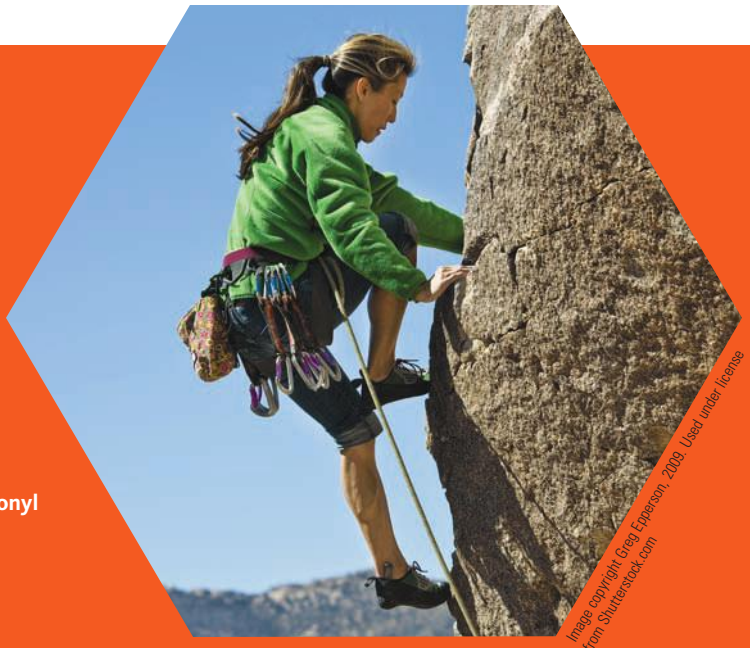
CHAPTER

11

The lives of rock climbers depend on their ropes, typically made of a nylon polymer prepared by a carbonyl condensation reaction.



Carbonyl Alpha-Substitution Reactions and Condensation Reactions

11.1 Keto–Enol Tautomerism
11.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions
11.3 Alpha Halogenation of Aldehydes and Ketones
11.4 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation
11.5 Reactivity of Enolate Ions
11.6 Alkylation of Enolate Ions
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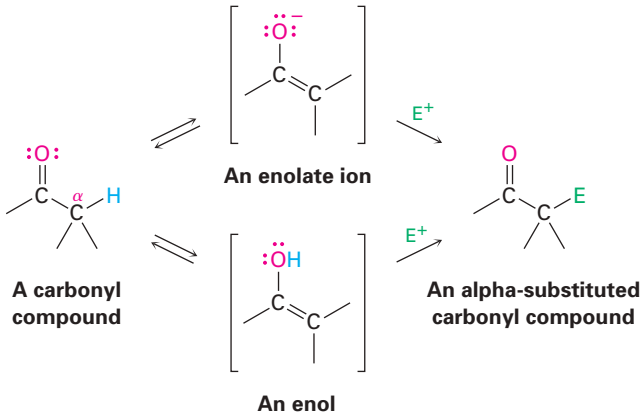
11.8 Condensations of Aldehydes and Ketones: The Aldol Reaction
11.9 Dehydration of Aldol Products: Synthesis of Enones
11.10 Condensations of Esters: The Claisen Condensation Reaction
11.11 Some Biological Carbonyl Reactions
Interlude—Barbiturates

Most of the chemistry of carbonyl compounds can be explained by just four fundamental reactions. We've already looked in detail at two of the four: the nucleophilic addition reaction of aldehydes and ketones (Chapter 9) and the nucleophilic acyl substitution reaction of carboxylic acid derivatives (Chapter 10). In this chapter, we'll look at the remaining two: the *alpha-substitution reaction* and the *carbonyl condensation reaction*.

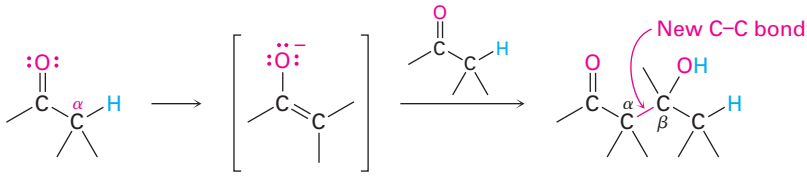
Alpha-substitution reactions occur at the position *next to* the carbonyl group—the α position—and result in the substitution of an α hydrogen atom by an electrophile (E) through either an *enol* or *enolate ion* intermediate.

OWL

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



Carbonyl condensation reactions take place between two carbonyl partners and involve a *combination* of α substitution and nucleophilic addition steps. One partner is converted into its enolate ion and undergoes an α-substitution reaction when it carries out a nucleophilic addition to the second partner. The product is a β-hydroxy carbonyl compound.



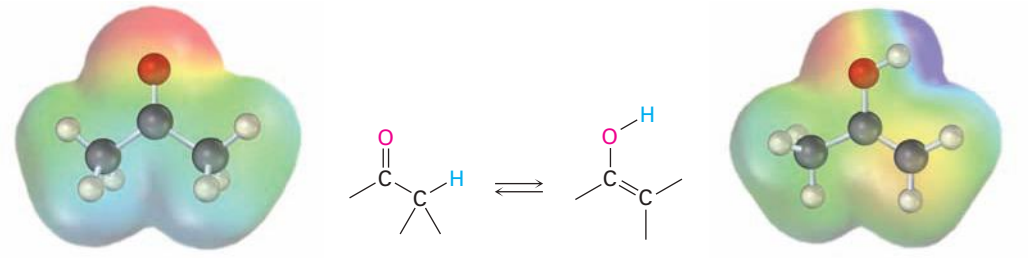
WHY THIS CHAPTER?

Many laboratory schemes, pharmaceutical syntheses, and biochemical pathways make frequent use of carbonyl α-substitution and carbonyl condensation reactions. Their great value is that they are two of the few general methods available for forming carbon–carbon bonds, thereby making it possible to build larger molecules from smaller ones. In this chapter, we'll see how these reactions occur.

11.1 Keto–Enol Tautomerism

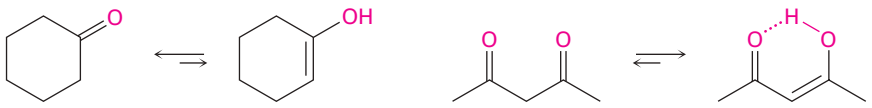
A carbonyl compound with a hydrogen atom on its α carbon rapidly equilibrates with its corresponding **enol** (*ene* + *ol;* unsaturated alcohol) isomer. This spontaneous interconversion between two isomers, usually with the change in position of a hydrogen, is called *tautomerism,* from the Greek *tauto,* meaning

"the same," and *meros,* meaning "part." The individual keto and enol isomers are called **tautomers**.



Keto tautomer **Enol tautomer**

Most monocarbonyl compounds exist almost entirely in the keto form at equilibrium, and it's usually difficult to isolate the pure enol. Cyclohexanone, for example, contains only about 0.0001% of its enol tautomer at room temperature, and the amount of enol tautomer is even less for carboxylic acids, esters, and amides. Only when the enol can be stabilized by conjugation or by intramolecular hydrogen bond formation does the enol sometimes predominate. Thus, pentane-2,4-dione is about 76% enol tautomer.



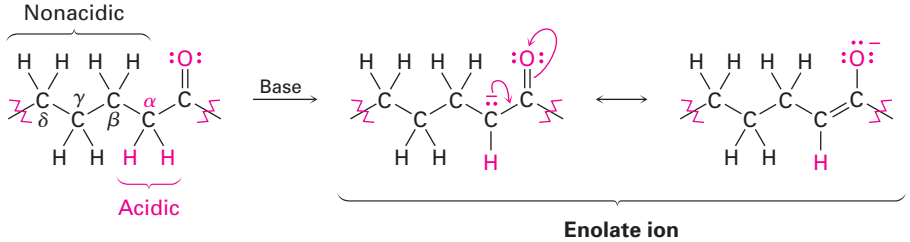
99.9999 % 0.0001 % 24 % 76 %

Cyclohexanone **Pentane-2,4-dione**

Keto–enol tautomerism of carbonyl compounds is catalyzed by both acids and bases. Acid catalysis involves protonation of the carbonyl oxygen atom (a Lewis base) to give an intermediate cation that loses H^+ from the α carbon to yield the enol (Figure 11.1a).

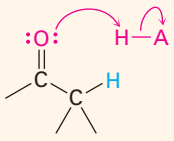
Base-catalyzed enol formation occurs because the presence of a carbonyl group makes the hydrogens on the α carbon weakly acidic. Thus, a carbonyl compound can act as an acid and donate one of its α hydrogens to a sufficiently strong base. The resultant resonance-stabilized anion, an **enolate ion**, is then protonated to yield a neutral compound. If protonation of the enolate ion takes place on the α carbon, the keto tautomer is regenerated and no net change occurs. If, however, protonation takes place on the oxygen atom, then an enol tautomer is formed (Figure 11.1b).

Note that only the protons on the α position of carbonyl compounds are acidic. The protons at beta (β), gamma (γ), delta (δ), and other positions aren't acidic because the resulting anions can't be resonance-stabilized by the carbonyl group.



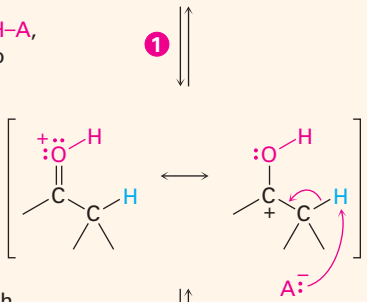
MECHANISM

(a) Acidic conditions

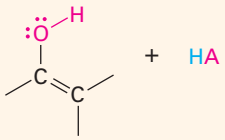


Keto tautomer

1. The carbonyl oxygen is protonated by an acid H–A, giving a cation with two resonance structures.

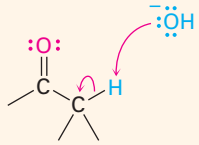


2. Loss of H^+ from the α position by reaction with a base A^- gives the enol tautomer and regenerates HA catalyst.



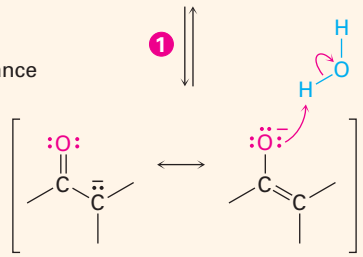
Enol tautomer

(b) Basic conditions



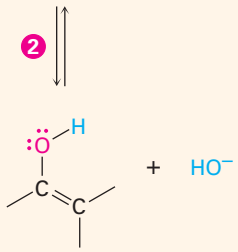
Keto tautomer

1. Base removes the acidic α hydrogen, yielding an enolate ion with two resonance structures.



Enolate ion

2. Protonation of the enolate ion on oxygen gives the enol and regenerates base catalyst.



Enol tautomer

Figure 11.1 Mechanism of enol formation under both acid-catalyzed and base-catalyzed conditions. **(a)** Acid catalysis involves initial protonation of the carbonyl oxygen followed by removal of H^+ from the α position. **(b)** Base catalysis involves initial deprotonation of the α position to give an enolate ion, followed by reprotonation on oxygen.

Worked Example 11.1

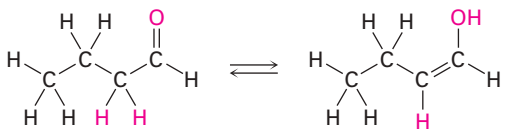
Drawing the Structure of an Enol Tautomer

Show the structure of the enol tautomer of butanal.

Strategy

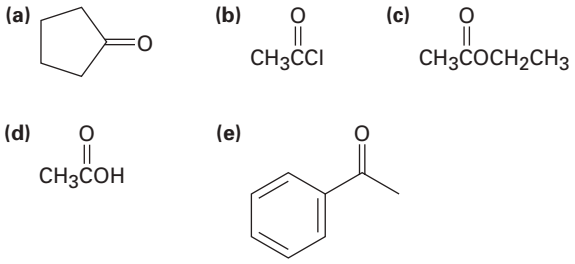
Form the enol by removing a hydrogen from the carbon next to the carbonyl carbon. Then draw a resonance structure that has a double bond between the two carbons, and replace the hydrogen on the carbonyl oxygen.

Solution



Butanal **Enol tautomer**

Problem 11.1 Draw structures for the enol tautomers of the following compounds:

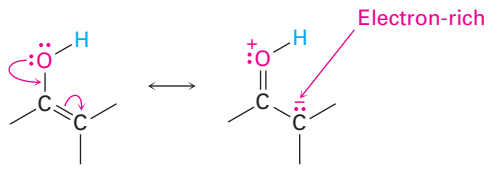


Problem 11.2 How many acidic hydrogens does each of the molecules listed in Problem 11.1 have? Identify them.

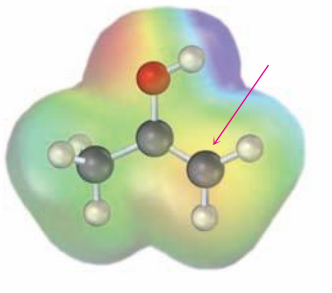
Problem 11.3 2-Methylcyclohexanone can form two enol tautomers. Show the structures of both.

11.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

What kind of chemistry do enols have? Because their double bonds are electron-rich, enols behave as nucleophiles and react with electrophiles in much the same way alkenes do (Section 4.1). But because of resonance electron donation from the neighboring oxygen, enols are more electron-rich and correspondingly more reactive than alkenes. Notice in the following electrostatic potential map that there is a substantial amount of electron density (yellow-red) on the α carbon.



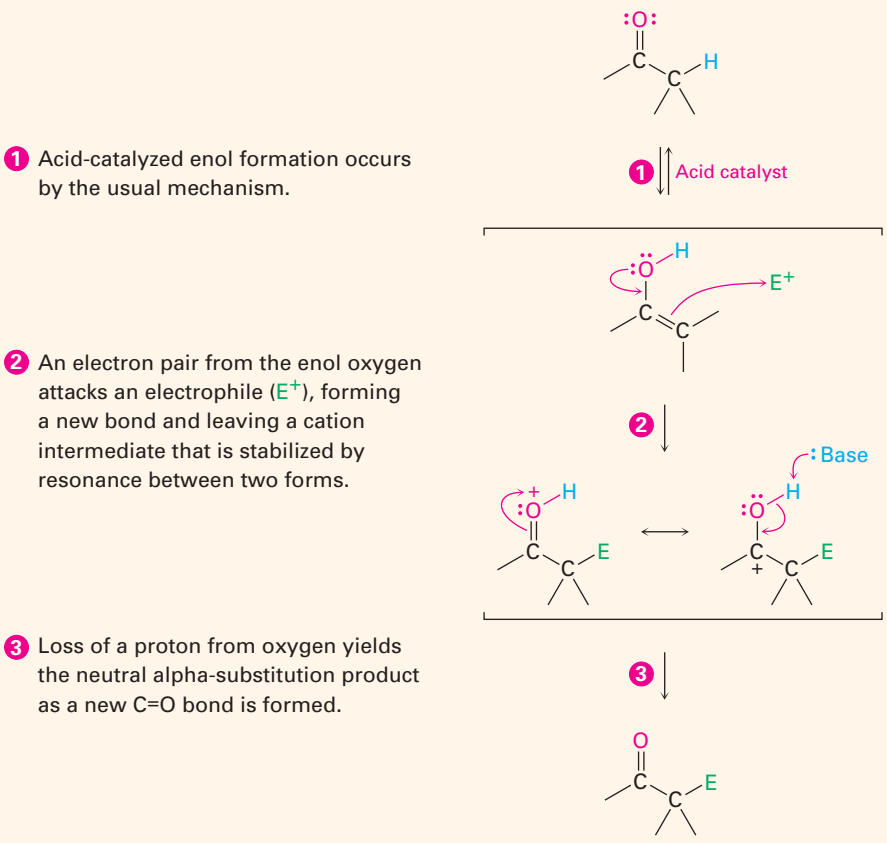
Enol tautomer



When an *alkene* reacts with an electrophile, such as Br_2, addition of Br^+ occurs to give an intermediate cation, and subsequent reaction with Br^- gives the addition product (Section 4.4). When an *enol* reacts with an electrophile, however, only the initial addition step is the same. Instead of reacting with Br^- to give an addition product, the intermediate cation loses the –OH proton to generate an α-substituted carbonyl compound. The general mechanism is shown in Figure 11.2.

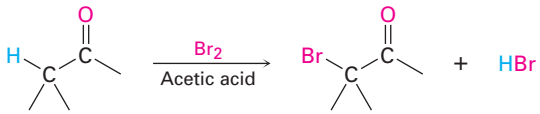
MECHANISM

Figure 11.2 The general mechanism of a carbonyl α-substitution reaction with an electrophile, E^+.



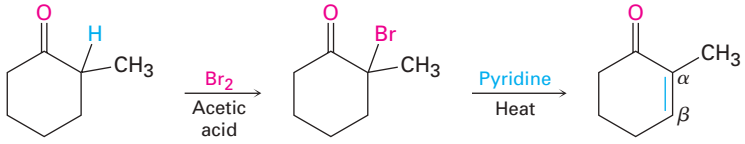
11.3 Alpha Halogenation of Aldehydes and Ketones

Aldehydes and ketones are halogenated at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution. Bromine in acetic acid solvent is most often used. The reaction is a typical α-substitution process that proceeds through an enol intermediate.



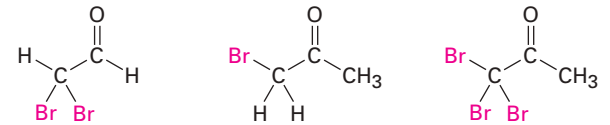
α-Bromo ketones are useful because they undergo elimination of HBr on treatment with base to yield α,β-unsaturated ketones. For example, 2-bromo-2-methylcyclohexanone gives 2-methylcyclohex-2-enone when heated in the

organic base pyridine. The reaction takes place by an E2 elimination pathway (Section 7.7) and is a good way to introduce a C=C bond into a molecule.



2-Methylcyclohexanone → **2-Bromo-2-methylcyclohexanone** → **2-Methylcyclohex-2-enone (63%)**

Ketone halogenation also occurs in biological systems, particularly in marine alga, where dibromoacetaldehyde, bromoacetone, 1,1,1-tribromoacetone, and other related compounds have been found.



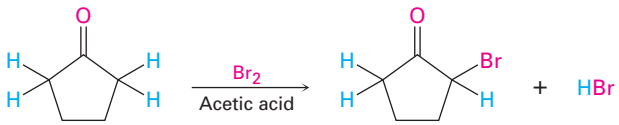
From the Hawaiian alga *Asparagopsis taxiformis*

Worked Example 11.2 Brominating a Ketone

What product would you obtain from the reaction of cyclopentanone with Br_2 in acetic acid?

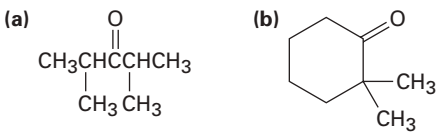
Strategy Locate the α hydrogens in the starting ketone, and replace one of them by Br to carry out an α-substitution reaction.

Solution



Cyclopentanone → **2-Bromocyclopentanone**

Problem 11.4 Show the products you would obtain by bromination of the following ketones:

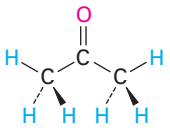


Problem 11.5 Show how you might prepare pent-1-en-3-one from pentan-3-one:

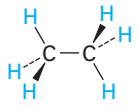
Pentan-3-one → **Pent-1-en-3-one**

11.4 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

As noted in Section 11.1, a hydrogen on the α position of a carbonyl compound is weakly acidic and can be removed by a strong base to give an enolate ion. In comparing acetone ($pK_a = 19.3$) with ethane ($pK_a \approx 60$), for instance, the presence of the carbonyl group increases the acidity of the ketone over the alkane by a factor of 10^{40}.



Acetone
($pK_a = 19.3$)



Ethane
($pK_a \approx 60$)

Why are carbonyl compounds acidic? The reason can be seen by looking at the orbital picture of an enolate ion in Figure 11.3. Abstraction of a proton from a carbonyl compound occurs when an α C–H bond is oriented roughly parallel to the p orbitals of the carbonyl group. The α carbon atom of the enolate ion is sp^2-hybridized and has a p orbital that overlaps the neighboring carbonyl p orbitals. Thus, the negative charge is shared by the electronegative oxygen atom, and the enolate ion is stabilized by resonance.

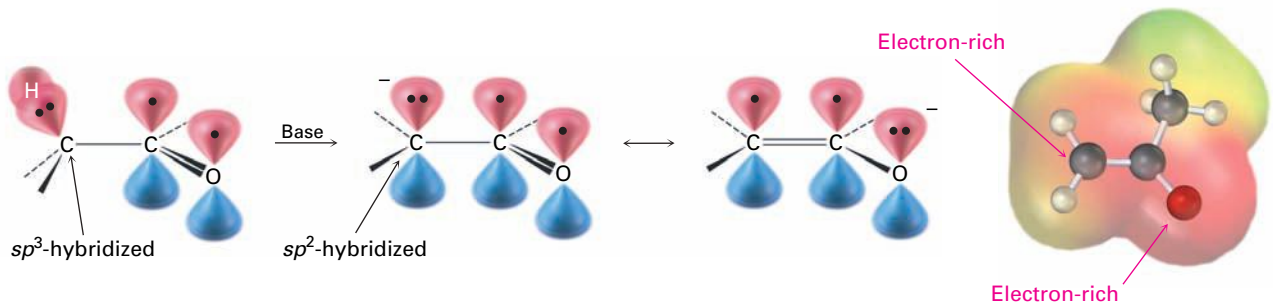


Figure 11.3 Mechanism of enolate ion formation by abstraction of an α hydrogen from a carbonyl compound. The enolate ion is stabilized by resonance and the negative charge (red) is shared by the oxygen and the α carbon atom, as indicated by the electrostatic potential map.

Because carbonyl compounds are only weakly acidic, a strong base is needed to form an enolate ion. If an alkoxide ion, such as sodium ethoxide, is used, ionization of acetone takes place only to the extent of about 0.1% because acetone ($pK_a = 19.3$) is a weaker acid than ethanol ($pK_a = 16$). If, however, a more powerful base such as sodium amide ($Na^+ \ ^-:NH_2$, the sodium salt of ammonia) is used, then a carbonyl compound is completely converted into its enolate ion. In practice, the strong base lithium diisopropylamide, abbreviated LDA, is commonly used. LDA is similar in its basicity to

sodium amide but is more soluble in organic solvents because of its two alkyl groups.

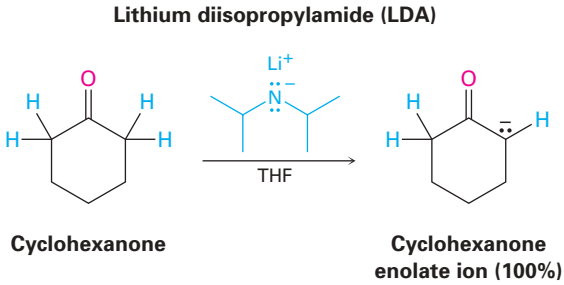


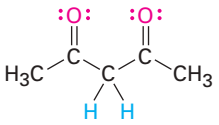
Table 11.1 lists the approximate pK_a values of some different types of carbonyl compounds and shows how these values compare with other common acids. Note that nitriles, too, are acidic and can be converted into enolate-like anions.

Table 11.1 Acidity Constants for Some Carbonyl Compounds

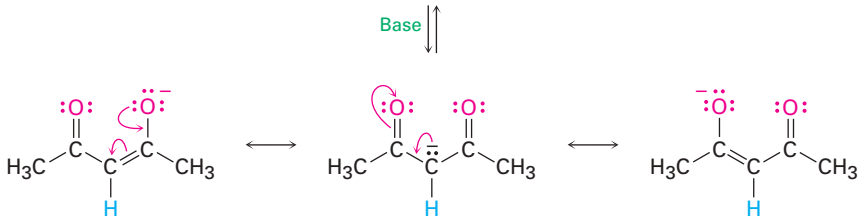
Functional group	Example	pK_a
Carboxylic acid	CH_3COH	5
1,3-Diketone	$CH_3CCH_2CCH_3$	9
3-Keto ester	$CH_3CCH_2COCH_3$	11
1,3-Diester	$CH_3OCCH_2COCH_3$	13
[Alcohol	CH_3OH	16]
Acid chloride	CH_3CCl	16
Aldehyde	CH_3CH	17
Ketone	CH_3CCH_3	19
Thioester	CH_3CSCH_3	21
Ester	CH_3COCH_3	25
Nitrile	$CH_3C{\equiv}N$	25
N,N-Dialkylamide	$CH_3CN(CH_3)_2$	30

When a C–H bond is flanked by *two* carbonyl groups, its acidity is enhanced even more. Thus, Table 11.1 shows that 1,3-diketones (called β-diketones), 3-keto esters (β-keto esters), and 1,3-diesters (malonic esters) are more acidic

than water. The enolate ions derived from these β-dicarbonyl compounds are stabilized by sharing of the negative charge by both neighboring carbonyl oxygens. The enolate ion from pentane-2,4-dione, for instance, has three resonance forms.



Pentane-2,4-dione (pK_a = 9)



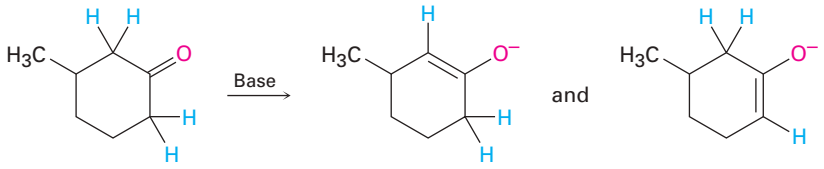
Worked Example 11.3 Forming an Enolate Ion from a Ketone

Draw structures of the two enolate ions you could obtain by reaction of 3-methylcyclohexanone with a strong base.

Strategy

Locate the acidic hydrogens, and remove them one at a time to generate the possible enolate ions. In this case, 3-methylcyclohexanone can be deprotonated either at C2 or at C6.

Solution

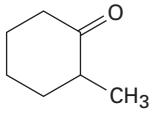


Problem 11.6 Identify all acidic hydrogens in the following molecules:

(a) CH_3CH_2CHO
(b) $(CH_3)_3CCOCH_3$
(c) CH_3CO_2H
(d) $CH_3CH_2CH_2C{\equiv}N$
(e) Cyclohexane-1,3-dione

Problem 11.7 Show the enolate ions you would obtain by deprotonation of the following carbonyl compounds:

(a) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H$ **(b)** $CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3$ **(c)**



Problem 11.8 Draw three resonance forms for the most stable enolate ion you would obtain by deprotonation of methyl 3-oxobutanoate.

$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_3$ **Methyl 3-oxobutanoate**

11.5 Reactivity of Enolate Ions

Enolate ions are more useful than enols for two reasons. First, pure enols normally can't be isolated but are instead generated only as short-lived intermediates in low concentration. By contrast, stable solutions of pure enolate ions are easily prepared from carbonyl compounds by treatment with a strong base. Second, enolate ions are more reactive than enols and undergo many reactions that enols don't. Whereas enols are neutral, enolate ions have a negative charge that makes them much better nucleophiles. Thus, the α position of an enolate ion is electron-rich and highly reactive toward electrophiles.

Because they are resonance hybrids of two nonequivalent forms, enolate ions can be looked at either as vinylic alkoxides (C=C—O$^-$) or as α-keto carbanions ($^-$C—C=O). Thus, enolate ions can react with electrophiles either on oxygen or on carbon. Reaction on oxygen yields an enol derivative, while reaction on carbon yields an α-substituted carbonyl compound (Figure 11.4). Both kinds of reactivity are known, but reaction on carbon is more common.

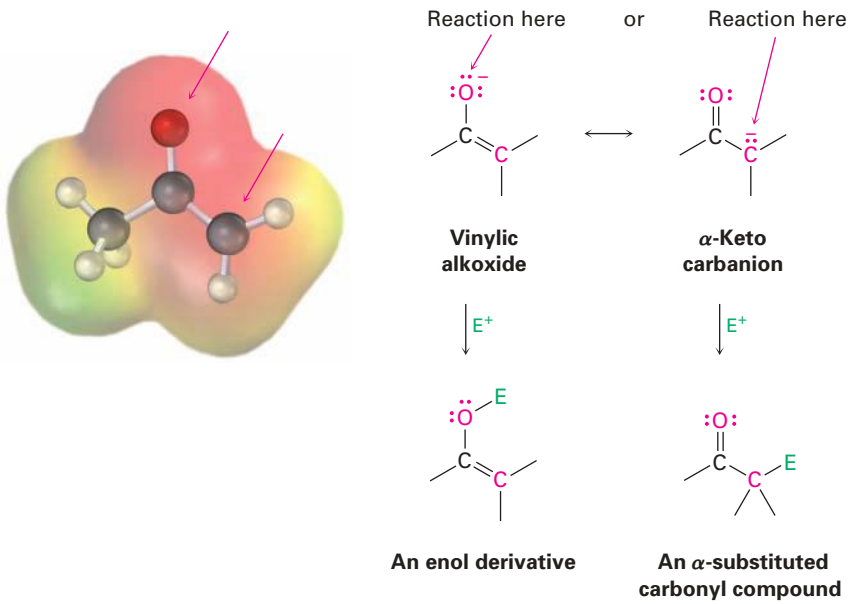
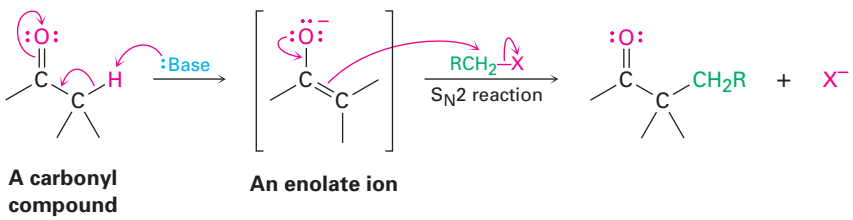


Figure 11.4 The electrostatic potential map of acetone enolate ion shows how the negative charge is delocalized over both the oxygen and the α carbon. As a result, two modes of reaction of an enolate ion with an electrophile E$^+$ are possible. Reaction on carbon to yield an α-substituted carbonyl product is more common.

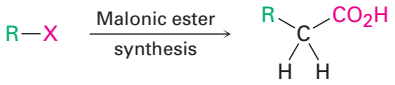
11.6 Alkylation of Enolate Ions

Perhaps the most useful reaction of enolate ions is their **alkylation** by treatment with an alkyl halide, thereby forming a new C–C bond and joining two smaller pieces into one larger molecule. Alkylation occurs when the nucleophilic enolate ion reacts with an electrophilic alkyl halide in an S_N2 reaction, displacing the halide ion in the usual way (Section 7.5).

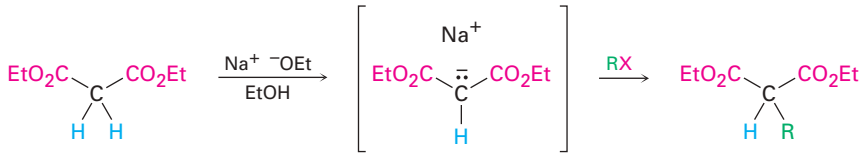


Like all S_N2 reactions, alkylations are successful only when a primary alkyl halide (RCH_2X) or methyl halide (CH_3X) is used, because a competing E2 elimination occurs if a secondary or tertiary halide is used. The leaving group halide can be Cl^-, Br^-, or I^-.

One of the best-known carbonyl alkylation reactions is the **malonic ester synthesis**, a method for preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms.

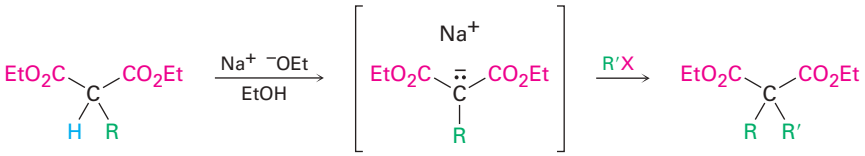


Diethyl propanedioate, commonly called diethyl malonate or *malonic ester,* is relatively acidic ($pK_a = 13$) because its α hydrogen atoms are flanked by two carbonyl groups. Thus, malonic ester is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol. The enolate ion, in turn, is readily alkylated by treatment with an alkyl halide, yielding an α-substituted malonic ester. Note in the following examples that the abbreviation "Et" is used for an ethyl group, $-CH_2CH_3$.



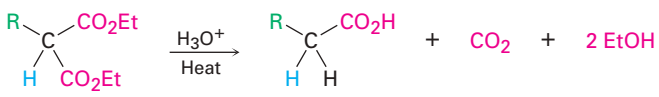
Diethyl propanedioate (malonic ester) | **Sodio malonic ester** | **An alkylated malonic ester**

The product of a malonic ester alkylation has one acidic α hydrogen remaining, so the alkylation process can be repeated to yield a dialkylated malonic ester.



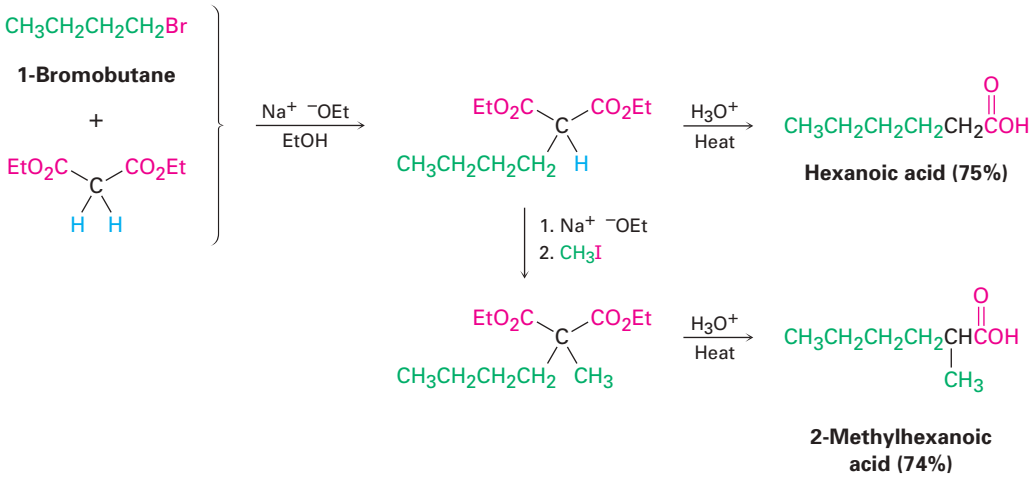
An alkylated malonic ester | **A dialkylated malonic ester**

On heating with aqueous hydrochloric acid, the alkylated (or dialkylated) malonic ester undergoes hydrolysis of its two ester groups followed by *decarboxylation* (loss of CO_2) to yield a substituted monocarboxylic acid. Decarboxylation is a unique feature of compounds like malonic acids that have a second carbonyl group two atoms away from the $-CO_2H$ and is not a general reaction of carboxylic acids.



An alkylated malonic ester | **A carboxylic acid**

The overall result of the malonic ester synthesis is to convert an alkyl halide into a carboxylic acid with a carbon chain that has been lengthened by two atoms ($RX \rightarrow RCH_2CO_2H$).



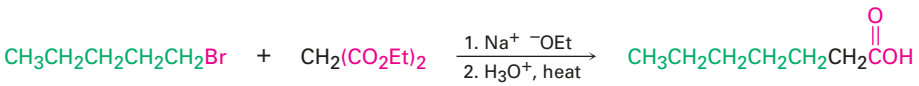
Worked Example 11.4 Using a Malonic Ester Synthesis

How would you prepare heptanoic acid by a malonic ester synthesis?

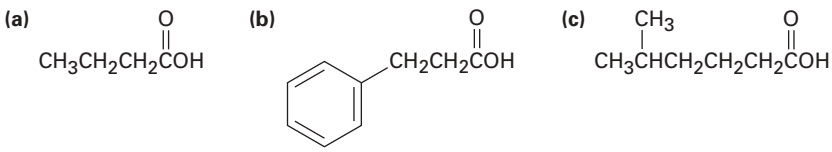
Strategy

The malonic ester synthesis converts an alkyl halide into a carboxylic acid having two more carbon atoms. Thus, a seven-carbon acid chain must be derived from a five-carbon alkyl halide such as 1-bromopentane.

Solution



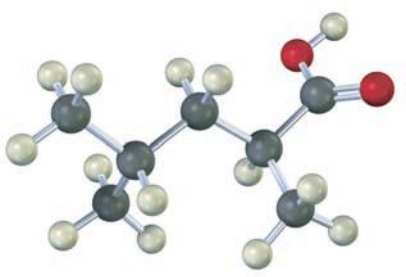
Problem 11.9 What alkyl halide would you use to prepare the following compounds by a malonic ester synthesis?



Problem 11.10 Show how you could use a malonic ester synthesis to prepare the following compounds:

(a) 4-Methylpentanoic acid **(b)** 2-Methylpentanoic acid

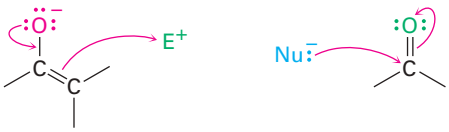
Problem 11.11 Show how you could use a malonic ester synthesis to prepare the following compound:



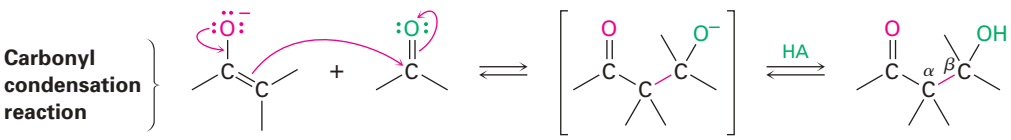
11.7 Carbonyl Condensation Reactions

By this point, we've seen that carbonyl compounds can behave as either electrophiles or nucleophiles. In an α-substitution reaction, the carbonyl compound behaves as a nucleophile after being converted into an enol or enolate ion. In a nucleophilic addition reaction or a nucleophilic acyl substitution reaction, however, the carbonyl group behaves as an electrophile by accepting electrons from an attacking nucleophile.

Carbonyl condensation reactions, the fourth and last general category of carbonyl-group reactions we'll study, involve *both* kinds of reactivity. These reactions take place between two carbonyl partners and involve a combination of nucleophilic addition and α-substitution steps. One partner (the nucleophilic donor) is converted into an enolate ion and undergoes an α-substitution reaction, while the other partner (the electrophilic acceptor) undergoes a nucleophilic addition reaction. There are numerous variations of carbonyl condensation reactions, depending on the two carbonyl partners, but the general mechanism remains the same.



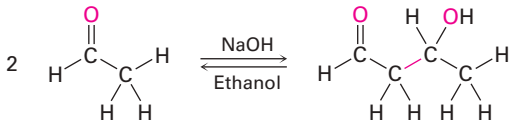
Nucleophilic enolate ion reacts with electrophiles | **Electrophilic carbonyl group reacts with nucleophiles**



Nucleophilic enolate ion | **Electrophilic carbonyl** | **Condensation product**

11.8 Condensations of Aldehydes and Ketones: The Aldol Reaction

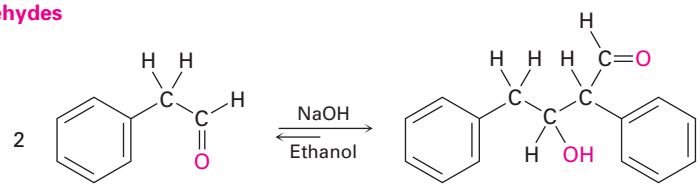
Aldehydes and ketones with an α hydrogen atom undergo a base-catalyzed carbonyl condensation reaction called the **aldol reaction**. The product is a β-hydroxy-substituted carbonyl compound. For example, treatment of acetaldehyde with a base such as sodium ethoxide or sodium hydroxide in a protic solvent leads to rapid and reversible formation of 3-hydroxybutanal, known commonly as *aldol* (*ald*ehyde + alcoh*ol*).



Acetaldehyde — **3-Hydroxybutanal (aldol)**

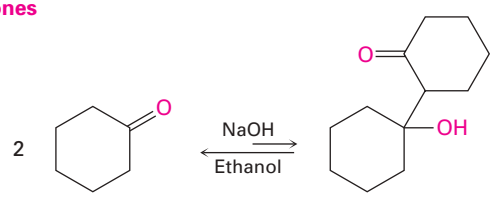
The exact position of the aldol equilibrium depends both on reaction conditions and on substrate structure. The equilibrium generally favors condensation product for aldol reaction of aldehydes with no α substituent (RCH_2CHO) but favors reactant for α-substituted aldehydes (R_2CHCHO) and for ketones.

Aldehydes



Phenylacetaldehyde (10%) — **(90%)**

Ketones



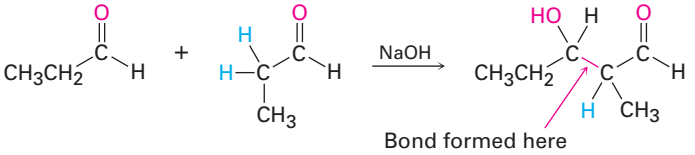
Cyclohexanone (78%) — **(22%)**

Worked Example 11.5 Predicting the Product of an Aldol Reaction

What is the structure of the aldol product derived from propanal?

Strategy An aldol reaction combines two molecules of reactant, forming a bond between the α carbon of one partner and the carbonyl carbon of the second partner.

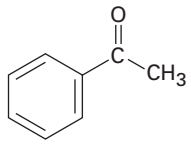
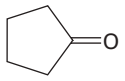
Solution



Problem 11.12 Which of the following compounds can undergo the aldol reaction, and which cannot? Explain.

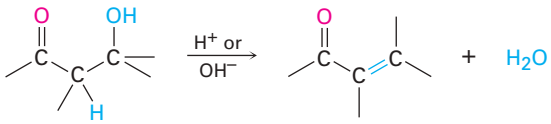
(a) 2,2-Dimethylcyclohexanone **(b)** Benzaldehyde
(c) 2,2,6,6-Tetramethylcyclohexanone **(d)** Formaldehyde

Problem 11.13 Show the product of the aldol reaction of the following compounds:

(a) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H$ **(b)**  **(c)** 

11.9 Dehydration of Aldol Products: Synthesis of Enones

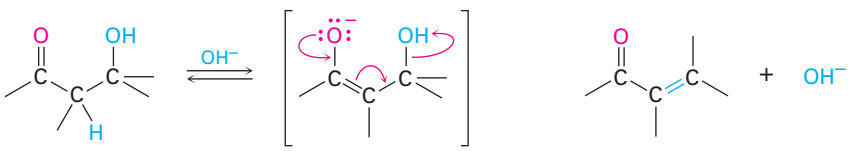
The β-hydroxy aldehydes and β-hydroxy ketones formed in aldol reactions are easily dehydrated to yield α,β-unsaturated products, or conjugated **enones** (*ene* + *one*). In fact, it's this loss of water that gives the aldol *condensation* its name, because water condenses out of the reaction.



A β-hydroxy ketone or aldehyde **A conjugated enone**

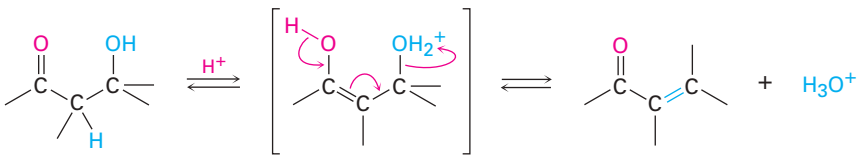
Most alcohols are resistant to dehydration by dilute acid or base because hydroxide ion is a poor leaving group (Section 8.4), but β-hydroxy carbonyl compounds dehydrate easily because of the carbonyl group. Under *basic* conditions, an α hydrogen is abstracted and the resultant enolate ion expels the OH^- leaving group in an E1cB reaction (Section 7.8). Under *acidic* conditions, an enol is formed, the –OH group is protonated, and H_2O is then expelled in an E1 or E2 reaction.

Base-catalyzed



Enolate ion

Acid-catalyzed



Enol

The reaction conditions needed for aldol dehydration are often only a bit more vigorous (slightly higher temperature, for instance) than the conditions

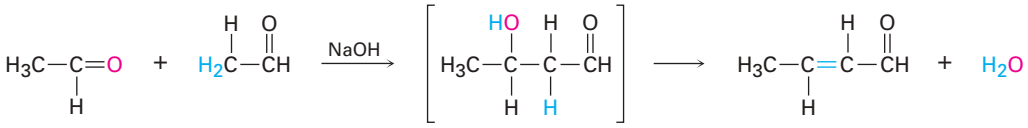
needed for the aldol condensation itself. As a result, conjugated enones are often obtained directly from aldol reactions without isolating the intermediate β-hydroxy carbonyl compounds.

Worked Example 11.6 **Dehydrating an Aldol Condensation Product**

What is the structure of the enone obtained from aldol condensation of acetaldehyde?

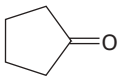
Strategy In the aldol reaction, H_2O is eliminated and a double bond is formed by removing two hydrogens from the acidic α position of one partner and the oxygen from the second partner.

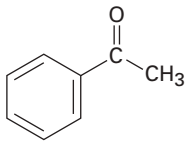
Solution

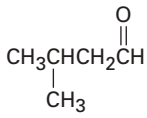


But-2-enal

Problem 11.14 Write the structures of the enone products you would obtain from aldol condensation of the following compounds:

(a) 

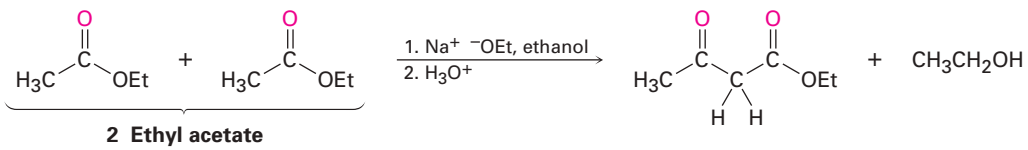
(b) 

(c) 

Problem 11.15 Aldol condensation of butan-2-one leads to a mixture of two enones (ignoring double-bond stereochemistry). Draw them.

11.10 Condensations of Esters: The Claisen Condensation Reaction

Esters, like aldehydes and ketones, are weakly acidic. When an ester with an α hydrogen is treated with a base such as sodium ethoxide, a carbonyl condensation reaction occurs to yield a β-keto ester. For example, ethyl acetate yields ethyl acetoacetate on treatment with base. This reaction between two ester molecules is known as the **Claisen condensation reaction**. We'll use ethyl esters, abbreviated "Et," for consistency, but other esters also work.



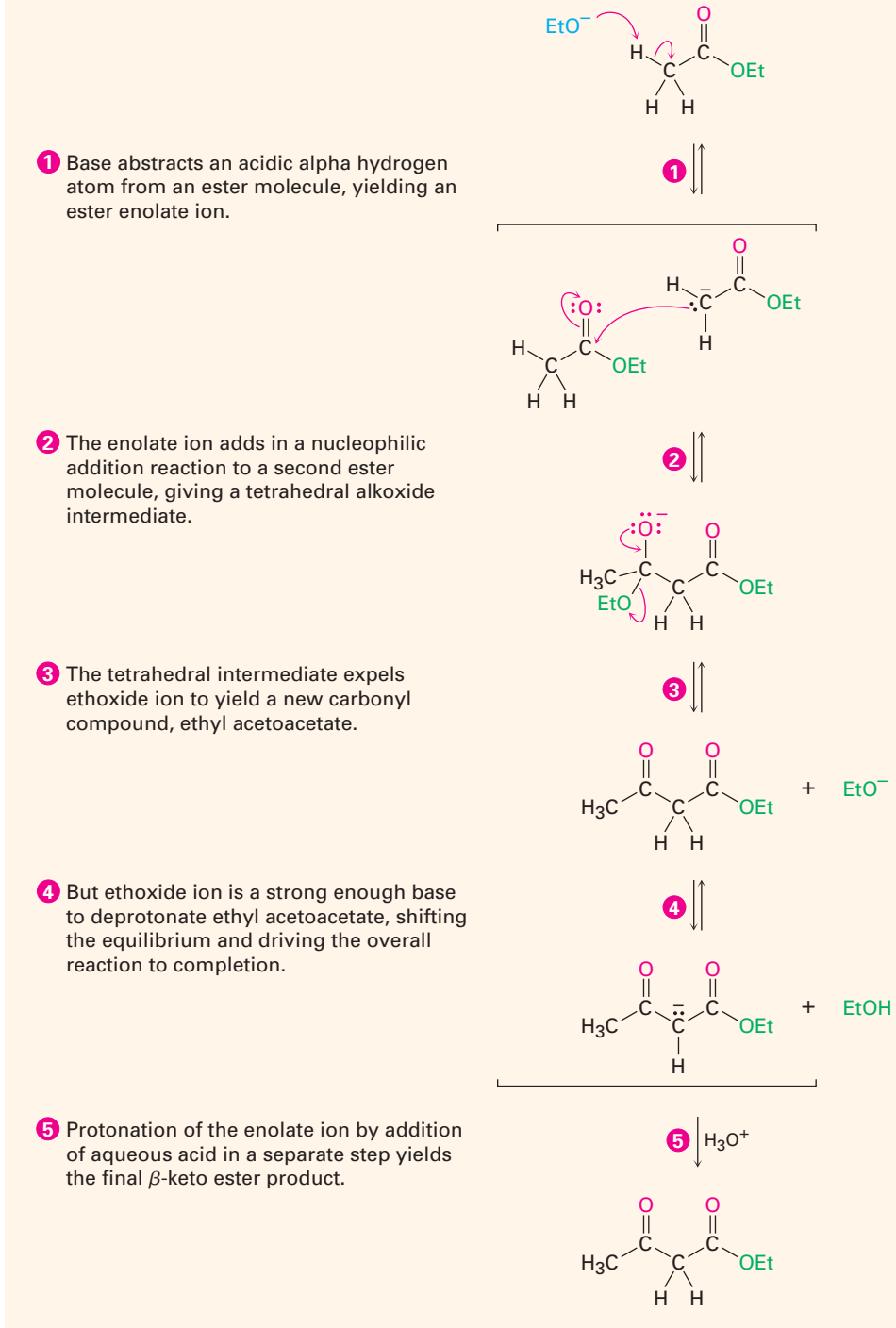
2 Ethyl acetate

Ethyl acetoacetate, a β-keto ester (75%)

The mechanism of the Claisen condensation is similar to that of the aldol condensation and involves the nucleophilic addition of an ester enolate ion to the carbonyl group of a second ester molecule (Figure 11.5). The only

MECHANISM

Figure 11.5 The mechanism of the Claisen condensation reaction.



difference between the aldol condensation of an aldehyde or ketone and the Claisen condensation of an ester involves the fate of the initially formed intermediate. The alkoxide intermediate in the aldol reaction is protonated to give an alcohol product—exactly the behavior previously seen for aldehydes and ketones (Section 9.5). The alkoxide intermediate in the Claisen reaction, however, expels an alkoxide leaving group to yield a nucleophilic acyl substitution product—exactly the behavior previously seen for esters (Section 10.9).

If the starting ester has more than one acidic α hydrogen, the β-keto ester product contains a highly acidic, doubly activated hydrogen atom that can be removed by base. This deprotonation of the product means that a full equivalent of base rather than a catalytic amount must be used in the reaction. The deprotonation drives the equilibrium completely to the product side so that high yields are usually obtained in Claisen condensations.

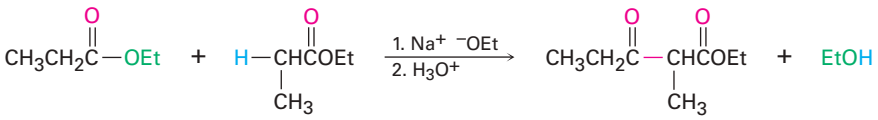
Worked Example 11.7 Predicting the Product of a Claisen Condensation

What product would you obtain from Claisen condensation of ethyl propanoate?

Strategy

The Claisen condensation of an ester results in the loss of one molecule of alcohol and the formation of a β-keto ester product in which an acyl group of one partner bonds to the α carbon of the second partner.

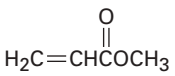
Solution

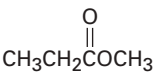


2 Ethyl propanoate — Ethyl 2-methyl-3-oxopentanoate

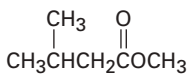
Problem 11.16 Which of the following esters can't undergo Claisen condensation? Explain.

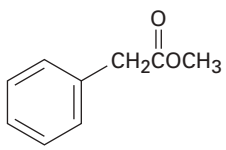
(a) 

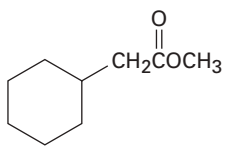
(b) 

(c) 

Problem 11.17 Show the products you would obtain by Claisen condensation of the following esters:

(a) 

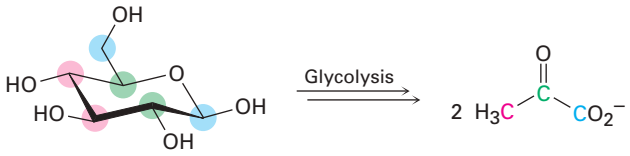
(b) 

(c) 

11.11 Some Biological Carbonyl Reactions

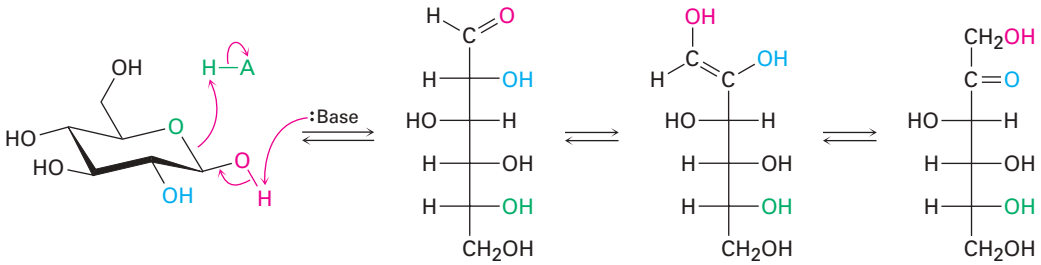
Biochemistry *is* carbonyl chemistry. Almost every metabolic process used by living organisms involves one or more of the four fundamental carbonyl-group reactions we've seen in the past three chapters. The digestion and metabolic breakdown of all the major classes of food molecules—fats, carbohydrates, and proteins—take place by nucleophilic addition reactions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Conversely, hormones and other crucial biological molecules are built up from smaller precursors by these same carbonyl-group reactions.

Take *glycolysis,* for example, the metabolic pathway by which organisms convert glucose to pyruvate as the first step in extracting energy from carbohydrates.



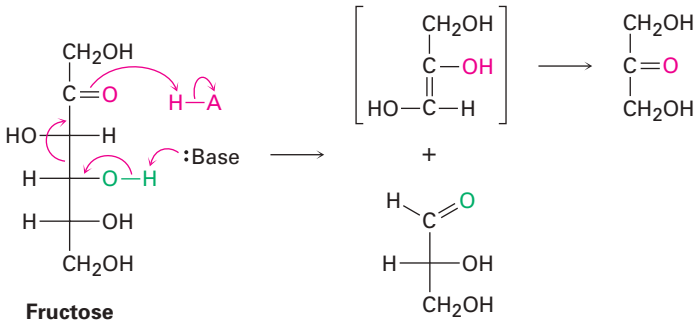
Glucose **Pyruvate**

Glycolysis is a ten-step process that begins with conversion of glucose from its cyclic hemiacetal form to its open-chain aldehyde form—a retro nucleophilic addition reaction. The aldehyde then undergoes tautomerization to yield an enol, which undergoes yet another tautomerization to give the ketone fructose.



Glucose (hemiacetal) **Glucose (aldehyde)** **Glucose (enol)** **Fructose**

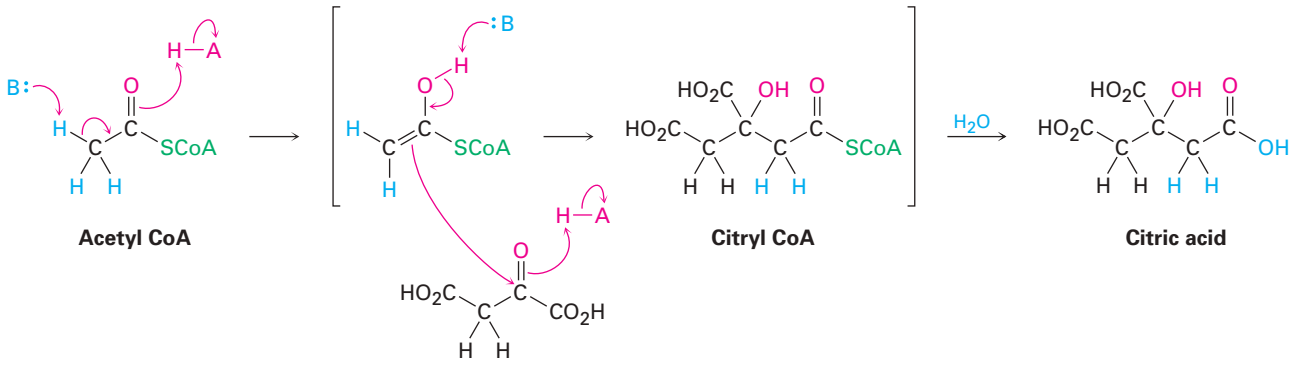
Fructose, a β-hydroxy ketone, is then cleaved into two three-carbon molecules—one ketone and one aldehyde—by a retro aldol reaction. Still further carbonyl-group reactions then occur until pyruvate results.



Fructose

As another example of a biological carbonyl reaction, nature uses the two-carbon acetate fragment of acetyl CoA as a major building block for synthesis.

Acetyl CoA can act not only as an electrophilic acceptor, being attacked by nucleophiles at the carbonyl group, but also as a nucleophilic donor by loss of its acidic α hydrogen. Once formed, the enol or enolate ion of acetyl CoA can add to another carbonyl group in a condensation reaction. For example, citric acid is biosynthesized by nucleophilic addition of acetyl CoA to the ketone carbonyl group of oxaloacetic acid (2-oxobutanedioic acid) in an aldol-like reaction.



Acetyl CoA **Citryl CoA** **Citric acid**

Oxaloacetic acid

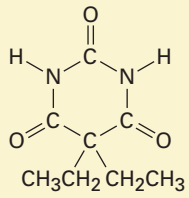
The few examples just given are only an introduction; we'll look at several of the major metabolic pathways and see more carbonyl-group reactions in Chapter 17. A good grasp of carbonyl chemistry is crucial to an understanding of biochemistry.

INTERLUDE

Barbiturates

Different barbiturates come in a multitude of colors, giving rise to similarly colorful street names when the drugs are abused.

Using herbal remedies to treat illness and disease goes back thousands of years, but the medical use of chemicals prepared in the laboratory has a much shorter history. The barbiturates, a large class of drugs with a wide variety of uses, constitute one of the earliest successes of medicinal chemistry. The synthesis and medical use of barbiturates goes back to 1904 when the Bayer company in Germany first marketed a compound called barbital, trade named Veronal, as a treatment for insomnia. Since that time, more than 2500 different barbiturate analogs have been synthesized by drug companies, more than 50 have been used medicinally, and about a dozen are still in use as anesthetics, anticonvulsants, sedatives, and anxiolytics.



Barbital (Veronal), the first barbiturate

The synthesis of barbiturates is relatively simple and relies on reactions that are now familiar: enolate alkylations and nucleophilic acyl substitutions.

continued

INTERLUDE

Starting with diethyl malonate, or malonic ester, alkylation of the corresponding enolate ion with simple alkyl halides provides a wealth of different disubstituted malonic esters. Reaction with urea (H_2NCONH_2) then gives the product barbiturates by a twofold nucleophilic acyl substitution reaction of the ester groups with the $-NH_2$ groups of urea (Figure 11.6). Amobarbital (Amytal), pentobarbital (Nembutal), and secobarbital (Seconal) are typical examples.

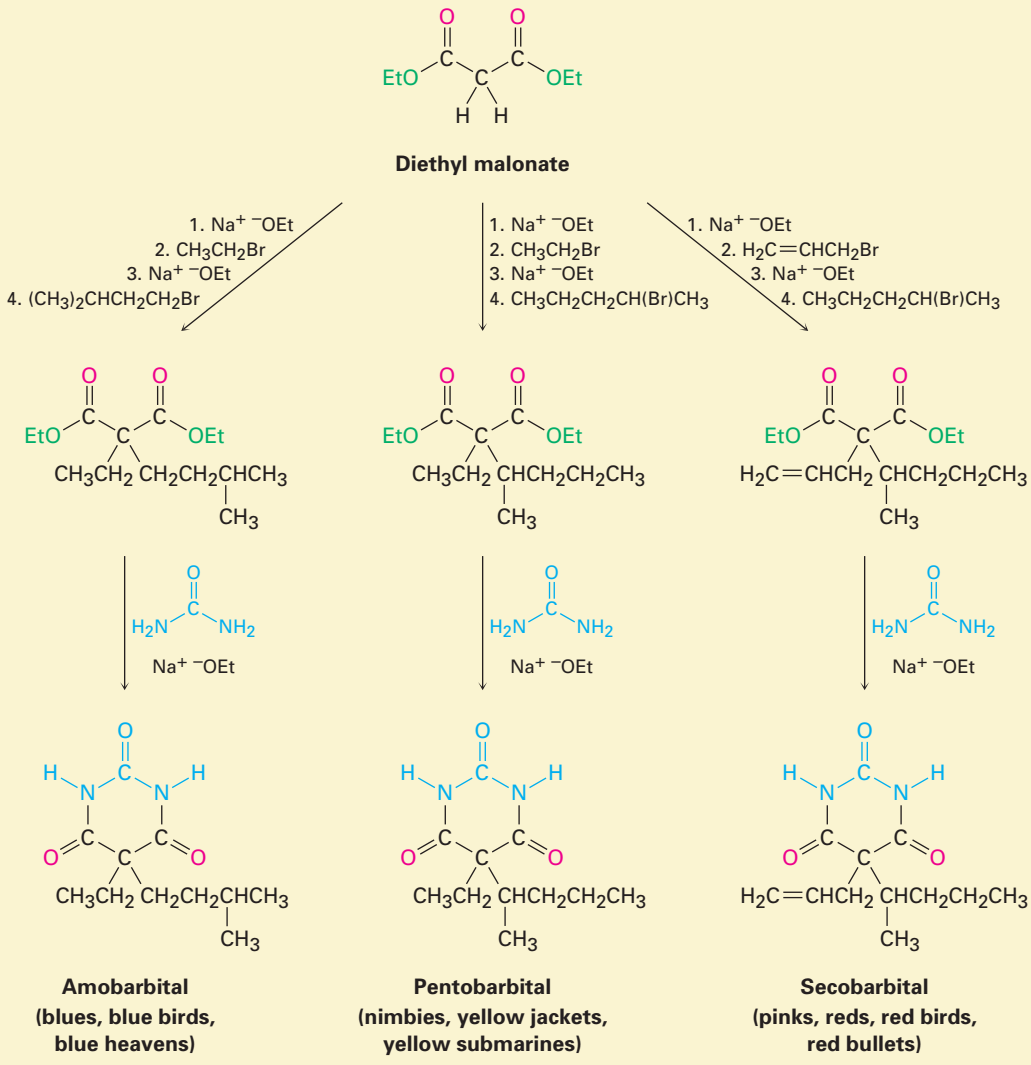


Figure 11.6 The synthesis of barbiturates relies on malonic ester alkylations and nucleophilic acyl substitution reactions. More than 2500 different barbiturates have been synthesized over the past 100 years. In addition to their legal medical uses, some barbiturates are also used illegally as street drugs under many colorful names.

In addition to their prescribed medical uses, many barbiturates have also found widespread illegal use as street drugs. Each barbiturate comes as a tablet of regulated size, shape, and color, and their street names often mimic those colors. Although still used today, most barbiturates have been replaced by safer, more potent alternatives with markedly different structures.

Summary and Key Words

aldol reaction 386
alkylation reaction 382
alpha-substitution reaction 372
carbonyl condensation reaction 373
Claisen condensation reaction 388
enol 373
enolate ion 374
enone 387
malonic ester synthesis 383
tautomers 374

Alpha substitution reactions and **carbonyl condensation** reactions are two of the four fundamental reaction types in carbonyl-group chemistry. Both are used in biosynthetic pathways and in the chemical laboratory for building up larger molecules from smaller precursors. In this chapter, we saw how and why these reactions occur.

Alpha-substitution reactions take place via **enol** or **enolate ion** intermediates and result in the replacement of an α hydrogen atom by another substituent. Carbonyl compounds are in rapid equilibrium with their enols, a process known as *tautomerism*. Enol **tautomers** are normally present to only a small extent, and pure enols usually can't be isolated. Nevertheless, enols react rapidly with a variety of electrophiles. For example, aldehydes and ketones are halogenated by reaction with Cl_2, Br_2, or I_2 in acetic acid solution.

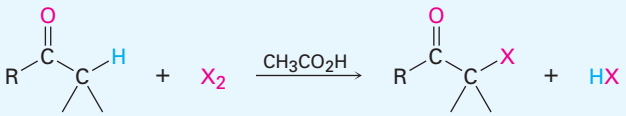
Alpha hydrogen atoms in carbonyl compounds are acidic and can be abstracted by bases to yield enolate ions. Ketones, aldehydes, esters, amides, and nitriles can all be deprotonated. The most important reaction of enolate ions is their S_N2 **alkylation** by reaction with alkyl halides. The nucleophilic enolate ion attacks an alkyl halide, displacing the leaving halide group and yielding an α-alkylated product. The **malonic ester synthesis**, which involves alkylation of diethyl malonate with an alkyl halide, is a good method for preparing a carboxylic acid from an alkyl halide.

A carbonyl condensation reaction takes place between two carbonyl components and involves a combination of nucleophilic addition and α-substitution steps. One carbonyl partner (the nucleophilic donor) is converted into its enolate ion, which then adds to the carbonyl group of the second partner (the electrophilic acceptor).

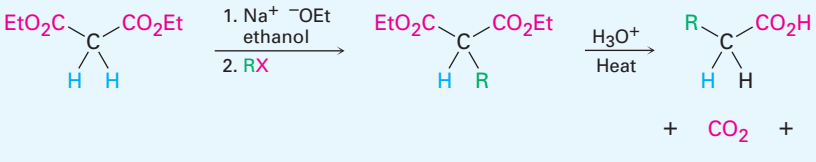
The **aldol reaction** is a carbonyl condensation that occurs between two aldehyde or ketone components. Aldol reactions are reversible, leading first to a β-hydroxy ketone and then to an α,β-unsaturated ketone, or **enone**. The **Claisen condensation reaction** is a carbonyl condensation reaction that occurs between two ester components and leads to a β-keto ester product.

Summary of Reactions

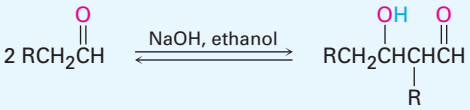
1. Halogenation of aldehydes and ketones (Section 11.3)



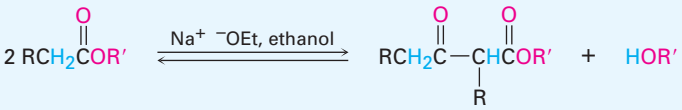
2. Malonic ester synthesis (Section 11.6)



3. Aldol reaction of aldehydes and ketones (Section 11.8)



4. Claisen condensation reaction of esters (Section 11.10)



Exercises

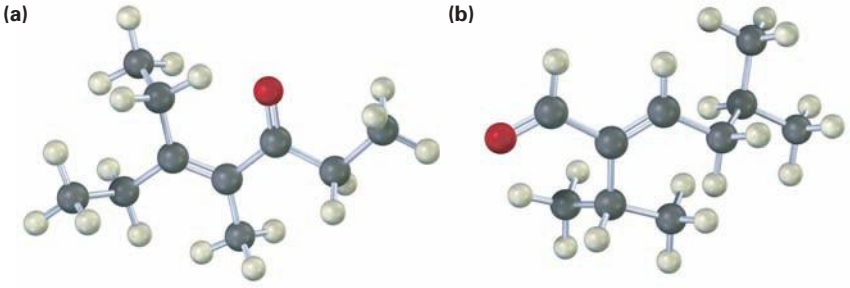
Visualizing Chemistry

(Problems 11.1–11.17 appear within the chapter.)

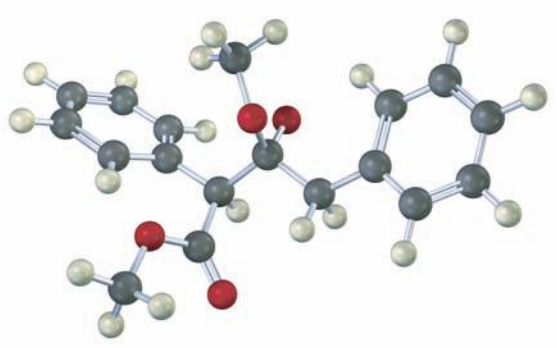
OWL

Interactive versions of these problems are assignable in OWL.

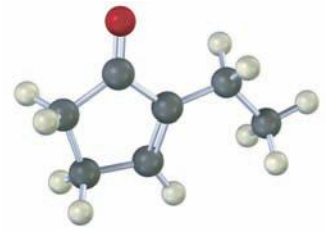
11.18 What aldehydes or ketones might the following enones have been prepared from by aldol reaction?



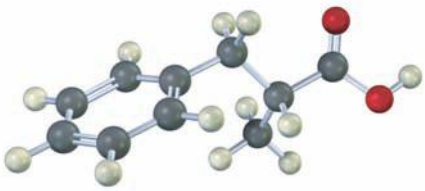
11.19 The following structure represents an intermediate formed by addition of an ester enolate ion to a second ester molecule. Identify the reactant, the leaving group, and the product.



11.20 The following molecule was formed by an *intramolecular* aldol reaction of a *dicarbonyl* compound. Show the structure of the dicarbonyl reactant.



11.21 Show the steps in preparing the following molecule using a malonic ester synthesis:

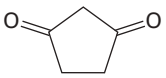


Additional Problems

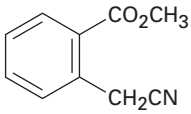
Acidity and Tautomerism

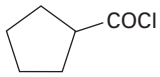
11.22 Indicate all acidic hydrogen atoms in the following molecules:

(a) $CH_3CH_2CHCCH_3$ (O above the second C; CH_3 below the CH)

(b) 

(c) $HOCH_2CH_2CC{\equiv}CCH_3$ (O above the CC)

(d) 

(e) 

(f) $CH_3CH_2CC{=}CH_2$ (O above the CC; CH_3 below the CC)

11.23 Draw structures for the monoenol tautomers of cyclohexane-1,3-dione. How many enol forms are possible, and which would you expect to be most stable? Explain.

11.24 Rank the following compounds in order of increasing acidity:

CH_3CH_2COH, CH_3CCH_3, CH_3CH_2OH, $CH_3CCH_2CCH_3$

11.25 Why do you suppose pentane-2,4-dione is 76% enolized at equilibrium although acetone is enolized only to the extent of about 0.0001%?

11.26 Write resonance structures for the following anions:

(a) $CH_3\overset{\overset{O}{\|}}{C}\overset{\cdot\cdot}{\underset{\cdot\cdot}{C}}H\overset{\overset{O}{\|}}{C}CH_3$ **(b)** $:\bar{C}H_2C{\equiv}N$ **(c)** $CH_3CH{=}CH\overset{\cdot\cdot}{\underset{\cdot\cdot}{C}}H\overset{\overset{O}{\|}}{C}CH_3$

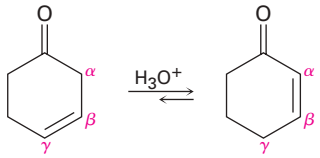
(d) $N{\equiv}\overset{\cdot\cdot}{\underset{\cdot\cdot}{C}}CHCO_2C_2H_5$

11.27 Why is an enolate ion generally more reactive than a neutral enol?

MECHANISMS

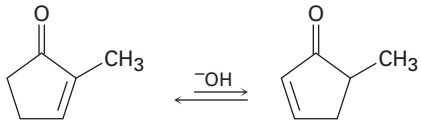
11.28 How do the mechanisms of base-catalyzed enolization and acid-catalyzed enolization differ?

11.29 Nonconjugated β,γ-unsaturated ketones such as cyclohex-3-enone are in an acid-catalyzed equilibrium with their conjugated α,β-unsaturated isomers. Propose a mechanism for the acid-catalyzed interconversion.

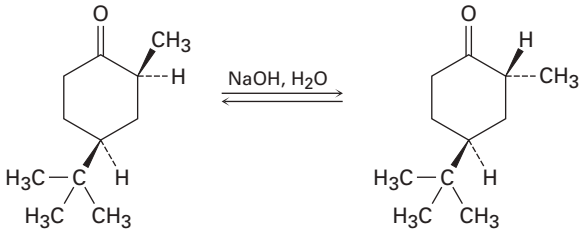


11.30 The α,β to β,γ interconversion of unsaturated ketones (see Problem 11.29) is catalyzed by base as well as by acid. Propose a mechanism.

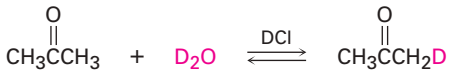
11.31 One consequence of the base-catalyzed α,β to β,γ isomerization of unsaturated ketones (see Problem 11.30) is that C5-substituted cyclopent-2-enones can be interconverted with C2-substituted cyclopent-2-enones. Propose a mechanism for this isomerization.



11.32 How can you account for the fact that *cis*- and *trans*-4-*tert*-butyl-2-methylcyclohexanone are interconverted by base treatment? Which of the two isomers is more stable, and why? (See Section 2.10.)



11.33 When acetone is treated with acid in deuterated water, D_2O, deuterium becomes incorporated into the molecule. Propose a mechanism.



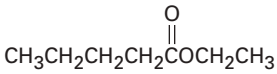
11.34 When optically active (*R*)-2-methylcyclohexanone is treated with aqueous HCl or NaOH, racemic 2-methylcyclohexanone is produced. Explain.

11.35 When optically active (*R*)-3-methylcyclohexanone is treated with aqueous HCl or NaOH, no racemization occurs. Instead, the optically active ketone is recovered unchanged. How can you reconcile this observation with your answer to Problem 11.34?

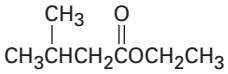
MALONIC ESTER SYNTHESIS

11.36 Which of the following esters can be prepared by a malonic ester synthesis? Show what reagents you would use.

(a)



(b)



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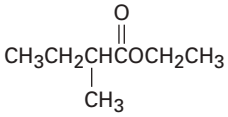
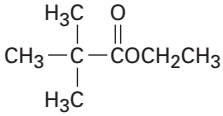
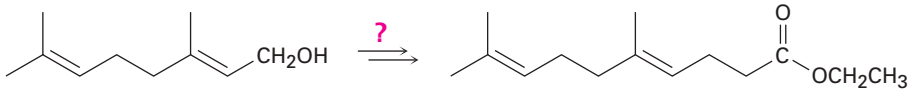


(d)



11.37 By starting with a *dihalide,* cyclic compounds can be prepared using the malonic ester synthesis. What product would you expect to obtain from the reaction of diethyl malonate, 1,4-dibromobutane, and 2 equivalents of base?

11.38 Show how you might convert geraniol, the chief constituent of rose oil, into ethyl geranylacetate.

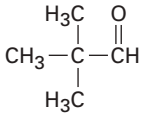


Geraniol **Ethyl geranylacetate**

ALDOL CONDENSATION

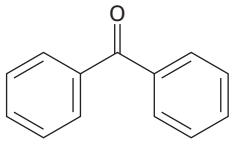
11.39 Which of the following compounds would you expect to undergo aldol condensation? Draw the product in each case.

(a)

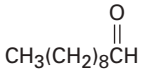


(b)

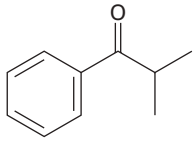
(c)



(d)



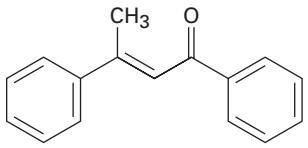
(e)



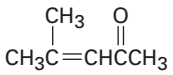
(f)

11.40 How might you prepare the following compounds using an aldol condensation reaction?

(a)



(b)



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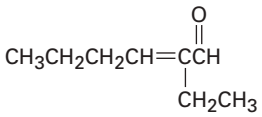
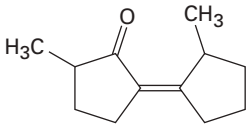


(d)



11.41 The aldol condensation reaction can be carried out intramolecularly by treatment of a diketone with base. What diketone would you start with to prepare 3-methylcyclohex-2-enone? Show the reaction.

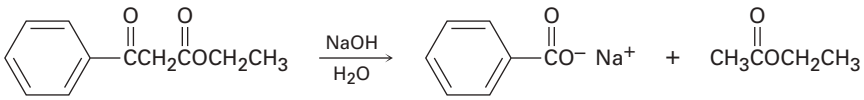
11.42 What product would you expect to obtain from intramolecular aldol condensation of hexanedial, $OHCCH_2CH_2CH_2CH_2CHO$? (See Problem 11.41.)

Claisen Condensation

11.43 If a 1:1 mixture of ethyl acetate and ethyl propanoate is treated with base under Claisen condensation conditions, a mixture of four β-keto ester products is obtained. Show their structures, and explain.

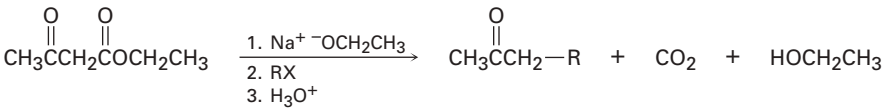
11.44 If a mixture of ethyl acetate and ethyl benzoate is treated with base, a mixture of two Claisen condensation products is obtained. Show their structures, and explain.

11.45 The Claisen condensation is reversible. That is, a β-keto ester can be cleaved by base into two fragments. Show the mechanism by which the following cleavage occurs:



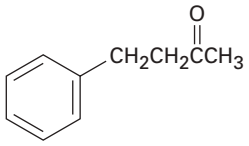
General Problems

11.46 The *acetoacetic ester synthesis* is closely related to the malonic ester synthesis, but involves alkylation with the anion of ethyl acetoacetate rather than diethyl malonate. Treatment of the ethyl acetoacetate anion with an alkyl halide, followed by decarboxylation, yields a ketone product:

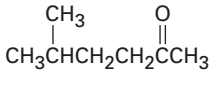


How would you prepare the following compounds using an acetoacetic ester synthesis?

(a)



(b)



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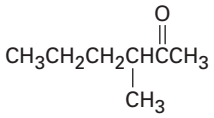
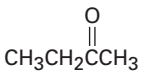
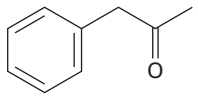
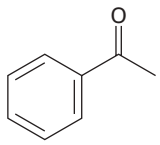
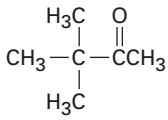


11.47 Which of the following compounds can't be prepared by an acetoacetic ester synthesis (see Problem 11.46)? Explain.

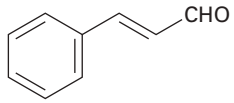
(a) 

(b) 

(c) 

(d) 

11.48 Cinnamaldehyde, the aromatic constituent of cinnamon oil, can be synthesized by a mixed aldol-like reaction between benzaldehyde and acetaldehyde. Formulate the reaction. What other product would you expect to obtain?

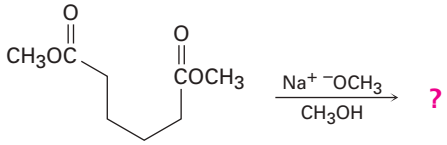


Cinnamaldehyde

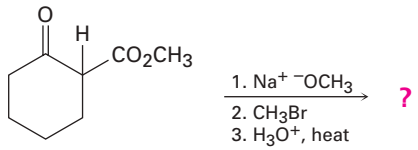
11.49 Butan-1-ol is synthesized commercially from acetaldehyde by a three-step route that involves an aldol reaction followed by two reductions. Show how you might carry out this transformation.

11.50 Monoalkylated acetic acids (RCH_2CO_2H) and dialkylated acetic acids (R_2CHCO_2H) can be prepared by malonic ester synthesis, but trialkylated acetic acids (R_3CCO_2H) can't be prepared. Explain.

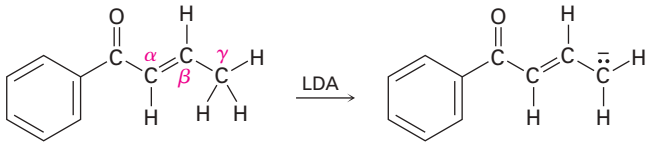
11.51 Just as the aldol condensation can be carried out intramolecularly on a diketone (Problem 11.41), so too can the Claisen condensation be carried out intramolecularly on a diester. Called the *Dieckmann cyclization,* reaction of a diester with base yields a cyclic β-keto ester product. What product would you expect to obtain in the following reaction?



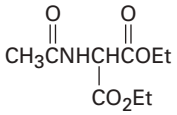
11.52 The cyclic β-keto ester formed in a Dieckmann cyclization reaction (Problem 11.51) can be converted by treatment with base into an anion and alkylated in a process much like that of the acetoacetic ester synthesis (Problem 11.46). Show the product of the following reaction:



11.53 Treatment of an α,β-unsaturated carbonyl compound with base yields an anion by removal of H^+ from the γ carbon. Why are hydrogens on the γ carbon atom acidic?

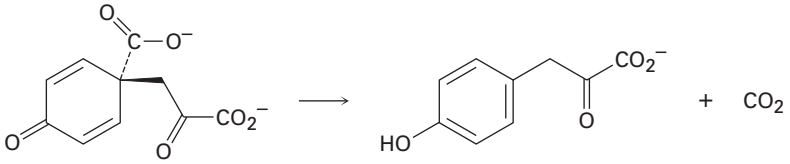


11.54 Amino acids can be prepared by reaction of alkyl halides with diethyl acetamidomalonate, followed by heating the initial alkylation product with aqueous HCl. Show how you would prepare alanine, $CH_3CH(NH_2)CO_2H$, one of the 20 amino acids found in proteins.

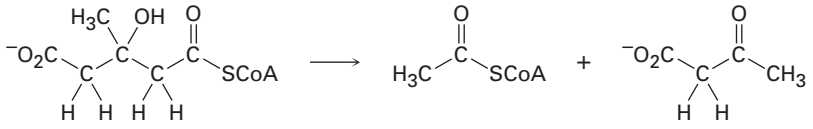


Diethyl acetamidomalonate

11.55 Using curved arrows, propose a mechanism for the following decarboxylation reaction, one of the steps in the biosynthesis of the amino acid tyrosine.

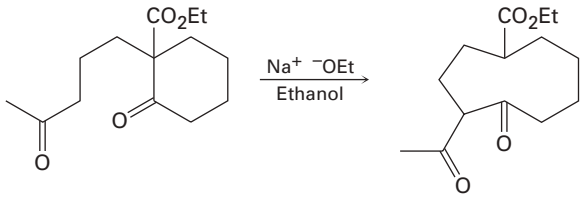


11.56 Leucine, one of the 20 amino acids found in proteins, is metabolized by a pathway that includes the following base-catalyzed step. Propose a mechanism.



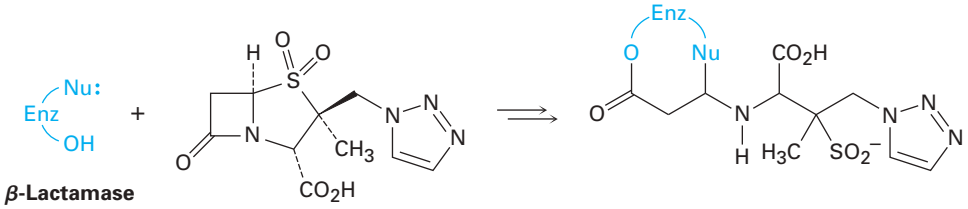
3-Hydroxy-3-methylglutaryl CoA **Acetyl CoA** **Acetoacetate**

11.57 The following reaction occurs in two steps: (1) An intramolecular aldol reaction to yield a cyclic β-hydroxy ketone and (2) a *retro* aldol-like reaction. Write both steps and show their mechanisms.



IN THE MEDICINE CABINET

11.58 Tazobactam inhibits the β-lactamase enzyme that gives many bacteria their resistance to penicillins. It functions by reacting irreversibly with the β-lactamase, thereby trapping and deactivating it.

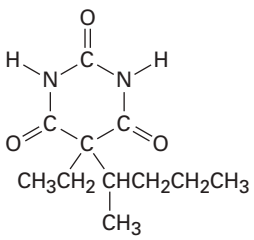


β-Lactamase **Tazobactam** **Trapped β-lactamase**

Formation of the tazobactam-trapped β-lactamase proceeds through the following steps. Show a mechanism for each.

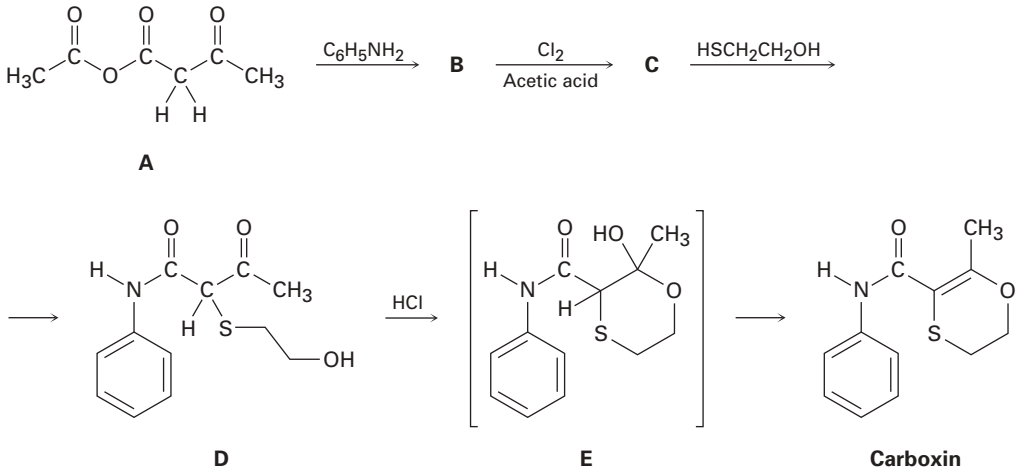
(a) Nucleophilic acyl substitution by a β-lactamase –OH group with tazobactam opens the four-membered cyclic amide (β-lactam) ring.
(b) Formation of an imine (C═N) occurs with expulsion of $-SO_2^-$ as leaving group.
(c) Rearrangement of the imine gives an α,β-unsaturated ester.
(d) Intramolecular conjugate addition by the Nu: group of β-lactamase to the α,β-unsaturated ester gives the final product.

11.59 Pentobarbital, first marketed as Nembutal and still used as an anticonvulsant and sedative, is administered as a racemate. Draw the *R*- and *S*-enantiomers of pentobarbital. Are both enantiomers likely to have the same biological activity?



Pentobarbital

IN THE FIELD **11.60** Carboxin, marketed as Vitavax, is a fungicide used on corn and wheat. A synthesis of carboxin is shown:



(a) Reaction of anhydride **A** with aniline ($C_6H_5NH_2$) gives an amide, **B**. Show the structure of **B** and the mechanism for its formation.

(b) Acid-catalyzed chlorination of **B** gives **C**. Show the structure of **C** and the mechanism for its formation.

(c) What kind of mechanism is involved in the reaction of **C** with $HSCH_2CH_2OH$ to give **D**?

(d) Formation of carboxin from **D** occurs through intermediate **E**. What new functional group appears in this intermediate? Show a mechanism for formation of **E**.

(e) The conversion of **E** to carboxin occurs through an enol intermediate. Show a mechanism for this reaction.