Indira Gandhi National
Open University
School of Sciences

BCHET-147

ORGANOMETALLICS, BIOINORGANIC CHEMISTRY, POLYNUCLEAR HYDROCARBONS AND UV, IR SPECTROSCOPY

Block

2

BIOINORGANIC CHEMISTRY

Course Design Committee

Dr Pritam Mukhopadhyay
School of Physical Sciences,
Jawaharlal Nehru University,
New Delhi

Dr. Preeti Malhotra
Department of Chemistry,
University of Delhi, Delhi

Dr. Sushmita Choudhury (Retd.)
Gargi College, University of Delhi,
New Delhi

Dr. Sangeeta Pandita
Department of Chemistry,
Zakir Husain Delhi College,
University of Delhi, Delhi

School of Sciences,
IGNOU, New Delhi 110068

Prof. M.S. Nathawat
Prof. Sunita Malhotra
Prof. Bharat Inder Fozdar
Prof. Javed A. Farooqi
Prof. Sanjiv Kumar
Prof. Lalita S. Kumar
Prof. Kamalika Banerjee

Block Preparation Team

Prof. Kamalika Banerjee
School of Sciences, IGNOU

Dr. Sushmita Choudhury (Retd.), (Editor)
Gargi College, University of Delhi,
New Delhi

Course Coordinator: Prof. Kamalika Banerjee

Production

Mr. Rajiv Girdher
AR (P), MPDD, IGNOU

Mr. Hemant Kumar
SO(P), MPDD, IGNOU

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BLOCK-2: BIOINORGANIC CHEMISTRY

This is the second block of this course and here you will be introduced to bioinorganic chemistry which is of immense interest as it involves living systems. This block has three units.

Unit 5 deals with bioinorganic chemistry followed by metals and non metals in biological system. The essential, non essential as well as trace and toxic metals have been discussed.

In unit 6 the sodium-potassium pump and the role of magnesium ions in chlorophyll have been dealt with.

In the last unit of this block, that is unit 7, the role of iron in oxygen transport along with details of hemoglobin and myoglobin have been discussed.

Expected Learning Outcomes

After studying this block, you will be able to

- understand the importance of bioinorganic chemistry;
- appreciate the presence of metals & non-metals in biological system;
- define the essential, non-essential, trace & toxic metals;
- describe the Na^+-K^+ Pump;
- understand the role of magnesium ions in chlorophyll;
- describe the salient features of hemoglobin; and
- discuss the special characteristic of myoglobin alongwith its structure.

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UNIT 5

METALS IN BIOLOGICAL SYSTEM

Structure

5.1 INTRODUCTION

The last block had four units where you learnt about the important inorganic reagents, organometallic compounds alongwith their nomenclature and the metal carbonyl compounds. The applications of inorganic chemistry to living systems is one of the most rapidly developing areas in modern inorganic chemistry. There are vital “inorganic” links in the processes that are discussed in this block on bioinorganic chemistry. Of course, this interdisciplinary subject is still in its developmental stage and is very futuristic in nature. Scientists are still trying to find out the answers to many unsolved puzzles of the living system. In this unit you will be studying about metals in biological system in details.

Expected Learning Outcomes

After studying this unit you should be able to:

- understand the importance of bioinorganic chemistry;
- appreciate the presence of metals & non-metals in biological system; and
- define the essential, non-essential, trace & toxic metals.

5.2 BIOINORGANIC CHEMISTRY

Bioinorganic chemistry involves the interface of inorganic chemistry and biology. The term “inorganic biochemistry” or “bioinorganic chemistry” is used in the latter part of the twentieth century which includes studies on the biological functions of typically “inorganic elements”, – the metals in particular. Many inorganic elements are essential to life processes. Different elements are taken up selectively by different cells and other components inside the cells, and utilized. The basics of coordination chemistry have been discussed in Units 4 and 5 of BCHCT 137 which you may recapitulate before reading this unit. Here you will be discussing the functions of the metals in the biological environment in context with the coordination chemistry which you may have learnt earlier. The mystery of living systems have always attracted scientists who tried to unravel it with the help of experimental research. In this process, model compounds with structures almost the same as in living systems have been tried to find the mechanism of reactions in natural systems. The term “bioinorganic” obviously has lot of contradictions. The source of this are the misconceptions that have been there when modern science evolved. In the early 19^{th} century, chemistry was still divided into “organic” chemistry which comprised of substances which were found in “organisms”, and an “inorganic” chemistry which comprised of “dead matter”. But then in 1828, synthesis of “organic” urea from “inorganic” ammonium cyanate (NH_4OCN) changed the basis of this terminology.

By 1960, bioinorganic chemistry became an independent and highly interdisciplinary research area.

Sophisticated and advanced analytical techniques have revealed that apart from carbon many metals and non-metals are present in biochemical processes and they are important for life. Even trace elements could be detected in these processes. Thus we can say that bioinorganic chemistry is mainly the study of the function of inorganic substances in living systems, alongwith the transport, speciation and thereby, mineralization of inorganic materials and their use in mechanical therapy and diagnosis.

The major areas of study of bioinorganic chemistry may be broadly identified as :

(i) biological functions of different elements which are mostly known to form inorganic compounds;

(ii) to find out if these elements and their compounds are toxic and how to overcome the toxic effects;

(iii) metal ion transport and storage in living systems;

(iv) use of metals as probes and drugs;

(v) artificial fixation of nitrogen and other applications.

The following two chemical processes involved in the chemistry of life in which metal ions play an active role are:

(i) Using solar energy to facilitate chemical reactions that produce oxygen and reduced organic compounds from carbon dioxide and water (photosynthesis)

(ii) Oxidation of organic matter to produce carbon dioxide, water and energy (respiration).

The "reaction flask" of living organisms is the cell. Each cell is characterized by an outer membrane whose function is to contain a highly organized chemical system and to monitor the influx of needed reagents. Within the cell membrane are several organelles immersed in cellular fluid, cytoplasm. Two of these organelles, the nucleus and mitochondria, are the focus of most of the chemistry. The nucleus is surrounded by a nuclear membrane, within which occur the process concerned with DNA-DNA replication, RNA synthesis and membrane synthesis. The other important organelles are the mitochondria within which occur the redox/electron transfer processes important in the combustion of glucose and synthesis of ATP. In animals the mitochondria are the sole centres of energy generation in the cell. The cells of green plants contain in addition chloroplasts which contain chlorophyll. This chlorophyll only enables the light sensitized phosphorylation reaction associated with ATP generation.

DNA is deoxyribose nucleic acid RNA is ribose nucleic acid. ATP is adenosine triphosphate.

In the dark, the mitochondria of plant cells maintain this regeneration though at a lower rate than in animals. This is because in green plant cells it is rarely found. The other organelles are lysosomes and golgi bodies involved in digestion and excretion respectively. The endoplasmic reticulum is an intracellular network of channels for transport of proteins synthesised by ribosomes that surround the surface of the channels.

An important feature of living systems is their unique dependence upon kinetic stability for their existence. Organisms must maintain steady states far from equilibrium by a continuous flow of nutrients and energy in a variable environment. All are thermodynamically unstable. They would burn up immediately to carbon dioxide and water if the system came to thermodynamic equilibrium. Thus to a living organism reaching equilibrium is equivalent to death. Life processes depend upon the ability to restrict these thermodynamic tendencies and allow kinetics to control and produce energy as needed. So, apart from capturing solar energy, it is important to use catalysts to release that energy in controlled manner. Examples of such catalysts are enzymes which control the synthesis and degradation of biologically important molecules. Metal ions play a crucial role for the activity of those enzymes. Metal containing compounds are also important in the process of chemical and energy transfer, reactions involving transport of oxygen to the site of oxidation and various redox reactions. Most of the reactions for obtaining energy for living systems are basically inorganic. The reactions are mediated and made possible by complex biochemical processes.

Inorganic elements can also be artificially introduced to the living system in diagnostic techniques like barium meal X-ray, MRI (Magnetic resonance imaging, suitable for paramagnetic metal ion) and as medicines e.g., platinum complexes in oncology, gold complexes in arthiritis and lithium salts as antidepressants. In these ways, bioinorganic chemistry provides many interesting insights about the functions of inorganic substances in living systems. In the next section you are going to study about the metals and non-metals in biological system.

Before moving to the next section, please try to solve the following SAQ.

SAQ 1

Give any two major areas of study of bioinorganic chemistry.

5.3 METALS & NON-METALS IN BIOLOGICAL SYSTEM

In this section you are going to study the metals and non-metals in biological system.

5.3.1 Essential, Non-essential Elements

Now let us discuss the essential elements in biological systems.

Essential elements are those elements which have a specific role indispensable to sustain life in a living organism. The normal functioning of the living system will suffer if there is absence or even deficiency of the element.

About thirty elements appear essential to some form of life (Table 5.1). The most abundant biological element is hydrogen which constitutes 63% of the atoms in a human body. Next comes oxygen (25 .5%), carbon (9.5%) and nitrogen (1.4%). The following seven elements in order of their abundance in humans are Ca, P, Na, K, S, Cl and Mg; together they constitute about 0.6%.

Table 5.1: Essential elements in living organisms

bulk elements : □; others are trace elements

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
□H												B	C	□N	□O	□F
□Na	□Mg												Si	P	□S	□Cl
□K	□Ca			V	Cr	Mn	Fe	Co	Ni	Cu	Zn			As	Se	Br
					Mo								Sn			I
					W											

There are nearly 40 elements in the periodic table which are biologically active. Any species responding to or involved in a biological system is termed biologically active. The heaviest biologically active metals and non-metals are molybdenum and iodine whilst the lightest counterparts are lithium and hydrogen. The following elements are essential of human life.

Metals: Na, Ca, Mg, V, Cr, Mn, Fe, Co, Cu, Zn, Mo, Sn.

Non metals: H, C, N, O, P, S, Se, F, Cl, Br, I.

The 11 most abundant elements are H, O, C, N, Na, K, Ca, Mg, P, S, Cl; the next seven are less abundant - Mn, Fe, Co, Cu, Zn, Mo and I whilst the remainder occur in ultratraces. The amount of these elements present in a 70 kg man are shown in Table 5.2 below.

Table 5.2: Amounts of essential elements present in a 70 kg man

Oxygen - 45.5 kg	Ca – 1050 g
Carbon – 12.6 kg	K – 140 g
Hydrogen – 7 kg	Na – 105 g
Nitrogen – 2.1 kg	Mg – 35 g
Phosphorus – 700 g	Fe – 4.2 g
	Zn – 2.3
	Mn, Cr, Mo, Co, Cu < 1g
	Eg. Cu – 0.11 g
	Mn – 0.02 g

Hydrogen, oxygen and carbon are present in water, carbohydrates, proteins etc. Nitrogen is an essential constituent of proteins. Phosphorus is present in ATP, ADP, DNA, RNA, bones, teeth etc. Sulphur is present in some amino acids and vitamins. Sodium, potassium, magnesium, chlorine are present in body fluids and cytoplasm. Sodium ion (Na^+) is the major component of extracellular fluid and potassium (K^+) of intracellular fluid. Together they act as charge carriers and are involved in osmotic balance. That is, they maintain a constant osmotic pressure on either side of cell membrane. The acid-base equilibrium is maintained by them. They also control sensitivity of nerves and muscles along with calcium ions (Ca^{2+}) and magnesium ions (Mg^{2+}). Calcium is required for bones and teeth and maintain correct rhythm of heart beat and converts fibrinogen to fibrin. It also stabilises protein structure. Mg^{2+} are found complexed with nucleic acids and are necessary for nerve-impulse transmission. All the phosphate transfer enzymes need Mg^{2+}. It is also an essential constituent of chlorophyll.

Manganese (Mn) and cobalt (Co) are present in enzymes, for example, arginase involved degradation of protein. Co is present in Vitamin B_{12}. Copper (Cu) is a constituent of metalloenzymes involved in electron transfer. Iron (Fe) is present in hemoglobin, myoglobin, cytochromes which act as O_2 carrier, O_2 storehouse and electron transfer respectively. Zinc (Zn) is present in enzymes particularly hydrolases and in insulin. Molybdenum (Mo) helps in nitrogen fixation in plants while iodine (I) is involved for proper functioning of thyroid gland.

We may classify the elements in a way that suggests their function in the complex dynamic system of a living cell. Let us now discuss a system that classifies elements according to their occurrence in three different biological environments.

- Firstly, it may be in the extracullar fluids and outer wall of cell-membrane – Na, Ca, Cu, Mo, Cl, Al.
- Secondly, it may be inside the cell, starting from inner wall of cell membrane in the aqueous phase known as cytoplasmic fluid - K, Mg, Co, Zn, P, S
- Also it may be present organelles inside the cell – K, Mg, Fe, Co, Zn, Mn, P, S

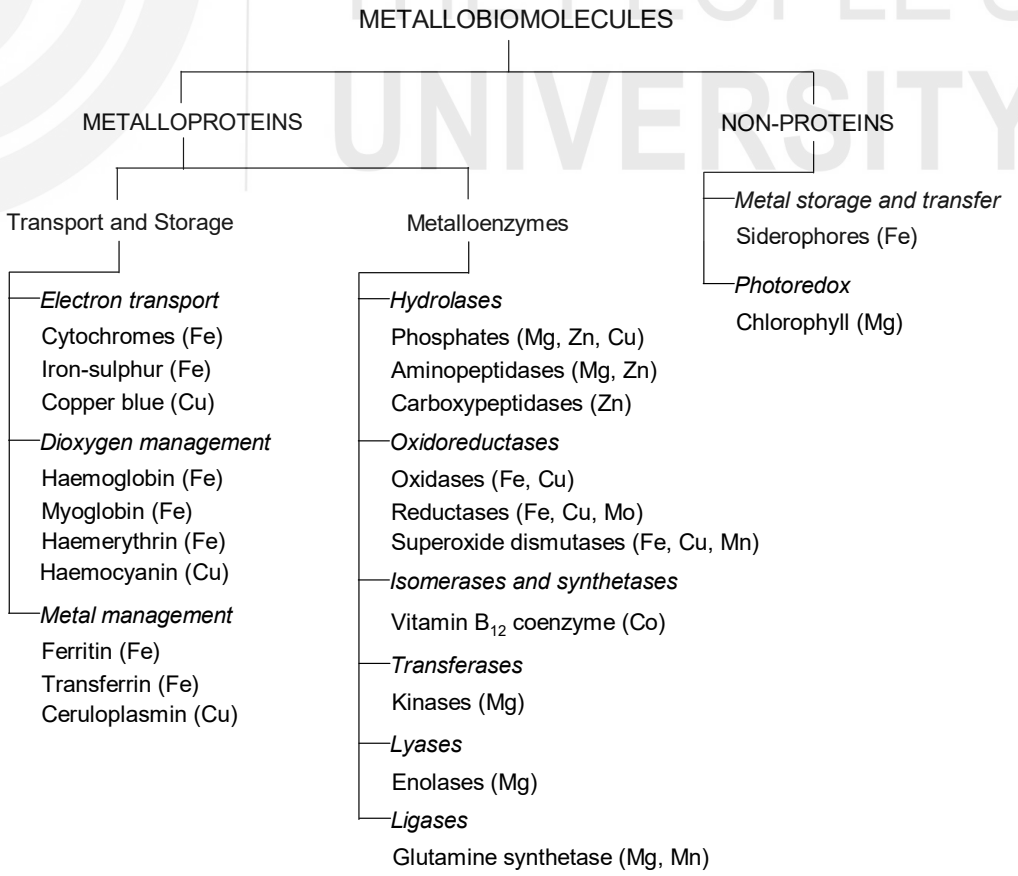
However, this classification is not very rigid.

Next, let us dscuss the classification of the elements on the basis of mechanism of action as:

- Essential elements: they are absolutely necessary for life processes and are needed in large quantites e.g. O, C, H, N, P, Na, K, Mg, Cl, Ca, S
- Trace elements: these are essential but are present in trace amounts - I, Fe, Cu, Zn, Co, Mn, Mo.
- Non-essential: they may be present in biosystem, but in their absence other elements may serve the same purpose e.g. Al, Ba, Sn, Sr.
- Toxic: they disturb the normal function of biological system e.g. Hg, Pb, Cd, As etc.

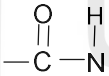
Next let us understand what are biomolecules. Biomolecules containing one or more metallic elements are called metallo biomolecules. These are natural products and usually complex coordination compounds, whose active sites are involved in different processes e.g., electron transfer, O_2 transfer, catalysis etc. Most biochemical processes are related to the chemistry of hydrogen and elements of the second and third periods of the periodic table. Every cell (animal, plant, microbial) contain the same elements in the same proportion. Six nonmetals (H, C, N, O, P, S) provide the structural elements to the protoplasm. The relative geochemical abundance and intrinsic chemical properties like, (i) small atomic radius, (ii) catenation, (iii) ability to from multiple bonds of these six elements suggest their unique suitability for building blocks of life. Table 5.3 gives an idea of the important metallobiomolecules

Table 5.3: Some representative examples of different metallobimolecules



The number of elements that are biologically important comprises a relative small fraction of the known elements. Geochemical abundance is an important parameter. All essential elements are abundant in the earth's crust. Four elements, Al, Si, Ti, Zr are abundant but not essential because at biological pH they form insoluble oxides. They also form very weak complexes with biological species. Natural abundance limits availability of elements for use in biosystem. The metals for importance in enzymes are mainly those of the first transition series and other elements of importance are relatively the light ones. Natural abundance of elements decreases with increase in atomic number. The heavier elements are not very important as far as biological activity is concerned. The conclusion is inescapable "Life evolved utilizing elements that are abundant and available to it and became dependent upon them". The rarer elements were not used by living systems because they were not available; neither did the system evolve mechanisms to cope with them. They were later introduced to the environment and ecosystem by human activities.

Most of essential metals except Na, K cannot occur in the biosystem in the free state as under the prevailing pH conditions they get hydrolysed and precipitated. They must be present and transported as complexes. Most of the essential and trace metals are transition metals which are capable of forming complexes and chelates with species like citrate, tartrate, lactate, amino acids present in the plasma. Many metal complexes of biological macromolecules have been isolated in the free state for example hemoglobin, myoglobin, cyanocobalamine, chlorophyll a, cytochrome-c etc. The presence of others or their formation as intermediate products taking part in metabolic processes of living system has been inferred from a catalytic study of enzymes.

A successful organism must have a subtle command over a complex pattern of reactions that proceed at high but controlled rates. Loss of this control leads to the organism's disease and death. Life depends on how these reactions are controlled and thus the role of catalysts is important. These catalysts are enzymes which are polypeptides i.e. macromolecules, formed from α-amino acids linked by a peptide bond  . The term "peptide residue" denotes that part of the amino acid that remains in the chain once the peptide link is formed by elimination of H_2O. Enzymes are named according to the reactions they catalyze e.g. hydrolase, oxidase, reductase etc.

The naturally occurring amino acids have different side chains eg. alkyls,-COOH, -NH_2, -OH, -SH. These functional groups confer hydrophobic and hydrophilic character, Bronsted acidity/basicity, Lewis acidity to complex with a metal. About 30% enzymes are metalloenzymes having a metal atom as the active site. The functional groups modify the immediate environment. The protein part of the enzyme is called apoenzyme and the non-protein part, the prosthetic group. Enzymes not only control the rate of a reaction but by favouring certain geometries in the Transition State (TS) can lower the activation energy to favour the formation of the desired product. Metal ions also occur in transport and storage proteins and in non-protein complexes.

Life originally appeared on earth in an overall reducing atmosphere. As shown by Miller and Urey (1953), lightning discharges through a mixture of methane, water, ammonia and hydrogen to produce significant amounts of amino acids

essential to life processes. Abelson and others later showed (1960s) that solar ultra violet radiation not filtered by the earth's ozonosphere acts on a mixture of carbon monoxide, carbondioxide, nitrogen and a small amount of hydrogen producing, among others, hydrogen cyanide. This molecule can subsequently give rise to glycine, adenine, and other biologically significant molecules. These compounds, formed in the primitive earth, might have undergone a series of complex chemical evolution over millions of years to produce living organisms which could replicate themselves and undergo biological evolutions (nearly 3.5 billion years ago). Photosynthetic organisms appeared approximately 2.5 billion years ago when the atmosphere became gradually rich in oxygen and ultimately sustained aerobic forms of life. The diverse biological world of today has largely developed with this form of life and is a unique example of nature's delicate balance between constructive and destructive oxidation by oxygen. The amazingly complex and yet precisely synchronized biological processes involve, in addition to H, C, N, O, and P, other elements abundant on the earth, particularly a large number of metals, in both bulk and in trace. As more and more finer details regarding these roles get unveiled, the emphasis on a particular area of study generates new terminologies to justify the thrust area.

5.3.2 Trace & Toxic Metals

The living system also requires small amounts of other elements as shown in Table 5.2. The requirement of these elements may be very low (i.e., 10^{-4} g mole or less in a 75 kg adult) or moderate (e.g., 10^{-1} g mole). All these elements are classed as essential trace elements of which in top priority; iron, copper and zinc. Elements present in exceedingly small amounts are called ultra-trace elements, for example, Mn, Mo, Co, Ni and V.

Hydrogen are involved in the biological system and the *s*-block elements sodium, magnesium, copper and calcium. Na, K, Ca and Mg, are the most abundant metal ions in living systems. They occur at fairly high concentration in most cells and constitute 99% of the metal content (more than 1% of the body weight) in man.

Hydrogen

It is the most abundant element in the biosphere. The small atoms can effectively “seal” the residual valences of carbon, nitrogen, and oxygen without any structural strain. When bonded to nitrogen and oxygen, hydrogen can form hydrogen bond; these weak but extensive bonds are crucial in stabilizing many biological systems, for example, the double helix of DNA. The weakness of the bonds is an advantage in such systems since the helix must unwind during replication. The life supporting properties of water and many other functions like operations of several enzyme are also dependent on hydrogen bond.

Sodium and Potassium

In spite of their established chemical similarity, the elements differ in their ability to penetrate cell membranes presumably due to their different ionic size. The metals also differ in their transport mechanism and efficiency to activate

enzymes. Sodium ions are more abundant outside the cells, for example in the blood plasma and in the extracellular fluid surrounding the cells. They participate in transmitting nerve signals and regulate the flow of water across cell membranes. The transport of sugars and amino acids into cells is also influenced by sodium ions (Na^+).

On the other hand, potassium ions occur at a higher concentration inside cells. They also activate many enzymes and participate in the oxidation of glucose to produce ATP. Both sodium and potassium ions are also involved in the transmission of nerve signals.

Magnesium

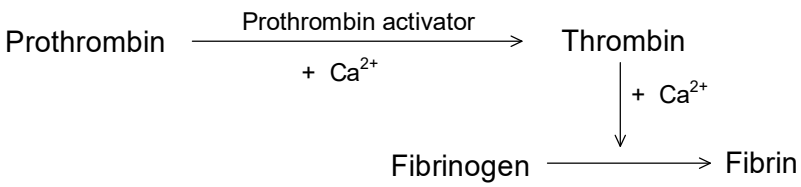
The involvement of magnesium in photosynthesis by plants is well-known. Magnesium is also an essential element for animal physiology. The major portion of magnesium is an adult human is in the skeleton while the rest is inside the cells. The Mg^{2+} ion in cells is the next most important cation after K^+. The small doubly charged cation has a high charge/size ratio and is strongly hydrated - mostly to $[Mg(H_2O)_6]^{2+}$ which binds the $ROPO_3H$ – groups in nucleotides (ATP, ADP) and polynucleotides (DNA, RNA). The ion may form strong complexes with oxygens on various phosphate groups; such complexes appear to be important in storing energy and use of the same when necessary. All enzymes utilizing ATP in phosphate transfer require Mg^{2+} as cofactor.

Intracellular magnesium ions are also essential to keep ribosomes intact. Ribosomes are RNA-protein complexes of particle size of about 20,000 pm diameter which occur in the cytoplasm and function as sites for protein synthesis.

Calcium

It is the major constituent of bones and teeth. It is also important in neuromuscular function, interneuronal transmission, maintenance of cell membrane integrity and blood coagulation. The calcium present in bones gets continuously solubilized and redeposited in our body to the extent of about 400 mg per day. The concentration of calcium ions (Ca^{2+}) in plasma is closely maintained around 100 mg/L by means of two hormones namely, calcitonin and parathyroid hormone. Together they help in building and mobilising bone structure.

Calcium ions in the cytoplasm of muscle fibres play an important regulatory role in muscle functioning. Clotting of blood is also influenced by the presence of Ca^{2+} ions. Blood contains prothrombin, a soluble protein. This is converted to the enzyme thrombin by the action of prothrombin activator in the presence of Ca^{2+} ion. Thrombin, again aided by Ca^{2+}, now clots the blood by converting its soluble fibrinogen into insoluble fibrin as shown below:



During the period of growth, deposition of bone must exceed resorption. With ageing, resorption predominates and causes loss of about 15-30 mg per day. Vitamin D promotes deposition of bone. This vitamin is synthesized by the action of ultra violet light on 7-dehydrocholesterol. So inadequate exposure to sunlight may result in diseases of the bone like ricket in childhood and softening of bones (osteomalacia) in later life.

It is interesting to note that the distribution of essential elements in the biosphere is not in harmony with the abundance of the elements in the earth‘s crust. About 88% of the earth‘s crust is made from the four most abundant elements oxygen, silicon, aluminium and iron. In living cells, more than 98% is derived from the four elements hydrogen, carbon, nitrogen and oxygen. On the other hand, the concentrations of different ions in sea-water show a similarities with those in living systems, for example, the blood plasma. Thus life probably originated in the sea and evolved thereafter. The process of evolution continued with the relatively abundant elements which were found suitable for sustained development of the process. The metal ions chosen were able to form thermodynamically stable units in the active centres of proteins (metalloproteins) or other biomolecules. At the same time, they had to be kinetically labile, be able to assemble and disassemble very fast under physiological conditions. Titanium and zirconium, in spite of their high abundance, are not found in living cells as the metals are readily precipitated as insoluble hydrated oxides at our body pH. Also the metals have a uniform high +4 oxidation state unsuitable for reversible electron transfer and other reversible biological processes.

The health response of an organism to an essential element follows the general type of curve shown in Fig. 5.1; details of the curve vary from one element to another. At and around zero intake of the element, the condition may be anything between bare survival to death. As the dose is slowly increased, the organism gradually reaches a stage of smooth functioning. But an excessive dose will gradually result in toxicity by the same element and ultimately lead to death. For some elements, the safe dose and the toxic dose may be quite close, for example 50 to 200 μg for selenium (Table 5.4).

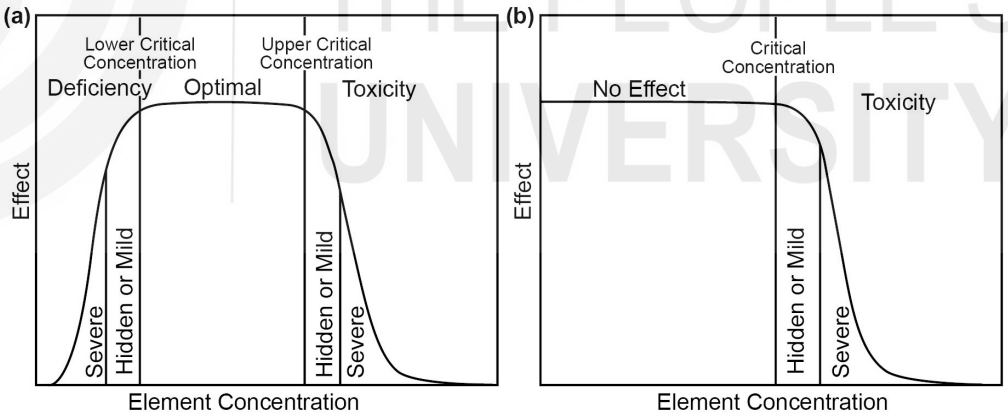


Fig. 5.2: Nature of variation of response to increasing dose of an essential element.

Table 5.4: Recommended daily doses of some elements for an adult human being (~70 kg)

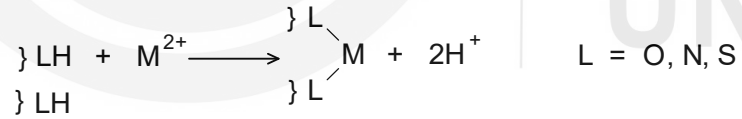
Element	Intake (per day)	Element	Intake (per day)
Iron	10 mg (male)	Fluorine	1.5-4.0 mg
	18 mg (female)	Molybdenum	150-500 μg
Zinc	15 mg	Iodine	150 μg
Manganese	2.5-5.0 mg	Chromium	50-200 μg
Copper	2.0-3.0 mg	Selenium	50-200 μg

Deficiency or excess of these elements may give rise to metabolic disorders, inhibited growth and other diseases.

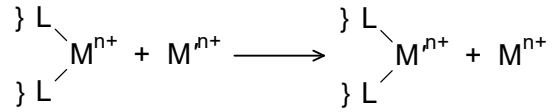
Sometimes one element strongly interferes with the uptake of another element an this is known as antagonism. The copper containing enzyme monoamine oxidase is involved in the cross-linking of polypeptide chains responsible for structural strength of arteries. As a consequence, copper deficiency in herbivorous animals causes anemia, loss of pigmentation and ultimately death owing to arterial lesions. However, even when the animals are supplied with pasture having a plentiful supply of copper, the take may be still hampered if the soil contains a high level of molybdenum – presumably owing to the formation of highly insoluble copper thiomolybdate in the gut.

Let us look into specific examples of toxicity of metal ion in biochemical system. Metal ions are essential for life processes only in limited quantity. The concentration of the essential metal ions inside the cell is controlled by enzyme regulated transport mechanisms and excess unused metal ion is ejected. The biosystem does not have transport mechanism for some (impurity) elements and these cause disorder. Such metal ions are toxic, the highly toxic ones are generally heavy metals of second and third transition series (soft acids) and metalloids like arsenic. Toxicity is of two types, namely chronic toxicity and acute toxicity. Chronic toxicity arises due to high rate of turnover of metal ion in the body. Whenever metal ions are in excess in the body, they are stored in specific sites to a limited extent and the excess metal ion interferes in body processes. Acute toxicity arises due to certain chemical activity like deactivation of enzymes and other biomolecules. Let us understand this in detail now.

(i) The metal may get bound to coordinating site of the enzymes, which are binding sites of essential metal ions. Thereafter the essential biological function of the enzyme is lost resulting in its deactivation



(ii) Deactivation of an enzyme can be due to displacement of metal ion present in the enzyme, which is essential for its catalytic activity by a toxic metal ion e.g. replacement of Zn^{2+} by Pb^{2+}, Cd^{2+}, Hg^{2+}.



As the external metal ion is not biochemically active, the activity of the enzyme is lost. Common example is Cd^{2+} replacing Zn^{2+}.

(iii) There may be cases when the external metal ion may change conformation of biomolecule and hence its biological activity.

(iv) The metal ion can get bound to DNA causing a change in base sequence, leading to transmission of wrong genetic information from

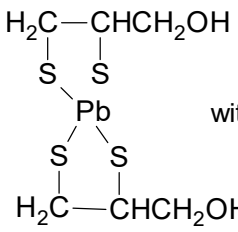
DNA which produces faulty protein and enzymes. This may give rise to birth defects too.

(v) The metal ion can bind to DNA stimulating its replication resulting in uncontrolled cell growth i.e., formation of malignant tumours.

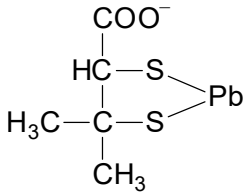
Lead

This enters the biosystem through food, water and air. Lead pollution can be caused by factories, particularly those manufacturing batteries. The antiknock compound $Pb(Et)_4$, namely tetraethyl lead used earlier in gasoline was present in exhaust gases of automobiles and was a source of lead (Pb) in the atmosphere. Lead is also present in paints and pigments. Lead gets deposited in the softer tissues and passes to the blood stream. Pb^{2+} has strong affinity for the –SH group of enzymes and hence gets bound to these and deactivates them. The principal indicators of lead level in human beings is lead in blood expressed as μg/mL or μmol/L. At concentration as low as 10 μg/mL it inhibits some enzymes when the concentration becomes higher, it affects digestive, muscular, nervous and other organs. Lead affects the biosynthesis of bones as Pb^{2+} replaces Ca^{2+} in bone. Deposition of lead in brain results to irreversible brain damage. Lead also damages kidney, liver and intestinal tract.

The major biochemical effect has been attributed to its influence with heme synthesis giving rise to hematological damage. It lowers the formation of δ-aminolevulinic acid (ALA) and its conversion to porphobilinogen is inhibited. Lead deactivates the enzyme ALA dehydrase and overall effect is disruption of synthesis of hemoglobin, other respiratory pigments and cyctochromes. Thereby deficiency of hemoglobin leads to anemia. Methods for removal of lead from the body depend on formation of coordination compounds which are excreted. Common antidotes are calcium sodium salt of EDTA ($CaNa_2EDTA$), succimer (Dimethyl succinic acid or DMSA), 2,3-dimercapto-1-propanol (British anti-Lewisite (BAL) and d-penicillamine. The probable coordination compounds of lead ions with some antidotes are shown below;



with BAL



with d-penicillanine

Arsenic

Arsenic (As) poisoning is caused through air and water (mainly ground water) pollution. Elemental arsenic is not absorbed through the intenstinal wall and is not toxic. As(III) is more toxic then As(V). Poisoning causes gastroenteritis, skin lesion and skin cancer. As(III) shows toxicity due to binding with the –SH group of the enzyme pyruvate dehydrogenase, which is essential for ATP synthesis. At higher concentration. As(III) causes coagulation of proteins probably by binding to –SH group of the proteins. It also binds to the protein keratin in the hair affecting its texture.

Excess arsenic affects the biosynthesis of ATP in another way. It is chemically similar to phosphorus and interferes in stepwise synthesis of ATP. In presence of AsO_3^{3-}, phosphorylation of glyceraldehyde-3-phosphate to give 1,3-disphosphoglycerate does not occur, rather 1-arseno-3-phosphoglycerate is formed and further oxidative phosphorylation leading to ATP formation does not occur. The main biochemical actions of arsenic are as follows:

- deactivation of enzymes e.g. pyruvate dehydrohenase system, citric acid cycle is also inhibited apart from others;
- coagulation of protein; and
- uncoupling of phosphorylation.

DMSA is dimethyl succinic acid.

A lethal dose of the more toxic form of arsenic is 125 mg/kg body weight but for less toxic forms it is upto 200 mg/kg body weight. The major antidotes for arsenic poisoning include chemicals having –SH groups which can bind to arsenic forming chelate e.g. (British anti-Lewisite (BAL), succimer (DMSA).

Cadmium

Cadmium (Cd) is a very toxic metal with a lethal dose of greater than 350 mg at a time. It enters the body system through the food chain (40 mg/day) and industrial fumes. Tobacco contains nearly 1μg Cd/g. Thus nearly 2-4 μg of Cd are inhaled per packet of cigarette. This is the major source of inhaled Cd. 25-50% of inhaled Cd is absorbed into the body while the absorption from food is almost 6%. Other sources of Cd are from plating, pigment and battery manufacturing industries. Inhaling Cd laden dust leads to respiratory problem. Cd accumulates in liver and kidneys and may produce irreversible damage. Certain compounds of Cd are carcinogenic. The main disease associated with Cd poisoning is Itai-Itai disease which was observed in the Jinzu river basin (Japan). This water was used for irrigation and patients developed this disease after eating rice grown on fields irrigated with this water. The disease is associated with brittle or hollow bones, high rate of fracture, osteoporosis and intense bone-associated pain. It is very interesting to note that Cd cannot pass through the placental membrane and thus cannot harm new born babies. Excess Cd can displace Zn from enzymes and deactivate them causing metabolic disorders. Regular intake of Zn provides protection against Cd poisoning.

The average amount of Cd accumulated in the body over a life time is nearly 30 mg. Metallothioneins (MTs) are low molecular weight cadmium binding proteins present in animal and human tissues. The deposited Cd is taken up by MTs and Cd binds to its –SH group thereby getting trapped and its toxicity controlled. The protein bound Cd gets accumulated in the kidneys and damages them. Long-term cadmium exposure gives rise to kidney or bone disease, reproductive toxicity and cancer in animals and human. Its antidotes are (British anti-Lewisite (BAL) and $CaNa_2EDTA$.

Mercury

Mercury (Hg) is the most toxic heavy metal and may enter the biological system as Hg vapour, mercury salts or alkyl/aryl mercury compounds. The major source is industrial processes involving mercury compounds and

organomercurials used as fungicides. Upto 80% of Hg may be absorbed depending on its chemical form. The methyl mercury compounds are most extensively absorbed while for inorganic mercury compounds the absorption is nearly 15% mercury in blood and hair can be used for estimating the body burden. A blood Hg level of 20 μg/100 mL corresponds to a daily consumption of 200-300 μg of Hg. The distribution of mercury in different organs follow the order liver, kidney, brain, heart, lungs. Its presence is least in the muscles.

The toxicity of Hg depends on its chemical form. In the liquid form it is not absorbed by the human systems and is not toxic. However Hg vapours is absorbed into the blood and enter the brain. Hg(II) is toxic but cannot enter the cell as it cannot pass through the membrane. Hg(I) forms and insoluble chloride with gastric juice in stomach and is not highly toxic. However Hg(I) can enter the cell and get oxidized to Hg(II) and show high toxicity. Hg(II) like Cd(II) and Pb(II) has affinity for –SH group of enzymes as well as proteins and can deactivate them. It also inhibits the synthesis of δ aminolevulinic acid by deactivating specific enzymes and thereby decreases synthesis of heme. It can also form bonds with heme and serum albumin. The most toxic species are the organomercurials headed by methyl mercury (CH_3Hg^+). Mercury salts are converted into methylmercury in the biochemical system by the action of Vit B_{12}. The Co–C bond in Vit B_{12} is weak and can be readily transferred to the substrate causing alkylation. This methylmercury is taken up by aquatic plants and fish and finally enters animals and human bodies. The higher toxicity of organomercurials is due to their nonpolar nature, this makes them fat soluble and they readily pass through the biological membrane and spread all over the body. The Hg–C bond does not break easily hence CH_3Hg^+ is not excreted and retained in kidneys, brain, heart and muscles. CH_3Hg^+ can penetrate through the placenta and get accumulated in foetal tissue. Methylmercury gets attached to the cell membrane and hence the transport of sugar through the membrane is lowered whereas external passage of potassium ions (K^+) is increased. Thus the brain cells do not get sufficient energy and K^+–controlled nerve impulse transmission is impaired leading to tumours and mental instability. Such effects are observed distinctly when the concentration of mercury in the brain exceeds 20 μg/g. The effect is more serious in babies. It may cause irreversible damage to central nervous system is irreversible leading to cerebral palsy, mental retardation and convulsions. CH_3Hg^+ poisoning also gives rise to segregation of chromosomes, chromosome breakage in cells and inhibited cell division.

The toxic effect of mercury was first realized when 121 persons in Japan were affected by a disease causing tremors and mental imbalance. They were residents near the Minamata bay where the effluents of the factory containing mercury compounds and CH_3Hg^+ was discharged. Though the concentration of CH_3Hg^+ was low it got accumulated in significant concentration in fish. People eating the fish were seriously affected and many babies were born with cerebral defects and this was referred as Minamata disaster.

So in this section you have learnt all about the metals and non metals in biological system. Before moving to the next section, please try to solve the following SAQ.

SAQ 2

What are the roles of sodium and potassium metals in biological system?

5.4 SUMMARY

In this unit, we first discussed the importance of bioinorganic chemistry. Then the different metals and non-metals in biological system along with the essential, non-essential, trace & toxic metals have been taken up. These will help you to understand the role of various metals in the biological system. In the next unit we will talk about the functions of *s*-block metals.

5.5 TERMINAL QUESTIONS

1. What is bioinorganic chemistry?
2. What is the role of manganese and cobalt in biological system?
3. Which metal ion has role in blood clotting and how does it do so?

5.6 ANSWERS

Self Assessment Questions

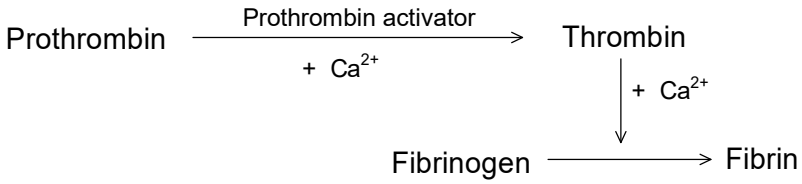
1. Any two areas may be given (from section 5.2)
2. The elements are similar chemically but differ in their ability to penetrate cell membranes presumably due to their different ionic size. They also differ in their transport mechanism and efficiency to activate enzymes. Sodium ions are more abundant outside the cells, (blood plasma and in the interstitial fluid surrounding the cells). They participate in transmitting nerve signals and regulate the flow of water across cell membranes. The transport of sugars and amino acids into cells is also influenced by Na^+ ions.

   But potassium ions occur at a higher concentration inside cells. They also activate many enzymes and participate in the oxidation of glucose to produce ATP. With sodium, K^+ ions are also involved in the transmission of nerve signals.

Terminal Questions

1. Bioinorganic chemistry involves the study and function of inorganic substances in living systems. It also deals with the transport, speciation and mineralization of inorganic materials and their use in mechanical therapy and diagnosis.
2. Manganese and cobalt are present in enzymes. The enzyme arginase have these metals and it has role in protein degradation. Co is present in Vitamin B_{12}.

3. Calcium ions play an important role in clotting of blood. Blood contains prothrombin, a soluble protein. This is converted to the enzyme thrombin by the action of prothrombin activator in the presence of Ca^{2+} ion. Thrombin, again aided by Ca^{2+}, now clots the blood by converting its soluble fibrinogen into insoluble fibrin.



UNIT 6

FUNCTIONS OF *s*–BLOCK METALS

Structure

6.1 INTRODUCTION

In the previous unit you were introduced to metals in biological system. Here you will be studying about the functions of *s*-block metals pertaining to bioinorganic chemistry especially about the Na^+-K^+ pump. After that the role of magnesium ions in chlorophyll will be discussed. In the next unit you will be learning about the role of iron in oxygen transport.

Expected Learning Outcomes

After studying this unit you should be able to:

- describe the Na^+-K^+ pump; and
- understand the role of magnesium ions in chlorophyll.

6.2 TRANSPORT OF METALS

Na^+-K^+ Pump

The sodium-potassium pump (also referred to as Na^+-K^+-ATPase pump). It is found in the cell membrane of all animal cells and deals with transport of these ions. The structure of the membrane and the presence of enzyme systems that operate the ion pump determine the permeability properties of cell membranes. The Na^+-K^+ pump coresponds to active transport i.e the transport of ions through membranes against the natural tendency of ions to diffuse

towards lower concentration. Whenever there is a charge distribution established across the membrane by active transport, an electrode potential develops. Also, there is a difference in chemical composition of the fluids inside and outside the cell.

Most animal cells have a higher concentration of potassium ions (K^+) inside the cell membrane than outside and a higher concentration of sodium ions (Na^+) outside the cell than inside. You will find that this concentration gradient is not maintained in dead cells. Also if cells are cooled to 0 ^oC then the flow of ions equalizes the gradient. The immediate source of energy to sustain this disequilibrium is ATP, huge amounts of which are consumed to maintain this gradient. Ion pumping occurs at a limited number of positions in the membrane. Three Na^+ ions are pumped outwards and two K^+ inwards for each molecule of ATP hydrolysed to ADP and inorganic phosphate. So, the ion in the membrane, which is to be transported, moves to the other side and gets released with the help of a carrier. The first clue came in 1957 when Jens Skou disovered an enzyme of molar mass 100 kg mol^{-1} that hydrolyses Mg-ATP only in the presence of Na^+ and K^+. It is to be noted here that ATP is a simplified notation. In cells it is present as Mg^{2+}-complex, the structure of which is given in Fig. 6.1 below.

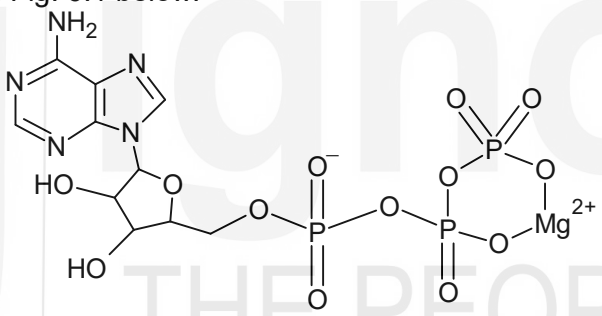


Fig. 6.1 : Structural formula of Mg^{2+}-complex of ATP.

The ability of the enzyme correlates quantitatively with the extent of ion transport. Another observation came that this enzyme ATPase is phosphorylated only in presence of Na^+ and Mg^{2+} ions. Moreover the phosphorylated product is hydrolysed if K^+ are present. These observations are summarized by the cycle of enzyme reactions shown in Fig. 6.2, it has been shown that the enzyme undergoes a conformational change during phosphorylation. E_1 and E_2 are two enzyme conformation. Using these clues a mechanism for the sodium-potassium pump was proposed as shown in Fig. 6.3.

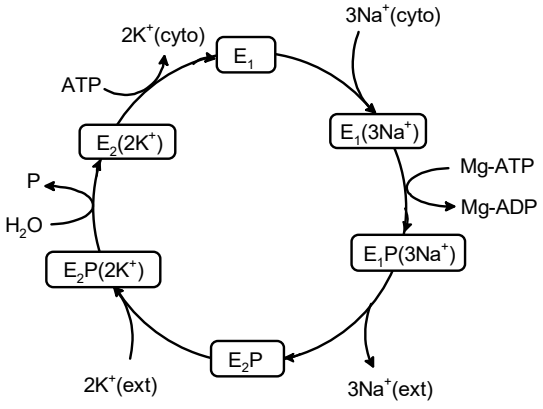


Fig. 6.2 : The cycle of enzyme reactions that accomplish sodium pumping.

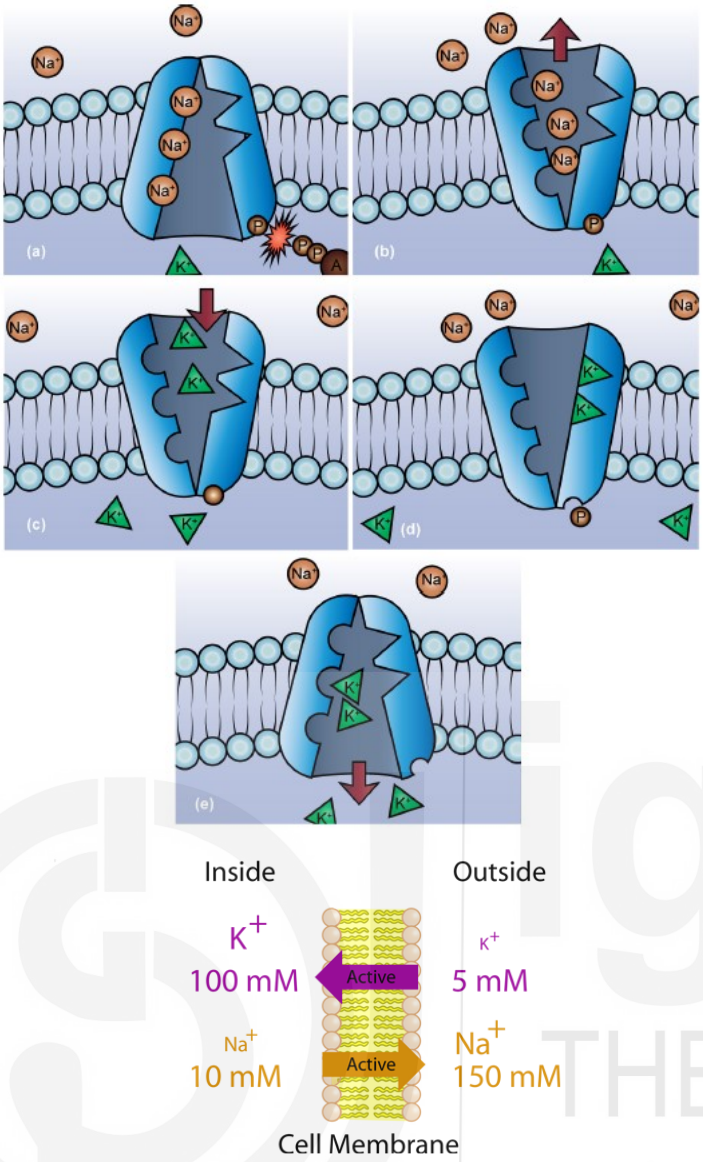


Fig. 6.3 : The Na^+-K^+ pump (The sodium-potassium pump moves toward an equilibrium state with the relative concentrations of Na^+ and K^+ shown at left).

ATP and three Na^+ bind to the inside of the membrane and the enzyme (E_1) gets phosphorylated. The product undergoes a conformation change – eversion (which is like motion through a revolving door) that brings the bound Na^+ to the outside of the cell membrane. There the three Na^+ are replaced by two K^+ ions. The attachment of K^+ triggers dephosphorylation and loss of ATP induces a conformational change that carries the K^+ to the interior of the cell where they are released. This process builds up a charge gradient because three Na^+ are expelled for two K^+ incorporated and so there is a net loss of positive ions, thus the resting membrane potential of the cell becomes slightly more negative. The overall reaction can be summarized by equation 6.1.

$$3Na^+(in) + 2K^+(out) + Mg^{2+}(in) + E\text{-}ATP + H_2O \longrightarrow 3Na^+(out) + 2K^+(in) + Mg^{2+}\text{-}ADP + HPO_4^{2-} + H^+ + E \quad \ldots (6.1)$$

Kinetic studies have confirmed that Mg-ATP is the substrate and free ATP binds to the enzyme and inhibits its activity. Cleavage of the phosphoryl group from ATP proceeds via, an S_N2 mechanism forming a 5 coordinate unstable

intermediate which breaks down completing hydrolysis. An observation supporting this is that minute (10^{-9} mol/L) constants of vanadate (VO_4^{3-}) inhibits the operation of ATPase. VO_4^{3-} binds to ATP and the five coordinate species formed does not break down, conformational changes do not occur and K^+ remain on the outside of the cell membrane.

The novel feature of active transport from an inorganic stand point is the selectivity of the complexation between K^+ and Na^+. You will not find this in simple systems. The question here is that why the enzyme is selective first to Na^+ and then to K^+ in different conformations. Group I cations are not strongly complexing and selectivity in simple system is based upon coulombic forces, differences in ionic radii and hydration enthalpy. Crown ethers are biochemically active ligands, increase permeability of cell membrane towards cation and show specificity (for example 18-Crown 6 (18C6) favours K^+ over Na^+ by factors of nearly 100). This reason of selectivity may be the reason that a ligand can adopt conformation providing chelating site of right size. Bases stronger than water will bind preferably to the smaller, harder acid Na^+ and vice versa. Displacement of water from the softer K^+ is easier. However such complexes where bases are weaker than water will be very weakly bound.

Two kinds of border guards control the movement of ions across cell membranes, namely ion channels and ion pumps. The ion channels allowing the passage of ion through membranes are typically constructed from protein polymers in helical conformation. These helices form the walls of the channels and their precise conformation produce specific geometrical arrangement of a number of potential ligand-metal binding sites.

The selective pm passage of large K^+ ions (ionic radius of 130 pm) over smaller Na^+ ions (100 pm) is a special feature of the potassium channel.

Channels for Na^+ transport are permeable to H^+ whereas K^+ channels are not. These facts can be explained by assuming that Na^+ channels are hydrated and larger. The more strongly hydrated Na^+ moves into the sites inside the channels while exchanging water ligands to bind to the water molecules of the channel in turn. Na^+ channels accept ions by coordination to H_2O molecules inside the channel. These water molecules can transport H^+. The K^+ channels are formed from ligand sites of protein and are dehydrated.

Thus you have learnt in this section that the main function of the sodium-potassium pump is to transport sodium ions out of the cell and potassium ions into the cell. As a result, the most important purpose served by this is that the neurons can function in this sort of condition. Also the cell's membrane potential becomes stable due to the differences in ion concentration.

In this context you should also understand the terms active transport and passive transport. Active transport gets powered by ATP and results in movement of ions inside the cell against the electrochemical gradient, with the help of a special membrane bound protein. After this establishment of an electrochemical gradient inside the cell, a cotransporter uses the same energy to bring in another ion against the concentration gradient. Passive transport involves specific channels for particular ions and carriers may bind to specific proteins and undergo conformational changes to deposit the bound protein inside the cell, which is known as facilitated diffusion. So this sort of passive diffusions takes place along the electrochemical gradient without the use of energy where ions move across the membrane through protein channels.

Before moving to the next section, please try to solve the following SAQ.

SAQ 1

Give the general principle of the sodium-potassium pump.

6.3 ROLE OF Mg^{2+} IONS IN CHLOROPHYLL

In this section we are going to study the role of Mg^{2+} ions in chlorophyll. For this, we are essentially going to study about photosynthesis. Photosynthesis involves a series of complex reactions in the chloroplasts of plants with the overall conversion of water and carbon dioxide to carbohydrates and dioxygen. The overall reaction may be written as

Porophine is a ring or four pyrrole rings linked by methine groups.

$$x CO_2 + x H_2O \longrightarrow (CH_2O)_x + x H_2O \quad \ldots (6.2)$$

All the oxygen comes from oxidation of H_2O. as shown by the use of labelled $H_2\overset{*}{O}$ ($O^* = {}^{18}O$):

Porphyrin is any class of heterocyclic compounds containing four pyrrole rings in a square. It is present in a form with a metal atom in its cavity at the centre, for example, in hemoglobin with iron.

$$x CO_2 + 2x H_2\overset{*}{O} \longrightarrow (CH_2O)_x + x\overset{*}{O}_2 + x H_2O \quad \ldots (6.3)$$

The reaction is endothermic to the extent of about 469 kJ per mole of CO_2 and is initiated by visible solar radiation in the range 600-700 nm. A part of the series of reactions may proceed in dark as well.

Plants absorb light with the help of chlorophylls which are magnesium porphyrin complexes (Fig. 6.4). Other variants of chlorophylls are also known in different algae.

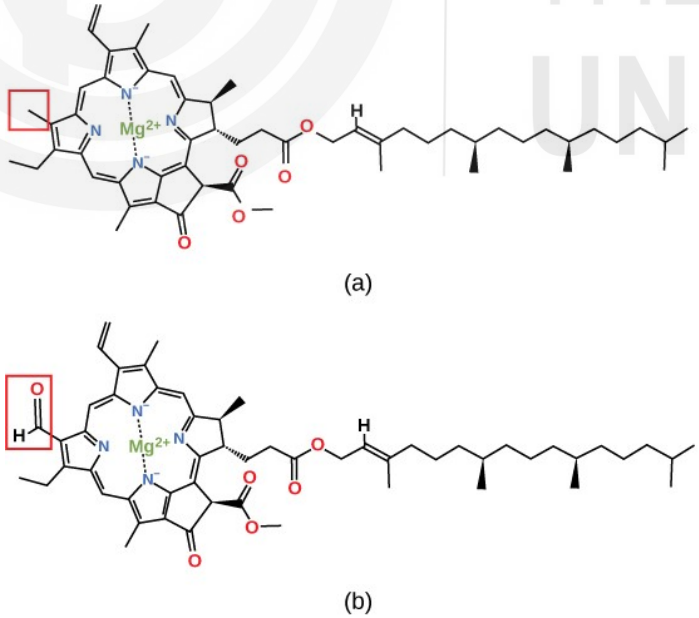


Fig.6.4: The chemical structure of (a) Chlorophyll a, (b) chlorophyll b, Chlorophyll a contains methyl group (-CH_3) and chlorophyll b contains aldehydic group (-CHO) instead.

The molecules are capable of absorbing photons around 700 nm and transmit the energy on to other species in the reaction sequence. The ability to absorb

photon may be due to the conjugated polyene structure of the porphyrin ring system (Fig. 6.4). Some chlorophylls (actually chlorophyll-protein complexes) act as antenna for solar radiation – also called light harvesting centres (LHC), which pass the photon energy in the reaction site through excitation transfer within picoseconds. Other pigments like carotenoids may also be present in LHC; which respond to radiations not absorbed by chlorophylls.

The overall photosynthetic conversion is the outcome of a series of complex reactions and involves light absorption at two different regions of wavelength – photosystem-I (PS I) and photosystem-II (PS II). PS-I is based on a special form of chlorophyll-a having absorption maxima at 700 nm (P-700) while PS II utilizes another form of chlorophyll-a having maxima at 680 nm (P-680).

Photosystem-II: A manganese cluster catalyzes the oxidation of water to oxygen; the metalloenzyme is called oxygen-evolving complex (OEC):

$$2H_2O \longrightarrow O_2 + 4H^+ + 4e \quad \ldots (6.4)$$

The electrons are excited photochemically by P-68O to the primary electron acceptor pheophytin. It is then transferred to photosystem I via the intermediacy of (i) cytochrome b_3, (ii) plastoquinone (iii) Rieske's Fe-S protein (iv) cytochrome *f* and (v) plastocyanin.

Photosystem-I: The electron received from PS-II is further excited by P-7OO and is ultimately used up in the reduction of CO_2 via (i) an Fe-S center (ii) Ferredoxin NADP reductase and (iii) NADPH. The electron flow also results in the formation of ATP from ADP.

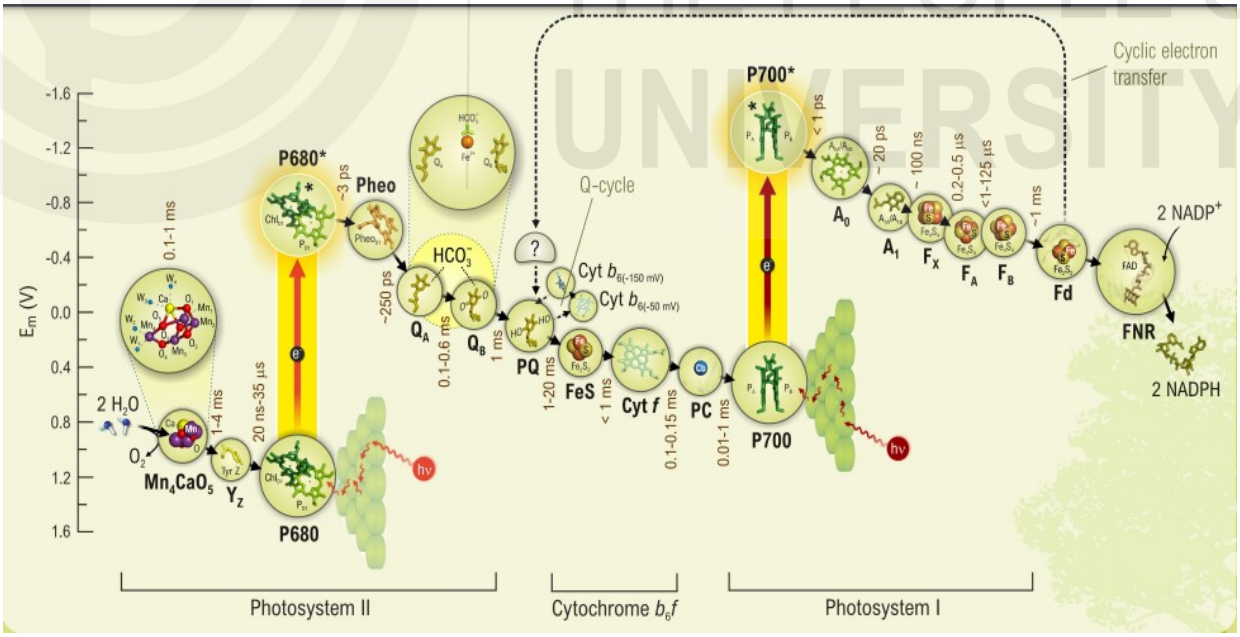


Fig.6.5 : Schematic representation of the main steps in photosynthesis (Z-scheme).

The main reactions which have been schematically represented as in Fig. 6.5 may be summarily represented as

PS-II : $2H_2O \longrightarrow O_2 + 4H^+ + 4e$] x 6

PS-I : $2NADP^+ + 2H^+ + 4e \longrightarrow 2NADPH$] x 6

Dark reaction : $12NADPH + 12H^+ + 6CO_2 \longrightarrow 12NADP^+ + 6H_2O + (CH_2O)_6$

Net reaction : $6H_2O + 6CO_2 \longrightarrow 6O_2 + C_6H_{12}O_6$ … (6.5)

The Mg^{2+} ion serves at least three purposes:

(i) it maintains the rigidity of the macrocyclic structure of chlorophyll and minimizes molecular vibrations; hence energy is not readily lost by thermal vibrations.

(ii) The H_2O molecules coordinated to it mediates H-bonding between adjacent chlorophyll molecules in a stack.

Before moving to the next section, please try to solve the following SAQ.

SAQ 2

What purpose does the magnesium ions serve in the process of photosynthesis?

6.4 SUMMARY

In this unit you have studied about the functions of *s*-block metals pertaining to bioinorganic chemistry especially about the Na^+-K^+ pump. Also, the role of magnesium ions in chlorophyll were discussed.

6.5 TERMINAL QUESTIONS

1. Explain the Na^+-K^+ pump with a suitable diagram.
2. Give the main reactions in photosynthesis.
3. In which proteins in an adult human iron storage and and transport takes place?

6.6 ANSWERS

Self Assessment Questions

1. The general principle of the sodium-potassium pump: Ion pumping occurs at a limited number of positions in the membrane. Three Na^+ ions are pumped outwards and two K^+ inwards for each molecule of ATP hydrolysed to ADP and inorganic phosphate. So, the ion in the membrane, which is to be transported, moves to the other side and gets released with the help of a carrier. These observations are summarized by the cycle of enzyme reactions (provide Fig. 6.3 here), it has been shown that the enzyme undergoes a conformational change during phosphorylation. E_1 and E_2 are two enzyme conformation. Using these clues a mechanism for the sodium-potassium pump was proposed.

2. The Mg^{2+} ion serves at least three purposes:

   i) it maintains the rigidity of the macrocyclic structure of chlorophyll and minimizes molecular vibrations; hence energy is not readily lost by thermal vibrations.

   ii) The H_2O molecules coordinated to it mediates H-bonding between adjacent chlorophyll molecules in a stack.

Terminal Questions

1. The permeability properties of cell membranes depend upon the structure of the membrane and the presence of enzyme system that operate the ion pump. The Na^+-K^+ pump coresponds to active transport i.e the transport of ions through membranes against the natural tendency to diffuse towards lower concentration. The charge distribution established across the membrane by active transport result in an electrode potential as well as difference in chemical composition of the fluids inside and outside the cell.

   Most animal cells have a higher concentration of potassium ions (K^+) inside the cell membrane than outside and a higher concentration of sodium ions (Na^+) outside the cell than inside. Three Na^+ ions are pumped outwards and two K^+ inwards for each molecule of ATP hydrolysed to ADP and inorganic phosphate. The simplest concept is that of a carrier in the membrane which can combine with the ion to be transported, carry it to the other side and release it. (Explain with the help of Fig. 6.3)

2. The main reactions may be summarily represented as

PS-II	:	$2H_2O \longrightarrow O_2 + 4H^+ + 4e\ ] \times 6$
PS-I	:	$2NADP^+ + 2H^+ + 4e \longrightarrow 2NADPH\ ] \times 6$
Dark reaction	:	$12NADPH + 12H^+ + 6CO_2 \longrightarrow 12NADP^+ + 6H_2O + (CH_2O)_6$
Net reaction	:	$6H_2O + 6CO_2 \longrightarrow 6O_2 + C_6H_{12}O_6$

3. For Fe-transport- Transferritin, for Fe-storage- Ferritin.

Source of Figures

Fig. 6.4
https://bio.libretexts.org/Bookshelves/Botany/Botany_(Ha_Morrow_and_Algiers)/Unit_3%3A_Plant_Physiology_and_Regulation/13%3A_Photosynthesis/13.05%3A_The_Light-dependent_Reactions,CC-BY-SA license)

Fig. 6.5
https://newmarketscientific.com/datasheets/Z-scheme%20poster-web.pdf

UNIT 7

ROLE OF IRON IN OXYGEN TRANSPORT

Structure

7.1 INTRODUCTION

In the previous unit, you have learnt about the functions of *s*-block metals pertaining to the living system especially about the sodium-potassium pump. The role of magnesium ions in chlorophyll has also been discussed. In this last unit of the block on bioinorganic chemistry you will be learning about the role of iron in oxygen transport. Hemoglobin and myoglobin will be discussed in detail as they are the best known iron porphyrin compounds. They are metalloproteins and are special as they serve the prupose of oxygen carriers. In this way, units 5, 6 and 7 will give you an insight of bioinorganic chemistry.

Expected Learning Outcomes

After studying this unit you should be able to:

- describe the salient features of hemoglobin; and
- discuss the special characteristics of myoglobin alongwith its structure.

7.2 HEMOGLOBIN

The commonest examples for bioinorganic chemistry in the context of carrying oxygen to the cells is hemoglobin. Before we learn about hemoglobin we should study about iron and its applications in the biosystem.

Even though iron is essential in small amounts for both plants and animals, large amounts of it is toxic. The human body contains nearly 4 g of iron (Fe) and it is the most important trace element, being involved in several processes as below:

(i) As an oxygen carrier in blood of birds, mammal, fish (hemoglobin)

(ii) For oxygen storage in muscles and tissue (myoglobin)

(iii) As an electron carrier in plants, animals, bacteria (cytochromes) and for electron transfer in plants and bacteria (ferredoxin)

(iv) Storage and scavenging of iron (Fe) in animals (ferritin and transferrin)

(v) As nitrogenase (enzyme in nitrogen (N_2) fixing bacteria)

(vi) As a number of other enzymes like aldehyde oxidase, peroxidase (decomposing of H_2O_2), succinic dehydrogenase (aerobic oxidation of carbohydrates).

An adult human contains about 5 litre of blood, each millilitre of which contains 5000 million blood cells; each cell contains 2.5×10^5 (0.25 million) hemoglobin molecules. The normal concentration of hemoglobin in blood of males is 14-16 g/dL and in females it is 13-15 g/dL. As the red blood cells is of short life span that is in the range of 100-120 days, about 1% of these hemoglobin molecules is replaced daily.

As you see that hemoglobin is essential for oxygen transport, whereas myoglobin is engaged in storage of oxygen in muscle tissues. It is used for the controlled release for oxidative phosphorylation as and when necessary. What is the commonality between hemoglobin and myoglobin? Well, the site of reversible binding of oxygen in both is heme (or haem), which is an Fe-protoporphyrin IX where iron is in the Fe^{2+} state.

In hemoglobin, a high-spin Fe^{2+} is coordinated by the four N-atoms of porphyrin and the fifth coordination position is bound to nitrogen atom of an imidazole group in the histidine residue.

Out of nearly 4 g of iron in the human body, 70% is in the form of hemoglobin, the red pigment in the erythrocytes that make up nearly 95% of the dry volume of red blood cells. Here you may note that most of the remaining iron is stored as ferritin. The function of hemoglobin is to pick up oxygen at the lungs. The arteries carry blood to different parts of the body e.g. the muscles, where oxygen is required. Here oxygen is transferred to a myoglyobin molecule and stored until it is required to release energy from glucose. When oxygen is removed from hemoglobin molecules, it gets replaced by a water molecule. Oxygenation of hemoglobin causes release of H^+ from a side chain.

Indirectly this helps to remove carbon dioxide ion from the tissues, since it is converted to the more soluble bicarbonate ion, that is HCO_3^-.

$$CO_2 + H_2O = HCO_3^- + H^+.$$

As deoxygenated hemoglobin absorbs the H^+, the equilibrium shifts towards the right and HCO_3^- is transported between folds of the globin chain and there

is no definite binding between hemoglobin and hydrogen carbonate. Thus, it acts as a carbon dioxide carrier by solubllising carbon dioxide as hydrogen carbonate. The transportation of carbon dioxide is by the amino acid side chain and not by heme group and the blood returns to the heart via the veins. It is pumped to the lungs where hydrogen carbonate is converted in carbon dioxide and the air is exhaled. The blood takes up oxygen and the process is repeated.

Hemoglobin binds carbon monoxide more strongly than oxygen.

The most striking feature regarding hemoglobin acting as an oxygen carrier is the complete reversibility of the process. If the oxygenated complex was too stable then huge amount of energy would be released in the lungs. Then there would be less energy left by the time oxygen is released in the muscles. The oxygenated form is called oxyhemoglobin and the deoxygenated form deoxyhemoglobin. The transfer of oxygen is remarkable as it involves Fe^{2+} and not Fe^{3+}. Ligands like CO, PF_3, CN^- bind with hemoglobin irreversibly. These ligands therefore prevent oxygen transfer and may result in death.

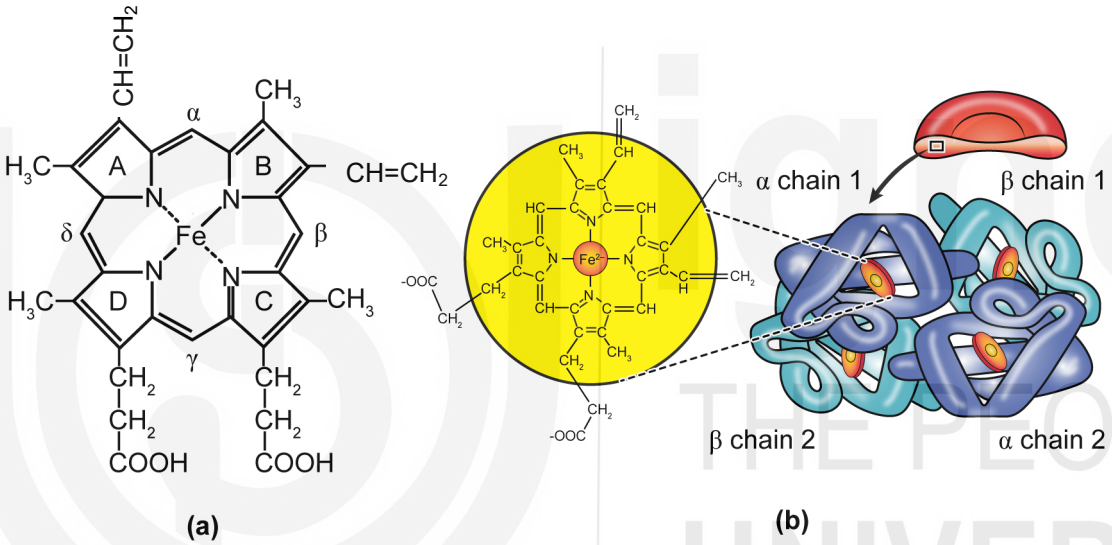


Fig. 7.3: Schematic diagram of haemoglobin showing (a) the heme, α chain 1, α chain 2, β chain 1 and β chain 2. (b) Structure of heme (haeme) containing a protoporphyrin IX, with iron at its centre.

Protoporphyrin IX consists of four pyrrole rings to which four methyl, two propionyl and two vinyl groups are attached.

Molecular mass of hemoglobin has a molar mass of nearly 65,000. It is a conjugated protein made up of four subunits which are four heme units. Each subunit comprises a porphyrin complex (prosthetic group) heme which consists of Fe^{2+} bound to four nitrogen atoms and it is associated with a globular protein called globin. Heme belongs to the class of metal porphyrins or metalloporphyrins. All hemoglobins carry the same heme as the prosthetic group which is iron protoporphyrin IX as shown in Fig. 7.3a. The basic frame work of all porphyrin is built of four pyrrole rings linked together in a larger ring like structure called porphin. By substitution of the eight hydrogen atoms about the edge of the porphin structure with various side chain and groups gives various porphyrin found in nature. Heme contain $-CH_3$ in 1,3,5 and 8, propionyl ($-CH_2CH_2$ COOH) in 6, 7 and vinyl in 2,4 positions. Each hemoglobin molecule has four heme groups bound to globin on the surface as shown in Fig. 7.4. For each heme unit of hemoglobin the four square planar positions of Fe^{2+} are occupied by the four nitrogens of the porphyrin ring with the fifth coordination site of Fe^{2+}, away from the ring occupied by the imidazole nitrogen of a histidine residue (proximal histidine) of the protein

(globin). Globin is made up of polypeptide chain of 141 (alpha) and 146 (beta) amino acids. The vacant sixth site, below the ring is occupied by a loosely held water molecule which is replaced by oxygen on oxygenation.

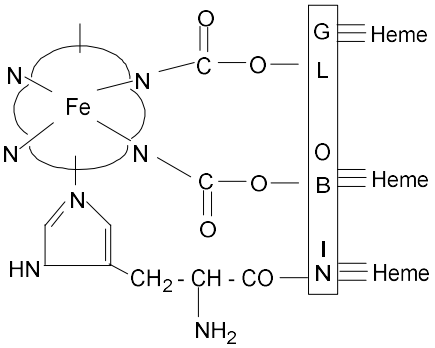


Fig. 7.4: Heme linked to the protein chain (GLOBIN).

The heme is further linked to the protein chain by condensation through the –COOH end of the two propionyl groups. Fe^{2+} in hemoglobin is in the high spin state but in oxyhemoglobin it is low spin. This highly complex molecule is entirely synthesised in the living system by series of condensation reactions beginning with glycine and succinate. The tetrahedral arrangement of hemoglobin subunits gives the tight spherical appearance. Each individual polypeptide is folded in a way so that the exposed surface has the maximum of polar residues and the non-polar interactions remain internal. Thus this large protein becomes water soluble. Heme is held within the cleft of the associated protein molecule namely globin with 150-160 amino acid residues. The polypeptides in hemoglobin are held together by hydrogen bonding, hydrophobic interactions and multiple ionic interactions. The α-chain consists of 141 amino acid residues in linear sequence. The β, ϒ and δ chains consist of 146 amino acids. In a helical arrangement, the 75% of the amino acids are in α or β-chains. The haemoglobin tetramer has two identical dimers (α, β) 1 and (α β) 2 [dimer1 and dimer2] which are held together by polar bonds. There is extensive hydrophobic interaction between the porphyrin part and the globin molecule, besides the covalent interaction between Fe^{2+} and the proximal histidine. This arrangement is considered as its quaternary structure of hemoglobin as depicted in Fig. 7.3.

In the free state octahedral Fe^{2+} in heme has its two coordination positions above and below the plane occupied by water molecules. The magnetic moment of heme shows presence of four unpaired electrons characetrisitic of a weak field octahedral complex of d^6 Fe^{2+}. It is very sensitive to oxygen and readily combines with it to form a labile Fe^{2+} oxygen complex (oxy-heme) intermediate which changes to the Fe^{3+} porphyrin complex which is hemin as shown in Fig. 7.5.

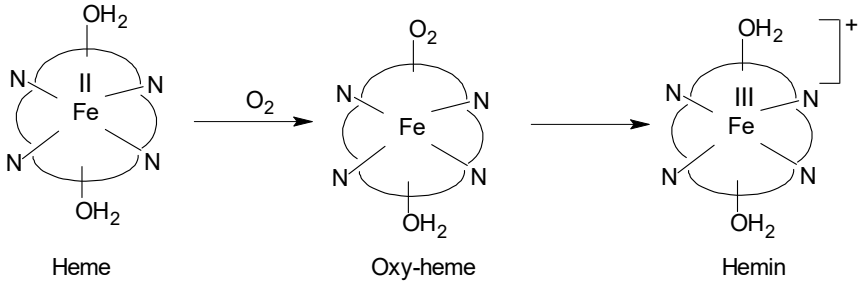


Fig. 7.5: Conversion of heme to hemin.

Now, let us understand how this conversion of heme to hemin is prevented in hemoglobin. In hemoglobin, the Fe^{2+} heme is enclosed in a hydrophobic pocket globin, which provides a medium of low dielectric constant and prevents water molecules or any polar solvent to occupy the sixth position which is occupied by a protein residue. It does not allow simultaneous coordination of oxygen and water which seems to be necessary for electron transfer to transform Fe^{2+} to Fe^{3+}. The access to the iron is reduced as the protein chain is folded about the heme groups. In the absence of globin, Fe^{2+} heme would get irreversibly oxidized to Fe^{3+} which would not be able to transport oxygen. Oxidation is irreversible and a μ-peroxo and finally μ-oxo Fe^{2+} heme dimer is formed as shown below:

$$Fe^{2+}\ \text{heme} + O_2 \longrightarrow Fe^{2+}\ \text{heme}\ O_2^-(\text{superoxide}) \longleftarrow$$

$$Fe^{3+}\ \text{heme}O_2^- + Fe^{2+}\ \text{heme} \longrightarrow \text{Heme}\ Fe^{3+}\ O - O Fe^{3+}\text{heme}$$

$$\downarrow$$

$$\text{Heme}\ Fe^{3+} - O - Fe^{3+}\ \text{heme}$$

This complex cannot carry oxygen reversibly and its formation would stop the transport of oxygen to cells and tissues and all body processes would come to a halt. The role of the globin chain is both chemical and steric.

- It provides a medium of low dielectric constant. Whereby charge separation as in μ-peroxo and μ-oxo dimer is not possible.
- It acts as a carrier of heme and stabilises the heme–oxygen complex such that oxidation of Fe^{2+} in heme is prevented.
- It does not allow simultaneous coordination of oxygen and water which is a prerequisite for oxidation of Fe^{2+} to Fe^{3+}.
- The heme is deep-buried in the protein fold and this prevents the peripheral attachment to Fe^{2+} and thus prevents its oxidation.
- The role of the fifth ligand i.e. histidine is to provide optimum electron density on iron. If the fifth ligand is highly basic then the electron density on Fe^{2+} increases and when oxygen is taken up the ineraction is so strong that the reaction is irreversible and hemoglobin no longer can act as an oxygen carrier. If the fifth ligand is weakly basic then the electron density on Fe^{2+} is not increased sufficiently and the bond between iron and oxygen is not strong and dissociation is rapid. Hence the fifth ligand should have sufficient basicity to maintain optimum bond strength between iron (Fe^{2+}) and oxygen.

There is another histidine situated in the oxygen binding pocket on the side away from the coordinated imidazole base. This is called the distal histidine. Neutron diffraction studies indicate the formation of a hemoglobin bond between the coordinated dioxygen molecule and the N-H proton of the histidine residue: This Fe–O–O…..H–N unit is accommodated very well as there is the angular bend at the coordinated dioxygen atom. This is established by crystallography. The double bond angle is equal to 120°. This coordination is favoured over straight as in CO due to the distal histidine. In carbon monoxide adduct of hemoglobin, X-ray data reveal a distorted structure

in which the Fe–C≡O angle is either bent or tilted off to the proximal histidine N–Fe (natural tendency for N–C=O bond is linear as in carbonyls) axis to avoid steric clash with the distal histidine bond. So you see, how intelligently nature created the Fe-porphyin centre so that oxygen binds to it rather than the toxic carbon monoxide. Here you must note that carbon monoxide often binds more tightly to metal complexes than does oxygen.

Next let us understand the Perutz mechanism in the context of oxygenation of hemoglobin. An interaction between an oxygen molecule and a heme group can affect the position of the protein chain attached to it, which in turn affects other protein chains through hydrogen bonds. The key or trigger to the Perutz mechanism is the high spin Fe^{2+} atom in an oxygenless heme. The hemoglobin has two conformational states. The deoxygenated form is more tense and is called the Tense (T) form, whereas the oxygenated form is the Relaxed (R) form (methemoglobin). The T state is controlled by the subunit-subunit interactions, but R state is more flexible due to the ability of oxygen binding. The radius of high spin Fe^{2+} is nearly 78 pm. The Fe-N bond distance in heme is nearly 218 pm. The size of the central hole is nearly 200 pm and so the Fe atom in the T form must lie above the plane of the heme group. The low spin Fe^{2+} is almost 17 pm smaller than the high spin Fe^{2+}; the Fe-N bond distance is almost exactly 200 pm and low spin Fe^{2+} fits smugly into the hole. Coordination with oxygen causes the Fe atom to drop into the plane of the heme group and the Fe^{2+} changes from high spin in T form to low in R form. Hemoglobin is made up of four subunits and when one subunit takes up an oxygen molecule, the Fe^{2+} contracts and fits into the plane of the ring. As this happens, the histidine residue bound in the fifth coordination site moves with it as shown in Fig. 7.6.

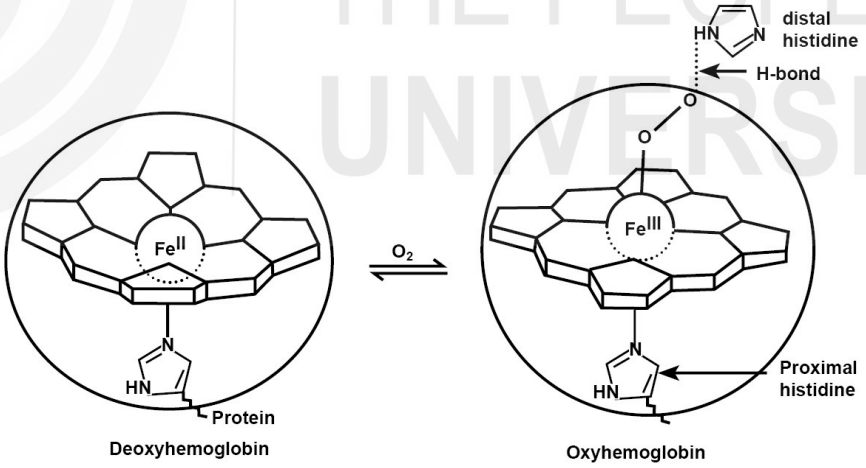


Fig. 7.6: Structural change in hemoglobin on reversible binding of O_2.

The distribution of electrons in the “Tense “ and “Relaxed” form, according to the octahedral symmetry of crystal field theory will be as following:

Since high spin Fe^{2+} contains two electrons in antibonding orbitals, it is larger than low spin Fe^{2+} which has all electrons in bonding orbitals. The Fe-N bond length is related to bond order. In T form two electrons are present in e_g orbitals which decreases the bond order and increases the bond length. Oxygen has π acid properties and is a strong ligand. It induces large crystal field splitting when coordinated to Fe^{2+}; thus the electrons are paired up in low lying t_{2g} orbitals resulting in a low spin complex.

Mechanical depiction of shrinkage of Fe^{2+} and movement into the porphyrin ring causes conformational changes in the globin chain. Since this chain is H-bonded to the other three units, it changes their conformation too and enhances their ability to attract oxygen. This phenomenon is called cooperative effect (allosteric effect). When oxygen pressure is high as in lungs, the oxygen uptake by hemoglobin increases due to cooperative interaction. In a similar way when the blood reaches the muscles where the oxygen pressure is low, once one oxygen is released, the others are released even more readily and the cooperative effect is in reverse order. The deoxygenated form of hemoglobin is also said to have a domed structure as is clear from the Fig. 7.7.

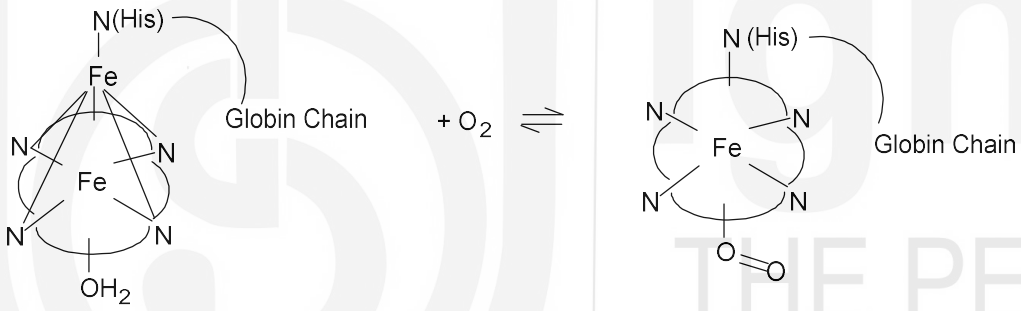


Fig. 7.7: The domed structure of the deoxygenated hemoglobin.

The affinity of hemoglobin for oxygen decreases with decreasing pH, i.e. oxygenation is pH dependent and is favoured at high pH. This is referred to as **Bohr effect**. There is long range electrostatic interaction of the type COO^{-}…….. NH_4^{+} and H-bonded interaction of the type O–H……$^{-}$OOC between the globin chains. Oxygenation of hemoglobin involves in breaking of these interactions and is pH dependent. With increase in pH, breaking of bonds gets favoured and oxygen uptake increases; while at low pH electrostatic interactions are strengthened resulting in lowering of oxygen uptake. So, in region of low pH, hemoglobin has a tendency to release oxygen. In the lungs, the pH is 7.4. The pH at which oxygen binding affinity is lowest is 6-6.5 and the working tissues provide this pH. Blood is well buffered by the presence of carbon dioxide. Carbon dioxide dissolves in water to form carbonic acid, assisted by the enzyme carbonic anhydrase.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \;; \qquad H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad \ldots(7.1)$$

In the muscles there is a good concentration of carbon dioxide and thereafter hemoglobin takes them up. The terminal amine group of protein picks up the H^+ produced (as a result of Eq. 7.1). When the supply of oxygen goes down, glucose undergoes incomplete oxidation to lactic acid. Thus the pH is lowered

leading to further release of oxygen from oxyhemoglobin. So in this section, you have learnt about the structure and functions of hemoglobin. Before moving to the next section try to answer the following SAQ.

SAQ 1

Explain with the help of a suitable figure, how the binding of oxygen takes place in oxyhemoglobin.

7.3 MYOGLOBIN

This is the last section in this block on bioinorganic chemistry where myoglobin, the oxygen carrier for getting oxygen into the cell for glucose oxidation will be taken up. It is the pigment in muscles resembling hemoglobin in its function. It is the simplest example of a respiratory heme protein and its molecule consists of only one polypeptide chain and one heme group. It has a molar mass of nearly 17000 and acts as an oxygen reservoir within the muscle fibre. It has a higher capability for oxygen binding than hemoglobin and can get oxygenated at any given pressure.

The molecule of myoglobin has a capability to bind oxygen. This capability is acquired by the presence of heme, a non-polypeptide prosthetic group consisting of protoporphyrin IX and a central iron atom. This complete structural arrangement is known as protoheme group as shown in Fig. 7.8 (b). This protoheme group is stabilized by histidine residue above (His 64) and below (His 93) as shown in Fig.7.8 (a). The two histidine residues located in the interior part of the molecule also facilitate the binding of iron and oxygen.

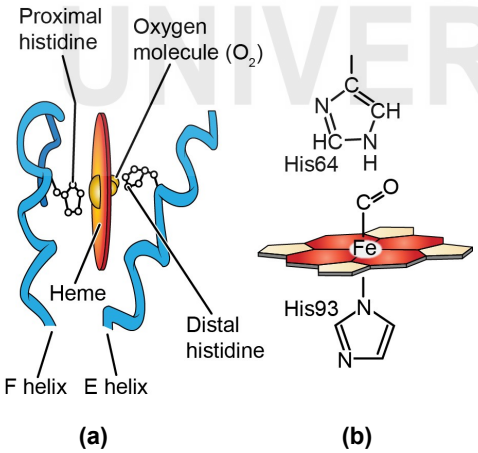


Fig. 7.8: (a) Schematic diagram of myoglobin, (b) Structure of myoglobin showing the protoheme group.

Hemoglobin is a tetramer with electrostatic interaction between different units resulting in a constraint in structure, thus the overall rate of binding with oxygen is less in hemoglobin than with myoglobin and this explains why myoglobin can take up oxygen at low pressure. The function of hemoglobin is to pick up oxygen at high oxygen partial pressure in the lungs and carry it without loss through the blood and release it to myoglobin. So, myoglobin must be having greater affinity for oxygen than hemoglobin at low pressure.

The loading tension refers to the tension of saturation of 95% of pigment with oxygen. The value (pO_2 in tissues is equal to 40mm of Hg) for hemoglobin is

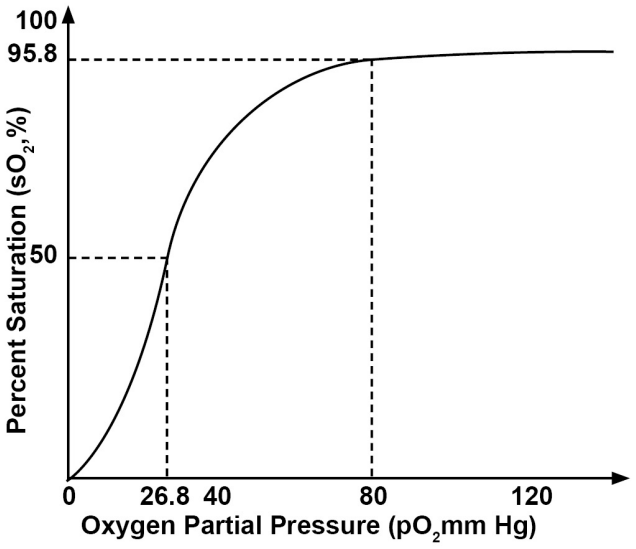


Fig. 7.9: Saturation of hemoglobin with oxygen against partial pressure of oxygen.

73 mm hemoglobin. In tissues pO_2 is low, so hemoglobin can give up oxygen.

The oxygen saturation of hemoglobin as a function of pO_2 is shown in Fig. 7.9. The oxygen saturation curves for hemoglobin and myoglobin have different shapes. It is hyperbolic for myoglobin and sigmoidal for hemoglobin as shown in Fig. 7.10. The isotherm for myoglobin is expected of this shape as the equilibrium is simple with one oxygen which binds to one iron. However the isotherm for hemoglobin has a different shape as the binding of oxygen at one subunit influences the oxygen binding to the other. The shapes of the oxygen saturation curves for myoglobin and hemoglobin are explained in terms of this equilibrium is shown in Fig. 7.10 where it shows the fractional oxygen saturation α as a function of the oxygen partial pressure at pH 7.2.

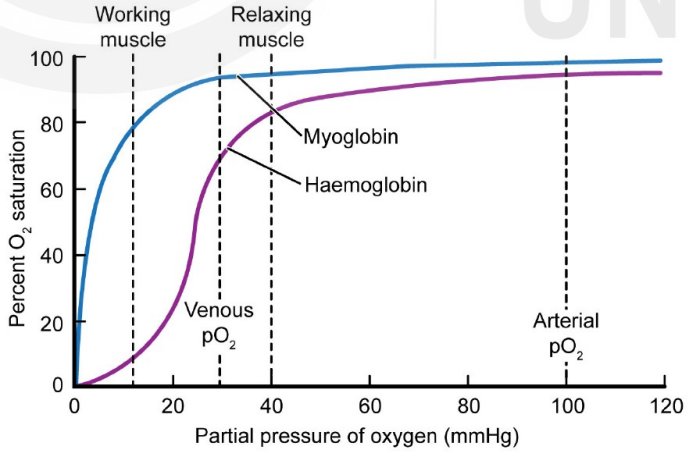


Fig. 7.10: Oxygen saturation curves for myoglobin and hemoglobin.

$$Mb + O_2 \rightarrow MbO_2 \; ; \qquad K = \frac{[Mb_2O_2]}{[Mb]p} \quad = \qquad \ldots(7.2)$$

p partial pressure O_2

α = fractional O_2 saturation = ratio of concentration of myoglobin present as oxymyoglobin (MbO_2) to the total myoglobin concentration.

$$\alpha = \frac{[MbO_2]}{[Mb]+[MbO_2]} = \frac{K[Mb]p}{[Mb]+K[Mb]p} = \frac{[Mb]Kp}{[Mb](1+Kp)} = \frac{Kp}{1+Kp} \quad \ldots(7.3)$$

Saturation factor = $\frac{\alpha}{1-\alpha} = \frac{[Kp/(1+Kp)]}{1-[Kp/(1+Kp)]} = \frac{Kp}{1+Kp} \div \frac{1+Kp-Kp}{1+Kp}$

$$= \frac{Kp}{1+Kp} \times \frac{1+Kp}{1} = Kp \quad \ldots(7.4)$$

This Kp shown in Eq. 7.4 is the saturation capacity, which when equal to 1 means that there is 100% saturation. In case of hemoglobin, the curve can be reproduced if dependence of α on partial pressure is represented as p^n.

$$Hb + nO_2 \rightarrow Hb(O_2)_n \quad K = \frac{[Hb(O_2)_n]}{[Hb]p^n} \quad \ldots(7.5)$$

$$\alpha = \frac{[Hb(O_2)_n]}{[Hb]+[Hb(O_2)_n]} = \frac{K[Hb]p^n}{[Hb]+K[Hb]p^n} = \frac{Kp^n}{1+Kp^n} \quad \ldots(7.6)$$

$$\Rightarrow \frac{\alpha}{1-\alpha} = Kp^n \quad \ldots(7.7)$$

If we take the logarithm of Eq. 7.7, we get

$$\log \frac{\alpha}{1-\alpha} = \log K + n \log p \quad \ldots(7.8)$$

The Eq. 7.8 is referred as Hill equilibrium. If $\log \frac{\alpha}{1-\alpha}$ is plotted against log p then the slope will be 1 for myoglobin as n = 1 and for hemoglobin it is 2.8 (n = Hill's constant). This plot is called Hill's curve. Hill's constant refers to the degree of cooperativity between different heme units. Since myoglobin is a monomer it does not have the feature of cooperativity. Hemoglobin picks up of oxygen in a stepwise manner. In this process, steric hindrance comes into play and so the maximum number of oxygen picked up is reduced to three.

Difference between hemoglobin (Hb) and myoglobin (Mb)

- In terms of its structure, hemoglobin is made up of four subunits, myoglobin has only one subunit
- Hemoglobin has constraint in structure due to electrostatic and other interactions between different subunits, myoglobin has no such constraint.
- Hemoglobin picks up oxygen only at high partial pressure whereas myoglobin can pick up oxygen at any pressure. The nature of oxygen binding curve of hemoglobin is sigmoidal whereas in myoglobin it is hyperbolic curve.
- The binding of oxygen to hemoglobin enhances binding of additional oxygen to the hemoglobin molecule. In other words oxygen binds cooperatively to hemoglobin whereas no such effect is noted in myoglobin.

- The affinity of hemoglobin for oxygen is dependent on pH whereas that of myoglobin is not affected by pH (Bohr Effect) .
- Dissociation of oxyhemoglobin is influenced by concentration of carbon dioxide [CO_2] and temperature (T). In muscular tissue both pressure of CO_2 and temperature are high. High pressure of CO_2 results in low pH and thus hemoglobin gives up oxygen readily.
- Affinity of hemoglobin for oxygen is controlled by 2,3-diphosphoglycerate present in red blood cell (RBC). Total hemoglobin has less affinity for 2,3-DPG in comparison to adult hemoglobin and hence higher affinity for oxygen. This facilitates transfer of oxygen from mother's oxyhemoglobin to fetal hemoglobin. Myoglobin is found in muscles.

So in this section, we have discussed about the structure and functions of myoglobin and also compared them with those of hemoglobin. Now, answer the following SAQ.

SAQ 2

Mention any three differences between hemoglobin and myoglobin.

7.4 SUMMARY

In this unit, you have studied the role of iron in oxygen transport. You have learnt about the different features of hemoglobin and myoglobin and compared them too. In this way, you have learnt all about bioinorganic chemistry with the help of units 5, 6 and 7 of this block. This brings us to the end of this section of inorganic chemistry.

7.5 TERMINAL QUESTION

1. What is the "cooperative effect" regarding the binding of oxygen with hemoglobin?
2. Give the relevant equations for the equilibrium constant regarding the oxygen binding by myoglobin.

7.6 ANSWERS

Self Assessment Questions

1. In oxyhemoglobin the plane of the porphyrin ring becomes nearer to the iron which was out of plane. This serves as a trigger for the cooperative binding of oxygen to the four subunits in hemoglobin. When there is no oxygen, these subunits interact between themselves so that the proximal histidine can not move the five coordinate iron towards the plane of the porphyrin.

2. The difference between hemoglobin and myoglobin are:

S.No.	Hemoglobin	Myoglobin
i)	Hemoglobin takes up oxygen only at high partial pressure	Myoglobin can take up oxygen at any pressure
ii)	Hemoglobin can take up oxygen in a particular pH	Myoglobin can take up oxygen at any pH
iii)	Hemoglobin has four heme groups per molecule	Myoglobin has only one heme group per molecule

Terminal Questions

1. When dissolved oxygen is present hemoglobin undergoes certain changes in its conformation. As one iron binds to an oxygen molecule, the additional oxygen molecule can be much easily binded to the hemoglobin because of certain changes in its molecular shape. So, total four irons of the hemoglobin can take up one oxygen each, and the equilibrium constant increase for each consecutive step. This triggering of binding of oxygen is known as cooperative effect. Similarly, the removal of one oxygen also helps in the removal of the remainder oxygens.

2. α = fractional O_2 saturation = ratio of concentration of myoglobin present as myoglobin O_2 to the total myoglobin concentration.

$$\alpha = \frac{[Mb_2O_2]}{[Mb]+[Mb_2]} = \frac{K[Mb]p}{[Mb]+K[Mb]p} = \frac{[Mb]Kp}{[Mb]+(1+Kp)} = \frac{Kp}{1+Kp}$$

$$= \frac{Kp}{1+Kp} \times \frac{1+Kp}{1} = Kp \Rightarrow \text{saturation capacity} = = 100\%$$

Further Reading

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