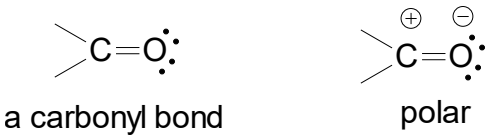
## CHAPTER ONE

# ALDEHYDES and KETONES

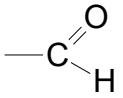
## 1.1 Introduction-The Carbonyl Bond (C=O)

The geometry of the carbonyl is determined by the $sp^2$–hybridized carbon. The molecule is planar around the trigonal $sp^2$ carbon.

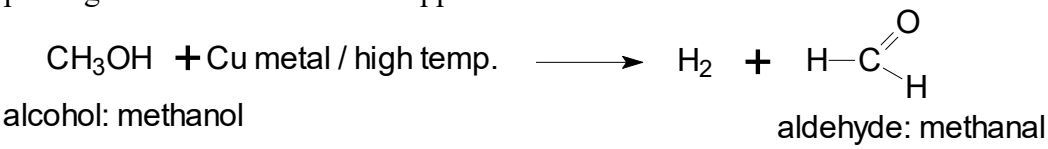



The C==O bond is composed of a sigma (σ) bond and a pi (π) bond. The oxygen atom has two pairs of unshared electrons. Because of the significant difference in electronegativity between carbon and oxygen, the carbonyl group is polarized in such a way that oxygen is slightly negative (δ-) and the carbon slightly positive (δ+). The carbonyl group is more polar than the C-O bond of the alcohol or ether molecule. The pi electrons in the carbonyl are drawn more easily to the electronegative oxygen than the sigma electrons in the C-O bond. Keeping polarity in mind will often be helpful in understanding the chemical reactivity of carbonyl containing compounds.

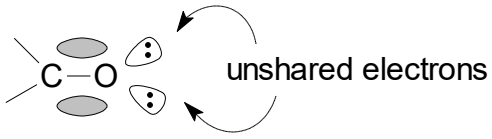
The name aldehyde is derived from alcohol dehydrogenated and may be represented as follows –CHO or in structural form as below.



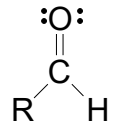
Aldehydes have the general formula R-CHO and the simplest, methanal, is prepared by passing methanol over heated copper metal.



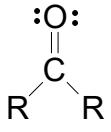

Aldehydes are very reactive compounds because they contain an aldehyde group or more generally the carbonyl group -C==O. An aldehyde has a hydrogen atom attached to the carbonyl group while a ketone has no hydrogen attached but two organic groups, R, which could be alkyl or aryl. Much of the chemistry of aldehydes and ketones involves addition reaction to the pi bond. Because of the presence of a hydrogen atom on the carbonyl group of aldehydes, they are easily oxidised while ketones are oxidised with difficulty. Aldehydes are more reactive towards nucleophilic addition.




carbonyl bond



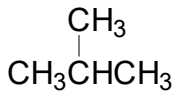

aldehyde



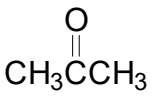

ketone

## 1.2 Physical Properties

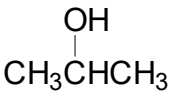
Aldehydes and ketones have higher boiling points than non-polar compounds of similar molecular weight. This is because they are polar and undergo intermolecular dipole-dipole attractions. To a limited extent aldehydes and ketones can solvate ions. An example is sodium iodide (NaI), which is soluble in acetone ($CH_3COCH_3$).



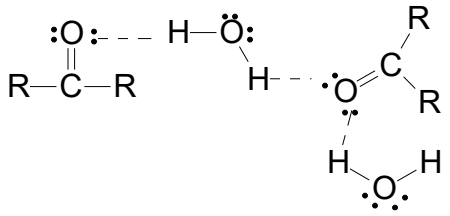

bp **$12^0$**

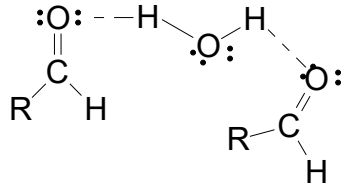



bp **$56^0$**




bp **$82^0$**





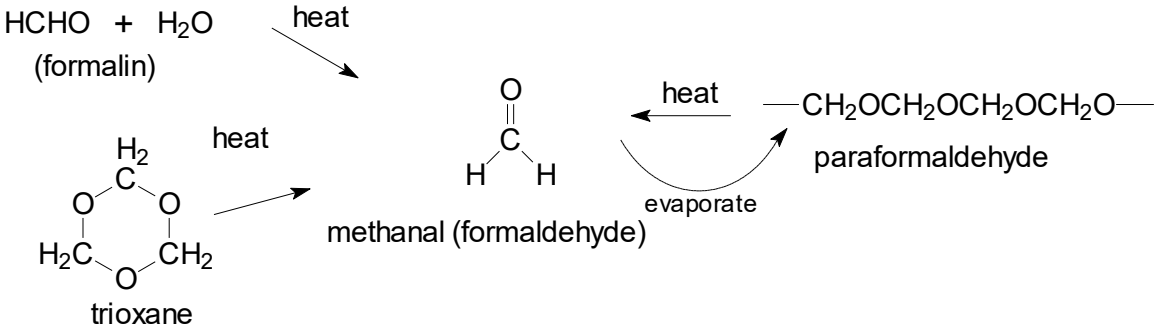
Because of unshared electrons on the oxygen, a carbonyl compound can form hydrogen bonds (but not with another carbonyl compound unless it has an acidic hydrogen available for hydrogen bonding). Aldehydes and ketones of low molecular weight, those with four or fewer carbons, can form hydrogen bonds with water and alcohols and are soluble.

## 1.3 Aldehydes

Methanal (formaldehyde): This is a colourless gas with a sharp penetrating odor (i.e. irritating to mucus membrane). It is readily soluble in water. When concentrated methanal solution is evaporated it forms a solid polymer known as paraformaldehyde (an acetal).
A solution of 37% methanal and 7-15% methanol in water is known as formalin. Methanal is conveniently shipped or stored as formalin or as a solid polymer (paraformaldehyde) or trimer - trioxane (mp $62^0$C).

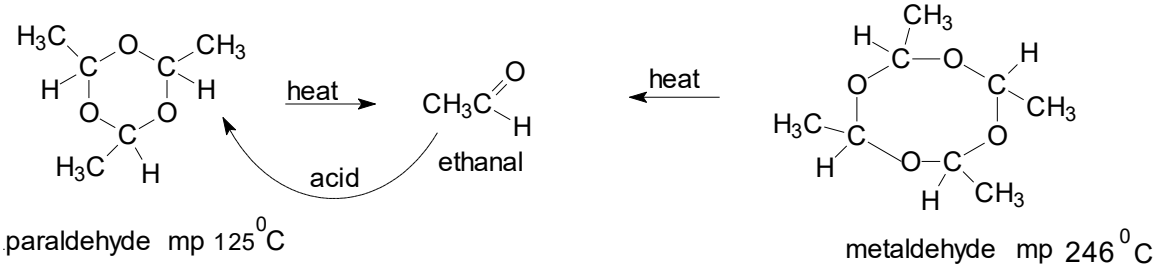
- Formalin acts as a disinfectant (a germicide).
- Is used in embalming fluid.
- Is used as a preservative of various tissues i.e. hardens tissues.

Formaldehydes gas and the polymer paraformaldehyde are used extensively as insecticides, fumigating agents and antiseptics. Large quantities of formaldehyde are used in the manufacture of synthetic (lightweight) resins (e.g. bakelite foam) and the syntheses of other organic compounds.




**Ethanal bp $20^0$ (acetaldehyde)** is also stored and shipped in a cyclic trimer paraldehyde or as a tetramer metaldehyde.

- It is a colourless liquid and has a characteristic sharp odor
- Produced by oxidation of ethanol or hydration of ethane.
- Ethanal is used in the production of ethanoic acid (acetic acid, vinegar), ethyl acetate, synthetic rubber, etc.
- Paraldehyde, (mp 125 o C; polymer of ethanol) an acetal (cyclic ether), is more stable than ethanol and serves as a source of the latter compound when heated. When three molecules of ethanal is heated with a trace of acid paraldehyde is formed.
- Paraldehyde–used to depress the central nervous system and to desensitize the gums of the mouth against heat or cold.
- It is an effective hypnotic or sleep producer but has been replaced by other drugs since it has an irritating odor and an unpleasant taste.

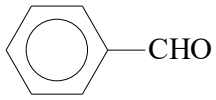



## 1.4 Nomenclature of Aldehydes

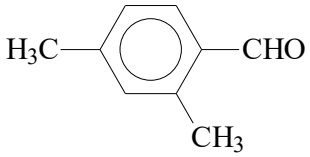
1) Pick the longest carbon chain containing the aldehyde or ketone group.
2) Number the chain so that the terminal aldehyde is always in position 1.

3) Locate and number the branched alkyl groups on the main chain.
4) For aldehydes change the alkane name by changing the "e" to "al"

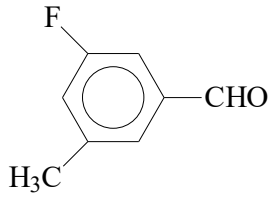
| Structure | IUPAC | common name. |
|---|---|---|
| a) HCHO | methanal | formaldehyde |
| b) $CH_3CHO$ | ethanal | acetaldehyde |
| c) $CH_3CH_2CHO$ | propanal | propionadehyde |
| d) $CH_3CH_2CH_2CHO$ | butanal | buytraldehyde |
| e) $CH_3CH_2CH(CH_3)CHO$ | 2–methylbutanal | |
| f) $CH_3CH_2CH_2CH(CH_2CH_2CH_3)CH(CH_3)CHO$ | 3-ethyl-2-methylhexanal (NOT 2-methyl-3-ethylhexanal!) | |
| g) $C_6H_5CHO$ | benzaldehyde | |
| h) $ClC_6H_5CHO$ | Chlorobenzaldehyde | |
| i) $HOC_6H_5CHO$ | Hydroxybenzaldehyde. | |
| j) $OHCCH_2CH(CH_3)CH_2C(C_2H_5)(CH_3)CH_2CH_2CH_3$ | 5-ethyl-3,5-dimethyloctanal | |
| k) $OHCCH_2CH_2CH_2CH_2CHO$ | hexanedial (the final e is retained in dial names) | |




benzaldehyde




2 , 4 – dimethylbenzaldehyde




3 – fluoro – 5 – methylbenzaldehyde

**Note**: Commas and hyphens should be used properly just like in naming of other organic compounds.

If two or more substitutes present: e.g. 2 methyl groups–dimethyl- or 3 ethyl groups-triethyl etc.
In alphabetizing, a prefix denoting the number of times a substituent is found (di, tr.) is disregarded, but m for methyl.
With 2 or more branches attached to a parent chain, more prefixes are added to the parent name. Use alphabetical order – ethyl, methyl, propyl etc.

## Nomenclature Priority

| | | |
|---|---|---|
| 1. | -COOH | carboxylic acid |
| 2. | COOR | ester |

| | | |
|---|---|---|
| 3. | -C=N | nitrile |
| 4. | -CHO | aldehyde |
| 5. | -CO- | ketone |
| 6. | ROH | alcohol |
| 7. | ArOH | phenol |
| 8. | -SH | thiol |
| 9. | -NR | amine |
| 10 | CH≡CH | alkynes |
| 11. | C=C | alkene |

12. R-, aryl, X- (Cl, Br, F, $NO_2$) etc. follow alphabetical order

The highest priority (COOH) is at the top. Two examples of compounds that have two functional groups are given below.

| | |
|---|---|
| $HOCH_2CH_2CH_2CH_2CHO$ | 5-hydroxypentanal |
| $CH_3CH=CHCHO$ | 2-butenal |

## 1.5 Nomenclature of Ketones

1 Find the largest continuous chain, which includes the carbonyl group.
2 Number the chain so that the carbonyl group has lowest possible number.
3 Locate and number the branched alkyl group on the main chain.
Change "e" of alkane to one.

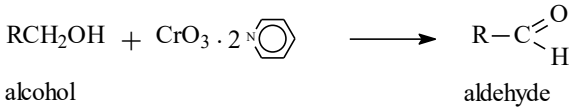
a) $CH_3COCH_3$ propanone [acetone (dimethylketone)]
b) $CH_3CH(CH_3)COCH_3$ 3-methyl-2-butanone
c) $CH_3COCH_2CH(CH_3)CH_3$ 4 -methyl–2- pentanone
d) $CH_3CH_2COCH(CH_2CH_3)CH_3$ 4–methyl–3-hexanone
e) $CH_3COCH(CH_3)CH_2CH(CH_2CH_3)CH_3$ 3,5-dimethyl-2-heptanone
f) $CH_3COCH_2COCH_3$ 2,4–pentanedione [The –e is retained]
g)$(CH_3)_2CHCOC(CH_3)_3$ 2,2,4 –trimethyl–3-pentanone

Many aldehydes and ketones have distinctive odors. Aldehydes are generally pungent-smelling and ketones are sweet smelling.

## 1.6 Preparation of Aldehydes and Ketones

### 1.6.1 Preparation of Aldehydes

Aldehydes are most commonly prepared by oxidation of an alcohol.
a) Oxidation of primary alcohols. Oxidation involves loss of one or more hydrogens (α–hydrogen) from the carbon bearing the –OH group.

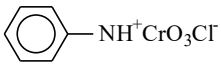



i) $CH_3CH_2OH + CrO_3 . 2$  $\longrightarrow CH_3C(=O)H$

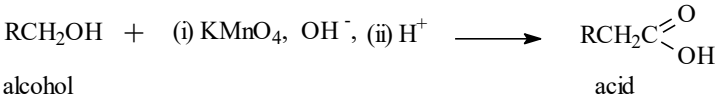
ethanol ethanal

ii) $CH_3(CH_2)_4CH_2OH + CrO_3 . 2$  $\longrightarrow CH_3(CH_2)_4C(=O)H$

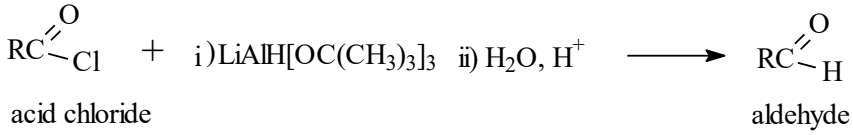
hexanol hexanal

Another reagent that can be used is pyridinium chlorochromate , 

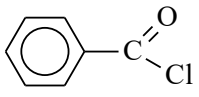
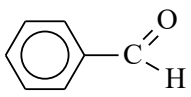
Common oxidising agents such as potassium permanganate $KMnO_4$ and aqueous $K_2Cr_2O_7$ and $CrO_3$ in glacial acetic acid are not used because they oxidise the primary aldehydes formed to acids.



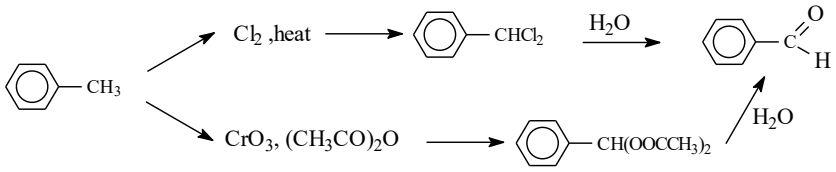

b) Reduction of acid chlorides

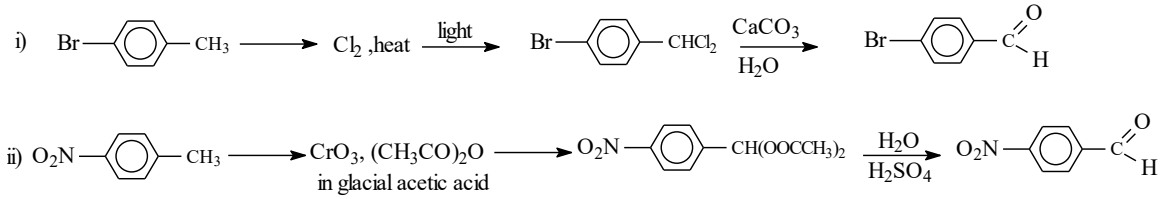



i) $CH_3CH_2C(=O)Cl$ + i) $LiAlH[OC(CH_3)_3]_3$ ii) $H_2O, H^+$ $\longrightarrow$ $CH_3CH_2C(=O)H$

ii)  i) $LiAlH[OC(CH_3)_3]_3$ ii) $H_2O, H^+$ $\longrightarrow$ 

c) Oxidation of methylbenzenes

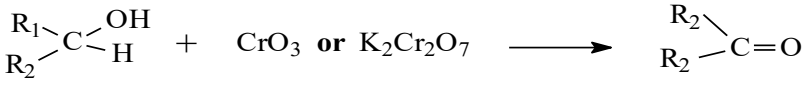


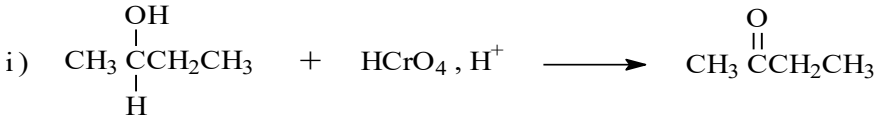



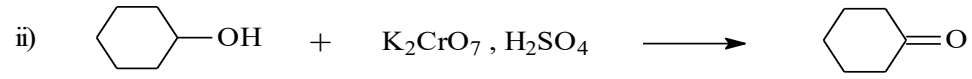

## 1.6.2 Preparation of Ketones

a) **Oxidation**

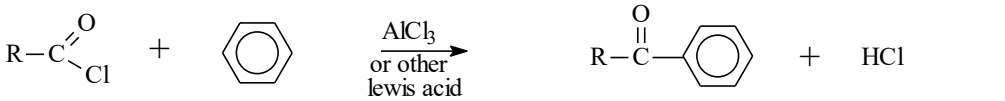
Oxidation of secondary alcohols using standard oxidizing agents gives excellent yields of ketones

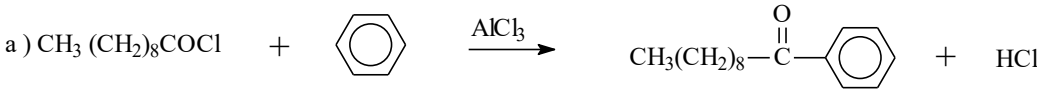


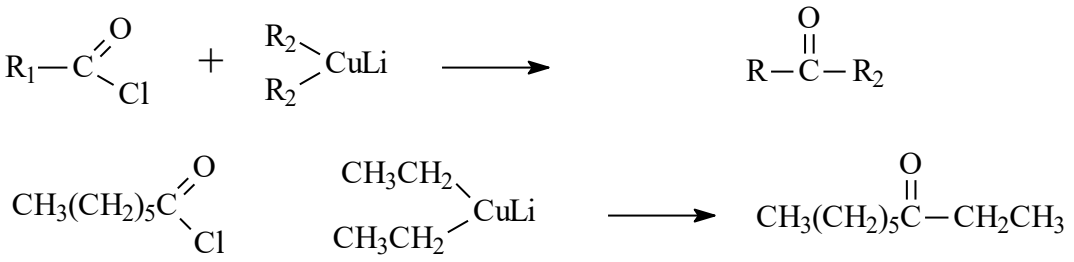




b) **Friedel–Crafts acylation**




c) **From acid chlorides and organo-copper compounds**




**Note**: Tertiary alcohols do not have an α hydrogen and are not oxidized or yield a mixture of products.

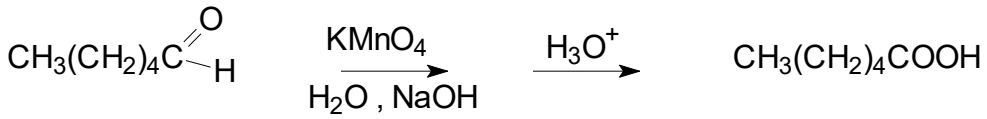
CHAPTER TWO

# REACTIONS OF ALDEHYDES AND KETONES

The major reactions of aldehydes and ketones include addition, reduction, oxidation and condensation reactions.

## 2.1 Oxidation Reactions

(a) **Aldehydes are easily oxidised to acids** as they have a hydrogen atom attached to the carbonyl carbon. Oxidation involves abstraction of the hydrogen atom. Most reagents that oxidize an alcohol also oxidise an aldehyde ($KMnO_4$, Cr(VI) reagents and nitric acid). Many aldehydes are oxidized by the oxidation in the air upon standing for long periods of time. This process, autoxidation of the aldehyde is responsible for the contamination of some aldehyde samples with appreciable amounts of carboxylic acids.




Ketones are not easily oxidized. Oxidation involves breaking the carbon-carbon bonds. They are resistant to mild oxidation with Cr (VI) reagents and acetone can even be used as a solvent for oxidation with such reagents. KMnO4 oxidizes ketones and is not a useful reagent for the preparation of ketones from secondary alcohols.

(b) **Mild oxidising agents e.g. Ag+ or $Cu^{2+}$**

(i) **Fehlings and Benedicts solutions** both contain the cupric ion, $Cu^{2+}$. Adding certain compounds with the aldehyde groups to either of these clear solutions causes a precipitate of cuprous oxide, $Cu_2O$. Benedicts solution contains sodium citrate to keep the cupric ion in solution, while Fehlings solution contains sodium tartrate and does not store as well. Simple sugars contain an aldehyde group and will reduce cupric ions ($Cu^{2+}$) to cuprous ($Cu^{+}$). Cuprous ions then form cuprous oxide, $Cu_2O$, an insoluble red precipitate.

$$CH_3CH_2CH_2CHO + Cu^{2+} \longrightarrow CH_3CH_2CH_2COOH + Cu_2O\ (s)$$

(ii) **Tollen's Reagent** - Ammonical silver nitrate solution (colourless solution).
Oxidation by silver ions require alkaline conditions to prevent the precipitation of insoluble silver oxide, so a complexing agent, $NH_3$ , is added. Aldehydes are oxidized to acids and silver ions (Ag+) are reduced to silver metal (Ag)– a positive test formation of a silver mirror on the wall of a test tube is observed.

Aldehyde + Silver ions (Ag+) ⟶ Ag(s) silver mirror + acid

RCHO + $Ag(NH_3)_2^+ + OH^-$ ⟶ Ag (s) + RCOOH

These tests can be used to find whether a large amount of glucose is present in urine.
The sugar glucose containing an aldehyde group gives a positive test with Benedicts, Fehlings and Tollens reagents.

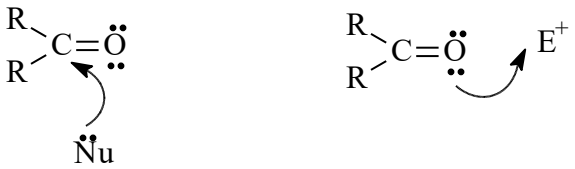
Example: With a 1 to 10 ratio of urine to Benedicts (blue colour) solution a green colour means about 0.25% glucose, a yellow-orange colour means about 1% glucose, and a brick-red colour indicates over 2% glucose.

$$\underset{\text{(glucose)}}{HOCH_2(CHOH)_4CHO} + 2Cu^{2+} + 4OH^- \longrightarrow \underset{\text{(gluconic acid)}}{HOCH_2(CHOH)_4COOH} + Cu_2O\ (s) + 2H_2O$$

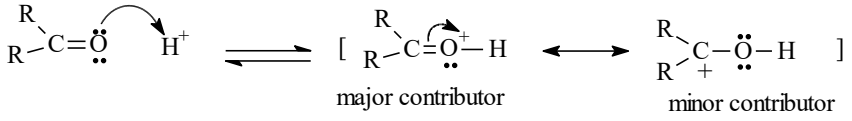
Tests a) and b) above are used to distinguish between an aldehydes and ketones as ketones test negative.

## 2.2 Addition Reactions of Aldehydes and Ketones

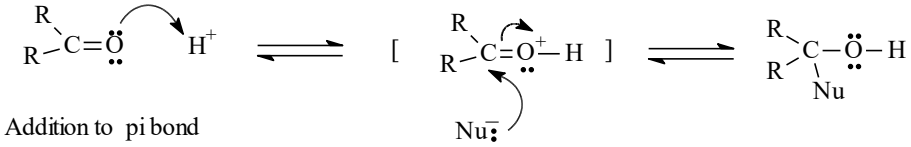
Aldehydes and ketones undergo addition reactions to the carbon-oxygen double bond. A carbonyl can be attacked either by a nucleophile (Nu) or an electrophile ($E^+$) because it is polar.



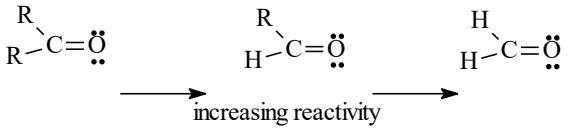

Many reactions involve initial protonation of the oxygen atom. -This enhances the charge of the carbonyl carbon so that it is more easily attacked by weaker nucleophiles.



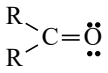

Resonance structures for a protonated carbonyl group




The relative reactivities of aldehydes and ketones in addition reactions maybe attributed partly to the amount of positive charge on the carbonyl. The greater charge means a higher reactivity.




A ketone is stabilised by neighbouring alkyl groups by the dispersal of positive charge.
Hence the carbonyl compound is mor stable and less reactive . Methanal is the most reactive.



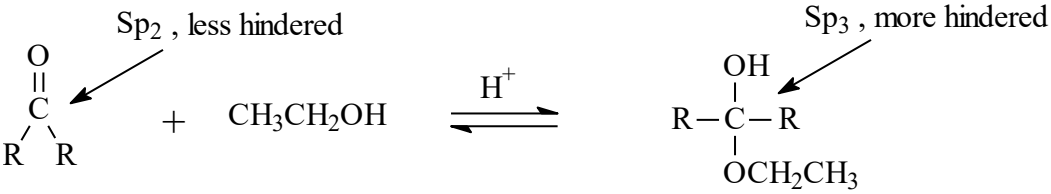
## Study Question:

List the following aldehydes in terms of increasing reactivity $CH_3CHO$, $ClCH_2CHO$, $Cl_2CH\ CHO$, $Cl_3CCHO$

**Answer:** $Cl_3CCHO$ most reactive

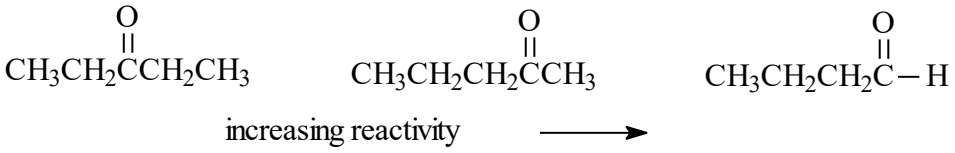
Cl– is an electron-withdrawing atom. The carbonyl carbon becomes increasingly positive as more Cl atoms are added to the α-carbon. Hence $CH_3CHO$ is least reactive.


Steric factor is also important in relative rates of aldehydes and ketones. The greater the steric hindrance, the less reactive the compounds are. Addition reactions of the carbonyl group lead to an increase in steric hindrance around the carbonyl carbon.



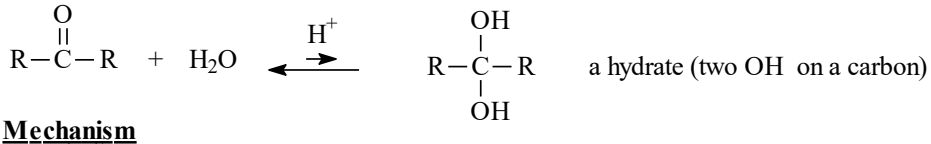

Bulky groups around the carbonyl group lead to more steric hindrance in the product (and in the transition state). The product is of higher energy due to steric repulsion. A more

hindered ketone is less reactive than an aldehyde or a less hindered ketone. Hence methanal is more reactive than other aldehydes.

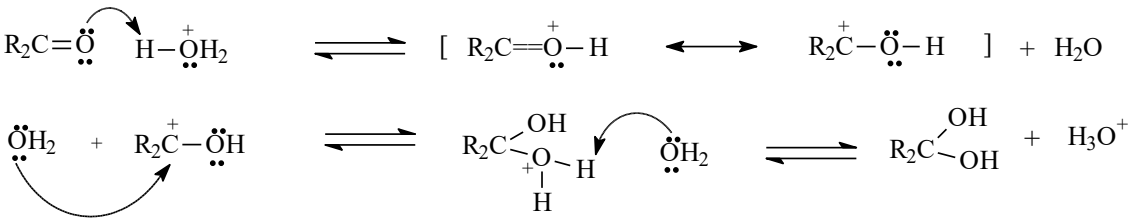



## 2.3 Addition of Water

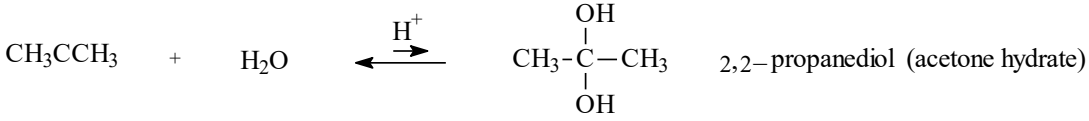
Acid catalysed hydration of carbonyl compounds yields **1,1-diol** called a gem-diol or **hydrate**. It is a reversible reaction and equilibrium lies on carbonyl side. The carbonyl group is first protonated by an acid in solution.



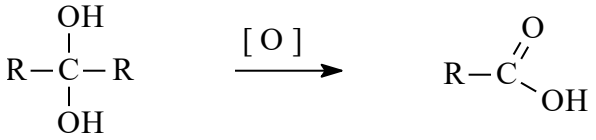

**Mechanism**




The nucleophile in this reaction is a water molecule which attacks the protonated carbonyl compound which then loses a proton completing the addition.



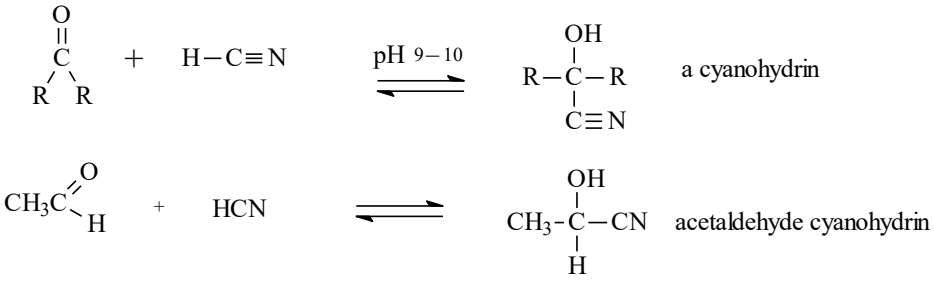

Stable hydrates are the exception rather than the rule. Hydrate formation is the reason that aldehydes are more easily oxidised to carboxylic acids in aqueous media than in non-aqueous media.



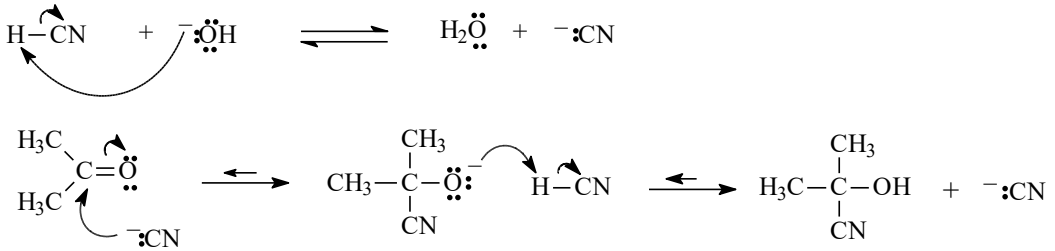

## 2.4 Addition of Hydrogen Cyanide (HCN)

HCN (bp 26 $^0$C) can be considered to be either a gas or a liquid with low boiling point. It is toxic and some people can detect the odour only at levels that may be lethal. HCN is obtained from the reaction of KCN or NaCN with a strong acid.

Hydrogen cyanide addition occurs under basic conditions. The product of HCN addition is a cyanohydrin. Cyanohydrins are a special class of nitriles (organic cyanides). HCN does not add directly to a carbonyl. Addition involves nucleophilic attack on the carbonyl carbon by the cyanide ion, which requires alkaline conditions. Acidic medium where the concentration of unionised HCN is highest retards the reaction. HCN, a weak acid is a poor source of cyanide ions.

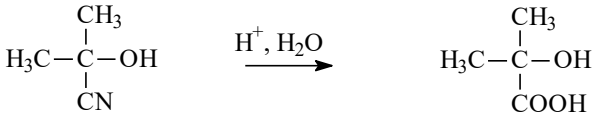


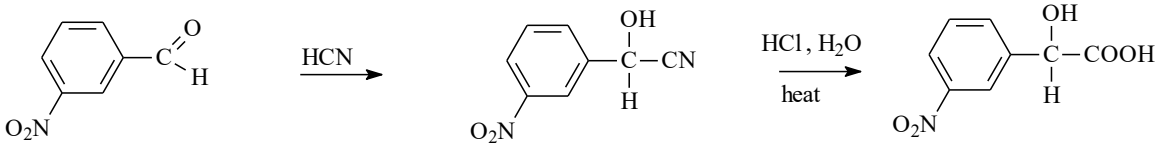

**Mechanism:**



The negatively charged oxygen essentially an alkoxide ion is a relatively strong base, and is protonated by either water or HCN to complete the addition.

A CN group can be hydrolysed to a carboxylic acid group.

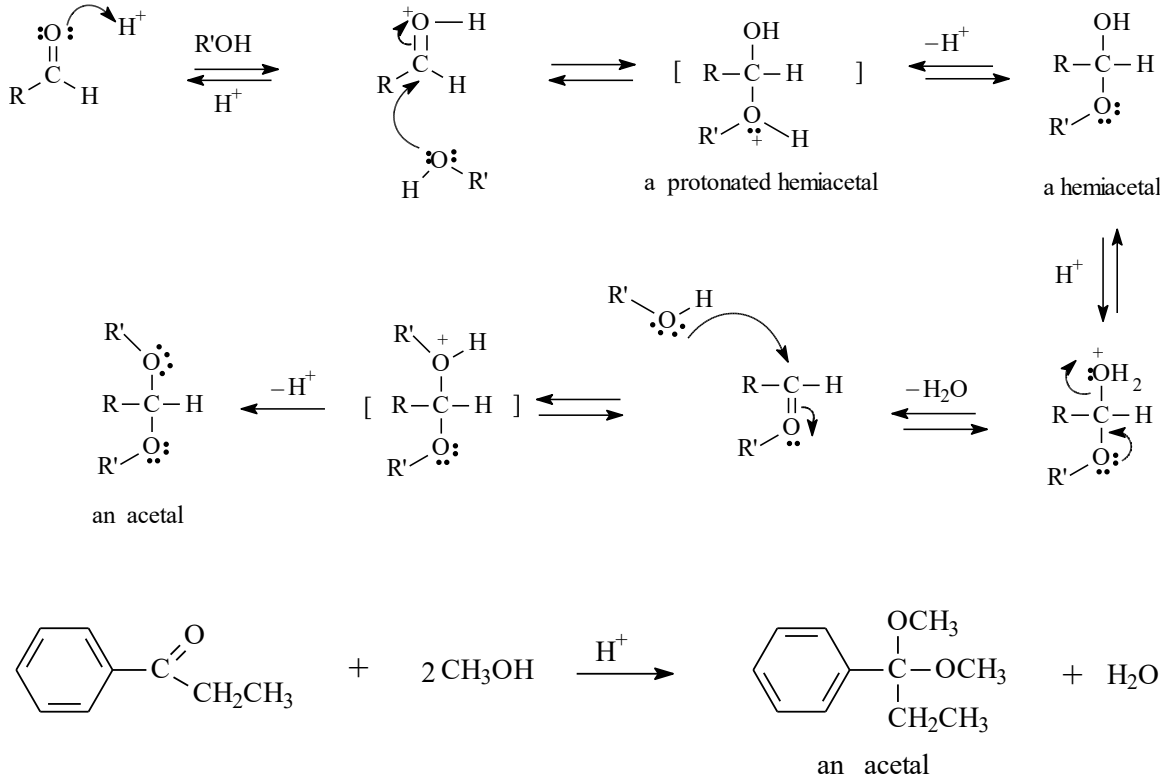



## 2.5 Addition of Alcohol

When an aldehyde or ketone reacts with a large excess of an alcohol in the presence of a trace of mineral acid, an acetal is formed. An acetal is simply a diether in which both ether oxygens are bound to the same carbon. Equilibrium lies on the aldehyde or ketone side of equilibrium. Acetal formation is therefore accomplished either by use of excess alcohol as the solvent, by removal of the water by-product, or both. The reaction is driven to the right by applying Le Chatelier's principle.

**Mechanisim**

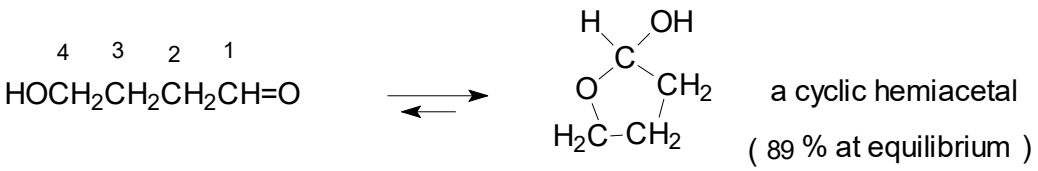


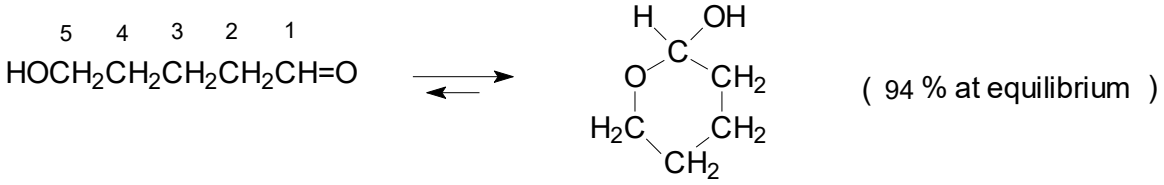




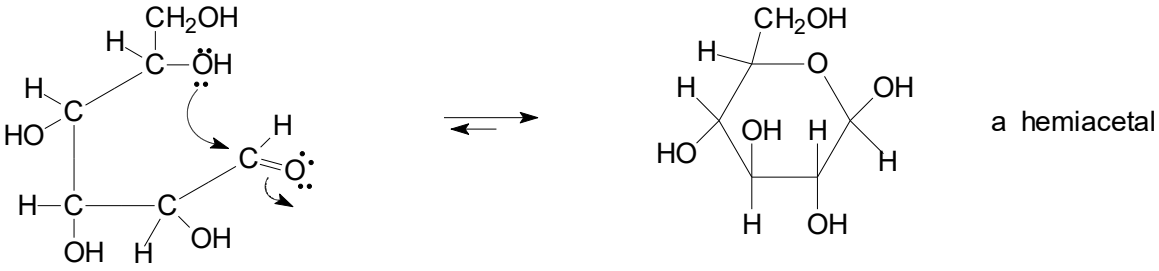
- In most cases a hemiacetal (half an acetal ) can not be isolated because they react further to yield acetals ( in alcohol solution) or decompose to aldehydes or ketones (in water)
- Acetals are stable in non-acidic (basic) solutions and can be isolated. Hence acetal hydrolysis (hydrolysis is a cleavage reaction involving water) to the corresponding carbonyl compound is acid catalysed since acetal formation is a reversible reaction.

An exception to the generality occurs if a molecule has a hydroxyl, OH, group in position 4 (γ) or 5 (δ) from the aldehyde or ketone, it undergoes intra molecular cyclisation to form a 5- or 6- membered hemiacetal rings. Most are stable and isolable compounds. They are favoured over open chain aldehyde forms.



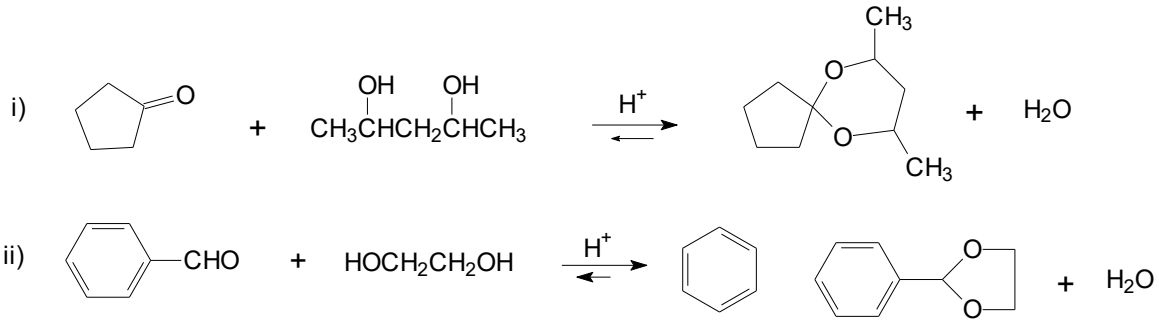




Sugars contain hydroxyl groups γ and δ to carbonyl groups. These are important biological examples, which form cyclic hemiacetals in water solution.



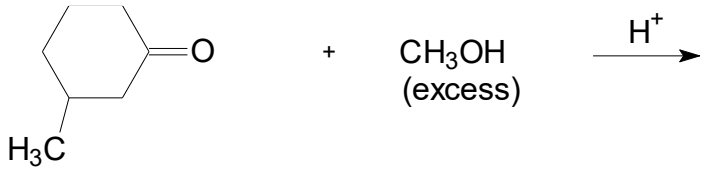

It is interesting to note that the polymers mentioned earlier, paraldehyde, trioxane, paraformaldehyde are cyclic acetals (alcohols are not involved in their formation).

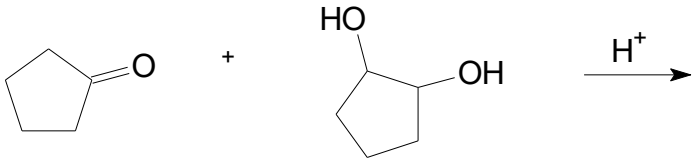
If a reaction occurs between an aldehyde or ketone with a 1,2- or 1,3- diol a cyclic acetal is formed in which the acetal group is part of a five- or six-membered ring.




## Study Questions

Complete the following reactions:

a) 

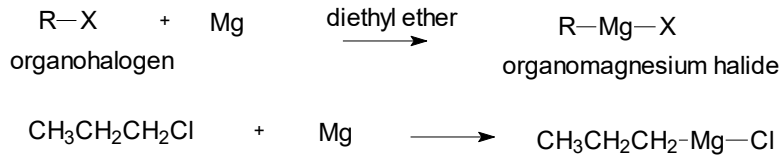

b) 


c) $HOCH_2CH_2CH(OH)CH_2COCH_3$ ⟶

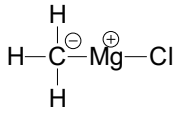
d) $CH(OH)CH_2CH(CH_3)CH_2CHO$ ⟶

## 2.6 Reaction with Grignard Reagents

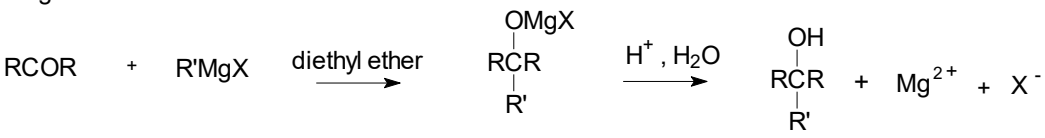
Grignard reagents are organomagnesium halides RMgX. Grignard reagents are prepared by a reaction between magnesium metal and an organohalogen compound in ether solvent. This reaction is named after a French chemist Victor Grignard who received the Nobel prize in 1912 for his work in this area. An important application of the Grignard reagent in organic chemistry is its addition to aldehydes and ketons in an ether solvent followed by hydrolysis to yield alcohols. The reaction is a nucleophilic addition reaction and is not a reversible reaction.



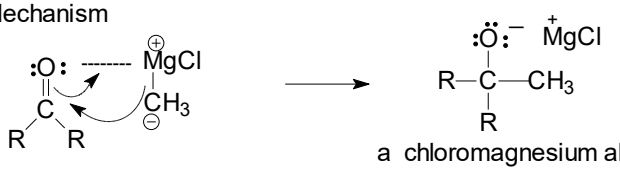

In most organic compounds, carbon carries either no partial charge or a partial positive charge. In Grignard reagents, carbon bonded to an electropositive element carries a partial negative charge. Hence the carbon is an extremely strong base and the alkyl or the aryl portion of the Grignard reagent can act as a nucleophile.



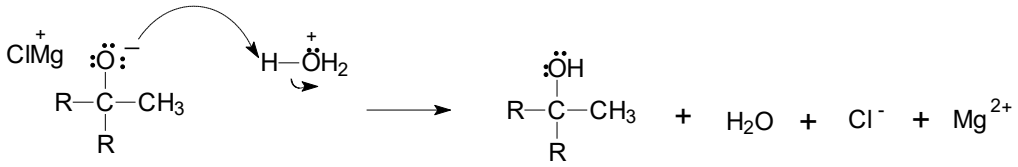
The general reaction involves two steps: Reaction with a Grignard reagent followed by hydrolysis of magnesium alkoxide.




Mechanism




a chloromagnesium alkoxide




The chloromagnesium alkoxide is the magnesium salt of an alcohol. Addition of dilute acid to the reaction mixture gives an alcohol.

The Grignard reaction is also an excellent way of increasing the carbon-carbon chain length.

a ) HCHO $\xrightarrow[(ii)\ H^+,\ H_2O]{(i)\ RMgX}$ $R-\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-H$ a primary alcohol

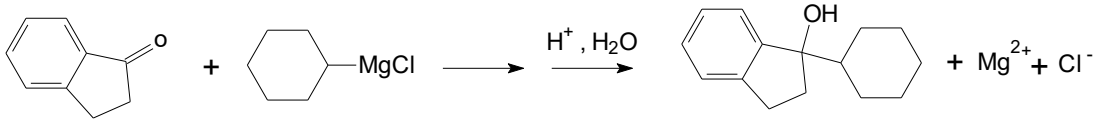
b ) R'CHO $\xrightarrow[(ii)\ H^+,\ H_2O]{(i)\ RMgX}$ $R'-\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-R$ a secondary alcohol

C ) R'COR" $\xrightarrow[(ii)\ H^+,\ H_2O]{(i)\ RMgX}$ $R'-\underset{R''}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-R$ a tertiary alcohol

The net effect of the Grignard reaction, followed by hydrolysis is addition of R—H ( R = an alkyl or aryl group) across the C=O double bond.


a ) $CH_3CH_2COCH_3$ + $CH_3CH_2CH_2MgBr$ $\longrightarrow$ $CH_3CH_2\underset{CH_2CH_2CH_3}{\overset{OMgBr}{\underset{|}{\overset{|}{C}}}}CH_3$ $\xrightarrow{H^+,\ H_2O}$ $CH_3CH_2\underset{CH_2CH_2CH_3}{\overset{OH}{\underset{|}{\overset{|}{C}}}}CH_3$ + $Mg^{2+}Br^-$

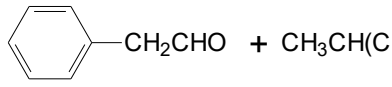
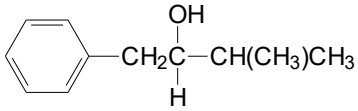
b ) $CH_3CHO$ + $CH_3MgI$ $\longrightarrow$ $CH_3\underset{CH_3}{\overset{OMI}{\underset{|}{\overset{|}{C}}}}-H$ $\xrightarrow{H^+,\ H_2O}$ $CH_3\underset{CH_3}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-H$ + $Mg^{2+}$ + $I^-$

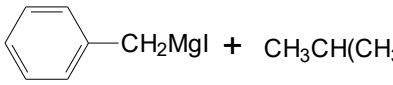
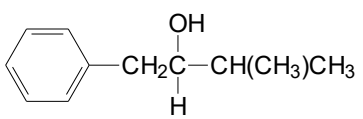
c ) 


It is possible to have more than one Grignard synthesis route to some alcohols.

A i ) $CH_3\ CH_2CH_2CHO$ + $CH_3MgBr$ $\longrightarrow$ $\xrightarrow{H^+,\ H_2O}$ $CH_3CH_2CH_2\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-CH_3$ 2 – pentanol

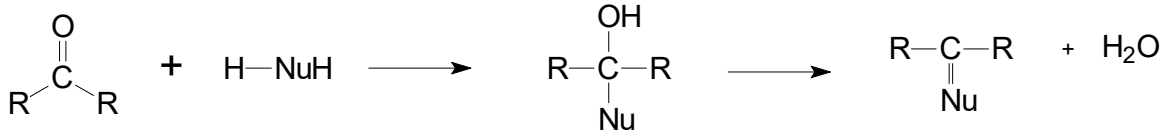
ii ) $CH_3CHO$ + $CH_3CH_2CH_2MgBr$ $\longrightarrow$ $\xrightarrow{H^+,\ H_2O}$ $CH_3\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-CH_2CH_2CH_3$ 2 – pentanol

B i )  + $CH_3CH(CH_3)MgI$ $\longrightarrow$ $\xrightarrow{H^+,\ H_2O}$ 

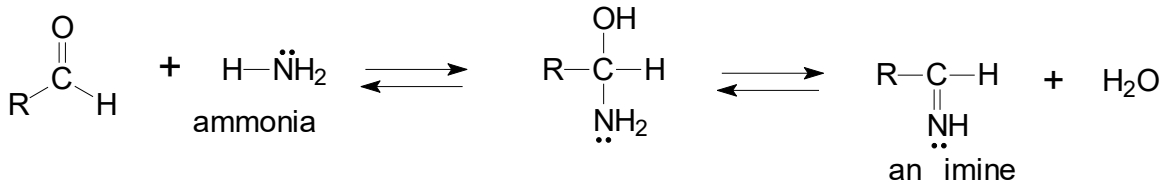

ii )  + $CH_3CH(CH_3)CHO$ $\longrightarrow$ $\xrightarrow{H^+,\ H_2O}$ 

## 2.7 Addition–Elimination Reactions

These are addition to an aldehyde or ketone followed by the elimination of water or other small molecule to yield a product containing a double bond.



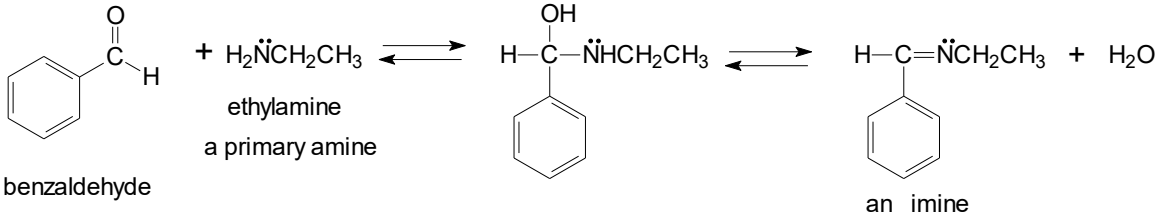

**a) Reaction with Ammonia**

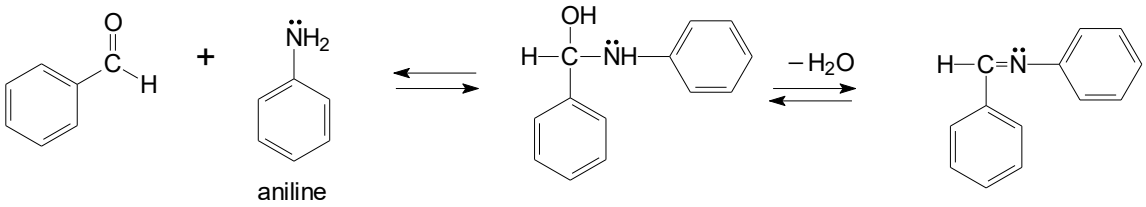


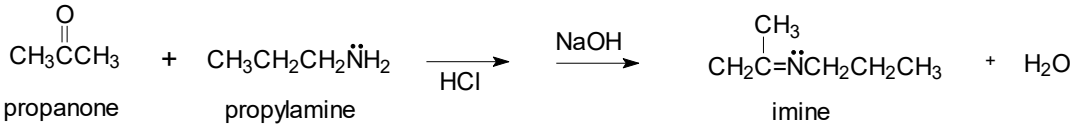

The product of the reaction of an aldehyde or ketone with ammonia, $NH_3$, is an imine. An **imine** is a nitrogen analogue of an aldehyde or ketone in which the C=O group is replaced by a C=NR group. Imines are sometimes called **Schiff bases**. Imines from ammonia are unstable and polymerise on standing.

**b) Reaction with Primary Amines**

A primary amine is an organic derivative of ammonia in which an alkyl or aryl group, RNH2, replaces only one hydrogen atom of ammonia. Primary amines form more stable imines. Aromatic aldehydes or aryl amines yield the most stable imines. Ketones do not form imines as readily as aldehydes do. Imine formation is a reversible reaction, which is driven to the product by the removal of water or the precipitation of the imine or both.

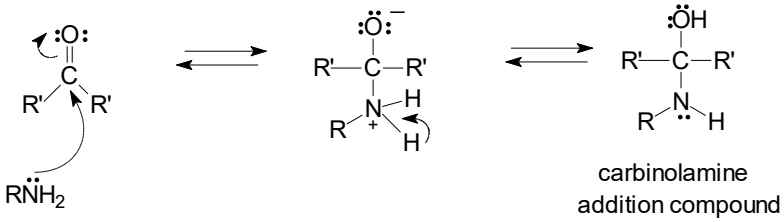


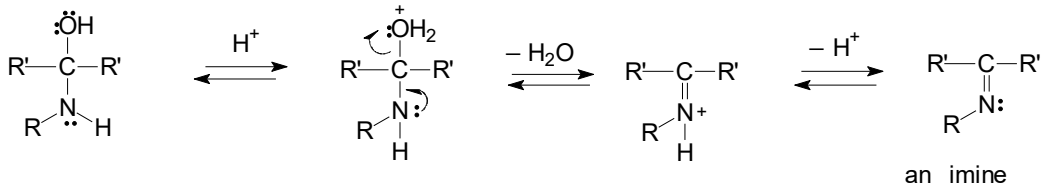




Mechanism: The mechanism is a two step process (i) addition and (ii) elimination.

(i) addition of nucleophile to the carbonyl group of aldehyde or ketone gives an unstable addition compound called a carbinolamine.




(ii) elimination of water from the addition compound



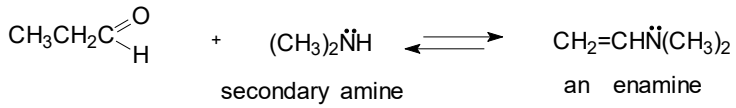

The carbinolamine undergo acid catalysed dehydration to yield an imine.

Imine formation is pH dependent. If the solution is too acidic, the nitrogen of the amine will be protonated and it will not be nucleophilic. The addition step will then be slowed down, but the rate of elimination step would be increased, as it requires protonation. Decrease in acidity causes the addition step to increase and the elimination step to go

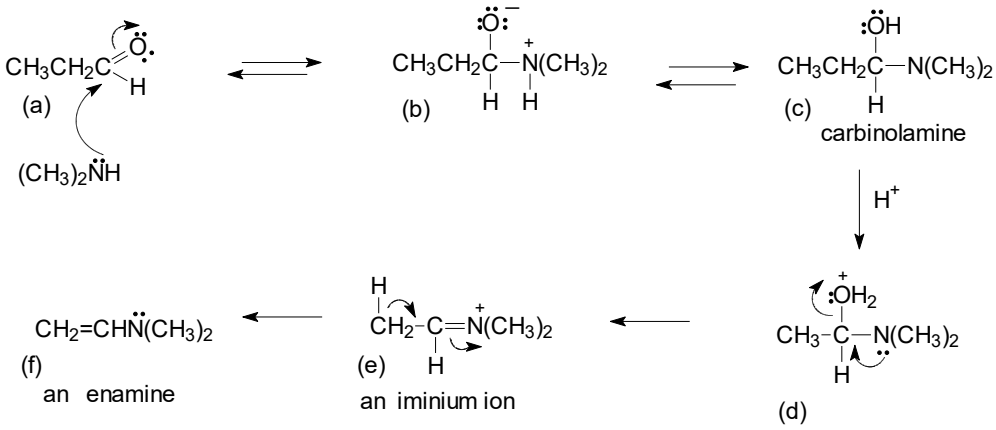
slower. Hence the optimum pH between the two extremes is pH between 3 and 4. At this pH some amines are protonated but some are free to initiate the nucleophilic addition. There is enough acid present so that elimination can proceed at a reasonable rate.

## c) Reactions with Secondary Amines

A secondary amine has the general structure $R_2NH$, in which alkyl or aryl groups formally replace two ammonia protons. The nitrogen of a secondary amine may be part of a ring. When an aldehyde or ketone with hydrogens react s with a secondary amine and **enamine** is formed via an intermediate iminium ion.



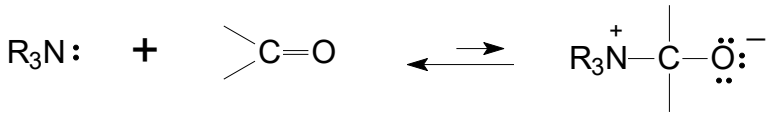

mechanism




Because the nitrogen in intermediate carbinolamine (c) does not have a proton, dehydration in the final product involves proton loss from the adjacent carbon (e) to yield enamine (f).

## d) Reactions with Tertiary Amines

The tertiary amine, $R_3N$ has all the protons of ammonia replaced by alkyl or aryl groups. Tertiary amines do not react with aldehydes and ketones to form stable derivatives. This is because the nitrogen of the tertiary amines do not have NH protons and cannot form intermediate carbinolamines such as (c) above in secondary amines. Hence their addition products break down to starting materials.



## Study Questions

1. Write IUPAC names for each of the following compounds

a ) $CH_3CH_2CH_2CH_2CHO$

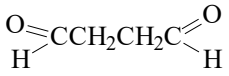
b) $CH_3CH_2COCH_2CH_3$

c) $CHOHCH_2CHClCH_2CH_2CHO$

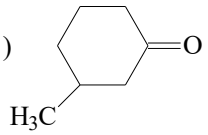
d) $CH_3CH_2CHBrCH_2CHO$

e ) $CH_2{=}CHCH_2COCH_3$

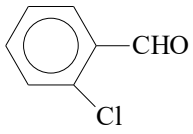
f )



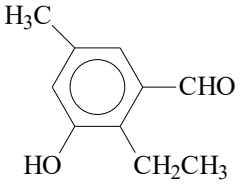
g )

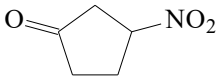


h )



i )





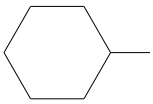
2.. Give the structures of the following compounds:

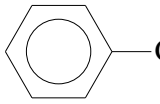
a) 4- methyl-2-pentanone
b) 3,5 – dimethyl-2-heptanone
c) 3- cyclohexen –1- one
d) 3 – hydroxyl- 2 – butanone
e) 3,4-dichloro-2-methylbutanal

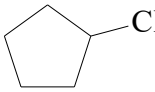
3. Show the mechanism of the following reactions:

a) $CH_3COCH_3$ + $CH_3OH$ , $H^+$

b) 1,3,4,5,6,-pentahydroxy-2-hexanone + $H^+$ , $H_2O$

c )  $CH_2CH_2OH$ + $CH_3CHO$ $\xrightleftharpoons{H^+}$

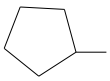
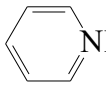
d )  $CHO$ + (i) HCN , $OH^-$ ⟶ (ii) $H^+$ , $H_2O$

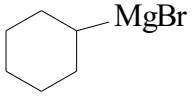
e )  $CHO$ + $CH_3CH_2MgCl$ $\xrightleftharpoons{H^+ , H_2O}$

4. Complete the following reactions:

a) $CH_3CH(OH)CH_2CH(OH)CH_3$ + $K_2CrO_7$ , $H_2SO_4$ ⟶

b) $CH_3CH_2CH_2OH$ + $HCrO_4$ , $H^+$ ⟶

c)  $CH_2CH_2OH$ +  $NH^+CrO_3Cl^-$ ⟶

d) $CH_3COCH_3$ +  ⟶

e) HCHO + $CH_3NH_2$ ⟶

f ) $CH_3COCH_3$ + $NH_2NHC_6H_5$ + $H^+$ ⟶

g) $CH_3CHO$ + $CH_3N(CH_2CH_3)_2$ ⟶

h ) $CH_3CH_2COCH_3$ + $I_2$ / $OH^-$ ⟶

CHAPTER THREE

# OTHER REACTIONS OF ALDEHYDES AND KETONES

## 3.1 The Alpha (α) Hydrogen (s)

An alpha (α) carbon atom is the one adjacent to a carbonyl group. Alpha (α) hydrogen is one on alpha carbon to a carbonyl group. Because carbon and hydrogen have comparable electronegativities, a carbon–hydrogen bond normally has little polarity and hydrogen atom bonded to carbon shows very low acidity. However, the situation is different for alpha hydrogen to the carbonyl group. The hydrogens are more acidic than acetylic, vinylic and alkane hydrogens, but less acidic than –OH hydrogen of alcohol.

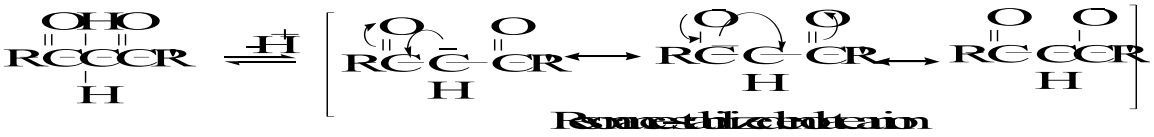
| Type of Bond | p$K_a$ |
|---|---|
| $CH_3CH_2O–H$ | 16 |
| $CH_3COCH_2–H$ | 20 |
| $CH_3C{\equiv}C–H$ | 25 |
| $CH_2{=}CH–H$ | 44 |
| $CH_3CH_2–H$ | 51 |

The alpha hydrogen of carbonyl compounds is relatively acidic due to:

(i) The electron-withdrawing inductive effect of the adjacent carbonyl group weakens the bond to the alpha hydrogen.

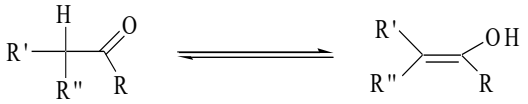
(ii) The negative charge on the resulting enolate anion is delocalized by resonance, thus stabilizing it relative to the anion from the other compounds like alkynes, alkenes and alkanes.[an enolate is an anion derived by loss of a hydrogen from a carbon alpha to a carbonyl group].

Consider a case whereby the hydrogen is lost from a carbon atom between two carbonyl groups. More than two resonance structures are involved and therefore better resonance-stabilized.



## 3.1.1 Tautomerism

A carbonyl compound with acidic alpha hydrogen may exist in two forms called **tautomers**. These are inter-convertible structural isomers that differ from one another only in the location of the double bond and the hydrogen atom relative to the oxygen atom.

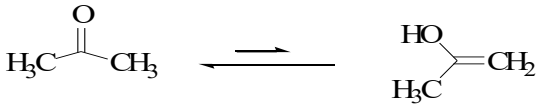



Keto form Enol form

As the hydrogen atom is in a different position, the two tautomeric forms are not resonance structures, but two different structures in equilibrium.

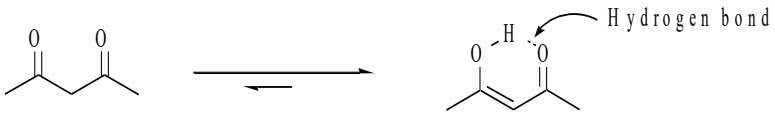
**Note:** Resonance structures vary only in the position of electrons.

Normally aldehydes and ketones exist primarily in the keto forms.




Keto form of Acetone Enol form of Acetone

However, there exist some carbonyl compounds that prefer enol forms to the keto forms. Consider 2,4-pentanedione for example.



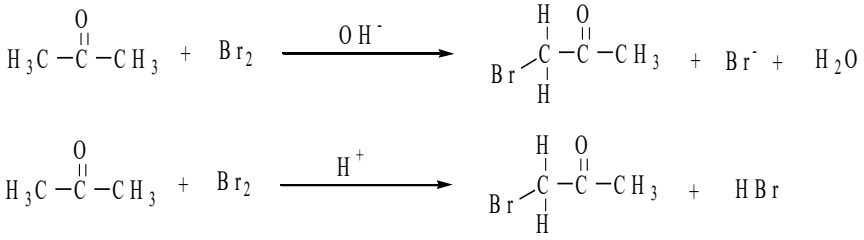

Keto form (20%) Enol form (80%)

The enol form of 2,4-pentanedione is favored over keto form due to:

(i) The enol form ends up with a conjugated double bond system thus stable.
(ii) The enol form can exhibit internal hydrogen bonding which also stabilize the tautomer.

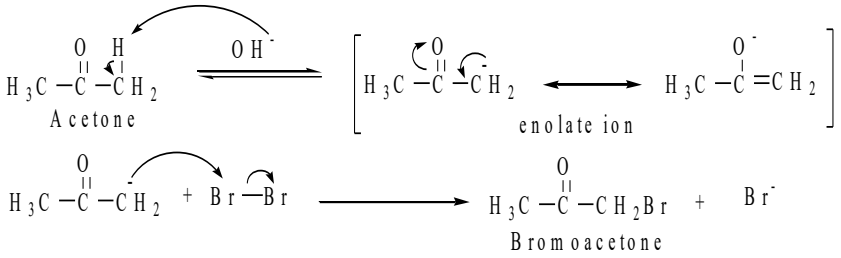
## 3.1.2 Alpha (α) halogenation

Aldehydes and ketones with at least one alpha-hydrogen react at alpha-carbon with bromine and chlorine to form alpha-haloaldehydes and alpha-haloketones. An acid or a base can catalyze the reaction.

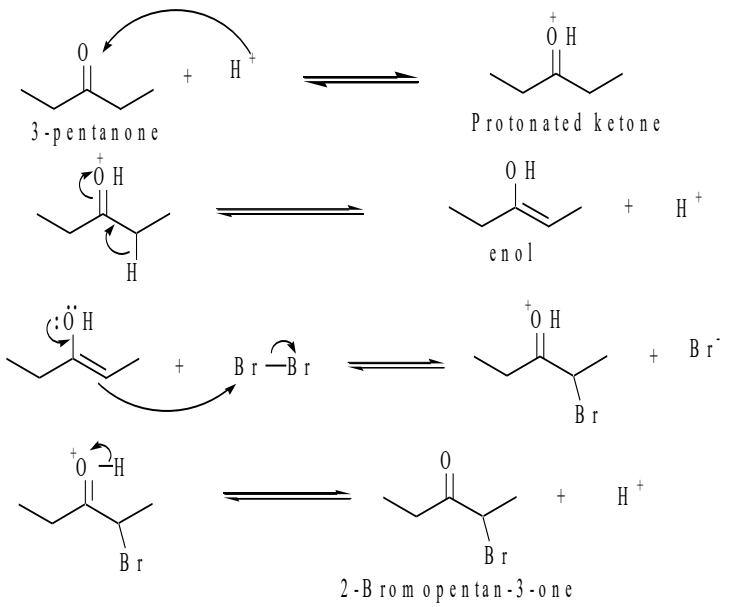


**Note**: In the basic medium, the base is a reactant but in acidic medium the acid is a catalyst.

The mechanism in basic media involves formation of an enolate ion as intermediate as also as the rate-determining step.



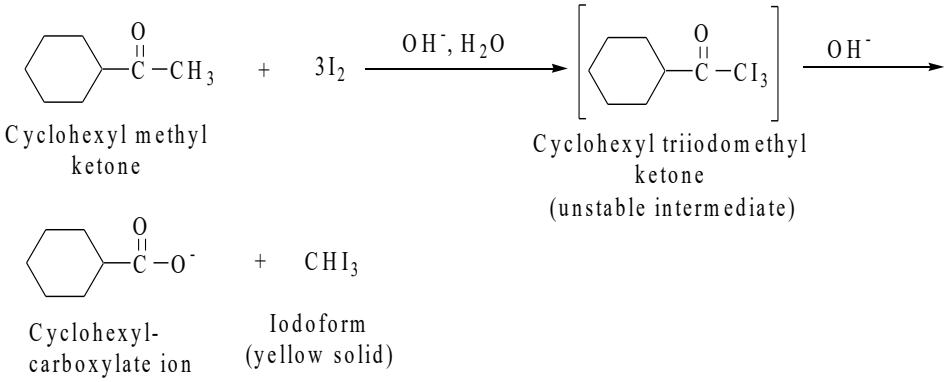

The mechanism in acidic medium proceeds by way of enol as the rate-determining step.




### 3.1.3 Haloform reaction (Iodoform test)

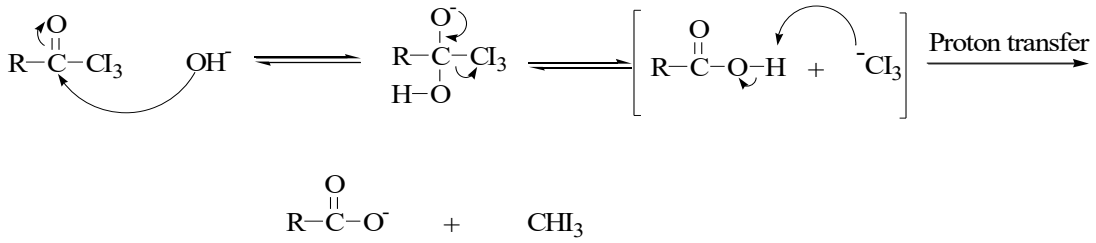
This is a characteristic reaction of compounds with a terminal methyl group bonded to a carbonyl group, like methyl ketones. The methyl is iodinated stepwise until the yellow solid of iodoform ($CHI_3$) is formed. The reaction is used for identification of such compound.

| **Note**: Ethanal (acetaldehyde) is the only aldehyde that gives a positive iodoform test. |
|---|




The intermediate, cyclohexyl triiodomethyl ketone is rendered unstable due to the fact that the moiety $CI_3$ is a good leaving group.

The mechanism of the reaction involves the attack by the hydroxyl ion on the carbonyl carbon leading to formation of a carboxylic acid and triiodomethyl anion. There is transfer of the hydrogen ion and exchange of anions due to stability factors.



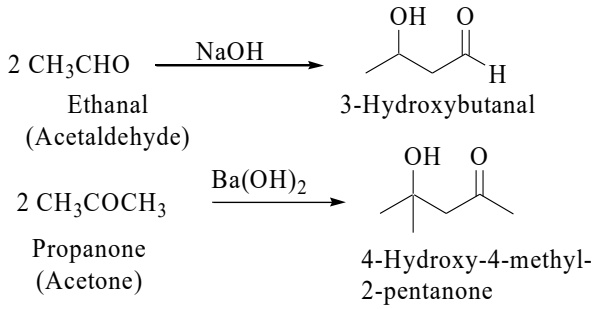

**Note**: As iodine is a mild oxidizing agent, secondary alcohols with a terminal methyl group also give a positive iodoform test.

An alcohol like 2-propanol is oxidized first by iodine to propanone (acetone). Later acetone is converted to the acetate ion and iodoform.

**Note**: Chlorine and bromine also react the same way as iodine but the resulting haloform products are non-distinctive clear liquids. For that reason, they are not useful for test purposes.

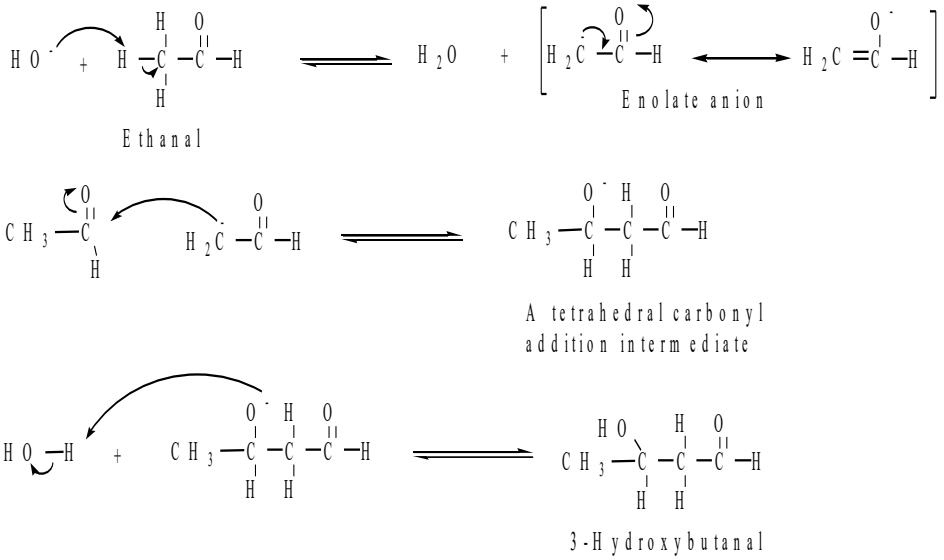
## 3.2 Aldol Condensation Reactions

Aldol condensation reaction involves coupling of two molecules of carbonyl compounds. The reaction can be catalyzed by either acid or base; with the base catalysis is more common. The products are either a β-hydroxyaldehyde or a β-hydroxyketone.

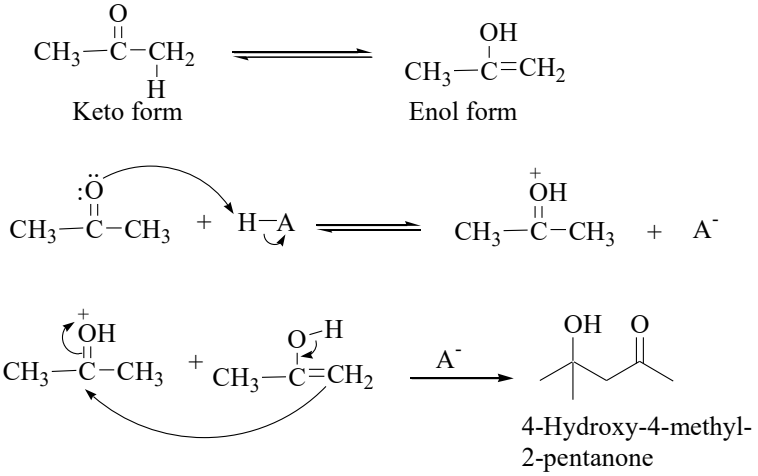



The key step in base-catalyzed Aldol reaction is nucleophilic addition of the enolate anion of one carbonyl-containing molecule to the carbonyl group of another to form a tetrahedral carbonyl addition intermediate. The hydroxyl ion is used as catalyst because it is generated later. The reaction is a three-step reaction. First step involves formation of a resonance stabilized enolate anion. Second step is a nucleophilic addition of the enolate anion to carbonyl carbon to form a tetrahedral carbonyl addition intermediate. The final step is the

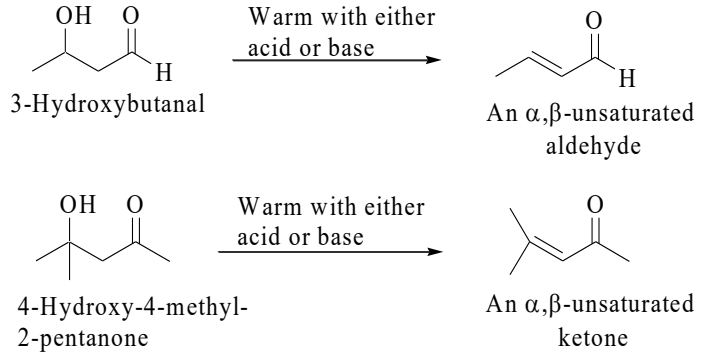
reaction of the tetrahedral carbonyl addition intermediate with a proton donor to form the Aldol product.



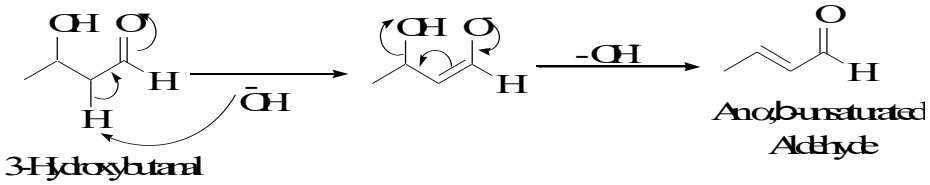

The mechanism of acid-catalyzed reaction involves two steps, the first of which is acid-catalyzed establishment of equilibrium between the keto and enol forms of the ketone or aldehyde. The second step is formation of the new carbon-carbon bond by attack of the enol on the carbon of the protonated carbonyl group.



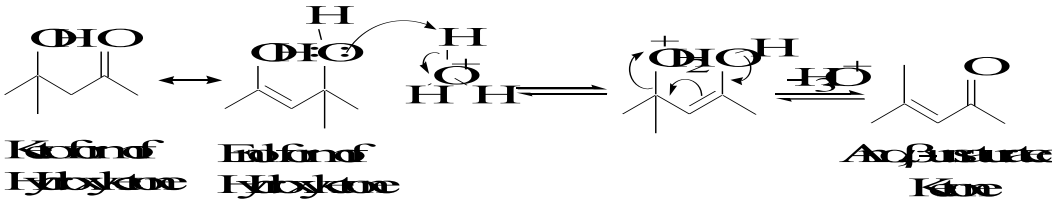

β-Hydroxyaldehydes and β-Hydroxyketones are very easily dehydrated where the conditions of aldol reaction are sufficient enough to cause dehydration, particularly the acid-catalyzed aldol reaction. Alternatively, warming the aldol product in dilute acid can bring about dehydration. The major product of dehydration is one with the carbon-carbon double bond being conjugated with the carbonyl group, giving an α,β-unsaturated aldehyde or ketone.




In base catalyzed dehydration, alpha hydrogen is removed to form a new enolate anion, which then expels the hydroxide ion.




In acid-catalyzed dehydration, proton transfer from protonated water ($H_3O^+$) to the hydroxyl ($OH^-$) group of the aldol product forms an oxonium ion. Loss of water from this protonated enol gives a protonated form of the product. Proton transfer from the protonated carbonyl group to water completes the dehydration of the aldol product.



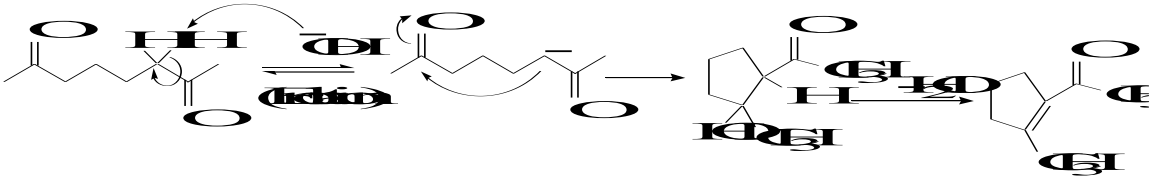

**Crossed aldol reaction** involves two different types of carbonyl compounds. The reaction involving acetone and formaldehyde (methanal) is a good example of a crossed aldol reaction. Note that methanal cannot provide an enolate anion because it has no α-hydrogen, but it can function as a good anion acceptor because its carbonyl group is unhindered.

A similar reaction will take place when acetone (or any other ketone) and benzaldehyde undergo aldol reaction.

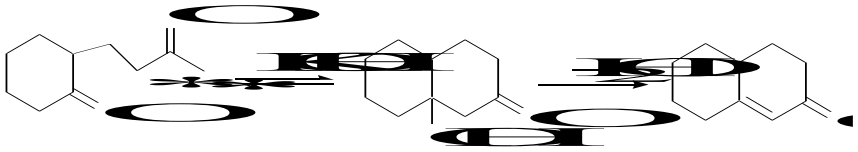
Consider the aldol reaction between acetone and acetaldehyde. Although is more favored in formation of enolate anion over acetaldehyde, there is possibility of acetaldehyde providing the enolate anion. A mixture of four aldol products is formed in such a case. A single product can be obtained by carrying out the enolation process first by use of suitable bases like lithium diisopropylamide (LDA) and later introducing the other carbonyl compound to come in as the enolate acceptor.

**Study Question**: Provide the structures and systematic names of the four aldol products of the reaction between acetone and acetaldehyde.

**Intramolecular aldol reaction** involves a dicarbonyl compound that provides both the enolate anion and the carbonyl group as the enolate acceptor. This type of reaction is useful for formation of five- and six-membered rings. Consider 2,7-octanedione;

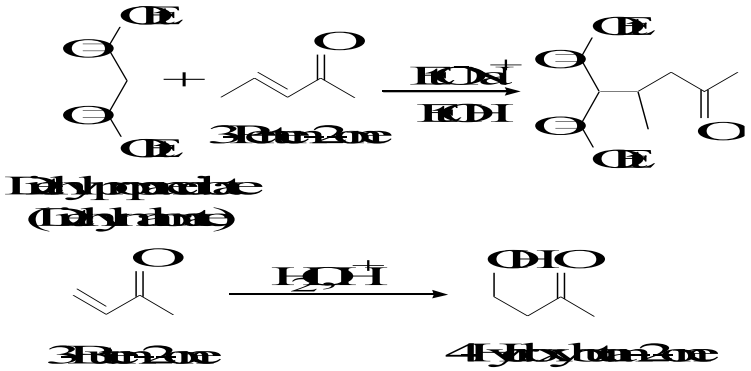


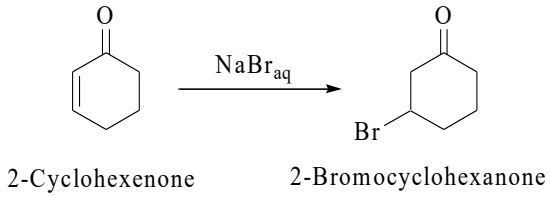
It should be noted that 2,7-octanedione can form two enolate anions; one that leads to formation of a five-membered ring as shown above, and the other involving the terminal methyl group that may lead to formation of a seven-membered ring. Formation of five- and six-membered rings is favored relative to formation of four- and seven membered rings. Smaller rings are formed faster than larger rings because reacting groups are closer together. However, the formation of three- and four-membered rings is not favored because of strain in the rings. Another example is illustrated below. There are options of forming two enolate anions leading to formation of six- or four-membered rings. But the six-membered ring is favored as the only product.



## 3.3 Michael Addition Reaction

Addition of enolate anion to α,β-unsaturated carbonyl compounds was first reported in 1887 by the American chemist, Arthur Michael.

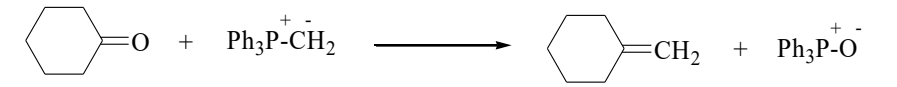





2-Cyclohexenone 2-Bromocyclohexanone

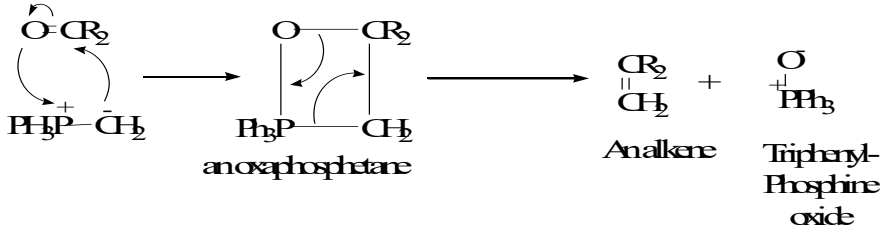
## 3.4 Wittig Reaction

Georg Wittig first reported the reaction in 1954 and is a important method for the synthesis of alkenes from aldehydes and ketones using compounds called phosphonium ylides. An ylide is a molecule that, when written in a Lewis structure showing all atoms with complete valence shells, has positive and negative charges on adjacent atoms. In the reaction, the C=O bond is converted to a C=C bond.




Cyclohexane | Triphenyl-phosphonium ylide | Methylene cyclohexane | Triphenyl-phosphine oxide

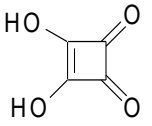
Phosphonium ylide react with the carbonyl group of aldehyde and ketone by a cycloaddition reaction to form a four-membered ring called an **oxaphosphetane**. On warming the oxaphosphetane fragment to give the products. The driving force for the reaction is formation of a very strong phosphorus-oxygen bond in triphenylphosphine oxide.

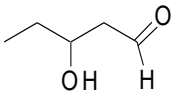


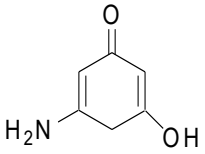

## Study Questions

[**Note**: Some questions below may require your further reading on other chapters (topics) in this text]

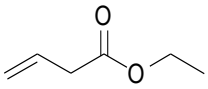
Q1.(a) Write systematic names for the following compounds.

(i) 

(ii) 

(iii) 

(iv) $(CH_3)_3CCO_2H$

(v) 

(b) Draw structures of each of the following compounds.

(i) 4- Methyl-4-hydroxy-2-pentanone (ii) (Trans)-2-Ethyl-2-butenal
(iii) *N*-Ethyl-*N*-methylpentanamide (iv) (Z)-3-Phenyl-2-pentanoic acid
(v) 3,6-Dichloro-2,5-dihyroxy-1,4-benzoquinone

Q2.

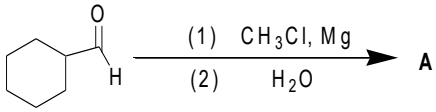
(a) Explain the following using appropriate equations and structures.

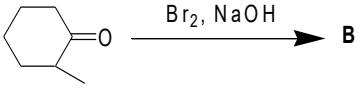
(i) Ethanal is more reactive than 4-heptanone towards nucleophilic addition reaction.

(ii) 1,2-Cyclohexanedione in hexane exists in about 100% in the enol form.

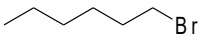
(iii) Aldehydes and ketones have lower boiling points than alcohols with comparable MW, but higher boiling points than hydrocarbons of comparable MW.

(b) Identify the major organic products A to D in the following transformations.

(i) 


(ii) 


(iii) $CH_3COCH_3 + CH_3CH_2NH_2 \longrightarrow$ **C**

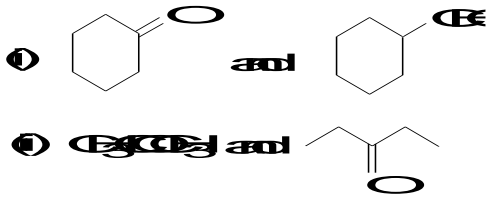
(iv) 


Q3

(a) Using Curly arrows, write possible reaction mechanisms for the following reactions.

(i) Base hydrolysis of ethyl ethanoate

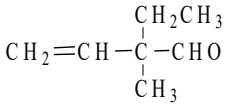
(b) Give simple visual chemical test you would use to differentiate between the following pairs of compounds.

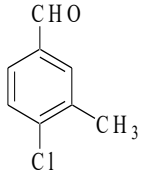


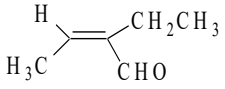
Q4. (a) Draw structures of each of the following compounds.

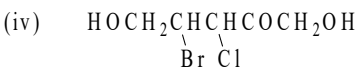
(iv) 5-Bromo-4-oxopentenal
(v) 3,5-Dimethyl-3-cyclohexenone
(vi) Phenyethanenitrile
(vii) 2-Butenedioc acid anhydride
(viii) Ethyldimethylphenylammonium nitrate

(b) Write systematic names for the following compounds.

(i) 

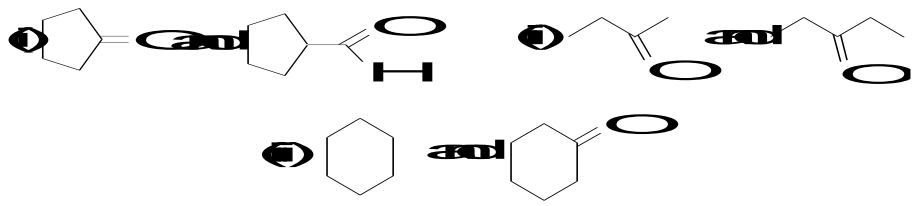
(ii) 

(iii) 

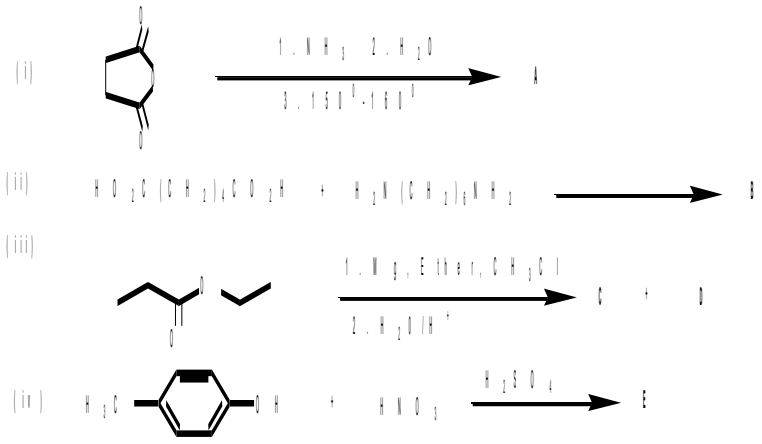
(iv) 

(v) $(CH_3)_3CCH_2COCH_2CH(CH_3)_2$

Q5. (a) Give simple visual chemical tests, including observations that you would use to differentiate between the following pairs of compounds.



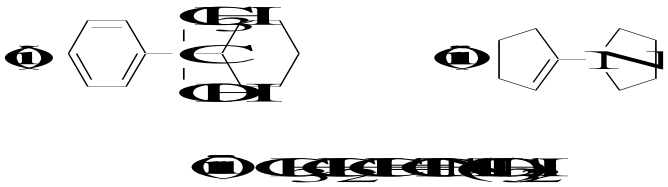
Q6.(b) Identify the major organic products A to E in the following transformations.



Q7 Explain the following using appropriate equations and/or structures.

(i) Methanal is more reactive than 2-butanone towards nucleophilic addition reaction.
(ii) In conversion of primary alcohols to aldehydes, special reagents are required.
(iii) Aldehydes and ketones have lower boiling point than alcohols but they have higher boiling points than hydrocarbons of comparable molecular weight.
(iv) Amines are more basic than amides and the basicity of an amine depends on the number of alkyl groups attached to nitrogen.

Q8 (a) Suggest the reagents from which the following compounds may be prepared.



## CHAPTER FOUR

# CARBOXYLIC ACIDS

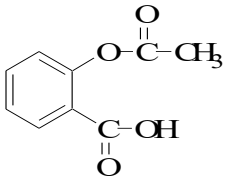
## 4.1 Introduction

Carboxylic acids are organic compounds that contain carbonyl and hydroxyl groups on the same carbon atom. They under go unique reactions due to interaction of the two groups.

There are three features that can be noted of the carboxylic group; that it is planar, polar and has increased number of lone pairs when compared with aldehydes and ketones.

Carboxylic acids are important biologically and commercially. A few examples are mentioned.

Aspirin, the all round painkiller contains both carboxyl group and an ester group.

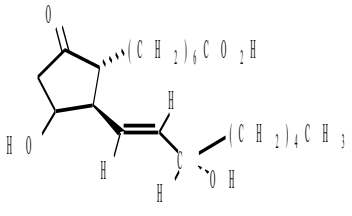


Aspirin

Oleic acid

Oleic acid is a fatty acid, a component of fats and oils. Base hydrolysis of fats, a process known as saponification, leads to formation of soap and the fatty acid moiety is one involved.

Prostaglandrins are carboxylic acids or their derivatives. They are responsible of hormonal activity.



Prostaglandrin $E_1$ ($PGE_1$)

As the carboxyl group is generally non-hindered, its reactions are not usually affected to a great extent by the rest of the molecule. Therefore the acids undergo similar reactions.

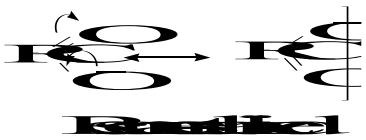
Acid strength is the extent of ionization of a Brϕnsted acid in water. That is the greater the ionization in water, the stronger is the acid and can be expressed in terms of Ka or pKa. Carboxylic acids are termed as weak acids, with an average pKa value of 5. Acids like Hydrochloric acid and nitric acid have a pKa value of 1.

$$pKa = -\log Ka \text{ (Like } pH = -\log [H^+]$$

**Note**: The lower the pKa value the stronger the acid.

This implies that when carboxylic acids aqueous media the three species, hydrogen ion, carboxylate ion and undissociated carboxylic acid molecules exist in equilibrium.

However, carboxylic acids are more acidic than phenol and alcohols. This is due to the fact that the resulting carboxylate ion is resonance stabilized.




## 4.2 Nomenclature of carboxylic acids

In naming of carboxylic acids by IUPAC system, the suffix ‘e’ in alkane is replaced with ‘oic acid’ to lead alkanoic acid and is derived from the name of the longest carbon chain that contains the carboxyl group. However, the ‘e’ is retained in dicarboxylic acids and other polyfunctional acids.

| | | |
|---|---|---|
| $HCO_2H$ | $CH_3CO_2H$ | $CH_3CH_2CO_2H$ |
| Methanoic acid | Ethanoic acid | Propanoic acid |

The chain is numbered, beginning with the carbon atom of the carboxylic group. If the carboxylic acid contains a carbon-carbon double or triple bond, change of infix from ‘an’ to ‘en’ and ‘yn’ to indicate the presence of multiple bond. The location of the multiple bond is indicated by a number with reference to the carboxyl group.

| | |
|---|---|
| $CH_3CH{=}CHCO_2H$ | $CH_2{=}CHCH_2CO_2H$ |
| 2-But**e**noic acid | 3-But**e**noic acid |

**Note**: Geometrical isomerism will be experienced in 2-butenoic acid.

In IUPAC system, a carboxyl group takes precedence over most other functional groups. For that the other groups are indicated by prefixes.

It will be noted that usage of trivial names has persisted in carboxylic acids such that the names are used for the simple carboxylic acids. These names were based on source of the acids. Table 1 below gives the IUPAC names, trivial names and occurrence of some selected acids.

Table 4.1. **Some Carboxylic acids and their common names**

| Structure | IUPAC Name | Common Name | Occurrence/Derivation |
|---|---|---|---|
| $HCO_2H$ | Methanoic acid | Formic acid | *Formica* (L), ant |
| $CH_3CO_2H$ | Ethanoic acid | Acetic acid | *Acetum* (L), vinegar |
| $CH_3CH_2CO_2H$ | Propanoic acid | Propionic acid | *Propion* (G), first fat |
| $CH_3(CH_2)_2CO_2H$ | Butanoic acid | Butyric acid | *Butyrum* (L), butter |
| $CH_3(CH_2)_3CO_2H$ | Pentanoic acid | Valeric acid | *Valeriana* (L), a flowering plant |
| $CH_3(CH_2)_4CO_2H$ | Hexanoic acid | Caproic acid | *Caper* (L), goat |
| $CH_3(CH_2)_6CO_2H$ | Octanoic acid | Caprylic acid | *Caper* (L), goat |
| $CH_3(CH_2)_8CO_2H$ | Decanoic acid | Capric acid | *Caper* (L), goat |
| $CH_3(CH_2)_{10}CO_2H$ | Dodecanoic acid | Lauric acid | *Laurus* (L), laurel plant |
| $CH_3(CH_2)_{12}CO_2H$ | Tetradecanoic acid | Myristic acid | *Myristikos* (G) fragrant |
| $CH_3(CH_2)_{14}CO_2H$ | Hexadecanoic acid | Palmitic acid | *Palma* (L), palm tree |
| $CH_3(CH_2)_{16}CO_2H$ | Octadecanoic acid | Stearic acid | *Stear* (G), solid fat |
| $CH_3(CH_2)_{18}CO_2H$ | Eicosanoic acid | Arachidonic acid | *Arachis* (G) peanut |

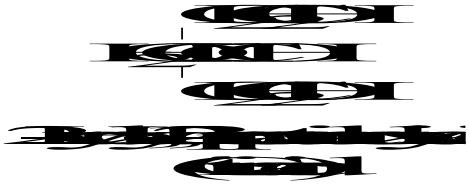
KEY: G (Greek); L (Latin)

**Note**: Pure ethanoic acid is viscous liquid that solidifies into an 'icy-looking solid and thus called **'Glacial' acetic acid.**

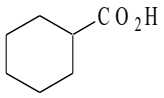
As was mentioned earlier, in dicarboxylic acids the 'e' in alkane is retained and the suffix '-dioic' acid added to the name of the longest carbon chain that contains both carboxylic

groups. The numbers for the position of the carboxyl groups are not indicated because they can only be at the ends of the parent chain. Like monocarboxylic acids, trivial names have persisted and are based on the source of a given dicarboxylic acid.

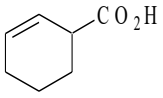
Tri- and higher carboxylic acids are named by using the suffixes '–tricarboxylic acid', '-tetracarboxylic acid', etc. Citric acid from citrus juices is a tricarboxylic acid.



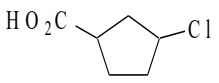
Carboxylic acid containing carboxyl group attached to a cycloalkane or cycloalkene ring is named by giving the name of the ring and adding the suffix 'carboxylic acid'. The atoms are numbered beginning with the carbon with carbon bearing the carboxyl group.



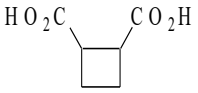
Cyclohexanecarboxylic acid
(Cyclohexylmethanoic acid)



2-Cyclohexenecarboxylic acid

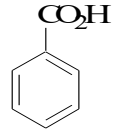


3-Chlorocyclopentanecarboxylic acid
(two structures: *Cis* and T*rans* isomers)

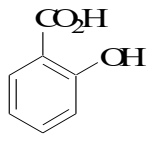


1,3-Cyclobutanedicarboxylic acid
(two structures: *Cis* and T*rans* isomers)

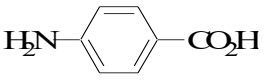
Benzoic acid is the simplest aromatic carboxylic acid. Derivatives are named by using numbers to show the location of substituents relative to the carboxyl group. Common names are also used for aromatic carboxylic acids. 2-Hydroxybenzoic acid is usually known as 'salicylic acid', name derived from the willow tree of the genus *Salix*.



Benzoic acid



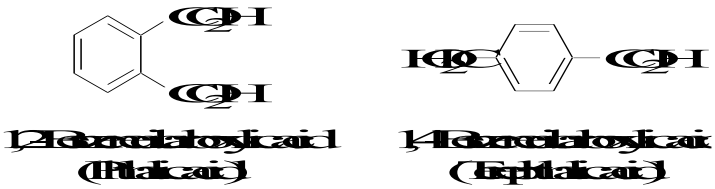
2-Hydroxybenzoic acid
(Salicylic acid)



4-Aminobenzoic acid

4-Aminobenzoic acid is a growth factor required by microorganisms for the synthesis of folic acid, complex group of compounds used in treatment of anaemia.

Aromatic dicarboxylic acids are named by adding the word ‘dicarboxylic acid’ to ‘benzene’. Again trivial names are commonly used.

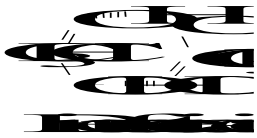


## 4.3 Physical Properties of carboxylic acids

Carboxylic acids with one to four carbon atoms are colourless liquids with sharp pungent (unpleasant) smell. Acids with five to nine carbon atoms may be liquids or solids depending on the isomeric forms. Those with more than ten carbon atoms are usually no-volatile solids and the odor diminishes due to low volatility.

Carboxylic acids interact with water molecules by hydrogen bonding through both hydroxyl and carbonyl groups. The solubility diminishes are the number of carbon atoms increases. This is because of increasing of the hydrophobic (‘water fearing’) hydrocarbon group. Thus lower members are highly miscible with water. The solubility of hexanoic acid in water is 1.0g/100mL water while that of decanoic acid is 0.2g/100 mL water.

Normally carboxylic acids have high boiling points than other types of organic compounds of comparable molecular weight such as alcohols, aldehydes and ketones. In their liquid and solid states, carboxylic acids are associated by hydrogen bonding into dimeric structures as illustrated with acetic acid in liquid state.

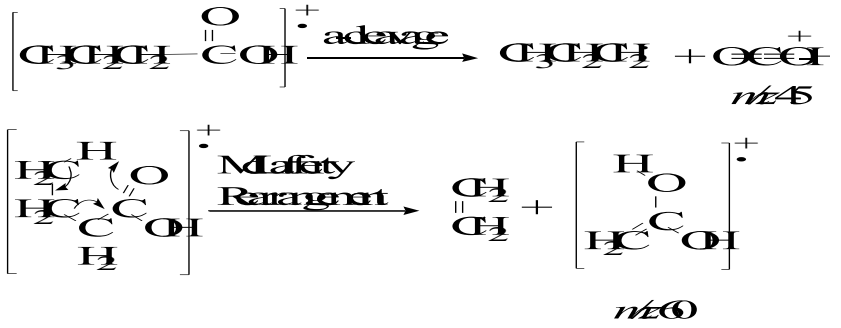


Carboxylic acids can be detected due to their odor. Hexanoic acid (caproic acid), for example, smells like goat (Goat sweat contains it). Dogs differentiate the odors of individual humans because of differing proportions of carboxylic acids in human sweat. Pentanoic acid (valeric acid) is a sex attractant of the sugar beet wireworm.

## 4.4 Spectroscopic Properties

### 4.4.1 Mass Spectrometry (MS)

The molecular peak from a carboxylic acid is generally observed, although it is often very weak. The most common fragmentation patterns are α-cleavage of the carboxyl group to give the ion $[CO_2H]^+$ of *m*/*z* 45 and McLafferty rearrangement, which is very often the base peak. Example is illustrated with butanoic acid.




### 4.4.2 Infrared Spectroscopy (IR)

The carboxyl group gives rise to two characteristic absorptions in the infrared spectrum. One of these occurs in the regions 1700-1725 $cm^{-1}$ and is associated with the stretching vibration of the carbonyl group. Note that the absorption is essentially the same range of absorption as for the carbonyl group of aldehydes and ketones but the peak is usually broader in the case of the carboxyl carbonyl because of intermolecular hydrogen bonding. The other absorption of importance for carboxylic acids is a peak between 2400 and 3400 $cm^{-1}$ due to the stretching vibration of the O-H group. The absorption is generally very broad due to hydrogen bonding between molecules of the carboxylic acid.

### 4.4.3 Nuclear Magnetic Resonance (NMR)

Hydrogens on the α-carbon to a carboxyl group give a signal in the proton NMR spectrum in the range δ 2.0-2.5. The hydrogen of the carboxyl group appears in the range δ 10-13.

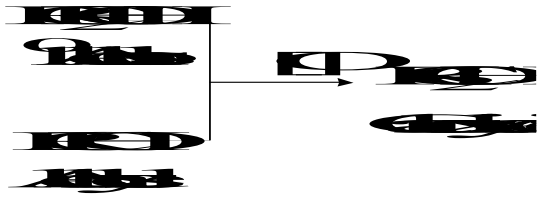
The carbon-13 absorption of the carboxyl carbon appears in the range δ 160-180 and is similar to that of carboxyl derivatives (esters, amides and acid anhydrides).

## 4.5 Preparation of Carboxylic Acids

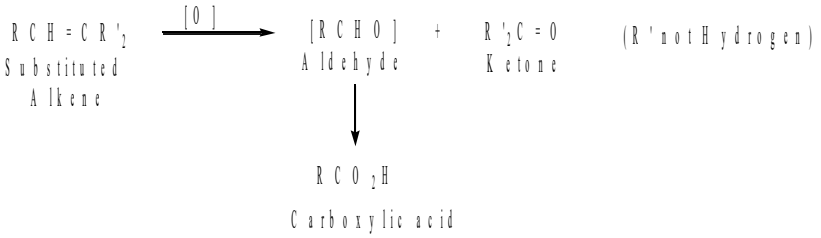
Three main types of reactions are involved in preparation of carboxylic acids. They are: oxidation reactions, Grignard reactions and hydrolysis reactions of carboxylic acids derivatives.

## 4.5.1 Oxidation Reactions

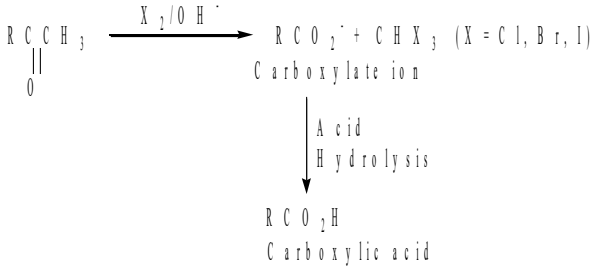
Oxidation reactions of primary alcohols and aldehydes lead to formation of carboxylic acids. Various common oxidizing agents can be used. They include potassium permanganate ($KMnO_4$), potassium dichromate ($K_2Cr_2O_7$), chromic acid ($H_2CrO_4$), manganese dioxide ($MnO_2$) and even hydrogen peroxide ($H_2O_2$).



When alkenes react with strong oxidizing agent oxidative cleavage leads to formation of oxidized products like carboxylic acid through fragmentation. This depends on the structural feature of the alkene. When the carbon atoms of the double bond are bonded to hydrogen atoms carboxylic acids are formed through aldehydes. However, if they are substituted ketones are formed.




Haloform reactions of methyl ketones form carboxylic acid with one carbon atom less. (Refer to the iodoform/haloform reaction of aldehydes and ketones).



### 4.5.2 Grignard Reactions

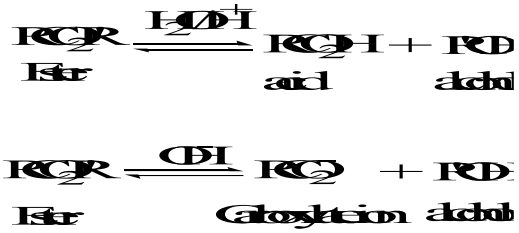
When the Grignard reagent is reacted with carbon dioxide followed by acid hydrolysis, carboxylic acid is formed. The acid that is formed is one carbon atom more that the starting alkyl halide.

Mechanism:

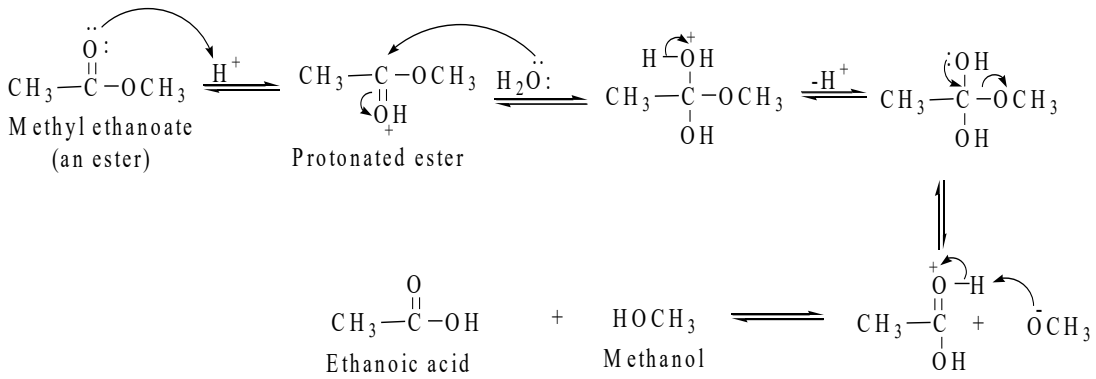
### 4.5.3 Hydrolysis of Acid Derivatives

### (a) Esters

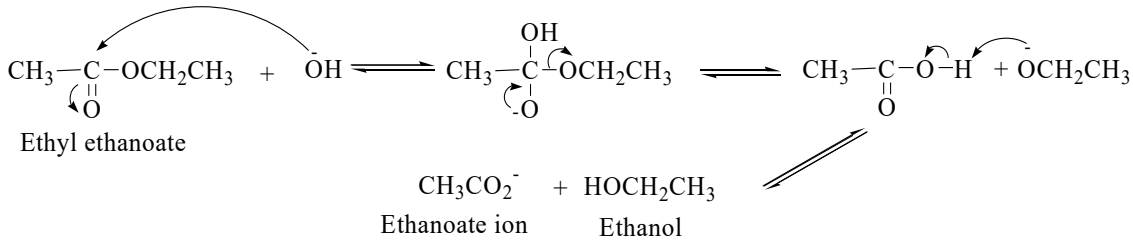
Esters differ from acids by replacement of the hydrogen of the hydroxyl group of acid with an alkyl or aryl group. Hydrolysis of ester can be performed under acidic or basic conditions. Both methods lead to formation of carboxylic acids.



The role of the acid catalyst is to protonate the carbonyl oxygen. In doing so, it increases the electrophilic character of the carbonyl carbon toward attack by water to form a **tetrahedral carbonyl addition intermediate**. Collapse of this intermediate gives the carboxylic acid and an alcohol. In this reaction, acid is a catalyst; it is consumed in the first step but is regenerated at the end of the reaction.




Base hydrolysis is by use of aqueous sodium hydroxide or potassium hydroxide is called saponification, a reference to the use of this reaction in the manufacture of soaps. Although the carbonyl carbon of the ester is not strongly electrophilic, hydroxyl ion is a good nucleophile and adds to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate, which in turn collapses to give a carboxylic acid and an alkoxide ion. The acid reacts with the alkoxide ion to form a carboxylic acid anion and an alcohol. The mechanism is illustrated below.




There are two major differences between hydrolysis of esters in aqueous acid and aqueous base.

1. For the hydrolysis of an ester in aqueous acid, acid is required in only catalytic amounts. For the hydrolysis in aqueous base, base is required in equimolar amounts because it is a reactant, not a catalyst.
2. Hydrolysis of an ester in aqueous acid is reversible while in aqueous base is irreversible.

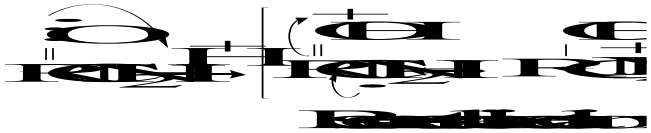
## (b) Amides

Amides are organic compounds where the hydroxyl group of the carboxylic acid is replaced with an amino group. That is, a nitrogen atom is directly bonded to the carbon of the carbonyl. When the nitrogen has two hydrogens, the amide is termed as primary ($1^0$) amide. When the nitrogen has one hydrogen atom and an alkyl (or aryl) group it is termed as a secondary ($2^0$) amide. If both hydrogens have been replaced with alkyl (or aryl) groups, the amide is termed as a tertiary ($3^0$) amide.

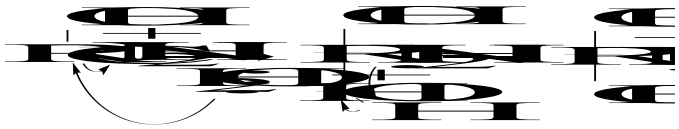
Amides undergo hydrolysis in hot aqueous acid to give a carboxylic acid and ammonium ion.

The steps in the mechanism of the acid hydrolysis of the amides are similar to that of ester. The mechanism is outline below.

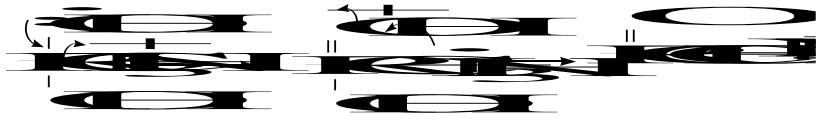
1st Step: Protonation of the amide at the carbonyl oxygen.



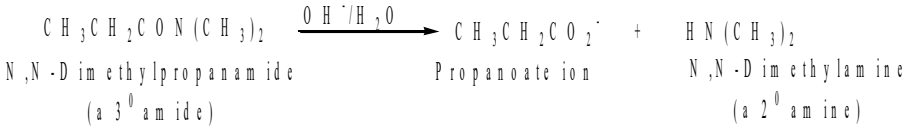
2nd Step: Addition of water to the carbonyl carbon followed by proton transfer gives a tetrahedral carbonyl addition intermediate.



3rd Step: Collapse of the tetrahedral carbonyl addition intermediate coupled with a proton transfer.

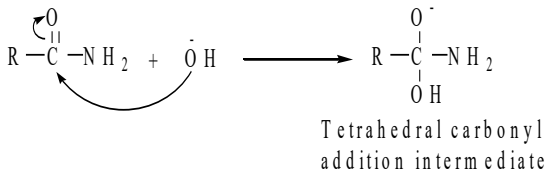


In aqueous base, the products of amide hydrolysis are carboxylic acid salt and ammonia or amine. Like the acid hydrolysis, vigorous conditions are required in base hydrolysis.

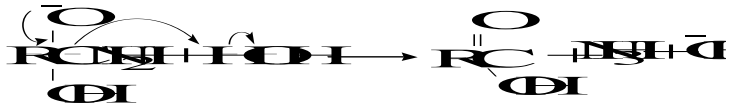


The mechanism for the base hydrolysis of amides is similar to that for the base hydrolysis of esters. In the mechanism, loss of nitrogen and transfer of proton from water to nitrogen are concerted so that the leaving group is ammonia, a weaker base and a better leaving group rather than amide ion ($NH_2^-$), a stronger base and a poorer leaving group. The mechanism is outlined below.

Step 1: Addition of hydroxide ion to the carbonyl carbon to give a tetrahedral carbonyl addition intermediate.




Step 2: Collapse of the tetrahedral carbonyl intermediate to form a carboxylic acid and ammonia.



Step 3: Proton transfer to form the carboxylate anion and water where the hydrolysis is driven to completion by the acid-base reaction

## (c) Acid (acyl) halides

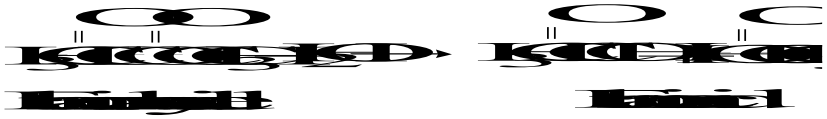
Acyl or acid halides are derivatives of carboxylic acids in which the hydroxyl group of the acid is replaced by a halogen. The most common ones are the acid chlorides.

Low-molecular-weight acid chlorides react very rapidly with water to form carboxylic acid and hydrogen chloride (HCl). Higher-molecular-weight acid halides are less soluble and consequently react less rapidly with water.

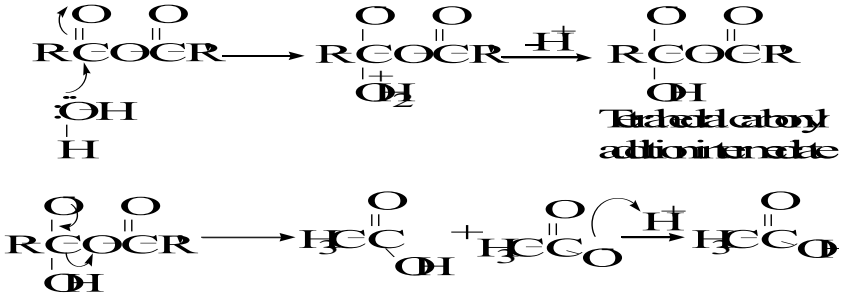
The carbonyl carbon is attacked by water directly leading to formation of tetrahedral carbonyl addition intermediate. The intermediate collapses to give hydrogen and chloride ions separately.

## (d) Acid anhydrides

These are organic compounds that have two acyl groups bonded to an oxygen atom. They are generally less reactive than acid chlorides. But lower molecular weight anhydrides readily react with water to form two molecules of carboxylic acids.

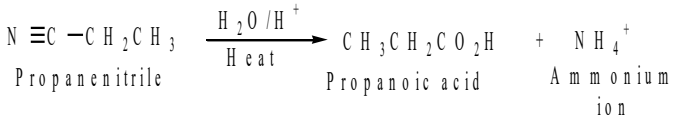


The mechanism is divided into two stages. The first one involves formation of the tetrahedral carbonyl addition intermediate and the second is the collapsing of the intermediate by elimination of acetate ion, which is a moderate base and a good leaving group.

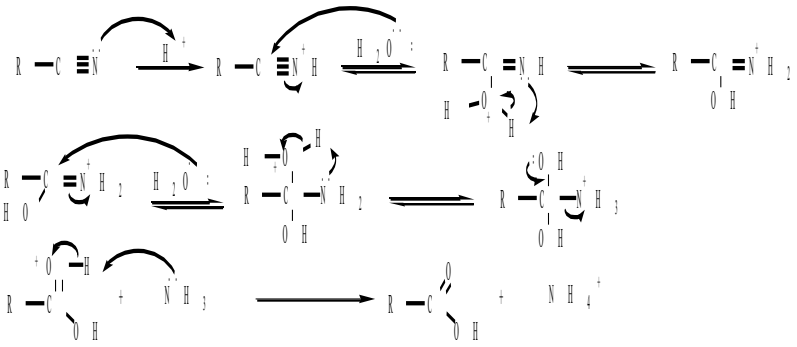


## (e) Nitriles

Organic compounds with a cyano (C≡N) group bonded to carbon are called nitriles compounds. The cyano group is hydrolyzed in aqueous acid to a carboxyl group and ammonium ion.

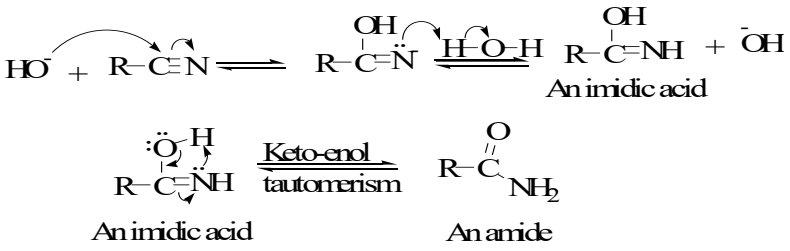


The mechanism involves addition of both hydrogen ions and water as the nitrogen-carbon bonds in the cyano group are removed as hydrogen atoms migrate from added water to nitrogen. The mechanism is illustrated below



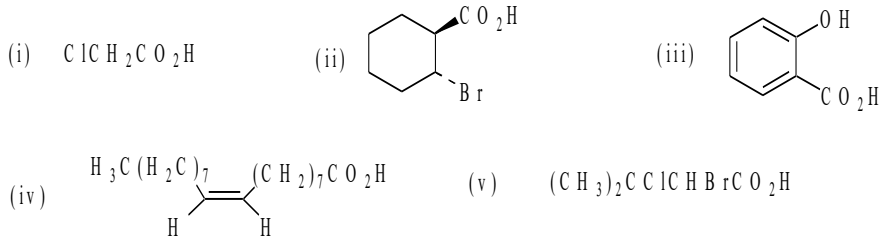
Nitrile compounds can also be hydrolysed in aqueous basic media. The products are a carboxylic acid anion and ammonia.

The basic hydrolysis involves initial formation of the anion of an imidic acid. Proton transfer from water leads to the intermediate undergoing keto-enol tautomerism to give an amide. Base hydrolysis of the amides was outline earlier to give carboxylic acid anion and ammonia.




## Study Questions

Q1. Write IUPAC names for the following compounds indicating stereochemistry where appropriate:




Q2. Draw structures of the following compounds:

(i) 3-methylbut-2-enoic acid
(ii) (Z)-3-Phenyl-2-pentenoic acid
(iii) 2-(N-Methylamino)propanoic acid

Q3. Ethanedioic acid has higher boiling point than ethanoic acid. Explain.

Q4. Using Curly arrows, write reaction mechanism of the following reactions:
(i) Acid hydrolysis of propanenitrile
(ii) Hydrolysis of butanoic methanoic anhydride
(iii) Base hydrolysis of ethyl ethanoate

## CHAPTER FIVE

# REACTIONS OF CARBOXYLIC ACIDS

## 5.1 Reaction with Bases

All carboxylic acids, whether soluble or insoluble in water, react with sodium hydroxide, potassium hydroxide and other strong bases to form water-soluble salts and water.

Sodium benzoate is a fungal growth inhibitor and often added to baked products. Carboxylic acids also react with sodium bicarbonate, ammonia and amines to form soluble salts. The reaction with sodium bicarbonate can be used to differentiate a carboxylic acid and phenol and alcohol, which are said to behave as acids. Phenol reacts with sodium hydroxide-a stronger base-but does not react with sodium bicarbonate-a weaker base. Alcohols on the other hand do not react with both sodium hydroxide and sodium bicarbonate.

Therefore a water insoluble compound that dissolves in aqueous sodium hydroxide but not in aqueous sodium bicarbonate is phenol. One that will dissolve with both is a carboxylic acid and one that does not dissolve in neither of the two is an alcohol.

**Note**. Salts of carboxylic acids are named in the same manner as salts of inorganic acids; the cation is named first and then the anion. The name of the anion is derived from the name of the carboxylic acid by dropping the suffix -**ic acid** and adding the suffix -**ate**.

## 5.2 Esterification of carboxylic acids

The reaction of a carboxylic acid with an alcohol by refluxing with in presence of an acid catalyst, commonly sulfuric acid, leads to formation of an ester. Esters have already been mentioned as derivatives of carboxylic acids, from which, acids are prepared by both acid and base hydrolysis. The method of formation of esters by the above method is known as **Fischer esterification**.

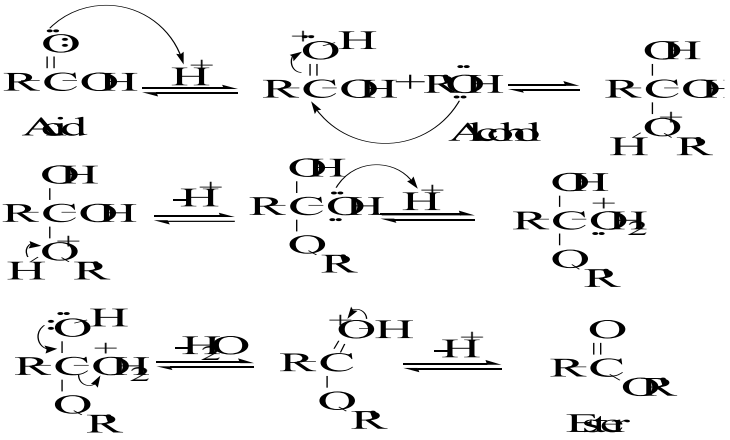
When acetic acid reacts with ethanol in presence of sulfuric acid forms ethyl acetate and water.

Acid catalyzed esterification is reversible with appreciable amounts of both the acid and alcohol at equilibrium. By control of the reaction conditions, it is possible to prepare the ester at high yield. If the alcohol is inexpensive compared to the carboxylic acid, a large excess of it can be used to drive the equilibrium to the right and achieve a high conversion of the carboxylic acid to its ester. Alternatively, water can be removed by azeotropic distillation and a Dean-Stark trap.

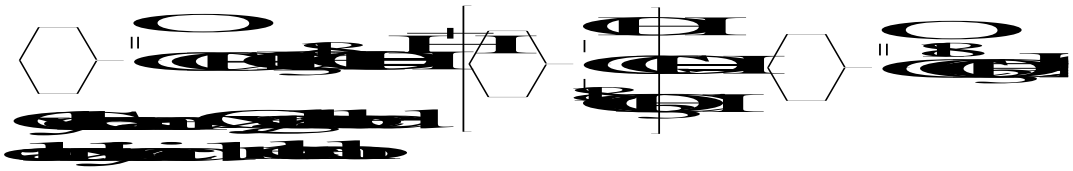
> Azeotrope is a liquid mixture with a constant composition and a boiling point that is different from that of any of its components. An azeotropic mixture boils at a constant temperature without change in composition.

The rate of esterification depends, on steric hindrance of both the alcohol and the carboxylic acid. For that methanol and methanoic acid would have higher reactivity as they are least hindered.

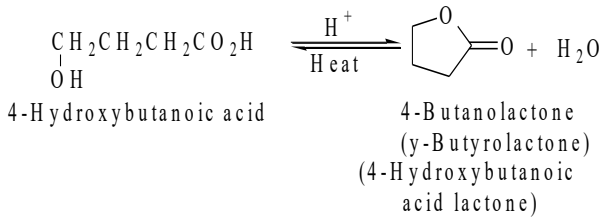
The reaction mechanism of esterification indicates protonation and deprotonation steps.



From the mechanism it is noted that the carbon-oxygen bond of the carboxylic acid and not oxygen-hydrogen nor carbon-oxygen bonds of the alcohol. When labeled alcohol $CH_3{}^{18}OH$ is used the $^{18}O$ stays with the methyl group.



Intra-esterification can take place when a hydroxylated carboxylic acid at γ or δ position with respect to carboxyl group is heated in presence of mineral acids like sulphuric acid. A **lactone**, cyclic ester is formed.




4-Hydroxybutanoic acid

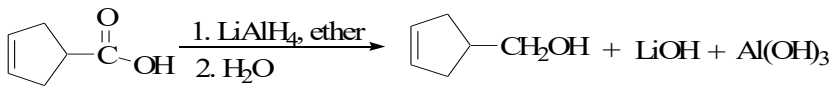
4-Butanolactone
(γ-Butyrolactone)
(4-Hydroxybutanoic
acid lactone)

5-Hydroxyhexanoic acid

5-Hydroxyhexanoic
acid lactone
(δ-Hexalactone)

## 5.3 Reduction of Carboxylic acids

The carboxyl group is one of the organic functional groups most resistant to reduction. It should be noted that, apart from carbon dioxide, carboxyl group is at its highest oxidation state. The group is not affected by catalytic hydrogenation under conditions that easily reduce aldehydes and ketones to alcohols. The most common reagent for the reduction of carboxylic acids to primary alcohols is the very powerful reducing agent lithium aluminium hydride ($LiAlH_4$). Carboxylic acids are not affected by the weaker sodium borohydride ($NaBH_4$). These hydrides do not affect a double bond unless it is conjugated to carbonyl functionalities.

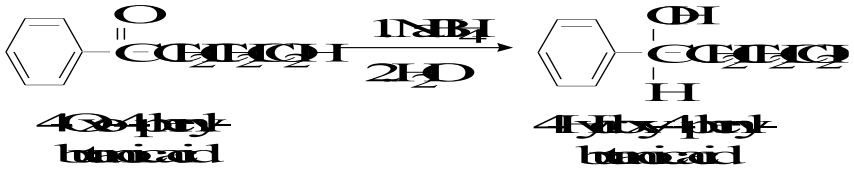



3-Cyclopentene
carboxylic acid

4-Hydroxymethyl-
cyclopentene

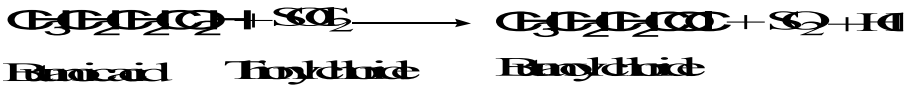
Selective reduction reaction can therefore take place affect one functionality leaving the other intact like the case above. Reduction of an aldehyde or ketone carbonyl group present

in a carboxylic compound can be carried out by use of catalytic reduction of by use of sodium borohydride. In both cases the carboxyl group is unaffected.

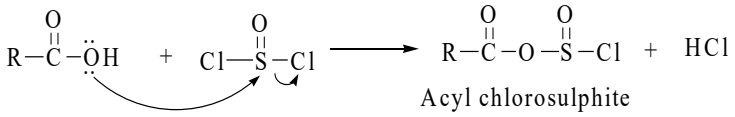


## 5.4 Acid (Acyl) halides formation

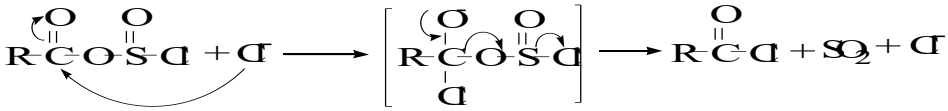
When a carboxylic acid is reacted with thionyl chloride ($SOCl_2$) an acyl or acid halide is formed.



The first step in the mechanism of the reaction involves formation of an acyl chlorosulphite, where the chlorosulphite group is a good leaving group.




The second step involves the attack by chloride ion on the carbonyl carbon of the acyl chlorosulphite to form a tetrahedral carbonyl addition intermediate, followed by its collapse to give the acid chloride

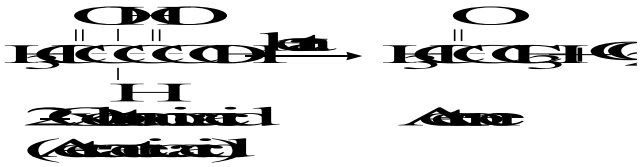


Carboxylic acids also react with phosphorus trichloride to form acyl halides.

It should be noted that a carboxylic acid with alpha (α) hydrogen(s) reacts with chlorine gas in presence of phosphorus trichloride to form alpha (α)-chloro acid. In this case phosphorus trichloride acts as a catalyst.

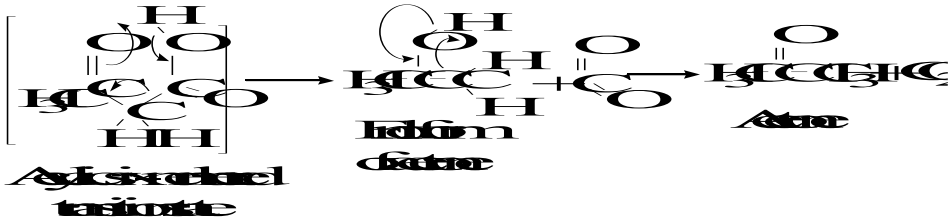
## 5.5 Decarboxylation of carboxylic acids

Decarboxylation is loss of carbon dioxide from the carboxyl group of a molecule. Almost all carboxylic acids when heated at high temperatures are bound to under go thermal decarboxylation. But at moderate heating carboxylic acids are resistant and melt or even boil without decarboxylation. However, exceptions are carboxylic acids that have a carbonyl group at beta (β) position with respect to the carboxyl group. When 3-oxobutanoic acid is heated moderately, it undergoes decarboxylation to give acetone and carbon dioxide.

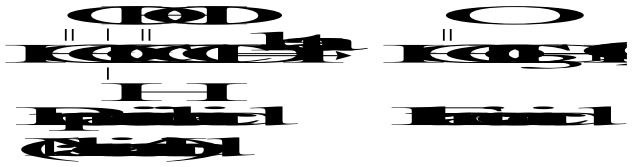


This is a unique property of 3-oxocarboxylic acids (β-ketoacids) and is not observed with other classes of ketoacids.

The mechanism of decarboxylation of a β-ketoacid involves rearrangement of six electrons in a cyclic six-membered transition state to give carbon dioxide and an enol. The enol is then converted to the keto form by keto-enol tautomerism.



Dicarboxylic acids (β-diacids) undergo similar reaction as the reaction is facilitated by the presence of any carbonyl group at the β position. Malonic acid and substituted malonic acids, for example, undergo decarboxylation on heating.



The mechanism is very similar to that of a β-ketoacid. The only difference is that the enol formed of carboxylic acid and rearranges itself to the form the carboxylic acid.

## CHAPTER SIX

# DERIVATIVES OF CARBOXYLIC ACIDS

## 6.1 Introduction

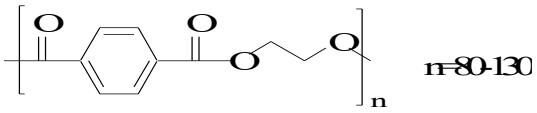
These are compounds that yield carboxylic acids upon reaction with water. They are: esters, amides, acid anhydrides, acid halides and nitriles. In nature esters are well represented by the waxes and fats and oils. Waxes are monoesters while fats and oils are triesters. Proteins represent amides as polyamides.

Acid halides are never found in nature while acid anhydrides are found rarely. They are readily attacked by water, thus would not be expected in the living cells of plants and animals. Cantharidin, a compound isolated from the Spanish fly, is an example of natural acid anhydride. It is toxic and irritant to the urinary tract. It is used to remove warts. The ancient Greek and Romans used dried flies as an aphrodisiac (substances, may it be drugs or foods, that excites sexual desires).

Cantharidin

## 6.2 Esters of Carboxylic Acids

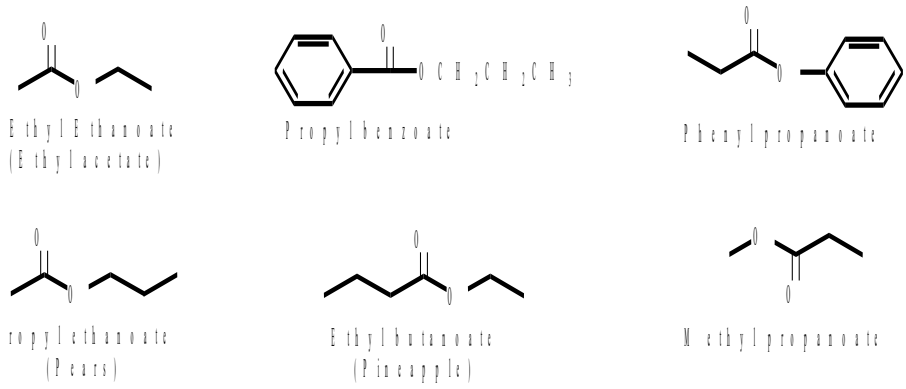
The functional group of a carboxylic acid ester is an acyl group bonded to –OR or –OAr. As mentioned earlier fats, oils and waxes have such groups, and represent esters in nature. Volatile esters give the pleasant aromas to many fruits and flowers. Some common synthetic polymers are esters, with a good examples being Dacron.



Dacron (Polyethylene terephthalate)

## 6.2.1 Nomenclature of Esters

Naming of esters is derived from the corresponding carboxylic acid. Like salts of carboxylic acids, esters are named by use of two words. The alkyl or aryl group bonded to oxygen is named first, followed by the name of the carboxylic acid in which the suffix '-ic acid' is replaced by the suffix –ate.

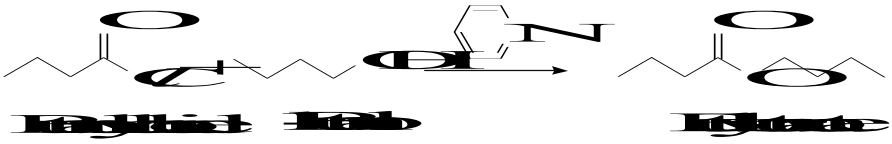



## 6.2.2 Preparation of Esters

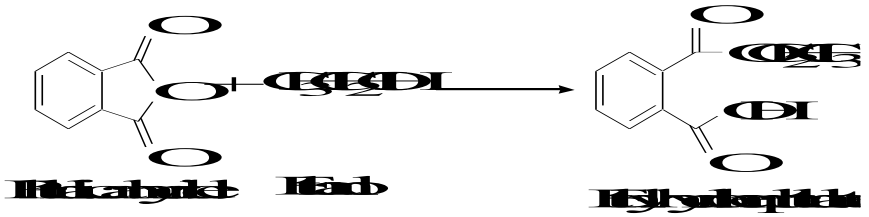
Esters can be prepared by use of various methods. The reaction between a carboxylic acid with an alcohol in presence of a mineral acid and heating leads to formation of an ester. As mentioned earlier this reaction is reversible, as same conditions are required to decompose the ester into the carboxylic acid and alcohol. Removal of any of the products would push the equilibrium to the right hand side. Normally water removed by azeotropic distillation.

4-Phenylbutanoic acid  Ethanol  Ethyl 4-phenylbutanoate

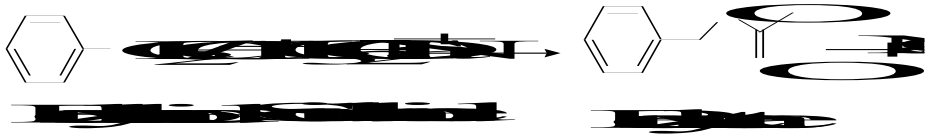
Acid (Acyl) halides react with alcohols to form the esters. The formed HX is normally removed by adding some amount of tertiary amine like pyridine.



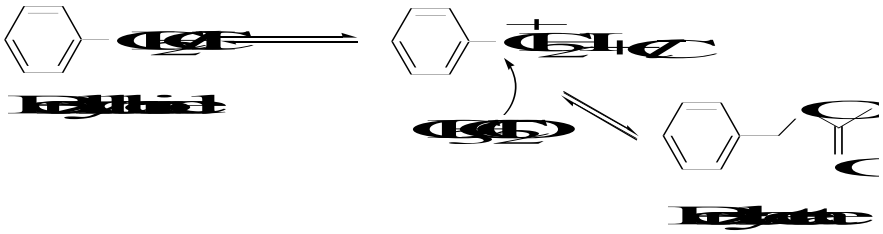
Esters can also be prepared by reacting acid anhydrides with alcohols.



The fourth method of preparing ester is the reaction of salts of carboxylic acid with alkyl halides.



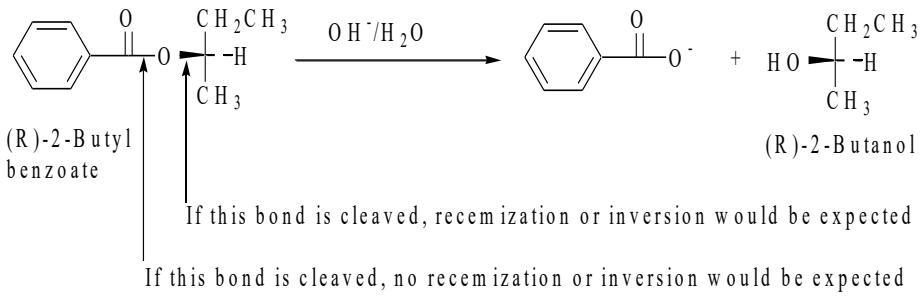
Reactive halides like tertiary or aromatic like benzyl chloride are preferred as the reaction is first order ($SN_1$ reaction).



## 6.2.3 Reactions of Esters

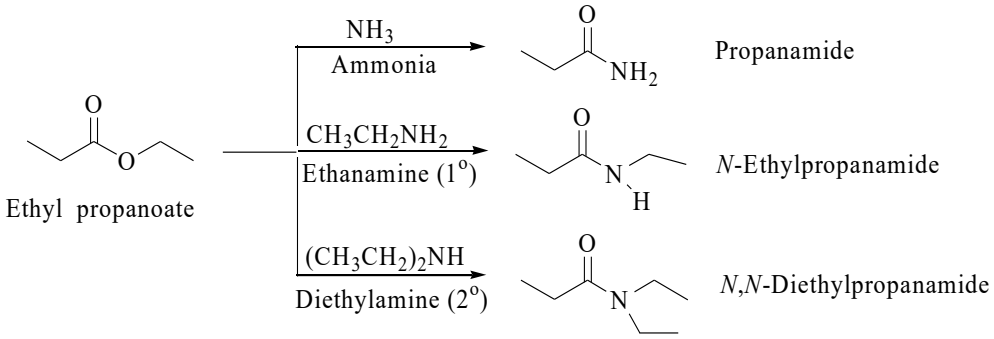
(**a**) **Hydrolysis**: Both acidic and basic hydrolysis of esters has been discussed earlier in the preparation of carboxylic acid. As mentioned, acidic hydrolysis is reversible while the basic hydrolysis is not. Alkaline hydrolysis is also termed as saponification because soap formation involves the method. In soap formation the carboxylic acid moiety has a long chained alkyl group.

**Note**: If the alcohol portion of the ester contains a chiral carbon, saponification proceeds with retention of configuration in the alcohol. This leads to the conclusion that carbonyl-oxygen bond is broken and not oxygen-alkyl bond.

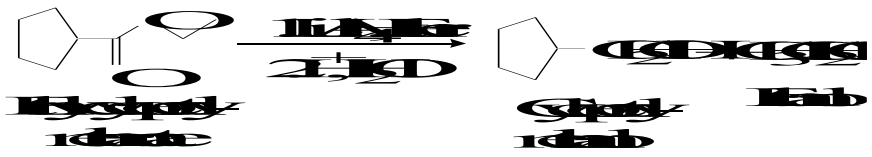



**(b) Transesterification:** This involves exchanging the alkyl or aryl group of a given ester in the alcohol moiety in presence of a mineral acid and heating. This can be done if there is need to introduce a bulkier alkyl group to an ester, to enhance boiling point, where the alkyl group is transferred from the alcohol.

**(c) Reaction with Ammonia, $1^0$ and $2^0$ amines:** As mentioned earlier, esters react with ammonia, primary and secondary amines to form corresponding amides. Note that in all cases alcohols are formed as the other product.

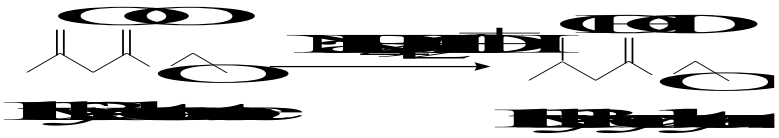



**(d) Reduction of Esters:** Esters react with lithium aluminum hydride ($LiAlH_4$) to form two alcohols: the one derived from the acyl group is primary alcohol and is usually the objective of the reduction.

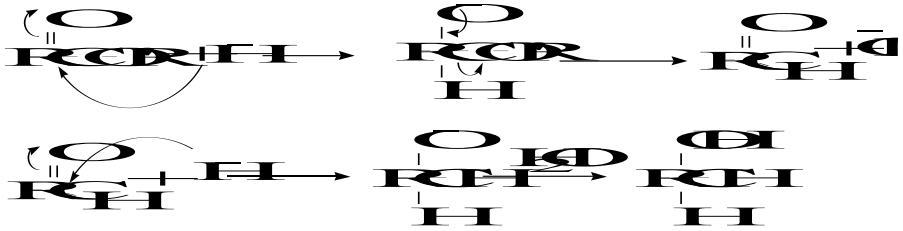


**Note**: Sodium borohydride ($NaBH_4$) is normally not used to reduce ester and other carboxylic acid derivatives because the reaction is very slow.

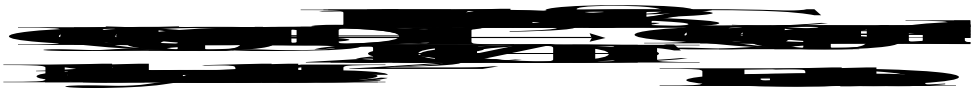
Lower reactivity of $NaBH_4$ towards esters makes it possible to effect reduction of a carbonyl of an aldehyde or ketone to an alcoholic group without reducing the carbonyl group of the ester or carboxylic acid in the same molecule.



Reduction of an ester by $LiAlH_4$ involves hydride ion transfer to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate. This intermediate then collapses by loss of alkoxide ion to give an aldehyde. A second hydride ion transfer to the new carbonyl group completes the reaction. Treatment of the resulting alkoxide ion with water or aqueous acid gives the product of the reduction.

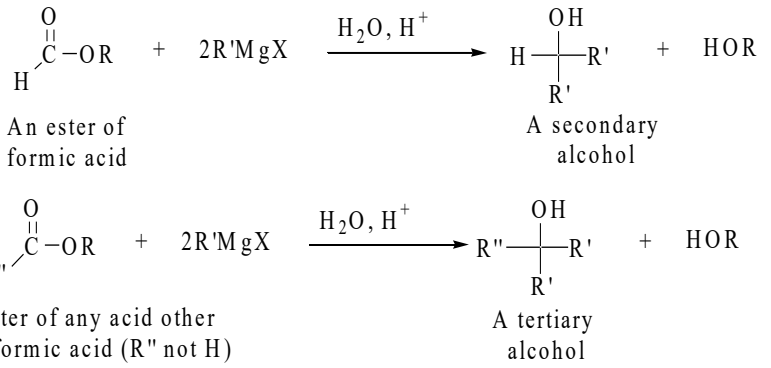


Modified hydride reducing agents like diisobutylaluminium hydride (DIBALH) have been used to reduce the acyl group of the ester to an aldehyde. The reactions are carried out in toluene or hexane at –78ºC (Dry/acetone temperature) followed by warming to room temperature and addition of aqueous acid to hydrolyze the aluminium salts and liberate the aldehyde. If the reaction is carried out at room temperature, the ester is reduced to a primary alcohol. At low temperature, the tetrahedral carbonyl addition intermediate does not eliminate alkoxide ion, and more reactive aldehyde is not formed until after workup, when the hydride ion has been destroyed. Thus, temperature control is critical for the selective reduction of an ester to an aldehyde.



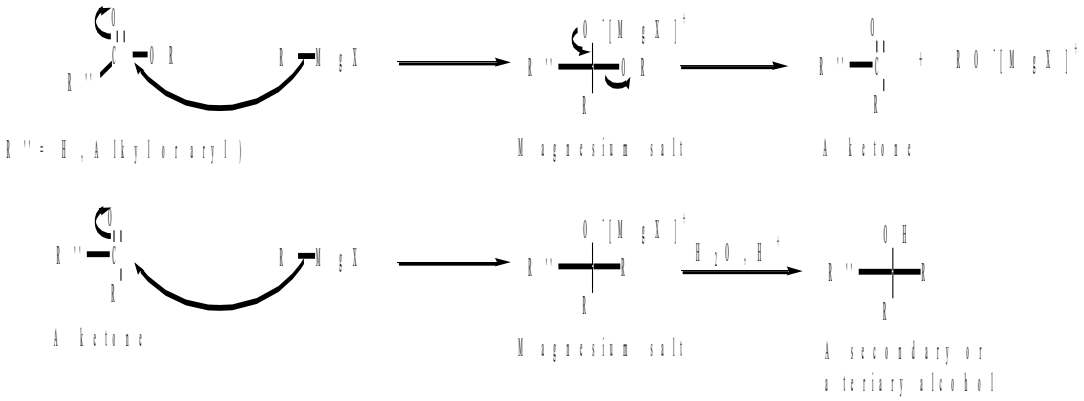
**(e)** **<u>Reaction with Grignard Reagent</u>**: Methanoic (formic) acid esters react with Grignard reagent followed by hydrolysis of the magnesium alkoxide salts in aqueous acid to give secondary alcohols as products of the acyl units of the esters. Other esters other

than methanoate react with Grignard reagent to give tertiary alcohols as products of the acyl units of the esters.



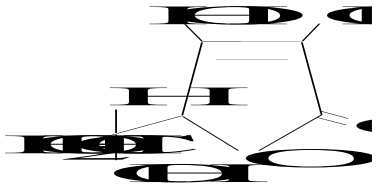

This is a double step reaction where the ester reacts with the one mole of Grignard reagent at the carbonyl carbon to form a tetrahedral carbonyl addition intermediate. As the alkoxide ion is a good leaving group, the addition intermediate collapses to give a carbonyl group containing compound and a magnesium salt.

The newly formed carbonyl compound then reacts with the other mole of Grignard reagent to form another tetrahedral carbonyl addition compound, which is hydrolyzed in aqueous acid to give the secondary or the tertiary alcohol.

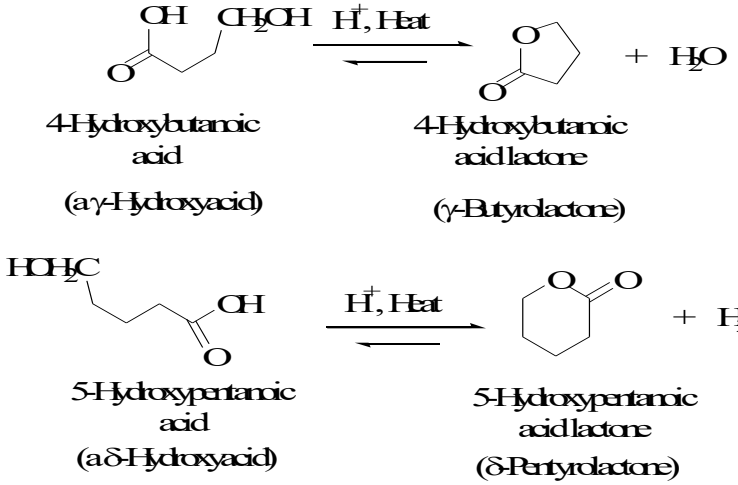


**Note:** The formed intermediate ketone is more reactive towards Grignard reaction than the ester, and therefore, esters cannot be used to prepare ketones using this method.

**(f) Lactones:** As mentioned earlier in the lactones are cyclic esters. A good example of a lactone is vitamin C (ascorbic acid).



Lactones are formed when carboxylic acids with γ or δ hydroxyl group undergo intramolecular esterification.



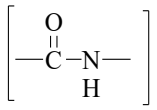

Carboxylic acids with hydroxyl groups at α or β positions do not form lactones. This is because of small strained rings that would result.

## 6.3 Amides

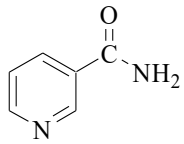
### 6.3.1 Introduction and nomenclature

Amides are compounds with trivalent nitrogen bonded to a carbonyl group. Amides are termed as derivatives of carboxylic acids because they yield carboxylic acid upon reaction with water (hydrolysis).

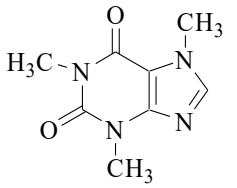
There are many compounds, which represent amides in nature. Proteins are compounds with polyamide (peptide) bonds. Many enzymes, biological catalysts, are proteins. Nicotinamide (a vitamin B) and Caffeine, a stimulant, are amides.



A peptide linkage in proteins

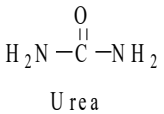


Nicotinamide

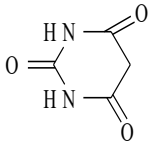


Caffeine

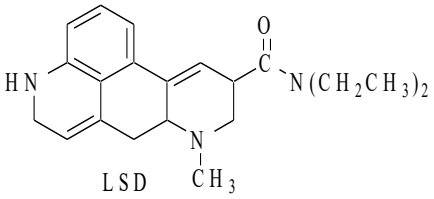
Urea, the major component of human urine, is also an amide. Higher animals excrete excess nitrogen in the metabolism of proteins as urea. It is used in synthesis of urea polymers. Barbiturate, a sedative, is made from urea. Lysergic acid diethylamide (LSD) also has an amide group.



Urea



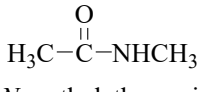
Barbiturate



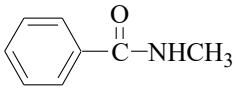
LSD

They are named by dropping the suffix -oic acid from name of parent carboxylic acid and adding –amide. If there is no substitution on the nitrogen, the amides are termed as primary (1°) amides.

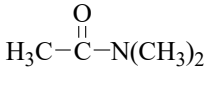
If the nitrogen atom of an amide is bonded to an alkyl or an aryl group, the group is named and its location on nitrogen is indicated by *N*- and is termed as secondary (2°) amides. Two alkyl or aryl groups are attached to nitrogen are indicated by *N,N*-di and are termed as tertiary (3°) amides. For that case, most peptides bonds of proteins are secondary amide links and lysergic acid diethylamide is a tertiary amide.



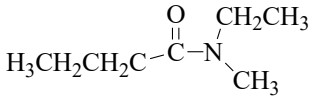
*N*-methylethanamide
($2^o$ amide)



*N*-Ethylbenzamide
($2^o$ amide)

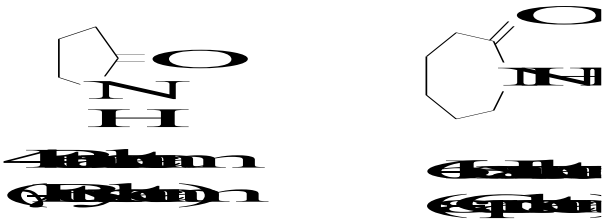


*N,N*-Dimethylethanamide
($3^o$ amide)

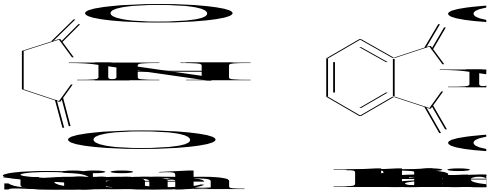


*N*-Ethyl-*N*-methylbutanamide
($3^o$ amide)

Cyclic amides are given a special name **lactams**. Caffeine is a good example of a lactam. Their names are derived in a manner similar to those of lactones, the cyclic esters, by replacing –lactone with –lactam.



When two acyl groups are bonded to nitrogen, the amide has a special name of **imide.** Barbiturate is a good example of an imide.



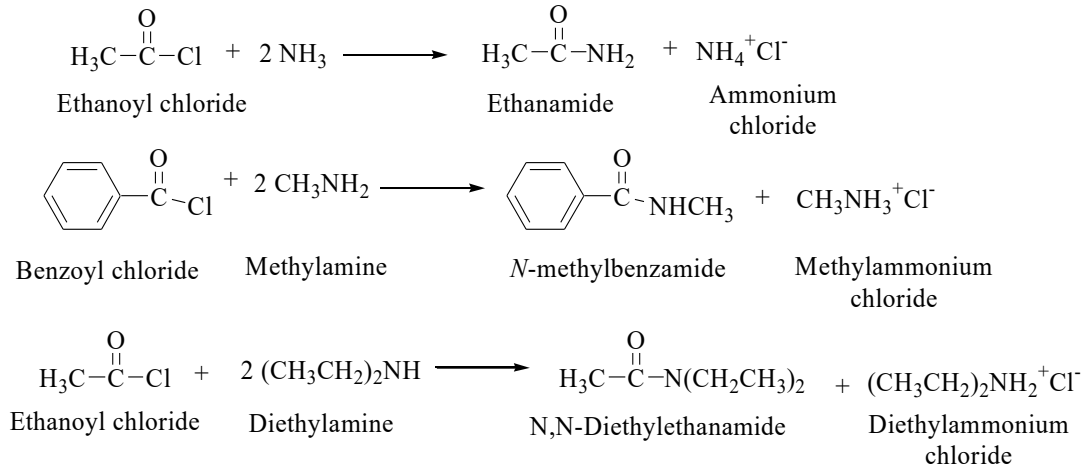
## 6.3.2 Preparation of amides

Amides are prepared from other derivatives of carboxylic acid (esters, acid halides and acid anhydride) reacted with ammonia or amines.

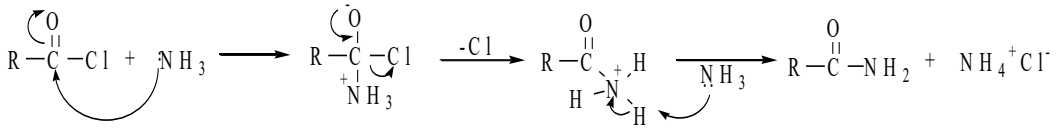
## (a) Amides from acid (acyl) halides

Acid halides react readily with ammonia, primary amine and secondary amines to form primary, secondary and tertiary amides, respectively.

**Note**: Two moles of ammonia or the amine are used; one to form the amide and the other to neutralize the hydrogen halide formed.

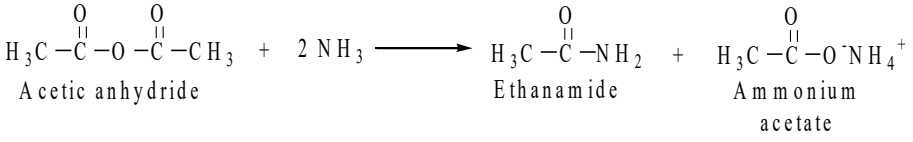



The mechanism of the reaction between acid halide and ammonia (or amine) starts with the addition of ammonia (or amine) to the carbon of carbonyl group.

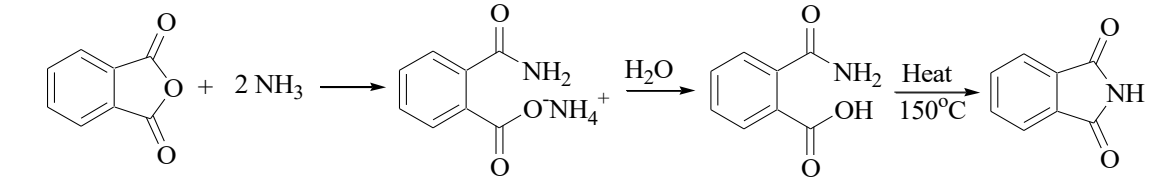


## (b) Amides from acid anhydrides

Acid anhydrides react with ammonia, primary amines and secondary amines to form primary, secondary and tertiary amides, respectively. As with acid halides, two moles are required: one to form the amide and the other to neutralize the carboxylic acid formed as by-product.




Cyclic acid anhydrides like phthalic anhydride reacts in a similar way but other derivatives of amides are formed thereafter as initial reaction involves ring opening. An ammonium salt of phthalamic acid is first formed. Hydrolysis of this salt forms phthalamic acid, a compound containing both amide and carboxylate groups. When phthalamic acid heated at 150-160$^{o}$C phthalimide, an imide, is formed.

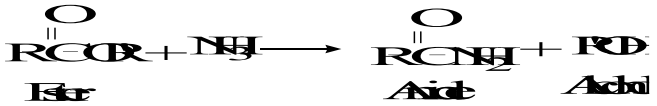



Phthalic anhydride | Ammonium salt of phthalamic acid | Phthalamic acid | Phthalimide

## (c) Amides from esters

Amides can also be prepared from esters. However, esters are less reactive towards ammonia, primary and secondary amines because an alkoxide anion is far poorer leaving group than either a halide ion (from acid halides) or a carboxylate ion (from acid anhydride). No extra mole of ammonia, primary or secondary amine is required here as the by-product is alcohol.

> **Note**: No extra mole of ammonia, primary or secondary amine is required in the reaction of esters because the byproduct is alcohol



Ester | Amide | Alcohol

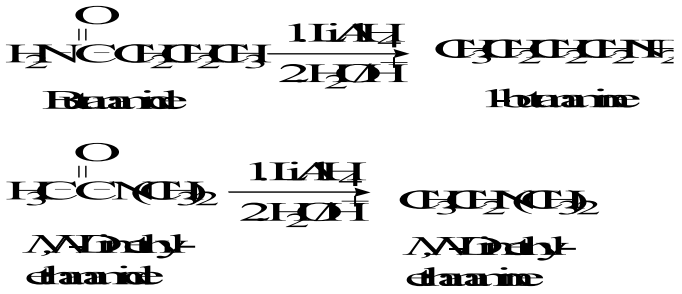
## 6.3.3 Reactions of amides

## (a) Reaction with water (hydrolysis)

See earlier notes on preparation of carboxylic acids.

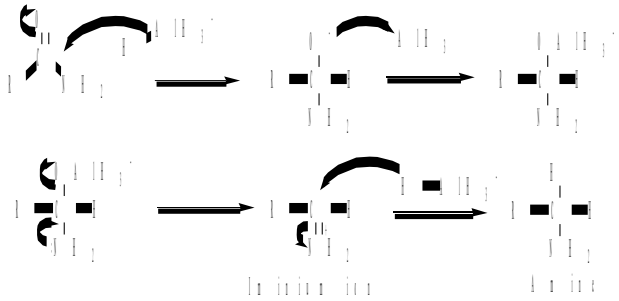
## (b) Reduction reaction

Amides are reduced by lithium aluminium hydride ($LiAlH_4$) to for primary, secondary or tertiary amines depending on the degree of substitution of the amide. Like other carboxylic acid derivatives, amides are not reduced by the sodium borohydride ($NaBH_4$).



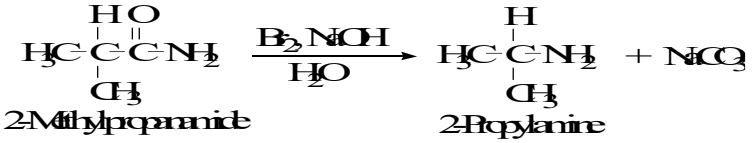
**Note**: Unlike other acid derivatives amides do not react with alcohols, ammonia, primary and secondary amines. They are termed as the least reactive of the functional derivatives of the carboxylic acids.

The mechanism involves transfer of the hydride from $AlH_4^-$ to the carbonyl carbon. Rearrangement of electron pairs leads to formation of iminium ion, which in turn takes another hydride to form the amine. $H_3AlO^-$ is a good leaving group.



## (c) The Hofmann Rearrangement

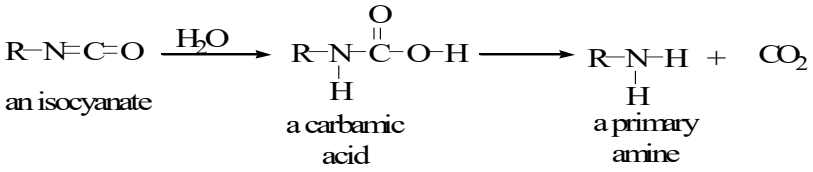
Primary amides react with bromine or chlorine in aqueous sodium or potassium hydroxide to form a primary amine with one carbon atom less. If the group involved is the chiral, then complete retention of configuration is realized.



The mechanism initially shows formation of an N-bromoamide through an amide anion after acid base reaction between the amide and the hydroxide ion.

The second step involves removal of second amide hydrogen followed by elimination of the bromine, as a bromide, to give an acyl nitrene, an unstable species containing a neutral, electron-deficient nitrogen atom. Migration of the alkyl or aryl group with its bonding electrons to nitrogen gives an isocyanate.

Third step involves the reaction of the isocyanate with water to form carbamic acid (functional group of a carboxyl group bonded to nitrogen). Carbamic acids are unstable species and undergo decarboxylation to give a primary amine and carbon dioxide, which is absorbed by the base to form carbonate.

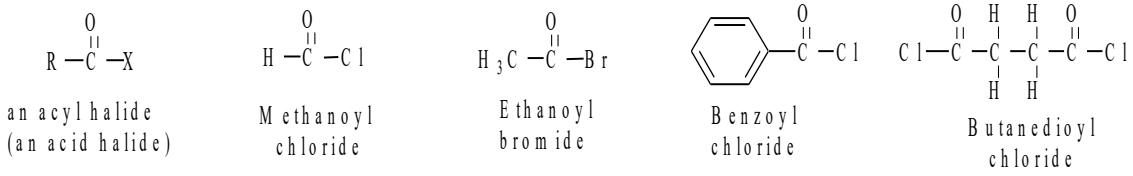



## 6.4 Acid halides

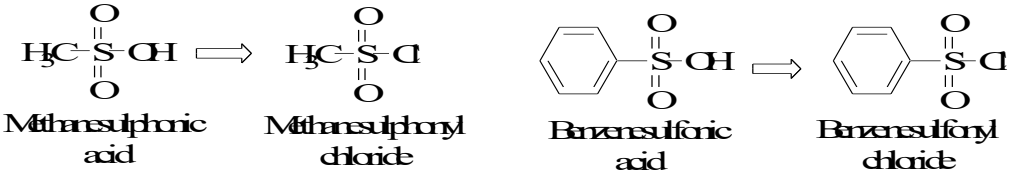
### 6.4.1 Introduction and Nomenclature

Acid (acyl) halides are derivatives of carboxylic acids in which the hydroxyl group of the carboxylic acid is replaced by a halogen, most commonly chlorine. The term acyl is used to represent a carbonyl group bonded to a hydrogen atom, an alkyl group or an aryl group. They are very reactive species that they are readily attacked by water, thus would not be expected in cells of plants and animals.

Acid halides are named by changing the suffix **–ic acid** in the name of the parent carboxylic acid to **–yl halide**.

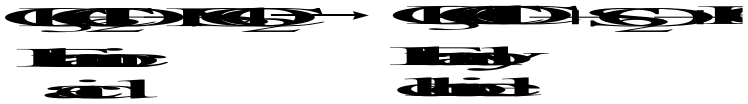



Sulphonic acids can also form acid halides. Replacement of the hydroxyl group in a sulphonic acid by chlorine forms **sulphonyl (sulphonyl) chloride**.




## 6.4.2 Preparation of acid halides

Reaction of carboxylic acids and thionyl chloride ($SOCl_2$) or phosphorus trichloride ($PCl_3$) lead to formation of acid chlorides. [For reaction mechanism see earlier notes on reactions of carboxylic acids]



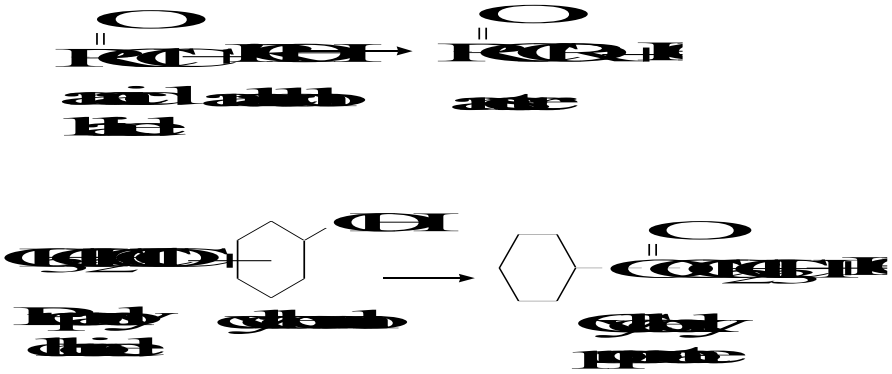
## 6.4.3 Reactions of acid halides

### (a) Reaction with water

Acyl halide, as mentioned earlier, reacts readily with water to form corresponding carboxylic acid. However, higher-molecular-weight acid halides are less soluble and consequently react less rapidly with water.

## (b) Reaction with alcohols

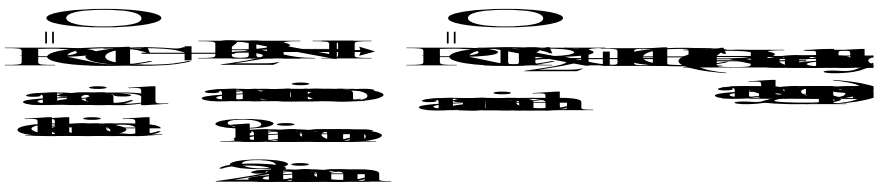
Acid halides react with alcohols to form esters. Although alcohols are weak nucleophiles, acid halides are so reactive that no mineral acid catalyst is required for the reactions.



When the alcohol or the resulting ester is sensitive to acid (HCl formed), the reaction is carried out in the presence of a tertiary amine to neutralize the HCl as it is formed. Amines mostly used for this purpose are pyridine and triethylamine.

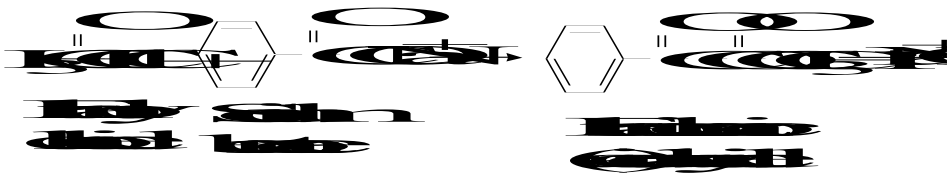
## (c) Reaction with ammonia and amines

Acid halides react readily with ammonia and primary or secondary amines to form amides. As was mentioned in preparation of amides, two equivalents of ammonia or amine are used; one to form the amide and the other to neutralize the hydrogen chloride formed. [For the reaction mechanism see earlier notes on preparation of amides].



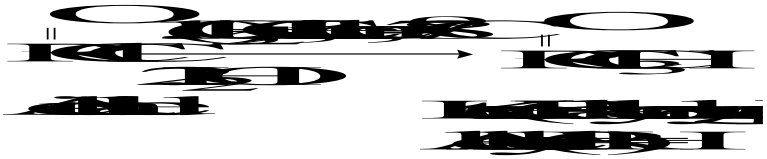
## (d) Reaction with salts of carboxylic acids

Sodium or potassium salts of carboxylic acids react with acid halides to form acid anhydrides. This reaction is of importance in preparation of mixed acid anhydride.



## (e) Reaction with lithium diorganocopper

Acid halides react with lithium diorganocopper (Gilman) reagent to give ketones. The reaction is carried out at –78°C in tetrahydrofuran (THF) or diethyl ether. Hydrolysis thereafter leads to formation of the ketone.



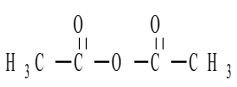
Under the above conditions the ketone (or aldehyde) does not react further. This contrasts the reaction of an ester with Grignard reagent where the intermediate ketone reacts with second mole of the Grignard reagent to give an alcohol. The reason for difference in reactivity is that the tetrahedral carbonyl intermediate is stable at –78°C and thus survives until the later to decompose to the ketone. These reagents of $R_2CuLi$ readily react with only acid chlorides. They do not react with esters, amides, acid anhydride or nitriles. Therefore, they can selectively react with the acid halide group leaving an ester group intact.

# 6.5 Acid anhydrides

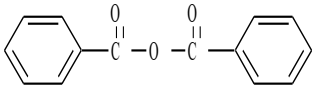
## 6.5.1 Nomenclature of acid anhydrides

Carboxylic acid anhydrides are organic compounds with two acyl groups bonded to an oxygen atom. They are called acid anhydrides because they are formally derived from two molecules of carboxylic acids losing a molecule of water. Symmetrical acid anhydrides are those with similar or identical acyl group. In other words they are made from identical carboxylic acids. Mixed acid anhydride has different acyl group or made from two different acids.

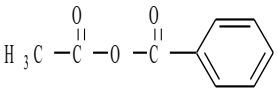
Acid anhydrides are named by replacing the word acid in the parent carboxylic acid by the word anhydride.



Ethanoic anhydride

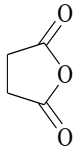


Benzoic anhydride

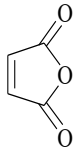


Ethanoic benzoic anhydride

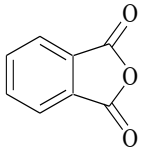
Cyclic acid anhydrides are named from the dicarboxylic acid from which they are derived. The most important three are shown below that are derived from butanedioic acid, 2-butenedioic acid and 1,2-benzenedioic acid, respectively.



Succinic anhydride
(Butanedioic anhydride)



Maleic anhydride
(2-Butenedioic anhydride)



Phthalic anhydride
(1,2-Benzenedioic anhydride)

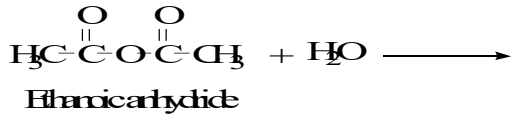
## 6.5.2 Preparation of acid anhydrides

Acid anhydrides are prepared from acid halides when reacted with carboxylic acid salts. [See reactions of acid halides]

## 6.5.3 Reactions of acid anhydrides

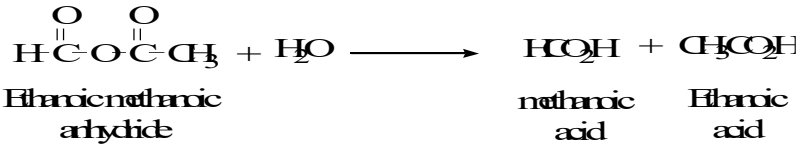
### (a) Reaction with water: Hydrolysis

They react with water to form two molecules of carboxylic acid. If the acid anhydride is symmetrical two identical carboxylic acids are formed. If it is a mixed acid anhydride, two different acids are formed. [For the mechanism see preparation of carboxylic acids].



Ethanoic anhydride

Ethanoic acid



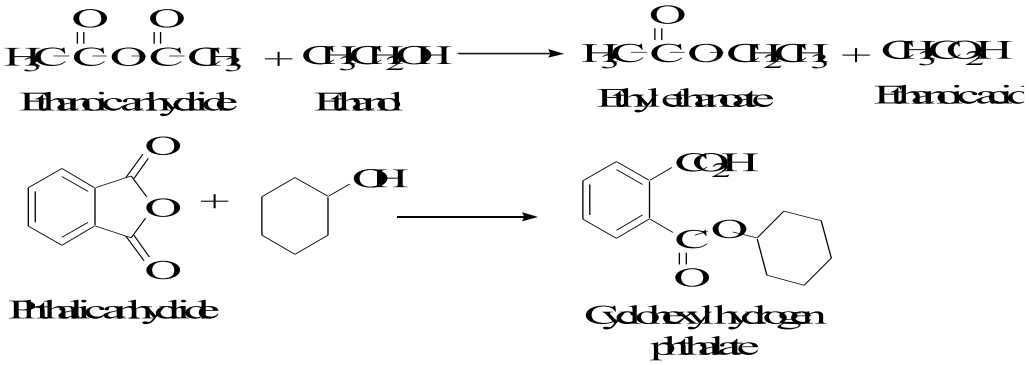
Ethanoic methanoic anhydride

methanoic acid

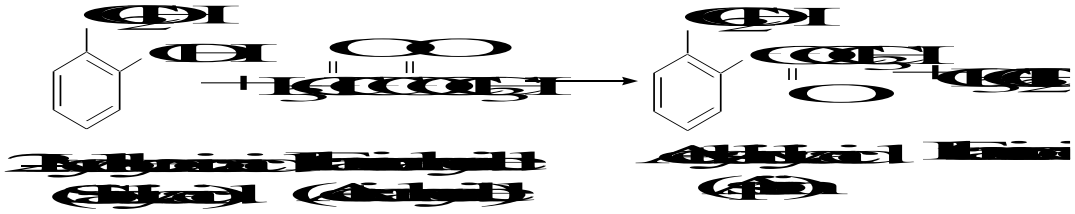
Ethanoic acid

### (b) Reaction with alcohols

Acid anhydrides react with alcohols to form one mole of ester and one mole of carboxylic acid. The reaction is not reversible and does not require mineral acid catalyst. It is therefore a useful method for synthesis of esters.



Aspirin is synthesized on industrial scale by the reaction of acetic anhydride and salicylic acid.



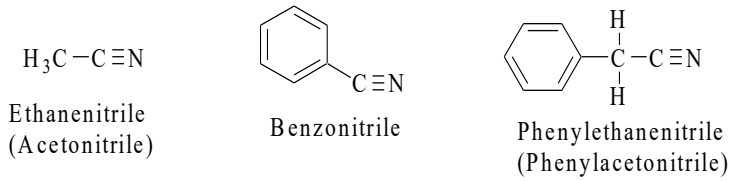
**(c) Reaction with ammonia and amines**

Acid anhydrides react with ammonia, primary amines and secondary amines to form primary amides, secondary amides and tertiary amides, respectively. [See notes on preparation of amides].

## 6.6 Nitriles

### 6.6.1 Introduction and nomenclature

Nitriles are compounds with a cyano (C≡N) group bonded to a carbon or to alkyl group. IUPAC naming of the nitriles is by adding the suffix –**nitrile** to the parent alkane. However, common names are derived by dropping the suffix –ic or oic from the name of the parent carboxylic acid and adding the suffix –**onitrile**.



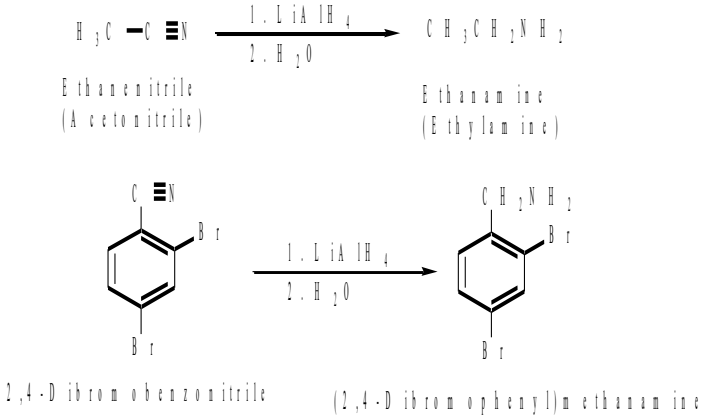

## 6.6.2 **Reactions of Nitriles**

### (a) Reaction with water (Hydrolysis)

The cyano group is hydrolyzed in aqueous acid form a carboxyl group and ammonium ion. In aqueous base, the cyano group is hydrolyzed to carboxylic acid anion and ammonia. [For equations and mechanisms for the reactions see earlier notes on preparation of carboxylic acids].

### (b) Reduction reactions

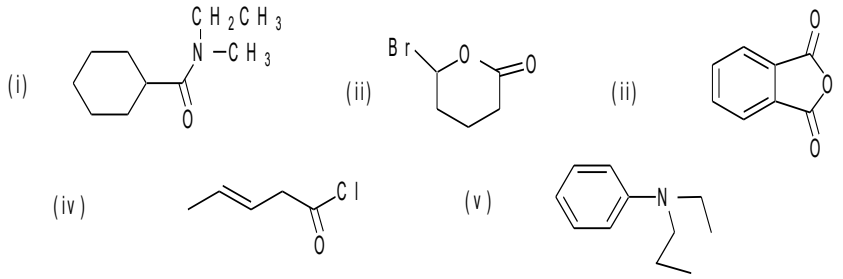
The cyano group reacts with lithium aluminium hydride ($LiAlH_4$) to form primary amino group.




## Study Questions

Q1.

(b) Write systematic names for the following compounds.




(c) Draw structures of each of the following compounds.

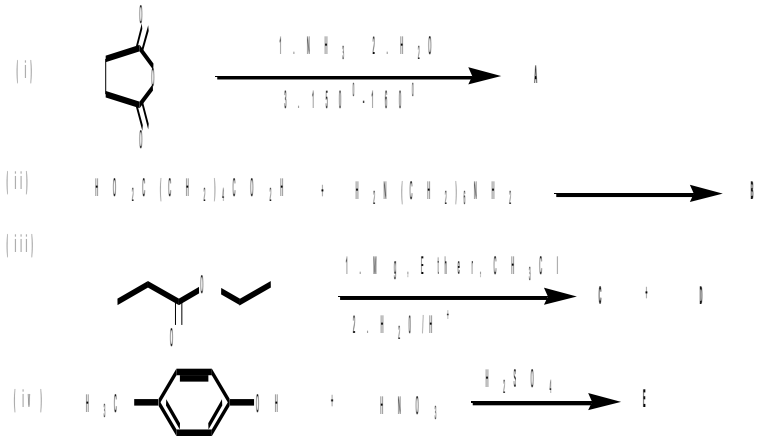
(i) Phenyethanenitrile (ii) 2-Butenedioc acid anhydride
(iii) 4-bromo-5-chloro-2-nitrophenol (iv) Benzyl ethanoate
(v) Ethyldimethylphenylammonium nitrate

Q2.

(c) Explain the following using appropriate equations, structures or resonance structures where applicable.

(i) Amines are more basic than amides and the basicity of an amine depends on the number of alkyl groups attached to nitrogen.
(ii) Amino groups in aniline, is *ortho-para* directors and activate benzene towards electrophilic substitution reactions.
(iii) Presence of an electron donating group at *ortho* or *para* positions reduce the acidic of phenol.

(d) Identify the major organic products A to E in the following transformations.



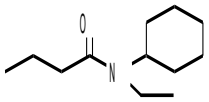
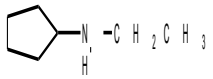

Q3

(b) Using Curly arrows, write possible reaction mechanisms for the following reactions.

(i) Hydrolysis of ethanoic methanoic anhydride.
(ii) Acid hydrolysis of propanenitrile.

Q4. (a) Write systematic names for the following compounds.

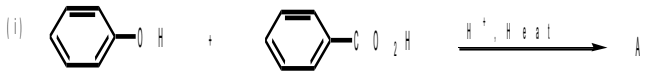
(i) $CH_2BrCHBrCO_2H$ (ii) $(CH_3)_3CCOCl$

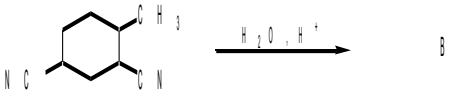
(iii)  (iv) 

(b) Draw structures of each of the following compounds.

(i) 1,3-Butanediamine
(ii) 2,2,3-Trichloropentanenitrile
(iii) Ethyl 3-methyl-3-butenoate
(iv) 4-Hydroxy-3-methylbutanoic acid lactone

Q5. Predict the major organic products A to D in the following transformations.

(i) 

(ii) 

(iii) 

(iv) 

Q6. Explain the following using appropriate equations and/or structures.
Boiling points of propylamine, *N*-methylethylamine and *N*,*N*,*N*-trimethylamine are 48, 37 and $3^0$C, respectively.

Q7. Using Curly arrows, write possible reaction mechanisms for the following reactions.