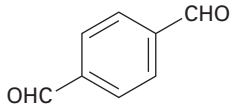
(d)



(e)



(f)



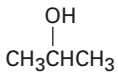
Reactions

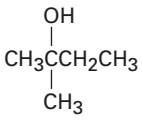
9.30 Predict the products of the reaction of phenylacetaldehyde, $C_6H_5CH_2CHO$, with the following reagents:

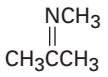
(a) $NaBH_4$, then H_3O^+
(b) aqueous acidic CrO_3
(c) NH_2OH
(d) CH_3MgBr, then H_3O^+
(e) CH_3OH, H^+ catalyst

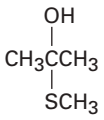
9.31 Answer Problem 9.30 for the reaction of acetophenone, $C_6H_5COCH_3$, with the same reagents.

9.32 Identify the nucleophile that has added to acetone to give the following products:

(a) 

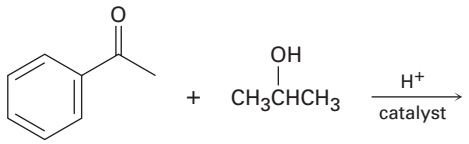
(b) 

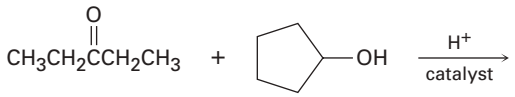
(c) 

(d) 

9.33 Show the products that result from the reaction of phenylmagnesium bromide with the following reagents:
(a) CH_2O **(b)** Benzophenone ($C_6H_5COC_6H_5$) **(c)** Pentan-3-one

9.34 Show the structures of the intermediate hemiacetals and the final acetals that result from the following reactions:

(a) 

(b) 

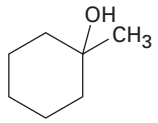
9.35 Reaction of butan-2-one with HCN yields a *cyanohydrin* product [$R_2C(OH)CN$] having a new chirality center. Explain why the product is not optically active.

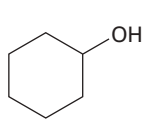
9.36 In light of your answer to Problem 9.35, what stereochemistry would you expect the product from the reaction of phenylmagnesium bromide with butan-2-one to have?

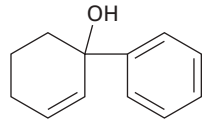
SYNTHESIS

9.37 Starting from cyclohex-2-enone and any other reagents needed, how would you prepare the following substances? More than one step may be required.

(a) 

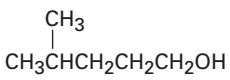
(b) 

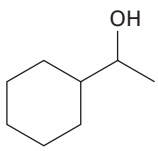
(c) 

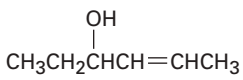
(d) 

9.38 Use a Grignard reaction on an aldehyde or ketone to synthesize the following compounds:
(a) Pentan-2-ol **(b)** 1-Phenylbutan-2-ol
(c) 1-Ethylcyclohexanol **(d)** Diphenylmethanol

9.39 How could you make the following alcohols using a Grignard reaction of an aldehyde or ketone? Show all possibilities.

(a) 

(b) 

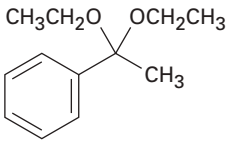
(c) 

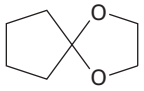
9.40 Which of the alcohols shown in Problem 9.39 could you make by reduction of a carbonyl compound? What carbonyl compound would you use in each case?

9.41 How could you convert bromobenzene into benzoic acid, $C_6H_5CO_2H$? (More than one step is required.)

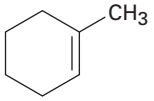
9.42 Show the structures of the alcohols and aldehydes or ketones you would use to make the following acetals:

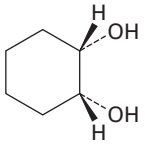
(a) $CH_3CH_2CHCH_2CHOCH_3$ (with CH_3 and OCH_3 substituents)

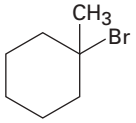
(b) 

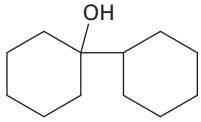
(c) 

9.43 How would you synthesize the following compounds from cyclohexanone?

(a) 

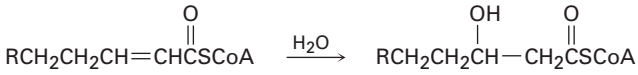
(b) 

(c) 

(d) 

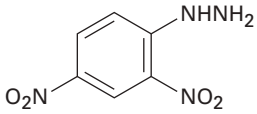
General Problems

9.44 One of the steps in the metabolism of fats is the reaction of an α,β-unsaturated acyl CoA with water to give a β-hydroxyacyl CoA. Propose a mechanism.



Unsaturated acyl CoA **β-Hydroxyacyl CoA**

9.45 Show the products from the reaction of pentan-2-one with the following reagents:

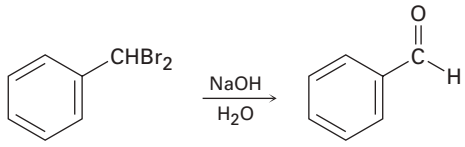
(a) NH_2OH **(b)** 

(c) CH_3CH_2OH, H^+

9.46 Draw the product(s) obtained by conjugate addition of the following reagents to cyclohex-2-enone:

(a) H_2O **(b)** NH_3 **(c)** CH_3OH **(d)** CH_3CH_2SH

9.47 How can you explain the observation that the S_N2 reaction of (dibromomethyl)benzene with NaOH yields benzaldehyde rather than (dihydroxymethyl)benzene?

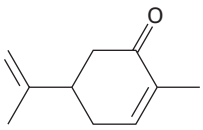


(Dibromomethyl)benzene **Benzaldehyde**

9.48 Carvone is the major constituent of spearmint oil. What products would you expect from the reaction of carvone with the following reagents?

(a) $LiAlH_4$, then H_3O^+ **(b)** C_6H_5MgBr, then H_3O^+

(c) H_2, Pd catalyst **(d)** CH_3OH, H^+

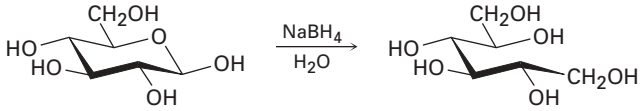


Carvone

9.49 Treatment of an aldehyde or ketone with a thiol (RSH) in the presence of an acid catalyst yields a *thioacetal,* $R'_2C(SR)_2$. To what other reaction is this thioacetal formation analogous? Propose a mechanism for the reaction.

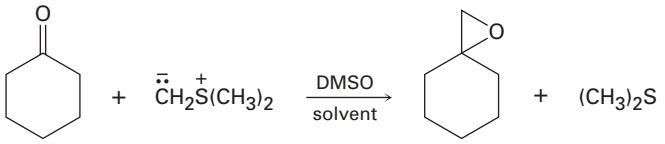
9.50 Treatment of an aldehyde or ketone with hydrazine, H_2NNH_2, yields an *azine,* $R_2C{=}N{-}N{=}CR_2$. Propose a mechanism.

9.51 When glucose is treated with $NaBH_4$, reaction occurs to yield *sorbitol,* a commonly used food additive. Show how this reduction occurs.



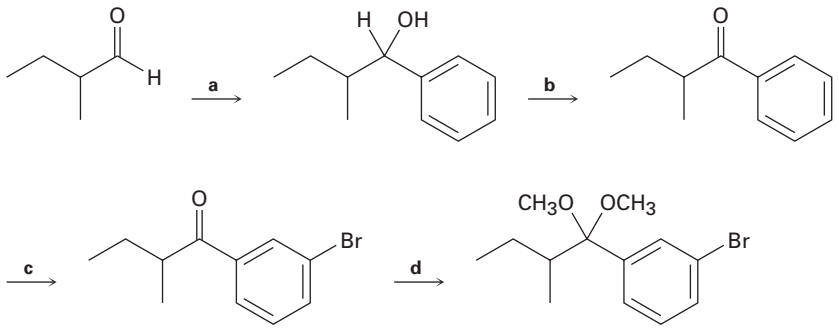
Glucose **Sorbitol**

9.52 Ketones react with dimethylsulfonium methylide to yield epoxides by a mechanism that involves (1) an initial nucleophilic addition followed by (2) an intramolecular S_N2 substitution. Show the mechanism.

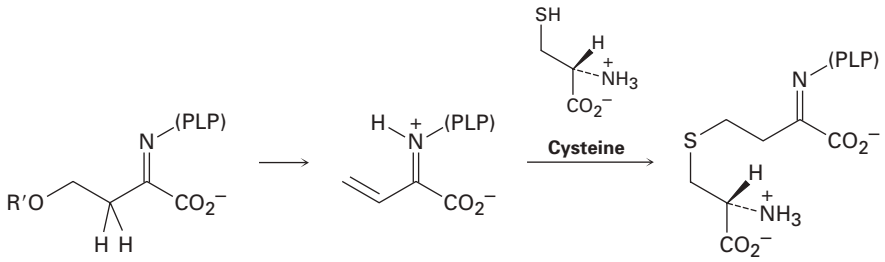


Dimethylsulfonium methylide

9.53 Identify the reagents **a** through **d** in the following scheme:

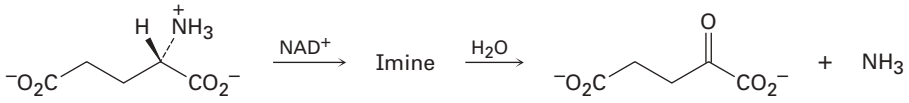


9.54 The amino acid methionine is biosynthesized by a multistep route that includes (1) reaction of a pyridoxal phosphate (PLP) imine to give an unsaturated imine followed by (2) reaction with the amino acid cysteine. What kinds of reactions are occurring in the two steps?



***O*-Succinylhomoserine–PLP imine** **Unsaturated imine**

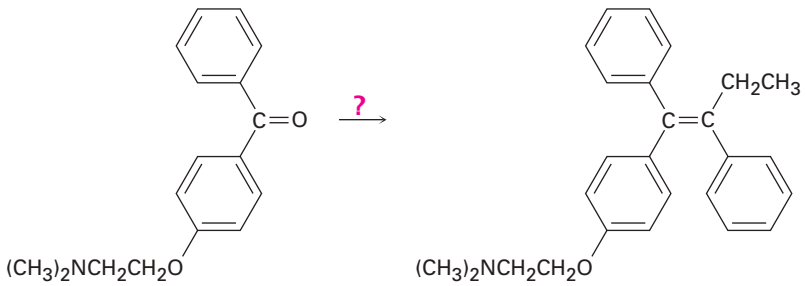
9.55 One of the biological pathways by which an amine is converted to a ketone involves two steps: (1) enzymatic oxidation of the amine to give an imine and (2) hydrolysis of the imine to give a ketone plus ammonia. Glutamate, for instance, is converted by this process into α-ketoglutarate. Show the structure of the imine intermediate, and propose a mechanism for the hydrolysis step (the exact reverse of imine formation).



Glutamate **α-Ketoglutarate**

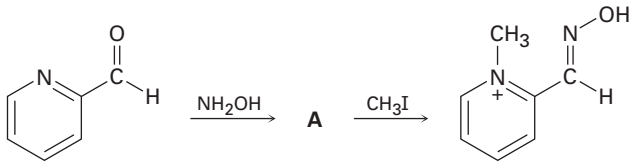
IN THE MEDICINE CABINET

9.56 Tamoxifen is a drug used in the treatment of breast cancer. How could you prepare tamoxifen from benzene, the following ketone, and any other reagents needed?



Tamoxifen

9.57 Pralidoxime iodide is a general antidote for poisoning by many insecticides. The drug is made in two steps starting with pyridine-2-carbaldehyde.



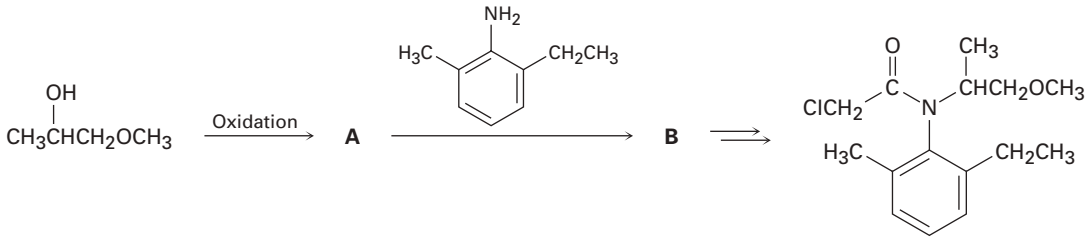
Pyridine-2-carbaldehyde **Pralidoxime iodide**

(a) Show the mechanism of the reaction of hydroxylamine (NH_2OH) with pyridine-2-carbaldehyde, and give the structure of **A**.

(b) Reaction of **A** with iodomethane to give pralidoxime iodide is an S_N2 reaction. Show the mechanism.

IN THE FIELD

9.58 Synthesis of the herbicide metolachlor, seen previously in Problems 2.74, 5.61, and 6.66, begins with an oxidation followed by an imine formation:



Metolachlor

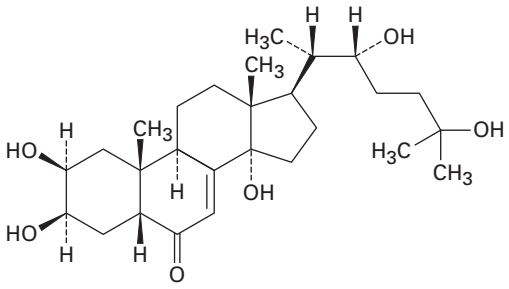
(a) The starting ether can be obtained by reacting an epoxide with sodium methoxide, $Na^{+-}OCH_3$. Propose a structure for the epoxide (commonly called propylene oxide).

(b) What is the structure of intermediate **A**?

(c) What oxidizing agent would you use to form **A**?

(d) What is the structure of imine **B**?

9.59 Many insecticides function by blocking cellular receptors for the insect molting hormone ecdysone.



Ecdysone

(a) Categorize each of the hydroxyl groups in ecdysone as primary, secondary, or tertiary.
(b) How many chirality centers does ecdysone have?
(c) Reduction of ecdysone with $NaBH_4$ occurs by both 1,2- and 1,4-addition of hydride ion. Neglecting stereochemistry, show the product formed by each pathway.
(d) Both 1,2- and 1,4-addition reduction pathways described in part **(c)** produce two stereoisomers, depending on which side of the molecule the hydride addition occurs from. What term describes the relationship between the two 1,2-addition products? Between the two 1,4-addition products? Between a 1,2- and a 1,4-addition product?