UNIT 15 MONOCARBOXYLIC AND SULPHONIC ACIDS

Structure

15.1 INTRODUCTION

Carboxylic acids are the compounds which contain the **carboxy** ($-\overset{\overset{O}{\|}}{C}OH$) functional group and can be represented either as $R\overset{\overset{O}{\|}}{C}OH$ or as RCOOH. The carboxylic acids not only form an important class of organic compounds but are also the parent compounds of a large group of compounds called the functional derivatives of carboxylic acids which can be further classified as acid halides, acid anhydrides, acid amides and esters. These classes of compounds will be discussed in Unit 17. Carboxylic acids also play an important role in various biological processes. In Unit 16, you will study about some such acids

Besides carboxylic acids, there is another important class of organic acids, called **sulphonic acids.** The sulphonic acids are the compounds which contain a $-SO_3H$ group, called the **sulphonic acid group.** Sulphonic acids are organic acids related to sulphuric acid. Sulphonic acids and carboxylic acids are closely related in their chemistry. Therefore, in this unit, we will first study the chemistry of carboxylic acids and then that of the sulphonic acids.

Objectives

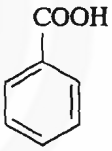
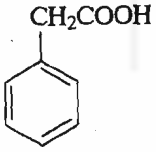
After studying this unit, you should be able to:

- list various methods of preparation of carboxylic acids,
- outline the synthesis of various carboxylic acids using the above methods starting from appropriate starting materials,
- predict and correlate the physical properties such as melting point, boiling point, solubility and spectral characteristics of carboxylic acids with their structures,
- describe the reactions of carboxylic acids,
- explain the preparation and reactions of sulphonic acids,
- describe the importance and uses of carboxylic and sulphonic acids, and
- explain how carboxylic and sulphonic acids can be identified in laboratory.

15.2 CARBOXYLIC ACIDS

You have already come across carboxylic acids in Unit 1. There you studied the nomenclature of monocarboxylic and dicarboxylic acids. Before studying the chemistry of monocarboxylic acids you can refresh your memory by going through the list of carboxylic acids given in Table 15.1.

Table 15.1 : Some Carboxylic Acids

Structure	IUPAC Name	Common Name
$HCOOH$	Methanoic acid	Formic acid
CH_3COOH	Ethanoic acid	Acetic acid
CH_3CH_2COOH	Propanoic acid	Propionic acid
$CH_3(CH_2)_2COOH$	Butanoic acid	Butyric acid
$CH_3(CH_2)_3COOH$	Pentanoic acid	Valeric acid
$CH_3(CH_2)_4COOH$	Hexanoic acid	Caproic acid
$CH_3(CH_2)_5COOH$	Heptanoic acid	Enanthic acid
$CH_3(CH_2)_6COOH$	Octanoic acid	Caprylic acid
$CH_3(CH_2)_7COOH$	Nonanoic acid	Pelargonic acid
$CH_3(CH_2)_8COOH$	Decanoic acid	Capric acid
$CH_3(CH_2)_{10}COOH$	Dodecanoic acid	Lauric acid
$CH_3(CH_2)_{12}COOH$	Tetradecanoic acid	Myristic acid
$CH_3(CH_2)_{14}COOH$	Hexadecanoic acid	Palmitic acid
$CH_3(CH_2)_{16}COOH$	Octadecanoic acid	Stearic acid
	Benzenecarboxylic acid	Benzoic acid
	Phenylethanoic acid	Phenylacetic acid

Aliphatic acids are also referred to as **fatty acids** because many of them were first obtained by the hydrolysis of fats and oils of vegetable or animal origin. Let us now study how monocarboxylic acids can be prepared.

15.3 PREPARATION OF MONOCARBOXYLIC ACIDS

Let us first have a look at Table 15.2 where various methods which can be used to prepare monocarboxylic acids have been listed. We will then discuss each one of them in more detail.

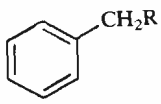
Table 15.2 : Some Methods of Preparation for Carboxylic Acids

1. **Oxidation of Alkenes**

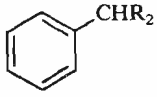
$$RCH = CHR' \xrightarrow[2.\ H^+,\ H_2O]{1.\ KMnO_4,\ OH^-,\ \Delta} RCOOH + R'COOH$$

$$RCH = CR'_2 \xrightarrow[2.\ H^+,\ H_2O]{1.\ KMnO_4,\ OH^-,\ \Delta} RCOOH + R'_2C = O$$

2. **Side-Chain Oxidation of Alkylbenzenes**

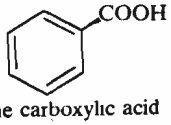


or



alkylbenzene

$\xrightarrow[2.\ H^+,\ H_2O]{1.\ KMnO_4,\ OH^-,\ \Delta}$



arene carboxylic acid

Other oxidising agents used are $Na_2Cr_2O_7$ and CrO_3, etc.

3. **Oxidation of Primary Alcohols**

$$\underset{\text{primary alcohol}}{R - CH_2OH} \xrightarrow[K_2Cr_2O_7,\ H_2SO_4]{KMnO_4 \text{ or}} \underset{\text{carboxylic acid}}{RCOOH}$$

4. **Oxidation of Aldehydes**

$$RCHO \xrightarrow[2.\ H^+,\ \text{heat}]{1.\ Ag_2O \text{ or } Ag(NH_3)_2^+\ OH^-} RCOOH$$

Other oxidising agents like $KMnO_4$ and chromic acid can be used.

5. **Oxidation of Methyl Ketones (Haloform reaction)**

$$RCCH_3 \xrightarrow[OH^-]{X_2} [RCOCX_3] \xrightarrow[2.\ H^+,\ H_2O]{1.\ OH^-} RCOOH + CHX_3$$

(O)

6. **Carbonation of Organometallic Reagents**

$$RMgX \xrightarrow{CO_2} RCO_2MgX \xrightarrow{H_2O,H^+} RCOOH + Mg(OH)X$$

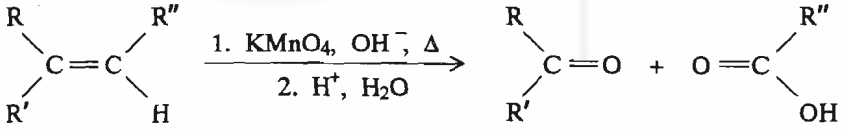
$$RLi \xrightarrow{CO_2} RCO_2Li \xrightarrow{H_2O,H^+} RCOOH$$

7. **Hydrolysis of Nitriles**

$$\underset{\text{nitrile}}{R - C{\equiv}N} \xrightarrow[H^+ \text{ or } OH^-]{H_2O} \underset{\text{amide}}{RCONH_2} \xrightarrow[H^+ \text{ or } OH^-]{H_2O} RCOOH$$

1. Oxidation of Alkenes

Basic potassium permanganate cleaves alkenes to two carbonyl compounds. If one of the substituents at the double bond is hydrogen, the cleavage product is an aldehyde which is rapidly oxidised to a carboxylic acid under the reaction conditions, i.e.



alkene ketone carboxylic acid

In this oxidation, each carbon of the double bond becomes the carbon atom of the carbonyl group and a hydrogen substituent on the double bond is replaced by a hydroxyl group.

Since the carboxylic acids are formed in these reactions as their potassium carboxylate salts, the acidification step is necessary in order to isolate the product as free acid.

The intermediate in this reaction may be a diol which is oxidised further with the cleavage of carbon-carbon bond.

The terminal CH_2 group of 1-alkene is completely oxidised to carbon dioxide and water. For example,

$$\underset{\text{1-tridecene}}{CH_3(CH_2)_{10}CH{=}CH_2} \xrightarrow[2.\ H^+,\ H_2O]{1.\ KMnO_4,\ OH^-,\ \Delta} \underset{\substack{\text{dodecanoic acid}\\(84\%)}}{CH_3(CH_2)_{10}COOH} + CO_2 + H_2O$$

Potassium permanganate is a dark purple crystalline solid which dissolves in water to give intense purple coloured solution. In permanganate anion, MnO_4^-, manganese has an oxidation state of +7. When used as an oxidising agent in basic solution, manganese reduces to MnO_2 which is obtained as brown precipitate. The oxidation state of Mn in MnO_2 is +4.

You may recall that alkenes can be oxidised to diols using cold dilute $KMnO_4$ (sub-Sec. 7.6.6, Unit 7, Block 2).

The terminal carbon of 1-alkenes contains two hydrogens on it, so it is oxidised to carbonic acid which is present as its potassium salt, i.e. potassium carbonate. This on acidification yields carbonic acid which decomposes into carbon dioxide and water.

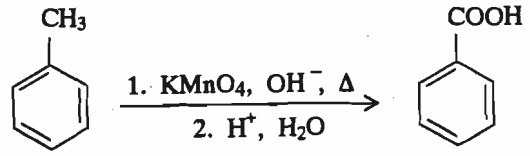
$$\underset{\substack{\text{potassium}\\\text{carbonate}}}{KOCOK} \xrightarrow{H^+} \underset{\substack{\text{Carbonic}\\\text{acid}}}{HOCOH} \longrightarrow \underset{\substack{\text{Carbon}\\\text{dioxide}}}{CO_2} + \underset{\text{water}}{H_2O}$$

Note that the acid produced from the terminal alkene contains one carbon less than the alkene.

2. Side Chain Oxidation of Alkylbenzenes

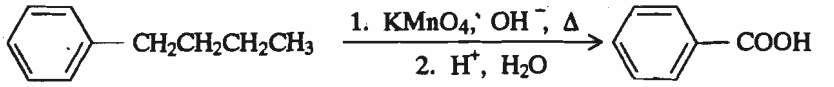
Aromatic carboxylic acids can be obtained by the oxidation of alkylbenzenes. The oxidation can be carried out by using potassium permanganate, Cr^{6+} derivatives such as sodium dichromate or aqueous nitric acid.

Note that the alkyl chain, regardless of length, is oxidised to a –COOH group. However, *tert*-alkyl substituents do not undergo oxidation under these conditions.



methylbenzene (toluene)

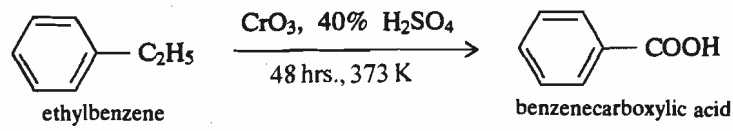
benzenecarboxylic acid (benzoic acid) (100%)



butylbenzene

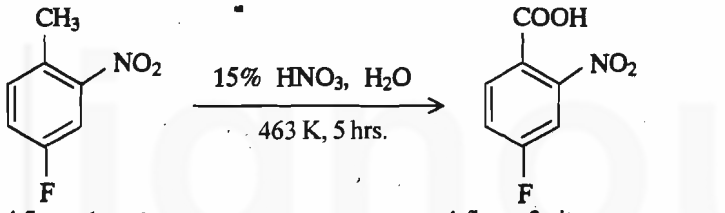
benzenecarboxylic acid

Side-chain oxidation of alkylbenzenes is important in certain metabolic processes. One way in which the body gets rid of foreign substances is by oxidation in the liver to compounds which are more easily excreted in the urine. Methylbenzene, for example, is oxidised to benzenecarboxylic acid which is easily eliminated.



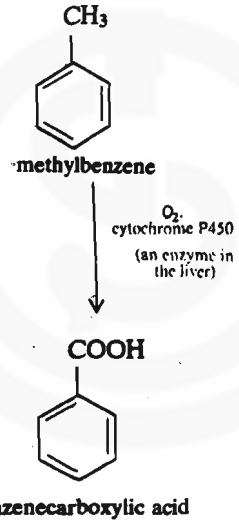
ethylbenzene

benzenecarboxylic acid



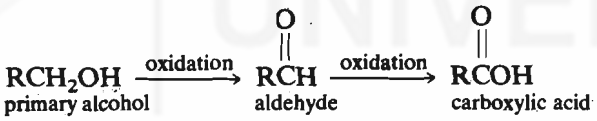
4-fluoro-1-methyl-2-nitrobenzene

4-fluoro-2-nitro-benzenecarboxylic acid (69%)

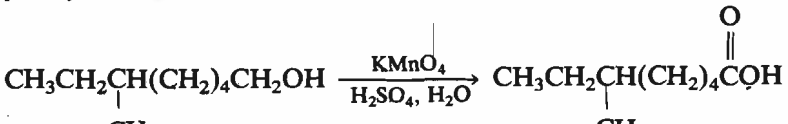


3. Oxidation of Primary Alcohols

You have studied in Block 3, Unit 12, sub-Sec. 12.6.2 that primary alcohols can be oxidised to carboxylic acids using $KMnO_4$, CrO_3, nitric acid etc. The carboxylic acid obtained contains the same number of carbon atoms as present in the starting alcohol. The initial product of oxidation is an aldehyde. However, when aqueous $KMnO_4$ is used, the aldehyde is rapidly oxidised and the carboxylic acid is obtained as the product.



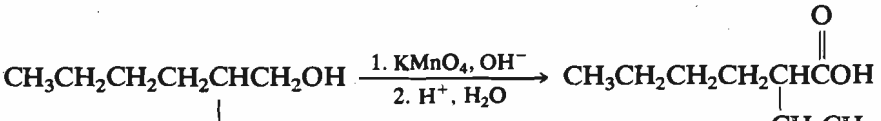
primary alcohol — aldehyde — carboxylic acid



6-methyl-1-octanol

6-methyloctanoic acid (66%)

When oxidation is carried out under basic conditions, the carboxylic acid is obtained as the carboxylate salt which on acidification yields carboxylic acid.

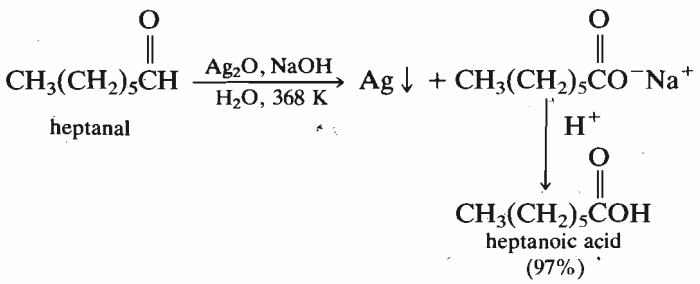


2-ethyl-1-hexanol

2-ethylhexanoic acid (74%)

4. Oxidation of Aldehydes

Aldehydes are readily oxidised to carboxylic acids by strong oxidising agents such as $KMnO_4$, CrO_3 and HNO_3 as discussed above. A mild oxidising agent used for this oxidation is moist silver oxide suspended in an aqueous base.



heptanal

heptanoic acid
(97%)

Silver oxide is usually prepared by mixing a solution of silver nitrate with sodium hydroxide. The precipitate obtained is filtered, washed with water and used as an aqueous suspension.

In this reaction, Ag(I) is reduced to metallic silver. When the reaction is carried out in a clean test-tube, a mirror is deposited on the walls of the tube. This reaction forms the basis of the *Tollens' test.*

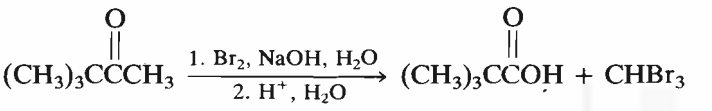
Tollens' test is a qualitative test for aldehydes. The compound is treated with ammoniacal silver nitrate in a clean test tube. Formation of a shiny mirror of silver on the walls of the test tube is taken as a positive indication of the presence of an aldehyde or other easily oxidisable group.

Silver oxide selectively oxidises the aldehyde functional group and the other sensitive groups such as double bonds and triple bonds are not affected.

Although this method gives the desired acid in good yields, its use is limited to small scale reactions because silver oxide is expensive.

5. Oxidation of Methylketones

The haloform reaction which you studied in sub-Sec. 14.4.2, Unit 14, Block 3, is occasionally used to prepare carboxylic acids from readily available methylketones.



3, 3-dimethyl-2-butanone

2, 2-dimethylpro--panoic acid
(71-74%)

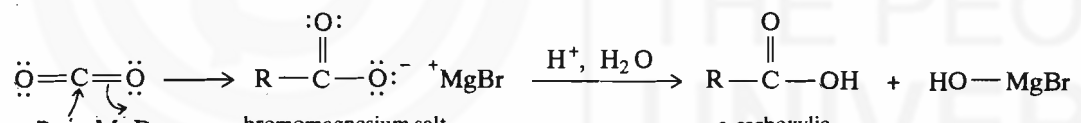
bromoform

Grignard reagents, RMgX, are named after the French Chemist Victor Grignard who discovered them in 1900 and for which he was awarded the Nobel prize in 1912.

6. Carbonation of Ogranometallic Reagents

Organometallic compounds such as Grignard reagents and organolithium compounds can be used for the synthesis of carboxylic acids.

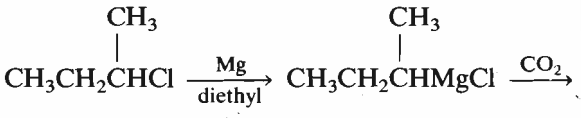
Organometallic reagents react with carbon dioxide to give salts of carboxylic acids. The salt is treated with a strong mineral acid to yield the carboxylic acid.



bromomagnesium salt of a carboxylic acid

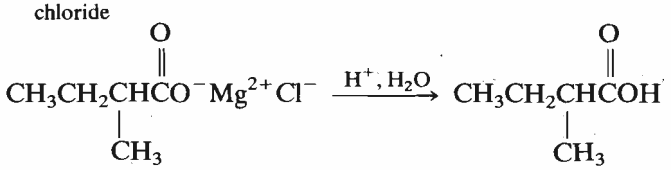
a carboxylic acid

Grignard reagents are usually prepared by the reaction of an alkyl or aryl halide with magnesium metal in an ether or hydrocarbon solvent.

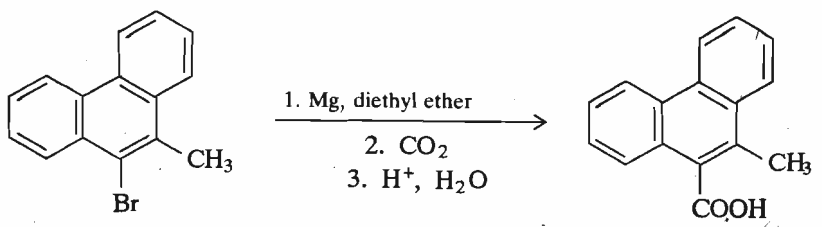


2-chlorobutane

2-butylmagnesium chloride



2-methylbutanoic acid
(~77%)

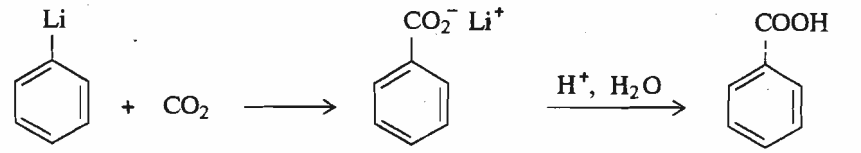


9-bromo-10-methylphenanthrene

10-methylphenanthrene-9-carboxylic acid (82%)

Note that the acid obtained contains one carbon atom more than the alkyl or aryl halide used to prepare the Grignard reagent.

A similar reaction occurs between carbon dioxide and organolithium compounds.



phenyllithium — benzenecarboxylic acid

7. Hydrolysis of nitriles

The reaction is of S_N2 type and is most effective with primary alkyl halides. It is slow with secondary alkyl halides. With tertiary alkyl halides, elimination occurs. Aryl and vinyl halides do not react.

DMSO, Dimethylsulphoxide, is the preferred solvent for this reaction, but alcohols and water-alcohol mixtures have also been used.

Primary and secondary alkyl halides may be converted to carboxylic acids containing one more carbon atom using a two step process. The first step involves the preparation of nitriles or alkyl cyanide. The nitrile on hydrolysis in acidic or basic conditions yields the carboxylic acid.

$$CH_3CH_2CH_2CH_2Br + NaCN \xrightarrow{DMSO} CH_3CH_2CH_2CH_2CN$$

1-bromobutane — pentanenitrile

$$CH_3CH_2CH_2CH_2CN \xrightarrow{KOH,\ H_2O,\ \Delta} CH_3CH_2CH_2CH_2COO^-K^+ \xrightarrow{H^+,\ H_2O} CH_3CH_2CH_2CH_2COOH$$

pentanoic acid (90%)

This method is complementary to carbonation of organometallic reagents as the hydroxy and carboxy groups present in the molecule do not need protection in this method.

SAQ 1

How will you prepare the following carboxylic acids using Grignard reagents?

a) 2, 2-dimethylpentanoic acid

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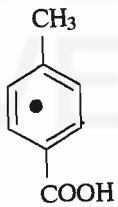
b) Hexanoic acid

.....

c) 4-methylbenzenecarboxylic acid,



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15.4 PHYSICAL PROPERTIES OF MONO-CARBOXYLIC ACIDS

Physical properties such as melting point, boiling point and water solubility of some straight chain carboxylic acids are listed in Table 15.3.

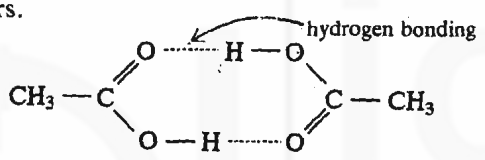
Table 15.3 : Physical Properties of Carboxylic Acids

Acid	Melting point/K	Boiling point/K	Solubility in $H_2O \times 10^2$ at 293K/kg dm^{-3}
Methanoic acid	281	374	∞
Ethanoic acid	289	391	∞
Propanoic acid	252	414	∞

Acid	Melting point/K	Boiling point/K	Solubility in $H_2O \times 10^2$ at 293K/kg dm^{-3}
Butanoic acid	268	437	∝
Pentanoic acid	239	459	4.97
Hexanoic acid	270	478	0.968
Heptanoic acid	265	496	0.244
Octanoic acid	290	512	0.068
Nonanoic acid	288	528	0.026
Decanoic acid	305	543	0.015
Benzenecarboxylic acid	395	522	0.21

You can see from Table 15.3 that the lower members are liquids at room temperature. Table 15.3 also shows that the carboxylic acids having an even number of carbon atoms have higher melting points as compared to the carboxylic acids having an odd number of carbon atoms. Thus, it illustrates the "saw-tooth" pattern which you studied in Block 1, Unit 4, Fig. 4.2. The higher members and aromatic acids are solid at room temperature.

Carboxylic acids are polar in nature. They can form hydrogen bonds in the solid as well as in the liquid state. As a result, they generally have high boiling points. In the solid state and under some conditions in gas and solution phase, carboxylic acids exist as hydrogen-bonded dimers.



dimer of ethanoic acid in vapour phase

Due to the hydrogen bonding lower members of this class show appreciable solubility in water. The first four monocarboxylic acids are miscible with water in all proportions. But, as the chain length increases, the water solubility decreases.

15.5 SPECTRAL PROPERTIES OF CARBOXYLIC ACIDS

Infrared spectra of carboxylic acids

The carboxy group consists of a carbonyl group and an attached hydroxy group. Characteristic stretching frequencies corresponding to both these groups are observed in the infrared spectra of carboxylic acids. This is illustrated in the infrared spectrum of propanoic acid as shown in Fig. 15.1.

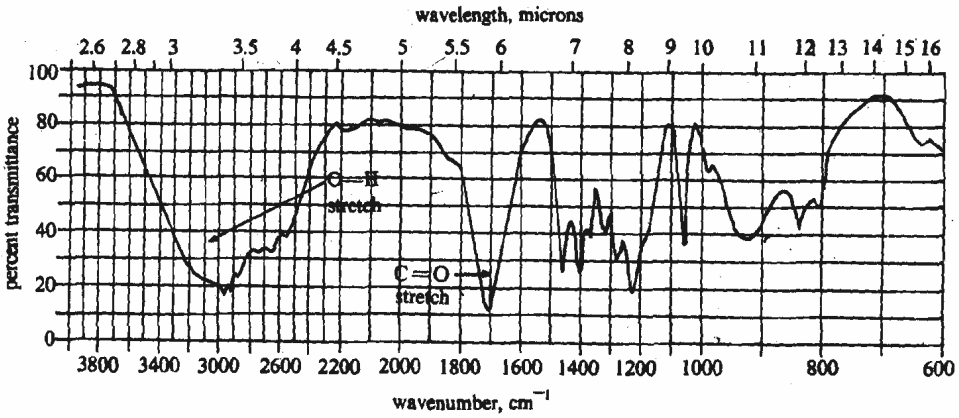


Fig. 15.1 : Infrared spectrum of propanoic acid.

The bands due to O–H stretching and C=O stretching are both broad due to hydrogen bonding.

The O–H stretching in carboxylic acids is observed as a broad band at wave numbers 2400 to 3600 cm^{-1} as shown in Fig. 15.1. The O–H stretching frequencies usually overlap with the C–H stretching frequencies of the molecules. The C=O stretching in carboxylic acids is observed near 1710 cm^{-1} (see Fig. 15.1). For acids in which the carbonyl group is conjugated with a double bond or with an aromatic ring, the C=O stretching appears between 1710–1680 cm^{-1}. For example, C=O stretching in benzenecarboxylic acid is observed at 1680 cm^{-1}.

NMR spectra of carboxylic acids

The hydroxyl proton (–O–H) of a carboxy group is normally the least shielded of all the hydrogens bonded to oxygen. It is observed downfield between δ 9–13 ppm depending upon the concentration, solvent and temperature which affect the extent of hydrogen bonding. As with other acidic protons (e.g. –OH protons of alcohols and phenols), the carboxy proton can be identified by adding D_2O to the sample. Hydrogen-deuterium exchange converts –COOH to –COOD and hence the signal corresponding to the –COOH proton disappears in the spectrum. The NMR spectrum of propanoic acid is shown in Fig. 15.2.

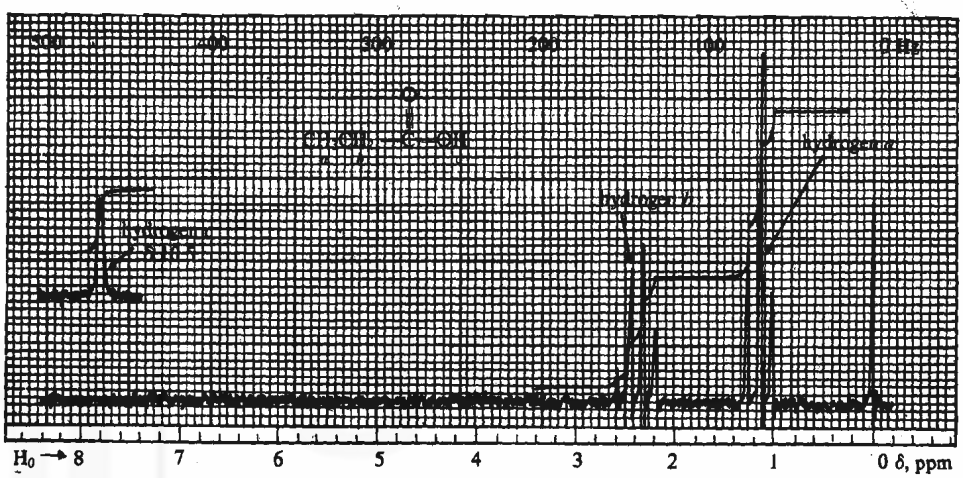


Fig. 15.2 : NMR spectrum of propanoic acid.

15.6 REACTIONS OF CARBOXYLIC ACIDS

The reactions of carboxylic acids are given below in Table 15.4 followed by their detailed discussion.

Table 15.4 : Reactions of Carboxylic acids

1. **As Acids**

$$RCOOH + NaOH \longrightarrow RCOO^- Na^+ + H_2O$$

$$RCOOH + NaHCO_3 \longrightarrow RCOO^- Na^+ + H_2O + CO_2$$

2. **As Bases**

$$R-C(=O)-\ddot{O}H + H^+ \rightleftharpoons R-C(=\overset{+}{O}-H)-\ddot{O}H$$

(resonance stabilised)

3. **Esterification**

$$RCOOH + R'OH \overset{H^+}{\rightleftharpoons} RC(=O)OR' + H_2O \text{ (Fischer Esterification)}$$

$$RCOOH + CH_2N_2 \longrightarrow RC(=O)CH_3 + N_2 \text{ (by diazomethane)}$$

4. **Conversion to amides**

$$RCOOH + NH_3 \rightleftharpoons RCOO^-\overset{+}{N}H_4 \xrightarrow{heat} RCONH_2 + H_2O$$

$$RCOOH + R'NH_2 \rightleftharpoons RCOO^-\overset{+}{N}H_3R' \xrightarrow{heat} RCONHR' + H_2O$$

$$RCOOH + R'_2NH \rightleftharpoons RCOO^-\overset{+}{N}H_2R'_2 \xrightarrow{heat} RCONR'_2 + H_2O$$

5. **Conversion to 2-halo acids**

$$R{-}CH_2COOH + X_2 \xrightarrow{\text{Red P}} R{-}\underset{\displaystyle X}{\underset{|}{CH}}COOH$$

$X_2 = Cl_2$ or Br_2

6. **Reduction**

$$RCOOH \xrightarrow[2.\ H^+,\ H_2O]{1.\ LiAlH_4} RCH_2OH$$

7. **Decarboxylation**

i) $$2\,R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}O^- \xrightarrow{\text{electrolysis}} R - R + 2\,CO_2$$

ii) $$\overset{\displaystyle O}{\overset{\|}{R}}COAg + Br_2 \xrightarrow[\Delta]{CCl_4} RBr + CO_2 + AgBr$$

8. **Conversion to alkanoyl halides**

$$RCOOH + SOCl_2 \longrightarrow RCOCl + SO_2 + HCl$$
$$RCOOH + PCl_3 \longrightarrow 3\,RCOCl + H_3PO_3$$
$$RCOOH + PCl_5 \longrightarrow 3\,RCOCl + POCl_3 + HCl$$

1. Acidity

As the name indicates, carboxylic acids are acidic. The acidity of carboxylic acids and various factors affecting it were discussed in Unit 5, Block 1. It was explained in Unit 5 that the carboxylate ion so produced is resonance stabilised.

Another aspect related to the acidity of carboxylic acids is salt formation. Carboxylic acids on treatment with bases such as NaOH yield salts.

$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\ddot{O}H + NaOH \longrightarrow R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\underset{\text{(salt)}}{\ddot{O}:^-}\,Na^+ + H_2O$$

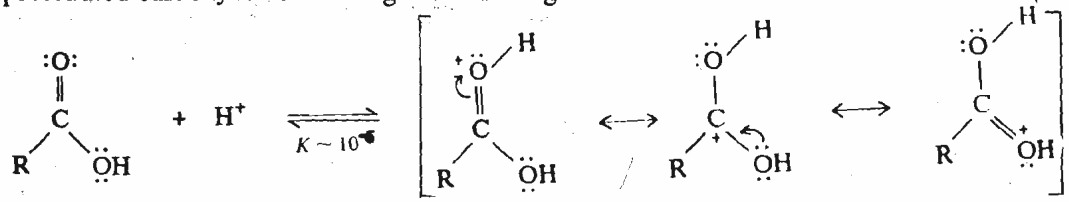
These salts are named by specifying the metal and replacing the **–ic acid** in the name of the acid by **–ate** ending.

Even a 5% sodium bicarbonate ($NaHCO_3$) solution is basic enough (pH = 8.5) to yield the sodium salt of a carboxylic acid. Thus, carboxylic acids react readily with aqueous solutions of sodium hydroxide and sodium bicarbonate to form soluble sodium salts.

Thus, water insoluble carboxylic acids can be differentiated from other water insoluble nonacidic substances. Water insoluble carboxylic acids will dissolve in either aqueous sodium hydroxide or sodium bicarbonate but the nonacidic compounds will not. After separating the basic aqueous solution, it can be acidified with mineral acid to yield the carboxylic acid.

2. Basicity of carboxylic acids

The carbonyl group of a carboxylic acid is weakly basic and its protonation yields the protonated carboxylic acid having the following three resonance contributors.



Such a protonation or basicity plays an important role in many reactions of the carboxylic acids and their derivatives about which you will study in the following units of this block.

3. Esterification

Carboxylic acids react with alcohols in the presence of an acid catalyst to yield esters. The reaction is known as **Fischer esterification**.

$$\underset{\text{carboxylic acid}}{RCOOH} + \underset{\text{alcohol}}{R'OH} \overset{H^+}{\rightleftharpoons} \underset{\text{ester}}{\overset{\displaystyle O}{\overset{\|}{R}}COR'} + \underset{\text{water}}{H_2O}$$

This reaction is an equilibrium process and can be driven in favour of the ester by removing the water formed. The second way of increasing the yield of an ester is by using one of the reactants in excess (Le Chatelier's principle). Generally, the cheaper of the two reactants is taken in excess. Thus, esterifications are often carried out by using the alcohol as the solvent.

A wide variety of esters can be prepared using this method. The common acid catalysts used are conc. sulphuric acid, hydrogen chloride or *p*-toluenesulphonic acid. Some examples of ester formation are given below.

$$CH_3\overset{\overset{O}{\|}}{C}OH + CH_3OH \xrightleftharpoons{H_2SO_4,\ \Delta} CH_3\overset{\overset{O}{\|}}{C}OCH_3 + H_2O$$

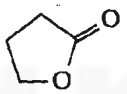
ethanoic acid — solvent — methyl ethanoate (85%)

$$BrCH_2COOH + CH_3CH_2OH \xrightleftharpoons{H_2SO_4,\ \Delta} BrCH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 + H_2O$$

bromoethanoic acid — ethanol (excess) — ethyl bromoethanoate (70%) — (remove)

When the carboxy and hydroxy groups are present in the same molecule, a lactone (cyclic ester) is obtained by intramolecular esterification. For example,

You will study more about lactones in sub-Sec. 16.3.2 of Unit 16.

$$HOCH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OH \xrightleftharpoons{H^+}$$ 

4-hydroxybutanoic acid — 2-oxacyclopentanone (γ-butyrolactone)

Before studying the mechanism of acid-catalysed esterification, it is interesting to know whether the oxygen of the water formed in the reaction comes from the alcohol or from the acid. In an experiment using isotopically labelled alcohol (having ^{18}O isotope) it was observed that oxygen in the water produced comes exclusively from the carboxylic acid. Thus, it was observed that,

$$RCOH + H^{18}OCH_3 \xrightleftharpoons{H^+} RC^{18}OCH_3 + H_2O$$

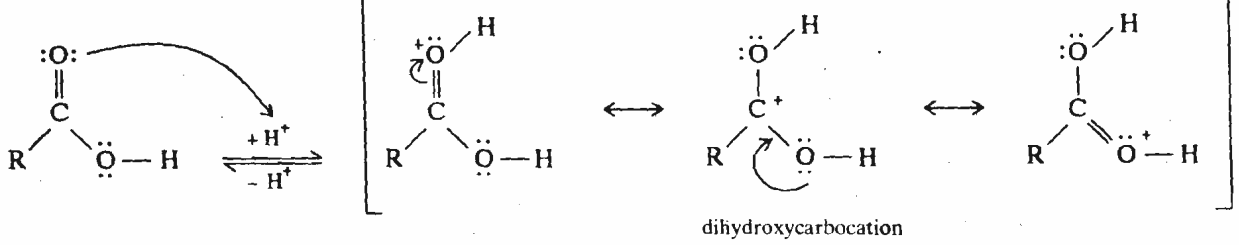
and not,

$$RCOH + H^{18}OCH_3 \not\rightleftharpoons RCOCH_3 + H_2{}^{18}O$$

A carboxylic acid does not react with an alcohol unless a strong acid is used as a catalyst. Protonation of the carboxy group makes the carbonyl (>C=O) group more electrophilic and enables it to react with the alcohol which is a weak nucleophile.

In other words, the alcohol oxygen is incorporated into the ester. This and other observations led to the following mechanism of esterification:

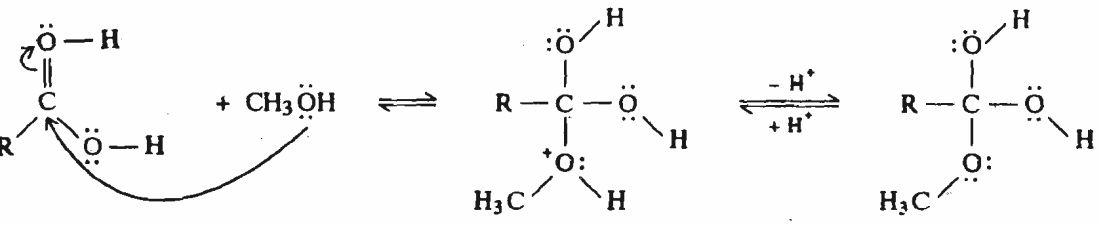
Step 1 : Protonation of the carboxy group



dihydroxycarbocation

The protonated carboxylic acid is susceptible to attack by nucleophiles such as alcohol, as shown in step 2.

Step 2 : Attack by alcohol



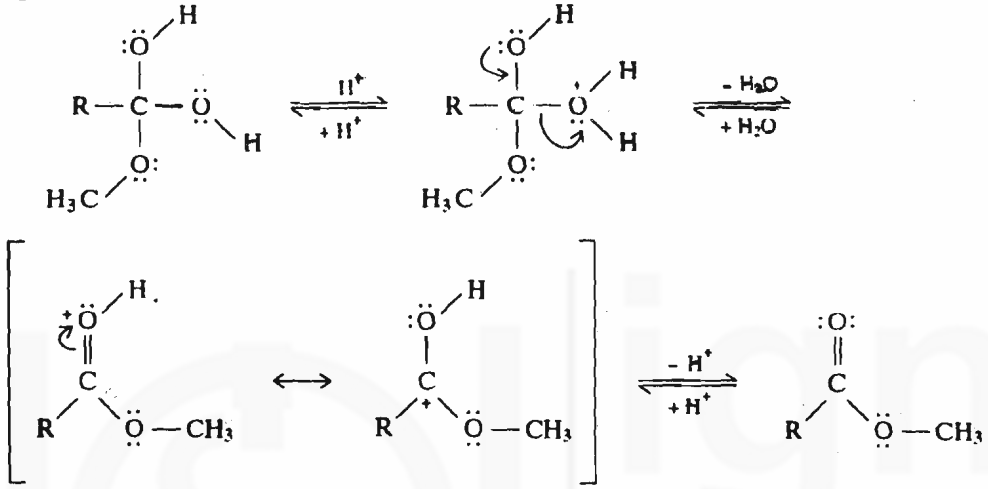
tetrahedral intermediate

Addition of alcohol to carboxylic acid to form the tetrahedral intermediate is analogous to the addition of an alcohol to an aldehyde or ketone to form a hemiacetal which you have studied in, Block 3, Unit 14, sub-Sec. 14.4.1.

Step 2 is the rate-determining step in esterification reactions.

Attack of the alcohol on the protonated carboxylic acid yields an initial adduct which on loss of a proton yields the **tetrahedral intermediate.** The tetrahedral intermediate eliminates water and yields the ester as shown in step 3.

Step 3 : Elimination of water and deprotonation

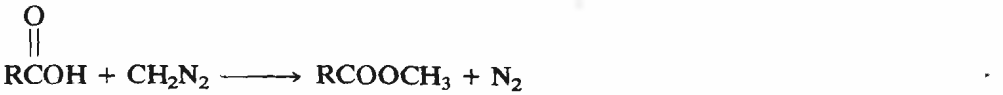


Tertiary alcohols and phenols cannot be used in acid catalysed esterification. Due to steric factors, tertiary alcohols react very slowly in the esterification reaction and they usually undergo elimination instead of esterification. For phenols also, the equilibrium constants of esterification are very low.

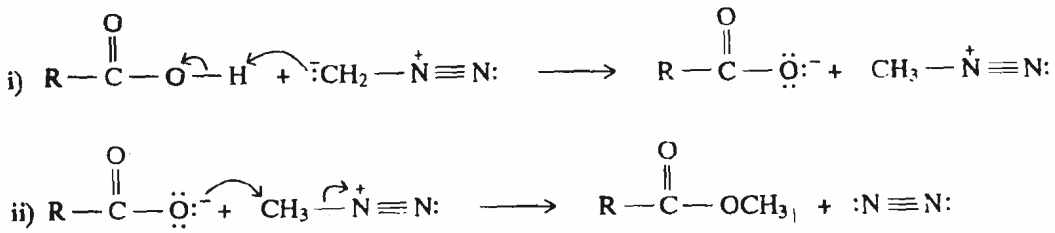
There are other ways of obtaining esters from tertiary alcohols and phenols about which you will study in Unit 17, sub-Sec. 17.5.2.

Another method of obtaining methyl esters from carboxylic acids involves the use of diazomethane, CH_2N_2. When a carboxylic acid is treated with diazomethane in ether solution, it is rapidly converted into a methyl ester.

Diazomethane is a toxic yellow gas. It is both explosive and allergenic. Therefore, this method can be used only for small scale preparations. But the esterification is so mild and free of side reactions that in many cases it is the method of choice for the synthesis of methyl esters.



The following mechanism can be written for this esterification.



Step (i) is an acid-base reaction about which you studied in Unit 5, Block 1.

The first step involves the protonation of diazomethane. Therefore, you can understand that acidity of carboxylic acid is important in this reaction. The resulting methyl diazonium ion has one of the best leaving groups, i.e., molecular nitrogen. Thus, an S_N2 reaction of the carboxylate ion with the methyldiazonium ion results in the displacement of N_2 and formation of an ester. **Note that here the oxygen of the carboxylate group acts as a nucleophile whereas in acid-catalysed esterification, the carbonyl group of the protonated carboxyl group behaves as an electrophile.** This illustrates two of the general ways in which carboxylic acids react.

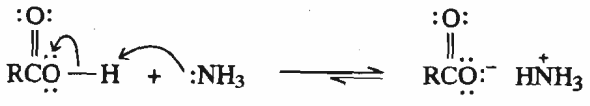
The nucleophilic nature of the carboxylate ion is also illustrated by the reaction of certain alkyl halides, particularly primary haloalkanes, with carboxylate ions. For example,

$$CH_3CH_2CH_2CH_2I + CH_3\overset{O}{\overset{\|}{C}}O^-\overset{+}{N}a \xrightarrow[373\ K]{CH_3COOH} CH_3CH_2CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3 + \overset{+}{N}a\ I^-$$

iodobutane — sodium ethanoate — butyl ethanoate (95%)

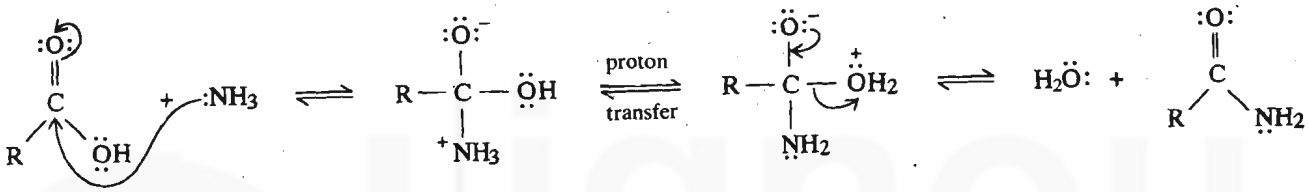
4. Amide formation

Carboxylic acids on reaction with ammonia or amines (primary or secondary) can lead to amides via the initial formation of ammonium salts.



ammonia — an ammonium alkanoate

On heating salt formation is reversed and nucleophilic attack by nitrogen on the carbonyl carbon takes place. The elimination of water then leads to the formation of an amide as shown below:



Some examples are given below:

$$CH_3CH_2CH_2COOH + NH_3 \xrightarrow{298\ K} CH_3CH_2CH_2COO^-\overset{+}{N}H_4$$

butanoic acid — ammonium butanoate

$$CH_3CH_2CH_2COO^-\overset{+}{N}H_4 \xrightarrow{458\ K} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2 + H_2O$$

ammonium butanoate — butanamide

$$CH_3CH_2CH_2COOH + (CH_3)_2NH \xrightarrow{428\ K} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}N(CH_3)_2 + H_2O$$

butanoic acid — *N, N*-dimethylamine — *N, N*-dimethylbutanamide (84%)

5. Formation of 2-halo acids

Aliphatic carboxylic acids react with bromine or chlorine in the presence of phosphorus (or a phosphorus halide) to give 2-halo acids. This reaction is known as **Hell-Vollhard-Zelinski** reaction after its discoverers.

Phosphorus reacts with Br_2 to give PBr_3.

$$CH_3CH_2CH_2CH_2COOH \xrightarrow[(PBr_3)]{Br_2,\ Catalytic\ Red\ P} CH_3CH_2CH_2\underset{Br}{C}HCOOH + HBr$$

pentanoic acid — 2-bromopentanoic acid

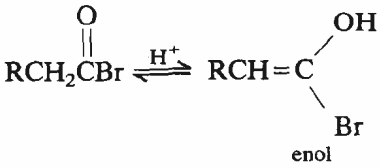
If more than one equivalent of halogen is used in the reaction, then 2,2-dihalo acids or 2,2,2-trihalo acids are obtained. The mechanism of this reaction is given below:

Step 1 : Alkanoyl bromide formation

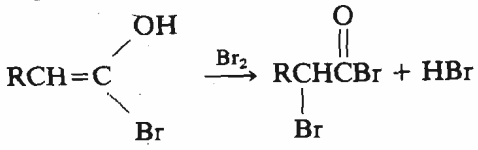
$$3\ RCH_2\overset{O}{\overset{\|}{C}}OH + PBr_3 \longrightarrow 3\ RCH_2\overset{O}{\overset{\|}{C}}Br + H_3PO_3$$

alkanoyl bromide

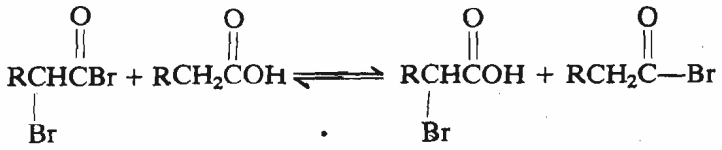
Step 2 : Enolisation



Step 3 : Bromination



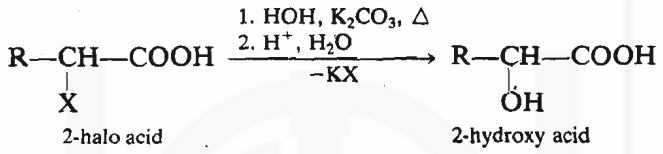
Step 4 : Exchange



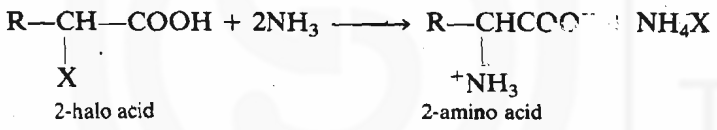
This can reenter the sequence at step 2.

The Hell-Volhard-Zelinsky reaction is of synthetic importance as the 2-halo acids obtained can further react with a variety of nucleophiles as shown below:

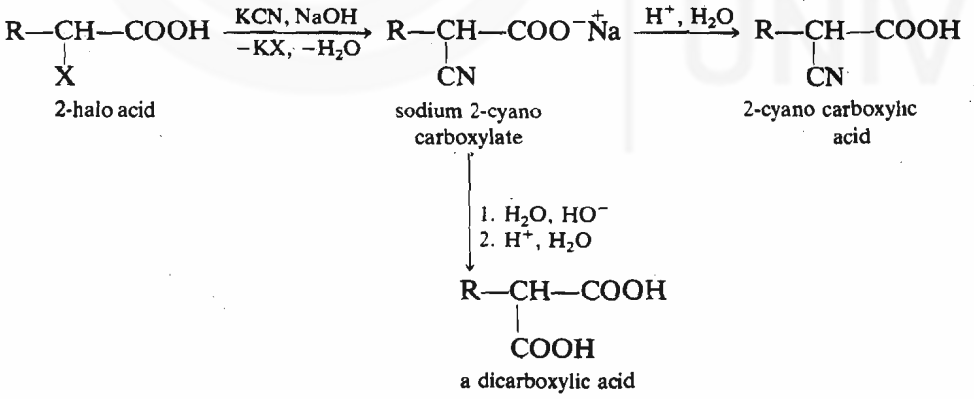
Conversion to 2–hydroxy acids:



Conversion to 2-amino acids:



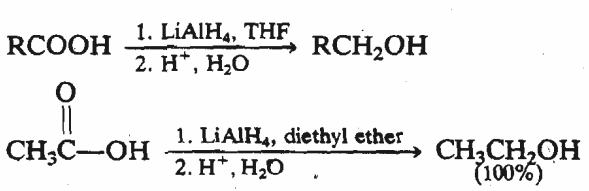
Conversion to 2–cyano carboxylic acid:

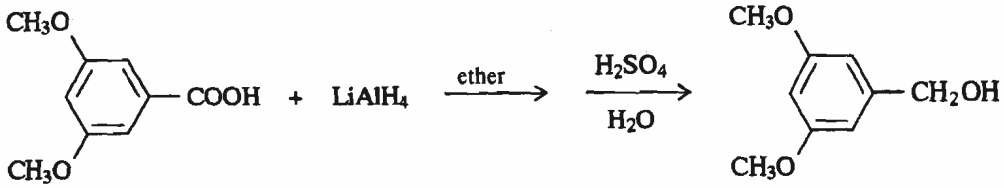


The cyano carboxylic acid can be subsequently hydrolysed to the dicarboxylic acid as shown above.

6. Reduction of Carboxylic acids

Carboxylic acids can be reduced by powerful reducing agents such as lithium aluminium hydride, $LiAlH_4$, to the primary alcohols.





(93%)

7. Decarboxylation

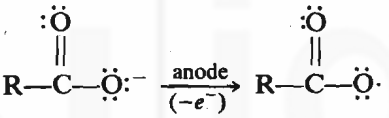
The loss of a molecule of carbon dioxide from a carboxylic acid is known as **decarboxylation.**

The simple aliphatic carboxylic acids do not decarboxylate easily and some structural features are required for it. For example, carboxylic acids having strongly electron-attracting groups at the 2-position, decarboxylate readily on heating at 373 to 423 K.

Among other carboxylic acids which decarboxylate readily are: i) 3-keto acids; ii) propanedioic acid (malonic acid) and its derivatives; and iii) carbonic acid derivatives. About these acids you will study in Unit 16, sub-Sec. 16.5.3 and Sec. 16.6.

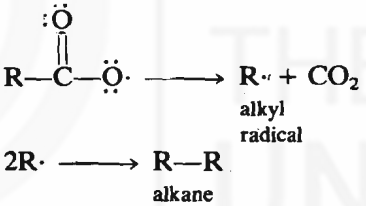
Decarboxylation reactions involving carboxyl radicals include **Kolbe electrolysis** and **Hunsdiecker reaction.**

In Kolbe electrolysis an aqueous solution of the sodium or potassium salt of a carboxylic acid is subjected to electrolysis. The carboxylate ion loses an electron at the anode to yield a carboxyl radical.



carboxylate ion carboxyl radical

The carboxyl radical then decarboxylates and the alkyl radicals so produced combine to yield an alkane.



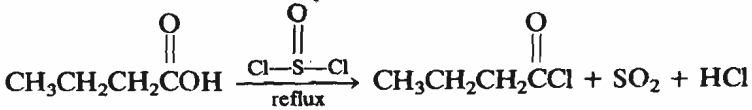
In the Hunsdiecker reaction, the silver salt of a carboxylic acid is heated with a halogen, usually bromine in CCl_4.

$$RCOO^-Ag^+ + Br_2 \longrightarrow RBr + CO_2 + AgBr$$

The reaction yields a bromoalkane having one carbon less than the starting acid.

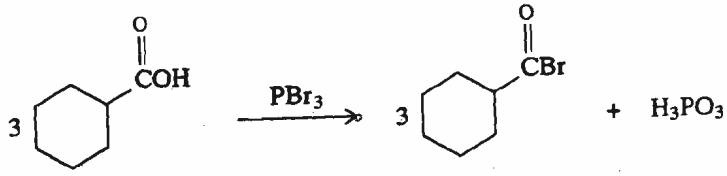
8. Formation of alkanoyl (acyl) halides

Carboxylic acids react with phosphorus trichloride (PCl_3), phosphorus pentachloride (PCl_5) or thionyl chloride ($SOCl_2$) to yield an alkanoyl chloride.



butanoic acid butanoyl chloride (85%)

An alkanoyl bromide can be obtained by the reaction of a carboxylic acid with PBr_3.



(90%)

SAQ 2

Write the product obtained when 2-methylpropanoic acid reacts with:

a) diazomethane in ether

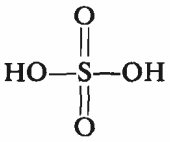
.....

b) butanol (as solvent), H_2SO_4

.....

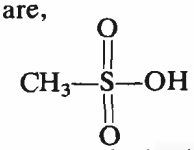
15.7 SULPHONIC ACIDS

It was stated earlier that sulphonic acids are organic acids related to sulphuric acid. Sulphuric acid can be written as shown below:

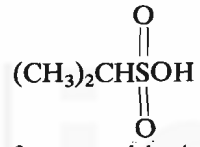


sulphuric acid

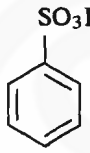
Replacement of one of the hydroxyl groups of sulphuric acid by an alkyl or aryl group leads to alkanesulphonic acid (RSO_3H) or arenesulphonic acid ($ArSO_3H$). Some examples are,



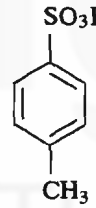
methanesulphonic acid



2-propanesulphonic acid



benzenesulphonic acid

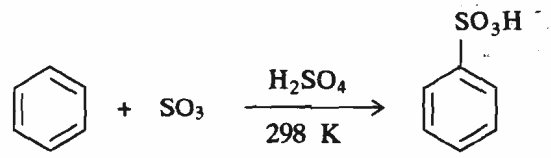


4-methylbenzenesulphonic acid
(*p*-toluenesulphonic acid)

You will now study about the representative arenesulphonic acid, i.e. benzenesulphonic acid.

15.7.1 Preparation of Benzenesulphonic Acid

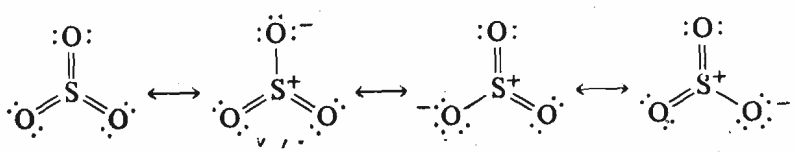
Benzenesulphonic acid can be prepared by the **sulphonation** of benzene. You have already studied about the sulphonation of aromatic compounds in sub-Sec. 9.6.3 of Unit 9, Block 2. Sulphonation involves electrophilic substitution by sulphur trioxide. The source of sulphur trioxide is usually fuming sulphuric acid or oleum which contains 10–30% SO_3 dissolved in concentrated H_2SO_4.



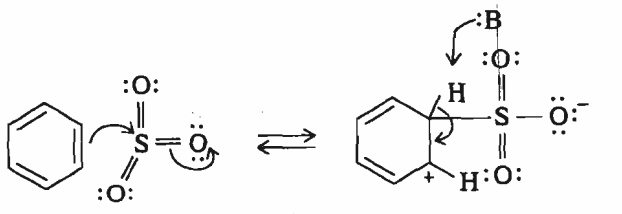
benzene — benzenesulphonic acid

The mechanism of sulphonation involves the following steps:

THE SULPHONATION REACTION

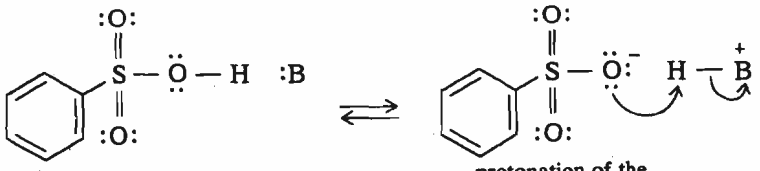


Resonance Contributors of Sulphur Trioxide



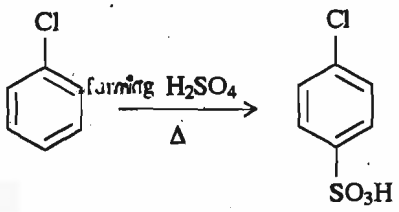
reaction of electrophile with the π electrons

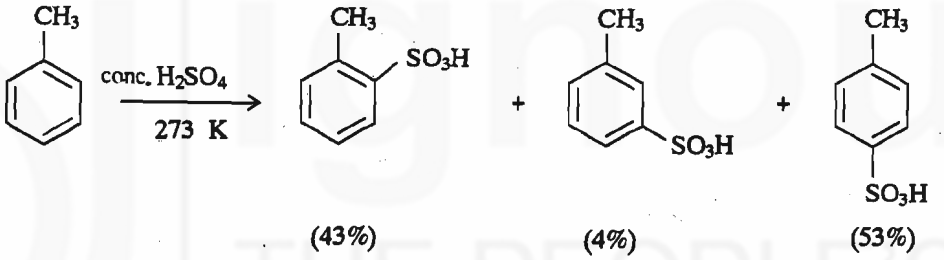
deprotonation of the cationic intermediate



protonation of the benzenesulphonate anion

Sulphonation is a general reaction and occurs with other substituted benzenes also. Examples are,





(43%) (4%) (53%)

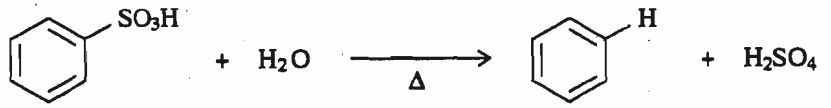
Sulphonation is a reversible reaction; therefore, to **sulphonate**, a high concentration of fuming sulphuric acid is employed. To **desulphonate**, dilute acid is used and superheated steam is passed through the mixture when the more volatile benzene is removed by steam distillation.

15.7.2 Reactions of Benzenesulphonic Acid

1. Desulphonation

The sulphonation reaction which you have studied above and also in Unit 9, is a reversible reaction. Thus, reversal of sulphonation or desulphonation can be achieved by heating the sulphonic acid with dilute sulphuric acid. Usually steam is also passed to carry out desulphonation.

Sulphonation and desulphonation reactions are useful in synthesis of organic compounds. For example, sulphonic acid group can be used as a protecting group to aromatic ring in substitution. This can thus influence the course of further reaction. Later it can be easily removed by desulphonation.

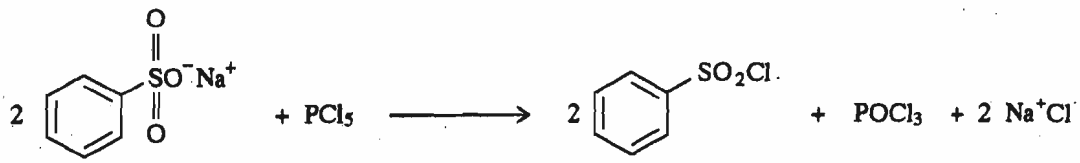


benzenesulphonic acid — water — benzene — sulphuric acid

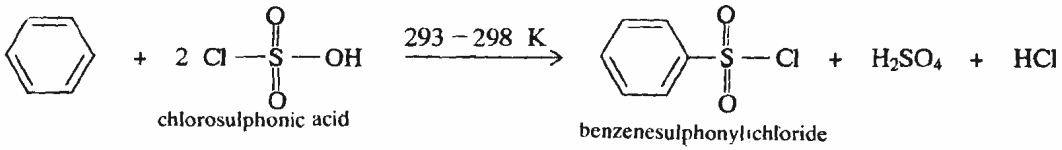
2. Formation of acid chloride

Similar to carboxylic acids, the acid chlorides of sulphonic acids, i.e., sulphonyl chlorides, can be prepared by heating the sulphonic acid with thionyl chloride or phosphorus pentachloride. Aromatic sulphonyl chlorides can also be prepared directly from aromatic compounds using chlorosulphonic acid.

4–Methylbenzenesulphonyl-chloride (*p*–toluene-sulphonyl chloride) is an important reagent in the laboratory.

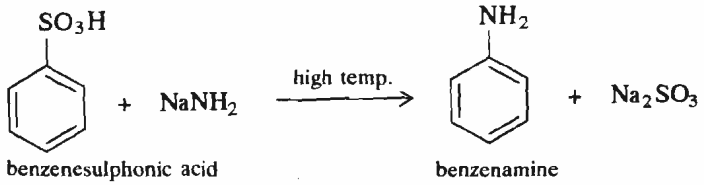


sodium benzenesulphonate — benzenesulphonyl chloride (80%)



3 Fusion with sodamide

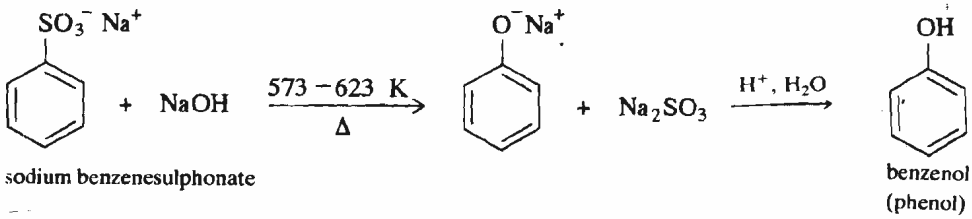
When sodium salt of benzenesulphonic acid is treated with sodamide, $NaNH_2$, benzenamine (aniline) is obtained as the product.



4. Fusion with alkali hydroxide

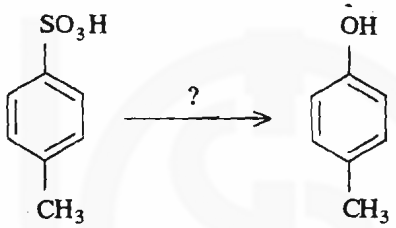
This is the oldest method for the preparation of benzenol.

Fusion of sodium salt of sulphonic acid with alkali hydroxide yields benzenol.



SAQ 3

How will you carry out the following conversion:



15.8 INDUSTRIAL USES OF CARBOXYLIC AND SULPHONIC ACIDS

1. Soaps and detergents

The sodium and potassium salts of long chain carboxylic acids were used as **soaps** until the 19th century. These molecules have an ionic **hydrophilic** *(water-loving)* carboxylate group and a nonpolar **lipophilic** *(fat–loving)* hydrocarbon chain. In aqueous solution, they form spherical aggregates known as **micelles**, as shown in Fig. 15.3.

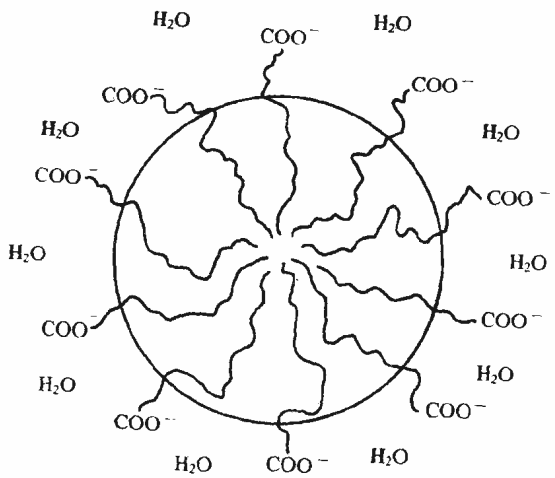


Fig. 15.3 : Schematic representation of a micelle.

The cleansing action of soap involves attracting nonpolar molecules as grease, oil etc. to the nonpolar centre of the micelle. The outer polar part of the micelle is attracted to water and the **solubilised** grease is washed away. This is shown in Fig. 15.4.

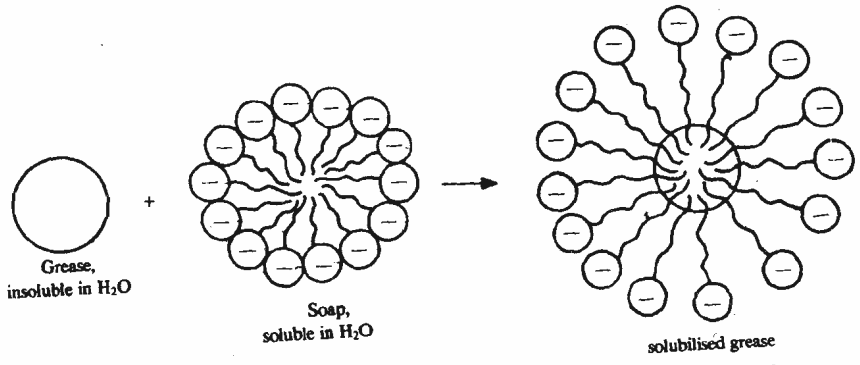
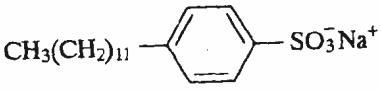


Fig. 15.4 : Cleansing action of soap.

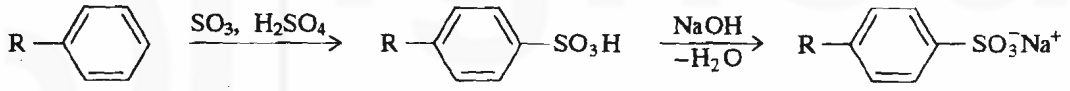
A major disadvantage of the carboxylate soaps is that they combine with calcium and magnesium ions often present in the water to form **insoluble scums.**

This problem was taken care of when synthetic detergents were marketed in 1933. The first detergents were alkylbenzenesulphonates. The advantages of these detergents is that they do not form insoluble scum with hard water. An example of a synthetic detergent is given below.



sodium 4–dodecylbenzenesulphonate

Until recently, long–chain branched alkylbenzenes were sulphonated to the corresponding sulphonic acids which were converted into sodium salts to be used as detergents.

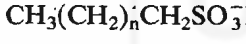


R = branched alkyl chain

Synthesis of alkylbenzenesulphonates

Biodegradable means degradation or breaking up into simple molecules by living organisms such as bacteria.

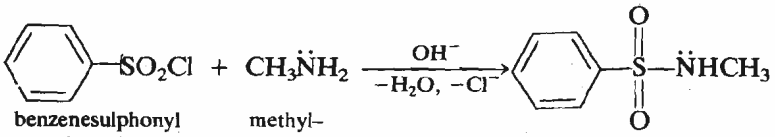
But these detergents are not readily biodegradable. After intensive research linear alkanesulphonate detergents were introduced which are biodegradable. The general structure of linear alkanesulphonates is given below:



alkanesulphonate detergent, n = 12 – 15

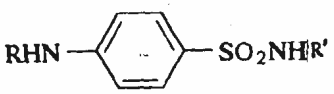
2. Sulphonamides as chemotherapeutic agents

Sulphonyl chlorides, which you studied in sub-Sec. 15.7.2, on treatment with ammonia or amines give the corresponding **sulphonamides**. For example,

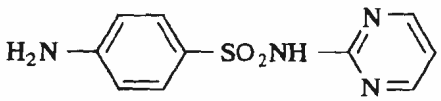


benzenesulphonyl chloride — methyl–amine — *N*–methylbenzenesulphonamide

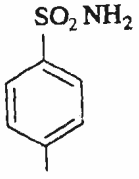
Many sulphonamides have important medicinal use as antibacterial agents. Some examples of such **sulpha drugs** are:



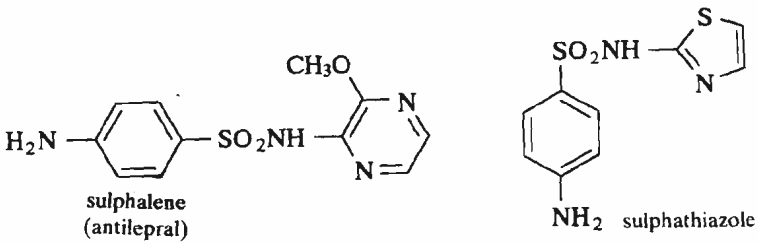
general structure



sulphadiazine
(antibacterial)



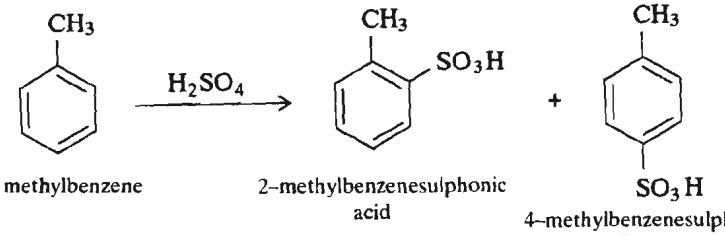
4–aminobenzenesulphonamide
or *p*-aminobenzenesulphonamide
(sulphanilamide)



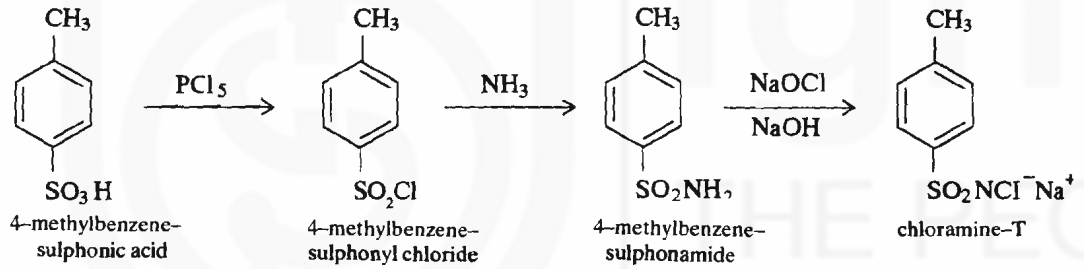
Sulpha drugs were used for treating human beings during 1930s and 1940s but now more effective antibiotics such as penicillins and tetracyclines have replaced them. These antibiotics will be dealt with in Unit 20.

3. Chloramine T

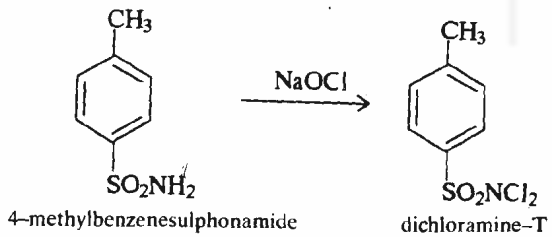
When methylbenzene is treated with concentrated sulphuric acid, a mixture of 2–methylbenzenesulphonic and 4–methylbenzenesulphonic acids is formed. Low temperatures (below 373 K) favour the formation of 2–methylbenzenesulphonic acid and high temperatures (above 373 K) favour the 4–methylbenzenesulphonic acid.



4–Methylbenzenesulphonic acid is used in the preparation of the antiseptics **Chloramine–T** and **Dichloramine–T**. Chloramine–T is the sodium salt of *N*–chloro–4–methylbenzenesulphonamide and is prepared as follows:

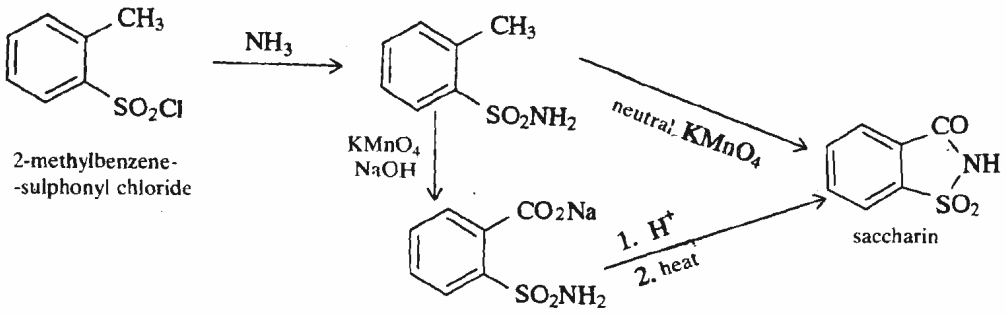


In addition to being used as an antiseptic, chloramine–T is also used as a laboratory reagent instead of hypochlorite salts, since it is stable and liberates hypochlorous acid when acidified. Dichloramine–T is obtained when 4– methylbenzenesulphonamide is treated with a large excess of sodium hypochlorite.

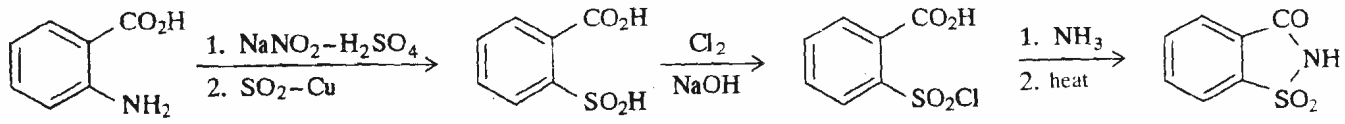


4. Saccharin

2–Methylbenzenesulphonyl chloride on treatment with ammonia, followed by oxidation of the amide by potassium permanganate, gives the corresponding benzoic acid. This, on heating, forms saccharin.



Although the above method was one of the first to be used industrially, other methods are now employed (e.g., from 2-aminobenzenecarboxylic acid (anthranilic acid).



2-aminobenzene--carboxylic acid

Saccharin is a crystalline solid, m.p. 497 K. It is about 550 times as sweet as sugar. It is used in place of sugar for many purposes, e.g., sweetening preserves, drinks, etc. It is also used as a substitute for sugar by diabetics and obese persons. In view of suspected carcinogenic properties, the use of saccharin has been discontinued in many countries.

SAQ 4

What is the difference between soaps and detergents?

.....

.....

15.9 LABORATORY DETECTION OF CARBOXYLIC AND SULPHONIC ACIDS

The solubility in sodium bicarbonate helps to distinguish carboxylic acids from most phenols. Except for di–and trinitrophenols, phenols do not dissolve in sodium bicarbonate.

Carboxylic acids and sulphonic acids are recognised by their acidic nature. They dissolve in aqueous sodium hydroxide and sodium bicarbonate. The reaction with sodium bicarbonate is accompanied by the evolution of bubbles of carbon dioxide. Further, the elemental analysis in case of sulphonic acids shows presence of sulphur.

Determination of the physical constants and formation of derivatives leads to final identification. The commonly prepared derivatives of carboxylic acid include amides and esters. Similarly, sulphonic acids can be converted into sulphonamides.

15.10 SUMMARY

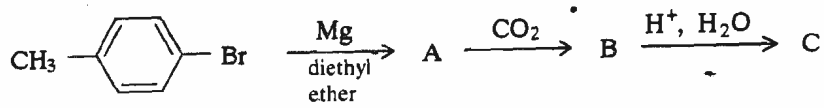
In this Unit, you have studied that

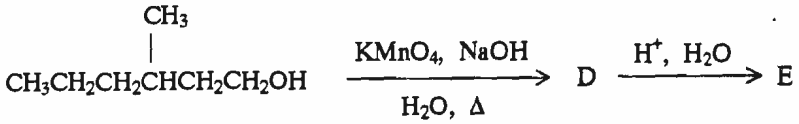
- carboxy group is the functional group of carboxylic acids and sulphonic acid group is the functional group of sulphonic acids.
- carboxylic acids with long unbranched carbon chains are called fatty acids.
- carboxylic acids can be prepared by the following methods:
  - i) Oxidation of alkenes.
  - ii) Side chain oxidation of alkylbenzenes.
  - iii) Oxidation of primary alcohols.
  - iv) Oxidation of aldehydes.
  - v) Oxidation of methylketones.
  - vi) Carbonation of organometallic reagents.
  - vii) Hydrolysis of nitriles.
- because of their acidity, carboxylic acids dissolve not only in aqueous sodium hydroxide but also in aqueous solutions of weaker bases such as sodium bicarbonate.
- carboxylic acids can be esterified using Fischer esterification or diazomethane.
- using appropriate reagents and conditions, carboxylic acids can be converted to:
  - i) amides.
  - ii) 2–halo acids.
  - iii) alcohols.
  - iv) alkanes.
  - v) alkanoyl halides.
- sulphonic acids can be obtained by the sulphonation reaction.
- sulphonation is a reversible reaction.

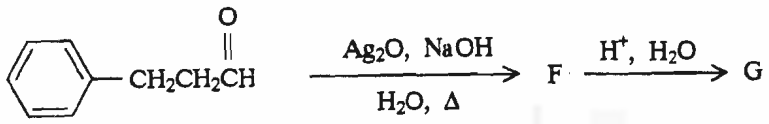
- benzenesulphonic acid can undergo:
  i) desulphonation
  ii) fusion with sodamide to give benzenamine and potassium hydroxide to yield benzenol.
- salts of carboxylic acids and sulphonic acids are used as soaps and detergents.
- sulphonic acids are also used in the preparation of chemotherapeutic agents such as sulphonamides and chloramine–T and also in the preparation of artificial sweetener, saccharin.

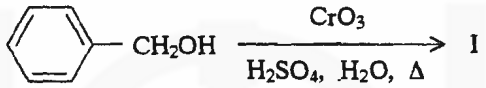
15.11 TERMINAL QUESTIONS

1) Assign structures to the compounds given in the following reactions:

a) 

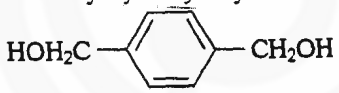
b) 

c) 

d) 

2) From a reaction mixture containing 4–bromomethylbenzene and 4–bromobenzenecarboxylic acid, how will you isolate pure acid?

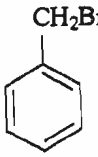
3) A carboxylic acid having molecular formula $C_8H_6O_3$ on reduction with $LiAlH_4$ followed by hydrolysis yielded the following product.



What is the structure of the acid?

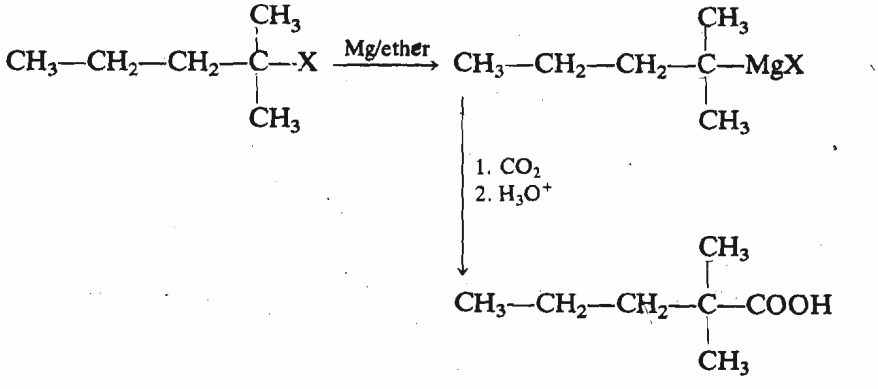
4) Using decarboxylation reactions, how will you obtain the following, using appropriate starting materials.

a) decane

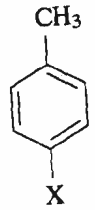
b) phenylmethyl (benzyl) bromide, 

15.12 ANSWERS

Self-Assessment Questions

1) a) 

b) Similar to (a) using $CH_3(CH_2)_4X$.

c) Similar to (a) starting with 

2) a) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-COOH + CH_2N_2 \longrightarrow \underset{\displaystyle CH_3}{\underset{|}{CH_3CH}}COOCH_3$

b) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-COOH + CH_3CH_2CH_2CH_2OH \longrightarrow$

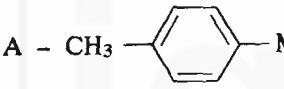
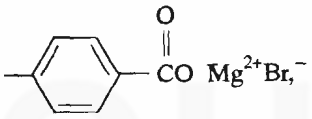
$$CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\overset{\displaystyle O}{\overset{\|}{C}}-OCH_2CH_2CH_2CH_3$$

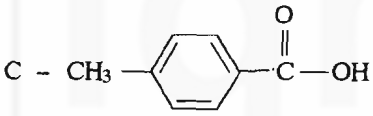
3) Fusing with NaOH / KOH at 500-600 K.

4) i) Soaps form insoluble scums with hard water whereas detergents do not,

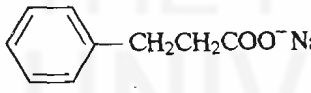
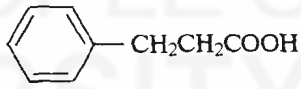
ii) Soaps are sodium or potassium salts of long chain carboxylic acids whereas detergents are sodium salts of sulphonic acids.

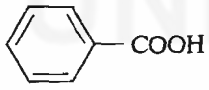
Terminal Questions

1) a) A –  , B – 

C – 

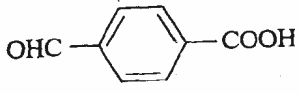
b) D– $CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COO^-Na^+$, E– $CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOH$

c) F –  , G – 

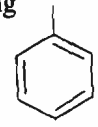
d) I – 

2) Dissolve the mixture in aqueous alkali, separate aqueous layer and acidify to get 4–bromobenzenecarboxylic acid.

3) Molecular formula, $C_8H_6O_3$



4) a) Kolbe Electrolysis of sodium or potassium salt of pentanoic acid.

b) heating  with Br_2 ; using Hunsdiecker reaction.

UNIT 16 SUBSTITUTED CARBOXYLIC ACIDS

Structure

16.1 INTRODUCTION

In Unit 15, you studied the chemistry of monocarboxylic acids in detail. In this unit, you will study the change in their properties caused by the introduction of a second functional group. The second functional group may be a halogen, a hydroxyl group, an amino group, a second carboxyl group, a carbonyl group or a double or triple bond. Corresponding to the above functional groups, we get haloacids, hydroxyacids, amino acids, dicarboxylic acids, keto acids and unsaturated acids, respectively. In this unit, we will study the chemistry of each of these classes.

Objectives

After studying this Unit, you should be able to:

- give the methods of preparation and reactions of halo acids,
- list a few naturally occurring hydroxy acids, write their structures and give their IUPAC names,
- outline the synthesis of hydroxy acids and write the products obtained from various hydroxy acids on treatment with aqueous acids,
- write structures of various amino acids and give their methods of preparation,
- explain the zwitterionic nature of amino acids,
- discuss the reactions of amino acids,
- outline the synthesis of a given dicarboxylic acid,
- explain the behaviour of various dicarboxylic acids on heating and discuss the other reactions shown by them,
- give examples of some keto acids,
- discuss the synthetic utility of ethyl 3–oxobutanoate and diethyl propanedioate, and
- describe the methods of preparation and reactions of unsaturated carboxylic acids.

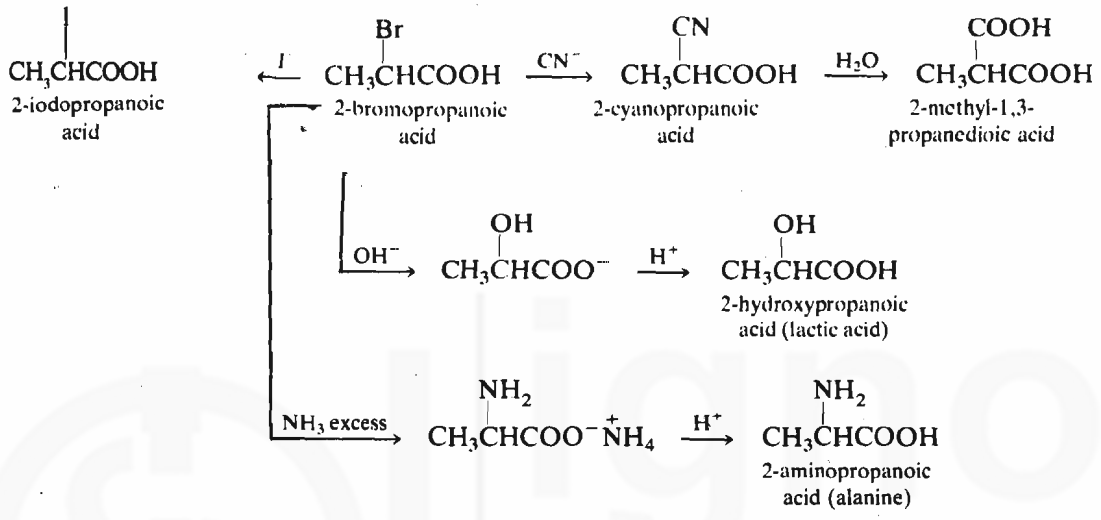
16.2 HALO ACIDS

You have already studied about halo acids in Unit 5, Block 1 and Unit 15. In Unit 5, sub-Sec. 5.4.1, we discussed the inductive effect of halogen atoms on the acidity of the carboxylic acids. In Unit 15, Sec. 15.6, the preparation of 2-halo acids using the Hell-Volhard-Zelinsky reaction was discussed. However, 3-halo acids can be obtained by the addition of hydrogen halide to 2 , 3-unsaturated acid. For example,

$$\underset{\text{propenoic acid}}{CH_2=CHCOOH} \xrightarrow{HBr} \underset{\text{3-bromopropanoic acid}}{BrCH_2CH_2COOH}$$

16.2.1 Reactions of the Halo Acids

The halogen atom of 2-halo acids is readily replaced by nucleophilic reagents such as CN^-, OH^-, I^- and NH_3. This yields a variety of 2-substituted acids as shown below:



3-Halo acids, however, undergo elimination of a molecule of HX when warmed with alcoholic KOH to give unsaturated acids.

$$\underset{\underset{\text{3-chlorobutanoic acid}}{\underset{Cl}{|}}}{CH_3CHCH_2COOH} \xrightarrow[KOH]{\text{alcoholic}} \underset{\text{but-2-enoic acid (crotonic acid)}}{CH_3CH=CH-COOH}$$

16.3 HYDROXY ACIDS

Many important hydroxy acids occur naturally. As stated earlier in case of saturated monocarboxylic acids in Unit 5, Block 1, the common names of hydroxy acids are also derived from the sources from which they were originally obtained. A few important hydroxy acids along with their natural source, common names and IUPAC names are listed in Table 16.1.

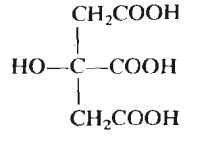
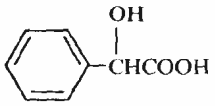
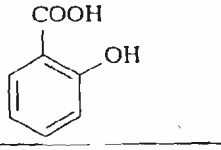
Table 16.1 : Hydroxy Acids

Structure	Source	Common Name	IUPAC Name
$HOCH_2COOH$	cane sugar juice	glycolic acid	hydroxyethanoic acid
$CH_3CHOHCOOH$	sour milk	lactic acid	2-hydroxypropanoic acid
$HOOCCH_2\underset{OH}{\underset{\vert}{C}}HCOOH$	fruit juices	malic acid	2-hydroxybutane-dioic acid
$HOOC\underset{OH}{\underset{\vert}{C}}H-\underset{OH}{\underset{\vert}{C}}HCOOH$	*dextro*-isomer found in fruits	tartaric acid	2 , 3-dihydroxy-butanedioic acid

Usually the hydroxy acids are named as derivatives of the parent acid. The position of the hydroxy group in the molecule is indicated by the Greek letters, i.e., α, β, γ, δ, ... The positions α β, γ, δ ... are as shown below:

... $CH_2-CH_2-CH_2-CH_2-COOH$

... δ γ β α

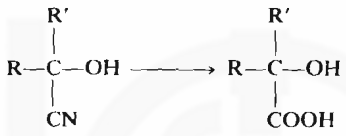
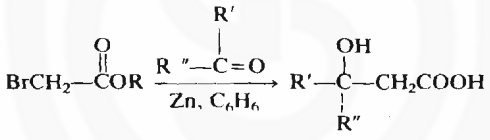
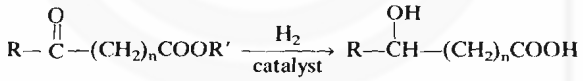
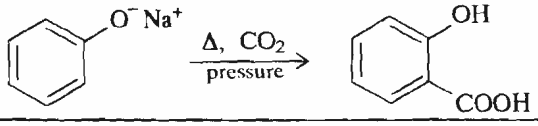
Structure	Source	Common Name	IUPAC Name
	*citrus* fruits	citric acid	2-hydroxy-1, 2, 3-propanetricarb-oxylic acid
	plums, peaches and other fruits	mandelic acid	2-hydroxy-2-phenylethanoic acid
	willow bark	salicylic acid	2-hydroxybenzene-carboxylic acid

Let us now study how hydroxy acids can be prepared in the laboratory.

16.3.1 Preparation of Hydroxy Acids

Table 16.2 gives briefly the methods of preparation of Hydroxy acids.

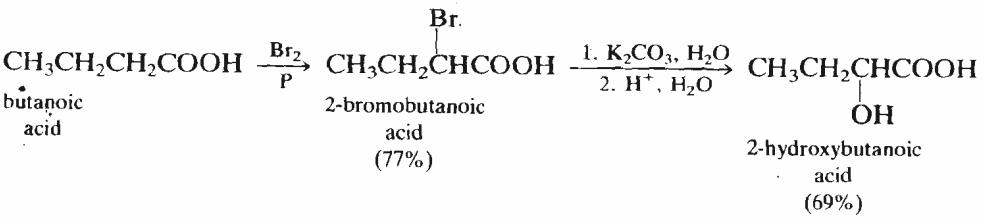
Table 16.2 : Methods of Preparation of Hydroxy Acids

	Comments
1. **From Halo acids** 	Can be used for 2-hydroxy acids but not for 3-hydroxy acids
2. **From Cyanohydrins** 	Works in acidic conditions only.
3. **From 2-Bromoesters and Carbonyl Compounds** 	Reformatsky reaction
4. **From Keto Esters** 	
5. **Kolbe Schmidt Reaction** 	Industrial method

Let us now study each of these methods in detail.

1. From Halo acids

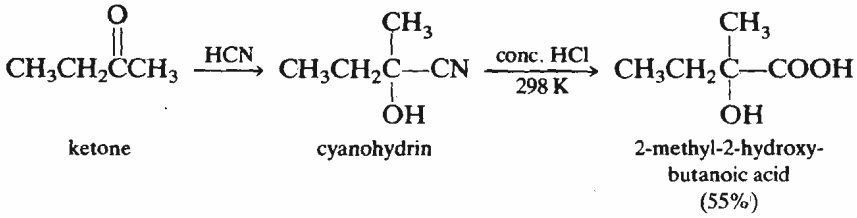
2-hydroxy (α-hydroxy) acids can be obtained by the hydrolysis of 2-halo acids. You may recall that 2-halo acids can in turn be obtained from the Hell-Volhard-Zelinsky reaction, (Sec. 15.6, Unit 15). Thus, a hydroxyl group can be introduced in the carboxylic acid in a two step process as shown below:



It was pointed out in the last section that 3-halo acids undergo elimination in base and yield unsaturated acids, therefore, a similar sequence cannot be used for the synthesis of 3-hydroxy acids.

2. By hydrolysis of cyanohydrins

Cynohydrins obtained from the reaction of HCN with aldehydes and ketones (sub-Sec. 14.4.1, Unit 14, Block 3) on hydrolysis yield hydroxy acids.

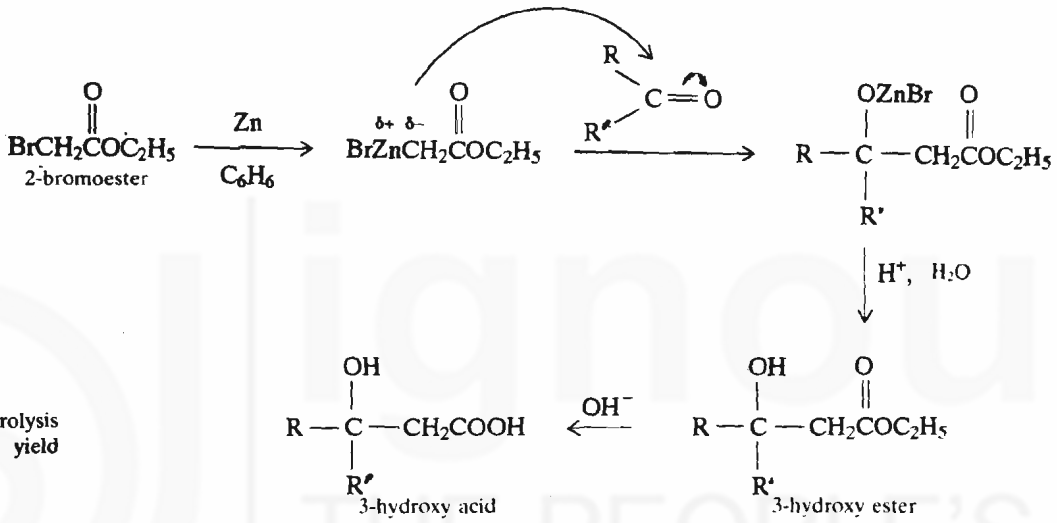


ketone — cyanohydrin — 2-methyl-2-hydroxy-butanoic acid (55%)

In the second step, it is necessary to hydrolyse the cyanohydrin under acidic conditions since under basic conditions, the first step of the reaction is reversed and the cyanohydrin intermediate returns the starting carbonyl compound.

3. Using 2-bromoesters and carbonyl compounds: Reformatsky reaction

2-Bromoesters react with aldehydes or ketones in the presence of zinc metal in nonhydroxylic solvents like benzene to yield 3-hydroxy esters.

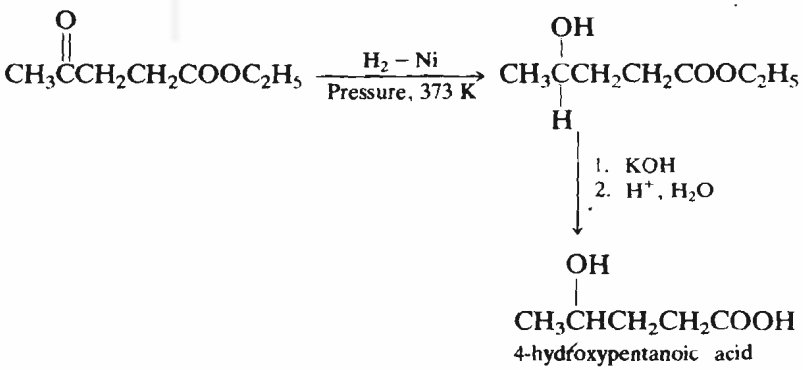


3-Hydroxy esters on hydrolysis under acidic conditions yield unsaturated esters.

The 3-hydroxy ester on alkaline hydrolysis finally yields 3-hydroxy acid.

4. By Catalytic reduction of keto esters

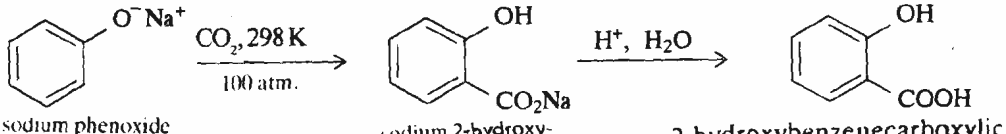
Hydroxy acids may also be prepared by catalytic reduction of the corresponding keto esters, e.g.,



5. Industrial preparation of 2-hydroxybenzenecarboxylic acid: Kolbe Schmidt reaction

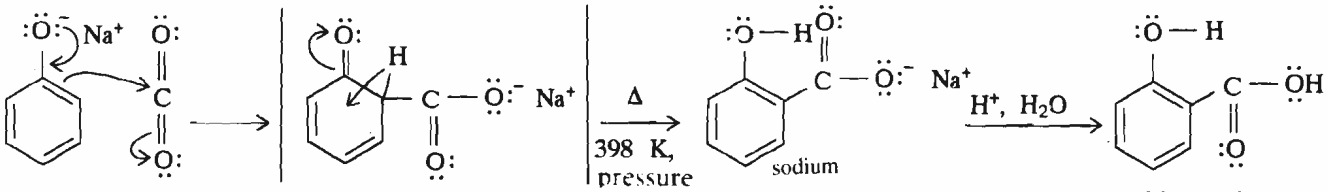
This reaction was also discussed in sub-Sec. 12.6.3, Unit 12, Block 3.

It involves heating the sodium salt of benzenol (phenol) with CO_2 under pressure.



sodium phenoxide — sodium 2-hydroxy-benzoate — 2-hydroxybenzenecarboxylic acid

It involves the initial absorption of CO_2 at room temperature to yield sodium phenyl carbonate as shown below:



sodium phenyl carbonate — 2-hydroxybenzoate — 2-hydroxybenzene-carboxylic acid

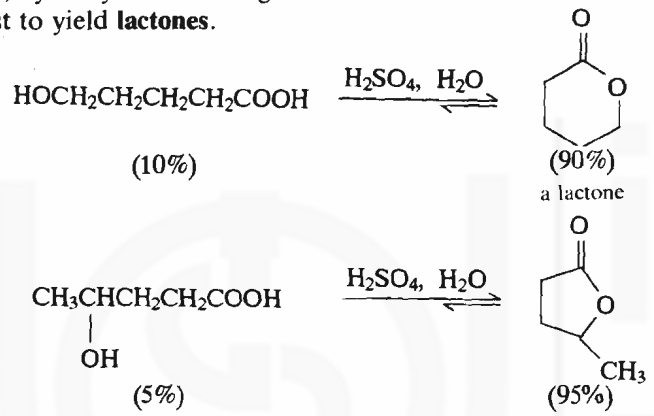
Sodium phenyl carbonate on heating to 398 K under pressure rearranges to sodium 2-hydroxybenzoate. Subsequent acidification yields 2-hydroxybenzenecarboxylic acid.

16.3.2 Reactions of Hydroxy Acids

Since the hydroxy acids contain a **hydroxy** and a **carboxy** functional group, they exhibit the reactions of these functional groups particularly when these groups are far apart. For example, the carboxy group can be converted into the ester, amide, nitrile or alkanoyl halide and the hydroxyl group can be transformed into an ester or an ether.

In addition to the above reactions which are characteristic of individual functional groups, hydroxy acids undergo intramolecular esterification in the presence of acid catalyst to yield **lactones**.

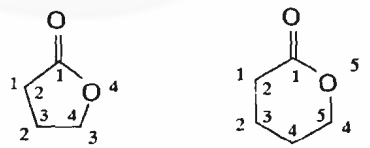
Lactones are cyclic esters.



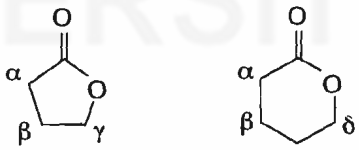
Lactone formation is favoured when the lactone formed is five or six-membered. Lactones containing five-membered rings are referred to as γ-lactones whereas the six-membered lactones are referred to as δ-lactones.

Reactions that are expected to produce hydroxy acids often yield lactones if a five or six membered lactone ring is possible.

A lactone can be named by replacing the *-oic acid* ending of the parent carboxylic acid by- *olide* and identifying its oxygenated atom by a number. This is illustrated below.



4-butanolide — 5-pentanolide

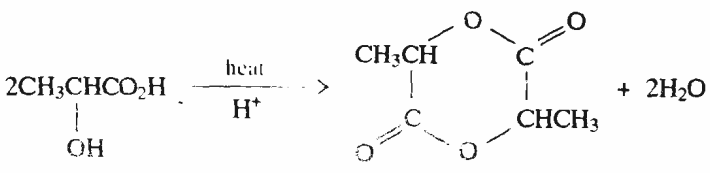


γ-lactone — δ-lactone

Lactones with four-membered rings (i.e., β-lactones) have been detected as highly reactive intermediates in some reactions. But, attempts to synthesise them from 3-hydroxy acids yield 2,3-unsaturated acids, i.e.,

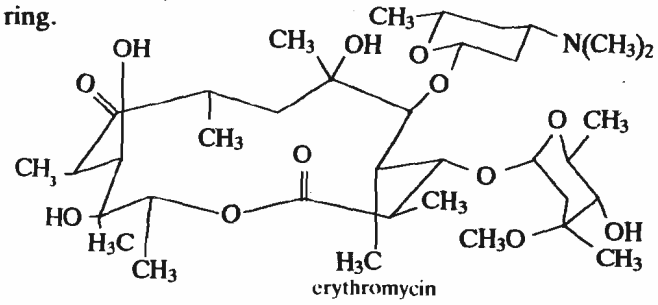
3-hydroxy acid

On the other hand, 2-hydroxy acids form a cyclic diester, called **lactide** as shown below:



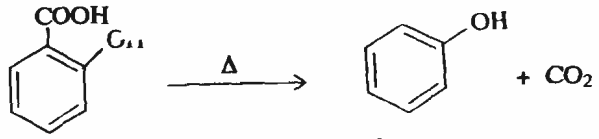
a lactide

Synthesis of large ring lactones called **macrocylic lactones** is of special synthetic interest because substituted macrocyclic lactones form the basic framework of many antibiotics of which erythromycin is one example. Erythromycin has a 14-membered lactone ring.



erythromycin

However, 2-hydroxybenzenecarboxylic acid on slow heating undergoes decarboxylation to yield benzenol.



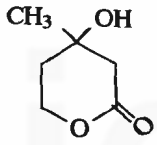
2-hydroxybenzenecarboxylic acid

benzenol

SAQ 1

Write the structure of the hydroxy acid from which the following lactones can be synthesised.

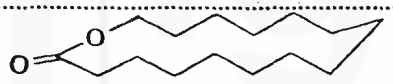
a)



mevalonolactone

(an intermediate in the biosynthesis of terpenes and steroids)

b)



1,5-pentadecanolide
(used in perfumes)

Proteins will be dealt in detail in Unit 20.

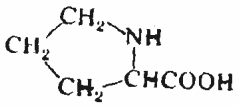
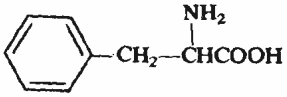
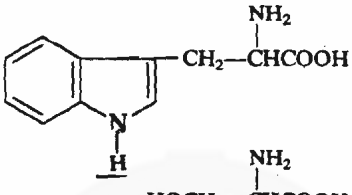
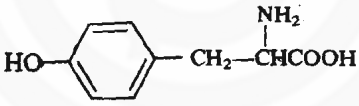
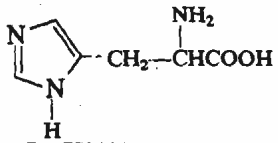
16.4 AMINO ACIDS

Amino acids are the compounds which contain both an amino group and a carboxy group in their molecules. They constitute a particularly important class of difunctional compounds as they are the building blocks of proteins.

While several hundred different amino acids are known to occur naturally, 20 of them deserve special mention as they are present in proteins. These amino acids are listed in Table 16.3. As given in this Table, for amino acids trivial names are common. The convention to use a three letter code, as an abbreviation, for each amino acid is also given in the table. These abbreviations are particularly useful in designating the sequence of amino acids in peptides and proteins which you will study in Unit 20.

Table 16.3 : Common Amino Acids found in Proteins

$R-\underset{\displaystyle NH_2}{\underset{\vert}{C}}HCOOH$	Name	Abbreviation
$H-\underset{\displaystyle NH_2}{\underset{\vert}{C}}HCOOH$	glycine	Gly
$CH_3-\underset{\displaystyle NH_2}{\underset{\vert}{C}}HCOOH$	alanine	Ala
$CH_3CH(CH_3)-\underset{\displaystyle NH_2}{\underset{\vert}{C}}HCOOH$	valine	Val

$R-CH(NH_2)COOH$	Name	abbreviation
$CH_3CH(CH_3)CH_2CH(NH_2)COOH$	leucine	Leu
$CH_3CH_2CH(CH_3)CH(NH_2)COOH$	isoleucine	Ile
$CH_3SCH_2CH_2CH(NH_2)COOH$	methionine	Met
	proline	Pro
	phenylalanine	Phe
	tryptophan	Trp
$HOCH_2CH(NH_2)COOH$	serine	Ser
$CH_3CH(OH)CH(NH_2)COOH$	threonine	Thr
$HSCH_2CH(NH_2)COOH$	cysteine	Cys
	tyrosine	Tyr
$H_2NCOCH_2CH(NH_2)COOH$	asparagine	Asn
$H_2NCOCH_2CH_2CH(NH_2)COOH$	glutamine	Gln
$HOCOCH_2CH(NH_2)COOH$	aspartic acid	Asp
$HOCOCH_2CH_2CH(NH_2)COOH$	glutamic acid	Glu
$H_2NCH_2CH_2CH_2CH_2CH(NH_2)COOH$	lysine	Lys
$H_2NC(=NH)NHCH_2CH_2CH_2CH(NH_2)COOH$	arginin	Arg
	histidine	His

Amino acids can be classified as α, β, γ, etc., depending upon the location of the amino group on the carbon chain containing the carboxy function. Some examples are illustrated below:

$H_2N-\underset{\alpha}{CH_2}COOH$
2-aminoethanoic acid
(α-amino acid)

$H_2N\underset{\gamma}{CH_2}\underset{\beta}{CH_2}\underset{\alpha}{CH_2}COOH$
4-aminobutanoic acid
(γ-amino acid)

$H_2N\underset{\beta}{CH_2}\underset{\alpha}{CH_2}COOH$
3-aminopropanoic acid
(β-amino acid)

Thus, the amino acids listed in Table 16.3 are α-amino acids or 2-amino acids.

Having learnt about some general aspects of the structure of amino acids, let us now focus our attention on the synthesis of 2-amino acids.

16.4.1 Synthesis of 2-amino Acids

2-Amino acids can be synthesised by using the methods given in Table 16.4.

Table 16.4 : Methods of preparation of 2-amino acids

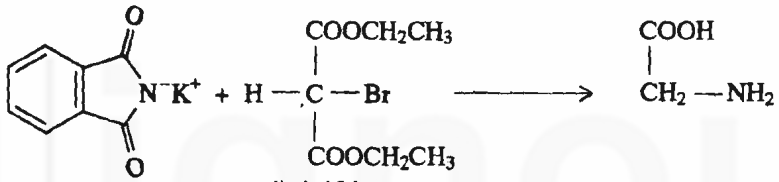
1. From 2-halo acids

$$R-\underset{X}{\underset{|}{C}}HCOOH + NH_3 \longrightarrow R-\underset{NH_2}{\underset{|}{C}}HCOOH$$

2. From aldehydes : Strecker Synthesis

$$R-CHO + NH_3 + HCN \longrightarrow R-\underset{NH_2}{\underset{|}{C}}H-COOH$$

3. By *N*-alkylation of 1,2-benzenedicarboxylic imide (phthalimide) anion.



diethyl 2-bromo-propanedioate

2-substituted amino acids can also be prepared.

1. From 2-halo acids

In Unit 15, Sec. 15.6, you studied that 2-halo acids can be obtained from carboxylic acids using the Hell-Volhard-Zelinsky reaction. These 2-halo acids on nucleophilic substitution by NH_3 yield 2-amino acids as shown below:

$$CH_3\underset{Br}{\underset{|}{C}}HCOOH + 2NH_3 \xrightarrow{H_2O} CH_3\underset{NH_2}{\underset{|}{C}}HCOOH + NH_4Br + NH_4Br$$

2-bromopropanoic acid — 2-aminopropanoic acid (65-70%)

2. From aldehydes : Strecker synthesis

It was pointed out in sub-Sec. 14.4.1, Unit 14, Block 3 that aldehydes on reaction with hydrogen cyanide yield a cyanohydrin. But, when the same reaction is carried out in the presence of ammonia, the first step is probably the initial formation of an imine from the reaction of the aldehyde with ammonia. The addition of hydrogen cyanide to the imine furnishes the corresponding 2-amino nitrile which on acidic or basic hydrolysis yields the 2-amino acid. This is also known as **Strecker synthesis**. The sequence of reactions involved in this synthesis is given below.

$$CH_3\overset{O}{\overset{\|}{C}}H \xrightarrow[-H_2O]{NH_3} CH_3\overset{NH}{\overset{\|}{C}}H \xrightarrow{HCN} CH_3-\underset{H}{\underset{|}{\overset{NH_2}{\overset{|}{C}}}}-CN \xrightarrow{H^+, H_2O} CH_3\underset{NH_2}{\underset{|}{C}}HCOOH$$

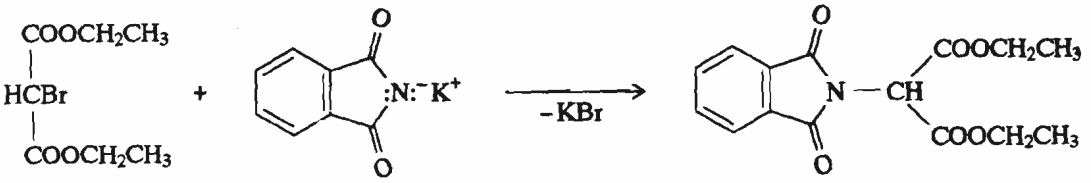
ethanal — imine — 2-aminopropane-nitrile — 2-aminopropanoic acid (55%)

3. From potassium phthalimide

Diethyl 2-bromopropanedioate can be prepared by the bromination of diethyl propanedioate.

This method is a modification of the Gabriel synthesis of amines which will be discussed in Unit 19, Sec. 19.6.

It involves the *N*-alkylation of 1,2-benzenedicarboxylic imide (phthalimide) anion with diethyl 2-bromopropanedioate as shown below:

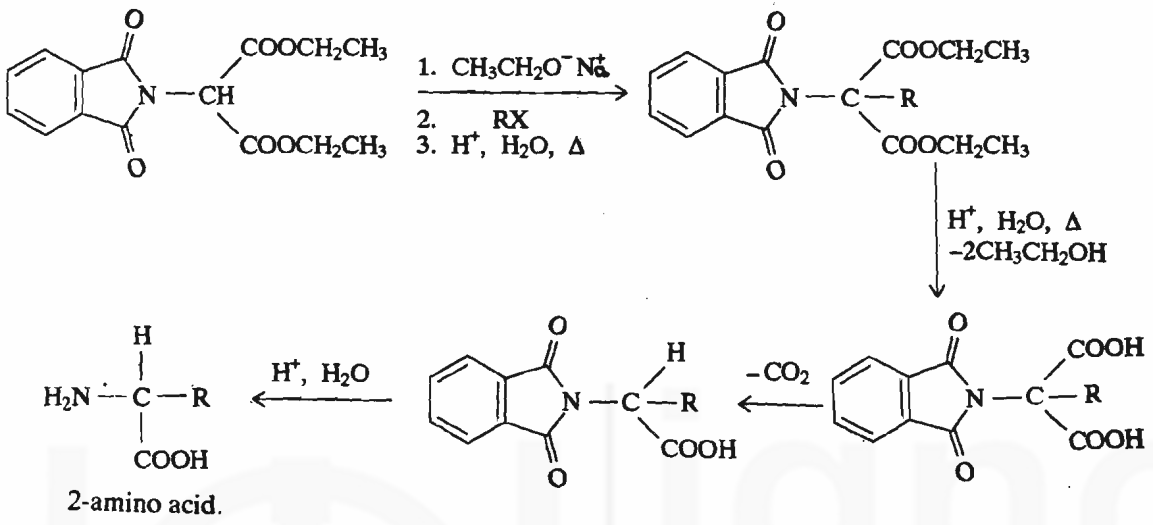


diethyl 2-bromo-propanedioate (diethyl 2-bromo-malonate)

potassium 1,2-benzene-dicarboxylic imide (potassium phthalimide)

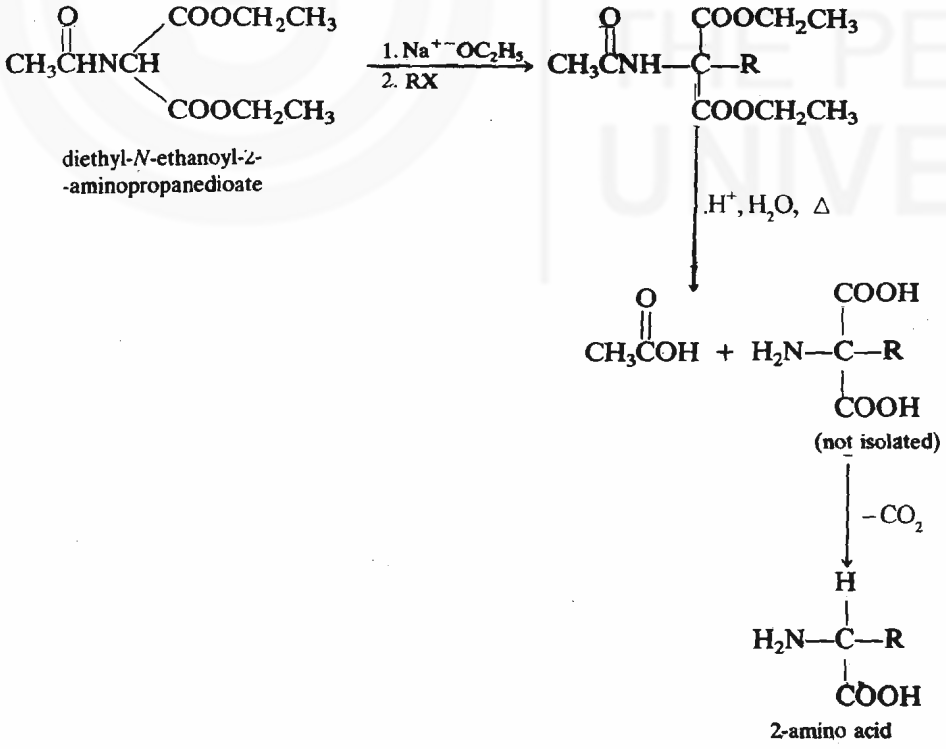
N-alkylated product (85%)

The advantage of this method is that the alkylated product obtained in the above reaction can be further alkylated to yield a variety of substituted amino acids by the following sequence of reactions.



Thus, we can get a variety of amino acids depending upon the nature of R.

A variation of the above method utilises diethyl *N*-ethanoyl-2-aminopropanedioate instead of the imide derivative. The sequence of reactions involved is shown below:



diethyl-*N*-ethanoyl-2-aminopropanedioate

16.4.2 Physical Properties of Amino Acids

1. Acid-base properties

Because amino acids contain both carboxy and amino groups in their molecules, they are *amphoteric* in nature, i.e. they behave both as acids and bases. Amino acids

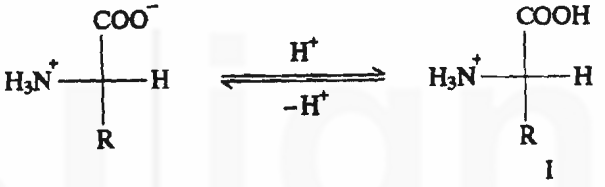
actually exist as *inner salts*, called **zwitterions**. A zwitterionic structure is possible for amino acids because the amino group is basic in nature and can accept a proton from the acidic carboxy group. A zwitterion can be represented as shown below.

a zwitterion

The highly polar nature of zwitterion allows the formation of strong crystal lattices similar to the ionic compounds. Amino acids, therefore, resist conversion from solid to liquid state and *do not melt* but decompose on heating.

The zwitterionic nature is also reflected in their higher solubility in water and low solubility in nonpolar solvents. In addition to the above observations, large dipole moments also indicate the zwitterionic nature of amino acids.

Let us now study the zwitterionic form of amino acids in more detail. You can see in the zwitterion shown above that the amino group is protonated and the carboxy group exists as carboxylate anion. Thus, the acidic group is a substituted ammonium ion and the basic group is the carboxylate anion. As a result,in strongly acidic medium i.e., at low pH, the carboxylate group will be protonated to yield the following species.

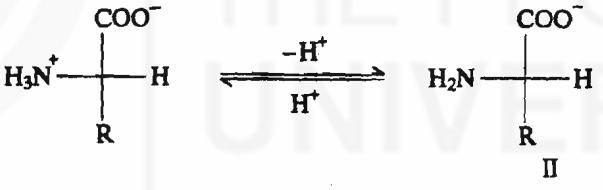


zwitterion

I

species present in strongly acidic medium

Let us next consider the species present in strongly basic medium, i.e. at higher pH of the solution. Under these conditions, the proton will be removed from the $\overset{+}{N}H_3$ group to yield the following species.

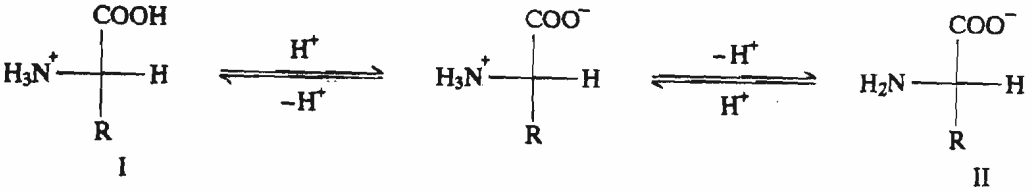


zwitterion

II

species present in strongly basic conditions

Thus, we can write a combined equation for the acid-base behaviour of the amino acids as shown below.



I

low pH (acidic conditions)

zwitterion

II

high pH (basic conditions)

You can see that a low pH, species I has a net positive charge and has two acidic sites ($\overset{+}{N}H_3$ and COOH). On the other hand, at high pH, species II has a net negative charge and has two basic sites (NH_2 and COO^-). It is clear from the above equation that the amino group will be first protonated and then the carboxylate anion. Also at some intermediate pH, the amino acid exists as a zwitterion *with no net charge*. The pH at which this occurs is known as **isoelectric point**, pH_i of the amino acid. At this pH, the amino acid is stationary in an electric field, i.e., it migrates neither to the negative pole nor to the positive pole because the charges on it are balanced.

Since there are two acidic sites in an amino acid, it has two pK_a values. The pK_a value corresponding to the more acidic site is referred to as pKa_1 and that corresponding to the less acidic site as pKa_2. Thus, for the simplest amino acid, glycine, we can write the two equilibria as follows:

$$H_3\overset{+}{N}CH_2COOH + H_2O \underset{pKa_1 = 2.4}{\rightleftharpoons} H_3\overset{+}{N}CH_2COO^- + H_3O^+$$

and

$$H_3\overset{+}{N}CH_2COO^- + H_2O \underset{pKa_2 = 9.8}{\rightleftharpoons} H_2NCH_2COO^- + H_3O^+$$

At this stage you can compare the pKa_1, with the pK_a of ethanoic acid which is equal to 4.76. This leads to the conclusion that due to the electron withdrawing nature of the protonated amino group, the acidity of amino acid is increased as compared to ethanoic acid. Table 16.5 lists the pK_a values and pH_i of some amino acids.

Table 16.5 : pK_a and pH_i values of some amino acids

Amino acid	pKa_1	pKa_2	pH_i
Glycine	2.34	9.60	5.97
Alanine	2.34	9.69	6.00
Valine	2.32	9.62	5.96
Leucine	2.36	9.60	5.98
Isoleucine	2.36	9.60	6.02
Methionine	2.28	9.21	5.74
Proline	1.99	10.60	6.30
Phenylalanine	1.83	9.13	5.48
Tryptophan	2.83	9.39	5.89
Asparagine	2.02	8.80	5.41
Glutamine	2.17	9.13	5.65
Serine	2.21	9.15	5.68
Threonine	2.09	9.10	5.60

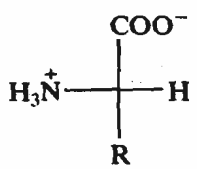
You can verify from Table 16.5 that $pH_i = \frac{pKa_1 + pKa_2}{2}$

The amino acids having acidic and basic side chains are characterised by three pK_a values. The third pK_a value, i.e., pKa_3 reflects the nature of the functional group present in the side chain.

2. Stereochemistry of amino acids

With the exception of 2-aminoethanoic acid (glycine), the 2-amino acids have at least one chiral centre.

According to the older D, L system of specifying the configuration (discussed in Sec. 3.3, Unit 3, Block 1), the 2-amino acids derived from animals or higher plants were found to have L configuration, i.e., they have the same relative configuration as L-glyceraldehyde. Thus, we can write the following Fischer projection formula of an L amino acid.

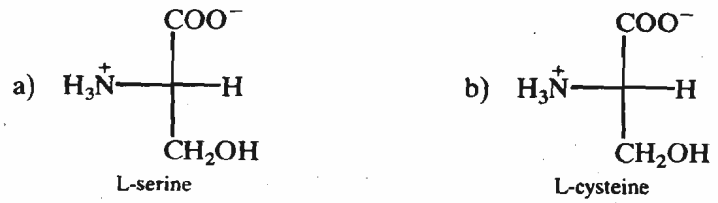


an L amino acid

On the basis of your knowledge about assigning the absolute configuration, can you attempt the following SAQ?

SAQ 2

What is the absolute configuration (*R* or *S*) of the following amino acids?



L-serine L-cysteine

.....

.....

Enzymes use up one enantiomer preferentially.

It is also worthwhile to mention here that the amino acids obtained by synthesis using the methods discussed before are racemic mixtures. Enantiomerically pure amino acids can be obtained by resolution of the racemic mixtures or by biological methods using enzymes.

3. Spectral properties of amino acids

Amino acids do not give any very useful absorptions in the ultraviolet spectra unless they possess aromatic groups such as those present in phenylalanine, tryptophan and tyrosine in which case they show λmax between 260 to 280 nm. However, these absorptions are more useful in monitoring the chemical and conformational changes in the proteins than in simple amino acids.

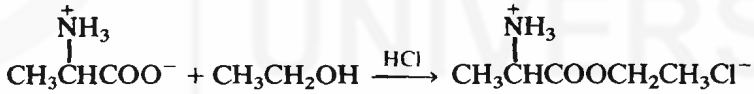
The infrared spectra of 2-amino acids show a strong absorption band near 1600 cm^{-1} due to the carboxylate anion. The N-H stretching (in $\overset{+}{N}H_3$) appears between 2600-3100 cm^{-1} as a strong broad band.

16.4.3 Reactions of Amino Acids

Amino acids undergo many of the reactions characteristic of the amino and carboxylic acid groups. For example, a typical reaction of the carboxy group is esterification and that of the amino functional group is alkanoylation. Let us now study these reactions in detail.

1. Esterification

The carboxy group of an amino acid can be esterified in the normal way using excess of an alcohol under acidic conditions.

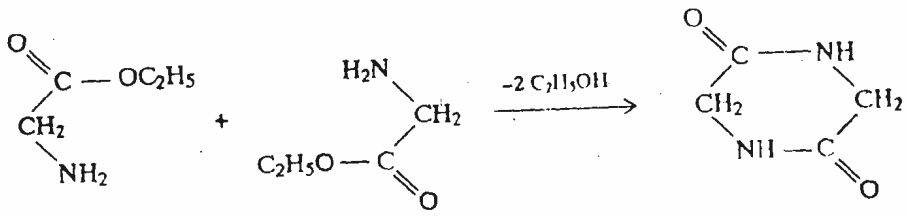


(90-95%)
hydrochloride salt of amino acid ester

Methyl, ethyl and benzyl esters are used as intermediates in the synthesis of peptides.

Neutralisation of the hydrochloride with alkali yields the ester.

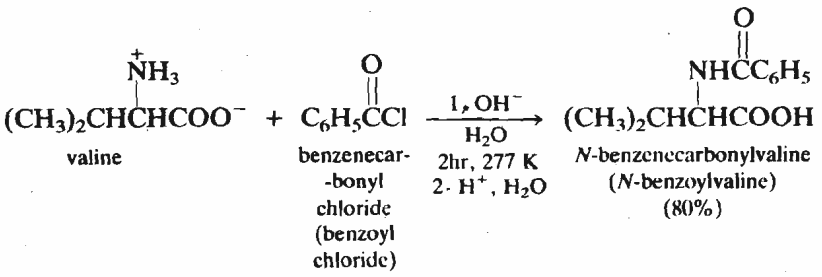
Esters of amino acids undergo intermolecular cyclisation to yield cyclic amides as shown below:

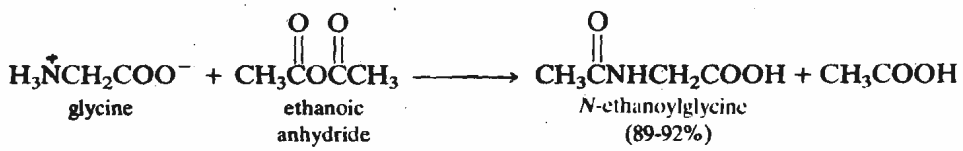


2,5-diazacyclohexane-1,4-dione (diketopiperazine)

2. Alkanoylation of amino acids

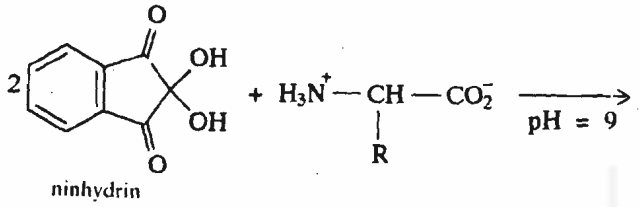
Alkanoylation of the amino group of an amino acid is carried out under basic conditions so that the free amino form is present in substantital concentration. Alkanoylation can be carried out by alkanoyl halides (acid chlorides) or carboxylic anhydrides. The product is finally obtained by acidifying the reaction mixture.

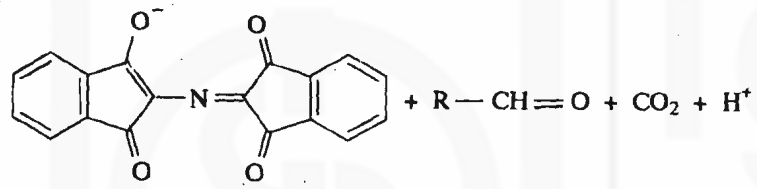




3. Reaction with Ninhydrin

When the aqueous solution of a 2-amino acid is treated with triketohydrindene hydrate (ninhydrin), a blue-violet colour is obtained.





Ruhemann's purple λ_{max} = 570 nm

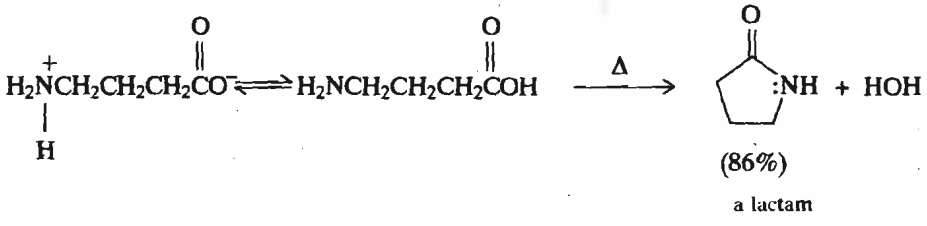
Ninhydrin test is given by amino acids containing primary amino group.

The blue-violet coloured compound formed is also known as *Ruhemann's purple.*

This is an important reaction used in the detection of small amounts of amino acids.

4. Formation of lactones

Some amino acids undergo cyclisation to yield cyclic amides, called **lactams.** See Sec. 17.8, Unit 17 for nomenclature of lactams.



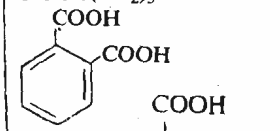
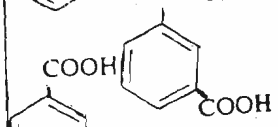
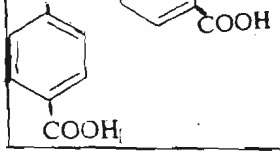
5. Formation of peptides

In addition to the above reactions, amino acids constitute the structural units of peptides and proteins about which you will study in Unit, 20, Sec. 20.3.

16.5 DICARBOXYLIC ACIDS

As the name indicates, dicarboxylic acids are the acids which contain two carboxy groups in their molecules. You may recall from Block 1, Unit 1, Sec. 1.6 that dicarboxylic acids are called alkanedioic acids in the IUPAC system of nomenclature. Table 16.6 lists the common as well as IUPAC names for some saturated aliphatic and aromatic dicarboxylic acids.

Table 16.6 : Some Dicarboxylic acids

Structure	Common name	IUPAC name
HOOCCOOH	oxalic acid	ethanedioic acid
$HOOCCH_2COOH$	malonic acid	propanedioic acid
$HOOC(CH_2)_2COOH$	succinic acid	butanedioic acid
$HOOC(CH_2)_3COOH$	glutaric acid	pentanedioic acid
$HOOC(CH_2)_4COOH$	adipic acid	hexanedioic acid
$HOOC(CH_2)_5COOH$	pimelic acid	heptanedioic acid
	phthalic acid	1,2-benzenedicarboxylic acid
	isophthalic acid	1,3-benzenedicarboxylic acid
	terephthalic acid	1,4-benzenedicarboxylic acid

Let us now study how dicarboxylic acids can be obtained.

16.5.1 Preparation of Dicarboxylic Acids

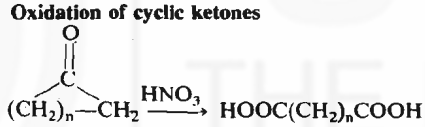
Table 16.7 : Methods of preparation of Dicarboxylic Acids

1. **By hydrolysis of nitriles**

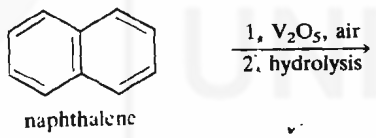
$$NC{-}CH_2{-}(CH_2)_n{-}COOH \xrightarrow{H^+/H_2O} HOOC{-}CH_2{-}(CH_2)_n{-}COOH$$

$$NC(CH_2)_nCN \xrightarrow{H^+/H_2O} HOOC(CH_2)_nCOOH$$

2. **Oxidation of cyclic ketones**



3. **Oxidation of naphthalene**



naphthalene — 1,2-benzenedicarboxylic acid

4. **Oxidation of dimethylbenzenes.**

Let us now study these methods in detail.

1. By hydrolysis of nitriles

You have earlier studied this method for the preparation of monocarboxylic acids in Sec. 15.3, Unit 15. It can also be applied to synthesise dicarboxylic acids. The starting material can be either a halo acid or a dibromoalkane. **For example,** chloroethanoic acid can be converted into cyanoethanoic acid which on hydrolysis yields the propanedioic acid.

$$\underset{\text{chloroethanoic acid}}{ClCH_2COOH} \xrightarrow{KCN} \underset{\text{cyanoethanoic acid}}{NCCH_2COOH} \xrightarrow[\text{hydrolysis}]{H_2O/H^+} \underset{\text{propanedioic acid}}{HOOCCH_2COOH}$$

The substitution by cyano group and hydrolysis can also be carried in a **single step** using NaOH and NaCN as shown below:

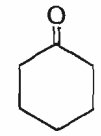
$$ClCH_2COOH + NaOH + NaCN \xrightarrow{H_2O} [NCCH_2COO^-Na^+] \xrightarrow[H_2O]{NaOH} Na^+\bar{O}OCCH_2COO^-Na^+ \xrightarrow{HCl} \underset{(77-82\%)}{HOOCCH_2COOH}$$

Similarly, 1,3-dibromopropane can be converted into 1,3-dicyanopropane which on acid hydrolysis yields pentanedioic acid as shown below:

$$\underset{\text{1,3-dibromopropane}}{BrCH_2CH_2CH_2Br} \xrightarrow[H_2O]{NaCN} \underset{\text{1,3-dicyanopropane (82\%)}}{NCCH_2CH_2CH_2CN} \xrightarrow{H^+,\ H_2O} \underset{\text{pentanedioic acid (84\%)}}{HOOCCH_2CH_2CH_2COOH}$$

2. By oxidation of cyclic ketones

Cyclic ketones on oxidation with nitric acid yield dicarboxylic acids. This is illustrated by the synthesis of hexanedioic acid from cyclohexanone.

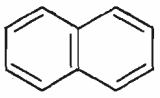


cyclohexanone

$$\xrightarrow{HNO_3} \underset{\text{hexanedioic acid}}{HOOCCH_2CH_2CH_2CH_2COOH}$$

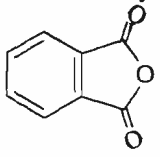
3. Oxidation of naphthalene

Vigorous oxidation of naphthalene yields the anhydride of 1,2-benzenedicarboxylic acid from which the acid can be obtained on hydrolysis.



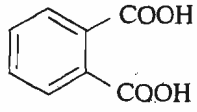
naphthalene

$\xrightarrow[\Delta]{V_2O_5,\ air}$



1,2-benzenedicarboxylic anhydride

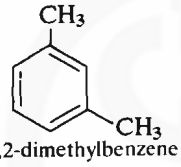
$\xrightarrow{hydrolysis}$



1,2-benzenedicarboxylic acid

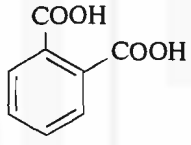
4. Oxidation of dimethylbenzenes

Alternatively, isomeric dimethylbenzenes can be oxidised to yield the corresponding benzenedicarboxylic acids.

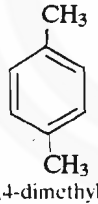


1,2-dimethylbenzene

$\xrightarrow{O_2,\ Co^{3+}}$

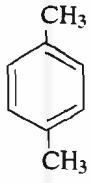


1,2-benzenedicarboxylic acid

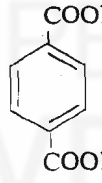


1,4-dimethylbenzene

$+ O_2 \xrightarrow[Co^{3+}]{CH_3COOH}$



$\xrightarrow[O_2,\ Co^{3+}]{CH_3COOH}$



1,4-benzenedicarboxylic acids

16.5.2 Physical Properties of Dicarboxylic Acids

Physical properties such as melting point and dissociation constants for some dicarboxylic acids are listed in Table 16.8.

Table 16.8 : Physical properties of some dicarboxylic acids

Acid	m.p./K	$k_1 \times 10^5$ at 298 K	$k_2 \times 10^5$ at 298 K
ethanedioic acid	462	5400.0	5.4
propanedioic acid	409 (decomposition)	140.0	0.20
butanedioic acid	458	6.2	0.23
pentanedioic acid	371	4.6	0.39
hexanedioic acid	425	3.7	0.24
1,2-benzene-dicarboxylic acid	504	130.0	0.39
1,3-benzene-dicarboxylic acid	618	29.0	2.5
1,4-benzene-dicarboxylic acid	sublimes	31.0	1.5

where k_1 and k_2 refer to the following equilibria, respectively.

$$HOOC(CH_2)_nCOOH \overset{k_1}{\rightleftharpoons} HOOC(CH_2)_nCOO^- + H^+$$

$$HOOC(CH_2)_nCOO^- \overset{k_2}{\rightleftharpoons} {}^-OOC(CH_2)_nCOO^- + H^+$$

You can refer back to sub-Sec 5.4.1 of Unit 5, Block 1 where we explained why k_2 of a dicarboxylic is less than k_1.

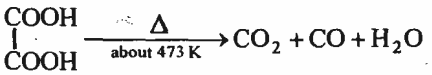
16.5.3 Reactions of Dicarboxylic Acids

1. Action of heat on dicarboxylic acids

The dicarboxylic acids undergo a variety of thermal reactions depending upon the length of the carbon chain separating the two carboxy groups. Let us study the effect of heat on some simple dicarboxylic acids.

i) Ethanedioic acid

It decomposes on heating to yield carbon dioxide, carbon monoxide and water.

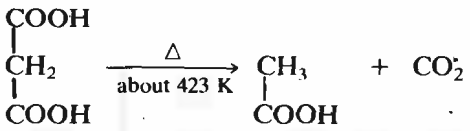


ethanedioic acid

ii) Propanedioic acid

It also decarboxylates on heating at 423 K to yield ethanoic acid.

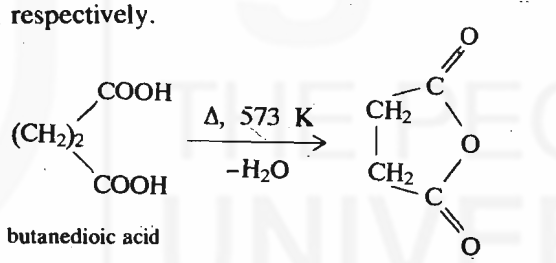
Decarboxylation is the characteristic feature of all those acids which have two carboxy groups on the same carbon atom as also of monocarboxylic acids having a strong electronegative group on the carbon atom next to the carboxy group.



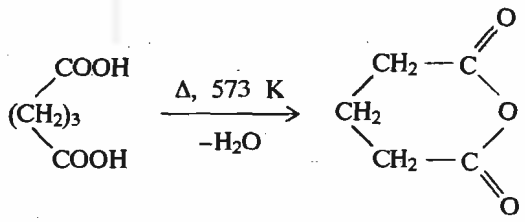
propanedioic acid — ethanoic acid

iii) Butanedioic and pentanedioic acids

These dicarboxylic acids form cyclic anhydrides containing five and six membered rings, respectively.



butanedioic acid — butanedioic anhydride

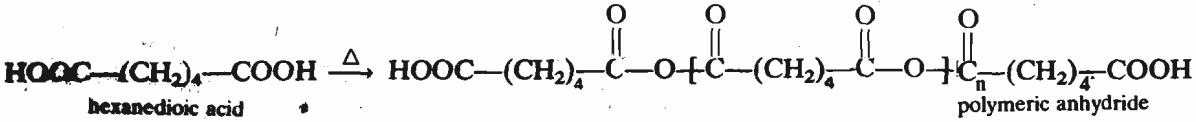


pentanedioic acid — pentanedioic anhydride

The formation of cyclic anhydrides is greatly aided by the use of dehydrating agents such as PCl_3, P_2O_5, $POCl_3$ and $SOCl_2$.

iv) Hexanedioic and higher dicarboxylic acids

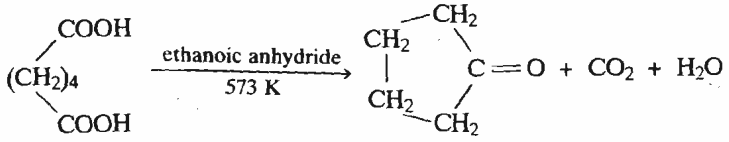
Only traces of a seven-membered ring compound, i.e., the corresponding anhydride is formed when hexanedioic acid is heated. Instead, the reaction yields a polymeric anhydride of relatively high molecular weight.



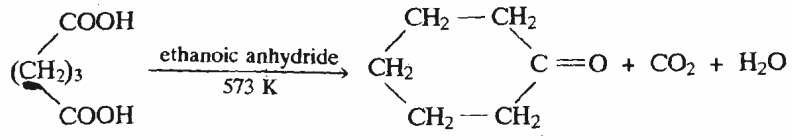
hexanedioic acid — polymeric anhydride

Dicarboxylic acids containing more than six carbon atoms behave in a similar fashion.

However, when hexanedioic and heptanedioic acids are heated with ethanoic anhydride and the product is distilled at 573 K, a cyclic ketone is obtained in each case.



hexanedioic acid — cyclopentanone

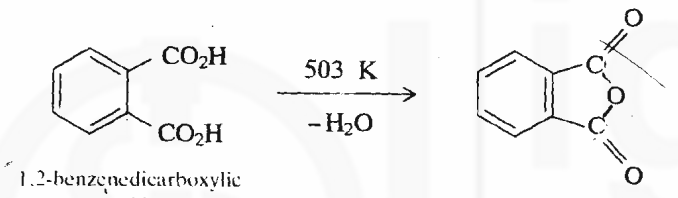


heptanedioic acid — cyclohexanone

Hexanedioic acid is used for the preparation of polyesters and is an intermediate in the manufacture of nylon 6,6 — a polyamide formed from hexanedioic acid and hexamethylene diamine, $NH_2(CH_2)_6NH_2$.

v) Benzenedicarboxylic acids

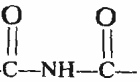
1,2-Benzenedicarboxylic acid forms a cyclic anhydride at its melting point. The two isomeric acids, 1,3-benzenedicarboxylic acid and 1,4-benzenedicarboxylic acid, evidently cannot form the anhydrides.

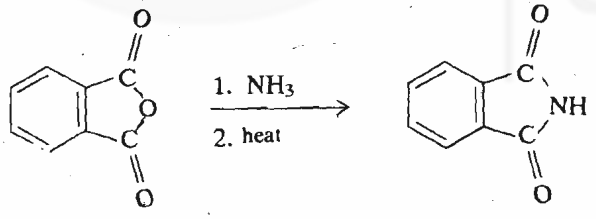


1,2-benzenedicarboxylic acid — cyclic anhydride

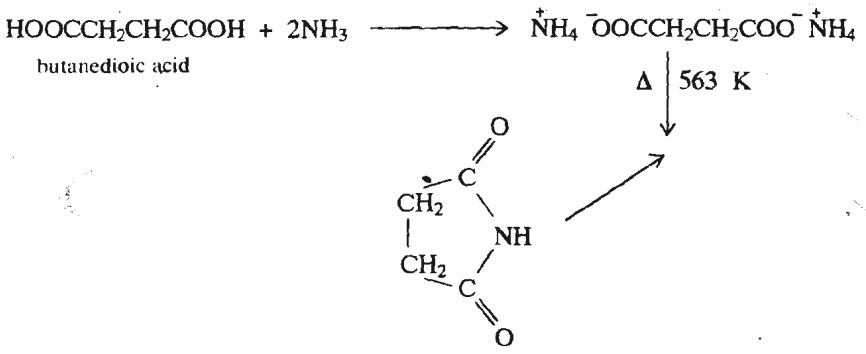
2. Formation of imides

Imides are the nitrogen analogs of anhydrides. They can be prepared by the reaction of ammonia or amines with anhydrides or by heating the ammonium salt of the dicarboxylic acid. The formation of cyclic imides from 1,2-benzenedicarboxylic anhydride and butanedioic acid is shown below:

Imides contain two alkanoyl (acyl) groups attached to a nitrogen, i.e., they contain  linkage.



1,2-benzenedicarboxylic anhydride — 1,2-benzenedicarboxylicimide (phthalimide) (97%)



butanimide (82-83%)

$CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$

diethyl propanedioate
(diethyl malonate)

3. An important derivative of propanedioic acid is its diethyl ester, called as diethyl propanedioate. It is a highly versatile reagent in organic synthesis about which you will study in Sec. 16.7 where we will also discuss the synthetic utility of ethyl-3-oxobutanoate which is a keto ester. But before that let us first study about keto acids.

16.6 KETO ACIDS

Keto acids are the compounds containing both the keto and the carboxy groups in their molecules. Depending upon the position of the keto group, keto acids are named as 2-oxo or 3-oxo alkanoic acids, etc.

$CH_3\overset{O}{\overset{\|}{C}}COOH$

2-oxopropanoic acid
(pyruvic acid)

$CH_3\overset{O}{\overset{\|}{C}}CH_2COOH$

3-oxobutanoic acid

2-Oxopropanoic acid is a physiologically important natural keto acid as the two molecules, 2-oxopropanoic acid and 2-hydroxypropanoic acid (lactic acid), are interconverted in the body by an enzyme present in the muscles called *lactic acid dehydrogenase*.

Lactic acid dehydrogenase reduces 2-oxopropanoic acid to 2-hydroxypropanoic acid during physical exercise. The enzyme reverses this process when the muscles rest.

$CH_3\overset{O}{\overset{\|}{C}}COOH \underset{}{\overset{\text{Lactic acid dehydrogenase}}{\rightleftharpoons}} HO\overset{H}{\underset{H_3C}{\diagdown\diagup}}C-COOH$

2-oxopropanoic acid

(*S*)-(+)-2-hydroxypropanoic acid
(lactic acid)

3-Oxobutanoic acid undergoes decarboxylation on mild heating.

$CH_3\overset{O}{\overset{\|}{C}}CH_2COOH \xrightarrow[-CO_2]{\text{heat}} CH_3\overset{O}{\overset{\|}{C}}CH_3$

3-oxobutanoic acid — propanone

Thus, 3-oxobutanoic acid due to its instability, is not of much importance whereas its esters, particularly ethyl 3-oxobutanoate, are of great synthetic utility about which you will study in the next section. You can see that there is a similarity in the structures of ethyl 3-oxobutanoate and diethyl propanedioate. Therefore, both undergo similar kinds of reactions to yield a large variety of new compounds about which you will now study.

$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$

ethyl 3-oxobutanoate

16.7 ETHYL 3-OXOBUTANOATE AND DIETHYL PROPANEDIOATE

Claisen condensation is the ester analog of the aldol condensation which you studied in sub-Sec. 14.4.2, Unit 14, Block 3.

3-Oxo esters are generally prepared by a condensation reaction, called **Claisen condensation**. Esters undergo self condensation on treatment with alkoxide bases to yield 3-oxo ester and an alcohol.

$2\,RCH_2\overset{O}{\overset{\|}{C}}OR' \xrightarrow[2.\ H^+,\ H_2O]{1.\ NaOR''} RCH_2\overset{O}{\overset{\|}{C}}\underset{R}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OR' + R'OH$

ester — 3-oxo ester

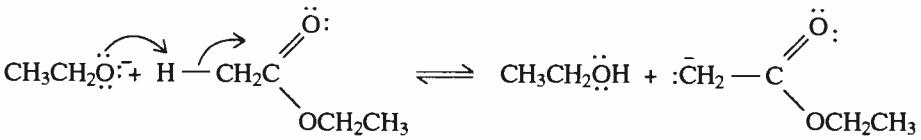
Thus, ethyl ethanoate reacts with sodium ethoxide to yield ethyl 3-oxobutanoate and ethanol.

$2\,CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[2.\ H^+,\ H_2O]{1.\ \overset{+}{N}a\bar{O}CH_2CH_3} CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2OH$

ethyl ethanoate — ethyl 3-oxobutanoate — ethanol

Ethyl 3-oxobutanoate is commonly known as ethyl acetoacetate or simply acetoacetic ester. The Claisen condensation, in general is also known as **acetoacetic ester condensation.**

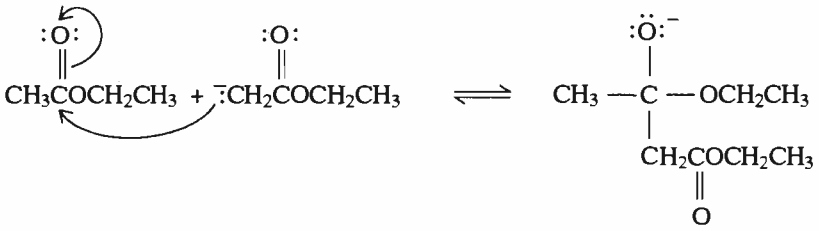
The reaction involves a series of equilibrium reactions. The first step is the abstraction of a proton from the ester by the base, i.e.,



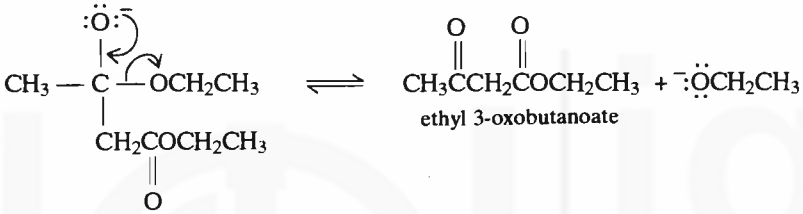
ethoxide ion | ethyl ethanoate | ethanol | anion of ethyl ethanoate (ester enolate)

The ester enolate being a powerful nucleophile attacks the carbonyl carbon of the second ester molecule as shown below:

Nucleophilic addition

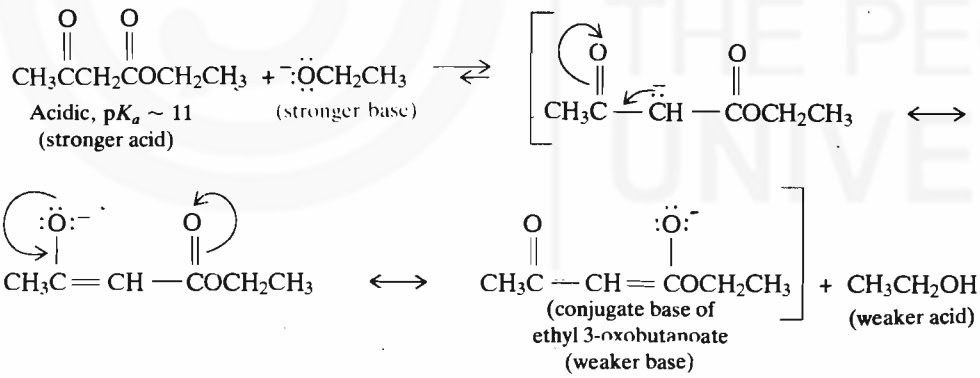


This is followed by the elimination of ethoxide ion to yield ethyl 3-oxobutanoate.



ethyl 3-oxobutanoate

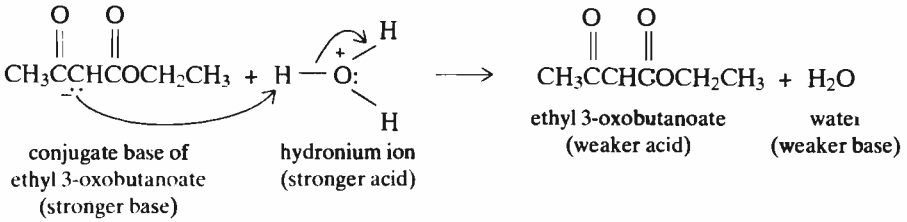
Ethyl 3-oxobutanoate so obtained is a stronger acid and hence, reacts with ethoxide ion to produce ethanol and the conjugate base of ethyl 3-oxobutanoate, as shown below:



Acidic, $pK_a \sim 11$ (stronger acid) | (stronger base) | (conjugate base of ethyl 3-oxobutanoate (weaker base)) | (weaker acid)

The equilibrium for this reaction lies towards the right hand side and provides the driving force for the reaction.

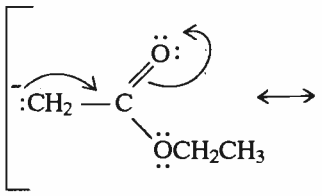
Subsequent acidification converts the above anion to its neutral form which is then isolated.

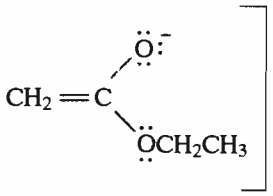


conjugate base of ethyl 3-oxobutanoate (stronger base) | hydronium ion (stronger acid) | ethyl 3-oxobutanoate (weaker acid) | water (weaker base)

The formation of the final enolate ion is crucial for the Claisen condensation to occur. If a stable anion is not formed by deprotonation, the product is obtained only in trace amounts at equilibrium. For example, if you write the similar steps starting from ethyl

The resonance structures of ester enolate





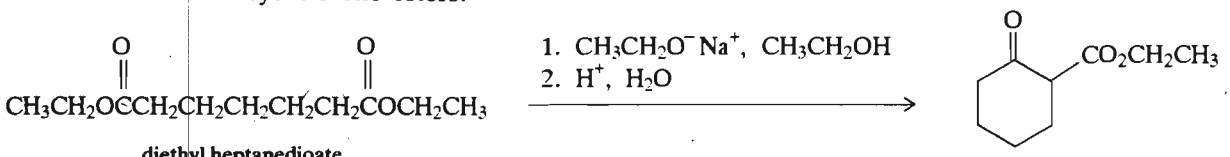
The acidic nature of hydrogen can be accounted on the basis of its position between two carbonyl groups.

2-methylpropanoate, $(CH_3)_2CHCOCH_2CH_3$, you will see that the product has no acidic hydrogen and formation of the final enolate is not possible. Hence, the esters having only one hydrogen adjacent to the carbonyl group of the ester do not undergo Claisen condensation.

A variety of 3-oxo esters can be synthesised using mixed Claisen condensations. Mixed Claisen condensation involves the reaction between two different esters. Can you predict how many 3-oxo esters will be obtained using mixed Claisen condensation? The answer is *four*. Thus, the resulting product is a mixture of four oxo esters. However, a selective mixed condensation is possible when one of the esters has no hydrogen adjacent to the carbonyl group of the ester and is thus incapable of forming the enolate. Some such esters are given below.

methanoate ester | carbonate ester | ethanedioate ester | benzoate ester

Intramolecular Claisen condensation is called **Dieckmann condensation** and yields cyclic 3-oxo esters.



diethyl heptanedioate

ethyl 3-oxocyclo-hexanecarboxylate (60%)

SAQ 3

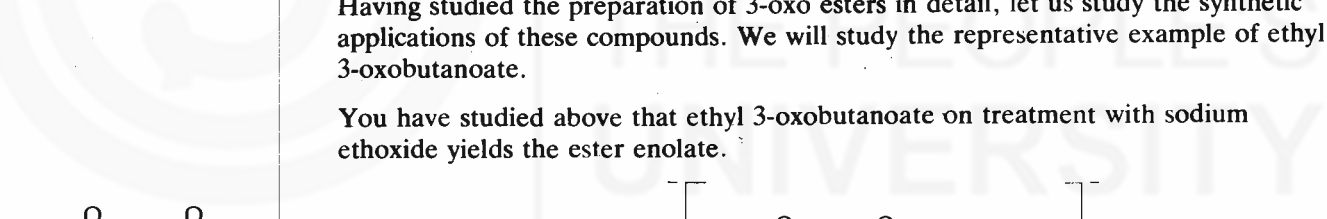
Write the possible series of reactions when ethyl 2-methylpropanoate is subjected to Claisen condensation and comment.

.....

.....

Having studied the preparation of 3-oxo esters in detail, let us study the synthetic applications of these compounds. We will study the representative example of ethyl 3-oxobutanoate.

You have studied above that ethyl 3-oxobutanoate on treatment with sodium ethoxide yields the ester enolate.



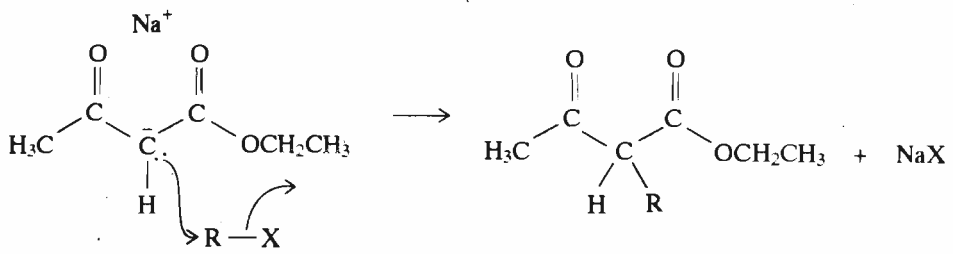
ethyl 3-oxobutanoate (Stronger acid) $K_a\ 10^{-11}$ (pK_a 11)

sodium ethoxide (stronger base)

sodium salt of ethyl ethanoate (weaker base) ester enolate

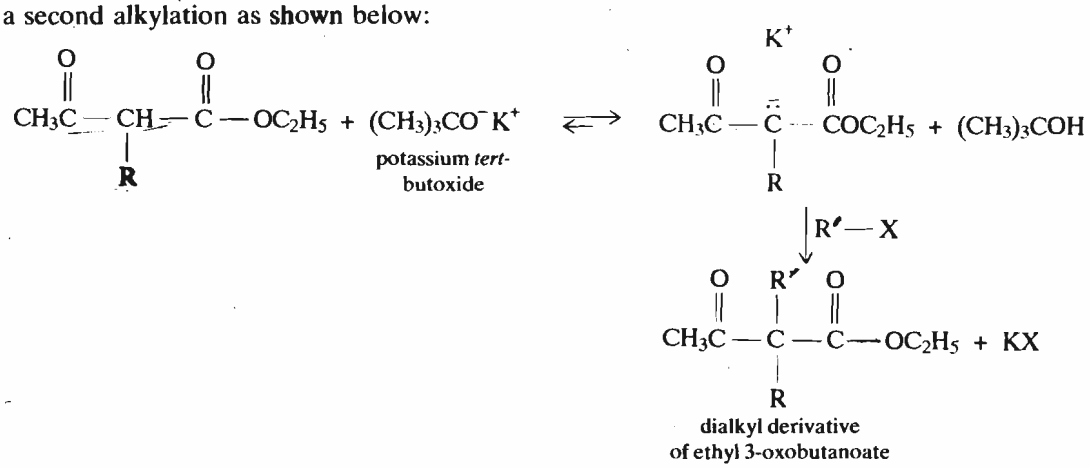
ethanol (weaker acid) $K_a\ 10^{-16}$ (pk_a 16)

The ester enolate is nucleophilic and can be alkylated on treatment with alkyl halide.

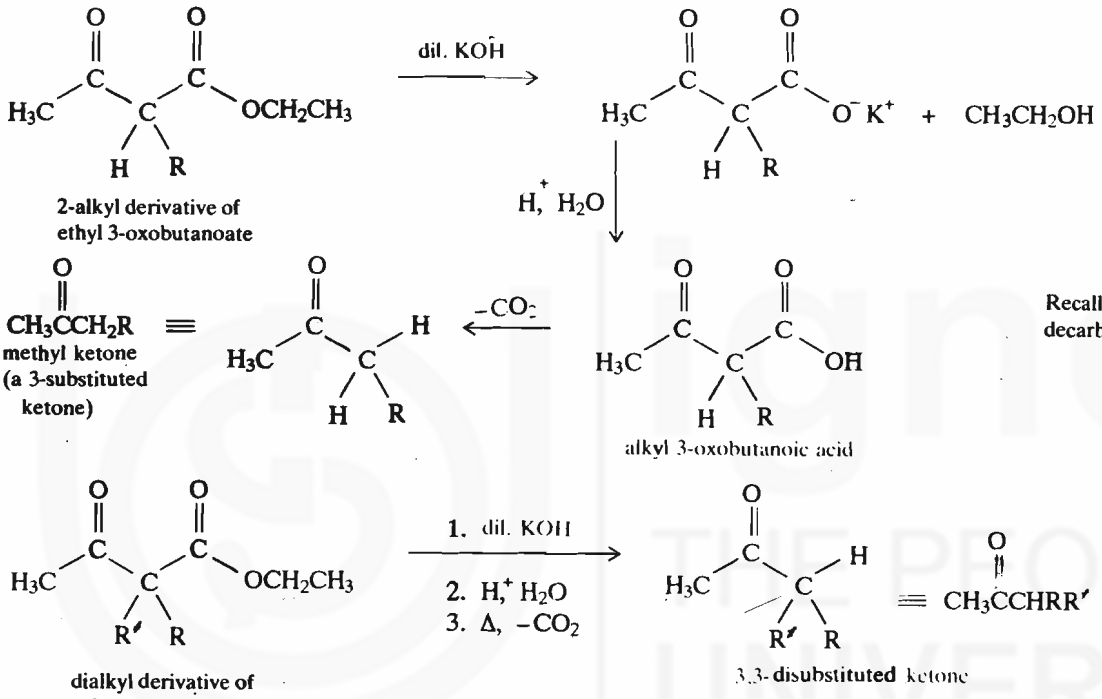


ethyl 2-alkyl-3-oxobutanoate

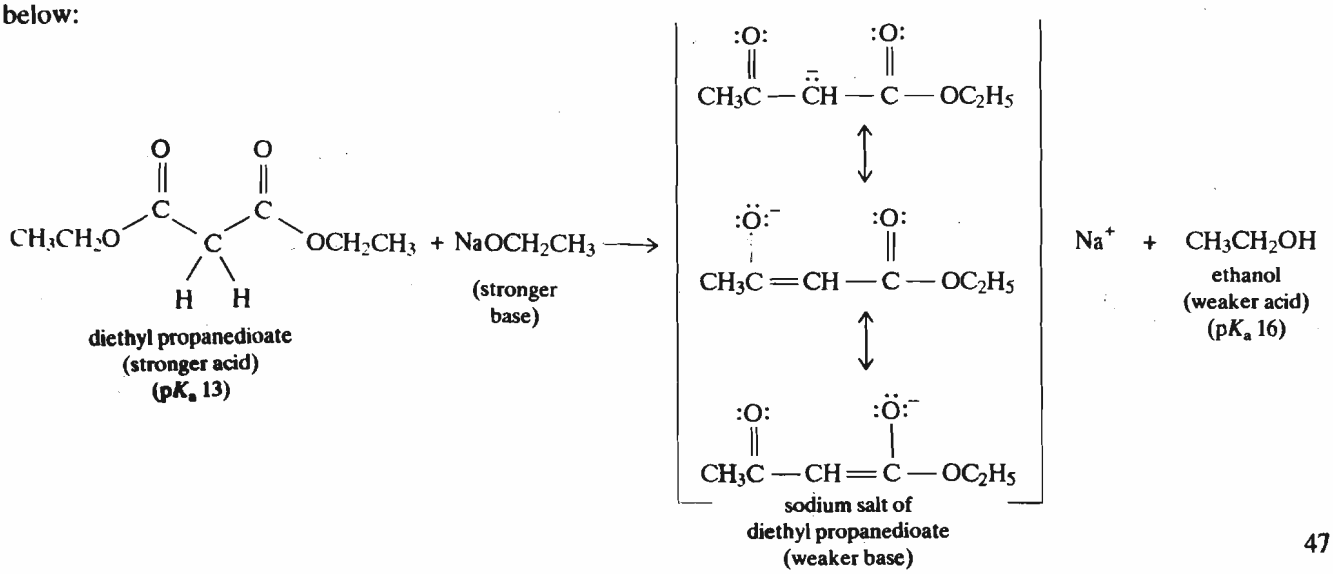
The 2-alkyl derivative still has one appreciably acidic hydrogen and we can carry out a second alkylation as shown below:



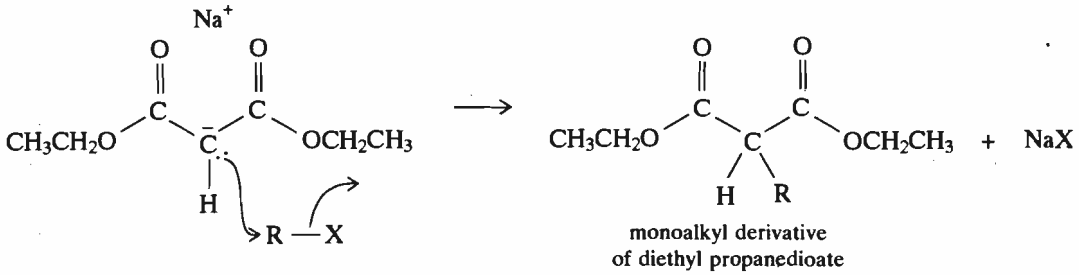
Sponification of mono- and dialkyl derivatives as obtained above, followed by acidification will yield mono- and disubstituted ketones, respectively.



Let us now consider the structure of diethyl propanedioate. You will find that it also has two acidic hydrogens flanked by the two carbonyl groups. When treated with a strong base, $Na^+ \overline{O}CH_2CH_3$, it yields an anion which is resonance stabilised as shown below:

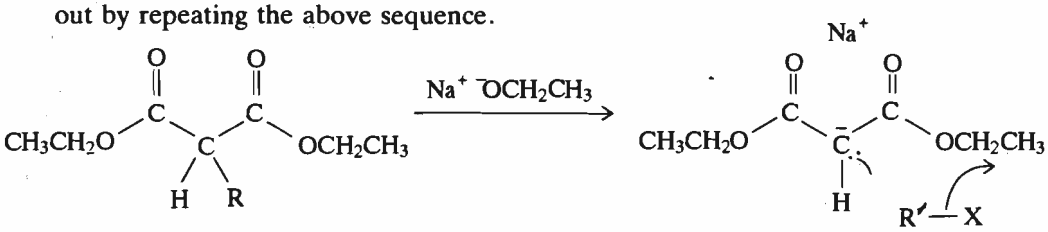


Treatment of the above anion with an alkyl halide leads to the alkylation at the carbon atom present between the two carbonyl carbons.



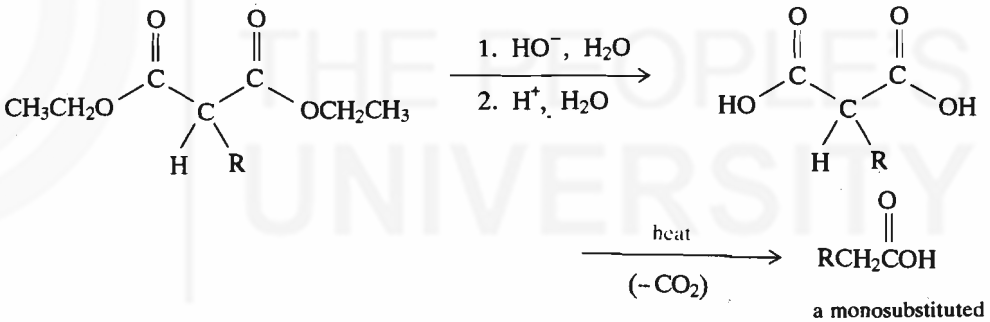
monoalkyl derivative of diethyl propanedioate

As in the case of ethyl 3-oxobutanoate, here also a second alkylation can be carried out by repeating the above sequence.

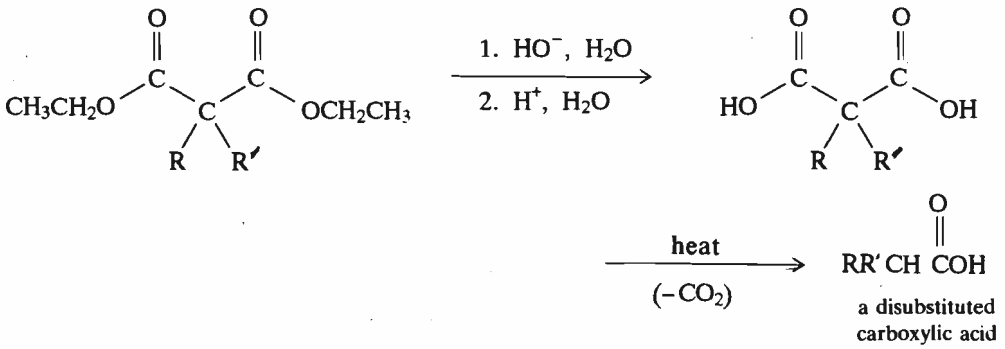


dialkyl derivative of diethyl propanedioate

When monoalkyl and dialkyl derivatives of diethyl propanedioate are hydrolysed by alkali and heated to 453 K they undergo decarboxylation to yield substituted carboxylic acids as shown below:



a monosubstituted carboxylic acid



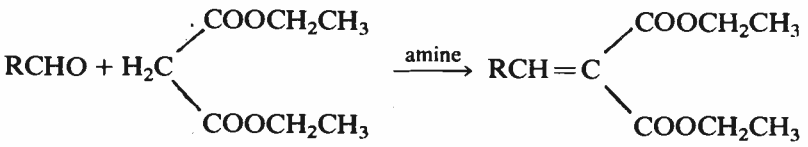
a disubstituted carboxylic acid

Thus, by suitably selecting the alkyl halides, we can synthesise a large variety of substituted carboxylic acids.

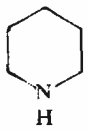
The synthesis of alkylated derivatives of diethyl propanedioate (malonic ester) is called **malonic ester synthesis.**

Reaction with aldehydes and ketones

Diethyl propanedioate readily reacts with aldehydes and ketones under basic conditions to give α, β-unsaturated diesters.

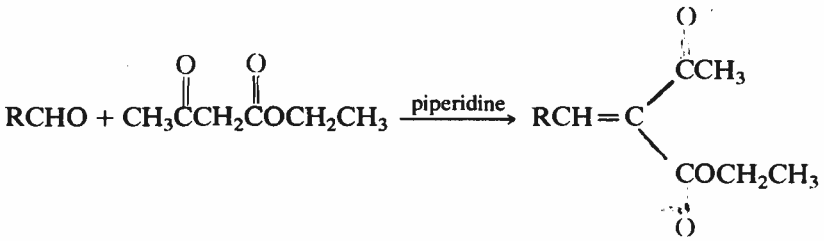


Amines such as piperidine are effective catalysts for this reaction which is called **Knoevenagel reaction.**



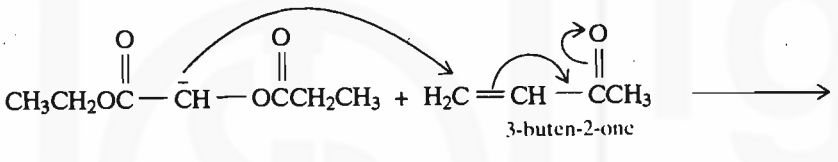
piperidine

A similar reaction is observed with ethyl 3-oxobutanoate also. This is as shown below:

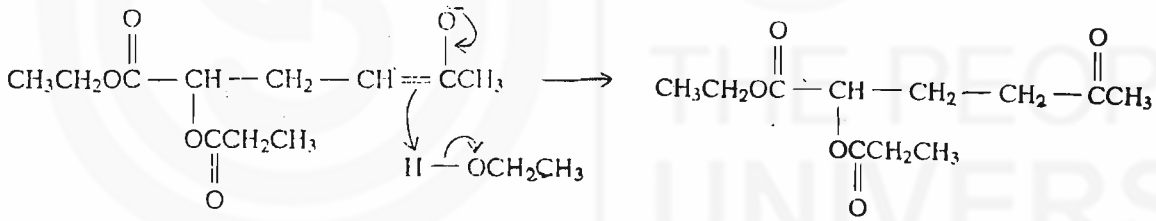


Reaction with α, β-unsaturated carbonyl compounds

Anions of ethyl 3-oxobutanoate and diethyl propanedioate react with α, β-unsaturated carbonyl compounds in the presence of catalytic amounts of a base by adding on to the β carbon atom. The reaction works with saturated aldehydes, ketones, nitriles, carboxylic acid derivatives such as esters, amides, etc., and is called **Michael addition.**

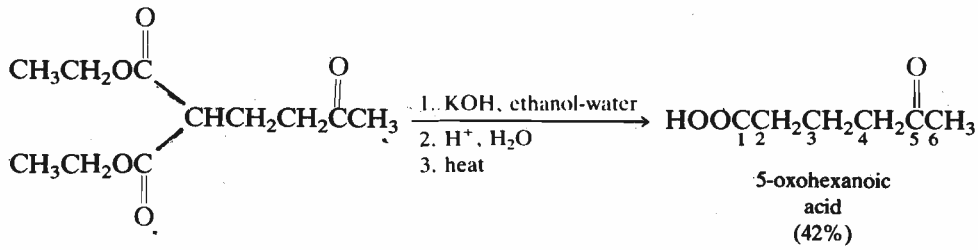


3-buten-2-one



diethyl 2-(3-oxobutyl) propanedioate (Michael adduct) (71%)

The Michael adduct so obtained on ester hydrolysis and decarboxylation yields a 5-keto acid.



5-oxohexanoic acid (42%)

Thus, you can see that we can synthesise a wide variety of compounds using diethyl propanedioate and ethyl 3-oxobutanoate.

Using the knowledge acquired in the above section, answer the following SAQ.

SAQ 4

Write the structural formulas for the products indicated by letters in the following equations.

a) $CH_2(COCH_2CH_3)_2 \xrightarrow[\text{ethanol}]{Na^+\bar{O}CH_2CH_3} A \xrightarrow{CH_3CH(Br)CH_3} B$

.....

b) $CH_3CH_2CH(COOCH_2CH_3)_2 \xrightarrow[\text{tert-butyl alcohol}]{(CH_3)_3C\bar{O}\,Na^+} C \xrightarrow{BrCH_2CH=CH_2} D$

.....

C) $CH_3COCH_2COCH_2CH_3 \xrightarrow[\text{ethanol}]{Na^+\bar{O}CH_2CH_3} E \longrightarrow F$ (E: $C_6H_5CH_2Br$)

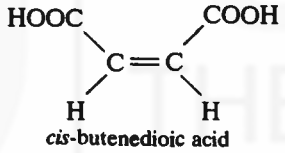
.....

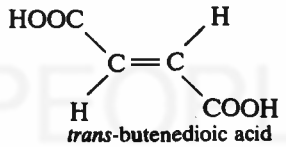
16.8 UNSATURATED CARBOXYLIC ACIDS

Unsaturated carboxylic acids contain a carboxy group and a double or/and a triple bon in their molecules. Some examples of unsaturated carboxylic acids are given below:

$CH_2^3=CH^2CH^1COOH$
propenoic acid
(acrylic acid)

$C_6H_5-CH=CHCOOH$
3-phenylpropenoic acid
(cinnamic acid)


cis-butenedioic acid
(maleic acid)


trans-butenedioic acid
(fumaric acid)

The geometric isomerism of butenedioic acid was discussed in Unit 2, Block 1.

16.8.1 Preparation of Unsaturated Carboxylic Acids

You can first have a look at the methods of preparation given in Table 16.9 before studying their details given below.

Table 16.9 : Methods of preparation of Unsaturated Carboxylic Acids

1. **From Alkenyl halides**

$R-CH=CH-(CH_2)_n-X \longrightarrow R-CH=CH-(CH_2)_n-COOH$

2. **Using Knoevenagel Condensation**

$R-CHO + CH_2(COOH)_2 \longrightarrow R-CH=CH-COOH$

3. **From Ketones**

$RCH_2-C(=O)-R' \longrightarrow RCH=C(R')-COOH$

4. **From aromatic aldehydes**

$ArCHO + R'CH_2COOCOCH_2R \longrightarrow ArCH=C(R)COOH$

5. **By oxidation of unsaturated aldehydes**

Some of the methods which were discussed for the preparation of saturated carboxylic acids can be used for the synthesis of unsaturated carboxylic acids also. For example, starting from appropriate halide.

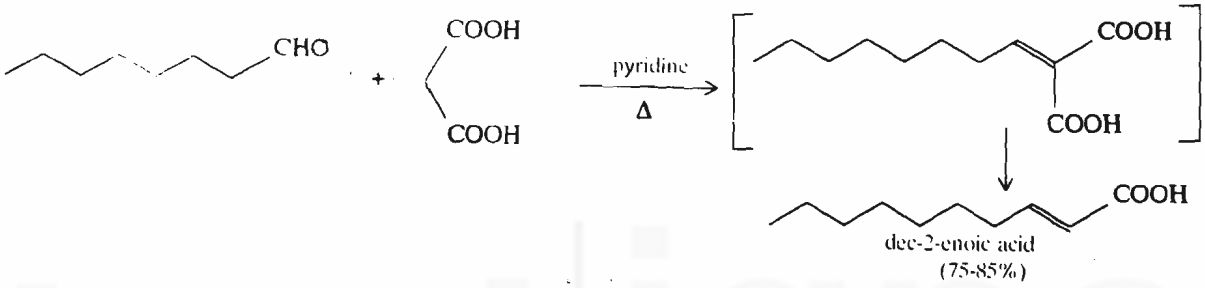
1. From alkenyl halides

Alkenyl halides containing the double bond at appropriate position can be converted into the nitrile which on hydrolysis yields the required unsaturated carboxylic acid.

$$CH_2{=}CHCH_2Cl \xrightarrow{CuCN} CH_2{=}CHCH_2CN \xrightarrow{aq.\ HCl} \underset{\text{but-3-enoic acid (52-62\%)}}{CH_2{=}CHCH_2COOH}$$

2. By Knoevenagel condensation

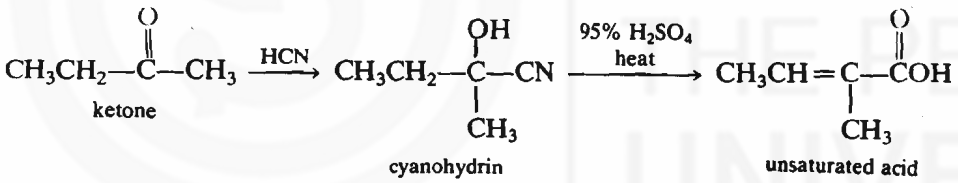
Knoevenagel condensation which you studied in the last section can also be used to prepare unsaturated carboxylic acids. A variation of this reaction involves the use of propanedioic acid which on condensation with a suitable aldehyde in the presence of catalytic amounts of a base followod by heating yields the unsaturated acid.



This reaction works best with aldehydes but the yields are generally low when ketones are used.

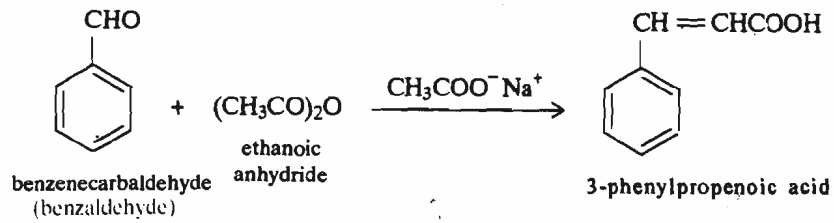
3. From ketones

The cyanohydrins obtained from ketones on acidic hydrolysis yield unsaturated carboxylic acids.



4. From aromatic aldehydes

Aromatic aldehydes on heating with anhydride of an aliphatic acid and the corresponding carboxylate salt are converted into 2,3-unsaturated carboxylic acids.



This reaction is also known as **Perkin Condensation.**

5. By oxidation of unsaturated aldehydes

Unsaturated aldehydes obtained from aldol condensation of aldehydes can be oxidised to unsaturated acids. Ammoniacal silver nitrate which is a mild oxidising agent is used in this oxidation.

$$\underset{\text{unsaturated aldehyde}}{CH_3CH{=}CHCHO} + 2Ag(NH_3)OH \rightarrow CH_3CH{=}CHCOO^-NH_4^+ + 2\,Ag + 3\,NH_3 + H_2O$$

$$CH_3CH{=}CHCOO^-NH_4^+ \xrightarrow{H^+} \underset{\text{unsaturated acid}}{CH_3CH{=}CHCOOH}$$

16.8.2 Reactions of Unsaturated Acids

Unsaturated carboxylic acids in which the two functional groups are isolated, show the characteristic properties associated with these functional groups. But, when these groups are sufficiently close, their interaction affects the reactivity and they exhibit some characteristic reactions which are given below:

1. Addition of halogen acids

2,3- and 3,4- unsaturated acids add on the halogen acid in such a way that the halogen atom is attached to the carbon atom which is farther away from the carboxy group, i.e., in anti-Markownikoff mode.

$$\underset{\text{propenoic acid}}{CH_2=CHCOOH} \xrightarrow{HBr} \underset{\text{3-bromopropanoic acid}}{BrCH_2CH_2COOH}$$

$$\underset{\text{3-pentenoic acid}}{CH_3CH=CHCH_2COOH} \xrightarrow{HBr} \underset{\text{4-bromopentanoic acid}}{CH_3CHBrCH_2CH_2COOH}$$

This can be attributed to the inductive effect of the carboxy group. But as you know, the inductive effect decreases with distance, therefore, in 4,5-unsaturated acids the addition of halogen acids is in accordance with the Markownikoff's rule.

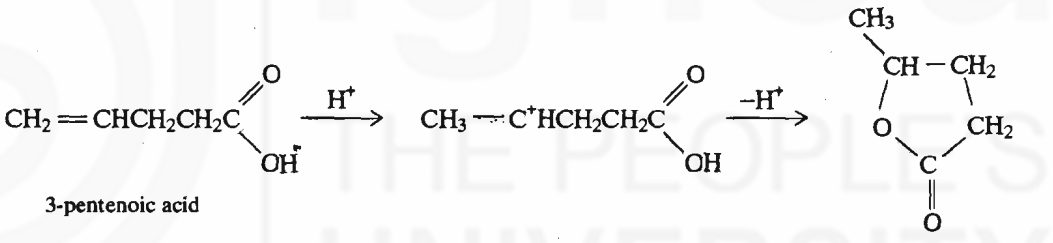
2. Migration of the double bond

2,3- and 3,4- unsaturated acids tend to interconvert by migration of the double bond.

$$RCH=CH-CH_2COO^- \underset{}{\overset{NaOH}{\rightleftharpoons}} RCH_2CH=CHCOO^-$$

3. Formation of lactones

The double bond and the carboxy group interact in the presence of acid catalysts to yield a lactone. Lactone formation occurs readily when a five-or six-membered ring can be formed.



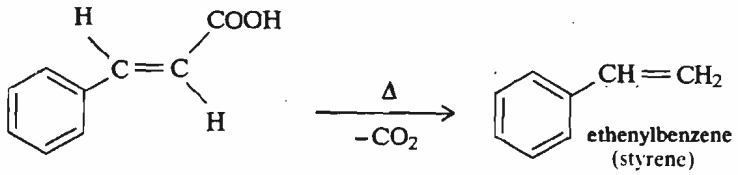
3-pentenoic acid

a lactone

4. Some reactions of 3-phenylpropenoic acid

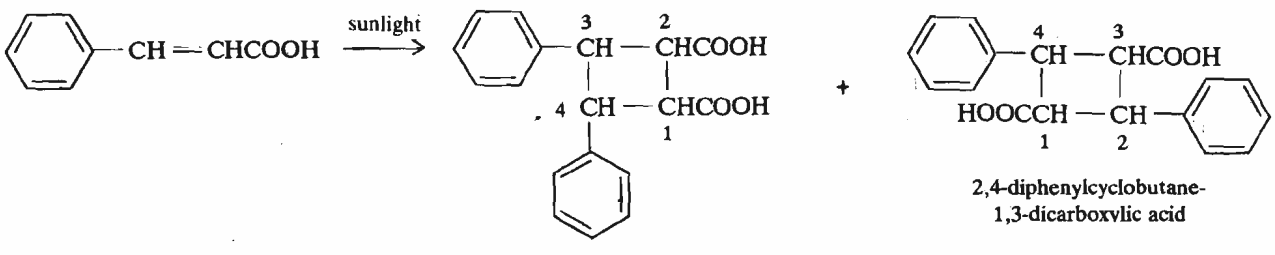
Cis- and *trans-* isomers of 3-phenylpropenoic acid exhibit some typical reactions which are discussed below:

a) The *trans-* isomer on dry distillation undergoes decarboxylation.



ethenylbenzene (styrene)

b) The *trans* isomer when exposed to sunlight dimerises.



3,4-diphenylcyclobutane-1,2-dicarboxylic acid

2,4-diphenylcyclobutane-1,3-dicarboxylic acid

c) The *cis*- isomer readily converts into the *trans*- isomer.

5. Reactions of *cis*- and *trans*- butenedioic acid

In addition to the other reactions like catalytic reduction to butanedioic acid and oxidation to 2,3-dihydroxybutanedioic acid, butenedioic acids yield acid anhydride. The formation of acid anhydrides was discussed in Unit 2, Block 1.

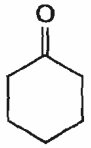
16.9 SUMMARY

In this unit, you studied that

- 2-halo acids undergo nucleophilic substitution reactions to yield 2-substituted acids whereas 3-halo acids undergo elimination to give unsaturated acids.
- hydroxy acids occur in nature and they can also be synthesised from halo acids, cyanohydrins, keto esters, from the reaction of bromoesters and carbonyl compounds, and by the Kolbe Schmidt reaction.. In addition to the usual reactions of the hydroxy and the carboxy group, they can also be converted to lactones, unsaturated acids or lactides depending upon the position of the hydroxy group relative to the carboxy group.
- 20 amino acids occurring in proteins are L amino acids.
- 2-amino acids can be synthesised from 2-halo acids, aldehydes (Strecker synthesis) and potassium 1,2-benzenedicarboxylic imide.
- amino acids exist as inner salts called *zwitterions*.
- the reactions of amino acids include the usual reactions of the carboxy and the amino group. For example, they undergo esterification (characteristic of the carboxy group) and alkanoylation (characteristic of the amino group) reactions. They give a blue-violet colour with ninhydrin, and some amino acid can also be converted to lactams.
- dicarboxylic acids can be obtained by the hydrolysis of nitriles and oxidation of cyclic ketones, naphthalene and dimethylbenzenes. They can be converted into anhydrides by heating or by their reaction with ethanoic anhydride depending upon the starting acid. Lower members, for example, ethanedioic and propanedioic acids undergo decarboxylation on heating.
- ethyl 3-oxobutanoate and diethyl propanedioate are versatile reagents in synthesis. They can be used to prepare mono-and di-substituted ketones and substituted carboxylic acids. They yield unsaturated esters on reaction with aldehydes and ketones. They undergo Michael addition with unsaturated aldehydes, ketones, nitriles and carboxylic acid derivatives and hence can be used to synthesise a large variety of organic compounds.
- Finally, the synthetic methods and reactions of some unsaturated acids were also discussed.

16.10 TERMINAL QUESTIONS

1) Write the products obtained when the following hydroxy acids are heated with acid.
   a) 2-hydroxybutanoic acid
   b) 3-hydroxybutanoic acid
   c) 4-hydroxybutanoic acid
2) Outline the Strecker synthesis of tyrosine.
3) Write the products from the following Knoevenagel condensation reactions:

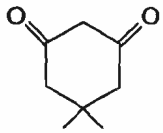
a)  + $N \equiv CCH_2C \equiv N \longrightarrow$

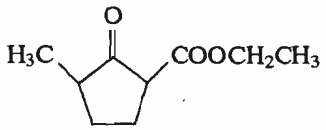
b) $CH_3CH_2CH_2CHO + N \equiv CCH_2COOCH_2CH_3 \longrightarrow$

c) $C_6H_5CHO + CH_3\overset{O}{\overset{\|}{C}}CH_2COOCH_2CH_3 \longrightarrow$

4) Give the products obtained from the following Michael additions :

a) $CH_3CH_2CH(COOCH_2CH_3)_2 + CH_2{=}CH\overset{O}{\overset{\|}{C}}H \xrightarrow{Na^+O^-CH_2CH_3}$

b)  $+ CH_2{=}CHC{\equiv}N \xrightarrow{Na^+O^-CH_3}$

c)  $+ CH_3CH{=}CHCOOCH_2CH_3 \xrightarrow{K^+O^-CH_2CH_3}$

5) Which one of the following esters cannot undergo the Claisen condensation reaction? Write the Claisen condensation products of the other two.

a) $CH_3CH_2CH_2CH_2COOCH_2CH_3$
ethyl pentanoate

b) $C_6H_5COOCH_2CH_3$
ethyl benzoate

c) $C_6H_5CH_2COOCH_2CH_3$
ethyl phenylethanoate

6) Using ethyl 3-oxobutanoate, how will you prepare the following ketones? Write the other reagents used in the reaction.

a) 1-phenyl -1,4-pentanedione

b) 4-phenyl -2-butanone

c) 5-hexen-2-one

7) How will you synthesise 3-methylpentanoic acid from diethyl propanedioate?

16.11 ANSWERS

Self Assessment Questions

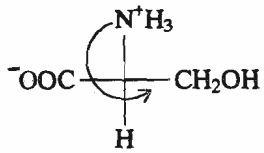
1) a) $HOCH_2CH_2-\overset{CH_3}{\overset{|}{\underset{OH}{\underset{|}{C}}}}-CH_2COOH$

b) $HOCH_2-(CH_2)_3-COOH$

2) a) The order of priority of substituents is

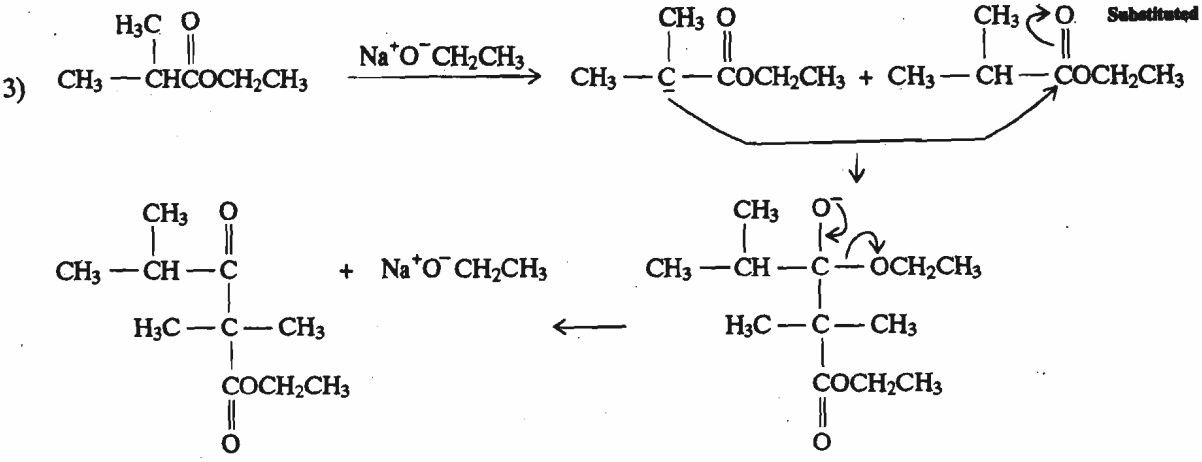
$$-\overset{+}{H_3}N > -COO^- > -CH_2OH > -H$$

The given Fischer projection can be converted to another Fischer projection given below by interchanging twice two substituents.

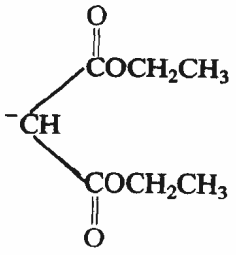


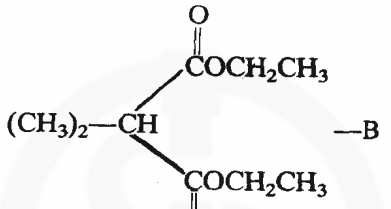
Overlooking H and moving from the substituents of highest priority to lower priority, the direction is anticlockwise, so the configuration is *S*.

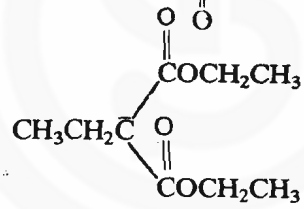
b) *R*

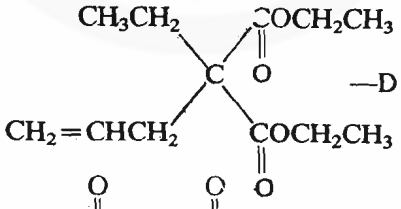
3) 

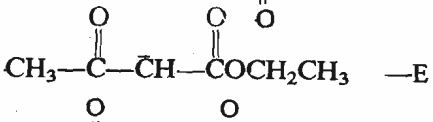
Since there is no hydrogen on the carbon atom adjacent to the ester carbonyl carbon, the equilibrium cannot shift towards the right hand side to yield the 3-oxo ester.

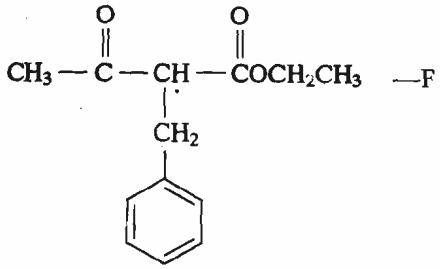
4) a)  —A

 —B

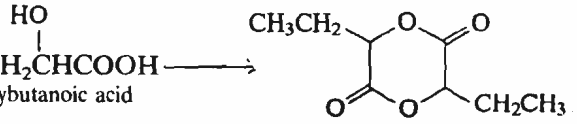
b)  —C

 —D

c)  —E

 —F

Terminal Questions

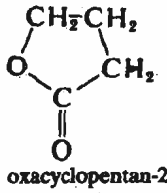
1) a) 

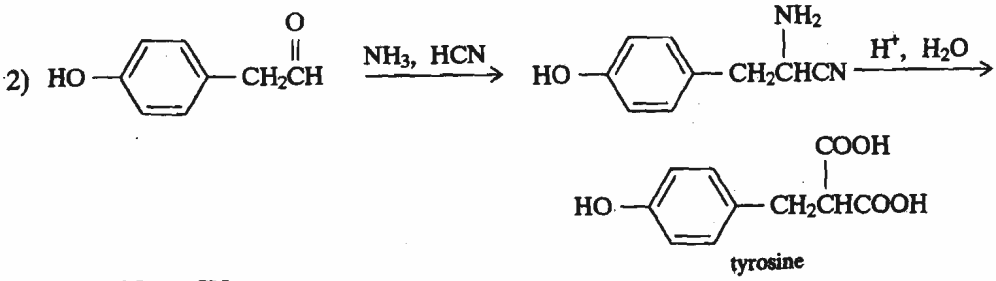
2- hydroxybutanoic acid

b) $CH_3\underset{\text{OH}}{\underset{|}{C}}HCH_2COOH \longrightarrow CH_3CH=CHCOH$ (with =O)

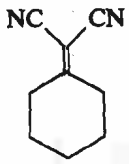
3-hydroxybutanoic acid

c) $HOH_2CCH_2CH_2COOH \longrightarrow$ oxacyclopentan-2-one (a lactone)

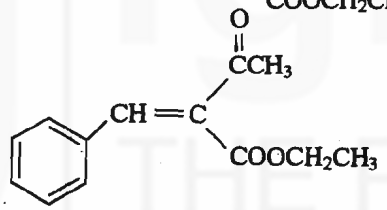


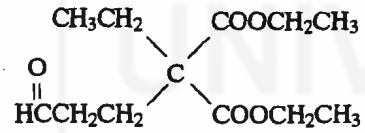
2) 

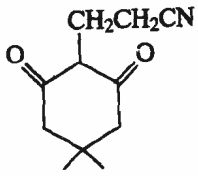
tyrosine

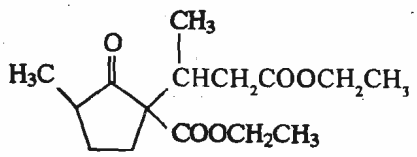
3) a) 

b) $CH_3CH_2CH_2CH=C(CN)(COOCH_2CH_3)$

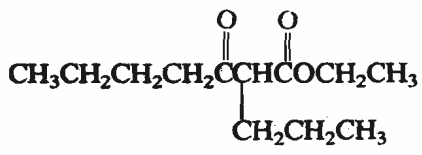
c) 

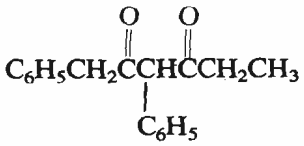
4) a) 

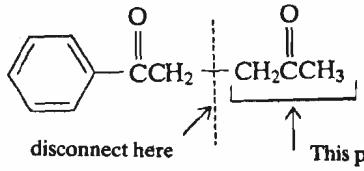
b) 

c) 

5) b) Ethyl benzoate cannot undergo the Claisen condensation. The Claisen condensation products of compounds given in (a) and (c) are given below.

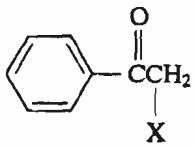
a) 

c) 

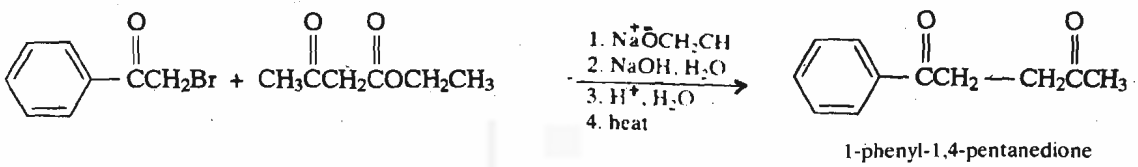
6) a) 

disconnect here
1-phenyl-
1,4-pentanedione

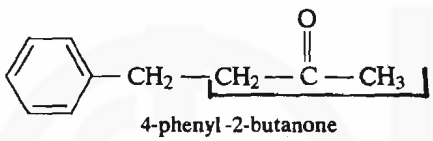
This part can be derived
from ethyl 3-oxobutanoate

Therefore, the required halide is, 

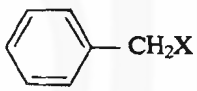
The reaction can be written as,

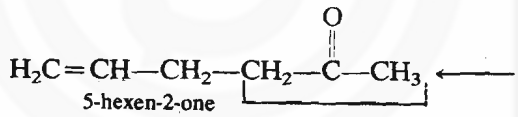


1-phenyl-1,4-pentanedione

b) 

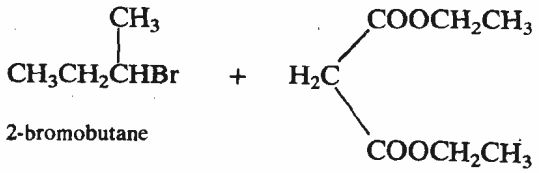
4-phenyl-2-butanone

The required halide is 

c) 

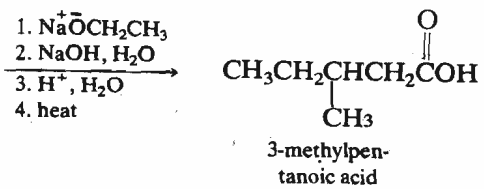
5-hexen-2-one

The required halide is
$H_2C=CH-CH_2X$

7) 

2-bromobutane

diethyl propanedioate



3-methylpen-
tanoic acid

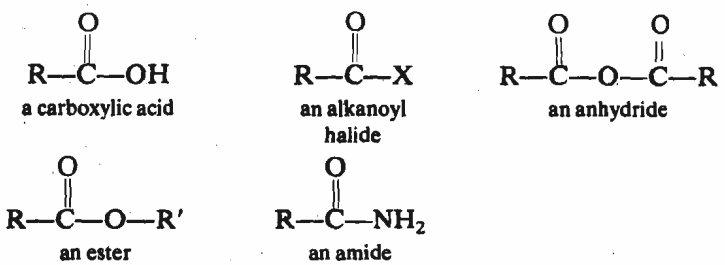
UNIT 17 FUNCTIONAL DERIVATIVES OF MONOCARBOXYLIC ACIDS

Structure

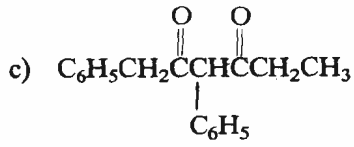
17.1 INTRODUCTION

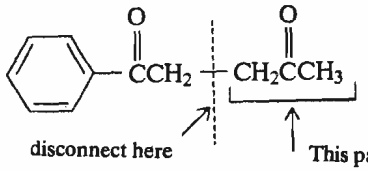
A **functional derivative** of a carboxylic acid is a compound which results on replacement of the hydroxyl group of the carboxylic acid by some other group, L. A characteristic feature of these derivatives is that they regenerate the carboxylic acid on hydrolysis, i.e.,

Various functional derivatives of carboxylic acids are possible depending upon the nature of L. The functional derivatives which you will study in this unit include carboxylic acid halides also called alkanoyl halides, anhydrides, esters and amides. These functional derivatives can be represented by the following structures.



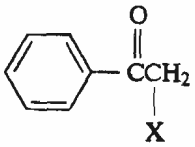
You can see that all of these derivatives contain a R—C— or alkanoyl group in their structure. While studying this unit, you will realise that there is not only a structural similarity among carboxylic acids and their derivatives but also a close relationship in their chemistry.

c) 

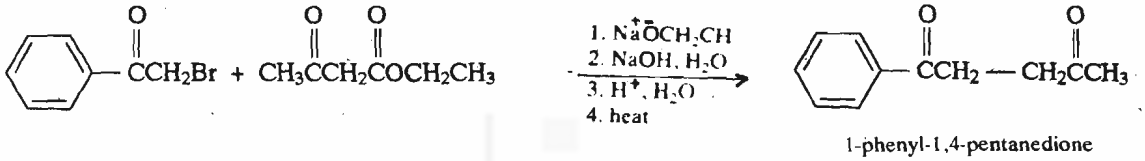
6) a) 

disconnect here
1-phenyl-
1,4-pentanedione

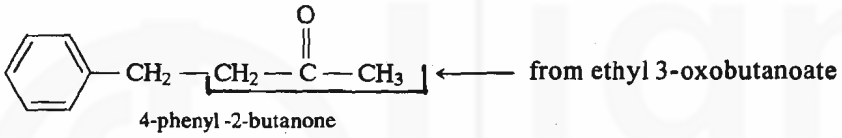
This part can be derived from ethyl 3-oxobutanoate

Therefore, the required halide is, 

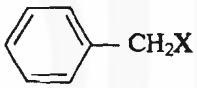
The reaction can be written as,

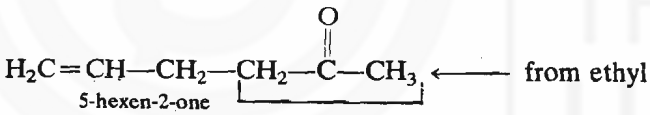


1-phenyl-1,4-pentanedione

b) 

4-phenyl -2-butanone

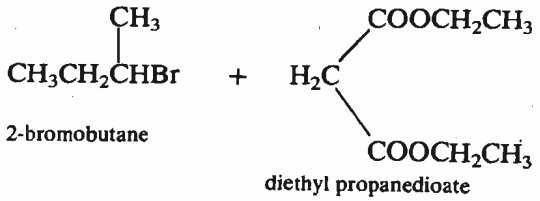
The required halide is 

c) 

5-hexen-2-one

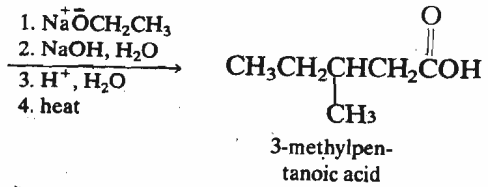
The required halide is

$H_2C=CH-CH_2X$

7) 

2-bromobutane

diethyl propanedioate



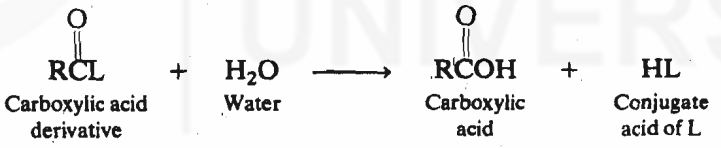
3-methylpen-
tanoic acid

UNIT 17 FUNCTIONAL DERIVATIVES OF MONOCARBOXYLIC ACIDS

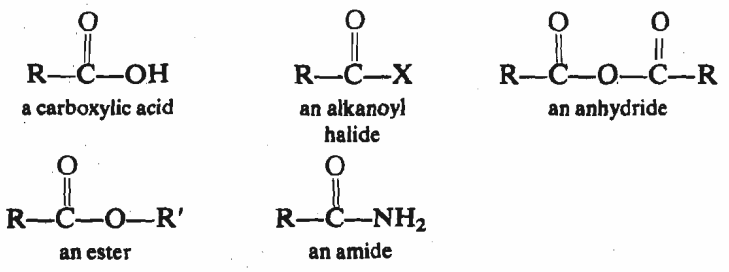
Structure

17.1 INTRODUCTION

A **functional derivative** of a carboxylic acid is a compound which results on replacement of the hydroxyl group of the carboxylic acid by some other group, L. A characteristic feature of these derivatives is that they regenerate the carboxylic acid on hydrolysis, i.e.,



Various functional derivatives of carboxylic acids are possible depending upon the nature of L. The functional derivatives which you will study in this unit include carboxylic acid halides also called alkanoyl halides, anhydrides, esters and amides. These functional derivatives can be represented by the following structures.



You can see that all of these derivatives contain a R—C— or alkanoyl group in their structure. While studying this unit, you will realise that there is not only a structural similarity among carboxylic acids and their derivatives but also a close relationship in their chemistry.

Objectives

After studying this Unit, you should be able to :

- define carboxylic acid derivatives,
- give examples of various carboxylic acid derivatives,
- comment on the acidic and basic behaviour of various carboxylic acid derivatives,
- correlate the reactivities of carboxylic acid derivatives with their structures,
- outline the synthesis of various carboxylic acid derivatives,
- explain the reactions of various carboxylic acid derivatives,
- compare the behaviour of various carboxylic acid derivatives, reaction conditions required in various nucleophilic addition-elimination reactions like hydrolysis, formation of amides, etc., and the nature of products obtained,
- describe the reactions of various carboxylic acid derivatives with organometallic reagents, and
- explain the reduction reactions undergone by carboxylic acid derivatives.

17.2 STRUCTURE OF CARBOXYLIC ACID DERIVATIVES

Similar to the structure of carbonyl compounds and carboxylic acids, the derivatives of carboxylic acids have a trigonal geometry, i.e., all the bonds to the carbonyl carbon are in the same plane. This is shown in Fig. 17.1.

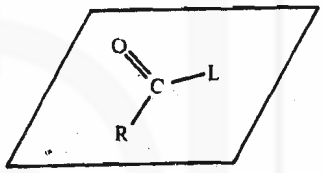


Fig. 17.1 : Planar arrangement of bonds to the carbonyl carbon in carboxylic acid derivatives.

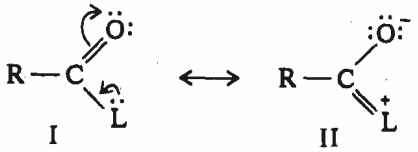
An important structural feature of carboxylic acid derivatives is that the atom attached to the $RC(=O)-$ group bears an unshared pair of electrons which is capable of interacting with the π electrons of the carbonyl group. This is shown in Fig. 17.2.

Individual *p* orbitals of a carboxylic acid derivative

Extended π system of a carboxylic acid derivative

Fig. 17.2 : The extended π electron system in carboxylic acid derivatives.

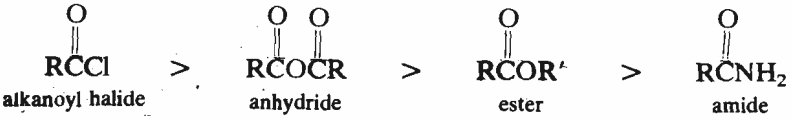
This electron delocalisation can be represented by the following resonance structures.



The extent of this electron delocalisation depends on the electron donating properties of L. Thus, a less electronegative L will donate the electrons more easily than a more electronegative L. The electron release from L reduces the polarisation of the carbonyl group, thereby, decreasing its electrophilic character. Thus, the greater the

electron release from L, the greater is its stabilising effect. Consequently, when L is more electronegative, the extent of resonance decreases and the reactivity increases. Thus, the reactivity of acid derivatives towards nucleophilic substitution reactions follows the following order:

A derivative higher in this order can be converted to the one lower but not vice-versa.



You will study the nucleophilic substitution reactions of acid derivatives in detail in the later sections of this unit.

The degree of resonance stabilisation is also reflected in the structural parameters and spectral characteristics of carboxylic acid derivatives about which you will study in the next section.

17.3 PHYSICAL PROPERTIES AND SPECTRAL CHARACTERISTICS OF CARBOXYLIC ACID DERIVATIVES

It was pointed out in the earlier section that the extent of resonance is reflected in the structural parameters. This can be understood when we compare the C-L bond lengths in various acid derivatives with the C-L bond lengths in the compounds of the type R-L. These bond lengths are listed in Table 17.1.

Table 17.1 : C-L Bond lengths of some carboxylic acid derivatives and of some compounds of R-L type

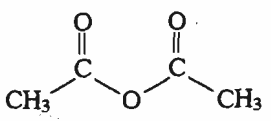
L	in R—C(=O)—L (pm)	in R—L (pm)
Cl	179	178
OCH_3	136	143
NH_2	136	147

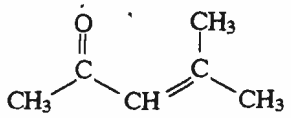
The bond lengths shown in Table 17.1 indicate that as we go from the most reactive alkanoyl halides to the much less reactive esters and amides, the C-L bond becomes shorter as compared to the normal C-L single bond. Thus, in amides the contribution of the dipolar structure II, is strong enough to impart a double bond character to the carbon-nitrogen bond. The double bond character is also indicated by a barrier of 75 to 84 kJ mol^{-1} to the rotation of the carbon-nitrogen bond.

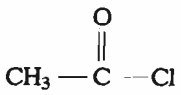
The other physical properties for various carboxylic acid derivatives are briefly stated below.

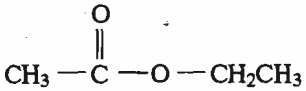
Alkanoyl halides and anhydrides

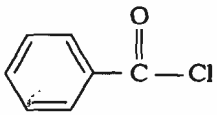
The lower members of these derivatives are dense, water-insoluble liquids with piercing odours. Their boiling points are not very different from those of other polar molecules of similar molecular weight and shape. Some examples are given below:

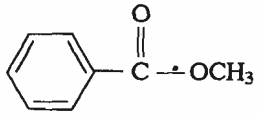

b.p. 413 K


b.p. 403 K


b.p. 324 K


b.p. 330 K


b.p. 470 K

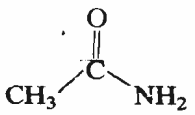

b.p. 486 K

Esters

The lower members of this class are volatile, fragrant liquids having lower density than water. Most esters are not soluble in water.

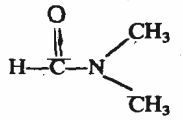
Amides

The lower members are water-soluble, polar in nature and have high boiling points. Primary and secondary amides associate to form hydrogen bonded dimers or higher aggregates in solid and liquid state.



ethanamide
m.p. 355 K
b.p. 494 K

A number of amides have high dielectric constants. *N, N*-dimethylmethanamide (commonly known as *N,N*-dimethylformamide, abbreviated as DMF) is widely used as polar aprotic solvent.



N,N-Dimethylmethanamide

Spectral Characteristics

The increased contribution of the dipolar resonance structure II, weakens the C=O bond resulting in a corresponding decrease in the carbonyl stretching frequency as shown in Table 17.2.

Table 17.2 : Carbonyl stretching frequencies of carboxylic acid derivatives, RCL

L	$\bar{\nu}_{c=o}$ (cm^{-1})	
Cl	1790-1815	
OCR	1740-1790 1800-1850	two bands are observed due to symmetric and asymmetric stretching.
OR	1735-1750	
NR_2'	1650-1690	

Primary and secondary amides show the N-H stretching absorption in the region 3200-3400 cm^{-1} and a strong N-H bending absorption near 1640 cm^{-1}.

The positions of signals in the NMR spectra of various carboxylic acid derivatives are given in Table 17.3.

Table 17.3 : The chemical shifts of the methyl protons in carboxylic acid derivatives

CH_3CL	δ ($-C\underline{H}_3$ protons)
CH_3COR	2.1
CH_3CCl	2.67
CH_3CNR_2	2.0

The N-alkyl protons of amides show chemical shifts in the range δ 2.6-3 and the N-H protons of primary and secondary amides show chemical shifts in the δ 7.5-8.5 region. The N-H signals, similar to O-H signals are broad and are D_2O exchangeable.

SAQ 1

The amide, $CH_3\overset{\overset{O}{\|}}{C}NH—CH_3$ showed three signals in its NMR spectrum at the following δ values:

1.97(s), 2.74(d) and 8.18 (broad D_2O exchangeable).

Assign these signals to the protons in the amide.

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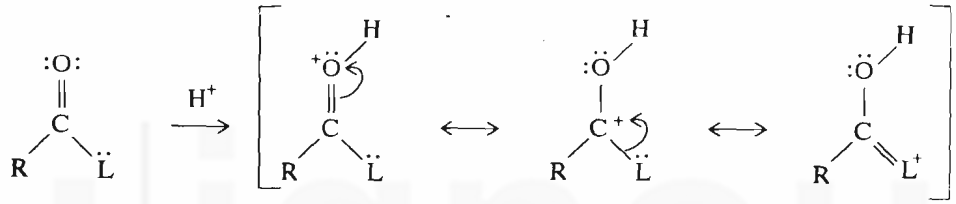
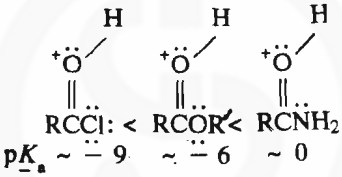
17.4 BASICITY AND ACIDITY OF CARBOXYLIC ACID DERIVATIVES

Carboxylic acid derivatives are weakly basic at the carbonyl oxygen which can be protonated using strong acids. This property is particularly useful in some of the acid-catalysed reactions of esters and amides.

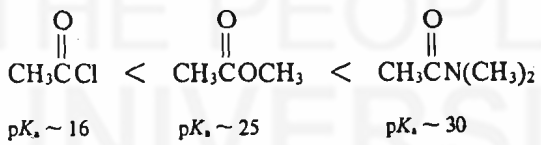


pK_a values of the conjugate acids of carboxylic acid derivatives

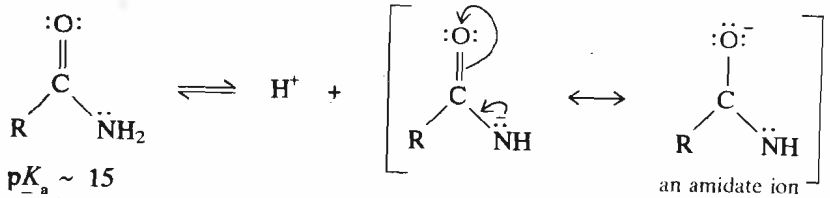


The pK_a values for the conjugate acids of carboxylic acid derivatives show that alkanoyl halides are the weakest bases as their conjugate acids have the lowest pK_a and are, therefore, strongest acids. Esters are about as basic as carboxylic acids whereas amides are the most basic.

The acidity of the hydrogens next to the carbonyl group shows the following order amongst carboxylic acid derivatives.



Primary and secondary amides are deprotonated at nitrogen to give an **amidate ion** which is resonance stabilised in the same way as the carboxylate ion.

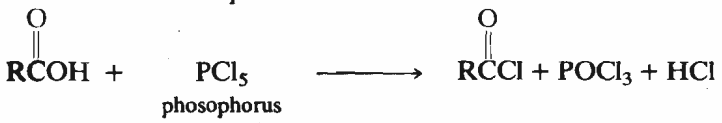


Let us now study about each of these derivatives in detail.

17.5 CARBOXYLIC ACID HALIDES

17.5.1 Preparation of Carboxylic Acid Halides

Carboxylic acid halides can be prepared from carboxylic acids using the acid chlorides of inorganic acids such as PCl_5 (acid chloride of phosphoric acid), PCl_3 (acid chloride of phosphorus acid) and $SOCl_2$ (acid chloride of sulphurous acid). The general reactions can be represented as shown below:



$$3\,RCOH + PCl_3 \longrightarrow 3\,RCCl + H_3PO_3$$

(PCl_3: phosphorus trichloride)

$$RCOH + SOCl_2 \longrightarrow RCCl + SO_2 + HCl$$

($SOCl_2$: thionyl chloride)

Carboxylic acid fluorides, bromides and iodides are prepared from carboxylic acid chlorides by reaction with HF, HBr and HI, respectively.

$$RCCl + HX \longrightarrow RCX + HCl$$

(HX = HF, HBr or HI)

17.5.2 Reactions of Carboxylic Acid Halides

The reactions of carboxylic acid halides are listed in Table 17.4.

Table 17.4 : Reactions of Carboxylic Acid Halides

A. Reactions with Nucleophiles

$$RCL + Nu^- \longrightarrow RCNu + L^-$$

where NuH = H_2O, RCOOH, ROH, ArOH, NH_3, NR_2 and organometallic reagents.

B. Reduction

$$RCL \xrightarrow[\text{or hydride reduction}]{H_2/\text{catalyst}} RCH$$

(RCH: aldehydes)

C. Friedal — Crafts reactions (discussed in Unit 9).

A. Reactions with nucleophiles

The reactions of carboxylic acid halides and other carboxylic acid derivatives with nucleophiles proceed via addition-elimination steps which leads to **nucleophilic substitution** at the carbonyl carbon. This is shown below.

$$RCL + :Nu^- \longrightarrow R-C(-O^-)(-L)-Nu \longrightarrow RCNu + L^-$$

Thus, the nucleophile $:Nu^-$ has substituted the group L in the carboxylic acid derivative.

Carboxylic acid halides react with a variety of nucleophilic reagents such as water, carboxylic acids, alcohols and phenols, amines and organometallic reagents. Let us study each of these reactions in detail using the examples of carboxylic acid chlorides as these are the most readily accessible among the halides.

1. Reaction with Water

It was pointed out earlier that carboxylic acid derivatives, on hydrolysis, yield carboxylic acids. Thus, carboxylic acid halides react with water to give carboxylic acids. For example,

$$CH_3CH_2CCl + HOH \longrightarrow CH_3CH_2COH + HCl$$

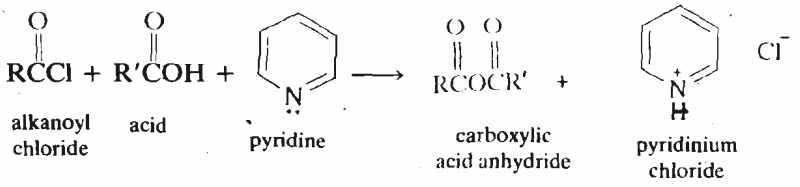
propanoyl chloride → propanoic acid (100%)

This reaction has little synthetic value because acid halides are themselves usually prepared from the acids.

Pyridine acts both as a catalyst as well as a base and neutralises the hydrogen chloride formed in the reaction.

2. Reaction with Carboxylic Acids

Carboxylic acid halides on reaction with carboxylic acids yield acid anhydrides, i.e.,



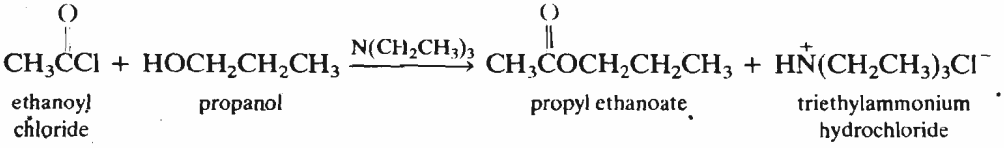
alkanoyl chloride — acid — pyridine — carboxylic acid anhydride — pyridinium chloride

Salts of carboxylic acids also react with carboxylic acid halides to yield the acid anhydrides. For example,

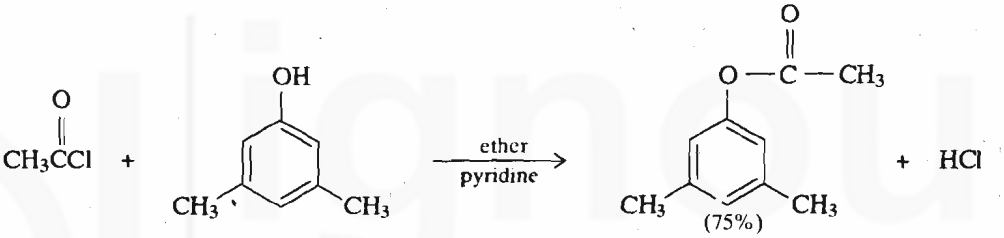
propanoyl chloride — (excess) sodium ethanoate — ethanoic propanoic anhydride

3. Reaction with alcohols and phenols

The reaction of carboxylic acid halides with alcohols and phenols yields esters. A base is usually added to neutralise the hydrogen chloride formed as a by-product. Usually pyridine, amines or alkali metal hydroxides are used as bases.

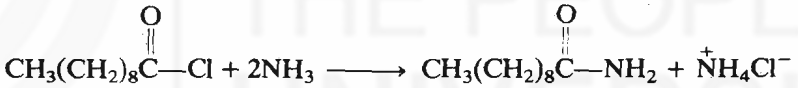


ethanoyl chloride — propanol — propyl ethanoate — triethylammonium hydrochloride

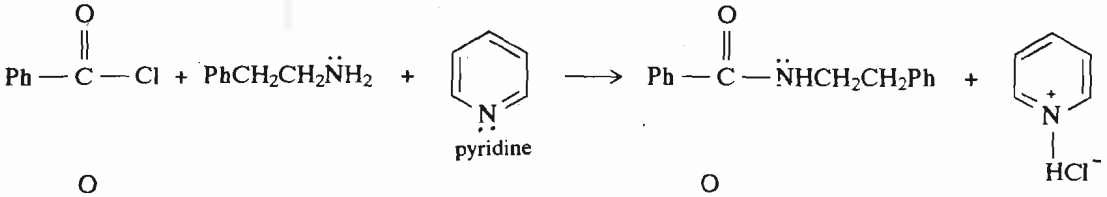


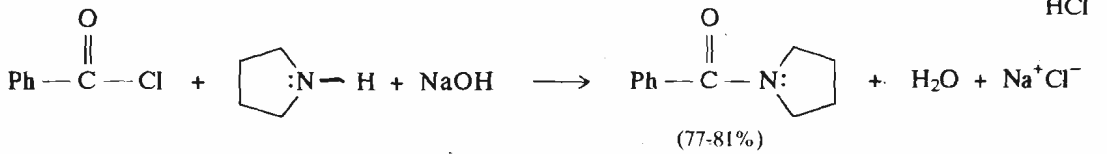
4. Reaction with ammonia and amines

Ammonia and primary and secondary amines react with carboxylic acid halides to yield amides. The reaction with ammonia yields a primary amide as shown below.

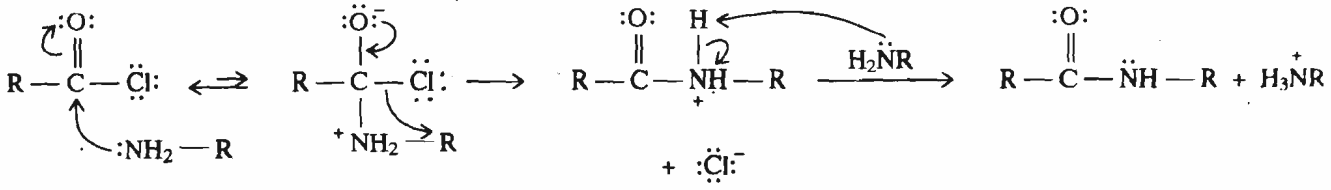


The reaction with primary amines yields a secondary amide whereas the reaction with secondary amines gives a tertiary amide.

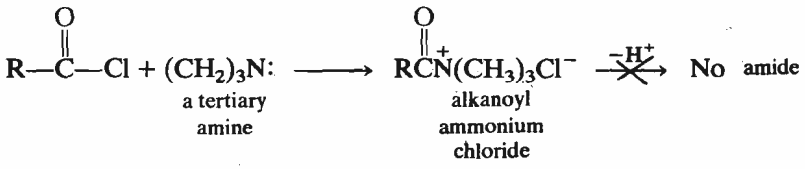




What about the tertiary amines? Do they react with carboxylic acid halides? Before finding an answer to these questions, let us first try to understand the mechanism of the amide formation which is given below:



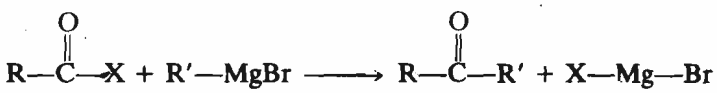
The last step in the mechanism involves loss of a proton from nitrogen which is not possible when the reaction is carried out with tertiary amines.



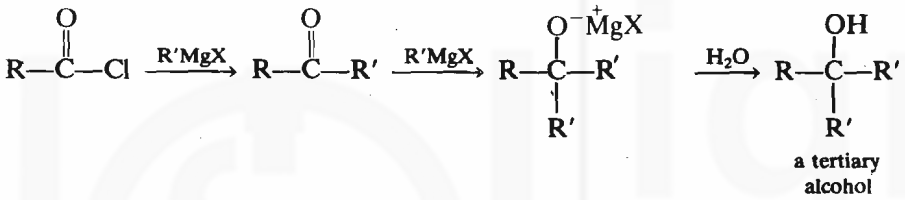
An important aspect of amide formation is that, for each equivalent of the amide formed, an additional equivalent of base is required to neutralise the hydrogen chloride formed. When the amine used in the reaction is cheap and readily available, it is used in excess to serve as a base also. When the amine used to form the amide is expensive and, hence, cannot be used in excess, a tertiary amine, which does not interfere with the reaction, can be used as a base.

5. Reaction with organometallic reagents

Carboxylic acid halides react with a number of organometallic compounds to yield ketones. When a Grignard reagent is used, the best results are obtained if the reaction is carried out at low temperature using *one* equivalent of the Grignard reagent.

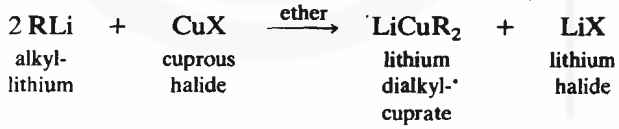


If an excess of the Grignard reagent is used, the ketone obtained reacts further to yield an alcohol as shown below:

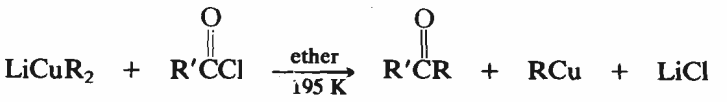


Thus, to synthesise a ketone from a carboxylic acid halide, the organometallic reagent used should be so chosen that it reacts much faster with the starting halide than it does with the product ketone. Two types of organometallic reagents which satisfy this requirement are organocuprate reagents and organocadmium reagents.

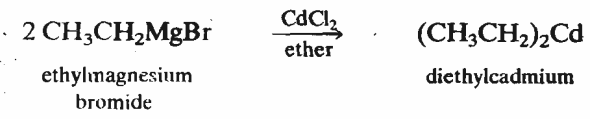
Organocuprate reagents such as dialkyl- and diaryl cuprates are prepared through the reaction of an alkyl- or aryllithium reagent with a cuprous salt.

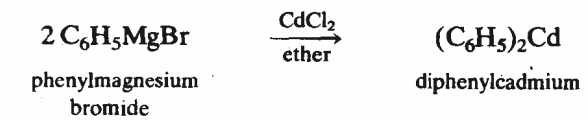


The reaction of a carboxylic acid halide with lithium diorganocuprate yields a ketone.

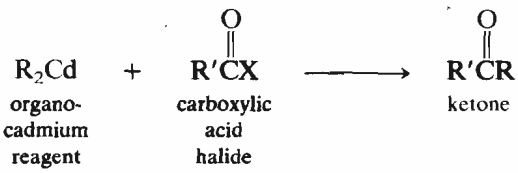


Organocadmium reagents such as dialkylcadmium and diarylcadmium are prepared by treating Grignard reagents with cadmium chloride.





The desired ketone can be prepared by the reaction of the suitable organocadmium reagent with a suitable carboxylic acid halide.

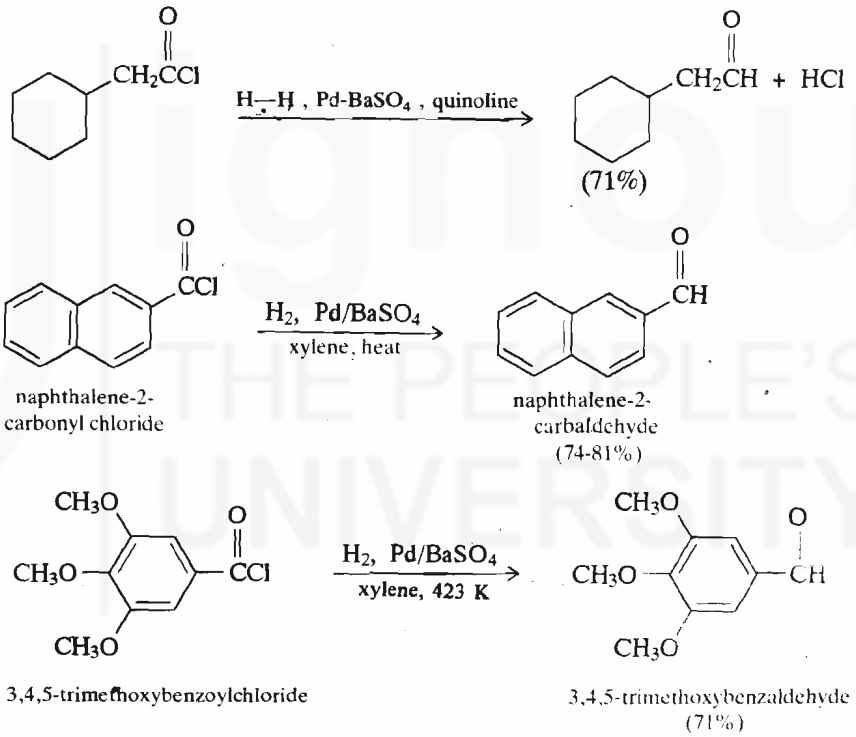


Secondary and tertiary alkylcuprates and also the secondary and tertiary alkylcadmium reagents are not stable and decompose readily and hence, cannot be employed for ketone synthesis. This then limits the synthetic utility of these reactions to primary alkyl and arylcuprates and to primary dialkyl or diarylcadmium reagents.

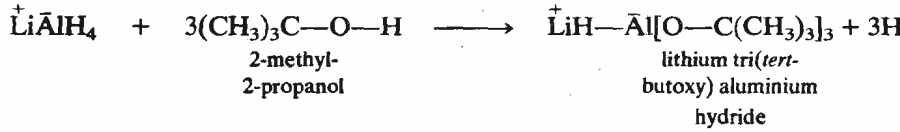
B. Reduction

Carboxylic acid halides can be reduced to aldehydes by either of two methods: the first method involves catalytic hydrogenation and the second involves hydride reduction.

In **catalytic reduction**, the carboxylic acid halide is hydrogenated using a special catalyst such as palladium deposited on barium sulphate **poisoned** with an amine such as quinoline. The poisoning of the catalyst moderates its effectiveness and hence inhibits the subsequent reduction of the product aldehyde to alcohol. This reaction is called the **Rosenmund reduction**.



The **hydride reduction** using ordinary reducing hydrides, such as sodium borohydride or lithium aluminium hydride, converts the aldehydes obtained in the reaction to alcohols. This over-reduction can be prevented by using a modified lithium aluminium hydride namely, lithium tri(*tert*-butoxy) aluminium hydride which is obtained by the reaction of lithium aluminium hydride with three equivalents of 2-methyl-2-propanol.



In lithium tri(*tert*-butoxy) aluminium hydride, three of the reactive hydride atoms of lithium aluminium hydride are replaced with alkoxy groups and hence, the one remaining hydride reduces only the most reactive functional groups. Because acid halides are more reactive towards nucleophiles than aldehydes, the reagent preferentially reduces the carboxylic acid halide rather than the product aldehyde.

$$RC(=O)Cl + LiAl[OC(CH_3)_3]_3H \xrightarrow[2.\ H^+,\ H_2O]{1.\ \text{ether}} RC(=O)H + LiCl + Al[OC(CH_3)_3]_3$$

C. Friedel-Crafts reactions

The Friedel-Crafts alkanoylation (acylation) of aromatic compounds using alkanoyl halides was dealt with in sub-Sec. 9.6.5 in Unit 9, Block 2.

SAQ 2

How will you convert butanoyl chloride into the following products.

a) $CH_3CH_2CH_2C(=O)OH$

.....

b) $CH_3CH_2CH_2C(=O)OC(=O)CH_3$

.....

c) $CH_3CH_2CH_2C(=O)-C_6H_5$

.....

d) $CH_3CH_2CH_2C(=O)N(CH_3)_2$

.....

e) $CH_3CH_2CH_2C(=O)CH_2CH_3$

.....

f) $CH_3CH_2CH_2C(=O)H$

.....

17.6 CARBOXYLIC ACID ANHYDRIDES

17.6.1 Preparation of Carboxylic Acid Anhydrides

Carboxylic acid anhydrides can be prepared using the methods listed in Table 17.5.

Table 17.5 : **Methods of preparation of Carboxylic acid anhydrides**

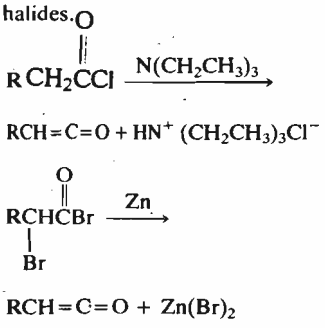
1. **From carboxylic acid halides and carboxylic acids** $RCOOH + R'COCl \xrightarrow{\text{pyridine}} RCO{-}O{-}COR' + HCl$
2. **From Ketene and carboxylic acids** $CH_2{=}C{=}O + RCOOH \longrightarrow RCO{-}O{-}COCH_3$ (used in commercial preparation of ethanoic anhydride)
3. **Using other anhydrides** $2\,R{-}COOH \xrightarrow[\text{or ethanoic anhydride}]{P_2O_5} R{-}CO{-}O{-}CO{-}R$

Let us now study these methods in detail.

1. From carboxylic acid halides

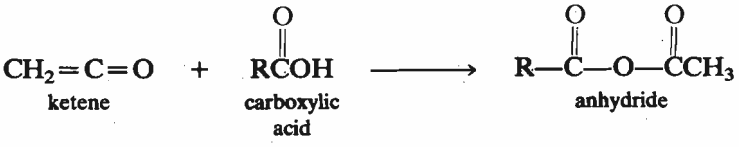
It was pointed out in the last section that carboxylic acid halides react with carboxylic acids or carboxylate salts to give carboxylic acid anhydrides. This reaction can be used to prepare both the simple and the mixed anhydrides.

A general method of preparation of substituted ketenes is based on the dehydrohalogenation of alkanoyl halides or the dehalogenation of 2-halo-alkanoyl halides.



2. From ketene and carboxylic acids

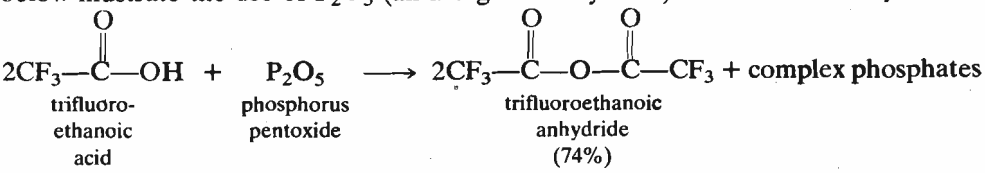
Carboxylic acid anhydrides can also be prepared by the reaction of ketene with carboxylic acids.

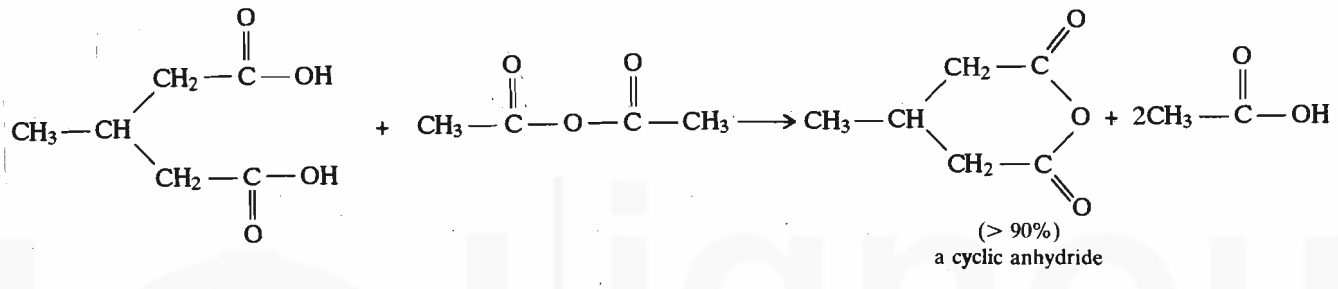


The commerical production of ethanoic anhydride, based on the above reaction, involves the use of ethanoic acid as the carboxylic acid.

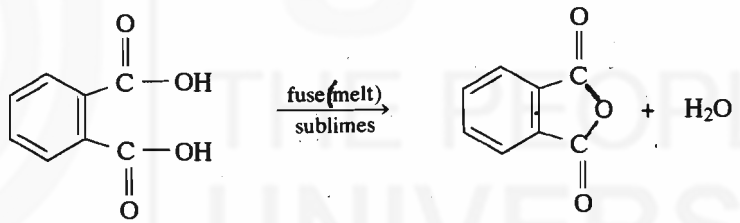
3. Using other anhydrides

Most anhydrides may themselves be used to form other anhydrides. Examples given below illustrate the use of P_2O_5 (an inorganic anhydride) and ethanoic anhydride.





Cyclic anhydrides containing five- and six-membered rings can also be readily prepared just by heating the dicarboxylic acid. For example, 1,2-benzenedicarboxylic acid gives 1,2-benzenedicarboxylic anhydride on heating.



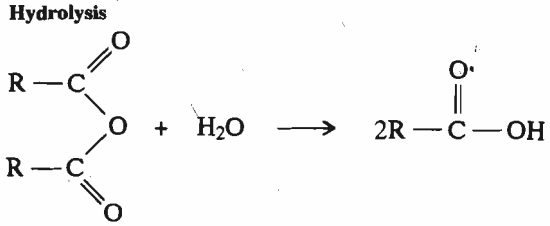
17.6.2 Reactions of Carboxylic Acid Anhydrides

Table 17.6 lists the reactions exhibited by carboxylic acid anhydrides.

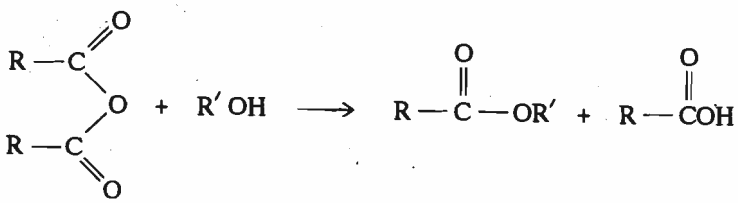
Table 17.6 : Reactions of Acid Anhydrides

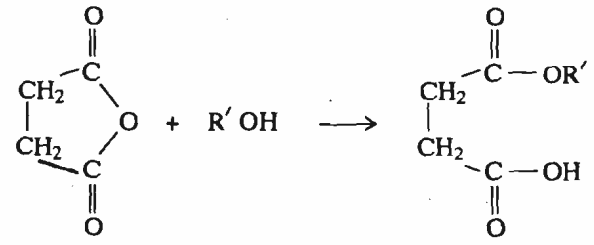
A. Reactions with nucleophiles

1. **Hydrolysis**

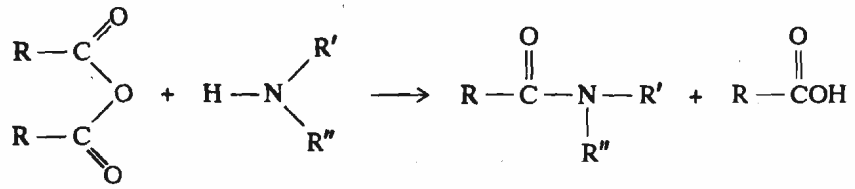


2. **Reaction with alcohol**

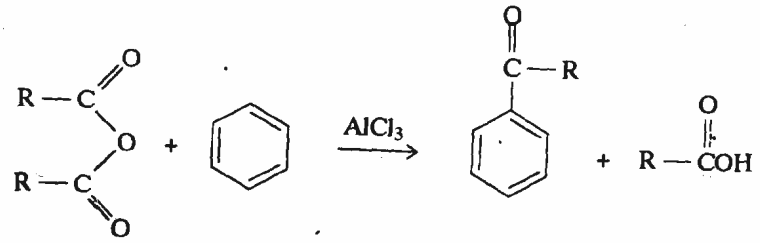




3. **Reaction with ammonia and amines**



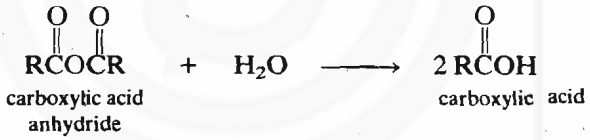
B. Friedel-Crafts alkanoylations



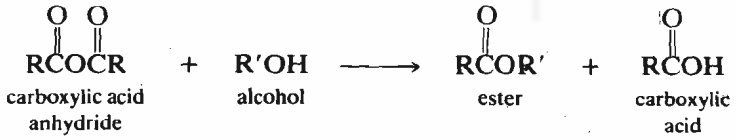
A. Reactions with nucleophiles

The reactions of carboxylic acid anhydrides with nucleophiles are analogous to those of the carboxylic acid halides with you have studied in the last section. The difference here is that the leaving group is a carboxylate ion instead of the halide ion in the case of carboxylic acid halides. The reactions of carboxylic acid anhydrides with water, alcohols and amines are given below:

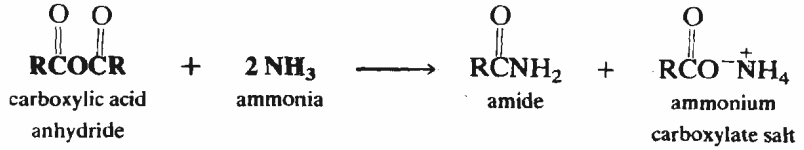
1. Hydrolysis

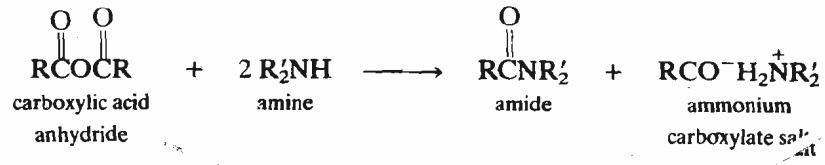


2. Reaction with alcohols



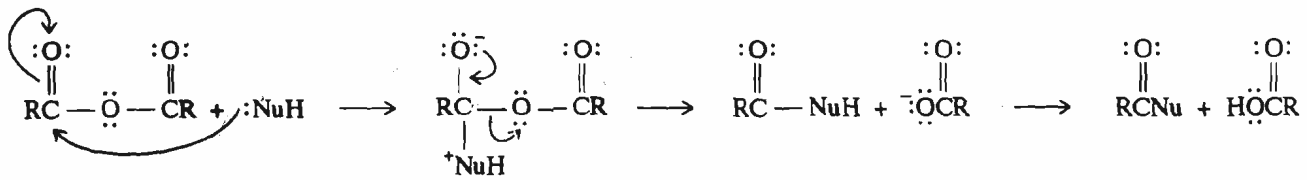
3. Reaction with ammonia and amines





The products in this reaction are amide and carboxylic acid. The carboxylic acid reacts with ammonia or amine to form a salt, therefore, two moles of ammonia or amines are required. Another alternative, as you have studied in the case of carboxylic acid halides is to use one equivalent of a tertiary amine.

The general nucleophilic addition-elimination of anhydrides is shown below:

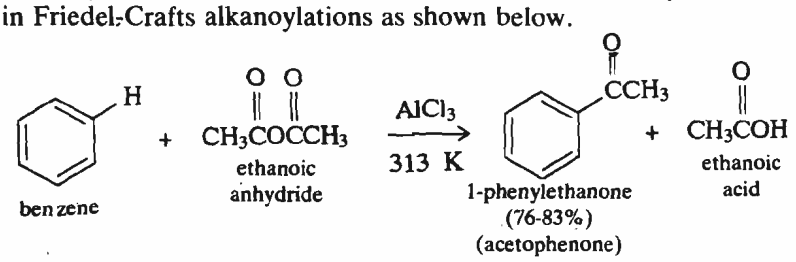


The nucleophilic reactions which you have just studied can be used to synthesise one carboxylic acid derivative from another, as you will study in the later sections.

If you recall the order of reactivities of various carboxylic acid derivatives given in Sec. 17.2 you will realise that the less reactive carboxylic acid derivatives can be synthesised from the more reactive ones but the reverse is usually difficult and requires special conditions or a catalyst.

B. Friedel-Crafts alkanoylations

Carboxylic acid anhydrides also serve as sources of alkanoyl cations and can be used in Friedel-Crafts alkanoylations as shown below.



SAQ 3

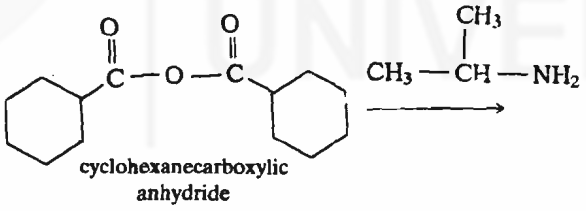
Write the products of the following reactions:

a) CH_3COCCH_3 (ethanoic anhydride) $\xrightarrow{H_2O}$

.....

b) $CH_3CH_2COCCH_2CH_3$ (propanoic anhydride) $\xrightarrow{CH_3OH}$

.....

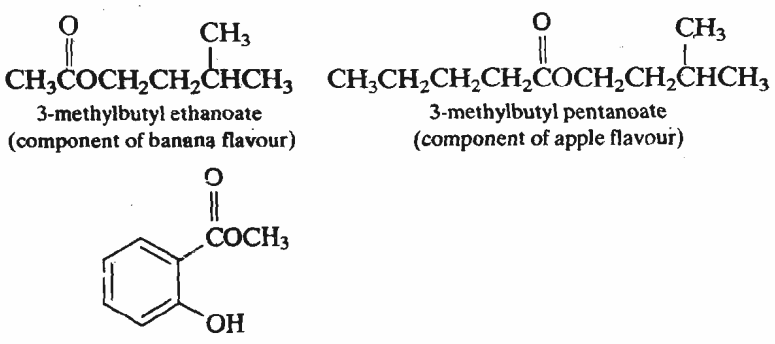
c) 

.....

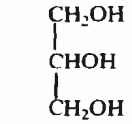
17.7 CARBOXYLIC ACID ESTERS

Carboxylic acid esters constitute a very important class of carboxylic acid derivatives. Some examples of naturally occurring esters are given below.

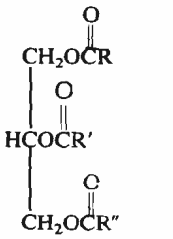
Esters have pleasing odors.



Triesters of 1,2,3-propanetriol (glycerol) constitute the oils and fats found in plants and animals.



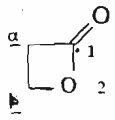
1,2,3-propanetriol (glycerol)



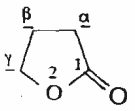
1,2,3-propanetriol triester (Triglyceride)

The nomenclature of esters was discussed in Unit 1, Block 1, where you studied that esters are named as **alkyl alkanoates**.

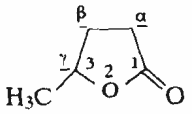
The systematic names of cyclic esters, i.e., lactones, which were not discussed there, are illustrated by the following examples.



2-oxacyclobutanone



2-oxacyclopentanone (γ-butyrolactone)



2-oxa-3-methylcyclopentanone (β-valerolactone)

Let us now study the methods of preparation of carboxylic acid esters.

17.7.1 Preparation of Carboxylic Acid Esters

Let us first list the methods of ester formation which you have already studied.

1) From the reaction of carboxylic acids and alcohols (Fischer esterification) : It was dealt with in detail in Sec. 15.6, Unit 15.

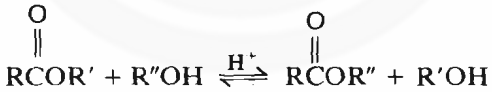
2) From carboxylic acids using diazomethane : It was also dealt with in Sec. 15.6, Unit 15.

3) From carboxylic acid halides : The reaction of carboxylic acid halides with alcohols and phenols also yields esters. It involves the use of a weak base. It was discussed in Sub-Sec. 17.5.2.

4) From carboxylic acid anhydrides : Carboxylic acid anhydrides react with alcohols in the presence of acid catalysts to give esters. This reaction was discussed in sub-Sec. 17.6.2.

In addition to the above methods, esters can also be prepared by ester interchange which is discussed below.

5) Ester interchange : Esters can also be obtained by ester interchange. When an ester reacts with an alcohol under acidic conditions or with an alkoxide ion under basic conditions, a new ester is formed. This is called **transesterification**. The general reaction can be represented as shown below:



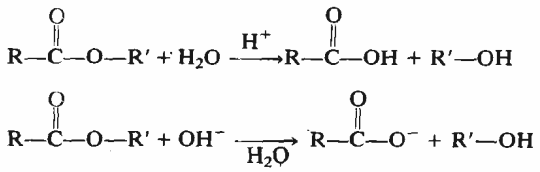
Transesterification will be discussed in detail under the reactions of esters in the next sub-section.

17.7.2 Reactions of Carboxylic Acid Esters

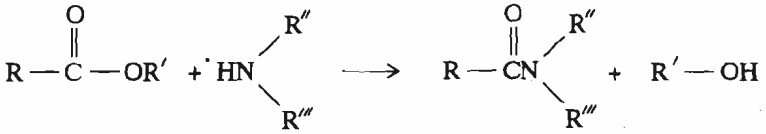
The reactions are listed in Table 17.7 followed by their detailed discussion.

Table 17.7 : Reactions of Esters

1. Hydrolysis

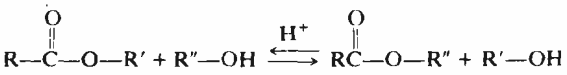


2. Conversion to amides

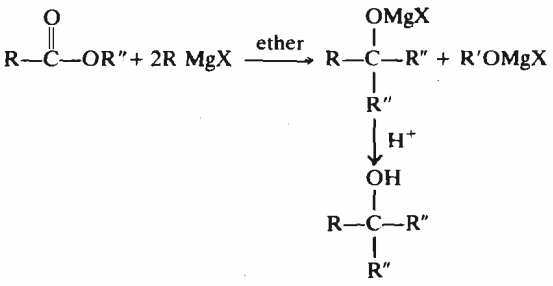


R″ and/or R‴ may be H

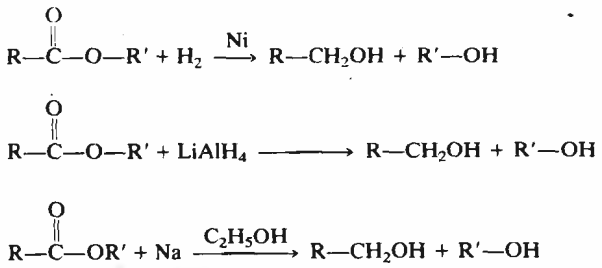
3. Conversion to other esters : transesterification



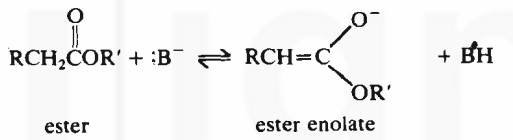
4. Reaction with Grignard reagents



5. Reduction



6. Formation of enolates

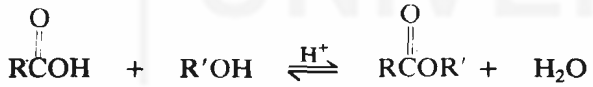


ester — ester enolate

1. Hydrolysis

In contrast to the hydrolysis of carboxylic acid halides and anhydrides, esters do not react with water unless a catalyst is present. Both acid-catalysed and base-catalysed hydrolysis reactions are possible.

The acid-catalysed hydrolysis is just the reverse of acid-catalysed formation of esters which was discussed in detail in Sec. 15.6, Unit 15. You studied in Sec. 15.6 that esterification is an equilibrium reaction, i.e.



acid — alcohol — ester

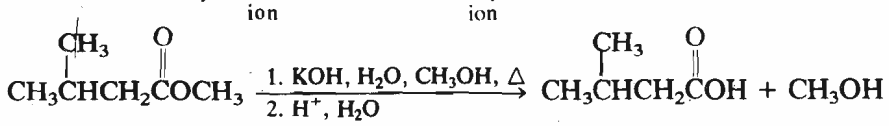
In esterification, either excess of the starting alcohol is used or water produced is removed from the reaction mixture to shift the equilibrium in the forward direction. But when ester hydrolysis is the objective, the reaction is carried out using excess of water in the presence of a mineral acid. Remember that acid-catalysed hydrolysis is an equilibrium process.

Base-catalysed hydrolysis of esters is called **sponification** because it was initially used in the manufacture of soaps from fats. This term is now sometimes used to refer to base-catalysed hydrolysis of any acid derivative.

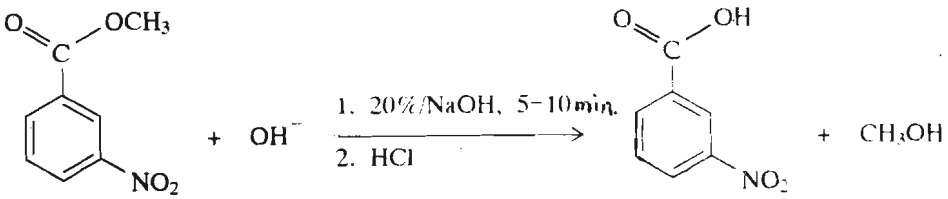
Base-catalysed hydrolysis of esters is faster than acid-catalysed hydrolysis.

In contrast to acid-catalysed hydrolysis, base-catalysed hydrolysis of esters is not an equilibrium process but is *irreversible* because the carboxylic acid produced on hydrolysis is converted to its anion under the basic conditions.

ester — hydroxide ion — carboxylate ion — alcohol



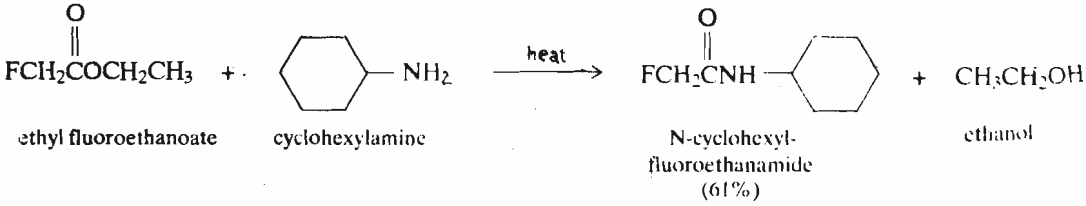
methyl 3-methyl-butanoate — 3-methylbutanoic acid — methanol



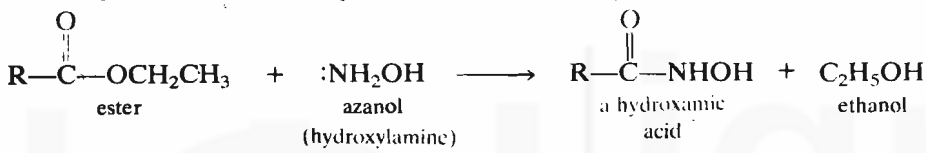
As shown in the above examples, a separate acidification step is required to get the free acid from the carboxylate ion.

2. Reaction with ammonia and amines : Conversion to amides

Esters react with ammonia and amines to give an amide and an alcohol.



The reaction of esters with azanol (hydroxylamine), ($:NH_2OH$) gives N-hydroxyamides. These compounds are known as **hydroxamic acids.**

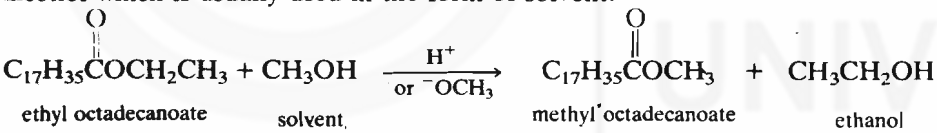


The hydroxamic acids form highly coloured complexes with ferric ion. This chemistry forms the basis of **hydroxamic test** used for the identification of esters.

3. Reaction with alcohols : Transesterification

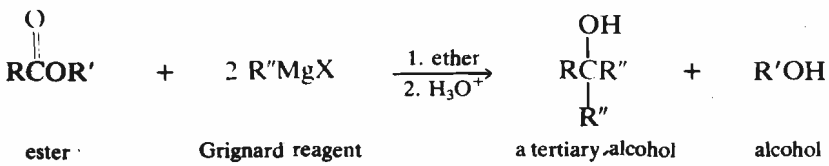
It was pointed out in the last sub-section that a new ester can be synthesised by the reaction of an ester with an alcohol by a process called *transesterification*.

Transesterification is an equilibrium reaction and requires a large excess of the alcohol which is usually used in the form of solvent.

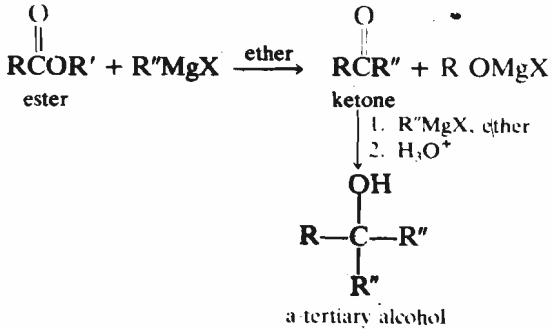


4. Reaction with Grignard reagents

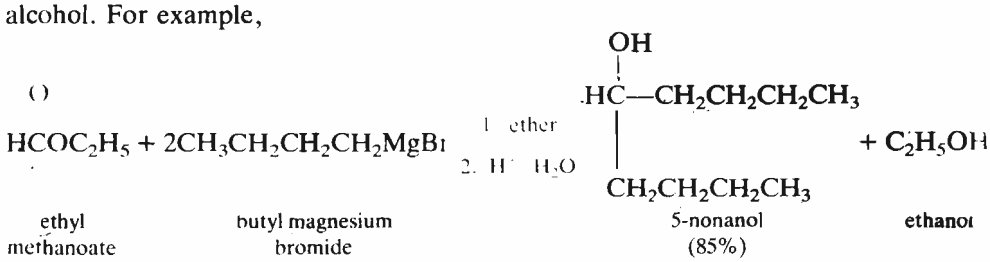
Esters react with two equivalents of a Grignard reagent to produce tertiary alcohols.



A ketone is an intermediate in the reaction but it reacts with the second equivalent of the Grignard reagent as soon as it is formed.



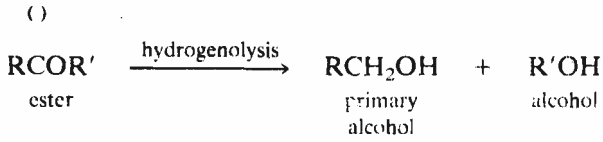
Obviously, methanoic esters on reaction with Grignard reagents yield a secondary alcohol. For example,



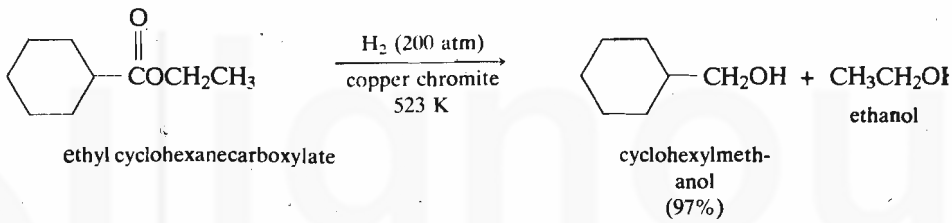
This reaction is a very important method for the synthesis of alcohols having two identical groups attached to carbon atom carrying the hydroxyl group.

5. Reduction

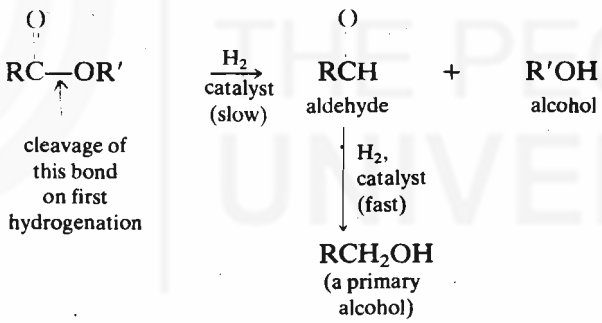
The hydrogenation of esters is accompanied by *cleavage* to yield two alcohols and is, therefore, referred to as **hydrogenolysis.**



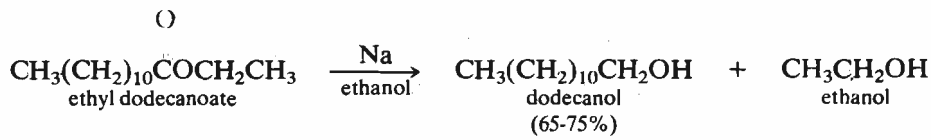
Hydrogenolysis is normally carried over a combination of copper-chromium oxides known as **copper chromite** at high temperature and pressure.



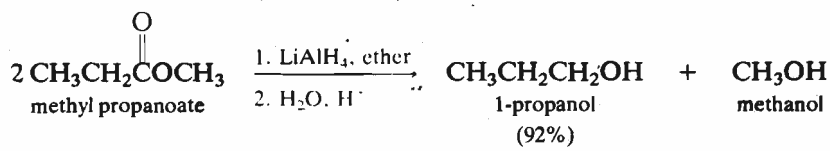
The reduction proceeds in two stages. The first stage involves the formation of an aldehyde which rapidly undergoes reduction to the primary alcohol.



Esters are also reduced by sodium in alcohol. This is a method of long standing and is known as **Bouveault-Blanc reduction**. It was the common laboratory method before the discovery of lithium aluminium hydride.



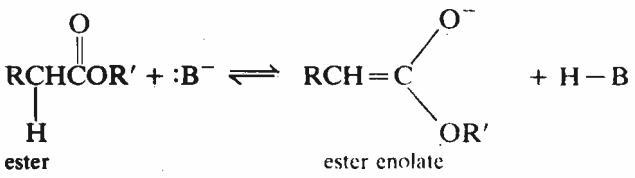
Reduction of esters using lithium aluminium hydride requires only 0.5 equivalent of $LiAlH_4$ because only two of the hydrogens are used per ester function.



This reduction proceeds via the formation of an aldehyde which reacts rapidly with $LiAlH_4$ and yields an alcohol after acidification.

6. Formation of enolates

When esters are treated with strong bases at low temperature, ester enolates are formed. This involves the abstraction of the acidic hydrogen from the carbon atom next to the ester function.



ester ester enolate

You have already studied the **Claisen condensation** involving ester enolates to yield 3-ketoesters such as ethyl 3-oxobutanoate in Sec. 16.7, Unit 16.

Having studied the reactions of esters, answer the following SAQ.

SAQ 4

Write the expected product(s) of the reaction between ethyl benzoate and the following reagents:

a) H^+, H_2O, heat

.....

b) NaOH, H_2O

.....

c) aqueous NH_3, heat

.....

d) i) $LiAlH_4$,
ii) H_3O^+

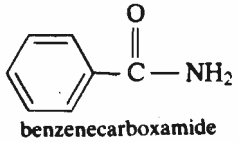
.....

e) i) excess $CH_3CH_2CH_2MgBr$
ii) H_2O, H^+

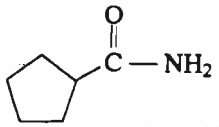
.....

17.8 AMIDES

You are aware from Sec. 1.6, Unit 1, Block 1, that amides can be named by replacing the *-ic* or *-oic acid* suffix of the carboxylic acid with the suffix *amide*. Thus, amides are named as **alkanamides**. Amides are also named as substituted **carboxamides**. The name of the group R in $R—\overset{O}{\overset{\|}{C}}—NH_2$ followed by the suffix carboxamide gives the name according to this system, examples being benzenecarboxamide and cyclopentanecarboxamide.



benzenecarboxamide

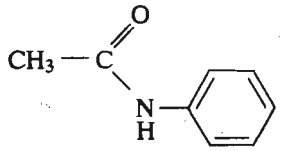


cyclopentanecarboxamide

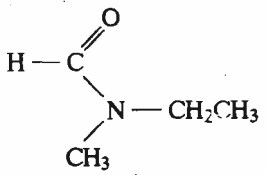
Amides can be classified as primary, secondary or tertiary according to the degree of substitution on the amide nitrogen.

$RCONH_2$	RCONHR'	RCONR'R"
a primary amide	a secondary amide	a tertiary amide

In the case of secondary and tertiary amides, the symbol *N* must precede the name of each different group attached to the nitrogen.

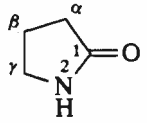


N-phenylethanamide

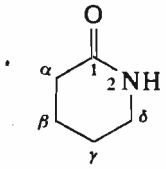


N-ethyl-*N*-methyl-methanamide

Cyclic amides are called **lactams**. The systematic names of some lactams are given below:



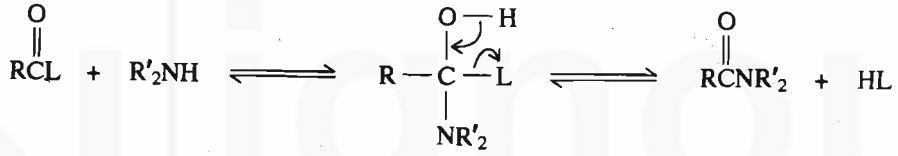
2-azacyclopentanone
(γ-butyrolactam)



2-azacyclohexanone
(δ-valerolactam)

17.8.1 Preparation of Amides

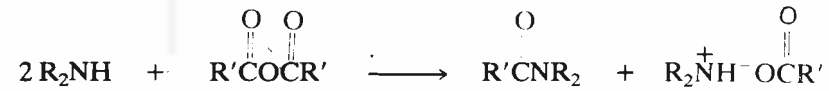
The formation of amides from carboxylic acid halides, anhydrides and esters was discussed in Secs. 17.5.2, 17.6.2 and 17.7.2, respectively. General reactions of the above carboxylic acid derivatives with amines (or ammonia) can be represented as shown below:



carboxylic acid derivative | amine | tetrahedral intermediate | amide | conjugate acid of the leaving group

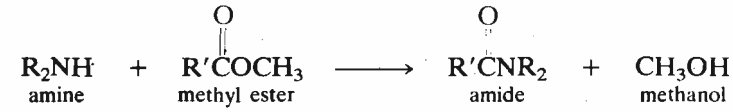
You will recall that two molar equivalents of amine are required in case of carboxylic acid halide and anhydride.

amine | carboxylic acid halide | amide | hydrochloride salt of amine



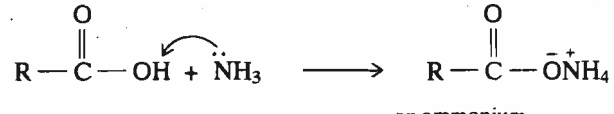
amine | carboxylic acid anhydride | amide | carboxylate salt of amine

But in the case of esters, no acid is formed, therefore, the reaction is carried out using the ester and the amine in 1:1 molar ratio to yield the amide.



amine | methyl ester | amide | methanol

In addition to the above methods, amides can also be prepared from ammonium carboxylates. Ammonium carboxylates are prepared by the reaction of ammonia with carboxyic acids.



an ammonium carboxylate

When dry ammonium carboxylates are heated, dehydration takes place to yield an amide.

$$R-\underset{\text{(solid)}}{\overset{O}{\overset{\|}{C}}}-O^{-}\overset{+}{N}H_4 \xrightarrow{\text{heat}} R-\overset{O}{\overset{\|}{C}}-NH_2 + H_2O$$

A similar sequence of reactions can be carried out using amines instead of ammonia.

This is a poor method of preparing amides. A much better method is to convert the acid into the acid halide which can yield the amide as discussed in Section 17.5.2, Unit 17.

You may recall from sub-Sec. 14.4.1, Unit 14, Block 3 that ketones react with RNH_2 compounds to yield condensation products. When azanol (hydroxylamine, $HO-NH_2$) reacts with ketones, an oxime is obtained as shown below.

$$\begin{matrix} R \\ \diagdown \\ C=O \\ \diagup \\ R' \end{matrix} + H_2N-OH \xrightarrow[H_2O]{H^+} \begin{matrix} R \\ \diagdown \\ C=N \\ \diagup \\ R' \end{matrix}\!\!\begin{matrix} OH \\ \diagup \end{matrix}$$

oxime

Oximes on heating with a strong acid rearrange to give amides.

$$\begin{matrix} R \\ \diagdown \\ C=N \\ \diagup \\ R' \end{matrix}\!\!\begin{matrix} OH \\ \diagup \end{matrix} \xrightarrow[\text{heat}]{H_2SO_4} R-\overset{O}{\overset{\|}{C}}-NHR'$$

oxime

This reaction is known as **Beckmann rearrangement.**

17.8.2 Reactions of amides

The reactions of amides are listed in Table 17.8.

Table 17.8 : Reactions of Amides

1. Hydrolysis

$$R-\overset{O}{\overset{\|}{C}}-\underset{R''}{\overset{|}{N}}R' + H_3O^+ \xrightarrow{H_2O} R-\overset{O}{\overset{\|}{C}}-OH + R'-\underset{R''}{\overset{|}{\overset{+}{N}}}H_2$$

$$R-\overset{O}{\overset{\|}{C}}-\underset{R''}{\overset{|}{N}}R' + OH^- \xrightarrow{H_2O} RC-O^- + R'-\underset{R''}{\overset{|}{N}}H$$

R, R′, and/or R″ may be H

2. Reduction

$$R-\overset{O}{\overset{\|}{C}}-NR'_2 \xrightarrow[\text{or } B_2H_6]{LiAlH_4} RCH_2NR'_2$$

3. Dehydration

$$R-\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[\text{heat}]{P_2O_5} R-C\equiv N$$
$$(-H_2O)$$

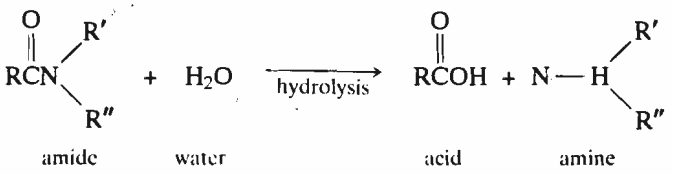
4. Hofmann rearrangement

$$R-\overset{O}{\overset{\|}{C}}-NH_2 \xrightarrow{Br_2,\ NaOH,\ H_2O} RNH_2 + O=C=O$$

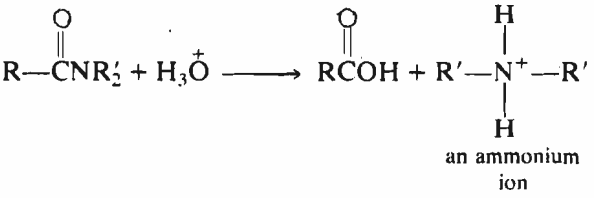
Amides are the least reactive among the carboxylic acid derivatives discussed so far. Therefore, their nucleophilic addition-elimination requires relatively vigrous reaction conditions. Let us understand this by taking the example of hydrolysis.

1. Hydrolysis of amides

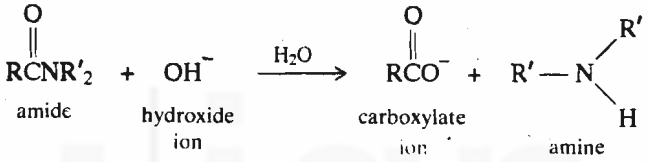
Hydrolysis of amides occurs only on prolonged heating in strongly acidic or basic aqueous conditions to yield an amine and a carboxylic acid.



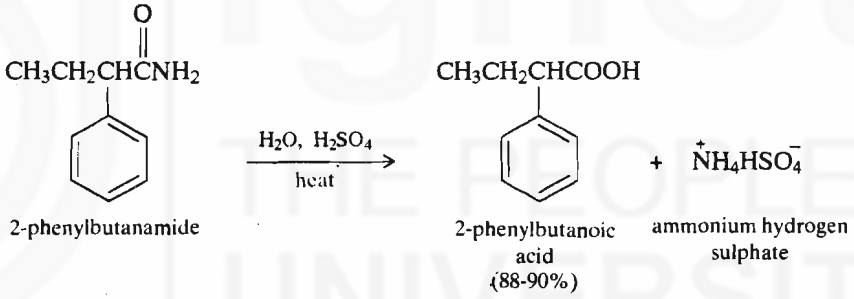
When the hydrolysis is carried out in acidic medium, the amine obtained is protonated to yield an ammonium ion, i.e.,

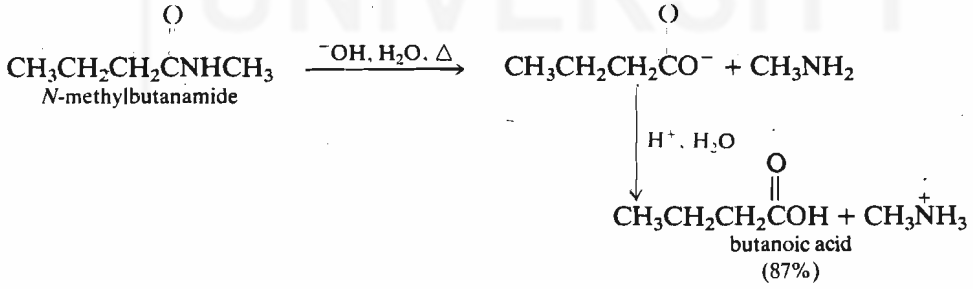


But when the hydrolysis is done using a base, the carboxylic acid obtained is deprotonated to give a carboxylate ion, as shown below:



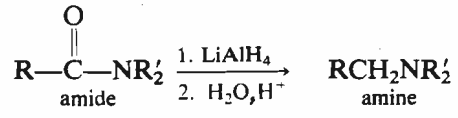
The following examples illustrate amide hydrolysis.

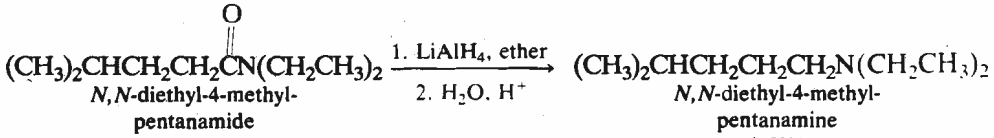




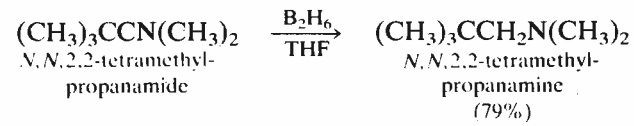
2. Reduction of amides

Amides can be converted into the corresponding amines on reduction with lithium aluminium hydride.





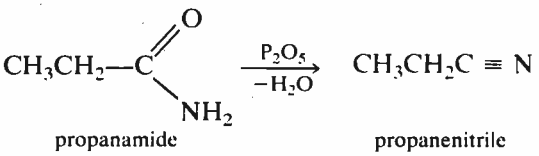
Diborane, B_2H_6, may also be used for the reduction of amides.



N,N,2,2-tetramethylpropanamide — *N,N,2,2*-tetramethylpropanamine (79%)

3. Dehydration of amides

Amides can be dehydrated, using a number of dehydrating agents like P_2O_5 or ethanoic anhydride, to the corresponding nitriles. For example,

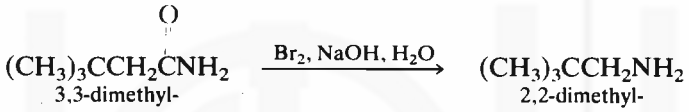


propanamide — propanenitrile (55-70%)

4. Hofmann rearrangement

Primary amides, $RCNH_2$, on treatment with bromine in basic solution undergo an interesting reaction to yield amines.

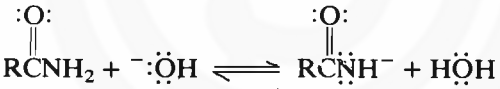
The overall reaction appears as if the carbonyl group is expelled from the amide to give an amine with one carbon atom less than the amide.



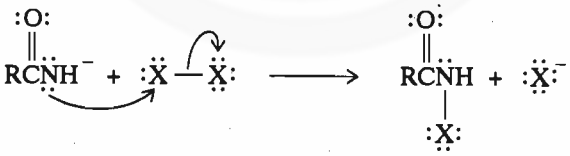
3,3-dimethylbutanamide — 2,2-dimethylpropanamine (94%)

The reaction proceeds via the following steps.

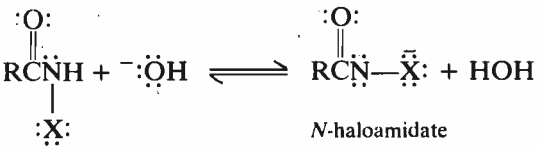
Step 1 Amidate formation



Step 2 Halogenation

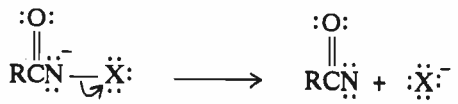


Step 3 *N*-Halo amidate formation

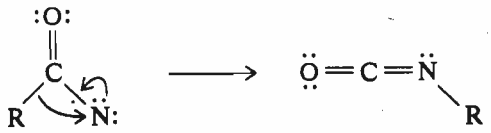


N-haloamidate

Step 4 Halide elimination

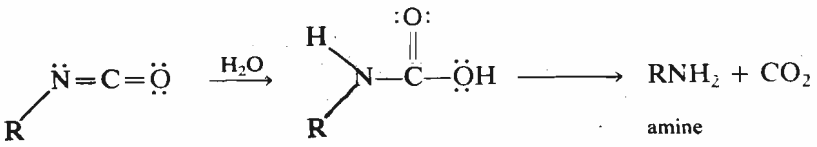


Step 5 Rearrangement



an isocyanate

Step 6 Hydrolysis to carbamic acid and decomposition



$$\ddot{N}=C=\ddot{O} \xrightarrow{H_2O} \text{N—C—ÖH} \longrightarrow RNH_2 + CO_2$$

After studying the chemistry of amides, answer the following SAQ

SAQ 5

Outline the synthesis of propanamine, $CH_3CH_2CH_2NH_2$ from butanoic acid.

.....

.....

17.9 SUMMARY

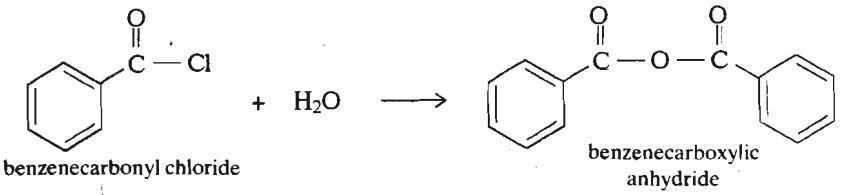
In this unit, you have studied that

- the functional derivatives of carboxylic acids are those derivatives which are formed by substitution of OH of the carboxy group and can be hydrolysed to yield caboxylic acids.
- various carboxylic acid derivatives can be arranged according to their reactivity in the following order:

  carboxylic acid > carboyxlic acid > esters > amides
  halides anhydrides
- the electrophilic reactivity of the carbonyl carbon in carboxylic acid derivatives is weakened by good electron-donating substituents. This also explains the increasing basicity in the series: carboxylic acid halides < anhydrides < esters < amides.
- carboxylic acid derivatives undergo nucleophilic substitution reactions by addition-elimination mechanism.
- one carboxylic acid derivative can be converted into another by nucleophilic addition-elimination and the more reactive derivative can be converted to the less reactive derivative easily but the reverse requires special conditions and suitable catalysts.
- carboxylic acid halides undergo nucleophilic substitution reactions with water, carboxylic acids, alcohols, amines and organometallic reagents.
- reactions of carboxylic acid anhydrides with water, alcohol and amines are similar to carboxylic acid halides.
- esters can be obtained from carboxylic acids, carboxylic acid halides and carboxylic acid anhydrides by reaction with alcohols.
- esters can be hydrolysed both in acidic and basic conditions and they react with amines to yield amides and alcohols. Their catalytic hydrogenation, reaction with Grignard reagents and $LiAlH_4$, yield alcohols.
- amides can be prepared by the reaction of ammonia or amines with carboxylic acid halides, anhydrides and esters. Their important reactions include hydrolysis, reduction, dehydration and Hofmann rearrangement.

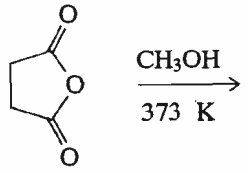
17.10 TERMINAL QUESTIONS

1) Benzenecarboxylic anhydride can be prepared by adding one molar equivalent of water to two molar equivalents of benzenecarbonyl chloride, i.e.,

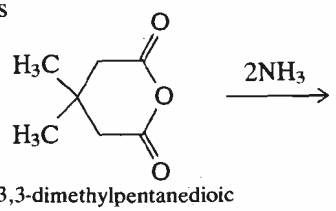


Explain how this reaction takes place.

2) Write products of the following reactions

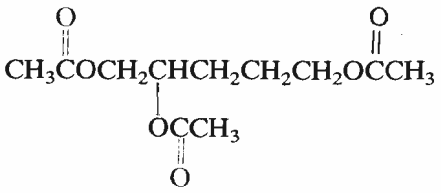
a) 

butanedioic anhydride

b) 

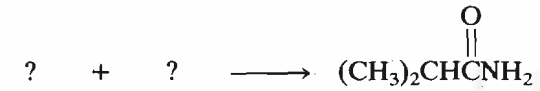
3,3-dimethylpentanedioic anhydride

3) The compound



on hydrolysis in acidic medium gave a compound of molecular formula $C_5H_{12}O_3$. Write the structure of this compound. What other compound is formed in this reaction?

4) Suggest suitable starting materials for the following reactions.

a) 

an acid halide

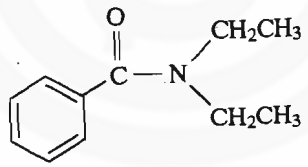
b) 

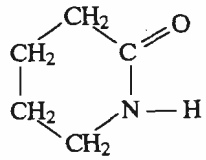
an acid anhydride

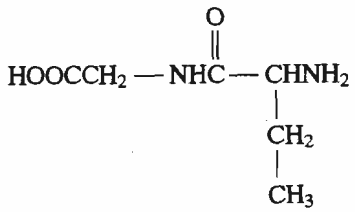
c) 

a methyl ester

5) Write the products of hydrolysis of the following compounds.

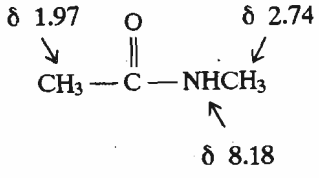
a) 

b) 

c) 

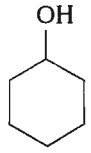
17.11 ANSWERS

Self Assessment Questions

1) 

2) a) H_2O

b) $CH_3\overset{\overset{O}{\|}}{C}O^- Na^+$

c) 

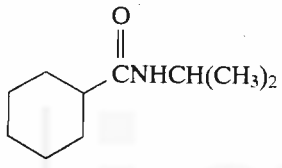
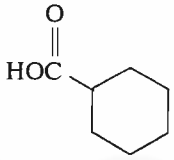
d) $(CH_3)_2NH$

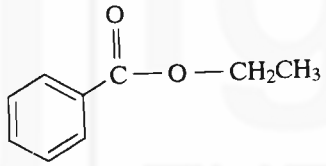
e) CH_3CH_2MgBr

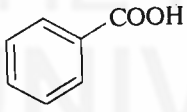
f) $LiAl[OC(CH_3)_3]_3H$

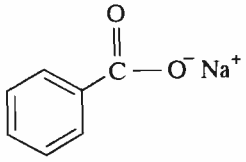
3) a) $2CH_3\overset{\overset{O}{\|}}{C}OH$
ethanoic acid

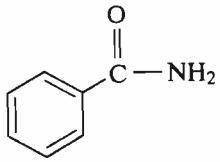
b) $CH_3CH_2\overset{\overset{O}{\|}}{C}OCH_3$ + $HO\overset{\overset{O}{\|}}{C}CH_2CH_3$
methyl propanoate — propanoic acid

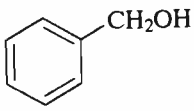
c)  + 
N-(1-methylethyl)-cyclohexanecarboxamide — cyclohexanecarboxylic acid

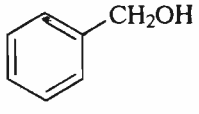
4) 
ethyl benzoate

a) $\xrightarrow{H^+, H_2O, \text{heat}}$  + CH_3CH_2OH

b) $\xrightarrow{NaOH, H_2O}$  + C_2H_5OH

c) $\xrightarrow{\text{aq. } NH_3, \text{ heat}}$  + CH_3CH_2OH

d) $\xrightarrow[2.\ H_2O,\ H^+]{1.\ LiAlH_4}$  + CH_3CH_2OH

e) $\xrightarrow[2.\ H_2O,\ H^+]{1.\ \text{excess } CH_3CH_2CH_2MgBr,}$  + CH_3CH_2OH

5) $CH_3CH_2CH_2COOH \xrightarrow[2.\ NH_3]{1.\ SOCl_2} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[H_2O]{Br_2,\ NaOH} CH_3CH_2CH_2NH_2$

butanoic acid — butanamide — propanamine

Terminal Questions

1) Benzenecarbonyl chloride on reaction with water yields benzenecarboxylic acid which further reacts with second molar equivalent of benzenecarbonyl chloride to yield benzenecarboxylic anhydride.

2) a) $HO\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$

b) $^{+}NH_4\ ^{-}O\overset{O}{\overset{\|}{C}}CH_2\overset{CH_3}{\overset{|}{C}}CH_2\overset{O}{\overset{\|}{C}}NH_2$ (with CH_3 branch)

3) $HOH_2C\underset{OH}{\underset{|}{C}}HCH_2CH_2CH_2OH$

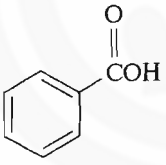
(molecular formula $C_5H_{12}O_3$)

The other product obtained is ethanoic acid.

4) a) $(CH_3)_2CH\overset{O}{\overset{\|}{C}}Cl$ and $2\ NH_3$

b) $CH_3\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}CH_3$ and $2\ CH_3NH_2$

c) $H\overset{O}{\overset{\|}{C}}OCH_3$ and $HN(CH_3)_2$

5) a)  + $NH(CH_2CH_3)_2$

b) $H_2NCH_2CH_2CH_2CH_2COOH$

c) $HOOCCH_2-NH_2$ + $HOOCCH(CH_2CH_3)-NH_2$

UNIT 18 NITRO COMPOUNDS

Structure

18.1 INTRODUCTION

In Unit 17, you studied the chemistry of carboxylic acid derivatives. In this unit, you will study a very important class of nitrogen containing organic compounds called nitro compounds. You may recall that the nomenclature of nitro compounds was discussed in Block 1, Unit 1, Sec. 1.6. The nitro group can be converted to many other functional groups which makes nitro compounds good starting materials for the synthesis of other organic compounds. Let us first study how nitro compounds can be prepared. Then, we will discuss various reactions of nitro compounds. Finally, the uses of nitro compounds will be explained.

Objectives

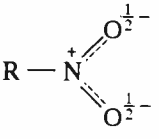
After studying this unit, you should be able to:

- outline the synthesis of a nitro compound,
- explain the acidic nature of nitro alkanes,
- write reduction products of nitro compounds in different reaction conditions, and
- list the uses of nitro compounds.

18.2 STRUCTURE AND PROPERTIES OF NITRO COMPOUNDS

The nitro group, $-NO_2$, which is the functional group of nitro compounds is a resonance hybrid of two equivalent contributing structures as shown below.

Thus, it can be represented by the following hydrid structure:



Remember that a similar resonance hydrid was written in the case of carboxylate ion.

Nitro Compound	*b.p./K*
nitromethane	374
nitroethane	387
2-nitropropane	393
1-nitropropane	404
nitrobenzene	484

You can see in the hydrid structure that there is a positive charge on the nitrogen atom and the negative charge is distributed equally on the two oxygen atoms. This separation of charge is reflected in the high dipole moment values for nitro compounds which range between 11.67×10^{-30} C m and 13.35×10^{-30} C m, depending upon the nature of the hydrocarbon group. Their polar nature is also indicated by their high boiling points.

5) $CH_3CH_2CH_2COOH \xrightarrow[2.\ NH_3]{1.\ SOCl_2} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[H_2O]{Br_2,\ NaOH} CH_3CH_2CH_2NH_2$

butanoic acid — butanamide — propanamine

Terminal Questions

1) Benzenecarbonyl chloride on reaction with water yields benzenecarboxylic acid which further reacts with second molar equivalent of benzenecarbonyl chloride to yield benzenecarboxylic anhydride.

2) a) $HO\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$

b) $^{+}NH_4{}^{-}O\overset{O}{\overset{\|}{C}}CH_2\overset{CH_3}{\overset{|}{C}}CH_2\overset{O}{\overset{\|}{C}}NH_2$ (CH₃ branch on the central C)

3) $HOH_2C\underset{OH}{\underset{|}{C}}HCH_2CH_2CH_2OH$

(molecular formula $C_5H_{12}O_3$)

The other product obtained is ethanoic acid.

4) a) $(CH_3)_2CH\overset{O}{\overset{\|}{C}}Cl$ and $2\ NH_3$

b) $CH_3\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}CH_3$ and $2\ CH_3NH_2$

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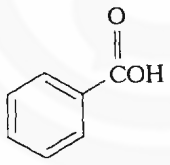
5) a)  + $NH(CH_2CH_3)_2$

b) $H_2NCH_2CH_2CH_2CH_2COOH$

c) $HOOCCH_2-NH_2 + HOOCCH(CH_2CH_3)-NH_2$

UNIT 18 NITRO COMPOUNDS

Structure

18.1 INTRODUCTION

In Unit 17, you studied the chemistry of carboxylic acid derivatives. In this unit, you will study a very important class of nitrogen containing organic compounds called nitro compounds. You may recall that the nomenclature of nitro compounds was discussed in Block 1, Unit 1, Sec. 1.6. The nitro group can be converted to many other functional groups which makes nitro compounds good starting materials for the synthesis of other organic compounds. Let us first study how nitro compounds can be prepared. Then, we will discuss various reactions of nitro compounds. Finally, the uses of nitro compounds will be explained.

Objectives

After studying this unit, you should be able to:

- outline the synthesis of a nitro compound,
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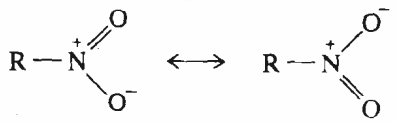
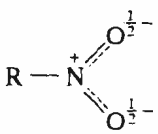


Thus, it can be represented by the following hydrid structure:



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nitromethane	374
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You can see in the hydrid structure that there is a positive charge on the nitrogen atom and the negative charge is distributed equally on the two oxygen atoms. This separation of charge is reflected in the high dipole moment values for nitro compounds which range between 11.67×10^{-30} C m and 13.35×10^{-30} C m, depending upon the nature of the hydrocarbon group. Their polar nature is also indicated by their high boiling points.

Spectral properties of nitro compounds

Aliphatic nitro compounds show an absorption near 270 nm in their ultraviolet spectrum due to $n \rightarrow \pi^*$ transitions. However, aromatic nitro compounds absorb at longer wavelengths, i.e., ~300 nm, due to the extended conjugation.

The infrared spectra of nitro alkanes show strong bands at about 1550 cm^{-1} and 1375 cm^{-1} whereas aromatic nitro compounds show these absorptions at slightly lower frequencies.

18.3 PREPARATION OF NITRO COMPOUNDS

The nitro compounds can be prepared by a number of methods. Let us now study these methods.

1. By direct nitration of hydrocarbons

Hydrocarbons can be nitrated using nitric acid. The reaction with aliphatic hydrocarbons requires high temperatures and is carried out in the vapour phase. For example,

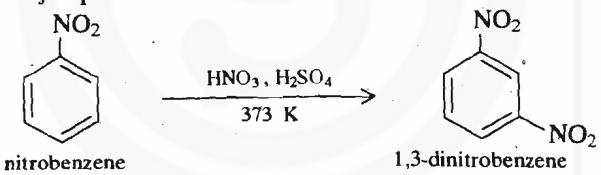
$$\underset{\text{methane}}{CH_4} + HNO_3 \xrightarrow{673\ K} \underset{\text{nitromethane}}{CH_3NO_2} + H_2O$$

Nitration is accompanied by oxidation.

You have studied, under the nitration of alkanes in sub-Sec. 6.6.2, Unit 6, Block 2, that nitration of higher alkanes yields a mixture of nitroalkanes which are separated using fractional distillation.

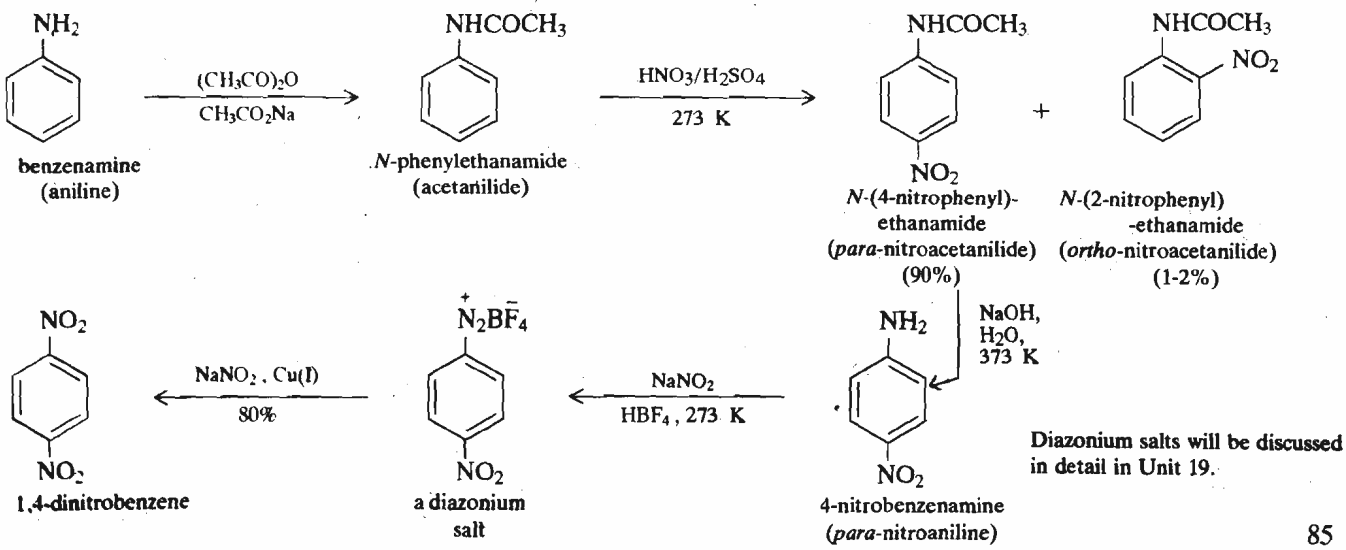
In contrast to this, nitration of aromatic compounds takes place readily in the liquid phase and can be carried out near room temperature or on a steam bath. You have already studied about the nitration of benzene in sub-Sec. 9.6.1, Unit 9, Block 2. You may recall that nitration of aromatic compounds is an electrophilic substitution reaction, the electrophile being the nitronium ion, NO_2^+.

The products of nitration of substituted benzenes depend upon the nature of the substituent groups already present in the molecule. The nitro group itself is *meta*-directing and, therefore, nitration of nitrobenzene yields 1,3-dinitrobenzene as the major product.



nitrobenzene — 1,3-dinitrobenzene

1,4-Dinitrobenzene can be prepared by starting with benzenamine. Since the amino group is *o*-, *p*- directing, nitration of benzenamine followed by the conversion of the amino group to nitro group, should give the desired compound. Benzenamine, however, is susceptible to oxidation, so the amino group is first protected by ethanoylation (acetylation). The sequence of reactions is outlined below:

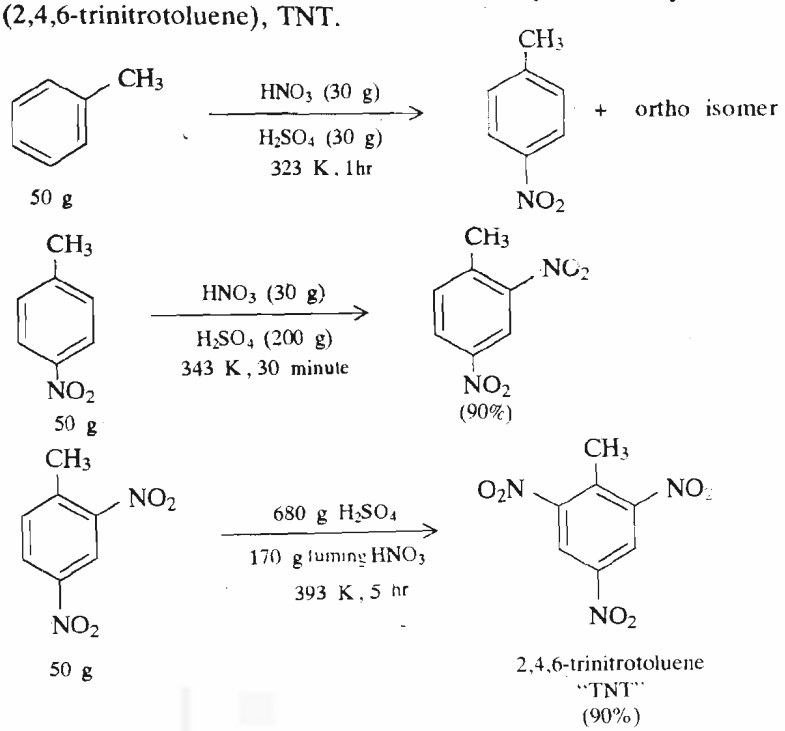


benzenamine (aniline) — *N*-phenylethanamide (acetanilide) — *N*-(4-nitrophenyl)-ethanamide (*para*-nitroacetanilide) (90%) — *N*-(2-nitrophenyl) -ethanamide (*ortho*-nitroacetanilide) (1-2%)

4-nitrobenzenamine (*para*-nitroaniline) — a diazonium salt — 1,4-dinitrobenzene

Diazonium salts will be discussed in detail in Unit 19.

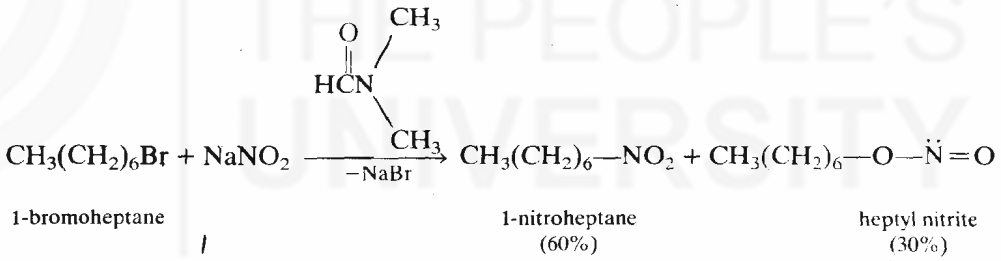
Nitration reactions to yield trinitro derivatives require very harsh reaction conditions, e.g. prolonged heating of the starting nitro compound with nitric acid in fuming sulphuric acid. But, by using activating groups further nitration is facilitated and methylbenzene can be converted more readily to 2-methyl-1,3,5-trinitrobenzene (2,4,6-trinitrotoluene), TNT.



TNT is an important explosive. It is relatively insensitive to shock and hence is used with a detonator. When mixed with ammonium nitrate it yields the explosive *amatol*.

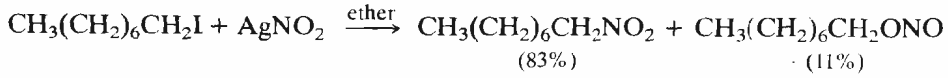
2. Substitution by nitrite ion

Some nitro compounds can be prepared by the reaction of alkyl halides with sodium nitrite using dimethylmethanamide as solvent.

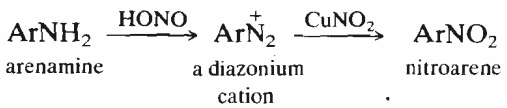


Some alkyl nitrite is usually obtained as by-product in this reaction.

Better yields of nitroalkanes are obtained when silver nitrite is used instead of sodium nitrite. But as you know, silver nitrite is expensive and is not economical for large scale production of nitro compounds.



Aryl nitro compounds or nitroarenes cannot be synthesised from aryl halide by a similar route. Instead, nitroarenes are prepared by displacement of the diazonium group. This will be dealt with in Unit 19. The reaction of arenamines to yield diazonium salts which can be used to prepare nitroarenes can be represented as shown below:



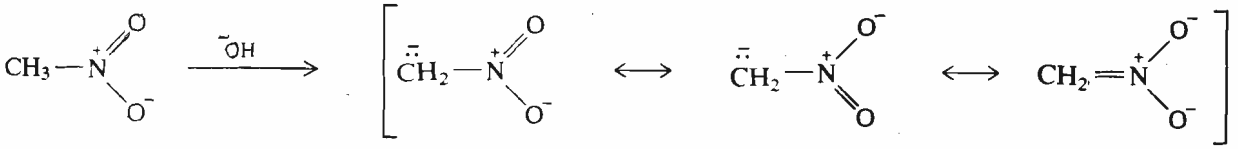
Let us now study the reactions of nitro compounds.

18.4 REACTIONS OF NITRO COMPOUNDS

1. As weak acids

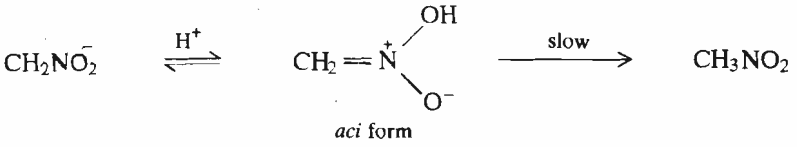
The hydrogen atoms bonded to the carbon atom carrying the nitro group are acidic in nature. Thus, nitro compounds dissolve in bases like sodium hydroxide. The anion so produced is resonance stabilised as shown below:

nitroalkane	pK_a
nitromethane	10.2
nitroethane	8.5
nitropropane	7.8



nitromethane — methylnitronate ion

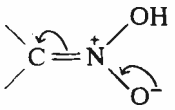
On acidification, the anion yields the acidic isomer of nitromethane known as the *aci* form which slowly changes to the more stable nitro form.



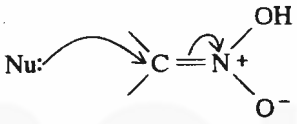
aci form

***The aci* form can behave both as a** nuclephile as well as an electrophile.

as nucleophile:

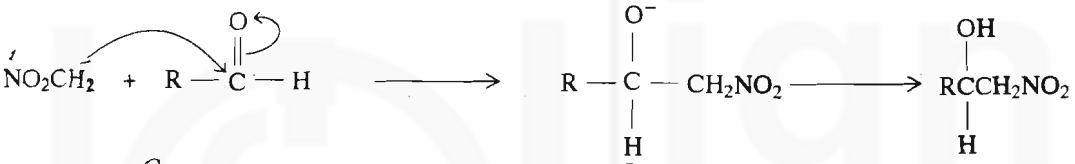


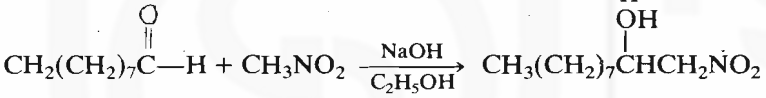
as electrophile:



2. Henry reaction

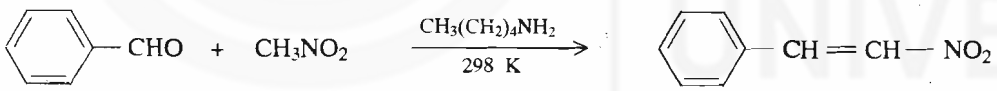
The anions obtained from nitroalkanes as explained above can undergo nucleophilic reactions with carbonyl compounds similar to the aldol type addition reaction.





1-nitro-2-decanol
(80%)

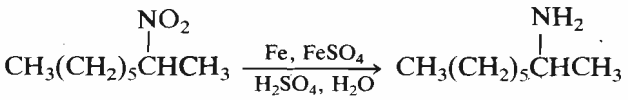
In case of aromatic aldehydes, the product obtained undergoes dehydration as shown below:



(75%)

3. Reduction

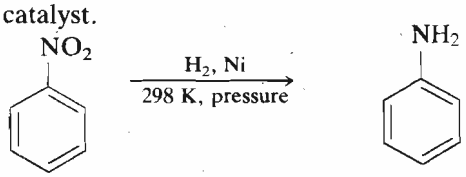
Nitro compounds can be reduced with a variety of reducing agents. Nitroalkanes can be converted to alkanamines as shown below:



2-nitrooctane — 2-octanamine
(90%)

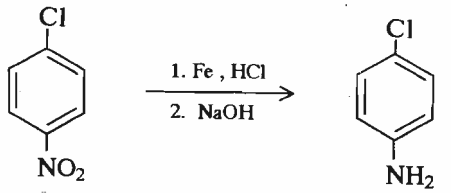
The product of reduction of aromatic nitro compounds depends on the reaction conditions employed. Catalytic reduction and reduction in acidic media yields aromatic amines.

Catalytic hydrogenation is carried out by using platinum, palladium or nickel as the catalyst.



nitrobenzene — benzenamine

For reduction in **acidic medium** a metal and an acid is used. Usually iron or zinc and hydrochloric acid are taken.



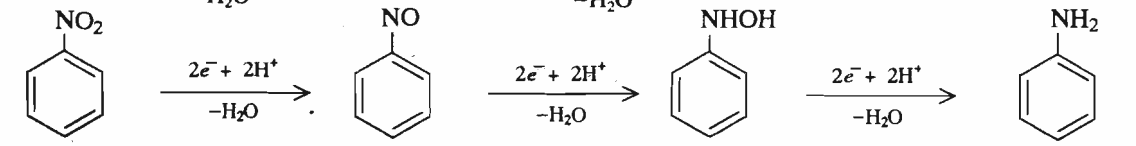
1-chloro-4-nitrobenzene 4-chlorobenzenamine

Reduction of a nitro compound to an amine requires six equivalents of the reducing agent, i.e.,

$$R—NO_2 + 6H^+ + 6\,e^- \longrightarrow RNH_2 + 2H_2O$$

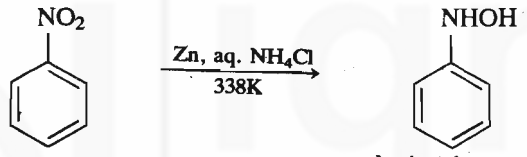
The reduction actually proceeds in a series of two-electron steps via the nitroso compounds (R—N=O) and *N*-substituted azanols (RNHOH) as successive intermediates.

$$RNO_2 \xrightarrow[-H_2O]{2[H]} RN{=}O \xrightarrow{2[H]} RNHOH \xrightarrow[-H_2O]{2[H]} RNH_2$$



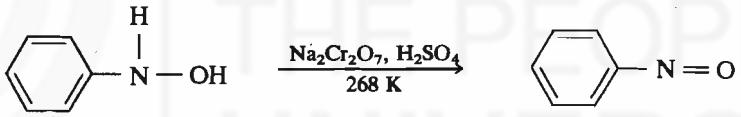
nitrobenzene nitrosobenzene *N*-phenylazanol benzenamine

Reduction can be stopped at the *N*-substituted azanol stage when reduction is carried out in **neutral conditions** using zinc and ammonium chloride.



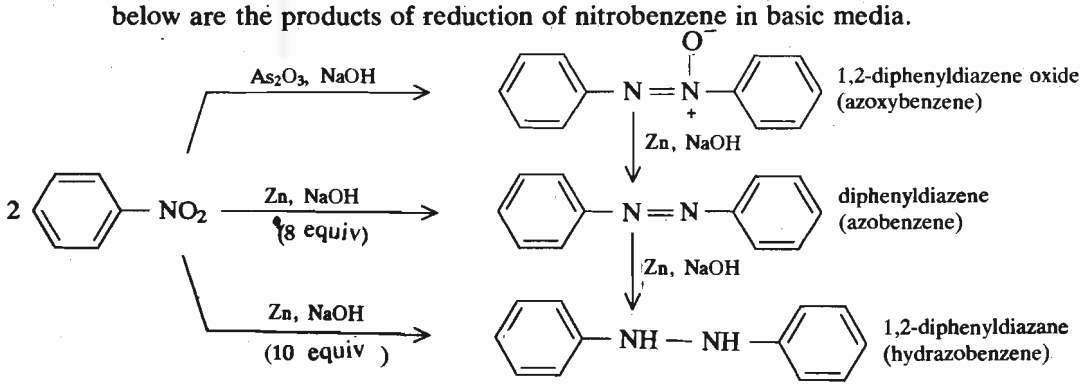
nitrobenzene *N*-phenylazanol (62-68%)

N-phenylazanol obtained above can be oxidised to nitrosobenzene.

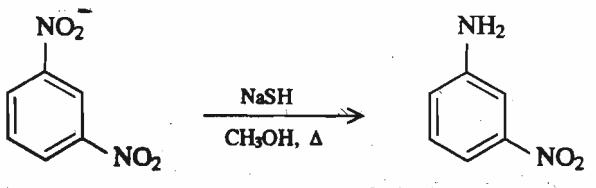


N-phenylazanol *N*-nitrosobenzene (65-70%)

Reduction of nitro compounds in **basic medium** gives binuclear compounds. Given below are the products of reduction of nitrobenzene in basic media.



Selective reduction of the nitro group is also possible as shown below:

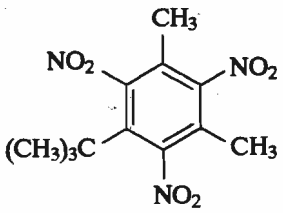


1,3-dinitrobenzene 3-nitrobenzenamine (79-85%)

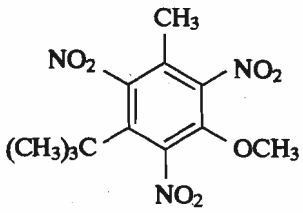
18.5 IMPORTANT USES OF NITRO COMPOUNDS

In addition to the synthetic utility of nitro compounds, you have studied that they are used in the preparation of explosives.

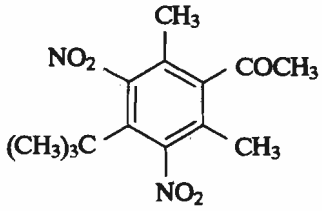
Several polynitro compounds possess an odour resembling musk and are used in perfumery. Some such examples are listed below:



musk xylol

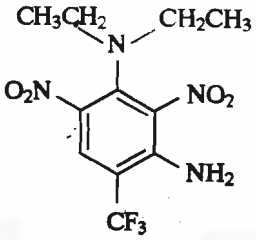


musk ambrette

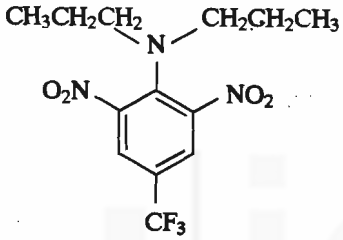


must ketone

Nitro compounds have important herbicidal uses. Some nitro compounds used as weedicides for the cotton, soyabean and peanut crops are shown below:



N^3,N^3-diethyl-6-trifluoromethyl-2,4-dinitro-1,3-benzenediamine (dinitramine)



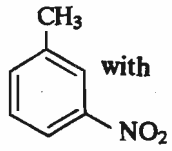
N,N-dipropyl-4-trifluoromethyl-2,6-dinitrobenzenamine (trifluralin)

18.6 SUMMARY

In this unit, you have studied that :

- Drastic conditions are required for the preparation of nitroalkanes whereas aromatic nitro compounds are easier to synthesise.
- Primary and secondary nitro compounds behave as weak acids and they show nitro—acinitro tautomerism.
- Nitro compounds react with carbonyl compounds in alkaline medium to yield aldol type products.
- Nitroalkanes can be reduced to alkanamines.
- Aromatic nitro compounds on catalytic reduction and reduction in acidic conditions yield amines whereas in neutral media the product is N-substituted azanol. The reduction in basic media leads to a series of bimolecular reduction products, depending upon the nature of the reducing agent.

18.7 TERMINAL QUESTIONS

1) Write equations for the reactions of 3-nitropentane with
   a) H_2/Catalyst
   b) dil. NaOH, HCHO
2) Write the major product of reduction of  with
   a) Zn/alc. NaOH
   b) Pt/H_2
   c) Zn/aq. NH_4Cl
   d) $SnCl_2$/HCl

18.8 ANSWERS

Terminal Questions

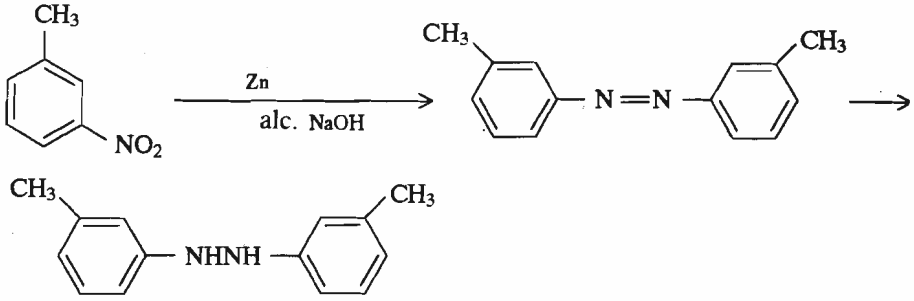
1) a) $CH_3CH_2\underset{\underset{NO_2}{|}}{C}HCH_2CH_3 \xrightarrow{H_2 / \text{Catalyst}} CH_3CH_2\underset{\underset{NH_2}{|}}{C}HCH_2CH_3$

3-nitropentane → 3-pentanamine

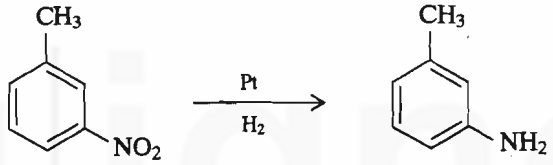
b) $CH_3CH_2\underset{\underset{NO_2}{|}}{C}HCH_2CH_3 \xrightarrow[\text{dil. NaOH}]{HC(=O)H} CH_3CH_2\underset{\underset{CH_2OH}{|}}{\overset{\overset{NO_2}{|}}{C}}CH_2CH_3$

3-nitropentane

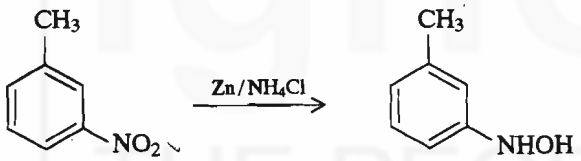
2) a)



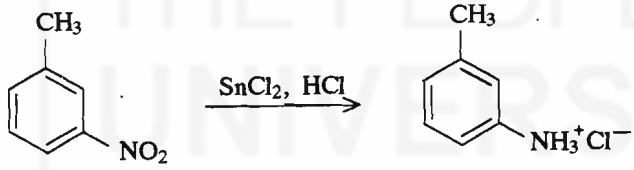
b)



c)



d)



UNIT 19 AMINO COMPOUNDS AND DIAZONIUM SALTS

Structure

19.1 INTRODUCTION

Amines represent one of the largest classes of nitrogen containing organic compounds. You are aware that amines are compounds in which one or more alkyl or aryl groups are attached to nitrogen. You have studied in Unit 18 that nitro compounds can be reduced to amines. In this unit, you will study other methods of preparation of amines. Because of the pair of nonbonding electrons on the nitrogen atom, amines are important organic bases. They behave as nucleophiles as you studied in their reactions with carboxylic acid derivatives. They react with nitrous acid which is electrophilic in nature. The reaction of primary aromatic amines and nitrous acid gives diazonium salts which can lead to a large variety of organic compounds. The reactions of diazonium salts will also be dealt with in this unit. Finally, you will study about the uses of amines and the methods employed for their detection in the laboratory.

Objectives

After studying this unit, you should be able to:

- classify amines as primary, secondary or tertiary,
- give systematic names of amines;
- correlate the physical properties of amines with their structures,
- outline the synthesis of amines using various methods,
- describe the reactions of amines,
- explain the synthetic uses of diazonium salts,
- list some important amines and their uses, and
- give methods of detection of amines in the laboratory.

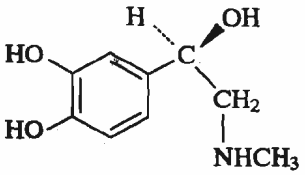
19.2 NATURAL OCCURRENCE AND NOMENCLATURE OF AMINES

Amines are widely distributed in nature. A large class of amines of plant origin is called **alkaloids.** *Strychnine* and *brucine* which you studied in Unit 3 with regard to the resolution of enantiomers are alkaloids. Some of the alkaloids have medicinal while others have poisonous properties. Examples of such alkaloids include ***quinine***, which is antimalarial and antimicrobial, *caffeine* and *atropine* which are used as stimulants.

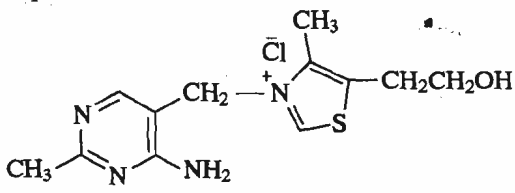
The term **alkaloid** was coined by F.W.A. Sertürner who in 1816, described morphine as basic and *alkali like.*

Alkaloids will also be discussed in Unit 20.

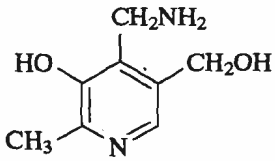
The alkaloids occurring in animals include many essential vitamins and hormones. Some examples are shown below.



adrenaline
(a hormone secreted by adrenal glands)

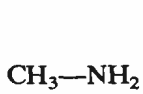


vitamin B_1
(thiamine chloride)



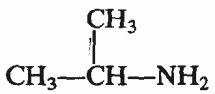
pyridoxamine
(one of the complex B_6 vitamins)

You may recall from Unit 1, Block 1, that amines can be classified as **primary, secondary** or **tertiary** depending on the number of alkyl or aryl groups attached to the nitrogen atom. When the substituents attached to the nitrogen are **alkyl** groups, the amine is called an **alkyl amine**. But the amines in which **at least one** of the substituents attached to the nitrogen atom is an **aryl** group, are called **aryl amines.** Examples of primary, secondary and tertiary, alkyl as well as aryl, amines are given below:



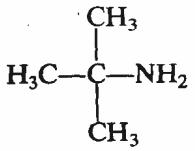
methylamine or methanamine

a primany alkyl amine



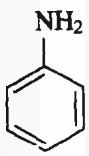
2-propanamine

a secondary alkyl amine



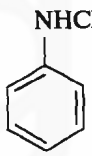
1,1-dimethylethanamine

a tertiary alkyl amine



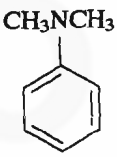
benzenamine (aniline)

a primary aryl amine



N-methylbenzenamine (*N*-methylaniline)

a secondary aryl amine



N,N-dimethylbenzenamine (*N,N*-dimethylaniline)

a tertiary aryl amine

The nomenclature of alkyl and aryl amines was discussed in Block 1, Unit 1, Sec 1.6, whereas the nomenclature of heterocyclic nitrogen compounds was discussed in Block 2, Unit 10, Sec. 10.2.

Why don't you check how much do you remember about the nomenclature of amines by answering the following SAQ.

SAQ 1

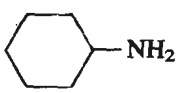
Write systematic names of the following amines:

a) $CH_3CH(CH_3)CH_2NH_2$

.....

b) $(CH_3CH_2)_3N$

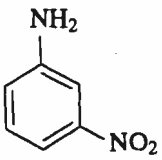
.....

c) 

.....

d) $H_2NCH_2CH(NH_2)CH_3$

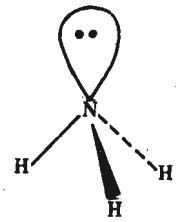
.....

e) 

If you don't feel confident that you can correctly name the amines, go back to Block 1, Unit 1, Sec. 1.6 to refresh your knowledge about nomenclature.

19.3 STRUCTURE OF AMINES

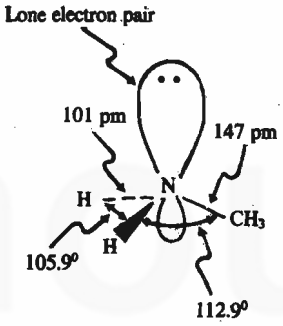
You may recall from your earlier studies that ammonia has a pyramidal shape. The HNH angle in ammonia, 107.3°, is very close to the angle of a tetrahedron, Hybridisation in ammonia can thus be described as nearly sp^3



ammonia

The structure of amines is similar to the structure of ammonia. Aliphatic amines have a pyramidal shape or if we regard the lone pair of electrons as a group, an approximately tetrahedral shape. The three vertices of the tetrahedron are occupied by three substituent groups and the fourth is occupied by the lone pair. If the three substituents are different then the nitrogen is *chiral*. This leads to the possibility of existence of enantiomers. The enantiomers of *N*-methylethanamine are shown in Fig. 19.1

The nearly tetrahedral structure of methanamine (methylamine)



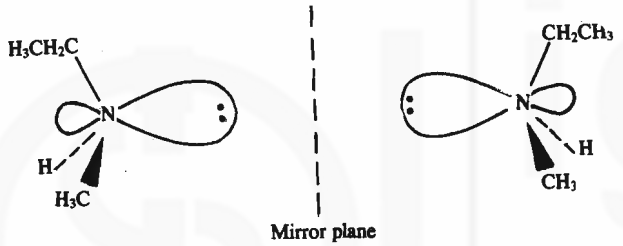


Fig. 19.1 : Enantiomers of *N*-methylethanamine.

But, in the absence of steric factors, amines undergo a *rapid inversion* at nitrogen via a planer transition state to yield their enantiomers, as is shown in Fig. 19.2. So it is not possible to isolate the enantiomers.

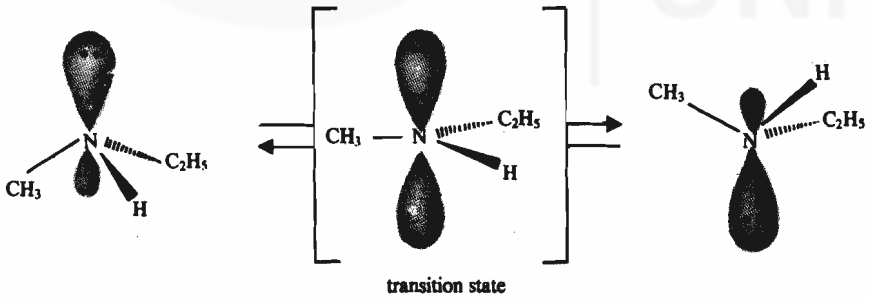
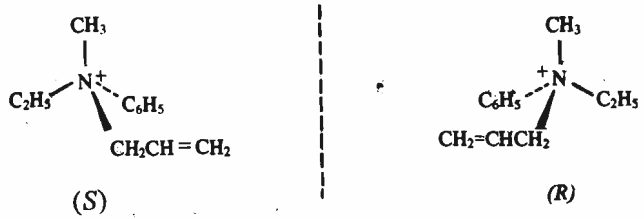
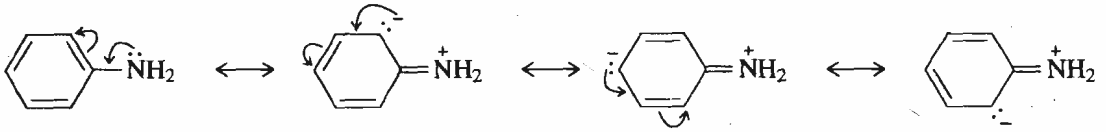


Fig. 19.2 : Inversion at nitrogen interconverts the enantiomers of *N*-methylethanamine.

Since such an inversion is not possible in quaternary ammonium compounds, they can be separated into enantiomers. The enantiomers of such a quaternary ammonium ion are shown below:

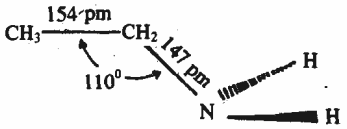


Aryl amines have larger HNH and HNC angles indicating that nitrogen in aryl amines is more nearly planer than in alkylamines. In aryl amines, the lone pair of electrons is delocalised with the π electrons of the aromatic ring. The resonance structures, thus, obtained are shown below for benzenamine.



You can see the double bond character of C-N bond in some of these resonance structures. Thus, C—N bond in benzenamine is shorter (140 pm) as compared to that in aliphatic amines (147 pm).

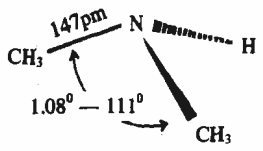
Let us now study the physical properties of amines and try to relate them to the structure of amines.



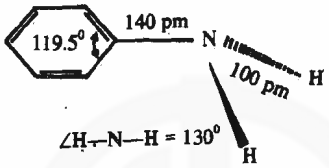
ethylamine

19.4 PHYSICAL PROPERTIES OF AMINES

The physical constants of some amines are given in Table 19.1.

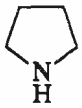


dimethylamine



benzenamine
(aniline)

Table 19.1 : Physical constants of amines

Amine	Molecular weight	Melting point /K	Boiling point /K
Primary amines			
CH_3NH_2	31	179	277
$CH_3CH_2NH_2$	45	192	290
$CH_3CH_2CH_2NH_2$	59	190	321
$CH_3CH_2CH_2CH_2NH_2$	73	224	351
$(CH_3)_2CHCH_2NH_2$	73	188	341
$(CH_3)_3CNH_2$	73	206	318
aniline, $C_6H_5NH_2$	93	267	467
o-nitroaniline	138	345	557
m-nitroaniline	138	387	579
p-nitroaniline	138	421	605
Secondary amines			
$(CH_3)_2NH$	45	181	280
$(CH_3CH_2)_2NH$	73	223	329
	70	275	336
N-methylaniline	106	216	469
N-ethylaniline	120	210	478
diphenylamine	169	327	575
Tertiary amines			
trimethylamine, $(CH_3)_3N$	59	156	276
triethylamine, $(C_2H_5)_3N$	101	159	363
N,N-dimethylaniline	121	276	467
triphenylamine	245	400	638

The physical constants of the amines listed in Table 19.1 show that most amines are liquids. Amines generally have unpleasant fishlike odours.

You can clearly visualise certain trends in the physical constants of amines as listed in Table 19.1 which you studied in Unit 4, Block 1.

Primary and secondary amines can participate in intermolecular hydrogen bonding. The N—H...H hydrogen bonds are weaker than O—H...O hydrogen bonds because nitrogen is less electronegative than oxygen. Thus, the boiling points of primary amines are intermediate between those of alcohols and alkanes of comparable molecular weight. The hydrogen bonding is also a factor governing the water solubility of amines.

SAQ 2

The melting point and boiling point of 2-nitrobenzenamine (*o*-nitroaniline) are lower than its 3-nitro (*meta*-) or 4-nitro (*para*-) isomer. Why?

.....

.....

19.5 SPECTRAL CHARACTERISTICS OF AMINES

UV spectra

The absorptions due to $n \rightarrow \sigma^*$ transitions of saturated amines occur at short wavelengths (~ 220 nm) and, therefore, are not of much use for identification purposes.

IR spectra

The infrared spectra of primary and secondary amines show a characteristic broad bond due to N—H stretching absorption in the region between 3300 to 3500 cm^{-1}, see Fig. 19.3. Primary amines show two bands in this region whereas secondary amines show only one band. The N—H bending absorption of primary amines is observed near 1600 cm^{-1}.

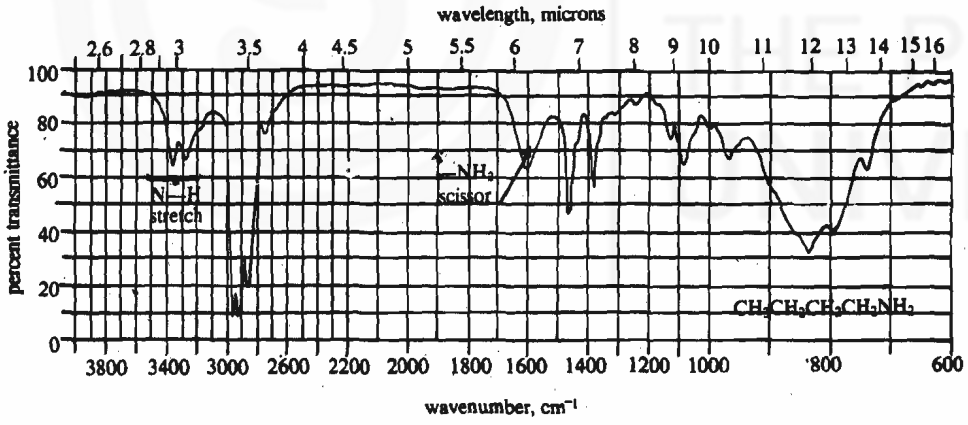
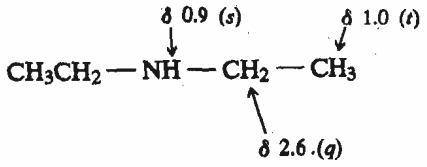


Fig. 19.3 : IR spectrum of butanamine.

NMR spectra

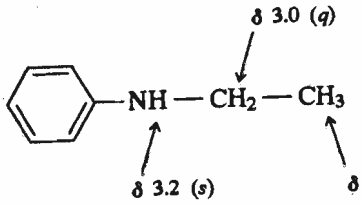
The H—C—N protons of alkylamines show absorption in the range δ 2.5-3.0. The absorption occurs further downfield in aromatic amines, i.e., near δ 3. The chemical shift of the N—H proton, like that of the O—H proton in alcohols, depends on the concentration of the amine and on other factors such as solvent and temperature. The N—H proton also undergoes chemical exchange as is observed in case of —OH protons of alcohols.

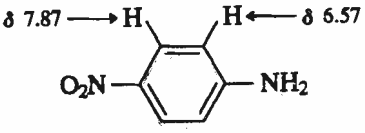


The absorption of protons of aromatic ring *ortho-* and *para-* to the amino nitrogen i shifted to higher field than that of the *meta*-protons indicating the increased electroı density at the *ortho*-and *para*-positions.

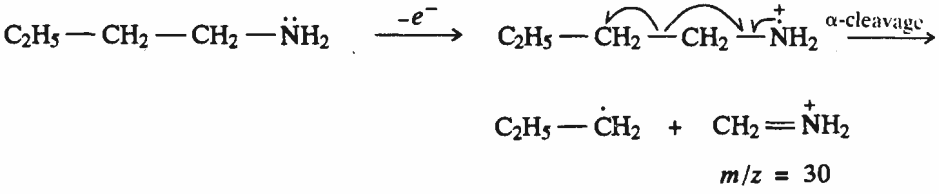
Mass spectra

The mass spectra of aliphatic amines show a peak a $m/z = 30$ due to the followin fragmentation from the M^+ ion:





For example,



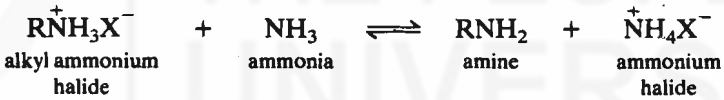
19.6 PREPARATION OF AMINES

The various methods used for the preparation of amines are discussed below:

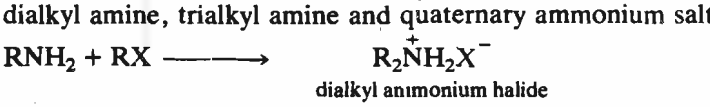
1) By direct alkylation of ammonia and other amines

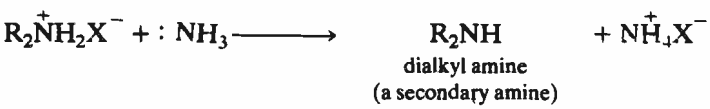
Ammonia and amines react with alkyl halides to yield amines. Let us understand this reaction with the example of ammonia and a primary alkyl halide.

This reaction follows the S_N2 path. If excess of ammonia is not used then the reaction stops at the stage of alkyl ammonium halide. In the presence of excess ammonia, another molecule of ammonia deprotonates the alkylammonium ion thereby liberating the free amine.

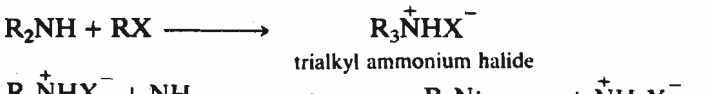


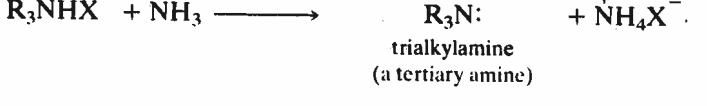
The resulting amine being a nucleophile reacts further with alkyl halide to yield dialkyl amine, trialkyl amine and quaternary ammonium salts as shown below.

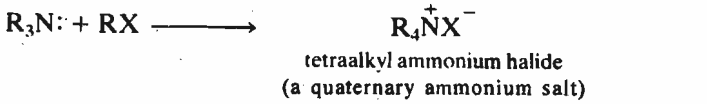




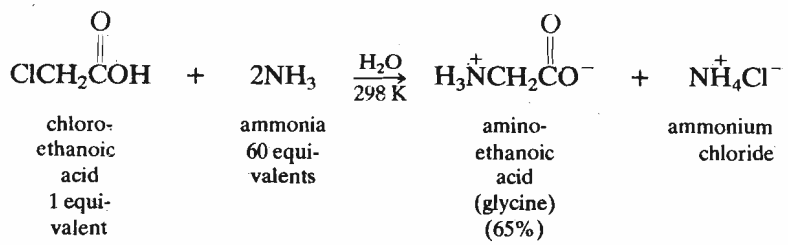
A secondary amine is a stronger nucleophile than a primary amine.

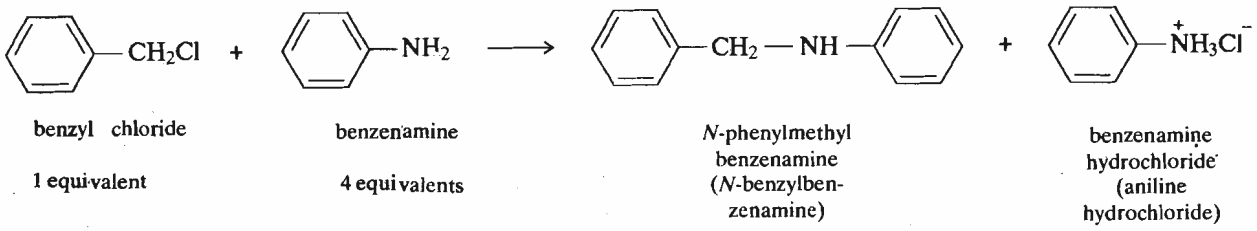






Thus, a mixture of products is formed which limits the synthetic value of this reaction for the synthesis of primary amines. The overalkylation may be suppressed by using a large excess of ammonia or amine provided the amine is inexpensive and the desired product can be easily separated from the reaction mixture. Some examples follow:



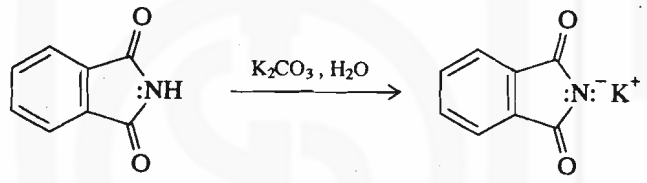


In many cases, even after using a large excess of the amine or ammonia, only moderate yields of desired amine are available. In such cases, indirect methods which give better yields are employed. One such method is the Gabriel synthesis which you will now study.

2. Indirect alkylation: The Gabriel synthesis

Pure primary amines can be prepared conveniently if the nitrogen atom is protected so that alkylation can take place only once.

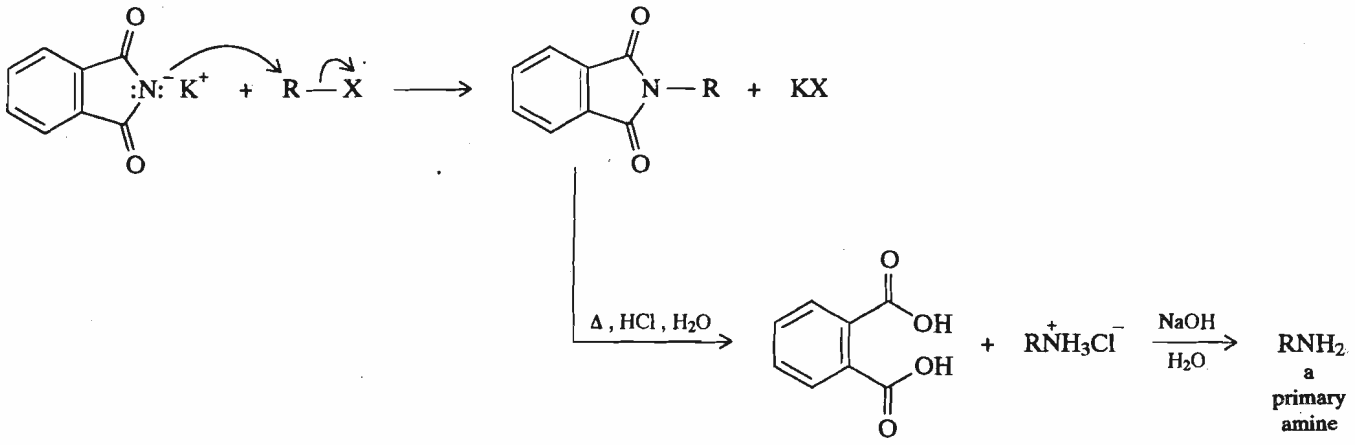
Such a protected nitrogen is present in 1,2-benzenedicarboxylic imide. Because the nitrogen atom has two adjacent carbonyl groups, the NH group is acidic enough (pK_a=8.3) to be deprotonated using a mild base to yield a nitrogen anion in a salt.



1,2-benzenedi-carboxylic imide (phthalimide)

potassium salt with nitrogen anion

The nitrogen anion is a good nucleophile and can undergo a wide variety of nucleophilic substitution reactions. It reacts with alkyl halides to yield *N*-alkyl derivative in good yield. *N*-alkyl derivative on acidic hydrolysis yields the ammonium salt from which the free amine can be liberated by treatment with a base. Such a sequence of reactions can be used to prepare amines which are difficult to prepare by simple alkylation of ammonia and is known as Gabriel synthesis.



The use of the Gabriel synthesis is limited to primary and unbranched secondary alkyl halides. However, tertiary alkyl halides undergo eliminations under these conditions.

3. Reduction of nitro compounds

The reduction of nitro compounds to yield primary amines was discussed in Unit 18, Sec. 18.4.

4. Reduction of nitriles

Nitriles can be reduced to primary amines by catalytic hydrogenation or by the reaction with $LiAlH_4$.

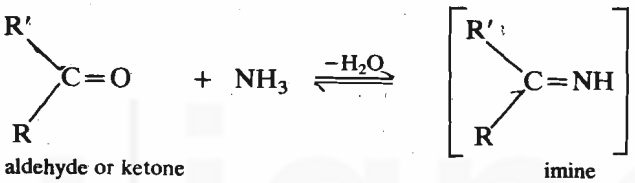
$$R{-}C{\equiv}N \xrightarrow[\text{or } LiAlH_4]{H_2/Pd{-}C} RCH_2NH_2$$

$$\underset{\text{butanenitrile}}{CH_3CH_2CH_2CN} \xrightarrow[\text{ether}]{\text{1. } LiAlH_4} \xrightarrow{\text{2. } H^+,\ H_2O} \underset{\substack{\text{butanamine}\\(57\%)}}{CH_3CH_2CH_2CH_2NH_2}$$

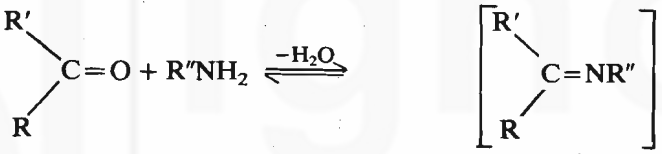
$$\underset{\text{pentanenitrile}}{CH_3CH_2CH_2CH_2CN} \xrightarrow{H_2\ /\ Ni} \underset{\substack{\text{pentanamine}\\(90\%)}}{CH_3CH_2CH_2CH_2CH_2NH_2}$$

5. Reduction of imines

Ammonia and primary amines condense with aldehydes and ketones to yield imines as shown below:

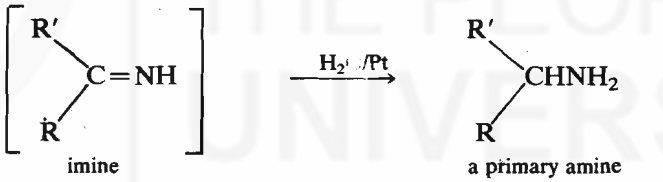


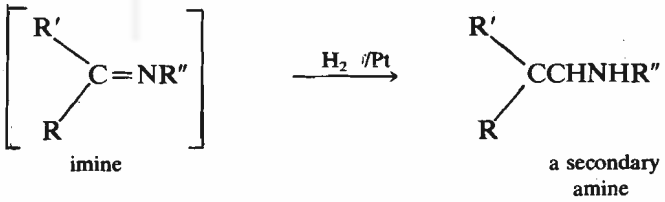
aldehyde or ketone — imine



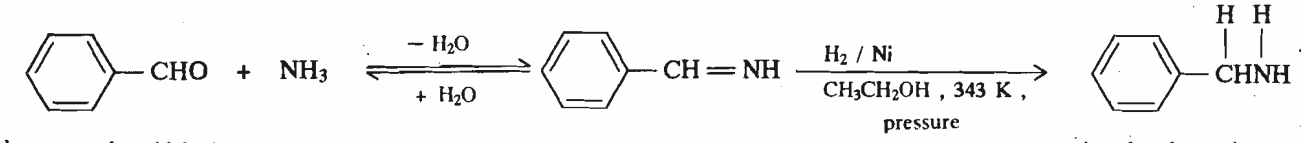
imine

The carbon nitrogen double bond of an imine can be reduced by catalytic hydrogenation to yield a primary or secondary amine.





Some examples are given below:



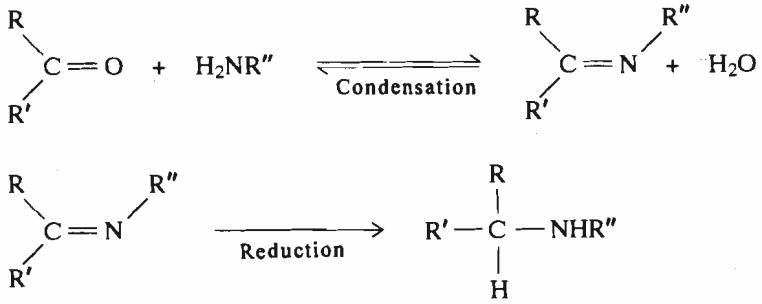
benzenecarboxaldehyde (benzaldehyde) — imine (not isolated) — phenylmethanamine (benzylamine) (89%)

$$(CH_3)_2CH\overset{\overset{O}{\|}}{C}H + CH_3CH_2CH_2CH_2NH_2 \xrightarrow[\text{ethanol}]{H_2,\ Pt} (CH_3)_2CHCH_2NHCH_2CH_2CH_2CH_3$$

2-methylpropanal — butanamine — *N*-2-methylpropylbutanamine

You can see that the carbonyl group is **reduced** in the above reaction and the amine is **alkylated**, hence, the reaction is also known as **reductive alkylation** or **reductive amination**.

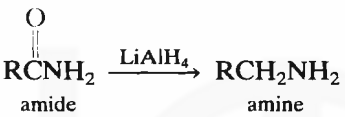
General Reductive Amination of a Ketone



What makes the reductive amination a useful synthetic procedure is that it can be carried out in a single operation involving the hydrogenation of a solution of the carbonyl compound and ammonia (or amine) in the presence of a catalyst without isolating the intermediate imine.

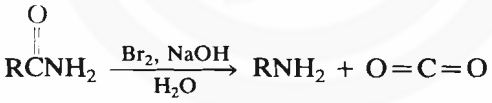
6. From amides

You are aware from Unit 17, Sec. 17.8, sub-Sec. 17.8.2 that amides can be reduced to amines, i.e.

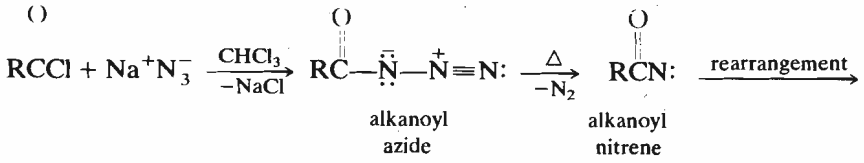


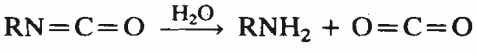
Depending upon the structure of the starting amide, primary, secondary or tertiary amines can be synthesised. Note that the same number of carbon atoms is present in the amine as in the starting amide.

Another method of preparing primary amines from amides is Hofmann rearrangement. The amine obtained contains one carbon atom less than the starting amide. Hofmann rearrangement was discussed in Unit 17, Sec. 17.8. The general reaction of Hofmann rearrangement is shown below :

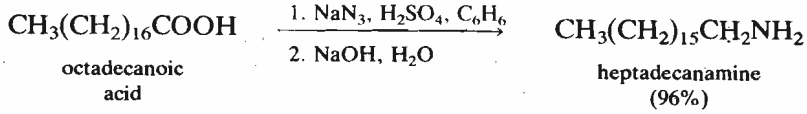


Similar transformation involving the reaction of an alkanoyl halide with sodium azide, NaN_3 to yield amines is known as **Curtius rearrangement**. This reaction proceeds via the following steps.



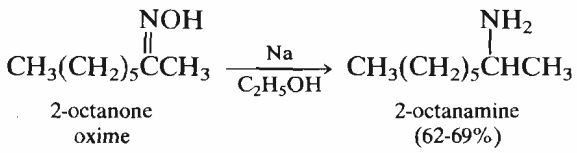


The same sequence of reactions is observed when the starting material is a carboxylic acid. A carboxylic acid when treated with sodium azide in acid catalyst yields an alkanoyl azide which finally yields the amine. This reaction is known as **Schmidt rearrangement**. An example of Schmidt rearrangement is shown below:



7. Reduction of oximes

It was pointed out in Block 3, Unit 14, Sec. 14.4 that aldehydes and ketones react with azanol (hydroxylamine) to yield **oximes**. Oximes so obtained can be reduced with $LiAlH_4$ or sodium in alcohol to yield primary amines.

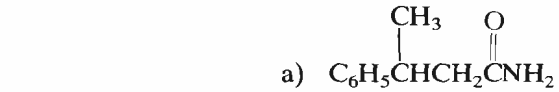


2-octanone oxime — 2-octanamine (62-69%)

Using the knowledge gained so far, answer the following SAQ.

SAQ 3

Write the products of reduction of the following amides with $LiAlH_4$.

a) 

3-phenylbutanamide

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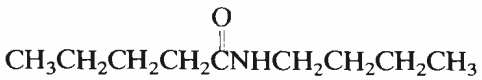
b) 

N-butylpentanamide

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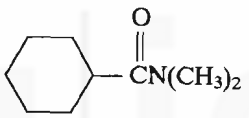
c) 

N,N-Dimethylcyclohexane carboxamide

.....

19.7 REACTIONS OF AMINES

1. As bases

Amines behave as Lewis bases because of the nonbonding electron pair on nitrogen. They react with a variety of acids by accepting a proton.

$$R\ddot{N}H_2 + HA \rightleftharpoons R\overset{+}{N}H_3 + :A^-$$

The aqueous solutions of amines are basic in nature due to the following equilibrium.

$$R\ddot{N}H_2 + H_2O \overset{K_{eq}}{\rightleftharpoons} R\overset{+}{N}H_3 + OH^-$$

where K_{eq} is the equilibrium constant.

You may recall from Block 1, Unit 5, Sec. 5.3, Eq. 5.6 that K_{eq} is related to the basicity constant, K_b, by the following expression.

$$K_b = K_{eq}[H_2O] = \frac{[R\overset{+}{N}H_3][OH^-]}{[R\ddot{N}H_2]}$$

Also,

$$pK_b = -\log K_b$$

It was also pointed out in Unit 5, Block 1 that it is convenient to refer to the base strength also in terms of the dissociation constant, K_a, of the corresponding ammonium ion, i.e.,

$$R\overset{+}{N}H_3 + H_2O \overset{K_a}{\rightleftharpoons} R\ddot{N}H_2 + H_3O^+$$

where $$K_a = \frac{[R\ddot{N}H_2][H_3\overset{+}{O}]}{[R\overset{+}{N}H_3]}$$

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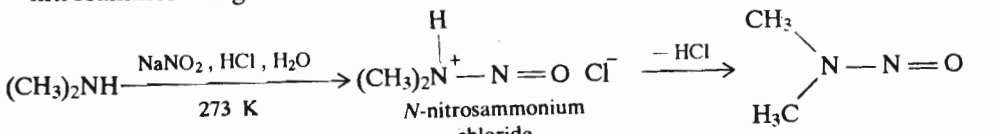
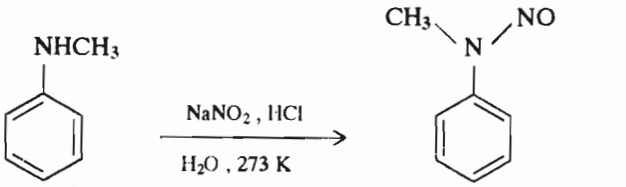
Nitrosation of secondary amines

Aliphatic and aromatic secondary amines react with nitrous acid to yield *N*-nitroso compounds, also known as **nitrosamines**. Nitrosamines usually separate from the reaction mixture as yellow oily liquids. Some examples of the formation of nitrosamines are given below:



Nitrosamines are very powerful **carcinogens.** Sodium nitrite, used as a preservative in meats and also the nitrites produced by the reduction of nitrate fertilisers, react with natural amines in the presence of the acid found in stomach to yield nitrosamines.

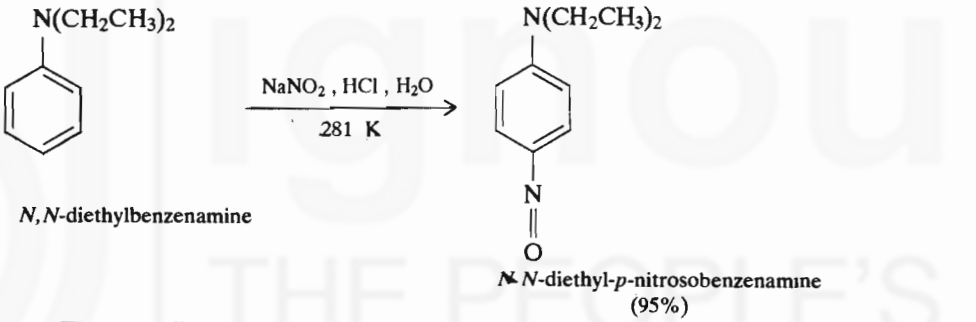
Dimethylamine and methylethylamine are found in tobacco smoke also.



Nitrosation of tertiary amines

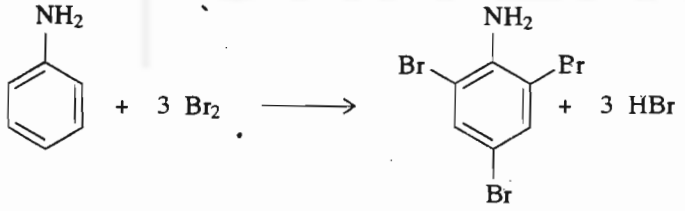
Tertiary aliphatic amines react with nitrous acid without the evolution of nitrogen to yield complex mixtures.

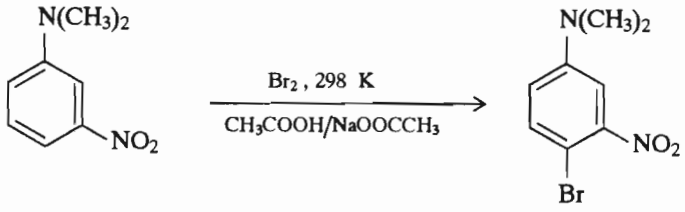
Tertiary aromatic amines react with nitrous acid to give C-nitroso aromatic compounds. Nitrosation takes place almost exclusively at the *para* position of the aromatic ring.

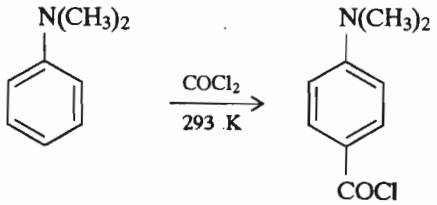


4. Electrophilic aromatic substitution

The amino group activates the aromatic ring towards substitution by electrophilic reagents and the reactions require mild conditions. The amino group is an *ortho-*, *para*-directing group, as is illustrated by the following examples:

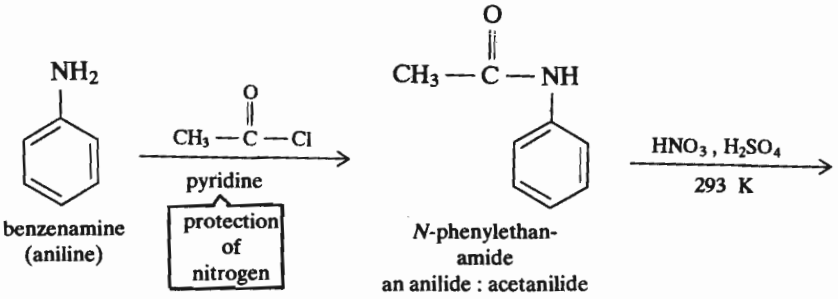






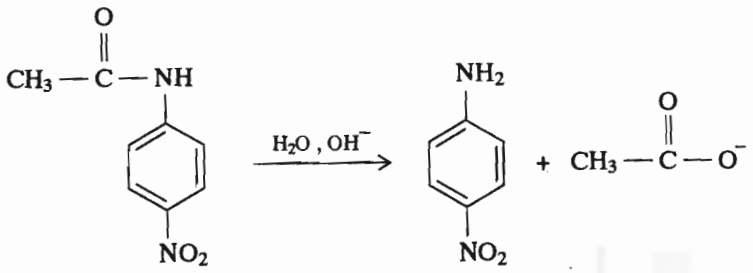
Since amino group is susceptible to attack by a wide variety of reagents such as oxidising agents, alkylating reagents and carbonyl compounds, it must be suitably protected.

The reactivity of the amino group is reduced when it is converted into an amide as is shown below:



benzenamine (aniline)

N-phenylethanamide
an anilide : acetanilide

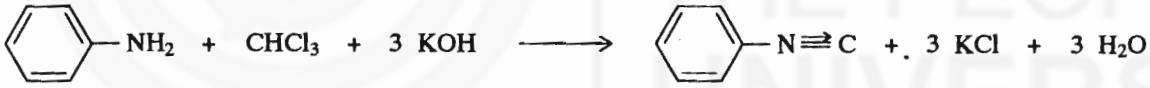


4-nitro-*N*-phenylethanamide
p-nitroacetanilide

4-nitrobenzenamine
(*p*-nitroaniline)

5. Isocyanide (carbylamine) reaction

Both aliphatic and aromatic primary amines react with chloroform in the presence of potassium hydroxide to produce an isocyanide that has a very nauseating odour. This reaction is so sensitive that it can be used as a test to detect the presence of very small amounts of primary amines as impurities in secondary and tertiary amines.



Caution : You should destroy the isocyanide by heating the reaction mixture with an acid before throwing the products into the laboratory sink.

SAQ 4

When 4-aminobenzenol reacts with one molar equivalent of ethanoic anhydride, a compound having molecular formula, $C_8H_9NO_2$ is formed which is soluble in alkali. Write its structure.

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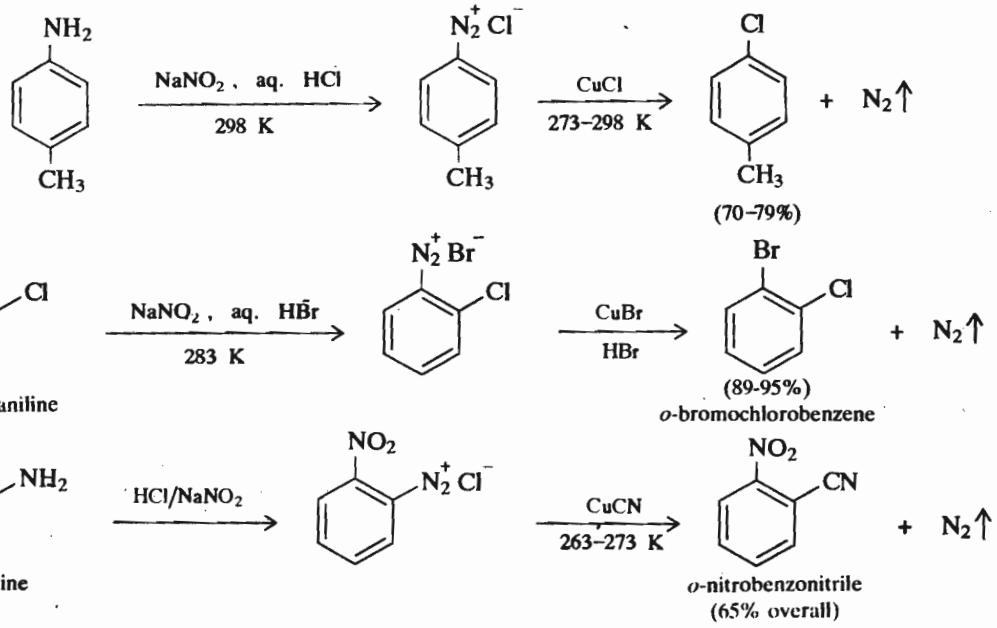
19.8 REACTIONS OF DIAZONIUM SALTS

You have studied the formation of diazonium salts in the last section. It has been pointed out there that arenediazonium salts are stable at temperatures below 278 K and can be used in the synthesis of aromatic compounds. You will now study various reactions undergone by arenediazonium salts.

1. The Sandmeyer Reaction

The reactions of diazonium salts involving cuprous salts are called **Sandmeyer reactions.**

Arenediazonium salts react with cuprous chloride, cuprous bromide and cuprous cyanide to give products in which the diazonium group has been replaced by −Cl, −Br and −CN groups, respectively.



Reactions similar to the Sandmeyer reactions may be accomplished by the use of copper powder as a catalyst for decomposing the diazonium salt. This method is particularly useful in cases where the corresponding cuprous salt cannot be prepared. This variation is called the **Gattermann reaction**.

$$ArN_2^+X^- \xrightarrow{NaNO_2,\ Cu} ArNO_2$$

$$ArN_2^+X^- \xrightarrow[Cu]{SO_2,\ H_2O} ArSO_2H$$

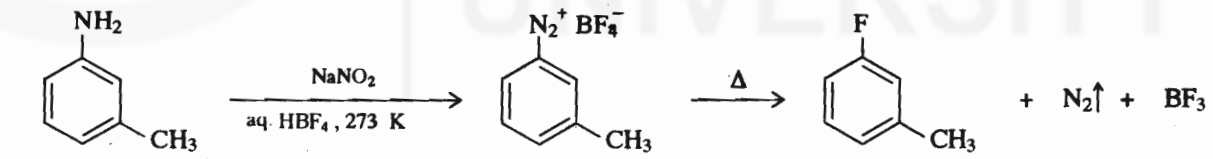
sulphinic acid

$$ArN_2^+X^- \xrightarrow{KOCN,\ Cu} Ar{-}N{=}C{=}O$$

aryl isocyanate

2. Formation of aryl fluorides

The diazotisation of an amine with sodium nitrite and fluoboric acid, HBF_4, yields fluoborate diazonium salt as a precipitate which is isolated and decomposed thermally to yield aryl fluorides. This reaction is also known as **Schiemann reaction**.

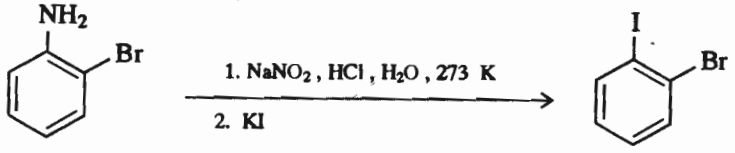


3-methylbenzenediazonium fluoborate (*m*-methylbenzenediazonium fluoborate) (76-84%)

3-methylfluorobenzene (*m*-fluorotoluene)

3. With potassium iodide

Diazonium salts react with potassium iodide to yield **aryl iodides.** The diazonium salt is prepared in the usual way and a solution of potassium iodide is then added and the reaction mixture is heated to yield the aryl iodide.

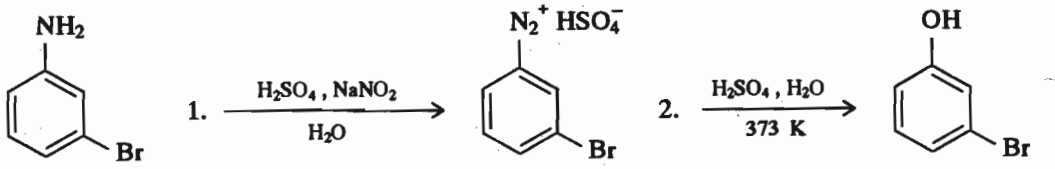


2-bromobenzenamine (*o*-bromoaniline)

2-bromoiodobenzene (*o*-bromoiodobenzene) (72-83%)

4. With water

The most general method for the preparation of phenols involves the heating of the diazonium salt in aqueous acid.

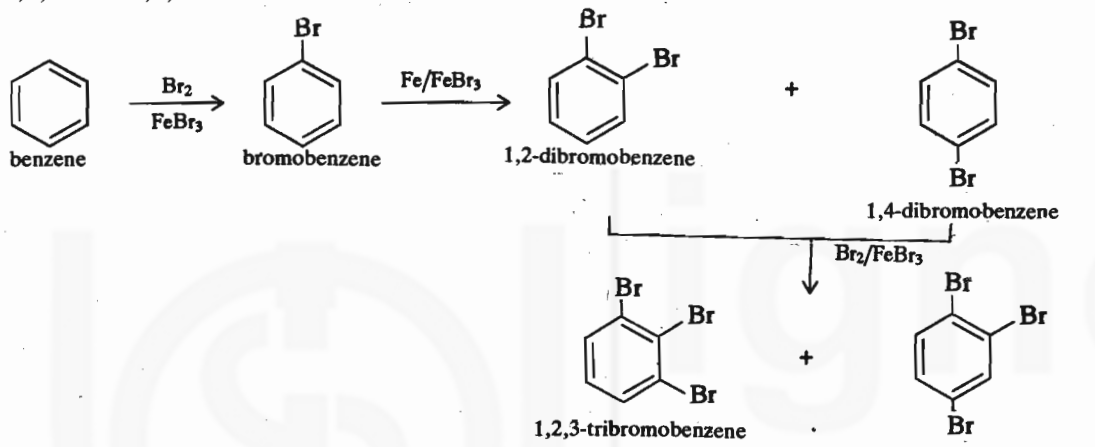


3-bromobenzenamine (*m*-bromoaniline)

3-bromobenzenol 3-bromophenol (*m*-bromophenol) (78%)

5. Replacement of diazonium group by hydrogen

When a diazonium salt is treated with hypophosphorous acid, H_3PO_2, the diazonium group is replaced by hydrogen. Reactions of this type are called **reductive deaminations**. This reaction is useful when we introduce an amino group into an aromatic ring to influence the orientation of a subsequent reaction. Later the amino group can be removed by converting it into the diazonium salt and then treating the diazonium salt with H_3PO_2. For example, direct bromination of benzene leads to 1,2,3- and 1,2,4-tribromobenzenes.



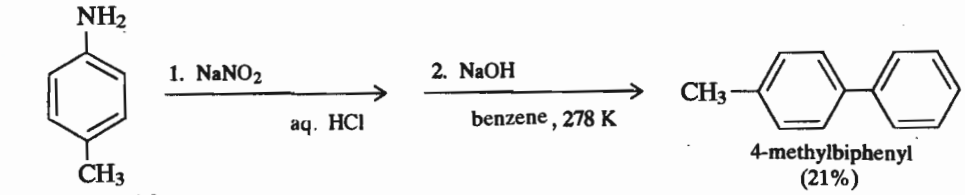
benzene — bromobenzene — 1,2-dibromobenzene + 1,4-dibromobenzene

1,2,3-tribromobenzene + 1,2,4-tribromobenzene

Thus, 1,3,5-tribromobenzene which cannot be prepared by direct bromination of benzene can be obtained by the reaction of the diazonium salt of tribromoaniline with H_3PO_2.

6. Arylation

Basic solutions of diazonium salts react with aromatic compounds in cold to yield biaryl compounds in which the diazonium group has been replaced by an aromatic ring. This is illustrated by the following example.



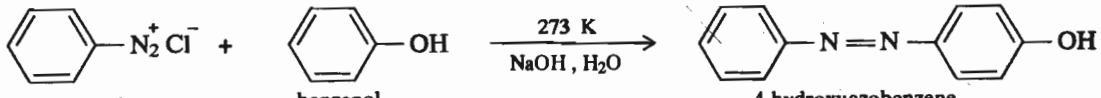
4-methylbenzenamine

4-methylbiphenyl (21%)

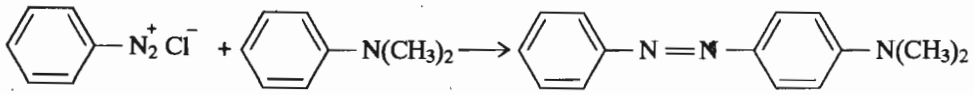
This reaction is called the **Gomberg-Bachmann reaction**.

7. Coupling Reactions

Arenediazonium salts are weak electrophiles and attack aromatic ring of highly activated compounds such as amines and phenols to yield azo compounds. This electrophilic aromatic substitution reaction is called **diazo coupling** and is shown below:



benzenediazonium chloride — benzenol (phenol) — 4-hydroxyazobenzene (orange)



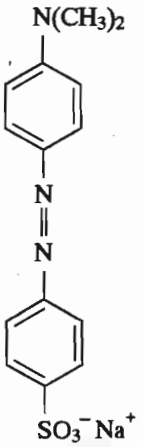
benzenediazonium chloride

N,N-dimethyl-benzenamine

4-dimethyl aminoazo benzene (butter yellow)

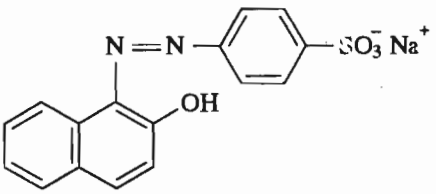
The azo compounds thus obtained are highly coloured and many of them are used as colouring agents and are called **azo dyes**. Butter yellow was once used as a food colouring agent. Azo dyes are also used as indicators and for textile dying. Some examples are given below:

Coupling takes place preferably at the *para* position, if it is free. If it is not, then, the coupling takes place at the *ortho* position.



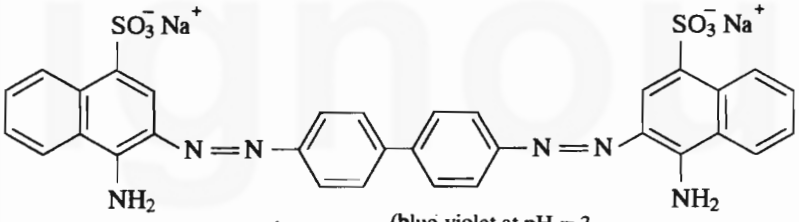
methyl orange (an indicator)

(red at pH = 3.1
yellow at pH = 4.4



Orange II

(an industrial dye for textiles)



Congo red

(blue-violet at pH = 3
red at pH = 5)

After studying the reactions of diazonium salts, answer the following SAQ.

SAQ 5

Write the starting materials required for the preparation of azo compounds methyl orange and congo red.

.....

.....

Before closing our discussion on amines, let us study the uses of amines and their detection in the laboratory.

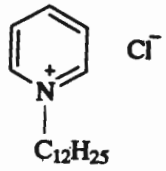
19.9 USES OF AMINES

Amines have diverse uses. You have already studied most of them in the discussion about amines in this unit. Let us now restate them.

1) Several amines are physiologically active and are used as drugs.
2) Some naturally occurring amines, particularly alkaloids are used as resolving agents for optically active compounds. You have studied them in Unit 3, Block 1 also.
3) It was also pointed out that quaternary ammonium salts also act as **phase transfe catalysts**. Quaternary ammonium salts are soluble in both water and organic solvents and thus act as mediators for reactions between species dissolved in immiscible liquids. Quaternary ammonium salts having long chain alkyl groups such as hexadecyl trimethylammonium chloride, $[C_{16}H_{33}N(CH_3)_3]^+ Cl^-$, have detergent properties. They are known as cationic surfactants or invert soaps

because the surface activity is found in a positive ion rather than in a negative ion as is the case with ordinary soaps. Most surface-active quaternary ammonium salts, such as dodecyl pyridinium chloride are potent germicides.

4) Diazonium salts available from amines can be used to synthesise a variety of aromatic compounds and azo dyes.



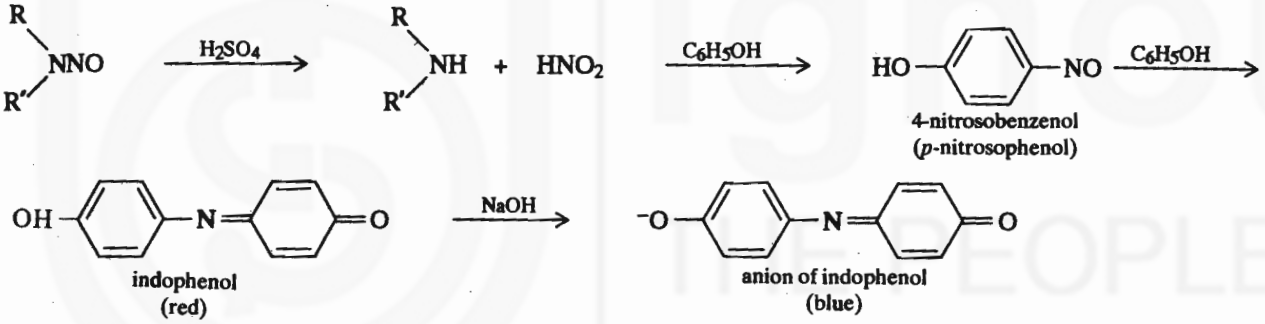
dodecyl pyridinium chloride

19.10 LABORATORY DETECTION OF AMINES

Amines are characterised by their basic nature. They dissolve in dilute aqueous acids. The elemental analysis of amines shows the presence of nitrogen.

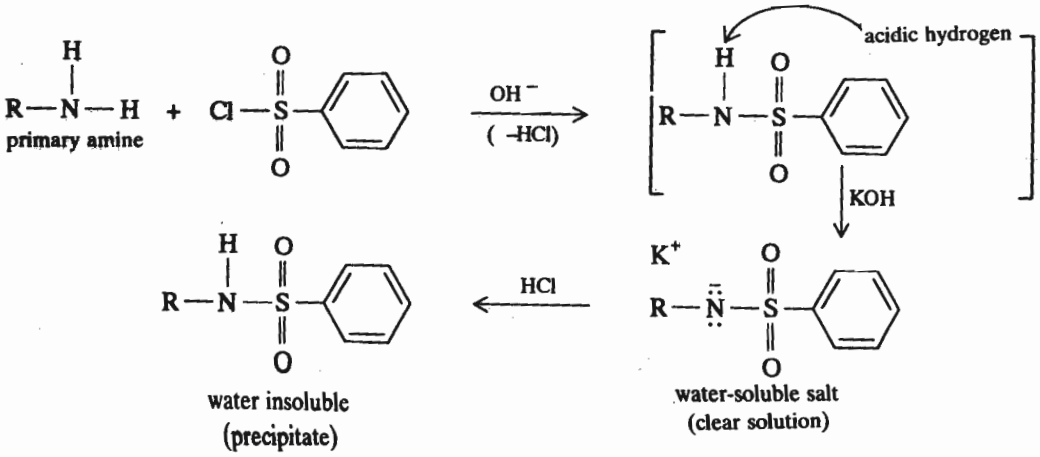
Amines can be characterised by their reaction with nitrous acid. The amine is dissolved in dilute HCl and an ice-cold solution of sodium nitrite is added to it. If a clear solution is obtained with the evolution of nitrogen, the amine is a **primary aliphatic** or **primary alkylaryl amine**. If no nitrogen is evolved, then a cold solution of 2-naphthol in sodium hydroxide solution is added to a portion of the above reaction mixture. If a coloured azo dye is formed, then the amine is a **primary aromatic amine**.

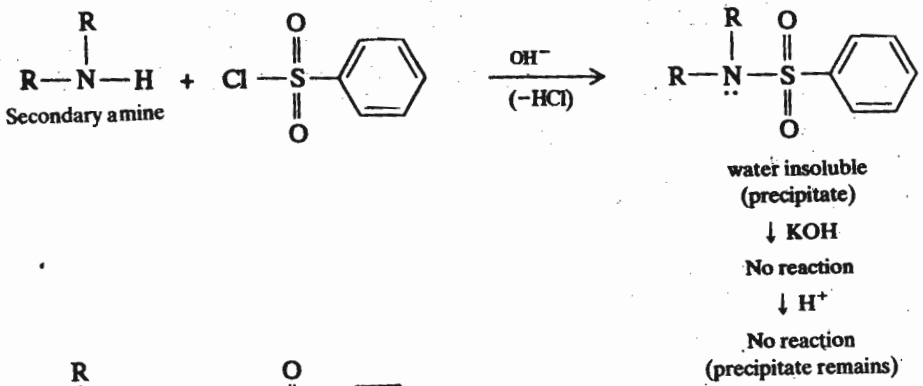
If a yellow oily substance separates out when cold sodium nitrite solution is added to the acidic solution of the amine, then the amine is a **secondary amine**. The formation of the oily nitrosamine is confirmed by the **Liebermann nitroso reaction**. The yellow oily substance is warmed with phenol and concentrated sulphuric acid. Sulphuric acid liberates nitrous acid from nitrosamine which reacts with phenol to yield *p*-nitrosophenol. The *p*-nitrosophenol reacts with another molecule of phenol to yield red coloured indophenol. In alkaline solution indophenol yields its anion which is blue in colour. The sequence of reactions which occur can be represented as shown below:

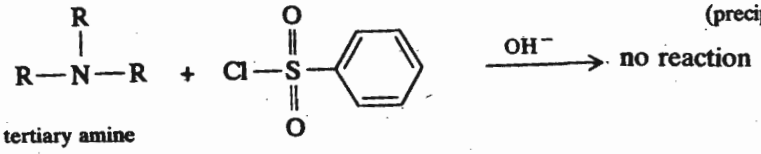


If a dark orange-red solution is obtained on treatment of the amine with nitrous acid and the colour changes to green on adding the alkali, then the amine is a **tertiary aromatic amine**.

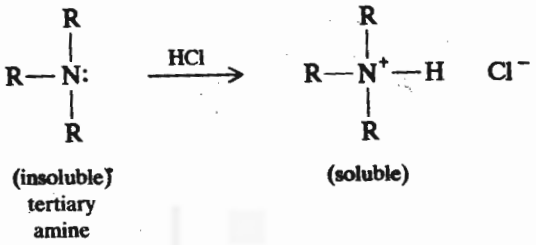
An efficient method to distinguish whether an amine is **primary, secondary** or **tertiary** is the **Hinsberg test**. This involves the reaction between an amine and benzenesulphonyl chloride in the presence of aqueous potassium hydroxide. Primary and secondary amines form substituted sulphonamides but tertiary amines do not. The sulphonamide from the primary amine may be further distinguished by the fact that it is soluble in potassium hydroxide, whereas the derivative from the secondary amine, having no acidic hydrogen, is insoluble in potassium hydroxide and, therefore, precipitates out. The reactions involved with each type of amine are shown below:







But amine will dissolve on acidification.



Let us now summarise what we have learnt in this unit.

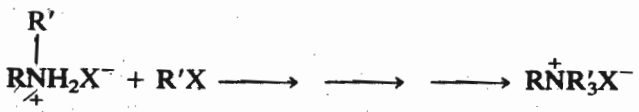
19.11 SUMMARY

In this unit, you have studied that

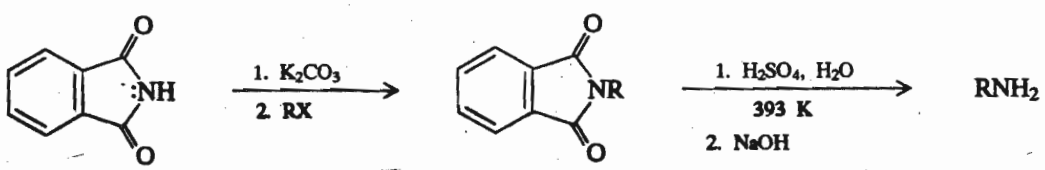
- amines are nitrogen-containing organic bases.
- amines can be classified as primary, secondary and tertiary according to the degree of the substitution at the nitrogen atom.
- amines have tetrahedral structure in which the nitrogen is sp^3 hybridised. One of the sp^3 hybrid orbitals is occupied by the unshared pair of electrons.
- trends in the physical properties of amines such as melting and boiling point can be explained on the basis of various factors you studied in Unit 4, Block 1.
- primary and secondary amines can be differentiated with the help of the infrared spectra.
- amines can be prepared by the following methods:

i) **By alkylation**

drawback: multiple alkylation.

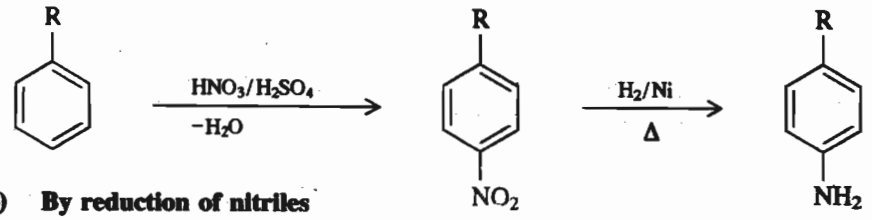


ii) **Gabriel synthesis of primary amines**



iii) Primary amines from nitro compounds

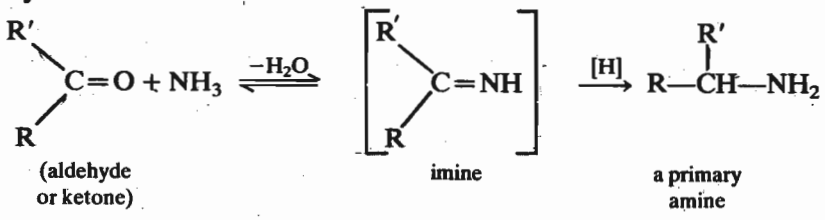
$$RX + NO_2^- \xrightarrow[-X^-]{S_N2} RNO_2 \xrightarrow[H^+]{Fe/FeSO_4} RNH_2$$

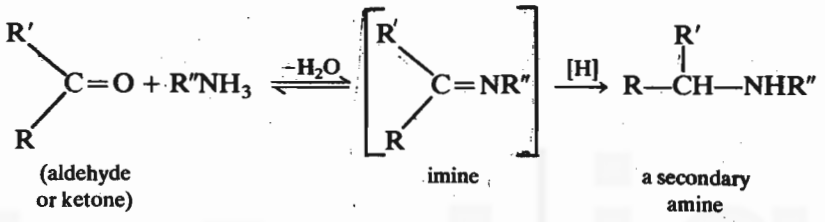


iv) By reduction of nitriles

$$RCN \xrightarrow[\text{or } H_2, \text{ Catalyst}]{LiAlH_4} RNH_2$$

v) By reduction of imines

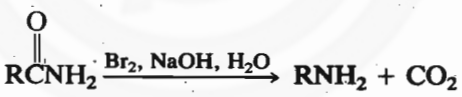




vi) From amides

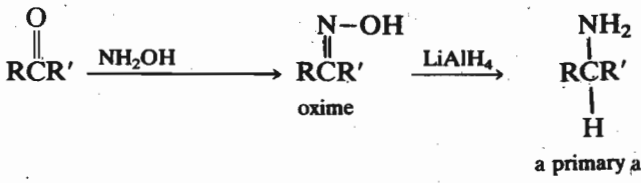
a) By reduction

b) By Hofmann rearrangement



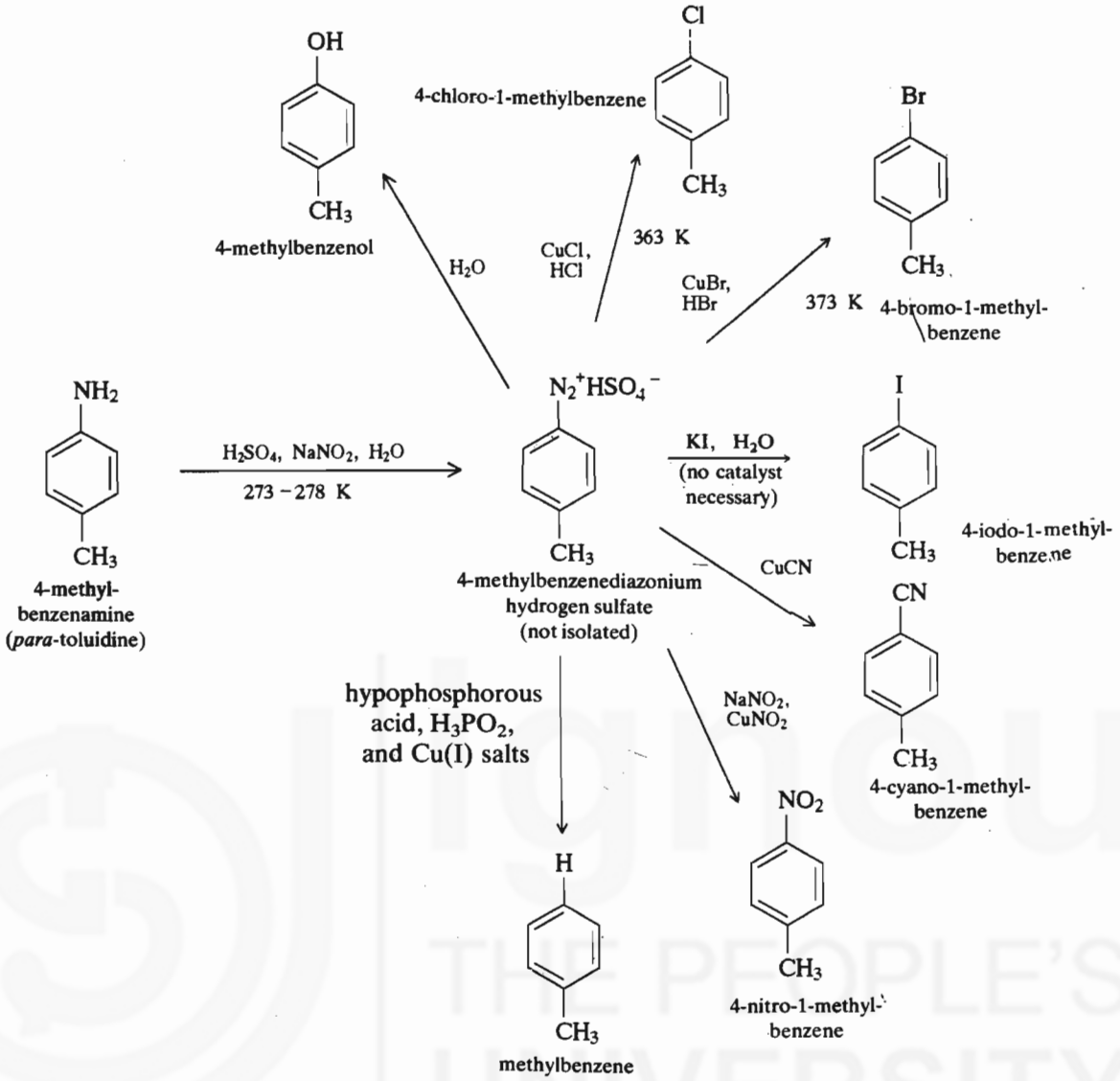
Similar transformations starting with alkanoyl halides (Curtius rearrangement) and carboxylic acids (Schmidt rearrangement) using sodium azide also yield amines.

vii) From Oximes



- Amines undergo the following reactions:
  - — they behave as bases in aqueous solutions and form salts with acids.
  - — they undergo alkylation with alkyl halides and alkanoylation with carboxylic acids and their derivatives.
  - — tertiary aliphatic amines can be oxidised to amine oxides which undergo Cope elimination on heating to yield an alkene and *N,N*-dialkylhydroxylamine.
  - — Oxidation of aromatic amines leads to a variety of oxidation products depending upon the oxidising agent and reaction conditions.
  - — **Amines** undergo **nitrosation reaction** with nitrous acid which gives various products depending upon whether the amine is primary, secondary or tertiary and is aliphatic or aromatic.

- amino group activates the aromatic ring towards electrophilic substitution reactions.
- Some of the reactions of diazonium salts can be summarised as follows:

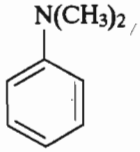


- Amines have various uses.
- Amines can be characterised in the laboratory by their reaction with nitrous acid and Hinsberg test.

19.12 TERMINAL QUESTIONS

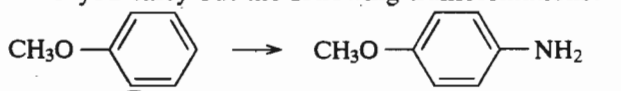
1) Name the following amines:

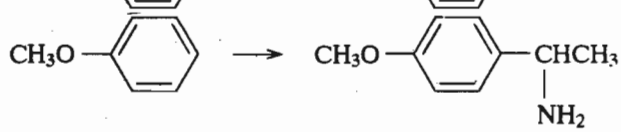
a) $CH_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_2CH_3$

b) 

c) $BrCH_2CH_2CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HNH_2$

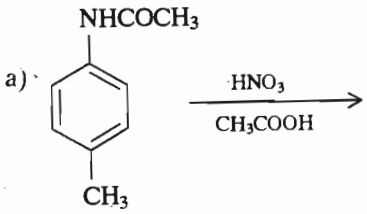
2) How will you carry out the following transformations?

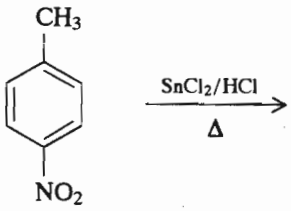
a) 

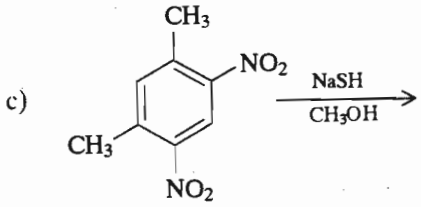
b) 

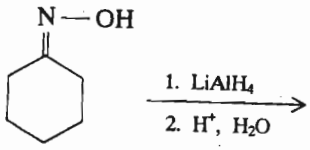
c) 

3) Complete the following reactions:

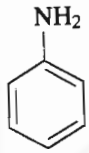
a) 

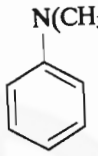
b) 

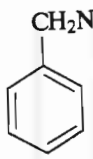
c) 

d) 

4) Write the products of nitrosation of the following compounds.

a) 

b) 

c) 

19.13 ANSWERS

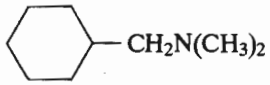
Self Assessment Questions

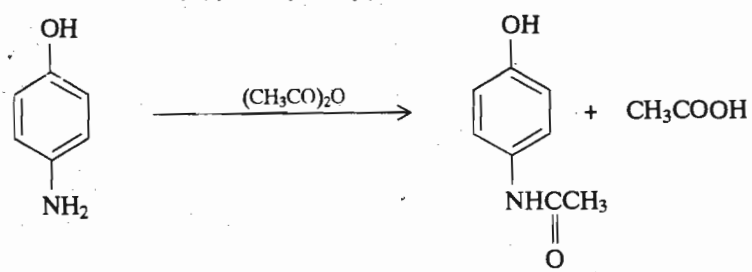
1) a) 2-methylpropanamine
   b) *N,N*-diethylethanamine or triethylamine
   c) cyclohexylamine
   d) 1,2-propanediamine
   e) 3-nitrobenzenamine or 3-nitroaniline

2) *o*-Nitroaniline can undergo **intramolecular** hydrogen bonding whereas its **meta-** and **para-** isomers show **intermolecular** hydrogen bonding. This leads to lower melting and boiling points for *o*-nitroaniline.

3) a) $C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2NH_2$
   3-phenyl-1-butanamine

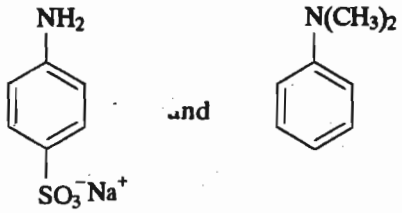
   b) $CH_3CH_2CH_2CH_2CH_2NHCH_2CH_2CH_2CH_3$
   N-butyl-1-pentanamine

   c) 
   N,N-dimethyl(cyclohexylmethyl)amine

4) 

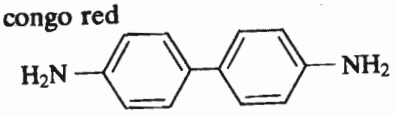
mol. formula – $C_8H_9NO_2$

5) For methyl orange:

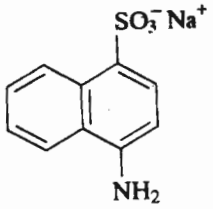


and

For congo red



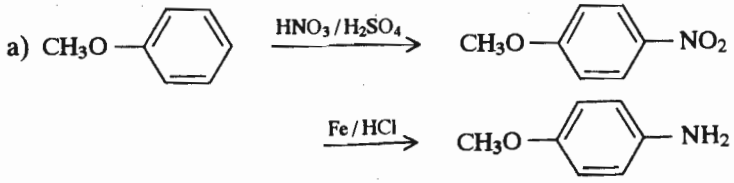
and 2 equivalents of



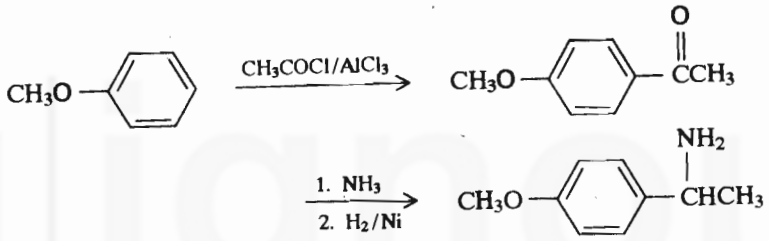
Terminal Questions

1) a) 2-butanamine
   b) *N,N*-dimethylbenzenamine
   c) 6-bromo-2-hexanamine

2) a)



b)



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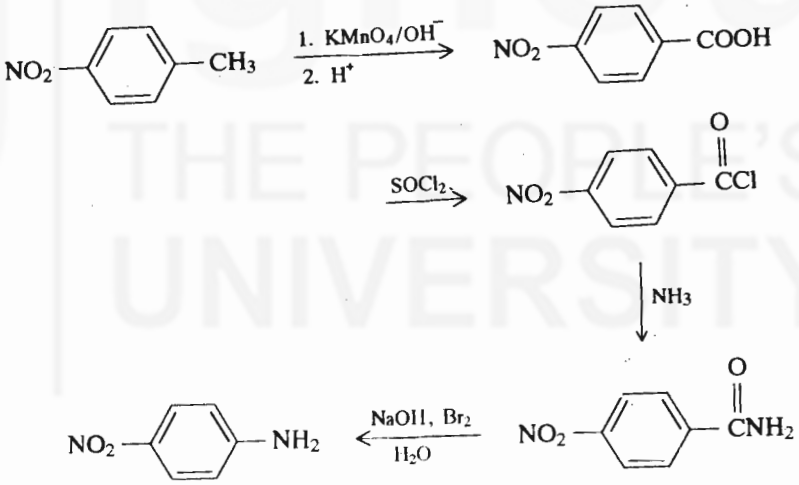

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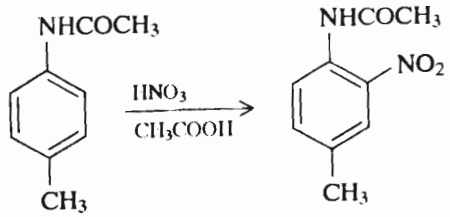

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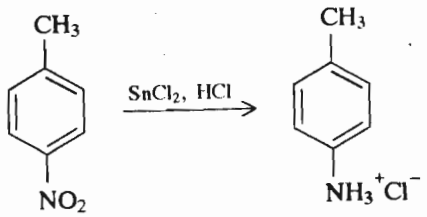
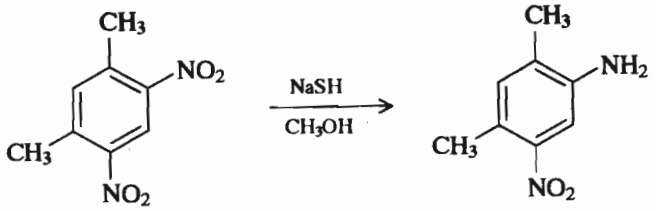
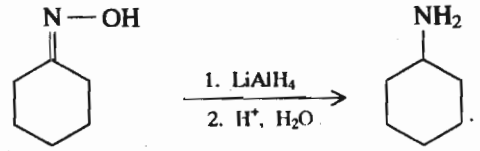
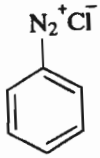
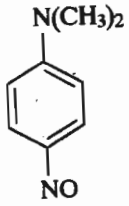


c) 

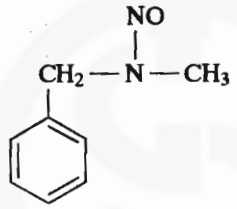
d) 

4) a) 

a diazonium salt

b) 

p-nitroso compound

c) 

N-nitroso compound

UNIT 20 NATURAL PRODUCTS

Structure

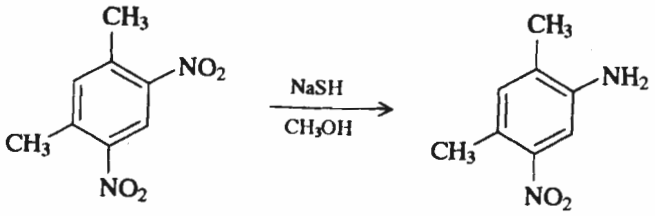
20.1 INTRODUCTION

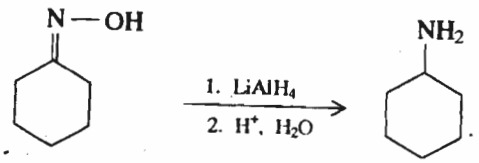
So far we have devoted much of our study of organic chemistry to describe the chemistry involved in the preparation and reactions of compounds containing different functional groups and correlating their behaviour with their structures. There is a unique and vast category of organic compounds produced by living organisms to which you have not yet been exposed. Such compounds are called **natural products**. There are many different classes of natural products. Natural products such as **carbohydrates, proteins, nucleic acids** and **fats** occur in almost all organisms and play an important and primary role in metabolic processes. These natural products are called **primary metabolites**. Another class of natural products, known as **secondary metabolites**, includes **terpenes, steroids** and **alkaloids.** The distribution of secondary metabolities is much more species-dependent. These compounds have been used as drugs, flavours, poisons, dyes and so on. This unit will be devoted to the basic concepts and genral chemistry associated with the natural products.

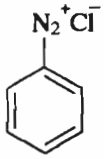
Objectives

After studying this unit, you should be able to:

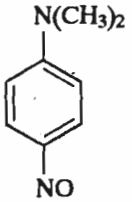
- classify a carbohydrate as monosaccharide, oligosaccharide (disaccharide, trisaccharide and so on) or a polysaccharide,
- write the structures of various carbohydrates,
- write the structures of nucleic acids and discuss the role of DNA in protein synthesis,
- explain the primary, secondary, tertiary and quaternary structure of peptides and proteins,
- list the acids present in oils and fats,
- define acid value, saponification value and iodine value.
- give some examples of terpenes belonging to each category of this class of compounds.

c) 

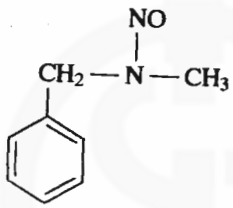
d) 

4) a) 

a diazonium salt

b) 

p-nitroso compound

c) 

N-nitroso compound

UNIT 20 NATURAL PRODUCTS

Structure

20.1 INTRODUCTION

So far we have devoted much of our study of organic chemistry to describe the chemistry involved in the preparation and reactions of compounds containing different functional groups and correlating their behaviour with their structures. There is a unique and vast category of organic compounds produced by living organisms to which you have not yet been exposed. Such compounds are called **natural products**. There are many different classes of natural products. Natural products such as **carbohydrates, proteins, nucleic acids** and **fats** occur in almost all organisms and play an important and primary role in metabolic processes. These natural products are called **primary metabolites**. Another class of natural products, known as **secondary metabolites**, includes **terpenes, steroids** and **alkaloids.** The distribution of secondary metabolities is much more species-dependent. These compounds have been used as drugs, flavours, poisons, dyes and so on. This unit will be devoted to the basic concepts and genral chemistry associated with the natural products.

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- explain the primary, secondary, tertiary and quaternary structure of peptides and proteins,
- list the acids present in oils and fats,
- define acid value, saponification value and iodine value.
- give some examples of terpenes belonging to each category of this class of compounds.

- describe the physiological activities of some alkaloids, and
- give names, structures and uses of some antibiotics.

20.2 CARBOHYDRATES

Carbohydrates received their name because of their general formula $C_x(H_2O)y$, according to which they appear to be **hydrates of carbon**.

Carbohydrates are widespread in nature. In plants, they constitute upto 80% of the dry weight. Carbohydrates occurring in plants include **cellulose** (which gives structural support to plants), **starch** (which serves as the reserved energy source) and **sugars** (like sucrose and glucose). Glucose is an essential constituent of blood in higher animals and occurs in polymeric form as glycogen, in liver and in muscles. Carbohydrates also occur in adenosine triphosphate which is involved in biological energy storage and transport systems. They are also present in the nucleic acids which control the production of enzymes and the transfer of genetic information.

In nature, carbohydrates are synthesised by a process called **photosynthesis**. In this process, sunlight impinging on chlorophyll present in the green plants is absorbed and the photochemical energy thus obtained is used to convert carbon dioxide and water into carbohydrates and oxygen. The overall process can be represented as follows:

$$x\,CO_2 + y\,H_2O \xrightarrow{\text{Sunlight, chlorophyll}} \underset{\text{carbohydrate}}{C_x(H_2O)_y} + x\,O_2$$

20.2.1 Classification and Structure of Carbohydrates

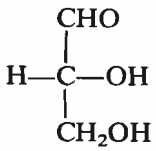
Carbohydrates are polyhydroxy aldehydes and ketones and substances which hydrolyse to polyhydroxy aldehydes and ketones.

The simplest carbohydrates are called **sugars** or **saccharides**, (Latin: *Saccharum*, sugar). Carbohydrates can be classified as **monosaccharides, oligosaccharides** and **polysaccharides**.

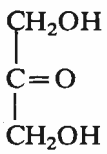
Sugars are crystalline substances having sweet taste and are soluble in water.

Monosaccharides

Monosaccharides are the simplest carbohydrates which cannot be hydrolysed into smaller and simpler carbohydrates. A monosaccharide may be further classified as an **aldose** or a **ketose** if it contains an *aldehyde* or a *keto* group, respectively. The simplest monosaccharides being 2,3-dihydroxypropanal (glyceraldehyde) and 1,3-dihydroxypropanone. Their structures are as shown below:



2,3-dihydroxylpropanal
(an aldose)



1,3-dihydroxypropanone
(a ketose)

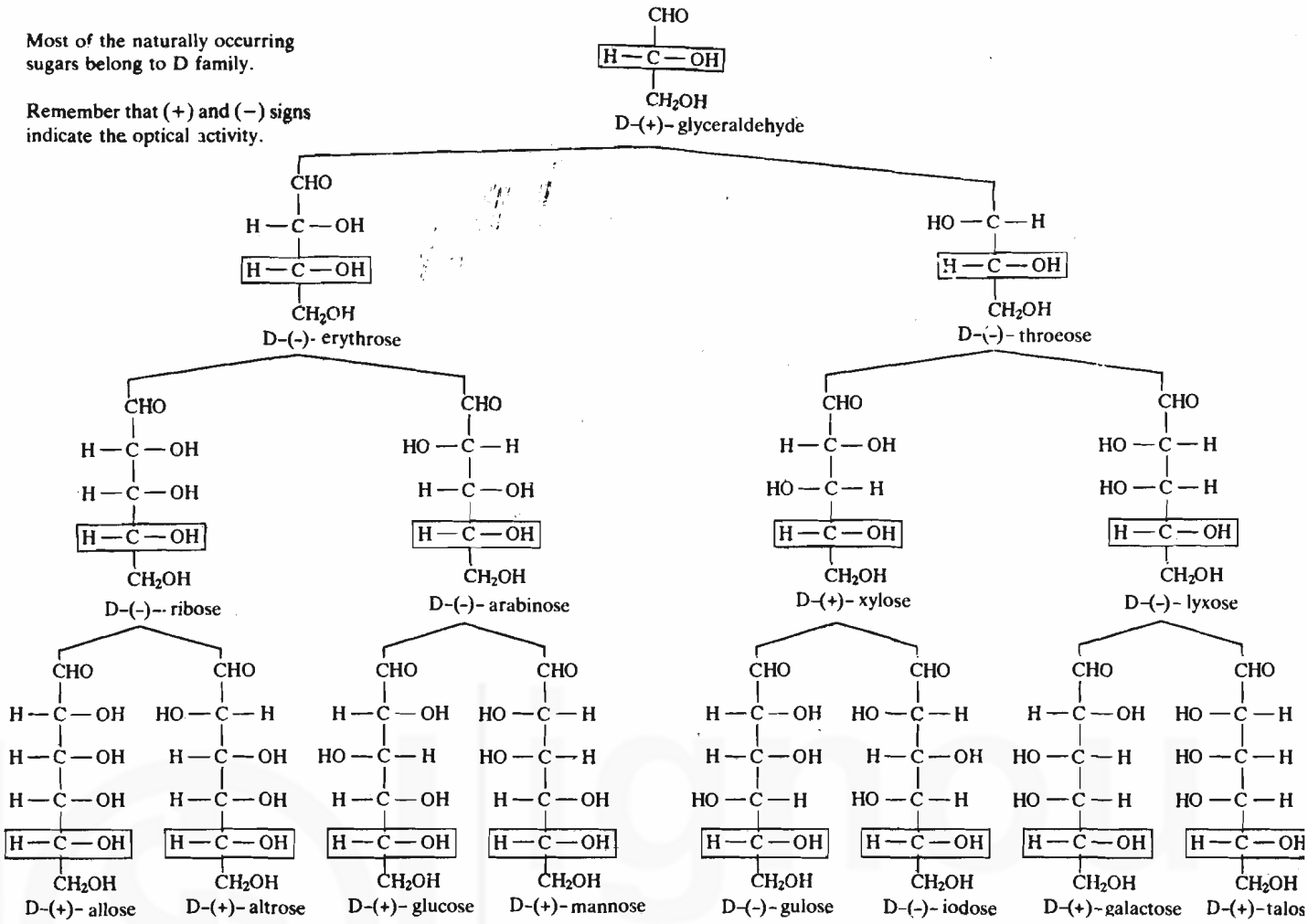
Depending upon the number of carbon atoms in the chain, sugars are called **trioses** (3 carbons), **tetroses** (4 carbons), **pentoses** (5 carbons), **hexoses** (6 carbons) and so on. Therefore, 2,3-dihydroxypropanal is an **aldotriose** and 1,3-dihydroxypropanone is a **ketotriose**.

It was pointed out in Unit 3 that monosaccharides can be classified as D or L depending upon whether the position of the hydroxyl group on carbon next to primary alcoholic group is right or left in the Fischer projection of the molecule projected vertically in such a way that the aldehyde function is on the top. The structures of aldoses belonging to D-family are given in Table 20.1.

Table 20.1 : The D-family aldoses

Most of the naturally occurring sugars belong to D family.

Remember that (+) and (−) signs indicate the optical activity.



Each of the D sugars shown in Table 20.1 has an enantiomeric L-counterpart.

You may recall that R, S system of assigning configurations was discussed in Unit 3, Block 1.

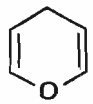
The absolute configurations are described by assigning the configuration to each stereocentre in the molecule. For example, D-(+)-glucose is (2*R*, 3*S*, 4*R*, 5*R*)—2, 3, 4, 5, 6-pentahydroxyhexanal.

As in the case of D-aldoses shown in Table 20.1, the Fischer projections of monosaccharides belonging to D-ketose series are shown in Table 20.2.

You are aware from seb-Sec. 14.4.1, Sec. 14.4, Unit 14, Block 3 that aldehydes and ketones form hemiacetals or hemiketals with alcohols. Since sugars are hydroxy carbonyl compunds, they are capable of forming intramolecular cyclic hemiacetals and hemiketals. While in principle, any one of the hydroxyl group could add to the carbonyl function; the formation of six-membered ring is preferred, although five-membered rings are also formed. This is shown below in case of glucose.

Cyclic Hemiacetal Formation by Glucose

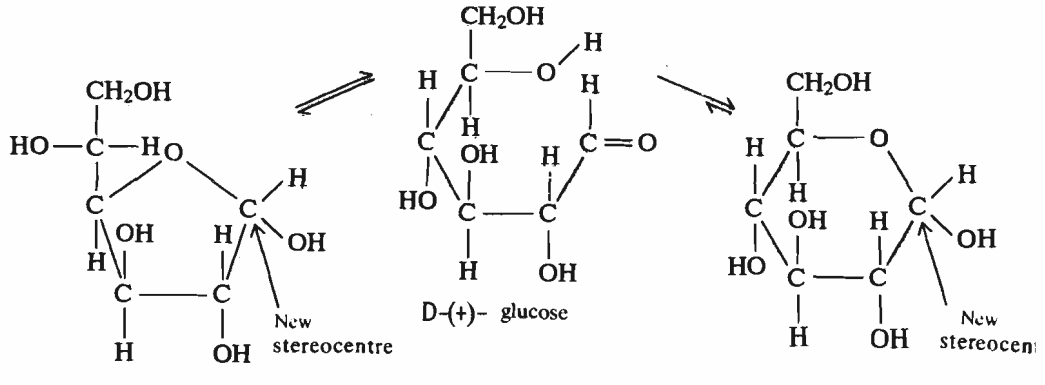
The name **pyranose** is derived from pyran, a six-membered cyclic ether.



pyran

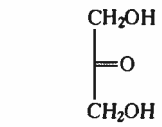
Similarly, **furanose** is derived from furan.

furan

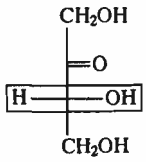


D-(+)-glucofuranose
less stable

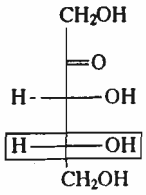
D-(+)-glucopyranose
more stable



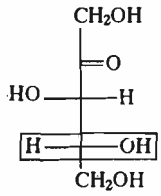
1,3-Dihydroxypropanone



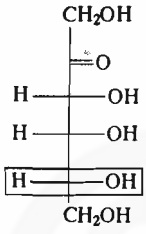
D-(−)-erythralose



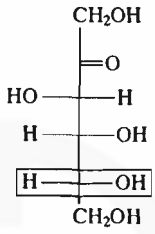
D-(+)-ribulose



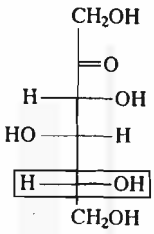
D-(+)-xylulose



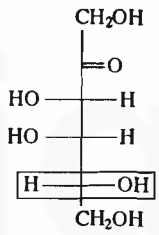
D-(+)-psicose



D-(−)-fructose

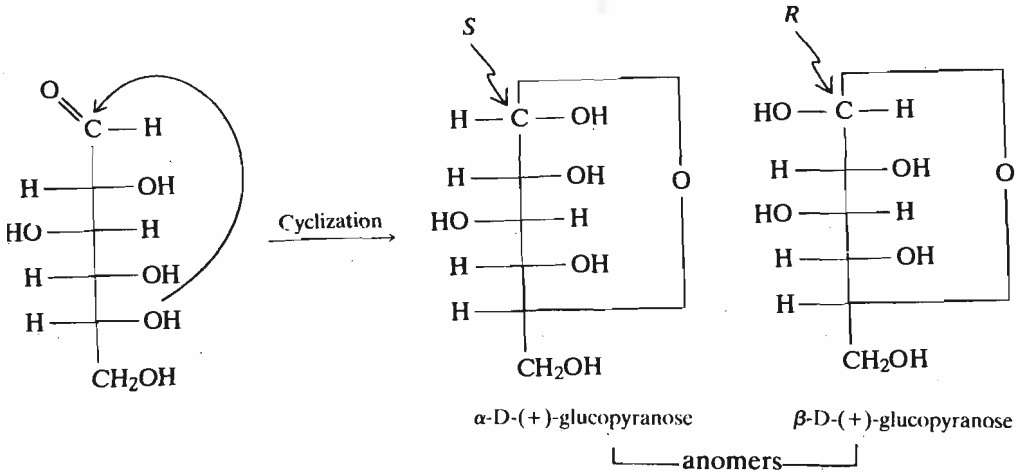


D-(+)-sorbose



D-(−)-tagatose

You can see that the formation of hemiacetal (or hemiketal) turns the carbonyl carbon into a new stereocentre. This leads to **two** new compounds which are diastereomers having different configurations at C-1. Such isomers are called **anomers** and the hemiacetal or hemiketal carbon (C-1) is called the **anomeric carbon.** The two anomers are differentiated by the Greek letters α and β. Thus, we can call the anomers of glucose as α-D-(+)-Glucopyranose and β−D−(+)−Glucopyranose. These anomers are represented below in the modified Fischer projections using elongated lines to indicate the new bonds formed.



α-D-(+)-glucopyranose β-D-(+)-glucopyranose

anomers

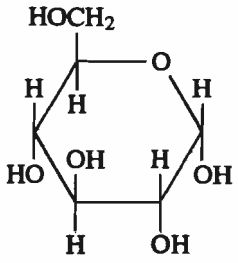
Note that in β-anomer the OH at C-1 is written to the left and that in the α-anomer is written to right.

Since these modified Fischer projections do not give the correct picture of the molecule in terms of bond lengths, Haworth introduced an alternate projection formula called **Haworth projections**. In Haworth projections, the cyclic ether is written as a planer pentagon or a hexagon having the anomeric carbon on the right and the ether oxygen at the top. The substituents located above and below the ring

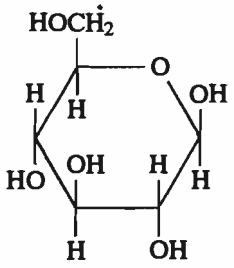
are joined by vertical lines to the ring carbons. The OH at the anomeric carbon (C–1) is shown up in the β-anomer and down in the α-anomer.

Haworth, the English Chemist, received the Nobel Prize in 1937 for his work in carbohydrate chemistry.

The Haworth projections of D-(+)-Glucose are shown below.



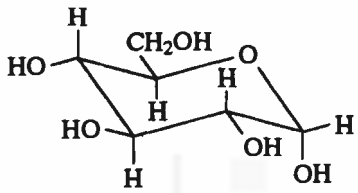
α-D-(+)-glucopyranose



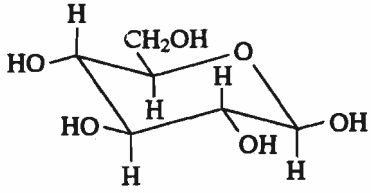
β-D-(+)-glucopyranose

Using our knowledge of conformations of cyclic systems gained in Unit 3, Block 1, we can write the chair conformations of the anomeric forms of D-(+)-glucose as given below.

Glucose exists mainly in the pyranose form whereas fructose forms an equilibrium mixture of pyranose and furanose forms in the ratio 70:30.

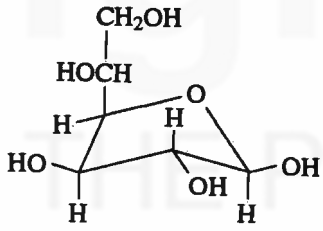


β-D-glucopyranose



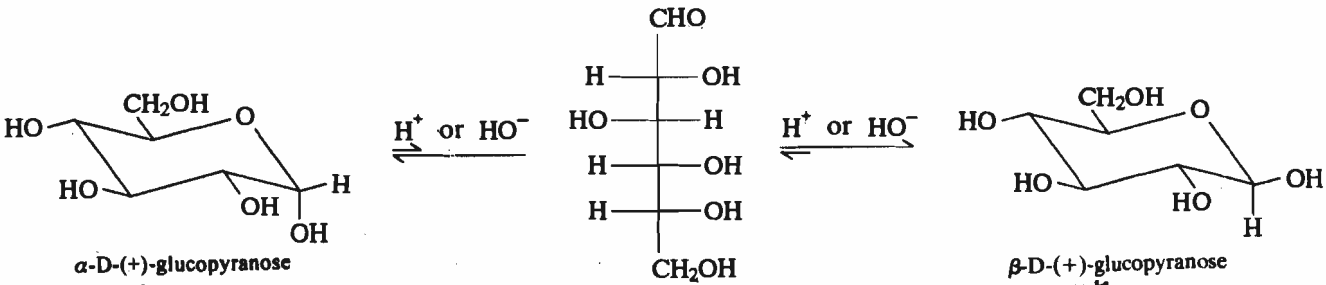
β-D-glucopyranose

The envelope conformation of the furanose form can be represented as shown below.



β-D-glucofuranose

Both α-D-(+)-glucopyranose.and β-D-(+)-glucopyranose are optically active but differ widely in their optical rotations. The α-D-(+)-glucopyranose has the specifice rotation of $[\alpha]_D^{298\,K} = +112°$ whereas β-D-(+)-glucopyranose has $[\alpha]_D^{298\,K} = +18.7°$. When dissolved in water, the optical rotation of the solution gradually changes with time until it reaches an equilibrium value of +52.7°. This is because α-D-(+)-glucopyranose rapidly establishes an equilibrium with a small amount of the open-chain aldehyde form which in turn undergoes renewed and reversible ring closure to the β-anomer.



α-D-(+)-glucopyranose
$[\alpha]_D^{298\,K} = +112°$
(36.4%)

aldehyde form
0.003%

β-D-(+)-glucopyranose
$[\alpha]_D^{298\,K} = +18.7°$
(63.6%)

This interconversion is called **mutarotation** and was first observed in 1846. It involves change of configuration at one stereocentre in a compound having more than one such centres.

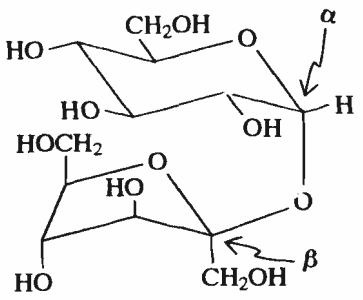
Mutarotation is catalysed by acids and bases.

In Latin, *mutare* means to **change**.

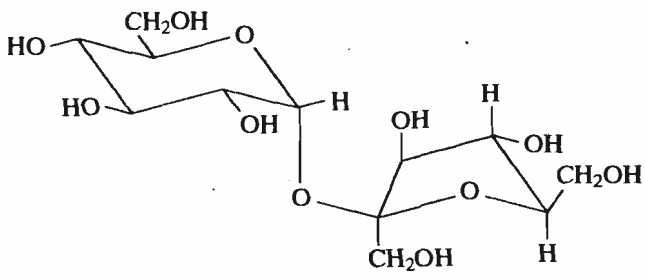
Oligosaccharides

Oligosaccharides are the carbohydrates that yield two to eight monosaccharide units on hydrolysis. Carbohydrates which yield *two* monosaccharide units on hyrolysis are called **disaccharides** and those which yield *three* monosaccharide units are called **trisaccharides** and so on.

The most familiar disaccharide is the table sugar called **sucrose**. It contains one unit each of glucose and fructose joined by acetal linkage as shown below in its structure. Sucrose is abundant in cane sugar and sugar beets where it is present to the extent of 14-20% by weight.



or

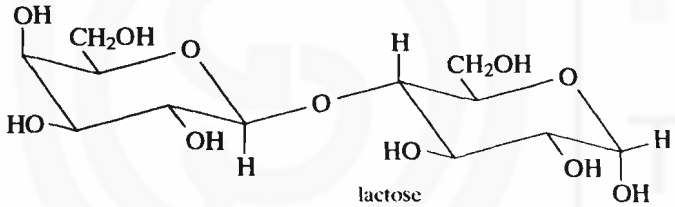


(sugars represented in usual way)

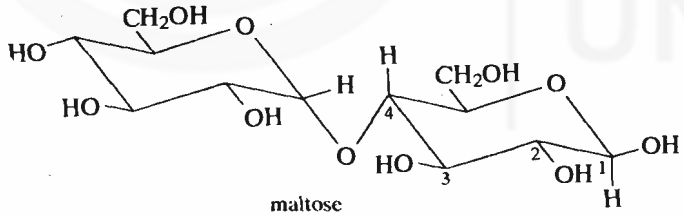
(sterically more favourable)

Sucrose an α-D-glucopyranosyl β-D-fructofuranoside

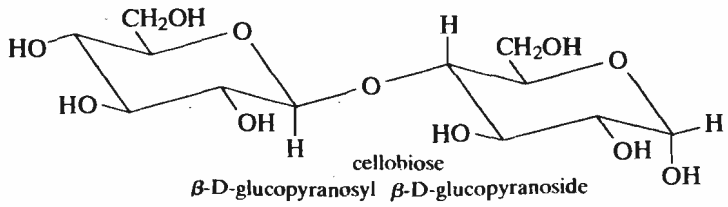
The other common disaccharides are **lactose, maltose** and **cellobiose**. Their structures are given below:



lactose
β-D-galactopyranosyl α-D-glucopyranoside



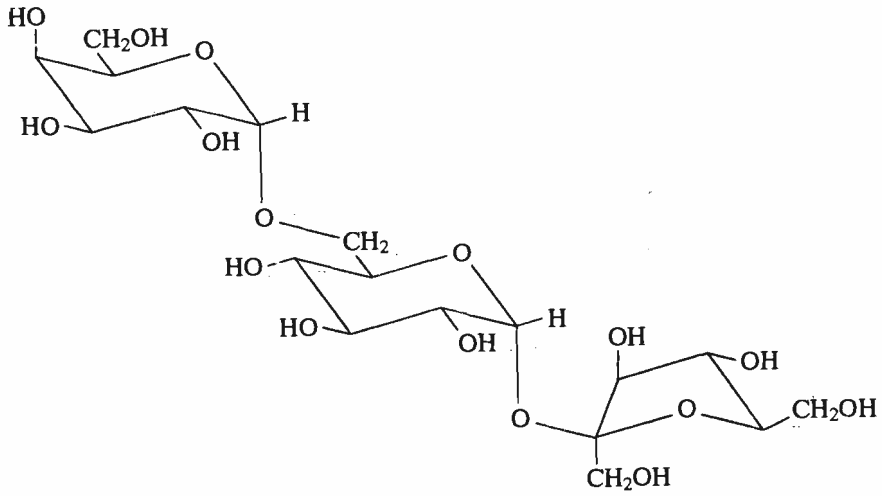
maltose
α-D-glucopyranosyl β-D-glucopyranoside



cellobiose
β-D-glucopyranosyl β-D-glucopyranoside

Lactose constitutes about 5% by weight of human and most animal milk. Maltose is obtained by enzymatic degradation of starch using the enzyme **amylase** whereas cellobiose is obtained by the hydrolysis of cellulose.

Raffinose is an example of a trisaccharide. It is found in sugar beets and also in cotton seeds. On hydrolysis, it yields one unit each of D-galactose, D-glucose and D-fructose which are joined together as shown below.

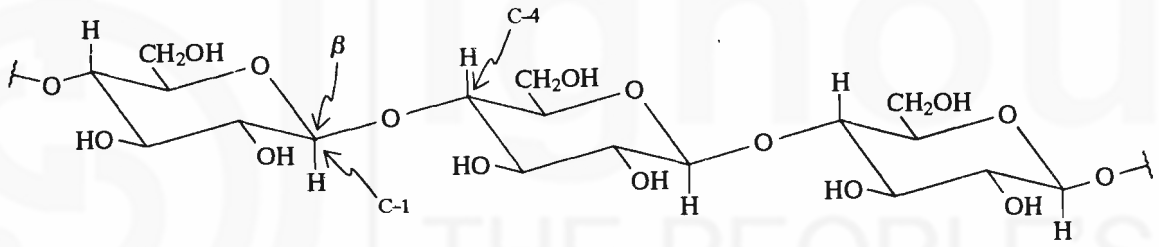


raffinose

Polysaccharides

Polysaccharides are the polymers of monosaccharides. The natural polysaccharides generally contain about 100-3000 monosaccharide units. The three most abundant natural polysaccharides-cellulose, starch and glycogen are derived from the same monomer, i.e., glucose.

Cellulose contains about 3000 monomeric units linked together and has a molecular weight of about 500,000. The individual units are linked by β-glycoside bonds which join the anomeric carbon of one unit to the C-4 hydroxyl of the next unit as shown below in the structure of cellulose.

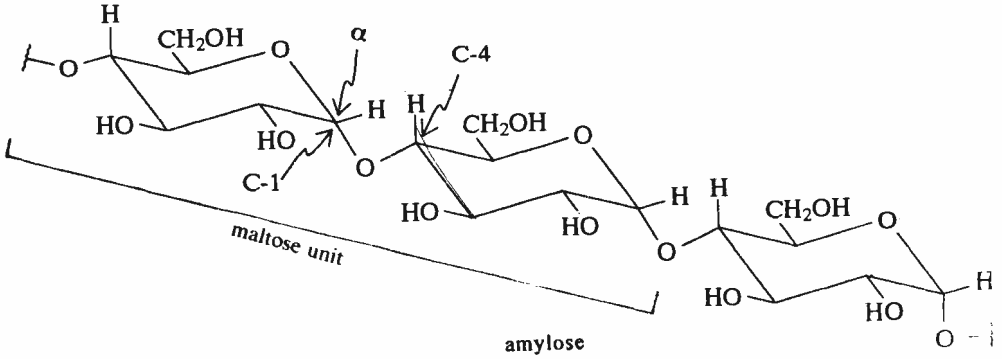


cellulose

Cellulose is abundant in trees and plants. Cotton fibre contains 90% cellulose by weight.

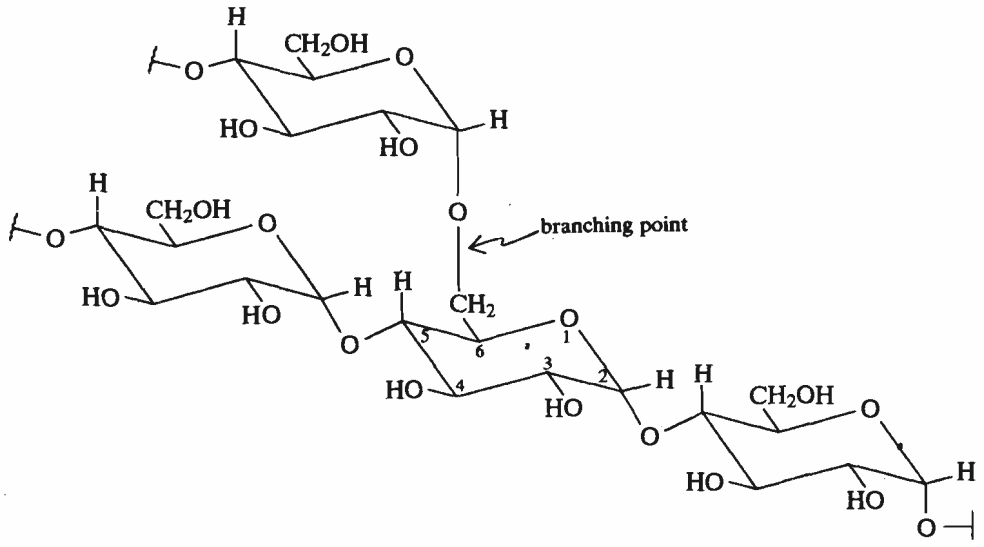
Unlike cellulose, **starch** contains glucose units linked by α-glucoside bonds. Major sources of starch are corn, potatoes, wheat and rice which constitute the chief carbohydrate sources for human beings. Starch is deposited in plants in the form of starch granules. The granules swell in hot water and can be separated into two major components: **amylose** (~ 20%) and **amylopectin** (~80%).

Amylose contains a few hundred units per molecule linked in an unbranched manner and has the molecular weight ranging between 1,50,000 – 6,00,000.



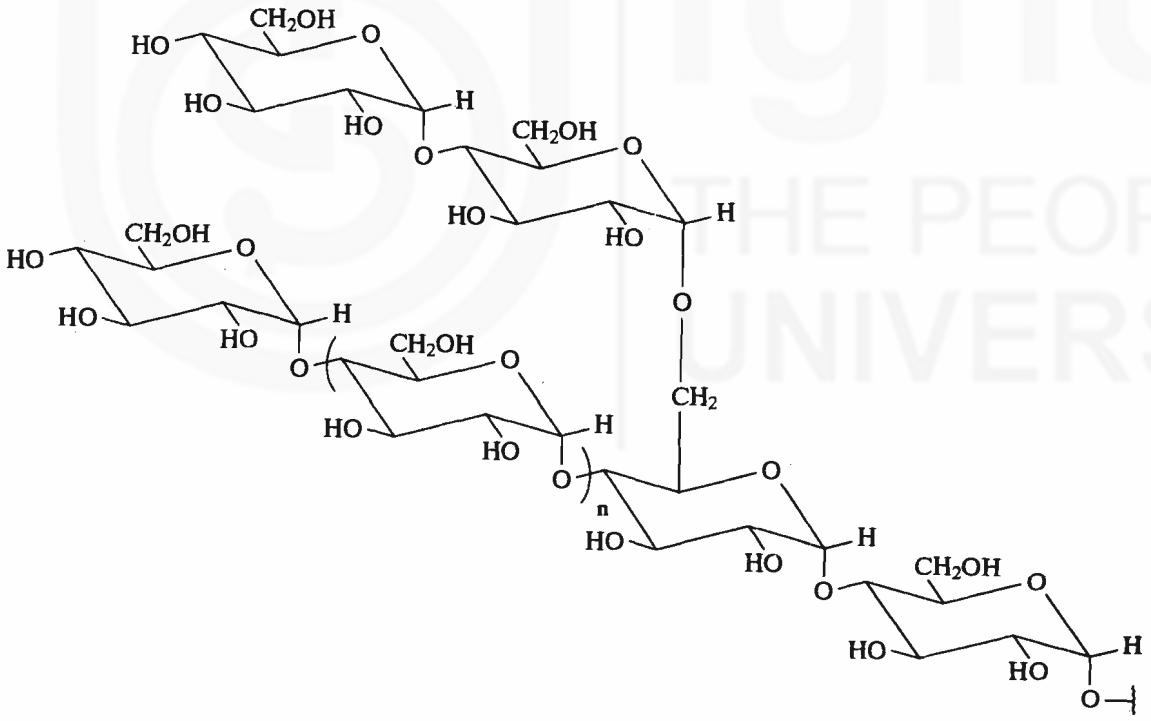
amylose

Amylopectin on the other hand is branched at the C-6 position. The branching occurs at about every twenty to twenty-five glucose units. Its molecular weight is in millions. A portion of the structure of amylopectin is shown below:



amylopectin

Glycogen is structurally similar to starch but has greater branching, i.e., one per ten glucose units. It is a source of stored energy in humans and accumulates in liver and muscles.



glycogen

SAQ 1

Write the hemiacetal formation for fructose.

.....

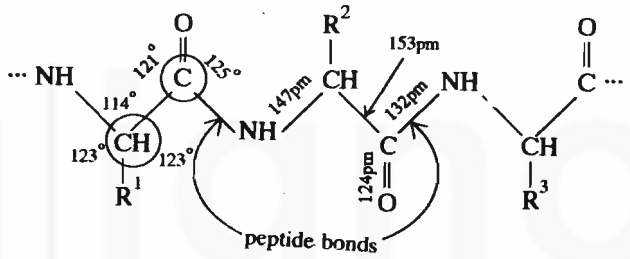
.....

.....

20.3 PEPTIDES AND PROTEINS

In the last section, you studied the polymers of monosaccharides which act as structural components in plants and serve as energy storage in animals. In this section, you will study another kind of natural polymers called **peptides** and **proteins.**

Peptides are biologically important polymers in which 2-amino acids are joined by the amide linkages, formed by the reaction of the carboxy group of one amino acid with the amino group of another amino acid. These amide linkages are also called **peptide bonds.** The general structure of a peptide is shown below:



general peptide structure

Remember that a three letter code to represent amino acids was given in Table 16.1, Sec. 16.4, Unit 16.

Peptides can be classified as **dipeptides, tripeptides** and **tetrapeptides**, depending on whether the number of amino acids is **two, three** or **four**, respectively. Peptides containing upto 50 amino acids are called **polypeptides.** *Bradykinin* is an important naturally occurring nonapeptide which is present in blood plasma and is involved in the regulation of blood pressure.

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg
bradykinin

Proteins are large polypeptides containing from about 50 to more than 8,000 amino acids per molecule. Proteins have diverse biological functions. As enzymes and hormones, proteins catalyse and regulate various reactions occurring in our body. As skin and hair, they give outer covering to our body and as muscles they provide movement. In the form of antibodies, they protect us from diseases. The oxygen present in the air we breath, is transported by the protein **hemoglobin**. The nucleoproteins in the genes supply and transmit the genetic information in cell division. In addition, proteins also provide structural support in combination with other substances.

After having an idea about the importance of proteins, you must be curious to know about the structure of peptides and proteins.

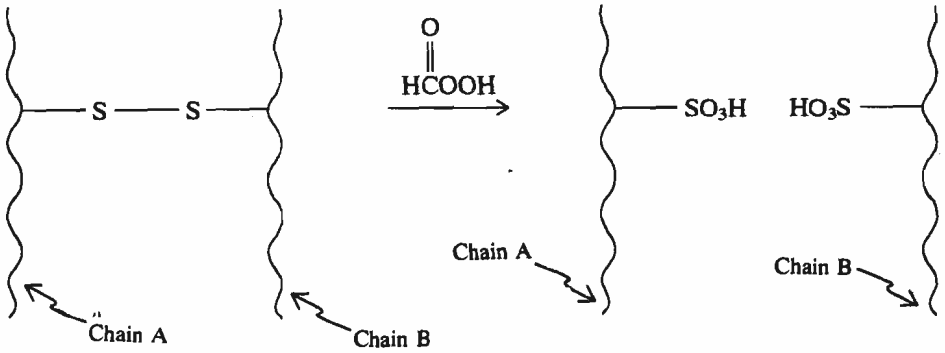
20.3.1 Structure of Peptides and Proteins

Since peptides and proteins contain a number of amino acids linked together, the first step in the determination of their structure requires a knowledge about which amino

acids are present and how they are linked together plus any *disulphide links* present in them. The order in which the amino acids are joined is called the **primary structure** of a peptide or protein.

Disulphide links hold peptide chains together in a protein molecule.

Determination of the primary structure involves oxidation of the disulphide bridges linking the chains in peptides or proteins to sulphonic acids using peroxymethanoic acid, as shown below:



Proteins can be degraded into peptides by **partial hydrolysis** using either dilute hydrochloric acid or enzymes. Peptides on **complete hydrolysis** by heating with 6 N HCl for 24 hours yield a mixture of all amino acids present. This mixture is then separated, taking advantage of the acid-base properties of amino acids, in an apparatus known as **amino acid analyser**. The separation involves ion-exchange chromatography. This analysis thus provides information about the amino acids present and their relative amounts.

The sequence of amino acids present in a peptide chain can be determined either by analysing the products of **partial hydrolysis** or by **end group analysis**. Let us understand these methods with the help of examples.

Partial Hydrolysis

In a particular case, partial hydrolysis of a tetrapeptide containing Ala, Gly, Phe and Val yielded a tripeptide Gly-Phe-Val and a dipeptide Ala-Gly.

$$\text{Tetrapeptide} \xrightarrow{\text{hydrolysis}} \text{Gly-Phe-Val} + \text{Ala-Gly}$$

Since the dipeptide shows that Ala is linked to Gly, the amino acids in the tetrapeptide are linked in the following sequence:

$$\text{Ala}\overset{a}{\text{—}}\text{Gly}\overset{b}{\text{—}}\text{Phe—Val}$$

Cleavage at *a* gives the tripeptide and that at *b* gives the dipeptide.

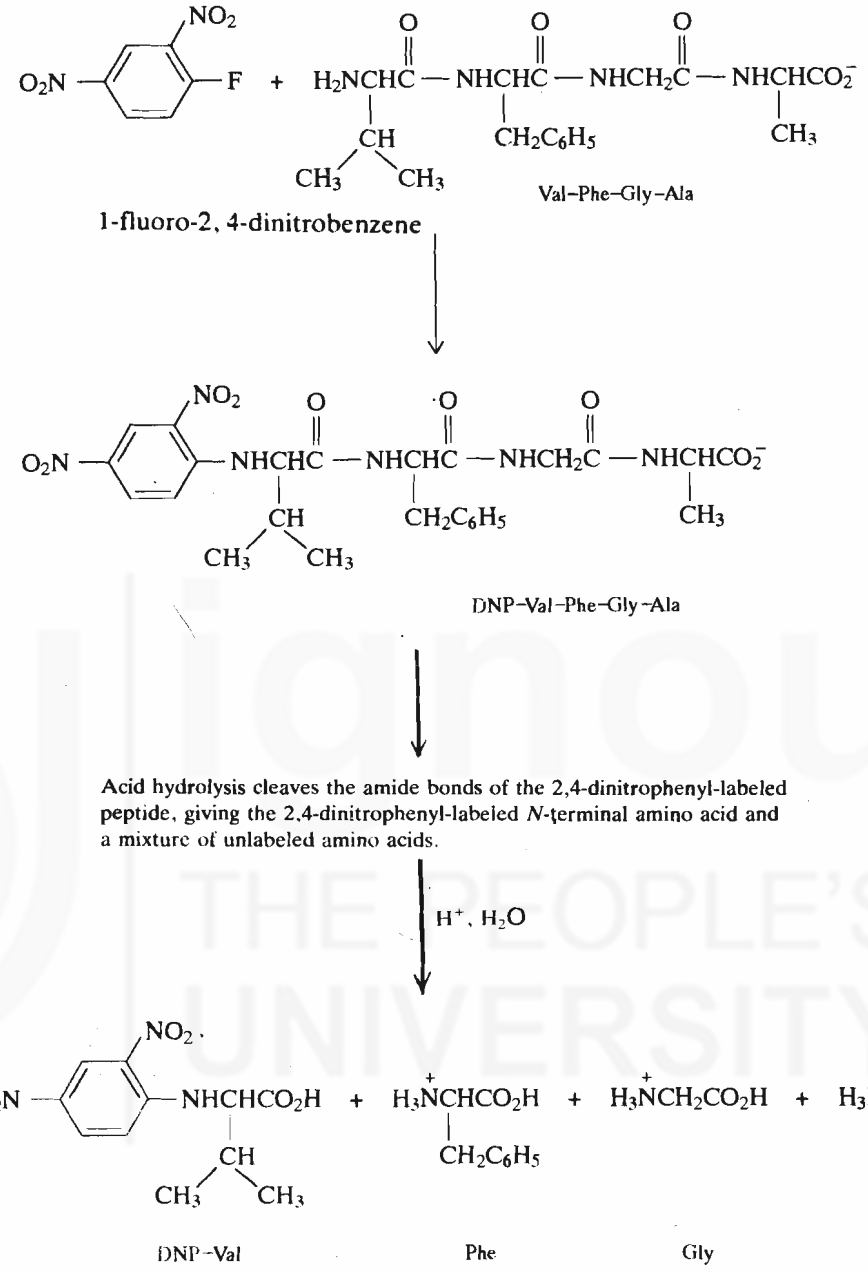
End Group Analysis

Let us first understand what is an end group? By convention, peptide structures are written in such a way that the amino group is at the left and the carboxy group is at the right. Thus, the amino end is called the **N-terminus** and the carboxy end is called the **C-terminus**, the end groups being amino and carboxy groups.

The amino groups of all the amino acids, except the N-terminal amino acid, are involved in the amide bond formation. Therefore, the amino group of the N-terminal

Sanger utilised this method in the determination of sequence of amino acids in insulin and was awarded Nobel Prize in 1958 for this pioneering work

amino acid is free and can react as a nucleophile. The **Sanger method** of identifying N-terminal amino acid involves the reaction of the free amino group in the peptide with 1-fluoro-2, 4-dinitrobenzene to yield a peptide in which the N-terminal nitrogen is tagged with a 2,4-dinitrophenyl group. After complete hydrolysis of the peptide, the tagged amino acid is identified by chromotographic methods. This procedure is illustrated below.

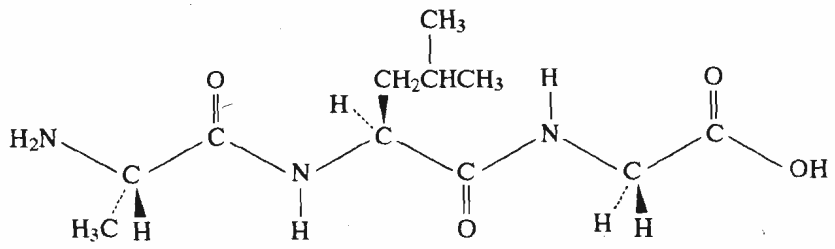


The drawback in this method is that complete degradation is required after the polypeptide is once tagged.

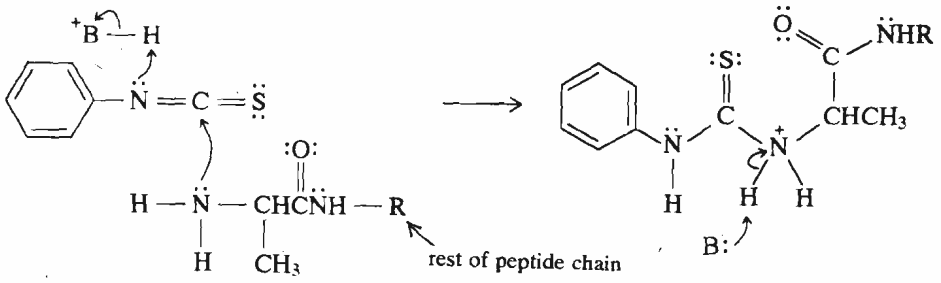
A more useful method is by the **selective removal** of the tagged terminal amino acid and leaving the remaining chain intact so that it can again be tagged with the reagent. One such method which enables identification of one amino acid in the sequence at a time is the **Edman degradation.**

In *Edman degradation,* the terminal amino group adds to phenyl isothiocyanate, $C_6H_5N{=}C{=}S$ to yield a thiourea derivative. Treatment with mild acid gives the tagged amino acid as a phenylthiohydantoin and the remainder of the peptide chain. The tagged amino acid is identified and the remaining peptide is again subjected to Edman degradation. This sequence is repeated till all the amino acids in the peptide are identified. An example using the peptide Ala-Leu-Gly is shown below:

Degradation of a peptide by Edman's reagent



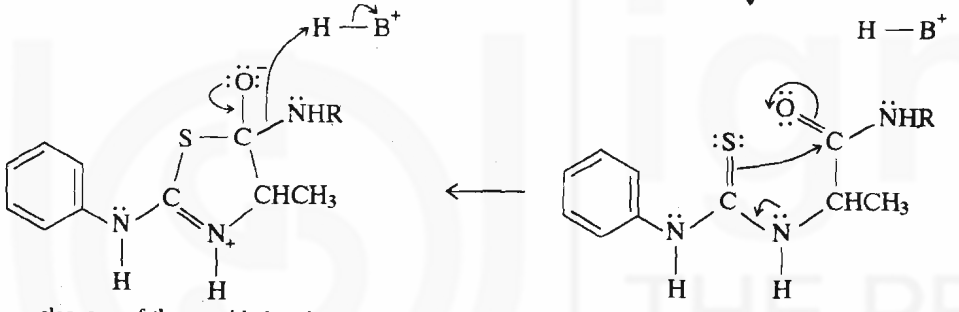
Ala-Leu-Gly
Peptide



nucleophilic attack by amino group on isothiocyanate with subsequent protonation of nitrogen

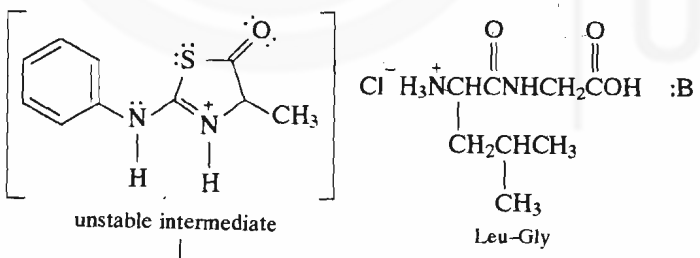
rest of peptide chain

deprotonation



cleavage of the peptide bond

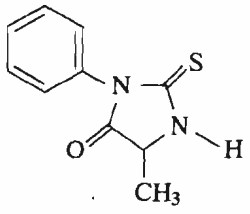
nucleophilic attack by sulphur on carbonyl group



unstable intermediate

Leu-Gly

△, rearrangment



phenylthiohydantoin derived from alanine

The amino acid at the C terminus is identified by **enzymatic hydrolysis**. The enzymes which are used are called **peptidases** or **proteases**. Thus, **carboxypeptidases** sequentially cleave the C-terminus amino acids and the amino acids so cleaved are monitored with time to know the sequence.

Certain peptidases which allow controlled hydrolysis by cleaving certain specific amide bonds, can also be used in sequence analysis. For example, **trypsin**, present in intestine, catalyses the hydrolysis of the peptide bonds involving carboxy groups of lysine or arginine. Similarly, **chymotrypsin** allows cleavage of the amide bonds of amino acids containing aromatic groups in their side chains, namely phenylalanine, tyrosine and tryptophan.

Till now you have learnt the primary structure of peptides and proteins. Let us now study their secondary structure, i.e., the spatial arrangement of the peptide chains.

Description of the conformational relationship of the nearest amino acids of a peptide is called its **secondary structure.** Two conformational arrangements called **α-helix** and **β-pleated sheet** are particularly stable.

The terms α and β-refer to two characteristic X-ray diffraction patterns. The α-type pattern was associated with right handed helix and β-type with the pleated sheet.

In a right handed helix, the chain turns in clockwise direction.

The α-helix conformation is shown in Fig. 20.1. In this the polypeptide chain forms a right handed coil having 3.7 amino acids per turn. This allows hydrogen bonding between each carbonyl oxygen and an amide hydrogen which stabilises the conformation. α-Helix is important in structural proteins such as α-keratins which constitute proteins of skin, nails, hair and feathers.

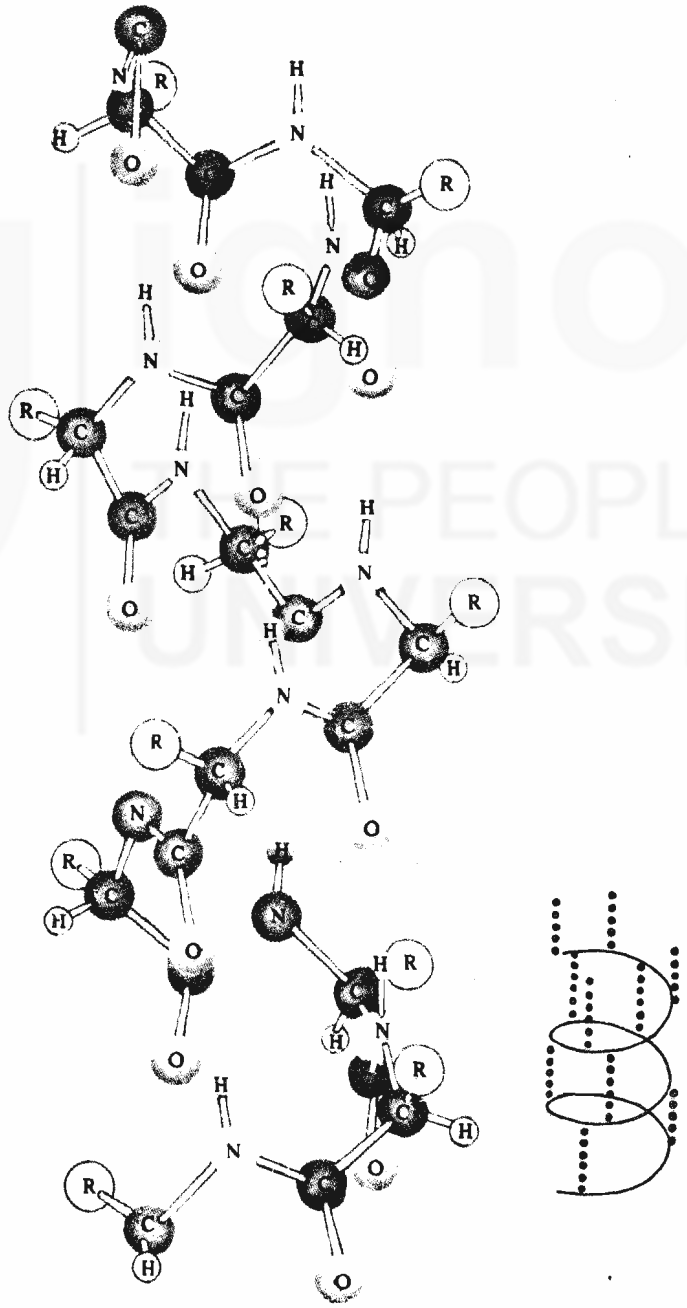


Fig. 20.1 : α-helix.

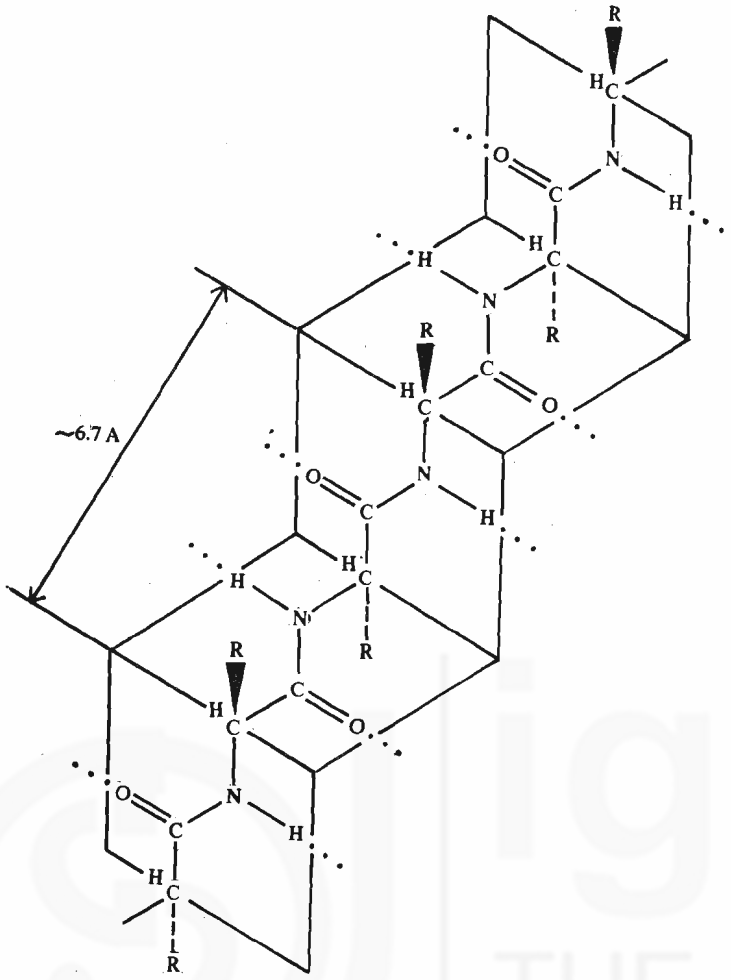


Fig. 20.2 : The β-pleated sheet in a polypeptide.

Note that the hydrogen bonds are formed between the carbonyl oxygen and the amide hydrogen of *two chains* in β-pleated sheet. You can see that the side chains alternate above and below the planes of the pleated sheets.

Tertiary structure refers to further folding of the peptide chain leading to its three-dimensional shape. Folding affects the physical and biological properties. Tertiary structure depends upon a variety of factors such as hydrogen bonding, van der Waal's forces and electrostatic forces. A protein adopts the tertiary structure in such a way that favourable interactions are maximised and the unfavourable ones are minimised. The tertiary structure of a protein is important in the sense that it defines an **active site** to fit in a substrate. This allows the specificity of enzyme action. The tertiary structure of **fibrous proteins** show a **superhelix** in which several α-helices are coiled, see Fig. 20.3.

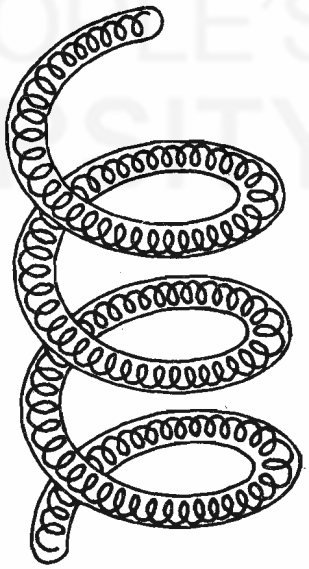


Fig. 20.3: A superhelix : helix within a helix.

Pronounced folding is observed in **globular proteins** in which the tertiary structure allows them to be spherical. The globular proteins perform a crucial part in chemical transport.

Some proteins such as hemoglobin have a **quaternary structure** in which two or more peptide chains combine to form an assembly. The manner in which these subunits are organised is referred to as the quaternary structure of the protein.

SAQ 2

Write the structure of the tripeptide Val-Phe-Ser.

.....

.....

.....

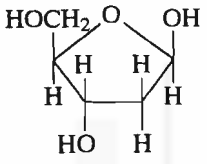
20.4 NUCLEIC ACIDS

Having studied the structure of peptides and proteins, let us now study the substances involved in the control of protein biosynthesis and transfer of genetic information. These are biological macromolecules present in the nuclei of the cells and are called **nucleic acids**. There are two major kinds of nucleic acids, **deoxyribonucleic acid (DNA)** and **ribonucleic acid (RNA)**. Nucleic acids are the natural polymers which contain **nucleotide** repeating units and are, therefore, also known as **polynucleotides.**

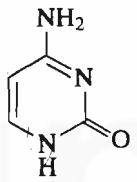
The prefix *deoxy* means without oxygen.

Nucleotides contain a **phosphate group** linked through a **sugar moiety** to a **nitrogen heterocycle.**

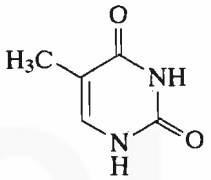
DNA contains the sugar *2-deoxyribose* and four nitrogen heterocyclic bases called *cytosine* (C), *thymine* (T), *adenine* (A) and *guanine* (G). Their structures are shown below:



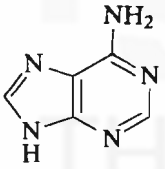
2-deoxyribose



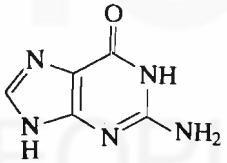
cytosine



thymine



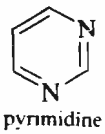
adenine



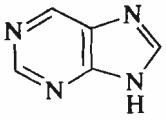
guanine

In RNA, the sugar moiety is ribose and the four bases present are cytosine, adenine, guanine and uracil. The structures of ribose and uracil are given below:

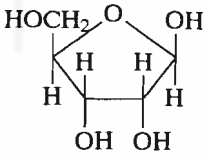
Note that the heterocyclic bases are derived from heterocyclic ring systems: pyrimidine and purine:



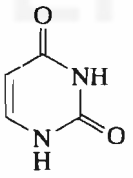
pyrimidine



purine



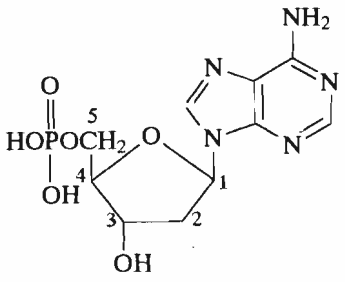
ribose



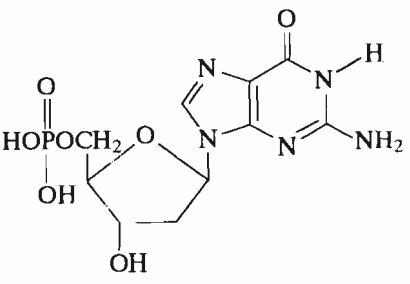
uracil

Thus, the nucleotides present in DNA and RNA can be written as follows:

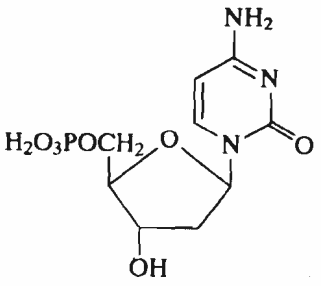
The Four Nucleotides of DNA



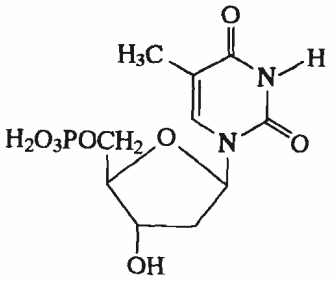
2-deoxyadenylic acid



2-deoxyguanidylic acid

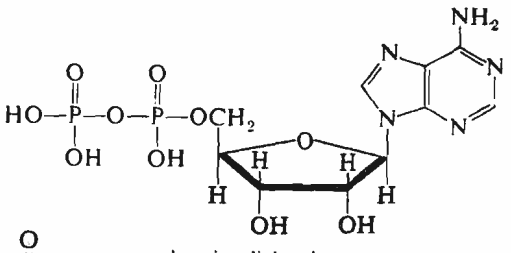


2-deoxycytidylic acid



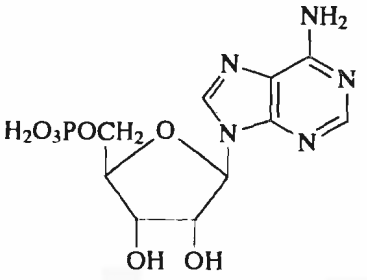
2-deoxythymidylic acid

Other important 5'-nucleotides of adenosine include adenosine diphosphate (ADP) and adenosine triphosphate (ATP).

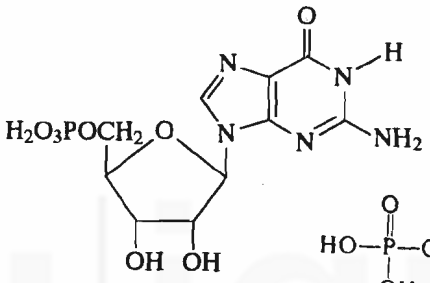


adenosine diphosphate
ADP

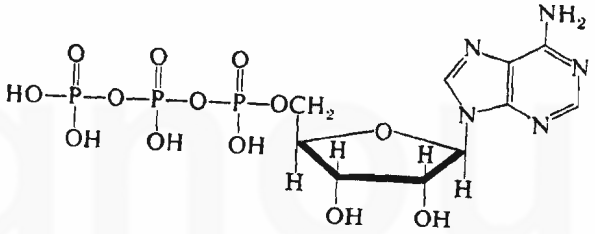
The Four Nucleotides of RNA



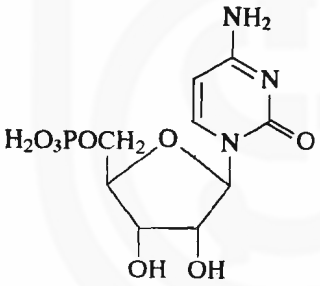
adenylic acid



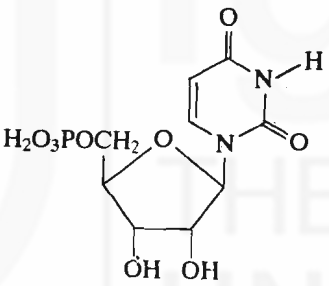
guanidylic acid



adenosine triphosphate
ATP

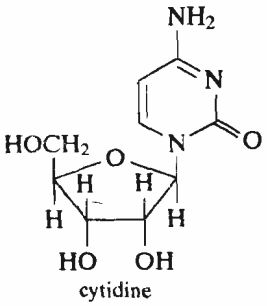


cytidylic acid

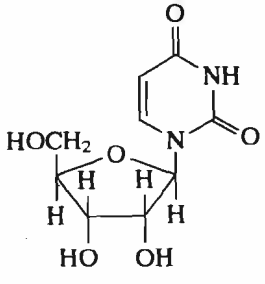


uridylic acid

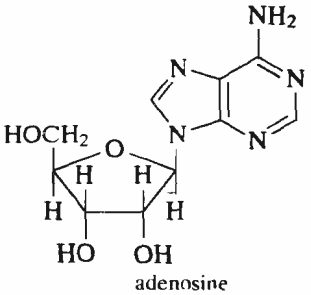
Base-catalysed hydrolysis of a nucleotide removes the phosphate group to yield a **nucleoside**. The nucleosides of RNA are shown below:



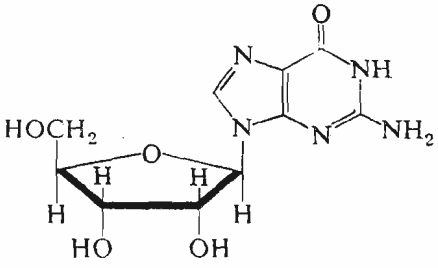
cytidine



uridine



adenosine



guanosine

20.4.1 Structure of Nucleic Acids

Nucleic acids are polynucleotides in which the phosphate esters link the 3′-hydroxyl of one sugar with 5′-hydroxyl of another, see Fig. 20.4 which shows a portion of a polynucleotide chain.

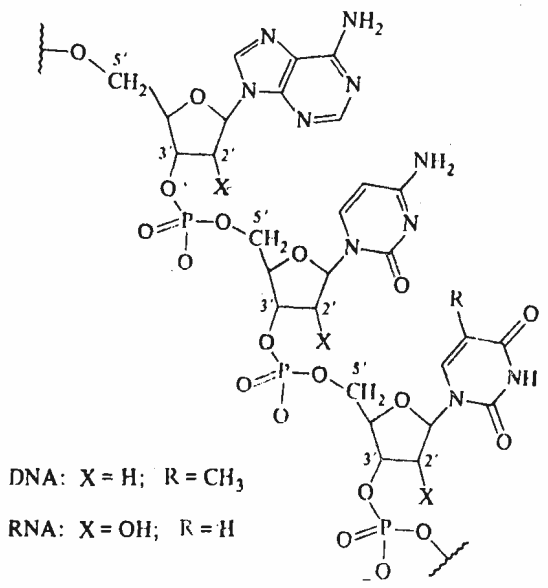


Fig. 20.4 : A portion of a polynucleotide chain.

You can see in Fig. 20.4 that there is a **backbone** of alternating sugar and phosphate units with bases protruding from the chain at regular intervals.

In 1950, Chargaff observed that the ratios of adenine to thymine and guanine to cytosine in DNA was always one to one which indicated the association of adenine to thymine and guanine to cytosine by hydrogen bonds as shown below in Fig. 20.5.

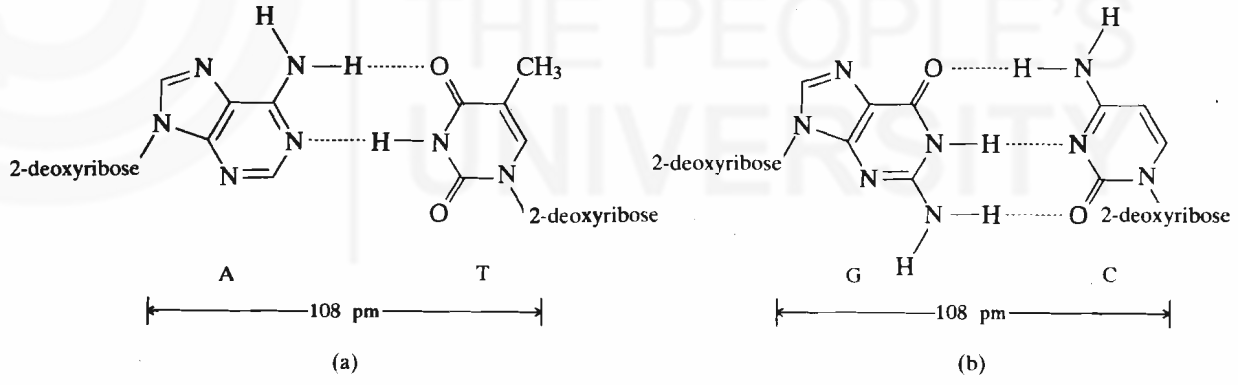


Fig. 20.5: Base pairing between (a) adenine and thymine and (b) guanine and cytosine.

J.D. Watson and F. Crick received Nobel Prize for medicine and physiology in 1962 for their work on structure of DNA.

This hydrogen bonding between the base pairs is a key element in the double helix structure of DNA proposed by Watson and Crick. Such a double helix is shown in Fig. 20.6.

20.4.2 Nucleic Acids and the Genetic Code

The sequence of nucleotides in DNA contains all the genetic information for cell duplication. At one stage of cell division, the double helix of DNA begins to unwind. Each of the separated chains function as a template upon which another chain, exactly complementary to itself, is constructed. This leads to two identical new double helices, each one of which passes the genetic information to the daughter cells. This is called **DNA replication** and is shown in Fig. 20.7.

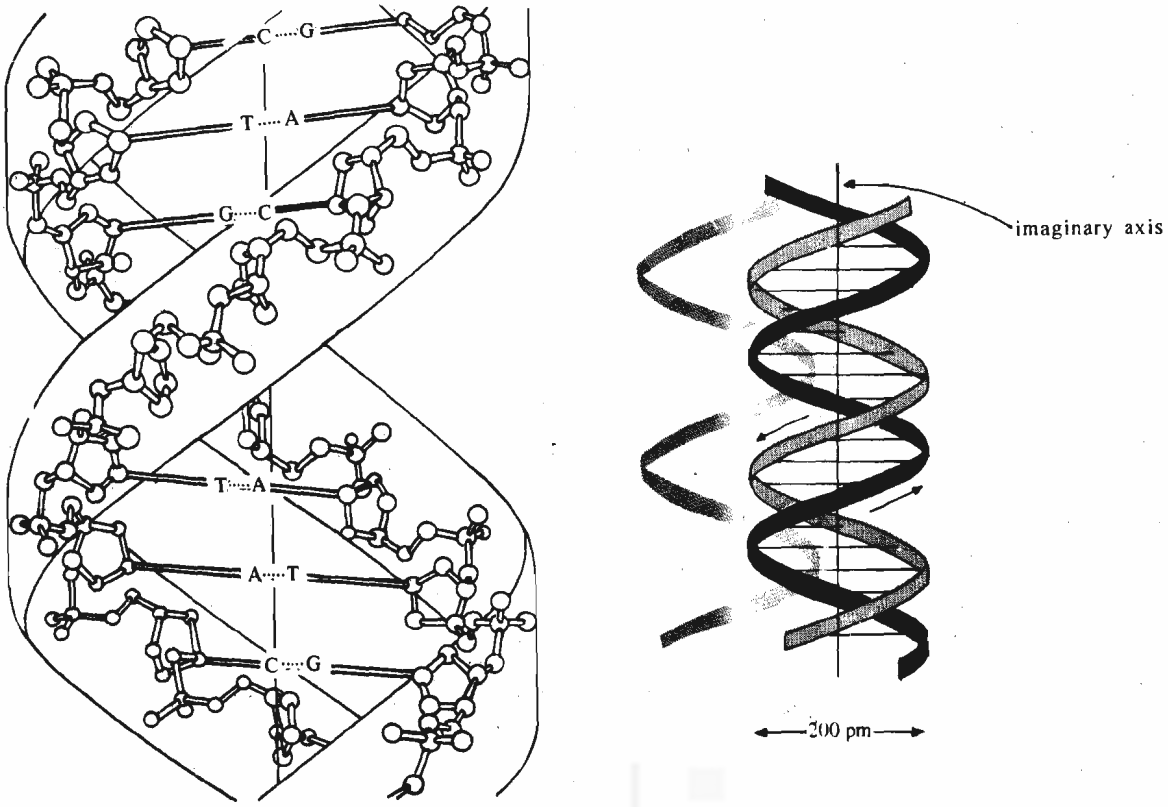


Fig. 20.6 : The double helix.

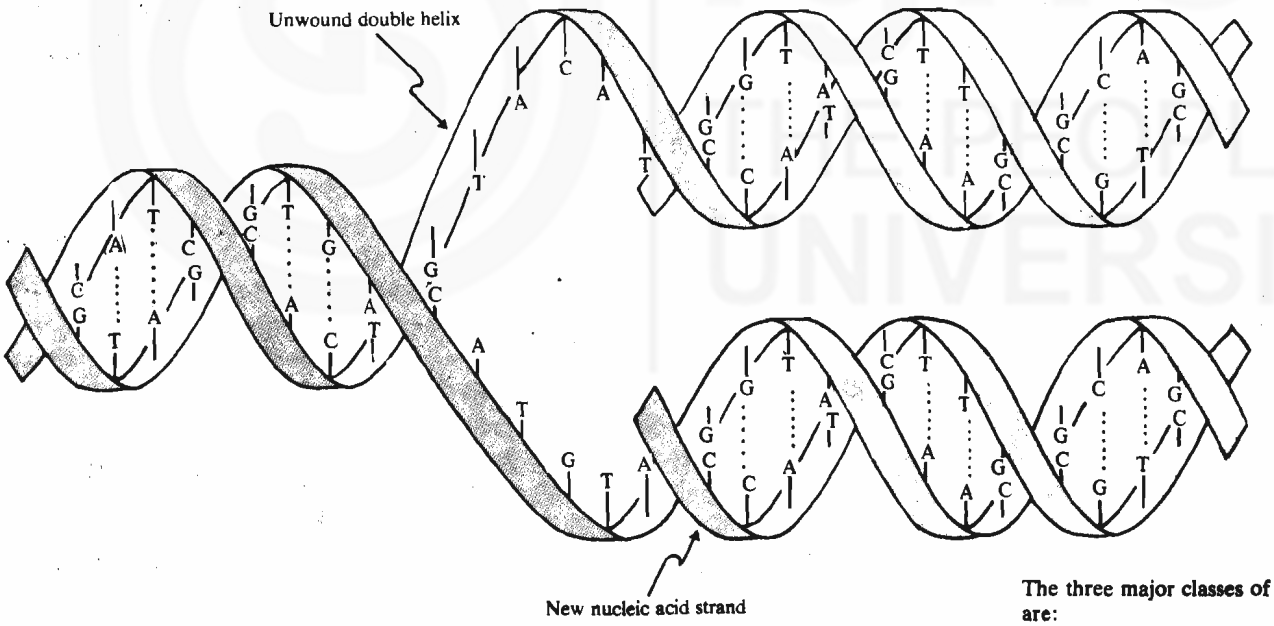


Fig. 20.7 : The DNA replication.

The synthesis of proteins involves the synthesis of a complementary strand of RNA, called **messenger RNA** by a process similar to replication of DNA. This process of formation of messenger RNA is called **transcription**. The messenger RNA sequence is used by the cell to direct the synthesis of a specific protein from the component amino acids by the process called **translation**. Each sequence of three bases, called a **codon**, specifies a particular amino acid. The 64 possible codons are listed in Table 20.3.

The three major classes of RNA are:

1) *Messenger RNA (m RNA):* It carries genetic information from DNA to the site of protein synthesis.
2) *Ribosomal RNA (r RNA):* It serves as structural material of ribosomes.
3) *Transfer RNA (t RNA):* It carries the amino acids to the ribosome for incorporation into the growing polypeptide chain.

Table 20.3 : The Codons for amino acids in protein synthesis

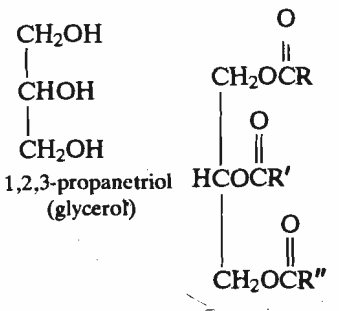
Amino acid	Base sequence	Amino acid	Base sequence	Amino acid	Base sequence
Ala	GCA GCC GCG GCU	His	CAC CAU	Ser	AGC AGU UCA UCG UCC UCU
Arg	AGA AGG CGA CGC CGG CGU	Ile	AUA AUC AUU	Thr	ACA ACC ACG ACU
Asn	AAC AAU	Leu	CUA CUC CUG CUU UUA UUG	Trp	UGG
Asp	GAC GAU	Lys	AAA AAG	Tyr	UAC UAU
Cys	UGC UGU	Met	AUG	Val	GUA GUG GUC GUU
Gln	CAA CAG	Phe	UUU UUC	Chain initiation	AUG
Glu	GAA GAG	Pro	CCA CCC CCG CCU	Chain termination	UGA UAA UAG
Gly	GGA GGC GGG GGU				

The *codons* are recognised by transfer RNA (t RNA) for a particular amino acid, and that amino acid is added to the growing peptide chain in the protein synthesis. The complete base sequence of the DNA in a cell defines its **genetic code**.

20.5 OILS AND FATS

In addition to carbohydrates and proteins, oils and fats constitute the basic food substances. They are the most concentrated form of energy. While carbohydrates serve as a source of readily available energy, an equal amount of fat gives more than twice amount of the energy. They make foods more palatable, add flavour to it and make it more satisfying.

Fats can be obtained from animal sources, i.e., from the fatty tissues of hogs, cattle, sheep and poultry. Butter is obtained from milk. Vegetable oils include oils from various plant seeds, primarily from soybean, cottonseed, corn, peanut, sunflower, olive, rapeseed, coconut, saflower and oil palm.



1,2,3-propanetriol triester
(triglyceride)

Oils and fats belong to a broader class of compounds called **lipids**. Lipids are naturally occurring substances which are soluble in organic solvents but are insoluble in water.

Oils and fats are esters of 1,2,3-propanetriol (glycerol) and long chain carboxylic acids. They are also called **triglycerides** or **glyceryl trialkanoates**.

The difference between oils and fats is that *fats* are **solid** at room temperature whereas *oils* are **liquids**. The acids found in fats are predominantly saturated in nature whereas those present in oils such as peanut oil, corn oil, coconut and soybean are unsaturated. Table 20.4 lists the saturated and unsaturated carboxylic acids commonly occurring in oils and fats.

Table 20.4 : Some representative fatty acids

Structural formula	Systematic name	Common name	m.p./K
Saturated fatty acids			
$CH_3(CH_2)_{10}COOH$	Dodecanoic acid	Lauric acid	
$CH_3(CH_2)_{12}COOH$	Tetradecanoic acid	Myristic acid	327
$CH_3(CH_2)_{14}COOH$	Hexadecanoic acid	Palmitic acid	336
$CH_3(CH_2)_{16}COOH$	Octadecanoic acid	Stearic acid	343
Unsaturated fatty acids			
$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	(*Z*)-9-Octadecanoic acid	Oleic acid	286
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$	(9*Z*, 12*Z*)-9, 12-Octadecadienoic acid	Linoleic acid	268
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7COOH$	(9*Z*, 12*Z*, 15*Z*)-9, 12, 15-Octadecatrienoic acid	Linolenic acid	257
$CH_3(CH_2)_4CH=CHCH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_3COOH$	(5*Z*, 8*Z*, 11*Z*, 14*Z*)-5, 8, 11, 14-Icosatetraenoic acid	Arachidonic acid	not accurately determined

You can see in Table 20.4 that melting points decrease with the increase in unsaturation. Thus, the melting points can be raised if the double bonds are hydrogenated. Industrially, this process is called **hardening**. The oil is heated to 423-473 K and hydrogen is passed under pressure in the presence of nickel catalyst to yield solid fats which are used in the manufacture of soap and as cooking medium for foods.

Certain unsaturated fatty acids are termed as *essential* because their absence in human diet may cause scaley skin, stunted growth and increased water loss from the skin.

Esters formed from cholesterol with saturated fatty acids are solids and, hence, deposit on the walls of blood vessels causing diseases of heart and arteries. Thus, for health considerations, the unsaturated vegetable oils are becoming increasingly popular over the animal fats and margarines which are rich in saturated fatty acids.

20.5.1 Analysis of Oils and Fats

In addition to their physical constants such as melting point, density and refractive index, oils and fats are characterised in terms of certain chemical tests which gives an idea about their nature. These tests involve the determination of **acid value, saponification value** and **iodine value.**

Acid value of an oil or a fat is the number of milligrams of potassium hydroxide required to neutralise one gram of an oil or a fat. This tells us about the amount of free acid present in the oil or fat.

Sponification value is the number of milligrams of potassium hydroxide required to neutralise the acids resulting from complete hydrolysis of one gram of the oil or fat. Since mineral oils which are hydrocarbons, do not react with alkali, this enables us to estimate the fat or oil present in a mixture of fatty oils and mineral oils.

The **iodine value** is the number of grams of iodine that combines with 100 grams of oil or fat. This indicates the degree of unsaturation of the acids present in oil or fat.

Till now you were studying about primary metabolites. We will now shift our focus to secondary metabolites such as terpenes, steroids and alkaloids. Finally, you will also study about *antibiotics* which are chemical substances produced by micro-organisms.

SAQ 3

What is the difference between an oil and a fat?

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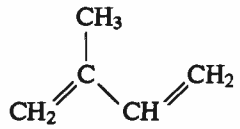
.....

20.6 TERPENES

The term *essential oil* has been applied in two different ways in the context of natural products. As used in the previous section with respect to fatty acids, **essential** meant

necessary. But it is also used as the adjective of the noun **essence**. Mixtures of **volatile, pleasant smelling** substances obtained by steam distillation of flowers, leaves or other parts of plants are called **essential oils**.

Essential oils have been used in perfumes and as flavours. Many of them also have medicinal uses. Very often, the principal volatile component of essential oils belongs to a class of compounds called **terpenes**.



2-methyl-1, 3-butadiene (isoprene)

Terpenes contain a characteristic structural unit called 2-methyl-1, 3-butadiene (**isoprene**) unit, therefore, they are also referred to as **isoprenoids**. Terpenes can be classified according to the number of carbon atoms present in their molecules as shown in Table 20.5.

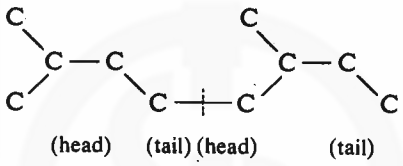
Table 20.5 : Classification of terpenes

Class	No. of carbon atoms
Monoterpene	10
Sesquiterpene	15
Diterpene	20
Sesterpene	25
Triterpene	30
Tetraterpene	40

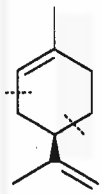
Structures of terpenes belonging to various classes are shown below.

Note the head to tail linkage of 2-methyl-1, 3-butadiene units in these structures.

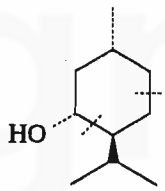
Monoterpenes



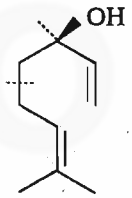
(head) (tail) (head) (tail)



R-(+)-limonene (from oil of oranges and lemon)

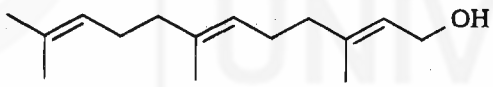


(−)-menthol (from peppermint oil)

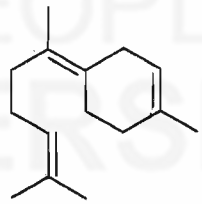


R-(−)-Linalool (from rose oil)

Sesquiterpenes

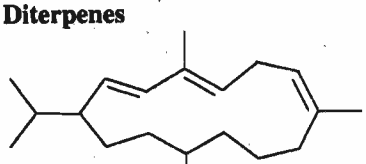


farnesol (from ambrette)

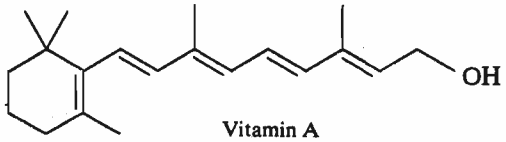


bisabolol (from chamomile and lavender oils)

Diterpenes

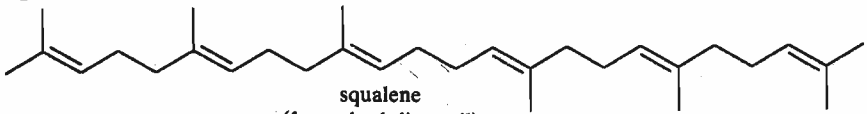


Cembrene (from pine)



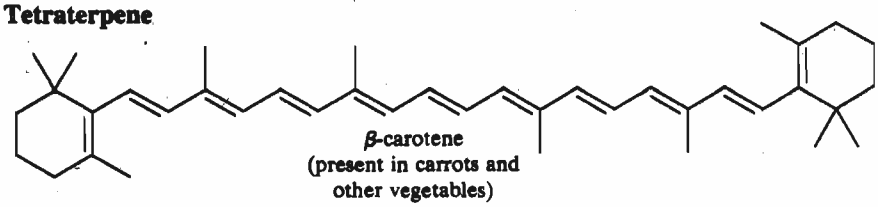
Vitamin A (present in mammalian tissue and fish oil)

Triterpene



squalene (from shark liver oil)

Tetraterpene



β-carotene (present in carrots and other vegetables)

SAQ 4

Mark 2-methyl-1, 3-butadiene units in β-carotene.

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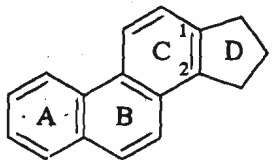
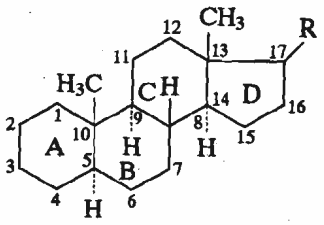
20.7 STEROIDS

Steroids are related to terpenes as they are bio-synthesised by a similar route.

The basic skeleton of steroids contains a hydrogenated 1,2-cyclopentenophenanthrene system.

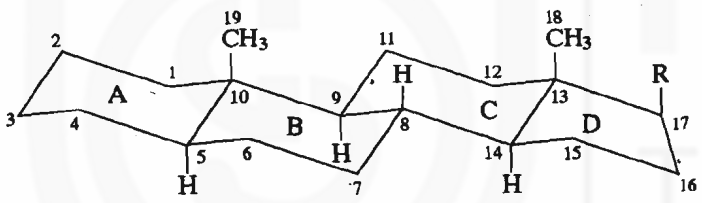


basic steroid ring structure

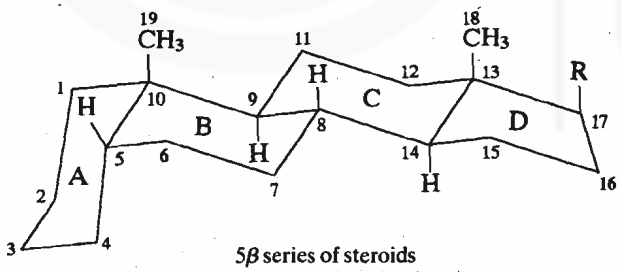


1,2-cyclopenteno-phenanthrene

In most steroids B, C and C, D ring junctions are *trans*. The A, B junction may be either *cis*- or *trans*-leading to two general groups of steroids having the three-dimensional structures as shown below.

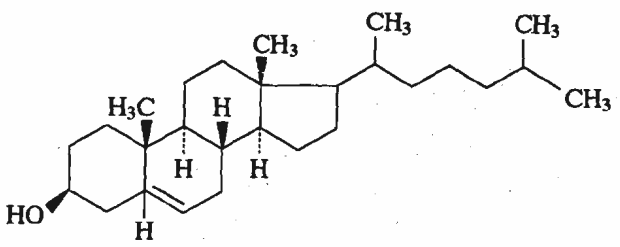


5α series of steroids
(all ring junctions are *trans*)



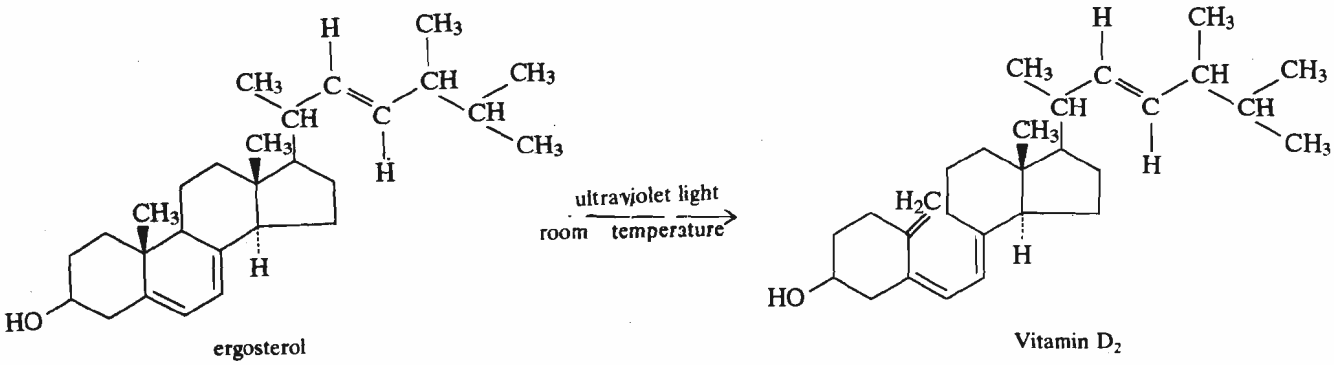
5β series of steroids
(A, B ring junction is *cis*)

Cholesterol is an important steroid. It is found in almost all animal tissues but is particularly abundant in the brain, spinal cord and gall stones. Its deposition in the arteries restricts the flow of blood causing high blood pressure and some forms of cardiovascular diseases.



Cholesterol

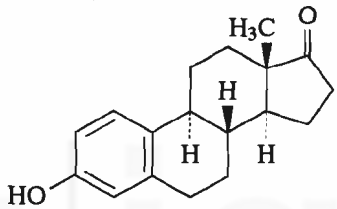
Although cholesterol is found only in animals, a large number of similar compounds are found in plants. These are called **phytosterols**. One such example is **ergosterol** which on irradiation yields calciferol, vitamin D_2.



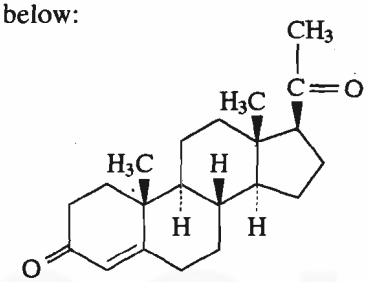
ergosterol

Vitamin D_2

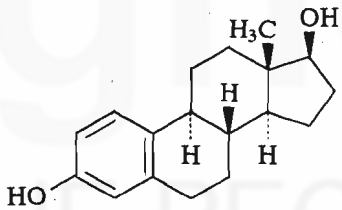
Among other important steroids are sex hormones and adrenocortical hormones. The examples of female sex hormones, called **estrogens**, include estrone, progesterone and estradiol. Their structures are shown below:



estrone

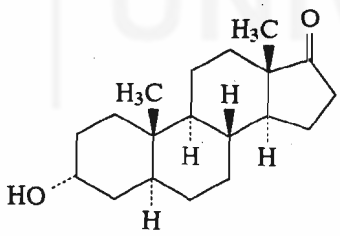


progesterone

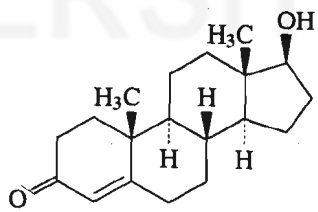


estradiol

The male sex hormones are called **androgens**. The examples are androsterone and testosterone.

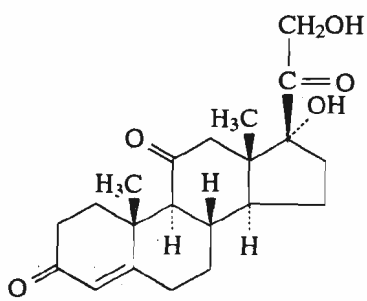


androsterone

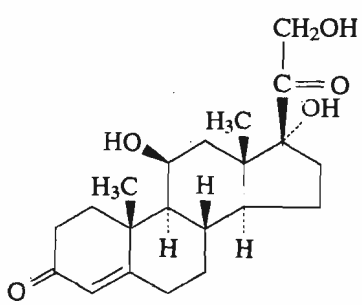


testosterone

The examples of adrenocortical hormones are cortisone and cortisol.



Cortisone



cortisol

They are involved in the regulation of a large number of biological activities such as metabolism of carbohydrates, proteins and lipids, water and electrolyte balance, and reactions to allergic and inflammatory phenomena. Cortisone has been used for the treatment of rheumatoid arthritis. Other steroids oxygenated at 11 position have also been used for treating asthama and the inflammations.

20.8 ALKALOIDS

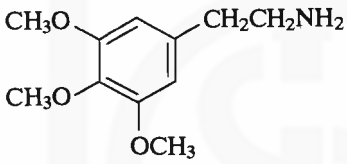
Alkaloids have been defined in Sec. 19.2, Unit 19, as amines of plant origin. They were called so because of their basic or **alkali like** properties.

Alkaloids are usually found in the seeds, roots, leaves or bark of the plants in the form of salts of acids. They can be extracted from dry, powdered plant material by extraction with methanol. After removal of the solvent, the residue is treated with inorganic acids which yield salts of the basic components.

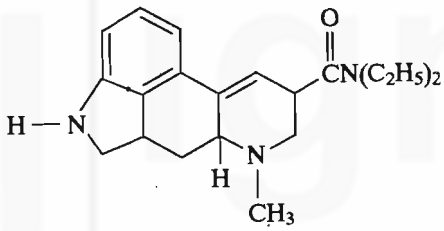
Free bases are liberated by treating the salts with sodium carbonate. Extraction of free bases using chloroform or ether yields a mixture which is separated into individual compounds by various methods including chromatographic methods.

Alkaloids can be classified, according to the nature of the basic structural moiety present in the molecule, into various groups. Representative alkaloids of some of these classes along with their physiological effects are given below:

1) Phenylethylamine alkaloids



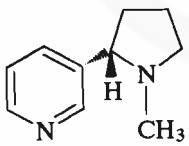
mescaline
(hellucinogen from various species of cactus)



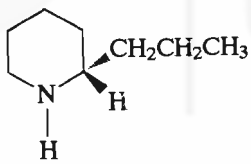
lysergic acid diethylamide
(LSD)
(hellucinogen)

Hallucinogens produce distortion of perception, vivid images or hallucinations.

2) Alkaloids containing a pyridine or piperidine ring

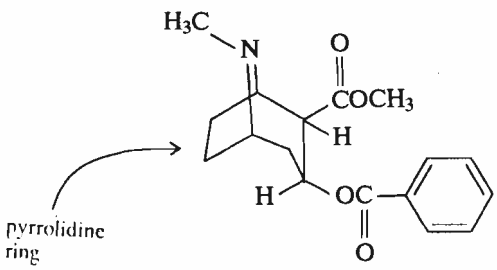


nicotine
(principal alkaloid of tobacco)

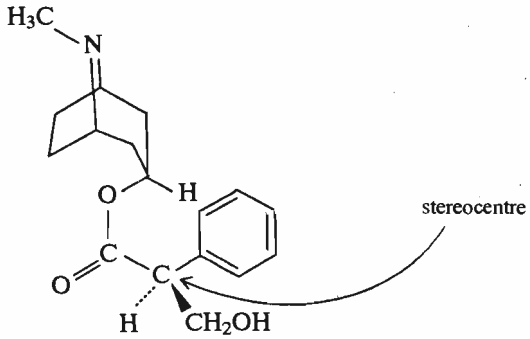


coniine
(from the posion hemlock)

3) Tropane alkaloids

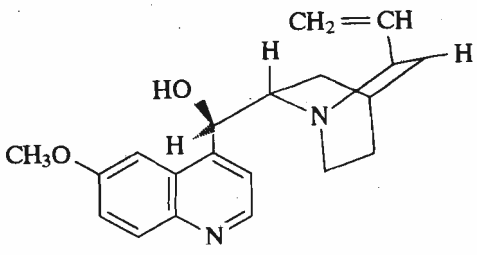


cocaine
(local anaesthetic, stimulant)
(from coca leaves)



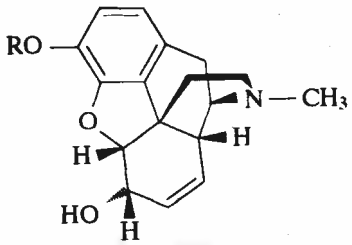
atropine
(a stimulant)

4) Quinoline alkaloids

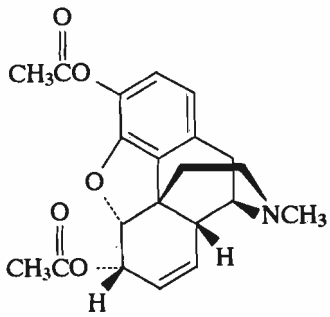


quinine
(antimicrobial, antimalarial)
(from cinchona bark)

5) Isoquinoline alkaloids

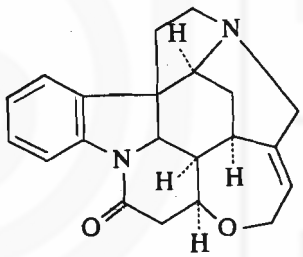


morphine (R=H)
codeine (R=CH_3)
(analgesic from opium)

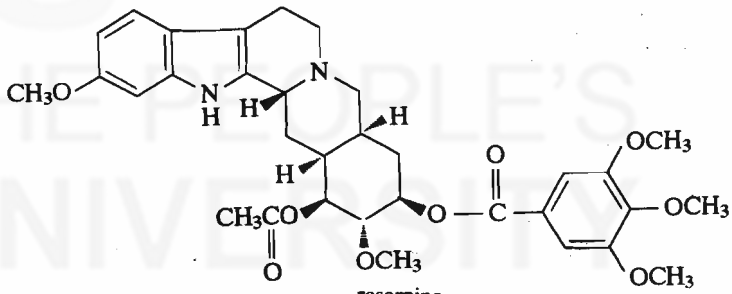


heroin
(diethanoyl derivative
of morphine)

6) Indole alkaloids



strychnine
(rodent poison,
resolving agent)
(from seeds of
strychnos nuxvomica)



reserpine
(tranquiliser, reduces
blood pressure)
(from Indian snake root
Rauwolfia serpentina)

SAQ 5

Write the structure of heterocyclic nucleus present in indole alkaloids and isoquinoline alkaloids.

.....

.....

.....

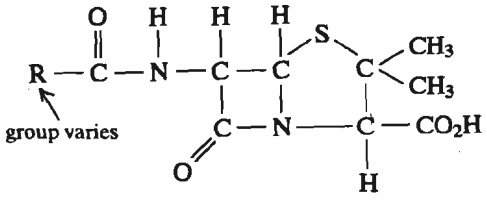
20.9 ANTIBIOTICS

In this section, you will study about the chemical substances produced by microorganisms which inhibit the growth or metabolism of other microorganisms, called *antibiotics*.

In Unit 16, you studied about treatment of bacterial infections by sulpha drugs.

The first antibiotic, **penicillin**, was discovered by Fleming in 1929 from the mold *Penicillium notatum*. It inhibited the growth of certain bacteria.

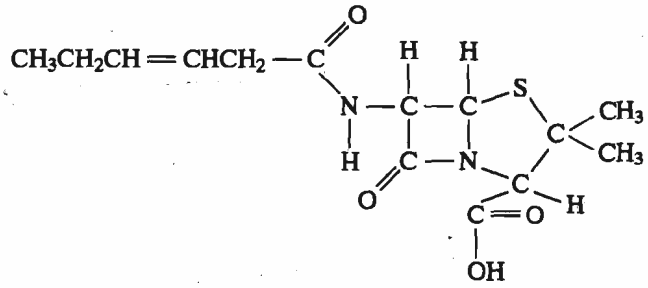
The general structure of penicillin is given below:



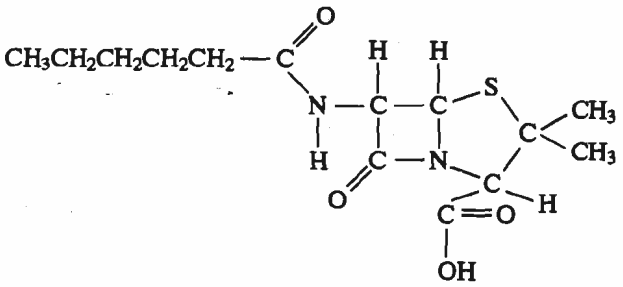
basic penicillin structure

Penicillin acts by inhibiting an enzyme which catalyses the synthesis of cell walls of reproducing bacteria. The new cells have defective cell walls and cell contents leak out, and the cell dies. Since the cell wall material of bacteria and of human beings is different, penicillin is used to treat bacterial infections in humans.

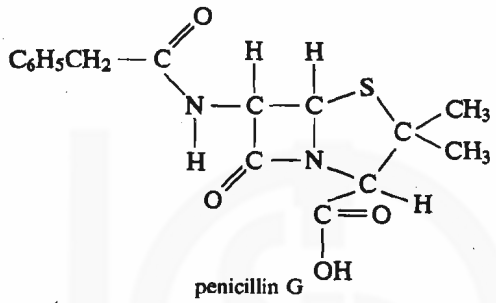
There are at least six natural penicillins depending upon the nature of group R. Their structures are shown below:



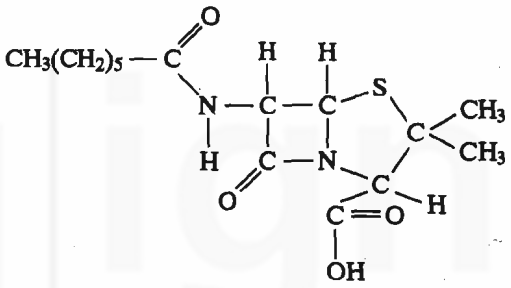
penicillin F (pent-2-enylpenicillin)



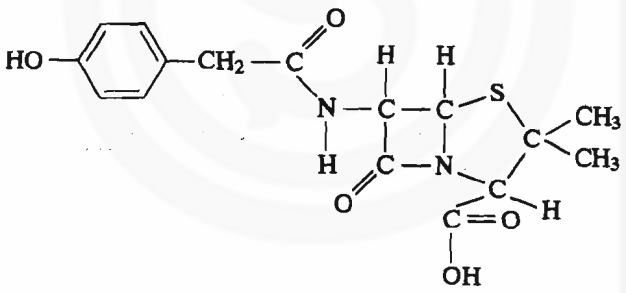
dihydro-F-penicillin



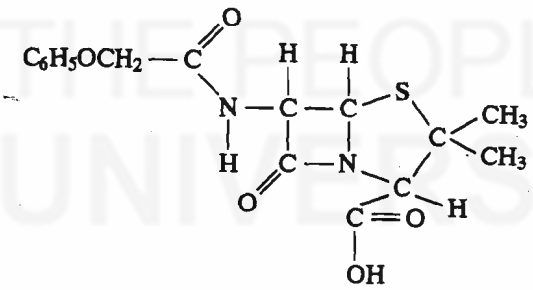
penicillin G
(Benzylpenicillin)



penicillin K (Heptyl penicillin)



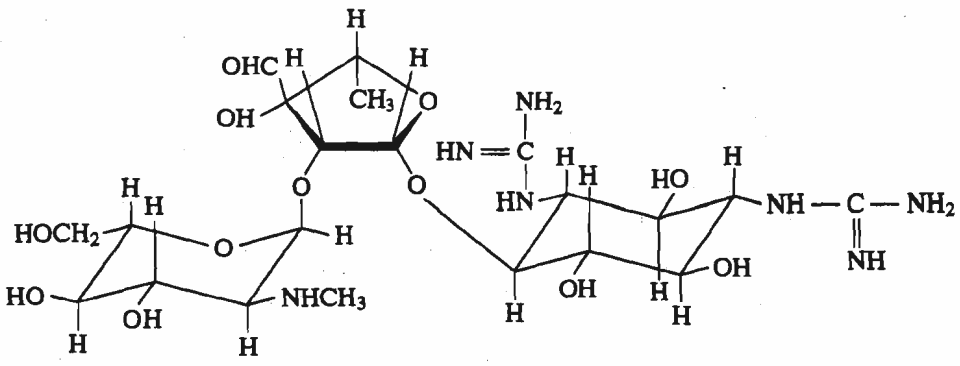
penicillin X (4-Hydroxybenzylpenicillin)



phenoxymethylpenicillin

Antibiotics include compounds having a wide range of structures. Some examples are streptomycin, chloroamphenicol and tetracycline antibiotics.

Streptomycin

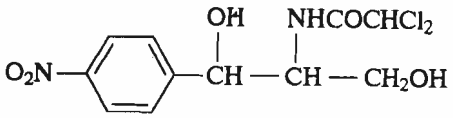


Streptomycin

Note that it contains two sugar units and a hexasubstituted cyclohexane unit.

It is used in the treatment of tuberculosis, meningitis and pnuemonia.

Chloramphenicol

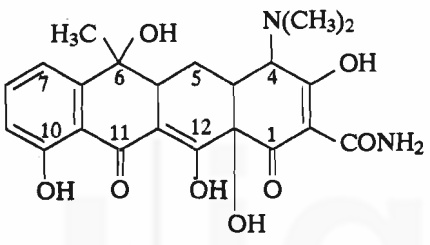


Chloramphenicol

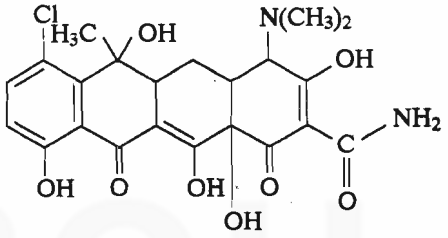
It is a broad spectrum antibiotic isolated in 1947. It is used in the treatment of typhoid, dysentery, acute fever and certain urinary infections.

Tetracylines

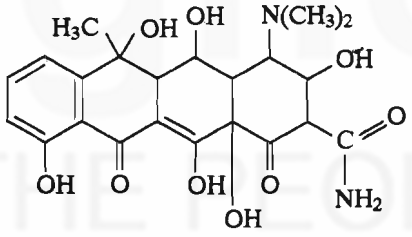
The basic nucleus of tetracycline antibiotics consists of four 6-membered rings fused to each other. Tetracycline, its 7-chloro derivative, aureomycin and its 5-hydroxy derivative, terramycin, are **broad spectrum** antibiotics which are used against a number of bacterial and viral diseases. Tetracyclines have also been used when the patient is allergic to penicillin.



tetracycline



aureomycin



terramycin

20.10 SUMMARY

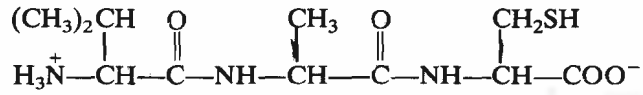
In this unit, you learnt that

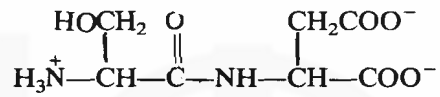
- Natural products such as carbohydrates, nucleic acids, proteins and fats have an important role in the functioning of organisms and are called **primary metabolites.** These are present in almost all organisms.
- Natural occurrence of **secondary metabolites** such as terpenes and alkaloids is species dependent and they also have a wide variety of characteristic uses.
- Carbohydrates are naturally occurring polyhydroxy carbonyl compounds and can be classified as monosaccharides, oligosaccharides (disaccharides, trisaccharides, etc.) and polysaccharides. The structures of carbohydrates belonging to each of the above classes were considered in detail.
- Two important nucleic acids are DNA and RNA.
- DNA has double helical structure and acts as a template during DNA replication and RNA Synthesis.
- DNA is indirectly involved in the protein synthesis. In protein synthesis, each amino acid is specified by a set of three consecutive RNA bases, called a codon. This base sequence or the genetic code in RNA is translated to a specific amino acid sequence in proteins.
- Oils and fats are esters of 1,2,3-propane-triol. They also constitute concentrated source of energy.

- Oils and fats are characterised by their acid values, sponification values and iodine values.
- 2-methyl-1, 3-butadiene is the characteristic structural unit in terpenes which are present in essential oils.
- Terpenes can be classified as mono-, sesqui-, di-, ses-, tri- and tetraterpenes. Various examples of these classes of terpenes were considered.
- Alkaloids are physiologically active basic compounds of plant origin. The examples of alkaloids illustrate that they can be classified into various categories depending upon the type of nucleus present in the molecule.
- Finally the natural products obtained from micro-organisms called antibiotics were discussed. Some examples were taken to show the wide variety of antibiotics and their uses.

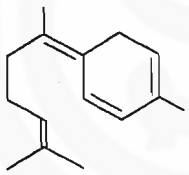
20.11 TERMINAL QUESTIONS

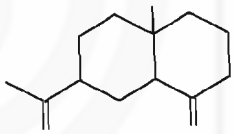
1) Write the structures and names of the D-aldoses which you have studied in Table 20.1.
2) What is the number of possible aldoheptoses?
3) Idenfity the peptide bonds in the following:

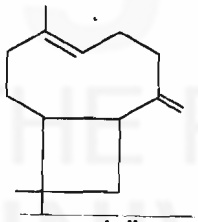
a) 

b) 

4) Define iodine value and give its significance.
5) Classify the following terpenes as monoterpenes, diterpenes and so on.

a) 
zingiberine
(from oil of ginger)

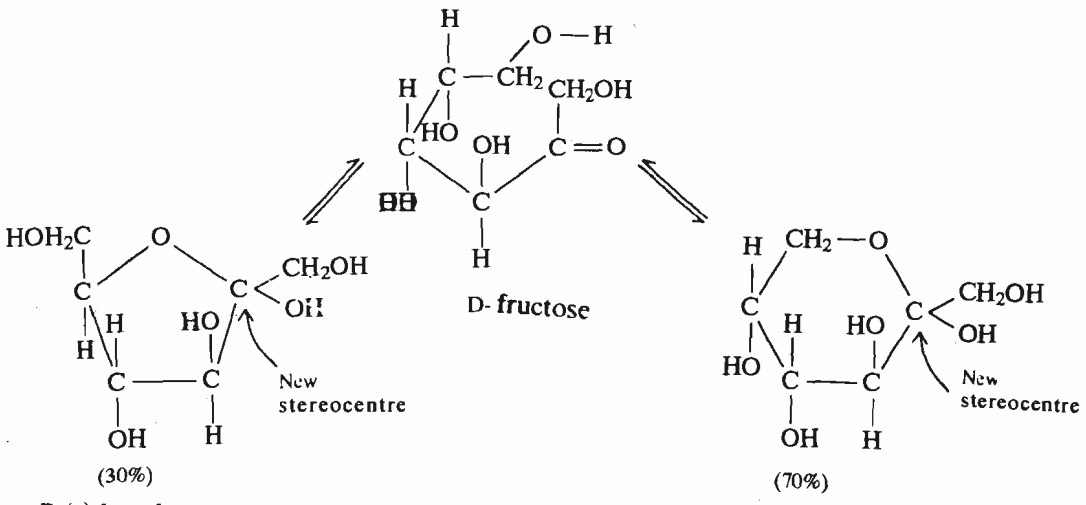
b) 
β-selinene
(from oil of celery)

c) 
caryophyllene
(from oil of cloves)

20.12 ANSWERS

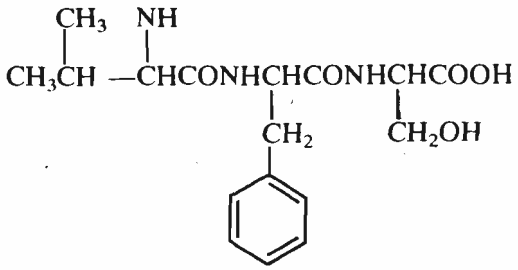
Self Assessment Questions

1) **Cyclic Hemiacetal Formation by Fructose**



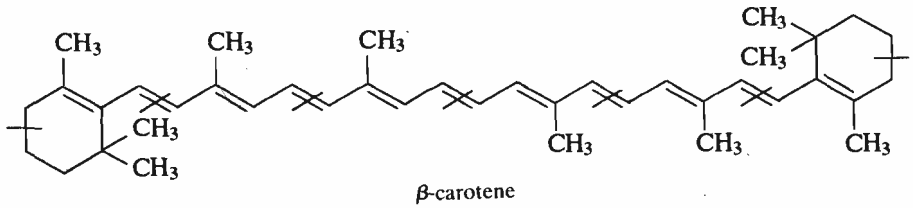
(30%)
D-(–)-fructofuranose

(70%)
D(–)-fructopyranose

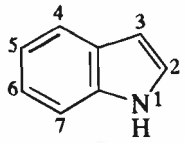
2) 

3) a) An oil is liquid at room temperature whereas a fat is solid.

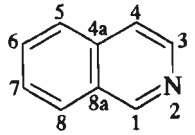
b) Oils are esters of unsaturated long chain carboxylic acids whereas fats are esters of saturated long chain carboxylic acids.

4) 

β-carotene

5) 

indole

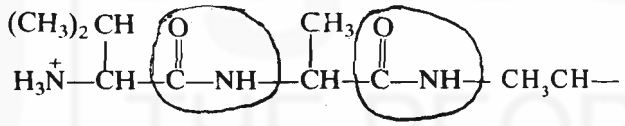


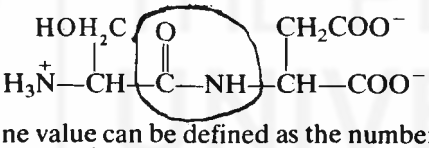
isoquinoline

Terminal Questions

1) See sub-Sec. 20.2.1.

2) 32, 16 D isomers and 16 L isomers.

3) a) 

b) 

4) Iodine value can be defined as the number of grams of iodine that combines with 100 gms of an oil or a fat. It indicates the amount of unsaturation in the carboxy part of the fat or oil.

5) a) Sesquiterpene b) Sesquiterpene
c) Sesquiterpene

Further Readings

1) *Organic Chemistry*, 6th Ed., By R.T. Morrison and R.N. Boyd, Prentice-Hall of India Pvt. Ltd.

2) *Text Book of Organic Chemistry*, 2nd Ed., by Lloyd N. Ferguson, Affiliated East-West Press Pvt. Ltd.

3) *Organic Chemistry*, Vol. I and II by S.M. Mukherji, S.P. Singh and R.P. Kapoor, Wiley Eastern Ltd.

4) *Text Book of Organic Chemistry*, 2nd Ed., by P.L. Soni and H.M. Chawla, Sultan Chand and Sons.