Chemistry Notes 97

Que 1. What is Iron Overload Disorder? What are the reasons for Iron Overload and how this disorder can be treated ?

Chemistry 1st Year End Sem. A2 Batch New (1)

Ans :- Iron overload means accumulation of iron in the body from any cause.

The most important causes are:-

(i) Hereditary haemochromatosis (HHC) which is a genetic disorder.
(ii) Transfusional iron overload, which can result from repeated blood transfusion.
(iii) Iron overload also occur when body is unable to produce Porphyrin in sufficient amount.
(iv) It may also be caused by improper regulation of Fe level by Ferritin and Transferritin production.

Problem:- Iron overload causes serious problems. Iron is potentially toxic because it has the ability to produce harmful radicals by reaction with oxygen.

Treatment:

This disorder can be treated by Chelation therapy in which a ligand is administered to the body which bind with iron and allow it to be excreted out of the body.

Que 2. What is Chelation Therapy? Write the application of Chelation Therapy. or

Define Chelation Therapy and write the application of Chelation Therapy.

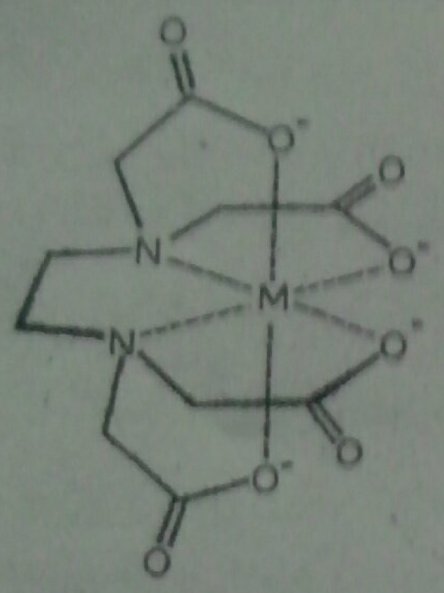
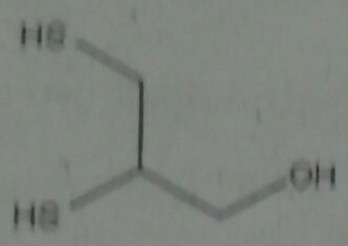
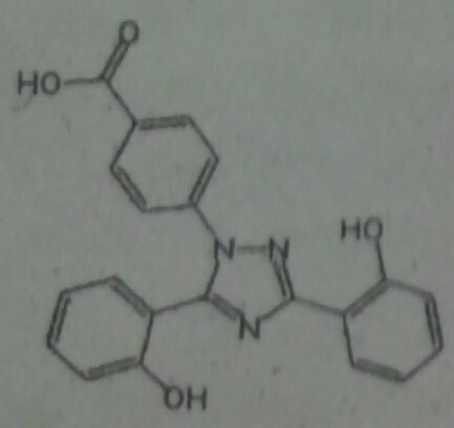
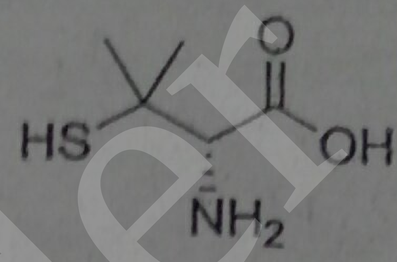
Chelation therapy is the administration of chelating agents to remove heavy metals from the body. Chelation therapy is used in clinical toxicology for the detoxification of heavy metals like lead, arsenic, mercury, and iron.

For example DMSA (dimercaptosuccinic acid) has been recommended for the treatment of lead poisoning in children. Similarly, $CaNa_2EDTA$ is also used in lead poisoning.

There are several chelating agents available which have different affinities for different metals. Common chelating agents with their application are as follow:

Sr. No	Chelating Agent	Uses/application in the treatment of
1	Deferoxamine and Deferasirox	Iron Overload and Acute Iron poisoning
2	Ethylenediamine tetraacetic acid (calcium disodium versante ($CaNa_2$-EDTA)	Lead poisoning
3	Dimercaptosuccinic acid (DMSA)	Lead, arsenic and mercury poisoning
4	Dimercaprol (British anti-Lewisite, BAL)	Lead, arsenic and mercury poisoning. Lewisite poisoning (for which it was developed as an antidote)
5	Penicillamine	Copper Toxicity

Structure of various Chelating agents used in Chelation Therapy:

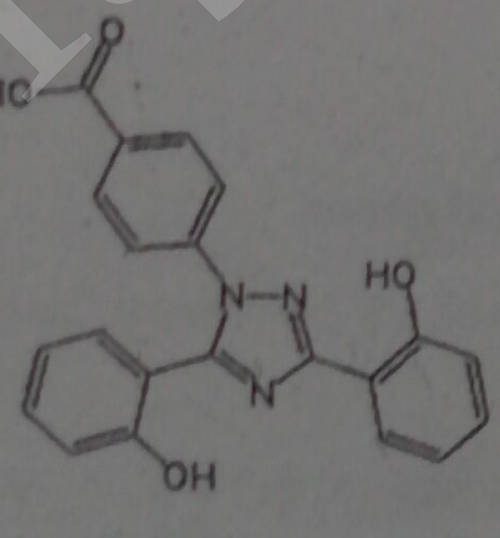
 Metal-EDTA chelate (Ethylenediamine tetraacetic acid)	 Dimercaprol or British anti-Lewisite (abbreviated as BAL)	DMSA (dimercaptosuccinic acid)
 Deferasirox	Deferoxamine	 Penicillamine

Que 3. What is Deferasirox ? Write the structure and function. What are the side effects of Deferasirox.

Deferasirox is an iron chelating agent which is administered orally. It was the first oral medication approved in the USA for this purpose. It is marketed as Exjade.

Function:- Its main use is to reduce chronic iron overload in patients who are receiving long-term blood transfusions due to chronic anemias.

Structure



Deferasirox

Side Effects: Kidney failure and cytopenias (Reduction in the number of blood cells eg RBC, WBC, Blood Platelets).

Que 4. What is the significance of Ferritin and Transferrins in biological system ?

Ans:- **Ferritin** is an intracellular protein that stores iron and releases it in a controlled fashion. The amount of ferritin stored reflects the amount of iron stored. This protein is produced by almost all living organisms, including algae, bacteria, higher plants, and

animals. In humans, it acts as a buffer against iron deficiency and iron overload. Ferritin that is not combined with iron is called apoferritin.

Transferrins are blood plasma glycoproteins that control the level of free iron in biological fluids. Transferrin glycoprotein binds iron very tightly, but reversibly. Human transferrin is encoded by the FT gene.

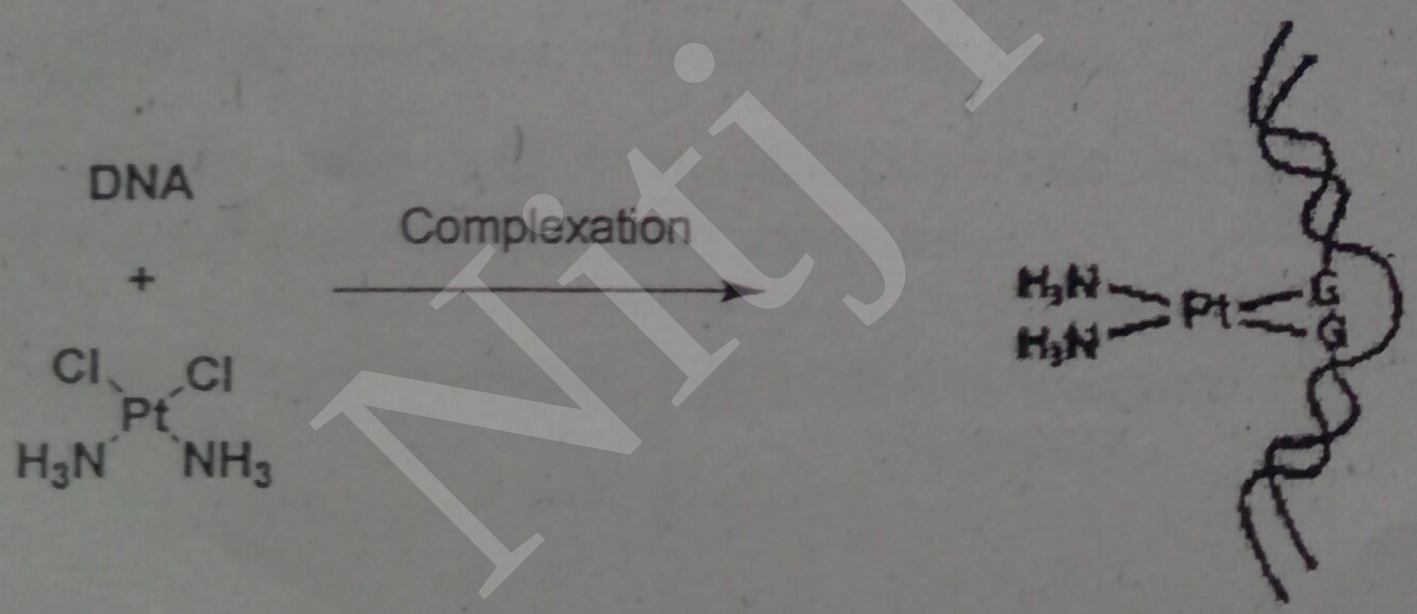
Que 5. What is Cis-Platin ? Write the molecular basis of mode of action of this drug.

Cis-Platin is a platinum complex that is used in the treatment of cancer.

Mode of action: The molecular basis of the chemotherapeutic action of cis-Platin and cis-Platin-like drug is thought to be formation of stable complex between Pt(II) and DNA of cancer cell.

Cis-Platin is administered to the blood of the patient and through blood it approaches the cancer cell. The cytoplasm of the cancer cell contains high concentration of Cl^- ions so the drug remains as such dichloro species in the cytoplasm. But once the drug crosses the nuclear membrane, where the concentration of Cl^- ions is less, the chlorine ligands are lost from the cis-platin. The resulting cationic species Pt(I) or Pt(II) is attracted electrostatically toward the DNA and inner sphere complexation occurs. It is observed that $-Pt(NH_3)_2$ fragment makes co-ordination complex to the N-atom of the nuclear bases (A, T, G, C).

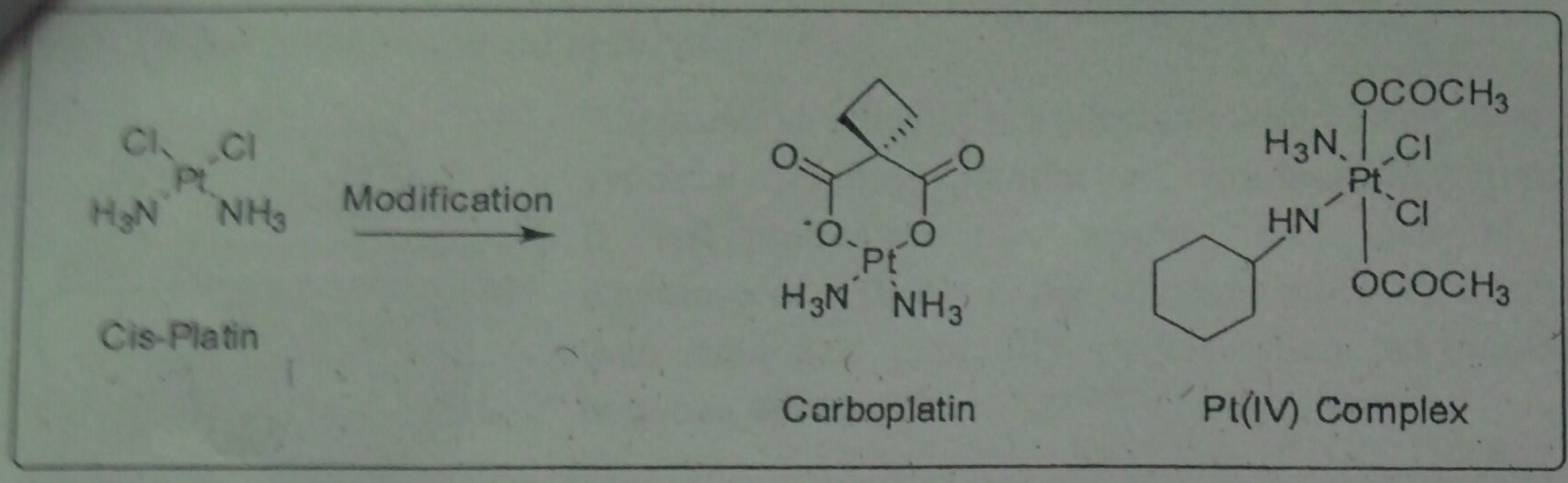
The studies show that complexation occurs preferably with N-atom of guanine bases of the same DNA strand leading to $[PtCl(guanine\text{-}DNA)(NH_3)_2]^+$ or $[Pt(guanine\text{-}DNA)(NH_3)_2]^{2+}$. The complexation with Pt causes DNA helix to bend and partially unwind. It is recognised by the proteins (High Mobility Group Proteins, HMG) and they make the DNA incapable of replication. It finally leads to the death of cancer cell and this way cancer is treated.



Inside the nuclear membrane

Side Effects:- Cis-Platin causes the serious damage to the kidney before it is excreted out of the body.

Modification in Cis-Platin: To remove the side effects of the Cis-Platin several modifications have been done. Carboplatin and Trinuclear Pt(II) and Pt(IV) complex are the examples of modified drugs which can be administered orally.



Que 6. What is Arthritis? What are the causes of Arthritis?

Arthritis :- Arthritis is a form of joint disorder that involves inflammation of joints and result in constant pain in the joints. The pain from arthritis is due to inflammation that occurs around the joint. The pain may be localized to the joint affected.

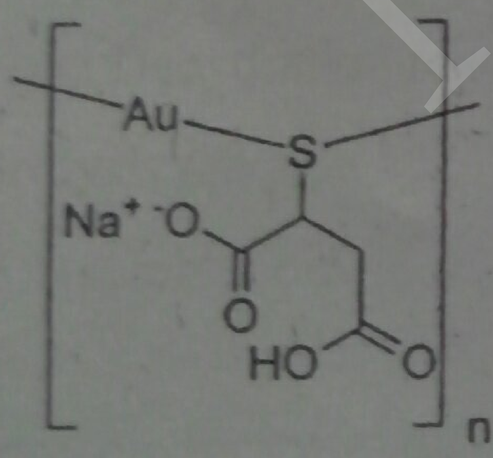
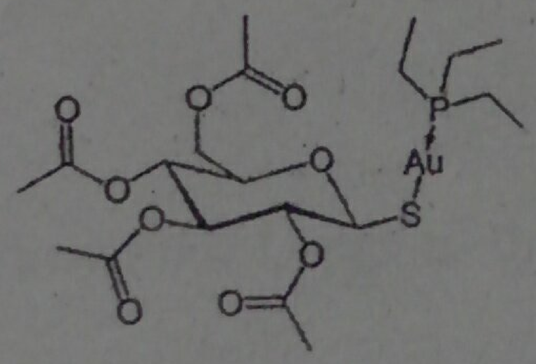
Cause:- The inflammation arises due to action of hydrolytic enzymes present in the Lysosomes.

Types:- There are over 100 different forms of arthritis. The most common form, osteoarthritis (degenerative joint disease), is a result of trauma to the joint, infection of the joint, or age. Other arthritis forms are rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases.

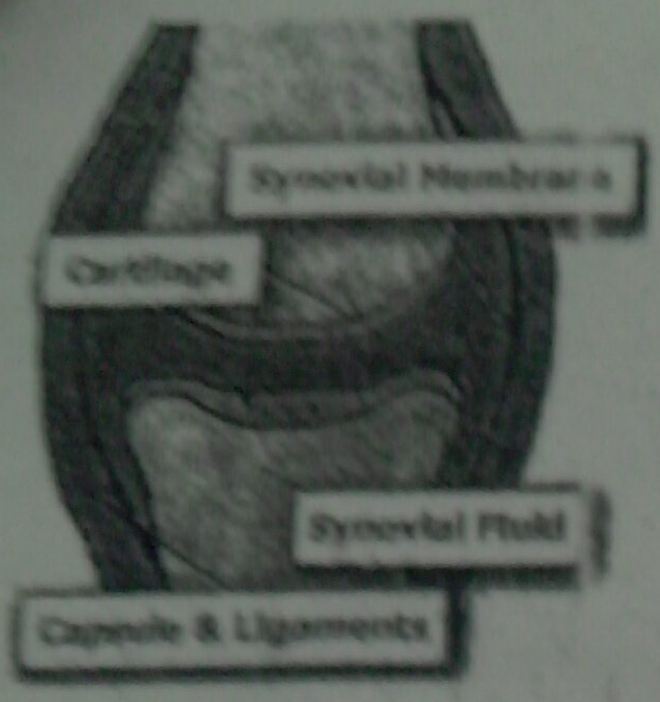
Treatment: Gold drugs are used in the treatment of rheumatoid arthritis. Commonly used gold drugs are Sodium aurothiomalate (Myocrisin), Sodium aurothioglucose (Solganol) and Auranofin.

Mechanism of Action of Gold drugs:- I). It is proposed that Gold accumulates in the Lysosomes and it inhibits the action of hydrolytic enzymes.

II). Second hypothesis is that Au(I) compounds deactivate singlet oxygen which is a harmful species that can be formed by oxidation of superoxide.

Name of Drug	Sodium Aurothiomalate (Myocrisin)	Sodium Aurothioglucose (Solganol)	Auranofin
Structure of Drug			
Application	Treatment of Rheumatoid arthritis	Rheumatoid arthritis	Rheumatoid arthritis

Que 7. What is Rheumatoid arthritis ?

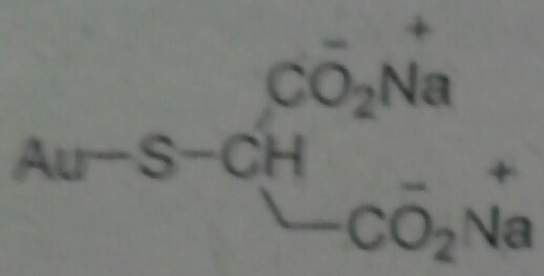


Rheumatoid arthritis is an inflammatory form of arthritis. The synovial membrane is attacked, resulting in swelling and pain. If left untreated the arthritis can lead to deformity. Rheumatoid arthritis is significantly more common in women than men and generally strikes when the patient is aged between 40 and 60.

Que 8.What is Myocrisin ? Write the structure, function and side effects of Myocrisin.

Myocrisin is a gold drug that is used in the treatment of Rheumatoid arthritis. It is proposed that Gold accumulates in the Lysosomes and it inhibits the action of hydrolytic enzymes.

Structure:



Disodium Aurothiomalate (Myocrisin)

Side Effects:

Skin rashes

Mouth ulcers

Blood disorders which may be serious

Lung disorders

Kidney disease

Que 9. Describe the role of following metals in Biological system :-

(1) Iron (Fe)

Ans:- 1. Iron exists in three oxidation states: Fe(II), Fe(III),: Fe(IV), There are several active sites in various enzymes which contain Fe and they catalyse several reactions like:- (a) Electron Transfer to Oxygenation Reactions

(b) Acid-Base reactions like: i) Reversible oxygen binding

ii) Hydration and Dehydration reaction

iii) Ester Hydrolysis reaction

(c) Fe (II) in Haemoglobin is responsible for transportation of oxygen from Lungs to the tissues.

(d) Fe is responsible for insertion of reactive oxygen atom into C-H bonds.

(2) Calcium (Ca)

Calcium is a critical mineral nutrient. However Calcium ions are important only in Eukaryotes.

Fuctions: (a) Calcium ions are important constituents of bones and teeth as $Ca_3(PO_4)_2$. Calcium is essential for the formation and maintenance of bones and teeth. This is due the insolubility of Calcium phosphate and calcium carbonate.

(b) Calcium ions are also required for intracellular signalling system. Movement of the calcium ion Ca^{2+} into and out of the cytoplasm functions as a signal for many cellular processes.

(c) Calcium supports bone health, especially in woman during and after menopause, for prevention and treatment of osteoporosis (the increased porosity of bones common during aging).

(d) Calcium also reduces muscle cramps and menstrual cramps.

(3) Cobalt (Co)

(a) Co is one of the most ancient biocatalyst.

(b) Cobalt is the active centre of coenzymes called cobalamins, the most common example of which is vitamin B_{12}.

Cobalamins are cofactors in enzymes that catalyse radical-based rearrangements and alkyl transfer reactions.

(4) Sodium (Na)

(a) Sodium is needed in larger amounts by animals, due to their use in generation and transmission of nervous impulses. Sodium and potassium maintain the potential difference across the cell membrane with the help of ion pumps.

(b) Sodium and Potassium ions are important agent in controlling cell structure through osmotic pressure.

(c) In animals, sodium ions are necessary for regulation of blood and body fluids, heart activity, and certain metabolic functions.

(5) Magnesium (Mg)

Magnesium is an essential element in biological systems. Magnesium occurs typically as the Mg^{2+} ion.

(a) It is present in every cell type in every organism. For example, ATP (adenosine triphosphate), the main source of energy in cells, must be bound to a magnesium ion in order to be biologically active. ATP is actually Mg-ATP.

(b) Similarly, magnesium plays a role in the stability of all polyphosphate compounds in the cells; including those associated with DNA- and RNA synthesis.

(c) Over 300 enzymes require the presence of magnesium ions for their catalytic action, including all enzymes utilizing or synthesizing ATP, or those that use other nucleotides to synthesize DNA and RNA.

(d) In plants, magnesium is necessary for synthesis of chlorophyll and photosynthesis.

(6) **Manganese (Mn)**

7

(a) Manganese exists in several oxidation states; most of them are very oxidising.

It acts as a catalyst in several oxidation-reduction (redox) reactions involving the positive reduction potential.

Manganese also functions in the oxygen-evolving complex of photosynthetic plants. Example is photosynthesis where H_2O is used as an e- donor and O_2 is released. In this reaction **Mn_4Ca,** a special cluster is involved.

(b) Manganese(II) ions also used as acid-base catalyst in several enzyme reactions.

(c) Manganese(II) ions function as cofactors for a large variety of enzymes with many functions. Manganese enzymes are particularly essential in detoxification of superoxide free radicals in organisms. I

(7) Nickel (Ni)

(a) Nickel is found in bacterial enzyme **hydrogenases** where Ni is present as +3 and +1 oxidation states.

(b) Coenzyme A Synthetase uses Ni to produce CO, and then react with it CH_3- to produce a C-C bond in the form of acetyl ester.

(c) Nickel is also found in the active site of **Urease enzyme** which was the first isolated enzyme in history.

(7) Zinc (Zn)

(a) Zinc act as an excellent Lewis acid in biological system and thus catalyse ester hydrolysis and peptide hydrolysis. This is because Zinc can form stable complexes with N- ans S- donor ligands.

(b) Alcohol dehydrogenase Enzyme in humans contain a zinc atom in the active site.

(c) Zinc deficiency in children causes growth retardation, delayed sexual maturation, infection susceptibility, and diarrhea, contributing to the death of about 800,000 children worldwide per year.

(8) Copper (Cu)

(a) The main role of copper is in electron transfer reactions and catalyses the redox reactions involving O_2.

(b) It is also used for reversible oxygen binding.

(c) Copper proteins have diverse roles in biological electron transport and oxygen transportation, processes that exploit the easy interconversion of Cu(I) and Cu(II).

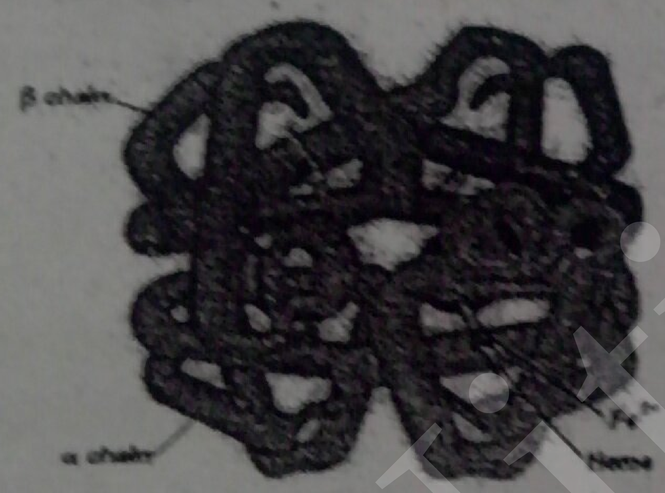
(d) The protein hemocyanin is the oxygen carrier in most molluscs and some arthropods such as the horseshoe crab. Because hemocyanin is blue, these organisms have blue blood, not the red blood found in organisms that rely on haemoglobin for this purpose.

(e) Copper is also a component of other proteins associated with the processing of oxygen. In Cytochrome c oxidase, which is required for aerobic respiration, copper and iron cooperate in the reduction of oxygen.

(f) Copper is also found in many superoxide dismutases, proteins that catalyze the decomposition of superoxides, by converting it to oxygen and hydrogen peroxide:

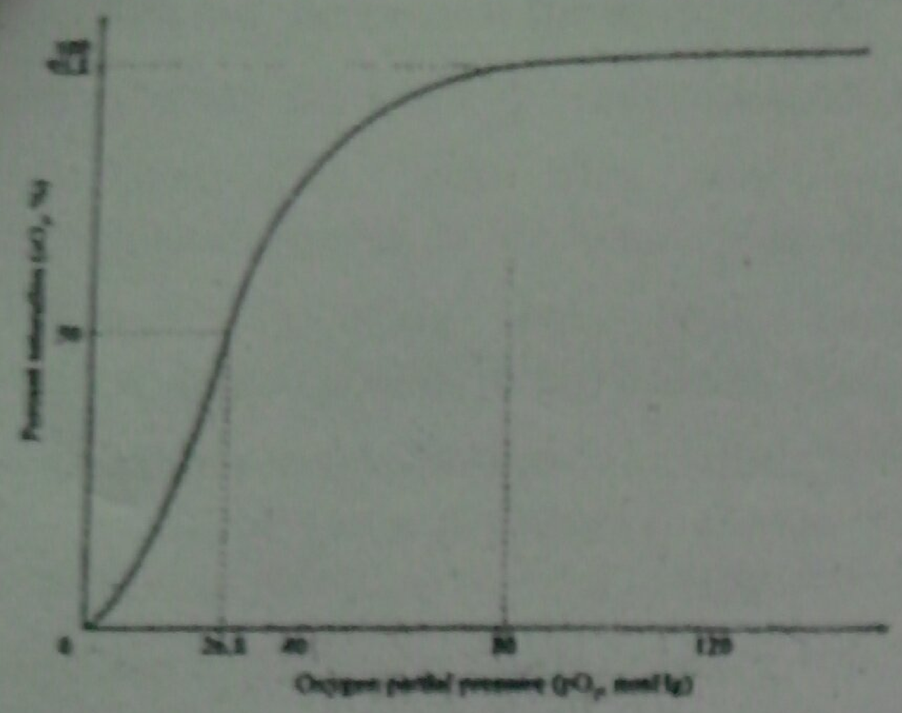
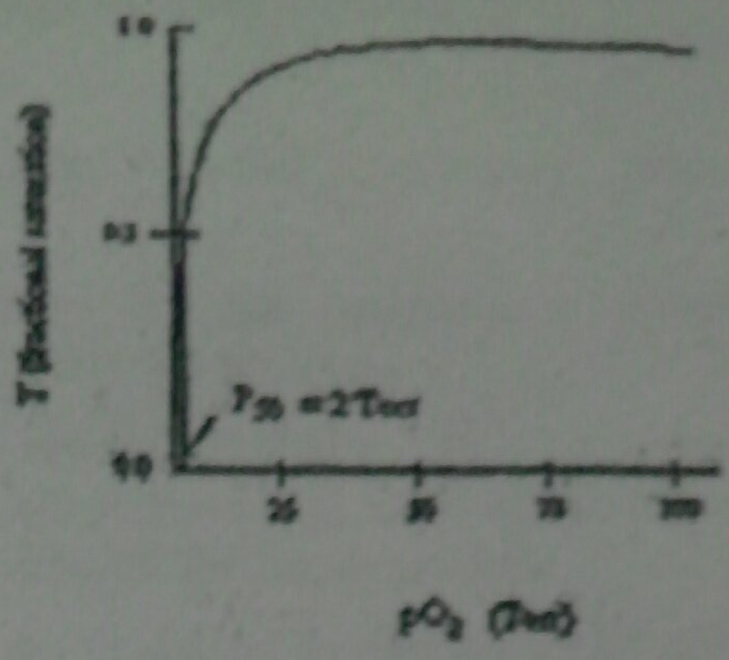
$$2\,HO_2 \xrightarrow{\text{superoxide dismutases}} H_2O_2 + O_2$$

Que 10. What are the structural differences between Hemoglobin(Hb) and Myoglobin(Mb).

Sr. No.	Hemoglobin(Hb)	Myoglobin(Mb)
1	Hemoglobin is a metallo-protein found in RBC (Red Blood Corpuscles).	Myoglobin is a metallo-protein found in muscles.
2	Hemoglobin is composed of Heme which is a non-protein part and four globin protein part.	Myoglobin has prosthetic heme group surrounded by apoprotein folds.
3	The protein of Hb has both tertiary and quaternary structure.	The protein of Mb has only tertiary structure.
4	Hb is tetrameric, it has two alpha chains and two beta chains ($\alpha_2\beta_2$).	Mb is monomeric and has only one alpha chain.
5	Each α-chain of protein has 141 amino acids and each β- chain has 146 amino acids.	The α-chain of protein has 153 amino acids.
6	Molecular weight of Hb is 68 KDA.	Molecular weight of Mb is 17 KDA.
		

Que 11. What are the functional differences between Hemoglobin(Hb) and Myoglobin(Mb).

Sr. No.	Hemoglobin(Hb)	Myoglobin(Mb)
1	The function of Hemoglobin is transportation of oxygen from Lungs to the tissue.	The function of Myoglobin is storage of oxygen in muscles.
2	Hemoglobin has comparatively less affinity for oxygen.	Myoglobin has high affinity for oxygen molecule.
3	One Hb can bind with four oxygen molecules, $Hb(O_2)_4$.	One Mb can bind with one oxygen molecule only to form MbO_2.
4	Hb shows co-operative binding with oxygen.	Mb doesn't shows co-operative binding with oxygen.
5	The oxygen binding curve is Sigmoidal or *S*-shaped in nature.	The oxygen binding curve is hyperbolic in nature.

	 The sigmoidal shape of hemoglobin's oxygen-dissociation curve results from cooperative binding of oxygen to hemoglobin.	

Que 12. Define Bohr Effect ?

Ans The Bohr Effect is the phenomenon of binding of oxygen to the haemoglobin with increase of H+ concentration. In other word, it is caused when the haemoglobin is exposed to increased partial pressure of CO_2. It is a change in the binding affinity of oxygen to haemoglobin. It is responsible for release of oxygen from the haemoglobin to the tissue which is due to increased of CO_2 and decreased in pH in the metabolically active cell. When a tissue is more active, the amount of carbon dioxide produced will be increased (pCO_2 is higher). Carbon dioxide reacts with water as shown in the following equation:

$$CO_2 + H_2O \xrightarrow{\text{Active Tissue}} H^+ + HCO_3^-$$

According to the Bohr Effect, Hemoglobin's oxygen binding affinity is inversely related both to acidity and to the concentration of carbon dioxide.

$$\text{Binding affinity (Hb)} = \frac{1}{\text{H+ ion conc}}$$

A decrease in blood pH or an increase in blood CO_2 concentration will result in hemoglobin proteins releasing their loads of oxygen and a decrease in carbon dioxide or increase in pH will result in hemoglobin picking up more oxygen. Since carbon dioxide reacts with water to form carbonic acid thus an increase in CO_2 concentration will results in a decrease in blood pH.

Que 13. Define the co-operative binding of haemoglobin with the oxygen.

Binding of oxygen to haemoglobin is known as co-operative binding because the binding of successive O_2 molecules facilitates binding of the next. Binding of the 1st O_2 molecule increases the affinity of haemoglobin for oxygen and hence facilitates the binding of the 2nd O_2 molecule. Binding of the 2nd O_2 molecule facilitates the binding of the 3rd O_2 molecule and so on. The affinity of haemoglobin for the 4th O_2 molecule is approximately 300 times that for the 1st. This co-operative binding explains the sigmoidal shape of the oxygen dissociation curve.

Que 14. What is the reason for co-operative Binding of Haemoglobin ?

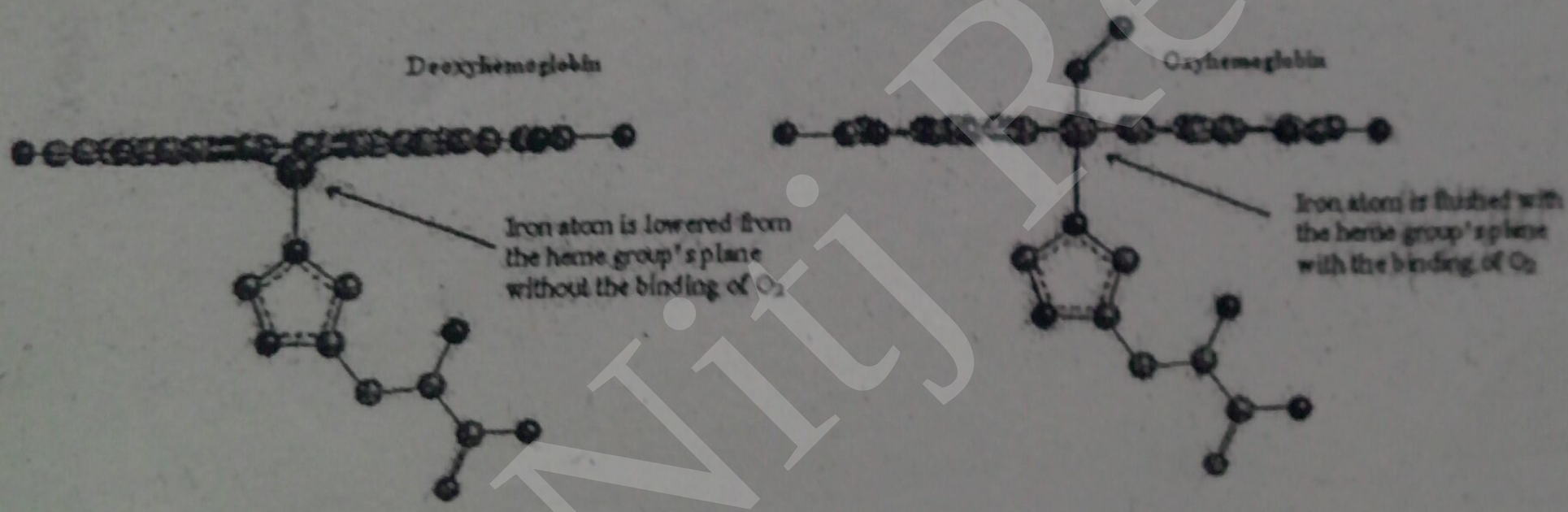
Haemoglobin can exist in two conformational states:

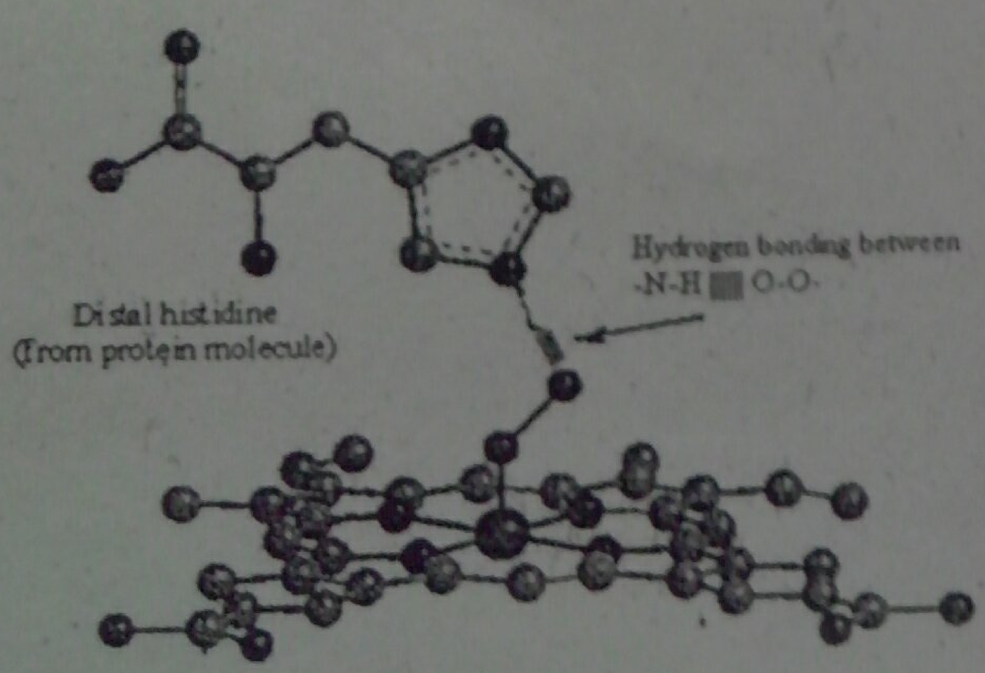
- Relaxed (R) state- this state corresponds to the quaternary structure of oxyhaemoglobin & favours oxygen binding
- Tense (T) state- this state corresponds to the quaternary structure of deoxyhaemoglobin & has a lower binding affinity for oxygen
- Deoxyhaemoglobin has four subunits which are interlinked through light salt bridges. Binding of oxygen causes a change in the conformational state of the haemoglobin molecule bringing about a change in the position of the haem groups.

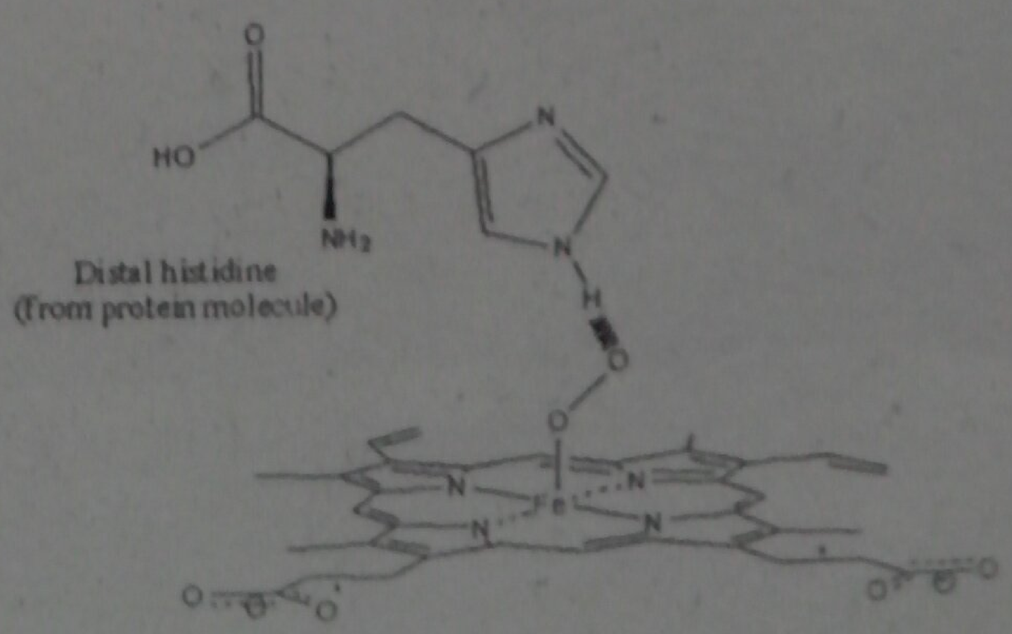
Transition from one state to another involves the breaking or formation of salt bridges between the polypeptide chains. Oxygenation cannot occur unless some of the salt bridges are broken so that the Iron atom can move into the plane of the heme group. The number of salt links that need to be broken for the binding of an oxygen molecule depends upon whether it is 1^{st}, 2^{nd}, or 3^{rd} or 4^{th} oxygen to be bound.

More salt links must be broken to permit the entry of 1^{st} oxygen molecule than the subsequent one. Because energy is required to break salt links, the binding of 1^{st} O2 molecule is less favourable than that of subsequent O2 molecule. Because Hb has four subunits, its binding can reflect multiple equilibria. When oxygen is taken up the 2 beta chains move closer together and when oxygen is released the chains move apart.

- The reaction of oxygen with the iron molecule of the haem group is an oxygenation reaction, not oxidative, and the iron remains in the ferrous (2+) state.







Que 15. What is the structure of Heme Group.

A heme group consists of an iron (Fe) ion held in a heterocyclic ring, known as a porphyrin. This porphyrin ring consists of four pyrrole molecules cyclically linked together (by methane bridges) with the iron ion bound in the center. The iron ion, which is the site of oxygen binding, coordinates with the four nitrogens in the center of the ring, which all lie in one plane. The iron is bound strongly (covalently) to the globular protein via the imidazole ring of F8 histidine residue (also known as the proximal histidine) below the porphyrin ring. A sixth position can reversibly bind oxygen by a coordinate covalent bond, completing the octahedral group of six ligands. Oxygen binds in an "end-on bent" geometry where one oxygen atom binds Fe and the other protrudes at an angle. When oxygen is not bound, a very weakly bonded water molecule fills the site, forming a distorted octahedron.