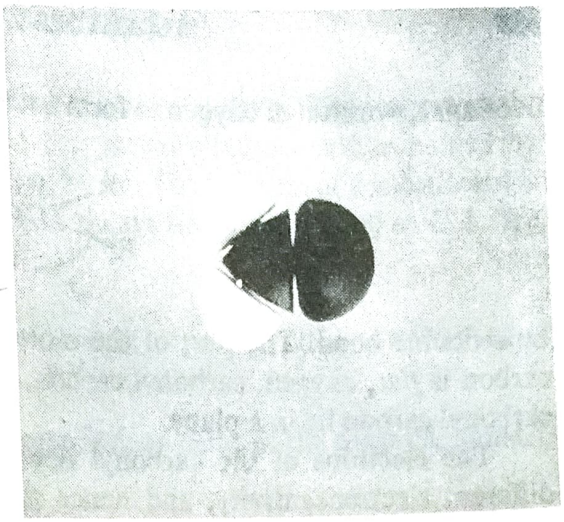
18

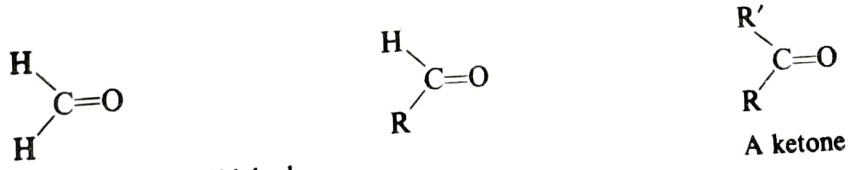


Aldehydes and Ketones

Nucleophilic Addition

18.1 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

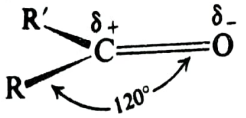
A ketone

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 (Sec. 1.10), 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 different 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. 18.1). The large dipole

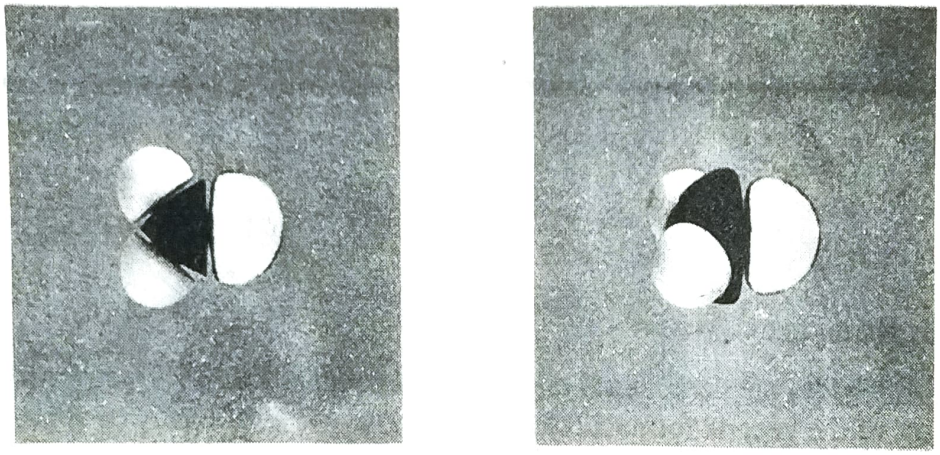
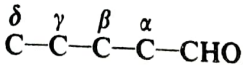


Figure 18.1 Electronic configuration and molecular shape: the carbonyl group. Model of formaldehyde, HCHO: two views.

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.

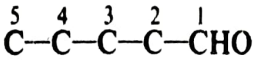
18.2 Nomenclature

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, see Sec. 19.2.) 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.



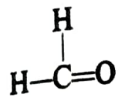
Used in common names

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

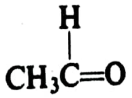


Used in IUPAC names

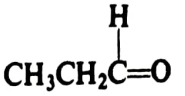
notice that C–2 of the IUPAC name corresponds to *alpha* of the common name.



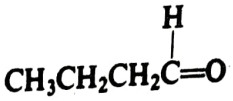
Formaldehyde
Methanal



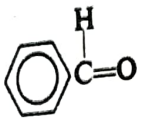
Acetaldehyde
Ethanal



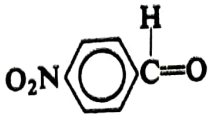
Propionaldehyde
Propanal



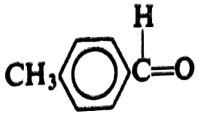
n-Butyraldehyde
Butanal



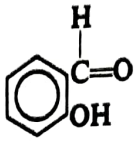
Benzaldehyde



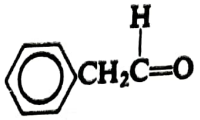
p-Nitrobenzaldehyde



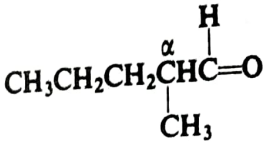
p-Tolualdehyde



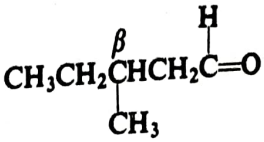
Salicylaldehyde
o-Hydroxybenzaldehyde



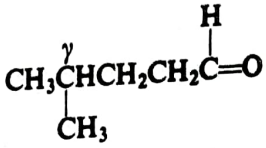
Phenylacetaldehyde
Phenylethanal



α-Methylvaleraldehyde
2-Methylpentanal



β-Methylvaleraldehyde
3-Methylpentanal

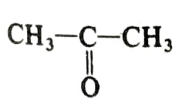


Isocaproaldehyde
γ-Methylvaleraldehyde
4-Methylpentanal

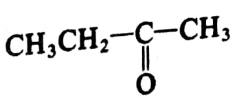
The simplest aliphatic ketone has the common name of *acetone*. For most other aliphatic **ketones** we name the two groups that are attached to carbonyl carbon, and follow these names by the word *ketone*. A ketone in which the carbonyl group is attached to a benzene ring is named as a *-phenone*, as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

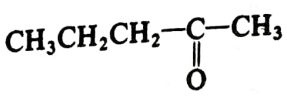
In certain polyfunctional compounds, the presence of a carbonyl group can be indicated by the prefix *oxo-*, with a number to show its position in the molecule.



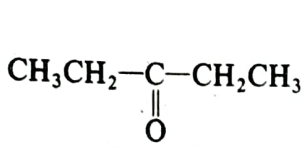
Acetone
Propanone



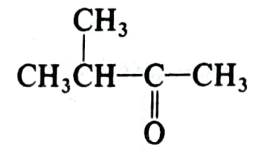
Ethyl methyl ketone
Butanone



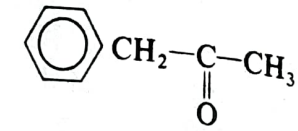
Methyl *n*-propyl ketone
2-Pentanone



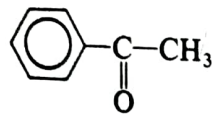
Diethyl ketone
3-Pentanone



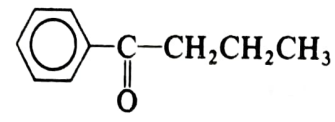
Isopropyl methyl ketone
3-Methyl-2-butanone



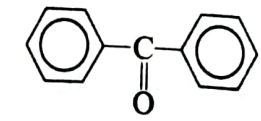
Benzyl methyl ketone
1-Phenyl-2-propanone



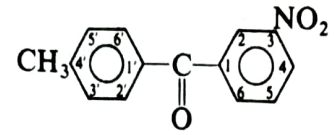
Acetophenone



n-Butyrophenone



Benzophenone



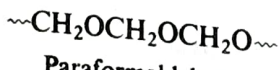
3-Nitro-4′-methylbenzophenone

18.3 Physical properties

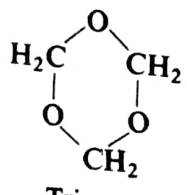
The polar carbonyl group makes aldehydes and ketones polar compounds, and hence they have higher boiling points than non-polar compounds of comparable molecular weight. By themselves, they are not capable of intermolecular hydrogen bonding since they contain hydrogen bonded only to carbon; as a result 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.



Paraformaldehyde

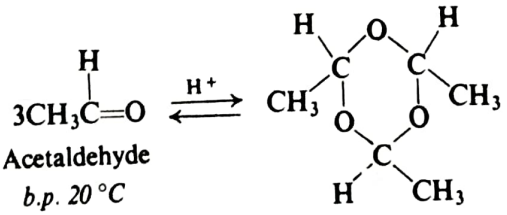


Trioxane

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

Table 18.1 ALDEHYDES AND KETONES

	M.p., °C	B.p., °C	Solubility, g/100 g H_2O
Formaldehyde	−92	−21	v.sol.
Acetaldehyde	−121	20	∞
Propionaldehyde	−81	49	16
n-Butyraldehyde	−99	76	7
n-Valeraldehyde	−91	103	sl.s.
Caproaldehyde		131	sl.s.
Heptaldehyde	−42	155	0.1
Phenylacetaldehyde		194	sl.s.
Benzaldehyde	−26	178	0.3
o-Tolualdehyde		196	
m-Tolualdehyde		199	
p-Tolualdehyde		205	
Salicylaldehyde (*o*-Hydroxybenzaldehyde)	2	197	1.7
p-Hydroxybenzaldehyde	116		1.4
Anisaldehyde	3	248	0.2
Vanillin	82	285	1
Piperonal	37	263	0.2
Acetone	−94	56	∞
Ethyl methyl ketone	−86	80	26
2-Pentanone	−78	102	6.3
3-Pentanone	−41	101	5
2-Hexanone	−35	150	2.0
3-Hexanone		124	sl.s
Isobutyl methyl ketone	−85	119	1.9
Acetophenone	21	202	
Propiophenone	21	218	



Acetaldehyde
b.p. 20 °C

Paraldehyde
b.p. 125 °C

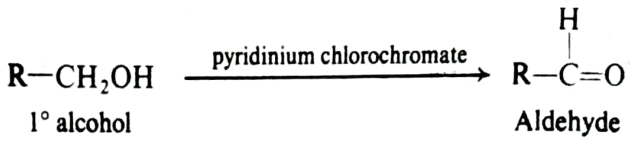
18.4 Preparation

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.

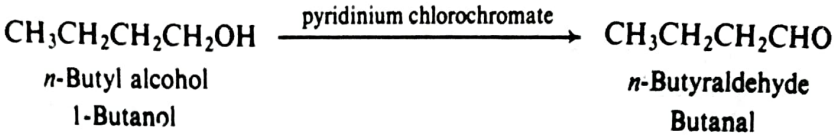
Industrial preparations often involve special methods, or the modification of laboratory methods by use of cheaper reagents: formaldehyde and acetone are made by oxidation of methanol and isopropyl alcohol, respectively, but by air in the presence of a catalyst. Some aldehydes are obtained by the oxo process, in which they are the initial products (Secs. 6.6 and 29.8).

PREPARATION OF ALDEHYDES

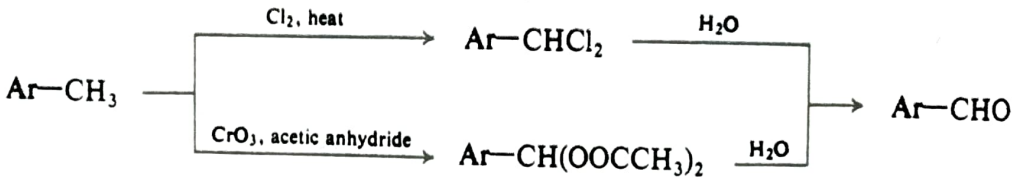
1. **Oxidation of primary alcohols.** Discussed in Secs. 6.15 and 18.4.



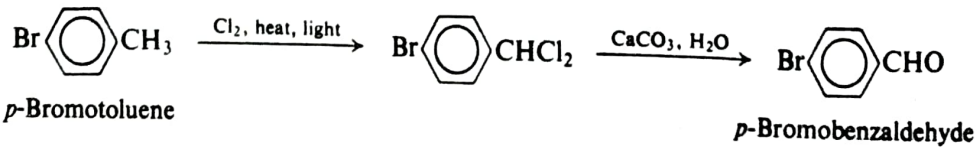
Example:

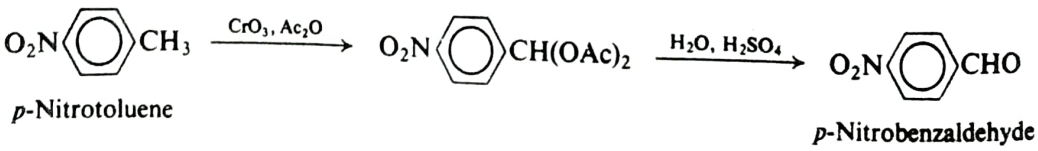


2. **Oxidation of methylbenzenes.** Discussed in Sec. 18.4.

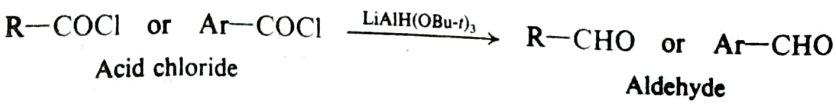


Examples:





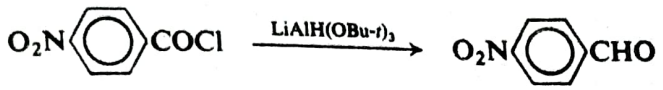
3. **Reduction of acid chlorides.** Discussed in Sec. 18.4.



CONTINUED

CONTINUED

Example:

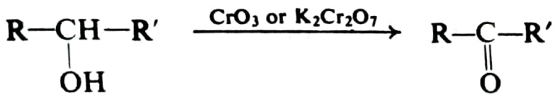


p-Nitrobenzoyl chloride — *p*-Nitrobenzaldehyde

4. **Reimer–Tiemann reaction. Phenolic aldehydes.** Discussed in Sec. 24.13.

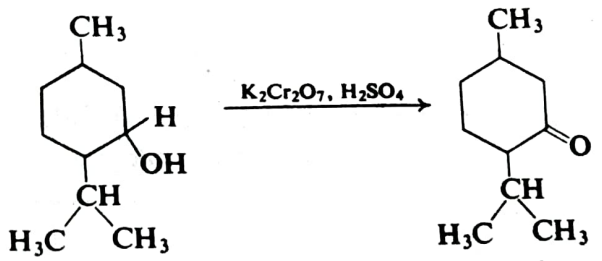
PREPARATION OF KETONES

1. **Oxidation of secondary alcohols.** Discussed in Secs. 6.15 and 18.4.



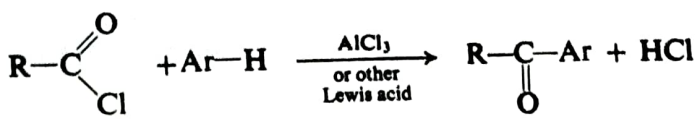
2° alcohol — Ketone

Example:



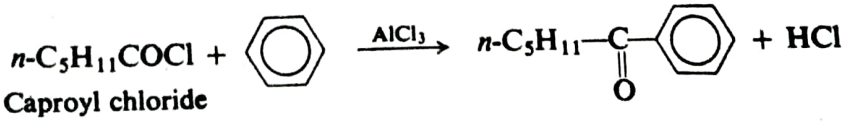
(−)-Menthol — (−)-Menthone

2. **Friedel–Crafts acylation.** Discussed in Sec. 18.5.



Acid chloride — Ketone

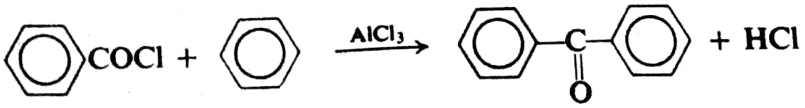
Examples:



Caproyl chloride

n-Pentyl phenyl ketone

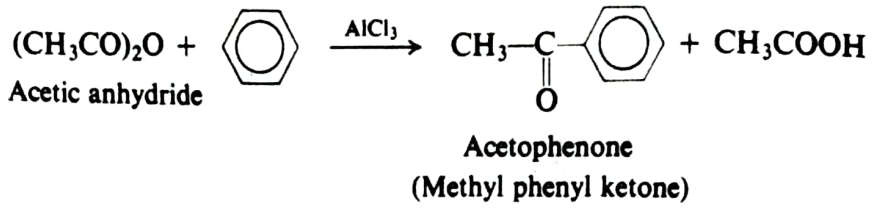
No rearrangement of n-pentyl group



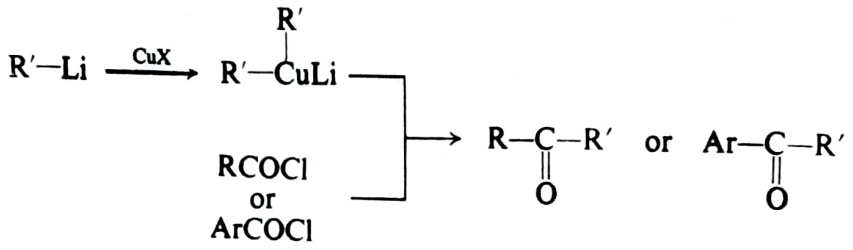
Benzoyl chloride — Benzophenone (Diphenyl ketone)

CONTINUED

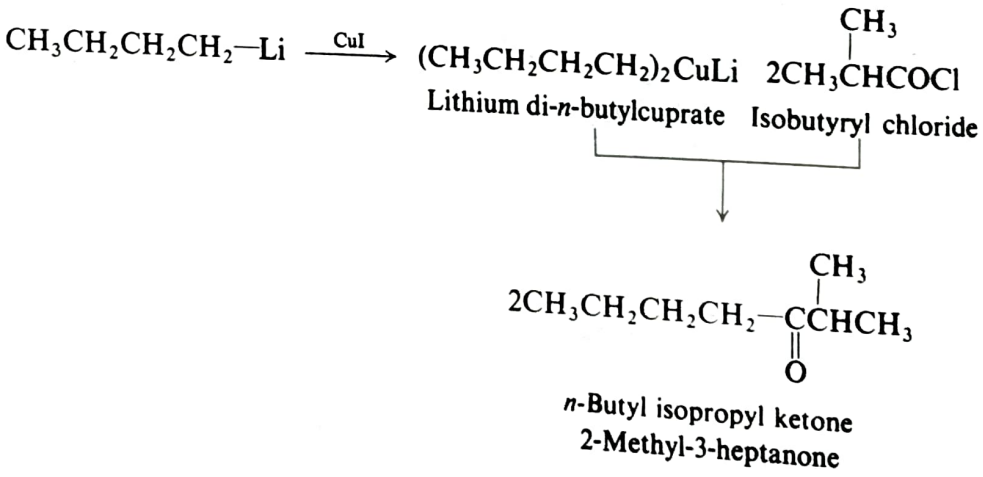
CONTINUED

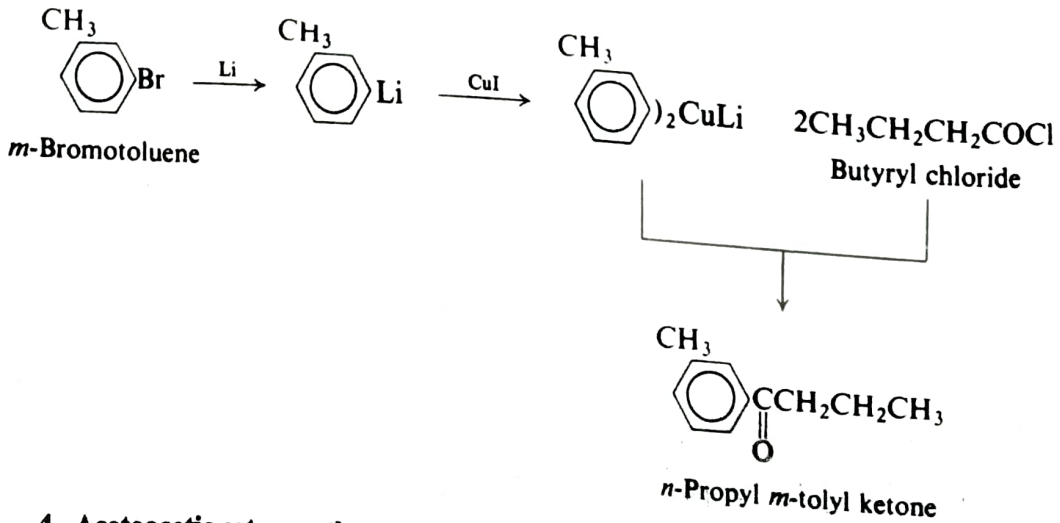


3. **Reaction of acid chlorides with organocopper compounds.** Discussed in Sec. 18.6.



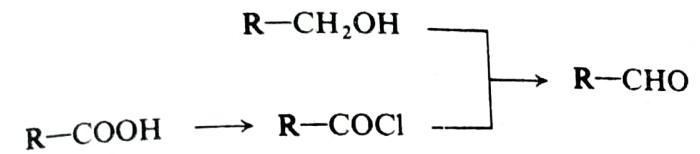
Examples:



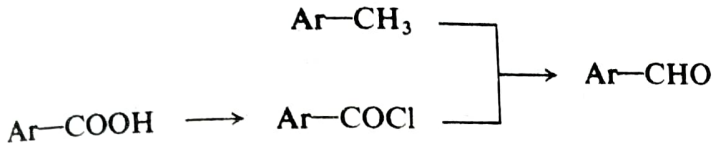


4. **Acetoacetic ester synthesis.** Discussed in Sec. 25.3.

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



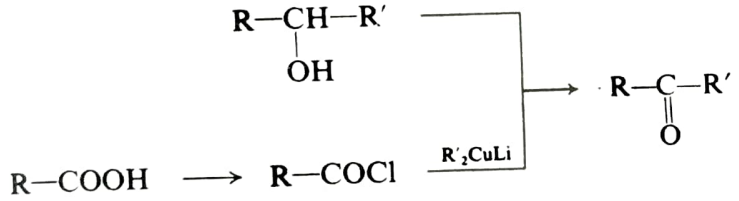
Preparation of aliphatic aldehydes



Preparation of aromatic aldehydes

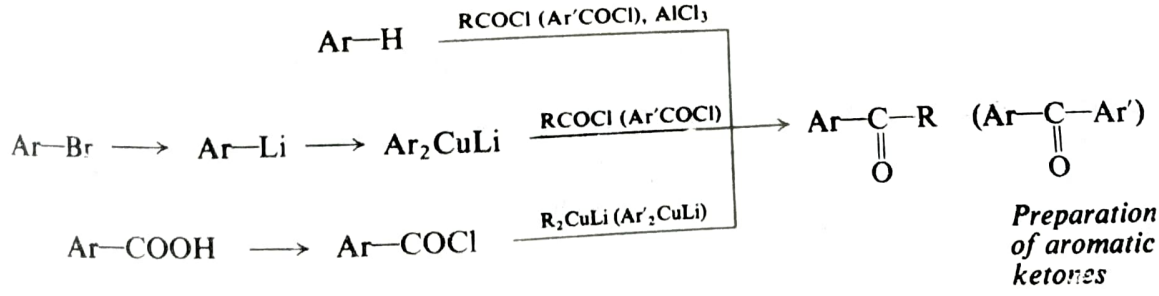
chlorides. There are, in addition, a number of methods by which the aldehyde group is introduced into an aromatic ring: for example, the Reimer–Tiemann synthesis of phenolic aldehydes (Sec. 24.13).

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



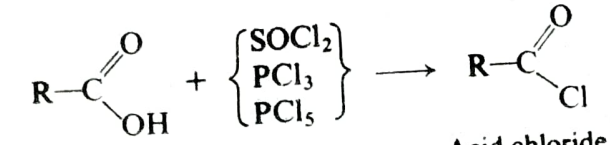
Preparation of aliphatic ketones

useful method for making complicated aliphatic ketones, the acetoacetic ester synthesis, will be discussed later (Sec. 25.3). **Aromatic ketones** containing a carbonyl group attached directly to an aromatic ring are conveniently prepared by Friedel–Crafts acylation (Sec. 18.5).



Preparation of aromatic ketones

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 (PCl_5). Since we already know several of the most

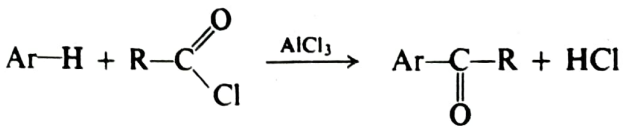


Carboxylic acid Acid chloride

important ways of making carboxylic acids—oxidation of primary alcohols (Sec. 6.15) and oxidation of toluenes (Sec. 16.11)—we can begin to fit these syntheses of carbonyl compounds into the overall framework of organic chemistry.

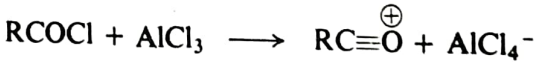
18.5 Preparation of ketones by Friedel–Crafts acylation

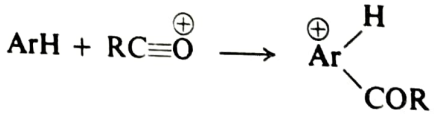
One of the most important modifications of the Friedel–Crafts reaction involves the use of acid chlorides rather than alkyl halides. An acyl group, RCO—, becomes attached to the aromatic ring, thus forming a ketone; the process is called **acylation**. As usual for the Friedel–Crafts reaction (Sec. 16.9), the aromatic ring undergoing substitution must be at least as reactive as that of a halobenzene; catalysis by aluminum chloride or another Lewis acid is required.

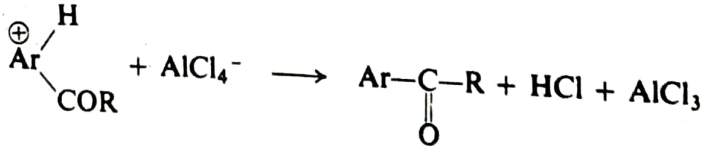


An acid chloride A ketone

The most likely mechanism for Friedel–Crafts acylation is analogous to the carbocation mechanism for Friedel–Crafts alkylation (Sec. 15.10), and involves the following steps:

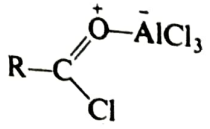
(1) 

(2) 

(3) 

This fits the pattern of electrophilic aromatic substitution, the attacking reagent this time being the **acylium ion**, $R-C\equiv\overset{\oplus}{O}$. The acylium ion is considerably more stable than ordinary carbocations since in it every atom has an octet of electrons.

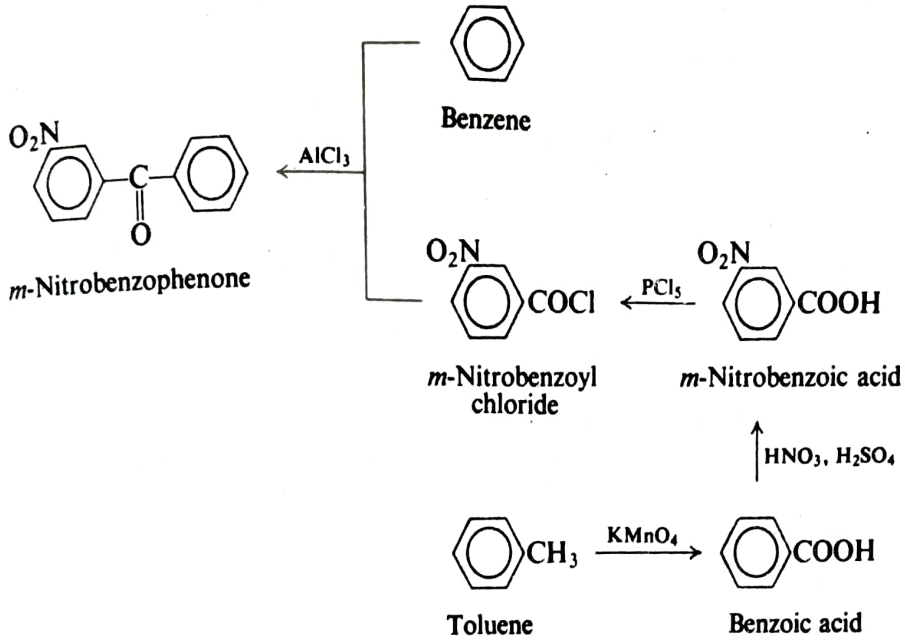
Alternatively, it may be that the electrophile is a complex between acid chloride and Lewis acid:

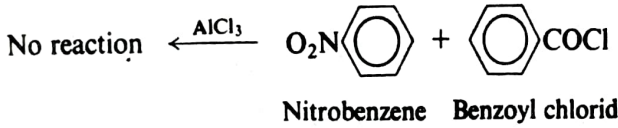


In this case, from the standpoint of the acid chloride, reaction is acid-catalyzed nucleophilic acyl substitution, of the kind discussed in Sec. 20.4, with the aromatic ring acting as the nucleophile.

In planning the synthesis of diaryl ketones, ArCOAr′, it is particularly important to select the right combination of ArCOCl and Ar′H. As shown below, in the preparation of *m*-nitrobenzophenone, for example, the nitro group can be

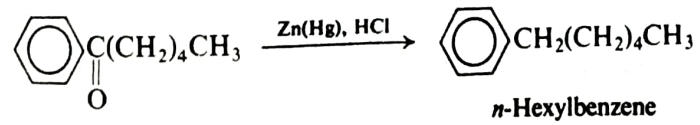
present in the acid chloride but not in the ring undergoing substitution, since as a strongly deactivating group it prevents the Friedel–Crafts reaction (Sec. 16.9).

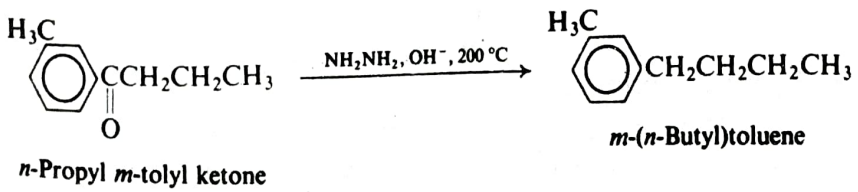




Friedel–Crafts acylation is one of the most important methods of preparing ketones in which the carbonyl group is attached to an aromatic ring. Once formed, these ketones may be converted into secondary alcohols by reduction, into tertiary alcohols by reaction with Grignard reagents, and into many other important classes of compounds, as we shall see.

Of particular importance is the conversion of the acyl group into an alkyl group. This can be accomplished by the **Clemmensen reduction** (amalgamated zinc and concentrated hydrochloric acid), or the **Wolff–Kishner reduction** (hydrazine and base). For example:





A straight-chain alkyl group longer than ethyl generally cannot be attached in good yield to an aromatic ring by Friedel–Crafts alkylation because of rearrangement (Sec. 16.8). Such a group is readily introduced, however, in two steps: (1) formation of a ketone by Friedel–Crafts acylation (or by the reaction of an organocopper compound with an acyl chloride, described in the following section); (2) Clemmensen or Wolff–Kishner reduction of the ketone.

18.6 Preparation of ketones by use of organocopper compounds

Treatment of alkyl or aryl halides with lithium metal gives organolithium compounds (Sec. 18.14) which, on treatment with a cuprous halide, form lithium organocuprates, R_2CuLi or Ar_2CuLi. Since the late 1960s such organocopper

$$RX \xrightarrow{Li} RLi \xrightarrow{CuX} R_2CuLi$$

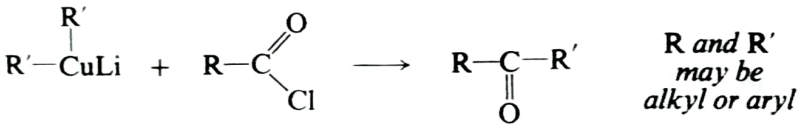
A lithium dialkylcuprate

$$ArX \xrightarrow{Li} ArLi \xrightarrow{CuX} Ar_2CuLi$$

A lithium diarylcuprate

compounds have found rapidly increasing application to organic synthesis because of their remarkable ability to form carbon–carbon bonds. We have already (Sec. 3.17) encountered their reaction with alkyl halides to form alkanes.

Lithium organocuprates react readily with acid chlorides to yield ketones. Here, as in its other reactions (Sec. 20.4), the acid chloride is undergoing nucleo-



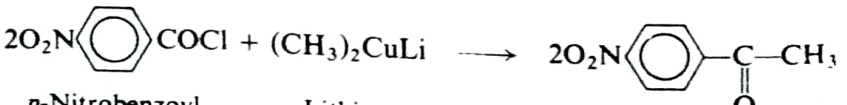
An acid chloride A ketone

philic substitution, the nucleophile being the basic alkyl or aryl group of the organometallic compound.

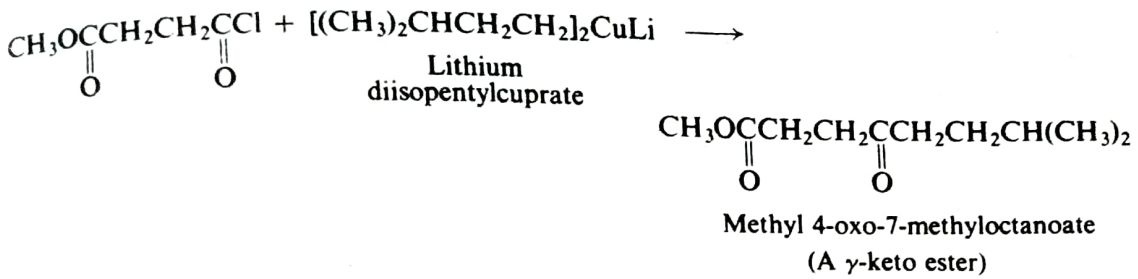
Grignard reagents (or organolithiums) react readily with acid chlorides, too, but the products are usually tertiary alcohols, formed by reaction of initially formed ketones with additional Grignard reagents (Sec. 18.14). (If tertiary alcohols are desired, they are better prepared from esters than from acid chlorides (Sec. 20.21).) Organocopper reagents are less reactive than Grignard reagents toward the carbonyl group of ketones, and reaction stops at the ketone stage.

It is interesting that organocopper compounds are *more* reactive than Grignard reagents toward many kinds of compounds—alkyl halides, for example, which in general are not attacked by Grignard reagents. Organocopper compounds are highly *selective* toward different functional groups, and this selectivity is a major factor in determining their usefulness.

This lower reactivity of organocopper compounds not only makes the synthesis of ketones possible, but in addition widens the applicability of the method. Organocopper reagents do not react with many of the functional groups with which Grignard reagents and organolithiums do react: $—NO_2$, —CN, —CO—, —COOR, for example. Consequently, the presence of one of these groups in the acid chloride does not interfere with the synthesis of a ketone (compare with Sec. 18.18). For example:



p-Nitrobenzoyl chloride Lithium dimethylcuprate *p*-Nitroacetophenone (Methyl *p*-nitrophenyl ketone)



Problem 18.1 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?

18.7 Reactions. Nucleophilic addition

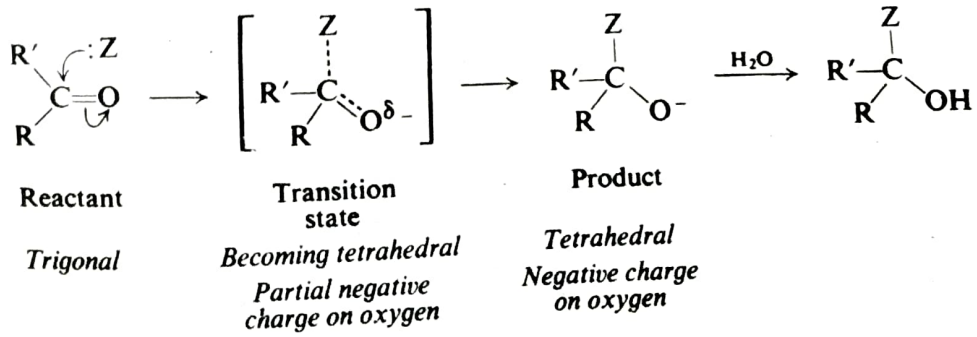
The carbonyl group, C=O, governs the chemistry of aldehydes and ketones. It does this in two ways: (a) by providing a site for nucleophilic addition, and (b) by increasing the acidity of the hydrogen atoms attached to the *alpha* carbon. Both these effects are quite consistent with the structure of the 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; in Sec. 21.1, we shall see how the acid-strengthening effect arises.

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 perpendicular 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.**

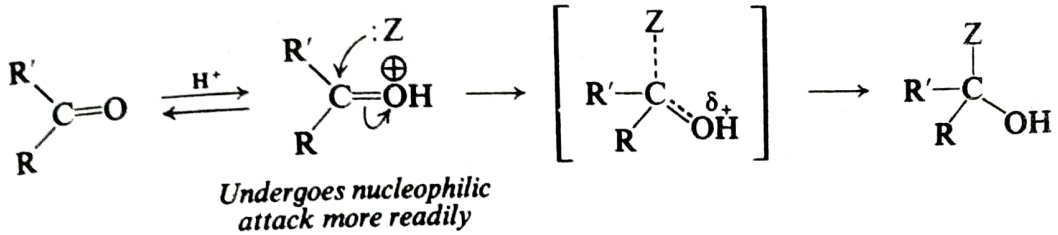
Nucleophilic addition



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

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

Acid-catalyzed nucleophilic addition



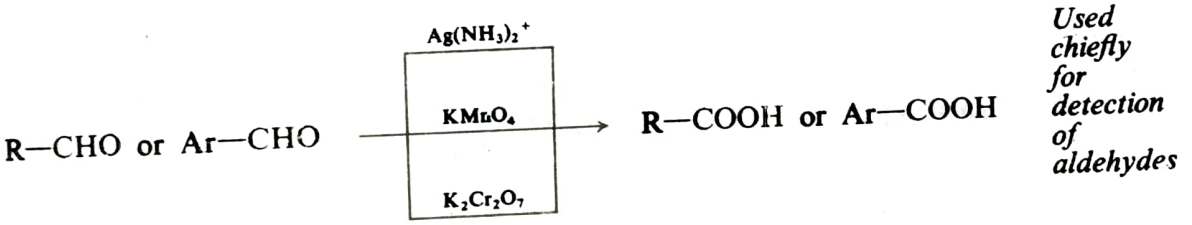
Undergoes nucleophilic attack more readily

acquire the π electrons without having to accept a negative charge. Thus nucleophilic addition to aldehydes and ketones can be catalyzed by acids (sometimes, by *Lewis* acids).

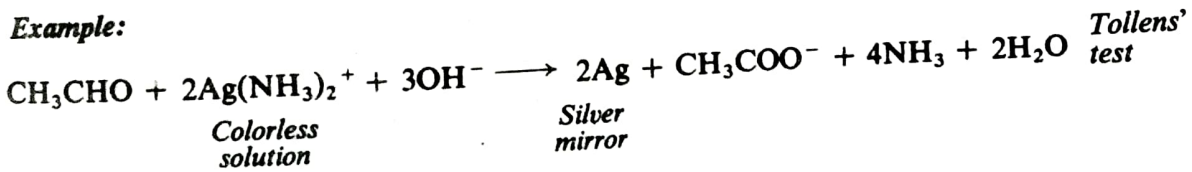
REACTIONS OF ALDEHYDES AND KETONES

1. Oxidation

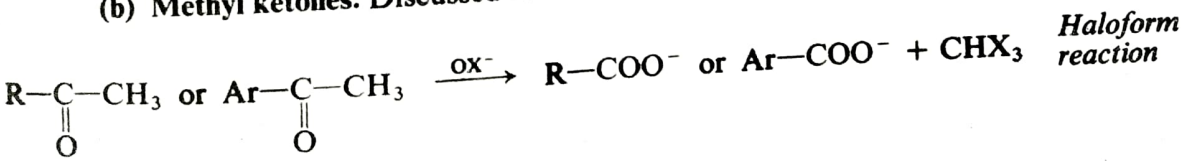
(a) Aldehydes. Discussed in Sec. 18.8.



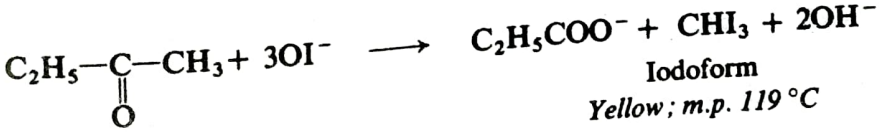
Example:

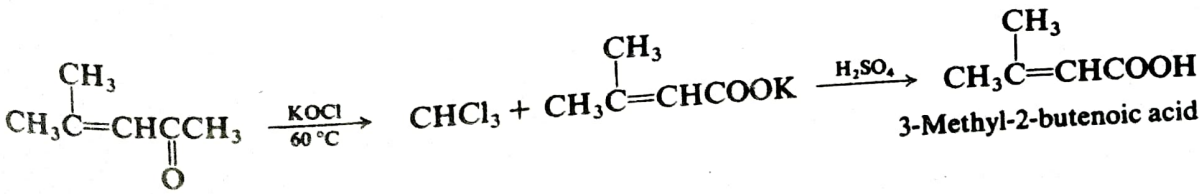


(b) Methyl ketones. Discussed in Sec. 18.21.



Examples:





4-Methyl-3-penten-2-one

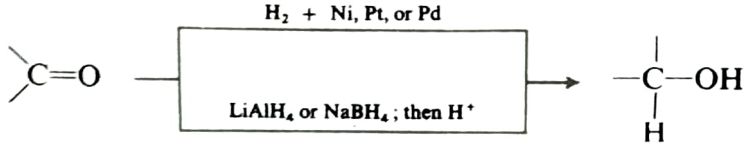
3-Methyl-2-butenoic acid

CONTINUED

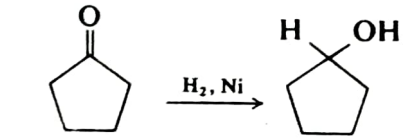
CONTINUED

2. Reduction

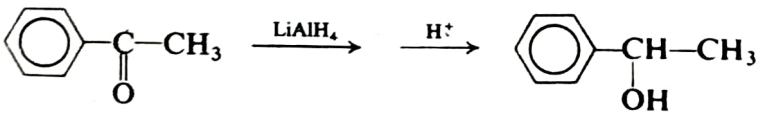
(a) **Reduction to alcohols.** Discussed in Sec. 18.9.



Examples:

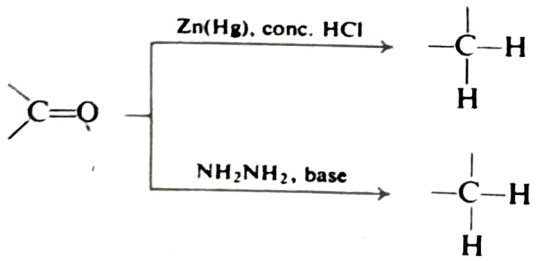


Cyclopentanone Cyclopentanol



Acetophenone α-Phenylethyl alcohol

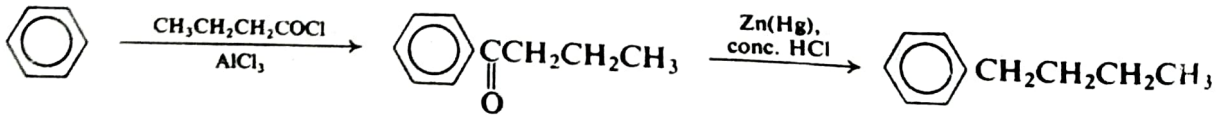
(b) **Reduction to hydrocarbons.** Discussed in Sec. 18.9.



Clemmensen reduction
for compounds sensitive to base

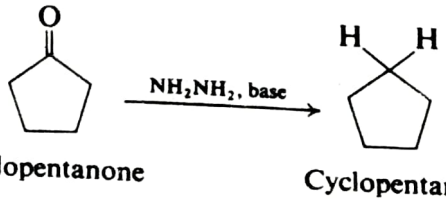
Wolff-Kishner reduction
for compounds sensitive to acid

Examples:



n-Butyrophenone
(Phenyl *n*-propyl ketone)

n-Butylbenzene



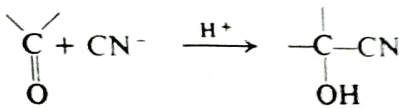
Cyclopentanone Cyclopentane

(c) **Reductive amination.** Discussed in Sec. 22.11.

CONTINUED

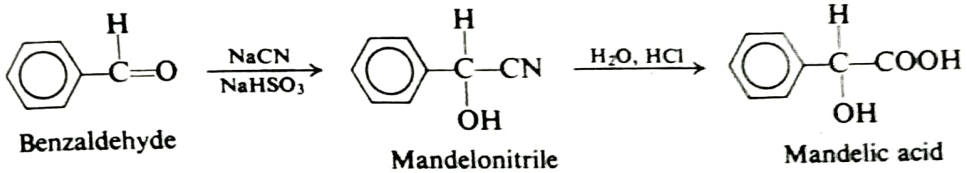
CONTINUED

3. Addition of cyanide. Cyanohydrin formation. Discussed in Sec. 18.10.

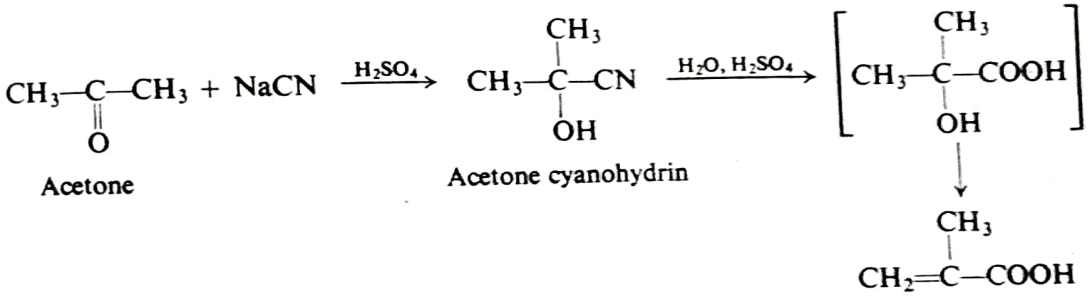


Cyanohydrin

Examples:



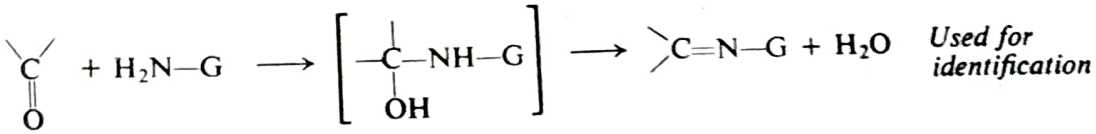
Benzaldehyde — Mandelonitrile — Mandelic acid



Acetone — Acetone cyanohydrin

Methacrylic acid
(2-Methylpropenoic acid)

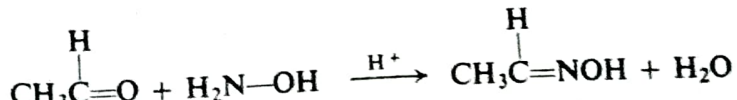
4. Addition of derivatives of ammonia. Discussed in Sec. 18.11.



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

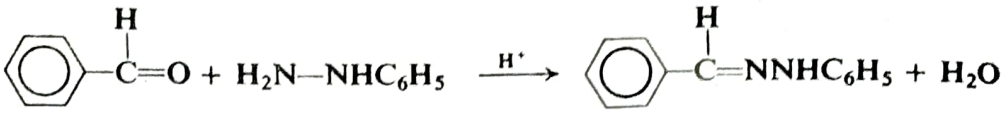
Examples:



Acetaldehyde — Hydroxylamine — Acetaldoxime

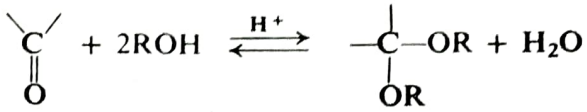
CONTINUED

CONTINUED



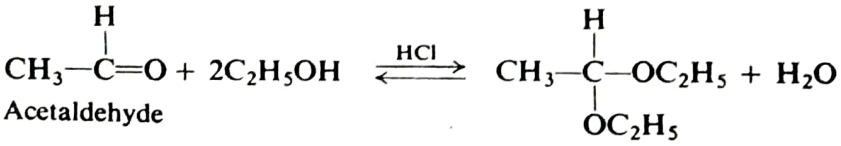
Benzaldehyde Phenylhydrazine Benzaldehyde phenylhydrazone

5. **Addition of alcohols. Acetal formation.** Discussed in Sec. 18.12.



An acetal

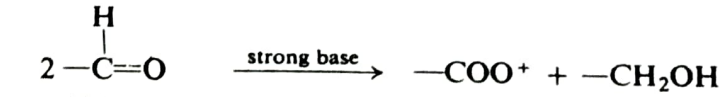
Example:



Acetaldehyde

Acetal
(Acetaldehyde diethyl acetal)

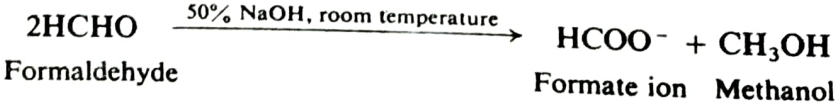
6. **Cannizzaro reaction.** Discussed in Sec. 18.13.



An aldehyde with no α-hydrogens

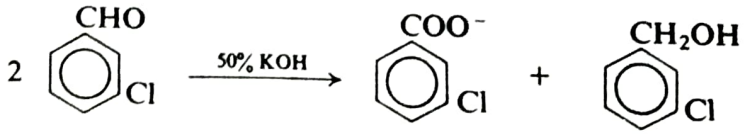
Acid salt Alcohol

Examples:



Formaldehyde

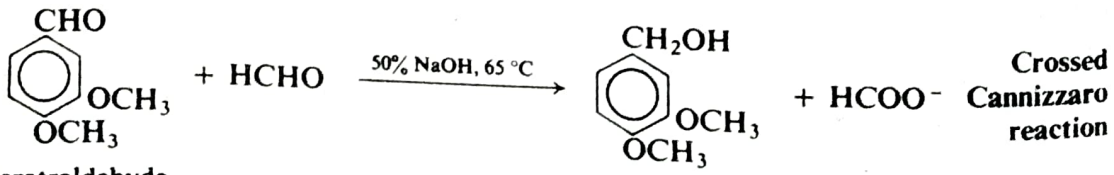
Formate ion Methanol



m-Chlorobenzaldehyde

m-Chlorobenzoate ion

m-Chlorobenzyl alcohol



Veratraldehyde
3,4-Dimethoxybenzaldehyde

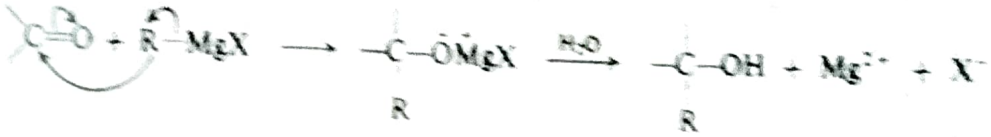
3,4-Dimethoxybenzyl alcohol

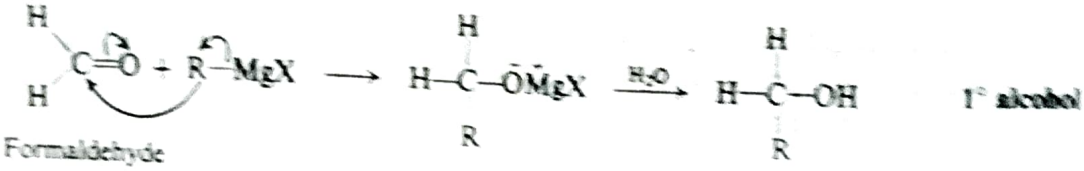
Crossed Cannizzaro reaction

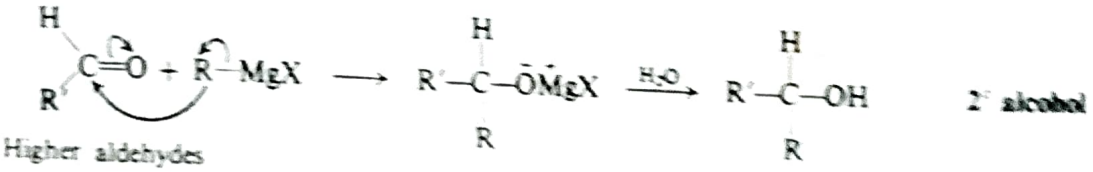
CONTINUED

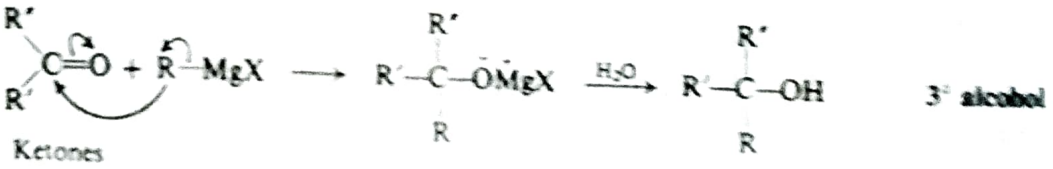
CONTINUED

7. **Addition of Grignard reagents.** Discussed in Secs. 18.14–18.17.

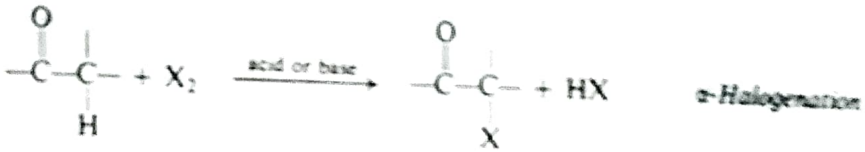








8. **Halogenation of ketones.** Discussed in Secs. 21.3–21.4.



$X_2 = Cl_2, Br_2, I_2$

9. **Addition of carbanions**

   (a) **Aldol condensation.** Discussed in Secs. 21.5–21.8.

   (b) **Reactions related to aldol condensation.** Discussed in Sec. 21.9.

   (c) **Wittig reaction.** Discussed in Sec. 21.10.

■

18.8 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, and 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).

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

(Oxidation by complexed cupric ion is a characteristic of certain substituted carbonyl compounds, and will be taken up with *carbohydrates* in Sec. 34.6.)

Oxidation by Tollens' reagent is useful chiefly for detecting aldehydes, and in particular for differentiating them from ketones (see Sec. 18.20). 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 (Sec. 21.6), where advantage is taken of the fact that Tollens' reagent does not attack carbon–carbon double bonds.

$$\underset{\alpha,\beta\text{-Unsaturated aldehyde}}{R\overset{\beta}{C}H{=}\overset{\alpha}{C}H{-}\overset{H}{\overset{|}{C}}{=}O} \xrightarrow{\text{Tollens' reagent}} \underset{\alpha,\beta\text{-Unsaturated acid}}{R\overset{\beta}{C}H{=}\overset{\alpha}{C}H{-}COOH}$$

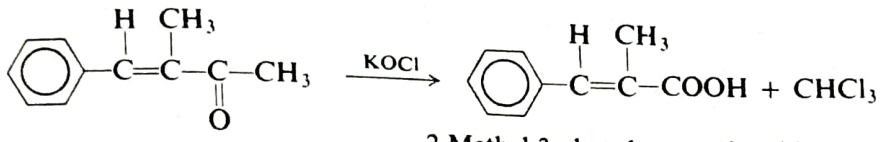
Oxidation of ketones requires breaking of carbon–carbon bonds, and (except for the haloform reaction) takes place only under vigorous conditions. Cleavage involves the double bond of the *enol* form (Sec. 12.10) and, where the structure

$$\underset{\text{Enol}}{-\overset{|}{C}-\overset{OH}{\overset{|}{C}}=C-} \rightleftharpoons \underset{\text{Ketone}}{-\overset{|}{C}-\overset{O}{\overset{\|}{C}}-\overset{|}{C}-} \rightleftharpoons \underset{\text{Enol}}{-C=\overset{OH}{\overset{|}{C}}-\overset{|}{C}-}$$

permits, occurs on either side of the carbonyl group; in general, then, mixtures of carboxylic acids are obtained (see Sec. 9.26).

Problem 18.2 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 (Sec. 18.20), this reaction is often useful in synthesis, hypohalite having the special advantage of not attacking carbon–carbon double bonds. For example:

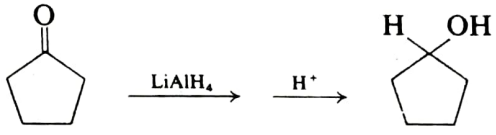


Available by aldol condensation
(Sec. 21.8)

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

18.9 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 (Sec. 21.7). For example:

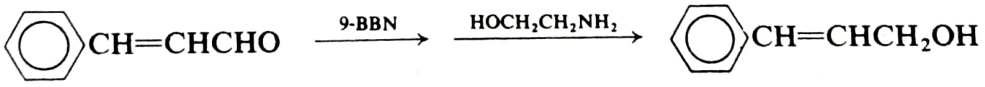


Cyclopentanone Cyclopentanol

$$CH_3CH{=}CHCHO \xrightarrow{H_2,\ Ni} CH_3CH_2CH_2CH_2OH$$

2-Butenal
Crotonaldehyde
From aldol condensation of acetaldehyde

n-Butyl alcohol

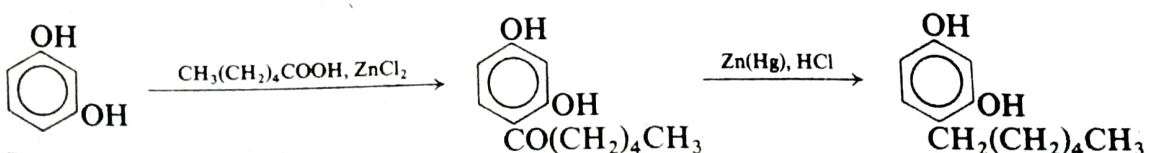


3-Phenylpropenal
Cinnamaldehyde
From aldol condensation of benzaldehyde and acetaldehyde
(Sec. 21.8)

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. One of these is shown above, and will be discussed in Sec. 21.7.

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

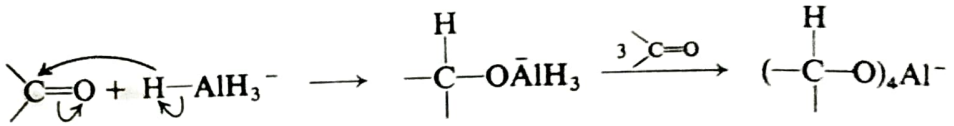
4-*n*-Hexylresorcinol
Used as an antiseptic

A special sort of oxidation and reduction, the *Cannizzaro reaction*, will be discussed in Sec. 18.13.

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

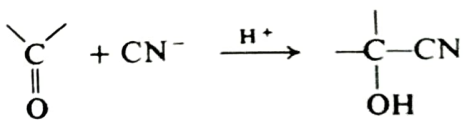
$$4R_2C{=}O + LiAlH_4 \longrightarrow (R_2CHO)_4AlLi \xrightarrow{H_2O} 4R_2CHOH + LiOH + Al(OH)_3$$

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



18.10 Addition of cyanide

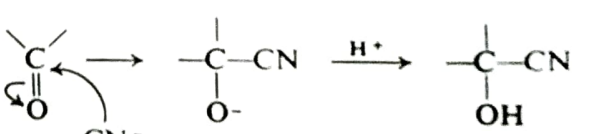
The elements of HCN add to the carbonyl group of aldehydes and ketones to yield compounds known as **cyanohydrins**:



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:

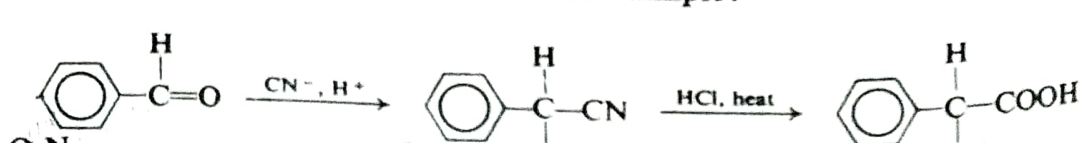


Nucleophilic reagent

Cyanohydrin

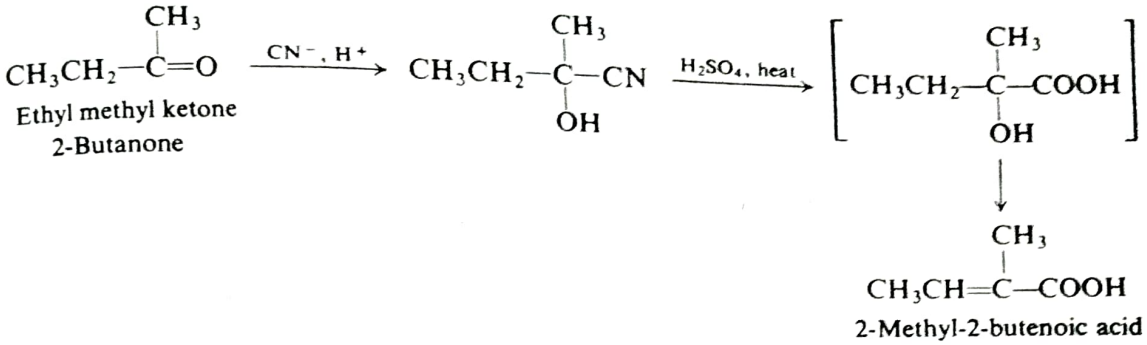
Although it is the elements of HCN that become attached to the carbonyl group, a highly acidic medium—in which the concentration of un-ionized HCN is highest—actually retards reaction. This is to be expected, since the very weak acid HCN is a poor source of cyanide ion.

Cyanohydrins are *nitriles* (see Sec. 19.8), 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:



m-Nitrobenzaldehyde

m-Nitromandelic acid



Problem 18.3 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.

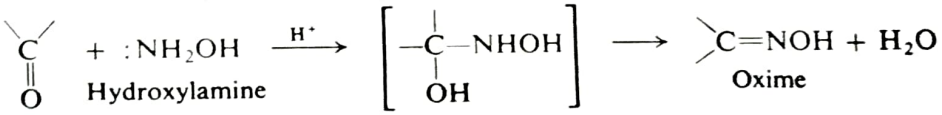
(a) Acetaldehyde; (b) benzaldehyde; (c) acetone.

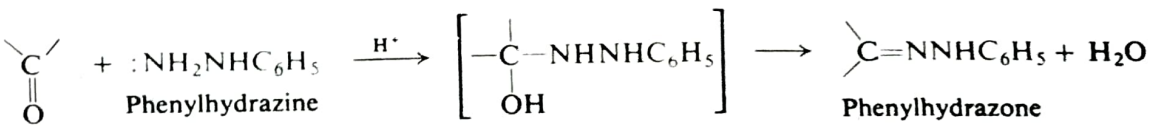
(d) *R*-(+)-glyceraldehyde, $CH_2OHCHOHCHO$; (e) (±)-glyceraldehyde.

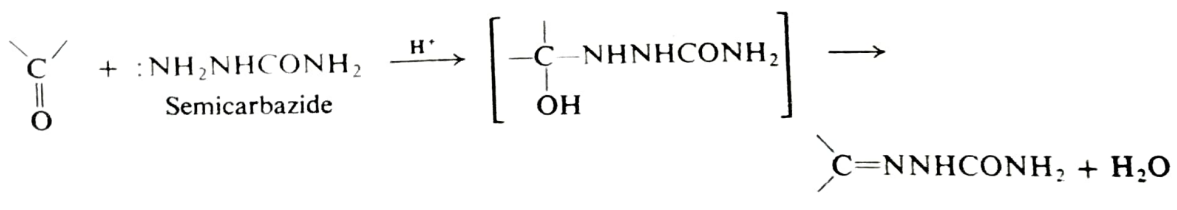
(f) How would your answer to each of the above be changed if each mixture were subjected to hydrolysis to hydroxy acids before fractionation?

18.11 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 (Sec. 18.20). 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:





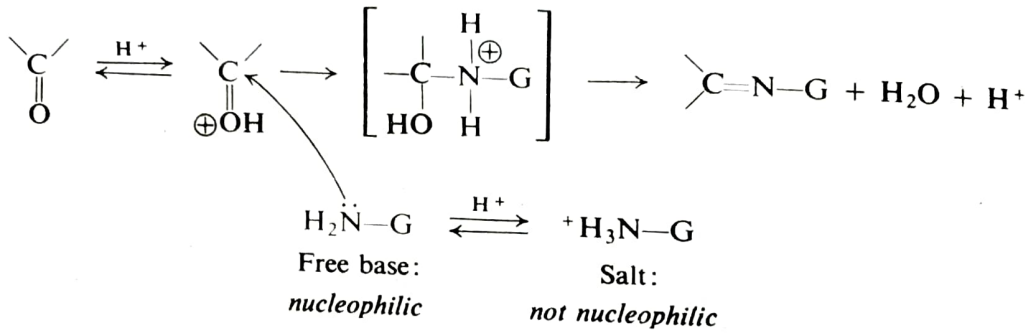


Like ammonia, these derivatives of ammonia are basic, and therefore react with acids to form salts: hydroxylamine hydrochloride, $HONH_3^+Cl^-$; phenylhydrazine hydrochloride, $C_6H_5NHNH_3^+Cl^-$; and semicarbazide hydrochloride, $NH_2CONHNH_3^+Cl^-$. The salts are less easily oxidized by air than the 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.

$$\underset{\substack{\text{Phenylhydrazine}\\\text{hydrochloride}\\\textit{Stronger acid}}}{C_6H_5NHNH_3^+Cl^-} + \underset{\substack{\text{Sodium}\\\text{acetate}\\\textit{Stronger base}}}{CH_3COO^-Na^+} \rightleftharpoons \underset{\substack{\text{Phenylhydrazine}\\\textit{Weaker base}}}{C_6H_5NHNH_2} + \underset{\textit{Weaker acid}}{CH_3COOH} + Na^+Cl^-$$

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.

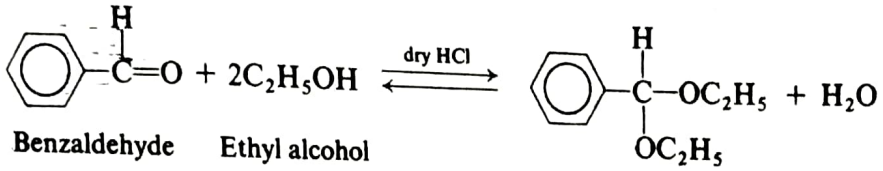
Problem 18.4 Semicarbazide (1 mol) is added to a mixture of cyclohexanone (1 mol) and benzaldehyde (1 mol). If the product is isolated immediately, it consists almost entirely of the semicarbazone of cyclohexanone; if the product is isolated after several hours, it consists almost entirely of the semicarbazone of benzaldehyde. How do you account for these observations? (*Hint*: See Sec. 11.23.)

18.12 Addition of alcohols. Acetal formation

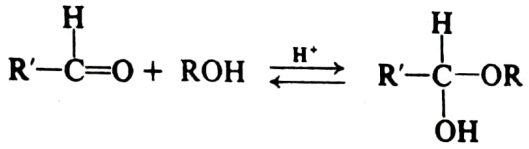
Alcohols add to the carbonyl group of aldehydes in the presence of anhydrous acids to yield **acetals**:

$$\underset{\text{Aldehyde}}{R'-\overset{\displaystyle H}{\overset{|}{C}}=O} + \underset{\text{Alcohol}}{2ROH} \xrightleftharpoons{\text{dry HCl}} \underset{\text{Acetal}}{R'-\overset{\displaystyle H}{\overset{|}{C}}(OR)_2} + H_2O$$

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, Sec. 6.9). (Simple *ketals* are usually difficult to prepare by reaction of ketones with alcohols, and are made in other ways.)

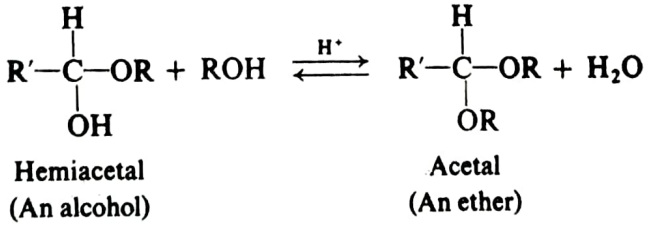


There is good evidence that in alcoholic solution an aldehyde exists in equilibrium with a compound called a **hemiacetal**:



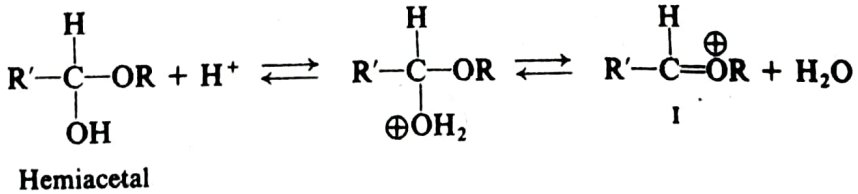
A hemiacetal is formed by the addition of the nucleophilic alcohol molecule to the carbonyl group; it is both an ether and an alcohol. With a few exceptions, hemiacetals are too unstable to be isolated.

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

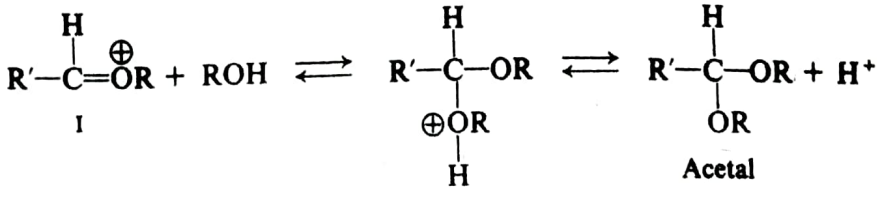


The reaction involves the formation (step 1) of the ion I, which then combines (step 2) with a molecule of alcohol to yield the protonated acetal. As we can see,

(1)



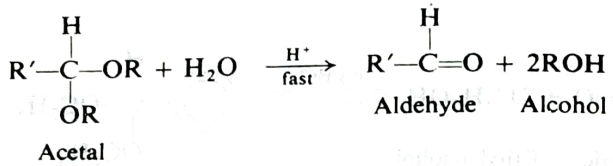
(2)



this mechanism is strictly analogous to the S_N1 route we have previously encountered (Sec. 6.18) for the formation of ethers.

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

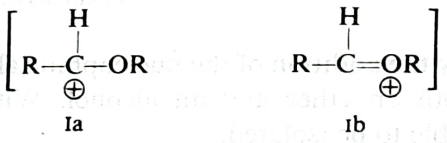
Acetals have the structure of ethers and, like ethers, are cleaved by acids and are stable toward bases. Acetals differ from ethers, however, in the extreme *ease* with which they undergo acidic cleavage; they are rapidly converted even at room



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

The heart of the chemistry of acetals is the "carbocation",



which is a hybrid of structures Ia and Ib. Contribution from Ib, in which every atom has an octet of electrons, makes this ion considerably more stable than ordinary carbocations. (Indeed, Ib *alone* may pretty well represent the ion, in which case it is not a carbocation at all but an *oxonium* ion.)

Now, generation of this cation is the rate-determining step both in formation of acetals (reading to the right in equation 1) and in their hydrolysis (reading to the left in equation 2). The same factor—the providing of electrons by oxygen—that stabilizes the ion also stabilizes the transition state leading to its formation. Generation of the ion is speeded up, and along with it the entire process: formation or hydrolysis of the acetal.

(Oddly enough, oxygen causes activation toward *nucleophilic* substitution here in precisely the same way it activates aromatic ethers toward *electrophilic* substitution (Sec. 15.18); the common feature is, of course, development of a positive charge in the transition state of the rate-determining step.)

We shall find the chemistry of hemiacetals and acetals to be fundamental to the study of carbohydrates (Chaps. 34 and 35).

(b) What structural factor favors this course of reaction? (c) To what family of compounds does II belong? (d) What will II yield upon treatment with acid? With base?

Problem 18.7 *Glyceraldehyde*, $CH_2OHCHOHCHO$, is commonly made from the acetal of acrolein, $CH_2{=}CH{-}CHO$. Show how this could be done. Why is acrolein itself not used?

Problem 18.8 How do you account for the following differences in ease of hydrolysis?

(a) $RC(OR')_3 \gg RCH(OR')_2 \gg RCH_2OR'$
An ortho ester — An acetal — An ether

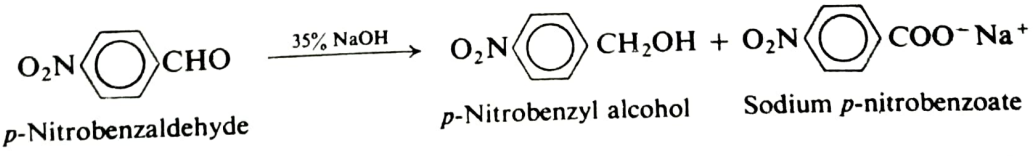
(b) $R_2C(OR')_2 > RCH(OR')_2 > H_2C(OR')_2$
A ketal — An acetal — A formal

Problem 18.9 The simplest way to prepare an aldehyde, $RCH^{18}O$, labeled at the carbonyl oxygen, is to allow an ordinary aldehyde to stand in $H_2{}^{18}O$ in the presence of a little acid. Suggest a detailed mechanism for this oxygen exchange.

18.13 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, Sec. 21.5.)

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

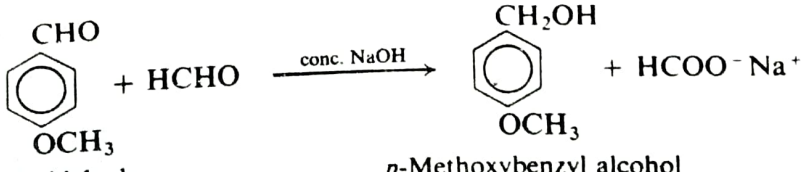


p-Nitrobenzaldehyde — *p*-Nitrobenzyl alcohol — Sodium *p*-nitrobenzoate

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:

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

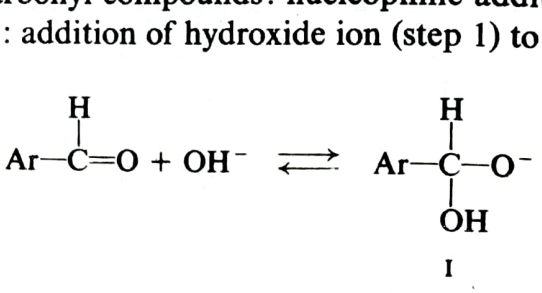
Such a reaction is called a **crossed Cannizzaro reaction**. For example:



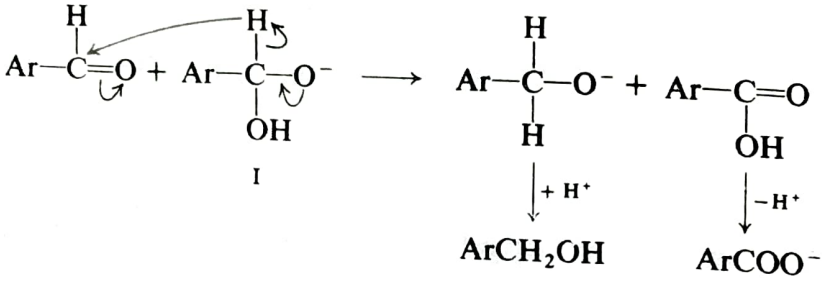
Anisaldehyde (*p*-Methoxybenzaldehyde) — *p*-Methoxybenzyl alcohol

Evidence, chiefly from kinetics and experiments with isotopically labe compounds, indicates that even this seemingly different reaction follows t familiar pattern for carbonyl compounds: nucleophilic addition. Two successi additions are involved: addition of hydroxide ion (step 1) to give intermediate

(1)

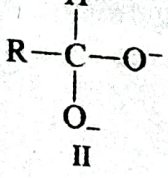


(2)



and addition of a hydride ion from I (step 2) to a second molecule of aldehyde. T presence of the negative charge on I aids in the loss of hydride ion.

Problem 18.10 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 18.11 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 18.12 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 18.13 Phenylglyoxal, C_6H_5COCHO, is converted by aqueous sodium hydroxide into sodium mandelate, $C_6H_5CHOHCOONa$. Suggest a likely mechanism for this conversion.

Problem 18.14 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.

18.14 Addition of Grignard reagents

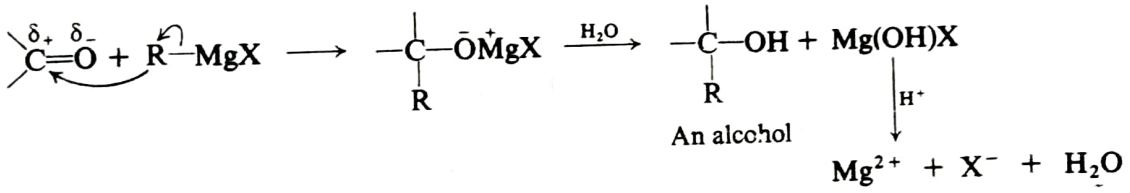
The Grignard reagent, we recall, has the formula RMgX, and is prepared by the reaction of metallic magnesium with the appropriate organic halide (Sec. 3.16). This halide can be alkyl (1°, 2°, 3°), allylic, aralkyl (e.g., benzyl), or aryl (phenyl or

$$RX + Mg \xrightarrow{\text{anhydrous ether}} RMgX$$

A Grignard reagent

substituted phenyl). 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.

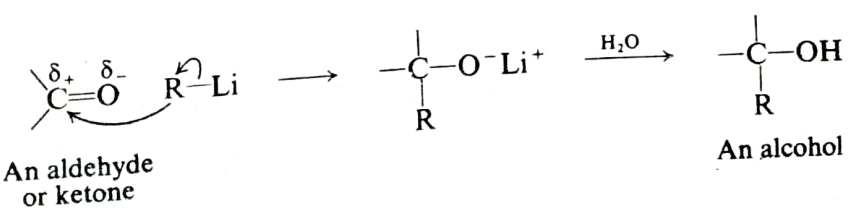
Grignard reagents are the classical reagents for such syntheses. Increasingly, however, *organolithium* compounds are being used instead, chiefly because they are less prone to unwanted side reactions. Organolithiums can be prepared in the same way as Grignard reagents, by reaction of the metal with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

$$RX + 2Li \xrightarrow{\text{anhydrous ether}} RLi + LiX$$

An organolithium

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.



An aldehyde or ketone

An alcohol

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.

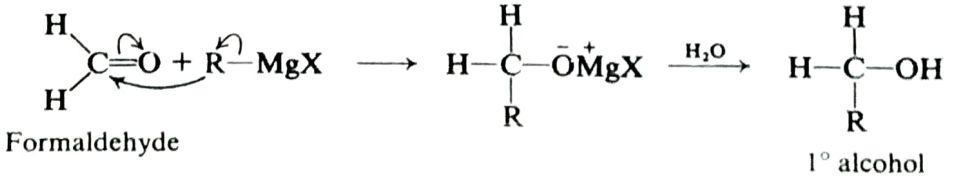
Problem 18.15 Write equations for the reaction of *n*-butyllithium with: (a) H_2O; (b) D_2O; (c) C_2H_5OH; (d) CH_3NH_2; (e) $C_2H_5C{\equiv}CH$; (f) CH_3CCH_3 (O above C).

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 (Sec. 12.13) 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.

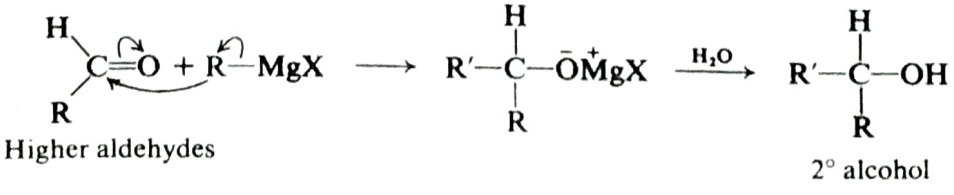
But this is only half the story. Not only does the Grignard synthesis involve formation of a carbon–carbon bond, but the product contains the highly versatile group, —OH. And now, as we shall soon see, the way is open to further synthesis, and the building of still bigger and more complicated structures.

18.15 Products of the Grignard synthesis

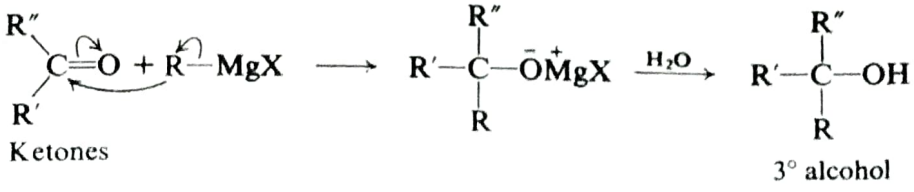
The class of alcohol that is obtained from a Grignard synthesis depends upon the type of carbonyl compound used: *formaldehyde*, HCHO, *yields primary alcohols*; *other aldehydes*, RCHO, *yield secondary alcohols*; and *ketones*, R_2CO, *yield tertiary alcohols*.



Formaldehyde — 1° alcohol



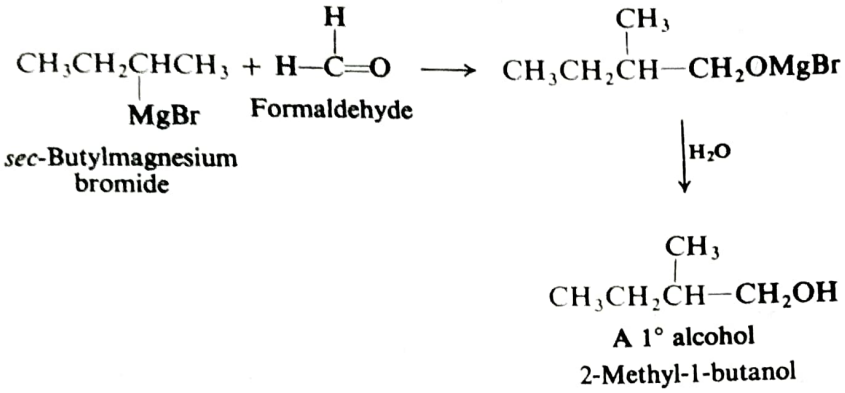
Higher aldehydes — 2° alcohol

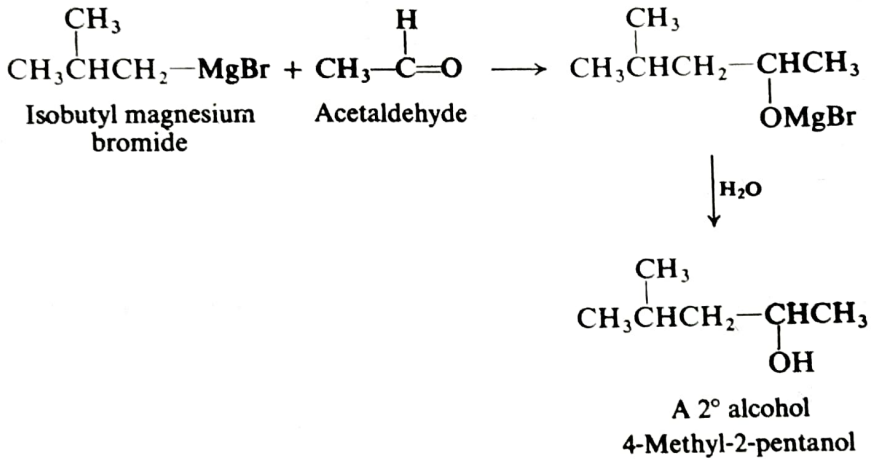


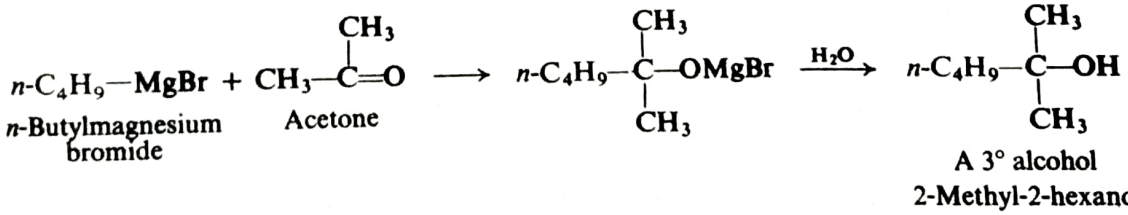
Ketones — 3° alcohol

This relationship arises directly from our definitions of aldehydes and ketones, and our definitions of primary, secondary, and tertiary alcohols. The number of hydrogens attached to the carbonyl carbon defines the carbonyl compound as

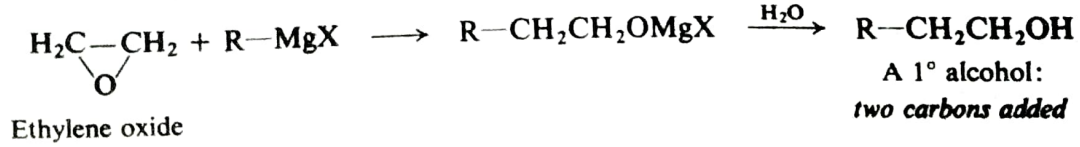
formaldehyde, higher aldehyde, or ketone. The carbonyl carbon is the one that finally bears the —OH group in the product; here the number of hydrogens defines the alcohol as primary, secondary, or tertiary. For example:





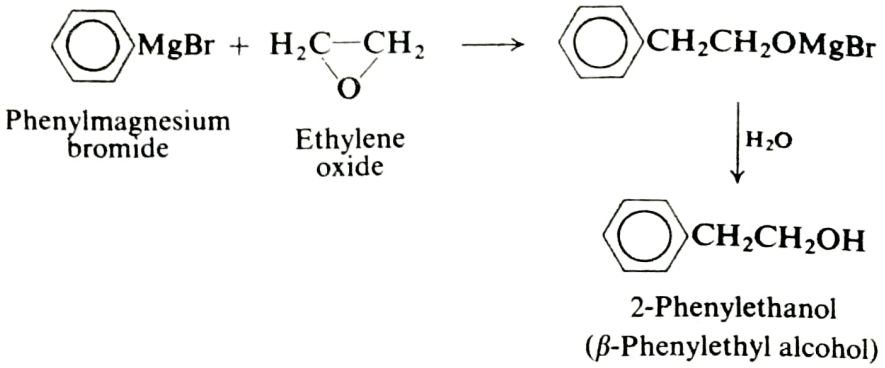


It is convenient at this point to bring in a related synthesis, one that utilizes *ethylene oxide* (Sec. 13.20) to make *primary alcohols containing two more carbons* than the Grignard reagent. Here, too, the organic group becomes attached to



carbon and magnesium to oxygen, this time with the breaking of a carbon–oxygen σ bond in a highly strained three-membered ring (Sec. 13.21).

For example:



Phenylmagnesium bromide

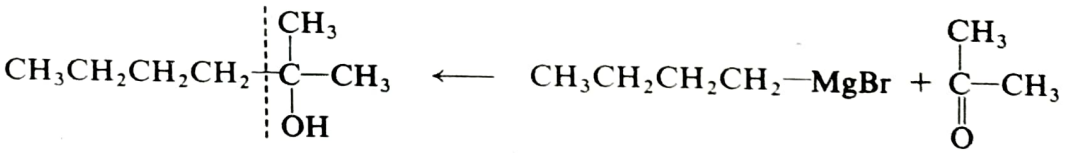
Ethylene oxide

2-Phenylethanol
(β-Phenylethyl alcohol)

18.16 Planning a Grignard synthesis

How do we decide which Grignard reagent and which carbonyl compound to use in preparing a particular alcohol? We have only to look at the structure of the alcohol we want. Of groups attached to the carbon bearing the —OH group, one must come from the Grignard reagent, the other two (including any hydrogens) must come from the carbonyl compound.

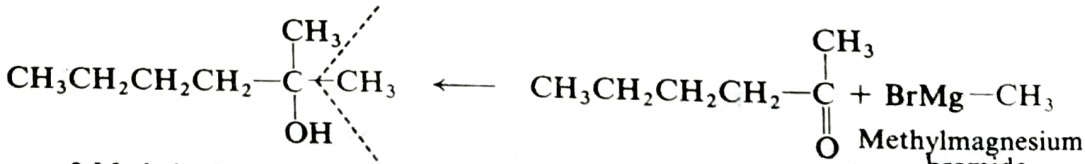
Most alcohols can be obtained from more than one combination of reagents; we usually choose the combination that is most readily available. Consider, for example, the synthesis of 2-methyl-2-hexanol:



2-Methyl-2-hexanol

n-Butylmagnesium bromide

Acetone



2-Methyl-2-hexanol

Methyl *n*-butyl ketone

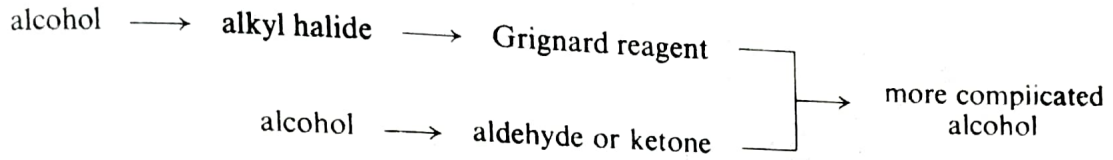
Methylmagnesium bromide

As shown, we could make this either from the four-carbon Grignard reagent and acetone, or from the methyl Grignard reagent and the six-carbon aliphatic ketone. Which combination do we pick? As we shall see below, it depends upon which reactants are *more readily available*.

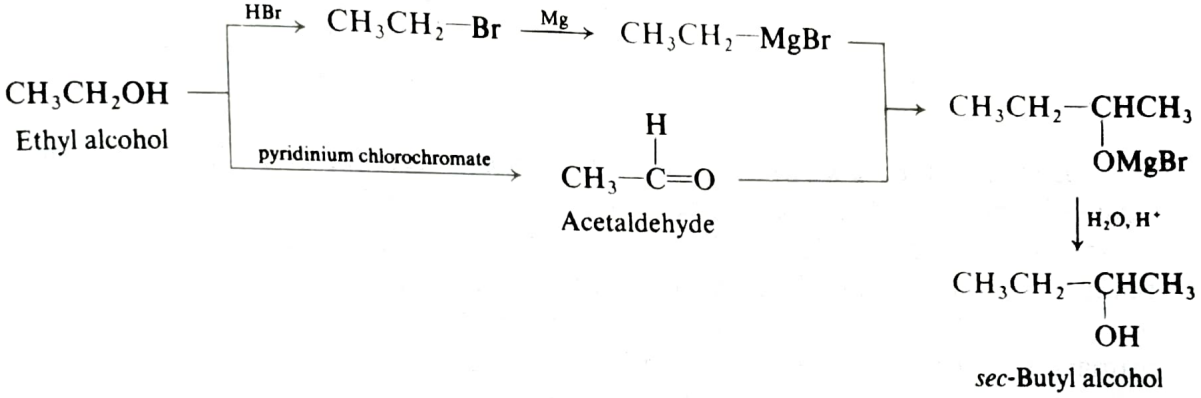
Problem 18.16 Give structures of the Grignard reagent and the substrate (aldehyde, ketone, or ethylene oxide) that would react to yield each of the eight isomeric pentyl alcohols of Problem 1(a), page 245. If more than one combination of reactants is possible, show each of the combinations.

Let us look at this matter of how we obtain the reactants for Grignard syntheses. We know that aldehydes and ketones are most often made from alcohols. We know that Grignard reagents are made from organic halides and that these, too, are most often made from alcohols. Finally, we know that the simple alcohols

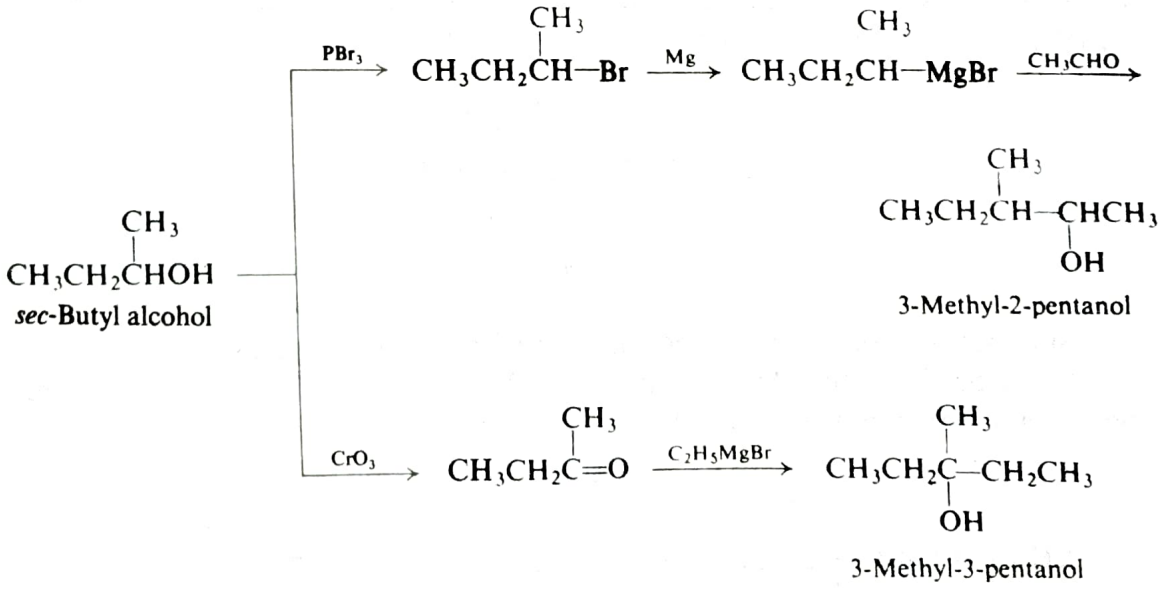
are among our most readily available compounds. We have available to us, then, a synthetic route leading from simple alcohols to more complicated ones.



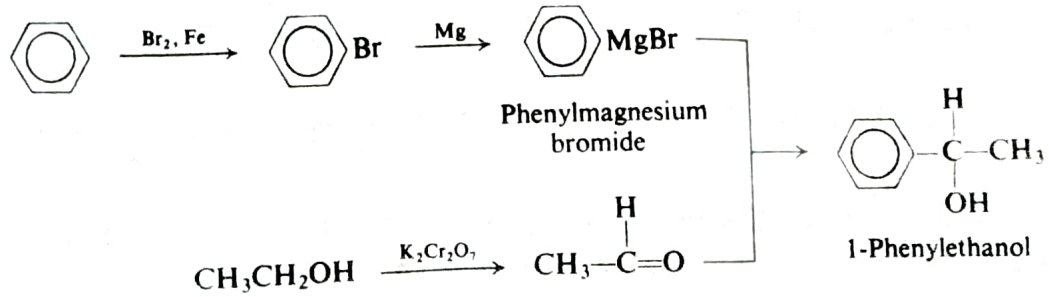
As a simple example, consider conversion of the two-carbon ethyl alcohol into the four-carbon *sec*-butyl alcohol:



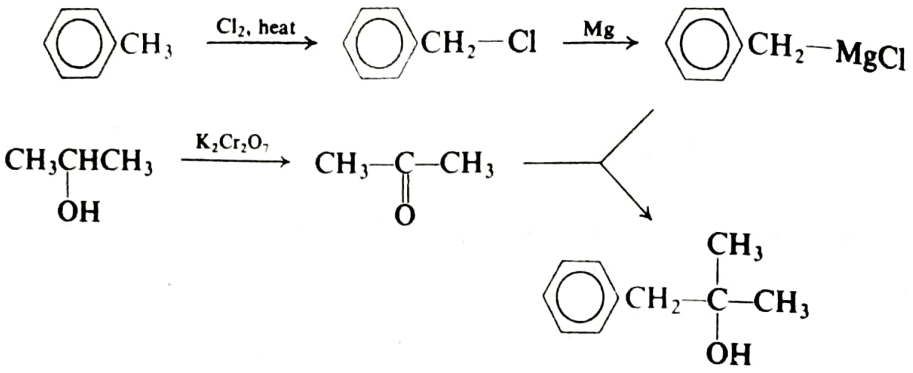
Using the *sec*-butyl alcohol thus obtained, we could prepare even larger alcohols:



By combining our knowledge of alcohols with what we know about alkylbenzenes and aromatic substitution, we can extend our syntheses to include aromatic alcohols. Starting from benzene we can make, for example, 1-phenylethanol,



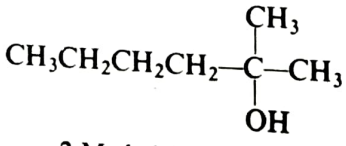
and from toluene we can make 2-methyl-1-phenyl-2-propanol.



2-Methyl-1-phenyl-2-propanol

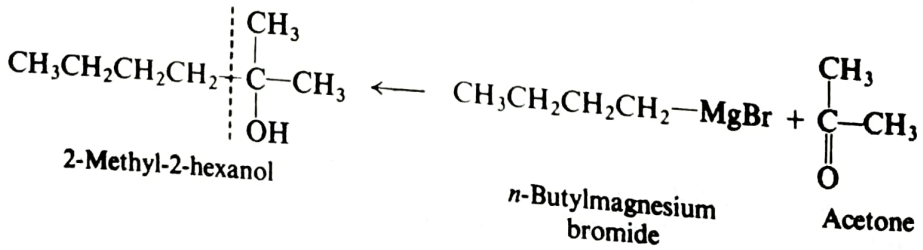
Granting that we know the chemistry of the individual steps, how do we go about planning a route to these more complicated alcohols? In almost every organic synthesis it is best to **work backwards** from the compound we want. There are relatively few ways to make a complicated alcohol; there are relatively few ways to make the Grignard reagent or the aldehyde or ketone; and so on back to our primary starting materials. On the other hand, alcohols can undergo so many different reactions that, if we go at the problem the other way around, we find a bewildering number of paths, few of which take us where we want to go.

Let us suppose (and this is quite reasonable) that we have available all alcohols of four carbons or fewer, and that we want to make, say, 2-methyl-2-hexanol. Let us set down the structure of this *target molecule*, and see what we need to make it.



2-Methyl-2-hexanol

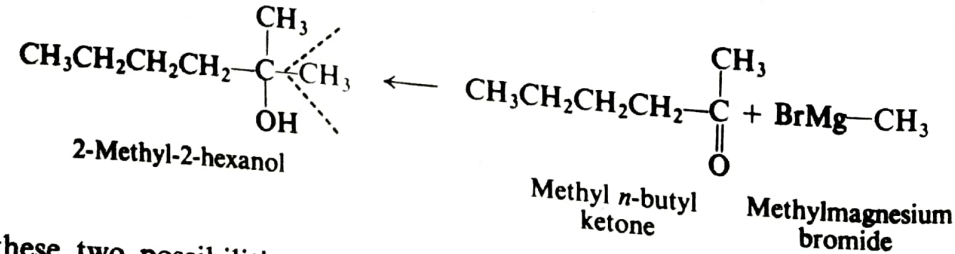
Since it is a tertiary alcohol, we must use a Grignard reagent and a ketone. But which Grignard reagent? And which ketone? Using the same approach as before, we see that there are two possibilities:



2-Methyl-2-hexanol

n-Butylmagnesium bromide

Acetone



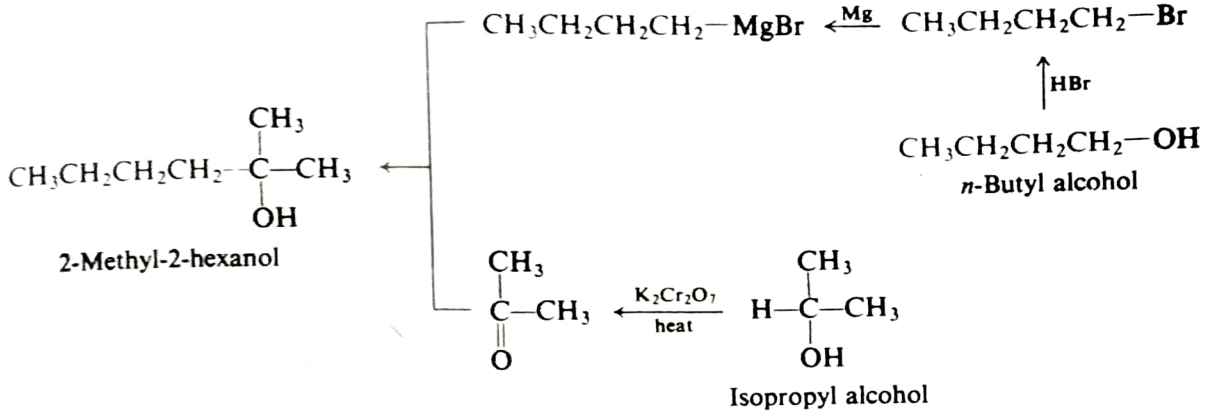
2-Methyl-2-hexanol

Methyl *n*-butyl ketone

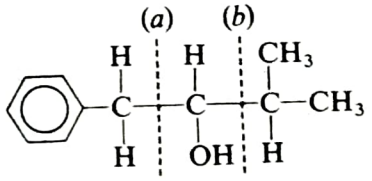
Methylmagnesium bromide

Of these two possibilities we would select the one involving the four-carbon Grignard reagent and the three-carbon ketone; now how are we to make *them*?

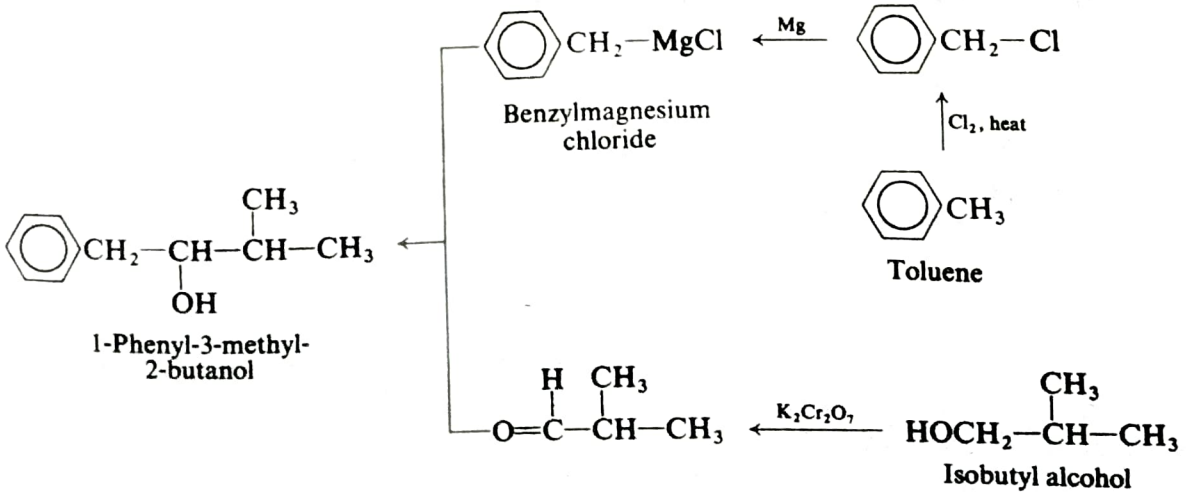
The Grignard reagent can be made only from the corresponding alkyl halide, *n*-butyl bromide, and that in turn most likely from an alcohol, *n*-butyl alcohol. Acetone requires, of course, isopropyl alcohol. Putting together the entire synthesis, we have the following sequence:



Let us consider that, in addition to our alcohols of four carbons or fewer, we have available benzene and toluene, another reasonable assumption, and that we wish to make, say, 3-methyl-1-phenyl-2-butanol. Again we set down the structure of the alcohol we want and work backwards to the starting materials. To make a secondary alcohol, we use a Grignard reagent and an aldehyde, and, as usual, there are two choices: we may consider the molecule to be put together either (*a*) between C–1 and C–2 or (*b*) between C–2 and C–3. Of the two possibilities we select the



first, since this requires a compound with only one carbon attached to the benzene ring, which we have available in toluene. We need, then, a four-carbon aldehyde and benzylmagnesium chloride. The aldehyde can be made from isobutyl alcohol. The benzylmagnesium chloride is, of course, made from benzyl chloride, which in turn is made from toluene by free-radical chlorination. Our synthesis is complete:



18.20 Analysis of aldehydes and ketones

Aldehydes and ketones are characterized through the addition to the carbonyl group of nucleophilic reagents, especially derivatives of ammonia (Sec. 18.11). An aldehyde or ketone will, for example, react with 2,4-dinitrophenylhydrazine to form an insoluble yellow or red solid.

Aldehydes are characterized, and in particular are differentiated from ketones, through their ease of oxidation: aldehydes give a positive test with Tollens' reagent (Sec. 18.8); ketones do not. A positive Tollens' test is also given by a few other kinds of easily oxidized compounds, e.g., certain phenols and amines; these compounds do not, however, give positive tests with 2,4-dinitrophenylhydrazine.

Aldehydes are also, of course, oxidized by many other oxidizing agents: by cold, dilute, neutral $KMnO_4$ and by CrO_3 in H_2SO_4 (Sec. 6.22).

A highly sensitive test for aldehydes is the *Schiff test*. An aldehyde reacts with the fuchsin–aldehyde reagent to form a characteristic magenta color.

Aliphatic aldehydes and ketones having an α-hydrogen react with Br_2 in CCl_4. This reaction is generally too slow to be confused with a test for unsaturation, and moreover it liberates HBr.

Aldehydes and ketones are generally identified through the melting points of derivatives like 2,4-dinitrophenylhydrazones, oximes, and semicarbazones.

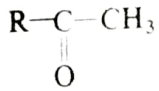
Methyl ketones are characterized through the *iodoform test* (see Sec. 18.21).

Problem 18.18 Make a table to show the response of each kind of compound we have studied so far toward the following reagents:

(a) cold concentrated H_2SO_4
(b) cold, dilute, neutral $KMnO_4$
(c) Br_2 in CCl_4
(d) CrO_3 in H_2SO_4
(e) cold fuming sulfuric acid
(f) $CHCl_3$ and $AlCl_3$
(g) sodium metal

18.21 Iodoform test

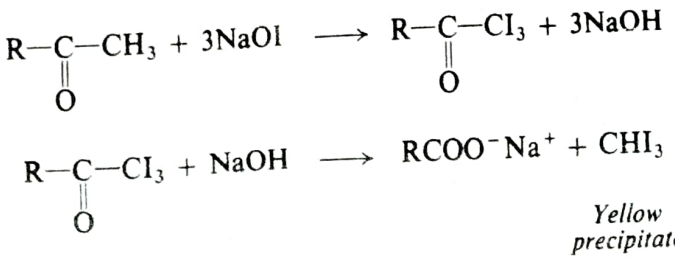
Whether or not a ketone is a *methyl* ketone is shown by the *iodoform test*. The ketone is treated with iodine and sodium hydroxide (sodium hypoiodite, NaOI); a ketone of the structure



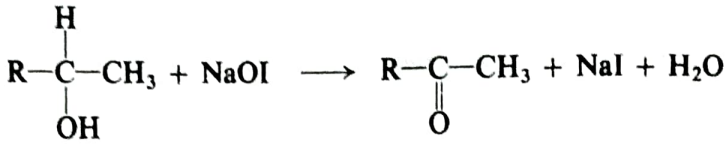
where R *is* H *or an alkyl or aryl group*

yields a yellow precipitate of iodoform (CHI_3, m.p. 119 °C).

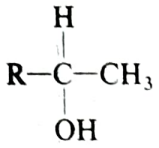
The reaction involves halogenation and cleavage:



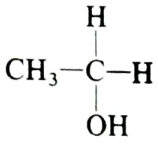
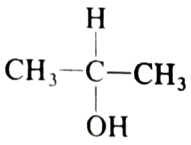
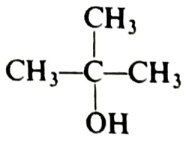
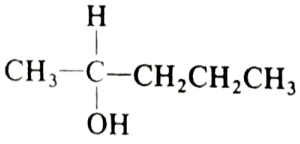
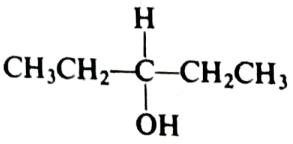
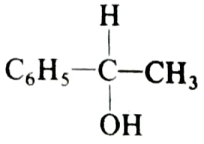
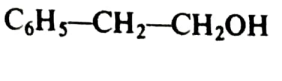
Hypohalites can not only halogenate but also oxidize:



As a result, an alcohol of the structure



is oxidized to a methyl ketone, and hence gives a positive test. For example:

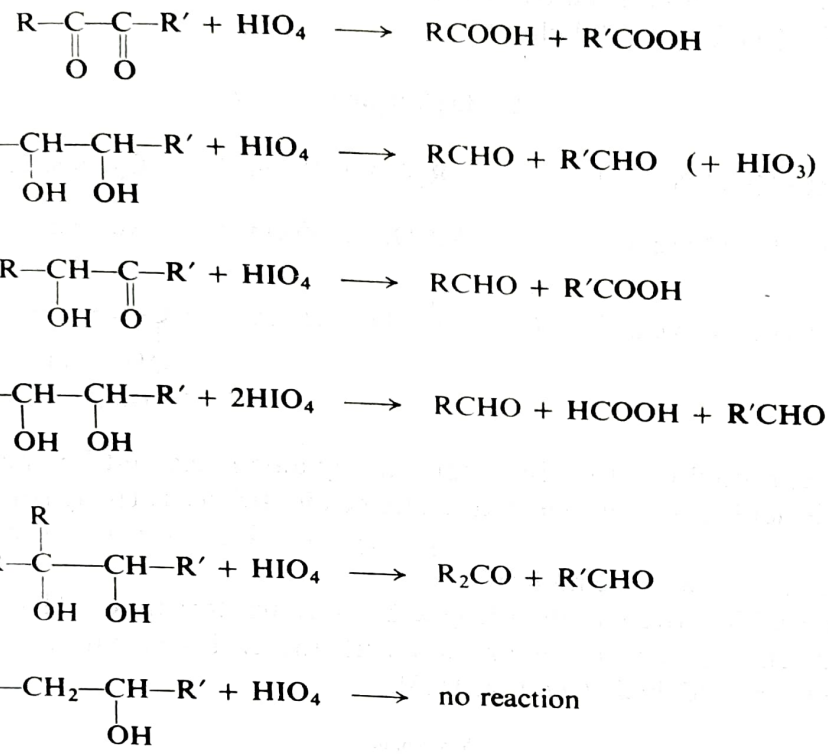
Gives positive iodoform test	Gives negative iodoform test
	Any other primary alcohol
	
	
	

In certain special cases this reaction is used, not as a test, but to synthesize the carboxylic acid, RCOOH. Here, hypobromite or the cheaper hypochlorite would probably be used.

In Problem 18, page 819, you will account for the regioselectivity of the halogenation—why the carbon that suffers the initial substitution is the preferred site of further substitution—and the ease of cleavage.

18.22 Analysis of 1,2-diols. Periodic acid oxidation

Upon treatment with periodic acid, HIO_4, compounds containing two or more =O or —OH groups attached to *adjacent* carbon atoms undergo oxidation with cleavage of carbon–carbon bonds. For example:



$$R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R' + HIO_4 \longrightarrow RCOOH + R'COOH$$

$$R-\underset{\underset{OH}{|}}{CH}-\underset{\underset{OH}{|}}{CH}-R' + HIO_4 \longrightarrow RCHO + R'CHO \quad (+ HIO_3)$$

$$R-\underset{\underset{OH}{|}}{CH}-\underset{\underset{O}{\|}}{C}-R' + HIO_4 \longrightarrow RCHO + R'COOH$$

$$R-\underset{\underset{OH}{|}}{CH}-\underset{\underset{OH}{|}}{CH}-\underset{\underset{OH}{|}}{CH}-R' + 2HIO_4 \longrightarrow RCHO + HCOOH + R'CHO$$

$$R-\underset{\underset{OH}{|}}{\overset{\overset{R}{|}}{C}}-\underset{\underset{OH}{|}}{CH}-R' + HIO_4 \longrightarrow R_2CO + R'CHO$$

$$R-\underset{\underset{OH}{|}}{CH}-CH_2-\underset{\underset{OH}{|}}{CH}-R' + HIO_4 \longrightarrow \text{no reaction}$$

The oxidation is particularly useful in determination of structure, as we shall find in our study of carbohydrates (Chaps. 34 and 35). Qualitatively, oxidation by HIO_4 is indicated by formation of a white precipitate ($AgIO_3$) upon addition of silver nitrate. Since the reaction is usually quantitative, valuable information is given by the nature and amounts of the products, and by the quantity of periodic acid consumed.

Problem 18.19 When one mole of each of the following compounds is treated with HIO_4, what will the products be, and how many moles of HIO_4 will be consumed?

(a) $CH_3CHOHCH_2OH$
(b) $CH_3CHOHCHO$
(c) $CH_2OHCHOHCH_2OCH_3$
(d) $CH_2OHCH(OCH_3)CH_2OH$
(e) *cis*-1,2-cyclopentanediol
(f) $CH_2OH(CHOH)_3CHO$
(g) $CH_2OH(CHOH)_3CH_2OH$

Problem 18.20 Assign a structure to each of the following compounds:

A + 1 mol HIO_4 $\longrightarrow$ $CH_3COCH_3 + HCHO$
B + 1 mol HIO_4 $\longrightarrow$ $OHC(CH_2)_4CHO$
C + 1 mol HIO_4 $\longrightarrow$ $HOOC(CH_2)_4CHO$
D + 1 mol HIO_4 $\longrightarrow$ $2HOOC—CHO$
E + $3HIO_4$ $\longrightarrow$ $2HCOOH + 2HCHO$
F + $3HIO_4$ $\longrightarrow$ $2HCOOH + HCHO + CO_2$
G + $5HIO_4$ $\longrightarrow$ $5HCOOH + HCHO$