In addition, the carbocation is destabilized by its unfavorable electrostatic interaction with the bond dipole of the carbonyl group—that is, with the partial positive charge on the carbonyl carbon atom.

PROBLEMS

22.16 What product is formed when
(a) phenylacetic acid is treated first with \( \text{Br}_2 \) and one equivalent of \( \text{PBr}_3 \), then with a large excess of ethanol?
(b) propionic acid is treated first with \( \text{Br}_2 \) and one equivalent of \( \text{PBr}_3 \), then with a large excess of ammonia?

22.17 Give the structure of the product expected in each of the following reactions.
(a) \[
\text{CH}_3\text{C} \text{H}_2\text{CCH}_2\text{Br} + \text{pyridine} \rightarrow \text{1-bromo-2-butane}
\]
(b) \[
\text{BrCH}_2\text{C} \text{H} \text{C} \text{H} \text{Ph} + \text{CH}_3\text{C} \text{O}^- \text{Na}^+ \rightarrow \text{\( \alpha \)-bromoacetophenone sodium acetate}
\]

22.18 Give a curved-arrow mechanism for the reaction in Eq. 22.34. Your mechanism should show why two equivalents of NaOH must be used.

22.4 ALDOL ADDITION AND ALDOL CONденСATION

A. Base-Catalyzed Aldol Reactions

In aqueous base, acetaldehyde undergoes a reaction called the aldol addition.

\[
2\text{H}_3\text{C} \text{CH} \xrightarrow{\text{NaOH}, \text{H}_2\text{O}} \text{H}_3\text{C} \text{CH} \xrightarrow{\text{OH}} \text{H}_3\text{C} \text{CH} \text{CH}_2 \text{CH} (50\% \text{ yield})
\]
The term **aldol** is both a traditional name for 3-hydroxybutanal and a generic name for $\beta$-hydroxy aldehydes. An **aldol addition** is a reaction of two aldehyde molecules to form a $\beta$-hydroxy aldehyde. The aldol addition is a very important and general reaction of aldehydes and ketones that have $\alpha$-hydrogens. Notice that this reaction provides another method of forming carbon–carbon bonds.

The base-catalyzed aldol addition involves an **enolate ion** as an intermediate. In this reaction, an enolate ion, formed by the reaction of acetaldehyde with aqueous NaOH, adds to a second molecule of acetaldehyde.

\[
\text{enolate ion} \quad \text{H}_2\text{C}CH\text{O} \quad \text{H}_2\text{C}CH + \text{H}_2\text{O} \quad (22.40a)
\]

The aldol addition is another nucleophilic addition to a carbonyl group. In this reaction, the nucleophile is an enolate ion. The reaction may look more complicated than some additions because of the number of carbon atoms in the product. However, it is not conceptually different from other nucleophilic additions, such as cyanohydrin formation.

**Cyanohydrin formation:**

**Aldol addition:**

- **nucleophile** + **aldehyde**
- **protonation**
- **addition**

\[
\text{H}_2\text{C}CH\text{O} + \text{H}_2\text{C}CH \quad \text{H}_2\text{C}CH\text{O} + \text{H}_2\text{C}CH \quad \text{H}_2\text{C}CH\text{O} + \text{H}_2\text{C}CH \quad (22.41)
\]

**PROBLEM**

22.19 Use the reaction mechanism to deduce the product of the aldol addition reaction of *(a)* phenylacetaldehyde; *(b)* propionaldehyde.

The aldol addition is reversible. Like many other carbonyl addition reactions (Sec. 19.7B), the equilibrium for the aldol addition is more favorable for aldehydes than for ketones.
In this aldol addition reaction of acetone, the equilibrium favors the ketone reactant rather than the addition product, diacetone alcohol. This product can be isolated in good yield only if an apparatus is used that allows the product to be removed from the base catalyst as it is formed.

Under more severe conditions (higher base concentration, or heat, or both), the product of aldol addition undergoes a dehydration reaction.

The sequence of reactions consisting of the aldol addition followed by dehydration, as in Eq. 22.43, is called the aldol condensation. (A condensation is a reaction in which two molecules combine to form a larger molecule with the elimination of a small molecule, in many cases water.)

The term aldol condensation has been used historically to refer to the aldol addition reaction as well as to the addition and dehydration reactions together. To eliminate ambiguity, aldol condensation is used in this text only for the addition-dehydration sequence. The term aldol reactions is used to refer generically to both addition and condensation reactions.

The dehydration part of the aldol condensation is a $\beta$-elimination reaction catalyzed by base, and it occurs in two distinct steps through an enolate-ion intermediate.

This is not a concerted $\beta$-elimination. In this respect, it differs from the E2 reaction. (See Problem 9.16, p. 402.)
A base-catalyzed dehydration reaction of simple alcohols is unknown; ordinary alcohols do not dehydrate in base. However, \( \beta \)-hydroxy aldehydes and \( \beta \)-hydroxy ketones do for two reasons. First, their \( \alpha \)-hydrogens are relatively acidic. Recall that base-promoted \( \beta \)-eliminations are particularly rapid when acidic hydrogens are involved (Secs. 17.3B and 9.5B). Second, the product is conjugated and therefore is particularly stable. To the extent that the transition state of the dehydration reaction resembles the \( \alpha,\beta \)-unsaturated ketone, it too is stabilized by conjugation, and the elimination reaction is accelerated (Hammond’s postulate).

The product of the aldol condensation is an \( \alpha,\beta \)-unsaturated carbonyl compound. The aldol condensation is an important method for the preparation of certain \( \alpha,\beta \)-unsaturated carbonyl compounds. Whether the aldol addition product or the condensation product is formed depends on reaction conditions, which must be worked out on a case-by-case basis. You can assume for purposes of problem-solving, unless stated otherwise, that either the addition product or the condensation product can be prepared.

### Musical History of the Aldol Condensation

Discovery of the aldol condensation is usually attributed solely to Charles Adolphe Wurtz, a French chemist who trained Friedel and Crafts. However, the reaction was first investigated during the period 1864–1873 by Aleksandr Borodin (1833–1887), a Russian chemist who was also a self-taught and proficient musician and composer. (Borodin’s musical themes were used as the basis of songs in the musical *Kismet*.) Borodin found it difficult to compete with Wurtz’s large, modern, well-funded laboratory. Borodin also lamented that his professional duties so burdened him with “examinations and commissions” that he could only compose when he was at home ill. Knowing this, his musical friends used to greet him, “Aleksandr, I hope you are ill today!”

### B. Acid-Catalyzed Aldol Condensation

Aldol condensations are also catalyzed by acid.

\[
2 \text{CH}_3\text{C} = \text{C} = \text{CH}_3 \xrightarrow{\text{acid}} \text{H}_3\text{C} = \text{C} = \text{C} = \text{CH}_3 + \text{H}_2\text{O} \tag{22.45}
\]

Acid-catalyzed aldol condensations, as in this example, generally give \( \alpha,\beta \)-unsaturated carbonyl compounds as products; addition products cannot be isolated.

In acid-catalyzed aldol condensations, the conjugate acid of the aldehyde or ketone is a key reactive intermediate.

\[
\text{H}_3\text{C} = \text{C} = \text{CH}_3 \xleftarrow{\text{H}} \text{H}_3\text{C} + \text{H}_2\text{O} \tag{22.46a}
\]

This protonated ketone plays two roles. First, it serves as a source of the enol, as shown in Eq. 22.17b on p. 1056. Second, the protonated ketone is the electrophilic species in the reaction. It reacts as an electrophile with the \( \pi \) electrons of the enol to give an \( \alpha \)-hydroxy carbocation, which is also the conjugate acid of the addition product.
As the second part of Eq. 22.46b shows, the \( \alpha \)-hydroxy carbocation loses a proton to give the \( \beta \)-hydroxy ketone product. Under the acidic conditions, this material spontaneously undergoes acid-catalyzed dehydration to give an \( \alpha,\beta \)-unsaturated carbonyl compound:

\[
\text{HO} - \text{C} - \text{CH}_2 - \text{C} - \text{CH}_3 + \text{H}_2\text{O} \rightarrow \text{CH}_3 \text{C} = \text{CH} - \text{C} - \text{CH}_3 + \text{H}_2\text{O}
\]

(22.46c)

This dehydration drives the aldol condensation to completion. (Recall that without this dehydration, the aldol condensation of ketones is unfavorable; Eq. 22.42).

Let’s contrast the species involved in the acid- and base-catalyzed aldol reactions. An enol, not an enolate ion, is the nucleophilic species in an acid-catalyzed aldol condensation. Enolate ions are too basic to exist in acidic solution. Although an enol is much less nucleophilic than an enolate ion, it reacts at a useful rate because the protonated carbonyl compound (an \( \alpha \)-hydroxy carbocation) with which it reacts is a potent electrophile. In a base-catalyzed aldol reaction, an enolate ion is the nucleophile. A protonated carbonyl compound is not an intermediate because it is too acidic to exist in basic solution. The electrophile that reacts with the enolate ion is a neutral carbonyl compound. To summarize:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Nucleophile</th>
<th>Electrophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-catalyzed aldol reaction</td>
<td>enolate ion</td>
<td>neutral carbonyl compound</td>
</tr>
<tr>
<td>Acid-catalyzed aldol condensation</td>
<td>enol</td>
<td>protonated carbonyl compound</td>
</tr>
</tbody>
</table>

C. Special Types of Aldol Reactions

Crossed Aldol Reactions  The preceding discussion considered only aldol reactions between two molecules of the same aldehyde or ketone. When two different carbonyl compounds are used, the reaction is called a crossed aldol reaction. In many cases, the result of a crossed aldol reaction is a difficult-to-separate mixture, as Study Problem 22.1 illustrates.
Study Problem 22.1
Give the structures of the aldol addition products expected from the base-catalyzed reaction of acetaldehyde and propionaldehyde.

Solution Such a reaction involves four different species: acetaldehyde (A) and its enolate ion (A'), as well as propionaldehyde (P) and its enolate ion (P'):

\[
\begin{align*}
A & : \text{CH}_3\text{CH} = \text{CHO} \\
A' & : \text{CH}_3\text{C} = \text{CHO} \\
P & : \text{CH}_3\text{CH}_2\text{CH} = \text{CHO} \\
P' & : \text{CH}_3\text{C} = \text{CHO}
\end{align*}
\]

Four possible addition products can arise from the reaction of each enolate ion with each aldehyde:

\[
\begin{align*}
A + A' & \rightarrow \text{CH}_3\text{CHCH}_2\text{CH} = \text{O} \\
P + A' & \rightarrow \text{CH}_3\text{CH}_2\text{CHCH} = \text{O} \\
A + P' & \rightarrow \text{CH}_3\text{CHCH}_2\text{CH} = \text{O} \\
P + P' & \rightarrow \text{CH}_3\text{C} = \text{CHO}
\end{align*}
\]

(Be sure you see how each product is formed; write a mechanism for each, if necessary.) Notice also a further complication: diastereomers are possible for the last two products because each has two asymmetric carbons.

Crossed aldol reactions that provide complex mixtures, such as the one in Study Problem 22.1, are not very useful because the product of interest is not formed in very high yield, and because isolation of one product from a complex mixture is in most cases extremely tedious. Although conditions that favor one product or another in crossed aldol reactions have been worked out in specific cases, as a practical matter, under the usual conditions (aqueous or alcoholic acid or base), useful crossed aldol reactions are limited to situations in which a ketone with α-hydrogens is condensed with an aldehyde that has no α-hydrogens. An important example of this type is the Claisen–Schmidt condensation. In a Claisen–Schmidt condensation, a ketone with α-hydrogens—acetone in the following example—is condensed with an aromatic aldehyde that has no α-hydrogens—benzaldehyde in this case.

\[
\text{PhCH} = \text{O} + \text{H}_2\text{C} = \text{C} = \text{CH}_3 \xrightarrow{\text{aq. NaOH}} \text{PhCH} = \text{C} = \text{C} = \text{CH}_3 + \text{H}_2\text{O} \quad (22.47)
\]

benzaldehyde acetone (excess)

(4-phenyl-3-buten-2-one)

(65–78% yield)

Notice that the addition product cannot be isolated in this reaction; the highly conjugated condensation product is formed as its most stable stereoisomer—the trans isomer in Eq. 22.47.

In view of the complex mixture obtained in the example used in Study Problem 22.1, it is reasonable to ask why only one product is obtained from the crossed aldol condensation in Eq. 22.47. The analysis of this case highlights several important principles of carbonyl–compound
reactivity. First, because the aldehyde in the Claisen–Schmidt reaction has no \( \alpha \)-hydrogens, it cannot act as the enolate component of the aldol condensation; consequently, two of the four possible crossed aldol products cannot form. The other possible side reaction is the aldol addition reaction of the ketone with itself, as in Eq. 22.42; why doesn’t this reaction occur? The enolate ion from acetone can react either with another molecule of acetone or with benzaldehyde. Recall that addition to a ketone occurs more slowly than addition to an aldehyde (Sec. 19.7C). Furthermore, even if addition to acetone does occur, the aldol addition reaction of two ketones is reversible (Eq. 22.42) and addition to an aldehyde has a more favorable equilibrium constant than addition to a ketone (Sec. 19.7B). Thus, in Eq. 22.47, both the rate and equilibrium for addition to benzaldehyde are more favorable than they are for addition to a second molecule of acetone. Thus, the product shown in Eq. 22.47 is the only one formed.

The Claisen–Schmidt condensation, like other aldol condensations, can also be catalyzed by acid.

A great deal of research has been devoted to finding solutions to the “crossed aldol” problem, particularly in the reactions of aldehydes with the enolate ions derived from ketones. Some of this work is described in Further Exploration 22.1.

**Intramolecular Aldol Condensation** When a molecule contains more than one aldehyde or ketone group, an intramolecular reaction (a reaction within the same molecule) is possible. In such a case, the aldol condensation results in formation of a ring. Intramolecular aldol condensations are particularly favorable when five- and six-membered rings can be formed because of the proximity effect (Sec. 11.7).

**PROBLEMS**

22.20 Predict the product(s) in each of the following aldol condensations.

(a) \( \text{Ph} \text{CH} = \text{O} + \text{H}_{3}\text{C} \rightarrow \text{C} \rightarrow \text{Ph} \xrightarrow{\text{H}_{2}\text{SO}_{4} / \text{CH}_{3}\text{CO}_{2}\text{H}} \text{Ph} \text{CH} = \text{C} \rightarrow \text{Ph} \) (95% yield)

(b) \( \text{PhCH} = \text{O} + \text{H}_{3}\text{C} \rightarrow \text{C} \rightarrow \text{CH}_{3} \xrightarrow{1) \text{NaOH} \ 2) \text{H}_{2}\text{O}^*} \)

(c) \( \text{Acetophenone} + \text{Hexanal} \xrightarrow{\text{NaOH}} \)

(d) \( \text{KOH} \)
22.21 A reverse aldol addition is an important step in the glycolytic pathway, the process by which hexoses (six-carbon sugars) are metabolized as energy sources. The following reaction is catalyzed by the enzyme aldolase.

\[
\begin{align*}
\text{fructose 1,6-diphosphate} & \quad \text{aldolase (an enzyme)} \\
\text{dihydroxyacetone phosphate} & \quad \text{glyceraldehyde-3-phosphate}
\end{align*}
\]

Give a curved-arrow mechanism for this reaction, using B as a base catalyst (which is part of the enzyme) and \( ^+\text{BH} \) as its conjugate acid.

D. Synthesis with the Aldol Condensation

The aldol condensation can be applied to the synthesis of a wide variety of \(\alpha,\beta\)-unsaturated aldehydes and ketones, and it is also another method for the formation of carbon–carbon bonds. (See the complete list in Appendix VI.) If you want to prepare a particular \(\alpha,\beta\)-unsaturated aldehyde or ketone by the aldol condensation, you must ask two questions: (1) What starting materials are required in the aldol condensation? (2) With these starting materials, is the aldol condensation of these compounds a feasible one?

The starting materials for an aldol condensation can be determined by mentally “splitting” the \(\alpha,\beta\)-unsaturated carbonyl compound at the double bond:

\[
\begin{align*}
\text{this portion is derived} & \quad \text{from the carbonyl} \\
\text{compound that reacts} & \quad \text{with the enolate} \\
\text{or enol} & \quad \text{implying}
\end{align*}
\]

\[
\begin{align*}
\text{this portion is derived} & \quad \text{from the enolate ion} \\
\text{or enol} & \quad \text{or enol}
\end{align*}
\]

That is, work backward from the desired synthetic objective by replacing the double bond on the carbonyl side by two hydrogens and on the other side by a carbonyl oxygen (\(\equiv\text{O}\)) to obtain the structures of the starting materials in the aldol condensation.

Knowing the potential starting materials for an aldol condensation is not enough; you must also know whether the condensation is one that works, or whether instead it is one that is likely
to give troublesome mixtures. (Review Study Problem 4.9 on p. 153). In other words, you can’t make every conceivable \(\alpha,\beta\)-unsaturated aldehyde or ketone by the aldol condensation—only certain ones. This point is illustrated in Study Problem 22.2.

### Study Problem 22.2

Determine whether the following \(\alpha,\beta\)-unsaturated ketone can be prepared by an aldol condensation.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{C} &= \text{CH} \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
\text{H}_3\text{C} & \quad \\
\end{align*}
\]

**Solution** Following the procedure in Eq. 22.50, analyze the desired product as follows:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{C} &= \text{CH} \quad \text{C} \quad \text{CH}_2\text{CH}_3 & \Rightarrow & \text{H}_3\text{C} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{C} &= \text{O} + \text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_2\text{CH}_3 \\
\text{acetone} & \quad \text{required starting materials} & \text{2-butane} \\
\end{align*}
\]

The desired product requires a crossed condensation between two similar ketones: acetone and 2-butane. The question, then, is whether the desired product is the only one that could form, or whether other competing aldol reactions would occur.

First, either acetone and 2-butane could serve as either the enolate component or the carbonyl component of the aldol addition, and there is no reason to presume that the desired reaction will be the only one observed. (This situation is analogous to the one presented in Study Problem 22.1.) To complicate matters even more, 2-butane has two nonequivalent \(\alpha\)-carbons at which enolate ions (or enols) could form. This opens yet other possibilities for aldol reactions and thus for complex product mixtures. Hence, the reaction of acetone and 2-butane would not be useful for preparing the desired ketone because a large number of constitutionally isomeric products would be expected.

### Problems

22.22 Some of the following molecules can be synthesized in good yield using an aldol condensation. Identify these and give the structures of the required starting materials. Others cannot be synthesized in good yield by an aldol condensation. Identify these, and explain why the required aldol condensation would not be likely to succeed.

(a) 
\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{C} & \quad \text{CH} \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{C}\text{H}_3 \\
\text{CH}_3 & \quad \\
\end{align*}
\]

(b) 
\[
\begin{align*}
\text{CH} & \quad \text{C} \quad \text{C} \quad \text{CH}_2\text{C}\text{H}_3 \\
\text{CH}_3 & \quad \\
\end{align*}
\]
22.23 Analyze the aldol condensation in Eq. 22.49 on p. 1069 using the method given in Eq. 22.50. Show that four possible aldol condensation products might in principle result from the starting material. Explain why the observed product is the most reasonable one.

22.5 CONDENSATION REACTIONS INVOLVING ESTER ENOLATE IONS

With this section, we begin the use of more compact abbreviations for several commonly occurring organic groups. These abbreviations, shown in Table 22.1, not only save space but also make the structures of large molecules less cluttered and easier to read. Just as Ph— is used to symbolize the phenyl ring, Me— can be used for methyl, Et— for ethyl, Pr— for propyl, and so on. Thus, ethyl acetate is abbreviated EtOAc; sodium ethoxide (Na$^+$ $\text{OC}_2\text{H}_5$) is simply written as NaOEt; and methanol is abbreviated as MeOH.

PROBLEM 22.24 Write the structure that corresponds to each of the following abbreviations. (See Table 22.1.)
(a) Et$_3$C—OH  (b) i-Pr—Ph  (c) i-BuOAc
(d) Pr—OH  (e) Ac$_2$O  (f) Ac—Ph

A. Claisen Condensation

The base-catalyzed aldol reactions discussed in the previous section involve enolate ions derived from aldehydes and ketones. This section discusses condensation reactions that involve the enolate ions of esters.

Ethyl acetate undergoes a condensation reaction in the presence of one equivalent of sodium ethoxide in ethanol to give ethyl 3-oxobutanoate, which is known commonly as ethyl acetoacetate.

\[
\text{ethyl acetate} \xrightarrow{\text{NaOEt, EtOH}} \text{ethyl acetoacetate} \quad (75\text{–}76\% \text{ yield})
\]