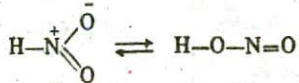
Chapter 31

Nitroalkanes, Diazoalkanes and Azides

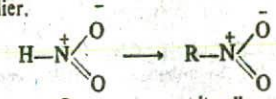
NITROALIKANES

Nitrous acid (HNO_2) exists in two tautomeric forms

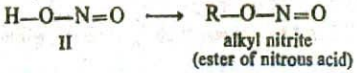


I II

The alkyl derivatives arising from form I are known as *Aliphatic Nitro compounds*. Those derived from form II are called *alkyl nitrites*, which are, in fact, the esters of nitrous acid and have been discussed earlier.



I nitroalkane



II alkyl nitrite (ester of nitrous acid)

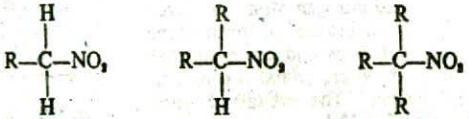
In nitroalkane molecule, nitrogen atom is attached directly to carbon of the alkyl group (C—N) and in alkyl nitrites it is attached to carbon through oxygen (C—O—N).

Nitroalkanes are correctly considered as the derivatives of alkanes in which a hydrogen atom is replaced by a nitro group, $-NO_2$.

alkane nitroalkane

The general formula of nitroalkanes is $R-NO_2$ where the nitro group ($-NO_2$) is the functional group.

Like alcohols, nitroalkanes are further divided into primary, secondary and tertiary nitroalkanes according as the nitro group is bonded to a primary (1°), secondary (2°), or a tertiary carbon atom.



1° nitroalkane 2° nitroalkane 3° nitroalkane

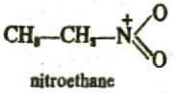
NOMENCLATURE

Aliphatic nitro compounds are solely named by the IUPAC system. The systematic name of a nitro compound is constructed by prefixing 'nitro' to the name of the alkane in which the $-NO_2$ group is substituted. The total name emerges as one word, the position of the $-NO_2$ group on the carbon chain being indicated by a number. For example,

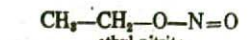
Formula	IUPAC Name	Formula	IUPAC Name
$CH_3—NO_2$	Nitromethane	$CH_3—\underset{\displaystyle NO_2}{\underset{\vert}{CH}}—CH_3$	2-Nitropropane
$CH_3—CH_2—NO_2$	Nitroethane	$\overset{1}{CH_3}—\overset{2}{\underset{\displaystyle NO_2}{\underset{\vert}{CH}}}—\overset{3}{\underset{\displaystyle CH_3}{\underset{\vert}{CH}}}—\overset{4}{CH_3}$	2-Nitro-3-methyl butane
$CH_3—CH_2—CH_2—NO_2$	1-Nitropropane		

ISOMERISM

Besides chain and position isomerism, nitroalkanes also show functional isomerism with alkyl nitriles. Thus nitroethane ($C_2H_5NO_2$) is isomeric with ethyl nitrite (C_2H_5ONO).

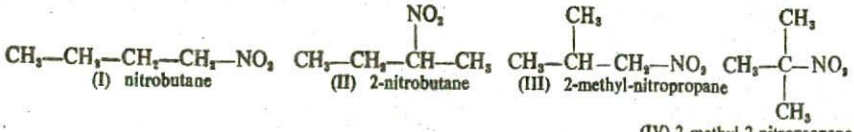


nitroethane



ethyl nitrite

The molecular formula $C_4H_9NO_2$ can represent the following isomeric niiroalkanes.



(I) nitrobutane (II) 2-nitrobutane (III) 2-methyl-nitropropane (IV) 2-methyl-2-nitropsopane

The structures I, II, III and IV represent chain isomers, while I and II represent position isomers.

STRUCTURE

In constructing the structure of a nitroalkane molecule, nitrogen atom plays the key role. The configuration of the valence shell of nitrogen in different states is as below.

N in ground state : $2s^2\ 2p_x^1\ 2p_y^1\ 2p_z^1$

N in excited state : $2s^1\ 2p_x^1\ 2p_y^1\ 2p_z^2$
(one s electron permoted to $2p_z$ orbital)

N in hybridized state : $2(sp^2)^1\ 2p_z^2$

As shown above, in the excited nitrogen atom the three half-filled orbitals $2s$, $2p_x$, $2p_y$ hybridize to form three $2sp^2$ orbitals. These lie in one plane and are inclined at angle of 120°. The unhybridized $2p_z$ orbital is perpendicular to the plane of sp^2 orbitals. The orbitals of hybridized nitrogen are shown in Fig. 33·1.

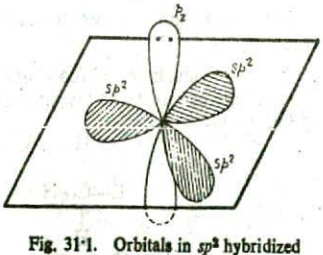


Fig. 31·1. Orbitals in sp^2 hybridized nitrogen.

In formation of nitroalkane molecule (RNO_2), of the three sp^2 orbitals of N atom one overlaps with sp^3 orbital of carbon of the alkyl group R to create a σ bond (R—N). The remaining two sp^2 orbitals form two σ bonds (N—O) by overlap with half-filled p_x orbitals on each of the oxygen atoms ($2s^2\ 2p_x^1\ 2p_y^1\ 2p_z^2$), Fig. 31·2. At this stage there is left on nitrogen one unhybridized p orbital ($2p_z^2$) with an unshared electron pair, and a half-filled p orbital ($2p_y$) on each oxygen atom. The two unused p_z orbitals of oxygen are equidistant from p_z orbital of nitrogen and parallel to it. These available p orbitals of nitrogen and the two oxygens overlap sidewise producing a delocalized cloud which encompasses all the three atoms (Fig. 31·2).

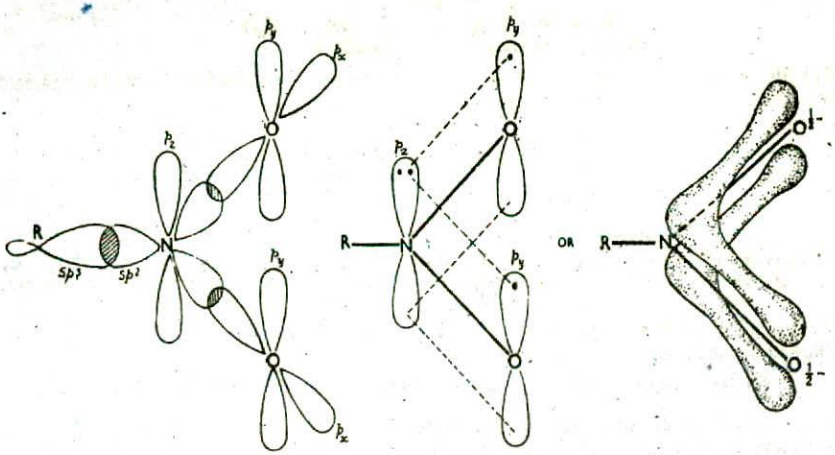
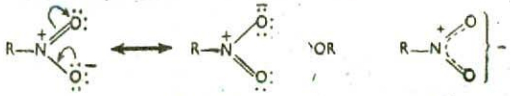


Fig. 31·2. Orbital structure of Nitroalkanes.

In terms of valence bonds, the structure of nitroalkanes may be written as

(classical) (polar)

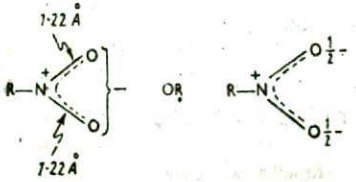
The polar structure is supported by a large dipole moment of the nitro group. Thus nitroalkane is represented as a resonance hybrid of the canonical forms I and II



I II III

RESONANCE HYBRID

The hybrid structure III suggests the equivalence of the two nitrogen-oxygen bonds. The spectroscopic and diffraction studies of nitroalkanes have shown that the bond distance for each of the N—O bonds is 1·22 Å, which is less than N—O single bond (1·36 Å) and N=O double bond (1·15 Å). This confirms the bond structure and distribution of charge in nitroalkane molecule.



METHODS OF PREPARATION

The general methods of preparation of nitroalkanes are listed below.

(I) **Vapour Phase Nitration of Alkanes.** Nitroalkanes are made industrially by passing a gaseous mixture of an alkane and nitric acid through a narrow metal tube at about 400°C.

$$\underset{\text{alkane}}{R{-}H} + \underset{\text{nitric acid}}{HO{-}NO_2} \xrightarrow{400^\circ} \underset{\text{nitroalkane}}{R{-}NO_2} + H_2O$$

With alkanes other than methane, a mixture of nitralkanes is obtained which can be separated by fractional distillation. For example,

$$CH_3{-}CH_3 \xrightarrow[400^\circ]{HONO_2} \underset{\text{nitroethane (73\%)}}{CH_3{-}CH_2{-}NO_2} + \underset{\text{nitromethane (27\%)}}{CH_3{-}NO_2}$$

$$\underset{\text{propane}}{CH_3{-}CH_2{-}CH_3} \xrightarrow[400^\circ]{HONO_2} \underset{\text{1-nitropropane (25\%)}}{CH_3{-}CH_2{-}CH_2{-}NO_2} + \underset{\text{2-nitropropane (40\%)}}{CH_3{-}\overset{NO_2}{\overset{|}{C}}H{-}CH_3} + \underset{\text{nitroethane (10\%)}}{CH_3{-}CH_2{-}NO_2} + \underset{\text{nitromethane (25\%)}}{CH_3{-}NO_2}$$

The nitroalkanes with less carbon atoms are produced by the initial rupture of C—C bonds followed by nitration.

Similarly *n*-butane yields nitromethane, nitroethane, 1-nitrobutane and 2-nitrobutane.

(2) **Action of Alkyl halides with Metal nitrites.** Nitroalkanes are obtained in the laboratory by the action of primary or secondary alkyl halides (bromides or iodides) on silver nitrite in ethanol.

$$\underset{1^\circ \text{ or } 2^\circ \text{ halide}}{R{-}Br} + AgNO_2 \longrightarrow \underset{\substack{\text{nitroalkane}\\(80\%)}}{R{-}NO_2} + AgBr$$

The product consists of 80 per cent nitroalkane along with 20 per cent of the isomeric alkyl nitrite (RO—N=O) which is also produced in the reaction. The components of the mixture can be easily separated by fractional distillation as the nitroalkane boils at a much higher temperature than the alkyl nitrite.

Silver nitrate is a costly reagent. By using sodium or potassium nitrite in a suitable solvent (dimethyl sulphoxide or *N, N*-dimethylformamide) nitroalkane may be obtained in 50-60 per cent yield.

$$\underset{1^\circ \text{ or } 2^\circ \text{ halide}}{R{-}Br} + \overset{+}{Na}\overset{-}{NO_2} \xrightarrow[\text{sulphoxide}]{\text{dimethyl}} \underset{(50-60\%)}{R{-}NO_2} + \overset{+}{Na}\overset{-}{Br}$$

Tertiary halides react with metal nitrites to form chiefly alkyl nitrites and alkenes, and are therefore not used.

(3) **Action of Sodium Nitrite with α-Halogeno Carboxylic acid salts.** A useful method for preparing lower nitroalkanes is to boil an aqueous solution of sodium nitrite ($Na^+NO_2^-$) with sodium salt of α-halogeno-carboxylic acid. Sodium nitrocarboxylate produced in the first instance decarboxylates to form the nitroalkane. For example,

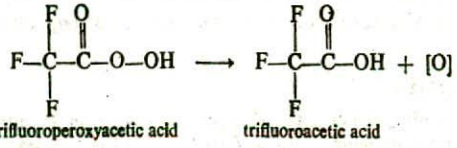
$$\underset{\text{sod chloroacetate}}{Cl{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}\overset{-}{O}\overset{+}{Na}} + \overset{+}{Na}\overset{-}{NO_2} \xrightarrow[aq.\text{ solution}]{\text{boil}} \underset{\text{sod nitroacetate}}{O_2N{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}\overset{-}{O}\overset{+}{Na}} + \overset{+}{Na}\overset{-}{Cl}$$

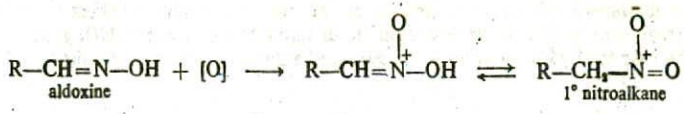
$$O_2N{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}\overset{-}{O}\overset{+}{Na} + H_2O \longrightarrow \underset{\text{nitromethane}}{CH_3{-}NO_2} + \overset{+}{Na}\overset{-}{HCO_3}$$

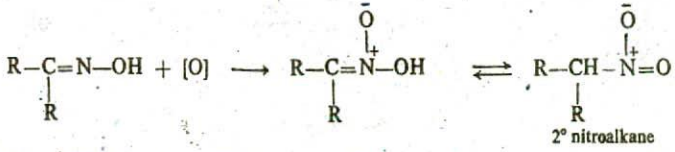
(4) **Hydrolysis of α-Nitroalkanes.** Levy and Scaife recently developed a method for preparing nitroalkanes by hydrolysing α-nitroalkenes in presence of acids. Thus,

$$\underset{\text{2-methyl-1-nitropropene}}{CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}NO_2} + H_2O \longrightarrow \underset{\text{acetone}}{CH_3{-}\overset{CH_3}{\overset{|}{C}}{=}O} + \underset{\text{nitromethane}}{CH_2{-}NO_2}$$

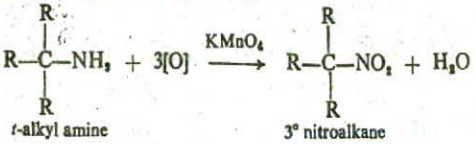
(5) Oxidation of Oximes. Primary and Secondary nitroalkanes are obtained in good yields by oxidising aldoximes and ketoximes respectively with the help of trifluoroperoxyacetic acid.







(6) Oxidation of *t*-Alkyl amines. Tertiary nitroalkanes are best prepared by oxidising *t*-alkyl amines with aqueous potassium permanganate.



PHYSICAL PROPERTIES

(1) The lower nitroalkanes are colourless pleasant smelling liquids at ordinary temperature.

(2) Nitromethane is about 10 per cent soluble in water but the higher alkanes are practically insoluble. This shows that they are less able than alcohols to form hydrogen bonds.

(3) Since they are polar molecules, nitroalkanes are useful solvents for polar and ionic compounds.

(4) They have abnormally high boiling points. Thus,

	bp°C		*bp°C*
Nitromethane, $CH_3—NO_2$	101	1-Nitropropane, $CH_3CH_2CH_2—NO_2$	112
Nitroethane, $C_2H_5—NO_2$	115	2-Nitropropane, $(CH_3)_2CH—NO_2$	120

This is explained by the fact that nitroalkanes are highly polar compounds as shown by their high dipole moments (3·6 D). Due to the appreciable electrostatic attraction between the polar molecules, they need a larger amount of energy (heat) in order to separate them.

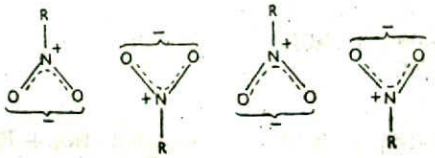


Fig. 31·3. Intermolecular association in nitroalkanes.

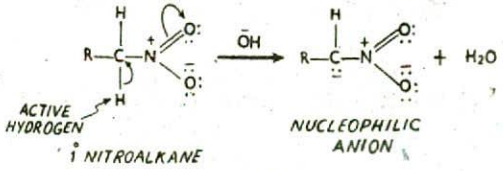
Nitroalkanes have much higher boiling points than the less polar isomeric alkyl nitrifes (CH_3—O—NO, bp −12° ; C_2H_5—O—NO, bp 17°).

(5) They are less toxic than isomeric nitrites and aromatic nitro compounds.

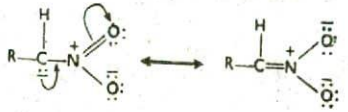
(6) Nitro groups of nitroalkanes can be identified by strong infrared bands at 1580 and 1275 cm^{-1}.

CHEMICAL PROPERTIES

The structure of nitro group indicates a positive charge on the nitrogen atom. Therefore it is a strongly electron-withdrawing group and is able to exert a strong inductive effect (−I) and mesomeric effect (−M). Because of this electron-withdrawal effect Primary and Secondary nitroalkanes possess active hydrogen atoms on carbon adjacent to NO_2 group. In the presence of a base the hydrogen atom is removed and a nucleophilic anion results.



The nucleophilic anion thus produced is resonance stabilized.

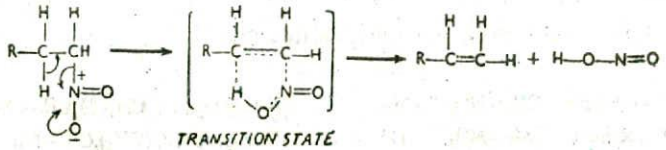


Therefore primary and secondary nitroalkanes are capable of undergoing nucleophilic addition reactions as also exhibiting tautomerism. Their important reactions are listed below.

(1) **Action of Heat.** Nitroalkanes are decomposed on moderate heating beyond 300°. Alkenes are formed with the elimination of nitrous acid.

$$\underset{\text{nitroalkane}}{R{-}CH_2{-}CH_2{-}NO_2} \xrightarrow[>300^\circ]{\Delta} \underset{\text{alkene}}{R{-}CH{=}CH_2} + HNO_2$$

MECHANISM. The reaction presumably takes place through a cyclic transition state, which results in *cis* elimination.

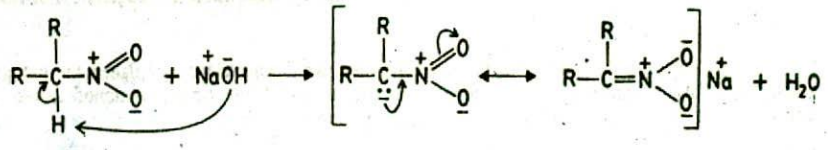


(2) **Formation of Salts.** The α-hydrogens of primary and secondary nitroalkanes are acidic in nature much in the same fashion as the α-hydrogen atoms of aldehydes and ketones. Thus they dissolve in NaOH or KOH solution forming salts.

$$\underset{\text{1° nitroalkane}}{R{-}CH_2{-}NO_2} + NaOH \longrightarrow \underset{\text{sodium salt}}{R{-}\overset{-}{C}H(\overset{+}{N}a){-}NO_2} + H_2O$$

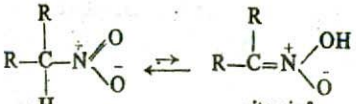
$$\underset{\text{2° nitroalkane}}{R{-}\overset{R}{\overset{|}{C}}H{-}NO_2} + NaOH \longrightarrow \underset{\text{sodium salt}}{R{-}\overset{R}{\overset{|}{\overset{-}{C}}}(\overset{+}{N}a){-}NO_2} + H_2O$$

The acidic behaviour and formation of salt is ascribed to strongly electron-withdrawing effect of NO_2 group and resonance stabilisation of the resulting anion.



I II

It is of interest that primary and secondary nitroalkanes exhibit tautomerism, the two tautomeric forms being derived by the addition of a proton (H^+) to the froms I and II of the anion of the salt shown above.

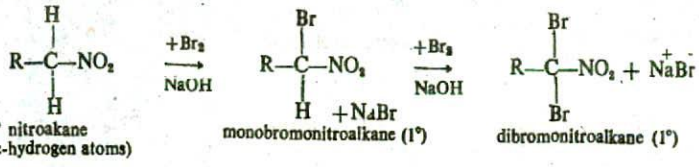


nitro form, or *iso* form — nitronic form, or *aci* form

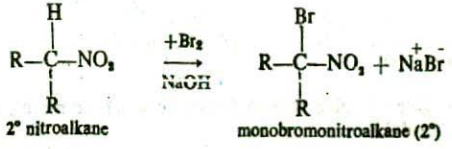
The tautomeric equilibrium lies almost entirely to the nitro form due to the resonance stablisation of the NO_2 group. That is why nitroalkanes are often called 'peseudo acids', the acid behaviour being shown only in presence of strong alkali when the *aci* (from acid) from exists. The *aci* form is also called nitronic acid.

The existence of the teutomeric mixture has been established by isolation of the *iso* and *aci* forms in the pure state. It is found that the *iso* form dissolves in NaOH solution slowly, while the *aci* form dissolves instantly. Nitro form gives no colour with ferric chloride, while the *aci* form produces reddish brown colour characteristic of enol structure (C=C−OH). Lastly, the acidification of sodium salt of a nitroalkane raises the electrical conductivity of the solution due to the production of the acid form but at once the conductivity falls due to the conversion of the *aci* form to unionised nitro form.

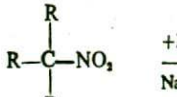
(3) **Halogenation.** Primary and Secondary nitroalkanes when treated with halogen (chlorine or bromine) in alkaline solution are readily halogenated. The α-hydrogens are thus replaced by the halogen.



1° nitroalkane (two α-hydrogen atoms) — monobromonitroalkane (1°) — dibromonitroalkane (1°)



2° nitroalkane — monobromonitroalkane (2°)

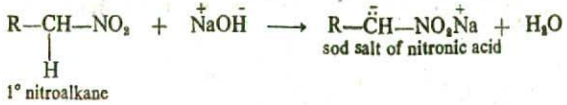


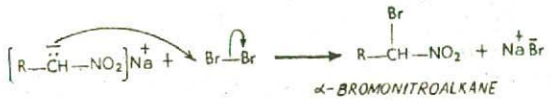
3° nitroalkane (one α-hydrogen atom) — *No action*

As shown above, primary nitroalkanes having two replaceable α-hydrogens can form mono- and dihalogen derivatives, while secondary nitroalkanes having one α-halogen can form monohalogen derivative only. Tertiary nitroalkanes with no replaceable hydrogen do not react at all.

In case of nitromethane, all the three H-atoms can be successively replaced by halogen atoms. Thus trichloronitromethane (**Chloropicrin**, an important insecticide) is manufactured by treating nitromethane with chlorine and sodium hydroxide.

MECHANISM. The halogen substitution reactions of nitroalkanes are accounted for as due to the inductive effect of the nitro group.

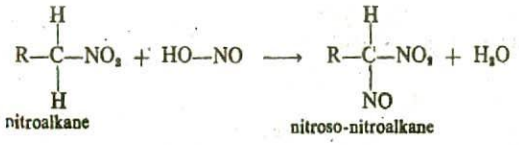


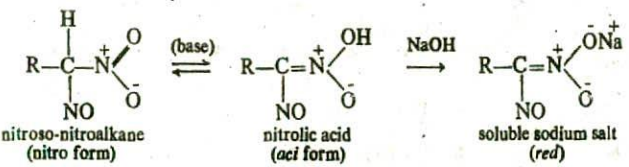


The above steps are repeated so as to form the dibromo derivative.

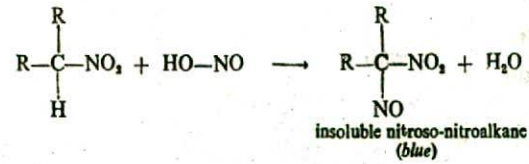
(4) **Reaction with Nitrous Acid.** Primary, secondary and tertiary nitroalkanes behave differently when treated with nitrous acid. The reactive hydrogen atoms on α-carbon to NO_2 group are involved in the reaction.

(*a*) A primary nitroalkane gives a blue nitroso-nitroalkane which in presence of NaOH solution produces a soluble sodium salt having red colonr.

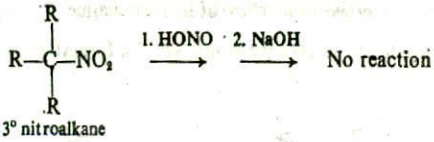




(*b*) A secondary nitroalkane gives a blue nitroso derivative which no more contains a replaceable H-atom and is, therefore, insoluble.

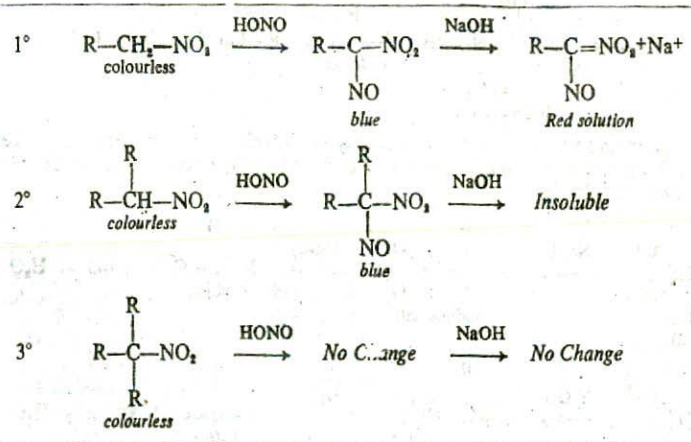


(*c*) A tertiary amine does not react since it has no reactive hydrogen on the α-carbon.



The reaction of nitrous acid on the three types (1°, 2°, 3°) of nitroalkanes serves as a test for their indentification.

Table. Identification of 1°, 2°, 3° nitroalkanes



Since nitroalkances can be formed from 1°, 2° and 3° alcohols by treatment with HI and th $AgNO_2$, the reaction with nitrous acid also forms the basis of the *Victor Meyer Test* for distiguishing 1°, 2° and 3° alcohols.

(5) **Reduction.** Nitroalkanes are reduced to a primary amine with hydrogen on Ra nickel, and with lithium aluminium hydride.

$$\underset{\text{nitroalkane}}{R{-}NO_2} + 3H_2 \xrightarrow{\text{Raney Ni}} \underset{\text{1° amine}}{R{-}NH_2} + 2H_2O$$

$$R{-}NO_2 \xrightarrow{LiAlH_4} R{-}NH_2$$

This reduction can also be effected with iron and hydrochloric acid.

$$R{-}NO_2 + 6H^+ + 6e^- \longrightarrow R{-}NH_2 + 2H_2O$$

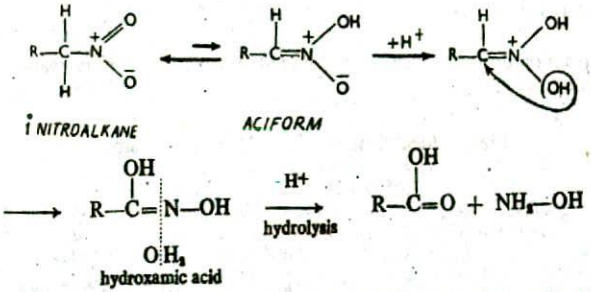
Now that nitroalkanes are becoming available in large quantities, this method can be used for the industrial production of primary amines.

(6) **Hydrolysis.** (*a*) Primary nitroalkanes on boiling with concentrated hydrochloric acid or sulphuric acid, are hydrolysed to form a carboxylic acid and hydroxylamine.

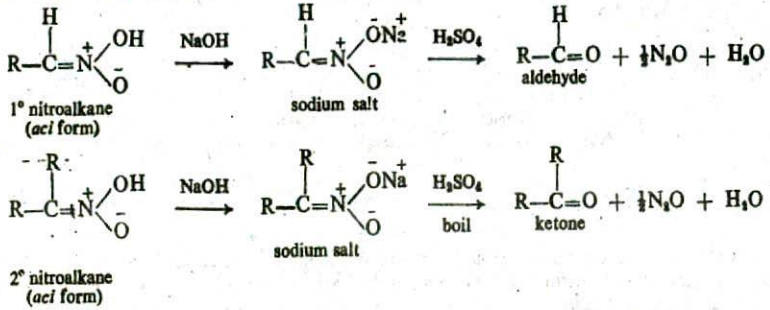
$$\underset{\text{1° nitroalkane}}{R{-}CH_2{-}NO_2} + H_2O \xrightarrow[\Delta]{H^+} \underset{\text{carboxylic acid}}{R{-}CO{-}OH} + \underset{\text{hydroxylamine}}{NH_2OH}$$

This reaction proceeds by oxidation of CH_2 group and reduction of NO_2 group, accompanied by C—N bond cleavage. It is used for the commercial production of hydroxylamine.

MECHANISM. The reaction is believed to take place through the formation of hydroxamic acid as

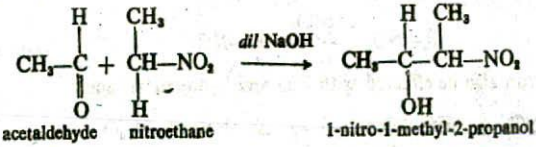


(*b*) Primary and Secondary nitroalkanes may be hydrolysed by first converting them to the salts of their *aci* forms by NaOH, which on boiling with 50 per cent H_2SO_4 produced aldehydes and ketones repectively.



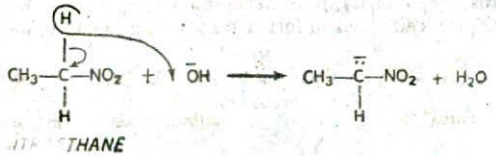
The above reaction, popularly known as **Nef Reaction,** has been usefully employed for the synthesis of aldehydes and ketones.

(7) **Condensation with Aldehydes and Ketones.** Primary and secondary nitroalkanes react with aldehydes and ketones in the presence of dilute alkali. This reaction which yields nitroalcohols is quite similar to aldol condensation. For example,

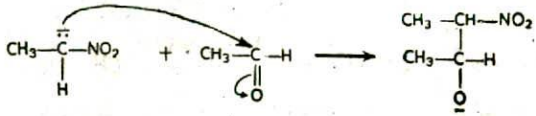


MECHANISM. This condensation reaction proceeds by the following steps.

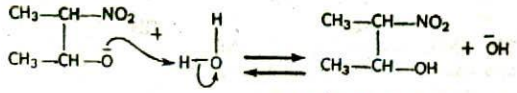
(*a*) Carbanion formation :



(*b*) **Nucleophilic attack at the carbonyl carbon :**



(*c*) **Proton take up from water :**



1-NITRO-1-METHYL-2-PROPANOL
(NITROALCOHOL)

USES OF NITROALKANES

(1) Since nitroalkanes have medium boiling points and do not have obnoxious smell, they are widely used as industrial solvents, particularly for plastics and dyes.

(2) They are used as fuel in small engines and are valuable constituents of rocket fuel.

(3) They form starting materials for the manufacture of primary amines and carboxylic acids, and many of their useful derivatives.

(4) They are intermediates in the production of detergents, propellants, explosives, pharmaceuticals and finish removers.

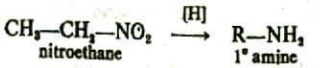
(5) Their reaction with nitrous acid forms the basis of the Victor Meyer Test for distinguishing between primary, secondary and tertiary amines.

How to Distinguish Nitroalkanes from Alkyl Nitrites

The two classes of compounds are functional isomers and can be distinguished from each other by specific chemical behavior.

nitroalkane — alkyl nitrite (*an ester*)

(1) **Reduction.** Nitroalkanes when reduced with hydrogen on Raney nickel, or with $LiAlH_4$ yield primary amines.

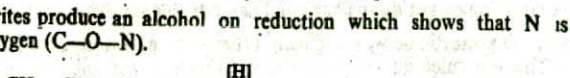


nitroethane — 1° amine

The fact that an amine is so produced demonstrates the presence of C—N bond in the original nitroalkane. The reduction of isomeric alkyl nitrite cannot lead to an amine.

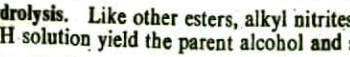
$$R—O—N=O \quad \textit{cannot form} \quad R—NH_2$$

Actually alkyl nitrites produce an alcohol on reduction which shows that N is bonded to carbon through oxygen (C—O—N).



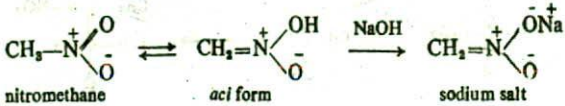
alkyl nitrite — 1° alcohol

(2) **Basic Hydrolysis.** Like other esters, alkyl nitrites (which are esters of nitrous acid) on boiling with NaOH solution yield the parent alcohol and sodium nitrite.



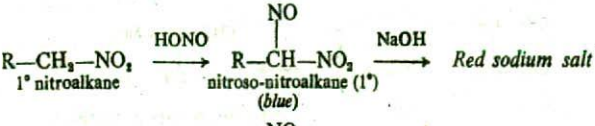
alkyl nitrites — alcohol

Nitroalkanes have no action with NaOH solution. However, 1° and 2° nitroalkanes form soluble sodium salts.

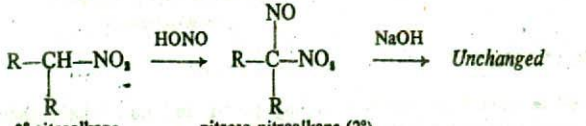


nitromethane *aci* form sodium salt

(3) **Reaction with Nitrous Acid.** Primary and secondary nitroalkanes when treated with nitrous acid form blue nitroso derivatives.

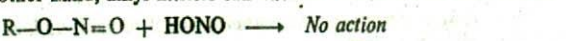


1° nitroalkane nitroso-nitroalkane (1°) (*blue*)



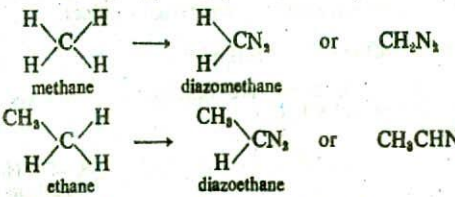
2° nitroalkane nitroso-nitroalkane (2°) (*blue*)

On the other hand, alkyl nitrites can have no reaction with nitrous acid



DIAZOALKANES

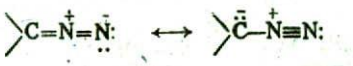
These are the derivatives of **alkanes** in which two hydrogen atoms on the same carbon have been replaced by the divalent **diazo group**, $>N_2$, (*di*=2 ; *azo*=N).



methane diazomethane

ethane diazoethane

The diazo group ($>N_2$) is the functional group which is represented as a resonance hybrid of two forms.

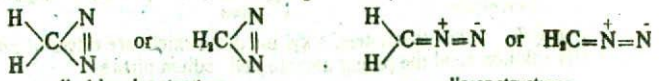


Here we will take up a detailed discussion of diazomethane, the simplest member of the class.

DIAZOMETHANE, CH_2N_2

It is the most important diazoalkane and has valuable synthetic applications.

Structure. Diazomethane was originally believed to possess a three-membered, diazirine ring structure. This was ruled out when electron-diffraction and dipole measurements proved that it has a linear structure with H—C—N angle as 120°.

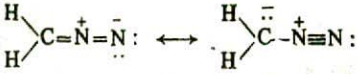


diazirine ring structure (*Incorrect for diazomethane*)

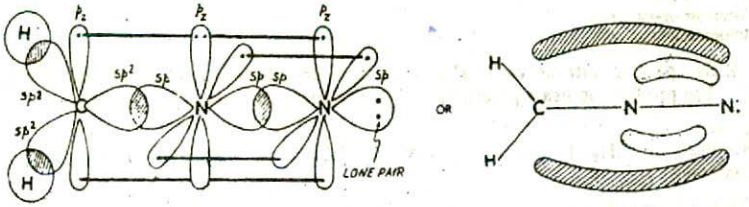
linear structure (*Correct for diazomethane*)

The structure of diazomethane is now represented in two way :

(*a*) As *Resonance Hybrid* of the extreme electronic states,



(*b*) As delocalised *Orbital Model*, carbon in its sp^2 state of hybridisation forms two σ bonds with H-atoms and one σ bond with one N-atom in *sp* state of hybridisation. The central



(I) (II)

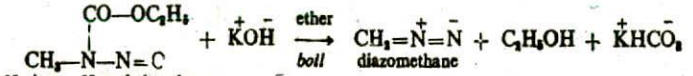
Fig. 31·1. Molecular Model of Diazomethane.

N-atom forms another σ bond with the second N-atom. This leaves a p_z orbital on carbon ; a p_y and p_z on the central N-atom containing two and one electrons. The terminal N-atom is left with one electron in p_y and p_z orbitals, and a lone pair in its *sp* orbital. The various overlaps are shown in Fig. 31·1 (I) The delocalised π molecular orbital over C—N—N system is shown in Fig. 31·1 (II)

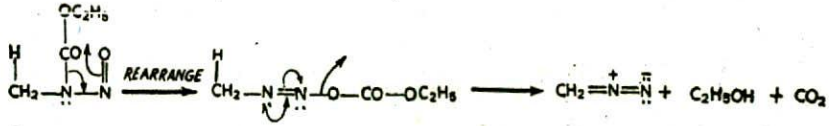
The above orbital structure justifies the linkage of both the nitrogen atoms with the same carbon atom.

Preparation. Diazomethane can be synthesised in a number of ways from *N*-nitroso-*N*-methyl compounds.

(1) By warming *N*-nitroso-*N*-methylurethane with KOH solution.

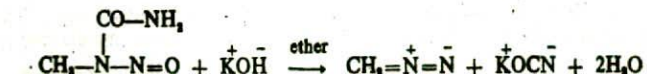


MECHANISM :

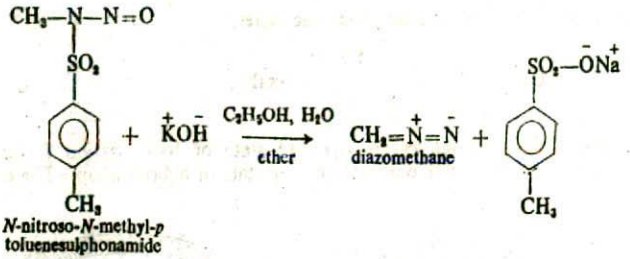


Similar mechanism can be visualised for other methods of synthesis listed below.

(2) By reaction of *N*-nitroso-*N*-methylurea with aqueous potassium hydroxide solution.



(3) By treatment of *N*-nitroso-*N*-methyl-*p*-toluenesulphonamide with ethanolic potassium hydroxide (*Commercial*).



(4) By passing nitrous oxide (N_2O) through an ethereal solution of methyllithium (CH_3Li). The product on heating decomposes to give diazomethane.

$$\underset{\text{nitrous oxide}}{\overset{+}{N}=\overset{-}{N}=O} + CH_3—Li \longrightarrow CH_3—N=N—OLi \xrightarrow{\Delta} CH_2=\overset{+}{N}=\overset{-}{N} + LiOH$$

This method has very recently been introduced by Muller.

Properties. (*Physical*). Diazomethane is an intensely yellow gas at ordinary temperature. n the liquid form it boils at $-24°$. It is extremely toxic and soluble in ether. It is prone to xplosive decomposition and is unstable even at room temperature. However, it is more stable a solution form and hence its various synthetic reactions are carried safely in ethereal solution.

(*Chemical*). (1) **Action of Heat or Light.** Diazomethane when supplied heat, or exposed) light decomposes to form methylene.

$$\underset{\text{diazomethane}}{CH_2=\overset{+}{N}=\overset{-}{N}} \xrightarrow[\Delta]{h\nu \text{ or}} \underset{\text{methylene}}{CH_2:} + N_2$$

ethylene is a very reactive reagent and adds to alkanes to yield higher homologues.

$$\underset{\text{alkane}}{R—R} + :CH_2 \longrightarrow \underset{\text{higher alkane}}{R—CH_2—R}$$

(2) **Reduction.** When reduced with sodium amalgam, it is converted to methyl hydrazine.

$$\underset{\text{diazomethane}}{CH_2=\overset{+}{N}=\overset{-}{N}} + 4[H] \xrightarrow{Na/Hg} \underset{\text{methylhydrazine}}{CH_3—NH—NH_2}$$

(3) **Reaction with Mineral Acids.** Hydrochloric acid and sulphuric acid convert diazomethane to diazonium salts which at once decompose to form methyl derivatives and nitrogen. Thus,

$$\underset{\text{diazomethane}}{CH_2=\overset{+}{N}=\overset{-}{N}} + HCl \longrightarrow \left[CH_3—\overset{+}{N}\equiv N\overset{-}{Cl}\right] \longrightarrow \underset{\text{methyl chloride}}{CH_3—Cl} + N\equiv N$$

(4) **Reaction with Carboxylic Acids.** Diazomethane reacts readily with carboxylic acids to form methyl esters, the H-atom of the —COOH group being converted to methyl group.

$$\underset{\text{carboxylic acid}}{\overset{O}{\overset{\|}{R—C—OH}}} + CH_2N_2 \xrightarrow{\text{ether}} \underset{\text{methyl ester}}{\overset{O}{\overset{\|}{R—C—OCH_3}}} + N_2$$

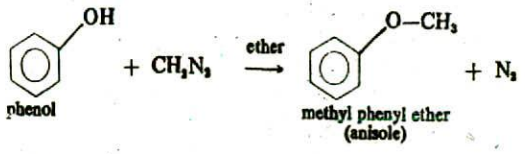
This is an excellent method for converting expensive organic acids to methyl esters. The fact hat the only by-product is nitrogen, makes this one of the cleanest synthetic organic reactions.

MECHANISM. The reaction takes place in two steps : (1) the transfer of an acid proton to diazomethane at the negative carbon of diazomethane, generating the nucleophile carboxylate on and a diazonium ion ; (2) the products of step 1 react together to form a new C—O bond, giving methyl ester and molecular nitrogen.

(1) $R-\overset{\overset{O}{\|}}{C}-\ddot{O}-H + \bar{C}H_2-\overset{+}{N}\equiv N: \longrightarrow R-\overset{\overset{O}{\|}}{C}-\bar{O}$ (CARBOXYLATE ION) $+ CH_3-\overset{+}{N}\equiv N:$ (DIAZONIUM ION)

(2) $R-\overset{\overset{O}{\|}}{C}-\bar{O} + CH_3-\overset{+}{N}\equiv N \longrightarrow R-\overset{\overset{O}{\|}}{C}-O-CH_3 + \ddot{N}\equiv\ddot{N}$ (METHYL ESTER)

(5) Reaction with Phenols. Like carboxylic acids, phenols are also methylated when treated with diazomethane to form methyl ethers. Thus,



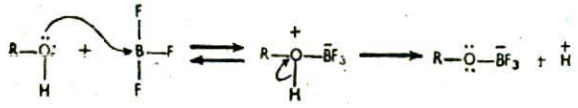
The reaction mechanism is similar to that of methylation of carboxylic acids.

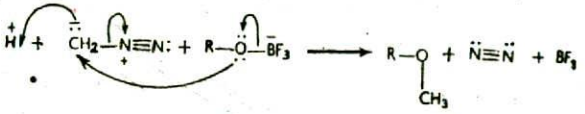
(6) Reaction with Alcohols and Amines. Diazomethane does not react with alcohols and amines ordinarily. But in the presence of a catalyst such as BF_3, a Lewis acid, the hydrogen of the —OH or >NH group is replaced by a methyl group.

$$\underset{\text{alcohol}}{R-O-H} + CH_2N_2 \xrightarrow{BF_3} \underset{\substack{\text{methoxyalkane}\\\text{(methyl ether)}}}{R-O-CH_3} + N_2$$

$$\underset{1^\circ\text{ amine}}{R-NH_2} + CH_2N_2 \xrightarrow{BF_3} \underset{N\text{-methylamine}}{R-NH-CH_3} + N_2$$

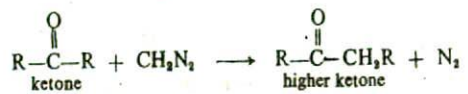
MECHANISM. The function of BF_3 is to increase the acidity of the alcohol or amine. The released H^+ promotes methylation as shown below.



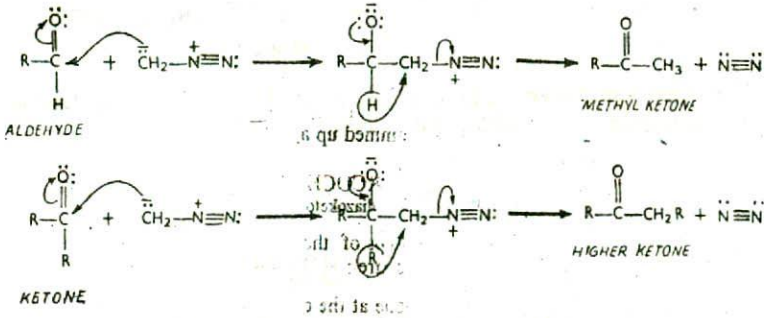


(7) Reaction with Carbonyl compounds. Diazomethane converts aldehydes into methyl ketones, while ketones are converted into their higher homologues.

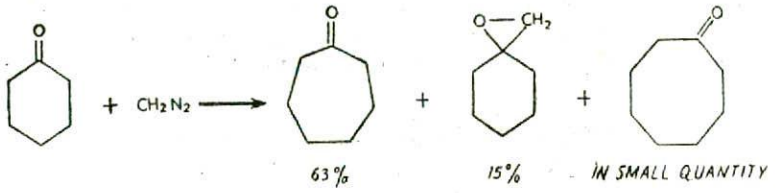
$$\underset{\text{aldehyde}}{R-\overset{\overset{O}{\|}}{C}-H} + CH_2N_2 \longrightarrow \underset{\text{methyl ketone}}{R-\overset{\overset{O}{\|}}{C}-CH_3} + N_2$$



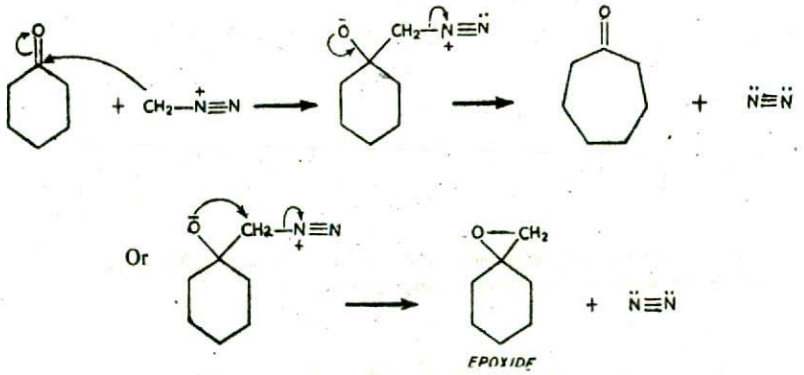
MECHANISM. The reaction proceeds by nucleophilic addition at the carbonyl group. The adduct then loses N_2 by rearrangement.



The most interesting application of this reaction is ring expansion. Thus cyclohexanone reacts with diazomethane to form cycloheptanone. The initial product again reacts with diazomethane to yield the corresponding epoxide and higher cyclonanones.



MECHANISM. It involves nucleophilic addition followed by either rearrangement or ring closure of the epoxide ring.



(8) **Reaction with Acid Chlorides.** Diazomethane reacts with an acid chloride (RCOCl) to form a diazomethyl ketone. This when heated with water in the presence of silver oxide (Ag_2O) yields a carboxylic acid containing one more carbon than the starting acid chloride.

$$\underset{\text{acid chloride}}{R{-}\overset{O}{\overset{\|}{C}}{-}Cl} + \underset{\text{diazomethane}}{2CH_2O_2} \longrightarrow \underset{\text{diazomethyl ketone}}{R{-}\overset{O}{\overset{\|}{C}}{-}CHN_2} + CH_3Cl + N_2$$

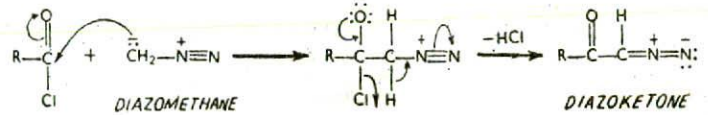
$$R{-}\overset{O}{\overset{\|}{C}}{-}CHN_2 + H_2O \xrightarrow[\Delta]{Ag_2O} \underset{\text{higher acid}}{R{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}OH} + N_2$$

The complete sequence of reactions for converting a given carboxylic acid to its next higher homologue (*Arudt-Eistert Synthesis*) is summed up as :

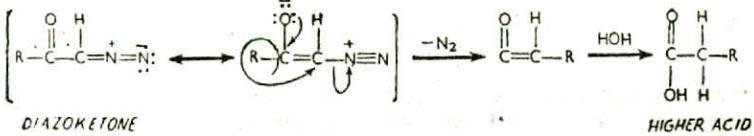
$$\underset{\text{acid}}{RCOOH} \xrightarrow{SOCl_2} \underset{\text{acid chloride}}{RCOCl} \xrightarrow{CH_2N_2} \underset{\text{diazoketone}}{RCOCHN_2} \xrightarrow{Ag_2O} \underset{\text{higher acid}}{RCH_2COOH}$$

MECHANISM. The two important steps of the reaction of acid chloride with diazomethane leading to the formation of higher acid are :

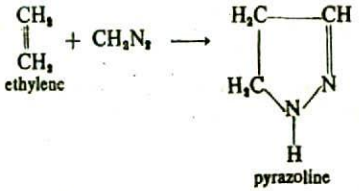
(*a*) Nucleophilic addition of diazomethane at the carbonyl carbon to form diazoketone.

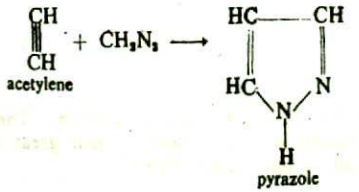


(*b*) Wolff's rearrangement leading to the formation of a ketone that reacts with water to produce the higher acid.

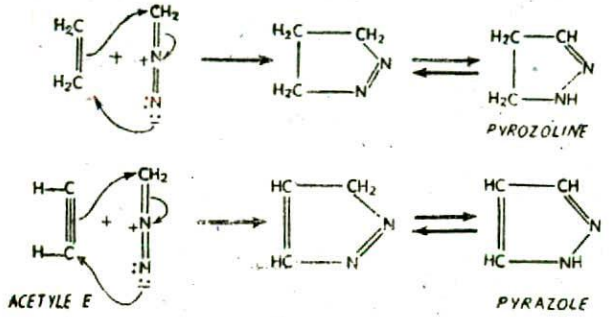


(9) **Addition to Ethylenic and Acetylenic pi bonds.** Diazomethane adds to ethylenic or acetylenic π bonds leading to the formation of heterocyclic compounds.





MECHANISM :



AZIDES

These are the derivatives of hydrozoic acid, N_3H, and are characterised by the presence of the function $-\ddot{N}=\overset{+}{N}=\ddot{N}$ (azido group). Azides are named in the same way as halides. The name of the substituent group is followed by the suffix *azide* as a separate word. Thus,

$$\underset{\text{alkyl azide}}{R-\ddot{N}=\overset{+}{N}=\ddot{N}:} \qquad \underset{\text{acyl azide}}{RCO-\ddot{N}=\overset{+}{N}=\ddot{N}:}$$

Alkyl azides are also named as '*Azido-alkane*'.

STRUCTURE

Like diazo group, the azido group is known to possess a linear structure. It may be represented as a resonance hybrid of the two extreme bond structures as

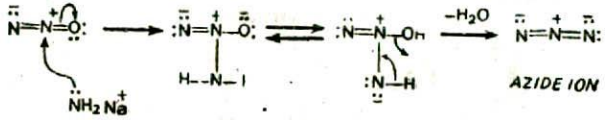
$$R-\ddot{N}=\overset{+}{N}=\ddot{N}: \longleftrightarrow R-\ddot{N}-N\equiv N:$$

Orbital overlaps in alkyl azide leading to delocalised π molecular orbital over the three nitrogen atoms is similar to that obtaining in diazo compounds.

Preparation. Alkyl azides may be conveniently obtained by the action of sodium azide (nitrous oxide and sodium azide) on alkyl sulphate.

$$\underset{\text{alkyl sulphate}}{R_2SO_4} + \overset{+}{Na}\overset{-}{N_3} \longrightarrow \underset{\text{alkyl azide}}{R-N=\overset{+}{N}=\ddot{N}:} + R\overset{-}{S}O_4\overset{+}{Na}$$

In the above reaction the azide ion acts as the nucleophile bringing about substitution. The azide ion formation from N_2O and $NaNH_2$, may occur as follows.



Properties. Azides are explosive just like diazo compounds. They possess very low boiling points indicating hydrogen bonding in them. Owing to their great chemical reactivity, they are used as synthetic reagents only in the solution state.

(1) **Reduction.** When reduced with H_2 in presence of Pt, or with $LiAlH_4$, alkyl azide yield primary amines.

$$R-\overset{\cdot\cdot}{N}=\overset{+}{N}=\overset{-}{\overset{\cdot\cdot}{N}}: + H_2 \xrightarrow{Pt} \underset{1^\circ \text{ amine}}{R-NH_2} + N_2$$

This method of preparation of primary amines is distinctly superior to the ammonlysis of halides, as it gives pure stuff.

(2) **Addition to Alkenes.** Like the diazo compounds, azides add to π bonds of alkanes (or alkynes) forming heterocyclic compounds.

1,2,3-TRIAZOLE

(3) **Pyrolysis or Photolysis.** By the action of heat or light, azides produce very reactive intermediates called nitrines (*Cf.* carbenes from diazo compounds).

$$R-\overset{\cdot\cdot}{N}=\overset{+}{N}=\overset{-}{\overset{\cdot\cdot}{N}}: \longleftrightarrow R-\overset{-}{\underset{\cdot\cdot}{N}}-\overset{+}{N}\equiv N \xrightarrow{h\nu} \underset{\text{a nitrene}}{R-\underset{\cdot\cdot}{N}} + N\equiv N$$

QUESTIONS

1. How is nitromethane prepared ?
2. How is nitroethane prepared ?
3. Describe the reactions of nitroalkanes. Differentiate between an alkyl nitrite and a nitroalkane.
4. Explain : Nitroethane has a higher boiling point than ethyl nitrite. *(Banaras BSc III, 1993)*
5. Explain : Nitromethane exhibits tautomerism.
6. Write a note on : Nitroalkanes.
7. How will you distinguish between nitroethane and ethyl nitrite ? *(Madras BSc, 1994; Udaipur BSc, 1994)*
8. How will you synthesise diazomethane from methylamine ? *(Vikram BSc, 1993)*
9. Discuss the structure of diazomethane. *(Kerala BSc, 1993)*
10. How is diazomethane prepared ? How does it react with hydrochloric acid ? *(Agra BSc, 1994)*
11. Describe the synthetic applications of diazomethane. *(Panjab BSc, 1994; Delhi BSc Hons, 1994)*

Chapter **32**

Carbohydrates

Carbohydrates constitute a major class of naturally occurring organic compounds. They include such well-known substances as sugars, starch, and cellulose. Table sugar, wood, cotton, potato starch, honey, and milk sugar are all carbohydrates familiar to most of us. They are essential to the maintenance of life in both plants and animals. They provide raw materials for many important industries including textiles, artificial silks, paper, films, plastics, lacquers, confections, drugs, fermentation and explosives.

Carbohydrates, as the name implies, are composed mainly of carbon, hydrogen and oxygen with the latter two elements in the ratio of 2 to 1 as in water. These compounds may be represented by the general formula $C_x(H_2O)_y$, where x and y may be same or different. For example, we can write glucose $C_6H_{12}O_6$ as $C_6(H_2O)_6$ and sucrose $C_{12}H_{22}O_{11}$ as $C_{12}(H_2O)_{11}$. Because of this fact they were considered, in early days, to be hydrates of carbon and for this reason were called carbohydrates. It is simply a coincidence that in carbohydrates hydrogen and oxygen are present in the ratio of 2 to 1.

It should be noted at this point that not all organic compounds containing hydrogen and oxygen in the proportion found in water are carbohydrates. For example, formaldehyde HCHO, for the present purpose written as $C(H_2O)$, acetic acid CH_3COOH written as $C_2(H_2O)_2$ and lactic acid $CH_3CHOHCOOH$, written as $C_3(H_2O)_3$, are not carbohydrates. Also, some carbohydrates, such as rhamnose ($C_6H_{12}O_5$), do not contain the usual proportions of hydrogen to oxygen. Further more, some carbohydrates are now known which contain nitrogen or sulphur in addition to carbon, hydrogen and oxygen.

Structurally, carbohydrates are polyfunctional compounds. They contain two types of functional groups, the hydroxyl group and the carbonyl group. *They are polyhydroxy aldehydes or polyhydroxy ketones or compounds which are converted to these on hydrolysis.* Since the carbonyl group, because of intramolecular cyclization with a hydroxyl group, may be a part of a ring structure, some carbohydrates are said to contain potential aldehyde or ketone groups.

Formation of Carbohydrates (*Photosynthesis*)

The formation of carbohydrates in nature occurs in green plants by a process called *photosynthesis*. Plants contain the green pigment *chlorophyll*, which catalyses the conversion of carbon dioxide and water into sugar. The reaction is thermodynamically unfavourable, but proceeds because the necessary energy is supplied by the sun in the form of light.

$$6CO_2 + 6H_2O + \textit{Solar Energy} \xrightarrow{\textit{Chlorophyll}} C_6(H_2O)_6 + 6O_2\uparrow$$

While plants build up carbohydrates from carbon dioxide and water, animals degrade carbohydrates by eating plants and combine the carbohydrates with oxygen from the air to carry out the reverse of photosynthesis.

CLASSIFICATION AND NOMENCLATURE OF CARBOHYDRATES

The names of most of carbohydrates are characterised by the ending '*-ose*'. Thus we have glucose, fructose, sucrose, cellulose, and so on.

The carbohydrates are divided into *three* major classes depending upon whether or not they undergo hydrolysis, and if they do, on the number of products formed.

1. **Monosaccharides***. The monosaccharides are polyhydroxy aldeyhydes or polyhydroxy ketones which cannot be decomposed by hydrolysis to give simpler carbohydrates. Examples are glucose and fructose, both of which have molecular formula, $C_6H_{12}O_6$.

$$\underset{\text{glucose or fructose}}{C_6H_{12}O_6} + H_2O \xrightarrow{H^+} \textit{No Reaction}$$

2. **Oligosaccharides**. The oligosaccharides (Greek, *oligo*, few) are carbohydrates which yield a definite number (2—9) of monosaccharide molecules on hydrolysis. They include,

(*i*) *Disaccharides*, which yield *two* monosaccharide molecules on hydrolysis. Examples are sucrose and maltose, both of which have molecular formula, $C_{12}H_{22}O_{11}$.

$$\underset{\text{sucrose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow{H^+} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6}$$

$$\underset{\text{maltose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow{H^+} 2\underset{\text{glucose}}{C_6H_{12}O_6}$$

(*ii*) *Trisaccharides*, which yield *three* monosaccharide molecules on hydrolysis. Example is, raffinose, which has molecular formula, $C_{18}H_{32}O_{16}$.

$$\underset{\text{raffinose}}{C_{18}H_{32}O_{16}} + 2H_2O \xrightarrow{H^+} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6} + \underset{\text{galactose}}{C_6H_{12}O_6}$$

(*iii*) *Tetrasaccharides*, etc.

3. **Polysaccharides**. The polysaccharides are carbohydrates of high molecular weight which yield many monosaccharide molecules on hydrolysis. Examples are starch and cellulose, both of which have molecular formula, $(C_6H_{10}O_5)_n$.

$$\underset{\substack{\text{starch or}\\ \text{cellulose}}}{(C_6H_{10}O_5)_n} + nH_2O \xrightarrow{H^+} \underset{\text{glucose}}{nC_6H_{12}O_6}$$

In general, the monosaccharides and oligosaccharides are crystalline solids, soluble in water and sweet to taste. They are collectively known as *sugars*. The polysaccharides, on the other hand, are amorphous, insoluble in water and tasteless. They are called **non-sugars**.

The carbohydrates may also be classified as either *reducing* or *non-reducing sugars*. All those carbohydrates which have the ability to reduce Fehling's solution and Tollen's reagent are referred to as reducing sugars, while others are non-reducing sugars. All monosaccharides and the disaccharides other than sucrose are reducing sugars.

MONOSACCHARIDES

The monosaccharides are the basis of carbohydrate chemistry since all carbohydrates are either monosaccharides or are converted into monosaccharides on hydrolysis. The monosaccha-

*Carbohydrates are also said to be Saccharides (Latin, *saccharon*, sugar).

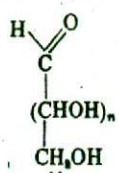
rides are polyhydroxy aldehydes or polyhydroxy ketones. There are, therefore, two main classes of monosaccharides.

(1) the **Aldoses**, which contain an aldehyde group (—C(=O)—H)

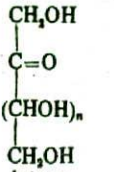
(2) the **Ketoses**, which contain a ketone group (—C(=O)—)

The aldoses and ketoses are further divided into sub-groups on the basis of the number of carbon atoms in their molecules, as *trioses*, *tetroses*, *pentoses*, *hexoses*, etc. To classify a monosaccharide completely, it is necessary to specify both, the type of the carbonyl group and the number of carbon atoms present in the molecule. Thus monosaccharides are generally referred to as *aldotrioses*, *aldotetroses*, *aldopentoses*, *aldohexoses*, *ketohexoses*, etc.

The aldoses and ketoses may be represented by the following general formulas.

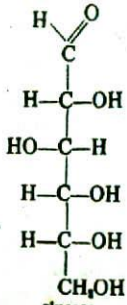


aldoses
(n = 1, 2, 3, 4, 5)

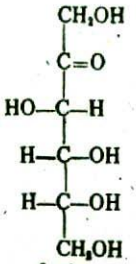


ketoses
(n = 0, 1, 2, 3, 4,)

Glucose and fructose are specific examples of an aldose and a ketose.



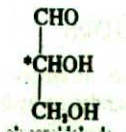
glucose
(an aldohexose)



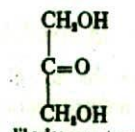
fructose
(a ketohexose)

STEREOCHEMISTRY OF MONOSACCHARIDES

Trioses : D and L Terminology. The simplest of all carbohydrates that fit the definition we have given for carbohydrates are the trioses, glyceraldehyde and dihydroxyacetone. Glyceraldehyde is an aldotriose, and dihydroxyacetone is a ketotriose.

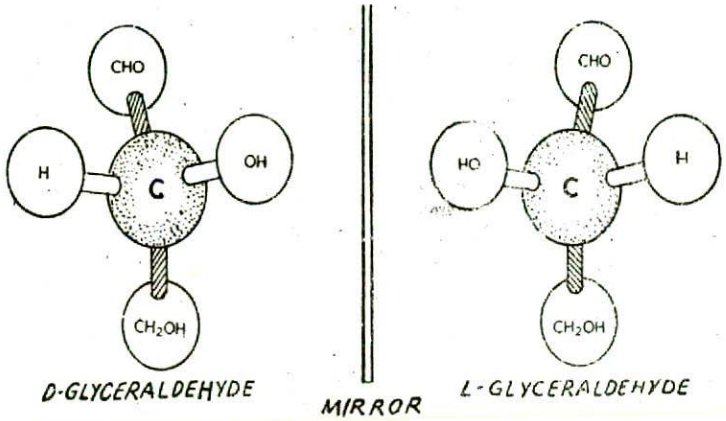


glyceraldehyde
(an aldotriose)



dihydroxyacetone
(a ketotriose)

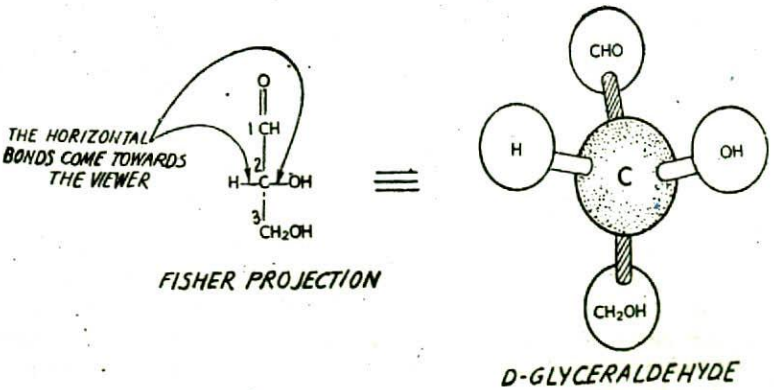
Glyceraldehyde contains one asymmetric carbon atom (marked by an asterisk) and can thus exist in two optically active forms, called the D-form and the L-form. The following figure contains the ball and stick models of the D- and L-forms of glyceraldehyde and shows the spatial relationship of the groups attached to the asymmetric carbon atom in each case.

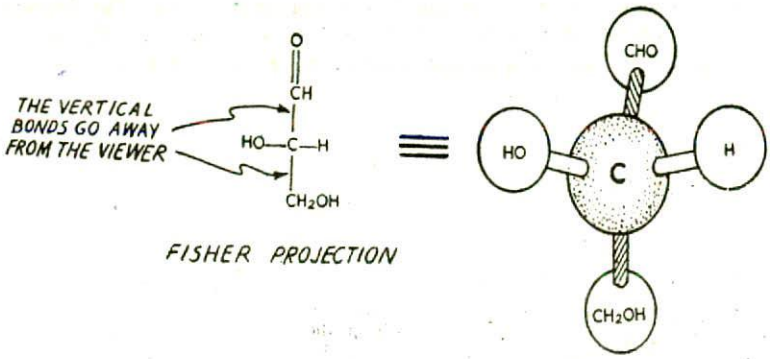


Clearly, the two forms are mirror images that cannot be superimposed, that is, **they are enantimers.**

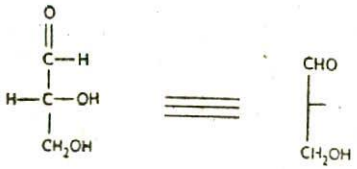
Rather than drawing out three-dimensional structures each time we wish to represent an optically active compound such as D- and L-glyceraldehyde, we can use a two-dimensional projection. One projection commonly used is called the **Fischer projection.**

In the Fischer projection, glyceraldehyde has the aldehyde group at the top. The horizontal bonds in the Fischer projection are defined as coming out towards the viewer. The vertical bonds go away from the viewer.

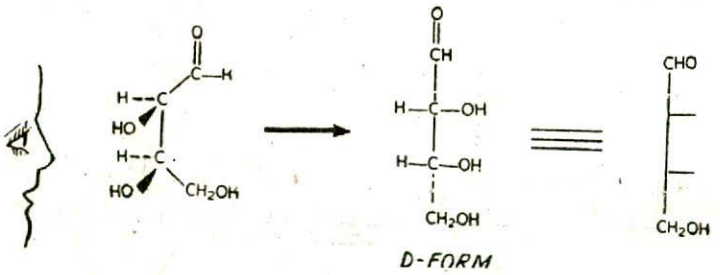




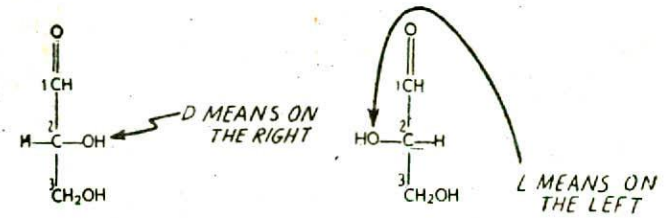
A simpler way of drawing Fischer projections is to use horizontal lines to show the positions of the hydroxyl groups on the asymmetric carbon atoms and omitting the hydrogen atoms. Thus, D-glyceraldehyde may be represented as follows.



The same rules apply for drawing Fischer projections of more complex molecules. For example, the Fischer projection of an aldotetrose molecule may be drawn as indicated below.

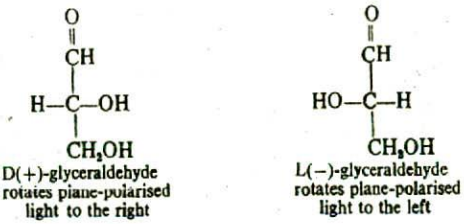


In the name D-glyceraldehyde, the prefix letter D means that the hydroxyl group on the carbon number 2 is projected to the *right* in the Fischer projection. The prefix letter L in the name L-glyceraldehyde means that the hydroxyl group is projected to the *left*. The prefixes D- and L- are used to tell us the absolute configuration, that is, the exact spatial relationship of the groups around the asymmetric carbon atom.



The two forms of glyceraldehyde are especially important because the more complex monosaccharides may be considered to be derived from them. They serve as a reference point for designating and drawing all other monosaccharides. In carbohydrate chemistry, the Fischer projection formulas are always written with the aldehyde or ketone groups at the top of the structure. By definition, *if the hydroxyl group on the asymmetric carbon atom farthest from aldehyde or ketone group projects to the right, the compound is a member of the D-family. If the hydroxyl group on the farthest asymmetric carbon projects to the left, the compound is a member of the L-family.*

As we have already stated in the chapter on stereochemistry an optically active compound is one that rotates the plane of polarised light to the right or to the left. If a compound rotates the plane-polarised light to the right, it is said to be *dextrorotatory* (Latin, *dexter*, right). This is indicated in the name of the compound by the prefix sign (+). If the compound rotates the plane-polarised light to the left, the compound is said to be *Laevorotatory* (Latin, *laeveus*, left). The prefix sign (−) is used to designate a levorotatory compound. D-glyceraldehyde rotates the plane-polarised light to the right. This can be indicated in the name by calling this compound D(+)-glyceraldehyde (pronounced, *dee* plus glyceraldehyde). Similarly, L-glyceraldehyde rotates the plane-polarised light to the left. This can be indicated in the name by calling this compound L(−)-glyceraldehyde (pronounced, *ell* minus glyceraldehyde).



At this stage it should be clearly understood that the letters D- and L- refer to the absolute configuration around the asymmetric carbon atom. The signs (+) and (−) refer to the direction of rotation of the plane-polarised light, which is a measured physical constant and cannot be obtained *by looking at the formula.* The two are not necessarily related. A compound in the D-family may rotate the plane-polarised light to the right or it may rotate it to the left.

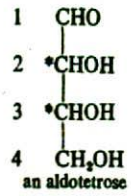
The maximum number of optical isomers of a sugar is related to the number of asymmetric carbon atoms in the molecule and may be calculated by the following simple equation.

Maximum Number of Optical Isomers $= 2^n$, where n = the number of asymmetric carbon atoms.

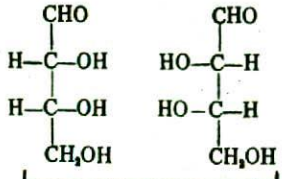
Since glyceraldehyde contains only one asymmetric carbon atom, the number of optical isomer is 2^1. We know that 2^1 is $= 2$, and we have seen that there are indeed two different glyceraldehydes.

Aldotetroses. If we examine the general formula of an aldotetrose, we see that they contain *two* asymmetric carbon atoms (marked by asterisks).

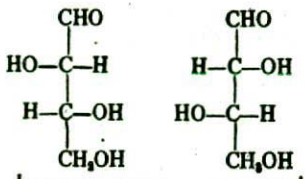
This means that 2^2 or 4 optical isomers are possible. They may be represented as the following two pairs :



an aldotetrose



mirror images
(*racemic pair*)
D(−)-erythrose L(+)-erythrose



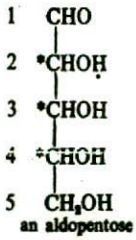
mirror images
(*racemic pair*)
D(−)-threose L(+)-threose

All four isomers have been prepared synthetically. The D- and L-erythrose are mirror images, that is, they are enantiomers. They have exactly the same degree of rotation but in opposite directions. Equal amounts of the two would constitute a *racemic mixture*, that is, a mixture that would allow a plane-polarised light to pass through the solution unchanged but could be separated into dextrotatory and and laevorotatory isomers, The same comments hold for D- and L-threose. However, D-erythrose and L-threose are not images, that is, they are *diastereomers* (optical isomers that are not mirror images are called diastereomers), and the degree of rotation of each would probably differ.

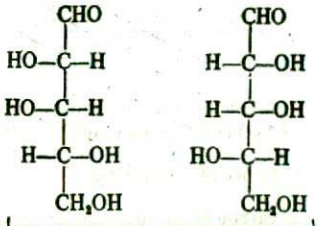
From the above formulas it can be seen that the D- and L-sugars conform to the definition previously given, and that no connection exists between a D-sugar and the term le- orotatory, and an L-sugar and the term laevorotatory.

Aldopentoses. If we examine the general formula of an aldopentose, we see that they contain *three* asymmetric carbon atoms.

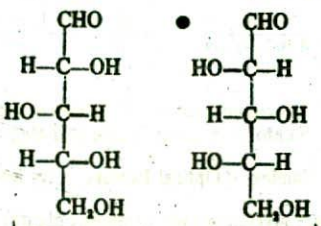
This means that 2^3 or 8 optical isomers are possible. They may be represented as the following four pairs :



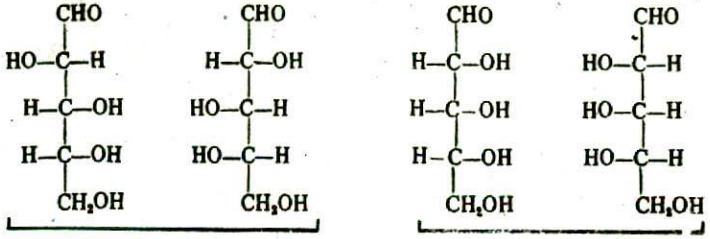
an aldopentose



mirror images
(*racemic pair*)
D(−)-lyxose L(+)-lyxose

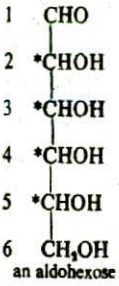


mirror images
(*racemic pair*)
D(−)-xylose L(−)-xylose

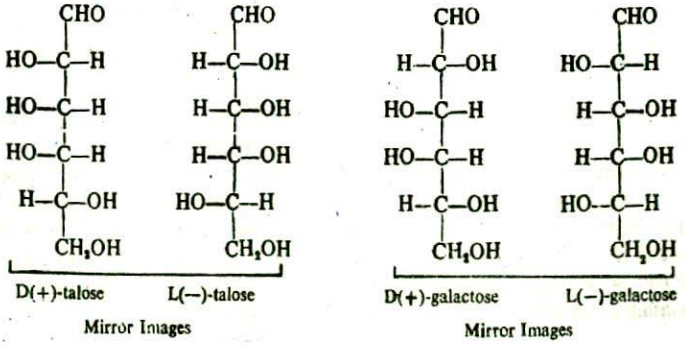


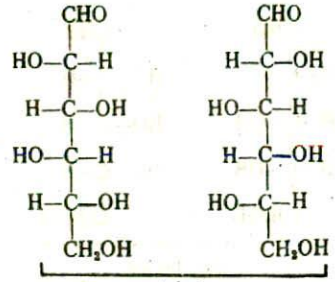
All eight isomers have been prepared synthetically. Of the D-pentoses, lyxose, arabinose, and ribose are laevorotatory, whereas D-xylose is dextrorotatory. Of the L-pentoses, lyxose, arabinose, and ribose are dextrorotatory, whereas L-xylose is laevorotatory. The aldopentoses which are found in nature are L-arabinose, D-xylose, and D-ribose.

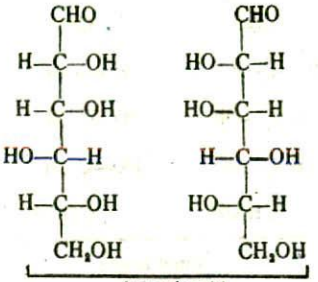
Aldohexoses : Epimers. If we examine the general formula of a hexoser, we see that it contains four asymmetric carbon atoms.

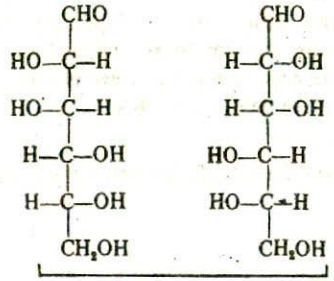


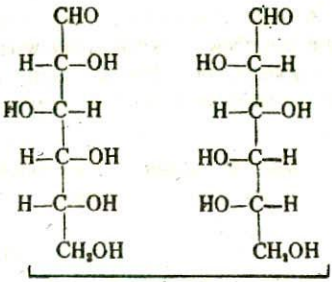
This means that 2^4 or 16 optical isomers are possible. They may be represented as the following eight pairs.

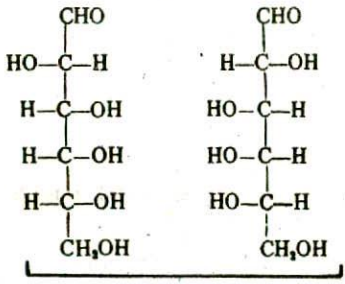


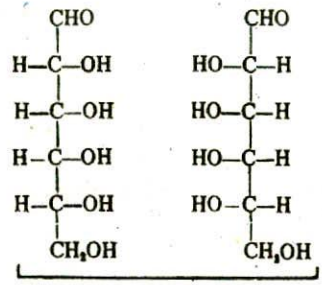




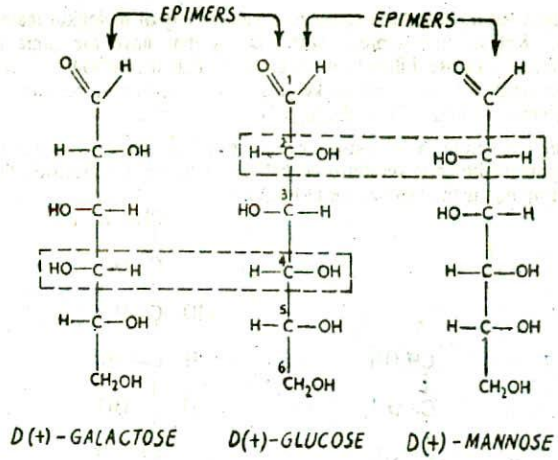








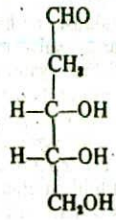
Only three of the sixteen possible aldohexoses are found in nature (all sixteen isomers have been prepared synthetically). They are D-glucose, D-mannose, and D-galactose. No one of these three optical isomers is a mirror image of any of the others, so all three are diastereomers of each other. Furthermore, D(+)-glucose differs from D(+)-mannose and D(+)-galactose only in configuration about one asymmetric carbon atom, carbon number 2 and 4 respectively. D(+)-Mannose and D(+)-galactose are said to be epimers of D(+)-glucose. *A pair of diastereomers that differ only in the configuration about a single carbon atom are said to be epimers.* No epimeric relationship exists between D(+)-mannose and D(+)-galactose.



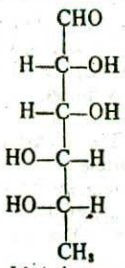
Other Aldoses.

The length of the carbon chain in monosaccharides has no theoretical limit. Aldoheptoses, octoses, nonoses, and decoses have been synthesised in the laboratory, and aldoheptoses have been obtained by the hydrolysis of certain polysaccharides of bacterial origin.

Deoxy Sugars. *Sugars in which one of the hydroxyl groups is replaced by a hydrogen atom are called deoxy sugars.* Examples are 2-deoxy-D-ribose and L(+)-rhamnose.



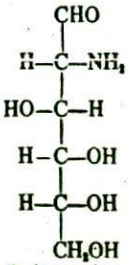
2-deoxy-D-ribose



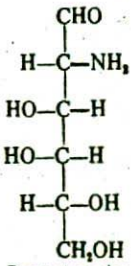
L(+)-rhamnose

2-Deoxy-D-ribose is of great biochemical importance and is found in combination in deoxy-ribonucleic acids (the DNA's), which play an important role in heredity.

Amino Sugars. *Sugars in which one of the hydroxyl groups is replaced by an amino group are called amino sugars.* Examples are D-glucosamine and D-galactosamine.



D-glucosamine

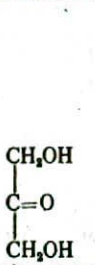


D-galactosamine

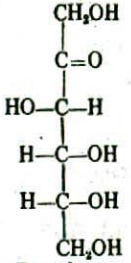
Both these sugars have been found in a wide variety of biological materials.

Ketoses. Ketoses are isomeric with aldoses that have the same number of carbon atoms. Structurally, a ketose differs from an aldose in that the carbonyl group never contains a terminal carbon atom. In the common ketoses the carbonyl group contains the second carbon atom (see the general formula of ketoses, page 746).

The simplest ketose is dihydroxyacetone which contains no asymmetric carbon atom. Of the various possible isomeric ketotetroses, ketopentoses, and ketohexoses, the most important naturally occurring one is the ketohexose D-fructose.



dihydroxyacetone



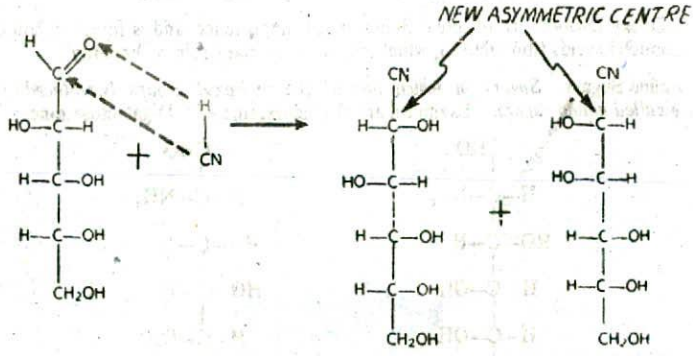
D(−)-fructose

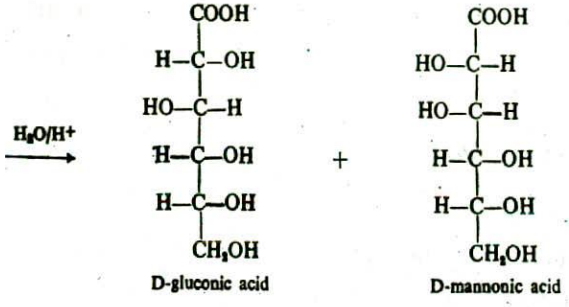
SYNTHESIS AND INTERCONVERSIONS OF MONOSACCHARIDES

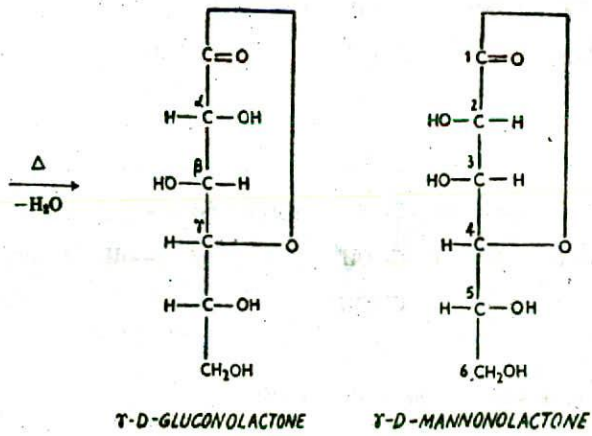
By means of the following methods it is possible to convert one monosaccharide into another. These interconversions are important for two main reasons : they are used in determining the relative configurations of monosaccharides, and they also provide routes to compounds which are unknown or very rare in nature.

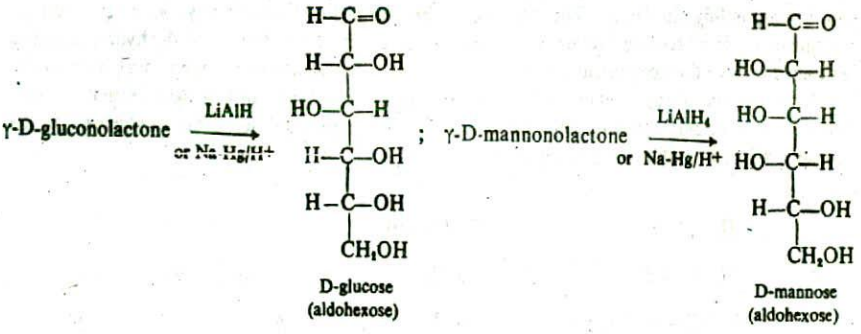
(1) Conversion of an Aldose into the Next Higher Aldose

(*a*) **Kiliani-Fischer Cyanohydrin Synthesis.** The aldose is first allowed to react with HCN. This process introduces a new asymmetric centre and results in the formation of two cyanohydrins (aldononitriles). It should be noted that these cyanohydrins differ only in configuration about the newly introduced asymmetric carbon atom (carbon number 2), and are, therefore, *epimers*. These cyanohydrins are next hydrolysed with dilute acid to give the corresponding aldonic acids. The aldonic acids on heating lose a molecule of water to give γ-lactones (1, 4-aldonolactones). These γ-lactones are solids and are separated by fractional crystallisation. The individual lactones can then be reduced with lithium aluminium hydride or sodium amalgam in a weakly acidic solution to give aldoses which contain one more carbon atoms than the original aldose. Thus D-arabinose may be converted into D-glucose and D-mannose as follows.

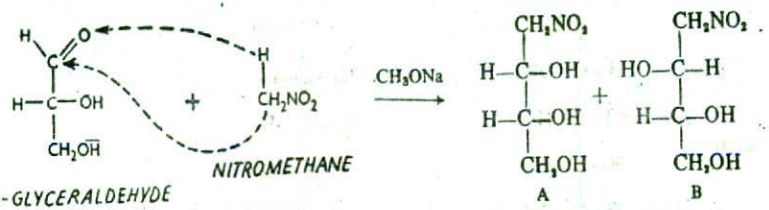


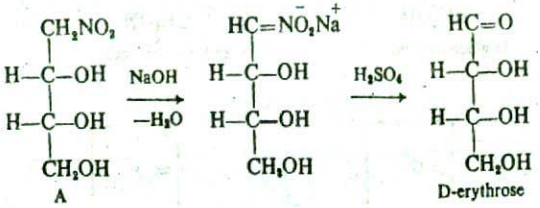


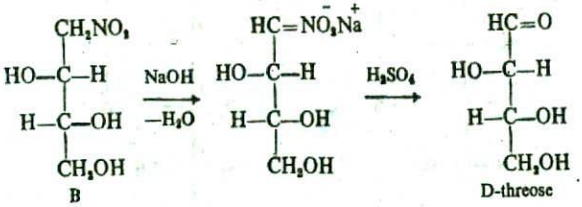




(*b*) **Sowden-Fischer Nitromethane Synthesis.** This is a more recent method and involves the reaction of an aldose with nitromethane in the presence of a base. This process introduces a new asymmetric centre and results in the formation of two different nitroalcohols, which are separated by fractional crystallisation. The individual nitroalcohols are next treated with sodium hydroxide solution to give the corresponding sodium salts, which may then be decomposed to give the higher aldoses. Thus, D-glyceraldehyde may be converted into D-erythrose and D-threose as follows.

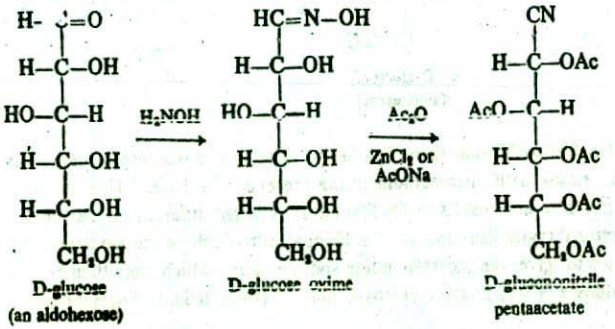


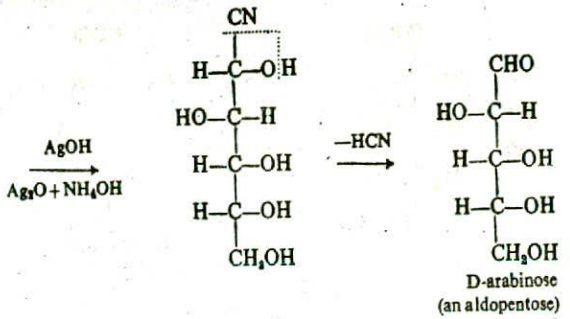




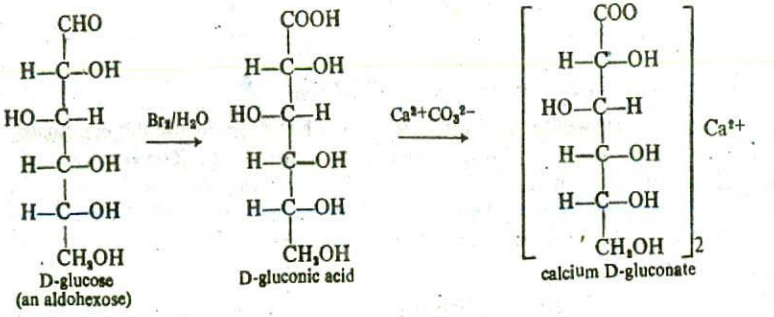
(2) Conversion of an Aldose into the Next Lower Aldose

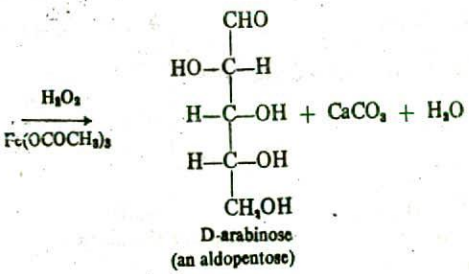
(*a*) **Wohl's Method.** In this method the aldose is first treated with hydroxylamine to give the corresponding aldoxime. The aldoxime is next warmed with acetic anhydride in the presence of zinc chloride or sodium acetate, so that the oxime group is dehydrated and the hydroxyl groups esterified to give the acetylated aldononitrile. This is next warmed with ammoniacal silver oxide, so that the acetyl groups are removed by hydrolysis and a molecule of hydrogen cyanide is eliminated to give an aldose having one carbon less than the original aldose. Thus D-glucose may be converted into D-arabinose as indicated below.





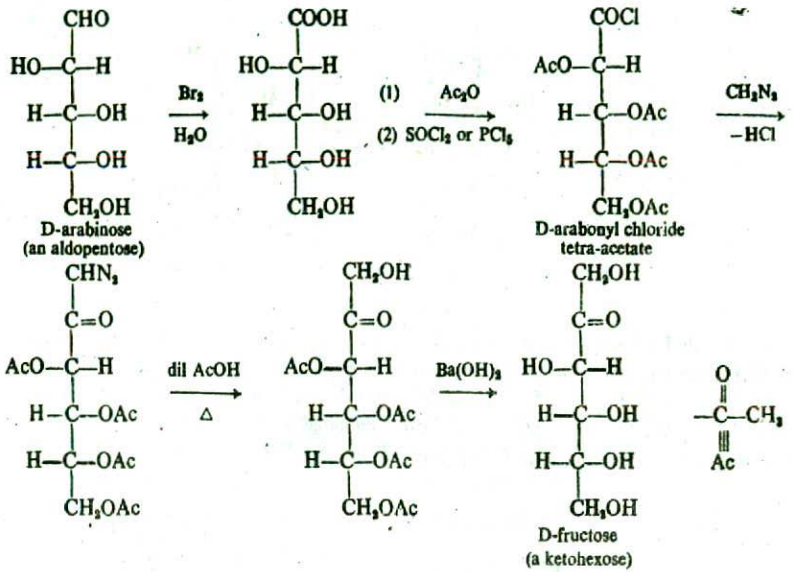
(*b*) **Ruff's Method.** In this method the aldose is first oxidised with bromine water to give the corresponding aldonic acid. The aldonic acid is next treated with calcium carbonate to give the calcium salt of the acid. This is then treated with hydrogen peroxide and ferric acetate (*Fenton's reagent*), so that CO_2 and H_2O are eliminated to give the next lower aldose. Thus D-glucose may be converted into D-arabinose as shown below.





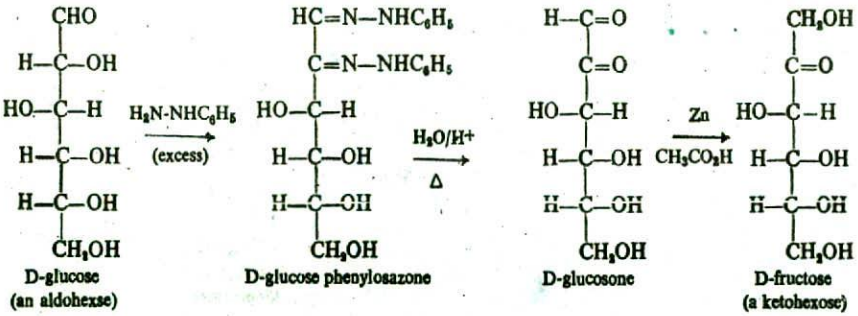
(3) Conversion of an Aldose into the Next Higher Ketose

Wolfrom's Method. In this method the aldose is oxidised to the corresponding aldonic acid, which is acetylated with acetic anhydride. The acetylated aldonic acid is then treated with thionyl chloride or PCl_5 to give the corresponding acid chloride. Treatment of this with diazomethane followed by heating with aqueous acetic acid and, finally, deacetylation by alkaline hydrolysis gives next higher ketose. Thus, D-arabinose may be converted into D-fructose as follows.

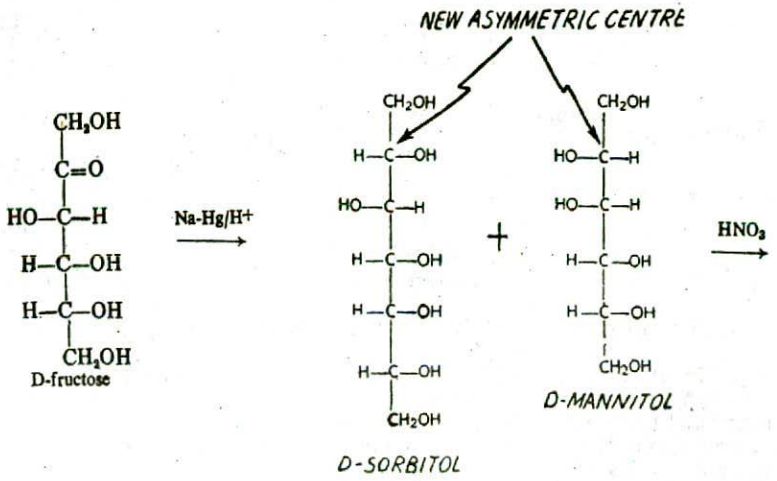


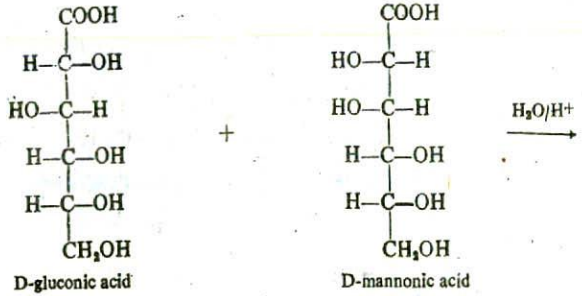
(4) Conversion of an Aldose into the Corresponding Ketose

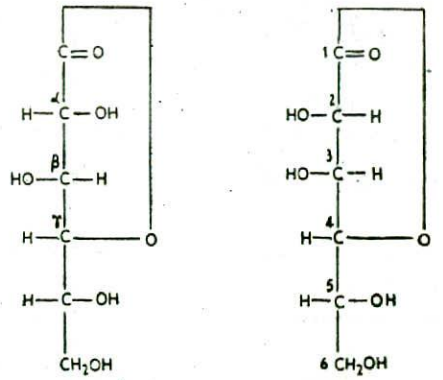
The aldose is first allowed to react with *excess* phenylhydrazine to give the corresponding osazone. The osazone is next hydrolysed with dilute hydrochloric acid to give the osone. This is then reduced with zinc and glacial acetic acid to give ketose which is isomeric with the original aldose. It should be noted that in glacial acetic acid, zinc reduces the aldehyde group in preference to the ketone group. Thus D-glucose may be converted into D-fructose as follows.

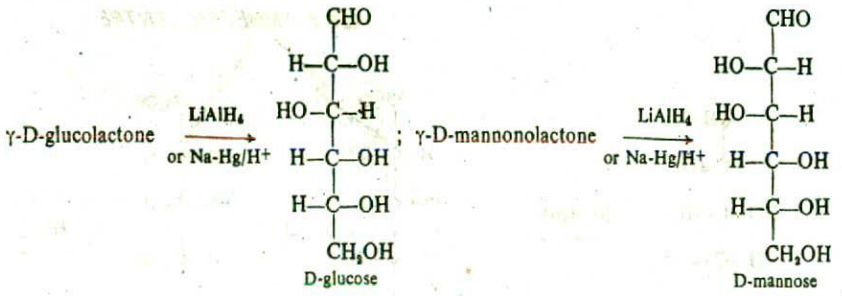


(5) Conversion of the Ketose into the Corresponding Aldose. The ketose is first reduced with sodium amalgam in the presence of a trace of acid. This process introduces a new asymmetric centre and results in the formation of two different polyhydric alcohols. These alcohols are next oxidised with nitric acid to give the corresponding monobasic aldonic acids. The aldonic acids on treatment with dilute HCl give γ-lactones. These lactones are solids, and are separated by fractional crystallisation. The individual lactones are then reduced with lithium aluminium hydride or sodium amalgam in a weakly acidic solution to yield aldoses which are isomeric with the original ketose. Thus D-fructose may be converted into D-glucose and D-mannose as shown below.


NEW ASYMMETRIC CENTRE
D-fructose
Na-Hg/H+
D-SORBITOL
D-MANNITOL
HNO3

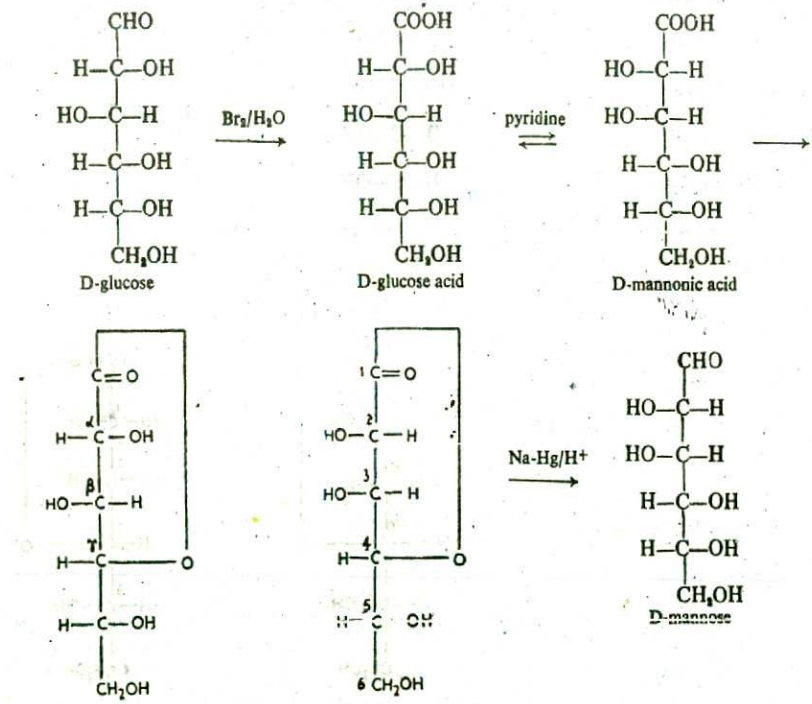

D-gluconic acid
D-mannonic acid
H2O/H+


γ-D-GLUCONOLACTONE
γ-D-MANNONOLACTONE



(6) Conversion of an Aldose into its Epimeric Aldose ; (Epimerisation)

The aldose is first oxidised with bromine water to give the corresponding aldonic acid, which is then heated in aqueous pyridine or quinoline to give an equilibrium mixture of the original acid and its isomer. These isomeric aldonic acids are identical in all respects except for the configuration about the asymmetric carbon number 2. They are, therefore, epimers (or more precisely C-2-epimers). These acids are next converted into lactones, separated and reduced to the original aldose and its C-2-epimer. Thus D-glucose may be converted into D-mannose as shown below.



This change of configuration of one asymmetric carbon atom in a compound containing two or more asymmetric carbon atoms is known as epimerisation.

D-GLUCOSE (*Dextrose, Grape Sugar, or Blood Sugar*), $C_6H_{12}O_6$

Occurrence. Glucose* occurs naturally both in a combined and free state. In the free state, it is present in most sweet fruits and in honey. Ripe grapes often contain as much as 20 to 30 per cent of glucose, and for this reason it is sometimes called *Grape Sugar*. Small quantities of glucose are also present in human blood and urine, but urine of sufferers from *diabetes* may contain as much as 8 to 10 per cent of glucose. In the combined state, it forms a major component of many disaccharides (*e.g.*, sucrose, maltose, and lactose), and polysaccharides (*e.g.*, starch, cellulose, and glycogen)

Preparation. (1) FROM SUCROSE (*Cane Sugar*). In the laboratory glucose is made by the hydrolysis of sucrose by boiling with dilute HCl or H_2SO_4 in alcoholic solution. Glucose and fructose are obtained in equal amounts. On cooling the resulting solution, glucose being much less soluble than fructose separates out.

$$\underset{\text{sucrose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow[\Delta]{H^+} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6}$$

(2) FROM STARCH. Commercially, glucose is obtained by the hydrolysis of starch by heating with very dilute (0·5 per cent) sulphuric acid at 120°C under a pressure of 2 to 3 atmospheres.

$$\underset{\text{starch}}{(C_6H_{10}O_5)_n} + n\,H_2O \xrightarrow[120°C\,;\,2\text{-}3\ \text{atmos}]{H^+} \underset{\text{glucose}}{n\,C_6H_{12}O_6}$$

The resulting solution is neutralised with calcium carbonate, and the precipitated calcium salts are filtered off. The filterate is decolourised by boiling with animal charcoal, and then concentrated under reduced pressure and crystallised.

(3) FROM CELLULOSE. Glucose may also be obtained by the hydrolysis of cellulose $(C_6H_{10}O_5)_n$ by heating with dilute H_2SO_4. The details of the procedure are the same as in the manufacture of glucose from starch.

STRUCTURE OF D-GLUCOSE

The structure of glucose has been derived from a consideration of facts and conclusions such as the following :

(1) Elemental analysis and molecular weight determination show that the molecular formula of glucose is $C_6H_{12}O_6$.

(2) Complete reduction of glucose with concentrated hydriodic acid in the presence of red phosphorous produces *n*-hexane (C_6H_{14}) as the major product. This indicates that the six carbon atoms in the glucose molecule form a consecutive, unbranched chain.

(3) Glucose readily dissolves in water to give a neutral solution. This indicates that the glucose molecule does not contain a carboxyl ($-\overset{\overset{O}{\|}}{C}-O-$) group.

(4) Glucose reacts with hydroxylamine to form a monoxime, or adds only one mole of hydrogen cyanide to give a cyanohydrin. These reactions indicate the presence of either an

*The name 'glucose', unqualified by prefix D- or L- could mean either of the two enantiomers. However, in this text book, unless otherwise specified, the name will be used in with reference to D-glucose only.

aldehyde ($-\overset{O}{\overset{\|}{C}}-H$) or a ketone ($-\overset{O}{\overset{\|}{C}}-$) group, *but not both.*

(5) Mild oxidation of glucose with bromine water gives gluconic acid, a monocarboxylic acid with molecular formula $C_6H_{12}O_7$. This indicates the presence of an aldehyde group since only the aldehyde group can be oxidised to an acid by gaining one oxygen atom without losing any hydrogen atoms, ($C_6H_{12}O_6 \longrightarrow C_6H_{12}O_7$; $-\overset{O}{\overset{\|}{C}}-H \longrightarrow -\overset{O}{\overset{\|}{C}}-OH$). Since the six carbon atoms in glucose form a consecutive, unbranched chain, the aldehyde group, must occupy one end of this chain.

(6) Further oxidation of gluconic acid with nitric acid gives glucaric acid, a dicarboxylic acid with molecular formula $C_6H_{10}O_8$. This indicates the presence of a primary alcohol group, since oxidation occurs with the loss of two hydrogens and gain of one oxygen atom.

$$C_6H_{12}O_7 \longrightarrow C_6H_{10}O_8 \; ; \; -CH_2OH \longrightarrow -\overset{O}{\overset{\|}{C}}-OH.$$

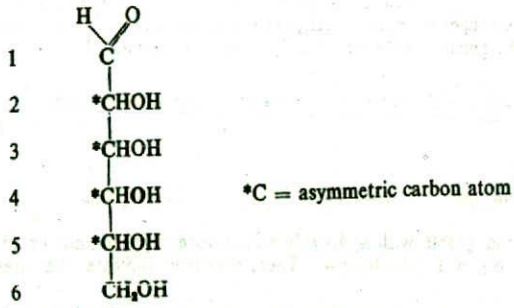
(7) Glucose reduces an ammonical solution of silver oxide (Tollen's reagent) to metallic silver, or a basic solution of cupric ion (*Fehling's solution*) to red cuprous oxide. These reactions further confirm the presence of a terminal aldehyde group.

(8) Glucose reacts with acetic anhydride in the presence of pyridine to form a pentaacetate. This reaction indicates the presence of five hydroxyl groups in a glucose molecule.

(9) Organic compounds with two hydroxyl groups attached to a single carbon atom are rare, and those which are known usually lose water to produce a carbonyl group.

This suggests that in glucose molecule, each one of the five hydroxyl groups is attached to a different carbon atom.

From the above evidence we conclude that glucose is a pentahydroxyhexanal (an aldohexose), and can be represented by the following gross structure.



glucose
(2,3, 4, 5, 6-pentahydroxyhexanal)

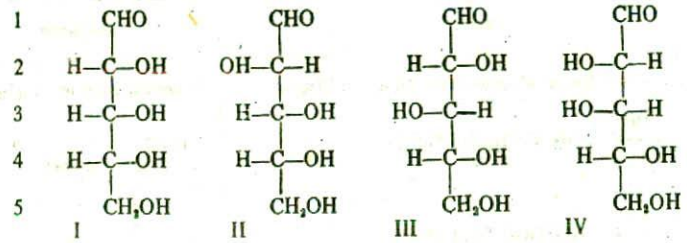
Table 32·1. Facts leading to the Structure of Glucose

	Fact	*Conclusion*
	⟶ Elemental Analysis and Molecular Weight	Molecular Formula : $C_6H_{12}O_6$
	HI/P ⟶ reduction $CH_3CH_2CH_2CH_2CH_2CH_3$ *n*-hexane	C–C–C–C–C–C (continuous chain)
	H_2O ⟶ NEUTRAL SOLUTION	$-C(=O)-O-$ absent
	NH_2OH ⟶ $HC{=}NOH$, $(CHOH)_4$, CH_2OH glucose oxime	$-C(=O)-H$ or $-C(=O)-$ present
CHO, CHOH, CHOH, CHOH, CHOH, CH_2OH glucose	HCN ⟶ 1 mole CN, $(CHOH)_5$, CH_2OH glucononitrile	$-C(=O)-H$ or $-C(=O)-$ confirmed
	Br_2/H_2O ⟶ mild oxidation $COOH$, $(CHOH)_4$, CH_2OH gluconic acid; HNO_3 ⟶ strong oxidation $COOH$, $(CHOH)$, $COOH$ glucaric acid	$-C(=O)-H$ and $-CH_2OH$ at the ends of the 6-carbon chain.
	$Ag(NH_3)OH$ ⟶ Tollen's reagent $Ag\downarrow$ silver mirror	Confirms $-C(=O)-H$
	$Cu(OH)_2/NaOH$ ⟶ Fehling's solution $Cu_2O\downarrow$ red ppt	Confirms $-C(=O)-H$
	$(CH_3CO)_2O$ ⟶ C_5H_5N CHO, $(CHOCOCH_3)_4$, CH_2OH glucose pentaacetate	Confirms five —OH groups in glucose on separate carbons.

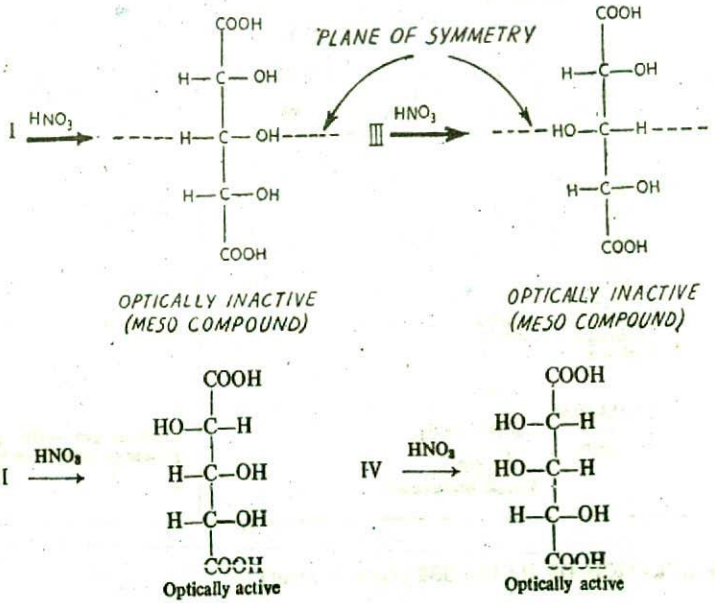
CONFIGURATION OF D-GLUCOSE (*Fischer's Proof*)

The above ructure has four unlike asymmetric carbon atoms (marked by asterisks). This representation of glucose is incomplete, because it does not give us any idea about the spatial arrangement of the hydroxyl groups and the hydrogen atoms around these four asymmetric centres. That is, we have yet to determine the relative configuration of the asymmetric centres and the absolute configuration of the molecule. The procedure given below is the one which was used by the great Emil Fischer.

A key compound in this determinatation is D-arabinose, an aldopentose, which must have one of the following structures (I—IV).

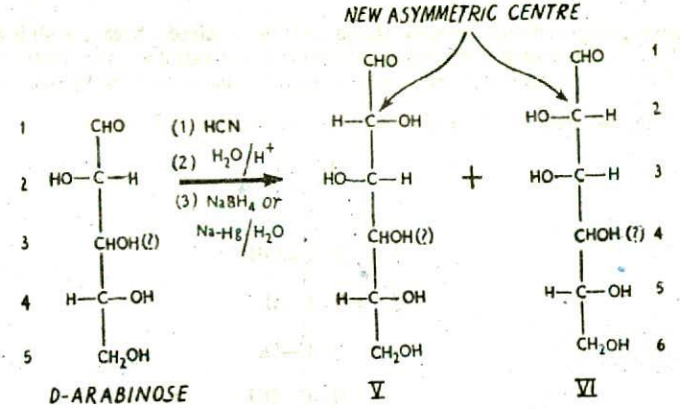


Oxidation of D-arabinose with nitric acid gives an optically active dicarboxylic acid. Under these conditions I and III would have given optically inactive *meso* diacids. It should be recalled that the *meso* compounds are those which contain two or more asymmetric centres but are optically inactive They contain an internal plane of symmetry such that one half of the molecule forms the mirror image of the other half. They are optically inactive because the optical activity due to one half is counterbalanced by the optical activity of the other half.

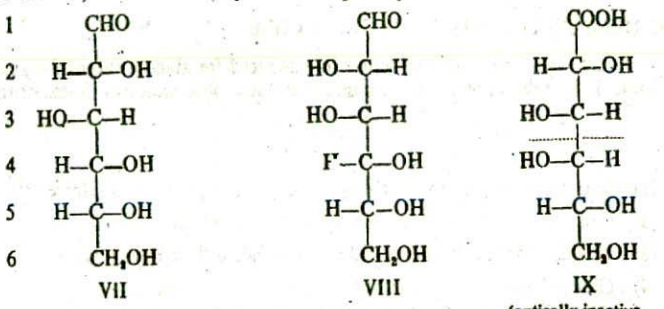


D-Arabinose is therefore either II or IV, and can be represented with configuration in *doubt* at C-3 for the time being.

When D-arabinose is subjected to the Kiliani-Fischer synthesis, it gives two sugars, glucose and mannose. These sugars differ only in configuration at C-2, which is the new asymmetric centre created in the chain-extension. Structures V and VI must therefore represent glucose and mannose. The next step is to determine the configuration at C-4 and then decide which is glucose and which is mannose.

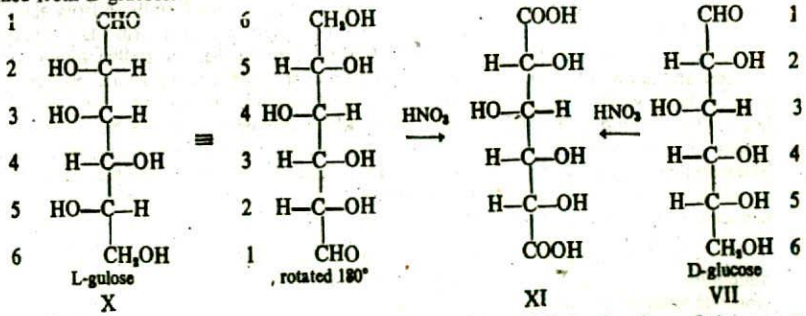


Both glucose and mannose on oxidation with nitric acid give diacids which are optically active. This means that the hydroxyl group C-4 is on the right, as in VII and VIII. If it were on the left, VII would have yielded an optically inactive *meso* diacid, IX.



Structures VII and VIII, then represent D-glucose and D-mannose. It only remains to decide whether VII is glucose and VIII is mannose, or the other way around.

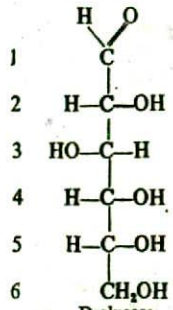
To decide this last point, we make use of another aldeohexose, L-gulose, X. This compound when oxidised with nitric acid yields the same dicarboxylic acid (XI) as that obtained from D-glucose.



L-Gulose when turned upside down (*i.e.*, rotated by 180° in the plane of the paper) has the same configuration at the asymmetric centres as does D-glucose, except that the aldehyde and the primary alcohol groups are interchanged. Oxidation converts these groups to

the carboxyl groups and thus the same diacid (XI) is obtained. Such a result is not possible with VIII, since the structure obtained by interchanging the ends does not represent a different sugar. Hence D-glucose is represented by structure VII, and D-mannose by structure VIII.

If follows from the above discussion that the structure of D-glucose is



D-glucose
(open-chain aldehyde form)

CYCLIC HEMIACETAL FORMS OF D-GLUCOSE

Although the open-chain structure just deduced for glucose successfully rationalises the data in Table 32·1, it does not explain a number of other observations. Some of these are given below.

(1) Glucose does not show carbonyl (—C—, with O) absorption in its infrared spectrum.

(2) Glucose does not give the Schiff's test for aldehydes.

(3) Glucose does not form an addition product with sodium bisulphite.

(4) Glucose pentaacetate does not react with hydroxylamine.

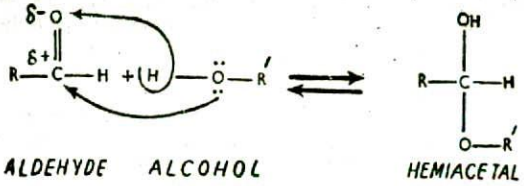
(5) Glucose does not react with Grignard reagents.

All these observations suggest the absence of a free aldehyde group.

(6) **Isolation of Two Crystalline Forms of D-Glucose** (*Mutarotation*). D-Glucose can be obtained in two different crystalline forms depending on how one recrystallises ordinary glucose. If ordinary D-glucose is crystallised from a concentrated aqueous solution at 30°C, the α-form of the sugar is obtained. Its melting point is 146°C and the specific rotation is +113°. However, if another portion of the same ordinary D-glucose is recrystallised from glacial acetic acid at temperatures higher than 100°C, the β-form is obtained. This form has a melting point of 150°C and a specific rotation of +19°. If either form of these crystalline forms is dissolved in water and allowed to stand, the specific rotation of the solution so prepared changes gradually until a final value of +53° is obtained. The final stage can be reached more rapidly either by heating the solution or by adding some catalyst which may be an acid or a base. *A spontaneous change of this kind in the specific rotation of a solution of an optically active compound is called* **Mutarotation** (Latin : *Mutare*, to change). This suggests that the two samples are different but in solution they form an equilibrium mixture. The structure of D-glucose that we have deduced does not explain this behaviour.

(7) Treatment of glucose with methanol in the presence of dilute HCl does not yield a dimethylacetal, as might be expected if glucose were an open-chain aldehyde. Instead, two isomeric monomethyl derivatives are obtained.

The structure we have deduced for D-glucose can be modified to accommodate these facts. Recall that aldehydes may react with alcohols to form unstable compounds called *hemiacetals*.



The glucose structure contains an aldehyde group and five hydroxyl groups in the same molecule. Consequently, there can be *intramolecular ineraction* between the carbonyl group and one of the hydroxyl groups. Of necessity, the reaction results in a ring, that is, the product is a *cyclic hemiacetal.*

We can apply our knowledge of stereochemistry to this problem in order to predict which of the five hydroxyl groups will participate in the reaction. Since we know that 5- and 6-membered rings are more stable than rings containing 3, 4, or 7 atoms (Baeyer Strain theory), we would predict that hydroxyl groups at C-4 and C-5 in the glucose molecule are likely to react to form the cyclic hemiacetal. The 6-membered ring system contains *less* bond angle strain than the 5-membered ring, and hence it is probable that the hydroxyl group at C-5 will react with the aldehyde group. The following figure illustrates this reaction. The long C—O—C bonds merely emphasise the points of attachment.

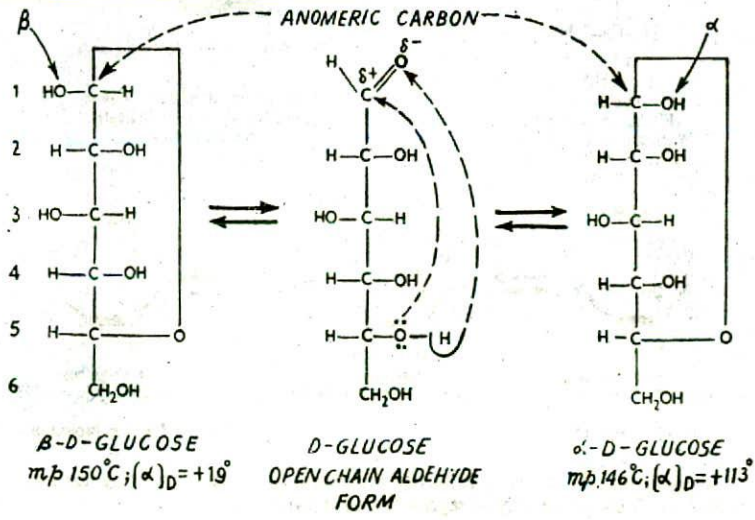


Fig. 32·1. Formation of the cyclic hemiacetal forms of D-glucose.

As a result of the cyclisation reaction, C-1 (hemiacetal carbon) becomes asymmetric. This simply means that when hydrogen of the hydroxyl group at C-5 adds to the oxygen of the planar aldehyde group, the —OH group formed may move either to left or right, and thus resulting in the formation of two isomers. The isomer having the hydroxyl group to the *left* of C-1 is designated β-D-glucose, the one having the hydroxyl group on the *right*, as α-D-glucose.

α-D-Glucose and β-D-glucose are not enantiomers (*i.e.*, are not mirror images of each other), since the configurations at C-2, C-3, C-4, and C-5 are the same. They are diastereomers. They differ only in configuration at C—1.

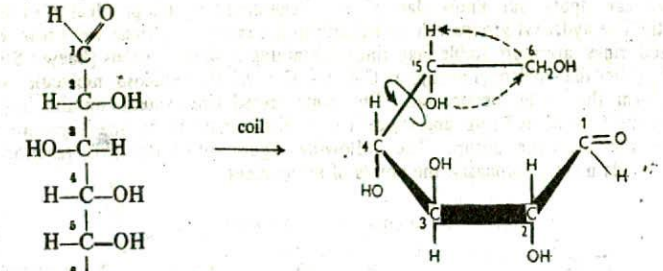
In carbohydrate chemistry, the diastereomers resulting from cyclisation are called **Anomers**. Anomers differ only in the configuration around C-1, and this carbon atom is referred to as the **Anomeric carbon**. The anomeric carbon can easily be distinguished from the other carbon atoms in the ring by the fact that it is joined to *two* oxygens.

Haworth Projections

The Fischer projections shown in figure 32·1 do not accurately describe the true shapes of the cyclic hemiacetal forms of glucose. A formulation suggested by the English chemist W.N. Haworth in which rings are written as *flat* or *planar* hexagons, is more correct.

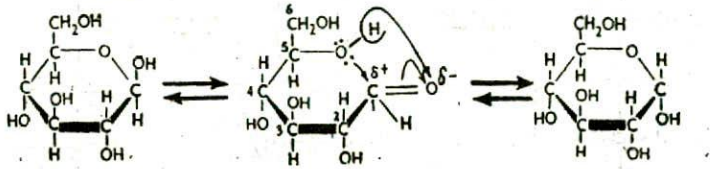
When a cyclic form of glucose is represented in this way the lower thickened edge of the ring is assumed to be nearest the reader. The groups projected to the *right* in the Fischer projection go *below* the plane of the ring, those to the *left* go *above*.

The following series of formulas should explain the relation between the two conventions without further comment.



D-glucose (Fischer Projection) When a model of this is made, it will coil as shown.

If the group attached at C-4 is pivoted as the arrows indicate : we get form A.

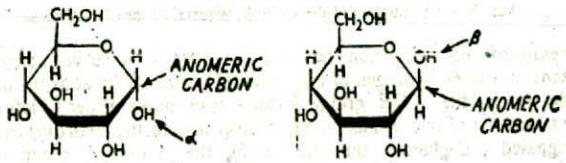


β-D-glucose mp 150°C ; $[\alpha]_D = +19°$ (Haworth Projection) B

D-glucose (Open-chain aldehyde form) A

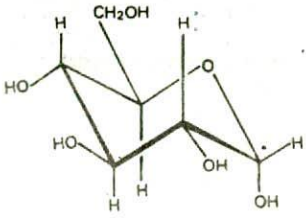
α-D-glucose mp 146° ; $[\alpha]_D = +113°$ (Haworth Projection) C

A simple way of drawing Haworth projections is to omit the ring carbons. Thus, α-D-glucose and β-D-glucose may be represented as shown below.

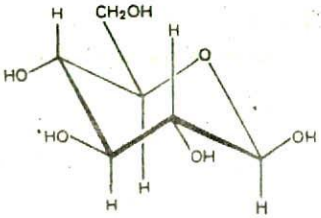


α-D-GLUCOSE β-D-GLUCOSE

Aactually, the cyclic forms of glucose preferentially exist in the non-planar chair conformations like those of cyclohexanes. This has been confirmed by X-ray studies.



α-D-Glucose



β-D-Glucose

Since it is inconvenient to draw such non-planar projections, we will use the planar Haworth projections.

EXPLANATION OF MUTAROTATION

The phenomenon of mutarotation can now be explained on the basis of the cyclic forms of glucose. The initial rotations of +113° or +19° are caused by the presence of α-D-glucose (+113°) or β-D-glucose (+19°), respectively. In the solid state these two forms of glucose are stable. However, when either form is placed in solution it slowly forms the other *via* the open-chain aldehyde form, and the gradual change in specific rotation is attributed to the establishment of equilibrium between the two forms. The final value +53° corresponds to the equilibrium mixture of the α- and β-forms (Fig. 32·2). This value is not an average of +19° and + 113°. This implies that the equilibrium mixture does not contain equal amounts of the two anomers. Calculations have shown that it contains 63% of β-form, 37% of the α-form (with less than 1% of the unisolable open-chain aldehyde form).

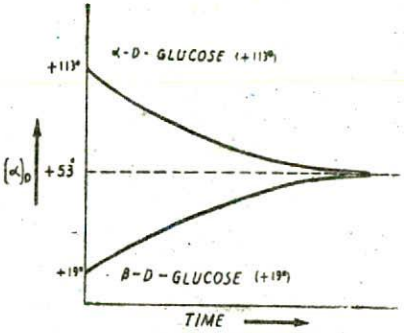
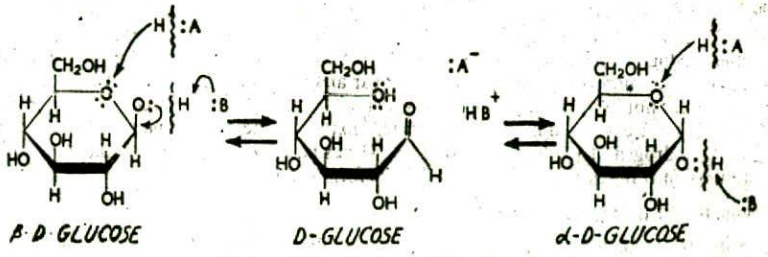


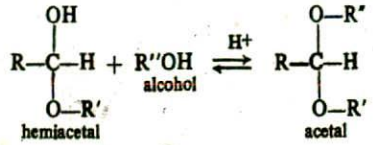
Fig. 32·2. The mutarotation of α-D-glucose and β-D-glucose.

MECHANISM. The mechanism of mutarotation is not completely understood. However, the generally accepted mechanism involves a simultaneous attack by an acid and a base (water is an amphoteric solvent) to yield the open-chain aldehyde form, which then recloses to give the other form.

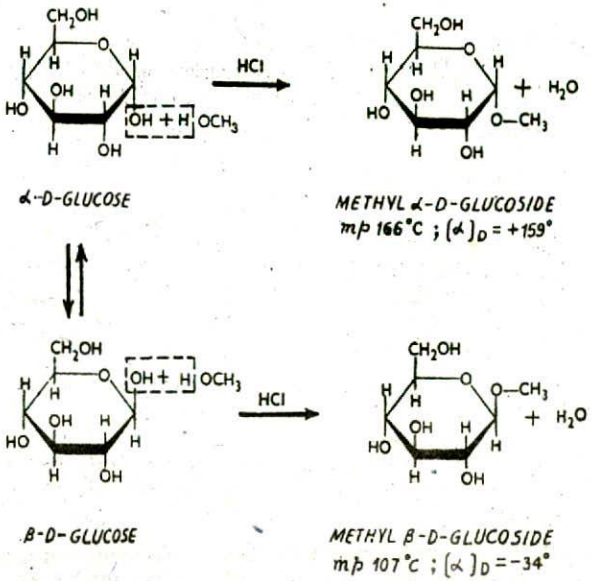


GLUCOSIDES

A hemiacetal can react with an alcohol in acidic solution to form an acetal.



Glucose itself is a hemiacetal. Therefore, the hemiacetal hydroxyl group (—OH at C-1) of glucose can and does react similarly to produce the corresponding acetal. However, when glucose is treated with methyl alcohol in the presence of HCl, two isomeric compounds are obtained. This is because when glucose is placed in solution both α- and β-forms of glucose are in equilibrium with each other, and each reacts separately to yield a different compound (This explains step 7 on page 766).



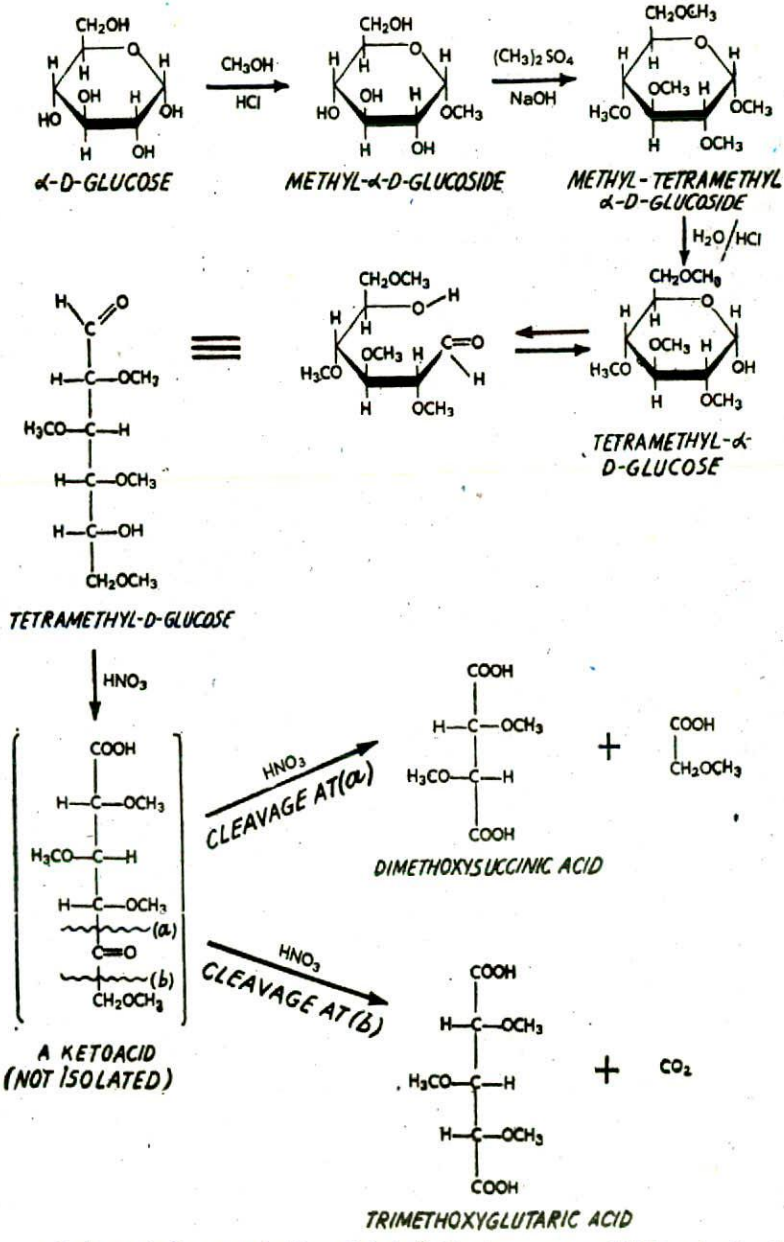
In carbohydrate chemistry, acetals derived from *glucose* are called **Glucosides**. The more general term, **Glycoside**, is used to refer the acetal which is obtained when any carbohydrate reacts with a hydroxy compound. Specific compounds may be named according to the sugar from which they are derived. For example, the acetal from *fructose* may be called **Fructoside**. The C—O—C linkage which joins the two components of an acetal is called the **Glycosidic linkage.**

The α- and β-methyl glucosides are crystalline, water-soluble compounds, and have properties analogous to the acetals. Like acetals, they are stable toward bases, but are hydrolysed in acid solution to yield the parent sugar and alcohol. They do not reduce Fehling's solution and do not mutarotate. This means that when either form is placed in water, it remains as such and is not converted into an equilibrium mixture of the two isomers. This is because the mobile hydrogen of the hydroxyl group at C-1 has now been replaced by the alkyl group ; the equilibrium through the open-chain aldehyde form is no longer possible.

Determination of the Ring Size

So far we have assumed that both α- and β-D-glucose have 6-membered ring structures. Alternatively, the hydroxyl groups at C-2, C-3, C-4, or C-6 could have

been involved in the ring closure, which makes possible the formation of 3-, 4-, 5-, or 7-membered rings. This problem was solved by W.N. Haworth and the method he used to determine the exact ring size in glucose, involves the following steps.



α-D-glucose is first treated with methyl alcohol in the presence of HCl to give the alkali stable methyl α-D-glucoside. The glucoside is then completely methylated by treatment wit

dimethyl sulphate in alkaline solution (*Denham Reaction*), or silver oxide and methyl iodide (*Purdie-Irwin Reaction*) to give methyl tetramethyl-α-D-glucoside. The hydrolysis of this with dilute HCl selectively removes the methoxy group at C-1 to give tetramethyl-α-D-glucose. This undergoes mutarotation to give the open-chain aldehyde form which is then oxidised with concentrated HNO_3, ultimately affording a mixture of dimethoxysuccinic acid and trimethoxyglutaric acid. Dimethoxysuccinic acid is obtained by cleavage at (*a*), and trimethoxyglutaric acid by cleavage at (*b*). The above sequence of reactions is given on page 771.

The isolation and identification of these diacids as dimethoxysuccinic acid and trimethoxyglutaric acid clearly shows that the ketone group must have been formed at C-5, and that α-D-glucose has a 6-membered ring structure. This has also been confirmed by X-ray analysis. Had the α-D-glucose possessed a 5-membered ring structure, a different set of diacids would have been obtained.

Convention for Indicating the Ring Size

The 6-membered ring that we have shown for α- or β-D-glucose is known as a pyran ring because *pyran* is the name of a hetero cyclic compound whose ring consists of five carbon atoms and one oxygen atom. The pyran ring is also present in many other carbohydrates. Any carbohydrate containing a 6-membered ring therefore is called *pyranose* (pyran + ose) and its glycosides are called *pyranosides*. Thus the size of the ring in α-D-glucose and in methyl α-D-glucoside can be indicated by naming these compounds as α-D-glucopyranose and methyl α-D-glucopyranoside.

PYRAN FURAN

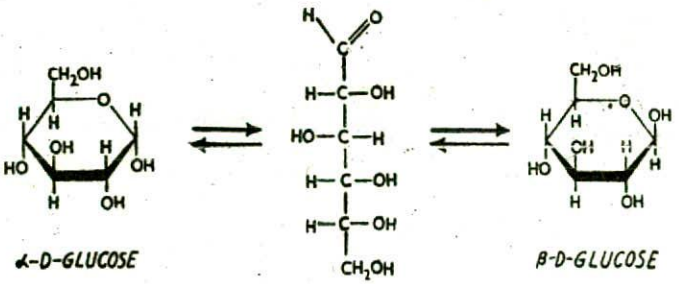
Five-membered ring structures are also common in sugars. A carbohydrate containing a 5-membered ring is called *furanose* (furan+ose) because *furan* is the name of a heterocyclic compound whose ring consists of four carbons and one oxygen atom. The glycosides of a furanose are called *furanosides*.

Physical Properties

Naturally occurring glucose (α-D-glucose) is a colourless, odourless, crystalline solid, mp 146°C. It is very soluble in water, sparingly soluble in alcohols, and insoluble in ether. An aqueous solution of glucose is dextrorotatory, and for this reason it is sometimes called *dextrose*.

Chemical Properties

In the solid state, the two cyclic forms of D-glucose (α-D-glucose and β-D-glucose) are stable. However, in solution, each form is in equilibrium with the other *via* the open-chain aldehyde form.



α-D-GLUCOSE D-GLUCOSE (OPEN CHAIN FORM) β-D-GLUCOSE

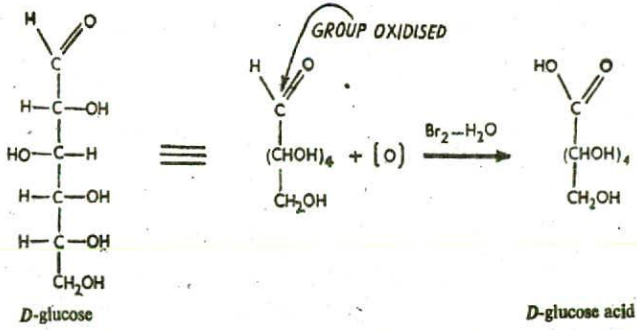
Because the above equilibrium reactions are fairly fast, glucose solutions can react as though they consisted of any of the three forms. Thus the reactions of glucose are of two types :

(*A*) *Reactions characteristic of the open-chain aldehyde form* ;

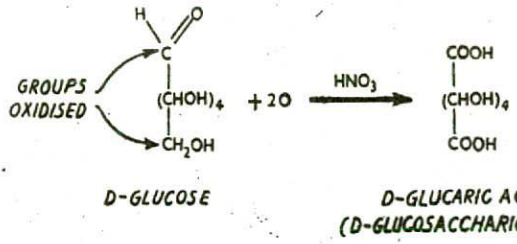
(*B*) *Reactions characteristic of the cyclic forms.*

(A) REACTIONS CHARACTERISTIC OF THE OPEN-CHAIN ALDEHYDE FORM OF GLUCOSE

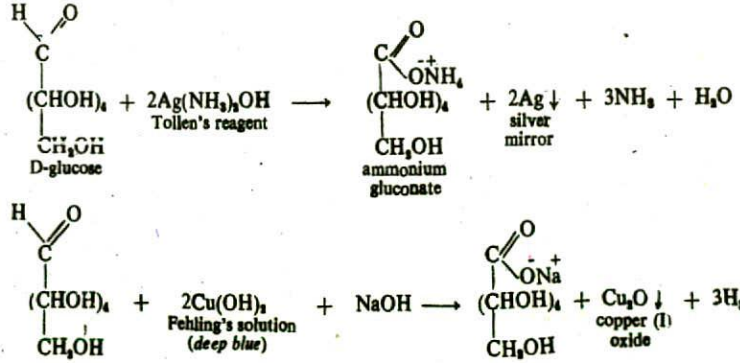
(1) **Oxidation.** Mild ox dation of D-glucose with bromine water gives a monocarboxylic acid called D-gluconic acid.



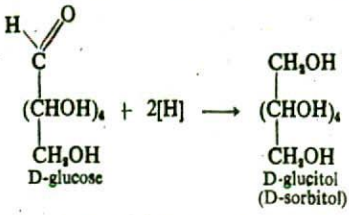
Drastic oxidation of glucose with conc HNO_3 yields a dicarboxylic acid called D-glucaric acid (or D-glucosaccharic acid).



(2) **Action as a Reducing Agent.** D-Glucose reduces an ammoniacal solution of silver oxide (*Tollen's reagent*) to silver, and an alkaline solution of cupric ion complexed with sodium potassium tartrate (*Fehling's solution*) to cuprous oxide.



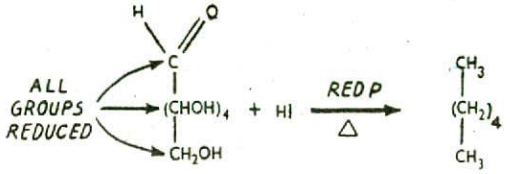
(3) **Reduction.** Mild reduction of D-glucose with sodium borohydride or sodium amalgam and water yields a hexahydroxy alcohol called D-sorbitol. Since names for the polyhydroxy alcohols may be derived from the names of the corresponding sugars by changing the suffix *-ose* to *-itol*, another name for this alcohol is D-glucitol.



D-glucose

D-glucitol
(D-sorbitol)

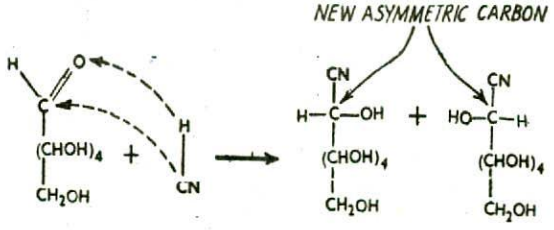
Drastic reduction of glucose with hydriodic acid and red phosphorous yields *n*-hexane.



D-GLUCOSE *n-HEXANE*

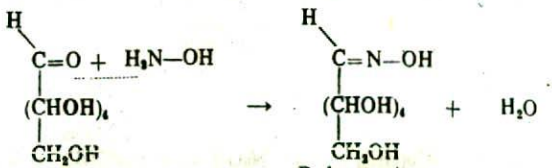
(4) **Reaction with Metallic Hydroxides.** D-glucose aqueous solution reacts with slaked lime to form a soluble compound called calcium D-glucosate, $C_6H_{11}O_6CaOH$. This compound is decomposed by carbon dioxide with the liberation of glucose. Barium hydroxide also reacts with glucose to give a similar soluble compound which is decomposed by carbon dioxide.

(5) **Reaction with Hydrogen Cyanide** (*Cyanohydrogenation*). D-glucose reacts with hydrogen cyanide to form two epimeric cyanohydrins, D-glucononitrile and D-mannononitrile. Two products are obtained as a result of introduction of a new asymmetric centre.



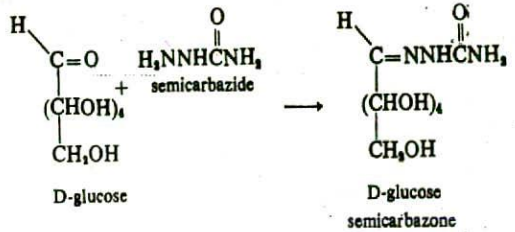
D-GLUCOSE *D-GLOCONO-NITRILE* *D-MANNONO-NITRILE*

(6) **Reaction with Hydroxylamine.** D-glucose undergoes a condensation reaction with hydroxylamine to form an oxime called D-glucose oxime.

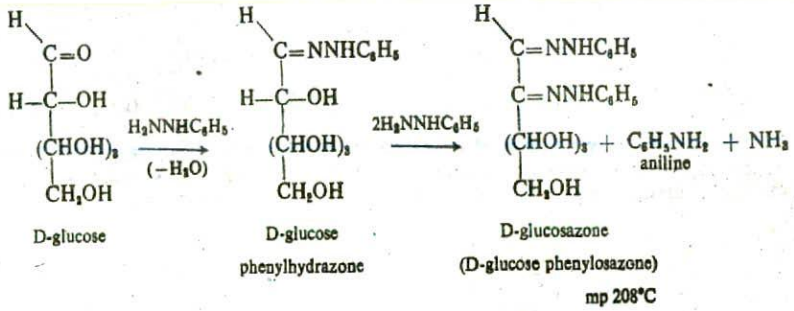


D-glucose D-glucose oxime

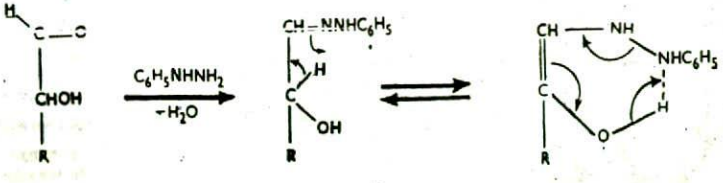
(7) Reaction with Semicarbazide. D-glucose also undergoes a condensation reaction with semicarbazide to form a semicarbazone called D-glucose semicarbazone.

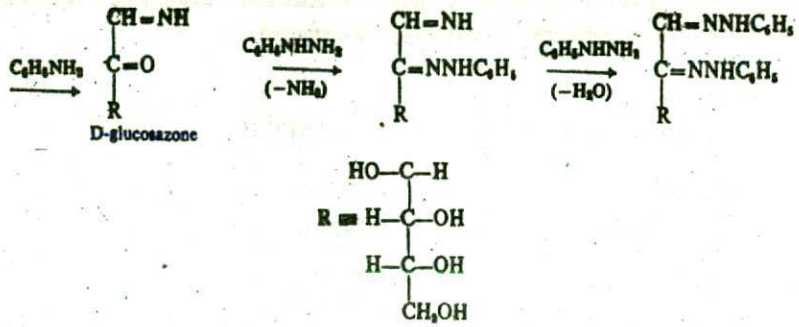


(8) **Reaction with Phenylhydrazine (Osazone Formation).** D-Glucose reacts with phenylhydrazine to give the soluble D-glucose phenylhydrazone. However, in the presence of excess phenylhydrazine the phenylhydrazone reacts further to form a dihydrazone called D-glucoseazone, aniline and ammonia. This reaction was discovered by Emil Fischer in 1887.

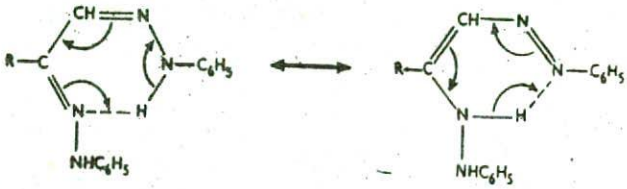


MECHANISM. The mechanism of osazone formation is uncertain, but the one proposed by Weygand and Semyakin (1965) is generally accepted. According to this mechanism, the first formed phenylhydrazone undergoes a re arrangement through a cyclic intermediate in which the secondary hydroxyl group at C-2 becomes a ketone group. This ketone group then condenses with phenylhydrazine to form the osazone.



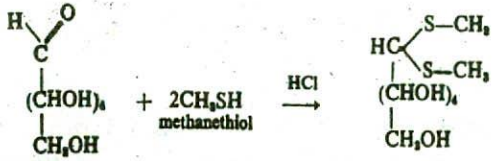


The reaction with phenylhydrazine stops at the osazone stage, apparently because hydrogen bonding permits resonance stabilisation in the form of a cyclic structure.

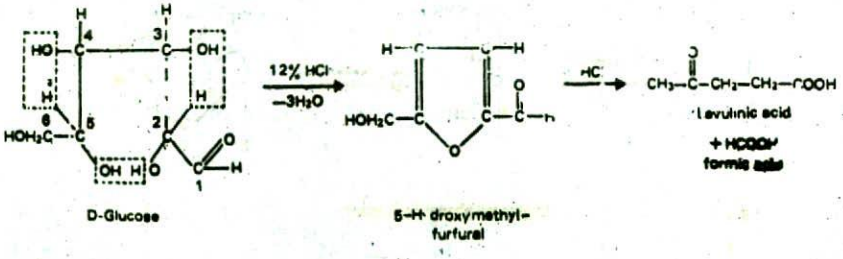


OSAZONE STABILISATION

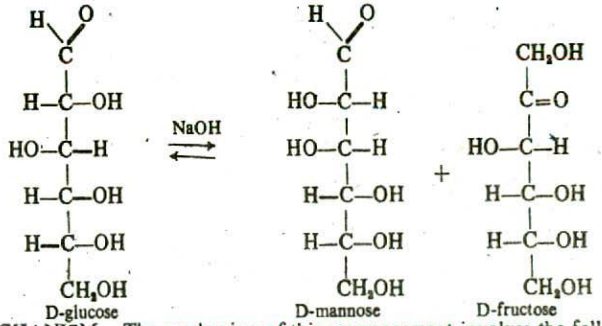
(9) **Reaction with Thiols (Dithioacetal Formation).** D-Glucose reacts with thiols in a normal way to form dithioacetals (mercaptals). Thus, when D-glucose is treated with methanethiol in the presence of an acid, it forms dimethyl dithioacetal (dimethyl mercaptal).



(10) **Action of Acids (Dehydration).** Although dilute acids have little effect on D-glucose, hot strong acids produce complex changes which involve dehydration. Thus when D-glucose is boiled with 12 per cent hydrochloric acid, it undergoes dehydration to give 5-hydroxymethylfurfural. This furfural further reacts with the hot acid to yield a mixture of levulinic acid, formic acid, and considerable amounts of dark resinous products of unknown structure called **Humins**.

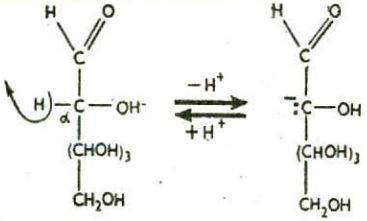


(11) Action of Alkalies (Lobry de Bruyn-van Ekenstein Rearrangement). The action of strong alkalis on D-glucose leads to brown resinous products. However, in weakly alkaline solutions, glucose undergoes rearrangement to give a mixture of D-mannose, D-glucose, and D-fructose. Mannose and fructose under the same conditions are also converted into the same mixture. The reaction is named *Lobry de Bruyn-van Ekenstein Rearrangement*, after its discoverers (1895).

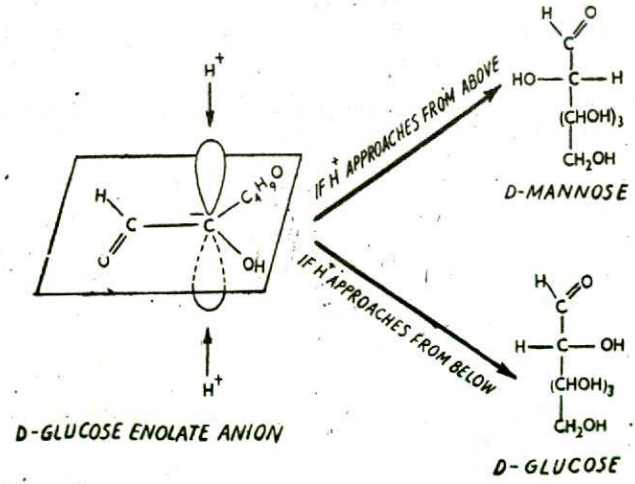


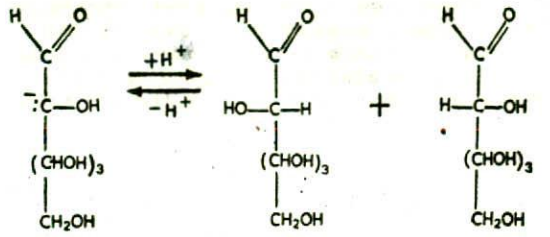
MECHANISM. The mechanism of this rearrangement involves the following steps.

Step 1. As with simple aldehydes and ketones, the hydrogen atom α to the carbonyl group of D-glucose is first removed by base (OH^-) to give an enolate anion.



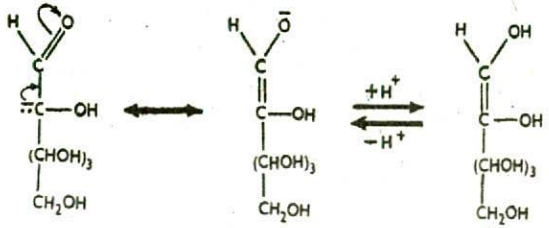
Step 2. This enolate anion has planar sp^2 geometry at C-2 and can be reprotonated at this carbon to form either D-mannose or D-glucose, depending upon the direction from which the incoming proton approaches the enolate anion.





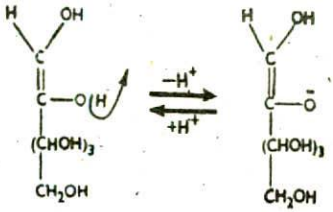
D-GLUCOSE ENOLATE ANION D-MANNOSE D-GLUCOSE

Step 3. D-glucose enolate anion, being resonance stabilised, can also be protonated on oxygen to form an *enediol*.



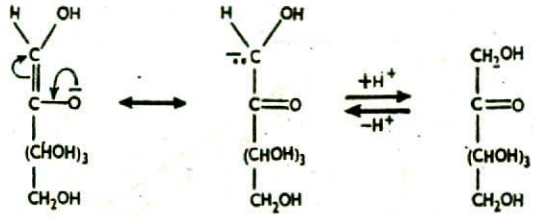
D-GLUCOSE ENOLATE ANION ENEDIOL

Step 4. Removal of a proton from the hydroxyl group at C-2 in enediol yields a new enolate anion.



ENEDIOL ENOLATE ANION

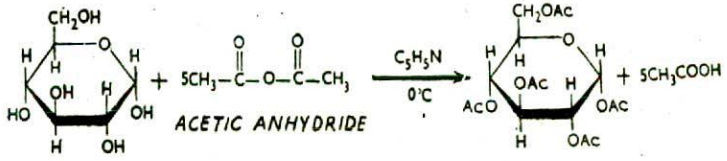
Step 5. This new enolate anion, being resonance stabilised, can also be reprotonated at C-1 to give D-fructose.



D-FRUCTOSE ENOLATE ANION D-FRUCTOSE

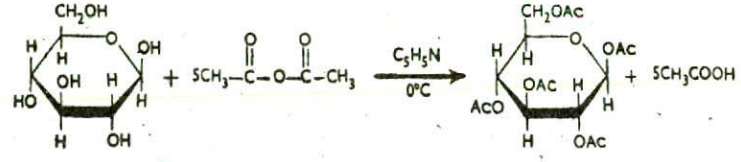
B. REACTIONS CHARACTERISTIC OF THE CYCLIC FORMS OF GLUCOSE

(12) Reaction with Acetic Anhydride (Acetylation). D-Glucose reacts with acetic anhydride, either in pyridine solution at 0°C, or by heating in the presence of sodium acetate to form two anomeric pentaacetates. This is because in solution, both α- and β-forms are in equilibrium with each other and each reacts separately to yield a different compound.



α-D-GLUCOSE

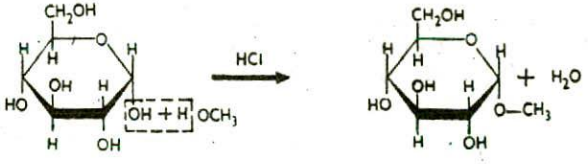
α-D-GLUCOSE PENTA ACETATE
mp 113°C; $[\alpha]_D = +102°$



β-D-GLUCOSE

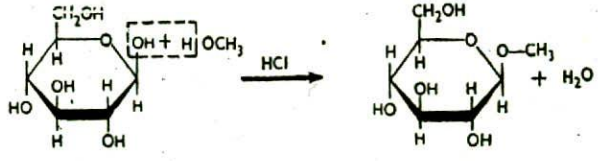
β-D-GLUCOSE PENTA ACETATE
mp 134°C; $[\alpha]_D = +4°$

(13) Reaction with Alcohols (Glucoside Formation). D-Glucose reacts with alcohols to form glucosides. Thus, when D-glucose is treated with methyl alcohol in the presence of HCl, it forms two anomeric glucosides (See page 770).



α-D-GLUCOSE

METHYL α-D-GLUCOSIDE
mp 166°C; $[\alpha]_D = +159°$

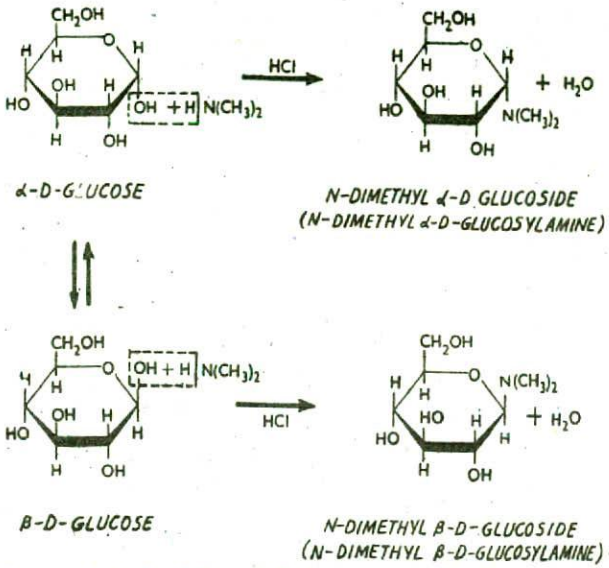


β-D-GLUCOSE

METHYL β-D-GLUCOSIDE
mp 107°C; $[\alpha]_D = -34°$

These methyl D-glucosides are used in the production of polyurethane foams.

(14) **Reaction with Amines (*N*-Glucoside Formation).** Instead of giving Schiff's bases, amines condense with glucose to form *N*-glucosides analogous to the ordinary glucosides from alcohols. Thus D-glucose reacts with dimethylamine in the presence of an acid to form two isomeric *N*-glucosides.



(15) **Fermentation.** A solution of D-glucose is readily fermented by the enzyme, *zymase* from yeast, the products being mainly ethyl alcohol and carbon dioxide.

$$\underset{\text{D-glucose}}{C_6H_{12}O_6} \xrightarrow{\text{zymase}} \underset{\text{ethyl alcohol}}{2\,C_2H_5OH} + 2CO_2\uparrow$$

The reaction is *anaerobic*, that is, it takes place in the absence of air. In the presence of air (oxygen), the alcohol may be oxidised further to acetic acid (Vinegar) or it may produce more carbon dioxide.

Uses af Glucose

Glucose is used in the making of candy, as a food, as a raw material in the preparation of vinegar, in flavouring syrups, in jellies, and in preservers. Glucose is also used as a reducing agent in the silvering of mirrors and in the reduction of indigo blue to indigo white.

D-FRUCTOSE (*Laevulose or Fruit Sugar*), $C_6H_{12}O_6$

Occurrence. Fructose occurs naturally both in a combined and free state. In the free state, it is present along with glucose in most sweet fruits and in honey. In the combined state, it forms a major component of many oligosaccharides (*e.g.*, sucrose). It is the sole constituent of inulin, a polysaccharide found in the artichokes and dahlias.

Preparation: (1) **From Sucrose** (*Cane Sugar*). In the laboratory fructose is prepared by hydrolysis of sucrose by boiling with dilute sulphuric acid.

$$\underset{\text{sucrose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow[\text{boil}]{H_2SO_4} \underset{\text{fructose}}{C_6H_{12}O_6} + \underset{\text{glucose}}{C_6H_{12}O_6}$$

On completion of the hydrolysis, the excess of sulphuric acid is neutralised with barium carbonate and the filtrate concentrated. It is cooled in ice and then calcium hydroxide is added to precipitate calcium fructosate, the calcium glucosate which is also formed remains in solu-

tion. The calcium fructosate is removed by filtration and converted to fructose by passing carbon dioxide through its suspension in water.

$$\underset{\text{calcium D-fructosate}}{C_6H_{11}O_6CaOH} + CO_2 \longrightarrow \underset{\text{fructose}}{C_6H_{12}O_6} + CaCO_3$$

After removal of the calcium carbonate by filtration, the solution is evaporated to a syrup. The addition of a crystal of fructose causes the syrup slowly to solidify, and the crystals obtained may be recrystallised from alcohol.

(2) **From Inulin.** Fructose is obtained commercially by the hydrolysis of inulin by heating with dilute sulphuric acid.

$$\underset{\text{inulin}}{(C_6H_{10}O_5)_n} + n\,H_2O \xrightarrow[\Delta]{H_2SO_4} \underset{\text{fructose}}{n\,C_6H_{12}O_6}$$

The resulting solution is neutralised with barium hydroxide and the precipitated barium sulphate removed by filtration. The solution thus obtained is concentrated under reduced pressure to yield the crystals of fructose.

STRUCTURE OF D-FRUCTOSE

The structure of fructose has been derived from a consideration of facts and conclusions such as the following.

(1) Elemental analysis and molecular weight determination show that the molecular formula of fructose is $C_6H_{12}O_6$.

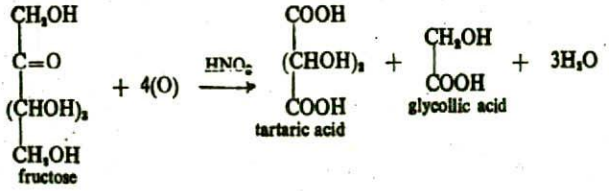
(2) Complete reduction of fructose with concentrated hydriodic acid in the presence of red phosphorous produces *n*-hexane (C_6H_{14}) as the major product. This indicates that the six carbon atoms in the fructose molecule form a consecutive, unbranched chain.

(3) Fructose readily dissolves in water to give a neutral solution. This indicates that the fructose molecule does not contain a carboxyl (—CO—O—) group.

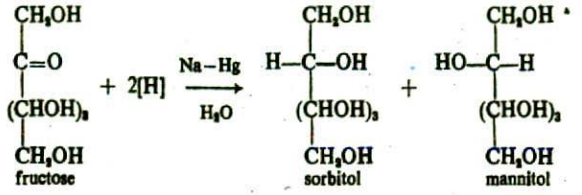
(4) Fructose reacts with acetic anhydride in the presence of pyridine to form a pentaacetate. This reaction indicates the presence of *five* hydroxyl groups in a fructose molecule. Since fructose is a stable compound, the five hydroxyl groups must be present on separate carbon atoms.

(5) Fructose reacts with hydroxylamine to form a monoxime, or adds only one mole of HCN to give a cyanohydrin. These reactions indicate the presence of either an aldehydic —CH=O or a ketonic >C=O group, *but not both.*

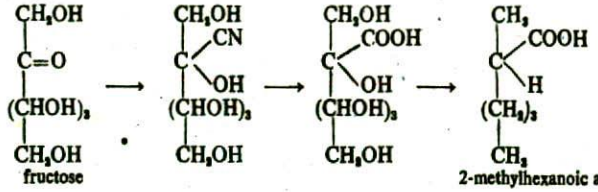
(6) Oxidation of fructose with concentrated nitric acid yields a mixture of glycollic acid and tartaric acid. Since this oxidation occurs with the rupture of the carbon chain, the carbonyl group must be present as a ketone group.



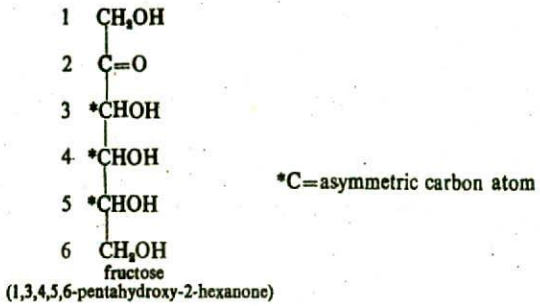
(7) Partial reduction of fructose with sodium amalgam and water produces a mixture of two epimeric alcohols, sorbitol and mannitol, because a new asymmetric centre has been created at C-2. This confirms the presence of a ketonic group.



(8) When fructose is treated with HCN, it forms an addition product which upon hydrolysis and subsequent reduction with hydriodic acid and red phosphorous gives 2-methylhexanoic acid. This indicates that the ketone group is adjacent to one of the terminal carbon atoms.



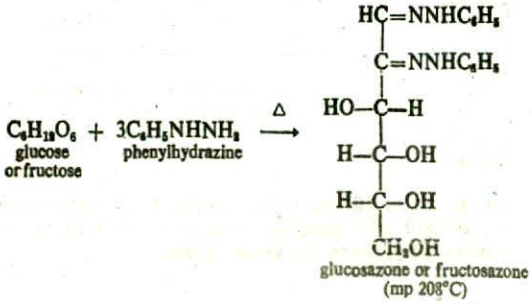
From the above evidences we conclude that fructose is a pentahydroxyhexanone (a ketohexose), and can be represented by the following gross structure.



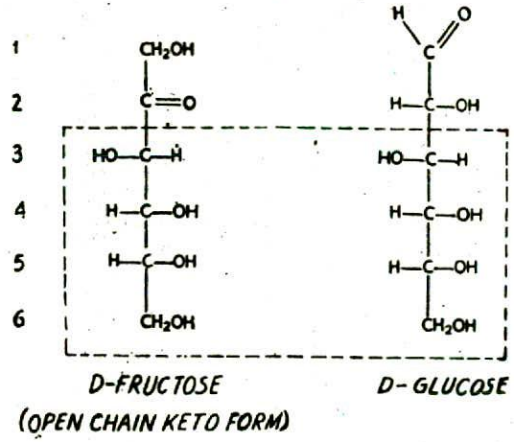
Configuration of D-Fructose

The above structure has *three* unlike asymmetric carbon atoms (marked by asterisks). This representation of fructose is incomplete, because we have yet to determine the configuration of these three asymmetric centres.

A key compound in this determination is D-glucose. It has been found that both fructose and glucose yield *identical osazones* when treated with excess phenylhydrazine.



Since osazone formation involves only the carbonyl and hydroxyl groups at C-1 and C-2, both fructose and glucose must have the same configuration at the remaining carbon atoms.

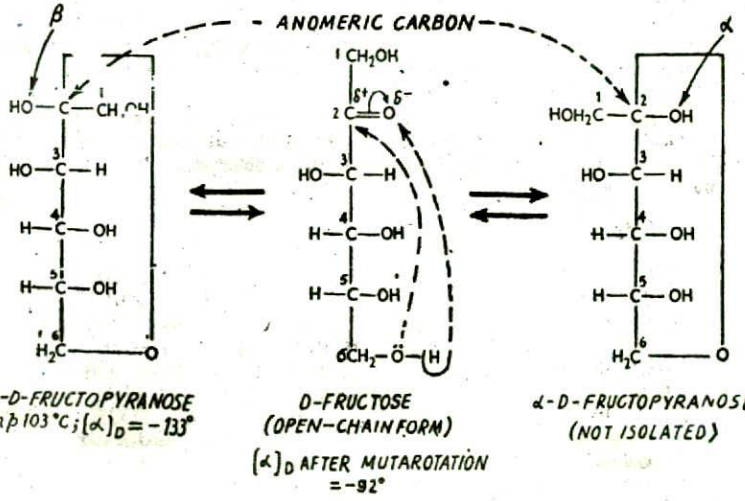


Cyclic Hemiketal Forms of D-Fructose

There are a number of observations that do not fit in well with the *open-chain* structure just deduced for fructose. Some of these are given below :

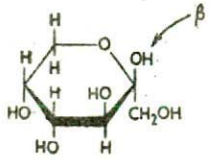
(1) Fructose does not show appreciable carbonyl absorption in its infrared spectrum.
(2) Fructose does not form an addition product with sodium bisulphite.
(3) Fructose pentaacetate does not react with hydroxylamine.
(4) Fructose does not react with Grignard reagents.
(5) Fructose shows mutarotation in aqueous solution.
(6) Treatment of fructose with methanol in the presence of dilute HCl yields a mixture of isomeric methyl fructosides.

To account for these facts, it has been proposed that in aqueous solution, fructose consists mainly of an equilibrium mixture of two anomeric 6-membered cyclic hemiketal forms as shown below.

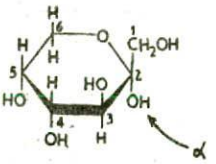


These two forms of fructose result from the *intramolecular interaction* between the carbonyl group at C-2 and the hydroxyl group at C-6. The isomer having the hydroxyl group to the *left* of the anomeric carbon (C-2) is designated β-D-fructopyranose and the one having the hydroxyl group on the *right* as α-D-fructopyranose.

Alternatively, these two cyclic forms of fructose can be better represented by the following Haworth projections.

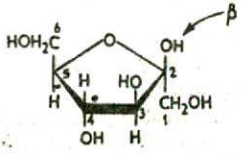


β-D-FRUCTOPYRANOSE

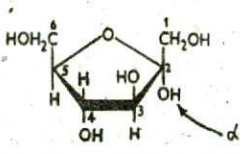


α-D-FRUCTOPYRANOSE

In the combined state, however (as for example in sucrose and inulin) fructose has been invariably found to possess 5-membered cyclic hemiketal structures.



β-D-FRUCTOFURANOSE



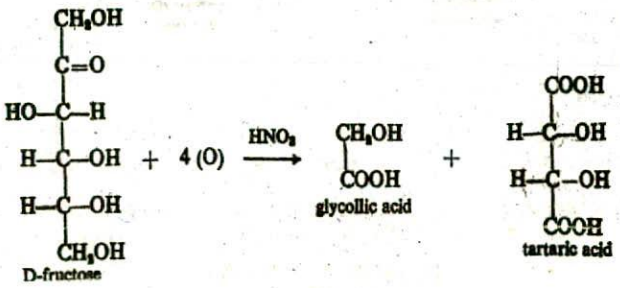
α-D-FRUCTOFURANOSE

Properties of Fructose

(Physical). Naturally occurring fructose (β-D-fructopyranose) is a colourless, crystalline solid, mp 102·4°C. It is very soluble in water, sparingly soluble in alcohol, and insoluble in ether. An aqueous solution of fructose is laevo-rotatory, and for this reason, it is sometimes called *laevulose.*

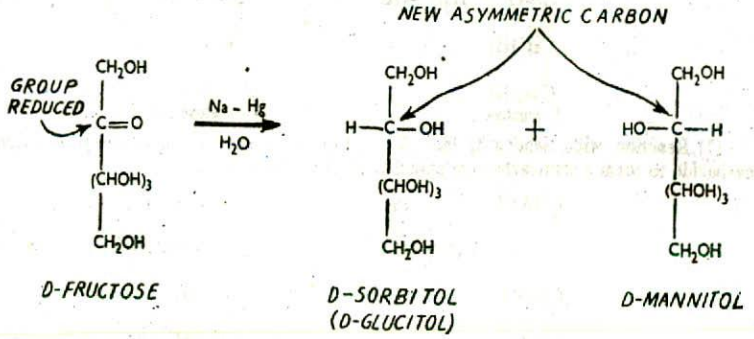
A. REACTIONS CHARACTERISTIC OF THE OPEN-CHAIN KETO FORM OF D-FRUCTOSE.

(1) Oxidation. D-Fructose does not react with mild oxidising agents such as bromine water. With stronger oxidising agents, such as concentrated nitric acid, the carbon chain is ruptured and a mixture of glycollic acid and tartaric acid is obtained.

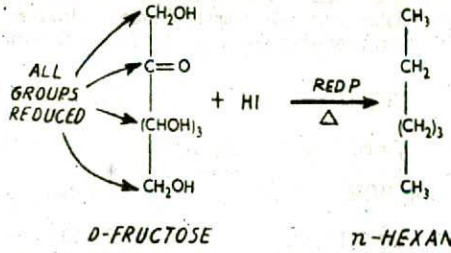


(2) **Action as a Reducing Agent.** D-fructose differs from simple ketones in being a strong reducing agent. It reduces Fehling's solution to cuprous oxide and ammoniacal silver oxide to silver. This is attributed to the fact that the secondary hydroxyl group adjacent to the carbonyl group (—OH at C-3) in fructose is readily oxidised by these mild oxidising agents.

(3) **Reduction.** Partial reduction of D-fructose with sodium amalgam and water produces a mixture of two epimeric polyhydroxy alcohols, D-sorbitol and D-mannitol. Two products are obtained due to the introduction of a new asymmetric centre at C-2.



Drastic reduction of fructose with hydriodic acid and red phosphorous yields *n*-hexane as the major product.



(4) **Reaction with Metallic Hydroxides.** D-Fructose in aqueous solution reacts with calcium hydroxide to form an *insoluble* compound called calcium fructosate, $C_6H_{11}O_6CaOH$. This compound is used in the separation of fructose from glucose. Barium hydroxide also reacts with fructose to yield a similar compound.

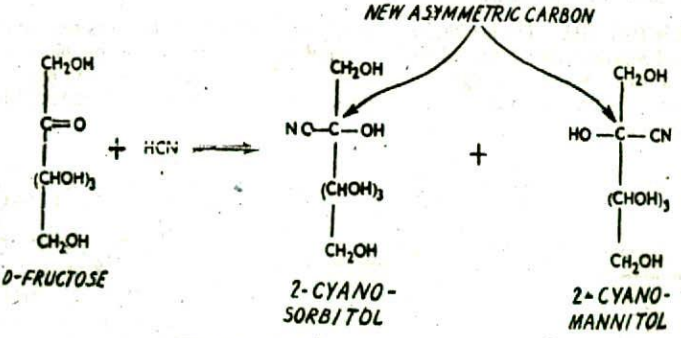
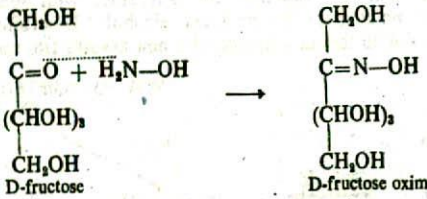


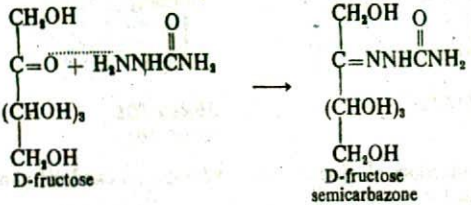
Fig. 32·1. Reaction of D-Fructose with HCN

(5) **Reaction with Hydrogen Cyanide** (*Cyanohydrogenation*). D-Fructose reacts with hydrogen cyanide to form two epimeric cyanohydrins, 2-cyanosorbitol and 2-cyanomannitol. Two products are obtained due to the introduction of a new asymmetric centre.

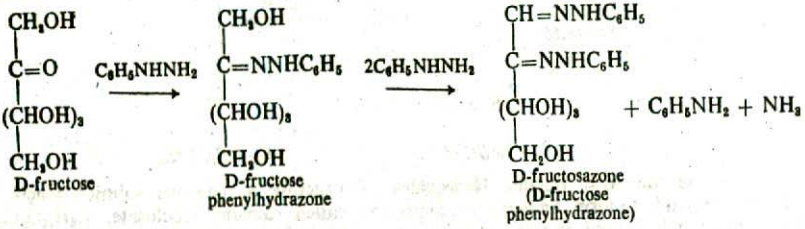
(6) **Reaction with Hydroxylamine.** D-Fructose undergoes a condensation reaction with hydroxylamine to form an oxime called D-fructose oxime.



(7) **Reaction with Semicarbazide.** D-fructose undergoes a condensation reaction with semicarbazide to form a semicarbazone called D-fructose semicarbazone.

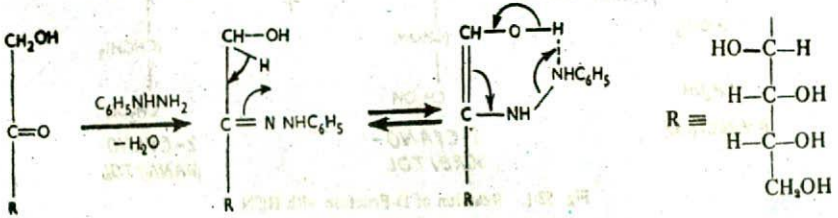


(8) **Reaction with Phenylhydrazine.** D-fructose undergoes a condensation reaction with phenylhydrazine to give the soluble D-fructose phenylhydrazone. However, in the presence of excess phenylhydrazine the phenylhydrazone reacts further to form D-fructosazone, aniline, and ammonia.

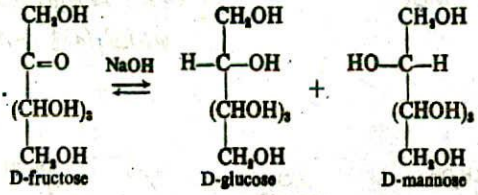


It should be noted that both D-glucose and D-fructose form identical osazones on treatment with excess phenylhydrazine.

MECHANISM. The mechanism of the above osazone formation has been proposed by Wegand and Semykin (1965). According to this mechanism the first D-fructose phenylhydrazone undergoes a rearrangement through a cyclic intermediate in which the primary hydroxyl group at C-1 becomes a carbonyl group and then condenses with another mole of phenylhydrazine to form the osazone.

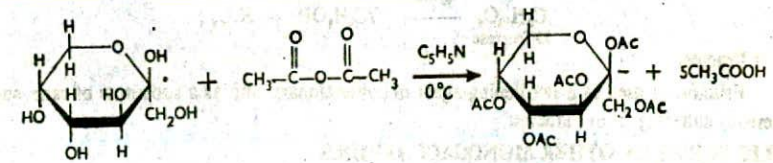


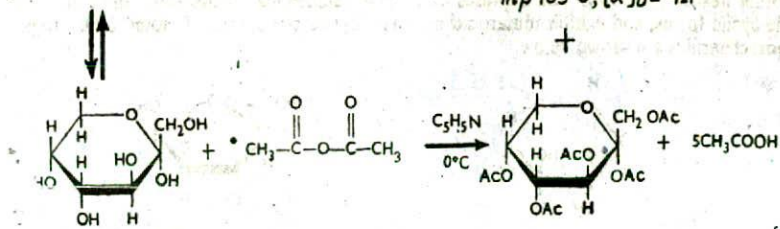
(9) **Action of Alkalis.** The action of strong alkalis on D-fructose leads to brown resinous products. However, in weakly alkaline solutions it undergoes *Lobry de Bruyn van Ekenstein rearrangement* to yield a mixture of D-glucose, D-mannose, and D-fructose. Under the same conditions D-glucose and D-mannose are converted into the same mixture



B. REACTIONS CHARACTERISTIC OF THE CYCLIC FORMS OF FRUCTOSE

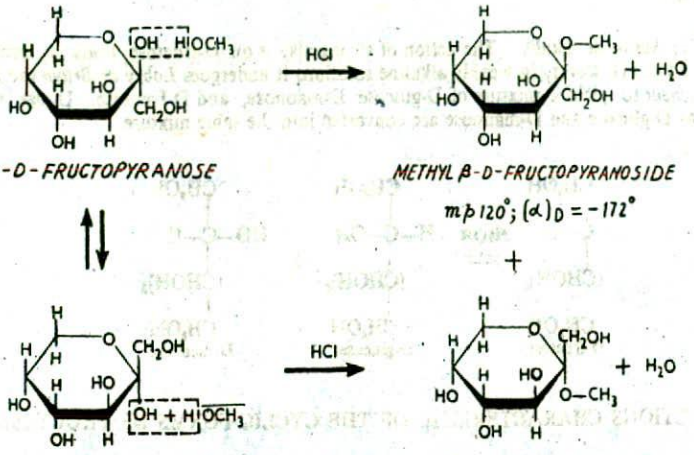
(10) **Reaction with Acetic Anhydride** (*Acetylation*). D-fructose reacts with acetic anhydride, either in pyridine solution at 0°C, or by heating in the presence of sodium acetate to form two anomeric pentaacetates. This is because in solution, both α- and β-forms are in equilibrium with each other and react separately to yield a different compound.





$$\text{Ac} \equiv -\overset{\overset{O}{\|}}{C}-CH_3$$

(11) **Reaction with Alcohols** (*Fructoside Formation*). D-fructose reacts with alcohols to form fructosides. Thus, when D-fructose is treated with methyl alcohol in the presence of HCl, it forms a mixture of methyl α-D-fructopyranoside and methyl β-D-fructopyranoside along with small amounts of the corresponding fructofuranosides.



β-D-FRUCTOPYRANOSE

METHYL β-D-FRUCTOPYRANOSIDE
m.p 120°; $(\alpha)_D = -172°$

+

α-D-FRUCTOPYRANOSE

METHYL α-D-FRUCTOPYRANOSIDE
m.p 102°C $(\alpha)_D = +90°$

(12) **Fermentation.** Like glucose, a solution of D-fructose is readily fermented by the enzyme, *zymase*, in yeast, to give mainly ethyl alcohol and carbon dioxide.

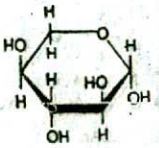
$$\underset{\text{D-fructose}}{C_6H_{12}O_6} \xrightarrow{\textit{zymase}} 2C_2H_5OH + 2CO_2\uparrow$$

Uses of Fructose

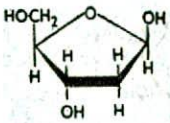
Fructose is used as a sweetening agent in confectionary and as a substitute of cane sugar for persons suffering from diabetes.

CYCLIC FORMS OF OTHER MONOSACCHARIDES

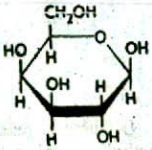
D-Glucose and D-fructose are not the only monosaccharides that exist in cyclic forms. All other hexoses, pentoses and heptoses undergo intramolecular cyclisation ; these also exist in stable cyclic forms, and exhibit mutarotation. The cyclic structures of some other important monosaccharides are shown below.



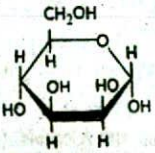
α-L-ARABINOSE
(α-L-ARABINOPYRANOSE)



2-DEOXY-β-D-RIBOSE
(2-DEOXY-β-D-RIBOFURANOSE)



β-D-GALACTOSE
(β-D-GALACTOPYRANOSE)



α-D-MANNOSE
(α-D-MANNOPYRANOSE)

DISACCHARIDES

When a hydroxyl group of one monosaccharide molecule acts as the alcohol to form a glycosidic linkage with the hemiacetal group of a second monosaccharide, the resulting glycoside is called a disaccharide. They are therefore acetals, formed from two monosaccharides by the elimination of one molecule of water. Conversely, hydrolysis of a disaccharide either by water in the presence of an acid or by enzymes yields two monosaccharides.

$$\underset{\text{monosaccharide}}{C_6H_{12}O_6} + \underset{\text{monosaccharide}}{C_6H_{12}O_6} \rightleftharpoons \underset{\text{disaccharide}}{C_{12}H_{22}O_{11}} + H_2O$$

Among the most common disaccharides are sucrose, lactose, maltose, and cellobiose. Of these, sucrose is the most important.

SUCROSE (*Cane Sugar or Beet Sugar*), $C_{12}H_{22}O_{11}$

Occurrence. Sucrose is the ordinary table sugar which we eat every day. It occurs in sugar cane (16 to 20 per cent), sugar beets (10 to 15 per cent), pineapples (10 to 12 per cent), maple sap (2 to 4 per cent), apricot, banana, mango, almonds, coffee, and honey.

Manufacture (Sugar Industry)

The two main commercial sources of sugar (sucrose) are sugar cane and sugar beet. Sugar cane grows in tropical countries, while sugar beet is produced in temperate climates. India is the biggest producer of sugar cane among all the Asian countries. Therefore, sugar cane is the chief raw material for sugar manufacture in India.

Ripe sugar cane is reaped from the field by hand-cutting or by modern mechanical harvesters. The leaves and tops are removed from cane which is then delivered at the factory within 42 hours from the time of cutting in the field. The stale cane deteriorates and sucrose content falls due to inversion.

The conventional method for the recovery of sugar from cane consists of the following steps :

(1) *Extraction of the Juice* (Crushing or Milling) ;
(2) *Purification of the Juice* (Clarification) ;
(3) *Concentration and Crystallisation* ; and
(4) *Separation and Drying of the Crystals.*

1. **Extraction of the Juice.** In the conventional method, the cane prepared in the manner described above is passed through a series of three-roller mills, numbering from four to seven. (Fig. 32·3).

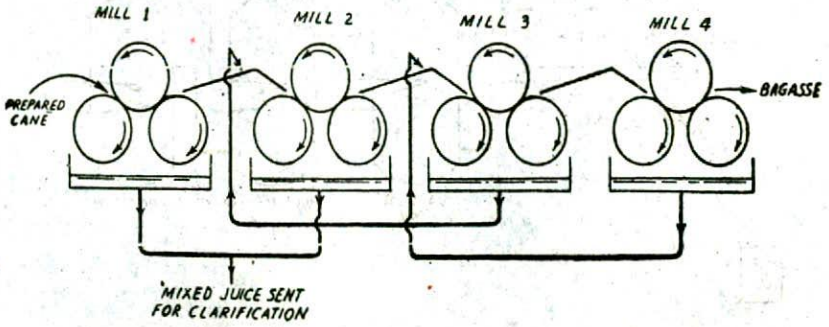


Fig. 32·2. Tandem or train of four three-roller mills used in traditional method for juice extraction. There are four three-roller mills connected each with metal plates over which the crushed, cane 'blanket' moves. Under each mill is placed a tray for collecting the expressed juice. Water is sprayed on to the exhausted fibre leaving the Mill 3. The fourth mill expresses as much as possible of the remaining juice mixed with water. This is sprayed on the partly exhausted fibre discharged from the Mill 2, while juice from Mill 3 is delivered immediately after the Mill 1.

The juice is thus expressed from the cane which travels as a continuous 'blanket' of fibrous mass from one mill to the other. Farther along the mill train, or trandem as it is called, water is sprayed onto the partly exhausted fibre (*imbibition*). The imbitition and circulation of

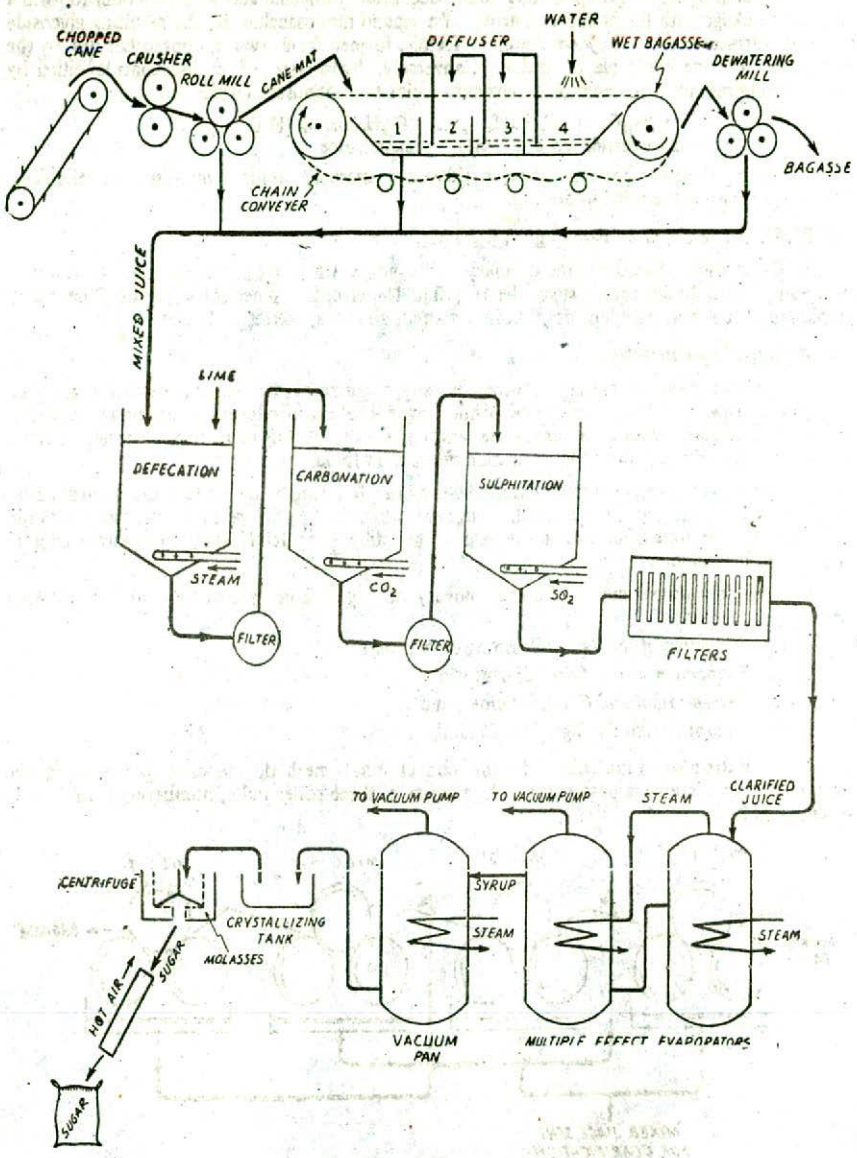


Fig. 32·4. Manufacture of Sugar

extracted juice in the trandem is done so as to ensure maximum recovery of sucrose from the canes. The cellulosic material discharged from the last mill is called *bagasse*. It is used as fuel under boilers and also in the manufacture of the insulating material known as *Celotex*.

The Modern Diffusion Process of Juice Extraction. In this process the crusher and the first three-roller mill used in the conventional method are retained. Therefore, the cane mat coming from the roller mill is passed into a long rectangular tank fitted with a chain conveyer below which there are a number of compartments. The sucrose is extracted from the partially exhausted cane mat as it passes on the conveyer by washing with cold or hot water and dilute juice by a countercurrent method. Water is sprayed onto the mat near the exit when almost all sucrose has been removed from it. The dilute juice from each compartment is used to spray on the preceding portion until the richest juice is delivered onto the mat near the entrance of the diffuser. The juice from compartment 1 and the mill is then pumped to the 'clarification unit'.

This method is called 'Diffusion Process' as it is believed that washing of the cane mat with hot water and juice extracts sucrose from even the unruptured cells by true diffusion. The sucrose extraction by this method is on the average 98 per cent compared to 90—94 per cent by the conventional milling.

2. **Purification of the Juice.** The mixed juice, or raw juice as it is called, from step (1) contains 15 to 20 per cent sucrose and much impurity. The impurity commonly includes organic acid (oxalic acid, citric acid and amino acids), mineral phosphates, proteins, and colloidal colouring matter. The raw juice is slightly acidic in reaction and is *at once* processed for purification or clarification by the following operations. Otherwise, the presence of acids causes further loss of sucrose by inversion.

(*i*) **Defecation.** The raw juice is transferred into tanks where it is heated by steam and treated with 2 to 3 per cent lime. This operation called *defecation* removes the organic acids and phosphates as insoluble calcium salts. The proteins and the colloidal colouring matter are also thrown out of the solution as thick scum appearing on the surface. The precipitated calcium salts and the scum are removed by filtration through canvas. For greater efficiency, rotary vacuum filters equipped with perforated metal screen cloth are used in modern practice.

(*ii*) **Carbonation.** The juice after *defecation* contains excess of lime and soluble calcium sucrosate. Carbon dioxide is then passed through it. This process known as *carbonation* removes the excess of lime and decomposes calcium sucrosate to give back sugar and calcium carbonate. Calcium carbonate is removed by filtration.

$$\underset{\text{calcium sucrosate}}{C_{12}H_{21}O_{11}CaOH} + CO_2 \longrightarrow \underset{\text{sucrose}}{C_{12}H_{22}O_{11}} + CaCO_3\downarrow$$

(*iii*) **Sulphitation.** The juice after *carbonation* is treated with sulphur dioxide. This operation known as *sulphitation* completes the neutralisation of lime and the decomposition of calcium sucrosate. In addition the colour of the juice is bleached. The clarified juice is filtered to remove precipitated calcium sulphite.

3. **Concentration and Crystallisation of the Juice.** The clarified juice is then concentrated by boiling under reduced pressure in *multiple effect evaporators*. In these, the steam produced in the first evaporator is used to boil the juice in the second kept at a lower pressure, the steam produced in the second being used to boil the juice in the third maintained at a still lower pressure, and so on.

The concentrated juice is finally passed to the *vacuum pans* where further evaporation reduces the water content from 6 to 8 per cent. Here partial separation of sugar crystals takes place. The contents of the pan, known as *massecuite* are discharged into a tank where crystals grow in size and form a thick *crop*.

4. **Separation and Drying of Crystals.** The *massecuite* is then charged into centrifugal machines by means of which sugar crystals are separated from the mother liquor. The crystals are here sprinkled with a little water to wash away any impurities sticking to their surface. The crystals are finally dried by dropping through a revolving cylinder where they meet a current of hot air coming up. The sugar thus obtained is about 96 per cent pure. For further purification it may be dissolved in hot water and recrystallised.

The mother liquor obtained after the removal of crystals is called *molasses*. It still contains large amounts of sugar and may be concentrated to get a fresh crop of crystals.

Molasses, which also contains glucose and fructose, is fermented to obtain alcohol. More recently, glycerol and citric acid have been prepared from molasses.

Sugar Industry in India

The sugar industry is one of the major and oldest industries of India. With the improvement in the quality of sugar cane and the setting up of new factories in the country the government has succeeded in stepping up the annual production of sugar to almost double of what it was five years back. In 1972-3 there were 212 factories and the total production was 43 lac tonnes. Further steps are being taken to increase the production to 60 lac tonnes by 1980. The biggest sugar producing state is Uttar Pradesh and then comes Maharashtra in order of annual production.

Sugar from Beets

The sugar beet is a temperate zone plant. It is grown largely in United States of America, China, Spain and Iran. Today sugar from beets accounts for about 41 per cent of the world's supply.

After plants have reached maturity, they are harvested by machines which remove the leaves, lift the root from the ground and conveyed to the nearest sugar factory. There the roots are washed with water so as to remove trash and earth. The various stages in the recovery of sugar from beets are :

(*i*) *Extraction of sugar solution by Diffusion*;
(*ii*) *Purification* ;
(*iii*) *Concentration and Crystallisation* ; *and*
(*iv*) *Separation and Drying of Crystals.*

The stages from (*ii*) to (*iv*) are the same as described under sugar manufacture from canes. Therefore, here we will discuss only stage (*i*).

Extraction of Sugar Solution. The washed beets are cut by specially shaped knives to give V-shaped slices, called *coseltes*. The crude sugar solution is extracted from coseltes by a percolating process in a series of large tanks known as *Diffusers*. Hot water is slowly pumped through these tanks containing *coseltes* and the extraction is conducted on countercurrent principle (Fig 32·5). Sugar is removed from the beet by a two fold process ; (*i*) Leaching ; and (*ii*) *Dialysis*. Leaching means simply washing out sugar with water. By dialysis we under stand a process by which the sugar passes through the cell wall membrane, leaving the larger colloidal material behind.

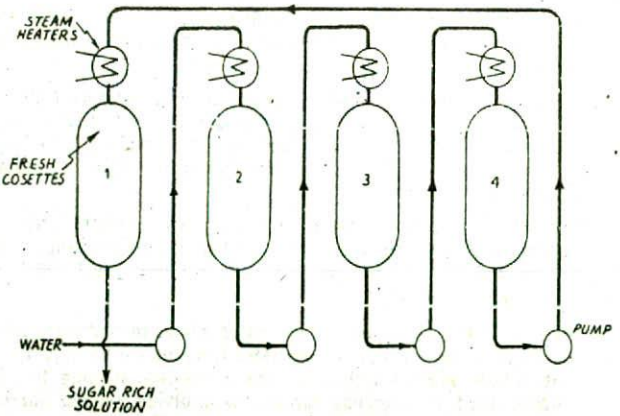


Fig. 32·5. Extraction of sugar solution from beets by circulation of hot water through a series of diffusers containing *coseltes*. The fresh water contacts the most depleted coseltes first (tank 2) and contacts the fresh coseltes (tank 1) last. Actually, the diffusers are emptied and recharged turn by turn in numerical order (1, 2, etc.); the sequence of entry of water and circulation of sugar solution through the diffusers is changed accordingly.

Structure of Sucrose

The structure of sucrose has been derived from a consideration of facts and conclusions such as the following.

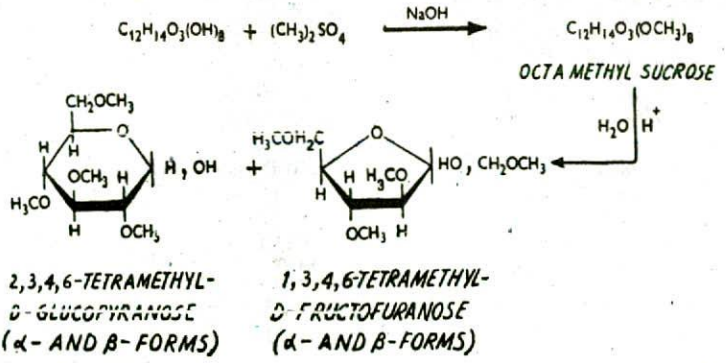
1. Elemental analysis and molecular weight determination show that the molecular formula of sucrose is $C_{12}H_{22}O_{11}$.

2. Sucrose reacts with acetic anhydride in the presence of sodium acetate to form sucrose octaacetate. This reaction indicates the presence of *eight* hydroxyl groups in a sucrose molecule. Since sucrose is a stable compound, the eight hydroxyl groups must be present on separate carbon atoms.

3. Hydrolysis of sucrose with dilute acids yields an equimolecular mixture of D-glucose and D-fructose. This indicates that the sucrose molecule is made up of one unit of each of these monosaccharides.

4. Sucrose does not reduce Tollen's reagent or Fehling's solution ; does not form an osazone (except on prolonged boiling, when glucosazone is formed due to hydrolysis of sucrose) ; does not form methyl glycosides ; and does not undergo mutarotation. All these observations indicate that the cyclic forms of glucose and fructose are joined together through glycosidic linkage at points where the carbonyl groups would otherwise become available, that is, C-1 in glucose and C-2 in fructose.

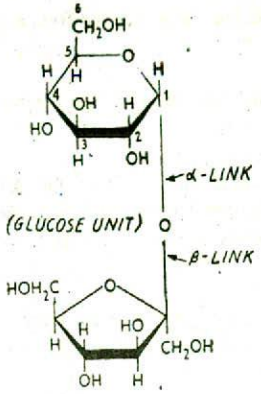
5. Sucrose reacts with dimethyl sulphate in an alkaline solution to form octamethyl-sucrose, which on hydrolysis yields a mixture of 2, 3, 4, 6-tetramethyl-D-glucopyranose and 1, 3, 4, 6-tetramethyl-D-fructofuranose. The formation of these compounds indicates that the glucose unit in sucrose has a pyranose form (6-membered ring), and the fructose unit the furanose form (5-membered ring).



6. Sucrose is hydrolysed by *maltase*, an enzyme that hydrolyses only α-glycosides. It is also hydrolysed by *invertase*, an enzyme that hydrolyses β- but not α-fructofuranosides. These observations indicate that sucrose is both an α-glucoside and a β-fructoside.

The above evidence clearly indicates that sucrose has the following structure :

It should be noted that the fructose unit in sucrose has the furanose form, but when sucrose is hydrolysed, it is the pyranose form of fructose which is obtained.



SUCROSE

Properties of Sucrose

(*Physical*). Sucrose is a colourless, odourless, crystalline solid, mp 184–5°C. It is very soluble in water, but only slightly soluble in alcohol. An aqueous solution of sucrose is dextrorotatory and does not exhibit mutarotation.

(*Chemical*). Sucrose is a non-reducing sugar. It does not react with Tollen's reagent, Fehling's solution, hydrogen cyanide, hydroxylamine or phenylhydrazine. However, it gives the following reactions.

(1) **Effect of Heat.** When sucrose is heated to 210°C, it forms a brown mass known as *caramel*, which because of its colour and characteristic flavour, is used as colouring and flavouring material in foods and candies. At higher temperatures, sucrose chars to almost pure carbon and gives vapour of carbon dioxide, carbon monoxide, methane, ethylene, acetylene, acetone, formic acid, acetic acid, ethanal, and acrolein.

(2) **Oxidation.** Oxidation of sucrose with concentrated nitric acid yields a mixture of oxalic acid, tartaric acid, and D-glucaric acid.

(3) **Reduction** (*Hydrogenation*). Reduction of sucrose with sodium borohydride or sodium amalgam in water under controlled conditions yields a mixture of D-sorbitol and D-mannitol.

(4) **Hydrolysis** (*Invert Sugar or Invertose*). Hydrolysis of sucrose with hot dilute acid yields D-glucose and D-fructose.

$$\underset{\substack{\text{sucrose}\\ [\alpha]_D=+66{\cdot}5^\circ}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow{H^+} \underbrace{\underset{\substack{\text{D-glucose}\\ [\alpha]_D=+53^\circ}}{C_6H_{12}O_6} + \underset{\substack{\text{D-fructose}\\ [\alpha]_D=-92^\circ}}{C_6H_{12}O_6}}_{\substack{\text{Invert Sugar}\\ [\alpha]_D=(+53^\circ)-(-92^\circ)=-39^\circ}}$$

Sucrose is dextrorotatory, its specific rotation being $+66{\cdot}5^\circ$, D-glucose is also dextrorotatory, $[\alpha]_D=+53^\circ$, but D-fructose has a large negative rotation, $[\alpha]_D=-92^\circ$. Since D-fructose has a greater specific rotation than D-glucose, the resulting mixture is laevorotatory. Because of this, the hydrolysis of sucrose is known as the **Inversion of Sucrose**, and the equimolecular mixture of glucose and fructose is known as **Invert sugar** or **Invertose**. The inversion (*i.e.* hydrolysis) of sucrose can also be brought about by the enzyme *invertase*, which is found in yeast.

(5) **Reaction with Metallic Hydroxides** (*Formation of Sucrosates*). Sucrose in aqueous solution reacts with hydroxides of calcium, strontium, and barium to produce insoluble compounds called sucrosates. These compounds are readily decomposed when carbon dioxide is passed into their aqueous suspensions. The strontium compound is used for isolating pure sucrose from non-crystallisable molasses.

$$\underset{\text{sucrose in molasses}}{C_{12}H_{22}O_{11}} + Sr(OH)_2 \xrightarrow{-H_2O} \underset{\text{strontium sucrosate}}{C_{12}H_{21}O_{11}SrOH\downarrow} \xrightarrow{CO_2} \underset{\text{pure sucrose}}{C_{12}H_{22}O_{11}} + SrCO_3\downarrow$$

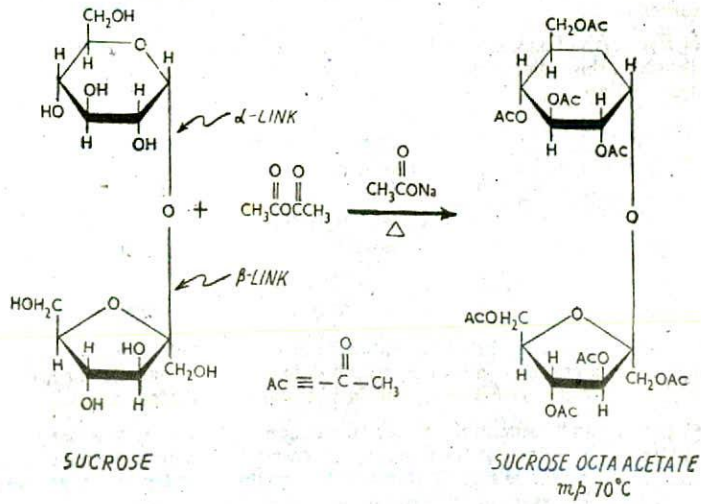


Fig. 32·6. Acetylation of Sucrose.

(6) **Reaction with Acetic Anhydride** (*Acetylation*). Sucrose reacts with acetic anhydride in the presence of sodium acetate to form sucrose octaacetate (see Fig. 32·6).

(7) **Fermentation**. An aqueous solution of sucrose is readily fermented by yeast to give ethyl alcohol and carbon dioxide. The enzyme *invertase* present in yeast first converts sucrose into glucose and fructose. These sugars are then decomposed by the enzyme *zymase* (also present in yeast) to give ethyl alcohol and carbon dioxide.

$$\underset{\text{sucrose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow{\textit{invertase}} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6}$$

$$\underset{\text{glucose or fructose}}{C_6H_{12}O_6} \xrightarrow{\textit{zymase}} 2C_2H_5OH + 2CO_2$$
ethyl alcohol

Uses of Sucrose

Sucrose is used as a food. It is an ingredient of jellies, jams, canned fruits, preserves, confections, condensed milk and other foods. It is used in the manufacture of sucrose octaacetate which is employed to denature alcohol to render paper transparent, to stiffen textiles and as an ingredient of nonaqueous adhesives.

LACTOSE (*Milk Sugar*), $C_{12}H_{22}O_{11}$

Occurrence. Lactose occurs in the milk of all animals. For example, cow's milk contains 4 to 6 per cent and human milk contains 5 to 8 per cent of this sugar. Unlike most other carbohydrates, it is found only in animals and not in plants.

Preparation. Lactose is obtained commercially from cow's milk after the removal of the emulsified fat and casein. The remaining *whey* is concentrated in vacuum pans, and the raw lactose which separates is eventually decolourised with animal charcoal

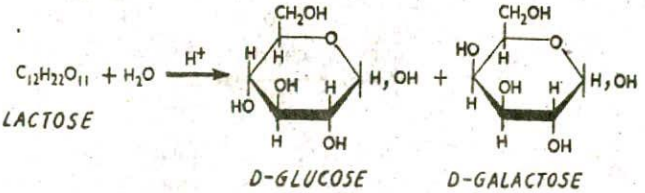
Structure of Lactose

The tructure of lactose has been derived as follows :

(1) Elemental analysis and molecular weight determination show that the molecular formula of lactose is $C_{12}H_{22}O_{11}$.

(2) Lactose reacts with acetic anhydride in the presence of sodium acetate to form lactose octaacetate. This reaction indicates the presence of *eight* hydroxyl groups in a lactose molecule. Since lactose is a stable compound, the eight hydroxyl groups must be present on separate carbon atoms.

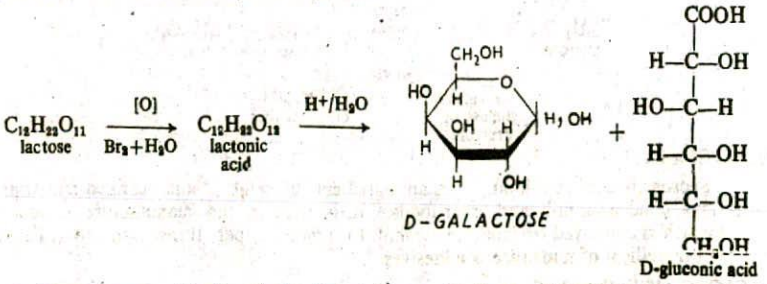
(3) Hydrolysis of lactose with dilute acid yields an equimolecular mixture of D-glucose and D-galactose. This indicates that the lactose molecule is made up of one unit of each of these monosaccharides.



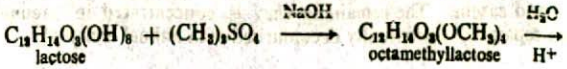
(4) Lactose reduces Tollen's reagent and Fehling's solution, reacts with hydrogen cyanide, and forms an osazone. All these reactions indicate that one free hemiacetal group must be present and this is in equilibrium with some of the free aldehyde form.

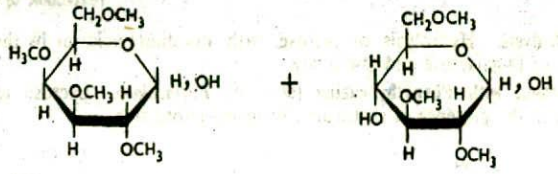
(5) Lactose can be isolated in two crystalline forms depending on how one recrystallises ordinary lactose. If it is recrystallised from a concentrated aqueous solution at ordinary temperatures, the α-form of the sugar is obtained. Its melting point is 223°C and the specific rotation is +90°. However, if another portion of ordinary lactose is recrystallised from water at temperatures higher than 95°C, the β-form is obtained. Its melting point is 252°C and the specific rotation is +35°. Both α- and the β-forms exhibit mutarotation until an equilibrium value of +55° is reached. This further confirms the presence of a free hemiactal group in lactose.

(6) Oxidation of lactose with bromine water gives lactonic acid, which on hydrolysis yields a mixture of D-galactose and D-gluconic acid. This indicates that it is the glucose unit that contains the free hemiacetal-aldehyde group.



(7) Lactose reacts with dimethyl sulphate in an alkaline solution to form octamethyl-lactose, which on hydrolysis yields a mixture of 2, 3, 4, 6-tetramethyl-D-galactose and 2, 3, 6-trimethyl-D-glucose. The formation of these compounds indicates that both units exist in 6-membered pyranose forms, and the glycosidic linkage involves the hydroxyl group at C-4 in glucose.

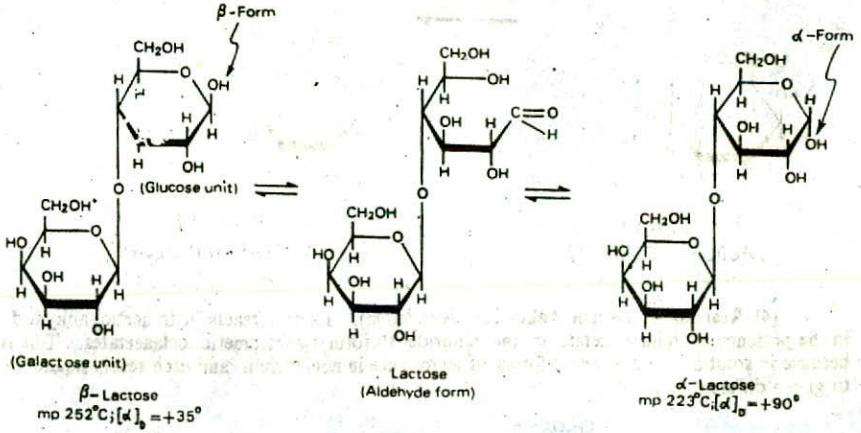




2,3,4,6-TETRAMETHYL-D-GALACTOSE (α- AND β-FORMS)

2,3,6-TRIMETHYL-D-GLUCOSE (α- AND β- FORMS)

(8) Lactose is also hydrolysed by *emulsin*, an enzyme that hydrolyses β-glycosides rather than α-glycosides. This indicates that lactose is a β-galactoside.

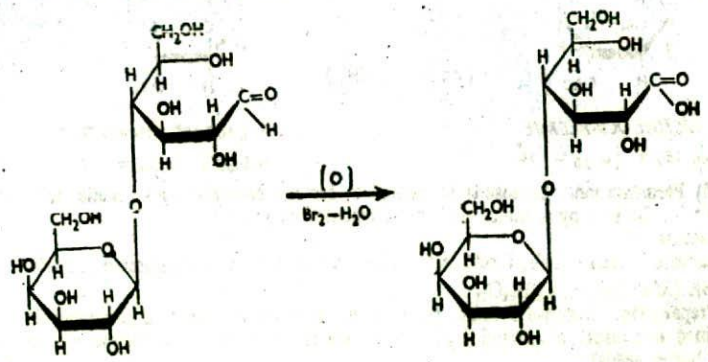


Properties of Lactose

(*Physical*). Lactose (α-form) is a colourless, odourless, crystalline solid, mp 223°C (with decomposition). It is soluble in water, but insoluble in alcohol and ether. An aqueous solution of lactose is dextrorotatory and exhibits mutarotation.

(*Chemical*). Lactose is a reducing sugar, that is, it reduces Fehling's solution and Tollen's reagent. Its reactivity is mainly due to the presence of a free hemiacetal-aldehyde group in the glucose unit of its molecule. Some of the more important reactions of lactose are given below.

(1) **Oxidation.** Oxidation of lactose with bromine water yields a monocarboxylic acid called lactonic acid or lactobionic acid.

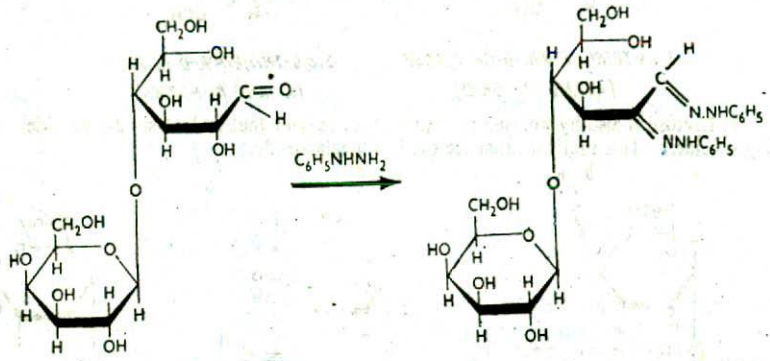


LACTOSE (ALDEHYDE FORM)

LACTONIC ACID

(2) **Hydrolysis.** Hydrolysis of lactose with hot dilute acid or by the enzyme *emulsin*, yields a mixture of D-galactose and D-glucose.

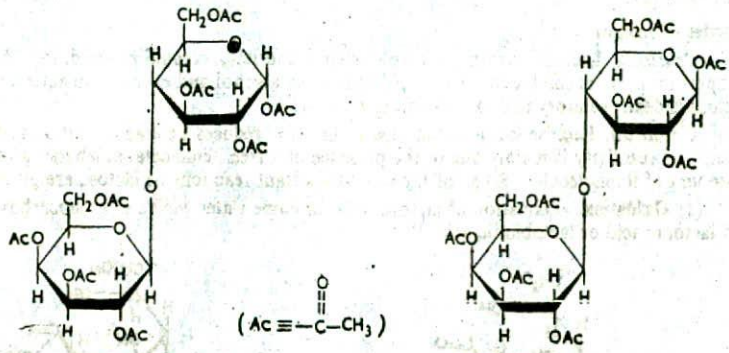
(3) **Reaction with Phenylhydrazine** (*Osazone Formation*). Lactose reacts with excess phenylhydrazine in the presence of acetic acid to form lactosazone.



LACTOSE
(ALDEHYDE FORM)

LACTOSAZONE
(LACTOSE PHENYLOSAZONE)
m.p 200°C

(4) **Reaction with Acetic Anhydride** (*Acetylation*). Lactose reacts with acetic anhydride in the presence of sodium acetate or zinc chloride to form two isomeric octaacetates. This is because in solution, both α- and β-forms of lactose are in equilibrium and each reacts separately to give a different compound.



α-LACTOSE OCTAACETATE
m.p 152°C; $[\alpha]_D = +54°$

β-LACTOSE OCTAACETATE
m.p 90°C; $[\alpha]_D = -4°$

(5) **Fermentation.** Lactose is fermented by certain bacteria to give lactic acid which is responsible for the souring of milk. It is not fermented by yeast.

Uses of Lactose

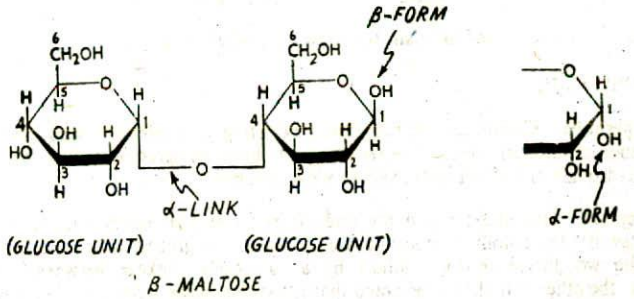
Lactose is used in baby foods and in pharmacy as a base for compressed tablets.

MALTOSE (*Malt Sugar*), $C_{12}H_{22}O_{11}$

Preparation. Maltose does not occur in the free state in nature to an appreciable extent. It is obtained as a result of partial hydrolysis of starch by *diastase*, an enzyme present in malt (sprouted barley seeds).

$$\underset{\text{starch}}{(C_6H_{10}O_5)_n} + H_2O \xrightarrow{\textit{diastase}} \underset{\text{maltose}}{C_{12}H_{22}O_{11}}$$

Structure. Hydrolysis of maltose with dilute acids yields only D-glucose. This indicates that the maltose molecule is made up of two glucose units. Other structural studies, similar to those described under lactose, indicate that the two glucose units are joined by an α-glycosidic linkage between C-1 of one unit and C-4 of the other.



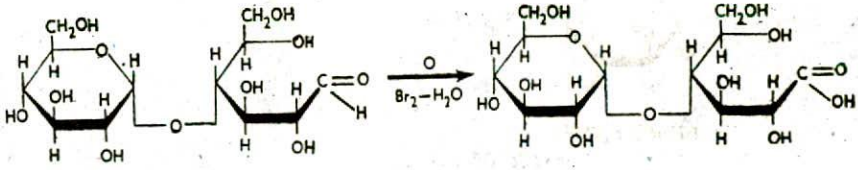
β-MALTOSE

Like lactose, maltose exists in α- and β-forms, each of which exhibits mutarotation. The values of specific rotation are: + 168° for α-maltose, +118° for β-maltose, and +136° for the equilibrium mixture.

Properties (*Physical*). Maltose (β-form) is a colourless, odourless, crystalline solid, mp 160°–5°C. It is soluble in water, but insoluble in alcohol or ether. An aqueous solution of maltose is dextrorotatory and exhibits mutarotation.

(*Chemical*). Maltose is a reducing sugar. Like lactose, its reactivity is also due mainly to the presence of a free hemiacetal group in one of the glucose units of its molecule.

(1) **Oxidation.** Oxidation of maltose with bromine water yields a monocarboxylic acid called maltonic acid or maltobionic acid.



MALTOSE (ALDEHYDE FORM) MALTONIC ACID

(2) **Hydrolysis.** Hydrolysis of maltose with hot dilute acids or by the enzyme *maltase* yields only D-glucose. The fact that it is hydrolysed by *maltase* (specific for α-glycosides) and not by *emulsin* (specific for β-glycosides) is an evidence for its α-glycosidic structure.

(3) **Reaction with Phenylhydrazine** (*Osazone Formation*). Maltose reacts with excess phenylhydrazine in the presence of acetic acid to form maltosazone, mp 206°C.

(4) **Reaction with Acetic anhydride** (*Acetylation*). Maltose reacts with acetic anhydride in the presence of zinc chloride or sodium acetate to give α-maltose octaacetate (mp 125°C; $[\alpha]_D$ = +123°) and β-maltose octaacetate (mp 160°C; $[\alpha]_D$ = +63°).

(5) **Fermentation.** An aqueous solution of maltose is fermented by yeast to give ethyl alcohol and carbon dioxide. The enzyme *maltase* present in yeast first converts maltose into glucose. This sugar is then decomposed by the enzyme *zymase* (also present in yeast) to give alcohol and carbon dioxide.

$$\underset{\text{maltose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow{\textit{maltase}} \underset{\text{glucose}}{C_6H_{12}O_6}$$

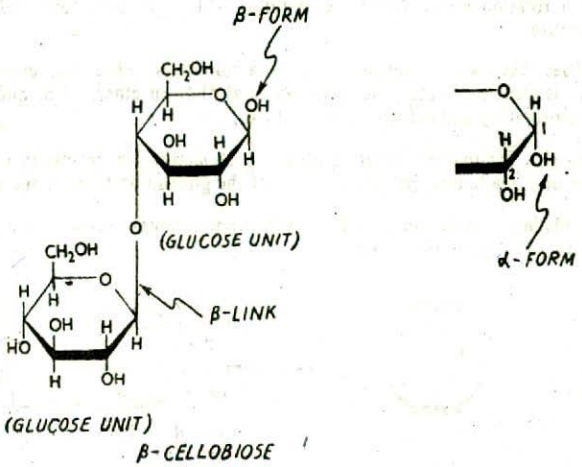
$$\underset{\text{glucose}}{C_6H_{12}O_6} \xrightarrow{\textit{zymase}} 2\underset{\text{ethyl alcohol}}{C_2H_5OH} + 2CO_2$$

Uses. Maltose is used in infant foods and in malted milk.

CELLOBIOSE, $C_{12}H_{22}O_{11}$

Preparation. Cellobiose is obtained by acetylating pure cellulose with acetic anhydride in the presence of sulphuric acid. The resulting cellobiose octaacetate is then hydrolysed with potassium hydroxide or sodium methoxide to yield cellobiose.

Structure. Hydrolysis with dilute acids or by the enzyme *emulsin* yields only D-glucose. This indicates that the cellobiose molecule is made up of two glucose units. Further experiments show that the two glucose units are joined by a β-glycosidic linkage between C-1 of one unit and C-4 of the other. It should be noted that it has the same structure as maltose, except for the type of the glycosidic linkage.



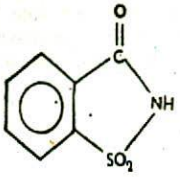
It exists in α- and β-forms, each of which exhibits mutarotation. The values of specific rotation are: $+72°$ for α-cellobiose, $+16°$ for β-cellulose and $+35°$ for the equilibrium mixture.

Properties (*Physical*). Cellobiose (β-form) is a colourless, crystalline solid, mp 225°C. It is soluble in water, but insoluble in ether. An aqueous solution of cellobiose is dextrorotatory and exhibits mutarotation.

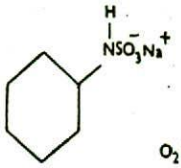
(*Chemical*). Like maltose, cellobiose is also a reducing sugar. It undergoes all the reactions of maltose.

SWEETNESS

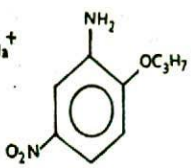
A sweet taste is a physiological property commonly associated with mono- and disaccharides. However, it is not a specific property of carbohydrates. Several organic compounds have been synthesised that are much sweeter than any known carbohydrate. Three of these have actually been sold commercially as sweetening agents. They are saccharin (*o*-sulphobenzimide), cyclamate (*N*-cyclohexylsulphamate), and nectarin (2-amino-4-nitropropoxybenzene).



SACCHARIN



CYCLAMATE



NECTARIN

The sweetness of a substance is tested by determining the minimum concentration of the substance in water which can be tasted. A solution of 5 g in 100 ml of water is prepared and tasted. This is then diluted by one-half, and tasted again. This process is continued until sweetness in the solution can no longer be detected, and the average concentration at which sweetness can be detected by a number of individuals is considered as a measure of sweetness. The adjoining table (Table 32·2 indicates the relative sweetness per gram of several compounds, compared to *sucrose* (table sugar) as standard.

Notice that the synthetic compounds are far superior sweetening agents, so that one teaspoon of nectarin is equivalent to five hundred teaspoons of sucrose. These compounds have no calorific value (food value) and therefore they are useful for those persons (for example, *diabetics*) who must reduce their carbohydrate intake. Unfortunately, these compounds are somewhat toxic and must be used with caution. The toxicity is approximately in the order of sweetness.

Table 32.2. Relative sweetness of some of the carbohydrates and other compounds.

Nectarin	50,000
Saccharin	36.000
Cyclamate	7,100
Fructose	173
Invertose (*Invert Sugar*)	123
Sucrose (*Table Sugar*)	100
Glucose	74
Xylose	40
Galactose	32
Maltose	32
Lactose	16

POLYSACCHARIDES

Polysaccharides are natural polymers in which hundreds or even thousands of monosaccharide units are joined together by glycosidic linkages. Among the most common polysaccharides are starch, dextrins, glycogen, inulin and cellulose. Of these, starch and cellulose are the most important.

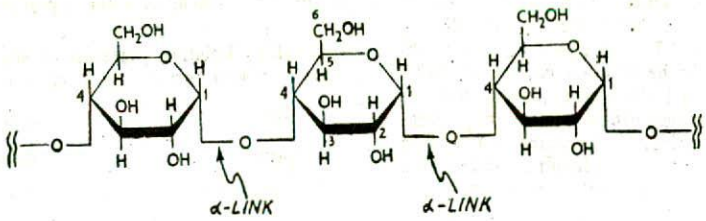
STARCH (*Amylum*), $(C_6H_{10}O_5)_n$

Occurrence. Starch is the most important source of carbohydrates in the human diet. It is found in most plants, particularly in the seeds, where it serves as the nutritional reserve carbohydrate. The chief commercial sources of starch are wheat, rice, maize, potatoes, barley, and arrowroot. Starch occurs in the form of granules, which vary in size and shape depending upon their plant source.

Manufacture. Commercially starch is extracted from wheat, maize, and rice. The grains are soaked in water to soften the crust. These are then crushed so as to break the cell walls containing starch. The pulp thus obtained is carried by a stream of water on to a fine sieve. The starch passes down in the form of a milky suspension, leaving behind the cell tissues which are used as fodder. The liquid containing starch is allowed to settle and starch separated by decantation. It is finally dried in the air or by gentle heating in ovens.

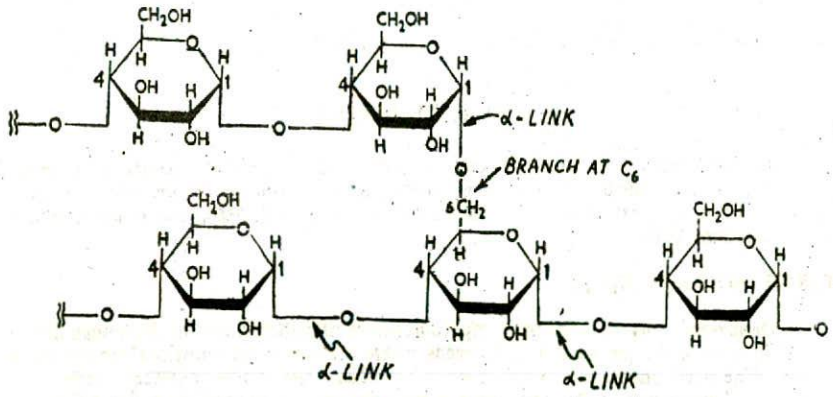
Structure. Starch is not a pure compound. It is a mixture of two polysaccharides, *amylose* and *amylopectin*, which can be separated from one another. Amylose is soluble in water and gives a deep blue colour with iodine, while amylopectin is insoluble and gives no colour. Natural starch consists of 10 to 20 per cent amylose, and 80 to 90 per cent amylopectin.

Amylose is a straight chain polysaccharide composed entirely of D-glucose units. These units are joined by α-glycosidic linkages between C-1 of one glucose unit and C-4 of the next glucose unit. The molecular weight of amylose ranges from 10,000 to 500,000 (60 to 300 D-glucose units).



AMYLOSE

Amylopectin is a branched chain polysaccharide. It is composed of chains of 24 to 30 D-glucose units joined by α-glycosidic linkages between C-1 of one glucose unit and C-4 of the next glucose unit. These chains in turn are connected to each other by 1, 6-linkages. The molecular weight of amylopectin ranges from 50,000 to 1,000,000 (300 to 6000 D-glucose units).



AMYLOPECTIN

Properties. Starch is a colourless amorphous powder. Like all organic compounds of high molecular weight, starch has no definite melting point. It is insoluble in cold water, but a special water-soluble form can be made. When a suspension of starch in water is heated, the starch granules swell and burst forming a viscous, opalescent solution which on cooling sets to a jelly and can be used as *starch paste*.

The main chemical properties of starch are given below :

(1) **Effect of Heat.** When starch is heated to 200°C, it decomposes to give *dextrins* and other compounds. Dextrins are glucose polysaccharides of intermediate size. They are used quite extensively in the manufacture of cheap adhesives because of their sticky properties when wet. Such adhesives are used on postage stamps and envelopes. When starched clothing is ironed, dextrins are produced on the surface from the heating of the starch. The dextrin coating gives the cloth a smooth and shiny finish.

(2) **Reaction with Iodine.** Starch reacts with iodine to give a deep blue colour. Thus, iodine is commonly used to test the presence of starch, and *vice versa*. The blue colour is due to the formation of an *inclusion complex* between iodine and the *amylose* fraction of starch. In forming this complex, the linear amylose molecule coils into a spiral that is held by hydrogen bonding between hydroxyl groups of adjacent loops. The iodine molecules then align themselves in the centre of the tube formed by the spiral (Fig. 32·7). This arrangement allows the interaction of the electron orbitals of many iodine atoms, which causes the light absorption that gives the complex its characteristic colour. Inclusion complexes are unusual in that they do not depend on ordinary chemical bonds to hold them together. They may be considered as molecular boxes with another molecule inside.

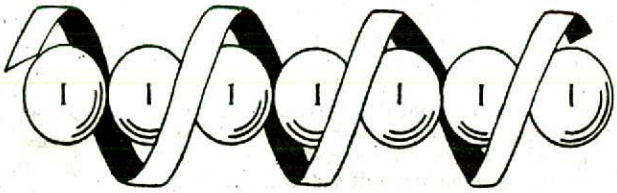


Fig. 32·7. **Amylose-iodine inclusion complex. The spheres represent iodine atoms, and the spiral tape represents the amylose molecule.**

(3) **Hydrolysis.** Hydrolysis of starch with hot dilute acids or by enzymes gives dextrins of varying complexity, maltose, and finally D-glucose.

Starch does not reduce Tollen's reagent and Fehling's solution, and it does not form an osazone with phenylhydrazine. It is not fermented by yeast.

Uses. Starch is used as food. It is encountered daily in the form of potatoes, bread, cakes, rice, etc. It is used in coating and sizing paper to improve the writing qualities. Starch is used to treat textile fibres before they are woven into cloth. This treatment strengthens the fibres so that they can be woven without breaking. It is used in laundering, and in the manufacture of dextrins, glucose, and ethyl alcohol. Starch is also used in the manufacture of starch nitrate (nitro starch), which is used as an explosive.

GLYCOGEN (*Animal Starch*), $(C_6H_{10}O_5)_x$

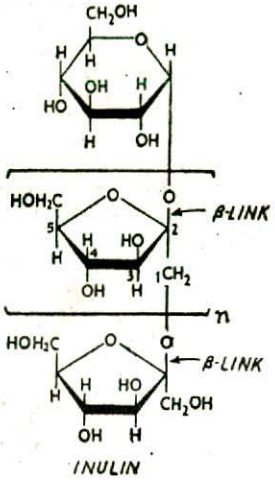
Glycogen is the reserve carbohydrate of animals. It is found in the liver and muscles, the former being a particularly rich source. It also occurs in yeast, mushrooms, and scallops. The structure of glycogen is similar to amylopectin in that it has 1, 6- as well as 1, 4-glycosidic linkages. Glycogen has been found to be even more branched in structure, with one branch for every 12 to 18 glucose units. The molecular weight of glycogen is higher than amylopectin, and it ranges from 1,000,000 to 5,000,000 (6,000 to 30,000 D-glucose units).

Glycogen is a colourless amorphous powder. It is soluble in water and gives a reddish-brown colour with iodine solution. Hydrolysis of glycogen with hot dilute acids yields D-glucose only. It does not reduce Fehling's solution, and does not form an osazone with excess phenylhydrazine. It is not fermented by yeast.

INULIN, $(C_6H_{10}O_5)_n$

Inulin is another reserve carbohydrate of plants. It is found in the roots of chicory, dahlia, dandelion and Jerusalem artichokes. It is a straight chain polysaccharide composed of about 30 D-fructofuranose units. These units are joined by β-glycosidic linkages between C-1 of one fructose unit and C-2 of the next fructose unit. There is evidence that one glucose unit terminates the chain of fructose units. The molecular weight of inulin is about 5,000 (30 D-fructofuranose units).

Inulin is a colourless amorphous powder. It forms a colloidal suspension in water and gives no colour with iodine. Hydrolysis of inulin with hot dilute acids yields D-fructose along with a very small amount of D-glucose. It does not reduce Fehling's solution, and does not form an osazone with excess phenylhydrazine. It is not fermented by yeast.

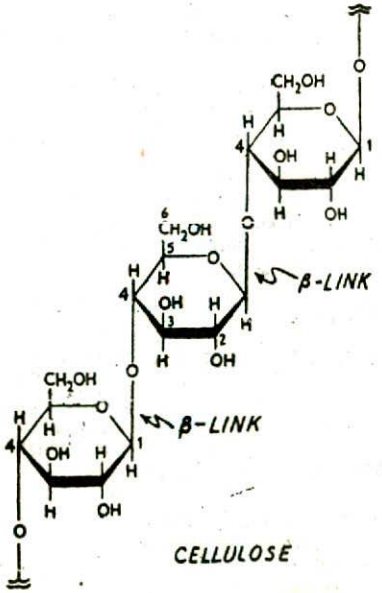


INULIN

CELLULOSE, $(C_6H_{10}O_5)_n$

Occurrence. Cellulose is the main constituent of the cell walls of plants and is very widely distributed. Cottonseeds contain 90 to 95 per cent, wood contains 45 to 50 per cent, flax contains 80 to 85 per cent, hemp contains 75 to 80 per cent, jute contains 60 to 65 per cent, and cereal straws contain 40 to 45 per cent of cellulose.

Preparation : (1) **From Cotton.** The chief impurities which are associated with raw cotton are waxes and fats. These impurities are removed by washing the raw cotton with alcohol and ether, and then treating with hot caustic soda solution. It is then washed with water, and dried to give pure amorphous cellulose.



CELLULOSE

(2) **From Wood.** The chief impurities which are associated with wood are lignin, hemicelluloses and resinous substances. These impurities are removed by digesting the wood chips under pressure with a solution of calcium hydrogen sulphite or an aqueous solution of sodium hydroxide and sodium sulphate. The cellulose separates as insoluble fibres which are thoroughly washed with water, bleached with chlorine or calcium hypochlorite, and dried. The cellulose thus obtained is known as *wood pulp*. More details of the process are given on page 808.

Structure. Cellulose is a straight-chain polysaccharide composed entirely of D–glucose units. These units are joined by β-glycosidic linkages between C-1 of one glucose unit and C-4 of the next glucose unit. The molecular weight of cellulose ranges from 50,000 to 500,000 (300 to 2500 D-glucose units).

Properties. Cellulose is a colourless amorphous solid. It has no melting point, and decomposes on strong heating. It is insoluble in water, and most organic solvents. However, it dissolves in a variety of special reagents such as an ammoniacal solution of cupric hydroxide (*Schweitzer's solution*), a solution of zinc chloride in HCl (*Cross and Bevan's reagent*), and a mixture of sodium hydroxide solution and carbon disulphide.

Cellulose is not hydrolysed so easily as starch but, on heating with dilute sulphuric acid under pressure, it yields D-glucose only. Cellulose does not reduce Tollen's reagent or Fehling's solution, and it does not form an osazone with phenylhydrazine. It is not fermented by yeast.

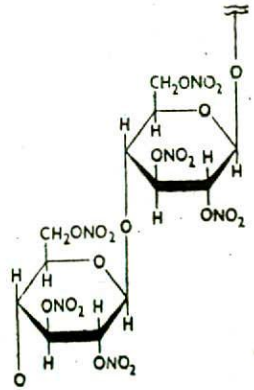
CHEMICAL DERIVATIVES OF CELLULOSE

Each glucose unit in the cellulose molecule has three free hydroxyl groups. Cellulose, therefore, has chemical properties similar to those of a trihydric alcohol. It forms esters with acids, ethers with other alcohols, and in general shows the chemistry of alcohols. Several industrially important derivatives of cellulose are made in this way.

(*a*) **Cellulose Nitrates.** Cellulose reacts with concentrated nitric acid in the presence of sulphuric acid to form esters known as cellulose nitrates or **Nitrocelluloses.** By varying the initial reaction conditions, some or all of the -OH groups in the cellulose molecule can be replaced by $-ONO_2$ groups.

When almost all of the $-OH$ groups are replaced in this way, the product obtained is known as **Gun Cotton.** It is approximately cellulose nitrate, that is, it contains three $-ONO_2$ groups per glucose unit. When only some of the $-OH$ groups are replaced, the product is known as **Pyroxylin.** It is approximately a mixture of cellulose dinitrate and cellulose mononitrate.

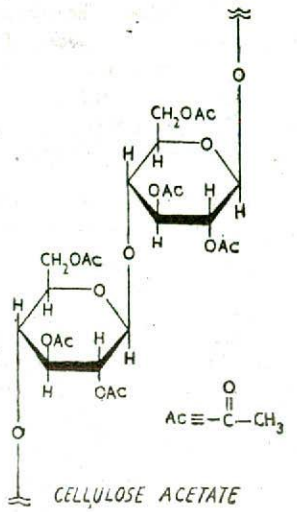
Gun cotton looks something like ordinary cotton but is highly explosive. It is used in the manufacture of smokeless gunpowder. Pyroxylin is used in the manufacture of plastics like **Celluloid** and **Collodion**, in photographic films, and lacquers.



CELLULOSE NITRATE (GUN COTTON)

(*b*) **Cellulose Acetate.** Cellulose reacts with acetic anhydride in the presence of acetic acid and a small amount of concentrated sulphuric acid to give cellulose acetate.

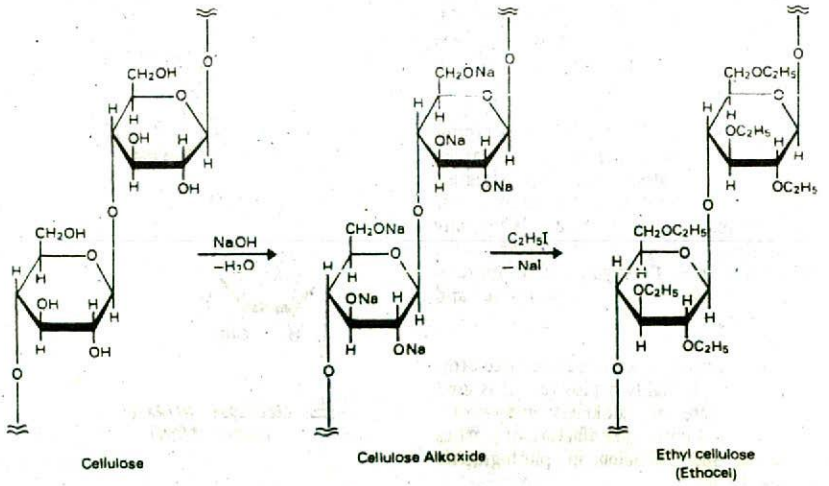
Cellulose acetate is used as moulding plastic for such objects as automobile steering wheels, horn buttons, and various gadgets in cars. Cellulose acetate can be dissolved in acetone to give a solution used in varnishes and lacquers. This solution can also be evaporated, after passing through a thin slit or fine holes, to give *sheets* or *films* or *fibres* of cellulose acetate. The sheets are used in the manufacture of **Shatter-proof Glass.** Shatter-proof glass is made by cementing together two sheets of glass with a sheet of cellulose acetate. The films are used in the manufacture of motion picture films and photographic films. The fibres are woven into cloth under the trade name of **Celanese.**



(*c*) **Ethyl Cellulose.** Cellulose reacts with ethyl iodide in the presence of sodium hydroxide to form an ether known as ethyl cellulose or *ethocel.* Celluiose first reacts with sodium hydroxide to give cellulose alkoxide which then forms the ether with ethyl chloride.

Ethyl cellulose is used as an emulsifying and thickening agent for creams, lotions, shampoos, and toothpastes. It is also used in the manufacture of paints, lacquers, varnishes, enamels, adhesives, films, moulded plastics and packaging sheets.

(*d*) **Mercerised Cotton.** When cotton, under tension, is treated with a strong solution of sodium hydroxide and then washed free of alkali, the product is known as *mercerised cotton.* The fibres swell, become semitransparent, and have a higher luster and a greater absorption capacity for dyes.



RAYONS (*Artificial Silks*)

Rayon is the name given to cover all fibres made by the chemical treatment of cellulose. Cotton linters or more commonly purified wood pulp are used as the sources of cellulose. Today, rayon is made by the following three methods.

(1) *Viscose Process* ;

(2) *Cuprammonium Process* ; and

(3) *Acetate Process.*

The principle in all three is the same, that is, a solution of cellulose is made and then forced through tiny jets, called *spinnerets.* The cellulose is precipitated from the stream of solution, or by allowing the solvent to evaporate in hot air. In all cases, the films are cylindrical and possess smooth surfaces, giving the high lustre characteristic of silk.

(1) **Viscose Process.** Cellulose is first treated with sodium hydroxide solution to give cellulose alkoxide. Upon treating the alkoxide with carbon disulphide, a susbtance known as *cellulose xanthate*, $C_6H_9O_4(OCS_1Na)_n$, is obtained. A very viscous solution of this in water is called **Viscose** from which the process gets its name. The viscose is carefully aged or ripened and then forced through fine openings in a *spinneret* into a bath of dilute sulphuric acid (Fig. 32·8). This reacts with cellulose xanthate to regenerate cellulose. The filaments of regenerated cellulose are washed, dried, and spun into thread or yarn for weaving. The finished product is called **Viscose Rayon.** More than 80 per cent of rayon is made by this method.

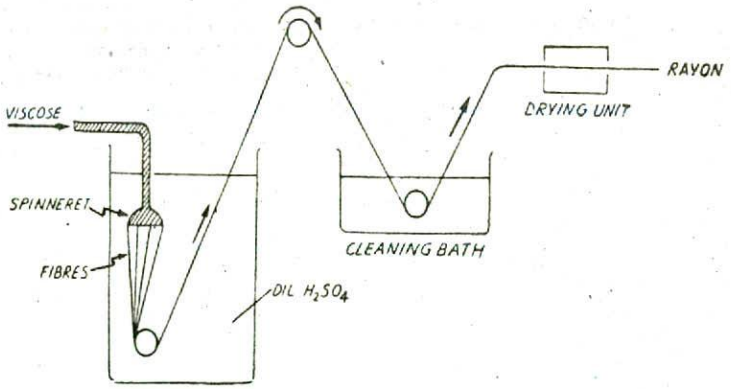


Fig. 32·8. Manufacture of Viscose Rayon.

If the cellulose xanthate solution is forced through a long narrow slit, a thin sheet of **Cellophane** is formed. The xanthate solution can also be made into sponges.

(2) **Cuprammonium Process.** Cellulose is first dissolved in an ammoniacal solution of cupric hydroxide (*Schweitzer's reagent*). The resulting solution is then forced through a spinneret into a bath of sulphuric acid. As the solution passes into the acid it is converted into cellulose threads which are dried, spun together and woven. The finished product is called **Cuprammonium Rayon** or **Cupra Silk.**

(3) **Acetate Process.** Cellulose is first treated with acetic anhydride in glacial acetic acid to form cellulose acetate. The cellulose acetate is soluble in acetone and gives a viscous solution, which is forced through a *spinneret* into hot air. The acetone evaporates and leaves threads of cellulose acetate, which are spun and woven. The finished product is called **Acetate Silk** or **Celanese.**

PAPER INDUSTRY

One of the most important uses of cellulose is for the manufacture of paper. The cellulose used is obtained from wood, cotton rags, waste paper, cereal straws, and similar materials. The most abundant source, of course, is wood, especially the soft wood. The modern method of making paper consists of the following steps.

(*i*) *Preparation of Wood Pulp* ;

and (*ii*) *Preparation of Paper.*

(1) **Preparation of Wood Pulp.** This can be achieved by any one of the following processes.

(*a*) **Mechanical Process.** In this process, wood after being barked, is pressed against a rotating stone or a steel pulping wheel in the same manner as grinding an axe against old-fashioned grind stone. As a result of this wood fibres are separated from each other. Water is added to the mill. It cools the pulping wheel and washes the wood pulp formed into a pot below the wheel.

(*b*) **Sulphite Process.** In this process, wood after being barked is cut into smaller chips by mechanical cutters. The chips are then digested with a solution of calcium hydrogen sulphite, $Ca(HSO_3)_2$ and then reduced to pulp mechanically. Lignin, hemicelluloses and resinous substances which are associated with wood are dissolved. Cellulose itself is not attacked in this process. The digesting is done in a steel vessel at a pressure of about 4 to 6 atmospheres and at a temperature of 150°C for about 10 hours. After the operation is finished the contents of the digester are washed thoroughly with water and bleached with liquid chlorine or calcium hypochlorite. They are then screened from coarser particles and dewatered by passing them through special filtering machines. The purified pulp is obtained in the form of white plates consisting of 89 to 90 per cent cellulose. The pulp produced by this method is known as the *sulphite pulp.*

(*c*) **Sulphate Process.** In this process, the cellulose is freed from lignin and other accompanying substances by digesting the wood chips with an aqueous solution of sodium sulphate. The digesting and the processing of the resulting pulp is carried in the same way as described for the sulphite process. The pulp obtained by this method is known as the **Soda pulp** or **Kraft pulp.**

Mechanical pulp is simply ground wood and contains most of the components of wood from which it was made, including lignin and cellulose. Paper, such as newsprint, is made from mechanical pulp and can be identified because it turns yellow with an aqueous solution of aniline. This is due to the high lignin content of the mechanical pulp. Sulphite pulp or soda pulp shows no such colour change with same treatment.

(2) **Preparation of Paper.** In the manufacture of paper the purified pulp is mixed with water in a pulp beater when pulp paste is obtained. Many substances, such as clay, rosin, dextrins, aluminium silicate, barium sulphate, or pigments are added to the pulp paste to prepare papers of special properties. For example, rosin and similar materials are used as 'sizes' to fill up the spaces between the cellulose fibres ; this prevents ink from spreading on the paper and gives it a smooth finish. Glazed paper contains clay or aluminium sulphate, and waxed paper contains paraffin.

Pulp paste containing a sizing material is fed on to a wire screen carried on an endless belt. This results in dewatering of pulp stock. To aid this process sometimes a suction box is added below the wire screen. When the matter reaches the end of the wire, sufficient water has been removed to make it a consistent mat and to enable it maintain its shape without support. It is then conveyed by means of belts made of felts through a series of rollers where it is further dewatered and made compact. It is then passed through driers which are made up of a series of steam-heated cast iron cylinders. After the drying operation, the paper is finished or polished by passing between a number of horizontal, highly polished, chilled cast iron rollers, known as *callenders.* It is then rolled on reels.

If the pulp is made into paper without a sizing material, the product is porous and resembles filter paper. When such a paper is immersed in about 75 per cent sulphuric acid for a short time and then washed with water, the so-called *parchment paper* is obtained.

Paper Industry in India

The production of paper in India dates back to 1881, when the Titaghur Paper Mills were established in Bengal. During World War II, the number of mills increased to 15 and the production reached 103,884 tonnes (1944-5). Rapid progress has been made since 1950. In 1972-73 there were 63 mills producing paper of all varieties and the total production was 825,000 tonnes.

QUALITATIVE TESTS FOR CARBOHYDRATES

(1) **Molisch's Test.** This is a general test for all carbohydrates larger than tetroses. The test is based on the fact that pentoses and hexoses are dehydrated by concentrated sulphuric acid to form furfural or hydroxymethylfurfural, respectively. Oligo- and polysaccharides first undergo hydrolysis with sulphuric acid to give pentoses and/or hexoses, which on subsequent dehydration yield furfurals. These furfurals condense with α-naphthol to give (Fig. 32·9) coloured complexes.

Place 20 mg of the compound in 1 ml of water. Add two drops of a 5 per cent solution of α-naphthol in methanol. By means of a dropper, allow 1 ml of concentrated sulphuric acid to flow down the side of the inclined tube so that the heavier acid forms the bottom layer. The development of a violet purple colour at the interface is the criterion of a positive test.

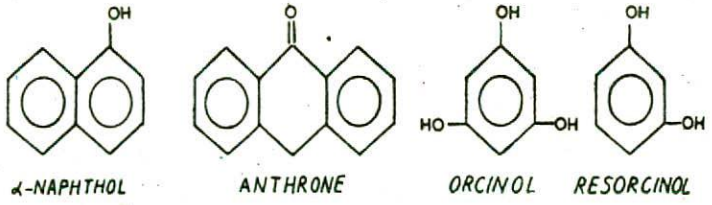


Fig. 32·9. Some of the test-reagents for carbohydrates.

(2) **Anthrone Test.** This is another general test for carbohydrates. The principle is the same as that outlined in the above test except that the furfurals are condensed with anthrone (10-keto-9, 10-dihydroanthracene) to form a coloured complex.

Place 20 mg of the compound in 1 ml of water. Add about 2 ml of the anthrone reagent (0·2 per cent in conc H_2SO_4), mix thoroughly and observe the colour change. The formation of blue-green complex indicates a positive test.

(3) **Fehling's Test.** This is a general test for all reducing carbohydrates. The test is based upon the fact that, in solution, these carbohydrates possess a free aldehyde group and are capable of reducing an alkaline solution of cupric ions.

Mix 3 ml each of Fehling's solution *A* (Dissolve 35 g of $CuSO_4.5H_2O$ in water and make up to 500 ml) and Fehling's solution *B* (Dissolve 120 g of KOH and 173 g of sodium potassium tartarate in water and make up to 500 ml). Add 5 drops of the sugar solution to the mixed Fehling's solution and boil. The formation of a red cuprous oxide precipitate is the criterion of a positive test.

(4) **Bial's Test.** (*Distinguishing Pentoses from Hexoses*). This test for pentoses is based on the reaction of the pentoses with hydrochloric acid to form furfural, which is then condensed with orcinol (Fig. 32·9) in the presence of ferric ions to form a blue-green complex. Other sugars may produce different colours.

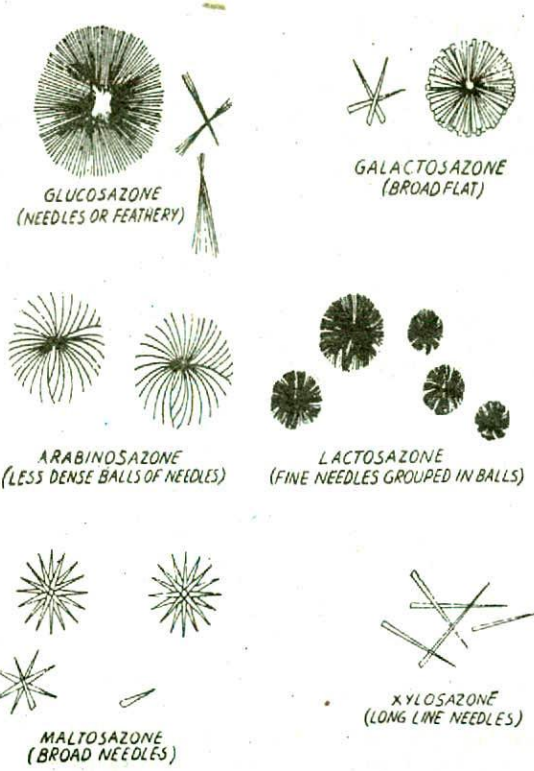


Fig. 32·1. Crystalline appearance of various osazones as seen under a microscope.

Place 20 mg of the sugar in 2 ml of water. Add about 5 ml of the orcinol reagent (Dissolve 1·5 g of orcinol in 5·00 ml of conc HCl and add 20 drops of 10 per cent solution of $FeCl_3$) and heat until boiling starts. A blue-green colour indicates a positive test.

(5) **Seliwanoff's Test** (*Distinguishing ketohexoses from aldohexoses*). This test is based on the fact that hot HCl dehydrates the ketohexoses to form hydroxymethylfurfural much faster than it acts upon the corresponding aldohexoses. In this test hydroxymethylfurfural is condensed with resorcinol to give a coloured complex.

Mix 1 ml of Seliwanoff's reagent (Dissolve 125 mg of resorcinol in 250 ml of dilute HCl) with 1 ml of about 5 per cent solution of the sugar in water. Heat the mixture to boiling. A colour develops within 2 minutes if the sugar is a ketose. Long standing or prolonged heating will develop the colour with aldohexoses.

(6) **Barfoed's Test** (*Distinguishing Monosaccharides from Disaccharides*). This test is based on the fact that the monosaccharides are more easily oxidised than the disaccharides. Barford's reagent will oxidise monosaccharides within 2 minutes, but it will not oxidise disaccharides unless heated for several minutes.

Place 2 ml of Barfoed's reagent (Dissolve 16·6 g of copper acetate in 245 ml of water and add 2·4 ml of glacial acetic acid) in a test tube and add 10 to 20 mg of the carbohydrate (or 1 ml of a dilute solution of it in water) to the reagent. Place the tube in a bath of boiling water for 3 minutes. Remove the tube from the bath and allow it to cool. A yellow-orange or orange-red precipitate is a positive test.

(7) **Osazone Formation** (*Identification of an Unknown Carbohydrate*). All reducing carbohydrates form crystalline osazones with excess phenylhydrazine. The osazone crystals have characteristic shapes and melting points which assist in the identification of the reducing sugar. Further evidence for identification is obtained by noting the time of formation of the crystals and whether the osazone is precipitated from the hot solution or only on cooling. It should be noted that in the formation of osazones, one hydroxy group next to the carbonise group is oxidised, and hence a number of isomeric sugars form the same osazone, for example, glucose, fructose, and mannose all produce the same osazone.

Dissolve 1 g of the unknown sugar in 10 ml of distilled water in a test-tube. Add 2·5 ml of phenylhydrazine and 3 ml of glacial acetic acid. Stopper the test-tube with a vented cork, and place it in a beaker of boiling water. Note the time of immersion and the time of precipitation of the osazone. Shake the tube occasionally.

Under these conditions, fructose osazone precipitates in 2 minutes, glucose and mannose in 4 min, xylose in 7 min, arabinose in 10 min, and galactose in 15 to 20 minutes. Lactose and maltose osazones are soluble in hot water and separate only on cooling.

After 30 minutes remove the test-tube from the hot water and allow it to cool. Carefully collect the crystals, and compare their shapes with those shown in figure 32·10.

QUESTIONS

1. What are carbohydrates ? How are they classified ? Give evidence on which the cyclic structure of glucose is based. How can glucose be converted into fructose ? Explain, giving equations, the reactions involved.

2. Discuss the structure of glucose. How will you convert glucose into fructose and *vice versa* ?

3. Describe the manufacture of sucrose from sugar-beet. How does sucrose react with (*a*) lime water ; (*b*) acetic anhydride ; (*c*) yeast ; (*d*) conc. HNO_3 ; and (*e*) conc. and hot H_2SO_4 ?

4. How may glucose be prepared from starch ? Discuss the structure of glucose, giving experimental evidence in support of it. Why was the open chain structure for glucose discarded in favour of cyclic one ?

5. What are carbohydrates ? How are they classified ? Describe the important properties of starch. *(Mysore BSc III, 1980)*

6. (*a*) Describe the important aspects of manufacture and refinement of cane sugar.
(*b*) Explain the preparation and utility of cellulose nitrate. *(Andhra BSc III, 1980)*

7. Explain: Fructose does not contain any reducing group but it reduces Tollen's reagent and Fehling solution. *(Guru Nanak Dev BSc III, 1980)*

8. What are the limitations of the open-chain structure of D(+)-glucose ?

How oes a cyclic structure of glucose overcome these limitations ? Discuss the evidence in support of the pyranose ring structure of D(+)-glucose. *(Banaras BSc III, 1980)*

9. Write about Kiliani Fischer synthesis for ascending the series of aldoses. *(Himachal BSc III, 1980)*

10. Point out one characteristic difference between the two compounds in each of the following pairs:

(*i*) Glucose and fructose (*ii*) Sucrose and maltose
(*iii*) Cellulose and starch *(Kerala BSc III, 1980)*

11. How are the following conversions effected ?
(*i*) Arabinose to glucose; and
(*ii*) Glucose to fructose. *(Calicut BSc III, 1980)*

12. (*a*) Discuss the objections advanced against open-chain formula of glucose.
(*b*) How does the ring structure in general overcome the objections ?
(*c*) Deduce the nature of the ring. *(Bombay BSc II, 1980)*

13. How has the configuration and the ring size of glucose been confirmed ? *(Punjabi BSc III, 1980)*

14. Starting from Glucose how will you prepare: (*i*) Sorbitol; (*ii*) Gluconic acid; (*iii*) Fructose. *(Annamali BSc III, 1980)*

15. (*a*) Why glucose and fructose give the same osazone ?
(*b*) How would you convert glucose into fructose and vice-versa.
(*c*) What happens when glucose reacts with.
(*i*) a reducing agent (*ii*) bromine water
(*iii*) dilute HNO_3 (*iv*) Phenylhydrazine
(*v*) CH_3OH + CHI. *(Meerut BSc III, 1980)*

16. (*a*) Write structural formulae of :
(*i*) α-D(—) fructofuranose
(*ii*) β-D(+) glucopyranose.
(*b*) Write equations to show the steps of the reaction of excess phenylhydrazine with:
(*i*) Glucose (*ii*) Fructose.

What information does this reaction provide about the configurational relation of these two sugars. *(Gorakhpur BSc II, 1981)*

17. Give definition and classification of Carbohydrates ? Give their preparation and discuss their stability in light of Baeyer's Strain theory. *(Aligarh BSc Hons, 1981)*

18. How is the structure of sucrose established ? *(North Bengal BSc Hons, 1981)*

19. What is mutarotation ? Explain with the help of an example. *(Panjab BSc Chem Engg, 1981)*

20. How can glucose be obtained from arabinose ?
(*b*) What happens when glucose is treated with:
(*i*) Phenylhydrazine (*ii*) Sodium amalgam and alcohol
(*iii*) Ammoniacal Silver nitrate (*iv*) Methanol and dry HCl.
(Nagpur BSc II, 1982)

21. (*a*) Define Carbohydrates. How are these classified ?
(*b*) How would you convert glucose into fructose ?
(*c*) Write ring structures of any two of the following:
(*i*) Sucrose (*ii*) Amylose (*iii*) Amylopectin. *(Himachal BSc III, 1982)*

22. (*a*) Explain briefly the utility of:
(*i*) HIO_4 in determining the size of the ring in glucose.
(*ii*) Cyclic pyranose (hemi ketal) structure in accounting for mutarotation in fructose.
(*iii*) How are reducing sugars different from non-reducing sugars ? Give one example of each. Write the structure of sucrose and maltose. What products are formed when the two are hydrolysed ? *(Delhi BSc Hons. 1982)*

23. (*a*) Discuss the evidence leading to the cyclic structure for D-(+) Glucose.
(*b*) Describe the conversion of aldohexoses into aldopentoses by Wohl's Degradation (Oxime method). *(Guru Nanak Dev BSc III, 1982)*

24. How is glucose prepared ? Write the Pyranose structure. What is the action of Phenylhydrazine on glucose ? How can fructose be converted into glucose ? *(Indore BSc III, 1982)*

25. (*i*) Criticize the following statement:
"Two hexoses that react with phenylhydrazine yield identical osazones are epimers".
(*ii*) Explain why maltose is a reducing sugar while sucrose is not. *(Kerala BSc III, 1982)*

26. (*a*) Illustrate with examples the detailed steps of Killani-Fischer Synthesis.
(*b*) Explain as to why a freshly prepared aqueous solution of glucose has an optical rotation of +112°. On standing at room temperature, the rotation comes down to +52·5° *(Jammu BSc III, 1982)*

27. (*a*) How are carbohydrates classified ?
(*b*) How is glucose converted into fructose ? *(Delhi BSc, 1994)*

28. Discuss the structure of glucose. *(Mangalore BSc, 1993; Osmania BSc Hons, 1994)*

29. (*a*) How will you prove that glucose has a ring structure ?
(*b*) What happens when fructose is treated with excess of phenylhydrazine ? *(Baroda BSc, 1993)*

30. Write a note on : Mutarotation. *(Delhi BSc Hons, 1994)*

31. What happens when glucose is treated with : (*a*) conc. HNO_3; and (*b*) methanol in the presence of HCl ? *(Vikram BSc, 1994)*

32. How is fructose obtained ? How does it react with :
(*a*) Na/C_2H_5OH (*b*) Hydrazine (*c*) conc. HNO_3 (*d*) Phenylhydrazine *(Meerut BSc, 1994)*

33. Describe Killiani reaction for stepping up the aldose series. *(Saugar BSc, 1993)*

34. Discuss the structure of fructose. *(North Eastern Hill BSc Hons, 1993)*

35. (*a*) What are reducing and non-reducing sugars. Give one example of each.
(*b*) Write a note on : Mutarotation. *(Dirbugarh BSc Hons, 1993)*

36. Give the mechanism of osazone formation of glucose.

37. What are carbohydrates ? How are they classified ? Discuss the structure of glucose. *(Delhi BSc Hons, 1993)*

38. How are carbohydrates classified ? Discuss the structure of fructose.

39. How will you synthesise fructose from glucose ? *(Jabalpur BSc, 1994)*

Chapter **33**

Amino Acids, Peptides and Proteins

Proteins are probably the most complex materials produced in nature. The name protein is derived from the Greek word *proteios*, meaning 'of prime importance'. The name is well chosen because proteins are the basis of protoplasm and are present in all living organisms. Without proteins life would not be possible. Proteins are present in muscle, skin, hair and other tissue that make up the bulk of the body's nonbony structure. As enzymes they catalyse biochemical reactions ; as harmones they regulate metabolic processes; and as antibodies they resist and nullify the effects of toxic substances.

Plants synthesise proteins from carbon dioxide, water, nitrates, sulphates, and phosphates. Animals cannot synthesise proteins from these inorganic materials. Animals obtain proteins by eating plants or other animals, which in turn have obtained proteins from plants.

All proteins contain the elements carbon, hydrogen, oxygen, nitrogen, and sulphur. They may contain phosphorus, and traces of other elements like iron, copper, iodine, manganese, and zinc. Most proteins do not show variation in their elementary composition. The average content of the five main elements is given in Table. 33·1.

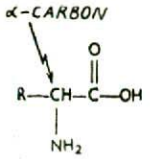
Table 33·1

Element	*Average Per Cent*
Carbon	53
Hydrogen	7
Oxygen	23
Nitrogen	16
Sulphur	1

Proteins have very high moleculur weights. Their molecular weights may range from 10,000 to over 50 million. All proteins yield amino acids upon complete hydrolysis. *Thus proteins may be defined as the high-molecular-weight organic materials which, upon complete hydrolysis, yield amino acids.*

AMINO ACIDS

Amino acids are organic acids having an amino ($-NH_2$) group attached to a chain containing an acid group. Although the amino group can be anywhere on the chain, amino acids derived from proteins have the amino group on the alpha (α) carbon, that is, the carbon atom next to the carboxyl group. These α-amino acids may be represented by the following general formula.



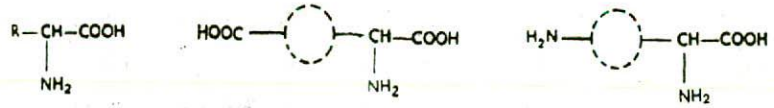
where R may be a hydrogen, a straight- or branched-chain aliphatic group, an aromatic ring or a heterocylic ring.

NOMENCLATURE OF AMINO ACIDS

About 30 amino acids have been obtained from hydrolysis of proteins, and 20 of these are relatively common. The names, structures, and 3-letter abbreviations of the common amino acids are given in Table 33·2. Notice that all the amino acids have trivial names, even those for which the systematic names whould not be cumbersome. Thus the compound $H_2N—CH_2—COOH$ is called *glycine* rather than α-aminoacetic acid or 2-aminoethanoic acid. The compound $CH_3—CH(NH_2)—COOH$ is called *alanine* rather than α-aminopropionic acid or 2-aminopropanoic acid. These trivial names usually reflect the origin or a property of the compound. Glycine, for example, is so named because it has a sweet taste (Gr *glykos*, sweet), and tyrosine was first obtained from cheese (Gr., *tyros*, cheese).

CLASSIFICATION OF AMINO ACIDS

Amino acids are classified as *neutral*, *acidic*, or *basic* according to the relative number of amino and carboxyl groups in the molecule. Neutral amino acids contain one amino group and one carboxyl group. Acidic amino acids contain one amino group and two carboxyl groups. Basic amino acids contain two amino groups and one carboxyl group. Examples of each type are given in Table 33·3.



ESSENTIAL AND NONESSENTIAL AMINO ACIDS

The body can synthesise some, but not all, of the amino acids that it needs for maintaining good health. Those amino acids that cannot be synthesised by the body and must be supplied in the diet are called **Essential Amino acids**. Experimental reasearch has indicated that the quantities of amino acids needed for the normal growth of children are far greater than the proportion needed for the good health in adults. Minimum daily requirements of all essential amino acids for human beings have not been established; requirements vary from 0·25 g to 1·5 g a day.

The amino acids that can be synthesised from other compounds by the tissues of the body are called **Nonessential Amino acids**. Remember that the essential amino acids are no more essential to our body than the nonessential amino acids. Both are equally needed for our growth and good health. The essential and nonessential amino acids are listed in Table 33·2.

Table 33·2. Essential and Nonessential Amino acids

Essential	*Nonessential*
Valine	Glycine
Leucine	Alanine
Isoleucine	Tyrosine
Phenylalanine	Serine
Tryptophan	Proline
Threonine	Hydroxypropine
Methionine	Cysteine
Lysine	Cystine
Arginine	Aspartic Acid
Histidine	Glutamic acid

Table 33·3. Amino acids Derived from Proteins

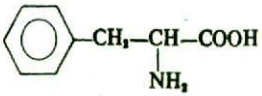
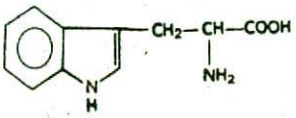
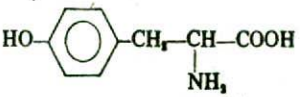
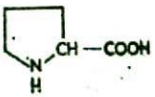
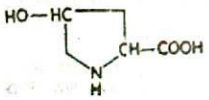
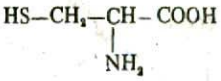
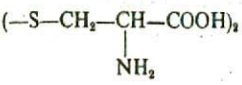
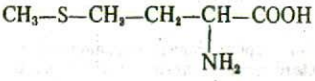
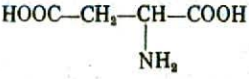
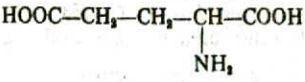
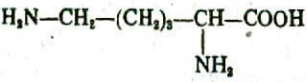
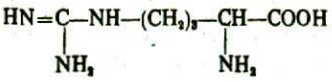
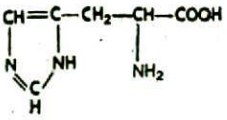
Name	*3-Letter Abbreviation*	*Structure*
NEUTRAL AMINO ACIDS		
Glycine	Gly	H_2N-CH_2-COOH
Alanine	Ala	$CH_3-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$
Valine	Val	$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$
Leucine	Leu	$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$
Isoleucine	Ile	$CH_3-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$
Phenylalanine	Phe	
Tryptophan	Try	
Tyrosine	Tyr	
Serine	Ser	$HO-CH_2-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$
Threonine	Thr	$CH_3-\underset{\displaystyle OH}{\underset{\vert}{CH}}-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$
Proline	Pro	

Table 33·3. *Continued*

Name	*3-Letter Abbreviation*	*Structure*
Hydroxyproline	Hyp	
Cysteine	Cys	
Cystine	Cys-Scy	
Methionine	Met	
ACIDIC AMINO ACIDS :		
Aspartic acid	Asp	
Glutamic acid	Glu	
BASIC AMINO ACIDS :		
Lysine	Lys	
Arginine	Arg	
Histidine	His	

OPTICAL ACTIVITY OF AMINO ACIDS

Glycine does not have an asymmetric carbon atom and, therefore, does not have optical isomers. Alanine and all other amino acids have an asymmetric carbon at position 2, the α-carbon atom. For this reason they are all optically active and exist in D and L forms, which are nonsuperimposable mirror image isomers. If the carboxyl group is written at the top, the D-form refers to the isomer with the $-NH_2$ group on the right; the L-form is the isomer with the $-NH_2$ group on the left (Fig. 33·1). The reference compound for this assignment is glyceraldehyde.

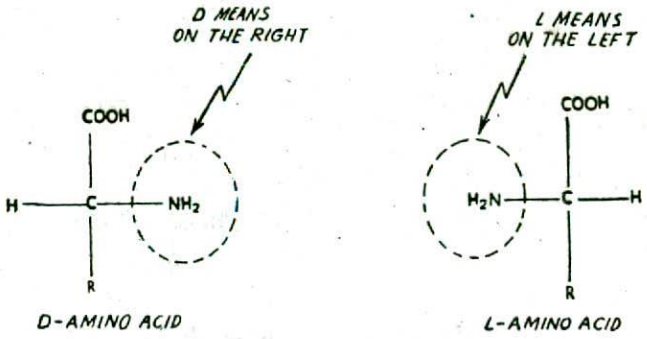


Fig. 33·1. Optical isomers of an amino acid. If the amino group on the asymmetric carbon atom projects to the right, the amino acid is said to be of D-configuration. If the amino group on the asymmetric carbon projects to the left, the amino acid is said to be of L-configuration.

Recall that the letters D and L refer only to the **relative** configuration around the asymmetric carbon atom and not to the direction of optical rotation. The direction of optical rotation is indicated by a (+) sign for a dextrorotatory amino acid and a (—) sign for a laevorotatory one.

Most of the naturally occurring amino acids have the L-configuration. The products of laboratory synthesis are generally optically inactive. This is due to the formation of racemates containing equal amounts of D- and L-forms. The optical rotation of amino acids depends upon the pH of the solution. In neutral solution, most of the amino acids are dextrorotatory.

SYNTHESIS OF α-AMINO ACIDS

α-Amino acids may be obtained :

(1) **By Hydrolysis of Proteins.** Proteins can be hydrolysed by refluxing with dilute hydrochloric acid to give a mixture of α-amino acids. The resulting mixture can be separated by : (*a*) Fractional crystallisation ; (*b*) Fractional distillation of their esters followed by hydrolysis (*Fischer's method*) ; (*c*) Selective precipitation as salts with phosphotungstic and picric acids ; (*d*) Distribution of amino acids between *n*-butanol saturated with water (*Dakin's method*) ; (*e*) Column, paper and gas chromatography ; and (*f*) Electrophoresis. Paper chromatography and electrophoresis are the most widely used techniques.

(2) **By Amination of α-Halo Acids.** α-Chloro or α-bromo carboxylic acids react with excess of liquid ammonia to form the ammonium salt of an amino acid. The free amino acid can be obtained by hydrolysis of the ammonium salt.

$$\underset{\text{chloroacetic acid}}{Cl{-}CH_2{-}COOH} + 3NH_3 \xrightarrow[(-NH_4Cl)]{50^\circ} H_2N{-}CH_2{-}COO^-NH_4^+ \xrightarrow[H_2O]{H^+} \underset{\text{glycine}}{H_2N{-}CH_2{-}COOH}$$

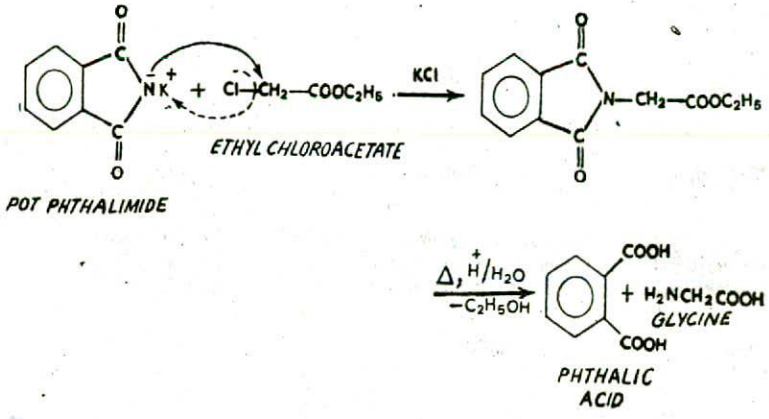
$$\underset{\text{α-bromopropionic acid}}{CH_3{-}\underset{Br}{\underset{|}{CH}}{-}COOH} + 3NH_3 \xrightarrow[(-NH_4Br)]{50^\circ} CH_3{-}\underset{NH_2}{\underset{|}{CH}}{-}COO^-NH_4^+ \xrightarrow[H_2O]{H^+} \underset{\text{alanine}}{CH_3{-}\underset{NH_2}{\underset{|}{CH}}{-}COOH}$$

The necessary α-halo acids may be prepared by the Hell-Volhard-Zelinsky halogenation of the corresponding unsubstituted carboxylic acids.

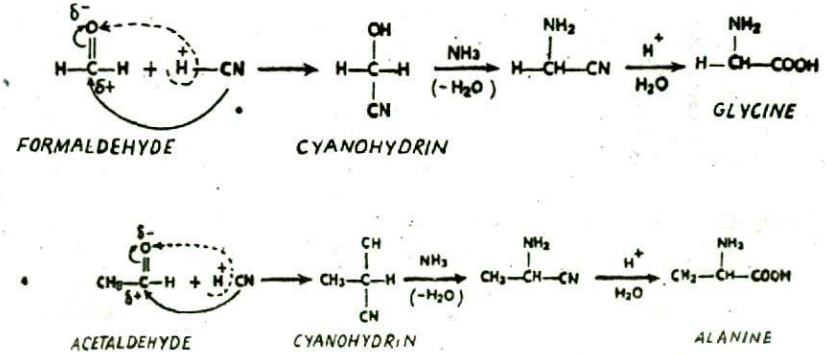
$$\underset{\text{acetic acid}}{CH_3{-}COOH} + Cl_2 \xrightarrow{P} \underset{\text{chloroacetic acid}}{Cl{-}CH_2{-}COOH} + HCl$$

$$\underset{\text{propionic acid}}{CH_3{-}CH_2{-}COOH} + Br_2 \xrightarrow{P} \underset{\text{α-bromopropionic acid}}{CH_3{-}\underset{\displaystyle Br}{\underset{|}{CH}}{-}COOH} + HBr$$

(3) **By Gabriel Synthesis.** An ester of α-halo acid is treated with potassium phthalimide to form the corresponding substituted phthalimide which on hydrolysis gives phthalic acid and an amino acid.



(4) **By Strecker Synthesis.** An aldehyde is treated with HCN to form the corresponding cyanohydrin which is made to react with ammonia to give an α-amino nitrile. Hydrolysis the nitrile yields an α-amino acid.

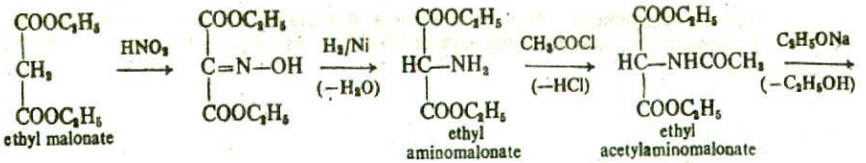


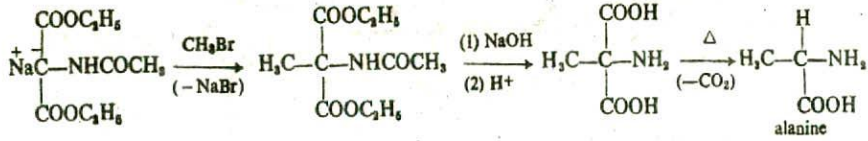
In practice the aldehyde is treated with a mixture of ammonium chloride and potassium cyanide in aqueous solution.

$$NH_4Cl + KCN \xrightarrow{aqueous} NH_4CN + KCl$$

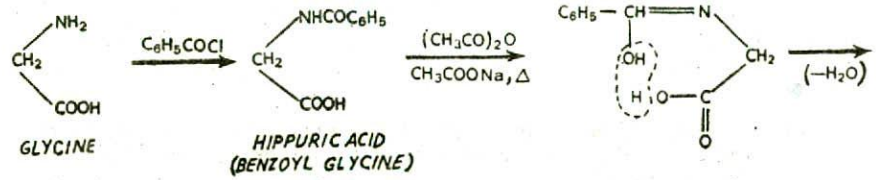
$$NH_4CN \xrightarrow{aqueous} NH_3 + HCN$$

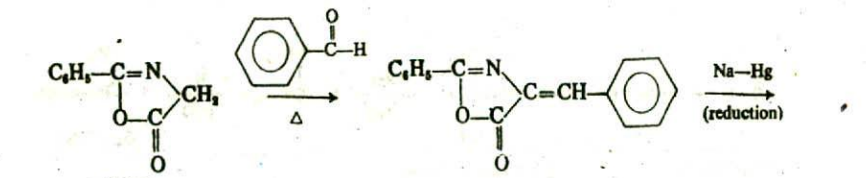
(5) **From Ethyl Malonate.** In three steps ethyl malonate is converted into ethyl acetylaminomalonate. This on treatment with sodium ethoxide in absolute alcohol forms a sodium salt which is made to react with an *alkyl halide* to give an alkyl-substituted ester. Saponification and decarboxylation of this ester yields an α-amino acid.

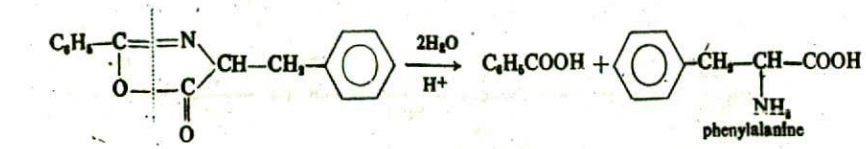




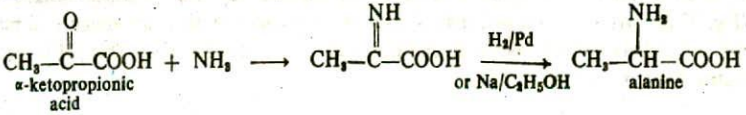
(6) **By Erlenmeyer Azlactone Synthesis.** Hippuric acid (benzoyl glycine) is treated with acetic anhydride in the presence of sodium acetate to form azlactone. This on condensation with *aldehydes* followed by reduction and subsequent hydrolysis yields an α-amino acid.





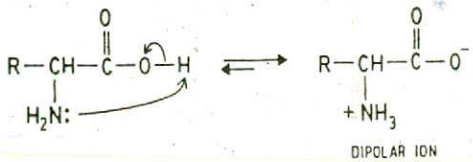


(7) **By Koop Synthesis.** α-Keto acids are treated with ammonia to form the corresponding imine which on catalytic reduction yields an amino acid.



PROPERTIES OF AMINO ACIDS

(*Physical*). Amino acids are generally colourless, crystalline solids having melting points (or decomposition points) above 200°C. They are soluble in water, but insoluble in non-polar organic solvents. These properties are not characteristic of most simple carboxylic acids or simple amines but are more like those of salts. The reason for this anomalous behaviour is that amino acids contain both an *acidic* carboxyl group and a *basic* amino group in the same molecule. In aqueous solution, the acidic carboxyl group can lose a proton and the basic amino group can gain a proton in a kind of internal acid-base reaction.

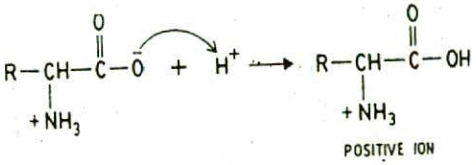


The product of this internal reaction is called a **Dipolar ion** or a **Zwitterion.** Although it is neutral overall, it contains both a positive and a negative charge.

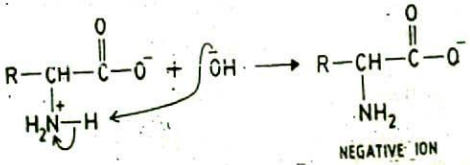
The dipolar ion is the more common form in which amino acids exist in aqueous solution or in the solid state. This has been confirmed by their IR spectrum ; it contains absorption peaks at 1600 and 1400 cm^{-1} corresponding to the stretching vibrations of the carboxylate ion. There is also a broad band at 3000—2500 cm^{-1} corresponding to the ammonium ion.

Amino acids in the dipolar-ion form are amphoteric. That is, they react with both acids and bases. The reaction with a base converts the ammonium substituent ($-NH_3^+$) to an amino group ($-NH_2$). The reaction with an acid converts the carboxylate substituent ($-COO^-$) to a carboxyl substituent ($-COOH$). Thus in acidic solution amino acids exist as positive ions (cations), while in basic solution they exist as negative ions (anions).

An Amino acid in Acidic solution :



An Amino acid in Basic solution :



We know that if a solution of charged ions is placed in an electric field, the negative ions (anions) migrate toward the positive electrode (the anode). The positive ions (cations) migrate toward the negative electrode (the cathode). A neutral molecule, of course, is attracted to neither electrode

In acidic solution, an amino acid exists as a positive ion and migrates toward the cathode. In basic solution, the amino acid exists as a negative ion and migrates toward the anode (Fig. 33·2). At a certain pH, that is, hydrogen ion concentration, the amino acid molecule would not migrate to either electrode and exist as a neutral dipolar ion. This pH is called the **Isoelectric Point** of that amino acid.

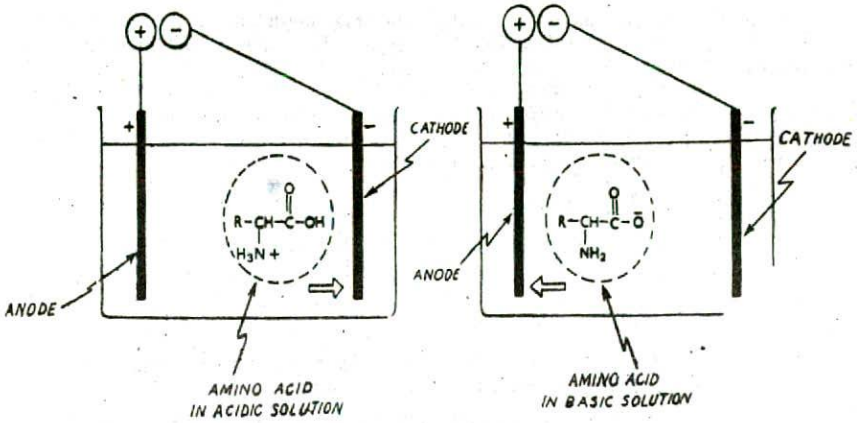


Fig. 33·2. Effect of an electric field on an amino acid in acidic and basic solutions

All amino acids do not have the same isoelectric point. The pH of the isoelectric point depends upon other functional groups in the amino acid structure. Neutral amino acids have isoelectric points from pH 5·5 to 6·3. Acidic amino acids have isoelectric points at a *low* pH, around 3. Basic amino acids have isoelectric points at a *high* pH, around 10. The isoelectric points of some amino acids are given in Table 33·3.

Amino acids have minimum aqueous solubility at their isoelectric points. This fact has been made use in the separation of α-amino acids from protein hydrolysates.

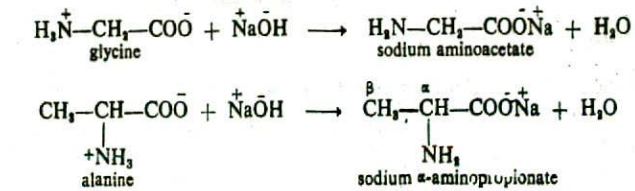
(*Chemical*). Amino acids show the characteristic reactions of amines and carboxylic acids. However, the properties of an individual group may sometimes be affected due the dipolar-ion formation. Some important reactions of amino acids are described below. Glycine and alanine are taken as examples.

Table 33·3. Isoelectric Points of Some Amino acids

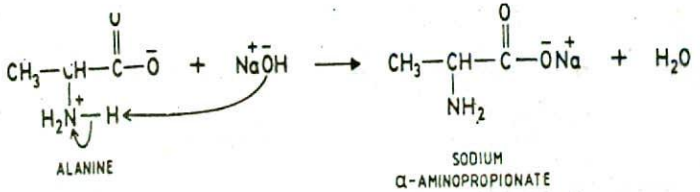
Amino Acid	*Isoelectric Point*
Neutral Amino Acids :	
Alanine	6·1
Valine	6·0
Serine	5·7
Threonine	5·6
Acidic Amino Acids :	
Aspartic acid	2·8
Glutamic acid	3·2
Basic Amino Acids :	
Lysine	9·7
Arginine	10·8

A. REACTIONS OF THE CARBOXYL GROUP

(1) **Reaction with Bases.** Amino acids react with bases to form the corresponding salts.

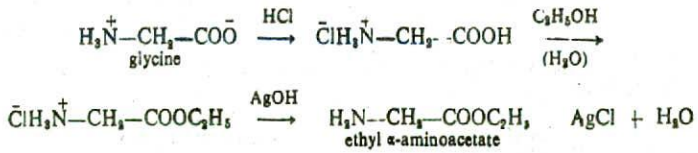


MECHANISM :

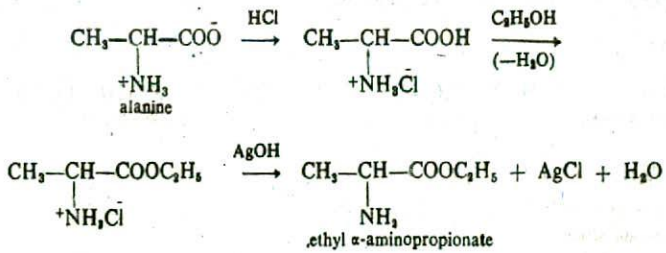


(2) **Esterification.** Amino acids can be esterified by boiling with an alcohol in the presence of anhydrous HCl. The hydrochloride of the ester is formed first, and the free ester may be obtained by treatment with silver hydroxide (*moist* Ag_2O)

Esterification of Glycine :

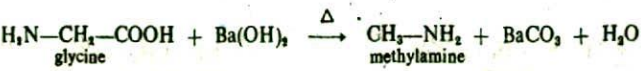


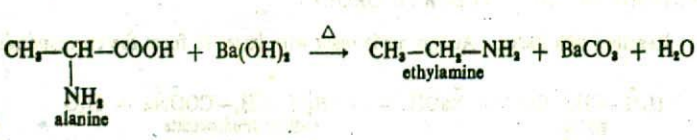
Esterification of Alanine :



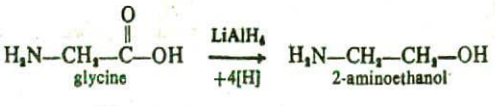
Notice that HCl first converts the dipolar ion into an acid which is subsequently esterified.

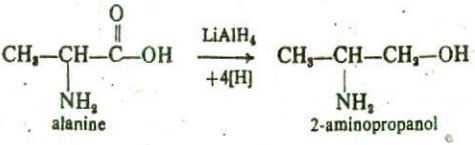
(3) **Decarboxylation.** Amino acids lose carbon dioxide and yield primary amines when heated with barium hydroxide solution.





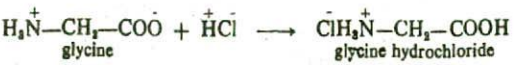
(4) **Reduction.** Amino acids undergo reduction with lithium aluminium hydride to form amino alcohols.

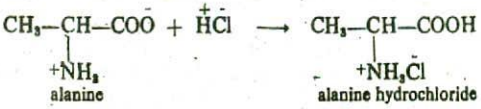




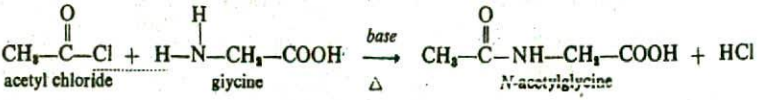
B. REACTIONS OF THE AMINO GROUP

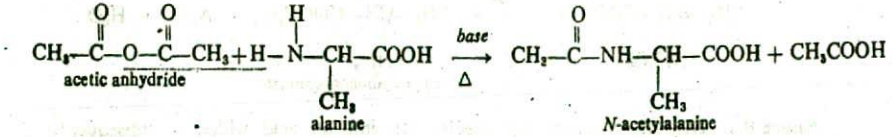
(5) **Reaction with Strong Acids.** Amino acids react with strong acids to give the corresponding salts.



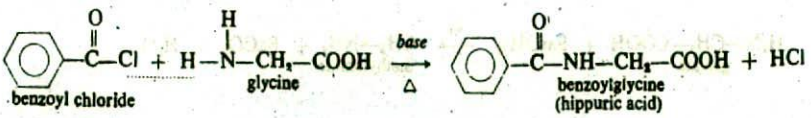


(6) **Acylation.** The amino group of amino acids can be acylated with acid anhydrides or acid halides to form *N*-acyl amino acids.





Similarly, benzoyl chloride and glycine yield benzoylglycine or hippuric acid. It is found in considerable quantities in the urine of the horse (Gr. *hippos*, horse).



(7) **Reaction with Nitrous Acid.** Like primary aliphatic amines, amino acids react with nitrous acid ($NaNO_2$+HCl) to form hydroxy acids and nitrogen.

$$\underset{\text{glycine}}{H_3\overset{+}{N}-CH_2-COO^-} + HONO \longrightarrow \underset{\text{glycollic acid}}{HO-CH_2-COOH} + N_2\uparrow + H_2O$$

$$\underset{\text{alanine}}{CH_3-\underset{\displaystyle {}^{+}NH_3}{\underset{|}{CH}}-COO^-} + HONO \longrightarrow \underset{\text{lactic acid}}{CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-COOH} + N_2\uparrow + H_2O$$

This reaction forms the basis of the *Van Slyke Method* for the estimation of amino acids. The nitrogen is evolved quantitatively and its volume measured. Notice that one-half of the evolved nitrogen comes from the amino group of the amino acid.

(8) **Reaction with Nitrosyl Halides.** Amino acids react with nitrosyl chloride (or bromide) to form the halo acids and nitrogen.

$$\underset{\text{glycine}}{H_2N-CH_2-COOH} + NOCl \longrightarrow \underset{\text{chloroacetic acid}}{Cl-CH_2-COOH} + N_2\uparrow + H_2O$$

$$\underset{\text{alanine}}{CH_3-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH} + NOBr \longrightarrow \underset{\text{α-bromopropionic acid}}{CH_3-\underset{\displaystyle Br}{\underset{|}{CH}}-COOH} + N_2\uparrow + H_2O$$

(9) **Reaction with Formaldehyde.** Amino acids react with formaldehyde to produee *N*-methylene amino acids.

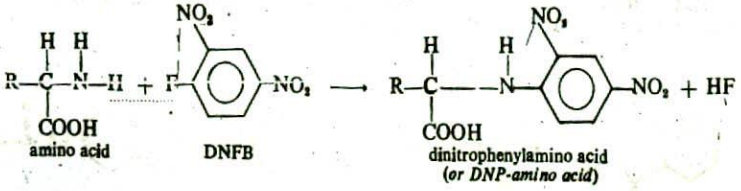
$$\underset{\text{formaldehyde}}{\begin{matrix}H\\H\end{matrix}\!\!>\!C=O} + \underset{\text{glycine}}{H_2N-CH_2-COOH} \longrightarrow \underset{\text{N-methyleneglycine}}{H_2C=N-CH_2-COOH} + H_2O$$

As a result of this reaction, the basic character of the amino acid is lost and the product is acidic in nature which can be titrated with alkalis in the usual manner.

$$H_2C=N-CH_2-COOH + \overset{+}{Na}\overset{-}{OH} \longrightarrow \underset{\text{sod salt of N-methyleneglycine}}{H_2N=N-CH_2-COO^-\overset{+}{Na}} + H_2O$$

This reaction forms the basis of *Sorenson Formol Titration Method* for the determination of neutralisation equivalents of amino acids.

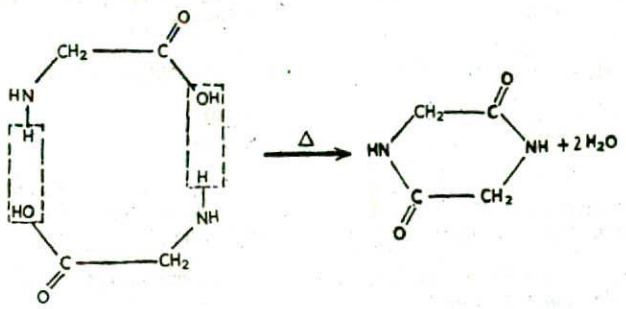
(10) **Reaction with 2,4-Dinitrofluorobenzene (DNFB).** 2,4-Dinitrofluorobenzene is also called *Sangar's reagent.* Amino acids react with this reagent to produce yellow coloured dinitrophenylamino acids or DNP-amino acids.



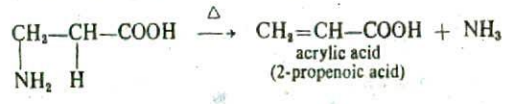
This reaction is very important in the determination of structure of peptides and proteins. The reagent reacts with the free amino group of terminal amino acid in a peptide or a protein and thus identifies the end amino acid in the structure.

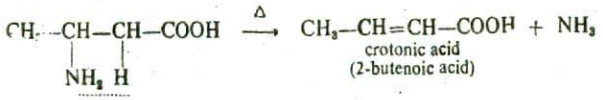
C. REACTIONS INVOLVING BOTH THE CARBOXYL AND THE AMINO GROUPS

(11) **Effect of Heat.** The behaviour of amino acids on heating varies with the number of carbon atoms between amino and carboxyl groups. α-Amino acids undergo dehydration on heating (200°C) to give diketopiperazines.

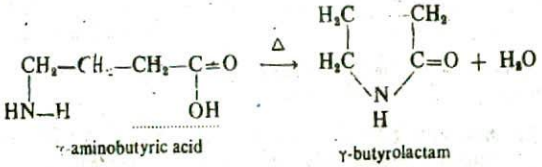


β Amino acids lose ammonia on heating to form α, β-unsaturated acids.

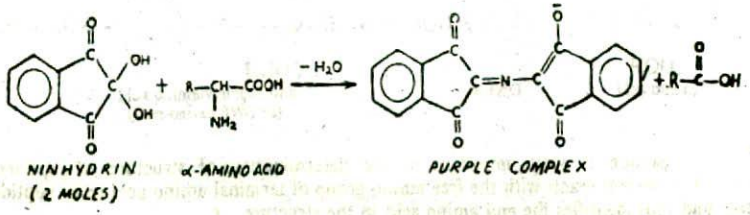




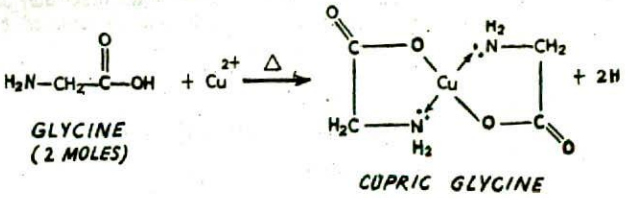
γ-Amino acids and δ-amino acids undergo intramolecular dehydration to form cyclic amides called **Lactams**.



(12) **Reaction with Ninhydrin.** All α-amino acids react with ninhydrin (triketohydrindene hydrate) to produce the same purple complex. This reaction is commonly used to test the presence of α-amino acids.

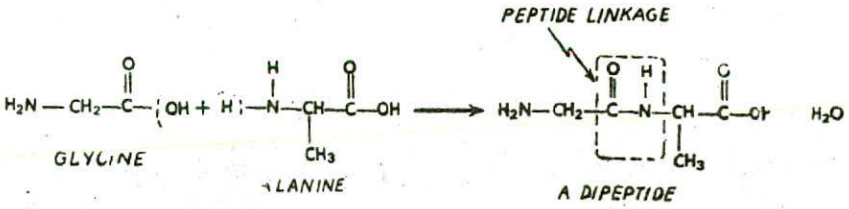


(13) **Reaction with Cupric Oxide.** Amino acids react with cupric oxide in water to produce deep blue complex salts.



PEPTIDES

Proteins are made of many α-amino acids bonded together by a peptide linkage formed between the amino group of one amino acid and the carboxyl group of another. When two amino acids combine in this way, the resulting product is called a **Dipeptide.**



When three amino acids combine, the product is called a **Tripeptide.** When four amino acids combine, the product is called a **Tetrapeptide.** When many amino acids combine in this way, the product is called a **Polypeptide.** Proteins are polypeptides containing at least 100 or more amino acids, but there is no clear dividing line between polypeptides and proteins.

N-TERMINAL AND C-TERMINAL AMINO ACID RESIDUES

In a peptide the amino acid that contains the free amino group is called the *N*-terminal residue. It is always written on the left-hand side of the polypeptide chain. Similarly, the amino acid that contains the free carboxyl group is called the *C*-terminal residue. It is always written on the right-hand side of the polypeptide chain. A tripeptide from glycine, alanine, and phenylalanine should thus be written as in the Fig. 33·3.

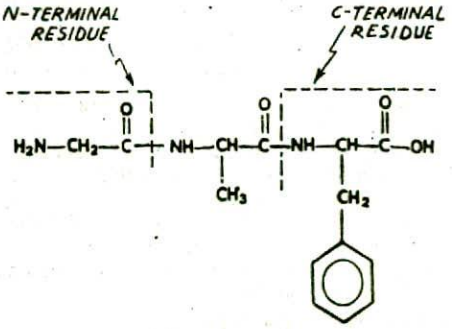
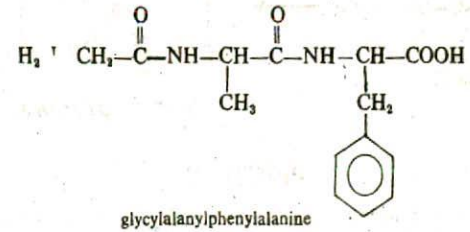


Fig. 33·3. A tripeptide from glycine, alanine, and phenylalanine. Glycine is the *N*-terminal amino acid and phenylalanine is the *C*-terminal amino acid.

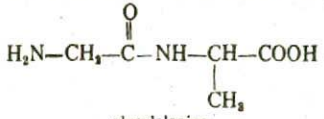
NOMENCLATURE OF PEPTIDES

Peptides are named by listing the amino acids present in the order they occur starting from the *N*-terminal amino acid. The typical amino acid suffix '*-ine*' is replaced by the suffix '*-yl*' for all amino acids except the *C*-terminal amino acid.



glycylalanylphenylalanine

(*A tripeptide from glycine, alanine, and phenylalanine*)



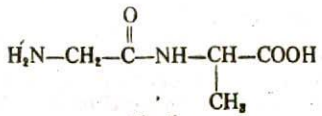
glycylalanine

(*A dipeptide from glycine and alanine*)

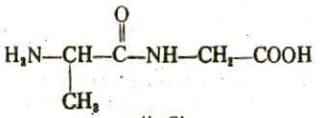
Peptide names formed in this way are not used very often. Instead, the standard 3-letter abbreviations are used (*See* Table 33.1). For example, glycylalanylphenylalanine may be represented as *Gly-Ala-Phe*.

VARIATIONS IN PEPTIDE AND PROTEIN STRUCTURES

There are two ways in which two amino acids can combine to form a dipeptide. For example, glycine and alanine may combine to give the dipeptide *Gly-Ala* or *Ala-Gly*. In the first, glycine is the *N*-terminal and alanine is the *C*-terminal. In the second, alanine is the *N*-terminal and glycine is the *C*-terminal.



Gly-Ala
(glycylalanine)



Ala-Gly
(alanylglycine)

Three amino acids can combine in six different ways to form six tripeptides. For example, glycine, alanine, and phenylalanine may combine to give the following tripeptides.

Gly-Ala-Phe	*Ala-Gly-Phe*	*Ala-Phe-Gly*
Phe-Ala-Gly	*Phe-Gly-Ala*	*Gly-Phe-Ala*

As the size of the peptide increases, the possibilities of variation in structure increase at an almost unbelievable rate. The different ways of combining the amino acids give rise to the fantastic number of variations possible in protein structure. For example, a decapeptide contains 10 amino acid units and has a molecular weight of something over 1000. It is far smaller than a protein. Even so, the number of different decapeptides that can be constructed (using each amino acid no more than once in each structure) is over 4 000,000,000,000. Most proteins have molecular weights of several thousands and some, many millions. Proteins can use the same amino acid more than once in a molecule and may also form cross-linked structures. The number of variations is beyond comprehension.

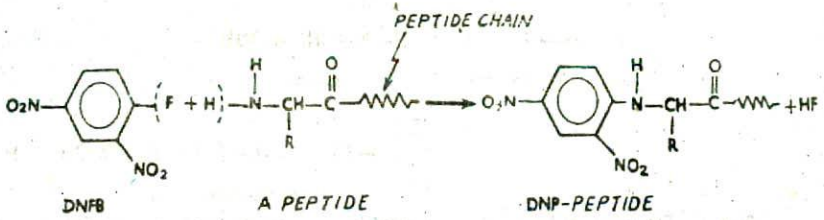
DETERMINATION OF STRUCTURE OF PEPTIDES

To determine the structure of a peptide (or a protein), we normally begin by carrying out its complete hydrolysis. The peptide is refluxed with dilute hydrochloric acid so that all the peptide linkages are broken. Analysis of the resulting solution tells us the kind and the

amounts of the amino acids present in the peptide. However, complete hydrolysis tells us nothing about the sequence of amino acids in the peptide.

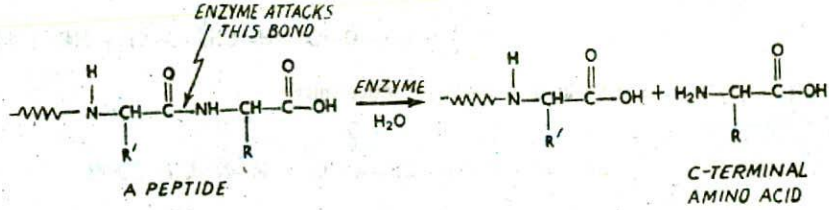
END-GROUP ANALYSIS

Identification of the *N*-terminal amino acid of the peptides can be accomplished by the *Sanger's method*. This involves the reaction of 2, 4-dinitrofluorobenzene (DNFB) with the free amino group of the *N*-terminal residue before the peptide is hydrolysed.



The dinitrophenyl (DNP) derivative of the *N*-terminal amino acid is coloured and can easily be isolated and identified.

Identification of the *C*-terminal amino acid can be accomplished by the enzyme *carboxypeptidase*. This enzyme selectively cleaves the *C*-terminal amino acid, which can be isolated and idetified.



The sequence of internal amino acids of the peptide can be determined from data obtained from partial hydrolysis of the peptide. Partial hydrolysis of the peptide cleaves it into *di-*, *tri-*, *tetra-*, and higher peptides. The tripeptide fragments are separated from the others and the *N*-terminal and *C*-terminal amino acids and the central amino acid in each tripeptide are identified. Once the structures of all the tripeptides are known, the information can be fitted together like a jigsaw puzzle, and the structure of the original peptide can be deduced.

As an example, let us take the case of an unknown tetrapeptide. Complete hydrolysis, separation, and analysis tells us that it contains alanine, isoleucine, and valine. We now subject the unknown peptide to end-group analysis. Treatment with DNFB followed by hydrolysis, gives us the DNP-derivative of alanine. Therefore, the *N*-terminal amino acid must be alanine. Treatment with *carboxypeptidase* gives us valine. Partial hydrolysis of the unknown tetrapeptide gives us two different tripeptides. These tripeptides are in turn subjected to complete hydrolysis and end-group analysis. By overlapping the pieces, we can determine the sequence of amino acids in the original tetrapeptide.

(1) Tetrapeptide $\xrightarrow[H_2O]{H^+}$ *Ala—Gly—Ile* + *Gly—Ile—Val*

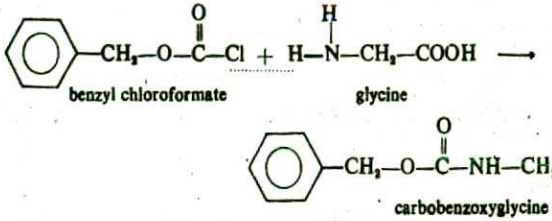
(2) *Ala—Gly—Ile*
Gly—Ile—Val

(3) *Structure* : *Ala—Gly—Ile—Val*

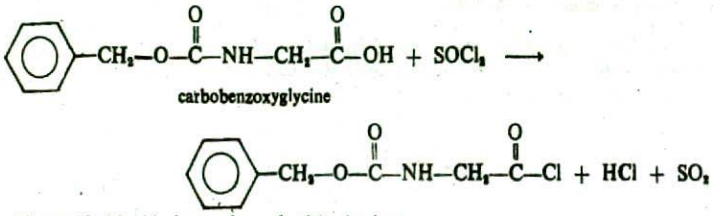
SYNTHESIS OF PEPTIDES

Specific peptides can be obtained by the following steps. Glycylalanine (*Gly—Ala*) is taken as an example.

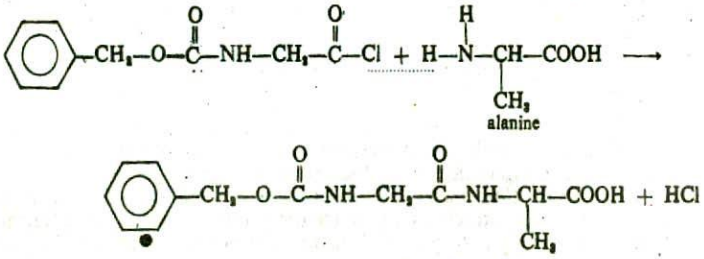
Step 1. The amino group of glycine is protected by treatment with benzyl chloroformate.



Step 2. The protected glycine is converted to the corresponding acid chloride by treatment with thionyl chloride.

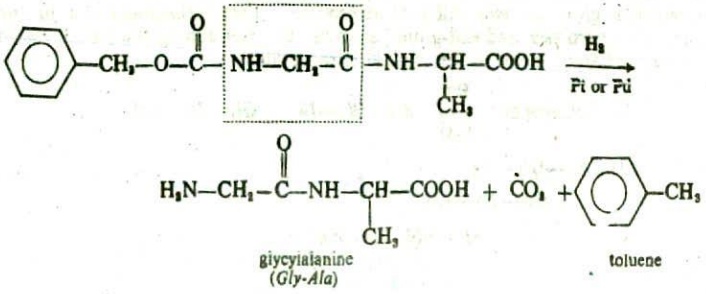


Step 3. The acid chloride is condensed with alanine.



If the amino group of glycine is not protected as in Step (1) and the reaction is carried straight with glycine acid chloride, two reactions will occur. Glycine acid chloride will react with the amino group of another molecule of glycine acid chloride as well as with alanine as in this step.

Step 4. The protecting group of glycine is removed by reduction.



If higher peptides are to be synthesised, the protecting group is left on the amino group and the carboxyl group of each new peptide is reacted with $SOCl_2$ and a new amino acid. Although the process of polypeptide synthesis is laborious, small proteins like ribonuclease with 124 amino acid units have been successfully synthesised.

PROTEINS

CLASSIFICATION

There are two methods for classifying proteins. One method classifies them according to composition as either *simple proteins* or *conjugated proteins*. The second method classifies them according to their physiological functions.

I. Classification According to Composition

(A) Simple Proteins. Simple proteins are those which yield only α-amino acids upon hydrolysis. They are further subdivided according to their solubility in various solvents and also whether they are coagulated by heat.

(1) *ALBUMINS.* Albumins are water-soluble proteins, which are coagulated by heat. They are found in plants and animals. Examples are egg-albumin and serum-albumin.

(2) *GLOBULINS.* Globulins are insoluble in water but soluble in dilute salt solutions, which are coagulated by heat. They are found in plants and animals. Examples are serum-globulin and vegetable-globulin.

(3) *SCLEROPROTEINS* (*Albuminoids*). Scleroproteins are insoluble in water and most other solvents. They are found only in animals. Example is keratin in hair and fingernails.

(4) *GLUTENINS.* Glutenins are insoluble in water but soluble in dilute acids and alkalis, which are coagulated by heat. Example is glutenin from wheat.

(5) *HISTONES.* Histones are soluble in water but insoluble in dilute ammonium hydroxide, which are not coagulated by heat. They are found in animals. Example is globin in haemoglobin.

(6) *PROLAMINES.* Prolamines are insoluble in water but soluble in 70 per cent ethanol, which are not coagulated by heat. Examples are *zein* from corn and *gliadin* from wheat.

(7) *PROTAMINES.* Protamines are soluble in water and dilute ammonium hydroxide, which are not coagulated by heat. Examples are *salmine* from salmon and *sturine* from sturgeon.

(B) Conjugated Proteins. Conjugated proteins are those which yield α-amino acids *plus* a nonprotein material upon hydrolysis. The nonprotein material is called the *prosthetic* group (Gr. *prosthesis*, an addition). The conjugated proteins are also subdivided into several classes according to the nature of the prosthetic group.

(1) *GLYCOPROTEINS.* Glycoproteins contain a carbohydrate derivative as their prosthetic group. *Mucin*, a constituent of saliva, is a glycoprotein.

(2) *PHOSPHOPROTEINS.* Phosphoproteins are proteins which contain α-amino acids linked to phosphoric acid. Casein, which is found in milk, is an example of this class.

(3) *CHROMOPROTEINS.* Chromoproteins consist of a pigmented prosthetic group combined with a simple protein. Haemoglobin and cytochromes are examples of chromoproteins.

(4) *NUCLEOPROTIENS.* Nucleoproteins are complex substances that occur abundantly in the nuclei of plant and animal cells. The prosthetic groups are nucleic acids. Examples of nucleoproteins are the *nuclein* and *nucleohistones* of glandular tissues, *yeast*, *chromosomes*, and other materials rich in cell nuclei.

(5) *LIPOPROTEINS.* Lipoproteins consist of cholestrol esters and phospholipids attached to protein molecules. They are found in brain and nerve tissue and are an integral part of cell membranes.

II. Classification According to Functions

The functional classification of proteins includes the following groups :

(1) Structural Proteins. These are fibrous proteins, such as collogen which comprises half of man's total protein in the form of skin, cartilage and bone.

(2) **Contractile Proteins.** Contractile proteins are found in muscles. Examples are *myosin, actin.*

(3) **Harmones.** Many proteins function as *harmones,* that is, as communication links between different parts of organism. *Insulin* is a common example of a protein harmone.

(4) **Enzymes.** Proteins of this group serve as catalyst for the chemical reactions in living organisms, rendering specificity and control to these reactions. *Pepsin,* and *trypsin* are examples of the class.

(5) **Antibodies.** When the body is invaded by infectious species that release foreign proteins or antigens, antibodies are produced to remove the invading species from the system. *Gamma globulins* present in the blood are examples of antibodies.

(6) **Blood Proteins.** The three major protein constituents of the blood are *albumins, hemoglobin* and *fibrinogen.* Their presence contributes to the maintenance of osmotic pressure, oxygen transport and blood coagulation respectively.

STRUCTURE OF PROTEINS

Proteins have definite three-dimensional structure. There are a number of factors which determine the exact shape of a protein. These are considered in terms of four levels of structural organisation called the primary, secondary, tertiary, and quaternary structures of the protein. Each succeeding level of organisation is more complex than the previous one and is a direct result of the chemical features of the previous levels.

(1) **Primary Structure.** The primary structure of proteins refers to the sequence of amino acids held together by peptide linkages. The amino acid sequence in proteins can be determined by the methods used for peptides. These methods have been applied to a number of proteins and several generalisations regarding the primary structure of proteins have been made. They are : (*a*) Proteins are made up of L-amino acids only ; (*b*) A protein may contain more than one amino acid chain. If so, the chains are usually bonded to each other at specific points by disulphide —S—S— linkages ; (*c*) Sequence of amino acids along the protein chains is essentially random. Repeating sequences within a protein molecule are not common ; and (*d*) Small variations in the sequence of amino acids have pronounced effects on the chemical and physical properties of protein.

(2) **Secondary Structure.** The secondary structure of a protein refers to the shape in which the long amino acid chain exists. Many proteins consist of amino acid chain coiled into a spiral known as a **helix.** Such a helix may be either right- or left-handed, as in the case of screws. The right-handed helix is known as the α-helix, and the left-handed helix is known as the β-helix. It has been found that an α-helix constitutes the mor estable arrangement. The spiral is held together by hydrogen bonds between N—H and C=O groups vertically adjacent to one another in the helix (Fig. 33·4). X-Ray studies have shown that there are approximately 3·6 amino acid units for each turn in the helix.

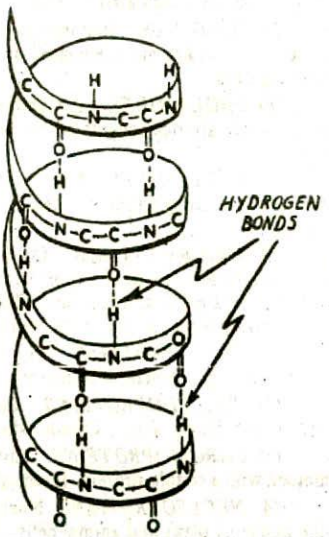


Fig. 33·4. Representation of an α-helix. Only the amino acids in the front portion are shown. The carbons holding the H and R groups are shown as C. The H and R groups are not shown for simplicity. Notice the hydrogen bonds between N—H and C=O groups.

(3) **Tertiary Structure.** An α-helix may be considered to be a piece of a rope which is free to bend, twist, and fold. The tertiary structure of a protein refers to the final three-dimensional shape that results from the twisting, bending, and folding of the protein helix.

(4) **Quaternary Structure.** Complex proteins are often formed from two or more amino acid chains rather than a single amino acid chain. Each chain is a complete protein with a characteristic primary, secondary, and tertiary structure. The quaternary structure refers to the way in which these amino acid chains of a complex protein are associated with each other.

PROPERTIES OF PROTEINS

Some of the general properties and reactions of proteins are described below.

(1) Most proteins are colourless amorphous substances with no definite melting points or boiling points. On heating they undergo decomposition. They are amphoteric in nature and, like amino acids, exist as *Dipolar ions* or *Zwitter ions*. Most proteins are laevorotatory.

(2) **Colloidal Nature.** Proteins form colloidal dispersions in water. Protein, being colloidal, will pass through a filter paper but not through a membrane. The inability of the protein to pass through a membrane is of great importance in the body. Proteins present in the bloodstream cannot pass through the cell membranes and should remain in the bloodstream. Since proteins cannot pass through membranes, there should be no protein material present in the urine. The presence of protein in the urine indicates damage to the membranes in the kidneys.

(3) **Isoelectric Point.** Proteins have isoelectric points in the same way as do amino acids. This is because of the presence on the protein chain of additional acidic or basic groups that are not involved in peptide linkages. The isoelectric points of some proteins are given in Table 32·4.

Table 32·4. Isoelectric Points of Some Proteins

Protein	*Isoelectric Point*
Casein	4·60
Gelatin	4·80 — 4·85
Serum albumin	4·88
Insulin	5·30 — 5·35
Serum globulin	5·50
Haemoglobin	6·79 — 6·83

Most proteins show minimum solubility and stability at their isoelectric points.

(4) **Precipitation.** Proteins are easily precipitated (or coagulated) by certain agents. Many of the normal functions in the body are essentially precipitation reactions ; for example, the clotting of blood or the precipitation of casein during digestion. Since animal tissues are chiefly protein in nature, reagents that precipitate protein will have a marked toxic effect if introduced into the body. Bacteria, which are mainly protein, are effectively destroyed when treated with suitable precipitants. Many of the common poisons and disinfectants act in this way. Precipitation of proteins is an irreversible change and the precipitated protein is said to be **Denatured.** Some of the common methods of protein precipitation are described below

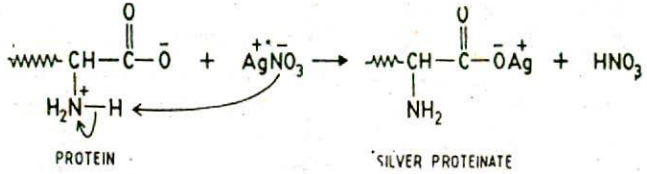
(*a*) *BY HEAT.* Heat coagulates almost all protein solutions. Egg-white, a substance containing a high percentage of protein, coagulates on heating. Heat coagulates and destroys protein present in bacteria. Hence sterilization of instruments and clothing for use in operating rooms of hospitals requires the use of high heats. Routine examinations of urine specimens for protein are made by heating the urine in a test tube to coagulate any protein that might be present.

(*b*) *BY ALCOHOL.* Alcohol coagulates all types of protein except prolamines. A 70 per cent solution of ethanol is used as a disinfectant because of its ability to coagulate the protein present in bacteria.

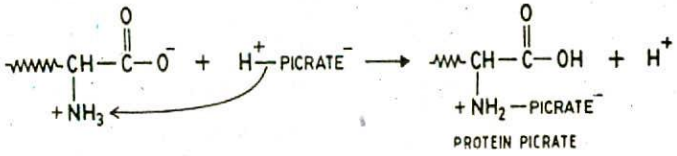
(c) *BY CONCENTRATED INORGANIC ACIDS.* Proteins are precipitated from their solutions by acids such as hydrochloric, sulphuric, and nitric acids. This forms the basis of **Heller's Ring Test** which is used to detect the presence of albumin in urine. Concentrated nitric acid is added slowly down the sides of a test tube containing the urine sample. If albumin is present, it will precipitate out as a white ring at the interface of the two liquids.

(d) *BY SALTS OF HEAVY METALS.* Heavy metal salts such as mercuric chloride or silver nitrate coagulate proteins. They are very poisonous if taken internally because they coagulate and destroy protein present in the body. The antidote for the mercuric chloride or silver nitrate, when these poisons are taken internally, is egg-white. The heavy metal salts react with the egg-white and precipitate out. The precipitates thus formed must be removed from the stomach by an emetic or else the stomach will digest the egg-white and return the poisonous material to the system.

Dilute silver nitrate solution is used as a disinfectant in the eyes of newborn infants. Strong solutions of silver nitrate are used to causterize fissures and destroy excessive granulation of tissues. The reaction of a protein with silver nitrate may be illustrated as follows.



(e) *BY ALKALOIDAL REAGENTS.* Alkaloidal reagents such as tannic acid and picric acid precipitate proteins from solutions. The reaction of a protein with picric acid may be illustrated as follows.



Tannic acid has been used extensively in the treatment of burns. When this substance is applied to a burn area, it causes the protein to precipitate as a tough covering, thus reducing the amount of water loss from the area. It also reduces exposure to air.

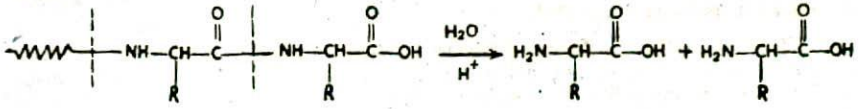
Newer drugs have taken the place of tannic acid for burns, but an old-fashioned remedy still in use for emergencies involves the use of strong tea (which contains tannic acid).

(f) *BY SALTING OUT.* Most proteins are insoluble in concentrated salt solutions and precipitate out unchanged. To separate a protein from a mixture of other substances, the mixture is placed in a concentrated salt solution. The protein precipitates out and is removed by filtration. The protein is then purified from the remaining salt solution by the process of dialysis. Dialysis is the separation of solution particles from colloidal particles by means of a membrane.

(g) *BY RADIATION.* Ultraviolet light or X-rays cause precipitation of proteins. The radiations provide kinetic energy to cause excessive vibration of atoms in protein molecules. As a result, hydrogen bonds and salt linkages are broken and coagulation occurs. Thus ultraviolet radiation destroys bacteria by denaturing some of their vital enzymes.

(5) **Hydrolysis.** Proteins can be hydrolysed by acids (HCl and H_2SO_4), alkalis (NaOH), or enzymes (*proteases*). The final products of hydrolysis are the amino acids, together with the prosthetic groups from any conjugated proteins present. Hydrolysis by alkalis causes racemisation of the optically active amino acids, whereas hydrolysis by acids does not. Hydrolysis by

enzymes is slow and often incomplete but does not cause racemisation or decomposition of the sensitive amino acids.



(6) **Oxidation.** Proteins are oxidised on burning and putrefaction. The products include nitrogen, amines, carbon dioxide and water. The bad smell produced during putrefaction of dead animals is largely due to the formation of amines and other nitrogen products by the bacterial oxidation of body proteins.

COLOUR TESTS FOR PROTEINS

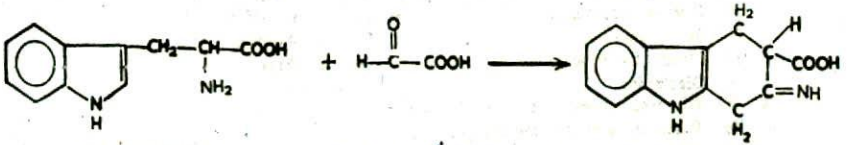
Proteins exhibit characteristic colour reactions when treated with certain reagents. Some of these reactions depend upon the presence of particular amino acids in the protein. Others are due to the peptide linkages between the amino acids. It may thus be necessary to try several tests before deciding whether a subtance is a protein or not.

(1) **Xanthoproteic Test.** When a protein is treated with concentrated nitric acid, a yellow colour is produced. The colour is turned to orange if the solution is made basic. Any one who has spilled nitric acid on his hands will recall the yellow colour produced by the reaction of the nitric acid with the protein of the skin. This test is given by a protein that consists of amino acids containing a benzene ring, such as *tyrosine* or *phenylalanine*.

(2) **Biuret Test.** When a protein is treated with a small amount of sodium hydroxide solution and a dilute solution of cupric sulphate is added drop by drop, a violet colour is produced. This test is given by all substances that contain two or more peptide linkages, that is, such substances as proteins or polypeptides. The colour is due to the formation of a coordination complex between Cu^{2+} and >C=O and —NH— groups of the peptide linkages. The biuret test is negative for amino acids, which do not contain a peptide linkage, or for dipeptides which contain only one peptide linkage.

(3) **Millon's Test.** Millon's reagent consists of mercury dissolved in nitric acid (forming, a mixture of mercuric and mercurous nitrates). When Million's reagent is added to a protein, a white precipitate forms. This white precipitate on heating turns to a brick-red colour This test is given by those proteins which yield *tyrosine* on hydrolysis.

(4) **Hopkins-Cole Test.** To a mixture of protein and a glyoxalic acid solution, concentrated sulphuric acid is added carefully down the sides of the test tube to form a layer. If tryptophan is present in the protein, a violet ring will appear between the two layers.



(5) **Sulphur Test.** When a sulphur-containing protein is heated with a mixture of sodium hydroxide and lead acetate solutions, a black precipitate of lead sulphide is formed.

(6) **Ninhydrin Test.** When proteins are boiled with a dilute aqueous solution of ninhydrin, a purple colour is produced. This test is given by α-amino acids, proteins, and dipeptides.

ISOLATION AND PURIFICATION OF PROTEINS

Most proteins occur as mixtures with other proteins. Their separation is difficult because proteins have similar properties. Column chromatography is commonly used to separate protein mixtures. Sometimes careful control of the pH of a solution of proteins also results in one being precipitated.

It is also difficult to determine whether a protein is pure or not. This is because most proteins do not have sharp melting points and decompose on heating. The most common method of testing the purity of a protein is by the use of *ultracentrifuge*. In this method, the protein is spun at a very high speed. Due to centrifugal force, the protein moves to the outer end of the spinning cell at a rate which depends upon its size. A special optical system enables the solution to be photographed during this process and reveals the moving protein. If impurities of different molecular weights are present, they will travel at different rates and consequently can be detected in the resulting photographs.

DETERMINATION OF PROTEINS

It is often desirable to know the protein content of various foods and biological material. The analysis of the protein content of such a material is based on its nitrogen content. Since the average nitrogen content of proteins is 16 per cent, the protein content of a substance may be obtained by multiplying its nitrogen value by the factor $100/16 = 6{\cdot}25$. For example, if a certain food contains 2 per cent nitrogen, on analysis its protein content would equal 2 times 6·25, or 12·5 per cent.

The total nitrogen content of proteins and peptides may be determined by the *Dumas method* or the *Kjeldahl method*. The aromatic amino acids in proteins absorb ultraviolet light at a wavelength of 2800 Å. The measurement of light absorption at 2800 Å is a convenient method for determining the amount of protein in solution.

INDUSTRIAL IMPORTANCE OF PROTEINS

Industrially, proteins have great importance. We are familiar with the use of leather made by tanning of hides. This is essentially a precipitation of the protein by tannic acid. Gelatin is obtained by heating bones, skin, and tendons in water. Gelatin is used in desserts, salads, candies, bakery goods, etc. Wool and silk are also protein materials.

Casein is another protein that has been used industrially for a long time. Casein plastics are used in the manufacture of buttons and buckles. Casein is also used in sizing of paper and in making casein glues, cosmetics, hard rubber, insecticide sprays, linoleum, paint, plywood, safety glass, and veneer. Casein forms the basis of artificial wool fibre known as *Lanital*.

The proteins of soyabeans are used in the manufacture of plastics and can be converted into filaments which may be spun and dyed.

QUESTIONS

1. What is meant by each of the following terms ? Where possible, illustrate each with a structure.
   (*a*) α-Amino acid
   (*b*) Essential amino acid
   (*c*) Basic amino acid
   (*d*) Neutral amino acid
   (*e*) Dipolar ion
   (*f*) Isoelectric point
   (*g*) N-Terminal residue
   (*h*) C-Terminal residue
   (*i*) Peptide linkage
   (*j*) Denaturation.
2. (*a*) Why α-amino acids (except glycine) are optically active ?
   (*b*) What are essential amino acids ?
   (*c*) Why are amino acids amphoteric ?
   (*d*) What is meant by the term *isoelectric point* in relation to amino acids ?
3. Write equations for the reaction of *glycine* or *alanine* with :
   (*a*) NaOH *aq.*
   (*b*) HCl *aq.*
   (*c*) C_2H_5OH, H^+, *heat*
   (*d*) HNO_2
   (*e*) Heat at 200°C
   (*f*) Formaldehyde
   (*g*) Ninhydrin
   (*h*) Benzyl chloroformate.

4. What are polypeptides ? Write series of equations to show how the peptide glycylalanine (*Gly-Ala*) can be synthesised from glycine and alanine. How would you determine the sequence of amino acids in peptides or proteins ?

5. (*a*) How are proteins classified ?
   (*b*) What percentage of protein is usually nitrogen ? What use is made of this fact ?
   (*c*) Describe at least three ways to coagulate a protein solution.
   (*d*) Describe two colour tests for proteins.

6. (*a*) When proteins are hydrolysed, what products are obtained ?
   (*b*) Why should protein not normally be found in urine ?
   (*c*) What is the antidote of $HgCl_2$ poisoning ? Why must the stomach be pumped afterwards ?
   (*d*) What is meant by the term *salting out* of a protein ?
   (*e*) What use is made of the fact that heat coagulates protein ?
   (*f*) What happens to the solubility of a protein at its isoelectric point ?

7. What are the principal properties of proteins ? How would you identify the given material as being a protein ?

8. Write short notes on the following:
   (*a*) Simple proteins ;
   (*b*) Conjugated proteins ;
   (*c*) End-group analysis ;
   (*d*) Primary structure of proteins ;
   (*e*) Secondary structure of proteins.

9. A person has a job that involves working with sodium hydroxide solutions. From standpoint of durability, would he be better off wearing cotton garments or silk garments ? Explain.

10. (*a*) What is the importance of amino acids to life ?
    (*b*) Give two general methods for the synthesis of α-amino acids.
    (*c*) Formulate the reaction of alanine with the following reagents:
    (*i*) ethanol; (*ii*) acetic anhydride; (*iii*) conc H_2SO_4; (*iv*) aq NaOH.
    (*Andhra BSc III, 1980*)

11. Give a brief account of general idea of the structure of proteins. (*Udaipur BSc III, 1980*)

12. (*a*) Briefly indicate how you could arrive at the primary structure of a protein.
    (*b*) Give a brief account of the secondary structure in peptides. (*Banaras BSc III, 1980*)

13. Why amino acids are weaker acids than the corresponding unsubstituted acids ? Explain the following with reference to amino acids and proteins:
    (*a*) Isoelectric point (*b*) Zwitter ion (*c*) Peptide linkage.
    (*Guru Nanak Dev BSc III, 1980*)

14. Write the structures of all the possible dipeptides obtainable from glycine and alanine.
    (*Kerala BSc II, 1980*)

15. How are proteins classified ? (*Bangalore BSc III, 1980*)

16. What are amino acids ? What is their importance ? Give formulae and names of any two amino acids. State the general methods for the preparation of amino acids. (*Panjab BSc III, 1981*)

17. Write notes on: (*i*) Zwitter ion (*ii*) Isoelectric point of amino acids. (*Annamalai BSc, 1980*)

18. What is peptide linkage ? How does it form a chain of protein ? Discuss the important characteristics of proteins. (*Maharishi Dayanand BSc III, 1980*)

19. Give the methods of preparation and properties of α-amino acids. How are they related to proteins ? (*Bundelkand BSc, 1981*)

20. (*a*) Outline the Strecker Synthesis for:
    (*i*) Phenylalanine (*ii*) Valine
    (*b*) Define the term 'Isoelectric Point' of an amino acid.
    (*c*) Indicate the name and structure of the organic reagent that is used to detect the presence of an amino acid in a given sample. (*Panjab BSc III, 198.*)

21. What are proteins ? Give three colour reactions of proteins. Explain what is meant by peptide linkage. (*Mysore BSc III, 1981*)

22. How can you distinguish between α, β and γ-amino acids ? (*Meerut BSc II, 1981*)

23. (*a*) What are amino acids ? Give two examples.
    (*b*) Give the methods of preparation of glycine.
    (*c*) What is the action of heat on glycine ? (*Saugar BSc II, 1981*)

24. (*a*) What do you understand by isoelectric point of amino acids ?

(*b*) Explain how peptides are formed from amino acids ?
(*c*) Give the dipolar-ion structure of α-aminopropionic acid. (*Punjabi BSc III, 1981*)

25. (*a*) What are α-amino acids ? How are proteins formed from them.
(*b*) Write short notes on: (*i*) Zwitter ion; (*ii*) Basicity of amines. (*Guru Nanak Dev BSc, 1981*)

26. Illustrate with equations, the Stracker Synthesis of alpha-amino acids. (*Kerala BSc III, 1982*)

27. Give action of heat on α, β, Υ-amino acids. (*Himachal BSc III, 1982*)

28. What are essential amino acids ? Name two of them and write their structures. (*Delhi BSc, 1982*)

29. (*a*) Explain how peptides are formed from amino acids.
(*b*) Explain clearly what you understand by isoelectric point of amino acids. (*Punjabi BSc III, 1982*)

30. Give any two methods of preparation of α-amino acids. (*Mysore BSc III, 1982*)

31. What is meant by denaturation of proteins ? Explain the term isoelectric point as applied to an amino acid. (*Poona BSc, 1994*)

32. How are proteins classified ? (*Patna BSc, 1993*)

33. How are polypeptides synthesised ? Explain giving necessary reactions, methods for determination of sequence of amino acids in polypeptides. (*Saugar BSc, 1994*)

34. Write a note on : Strecker's synthesis of amino acids. (*Madurai BSc, 1993*)

35. Write a note on : Isoelectric point of amino acids. (*Kakatiya BSc, 1993; Anna BSc, 1994*)

36. What are α-amino acids ? Give their synthesis and important properties. (*Madras BSc, 1994*)

37. What are proteins ? How are they classified ? Describe their general properties, tests, and uses. (*Devi Ahilya BSc, 1993*)

38. (*a*) Describe any four general properties of proteins.
(*b*) What is a peptide bond ?
(*c*) How is alanine prepared ? (*Nagpur BSc, 1994*)

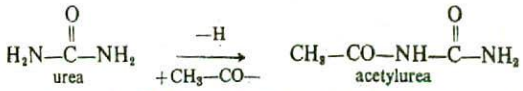
39. (*a*) Give three important general methods for the synthesis of amino acids.
(*b*) Give a brief account of the classification of proteins.
(*c*) What happens when amino acids are reacted with ninhydrin and nitrous acid ? (*North Bengal BSc Hons, 1993*)

Chapter **33A**

Ureides and Purines

A. THE UREIDES

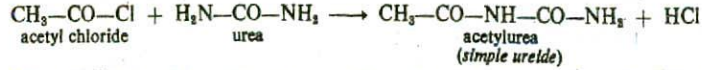
Acyl derivatives of urea are called **Ureides** *e.g.*. acetylurea,

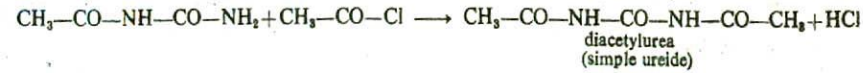


The ureides are classified as : (*a*) *Simple Ureides* or *Open-Chain Ureides* ; and *Cyclic Ureides*.

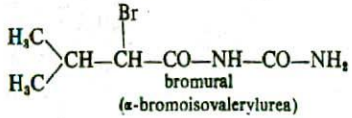
SIMPLE UREIDES

They may be prepared by the action of acyl chlorides or acid anhydrides of monocarboxylic acids on urea. Thus,



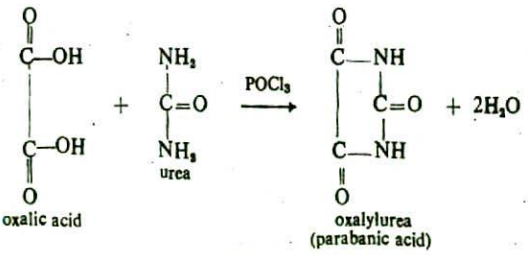


The simple ureides resemble the amides ($R-CO-NH_2$) in properties. Many of these simple ureides are useful drugs *e.g.*, *bromural*.

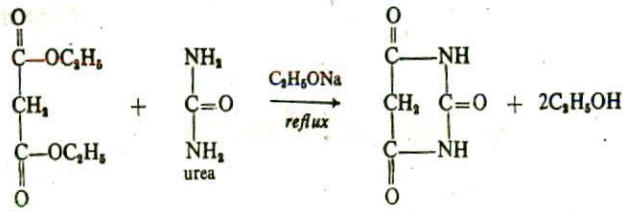


CYCLIC UREIDES

They may be prepared by the action of dicarboxylic acids on urea in the presence of phosphoryl chloride *e.g.*, oxalic acid forms parabanic acid (*oxalylurea*).



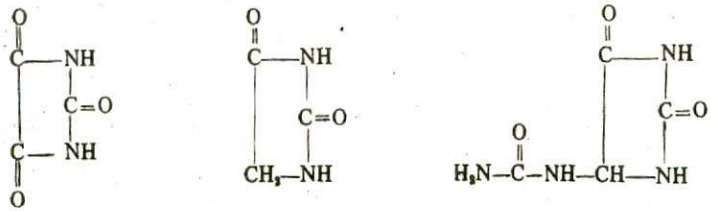
The cyclic ureides may also be obtained by refluxing a di-ester with urea in ethanolic solution containing sodium ethoxide *e.g.*, malonic acid forms *barbituric acid* (malonylurea).



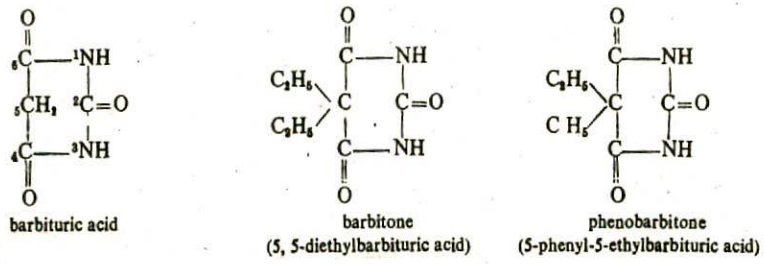
TYPES OF CYCLIC UREIDES

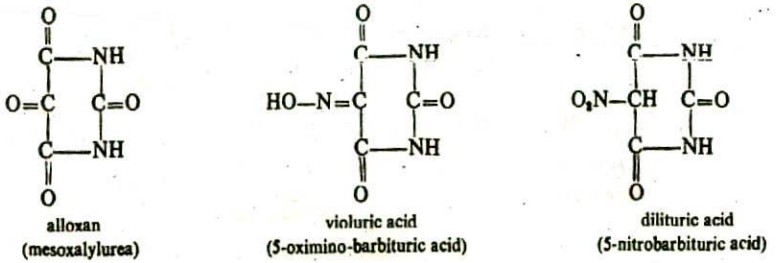
There are two types of cyclic ureides known :

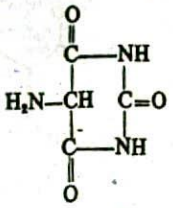
(1) **Five-membered Cyclic Ureides.** These include :



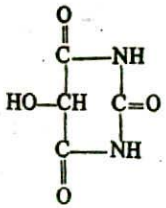
(2) **Six-membered Cyclic Ureides.** These include :



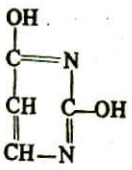




uramil
(5-amino-barbituric acid)



dialuric acid
(5-hydroxybarbituric acid)



uracil
(2, 6-dihydroxy-pyrimidine

Ureides are beautifully crystalline compounds. They are hydrolysed by alkalis to form the parent acid and urea. The cyclic ureides are acidic owing to enolisation and hence they form metallic salts. Many of them are excellent drugs.

B. THE PURINES

Uric acid and other closely related compounds such as caffeine, adenine, guanine, xanthine, hypoxanthine form a group of complex cyclic ureides. They are all derived from the same parent substance 'Purine' and are, therefore, named as **Purines**. Purines may be thought of as cyclic diureides since they could be considered as built from two molecules of urea and one of a dicarboxylic acid.

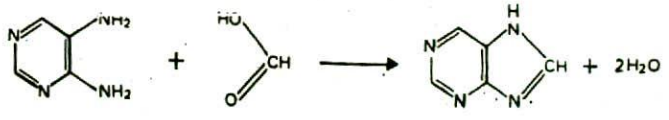
PURINE

The parent substance of the class of compounds known as purines, is a tautomeric form of the following two structures.

Purine is a colourless solid, mp 216—217°C. It is highly soluble in water and has both acidic and basic properties. For the purpose of naming its derivatives, the skeleton of purine is numbered as shown above.

Synthesis. Purine does not occur in nature. It can be synthesised by the following methods.

(1) *Albert and Brown* (1954) :

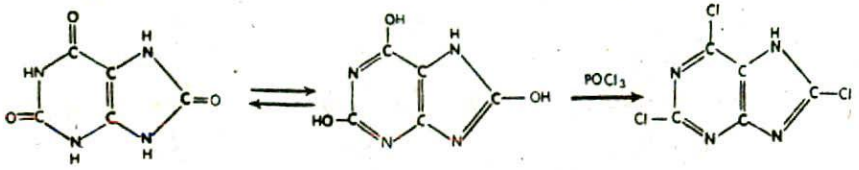


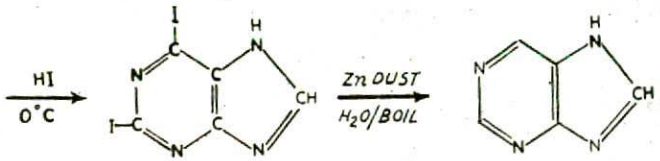
4,5-Diamino-pyrimidine

Formic acid

Purine

(2) *From uric acid* :

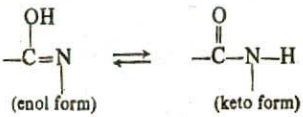




CLASSIFICATION OF PURINES

The natural purines are either the hydroxy or the amino derivatives of the parent substance purine. Thus they can be divided into t o types.

(1) **Oxypurines**. These are the hydroxy derivatives of purine, and are so named since they can exhibit keto-enol tautomerism.

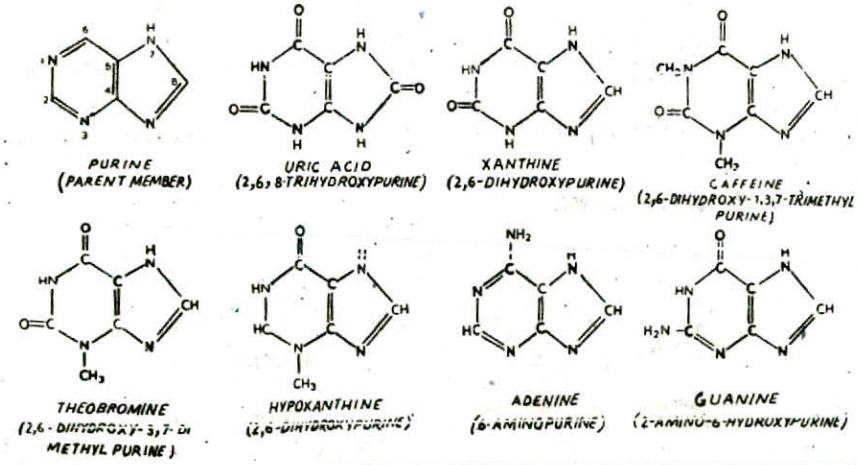


Examples of oxypurines are uric acid, xanthine and its bases (caffeine, theobromine) and hypoxanthine.

(2) **Aminopurines**. These are the amino derivatives of purine *e.g.*, adenine, guanine.

Table. PURINE AND ITS DERIVATIVES

(Derived names indicating relationship with the parent member, purine, are given in brackets)



Uric acid and caffeine are by far the most important of the purines, and will be discussed in detail.

URIC ACID, *2, 6, 8-Trihydroxypurine*

It is so named as it was first isolated by Scheel and Bergmann (1776) from human urine. It is produced in the body of man by the degradation of certain proteins. Normally only traces of it are present in the blood, and small quantities are excreted in urine. Owing to its small solubility, any temporary excess of uric acid in the blood deposits in the joints (*gout*) or in the tissues (*rheumatism*). It may sometimes accumulate in the bladder or kidneys, forming stones.

Uric acid is the chief constituent of the excreta of birds and reptiles. 'Guano' which is the excreta of certain sea birds, is an excellent source of uric acid.

Preparation. Uric acid may be obtained from human urine or *Guano* in which it is present mostly as ammonium salt.

(1) FROM HUMAN URINE. Uric acid may be isolated from human urine by concentrating it and adding concentrated hydrochloric acid. The crystals of uric acid separate out on cooling.

$$\text{Human Urine} \xrightarrow[2.\ Cool]{1.\ Concentrate/HCl} \text{Uric acid Crystals}$$

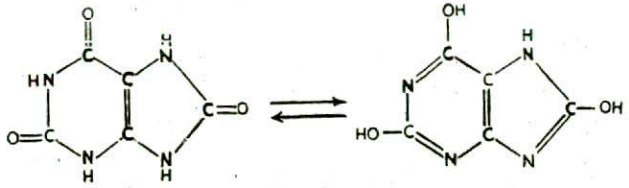
(2) FROM GUANO. Uric acid is prepared on a large scale from the excrement of birds and snakes (*guano*). The dry excrement is powdered and boiled with sodium hydroxide solution, until the evolution of ammonia ceases. The hot solution of sodium urate thus obtained is then filtered and poured into hydrochloric acid.

$$\text{Ammonium Urate} \xrightarrow[(-NH_3)]{NaOH} \text{Sodium Urate} \xrightarrow[Cool]{HCl} \underset{(crystals)}{\text{Uric Acid}} + NaCl$$

The uric acid separates as a fine crystalline mass on allowing the solution to stand in cold. It is filtered and dried in air.

Properties (*Physical*). Uric acid is a white crystalline solid having no taste or smell. It decomposes when heated, so that it has no melting point. It is very slightly soluble in water, insoluble in ethanol or water, but soluble in glycerol, hot alkali, etc.

(*Chemical*). Uric acid behaves as a weak tribasic acid due to enolisation.

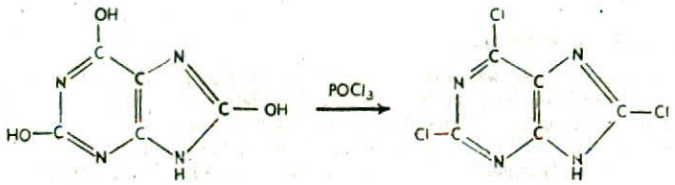


KETONIC FORM

ENOLIC FORM
(2,6,8-TRIHYDROXYPURINE)

With sodium carbonate, it gives an acid salt, while with sodium hydroxide a normal salt is produced. The acid salts are sparingly soluble in water while normal salts are moderately soluble in water. Lithium salts are freely soluble. That is why 'lithiated water' is often used as a remedy in cases of rheumatism and gout to secure the elimination of uric acid.

It reacts with phosphorus oxychloride to form 2, 6, 8-trichloropurine, indicating thereby the existence of a trienolic form of uric acid.



URIC ACID (TRIENOLIC FORM) 2,6,8-TRICHLOROPURINE

Constitution of Uric Acid

(1) Molecular formula of uric acid as deduced from its analytical data and molecular weight determination is $C_5H_4N_4O_3$.

(2) **Presence of four imino groups** (>NH). On exhaustive methylation, uric acid gives tetramethyluric acid in which all the four hydrogen atoms of uric acid have been replaced by methyl groups. When subjected to hydrolysis with dilute hydrochloric acid, tetramethyluric acid loses all the four nitrogen atoms as methylamine, It indicates that in tetramethyluric acid all the methyl groups are directly linked to nitrogen atoms. Therefore, it stands to reason that all the four hydrogen atoms of uric acid molecule must be attached to nitrogen atoms.

$$\underset{\text{uric acid}}{C_5O_3(N{-}H)_4} \xrightarrow[\text{methylation}]{\text{exhaustive}} \underset{\text{tetramethyluric acid}}{C_5O_3(N{-}CH_3)_4} \xrightarrow[\text{dil HCl}]{H_2O} \underset{\text{methylamine}}{4\,CH_3{-}NH_2} + \ldots$$

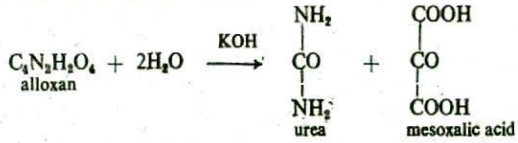
This shows that uric acid contains four imino groups (−NH−).

(3) **Presence of Alloxan and Urea units.** On oxidation with dilute nitric acid, uric acid forms alloxan and urea in equimolecular proportions.

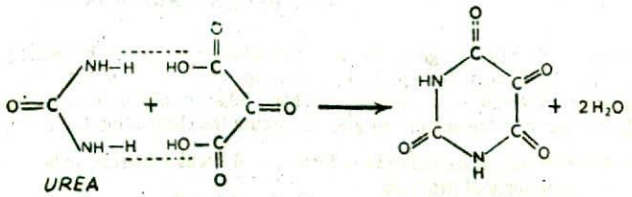
$$\underset{\text{uric acid}}{C_5H_4N_4O_3} + H_2O + [O] \xrightarrow{HNO_3} \underset{\text{alloxan}}{C_4N_2H_2O_4} + \underset{\text{urea}}{NH_2{-}CO{-}NH_2}$$

Since urea is a known compound, the structure of uric acid rests on the elucidation of that of alloxan.

(4) **Structure of Alloxan.** When hydrolysed with alkali, alloxan produces one molecule of urea and one molecule of mesoxalic acid.



Since alloxan contains no free amino group or carboxyl group, the products of hydrolysis suggest that alloxan is mesoxalyl urea. The structure of alloxan has been confirmed by its synthesis (Liebig and Wohler, 1838).



UREA MESOXALIC ACID ALLOXAN

The formation of alloxan from uric acid suggests that the latter contains a six-membered ring.

(5) **Presence of Allantoin unit.** On oxidation with an aqueous suspension of lead dioxide or alkaline potassium permanganate, uric acid forms allantoin and carbon dioxide.

$$\underset{\text{uric acid}}{C_5H_4N_4O_3} + H_2O + [O] \xrightarrow[\bar{O}H]{KMnO_4} \underset{\text{allantoin}}{C_4H_6N_4O_3} + CO_2$$

(6) **Structure of Allantoin.** (*i*) When hydrolysed with alkali, allantoin forms two molecules of urea and one molecule of glyoxylic acid.

$$\underset{\text{allantoin}}{C_4H_6N_4O_3} + 2H_2O \xrightarrow{\bar{O}H} 2\,\underset{\text{urea}}{NH_2—CO—NH_2} + \underset{\text{glyoxylic acid}}{OHC—COOH}$$

The formation of these hydrolytic products suggests that allantoin is the diureide of glyoxylic acid.

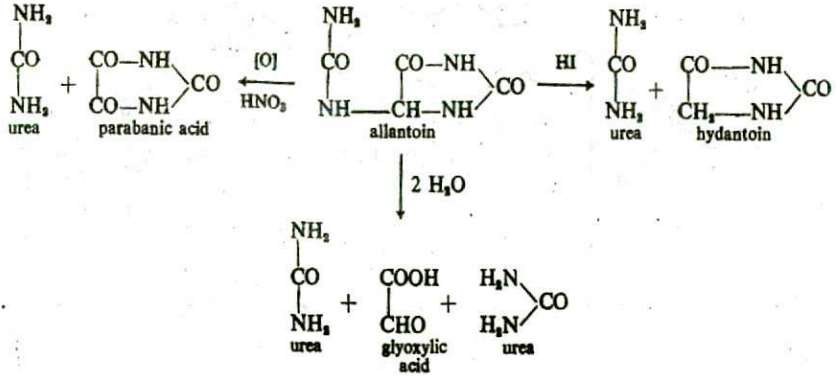
(*ii*) On oxidation with nitric acid, allantoin forms urea and parabanic acid in equimolecular proportions.

$$\underset{\text{allantoin}}{C_4H_6N_4O_3} + [O] \xrightarrow{HNO_2} \underset{\text{urea}}{NH_2—CO—NH_2} + \underset{\text{parabanic acid}}{C_3H_2N_2O_3}$$

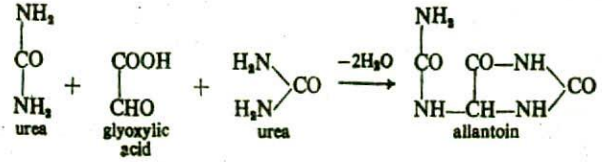
(*iii*) When reduced with concentrated hydriodic acid at 100°C, allantoin produces urea and hydantoin.

$$\underset{\text{allantoin}}{C_4H_6N_4O_3} + 2[H] \xrightarrow{HI} \underset{\text{urea}}{NH_2—CO—NH_2} + \underset{\text{hydantoin}}{C_3H_4N_2O_3}$$

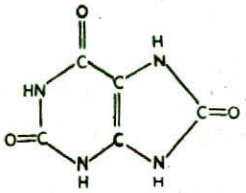
The reactions of allantoin stated above can, therefore, be formulated as follows :



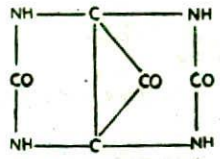
(*iv*) The structure of allantoin has been confirmed by its synthesis, by heating urea with glyoxylic acid.



(7) **How Structure of Uric acid was arrived at ?** In the formation of allantoin from uric acid (step 5) by oxidation, one carbon atom is lost from the latter as carbon dioxide. The problem, then is to fit one carbon atom into the allantoin structure so as to construct the uric acid molecule. Also, the structure of uric acid so constructed, must give alloxan on oxidation with nitric acid (step 3). In view of the above facts, two structures were proposed for uric acid ; one by Medicus (1875) and the other by Fitting (1878). Both these structures agreed with the facts known upto that time. Medicus formula was found to be correct by Fischer's work.

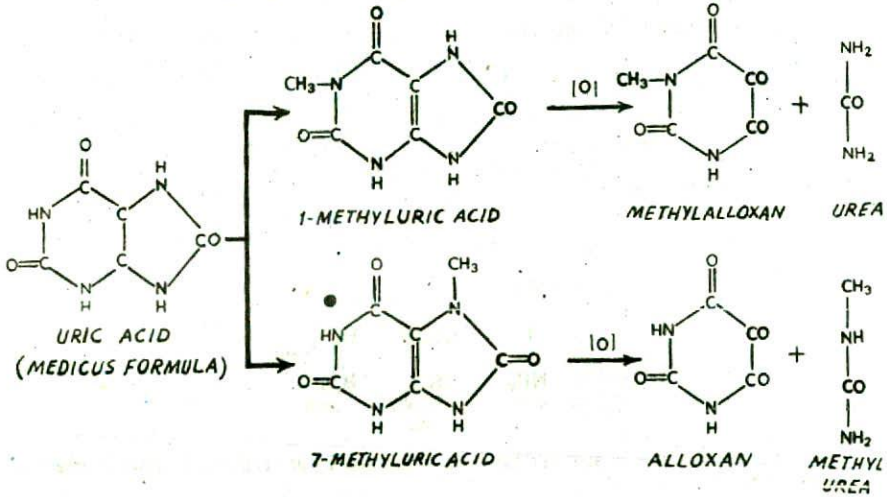


MEDICUS FORMULA (1875)



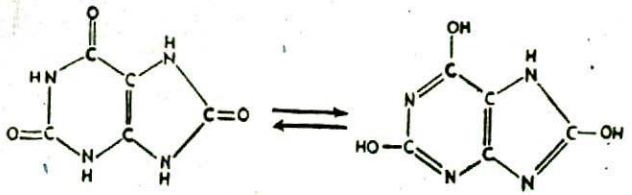
FITTIG FORMULA (1878)

Fischer (1884) prepared two isomeric monomethyluric acids. One of these gave methylalloxan and urea on oxidation with nitric acid, and the other gave alloxan and methylurea. Fittig's formula, which is symmetrical, can form only one monomethyluric acid and hence this structure is untenable. On the other hand, the Medicus formula satisfies the existence of two isomeric monomethyl derivatives.



Moreover, [the] Medicus formula [explains the] existence of four monomethyl, six dimethyl and four trimethyl derivatives. All of these have been prepared by Fischer, thus giving powerful support to the Medicus formula.

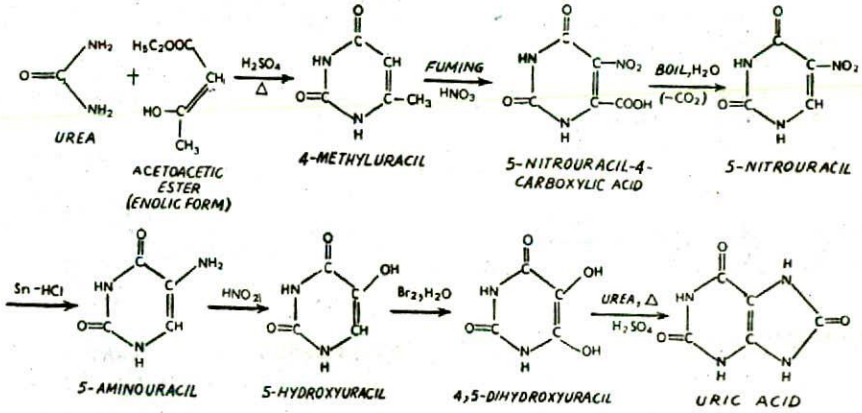
(8) **Tautomeric Structure.** As already mentioned, uric acid reacts with phosphoryl chloride to form a trichloro derivative, This shows the presence of three hydroxy groups in the molecule. To explain the presence of three hydroxy groups and the acidic character, uric acid is supposed to have a tautomeric structure.



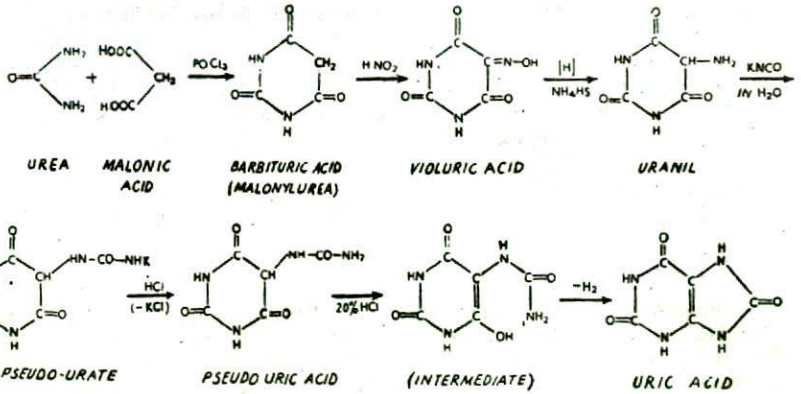
It has been established by examination of the infrared spectrum that uric acid exhibits keto-enol tautomerism, and that the keto form predominates in the equilibrium mixture.

(9) **Synthetic Evidence.** The structure of uric acid has been confirmed by its synthesis accomplished by various workers.

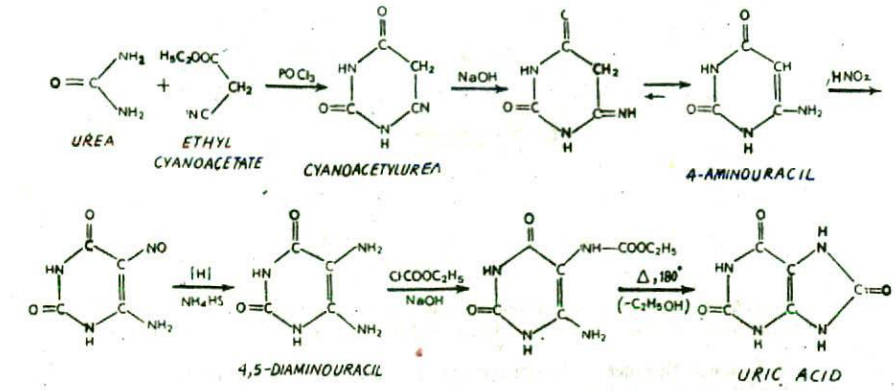
(*i*) *Behrend and Roosen's Synthesis* (1888)



(*ii*) *Fischer's Synthesis* (1895)



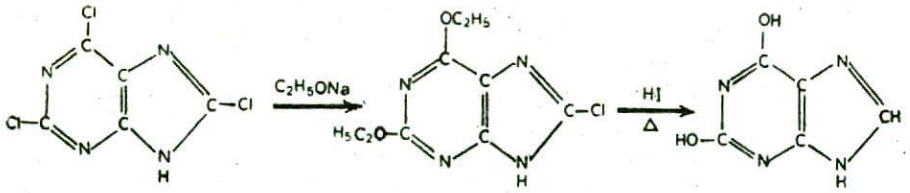
(*iii*) *Traube's Synthesis* (1900). It is the most important method as it can be used to prepare any purine derivative The starting materials are urea and ethyl cyanoacetate.



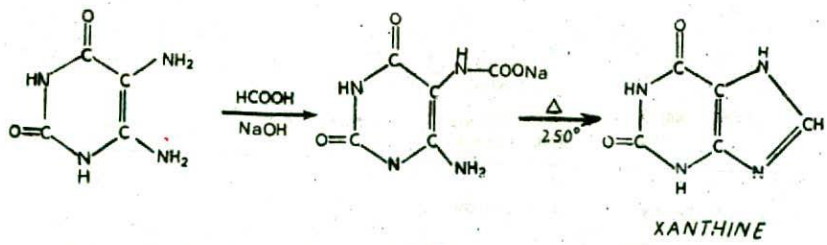
XANTHINE, *2,6-Dihydroxypurine*

This important purine derivative is present in the blood and is excreted in urine. It also occurs in tea extract and sprouting seedlings. It is the parent compound of three important bases, caffeine, theobromine and theophylline.

Preparation. (1) Xanthine may be prepared from 2, 6, 8-trichloropurine obtained by the action of $POCl_3$ on uric acid.

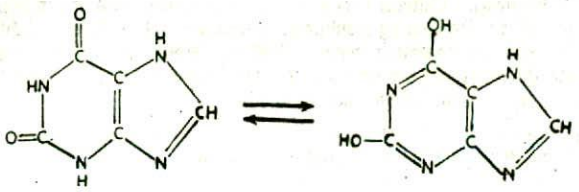


(2) It may also be synthesised by a method analogous to that of Traube for uric acid. 4, 5-diaminouracil as obtained in uric acid synthesis is treated with formic acid and sodium hydroxide. The sodium salt thus produced is heated at 250° to give Xanthine.



Properties. Xanthine crytallises well. It is very sparingly soluble in water. Chemically it resembles uric acid and forms salts with alkalis, and also with hydrocloric acid and nitric acid. When oxidised with potassium chlorate in hydrochloric acid solution, xanthine forms alloxan and urea.

Like other hydroxy derivatives of purine, xanthine exhibits tautomerism.



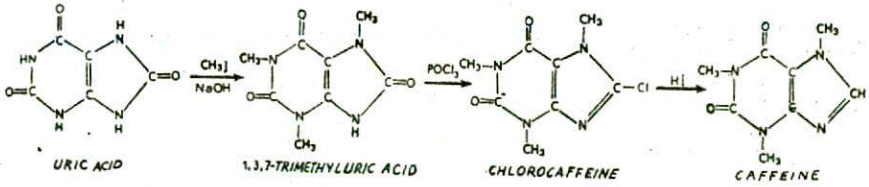
KETO FORM ENOL FORM

CAFFEINE, *2, 6-Dihydroxy-1, 3, 7-Trimethylpurine; 1, 3, 7-Trimethylxanthine.*

It is the component of tea and coffee responsible for the stimulating action of these beverages on the nerves and heart. It occurs in dried tea leaves to the eaxtent of 5 per cent, and in coffee up to 1—2 per cent. It is also called **Theine.**

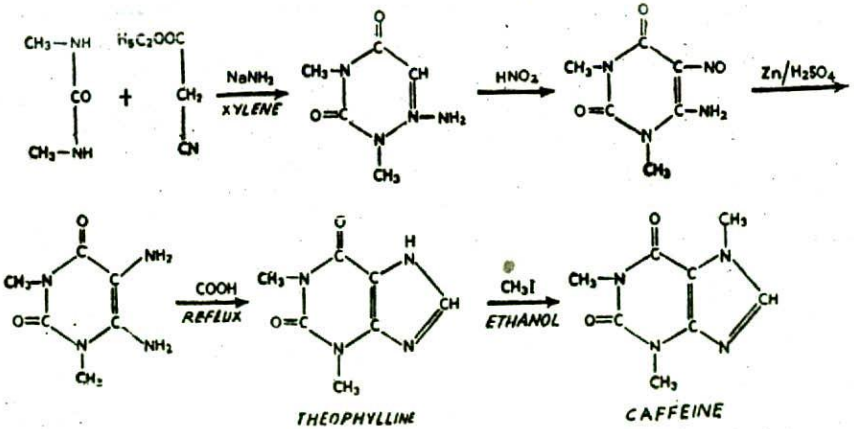
Preparation. (1) FROM TEA LEAVES. Caffeine is extracted from tea leaves. These are boiled with water and filtered. The filtrate contains caffeine along with proteins and tannins. It is treated with basic lead acetate when proteins and tannins are precipitated. The precipitate is filtered off and the solution is treated with sulphuric acid to remove any excess of lead as insoluble lead sulphate. The resulting solution is decolourised with animal charcoal and caffeine extracted from it with chloroform is distilled off. The residue of caffeine is recrytallised from water.

(2) SYNTHESIS FROM URIC ACID. Uric acid is produced commercially from uric acid by a synthetic method given by Fisher in 1899. Uric acid is treated with methyl iodide in alkaline solution to from 1,3,7-trimethyluric acid. This on heating with $POCl_3$ gives chlorocaffeine which on reduction with hydrogen iodide yields caffeine.



URIC ACID 1,3,7-TRIMETHYLURIC ACID CHLOROCAFFEINE CAFFEINE

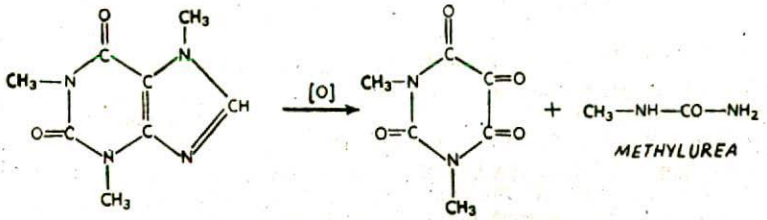
(3) TRAUBE'S SYNTHETIC METHOD. Caffeine is produced on large scale by a synthetic procedure stated below.



THEOPHYLLINE CAFFEINE

Properties. (*Physical*). Caffeine crystallises in silky needles with one molecule of water of crystallisation, mp 236°C. On heating it sublimes unchanged. It is fairly soluble in chloroform and ethanol but sparingly soluble in water and ether. When administered orally, caffeine and its salts stimulate the heart and the nerves. We take caffeine when we drink tea or coffee. This is why these beverages relieve fatigue and quicken brain.

(*Chemical*). Caffeine is a weak base with bitter taste and forms salts with strong acids. On oxidation with potassium chlorate in hydrochloric acid, it gives dimethylalloxan and methylurea.



CAFFEINE DIMETHYLALLOXAN METHYLUREA

QUESTIONS

1. What are Ureides ? Give examples.
2. How are ureides classified ? Give the structural formula and name of one member of each class.
3. What are Cyclic ureides ? Write the structures of : parabanic acid, hydantoin, allantoin, barbitone, phenobarbitone, alloxan, dilituric acid.
4. What are Purines and how they are named ? Give the preparation, properties and synthesis of purine.
5. How are Purines classified ? Give the systematic name and write the structural formulas of : uric acid, xanthine, caffeine, theobromine and adenine.
6. How is uric acid manufactured from Guano ? Discuss its physical and chemical properties.
7. Discuss in detail the constitution of Uric acid.
8. Give synthetic evidence in favour of the accepted structure of Uric acid.
9. Give the various stages envolved in the Fischer's synthesis of Uric acid.
10. Write a note on Xanthine.
11. How is caffeine prepared from tea leaves ? Give its synthesis from Uric acid. What is the chief use of this compound ?
12. Sketch the evidence that establishes the structure of uric acid. Describe one method of its synthesis.
13. (*a*) Give analytical evidence to establish the structure of caffeine.
(*b*) How is uric acid converted into caffeine ? (*Bombay BSc, 1992*)
14. What are purines ? How will convert : (*a*) Urea into uric acid; and (*b*) Uric acid into purine. (*North Eastern Hill BSc Hons, 1993*)
15. What are purines ? Show how caffeine, theophylline, and theobromine are related to uric acid. (*Bombay BSc, 1994*)

AROMATIC COMPOUNDS

Chapter 34

Introductory—Coal and Petroleum as Sources of Aromatic Compounds

SCOPE AND SIGNIFICANCE OF THE TERM 'AROMATIC'

Hitherto we have studied only the *Aliphatic compounds* in which the carbon skeleton is made of open chains of carbon atoms or rings as in cycloalkanes. Besides the aliphatic compounds there were known since very early days of the history of organic chemistry, a large number of compounds having distinctly characteristic behaviour. Such compounds were highly unsaturated and yet came to be known as very stable. Since most of them possessed pleasant odour, this new class of compounds were named as **Aromatic Compounds** (Gr, *aroma*-sweet smelling). The fragrance of Oil of wintergreen, Oil of bitter almonds, Cinnamon oil, Clove oil, Turpentine oil etc., was attributed to the presence of certain aromatic compounds in them. However, the analytical study of the 'aromatic compounds' later on revealed that *the fundamental difference between them and aliphatic compounds was of structure rather than of fragrance.*

Loschmidt in 1861 pointed out that all aromatic compounds were the derivatives of a cyclic hydrocarbon *benzene* which had a sextet of carbons bonded to each other in a specific fashion :

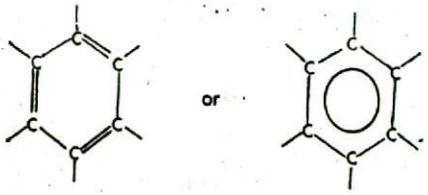


Fig. 34·1. Structural unit present in all aromatic compounds.

The presence of this structural unit (the benzene ring) in a compound conferred on it the characteristic aromatic character. Thus the carbocyclic compounds which contain at least a benzene ring, or resemble benzene in chemical behaviour, are said to belong to the **Aromatic Series.** The scope of the term 'aromatic' is now not limited to the *benzenoid compounds* only, but also includes *non-benzenoid compounds* which do not have a carbon sextet and yet possess aromatic character. These non-benzenoid aromatic (such as pyridine) compounds eventhough

lack the presence of a benzene ring, are found to have similarities in electronic configuration to the benzenoid compounds. These determined their aromatic character.

Like the aliphatic compounds, aromatic compounds include hydrocarbons, hydroxy derivatives, ethers, aldehydes, ketones, carboxylic acids, amines etc. We shall study the synthesis and properties of these classes of compounds in detail in the following chapters.

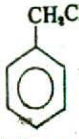
NOMENCLATURE OF AROMATIC COMPOUNDS

(1) **Hydrocarbons.** Aromatic hydrocarbons in general are referred to as *Arenes*. These are further divided into two classes :

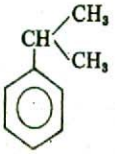
(*a*) MONOCYCLIC ARENES. These include benzene and its derivatives in which one or more hydrogen atoms of the ring have been replaced by alkyl, alkenyl, alkynyl, or aryl groups.

(*i*) *Monosubstituted benzenes* are named in a straightforward manner by prefixing the name of the substituent group to the word 'benzene'. These IUPAC names are used in general, but trivial names are retained, particularly for the important lower members. Thus,

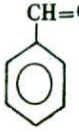
toluene
(methylbenzene)



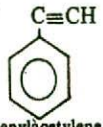
ethylbenzene



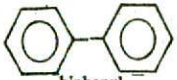
cumene
(isopropylbenzene)

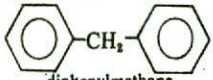


styrene
(vinylbenzene)



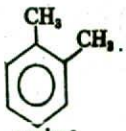
phenylacetylene
(ethynylbenzene)


biphenyl
(phenylbenzene)

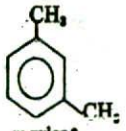


diphenylmethane
(benzylbenzene)

(*ii*) *Disubstituted benzenes.* The most important hydrocarbons of this type are dimethylbenzenes whose trivial names are *xylenes*. Since these exhibit position isomerism, there are three xylenes which are listed below.



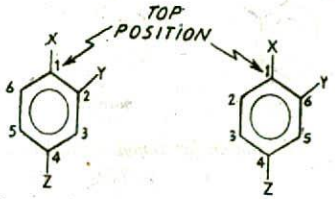
o-xylene



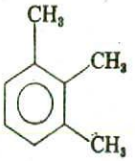
m-xylene

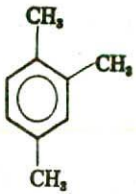
p-xylene

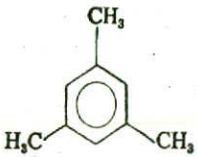
(*iii*) *Polysubstituted benzenes.* They are by and large named according to the IUPAC system, unless they have recognised trivial names. One of the substituent groups (X) is placed at the top of the hexagon and numbered 1. The relative positions of the remaining substituents (Y and Z) are indicated by numbering the ring from 2 to 5 either clockwise or anticlockwise whichever procedure gives lower numbers to the substituents Y and Z



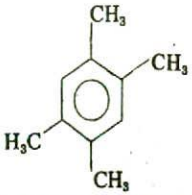
In the above illustration the positions of substituents get 1, 2, 4-numbers by clockwise procedure, and 1, 4, 6-by anticlockwise procedure. Therefore, the derivative will be correctly named as 1, 2, 4-triderivative (lower numbers). Thus the names of various position isomers of trimethylbenzenes are correctly given as :

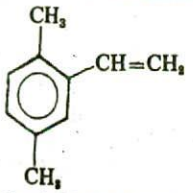

1, 2, 3-trimethylbenzene

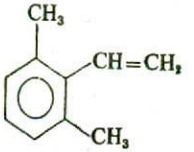

1, 3, 4-trimethylbenzene


1, 3, 5-trimethylbenzene (mesitylene)

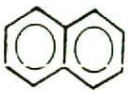
The higher polysubstituted benzenes are named mostly by the IUPAC system. The substituents are arranged in alphabetical order if they are different. Thus,


1, 2, 4, 5-tetramethylbenzene (durene)

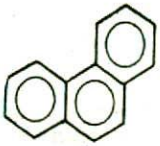

1, 4-dimethyl-2-vinylbenzene


1, 3-dimethyl-2-vinylbezene

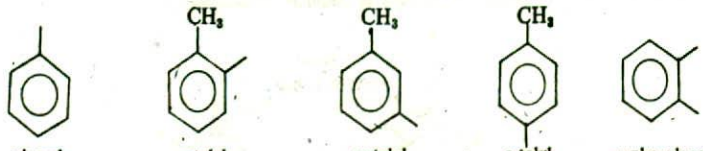
(*b*) **Fused Polycyclic Arenes.** A number of polycyclic arenes are known which contain two or more benzene rings fused in ortho positions. Some important members of this class known by their trivial names are :


NAPHTHALENE


ANTHRACENE


PHENANTHRENE

(2) **Functional Derivatives of Arenes.** As already stated, arenes form almost all classes of functional derivatives as do alkanes. The IUPAC names of these compounds are given either as the substitution products of arenes or by naming the aryl group followed by the name of the function. The groups (or radicals) derived from benezene and toluene by removal of hydrogen atoms are :

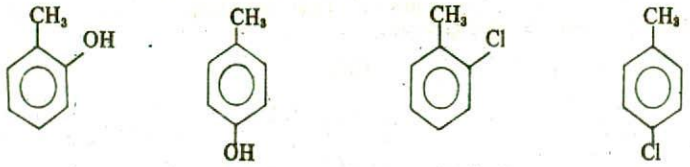


phenyl (Ph or ϕ) | *o*-tolyl | *m*-tolyl | *p*-tolyl | *o*-phenylene

(*i*) *The Monosubstitution functional derivatives* of benzene are listed below.

ϕ—Cl	ϕ—SO_3H	ϕ—NO_2	ϕ—NH_2	ϕ—OH	ϕ—CHO	ϕ—COOH
chlorobenzene	benzenesulphonic acid	nitrobenzene	aniline	phenol	benzaldehyde	benzoic acid

In case of monosubstitution products of toluene, the systematic names are used, unless the derivative has a recognised trivial name. Sometimes the name of the derivative is given by writing the name of the tolyl group followed by the name of the functional group. Thus,



o-cresol (2-hydroxytolucne) | *p*-cresol (4-hydroxytoluene) | *o*-tolyl chloride (2-chlorotoluene) | *p*-tolyl chloride (4-chlorotoluene)

In tri- or tetra-substitution products, the IUPAC rules cited while naming polysubstituted arenes are used. For example,

1, 2, 3-trichlorobenzene | 1, 2, 4-trichlorobenzene | 1, 3, 5-trichlorobenzene (mesitylene)

The detailed nomenclature of the various classes of compounds will be taken up under the relavent chapters.

SOURCES OF AROMATIC COMPOUNDS

Aromatic compounds or Aromatics, as they are called in brief, are obtainable both from the animal and vegetable sources. Coal and petroleum reserves derived from prehistoric forests by a process of decay and transformation under action of heat proved to be the biggest sources of aromatics. Up to the middle of this century, the chief sources of benzene and other aromatic compounds were coal tar and coke-oven gas produced by heating coal out of contact with air. With the rapid growth of petroleum refining industry during recent years, the emphasis has abruptly shifted from coal to petroleum as the potent source of aromatics. The most aromatic chemicals which were earlier obtained from coal tar are now produced synthetically from petroleum.

In India the petroleum refining industry has developed tremendously and provides *naphtha* for the production of aromatics. This added to their availability as coke-oven by products. However, on account of the high cost of crude petroleum, Government of India is trying to step up the production of ethylene from ethanol to meet the increasing demand of aromatics.

AROMATICS FROM COAL

Coal was formed from the remains of trees and ferns which grew in swamps some 500 million years ago. Initially, bacterial and chemical action on such plant debris produced PEAT as an intermediate product. The deposition of minerals caused the peat to sink. Peat, which is composed of dead leaves, stems and roots of plants, is mainly cellulose $(C_6H_{10}O_5)_n$. As a result of high pressure and temperature during geological changes under earth's surface, peat was transformed into coal. Thus coal is the product of the following sequence of changes which take place with the passage of time.

$$\underset{\text{(Dead plant material)}}{\text{PEAT}} \xrightarrow[\text{pressure}]{\Delta} \underset{\text{(Brown Coal)}}{\text{LIGNITE}} \xrightarrow[\text{pressure}]{\Delta\Delta} \underset{\text{(Household Soft Coal)}}{\text{BITUMINOUS COAL}} \xrightarrow[\text{pressure}]{\Delta\Delta\Delta} \underset{\text{(Hard Coal)}}{\text{ANTHRACITE}}$$

The transformation of plant material to coal by the above stages is due to progressive decomposition by heat and pressure. Therefore the original material (cellulose) lost moisture, and the gases, hydrogen and oxygen, and became richer in carbon at each stage listed above. The final product, coal, has the appoximate chemical formula $(C_3H_4)n$ which shows that it is hydrogen-deficient hydrocarbon stuff. Thus the basic structure of coal is probably built up of a large number of interlocked benzene rings, upto thirty in high ranking coal. Hydrogen is present in the aliphatic side-chains. Besides carbon and hydrogen, coal may also contain small percentages of other elements as shown in the Table below.

Table. Approximate Composition (percentages) of various types of coal

Elements	*Peat*	*Lignite*	*Bituminous*	*Anthracite*
Carbon	54·0	64·0	84·0	93·0
Hydrogen	5·5	5·0	4·5	3·3
Oxygen	35·0	26·0	8·0	2·0
Nitrogen	2.0	1·3	1·3	1·3
Sulphur	3·5	3·3	1·5	0·5

Peat and lignite are both rich in oxygen and appreciably less aromatic than bituminous coal. Of all these varieties of coals, bituminous coals are most important and sufficiently rich in aromatic compounds.

The main use of bituminous coal is the manufacture of smokeless industrial fuel COKE, required for Iron and Steel industry, and COKE-OVEN GAS consumed as a household fuel. In processing coal for coke and coke-oven gas by destructive distillation, a portion of coal is left as a tarry residue COAL TAR, which is a major source of coal-based aromatic chemicals.

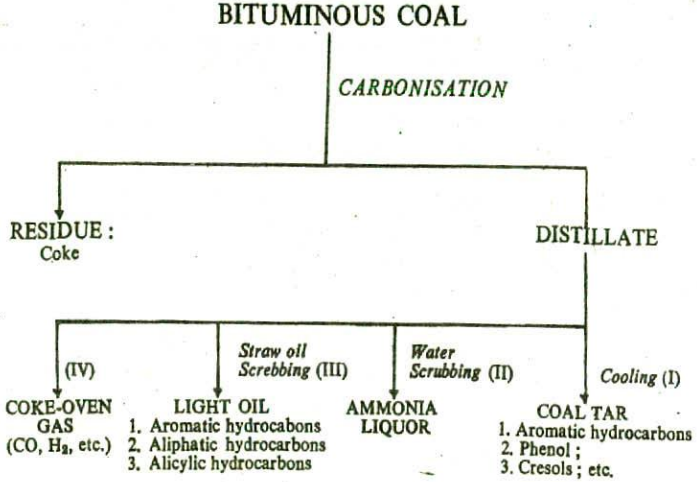
The manufacture of coal gas is obsolete since 'natural gas' is available in free supply in cylinders for use in domestic stoves. Natural gas is convenient to handle and non-poisonous, while coal gas is poisonous. Therefore, carbonisation of coal is now mainly carried for the production of coke and the recovery of coal chemicals.

CARBONISATION OF COAL

The chief industrial method of obtaining aromatic compounds from bituminous coal is thermal decomposition. This process called CARBONISATION is now carried mainly with the object of manufacture of coke for Iron and Steel industry. This process is also the main source of coal-based organic chemicals.

Coal is known to have a sieve carbon structure in which complex aromatic molecules are trapped. When coal is heated, these trapped molecules are released. These released molecules at high temperatures employed during carbonisation, further undergo thermal cracking to yield simple volatile aromatics and gaseous products.

Actually when heated above 400° in closed ovens or retorts, coal softens and becomes plastic. Then volatile materials are evolved as distillate, leaving involatile residue which coalesces, swells and finally solidifies to form coke. The main products of carbonisation of bituminous coal are indicated below.



The exact nature and proportions of the by-products obtained by carbonisation of coal are determined by the temperature conditions employed for the process. Actually, carbonisation is carried in two ways depending upon whether coke or the volatile materials are required as the main product.

(*a*) *Low-temperature Carbonisation* (450—700°C) ;

(*b*) *High-temperature Carbonisation.* (900—1100°C).

The by-products from either process are of the same type as indicated in the chart given above, although their proportions will vary with the process and the type of coal carbonised. For example, ONE TON of Bituminous coal yields the various products in the following proportions.

	I	II	III	IV	V
	Coal Tar	Ammonia	Light Oil	Coke-Oven Gas	Coke
Low-temp carbonisation	17—90 gal	2·5 lb	2·5—3·5 gal	4000 scf	0·75 tons
High-temp carbonisation	6—7 gal	3—4 lb	3 gal	10,000 scf	0·7—0·8 tons

(1) *COAL TAR.* It is obtained in a much greater proportion from low-temp carbonisation, which is an excellent source of naphtha and small amounts of numerous aromatics. From high-temp-carbonisation coal tar is obtained in poor yield and small amounts of aromatics can be recovered from it.

(2) *AMMONIA.* High-temp carbonisation yields less of ammonia gas. Ammonia gas is converted into the fertiliser ammonium sulphate, by reaction with sulphuric acid, and subsequent separation of the solid substance in a centrifuge.

(3) *LIGHT OIL.* The light oil obtained from high-temp carbonisation is a rich source of Benzene (72%), Toluene (13%), and Xylenes (4%). BTX is the trade name for a mixture of these hydrocarbons.

The light oil derived from low-temp carbonisation, on the other hand, is rich in alkanes (46% vol), alkenes (16%), cycloalkanes (8%), cycloalkenes (9 %), and contains some aromatics (16%).

(4) *COKE-OVEN GAS.* Low-temp carbonisation gas contains mainly methane and higher alkanes (65% vol), alongwith H_2 (10%), CO (5%), CO_2 (9%), etc. It can be used for supply as 'coal gas' for domestic consumption.

High-temp carbonisation gas is made of hydrogen (50% vol), alkanes (34%), CO (8%), CO_2 (3%), etc. This can be used as reducing fuel gas in metallurgical operations.

(5) *COKE.* Low-temp carbonisation coke contains 8—20% volatile matter and is used as smokeless domestic fuel. The hard coke produced by high-temp carbonisation process is largely used for metallurgical purposes.

As clear from above, coal tar and light oils are the products of coal carbonisation which are, in fact, the potent sources of aromatic hydrocarbons and their derivatives. It will be worthwhile to have a knowledge of the relative amounts of aromatics available in the low and high-temp carbonisation processes.

Table : The composition of coal tar and light oil produced by low-temp and high-temp carbonisation of ONE TON of Bituminous coal.

Product	*Low-temp Carbonisation*		*High-temp Carbonisation*	
COAL TAR	Aromatic hydrocarbons (BTX)	< 0·5%	Aromatic hydrocarbons (BTX)	0·6%
	Cresols	3·5	Cresols	1·0
	Xylenols	6·5	Xylenols	0·5
	Other phenols	13·0	Other phenols	1·5
	Naphtha	36·0	Naphthalene	8·9
	Other aromatics	3·0	Other aromatics	10·0
	Pitch	26·0	Pitch	60·0
LIGHT OIL	Alkanes	46 vol %	Benzene	72%
	Alkenes	16	Toluene	13
	Cycloalkanes	8	Xylenes	4
	Cycloalkenes	9	Alicyclics	5
	Aromatics	16	Aliphatics	6
	Others	5		

COAL GAS MANUFACTURE AND RECOVERY OF AROMATICS

As stated earlier, coal gas can be produced by low-temperature carbonisation of bituminous coal. It was long used as a domestic fuel. Since the availability of bottled 'natural' or refinery gas, the manufacture of gas by carbonisation has become obsolete in advanced petroleum countries like USA, USSR, etc. However, the present petroleum crisis, particularly in India, has once again diverted the attention to 'coal gas'. At persent only the cities of Bombay and Calcutta have gas plants that supply gas as a domestic fuel on a very limited scale. However, a high powered committee set up by Govt. of India in Nov. 1984, have prepared a plan to have plants to supply coal gas to families in Calcutta to start with.

The plant used for the manufacture of coal gas is shown in Fig. 34·2.

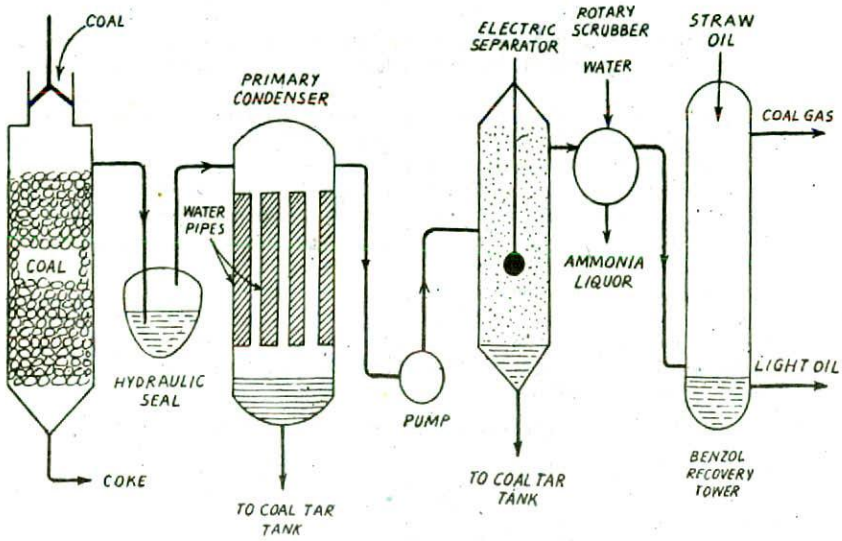


Fig. 34·2. Diagram of a Coal-Gas plant.

The coal is heated in large vertical iron RETORTS at about 600°C, by burning producer gas. The gases (H_2, CH_4, CO, CO_2, C_2H_4, C_6H_6, NH_3, H_2S), water vapours, vapours of aromatics, coal dust etc pass out of the retort. The residue in the retort is coke, used as domestic fuel.

The gases, vapours and dust first pass through the HYDRAULIC SEAL where they are partially cooled and tar separated to some extent. The purpose of the seal is to act as valve and not to allow the gases and vapours to return to the retort when it is opened for cleaning. The gases, the volatile organic matter and coke dust, are then passed through 'PRIMARY CONDENSER' fitted with cold-water pipes. Tar is condensed here and collects at the bottom, and is led to the tar-tank. The remaining gases, vapours and smoke are made to pass through a PUMP which helps keeping them circulating. The ELECTRICAL SEPARATOR precipitates smoke and particles of organic matter which settle down and are taken to coal-tar tank. The uncondensed gases that escape from the electrical separator are scrubbed with water by a ROTARY SCRUBBER, removing ammonia as *ammonia liquor*. This is later reacted with sulphuric acid to get the fertiliser *ammonium sulphate*.

The cooled gases free from ammonia are then scrubbed with straw oil in 'BENZOL RECOVERY TOWER'. The *light oil* collecting at the base of the tower is fractionated to recover benzene, while coal gas leaves near the top through exit pipe. Before distribution for domestic use, the coal gas is passed over iron oxide to remove hydrogen sulphide gas. If not removed, H_2S burns alongwith coal gas to produce SO_2 gas which is poisonous.

FRACTIONAL DISTILLATION OF COAL TAR

Practically all the tar in USA, and in most other countries is produced by high-temperature carbonisation in coke-ovens by the steel industry. About 16 per cent of the tar is burned as fuel in furnaces, while the remaining 84 per cent is processed for the recovery of aromatics.

The dark-brown sticky liquid called coal tar is a mixture of several aromatic hydrocarbons, phenols, bases etc. The first step in the separation of coal tar into its components is

distillation in a fractionating column. Four main fractions are usually collected, leaving behind, a residue of pitch which is mostly used for road surfacing.

Table. Fractions obtained in Coal-tar Distillation

Fraction	*Temp. Range*	*% age by volume*	*Chief Constituents*
I. LIGHT OIL	<170°C	5	Benzene, toluene, xylene
II. MIDDLE OIL	170—230°C	7·5	Phenol, cresols, naphthalene
III. HEAVY OIL	230—270°C	10	Cresols, naphthalene
IV. ANTHRACENE OIL	270—400°C	20	Anthracene
V. PITCH	*Residue left*	≈ 57·5	

The above fractions collected at different temperatures are worked-up for the recovery of their aromatic components.

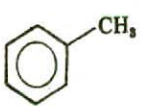
FRACTION I — Light Oil

The fraction up to about 170°C is called *Light Oil* because it is lighter than water. Besides the hydrocarbons, benzene, toluene, and xylenes (BTX), light oil also contains traces of acidic substances phenol and cresols, and basic substances pyridine and methylpyridines.

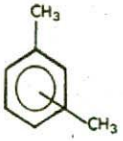
The main constituents of light oil are stated below—

NEUTRAL

benzene



toluene

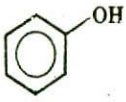


xylenes

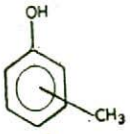
thiophene

pyrrole

ACIDIC



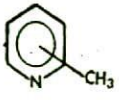
phenol



cresols

BASIC

pyridine



methylpyridines

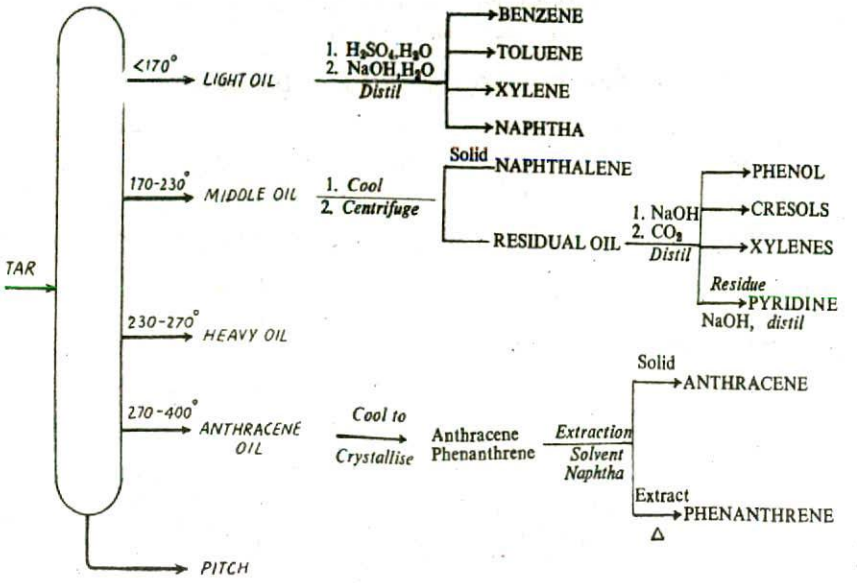


Fig. 34.3 Separation of constituents of Coal Tar.

To isolate the above components, light oil is washed with concentrated sulphuric acid which removes alkenes, basic substances such as pyridine and thiophene. This is followed by treatment of the oil with dil NaOH which removes acidic compounds, phenols. In fact the sequence of operations is as follows :

LIGHT OIL $\xrightarrow{H_2SO_4}$ $\xrightarrow{H_2O}$ $\xrightarrow{NaOH}$ $\xrightarrow{H_2O}$

The purified oil is then dried and subjected to further fractionation to get the following products.

(*i*) Benzene (bp 80°) ; (*ii*) toluene (bp 110°) ; (*iii*) a mixture of *o*-, *m*-, and *p*-xylenes (bp 135—145°) ; and (*iv*) a residue *Solvent Naphtha*. The solvent naphtha consisting of cumene and higher benzene homologues *e.g.*, mesitylene, is used, almost exclusively as a solvent for paints, resins, rubber, etc.

FRACTION II — Middle Oil

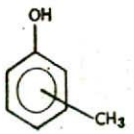
The fraction collected between 170°—230°C is called *Middle Oil* (being in the middle of light oil and heavy oil fractions), or *Carbolic Oil*. It consists chiefly of naphthalene, phenol or carbolic oil, cresols, pyridine and methylpyridines.

NEUTRAL :

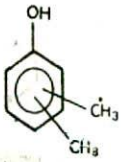
naphthalene

ACIDIC :

phenol



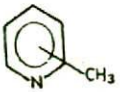
cresols



xylenols

BASIC :

pyridine



methylpyridines

On cooling the Middle Oil, crystals of crude naphthalene are deposited which are removed by centrifugation. Naphthalene thus obtained is purified by treating, while molten, with aqueous NaOH, H_2O, aqueous H_2SO_4, and H_2O. Thereafter it is dried and finally sublimed to get refined naphthalene.

The oil from which naphthalene has been separated is treated with warm aqueous sodium hydroxide to remove phenols (acidic substances). The resulting solution is saturated with carbon dioxide which sets free the phenols. The mixture of phenols is washed with water and fractionally distilled to yield phenol (bp 183°), a mixture of isomeric cresols (bp 191—201°), and xylenols (bp 210—225°). All these products are valuable disinfectants and are also important intermediates for the manufacture of industrical chemicals *e.g.*, salicylic acid, aspirin, phenacetin, many dyes, and explosives.

After the extraction of phenols, the remaining oil is washed with dilute H_2SO_4 which removes tar bases as their salts. The resulting salt solution is treated with NaOH and distilled to obtain pyridine. The residual oil is mixed with heavy oil fraction.

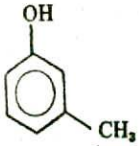
FRACTION III — Heavy Oil

This fraction of coal tar, also called *Creosote Oil*, is obtained between 230—270°C. Since it is heavier than water, it is named as *Heavy Oil*. The main constituents of Heavy Oil are :

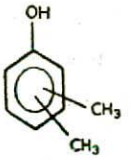
NEUTRAL :

naphthalene

ACIDIC :



cresols



xylenols

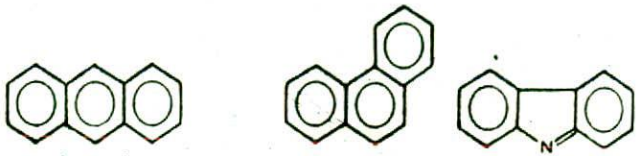
BASIC :

quinoline

Heavy Oil may be treated in much the same way as the Middle Oil to yield naphthalene, cresols and quinoline. Since these compounds can be conveniently produced by simpler synthetic methods, this fraction is not worked for their recovery. Heavy Oil finds a principal use as a wood preservative under the name *Creosote Oil*.

FRACTION IV—Anthracene Oil

This fraction distilling between 270—400°C gets its name from its chief ingredient *anthracene*. Phenanthrene and carbazole are the other two neutral components of *Anthracene Oil*.



Since the oil shows green fluorescence, it is also called *Green Oil*. For isolating anthracene, the oil is run into tanks and allowed to cool. The crystals of anthracene are formed, which are separated from the oil by filtration under pressure. On digesting these with solvent naphtha, phenanthrene dissolves in preference, leaving behind anthracene and carbazole. The solid mass is then extracted with pyridine to remove carbazole, and the residue is sublimed to yield 85—90% pure anthracene. This hydrocarbon is the starting material for *alizarin dyes*.

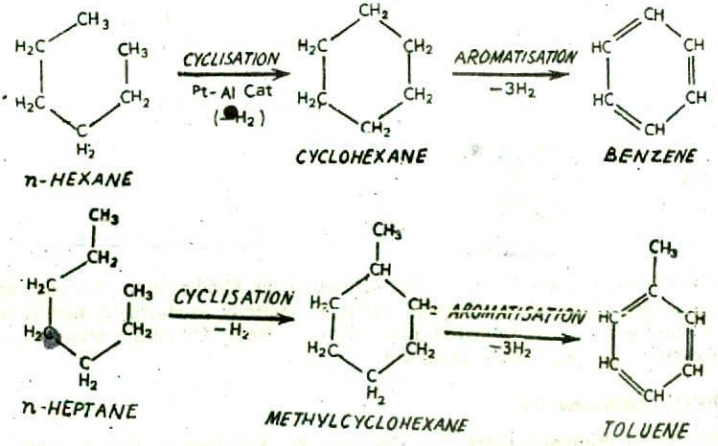
FRACTION V—Pitch. The residue in the still is called *Pitch*. Although most of it is carbon, (92—94%), it contains a number of five and six-membered fused ring compounds. It also contains some percentage of tar oils which determines the softening temperature range of the pitch. Pitch is used for : (*i*) making varnishes and water-proofing of roofs ; (*ii*) for making tarred paper and road surfacing ; (*iii*) for making acid-resistant stoneware ; and (*iv*) as pulverised fuel.

AROMATICS FROM PETROLEUM

As mentioned earlier, benzene, toluene, naphthalene, and several other aromatic compounds were originally obtained by the distillation of coal tar, derived as a byproduct in the manufacture of coke for steel. This was the only source of all aromatic compounds until 1940. In the past 30 years, the demand for aromatic compounds has far outstripped the amount available from coal tar. The major source of aromatic hydrocarbons is now petroleum industry.

Aromatics are present in very small quantities (10—12%) in the naphtha fraction (40-150°C) of petroleum. Straight separation of aromatics from petroleum is, therefore, not economically profitable. The following processes are generally employed for the large scale production of aromatics from petroleum.

(1) **Catalytic Reforming.** It is the process of converting C_6—C_9 aliphatic hydrocarbons present in petroleum naphtha into aromatic hydrocarbons. The C_6—C_8 fraction of light naphtha at 500°C and 25-35 atm pressure over a platinum-alumina catalyst gives a 45—55% yield of aromatics rich in benzene, toluene, and xylenes.



Middle distillates from petroleum may be similarly reformed to naphthalenes. Recently a new catalyst platinium-rhenium-alumina, has been introduced which functions satisfactorily at 10—20 atm pressure and increases the yield of aromatics to 25%.

An illustrative diagram of Benzene-Toluene-Xylene (BTX) is given in Fig. 34·4.

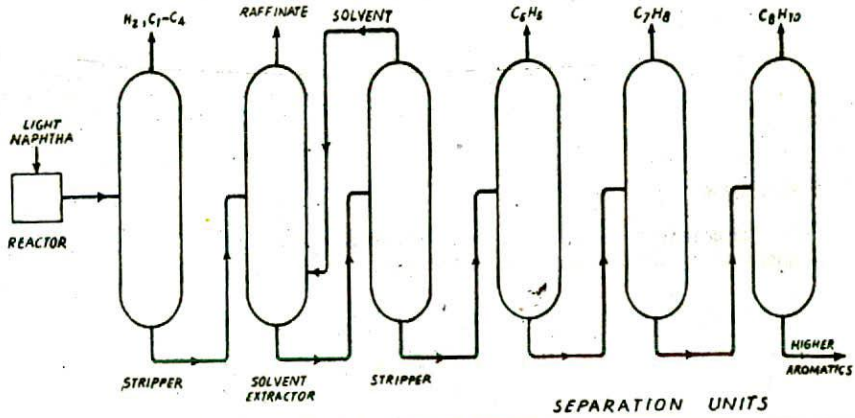
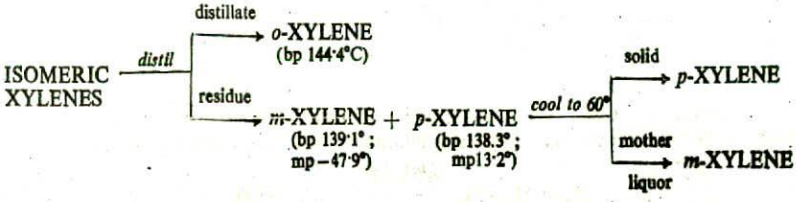


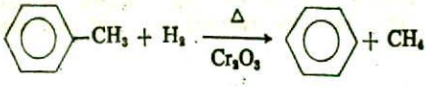
Fig. 34·4. Catalytic Reforming

Light naphtha fraction (C_6-C_8) of petroleum is first passed through a REFORMER having a fixed bed of platinum-alumina catalyst. Here the higher alkanes present in naphtha undergo reactions (cracking, cyclisation, aromatisation etc.) to reform benzene and its homologues (C_6 — C_8). The product mixture then goes to the STRIPPER, where the gaseous components (H_2, C_1-C_4) are removed. The mixture freed from gases is treated with a suitable solvent to extract the aromatics with which it forms less volatile azeotropic mixture. The relatively volatile nonaromatics (*reffinate* ; C_5 alkanes) escape at the head of the SOLVENT EXTRACTOR. The most commonly used solvent for extraction is diethylene glycol-water mixture (**Udex Process**). The extract containing the aromatics is sent to the stripper for the recovery of the solvent which is reused. The extract freed from the solvent is finally fractionated in the SEPARATION UNITS for the recovery of benzene, toluene, and xylenes. The separation of isomeric xylenes is difficult and is accomplished by the following procedure.

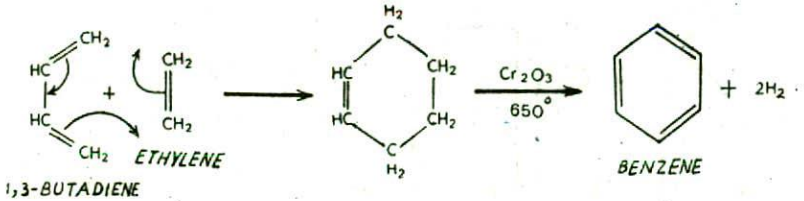


Benzene and Toluene are used as raw materials for the preparation of a large number of derivatives, drugs, explosives, plastics, etc. The *o*- and *p*-xylenes are convenient starting points for the the manufacture of phthalic and terephthalic acids.

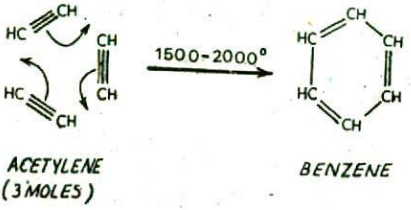
The mixture of BTX obtained by the selective solvent extraction described above, yields benzene, toluene and xylenes, but the yield of benzene is far less than the other two components. Since benzene is the most needed aromatic, toluene and xylenes are converted into benzene by heating with hydrogen obtained from the STRIPPER in the presence of Cr_2O_3 catalyst. This reaction known as **Hydrodealkylation** may be illustrated as



(2) **High-temperature Cracking.** Kerosene and other medium boiling fractions of petroleum are subjected to cracking, by passing through tubes packed with metal oxide catalyst at about 65°C. The reactions involved are dehydrogenation and rupture of C—C bonds to form alkenes. These undergo cyclisation and aromatisation to give a mixture of liquid aromatic hydrocarbons. Thus,



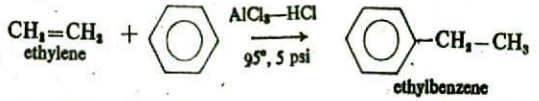
(3) **Polymerisation.** Acetylene, a petroleum product, when passed through a red-hot brick chequer work surface, polymerises to form benzene.



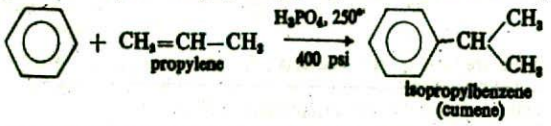
Acetylene in turn is produced by passing rapidly a liquid petroleum fraction through the brick chequer work in the first step of the process.

(4) **Alkylbenzene Synthesis.** A number of higher homologues of benzene have been very recently obtained by synthetic reactions from petroleum products. For example,

(*a*) *Ethylbenzene Synthesis.* When a mixture of benzene and ethylene derived from petroleum sources, is passed over liquid $AlCl_3$—HCl catalyst at 95°C and 5 psi pressure, ethylbenzene is formed.



(*b*) *Cumene Synthesis.* Isopropylbenzene or cumene is synthesised from benzene and propylene (obtained from petroleum) by using phosphoric acid as the catalyst at 250°C.



PROSPECTS OF AROMATICS FROM COAL AND PETROLEUM IN INDIA.

At present the whole world is in the grip of 'Petroleum Crisis' and the slogan 'Back to King Coal' is raging round in all the industrial countries of the world. India is no exception.

Government of India is making frantic efforts to explore the possibilities of finding new petroleum or *Natural gas* deposits, but not with much success. If atomic energy could be made available in the near future, some petroleum and coal could be diverted to meet the great demand for aromatics.

Total coal resources in India have been estimated by the Geographical servey of Indi to be 32 billion tons. The production of bituminous coal is at the rate of 0·06 billion tons pe annum ; indicating about 500 years supply. In 1974 India produced 9069,000 tonnes coa Government of India is trying to set up coke ovens near big cities, to provide gas and cok required for iron and steel industry. Aromatics will be obtained as byproducts. The productio of naphtha by petroleum refineries started yielding fair yields of benzene and other aromatic but this source has also declined. Production of acetylene from calcium carbide and ethylen from ethanol are perhaps the only substances which are being converted into aromatics. Th total 'aromatics' production both from coal and petroleum sources in 1973-74 touched 100,00 tonnes. Some of the organic chemicals synthesised are detailed below.

Styrene	*DMT*	*Phenol*	*Phthalic anhydride*	*Aniline*
30,000	22,000	18,000	20,000	6,000 tonnes

The Indian Petrochemicals Corporation, near Baroda, commissioned its plant for pro ducing mixed xylenes in 1974, and has so far supplied 3,000 tonnes of xylenes to customers i the country and 2,587 tonnes to Italy.

QUESTIONS

1. What do you mean by the term 'Aromatic' ?

2. Discuss the formation of coal in nature ? Mention the stages through which wood was finally converted into coal in prehistoric times.

3. What is the chemical composition of coal ? Which variety of coal is particularly rich ir aromatics ?

4. What do you understand by low-temperature carbonisation of coal. Give one of its applications.

5. How is coal gas manufactured ? Why is it obsolete in USA and other advanced countries ? Give the scope of this industry in India.

6. Name the main products obtained by the carbonisation of coal. 'High-temperature carbonisation light oils are worked for the recovery of aromatics'. Elucidate.

7. How is the destructive distillation of coal-tar carried to recover aromatic hydrocarbons, and phenols from it ? Write down the structural formulae of all aromatics present in each fraction.

8. Discuss briefly low-temperature carbonisation of coal.

9. Write an essay on coal-tar distillation.

10. Discuss coal-tar distillation. Give important uses of various products obtained.

11. Write a note on 'Chemicals from aromatic hydrocarbons in petrochemical industry.'

12. How are benzene and toluene obtained from coal-tar ?

13. How is pure napnthalene obtained from the middle oil fraction of coal tar distillation ?

14. Describe the method for the high temperature carbonisation of coal. What are the products obtained from it ? Mentic one use of each product. *(Nehu BSc Hons, 199*

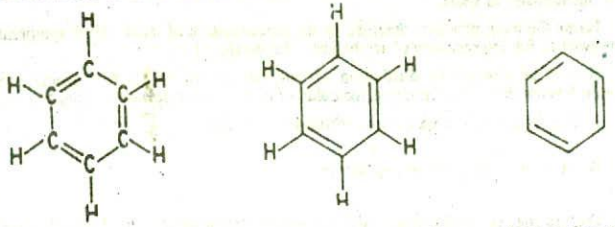
Chapter 35

Benzene and its Homologues

Benzene and all other aromatic hydrocarbons which are structurally related to benzene, are now designated as **Arenes**. These are further subdivided into *monocyclic*, *bicyclic* and *tricyclic arenes* according to the number of six-carbon benzene structural units present in their molecules. In this chapter we will discuss the **Monocyclic Arenes** or benzene and its homologues.

STRUCTURE OF BENZENE

The structure of benzene presented a major challenge to organic chemists ever since the pure material was first isolated in 1825 by Michael Faraday. He found that the vapour density of benzene was 39 so that its molecular formula was established to be C_6H_6. It was not until 1865 that the German chemist August Kekule suggested that the benzene mlecule is made up of a hexagon of six carbon atoms, joined alternately by double and single bonds, and with a hydrogen atom attached to each carbon atom.



Six carbon atoms joined by double and single bonds in alternate positions, each carrying a hydrogen atom.

(Carbon atoms are understood to be present at each corner of the hexagon)

(one carbon atom carrying one hydrogen atom is understood to be present at each corner)

Fig. 35·1. Kekule's Benzene Structure.

The above cyclic structure of benzene containing three conjugated double bonds is frequently referred to as **Kekule's Formula**. There is no doubt that during the hundred years which followed the discovery of benzene, experimental evidence for and against Kekule's formula was offered by several workers, but the original brilliant intution of Kekule perhaps best explained the chemistry of benzene. Even at present the chemists use Kekule's formula as frequently as before, and the modern molecular orbital concept has only modified it so as to fit it into a formal, logical and precise theory.

A. Facts that Supported Kekule Formula

The various facts advanced by chemists from time to time may be briefly summarised as follows.

(1) The molecular formula of benzene C_6H_6 as compared to that of hexane (C_6H_{14}), at once suggests that it is a highly unsaturated compound. The obvious conclusion was that the

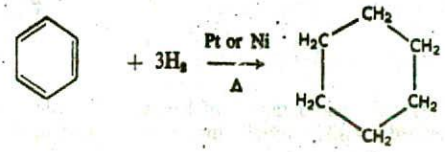
six carbon atoms in benzene were linked by double or triple bonds so as to form a straight chain or a closed ring as proposed by Kekule.

(2) **Open-Chain Structure untenable.** The possible open-chain structures for benzene could be as

$H_2C{=}CH{-}C{\equiv}C{-}CH{=}CH_2$ (I) $\quad HC{\equiv}C{-}CH_2{-}CH_2{-}C{\equiv}CH$ (II) $\quad H_3C{-}C{\equiv}C{-}C{\equiv}C{-}CH_3$ (III)

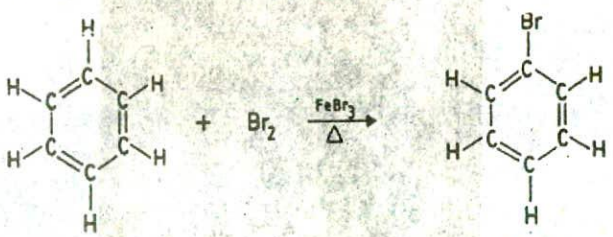
All these structures were ruled out because benzene did not give the usual reactions of alkenes and alkynes. For example, benzene does not react with aqueous potassium permanganate by oxidation, or with bromine in carbon tetrachloride to form the addition products. All known straight-chain structures as I, II or III, containing double or triple bonds, react with these reagents readily at room temperature.

(3) **Evidence in Favour of Ring Structure.** (*a*) Catalytic hydrogenation of benzene yielded cyclohexane,

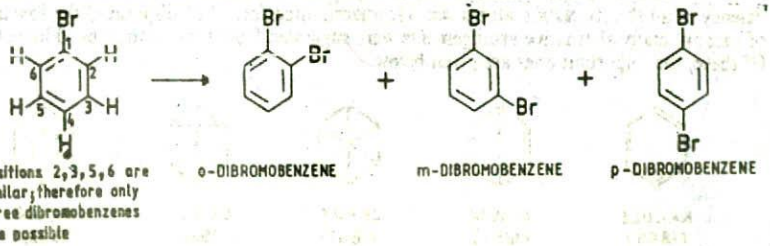


Since hydrogenation cannot bring about any major structural change in the carbon frame work, the above reaction demonstrated the presence of a closed ring of six carbon atoms in benzene molecule.

(*b*) It was noted that benzene gave substitution reactions to form one and only one monosubstitution product. Thus when heated to its boiling point in the presence of ferric bromide, benzene gives C_6H_5Br, when just one hydrogen atom is replaced by Br. This could be possible only if the six carbons in benzene are joined to each other to form a closed ring, and that one hydrogen atom is attached to each carbon.

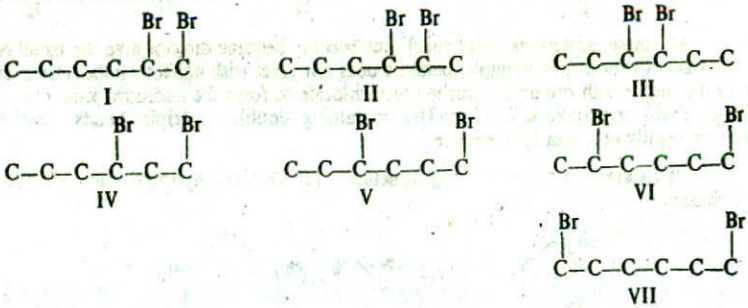


(*c*) Benzene forms three *di*- and three *tri*-substitution products, which were again explained on the basis of the ring structure of its molecule. Thus,



Proceeding similarly it can be shown that if a third bromine atom be introduced in the above dibromobenzenes, only three trisubstitution products would be obtained.

The formation of three *di-* and three *tri*-substitution products is possible if benzene has a ring formula. A straight-chain of six carbons, each carrying one hydrogen atom, would give as many as seven dibromo derivatives.



(*d*) Lonsdale (1929) took 'photographs' of hexamethylbenzene with the help of X-ray *diffraction camera* and provided a 'visible proof' that benzene ring indeed consisted of a planar ring of six carbon atoms.

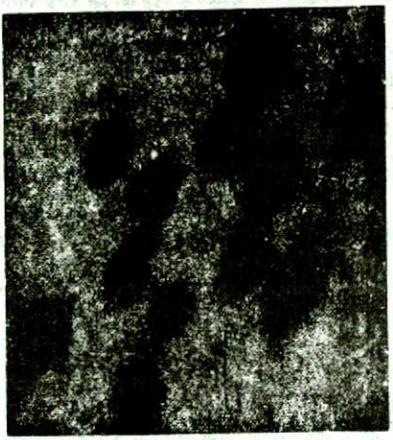


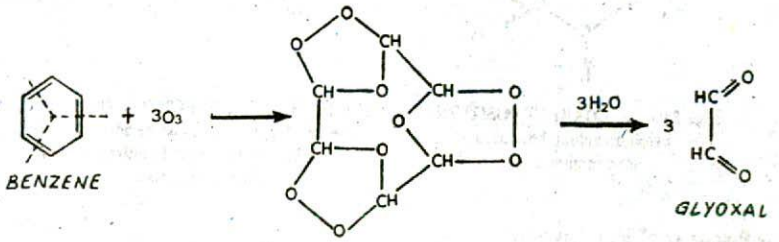
Fig. 35·2. X-ray Diffraction photograph of hexamethylbenzene, showing that benzene ring is made of six carbon atoms (black spots), while the outer spots represent the carbons of the six methyl groups attached to these carbon atoms.

(4) Bond Structure of Benzene. In the ring formula of benzene discussed above, the fourth valency of all the six carbon atoms was left unaccounted for. For disposal of the fourth valency of carbon, many alternative arrangements were suggested from time to time by different workers. Of these, the important ones are given below.

KAKULE (1865) DEWAR (1867) CLAUS (1867) CLAUS (1867) BAYER (1892)

The most important of these formulae was that put forth by Kekule which, in fact, formed the basis of the modern structure of benzene. All the other formulae were dropped for one reason or the other.

(5) Under suitable conditions benzene combined with three molecules of hydrogen and chlorine to form respectively cyclohexane, C_6H_{12}, and benzene hexachloride $C_6H_6Cl_6$. This proved the presence of three double bonds in the benzene ring. Further, on ozonolysis benzene formed three molecules of glyoxal and this showed that the three double bonds in benzene are present in alternate positions.



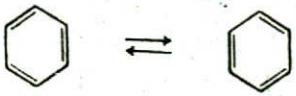
B. Objections to Kekule's Formula

(1) It admits the formation of two ortho disubstitution products for similar substituents. Thus the two *o*-dibromobenzenes possible would be :

I. (two Br atoms are attached to carbons containing a single bond)

II. (two Br atoms are attached to carbons containing a double bond)

However, actually only one *o*-dibromobenzene is known. Kekule himself replied to this objection by proposing that the double bonds in benzene ring were continuously oscillating back and forth between two adjacent positions.



Since the positions of the double bonds were not fixed, the question of formation of two dibromobenzenes did not arise.

(2) The X-ray diffraction measurements have shown that benzene ring indeed consists of a planar ring of six carbon atoms, and also that the ring carbon-carbon bonds are equal in length. These dimensions are now accurately known. The bond angles of benzene are 120°, the carbon-carbon distances are all 1·40 Å and carbon-hydrogen distances are 1·09 Å. The carbon-carbon distances in benzene are different from the normal carbon-carbon length in alkanes (1·54 Å) and the normal carbon-carbon double-bond length in alkenes (1·34 Å). These findings depict the actual position as in Fig 35·3 A, while the position if Kekule formula were correct in Fig. 35·3 B.

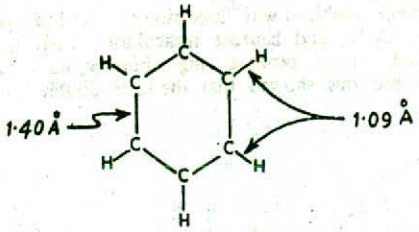


Fig. 35·3 A. CORRECT POSITION based on actual diffraction measurements.

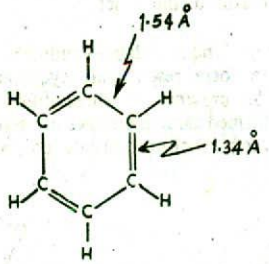
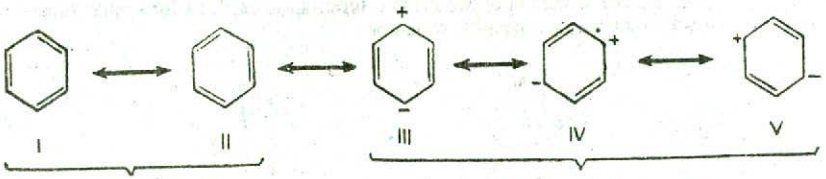


Fig. 35·3 B. INCORRECT POSITION presuming benzene to be cyclo-hexatriene which is disproved by diffraction measurements.

C. The Resonance Hybird Structure

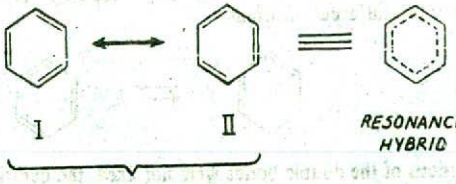
We get to the true picture of the structure of benzene by the application of the theory of resonance which was proposed in 1933. According to this theory, benzene is a resonance hybird of the following canonical forms.



Kekule Structures (most important contributors)

Charge-separated Dewar's Structures (least important contributors)

Since forms I and II are most important contributors, for simplyfying, benzene is represented as a hybrid structure of these canonical forms.



It would not be incorrect to say that the resonance between Kekule forms described above, was, in fact, brilliantly conceived some fifty years earlier. It was to explain the existence of one dibromobenzene only, that he had proposed the oscillation of single and double bonds between adjacent positions on the ring. However, the concept of resonance is imaginary and the canonical forms mentioned above actually do not exist. It is the resonance hybrid structure which is a reality. Since the π electrons are delocalised in the hybrid structure, each of the carbon-carbon bonds in benzene ring has a character intermediate between that of a σ bond and π bond.

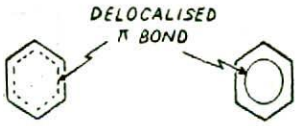
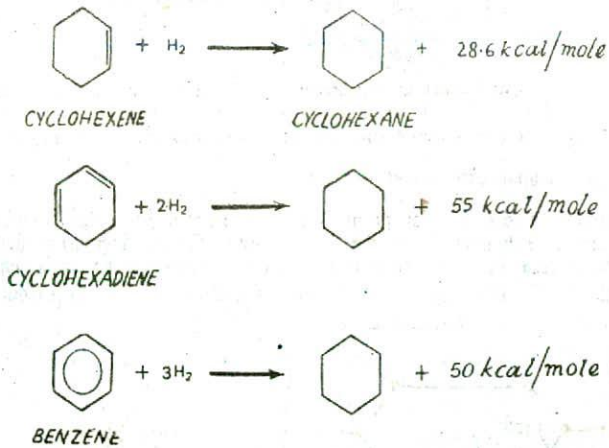


Fig. 35·4. Resonance hybrid of benzene which truly depicts the structure of benzene.

(*a*) RESONANCE HYBRID STRUCTURE CONFORMS TO X-RAY DIFFRACTION RESULTS. The fact that benzene is a resonance hybrid of the two Kekule forms, is in conformity with the results of X-ray diffraction experiments : (*i*) the carbon-sextet is flat ; and (*ii*) all the carbon-carbon bond lengths are equal (1·40Å) and are intermediate between those of an ordinary σ bond (1·54Å) and double bond (1·34°).

(*b*) RESONANCE THEORY EXPLAINS ELEGANTLY THE STABILITY OF BENZENE RING. The resonance hybrid structure of benzene, explained admirably the unusual stability of the benzene ring, a problem that had baffled the chemists for over half-a-century. The resonance stabilisation energy or 'resonance energy' which is really responsible for the unusual stability of benzene, could be calculated indirectly from the measurements of heat of combustion or heat of hydrogenation as follows.

The addition of hydrogen to a double bond is an exothermic reaction. Since heat is given out on hydrogenation, it implies that for the product in each case listed below, the energy is lower (more stable) than the original compound.



The heat of hydrogenation of one double bond in cyclohexene is 28·6 kcal/mole, which is nearly twice that of cyclohexadiene (55·0 kcal/mole) as here two double bonds are hydrogenated. Taking for granted that Kekule structure of benzene with three double bonds is correct, its heat of hydrogenation would be expected to be $3 \times 28{\cdot}6 = 85{\cdot}8$ kcal/mole. But when benzene is actually hydrogenated, only 50 kcal/mole are evolved. Thus thermodynamically benzene is more stable than the imaginary Kekule structures could predict. The difference, $(85{\cdot}8 - 50) = 35{\cdot}8$ kcal/mole, between the calculated and observed values is the resonance stabilisation energy of real benzene (resonance hybrid). These data are summarised in Fig. 35·5. The hydrogenation results prove clearly that benzene is correctly represented by the hybrid structure, and that Kekule formula is incorrect.

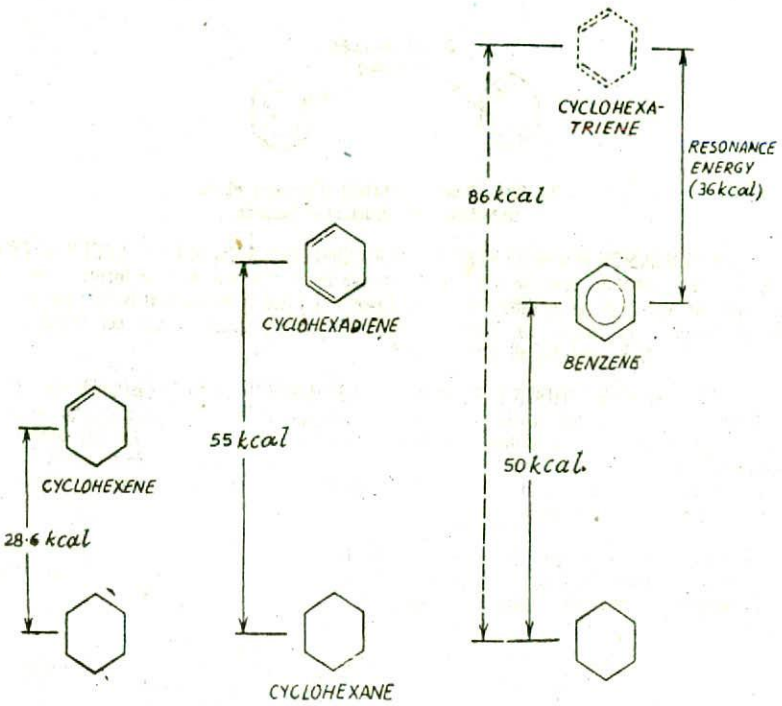


Fig. 35·5. Heats of hydrogenation of cyclohexene, cyclohexadiene, as also of hypothetical Kekule structure (cyclohexatriene), and real benzene (hybrid structure). Here are depicted beautifully the relative energies of these compounds, as also the resonance energy of benzene.

D. The Molecular Orbital Structure of Benzene

The stucture of benzene can probably be best described by using the molecular-orbital approach. We have already studied with the help of X-ray diffraction measurements that benzene consists of a planar hexagon of six-carbon atoms, having all carbon-carbon bonds equal in length (1·40 Å) and C—C—C bond angles of 120° each. Therefore, it stands to reason that each of

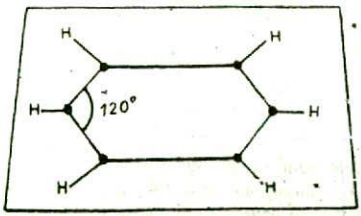


Fig. 35·6. Planar framework of benzene shown by X-ray diffraction measurements, having all C—C bonds of 1·4 Å and bond angles of 120°.

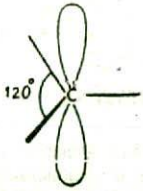


Fig. 35·7. An sp^2 hybridised carbon with sp^2 orbitals shown by lines in one plane and unused half-filled p orbital standing at right angle to the plane.

the six crabon atoms in benzene ring is in a state of sp^2 hybridisation (trigonal hybridisation) as shown in Fig. 35·6. Evidently the ring system is constructed from six sp^2 hybridised carbons,

by the overlapping of the two hybrid orbitals, each to each, to from a σ bond structure. This is a planar hexagon as visualised in Fig. 35·8 given blow.

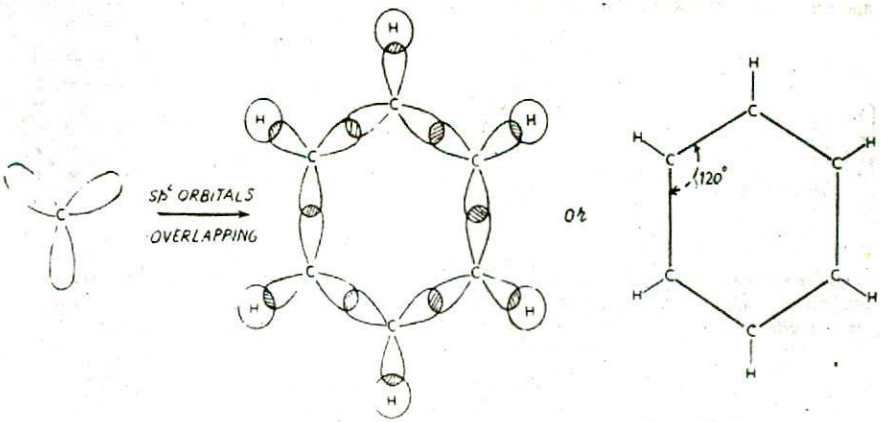


Fig. 35·8. σ-bond structure of benzene, constructed from six sp^2 hybridised carbon atoms ; the in-plane sp^2 orbitals interlocking to form a planar hexagon; the third hybrid orbital of each carbon forming a σ bond with a hydrogen atom.

As shown in Fig. 35·8 each carbon of the planar hexagon will have an unused *p* orbital disposed at right angle to the plane of the hexagon. The *p* orbitals on the six carbon atoms are perfectly aligned for side-side overlap. Since the system is completely symmetrical, the *p* orbitals can overlap equally well with either neighbour to give two molecular orbitals (*a*) and (*b*) analogous to the two classical Kekule structures.

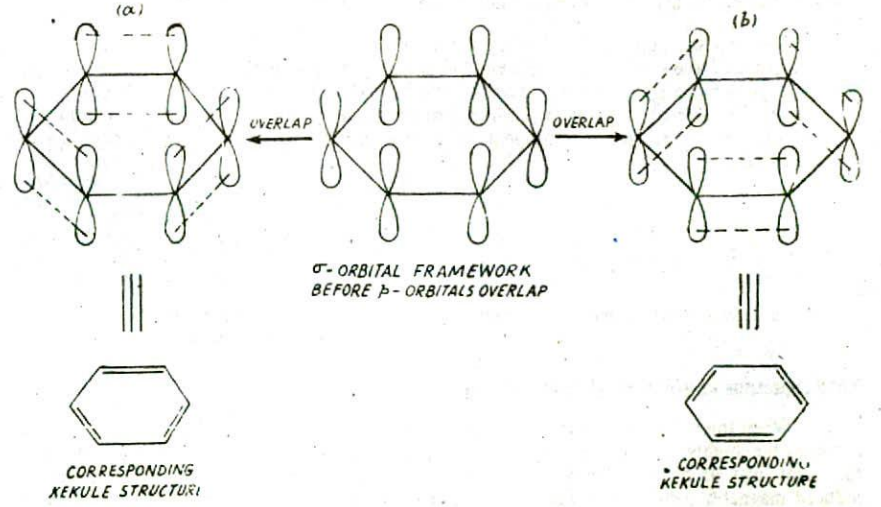
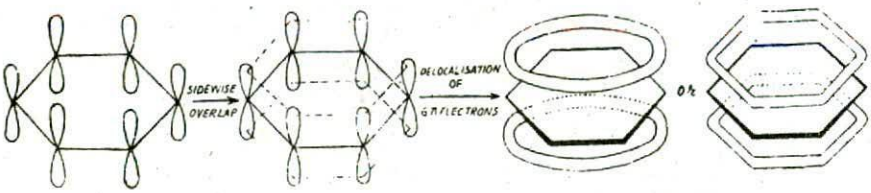


Fig. 35·9

As visualised above, the two Kekule structures correspond to localised π bond formation in one of the two ways as shown in Fig. 35·9. Since internuclear distances between the carbon atoms of the hexagon are equal, there appears to be no good reason why any one particular *p* orbital should overlap in one direction specifically rather than in both directions

Thus each of *p* orbital on the six carbons can overlap on either side with adjacent *p* orbital. There results a molecular orbital which is actually made of two continuous rings, one ring above and one below the plane of hexagon (Fig. 35·10).



Separate *p* orbitals on benzene ring may overlap on either side

The six *p* orbitals are delocalised, the lobes above and below the ring separately.

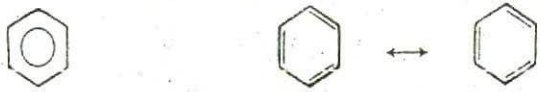
π molecular orbitals of benzene having a continuous annular cloud, one above and one below the carbon sextet.

Fig.35·10. Formation of continuous π electron annular clouds in benzene molecule.

The π electrons are now said to be completely delocalised and can freely move about the six positive carbon nuclei instead of any two as in Kekule structure. The amount of energy by which the total energy of the system is less than that of the arrangement corresponding to Kekule formula, called the delocalisation or resonance energy, actually accounts for the stability of the benzene ring.

The aromatic hydrocarbons resist addition and oxidation reactions since these destroy the extensive overlap and the stability of the system. The negative π electron clouds of benzene impart to it nucleophilic character. Thus benzene mainly gives electrophilic substitution reactions in which process the aromatic system remains intact.

The ring-like molecular orbital structure or resonance hybrid structure, both give the correct picture of the structure of benzene. Thus benzene is generally represented in a simple way by a regular hexagon with an inscribed circle that symbolises the three delocalised π orbitals or 6π electrons. This is the representation of benzene, which we shall adopt in this text. However, for the purpose of clarity in showing reaction mechanisms Kekule formula is still used.



I. Simplified representation of benzene

Kekule structure equivalent to structure I ; the two canonical forms

NMR Spectrum supports the Molecular Orbital Structure of Benzene.

When the magnetic field is applied at right angles to the plane of the π system of benzene it causes the highly mobile delocalised electron to circulate around their orbital, much in the same way as do electrons in a loop of wire. This 'ring current' in turn generates an induced magnetic field around the benzene ring. The induced magnetic field is opposed to the applied field inside the ring but in the return path of the lines of force outside the ring, the applied field is reinforced. In this way the protons situated outside the ring are subjected to increased magnetic field. The chemical shifts of aromatic protons are, therefore, observed at lower magnetic field than those for hydrogen atoms attached to doubly bonded carbons of ethylene, where they are not subjected to the effects of 'ring currents'. This is, in fact, one useful criterion of aromaticity.

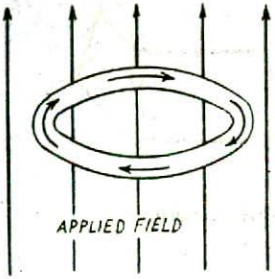


Fig.35·11. Applied field causes the π electrons to flow around the orbital, producing 'ring current'.

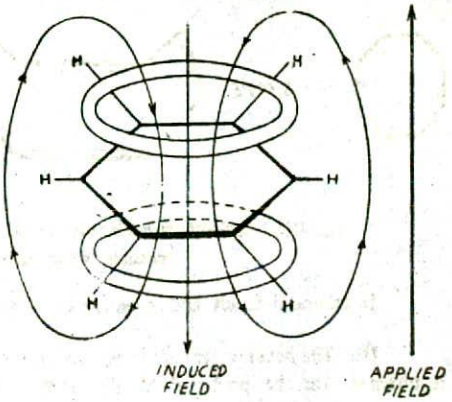


Fig.35·12. The induced magnetic field due to 'ring current' strengthens applied field around the protons outside the ring which gives higher δ value.

AROMATICITY

We have already observed that benzene and numerous other structually related compounds exhibit distinctly different physical and chemical properties as compared to aliphatic compounds. These benzenoid compounds even though highly unsaturated and possessing π bonds, resist addition and oxidation reactions, and instead undergo substitution reactions. While the benzene ring shows unusual stability, a substituent such as Cl, OH or NH_2 directly attached to the ring behaves very differently than the counterparts in the aliphatic series. Thus the term 'aromatic character' or **Aromaticity** was adopted to signify the characteristic physical and chemical behaviour of benzene and the related compounds.

Originally the aromatic character was attributed to the presence of a planar, cyclic conjugated π bond system as in benzene. Thus cyclic polyenes possessing alternate double and single bonds, with a planar carbon skeleton were shown to have aromatic character.

It was Robinson who first pointed out that the presence of alternate double and single bonds conferred *aromaticity* on the benzene ring owing to delocalisation of the six π electrons over the carbon-sextet. Thus the *aromaticity* of benzene was attributed to the six carbon planar hexagon having a sextet of π electrons in a continuous cloud above and below it.

Modern Theory of Aromaticity. The modern theory of aromaticity was advanced by Eric Huckel in 1931. He based it on molecular orbital calculations, extending the scope of the theory to larger or smaller rings than of benzene. The modern theory of aromaticity embraces polynuclear compounds, cyclic ions, and heterocyclic ring systems. The fundamental conccpts of this theory are :

I. *The complete delocalisation of π electrons of the ring systems makes them wholly aromatic in character.* As seen in case of benzene, the delocalisation of π electrons is caused by side-side overlapping of available *p* orbitals (each containing one electron) present on the carbons constituting the ring.

II. *The ample delocalisation of the π electrons is possible only if the ring is flat or coplanar, so as to allow cyclic overlap of p orbitals.*

Thus benzene having a coplanar ring is aromatic, while 1, 3, 5, 7-cyclooctatetrene being nonpolar lacks aromaticity.

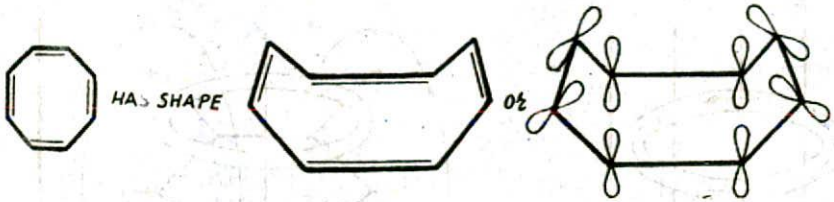


Fig.35·13. Cyclooctatetrene is nonpolar and hence complete side-side overlap is not possible, which makes it non-aromatic

In general five, six and seven carbon-rings being flat show aromatic character.

III. *The bonding orbitals in the conjutated ring system should be completely filled.* This requirement can be predicted by **Huckel Rule** or **4n+2 Rule.** According to this rule, in a cyclic system of overlapping *p* orbitals if the number of π electrons is $4n+2$, the system will have aromatic character, otherwise not. Here $n=0$, 1, 2, 3 etc. Thus :

(*a*) benzene, naphthalene and anthracene containing 6, 10 and 14 π electrons respectively satisfy Huckel Rule and are aromatic.

benzene	naphthalene	anthracene
6 π electrons	10π electrons	14π electrons
(n=1 ; 4×1+2=6)	(n=2 ; 4×2+2=10)	(n=3 ; 4×3+2=14)
4n+2 rule satisfied	4n+2 rule satisfied	4n+2 rule satisfied
AROMATIC	AROMATIC	AROMATIC

(*b*) 1, 3-cyclobutadiene and 1, 3, 5, 7-cyclooctatetrene containing 4π electrons and 8π electrons respectively do not satisfy Huckel Rule and are nonaromatic.

1, 3-cyclobutadiene	1, 3, 5, 7-cyclooctatetrene
4π electrons	8π electrons
(4n+2 rule not satisfied)	(4n+2 rule not satisfied)
NONAROMATIC	NONAROMATIC

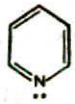
IV. *The cyclic systems formed by loss of a proton, which are ionic in character that obey Huckel Rule also exhibit aromaticity.* Thus cycloheptatrienyl (tropylium) cation, and cyclopentadienyl anion, both having 6π electrons (n=1), are aromatic. Even the cyclopropenyl cation which has 2π electrons (n=0) displays armoaticity.

cycloheptatrienyl cation
6π electrons
(n=1 ; 4×1+2=6)
AROMATIC

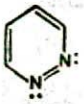
cyclopentadienyl anion
6π electrons
(n=1 ; 4×1+2=6)
AROMATIC

cyclopropenyl cation
2π electrons
(n=0 ; 4×0+2=2)
AROMATIC

V. Huckel enlarged the scope of his rule so as to embrace the heterocyclic ring systems as well. Thus for pyridine and pyridiazine, n=1. They have six π electrons each and satisfy Huckel rule and are aromatic.



pyridine
(6π electrons)
AROMATIC



pyridiazine
(6π electrons)
AROMATIC

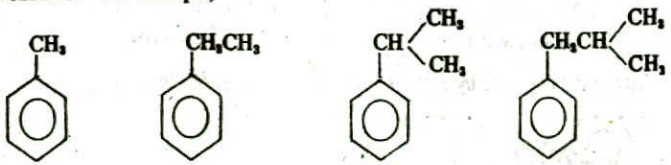
VI. Huckel extended the application of his rule to non-benzenoid heterocyclic aromatic systems also with some modification. Thus for furan, thiophene and pyrrole, n=1. Here, the hetero atoms contribute the nonbonded p orbital pair of electrons lying inside the ring which is counted towards deciding the aromaticity of these compounds.

It may be noted that in each of above compounds there are four π electrons and two p electrons on the hetero atom inside the ring. Therefore here the aromaticity is shown by compounds in which π-electron system remains unchanged.

NOMENCLATURE

The trivial name of the parent monocyclic arene is benzene. The other members of this class are to a large extent assigned the systematic IUPAC names. However IUPAC has adopted the trivial names of lower arenes particularly, which have become popular by long usage. This has been done for brevity and convenience. Thus methylbenzene is invariably named as *toluene*.

In the IUPAC system, arenes of this class are named in a straight forward manner as substituted-benzenes. For example,



methylbenzene
TOLUENE

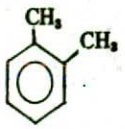
ethylbenzene

isopropylbenzene
CUMENE

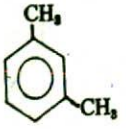
isobutylbenzene

The common names are written in capital letters for the reader.

When there are two substituents on the benzene ring, then positions are indicated by numbers, or by the prefixes *ortho* (*o*-), *meta* (*m*-) and *para* (*p*-). Thus the isomeric dimethylbenzenes are named as



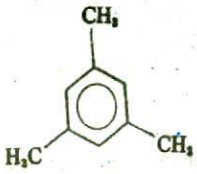
1, 2-dimethylbenzene, *o*-XYLENE



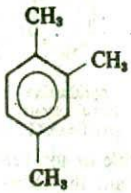
1, 3-dimethylbenzene, *m*-XYLENE

1, 4-dimethylbenzene *p*-XYLENE

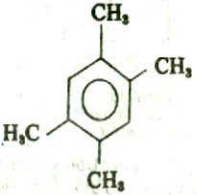
If there are three or more substiuent groups present on the ring, the arenes are preferably designated by IUPAC names. One of the groups is written at the top position of the hexagon, which becomes number 1. The six carbon atoms of the benzene are then numbered from 1 to 6 around the ring so that the substituent groups get the lower numbers. The substituent groups are preferably named in the alphabetical order. Thus,



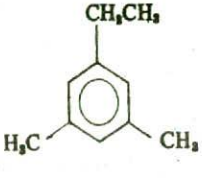
1, 3, 5-trimethylbenzene, MESITYLENE



1, 2, 4-trimethylbenzene NOT 1, 3, 4-trimethylbenzene



1, 2, 4, 5-tetramethylbenzene, NOT 1, 3, 4, 6-tetramethylbenzene DURENE



1-ethyl-3, 5-dimethylbenzene

Aryl Groups (Ar). The hydrocarbon group left after the removal of a hydrogen atom of the benzene itself is called phenyl group, which is often abbreviated as the symbol ϕ, Ph, or C_6H_5—. Thus toluene can be represented as :

$C_6H_5-CH_3$ Ph—CH_3 ϕ—CH_3

The symbol Ar is used to represent any aromatic (Ar) group just as R is used to represent any alkyl group. The common aryl groups which have trivial name are :

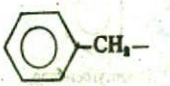
phenyl ϕ or Ph

o-tolyl

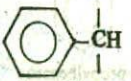
m-tolyl

p-tolyl

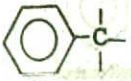
The groups derived by removal of hydrogen atom of the CH_3—group of toluene are :



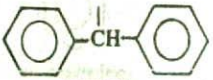
benzyl



benzylidene (formerly benzal)



benzo

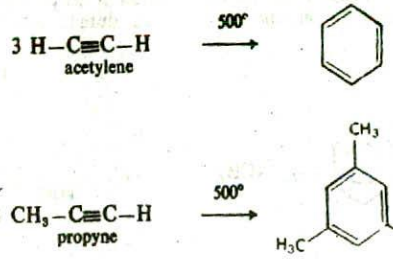


benzhydry

GENERAL SYNTHETIC METHODS OF PREPARATION

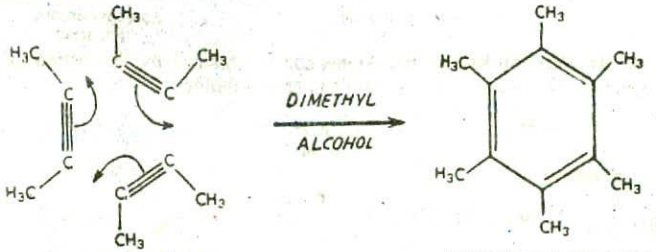
While benzene and its homologues are mostly obtained by distillation of coal-tar or from the petroleum fraction, the general methods for their synthesis are listed below. However, these methods are not widely used.

(1) **From Alkynes.** Benzene and many of its homologues can be prepared by polymerisation of appropriate alkynes. Acetylenes will polymerise at high temperature to yield arenes. Thus,



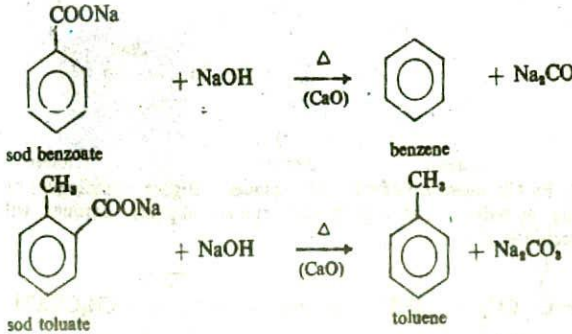
mesitylene

Recently catalysts *e.g.*, cobalt carbonyls and other metal complexes, have been found to catalyse the trimerisation of acetylenes in solution at low temperatures. Thus hexamethylbenzene has been prepared from 2-butyne in the presence of dimesityl cobalt (1961).

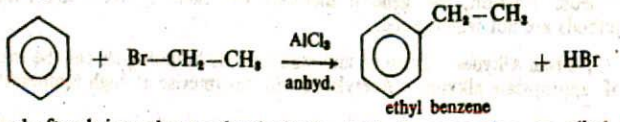


Very recently this method has been used for the large scale production of benzene from acetylene derived from petroleum sources.

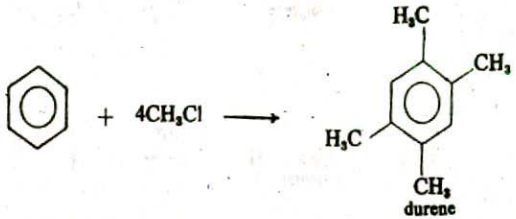
(2) **Decarboxylation of Aromatic acids.** Arenes can be prepared by heating aromatic acids or their sodium salts with sodalime.



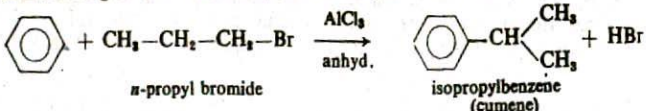
(3) **By Friedel-Crafts Reaction.** Alkylbenzenes can be best prepared by the action of alkyl halides on benzene and its homologues in the presence of anhydrous aluminium chloride as catalyst. For example,



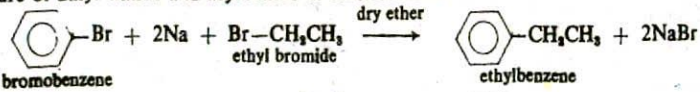
This method often brings about polysubstitution in the benzene ring, as alkyl benzenes are more easily substituted than benzene itself. Thus durene can be made straightaway by Friedel-Crafts Reaction.

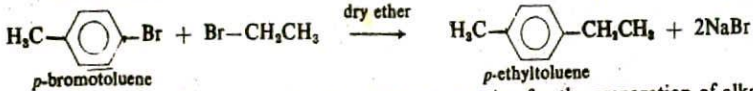


The higher normal alkyl halides undergo isomerisation and that these groups are introduced in the benzene ring in their secondary and tertiary forms. Thus,



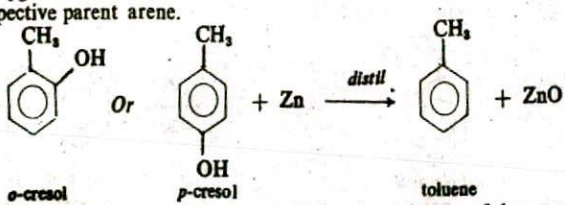
(4) **By Wurtz-Fitting Reaction.** Arenes con be obtained by the action of sodium metal on a mixture of alkyl halide and aryl halide in ether solution.



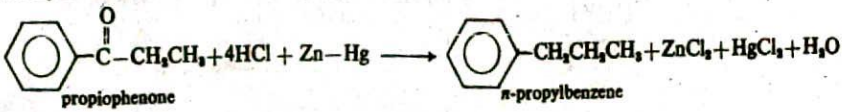


This method is, in fact, an extension of Wurtz reaction for the preparation of alkanes. It may be noted that in the reaction cited above from bromobenzene, diphenyl ($C_6H_5-C_6H_5$), and *n*-butane ($CH_3CH_2CH_2CH_3$) are also formed, but these can be easily separated by distillation because of their widely different boiling points.

(5) **By Deoxygenation of Phenols.** When distilled with zinc dust, phenols are deoxygenated to yield the respective parent arene.

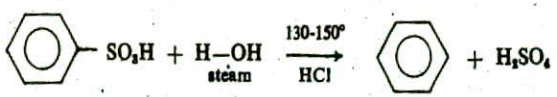


(6) **By Clemmensen Reduction of Ketones.** Higher homologues of benzene can be prepared easily by reduction of appropriate aromatic-aliphatic ketones with zinc amalgam and conc hydrochloric acid.



The ketone required for the reaction is prepared by the action of the corresponding acyl halide and arene in the presence of anhydrous aluminium chloride.

(7) **By Hydrolysis of Sulphonic acids.** Arenes can be produced from aromatic sulphonic acids by treating them with superheated steam at 130–150° in the presence of hydrochloric acid.



benzenesulphonic acid — benzene

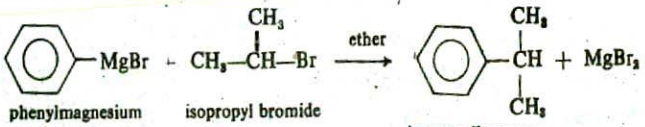
This method is helpful in separating arenes from alkanes which do not undergo sulphonation under similar conditions.

(8) **By Reduction of Diazonium Salts.** Aryldiazonium salts when reduced with hypophosphorus acid (H_3PO_2), yield corresponding arenes.

benzenediazonium chloride — benzene

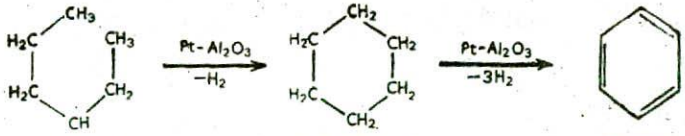
This reaction can be used for knocking out $-NH_2$ group from aromatic amino derivatives.

(9) **From Grignard Reagents.** The homologues of benzene can be synthesised by the action of an alkyl halide on Grignard reagent.



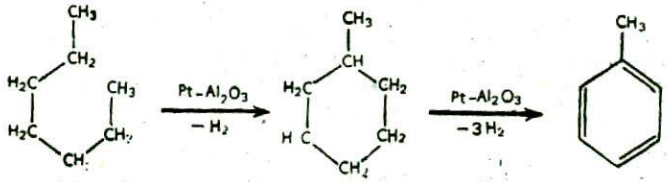
phenylmagnesium bromide — isopropyl bromide — isopropylbenzene

(10) **Cyclisation and Aromatisation of long-chain Alkanes.** Arenes are now synthesised on a large scale by passing the vapour of normal alkanes containing six to nine carbons over a metal catalyst (platinum supported on Al_2O_3) at 500°C. The reaction first involves cyclisation and is followed by aromatisation by loss of hydrogen.



n-HEXANE — CYCLOHEXANE — BENZENE

In a similar way, toluene is prepared from *n*-heptane and xylenes from *n*-octane.



n-HAPTANE — METHYLCYCLOHEXANE — TOLUENE

This method is now being used for the industrial production of benzene, toluene and xylenes.

PHYSICAL PROPERTIES

(1) Monocyclic arenes are colourless mobile liquids which have pleasant odours. The higher homologues are crystalline solids.

(2) They are lighter than and insoluble in water but are miscible in all proportions with organic solvents such as ethanol, ether, petrol, etc.

(3) They dissolve fats and many other organic substances which are insoluble in water.

(4) The lower members are quite toxic, and prolonged inhalation of their vapours should be avoided.

(5) Their boiling points increase fairly regularly with the rise of molecular weight. The melting points do not exhibit a regular gradation. These are highly dependent on molecular symmetry than on molecular weight. Benzene thus melts at 100°C higher than toluene, and the more symmetrical *p*-xylene has a higher melting point than either the *o*- or the *m*-isomer.

Table. Physical Properties of some Arenes

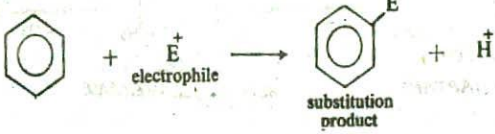
Name	*Structure*	*mp* °C	*bp*°C	*Density of liquid at 20°C*
Benzene	C_6H_6	5·5	80	0·8790
Toluene	$C_6H_5-CH_3$	−95	111	0·8660
Ethylbenzene	$C_6H_5-CH_2CH_3$	−94	136	0.8669
n-Propylbenzene	$C_6H_5-CH_2CH_2CH_3$	−99	159	0·8617
Isopropylbenzene	$C_6H_5-CH(CH_3)_2$	−96	152	0·8620
o-Xylene	$CH_3-C_6H_4-CH_3$ 1, 2-	−25	144	0·8968
m-Xylene	$CH_3-C_6H_4-CH_3$ 1, 3-	−47	139	0·8811
p-Xylene	$CH_3-C_6H_4-CH_3$ 1, 4-	−13	138	0·8541
Mesitylene	$C_6H_3(CH_3)_3$ 1, 3, 5-	−50	165	0·8634
Durene	$C_6H_2(CH_3)_4$ 1, 2, 4, 5-	80	191	—

CHEMICAL PROPERTIES

By far the most characteristic and useful reactions of arenes are those in which a hydrogen of the aromatic ring is substituted by an atom or group Y.

$$Ar-H \xrightarrow[\text{substitution}]{\text{aromatic}} Ar-Y$$

Such aromatic substitution reactions are, in fact, initiated by the attack of an electrophile (E^+) on the ring followed by the elimination of a proton (H^+). Thus,



The substitution reactions of aromatic ring caused by the presence of an active spieces, the electrophile (E^+), are commonly referred to as the **Electrophilic Substitution Reactions.**

GENERAL MECHANISM OF ELECTROPHILIC SUBSTITUTION

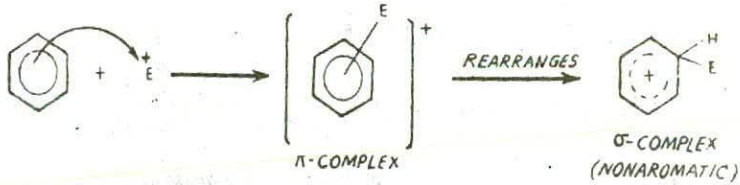
The benzene ring with its π electrons behaves as an electron-rich system. The electrons in the π clouds are readily available to form new bonds with electron-deficient spieces, the electrophile (E^+). The various electrophilic substitution reactions follow the same mechanistic pathway.

STEP 1. Generation of electrophiles either by *spontaneous dissociation* of the reagent (E—Nu) or by *acid-catalysed dissociation.*

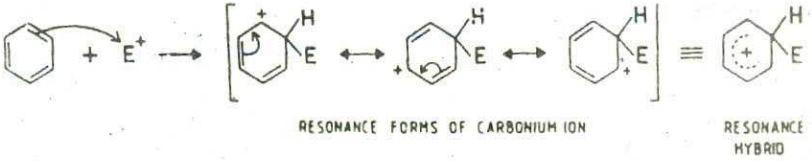
$$E{-}Nu \rightleftharpoons E^+ + Nu^- \qquad \text{(spontaneous dissociation)}$$

$$E{-}Nu + \underset{\text{(Lewis acid)}}{A} \rightleftharpoons E{-}\overset{+}{N}u{-}\bar{A} \rightleftharpoons E^+ + Nu{-}\bar{A} \qquad \text{(acid-catalysed dissociation)}$$

STEP 2. Formation of π-complex due to a loose association of the electrophile (E^+) with the aromatic ring. In this π-complex, the electrophile is not attached to any specific position of the ring, but later arranges to give the σ-complex.

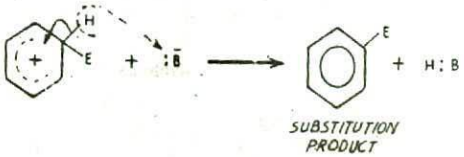


In fact the σ-complex is a resonance-stabilised carbonium ion produced by the attack of the electrophile on the benzene ring.

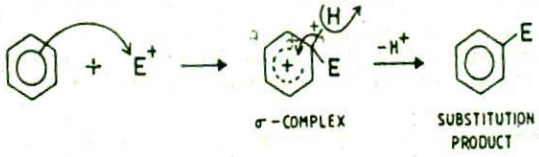


In the mechanism of the reactions that we will consider in this chapter, formation of the π-complex will be omitted for brevity. We will, therefore, write this step as

STEP 3. A proton (H^+) is then eliminated from the σ-complex by a base ($:\bar{B}$) to yield the final substitution product.

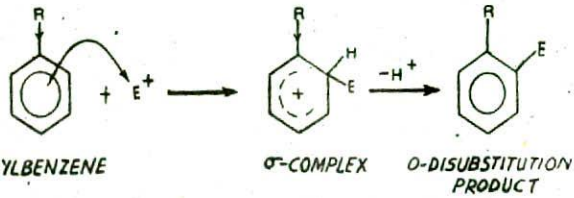


The *Overall Mechanism* of aromatic electrophilic substitution, putting the steps (2) and (3) together may be stated as

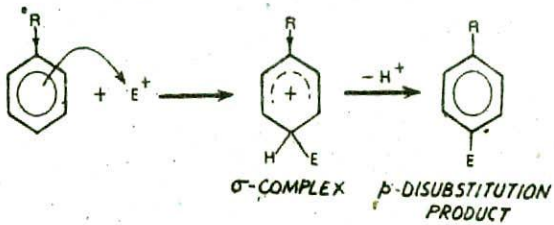


Alkyl benzenes, like benzene, undergo typical electrophilic substitution reactions As the alkyl groups are electron-pumping in nature, the electron density of π ring system increases in ortho and para positions. Thus the substitution reactions in alkylbenzenes proceed more readily than in benzene itself, and in ortho and para positions. The reaction mechanism is the same as already described for benzene.

Ortho-attack by E^+:

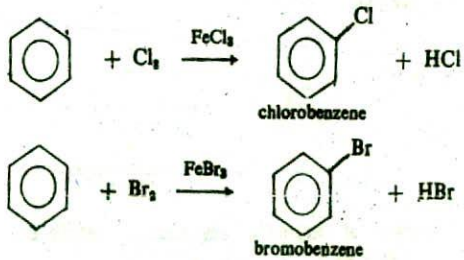


Para-attack by E^+:

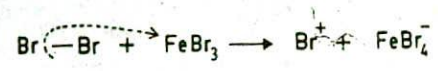


A. ELECTROPHILIC SUBSTITUTION REACTIONS OF ARENES

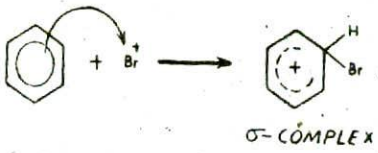
(1) **Halogenation.** (*a*) Benzene reacts with chlorine or bromine in the presence of a Lewis acid catalyst such as $AlCl_3$, $FeCl_3$ or $FeBr_3$ when substitution in the ring takes place, a proton being lost as HCl or HBr.



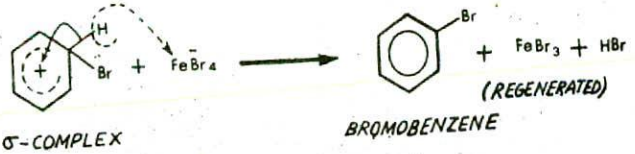
MECHANISM. (*i*) Generation of the electrophile Br^+



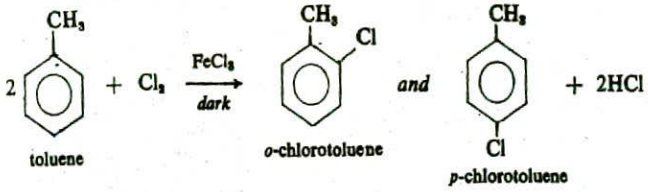
(*ii*) Formation of σ-complex



(*iii*) Elimination of a proton

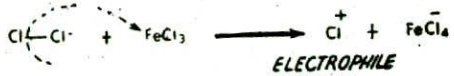


(*b*) **Halogenation of Toluene.** (*a*) When toluene is treated with chlorine or bromine in dark and in the presence of a Lewis acid catalyst ($FeCl_3$, $FeBr_3$), it undergoes halogenation in the ring in ortho and para position.

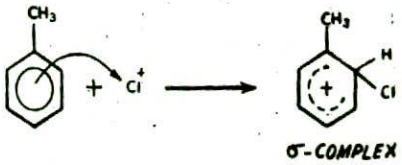


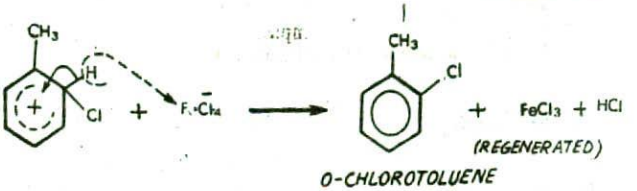
MECHANISM. The mechanism of formation of ortho and para chlorination/bromination product is the same as described for benzene. Thus *o*-chlorotoluene is produced by the steps :

(*i*) Generation of electrophile Cl^+

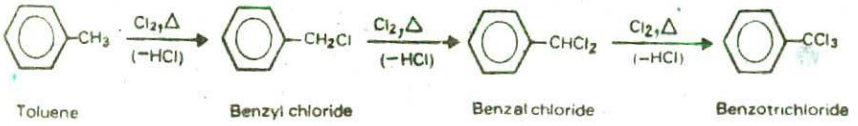


(*ii*) Formation of σ-complex



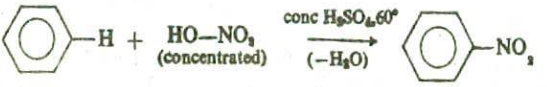
(iii) 

The para isomer is also produced by similar steps. (*b*) When chlorine or bromine is passed into boiling toluene, it attacks the side-chain and the hydrogen atoms of the CH_3 group are successively replaced.

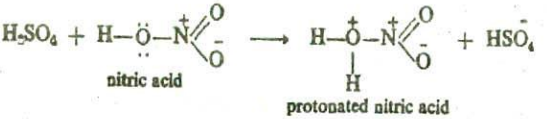


The substitution can be stopped at any stage by observing the increase of weight of the product. Substitution in side-chain is favoured by sunlight or UV-light and mechanistically resembles the halogenation of alkanes.

(2) **Nitration.** (*a*) Benzene reacts with nitric acid in presence of sulphuric acid to form nitrobenzene



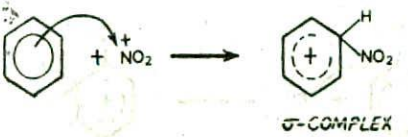
MECHANISM. (*i*) Generation of the electrophile nitronium ion by the protonation of concentrated nitric acid by sulphuric acid.



The overall reaction is :

$$HNO_3 + H_2SO_4 \longrightarrow \underset{\text{electrophile}}{NO_2^+} + HSO_4^- + H_2O$$

(*ii*) **Formation of σ-complex or stable resonance hybrid.**

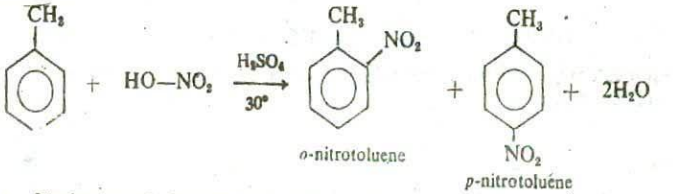


(*iii*) **Elimination of proton from σ-complex**

NITROBENZENE

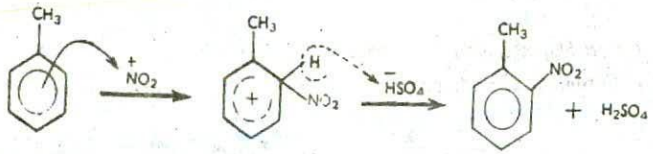
On prolonged treatment with nitrating mixture and at higher temperatures di- and trinitrobenzene can be obtained. The mechanism of the reaction remains the same as described above and the incoming nitro group occupies the meta position relative to the previous one.

(*b*) Toluene when treated with concentrated nitric acid and sulphuric acid gives *o*- and *p*-nitrotoluene.



o-nitrotoluene *p*-nitrotoluene

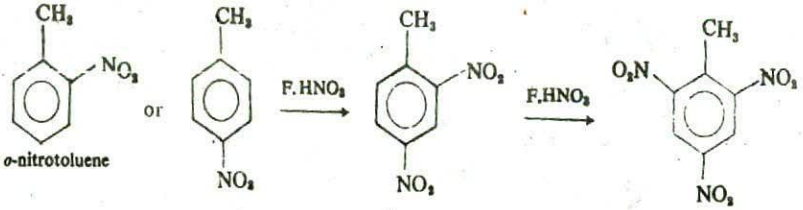
The *Mechanism* of the reaction remains the same as for benzene, except that the electrophile is attached to electron-rich sites (ortho and para).



TOLUENE *σ- COMPLEX* *O-NITROTOLUENE*

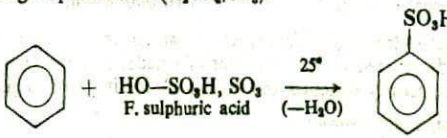
Nitration of toluene is easier than that of benzene, because CH_3 is an electron-releasing group and makes the π ring system electron-rich

Further nitration of toluene in the presence of fuming nitric acid yields 2, 4, 6-trinitrotoluene (TNT).



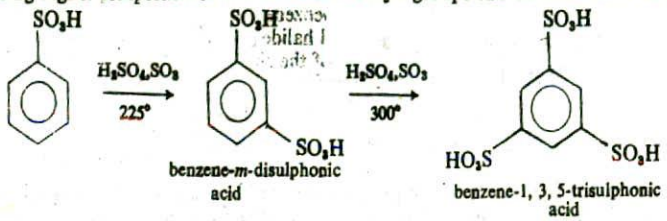
o-nitrotoluene *p*-nitrotoluene 2, 4-dinitrotoluene 2, 4, 6-trinitrotoluene

(3) **Sulphonation.** (*a*) Benzene may be sulphonated by treating it with concentrated sulphuric acid or fuming sulphuric acid ($H_2SO_4.SO_3$).



benzenesulphonic acid

By using higher temperatures two or three $-SO_3H$ groups can be introduced in the ring.

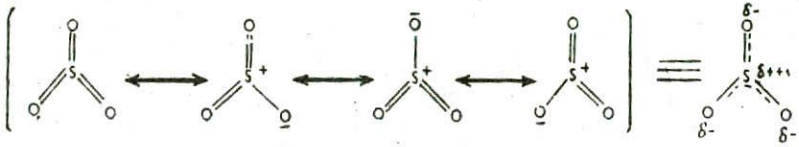


MECHANISM. Sulphonation of benzene to give benzenesulphonic acid follows the steps :

(*i*) Generation of the electrophile

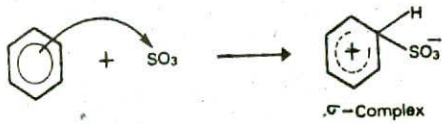
$$2H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^- + SO_3$$

Although SO_3 is a neutral molecule, its sulphur atom carries a positive charge due to resonance of the molecule.

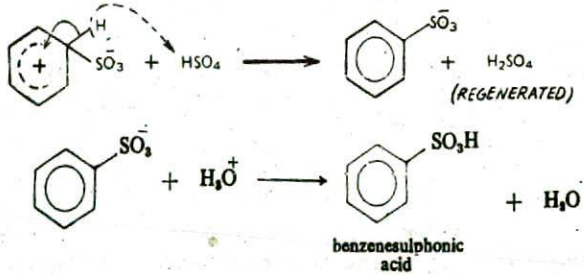


Therefore SO_3 acts as an electrophile.

(*ii*) Formation of σ-complex



(*iii*) Elimination of proton (H^+)



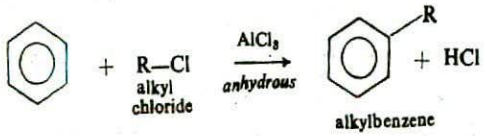
The similar mechanisms apply to *di-* and *tri*-sulphonation.

(4) Friedel-Crafts Reaction. This reaction, which now occupies prestigious positic organic synthesis, was discovered in 1877 by Charles Friedel and M. Crafts. Since then the s of the reaction has been greatly widened and we can divide it into two general types ·

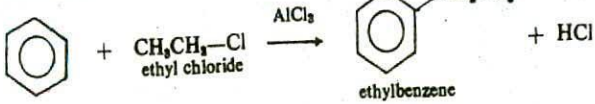
(*a*) ***Friedel-Crafts Alkylation*** ;

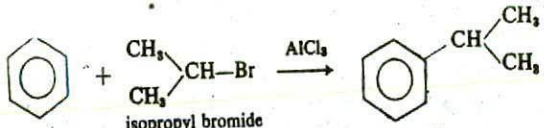
and (*b*) ***Friedel-Crafts Acylation.***

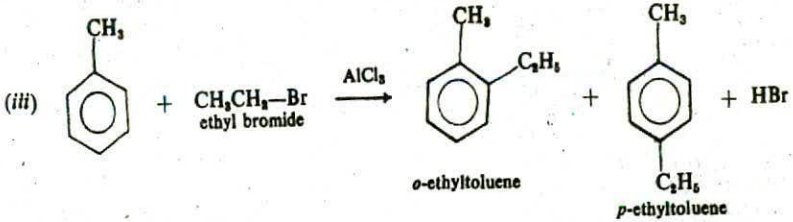
Friedel-Crafts Alkylation. This reaction involves the introduction of an alkyl group in the benzene ring for the synthesis of alkylbenzenes which are not ordinarily available. For illustration, when benzene reacts with an alkyl halide (RCl or RBr) in the presence of anhydrous $AlCl_3$ as catalyst, one of the hydrogen atoms of the ring is substituted by the alkyl group R.

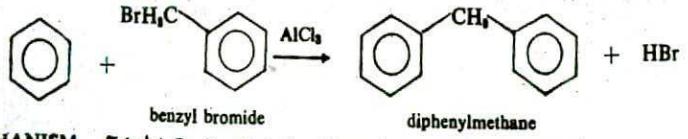


The alkylating agent used in Friedel-Crafts alkylation is an alkyl halide. The catalyst employed is a Lewis acid which may be $AlCl_3$, BF_3, $FeCl_3$, HF etc. Some examples illustrating the reaction to form arenes are :

(*i*)


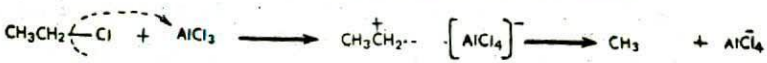
(*ii*)


(*iii*)


(*iv*)


MECHANISM. Friedel-Crafts alkylation is an electrophilic substitution reaction and proceeds by the following steps.

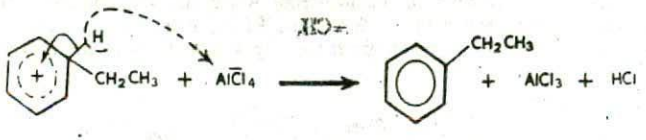
(*i*) Generation of the electrophile which in this case is a carbonium :



(*ii*) Formation of the σ-complex

σ- COMPLEX

(*iii*) Elimination of proton (H^+) from σ-complex

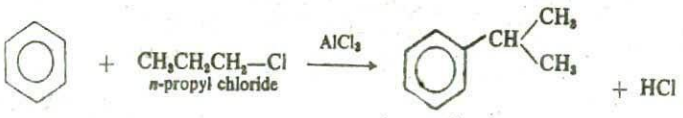


ethylbenzene

Drawbacks of Friedel-Crafts Alkylation

Although, the Friedel-Crafts alkylation reaction is very advantageous for attaching an alkyl group to an aromatic ring, it suffers from the following limitations.

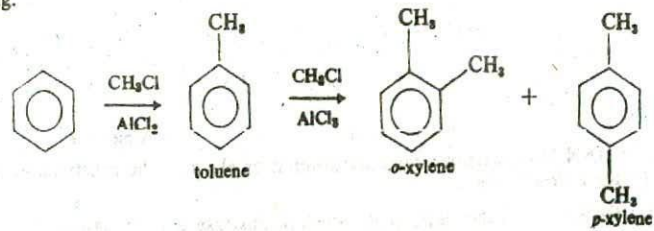
(*i*) *Rearrangement of the Alkyl group.* It is difficult to introduce an alkyl group higher than CH_3CH_2— group as it tends to undergo skeletal rearrangement. For example, alkylation of benzene with *n*-propyl chloride gives isopropylbenzene, and not *n*-propylbenzene.



isopropylbenzene (cumene)

This is due to the fact that *n*-propylcarbonium that results from interaction with $AlCl_3$, undergoes rearrangement to give more stable isopropyl carbonium ion, which electrophile then attacks benzene as usual to form isopropylbenzene.

(*ii*) *Polyalkylation.* The introduction of an alkyl group in benzene activates the ring for further electrophilic substitution. Thus more than one alkyl groups get attached to the aromatic ring.

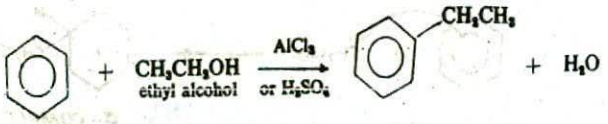


toluene *o*-xylene *p*-xylene

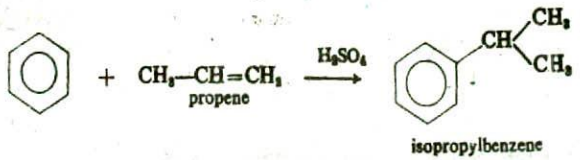
(*iii*) *Hindrance due to meta orienting groups.* The presence of a meta-orienting group in the aromatic ring hinders the Friedel-Crafts alkylation as such a group lowers the electron-density in the ring. Thus nitrobenzene does not respond to Friedel-Crafts reaction.

Extension of Friedel-Crafts Alkylation

The reagents like alkenes and alcohols are also now used in place of alkyl halide. Thus,

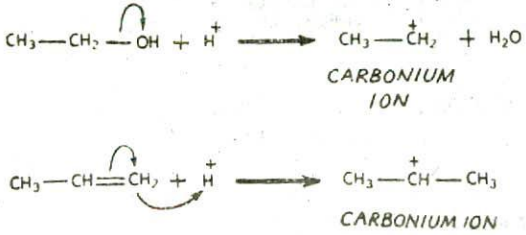


ethylbenzene

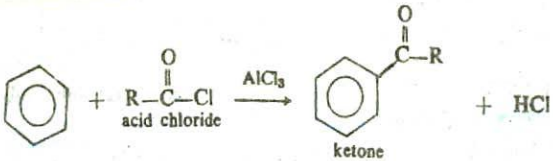


isopropylbenzene

The alcohol or the alkene provides the carbonium ion which servs as electrophile to initiate the mechanism of electrophilic substitution.

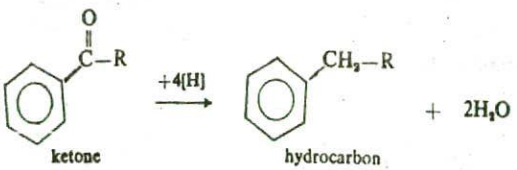


Friedel-Crafts Acylation. This reaction involves the introduction of an acyl group (RCO—) in the aromatic ring in the presence of anhydrous $AlCl_3$ (or other Lewis acid catalysts : BF_3, $FeCl_3$, $ZnCl_2$). The acylating agents employed are acid chlorides, acid anhydrides and esters.



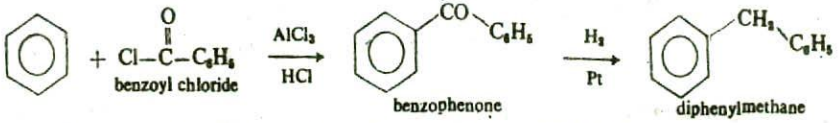
ketone

Friedel-Crafts Acylation reaction can be used in preference to the Friedel-Crafts alkylation as it is free from the two chief drawbacks of the latter : skeletal rearrangement and polysubstitution. The ketone obtained can be conveniently reduced to give the required hydrocarbon.



ketone hydrocarbon

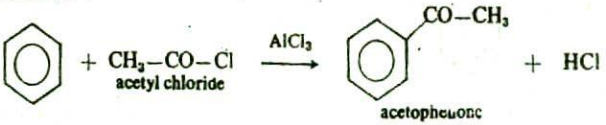
For example,



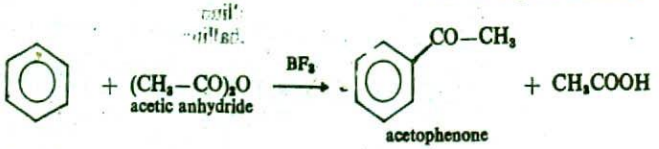
benzophenone diphenylmethane

Some examples indicating the synthetic applications of Fridel-Crafts Acylation reaction are listed below.

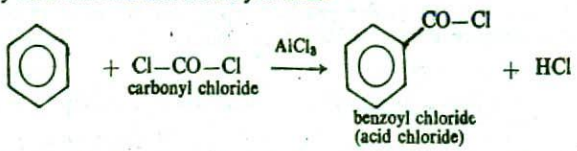
(*i*) ***Synthesis of Ketones*** :



acetophenone



(*ii*) *Synthesis of Acid chlorides and Carboxylic acids.*

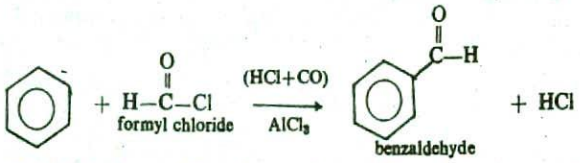


The acid chloride upon hydrolysis would yield the corresponding carboxylic acid.

$$\underset{\text{benzoyl chloride}}{C_6H_5-CO-Cl} + H_2O \longrightarrow \underset{\text{benzoic acid}}{C_6H_5-CO-OH} + HCl$$

(*iii*) *Synthesis of Aldehydes (Formylation)*

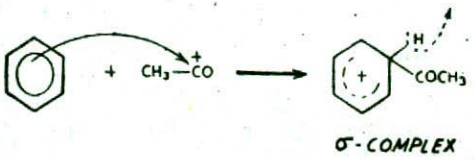
Here the arene is treated with hydrogen chloride and carbon monoxide in the presence of $AlCl_3$, when formylation occurs.



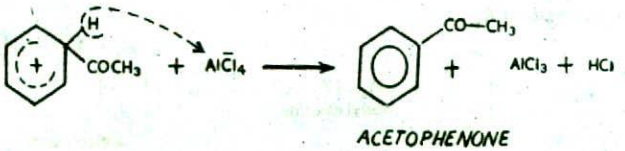
MECHANISM. Friedel-Crafts acylation is an electrophilic substitution reaction and follows the pathway sketched below.

(*i*) Generation of electrophile which is an acylium ion

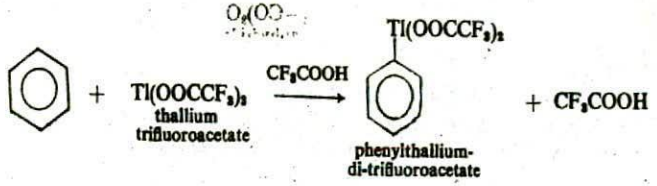
(*ii*) Formation of σ-complex



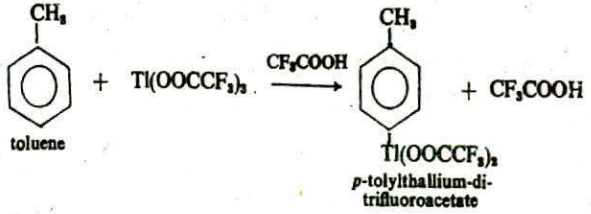
(*iii*) Elimination of proton ($\overset{+}{H}$)



(5) **Thallation.** Arenes react with thallium trifluoroacetate, $Tl(OOCCF_3)_3$, dissolved in trifluoroacetic acid (CF_3COOH), to form arylthallium-di-trifluoroacetates which are stable crystalline compounds.

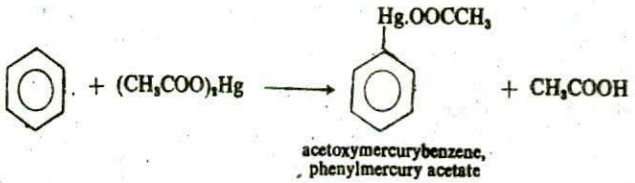


Similarly, thallium gives *p*-tolylthallium di-trifluoroacetate.



This reaction is believed to proceed by the electrophilic attack on the benzene ring by the Lewis acidic thallium.

(6) **Mercuration.** Arenes when heated with mercuric acetate undergo mercuration whereby a hydrogen atom of the benzene ring is replaced by acetoxy-mercuric group. $-Hg.OOCCH_3$

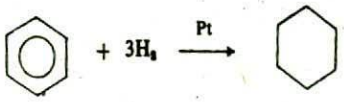


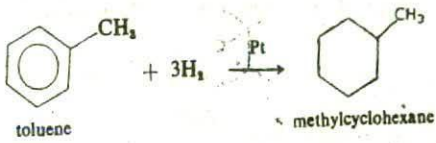
Since the mercury atom directly bonded to carbon can be readily replaced by other atoms or groups, this reaction is now increasingly used as a synthetic method as also for the preparation of valuable *mercurial drugs*.

B. ADDITION REACTIONS

Benzene and its derivatives are far less prone to undergo addition reactions than alkenes or alkynes. This is so because their special stability arising from aromaticity is lost in the addition process. However, arenes undergo the following addition reactions.

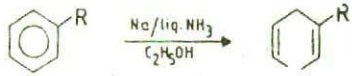
(7) **Catalytic Hydrogenation.** Benzene in the presence of molecular hydrogen and finely divided platinum yields cyclohexane.



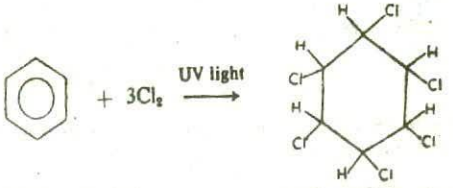


toluene methylcyclohexane

A recent technique for the partial reduction of aromatic rings, is with **sodium** metal in ammonia-alcohol mixture (***Birch reduction***). For example.



(8) **Addition of Halogens.** Under the influence of ultraviolet light, arenes add three molecules of chlorine (or bromine) to form hexachlorohexane.



hexachlorocyclohexane
(benzenehexachloride)

On chlorine addition of benzene, nine noninterconvertible stereoisomers of the hexachlorocyclohexane products are possible. Of these eight have been characterised. The *gamma isomer*, known as **Lindane**, is a useful insecticide. The commercial products are. in fact, mixtures of all the isomers but only the γ-isomer has the insecticide property. A simplified chair form formula of the γ-isomer is given in Fig. 35·14

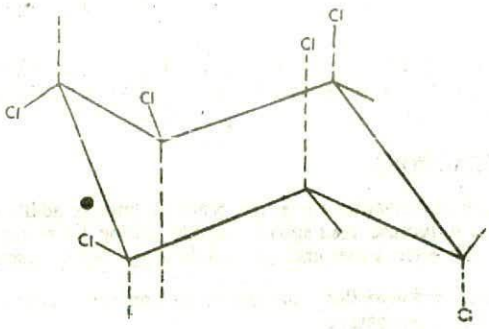
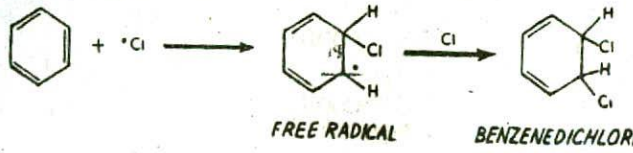


Fig. 35·14. Structural formula of γ-isomer of hexachlorocyclohexane.

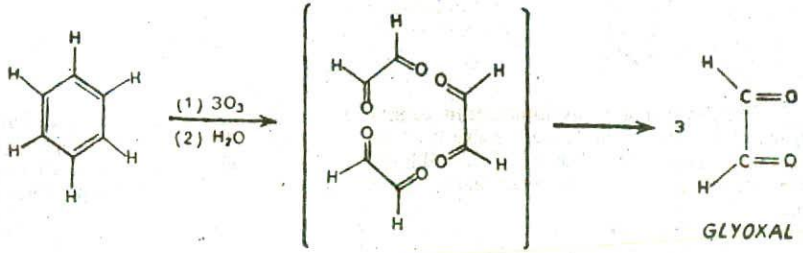
MECHANISM. The addition of halogen to benzene ring is considered to follow the mechanism given below.

$$Cl_2 \xrightarrow{h\nu} 2 \cdot Cl \quad \text{(free radical)}$$



The above steps are repeated twice again to yield benzenehexachloride.

(9) **Ozonide Formation.** Benzene and its derivatives, add three molecules of ozone to form unstable triozonides. The triozonide obtained from benzene is unstable and on hydrolysis yields three molecules of glyoxal.

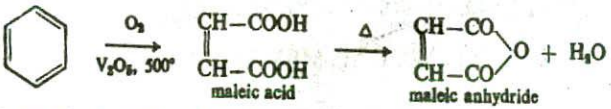


Formation of three molecules of glyoxal by rupture of benzene ring at the double bonds accompanied by oxidation. The unstable triozonide is not shown.

The mechanism of ozonolysis through the formation of ozonide at each double bond is the same as for alkenes. It points to unsaturation in the benzene ring.

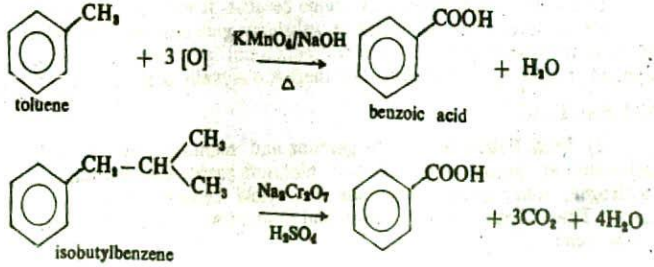
C. OTHER REACTIONS

• (10) **Oxidation Reactions.** (*a*) Benzene is very stable to oxidising agents like hot potassium permanganate and sodium dichromate plus H_2SO_4. However, vapour phase oxidation of benzene is quickly brought about by passing its vapour mixed with oxygen over vanadium pentoxide at 500°C. The ring gets ruptured to yield maleic anhydride.

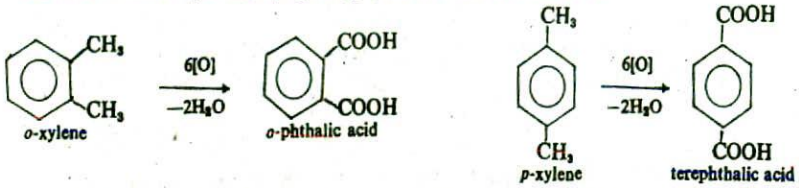


This reaction is employed for the manufacture of maleic anhydride.

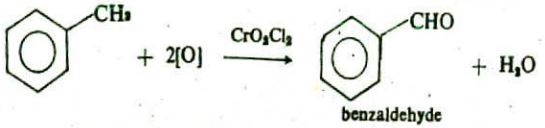
(*b*) **ALKYLBENZENES.** When oxidised under strenuous conditions ($KMnO_4/NaOH$; $Na_2Cr_2O_7/H_2SO_4$), the entire side-chain, regardless of length, is oxidised to a —COOH group. Thus :



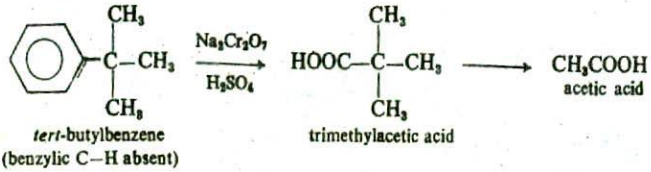
The three isomeric xylenes, $C_6H_4(CH_3)_2$, yield the corresponding phthalic acids.



TOLUENE on mild oxidation with an oxidant such as chromyl chloride gives benzaldehyde (*Etard Reaction*).



The conversion of alkylbenzenes to benzoic acid with strong oxidants as stated above, suggests that benzene ring is more stable than the side-chains. This is correct so long as the side-chain contains at least one benzylic C—H bond. If the side-chain contains no C—H bond at the root carbon, it is far more resistant to oxidative cleavage, and benzoic acid is not formed Thus,



The appearance of —COOH group on the aromatic ring by strenuous oxidation. tells the point or points where the side-chain was attached.

(11) **Combustion.** Arenes burn with a sooty flame giving carbon dioxide and water vapour.

$$2C_6H_6 + 15O_2 \longrightarrow 12CO_2 + 6H_2O$$

$$C_6H_5{-}CH_3 + 9O_2 \longrightarrow 7CO_2 + 4H_2O$$

INDIVIDUAL MEMBERS

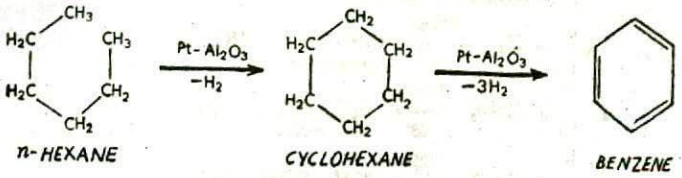
BENZENE, C_6H_6

Benzene is the simplest member which heads the class of aromatic hydrocarbons. It was first isolated by Faraday (1825) from oil condensed in cylinders containing compressed *illuminating gas* produced by destructive distillation of vegetable oils. Hofmann (1849) separated benzene from coal-tar.

This hydrocarbon derived its name because it was obtained by the decarboxylation of benzoic acid isolated from the aromatic substance *gum benzoin*. Its industrial name is 'benzol'. Benzene is an exceedingly important compound not only because it is the parent of all aromatic compounds but because numerous of these are actually prepared from them.

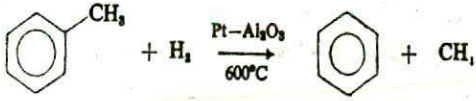
MANUFACTURE

(1) **From Petroleum.** If the gasoline and naphtha fraction obtained by the distillation of petroleum are passed over a catalyst, platinum suspended on alumina, In presence of excess of hydrogen, *n*-hexane and *n*-heptane *etc.*, yield benzene, toluene and other homologues of benzene. Thus *n*-hexane on cyclisation and aromatisation in the presence of platinum catalyst forms benzene



This process known as PLATFORMING is now used for the large scale production of benzene and its homologues (benzene, toluene, xylenes). Benzene is obtained from the resulting mixture by solvent extraction and by fractional distillation. 90% of commercial benzene is now obtained from petroleum.

(2) **From Toluene by Hydrodealkylation.** Toluene is the major product obtained from petroleum sources. Therefore it is converted to benzene, which is in much greater demand, by *hydrodealkylation.*

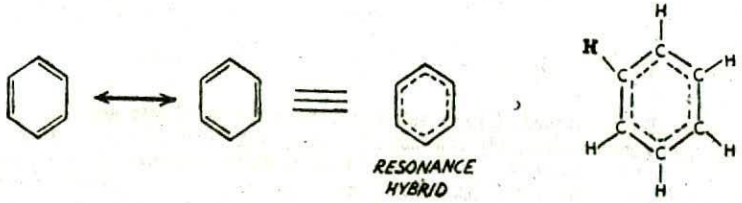


(3) **Distillation of Coal-tar.** At one time light oil obtained by the distillation of coal tar done with a purpose of preparing coal-gas, was the only source of benzene. Now high-temperature carbonisation of coal has been introduced for producing coke for metallurgical sources, and benzene may be recovered from the fuel gas, so obtained. At present less than 10% of the total production of benzene comes from this source.

The manufacture of benzene from coal and petroleum sources has already been discussed in detail.

Properties. (*Physical*). Benzene is a colourless, highly refractive, mobile liquid, mp 5·5° bp 80°, sp gr 0·8790 at 20°. It has a characteristic odour which is not unpleasant. It is insoluble in water and soluble in all organic solvents such as ether, ethanol, and petrol. It is itself a very good solvent for organic compounds like fats, resins etc. Both the liquid and vapour benzene is highly poisonous and must be used with care.

(*Chemical*). We have already discussed that benzene molecule is made of a six-carbon ring carrying one hydrogen on each carbon with a delocalised π orbital. It could be represented as resonance hybrid of the two Kekule forms.



Thus benzene ring being stable, the H atoms are capable of undergoing substitution. The double-bond character of each bond is intermediate between that of ordinary C—to—C double bond in alkenes and a single C—to—C bond in alkanes. Therefore while benzene can form addition products, it can also undergo oxidation under vigorous conditions. We have, in fact, discussed these reactions of benzene under the Chemical Properties of Arenes. Here we will sketch the same in a summary form by way of recapitulation.

benzene

(a) Electrophilic Substitution Reactions :

1. $+ Cl_2 \xrightarrow{FeCl_3} C_6H_5—Cl + HCl$ (chlorobenzene)

2. $+ HNO_3 \xrightarrow[60°]{H_2SO_4} C_6H_5—NO_2 + H_2O$ (nitrobenzene)

3. $+ H_2SO_4 \xrightarrow{25°} C_6H_5—SO_3H + H_2O$ (benzenesulphonic acid)

4. $+ C_2H_5Br \xrightarrow{AlCl_3} C_6H_5—C_2H_5 + HBr$ (ethylbenzene)

5. $+ CH_3COCl \xrightarrow{AlCl_3} C_6H_5—CO—CH_3 + HCl$ (acetophenone)

6. $+ (CH_3COO)_2Hg \longrightarrow C_6H_5—Hg—OOCCH_3 + CH_3COOH$

7. $+ Tl(OOCCF_3)_3 \xrightarrow{CF_3COOH} C_6H_5—Tl(OOCCF_3)_2 + CF_3COOH$

(b) Addition Reactions :

8. $+ 3H_2 \xrightarrow{Pt}$ (cyclohexane)

9. $+ 3Cl_2 \xrightarrow{UV\ light}$ (hexachlorocyclohexane)

10. $+ 3O_3 \longrightarrow C_6H_6(O_3) \xrightarrow{H_2O} 3\ OHC—CHO$ (triozonide → glyoxal)

(c) Other Reactions :

11. $+ O_2 \xrightarrow[500°]{V_2O_5}$ (maleic acid) $\xrightarrow{\Delta}$ (maleic anhydride) $+ H_2O$

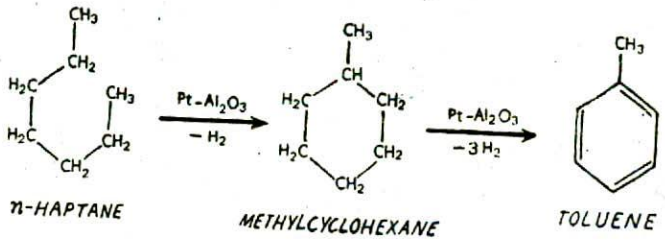
12. $+ 15/2\ O_2 \xrightarrow{combustion} 6CO_2 + 3H_2O + 788\ Kcal$

Uses. Benzene is used : (1) as a solvent for the extraction of fats and oils ; (2) for dry-cleaning of woolen clothes ; (3) as a motor fuel along with petrol ; (4) as a starting material for its various derivatives, and for dyes, drugs, perfumes, explosives etc. ; (5) for the preparation of styrene and polystyrene, and cyclohexane, required in the manufacture of plastics; (6) for making phenol needed for producing Bakelite ; and (7) for the manufacture of maleic anhydride by catalytic oxidation.

TOLUENE, *Methylbenzene*, $C_6H_5—CH_3$

It is the simplest homologue of benzene. It takes its name from *Tolu balsan* from which it was first obtained by distillation. Its industrial name is 'toluol'.

Preparation Toluene is prepared from petroleum and coal by the same methods as employed for benzene. *n*-Heptane derived from petroleum fractions (gasoline and naphtha) is converted to toluene by passing its vapours over the platinum catalyst ($Pt\text{-}Al_2O_3$).

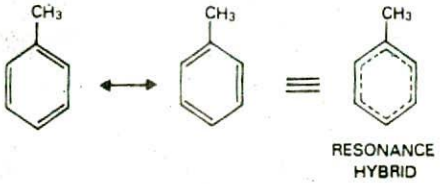


In 1970, the U.S. production from petroleum was 850 million gallons, only about 2% coming from coal.

Properties (*Physical*). Like benzene, toluene is a colourless mobile liquid, mp −95°, bp 111°, sp gr 0·866 at 20°. It has an odour similar to benzene. It is insolube in water but is soluble in organic solvents such as ethanol, ether and petroleum. Toluene itself is a good solvent for many organic substances.

It may be noted that the melting point of toluene is lower than that of benzene, although it has the higher formula weight. This is so because the planar symmetrical molecules of benzene can pack closely in the crystal and the cohesive forces are strong, whereas the methyl group in toluene does not permit such close packing.

(*Chemical*). Toluene, like benzene, may be represented as a resonance hybrid of two canonical forms.

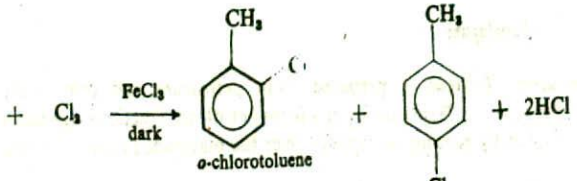


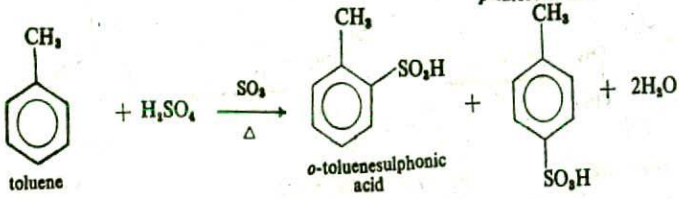
Since CH_3 group is an electron-releasing group, it increases the overall electron density of the ring. Thus toluene gives all the reactions of benzene ring more readily.

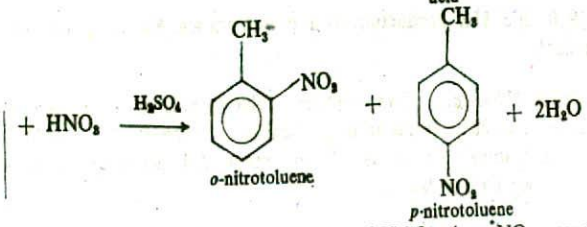
Toluene undergoes three types of reactions : (*i*) Electrophilic substitution in the rings; (*ii*) Addition to the ring; and (*iii*) Substitution in the methyl group.

A. Electrophilic Substitution Reactions

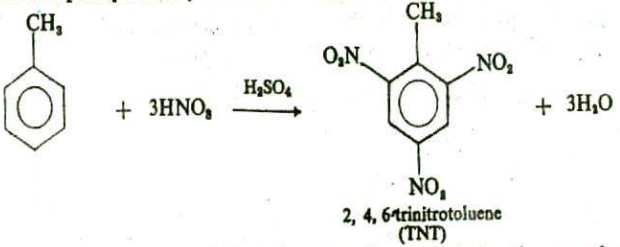
Toluene gives all the electrophilic substitution reactions which benzene does. The incoming substituent goes to the ortho and para positions. These reactions have already been discussed in detail as also their mechanism. They will be listed here for recapitulation.





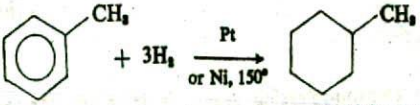


On prolonged reaction of toluene with HNO_3 and H_2SO_4, three NO_2 groups occupying both ortho positions and para position yield the traditional explosive TNT.



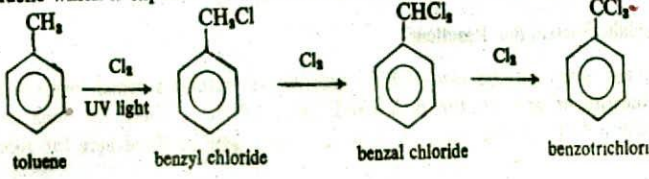
This explosive, which at one time epitomized the horrors of war and destruction, now has faded into insignificance in the face of the hydrogen bomb which is as destructive as millions of tons of TNT.

B. Addition Reactions



C Substitution in CH_3 group

(1) We have seen that when chlorine is passed through toluene at room temperature in the presence of a catalyst ($FeCl_3$, $AlCl_3$), the electrophilic substitution takes place in the ring, forming *o*-choloro and *p*-chloro toluenes. On the other hand if chlorine is passed through boiling toluene which is exposed to ultraviolet light, substitution in the side-chain occurs



These products separately upon hydrolysis yield respectively benzyl alcohol, benzaldehyde, and benzoic acid.

The oxidation of CH_3 group gives CHO group or COOH group, depending on the oxidant used.

$$C_6H_5-CH_3 \xrightarrow{CrO_2Cl_2} C_6H_5-CHO$$
benzaldehyde

$$C_6H_5-CH_3 \xrightarrow[\text{alkaline}]{KMnO_4} C_6H_5-COOH$$
benzoic acid

Uses. Toluene is used : (1) for blending petrol; (2) as a solvent for synthetic resins, surface coatings, and adhesives; (3) for the preparation of benzyl chloride, benzal chloride and benzotrichloride, which upon hydrolysis give benzyl alcohol, benzaldehyde, benzoic acid, of these large amounts of benzyl chloride are consumed for making benzyl phthalate plasticisers for vinyl floor tiles; (4) for the production of the high explosive TNT, which is still important; and (5) large amounts of toluene obtained from coal and petroleum sources are converted into benzene by hydrodealkylation.

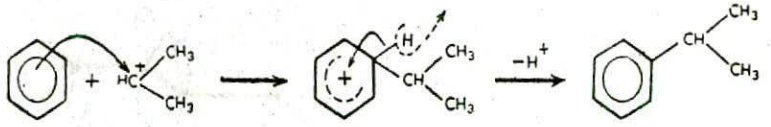
CUMENE, *Isopropylbenzene*, $C_6H_5-CH(CH_3)_2$

Cumene is synthesised by Friedel-Crafts reaction in which benzene is alkylated with propylene.

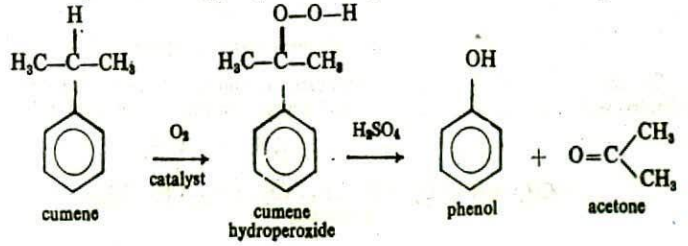
$$CH_3-CH=CH_2 + C_6H_6 \xrightarrow[\text{or } AlCl_3]{H_2SO_4} C_6H_5-CH(CH_3)_2$$
propene — cumene

The propene provides the carbonium ion which is necessary for electrophilic substitution in the benzene ring.

$$CH_3-CH=CH_2 \xrightarrow{H^+} CH_3-\overset{+}{C}H-CH_3$$



Properties. Cumene is a colourless liquid, bp 153°. It has recently become a source of commercial phenol. When oxygen is bubbled at 130°, through an emulsion containing cumene and metal catalyst, cumene hydroperoxide is formed. The cumene hydroperoxide in the presence of 10% sulphuric acid splits to from acetone and phenol

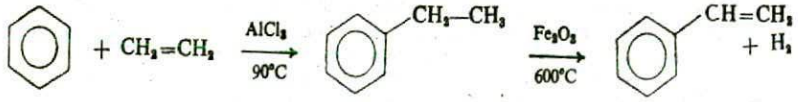


This reaction has been recently (1950) used for the industrial production of phenol and acetone which is produced as a side-product.

STYRENE, *Vinylbenzene, Phenylethylene*, $C_6H_5—CH=CH_2$

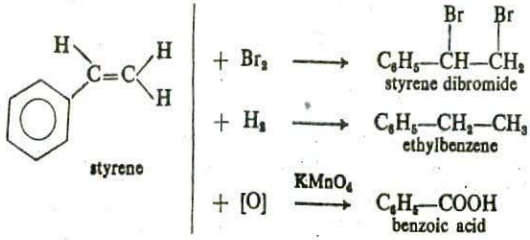
It occurs in coal-tar and the plant *storax* (hence its name).

Preparation. Styrene is manufactured by the reaction of benzene with ethylene in liquid phase using $AlCl_3$ as catalyst at 90°C at moderate pressure. The ethylbenzene thus obtained is dehydrogenated at 600°C over a catalyst (Fe_2O_3, ZnO or MgO) supported on alumina.



benzene ethylbenzene styrene

Properties. Styrene is a colourless liquid, bp 145°C. It behaves largely like ethylene at the double bond of the side chain. It adds bromine to form the dibromide and hydrogen to form ethylbenzene.



The stability of benzene ring as an independent unit from side-chain (—CH=CH$_2$) is justified. The overlap of π-electron clouds of the first *p* orbital of vinyl group and that of the *p* orbital on the adjoining carbon of the ring will not be possible, as the two are placed in different planes.

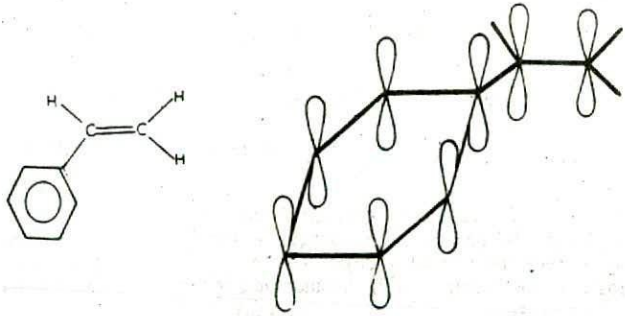
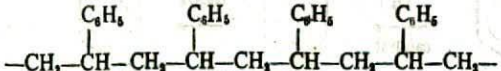


Fig. 35·17. The π-electronic system of styrene.

Styrene polymerises rapidly when exposed to sunlight to form metastyrene, $(C_8H_8)_n$. When heated with dibenzoyl peroxide (initiator), styrene polymerises to form polystyrene.

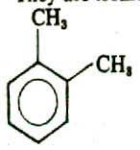


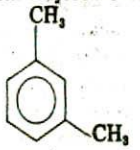
polystyrene

Uses. Styrene is used for : (1) making plastics and SBR rubber ; and (2) polystyrene for making light-weight packaging materials and a wide variety of household goods such as egg boxes and lining material for refrigerators.

XYLENES, *Dimethylbenzenes*, $CH_3—C_6H_4—CH_3$

The three position isomers *o*-, *m*-, and *p*-xylenes are present in coal-tar in very small amounts (about 1%). They are isomeric with ethylbenzene.

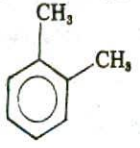

o-xylene

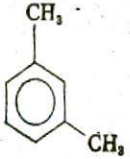

m-xylene


p-xylene

Isolation from Light Naphtha. The three isomeric xylenes are now produced industrially by reforming $C_6 - C_8$ petroleum fraction of light naphtha at 400-500°C at 25-35 atm pressure over a platinum-alumina catalyst. The cyclisation and aromatisation gives a mixture of benzene, toluene and xylenes. In the BTX plant the aromatics produced by reforming are extracted with diethylene glycol and refractionated. The C_9H_{10} fraction is subjected to distil *o*-xylene, and an apparently inseparable mixture of the *m*- and *p*-isomer. When the mixture is cooled to —60°C, pure *p*-xylene (mp —13°C) separates as a crystalline solid, leaving the mother liquor rich in *m*-xylene.

Properties. The three xylenes are colourless, mobile liquids having rather pleasant odours. Their boiling and melting points are listed below.

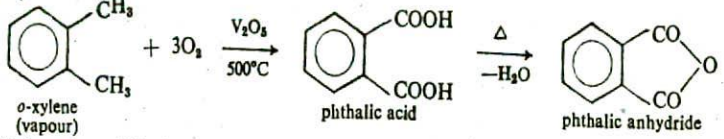

mp —25°C
bp 144°C


mp —47°C
bp 139°C


mp —130°C
bp 138°C

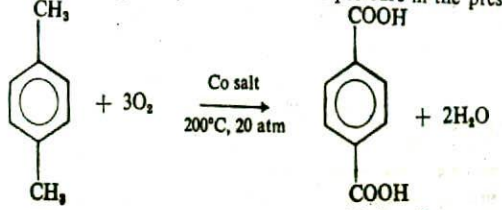
The xylenes form substitution products much in the same way as toluene. On oxidation with alkaline or acid $KMnO_4$, or acid $K_2Cr_2O_7$, the methyl groups are converted to COOH groups.

o-Xylene on oxidation with air in the presence of V_2O_5 gives phthalic anhydride (*Commercial*).



o-xylene (vapour) — phthalic acid — phthalic anhydride

p-Xylene is oxidised to terephthalic acid on a large scale by one of the most recent methods, by passing air into the liquid hydrocarbon under pressure in the presence of a cobalt salt catalyst.



terephthalic acid

Uses. (1) A mixture of xylenes as such (*Xylol*) is used as a solvent diluent for making lacquers ; (2) *o*-xylene is the raw material for the manufacture of phthalic anhydride ; and (3) *p*-xylene is used for production of polyester fibers (Dacron, Terylene).

QUESTIONS

1. What are the arenes ? Give one example of each of the monocyclic, dicyclic and tricyclic arenes.
2. Discuss in detail the Kekule structure of benzene, giving arguments for and against its validity.
3. "Benzene is a resonance hybrid of the two structures proposed by Kekule" Comment.
4. Derive the molecular orbital structure of benzene. What evidence could be cited in support of it ?
5. Define the term 'AROMATICITY'. Discuss the modern theory of aromaticity, making a special mention of Huckel Rule. Does this rule apply strictly in case of pyridine and pyrrole ?
6. State the IUPAC system as applied to the naming of arenes. Give four examples for illustration of this system.
7. What are the aryl groups ? Give names of aryl groups derived from benzene and toluene.
8. Discuss concisely the methods of synthesis of benzene and its homologues, making a special mention of Friedel-Crafts reaction and Wurtz-Fittig reaction.
9. Describe the physical characteristics of monocyclic arenes. How do you explain "Benzene and its homologues show regularity in the increase of boilling points, while their melting points do not exhibit regular gradation."
10. What do you understand by the term 'Electrophilic substitution' of arenes ? Discuss its mechanism
11. List the electrophilic substitution reactions of benzene and toluene and their mechanisms.
12. Write notes on : (*a*) nitration ; (*b*) sulphonation ; and (*c*) Friedel-Crafts alkylation, giving their detailed mechanisms.
13. State the addition reactions of benzene, particularly those with halogens and ozone.
14. Give the general reactions of arenes, writing equations taking examples of benzene and toluene only.
15. How is benzene prepared industrially from petroleum and coal-tar ? Make a special reference to the process of 'platforming' as applied to the production of benzene.
16. Give the method of production, properties and uses of toluene.
17. Write short notes on : (*a*) Cumene ; and (*b*) Styrene. Draw the orbital structure of styrene on paper.
18. How are xylenes obtained from petroleum ? How will you distinguish between the ortho and para xylenes ?
19. Explain the mechanism of electrophilic substitution in Benzene. (*Kurukshetra BSc III, 1980*)
20. Explain Friedel Crafts alkylation of benzene with the help of its mechanism. (*Himachal BSc II, 1980*)
21. Explain: Electrophilic substitution occurs more easily in toluene than in benzene. (*Andhra BSc II, 1980*)
22. (*a*) Starting from benzene or toluene, how would you synthesise the following compounds Discuss most likely mechanism of each reaction:
    (*i*) p-Nitrotoluene (*ii*) Acetophenone. (*Punjab BSc II, 8980*)
23. Discuss the mechanism of: (*i*) Friedel-Crafts reaction; (*ii*) Aromatic nitration. (*Madras BSc III 1980*)
24. Discuss the mechanism of nitration and acetylation of benzene. (*Punjabi BSc, 1980*)
25. (*a*) What are the special features of aromatic character ?
    (*b*) Explain the mechanism of alkylation of benzene. (*Mysore BSc II, 1980*)
26. What are the modern views about the structure of Benzene ? Give some examples of nonbenezenoid aromatic compounds.
    Discuss the mechanism of electrophilic substitution in aromatic compounds. (*Banaras BSc II, 1980*)
27. What is the criterion of aromaticity according to Huckel's rule ? (*Kerala BSc II, 1980*)
28. Give the mechanism of chlorination of aromatic hydrocarbons. (*Calicut BSc III, 1980*)
29. Write an account of the mechanism of aromatic substitution with reference to nucleophile and electrophile and illustrate your answer with suitable examples. (*Jammu BSc II, 1980*)
30. Give the modern views about the structure of Benzene. (*Delhi BSc III 1980*)
31. What structural features are necessary for a molecule to be aromatic ? (*Punjab BSc Chem Engg. 1980*)

32. Discuss the mechanism of sulphonation in benzene. *(Jammu BSc, 1980)*

33. What is meant by electrophilic substitution. Illustrate your answer with reference to rections of benzene. *(Annamali BSc III, 1980)*

34. How is the structure of benzene explained by: (*i*) Resonance; (*ii*) Molecular Orbital theory. *(Gorakhpur BSc III, 1981)*

35. Define aromaticity and explain Huckel's rule. Will cyclooctatetraene show aromatic character ? *(Guru Nanak Dev BSc II, 1981)*

36. How would you introduce the following in an aromatic ring ?
(*i*) —Cl; (*ii*) —COOH; (*iii*) —$COCH_3$. *(Manipur BSc Hons, 1981)*

37. (*a*) What is aromaticity ?
(*b*) Which of the following compounds will show aromaticity. Give reasons.
(*i*) Benzene (*ii*) Cyclooctatetraene (*iii*) Cyclopentadiene (*iv*) Pyrrole.
(Panjab BSc Chem Engg, 1981)

38. Discuss the aromaticity of Benzene with reference to :
(*i*) Heat of hydrogenation and combustion
(*ii*) Resonance
(*iii*) Bond lengths
(*iv*) Huckle Rule. *(Nagpur BSc, 1981)*

39. How is toluene converted into:
(*i*) Ortho and para-chlorotoluenes.
(*ii*) Benzyl chloride ? *(Gulbarga BSc II, 1981)*

40. Explain: "Benzene is planar and symmetrical molecule more susceptible for substitution rather than addition." *(Osmania BSc II, 1981)*

41. Discuss the present-day position regarding the structure of benzene. Explain fully the term aromaticity. *(Rajasthan BSc III, 1981)*

42. Explain with examples Friedel & Crafts alkylation and acylation reactions. *(Bangalore BSc II, 1981)*

43. Describe the structure of benzene in terms of resonance and orbital concept. *(Madras BSc II, 1982)*

44. (*a*) How does chlorine act on toluene under different conditions ?
(*b*) How would you convert the following into benzene:
(*i*) Phenol (*ii*) Toluene. *(Gulbarga BSc II, 1982)*

46. Discuss the molecular orbital structure of benzene. *(Marathwada BSc, 1994; Bangalore BSc, 1994)*

47. Discuss the mechanism of chlorination of benzene. *(Goa BSc, 1993)*

48. Discuss the mechanism of sulphonation of benzene. *(North Eastern Hill BSc Hons, 1993)*

49. Discuss the mechanism of Friedel and Crafts reactions. *(Delhi BSc, 1994; Madras BSc, 1994)*

50. Write a note on : Aromaticity. *(Magadh BSc Hons, 1994)*

51. Explain the aromatic character of pyrrole and furan. *(Panjab BSc, 1994)*