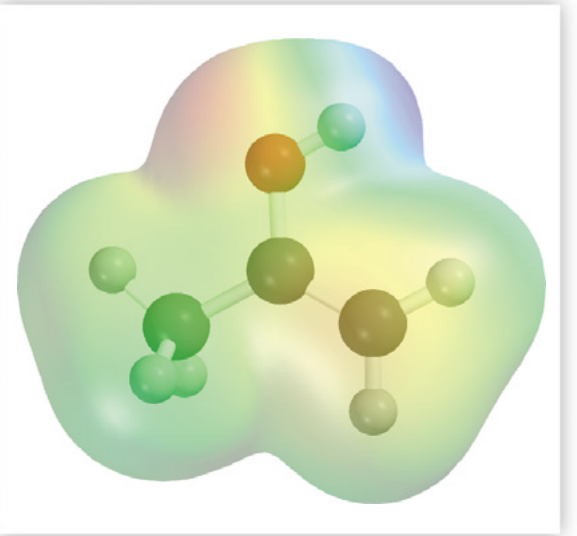
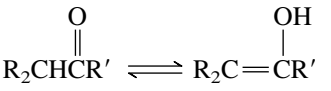


CHAPTER 18

ENOLS AND ENOLATES

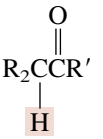
In the preceding chapter you learned that nucleophilic addition to the carbonyl group is one of the fundamental reaction types of organic chemistry. In addition to its own reactivity, a carbonyl group can affect the chemical properties of aldehydes and ketones in other ways. Aldehydes and ketones are in equilibrium with their **enol** isomers.



Aldehyde or ketone — Enol

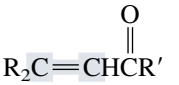
In this chapter you'll see a number of processes in which the enol, rather than the aldehyde or a ketone, is the reactive species.

There is also an important group of reactions in which the carbonyl group acts as a powerful electron-withdrawing substituent, increasing the acidity of protons on the adjacent carbons.



This proton is far more acidic than a hydrogen in an alkane.

As an electron-withdrawing group on a carbon–carbon double bond, a carbonyl group renders the double bond susceptible to nucleophilic attack:

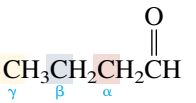


Normally, carbon–carbon double bonds are attacked by electrophiles; a carbon–carbon double bond that is conjugated to a carbonyl group is attacked by nucleophiles.

The presence of a carbonyl group in a molecule makes possible a number of chemical reactions that are of great synthetic and mechanistic importance. This chapter is complementary to the preceding one; the two chapters taken together demonstrate the extraordinary range of chemical reactions available to aldehydes and ketones.

18.1 THE α-CARBON ATOM AND ITS HYDROGENS

It is convenient to use the Greek letters α, β, γ, and so forth, to locate the carbons in a molecule in relation to the carbonyl group. The carbon atom adjacent to the carbonyl is the α-carbon atom, the next one down the chain is the β carbon, and so on. Butanal, for example, has an α carbon, a β carbon, and a γ carbon.



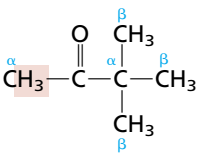
Carbonyl group is reference point; no Greek letter assigned to it.

Hydrogens take the same Greek letter as the carbon atom to which they are attached. A hydrogen connected to the α-carbon atom is an α hydrogen. Butanal has two α protons, two β protons, and three γ protons. No Greek letter is assigned to the hydrogen attached directly to the carbonyl group of an aldehyde.

PROBLEM 18.1 How many α hydrogens are there in each of the following?

(a) 3,3-Dimethyl-2-butanone
(b) 2,2-Dimethylpropanal
(c) Benzyl methyl ketone
(d) Cyclohexanone

SAMPLE SOLUTION (a) This ketone has two different α carbons, but only one of them has hydrogen substituents. There are three equivalent α hydrogens. The other nine hydrogens are attached to β-carbon atoms.

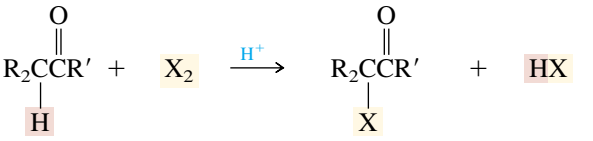


3,3-Dimethyl-2-butanone

Other than nucleophilic addition to the carbonyl group, the most important reactions of aldehydes and ketones involve substitution of an α hydrogen. A particularly well studied example is halogenation of aldehydes and ketones.

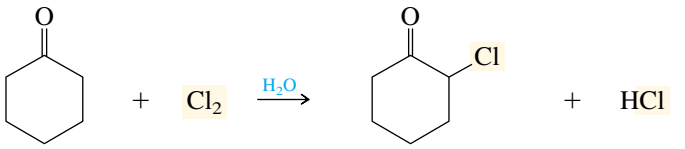
18.2 α HALOGENATION OF ALDEHYDES AND KETONES

Aldehydes and ketones react with halogens by *substitution* of one of the α hydrogens:



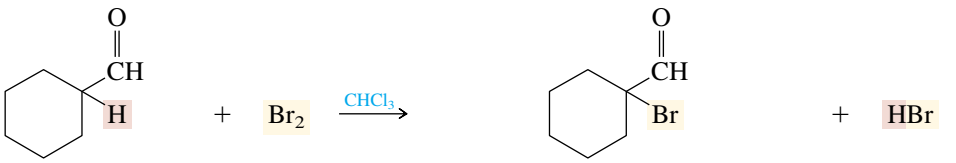
Aldehyde or ketone — Halogen — α-Halo aldehyde or ketone — Hydrogen halide

The reaction is *regiospecific* for substitution of an α hydrogen. None of the hydrogens farther removed from the carbonyl group are affected.



Cyclohexanone — Chlorine — 2-Chlorocyclohexanone (61–66%) — Hydrogen chloride

Nor is the hydrogen directly attached to the carbonyl group in aldehydes affected. Only the α hydrogen is replaced.



Cyclohexanecarbaldehyde — Bromine — 1-Bromocyclohexanecarbaldehyde (80%) — Hydrogen bromide

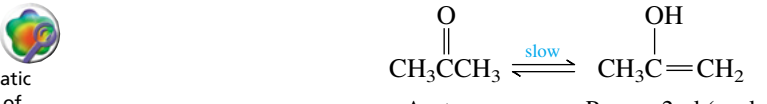
PROBLEM 18.2 Chlorination of 2-butanone yields two isomeric products, each having the molecular formula C_4H_7ClO. Identify these two compounds.

α Halogenation of aldehydes and ketones can be carried out in a variety of solvents (water and chloroform are shown in the examples, but acetic acid and diethyl ether are also often used). The reaction is catalyzed by acids. Since one of the reaction products, the hydrogen halide, is an acid and therefore a catalyst for the reaction, the process is said to be **autocatalytic.** Free radicals are *not* involved, and the reactions occur at room temperature in the absence of initiators. Mechanistically, acid-catalyzed halogenation of aldehydes and ketones is much different from free-radical halogenation of alkanes. Although both processes lead to the replacement of a hydrogen by a halogen, they do so by completely different pathways.

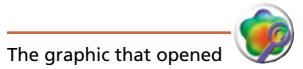
18.3 MECHANISM OF α HALOGENATION OF ALDEHYDES AND KETONES

In one of the earliest mechanistic investigations in organic chemistry, Arthur Lapworth discovered in 1904 that the rates of chlorination and bromination of acetone were the same. Later he found that iodination of acetone proceeded at the same rate as chlorination

and bromination. Moreover, the rates of all three halogenation reactions, although first-order in acetone, are independent of the halogen concentration. *Thus, the halogen does not participate in the reaction until after the rate-determining step.* These kinetic observations, coupled with the fact that substitution occurs exclusively at the α-carbon atom, led Lapworth to propose that the rate-determining step is the conversion of acetone to a more reactive form, its enol isomer:

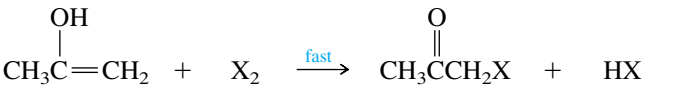


Acetone — Propen-2-ol (enol form of acetone)



The graphic that opened this chapter is an electrostatic potential map of the enol of acetone.

Once formed, this enol reacts rapidly with the halogen to form an α-halo ketone:

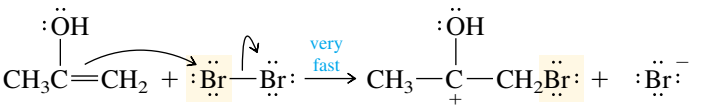


Propen-2-ol (enol form of acetone) — Halogen — α-Halo derivative of acetone — Hydrogen halide

PROBLEM 18.3 Write the structures of the enol forms of 2-butanone that react with chlorine to give 1-chloro-2-butanone and 3-chloro-2-butanone.

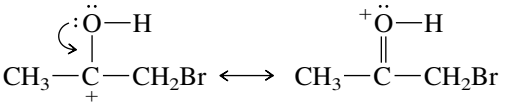
Lapworth was far ahead of his time in understanding how organic reactions occur. For an account of Lapworth's contributions to mechanistic organic chemistry, see the November 1972 issue of the *Journal of Chemical Education,* pp. 750–752.

Both parts of the Lapworth mechanism, enol formation and enol halogenation, are new to us. Let's examine them in reverse order. We can understand enol halogenation by analogy to halogen addition to alkenes. An enol is a very reactive kind of alkene. Its carbon–carbon double bond bears an electron-releasing hydroxyl group, which activates it toward attack by electrophiles.



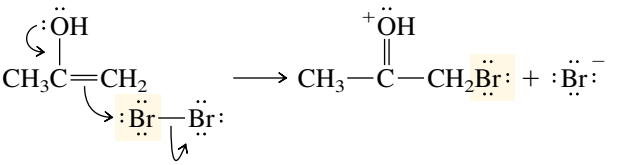
Propen-2-ol (enol form of acetone) — Bromine — Stabilized carbocation — Bromide ion

The hydroxyl group stabilizes the carbocation by delocalization of one of the unshared electron pairs of oxygen:



Less stable resonance form; 6 electrons on positively charged carbon. — More stable resonance form; all atoms (except hydrogen) have octets of electrons.

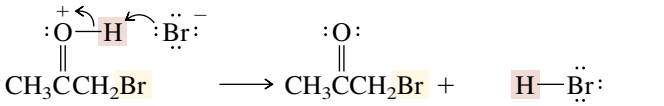
Participation by the oxygen lone pairs is responsible for the rapid attack on the carbon–carbon double bond of an enol by bromine. We can represent this participation explicitly:



Writing the bromine addition step in this way emphasizes the increased nucleophilicity of the enol double bond and identifies the source of that increased nucleophilicity as the enolic oxygen.

PROBLEM 18.4 Represent the reaction of chlorine with each of the enol forms of 2-butanone (see Problem 18.3) according to the curved arrow formalism just described.

The cationic intermediate is simply the protonated form (conjugate acid) of the α-halo ketone. Deprotonation of the cationic intermediate gives the products.



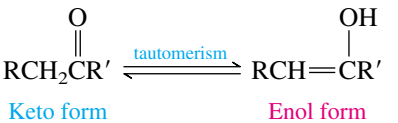
Cationic intermediate Bromoacetone Hydrogen bromide

Having now seen how an enol, once formed, reacts with a halogen, let us consider the process of enolization itself.

18.4 ENOLIZATION AND ENOL CONTENT

Enols are related to an aldehyde or a ketone by a proton-transfer equilibrium known as **keto–enol tautomerism.** (*Tautomerism* refers to an interconversion between two structures that differ by the placement of an atom or a group.)

The keto and enol forms are constitutional isomers. Using older terminology they are referred to as *tautomers* of each other.



Keto form Enol form

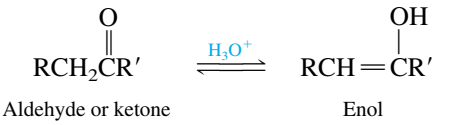
The mechanism of enolization involves two separate proton-transfer steps rather than a one-step process in which a proton jumps from carbon to oxygen. It is relatively slow in neutral media. The rate of enolization is catalyzed by acids as shown by the mechanism in Figure 18.1. In aqueous acid, a hydronium ion transfers a proton to the carbonyl oxygen in step 1, and a water molecule acts as a Brønsted base to remove a proton from the α-carbon atom in step 2. The second step is slower than the first. The first step involves proton transfer between oxygens, and the second is a proton transfer from carbon to oxygen.

You have had earlier experience with enols in their role as intermediates in the hydration of alkynes (Section 9.12). The mechanism of enolization of aldehydes and ketones is precisely the reverse of the mechanism by which an enol is converted to a carbonyl compound.

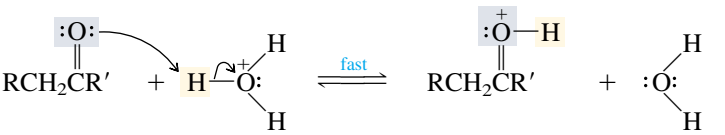
The amount of enol present at equilibrium, the *enol content,* is quite small for simple aldehydes and ketones. The equilibrium constants for enolization, as shown by the following examples, are much less than 1.

FIGURE 18.1 Mechanism of acid-catalyzed enolization of an aldehyde or ketone in aqueous solution.

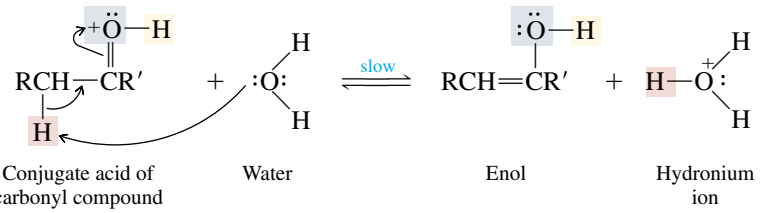
Overall reaction:

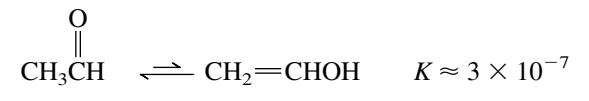


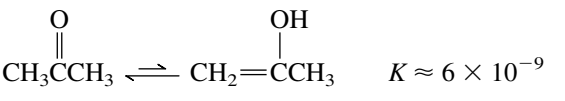
Step 1: A proton is transferred from the acid catalyst to the carbonyl oxygen.



Step 2: A water molecule acts as a Brønsted base to remove a proton from the α carbon atom of the protonated aldehyde or ketone.

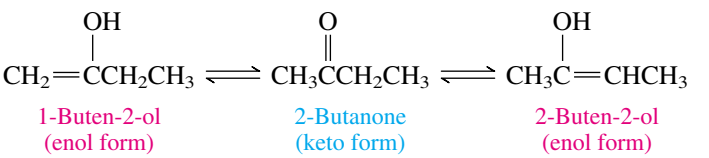






In these and numerous other simple cases, the keto form is more stable than the enol by some 45–60 kJ/mol (11–14 kcal/mol). The chief reason for this difference is that a carbon–oxygen double bond is stronger than a carbon–carbon double bond.

With unsymmetrical ketones, enolization may occur in either of two directions:



The ketone is by far the most abundant species present at equilibrium. Both enols are also present, but in very small concentrations.

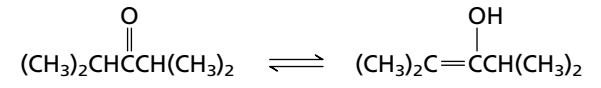
PROBLEM 18.5 Write structural formulas corresponding to

(a) The enol form of 2,4-dimethyl-3-pentanone

(b) The enol form of acetophenone

(c) The two enol forms of 2-methylcyclohexanone

SAMPLE SOLUTION (a) Remember that enolization involves the α-carbon atom. The ketone 2,4-dimethyl-3-pentanone gives a single enol, since the two α carbons are equivalent.

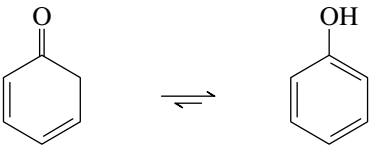


2,4-Dimethyl-3-pentanone (keto form) ⇌ 2,4-Dimethyl-2-penten-3-ol (enol form)

It is important to recognize that an enol is a real substance, capable of independent existence. An enol is *not* a resonance form of a carbonyl compound; the two are constitutional isomers of each other.

18.5 STABILIZED ENOLS

Certain structural features can make the keto–enol equilibrium more favorable by stabilizing the enol form. Enolization of 2,4-cyclohexadienone is one such example:

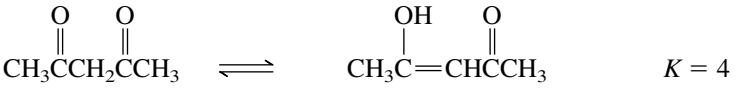


2,4-Cyclohexadienone (keto form, not aromatic) ⇌ Phenol (enol form, aromatic)

K is too large to measure.

The enol is *phenol,* and the stabilization gained by forming an aromatic ring is more than enough to overcome the normal preference for the keto form.

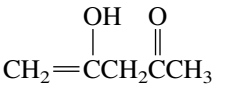
A 1,3 arrangement of two carbonyl groups (compounds called **β-diketones**) leads to a situation in which the keto and enol forms are of comparable stability.



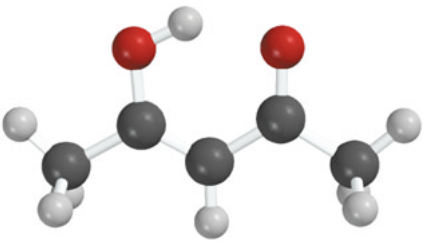
2,4-Pentanedione (20%) (keto form) ⇌ 4-Hydroxy-3-penten-2-one (80%) (enol form) $K = 4$

The two most important structural features that stabilize the enol of a β-dicarbonyl compound are (1) conjugation of its double bond with the remaining carbonyl group and (2) the presence of a strong intramolecular hydrogen bond between the enolic hydroxyl group and the carbonyl oxygen (Figure 18.2).

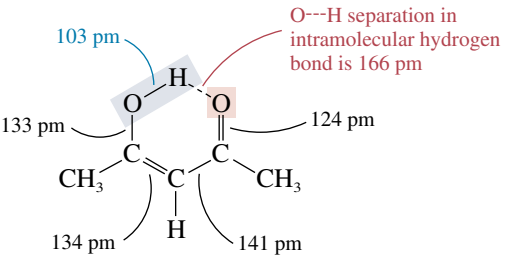
In β-diketones it is the methylene group flanked by the two carbonyls that is involved in enolization. The alternative enol



4-Hydroxy-4-penten-2-one



(*a*)



(*b*)

FIGURE 18.2 (*a*) A molecular model and (*b*) bond distances in the enol form of 2,4-pentanedione.

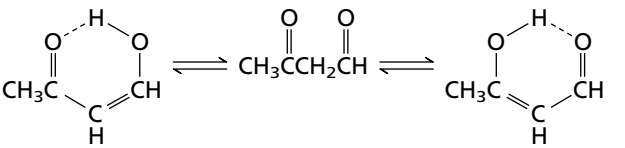
does not have its carbon–carbon double bond conjugated with the carbonyl group, is not as stable, and is present in negligible amounts at equilibrium.

PROBLEM 18.6 Write structural formulas corresponding to

(a) The two most stable enol forms of CH_3CCH_2CH (O, O)

(b) The two most stable enol forms of 1-phenyl-1,3-butanedione

SAMPLE SOLUTION (a) Enolization of this 1,3-dicarbonyl compound can involve either of the two carbonyl groups:

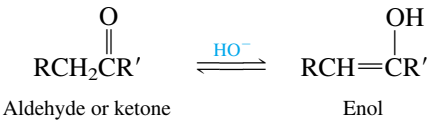


Both enols have their carbon–carbon double bonds conjugated to a carbonyl group and can form an intramolecular hydrogen bond. They are of comparable stability.

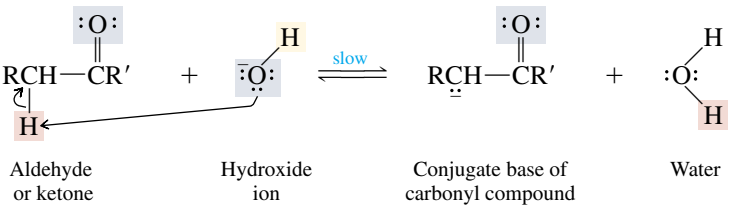
18.6 BASE-CATALYZED ENOLIZATION: ENOLATE ANIONS

The proton-transfer equilibrium that interconverts a carbonyl compound and its enol can be catalyzed by bases as well as by acids. Figure 18.3 illustrates the roles of hydroxide ion and water in a base-catalyzed enolization. As in acid-catalyzed enolization, protons are transferred sequentially rather than in a single step. First (step 1), the base abstracts

Overall reaction:



Step 1: A proton is abstracted by hydroxide ion from the α carbon atom of the carbonyl compound.



Step 2: A water molecule acts as a Brønsted acid to transfer a proton to the oxygen of the enolate ion.

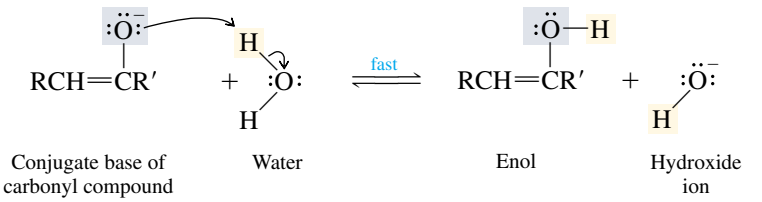
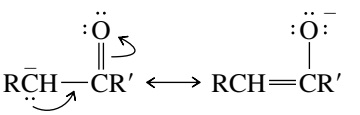


FIGURE 18.3 Mechanism of the base-catalyzed enolization of an aldehyde or ketone in aqueous solution.

a proton from the α-carbon atom to yield an anion. This anion is a resonance-stabilized species. Its negative charge is shared by the α-carbon atom and the carbonyl oxygen.



Electron delocalization in conjugate base of ketone

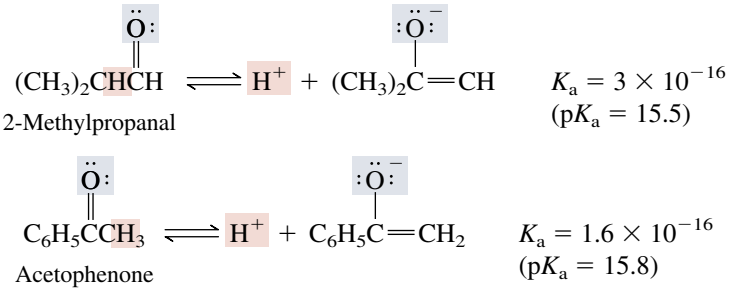
Protonation of this anion can occur either at the α carbon or at oxygen. Protonation of the α carbon simply returns the anion to the starting aldehyde or ketone. Protonation of oxygen, as shown in step 2 of Figure 18.3, produces the enol.

The key intermediate in this process, the conjugate base of the carbonyl compound, is referred to as an **enolate ion,** since it is the conjugate base of an enol. The term "enolate" is more descriptive of the electron distribution in this intermediate in that oxygen bears a greater share of the negative charge than does the α-carbon atom.

The slow step in base-catalyzed enolization is formation of the enolate ion. The second step, proton transfer from water to the enolate oxygen, is very fast, as are almost all proton transfers from one oxygen atom to another.

Examine the enolate of acetone on *Learning By Modeling.* How is the negative charge distributed between oxygen and the α carbon?

Our experience to this point has been that C—H bonds are not very acidic. Compared with most hydrocarbons, however, aldehydes and ketones have relatively acidic protons on their α-carbon atoms. Equilibrium constants for enolate formation from simple aldehydes and ketones are in the 10^{-16} to 10^{-20} range (pK_a = 16–20).

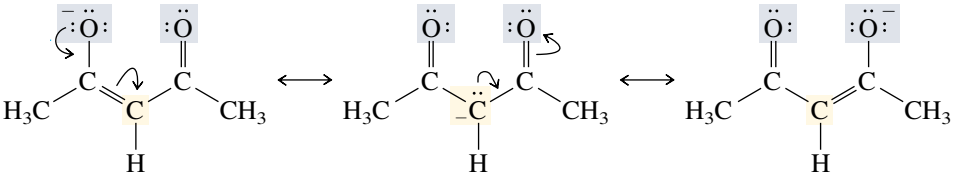


Delocalization of the negative charge onto the electronegative oxygen is responsible for the enhanced acidity of aldehydes and ketones. With K_a's in the 10^{-16} to 10^{-20} range, aldehydes and ketones are about as acidic as water and alcohols. Thus, hydroxide ion and alkoxide ions are sufficiently strong bases to produce solutions containing significant concentrations of enolate ions at equilibrium.

β-Diketones, such as 2,4-pentanedione, are even more acidic:

Learning By Modeling contains molecular models of the enolates of acetone and 2,4-pentanedione. Compare the two with respect to the distribution of negative charge.

In the presence of bases such as hydroxide, methoxide, and ethoxide, these β-diketones are converted completely to their enolate ions. Notice that it is the methylene group flanked by the two carbonyl groups that is deprotonated. Both carbonyl groups participate in stabilizing the enolate by delocalizing its negative charge.

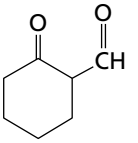


PROBLEM 18.7 Write the structure of the enolate ion derived from each of the following β-dicarbonyl compounds. Give the three most stable resonance forms of each enolate.

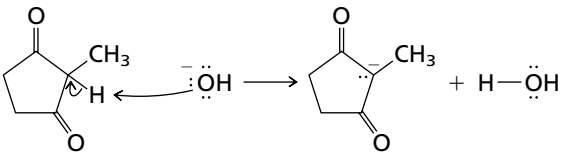
(a) 2-Methyl-1,3-cyclopentanedione

(b) 1-Phenyl-1,3-butanedione

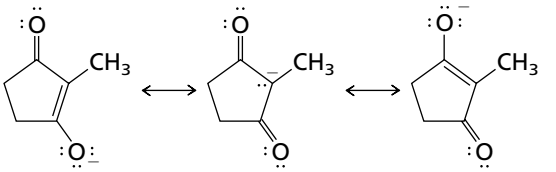
(c)



SAMPLE SOLUTION (a) First identify the proton that is removed by the base. It is on the carbon between the two carbonyl groups.



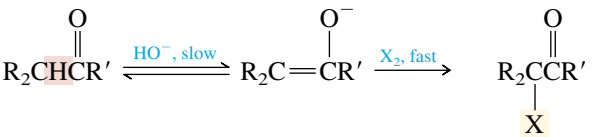
The three most stable resonance forms of this anion are



Enolate ions of β-dicarbonyl compounds are useful intermediates in organic synthesis. We shall see some examples of how they are employed in this way later in the chapter.

18.7 THE HALOFORM REACTION

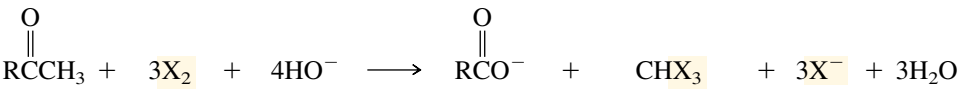
Rapid halogenation of the α-carbon atom takes place when an enolate ion is generated in the presence of chlorine, bromine, or iodine.



Aldehyde or ketone — Enolate — α-Halo aldehyde or ketone

As in the acid-catalyzed halogenation of aldehydes and ketones, the reaction rate is independent of the concentration of the halogen; chlorination, bromination, and iodination all occur at the same rate. Formation of the enolate is rate-determining, and, once formed, the enolate ion reacts rapidly with the halogen.

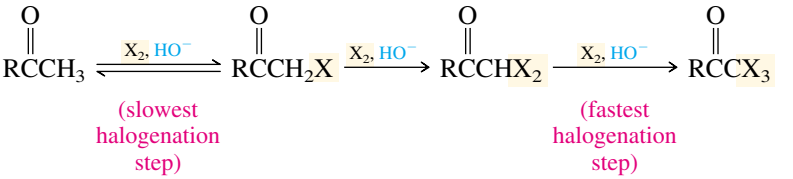
Unlike its acid-catalyzed counterpart, α halogenation in base cannot normally be limited to monohalogenation. Methyl ketones, for example, undergo a novel polyhalogenation and cleavage on treatment with a halogen in aqueous base.



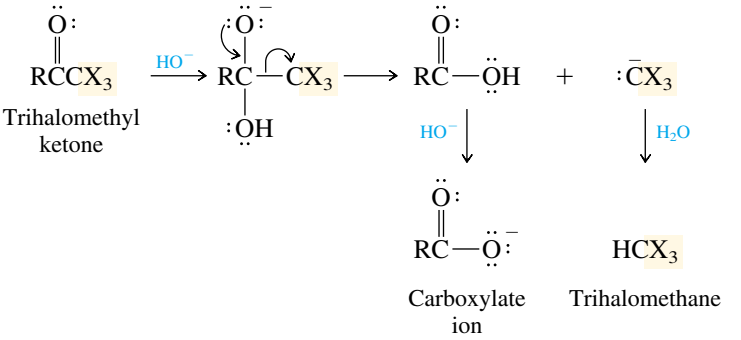
Methyl ketone — Halogen — Hydroxide ion — Carboxylate ion — Trihalomethane — Halide ion — Water

This is called the *haloform reaction* because the trihalomethane produced is chloroform, bromoform, or iodoform, depending, of course, on the halogen used.

The mechanism of the haloform reaction begins with α halogenation via the enolate. The electron-attracting effect of an α halogen increases the acidity of the protons on the carbon to which it is bonded, making each subsequent halogenation *at that carbon* faster than the preceding one.

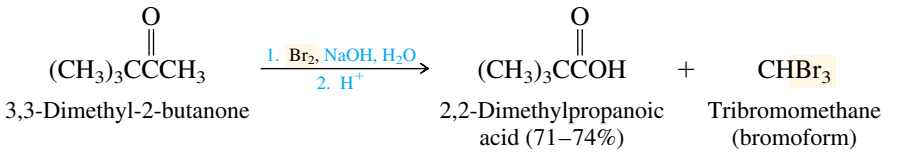


The trihalomethyl ketone ($RCCX_3$) so formed then undergoes nucleophilic addition of hydroxide ion to its carbonyl group, triggering its dissociation.



The three electron-withdrawing halogen substituents stabilize the negative charge of the trihalomethide ion ($^{-}$:CX_3), permitting it to act as a leaving group in the carbon–carbon bond cleavage step.

The haloform reaction is sometimes used for the preparation of carboxylic acids from methyl ketones.



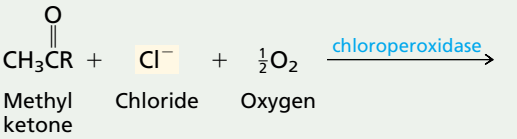
The methyl ketone shown in the example can enolize in only one direction and typifies the kind of reactant that can be converted to a carboxylic acid in synthetically acceptable yield by the haloform reaction. When C-3 of a methyl ketone bears enolizable hydrogens, as in $CH_3CH_2CCH_3$, the first halogenation step is not very regioselective and the isolated yield of $CH_3CH_2CO_2H$ is only about 50%.

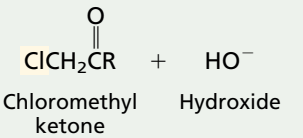
The haloform reaction, using iodine, was once used as an analytical test in which the formation of a yellow precipitate of iodoform was taken as evidence that a substance was a methyl ketone. This application has been superseded by spectroscopic methods of structure determination. Interest in the haloform reaction has returned with the realization that chloroform and bromoform occur naturally and are biosynthesized by an analogous process. (See the boxed essay "The Haloform Reaction and the Biosynthesis of Trihalomethanes.")

THE HALOFORM REACTION AND THE BIOSYNTHESIS OF TRIHALOMETHANES

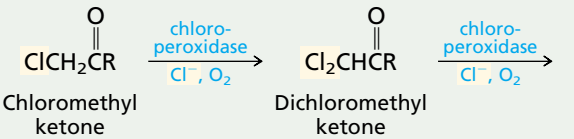
Until scientists started looking specifically for them, it was widely believed that naturally occurring organohalogen compounds were rare. We now know that more than 2000 such compounds occur naturally, with the oceans being a particularly rich source.* Over 50 organohalogen compounds, including $CHBr_3$, $CHBrClI$, $BrCH_2CH_2I$, CH_2I_2, $Br_2CHCH{=}O$, I_2CHCO_2H, and $(Cl_3C)_2C{=}O$, have been found in a single species of Hawaiian red seaweed, for example. It is not surprising that organisms living in the oceans have adapted to their halide-rich environment by incorporating chlorine, bromine, and iodine into their metabolic processes. Chloromethane (CH_3Cl), bromomethane (CH_3Br), and iodomethane (CH_3I) are all produced by marine algae and kelp, but land-based plants and fungi also contribute their share to the more than 5 million tons of the methyl halides formed each year by living systems. The ice plant, which grows in arid regions throughout the world and is cultivated as a ground cover along coastal highways in California, biosynthesizes CH_3Cl by a process in which nucleophilic attack by chloride ion (Cl^-) on the methyl group of *S*-adenosylmethionine is the key step (Section 16.17).

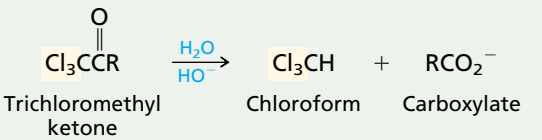
Interestingly, the trihalomethanes chloroform ($CHCl_3$), bromoform ($CHBr_3$), and iodoform (CHI_3) are biosynthesized by an entirely different process, one that is equivalent to the haloform reaction (Section 18.7) and begins with the formation of an α-halo ketone. Unlike the biosynthesis of methyl halides, which requires attack by a halide nucleophile (X^-), α halogenation of a ketone requires attack by an electrophilic form of the halogen. For chlorination, the electrophilic form of the halogen is generated by oxidation of Cl^- in the presence of the enzyme *chloroperoxidase.* Thus, the overall equation for the enzyme-catalyzed chlorination of a methyl ketone may be written as





Further chlorination of the chloromethyl ketone gives the corresponding trichloromethyl ketone, which then undergoes hydrolysis to form chloroform.





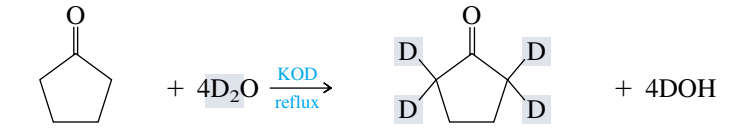
Purification of drinking water, by adding Cl_2 to kill bacteria, is a source of electrophilic chlorine and contributes a nonenzymatic pathway for α chlorination and subsequent chloroform formation. Although some of the odor associated with tap water may be due to chloroform, more of it probably results from chlorination of algae-produced organic compounds.

*The November 1994 edition of the *Journal of Chemical Education* contains as its cover story the article "Natural Organohalogens. Many More Than You Think!"

18.8 SOME CHEMICAL AND STEREOCHEMICAL CONSEQUENCES OF ENOLIZATION

A number of novel reactions involving the α-carbon atom of aldehydes and ketones involve enol and enolate anion intermediates.

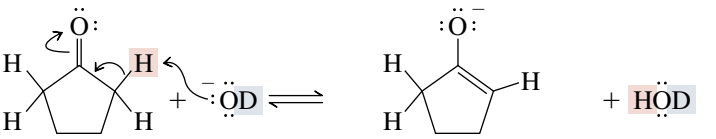
Substitution of deuterium for hydrogen at the α-carbon atom of an aldehyde or a ketone is a convenient way to introduce an isotopic label into a molecule and is readily carried out by treating the carbonyl compound with deuterium oxide (D_2O) and base.



Cyclopentanone Cyclopentanone-2,2,5,5-d_4

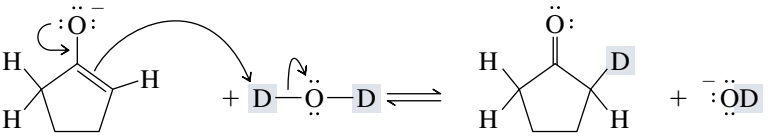
Only the α hydrogens are replaced by deuterium in this reaction. The key intermediate is the enolate ion formed by proton abstraction from the α-carbon atom of cyclopentanone. Transfer of deuterium from the solvent D_2O to the enolate gives cyclopentanone containing a deuterium atom in place of one of the hydrogens at the α carbon.

Formation of the enolate



Cyclopentanone Enolate of cyclopentanone

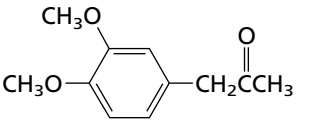
Deuterium transfer to the enolate



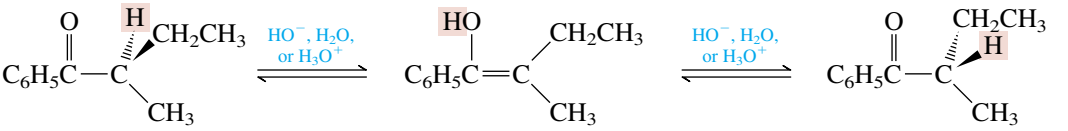
Enolate of cyclopentanone Cyclopentanone-2-d_1

In excess D_2O the process continues until all four α protons are eventually replaced by deuterium.

PROBLEM 18.8 After the compound shown was heated in D_2O containing K_2CO_3 at 70°C the only signals that could be found in its ^1H NMR spectrum were at δ 3.9 ppm (6H) and δ 6.7–6.9 ppm (3H). What happened?



If the α-carbon atom of an aldehyde or a ketone is a stereogenic center, its stereochemical integrity is lost on enolization. Enolization of optically active *sec*-butyl phenyl ketone leads to its racemization by way of the achiral enol form.



(*R*)-*sec*-Butyl phenyl ketone Enol form [achiral; may be converted to either (*R*)- or (*S*)-*sec*-butyl phenyl ketone] (*S*)-*sec*-Butyl phenyl ketone

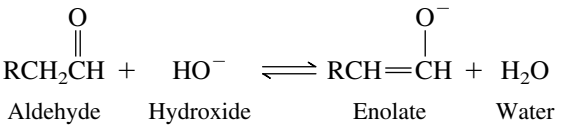
Each act of proton abstraction from the α-carbon atom converts a chiral molecule to an achiral enol or enolate anion. Careful kinetic studies have established that the rate of loss

of optical activity of *sec*-butyl phenyl ketone is equal to its rate of hydrogen–deuterium exchange, its rate of bromination, and its rate of iodination. In each case, the rate-determining step is conversion of the starting ketone to the enol or enolate anion.

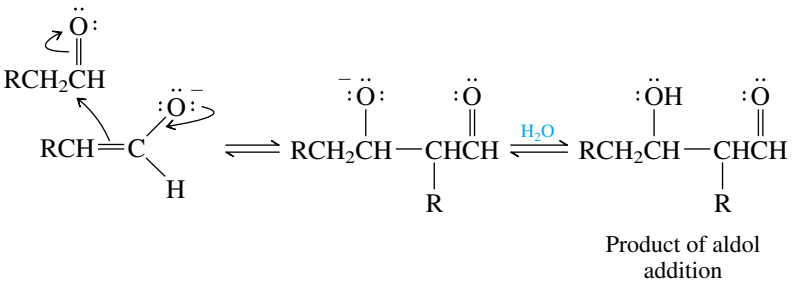
PROBLEM 18.9 Is the product from the α chlorination of (*R*)-*sec*-butyl phenyl ketone with Cl_2 in acetic acid chiral? Is it optically active?

18.9 THE ALDOL CONDENSATION

As noted earlier, an aldehyde is partially converted to its enolate anion by bases such as hydroxide ion and alkoxide ions.



In a solution that contains both an aldehyde and its enolate ion, the enolate undergoes nucleophilic addition to the carbonyl group. This addition is analogous to the addition reactions of other nucleophilic reagents to aldehydes and ketones described in Chapter 17.



The alkoxide formed in the nucleophilic addition step then abstracts a proton from the solvent (usually water or ethanol) to yield the product of **aldol addition.** This product is known as an *aldol* because it contains both an aldehyde function and a hydroxyl group *(ald + ol = aldol).*

An important feature of aldol addition is that carbon–carbon bond formation occurs between the α-carbon atom of one aldehyde and the carbonyl group of another. This is because carbanion (enolate) generation can involve proton abstraction *only* from the α-carbon atom. The overall transformation can be represented schematically, as shown in Figure 18.4.

Some of the earliest studies of the aldol reaction were carried out by Aleksander Borodin. Though a physician by training and a chemist by profession, Borodin is remembered as the composer of some of the most familiar works in Russian music. See pp. 326–327 in the April 1987 issue of the *Journal of Chemical Education* for a biographical sketch of Borodin.

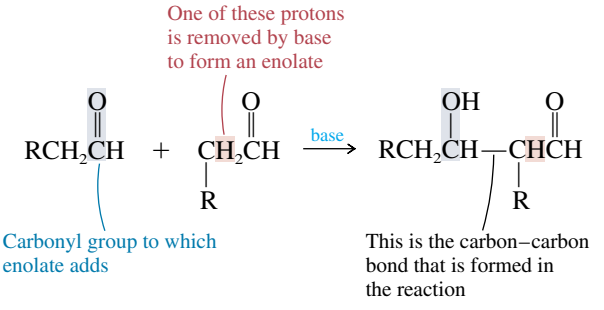
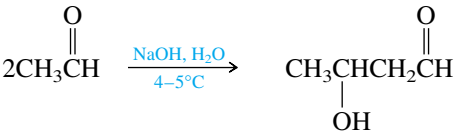
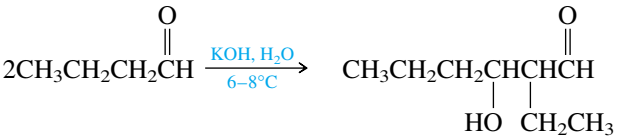


FIGURE 18.4 The reactive sites in aldol addition are the carbonyl group of one aldehyde molecule and the α-carbon atom of another.

Aldol addition occurs readily with aldehydes:



Acetaldehyde — 3-Hydroxybutanal (50%) (acetaldol)



Butanal — 2-Ethyl-3-hydroxyhexanal (75%)

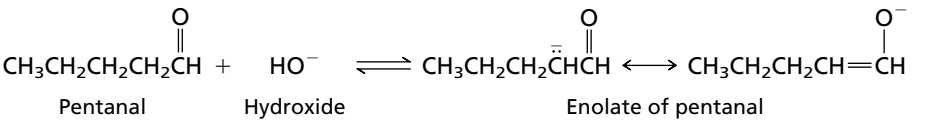
PROBLEM 18.10 Write the structure of the aldol addition product of

(a) Pentanal, $CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H$

(c) 3-Methylbutanal, $(CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}H$

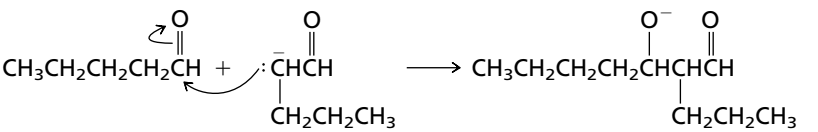
(b) 2-Methylbutanal, $CH_3CH_2\underset{CH_3}{\overset{O}{\overset{\|}{C}}}HCH$

SAMPLE SOLUTION (a) A good way to correctly identify the aldol addition product of any aldehyde is to work through the process mechanistically. Remember that the first step is enolate formation and that this *must* involve proton abstraction from the α carbon.

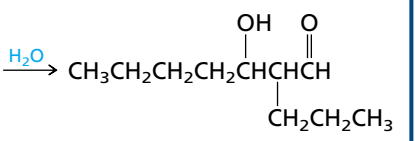


Pentanal — Hydroxide — Enolate of pentanal

Now use the negatively charged α carbon of the enolate to form a new carbon–carbon bond to the carbonyl group. Proton transfer from the solvent completes the process.

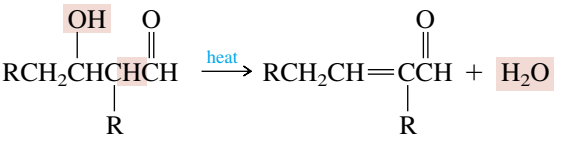


Pentanal — Enolate of pentanal



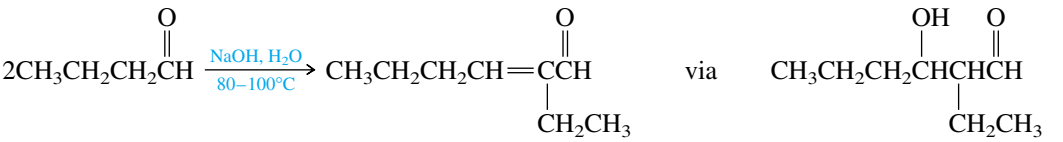
3-Hydroxy-2-propylheptanal (aldol addition product of pentanal)

The β-hydroxy aldehyde products of aldol addition undergo dehydration on heating, to yield *α,β-unsaturated aldehydes:*



β-Hydroxy aldehyde | α,β-Unsaturated aldehyde | Water

Conjugation of the newly formed double bond with the carbonyl group stabilizes the α,β-unsaturated aldehyde, provides the driving force for the dehydration, and controls its regioselectivity. Dehydration can be effected by heating the aldol with acid or base. Normally, if the α,β-unsaturated aldehyde is the desired product, all that is done is to carry out the base-catalyzed aldol addition reaction at elevated temperature. Under these conditions, once the aldol addition product is formed, it rapidly loses water to form the α,β-unsaturated aldehyde.



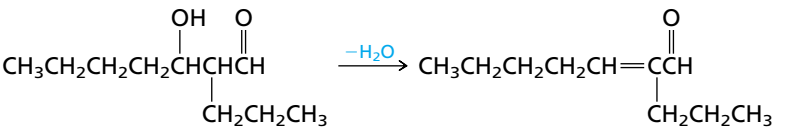
Butanal | 2-Ethyl-2-hexenal (86%) | 2-Ethyl-3-hydroxyhexanal (not isolated; dehydrates under reaction conditions)

Reactions in which two molecules of an aldehyde combine to form an α,β-unsaturated aldehyde and a molecule of water are called **aldol condensations.**

Recall from Section 15.7 that a condensation is a reaction in which two molecules combine to give a product along with some small (usually inorganic) molecule such as water.

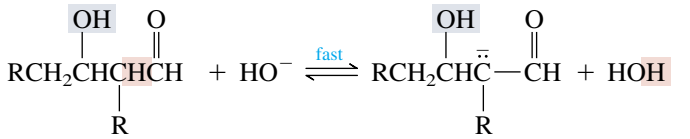
PROBLEM 18.11 Write the structure of the aldol condensation product of each of the aldehydes in Problem 18.10. One of these aldehydes can undergo aldol addition, but not aldol condensation. Which one? Why?

SAMPLE SOLUTION (a) Dehydration of the product of aldol addition of pentanal introduces the double bond between C-2 and C-3 to give an α,β-unsaturated aldehyde.

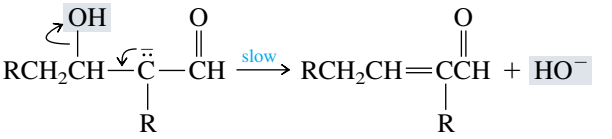


Product of aldol addition of pentanal (3-hydroxy-2-propylheptanal) | Product of aldol condensation of pentanal (2-propyl-2-heptenal)

The point was made earlier (Section 5.9) that alcohols require acid catalysis in order to undergo dehydration to alkenes. Thus, it may seem strange that aldol addition products can be dehydrated in base. This is another example of the way in which the enhanced acidity of protons at the α-carbon atom affects the reactions of carbonyl compounds. Elimination may take place in a concerted E2 fashion or it may be stepwise and proceed through an enolate ion.

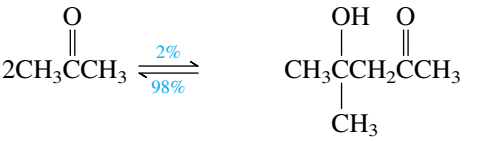


β-Hydroxy aldehyde — Enolate ion of β-hydroxy aldehyde



Enolate ion of β-hydroxy aldehyde — α,β-Unsaturated aldehyde

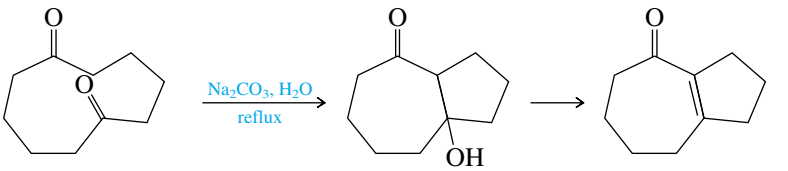
As with other reversible nucleophilic addition reactions, the equilibria for aldol additions are less favorable for ketones than for aldehydes. For example, only 2% of the aldol addition product of acetone is present at equilibrium.



Acetone — 4-Hydroxy-4-methyl-2-pentanone

The situation is similar for other ketones. Special procedures for aldol addition and self-condensation of ketones have been developed, but are rarely used.

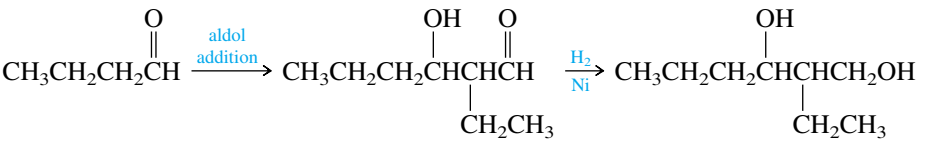
Aldol condensations of dicarbonyl compounds—even diketones—occur intramolecularly when five- or six-membered rings are possible.



1,6-Cyclodecanedione — Not isolated; dehydrates under reaction conditions — Bicyclo[5.3.0]dec-1(7)-en-2-one (96%)

Aldol condensations are one of the fundamental carbon–carbon bond-forming processes of synthetic organic chemistry. Furthermore, since the products of these aldol condensations contain functional groups capable of subsequent modification, access to a host of useful materials is gained.

To illustrate how aldol condensation may be coupled to functional group modification, consider the synthesis of 2-ethyl-1,3-hexanediol, a compound used as an insect repellent. This 1,3-diol is prepared by reduction of the aldol addition product of butanal:



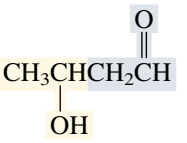
Butanal — 2-Ethyl-3-hydroxyhexanal — 2-Ethyl-1,3-hexanediol

PROBLEM 18.12 Outline a synthesis of 2-ethyl-1-hexanol from butanal.

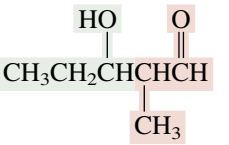
The carbon–carbon bond-forming potential of the aldol condensation has been extended beyond the self-condensations described in this section to cases in which two different carbonyl compounds react in what are called *mixed aldol condensations.*

18.10 MIXED ALDOL CONDENSATIONS

Mixed aldol condensations can be effective only if we limit the number of reaction possibilities. It would not be useful, for example, to treat a solution of acetaldehyde and propanal with base. A mixture of four aldol addition products forms under these conditions. Two of the products are those of self-addition:

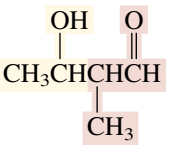


3-Hydroxybutanal
(from addition of enolate of acetaldehyde to acetaldehyde)

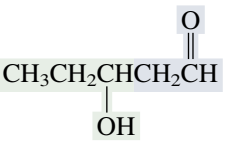


3-Hydroxy-2-methylpentanal
(from addition of enolate of propanal to propanal)

Two are the products of mixed addition:



3-Hydroxy-2-methylbutanal
(from addition of enolate of propanal to acetaldehyde)

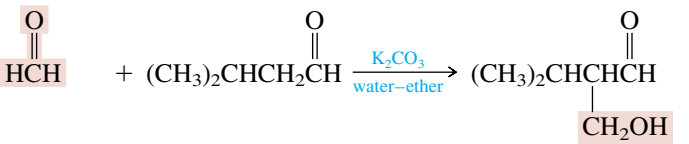


3-Hydroxypentanal
(from addition of enolate of acetaldehyde to propanal)

The mixed aldol condensations that are the most synthetically useful are those in which:

1. Only one of the reactants can form an enolate; or
2. One of the reactants is more reactive toward nucleophilic addition than the other.

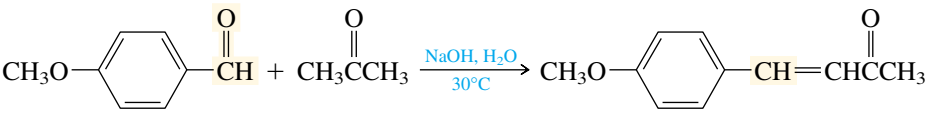
Formaldehyde, for example, cannot form an enolate but can react with the enolate of an aldehyde or ketone that can.



Formaldehyde 3-Methylbutanal 2-Hydroxymethyl-3-methylbutanal (52%)

Indeed, formaldehyde is so reactive toward nucleophilic addition that it suppresses the self-condensation of the other component by reacting rapidly with any enolate present.

Aromatic aldehydes cannot form enolates, and a large number of mixed aldol condensations have been carried out in which an aromatic aldehyde reacts with an enolate.



p-Methoxybenzaldehyde Acetone 4-*p*-Methoxyphenyl-3-buten-2-one (83%)

Mixed aldol condensations in which a ketone reacts with an aromatic aldehyde are known as *Claisen–Schmidt condensations.*

Recall that ketones do not readily undergo self-condensation. Thus, in the preceding example, the enolate of acetone reacts preferentially with the aromatic aldehyde and gives the mixed aldol condensation product in good yield. Mixed aldol condensations using aromatic aldehydes always involve dehydration of the product of mixed addition and yield a product in which the double bond is conjugated to both the aromatic ring and the carbonyl group.

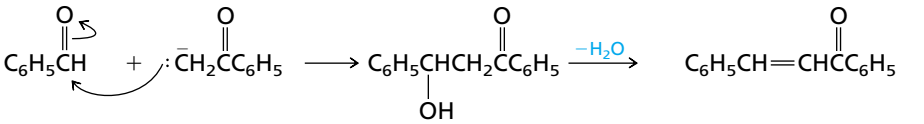
PROBLEM 18.13 Give the structure of the mixed aldol condensation product of benzaldehyde with

(a) Acetophenone, $C_6H_5\overset{\overset{O}{\|}}{C}CH_3$

(b) *tert*-Butyl methyl ketone, $(CH_3)_3\overset{\overset{O}{\|}}{C}CCH_3$

(c) Cyclohexanone

SAMPLE SOLUTION (a) The enolate of acetophenone reacts with benzaldehyde to yield the product of mixed addition. Dehydration of the intermediate occurs, giving the α,β-unsaturated ketone.



Benzaldehyde Enolate of acetophenone 1,3-Diphenyl-2-propen-1-one

As actually carried out, the mixed aldol condensation product, 1,3-diphenyl-2-propen-1-one, has been isolated in 85% yield on treating benzaldehyde with acetophenone in an aqueous ethanol solution of sodium hydroxide at 15–30°C.

18.11 EFFECTS OF CONJUGATION IN α,β-UNSATURATED ALDEHYDES AND KETONES

Aldol condensation offers an effective route to α,β-unsaturated aldehydes and ketones. These compounds have some interesting properties that result from conjugation of the carbon–carbon double bond with the carbonyl group. As shown in Figure 18.5, the π systems of the carbon–carbon and carbon–oxygen double bonds overlap to form an extended π system that permits increased electron delocalization.

This electron delocalization stabilizes a conjugated system. Under conditions chosen to bring about their interconversion, the equilibrium between a β,γ-unsaturated ketone and an α,β-unsaturated analog favors the conjugated isomer.

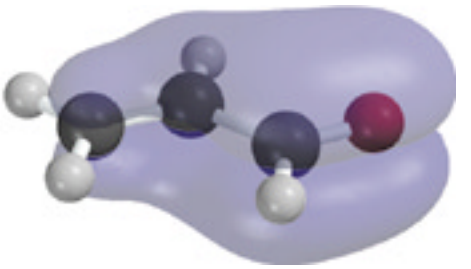
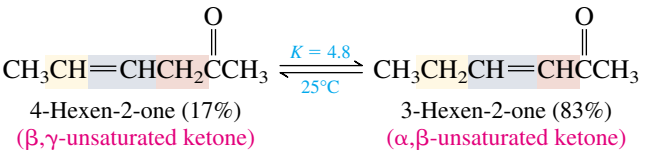


FIGURE 18.5 Acrolein ($H_2C{=}CHCH{=}O$) is a planar molecule. Oxygen and each carbon are sp^2-hybridized, and each contributes one electron to a conjugated π electron system analogous to that of 1,3-butadiene.



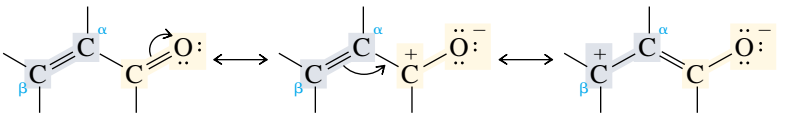
4-Hexen-2-one (17%)
(β,γ-unsaturated ketone)

3-Hexen-2-one (83%)
(α,β-unsaturated ketone)

Figure 3.17 (page 107) shows how the composition of an equilibrium mixture of two components varies according to the free-energy difference between them. For the equilibrium shown in the accompanying equation, $\Delta G° = -4$ kJ/mol (−1 kcal/mol).

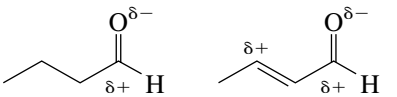
PROBLEM 18.14 Commercial mesityl oxide, $(CH_3)_2C{=}CHCCH_3$, is often contaminated with about 10% of an isomer having the same carbon skeleton. What is a likely structure for this compound?

In resonance terms, electron delocalization in α,β-unsaturated carbonyl compounds is represented by contributions from three principal resonance structures:



Most stable structure

The carbonyl group withdraws π electron density from the double bond, and both the carbonyl carbon and the β carbon are positively polarized. Their greater degree of charge separation makes the dipole moments of α,β-unsaturated carbonyl compounds significantly larger than those of comparable aldehydes and ketones.



Butanal
μ = 2.7 D

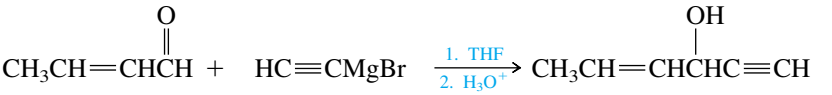
trans-2-Butenal
μ = 3.7 D

The diminished π electron density in the double bond makes α,β-unsaturated aldehydes and ketones less reactive than alkenes toward electrophilic addition. Electrophilic reagents—bromine and peroxy acids, for example—react more slowly with the carbon–carbon double bond of α,β-unsaturated carbonyl compounds than with simple alkenes.

On the other hand, the polarization of electron density in α,β-unsaturated carbonyl compounds makes their β-carbon atoms rather electrophilic. Some chemical consequences of this enhanced electrophilicity are described in the following section.

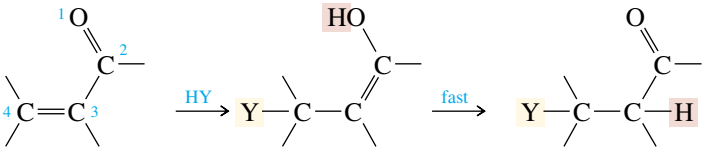
18.12 CONJUGATE ADDITION TO α,β-UNSATURATED CARBONYL COMPOUNDS

α,β-Unsaturated carbonyl compounds contain two electrophilic sites: the carbonyl carbon and the carbon atom that is β to it. Nucleophiles such as organolithium and Grignard reagents and lithium aluminum hydride tend to react by nucleophilic addition to the carbonyl group, as shown in the following example:

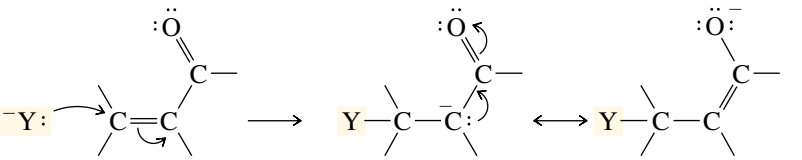


This is called *direct addition,* or *1,2 addition.* (The "1" and "2" do not refer to IUPAC locants but are used in a manner analogous to that employed in Section 10.10 to distinguish between direct and conjugate addition to conjugated dienes.)

With certain other nucleophiles, addition takes place at the carbon–carbon double bond rather than at the carbonyl group. Such reactions proceed via enol intermediates and are described as *conjugate addition,* or *1,4-addition,* reactions.



The nucleophilic portion of the reagent (Y in HY) becomes bonded to the β carbon. For reactions carried out under conditions in which the attacking species is the anion $:Y^-$, an enolate ion precedes the enol.

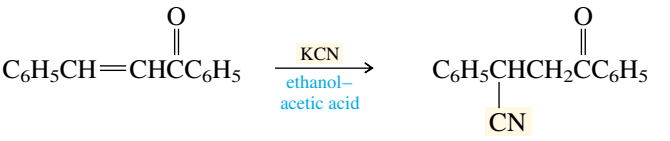


Enolate ion formed by nucleophilic addition of $:Y^-$ to β carbon

Ordinarily, nucleophilic addition to the carbon–carbon double bond of an alkene is very rare. It occurs with α,β-unsaturated carbonyl compounds because the carbanion that results is an enolate, which is more stable than a simple alkyl anion.

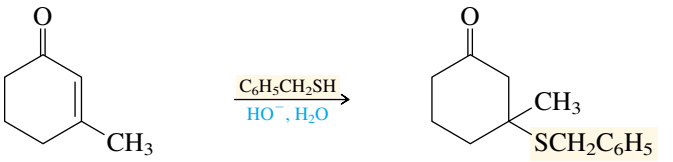
Hydrogen cyanide and alkanethiols have K_a values in the 10^{-9}–10^{-10} range (pK_a = 9–10), and K_a for acetylene is 10^{-26} (pK_a = 26).

Conjugate addition is most often observed when the nucleophile ($Y:^-$) is weakly basic. The nucleophiles in the two examples that follow are $^-:C{\equiv}N:$ and $C_6H_5CH_2\ddot{S}:^-$, respectively. Both are much weaker bases than acetylide ion, which was the nucleophile used in the example illustrating direct addition.



1,3-Diphenyl-2-propen-1-one

4-Oxo-2,4-diphenylbutanenitrile
(93–96%)



3-Methyl-2-cyclohexenone

3-Benzylthio-3-methylcyclohexanone
(58%)

One explanation for these observations is presented in Figure 18.6. Nucleophilic addition to α,β-unsaturated aldehydes and ketones may be governed either by *kinetic control* or by *thermodynamic control* (Section 10.10). 1,2 Addition is faster than 1,4 addition and, under conditions in which the 1,2- and 1,4-addition products do not equilibrate, is the predominant pathway. Kinetic control operates with strongly basic nucleophiles to give the 1,2-addition product. A weakly basic nucleophile, however, goes on and off the carbonyl carbon readily and permits the 1,2-addition product to equilibrate with the more slowly formed, but more stable, 1,4-addition product. Thermodynamic control is observed with weakly basic nucleophiles. The product of 1,4 addition, which retains the carbon–oxygen double bond, is more stable than the product of 1,2 addition, which retains the carbon–carbon double bond. In general, carbon–oxygen double bonds are more stable than carbon–carbon double bonds because the greater electronegativity of oxygen permits the π electrons to be bound more strongly.

PROBLEM 18.15 *Acrolein* ($CH_2{=}CHCH{=}O$) reacts with sodium azide (NaN_3) in aqueous acetic acid to form a compound, $C_3H_5N_3O$ in 71% yield. Propanal ($CH_3CH_2CH{=}O$), when subjected to the same reaction conditions, is recovered unchanged. Suggest a structure for the product formed from acrolein, and offer an explanation for the difference in reactivity between acrolein and propanal.

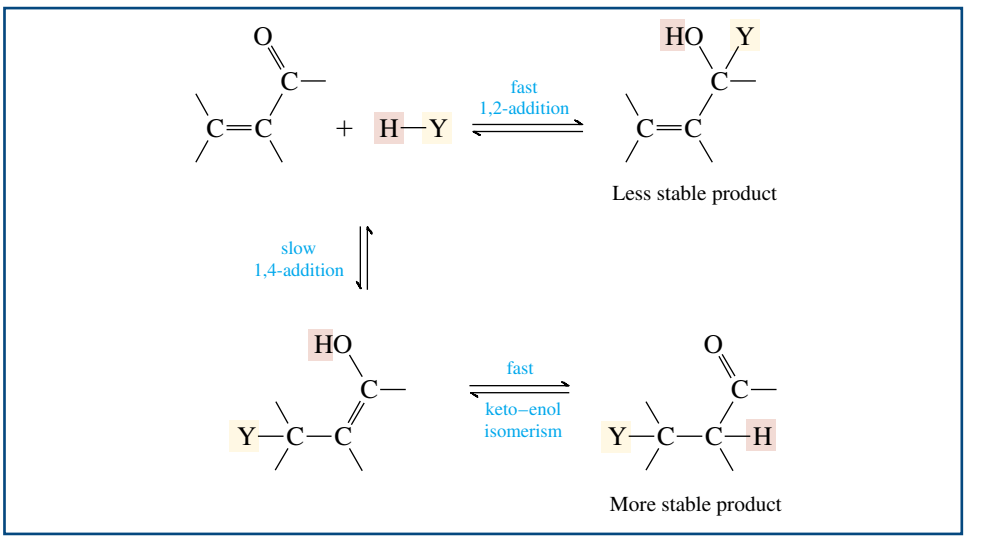
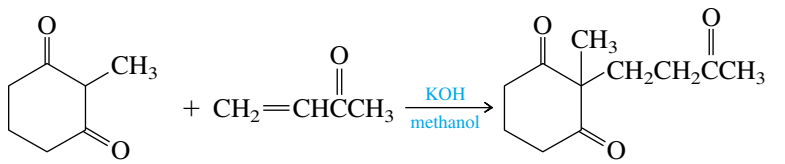


FIGURE 18.6 Nucleophilic addition to α,β-unsaturated aldehydes and ketones may take place either in a 1,2- or 1,4 manner. Direct addition (1,2) occurs faster than conjugate addition (1,4) but gives a less stable product. The product of 1,4 addition retains the carbon–oxygen double bond, which is, in general, stronger than a carbon–carbon double bond.

18.13 ADDITION OF CARBANIONS TO α,β-UNSATURATED KETONES: THE MICHAEL REACTION

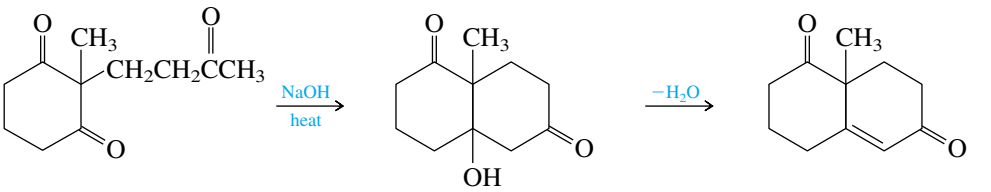
Arthur Michael, for whom the reaction is named, was an American chemist whose career spanned the period between the 1870s and the 1930s. He was independently wealthy and did much of his research in his own private laboratory.

A synthetically useful reaction known as the **Michael reaction,** or **Michael addition,** involves nucleophilic addition of carbanions to α,β-unsaturated ketones. The most common types of carbanions used are enolate ions derived from β-diketones. These enolates are weak bases (Section 18.6) and react with α,β-unsaturated ketones by *conjugate addition.*



2-Methyl-1,3-cyclohexanedione | Methyl vinyl ketone | 2-Methyl-2-(3′-oxobutyl)-1,3-cyclohexanedione (85%)

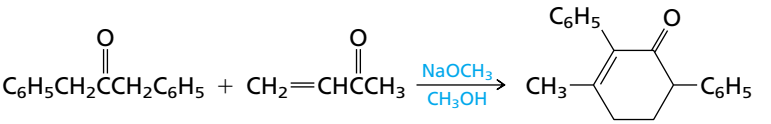
The product of Michael addition has the necessary functionality to undergo an intramolecular aldol condensation:



2-Methyl-2-(3′-oxobutyl)-1,3-cyclohexanedione | Intramolecular aldol addition product; not isolated | Δ^4-9-Methyloctalin-3,8-dione

The synthesis of cyclohexenone derivatives by Michael addition followed by intramolecular aldol condensation is called the **Robinson annulation,** after Sir Robert Robinson, who popularized its use. By *annulation* we mean the building of a ring onto some starting molecule. (The alternative spelling "annelation" is also often used.)

PROBLEM 18.16 Both the conjugate addition step and the intramolecular aldol condensation step can be carried out in one synthetic operation without isolating any of the intermediates along the way. For example, consider the reaction

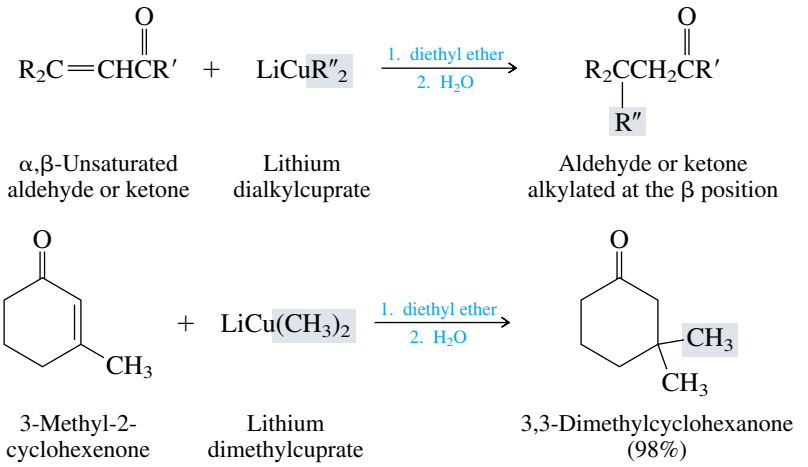


Dibenzyl ketone | Methyl vinyl ketone | 3-Methyl-2,6-diphenyl-2-cyclohexen-1-one (55%)

Write structural formulas corresponding to the intermediates formed in the conjugate addition step and in the aldol addition step.

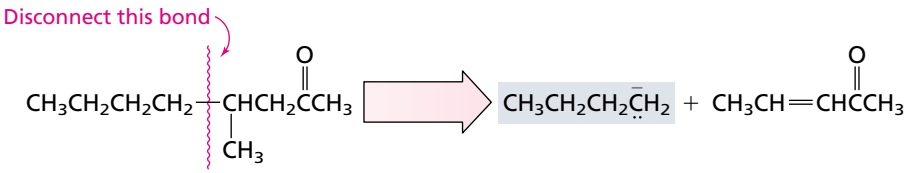
18.14 CONJUGATE ADDITION OF ORGANOCOPPER REAGENTS TO α,β-UNSATURATED CARBONYL COMPOUNDS

The preparation and some synthetic applications of lithium dialkylcuprates were described earlier (Section 14.11). The most prominent feature of these reagents is their capacity to undergo conjugate addition to α,β-unsaturated aldehydes and ketones.



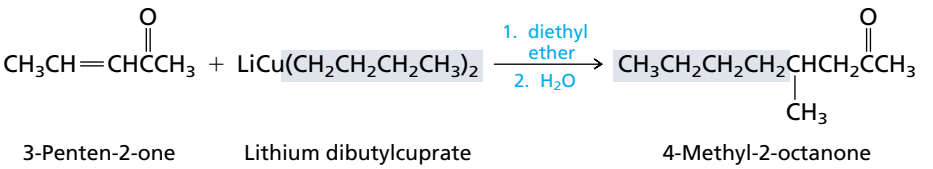
PROBLEM 18.17 Outline two ways in which 4-methyl-2-octanone can be prepared by conjugate addition of an organocuprate to an α,β-unsaturated ketone.

SAMPLE SOLUTION Mentally disconnect one of the bonds to the β carbon so as to identify the group that comes from the lithium dialkylcuprate.



4-Methyl-2-octanone

According to this disconnection, the butyl group is derived from lithium dibutylcuprate. A suitable preparation is

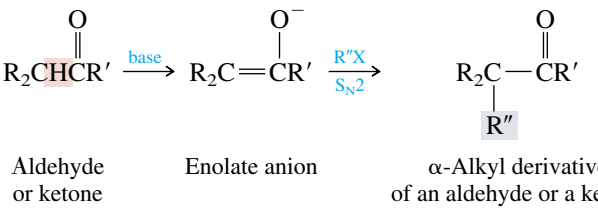


Now see if you can identify the second possibility.

Like other carbon–carbon bond-forming reactions, organocuprate addition to enones is a powerful tool in organic synthesis.

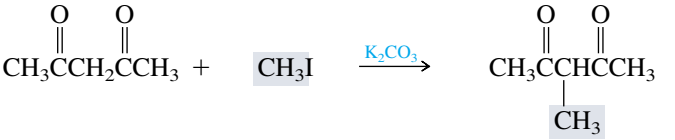
18.15 ALKYLATION OF ENOLATE ANIONS

Since enolate anions are sources of nucleophilic carbon, one potential use in organic synthesis is their reaction with alkyl halides to give α-alkyl derivatives of aldehydes and ketones:



Alkylation occurs by an S_N2 mechanism in which the enolate ion acts as a nucleophile toward the alkyl halide.

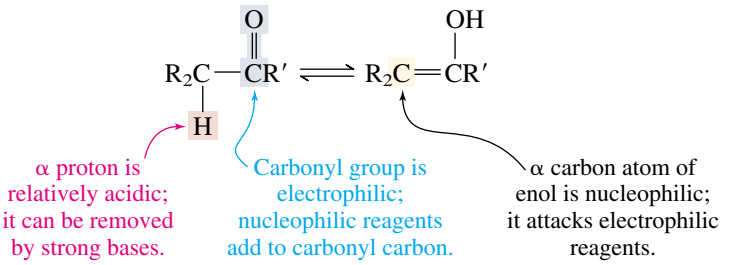
In practice, this reaction is difficult to carry out with simple aldehydes and ketones because aldol condensation competes with alkylation. Furthermore, it is not always possible to limit the reaction to the introduction of a single alkyl group. The most successful alkylation procedures use β-diketones as starting materials. Because they are relatively acidic, β-diketones can be converted quantitatively to their enolate ions by weak bases and do not self-condense. Ideally, the alkyl halide should be a methyl or primary alkyl halide.



18.16 SUMMARY

Section 18.1 Greek letters are commonly used to identify various carbons in aldehydes and ketones. Using the carbonyl group as a reference, the adjacent carbon is designated α, the next one β, and so on as one moves down the chain. Attached groups take the same Greek letter as the carbon to which they are connected.

Sections 18.2–18.15 Because aldehydes and ketones exist in equilibrium with their corresponding enol isomers, they can express a variety of different kinds of chemical reactivity.



Reactions that proceed via enol or enolate intermediates are summarized in Table 18.1.

PROBLEMS

18.18 (a) Write structural formulas or build molecular models for all the noncyclic aldehydes and ketones of molecular formula C_4H_6O.

(b) Are any of these compounds stereoisomeric?

(c) Are any of these compounds chiral?

(d) Which of these are α,β-unsaturated aldehydes or α,β-unsaturated ketones?

(e) Which of these can be prepared by a simple (i.e., not mixed) aldol condensation?

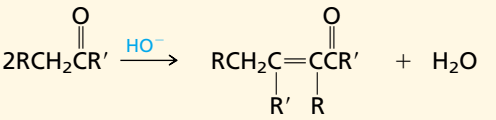
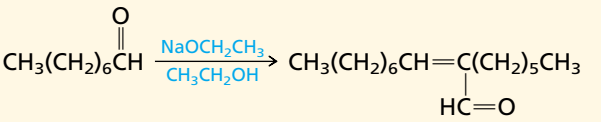
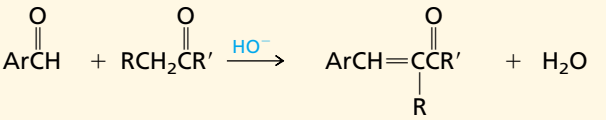
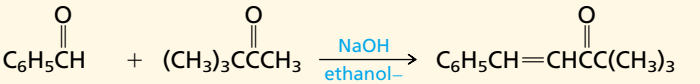
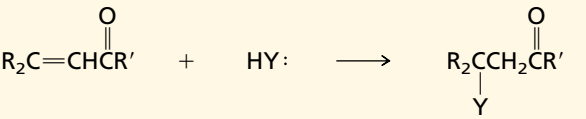
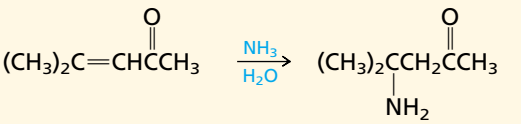
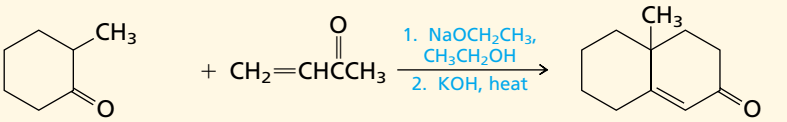
18.19 The main flavor component of the hazelnut is (2*E*,5*S*)-5-methyl-2-hepten-4-one. Write a structural formula or build a molecular model showing its stereochemistry.

TABLE 18.1 Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates

Reaction (section) and comments	General equation and typical example
α Halogenation (Sections 18.2 and 18.3) Halogens react with aldehydes and ketones by substitution; an α hydrogen is replaced by a halogen. Reaction occurs by electrophilic attack of the halogen on the carbon–carbon double bond of the enol form of the aldehyde or ketone. An acid catalyst increases the rate of enolization, which is the rate-determining step.	$R_2CHCR' + X_2 \longrightarrow R_2CCR' + HX$ (X on α-C) Aldehyde or ketone; Halogen; α-Halo aldehyde or ketone; Hydrogen halide $Br\text{-}C_6H_4\text{-}COCH_3 + Br_2 \xrightarrow{\text{acetic acid}} Br\text{-}C_6H_4\text{-}COCH_2Br + HBr$ *p*-Bromoacetophenone; Bromine; *p*-Bromophenacyl bromide (69–72%); Hydrogen bromide
Enolization (Sections 18.4 through 18.6) Aldehydes and ketones exist in equilibrium with their enol forms. The rate at which equilibrium is achieved is increased by acidic or basic catalysts. The enol content of simple aldehydes and ketones is quite small; β-diketones, however, are extensively enolized.	$R_2CH\text{—}CR' \rightleftharpoons R_2C{=}CR'$ (OH) Aldehyde or ketone; Enol Cyclopentanone $\overset{K}{\rightleftharpoons}$ Cyclopenten-1-ol; $K = 1 \times 10^{-8}$
Enolate ion formation (Section 18.6) An α proton of an aldehyde or a ketone is more acidic than most other protons bound to carbon. Aldehydes and ketones are weak acids, with K_a's in the range 10^{-16} to 10^{-20} (pK_a 16–20). Their enhanced acidity is due to the electron-withdrawing effect of the carbonyl group and the resonance stabilization of the enolate anion.	$R_2CHCR' + HO^- \rightleftharpoons R_2C{=}CR' + H_2O$ (O: on α-C) Aldehyde or ketone; Hydroxide ion; Enolate anion; Water $CH_3CH_2CCH_2CH_3 + HO^- \rightleftharpoons CH_3CH{=}CCH_2CH_3 + H_2O$ (O: on α-C) 3-Pentanone; Hydroxide ion; Enolate anion of 3-pentanone; Water
Haloform reaction (Section 18.7) Methyl ketones are cleaved on reaction with excess halogen in the presence of base. The products are a trihalomethane (haloform) and a carboxylate salt.	$RCCH_3 + 3X_2 \xrightarrow{HO^-} RCO^- + HCX_3$ Methyl ketone; Halogen; Carboxylate ion; Trihalomethane (haloform) $(CH_3)_3CCH_2CCH_3 \xrightarrow[2.\ H^+]{1.\ Br_2,\ NaOH} (CH_3)_3CCH_2CO_2H + CHBr_3$ 4,4-Dimethyl-2-pentanone; 3,3-Dimethylbutanoic acid (89%); Bromoform

(Continued)

TABLE 18.1 Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates *(Continued)*

Reaction (section) and comments	General equation and typical example
Aldol condensation (Section 18.9) A reaction of great synthetic value for carbon–carbon bond formation. Nucleophilic addition of an enolate ion to a carbonyl group, followed by dehydration of the β-hydroxy aldehyde, yields an α,β-unsaturated aldehyde.	 Aldehyde — α,β-Unsaturated aldehyde — Water  Octanal — 2-Hexyl-2-decenal (79%)
Claisen–Schmidt reaction (Section 18.10) A mixed aldol condensation in which an aromatic aldehyde reacts with an enolizable aldehyde or ketone.	 Aromatic aldehyde — Aldehyde or ketone — α,β-Unsaturated carbonyl compound — Water  Benzaldehyde — 3,3-Dimethyl-2-butanone — 4,4-Dimethyl-1-phenyl-1-penten-3-one (88–93%)
Conjugate addition to α,β-unsaturated carbonyl compounds (Sections 18.11 through 18.14) The β-carbon atom of an α,β-unsaturated carbonyl compound is electrophilic; nucleophiles, especially weakly basic ones, yield the products of conjugate addition to α,β-unsaturated aldehydes and ketones.	 α,β-Unsaturated aldehyde or ketone — Nucleophile — Product of conjugate addition  4-Methyl-3-penten-2-one (mesityl oxide) — 4-Amino-4-methyl-2-pentanone (63–70%)
Robinson annulation (Section 18.13) A combination of conjugate addition of an enolate anion to an α,β-unsaturated ketone with subsequent intramolecular aldol condensation.	 2-Methylcyclohexanone — Methyl vinyl ketone — 6-Methylbicyclo[4.4.0]-1-decen-3-one (46%)

(Continued)

TABLE 18.1 Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates *(Continued)*

Reaction (section) and comments	General equation and typical example
Conjugate addition of organocopper compounds (Section 18.14) The principal synthetic application of lithium dialkylcuprate reagents is their reaction with α,β-unsaturated carbonyl compounds. Alkyl-ation of the β carbon occurs.	$R_2C{=}CHCR'$ (α,β-Unsaturated aldehyde or ketone) + R''_2CuLi (Lithium dialkylcuprate) → 1. diethyl ether 2. H_2O → $R_2C(R'')-CH_2CR'$ (β-Alkyl aldehyde or ketone) 6-Methylcyclohept-2-enone → 1. $LiCu(CH_3)_2$ 2. H_2O → 3,6-Dimethylcycloheptanone (85%)
α Alkylation of aldehydes and ketones (Section 18.15) Alkylation of simple aldehydes and ketones via their enolates is difficult. β-Diketones can be converted quantitatively to their enolate anions, which react efficiently with primary alkyl halides.	$RCCH_2CR$ (β-Diketone) → $R'CH_2X$, HO^- → $RCCHCR$ with CH_2R' (α-Alkyl-β-diketone) 2-Benzyl-1,3-cyclohexanedione + $C_6H_5CH_2Cl$ (Benzyl chloride) → $KOCH_2CH_3$, ethanol → 2,2-Dibenzyl-1,3-cyclohexanedione (69%)

18.20 The simplest α,β-unsaturated aldehyde *acrolein* is prepared by heating glycerol with an acid catalyst. Suggest a mechanism for this reaction.

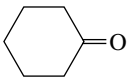
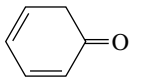
$$HOCH_2CH(OH)CH_2OH \xrightarrow[\text{heat}]{KHSO_4} CH_2{=}CHCH{=}O + H_2O$$

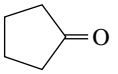
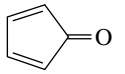
18.21 In each of the following pairs of compounds, choose the one that has the greater enol content, and write the structure of its enol form:

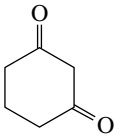
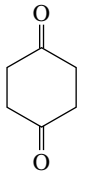
(a) $(CH_3)_3CCH{=}O$ or $(CH_3)_2CHCH{=}O$

(b) $C_6H_5CC_6H_5$ (O) or $C_6H_5CH_2CCH_2C_6H_5$ (O)

(c) $C_6H_5\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}C_6H_5$ or $C_6H_5CH_2\overset{O}{\overset{\|}{C}}CH_2C_6H_5$

(d)  or 

(e)  or 

(f)  or 

18.22 Give the structure of the expected organic product in the reaction of 3-phenylpropanal with each of the following:

(a) Chlorine in acetic acid

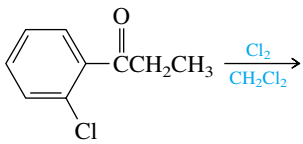
(b) Sodium hydroxide in ethanol, 10°C

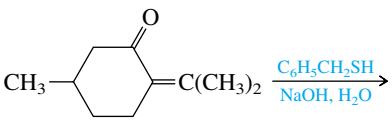
(c) Sodium hydroxide in ethanol, 70°C

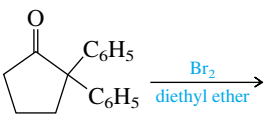
(d) Product of part (c) with lithium aluminum hydride; then H_2O

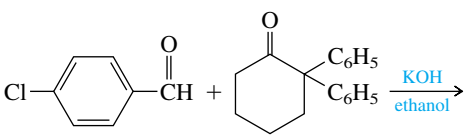
(e) Product of part (c) with sodium cyanide in acidic ethanol

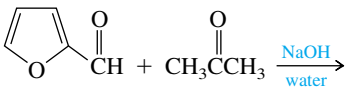
18.23 Each of the following reactions has been reported in the chemical literature. Write the structure of the product(s) formed in each case.

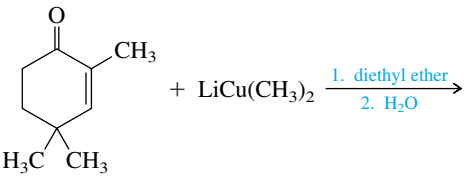
(a) 

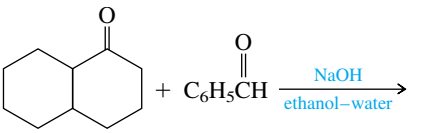
(b) 

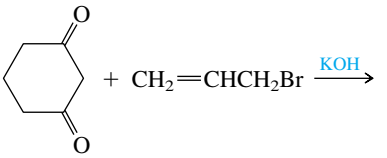
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

18.24 Show how each of the following compounds could be prepared from 3-pentanone. In most cases more than one synthetic transformation will be necessary.

(a) 2-Bromo-3-pentanone

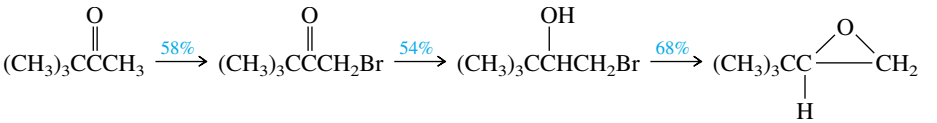
(b) 1-Penten-3-one

(c) 1-Penten-3-ol

(d) 3-Hexanone

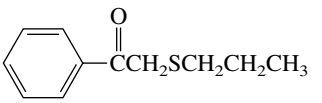
(e) 2-Methyl-1-phenyl-1-penten-3-one

18.25 (a) A synthesis that begins with 3,3-dimethyl-2-butanone gives the epoxide shown. Suggest reagents appropriate for each step in the synthesis.

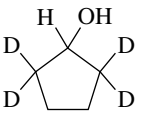


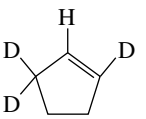
(b) The yield for each step as actually carried out in the laboratory is given above each arrow. What is the overall yield for the three-step sequence?

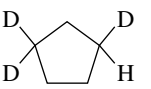
18.26 Using benzene, acetic anhydride, and 1-propanethiol as the source of all the carbon atoms, along with any necessary inorganic reagents, outline a synthesis of the compound shown.

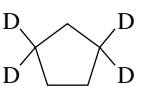


18.27 Show how you could prepare each of the following compounds from cyclopentanone, D_2O, and any necessary organic or inorganic reagents.

(a) 

(b) 

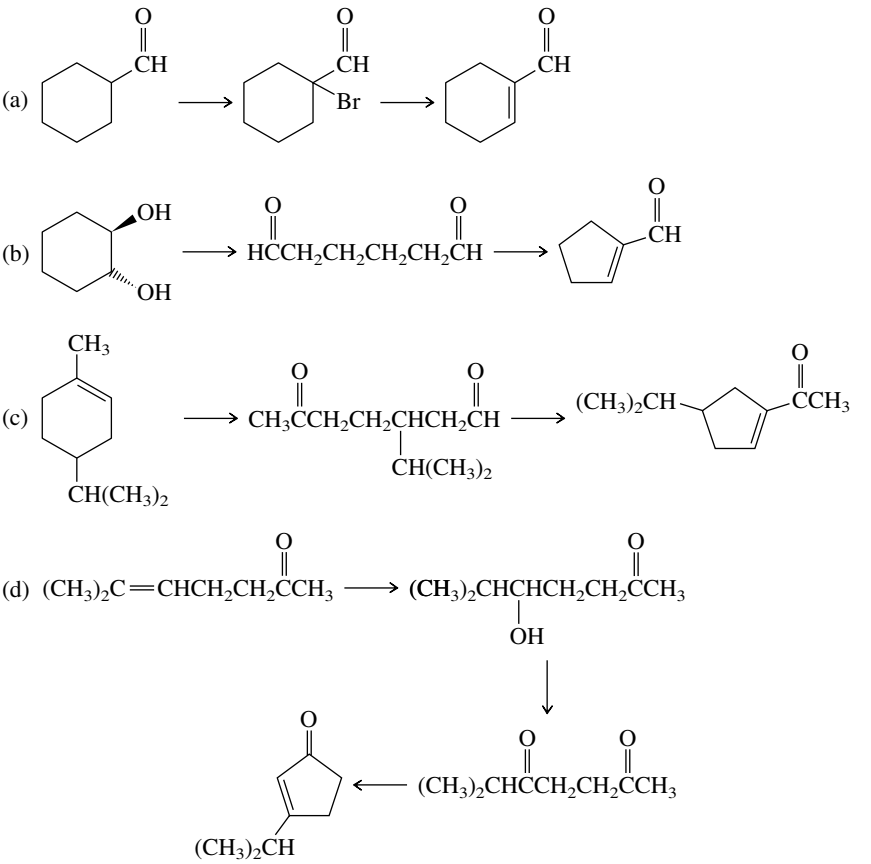
(c) 

(d) 

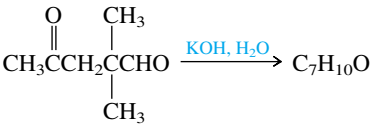
18.28 (a) At present, butanal is prepared industrially by hydroformylation of propene (Section 17.4). Write a chemical equation for this industrial synthesis.

(b) Before about 1970, the principal industrial preparation of butanal was from acetaldehyde. Outline a practical synthesis of butanal from acetaldehyde.

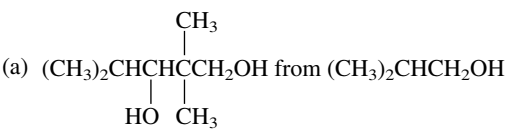
18.29 Identify the reagents appropriate for each step in the following syntheses:



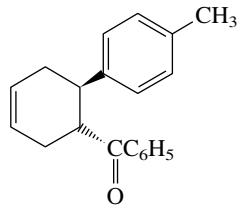
18.30 Give the structure of the product derived by intramolecular aldol condensation of the keto aldehyde shown:



18.31 Prepare each of the following compounds from the starting materials given and any necessary organic or inorganic reagents:

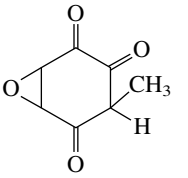


(b) $C_6H_5CH{=}CCH_2OH$ from benzyl alcohol and 1-propanol

(c) 

from acetophenone, 4-methylbenzyl alcohol, and 1,3-butadiene

18.32 *Terreic acid* is a naturally occurring antibiotic substance. Its actual structure is an enol isomer of the structure shown. Write the two most stable enol forms of terreic acid, and choose which of those two is more stable.

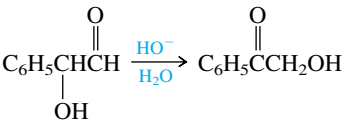


18.33 In each of the following, the indicated observations were made before any of the starting material was transformed to aldol addition or condensation products:

(a) In aqueous acid, only 17% of $(C_6H_5)_2CHCH{=}O$ is present as the aldehyde; 2% of the enol is present. Some other species accounts for 81% of the material. What is it?

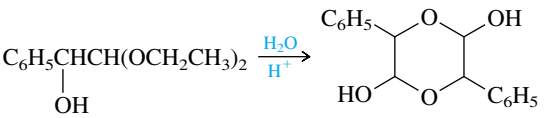
(b) In aqueous base, 97% of $(C_6H_5)_2CHCH{=}O$ is present as a species different from any of those in part (a). What is this species?

18.34 (a) For a long time attempts to prepare compound A were thwarted by its ready isomerization to compound B. The isomerization is efficiently catalyzed by traces of base. Write a reasonable mechanism for this isomerization.



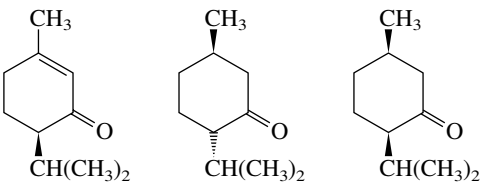
Compound A Compound B

(b) Another attempt to prepare compound A by hydrolysis of its diethyl acetal gave only the 1,4-dioxane derivative C. How was compound C formed?



Compound C

18.35 Consider the ketones piperitone, menthone, and isomenthone.



(−)-Piperitone Menthone Isomenthone

Suggest reasonable explanations for each of the following observations:

(a) Optically active piperitone ($\alpha_D - 32°$) is converted to racemic piperitone on standing in a solution of sodium ethoxide in ethanol.

(b) Menthone is converted to a mixture of menthone and isomenthone on treatment with 90% sulfuric acid.

18.36 Many nitrogen-containing compounds engage in a proton-transfer equilibrium that is analogous to keto–enol tautomerism:

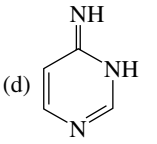
$$HX{-}N{=}Z \rightleftharpoons X{=}N{-}ZH$$

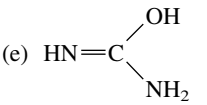
Each of the following compounds is the less stable partner of such a tautomeric pair. Write the structure of the more stable partner for each one.

(a) $CH_3CH_2N{=}O$

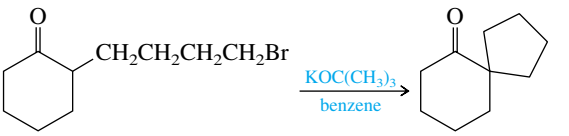
(b) $(CH_3)_2C{=}CHNHCH_3$

(c) $CH_3CH{=}\overset{+}{N}(O^-)OH$

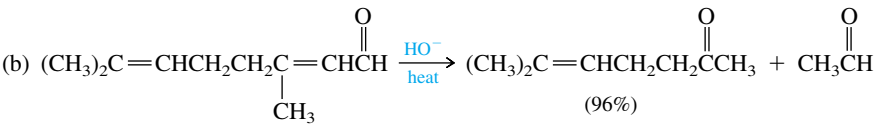
(d) 

(e) 

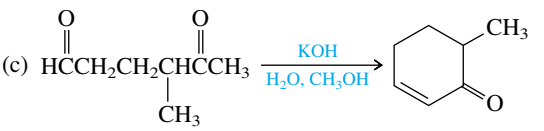
18.37 Outline reasonable mechanisms for each of the following reactions:

(a) 

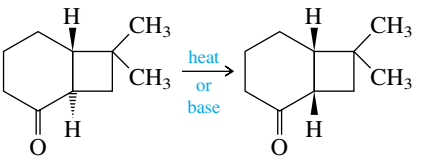
(76%)

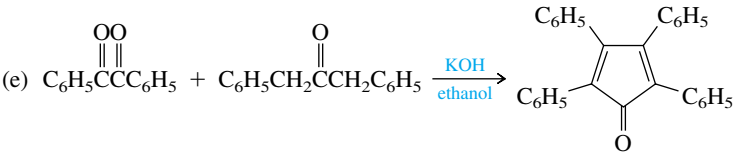
(b) 

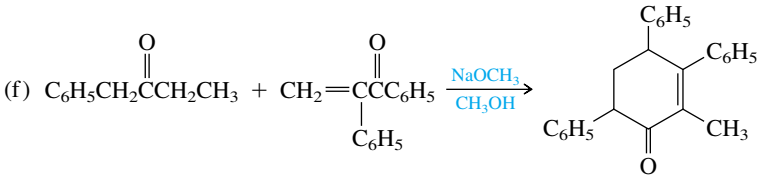
(96%)

(c) 

(40%)

(d) 

(e) 

(f) 

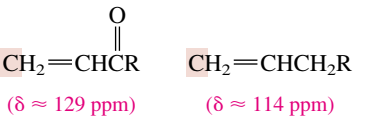
18.38 Suggest reasonable explanations for each of the following observations:

(a) The C=O stretching frequency of α,β-unsaturated ketones (about 1675 cm^{-1}) is less than that of typical dialkyl ketones (1710–1750 cm^{-1}).

(b) The C=O stretching frequency of cyclopropenone (1640 cm^{-1}) is lower than that of typical α,β-unsaturated ketones (1675 cm^{-1}).

(c) The dipole moment of diphenylcyclopropenone (μ = 5.1 D) is substantially larger than that of benzophenone (μ = 3.0 D)

(d) The β carbon of an α,β-unsaturated ketone is less shielded than the corresponding carbon of an alkene. Typical ^{13}C NMR chemical shift values are



18.39 Bromination of 3-methyl-2-butanone yielded two compounds, each having the molecular formula C_5H_9BrO, in a 95:5 ratio. The ^1H NMR spectrum of the major isomer A was characterized by a doublet at δ 1.2 ppm (6 protons), a septet at δ 3.0 ppm (1 proton), and a singlet at δ 4.1 ppm (2 protons). The ^1H NMR spectrum of the minor isomer B exhibited two singlets, one at δ 1.9 ppm and the other at δ 2.5 ppm. The lower field singlet had half the area of the higher field one. Suggest reasonable structures for these two compounds.

18.40 Treatment of 2-butanone (1 mol) with Br_2 (2 mol) in aqueous HBr gave $C_4H_6Br_2O$. The ^1H NMR spectrum of the product was characterized by signals at δ 1.9 ppm (doublet, 3 protons), 4.6 ppm (singlet, 2 protons), and 5.2 ppm (quartet, 1 proton). Identify this compound.

18.41 2-Phenylpropanedial [$C_6H_5CH(CHO)_2$] exists in the solid state as an enol in which the configuration of the double bond is *E*. In solution ($CDCl_3$), an enol form again predominates but this time the configuration is *Z*. Make molecular models of these two enols, and suggest an explanation for the predominance of the *Z* enol in solution. (*Hint:* Think about intermolecular versus intramolecular hydrogen bonding.)