Syllabus

B.Sc. IIIrd Year (M.D.U.)

SIXTH SEMESTER

Organic Chemistry

SECTION–A

Heterocyclic Compounds-I

Introduction : Molecular orbital picture and aromatic characteristics of pyrrole, furan, hiophene and pyridine. Methods of synthesis and chemical reactions with particular mphasis on the mechanism of electrophilic substitution. Mechanism of nucleophilic ubstitution reactions in pyridine derivatives. Comparison of basicity of pyridine, piperidine and pyrrole.

SECTION–B

1. Heterocyclic Compounds - II

Introduction to condensed five and six-membered heterocycles. Preparation and reactions of indole, quinoline and isoquinoline with special reference to Fisher indole synthesis, Skraup synthesis and Bischler-Napieralski synthesis. Mechanism of electrophilic substitution reactions of, quinoline and isoquinoline.

2. Organosulphur Compounds

Nomenclature, structural features, Methods of formation and chemical reactions of thiols, thioethers, sulphonic acids, sulphonamides and sulphaguanidine. Synthetic detergents alkyl and aryl sulphonates.

SECTION–C

1. Organic Synthesis *via* Enolates

Acidity of α-hydrogens, alkylation of diethyl malonate and ethyl acetoacetate. Synthesis of ethyl acetoacetate : the Claisen condensation. Keto-enol tautomerism of ethyl acetoacetate.

2. Synthetic Polymers

Addition or chain-growth polymerization. Free radical vinyl polymerization, ionic vinyl polymerization, Ziegler-Natta polymerization and vinyl polymers.

Condensation or step growth polymerization. Polyesters, polyamides, phenol formaldehyde resins, urea formaldehyde resins, epoxy resins and polyurethanes.

Natural and synthetic rubbers.

SECTION–D

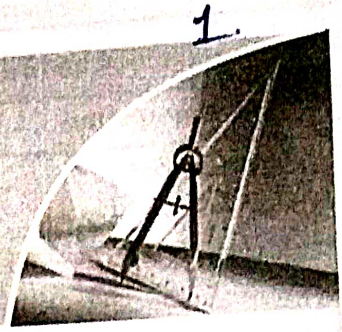
Amino Acids, Peptides and Proteins

Classification of amino acids, Acid-base behavior, isoelectric point and electrophoresis. Preparation of α-amino acids.

Structure and nomenclature of peptides and proteins. Classification of proteins. Peptide structure determination, end group analysis, selective hydrolysis of peptides. Classical peptide synthesis, solid-phase peptide synthesis. Structures of peptides and proteins : Primary and secondary structure.

Chapter 1

Organosulphur Compounds

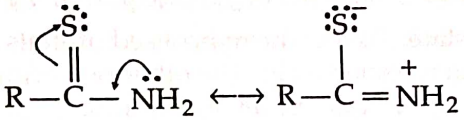


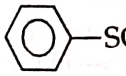
1.1. INTRODUCTION

Sulphur is known to form many organic compounds which may be considered as sulphur-containing counter parts of compounds having oxygen. For instance thiols (R — S— H) are sulphur analogues of alcohols (R — O — H) and thioethers (R — S — R') are sulphur analogues of ethers (R—O—R'). The chemical behaviour of these sulphur compounds is quite similar to corresponding compounds containing oxygen.

Sulphur (atomic number 16) lies below oxygen in the periodic table. Compared to oxygen, its atomic size is quite large. As a result, organic compounds which are sulphur-containing counterparts of carbonyl compounds (*i.e.* compounds having carbon-sulphur double bond, C = S) are not known to exist commonly. This is due to the reluctance of **large sized** sulphur atoms to form π bonds by **sideways overlap** of its 3*p* orbitals with the *p*-orbitals of the other atoms. Thus sulphur atoms neither form 3*p*-3*p* π bonds amongst themselves (*remember that sulphur exists in cyclic S_8 structure having only σ bonds*) nor do they form stable π bonds with other atoms such as carbon by 3*p*-2*p* overlapping.

It may be pointed out, however, that some thiocarbonyl compounds such as thiocarbamides do exist in a relatively stable form. This may be due to resonance which decreases the double bond character of thiocarbonyl (*i.e.* C = S) group as shown below :



It is interesting to note that there also exist many organosulphur compounds containing sulphur-oxygen bonds with large double bond character. Sulphoxides such as dimethylsulphoxide $(CH_3)_2$ SO and sulphonic acids such as benzene sulphonic acid  are common examples of such compounds. The formation of such compounds can be explained in terms of **pπ-dπ** bonding as explained a little later by considering the structural features of sulphonic acids.

THIOLS

Thiols or thioalcohols are sulphur-containing counterparts of alcohols. They contain the group **— SH** in their molecules and may be represented as **R—SH.** The prefix **thio** indicates that sulphur has replaced oxygen of the alcohols.

Thiols react with mercuric oxide to form mercuric salts and are, therefore, also known as **mercaptans** (*mercurium* = mercury ; *captans* = catching).

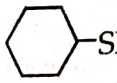
They may also be treated as alkyl derivatives of hydrogen sulphide and are, therefore, sometimes referred to as **hydrosulphides.**

1.2. NOMENCLATURE

In the **common system,** thiols are named by adding the word **mercaptan** (*as a separate word*) to the name of alkyl group attached to — SH.

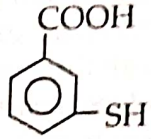
In the **IUPAC system,** they are named in the same way as alcohols except that the suffix used is **thiol** (in place of *-ol*).

The common and IUPAC names of a few thiols are given below :

Compound	Common Name	IUPAC Name
CH_3SH	Methyl mercaptan	Methanethiol
$CH_3—CH_2SH$	Ethyl mercaptan	Ethanethiol
$CH_3—\underset{\displaystyle SH}{\underset{\vert}{CH}}—CH_3$	Isopropyl mercaptan	Propane-2-thiol
$CH_3CH_2CH_2CH_2SH$	*n*-Butyl mercaptan	Butane-1-thiol
	Cyclohexyl mercaptan	Cyclohexanethiol

In compounds which also contain other functional groups of higher priority, — SH group is denoted by the prefix **mercapto.** It may be noted that — OH group is assigned higher priority than — SH both in numbering and naming. Thus we have :

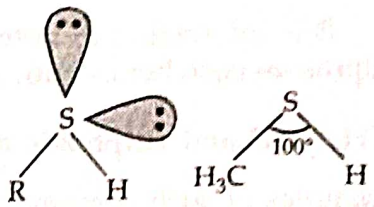
$HSCH_2CH_2OH$
2–Mercaptoethanol



3-Mercaptobenzoic acid

1.3. STRUCTURAL FEATURES

Sulphur (electronic configuration $3s^2, 3p_x^2, 3p_y^1, 3p_z^1$) takes part in the formation of thioalcohols in sp^3 hybridised form in the ground state. Two of the hybridised orbitals having one electron each form σ bonds with carbon and hydrogen respectively. The other two orbitals contain a lone pair of electrons in each of them. Therefore as in case of alcohols, thiol molecules also have bent structure although the C—S— H bond angle is lesser than C—O—H angle in alcohols. For example, methanethiol may be represented as :



Like alcohols, thiols are also polar compounds although the degree of polarity of S—H bond is very low as compared to the high degree of polarity of O—H bond. This is because the electronegativity of sulphur is much less than that of oxygen.

1.4. METHODS OF FORMATION

Thiols may be prepared by the following methods of preparation :–

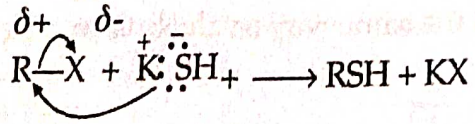
1. From alkyl halides. Thiols can be prepared by heating alkyl halides with excess of potassium or sodium hydrosulphide.

$$R—X + KSH \longrightarrow RSH + KX$$

For example :

$$C_2H_5I + KSH \longrightarrow \underset{\text{Ethanethiol}}{C_2H_5SH} + KI$$

Mechanism. The reaction is a typical nucleophilic substitution reaction of alkyl halides with hydrosulphide anion, $\bar{S}H$.



If hydrosulphide is not used in excess, considerable amount of thioethers may also be formed by further reaction as shown below :

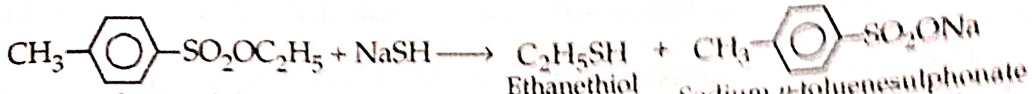
$$RSH + KSH \rightleftharpoons RS^-K^+ + H_2S$$
$$RS^-K^+ + RX \longrightarrow \underset{\text{Dialkyl thioether}}{RSR} + KX$$

(2) From sodium alkyl sulphates or p-toluenesulphonic esters.

Thiols can also be prepared by heating sodium hydrosulphide with sodium alkyl sulphates or *p*-toluenesulphonic esters.

For example :

$$\underset{\text{Sodium ethyl sulphate}}{C_2H_5OSO_3Na} + NaSH \longrightarrow \underset{\text{Ethanethiol}}{C_2H_5SH} + Na_2SO_4$$



Ethyl *p*-toluenesulphonate — Ethanethiol — Sodium *p*-toluenesulphonate

(3) From alcohols

(i) By passing a mixture of alcohol vapours and hydrogen sulphide over heated thoria catalyst.

$$ROH + H_2S \xrightarrow{ThO_2,\ 675\ K} RSH + H_2O$$

For example : $CH_3CH_2CH_2OH + H_2S \xrightarrow{ThO_2,\ 675\ K} \underset{\text{Propane-1-thiol}}{CH_3CH_2CH_2SH} + H_2O$

(ii) By heating an alcohol with phosphorus penta or tri sulphide.

$$5ROH + P_2S_5 \longrightarrow 5RSH + P_2O_5$$

For example :

$$5C_2H_5OH + P_2S_5 \longrightarrow \underset{\text{Ethane thiol}}{5C_2H_5SH} + P_2O_5$$

(4) From Grignard reagents. Reaction of Grignard reagent with sulphur followed by hydrolysis also leads to the formation of thiols.

$$R-MgX + S \xrightarrow{\text{Ether}} R-SMgX \xrightarrow{H_3O^+} RSH + Mg(OH)X$$

For example :

$$C_2H_5MgBr + S \xrightarrow{\text{Ether}} C_2H_5MgBr \xrightarrow{H_3O^+} \underset{\text{Ethane thiol}}{C_2H_5SH} + Mg(OH)Br$$

(5) From alkenes. Alkenes add on hydrogen sulphide to form thiols in accordance with Markownikoff's rule. For example,

$$\underset{\text{Propene}}{CH_3-CH=CH_2} + H_2S \xrightarrow{NiS,\ 575\ K} \underset{\text{Propane-2-thiol}}{CH_3-CHS-CH_3}$$

In the presence of organic peroxide, however, anti-Markownikoff's addition takes place.

(6) Hydrolysis of thioesters. When hydrolysed in acidic or basic medium, thioesters yield thiols.

$$R-\overset{\overset{O}{\|}}{C}-SR' + H_2O \xrightarrow{OH^- \text{ or } H^+} RCOOH + R'SH$$

For example :

$$CH_3-\overset{\overset{O}{\|}}{C}-SC_2H_5 + H_2O \xrightarrow{OH^- \text{ or } H^+} \underset{\text{Ethanethiol}}{CH_3COOH} + C_2H_5SH$$

Ethyl thioacetate

(7) By reaction between alkyl halide and thiourea. Probably the best method for the laboratory preparation of thiols is by reaction between alkyl halide and thiourea $[(NH_2)_2 C = S]$, which is a strong nucleophile. A nucleophilic substitution reaction takes place to form an intermediate S-alkyl isothiouronium salt. This salt on hydrolysis with a base gives thiol in excellent yield. For example :

$$\underset{n\text{-Butyl bromide}}{CH_3(CH_2)_2CH_2-Br} + :\ddot{S}=C\begin{matrix}NH_2\\NH_2\end{matrix} \longrightarrow \left[CH_3(CH_2)_2CH_2-\overset{+}{S}=C\begin{matrix}NH_2\\NH_2\end{matrix}\right] Br^- \xrightarrow[(ii)\ H_3O^+]{(i)\ OH^-}$$

S-Alkyl iso thiouronium bromide

$$\underset{\text{Butane-1-thiol}}{CH_3(CH_2)_2CH_2SH} + O=C\begin{matrix}NH_2\\NH_2\end{matrix}$$

Urea

1.5. PHYSICAL PROPERTIES

(1) Physical State. Methanethiol is a gas while higher thiols are colourless volatile liquids at room temperature. Lower members have extremely strong and offensive smell while higher members have mild odour. (The odour of freshly chopped onions is due to propane-1-thiol while that of garlic is partly due to prop-2-ene-1-thiol ($CH_2 = CH - CH_2SH$)

Small quantities of ethanethiol are added to LPG to serve as odour based warning against leakage of the gas.

(2) Boiling points. Due to lack of intermolecular hydrogen bonding in them, boiling points of lower thiols are lesser than those of corresponding alcohols. However, thiols having eight or more carbon atoms have slightly higher boiling points than corresponding alcohols. This is because the molecular masses of thiols are somewhat higher than those of alcohols while the hydrogen bonding in higher alcohols is not significant.

(3) Solubility. Thiols are practically insoluble in water. This is due to non-formation of hydrogen bonding between thiols and water.

1.6. CHEMICAL PROPERTIES

The chemical behaviour of thiols is, in general, similar to that of alcohols but the two classes of compounds also differ from each other in certain respects. The differences in their behaviour are essentially due to following reasons :

(*i*) Sulphur atom has larger size and smaller electronegativity than oxygen.

(*ii*) Sulphur can be easily oxidised to higher oxidation states.

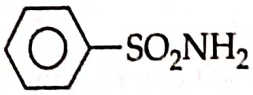
The important reactions of thiols are discussed below :

(1) Acidic nature. Thiols are **weakly acidic** in nature but their acidic character is considerably stronger than that of alcohols (*e.g.*, pk_a of C_2H_5SH is 8·5 while that of C_2H_5OH is 15·9)

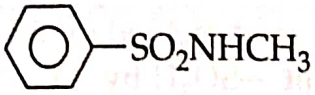
1.17. SULPHONAMIDES

Sulphonamides are derivatives of sulphonic acids in which —OH group of the sulphonic acid has been replaced by —NH_2 group. Substituted sulphonamides carry the group —NHR or —NR_2 in place of —NH_2.

For example :



Benzenesulphonamide



N-Methylbenzenesulphonamide

1.17.1. PREPARATION

Sulphonamides are generally prepared by the action of ammonia on corresponding sulphonyl chlorides. For example :

Benzene sulphonyl chloride

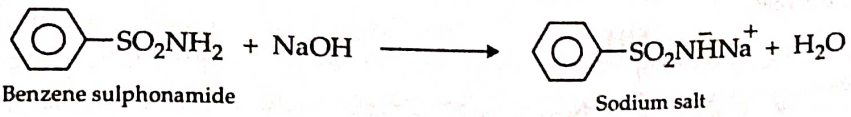
Benzene sulphonamide

1.17.2 PROPERTIES

(1) *Sulphonamides* are well-defined crystalline solids and are, therefore, used to characterise *sulphonic acids.*

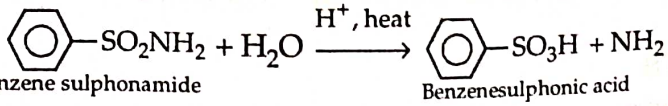
(2) *They are weakly* acidic in nature and react with strong alkalies to form water soluble salts.

For example :



Benzene sulphonamide — Sodium salt

(3) They are hydrolysed on heating with aqueous acids to form sulphonic acid and ammonia. For example :

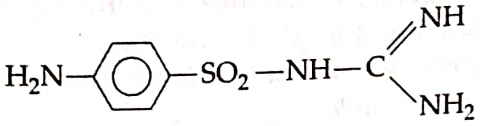


Benzene sulphonamide — Benzenesulphonic acid

1.17.3. USES

They are used as laboratory reagents and in the manufacture of dyes and drugs called sulpha drugs.

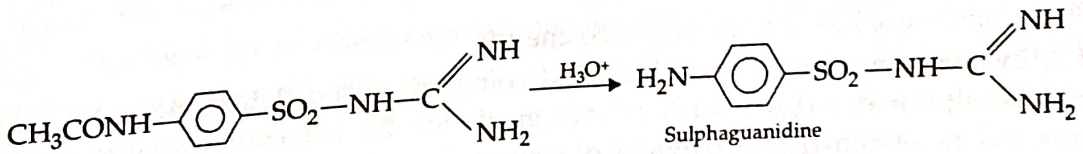
1.18. SULPHAGUANIDINE



Synthesis. It can be synthesised by the following methods :

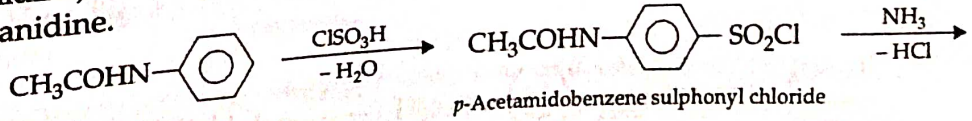
(1) *p*-Acetamidobenzene sulphonyl chloride (obtained by the action of chlorosulphonic acid on acetanilide) is treated with guanidine ($H_2N—\overset{\overset{NH}{\|}}{C}—NH_2$) in the presence of 2-propanol at a temperature below 253 K. The product formed is heated with a dilute mineral acid to hydrolyse the acetyl group and get sulphaguanidine.

Acetanilide — *p*-Acetamidobenzene sulphonyl chloride

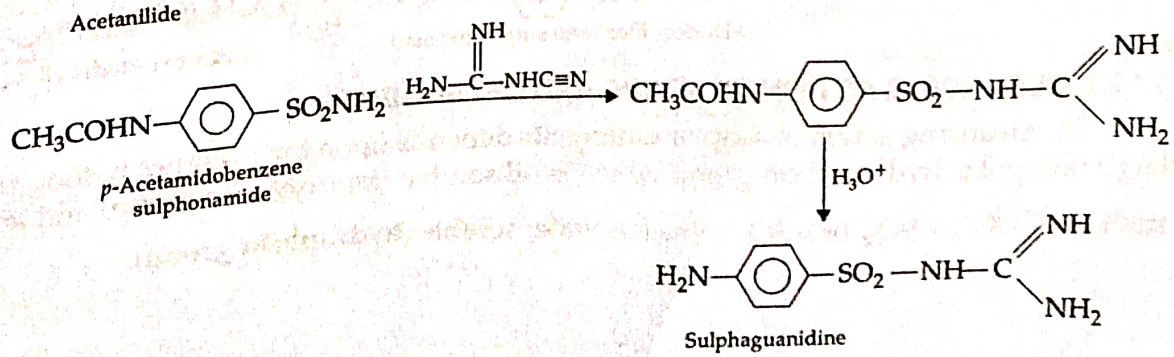


p-Acetamidobenzene sulphonyl guanidine — Sulphaguanidine

(2) *p*-Acetamidobenzene sulphonamide is first obtained by the action of chlorosulphonic acid on acetanilide followed by reaction with ammonia. It is then heated with dicyanodiamine (*i.e.* N-cyanoguanidine) and the resulting acetyl derivative is hydrolysed by heating with a mineral acid to get sulphaguanidine.

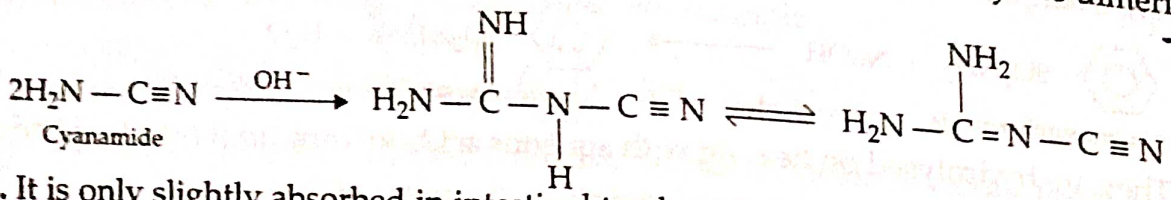


Acetanilide — *p*-Acetamidobenzene sulphonyl chloride



p-Acetamidobenzene sulphonamide — Sulphaguanidine

Cyanoguanidine used in the reaction is a tautomeric mixture obtained by the dimerisation of cyanamide in the presence of a base.



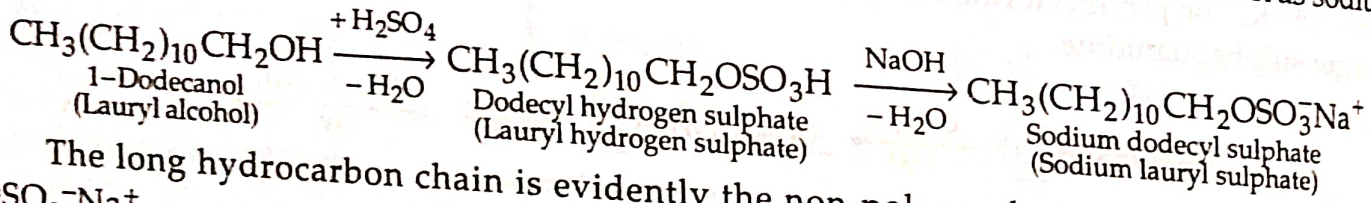
Uses. It is only slightly absorbed in intestinal track and is, therefore, used in the treatment of bacillary dysentry.

1.19. SYNTHETIC DETERGENTS

Synthetic detergents, or *soapless soaps*, as they are sometimes called, *are synthetic substances that are being increasingly employed as cleansing agents these days.* Unlike soap, detergents can be used satisfactorily even in hard water since they do not form curd like precipitate in such water. Huge quantities of different types of detergents, which differ chemically from soap as well as from one another, are now being manufactured and used all over the world. However, all these detergents are similar to soap in that their molecules also have a large non-polar hydrocarbon end that is oil soluble and an ionic end that is water-soluble.

The typical synthetic detergents are either salts of alkyl sulphates or alkylbenzene sulphonates as described below.

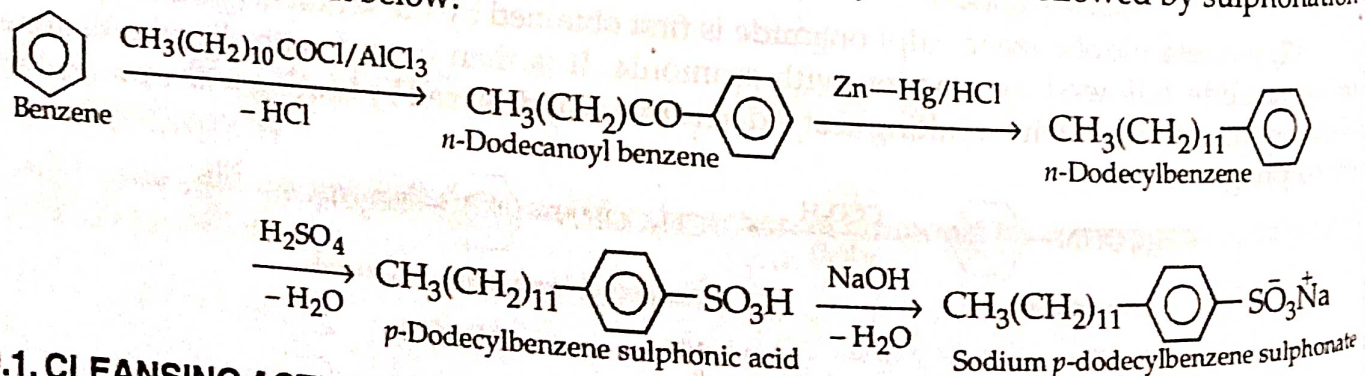
(1) Sodium alkyl sulphates. These detergents consist of sodium alkyl sulphates obtained from long chain alcohols. The first such detergent was made from a 12-carbon straight chain alcohol, 1-dodecanol (or lauryl alcohol). The alcohol was treated with concentrated sulphuric acid to form a sulphate ester which was neutralised with sodium hydroxide to obtain a detergent known as sodium dodecyl sulphate **(SDS)** as shown below :



The long hydrocarbon chain is evidently the non-polar end while the polar end is $-OSO_3^-Na^+$.

SDS is mainly used in shampoos and cosmetics.

(2) Alkyl benzenesulphonates. The most commonly used detergents these days are linear alkylbenzenesulphonates **(LAS)** such as sodium dodecylbenzenesulphonates. They are anionic detergents and are obtained by conversion of benzene into alkyl benzene followed by sulphonation and neutralisation as shown below.



1.19.1. CLEANSING ACTION OF SOAPS AND DETERGENTS

The cleansing action of soap or detergents depends upon the presence in their molecules of a large non polar hydrocarbon group which is oil soluble (***hydrophobic*** group) and an ionic group such as $-COO^-$, $-SO_4^-$ or $-SO_3^-$ which is water soluble (**hydrophilic group**).

The dirt is generally held to a dirty surface by a thin film of oil or grease which is non-polar. When the dirty surface is placed in soap or detergent solution, the non-polar hydrocarbon ends of the soap or detergent dissolve in oil or grease.

The ionic ends of the soap or detergent molecules are left projecting into the surrounding water layer (Fig. 1.1). Due to the negative charge of ions, an ionic atmosphere developes around the oil or grease droplets. Repulsion between similar charges prevents the oil droplets from coming together and coalescing. The net result is that droplets of oil or grease get dispersed in water to form an emulsion and in this way dirt portion comes out and is washed away by water.

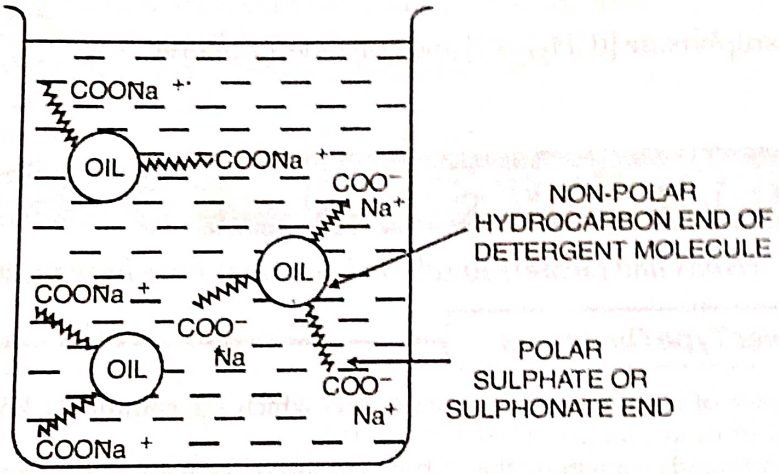


Fig. 1.1. Emulsifying action of soap.

Thus cleansing action of soap or detergent is fundamentally due to its property to act as an *emulsifying agent* in the formation of emulsion of oil or grease in water.

Chapter 2

Heterocyclic Compounds

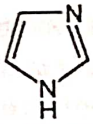
2.1. INTRODUCTION

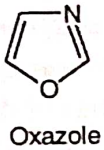
Heterocyclic compounds or heterocyclics are ring compounds having atoms of two or more elements in the ring (Greek *hetero* = different). Besides carbon atoms, the other atoms (called **hetero** atoms) usually present in the heterocyclic rings are nitrogen, oxygen and sulphur although sometimes rings containing other atoms such as phosphorus, boron, tin and silicon are also encountered. For example, we have :


Pyrrole


Furan


Thiophene


Imidazole


Oxazole


Pyridine


Pyran


Pyrimidine


Pyrazine

2.1.1. Classification

Heterocyclic compounds are usually classified on the basis of size of the heterocyclic ring and the number of hetero atoms present. The more important classes of heterocyclic compounds are as follows :

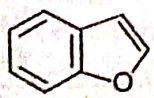
(1) **Five membered rings with one hetero atom.** Pyrrole, furan and thiophene are examples of this type of compounds.

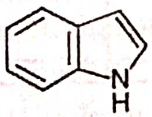
(2) **Six membered rings with one hetero atom.** Pyridine and pyran are common examples of this class of heterocyclics.

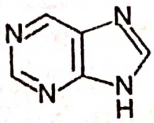
(3) **Five membered rings with two hetero atoms.** Imidazole and oxazole afford examples of heterocyclics of this type.

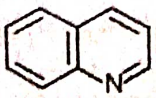
(4) **Six membered rings with two hetero atoms.** Pyrimidine and pyrazine belong to this class of compounds.

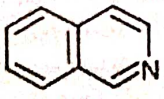
(5) **Heterocyclic ring condensed with benzene ring.** These are condensed ring heterocyclic compounds made up of two or more rings, at least one of which must be heterocyclic. A few examples of such heterocyclics are given below.

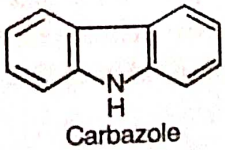

Benzofuran


Indole

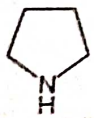

Purine


Quinoline

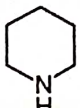

Iso- quinoline

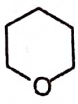

Carbazole

(6) **Non–aromatic heterocyclics.** All the examples of different types of heterocyclic compounds given above are aromatic in nature (as will be explained a little later). In addition to these, there are heterocyclic compounds which may be considered as non–aromatic or aliphatic heterocyclics. For example :


Pyrrolidine


Tetrahedrofuran


Piperdine


Tetrahydropyran

2.1.2. NOMENCLATURE

Most of the heterocyclic compounds have, over the years, acquired common names, such as those used above, which have become very popular. However IUPAC has also adopted certain rules for naming heterocyclic compounds. We are giving below a brief description of the IUPAC nomenclature of monocyclic ring systems having one or more heteroatoms.

(*i*) *The size of the ring is indicated by a* **stem.**

(*ii*) *Derived from the stem is a* **suffix** *which depends upon the unsaturated or saturated nature of the ring* and whether the ring contains nitrogen or not.

(*iii*) *Heteroatom present in the ring is denoted by a* **prefix.**

The stems for rings of different sizes, corresponding suffixes (for unsaturated rings only) and the prefixes for different heteroatoms for 4–7 atom rings are given below in tables 3.1 and 3.2 respectively.

Table 2.1. *Stems for rings of different sizes and corresponding suffixes for unsaturated rings only.*

Ring size	Stem	Suffix (unsaturated rings only)	
		Rings containing nitrogen	Rings not containing nitrogen
3	– ir –	– irine	– irene
4	– et –	– ete	– et
5	– ol –	– ole	– ole
6	– in –	– ine	– in
7	– ep –	– epine	– epin

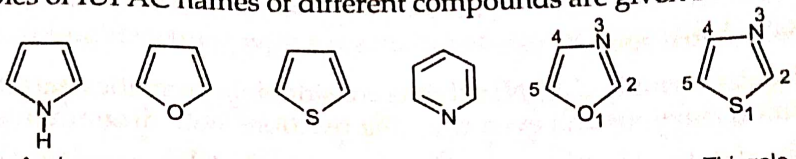
Table 2.2. *Prefixes for different heteroatoms*

Heteroatom	Prefix
Oxygen	Oxa
Sulphur	Thia
Nitrogen	Aza
Phosphorus	Phospha
Boron	Bora

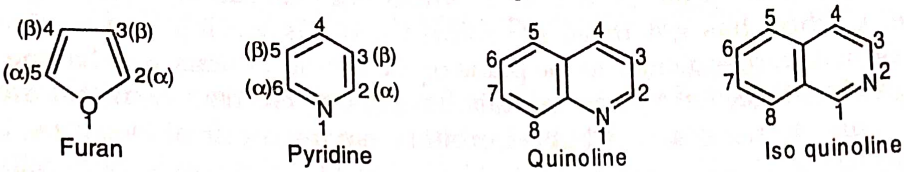
(*iv*) *The complete name of the heterocyclic compound is written by combining the prefix and the suffix. In doing so, the terminal "***a***" of the prefix is generally dropped.*

(*v*) *In rings containing two or more different heteroatoms oxygen takes precedence over sulphur and sulphur over nitrogen both in naming and numbering of atoms.*

A few examples of IUPAC names of different compounds are given below.



Derivatives of heterocyclics. In naming the derivatives of simple heterocyclic compounds, the positions of substituents are denoted by numbers (or less commonly, by Greek letters) *The numbering is done in such a way that the* **hetero atom** *gets the* **lowest number** *and further numbering is continued* to give the substituents or other heteroatoms the minimum number possible.An important exception to this rule is **isoquinoline** in which heteroatom does not get the lowest number as shown below.



The chemistry of heterocyclic compounds may resemble that of aliphatic or aromatic compounds depending upon the extent of unsaturation present. In this chapter we shall be mainly concerned with the chemistry of heterocyclics which exhibit aromatic character.

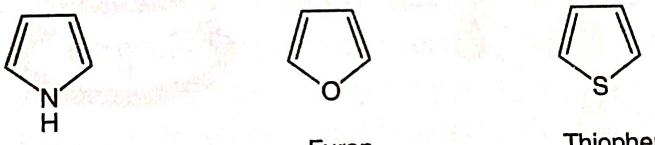
FIVE MEMBERED HETEROCYCLIC

The simplest five–membered heterocylic compounds are pyrrole, furan and thiophene, each of which contains only one hetero atom.

We begin the study of these compounds by first taking up their structures.

2.2. STRUCTURES OF PYRROLE, FURAN AND THIOPHENE : AROMATIC CHARACTER

Pyrrole, furan and thiophene have the molecular formulae C_4H_5N, C_4H_4O and C_4H_4S respectively. Keeping in view the tetracovalency of carbon and the valency of the hetero atom present, they may be represented by diene like structures as shown below.



According to the above structures, these compounds should exhibit the reactions of a **conjugated diene** and of an amine (in case of pyrrole), an ether (in case of furan) or a thioether (in case of thiophene).

In actual practice they have, no doubt, some tendency to undergo the expected reactions such as addition reactions. But, at the same time, they have considerable aromatic character and they undergo electrophilic substitution reactions such as halogenation, nitration sulphonation and Friedel–Crafts reaction and even coupling with diazonium salts. Moreover, heats of combustion of these compounds indicate that they are resonance stabilised to the extent of 65–125 kJ mol^{-1}. These values, though somewhat lesser than that of benzene (151 kJ mol^{-1}), are quite substantial and much greater than that of conjugated dienes (about 12.5 kJ mol^{-1}).

It is evident that the extra stabilities of pyrrole, furan and thiophene rings and their aromatic character cannot be justified in terms of structures given above. Let us, therefore, approach the problem from molecular orbital and resonance points of view.

2.2.1. Structure of Pyrrole

12

It has already been stated above :

(*i*) Pyrrole (molecular formula C_4H_5N) exhibits considerable aromatic character and undergoes electrophilic substitution reactions and even coupling reactions with diazonium salts.

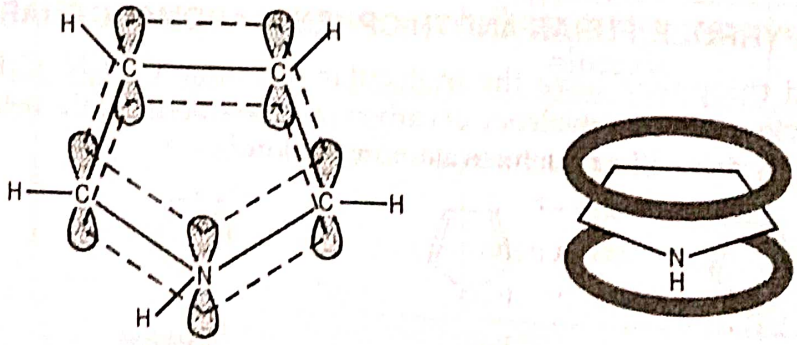
(*ii*) It is resonance stabilised to the extent of about 100 kJ mol^{-1} as compared to 151 kJ mol^{-1} for benzene and only 12.5 kJ mol^{-1} for conjugated dienes.

(*iii*) Unlike amines, pyrrole lacks basic character and is practically neutral.

These observations are not consistent with the diene structure given above.

Molecular orbital structure. According to molecular orbital concept, the carbon and nitrogen atoms of pyrrole constitute a flat pentagon in which both carbon and nitrogen atoms are in sp^2 *hybridised* state. Carbon has got three sp^2 hybrid orbitals having one electron each and an unhybridised *p* orbital, perpendicular to the plane of the hybrid orbitals, also having an odd electron. Similarly nitrogen has three sp^2 hybrid orbitals having one electron each and an unhybridised *p* orbital, perpendicular to the plane of hybrid orbitals, having a *pair* of electrons. Both carbon and nitrogen use their sp^2 orbitals to form C–H, N–H, C–C and C–N σ bonds. Naturally all these bonds lie in the same plane so that pyrrole is a flat molecule.

There remain now the unhybridised *p* orbitals of the four carbon atoms, each having one **electron** and the unhybridised *p* orbital of nitrogen having **two electrons.** These *p* orbitals overlap one another sideways (Fig. 2.1 *a*) to form a cyclic delocalised π molecular orbital containing six electrons and embracing all the five atoms of the ring. The delocalised electrons are present in the form of two π electron clouds, one above and one below the plane of the ring as shown in Fig. 2.1 *b*.



(*a*) Sideways overlap of *p*-orbitals of carbon and nitrogen

(*b*) π-Electron clouds above and below the plane of the ring

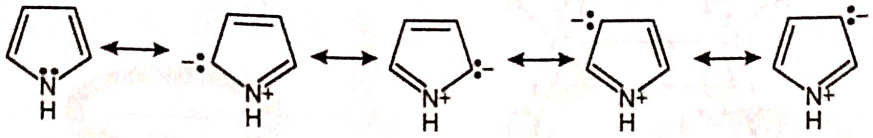
Fig. 2.1. Molecular orbital picture of pyrrole.

It is the presence of these electron clouds of six delocalised electrons, in accordance with Huckel's $(4n + 2)$ π electron rule, which is responsible for the stability and aromatic character of pyrrole.

It may be noted that nitrogen had to contribute both the *p* electrons in the formation of electron cloud. Therefore, nitrogen is not left with any unshared electrons for sharing with acids. As such, *in contrast to amines, pyrrole has very little basic character.*

Since each carbon atom contributes one electron towards the electron cloud while nitrogen contributes two electrons, the electron density at the carbon atoms of pyrrole ring is somewhat greater than that in case of benzene. Therefore, *pyrrole is more susceptible to electrophilic attack than benzene.* Thus it undergoes reactions like nitrosation and coupling with diazonium salts which are given only by activated substituted benzenes such as phenols and amines.

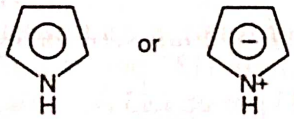
Resonance structure. In terms of resonance theory pyrrole is considered to be a resonance hybrid of following contributing structures with a resonance energy of about 100 kJ mol^{-1}.



It may be seen that in contrast to benzene which has **two** contributing structures, which do any carry any charge pyrrole has **only one** contributing structure without involving charge separation. In other words, pyrrole has only one relatively more stable contributing structure as against two in case of benzene. That is why resonance energy of pyrrole is much lesser than that of benzene.

Measurement of bond lengths lends support to the resonance hybrid structure of pyrrole. Thus the carbon–nitrogen bond length in pyrrole is 138 pm or 1.38 Å which is much shorter than carbon–nitrogen single bond length of 148 pm or 1.48 Å. This clearly indicates that carbon–nitrogen bond in pyrrole has got some double bond character. Studies involving measurements of dipole moments and UV and PMR spectra further confirm the resonance hybrid structure.

In the light of above discussion, pyrrole can be best represented as :



2.2.2. Structure of Furan

As already stated, furan (molecular formula C_4H_4O) could be represented by a diene–like structure (*please see page 2/3*) on the basis of tetracovalency of carbon and divalent nature of oxygen.

But in actual practice furan does not behave in keeping with the above structure. On the other hand it exhibits considerable aromatic character since it undergoes electrophilic substitution reactions such as nitration, sulphonation, halogenation and Friedel Crafts reaction. At the same time its heat of combustion shows that it is resonance stabilised by almost 65 kJ mol^{-1} as against the resonance stabilisation of conjugated dienes by only about 12.5 kJ mol^{-1}.

Hence furan cannot have the diene structure.

Molecular orbital structure. Since furan is considerably aromatic in nature, it would be quite appropriate to represent its structure in terms of orbital theory. Like pyrrole, furan has a flat pentagonal ring involving sp^2 *hybridised* carbon and oxygen atoms. Carbon has one electron each in its hybridised orbitals as well as unhybridised orbital. Of the hybrid orbitals of oxygen two have got one electron each while the third has a pair of electrons. The unhybridised *p* orbital also has a pair of electrons. Carbon uses its hybridised orbitals in the formation of C–C, C–H and C–O σ bonds. Two of the hybrid orbitals of oxygen having one electron each are also involved in the formation of σ bonds with adjacent carbon atoms.

The unhybridised orbital of oxygen having two electrons and the unhybridised orbitals of the four carbons having one electron each form delocalised electron cloud having six electrons by

sideways overlapping. But the pair of electrons in the third sp^2 orbital of oxygen is left unshared. The orbital picture of furan may, therefore, be depicted as shown in Fig. 5.2.

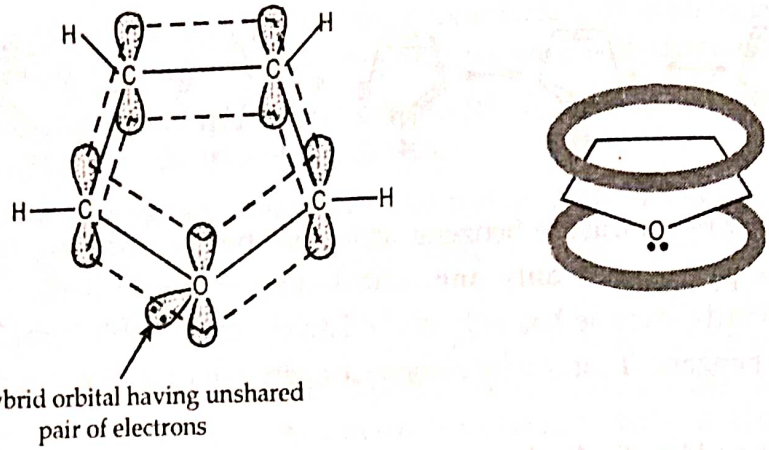
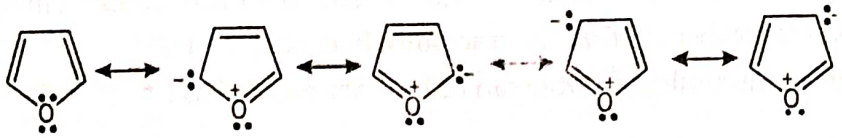


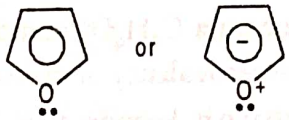
Fig. 2.2. Orbital picture of furan.

Resonance structure. According to the resonance concept, furan is considered to be a resonance hybrid of the following contributing structures. Its resonance energy is about 65 kJ mol^{-1}.



The resonance hybrid structure of furan is confirmed by its bond length determination. In particular the carbon–oxygen bond length (137 pm or 1.37 Å) in furan is shorter than a normal carbon–oxygen single bond length (143 pm or 1.43 Å). This clearly shows that this bond has some double bond character as required by the resonance hybrid concept.

In general furan is usually represented as shown below.



2.2.3. Structure of Thiophene

The structure of thiophene has been elucidated along the same lines as that of furan as described below. On the basis of tetracovalency of carbon and divalent nature of sulphur, thiophene (molecular formula C_4H_4S) can be assigned a diene like structure. (*Please see page 2/3*)

But the actual behaviour of thiophene resembles aromatic compounds rather than conjugated dienes. For instance it undergoes typical electrophilic substitution reactions such as nitration, sulphonation, halogenation and Friedel Crafts reaction. Its heat of combustion indicates that it is resonance stabilished by about 125 kJ mol^{-1} as compared to only 12.5 kJ mol^{-1} for conjugated dienes.

Therefore thiophene cannot have the diene structure given above.

Orbital strucuture. In view of its aromatic character and its similarity to furan, thiophene was assigned an orbital structure similar to that of furan. Thus thiophene has a flat pentagonal ring of sp^2 *hybridised* carbon and sulphur atoms. There is a cyclic electron cloud having six electrons lying above and below the plane of the ring.

Like the oxygen atom of furan, two of the hybrid orbitals of sulphur have got one electron each while the third has got a pair of electrons. The two hybrid orbitals of sulphur having one electron

each participate in formation of σ bonds with adjacent carbon atoms. The three hybrid orbitals of each carbon also form C–C, C–H and C–S σ-bonds.

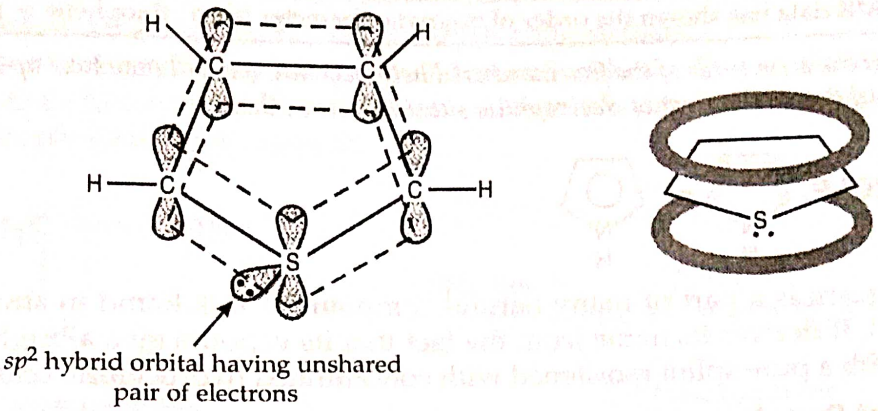
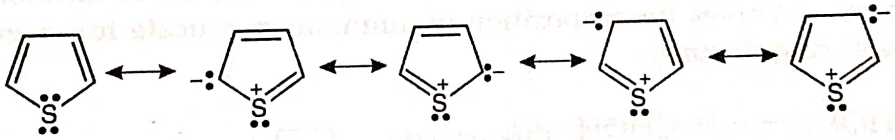


Fig. 2.3. Orbital picture of thiophene.

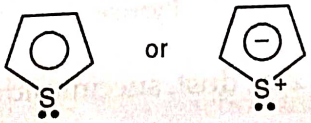
The unhybridised *p* orbital of sulphur containing two electrons and the unhybridised *p*–orbitals of the four carbons each having one electron form the delocalised electron cloud by sideways overlapping. However, the electron pair in the third sp^2 orbital of sulphur is left unshared. In this way, orbital picture of thiophene may be represented as given in Fig. 2.3.

Resonance structure. In terms of resonance, thiophene is considered to be a resonance hybrid of the following contributing structures with a resonance energy of about 125 kJ mol^{-1}.



The resonance hybrid structure gets confirmed by the determination of dipole moment and bond lengths of the molecule.

In general thiophene is represented as :



2.2.4. Relative Aromatic Character of Pyrrole, Thiophene and Furan

It is evident from the above discussion on the structures of pyrrole, thiophene and furan that each of these compounds consists of a *flat ring* of four carbon atoms and a hetero atom with a *cyclic electron cloud of six delocalised π-electrons.* This is in keeping with Huckel's rule. As such, all these compounds exhibit aromatic character.

It may also be noted that :

(*i*) Of the five contributing structures of each of these heterocyclics, there is only one structure in each case which does not involve any charge separation and makes major contribution to the resonance hybrid. As against this, both the contributing structures of benzene are uncharged and equally stable. As a result the resonance energies of these compounds are considerably lesser than that of benzene. In other words, their aromatic character is lesser than that of benzene.

(*ii*) The electronegativities of the heteroatoms present in pyrrole, furan and thiophene are in the order O > N > S. This means that oxygen has the least tendency to release its pair of electrons to

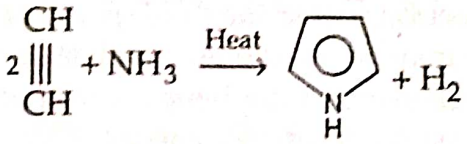
2.3. PYRROLE, AZOLE,  or 

Pyrrole ring system is a part of many natural compounds. It is found in small quantities in coal tar and bone oil. It derives its name from the fact that its vapours give a bright red colour on coming in contact with a pure splint moistened with concentrated hydrochloric acid.

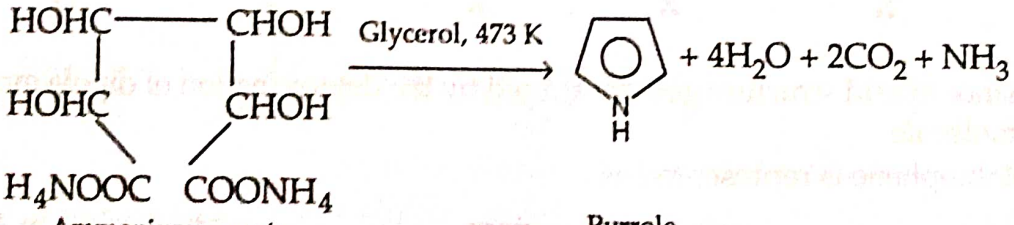
2.3.1. Preparation of Pyrrole and its Derivatives

Pyrrole can be prepared by the following methods.

(1) **From acetylene.** When a mixture of acetylene and ammonia is passed through a red hot tube, pyrrole is formed.

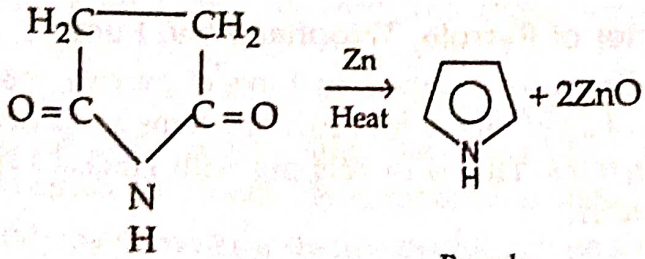


(2) **From ammonium mucate.** When heated with glycerol at 473 K, ammonium mucate gives pyrrole. The process involves decomposition of ammonium mucate followed by dehydration, decarboxylation and ring closure.



Ammonium mucate — Pyrrole

(3) **From succinimide.** On distillation with zinc dust, succinimide yields pyrrole.



Succinimide — Pyrrole

(4) **From furan.** When heated to 753–763 K, a mixture of furan, ammonia and steam in the presence of alumina catalyst yields pyrrole. This is used as a method for the manufacture of pyrrole.

2.3.2. Physical Properties

Pyrrole, when freshly distilled is a colourless liquid (b.p. 404 K) which rapidly turns brown on exposure to air. It has a chloroform like odour.

It is sparingly soluble in water but freely soluble in alcohol and ether.

2.3.3. Chemical Properties

The chemical behaviour of pyrrole is maked by its considerable aromatic character as typified by its ability to exhibit electrophilic substitution reactions. However it does undergo some addition reactions as well.

The important reactions of pyrrole are discussed below.

(1) Electrophilic substitution reactions. Pyrrole readily undergoes electrophilic substitution reactions. In fact, as already explained, there is greater electron density at the carbon atoms of the heterocyclic ring as compared with benzene. Therefore pyrrole is more reactive than benzene and resembles activated benzene derivatives such as aniline and phenol in undergoing electrophilic substitution reactions.

The electrophilic substitution of pyrrole occurs preferably at the α or 2–position although the β or 3–position is attacked when the α-positions are blocked. (The reasons for this are explained a little later)

The principal electrophilic substitution reactions of pyrrole are summarised in Fig. 2.4.

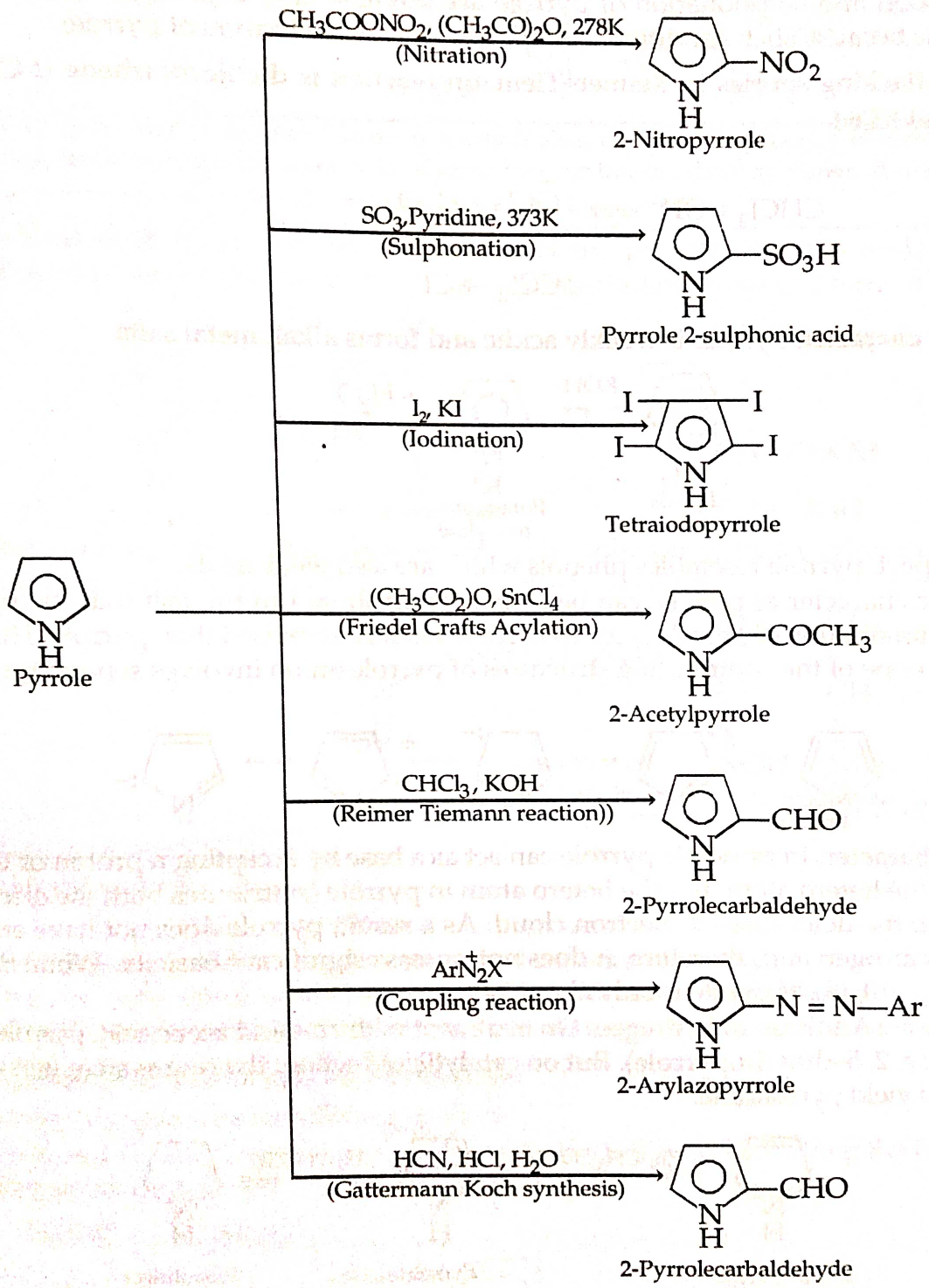
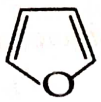


Fig. 2.4 Electrophilic substitution reactions of pyrrole.

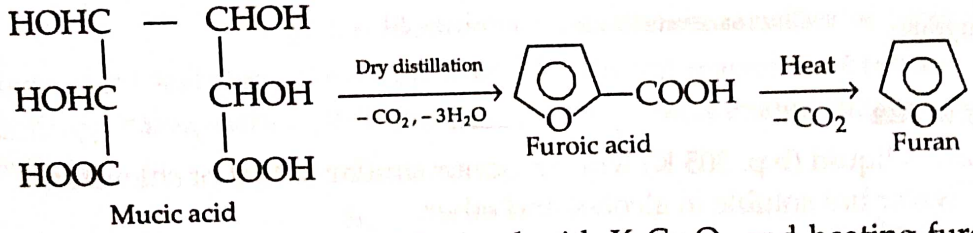
2.4. FURAN, OXOLE,  or 

Furan is the simplest heterocyclic compound containing an oxygen atom. It occurs alongwith methyl furan in very small quantities in wood tar. When brought in contact with pine splint moistented with concentrated hydrochloric acid, furan vapours produce a green colour.

2.4.1. Preparation of Furan and its Derivatives

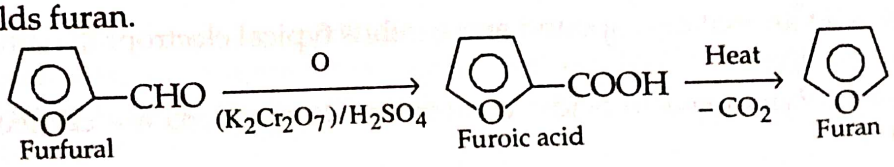
Furan can be prepared by the following methods :

(1) **From mucic acid.** Dry distillation of mucic acid followed by heating the furoic acid formed at its boiling point gives furan.



Mucic acid — Furoic acid — Furan

(2) **From furfural.** Oxidation of furfural with $K_2Cr_2O_7$ and heating furoic acid formed at its boiling point yields furan.



Furfural — Furoic acid — Furan

(3) **Decarbonylation of furfural.** On a commercial scale, furan is usually obtained by the decarbonylation (*i.e.* removal of carbonyl group) of furfural by heating it in steam in the presence of silver oxide catalyst.

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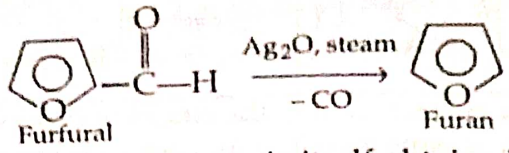
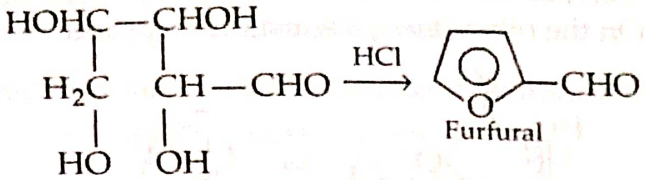


Furfural Furan

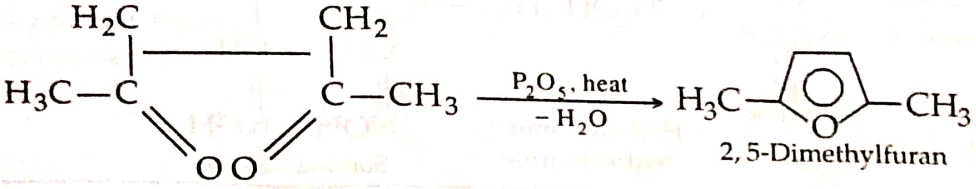
Furfural required for this purpose is itself obtained by the treatment of pentoses (present in oathuls) with concentrated hydrochloric acid.



Pentose (From oathuls) Furfural

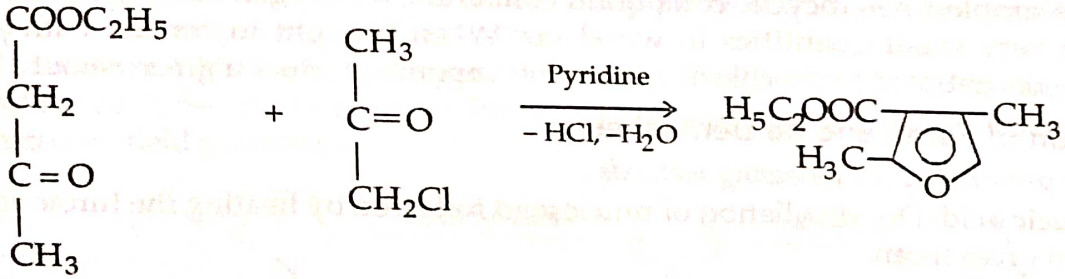
Furan **derivatives** *are usually prepared by the following two methods :*

(4) **Dehydration of 1, 4–dicarbonyl compounds : Paal–Knorr Synthesis.** This is a general method for the preparation of furan derivatives. It involves the action of a dehydrating agent such as P_2O_5, $ZnCl_2$ or H_2SO_4 on a 1,4–dicarbonyl compound which can undergo enolisation. For example :



Acetonyl acetone 2, 5-Dimethylfuran

(5) **Feist–Benary synthesis.** This method involves the reaction between a β-ketoester and an α-haloketone. For example :



Ethyl acetoacetate (or Ethyl β-ketobutyrate) α-Chloroacetone

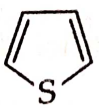
2.4.2. Physical Properties

Furan is a colourless liquid (b.p. 305 K) with an odour similar to that of chloroform. It is insoluble in water but soluble in alcohol and ether.

2.4.3. Chemical Properties

Furan behaves as an aromatic compound and exhibits typical electrophilic substitution reactions mainly at the α- or 2–position.

Since furan gets polymerised in acidic conditions, its reactions are carried out in properly selected conditions.

2.5. THIOPHENE, THIOLE,  or 

Thiophene (also spelt as **thiophen**) is a five membered heterocyclic compound containing sulphur as the hetero atom. It occurs in very small quantities in the light oil fraction of coal–tar distillation.

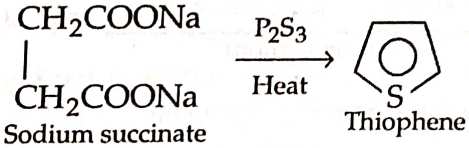
When benzene is isolated from light oil, thiophene passes on as an impurity in benzene since the boiling point of benzene (353 K) and thiophene (357 K) are very close together.

To separate thiophene from benzene, impure benzene is shaken with *cold* concentrated sulphuric acid. As a result thiophene gets converted into water soluble thiophene–2–sulphonic acid while benzene remains uneffected. Thiophene sulphonic acid is separated from benzene (which is insoluble in water) and treated with superheated steam to recover thiophene.

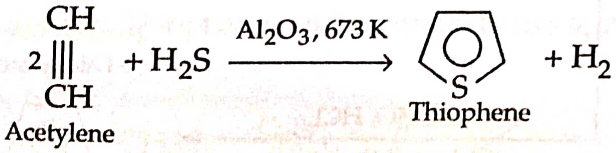
2.5.1. Preparation of Thiophene and its Derivatives

Thiophene can be prepared by the following methods :

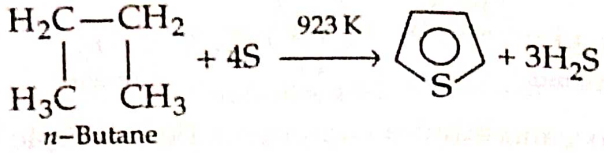
(1) **From sodium succinate.** Thiophene can be prepared in the **laboratory** by heating sodium succinate with phosphorus trisulphide.



(2) **From acetylene.** On a **commercial scale,** thiophene is obtained by passing a mixture of acetylene and hydrogen sulphide over heated alumina.

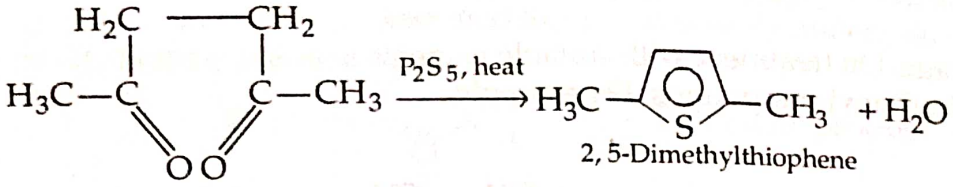


(3) **From *n*–butane.** Another method of obtaining thiophene on a **commercial scale** is by reaction of sulphur and *n*–butane at 923 K.



n–Butane

(4) **From 1, 4–dicarbonyl compounds : Paal–Knorr Synthesis.** This is a general method for the synthesis of thiophene derivatives. It involves the action of heat on enolisable 1, 4–dicarbonyl compounds in the presence of phosphorus pentasulphide. For example,



Acetonyl acetone

2, 5-Dimethylthiophene

2.5.2. Physical Properties

Thiophene is a colourless mobile liquid (b.p. 357 K) having a benzene like smell.

It is insoluble in water but soluble in alcohol and ether.

2.5.3. Chemical Properties

Thiophene, like pyrrole and furan, exhibits aromatic character although it is less reactive than the other two five–membered heterocyclics.

It does not show basic properties and is much more stable to acids than pyrrole or furan.

The important reactions of thiophene are given below.

(1) **Electrophilic substitution.** As in the case of pyrrole and furan, thiophene undergoes electrophilic substitution predominantly at α- or 2–position. Some of its electrophilic reactions are summed up in Fig. 2.6.

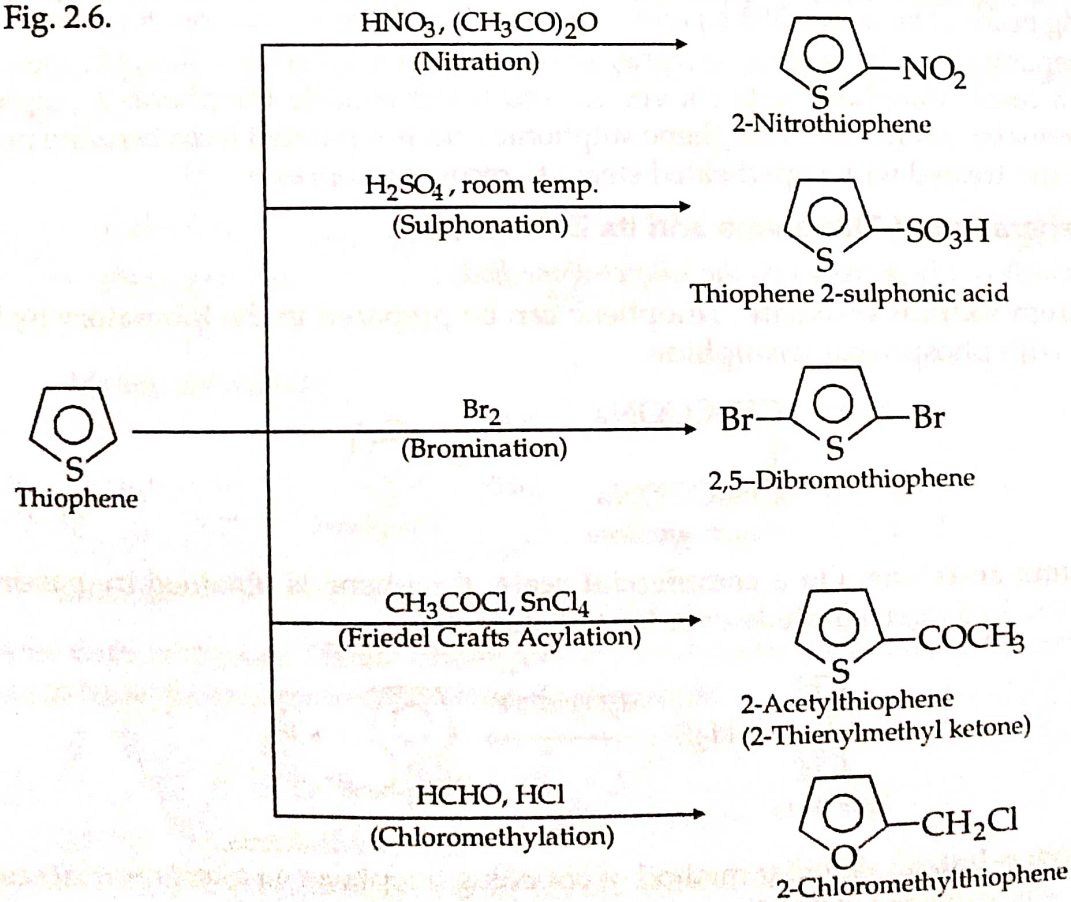
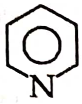


Fig. 2.6. Electrophilic substitution reactions of thiophene.

2.7. PYRIDINE,  or 

Pyridine (C_5H_5N) is the most important six–membered heterocyclic compound which contains a ring made of five carbon atoms and one nitrogen atom. It is found to be present in coal–tar and bone oil. Moreover, the pyridine ring system is also present in a number of natural products such as vitamins like *nicotinic acid* and *pyridoxine* and alkaloids like *nicotine* and *piperine*.

We would now consider the important aspects of the chemistry of pyridine.

2.7.1. Structure of Pyridine

The main points leading to the structure elucidation of pyridine are presented below.

(1) **Molecular formula.** On the basis of elemental analysis and molecular weight determination, the molecular formula of pyridine has been established to be C_5H_5N.

(2) **Chemical behaviour.** (*i*) Pyridine is a basic substance and forms salts with acids. For example :

$$\underset{\text{Pyridine}}{C_5H_5N} + HCl \longrightarrow \underset{\text{Pyridine hydrochloride}}{C_5H_5N.HCl}$$

(*ii*) It reacts with **equimolar** quantities of methyl iodide to form a quaternary ammonium salt.

$$\underset{\text{Pyridine}}{C_5H_5N} + CH_3I \longrightarrow \underset{\text{Methylpyridinium iodide}}{[C_5H_5N^+(CH_3)]\,I^-}$$

(*iii*) It does not react with acetyl chloride or nitrous acid.

The above reactions indicate that pyridine is a base containing a tertiary nitrogen atom.

(*iv*) Although its molecular formula C_5H_5N suggests a high degree of unsaturation, yet pyridine resists addition reactions and is stable towards usual oxidising agents.

(*v*) Like benzene, pyridine exhibits aromatic character and undergoes electrophilic substitution reactions such as halogenation, nitration and sulphonation.

(*vi*) The alkyl, hydroxy and amino derivatives of pyridine behave like corresponding derivatives of benzene.

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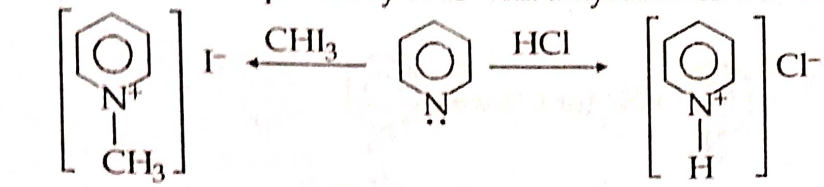
7.3. Physical Properties of Pyridine

Pyridine is a colourless hygroscopic liquid (b.p. 388 K) having a characteristic unpleasant smell. It is miscible with water and is itself a good solvent for many organic compounds.

7.4. Chemical Properties of Pyridine

The outstanding features of the chemical behaviour of pyridine are its basicity and its tendency o undergo electrophilic and nucleophilic substitution reactions as discussed below.

(1) **Basicity.** Due to the presence of a lone pair of electrons on nitrogen, pyridine acts as a base nd can form salts with acids and quatenary salts with alkyl halides. For example :



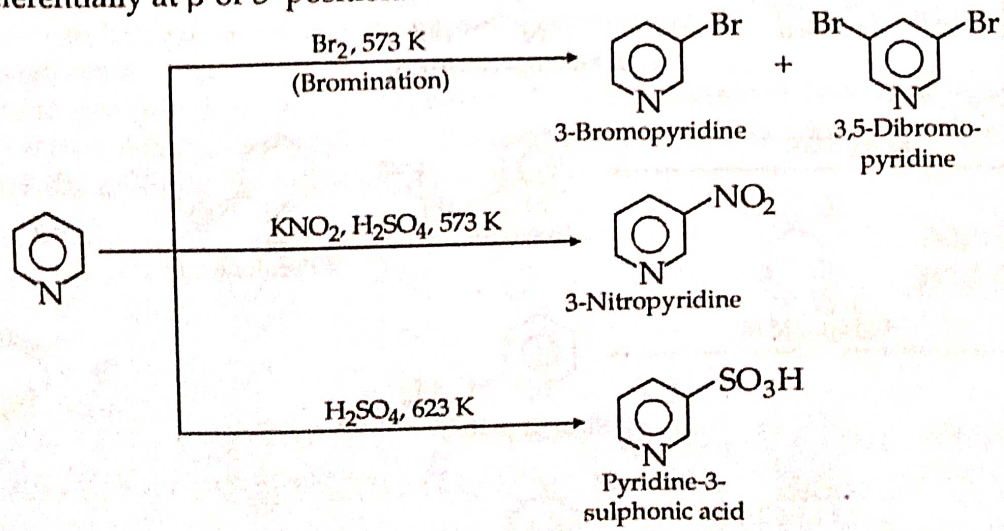
N-Methylpyridinium Iodide (Quaternary salt) — Pyridine hydrochloride

The basicity of pyridine ($pk_b \sim 8.7$) is comparable to that of aniline ($pk_b \sim 9.4$) but is much weaker than that off aliphatic tertiary amines ($pk_b \sim 4$).

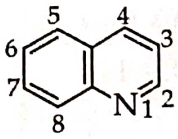
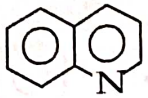
The fact that pyridine is much weaker base than aliphatic tertiary amines can be accounted for in terms of the state of hybridisation of the orbitals containing the lone pair of electrons. In aliphatic tertiary amines, unshared pair of electrons of nitrogen is in an sp^3 hybrid orbital while in case of pyridine the unshared pair is in an sp^2 hybrid orbital. Since the electrons in an sp^2 orbital are held more tightly by the nucleus than the electrons in an sp^3 orbital, they are less available for sharing with acids which is responsible for the decreased basicity.

> It may be noted that pyridine is more basic than pyrrole. This is because, as already stated, there is a lone pair of electrons on the nitrogen atom of pyridine while the nitrogen atom of pyrrole is not left with any lone pair of electrons.

(2) **Electrophilic substitution.** Pyridine is not very reactive towards electrophilic substitution reactions. Thus it undergoes electrophilic substitutions like halogenation, nitration and sulphonation only under drastic conditions and does not undergo Friedel–Crafts reaction at all. The substitution occurs preferentially at β-or 3–position.



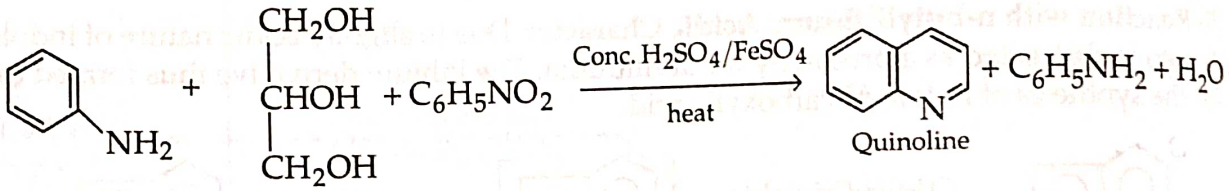
Explanation of low reactivity of pyridine. The low reactivity of pyridine towards electrophilic substitution can be understood in terms of its structure. As already mentioned the six

2.10. QUINOLINE,  or 

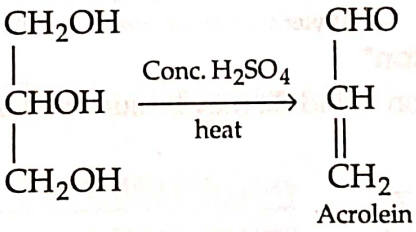
Quinoline is an important six-membered condensed ring heterocyclic which was first obtained from the alkaloid **quinine** by alkaline decomposition. It is present in coal tar and bone oil. These days it is either isolated from coal tar or prepared synthetically from benzene derivatives by different methods.

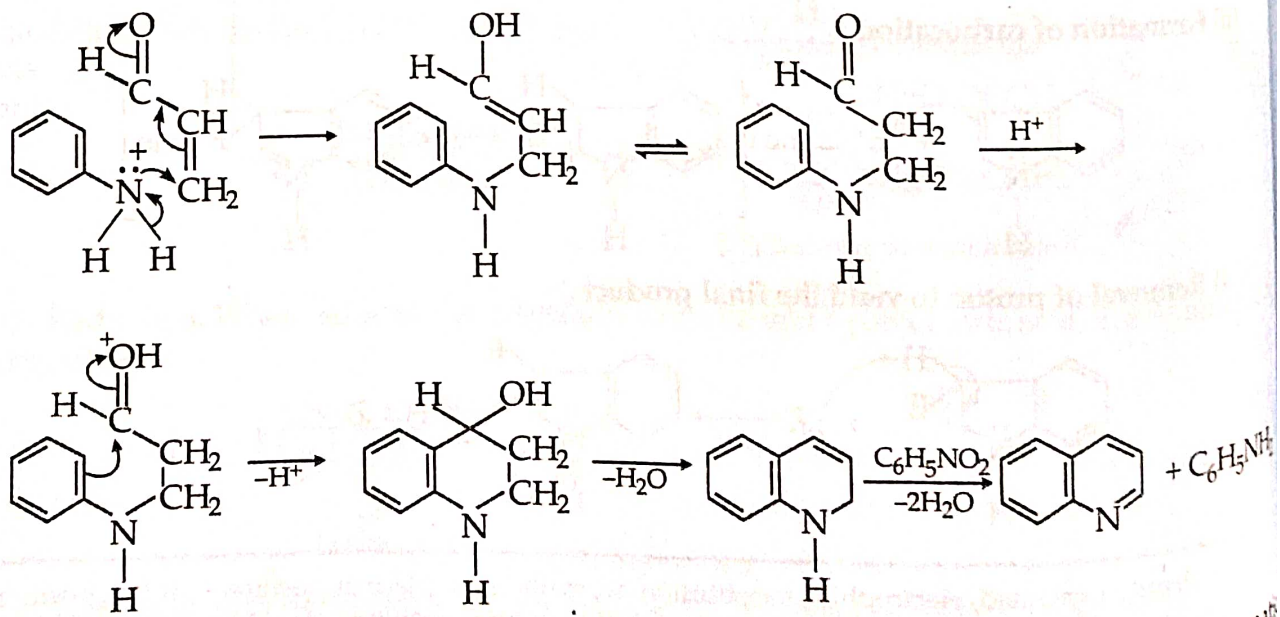
2.10.1. Preparation of Quinoline and its Derivatives

(1) **The Skraup synthesis.** This is the most widely used method for the preparation of quinoline. It is carried out by heating aniline with glycerol and concentrated sulphuric acid in the presence of nitrobenzene (which acts as an oxidising agent) and ferrous sulphate (which makes the reaction less violent).

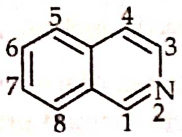
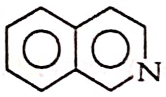


Mechanism. The first step in the reaction is the dehydration of glycerol into acrolein. This undergoes condensation with aniline via 1, 4-addition process to form 1, 2-dihydroquinoline. The dihydro product gets oxidised by nitrobenzene to yield quinoline.





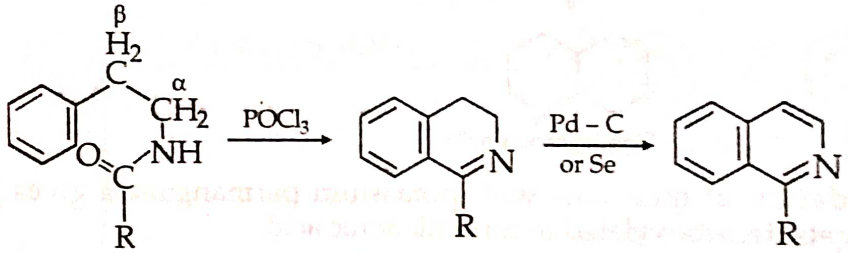
Quinoline derivatives can be prepared by this reaction by taking a suitable primary aromatic amine having at least one vacant ortho position and condensing it with α, β-unsaturated carbonyl compound in the presence of concentrated sulphuric acid (condensing agent) and nitrobenzene (oxidising agent).

2.11. ISOQUINOLINE,  or 

Isoquinoline is a degradation product of many alkaloids and also occurs, along with quinoline, in coal tar and bone oil. It is a rare example of a heterocyclic compound in which numbering does not start at the hetero atom.

2.11.1. Preparation of Isoquinoline and its Derivatives

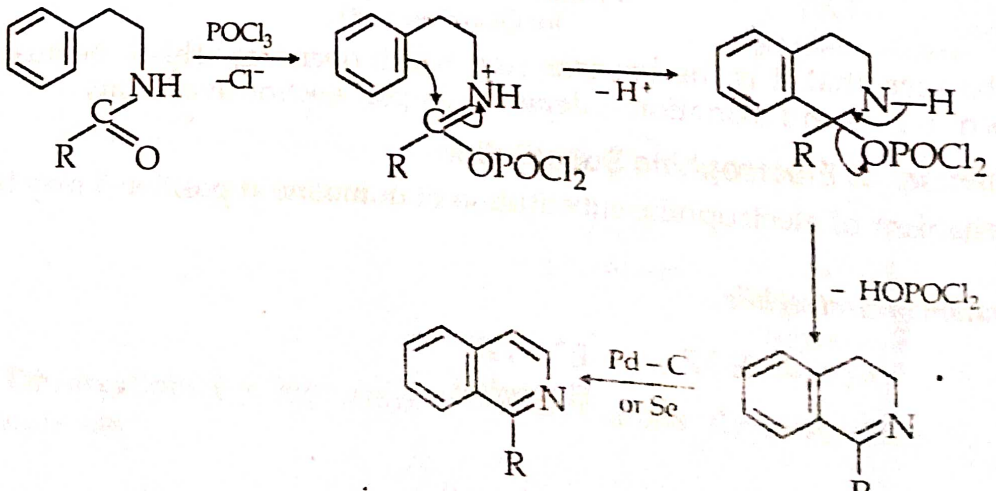
(1) **The Bischler-Napieralski synthesis.** This method involves the cyclodehydration of a β-phenylethylamine by heating with phosphoryl chloride ($POCl_3$) or phosphorus pentachloride to get 3, 4-dihydroisoquinoline. This on dehydrogenation forms isoquinoline.



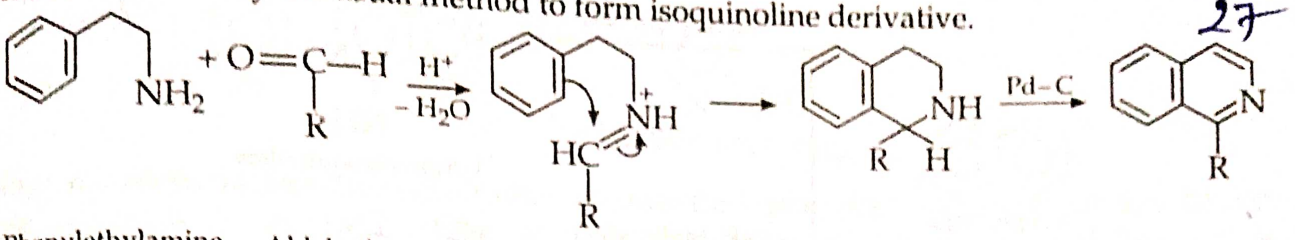
β-Phenylethylamide 1-Alkyl-3, 4-di-hydroisoquinoline 1-Alkyl-isoquinoline

The β-phenylethylamide itself is obtained from aromatic aldehydes.

Mechanism. The mechanism of the reaction may be depicted as follows :

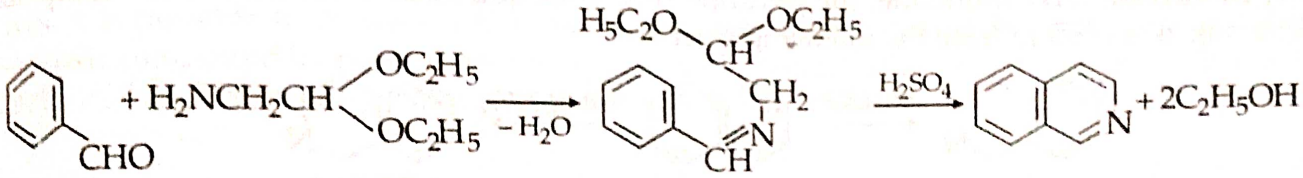


(2) **The Pictet-Spengler synthesis.** This method involves the condensation between a β-rylethylamine and an aldehyde in the presence of excess of hydrochloric acid at 373 K. As a result, 1, 2, 3, 4-tetrahydroisoquinoline is formed via a protonated imine intermediate. The tetrahydro product is then oxidised by the usual method to form isoquinoline derivative.



β-Phenylethylamine | Aldehyde | Protonated amine | 1-Alkyl-1, 2, 3, 4-tetrahydroisoquinoline | 1-Alkyl-isoquinoline

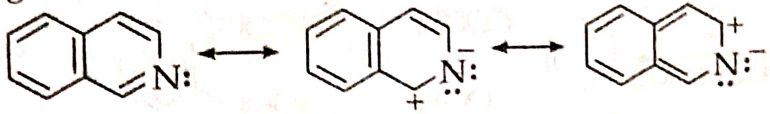
(3) **The Pomeranz-Fritsch synthesis.** In this synthesis, an aromatic aldehyde is condensed with an aminoacetal to form a Schiff's base. This is cyclised in the presence of sulphuric acid to get isoquinoline.



Aminoacetal

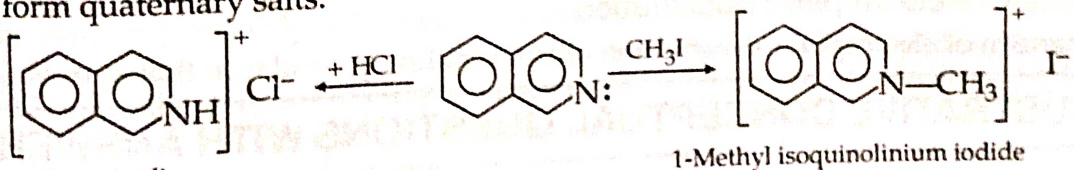
2.11.2. Properties of Isoquinoline

Isoquinoline is a colourless liquid (b.p. 516 K) which is a resonance hybrid of the following main contributing structures.



Its important reactions are given below.

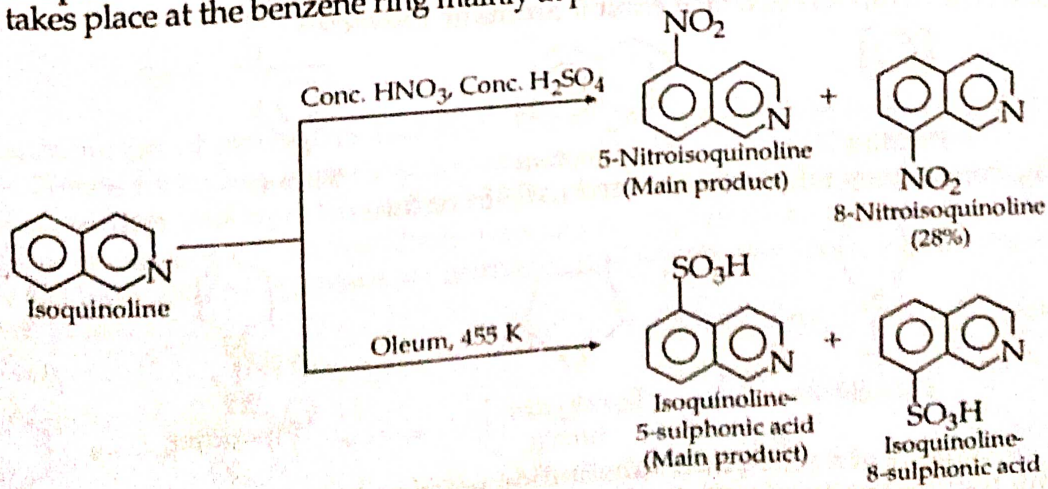
(1) **Basicity.** It is a fairly basic compound and reacts with acids to form salts and with alkyl halides to form quaternary salts.



Isoquinoline hydrochloride

1-Methyl isoquinolinium iodide

(2) **Electrophilic substitution.** As in the case of quinoline, electrophilic substitution in isoquinoline takes place at the benzene ring mainly at position-5 and to a lesser extent at position-8.



Isoquinoline

5-Nitroisoquinoline (Main product)

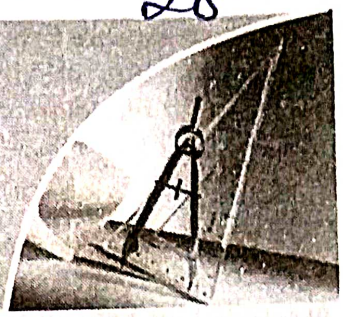
8-Nitroisoquinoline (28%)

Isoquinoline-5-sulphonic acid (Main product)

Isoquinoline-8-sulphonic acid

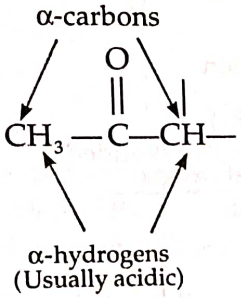
Chapter 3

Organic Synthesis Via Enolates



3.1. INTRODUCTION

It has been already learnt during the study of aldehydes and ketones that the hydrogen atoms attached to carbon atoms adjacent to carbonyl group are unusally acidic in nature. These hydrogens are called **α-hydrogens** and the carbon to which they are attached is called **α-carbon.**



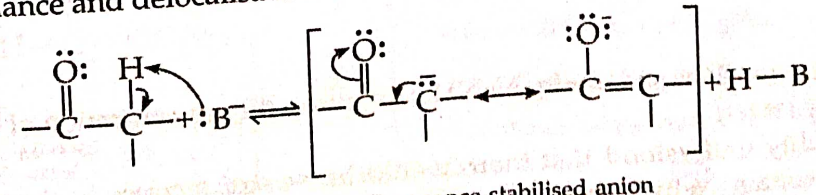
When we say that α-hydrogens are unusally acidic, it means that they have a much greater tendency to be released as protons than the hydrogen atoms of ordinary carbon-hydrogen bonds. This is evident from the fact that the pK_a values for the hydrogens of simple aldehydes and ketones are nearly 20 ($K_a = 10^{-20}$) while the pK_a values of acetylenic hydrogens HC ≡ C—H are around 25 ($K_a = 10^{-25}$), of vinylic hydrogens ($CH_2 = CH - H$) are around 40 ($K_a = 10^{-40}$) and of alkane hydrogens ($CH_3—CH_2—H$) are around 45 ($K_a = 10^{-45}$).

In this chapter, we shall study how the acidic nature of α-hydrogens leads to the formation of **enolates** which are used as nucleophiles in S_N^2 reactions employed in the synthesis of a number of organic compounds. We shall also study the participation of 1, 3-dithianes and enamines as nucleophiles in many synthetic reactions.

3.2. ACIDITY OF HYDROGENS : FORMATION OF ENOLATES

We have referred above to the acidic nature of hydrogen alpha to a carbonyl group. Let us try to find the cause of this.

Due to very small difference in the electronegativities of carbon and hydrogen, a C—H bond is normally almost non-polar in nature. But the presence of an adjacent carbonyl group (which is a strongly electron withdrawing group) polarises the electron pair of the C—H bond so that hydrogen may be removed as a proton by a strong base. At the same time, the anion that is produced gets stabilised by resonance and delocalisation of its negative charge as shown below :



Resonance stabilised anion

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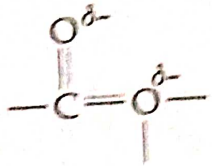
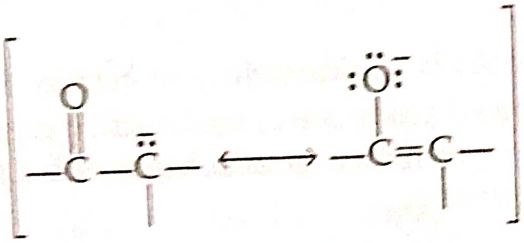
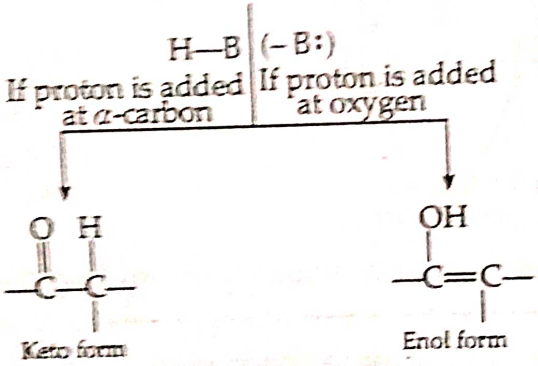
The resonance hybrid of the above structures may be represented as :



When the resonance stabilised anion reacts with a proton donor, there are two possibilities Addition of proton may take place at the carbon to give the original carbonyl compound (which also called the keto form). Alternatively, the addition of proton may occur at oxygen to give an eno

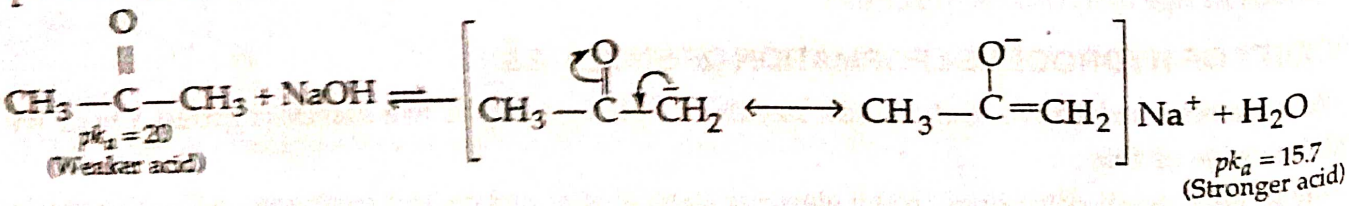


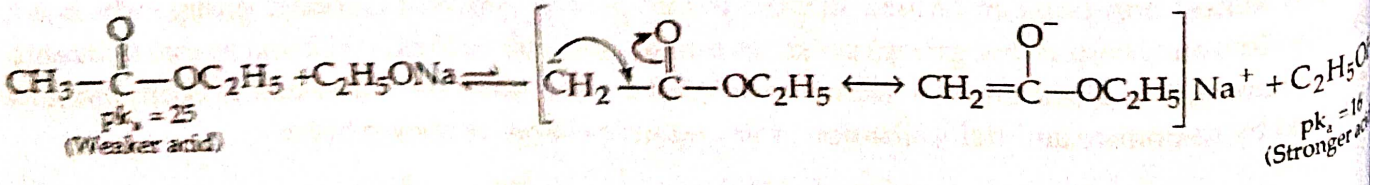
Enolate anion



The resonance stabilised anion is called **enolate anion** because it can give rise to enol.

The presence of carbonyl group, no doubt, makes the α-hydrogens unusually acidic as compare to hydrogens of an ordinary C—H bond. But the acidic character of simple carbonyl compounds i very weak with pK_a values of nearly 20. Therefore, the removal of proton and formation of enolat anion can be brought about only by strong bases such as alkali metal hydroxides or alkoxides. Bu even then the position of equilibrium in the reversible reaction favours the reactants rather than th products so that enolate ions are formed in low concentration





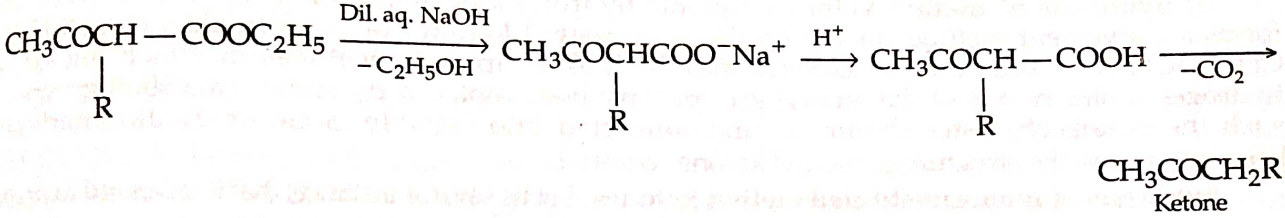
If stronger bases such as sodamide ($NaNH_2$) are used, the concentration of enolate ion formed would be relatively larger.

It can be readily understood that there would be *marked increase in the acidity of a carbonyl compound* when it contains a hydrogen alpha to **two carbonyl groups.** This is because in such cases

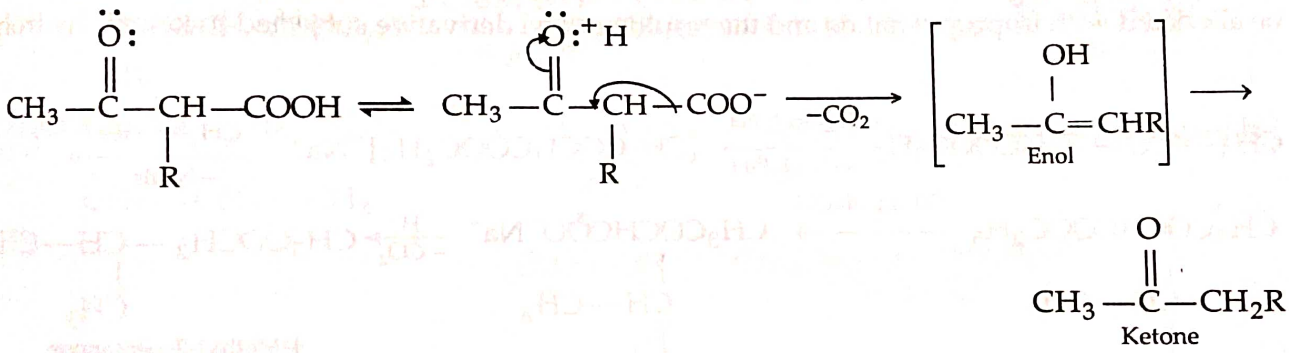
3.4.2. Acetoacetic Ester Synthesis

Acetoacetic ester is a very versatile synthetic reagent and the syntheses of a large variety of organic compounds with the help of acetoacetic ester is known as **acetoacetic ester synthesis.** An important reason at the back of synthetic utility of acetoacetic ester is that the ester itself and its alkyl derivatives can be hydrolysed in two different ways as described below.

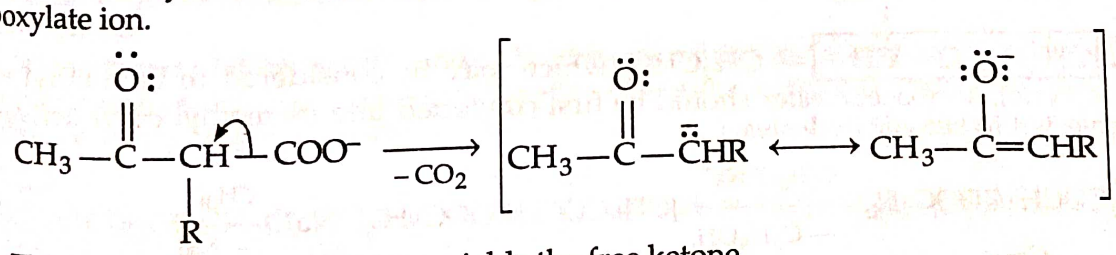
(*i*) **Ketonic hydrolysis.** When hydrolysed by dilute aqueous alkali (or acid), acetoacetic ester or its mono- or di-alkyl derivatives form the corresponding acids which readily undergo decarboxylation to yield ketones. That is why such hydrolysis is termed **ketonic hydrolysis.** Thus we have :



It is believed that decarboxylation of acetoacetic acid or its alkyl derivatives involves the transfer of carboxylic hydrogen to the keto group, eiter just before or simultaneously with the loss of carbon dioxide.

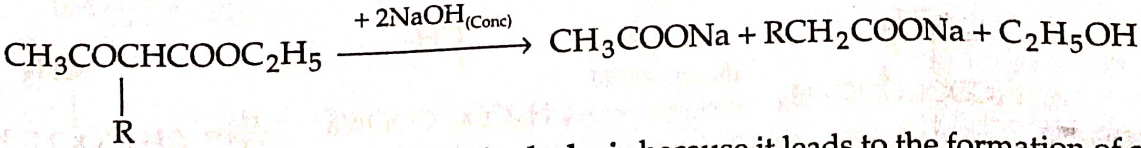


Quite often, the decarboxylation takes place even before the acidification of sodium salt formed on hydrolysis, *i.e.*, the carboxylate ion itself may decarboxylate. This is because loss of carbon dioxide from the carboxylate ion yields a carbanion which is more resonance stabilised relative to the carboxylate ion.



This carbanion on acidification yields the free ketone.

(*ii*) **Acid hydrolysis.** When the hydrolysis of acetoacetic ester or its alkyl derivatives is carried out with concentrated alkali, the ester molecule gets cleaved to form two molecules of carboxylic acids in the form of their salts.



This type of hydrolysis is known as **acid hydrolysis** because it leads to the formation of acids.

In the light of above discussion it may be concluded that the synthetic utility of acetoacetic ester is due to the following reasons.

3.5. SYNTHESIS OF ETHYL ACETOACETATE : THE CLAISEN CONDENSATION

Ethyl acetoacetate is obtained by the condensation of two molecules of ethyl acetate in presence of sodium ethoxide. The sodium salt initially formed is acidified to get ethyl acetoace

$$2CH_3COOC_2H_5 + C_2H_5O^-Na^+ \longrightarrow [CH_3COCHCOOC_2H_5]^-Na^+ + C_2H_5OH$$

Ethyl acetate — Sodium ethoxide

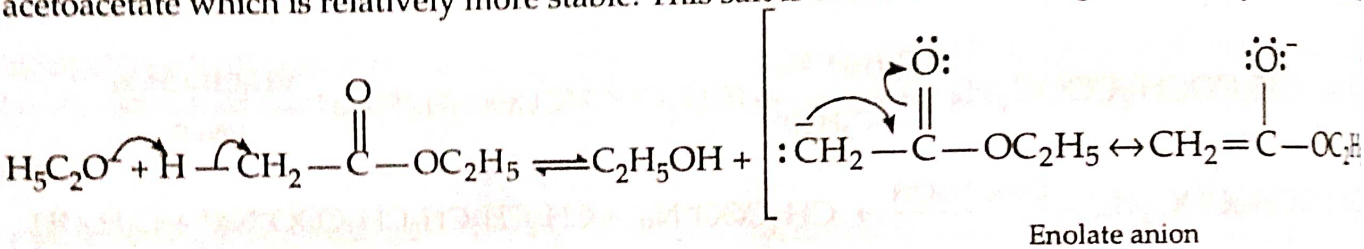
$$[CH_3COCHCOOC_2H_5]^-Na^+ \xrightarrow{H^+} CH_3COCH_2COOC_2H_5$$

Ethyl acetoacetate

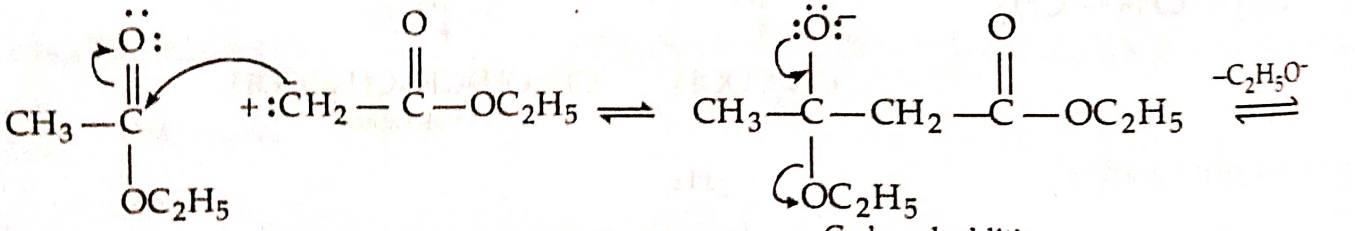
The reaction is known as Claisen condensation.

Mechanism. In the first step of Claisen condensation, the ethoxide ion removes a pro from the α-carbon of ethyl acetate to form a **resonance stabilised enolate anion.** This stron nucleophilic anion attacks the carbonyl carbon of a second molecule of the ester to form a carbo addition intermediate. This intermediate eliminates ethoxide ion to form the ketoester i.e. et acetoacetate in this case.

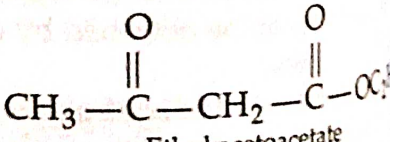
Ethyl acetoacetate formed reacts with ethoxide ion to form ethanol and enolate salt of et acetoacetate which is relatively more stable. This salt is then acidified to get free ethyl acetoace



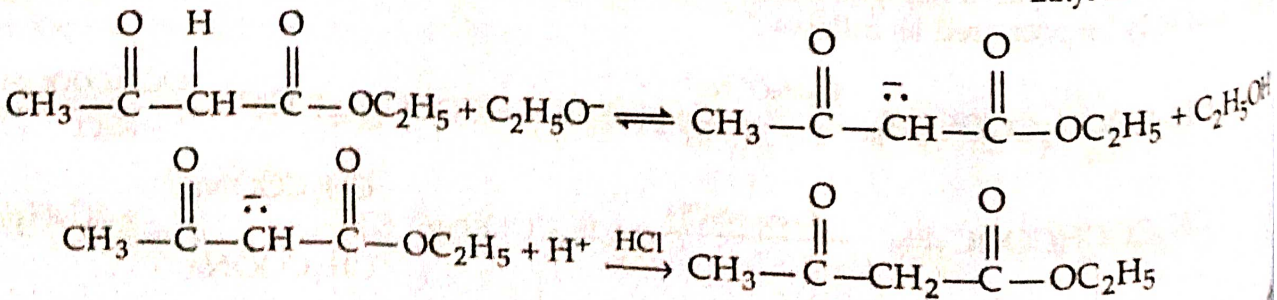
Enolate anion



Carbonyl addition intermediate



Ethyl acetoacetate

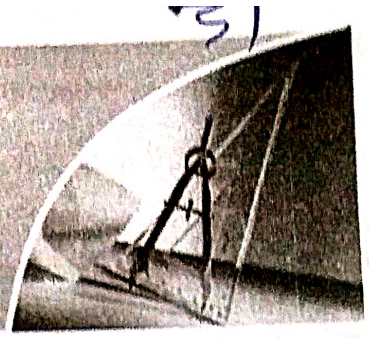


Ethyl aceto acetate

It may be noted that the first step of Claisen condensation, *i.e.* removal of a proton from carbon by a base to form a resonance stabilised enolate anion, resembles the first step of condensation. Similarly the attack of nucleophilic enolate anion on the carbonyl carbon of the second molecule of ester also resembles the condensation step of aldol condensation. However, condensation finally leads to the formation of an addition product while Claisen condensa results in the formation of an acyl substitution product.

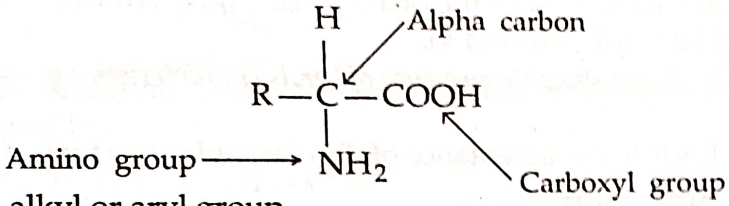
Chapter 4

Amino Acids, Peptides and Proteins



4.1. INTRODUCTION

Amino acids, as the name indicates, are *compounds which contain both an* **amino group** and *an* **acidic group** (such as carboxylic acid or sulphonic acid group) *in their molecules*. For the present, however, we shall be mainly concerned with amino carboxylic acids. In these acids, the amino group ($-NH_2$) may be attached to any carbon atom other than that of carboxyl group (—COOH). If it is bonded to the carbon atom adjacent to the carboxyl group, the acid is known as α-amino acid while the other successive positions of the $-NH_2$ group along the carbon chain with respect to the —COOH group are denoted by β, γ, etc. Thus an α-amino acid may be represented as :



where R is an alkyl or aryl group.

α-Amino acids command the maximum importance because they are the constituent units of proteins which are very important biomolecules.

In this chapter, we shall first deal with the chemistry of amino acids and then we shall discuss as to how amino acids combine to form polypeptides and proteins. Structure elucidation of peptides and proteins at different levels will also be taken up. This will be followed by a brief description of another class of biomolecules called nucleic acids.

AMINO ACIDS

α-Amino carboxylic acids constitute one of the most important classes of compounds because they serve as the building blocks of peptides and proteins. All naturally occurring amino acids have the amino group at α-position with respect to the amino group.

4.2. NOMENCLATURE OF α-AMINO ACIDS

Although amino acids can be named by IUPAC system, they are usually referred to by **common names**. The common names generally have the ending **'ine'**. Each name has been further given a **standard abbreviation** usually consisting of its first three letters. For example.

	CH_2COOH $\lvert$ NH_2	$CH_3—CH—COOH$ $\lvert$ NH_2	$(CH_3)_2CHCOOH$ $\lvert$ NH_2
(*IUPAC name*) :	2-Aminoethanoic acid	2-Aminopropanoic acid	2-Amino-2-methylpropanoic acid
(*Common name*) :	**Glycine**	**Alanine**	**Valine**
(*Abbreviation*) :	**Gly**	**Ala**	**Val**

4.3. STRUCTURE OF α-AMINO ACIDS

α-Amino carboxylic acids are generally represented as containing an amino group and a carboxyl group. That is :

$$R—\underset{\displaystyle NH_2}{\underset{|}{CH}}—COOH$$

However, in actual practice, the amino group (a basic group) and the carboxyl group (an acidic

$^{+}NH_3$

4.3.1. Evidence in favour of dipolar ionic structure

The absence of free amino and carboxyl groups in amino acids and the existence of dipolar ionic structure is supported by the following facts :

(*i*) *Unlike amines and carboxylic acids, the amino acids are non-volatile crystalline solids which melt with decomposition at fairly high temperatures.* The high melting points of amino acids can be attributed to the large inter-molecular forces arising from the electrostatic interactions of dipolar ions.

(*ii*) *The amino acids are practically insoluble in non-polar organic solvents such as ether and benzene but are soluble in polar solvents like water.*

(*iii*) *Their aqueous solutions behave like solutions of substances having high dipole-moments.*

(*iv*) *They have very low acidity and basicity constants.* For instance, the values of K_a and K_b for glycine (*i.e.* aminoacetic acid) are 1.6×10^{-10} ($pK_a = 9.8$) and 2.5×10^{-12} ($pK_b = 11.6$) respectively. In contrast, most carboxylic acids have K_a's of the order of 10^{-5} (pK_a around 5) and most aliphatic amines have K_b of the order of 10^{-4} (pK_b around 4).

(*v*) *Their spectroscopic studies do not show the presence of bands characteristics of —NH_2 and —COOH groups.*

The evidence cited above leads to the acceptance of dipolar ionic structure of amino acids.

4.4. CLASSIFICATION OF AMINO ACIDS

As already stated, amino acids can be broadly classified as α, β, γ and so on according to the position of amine group on the carbon chain with respect to the carboxylic group. For example :

H_2NCH_2COOH	$H_2NCH_2CH_2COOH$	$H_2NCH_2CH_2CH_2COOH$
2–Aminoethanoic acid or α-Aminoacetic acid	3–Aminopropanoic acid or β-Aminopropionic acid	4-Aminobutanoic acid or -Aminobutyric acid

The number of amino acids which are known to occur **naturally** is very large. But 20 of them command special importance because they are commonly found in proteins. All 20 of these protein derived acids are α-amino acids and **all but one** contain a primary amino group and have the general structure :

$$R-\overset{\alpha}{C}H(^{+}NH_3)-COO^{-}$$

The only exception is **proline** in which amino group is secondary and nitrogen and α-carbon are part of a pyrrolidene ring.

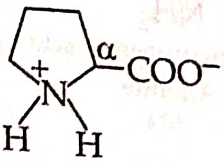


Table 6.1. on page 4 gives the **names,** *three letter abbreviations of the names,* **a one letter code** (in parenthesis) and **structural formulae** *of the 20 most important amino acids in alphabetical order.*

4.4.1. Classification of Protein derived Amino acids

The amino acids listed in table 4.1 can be further classified in several different ways as described below.

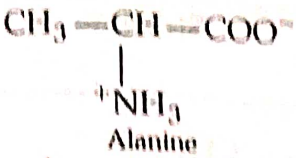
(1) Essential and non-essential amino acids. *Ten of the amino acids* (marked* in the table) *which*

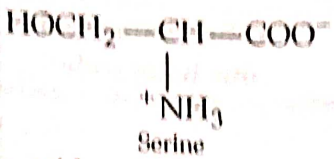
are very important for the growth of young animals cannot be synthesised by animals from other materials in the diet. These acids are termed **essential** or **indispensable amino acids** ; *they must be present in the diet as such.* Lack of these acids in the diet can cause diseases such as *kwashiorkar*.

The acids which can be synthesised by our bodies and may not be present in the diet as such are called **non-essential amino acids.**

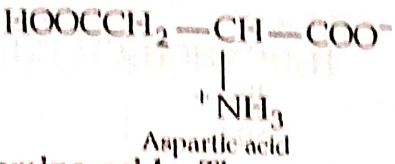
(2) **Classification according to neutral, acidic or basic character.** Amino acids can also be classified according to the number of acidic and basic groups present in them.

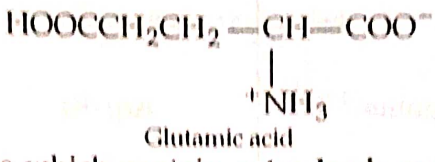
(*i*) **Neutral amino acids.** These are amino acids which contain **one acidic** and **one basic** group. For example :


Alanine

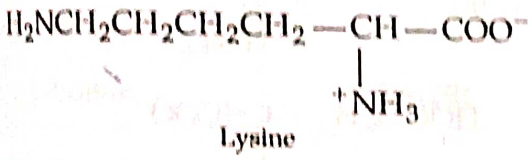

Serine

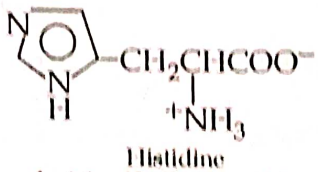
(*ii*) **Acidic amino acids.** These are amino acids which contain extra acidic group in their molecules. For example :


Aspartic acid


Glutamic acid

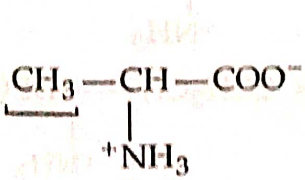
(*iii*) **Basic amino acids.** These are amino acids which contain **extra basic group** in their molecules. For example :

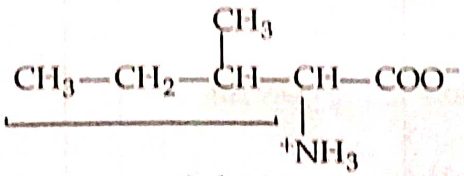

Lysine


Histidine

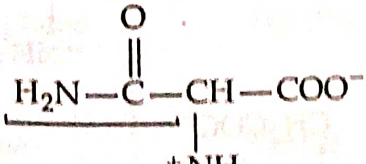
(3) **Classification according to the nature of side chain.** In this classification, amino acids have been classified into four categories.

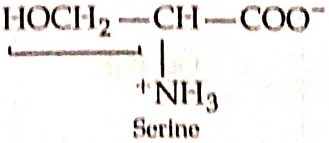
(*i*) **Amino acids having non-polar side chains.** For example :


Alanine

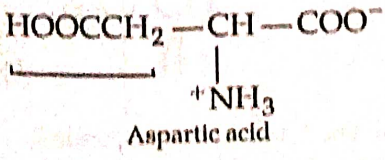

Isoleucine

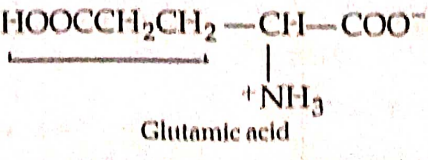
(*ii*) **Amino acids having polar but unionised side chains.** For example :


Asparagine


Serine

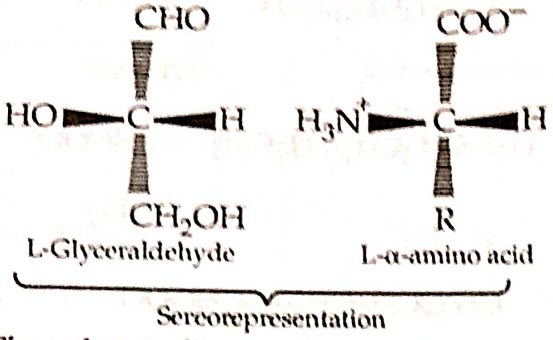
(*iii*) **Amino acids having acidic side chains.** For example :

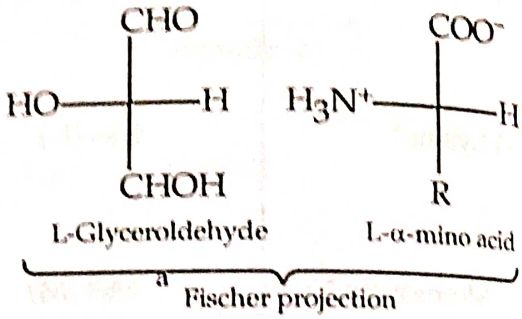

Aspartic acid


Glutamic acid

4.5. STEREOCHEMISTRY OF AMINO ACIDS*

With the exception of glycine, all α-amino acids have four different groups attached to α-carbon atom. This carbon, therefore, serves as a stereocentre and amino acids are chiral in nature. Two different enantiomeric forms of each amino acid are, therefore, possibe. But it is interesting to note that almost all α-amino acids derived from proteins belong to the same stereochemical family *i.e.* they have the same relative configuration at the α-carbon atom. The configuration is analogous to that of L-(–) glyceraldehyde and may be depicted as follows in terms of stereopresentation and Fischer projection formula.





Thus almost all naturally occuring amino acids belong to the L-series and are often referred to as **L-amino acids.**

It may also be pointed out that in terms of R, S notation the L α-amino acids usually have the S configuration.

4.6. ACID-BASE BEHAVIOUR OF AMINO ACIDS

It has already been studied that in the dry solid state, amino acids exist as dipolar ions or zwitterions having the structure $R-\underset{\displaystyle {}^{+}NH_3}{\underset{|}{CH}}-COO^-$. These zwitterions are amphoteric in nature. They can react either as acids having very low values of K_a or as bases having very low values of K_b. The exceptionally low values of K_a and K_b of amino acids are quite consistent with the zwitterionic strucuture. *According to this strucutre, it is a* **substituted ammonoium ion,** $-NH_3$ (not the carboxylic group) *which acts as a proton donor* and is *therefore the acidic centre. Similarly, it is a* **carboxylate ion,** $-COO^-$ (not the amino group) *which acts as the proton acceptor and is therefore the basic centre.*

Thus K_a actually refers to the acidity of a substituted ammonium ion as represented below.

$$R-\underset{\displaystyle {}^{+}NH_3}{\underset{|}{CH}}-COO^- + H_2O \rightleftharpoons H_3O^+ + R-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COO^-$$

$$K_a = \frac{[H_3O^+]\left[R-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COO^-\right]}{\left[R-\underset{\displaystyle {}^{+}NH_3}{\underset{|}{CH}}-COO^-\right]}$$

* Not included in syllabus.

For **diamino monocarboxylic acids** (such as lysine), the isoelectric point is at a *p*H much higher than 6. For example, isoelectric points of **lysine** and **arginine** are 9.74 and 10.70 respectively.

For **monoamino dicarboxylic acids** (such as aspartic acid) the isoelectric point is at a *p*H of much less than 6. For example, isoelectric points of **aspartic acid** and **glutamic acid** are 2.87 and 3.22 respectively.

It may also be noted that at the isoelectric point the solubility of amino acids is minimum. This is because at this point there is maximum concentration of relatively less soluble dipolar ion.

Isoelectric points of some amino acids are given in table 4.2.

Table 4.2. *Isoelectric points of some α-amino acids*

Amino acid		Isoelectric point
Alanine	Neutral	6.02
Valine		5.97
Leucine		5.98
Serine		5.70
Threonine		5.60
Aspartic acid	Acidic	2.87
Glutamic acid		3.22
Lysine	Basic	9.74
Arginine		10.70

4.7.1. Electrophoresis

Electrophoresis is *a process of separation and purification of compounds on the basis of movement of charged particles in an electric field.* Let us illustrate the process by considering the separation of a mixture of amino acids into its pure constituents.

To carry out electrophoresis, a strip of paper, a suitable plastic or cellulose acetate is used as a solid support. In paper electrophoresis, for example, a solution of different amino acids (which are to be separated from each other) is placed near the centre of strip of paper. The strip is then moistened with an aqueous buffer having a particular predetermined *p*H (which depends upon the isoelectric points of the acids to be separated). The ends of the strip are connected to the electrodes. When an electric field is applied, this is what happens :

(*i*) *The amino acids whose isoelectric point is* **below the pH** *of the buffer start migrating slowly towards the positive electrode because they exist mainly in the* **anionic form.**

(*ii*) *The amino acids having isoelectric point* **higher than the pH** *of the buffer migrate towards the negative electrode because they exist mainly in the* **cationic form.**

(*iii*) *The amino acids whose isoelectric point* **corresponds to the pH** *of the buffer do not migrate from the origin because they have* **no net charge.**

Different amino acids migrate at different rates depending upon the isoelectric point of the acid and its charge density. In this way, different amino acids get separated from each other. After the separation is complete, the strip is dried and sprayed with a dye (such as ninhydrin) when the separated components become visible.

Thus if a mixture of alanine (*p*I = 6.02), aspartic acid (*p*I = 2.87) and lysine (*p*I = 9.74) is to be separated, it is subjected to electrophoresis in a buffer having *p*H = 6.0. At this *p*H aspartic acid

would migrate towards the positive electrode, alanine would remain at the origin while lysine would move towards the negative electrode. This is shown below in fig. 4.1.

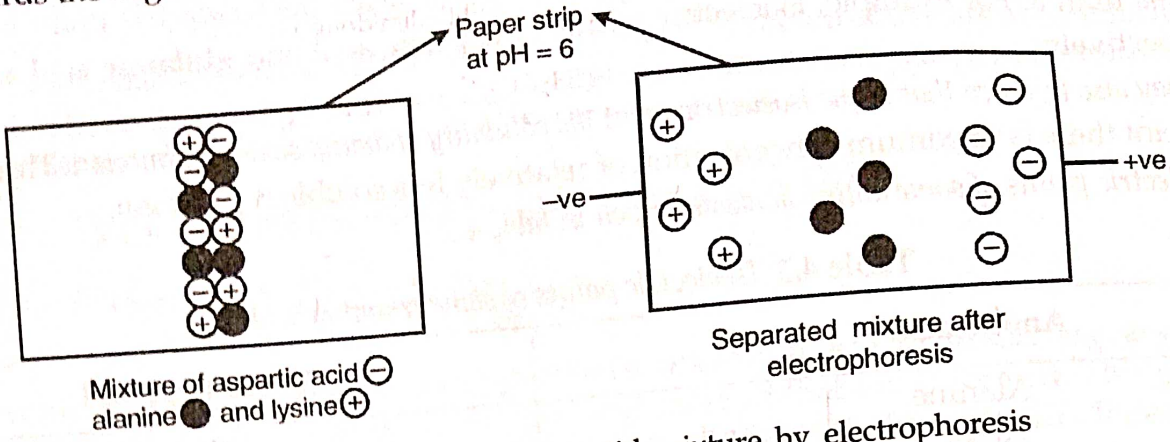


Fig. 4.1. Separation of amino acid mixture by electrophoresis

4.8. PREPARATION OF α-AMINO ACIDS

Proteins constitute the most important natural sources for α-amino acids. On hydrolytic degradation, proteins yield mixtures of α-amino acids from which the different acids can be separated by employing methods such as **paper chromatography and electrophoresis.**

Apart from their preparation from proteins, a number of synthetic methods are also available for the formation of α-amino acids. The important synthetic methods are described below.

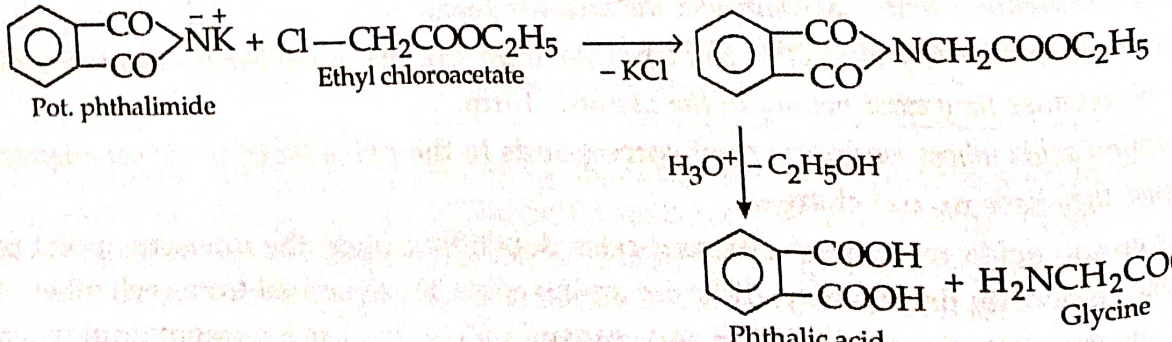
(1) **Direct amination of α-halo acids.** When treated with excess of concentrated aqueous ammonia, an α-chloro or α-bromo carboxylic acid undergoes nucleophilic substitution to give rise to ammonium salt of an α-amino acid. Hydrolysis of this salt yields an α-amino acid. For example :

$$CH_3CH(Cl)COOH + NH_3\ (excess) \xrightarrow[-NH_4Cl]{} CH_3CH(NH_2)COO^-NH_4^+ \xrightarrow{H_3O^+} CH_3CH(NH_2)COOH$$

a-Chloropropionic acid — Alanine

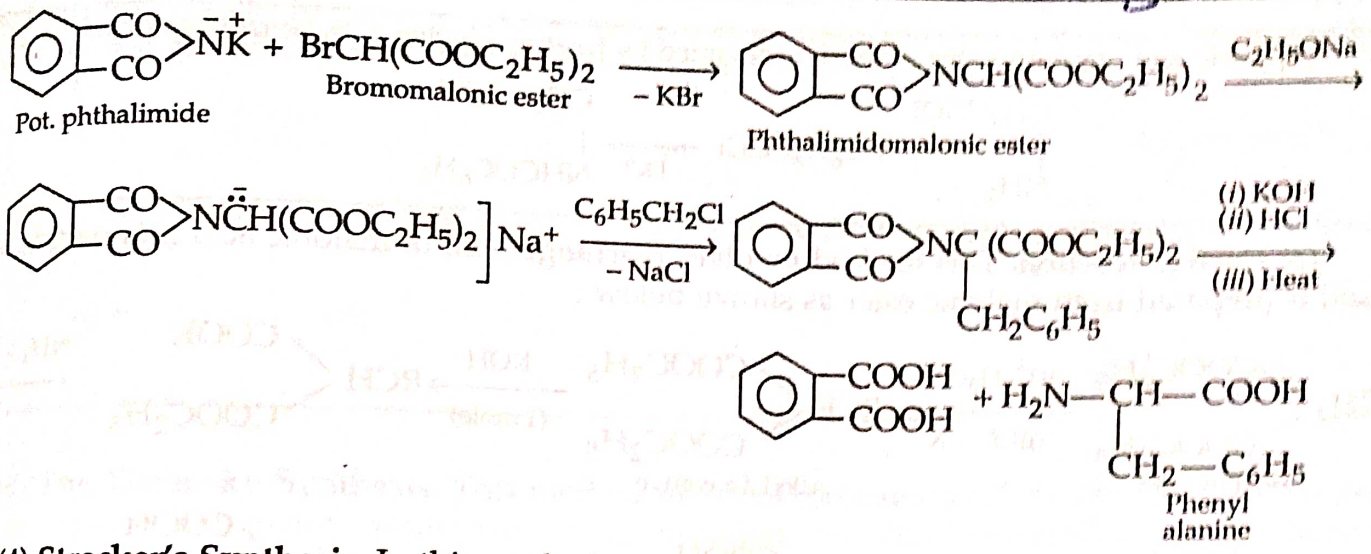
The α-haloacids required in this reaction are usually obtained by direct halogenation of carboxylic acids by Hell–Volhard–Zelinsky reaction.

(2) **Gabriel phthalimide synthesis.** This method involves reaction between an ester of α-halo acid and potassium phthalimide followed by hydrolysis of the product formed. For example:



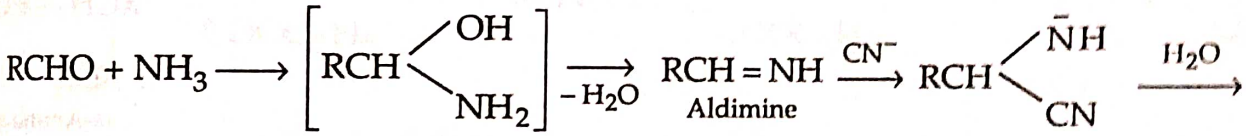
Pot. phthalimide — Phthalic acid

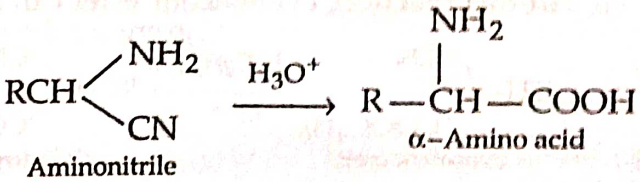
(3) **Phthalimidomalonic ester synthesis.** This method is a combination of malonic ester synthesis and Gabriel phthalimide synthesis. It involves the action of potassium salt of phthalimide on bromomalonic ester to form phthalimidomalonic ester. This is then heated with the required alkyl halide and the product hydrolysed to get α-amino acid. For example :



(4) **Strecker's Synthesis.** In this method an aldehyde is treated with a mixture of ammonium chloride and potassium cyanide. The aminonitrile thus formed is then hydrolysed to get α-amino acid. The reaction probably takes place as follows :

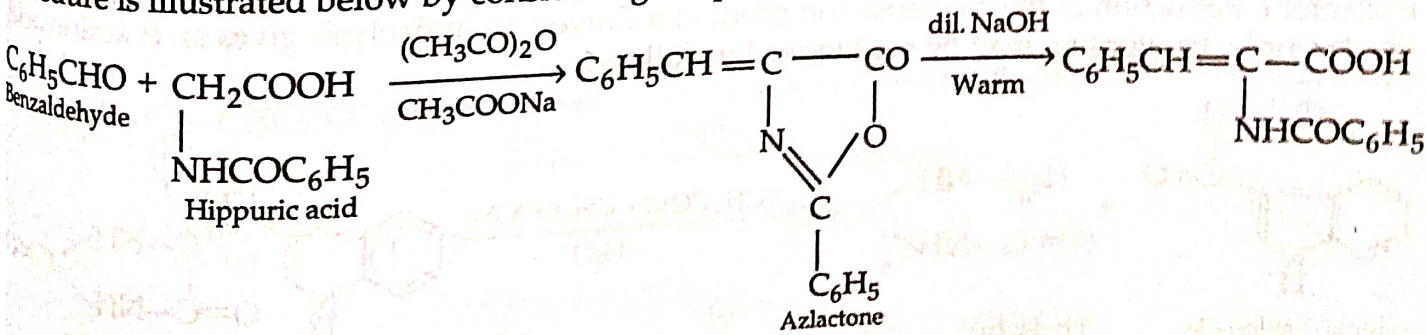
$$NH_4Cl + KCN \rightleftharpoons NH_3 + HCN + KCl$$

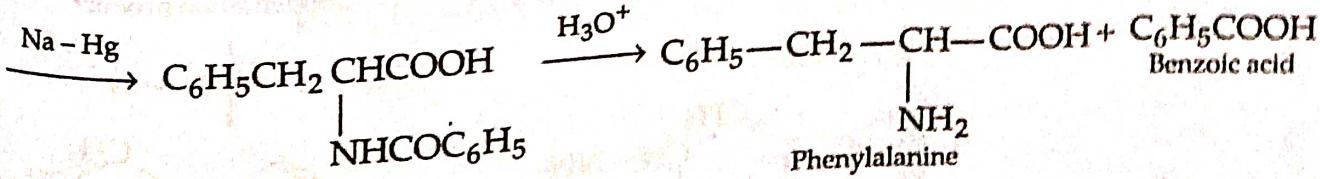




(5) **Erlenmeyer azlactone synthesis.** This method consists in heating an aromatic aldehyde with hippuric acid (*i.e.* benzoyl glycine) in the presence of acetic anhydride and sodium acetate when azlactone (*i.e.* 5-oxazolone) is formed. This on warming with 1% NaOH solution followed by reduction and hydrolysis gives the α-amino acid.

The method is employed in the preparation of aromatic amino acids and the complete procedure is illustrated below by considering the preparation of phenylalanine.





4.8. PHYSICAL PROPERTIES OF α-AMINO ACIDS

As already mentioned, amino acids are generally crystalline solids which behave in salt like manner. They melt with decomposition at high temperature.

They are soluble in polar solvents like water but are practically insoluble in organic solvents like benzene, ether and alcohol.

Their aqueous solutions behave like solutions of substances having high dipole moments.

All these characteristics have already been explained in terms of their 'dipolar ionic' structure (section 4.3).

4.9. CHEMICAL PROPERTIES OF α-AMINO ACIDS*

It has been already stated that the dipolar ionic structure (I) of amino acids exists in equilibrium with the ions (II) and (III) which have free amino and carboxyl groups respectively. As such amino acids can still display the characteristics reactions of amines as well as carboxylic acids.

$$\underset{\text{(II)}}{\text{RCHCOO}^-\\ |\\ \text{NH}_2} \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \underset{\text{(I)}}{\text{RCHCOO}^-\\ |\\ {}^+\text{NH}_3} \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} \underset{\text{(III)}}{\text{RCHCOOH}\\ |\\ {}^+\text{NH}_3}$$

It may be seen that in basic solution, the above equilibrium is predominantly in favour of the ion (II) so that reactions involving amino group are carried out in basic solution. Similarly reactions involving the carboxyl group are carried out in acidic solution because in that case the equilibrium is strongly in favour of the ion (III).

A few reactions of the amino and carboxyl groups are described below for the sake of illustration.

4.9.1. Reactions due to Amino Group

Amino acids undergo the usual reactions characteristics of amino group as described below.

(1) **Reaction with mineral acids.** Amino acids react with mineral acids to form corresponding salts.

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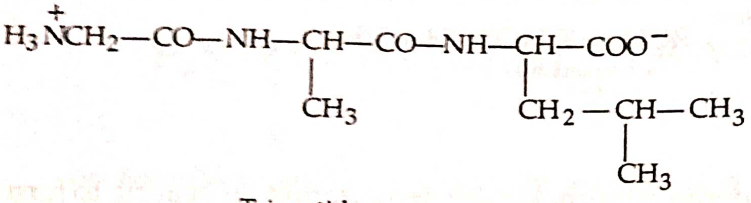
* Not included in the syllabus.

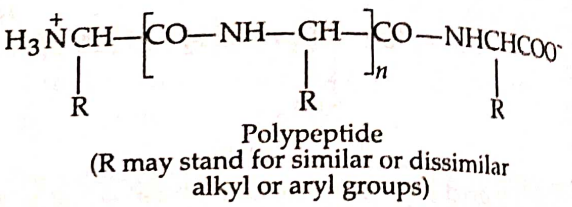
4.10. CLASSIFICATION AND NOMENCLATURE OF PEPTIDES

4.10.1. Classification

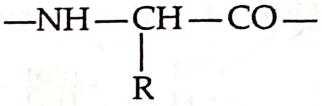
Peptides are classified as **dipeptides, tripeptides, tetrapeptides** and finally **polypeptides** according as the number of amino acid residues per molecule is two, three, four or more than ten. For example, glycylglycine (shown above) is a dipeptide, glycylalanylleucine is a tripeptide while a polypeptide may be represented as shown below.



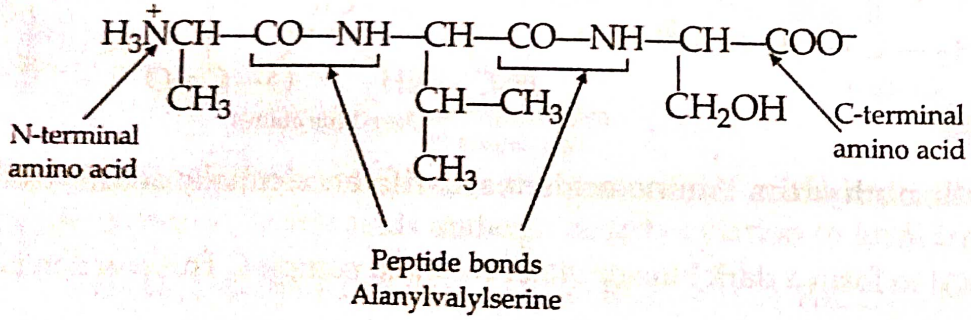
Tripeptide
Glycylalanylleucine (Gly-Ala-Leu)



Polypeptide
(R may stand for similar or dissimilar alkyl or aryl groups)

The repeating unit in the polypeptide chain is 

It may be seen that the peptides have a free — $\overset{+}{N}H_3$ on one end and a free — COO^- group on the other. The amino acid having the free — $\overset{+}{N}H_3$ group is called **N-terminal amino acid residue** while the amino acid having the free group —COO^- is called the **C-terminal amino acid residue.** In writing of formulae of peptides, we always start from the left with the N-terminal amino acid residue and then proceed to the right towards the C-terminal amino acid residue.

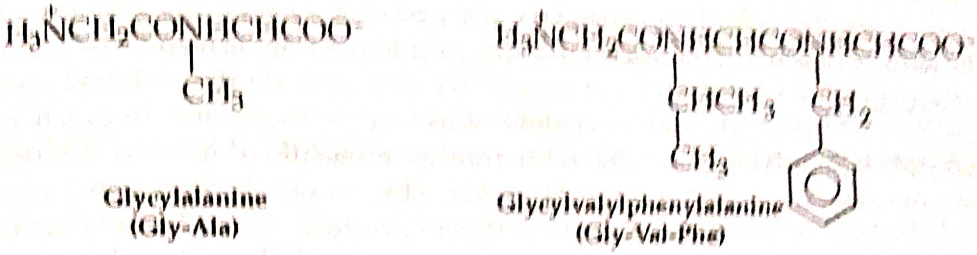


It may be noted that there is no sharp dividing line between a polypeptide and a protein. However, the usual convention is that *peptides of molecular mass upto 10,000 are known as* **polypeptides** ; *above 10,000 they are considered as* **proteins.**

4.10.2. Nomenclature

For naming the peptides, the names of constituent amino acids are written starting from N-terminus and proceeding to C-terminus.

The suffix "**ine**" of the names of all amino acids except the C-terminus acid is replaced by "**yl**". Sometimes the names of polypeptides are abbreviated by using three letter abbreviations for constituent amino acids. For example :



Glycylalanine (Gly-Ala)

Glycylvalylphenylalanine (Gly-Val-Phe)

4.11. GEOMETRY OF PEPTIDE BOND

It was shown by Lewis Pauling that the peptide bond is **planar** in nature. The four atoms of the peptide bond and the two α-carbons linked to it lie in the same plane with hydrogen (of NH) and oxygen of (CO) in **trans** position with respect to each other. The carbon-nitrogen bond distance has been found to be 132 pm or 1.32 Å (compared to usual carbon-nitrogen single bond distance of 147 pm or 1.47 Å) indicating that carbon nitrogen bond has about 50% double bond character. Furthermore, bond angle measurements have revealed that the angles of the bonds to nitrogen are similar to those about the trigonal carbon atoms as shown in Fig. 6.2.

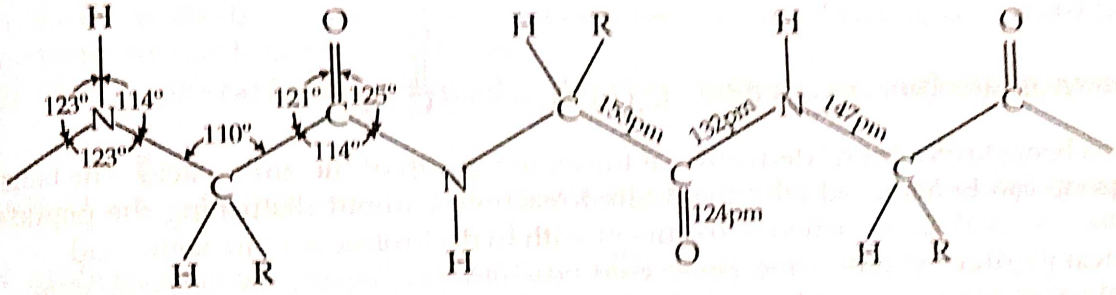


Fig. 4.2. Geometry of peptide bond

Since carbon-nitrogen bond has about 50% double bond character, the peptide bond may be represented as a resonance hybrid of following structures.

4.12. SYNTHESIS OF PEPTIDES FROM AMINO ACIDS

One of the notable achievements in the field of protein chemistry is the synthesis of some of the polypeptides in the laboratory in recent years. Theoretically it seems very simple to synthesise polypeptides by the condensation of similar or dissimilar amino acids in such a way that the carboxyl group of one molecule of an amino acid condenses with the amino group of a neighbouring molecule. But in actual practice this cannot be done so easily because of certain problems. We shall now briefly discuss what are these problems and how were these overcome in the earlier attempts to synthesise peptides called **classical synthesis** or **solution phase synthesis** of peptides. This will be followed by the description of modified procedure developed for this purpose.

4.12.1. Classical Peptide Synthesis

The essential considerations involved in the formation of di–, tri– and higher peptides by the condensation of amino acid molecules and the experimental procedure followed are given below.

The condensation reaction between two amino acid molecules to form peptide linkage is an endothermic reaction and does not take place easily. Therefore, what is done in actual practice is that the carboxylic group of one amino acid molecule is **activated** by conversion of the amino group into acid chloride. This is then reacted with the amino group of another amino acid molecule.

But there is another problem caused by the presence of both the acid group and the amino group in the same molecule. To understand this problem, let us consider the synthesis of a simple dipeptide, alanylglycine (Ala—Gly). Let us say, we first activate the carboxyl group of alanine by converting it into acid chloride and then allow it to react with glycine. In practice, alanyl chloride can react not only with glycine but also with another molecule of its own. Therefore, the reaction would yield not only Ala—Gly but also Ala—Ala. This would mean that the yield of the desired product would be low. At the same time, the different products formed would have to be separated which itself is quite difficult.

To overcome this problem what is done is to "**protect**" the amino group of the first amino acid before the acid is converted into the chloride. This involves the conversion of amino group into some other group (of low nucleophilicity) which would not react with the chlorinating agent or with the acid chloride formed. The usual method of protecting the amino group by acetylation or benzoylation is not feasible here. This is because attempts to remove the protecting acetyl or benzoyl group from the acetylated peptide formed lead to the cleavage of peptide bond as well. A suitable protecting group is that which can be easily introduced in the starting amino acid and can be removed after the reaction without disturbing the peptide bond formed. A number of reagents have been developed for this purpose. One such reagent is benzyloxycarbonyl chloride

(earlier known as carbobenzoxy chloride), $C_6H_5CH_2-O-\overset{\overset{O}{\|}}{C}-Cl$.

It forms benzyloxycarbonyl derivative of the amino group of the amino acid. The benzyloxycarbonyl group can be removed after the desired reaction, without disturbing the peptide bond formed, either on catalytic reduction or treatment with hydrobromic acid in acetic acid.

A **typical peptide synthesis** *from amino acids may, therefore, involve the following steps :*

(*i*) **Protection** *of amino group in one of the amino acids with benzyloxycarbonyl group or any other suitable protecting group.*

(*ii*) **Activation** *of the carboxyl group of the above protected acid by conversion into acid chloride.*

(*iii*) **Formation** *of peptide linkage by reaction of the acid chloride with another amino acid molecule.*

(*iv*) **Removal** *of the protecting group without disturbing the peptide bond.*

Let us illustrate the above synthetic route by considering the synthesis of glycylalanine (a dipeptide).

(*i*) Protection of amino group.

$$\underset{\text{Benzyloxycarbonyl chloride}}{C_6H_5CH_2OCOCl} + \underset{\text{Glycine}}{H_3\overset{+}{N}CH_2COO^-} \xrightarrow{-HCl} \underset{\text{N-Benzyloxycarbonyl glycine}}{C_6H_5CH_2OCONHCH_2COOH}$$

(*ii*) Formation of acid chloride :

$$C_6H_5CH_2OCONHCH_2COOH + SOCl_2 \xrightarrow[-SO_2,\ -HCl]{} \underset{\text{Acid chloride of N-benzyloxycarbonyl glycine}}{C_6H_5CH_2OCONHCH_2COCl}$$

(*iii*) Formation of peptide linkage :

$$C_6H_5CH_2OCONHCH_2COCl + H_3\overset{+}{N}\underset{\underset{\text{Alanine}}{CH_3}}{CHCOO^-} \xrightarrow{-HCl} \underset{\underset{\text{N-Benzyloxycarbonyl glcylalanine}}{CH_3}}{C_6H_5CH_2OCONHCH_2CONHCHCOOH}$$

PROTEINS

Proteins are extremely complex natural polymers which are ranked *first* amongst the chemical substances essential for the growth and maintenance of life (Greek *proteios* = first) and that is why they were given the name proteins (Mudlar, 1839). They are present in all living cells ; being found in almost every part of every plant and animal. In human beings, for instance, they are main ingredients of muscles, skin, hair, nails, blood tendons, arteries and connective tissue.

The proteins in different plants and animals and even the proteins in different tissues of a particular plant or animal differ from one another in their composition and biological functions. However, in elementary composition proteins are made up of carbon, hydrogen, oxygen, nitrogen and also sulphur in many cases. Phosphorus, iron, magnesium etc. are also present in some proteins. The molecular masses of proteins are very high and values running into millions have been reported for some proteins.

Plants synthesise proteins from carbon dioxide, water and inorganic nitrogenous substances. Animals, on the other hand, have to mainly depend upon the plants for their protein supply.

From chemical point of view, proteins are essentially polypeptides having molecular mass more than 10,000.

4.13. CLASSIFICATION OF PROTEINS

Proteins are arbitrarily classified in many different ways. Two of the widely used systems of classification are given below.

4.13.1. Classification According to Three Dimensional Structure

According to one system of classification, proteins are divided into two main classes depending upon their three dimensional structure. These classes are :

(1) **Fibrous proteins.** These proteins consist of linear, threadlike molecules which tend to lie side by side to form fibres. The peptide chains in them are mostly held together by strong *intermolecular* hydrogen bonds. They are tough and insoluble in water.

They serve as the chief structural material of animal tissue. Important examples of fibrous proteins are *keratin* in skin, hair, nails, wool, horn and feathers ; *collagen* in tendon ; *fibroin* in silk and *myosin* in muscles.

(2) **Globular proteins.** These proteins consist of polypeptide molecules that are extensively folded into compact units which approach spheroidal shapes. The peptide chains in them are stabilised by *intramolecular* hydrogen bonds. They are generally soluble in water or aqueous solution of acids, bases or salts.

The function of these proteins is to maintain and regulate life processes. Thus this class of proteins includes all *enzymes*, many hormones (*e.g. insulin* from the pancreas and *thyroglobulin* from the thyroid gland), *haemoglobin* which transports oxygen from the lungs to tissues, *albumin* from eggs, etc.

Table 4.3. *Comparison of fibrous and globular proteins*

Fibrous proteins	*Globular proteins*
(i) These proteins consist of linear thread-like molecules whch lie side by side.	These proteins consist of molecules which are extensively folded into compact units approaching almost spherical shapes.
(ii) There is extensive formation of hydrogen bonding between neighbouring chains.	Hydrogen bonding and van der Waal's interactions exist between different parts of polypeptide chain.
(iii) They are insoluble in water.	They are soluble in water.
(iv) They are stable towards small changes in temperature and pH.	They are very sensitive to changes in temperature and pressure.

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4.13.2. Classification According To Hydrolysis Products

According to this system of classification, proteins are classified according to their composition and hydrolysis products.

(1) **Simple proteins.** These are the proteins which on hydrolysis yield only amino acids. These important examples are : *albumins* (such as egg albumin, lactalbumin, serum albumin), *globulins* (such as glutenin in wheat and coryzenin in rice.)

(2) **Conjugated proteins.** These are the proteins in which a protein part is united with some non-protein part called **prosthetic group.** The prosthetic part is mostly concerned with the special biological functions of the protein.

The conjugated proteins may be further divided into different classes depending upon the nature of prosthetic group. Thus we have :

(*i*) **Nucleoproteins** such as *nuclein* of glandular tissue (prosthetic group being nucleic acids).

(*ii*) **Glyco proteins** such as *mucin* which is a constituent of saliva (prosthetic group being some carbohydrate).

(*iii*) **Chromo proteins** such as haemoglobin and chlorophyll (prosthetic group being some pigment having some metal such as Fe, Cu, Mn etc. in its structure) and so on.

(3) **Derived proteins.** These are the degradation products obtained by the partial hydrolysis of simple or conjugated proteins. For example, we have proteoses, peptones, peptides, etc.

4.14. GENERAL CHARACTERISTICS OF PROTEINS*

The important characteristics of proteins may be summarised as follows :

(1) **Elemental composition.** The elements generally present in poteins are carbon, hydrogen, oxygen and nitrogen. Their approximate composition is almost always : C = 51–52%, O = 22–24% N = 16% H = 7%. Sulphur and phosphorus, when present, occur to the extent of 1% and 0.5 respectively.

(2) **High molecular mass.** The molecular masses of proteins are very high and values running into several millions have been reported for certain proteins. The reported molecular masses of some proteins are : egg albumin 34,000–44,000 ; milk globulin 35,000–40,000 ; haemoglobin 65,000–70,000 and casein 75,000–100,000.

(3) **Physical state.** Proteins are generally colourless, tasteless, amorphous solids having no definite melting point. Some of them have, however, been obtained in crystalline form.

They are usually **colloidal** in character and have a strong tendency to adsorb other substances. By making use of their readiness to form colloidal solutions, proteins can be separated from soluble crystalline salts by the process of dialysis.

(4) **Amphoteric nature.** Like amino acids, proteins exist as amphoteric dipolar ions capable of reacting with both acids and bases.

(5) **Optical activity.** All proteins are optically active and further all of them have the L-configuration as they are composed of L-amino acids.

(6) **Isoelectric point.** Like amino acids, there exists for each protein an isoelectric point *i.e.* certain *p*H, at which its ionisation is minimum and it is least soluble. For example, casein has its isoelectric point at *p*H 4.6. This property of proteins is often utilised in their isolation.

(7) **Hydrolysis.** All proteins can be hydrolysed in the presence of acids, alkalies or enzymes. The hydrolysis proceeds slowly and in stages and the end products are simple amino acids. The sequence of hydrolytic products may be shown by the following scheme in which each type of product is less complex than the preceding one.

Proteins ⟶ *Proteoses* ⟶ *Polypeptides* ⟶ *Simple peptides* ⟶ *Amino acids.*

Conjugated proteins also yield products other than peptides or amino acids.

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*Sections 4.14, 4.15, 4.16 are not included the syllabus. These have been given here only to provide general information.

(8) **Denatuation.** Proteins are extremely sensitive to the action of heat, acids, alkalies, salts of heavy metals and many other reagents. When treated in this way, proteins are rendered insoluble and lose their biological activity. This phenomenon is known as **denaturation** and the modified proteins thus produced are called **denatured proteins.** Denaturation is accompanied by changes in properties such as conformation and optical rotation as well. Two very common examples of denaturation of proteins are : coagulation of egg white by the action of heat and curdling of milk.

Due to the mild conditions under which denaturation takes place, the covalent bonds are not affected so that the primary polypeptide structure remains intact. But the tertiary structure gets unfolded from a well-defined shape to randomly coiled structure.

Denaturation is generally irrevesible in nature. For example a coagulated egg cannot change into uncooked egg by cooling. Similarly curdled milk does not change into original homogenous form.

Renaturation. Proteins can also be precipitated or coagulated from their solutions by saturating the solution with soluble salts like ammonium sulphate, magnesium sulphate or by addition of water, alcohol, acetone, etc. This is **reversibe** denaturation and the original colloidal form can be re-obtained upon the removal of the reagent. This process is known as **renaturation.** It is accompanied by the complete recovery of original biological activity and tertiary structure.

4.15. ANALYSIS OF PROTEINS*

Proteins give a number of colour reactions that are used in their analysis. These reactions are, however, essentially the tests of certain amino acids and other reactive groups and are, therefore, employed collectively to analyse the nature of proteins.

The important tests are described below :

(1) **Biuret test.** This test consists in adding a drop of copper sulphate solution to an alkaline solution of protein when a bluish violet colour develops. The test is also given by the bigger hydrolytic products of proteins such as proteoses and peptones.

(2) **Ninhydrin test.** Proteins as well as amino acids produce a blue to red violet colouration when treated with ninhydrin, *i.e.* triketohydrindene hydrate.

(3) **Heller's test.** When concentrated nitric acid is poured along the sides of a test tube containing protein solution, a white precipitate appears at the junction of the two layers. This test is commonly employed for detecting albumin in urine.

(4) **Xanthoproteic test.** When warmed with concentrated nitric acid, certain proteins (such as the skin of the hand) produce a yellow colour. The test is given by proteins containing tyrosine or tryptophane.

(5) **Millon's test.** On treatment with a solution of mercury in nitric acid (which furnishes a mixture of mercuric and mercurous nitrates), proteins containing tyrosine produce a white precipitate turning to red.

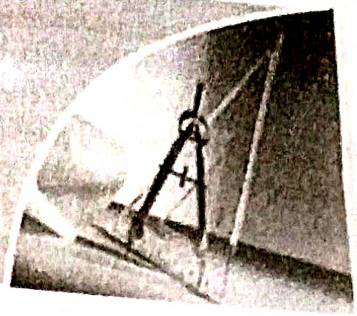
(6) **Mollisch's Test.** When concentrated sulphuric acid is added dropwise to an alcoholic solution of α-naphthol and protein taken in a test tube, a violet colour is formed at the junction of two layers. This test is given by glyco proteins.

4.16. BIOLOGICAL IMPORTANCE OF PROTEINS*

Proteins are very essential for animal life as they serve many useful functions in the body. But before they can be utilised by the body, they must be hydrolysed into their constituent amino acids. Hydrolysis starts in the stomach where hydrochloric acid and the enzyme *pepsin* break the protein into lower molecular mass polypeptides. In the intestine, the enzymes *trypsin* and *erepsin* complete the hydrolysis to form amino acids. The amino acids are assimilated in the blood stream and carried to the cells in various parts of the body. There some of the amino acids are converted back into specific proteins which the body requires for its continued well being while others get burnt as fuels

Chapter 5

Synthetic Polymers



5.1. INTRODUCTION

Polymers are very large molecules with very high molecular masses which are composed of many small repeating units joined together in a regular way (Greek *poly* = many, *mers* = parts).

The simple molecules from which the repeating structural units are derived are called **monomers** and the process of formation of polymers from the simple starting molecules (*i.e., the monomers*) is known as **polymerisation.** Polyethylene $+CH_2-CH_2+_n$ for instance, affords an important example of a widely used polymer obtained by the polymerisation of the monomer, ethylene ($CH_2=CH_2$).

In addition to the repeating structural units, a polymer generally contains two kinds of end groups. For example in case of polyethylene the end group may be CH_3CH_2- and $-CH=CH_2$ so that polyethylene may be repesented as :

$$CH_3CH_2+CH_2-CH_2+_{n-2}CH=CH_2$$

However, the nature of end groups depends upon the method of preparation of the polymer and in many cases the end groups are not known with certainty. As such polymers are often written in terms of recurring units only such as $+CH_2-CH_2+_n$ in case of polyethylene.

Homopolymers and Copolymers.

Homopolymers. *A polymer which is obtained from only one type of monomer molecules is known as* **homopolymer.** For example, polyethylene is a homopolymer obtained by the polymerisation of only one type of monomer molecules *i.e.* ethylene.

Copolymer. *A polymer made from two or more types of monomer molecules is referred to as a* **copolymer** (Latin *cum* = together). For example, nylon 66 $+\left[\begin{matrix}O\\\|\\C\end{matrix}-(CH_2)_4-\begin{matrix}O\\\|\\C\end{matrix}-NH(CH_2)_6NH\right]+_n$ is a copolymer obtained from adipic acid and hexamethylene diamine.

Properties of Polymers. The properties of a polymer are very much dependent upon the kinds of monomers from which the polymer is obtained and upon its molecular mass. By varying these, it is possible to have polymers having tailor-made properties. Thus, we have many polymeric products which are tough, flexible and resistant to most of the chemical reagents. On the other hand, we also have polymers which have a waxy feel and are insoluble in most of the solvents. There are still others which have excellent thermal and electrical properties.

It is not surprising, therefore, that a large part of modern chemical industry deals with the discovery and production of polymeric materials.

It may be pointed out that apart from man made or **synthetic polymers**, *there are many polymers of* **natural origin** *such as proteins, cellulose and starch.* We also have *semi-synthetic polymers* which are obtained by chemical modification of naturally occurring polymers. For example, rayon (cellulose diacetate), gun-cotton (cellulose trinitrate) and vulcanised rubber belong to this class. However, in this chapter we shall be dealing with synthetic polymers only.

Polymers and macromolecules. Even though the terms polymers and macromolecules are often used interchangeably, there is a fine distinction between the two.

A polymer always consists of very large number (running into hundreds) of repeating monomer units. On the other hand, a macromolecule is a giant molecule which may or may not contain repeating monomer units. For example, chlorophyll is a macromolecule but not a polymer because it does not contain repeating monomers. In contrast, polythene may be regarded as a polymer as well as a macromolecule because it is made up of a large number of repeating monomer units. In other words, it may be said that all polymers are macromolecules *but all macromolecules are not polymers.*

5.2. PREPARATION OF SYNTHETIC POLYMERS

The preparation of synthetic polymers involves two essential requirements. These are :

(*i*) *The monomers used in polymerisation should be of the highest purity and*

(*ii*) *The reaction conditions should be carefully controlled.*

This is because the reactions involved in polymerisation must proceed in almost quantitative yields. Any undesirable side reaction can stop polymer chains from growing further and thus prevent the formation of high molecular mass polymers.

The processes involved in the synthesis of polymers can be broadly divided into two categories. These are :

(*i*) Addition or chain-growth polymerisation and

(*ii*) Condensation or step-growth polymerisation

Let us discuss the two types one by one.

5.3. ADDITION OR CHAIN GROWTH POLYMERISATION

This type of polymerisation involves the addition together of the molecules of the monomer or monomers to form a large polymeric molecule in which the molecular formula of the repeating structural unit is the same as that of the starting monomer. Polymers thus formed are referred to as **addition or chain-growth polymers.**

Addition or chain growth polymerisation generally takes place among molecules containing carbon-carbon double bonds. The reaction is started by a suitable *initiator* which adds to a carbon-carbon double bond to form a reactive intermediate. This intermediate adds to a second molecule of monomer to form a new intermediate which, in turn, adds to third monomer unit and so on. In this way, the polymer chain keeps on growing by the successive addition of monomers, one at a time, to the reactive end of the chain. The complete process is sometimes also referred to as **vinyl polymerisation.**

Depending upon the monomer taken and the initiator used in the above polymerisation the reactive intermediates may be free radicals, carbocations or carbanions. Some of the well-known polymers formed by this method are polyethylene $\left[CH_2 - CH_2 \right]_n$, polypropylene

$\left[\begin{array}{l} CH_2 - CH \\ \quad\quad | \\ \quad\quad CH_3 \end{array} \right]_n$, polyvinyl chloride, $\left[\begin{array}{l} CH_2 - CH \\ \quad\quad | \\ \quad\quad Cl \end{array} \right]_n$ and polyacrylonitrile

$\left[\begin{array}{l} CH_2 - CH \\ \quad\quad | \\ \quad\quad CN \end{array} \right]_n$. Let us now discuss in detail the mechanism of chain growth or vinyl polymerisation by starting with free radical vinyl polymerisation.