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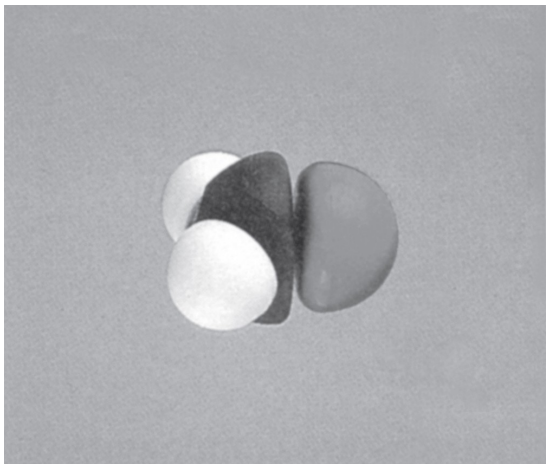
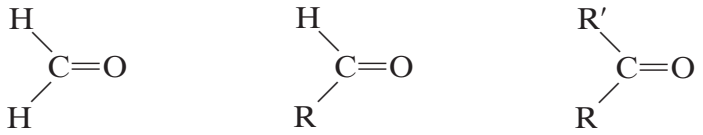


Aldehydes and Ketones
Nucleophilic Addition

12.1 Structure

Aldehydes are compounds of the general formula RCHO; ketones are compounds of the general formula RR′CO. The groups R and R′ may be aliphatic or aromatic. (In one aldehyde, HCHO, R is H.)



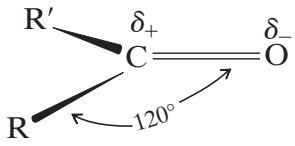
Aldehydes A ketone

Both aldehydes and ketones contain the carbonyl group, C═O, and are often referred to collectively as **carbonyl compounds**. *It is the carbonyl group that largely determines the chemistry of aldehydes and ketones.*

It is not surprising to find that aldehydes and ketones resemble each other closely in most of their properties. However, there is a hydrogen atom attached to the carbonyl group of aldehydes, and there are two organic groups attached to the carbonyl group of ketones. This difference in structure affects their properties in two ways: (a) aldehydes are quite easily oxidized, whereas ketones are oxidized only with difficulty; (b) aldehydes are usually more reactive than ketones toward nucleophilic addition, the characteristic reaction of carbonyl compounds.

Let us examine the structure of the carbonyl group. Carbonyl carbon is joined to three other atoms by σ bonds; since these bonds utilize sp^2 orbitals, they lie in a

plane, and are 120° apart. The remaining *p* orbital of the carbon overlaps a *p* orbital of oxygen to form a π bond; carbon and oxygen are thus joined by a double bond.



The part of the molecule immediately surrounding carbonyl carbon is *flat*; oxygen, carbonyl carbon, and the two atoms directly attached to carbonyl carbon lie in a plane.

The electrons of the carbonyl double bond hold together atoms of quite differ-ent electronegativity, and hence the electrons are not equally shared; in particular, the mobile π cloud is pulled strongly toward the more electronegative atom, oxygen.

The facts are consistent with the orbital picture of the carbonyl group. Electron diffraction and spectroscopic studies of aldehydes and ketones show that carbon, oxygen, and the two other atoms attached to carbonyl carbon lie in a plane; the three bond angles of carbon are very close to 120° (see Fig. 12.1).The large dipole moments (2.3–2.8 D) of aldehydes and ketones indicate that the electrons of the carbonyl group are quite unequally shared. We shall see how the physical and chemical properties of aldehydes and ketones are determined by the structure of the carbonyl group.

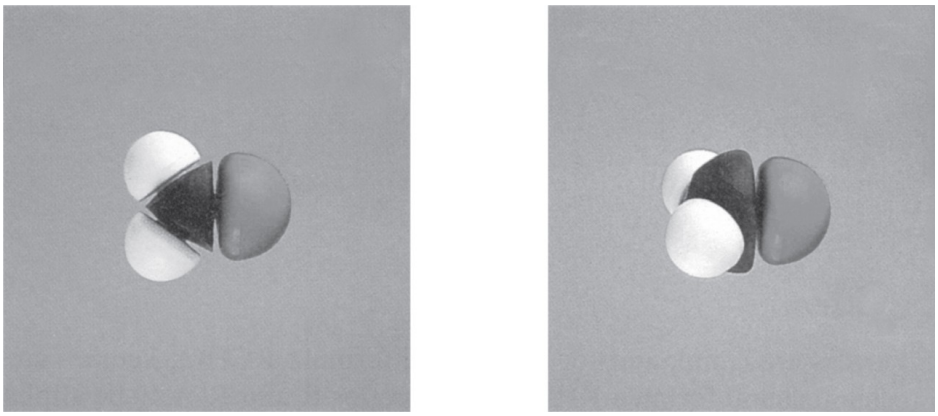


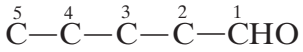
Figure 12.1 Electronic configuration and molecular shape: the carbonyl group. Model of formaldehyde, HCHO: two views.

12.2 Nomenclature

The common names of **aldehydes** are derived from the names of the corresponding carboxylic acids by replacing *-ic acid* by *-aldehyde*. (For the common names of carboxylic acids.) Branched-chain aldehydes are named as derivatives of straight-chain aldehydes. To indicate the point of attachment, the Greek letters, α-, β-, γ-, δ-, etc., are used; the α-carbon is the one bearing the —CHO group.

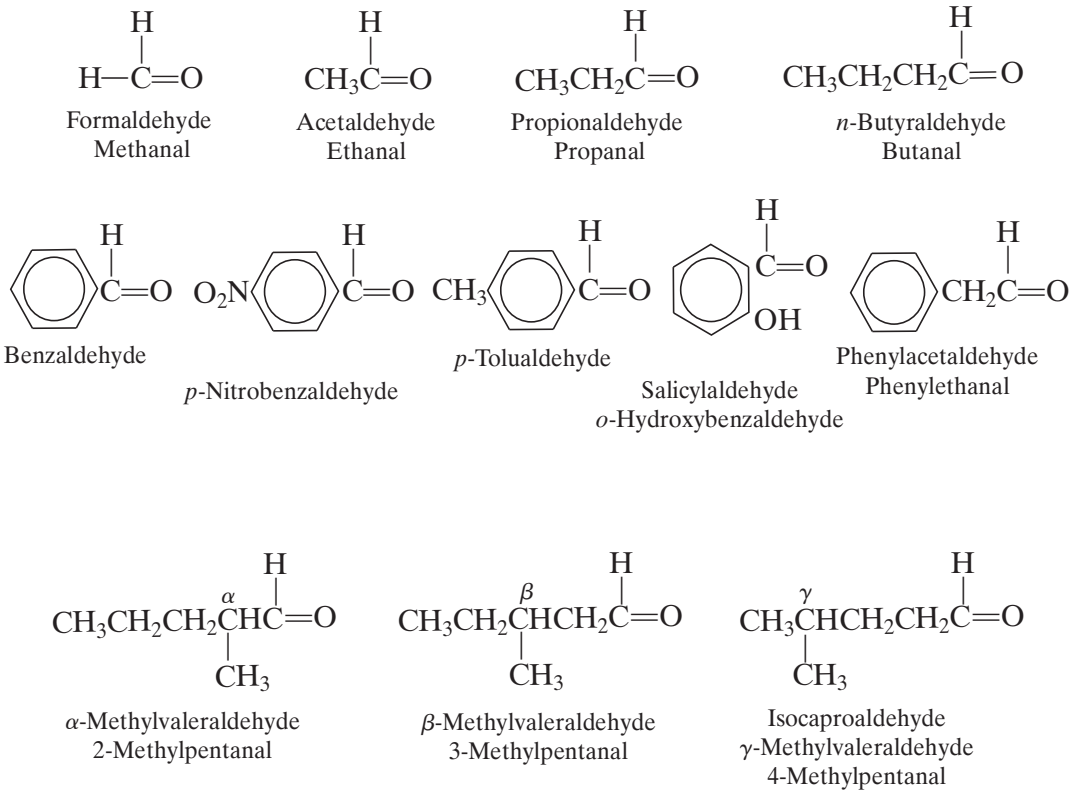
$$\overset{\delta}{\text{C}}—\overset{\gamma}{\text{C}}—\overset{\beta}{\text{C}}—\overset{\alpha}{\text{C}}—\text{CHO}$$ *Used in common names*

The IUPAC names of aldehydes follow the usual pattern.The longest chain carrying the —CHO group is considered the parent structure and is named by replacing the *-e* of the corresponding alkane by *-al*. The position of a substituent is indicated by a number, the carbonyl carbon always being considered as C–1. We



Used in IUPAC names

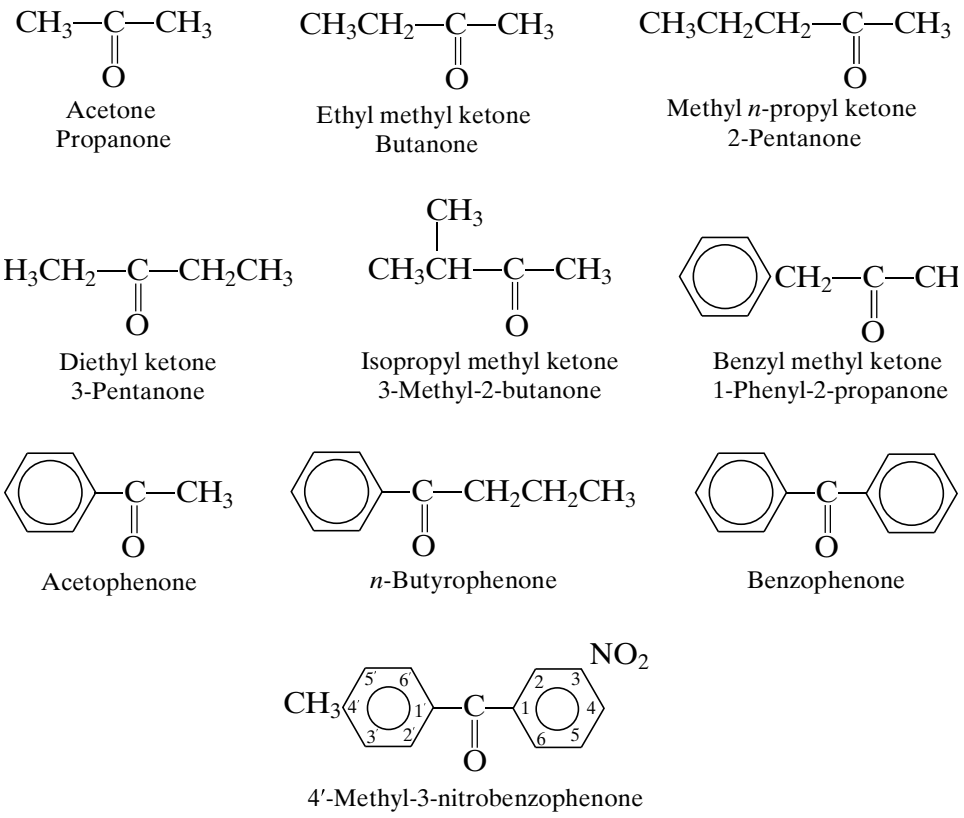
notice that C–2 of the IUPAC name corresponds to *alpha* of the common name.



The simplest aliphatic ketone has the common name of *acetone*. For most other aliphatic **ketones** we name the two groups that are attached to carbonyl carbon, and follow these names by the word *ketone*. A ketone in which the carbonyl group is attached to a benzene ring is named as a *-phenone*, as illustrated below.

According to the IUPAC system, the longest chain carrying the carbonyl group is considered the parent structure, and is named by replacing the *-e* of the corresponding alkane with *-one*. The positions of various groups are indicated by numbers, the carbonyl carbon being given the lowest possible number.

In certain polyfunctional compounds, the presence of a carbonyl group can be indicated by the prefix *oxo-*, with a number to show its position in the molecule.

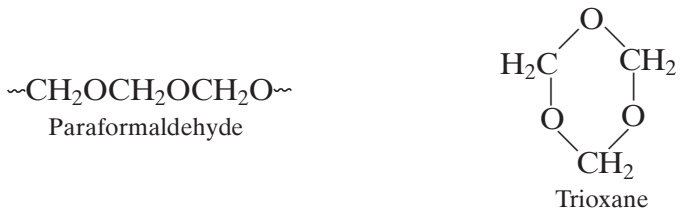


12.3 Physical properties

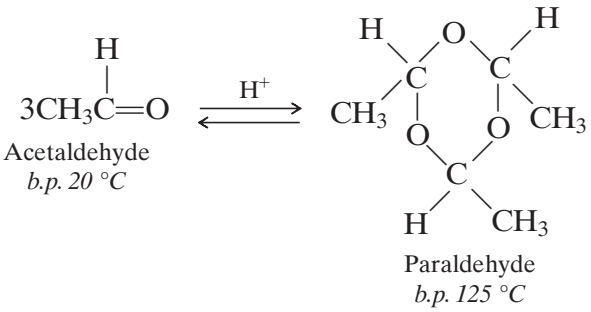
The polar carbonyl group makes aldehydes and ketones polar compounds, and hence they have higher boiling points than non-polar compounds of comparable molecular weight. By themselves, they are not capable of intermolecular hydrogen bonding since they contain hydrogen bonded only to carbon; as a result they have lower boiling points than comparable alcohols or carboxylic acids. For example, compare *n*-butyraldehyde (b.p. 76 °C) and ethyl methyl ketone (b.p. 80 °C) with *n*-pentane (b.p. 36 °C) and diethyl ether (b.p. 35 °C) on the one hand, and with *n*-butyl alcohol (b.p. 118 °C) and propionic acid (b.p. 141 °C) on the other.

The lower aldehydes and ketones are appreciably soluble in water, presumably because of hydrogen bonding between solute and solvent molecules; borderline solubility is reached at about five carbons. Aldehydes and ketones are soluble in the usual organic solvents.

Formaldehyde is a gas (b.p. –21 °C), and is handled either as an aqueous solution (*Formalin*), or as one of its solid polymers: *paraformaldehyde*, $(CH_2O)_n$, or *trioxane*, $(CH_2O)_3$. When dry formaldehyde is desired, as, for example, for reaction with a Grignard reagent, it is obtained by heating paraformaldehyde or trioxane.



Acetaldehyde (b.p. 20 °C) is often generated from its higher-boiling trimer by heating the trimer with acid:



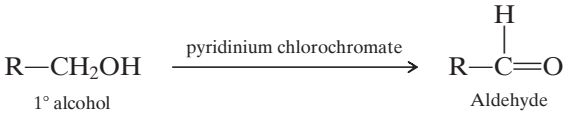
12.4 Preparation

A few of the many laboratory methods of preparing aldehydes and ketones are outlined below; many of these are already familiar to us. Some of the methods involve oxidation or reduction in which an alcohol, hydrocarbon, or acid chloride is converted into an aldehyde or ketone of the same carbon number. Other methods involve the formation of new carbon–carbon bonds, and yield aldehydes or ketones of higher carbon number than the starting materials.

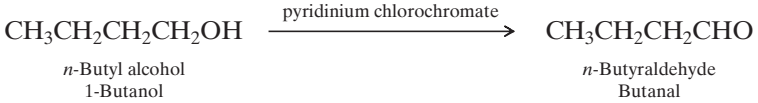
Industrial preparations often involve special methods, or the modification of laboratory methods by use of cheaper reagents: formaldehyde and acetone are made by oxidation of methanol and isopropyl alcohol, respectively, but by air in the presence of a catalyst. Some aldehydes are obtained by the oxo process, in which they are the initial products.

PREPARATION OF ALDEHYDES

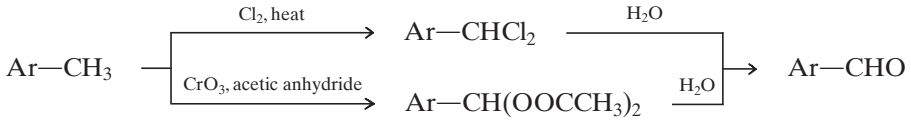
1. Oxidation of primary alcohols.



Example:



2. Oxidation of methylbenzenes.



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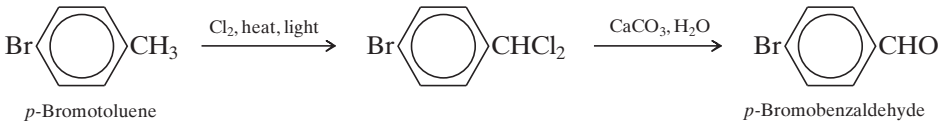
Examples:



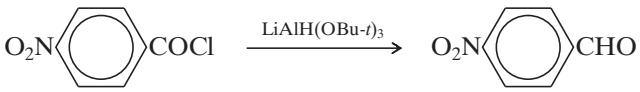
p-Bromotoluene *p*-Bromobenzaldehyde

p-Nitrotoluene *p*-Nitrobenzaldehyde

3. Reduction of acid chlorides.

Acid chloride Aldehyde

Example:

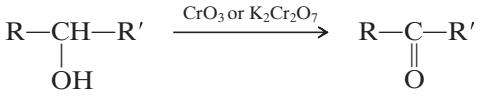


p-Nitrobenzoyl chloride *p*-Nitrobenzaldehyde

4. Reimer–Tiemann reaction. Phenolic aldehydes.

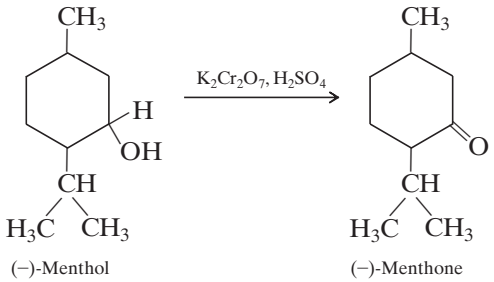
PREPARATION OF KETONES

1. Oxidation of secondary alcohols.



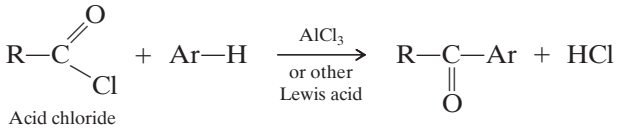
2° alcohol Ketone

Example:



(−)-Menthol (−)-Menthone

2. Friedel–Crafts acylation.



Acid chloride Ketone

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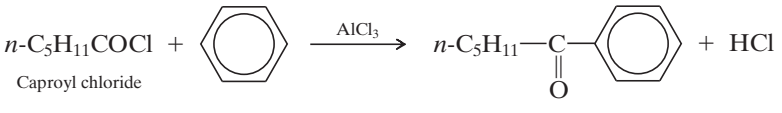
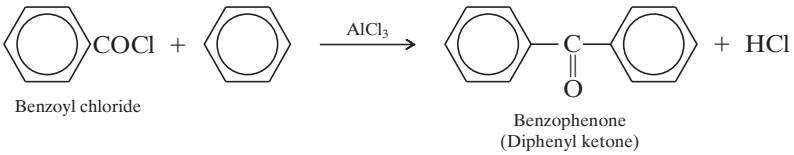
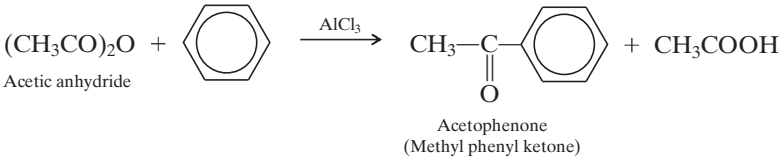
Examples:

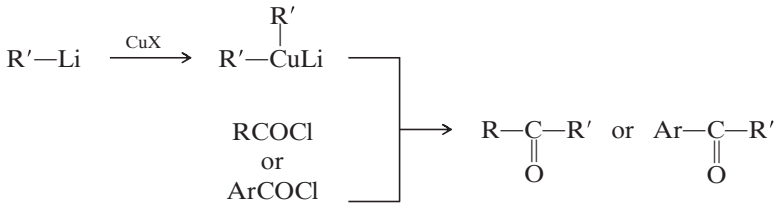


No rearrangement of n-pentyl group

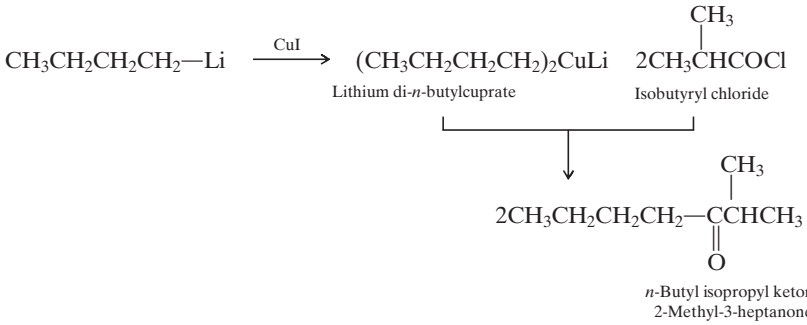


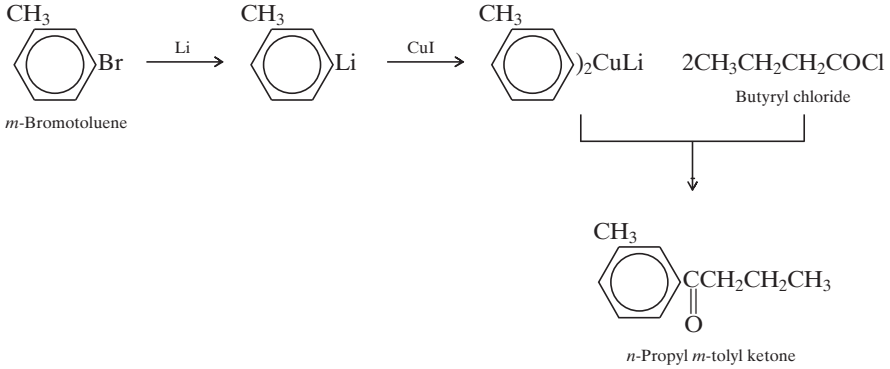


3. Reaction of acid chlorides with organocopper compounds.



Examples:





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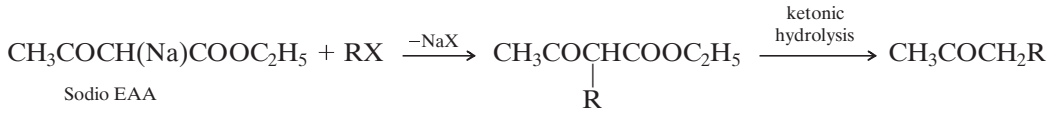
4. Acetoacetic ester synthesis.



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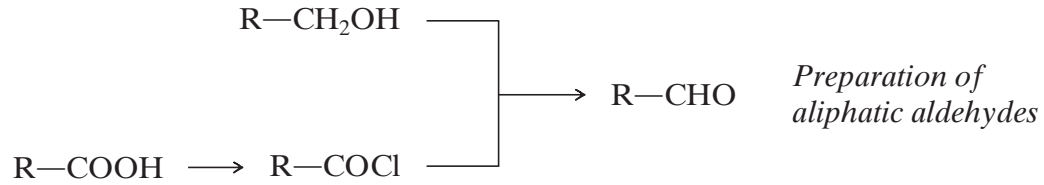
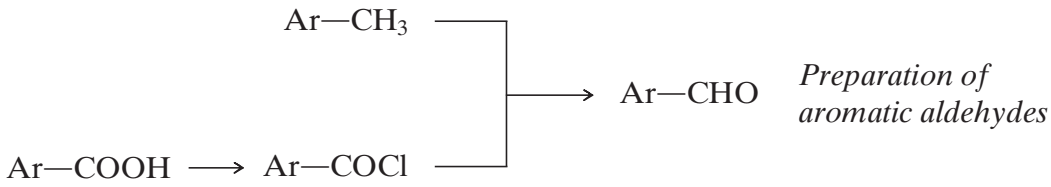
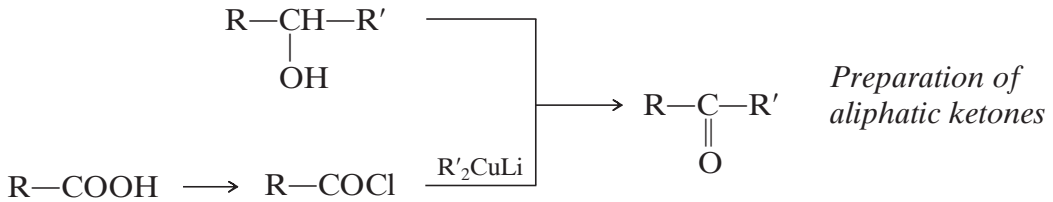
Depending upon the availability of starting materials, **aliphatic aldehydes** can be prepared from alcohols or acid chlorides of the same carbon skeleton, and **aromatic aldehydes** can be prepared from methylbenzenes or aromatic acid chlorides. There are, in addition, a number of methods by which the aldehyde



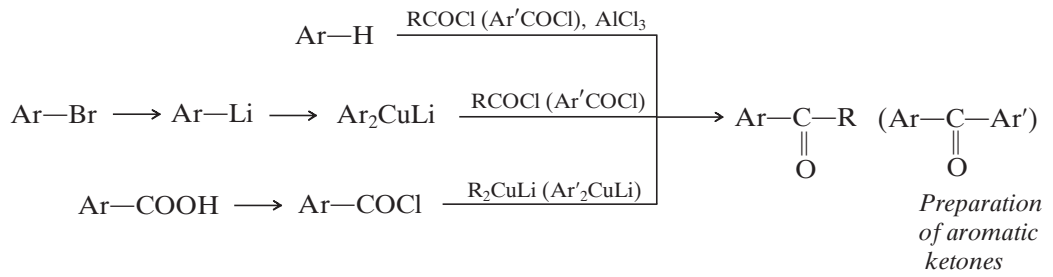


group is introduced into an aromatic ring: for example, the Reimer–Tiemann synthesis of phenolic aldehydes.

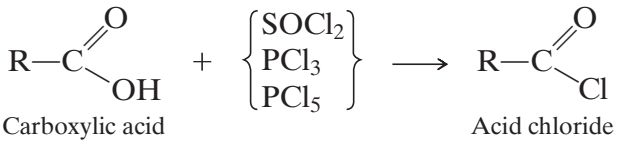
Aliphatic ketones are readily prepared from the corresponding secondary alcohols, if these are available. More complicated aliphatic ketones can be prepared by the reaction of acid chlorides with organocopper compounds. A particularly useful



method for making complicated aliphatic ketones is the acetoacetic ester synthesis. **Aromatic ketones** containing a carbonyl group attached directly to an aromatic ring are conveniently prepared by Friedel–Crafts acylation.



As we see, important precursors of both aldehydes and ketones are *acid chlorides*. These are conveniently made from the corresponding carboxylic acids by treatment with thionyl chloride ($SOCl_2$),phosphorus trichloride (PCl_3), or phosphorus pentachloride (PCI_5). Since we already know several of the most important ways of



Carboxylic acid Acid chloride

making carboxylic acids—oxidation of primary alcohols and oxidation of toluenes—we can begin to fit these syntheses of carbonyl compounds into the overall framework of organic chemistry.

Problem 12.1 Would it be feasible to make *p*-nitroacetophenone via a reaction between lithium di(*p*-nitrophenyl)cuprate, $(p\text{-}O_2NC_6H_4)_2CuLi$, and acetyl chloride?

12.5 Reactions. Nucleophilic addition

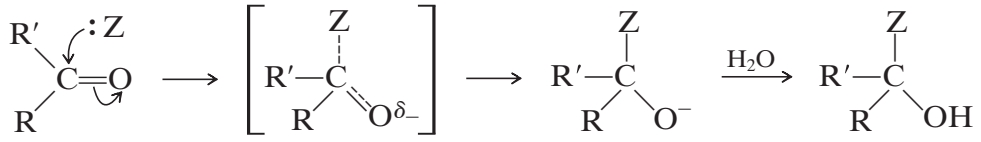
The carbonyl group, C═O, governs the chemistry of aldehydes and ketones. It does this in two ways: (a) by providing a site for nucleophilic addition, and (b) by increasing the acidity of the hydrogen atoms attached to the *alpha* carbon. Both these effects are quite consistent with the structure of the carbonyl group and, in fact, are due to the same thing: the ability of oxygen to accommodate a negative charge.

In this section, we shall examine the carbonyl group as a site for nucleophilic addition.

The carbonyl group contains a carbon–oxygen double bond; since the mobile π electrons are pulled strongly toward oxygen, carbonyl carbon is electron-deficient and carbonyl oxygen is electron-rich. Because it is flat, this part of the molecule is open to relatively unhindered attack from above or below, in a direction perpendi-cular to the plane of the group. It is not surprising that this accessible, polarized group is highly reactive.

What kind of reagents will attack such a group? Since the important step in these reactions is the formation of a bond to the electron-deficient (electrophilic) carbonyl carbon, the carbonyl group is most susceptible to attack by electron-rich, nucleophilic reagents, that is, by bases. **The typical reaction of aldehydes and ketones is nucleophilic addition**.

Nucleophilic addition



Reactant Transition state Product

Trigonal *Becoming tetrahedral Partial negative charge on oxygen* *Tetrahedral Negative charge on oxygen*

As might be expected, we can get a much truer picture of the reactivity of the carbonyl group by looking at the transition state for attack by a nucleophile. In the reactant, carbon is trigonal. In the transition state, carbon has begun to acquire the tetrahedral configuration it will have in the product; the attached groups are thus being brought closer together. We might expect moderate steric hindrance in this reaction; that is, larger groups (R and R′) will tend to resist crowding more than smaller groups. But the transition state is a relatively roomy one compared, say, with the transition state for an S_N2 reaction, with its pentavalent carbon; it is this comparative uncrowdedness that we are really referring to when we say that the carbonyl group is "accessible" to attack (see Fig. 12.2).

In the transition state, oxygen has started to acquire the electrons—and the negative charge—that it will have in the product. *It is the tendency of oxygen to acquire electrons—its ability to carry a negative charge—that is the real cause of the reactivity of the carbonyl group toward nucleophiles.* (The polarity of the carbonyl group is not the *cause* of the reactivity; it is simply another *manifestation* of the elec-tronegativity of oxygen.)

Aldehydes generally undergo nucleophilic addition more readily than ketones. This difference in reactivity is consistent with the transition states involved, and seems to be due to a combination of electronic and steric factors. A ketone contains

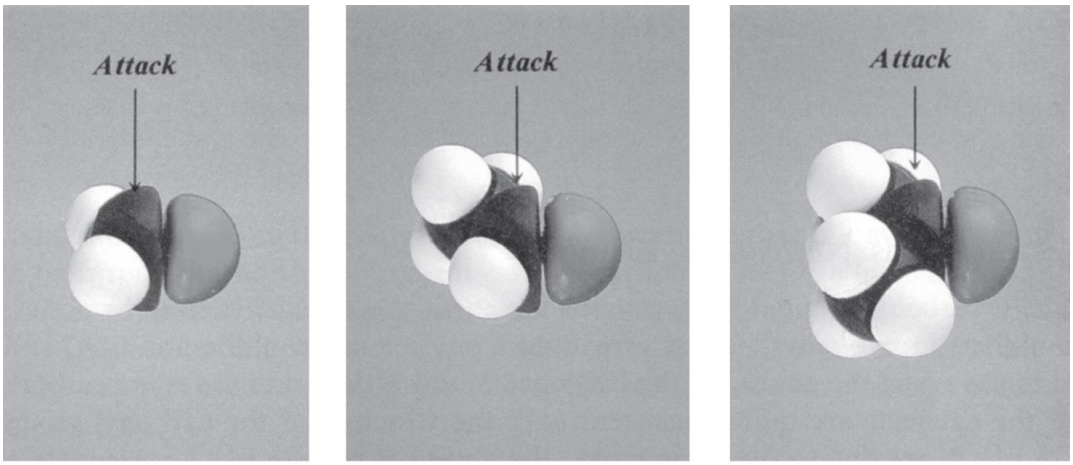
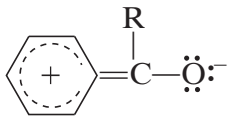


Figure 12.2 Molecular structure and reactivity: nucleophilic attack on the carbonyl group. Models of: (*a*) formaldehyde, HCHO; (*b*) acetaldehyde, CH_3CHO; (*c*) acetone, CH_3COCH_3. The flat carbonyl group is open to attack from above (or below). As hydrogen is replaced by the larger methyl, moderate crowding lowers reactivity.

a second alkyl or aryl group where an aldehyde contains a hydrogen atom. A second alkyl or aryl group of a ketone is larger than the hydrogen of an aldehyde, and resists more strongly the crowding together in the transition state (Fig. 12.2). An alkyl group releases electrons, and thus destabilizes the transition state by intensifying the negative charge developing on oxygen.

An aryl group has an electron-withdrawing inductive effect, and we might have expected it to stabilize the transition state and thus speed up reaction; however, it seems to stabilize the *reactant* even more, by resonance (contribution by I), and thus causes net deactivation.



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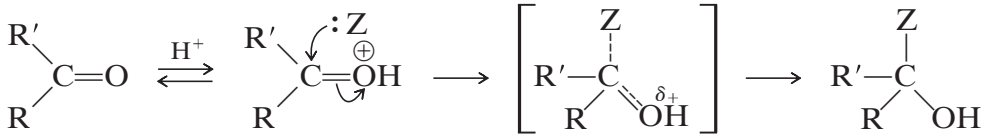
If acid is present, hydrogen ion becomes attached to carbonyl oxygen. This prior protonation lowers the E_{act} for nucleophilic attack, since it permits oxygen to acquire

Acid-catalyzed nucleophilic addition



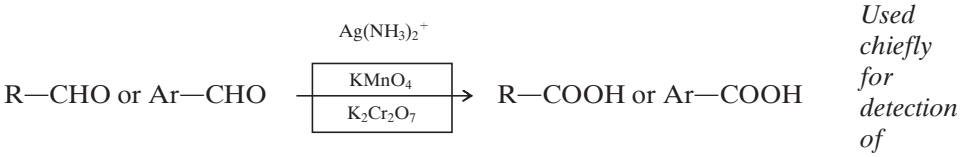
Undergoes nucleophilic attack more readily

the π electrons without having to accept a negative charge. Thus nucleophilic addi-tion to aldehydes and ketones can be catalysed by acids (sometimes, by *Lewis* acids).

REACTIONS OF ALDEHYDES AND KETONES

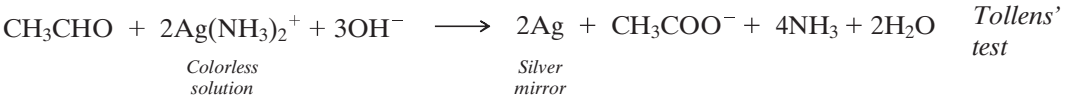
1. Oxidation

(a) Aldehydes.



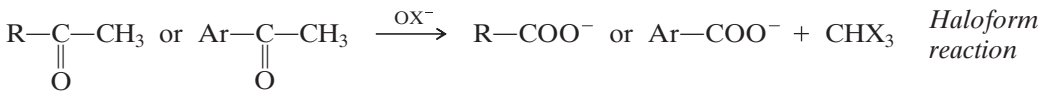
Used chiefly for detection of aldehydes

Example:



Tollens' test

(b) Methyl ketones.



Haloform reaction

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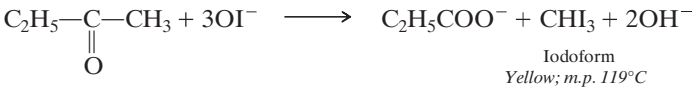
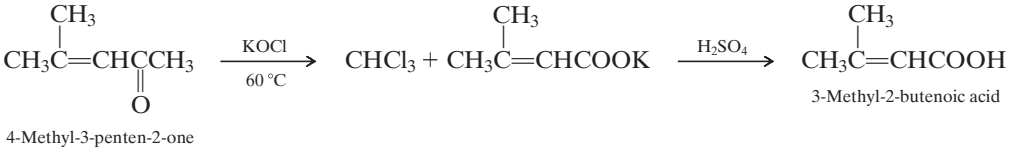
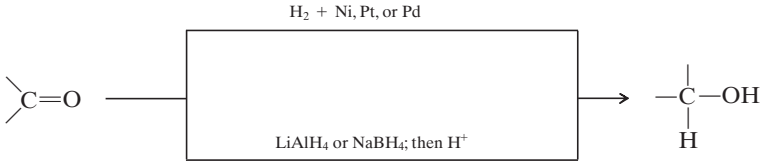
Examples:





2. Reduction

(a) Reduction to alcohols.



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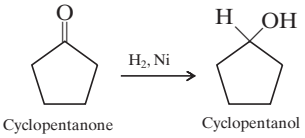
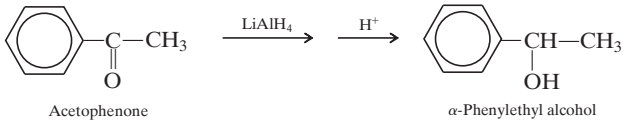
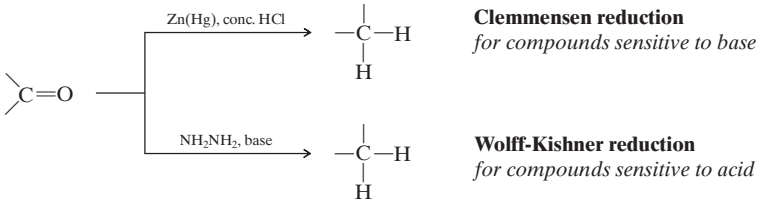




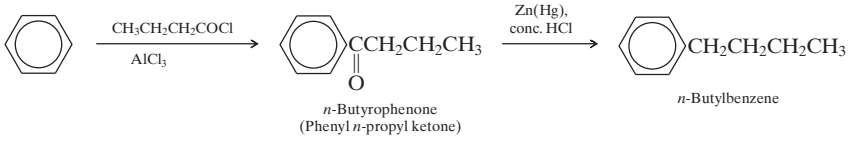
(b) Reduction to hydrocarbons.

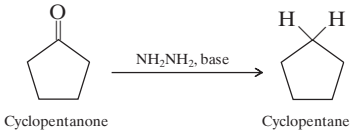


Clemmensen reduction
for compounds sensitive to base

Wolff-Kishner reduction
for compounds sensitive to acid

Examples:





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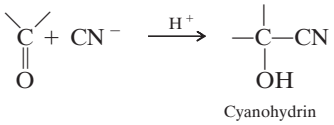
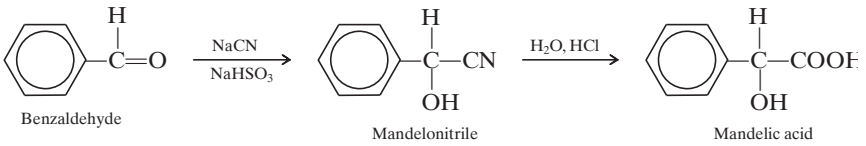
(c) Reductive amination.

3. Addition of cyanide. Cyanohydrin formation.

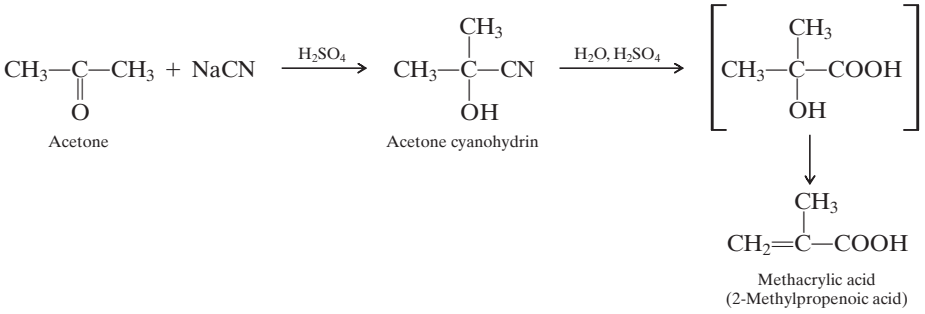


Cyanohydrin

Examples:

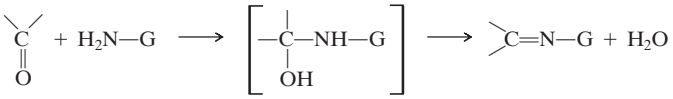


Benzaldehyde Mandelonitrile Mandelic acid



Acetone Acetone cyanohydrin Methacrylic acid (2-Methylpropenoic acid)

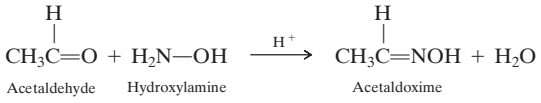
4. Addition of derivatives of ammonia.



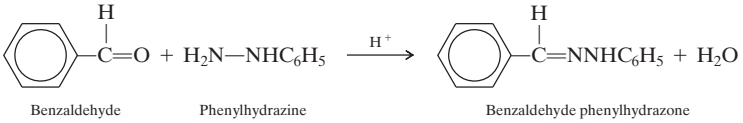
Used for identification

H_2N—G		Product	
H_2N—OH	Hydroxylamine	C=N—OH	Oxime
H_2N—NH_2	Hydrazine	C=N—NH_2	Hydrazone
H_2N—NHC_6H_5	Phenylhydrazine	C=N—NHC_6H_5	Phenylhydrazone
H_2N—$NHCONH_2$	Semicarbazide	C=N—$NHCONH_2$	Semicarbazone

Examples:



Acetaldehyde Hydroxylamine Acetaldoxime



Benzaldehyde Phenylhydrazine Benzaldehyde phenylhydrazone

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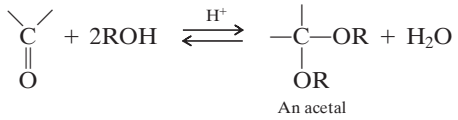
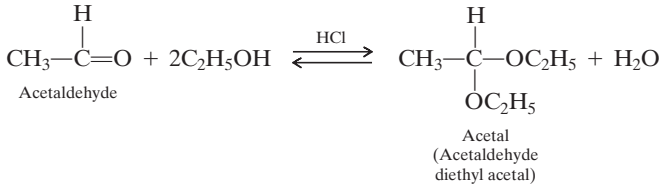
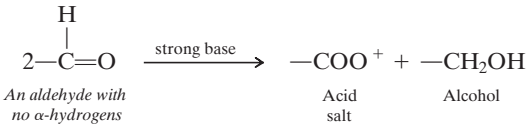
5. Addition of alcohols. Acetal formation.



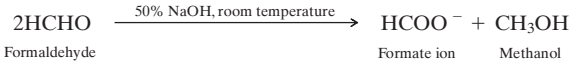
Example:

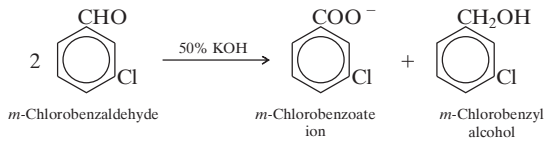


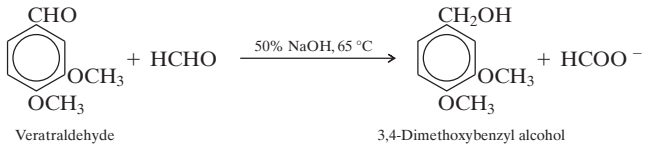
6. Cannizzaro reaction.



Examples:

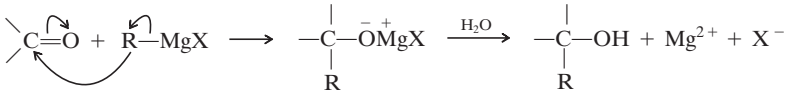


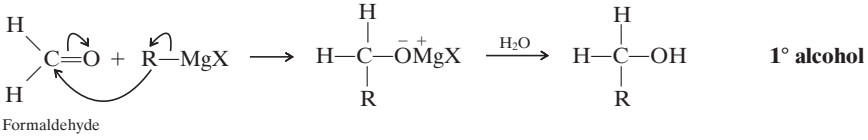




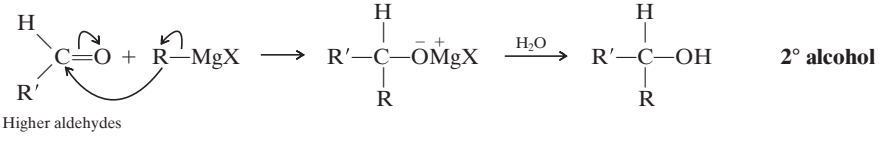
Crossed Cannizzaro reaction

7. Addition of Grignard reagents.





1° alcohol



2° alcohol

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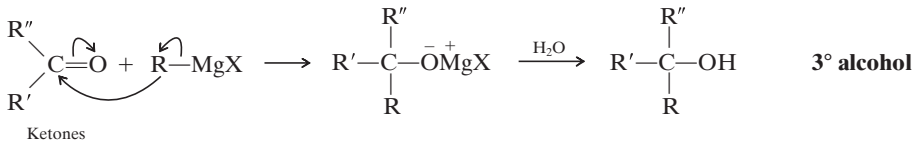
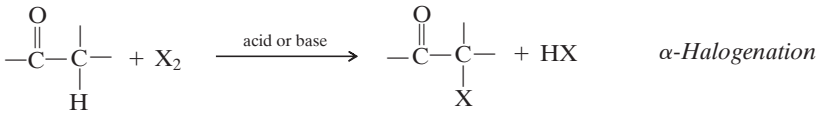


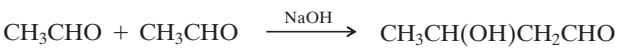
8. Halogenation of ketones.



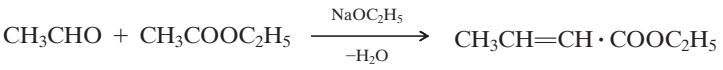
$X_2 = Cl_2, Br_2, I_2$

9. Addition of carbanions.

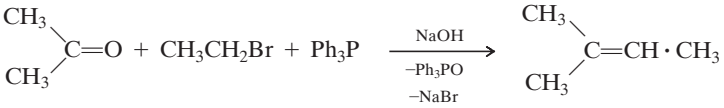
(a) Aldol condensation.



(b) Reactions related to aldol condensation.



(c) Wittig reaction.



■

12.6 Oxidation

Aldehydes are easily oxidized to carboxylic acids; ketones are not. Oxidation is the reaction in which aldehydes differ most from ketones, and this difference stems directly from their difference in structure: by definition, an aldehyde has a hydrogen atom attached to the carbonyl carbon, and a ketone has not. Regardless of exact mechanism, this hydrogen is abstracted in oxidation, either as a proton or as an atom, but the analogous reaction for a ketone—abstraction of an alkyl or aryl group—does not take place.

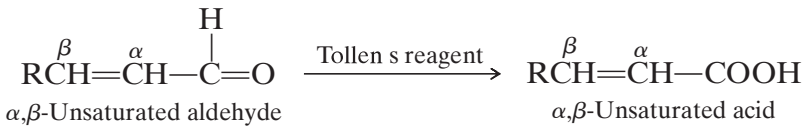
Aldehydes are oxidized not only by the same reagents that oxidize primary and secondary alcohols—permanganate and dichromate—but also by the very mild oxidizing agent silver ion. Oxidation by silver ion requires an alkaline medium; to prevent precipitation of the insoluble silver oxide, a complexing agent is added: ammonia.

Tollens' reagent contains the silver ammonia ion, $Ag(NH_3)_2^+$. Oxidation of the aldehyde is accompanied by reduction of silver ion to free silver (in the form of a *mirror* under the proper conditions).

$$\underset{}{RCHO} + \underset{\textit{Colorless solution}}{Ag(NH_3)_2^+} \longrightarrow \underset{}{RCOO^-} + \underset{\textit{Silver mirror}}{Ag}$$

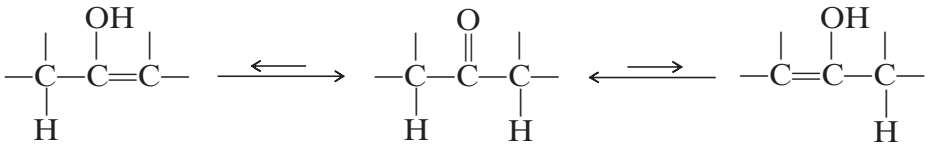
(Oxidation by complexed cupric ion is a characteristic of certain substituted carbonyl compounds, and will be taken up with *carbohydrates*.)

Oxidation by Tollens' reagent is useful chiefly for detecting aldehydes, and in particular for differentiating them from ketones. The reaction is of value in synthesis in those cases where aldehydes are more readily available than the corresponding acids: in particular, for the synthesis of unsaturated acids from the unsaturated aldehydes obtained from the aldol condensation, where advantage is taken of the fact that Tollens' reagent does not attack carbon–carbon double bonds. It is a chemoselective oxidant.



α,β-Unsaturated aldehyde — α,β-Unsaturated acid

Oxidation of ketones requires breaking of carbon–carbon bonds, and (except for the haloform reaction) takes place only under vigorous conditions. Cleavage involves the double bond of the *enol* form and, where the structure permits, occurs



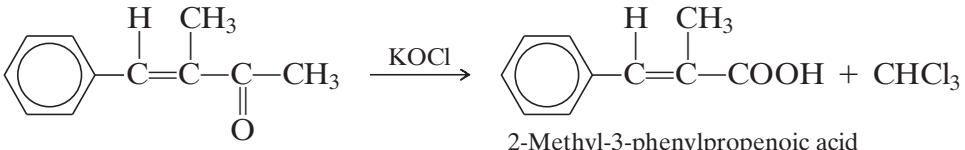
Enol — Ketone — Enol

on either side of the carbonyl group; in general, then, mixtures of carboxylic acids are obtained.

Problem 12.2 Predict the product(s) of vigorous oxidation of: (a) 3-hexanone; (b) cyclohexanone.

Methyl ketones are oxidized smoothly by means of hypohalite in the haloform reaction. Besides being commonly used to detect these ketones, this reaction is often

useful in synthesis, hypohalite having the special advantage of not attacking carbon–carbon double bonds. For example:

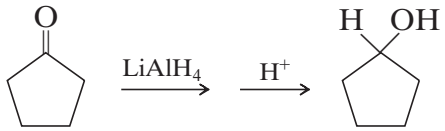


Available by aldol condensation

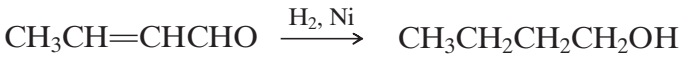
2-Methyl-3-phenylpropenoic acid
α-Methylcinnamic acid

12.7 Reduction

Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, either by catalytic hydrogenation or by use of chemical reducing agents like lithium aluminum hydride, $LiAlH_4$. Such reduction is useful for the preparation of certain alcohols that are less available than the corresponding carbonyl compounds, in particular carbonyl compounds that can be obtained by the aldol condensation. For example:

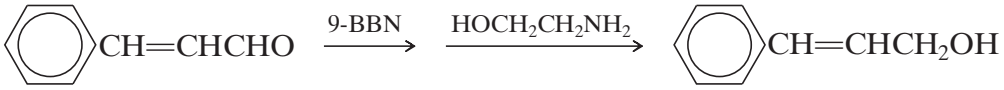


Cyclopentanone Cyclopentanol



2-Butenal
Crotonaldehyde
From aldol condensation of acetaldehyde

n-Butyl alcohol



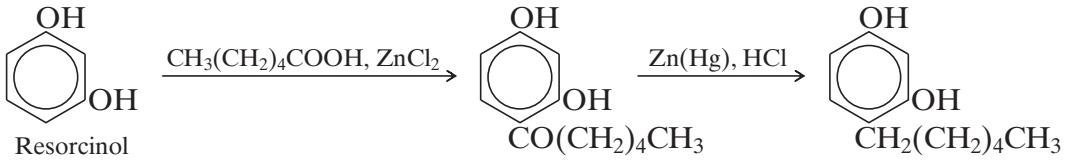
3-Phenylpropenal
Cinnamaldehyde
From aldol condensation of benzaldehyde and acetaldehyde
(Sec.)

3-Phenyl-2-propen-1-ol
Cinnamyl alcohol

To reduce a carbonyl group that is conjugated with a carbon–carbon double bond without reducing the carbon–carbon double bond, too, requires a *regioselective* reducing agent.

Aldehydes and ketones can be reduced to hydrocarbons by the action (a) of amalgamated zinc and concentrated hydrochloric acid, the **Clemmensen reduction**; or (b) of hydrazine, NH_2NH_2, and a strong base like KOH or potassium *tert*-butoxide, the **Wolff–Kishner reduction**. These are particularly important when applied to the alkyl aryl ketones obtained from Friedel–Crafts acylation, since this

reaction sequence permits, indirectly, the attachment of straight alkyl chains to the benzene ring. For example:



Resorcinol

4-*n*-Hexylresorcinol
Used as an antiseptic

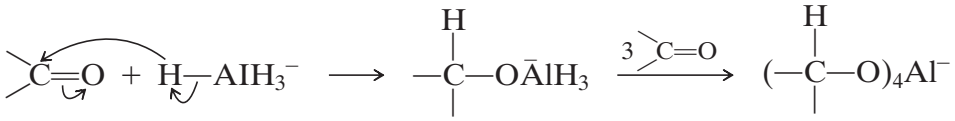
A special sort of oxidation and reduction is the *Cannizzaro reaction*. For example:

$$HCHO + HCHO \xrightarrow{\text{conc. NaOH}} CH_3OH + HCOOH$$

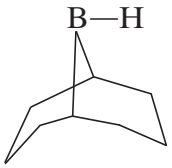
Let us look a little more closely at reduction by metal hydrides. Alcohols are formed from carbonyl compounds, smoothly and in high yield, by the action of such compounds as lithium aluminum hydride. $LiAlH_4$. Here again, we see nucleophilic

$$4R_2C{=}O + LiAlH_4 \longrightarrow (R_2CHO)_4AlLi \xrightarrow{H_2O} 4R_2CHOH + LiOH + Al(OH)_3$$

addition: this time the nucleophile is hydrogen transferred with a pair of electrons—as a hydride ion, $H{:}^-$—from the metal to carbonyl carbon:



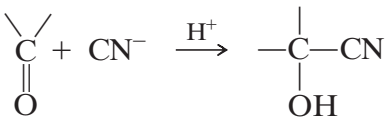
Complex metal hydride reductants have been so developed that some of them can chemoselectively reduce aldehydes in preference to ketones, for example, 9-borabicyclo-[3,3,1]-nonane (9-BBN) can selectively reduce an aldehyde in the presence of a ketone.



9-BBN

12.8 Addition of cyanide

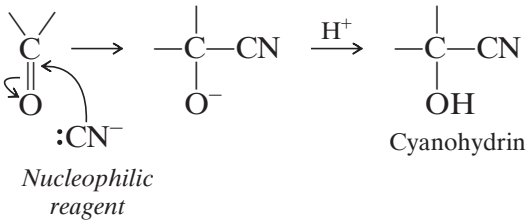
The elements of HCN add to the carbonyl group of aldehydes and ketones to yield compounds known as **cyanohydrins**:



A cyanohydrin

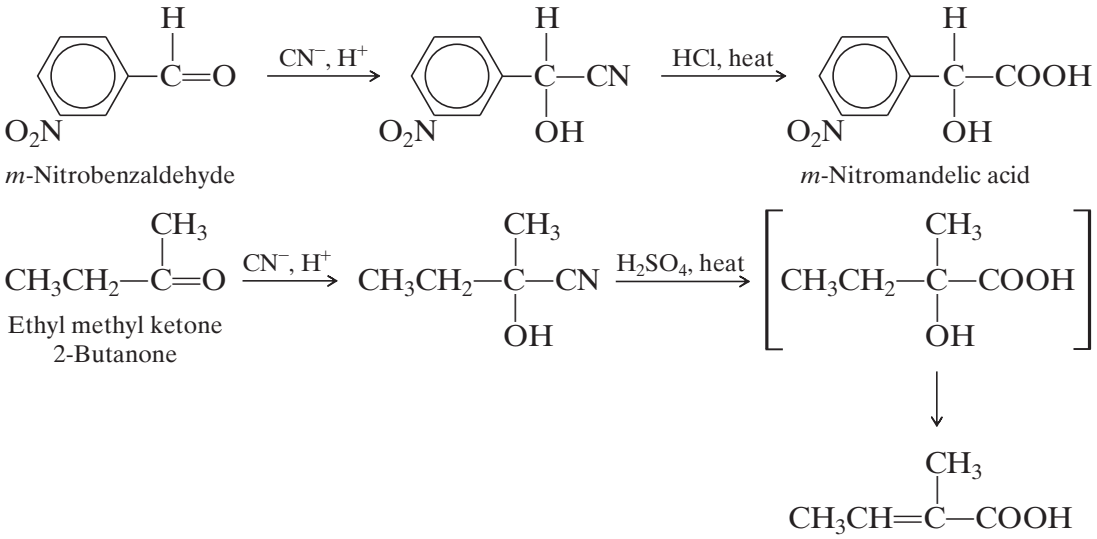
The reaction is often carried out by adding mineral acid to a mixture of the carbonyl compound and aqueous sodium cyanide.

Addition appears to involve nucleophilic attack on carbonyl carbon by the strongly basic cyanide ion; subsequently (or possibly simultaneously) oxygen accepts a hydrogen ion to form the cyanohydrin product:



Although it is the elements of HCN that become attached to the carbonyl group, a highly acidic medium—in which the concentration of un-ionized HCN is highest—actually retards reaction. This is to be expected, since the very weak acid HCN is a poor source of cyanide ion.

Cyanohydrins are *nitriles*, and their principal use is based on the fact that, like other nitriles, they undergo hydrolysis; in this case the products are α-hydroxy acids or unsaturated acids. For example:



Problem 12.3 Each of the following is converted into the cyanohydrin, and the products are separated by careful fractional distillation, crystallization, or chromatography. For each reaction tell how many fractions will be collected, and whether each fraction, as collected, will be optically active or inactive, resolvable or non-resolvable.

(a) Acetaldehyde; (b) benzaldehyde; (c) acetone.

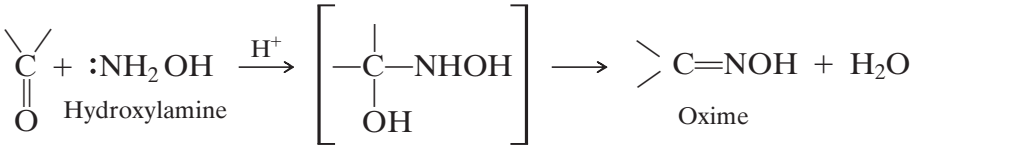
(d) *R*-(+)-glyceraldehyde, $CH_2OHCHOHCHO$; (e) (±)-glyceraldehyde.

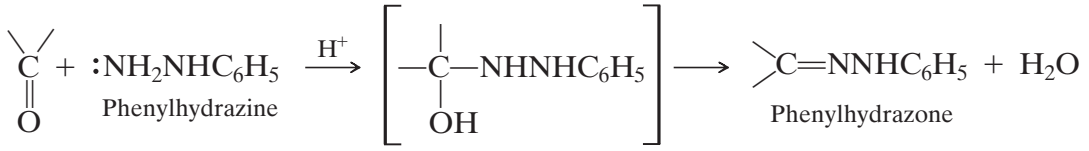
(f) How would your answer to each of the above be changed if each mixture were subjected to hydrolysis to hydroxy acids before fractionation?

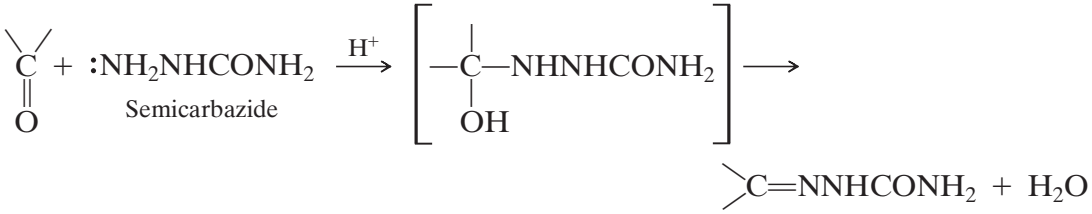
12.9 Addition of derivatives of ammonia

Certain compounds related to ammonia add to the carbonyl group to form derivatives that are important chiefly for the characterization and identification of aldehydes and ketones. The products contain a carbon–nitrogen double bond

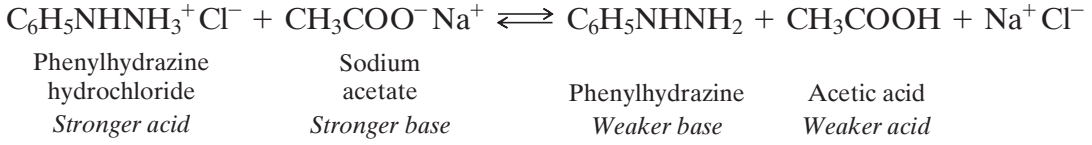
resulting from elimination of a molecule of water from the initial addition products. Some of these reagents and their products are:



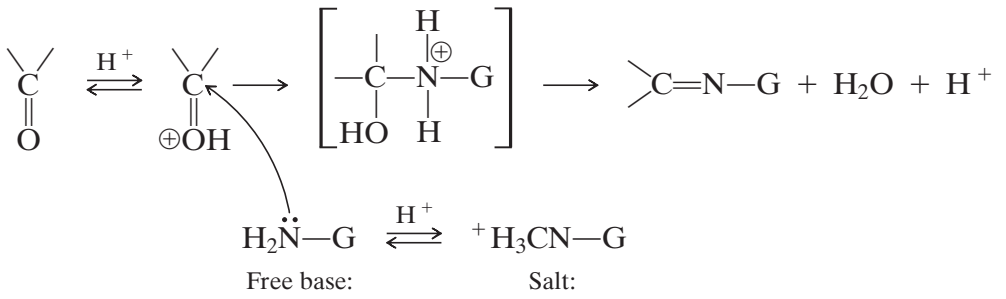




Like ammonia, these derivatives of ammonia are basic, and therefore react with acids to form salts: hydroxylamine hydrochloride, $HONH_3^+Cl^-$; phenylhydrazine hydrochloride, $C_6H_5NHNH_3^+Cl^-$; and semicarbazide hydrochloride, $NH_2CONHNH_3^+Cl^-$. The salts are less easily oxidized by air than the free bases, and it is in this form that the reagents are best preserved and handled.When needed, the basic reagents are liberated from their salts in the presence of the carbonyl compound by addition of a base, usually sodium acetate.



It is often necessary to adjust the reaction medium to just the right acidity. Addition involves nucleophilic attack by the basic nitrogen compound on carbonyl carbon. Protonation of carbonyl oxygen makes carbonyl carbon more susceptible to nucleophilic attack; in so far as the carbonyl compound is concerned, then, addition will be favored by high acidity. But the ammonia derivative, $H_2N—G$, can also undergo protonation to form the ion, $^+H_3N—G$, which lacks unshared electrons and

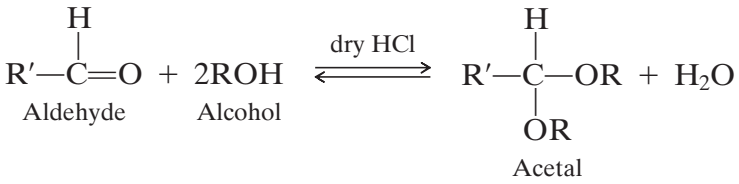


is no longer nucleophilic; in so far as the nitrogen compound is concerned, then, addition is favored by low acidity. The conditions under which addition proceeds most rapidly are thus the result of a compromise: the solution must be acidic enough for an appreciable fraction of the carbonyl compound to be protonated, but not so acidic that the concentration of the free nitrogen compound is too low. The exact conditions used depend upon the basicity of the reagent, and upon the reactivity of the carbonyl compound.

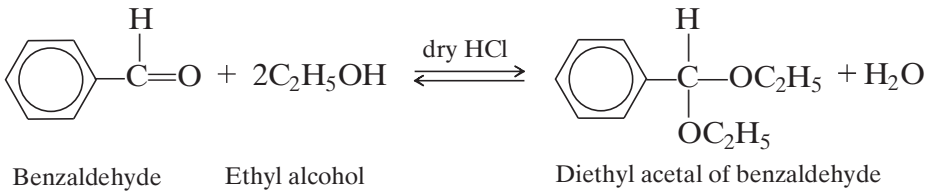
Problem 12.4 Semicarbazide (1 mol) is added to a mixture of cyclohexanone (1 mol) and benzaldehyde (1 mol). If the product is isolated immediately, it consists almost entirely of the semicarbazone of cyclohexanone; if the product is isolated after several hours, it consists almost entirely of the semicarbazone of benzaldehyde. How do you account for these observations?

12.10 Addition of alcohols. Acetal formation

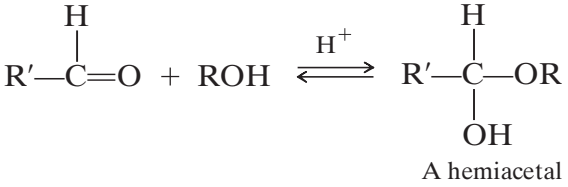
Alcohols add to the carbonyl group of aldehydes in the presence of anhydrous acids to yield **acetals**:



The reaction is carried out by allowing the aldehyde to stand with an excess of the anhydrous alcohol and a little anhydrous acid, usually hydrogen chloride. In the preparation of ethyl acetals the water is often removed as it is formed by means of the azeotrope of water, benzene, and ethyl alcohol (b.p. 64.9 °C). (Simple *ketals* are usually difficult to prepare by reaction of ketones with alcohols, and are made in other ways.)

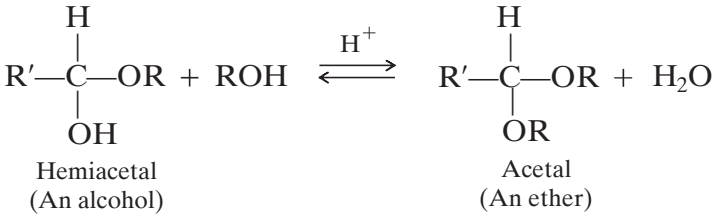


There is good evidence that in alcoholic solution an aldehyde exists in equili-brium with a compound called a **hemiacetal**:

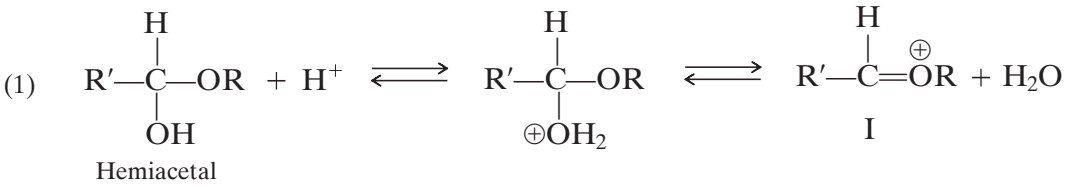


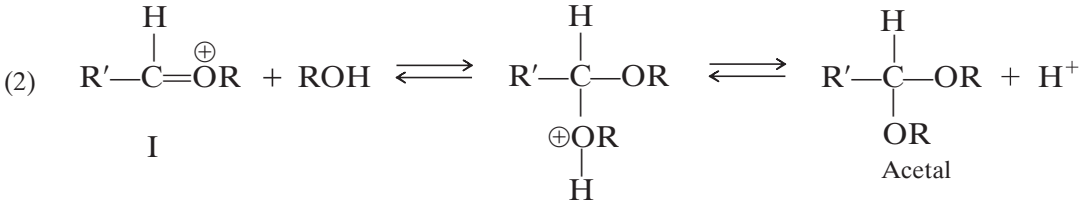
A hemiacetal is formed by the addition of the nucleophilic alcohol molecule to the carbonyl group; it is both an ether and an alcohol. With a few exceptions, hemiacetals are too unstable to be isolated.

In the presence of acid the hemiacetal, acting as an alcohol, reacts with more of the solvent alcohol to form the acetal, an ether:



The reaction involves the formation (step 1) of the ion I, which then combines (step 2) with a molecule of alcohol to yield the protonated acetal. As we can see,

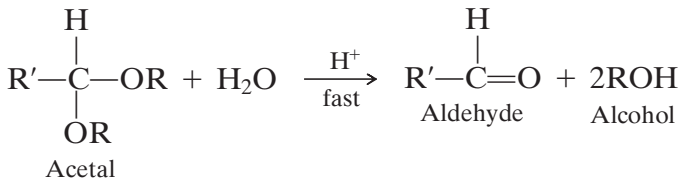




this mechanism is strictly analogous to the S_N1 route we have previously encountered for the formation of ethers.

Acetal formation thus involves (a) nucleophilic addition to a carbonyl group, and (b) ether formation via a carbocation.

Acetals have the structure of ethers and, like ethers, are cleaved by acids and are stable toward bases. Acetals differ from ethers, however, in the extreme *ease* with which they undergo acidic cleavage; they are rapidly converted even at room



temperature into the aldehyde and alcohol by dilute mineral acids. The mechanism of hydrolysis is exactly the reverse of the one by which acetals are formed.

Problem 12.5 Account for the fact that anhydrous acids bring about formation of acetals whereas aqueous acids bring about hydrolysis of acetals.

12.11 Cannizzaro reaction

In the presence of concentrated alkali, aldehydes containing no α-hydrogens undergo self-oxidation-and-reduction to yield a mixture of an alcohol and a salt of a carboxylic acid. This reaction, known as the **Cannizzaro reaction**, is generally brought about by allowing the aldehyde to stand at room temperature with concentrated aqueous or alcoholic hydroxide. (Under these conditions an aldehyde containing α-hydrogens would undergo aldol condensation faster.)

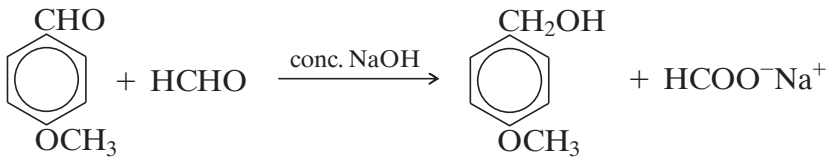
$$\underset{\text{Formaldehyde}}{2HCHO} \xrightarrow{50\%\ NaOH} \underset{\text{Methanol}}{CH_3OH} + \underset{\text{Sodium formate}}{HCOO^-Na^+}$$

p-Nitrobenzaldehyde — *p*-Nitrobenzyl alcohol — Sodium *p*-nitrobenzoate

In general, a mixture of two aldehydes undergoes a Cannizzaro reaction to yield all possible products. If one of the aldehydes is formaldehyde, however, reaction yields almost exclusively sodium formate and the alcohol corresponding to the other aldehyde:

$$ArCHO + HCHO \xrightarrow{conc.\ NaOH} ArCH_2OH + HCOO^-Na^+$$

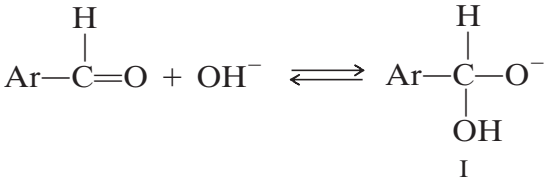
Such a reaction is called a **crossed Cannizzaro reaction**. For example:



Anisaldehyde (*p*-Methoxybenzaldehyde) — *p*-Methoxybenzyl alcohol

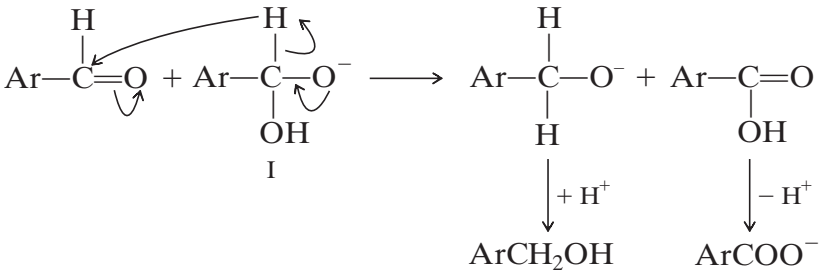
Evidence, chiefly from kinetics and experiments with isotopically labeled compounds, indicates that even this seemingly different reaction follows the familiar pattern for carbonyl compounds: nucleophilic addition. Two successive additions are

(1)



I

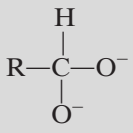
(2)



I

involved: addition of hydroxide ion (step 1) to give intermediate I; and addition of a hydride ion from I (step 2) to a second molecule of aldehyde. The presence of the negative charge on I aids in the loss of hydride ion.

Problem 12.6 In the case of some aldehydes there is evidence that intermediate II is the hydride donor in the Cannizzaro reactions, (a) How would II be formed from I?



II

(b) Why would you expect II to be a better hydride donor than I? (*Hint*: What is one product of the hydride transfer from II?)

Problem 12.7 Suggest an experiment to prove that a hydride transfer of the kind shown in step (2) is actually involved, that is, that hydrogen is transferred from I and not from the solvent.

Problem 12.8 From examination of the mechanism, can you suggest one factor that would tend to make a crossed Cannizzaro reaction involving formaldehyde take place in the particular way it does?

Problem 12.9 Phenylglyoxal, C_6H_5COCHO, is converted by aqueous sodium hydroxide into sodium mandelate, $C_6H_5CHOHCOONa$. Suggest a likely mechanism for this conversion.

Problem 12.10 In the **benzilic acid rearrangement**, the diketone *benzil* is converted by sodium hydroxide into the salt of *benzilic acid*.

$$\underset{\text{Benzil}}{C_6H_5COCOC_6H_5} \xrightarrow{OH^-} (C_6H_5)_2C(OH)COO^- \xrightarrow{H^+} \underset{\text{Benzilic acid}}{(C_6H_5)_2C(OH)COOH}$$

If sodium methoxide is used instead of sodium hydroxide, the ester $(C_6H_5)_2C(OH)COOCH_3$ is obtained. Suggest a possible mechanism for this rearrangement.

12.12 Addition of Grignard reagents

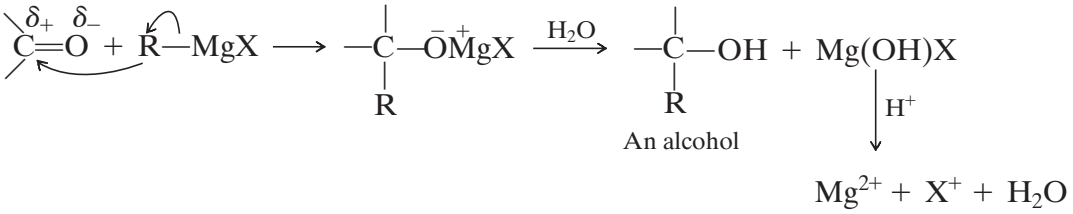
The Grignard reagent, we recall, has the formula RMgX, and is prepared by the reaction of metallic magnesium with the appropriate organic halide. This halide can be alkyl (1°, 2°, 3°), allylic, aralkyl (e.g., benzyl), or aryl (phenyl or substituted phenyl).

$$RX + Mg \xrightarrow{\text{anhydrous ether}} \underset{\substack{\text{A Grignard}\\ \text{reagent}}}{RMgX}$$

The halogen may be —Cl, —Br, or —I. (Arylmagnesium *chlorides* must be made in the cyclic ether tetrahydrofuran instead of diethyl ether.)

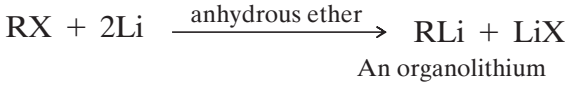
One of the most important uses of the Grignard reagent lies in its reaction with aldehydes and ketones. The carbon–magnesium bond of the Grignard reagent is a

highly polar bond, carbon being negative relative to electropositive magnesium. It is not surprising, then, that in the addition to carbonyl compounds, the organic group becomes attached to carbon and magnesium to oxygen. The product is the magnesium



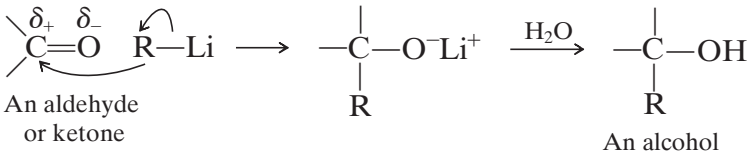
salt of the weakly acidic alcohol and is easily converted into the alcohol itself by the addition of the stronger acid, water. Since the Mg(OH)X thus formed is a gelatinous material difficult to handle, dilute mineral acid (HCl, H_2SO_4) is commonly used instead of water, so that water-soluble magnesium salts are formed.

Grignard reagents are the classical reagents for such syntheses. Increasingly, however, *organolithium* compounds are being used instead, chiefly because they are less prone to unwanted side reactions. Organolithiums can be prepared in the same way as Grignard reagents, by reaction of the metal with organic halides. Because



lithium is more electropositive than magnesium, carbon–lithium bonds are more polar than carbon–magnesium bonds; carbon is more negative—more carbanion-like—and organolithiums are in general somewhat more reactive than Grignard reagents.

Organolithiums react with aldehydes and ketones in the same manner that we have shown for Grignard reagents, and yield the same kinds of products. We shall consider this reaction to be an extension of Grignard's original synthesis. We shall



refer to the general method as the *Grignard synthesis of alcohols*, and often discuss it in terms of organomagnesium reagents; it should be understood, however, that most of what we say applies to the analogous synthesis involving organolithiums.

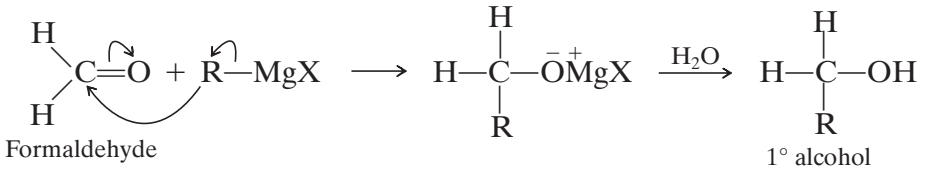
Problem 12.11 Write equations for the reaction of *n*-butyllithium with: (a) H_2O; (b) D_2O; (c) C_2H_5OH; (d) CH_3NH_2; (e) $C_2H_5C{\equiv}CH$; (f) $CH_3\overset{\overset{O}{\|}}{C}CH_3$.

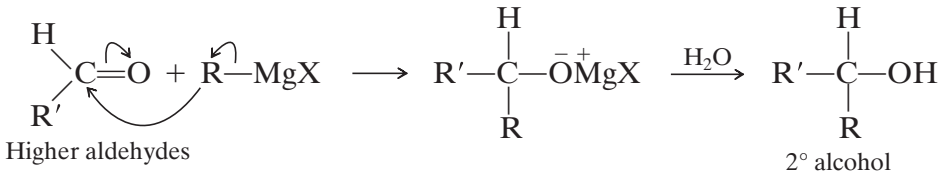
Now, why is the Grignard synthesis so important? Because it enables us to take two organic molecules and convert them into a bigger one. To do this, *we form a carbon–carbon bond*. Once again we join together electrophilic carbon and

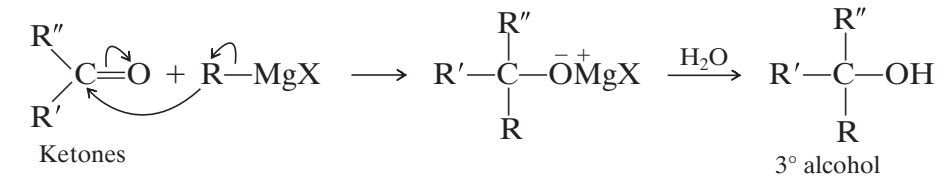
nucleophilic carbon. This time, electrophilic carbon is furnished by the carbonyl group. For nucleophilic carbon we turn again to the carbanion-like organic group of an organometallic compound: a Grignard reagent or an organolithium. The Grignard reaction is thus an example of the typical reaction of aldehydes and ketones: nucleophilic addition.

But this is only half the story. Not only does the Grignard synthesis involve formation of a carbon–carbon bond, but the product contains the highly versatile group, —OH. And now, as we shall soon see, the way is open to further synthesis, and the building of still bigger and more complicated structures.

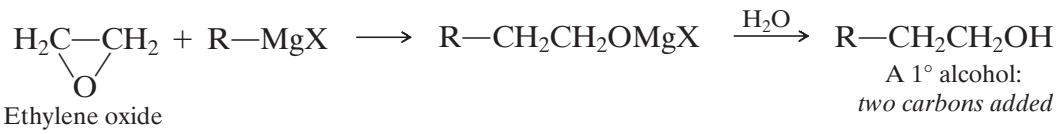
The class of alcohol that is obtained from a Grignard synthesis depends upon the type of carbonyl compound used: *formaldehyde*, HCHO, *yields primary alcohols; other aldehydes*, RCHO, *yield secondary alcohols;* and *ketones*, R_2CO, *yield tertiary alcohols*.



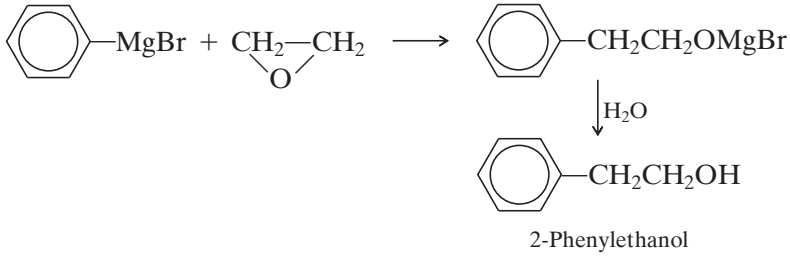




It is convenient at this point to bring in a related synthesis, one that utilizes *ethylene oxide* to make *primary alcohols containing two more carbons* than the Grignard reagent. Here, too, the organic group becomes attached to carbon and



magnesium to oxygen, this time with the breaking of a carbon–oxygen σ bond in a highly strained three-membered ring. For example,



12.13 Limitations of the Grignard synthesis

The very reactivity that makes a Grignard reagent so useful strictly limits how we may use it. We must keep this reactivity in mind when we plan the experimental conditions of the synthesis, when we select the halide that is to become the Grignard reagent, and when we select the compound with which it is to react.

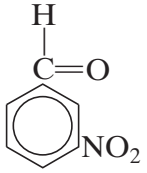
In our first encounter with the Grignard reagent, we allowed it to react with water to form an alkane; the stronger acid, water, displaced the extremely weak acid, the alkane, from its salt. In the same way, *any* compound containing hydrogen attached to an electronegative element—oxygen, nitrogen, sulfur, or even triply bonded carbon—is acidic enough to decompose a Grignard reagent. A Grignard reagent reacts rapidly with oxygen and carbon dioxide, and with nearly every organic compound containing a carbon–oxygen or carbon–nitrogen multiple bond.

How does all this affect our reaction between a Grignard reagent and, say, an aldehyde? First of all, alkyl halide, aldehyde, and the ether used as solvent must be scrupulously dried and freed of the alcohol from which each was very probably made; a Grignard reagent will not even form in the presence of water. Our apparatus must be completely dry before we start. We must protect the reaction system from the water vapor, oxygen, and carbon dioxide of the air: water vapor can be kept out by use of calcium chloride tubes, and oxygen and carbon dioxide can be swept out of the system with dry nitrogen. Having done all this we may hope to obtain a good yield of product—providing we have properly chosen the halide and the aldehyde.

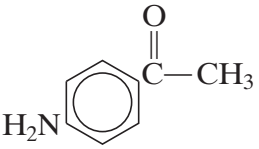
We cannot prepare a Grignard reagent from a compound (e.g., $HOCH_2CH_2Br$) that contains, in addition to halogen, some group (e.g., —OH) that will react with a Grignard reagent; if this were tried, as fast as a molecule of Grignard reagent formed it would react with the active group (—OH) in another molecule to yield an undesired product ($HOCH_2CH_2—H$).

We must be particularly watchful in the preparation of an arylmagnesium halide, in view of the wide variety of substituents that might be present on the benzene ring. Carboxyl (—COOH), hydroxyl (—OH), amino ($—NH_2$), and $—SO_3H$ all contain hydrogen attached to oxygen or nitrogen, and therefore are so acidic that they will decompose a Grignard reagent. We have just learned that a Grignard reagent adds to the carbonyl group (C=O), and we shall learn that it adds similarly to —COOR and —C≡N groups. The nitro ($—NO_2$) group oxidizes a Grignard reagent. It turns out that only a comparatively few groups may be present in the halide molecule from which we prepare a Grignard reagent; among these are —R, —Ar, —OR, and —Cl (of an aryl chloride).

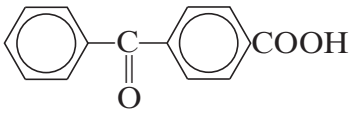
By the same token, the aldehyde (or other compound) with which a Grignard reagent is to react may not contain other groups that are reactive toward a Grignard reagent. For example, a Grignard reagent would be decomposed before it could add to the carbonyl group of:



m-Nitrobenzaldehyde



p-Aminoacetophenone



p-Benzoylbenzoic acid

These may seem like severe limitations, and they are. Nevertheless, the number of acceptable combinations is so great that the Grignard reagent is one of our most valuable synthetic tools. The kind of precautions described here must be taken in any kind of organic synthesis: we must not restrict our attention to the group we happen to be interested in, but must look for possible interference by other functional groups.

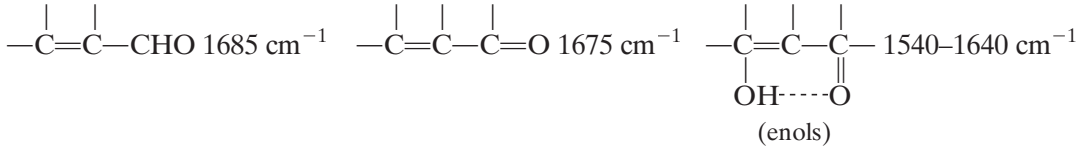
Even when we do see the possibility of interference, there is often something positive that we can do. We may be able to introduce—temporarily—a *protecting group* to prevent an unwanted reaction. Let us look at just one example of such a group, one whose use depends upon some of the carbonyl chemistry we have been learning in this chapter.

12.14 Spectroscopic analysis of aldehydes and ketones

Infrared Infrared spectroscopy is by far the best way to detect the presence of a carbonyl group in a molecule. The strong band due to C=O stretching appears at about 1700 cm^{-1}, where it is seldom obscured by other strong absorptions; it is one of the most useful bands in the infrared spectrum, and is often the first one looked for (see Fig. 12.3, below).

C=O **stretching,** *strong*

RCHO 1725 cm^{-1}	R_2CO 1710 cm^{-1}	Cyclobutanones 1780 cm^{-1}
ArCHO 1700 cm^{-1}	ArCOR 1690 cm^{-1}	Cyclopentanones 1740 cm^{-1}



The carbonyl band is given not only by aldehydes and ketones, but also by carboxylic acids and their derivatives. Once identified as arising from an aldehyde or ketone (see below), its exact frequency can give a great deal of information about the structure of the molecule.

The —CHO group of an aldehyde has a characteristic C—H stretching band near 2720 cm^{-1}; this, in conjunction with the carbonyl band, is fairly certain evidence for an aldehyde (see Fig. 12.3).

Carboxylic acids and esters also show carbonyl absorption, and in the same general region as aldehydes and ketones. Acids, however, also show the broad O—H band. Esters usually show the carbonyl band at somewhat higher frequencies than ketones of the same general structure; furthermore, esters show characteristic C—O stretching bands.

NMR The proton of an aldehyde group, —CHO, absorbs far downfield, at δ 9–10. Coupling of this proton with adjacent protons has a small constant (J 1–3 Hz), and the fine splitting is often seen superimposed on other splittings.

CMR Carbonyl carbon is both sp^2-hybridized and attached to electronegative oxygen, and as a result is powerfully deshielded. It absorbs *farther*

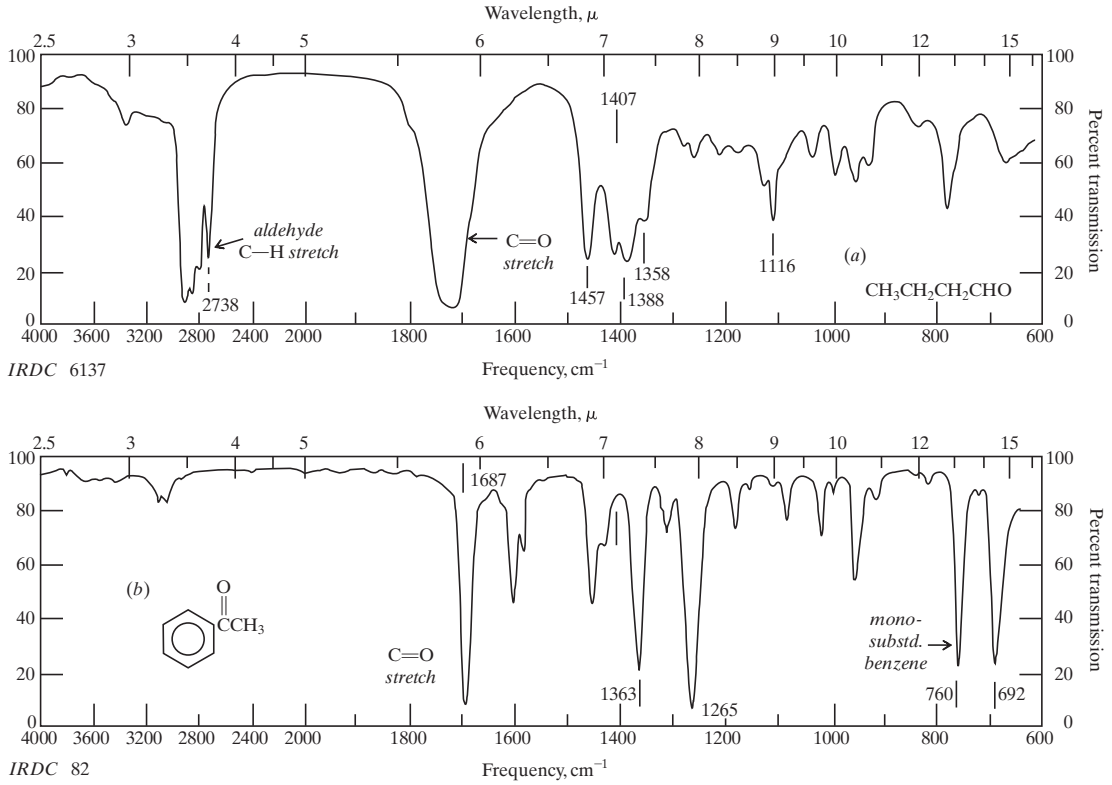


Figure 12.3 Infrared spectra of (*a*) *n*-butyraldehyde and (*b*) acetophenone.

downfield than any other kind of carbon: in the range δ 190–220 for aldehydes and ketones.

Carboxylic acids and their derivatives also contain carbonyl carbon, and here, too, absorption is far downfield, although not so far as for aldehydes and ketones: in the range δ 150–185.

As an electronegative substituent, the carbonyl group strongly deshields adjacent carbons.

Ultraviolet The ultraviolet spectrum can tell a good deal about the structure of carbonyl compounds: particularly, as we might expect from our earlier discussion, about conjugation of the carbonyl group with a carbon–carbon double bond.

Saturated aldehydes and ketones absorb weakly in the near ultraviolet. Conjugation moves this weak band (the R band) to longer wavelengths (*Why*?) and, more important, moves a very intense band (the K band) from the far ultraviolet to the near ultraviolet.

—C=O	—C=C—C=O	
λ_{max} 270–300 nm	λ_{max} 300–350 nm	λ_{max} 215–250 nm
ϵ_{max} 10–20	ϵ_{max} 10–20	ϵ_{max} 10 000–20 000

The exact position of this K band gives information about the number and location of substituents in the conjugated system.

12.15 α,β-Unsaturated Carbonyl Compounds (Conjugate Addition)

12.15.1 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.

Problem 12.12 What will be the products of the following reactions?

(a) $CH_3CH{=}CHCOOH + H_2 + Pt$

(b) $CH_3CH{=}CHCOOC_2H_5 + OH^- + H_2O + \text{heat}$

(c) $C_6H_5CH{=}CHCOCH_3 + I_2 + OH^-$

(d) $CH_3CH{=}CHCHO + C_6H_5NHNH_2 + \text{acid catalyst}$

(e) $CH_3CH{=}CHCHO + Ag(NH_3)_2^+$

(f) $C_6H_5CH{=}CHCOC_6H_5 + O_3$, followed by $Zn + H_2O$

(g) $CH_3CH{=}CHCHO + \text{excess } H_2 + Ni, \text{ heat, pressure}$

(h) *trans*-$HOOCCH{=}CHCOOH + Br_2/CCl_4$

(i) *trans*-$HOOCCH{=}CHCOOH + \text{cold alkaline } KMnO_4$

Problem 13.13 What are A, B, and C, given the following facts?

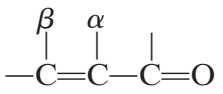
(a) Cinnamaldehyde ($C_6H_5CH{=}CHCHO$) + H_2 + Ni, at low temperatures and pressures $\longrightarrow$ A

(b) Cinnamaldehyde + H_2 + Ni, at high temperatures and pressures $\longrightarrow$ B

(c) Cinnamaldehyde + 9-BBN, followed by $HOCH_2CH_2NH_2$ $\longrightarrow$ C

	A	B	C
$KMnO_4$ test	positive	negative	positive
Br_2/CCl_4 test	negative	negative	positive
Tollens' test	positive	negative	negative
2,4-$(NO_2)_2PhNHNH_2$	positive	negative	negative

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, such



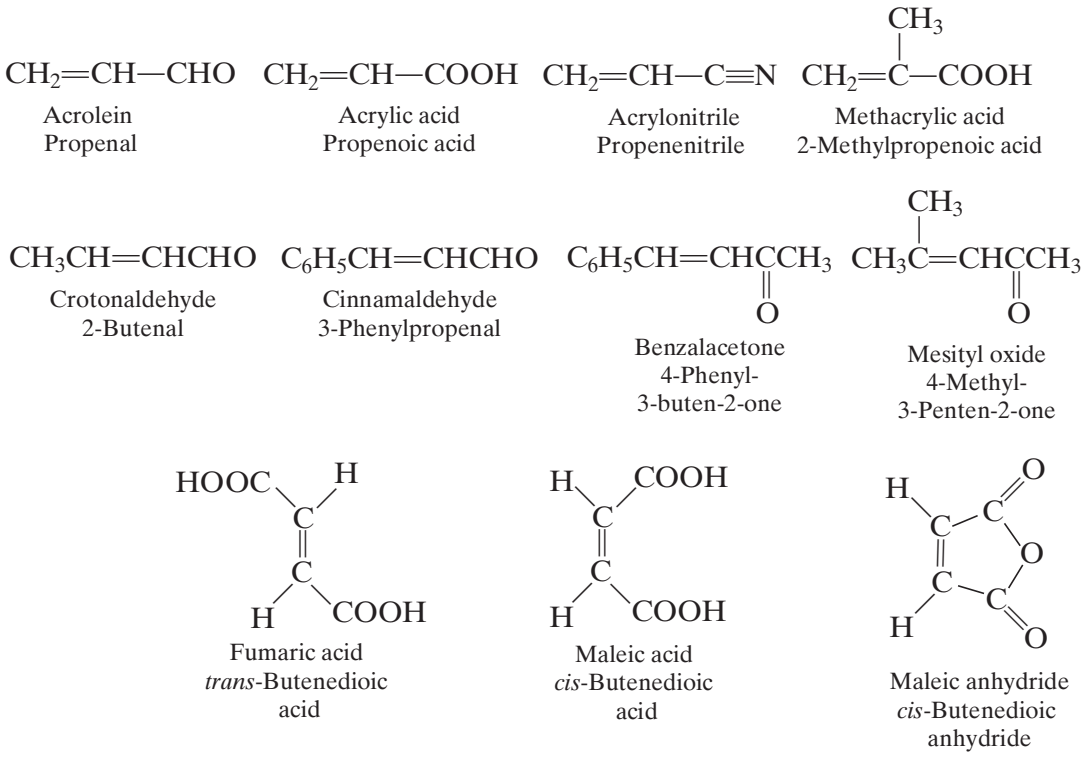
α,β-Unsaturated carbonyl compound
Conjugated system

compounds possess not only the properties of the individual functional groups, but certain other properties besides. In this chapter we shall concentrate on the α,β-unsaturated compounds, and on the special reactions characteristic of the conjugated system.

Table 12.1 α,β-UNSATURATED CARBONYL COMPOUNDS

Name	Formula	M.p., °C	B.p., °C
Acrolein	$CH_2{=}CHCHO$	–88	52
Crotonaldehyde	$CH_3CH{=}CHCHO$	–69	104
Cinnamaldehyde	$C_6H_5CH{=}CHCHO$	–7	254
Mesityl oxide	$(CH_3)_2C{=}CHCOCH_3$	42	131
Benzalacetone	$C_6H_5CH{=}CHCOCH_3$	42	261
Dibenzalacetone	$C_6H_5CH{=}CHCOCH{=}CHC_6H_5$	113	
Benzalacetophenone (Chalcone)	$C_6H_5CH{=}CHCOC_6H_5$	62	348
Dypnone	$C_6H_5C(CH_3){=}CHCOC_6H_5$		150–5[1]
Acrylic acid	$CH_2{=}CHCOOH$	12	142
Crotonic acid	*trans*-$CH_3CH{=}CHCOOH$	72	189
Isocrotonic acid	*cis*-$CH_3CH{=}CHCOOH$	16	172*d*
Methacrylic acid	$CH_2{=}C(CH_3)COOH$	16	162
Sorbic acid	$CH_3CH{=}CHCH{=}CHCOOH$	134	
Cinnamic acid	*trans*-$C_6H_5CH{=}CHCOOH$	137	300
Maleic acid	*cis*-$HOOCCH{=}CHCOOH$	130.5	
Fumaric acid	*trans*-$HOOCCH{=}CHCOOH$	302	
Maleic anhydride		60	202
Methyl acrylate	$CH_2{=}CHCOOCH_3$		80
Methyl methacrylate	$CH_2{=}C(CH_3)COOCH_3$		101
Ethyl cinnamate	$C_6H_5CH{=}CHCOOC_2H_5$	12	271
Acrylonitrile	$CH_2{=}CH{-}C{\equiv}N$	–82	79

Table 12.1 lists some of the more important of these compounds. Many have common names which the student must expect to encounter. For example:



12.15.2 Preparation

There are several general ways to make compounds of this kind: the **aldol condensation**, to make unsaturated aldehydes and ketones; **dehydrohalogenation of α-halo acids** and the **Perkin condensation**, to make unsaturated acids. Besides these, there are certain methods useful only for making single compounds.

All these methods make use of chemistry with which we are already familiar: the fundamental chemistry of alkenes and carbonyl compounds.

Problem 12.14 Outline a possible synthesis of:

(a) crotonaldehyde from acetylene
(b) cinnamaldehyde from compounds of lower carbon number
(c) cinnamic acid from compounds of lower carbon number
(d) 4-methyl-2-pentenoic acid via a malonic ester synthesis

Problem 12.15 The following compounds are of great industrial importance for the manufacture of polymers: acrylonitrile (for Orlon), methyl acrylate (for Acryloid), methyl methacrylate (for Lucite and Plexiglas). Outline a possible industrial synthesis of: (a) acrylonitrile from ethylene; (b) methyl acrylate from ethylene; (c) methyl methacrylate from acetone and methanol. (d) Polymerization of these compounds is similar to that of ethylene, vinyl chloride, etc. Draw a structural formula for each of the polymers.

Problem 12.16 Acrolein, $CH_2{=}CHCHO$, can be prepared by heating glycerol with sodium hydrogen sulfate, $NaHSO_4$. (a) Outline the likely steps in this synthesis, which involves acid-catalyzed dehydration and keto–enol tautomerization. (*Hint*: Which —OH is easier to eliminate, a primary or a secondary?) (b) How could acrolein be converted into acrylic acid?

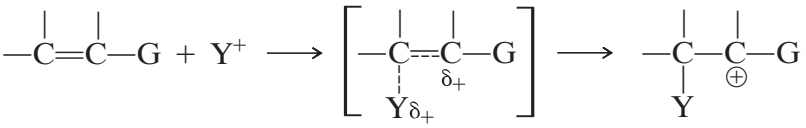
Problem 12.17 Outline all steps in each of the following syntheses:

(a) HOOC—CH=CH—CH=CH—COOH from adipic acid
(b) $CH_3COCH{=}CH_2$ from acetone and formaldehyde
(c) $CH_3COCH{=}CH_2$ from vinylacetylene

12.15.3 Interaction of functional groups

We have seen that, toward electrophilic addition, a carbon–carbon double bond is activated by an electron-releasing substituent and deactivated by an electron-withdrawing substituent. The carbon–carbon double bond serves as a source of electrons for the electrophilic reagent; the availability of its electrons is determined by the groups attached to it. More specifically, an electron-releasing substituent stabilizes the transition state leading to the initial carbocation by dispersing the developing positive charge; an electron-withdrawing substituent destabilizes the transition state by intensifying the positive charge.

Electrophilic addition



G *releases electrons: activates*
G *withdraws electrons: deactivates*

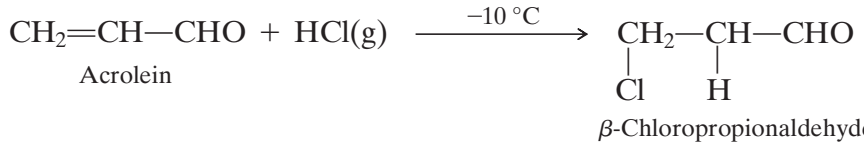
The C=O, —COOH, —COOR, and —CN groups are powerfully electron-withdrawing groups, and therefore would be expected to deactivate a carbon–carbon double bond toward electrophilic addition. This is found to be true: α,β-unsaturated ketones, acids, esters, and nitriles are in general less reactive than simple alkenes toward reagents like bromine and the hydrogen halides.

But this powerful electron withdrawal, which deactivates a carbon–carbon double bond toward reagents seeking electrons, at the same time *activates* toward reagents that are electron-rich. As a result, the carbon–carbon double bond of an α,β-unsaturated ketone, acid, ester, or nitrile is susceptible to nucleophilic attack, and undergoes a set of reactions, **nucleophilic addition**, that is uncommon for the simple alkenes. As we shall see, this reactivity toward nucleophiles is primarily due, not to a simple inductive effect of these substituents, but rather to their *conjugation with* the carbon–carbon double bond.

12.15.4 Electrophilic addition

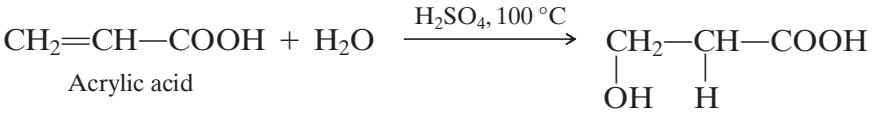
The presence of the carbonyl group not only lowers the **reactivity** of the carbon–carbon double bond toward electrophilic addition, but also controls the **orientation** of the addition.

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:



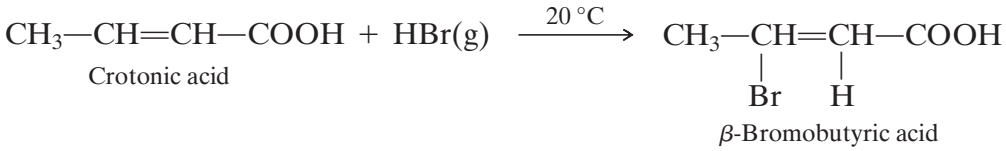
Acrolein

β-Chloropropionaldehyde



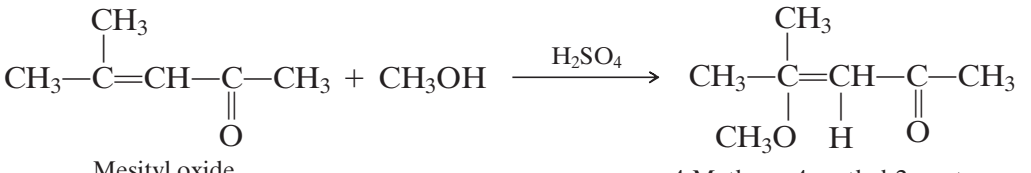
Acrylic acid

β-Hydroxypropionic acid



Crotonic acid

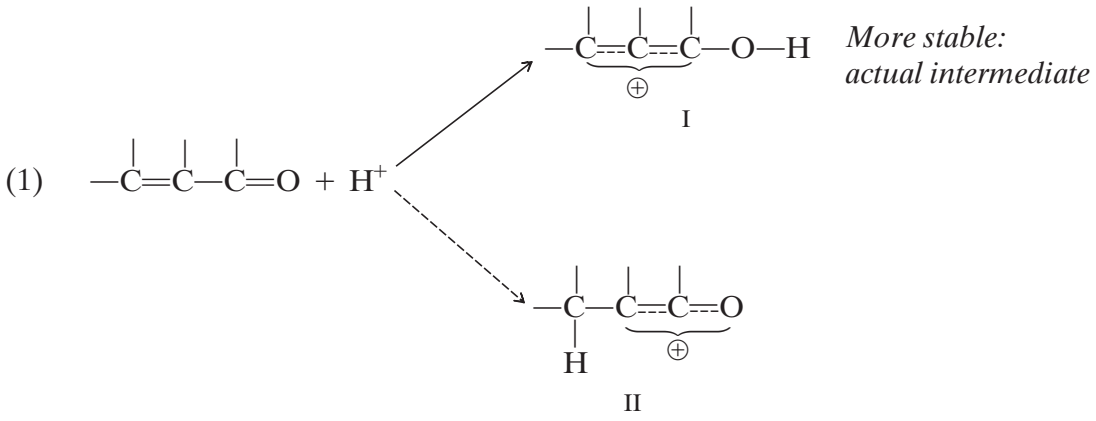
β-Bromobutyric acid



Mesityl oxide

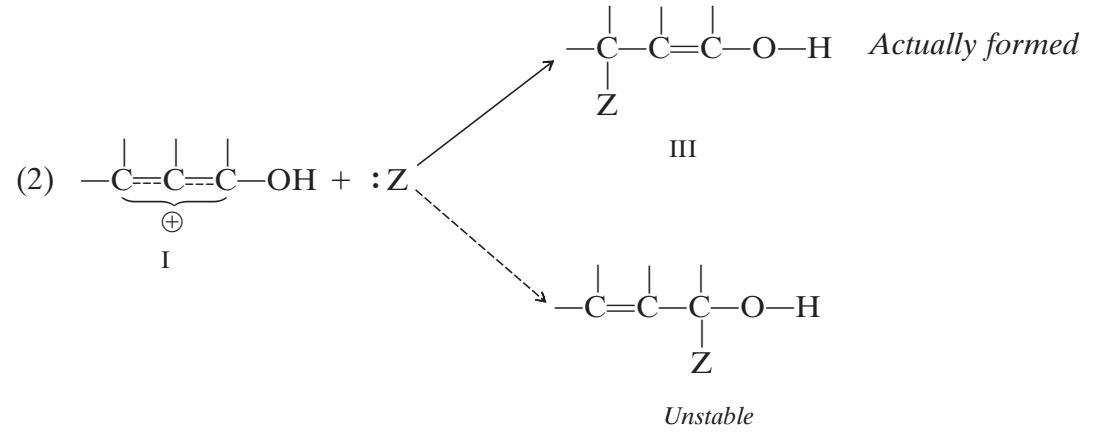
4-Methoxy-4-methyl-2-pentanone

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.

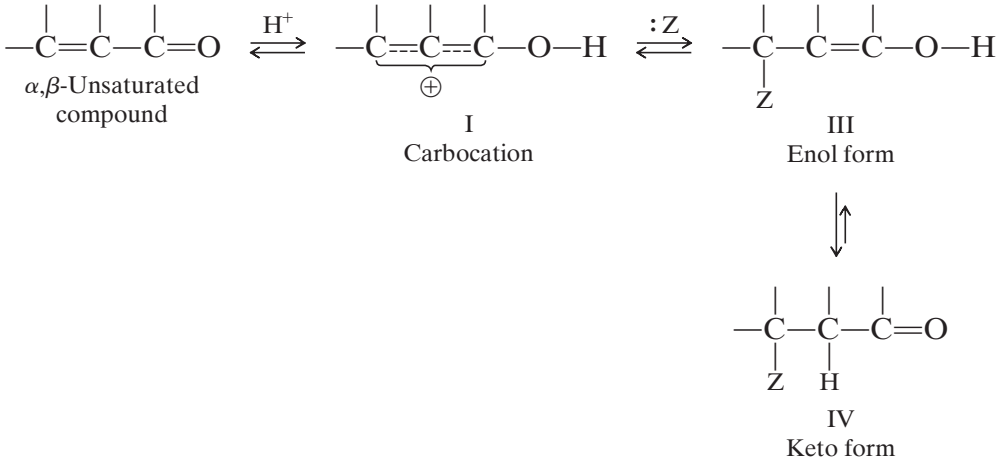


Of the two, I is the more stable, since the positive charge is carried by carbon atoms alone, rather than partly by the more highly electronegative oxygen atom.

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.

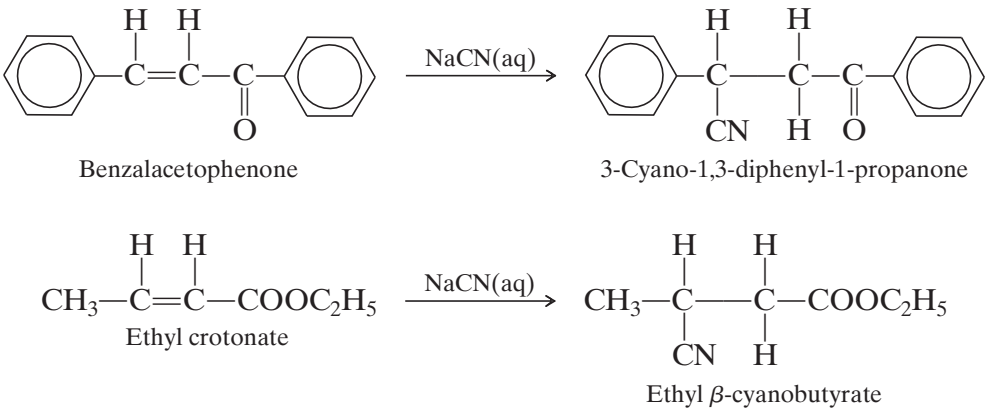


Of the two possibilities, only addition to the β-carbon yields a stable product (III), which is simply the enol form of the saturated carbonyl compound. The enol form then undergoes tautomerization to the keto form to give the observed product (IV).

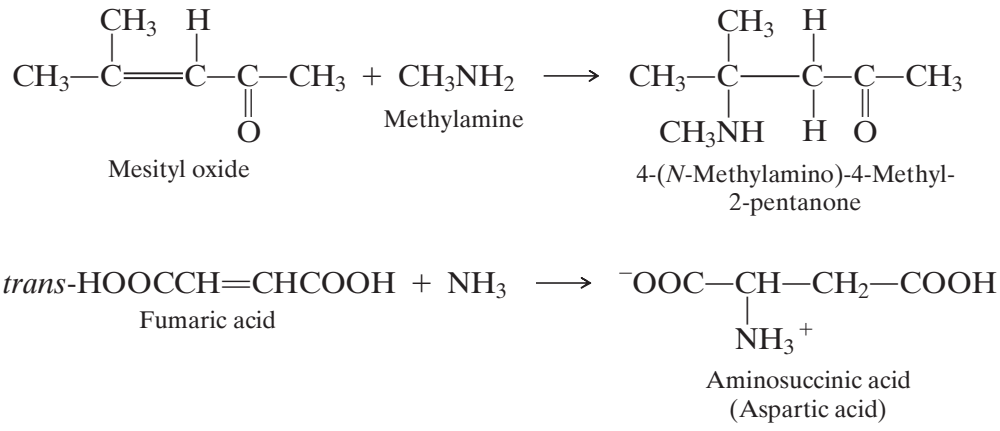


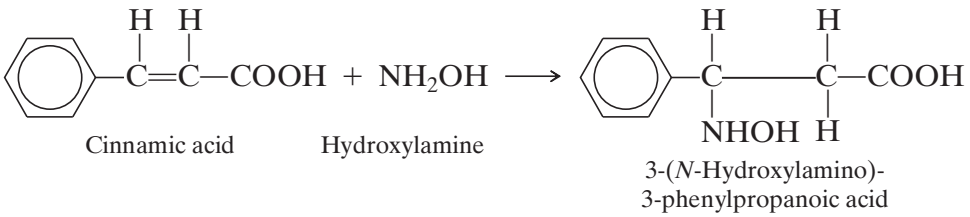
12.15.5 Nucleophilic addition

Aqueous sodium cyanide converts α,β-unsaturated carbonyl compounds into β-cyano carbonyl compounds. The reaction amounts to addition of the elements of HCN to the carbon–carbon double bond. For example:

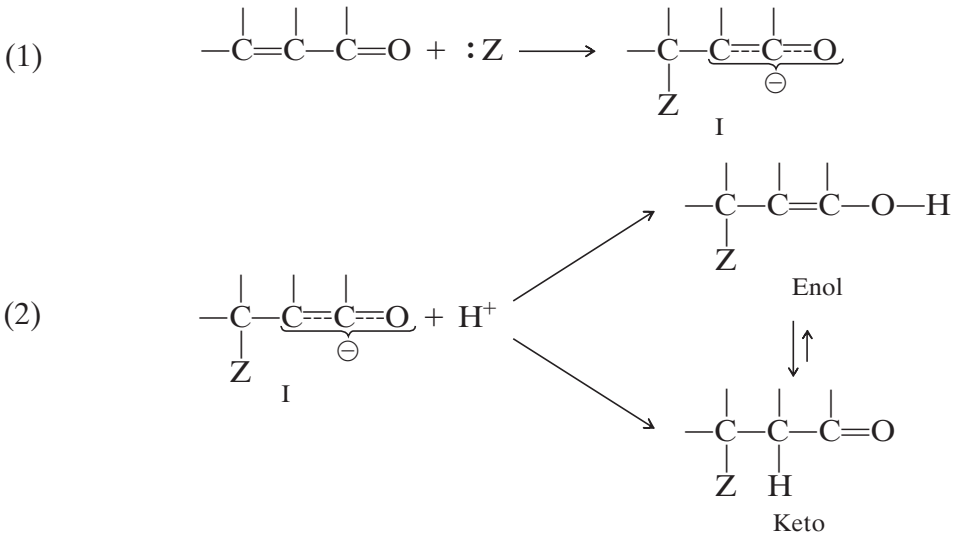


Ammonia or certain derivatives of ammonia (amines, hydroxylamine, phenyl-hydrazine, etc.) add to α,β-unsaturated carbonyl compounds to yield β-amino carbonyl compounds. For example:





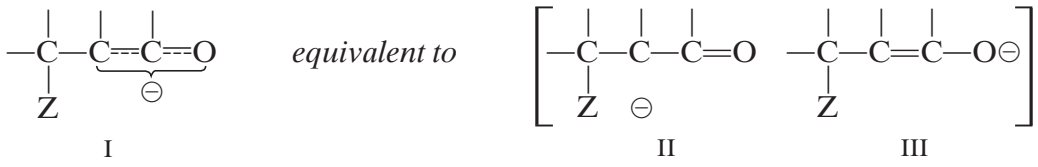
These reactions are believed to take place by the following mechanism:



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.

In the examples we have just seen, the nucleophilic reagent, :Z, is either the strongly basic anion, $:CN^-$, or a neutral base like ammonia and its derivatives, $:NH_2—G$. These are the same reagents which, we have seen, add to the carbonyl group of simple aldehydes and ketones. (Indeed, nucleophilic reagents rarely add to the carbon–carbon double bond of α,β-unsaturated *aldehydes*, but rather to the highly reactive carbonyl group.)

These nucleophilic reagents add to the conjugated system in such a way as to form the most stable intermediate anion. The most stable anion is I, which is a hybrid of II and III.

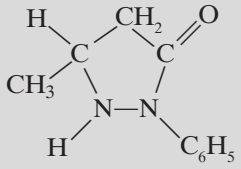


As usual, initial addition occurs to an *end* of the conjugated system, and in this case to the particular end (β-carbon) *that enables the electronegative element oxygen to accommodate the negative charge*.

The tendency for α,β-unsaturated carbonyl compounds to undergo nucleophilic addition is thus due, not simply to the electron-withdrawing ability of the carbonyl group, but to the existence of the conjugated system that permits formation of the resonance-stabilized anion I. The importance in synthesis of α,β-unsaturated aldehydes, ketones, acids, esters, and nitriles is due to the fact that they provide such a conjugated system.

Problem 12.18 Draw structures of the anion expected from nucleophilic addition to each of the other positions in the conjugated system, and compare its stability with that of I.

Problem 12.19 Treatment of crotonic acid, $CH_3CH{=}CHCOOH$, with phenylhydrazine yields compound IV.



IV

To what simple class of compounds does IV belong? How can you account for its formation?

Problem 12.20 Treatment of acrylonitrile, $CH_2{=}CHCN$, with ammonia yields a mixture of two products: β-aminopropionitrile, $H_2NCH_2CH_2CN$, and di(β-cyano-ethyl)amine, $NCCH_2CH_2NHCH_2CH_2CN$. How do you account for their formation?

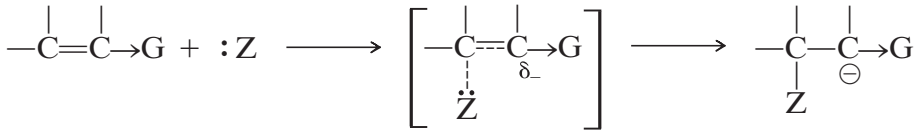
Problem 12.21 Treatment of ethyl acrylate, $CH_2{=}CHCOOC_2H_5$, with methylamine yields $CH_3N(CH_2CH_2COOC_2H_5)_2$. How do you account for its formation?

12.15.6 Comparison of nucleophilic and electrophilic addition

We can see that nucleophilic addition is closely analogous to electrophilic addition: (a) addition proceeds in two steps; (b) the first and controlling step is the formation of an intermediate ion; (c) both orientation of addition and reactivity are determined by the stability of the intermediate ion, or, more exactly, by the stability of the transition state leading to its formation; (d) this stability depends upon dispersal of the charge.

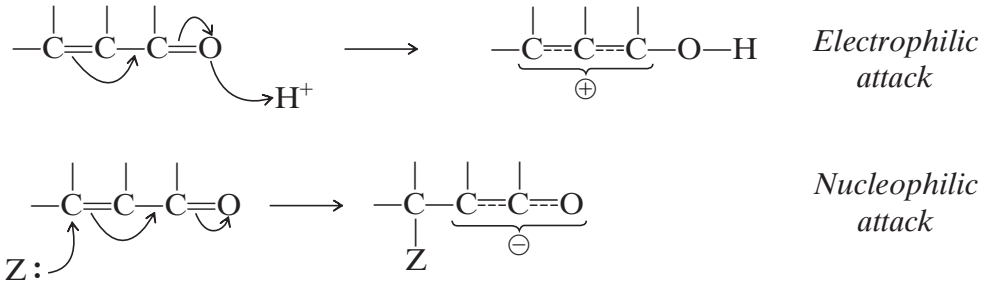
The difference between nucleophilic and electrophilic addition is, of course, that the intermediate ions have opposite charges: negative in nucleophilic addition, positive in electrophilic addition. As a result, the effects of substituents are exactly opposite. Where an electron-withdrawing group deactivates 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



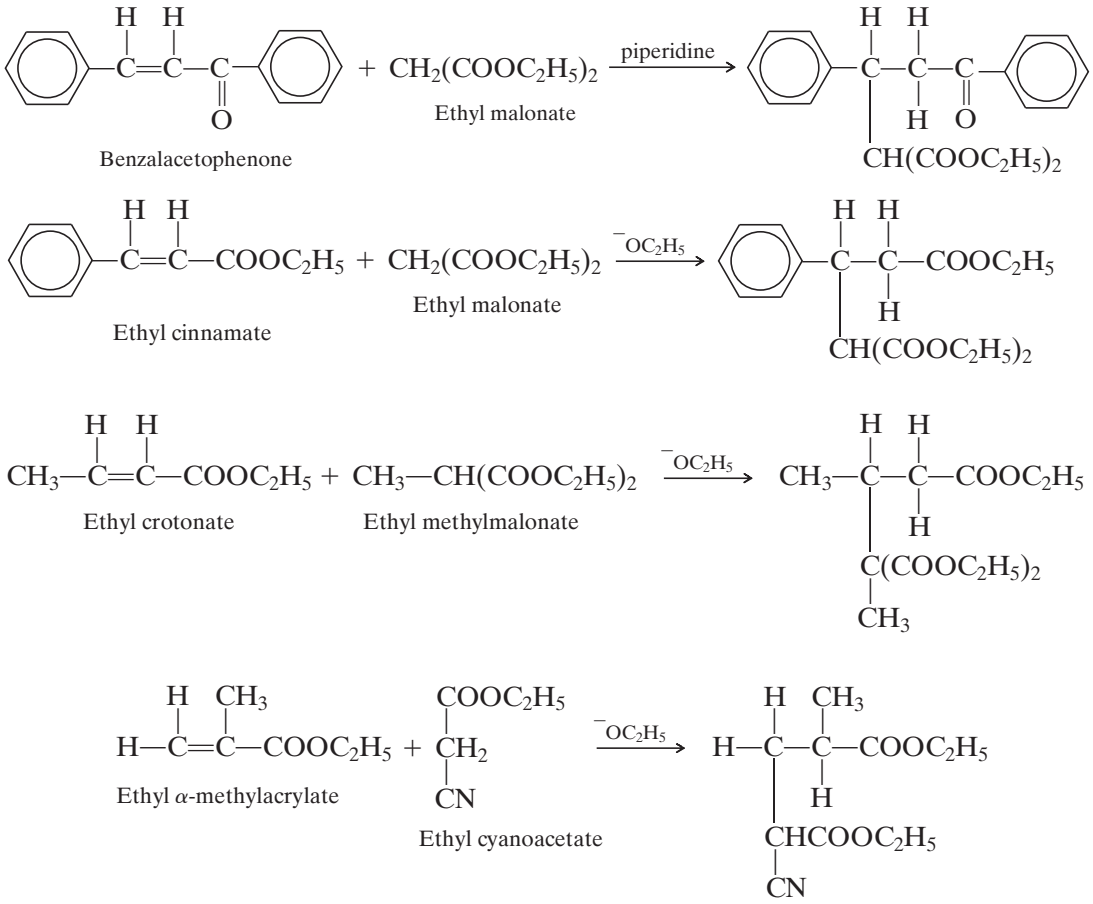
G *withdraws electrons: activates*

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.



12.15.7 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, it results in formation of carbon–carbon bonds. For example:



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

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

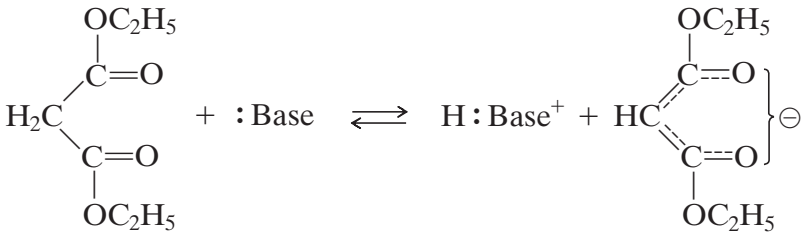
(2) $—C=C—C=O + CH(COOC_2H_5)_2^- \longrightarrow —C—C=C=O$ (⊖ on the conjugated system; $CH(COOC_2H_5)_2$ on the α-carbon)

Nucleophilic reagent

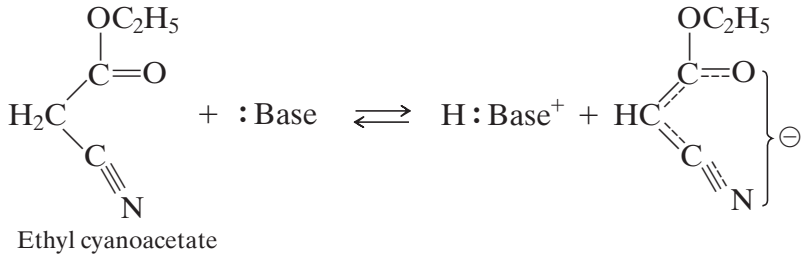
(3) $—C—C=C=O + H:Base^+ \longrightarrow —C—C—C=O + :Base$ ($CH(COOC_2H_5)_2$ on the α-carbon; H on the β-carbon)

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.

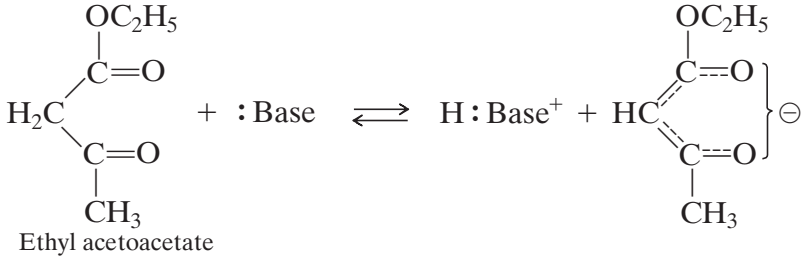
In general, the compound from which the carbanion is generated must be a fairly acidic substance, so that an appreciable concentration of the carbanion can be obtained. Such a compound is usually one that contains a $—CH_2—$ or —CH— group flanked by two electron-withdrawing groups which can help accommodate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



Ethyl malonate



Ethyl cyanoacetate



Ethyl acetoacetate

Ammonia and primary and secondary amines are especially powerful catalysts for the Michael addition. They appear to play a specific role in this reaction: not just to abstract a proton from the reagent to generate a carbanion, but to react with the carbonyl group of the substrate to form an intermediate imine or iminium ion that is particularly reactive toward nucleophilic addition.

Problem 12.22 Predict the products of the following Michael additions:

(a) ethyl crotonate + malonic ester $\longrightarrow$ A $\xrightarrow{OH^-}$ $\xrightarrow{H^+}$ $\xrightarrow{heat}$ B

(b) ethyl acrylate + ethyl acetoacetate $\longrightarrow$ C $\xrightarrow{H_2O_2H^+}$ D

(c) methyl vinyl ketone + malonic ester $\longrightarrow$ E

(d) benzalacetophenone + acetophenone $\longrightarrow$ F

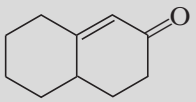
(e) acrylonitrile + allyl cyanide $\longrightarrow$ G $\xrightarrow{H_2O_2H^+}$ $H + 2NH_4^+$

(f) $C_2H_5OOC—C\equiv C—COOC_2H_5$ (1 mol) + ethyl acetoacetate (1 mol) $\longrightarrow$ I

(g) I $\xrightarrow{\text{strong } OH^-, H_2O}$ $\xrightarrow{H^+}$ $J + CH_3COOH$

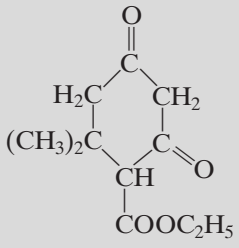
Problem 12.23 Formaldehyde and malonic ester react in the presence of ethoxide ion to give K, $C_8H_{12}O_4$. (a) What is the structure of K? (b) How can K be converted into L, $(C_2H_5OOC)_2CHCH_2CH(COOC_2H_5)_2$? (c) What would you get if L were subjected to hydrolysis, acidification, and heat?

Problem 12.24 Show how a Michael addition followed by an aldol condensation can transform a mixture of methyl vinyl ketone and cyclohexanone into $\Delta^{1,9}$-octalone.



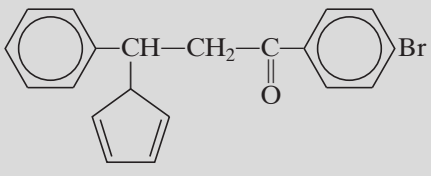
$\Delta^{1,9}$-Octalone

Problem 12.25 When mesityl oxide, $(CH_3)_2C=CHCOCH_3$, is treated with ethyl malonate in the presence of sodium ethoxide, compound M is obtained, (a) Outline the steps in its formation, (b) How could M be turned into 5,5-dimethyl-1,3-cyclohexanedione?



M

Problem 12.26 In the presence of piperidine, 1,3-cyclopentadiene and benzal-*p*-bromoacetophenone yield N. Outline the steps in its formation.



N

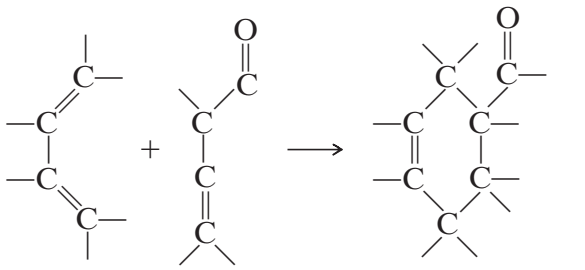
Problem 12.27 (a) Using as your example the addition of ethyl malonate to benzalacetophenone in the presence of dimethylamine, show how an iminium ion might be formed and act as an intermediate in this reaction.

(b) How do you account for the high reactivity toward nucleophilic addition of such an iminium ion?

(c) Why do tertiary amines not show specific catalytic action in the Michael addition?

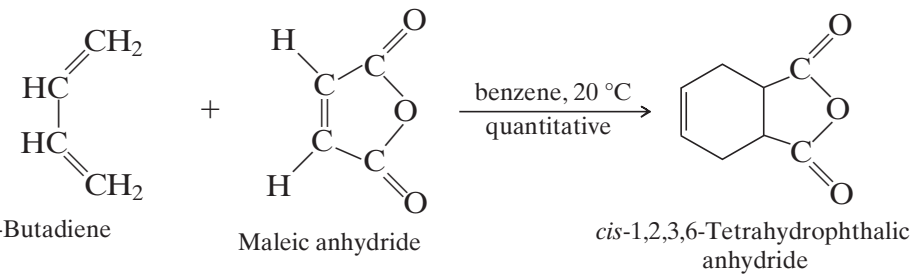
12.15.8 The Diels–Alder reaction

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*, which is discussed further in later chapters. Since reaction involves a system of four π electrons (the diene) and a system of two π electrons (the dienophile), it is known as a [4 + 2] cycloaddition.

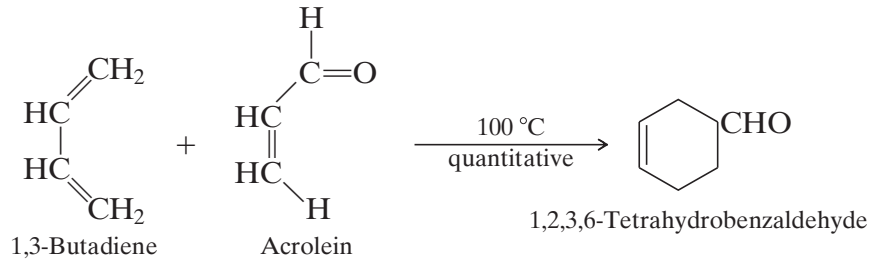
The Diels–Alder reaction is useful not only because a ring is generated, but also because it takes place so readily for a wide variety of reactants. Reaction is favored by electron-withdrawing substituents in the dienophile, but even simple alkenes can react. Reaction often takes place with the evolution of heat when the reactants are simply mixed together. A few examples of the Diels–Alder reaction are:



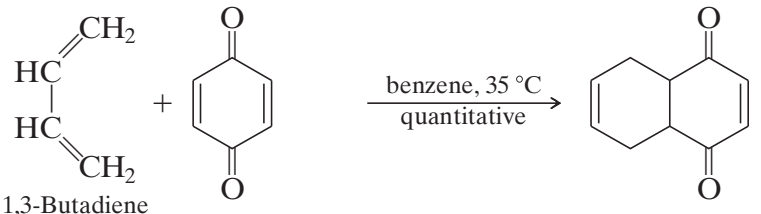
1,3-Butadiene

Maleic anhydride

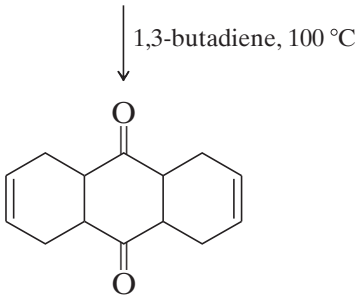
cis-1,2,3,6-Tetrahydrophthalic anhydride



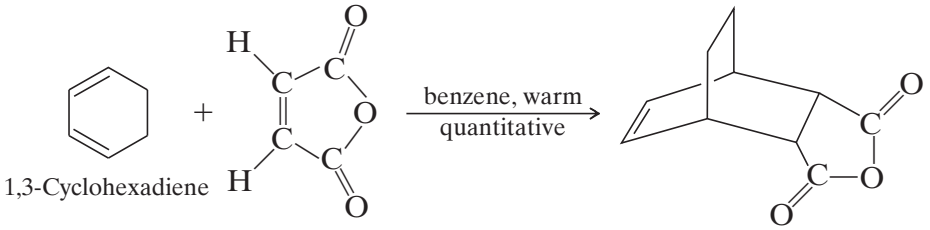
1,3-Butadiene Acrolein 1,2,3,6-Tetrahydrobenzaldehyde



1,3-Butadiene *p*-Benzoquinone 5,8,9,10-Tetrahydro-1,4-naphthoquinone

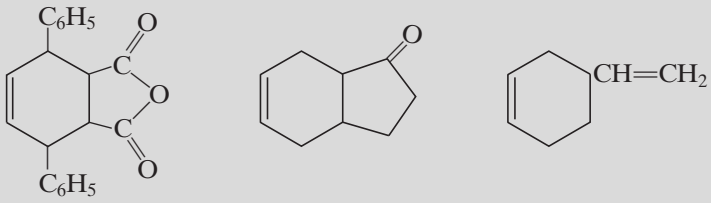


1,4,5,8,11,12,13,14-Octahydro-9,10-anthraquinone

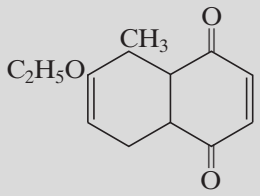


1,3-Cyclohexadiene Maleic anhydride

Problem 12.28 From what reactants could each of the following compounds be synthesized?

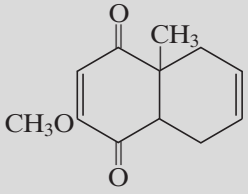


Problem 12.29 (a) In one synthesis of the hormone *cortisone* (by Lewis Sarett of Merck, Sharp and Dohme), the initial step was the formation of I by a Diels–Alder reaction. What were the starting materials?



I

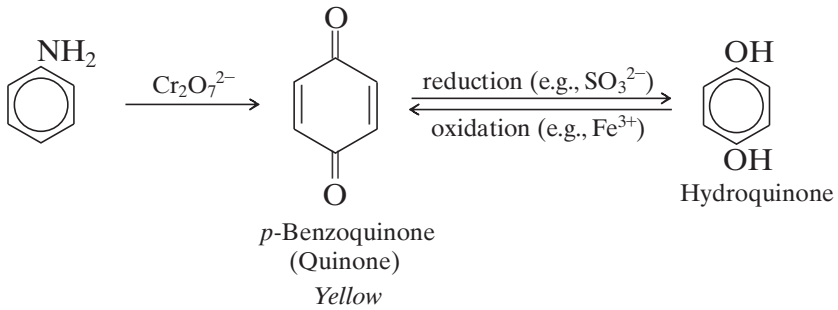
(b) In another synthesis of cortisone (by R. B. Woodward, p. 1004), the initial step was the formation of II by a Diels–Alder reaction. What were the starting materials?



II

12.15.9 Quinones

α,β-Unsaturated ketones of a rather special kind are given the name of **quinones**: these are cyclic diketones of such a structure that they are converted by reduction into hydroquinones, phenols containing two —OH groups. For example:



Because they are highly conjugated, quinones are colored: *p*-benzoquinone, for example, is yellow.

Also because they are highly conjugated, quinones are rather closely balanced, energetically, against the corresponding hydroquinones. The ready interconversion provides a convenient oxidation–reduction system that has been studied intensively. Many properties of quinones result from the tendency to form the aromatic hydroquinone system.

Quinones—some related to more complicated aromatic systems—have been isolated from biological sources (molds, fungi, higher plants). In many cases they seem to take part in oxidation–reduction cycles essential to the living organism.

Problem 12.30 When *p*-benzoquinone is treated with HCl, there is obtained 2-chloro–hydroquinone. It has been suggested that this product arises via an initial 1,4-addition. Show how this might be so.

Problem 12.31 (a) Hydroquinone is used in photographic developers to aid in the conversion of silver ion into free silver. What property of hydroquinone is being taken advantage of here?

(b) *p*-Benzoquinone can be used to convert iodide ion into iodine. What property of the quinone is being taken advantage of here?

Problem 12.32 How do you account for the fact that the treatment of phenol with nitrous acid yields the mono-oxime of *p*-benzoquinone?

EXERCISE

1. Neglecting enantiomerism, give structural formulas, common names, and IUPAC names for:

(a) the seven carbonyl compounds of formula $C_5H_{10}O$
(b) the five carbonyl compounds of formula C_8H_8O that contain a benzene ring

2. Give the structural formula of:

(a) acetone
(b) benzaldehyde
(c) isobutyl methyl ketone
(d) trimethylacetaldehyde
(e) acetophenone
(f) 4-methylpentanal
(g) phenylacetaldehyde
(h) benzophenone
(i) α,γ-dimethylcaproaldehyde
(j) 3-methyl-2-pentanone
(k) 2-butenal
(l) 4-methyl-3-penten-2-one
(m) 1,3-diphenyl-2-propen-1-one
(n) 3-hydroxypentanal
(o) benzyl phenyl ketone
(p) *p,p′*-dihydroxybenzophenone
(q) *m*-tolualdehyde

3. Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetaldehyde with:

(a) Tollens' reagent
(b) CrO_3/H_2SO_4
(c) cold dilute $KMnO_4$
(d) $KMnO_4$, H^+, heat
(e) H_2, Ni, 20 lb/in^2, 30 °C
(f) $LiAlH_4$
(g) $NaBH_4$
(h) C_6H_5MgBr, then H_2O
(i) isopropylmagnesium chloride, then H_2O
(j) $HC{\equiv}CLi$, then H_2O
(k) CN^-, H^+
(l) hydroxylamine
(m) phenylhydrazine
(n) 2,4-dinitrophenylhydrazine
(o) semicarbazide
(p) ethyl alcohol, dry HCl(g)

4. Answer Problem 3 for cyclohexanone.

5. Write balanced equations, naming all organic products, for the reaction (if any) of benzaldehyde with:

(a) conc. NaOH
(b) formaldehyde, conc. NaOH
(c) CN^-, H^+
(d) product (c) + H_2O, H^+, heat
(e) CH_3MgI, then H_2O
(f) product (e) + H^+, heat
(g) $(CH_3)_2{}^{14}CHMgBr$, then H_2O
(h) $H_2{}^{18}O$, H^+

6. Give structures of the Grignard reagent and the substrate (aldehyde, ketone, or ethylene oxide) that would react to yield each of the following alcohols. If more than one combination of reactants is possible, show each of the combinations.

(a) 1-phenyl-1-propanol
(b) 2-phenyl-2-propanol
(c) 1-phenyl-2-propanol
(d) 3-phenyl-1-propanol

(e) 1-methylcyclohexanol
(d) cyclohexylmethanol
(g) 1-cyclohexylethanol
(h) 2,4-dimethyl-3-pentanol
(i) 1-(*p*-tolyl)ethanol
(j) 1-pentyn-3-ol
(k) 3-pentyn-2-ol

7. Write equations for all steps in the synthesis of the following from propionaldehyde, using any other needed reagents:

(a) *n*-propyl alcohol
(b) propionic acid
(c) α-hydroxybutyric acid
(d) *sec*-butyl alcohol
(e) 1-phenyl-1-propanol
(f) ethyl methyl ketone
(g) 2-methyl-3-pentanol

8. Write equations for all steps in the synthesis of the following from acetophenone, using any other needed reagents:

(a) ethylbenzene
(b) benzoic acid
(c) α-phenylethyl alcohol
(d) 2-phenyl-2-butanol
(e) 1,1-diphenylethanol
(f) α-hydroxy-α-phenylpropionic acid

9. Outline all steps in a possible laboratory synthesis of each of the following from benzene, toluene, and alcohols of four carbons or fewer, using any needed inorganic reagents:

(a) isobutyraldehyde
(b) phenylacetaldehyde
(c) *p*-bromobenzaldehyde
(d) ethyl methyl ketone
(e) 2,4-dinitrobenzaldehyde
(f) *p*-nitrobenzophenone
(g) 2-methyl-3-pentanone
(h) benzyl methyl ketone
(i) *m*-nitrobenzophenone
(j) *n*-propyl *p*-tolyl ketone
(k) α-methylbutyraldehyde
(l) *n*-butyl isobutyl ketone
(m) *p*-nitroacetophenone
(n) 3-nitro-4′-methylbenzophenone
(o) *p*-nitropropiophenone

10. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer.

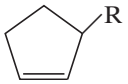
(a) 2,3-dimethyl-2-butanol
(b) 2-phenyl-2-propanol
(c) 2-phenylpropene
(d) 2-methyl-1-butene
(e) isopentane
(f) 1,2-dibromo-2-methylbutane
(g) 3-hexanol
(h) 3-hexanone
(i) 4-ethyl-4-heptanol
(j) 2-bromo-2-methylhexane
(k) 1-chloro-1-phenylethane (α-phenylethyl chloride)
(l) *n*-butylbenzene
(m) α-hydroxy-*n*-valeric acid
(n) 2-methylheptane
(o) 2,3,5-trimethyl-3-hexanol
(p) *p*-nitro-α-hydroxyphenylacetic acid
(q) 1,2-diphenyl-2-propanol
(r) 1-*p*-bromophenyl-1-phenyl-1-propanol
(s) 3-methyl-2-butenoic acid

11. Compounds "labeled" at various positions by isotopic atoms are useful in determining reaction mechanisms and in following the fate of compounds in biological systems. Outline a possible synthesis of each of the following labeled compounds using $^{14}CH_3OH$ as the source of ^{14}C, and D_2O as the source of deuterium.

(a) 2-methyl-1-propanol-1-^{14}C, $(CH_3)_2CH^{14}CH_2OH$
(b) 2-methyl-1-propanol-2-^{14}C, $(CH_3)_2{}^{14}CHCH_2OH$
(c) 2-methyl-1-propanol-3-^{14}C, $^{14}CH_3CH(CH_3)CH_2OH$
(d) propene-1-^{14}C, CH3CH=$^{14}CH_2$
(e) propene-2-^{14}C, $CH_3{}^{14}CH{=}CH_2$
(f) propene-3-^{14}C, $^{14}CH_3CH{=}CH_2$
(g) C_6H_5D
(h) $CH_3CH_2CHD^{14}CH_3$

12. When *trans*-2-methylcyclopentanol is treated with tosyl chloride and the product with potassium *tert*-butoxide, the only alkene obtained is 3-methylcyclopentene. (a) What is the

stereochemistry of this reaction? (b) This is the final step of a general synthetic route to 3-alkylcyclopentenes, starting from cyclopentanone. Outline all steps in this route, carefully choosing



your reagents in each step, (c) What advantage does this sequence have over an analogous one involving an intermediate halide instead of a tosylate?

13. (a) What are A, B, and C?

$$C_6H_5C(CH_3)_2CH_2COOH + PCl_3 \longrightarrow A\,(C_{11}H_{13}OCl)$$
$$A + AlCl_3/CS_2 \longrightarrow B(C_{11}H_{12}O)$$
$$B + N_2H_4,\ OH^-,\ \text{heat, high-boiling solvent} \longrightarrow C\,(C_{11}H_{14})$$

C gave the following proton NMR spectrum:

a singlet, δ 1.22, 6H
b triplet, δ 1.85, 2H, $J = 7$ Hz
c triplet, δ 2.83, 2H, $J = 7$ Hz
d singlet, δ 7.02, 4H

(b) C was also formed by treatment of the alcohol D($C_{11}H_{16}O$) with concentrated sulfuric acid. What is the structure of D?

14. Give stereochemical formulas for compounds E–J.

R-(+)-*glyceraldehyde* ($CH_2OHCHOHCHO$) + CN^-,H^+ $\longrightarrow$ E + F
(both E and F have the formula $C_4H_7O_3N$)
E + F + OH^-, H_2O, heat; then H^+ $\longrightarrow$ G + H (both $C_4H_8O_5$)
G + HNO_3 $\longrightarrow$ I ($C_4H_6O_4$), *optically active*
H + HNO_3 $\longrightarrow$ J($C_4H_6O_4$), *optically inactive*

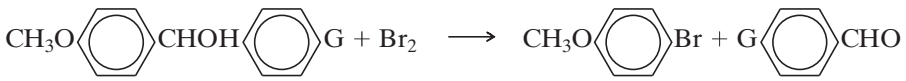
15. (a) *cis*-1,2-Cyclopentanediol reacts with acetone in the presence of dry HCl to yield compound K, $C_8H_{14}O_2$, which is resistant to boiling alkali, but which is readily converted into the starting materials by aqueous acids. What is the most likely structure of K? To what class of compounds does it belong?

(b) *trans*-1,2-Cyclopentanediol does not form an analogous compound. How do you account for this fact?

16. The oxygen exchange can be carried out by use of hydroxide ion instead of hydrogen ion as catalyst. Suggest a detailed mechanism for exchange under these conditions.

17. Vinyl alkyl ethers, RCH=CHOR′, are very rapidly hydrolyzed by dilute aqueous acid to form the alcohol R′OH and the aldehyde RCH_2CHO. Hydrolysis in $H_2{}^{18}O$ gives alcohol R′OH containing only ordinary oxygen. Outline all steps in the most likely mechanism for the hydrolysis. Show how this mechanism accounts not only for the results of the tracer experiment, but also for the extreme ease with which hydrolysis takes place.

18. On treatment with bromine, certain diarylmethanols (I) are converted into a 50 : 50 mixture of aryl bromide (II) and aldehyde (III).



I II III

Whether G is $-NO_2$, —H, —Br, or $-CH_3$, bromine appears *only* in the ring containing the $-OCH_3$ group. The rate of reaction is affected moderately by the nature of G, decreasing along the series: G = $-CH_3$ > —H > —Br > $-NO_2$. The rate of reaction is slowed down by the presence of added bromide ion.

Outline all steps in the most likely mechanism for this reaction. Show how your mechanism accounts for each of the above facts.

19. A naïve graduate student needed a quantity of benzhydrol, $(C_6H_5)_2CHOH$, and decided to prepare it by the reaction between phenylmagnesium bromide and benzaldehyde. He prepared a mole of the Grignard reagent. To insure a good yield, he then added, not one, but *two* moles of the aldehyde. On working up the reaction mixture, he was at first gratified to find he had obtained a good yield of a crystalline product, but his hopes were dashed when closer examination revealed that he had made, not benzhydrol, but the ketone benzophenone. Bewildered, the student made the first of many trips to his research director's office.

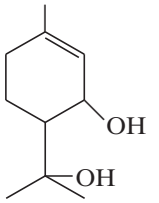
He returned shortly, red-faced, to the laboratory, carried out the reaction again using equimolar amounts of the reactants, and obtained a good yield of the compound he wanted.

What had gone wrong in his first attempt? How had his generosity with benzaldehyde betrayed him? (Examine the structure of the initial addition product.)

20. (a) How do you account for the extreme ease with which *tetrahydropyranyl* ethers undergo hydrolysis in dilute aqueous acid? (b) Predict the products of such hydrolysis of EtO–THP.

21. Suggest a mechanism for the following reaction.

$$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO + H_3O^+ \longrightarrow$$



3,8-Carvomenthenediol

The ring-closing step can be considered as either nucleophilic addition or electrophilic addition depending on one's point of view. Show how this is so, identifying both the electrophile and the nucleophile.

22. Assign structures to compounds L through R.

(*R*)-(+)-1-bromo-2, 4-dimethylpentane + Mg $\longrightarrow$ L
L + $(CH_3)_2CHCH_2CHO$, then H_2O $\longrightarrow$ M($C_{12}H_{26}O$), *a mixture*
M + CrO_3 $\longrightarrow$ N($C_{12}H_{24}O$)
N + CH_3MgBr, then H_2O $\longrightarrow$ O($C_{13}H_{28}O$), *a mixture*
O + I_2, heat $\longrightarrow$ P($C_{13}H_{26}$), *a mixture*
P + H_2, Ni $\longrightarrow$ Q($C_{13}H_{28}$) + R($C_{13}H_{28}$)
Optically active *Optically active*

23. Describe a simple chemical test that would serve to distinguish between:

(a) *n*-valeraldehyde and diethyl ketone
(b) phenylacetaldehyde and benzyl alcohol
(c) cyclohexanone and cyclohexyl methyl ether
(d) 2-pentanone and 3-pentanone
(e) propionaldehyde and diethyl ether
(f) diethyl acetal and *n*-valeraldehyde
(g) diethyl acetal and di-*n*-propyl ether
(h) methyl *m*-tolyl ketone and propiophenone
(i) 2-pentanone and 2-pentanol
(j) paraldehyde and diisobutyl ether
(k) dioxane and trioxane

Tell exactly what you would *do* and *see*.

24. *Citral*, $C_{10}H_{16}O$, is a terpene that is the major constituent of lemongrass oil. It reacts with hydroxylamine to yield a compound of formula $C_{10}H_{17}ON$, and with Tollens' reagent to give a silver

mirror and a compound of formula $C_{10}H_{16}O_2$. Upon vigorous oxidation citral yields acetone, oxalic acid (HOOC—COOH), and levulinic acid ($CH_3COCH_2CH_2COOH$).

(a) Propose a structure for citral that is consistent with these facts and with the isoprene rule.

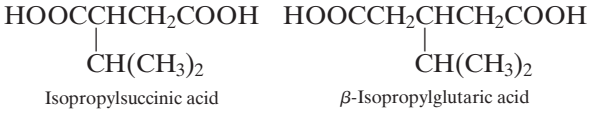
(b) Actually citral seems to consist of two isomers, citral *a*(*geranial*) and citral *b*(*neral*), which yield the same oxidation products. What is the most likely structural difference between these two isomers?

(c) Citral *a* is obtained by mild oxidation of geraniol; citral *b* is obtained in a similar way from nerol. On this basis assign structures to citral *a* and citral *b*.

25. (+)-*Carvotanacetone*,$C_{10}H_{16}O$, is a terpene found in thuja oil. It reacts with hydroxylamine and semicarbazide to form crystalline derivatives. It gives negative tests with Tollens' reagent, but rapidly decolorizes cold dilute $KMnO_4$.

Carvotanacetone can be reduced successively to *carvomenthone*, $C_{10}H_{18}O$, and *carvomenthol*, $C_{10}H_{20}O$. Carvomenthone reacts with hydroxylamine but not with cold dilute $KMnO_4$. Carvomenthol does not react with hydroxylamine or cold dilute $KMnO_4$, but gives a positive test with CrO_3/H_2SO_4.

One set of investigators found that oxidation of carvotanacetone gave isopropylsuccinic acid and pyruvic acid, $CH_3COCOOH$; another set of investigators isolated acetic acid and β-isopropylglutaric acid.



Isopropylsuccinic acid — β-Isopropylglutaric acid

What single structure for carvotanacetone is consistent with all these facts?

26. Upon treatment with mineral acids, 2,3-dimethyl-2,3-butanediol (*pinacol*) is converted into *tert*-butyl methyl ketone. Using only familiar steps, suggest a likely mechanism for this reaction, which is one example of the **pinacol rearrangement**. (*Hint*: There are four steps, two of which are equilibria.)

27. The sex attractant of the Douglas-fir tussock moth has been synthesized in the following way. Give the structure of the sex attractant and all intermediate compounds.

1-heptyne + $LiNH_2$ ⟶ S($C_7H_{11}Li$)
S + 1-chloro-3-bromopropane ⟶ T($C_{10}H_{17}Cl$)
T + Mg; then *n*-$C_{10}H_{21}CHO$; then H^+ ⟶ U($C_{21}H_{40}O$)
U + H_2, Lindlar catalyst ⟶ V($C_{21}H_{42}O$)
V + CrO_3 ⟶ sex attractant ($C_{21}H_{40}O$)

28. An insect pheromone that we have already encountered has been made in the following way. (*Useful information*: An alcohol, ROH, is often converted into its acetate, CH_3COOR, by treatment with acetyl chloride, CH_3COCl.)

1,8-octanediol + HBr ⟶ W($C_8H_{17}OBr$)
W + DHP + H^+ ⟶ X($C_{13}H_{25}O_2Br$)
X + HC≡CLi ⟶ Y($C_{15}H_{26}O_2$)
Y + $LiNH_2$, then C_2H_5Br ⟶ Z($C_{17}H_{30}O_2$)
Z + H_2O, H^+ ⟶ AA($C_{12}H_{22}O$)
AA + CH_3COCl ⟶ BB($C_{14}H_{24}O_2$)
BB + H_2, Lindlar catalyst ⟶ the pheromone($C_{14}H_{26}O_2$)

(a) Give the structure of the pheromone and all intermediate compounds.

(b) For maximum biological activity there should be present 4% of its geometric isomer. How could you modify the above synthesis to obtain this isomer?

29. The sex attractant of the pink bollworm moth is an approximately 50 : 50 mixture of two geometric isomers, and is known as *gossyplure*. One component has been synthesized in the following way. (*Useful information*: An alcohol, ROH, is often converted into its acetate, CH_3COOR, by treatment with acetyl chloride, CH_3COCl.)

1-hexyne + *n*-BuLi; then ethylene oxide; then H^+ ⟶ CC($C_8H_{14}O$)
CC + H_2, Lindlar catalyst ⟶ DD($C_8H_{16}O$)

$DD + PBr_3 \longrightarrow EE(C_8H_{15}Br)$
6-bromo-1-hexanol + DHP + $H^+ \longrightarrow FF(C_{11}H_{21}O_2Br)$
$FF + HC{\equiv}CLi \longrightarrow GG(C_{13}H_{22}O_2)$
GG + *n*-BuLi; then EE $\longrightarrow HH(C_{21}H_{36}O_2)$
HH + H_2, Lindlar catalyst $\longrightarrow II(C_{21}H_{38}O_2)$
II + $H_2O, H^+ \longrightarrow JJ(C_{16}H_{30}O)$
JJ + $CH_3COCl \longrightarrow$ the pheromone$(C_{18}H_{32}O_2)$

(a) What is the structure of the pheromone just formed?
(b) This synthesis has been modified to obtain each of the geometric isomers of the compound in (a), one of which is the other component of the natural pheromone. Show how this could be done.

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

31. 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

32. 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 + $CHCl_3$

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

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

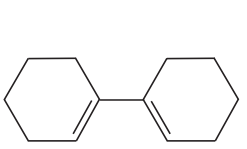
dibenzalacetone + 2 mol ethyl malonate $\longrightarrow$ A (no unsaturation)
dibenzalacetone + 1 mol ethyl malonate $\longrightarrow$ B (one carbon–carbon double bond)
dibenzalacetone + 1 mol ethyl malonate $\longrightarrow$ C (no unsaturation)

What are A, B, and C?

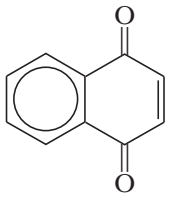
35. *Spermine*, $H_2NCH_2CH_2CH_2NHCH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$, found in seminal fluid, has been synthesized from acrylonitrile and 1,4-diaminobutane (putrescine). Show how this was probably done.

36. 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



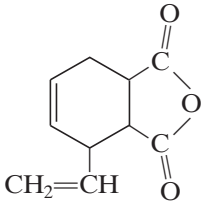
I



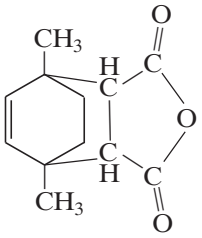
II

37. From what reactants could the following be synthesized by the Diels-Alder reaction?

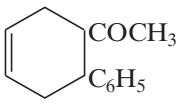
(a)



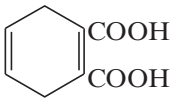
(b)



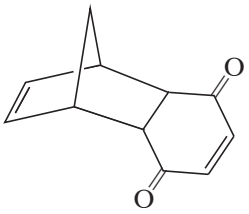
(c)



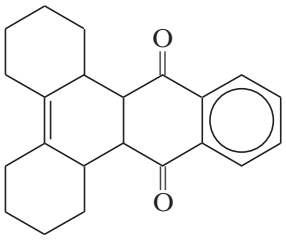
(d)



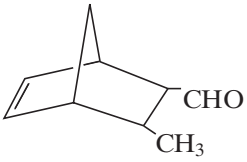
(e)



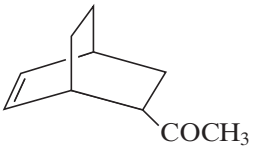
(f)



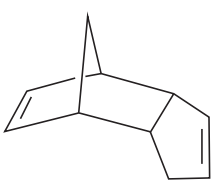
(g)



(h)



(i)



38. The following observations illustrate one aspect of the stereochemistry of the Diels–Alder reaction:

maleic anhydride + 1,3-butadiene $\longrightarrow$ D ($C_8H_8O_3$)
D + H_2O, heat $\longrightarrow$ E($C_8H_{10}O_4$)
E + H_2,Ni $\longrightarrow$ F($C_8H_{12}O_4$), m.p. 192 °C
fumaryl chloride (*trans*-ClOCCH=CHCOCl) + 1,3-butadiene $\longrightarrow$ G ($C_8H_8O_2Cl_2$)
G + H_2O, heat $\longrightarrow$ H($C_8H_{10}O_4$)
H + H_2, Ni $\longrightarrow$ I($C_8H_{12}O_4$), m.p. 215 °C
I can be resolved; F cannot be resolved.

Does the Diels–Alder reaction involve a *syn*-addition or an *anti*-addition?

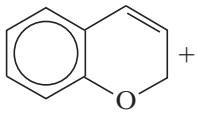
39. On the basis of your answer to Problem 38, give the stereochemical formulas of the products expected from each of the following reactions. Label *meso* compounds and racemic modifications.

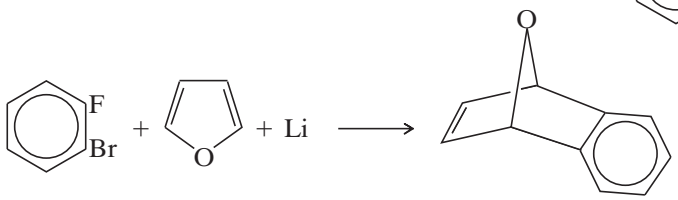
(a) crotonaldehyde (*trans*-2-butenal) + 1,3-butadiene
(b) *p*-benzoquinone + 1,3-butadiene
(c) maleic anhydride + 1,3-butadiene, followed by cold alkaline $KMnO_4$
(d) maleic anhydride + 1,3-butadiene, followed by hot $KMnO_4$ $\longrightarrow$ $C_8H_{10}O_8$

40. Account for the following observations:

(a) Dehydration of 3-hydroxy-2,2-dimethylpropanoic acid yields 2-methyl-2-butenoic acid.

(b) $C_2H_5OOC—COOC_2H_5$ (Ethyl oxalate) + $CH_3CH=CHCOOC_2H_5$ (Ethyl crotonate) $\xrightarrow{OC_2H_5^-}$ $C_2H_5OOC—C(=O)—CH_2CH=CHCOOC_2H_5$

(c) $CH_2=CH—\overset{+}{P}Ph_3\,Br^-$ + salicylaldehyde + a little base $\longrightarrow$  + Ph_3PO

(d) 

(d) benzil ($C_6H_5COCOC_6H_5$) + dibenzyl ketone ($C_6H_5CH_2COCH_2C_6H_5$) + base $\longrightarrow$ S ($C_{29}H_{20}O$), "tetracyclone"

S + maleic anhydride $\longrightarrow$ T ($C_{33}H_{22}O_4$)

T + heat $\longrightarrow$ CO + H_2 + U ($C_{32}H_{20}O_3$)

(e) S + $C_6H_5C{\equiv}CH$ $\longrightarrow$ V($C_{37}H_{26}O$)

V + heat $\longrightarrow$ CO + W ($C_{36}H_{26}$)

(f) acetone + $BrMgC{\equiv}COC_2H_5$, then H_2O $\longrightarrow$ X($C_7H_{12}O_2$)

X + H_2, Pd/$CaCO_3$ $\longrightarrow$ Y($C_7H_{14}O_2$)

Y + H^+, warm $\longrightarrow$ Z (C_5H_8O), β-methylcrotonaldehyde

(g) ethyl 3-methyl-2-butenoate + ethyl cyanoacetate + base $\longrightarrow$ A A ($C_{12}H_{19}O_4N$)

AA + OH^-, heat; then H^+; then heat $\longrightarrow$ BB($C_7H_{12}O_4$)

(h) mesityl oxide + ethyl malonate + base $\longrightarrow$ CC ($C_{13}H_{22}O_5$)

CC + NaOBr, OH^-, heat; then H^+ $\longrightarrow$ $CHBr_3$ + BB ($C_7H_{12}O_4$)

(i) $CH_3C{\equiv}CNa$ + acetaldehyde $\longrightarrow$ DD (C_5H_8O)

DD + $K_2Cr_2O_7$, H_2SO_4 $\longrightarrow$ EE (C_5H_6O)

(j) 3-pentyn-2-one + H_2O, Hg^{2+}, H^+ $\longrightarrow$ FF($C_5H_8O_2$)

(k) mesityl oxide + NaOCl, then H^+ $\longrightarrow$ GG ($C_5H_8O_2$)

(l) methallyl chloride (3-chloro-2-methylpropene) + HOCl $\longrightarrow$ HH ($C_4H_8OCl_2$)

HH + KCN $\longrightarrow$ II($C_6H_8ON_2$)

II + H_2SO_4, H_2O, heat $\longrightarrow$ JJ ($C_6H_8O_4$)

(m) ethyl adipate + NaOEt $\longrightarrow$ KK ($C_8H_{12}O_3$)

KK + methyl vinyl ketone + base $\xrightarrow{\text{Michael}}$ LL($C_{12}H_{18}O_4$)

LL + base $\xrightarrow{\text{aldol}}$ MM($C_{12}H_{16}O_3$)

(n) hexachloro-1,3-cyclopentadiene + CH_3OH + KOH $\longrightarrow$ NN ($C_7H_6Cl_4O_2$)

NN + $CH_2{=}CH_2$, heat, pressure $\longrightarrow$ OO ($C_9H_{10}Cl_4O_2$)

OO + Na + *t*-BuOH $\longrightarrow$ PP ($C_9H_{14}O_2$)

PP + dilute acid $\longrightarrow$ QQ (C_7H_8O), *7-ketonorbornene*

(o) ethyl acetamidomalonate [$CH_3CONHCH(COOC_2H_5)_2$] + acrolein $\xrightarrow{\text{Michael}}$ RR($C_{12}H_{19}O_6N$)

RR + KCN + acetic acid $\longrightarrow$ SS ($C_{13}H_{20}O_6N_2$)

SS + acid + heat $\longrightarrow$ TT ($C_{13}H_{18}O_5N_2$)

TT + H_2, catalyst, in acetic anhydride $\longrightarrow$ [UU ($C_{13}H_{24}O_5N_2$)]

UU $\xrightarrow{\text{acetic anhydride}}$ VV ($C_{15}H_{26}O_6N_2$)

VV + OH^-, heat; then H^+; then heat $\longrightarrow$ WW ($C_7H_{16}O_2N_2$)

(p) acrylonitrile + ethyl malonate $\xrightarrow{\text{Michael}}$ XX ($C_{10}H_{15}O_4N$)

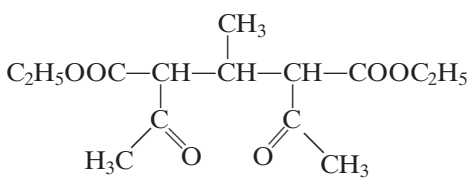
XX + H_2, catalyst $\longrightarrow$ [YY ($C_{10}H_{19}O_4N$)] $\longrightarrow$ ZZ($C_8H_{13}O_3N$)

ZZ + SO_2Cl_2 in $CHCl_3$ $\longrightarrow$ AAA ($C_8H_{12}O_3NCl$)

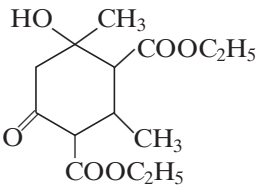
AAA + HCl, heat $\longrightarrow$ BBB ($C_5H_{10}O_2NCl$)

BBB $\xrightarrow{\text{base}}$ CCC ($C_5H_9O_2N$)

43. Treatment of ethyl acetoacetate with acetaldehyde in the presence of the base piperidine was found to give a product of formula $C_{14}H_{22}O_6$. Controversy arose about its structure: did it have open-chain structure III or cyclic structure IV, each formed by combinations of aldol and Michael condensations?



III



IV

(a) Show just how each possible product could have been formed.
(b) Then the NMR spectrum of the compound was found to be the following:

a complex, δ 0.95-1.10, 3H
b singlet, δ 1.28, 3H
c triplet, centered at δ 1.28, 3H
d triplet, centered at δ 1.32, 3H
e singlet, δ 2.5, 2H
f broad singlet, δ 3.5, 1H
g complex, δ 2–4, total of 3H
h quartet, δ 4.25, 2H
i quartet, δ 4.30, 2H

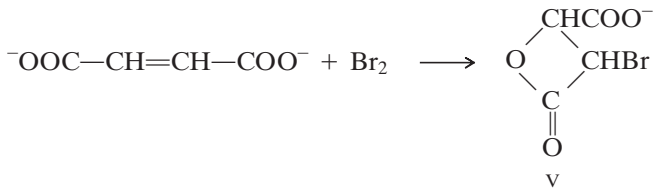
Which structure is the correct one? Assign all peaks in the spectrum. Describe the spectrum you would expect from the other possibility.

44. In connection with his new research problem, our naïve graduate student needed a quantity of the unsaturated alcohol $C_6H_5CH{=}CHC(OH)(CH_3)(C_2H_5)$. He added a slight excess of benzalacetone, $C_6H_5CH{=}CHCOCH_3$, to a solution of ethylmagnesium bromide, and, by use of a color test, found that the Grignard reagent had been consumed. He worked up the reaction mixture in the usual way with dilute acid. Having learned a little (but not much) from his earlier sad experiences, he tested the product with iodine and sodium hydroxide; when a copious precipitate of iodoform appeared, he concluded that he had simply recovered his starting material.

He threw his product into the waste crock, carefully and methodically destroyed his glassware, burned his laboratory coat, left school, and went into politics, where he did quite well; his career in Washington was marred only, in the opinion of some, by his blind antagonism toward all appropriations for scientific research and his frequent attacks—alternately vitriolic and caustic—on the French.

What had he thrown into the waste crock? How had it been formed?

45. β-Lactones cannot be made from β-hydroxy acids. The β-lactone V was obtained, however, by treatment of sodium maleate (or sodium fumarate) with bromine water.



V

This experiment, reported in 1937 by P. D. Bartlett and D. S. Tarbell was an important step in the establishment of the mechanism of addition of halogens to carbon–carbon double bonds. Why is this so? How do you account for the formation of the β-lactone?

46. Give the likely structures for GGG and HHH.

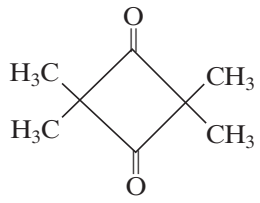
1,3-butadiene + propiolic acid ($HC{\equiv}CCOOH$) $\longrightarrow$ DDD ($C_7H_8O_2$)
DDD + 1 mol $LiAlH_4$ $\longrightarrow$ EEE ($C_7H_{10}O$)
EEE + methyl chlorocarbonate (CH_3OCOCl) $\longrightarrow$ FFF ($C_9H_{12}O_3$)
FFF + heat (short time) $\longrightarrow$ toluene + GGG (C_7H_8)
GGG + tetracyanoethylene $\longrightarrow$ HHH($C_{13}H_8N_4$)

Compound GGG is not toluene or 1,3,5-cycloheptatriene; on standing at room temperature it is converted fairly rapidly into toluene. Compound GGG gives the following spectral data. Ultraviolet: λ_{max} 303 nm, ϵ_{max} 4400. Infrared: strong bands at 3020, 2900, 1595, 1400, 864, 692, and 645 cm^{-1}; medium bands at 2850,1152, and 790 cm^{-1}.

47. Give structures of compounds III through KKK, and account for their formation:

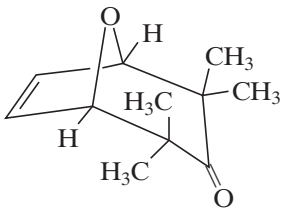
cyclopentanone + pyrrolidine, then acid $\longrightarrow$ III($C_9H_{15}N$)
III + $CH_2{=}CHCOOCH_3$ $\longrightarrow$ JJJ ($C_{13}H_{21}O_2N$)
JJJ + H_2O, H^+, heat $\longrightarrow$ KKK ($C_9H_{14}O_3$)

48. Irradiation by ultraviolet light of 2,2,4,4-tetramethyl-1,3-cyclobutanedione (VI) produces tetramethylethylene and two moles of carbon monoxide. When the irradiation is carried out in furan (VII), there is obtained a product believed to have the structure VIII.



VI

VII



VIII

(a) Chief support for structure VIII comes from elemental analysis, mol. wt. determination, and NMR data:

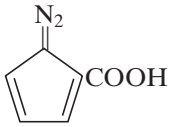
a singlet, δ 0.85, 6H
b singlet, δ 1.25, 6H
c singlet, δ 4.32, 2H
d singlet, δ 6.32, 2H

Show how the NMR data support the proposed structure. Why should there be two singlets of 6H each instead of one peak of 12H?

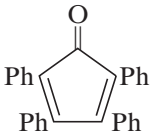
(b) It is proposed that, in the formation of tetramethylethylene, one mole of carbon monoxide is lost at a time. Draw electronic structures to show all steps in such a two-stage mechanism. How does the formation of VIII support such a mechanism?

49. In the reaction of benzaldehyde with semicarbazide to form the semicarbazone the anilinium ion is a *much* more effective catalyst than acarboxylic acid of the same acidity. How might you account for this?

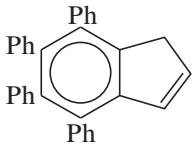
50. When the sodium salt of diazocyclopentadiene-2-carboxylic acid (IX) is heated above 140 °C, N_2 and CO_2 are evolved. If IX is heated in solution with tetracyclone (X), CO is evolved



IX



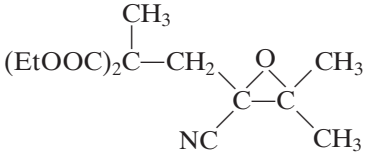
X



XI

as well, and 4,5,6,7-tetraphenylindene (XI) is obtained. Show all steps in a likely mechanism for the formation of XI. Of what special theoretical interest are these findings?

51. When ethyl methylmalonate, acetone, and α-chloroacrylonitrile (CH_2=CClCN) are allowed to react in the presence of base, there is obtained the epoxy compound XII. Show all steps in a likely mechanism for the formation of XII.



XII