A. Conjugate Addition to α,β-Unsaturated Carbonyl Compounds

The conjugated arrangement of C═C and C═O bonds endows α,β-unsaturated carbonyl compounds with unique reactivity, which is illustrated by the reaction of an α,β-unsaturated ketone with HCN.

\[
\text{Ph} \text{C} \text{C} \text{Ph} + \text{HCN} \xrightarrow{35 \degree \text{C} \text{E} \text{O} \text{H}} \text{Ph} \text{C} \text{C} \text{Ph} \text{CN} \quad (\text{trans isomer}) \quad \frac{\text{Na}^+ \cdot \text{CN}}{\text{EtOH}} \quad (93\% \text{ yield})
\]

In this reaction, the elements of HCN appear to have added across the C═C bond. Yet this is not a reaction of ordinary double bonds:

\[
\text{CH}_3\text{CH}═\text{CH}_2 + \text{HCN} \xrightarrow{\text{Na}^+ \cdot \text{CN} \text{EtOH}} \text{no reaction} \quad (22.77)
\]

Nucleophilic addition to the double bond in an α,β-un saturated carbonyl compound occurs because it gives a resonance-stabilized enolate ion intermediate:

\[
\begin{align*}
\text{Ph} \text{C} \text{C} \text{Ph} & \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \\
\text{enolate ion} & \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph}} \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}}
\end{align*}
\]

(Nucleophilic addition to the alkene in Eq. 22.77, in contrast, would give a very unstable alkyl anion.) The enolate ion can be protonated on either oxygen or carbon. In either case, a carbonyl group is eventually regenerated because enols spontaneously form carbonyl compounds (Sec. 22.2). The overall result of the reaction is net addition to the double bond.

\[
\begin{align*}
\text{Ph} \text{C} \text{C} \text{Ph} & \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \\
\text{enolate ion} & \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}}
\end{align*}
\]

(22.78a)

\[
\begin{align*}
\text{Ph} \text{C} \text{C} \text{Ph} & \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \\
\text{enolate ion} & \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}} \quad \xrightarrow{\text{Ph} \text{C} \text{C} \text{Ph} \text{CN}}
\end{align*}
\]

(22.78b)
Nucleophilic addition to the carbon–carbon double bonds of α,β-unsaturated aldehydes, ketones, esters, and nitriles is a rather general reaction that can be observed with a variety of nucleophiles. Some additional examples follow; try to write the mechanisms of these reactions.

**Conjugate additions to α,β-unsaturated esters:**

\[
\text{ethyle crotonate} + \text{Na}^+ \text{CN} \xrightarrow{\text{heat}} \text{ethyl } \beta\text{-cyanobutyrate} + \text{Na}^+ \text{EtOH/H}_2\text{O} \quad (\text{ester saponification})
\]

\[
\text{sodium } \beta\text{-cyanobutyrate} \xrightarrow{\text{H}_2\text{O}^+} \alpha\text{-methylsuccinic acid} \quad (66–70\% \text{ yield})
\]

\[
\text{(CH}_3\text{)}_2\text{SH} + \text{H}_2\text{C}==\text{CH}==\text{CO}_2\text{Me} \xrightarrow{\text{NaOMe}} \text{(CH}_3\text{)}_2\text{S}==\text{CH}_2==\text{CH}_2==\text{CO}_2\text{Me} \quad (97\% \text{ yield})
\]

**Conjugate addition to an α,β-unsaturated ketone:**

\[
\text{CONJUGATE ADDITION REACTIONS CONJUGATE ADDITION REACTIONS}
\]

**Conjugate addition to an α,β-unsaturated nitrile:**

\[
\text{methanethiol} + \text{H}_2\text{C}==\text{CH}==\text{CN} \xrightarrow{\text{NaOMe MeOH}} \text{CH}_2\text{S}==\text{CH}_2==\text{CH}_2==\text{CN} \quad (91\% \text{ yield})
\]

Notice that the addition of cyanide in Eq. 22.79 forms a new carbon–carbon bond, and that the nitrile group can then be converted into a carboxylic acid group by hydrolysis. The addition of a nucleophile to acrylonitrile (as in Eq. 22.82) is a useful reaction called cyanoethylation.
Because quinones (Sec. 18.7) are $\alpha,\beta$-unsaturated carbonyl compounds, they also undergo similar conjugate-addition reactions.

$$\text{quinone} + \text{CH}_3\text{SH} \xrightarrow{0^\circ \text{C}} \text{MeOH} \quad \text{enol}$$

In this example, the reaction is driven to completion by enolization of the ketone in brackets to the phenol, which is aromatic. (See Eq. 22.14, p. 1054; and see also the sidebar, “Poison Ivy and Itchy Quinones,” on p. 866, for a similar case.)

The preceding examples occur under basic or neutral conditions, but acid-catalyzed additions to the carbon–carbon double bonds of $\alpha,\beta$-unsaturated carbonyl compounds are also known.

$$\text{H}_2\text{C}==\text{CH} \text{CO}_2\text{Me} + \text{HBr} \xrightarrow{\text{Et}_3\text{O}} \text{Br}\text{CH}_2\text{CH}_2\text{CO}_2\text{Me} \quad \text{methyl acrylate} \quad \text{methyl } \beta\text{-bromopropionate}$$

$$\text{H}_2\text{C}==\text{CH}==\text{CH}==\text{O} + \text{HCl} \xrightarrow{-15^\circ \text{C}} \text{Cl}\text{CH}_2\text{CH}_2==\text{CH}==\text{O} \quad \text{(80–84% yield)}$$

Although such reactions appear to be nothing more than simple additions to the carbon–carbon double bond, this is not the case. The more basic site of an $\alpha,\beta$-unsaturated carbonyl compound is not the double bond, but rather the carbonyl oxygen. Protonation on the carbonyl oxygen is followed by a reaction with the halide ion. The electrophilic oxygen can accept electrons as a result of a nucleophilic reaction of the halide ion either at the carbonyl carbon or, because of the conjugated arrangement of $\pi$ bonds, at the $\beta$-carbon:

$$\text{H}_2\text{C}==\text{CH}==\text{CH}==\text{O} + \text{H}_2\text{C}==\text{CH}==\text{CH}==\text{O} \rightarrow \text{H}_2\text{C}==\text{CH}==\text{CH}==\text{O}$$

(22.86)
A reaction of \( \text{Br}^- \) at the carbonyl carbon yields a relatively unstable tetrahedral addition intermediate; a reaction at the \( \beta \)-carbon yields an enol, which rapidly reverts to the observed carbonyl product.

An addition to the double bond of an \( \alpha,\beta \)-unsaturated carbonyl compound is an example of conjugate addition. The mechanism of the conjugate addition of HBr shown in Eq. 22.86 is similar to the conjugate addition of HBr to 1,3-butadiene (Sec. 15.4A); both involve carbocation intermediates. However, the nucleophilic conjugate addition, such as the addition of cyanide in Eq. 22.79, has no parallel in the reactions of simple conjugated dienes.

### B. Conjugate Addition Reactions versus Carbonyl-Group Reactions

Any conjugate addition reaction competes with a carbonyl-group reaction. In the case of aldehydes and ketones, conjugate addition competes with addition to the carbonyl group. (\( \text{Nuc} = \text{nucleophile} \); for example, in cyanide addition, \( \text{H}^- \text{Nuc} = \text{H}^-\text{CN} \).)

\[
R-\text{CH}=\text{CH}-\text{C}=\text{R} + \text{H}^-\text{Nuc} \quad \rightarrow \quad R\text{-CH}-\text{CH}_2-\text{C}=\text{R} \quad \text{(conjugate addition)}
\]

\[
R-\text{CH}=\text{CH}-\text{C}=\text{R} + \text{H}^-\text{Nuc} \quad \rightarrow \quad R-\text{CH}=\text{CH}-\text{C}=\text{R} \quad \text{(carbonyl addition)}
\]  

In the case of esters, conjugate addition competes with nucleophilic acyl substitution.

\[
R-\text{CH}=\text{CH}-\text{C}=\text{OEt} + \text{H}^-\text{Nuc} \quad \rightarrow \quad R\text{-CH}-\text{CH}_2-\text{C}=\text{OEt} \quad \text{(conjugate addition)}
\]

\[
R-\text{CH}=\text{CH}-\text{C}=\text{OEt} + \text{H}^-\text{Nuc} \quad \rightarrow \quad R-\text{CH}=\text{CH}-\text{C}=\text{Nuc} + \text{EtOH} \quad \text{(nucleophilic acyl substitution)}
\]

When can we expect to observe conjugate addition, and when can we expect reactions at the carbonyl carbon?

Consider first the reactions of aldehydes and ketones. Relatively weak bases that give reversible carbonyl-addition reactions with ordinary aldehydes and ketones tend to give conjugate addition with \( \alpha,\beta \)-unsaturated aldehydes and ketones. Among the relatively weak bases in this category are cyanide ion, amines, thiolate ions, and enolate ions derived from \( \beta \)-dicarbonyl compounds. Conjugate addition is observed with these nucleophiles because the conjugate-addition products are more stable than the carbonyl-addition products. If carbonyl addition is reversible—even if it occurs more rapidly—then conjugate addition can drain the
carbonyl compound from the addition equilibrium, and the conjugate-addition product is formed ultimately.

This, then, is another case of kinetic versus thermodynamic control of a reaction (Sec. 15.4C). The conjugate-addition product is the thermodynamic (more stable) product of the reaction.

The greater stability of the conjugate-addition product can be understood with a bond energy argument. Conjugate addition retains a carbonyl group at the expense of a carbon–carbon double bond. Carbonyl addition retains a carbon–carbon double bond at the expense of a carbonyl group. Because a C=O bond is considerably stronger than a C=C bond (Table 5.3, p. 213), conjugate addition gives a more stable product. (Other bonds are broken and formed as well, but the major effect is the relative strengths of the two kinds of double bonds.) These same factors are reflected in the relative heats of formation of the isomers allyl alcohol and propionaldehyde:

$$\begin{align*}
\Delta H_f^{\circ} & \text{ allyl alcohol} \\
& = -124 \text{ kJ mol}^{-1} \\
& = (-29.6 \text{ kcal mol}^{-1}) \\
\Delta H_f^{\circ} & \text{ propionaldehyde} \\
& = -189 \text{ kJ mol}^{-1} \\
& = (-45.2 \text{ kcal mol}^{-1})
\end{align*}$$

As Eq. 22.89 suggests, carbonyl addition is in many cases the kinetically favored process; that is, it is faster than conjugate addition. When nucleophiles are used that undergo irreversible carbonyl additions, then the carbonyl addition product is observed rather than the conjugate addition product. This is exactly what happens with very powerful nucleophiles such as LiAlH$_4$ and organolithium reagents: These species add irreversibly to carbonyl groups and form carbonyl-addition products whether the reactant carbonyl compound is $\alpha,\beta$-unsaturated or not. (These reactions are discussed further in Secs. 22.9 and 22.10A.)

Many of the same nucleophiles that undergo conjugate addition with aldehydes and ketones also undergo conjugate addition with esters. In contrast, stronger bases that react irreversibly at the carbonyl carbon react with esters to give nucleophilic acyl substitution products. Thus, hydroxide ion reacts with an $\alpha,\beta$-unsaturated ester to give products of saponification, a nucleophilic acyl substitution reaction, because saponification is not reversible. Likewise, LiAlH$_4$ reduces $\alpha,\beta$-unsaturated esters at the carbonyl group because the reaction of hydride ion at the carbonyl group is irreversible.

To summarize: Conjugate addition usually occurs with nucleophiles that are relatively weak bases. Stronger bases give irreversible carbonyl addition or nucleophilic acyl substitution reactions.
22.8 CONJUGATE-ADDITION REACTIONS

PROBLEMS

22.42 Give the product expected when methyl methacrylate (methyl 2-methylpropenoate) reacts with each of the following reagents.
(a) $\text{CN}^{-}$ and HCN in MeOH
(b) $\text{C}_2\text{H}_5\text{SH}$ and NaOMe catalyst in MeOH
(c) HBr
(d) NaOH

22.43 Give a curved-arrow mechanism for each of the following reactions.
(a) $\text{MeNH}_2 + 2\text{H}_2\text{C}═\text{CH}—\text{CO}_2\text{Me}$ →

(b) $\text{H}_2\text{C}═\text{CH}——\text{CH}_3 + \text{Ph—SH}$ →

(c) $\text{EtO}_2\text{C}═\text{C}—\text{CO}_2\text{Et}$ →

C. Conjugate Addition of Enolate Ions

Enolate ions, especially those derived from malonic ester derivatives, $\beta$-keto esters, and the like, undergo conjugate-addition reactions with $\alpha,\beta$-unsaturated carbonyl compounds, as in the following example:

$$\text{HO}═\text{C—C}═\text{CH}—\text{CH}_2 + \text{CH}_2(\text{CO}_2\text{Et})_2 \xrightarrow{\text{NaOEt catalyst} \ EtOH} \text{H}_2\text{C}—\text{C}═\text{CH}_2\text{CH}═\text{CH}_2(\text{CO}_2\text{Et})_2$$  (22.91)

The mechanism of this reaction follows exactly the same pattern established for other nucleophilic conjugate additions; the nucleophile is the enolate ion formed in the reaction of ethoxide with diethyl malonate (Eq. 22.64a, p. 1084). Notice that, in contrast to the Claisen ester condensation (Sec. 22.5A), this reaction requires only a catalytic amount of base. The reaction does not rely on ionization of the product to drive it to completion. It goes to completion because a carbon–carbon $\pi$ bond in the starting $\alpha,\beta$-unsaturated carbonyl compound is replaced by a stronger carbon–carbon $\sigma$ bond.
Conjugate additions of carbanions to $\alpha,\beta$-unsaturated carbonyl compounds are called Michael additions, after Arthur Michael (1853–1942), a Harvard professor who investigated these reactions extensively.

Proper planning is needed to use a Michael addition in a synthesis. The product of a given Michael addition might originate from two different pairs of reactants. For example, in the reaction shown in Eq. 22.92, the same product (in principle) might be obtained by the Michael addition reaction of either of the following pairs of reactants (convince yourself of this point):

Which pair of reactants should be used? To answer this question, use the result in Sec. 22.8B: Weaker bases tend to give conjugate addition, and stronger bases tend to give carbonyl-group reactions. Hence, to maximize conjugate addition, choose the pair of reactants with the less basic enolate ion—pair (b) in the foregoing example.

In one useful variation of the Michael addition, called the Robinson annulation, the immediate product of the addition can be subjected to an aldol condensation that closes a ring. (An annulation is a ring-forming reaction, from the Latin annulus, meaning “ring.”)
(Write the curved-arrow mechanisms of these reactions.) This type of reaction was named for Sir Robert Robinson (1886–1975), a British chemist at Oxford University who pioneered its use. (Robinson received the 1947 Nobel Prize in Chemistry for his work in alkaloids, which are discussed in Sec. 23.12B.)

**Study Problem 22.6**

Outline a synthesis of tricarballylic acid from diethyl fumarate and any other reagents.

![diagram of synthesis](image)

**Solution**

Two of the carboxylic acid groups required in the target are already in place as the ester units in diethyl fumarate. A Michael addition of some species that could be converted into a \( \text{CH}_2\text{CO}_2\text{H} \) group is required. Notice that the desired product is conceptually a substituted acetic acid:

\[
\text{HO}_2\text{C} \rightarrow \text{CH} \rightarrow \text{CH}_2 \rightarrow \text{CO}_2\text{H} \\
\text{CH}_2 \rightarrow \text{CO}_2\text{H} \\
\text{substituted acetic acid}
\]

Recall that one way of preparing substituted acetic acids is the malonic ester synthesis (Sec. 22.7A). A variation of the malonic ester synthesis can be employed here in which alkylation of the conjugate-base anion of diethyl malonate is carried out by a Michael addition with diethyl fumarate instead of an \( \text{S}_2 \) reaction with an alkyl halide.

\[
\text{CH}_2(\text{CO}_2\text{Et})_2 \xrightarrow{\text{NaOEt}} \text{CH}(\text{CO}_2\text{Et})_2 \\
\xrightarrow{\text{EtOH, Michael addition}} \text{EtO}_2\text{C} \rightarrow \text{CH} \rightarrow \text{CH}_2 \rightarrow \text{CO}_2\text{Et} \\
\text{CH}(\text{CO}_2\text{Et})_2
\]

Saponification of all four ester groups, protonation, and decarboxylation should yield the desired tricarboxylic acid:

\[
\text{EtO}_2\text{C} \rightarrow \text{CH} \rightarrow \text{CH}_2 \rightarrow \text{CO}_2\text{Et} \\
\text{CH} \rightarrow \text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\xrightarrow{1) \text{NaOH}, 2) \text{H}_2\text{O}^+} \\
\text{HO}_2\text{C} \rightarrow \text{CH} \rightarrow \text{CH}_2 \rightarrow \text{CO}_2\text{H} \\
\text{CH} \rightarrow \text{CO}_2\text{H} \\
\text{CO}_2\text{H} \\
\text{heat} \xrightarrow{} \text{HO}_2\text{C} \rightarrow \text{CH} \rightarrow \text{CH}_2 \rightarrow \text{CO}_2\text{H} + \text{CO}_2 \\
\text{CH}_2 \rightarrow \text{CO}_2\text{H}
\]
22.44 Provide structures for the missing nucleophiles that could be used in the following transformations.

(a) \[ Y + H_2C=CH-CN \xrightarrow{NaOEt, \text{EtOH}} H_2C=CH-CO_2H \]

(b) \[ X + H_2C=CHCO_2Et \xrightarrow{NaOEt, \text{EtOH}} HO_2CCH_2CH_2CH_2CO_2H \]

22.45 Give a curved-arrow mechanism for each of the following reactions. In each reaction identify the intermediate indicated by \( A \) or \( B \).

(a) \[ \begin{array}{c}
\text{CH}=O \\
\text{KOH} \text{(cat.)}
\end{array} \xrightarrow{\text{KOH, MeOH}} \text{A} \quad \text{(C}_{10}\text{H}_{16}\text{O}_2) \quad \text{(C}_{10}\text{H}_{16}\text{O}_2) \quad + \text{H}-\text{C}=\text{O}^- \]

(b) \[ \text{CH}_2(\text{CO}_2\text{Et})_2 + H_2C=CH=CH_2 \xrightarrow{\text{NaOEt, EtOH}} \text{B} \quad \text{NaOEt (1 equiv.)} \quad \text{H}_2\text{O}^+ \]

22.9 REDUCTION OF \( \alpha,\beta \)-UNSATURATED CARBONYL COMPOUNDS

The carbonyl group of an \( \alpha,\beta \)-unsaturated aldehyde or ketone, like that of an ordinary aldehyde or ketone (Sec. 19.8), is reduced to an alcohol with lithium aluminum hydride.

\[ \begin{array}{c}
\text{O} \\
\text{CH}_3 \\
\text{ether}
\end{array} \xrightarrow{\text{LiAlH}_4} \text{H}_2\text{O}^+ \quad \begin{array}{c}
\text{HO} \\
\text{H} \\
\text{CH}_3
\end{array} \quad \text{(98% yield)} \quad (22.94) \]

This reaction, like other LiAlH\(_4\) reductions, involves the nucleophilic reaction of hydride at the carbonyl carbon and is therefore a carbonyl addition.

The reason that carbonyl addition, rather than conjugate addition, is observed follows from the discussion in Sec. 22.8B. Carbonyl addition is not only faster than conjugate addition but, in this case, is also irreversible. It is irreversible because hydride is a very poor leaving group.