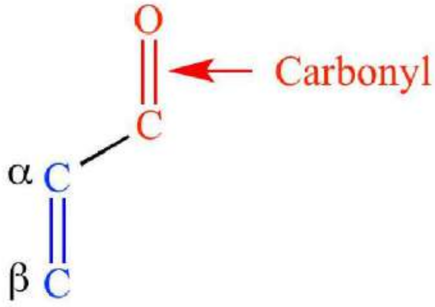
α, β-Unsaturated Carbonyl Compounds

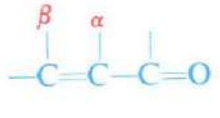
Conjugate Addition



Structure and properties

In general, a compound that contains both a carbon–carbon double bond and a carbon–oxygen double bond has properties that are characteristic of both functional groups. At the carbon–carbon double bond an unsaturated ester or unsaturated ketone undergoes electrophilic addition of acids and halogens, hydrogenation, hydroxylation, and cleavage; at the carbonyl group it undergoes the nucleophilic substitution typical of an ester or the nucleophilic addition typical of a ketone.

In the α,β-unsaturated carbonyl compounds, the carbon–carbon double bond and the carbon–oxygen double bond are separated by just one carbon–carbon single bond; that is, the double bonds are *conjugated*. Because of this conjugation,



$$-\overset{\beta}{\underset{|}{C}}=\overset{\alpha}{\underset{|}{C}}-\overset{|}{C}=O$$

α,β-Unsaturated carbonyl compound
Conjugated system

such compounds possess not only the properties of the individual functional groups, but certain other properties besides.

For example

$CH_2{=}CH{-}CHO$

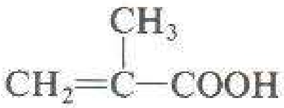
Acrolein
Propenal

$CH_2{=}CH{-}COOH$

Acrylic acid
Propenoic acid

$CH_2{=}CH{-}C{\equiv}N$

Acrylonitrile
Propenenitrile



$CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}COOH$

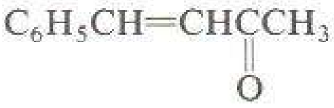
Methacrylic acid
2-Methylpropenoic acid

$CH_3CH{=}CHCHO$

Crotonaldehyde
2-Butenal

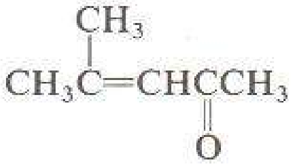
$C_6H_5CH{=}CHCHO$

Cinnamaldehyde
3-Phenylpropenal



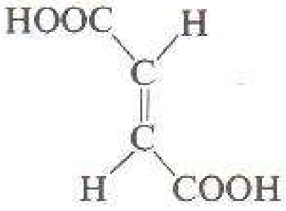
$C_6H_5CH{=}CH\underset{\underset{O}{\|}}{C}CH_3$

Benzalacetone
4-Phenyl-
3-buten-2-one

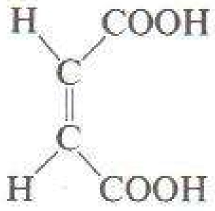


$CH_3\overset{CH_3}{\overset{|}{C}}{=}CH\underset{\underset{O}{\|}}{C}CH_3$

Mesityl oxide
4-Methyl-
3-penten-2-one



Fumaric acid
trans-Butenedioic
acid



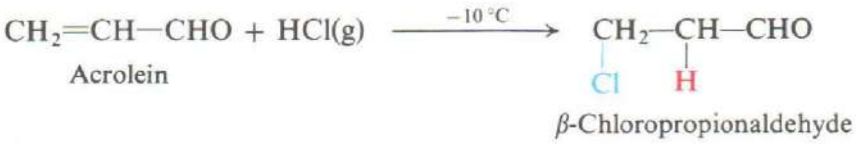
Maleic acid
cis-Butenedioic
acid

Maleic anhydride
cis-Butenedioic
anhydride

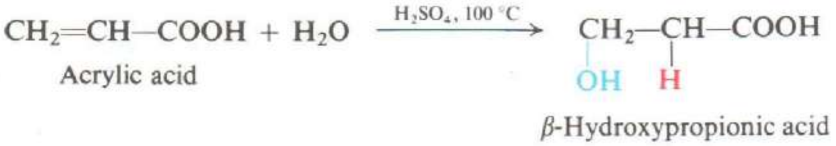
Electrophilic addition

The presence of the carbonyl group not only lowers the **reactivity** of the carbon–carbon double bond toward electrophilic addition, but also controls the **orientation** of the addition.

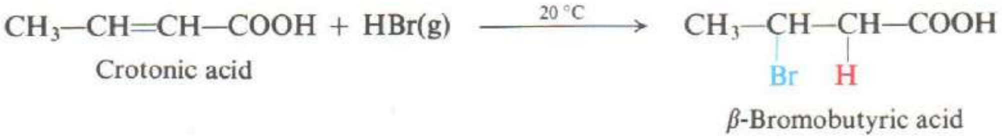
In general, it is observed that addition of an unsymmetrical reagent to an α,β-unsaturated carbonyl compound takes place in such a way that hydrogen becomes attached to the α-carbon and the negative group becomes attached to the β-carbon. For example:



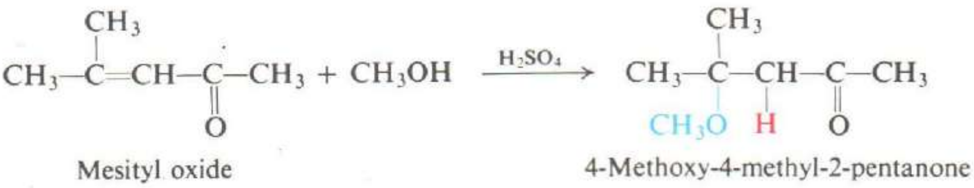
$$\underset{\text{Acrolein}}{CH_2{=}CH{-}CHO} + HCl(g) \xrightarrow{-10\ ^\circ C} \underset{\beta\text{-Chloropropionaldehyde}}{\underset{Cl}{CH_2}{-}\underset{H}{CH}{-}CHO}$$



$$\underset{\text{Acrylic acid}}{CH_2{=}CH{-}COOH} + H_2O \xrightarrow{H_2SO_4,\ 100\ ^\circ C} \underset{\beta\text{-Hydroxypropionic acid}}{\underset{OH}{CH_2}{-}\underset{H}{CH}{-}COOH}$$



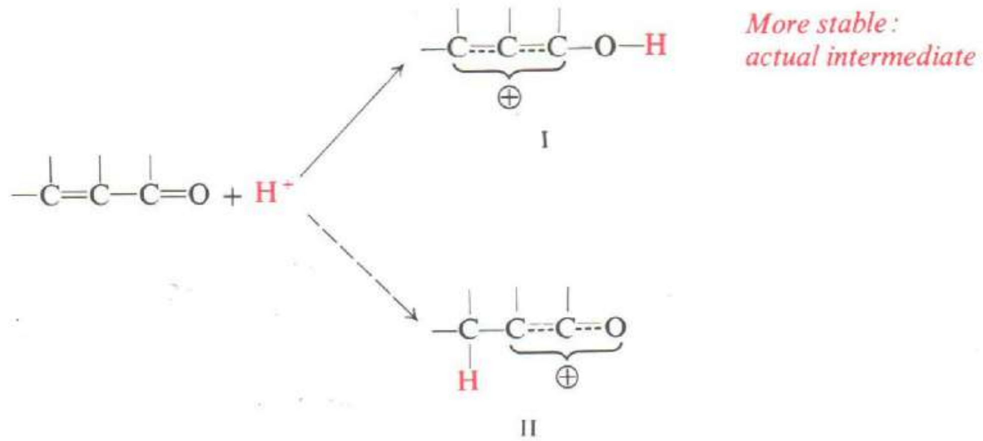
$$\underset{\text{Crotonic acid}}{CH_3{-}CH{=}CH{-}COOH} + HBr(g) \xrightarrow{20\ ^\circ C} \underset{\beta\text{-Bromobutyric acid}}{CH_3{-}\underset{Br}{CH}{-}\underset{H}{CH}{-}COOH}$$



$$\underset{\text{Mesityl oxide}}{CH_3{-}\overset{CH_3}{C}{=}CH{-}\underset{O}{\overset{}{\underset{\|}{C}}}{-}CH_3} + CH_3OH \xrightarrow{H_2SO_4} \underset{\text{4-Methoxy-4-methyl-2-pentanone}}{CH_3{-}\underset{CH_3O}{\overset{CH_3}{C}}{-}\underset{H}{CH}{-}\underset{O}{\underset{\|}{C}}{-}CH_3}$$

Electrophilic addition to simple alkenes takes place in such a way as to form the most stable intermediate carbocation. Addition to α,β-unsaturated carbonyl compounds, too, is consistent with this principle; to see that this is so, however, we must look at the conjugated system as a whole. As in the case of conjugated dienes , addition to an *end* of the conjugated system is preferred, since this yields (step 1) a resonance-stabilized carbocation. Addition of a proton to the carbonyl oxygen end would yield cation I; addition to the β-carbon end would yield cation II.

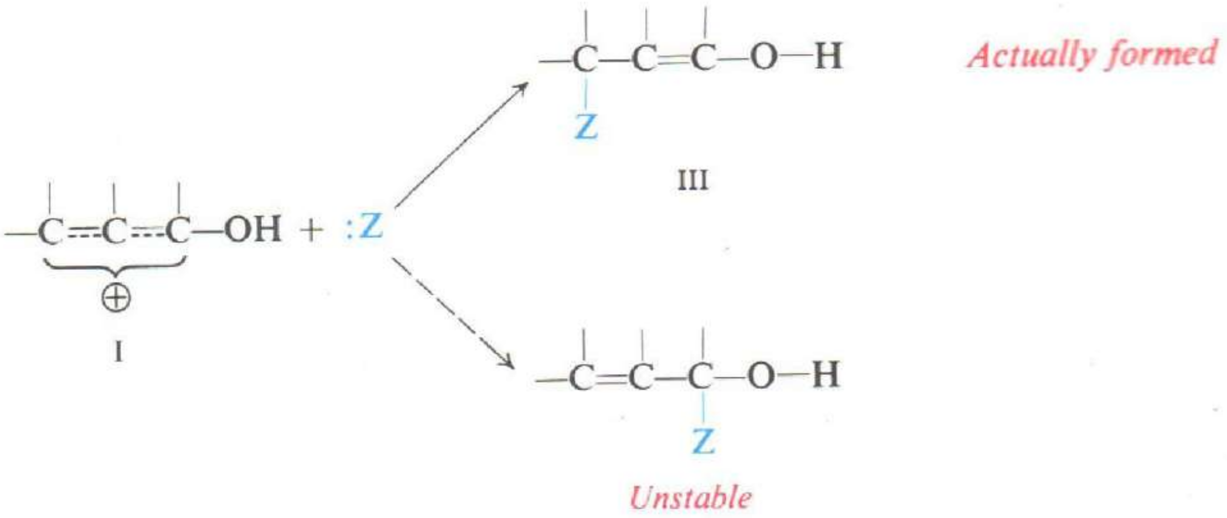
(1)



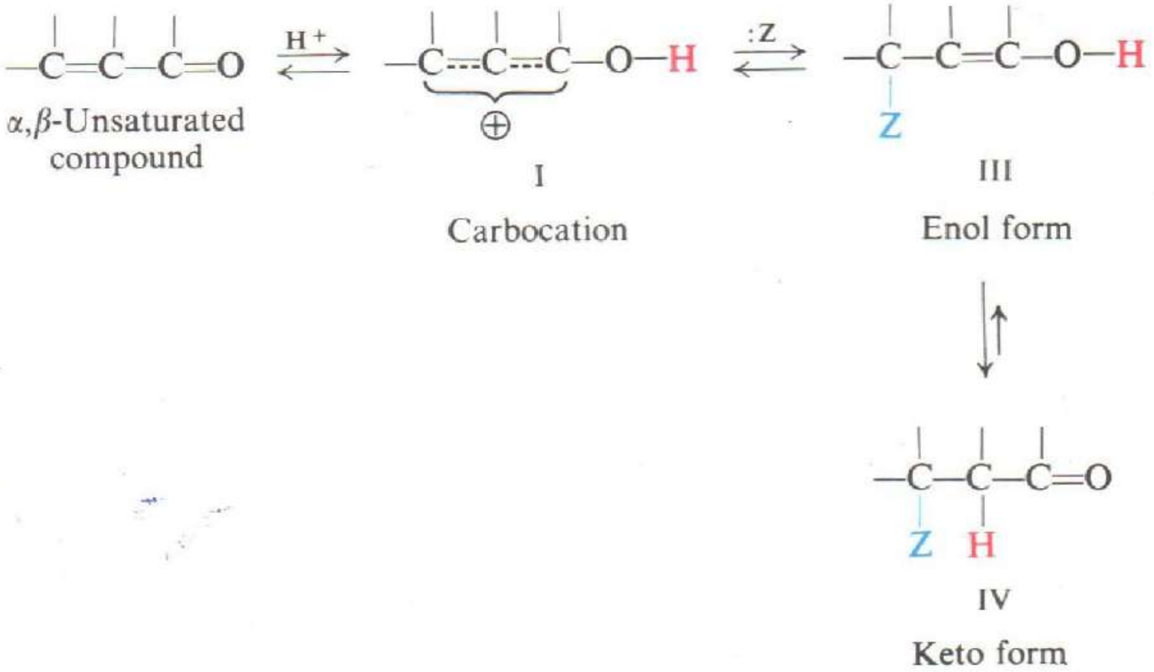
Of the two, I is the more stable, since the positive charge is carried by carbon atoms alone, rather than partly by the more highly electronegative oxygen atom.

In the second step of addition, a negative ion or basic molecule attaches itself either to the carbonyl carbon or to the β-carbon of the hybrid ion I.

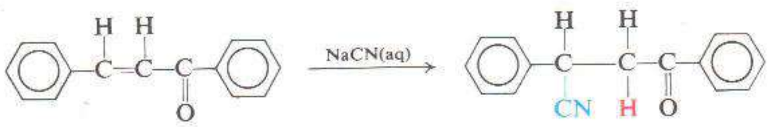
(2)



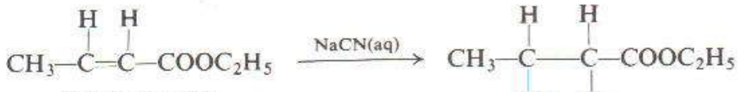
Of the two possibilities, only addition to the β-carbon yields a stable product (III), which is simply the enol form of the saturated carbonyl compound. The enol form then undergoes tautomerization to the keto form to give the observed product (IV).



Nucleophilic addition

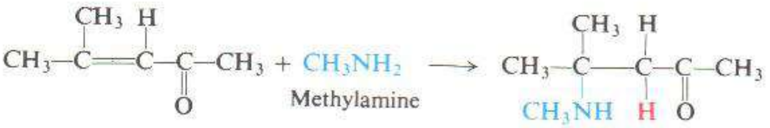


Benzalacetophenone 3-Cyano-1,3-diphenyl-1-propanone



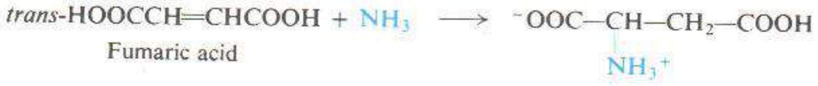
$$CH_3-\overset{H}{C}=\overset{H}{C}-COOC_2H_5 \xrightarrow{NaCN(aq)} CH_3-\underset{CN}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-COOC_2H_5$$

Ethyl crotonate Ethyl β-cyanobutyrate



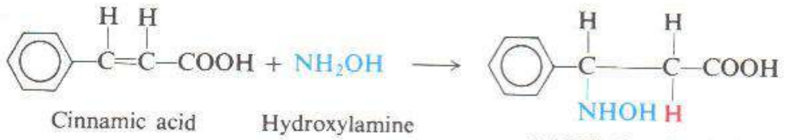
$$CH_3-\overset{CH_3}{C}=\overset{H}{C}-\underset{O}{\overset{\|}{C}}-CH_3 + CH_3NH_2 \longrightarrow CH_3-\underset{CH_3NH}{\overset{CH_3}{C}}-\underset{H}{\overset{H}{C}}-\underset{O}{\overset{\|}{C}}-CH_3$$

Mesityl oxide Methylamine 4-(*N*-Methylamino)-4-methyl-2-pentanone



$$trans\text{-}HOOCCH{=}CHCOOH + NH_3 \longrightarrow {}^-OOC-\underset{NH_3^+}{CH}-CH_2-COOH$$

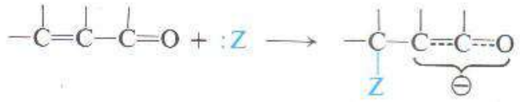
Fumaric acid Aminosuccinic acid (Aspartic acid)



Cinnamic acid Hydroxylamine 3-(*N*-Hydroxylamino)-3-phenylpropanoic acid

These reactions are believed to take place by the following mechanism:

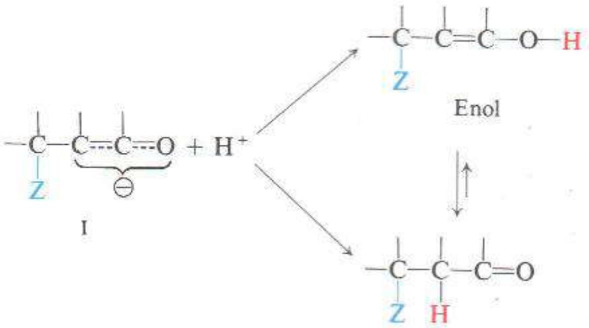
(1)



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O + :Z \longrightarrow -\underset{Z}{\overset{|}{C}}-\underbrace{\overset{|}{C}\cdots\overset{|}{C}\cdots O}_{\ominus}$$

I

(2)



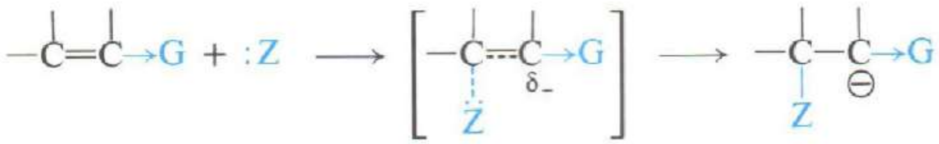
$$-\underset{Z}{\overset{|}{C}}-\underbrace{\overset{|}{C}\cdots\overset{|}{C}\cdots O}_{\ominus} + H^+ \longrightarrow -\underset{Z}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}-O-H \;\text{or}\; -\underset{Z}{\overset{|}{C}}-\underset{H}{\overset{|}{C}}-\overset{|}{C}=O$$

I Enol Keto

The nucleophilic reagent adds (step 1) to the carbon–carbon double bond to yield the hybrid anion I, which then accepts (step 2) a proton from the solvent to yield the final product. This proton can add either to the α-carbon or to oxygen, and thus yield either the keto or the enol form of the product; in either case the same equilibrium mixture, chiefly keto, is finally obtained.

The difference between nucleophilic and electrophilic addition is, of course, that the intermediate ions have opposite charges: negative in nucleophilic addition, positive in electrophilic addition. As a result, the effects of substituents are exactly opposite. Where an electron-withdrawing group deactivates a carbon–carbon double bond toward electrophilic addition, it activates toward nucleophilic addition. An electron-withdrawing group stabilizes the transition state leading to the formation of an intermediate anion in nucleophilic addition by helping to disperse the developing negative charge:

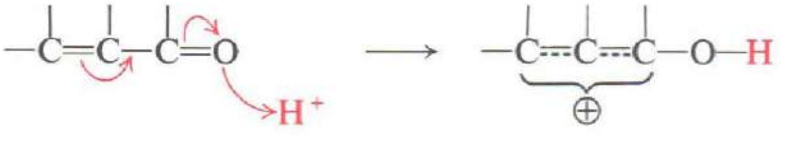
Nucleophilic addition



$$-\overset{|}{C}=\overset{|}{C}\rightarrow G + :Z \longrightarrow \left[-\underset{\vdots\atop Z}{\overset{|}{C}}\cdots\underset{\delta_-}{\overset{|}{C}}\rightarrow G\right] \longrightarrow -\underset{Z}{\overset{|}{C}}-\underset{\ominus}{\overset{|}{C}}\rightarrow G$$

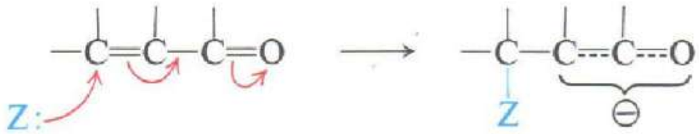
G *withdraws electrons: activates*

Addition to an α,β-unsaturated carbonyl compound can be understood best in terms of an attack on the entire conjugated system. To yield the most stable intermediate ion, this attack must occur at an end of the conjugated system. A nucleophilic reagent attacks at the β-carbon to form an ion in which the negative charge is partly accommodated by the electronegative atom oxygen; an electrophilic reagent attacks oxygen to form a carbocation in which the positive charge is accommodated by carbon.



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O \quad H^+ \longrightarrow \underbrace{-\overset{|}{C}\cdots\overset{|}{C}\cdots\overset{|}{C}}_{\oplus}-O-H$$

Electrophilic attack

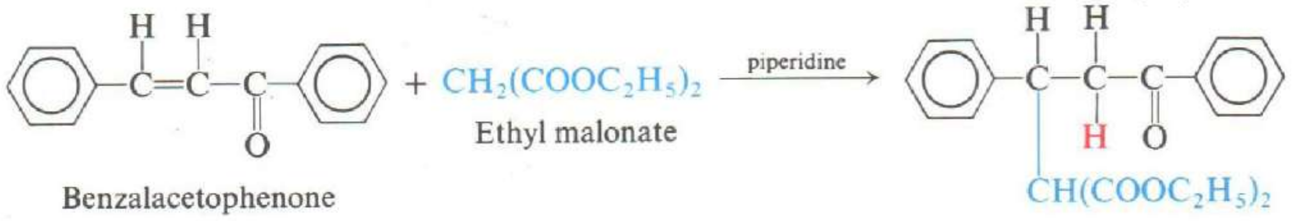


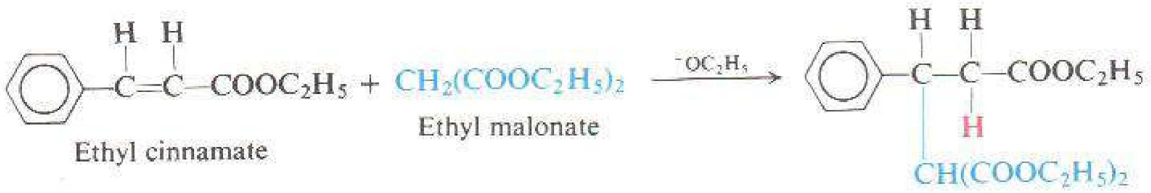
$$Z: \quad -\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O \longrightarrow -\underset{Z}{\overset{|}{C}}-\underbrace{\overset{|}{C}\cdots\overset{|}{C}\cdots O}_{\ominus}$$

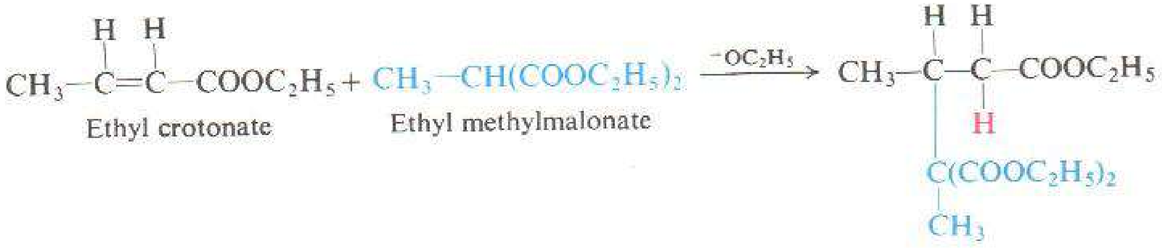
Nucleophilic attack

27.7 The Michael addition

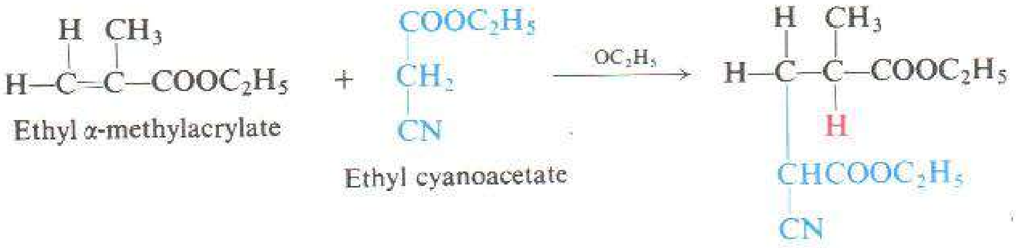
Of special importance in synthesis is the nucleophilic addition of carbanions to α,β-unsaturated carbonyl compounds known as the **Michael addition**. Like the reactions of carbanions that we studied in Chapter 25, it results in formation of carbon–carbon bonds. For example:







$$CH_3-\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}-COOC_2H_5 + CH_3-CH(COOC_2H_5)_2 \xrightarrow{^-OC_2H_5} CH_3-\underset{\underset{\underset{CH_3}{|}}{\underset{|}{C(COOC_2H_5)_2}}}{\overset{H}{\overset{|}{C}}}-\underset{H}{\overset{H}{\overset{|}{C}}}-COOC_2H_5$$

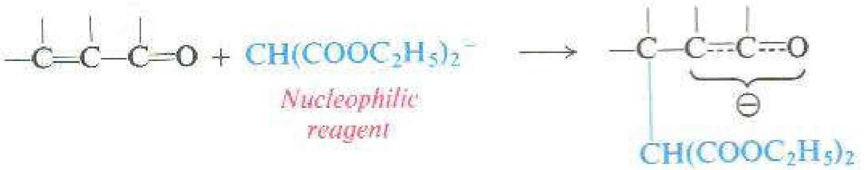


$$H-\overset{H}{\overset{|}{C}}=\overset{CH_3}{\overset{|}{C}}-COOC_2H_5 \quad + \quad \begin{array}{c}COOC_2H_5\\|\\CH_2\\|\\CN\end{array} \xrightarrow{^-OC_2H_5} H-\underset{\underset{\underset{CN}{|}}{\underset{|}{CHCOOC_2H_5}}}{\overset{H}{\overset{|}{C}}}-\underset{H}{\overset{CH_3}{\overset{|}{C}}}-COOC_2H_5$$

The Michael addition is believed to proceed by the following mechanism (shown for malonic ester):

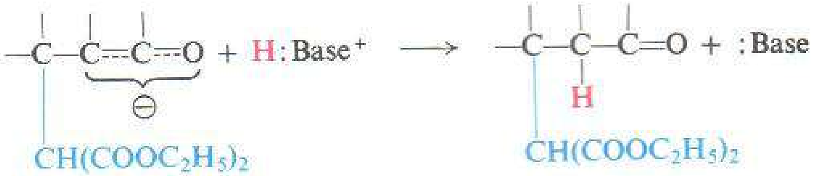
(1) $H-CH(COOC_2H_5)_2 + :Base \longrightarrow H:Base^+ + CH(COOC_2H_5)_2^-$

(2)



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O + CH(COOC_2H_5)_2^- \longrightarrow -\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}\cdots\overset{|}{C}\cdots O}_{\ominus}$$

(3)



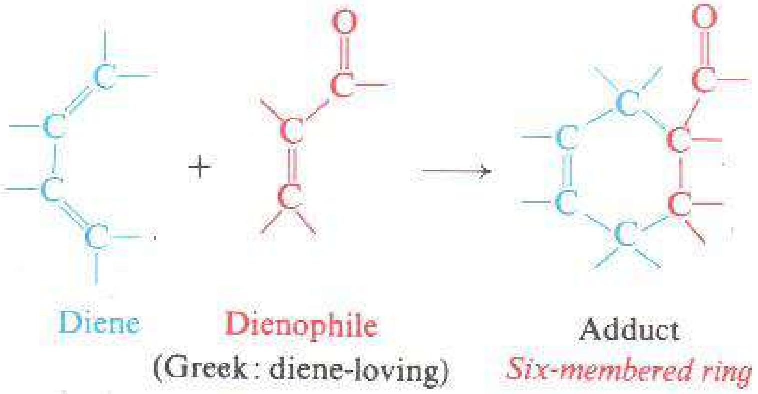
$$-\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underbrace{\overset{|}{C}\cdots\overset{|}{C}\cdots O}_{\ominus} + H:Base^+ \longrightarrow -\underset{\underset{CH(COOC_2H_5)_2}{|}}{\overset{|}{C}}-\underset{H}{\overset{|}{C}}-\overset{|}{C}=O + :Base$$

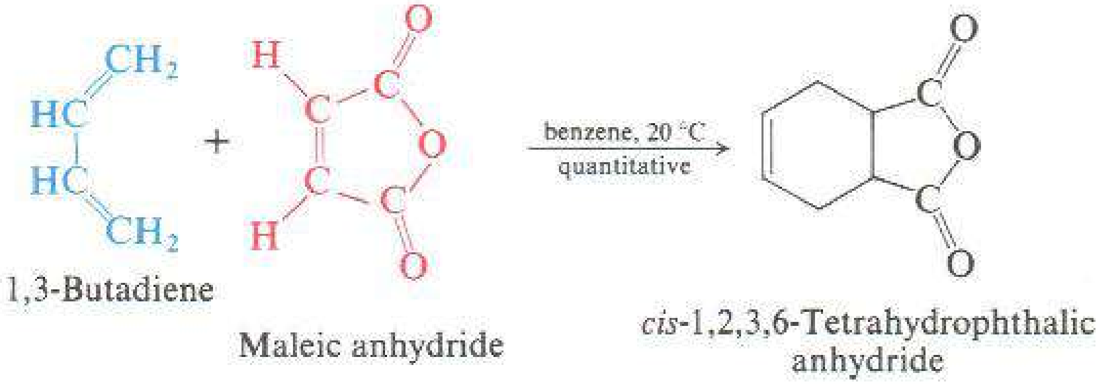
The function of the base is to abstract (step 1) a proton from malonic ester and thus generate a carbanion which, acting as a nucleophilic reagent, then attacks (step 2) the conjugated system in the usual manner.

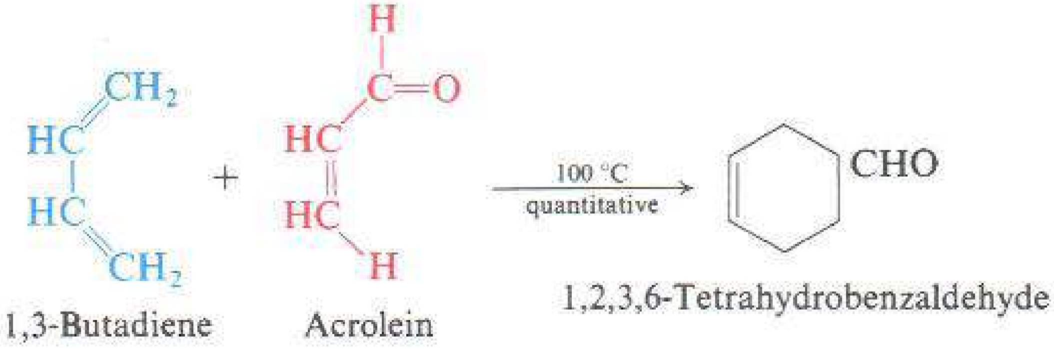
In general, the compound from which the carbanion is generated must be a fairly acidic substance, so that an appreciable concentration of the carbanion can be obtained. Such a compound is usually one that contains a $—CH_2—$ or $—CH—$ group flanked by two electron-withdrawing groups which can help accommodate the negative charge of the anion. In place of ethyl malonate, compounds like ethyl cyanoacetate and ethyl acetoacetate can be used.

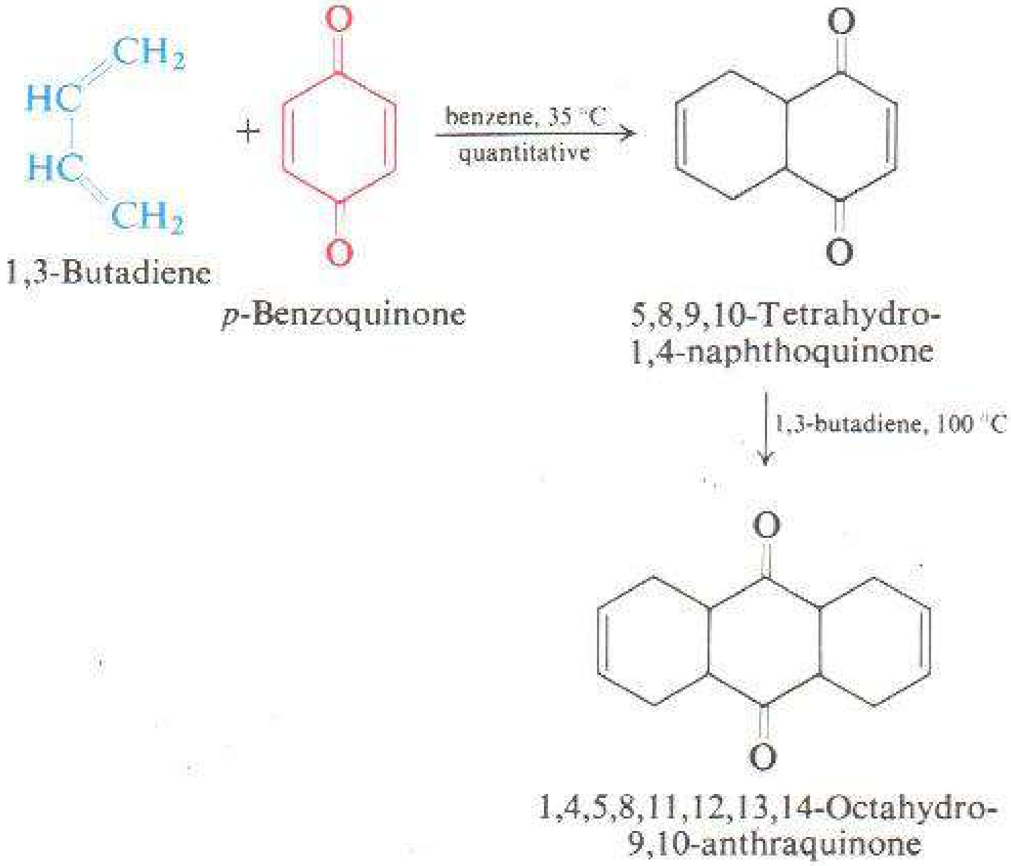
The Diels–Alder reaction

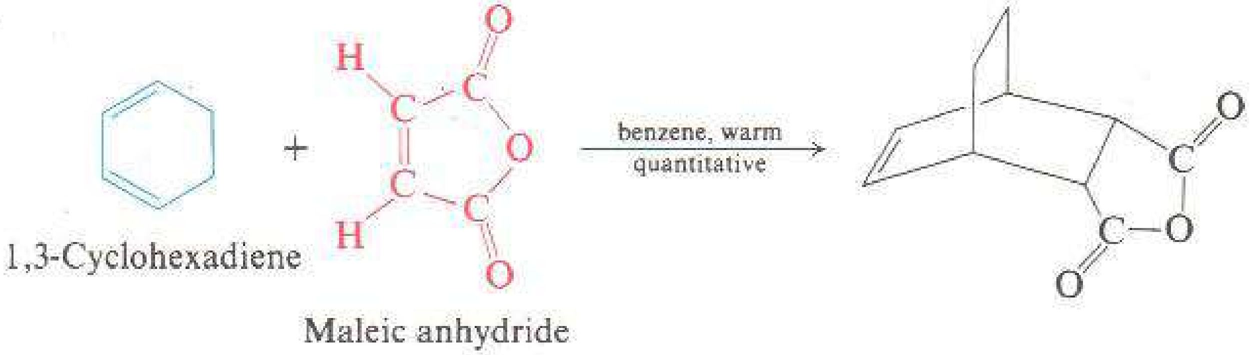
α,β-Unsaturated carbonyl compounds undergo an exceedingly useful reaction with conjugated dienes, known as the **Diels–Alder reaction**. This is an addition reaction in which C–1 and C–4 of the conjugated diene system become attached to the doubly bonded carbons of the unsaturated carbonyl compound to form a six-membered ring. A concerted, single-step mechanism is almost certainly involved; both new carbon–carbon bonds are partly formed in the same transition state, although not necessarily to the same extent. The Diels–Alder reaction is the most important example of *cycloaddition*.



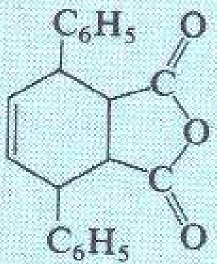

1,3-Butadiene
Maleic anhydride
benzene, 20 °C
quantitative
cis-1,2,3,6-Tetrahydrophthalic anhydride

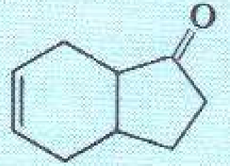

1,3-Butadiene
Acrolein
100 °C
quantitative
1,2,3,6-Tetrahydrobenzaldehyde

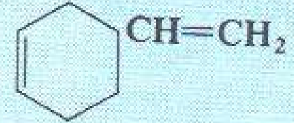

1,3-Butadiene
p-Benzoquinone
benzene, 35 °C
quantitative
5,8,9,10-Tetrahydro-1,4-naphthoquinone
1,3-butadiene, 100 °C
1,4,5,8,11,12,13,14-Octahydro-9,10-anthraquinone


1,3-Cyclohexadiene
Maleic anhydride
benzene, warm
quantitative

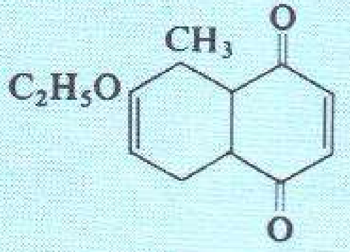
Problem [redacted] From what reactants could each of the following compounds be synthesized?





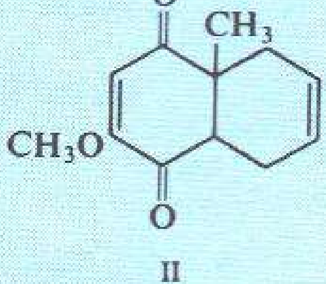


Problem 27.18 (a) In one synthesis of the hormone *cortisone* (by Lewis Sarett of Merck, Sharp and Dohme), the initial step was the formation of I by a Diels–Alder reaction. What were the starting materials?



I

(b) In another synthesis of cortisone (by R. B. Woodward, p. 1004), the initial step was the formation of II by a Diels–Alder reaction. What were the starting materials?



II

PROBLEMS

1. Outline all steps in a possible laboratory synthesis of each of the unsaturated carbonyl compounds in Table 27.1, p. 972, using any readily available monofunctional compounds: simple alcohols, aldehydes, ketones, acids, esters, and hydrocarbons.

2. Give the structures of the organic products expected from the reaction of benzalacetone, $C_6H_5CH{=}CHCOCH_3$, with each of the following:

(a) H_2,Ni
(b) 9-BBN, then $HOCH_2CH_2NH_2$
(c) NaOI
(d) O_3, then Zn, H_2O
(e) Br_2
(f) HCl
(g) HBr
(h) H_2O, H^+
(i) CH_3OH, H^+
(j) NaCN(aq)
(k) CH_3NH_2
(l) aniline
(m) NH_3
(n) NH_2OH
(o) benzaldehyde, base
(p) ethyl malonate, base
(q) ethyl cyanoacetate, base
(r) ethyl methylmalonate, base
(s) ethyl acetoacetate, base
(t) 1,3-butadiene
(u) 1,3-cyclohexadiene
(v) 1,3-cyclopentadiene

3. In the presence of base the following pairs of reagents undergo Michael addition. Give the structures of the expected products.

(a) benzalacetophenone + ethyl cyanoacetate
(b) ethyl cinnamate + ethyl cyanoacetate
(c) ethyl fumarate + ethyl malonate
(d) ethyl acetylenedicarboxylate + ethyl malonate
(e) mesityl oxide + ethyl malonate
(f) mesityl oxide + ethyl acetoacetate
(g) ethyl crotonate + ethyl methylmalonate
(h) formaldehyde + 2 mol ethyl malonate
(i) acetaldehyde + 2 mol ethyl acetoacetate
(j) methyl acrylate + nitromethane
(k) 2 mol ethyl crotonate + nitromethane
(l) 3 mol acrylonitrile + nitromethane
(m) 1 mol acrylonitrile + $CHCl_3$

4. Give the structures of the compounds expected from the hydrolysis and decarboxylation of the products obtained in Problem 3, parts (a) through (i).

5. Depending upon reaction conditions, dibenzalacetone and ethyl malonate can be made to yield any of three products by Michael addition.

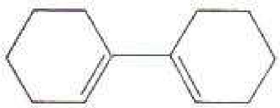
dibenzalacetone + 2 mol ethyl malonate $\longrightarrow$ A (no unsaturation)
dibenzalacetone + 1 mol ethyl malonate $\longrightarrow$ B (one carbon–carbon double bond)
dibenzalacetone + 1 mol ethyl malonate $\longrightarrow$ C (no unsaturation)

What are A, B, and C?

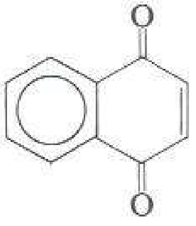
6. *Spermine*, $H_2NCH_2CH_2CH_2NHCH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$, found in seminal fluid, has been synthesized from acrylonitrile and 1,4-diaminobutane (putrescine). Show how this was probably done.

7. Give the structure of the product of the Diels–Alder reaction between:

(a) maleic anhydride and isoprene
(b) maleic anhydride and 1,1′-bicyclohexenyl (I)
(c) maleic anhydride and 1-vinyl-1-cyclohexene
(d) 1,3-butadiene and methyl vinyl ketone
(e) 1,3-butadiene and crotonaldehyde
(f) 2 mol 1,3-butadiene and dibenzalacetone
(g) 1,3-butadiene and β-nitrostyrene ($C_6H_5CH{=}CHNO_2$)
(h) 1,3-butadiene and 1,4-naphthoquinone (II)
(i) *p*-benzoquinone and 1,3-cyclohexadiene
(j) *p*-benzoquinone and 1,1′-bicyclohexenyl (I)
(k) *p*-benzoquinone and 2 mol 1,3-cyclohexadiene
(l) *p*-benzoquinone and 2 mol 1,1′-bicyclohexenyl (I)
(m) 1,3-cyclopentadiene and acrylonitrile
(n) 1,3-cyclohexadiene and acrolein



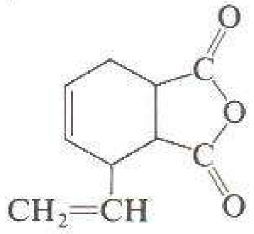
I



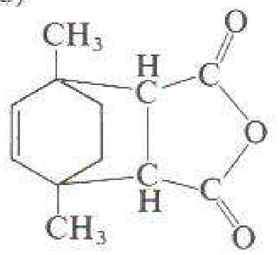
II

8. From what reactants could the following be synthesized by the Diels–Alder reaction?

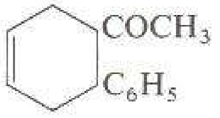
(a)



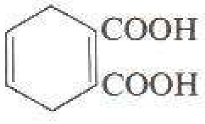
(b)



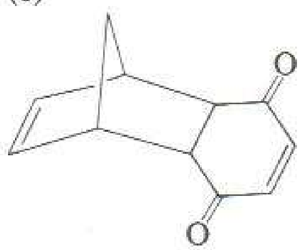
(c)



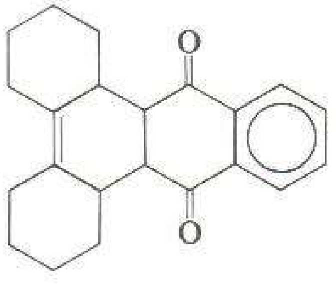
(d)



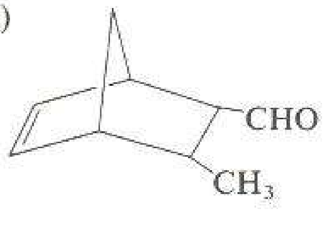
(e)



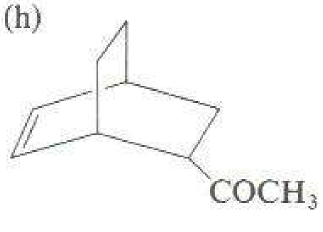
(f)



(g)



(h)



(i)