DIRECTORATE OF DISTANCE EDUCATION

M.Sc. (CHEMISTRY)

III – SEMESTER

34432

ADVANCED ORGANIC CHEMISTRY
SYLLABUS - BOOK MAPPING TABLE

34432 - ADVANCED ORGANIC CHEMISTRY

SYLLABUS

Unit-1: Oxidizing reagents in organic synthesis -1
Metal based and non-metal based oxidations of (i) alcohols to carbonyls (Cr, Mn, hypervalent iodine and TEMPO based reagents). (ii) Phenols (Fremy’s salt, silver carbonate) (iii) Alkenes to epoxides (peroxides/per acids based), Sharpless asymmetric epoxidation.

Unit-2: Oxidizing reagents in organic synthesis -2
(i) Alkenes to diols (Mn, Os based), Sharpless asymmetric dihydroxylation, Prevost reaction and Woodward modification, (ii) Alkenes to carbonyls with bond cleavage (Os and Ru, ozonolysis) (iii) Alkenes to alcohols/carbonyls without bond cleavage (hydroboration-oxidation, Wacker oxidation, Se) (iv) ketones to ester/lactones (Baeyer- Villiger).

Unit-3: Reducing reagents in organic synthesis -1
Catalytic hydrogenation- Heterogeneous: Pd/Pt/Rh/Ni, Homogeneous, Wilkinson, Li/Na/Ca in liquid ammonia - Birch, Pinacol formation, McMurry, Acyloin formation, dehalgenation and deoxygenations.

Unit-4: Reducing reagents in organic synthesis -2
Hydride transfer reagents from Group III and Group IV in reductions – LiBH4, NaBH4, triacetoxyborohydride, L-selectride, K-selectride, Luche reduction; LiAlH4, DIBAL-H; Trialkylsilanes, Meerwein-Pondorff-Verley reduction - Stereo/Enantioselectiviey reductions -Chiral Boranes, Corey-Bakshi-Shibata

Unit-5: Retrosynthetic Analysis
Basic principles and terminology of retrosynthesis, synthesis of aromatic compounds, one group and two group C-X disconnections, one group C-C and two group C-C disconnections, amine and alkene synthesis, important strategies of retrosynthesis, functional group transposition, important functional group interconversion.

Unit-6: Functional group protection
Protection and deprotection of hydroxy, carboxyl, carbonyl, carboxy amino groups and carbon-carbon multiple bonds; chemo- and regioselective protection and depretection; illustration of protection and deprotection in synthesis.
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Unit – 7: Heterocyclic compounds
Synthesis, structure and reactivity of Indole, Oxazole, Flavone and Anthocyanin.

Unit – 8: Carbohydrates
Configuration and conformation of disaccharides - Maltose and cellobiose – Polysaccharides - starch and cellulose.

Unit – 9: Proteins and enzyme
Aspects of structure and classification of proteins.-Primary, secondary and tertiary structure- end group analysis -Solid phase peptide synthesis. Enzyme-coenzyme.

Unit – 10: Nucleic acids
Aspects of structure and classification DNA and RNA. DNA replication and RNA transcription and translation

Unit – 11: Alkaloids
Structure and synthesis of Morphine and Atropine, Biosynthesis of Alkaloids.

Unit – 12: Terpenes
Structure and synthesis of a-Pinene, Camphor and Zingiberene. Biosynthesis of terpenes.

Unit – 13: Vitamins
Chemistry and physiological action of ascorbic acid, thiamin, riboflavin and pyridoxine – Elementary aspect of vitamin A, E, K and B12.

Unit – 14: Cholesterol and steroid
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Model Question Paper
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Model Question Paper
UNIT-1  OXIDIZING REAGENTS IN ORGANIC SYNTHESIS -1

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1.10 Further readings

1.1 INTRODUCTION

Oxidation is the loss of electrons during a reaction by a molecule, atom or ion. Oxidation occurs when the oxidation state of a molecule, atom or ion is increased. The opposite process is called reduction, which occurs when there is a gain of electrons or the oxidation state of an atom, molecule, or ion decreases. An oxidation-reduction (redox) reaction is a type of chemical reaction that involves a transfer of electrons between two species. An oxidation-reduction reaction is any chemical reaction in which the oxidation number of a molecule, atom, or ion changes by gaining or losing an electron. In practice, a series of functional groups have been qualitatively identified in the order of increasing oxidation state. Then, oxidation is referred to as the conversion of one functional group higher in...
the sequence to another lower in the list. Conversion within a group is neither oxidation nor reduction. This module has been organized based on the reagent that is used for oxidation reactions.

1.2 OBJECTIVES
After going through this unit, you will be able to

- Understand the concept of oxidation reagent
- Discuss the various oxidizing reagent for compound.
- Oxidizing reagent is one of the major source are synthesis of any organic compound.
- This unit fully covered on the Alcohol to carbonyl, Phenols, and Alkene to epoxide based various reagent discuss from reactant and mechanism

1.3 ALCOHOL TO CARBONYL

1.3.1 Metal based oxidation

1.3.1.1 Chromium
Chromium is the 21st most abundant element in Earth’s crust with atomic number 24. Naturally occurring chromium composed of three stable isotopes; $^{52}$Cr, $^{53}$Cr and $^{54}$Cr with $^{52}$Cr being most abundant. It has an electronic configuration of $3d^54s^1$ and exhibits a wide range of oxidation states, where the +3 and +6 states are commonly observed. This section describes some of the important chromium mediated/catalyzed oxidation of organic substrates.

Chromic Acid Oxidation (Jones Oxidation)
The combination of CrO$_3$ and sulfuric acid is often referred as Jones reagent, and the oxidation of alcohols with this reagent in acetone is called Jones oxidation. The reagent is selective as it is useful for the oxidation of alcohols, which contain carbon-carbon double or triple bonds, allylic or benzylic C-H bonds the reaction is carried at 0-20 °C to give the corresponding carbonyl compounds.

Mechanism

In aqueous acid, CrO$_3$ forms chromic acid, which oxidizes the alcohols to carbonyl compounds.
Pyridinium Chlorochromate (PCC) Oxidation

This reagent is obtained by adding pyridine to a solution of CrO₃ in hydrochloric acid. PCC oxidizes primary and secondary alcohols to aldehydes and ketones, respectively. As PCC is slightly acidic so it may affect the acid sensitive groups. The powdered NaOAc is used along with PCC for the oxidation of the substrate containing acid labile groups. PCC is commercially available and could also be prepared.
Collins-Ratcliff Oxidation

The 1:2 mixture of CrO₃ and pyridine in dichloromethane (DCM) is known as Collins reagent or Collin-Ratcliff reagent. It also oxidizes the primary alcohols and secondary alcohols to aldehydes and ketones, respectively. This reaction works under mild reaction condition without affecting other functional groups and the only disadvantage is the excess use of the reagent.

1.3.1.2 Manganese Reagent as Oxidation

Manganese is a useful selective oxidizing reagent in organic synthesis. It is commercially available, and it can also be prepared by the reaction of MnSO₄•4H₂O with KMnO₄ in aqueous NaOH.

Oxidation of Alcohols

MnO₂ can selectively oxidize allylic and benzylic alcohols to the corresponding carbonyl compounds.
Furthermore, at elevated temperature, saturated secondary alcohols can be oxidized to ketones.

Oxidation of Aldehydes to Esters (Corey-Gilman-Ganem Oxidation)

The aldehydes can be selectively oxidized to esters in presence of \( \text{MnO}_2 \) and hydrogen cyanide in methanol at ambient temperature. The aldehyde undergoes reaction with HCN to give cyanohydrins, which proceeds further oxidation to acyl cyanide. The latter on alcoholysis leads to corresponding-unsaturated carboxylic ester.

Mechanism:

1.3.2 Non-Metal Based Oxidation

1.3.2.1 Hypervalent Iodine

Carbonyl oxidation with hypervalent iodine reagents involves the functionalization of the \( \alpha \) position of carbonyl compounds through the intermediacy of a Hypervalent iodine(III) enolate species. This electrophilic intermediate may be attacked by a variety of nucleophiles or undergo rearrangement or elimination. Hypervalent iodine(III) compounds are attractive oxidizing agents because of their stability and selectivity. In the presence of enolizable carbonyl compounds, they are able to accomplish oxidative functionalization of the \( \alpha \) position. A key iodine (III) enolate intermediate forms, which then undergoes either nucleophilic substitution (\( \alpha \)-functionalization), elimination (dehydrogenation), or rearrangement. Common hypervalent iodine reagents used to effect these transformations include iodosylbenzene (PhIO), iodobenzene diacetate (PhI(OAc)\(_2\)), Koser's reagent (PhI(OTs)OH), and (dichloriodo)benzene (Cl\(_2\)IPh).
Notes

Prevailing Mechanism

The mechanism of carbonyl oxidation by iodine (III) reagents varies as a function of substrate structure and reaction conditions, but some generalizations are possible. Under basic conditions, the active iodinating species are iodine (III) compounds in which any relatively acidic ligands on iodine (such as acetate) have been replaced by alkoxide. In all cases, the α carbon forms a bond to iodine. Reduction of iodine (III) to iodine (I) then occurs via attack of a nucleophile on the now electrophilic α carbon. Under basic conditions, nucleophilic attack at the carbonyl carbon is faster than attack at the α carbon. Iodine displacement is actually accomplished intramolecularly by the carbonyl oxygen, which becomes the α-hydroxyl oxygen in the product.

Rearrangements of the iodine (III) enolate species have been observed. Under acidic conditions, oxidations of aryl enol ethers lead to α-aryl esters via 1,2-aryl migration. Ring-contractive Favorskii rearrangements may take place under basic conditions.

1.3.2.2 TEMPO (1.4. 2. 2, 2, 6, 6-Tetramethylpiperidin-1-oxyl)

TEMPO is organic heterocyclic compound bearing a radical oxygen atom. This compound was prepared by Lebedev and Kazarnowskii in 1960 from the oxidation of 2,2,6,6-tetramethylpiperidine. In conjunction with other oxidizing agents, this reagent provides mild conditions for oxidations. (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl, commonly known as TEMPO, is a chemical compound with the formula (CH₂)₃(CMe₂)₂NO.
This heterocyclic compound is a red-orange, sublimely solid. As a stable radical, it has applications in chemistry and biochemistry. TEMPO is used as a radical marker, as a structural probe for biological systems in conjunction with electron spin resonance spectroscopy, as a reagent in organic synthesis, and as a mediator in controlled radical polymerization.

**Structure**

![TEMPO Structure](image)

**Reaction**

![Reaction Diagram](image)

**Oxidation of Alcohols**

TEMPO is a mild catalyst for the oxidation of alcohols to give carbonyl compounds. NaOCl is usually used as a co-oxidant for the regeneration of the catalyst. The reactions with primary alcohols exhibit greater reactivity compared to secondary alcohols. Thus, primary alcohols could be chemoselectively oxidized in the presence of secondary alcohols.

**Mechanism**

The oxidation of nitroxyl radical gives the oxoammonium ion, which is the active species, in the TEMPO catalyzed reactions.
Phenols could be oxidized to a variety of products depending on the nature of substituent present in the aromatic ring. For example, 2,6-disubstituted phenols when treated with Ag$_2$CO$_3$ undergoes dimerization to provide diphenooquinones, while substituted 1,4-catecols are oxidized to give substituted benzoquinones.

The hydroxyl group is a strongly activating making phenols substrates for electrophilic halogenation, nitration, sulfonation, and friedel crafts reaction.

### 1.4.1 Fremy's salt

Frémy's salt is a chemical compound with the formula (K$_4$[ON(SO$_3$)$_2$]$_2$), sometimes written as (K$_2$[NO(SO$_3$)$_2$]). It a bright yellowish-brown solid, but its aqueous solutions are bright violet. The related sodium salt, i.e. disodium nitrosodisulfonate (NDS, Na$_2$ON(SO$_3$)$_2$). Regardless of the cations, the salts are distinctive because aqueous solutions contain the radical [ON(SO$_3$)$_2$]$^2$.
Fremys salt [(KSO3)2NO] works under mild conditions through a radical mechanism.

1.4.2 Silver carbonate

Fétizon oxidation is the oxidation of primary and secondary alcohols utilizing the compound silver(I) carbonate absorbed onto the surface of celite also known as Fétizon's reagent. First employed by Marcel Fétizon in 1968, it is a mild reagent, suitable for both acid and base sensitive compounds. Its great reactivity with lactols makes the Fétizon oxidation a useful method to obtain lactones from a diol. The reaction is inhibited significantly by polar groups within the reaction system as well as steric hindrance of the α-hydrogen of the alcohol.

Silver based catalysts are considerably investigated for the oxidation of alcohols to carbonyl compounds. For example, silver carbonate (Ag₂CO₃) has been used for the oxidation of primary and secondary alcohols to give aldehydes and ketones, respectively.

Ag₂CO₃ supported on celite is known as Fétizon’s reagent. This reagent oxidizes alcohols selectively under mild reaction conditions. The reaction is performed under a polar solvents such as benzene, heptane but the polar solvents hinder the oxidation.
Mechanism

\[
\begin{array}{c}
\text{Ox} \quad \text{H}_2\text{O} \\
\text{Ag}^+ \\
\text{H}^+
\end{array}
\rightarrow
\begin{array}{c}
\text{Ag}^2+ \\
\text{Ag}^2+ \\
\text{CO}_2 + \text{H}_2\text{O} + 2\text{Ag}^0
\end{array}
\]

Check your progress

4. What are the fremy’s salt?

5. What type of reagent based on silver carbonate oxidation of alcohol to carbonyl Compound?

1.5 ALKENES TO EPOXIDES

1.5.1 Peroxides

Peroxides are important oxidizing agent for the organic compounds. Aqueous H2O2 and t-BuO2H are commonly used hydroperoxide, which are commercially available. The lecture will discuss some of the important oxidation reactions performed with peroxide reagents.

Epoxidation of Allylic Alcohols

Epoxidation of allylic alcohols is one of the most important processes in oxidation chemistry. Metal alkoxides with t-BuOOH (TBHP) provide an excellent method for the epoxidation of allylic alcohols. The double bond selectively undergoes oxidation without affecting the OH group.

Epoxidation of allylic alcohols is one of the most important processes in oxidation chemistry. Metal alkoxides with t-BuOOH (TBHP) provide an excellent method for the epoxidation of allylic alcohols. The double bond selectively undergoes oxidation without affecting the OH group.
In addition to these homogeneous processes, effort has also been made to develop heterogeneous catalysts for the epoxidation of allylic alcohols with hydro peroxides. TiO$_2$-SiO$_2$ has been found to be superior to V2O$_5$-SiO$_2$ and MoO$_3$-SiO$_2$ for this purpose. Both TBHP and H$_2$O$_2$ (aqueous and urea H$_2$O$_2$) have been employed as terminal oxidant. These systems also work for the epoxidation of unfunctionalized alkenes. Epoxidation of unsaturated carbonyl compound Alkaline H$_2$O$_2$ is used for the epoxidation of unsaturated carbonyl compounds. The method is straightforward and the products are obtained in high yield.

![Chemical structure](image1)

1.5.2 Peracids

A number of peracids having the general formula, RCO$_3$H have been used for the oxidation of organic compounds. Some of the common peracids are peracetic acid (CH$_3$CO$_3$H), perbenzoic acid (PhCO$_3$H), trifluoroacetic acid (CF$_3$CO$_3$H) and $m$-chloroperbenzoic acid ($m$-ClC$_6$H$_4$CO$_3$H). Peracids are usually prepared *in situ* by the oxidation of carboxylic acid with hydrogen peroxide.

**Epoxidation of Alkenes**

Epoxides are useful building blocks in organic synthesis as they react with a variety of nucleophiles resulting in opening epoxide ring. An effective route for the synthesis of epoxides is the direct conversion of alkenes to epoxides using peracids as oxidizing agent. $m$-CPBA is often used for this purpose because it is available commercially as a colorless crystalline solid. The reaction is carried out at ambient conditions in chlorinated solvent such as dichloromethane. $m$-Chlorobenzoic acid is produced as a by-product, which can be removed by washing the reaction mixture with saturated NaHCO$_3$ solution.

![Chemical structure](image2)

The reaction is stereospecific leading to the *syn* addition of the oxygen atom to alkene. Thus, *cis* alkene gives *cis*-epoxide and *trans* alkene gives *trans*-epoxide.
In case of cyclic alkenes that are conformationally rigid, the reagent approaches from the less hindered side of the double bond. This is illustrated in the oxidation of norbornene.

A suitable substituent particularly at the allylic position may control the direction of the new epoxide group. This is due to the transition state electronic interaction between electron deficient m-CPBA and the direction group.

Mechanism
The reaction proceeds through a concerted pathway (Scheme 7). The reaction involves addition of an oxygen atom to the double bond with simultaneous proton transfer from oxygen to carbonyl oxygen.

1.5.3 Sharpless asymmetric Epoxidation
Asymmetric epoxidation is one of the most selective methods for the formation of enantiomeric products. The asymmetric epoxidation of allylic alcohols with t-BuOOH, Ti(OPr)$_4$ and tartrate ester, called Sharpless asymmetric epoxidation, provides the epoxides with high enantiomeric excess and yield. This reaction has been used for the synthesis of many important natural products and biologically active molecules.
The mnemonic rule for the absolute configuration of the epoxy alcohol is as follows, if the CH2OH group is in lower right or upper left of the double bond then the epoxide is formed at the upper face of the double bond when (+)-L-diethyl tartrate is used and at lower face when (-)-D-diethyl tartrate is used. The reaction works catalytically when 3Å or 4Å molecular sieves are used as an additive.

Epoxidation of alkene

Pd(OAc)\textsubscript{2} in combination with azibenzil has been reported for the epoxidation of alkenes in the presence of molecular oxygen. The aliphatic alkenes undergo epoxidation with moderate to good yield, while aromatic alkenes undergo C-C cleavage.

Mechanism
Check your progress

6. Epoxidation definition
7. Sharpless asymmetric Epoxidation definition?
8. What are the major product of below the reaction?

1.6 ANSWER TO CHECK YOUR PROGRESS QUESTION

1. Manganese is most power full oxidation agent in organic synthesis because it’s higher oxidation state. +2, +3, +4…..+7. Then commercially available for and it can also be prepared by the reaction of MnSO4.4H2O with KMnO4 in aqueous NaOH.

2. Hypervalent Iodine Compounds. Weaker and longer than covalent linkages, hypervalent bonds are the result of a linear three-center, four-electron (3c-4e) electronic distribution (hypervalent model). Common hypervalent iodine reagents used to effect these transformations include iodosylbenzene (PhIO), iodobenzene diacetate (PhI(OAc)2), Koser's reagent (PhI(OTs)OH), and (dichloroiodo)benzene (Cl2IPh).then hypervalent iodine react with carbonyl compound.

3. TEMPO structure

4. Frémy's salt is a chemical compound with the formula (K4[ON(SO3)2]2), sometimes written as (K2[NO(SO3)]). It a bright yellowish-brown solid, but its aqueous solutions are bright violet. The related sodium salt, i.e. disodium nitrosodisulfonate (NDS, Na2ON(SO3)2).Regardless of the cations, the salts are distinctive because aqueous solutions contain the radical [ON (SO3)2].
5. Ag₂CO₃ supported on celite is known as Fétizon’s reagent.

6. Epoxidation is the chemical reaction which converts the carbon–carbon double bond into epoxides (epoxides), using a variety of reagents including air oxidation, hypochlorous acid, hydrogen peroxide, and organic peracids.

7. Asymmetric epoxidation is one of the most selective methods for the formation of enantiomeric products. The asymmetric epoxidation of allylic alcohols with t-BuOOH, Ti(OPr)₄, and tartrate ester, called Sharpless asymmetric epoxidation, provides the epoxides with high enantiomeric excess and yield.

8. [Diagram of epoxidation reaction]

**1.7 SUMMARY**

The oxidation of alkene with potassium permanganate provides an alternative method for Dihydroxylation, avoiding the use of toxic and expensive reagent osmium tetroxide. The reaction needs careful control to avoid over-oxidation and best result are obtained in alkaline solution, using water or aqueous-soluble organic solvents (e.g., acetone, ethanol, t-BuOH). Oxidation to quinones using hypervalent iodine reagents, in particular PhI(OAc)₂ or PhI(OCOCF₃)₂, has been finding increasing use in synthesis of organic compound. The use of TEMPO is particularly convenient for the oxidation of primary alcohol in carbohydrate, avoiding the need for protection of the secondary alcohols. The silver carbonate oxidation mild condition alcohol to aldehyde and ketone this called Fétizon’s reagent. Then finally any organic compound synthesis used in oxidation reagent. They are not used any oxidation reagent, does not possible to several compound.

**1.8 KEY WORDS**
- Metal based oxidation
- Chromium
- Manganese
- Non-metal based oxidation
- Hypervalent iodine
- TEMPO
- Epoxidation
- Peroxide

**1.9 SELF ASSESSMENT QUESTION AND EXERCISES**

1. What do you understand by oxidation reaction?
2. What are the reagent of alkene to carbonyl based? Explain.
3. Hypervalent iodine mechanism explain?
4. Why TEMPO is mild oxidation? What are the reasons?

5. Give the major product in the following reaction?

a)

b)

c)

1.10 FURTHER READINGS


UNIT-2 OXIDIZING REAGENTS IN ORGANIC SYNTHESIS -2

Structure

2.1 Introduction
2.2 Objective
2.3 Alkene to Diols
   2.3.1 Osmium
   2.3.2 Manganese
   2.3.3 Sharpless asymmetric dihydroxylation
   2.3.4 Prevost reaction
   2.3.5 Woodward modification
2.4 Alkene to carbonyls with bond cleavage
   2.4.1 Osmium
   2.4.2 Ruthenium
   2.4.3 Ozonolysis
2.5 Alkene to alcohol/carbonyls without bond cleavage
   2.5.1 Hydroboration oxidation
   2.5.2 Wacker oxidation
   2.5.3 Selenium oxidation
2.6 Ketone to ester/ lactones
   2.6.1. Baeyer –Villiger
2.7 Answer to check your progress question
2.8 Summary
2.9 Keywords
2.10 Self-assessment question and exercises
2.11 Further readings
2.1 INTRODUCTION

The definition of oxidation and reduction respectively refer to the loss and gain of electrons, or an increase in oxidation number (oxidation) and a decrease in oxidation number (reduction). In organic chemistry, the gain of oxygen or loss of hydrogen is often referred to as oxidation. The oxidation is the loss of electrons during a response by a particle, atom or molecule. Oxidation happens when the oxidation condition of atom, molecule or particle is expanded. The contrary procedure is called decrease, which happens when there is an increase of electrons or the oxidation condition of an atom, particle, or molecule diminishes. An oxidation-decrease (redox) response is a kind of substance response that includes an exchange of electrons between two species. An oxidation-decrease response is any concoction response wherein the oxidation number of a particle, atom, or molecule changes by picking up or losing an electron. Practically speaking, a progression of useful gatherings has been subjectively distinguished in the request for expanding oxidation state. At that point, oxidation is alluded to as the transformation of one practical gathering higher in the arrangement to another lower in the rundown. Change inside a gathering is neither oxidation nor decrease. This module has been composed dependent on the reagent that are utilized for oxidation responses. In practice, a series of functional groups have been qualitatively identified in the order of increasing oxidation state. Then, oxidation is referred to as the conversion of one functional group higher in the sequence to another lower level.

2.2 OBJECTIVES

After going through this unit, you will be able to

- Understand the concept of oxidation reagent
- Discuss the various oxidizing reagent with mechanism for compound.
- Oxidizing reagent is one of the major source are synthesis of any organic compound.

2.3 ALKENES TO DIOL

2.3.1 Osmium (Os)

Osmium is the densest (density 22.59 g cm-3) transition metal naturally available. It has seven naturally occurring isotopes, six of which are stable: 184 Os, 187 Os, 188 Os, 189 Os, 190 Os, and 192 Os. It forms compounds with oxidation states ranging from -2 to +8, among them, the most common oxidation states are +2, +3, +4 and +8. Some important osmium catalyzed organic oxidation reactions follow

Dihydroxylation (diols) of Alkenes

In Cis-1,2-dihydroxylation of alkenes is a versatile process, because cis-1,2-diols are present in many important natural products and biologically active molecules. There are several methods available for cis-
1,2-dihydroxylation of alkenes, among them, the OsO₄-catalyzed reactions are more valuable. The use of tertiary amine such as triethyl amine or pyridine enhances the rate of reaction. Catalytic amount of OsO₄ can be used along with an oxidizing agent, which oxidizes the reduced osmium (VI) into osmium (VIII) to regenerate the catalyst. A variety of oxidizing agents, such as hydrogen peroxide, metal chlorates, tert-butyl hydroperoxide, N-methylmorpholine-N-oxide, molecular oxygen, sodium periodate and sodium hypochlorite, have been found to be effective.

Mechanism
2.3.2 Manganese Oxidants

Manganese (Mn) is the 12th most abundant element (0.1%) on earth’s crust with atomic number 25. Though manganese exists with the oxidation states from −3 to +7, the common oxidation states are +2, +3, +4, +6 and +7. The +2 oxidation state, which has a pale pink color due to spin forbidden d-d transition is found in living organisms for essential functions. The manganese in the oxidation state +7 is deep purple in colour and a strong oxidizing agent (Mn⁷⁺ + 5e⁻ → Mn²⁺).

Manganese (III) Reagents and Catalysts

Dilute solutions of KMnO₄ convert alkenes into diols.

\[
\text{KMnO}_4 \quad \rightarrow \quad \text{HO} \quad \text{OH}
\]

Dihydroxylation of alkenes using alkaline KMnO₄ is a stereoselective syn-addition of two hydroxyl groups across a double bond.

Oxidation of Alcohols

MnO₂ can selectively oxidize allylic and benzylic alcohols to the corresponding carbonyl compounds. The advantage of this method is that the reaction takes place under mild and neutral conditions, also carbon-carbon double and triple bonds are unaffected.

\[
\text{solvent free, rt}
\]

\[
\text{CHO}
\]
Comparison of mechanism for Mn and Os react with alkene to diol

2.3.3 Sharpless Asymmetric Dihydroxylation

Although osmylation of alkenes is an attractive process for the conversion of alkenes to 1,2-diols, the reaction produces racemic products. Sharpless group attempted to solve this problem by adding chiral substrate to the osmylation reagents, with the goal of producing a chiral osmatic intermediate. The most effective chiral additives were found to be the cinchona alkaloids, especially esters of dihydorquinidines such as DHQ and DHQD. The % of the diol product is good to excellent with a wide range of alkenes.
If the alkene is oriented as shown in the natural dihydroquinidine (DHQD) ester forces delivery of the hydroxyls from the top face (\( \beta \)-attack). Conversely, the reactions are generally carried out in a mixture of tert-butyl alcohol and water at ambient temperature.

2.3.4 Prevost Reaction

The Prevost reaction allows the synthesis of anti-diols from alkenes by the addition of iodine followed by nucleophilic displacement with benzoate in the absence of water. Hydrolysis of the intermediate diester gives the desired diol.

Mechanism of the Prevost Reaction

The initial addition of iodine leads to a cyclic iodonium ion, which is opened through nucleophilic substitution by benzoate anion.
A neighbouring group participation mechanism prevents the immediate nucleophilic substitution of iodine by a second equivalent of benzoate that would lead to a syn-substituted product. Instead, a cyclic benzoxonium ion intermediate is formed.

Opening of this intermediate by a second addition of benzoate gives the anti-substituted dibenzoate.

### 2.3.5 Woodward Modification

The Woodward modification allows the synthesis of syn-diols from alkenes by the addition of iodine followed by nucleophilic displacement with acetate in the presence of water. Hydrolysis of the intermediate ester gives the desired diol. The Prévost reaction gives anti-diols.

**Mechanism of the Woodward Modification**

The similar to the Prévost Reaction, initially addition of iodine leads to a cyclic iodonium ion that is opened through nucleophilic substitution by acetate anion.
A cyclic acetoxonium ion is formed in contrast to the course of the Prévost reaction, where water appears to add readily as a nucleophile to the partially positive carbon atom of the intermediate. The cyclic orthoacetate is then cleaved to a monoacylated diol. The desired diol can be isolated after hydrolysis.

Woodward noted that his modification of the Prévost reaction offers the opposite facial selectivity as compared to oxidations with OsO₄ in the hydroxylation of synthetic steroid intermediates. Here, the steric approach factors first direct the stereochemistry of the iodination, which is followed by hydroxylation from the opposite face, whereas OsO₄ leads to the isomeric cis-diol by direct attack from the most accessible face.

Check your progress

1. Give the product of the reaction?

2. What is the main function of provost reaction?

3. Difference between the Prevost and Woodward reaction?

2.4 ALKENE TO CARBONYLS WITH BOND CLEAVAGE

2.4.1 Osmium

The osmium-catalyzed oxidation of alcohols and Dihydroxylation of alkenes has been explored with molecular oxygen as terminal oxidant.
For example, K₂OsO₄(HO)₄ in combination with DABCO has been found to catalyze the oxidation of cylo octanol to cylo octanone in the presence of molecular oxygen. This reaction condition has been demonstrated as effective system styrene to afford the corresponding 1,2-diol in high yield.

2.4.2 Ruthenium

RuCl₃ - the most used reagent and it is used mainly catalytically in oxidation reactions. By means of stoichiometric quantities of an oxidizing agent such as Ozone or NaIO₄ it is oxidized in catalytic cycles to ruthenium tetroxide. RuO₄ reacts similar to OsO₄, but with a smaller efficiency. However, the use of Ru compounds as reagents is clearly cheaper.

Oxidation of Alcohols

Ruthenium catalyzed aerobic oxidation of alcohol has been extensively studied. RuCl₃·H₂O has been used for the oxidation of secondary alcohols to give ketones in the presence of oxygen.
2.4.3 Ozonolysis

Ozonolysis involves the cleavage of olefins with ozone. It forms either carbonyl compound or carboxylic acid.

Ozonolysis is an oxidative cleavage (like permanganate). But, it is comparatively mild reaction and no over oxidation is seen.

The reactions of alkenes with ozone can produce alcohols, aldehydes, ketones and carboxylic acids depending on the reaction conditions. This degradation of alkenes with ozone is called Ozonolysis. The reaction is performed in common solvents such as dichloromethane, methanol and acetone at \(-78\) °C. A reductive work up with Me2S or PPh3 or thiourea or zinc dust produces aldehydes and ketones, whereas sodium borohydride (NaBH4) produces alcohols and the oxidative work up with \(H_2O_2\) provides acids.

Ozonolysis of simple alkenes leads to the formation of two carbonyl fragments and carbon monoxide.
4. Write the major product of the following reaction?

a) 

\[
\begin{align*}
\text{Oxidizing Reagents in} \\
\text{Organic Synthesis -2} \\
\text{NOTES} \\
\text{Check your progress} \\
\text{4. Write the major product of the following reaction?} \\
\text{a)} \\
\begin{align*}
\text{alkene to alcohol/carbyliys without} \\
\text{bond cleavage} \\
\text{2.5.1 Hydroboration Oxidation} \\
\text{The hydroboration oxidation reaction is a two-step hydration} \\
\text{reaction that converts an alkene into an alcohol. The process results in the} \\
\text{syn addition of a hydrogen and a hydroxyl group where the double bond} \\
\text{had been. Hydroboration—oxidation is an anti-Markovnikov reaction, with} \\
\text{the hydroxyl group attaching to the less-substituted carbon. The reaction}
\end{align*}
\end{align*}
\]
thus provides a more stereospecific and complementary regiochemical alternative to other hydration reactions such as acid-catalyzed addition and the oxymercurio–reduction process. Tetrahydrofuran (THF) is the archetypal solvent used for hydroboration.

The general form of the reaction is as follows:

Hydroboration Oxidation Mechanism:

The 'H' atom in the reaction comes from B₂H₆, the 'O' atom comes from hydrogen peroxide (H₂O₂) whereas the O attached 'H' atom comes from the solvent (refer mechanism).

2.5.2 Wacker Oxidation

Wacker oxidation of alkenes to aldehydes or ketones is one of the most important industrial processes. In Wacker process, Pd catalyst is used in combination with O₂ and copper salt to transform alkenes to aldehydes and ketones. In these reactions, copper (II) oxidizes the reduced Pd(0) to palladium (II) to regenerate the catalyst, while the reduced copper(I) is reoxidized to copper(II) by oxygen. The oxygen incorporated in the alkene to give the carbonyl compound is obtained from water.
Mechanism

The palladium catalyzed oxidation of alcohols to carbonyl compounds with molecular oxygen can be explained the palladium complex acts as an active catalyst and oxidizes the alcohols to carbonyl compounds. The reduced Pd (0) is reoxidized to Pd (II) by molecular oxygen to complete the catalytic cycle.

2.5.3 Selenium Oxidation

Selenium dioxide (SeO₂) is a colorless crystalline solid. It is soluble in solvents like dioxane, ethanol, acetic acid and acetic anhydride. It is extremely poisonous and should be carefully handled while working with it. However, it is very selective oxidant.

Allylic Oxidation

Allylic oxidation is an important organic transformation because it provides a direct access to the allylic alcohols from the readily available alkenes. SeO₂ is found to be an effective reagent for this transformation. The stoichiometric as well as catalytic amount of SeO₂ can be used but the later requires an oxidant such as t-BuOOH to reoxidized the reduced selenium (II) to SeO₂. The reactivity order in ethanol solvent is as follows CH₂> CH₃> CH but the order may change depending on the reaction conditions.
Oxidizing Reagents in Organic Synthesis

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Mechanism

The reaction proceeds via ene reaction of allylic compounds with SeO₂ to afford allylic selenic acid that undergoes [2,3]-sigmatropic rearrangement to give selenium ester, which on hydrolysis gives the desired alcohol.

Oxidation of Carbonyl Compounds (Riley Oxidation)

SeO₂ oxidizes active methylene or methyl group present adjacent to the carbonyl group to give 1,2-dicarbonyl compounds. This reaction is called Riley oxidation. It has been widely used for the synthesis of natural products and biologically active compounds.

Mechanism

The proposed mechanism is similar to that of allylic oxidation i.e. ene reaction followed by [2,3]-sigmatropic rearrangement and then elimination gives the desired 1,2-dicarbonyl compounds.
2.6 KETONE TO ESTER/ LACTONES

2.6.1 Baeyer-Villiger Oxidation

Ketones undergo reaction with peracids to give esters by insertion of oxygen. The reaction is known as Baeyer-Villiger oxidation.

Mechanism

The first step involves protonation of carbonyl oxygen. The addition of peracids to the protonated carbonyl group gives a tetrahedral intermediate. Elimination of the carboxylate anion and migration of R to the electron deficient oxygen atom occur simultaneously. The resulting protonated form of the ester loses a proton to yield ester. It is believed that the loss of carboxylate anion and migration of R are concerted. The labeling study with O\textsuperscript{18} suggests that the carbonyl oxygen of the ketones becomes the carbonyl oxygen of the ester.

Applications

Baeyer-Villiger oxidation has great synthetic applications as the reaction allows the conversion of ketones to esters. The reaction works well with cyclic and acyclic ketones. For some examples,
Under these conditions, 1,2-diketones proceed reaction to give anhydride.

Baeyer-Villiger oxidation is a very useful protocol for the synthesis of large ring lactones that are otherwise difficult to prepare by intramolecular esterification of long-chain hydroxyacids. For example, cyclopentadecanone can be readily oxidized to the corresponding lactone in good yield.
Check your progress

5. What are the different between Hydroboration and Wacker oxidation?

6. Give the product of the reaction?

\[
\text{Me} \quad \xrightarrow{\text{MeCO}_3\text{H}} \quad \text{AcOH}
\]

7. Ketones undergo reaction with peracids to give esters which type of oxidation?

2.7 ANSWER TO CHECK YOUR PROGRESS QUESTION

1.

2. The provost reaction main function of anti-diols from alkene.

3. **Prevost Reaction:** The Prevost reaction allows the synthesis of *anti-diols from alkenes* by the addition of iodine followed by nucleophilic displacement with benzoate in the absence of water. Hydrolysis of the intermediate diester gives the desired diol.

**Woodward Reaction:** The Woodward reaction allows the synthesis of *syn-diols from alkenes* by the addition of iodine followed by nucleophilic displacement with acetate in the presence of water. Hydrolysis of the intermediate ester gives the desired diol.

4. a)

\[
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^4
\]

b)
5. **Hydroboration Oxidation** reaction is a two-step hydration reaction that converts an alkene into an alcohol. Hydroboration–oxidation is an anti-Markovnikov reaction, with the hydroxyl group attaching to the less-substituted carbon.

**Wacker Oxidation** of alkenes to aldehydes or ketones is one of the most important industrial processes. In these reactions, copper (II) oxidizes the reduced Pd(0) to palladium (II) to regenerate the catalyst.

6.  

7. **Baeyer-Villiger oxidation**

---

### 2.8 SUMMARY

For the practical purpose most organic chemists mean by oxidation either addition of oxygen to the substrate (such as epoxidation of an alkene), removal of hydrogen (such as the conversion of alcohol to aldehyde or ketone), or removal of one electron (such as the conversion of phenoxy anion to the phenoxy radical). In fact, some excellent alternative mild method have been reported the popular approach is the use of catalytic tetroxide and sodium periodate (NaIO₄). Example of oxidation reaction of alkene have been described carbonyl compound with bond cleavage and without bond cleavage, including Dihydroxylation, epoxidation, and Wacker oxidation. The controlled oxidation of unactivated, saturated CH₃, CH₂ and CH group is not uncommon in nature under the influence of oxidation enzymes, but there are very few methods for effecting controlled reaction of this kind in laboratory.

### 2.9 KEY WORDS

**Alkene to diols**: OsO₄, MnO₄
**Sharpless Asymmetric:** Sharpless asymmetric dihydroxylation (also called the Sharpless bishydroxylation) is the chemical reaction of an alkene with osmium tetroxide in the presence of a chiral quinine ligand to form a vicinal diol.

**Selenium Dioxide:** Selenium dioxide (SeO₂) is a colorless crystalline solid. It is soluble in solvents like dioxane, ethanol, acetic acid and acetic anhydride. It is extremely poisonous and should be carefully handled while working with it. However, it is very selective oxidant.

**Baeyer–villiger oxidation:** Ketones undergo reaction with peracids to give esters by insertion of oxygen. The reaction is known as Baeyer-Villiger oxidation.

### 2.10 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Why this oxidizing reagent for (OsO₄, MnO₄) specifically alkene to converted diols. What is the mechanism with explain?

2. Ozonolysis definition.

3. What are the Riley oxidation?

4. Baeyer-Villiger application.

5. Give the major product for the following reaction

   a)

   ![Diagram](image)

   b)

   ![Diagram](image)

   c)

   ![Diagram](image)

   d)
2.11 FURTHER READINGS


**********
UNIT-3  REDUCING REAGENTS IN ORGANIC SYNTHESIS - 1

3.1 INTRODUCTION

There must be few organic syntheses of any complexity that do not involve a reduction at some stage. Reduction is used in the sense of addition of hydrogen to an unsaturated group (such as carbon–carbon double bond, a carbonyl group or an aromatic ring) or addition of hydrogen with concomitant fission of a bond between two atoms (such as the reduction of a disulfide to a thiol or of an alkyl halide to a hydrocarbon).
The substance which loses electrons to the other substance and gets oxidized to the higher valency state is known as reducing agent.

A reducing agent is one of the reactants of an oxidation-reduction reaction which reduces the other reactant by giving out electrons to the reactant. If the reducing agent does not pass electrons to other substance in a reaction, then the reduction process cannot occur. The reducing agents give away electrons. The metals of the s-block in the periodic table are said to be good for reducing agents. These agents have an opposite effect to measuring the agents which tend to strengthen. The reducing agent after losing electrons gets oxidized and also causes the opposite reactant to get reduced by supplying electrons. All the good reducing agents have the atoms which have low electro negativity and a good ability of an atom or a molecule to attract the bonding electrons and the species having very small ionization energies. These usually serve as good reducing agents. All the oxidation and reduction reactions involve the transfer of electrons. When some substance is oxidized, it is said to lose electrons and the substance which receives electrons is said to be reduced. If the substance has a strong tendency to lose electrons, then it is said to be strong reducing agent as it will reduce the other substances by giving electrons. The more strong reducing agent, the weaker is the corresponding oxidizing agent. Fluorine gas is known to be a strong oxidizing agent and whereas F⁻ is said to be a weak reducing agent. We also know that – the weaker an acid then stronger is the conjugate base. In a similar way, the weaker the oxidizing agent then the more strong is the corresponding reducing agent as shown in the figure below.

![Redox Reaction]

The example of Reducing Agents are the common reducing agents include metals such as Na, Fe, Zn, Al and non-metals such as C, S, H₂. Some of the compounds and also the Hydracids such as HCl, HI, HBr, H₂S behave as good reducing agents. A brief explanation over some of the reducing agents are given below:

- **Lithium**– Lithium is a chemical element with atomic number 3 and a symbol Li. It appears like a soft and silvery-white metal and belongs to the alkali metal group of the periodic table. It is said to be a strong reducing agent when placed in solutions.
- **Iodides**– The salts of Iodides are said to be mild reducing agents. They react with oxygen to give out iodine. These also possess various antioxidant properties.
- **Reducing sugars**– Reducing sugars are those which behave in a similar as that of the reducing agents because of the free ketone group or a free aldehyde group present. All monosaccharides along with disaccharides, polysaccharides, oligosaccharides are...
said to be reducing sugars.

### 3.2 OBJECTIVES

After going through this unit, you will be able to:

- Identify organic reactions as being oxidations, reductions, or neither.
- Rank given compounds in order of their reduction level.
- Hydrogenation results in higher electron density on a carbon atom(s).
- We consider process to be one of reduction of the organic molecule.
- When a carbon atom in an organic compound gains a bond to hydrogen.

### 3.3 DEFINE: REDUCTION

Reduction involves a half-reaction in which a chemical species decreases its oxidation number, usually by gaining electrons. The other half of the reaction involves oxidation, in which electrons are lost. Together, reduction and oxidation form redox reactions (reduction-oxidation = redox).

### 3.4 CATALYTIC HYDROGENATION

Many different catalysts have been used for catalytic hydrogenations; they are mainly finely divided metals, metallic oxides or sulfides. The most commonly used in the laboratory are the platinium metals (platinium, palladium and increasingly, rhodium and ruthenium) and nickel. The catalysts are not specific and may be used for a variety of different reductions. The most widely used are palladium and platinium catalysts. They are used either as the finely divided metal or, more commonly, supported on a suitable carrier such as activated carbon, alumina or barium sulfate.

In general, supported metal catalysts, because they have a larger surface area, are more active than the unsupported metal, but the activity is influenced strongly by the support and by the method of preparation, and this provides a means of preparing catalysts of varying activity. Platinium is often used in the form of its oxide PtO₂ (Adams catalyst), which is reduced to metallic platinium by hydrogen in the reaction medium. For example, reduction of the dihydropyrrole 1 occurs with good selectivity under these conditions.

```
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{Me} & \quad \text{H}
\end{align*}
```

Most platinum metal catalysts (with the exception of Adams catalyst) are
stable and can be kept for many years without appreciable loss of activity, but they can be deactivated by many substances, particularly by compounds of divalent sulfur. Catalytic activity is sometimes increased by addition of small amounts of platinium or palladium salts or mineral acid. The increase in the activity may simply be the result of neutralization of alkaline impurities in the catalyst.

**Catalytic Hydrogenation**

The many methods available for reduction of organic compounds, catalytic hydrogenation is one of the most convenient. Reduction is carried out easily by simply stirring or shaking the substrate with the catalyst in a suitable solvent (or even without a solvent if the substance being reduced is a liquid) in an atmosphere of hydrogen gas. An apparatus can be used that measures the uptake of hydrogen. At the end of the reaction, the catalyst is filtered off and the product is recovered from the filtrate, often in a high state of purity. The method is easily adapted for work on a micro scale, or on a large, even industrial scale. In many cases reaction proceeds smoothly at or near room temperature and at atmospheric or slightly elevated pressure. In other cases, high temperatures (100-200 °C) and pressures (100-300 atmospheres) are necessary, requiring special high-pressure equipment.

Catalytic hydrogenation may result simply in the addition of hydrogen to one or more unsaturated groups in the molecule or it may be accompanied by fission of a bond between atoms. The latter process is known as hydrogenolysis. Most of the common unsaturated groups in organic chemistry, such as alkenes, alkynes, carbonyl groups, nitriles, nitro groups and aromatic rings can be reduced catalytically under appropriate conditions, although they are not all reduced with equal case. Certain groups, notably allylic and benzylic hydroxyl and amino groups and carbon – halogen single bonds readily undergo hydrogenolysis, resulting in cleavage of the bond between the carbon and the heteroatom. Much of the usefulness of the benzyloxy carbonyl protecting group (especially in peptide chemistry) is the result of the case by which it can be removed by hydrogenolysis over a palladium catalyst. Hydrogenolysis of the C-O bond gives toluene and an intermediate carbamic acid that loses carbon dioxide to give the deprotected amine product.

An alternative procedure that is sometimes advantageous is “catalytic transfer hydrogenation” in which hydrogen is transferred to the substrate from another organic compound. The reduction is carried out simply by warming the substrate and hydrogen donor (such as isopropanol or a salt of formic acid) together in the presence of a catalyst, usually palladium. Catalytic – transfer hydrogenation can show different selectivity towards functional groups from that shown in catalytic reduction with molecular hydrogen.
3.5 HETEROGENEOUS HYDROGENATION

Catalytic hydrogenation is one of the most convenient methods for the reduction of organic compounds. The method consists in stirring the substrate with a catalyst in a suitable solvent in an atmosphere of hydrogen. The apparatus used is such that the uptake of hydrogen can be measured. After the reduction is complete, the catalyst is removed by filtration and the reduced product is obtained in pure state by removal of the solvent from the filtrate. Common unsaturated groups such as C-C double bond, C-C triple bond, carbonyl group, carboxylic group, nitrile group, nitro group and aromatic and heterocyclic nuclei can be reduced catalytically under appropriate conditions.

A number of catalysts have been used for catalytic hydrogenation. They are used mainly as finely divided metals, metallic oxides or sulfides. The most important catalyst is the platinum (platinum, palladium, rhodium and ruthenium), nickel and copper chromite. The catalytic reduction takes place between gaseous hydrogen and an organic compound. The reduction takes place at the surface of the catalyst which adsorbs both hydrogen and the organic compound and facilitates their contact. Transfer of hydrogen takes place from the catalyst to the molecule, resulting in reduction. In general it is found that hydrogenation takes place by the addition of hydrogen atoms to the less hindered side of the unsaturated site.

PLATINUM

Platinum is used in the form of its oxide, PtO₂ (Adam’s catalyst). During reductions, the oxide is reduced by hydrogen in the reduction medium. The platinum metal catalysts can be prepared by the reduction of a metallic salt in the presence of a suitable support. Effective platinum catalysts can also be obtained by reduction of metal salts with sodium borohydride or a trialkylsilane.

PALLADIUM

Palladium is the most widely used both in industrial and academic laboratories on both a minute and very large scale. Palladium catalysts resemble platinum catalysts in activity and usefulness. It is obtained by the reduction of palladium chloride with sodium borohydride.

Palladium supported catalysts commonly used are palladium on charcoal, CaCO₃ or BaSO₄. It increases the contact of catalysts with hydrogen. Palladium on BaSO₄ deactivated by sulfur compound or quinoline is used for the Rosenmund reduction. Palladium on CaCO₃ deactivated by lead acetate is known as Lindlar’s catalyst and is used for partial reduction of triple bonds to double bonds.

NICKEL

Nickel catalysts are extensively used in the laboratory as well as in the industry. The most important catalyst is Raney nickel which is obtained by the Raney’s process. In this process, an alloy containing 50% of Ni and 50% of Al (known as Ni-Al Alloy) is heated with aqueous
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NaOH solution at 50-100 °C. by this process Al dissolves and Ni is left behind in the form of very fine particles. It is filtered and washed repeatedly with water and finally with alcohol. It is stored in absolute alcohol.

Check Your Progress

1. What is reduction
2. What is mean by hydrogenation

3.6 HOMOGENEOUS CATALYSTS

Dissolve in the solvent to make a homogeneous (one phase) solution. These catalysts are usually a transition metal complex that can bind both hydrogen and the alkenes reactant as ligands (many are based on Rh or Ru complexes). Hydrogen is transferred internally to the alkene by a rearrangement (insertion).

3.7 WILKINSON CATALYST

RhCl (PPh₃)₃ was the first highly active homogeneous hydrogenation catalyst and was discovered by Geoffrey Wilkinson (Nobel prize winner for Ferrocene) in 1964.

\[ \text{RhCl}_3 \cdot \text{H}_2\text{O} + \text{XS} \text{PPh}_3 \rightarrow \text{RhCl} (\text{PPh}_3)_3 + \text{Ph}_3\text{P = O + Oxidized Solvent} \]

Wilkinson’s Catalyst is a Rh(I) complex, Rh(PPh₃)₃Cl containing three phosphine ligands and one chlorine. As a result of the olefin insertion (hydrogen migration) we obtain Rh (III), 16e-, five coordinate species. A solvent occupies the sixth coordination site to take it to a 18e-species. Reductive elimination occurs to give the hydrogenated product and the catalytically active species. The complex RhCl(PPh3)3 (also known as Wilkinson’s catalyst) became the first highly active homogeneous hydrogenation catalyst that compared in rates with heterogeneous counterparts.

3.8 BIRCH REDUCTION

In Birch reduction, aromatic rings are reduced to 1,4-dienes by alkali metals in liquid ammonia. The reaction is carried out at -33°C (boiling point of ammonia). Co-solvents like Et₂O, THF, DME etc., are added to improve the solubility of organic compounds at this temperature.

The electron-withdrawing groups promote ipso & para reduction. These groups activate the ring towards birch reduction. Initially the protonation occurs para to the electron withdrawing groups. For example of -COOH, -CONH₂, aryl group etc. The electron-donating groups promote ortho & Meta reduction. They deactivate the ring for overall reduction compared to the electron withdrawing group. For example of -
R, -OR, -NR₂, -SR, PR₂, -CH₂OH, -CHO, -C(O)R, CO₂R etc.

**Mechanism of Birch Reduction**

The alkali metal donates an electron to the aromatic compounds, forming the alkali metal cation and a radical anion(1). Radical anion is very basic and abstracts a proton from protic solvent to give a radical (2), which picks up another electron to give an anion(3). Its quenched again by the proton source (ethanol) to give unconjugated dihydro compounds (4). The last double bond is often left unreduced in the ring.

![Mechanism of Birch Reduction diagram]

### 3.9 PINACOL FORMATION

This reaction involves the reductive homo-coupling of a carbonyl compound to produce a symmetrically substituted 1,2-diol. The first step is single electron transfer of the carbonyl bond, which generates radical ion intermediates that couple via carbon-carbon bond formation to give a 1,2-diol. The example depicted above shows the preparation of Pinacol itself.

![Pinacol Formation diagram]

**Check Your Progress**

3. Write the reaction of Wilkinson’s Catalyst

4. How to react the carbonyl compound in Pinacol formation.

### 3.10 McMURRY REDUCTION

This reductive coupling involves two steps. The coupling is induced by single electron transfer to the carbonyl groups from alkali metal (see Pinacol Coupling), followed by deoxygenation of the 1,2-diol with low-valent titanium to yield the alkene. The McMurry Reaction works well to produce symmetric products or rings.
Mechanism of McMurry Reduction

3.11 ACYLOIN FORMATION OF REDUCTION

Acyloin condensation reaction. When carboxylic acid esters are refluxed with metallic sodium in apotic solvents such as ether, benzene, toluene or xylene, free from oxygen then α-hydroxy ketones also known as acyloins are formed.

Mechanism of Acyloin formation of Reduction

The mechanism of the following reaction is not well understood yet it has been assumed that the reaction went through by a DIKETONE intermediate as these diketone has been isolated in small amounts as by-product. Since, the reaction proceeds in the presence of metallic Sodium, a radical reaction happens. The metallic sodium donates its electron to the carboxyl to give an ionic complex. Now, with the loss of alkoxy groups from produces the 1,2-diketone. Further, reduction gives sodium salt of enediol. Finally, addition of acid yields 1,2-diol which tautomerizes to ACYLOIN at . As, the miniscule trace of oxygen can reduce the yield, the whole reaction is carried out in oxygen free nitrogen.
Check Your Progress
5. How many steps involved in McMurry Reduction?
6. What are solvents used to Acyloin formation of Reduction?

3.12 DEHALGENATION

Alkyl bromides and iodides are reduced efficiently to the corresponding alkanes in a free-radical chain mechanism with tri-n-butyl tin hydride. The reduction of chlorides usually requires more forcing reaction conditions and alkyl fluorides are practically unreactive. The reactivity of alkyl halides parallels the thermodynamic stability of the radical produced and follows the order: tertiary > secondary > primary. Triethylboron-oxygen is a highly effective free-radical initiator. Reduction of bromides and iodides can occur at −78 °C with this initiator.

3.13 DEOXYGENATIONS

A vicinal diol is treated with ethyl orthoformate at high temperature (140-180 °C), followed by pyrolysis of the resulting cyclic orthoformate (160-220 °C) in the presence of a carboxylic acid (typically acetic acid). The elimination is stereo specific. Not suitable for highly functionalized substrates.

Check Your Progress
7. What is mean by dehalgenation?
8. What are the uses of deoxygenations?

3.14 ANSWER TO CHECK YOUR PROGRESS

1. Reduction involves a half-reaction in which a chemical species
Reducting Reagents in Organic Synthesis - I

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decreases its oxidation number, usually by gaining electrons. The other half of the reaction involves oxidation, in which electrons are lost.

2. Hydrogenation is one of the most convenient. Reduction is carried out easily by simply stirring or shaking the substrate with the catalyst in a suitable solvent (or even without a solvent if the substance being reduced is a liquid) in an atmosphere of hydrogen gas. An apparatus can be used that measures the uptake of hydrogen.

3. \( \text{RhCl}_3 \text{H}_2\text{O} + \text{XS PPh}_3 \rightarrow \text{RhCl (PPh}_3)_3 + \text{Ph}_3\text{P} = \text{O} + \text{Oxidized Solvent} \)

4. Pinacol reaction involves the reductive homo-coupling of a carbonyl compound to produce a symmetrically substituted 1,2-diol.

5. The McMurry Reaction are reductive coupling involves two steps. The coupling is induced by single electron transfer to the carbonyl groups from alkali metal (see Pinacol Coupling), followed by deoxygenation of the 1,2-diol with low-valent titanium to yield the alkene.

6. Acyloin condensation reaction are involved to the solvents such as ether, benzene, toluene or xylene, free from oxygen then \( \alpha \)-hydroxy ketones also known as acyloins are formed.

7. Dehalgenation is a chemical reaction that involve the cleavage of C–halogen bond to form product. It can be divided into two subclasses: Reductive dehalgenation and hydro dehalgenation.

8. Deoxygenations reaction are used to the organic compounds, removal of oxygen, \( \text{CO}_2 \) absorption, \( \text{H}_2\text{S} \) absorption into amines and ethanol/methanol distillation etc.

3.15 SUMMARY

In this unit, you have learnt about the meaning, definition, objectives of the reduction processes. This knowledge would make you understand what reduction reaction of organic synthesis is and how it can react the mechanism of some reduction reactions. The reaction and mechanisms are very useful to gain the knowledge in experimental skills. This content might play very important role in your practical knowledge and development of our creativity.

3.16 KEY WORDS

- Homogeneous
- Heterogeneous
- Wilkinson
- Dehalgenation

3.17 SELF-ASSESSMENT QUESTION AND EXERCISES
1. Explain the birch reduction of reaction and mechanism.

2. Compare the deoxygenations and Pinacol coupling reaction with suitable examples.

3.18 FURTHER READINGS


UNIT- 4  REDUCING REAGENTS IN ORGANIC SYNTHESIS - 2

Structure

4.1 Introduction

4.2 Objectives

4.3 Lithium borohydride

4.4 Sodium borohydride

4.5 Triacetoxyborohydride

4.6 L and K – Selectride

4.7 Luche Reduction

4.8 Lithium aluminium hydride

4.9 Diisobutyl aluminium hydride

4.10 Trialkylsilanes

4.11 Meerwein- Pondorff - Verley reduction

4.12 Enantioselective reduction Chiral Boranes

4.13 Corey–Bakshi–Shibata

4.14 Answer to check your progress question

4.15 Summary

4.16 Keywords

4.17 Self-assessment question and exercises

4.18 Further readings

4.1  INTRODUCTION

Reductions are generally effected either by catalytic hydrogenation or by a reducing agent (such as lithium aluminum hydride). Complete reduction of an unsaturated compound can generally be achieved without undue difficulty, but the aim is often selective reduction of one group in a molecule in the presence of other unsaturated groups. The method of choice in a particular case will often depend on the selectivity required and on the stereochemistry of the desired product. Reduction is a addition of Hydrogen’s or loss of Oxygen atoms called as reduction. Addition of electrons called reduction, Chemical used in reduction reaction called
Reducing Reagents in Organic Synthesis

4.2 OBJECTIVES

After going through this unit, you will be able to

- The compound has been hydrogenated, or reduced.
- Carbon atom loses a bond to hydrogen and gains a bond to a heteroatom.
- The process of dehydrogenation the carbon atom undergoes an overall loss of electron.
- Density - and loss of electrons is oxidation.

4.3 LITHIUM BOROHYDRIDE

Lithium borohydride is commonly used for the selective reduction of esters and lactones to the corresponding alcohols in the presence of carboxylic acids, tertiary amides, and nitriles. Aldehydes, ketones, epoxides, and several other functional groups can also be reduced by lithium borohydride. The reactivity of lithium borohydride is dependent on the reaction medium and follows the order: ether > THF > 2-propanol. This is attributed to the availability of the lithium counter ion for coordination to the substrate, promoting reduction. Lithium borohydride is commercially available in solid form and as solutions in many organic solvents (e.g. THF). Both are inflammable and should be stored protected from moisture.

\[
\text{LiH} + \text{BH}_3 \rightarrow \text{Li}^+ \text{B} \quad \text{H}_4
\]

4.4 SODIUM BOROHYDRIDE

Sodium borohydride reduces aldehydes and ketones to the corresponding alcohols at or below 25 °C. Under these conditions, esters, epoxides, lactones, carboxylic acids, nitro groups, and nitriles are not reduced. Sodium borohydride is commercially available as a solid, in powder or pellets, or as a solution in various solvents. Typically, sodium borohydride reductions are performed in ethanol or methanol, often with an excess of reagent (to counter the consumption of the reagent by its reaction with the solvent).

\[
\text{NaH} + \text{BH}_3 \rightarrow \text{Na}^+ \text{BH}_4
\]
4.5 TRIACETOXY BOROHYDRIDE

Sodium Triacetoxyborohydride, also known as sodium triacetoxyhydroborate, commonly abbreviated STAB, is a chemical compound with the formula Na(CH₃COO)₃BH. Like other borohydrides, it is used as a reducing agent in organic synthesis. This colorless salt is prepared by protonlysis of sodium borohydride with acetic acid.

\[
\begin{align*}
\text{NaBH(OAc)}_3 + \text{R}_3\text{N}\text{H} & \quad \text{1 - 2 eq. AcOH} \\
& \quad \text{DCE or THF, r.t., 0.5 - 75 h}
\end{align*}
\]

4.6 L AND K – SELECTRIDE

The reagents having the formula M[HB (sec-Bu)₃] are used as reducing agents. There are three types with different cations: L-Selectride (lithium) and K-Selectride (potassium). Because of the sec-butyl groups, these reducing agents are sensitive to steric influences and often allow for chemo- and stereoselective reductions. L-selectride is an organoborane. It is used in organic chemistry as a reducing agent, for example in the reduction of a ketone, as part of over man’s synthesis of strychnine.
Under certain conditions, L-selectride can selectively reduce enones by conjugate addition of hydride, owing to the greater steric hindrance the bulky hydride reagent experiences at the carbonyl carbon relative to the (also-electrophonic) β-position. L-Selectride can also stereoselectively reduce carbonyl groups in a 1,2-fashion, again due to the steric nature of the hydride reagent. N-selectride and K-selectride are related compounds, but instead of lithium as cation they have sodium and potassium cations respectively. These reagents can sometimes be used as alternatives to, for instance, sodium amalgam reductions in inorganic chemistry. A preitant is another synthesis example where L-selectride was used.

**Check Your Progress**

3. Write the chemical formula of Sodium triacetoxyhydroborate?

4. What are the difference between L and K Selectride?

**4.7 LUCHE REDUCTION**

Luche reduction is the selective organic reduction of α,β-unsaturated ketones to allylic alcohols with sodium borohydride (NaBH$_4$) and lanthanide chlorides, mainly cerium (III) chloride (CeCl$_3$), in methanol or ethanol. The Luche reduction can be conducted chemoselectively toward ketone in the presence of aldehyde or toward α,β-unsaturated ketone in the presence of non-conjugated ketone. An enone forms an allylic alcohol in a 1,2-addition, and the competing conjugate 1,4-addition is suppressed.
The selectivity can be explained in terms of the HSAB theory: carbonyl groups require hard nucleophiles for 1,2-addition. The hardness of the borohydride is increased by replacing hydride groups with alkoxide groups, a reaction catalyzed by the cerium salt by increasing the electrophilicity of the carbonyl group. This is selective for ketones because they are more Lewis basic. In one application, a ketone is selectively reduced in the presence of an aldehyde. Actually, in the presence of methanol as solvent, the aldehyde forms methyl acetal that is inactive in the reducing conditions.

**Mechanism of the Luche Reduction**

CeCl₃ is a selective Lewis acid catalyst for the methanolysis of sodium borohydride. The resulting reagents, various sodium methoxyborohydrides, are harder reducing agents (according to HSAB principles) and therefore effect an 1,2-reduction with higher selectivity.

\[
\text{NaBH}_4 + n \text{MeOH} \xrightarrow{\text{CeCl}_3 (\text{cat.})} \text{NaBH}_{(4-n)}(\text{OMe})_n + n \text{H}_2
\]

### 4.8 LITHIUM HYDRIDOALKOXY ALUMINATES

Lithium aluminium hydride itself is a powerful and versatile reducing agent. More selective reagents can be obtained by modification of lithium aluminium hydride by treatment with alcohols or with aluminium chloride. One such reagent is the sterically bulky lithium hydridotri-tributoxyaluminate, which is readily prepared by action of the stoichiometric amount of t-butyl alcohol on lithium aluminium hydride.

\[
\text{LiAlH}_4 + 3\text{ROH} \rightarrow \text{LiAlH(OR)}_3 + 3\text{H}_2
\]
Analogous reagents are obtained in the same way from other alcohols, and by replacement of only one or two of the hydrogen atoms of the hydride by alkoxy groups (Rerick in 1968; Brown and Krishnamurthy in 1979).

Lithium hydrotri-t-butoxyaluminate is a much milder reducing agent than lithium aluminium hydride itself. Thus, although aldehydes and ketones are reduced normally to alcohols, carboxylic esters and epoxides react only slowly, and halides, nitriles and nitro groups are not attacked. Aldehydes and ketones can thus be selectively reduced in presence of these groups good example as, One of the most useful applications of the alkoxy reagents is in the preparation of aldehydes from carboxylic acids by partial reduction of the acid chlorides or dimethylamides. Acid chlorides are readily reduced with lithium aluminium hydride itself or with sodium borohydride to the corresponding alcohols, but with one equivalent of the tri-t-butyli compound high yields of the aldehyde can be obtained in the presence of a range of other functional group. Although esters in general, are reduced only slowly, phenyl esters are converted into aldehyde with LiAlH (OC₄H₉)₃. Thus, phenyl cyclohexane carboxylate gives formylcyclohexane in 60% yield.

Reduction of tertiary amides with excess of lithium aluminium hydride, affords the corresponding amides in good yield. Reaction Is believed to proceed through an aldehyde –ammonia derivative. with the less active LiAlH (OC₂H₅)₃ (the tri-t-butoxy compound is ineffective in this case) reaction stops at the aldehyde -ammonia stage and hydrolysis of the product affords the corresponding aldehyde.

Similarly, reduction of nitriles with lithium aluminium hydride affords a primary amine by way of the imine salt.with lithium hydridotriethoxy aluminate , however reaction stops at the imine stage, and hydrolysis gives the aldehyde. By this trimethylacetonitrile was converted into trimethylacetalddehyde in 75% yield. Because of the steric effect of the alloy groups the hydridoalkoxyaluminates are more stereoselective in their action than its lithium aluminium hydride itself. But there is no very clear correlation between the size of the alkoxy groups and the selectivity of the reductions. It is complicated by the facts that some of the alkoxy compounds disproportionate readily, with regeneration of the reactive tetrahydroaluminate ion. Concentration effects may also have to
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Thus, in the reduction of 3,3,5-trimethylcyclohexanone, lithium hydridotri methoxy aluminate LiAlH(OCH₃)₃ was, as expected, more stereoselective than lithium aluminium hydride, but it was also more selective than the apparently more bulky tri-t-butyl compound LiAlH(OCH₃-t)₃. The reason is that in tetrahydrofuran, the usual solvent, the trimethoxy compound is dimeric or trimetric, whereas the tri-t-butyl compound is monomeric. The selectivity obtained with the trimethoxy compound depends on its concentration. Further useful modification of the properties of lithium aluminium hydride is achieved by addition of aluminium chloride in various properties. This serves to release mixed chloride-hydrides of aluminium.

\[
3\text{LiAlH}_4 + 3\text{AlCl}_3 \rightarrow 3\text{LiCl} + 4\text{AlH}_4
\]

The general effect of the addition of aluminium chloride is to lower the reducing power of lithium aluminium hydride and in consequence to produce reagents which are more specific for particular reactions. For example, the carbon halogen bond is often inert to the mixed hydride reagents. Advantage is taken of this in the reduction of polyfunctional compounds in which retention of halogen is desired, as in the conversion of methyl 3-bromopropionate into 3-bromopropanol; lithium aluminium hydride alone produces propanol.

\[
\text{Br CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \rightarrow \text{LiAlH}_4 - \text{AlCl}_3 \rightarrow \text{Br CH}_2\text{CH}_2\text{CH}_2\text{OH}
\]

Similarly, nitro groups are not so easily reduced as with lithium aluminium hydride itself, and p-nitrobenzaldehyde can be converted into p-nitrobenzyl alcohol in 75% per cent yield. Aldehydes and ketones are reduced to carbinols, and there is no advantage in the use of mixed hydrides in these cases, although it should be noted that the stereochemical result obtained in the reduction of cyclic ketones may not be the same as with lithium aluminium hydride itself. With diaryl ketones and with aryl alkyl ketones, however, the carbonyl group is reduced to methylene in high yield, and this procedure offers a useful alternative to the Clemmensen or Huang-Minlon methods for reduction of this type of ketone.

Reduction with lithium aluminium hydride-aluminium chloride also provides an excellent route from α, β-unsaturated carbonyl compounds to unsaturated alcohols which are difficult to prepare with lithium aluminium hydride alone because of competing reduction of the carbon-carbon double bond. The effective reagent is thought to be aluminium hydride formed in situ from lithium aluminium hydride and aluminium chloride.

4.9 DIISOBUTYL ALUMINIUM HYDRID

This derivative of aluminium hydride is available commercially.
solution in toluene or hexane. It is versatile reducing reagent (ef.Winterfeldt,1975). At ordinary temperatures esters and ketones are reduced to alcohol nitriles give amines and epoxides are cleaved to alcohols. It finds its greatest use, probably, in the preparation of aldehydes. At low temperatures esters and lactones are reduced directly to aldehydes, and nitriles and amides which are readily converted into the aldehydes by hydrolysis. DIBAL is a strong, bulky reducing agent. It’s a neutral aluminium hydride containing only one hydride species. It’s a convenient reagent for reducing carboxylic acids to alcohols. It’s most useful for the reduction of esters to aldehydes. Unlike lithium aluminium hydride, it will not reduce the aldehyde further if only one equivalent is added. It can reduce esters to alcohols and aldehydes selectively. Amides and nitriles also yield aldehydes. DIBAL is most notable for what it does not do. It reduces esters, but not to alcohols – it stops at the aldehyde stage. Let’s have a look. At low temperatures, DIBAL reduces esters to the corresponding aldehydes, and lactones to Lactols. Typically, toluene is used as the reaction solvent, but other solvents have also been employed, including dichloromethane.

Mechanism of Diisobutyl aluminium hydrid

DIBAL is a little bit unusual compared to NaBH₄. Whereas NaBH₄ is considered a “nucleophilic” reductant – that is, it delivers hydride (H⁻) directly to a carbonyl carbon DIBAL is an “electrophilic” reductant. That is, the first step in the reaction is coordination of a lone pair from the carbonyl oxygen (a nucleophile) to the aluminum (electrophile). It is only after coordinating to its carbonyl host that DIBAL delivers its hydride to the carbonyl carbon, resulting in formation of a neutral hemiacetal intermediate that is stable at low temperatures. Quenching of the reaction then breaks down the hemiacetal, resulting in isolation of the aldehyde.
4.10 TRIALKYLSILANES

The addition of Si-H to unsaturated substrates is a useful method of reduction in some cases, and is also an important route to complex organosilanes. Addition can be brought about under catalytic or ionic conditions.

Silanes will reduce a variety of functional groups in the presence of transition metal catalysts (Colvin, 1978; Flemming, 1979). Alkynes undergo cis addition to give vinylsilanes, ketones give ethers of the corresponding secondary alcohol and aromatic Schiff bases are readily reduced to secondary amines. A useful reaction is the conversion of acid chlorides into aldehydes, which provides an alternative to the Rosenmund reduction and reduction with complex hydrides (cf. p. 471) (Citron, 1969). Reaction of αβ-unsaturated aldehydes and ketones with triethylsilane in the presence of [(C₆H₅)₃P]₃RhCl gives the silyl enol ether of the corresponding saturated compound, and hence, on hydrolysis, the saturated carbonyl compound.
Silanes serve, depending upon the type of the silane, as a radical H-donor or as a hydride donor. The range reaches from simple alkylsilanes (Et₃SiH), alkylsiloxanes (PMHS, DEMS), over different phenylsilanes (such as PhSiH₃) and halosilanes (such as trichlorosilane) up to tris (trimethylsilyl) silane, which is due to its structure an outstanding radical reducing agent.

Check Your Progress

5. What are the properties of Lithium aluminium hydride?
6. What is use of Silanes?

4.11 MEERWEIN PONDORFF VERLEY REDUCTION

The Meerwein–Pondorff–Verley (MPV) reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminum alkoxide catalysis in the presence of a sacrificial alcohol. The beauty of the MPV reduction lies in its high chemo selectivity, and its use of a cheap environmentally friendly metal catalyst.

Mechanism of Meerwein – Pondorff – Verley Reduction
4.12 ENANTIOSELECTIVELY REDUCTION CHIRAL BORANE

Carbonyl reduction, the net addition of H₂ across a carbon-oxygen double bond, is a straightforward way to generate alcohols. Stoichiometric reducing agents to accomplish this task include lithium aluminium hydride, sodium borohydride, alkoxy borohydrides, alkoxy aluminium hydrides, and boranes. Initial efforts toward enantioselectivity ketone reductions focused on the development of chiral, non-racemic reducing agents. Although stoichiometric chiral reducing agents often afford products with high enantioselectivity, the necessity of a stoichiometric amount of chiral material is a disadvantage of these reagents.

The catalytic, asymmetric reduction of ketones may be accomplished through the use of catalytic amounts of an oxazaborolidine catalyst in conjunction with borane or catecholborane as the stoichiometric reducing agent. Oxazaborolidine remain in common use for reductions of simple ketones.

More recently, efforts in the field of enantioselectively reduction have focused on the development of transition metal catalyzed reactions, which employ cheap reductants such as hydrogen gas (H₂), formic acid (HCO₂H), or isopropanol ((CH₃)₂CHOH). The latter two reagents are used for transfer hydrogenations, which represent the formal transfer of an H₂molecule from the reductant to the substrate. Asymmetric induction in transition metal catalyzed reactions is achieved through the use of a chiral Lewis basic ligand in catalytic amounts. For ketone substrates that can chelate the metal catalyst, enantioselectivities of transition metal catalyzed reactions may be higher (and side reactions less prevalent) than the corresponding oxazaborolidine reductions.
Mechanism of Enantioselective reduction

The mechanism of enantioslecttive reductions has been supported by *initio* calculations. Coordination of borane to the oxazaborolidine nitrogen generates the complex I, which then coordinates a molecule of ketone to yield complex II. In the transition state for hydride transfer (II → III), the large substituent of the ketone is aligned inward to avoid steric interactions with the outward-pointing R group of the oxazaborolidine, which is often tethered to the nitrogen atom. After hydride transfer, complex III releases the product and coordinates a second molecule of borane.

![Mechanism of Enantioselective reduction](image)

Check Your Progress

7. What are benefits of MPV Reduction?
8. What is mean by Enantioselective Reduction?

### 4.13 COREY–BAKSHI–SHIBATA

The Corey–Itsuno reduction, also known as the Corey–Bakshi–Shibata (CBS) reduction, is a chemical reaction in which an achiral ketone is enantioselectively reduced to produce the corresponding chiral, non-racemic alcohol.
Mechanism of Corey–Bakshi–Shibata (CBS) reduction
4.14 ANSWER TO CHECK YOUR PROGRESS QUESTION

1. Lithium borohydride is commonly used for the selective reduction of esters and lactones to the corresponding alcohols in the presence of carboxylic acids, tertiary amides, and nitriles. Aldehydes, ketones, epoxides, and several other functional groups can also be reduced by lithium borohydride.

2. Under these conditions, esters, epoxides, lactones, carboxylic acids, nitro groups, and nitriles are not reduced.

3. Chemical formula of Sodium triacetoxyhydroborate Na(CH₃COO)₃BH.

4. Difference between L and K Selectride are L is an organoborane. It is used as a reducing agent and it’s used as a cations. K Selectride also reducing agent. In K Selectride, potassium is used as a cation.

5. It is colorless and odorless, solid crystalyst. It reacts with H₂O, including atmosphere moisture.

6. Salines are used in some fibreless and composites to improve mechanical strength and electrical properties.

7. MPV reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminum alkoxide catalysis in the presence of a sacrificial alcohol.

8. Enantioselectivity reductions focused on the development of chiral, non-racemic reducing agents.

9. CBS catalyst means reduce the achiral ketone to chiral alcohols using alkoxy – amine borane complexes in enantio selectivity and in high yield.

4.15 SUMMARY

A reduction reaction is a type of chemical reaction that involves a transfer of electrons between two species. We can tell there has been a transfer of electrons if there is any change in the reduction number between the reactants and the products.

These reactions need organic matter, bacteria, and no oxygen to be
present in order to occur. The amount of low Chroma color in soil is usually related to how long it has been reduced and not how long it has been saturated. However, some sandy soils are naturally low in iron and have low Chroma colors not related to reduction. Reduction reaction are essential to normal cellular function and the ability to measure reductive reaction changes is crucial in understanding how such changes affect metabolic pathways, cellular repair, and other important cellular mechanisms. Additionally, it is extra ordinarily helpful if a sensor is ratio metric, resistant to pH variations, and nontoxic to the cell.

4.16 KEY WORDS

- Reducing reagent
- Luche reduction
- Trialkysilane
- Lithium borohydride
- Diisobutyl aluminium hydride

4.17 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Define Luche Reduction and explain the mechanism?
2. Explain the mechanism of MPV
3. Explain reaction mechanism for CBS reduction?
4. Differ the Luche and CBS reduction
5. Which is best reduction reagent in organic chemistry
6. Explain the mechanism of Group 3 reduction
7. Explain reaction mechanism for group 4 reduction
8. Differ the L- and K- selectride
9. Which is best method for reduction of drug molecule?
10. Explain Stereoselective reduction
11. Describe hydride transfer reagents
12. Compare and contrast MVP and CBS reduction
13. Briefly account the catalytic reduction reactions
14. How can you claim reduction in your compound
4.18 FURTHER READINGS


UNIT- 5 RETROSYNTHETIC ANALYSIS

Structure

5.1 Introduction
5.2 Objectives
5.3 Basic principle and terminology of retrosynthesis
5.4 Synthesis of aromatic compounds
   5.4.1 One group and two group C-C disconnections
   5.4.2 One group and two group C-X disconnections
5.5 Amine and alkenes synthesis
5.6 Important strategies of retrosynthesis
5.7 Functional group transposition
5.8 Important functional group interconversion
5.9 Answers to check your progress questions
5.10 Summary
5.11 Keywords
5.12 Self-Assessment questions and exercises
5.13 Further readings

5.1 INTRODUCTION

Retrosynthetic analysis (retrosynthesis) is a technique for planning a synthesis, especially of complex organic molecules, whereby the complex target molecule (TM) is reduced into a sequence of progressively simpler structures along a pathway which ultimately leads to the identification of a simple or commercially available starting material (SM) from which a chemical synthesis can then be developed. Retrosynthetic analysis is based on known reactions (e.g. the Wittig reaction, oxidation, reduction etc). The synthetic plan generated from the retrosynthetic analysis will be the roadmap to guide the synthesis of the target molecule.

5.2 OBJECTIVES

After going through this unit, you will be able to

- get a pure sample of the desired organic compound.
Retrosynthetic analysis is a technique for solving problems in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures regardless of any potential reactivity/interaction with reagents. Each precursor material is examined using the same method. This procedure is repeated until simple or commercially available structures are reached. These simpler/commercially available compounds can be used to form a synthesis of the target molecule. E.J. Corey formalized this concept in his book The Logic of Chemical Synthesis. The power of retrosynthetic analysis becomes evident in the design of a synthesis. The goal of retrosynthetic analysis is structural simplification. Often, a synthesis will have more than one possible synthetic route. Retrosynthesis is well suited for discovering different synthetic routes and comparing them in a logical and straightforward fashion. A database may be consulted at each stage of the analysis, to determine whether a component already exists in the literature. In that case, no further exploration of that compound would be required. If that compound exists, it can be a jumping point for further steps developed to reach a synthesis. The definition of some terminologies in Retrosynthesis are given below:

1. **Disconnection**

   A retrosynthetic step involving the breaking of a bond to form two (or more) synthons.

2. **Retron**

   A minimal molecular substructure that enables certain transformations.

3. **Retrosynthetic tree**

   A directed acyclic graph of several (or all) possible retrosynthesis of a single target.

4. **Synthon**

   A fragment of a compound that assists in the formation of a synthesis, derived from that target molecule. A synthon and the corresponding commercially available synthetic equivalent are shown below:
5. Target

The desired final compound.

6. Transform

The reverse of a synthetic reaction; the formation of starting materials from a single product.

Example

An example will allow the concept of retrosynthetic analysis to be easily understood.

In planning the synthesis of phenyl acetic acid, two synthase are identified. A nucleophilic "-COOH" group, and an electrophilic "PhCH$_2^+$" group. Of course, both synthons do not exist per se; synthetic equivalents corresponding to the synthons are reacted to produce the desired product. In this case, the cyanide anion is the synthetic equivalent for the −COOH synthon, while benzyl bromide is the synthetic equivalent for the benzyl synthon.

The synthesis of phenylacetic acid determined by retrosynthetic analysis is thus:

PhCH$_2$Br + NaCN → PhCH$_2$CN + NaBr

PhCH$_2$CN + 2 H$_2$O → PhCH$_2$COOH + NH$_3$
In fact, phenylacetic acid has been synthesized from benzyl cyanide, itself prepared by the analogous reaction of benzyl chloride with sodium cyanide. The terminology used in Retrosynthesis as opposed to synthesis is summarized below:

<table>
<thead>
<tr>
<th>Terms for Retrosynthesis</th>
<th>Synthesis</th>
<th>Retrosynthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarting structure</td>
<td>Starting material</td>
<td>Target</td>
</tr>
<tr>
<td>Indicated by</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural features required</td>
<td>Functional group</td>
<td>Retron</td>
</tr>
<tr>
<td>Product after the step</td>
<td>Intermediate</td>
<td>Precursor synthon</td>
</tr>
<tr>
<td>Ending structure</td>
<td>Desired product</td>
<td>Most probable target</td>
</tr>
<tr>
<td>Reactions</td>
<td>Reaction = forward</td>
<td>Transform = backward</td>
</tr>
</tbody>
</table>

**Terminology of retrosynthesis**

1. **Target**
   - The molecule whose synthesis is being planned is the desired final compound/product.
   - The target molecule is the molecule under investigation. For example, in this case, it would mean the molecule you are looking for to help you make a diagnosis.
   - The reporter molecules would bind to the target molecules (if present) and would help you detect its presence.

2. **Retron**
   - A minimum molecular structure that enables certain transformations is known as retron. Product of a reaction that are
present in a molecule but may not indicate the strength of the transformation.

3. Synthon

- Synthon is an idealized fragments usually cation or anion resulting from a disconnection. It may or may not be a intermediate in the corresponding reaction.

4. Synthetic equivalent

- A real chemical compound used as an equivalent of a synthon. A reagent carrying out the function of a synthon which cannot itself be used, often because it is too unstable.

Check your progress

1. What are the terminologies of retrosynthesis?
2. What is synthon?
3. What is synthetic equivalent?

5.4 SYNTHESIS OF AROMATIC COMPOUNDS

5.4.1 ONE GROUP C-C DISCONNECTION

The disconnections we have made so far have all been of C–O, C–N, or C–S bonds, but, of course, the most important reactions in organic synthesis are those that form C–C bonds. We can analyze C–C disconnections in much the same way as we’ve analyzed C–X disconnections. Consider, for example, how you might make this simple compound, which is an intermediate in the synthesis of a carnation perfume.

The only functional group is the triple bond, and we shall want to use the chemistry of alkynes to

Show us where to disconnect. You know that alkylation of alkynes is a reliable reaction, so a sensible disconnection is next to the triple bond.
Alkynes are particularly valuable as synthetic intermediates because they can be reduced either to cis or to trans double bonds.

It’s often a good idea to start retrosynthetic analysis of target molecules containing isolated double bonds (conjugated dienes) by considering FGI to the alkyne because C–C disconnections can then become quite easy.

This cis-alkene is a component of violet oil, and is an intermediate in the synthesis of a violet oil component. FGI to the alkyne reveals two further disconnections that make use of alkyne alkylations.

The reagent we need for the first of these is, of course, the epoxide as there is a 1,2-relationship between the OH group and the alkyne.

After disconnecting the ester, FGI on the trans double bond gives an alkyne.

Two group C–C disconnection

It’s not only Grignard reagents that will react with aldehydes or ketones to make alcohols: enolates will too we spent discussing this reaction, the aldol reaction, its variants, and ways to control it.

The aldol reaction is extremely important in organic synthesis because it makes compounds with
two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule think aldol! In disconnection terms we can represent it like this.

We call this disconnection a **two-group C–C disconnection**, because we are using the OH and the C=O groups together to guide our disconnection. The disconnection gives us a d2 synthon for which we shall use an enolate equivalent, and an a1 synthon, for which we shall use an aldehyde or a ketone.

The β-hydroxy carbonyl products of aldol reactions are often very easily dehydrated to give unsaturated carbonyl compounds and, if you spot ana,b-unsaturated carbonyl group in the molecule, you should aim to make it by an aldol reaction. You will first need to do an FGI to the b-hydroxy carbonyl compound, then disconnect as before.

This aldehyde is an intermediate in the synthesis of the tranquillizer oxanamide. Because both components of the aldol reaction are the same, no special precautions need to be taken to prevent side-reactions occurring. In the synthesis, the dehydration happened spontaneously.

Because this disconnection of unsaturated carbonyl compounds is so common, it’s often written using a shorthand expression.
5.4.2 One group C-X disconnection

We continue with ethers amides and sulphides because the position of disconnection is again easily decided we disconnect a bond joining carbon to the heteroatom (X). This approach is fundamental to synthetic design and is a one group disconnection since we need to recognize only one functional group to know that we can make the disconnection. The label C-X, C-N can be used.

$$R \text{--X} \rightarrow C-X \xrightarrow{R} X^- + R^+ = RY \quad Y = Br, OTs$$

(1) (2)

The corresponding reactions are mostly ionic and involve nucleophilic heteroatom as in alcohol (ROH), amine (RNH2), sulfide (RSH). The disconnection will therefore give the cationic carbon synthon (1). The reagent for (1) will usually have a good leaving group attached to R (2).

In the other word, the reaction is a substitution of some kind and the reagents will be alkyl halides, acid chloride are best reagents this will be chosen to undergo substitution mostly.

$$R \text{--X} \rightarrow C-X \xrightarrow{R} O \quad + \quad XH$$

(1)

Acid groups are always easy to disconnect because we have chosen the bond between the carbonyl and heteroatom group.

Examples

**Ester disconnection**

$$\text{Ph} \text{--O} \text{Ph} \xrightarrow{C-O} \text{Ph} \text{--OH} \quad + \quad \text{Ph}$$

(3)

**Ethers and sulfides**
Two group C-X disconnection

We have done a single functional group disconnection corresponds to the reliable reaction. An important extension of this method is to use one functional group to help disconnect another elsewhere in the molecule.

One example we have already met is the synthesis of acetal (1). These compound have four C-O bonds all the candidates for disconnection if we regard the compound as an ether. If we recoganise that one carbon atom (marked as 2) has two C-O bonds we can use one oxygen atom to help disconnect the other (2) and discover that we have an acetal. Both C-O bonds should therefore be disconnected and we can label the operation to show that what we mean.

If one of the heteroatom is present as OH in a reaction only one functional group is initiated to do the disconnection.

Aromatic compounds can be synthesized easily because the bond to be disconnected is always the bond that joining the aromatic ring to the rest of the molecule all we have to decide is when to make the disconnection and exactly which starting material to use. We shall use the technical terms disconnection, functional group intercoversion (FGI), and synthon.
We know that esters are made up of alcohol and acids so we can write a C-O disconnection. Usually, disconnection will be labeled to show

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CO}_2\text{Et} \\
\xrightarrow{\text{C-O}} & \quad \text{H}_2\text{N} \quad \text{CO}_2\text{H} \\
& \quad + \text{EtOH}
\end{align*}
\]

In this step we must do the FGI to change the functional groups into others which can be disconnected. Aromatic acids can be made by the oxidation of methyl groups and amino groups by the reduction of nitro groups.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{FGI} \\
\xrightarrow{\text{O}_2\text{N}} & \quad \text{CO}_2\text{H} \\
& \quad \text{FGI} \\
\text{CH}_3 & \quad \text{O}_2\text{N} \\
\xrightarrow{\text{C-N}} & \quad \text{CH}_3 \\
& \quad \text{Nitration}
\end{align*}
\]

Now disconnection of the nitro group is rational because we know that nitration of toluene occurs easily and toluene is available.

\[
\begin{align*}
\text{OH} & \quad \text{Br} \\
\xrightarrow{\text{Me}} & \quad \text{Me} \quad \text{NH}_2 \\
& \quad \text{C-Br} \\
& \quad \text{bromination}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{FGI} \\
\xrightarrow{\text{C-N}} & \quad \text{NO}_2 \\
& \quad \text{nitrilation}
\end{align*}
\]

The amine group was protected as amide to prevent the bromine added to the other ortho position as well.
Retrosynthetic Analysis

NOTES

In this example motioned above we can disconnect the nitro group first but Friedel crafts reaction is most preferable to Para position due to presence of large electrophile.

Check your progress

4. Write a short note on one group C-C disconnection?
5. Write done the two group C-C disconnection?
6. Write short note on one group C-X disconnection?

5.5 AMINE AND ALKENE SYNTHESIS

The synthesis of amines warrants a separate chapter because the C-X disconnection (1a) used for ethers, sulphides, and the like is not satisfactory. The problem is that the product (1) of the inductive effect of the methyl group and reacts further to give (3) and even (4).

Analysis

\[ \text{R} \equiv \text{NHMe} \xrightarrow{\text{C-N}} \text{RNH}_2 + \text{MeI} \quad \text{NOT useful} \]

Synthesis

\[ \begin{align*}
\text{RNH}_2 & \xrightarrow{\text{MeI}} \text{RNHMe} \\
\text{RNHMe} & \xrightarrow{\text{MeI}} \text{RNMe}_2 \\
\text{RNMe}_2 & \xrightarrow{\text{MeI}} \text{RNMe}_3^+ \\
\end{align*} \]

It is no use adding only one equivalent of MeI since the molecule of (1) formed in the reaction will complete with (2) for MeI.

This reaction can occasionally be used if the product is less reactive than the starting material for electronic or steric reasons, or if it is intermolecular. This second example (6) is from the salbutamol synthesis discussed. Unless you can see a specific reason for success, avoid the reaction.
The general answer to this problem is to avoid alkyl halides and to use instead electrophiles which give relatively uncreative products with amines. The best example are acyl halides, aldehydes, and ketones. The products, amines (7) and (9) imines, can be reduced to amines. The amide method inevitably produces a \( \text{CH}_2 \) group (8) next to the nitrogen atom, but the imine route is suitable for amines with branched chains (10).

A preliminary FGI is therefore needed before we apply the C-N disconnection. Amine (11) could be disconnected by either method. It has been synthesized by route (b), the reduction being carried out without isolating the imine.

**Analysis**

**Synthesis**

An example more suited to the amide approach is the cyclic amine (12). We choose the exocyclic \( \text{CH}_2 \) group as a side for FGI since the cyclic amine piperidine (13) is readily available.
Catalytic reduction was used in the published synthesis: LiAlH₄ would be a commoner choice nowadays.

Catalytic reduction was used in the published synthesis: LiAlH₄ would be a commoner choice nowadays.

Primary amines RNH₂

Unsubstituted imines (14) are unstable and cannot usually be made in good yield, but primary amine can still be made in a one-step reductive amination in which the imine is not isolated.

Primary amines are not usually made by reduction of amides (15) but by other reductive processes which are minor variations on this scheme. For unbranched amines (16) we can reduce cyanides (17). This method is especially suitable for benzylic amines since aryl cyanides can be made from diazonium salts and for the homologous amines (18) since cyanides ion react easily with benzyl halides.
Disconnection again requires a preliminary FGI. We have already met examples.

For branched chain primary amines (20), oximes (19) are good intermediates since they can be made easily from ketone and reduction cleaves the weak N-O bond as well as reducing the C-N bond. FGI is again required before disconnection.

The synthesis of Fenfluramine (21), a drug acting on the central nervous system, illustrates two amine disconnections. The ethyl group can be removed by the amide method leaving the branched chain primary amine (22) available from the ketone (23) by the oxime method.

**Fenfluramine: Analysis**

(21) 

(22) 

(23)
Neither oxime nor amide need be isolated the published synthesis uses different method of reduction in the case, no doubt developed by experiment.

\[
\begin{align*}
\text{F}_3\text{C} & \quad \xrightarrow{1.\text{NH}_2\text{OH}} \quad \text{1. MeCOCl} \\
\text{1. H}_2\text{,cat} & \quad \xrightarrow{2.\text{LiAlH}_4} \quad \text{TM(21)} \\
\end{align*}
\]

The alkylation and reduction of aliphatic nitro compounds is one route to t-AlkNH₂ and is discussed. Another route uses the Ritter reaction followed by hydrolysis of the amide.

\[
\begin{align*}
\text{R}^1\text{CH}_2\text{NO}_2 & \quad \xrightarrow{\text{R}^1,\text{NO}_2} \quad \text{R}^1,\text{NH}_2 \\
\text{H}_2\text{,cat} & \quad \xrightarrow{\text{HO}^-/\text{H}_2\text{O}} \\
\text{MeCN} & \quad \xrightarrow{\text{Ritter}} \quad \text{NHCOMe} \\
\end{align*}
\]

**Alkene Synthesis**

Alkenes can be made by the dehydration of alcohols, usually under acidic conditions, the alcohol (1) being assembled by the usual methods. This route is particularly good for cyclic or branched olefins (2).

\[
\begin{align*}
\text{O} & \quad \xrightarrow{\text{RMgBr}} \quad \text{R} \quad \xrightarrow{\text{H}^+} \quad \text{R} \\
\text{R} \quad \text{OH} & \quad \xrightarrow{\text{H}^+} \quad \text{R} \\
\text{(1)} & \quad \xrightarrow{\text{(2)}} \\
\end{align*}
\]

When Zimmermann wished to study the photochemistry of a series of alkene of general structure (3), he could have put the OH group at either end of the double bond. Putting OH at the branch point is better strategy as disconnection of the alcohol (4) the gives simpler starting materials.
The dehydration of this tertiary alcohol (4) will be very rapid by an E1 mechanism and there is doubt about the position or geometry of there is no doubt about the position or geometry of the double bond.

**Synthesis**

\[
\text{EtO}_2\text{C}\quad \text{R} \quad \xrightarrow{\text{PhMgBr}} \quad \xrightarrow{\text{POCl}_3} \quad \text{TM(3)}
\]

Elimination reaction on alkyl halides follow essentially the same strategy as the halide is usually made from an alcohol. Eliminations of primary groups are better done this way with base instead of acid catalysis.

**Analysis**

\[
\text{R} \quad \xrightarrow{\text{FGI}} \quad \text{R} \quad \xrightarrow{\text{FGI}} \quad \text{OH}
\]

\[
\text{e.g. 1,2} \quad \text{C-C}
\]

**Synthesis**

\[
\text{R} \quad \text{OH} \quad \xrightarrow{\text{PBr}_3} \quad \text{Br} \quad \xrightarrow{\text{t-BuO}^-} \quad \text{TM(5)}
\]

Dienes can be made by this approach if vinly grignards are used because the vinyl group blocks dehydration in one direction and make the reaction faster by E1 as the intermediate is an allylic cation. An interesting example is the four-membered ring compound (6): note that the OH group is again added at the branch point.
The Wittig Reaction

These methods of olefin synthesis have now largely been superseded by the wittig method which gives total control over the position of the double bond and partial control over its geometry. This reaction may be new to you: its mechanism follows.

The Wittig reagent

The wittig reaction forms both $\sigma$and $\pi$ bonds in one reaction so the disconnection is at the double bond with a nearly free choice of which end come from the alkyl halide (7) and which from the carbonyl compound. Hence the exo-olefin (9), all but impossible to make elimination, is easily made by either wittig route. Route (a) is perhaps easier as cyclohexanone is easier to handle than formaldehyde.
Branched chains (10) are no trouble as either a secondary halide (11) or a ketone can be used. This is another case where dehydration of even the branch point alcohol (12) would give a mixture of positional isomers.

Substituted alkenes (13) can be made by the Wittig reaction: the more reaction phosphate ester (14) is often used when there is a stabilizing group present.
5.6 IMPORTANT STRATEGIES OF RETROSYNTHESIS

1. Functional groups based strategies

Functional groups in the target structure may direct the transform search in several ways:

- Removal of reactive and masked functionality.
- Disconnection based on the location of functional groups.
- Reconnection of functional groups to form rings retrosynthetically

The reductive strategy is constrained by strategic rules. Clearly, it is not practical to attempt every possible reconnection.

2. Topological strategies

The disconnection of specific, so-called ‘strategic’ bonds can lead to major molecular simplification. There are several types of strategic bonds:

- Bonds in (poly)cyclic ring systems
- Bonds in (poly)fused ring systems
- Bonds connecting chains to rings
- Bonds connecting chains to other chains
- Bonds connecting chains to functional groups

Heuristics (empirical rules) have been devised to select these types of bonds from any target structure. It is also possible to identify rings which should be disassembled early in the
retrosynthetic process, or rings which should be kept intact during these stages.

3. **Transform-based strategies**

A very useful guidance for retrosynthetic analysis can be provided by the application of a powerfully simplifying transform -- corresponding to a reaction effecting a considerable increase in complexity. Very often such an application is suggested by the presence of (functionalized) rings of specific sizes in the target molecule. Some powerfully simplifying transforms are:

- Diels-Alder
- Hetero Diels-Alder
- Robinson annulation
- Birch reduction
- Internal ene reaction
- Halolactonization

4. **Structure-goal strategies**

The analysis can also be directed towards a particular structure.

- Starting material
- Chiral building block
- Retron-containing structure
An analysis directed towards such a structure-goal does not need to be purely retrosynthetic. It can even be synthetic, but probably the most efficient search would be a bidirectional one.

5. Stereochemical strategies

Here the focus is on removal of stereocenters under stereocontrol. Stereocontrol can be achieved through either mechanistic control or substrate control. Reconnections that move stereocenters from chains (where they are difficult to introduce) into rings (where introduction is usually much easier) can also be considered stereochemically strategic.

5.7 FUNCTIONAL GROUP TRANSPOSITION (FGT)

Functional group transpositions (FGT) are frequently employed. But in fact any transform which assists in ‘setting up’ the retron for a goal transform can be thought of as a subgoal transform. Examples of each type are given below:

5.8 FUNCTIONAL GROUPS INTER CONVERSION

The antihypertensive drug of ornine contains an amide and an amine functional group, and we need to decide which to disconnect first. If we disconnect the secondary amine first (b), we will have chemo selectivity problems constructing the amide in the presence of the resulting NH₂ group.
Yet disconnection (a), on the face of it, seems to pose an even greater problem because we now have to construct an amine in the presence of an acyl chloride! However, we shall want to make the acyl chloride from the carboxylic acid, which can then easily be disconnected to 2-aminobenzoic acid (anthracitic acid) and 4-chloropyridine.

The retrosynthetic transformation of an acyl chloride to a carboxylic acid is not really a disconnection because nothing is being disconnected. We call it instead a functional group interconversion, or FGI, as written above the retrosynthetic arrow. Functional group interconversions often aid disconnections because the sort of reactive functional groups (acyl chlorides, alkyl halides) we want in starting materials are not desirable in compounds to be disconnected because they pose chemoselectively problems. They are also useful if the target molecule contains functional groups that are not easily disconnected.

By using an appropriate reagent or series of reagents, almost any functional group can be converted into any other. You should already have a fair grasp of reasonable functional group interconversions. They mostly fall into the categories of oxidations, reductions, and substitutions.

The synthesis of amines poses a special problem because only in certain
cases is the obvious disconnection successful.

The problem is that the product is usually more reactive than the starting material and there is a danger that multiple alkylation will take place.

The few successful examples you have seen so far in this chapter have been exceptions, either for steric or electronic reasons, and from now on we advise you to avoid disconnecting an amine in this way. Sometimes further alkylation is made unfavorable by the increased steric hindrance that would result: this is probably the case for the cetaben ethyl ester we made by this reaction.

If the alkylating agent contains an inductive electron-withdrawing group, the product may be less reactive than the starting material benzylamine was only alkylated once by the alkyl bromide in the synthesis of ICI-D7114 on p. 000 because of the electron-withdrawing effect of the aryloxy group.

What are the alternatives? There are two main ones, and both involve functional group interconversion, with the reactive amine being converted to a less reactive derivative before disconnection. The first solution is to convert the amine to an amide and then disconnect that. The reduction of amide to amine is quite reliable, so the FGI is a reasonable one.

This approach was used in a synthesis of this amine, though in this case catalytic hydrogenation was used to reduce the amide.
The second alternative is to convert to an imine, which can be disconnected to amine plus carbonyl compound. This approach is known as reductive amination.

Ocfentanil is an opioid painkiller that lacks the addictive properties of morphine. Disconnection of the amide gives a secondary amine that we can convert to an imine for disconnection to a ketone plus 2-fluoro aniline.

The synthesis is straightforward: a reductive amination followed by acylation of the only remaining NH group. The tertiary amine in the left-hand ring interferes with neither of these reactions.
There are several conceivable routes to the retroactive drug Fenfluramine analysis, which uses both the amide and the imine FGI methods, is shown below and this was the route used to make the drug. Notice that the oxime was used instead of the imine. N-substituted imines are very unstable, and the much more stable, indeed isolable oxime serves the same purpose. Oximes are generally reduced with LiAlH₄.

You should now be able to suggest a plausible analysis of the secondary amine terodilin. This is the structure; write down a retrosynthetic analysis and suggested synthesis before looking at the actual synthesis below. You should find yourself quite restricted in choice: the amide route clearly works only if there is a CH₂ group next to the nitrogen (this comes from the C=O reduction), so we have to use an imine.

In the synthesis of terodilin, it was not necessary to isolate the imine reduction of imines is faster than reduction of ketones, so formation of the imine in the presence of a mild reducing agent (usually NaCNBH₃ or catalytic hydrogenation) can give the amine directly.

Check your progress

7. What is a Transform-based strategy of retrosynthesis?
8. Write Functional group transposition.
5.9 ANSWERS TO CHECK YOUR PROGRESS QUESTIONS

1. The molecule whose synthesis is being planned is the desired final compound. The target molecule is the molecule under investigation. For example, in this case, it would mean the molecule you are looking for to help you make a diagnosis.

2. Synthon: A fragment of a compound that assists in the formation of a synthesis, derived from that target molecule.

3. A synthon and the corresponding commercially available synthetic equivalent.

4. The disconnections we have made so far have all been of C–O, C–N, or C–S bonds, but, of course, the most important reactions in organic synthesis are those that form C–C bonds. We can analyze C–C disconnections in much the same way as we’ve analyzed C–X disconnections. Consider, for example, how you might make this simple compound, which is an intermediate in the synthesis of a carnation perfume.

5. It’s not only Grignard reagents that will react with aldehydes or ketones to make alcohols: enolates will too. We spent discussing this reaction, the aldol reaction, its variants, and ways to control it.

The aldol reaction is extremely important in organic synthesis because it makes compounds with two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule think aldol! In disconnection terms we can represent it like this.
6. We have done a single functional group disconnection corresponds to the reliable reaction. An important extension of this method is to use one functional group to help disconnect another elsewhere in the molecule.

7.

- Robinson annulation
- Birch reduction
- Internal ene reaction
- Halolactonization

8. Functional group transpositions (FGT) are frequently employed. But in fact any transform which assists in ‘setting up’ the retron for a goal transform can be thought of as a sub-goal transformed.

5.10 SUMMARY

Retrosynthetic analysis is one of the main tasks in the planning of organic synthesis and a milestone in the computer-aided synthesis design. Different approaches have been proposed and several software systems have been developed as a solution to this issue, including rule-based expert systems, algorithms that use principles of physical chemistry to predict energy barriers of a reaction and machine learning techniques. It should consist of transforms that correspond to generic chemical reactions (or chemical transformations; and (2) the dataset should be presented in computer-readable form, in which transforms can be easily stored, processed, and applied. In accordance with “Nomenclature for organic chemical transformations” and the terminology used in retrosynthetic analysis, we distinguish the following terms: (i) chemical reaction—typically describing a specific chemical reaction with concrete reactants, products, agents and conditions; (ii) chemical transformation describing a generic chemical reaction, i.e., the chemical transformation can be related to a set of many ordinary reactions which share the same reaction center; and (iii) transform is a retro-reaction the reverse transformation of a generic chemical reaction.

5.11 KEYWORDS

- Terminology of retrosynthesis.
- One group and two group C-X disconnections.
- Amine and alkenes synthesis
- Functional group transposition
- Strategies of retrosynthesis

5.12 SELF ASSESSMENT QUESTIONS AND EXERCISES

1. What is the retron?

2. What is retrosynthetic free?
3. Write the synthesis of aldol product in two group C-C disconnection method?

4. Write the synthesis of aromatic compounds?

5. Write the witting reaction by retrosynthesis mythologies?

6. Write done the synthesis of amine by retrosynthesis method?

7. What are the important strategies of retrosynthesis?

8. What is functional group interconversion?

9. Write done the topological strategies?

5.13 FURTHER READINGS


UNIT- 6 FUNCTIONAL GROUP PROTECTION

Structure

6.1 Introduction

6.2 Objectives

6.3 Protection and deprotection

   6.3.1 Hydroxy
   6.3.2 Carboxyl
   6.3.3 Carbonyl
   6.3.4 Carboxyl amino groups
   6.3.5 Carbon - Carbon multiple bonds

6.4 Chemo-regioselectivity protection and deprotection

6.5 Illustration of protection and deprotection in synthesis

6.6 Answers to check your progress Questions

6.7 Summary

6.8 Keywords

6.9 Self-assessment question and exercises

6.10 Further readings

6.1 INTRODUCTION

Protection and deprotection is an important part of organic synthesis. During the course of synthesis, we many times desire to perform reaction at only one of the two functional groups in any single organic molecules. For example, in an organic compound possessing two functional groups like ester and ketone, we have to perform reaction at only ester group, them the keto group needs to be protected. If we want to reduce the ester group, then keto group will also get reduced. To avoid this type of complications, protection and deprotection of functional groups are necessary

The plants, animals or microorganisms produce a number of chiral and achiral complicated structures. Some of the groups of compounds include antibiotics, alkaloids, chlorophyll, steroids, biopolymers,
carbohydrates, fats, vitamins, dyes etc. The chemist determines the structures of these compounds and try to synthesize them using disconnection approaches. The synthesis of these compounds becomes important due to their wide applications. Synthesis from simple starting materials with predictable regioselectivity and stereochemistry requires the utility of retrosynthetic analysis.

There are two types of selectivity possible for this synthesis:

(i) Chemoselectively is deciding which group reacts.

(ii) Regioselectivity is where the reaction takes place in that group.

Selectivity can be attained by selecting appropriate starting materials, reagents, solvents, reaction conditions and most importantly protecting and deprotection methods.

### 6.2 OBJECTIVES

After going through this unit, you will be able to

- Understand the types of selectivity.
- Explain chemoselectivity in retroanalysis.
- Understand the stereoselectivity in retroanalysis.
- Design the synthesis of chiral and achiral molecules.
- Know about protecting groups.
- Study the characteristics of protecting groups.
- Understand the functional group protection.
- Know the protection of important functional groups.

### 6.3 PROTECTION AND DEPROTECTION

#### 6.3.1 Hydroxy

Methyl ethers and simple amides are easy to synthesize and are quite resistant to variety of reagents. From below reaction, we can see that reaction takes place to turn R1 in 13 into R2 in 16. But the protection is not very helpful as extreme conditions are required to remove them. These can be used when the molecule is stable enough to bear deprotection condition.

```
R1-OH  \xrightarrow{\text{base}}  \xrightarrow{\text{reaction}}  \xrightarrow{\text{HI reflux}}  R1-OMe  \rightarrow  R2-OMe  \rightarrow  R2-OH
```

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<th>14</th>
<th>15</th>
<th>16</th>
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</table>

The Achilles Heel Strategy

The Achilles Heel for the functional group ether is the use of tetrahydropyryl group (THP group). This converts ether into an acetal. The compound used to give THP derivative is dihydropyran, DHP 24. The protonation of 24 yield the compound with positive charge on oxygen 25. This is further reacted with alcohol (ROH) to give the acetal 26. The compound 2-methoxytetrahydropyran (when R = CH₃) is known as the ‘the THP derivative’. For deprotection of alcohol from the protecting group, hydrolysis only requires the weak

There is another way to make an ether easier to eliminate is to convert it into benzylic form as given. The alcohol can be protected as benzylic ether and easily deprotected to give the desired product. For example, the alcohol 27 on reaction with benzyl chloride in the presence of base like sodium hydride (NaH) gives the alcohol protected as benzylic ether 28. We can do any reaction on the protected alcohol group and deprotection will be done by simple hydrogenation in the presence of catalyst.

Other popular method to protect the alcohol group is to convert them to trimethylsilyl ether. This can be done by treating the alcohol with chlorotrimethylsilane and a tertiary amine.

6.3.2 Carboxyl

The common ester protecting groups for carboxylic acids are methyl, ethyl and benzyl esters.

Methyl esters:

Formation:

\[ R-\text{CO}_2\text{H} + \text{H}_2\text{C}=\text{N}_2 \rightarrow R-\text{C}=\text{OCH}_3 + \text{N}_2 \]

Diazomethane
Cleavage:

\[
\text{LiOH} \quad \overset{\text{R-C-OCH}_3}{\text{H}_2\text{O}_2} \quad \text{R-CO}_2\text{H} \quad + \quad \text{CH}_3\text{OH}
\]

Ethyl and benzyl esters are prepared based on the following rationale:

\[
\text{R-CO}_2\text{H} \quad + \quad \text{R}'\text{OH} \quad \overset{\text{HCl}}{\longrightarrow} \quad \text{R-C-OR}' \quad + \quad \text{H}_2\text{O}
\]

Best approach:

Milder conditions for esterification:

\[
\text{R-CO}_2\text{H} \quad + \quad \text{R}'\text{OH} \quad \overset{\text{DCC}}{\longrightarrow} \quad \text{R-C-OR}' \quad + \quad \text{DCHU}
\]

\[\text{DCC} = 1,3-\text{Dicyclohexyl carbodiimide}\]

Ethyl Ester:

Formation:

\[
\text{R-CO}_2\text{H} \quad + \quad \text{CH}_3\text{CH}_2\text{OH} \quad \overset{\text{DCC}}{\longrightarrow} \quad \text{R-C-OCH}_2\text{CH}_3
\]

Cleavage:

\[
\text{LiOH} \quad \overset{\text{R-C-OCH}_2\text{CH}_3}{\text{H}_2\text{O}_2} \quad \text{R-CO}_2\text{H} \quad + \quad \text{CH}_3\text{CH}_2\text{OH}
\]

Benzyl esters:

Formation:

\[
\text{R-CO}_2\text{H} \quad + \quad \text{PhCH}_2\text{OH} \quad \overset{\text{DCC}}{\longrightarrow} \quad \text{R-C-OCH}_2\text{Ph}
\]

\[
\text{BnOH} \quad \text{R-C-Obn}
\]
Cleavage:

By hydrogenolysis: A very mild method for most functional groups except with alkynes, alkenes and nitriles.

6.3.3 Carbonyl

The protecting groups allow the masking of a particular functional group where a specified reaction is not to be performed. The protection is required as it interferes with another reaction. Let us take the example of reduction of the keto-ester 1 to the alcohol 2 with a nucleophilic reagent such as NaBH₄ that attacks only the more electrophilic ketone. In order to make alcohol 3 by the reduction of ester, it is important to protect the ketone as an acetal 4 that allows the reduction of the ester with the more nucleophilic LiAlH₄.

In another example, 3-oxocyclohexanecarboxylic acid methyl ester (6) undergoes reduction with lithium aluminium hydride (LiAlH₄) to 3-hydroxymethylcyclohexanol (7). If we want to go for selective reduction, then the role of protection and deprotection comes.

During the protection, ketone from the compound 3-oxocyclohexanecarboxylic acid methyl ester (6) forms ketal on reaction with methanol (CH₃OH) under acidic conditions. The protection reaction can be reversed by treatment with water under acidic conditions.
The characteristics of protecting group are as follows:

1. It must be easy to put in

2. It must be resistant to reagents that would attack the unprotected function group.

3. It must be easily removed

### 6.3.4 Amino groups

**Tert-butyloxycarbonyl (BOC)**

**Formation:**

**Cleavage:**

**Benzoxycarbonyl protecting group (CBZ)**

**Formation:**
6.3.5 Protection of Triple bonds

Masking the potentially acidic proton of 1-alkyne (pKa 25) is readily achieved by their conversion to the corresponding 1-silyl-1-alkynes compound.

It can be removed under various conditions. MeONa in MeOH, n-Bu₄NF in THF, AgNO₃ in EtOH Protection of an internal triple bond

Dicobaltoctacarbonyl complex
Chemoselectivity plays important role in organic synthesis. This is helpful in those molecules which possess more than one functional group. The selective reactivity of one functional group in the presence of others is controlled by chemoselectivity. The chemoselectivity is supported by protection and deprotection. Following examples will explain the chemoselectivity in organic reactions.

**Selective Reduction**

The selection of proper reagent plays important role in chemoselectivity. The selective reduction of either the double bond or the carbonyl group in cyclopent-2-enone (1) is reagent specific. For the chemoselective reduction of bond over bond is performed by catalytic hydrogenation (Figure 1). Hence, the reaction of cyclopent-2-enone (1) with hydrogen in the presence of palladium (H\textsubscript{2}/Pd) gives cyclopentanone (2).

\[
\text{H}_2/\text{Pd} \rightarrow \text{H}_2/\text{Pd}
\]

The reduction of bond over bond is performed by reducing agent sodium borohydride (Figure 2). The reaction of cyclopent-2-enone (1) with sodium borohydride (NaBH\textsubscript{4}) gives cyclopent-2-enol (3). In this case, only the carbonyl group (\(>\text{C}=\text{O}\)) is selectively reduced to hydroxyl group (\(-\text{OH}\)). Whereas, in the former case (figure 1) the double bond is selectively reduced to single bond.

\[
\text{NaBH}_4,\text{CeCl}_3 \rightarrow \text{NaBH}_4,\text{CeCl}_3
\]

Another example of chemoselectivity is the chemoselective reduction of unsaturated esters in presence of alkenes. The reduction of the compound 4 with magnesium (Mg) in the presence of methanol reduced the double bond present at the, position of the, unsaturated esters giving the product 5.
Regioselectivity protection and deprotection:

Regioselectivity gives preference for bond making at a particular place when there is possibility of bond formations at other possible positions also. In other words, there is a preference of one reactive site with respect to other reactive site. The best example to explain this is Markovnikov and anti-Markovnikov addition reactions.

The reaction of hydrobromic acid (HBr) with styrene (vinyl benzene, 6) gives 1-bromoethylbenzene (8) through Markovnikov addition (Figure 4). The same reaction, if performed in the presence of peracids undergoes Anti-Markovnikov addition to give 2-bromoethylbenzene (7). These information of regioselectivity is important for the retrosynthetic analysis.

Birch reduction is another important example of regioselectivity. In this reduction method, aromatic rings undergo a 1, 4-reduction to provide unconjugated cyclohexadienes. This reaction is performed by sodium or lithium metal in liquid ammonia and in the presence of an alcohol. Here, the site of reduction is dependent upon the type of substitution present in the aromatic ring. Without any substitution in the aromatic ring, the reduction of simple benzene (9) gives cyclohexadiene (10).
The regioselectivity in Birch reduction when electron donating (-OCH₃) (Figure 6) and electron withdrawing (-COOH) (Figure 7) groups are attached. The preference is based on the mechanism of the reaction where the radical-anion is protonated initially determines the structure of the product. While performing the retrosynthetic analysis, these preferences play important role in the synthetic design of any molecule(s).

6.5 ILLUSTRATION OF PROTECTION AND DEPROTECTION IN SYNTHESIS

**Protecting group:** A temporary group added during organic synthesis to prevent a portion of a molecule from reacting (i.e., it assists chemoselectively). Protection is usually considered an undesirable synthetic strategy because it adds two steps (protection and deprotection) to the length of the overall synthesis, and because the added steps usually cause a decrease in overall yield and reduces atom economy. A painter's drop cloth is a useful metaphor: It prevents paint from getting on undesired areas (such as the floor) but adds extra time, effort, and cost to the painting process because the drop cloth must be put down before painting, and picked up afterward, and because the drop cloth adds cost to the process, and increases waste.
In the following reaction, without a protecting group, both the alcohol and aldehyde are oxidized by reagent. In this oxidation process is not chemoselective. When the alcohol is protected with a tBDMS group, only the aldehyde is oxidized by Jones reagent. Thanks to the protecting group the oxidation is now chemoselective, but the synthesis is now two steps longer because of the protection and deprotection steps.

**Check your progress**

1. Protection and deprotection definition.
2. Any example of the carboxyl amino group protection formation?

### 6.6 ANSWERS TO CHECK YOUR PROGRESS QUESTIONS

1. **Protection and deprotection**: A protecting group or protective group is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a subsequent chemical reaction. It plays an important role in multistep organic synthesis. This step is called deprotection.

2.
3. **Chemoselectivity** refers to the selective reactivity of one functional group in the presence of others; often this process in convoluted and protecting groups are on the molecular connectivity alone. Such predictions based on connectivity are generally considered plausible, but the physical outcome of the actual reaction is ultimately dependent on a number of factors that are practically impossible to predict to any useful accuracy.

**Regioselectivity** is the preference of one direction of chemical bond making or breaking over all other possible directions. It can often apply to which of many possible positions a reagent will affect, such as which proton a strong base will abstract from an organic molecule.

### 6.7 SUMMARY

Protection and deprotection is an important part of organic synthesis. Protecting groups allow masking the distinctive chemistry of a functional group as it interferes with another reaction. Ethers and Amides are used as protecting groups when the molecule is stable enough to bear deprotection condition. Alcohols are usually protected as ethers where as amines are protected as amide and Retrosynthetic analysis provides important inputs for synthesis from simple starting materials with predictable regioselectivity and stereochemistry. There are three types of selectivity possible for any synthesis; chemoselectivity, regioselectivity and stereoselectivity. Chemoselectivity refers to selective reactivity of one functional group in the presence of others. The selection of proper reagent plays important role in chemoselectivity. Regioselectivity gives preference for bond making at a particular place when there is possibility of bond formations at other possible positions also Markovnikov and anti-Markovnikov addition reactions are examples of regioselective reactions. Birch reduction is another example of regioselective reaction. Stereoselectivity is the preferential formation of one stereoisomer in a chemical reaction.

### 6.8 KEYWORDS

- Protection
- Deprotection
- Chemoselectivity
- Regioselectivity
Functional Group
Protection

NOTES

6.9 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Carboxyl group and ester and carbonyl group based on protection and deprotection formation?
2. Ketone given the more explanation?
3. Deprotection formation of amino group.
4. Regioselectivity of protection and deprotection.

6.10 FURTHER READINGS


UNIT-7 HETEROCYCLIC COMPOUNDS

Structure
7.1 Introduction
7.2 Objectives
7.3 Indole
  7.3.1 Fischer’s indole synthesis
  7.3.2 Madelung synthesis
  7.3.3 Reissert synthesis
7.4 Oxazole
7.5 Flavone
  7.5.1 Kostanecki’s synthesis
  7.5.2 Robinson’s synthesis
  7.5.3 Modified claisen’s’ condensation
  7.5.4 Baker-Venkatraman synthesis
  7.5.5 Wheeler’s synthesis
7.6 Anthocyanin
7.7 Answer to check your progress question
7.8 Summary
7.9 Keywords
7.10 Self-assessment question and exercises
7.11 Further readings

7.1 INTRODUCTION
Heterocyclic compounds are cyclic compounds with the ring containing carbon and other elements, the commonest being oxygen, nitrogen and sulphur. There are a number of heterocyclic ring which are easily opened and do not possess any aromatic properties, e.g., ethylene oxide, γ and δ - lactones, etc. There are not considered to be heterocyclic compounds. Heterocyclic are those compounds with five or six membered heterocyclic rings which are stable, contain conjugated double bonds, and exhibit aromatic character. E.g: Indole, Oxazole, Thialoze, etc.

7.2 OBJECTIVES
After going through this unit, you will be able to

❖ Synthesis of Indole, Oxazole, flavones and anthocyanin compounds.
❖ Reactions of heterocyclic compounds.
Heterocyclic Compounds

- Physical properties of heterocyclic compounds.
- Describe the physicochemical properties of heterocyclic compounds.
- Synthesis methods

## 7.3 INDOLE (2, 3-BENZOPYRROLE, C$_8$H$_7$N)

Indole belongs to pyrrole derivative. It is benzopyrrole. It occurs in coal-tar, jasmine flowers and orange blossom oil. Indole is the parent substance for Indigotin. Its melting point is 52°C.

![Indole structure](image)

### 7.3.1 Fischer’s Indole synthesis

This is the most important method of preparing indole and it is carried out by heating the phenylhydrazone or substituted phenylhydrazone of an appropriate aldehyde, ketone or ketonic acid with zinc chloride, polyphosphoric acid, and sulphuric acid in ethanol.

![Fischer's Indole synthesis](image)
**7.3.2 Madelung Synthesis**

This synthesis involves the cyclisation of o-acyl amido toluene by means of a strong base e.g., indole (from O-formamidotoluene) and 2-methylindole (from O-acetamidotoluene).

![Madelung Synthesis](image)

The possible mechanism for the above reaction is:

![Mechanism](image)

**7.3.3 Reissert synthesis**

This is the simple and good method and it is carried out with o-nitro toluene (or its substituted derivatives) and ethyl oxalate in the presence of sodium ethoxide.

![Reissert Synthesis](image)

**Properties**

Indole resembles Pyrrole in many of its properties.

a) Electrophilic substitution normally occurs in the 3 – position, but if it is occupied then 2-substitution occurs. If both 2 and 3-position are
blocked, then the benzene ring is attached at the 6-position.

b) Indole undergoes Gattermann reaction to form Indole-3-aldehyde

\[
\text{Indole} \xrightarrow{\text{Gattermann reaction}} \text{Indole-3-aldehyde}
\]

\[
\text{Indole} + \text{HCHO} + \text{CH}_3\text{NCH}_3 \rightarrow \text{Gramine}
\]

c) Indole undergo Mannich reaction with formaldehyde and dimethylamine to form Gramine (3-dimethyl amino ethyl indole)

d) Indole is reduced electrolytically, by tin and hydrochloric acid or by zinc dust and phosphoric acid to form 2-3 dihydro indoles (indoline).
d) Indole behaves in some ways as a tautomeric substance, the tautomer is known as indolenine.

\[
\begin{array}{c}
\text{indolenine} \\
\end{array}
\]

**Check your progress**

1. Write short notes on: Fischer’s Indole synthesis.
2. What is Heterocyclic compound?
3. Write about Reissert synthesis?

## 7.4 OXAZOLE

### Preparation:

(i) Oxazole may be prepared by the reaction between an acid amide and an \( \alpha \)-halogen ketone.

\[
\text{Ph} \quad \text{C} \quad \text{Ph} \\
\text{CH}_2\text{Br} \quad \text{OH} \\
\text{C} \quad \text{CH}_3 \quad + \\
\text{NH} \quad \text{C} \quad \text{CH}_3 \\
\text{O} \quad \text{HBr} \\
\text{O} \\
\text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{N} \quad \text{CH}_3 \\
\text{O} \\
\text{H}_2\text{O} \\
\text{Oxazole} \\
\text{(substituted)}
\]

(ii) Oxazole may be prepared by the action of acid on an \( \alpha \)-acylamino ketone.
(iii) Oxazole has been prepared by Cornforth et al by the following method.

Properties:

(i) Boiling point of oxazole is 69°C.

(ii) Oxazoles are stable towards alkalis.

(iii) Oxazoles are basic and possess aromatic properties, and the stability of the ring towards concentrated acids depends on the nature of the substituents in the ring, eg.
Check your progress

5. Any three properties Oxazole.
6. How to prepare Oxazole from α-acylamino ketone.

7.5 FLAVONES

The flavones, which are also known the anthoxanthins, are yellow pigments which occur in plant kingdom either in the Free State or as glycosides or associated with tannins. Chemically, the flavones are hydroxylated derivative of flavone (2-phenyl-4-chromone) which is partially alkylated.

In most of the flavones, position 5 and 7 are hydroxylated and also one or more of positions 3, 4 and 5 are also hydroxylated. Further position 3’ and 5’ are often methylated where as positions 5, 7 and 4’ are usually unmethylated.

When a flavone is hydrolysed with mineral acid, it yields anthoxanthidine (a glycon) and one or more molecules of sugar. The sugars are generally glucose, rhamnose etc., some important flavones are flavone, chrysin, Apigenin etc.

FLAVONE, C_{15}H_{10}O_{2}

This occurs naturally as dust on flowers, leaves etc.

Constitution:

The structure of flavone has been elucidated on the basis of following analytical and synthetic evidences.

(i) From analytical data and molecular weight determination the molecular formula of flavone has been found to be C_{15}H_{10}O_{2}.

(ii) When acetylated, flavone does not yield any acetyl derivative, indicating the absence of any –OH group.
(iii) When fused with KOH, it yields phenol and benzoic acid.

\[
C_{15}H_{10}O_2 \xrightarrow{\text{KOH fusion}} \text{phenol} + \text{benzoic acid}
\]

(iv) When flavone (I) is boiled with alcoholic potash; it yields a mixture of four compounds, salicylic acid (II) acetophenone (III), O-hydroxy acetophenone (IV) and benzoic acid (V).

The formation of the products, which are produced in pairs II and III, and IV and V can be explained on the basis of the fact that the opening of the pyrone ring of flavone I produces O-hydroxy-dibenzoylmethane (IA) which then undergoes scission in two different ways to yield two pairs of products.

The intermediate O-hydroxy dibenzoyl methane can be isolated either by heating flavone with a methanolic solution of barium hydroxide or by the action of sodium peroxide on flavone in pyridine.

**Synthesis**

Finally the structure (I) for flavone has been confirmed by its various syntheses.

**7.5.1 Kostanecki’s synthesis**

Methyl-O-methoxy benzoate is condensed with acetophenone in the presence of sodium, followed by treatment with HI.
This synthesis is an example of the claisen’s condensation. It is a reversal of the formation of II and III.

### 7.5.2 Robinson’s synthesis

In this o-hydroxy acetophenone when heated at 180° with benzoic anhydride and sodium benzoate yields flavone. This is a reversal of the formation of IV and V.
7.5.3 Modified Claisen’s’ condensation

This method involves the condensation of 2-methoxy acetophenone with ethyl benzoate in the presence of sodium, followed by treatment with HI. This is also a reversal of the formation of IV and V.

7.5.4 Baker-Venkatraman synthesis

This synthesis involves the Baker-Venkatraman rearrangement in which the isomerisation of o-benzoyl oxyacetophenone to an o-hydroxy-β-diketone by a base takes place.

7.5.5 Wheeler’s synthesis

This synthesis involves the sing expansion of 2-benzylidene coumaran – 3- ones.
Most of the flavones are yellow solids which are soluble in water, ethanol and dilute acids and alkalis. The oxonium salts are more highly coloured than the tree bases and they do not occur naturally as salts. The structure of flavone salts is not certain, they are probably represented as the resonance hybrid (VII)
The anthocyanins are the water soluble pigments which are largely responsible for the attractive colours of flowers, leaves, fruits, fruit juice and wines. These generally occur in the aqueous cell sap. Chemically anthocyanins are glycosides and their aglycons, i.e., the sugar free pigments are known as the anthocyanidins. Furthermore, the various anthocyanins were shown to possess the same carbon skeleton and differed only in the nature of substituent groups. The anthocyanin pigments are amphoteric, their acid salts are usually red, their metallic salts are blue and in neutral solution the anthocyanins are violet. In addition to anthocyanin, the colour of the flowers depends on the presence of Co-pigments such as flavones, flavonols, etc., to metal chelation particularly with Fe and Al.

In all the anthocyanin and anthocyanidine, the fundamental nucleus is benzo pyrylium chloride where as the parent compound is 2-phenyl benzo pyrylium chloride or flavylium chloride.

\[
\begin{align*}
\text{Benzopyrylium cation} & \\
\text{Flavylium chloride} & \\
\text{The flavylium cation can be represented by the following resonating structures.} \\
\end{align*}
\]

All the anthocyanins and anthocyanidine have been considered to be derivatives if 3, 5, 7- trihydroxy flavylium chloride. However, they differ in the number, nature and position of other hydroxyl group, methoxy groups and sugar residue. Various sugars moiety are found in anthocyanin.
The most common are glucose, galactose and rhamnose. Some pigments are glycosides and also acylated derivatives. In general the most common acids are derivatives of cinnamic acid.

\[
\text{R} \quad \text{HO-} - \text{CH=CH-COOH}
\]

Where \( R = H; P = \text{Coumaric acid}, R = \text{OH}; \text{Caffeic acid and R = OCH}_3; \text{Ferulic acid.} \) Pelargonidin, cyandin, Delphinine, Peonidin are the common anthocyanidine exists in nature as chlorides.

**Structure of anthocyanins:**

The various steps involved in the determination of structure of anthocyanins are.

**Hydrolysis:**

Hydrolysis of anthocyanin with dilute hydrochloride acid yield anthocyanidine (aglycon) and a sugar residue. Then the anthocyanidine is isolated as the chloride.

\[
\begin{align*}
\text{Dil.HCl} \\
\text{Anthocyanin} & \rightarrow \text{Anthocyanidine + Sugar} \\
\text{Hydrolysis} \\
\text{HCl} & \\
\text{C}_{27}\text{H}_{31}\text{O}_{16}\text{Cl} + 2\text{H}_2\text{O} & \rightarrow \text{C}_{15}\text{H}_{11}\text{O}_{6}\text{Cl} + 2\text{C}_{6}\text{H}_{12}\text{O} \\
\text{Cyanidin chloride} & + \text{Glucose}
\end{align*}
\]

**Structure of Sugar**

The sugar moiety is separated, identified and then estimated by employing the usual methods of sugar chemistry. If it is necessary, the structure of sugar moieties also ascertained. The sugars found in anthocyanins are glucose, galactose and rhamnose.

**Structure of anthocyanidin**

a) From analytical data and molecular weight determination the molecular composition of anthocyanidin is determined.

b) The number of hydroxyl groups in anthocyanidin is determined by employing acetylation and zerewitinoff’s method.

c) The number of methoxy groups is determined by Zeisel’s method.

d) In order to know its exact structure, anthocyanidin is fused with hot potassium hydroxide to yield products whose structures are
identified by the traditional methods. In most of the anthocyanidins, the products obtained are phloroglucinol.

Ex: Cyanidin chloride when fused with conc. KOH yields phloroglucinol and protocatechuic acid.

\[
\text{Cyanidin Chloride} \xrightarrow{\text{Conc. KOH}} \text{Phloroglucinol} + \text{Protocatechuic acid}
\]

This method is used for the degradation of cyanidin, pelargonidin and delphinidin chlorides. This method cannot be used for the degradation of anthocyanidins which contain methoxy groups (e.g., Peonidin, malvidin, and hirsutidin chlorides).

The reason is that when they are fused with conc. KOH it degrades the anthocyanidins and also demethylates them at the same time. Thus the methoxy group present in the original anthocyanidins is rendered uncertain.

To overcome this difficulty Karrer et al devised a better method in which anthocyanidin is degraded with a 10% solution of barium hydroxide or sodium hydroxide in an atmosphere of hydrogen. In this method the methoxy groups remain unaffected.

Ex: Maldivian chloride.

\[
\text{Malvidin Chloride} \xrightarrow{\text{10\% Ba(OH)\text{\textsubscript{2}}}} \text{Phloroglucinol} + \text{Syringic acid}
\]

**Position of sugar Residue in Anthocyanins:**

The exact position of anthocyanin is ascertained by the following methods; In this method the anthocyanin is methylated by dimethyl sulphate and sodium hydroxide. Then the methylated product is hydrolysed with 10% HCl to remove the sugar residue, thus giving the formation if anthocyanidin. Then it is hydrolysed with barium hydroxide solution in an atmosphere of hydrogen, the positions of the free hydroxyl group indicates the points of attachment of the sugar residue.
Where G – represents sugar residue.

In some cases, this method is not very reliable and the interpretation of the results is uncertain. The problem is which of the two hydroxyl groups in monomethyl phloroglucinol was originally attached to the sugar moiety G. The above results do not lead to a definite answer, since had the structure of the anthocyanin been (IV) instead of (I) and (III) would still have been formed.

**Karrer’s second method**

In this method anthocyanin is degraded by 15% hydrogen peroxide in acetic acid, which opens the heterocyclic by breaking the bond between carbon atom 2 and 3 without causing the removal of either the sugar residue or the methoxy groups, thus,

If the anthocyanin (V) has the glucose residue in the 3-position, then this glucose residue in (VI) is readily hydrolysed by dilute ammonia. If the glucose residue is present in V is in either the 5th or 7th position, then this glucose residue in VI is remove only by heating with dilute hydrochloric acid. Thus position 3 can be distinguished from position 5th or 7th. However 5th and 7th cannot be distinguished from each other.
Robinson’s Method

This method is applicable to anthocyanins which have a free hydroxyl group in the 3-position. Such anthocyanins are rapidly decolorized by ferric chloride due to the oxidation of anthocyanins.

Enzymatic hydrolysis

The next part is to know whether the sugar linkage to anthocyanin is α or β. This has been ascertained by carrying out the hydrolysis of anthocyanin with the enzymes maltase (α-linkage) and emulsion (β-linkage). Final conclusion about the positions and nature of the linkages of the sugar residue has been arrived at by the synthesis of anthocyanin. In general it has been found that glucose residues are linked at positions 3 or 3, 5 and the linkage is usually β in nature. The various methods for the synthesis of anthocyanidins are as follows:

In this synthesis, the starting material is coumarin or its derivatives.

Robinson’s synthesis:

Robinson has introduced a number of methods where by all anthocyanidins can be prepared. The basic reaction of these methods is the condensation between –o- hydroxy benzaldehyde and acetophenone in ethyl acetate solution which is then saturated with hydrogen chloride.
This method was used to prepare the anthocyanidins in which the substituents were either all hydroxyl group or all methoxy groups.

This method is used to prepare anthocyanidins having both hydroxyl and methoxy substituent groups. For example, peonidin chloride (I) is prepared by the following method.
9. What is anthocyanins?

10. Write Robinson’s synthesis?

---

**Check your progress**

---

**7.7 ANSWER TO CHECK YOUR PROGRESS QUESTION**

1. This is the most important method of preparing indole and it is carried out by heating the phenylhydrazone or substituted phenylhydrazone of an appropriate aldehyde, ketone or ketonic acid with zinc chloride, polyphosphoric acid, and sulphuric acid in ethanol.
2. Heterocyclic compounds are cyclic compounds with the ring containing carbon and other elements, the commonest being oxygen, nitrogen and sulphur. There are a number if heterocyclic ring which are easily opened and do not possess any aromatic properties, e.g., ethylene oxide, γ and δ - lactones, etc

3. This is the simple and good method and it is carried out with o-nitrotoluene (or its substituted derivatives) and ethyl oxalate in the presence of sodium ethoxide.

4. Oxazole is the parent compound for a vast class of heterocyclic aromatic organic compounds. These are azoles with oxygen and nitrogen separated by one carbon. Oxazoles are aromatic compounds but less so than the thiazoles. Oxazole is a weak base; its conjugate acid has a pKₐ of 0.8, compared to 7 for imidazole.

5.  
   (i) Boiling point of oxazole is 69°C.  
   (ii) Oxazoles are stable towards alkalis.  
   (iii) Oxazoles are basic and possess aromatic properties, and the stability of the ring towards concentrated acids depends on the nature of the substituents in the ring.

6. Oxazoles may be prepared by the action of acid on an α - acylamino ketone.
7. In this o-hydroxy acetophenone when heated at 180° with benzoic anhydride and sodium benzoate yields flavone. This is a reversal of the formation of IV and V.

8. This synthesis involves the Baker-venkatraman rearrangement in which the isomerisation of o-benzoyl oxyacetophenone to an o-hydroxy-β-diketone by a base takes place.

9. The anthocyanins are the water soluble pigments which are largely responsible for the attractive colours of flowers, leaves, fruits, fruit juice and wines. These generally occur in the aqueous cell. Chemically anthocyanins are glycosides and their aglycons, i.e., the sugar free pigments are known as the anthocyanidins.

10. Enzymatic hydrolysis
The next part is to know whether the sugar linkage to anthocyanin is \( \alpha \) or \( \beta \). This has been ascertained by carrying out the hydrolysis of anthocyanin with the enzymes maltase (\( \alpha \)-linkage) and emulsion (\( \beta \)-linkage).

This method has very limited application.

### 7.8 SUMMARY

After compiling the above material a number of conclusions can be drawn regarding the abundance of certain heterocyclic and the frequency and nature of typical chemical transformations applied in current drug syntheses. Amongst the aromatic heterocycles encountered in drug molecules in this review pyridines and pyrimidines are most common and are followed by purines. It is likely this results from the abundance of these heterocycles in natural products such as alkaloids and important cofactors/vitamins (pyridines) and nucleotides (pyrimidines and purines).

Furthermore, this might suggest a classical approach to drug design where substrate analogues gain inspiration from existing natural ligands. The use of robust scaffold hopping methods and more advanced design parameters have inspired novel heterocyclic approaches with distinct physicochemical advantages.

Interestingly, many of these newer scaffolds were originally thought to be synthetically intractable and hence were overlooked for many years. Nevertheless, the drive for novel patent positions has resulted in the discovery of several new heterocyclic syntheses.

### 4.9 KEY WORDS

- Heterocyclic Compound,
- Indole,
- Oxazole,
- Anthocyanins,
- Flavones.

### 7.10 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Write a note on Madelung synthesis?

2. How to react with indole in \( Br_2 \)?
3. Electrolytic reduction Sn/HCl

4. How to prepared Oxazole from acid amide?

5.

6. Write done the Kostanecki’s synthesis.

7.

7.11 FURTHER READINGS

UNIT- 8 CARBOHYDRATES

Structure

8.1 Introduction
8.2. Objective
8.3 Definition
   8.3.1 Monosaccharide
   8.3.2 Oligosaccharides
   8.3.3 Polysaccharides
8.4 Configuration and conformation of disaccharides
   8.4.1 Maltose
   8.4.2 Cellobiose
8.5 Configuration and conformation of Polysaccharides
   8.5.1 Starch
   8.5.2 Cellulose
8.6 Answer to check your progress question
8.7 Summary
8.8 Key words
8.9 Self-assessment question and exercises
8.10 Further readings

8.1 INTRODUCTION

Carbohydrates represent a broad group of substances which include the sugars, starches, gums and cellulosics. The common attributes of carbohydrates are that they contain only the elements carbon, hydrogen and oxygen, and that their combustion will yield carbon dioxide plus one or more molecules of Water.

The simplest carbohydrates are the three-carbon sugars which figure importantly in intermediary metabolism and the most complex are the naturally occurring polysaccharides, primarily of plant, origin. In the diet of animals and fish, two classes of polysaccharides are significant:
Carbohydrates

(a) Structural polysaccharides which are digestible by herbivorous species - cellulose, lignin, dextran’s, mannans, inulin, pentosans, pectic acids, alginic acids, agar and chitin; and

(b) Universally digestible polysaccharides - principally starch. Carbohydrates make up three-fourths of the biomass of plants but are present only in small quantities in the animal body as glycogen, sugars and their derivatives. Glycogen is often referred to as animal starch because it is not present in plants. Derived mono-saccharides such as the sugar acids, amino sugars and the deoxysugars are constituents of all living organisms.

8.2 OBJECTIVES

After Interacting with this learning object, learner will be able to

- Describe Monosaccharides.
- Describe Disaccharides and Polysaccharides
- Draw the complete structure of D-glucose, both its straight chain and it’s a and b cyclic forms. Describe the structural features which determine its form and its classifications as a D sugar, an aldohexose, and a reducing sugar. Know the numbering system for the carbon atoms.
- Draw the complete structure of D-fructose, both its straight chain and it’s a and b cyclic forms. Describe the structural features which determine its form and its classifications as a D sugar, a ketohexose, and a reducing sugar
- Draw the complete structure of sucrose. Be able to describe the structural features that make it a disaccharide and a non-reducing sugar. Identify the a-glucosidic and the b-fructosidic bonds. Know the kinds of reactions involved in the formation of a disaccharide from monosaccharides and vice versa.

8.3 DEFINITION

There are polyhydroxy compounds that has an –CHO or a –CO function present either free or as hemiacetal or aceta.

Classification:

There are classified into three types.

1. Mono saccharide
2. Oligo saccharide
3. Poly saccharide

8.3.1 Mono saccharide

These are single unit and can’t be broken by hydrolysis. Example: Glucose & Fructose.
8.3.2 Oligo saccharide

They contain more than two to 10 units of monosaccharide. If two monosaccharide units are present, they are called disaccharide and these containing 3 units are called trisaccharide, etc.

Example 1: Hydrolysis of sucrose can be explained as follows.

\[
\text{C}_{12}\text{H}_{22}\text{O}_{11} + \text{H}_2\text{O} \xrightarrow{\text{H}^+} \text{C}_6\text{H}_{12}\text{O}_6 + \text{C}_6\text{H}_{12}\text{O}_6
\]

Disaccharide (sucrose)    Glucose    Fructose

Example 2: Raffinose forms trisaccharide (C_{18}H_{32}O_{16}).

8.3.3 Polysaccharides

They contain more than 10 monosaccharides units in the molecule. One molecule upon hydrolysis gives a very large number of monosaccharides.

Example:

\[
(\text{C}_9\text{H}_{10}\text{O}_5) + \text{H}_2\text{O} \xrightarrow{\text{H}^+} n(\text{C}_9\text{H}_{10}\text{O}_5)
\]

(OR)

Non-sugars like starch, dextrin and cellulose, one molecule of which on hydrolysis yields a large number of monosaccharides molecules are polysaccharide. These are further classified into two types.

Homo polysaccharides which on hydrolysis yield only one kind of sugar.

(i) Hetro polysaccharides which on hydrolysis yield more than one kind of sugar.

Check your progress

1. Define Carbohydrates?
2. What is the classification of carbohydrates?
3. Define Polysaccharides?

8.4 CONFIGURATION AND CONFORMATION OF DISACCHARIDES

D & L Designation
Let us consider glyceraldehydes, it has asymmetric carbon atom. So if exists in two enantiomers (Mirror images).

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\text{H} - \text{C} - \text{OH} & \quad \text{O} - \text{H} - \text{C} - \text{H} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

D-configuration L-configuration

Enantiomers which rotate plane polarized light to the right written as (+) glyceraldehyde. Other that rotates plane polarized light to the left is (-) glyceraldehyde.

Rasonaff found that the enantiomers units –OH on the R.H.S can be designated as D configured molecules while the groups with –OH on the L.H.S can be designated as L configured molecules. Thus, sugars are designated as D\&L firmly, taking the configuration of glyceraldhyde as stand sugars.

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

**Definitions for D-sugars**

The sugars having the same configurations as of D-glyceraldehyde at the asymmetric carbon atom most distant from the carbonyl are designated as D-sugars.

**Representation of D-sugars**

Generally sugars are represented by two ways,

1. Fischer projection
2. Haworth representation

**1. Fischer projection**

Glucose forms hemiacetal by reaction of –CHO group. From C–1 with H of C–5 atom
2. Haworth synthesis
The groups which are present on the L.H.S of the Fischer’s formulae, above the plane of the ring. While, those on the R.H.S below the plane of the ring with terminal –CH₂OH group at the top of the C–5.

8.4.1 Maltose (Malt Sugar C₁₂H₂₂O₁₁)
It is composed of two α-D-glucose joined by an α –glycosidic linkage between C–1 of one unit & C–4 of other unit.

Constitution of Maltose or Structure of Maltose

- Molecular formula is C₁₂H₂₂O₁₁.
- On acid hydrolysis, it forms only D–glucose indicating the presence of glucose monosaccharide units.
• It forms oxime, phenyl hydrazone, semicarbazide on reaction with hydroxyl amine, phenyl hydrazine & semicarbazide respectively.
• It also reduces fehling’s solution & Tollen’s reagent indicating the presence of –CHO groups.
• Maltose is hydrolyzed by enzyme maltase and not by emulsion, indicating that the linkage between two glucose units in maltose is α–linkage.

![Diagram of Carbohydrates]

• The ring size of monosaccharide units is confirmed by the following reactions.
• It reacts with bromine water to give maltobionic acid III.
• Maltobionic acid on methylation gives methyl ether of octamethylmaltobionic acid (IV). This on vigorous hydrolysis gives 2, 3, 4, 6-tetra-O-methyl-DGlucopyranose (VI) & 2, 3, 5, 6-tetra-O-methylgluconic acid (V). The presence of free –OH groups in these products at positions C-1 & C-4 respectively indicates C-1, C-4 glucosidic linkage between two glucose units. V can be obtained only if maltose has structure I; structure II would have given 2, 3, 4, 6-tetra-O-methyl-O-glucopyranose. Thus, maltose is I & not II.

This specific rotation of maltose also proves the structure I. This confirms (scheme 6) the presence of α-glycosidic linkage.
Scheme 6: Conformation for Maltose

Since maltose is a reducing sugar its C₁ is free. It forms an osazone, therefore its C₂ is also free, i.e. not combined with an alkoxy group. The ring size of maltose is further confirmed by Zemplen & Wohl’s method (Degradation reaction). The structure of maltose is further confirmed by its synthesis (scheme 7).
Scheme 7: Conformation of Maltose by synthesis

8.4.2 Celllobiose

It is composed of α-D-glucose and β-D-glucose units joined by β-D-glycosidic linkage between C-4 of α-D-glucose unit and C-1 of β-D-glucose unit.
Constitution of Cellobiose (same as Maltose)

1) Molecular formulae is C_{12}H_{22}O_{11}
2) It reacts with hydroxyl amine, phenyl hydrazine, and semicarbazide to form an axime, phenyl hydrazone & semicarbazide respectively. It also reduces to Fehling’s solution. Indicating the presence of CHO group.
3) On acid hydrolysis, it gives D-glucose units indicating the presence of glucose monosaccharide units.
4) Hydrolysed by the enzyme and not by emulsion indicating that there is α-linkage between two glucose units.
5) It reacts with Br_2 / H_2O to form cellobionic acid.
6) It reacts with Me_2SO_4 to form 2, 3, 4, 6-tetraO-methyl-D-glucopyronose and 2, 3, 5, 6-tetra-methyl gluconic acid, the presence of free hydroxyl group at C_1 & C_4 indicates the linkage is between C_1 & C_4 of the two monosaccharide units.

Synthesis of cellobiose

It is obtained by treating with 2, 3, 4, 6-tetra-O-actyl-α-D-glucopyranosyl bromide with 1, 2, 3, 6-tetra-O-acetyl-β-glucopyranose to form cellobiose acetate which on hydrolysis gives cellobiose (scheme 8).
Check your progress

4. Define Disaccharaides.
5. Write a short note on d & l designation.
6. Draw the Strutures of Maltose and cellobiose.
7. Write the synthesis of cellobiose.

8.5 CONFIGURATION AND CONFORMATION OF POLYSACCHARIDES

8.5.1. Starch

Starch consists of two structurally different polysaccharidea viz. a microcrystalline structure called α -amylase, and an amorphous material called β -amyllosse. The B-fraction or more commonly as amylopectin (B). Most of the starches of consist of nearly 20% amylase (A) and 80% amylopectin (B).
Constitution of Amylose:

1. Its empirical formula is \((\text{C}_6\text{H}_{10}\text{O}_5)\) \(_n\).
2. On complete acidic hydrolysis amylose gives D-glucose in quantitative yield. This indicates that amylose is composed of only D-glucose units.
3. Diastase enzymatic hydrolysis of amylose gives maltose. Now since maltose is 4-O-(\(\alpha\)-D-glucopyranosyl)-D-glucopyranose, all the glucose units in starch are linked through \(\text{C}_1\alpha\) and \(\text{C}_4\). Hence amylose possesses the following structure (scheme) which explains the hydrolysis products.

![Scheme 9: Conformation of starch amylase](image)

As that amylose has a chain length of 300-350 glucose units as no dimethylglucose is obtained, the chain must be linear and not branched. The chain length (300-350) of glucose units is confirmed by its molecular weight determined by physical methods. While the linear nature of amylose molecule is indicated by the fact amylose acetate forms film and fibres like cellulose.

4. X-ray analysis of the amylose-iodine complex has revealed that the amylase molecule is in the form of a helix (but not in straight chain).

Constitution of Amylopectin

1. Its empirical formula is \((\text{C}_6\text{H}_{10}\text{O}_5)\) \(_n\).
2. On complete acidic hydrolysis, amylpectin yields D-glucose quantitatively again indicating that amylpectin is also composed of only D-glucose units.
3. Diastase (\(\beta\)-amylase) hydrolysis amylpectin to give 55% yield of maltose and a high molecular weight compound called limit dextrin. This indicates that amylpectin has some other linkages (which are not attacked by \(\beta\)-amylase) in addition to 1, 4-linkages (which are attacked by \(\delta\)-amylase).
4. Fully methylated amylopectin on hydrolysis gives: (a) 90% of 2, 3, 6-tri-O-methyl glucose, (b) 4% of 2, 3-di-O-methyl glucose. The reaction leads to the following important conclusions.

(i) The yield (4%) of tetra-O-methyl glucose indicates that the average chain length of branches is about 25 glucose units.

(ii) The formation of 2, 3-dimethyl glucose suggests that amylopectin is a branched polymer. Osmotic pressure measurements of amylopectin give a molecular weight of about 500,000 than corresponds to nearly 3000 glucose units. Amylopectin has nearly 120 branches.

5. Partial enzymatic hydrolysis of amylopectin also gives a small amount of isomaltose indicating that in branching C₁ of one glucose unit and C₆ of the other glucose unit are involved, i.e., branching involves 1, 6-linkages.

6. On the basis of the above points, structure of amylopectin may be represented as follows (scheme 10).

The presence of 1, 6-linkages is further confirmed by periodate oxidation method.

6. On the basis of the above points, structure of amylopectin may be represented as follows (scheme 10).

Scheme 10: Conformation of Starch amylopectine

7. The detailed structure of amylopectin regarding the points of origin of the branches is still not settled.
8.5.2 Cellulose

Constitution of cellulose

1. Molecular formula is \((C_6H_{10}O_5)_n\).

2. Acid hydrolysis of cellulose gives 96% D-glucose. This indicates that cellulose is made up of D-glucose unit.

3. From nitration & acetylation studies it is found that there are 3 free hydroxyl groups in each glucose unit.

4. Complete methylation of cellulose followed by acid hydrolysis gives 96% yield of 2:3:6-tri-O-methyl-D-glucose (all the remaining glucose units) 0.6% of 2:3:4:6-tetra-O-methyl-D-glucose without any dimethyl glucose. These facts suggest that it is a straight linear open chain polymer of glucose units.

5. The above hydrolysis products led to the following conclusions.

   i. The formation of 2, 3, 6-trimethyl glucose indicates that in cellulose free OH groups are present on C₂, C₃ and C₆. Hence in cellulose the two glucose units may be linked through C₁ and C₄ (if glucose units are present as pyranose) or through C₁ and C₅ (if glucose units are present as furanose). But since the cellulose is not easily hydrolysed, the glucose units must be in the form of pyranose rings. I.e. the two glucose units are linked through C₁ and C₄.

   ii. The yield (0.6%) of about 2, 3, 4, 6-tetra methyl glucose indicates that cellulose has a chain length of 100 to 200 glucose units.

   iii. The failure to isolate any dimethyl-D-glucose indicates that cellulose is a linear polymer.

6. Acetolysis (simulatenous acetylation and hydrolysis) of cellulose with a mixture of acetic anhydride and sulphuric acid gives cellobiose octaacetate. This suggests that cellulose that is composed of cellobiose units.

7. Gentle acidic hydrolysis of cellulose, gives in addition to cellobiose cello-triose, tetrose, -pentose, -hexose and -heptose and in all of these the C₁-C₄ links have been found to be β.

8. Since cellulose forms colloidal solution in the solvents in which glucose is soluble, the cellulose is a very large molecule. Also since cellulose forms fibers (example rayon) it is a linear molecule which has been confirmed by X-ray analysis.

9. Thus, on the basis of above point’s cellulose may be assigned the following structure (scheme 11).
Scheme 11: Conformation of Cellulose

10. The cellulose molecule is not planar, but has a screw-axis, each glucose unit being at right angle to the previous one. The absence of free rotation the C-O-C link due to steric effect and the close packing of atom give rise to a rigid chain molecule.

11. The chain length or molecular size is achieved by determining the molecular weight of the cellulose which has been found to be 100 to 200 glucose units.

The method consists in complete methylation, followed by hydrolysis with dilute acid to cleave all the glycosidic linkages. Thus the non-reducing end will give 2, 3, 4, 6-tetra-O-methyl-D-glucose, while the all other units will be hydrolysed to 2, 3, 6-tri-O-methyl-D-glucose is given below:
The two methylated sugars obtained by hydrolysis were separated by vacuum distillation. Hence, by knowing the percentage (or ratio of tetramethyl / trimethyl derivative) of the tetramethyl derivative, the length of the chain is estimated. The results obtained by this method indicate the presence of a chain having 100 to 200 D-glucose.

Check your progress
8. Write the structure of cellulose?
9. Write a short note on starch?

8.6 ANSWER TO CHECK YOUR PROGRESS QUESTION

1. There are polyhydroxy compounds that has an –CHO or a –CO function present either free or as hemiacetal or aceta.

2. There are classified into three types.
   1. Mono saccharide
   2. Oligo saccharide
   3. Poly saccharide

3. They contain more than 10 monosaccharides units in the molecule. One molecule upon hydrolysis gives a very large number of monosaccharides.

Example:

\[ \left( C_6H_{12}O_6 \right) + H_2O \xrightarrow{H^+} n(C_6H_{10}O_5) \]

4. A disaccharide (also called a double sugar or bivose) is the sugar formed when two monosaccharides (simple sugars) are joined by glycosidic linkage. Like monosaccharides, disaccharides are soluble in water. Three common examples are sucrose, lactose, and maltose.
5. Let us consider glyceraldehydes, it has asymmetric carbon atom. So if exists in two enantiomers (Mirror images).

\[ \text{CHO} \quad \text{CHO} \]
\[ \text{H} - \text{C} - \text{OH} \quad \text{O} - \text{H} - \text{C} - \text{H} \]
\[ \text{CH}_2\text{OH} \quad \text{CH}_2\text{OH} \]

D-configuration                       L-configuration

Enantiomers which rotate plane polarized light to the right written as (+) glyceraldehyde. Other that rotates plane polarized light to the left is (-) glyceraldehyde.

Rasonaff found that the enantiomers units –OH on the R.H.S can be designated as D configurated molecules while the groups with –OH on the L.H.S can be designated as L configurated molecules. Thus, sugars are designated as D&L firmly, taking the configuration of glyceraldehyde as stand sugars.

6.

\[ \text{HO} - \text{HO} - \text{OH} \]
\[ \text{HO} - \text{HO} - \text{OH} \]

Maltose

\[ \text{HO} - \text{HO} - \text{OH} \]
\[ \text{HO} - \text{HO} - \text{OH} \]

Cellubiose

7. Starch or amyylum is a polymeric carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. This polysaccharide is produced by most green plants as energy storage. It is the most common carbohydrate in human diets and is contained in large amounts in staple foods like potatoes, wheat, maize (corn), rice, and cassava.
Carbohydrates

NOTES

8. Cellulose

9. Starch

**8.7 SUMMARY**

Carbohydrates, a large group of biological compounds containing carbon, hydrogen, and oxygen atoms, include sugars, starch, glycogen, and cellulose. All carbohydrates contain alcohol functional groups, and either an aldehyde or a ketone group (or a functional group that can be converted to an aldehyde or ketone). The simplest carbohydrates are monosaccharides. Those with two monosaccharide units are disaccharides, and those with many monosaccharide units are polysaccharides. Most sugars are either monosaccharides or disaccharides. Cellulose, glycogen, and starch are polysaccharides A sugar is designated as being a D sugar or an L sugar according to how, in a Fischer projection of the molecule, the hydrogen atom and OH group are attached to the penultimate carbon atom, which is the carbon atom immediately before the terminal alcohol carbon atom. If the structure at this carbon atom is the same as that of D-glyceraldehyde (OH to the right), the sugar is a D sugar; if the configuration is the same as that of L-glyceraldehyde (OH to the left), the sugar is an L sugar.

**8.8 KEY WORDS**

- Carbohydrates
- Maltose Cellobiose
- Polysaccharides
- Starch
- Cellulose.
8.9 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Explain the configuration and conformation of cellobiose and cellulose.
2. Establish the structure of starch.
3. Discuss the salient feature of the structure of maltose.
4. Explain the configuration and conformation of sucrose and cellulose.
5. What are the differences between the starch and cellulose?
6. Discuss the conformation of maltose using Haworth synthesis.
7. Establish the structure of cellulose.

8.10 FURTHER READINGS

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UNIT-9 PROTEINS AND ENZYMES

9.1 INTRODUCTION

Proteins are large biomolecules, or macromolecules, consisting of one or more long chains of amino acid residues. Proteins perform a vast array of functions within organisms, including catalyzing metabolic reactions, DNA replication, responding to stimuli, providing structure to cells and organisms, and transporting molecules from one location to another. The molecules upon which enzymes may act are called substrates, and the enzyme converts the substrates into different molecules known as products. Almost all metabolic processes in the cell need enzyme catalysis in order to occur at rates fast enough to sustain life.

9.2 OBJECTIVES

After going through this unit, you will be able to
Proteins and Enzymes

NOTES

- Understand the concept of proteins & enzymes.
- Discuss the various processes for synthesis of proteins.
- Nucleic acid is one of the major sources for proteins.
- This unit fully covered on all the aspects and structures of enzymes & coenzymes.

9.3 ASPECTS OF STRUCTURE AND CLASSIFICATION OF PROTEINS

The structure of a protein is mainly referred to the number, nature and sequence of amino acids along with peptide chains. The questions about primary structure which can be asked and which must be answered to provide an understanding of protein structure are as follows

9.3.1 Primary structure

The primary structure of protein is defined as the linear sequence of amino acid residues making up its polypeptide chain. The protein may be formed of one or more polypeptide chains. The amino acids are arranged in specific sequence in polypeptide chain. The amino acid residues are linked by peptide bonds. The peptide bond is formed between the carboxyl group of one amino acid and the amino group of adjacent amino acid. Sometimes the adjacent polypeptide chains are linked by disulfide bonds.

Many structural proteins which form fibers are linear and unfolded types. Example: Silk fibroin.

The peptide bond is a repeating unit. Two amino acids give a dipartite; three amino acids give a tripartite, four amino acids give a tetrapeptide and so on. Less than 10 amino acids form oligopeptide.

More than 10 amino acids from a polypeptide. Each polypeptide chain of any length has at one end an N-terminal amino acid containing a free amino group and at the other end a C-terminal amino acid containing a free carboxyl group. The amino acids in a polypeptide chain are numbered form the N-terminal end.

Thus, the primary structure has the following salient features.

- Primary structure refers to the linear sequence of amino acid residues.
The proteins are linear and unfold
The protein is formed of one or more polypeptide chains.
The amino acid residues are linked by repeating peptide bonds
The adjacent polypeptide chains are linked by disulfide bonds
Most of the structural proteins which are in the form of fibers exhibit primary structure. Example: Fibroin of silk.

9.3.2. Secondary structure of protein

The primary structure gives only a partial picture of the protein molecule and tells nothing about its conformation. However, the secondary of protein gives the way in which the various atoms of the long polypeptide chain is arranged in space (conformation). The covalent backbone of a polypeptide chain is single-bonded and hence a protein is expected to have an infinite number of conformations due to free rotation about a single bond. However a polypeptide chain of a protein has only conformation. This is due to the fast that the C-H bond has some double bond character and cannot rotate freely. If the chain assumes a linear structure, the bulky side chains (R) would impose a sterical strain and make the molecule unstable. But the peptide chain is sufficiently stable so that the protein can be isolated and retained in its native state. Linus Pauling explained the stability of protein by proposing the helical structure. A helix may be visualized as a spring or spiral stair case. When polypeptide chain is coiled into a spiral, the bulky R groups of the α-carbon extend outward into sterically favored positions. This conformation referred to as α–helix (Fig.1).

![Figure 1: α- helix of secondary structure of protein](image)

The α–helix may be right handed or left handed. In all natural proteins, the α–helix is right handed.

The α–helix arrangement allows every peptide bond of the chain to participate in intrachain H-bonding (Fig 2). The H-bonds are formed between the –CO group of one amino acid residue and the –NH group of the fourth amino acid residue in the chain.
The α–helix structure is very common in fibrous protein (e.g. α–keratin).

![Figure 2: α- helix structure of intrachain H-bonding](image)

### 9.3.3. Tertiary structure of protein

The fibrous proteins have relatively simple structures primary and secondary structures. However, the globular proteins have three – dimensional tertiary structure. It refers to the folding of the secondary helical structure in three dimensions to form a compact spherical shape. The tertiary structure is stabilized by four major types of bonds. They are,

- Hydrogen bonds between peptide groups, as in α–helical structure and hydrogen bonds between R groups.
- Ionic bonds between –NH₃⁺ and –COO⁻ groups.
- Non-ionic hydrophobic bonds between non-polar R groups.
- Disulphide bonds between sulphur containing amino acid residues.

### Check your progress

1. How to identify the primary structure of proteins?
2. Define the α–helical structure and arrangement in secondary structure of proteins?

### 9.4 END GROUP ANALYSIS

Chemists have developed a series of reagents that react selectively with the N-terminal amino acid of a polypeptide, transforming it into some derivative that can be separated from all of the other amino acids in the chain and identified. One of the most useful of these is 2,4-dinitrofluorobenzene, Sanger’s reagent, developed by Frederick Sanger’s during his determination of the structure of insulin. Sanger was given the Nobel Prize in 1958 for being the first to establish the sequence of amino acids in a protein.
2, 4-dinitrofluorobenzene is an aryl halide with nitro groups on the aromatic ring in positions that activate the halogen toward nucleophilic substitution. The free amino group of the N-terminal amino acid displaces fluoride ion from the reagent, forming a dinitroarylamino group. Complete hydrolysis of the peptide gives free amino acids from all of the residues except the N-terminal one, which turns up labeled with the aryl group. The process is illustrated for the tripeptide Ser-Gly-Val (scheme 3), which is written in the form in which the amino group is not protonated.

![Scheme 3: Analysis of End group](image)

The presence of the dinitrophenyl group on the nitrogen of from serine converts the compound from an alkyl amine and changes its acid-base properties drastically. The derivative of serine behaves differently than serine does with all techniques used to separate amino acid and is
Proteins and Enzymes

NOTES

9.5 SOLID PHASE PEPTIDE SYNTHESIS

A recent technique for the synthesis of polypeptides was devised by R.B. Merrifield and coworkers. The peptide, according to this method is synthesized on the surface of an insoluble polymer. One of the common polymers used is polystyrene in which some of the benzene rings are chloromethylated, i.e., linked to \(-\text{CH}_2\text{Cl}\) group. The polymer is cross-linked with about 2% of divinylbenzene. This polymer may be designated as ClCH_2-polymer (Scheme 1). The C-terminal end of the amino acid is bound to the polymer by shaking a basic solution of the amino acid in ethyl acetate with the insoluble polymer. An S_N2 attack of the carboxylate ion takes place at the benzyl carbon removing the halogen and the result is a polymer bound amino acid derivative. This polymer derivative is then condensed with an N-protected amino acid using dicyclohexylcarbodiimide (DCC). The amino acid gets attached to the growing peptide and the latter is separated by filtration. The protecting group is removed by adding a strong anhydrous acid, usually trifluoroacetic acid. This process is repeated by adding another N-protected amino acid followed by condensation in the presence of DCC. After the desired polypeptide is built it is removed from the resin by adding anhydrous hydrogen fluoride. This does not affect the peptide bond. The synthetic peptide is eventually purified by a suitable chromatographic method.

\[
\text{\textit{Scheme 1: Insoluble Polymer, ClCH}_2-\text{Polymer}}
\]

The Merrifield method is very efficient and polypeptides containing a large number of amino acid can be prepared in good yields. Furthermore, since the process involves the repetition of a small number of simple and similar steps, this can be carried out by an automatically machine.

Merrifield and coworkers synthesized the Nona peptidebradykininby this automated procedure with an overall yield of 85%. They also synthesized bovine pancreatic ribonuclease containing 124 amino acids, the first protein to be synthesized artificially from its amino acid components (scheme 2):
Polymer-bound amino acid derivative

\[
\text{Polymer-bound amino acid derivative}
\]

\[
\text{t-Butoxyazidoformate} \quad \text{N-protected amino acid}
\]

Scheme 2: synthesis of solid phase peptide
3. Explain the end group analysis for the given compound 2,4-dinitrofluorobenzene?

9.6 ENZYMES

Enzymes are complex organic substances produced by living cells. They catalyse biological reactions. They are therefore, called biocatalysts. Chemically, enzymes are proteins with high molecular weight ranging from 12,000 to more than a million.

Mechanism of Enzyme:

Enzymes contain true activity centers in the form of the three-dimensional structures. The “active site” is the part of the enzyme molecule that combines with the substrate. The number of active sites per molecule is very small, generally only one. In order to catalyze a reaction, the enzyme molecule has to form a complex with the substrate. The binding sites of the enzyme recognize the corresponding domain of the molecule. This makes the enzyme specific towards the substrates and allows proper orientation of both the molecules so that the reactive sites of the enzyme molecule have access to the appropriate part of the substrate molecule. Thus, enzyme catalysis operates to form an enzyme substrate complex. An enzyme is absorbed onto a substrate surface in “lock and key fashion”. A schematic representation is given in figure 3.

![Figure 3: Lock and key mechanism for Enzyme](image-url)
Salient features of enzymes

1. Most enzymes are crystalline solids soluble in water.
2. They are colloidal in nature and do not pass through dialyzing membranes.
3. Enzymes have high molecular weights ranging from 12,000 to more than a million. For example, the enzyme pepsin has a molecular weight of 39,200.
4. The low molecular weight enzymes like amylase, urease etc. are simply proteins. However, most of the enzymes consist of two parts:
   i) Apoenzyme (protein part)
   ii) Co-enzyme (non-protein part)

   In many enzymes, the co-enzymes are tightly and permanently, bound to the protein part. In these cases, the co-enzymes are known as prosthetic groups. The apoenzyme alone can not catalyse any chemical reaction. It requires coenzyme for the action.
5. The enzyme activity depends upon temperature. At very low temperature, the rate of enzyme activity is very low. But it increases with increase of temperature. However, beyond a particular temperature, the enzyme loses its activity. That is, the enzyme is denatured. The optimum temperature for enzyme action is about 20-40°C.
6. The enzyme action is greatly influenced by pH of the medium. The optimum pH for most of the enzymes action is about 7.
7. The enzyme activity is enhanced by certain inorganic (e.g. Fe²⁺, Mn²⁺, Zn²⁺ etc) ions. These are called co-factors. For example, Fe²⁺ or Fe³⁺ is the co-factor in the enzyme cytochrome oxidase.
8. Enzymes work even when they are present in traces. The number of moles of a substance converted by one mole of an enzyme is called turnover number. The turnover number of enzymes is in the order 100-3,00,00.
9. The concentration of the substrate has significant effect on the enzymes activity. High substrate concentration renders the enzyme inactive. This is due to the saturation of active sites of the enzymes by substrate molecules.
10. Enzymes are highly specific in their action. Thus, an enzyme which acts on a particular substrate will not act on any other substrate. For example, urease hydrolysis urea only, phosphates hydrolyse only phosphate esters, maltose hydrolyses only maltose.
Applications of Enzymes:

Enzymes play a vital role in chemical and biochemical processes.

1. Role of Enzymes in Chemical reactions:

   i. Alcohol beverages are produced by the fermentation of sugar using the enzymes invertase and zymase derived from yeast cells.

   ii. Citric acid is obtained from sugar by the action of enzymes derived from certain molds. E.g. citromycesprefferianus.

   iii. Lactic acid is manufactured by the fermentation of sugar with sour milk which contains the enzyme bacillus acidilacti.

   iv. Vinegar is prepared from alcohol by the enzymatic action of micodermaaceti.

   v. Enzymes are widely used in tanning of leather, curing of tobacco, banking of bread and ripening of cheese.

2. Role of Enzymes in Biochemical reactions:

   The biochemical reactions like digestion, metabolism etc are regulated by enzymes.

   i. Digestion is a process of breaking of food materials with the help of enzymes. The enzyme amylase breaks down starch into maltose, pepsin and trypsin decompose proteins into amino acids and lipase hydrolyses fats.

   ii. The digested food undergoes chemical changes to liberate energy which is utilized by the body. This process is known as energy metabolism or catabolism. For example, glucose is oxidized to pyruvic acid which then decomposes with the liberation of energy. The biochemical change is brought about by the enzymes oxidases.

   iii. The enzyme activity in body fluids like plasma and serum throws light on the pathological conditions.

   iv. Most of the vitamins act as co-enzymes in life processes. Their presence prevents deficiency diseases in living organisms.

   v. The enzyme lysozyme, present in tears, is capable of destroying the cell walls of certain bacteria which cause eye infection.

   vi. The enzyme thrombin is used to prevent colt formation in blood vessels (veins).

   vii. Trypsin is an enzyme which promotes healing of wounds by dissolving blood clots.
9.7 COENZYMES

A coenzyme may be defined as a non-protein organic substance loosely attached to the enzyme and can be separated by dialysis and is essential for enzyme action.

Example: NAD, NADP, ATP, UDP, CoA, TPP, FAD, FMN, Ubiquinone (CoQ), etc.,

Chemically enzymes are proteins. Some enzymes are simple proteins and others are conjugated proteins. The conjugated protein enzymes are made up of two components, namely a protein part called apoenzyme and a non-protein part. The two components together form a holoenzyme.

\[ \text{Holoenzyme} \leftrightarrow \text{Apoenzyme} + \text{Non-protein} \]

The non-protein part of enzyme may be firmly bound to the enzyme and cannot be separated by dialysis. This tightly bound non-protein part of the enzyme is called prosthetic group.

\[ \text{Holoenzyme} \leftrightarrow \text{Apoenzyme} + \text{Prosthetic group} \]

In some enzymes, the non-protein part is loosely attached to the enzyme and it can be reversibly removed from the enzyme by dialysis. This loosely bound non-protein part of the enzyme is called coenzyme.

\[ \text{Holoenzyme} \leftrightarrow \text{Apoenzyme} + \text{Coenzyme} \]

The coenzyme is also called co-substrate or co-factor. It is an organic substance. It is a small molecule with low molecular weight. Hence it can be separated by dialysis. Coenzymes are heat stable. Most of them are derivatives of Vitamin B complex. They are necessary for enzyme action and they accelerate the reaction rate.

**Mechanism of Coenzyme Action**

The coenzyme helps the enzyme to combine with the substrate and at the end the substrate is cleaved. One of the cleavage products is transferred to the coenzyme. Finally the coenzyme is released from the product and is ready for further enzyme action (Fig 4).
Classification of Coenzymes

Coenzymes are classified into three groups on the basis of their functions. They are,
1. Hydrogen transferring coenzymes
2. Group transferring coenzymes
3. Isomerase coenzymes.

Hydrogen Transferring Coenzymes

Certain coenzymes transfer hydrogen atoms or electrons from one substrate to another. These coenzymes are called hydrogen transferring coenzymes.
Examples: NAD, NADP, FMN, FAD, Ubiquinone (Q), etc.

1. Group Transferring Coenzymes

These coenzymes are involved in group transfer.
Examples: CDP, UDP, CoA, TPP, etc.

2. Isomerase’s Coenzymes

These coenzymes are responsible for the interconversion of isomers.
Examples: UDP, TPP, etc.

Some common coenzymes
1. Nicotinamide Adenine Dinucleotide (NAD)
2. Flavin Adenine Dinucleotide (FAD)
3. Coenzyme A (CoA)
4. Adenosine Triphosphate (ATP)
5. Thiamine Pyrophosphate (TPP)

Salient features of Coenzymes

1. Coenzymes are non-protein organic substances loosely attached to enzymes and are easily separable by dialysis and are inevitable for enzyme action.
2. Coenzymes are also called co-substrates
3. They are small molecules with low molecular weight. They can be reversibly separated from enzymes by dialysis.
4. They are heat-stable.
5. They are closely related to vitamins and are derivatives of Vitamin B complex
6. They function as catalysts and are essential for enzyme action. They accelerate the rate of reaction.
7. An essential component of most of coenzymes is phosphate in the form of nucleotides
8. Coenzymes are usually not firmly attached to the enzyme protein. But they exist in the Free State in the solution. They contact the enzyme protein only at the time of enzyme action.
9. The Coenzyme is repeatedly used to split many molecules of substrates. Both apoenzyme and coenzyme are regenerated at their original forms at the end of the reaction.
10. The coenzymes act as intermediate carriers of hydrogen atoms in the biological oxidation reduction reactions.

Check your progress

4. What is an enzyme?
5. Explain the classification of co-enzyme?

9.8 ANSWER KEY TO CHECK YOUR PROGRESS

1. Protein primary structure is the linear sequence of amino acids in a peptide or protein. By convention, the primary structure of a protein is reported starting from the amino-terminal (N) end to the carboxyl-terminal (C) end. Protein biosynthesis is most commonly performed by ribosomes in cells.

2. The α–helix arrangement allows every peptide bond of the chain to participate in intrachain H-bonding. The H-bonds are formed between the –CO group of one amino acid residue and the –NH group of the fourth amino acid residue in the chain. The α–helix structure is very common in fibrous protein (e.g. α–keratin).

3. The presence of the dinitrophenyl group on the nitrogen of from serine converts the compound from an alkyl amine and changes its acid-base properties drastically. The derivative of serine behaves differently than serine does with all techniques used to separate amino acid and is easily identified by comparing it to an authentic sample of N–2, 4 dinitrophenylserine.
4. Enzyme are macromolecular biological catalysts that accelerate chemical reactions. The molecules upon which enzymes may act are alled substrates, and the enzyme converts the substrates into different molecules known as products. Almost all metabolic processes.

5. i) Hydrogen transferring coenzymes
   ii) Group transferring coenzymes
   iii) Isomerase coenzymes

9.9 SUMMARY

This chapter briefly describes about the structure and properties of proteins and enzymes. Proteins are a group or the combine structure of amino acids which in turn helps us in day to day life as muscle builder. The structure of a protein is mainly referred to the number, nature and sequence of amino acids along with peptide chains. Primary structure refers to the linear sequence of amino acid residues. Enzymes are complex organic substances produced by living cells. They catalyse biological reactions. They are therefore, called biocatalysts. A coenzyme may be defined as a non-protein organic substance loosely attached to the enzyme and can be separated by dialysis and is essential for enzyme action.

9.10 KEYWORDS

- Proteins
- Amino acids
- Enzymes
- Co-enzymes.
- Peptide

9.11 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Explain the secondary structure and tertiary structures of proteins

2. Explain the importance of end group analysis of peptides.

3. Explain the mechanism of Enzyme

4. Write notes on solid phase peptide synthesis

5. What is mean by coenzyme? Give examples.

6. What is a protein?
9.12 FURTHER READINGS

UNIT-10  NUCLEIC ACIDS

Structure

10.1 Introduction
10.2 Objectives
10.3 Deoxyribonucleic acids (DNA)
10.4 Ribonucleic acid (RNA)
10.5 Difference between DNA and RNA
10.6 Answer key to check your progress
10.7 Summary
10.8 Keywords
10.9 Self-assessment question and exercises
10.10 Further readings

10.1 INTRODUCTION

In this chapter we had discussed about nucleic acid. Nucleic acids are the biopolymers, or small biomolecules, essential to all known forms of life. The term nucleic acid is the overall name for DNA and RNA. They are composed of nucleotides, which are the monomers made of three components: a 5-carbon sugar, a phosphate group and a nitrogenous base. If the sugar is a compound ribose, the polymer is RNA (ribonucleic acid); if the sugar is derived from ribose as deoxyribose, the polymer is DNA (deoxyribonucleic acid). Nucleic acids are the most important of all biomolecules. They are found in abundance in all living things, where they function to create and encode and then store information in the nucleus of every living cell of every life-form organism on Earth. In turn, they function to transmit and express that information inside and outside the cell nucleus to the interior operations of the cell and ultimately to the next generation of each living organism. The encoded information is contained and conveyed via the nucleic acid sequence, which provides the 'ladder-step' ordering of nucleotides within the molecules of RNA and DA.
10.2 OBJECTIVES

After going through this unit, you will be able to:

- Understand the concept of deoxy and ribo nucleic acids
- Discuss the various process for synthesis of proteins.
- Nucleic acid is one of the major source are DNA, RNA synthesis.
- This unit fully covered on all the aspects and structures of DNA & RNA.

10.3 DEOXYRIBONUCLEIC ACID (DNA)

Living organisms contains two types of nucleic acids. They are,

1. Deoxyribonucleic acid (DNA)
2. Ribonucleic acid (RNA)

They differ only in the nature of sugar molecule present. DNA contains deoxyribose sugar whereas RNA contains ribose sugar.

Components of nucleic acids

Nucleic acid is a long chain polymer. It is composed of a large number of monomeric units called nucleotides. Each nucleotide consists of a nucleoside and a phosphate group. A nucleoside is formed of a five carbon sugar (pentose) and nitrogenous base. There are two types of nitrogenous bases. They are the purines and pyrimidines.

Purines are bicyclic heterocyclic compounds. They have two rings in the structure. One is a five membered ring and other is a six membered ring. Examples: Adinine and guanine.

Pyrimidine are six membered heterocyclic compounds. Cytosine, thymine and uracil are the important pyrimidines.

Sugar + Nitrogenous base = Nucleoside
Nucleoside + Phosphoric acid = Nucleotide
Polynucleotide = Nucleic acid.

Structure of DNA

DNA is made up of three chemical components namely,

i. Sugar

ii. Nitrogenous base

iii. Phosphoric acid
Sugar: The sugar present in DNA is deoxyribose. It is a pentose having the structure as given below:

![Deoxyribose structure]

Nitrogenous base: In DNA, four different nitrogenous bases are present. They combine with the sugar molecule to form four types of nucleosides.

i. Deoxyadenosine (Deoxyribose + Adenine)

ii. Deoxyguanosine (Deoxyribose + Guanin)

iii. Deoxycytidine (Deoxyribose + Cytosine)

iv. Deoxythymidine (Deoxyribose + Thymine)

Phosphoric acid: The nucleosides combine with phosphoric acid to form four types of nucleotides.

i. Deoxyadenylic acid

ii. Deoxyguanylic acid

iii. Deoxycytidylic acid

iv. Deoxythymidylic acid

Watson and Crick model of DNA

1. The DNA molecule (Fig.5) has two polynucleotide chains.

2. The two chains are twisted around each other in opposite direction to form a right handed double helix.

3. The two chains are held together by hydrogen bonds between bases. A purine pairs with a pyrimidine. For example, adenine (purine) of one chain always pairs with thymine (pyrimidine) of another chain by two hydrogen bonds,

$A = \cdots \cdots T \quad \text{or} \quad T = \cdots \cdots A$

Similarly, guanine (purine) of one chain always pairs with cytosine (pyrimidine) of another chain by three hydrogen bonds.

$G = \cdots \cdots C \quad \text{or} \quad C = \cdots \cdots G$

1. The two chains are complementary to each other. If the sequence of base in one chain is A,G,A,T,G,C then the sequence of base in the second chain is T,C,T,A,C,G
S- Sugar unit  P- Phosphate group  
A- Adenine  G- Guanine  
C- Cytosine  T- Thymine

Figure 5: Structure of DNA

Biological importance of DNA

1. **Synthesis of protein**
   
   Nucleic acids synthesize the various proteins of the protoplasm.

2. **Replication**
   
   During cell division DNA divides and offers exact copies to the daughter cells.

3. **Genetic information**
   
   DNA contains genetic information. DNA transfers characters from parents to offspring.

4. **Mutation**
   
   DNA produces mutations resulting in new characters.

### 10.4 RIBONUCLEIC ACID (RNA)

Transcription and Translation are very common terms in Biology. Transcription is the first step of gene expression process and it is the synthesis from RNA from DNA where the code in DNA is converted into complementary RNA code. Translation is the synthesis of protein from mRNA.

**Transcription:** It is the first step of gene expression process in which synthesis of the genetic instructions written in the genome. Transcription
occurs in the nucleus. The enzymes responsible for transcription are transcriptase and RNA polymerase. It occurs in the G1 and G2 phases of the cell cycle.

Transcription comprises the unwinding and splitting of those genes which are to be transcribed. Transcribed RNA strand gets separated from its DNA template strand. The product move from the nucleus to the cytoplasm and no primer is required and gets degraded after their function is completed. It results in the formation of the RNA molecule from a section of one strand which includes tRNA, rRNA, mRNA and non-coding RNA.

Translation: It synthesizes the proteins, that are used for millions of cellular functions. Translation is the second step of the gene expression process. It synthesizes proteins from RNA which are copied from genes. A template is an mRNA. It occurs in the cytoplasm. The enzymes responsible for the process are ribosomes. Translation occurs when ribosome sub-units, initiation factors, and t-RNA bind the mRNA near the AUG start codon and finally produces proteins. Translation is inhibited by anisomycin, cycloheximide, chloramphenicol, tetracycline, streptomycin, erythromycin and puromycin. Now, look at the difference between transcription and translation for complete knowledge.

**Purpose** - The purpose of transcription is to make RNA copies of individual genes that the cell can use in the biochemistry while the purpose of translation is to synthesize proteins which are used for cellular functions.

**Occurrence** - Transcription occurs in the nucleus while translation occurs in the cytoplasm.

**Enzyme** - The enzymes responsible for the transcription are transcriptase and RNA polymerase and enzymes responsible for the translation process are ribosomes.

**Template** - Template in transcription is the genes in the genome whereas the template in translation is the mRNA.

**Primer** - Primer is not required in transcription while in translation primer is required.

**Structure of RNA**

Structure of RNA is different from that of DNA in three respects.

1. DNA is a double stranded α-helix whereas RNA is mostly singlestrandedα-helix
2. RNA has the pyrimidine base uracil in the place of thymine of DNA
3. DNA has deoxyribose sugar whereas RNA has ribose sugar as given below:
Biological importance of RNA:

- RNA are the main components of protein synthesis.
- In many viruses, the RNA functions as the genetic material.
- The rRNA present in the chromatin fibres initiates the replication of DNA.
- RNA is associated with memory storage functions in the brain.

### 10.5 DIFFERENCE BETWEEN DNA AND RNA

<table>
<thead>
<tr>
<th></th>
<th>DNA</th>
<th>RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>It is mainly present in the nucleus</td>
<td>It is present both in nucleus and cytoplasm</td>
</tr>
<tr>
<td>2</td>
<td>It has double stranded α-helix structure</td>
<td>It has single stranded α-helix structure</td>
</tr>
<tr>
<td>3</td>
<td>It has thymidine as one of the nitrogenous bases</td>
<td>Instead of thymidine it has uracil</td>
</tr>
<tr>
<td>4</td>
<td>It has deoxyribose sugar</td>
<td>It has ribose sugar</td>
</tr>
<tr>
<td>5</td>
<td>It is denatured on heating</td>
<td>It is no denatured by heat</td>
</tr>
<tr>
<td>6</td>
<td>It has to do only one type of function</td>
<td>It has to do many functions</td>
</tr>
<tr>
<td>7</td>
<td>It does not depend on RNA for its formation</td>
<td>It depends on DNA for its formation</td>
</tr>
<tr>
<td>8</td>
<td>It does not help enzymatic action</td>
<td>It helps some enzymes for their action.</td>
</tr>
</tbody>
</table>
Check your progress

1. Draw the structure of DNA?
2. What is meant by purines and pyrimidines?
3. Explain the term transcription and translation?
4. Explain
   a. ATGC.
   b. Replication.
   c. Mutation.

10.6 ANSWER KEY TO CHECK YOUR PROGRESS

1.

![DNA structure]

S- Sugar unit  P- Phosphate group
A- Adenine    G- Guanine
C- Cytosine   T- Thymine

Structure of DNA

2. Purines
   Purines are bicyclic heterocyclic compounds. They have two rings in the structure. One is a five membered ring and other is a six membered ring. Examples: Adinine and guanine.

Pyrimidine
   Pyrimidine are six membered heterocyclic compounds. Cytosine, thymine and uracil are the important pyrimidines.

3. The process by which DNA is copied to RNA is called transcription, and that by which RNA is used to produce proteins is called translation.

4. i) A- Adenine   G- Guanine
    C- Cytosine  T- Thymine

   ii) Replication:
       During cell division DNA divides and offers exact copies to the daughter cells.

   iii) Mutation:
       DNA produces mutations resulting in new characters.

10.7 SUMMARY

This unit briefly tells about DNA and RNA. DNA contains deoxyribose sugar whereas RNA contains ribose sugar. DNA is made up of
three chemical components namely Sugar, nitrogenous base and phosphoric acid. Nucleic acid is a long chain polymer. It is composed of a large number of monomeric units called nucleotides. Each nucleotide consists of a nucleoside and a phosphate group. DNA is a double stranded α-helix whereas RNA is mostly single stranded α-helix RNA has the pyrimidine base uracil in the place of thymine of DNA.

10.8 KEYWORDS

- DNA
- RNA
- Nucleic acid
- Purines
- Pyrimidines.

10.9 SELF ASSESSMENT QUESTIONS AND EXERCISES

1) What is meant by replication of DNA? Explain its consequences.
2) What the different types of RNA?
3) Write the biological importance of RNA
4) Enumerate the essential differences between the DNA and RNA
5) Discuss the structure of DNA
6) Write the biological importance of RNA and DNA
7) Discuss the structure of DNA using Watson crick model.

10.10 FURTHER READINGS

UNIT- 11 ALKALOIDS

Structure

11.1 Introduction
11.2 Objectives
11.3 Phenanthrene Alkaloids
  11.3.1 Morphine
  11.3.2 Morison waite and Shavel synthesis
11.4 Atropine
11.5 Synthesis of tropic acid
  11.5.1 Mackenzie and wood synthesis
  11.5.2 Muller and Wislicenus Synthesis
  11.5.3 Blicke synthesis
  11.5.4 WillStatter’s Synthesis
  11.5.5 Elming Synthesis
  11.5.6 Robinson Synthesis
11.6 Biosynthesis of Alkaloids
11.7 Answer to check your progress question
11.8 Summary
11.9 Keywords
11.10 Self-assessment question and exercises
11.11 Further readings

11.1 INTRODUCTION

The term alkaloid or alkali-like was proposed by W. Meissner in 1819 for the basic nitrogen containing compounds of plant origin. Alkaloids are usually found in the seeds, root, leaves or bark of the plant and generally occur as salts of various plant acids. E.g., acetic, oxalic, citric, malic tartaric acids etc. Alkaloids are usually colorless, crystalline, non-volatile solids which are insoluble in water, but are soluble in ethanol, ether, chloroform, etc. Some alkaloids are liquids which are soluble in water. E.g., conine and nicotine, and a few are coloured, e.g., berberine is yellow. Most alkaloids have a bitter taste and are optically active.
They are generally tertiary nitrogen compounds and contain one or two nitrogen atoms usually in the tertiary state in a ring system, most of the alkaloids also contain oxygen.

## 11.2 OBJECTIVES

After going through this unit, you will be able to

- To know what are the characteristics of alkaloids
- To know the different sources of alkaloids
- To determine the importance of alkaloids and to identify their applications in pharmacy.
- To know the different test in determining the presence of alkaloids.

## 11.3 PHENANTHRENE ALKALOIDS

### 11.3.1 Morphine

Morphine is the most important among the opium alkaloids, the amount being nearly 3 to 23%. It was the first alkaloid to be isolated from serturr plant. Due to the presence of phenanthrene nucleus, these alkaloids are also known as phenanthrene alkaloids. The morphine alkaloids have been subjected to a detailed study than those of any other group because of the analgesic properties of morphine and also this alkaloid undergo a variety of molecular rearrangement.

### Constitution

1. The molecular formula of morphine is C_{17}H_{19}NO_{3}.

2. Morphine takes up one mole of methyl Todid to form quaternary ammonium salt showing that nitrogen is present as tertiary one. The tertiary nature of the nitrogen is confirmed by Hofmann degradation of codeine derivative which further indicates that nitrogen is in the ring.

3. Morphine on acetylation or benzoylation gives the diacetyl (heroin) or dibenzoyl derivative indicating the presence of two hydroxyl groups.

4. It exhibits the characteristic property of the phenolic group, viz. Colouration with FeCl\textsubscript{3} and solubility in aqueous sodium hydroxide to form monosodium salt which is reconverted into morphine by passing CO\textsubscript{2}. Hence one of the hydroxyl group must be phenolic one.

5. On treatment with halogen acids, morphine forms monohalogeno product indicating that an alcoholic hydroxyl group is present in morphine. It is further confirmed by the following facts.
Morphine on methylation with methyl iodide gives monomethyl product which does not give any colour with FeCl₃ indicating that it is the phenolic hydroxyl group that is methylated. The methylated morphine on chromic acid oxidation gives a ketone codeinone showing that the monomethylated morphine or codeine has a secondary alcoholic group.

6. From the unreactivity of the third oxygen atom and the degradation products of morphine it was concluded that the third oxygen atom is present as an either linkage.

7. On catalytic (palladium) reduction codeine gives isolated dihydro products, C₁₈ H₂₃ O₃ N suggesting the presence of an isolated ethylenic bond.

8. Morphine is brominated to a bromo derivative along with the evolution of a mole of hydrogen bromide, which suggests that morphine possesses a benzene nucleus.

9. Morphine on distillation with zinc dust gives phenanthrene indicating that the latter nucleus is present in morphine molecule.

10. Codeine, C₁₈ H₂₁, NO₃ is treated with methyl Iodide to form codeine methiodide, C₁₉ H₂₄ O₃ NI, which on heating with alkali give α- codeimethine, C₁₉ H₂₃ NO₃ (Hofmann degradation).

\[
\text{C}_{18} \text{H}_{21} \text{NO}_3 \xrightarrow{\text{CH}_3 \text{I}} \text{C}_{19} \text{H}_{24} \text{NO}_3 \text{I} \xrightarrow{\text{alkali}} \text{C}_{19} \text{H}_{23} \text{NO}_3
\]

Now as these changes correspond to the Hofmann degradation of N-methyl piperidine, the nitrogen atom must be present in a ring.

11. α- Codeimethine on heating with alkali suffers on double bond shift to give isomeric β- Codeimethine. When either of these isomers is treated with methyl iodide followed by alkali, methyl morphenol is formed as the main product along with trimethylamine and ethylene. The methyl morphenol when heated with hydrobromic acid gives morphenol which on reduction with sodium and alcohol gives morphol.

12. Since morphol is obtained by the reduction of morphenol which on fusion with KOH affords 3,4, 5- dihydroxy phenanthrene the morphenol will be having the following structure.
The structure of morphenol and its formation from codeine establishes the position of two of the three oxygen atoms of morphine.

13. Codeine methiodide and codeinone methiodide on heating separately with a mixture of Ac₂O-AcONa gives 3-methoxy -4-acetoxy phenanthrene and 3-methoxy -4,6-diacetoxy phenanthrene respectively.

14. The presence of an additional acetoxy group in position 6 in the latter indicates that in the former the secondary alcoholic group is lost as water molecule during dehydrogenation to the aromatic product while in the latter case the ketonic group (in the place of secondary alcoholic group) enolizes during the route to aromatic product and hence it appears as acetoxy group in the final product.

Thus the position of all the three oxygen function in morphine has been established (is) one (phenolic) at C₃, the other (ether linkage) between C₄ and C₅ and third (secondary alcoholic) at C₆ of the phenanthrene nucleus.

15. Morphine forms monobromo derivative with bromine and monosodium salt with sodium hydroxide, it possesses only one benzenoid nucleus. Further as ethylene is formed as one of the products during the exhaustive methylation of codeimethines and
dimethylamino ethanol is formed, a -CH₂-CH₂-Nme chain must be present in morphine. Further as it contains a double bond and a tertiary nitrogen atom the partial structure for morphine may be written as

\[ + \text{NMe-CH₂-CH₂-} + \text{one double bond formed as ethylene} \]

Hence, it is important to assign the positions of the double bond and the chain –CH₂-CH₂-NMe in such a manner to explain all the reactions of morphine.

16. Point of attachment of –CH₂-CH₂-N¹ Me chain

Codeine on oxidation with chromic acid gives some hydroxy codeine along with codeinone. The hydroxy codeine on Hofmann degradation gives a ketocodeimethane which on heating with AC₂O affords a methoxy diacetoxy phenanthrene. The methoxy diacetoxy phenanthrene on further oxidation gives a quinone with the loss of an acetoxy group.

Codeine $\xrightarrow{\text{CrO}_3}$ Hydroxy codeine $\rightarrow$ Ketocodeimethine $\rightarrow$

Methoxy diacetoxy phenanthrene $\xrightarrow{[O]}$ Methoxy acetoxy phenanthrene

The loss of an acetyl group during the last oxidation indicates that one of the two acetoxy groups in methoxy diacetoxy phenanthrene must be present either at position 9 or 10. Since this acetoxy group is introduced via the ketonic group during aromatization with AC₂O, the ketonic group in keto Codeimethine and hence the new hydroxyl group in hydroxy codeine must be at position C₉ or C₁₀. As the new secondary alcoholic group of hydroxy codeine is converted into ketonic group during Hofmann degradation, the double bond must be introduced between C₉ and C₁₀ during fission of the nitrogen ring and thus the nitrogen must be liked at C₉ or C₁₀. The exact point of linkage i.e., C₉ is established only after the synthesis of morphine. Thus the part structure of hydroxy codeine may be represented by the following reaction.
As the side chain having nitrogen is always elimination with the aromatization of the nucleus. Gulland and Robinson stated that, “the formation of the phenanthrene derivative can take place for structural reasons unless the ethamine chain is displaced”, since the nitrogen end of the side chain had previously been shown to be attached at C9, the carbon end of the side chain must be located at an angular position, so that its extrusion. From that position becomes essential for aromatization. Out of two such possible positions, viz., C13 and C14, the C13 position is selected on the basis that such structure explains the rearrangement of thebaine to thebenine and hence the partial structure of morphine can be written as

17. Position of double bond

Codeine on treatment with PCl₅ yields α- chloro iodide which on further treatment with aqueous acetic acid solution affords a mixture of codeine, iso- codeine, pseudocodiene and allopseudocodeine (positional isomers).

Codeine and isocodeine gives the same ketone on oxidation indicating that they differ only in the position of the hydroxyl group at C₆, while pseudocodiene and allopseudocodeine give the same ketone on oxidation again suggesting that these two differ only in the position of the -OH group which is at C₈. These changes can be explained if the double
bond is in between C<sub>7</sub> and C<sub>8</sub>. Thus, the structure of morphine and codeine.

### 11.3.2 Morison Waite and Shavel synthesis

**b) Morrison, Waite and Shavel synthesis**

![Chemical structure diagrams for the Morison Waite and Shavel synthesis](image-url)
Properties

1. The melting point of Morphine is 254°C.
2. It is bitter in taste and levorotatory alkaloid.
3. It is insoluble in water and slightly soluble in most of the organic solvents.
4. When heated with concentrated hydrochloric acid, morphine undergoes rearrangement to form apomorphine.

Uses

1. It is used as an analgesic and sedative which even today has no substitute in controlling severe pain.
2. It has a marked depressant action on various parts of the nervous system. But as it is habit forming, it must be used with great care.

3. The diacetyl derivative of morphine is used in medicine under the name of heroin, but the derivative is more habit forming than the morphine itself.

11.4 ATROPINE

Atropine is the alkaloid of the members of the solanaceae family, such as Atropa belladonna (deadly night shade), Datura stramonium (thorn apple) and Hyoscyamus niger (henbane). Atropine is isolated from the juice of the deadly night shade.

Constitution

1. The molecular composition of atropine in \( \text{C}_{17}\text{H}_{23}\text{NO}_3 \).

2. On hydrolysis it gives an alcohol, tropine, \( \text{C}_8\text{H}_{15}\text{NO} \) and (±) tropic acid \( \text{C}_9\text{H}_{10}\text{O}_3 \) indicating that atropine is an ester (tropic acid) is tropine tropate.

\[
\text{C}_{17}\text{H}_{23}\text{NO}_3 + \text{H}_2\text{O} \rightarrow \text{C}_8\text{H}_{15}\text{NO} + \text{C}_9\text{H}_{10}\text{O}_3
\]

Hence the constitution of atropine is resolved into two parts; the structure of tropic acid and tropine.

3. Constitution of tropic acid

   (i) Tropic acid \( \text{C}_9\text{H}_{10}\text{O}_3 \) is found to possess one alcoholic and one carboxylic group by usual tests.

   (ii) On strong heating it loses a molecule of water to form atropic acid \( \text{C}_9\text{H}_8\text{O}_2 \) which on oxidation gives benzoic acid.

The formation of benzoic acid suggests that atropic acid and tropic acid, both contains a benzene ring with one side chain. Thus the atropic acid \( \text{C}_9\text{H}_8\text{O}_2 \), having a benzene nucleus, one carboxyl group and a double bond. It can be represented in two ways as

   (iii) Since atropic acid is formed by the dehydration of tropic acid, addition of a molecule of water to the atropic acid
would therefore give tropic acid. The two possible structures of tropic acid are.

### 11.5 SYNTHESIS OF TROPIC ACID

#### 11.5.1 Mackenzie and wood synthesis

Tropic acid is synthesized from acetophenone.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{COC}_2\text{H}_5 & \xrightarrow{\text{HCl}} \text{C}_6\text{H}_5\text{COO}_2\text{H}_2 \\
\text{C}_6\text{H}_5\text{C} & \xrightarrow{\text{CH}_3\text{CN}} \text{C}_6\text{H}_5\text{C} & \xrightarrow{\text{CH}_3\text{O}} \\
\text{Heat} & \xrightarrow{\text{H}_2\text{O}} \text{C}_6\text{H}_5\text{COH}_2 & \xrightarrow{\text{Na}_2\text{CO}_3} \text{C}_6\text{H}_5\text{C}_2\text{H}_5
\end{align*}
\]

The addition of hydrogen chloride takes place contrary to Markownikoff’s rule. If the addition takes place according to the rule, the final product would be atrolactic acid. (±) Tropic acid has been resolved by means of quinine.

#### 11.5.2 Muller and Wislicenus Synthesis

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{CN} & \xrightarrow{\text{H}^+} \text{C}_6\text{H}_5\text{C} & \xrightarrow{\text{C}_2\text{H}_5\text{ONa}} \\
\text{Al-Ag moist ether} & \xrightarrow{\text{C}_6\text{H}_5\text{COH}_2} \text{C}_6\text{H}_5\text{C} & \xrightarrow{\text{Na}_2\text{CO}_3} \\
\text{C}_6\text{H}_5\text{CHO} & \xrightarrow{\text{CH}_3\text{OH}} \text{C}_6\text{H}_5\text{COH}_2 & \xrightarrow{\text{C}_6\text{H}_5\text{CH}_2\text{OH}_2}
\end{align*}
\]

#### 11.5.3 Blicke Synthesis

Tropic acid is also synthesized from phenyl acetic acid. This reaction is known as Blicke synthesis.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{COOH} & \xrightarrow{(\text{CH}_3)_2\text{CHMgCl}} \text{C}_6\text{H}_5\text{CH}_2\text{COOH} & \xrightarrow{\text{HCHO}} \\
\text{C}_6\text{H}_5\text{CH}_2\text{COOH} & \xrightarrow{(\text{CH}_3)_2\text{CHMgCl}} \text{C}_6\text{H}_5\text{CH}_2\text{COOH} & \xrightarrow{\text{HCHO}}
\end{align*}
\]

### Constitution of tropine (tropanol)

i. The molecular formula for tropine is \(\text{C}_8\text{H}_{15}\text{NO}\) and it is found to be a saturated secondary alcohol having tertiary nitrogen in the form of \(-\text{NCH}_3\) group (Herzig-Meyer Method).

ii. Tropine on treatment with hydroiodic gives tropine iodide which on reduction with Zinc and HCl affords tropane. Tropane hydrochloride on distillation followed by zinc dust distillation yield 2-ethylypyridine through nortropane.
On the basis of these reactions, Landenburg proposed that tropine is a reduced pyridine derivative. It may be either the following structure.

iii) Tropine (C₈H₁₅NO), on oxidation with chromic acid gives a ketone tropinone C₈H₁₃NO, which on further oxidation yields a dicarboxylic acid tropinic acid, C₈H₁₃O₄N. This change suggests that the ketonic group in tropinone and hence alcoholic group in tropine must be present in a single system and thus Ladenburg structure was discarded. Furthermore, as the tropinone forms a dibenzylidene derivative with C₆H₅CHO it must have –CH₂-CO-CH₂-group.

Tropinic acid was degraded by exhaustive methylation to piperylene carboxylic acid which on reduction gives pimelic acid.

iv) Tropinic acid was degraded by exhaustive methylation to piperylene carboxylic acid which on reduction gives pimelic acid.

The formation of pimelic acid suggests that tropinic acid must contain a seven-carbon chain and tropinone a seven-carbon ring. Further, as tropinic acid contains -COOH and –CH₂COOH (both from the oxidation of –CH₂-CO-CH₂-group), three and four membered ring structures are not possible for tropinic acid. The presence of five membered ring in tropinic acid is confirmed by its oxidation with chromic oxide in H₂SO₄ under drastic condition which gives N-methyl succinimide.
(v) Thus on the basis of the structure of tropinic acid, tropinone and tropine must be as follows.

11.5.4 Will Statter’s Synthesis
11.5.5 Elming Synthesis

Tropinone (81% yield) is obtained by condensing methylamine, acetone dicarboxylic acid and succindialdehyde generated in situ by the action of an acid on 2,5-dimethoxy tetrahydrofuran.

By knowing the structure of tropic acid and tropine the structure of atropine may be written as below. It is confirmed by the fact that tropine and tropic acid when heated in presence of hydrogen chloride (fischer-speier esterification) give atropine.
11.5.6 Robinson Synthesis

Robinson obtained tropinone by keeping a mixture of succindialdehyde, methylamine and acetone in water for 30 minutes.

\[
\begin{align*}
\text{CHO} + \text{CH}_2\text{NH}_2 & \rightarrow \text{CHO} + \text{CH} = \text{NHCH}_3^+ \rightarrow \text{CHO} \ \text{enolic form} \ \text{of acetone} \\
\rightarrow \text{NCH}_3 & \rightarrow \text{NCH}_3 \text{O} \\
\end{align*}
\]

Tropinone

When the above synthesis is carried out at pH about 7 the yield of tropinone is 70 – 85%.

Properties

1. The melting point of Atropine 115°C.

2. It is optically inactive and is a strong poison with a sharp bitter taste.

3. Atropine is the racemic modifikaton of hyoscyamine which is laevo-rotatory and it is believed that the atropine does not exist in the nature but it is formed during the isolation of hyoscyamine.

Uses

(i) Atropine has a dilating action on pupils of the eyes and hence it is used in ophthaquinology. For this purpose one part of atropine in 130,000 parts of water is sufficient to cause the dilatation of the pupils of the eyes of cats.

(ii) When taken internally atropine first stimulates and then depresses the central nervous system.

11.6 BIOSYNTHESIS OF ALKALOIDS

In spite of the large numbers and great diversity of alkaloid structures, it is possible to discuss a few general principles that are applicable to the biosynthesis of many different alkaloids. The assumptions of Robinson’s scheme of biosynthesis are important and are summarized as follows.

(i) The fundamental skeletons of alkaloids are derived from common acids and other small biological molecules.
(ii) A few simple types of reactions suffice to form complex structures from these starting materials.

eg. The aldol condensation.

\[ \text{C} = \text{O} + \text{H} - \text{C} - \text{X} \rightarrow \text{OH} \]
\[ \text{C} - \text{C} - \text{X} \]

The carbinolamine condensation

\[ \text{N} - \text{C} - \text{OH} + \text{H} - \text{C} - \text{X} \rightarrow \text{N} - \text{C} - \text{C} - \text{X} \]

The aldehyde – amine condensation

\[ \text{N} - \text{H} + \text{O} = \text{C} - \rightarrow \text{N} - \text{C} - \text{H} \]

Where X is the activating group like carbonyl group.

(iii) The most common amino acid that act as precursors in alkaloid biosynthesis is given below.

\[ \text{H}_2\text{N}(\text{CH}_2)_3\text{CH}(\text{NH}_2)\text{COOH} \rightarrow \text{N} \]

Ornithine pyrrolidine alkaloids

\[ \text{H}_2\text{N}(\text{CH}_2)_4\text{CH}(\text{NH}_2)\text{COOH} \rightarrow \text{N} \]

Lysine piperine alkaloids

\[ \text{R} - \text{C} - \text{C} - \text{N} \]

Isoquinoline alkaloids

R = H Phenylalanine
R = OH Tyrosine

\[ \text{H}_2\text{N}(\text{CH}_2)\text{CH}(\text{NH}_2)\text{COOH} \rightarrow \text{C} - \text{C} - \text{N} \]

Tryptophan Ergot alkaloids

A number of experiments were attempted to demonstrate that with low concentrations and under mild conditions of temperature and pH it becomes possible to carry out reactions of the hypothetical precursors to form complex structures which are resembling alkaloids.
Many types of reactions have been postulated for the biosynthetic conversion of amino acids into alkaloids.

a) **Decarboxylation**: This results in the formation of amine.

\[
R \text{CH (NH}_2\text{) COOH} \rightarrow R\text{CH}_2\text{NH}_2 + \text{CO}_2.
\]

b) **Oxidative deamination**: This reaction results in the formation of an aldehyde.

\[
R\text{CH (NH}_2\text{) COOH} \rightarrow R\text{COOCH} \rightarrow R\text{CHO}
\]

\[
R\text{CH (NH}_2\text{) COOH} \rightarrow R\text{CH}_2\text{NH}_2 \rightarrow R\text{CHO}
\]

**Schiff base formation**:

\[
R\text{CHO} + R^2\text{NH}_2 \rightarrow R^1\text{CH} = NR^2
\]

c) **Mannich reactions**: This is the reaction between a molecule with an active hydrogen, an aldehyde, and an amine. A Mannich intermediate is formed.

\[
R\text{CHO} + (C_2H_5)_2\text{NH} \rightarrow (C_2H_5)_2N^+ = CH_2 + H_2O
\]

This intermediate is a quaternary Schiffs base. It proceeds by the following steps.

\[
\begin{align*}
\text{I} & \rightarrow \text{II} \\
\text{CH}_3 & \equiv \text{CH}_2 + \text{NH}_2^+ \\
\text{II} & \rightarrow \text{I}
\end{align*}
\]

The reaction involved in the formation of I and II are important because they lead to the formation of a carbon-Nitrogen bond. The synthesis of Pyrrolidine and piperidine alkaloids involves Mannich reaction.

d) **Diamine oxidase**

According to Mann, smithies, Hasse and Maisack, cyclic compounds were formed as the result of the action of diamine oxidase in alkaloids such as cadaverine and putrescine.

This reaction involves the initial formation of an amine and ring closure with loss of ammonia or formation of an aldehyde and ring closure with loss of water.

eg: 1,4 diamino butane in putrescine alkaloid.
1. Define Morphine.

2. Draw the structure of tropine.

3. Robinson uses.

4. Write the any One example of Diamine Oxidase?

5. Mention the any Two importance of Biosynthesis?

11.7 ANSWER TO CHECK YOUR PROGRESS QUESTION

1. Morphine is the most important among the opium alkaloids, the amount being nearly 3 to 23%. It was the first alkaloid to be isolated from serturr plant. Due to the presence of phenanthrene nucleus, these alkaloids are also known as phenanthrene alkaloids.

2.

3. Robinson uses

   - Atropine has a dilating action on pupils of the eyes and hence it is used in ophthaquinology.
   - For this purpose one part of atropine in 130,000 parts of water is sufficient to cause the dilatation of the pupils of the eyes of cats.
   - The fundamental skeletons of alkaloids are derived from common acids and other small biological molecules.

4. 1,4 diamino butane in putrescine alkaloids.

5. The aldol condensation and carbinolamine condensation

\[
\begin{align*}
\text{C=O} + H\text{C} \rightarrow \text{C} & \rightarrow \text{OH} \\
\text{C} & \rightarrow \text{C} \rightarrow \text{X} \rightarrow \text{X}
\end{align*}
\]
11.8 SUMMARY

Alkaloids is a Basic nitrogenous compounds of plant origin that are physiologically active. They are occur in plants, some in animals (fungi and bacteria) – almost all have been reproduced in the lab by chemical synthesis and possess basic properties, due to nitrogen. Possess marked physiologic activity of insoluble/ sparingly soluble in water and few are amorphous and liquid, most are crystalline solids, free alkaloids – sol. In ether, chloroform, relatively non-polar immiscible solvents and alkaloidal salts are insoluble. For identification: Mayer’s, Dragendorff’s, Wagner’s reagents.

11.9 KEYWORDS

- Morphine
- Atropine
- Alkaloids
- Tropic acid
- Biosynthesis

11.10 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Write the structure of Morphine.

2. Write the Gates et al synthesis.

3. What are the solvent are used to Morison and Waite synthesis?


5. Mention the Mechanism Will Statter’s synthesis.

6. Write the Schiff base formation:

\[ RCHO + R^2NH_2 \rightarrow ? \]

11.11 FURTHER READINGS


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UNIT-12 TERPENES

Structure

12.1 Introduction
12.2 Objectives
12.3 α - Pinene
12.4 Camphor
12.5 Zingiberene
12.6 Biosynthesis of Terpenoids
12.7 Answer to check your progress question
12.8 Summary
12.9 Keywords
12.10 Self-assessment question and exercises
12.11 Further readings

12.1 INTRODUCTION

Terpenes or Terpenoids form a group of compounds the majority of which occur in the plant kingdom. The term ‘terpene’ was employed to describe a mixture of isomeric hydro carbons of the molecular formula C_{10}H_{16} occurring in the turpentine and many essential oils which are obtained from the sap and tissues of certain plants and trees. The oxygenated derivatives like alcohols, aldehydes, ketones etc., were called as Camphors. The terms ‘terpenes’ and camphors were amalgamated into a single term called terpenoids. The modern definition for terpenoids is as follows: “It includes hydrocarbons of plant origin of the general formula (C_{5}H_{8})_{n} as well as their oxygenated, hydrogenated and dehydrogenated derivatives”. As terpenoids are composed of isoprene units, these are sometimes called isoprenoids: The simpler mono and sesqui terpenoids are the chief constituents of the essential oils; these are the volatile oils obtained from the sap of the trees. The di and tri terpenoids which are not steam volatile are obtained from plant and tree gums and resins. The tetra terpenoids form a group of compounds known as carotenoids. Rubber is the most important polyterpenoid.

In the recent past, biological activity of various substances has been related with terpenoids. Many sesqui-terpenes and di-terpenes are used as antibiotics. Several sesqui-terpenes have been found to be active against experimental tambours are the plant growth hormones like gibberellins and
diterpenoids. As some terpenoids exhibit biological activity viz., insecticidal, or antiseptic, those are used in pharmacy.

The thermal decomposition of almost all terpenoids gives isoprene as one of the products, and this led to the suggestion that the skeleton structures of all naturally occurring terpenoids can be built up of isoprene units, this is known as the isoprene rule and was first pointed out by Wallach. Furthermore, Ingold points out that the isoprene units in natural terpenoids were joined “head to tail” and the head being the branched end of isoprene. Let us discuss the structure and synthesis of certain terpenoids.

12.2 OBJECTIVES

After going through this unit, you will be able to

- To know the terpene are a combination of carbon and Hydrogen.
- All terpene are derived from the union of five carbon elements that have branched carbon sketon of isopentane.
- All terpene are a occasionally referred to as isoprenoids.
- To know the cumene is a terpene that have been used in bioremediation studies.
- The carbon cation can lose a proton to give a double bonds.

12.3 \(\alpha\) - PINENE, \(\text{C}_{10}\text{H}_{16}\)

It is the most important member of Pinene class which is the chief constituent of the oil of turpentine. It occurs in both the (+) and (-) form in all turpentine oils. It is a bicyclic monoterpen compound.

The inactive or (±) isomer is obtained from turpentine oil which is the volatile fraction obtained by steam distillation of oleoresin produced by pine trees. The inactive \(\alpha\) - Pinene is separated by repeated fractional distillation of turpentine oil. Then, the purification of \(\alpha\) - pinene so obtained is done by formation of its crystalline nitrosyl chloride derivative with nitrosyl chloride. This additional product is then decomposed by aniline to yield pure \(\alpha\) - pinene.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Or} \\
\text{CH}_3 & \quad \alpha\text{-pinene}
\end{align*}
\]

\(\alpha\) - Pinene is a liquid which boils at 156°C. When \(\alpha\) - pinene is exposed to air, it undergoes autoxidation.
Structure of $\alpha$ - Pinene

The analytical evidence for the structure of $\alpha$ - pinene may conveniently be divided into two sections, each section leading independently to the structure, and the two taken together are giving very powerful evidence for the structural assignment.

Method: I

(i) Molecular Formula

From analytical data and molecular weight determination, the formula of $\alpha$ - pinene has been found to be $C_{10}H_{16}$.

(ii) Presence of a double bond

As $\alpha$ - pinene adds on two bromine atoms, this means that $\alpha$ - pinene contains one double bond. This is further revealed by the fact that it forms addition crystalline derivative with nitrosochloride.

(iii) Presence of a bicyclic compound

The molecular formula of $\alpha$ - pinene is $C_{10}H_{16}$ and it contains one triple bond. Therefore, its parent hydrocarbon is $C_{10}H_{18}$ which corresponds to the general formula $C_nH_{2n+2}$ of compounds containing two rings, Therefore, it follows that $\alpha$ - pinene is bicyclic.

(iv) Presence of six membered ring

When $\alpha$ - pinene is heated with alcoholic sulphuric acid, it yields $\alpha$ - terpineol.
The formation of α-terpineol from α-pinene leads to the following facts:

a) In α-pinene, a six-membered ring having the double bond of α-terpineol is present.

b) In α-terpineol, the hydroxyl group is present at C₆. But this is not present in α-pinene. Therefore, it means that the carbon atom is C₆ must be involved in the formation of the second ring of α-pinene. There are three possible points of union for this C₆, giving rise to two three-membered and one four-membered ring (as represented by dotted lines in the following structure), and at the same time the position of the double bond in α-pinene has been shown by conversion into α-terpineol. The exact structure of the second ring, ie., whether 4- or 3-membered is established by the oxidative degradation of α-pinene.

Actually there are four possible points for union of C₆. Out of these, three are shown in structure (I) where as the fourth being at the double bond to form a four membered ring. However, the fourth was rejected on the basis of Bredt’s rule, which states that “a double bond cannot be formed by a carbon atom occupying the bridge head of a bicyclic system”. According to this rule the structure (IA) cannot exist because it has a large amount of strain.

(C) The gem-dimethyl group (-CH-Me₂) of α-terpineol is not present in the six-membered ring of α-pinene and therefore it must be present in other ring.

(v) **Oxidative degradation of α-pinene**

The nature of the second ring was shown to be four membered in α-pinene by Baeyer on the bases of the following series of reactions.
The above set of oxidative degradation led to the following conclusions:

a) When $\alpha$-pinene (I) is oxidized to pinene glycol (II) the double bond of $\alpha$-pinene is hydroxylated.

b) The oxidation of pinene glycol (II) to pinonic acid (III) occurs due to scission of the glycol bond. At the same time, a small amount of pinoylformic acid is also formed, i.e., MeCO of pinonic acid is now HOOC-CO.

c) The formation of pinic acid (IV) and bromoform indicates the presence of an acetyl group in pinonic acid.

d) Pinic acid has been shown to be a saturated dicarboxylic acid. When this is treated first with bromine, then with barium hydroxide and finally with the oxidizing agent like PbO$_2$ yields cis-norpinic acid C$_6$H$_{12}$O$_4$.

As cis-norpinic acid has been shown to be a saturated dicarboxylic acid, its formula may be written as C$_6$H$_{10}$ (COOH)$_2$. But $\alpha$-pinene contains two methyl groups attached to a carbon atom in the second ring (I) and its six membered ring containing the double bond has been opened by the above oxidation. Therefore, the norpinic acid may be written as (CH$_3$)$_2$.

If methyl and carboxyl groups are considered as substituents, the parent saturated hydrocarbon from which norpinic acid has been derived is C$_4$H$_8$, corresponding to cyclobutane dicarboxylic acid. On this base, pinic acid would be a cyclobutane derivative with one side chain of – CH$_2$ COOH.

Therefore, Baeyer argued that pinic and norpinic acids possessed a cyclobutane ring and postulated the structures (I) to (v) to explain the above reactions by accepting structure (I) for $\alpha$-pinene.
In order to confirm the above reactors, the synthesis of norpinic acid was carried out by Kerr.

The norpinic acid obtained by this method was trans-isomer. This is readily converted into cis isomer by heating the trans acid with acetic

The norpinic acid obtained by this method was trans-isomer. This is readily converted into cis isomer by heating the trans acid with acetic
anhydride. The cis-anhydride of norpinic acid which upon hydrolysis gives the cis norpinic acid.

**Method II - (WAGNER’S METHOD)**

(i) **Molecular Formula**

The molecular formula has been found to be $C_{10}H_{16}$.

(ii) **Presence of double bond**

$\alpha$ - pinene adds on to one mole of bromine which shows that it contains one double bond.

(iii) **As bicyclic compound**

When nitrosyl chloride is added to $\alpha$ - pinene, $\alpha$ - pinene nitroschloride is obtained along with the by products. This latter when steam distilled yields pinol, $C_{10}H_{16}O$. Pinol contains one double bond because it adds on to one mole of bromine to form pinol dibromide. When pinol dibromide is treated with lead hydroxide it forms pinol glycol $C_{10}H_{16}O(OH)_2$, which upon oxidation yields terpenylic acid.

Pinol (VIII) is also obtained by the action of sodium ethoxide on $\alpha$ - terpineol dibromide (VII). Further, pinol glycol (IX) which upon further oxidation yields terpenylic acid (X).

All these facts can be explained if (VI) being the structure of $\alpha$ - terpineol.

Further support for pinol (VIII) is derived from the fact that sobrerol (pinol hydrate) gives a tetrahydric alcohol, Sotrerythritol.
Sobrerol is itself prepared by treating pinol with hydrogen bromide followed by sodium hydroxide. These reactions may be written as

All the above reactions of \( \alpha \) - pinene could be explained if the formula of \( \alpha \) - pinene is considered to be (I) as given by Wager. However, Wagner’s work provides no direct evidence for the existence of the cyclobutane ring which was provided by Baeyer in method I.

**Total synthesis of \( \alpha \) -Pinene**

Finally, the structure (I) for \( \alpha \) - pinene has been confirmed by its synthesis. Guba et al. Synthesized pinic acid from norpinic acid. Rao synthesized pinonic acid from synthetic pinic acid. Ruzicka et al. Synthesized \( \alpha \) - pinene from pinonic acid. Thus a total synthesis of \( \alpha \) - pinene is achieved.

The various steps for the synthesis of \( \alpha \) - pinene are as follows:
In the above synthesis a mixture of two compounds α and δ-pinene are obtained. They are distinguished on the basis of evidence that diazoacetic ester, combines with compound having a double bond to form pyrasoline derivatives and these on heating alone or with copper powder decompose to produce cyclopropane derivatives.

When the two pinenes are subjected to the above treatment and the resulting compounds, 1,2,3-tricarboxylic acid and δ-pinene yields cyclopropane-1,2,3-tricarboxylic acid. These products are in accord with structures assigned to α - pinene and δ -pinene.
Stereo Chemistry

Examination of \( \alpha \)-pinene structure shows that two dissimilar chiral centres are present, thus, two pairs of enantiomers are possible. However, only one pair is known because the four-membered ring can only be fused to the six-membered one in the cis–position and trans position is impossible. Thus, only the enantiomer of cis-isomer is known.

12.4 CAMPHOR \( \text{C}_{10} \text{H}_{16} \text{O} \)

This occurs in nature in the camphor tree of Formosa in Japan. When wood and leaves of camphor trees are boiled with water in a vessel covered with a dome, camphor sublimes and collects on the surface of the dome. Further purification of camphor is done by republication.

Camphor is a solid having melting point of 180\(^\circ\)C and is optically active, the (+) and (-) forms occur naturally whereas racemic camphor is the usual form of synthetic camphor which is obtained from \( \alpha \)-pinene.

Camphor is used as a plasticizer for the manufacture of celluloid and photographic films. It is used for the manufacture of smokeless powders and explosives. It is used as a mild disinfectant and stimulant for the heart muscles.

It is an effective insect repellent.

Constitution of Camphor

The structure of camphor was successfully elucidated by Bredt on the basis of following analytical and synthetic evidences.

1. Molecular Formula

From analytical data and molecular weight determination, the molecular formula of camphor is \( \text{C}_{10} \text{H}_{16} \text{O} \).

2. Saturated Characteristics

Camphor does not add reagents like bromine, nitrosyl chloride, etc. It forms mono substitution products like mono bromo camphor, monochlorocamphor, camphor sulphonic acid. The formation of these products reveals that camphor is a saturated compound and does not contain any double bond. This is further supported by the facts that it does not react with 1% alkaline KMnO\(_4\).

3. Presence of a keto group

The nature of oxygen atom is found to be Cyclic Ketonic on the basis of following facts:

a) It forms an oxime with hydroxylamine
Terpenes

\[
\text{C}_{10}\text{H}_{16}\text{O} + \text{H}_{2}\text{NOH} \rightarrow \text{C}_{10}\text{H}_{16} = \text{NOH}
\]

Camphor  Camphor Oxime

b) It forms semi carbazone with semi carbazide

c) It forms phenyl hydrazone with phenyl hydrazine

d) Camphor when oxidized with nitric acid, yields a dicarboxylic acid called camphoric acid without loss of carbon atoms.

e) Camphor when reduced with sodium amalgam, yields a secondary alcohol called borneol. Hence camphor must be a cyclic ketone.

f) When camphor is distilled with iodine, it yields Carvacrol.

\[
\text{Camphor} \xrightarrow{\text{I}_2} \text{OH}
\]

The presence of phenolic group in carvacrol reveals the presence of ketonic group in camphor.

4. Bicyclic system

The molecular formula of saturated parent hydrocarbon of camphor is \( \text{C}_{10}\text{H}_{18} \) which corresponds to the general \( \text{C}_n\text{H}_{2n-2} \) of bicyclic compounds and therefore, camphor is a bicyclic compound.

5. Presence of –\( \text{CH}_2\text{CO} \) group

(a) When camphor is treated with amyl nitrite and hydrochloric acid, it yields an iso-nitroso (oximino) camphor in which two hydrogen atoms have been replaced by \( =\text{NOH} \) group. This reaction reveals that the \( >\text{C}=\text{O} \) group is directly attached to \( -\text{CH}_2 \) Group.

\[
\begin{align*}
\text{C}_8\text{H}_{14} & \xrightarrow{\text{amyl nitrite}} \text{C}_8\text{H}_{14} \xrightarrow{\text{HCl}} \text{C}_8\text{H}_{14} \\
\text{C}=\text{O} & \xrightarrow{\text{amyl nitrite}} \text{C}=\text{NOH} \xrightarrow{\text{HCl}} \text{C}=\text{O}
\end{align*}
\]

Camphor  Isonitroso camphor

(b) Isonitroso camphor when hydrolysed yields camphor quinone, thus confirming the presence of a \( -\text{CO-CH}_2 \) group.
Equation: 13

(c) When camphor is treated with benzaldehyde, it yields a benzylidene derivative. This reaction is characteristic of the reactive methylene group attached to a C=O group. This shows that camphor contains –CH₂CO group.

(d) The presence of –CO-CH₂ group in a ring of camphor has been further confirmed when camphor is oxidized it yields camphoric acid, a dibasic acid having the same number of carbon atoms. The oxidation takes place by opening of the ring.

6. Presence of a six membered ring

When camphor is distilled with Zinc chloride or phosphorous pentoxide, it yields p-cymene. This reveals the presence of six-membered ring, methyl and gem-dimethyl group in camphor.
When camphor is heated with hydrochloric acid it yields tetra and hexa–hydrom-xylene, confirming that camphor contains a six membered ring.

7. Nature of the carbon frame in camphor

When camphor is oxidized with nitric acid, it yields a crystalline dibasic acid, camphoric acid, C_{10}H_{16}O_4. As camphoric acid possesses the same number of carbon atom as camphor, it means that the keto group must be present in one of the rings in camphor.

Further camphoric acid is a dicarboxylic acid and its molecular refracti...
(e) When camphoronic acid is distilled at atmospheric pressure it yields isobutyric acid (II), trimethyl succinic acid (III), carbon dioxide and carbon.

\[
\text{Camphoronic acid} \xrightarrow{\text{heat}} \text{iso-butyric acid} + \text{trimethyl succinic acid} + \text{CO}_2 + \text{C}
\]

In order to explain the formation of these products, Bredt suggested that camphoronic acid is \(\alpha, \alpha, \beta\)-tri carboxylic acid (I)

\[
\begin{align*}
\text{HOOC} - \text{C} - \text{COOH} & \quad \xrightarrow{\Delta} \quad \text{CO}_2 + 2\text{CH}_3\text{C} - \text{COOH} \\
\text{COOH} & \quad \xrightarrow{\Delta} \quad \text{CO}_2 + \text{H} - \text{C} - \text{COOH}
\end{align*}
\]

f) The structure (I) for camphoronic acid is confirmed by its synthesis given by Perkin Junior and Thorpe. In this synthesis, auto acetic ester is converted into dimethyl derivative which is then subjected to reformat sky reaction with ethyl bromo acetate. The product so obtained is converted into halide and then into a cyanide. This on hydrolysis yield camphoronic acid.
9. Structure of camphoric acid

a) The molecular formula of camphoric acid is $\text{C}_{10}\text{H}_{10}\text{O}_4$

b) Camphoric acid has been shown to be a saturated dicarboxylic acid

c) Its molecular formula is $(\text{CH}_3)_3\text{C}_5\text{H}_5(\text{COOH})_2$ and its parent hydrocarbon is $\text{C}_5\text{H}_{10}$ which corresponds to the general formula $\text{C}_n\text{H}_{2n}$ for a monocyclic derivative and hence camphoric acid is a monocyclic derivative. Thus the oxidation of camphoric acid to camphoronic acid is given as follows.

$$ \begin{align*}
\text{C} + \text{C} \quad &\xrightarrow{[\text{O}]} \quad \text{H}_2\text{C} -\text{C} -\text{COOH} \\
\text{CH}_3 &\quad \quad \text{HOOC} \quad \text{C} \quad \text{(CH}_3\text{)}_2 \quad \text{COOH} + 2\text{CO}_2
\end{align*} $$

Camphorinic acid

The selection structure (IV) plus one carbon, having arrangement with two carboxyl groups, will lead to the structure of camphoric acid.

d) Camphoric acid is able to form a monoester readily & forms diester with difficulty, this shows that the two carboxyl groups are not similar i.e., one is primary or secondary, and the other is tertiary. This is confirmed that camphoric anhydride forms only one monobromo derivatives with phosphorous / bromine. The formation of mono derivative is only possible if one of the carboxyl groups is secondary, i.e., the carbon atom of one carboxyl group must be $\text{C}-\text{H}$. Thus, the position of the one carboxyl group is ascertained.
e) The second carboxyl group is such that when occurs the opening of cyclopentane ring of camphoric acid to yield camphoronic acid, one carbon atom is readily lost. If this is taken into account, then, there are two structures for camphoric acid. The structures are V and VI. The structure V may also be written (VA).

10) Structure of Camphor

The camphoric acid is obtained by the oxidation of –CH2-COOH-group of camphor. Therefore, the structure of camphor would be obtained by joining the carbon atoms of the carboxyl groups in camphoric acid. Hence, the structure of camphor obtained by from (VA) would contain a six membered ring with a gem-dimethyl group. But, this Structure could not explain the conversion of camphor into β-cymene. Thus, structure V and VA were rejected.

The structure VI would be the correct structure for camphoric acid which was obtained by the oxidation, to reveal the relationship between camphor, camphoric acid and camphoronic acid.
Bredt also proposed structure (VIII) for camphor. This structure failed when camphor was distilled with iodine to yield carvocrol (XI). The formation of carvocrol (XI) can be explained only on the basis of structure VII but not on (VIII).
Thus, the structure of camphoric acid (VI) and camphor (VII) were confirmed by synthesis.

11) Synthesis of (+) camphoric acid

Synthesis of camphoric acid was given by Komppa. It involves two steps.

(i) First Step: It involves the preparation of 3,3-dimethyl glutaric acid from mesityl ketone and ethyl malonate.

\[
\text{(CH}_2\text{)}_2\text{C}=\text{CHCOCH}_3 + \text{CH}_2\text{(COOC}_2\text{H}_5\text{)}_2 \xrightarrow{\text{C}_2\text{H}_5\text{ONa}} \text{[\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \\
\text{COOC}_2\text{H}_5 \\
\text{COOC}_2\text{H}_5
\end{array}]}
\]

(ii) Second Step:

This step involves the conversion of 3,3 dimethyl glutaric acid into camphoric acid.
There are two geometrical isomeric form of camphoric acid is cis and trans. They are (+) – is camphoric acid and (-) form is isocamphoric acid. Camphoric acid is cis form which yield anhydride on heating, whereas iso camphoric is trans form which does not yield anhydride.

12) Synthesis of Camphor

Camphor was synthesized from camphoric acid by Haller. Money et al synthesized camphor from dihydrocarvone.
a) Haller synthesis

![Chemical diagram of Haller synthesis process]

b) Money et al synthesis

Camphor is synthesized from dihydro carvone.

![Chemical diagram of Money et al synthesis process]

13) Commercial synthesis of Camphor

On a large scale, camphor is prepared from α- Pinene.
14) Reactions of camphor

(i) Fission reaction

When camphor is heated with KOH, fission takes place and it yields a mixture of camphoric and iso camphoric acid.

(ii) Reduction reaction

When camphor is reduced, it yields a mixture of isomeric alcohols, borneol and isoborneol, the relative proportion of borneol and isoborneol depends upon the nature of the reducing agent.
Stereo chemistry of camphor

Camphor contains two dissimilar chiral centres. Therefore two pairs of enantiomers are known. Only one pair of enantiomer due to cis form is possible because other pair of enantiomer is not possible due to the impossibility of the trans fusion of the gem-dimethyl methylene bridge to the cyclohexane ring.

Camphor as well as its derivatives exists in the boat conformation. Since, the gem-dimethyl bridge must exhibit the boat form.

12.5 ZINGIBERENE $C_{15}H_{24}$

It is a monocyclic sesquiterpenoid which occurs in the (-) form in ginger oil. It is an optically active liquid having a boiling point of 134°c at 14mm pressure.

Constitution

1. Based on analytical data and molecular weight determination, the molecular formula of Zingiberene has been found to be $C_{15}H_{24}$.

2. As zingiberene forms dihydro chloride with Hydrogen Chloride this shows that it contains two double bonds.

$$C_{15}H_{24} + 2HCl \rightarrow C_{15}H_{26}Cl_2$$

Zingiberene  Zingiberene dihydro chloride.

3. Molecular refraction reveals the presence of three double bonds. This has been confirmed by the fact that zingiberene when reduced with hydrogen in the presence of Pt catalyst yields hexa hydro zingiberene $C_{15}H_{30}$

$$C_{15}H_{24} + 3H_2 \xrightarrow{Pt} C_{15}H_{30}$$

Zingiberene  Black Hexahydro zingiberene
4. As the parent hydrocarbon of zingiberene possesses the formula \( \text{C}_{15}\text{H}_{30} \) which corresponds to \( \text{C}_n\text{H}_{2n} \) for monocyclic compounds and therefore zingiberene is a monocyclic compound.

5. Zingiberene when reduced by means of sodium and ethanol yields dihydro zingiberene \( \text{C}_{15}\text{H}_{26} \). This reaction shows that two of the double bonds are probably conjugated. This has been confirmed by

(i) Formation of an adduct with maleic anhydride.

(ii) Zingiberene shows optical exaltation whereas dihydro zingiberene does not show. Dihydro zingiberene has molecular refraction of 68.37 which is similar to calculated value 68.25 of dihydro zingiberene on the assumption that dihydro zingiberene contains isolated double bonds which are produced by the reduction of one of the conjugated double bonds of zingiberene.

\[
\text{C}_{15}\text{H}_{24} + 4 \text{[H]} \rightarrow \text{C}_{15}\text{H}_{26}
\]

Zingiberene \hspace{1cm} dihydro zingiberene

(Shows optical exaltation)(does not shows opticalexaltation)

(iii) The \( \lambda_{\text{max}} \) of zingiberene is 260 nm. The calculated value of \( \lambda_{\text{max}} \) for the homo annular conjugated diene system is 253 nm, and the value for a hetero annular system is 214 nm. Therefore, \( \lambda_{\text{max}} \) also favours the conjugated system of double bonds in zingiberene.

6. When zingiberene is heated with sulphur, it undergoes dehydrogenation to form cadalene. The structure of cadalene is 1,6 – dimethyl -4-iso propynaphthalene.

Therefore, in zingiberene the following cadalene carbon skeleton must be present.
7. When zingiberene is ozonolysed, it yields acetone, laevulic acid and succinic acid. But these products are also obtained from bisabolene. This shows that both zingiberene and bisabolene must have the same carbon skeleton.

The above carbon skeleton of zingiberene has been confirmed by the fact that Hexahydro zingiberene when dehydrogenated over palladised charcoal yields 6-p-tolyl-2-methyl heptane which open oxidation with chromic acid yields acetic acid, oxalic acid and terephthalic acid.

8. During ozonolyses of zingiberene one of the products formed is acetone. The formation of this product reveals that one of the double bond must be present as isopropylidiene group i.e.,
9. When the oxidation of dihydro zingiberene (I) is carried out with permanganate, it yields a keto-dicarboxylic acid, C_{12}H_{20}O_{5} (II). This keto-dicarboxylic acid when oxidised with sodium hypobromite yields a tricarboxylic acid, C_{11}H_{18}O_{6} (III) along with bromoform. The formation of bromoform reveals that the compound (III) must have a methyl ketone group (CH_{2}CO). Now if (I) is considered to be the structure of dihydro zingiberene, the following reactions may be summerised as follows,

\[
\text{dihydrozingiberene} \xrightarrow{\text{Kmno}_{4}} \text{C}_{12}\text{H}_{20}\text{O}_{5} \xrightarrow{\text{NaOBr}} \text{C}_{11}\text{H}_{18}\text{O}_{6} + \text{CHBr}_{3}
\]

10. With methyl acetylene dicarboxylate, Zingiberene forms an adduct but when hydrolysed it yields 1,6 dimethylocta-3-6-diene, and methyl 1,4- methyl phthalate. All the reaction could be explained if structure (IV) is the correct structure of zingiberene.

11. Finally the structure (iv) of zingiberene has been confirmed by its synthesis given by Battacharya and Mukerjee from methyl heptone and P-methoxy methyl magnesium bromide.
12) Stereochemistry

The structure (IV) of zingiberene is found to contain two chiral centres. As the acyclic chiral centre is stereochemically related to that in (+) citronellal where as the cyclic centre to that in (-) α - phellandrene. It means that (-) -zingiberene possesses the absolute configuration (IV)

12.6 BIOSYNTHESISOF TERPENOIDS

Biosynthesis of Terpenoids

(i) According to the special isoprene rule, terpenoids are built of isoprene units which are joined head to tail. This led to the belief that isoprene CH$_2$ = C(CH$_3$) CH=CH$_2$ is the Precursor of all the terpenoids.

(ii) Isoprene itself has never been isolated from natural resources. Therefore, the isoprene hypothesis was discarded but this hypothesis indicates that all the terpenoids contain at least C$_5$ until if not isoprene units. Bonner proved experimentally that C$_2$ units of terpenoids are synthesized in plants from C$_2$.

(iii) The bio synthesis of terpenoids can be explained in three steps.

(a) The formation of a biological isopentane unit (C$_5$) from acetate.

(b) The condensation of this unit to form cyclic terpenoids

(c) The conversion of acyclic into cyclic terpenoids.
(A) Biosynthesis of $C_5$ unit

i. Bonner proved that $C_5$ units of terpenoids are synthesized in plants from $C_2$ units. He employed isotopically labeled acetate $C_2$ and showed that this acetate gets incorporated into the ruler (Poly terpenoids. This study reveals that the rubber is biosynthesized in plants from acetate ($C_2$)

ii. In plants the acetate is converted into mevalonic acid.

iii. With COA-SH, the acetate is first converted into active acetate or acetyl –SCOA. The two molecules of active acetate undergo condensation to form acetoacetyl –SCOA which on further combination with another molecule of active acetate yields hydroxymethyl glutaryl –SCOA (HMG-SCOA). This is then reduced step wise (via-mevaldic acid) to mevalonic acid (MVA).

iv. According to Brodie and coworkers, the precursors for biosynthesis of mevalonic acid are acetate and malonate.

The formation of mevalonic acid as an intermediate in the biosynthesis of terpenoid is supported by the following facts.

(a) Wolf isolated mevalonic acid from natural sources. Mevalonic acid is also formed from leucine.

(b) When synthetic mevalonic acid labeled with $^{14}$C is injected into plants, it is found incorporated into $\alpha$- pinene and rubber.

v. Mevalonic acid has been shown by tracer studies to be an efficient precursor of terpenes and steroids. Mevalonic acid has six carbon atoms while the isoprene unit has five carbon atoms. Therefore, if mevalonic acid is the precursor of isoprene units, it must lose one carbon atom at some stage.

vi. Synthesis of mevalonic acid labeled at the carboxyl group with $^{14}$C, and use of this material as a unlabelled Cholesterol. Hence, the carboxyl carbon is the one which has been lost.

vii. The conversion of mevalonic acid into “biological isoprene unit” has been shown to proceed by stepwise phosphorylation of both
alcohol group, then elimination and decarboxylation to yield 3-methyl-3-butanyl pyrophosphate (I)

viii. The formation of 3methyl-3-butanyl pyrophosphate (I) as the intermediate product has been proved on the basis of experiments carried out by Lynene et al. In which they were successful in converting 3-methyl-3-butenyl pyrophosphate into rubber (Poly terpenoids)

By using two kinds of labeled acetic acid \([^{14}CH_3COOH\text{ and } CH_3^{14}COOH]\), the following carbon atom distribution has been shown in \(C_5\) unit.

Where \(C_a\) represents the carbon atom derived from methyl group of \(^{14}CH_3\) COOH and \(C_b\) represents the carbon atom derived from carbonyl group of \(^{14}CH_3\) COOH.

From the above, the biogenetic isoprene unit is 3-methyl-3-butenyl pyrophosphate (I). However, its participation in the biosynthesis of terpenoids involves its equilibration, in the presence of the appropriate enzyme, with 3-methyl-2-butenyl (\(\beta,\beta\) - dimethyl allyl) Pyro phosphate (II).
ix. In addition to the isoprene and special isoprene rule, another rule known as biogenetic isoprene rule has been formulated on the basis of biosynthetic studies. According to this rule, the members of the isopentane group should be derivable from simple hypothetical precursors like geraniol, farnesol and squalene.

The biogenetic isoprene rule also takes into account that such compounds have originated from regular isoprenoid precursors which by rearrangement or degradation yield products which do not obey the isoprene rule (e.g: gibberellins)

B) Condensation of C5 units to form the Acyclic Terpenoids

(i) The experimental evidence so far available supports the fact that units (I) and (II) may undergo an enzyme-induced carbocation type of polymerization to form geranyl pyrophosphate. In this polymerization, (I) is acting as the nucleophilic reagent and (II) as the electrophilic reagent to give head to tail union.

(ii) Formation of a cis double bond in gerenyl pyrophosphate (III) gives rise to nerylpyro phosphate(IV).

(iii) Neryl pyrophosphate acts as a precursor for the biosynthesis of acyclic terpenoids.
(iv) The continuation of head-to-tail addition of five-carbon units to geranyl (or neryl) pyrophosphate can proceed in the same way to farnesyl pyrophosphate.

(C) Conversion of Acyclic into Cyclic Terpenoids

Geranyl pyrophosphate via the cis-isomer neryl pyrophosphate and farnesyl pyrophosphate formed as above serve as the key substances in the biosynthesis of cyclic mono-, sesqui-, di-, tri-, and tetra-terpenoids. ex: α - Terpinene, α - pinene.

α - Terpinene, a mono-terpenoid

Geranyl pyrophosphate serves as the precursor for the biosynthesis of monocyclic terpenoid via the cis isomer neryl pyrophosphate. The mechanism takes place via ionic intermediates.
Terpenes

NOTES

Check Your Progress

1. What is the role of Wagner work in terpene?
2. Draw the chemical reaction of \( \alpha \)-pinene to camphene.
3. Give the major product in the following reaction
4. Mention the role of Mevalonic acid to terpene.

12.7 ANSWER TO CHECK YOUR PROGRESS QUESTION

1. The reactions of \( \alpha \)-pinene could be explained if the formula of \( \alpha \)-pinene is considered to be (I) as given by Wager. However, Wagner’s work provides no direct evidence for the existence of the cyclobutane ring which was provided by Baeyer in method I.

2. 

3. \( \text{C}_{15} \text{H}_{24} + 2\text{HCl} \rightarrow \text{C}_{15} \text{H}_{26} \text{Cl}_2 \).

4. Mevalonic acid has been shown by tracer studies to be an efficient precursor of terpenes and steroids. Mevalonic acid has six carbon atoms while the isoprene unit has five carbon atoms.

12.8 SUMMARY

Terpenes are unsaturated compounds formed by joining together isoprene units. They are components in a wide variety of fruit and floral flavors and aromas. Terpene can be oxidized with in plants to produce the compounds responsible for the distinctive aroma of spices. It is a natural organic compound, they are used in perfumes, essential oils and medicines. Common
spices containing terpenes include cloves, cinnamon and ginger. The can oxidized to a form terpenoids. It was containing oxygen or other functional groups are known as terpenoids. Isoprene units can be linked to head and tail to form linear terpenes and in rings to form cyclic terpenes. They have not any side effect because its presence in plants and give it’s the special aromatic odor. However terpenes like any compound else should not used excessively because that reduces the advantages of terpenes.

### 12.9 KEY WORDS

- Camphor
- Zingiberene
- Pinene

### 12.10 SELF-ASSESSMENT QUESTION AND EXERCISES

1. What are the properties and uses of terpenes?
2. Difference between terpenes and terpenoid.
3. What are types of terpene?
4. Write the notes on mevalonic acid?
5. Explain the Wagner work to terpenes.

### 12.11 FURTHER READINGS

UNIT - 13 VITAMINS

Structure
13.1 Introduction

13.2 Objectives

13.3 Chemistry and physiological action
   13.3.1 Ascorbic acid
   13.3.2 Thiamin
   13.3.3 Riboflavin
   13.3.4 Pyridoxine

13.4 Elementary aspect of vitamins
   13.4.1 Vitamin-A
   13.4.2 Vitamin-E
   13.4.3 Vitamin –K
   13.4.4 Vitamin –B₁₂

13.5 Answer to check your progress question

13.6 Summary

13.7 Keywords

13.8 Self-assessment question and exercises

13.8. Further readings

13.1 INTRODUCTION

Vitamins are organic compounds required by the body in small amounts for normal growth various metabolic process, maintains of animal and including man. They are defined as potent organic compounds occurring in varying and minute proportion in food, which must be available the organisms in order that physiological process is essential to life many precede normally.
Classification of vitamins

Vitamins are classified into two types

1. **Fat soluble vitamins.**
   
   (Example: Vitamin A, D, E and K) and

2. **Water soluble vitamins.**
   
   (Example: Vitamin B and C)

   - There absence causes deficiency diseases
   - All contain C, H and O. It can also contain some N and S.
   - Each have a unique Chemical structure. It singular unit.
   - Perform numerous essential functions, some with more than one role in metabolism.
   - There either participate the production of co-enzyme (examples: B₁, B₂, B₆, B₁₂ and D) or act as regulate as biochemical processes
   - Vitamins also acts as redox agents (examples: A, C, E and K)
   - They also act as nuclear reagents (examples: Biotin, tollic acid)
   - Plant synthesis all vitamins (animals cannot synthesis all vitamins)
   - Vitamins are also known as accessory dietary factors
   - Vitamins are necessary to body only in small amounts

Vitamins are named with alphabet in the order of their discovery. Examples: Vitamin A, B₁, B₂, B₆, B₁₂, C, D and etc…

### 13.2 OBJECTIVES

After going through this unit, you will be able to

- Identify potential vitamin or minerals deficiencies for athletes
- Provide recommendations for improving vitamin & mineral intake.
- Evaluate need and appropriateness of supplements
Know the role of vitamins and minerals in energy system and important for sports performance.

Understand free radicals & antioxidants in relation to exercise.

13.3 CHEMISTRY AND PHYSIOLOGICAL ACTION OF ASCORBIC ACID

Chemical name : Ascorbic acid

Molecular formula: C\textsubscript{6}H\textsubscript{8}O\textsubscript{6}

Molecular mass : 176.12 g/mole.

Chemical name : 2-oxo-1-threo-hexone-1, 4-lactone-2, 4-dihydroxy-5-\{(s)-1, 2- dihydroxyethyl\} furan 2(5H) one.

Structure :

Ascorbic acid widely present in nature, mostly found in fresh fruits and vegetables.

Animal source of Ascorbic acid like fish, meat, poultry, eggs, dairy products not contain significant amount they comprise smaller amount of Vitamin C. It is very labile molecule and lost during preparation, cooking, storage. Ascorbic acid is commonly found in L-(+)-ascorbic acid. It is highly reducing agent this chemical behavior of Ascorbic acid is due to enediol structure conjugated with a carbonyl group (a lactone) which make this very sensitive to different ways of degradation.

- To prevent the loss of Vitamin C
- Take raw form of fruits and vegetables.
- Steam or boil the food for short time.

All plants and animals synthesis Ascorbic acid by D- glucose or D-glalactose and in animals this phenomenon is done in liver. Synthetic Ascorbic acid is available in a wide variety of supplements like, tablets, capsules, chewable tablets, crystalline powder, effervescent tablets and liquid form.
13.3.1 Ascorbic acid

Synthesis of Ascorbic acid

\[
\begin{align*}
D\text{-}Glucose & \xrightarrow{\text{Hydrogenation}} D\text{-}Sorbitol \\
D\text{-}Sorbitol & \xrightarrow{\text{Oxidation (by Acetobacter suboxydans)}} L\text{-}Sorbose \\
L\text{-}Sorbose & \xrightarrow{\text{Air oxidation (Carboxyl group add on C3)}} \text{Diacette-2-keto-L-gulonic acid} \\
\text{Diacette-2-keto-L-gulonic acid} & \xrightarrow{\text{Heating (with hydrochloric acid)}} L\text{-}Ascorbic acid
\end{align*}
\]

Metabolism of ascorbic acid

Ascorbic acid is an electron donor (antioxidant) this function of this preform all type of biochemical and molecular role in body. It should be easily available through the different source of food which is important for human diet and easily absorbed by the active transport system in the intestine.

In normal required amount it should be easily absorbed in body about 80-85% but it cannot be store in body. If its quantity increases the rate of absorption rapidly declines and. Ascorbic acid is not protected for long time because it is very sensitive to air, temperature, light and moisture. By all these factors its shows maillard degradation reaction and organoleptic properties of Vitamin C changed. The major metabolites of Ascorbic acid are dehydroascorbic acid, 2, 3 diketogluconic acid and oxalic acid. The main route of elimination of Ascorbic acid is renal through urine.

Physiological functions of ascorbic acid

The Physiological functions of Ascorbic acid is totally depends on redox property of Vitamin. This Vitamin is the co-factor for hydroxylases and monooxygenase enzyme involved in the synthesis of collagen, caritine and neurotransmitters. Ascorbic acid is also important for maintain the enzyme prolyl and lysyl hydroxylase. Its deficiency results in reduced hydroxylation of proline and lysine, thus affecting collagen synthesis. Ascorbic acid is essential for the synthesis of muscle caritine (β-hydroxyl butyric acid) 18. Caritine is used for energy production through fatty acid
into mitochondria. In addition, Ascorbic acid catalyzes other enzymatic reactions involving amidation necessary for maximal activity of hormones oxytocin, vasopressin, cholecystokinin and alpha-melanotripin. Deficiency of Ascorbic acid is also cause cholesterol gall stones.

13.3.2 Thiamin

**Chemical name**: Thiamin / Aneurin

**Molecular formula**: \( \text{C}_\text{12}\text{H}_{18}\text{ON}_4\text{SCl}_2 \)

**Structure**:

![Thiamin Structure](image)

**Daily requirement**: 1.0 mg

**Deficiency diseases**: Beri-Beri, impairment of nervous systems, loss of appetite, weight loss, fatigue hear disorder.

**Sources**: It occurs in rice polishing, yeast, wheat, nuts, egg, milk, green vegetables, peas and beans.

**Structural Elucidation**

- Molecular formula of this compound was found to be \( \text{C}_\text{12}\text{H}_{18}\text{ON}_4\text{SCl}_2 \).
- When thiamine is treated with \( \text{Na}_2\text{SO}_3 \) saturated with \( \text{SO}_2 \) at room temperature gives two products A&B.

\[
\text{C}_\text{12}\text{H}_{18}\text{Cl}_2\text{O}_4\text{S} + \text{Na}_2\text{SO}_3 \xrightarrow{\text{SO}_2} \text{C}_6\text{H}_9\text{N}_3\text{O}_2\text{S} + \text{C}_6\text{H}_9\text{N}_3\text{O}_3\text{S} + 2\text{NaCl}
\]

I. Constitution of compound A

1. Molecular formula is \( \text{C}_6\text{H}_9\text{NOS} \)
2. **Presence of Tertiary Nitrogen**: It forms quaternary ammonium salt with one mole of methyl iodine which indicates the fact that the nitrogen atom present here is tertiary type.

3. **Presence of Primary -OH group**: Then compound is treated with HCl, the OH group is replaced by Cl to give a chloro derivative. The UV spectrum of this compound has been found to be the same as that of A, which indicates the presence of primary -OH group.

4. **Presence of sulphur in Heterocyclic Ring**: The absorption spectrum of A is similar to that of thiazone ring. It indicates that the sulphur atom present in heterocyclic ring.

5. **Oxidation**: Compound A on oxidation with HNO₃ and gives C₅H₅NO₂S which has been identified as 4-methyl-thiazole 5-carboxylic group but the side chain must contain OH group. The side chain could be either –CH₂CH₂OH (or) –CHOHCH₃ group. Based on the above information the following two structures, structure I and structure II are given below.

![Structure I and Structure II](image)

But compound A is optically inactive. This could be explaining only by structure proof because it is optically inactive. Therefore the structure II is confirmed by synthesis. Compound A is synthesized by following method.

II. **Constitution of compound B**

1. **Molecular formula** is C₆H₉N₃O₃S

2. **Presence of Sulphonic acid**: When compound B is treated with water under pressure at 200°C gives out sulfuric acid, which indicates the presence of sulfonic acid.
3. **Presence of Amino group:** Compound B reacts with Nitrous acid (HNO$_2$) gives out nitrogen gas. This indicates the presence of one or more amino group.

4. **Presence of Pyrimidine group:** The above reaction evolution of nitrogen was slow and the reaction of B with benzoyl chloride ($C_6H_5COCl$) was also slow. This suggests that ‘B’ contains the pyrimidine structure. On heating the compound B with HCl at 150$^\circ$C under pressure gives compound C and NH$_3$ by the replacement –NH$_2$ group by OH group. This is a characteristic reaction for pyrimidine group UV spectrum of compound ‘C’ is similar that of the pyrimidine having –OH group at position 4. This suggests that compound B should probably a 4-amino pyrimidine. When it is reduced with Na and liquid NH$_3$, it gives 4-amino-2, 5-dimethyl pyrimidine. This is confirmed by its synthesis.

![](image1.png)

5. **Position of sulphonic acid**

When 4-amino 2, 5-dimethyl pyrimidine is treated with sodium sulphide. It gives 4-hydroxy-2-methyl pyrimidine-5-methyl sulphonic acid, which was identical; the above structure is given below.

![](image2.png)

Thus compound B possess as the following structure

![](image3.png)

Structure B is confirmed by following synthesis.
6. Attachment of A and B in Thiamine

Thiamine does not possess SO\textsubscript{3}H group. But it gets introduced into the compound. When thiamine is treated with sodium sulfate (Na\textsubscript{2}SO\textsubscript{3}) which indicates the point of attachment of B is at the methylene group in position 5, should be linked to the compound (A) by means of methylene bridge.

Fragment (B) must be linked to nitrogen atom of fragment (A). The nitrogen atom thiazole ring is in a quaternary state and so the accounts for the thiamine hydrochloride. It compound B is connected to A through the carbon atom, it could not be easy to account for the fission of the C-C bond by means of Na and liquid NH\textsubscript{3}, also does not form di-hydrochloride. Based on the above information the following structure is proposed for vitamin B\textsubscript{1},

![Structure of vitamin B\textsubscript{1}]

**Synthesis**

![Synthesis of thiamine]
Vitamins

NOTES

13.3.3 Riboflavin

IUPAC name: 6, 7-dimethyl-9-[ribityl] iso-alloxazine

Chemical name: Riboflavin

Molecular formula: \( C_{17}H_{20}O_{6}N_{4} \)

Daily requirement: 2.0 mg

Deficiency diseases: Skin diseases like dermatitis, sore tongue, fissuring of the corners of the mouth and lips.

Sources: It occurs in yeast, liver, kidney, heart, wheat, milk, green vegetable, rice polishing, leaf vegetables, potato, nuts and egg.

Structural Elucidation

1. A solution of Riboflavin in sodium hydroxide (NaOH) is exposed to light, it is lumihactoflavin. Lumi-lactoflavin as the molecular formula is \( C_{13}H_{12}N_{4}O_{2} \).

   \[
   \begin{align*}
   C_{17}H_{20}O_{6}N_{4} & \xrightarrow{\text{NaOH, light}} C_{13}H_{12}N_{4}O_{2} \\
   \text{Riboflavin} & \quad \text{Lumi-lactoflavin}
   \end{align*}
   \]

2. On boiling with \( \text{Ba(OH)}_{2} \) solution it gives urea and Barium salt of a \( \beta \)-Keto carboxylic acid (I).

   \[
   \begin{align*}
   C_{17}H_{20}O_{6}N_{4} & \xrightarrow{2\text{Ba(OH)}_{2}} H_{2}N-\text{CO-}NH_{2} + [C_{12}H_{2}N_{2}O_{3}] \\
   \text{Riboflavin} & \quad \text{urea I}
   \end{align*}
   \]

3. The Barium salt of (I) on acidification eliminates a molecule of \( \text{CO}_2 \) immediately forms compound (II).
4. The compound shows the properties of the lactone on vigorous hydrolysis with NaOH solution, the compound (II) forms glyoxalic acid and compound (III).

\[
\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3 \xrightarrow{\text{acidification}} \text{C}_{11}\text{H}_{12}\text{N}_2\text{O} \xrightarrow{-\text{CO}_2} \]

\[
\text{C}_{11}\text{H}_{12}\text{N}_2\text{O} \xrightarrow{\text{NaOH}} \text{CHO} + \text{COOH} + \text{C}_9\text{H}_{14}\text{N}_2
\]

Glyoxalic acid  \(\text{III}\)

Compound (III) was shown to be an aromatic diamino compound. Compound (III) gives a blue precipitate with FeCl₃. This reaction and it is the characteristic reaction of mono-O-phenylene diamine. Therefore, compound (III) contains, the nucleus of compound (IV), comparing the formula of compound (III) and compound (IV) is clear that, comparing the formula of compound (III) and compound (IV) is clear that we have to account for 3 carbon and 4 H atoms. This can be done by assuming the presence of an ethyl group or of two methyl group in compound (IV). The structure (III) is confirmed by following synthesis,

**Synthesis of riboflavin**

\[
\text{HC}_3\text{H}_2\text{C} \xrightarrow{\text{HNO}_3} \text{HC}_3\text{H}_2\text{C} \xrightarrow{\text{NH}_3 \text{EtOH}} \text{HC}_3\text{H}_2\text{C}
\]

Tosylchloride
Then I must be as follows,

\[ \text{TS} \rightarrow \text{H}_{2}\text{SO}_{4} \]

So, II must be as follows,

From the above reaction the structure of lumi-lactoflavin is known as follows,

The structure of lumi-lactoflavin is confirmed by the following synthesis.
The side chain of Riboflavin

- When a neutral solution of lactoflavin is exposed lumi-chorme is obtained. Its molecular formula is shown be \( \text{C}_{12}\text{H}_{10}\text{N}_{4}\text{O}_{2} \). Analytical work similar to that describe for lumi-lactoflavin shown that the structure of the lumi-chorme is 6, 7-dimethyl alloxazine (A).

- The structure (B), alloxazine is a tautomer of A. This lumi-lactoflavin with a hydrogen atom instead of a methyl group at position 9. This suggests that Reboflavin contains a side chain attached to be position 9.

- B-zerewittin off procedure shows that riboflavin, containing 5 active ahydrogen atoms. Therefore the molecule contains 4 hydroxy groups, the 5th active hydrogen is the one of the NH group of position 3. The silver salt of Riboflavin, silver atom in the place of hydrogen of NH group in position 3, from tetracetate. This facts also supports the presence of 4 hydroxy groups.

- On oxidation with Lead tetra acetate forms formaldehyde. Therefore the side chain contains a terminal \(-\text{CH}_{2}\text{OH}\) group.

- Riboflavin forms a di-isopropylidine derivative. Therefore there are two 1, 2 glycol systems.

- Based on the above information the following structure is proposed by Riboflavin.
The above structure is conformed by following synthesis.

13.3.4 Pyridoxine

Chemical name: Ergocalciferol
Molecular formula: C_{28}H_{44}O
Daily requirement: 12.0 mg
Deficiency diseases: Rickets, impairment of both teeth & bones.
Sources: Fish liver oils, egg yark, and milk.
1. **Presence of secondary Alcoholic group**

Formation of monoester on esterification and formation of ketone on oxidation indicate the presence of secondary alcoholic group.

\[
\text{C}_{28}\text{H}_{44} \xrightarrow{(O)} \text{Ketone}
\]

2. **Nature of side chain**

On ozonolysis it gives methyl-iso propyl acetaldehyde which is also obtained by Ozonolysis of Ergosterol. It indicates the side chain is same as that of Ergosterol.

\[
\text{C}_{28}\text{H}_{44} \xrightarrow{\text{Ozonolysis}} \text{methyl-iso-propyl acetaldehyde}
\]

3. **Presence of 4-Double bonds**

On catalytic reduction it takes up 4 molecules of hydrogen to form octa hydro ergocalciferol which indicates the presence of 4-double bonds out of this one is presence in side chain.

\[
\text{C}_{28}\text{H}_{44} \xrightarrow{\text{Reduction}} \text{Octa hydro ergocalciferol}
\]
And other three is in the nucleus of the vitamin. UV spectrum and the formation of adduct (combination of donor and acceptor compound) with Maleic anhydride conforms the above fact.

\[
\text{Maleic anhydride} \quad \text{adduct formation}
\]

4. Presence of 3-Rings

The molecular formula of the parent hydrocarbon of vitamin D₂ is \( \text{C}_{28}\text{H}_{52} \), which corresponds to the general formula of \( \text{C}_n\text{H}_{2n-4} \). From this it is understood that the compound is tricyclic one.

It does not form Diel’s Hydrocarbon when distilled with selenium, it indicates that it does not contain 4-cyclic ring system of Heterosterol and one of the rings Ergosterol has been opened in the formation of vitamin D₂. This is confirmed by following reaction.

i. Formation of formaldehyde shows the presence of methylene group is found to be C-10 based on the fact that the ring B is opened at C-9 and C-10.

ii. The formation keto acid suggest that the ring B is opened at C-9, C-10 and that there are two double bonds at C-7, C-8, C-22 and C-23.

iii. The position of the later double bond is confirmed by the isolation of methyl isopropyl acetaldehyde. Based on all of the above facts, the structure vitamin D₂ represent as given below.
Synthesis of vitamin D

Check your progress

1. Definition of vitamins.
2. Physiological function of ascorbic acid?
3. Draw the structure of thiamin
4. Source of riboflavin?

13.4. ELEMENTARY ASPECT OF VITAMINS

13.4.1. Vitamins-A

They are two general types

- Pre-formed retinoids are found in animal products
- Precursor’s carotenoids are found in plant products beta carotene, lutein, lycopene, others must be converted to retinoids absorbed and converted by intestinal cells
Absorption of Vitamin A

The required bile, digestive enzymes, integration into micelles have dependent on the fat in the diet. Olestra 90% of retinoids can be absorbed. Only ~3% of carotenoids are absorbed so eat your carrots. Intestinal cells can convert carotenoids to retinoids.

Transport in body/storage

Liver stores 90% of vitamin A in the body polar bear liver.
- Reserve is adequate for several months.
- Transported via chylomicrons to the liver.
- Transported from the liver as retinol via retinol-binding protein to target tissue.
- Carotenoids can be transported via VLDL.

Functions of Vitamin A

Night and color vision xerophthalmia Cell health and maintenance epithelial cell differentiation and division cells deteriorate without V[A follicular hyperkeratosis Antioxidant.

Source of vitamin

Retinoids – animals: Liver, fish oils, fortified milk, eggs 50% of vitamin A intake is from these sources.

Carotenoids – plants: Dark green leafy yellow orange the other 50%.

Deficiency
- Chronic Deficiency => Night Blindness.
- Prolonged deficiency => Xerophthalmia – pathologic dryness of conjunctiva and cornea of eye.
- Deficiency can lead to keratinization of epidermis
- Epithelial cells cannot secrete mucus and unable to function properly, promoting infection.

13.4.2 Vitamin E

Vitamin E is a group of eight fat soluble compounds. That include four tocopherols and four tocotrienols. which is rare and usually due to an underlying problem with digesting dietary fat rather than from a diet low in is a fat-soluble antioxidant protecting cell membranes from reactive oxygen species. Alpha-tocopherol most active form in body and synthetic form in supplements only ½ as active.

Function
Vitamin E may have various roles as a vitamin. Many biological functions have been postulated, including a role as a fat-soluble antioxidant.

In this role, vitamin E acts as a radical scavenger, delivering a hydrogen (H) atom to free radicals. At 323 kJ/mol, the O-H bond in tocopherols is about 10% weaker than in most other phenols.

This weak bond allows the vitamin to donate a hydrogen atom to the peroxyl radical and other free radicals, minimizing their damaging effect.

The thus-generated tocopheryl radical is recycled to tocopherol by a redox reaction with a hydrogen donor, such as vitamin C. As it is fat-soluble, vitamin E is incorporated into cell membranes, which are therefore protected from oxidative damage.

Vitamin E affects gene expression and is an enzyme activity regulator, such as for protein kinase C (PKC) – which plays a role in smooth muscle growth – with vitamin E participating in deactivation of PKC to inhibit smooth muscle growth.

General chemical structure of tocopherols

![Chemical structure of tocopherols](image)

**Alpha-tocopherol**

![Structure of Alpha-tocopherol](image)

**Toxicity and Deficiency**

- No risk of too much vitamin E from food sources
- Too much synthetic form may risk of a hemorrhage.
- Deficiency Symptoms in Adults
- Mild Anemia, Fragile RBCs
- Neurological Damage
- Disorders related to Reproduction and Infertility
Muscle, liver, bone marrow brain abnormalities

Decrease in Sex Drive

13.4.3 Vitamin K

Vitamin K plays a key role in helping the blood clot, preventing excessive bleeding. Unlike many other vitamins, vitamin K is not typically used as a dietary supplement. Vitamin K is actually a group of compounds. The most important of these compounds appears to be vitamin K1 and vitamin K2. Vitamin K1 is obtained from leafy greens and some other vegetables. Vitamin K2 is a group of compounds largely obtained from meats, cheeses, and eggs, and synthesized by bacteria.

There are three categories

i. Menaquinone from intestinal bacteria. K1

ii. Phylloquinone is found in green plants. K2

iii. Menadione

Vitamin K1 is the main form of vitamin K supplement available in the U.S. Recently, some people have looked to vitamin K2 to treat osteoporosis and steroid-induced bone loss, but the research is conflicting. At this point there is not enough data to recommend using vitamin K2 for osteoporosis.

Vitamin K Absorption and Transport

1. Most absorbed in Jejunum.
2. We only get ~10% vitamin K from our bacteria.
3. Into chylomicrons and to liver.
4. When a diet is deficient in vitamin K storage forms are transported by VLDL, LDL, and HDL.
5. Uses of vitamin K for cancer, for the symptoms of morning sickness, for the removal of spider veins, and for other conditions are unproven.

Take drugs that interfere with vitamin K absorption

1. Are severely malnourished
2. Drink alcohol heavily
3. Stored mostly in liver

Natural Foods Rich in Vitamin K1 and K2

- Green Leafy Vegetables (Kale) ½ c: 444 mcg (over 100% DV)
- Natto (Fermented soy) 2 oz: 500 mcg (over 100% DV)
- Spring Onions (Scallions) ½ c: 103 mcg (over 100% DV)
- Brussels Sprouts ½ c: 78 mcg (98% DV)
- Cabbage ½ cup: 82 mcg (over 100% DV)
Vitamins

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- Broccoli ½ c: 46 mcg (58% DV)
- Dairy (Fermented) ½ c: 10 mcg (10% DV)
- Prunes ½ c: 52 mcg (65% DV)
- Cucumbers 1 med: 49 mcg (61% DV)
- Dried basil 1 Tbsp: 36 mcg (45% DV)

13.4.4 Vitamin B 12

Vitamin B-12 is a water-soluble vitamin, like all other B-vitamins. This means it can dissolve in water and travel through the bloodstream. The human body can store vitamin B-12 for up to four years. Any excess or unwanted vitamin B-12 is excreted in the urine. Vitamin B-12 is the largest and most structurally complicated vitamin. It occurs naturally in meat products and can only be industrially produced through bacterial fermentation synthesis.

Foods

Vitamin B-12 can be found naturally in animal products, such as fish, meat, eggs, and dairy products. It does not typically occur in plant foods.

Good dietary sources of vitamin B-12 include

- Beef, pork, ham, poultry, lamb
- Fish, especially haddock and tuna
- Dairy products, such as milk, cheese, and yogurt
- Some nutritional yeast products
- Egg

Some types of soya milk and breakfast cereals are fortified with vitamin B-12. It is always better to maintain a balanced diet and receive healthful amounts of nutrients before active treatment is required. The symptoms of deficiency are easily avoided with a healthful diet.

Benefits

- Vitamin B-12 is crucial to the normal function of the brain and the nervous system. It is also involved in the formation of red blood cells and helps to create and regulate DNA.
- The metabolism of every cell in the body depends on vitamin B-12, as it plays a part in the synthesis of fatty acids and energy production. Vitamin B-12 enables the release of energy by helping the human body absorb folic acid.
The human body produces millions of red blood cells every minute. These cells cannot multiply properly without vitamin B-12. The production of red blood cells reduces if vitamin B-12 levels are too low. Anemia can occur if the red blood cell count drops.

**Deficiency**

- Infants who lack vitamin B-12 may demonstrate unusual movements, such as face tremors, as well as reflex problems, feeding difficulties, irritation, and eventual growth problems if the deficiency is left untreated.
- Vitamin B-12 deficiency carries a serious risk of permanent nerve and brain damage. Some people with insufficient vitamin B-12 have a higher risk of developing psychosis, mania, and dementia.
- Insufficient vitamin B-12 can also lead to anemia. The most common symptoms of anemia are fatigue, shortness of breath, and an irregular heartbeat. People with anemia might also experience:
  - a sore mouth or tongue
  - weight loss
  - pale or yellowing skin
  - diarrhea
  - menstrual problems

Vitamin B-12 deficiency also leaves people more susceptible to the effects of infections.

### Check your progress

5. Function of vitamin –A

6. What are the natural foods in vitamin K?

7. Benefit the vitamin B₁₂

### 13.5 ANSWER TO CHECK YOUR PROGRESS QUESTION

1. Vitamins are organic compounds required by the body in small amounts for normal growth various metabolic process, maintains of animal and including man. They are defined as potent organic compounds occurring in varying and minute proportion in food, which must be available the organisms in order that physiological process is essential to life many precede normally. Vitamins are classified in to two types: **Fat soluble vitamins.** (Example: Vitamin
A, D, E and K) **Water soluble vitamins.** (Example: Vitamin B and C)

2. The Physiological functions of Ascorbic acid is totally depends on redox property of Vitamin. This Vitamin is the co-factor for hydroxylases and monoxygenase enzyme involved in the synthesis of collagen, caritine and neurotransmitters. Ascorbic acid is also important for maintain the enzyme prolyl and lysyl hydroxylase. Its deficiency results in reduced hydroxylation of proline and lysine, thus affecting collagen synthesis. Ascorbic acid is essential for the synthesis of muscle caritine (β-hydroxyl butyric acid).

3. Structure:

   ![thiamine]

4. Source of riboflavin: It occurs in yeast, liver, kidney, heart, wheat, milk, green vegetable, rice polishing, leaf vegetables, potato, nuts and egg.

5. Functions of Vitamin A: Night and color vision xerophthalmia Cell health and maintenance epithelial cell differentiation and division cells deteriorate without V [A follicular hyperkeratosis Antioxidant.

6. Green Leafy Vegetables (Kale) ½ c: 444 mcg (over 100% DV) Natto (Fermented soy) 2 oz: 500 mcg (over 100% DV) Spring Onions (Scallions) ½ c: 103 mcg (over 100% DV)

7. Vitamin B-12 is crucial to the normal function of the brain and the nervous system. It is also involved in the formation of red blood cells and helps to create and regulate DNA. The metabolism of every cell in the body depends on vitamin B-12, as it plays a part in the synthesis of fatty acids and energy production. Vitamin B-12 enables the release of energy by helping the human body absorb folic acid.

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**13.6 SUMMARY**

Fat-soluble vitamins: These vitamins dissolve in fats (lipids). They are stored in the liver and in fatty tissues. If too much of the fat-soluble vitamins A or D are consumed, they can accumulate and may have harmful effects. Because fats in foods help the body absorb fat-soluble vitamins, a low-fat diet may result in a deficiency. Some disorders interfere with absorption of fats and thus of fat-soluble vitamins. Examples are chronic diarrhea, Crohn disease, cystic fibrosis, certain pancreatic disorders, and blockage of the bile ducts. Some drugs, such as mineral oil, have the same effect. Fat-soluble vitamins dissolve in mineral oil, which the body does not absorb. So when people take mineral oil, it carries these vitamins.
unabsorbed out of the body. Cooking does not destroy fat-soluble vitamins. Water-soluble vitamins: These vitamins dissolve in water. They are eliminated in urine and tend to be eliminated from the body more quickly than fat-soluble vitamins. Water-soluble vitamins are more likely to be destroyed when food is stored and prepared. The following can help prevent the loss of these vitamins: Refrigerating fresh produce, Storing milk and grains out of strong light, using the cooking water from vegetables to prepare soups.

13.7 KEY WORDS

- Vitamins
- Riboflavin
- Thiamin
- Structural Elucidation
- Deficiency

13.8 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Why do people take vitamin k?
2. Structural elucidation of riboflavin
3. Deficiency of pyridoxine?
4. Source of vitamin
5. What are the foods available for vitamin B₁₂?
6. Synthesis of thiamin?

13.8 FURTHER READINGS

UNIT- 14 CHOLESTEROL AND STEROID

Structure

14.1 Introduction
14.2 Objectives
14.3 Structural elucidation of cholesterol
14.4 Biosynthesis of cholesterol
14.5 Structural elucidation of progesterone
14.6 Synthesis of progesterone
14.7 Answer to check your progress question
14.8 Summary
14.9 Keywords
14.10 Self-assessment question and exercises
14.11 Further readings

14.1 INTRODUCTION

Cholesterol, triglycerides, and high-density lipoproteins are important constituents of the lipid fraction of the human body. Cholesterol is an unsaturated alcohol of the steroid family of compounds. It is essential for the normal function of all animal cells and fundamental element of their cell membranes. It is also a precursor of various critical substances such as adrenal and gonadal steroid hormones and bile acids. Triglycerides are fatty acid esters of glycerol and represent the main lipid component of dietary fat and fat depots of animals. Steroids are members of a large class of organic compounds occurring widely in animals and plants. They have 1, 2 cyclopentanone perhydro phenanthrene nucleus in their structure. The steroids include variety of compounds namely sterols, sex hormone, Bile acids, vitamin-D, certain atrinal and cortical hormones etc. Cholesterol and triglycerides, being nonpolar lipid substances (insoluble in water), need to be transported in the plasma associated with various lipoprotein particles. Plasma lipoproteins are separated by hydrated density; electrophoretic mobility; size; and their relative content of cholesterol, triglycerides, and protein into five major classes: chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Sterols, another name is also known as steroid alcohols, are a subgroup of the steroids and an important class of organic molecules. They occur naturally in plants, animals, and fungi, and can be also produced by some bacteria. The most familiar type of animal sterol is cholesterol,
which is vital to cell membrane structure, and functions as a precursor to fat-soluble vitamins and steroid hormones.

### 14.2 OBJECTIVES

At the end of the lesson, participants should be able to

- Define cholesterol as the most important animal steroid.
- Know the bio synthesis steps for cholesterol.
- Identify the regulation and elucidation of cholesterol and progesterone.
- Describe the relationship between cholesterol and progesterone.

### 14.3 STRUCTURAL ELUCIDATION OF CHOLESTEROL

1. Structure of the nucleus
   i. Analysis and molecular weight determination corresponds to the molecular formula \( C_{27}H_{46}O \).
   ii. On acetylation, it gives monoacetate, indicating the presence of one \(-OH\) group.
   iii. It takes up two bromine atoms to give dibromocholesterol, indicating the presence of one double bond.
   iv. On reduction, it gives cholestanol, which on oxidation gives cholestanone, cholestanone on reduction gives cholestane.

\[
\begin{align*}
  \text{Cholesterol} & \xrightarrow{\text{H/Pr}} \text{Cholestanol} \\
  \text{I} & \xrightarrow{\text{CrO}_3} \text{Cholestanone} \\
  \text{II} & \xrightarrow{\text{Zn/Hg}} \text{Cholestane} \\
  \text{III} & \xrightarrow{\text{IV}}
\end{align*}
\]

- a) Conversion of I to II shows the presence of double bond.
- b) Oxidation of II to III shows that cholesterol is secondary alcoholic group in nature.
- c) Cholestanone (IV) is a saturated hydrocarbon and corresponds to the general formula \((C_{27}H_{48})_nH_{2n-6}\) and it is tetracyclic.
v. The formation of Diel’s hydrocarbon shows that cholesterol (in general steroids) contains cyclopentenophenanthrene nucleus.

vi. The size of the rings is explained by Blanc’s Rule.
   a) The 1, 5-dicarboxylic acids on heating with acetic anhydride forms a cyclic anhydride indicating the presence of a five membered ring.
   b) The 1, 6-dicarboxylic acids form cyclophentanone with elimination of CO$_2$ indicating the presence of six membered ring.

**Ring A**

Cholesterol & the cholic acids were converted into the dicarboxylic acid (A) which gave a cyclopentanone derivative on heating with acetic anhydride. Therefore the ring A is six membered.

- Conversion of III to IV indicates the presence of keto group in the ring.
- Conversion of IV to V indicates V is either 1, 6 or 1, 7-dicarboxylic acids (From Blanc’s rule).
- Cholestanone undergoes oxidation to give two isomeric dicarboxylic acids, this indicates that the keto group in cholestanone is flanked on either side by a methylene group (−CH$_2$COCH$_2$−). Therefore the hydroxyl group must be present in ring A at position 3.

**Ring B**

Cholestrol was converted into the tricarboxylic acid (B) which gave the cyclopentanone derivative. Hence, ring (B) is six membered.
Deoxycholic acid was converted into dicarboxylic acid (C) which gave a cyclic anhydride.

This reaction results in the form of seven membered cyclic anhydride. In this case, Blanc’s rule fails. But, it is six membered ring.

Ring D

5β-cholestan(e (coprostan(e) was converted into etiobilianic acid and this gave a cyclic anhydride. Hence, ring D is five membered.

2. Position of Double bond

Consider the following reaction for the position of double bond
The above reaction leads to the following outcome:

a) Conversion of I to II indicates the double bond in I is hydroxylated.

b) Conversion of II to III indicates that (of the three –OH groups present in II) the two –OH groups are secondary and the 3rd –OH group is tertiary in nature.

3. Position of hydroxyl group (–OH) and double bond

Consider the following reaction, Oxidation of IV to V (without loss of C-atom) shows that the two keto groups in IV must be present in different rings. Also it follows that the –OH group & the double bond in cholesterol must be in different rings.

(d.) Conversion of IV to VI indicates the two ketonic groups are in γ-position (γ-diketone) with respect to each other. This is possible only if the double bond is present in the position of V and VI the –OH group at position III.
### 4. Nature and position of the side chain

The formation of this volatile ketone (isohexyl methyl ketone) in the above reaction shows that this ketone is the side chain being at the carbon of the keto group (non-volatile). The above reactions do not show where the side chain is attached to the nucleus. If we assume, that it must be attached to C-17 in the above reaction can be formulated.

### 5. Nature of side chain

**Barbier-wieland Degradation**

Conversion of $5\beta$-cholestane to etiobilianic acid.
**B.W Degradation**

\[
\begin{align*}
\text{CH}_2 \quad \text{CH}_2 \quad \text{COOH} & \quad \xrightarrow{\text{B.W.}} \quad \text{CH}_2 \quad \text{COOH} \\
\text{CH}_2 & \quad \xrightarrow{\text{B.W.}} \quad \text{COOH}
\end{align*}
\]

a) The formation of acetone shows that the side chain terminates in an isopropyl group.

b) The conversion of IV to V shows that there is an alkyl group on the \(\alpha\)-carbon in the former compound IV.

c) Conversion of V to VI ketone is oxidized to 5β-etiamic with the loss of one carbon atom. Therefore the ketone must be a methyl ketone. So the alkyl group on \(\alpha\)-carbon atom in bis nor-5β-cholanic acid is a methyl group.

d) Now the carboxyl group in etianic acid is directly attached the nucleus. This is shown by the conversion of V to VI. The ketone etiocholanone obtained by step VI. On oxidation with \(\text{HNO}_3\) gives a dicarboxylic acid etiobilianic acid without any loss of carbon atom. Thus etiocholanone must be a cyclic ketone. Hence, it follows that there are 8-carbon atoms in the side chain which is represented by the following structure.

\[
\text{Ar} \quad \text{CH} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH} \quad (\text{CH}_3)_2
\]

6. **Position of the side chain**

The dicarboxylic acid of etiobilianic acid an anhydride when heated with \(\text{Ac}_2\text{O}\). Thus, the ketone etiocholanone is probably a five membered ring. And the side chain is attached to the five membered ring D.

7. **Actual point of attachment**

The formation of Diel’s hydrocarbon from cholesterol shows that the side chain is C-17. Since, Selenium-dehydrogenation the side chain to a methyl group. The position of C-17 is also supported by X-ray diffraction studies and surface film measurements. When the anhydride of etiobilianic acid is distilled with \(\text{Se},1,2\)-dimethyl phenanthrene is obtained. This shows the presence of phenanthrene nucleus in cholesterol and also gives evidence for the position of the C-13 angular methyl group.

**14.4 BIOSYNTHESIS OF CHOLESTEROL**

Bio-synthesis of cholesterol can be studied in three parts

1. Synthesis of mevalonic acid from acetyl CoA

2. Synthesis of squalene from mevalonic acid

3. Conversion of squalene to cholesterol
1. Acetyl CoA to Mevalonic Acid

Initially two molecules of acetyl CoA derived from fatty acid oxidation condense in the presence of acetyl CoA-acetyl CoA transferase, to form acetoacetyl CoA. Squalene of reactions are shown below:

\[
CH_3CO-CO-S-CoA + CH_3CO-S-CoA \rightarrow CH_3COCH_2CO-S-CoA + CoASH \quad (1)
\]

\[
CH_3CO-S-CoA + CH_3COCH_2CO-S-CoA \rightarrow \text{(acetoacetyl CoA)} \quad \text{(3-hydroxy-3-methylglutaryl CoA)}
\]

\[
\text{HOOCCCH_2CH_2CO-S-CoA} + \text{NADPH} + H^+ \rightarrow \text{HOOCCCH_2CH_2CO-S-CoA} + \text{NADP}^+ + \text{CoASH}
\]

\[
\text{HOOCCCH_2CH_2CO-S-CoA} \rightarrow \text{HOOCCCH_2CH_2CO-S-CoA} + \text{NADPH} + H^+
\]

\[
\text{Mevalonate 5-diphosphate}
\]

2. Synthesis of Squalene

3-Hydroxy-3-Methylglutaryl (HMG) CoA is formed in cytosol as well as mitochondria, but in cytosol it is used for steroid synthesis. Mevalonic acid is phosphorylated by two molecules of ATP in two successive steps:

\[
\text{HOOC-C}_2\text{H}_4\text{O-C}_2\text{H}_4\text{OH} + 2\text{ATP} \rightarrow \text{HOOC-C}_2\text{H}_4\text{O-C}_2\text{H}_4\text{OH} + 2\text{ADP}
\]

Mevalonate 5-diphosphate is decarboxylated:

\[
\text{HOOC-C}_2\text{H}_4\text{O-C}_2\text{H}_4\text{OH} + 2\text{ATP} \rightarrow \text{CH}_3\text{C}=\text{CH-C}_2\text{H}_2\text{O-P}O_2H_3 + \text{CO}_2 + \text{H}_2O + \text{ADP} + \text{Pi}
\]

Isopentyl diphosphate is a donor of prenyl groups which can exist in another isomer, dimethylallyl diphosphate:

\[
\text{CH}_3\text{C}=\text{CH-C}_2\text{H}_2\text{O-P}O_2H_3 \rightarrow \text{CH}_3\text{C}=\text{CH-C}_2\text{H}_2\text{O-P}O_2H_3 + \text{Pi}
\]

\[
\text{CH}_3\text{C}=\text{CH-C}_2\text{H}_2\text{O-P}O_2H_3 + \text{Pi} \rightarrow \text{CH}_3\text{C}=\text{CH-C}_2\text{H}_2\text{O-P}O_2H_3
\]

Geranyl diphosphate
One molecule of isopentyl diphosphate reacts with another molecule of dimethylallyl diphosphate to produce geranyl diphosphate, which condenses with another molecule of isopentyl diphosphate to form farnesyl diphosphate with the elimination of PPI (pyro phosphate of inorganic compound) at each step:

\[
\text{Geranyl diphosphate} + \text{Isopentyl diphosphate} \rightarrow \text{Farnesyl diphosphate}
\]

Now, two molecules of farnesyl diphosphate are condensed head-to-head to make a steroid ring of squalene as given below:

3. Squalene to cholesterol

Squalene is a 30-C structure which is transformed into lanosterol by microsomal enzymes and subsequently converted to cholesterol by removal of three methyl groups and saturation of double bonds in the side chain as given below:
Regulation of cholesterol synthesis

Certain quantity of cholesterol is ingested in the diet by human beings, but still about 2.0 g of cholesterol per day is synthesized in body tissues. It has been estimated that the half-life of cholesterol in rats is about 6 days and about 32 days in extrahepatic tissues. Excessive fatty acid oxidation, as occurs in diabetes, results in higher rate of cholesterol synthesis that subsequently appears in the blood. However, rate of synthesis is controlled by a rate-limiting step in which HMG CoA Reductase catalyzes the reduction of HMG CoA in endoplasmic reticulum. Concentration of cholesterol is not known to be effective in inhibiting cholesterol synthesis, though fasting certainly has an inhibitory effect.

14.5 STRUCTURAL ELUCIDATION OF ROGESTERONE

The main source of this hormone is corpus luteum but it also found in placenta, pregnancy urine and atrenal cortex.
Structure Elucidation

1) The molecular formula is C_{22}H_{30}O_{2}.
2) It shows the presence of 2 ketonic groups as it forms dioxime etc.
3) On catalytic reduction it forms dihydro progesterone indicating the presence of one double bond.
4) On catalytic reduction it takes up 3 molecules of hydrogen forming diol’s showing these by the presence of one double bond because 2 H molecules are utilized in the formation of two CHOH groups.
5) Therefore the parent hydro carbon of progesterone C_{22}H_{36} which corresponds to general formula C_{n}H_{2n-6} for tetra cyclic compounds.
6) X-ray analysis shows the presence of steroids nucleus which is further confirmed by synthesis, Cholesterol and Sigidosterol.

- This hormone is very sensitive to alkali indicating the presence of α, β-unsaturated ketonic group. It is also confirmed by UV absorption spectrum (λ_{max} = 240nm). This suggests the position of the double bond is between 4 and 5.

- Progestrone undergoes haloform with reaction of NaOH and halogen to form haloform, which shows the presence of >C = O group (or) methyl group.

- On the above basis progesterone may be assign in the following structure,

- The above structure is confirmed by following synthesis from cholesterol.
14.6 SYNTHESIS OF PROGESTERONE

Check your progress

1. What is Blanc’s rule?
2. Draw the structure of Progesterone.
3. Structural elucidation of cholesterol?
4. What are the three types of Bio-synthesis of cholesterol?
5. Synthesis of Squalene.

14.7 ANSWER TO CHECK YOUR PROGRESS QUESTION

1. Blanc’s rule: The 1, 5-dicarboxylic acids on heating with acetic anhydride forms a cyclic anhydride indicating the presence of a five membered ring. The 1, 6-dicarboxylic acids form cyclophapentanone with elimination of CO₂ indicating the presence of six membered ring.

2. Structure of Progesterone
4. Bio-synthesis of cholesterol can be studied in three parts
   1. Synthesis of mevalonic acid from acetyl CoA
   2. Synthesis of squalene from mevalonic acid
   3. Conversion of squalene to cholesterol

5. 3-Hydroxy-3-Methylglutaryl (HMG) CoA is formed in cytosol as well as mitochondria, but in cytosol it is used for steroid synthesis. Mevalonic acid is phosphorylated by two molecules of ATP in two successive steps:

14.8 SUMMARY

Cholesterol is a waxy, fat-like substance that's found in all the cells in your body. Your body needs some cholesterol to make hormones, vitamin D, and substances that help you digest foods. Your body makes all the cholesterol it needs. Cholesterol is also found in foods from animal sources, such as egg yolks, meat, and cheese. If you have too much cholesterol in your blood, it can combine with other substances in the blood to form plaque. Plaque sticks to the walls of your arteries. This buildup of plaque is known as atherosclerosis. It can lead to coronary artery disease, where your coronary arteries become narrow or even blocked.

14.9 KEYWORDS

- Cholesterol
- Progesterone
- Structural elucidation
- Barbier-wieland Degradation
- Steroid

14.10 SELF-ASSESSMENT QUESTION AND EXERCISES

1. Explain the structure of cholesterol.
2. Discuss the position of Double bond in cholesterol
3. Discuss the nature of Ring A, B and D of cholesterol.
4. Synthesis of progesterone from cholesterol
5. Structural elucidation of progesterone?

14.11 FURTHER READINGS

2. Behrman EJ, Gopalan V, Scovell WM (ed.). "Cholesterol and Plants".
Answer to all questions (10 × 2 = 20)
1. What is the importance of Sharpless asymmetric epoxidation?
2. Write hydroboration oxidation
3. How will you run Corey-Bakshi-Shibata reaction?
4. What is the terminology used in retrosynthesis?
5. Why need for protection compound?
6. Define terpene, terpenoid, isoprene and isoprene unit
7. How can you differ Maltose and cellobiose?
8. What are the main steps are followed in biosynthesis of alkaloids?
9. Draw the structure of any two vitamins
10. Progesterone is which type of hormone and draw the structure?

SECTION - B

Answer all questions (5 × 5 = 25)
11. (a). Describe the role of chromium in oxidation of alcohol to carbonyl

    Or

    (b). Compare and contrast metal based and non-metal based oxidations

12. (a). Write a reaction with mechanism of prevost reaction

    Or

    (b). Briefly discuss catalytic hydrogenation

13. (a). How will you protect and deprotect the organic compounds

    Or

    (b). Chemical and physiological action of riboflavin?

14. (a). Write a structural elucidation and stereochemistry of morphine?

    Or

    (b). Discuss the structure compound?

15. (a). Write about RNA transcription and translation

    Or

    (b). What are the classification of vitamin and discuss fat soluble vitamins
SECTION - C

Answer any three questions (3 × 10 = 30)

16. How the alkene to carbonyls compound based with bond cleavage using osmium and ruthenium oxidizing agent?
17. Discuss the retrosynthetic analysis of one and two group C-X disconnection with an example.
18. Explain the synthesis, structure and reactivity of indole, and oxazole.
19. Explain the biosynthesis of terpenoids.
20. What is cholesterol? Explain the structural elucidation of cholesterol.