INORGANIC BIOCHEMISTRY

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Inorganic biochemistry is a branch of chemistry that deals with the study of the role of metals in biology or biological system. Inorganic biochemistry includes the study of both natural phenomena (behaviour of metalloproteins as well as artificially introduced metals (essential or non-essential metals in medicine and toxicology). Many biological processes like respiration depend upon the molecules which fall within the boundries of inorganic chemistry. This particular discipline also includes the study of inorganic models that mimics the behaviour of metalloproteins. As a mixture of biochemistry and inorganic chemistry, inorganic biochemistry is very important in elucidating the involvement of electron transfer proteins, substrate bindings and activation, atom and group transfer chemistry and metal properties in biological chemistry. It's also involve the study of role of metal species in biological systems.

Essential and trace elements in biological processes:

An essential elements is required for the maintenance of life and its absence results in several malfunctions of the organs or death. A total of 112 elements are known, of which 30 elements are essential for life processes in plants and animals.

Chemical elements essential to life forms can be categories into four major groups:

1. Bulk elements: (H/H^+ , C , N , O , P , S).
2. Macro minerals and ions (Na/Na^+ , K/K^+ , Mg/Mg^{+2} , Ca/Ca^{+2} , Cl^- , PO_4^{-3} , SO_4^{-2}).
3. Trace elements Fe / Fe^{II} , Fe^{III} , Fe^{IV} , Zn/Zn^{II} , Cu/Cu^{I} , Cu^{II} , Cu^{III}.

4. Ultratrace elements: non metals (F, F^- , I , I^- , Se/Se^{-2} , Si/Si^{IV} , As , B)

   and metals (Mn/Mn^{II} / Mn^{III} , Mn^{IV} , Mo/Mo^{IV} , Mo^{II}, Mo^{IV} , Co/Co^{II}, Co^{III} , Cr/Cr^{III} , Cr^{VI} , V/V^{III} , V^{V} , V^{VI}, Ni^{I} , Ni^{II} , Cd/Cd^{II} , Sn/Sn^{II} , Sn^{III}, Pb/Pb^{II} , Li/Li^+.

Criteria for essential elements:

1. Removal of the element from the diet causes a physiological deficiency.
2. The deficiency is relieved by the addition of that element in the diet.
3. A specific biological function is associated with a particular element.

Table (1): the approximate percentages of some selected essential elements by weight for adult human.

Elements	Percentage (by weight)
Oxygen	53.6
Carbon	16.0
Hydrogen	13.4
Nitrogen	2.4
Sodium, potassium, Sulfur	0.10
Chlorine	0.09
Magnisium	0.04
Iron	0.005
Zinc	0.003
Copper, Bromine	2×10^{-4}
Selenium, Manganese, Arsenic, Nickel	2×10^{-3}
Lead, Cobalt	9×10^{-6}

Macro minerals and ions:

- **Sodium (Na):**

Sodium is the major component of extracellular fluid. It mainly exists as chloride and bicarbonate. It is the primary cation (positive ion) in extracellular fluids such as blood plasma of animals and humans. These fluids transport nutrients and wastes. Sodium regulates acid base equilibrium in biological systems. It also helps in maintaining osmotic pressure of the body fluid and thus, protect the body against fluid loss. Sodium regulates osmotic pressure the body. Many enzyme reactions are controlled by Na^+ ion.

- **Potassium (K)**

Potassium is a very important element required for the proper function of all cells, tissues and organs in the human body. It is an electrolyte that conducts electricity in the body, along with sodium chloride, calcium, and magnesium, Various functions of potassium in biological systems are as follows:

1. Potassium plays a key role in skeletal and cardiac systems and smooth muscle contraction.
2. It also regulates acid base equilibrium like sodium in extracellular fluid.
3. Potassium controls osmotic pressure and water reaction.
4. It is important for metabolic function such as protein biosynthesis by ribosome.

The Na^+/K^+ Pump (Na^+/K^+ ATPase)

The enzyme that maintains the concentration diferential of Na^+ and K^+ inside and outside a cell, is an example of the high discrimination between alkali metal ions that has evolved with biological ligands. The ions are pumped against their concentration gradients by coupling the process 0to ATP hydrolysis.

- **Magnesium (Mg)**

Magnesium ions (Mg^{+2}) are important because of their role in the normal functioning of muscle and nerve tissue, bone formation and as a component of many coenzymes. Green plants conduct the process of photosynthesis in the presence ef sunlight and the magnesium containing pigment chlorophyll porphyrin^{-2} forms an magnesium complex which is chlorophyll in plants. Chlorophyll responsible for photosynthesis in plants. Photosynthesis is a series of redox reaction and it converts water and carbon dioxide into glocouse and oxygen.

$$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$$

The role of the magnesium in chlorophyll:

1. Makes the molecule rigid to prevent degradation due to vibrations.
2. It enhances the rate (catalyses) at which the short lived chlorophyll molecule in the singlet excited state is transformed to the chlorophyll molecule in the triplet state.

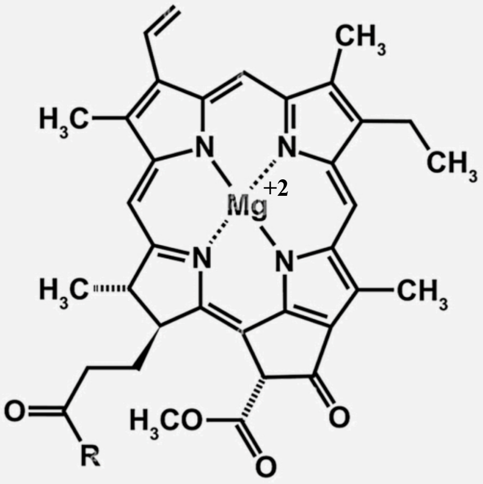


Figure (1): Chlorophyll Structure

- **Calcium (Ca):**

Large amount of Calcium present in the bone tissue. The approximate composition of bone crystals corresponds to $Ca_{10} (PO_4)_5 (OH)_2$. Calcium is involved in enzymatic system. It plays a role in regulating muscle contraction, transmitting nervous pulses and acts as an agent of blood coagulation calcium enters the body with food in the form of neutral phosphate which is converted into the readily soluble acid phosphates, $CaHPO_4$ and $Ca (H_2 PO_4)_2$ by the acidity in the digestive tract. These acid phosphates are absorbed in the intestine and pentrate the blood plasma the concentration of Ca^{+2} ions in human blood between 8.8 - 10.8mg/L. Nearly half of this calcium is in the form of aqua-ions. Capable of permeating membranes while the rest is bound with albumin and does not pass across membranes.

Along with K^+ and Mg^{+2}, the Ca^{+2} ions effect the rate of muscular contraction including that of cardioc muscle and the action of cardiac glycosides. An overdose of glycosides leads to cardiac arrest. Injection of K^+ and Mg^{+2} ions into the cardiac muscle mitigates the action of glycosides while that of Ca^{+2} enhances it. Excess calcium present in the body leads to the formation of stone, deposition of salts, etc.

- **Chloride (Cl^-):**

Cl^- are important in the acid-base balance of blood and the water balance of the body and in the formation of hydrochloric acid in the stomach. They are found in intracellular and extracellular fluids.

- **Phosphate (PO_4^{-3}):**

Phosphate ions have more roles than any other inorganic ions in mammals. They are important for the formation of bones and teeth, as a buffer in blood, Their role in muscle contraction and nerve impulses, as compounent of many coenzymes, for their role in transfer and storag energy in ATP and as a component of DNA and RNA.

Trace Metals

Zinc (Zn)

Zinc was shown in 1934 to be essential for the normal growth and development of mammals, and present to the extent of 1.4 to 2.3 gm in the human body. Although Zinc (II) is a d^{10} ion it has many similarities to the transition metal ions. In aqueous solution, oxidation states other than Zn (II) do not occur Zn (II) acts predominantly as a Lewis acid, and is found in many metalloenzymes such as carboxypeptidase and carbonic anhydrase. Zinc complexes are generally good buffers, and are used in PH control in vivo. In the body there are about 18 Zinc metalloenzyme and about 14 zinc ion activated enzymes. Zn (II) being a symmetrical d^{10} ion is fairly hard, and interacts strongly with oxygen and nitrogen donors.

- **Iron Fe:**

Iron is the most abundant transition metal in the human body 4.2 to 6.1 g. in the average man. In aqueous solution, Fe (II) and Fe (III) are the normal oxidation states. In haemoglobin and myoglobin (the oxygen binding proteins of blood and muscle) iron is present as Fe (II) in protoporphyrin.

In the catalase, which are very large molecules (M= 247.500) and oxidases, iron is present as Fe(III). Catalase catalyses the decomposition of hydrogen peroxide.

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

For redox system such as the cytochroms or ferredoxins the redox potential is tuned by the ligands present.

- **Copper (Cu)**

Copper is known in two oxidation state in solution Cu (I) and Cu(II) However some Cu (II) complexes of tripeptides can be oxidized by air to Cu (III) species, and so Cu (III) may be of biological importance. The relative gain in crystal field stabilization energy for the change from d^a Cu (II), to d^8 Cu (III) is an important factor in the overall thermodynamic stability of the Cu (III)-peptide complexes.

It would be expected that copper's main role in vevo would be in redox reactions copper is present in about 12 enzymes whose functions range from the utilization of iron to the pigmentation_ of the skin.

- **Molybdenum (Mo):**

Molybdenum is the only element of the second transition series Known to be essential to life Molybdenum is probably absorbed into living system as the tetrahedral molybdate anion MoO_4^{-2} which is present in soution at PH 7 or above. A well-developed Mo chemistry is known Mo(0) to Mo (VI) Although the other metals in the same triad chromium and tungsten display a similar range of oxidation states, these oxidation state are less readily accessible to biological systems for example Cr (III) is too difficult to oxidise and W(VI) too difficult to reduce Molybdenum was shown to be essential for biological nitrogen fixation (the reduction of N_2 to ammonia) which occurs in many legumes (peas, beans etc.). The major source of nitrogen for non-leguminous plants is the nitrate ion NO_3^- Another molybdenum containing enzyme nitrate reductase catalyses the reduction of NO_3^- to NO_2^- in the first step in this pathway for assimilation of inorganic nitrogen. Molybdenum enzyme also play several important roles in animal metabolism.

- **Manganese (Mn).**

Manganese (II) is found in a variety of enzymes such as pyruvate Carboxylase and oxaloacetate decarboxylase, where it functions primarily as a Lewis acid. Manganese containing superoxide dismutases. has been isolated from a variety of organisms. A diamine oxidase which contains manganese is also known. Manganese is also required for photosynthetic oxygen evolution, also appears to play an important role in several metabolic processes such as bone growth, glucose tolerance, reproduction, and development of the inner ear.

- **Cobalt (Co):**

Unique biological role in cobalamin (B_{12}-Coenzymes). Cobalt is present as a central atom of Vitamin B_{12}. Ruminants can synthesize Vitamin B_{12} in their rumen. Vitamin B_{12} is necessary for a functioning energy (utilization of propionic acid gluco neogenesis) and protein metabolism. (methionine formation) in the liver. A prolonged deficiency of cobalt leads to a decrease in feed intake, limited growth and reduced milk yield.

Chromium (Cr), Vanadium (V) and Nickel (Ni) small quantities uncertain biological roles, sugar metabolism (Cr), Ni only in plants and bacteria (role in CH_4 production) and SOD enzymes.

Table (2): Average element compositions of a 70 kg man

Elements	g
Na	70
K	250
Mg	42
Ca	1700
Mn	<1
Fe	6
Co	<1
Ni	<1
Cu	<1
Zn	<1-2
Mo	<1
H	6580
E	12590
N	1815
O	43550
P	680
S	100
Cl	115
I	<1

Transition metals in the biological system:

The role of the Central metal in biomolecules:

1. Metal ions can have structural roles, catalytic roles, or both.
2. Metals that have catalytic roles will be present at the active site of the biomolecule which will likely be a metalloprotein (a metalloenzyme).

3. The reactivity of a metalloprotein is defined by the nature of the metal, particularly it's electronic structure and oxidation state.
4. This in turn, is determined by its coordination environment (ligand donor atoms) and molecular geometry, which is Provided by the architecture of the protein surrounding the metal.

The importance of the electronic structure of the metal center:

1. The electronic structure and spin state of a metal center defines its chemical reactivity as a redox center (i.e., it controls its efficiency at accepting or donating electrons).
2. The electronic structure of a metal center defines its chemical reactivity as a Lewis acid (electron pair accepter) which enable it to bind ligands (O_2, N_2, CO, …) for transport, activation and reaction.
3. The electronic structure and spin state of a metal center its investigation and characterization through electronic Mossbauer and EPR spectroscopy and through magnetic measurements. Metal ions coordinate to proteins, nuclic acids and lipids.

Transition metals are extremely good catalytic active sites in enzymes because they:

1. Are stable in a variety of geometries and coordination number.
2. Have multiple coordination sites.
3. Are stable in a variety of oxidation states.
4. Are able to change the reactivity of ligands.
5. Have weak coordinate bonds (where needed).
6. Are capabe of stabilizing intermediates.

Uptake and Storage of Transition Metals.

Uptake and storag of Iron (Fe).

There are three possible dietary levels for any essential element: deficient, optimal, and toxic, in order of increasing concentration in the diet. If the concentration of an essential element in the diet is too low, an organism must be able to extract the element from the environment and concentrate it. If the concentration of an essential element in the diet is too high, an organism must be able to limit its intake to avoid toxic effects. Moreover, organisms must be able to switch off the uptake process rapidly if dietary levels rise suddenly, and they must be able to store essential elements for future use.

Three distinct steps are involved in transition metal uptake. First, the metal must be "mobilized" from the environment and brought into contact with a cell in a form that can be absorbed.

Second, the metal must be transported across the cell membrane into the cell.

Third, the element must be transported to its point of utilization within a cell or to other cells within the organism. In our discussion, we focus on the uptake, transport, and storage of iron, which illustrates the most important points. Because iron deficiency (anemia) is the most widespread nutritional deficiency known in humans, the uptake of iron is especially well understood.

The solubility of metal ions such as Fe^{3+}, which form highly insoluble hydroxides, depends on the pH and the presence of complexing agents. In an oxygen-containing atmosphere, iron exists as Fe(III) because of the positive reduction potential of Fe^{3+}

$$(Fe^{3+} + e^{-} \rightarrow Fe^{2+},\ E^{\circ} = +0.77\ V)$$

Because ferric hydroxide $[Fe\ (OH)_3]$ is highly insoluble ($K_{sp} \approx 1\times10^{-39}$), the equilibrium concentration of $Fe^{3+}(aq)$ at pH 7.0 is very low, about 10^{-18} M. You would have to drink 2×10^{13} L of iron-saturated water per day (roughly 5 ml^3) to consume the recommended daily intake of Fe for humans, which is about 1 mg/day. Animals such as humans can overcome this problem by consuming concentrated sources of iron, such as red meat, but microorganisms cannot.

Consequently, most microorganisms synthesize and secrete organic molecules called siderophores to increase the total concentration of available iron in the surrounding medium. Siderophores are generally cyclic compounds that use bidentate ligands, such as the hydroxamate and catecholate groups shown here, to bind Fe^{3+} in an octahedral arrangement.

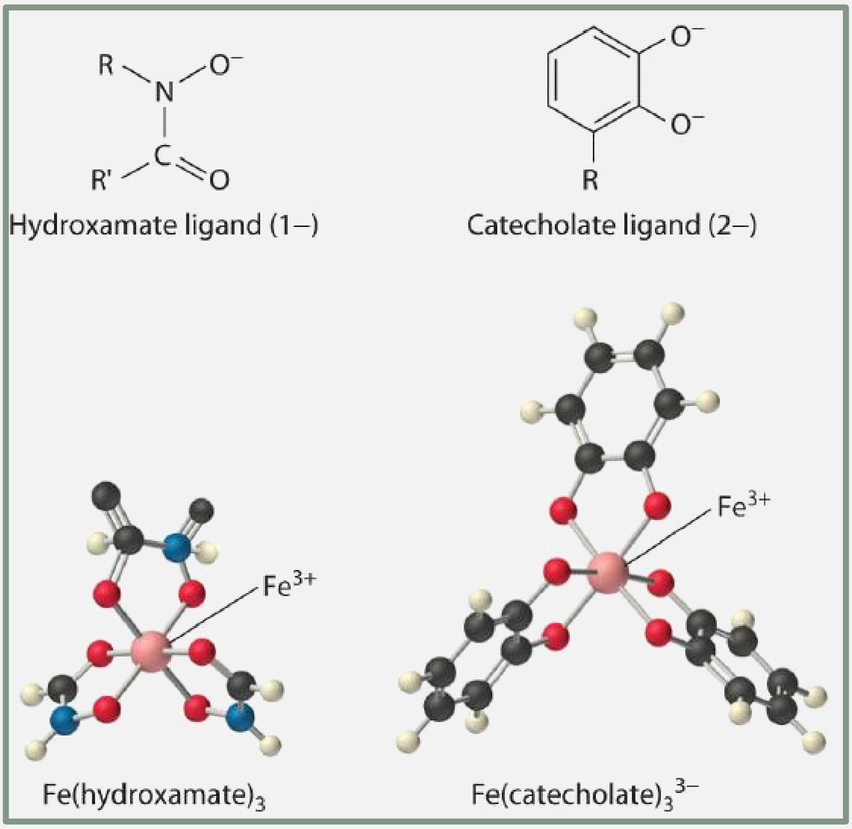


Figure (2): Iron complexes in biological systems. Iron(III) forms very stable octahedral complexes with hydroxamate and catecholate ligands.

The stability of the resulting Fe^{+3} complex due to the chelate effect, the formation constants for the Fe^{3+} complexes of ferrichrome and enterobactin are about 10^{32} and 10^{40}, respectively, which are high enough to allow them to dissolve almost any Fe (III) compound.

Siderophores increase the $[Fe^{3+}]$ in solution, providing the bacterium that synthesized them (as well as any competitors) with a supply of iron. In addition, siderophores neutralize the positive charge on the metal ion and provide a hydrophobic "wrapping" that enables the Fe^{3+}–siderophore complex to be recognized by a specific protein that transports it into the interior of a cell. Once it is inside a cell, the iron is reduced to Fe^{2+}, which has a much lower affinity for the siderophore and spontaneously dissociates. In contrast, multicellular organisms can increase the concentration of iron in their diet by lowering the pH in the gastrointestinal tract.

At pH 1.0 (the approximate pH of the stomach), most Fe(III) salts dissolve to form $Fe^{3+}(aq)$, which is absorbed by specific proteins in the intestinal wall. A protein called transferrin forms a complex with iron (III), allowing it to be transported to other cells. Proteins that bind tightly to Fe(III) can also be used as antibacterial agents because iron is absolutely essential for bacterial growth. For example, milk, tears, and egg white all contain proteins similar to transferrin, and their high affinity for Fe^{3+} allows them to sequester iron, thereby preventing bacteria from growing in these nutrient-rich media. Iron is released from transferrin by reduction to Fe^{2+}, and then it is either used immediately (e.g., for the synthesis of hemoglobin) or stored in a very large protein called ferritin for future use. Ferritin uses oxygen to oxidize Fe^{2+} to Fe^{3+}, which at neutral pH precipitates in the central cavity of the protein as a polymeric mixture of $Fe(OH)_3$ and $FePO_4$. Because a fully loaded ferritin molecule can contain as many as 4500 Fe atoms, which corresponds to about 25% Fe by mass, ferritin is an effective way to store iron in a highly concentrated form. When iron is needed by a cell, the Fe^{3+} is reduced to the much more soluble Fe^{2+} by a reductant such as ascorbic acid (vitamin C). The structure of ferritin contains channels at the junctions of the subunits, which provide pathways for iron to enter and leave the interior of a molecule.

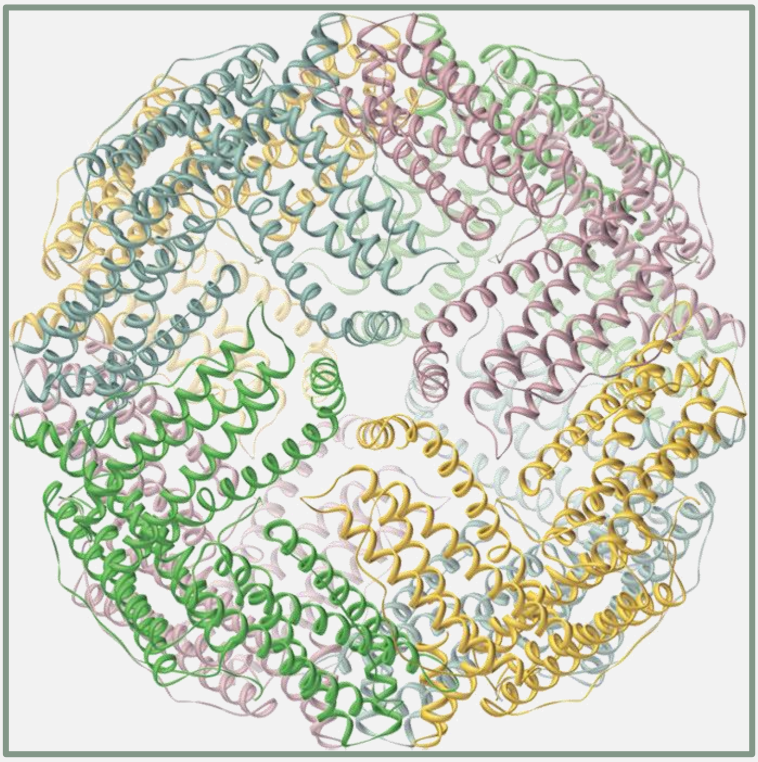


Figure (3): ferritin, an Iron storge protein. A schematic drawing of the structure of iron-loaded ferritin, showing the almost spherical protein shell inside which the iron hydroxide/phosphate core is formed.

Metalloproteins and Metalloenzymes.

A protein that contains one or more metal ions tightly bound to amino acid side chains is called a metalloprotein; some of the most common ligands provided by amino acids are shown here. A metalloprotein that catalyzes a chemical reaction is a metalloenzyme. Thus all metalloenzymes are metalloproteins, but the converse is not true. Recent estimates suggest that more than 40% of all known enzymes require at least one metal ion for activity, including almost all the enzymes responsible for the synthesis, duplication, and repair of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid).

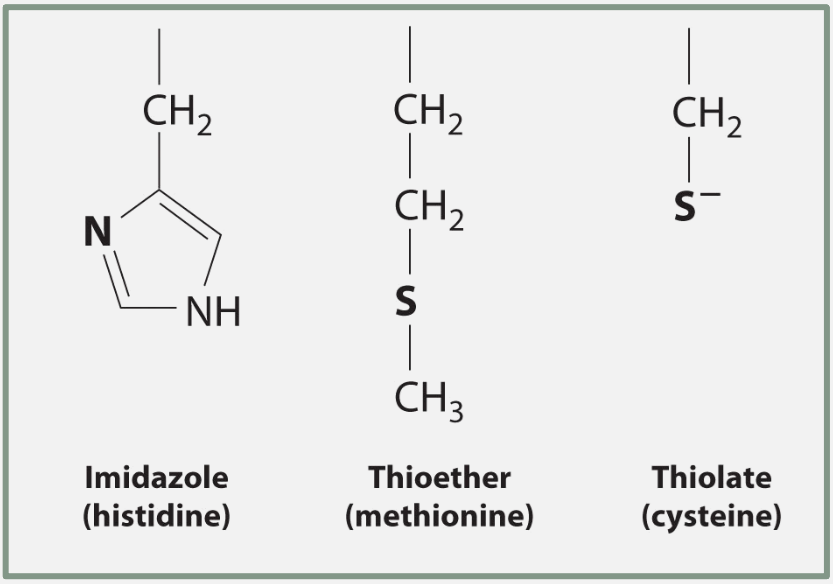


Figure (4): Most common ligands provided by amino acids

Electron-Transfer Proteins:

Proteins whose function is to transfer electrons from one place to another are called electron-transfer proteins. Because they do not catalyze a chemical reaction, electron-transfer proteins are not enzymes; they are biochemical reductants or oxidants consumed in an enzymatic reaction. The general reaction for an electron-transfer protein is as follows:

$$M^{n+} + e^{-} \Leftrightarrow M^{(n-1)+}$$

Because many transition metals can exist in more than one oxidation state, electron-transfer proteins usually contain one or more metal ions that can undergo a redox reaction. Incorporating a metal ion into a protein has three important biological consequences:

1. The protein environment can adjust the redox potential ($E^{0\prime}$), of the metal ion over a rather large potential range, whereas the redox potential of the simple hydrated metal ion [$M_n^+(aq)$], is essentially fixed.
2. The protein can adjust the structure of the metal complex to ensure that electron transfer is rapid.
3. The protein environment provides specificity, ensuring that the electron is transferred to only the desired site.

Three important classes of metalloproteins transfer electrons: blue copper proteins, cytochromes, and iron–sulfur proteins, which generally transfer electrons at high (> 0.20 V), intermediate (±0 V), and low (−0.20 to −0.50 V) potentials, respectively.

Although these electron-transfer proteins contain different metals with different structures, they are all designed to ensure rapid electron transfer to and from the metal.

Thus when the protein collides with its physiological oxidant or reductant, electron transfer can occur before the two proteins diffuse apart. For electron transfer to be rapid, the metal sites in the oxidized and reduced forms of the protein must have similar structures.

Table (3): Some Properties of the Most Common Electron-Transfer Proteins

Protein	Metal center	m/e^- transferred	Reduction potential
Iron – sulfur proteins	$[Fe\ (SR)_4]^{2}$	Fe 1	–0.1 to + 0.1
	$[(RS)_2\ Fe\ S_2\ Fe\ (SR)_2]^{2}$	Fe 2	–0.2 to – 0.4
	$[Fe_3\ S_4\ (SR)_3]^{3-}$	Fe 3	–0.1 to – 0.2
	$[Fe_4\ S_4\ (SR)_4]^{2-}$	Fe 4	–0.3 to –0.5
Cytochromes	Fe – heme (low spin)	Fe 1	~0
Blue copper proteins	$[Cu\ (Im)_2\ (SR)\ (SR_2)]^{-}$	Cu 1	≥+0.20

*** SR= A sulfur bound to an organic group.**
*** Im= Imidazole.**

Blue Copper Proteins

Blue copper proteins were first isolated from bacteria in the 1950s and from plant tissues in the early 1960s. The intense blue color of these proteins is due to a strong absorption band at a wavelength of about 600nm. Although simple Cu^{2+} complexes, such as $[Cu\ (H_2O)_6]^{2+}$ and $[Cu(NH_3)_4]^{2+}$, are also blue due to an absorption band at 600 nm, the intensity of the absorption band is about 100 times less than that of a blue copper protein. Moreover, the reduction potential for the Cu^{2+}/Cu^{+} couple in a blue copper protein is usually +0.3 to +0.5 V, considerably more positive than that of the aqueous Cu^{2+}/Cu^{+} couple (+0.15 V). The copper center in blue copper proteins has a distorted tetrahedral structure, in which the copper is bound to four amino acid side chains.

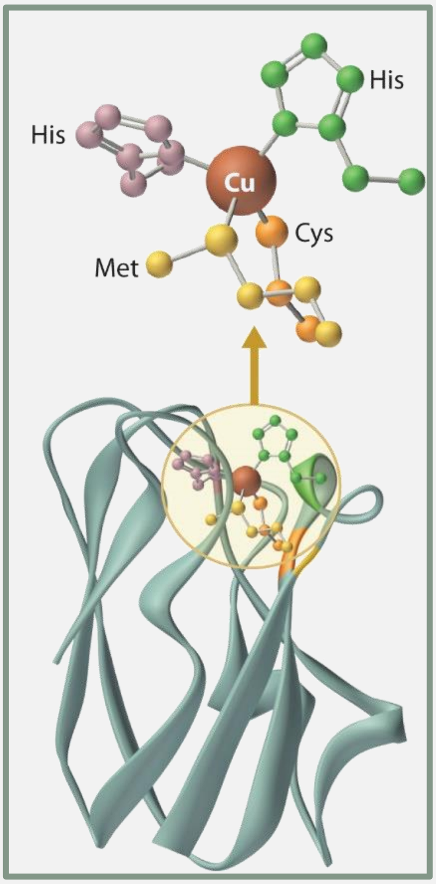


Figure (5): the copper is coordinated by four ligands (two histidine imidazole nitrogen atoms, a cysteine thiolate sulfur and a thioether sulfur of methionine in a roughly tetrahedral arrangement)

Although the most common structures for four-coordinate Cu^{2+} and Cu^{+} complexes are square planar and tetrahedral, respectively, the structures of the oxidized (Cu^{2+}) and reduced (Cu^{+}) forms of the protein are essentially identical. Thus the protein forces the Cu^{2+} ion to adopt a higher-energy structure that is more suitable for Cu^{+}, which makes the Cu^{2+} form easier to reduce and raises its reduction potential.

Moreover, by forcing the oxidized and reduced forms of the metal complex to have essentially the same structure, the protein ensures that electron transfer to and from the copper site is rapid because only minimal structural reorganization of the metal center is required. Kinetics studies on simple metal complexes have shown that electron-transfer reactions tend to be slow when the structures of the oxidized and reduced forms of a metal complex are very different, and fast when they are similar. You will see that other metal centers used for biological electron-transfer reactions are also set up for minimal structural reorganization after electron transfer, which ensures the rapid transfer of electrons.

Cytochromes

The cytochromes (from the Greek cytos, meaning “cell”, and chroma, meaning “color”) were first identified in the 1920s by spectroscopic studies of cell extracts. Based on the wavelength of the maximum absorption in the visible spectrum, they were classified as cytochromes a (with the longest wavelength), cytochromes b (intermediate wavelength), and cytochromes c (shortest wavelength). It quickly became apparent that there was a correlation between their spectroscopic properties and other physical properties. For examples, cytochromes c are generally small, soluble proteins with a reduction potential of about +0.25 V, whereas cytochromes b are larger, less-soluble proteins with reduction potentials of about (0 V).

All cytochromes contain iron, and the iron atom in all cytochromes is coordinated by a planar array of four nitrogen atoms provided by a cyclic tetradentate ligand called a porphyrin. The iron–porphyrin unit is called a heme group.

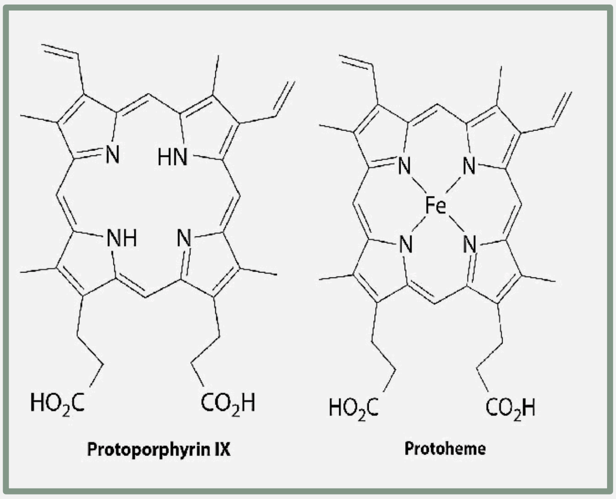


Figure (6): Structures of Protoporphyin IX and Protoheme

The structures of a typical porphyrin (protoporphyrin IX) and its iron complex (protoheme) are shown here. In addition to the four nitrogen atoms of the porphyrin, the iron in a cytochrome is usually bonded to two additional ligands provided by the protein (such as the nitrogen atom of a histidine imidazole and the sulfur atom of a methionine thioether) in cytochrome (C).

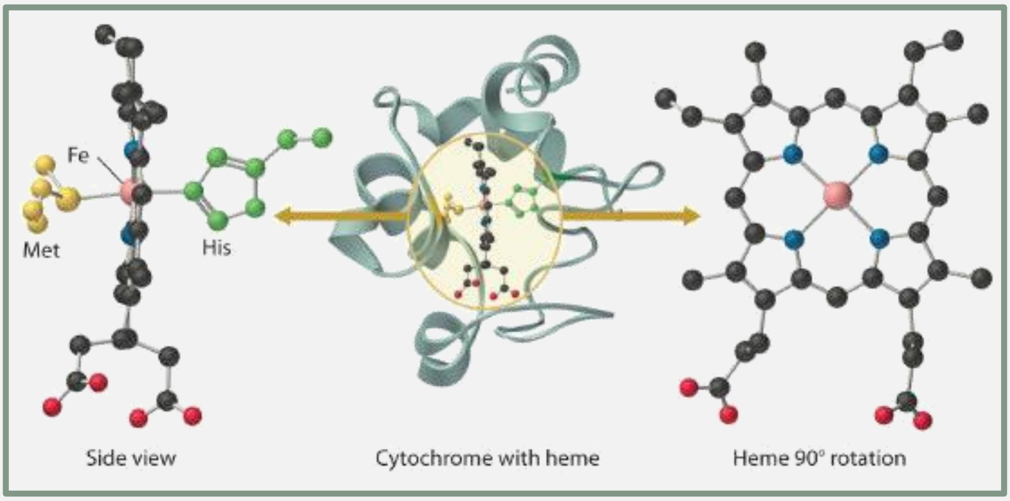


Figure (7): A Cytochrome c. In a cytochrome c, the heme iron is coordinated to the nitrogen atom of a histidine imidazole and the sulfur atom of a methionine thioether, in addition to the four nitrogen atoms provided by the porphyrin.

In contrast to the blue copper proteins, two electron configurations are possible for both the oxidized and reduced forms of a cytochrome, and this has significant structural consequences. Thus Fe^{2+} is d^6 and can be either high spin (with four unpaired electrons) or low spin (with no unpaired electrons). Similarly, Fe^{3+} is d^5 and can also be high spin (with five unpaired electrons) or low spin (with one unpaired electron). In low-spin heme complexes, both the Fe^{2+} and the Fe^{3+} ions are small enough to fit into the "hole" in the center of the porphyrin; hence the iron atom lies almost exactly in the plane of the four porphyrin nitrogen atoms in both cases. Because cytochromes b and c are low spin in both their oxidized and reduced forms, the structures of the oxidized and reduced cytochromes are essentially identical. Hence minimal structural changes occur after oxidation or reduction, which makes electron transfer to or from the heme very rapid.

Iron–Sulfur Proteins.

Although all known bacteria, plants, and animals use iron–sulfur proteins to transfer electrons, the existence of these proteins was not recognized until the late 1950s. Iron–sulfur proteins transfer electrons over a wide range of reduction potentials, and their iron content can range from 1 to more than 12 Fe atoms per protein molecule. In addition, most iron–sulfur proteins contain stoichiometric amounts of sulfide (S^{2-}).

These properties are due to the presence of four different kinds of iron–sulfur units, which contain one, two, three, or four iron atoms per Fe–S complex. In all cases, the Fe^{2+} and Fe^{3+} ions are coordinated to four sulfur ligands in a tetrahedral environment. Due to tetrahedral coordination by weak-field sulfur ligands, the iron is high spin in both the Fe^{3+} and Fe^{2+} oxidation states, which results in similar structures for the oxidized and reduced forms of the Fe–S complexes. Consequently, only small structural changes occur after oxidation or reduction of the Fe–S center, which results in rapid electron transfer.

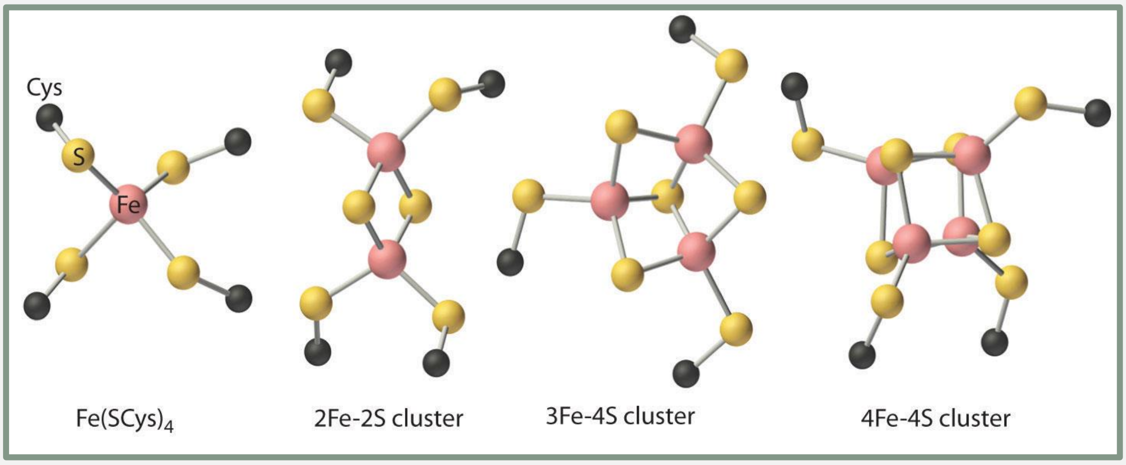


Figure (8): Fe–S Centers in Proteins: Four kinds of iron–sulfur centers, containing one, two, three, and four iron atoms, respectively, are known in electron-transfer proteins. Although they differ in the number of sulfur atoms provided by cysteine thiolates versus sulfide, in all cases the iron is coordinated to four sulfur ligands in a roughly tetrahedral environment.

Reactions of small Molecules.

Although small mole ales such as O_2, N_2 and H_2, do not react with organic compounds under ambient conditions, they do react with many transition metal complexes. Consequently, virtually all organisms use to metalloproteins to bind, transport, and calalyze the reactions of these molecules. Probably the best-known example is hemoglobin, which is wed to transport O_2 in many multicellular organisms.

Oxygen Transport

Many microorganisms and most animals obtain energy by respiration, the oxidation of organic or inorganic molecules by O_2. At 25°C, however, the concentration of dissolved oxygen in water in contact with air is only about 0.25 mm. Because of their high surface area-to-volume ratio, aerobic microorganisms can obtain enough oxygen for respiration by passive diffusion of O_2 through the cell membrane. As the size of an organism increases, however, its volume increases much more rapidly than its surface area, and the need for oxygen depends on its volume. Consequently, as a multicellular organism grows larger, its need for O_2 rapidly outstrips the supply available through diffusion. Unless a transport system is available to provide an adequate supply of oxygen for the interior cells, organisms that contain more than a few cells cannot exist. In addition, O_2 is such a powerful oxidant that the oxidation reactions used to obtain metabolic energy must be carefully controlled to avoid releasing so much heat that the water in the cell boils.

Consequently, in higher-level organisms, the respiratory apparatus is located in internal compartments called mitochondria, which are the power plants of a cell. Three different chemical solutions to the problem of oxygen transport have developed independently in the course of evolution.

Mammals, birds, reptiles, fish, and some insects use a heme protein called hemoglobin to transport oxygen from the lungs to the cells, and they use a related protein called myoglobin to temporarily store oxygen in the tissues. Several classes of invertebrates, including marine worms, use an iron-containing protein called hemerythrin to transport oxygen, whereas other classes of invertebrates (arthropods and mollusks) use a copper-containing protein called hemocyanin. Despite the presence of the hemprefix, hemerythrin and hemocyanin do not contain a metal–porphyrin complex.

Table (4): **Some Properties of the Three Classes of Oxygen-Transport Proteins**

Protein	Source	M per Subunit	M per O_2 Bound	Color (deoxy form)	Color (oxy form)
hemoglobin	mammals, birds, fish, reptiles, some insects	1 Fe	1 Fe	red-purple	red
hemerythrin	marine worms	2 Fe	2 Fe	colorless	red
hemocyanin	mollusks, crustaceans, spiders	2 Cu	2 Cu	colorless	blue

Hemoglobin and Myoglobin.

Hemoglobin (denoted as Hb) and Myoglobin (Mb) are dioxygen (O_2) binding metalloproteins containing an iron porphyrin system, heme, both of them contain Fe (II) ion.

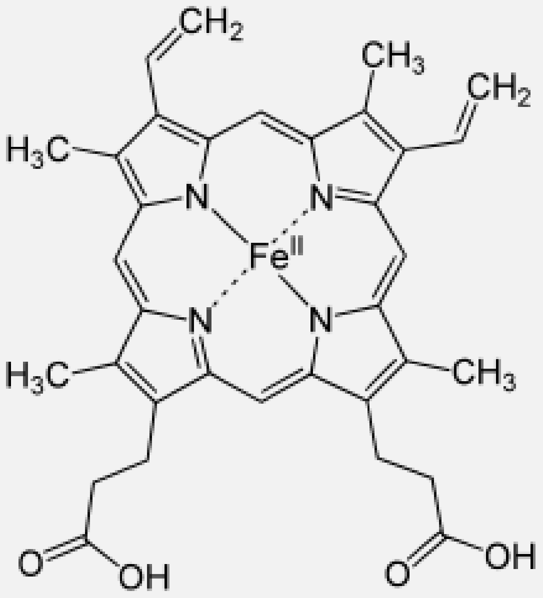
Hemoglobin is present in Red blood cells (RBC) and helps in transport of dioxygen from Lungs to tissues whereas Myoglobin stores dioxygen and is present in muscles.

Structure of Hemoglobin & Myoglobin.

Hemoglobin consists of two subunits of 141 amino acids and two subunits of 146 amino acids, it’s called a tetramer because of its four subunits. The functional unit is an iron-porphyrin complex (heme), is contains foun heme units.

Myoglobin, is relatively small protein that contains 153 amino acids. It has only one heme unit.

Heme is a porphyrin ring system made up of four pyrrole rings with an Fe (II) ion coordinated to nitrogen’s of pyrrole rings.



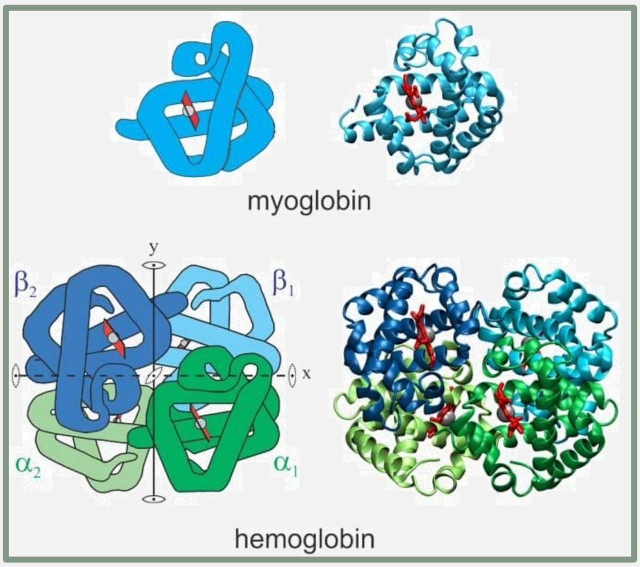


Figure (9): Hemoglobin and Myoglobin

Hemoglobin and Myoglobin exist in two forms:

1. **Deoxy form:** No oxygen is bound to iron
2. **Oxy form:** dioxygen is bounds to iron

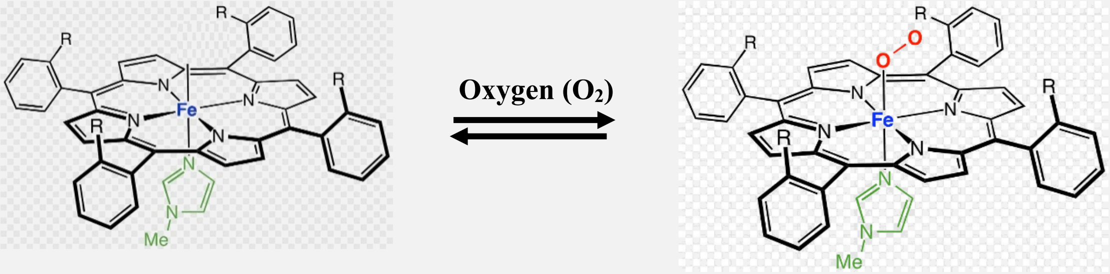
In deoxy hemoglobin, four of the coordinated sits of iron are occupied by nitrogen's of porphyrin ring, the fifth site is occupied by histidine residue (Called proximed histidine).

In oxyhemoglobin (hemoglobin coordinated to dioxygen) the sixth coordinated position of iron is occupied by dioxygen in bent geometry.

Functioning of Hemoglobin-A Bioinorganic perspective.

In deoxyhemoglobin, the porphyrin ring is dome Shaped. The Fe(III) is in high spin state and is paramagnetic. Its five coordinated, the size is 0.78 A°, Because high spin Fe^{2+} is too large to fit into the hole in the center of the porphyrin, thus is positioned above the plane of the porphyrin ring. However in oxyhemoglobin (O_2 binds to deoxy hemoglobin) the Fe is converted from five coordinate (high spin) to six coordinate (Low spin).

Because Low spin Fe^{3+} is smaller than high spin Fe^{2+}, the size of iron ion is reduced to 0.61A° and can fit into the cavity of planar Porphyrin ring and hence maves into the plane of the porphyrin ring to form an octahedral complex. The figer below shows the structures of Deox hemoglobin and oxyhemoglobin



deoxy hemoglobin **oxyhemoglobin**

Figure (10): deoxy hemoglobin and oxyhemoglobin

The nature of Fe in oxyhemoglobin or in oxymyoglobin is controversial:

According to old Pouling model, there is low spin Fe (II) ion that is bound to singlet O_2 in oxy-Hb, both are diamagnetic.

However, according to Weiss model, there is Fe (III) ion bound to superoxide radical anion (O^{-2}) through both are paramagnetic a strong paramagnetic coupling between them enswes diamagnetic behavior. This model is supported by the O–O stretching frequency at 1105cm^{-1} in resonance raman spectrum that is consistent with the fact that O_2 is in superoxide form. this deems to be more accurant and modern exclamation.

The shape of the O_2-binding curve of myoglobin.

This can be described mathematically by the following equilibrium:

$$MbO_2 \rightleftharpoons Mb + O_2$$

$$K_{diss} = \frac{[Mb][O_2]}{[MbO_2]}$$

In contrast, the O_2-binding curve of hemoglobin is S shaped. As shown in the curves, at low oxygen pressures, the affinity of deoxyhemoglobin for O_2 is substantially lower than that of myoglobin, whereas at high O_2 pressures the two proteins have comparable O_2 affinities. The physiological consequences of the unusual S-shaped O_2-binding curve of hemoglobin are enormous. In the lungs, where O_2 pressure is highest, the high oxygen affinity of deoxyhemoglobin allows it to be completely loaded with O_2, giving four O_2 molecules per hemoglobin. In the tissues, however, where the oxygen pressure is much lower, the decreased oxygen affinity of hemoglobin allows it to release O_2, resulting in a net transfer of oxygen to myoglobin.

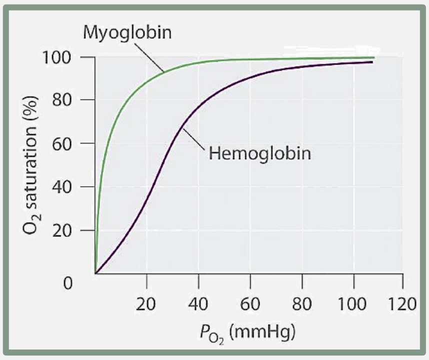


Figure (11): The O_2-Binding Curves of Myoglobin and Hemoglobin. The curve for myoglobin can be described by a simple equilibrium between deoxy- and oxymyoglobin, but the S-

shaped curve for hemoglobin can be described only in terms of a cooperative interaction between the four hemes.

The S-shaped O_2-binding curve of hemoglobin is due to a phenomenon called cooperativity, in which the affinity of one heme for O_2 depends on whether the other hemes are already bound to O_2. Cooperativity in hemoglobin requires an interaction between the four heme groups in the hemoglobin tetramer, even though they are more than 3000 pm apart, and depends on the change in structure of the heme group that occurs with oxygen binding. The structures of deoxyhemoglobin and oxyhemoglobin are slightly different, and as a result, deoxyhemoglobin has a much lower O_2 affinity than myoglobin, whereas the O_2 affinity of oxyhemoglobin is essentially identical to that of oxymyoglobin. Binding of the first two O_2 molecules to deoxyhemoglobin causes the overall structure of the protein to change to that of oxyhemoglobin; consequently, the last two heme groups have a much higher affinity for O_2 than the first two.

Hemerythrin

Hemerythrin is used to transport O_2 in a variety of marine invertebrates. It is an octamer (eight subunits), with each subunit containing two iron atoms and binding one molecule of O_2. Deoxyhemerythrin contains two Fe^{2+} ions per subunit and is colorless, whereas oxyhemerythrin contains two Fe^{3+} ions and is bright reddish violet. These invertebrates also contain a monomeric form of hemerythrin that is located in the tissues, analogous to myoglobin. The binding of oxygen to hemerythrin and its release can be described by the following reaction, where the HO_2^- ligand is the hydroperoxide anion derived by the deprotonation of hydrogen peroxide (H_2O_2):

$$2\,Fe^{2+} + O_2 + H^+ \rightleftharpoons 2\,Fe^{3+}\text{–}O_2H$$

The uptake of O_2 by hemerythrin is accompanied by two electron oxidation of the diferrous center to produce a hydroperoxide $(OOH)^-$ complex.

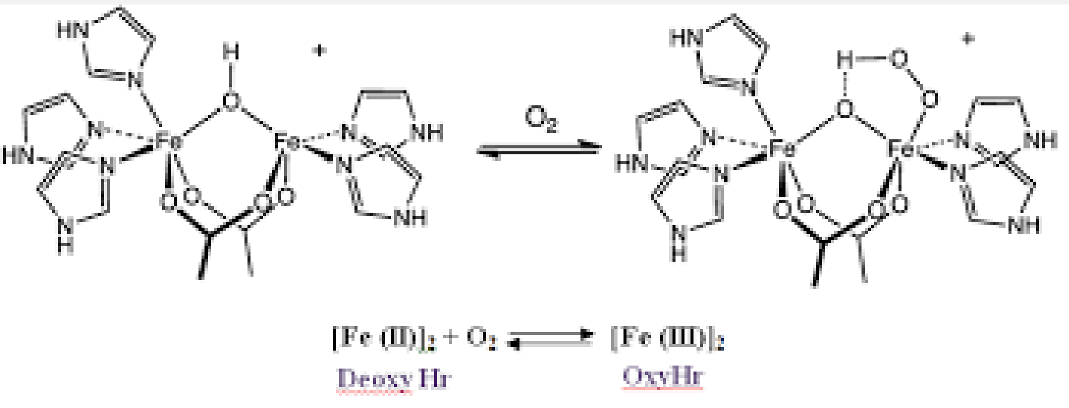


Figure (12): Hemerythrin Structure

Hemocyanin

Hemocyanin is used for oxygen transport in many arthropods (spiders, crabs, lobsters, and centipedes) and in mollusks (shellfish, octopi, and squid); it is responsible for the bluish-green color of their blood. The protein is a polymer of subunits that each contain two copper atoms (rather than iron), with an aggregate molecular mass of greater than 1,000,000 amu. Deoxyhemocyanin contains two Cu^+ ions per subunit and is colorless, whereas oxyhemocyanin contains two Cu^{2+} ions and is bright blue. As with hemerythrin, the binding and release of O_2 correspond to a two-electron reaction:

$$2\,Cu^{+} + O_2 \rightleftharpoons Cu^{2+}-O_2^{2-}-Cu^{2+}$$

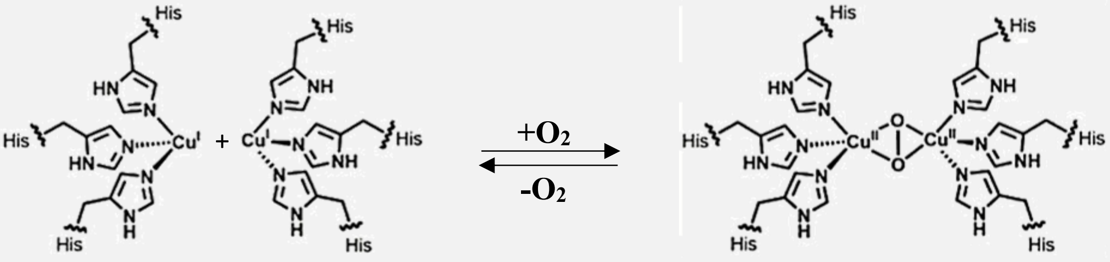


Figure (13): Hemocyanin structure

Although hemocyanin and hemerythrin perform the same basic function as hemoglobin, these proteins are not interchangeable. In fact, hemocyanin is so foreign to humans that it is one of the major factors responsible for the common allergies to shellfish.

Table (5): Difference Between Hemocyanin and Hemoglobin

Feature	Hemocyanin	Hemoglobin
Found in	Mollusks and arthropods	Vertebrates, including humans
Metal ion	Copper	Iron
Oxygen Binding	Binds oxygen directly to copper ions	Binds oxygen to iron in the heme group
Color change	Changes from colorless to blue when oxygenated	Changes from darker to bright red when oxygenated
Molecular Structure	Made up of multiple subunits, each with two copper atoms	Consists of four protein subunits, each with one iron atom
Function	Transports oxygen	Transports oxygen, also aids in carbon dioxide removal from the body
Thermal Adaptation	More efficient in colder, oxygen-rich environments	Functions effectively across a wide range of temperatures

Superoxide dismutase (SOD):

An enzyme that alternately catalyzes the dismutation (or partitioning) of the superoxide (O_2^-) radical into either ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2).

Superoxide is produced as a by-product of oxygen metabolism and, if not regulated, causes many types of cell damage.

Thus, SOD is an important antioxidant, defense in nearly all living cells exposed to oxygen.

This SOD-Calulyzed dismutation of superoxide may be written for Cu–SOD with +2 the following reactions:

$$Cu - SOD + O_2 \rightarrow Cu^{+1} - SOD + O_2$$

(Reaction of copper oxidation of superoxide)

$$Cu^{+1} - SOD + O_2 + O_2 + 2H^{+} \rightarrow Cu^{+2} - SOD + H_2O_2$$

(Oxidation of copper, reduction of superoxide)

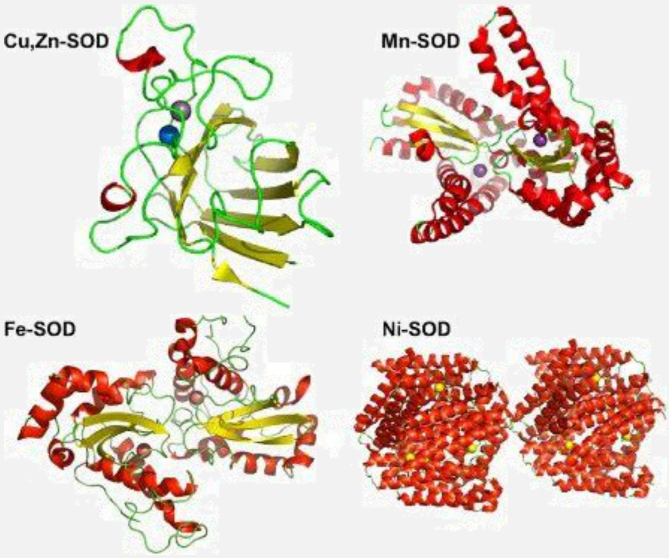


Figure (14): Superoxide dismutase

Zinc metalloenzymes:

More than 30 zinc metalloenzymes are Known, Zinc metalloenzyme are used as carboxypeptidase, this enzyme in the pancrease of mammals catalyses the hydrolysis of peptides.

$$R - C(O)N - R_2 + H_2O \rightarrow R - 0_2^- + NH_2 - R_2$$

Fanction of Zn in metalloenzymes:

1. Structure–promoter.
2. Substrate binder.
3. Lewis acid.

Enzymes Involved in Oxygen Activation:

Many of the enzymes involved in the biological reactions of oxygen contain metal centers with structures that are similar to those used for O_2 transport. Many of these enzymes also contain metal centers that are used for electron transfer, which have structures similar to those of the electron-transfer proteins discussed previously. In this section, we briefly describe two of the most important examples: dioxygenases and methane monooxygenase.

Dioxygenases are enzymes that insert both atoms of O_2 into an organic molecule. In humans, dioxygenases are responsible for cross-linking collagen in connective tissue and for synthesizing complex organic molecules called prostaglandins, which trigger inflammation and immune reactions. Iron is by far the most common metal in dioxygenases; and the target of the most commonly used drug in the world, aspirin, is an iron enzyme that synthesizes a specific prostaglandin.

Aspirin inhibits this enzyme by binding to the iron atom at the active site, which prevents oxygen from binding.

Methane monooxygenase catalyzes the conversion of methane to methanol. The enzyme is a monooxygenase because only one atom of O_2 is inserted into an organic molecule, while the other is reduced to water:

$$\mathrm{CH_4 + O_2 + 2\,e^- + 2\,H^+ \rightarrow CH_3OH + H_2O}$$

Because methane is the major component of natural gas, there is enormous interest in using this reaction to convert methane to a liquid fuel (methanol) that is much more convenient to ship and store.

Because the C–H bond in methane is one of the strongest C–H bonds known, however, an extraordinarily powerful oxidant is needed for this reaction. The active site of methane monooxygenase contains two Fe atoms that bind O_2, but the details of how the bound O_2 is converted to such a potent oxidant remain unclear.

Enzymes that use metals to generate Organic radicals:

An organic radical is an organic species that contains one or move unpaired electrons. Chemists often consider organic radicals to be highly reactive species that produce undesirable reactions. For example, they have been implicated in some of the irreversible chemical changes that accompany aging. It is surprising, however that organic radicals are also essential components of many important enzymes almost all of which use a metal ion to generate the organic radical within the enzyme. These enzymes are involved in the synthesis of hemoglobin and DNA among other important biological molecules, and they are the targets of pharmaceuticals for the treatment of diseases. such as anemia sickle-cell anemia, and cancer, here we discuss one class of radical enzymes that use vitamin B_{12}.

Vitamin B_{12} was discovered in the 1940s as the active agent in the cure of pernicious anemia, which does not respond to increased iron in the diet. Humans need only tiny amounts of vitamin B_{12}, and the average blood concentration in a healthy adult is only about 3.5×10^{-8} M. The structure of vitamin B_{12}:

A tetradentate ligand corrin coordinates (bonds) with cobalt cation to form cobalamin which is vitamin B_{12}.

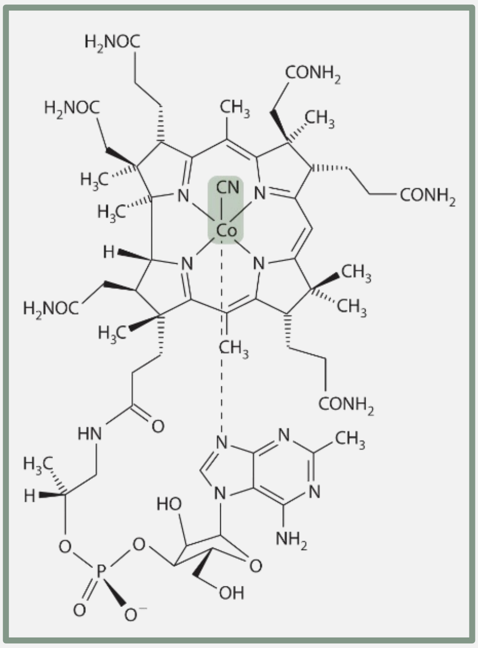


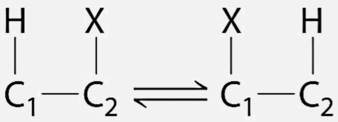
Figure (15): Vitamin B_{12} In the body, the axial cyanide ligand found in the vitamin is replaced by a complex organic unit. Heterolytic cleavage of the Co–C bond in the resulting organometallic complex generates an organic radical for the catalysis of rearrangement reactions.

In fact, vitamin B_{12} has been called the most complex nonpolymeric biological molecule known and was the first naturally occurring organometallic compound to be isolated. When vitamin B_{12} (the form present in vitamin tablets) is ingested, the axial cyanide ligand is replaced by a complex organic group.

The cobalt–carbon bond in the enzyme-bound form of vitamin B_{12} and related compounds is unusually weak, and it is particularly susceptible to homolytic cleavage Co^{3+}–CH_2R bond produces two species, each of which has an unpaired electron:

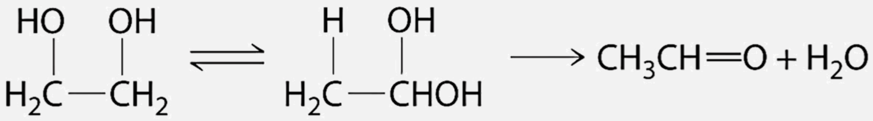
$$CoCH - 2R \rightarrow Co^{2+} + CH - 2R$$

a d^7 Co^{2+} derivative and an organic radical, $\cdot CH_2R$, which is used by vitamin B_{12}-dependent enzymes to catalyze a wide variety of reactions. Virtually all vitamin B_{12}-catalyzed reactions are rearrangements in which an H atom and an adjacent substituent exchange positions:



$$\begin{array}{ccc} H & & X \\ | & & | \\ C_1 & - & C_2 \end{array} \rightleftharpoons \begin{array}{ccc} X & & H \\ | & & | \\ C_1 & - & C_2 \end{array}$$

In the conversion of ethylene glycol to acetaldehyde, the initial product is the hydrated form of acetaldehyde, which rapidly loses water:



$$\begin{array}{ccc} HO & & OH \\ | & & | \\ H_2C & - & CH_2 \end{array} \rightleftharpoons \begin{array}{ccc} H & & OH \\ | & & | \\ H_2C & - & CHOH \end{array} \longrightarrow CH_3CH{=}O + H_2O$$

The enzyme uses the $\cdot CH_2R$ radical to temporarily remove a hydrogen atom from the organic substrate, which then rearranges to give a new radical. Transferring the hydrogen atom back to the rearranged radical gives the product and regenerates the $\cdot CH_2R$ radical.

The metal is not involved in the actual catalytic reaction; it provides the enzyme with a convenient mechanism for generating an organic radical, which does the actual work. Many examples of similar reactions are now known that use metals other than cobalt (Co) to generate an enzyme-bound organic radical.

Metal Ions as Lewis Acids:

Reactions catalyzed by metal ions that do not change their oxidation states during the reaction are usually group transfer reactions, in which a group such as the phosphoryl group (-PO_3^{2-}) is transferred. These enzymes usually use metal ions such as Zn^{2+}, Mg^{2+} and Mn^{2+} and they range from true metalloenzymes, in which the metal ion is tightly bound, to metal activated enzymes, which require the addition of metal ions for activity. Because tight binding, usually the result of specific metal-ligand interactions, metalloenzymes tend to be rather specific for a particular metal ion. In contrast, the binding of metal ions to metal-activated enzymes is largely electrostatic in nature, consequently several different metal ions with similar charges and sizes can often be used to give active enzyme.

A metal ion that acts as a Lewis acid can catalyze a group transfer reaction in many different ways, but we will focus only one of these, using a zinc enzyme as an example carbonic anhydrase is found in red blood cells and catalyzes the reaction of CO_2 with water to give carbonic acid.

$$CO_{2(g)} + H_2O_{(g)} \rightleftarrows H^+_{(aq)} + HCO^-_{3(aq)}$$

Although this reaction occurs spontaneously in the absence of a catalyst, it is too slow to absorb all the CO_2 generated during respiration. Without a catalyst, tissues would explode due to the buildup of excess CO_2 pressure. Carbonic anhydrase contains a single Zn^{+2} ion per molecule, which is coordinated by three histidine imidazol ligands and a molecule of water. Because Zn^{2+} is a Lewis acid, the Pka of the Zn^{+2}–OH_2 unit is about & versus 14 for pure water.

Thus at pH 7–8 a significant fraction of the enzyme molecules contain the Zn^{2+}–OH_2 group, which is much more reactive than bulk water. When carbon dioxide binds in a nonpolar site next to the Zn^{2+}–OH^- unit, it reacts rapidly to give a coordinated bicarbonate ion that dissociates from the enzyme.

$$Zn^{2+} - OH^{-} + CO_2 \rightleftarrows Zn^{2+} - CO_2H^{-} \rightleftarrows Zn^{2+} + HCO_3^{-}$$

The Zinc ion lies in a deep pocket weated by the Coiled apoenzyme and is coordinated with the three nitrogen atoms of the three imidazole rings of histidine groups of the apoenzyme the fourth coordination site is perhaps occupied by a water molecule when the enzyme is at rest, the stereochemistry of zinc in the enzyme is tetrahedral.

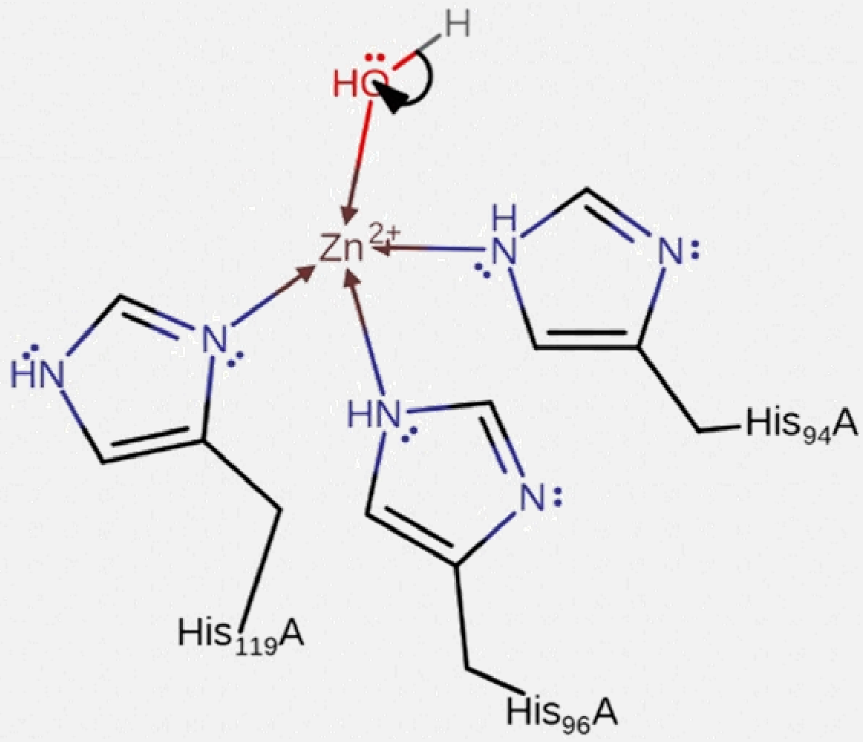


Figure (16): Zn^{2+} ion in carbonic anhydrase

The Lewis acidity of Zn^{2+} ion in carbonic anhydrase polarizes the coordinated H_2O molecule to the point of Loss H^+ ion to form coordinate OH group, H is the hydroxy form of the enzyme which is believed to reversibly hydrate CO_2 to HCO_3^-.

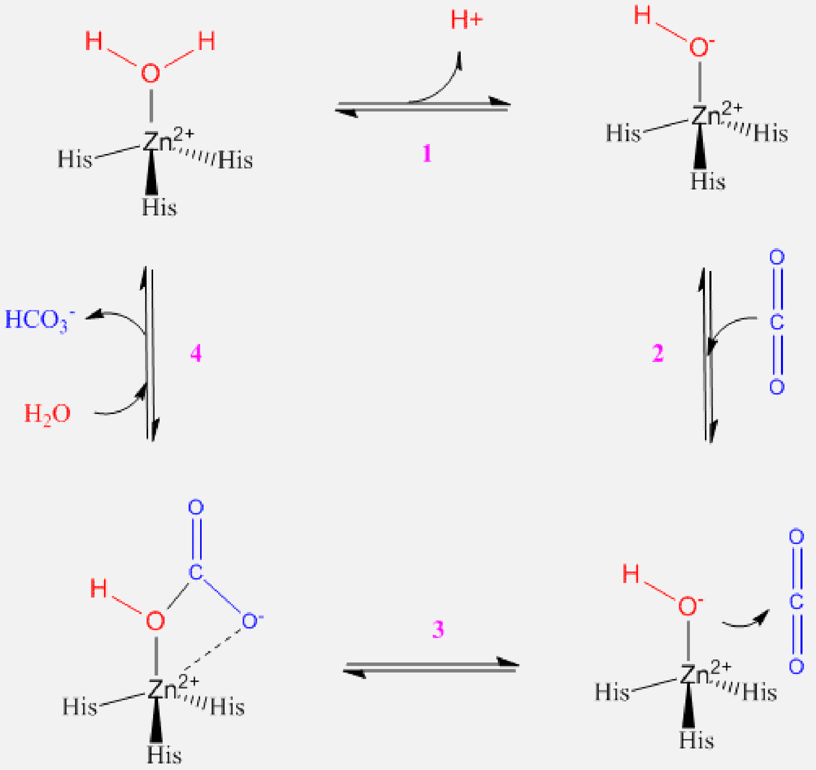


Figure (17): Mechanism of the formation of hydrogen carbonate catalyzed by carbonic anhydrase.

Metals in Medicine:

Metals in medicine are used in organic system for diagnostic and treatment purposes. Inorganic elements are also essential for organic life as cofactors in enzymes (Metalloproteins) when metals are scarce or high quantities equilibrium is set out of balance and must be returned to its natural state via interventional and natural methods.

Toxic metals:

Metals can be toxic in high quantities. Either ingestion or faulty metabolic pathway's can lead to metal poisoning sources of toxic metals include cadmium from tobaco, arsenic from agriculture and mercury volcanoes and forest fires. Nature in the form of trees and plants. Is able to trap many toxins and can bring abnormally high levels back into equilibrium. Toxic metal poisoning is usually treated with some type of chelating agent. Heavy metals poisoning, e.g. Hg, Cd, Pb, are particulary pernicious.

Examples of specific types of toxic metals include.

Copper (Cu)

Copper toxicity usually presents itself as a side effect I of low levels of the protein ceruloplasmin which normally is involved in copper storage. This is referred to as Wilson's disease. Wilson's disease is an autosomal recessive genetic disorder whose mutation causes the ATP that transports copper into bile and ultimately incorporates it into ceruloplasmin to malfunction.

Plutonium (Pu):

Ever since the nuclear age plutonium poisoning is a potential danger, especially among nuclear reactor employees, inhalation of Pu dust is, particularly dangerous due to its intense alpha particle emission. There have been very few cases of plutonium poisoning.

Mercury (Hg):

Mercury is usually ingested from agricultural source or other environmental sources. Mercury poisoning can lead to neurological disease and Kidney failure if left untreated.

Iron (Fe):

Iron Toxicity, iron poisoning, or iron overload is well known. Iron does test only very weakly positive for the ames test for cancer, however, since it is such a strong catalyst and essential for the production of ATP and consequently DNA production, any excess soluble iron is toxic especially over time. Too much iron deposited in tissues or high levels in the blood stream has been successfully linked to a vast majority of human diseases from Alzheimer's to malaria. In botany, iron is a severs problem for the irrigation of plants like rice, maize, or wheat in sub-Saharan Africa whose subterranean water contains excessive amounts of iron which then poisons these crops.

Nickel (Ni)

Allergies to nickel, particularly form skin to metal contact via jewelry are common.

Lead and Cadmium (Pb and Cd):

Lead and cadmium poisoning can head to gastrointestinal, kidney, and neurological dysfunction The use of unleaded paints and gas has successfully decreased the number of cases of lead heavy metal Poisoning.

Zinc, Magnesium, Chromium. (Zn, Mg, Cr):

Metal fume fever can be caused by ingestion of the fumes of these metals and leads to fume Tike symptoms.

Metal anemia

Humans need a certain amount of certain metals to function normally. Anemia symptoms are caused by lack of a certain essential metal. Anemia can be associated with malnourishment of faulty metabolic processes, usually caused by a genetic defect.

Examples of specific types of metal anemia include:

Iron:

Common simple anemia (iron deficiency) resuls in the loss of functional heme proteins (hemoglobin, myoglobin, etc.) which are responsible for oxygen transport or utilization of oxygen. Pernicious anemia) comes from a lack of vitamin B_{12} (which contains a cobalt complex called cobalamin), which then in turn interferes with the function of red blood cells.

Copper:

Copper anemia in infants results from infants with a poor diet and can cause heart disease.

Zine

Zinc anemia is mostly due to diet can result in growth retardation.

Metal in diagnosis:

- Metal ions are often used for diagnostic medical imaging.
- Metal complexes can be used either for radioisotope imaging (from their emitted radiation).

Example of metals used for diagnosis:

Technetium (^{99}TC)

Is the most commonly used radioisotope agent for imaging purposes. It has a short half-life, emits only ɤ ray photons, and does not emit β or α particles and thus is particularly suitable as an imaging radioisotops.

Gadolinium Gd (III), Iron Fe (III), Manganese Mn (II) for MRI imaging Paramagnetic metals are needed for contrast imaging. Gd (III), Fe(III) and Mn (II) are all paramagnetic metals that are able to alter the tissue relaxation times and produce Contrast image.

Cobalt: Co (III)

Is used with the compound bleomycin (BLM) which is an antibiotic, to be selectively be taken up by tumor cells. The use of Co results in the best blood to tumor distribution ratio, but its half-life is too long to be conducive for imaging purposes.

Metals is treatment:

Metals have been used in treatment since ancient times Sodium vanadate has been used since the early 20th Century to treat rheumatoid arthritis.

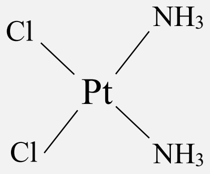
Recently metals have been used to treat cancer, by specifically attacking cancer cells and interacting directly with DNA. The positive charge on most metals can interact with the negative charge of the phosphate backbone of DNA.

Some drugs developed that include metals interact directly with other metals already present in protein active sites. While other drugs can use metals to interact with amino acids with the highest reduction potential.

Platinum (Pt):

Platinum based compounds have been shown to specifically effect head and neck tumors.

Ex. Cisplatin



Gold (Au):

Gold salt complexes have been used to treat rheumatoid arthritis

Zinc (Zn):

Zinc can be used topically to heal wounds, Zn^{2+} can be used to treat the herpes virus.

Silver (Ag):

Silver has been used to prevent infection at the bum sit for burn wound patients.

Tungsten (W):

Tungsten polyoxoanions can be used to treat AIDS.