# Bioinorganic Chemistry

# Syllabus

- Metal ions in biological system
- Trace and Bulk metal ions
- Hemoglobin and myoglobin (elementary idea only)

- When one considers the chemistry of biological processes, the boundary between inorganic and organic chemistry is blurred
- The bulk biological elements that are essential to all life include C, H, N, O (the four most abundant elements in biological systems) along with Na, K, Mg, Ca, P, S and Cl
- The fundamental elements that make up the building blocks of biomolecules (e.g. amino acids, peptides, carbohydrates, proteins, lipids and nucleic acids) are C, H, N and O, with P playing its part

- The roles of the less abundant, but nonetheless essential, elements include osmotic control and nerve action (Na, K and Cl)
- $Mg^{2+}$ in chlorophyll, $Mg^{2+}$ containing enzymes involved in phosphate hydrolysis
- Structural functions of $Ca^{2+}$ (e.g. bones, teeth, shells) and triggering actions of $Ca^{2+}$ (e.g. in muscles)
- The trace metals are V, Cr, Mn, Fe, Co, Ni, Cu, Zn and Mo, while trace non-metals comprise B, Si, Se, F and I

- So the chemical elements essential to life forms can be divided into the following
- (i) Bulk elements: C, H, N, O, P, S
- (ii) Macrominerals and ions: Na, K, Mg, Ca, Cl, $PO_4^{3-}$, $SO_4^{2-}$
- (iii) Trace elements: Fe, Zn, Cu
- (iv) Ultratrace elements comprises of
    - (a) Non-metals: F, I, Se, Si, As, B
    - (b) Metals: Mn, Mo, Co, Cr, V, Ni, Cd, Sn, Pb, Li

| | |
|---|---|
| $Na^+$ and $K^+$ | Most important free intra- and extracellular cations. Regulation of the osmotic pressure, membrane potentials, enzyme activity, signalling. |
| $Mg^{2+}$ | Chlorophyll; anaerobic energy metabolism (ATP > ATP). |
| $Ca^{2+}$ | Signalling, muscle contraction, enzyme regulation. Main inorganic part of the endoskeletons (bones, teeth, enamel: hydroxyapatite; $Ca_5(PO_4)_3(OH)$). Exoskeletons of mussels, shells, corals, sea urchins etc: aragonite or calcite; $CaCO_3$) |
| $V^{IV/V}$, $Mo^{IV/VI}$, $W^{IV/VI}$, $Mn^{II/III/IV}$, $Fe^{II/III}$, $Ni^{I/II/III}$, $Cu^{I/II}$ | Active centres in electron-transport (redox) enzymes, oxygenases, dismutases. |
| Fe and Cu | Transport of oxygen |
| $Fe^{3+}$ | Iron-storage proteins (ferritins) |
| $Fe^{2+}$ + $Fe^{3+}$ | Orientation of magnetobacteria, pigeons, bees in Earth's magnetic field |
| Co | Synthases and isomerases (cobalamines, e.g. vitamin-B12); methylation of inorganics |
| $Zn^{2+}$ | In the active centre of hydrolases, carboanhydrase, alcohol dehydrogenase, synthases; genetic transciption (zinc fingers), stabilisation of tertiary and quartary structures of proteins; repair enzymes |
| $Si^{IV}$ ("silicate") | Involved in the built-up of bones. In the form of $SiO_2$/silica-gels as support in monocotyledonous plants (like grass) and the shells of diatoms |
| $P^V$ (phosphate) | Constituent in hydroxi- and fluorapatite ($Ca_5(PO_4)_3(OH/F)$); energy metabolism (ATP), NADPH, activation of organic substrate; phospholipids in cell membranes; phosphate esters (DNA, RNA,…). |
| $Se^{2-}$ | Selenocystein in special enzymes (e.g. glutathionperoxidase) |
| $F^-$ | Fluorapatite ($Ca_5(PO_4)_3F$) in dental enamel |
| $Cl^-$ | Along with hydrogencarbonate the most important free anion. |
| I | Constituent of thyroid hormones (such as thyroxine). |

| *Metal* | *Compounds and Actions* |
|---|---|
| Fe (heme) | Hemoglobin, peroxidase, catalase, cytochrome P-450, tryptophan dioxygenase, cytochrome *c*, nitrite reductase |
| Fe (non-heme) | Pyrocatechase, ferredoxin, hemerythrin, transferrin, aconitase, nitrogenase |
| Cu | Tyrosinase, amine oxidases, laccase, ascorbate oxidase, ceruloplasmin, superoxide dismutase, plastocyanin, nitrite reductase |
| Co ($B_{12}$ coenzyme) | Glutamate mutase, dioldehydrase, methionine synthetase |
| Co(II) (non-corrin) | Dipeptidase |
| Zn(II) | Carbonic anhydrase, carboxypeptidase, alcohol dehydrogenase, DNA polymerase |
| Mg(II) | Activates phosphotransferases and phosphohydrases, DNA polymerase |
| K(I) | Activates pyruvate phosphokinase and K-specific ATPase |
| Na(I) | Activates Na-specific ATPase |
| Mo | Nitrogenase, nitrate reductase, xanthine oxidase, formate dehydrogenase, sulfite oxidase, DMSO reductase |
| W | Aldehyde ferredoxin oxidoreductase |

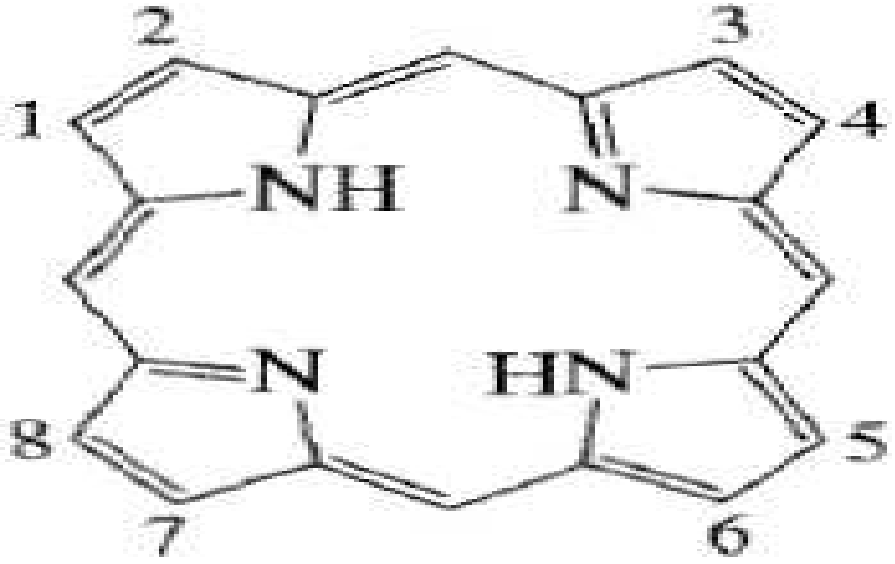
| Metal | Mass / mg | Biological roles |
|---|---|---|
| V | 0.11 | Enzymes (nitrogenases, haloperoxidases) |
| Cr | 14 | Claimed (not yet proven) to be essential in glucose metabolism in higher mammals |
| Mn | 12 | Enzymes (phosphatase, mitochondrial superoxide dismutase, glycosyl transferase); photoredox activity in Photosystem II (see *equation 21.53* and discussion) |
| Fe | 4200 | Electron-transfer systems (Fe–S proteins, cytochromes); $O_2$ storage and transport (haemoglobin, myoglobin, haemerythrin); Fe storage (ferritin, transferritin); Fe transport proteins (siderophores); in enzymes (e.g. nitrogenases, hydrogenases, oxidases, reductases) |
| Co | 3 | Vitamin $B_{12}$ coenzyme |
| Ni | 15 | Enzymes (urease, some hydrogenases) |
| Cu | 72 | Electron transfer systems (blue copper proteins); $O_2$ storage and transport (haemocyanin); Cu transport proteins (ceruloplasmin) |
| Zn | 2300 | Acts as a Lewis acid (e.g. in hydrolysis processes involving carboxypeptidase, carbonic anhydrase, alcohol dehydrogenase); structural roles |
| Mo | 5 | Enzymes (nitrogenases, reductases, hydroxylases) |

| | |
|---|---|
| V | Accumulated by a few organisms, and has been shown to be essential for growth in rats and chicks |
| Mn, Fe, Cu, Ni, Zn | Essential to all organisms |
| Co | Essential to mammals and many other organisms |
| Mo | Essential to all organisms although green algae may be an exception |
| B | Essential to green algae and higher plants, but its role is unknown |
| Si | Exoskeletons of marine diatoms composed of hydrated silica, but its role in other biological systems is less well defined |
| Se | Essential to mammals and some higher plants |
| F | Its role is not fully established but its deficiency causes dental caries |
| I | Essential to many organisms. |

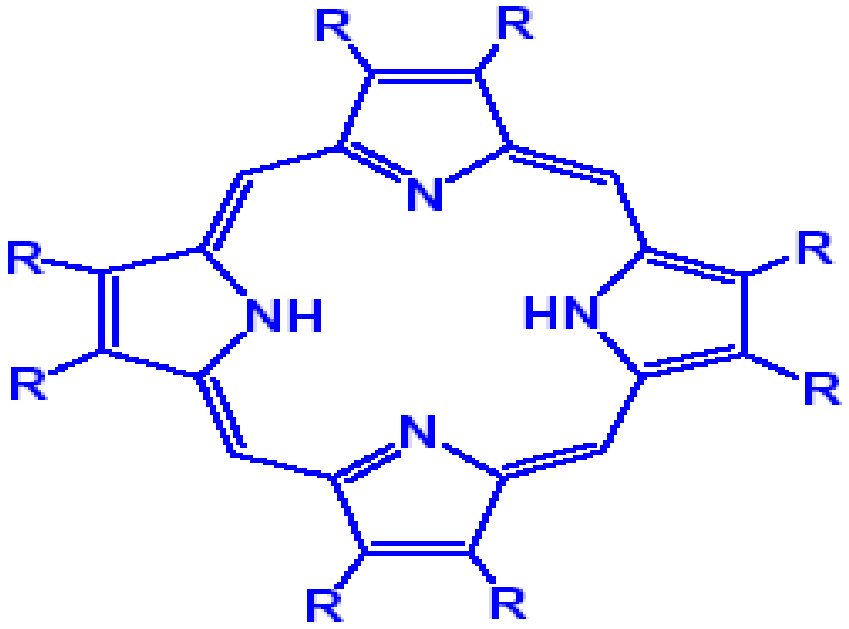
- The average amount of iron in the human body (70 kg) is ca. 5 g; iron is thus the most abundant transition metal in our organism
- About 70% of this amount is used for oxygen transport and storage (haemoglobin, myoglobin)
- Almost 30% are stored in ferritins (iron storage proteins)
- About 1% is bound to the transport protein transferrin and to various iron dependent enzymes

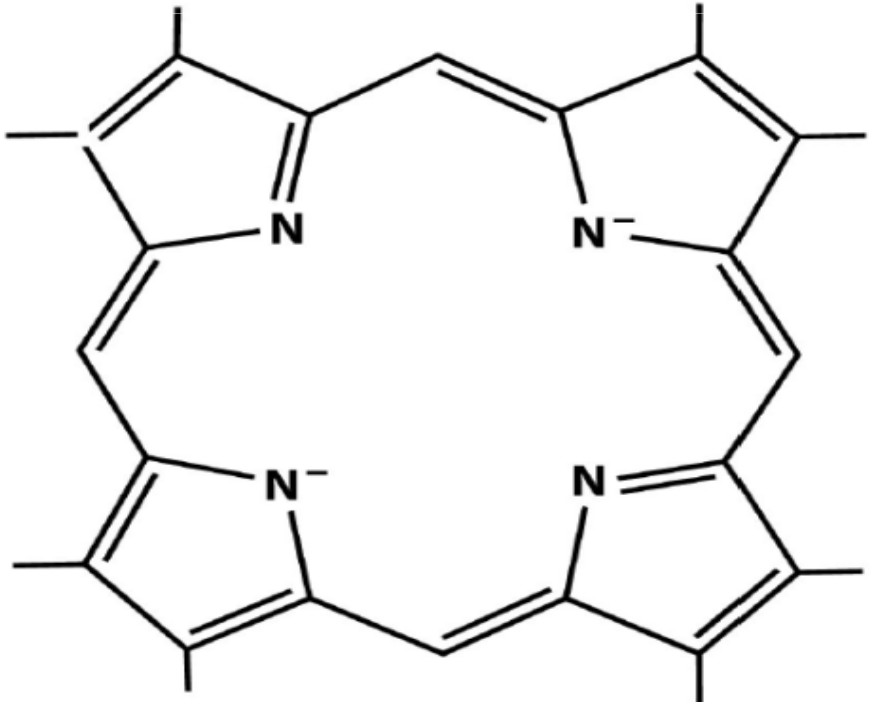
## Porphyrins

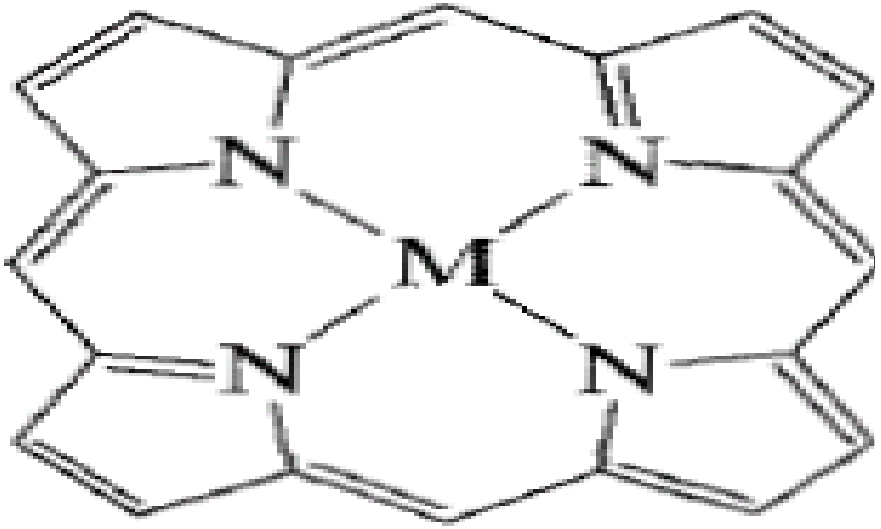
- One of the most important groups of compounds is the porphyrins, in which a metal ion is surrounded by the four nitrogens of a porphine ring in a square-planar geometry and the axial sites are available for other ligands
- Different side chains, metal ions, and surrounding species result in very different reactions and roles for these compounds




Porphine



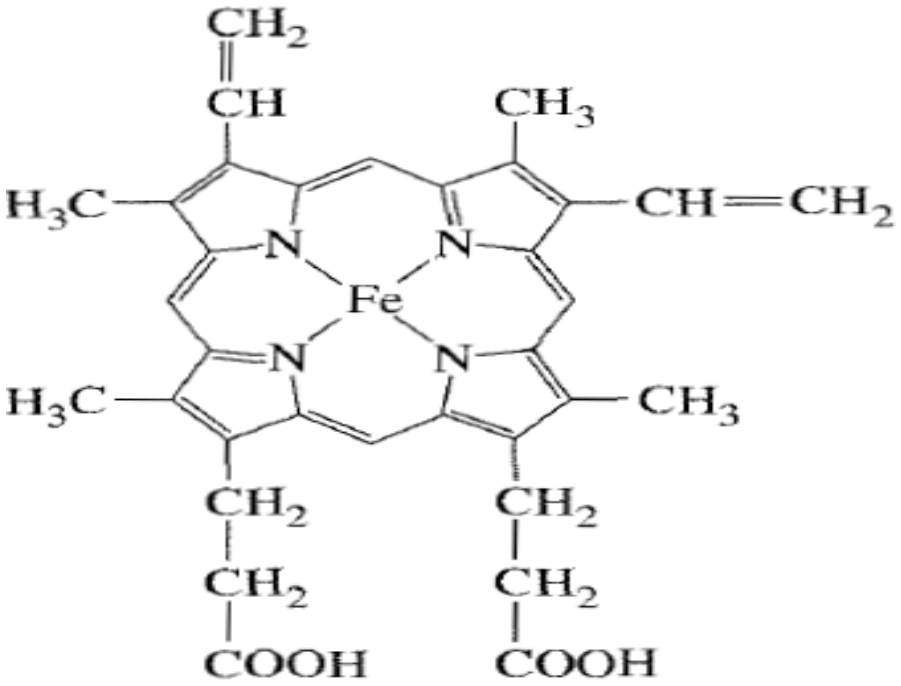



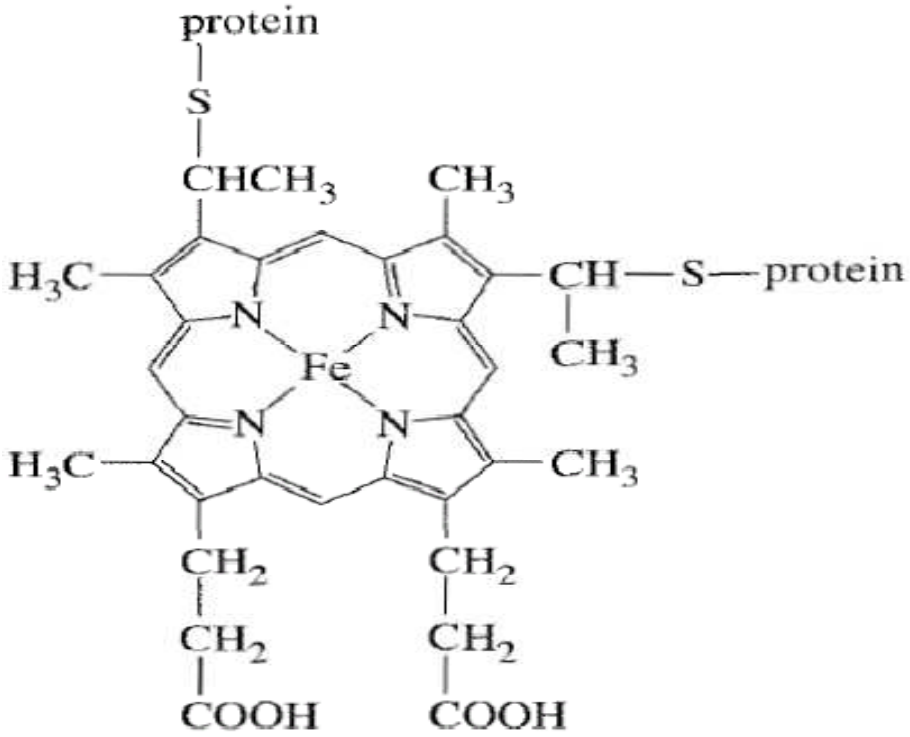

Metalloporphyrin

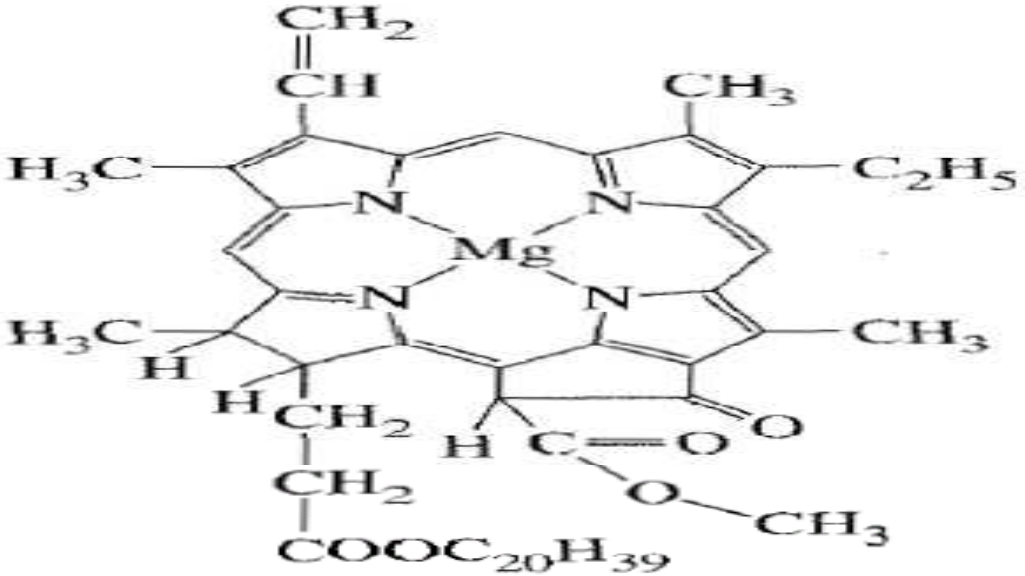
# Porphyrins are found in many metalloenzyme

| | Enzyme | Function |
|---|---|---|
| Fe-porphyrin | Cytochrome | Electron transfer |
| Fe-porphyrin | Hemoglobin & Myoglobin | Dioxygen carrier |
| Mg-porphyrin | Chlorophyll | Photosynthesis |




Fe-protoporphyrin IX




Chlorophyll *a*

## ➢ Oxygen transport

- In the pulmonary alveoli, $O_2$ is taken up by haemoglobin (Hb) and 1 L of blood can dissolve 200 ml of oxygen
- Simultaneously, hydrogencarbonate is converted to carbonic acid, which in turn is catalytically degraded into $CO_2$ and $H_2O$ (by the zinc enzyme carbonic anhydrase)

$$\underset{\text{Desoxi-Hb}}{Hb{\cdot}H^+} + O_2 + HCO_3^- \leftrightarrows \underset{\text{Oxi-Hb}}{Hb{\cdot}O_2} + H_2CO_3$$

$$H_2CO_3 \leftrightarrows H_2O + CO_2$$

- After transport of $O_2$ by haemoglobin in the blood stream, the oxygen is transferred to tissue myoglobin (Mb), Mb has a higher affinity to $O_2$ than Hb

## ➢ Iron Porphyrins

- Hemoglobin and Myoglobin: The best known iron porphyrin compounds are hemoglobin and myoglobin, oxygen transfer and storage agents in the blood and muscle tissue, respectively
- Each of us has nearly 1 kg of hemoglobin in our body, picking up molecular oxygen in the lungs and delivering it to the rest of the body

- Each hemoglobin molecule is made up of four globin protein subunits, two α and two β
- In each of these, the protein molecule partially encloses the heme group, bonding to one of the axial positions through an imidazole nitrogen
- The other axial position is vacant or has water bound to it (the imidazole ring from histidine is too far from the iron atom to bond)

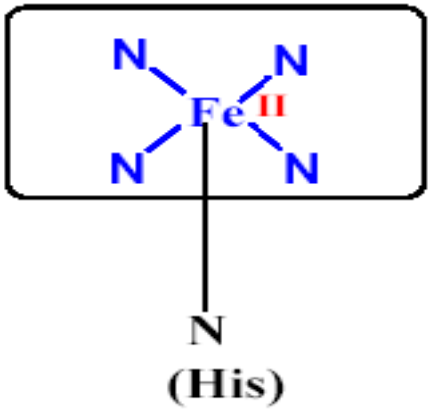
- When dissolved oxygen is present, it can occupy this position, and subtle changes in the conformation of the proteins result
- As one iron binds an oxygen molecule, the molecular shape changes to make binding of additional oxygen molecules easier

$$Hb + O_2 \rightleftharpoons HbO_2$$

$$HbO_2 + O_2 \rightleftharpoons Hb(O_2)_2$$

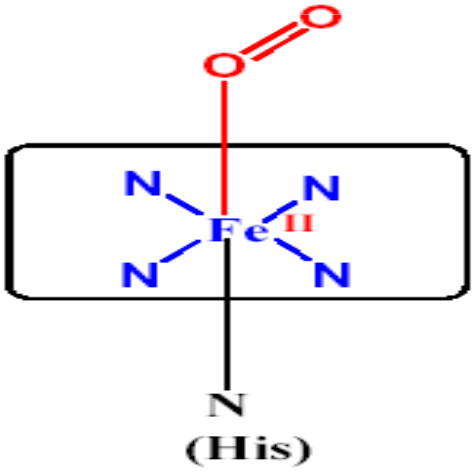
$$Hb(O_2)_2 + O_2 \rightleftharpoons Hb(O_2)_3$$

$$Hb(O_2)_3 + O_2 \rightleftharpoons Hb(O_2)_4$$




High Spin
paramagnetic
$t_{2g}^4\ e_g^2$

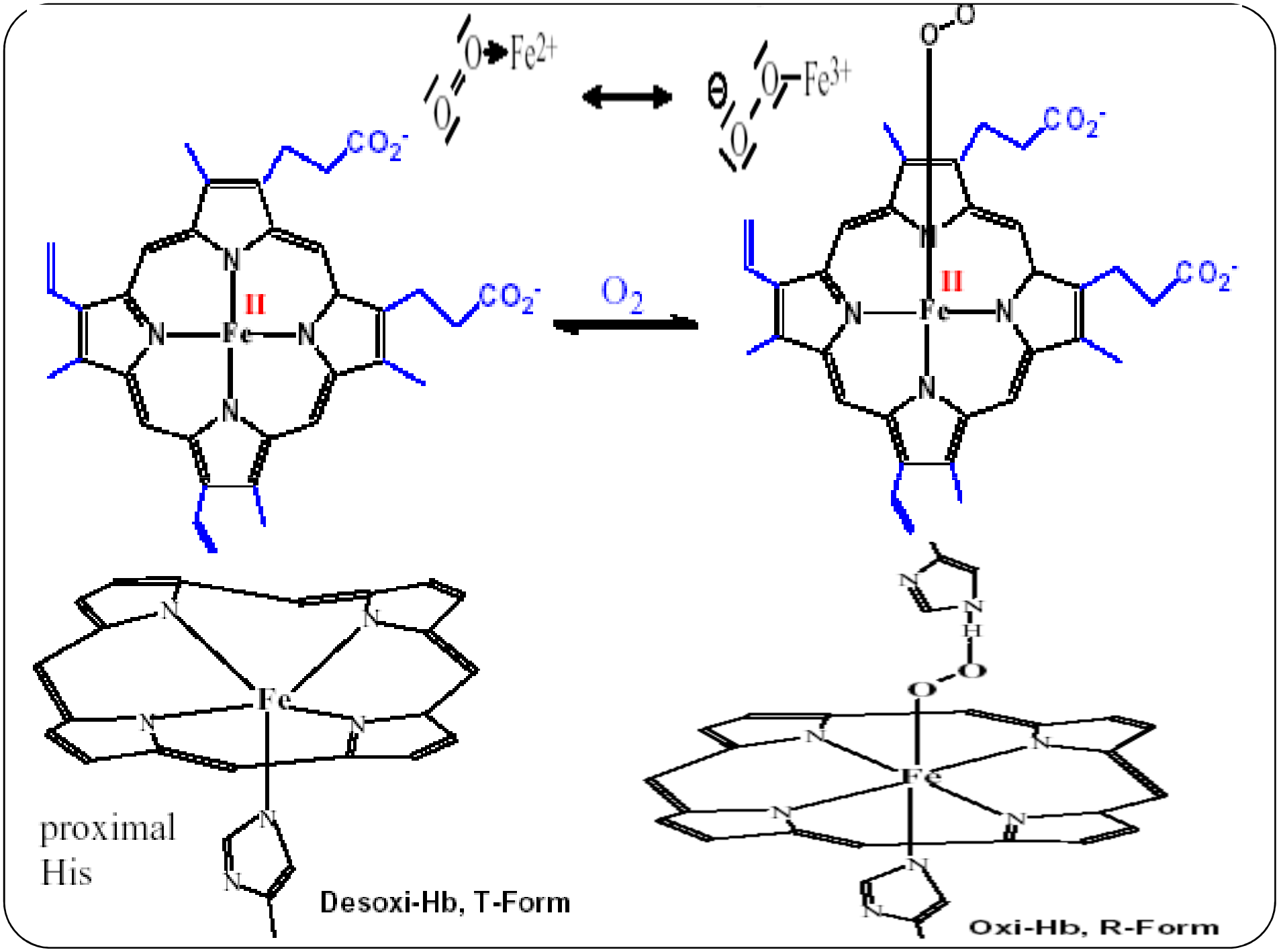
***Deoxyhemoglobin***




Low Spin
diamagnetic
$t_{2g}^6\ e_g^0$

***Oxyhemoglobin***

- The four irons can each carry one $O_2$, with generally increasing equilibrium constants: In hemoglobin, the Fe(I1) is about 70 pm out of the plane of the porphyrin nitrogens in the direction of the imidazole nitrogen bonding to the axial position
- When oxygen bond to the sixth position, the iron becomes coplanar with the porphyrin, oxygen bonds at an angle of approximately 130°, also with considerable back π bonding (as nearly that of Fe(II1) - $O_2^-$)


Fe2+
Fe3+
CO2-
CO2-
O2
II
N
Fe
proximal
His
Desoxi-Hb, T-Form
Oxi-Hb, R-Form

- As soon as some oxygen has been bound to the molecule, all four irons are readily oxygenated
- In a similar fashion, initial removal of oxygen triggers the release of the remainder and the entire load of oxygen is delivered at the required site, this effect is also favored by pH changes caused by increased $CO_2$ concentration in the capillaries
- As the concentration of $CO_2$ increases, formation of bicarbonate causes the pH to decrease and the increased acidity favors release of $O_2$ from the oxyhemoglobin, called the Bohr effect

$$2\,H_2O + CO_2 \rightleftharpoons HCO_3^- + H_3O^+$$

- Myoglobin has only one heme group per molecule and serves as an oxygen storage molecule in the muscles. The myoglobin molecule is similar to a single subunit of hemoglobin
- Bonding between the iron and the oxygen molecule is similar to that in hemoglobin, but the equilibrium is simpler because only one oxygen molecule is bound
- When hemoglobin releases oxygen to the muscle tissue, myoglobin picks it up and stores it until it is needed

- The Bohr effect and the cooperation of the four hemoglobin binding sites make the transfer more complete when the oxygen concentration is low and the carbon dioxide concentration is high
- The opposite conditions in the lungs promote the transfer of oxygen to hemoglobin and the transfer of $CO_2$ to the gas phase in the lungs
- Myoglobin binds $O_2$ more strongly than the first $O_2$ of hemoglobin $\mathrm{Mb} + \mathrm{O_2} \rightleftharpoons \mathrm{MbO_2}$

The end