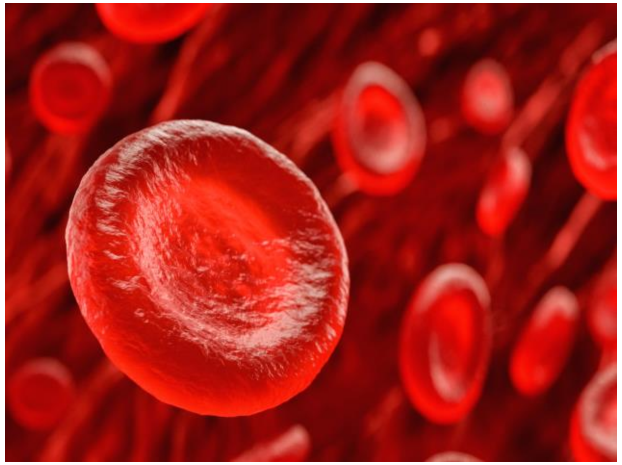
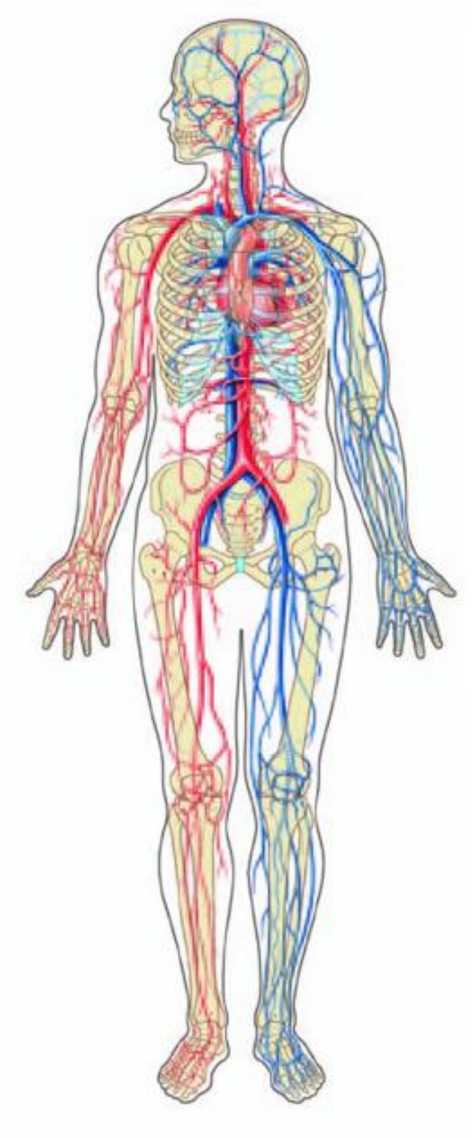
Oxygen carriers and oxygen transport proteins

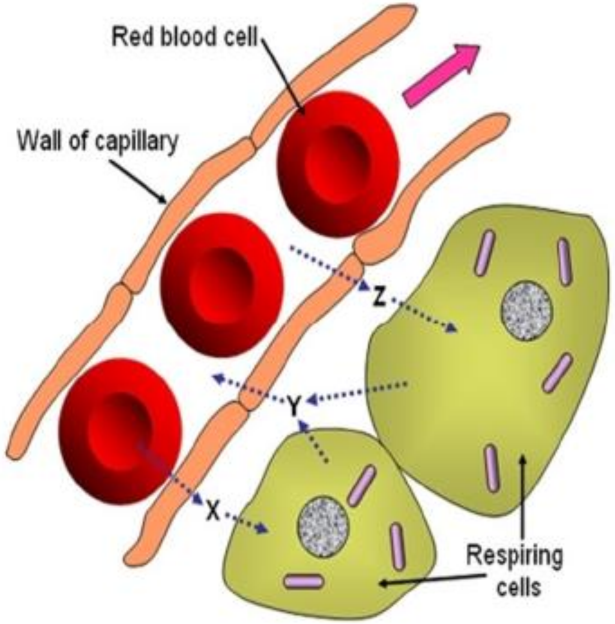
MSc Chemistry

St. Mary's College, Manarcaud



Myoglobin (Mb) and Hemoglobin (Hb) have related, but different, roles in the body



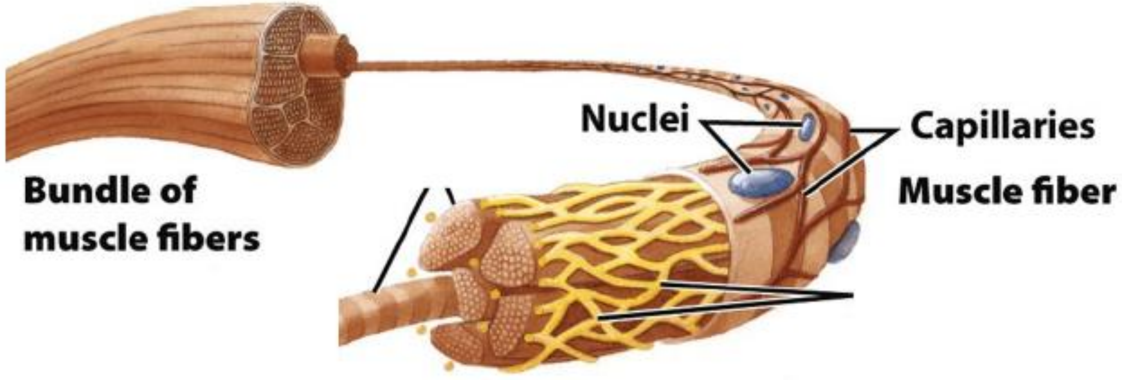


Hemoglobin:

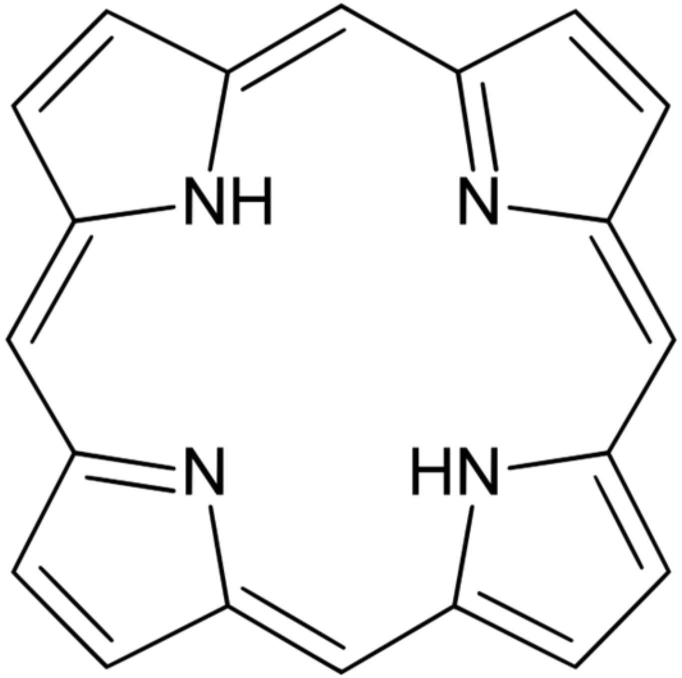
- Found in red blood cells
- Promotes diffusion of O_2 throughout the body (binds O_2 at lungs, releases at tissues)

Myoglobin:

- Found in muscle cells
- Promotes diffusion of O_2 into and throughout muscle cell

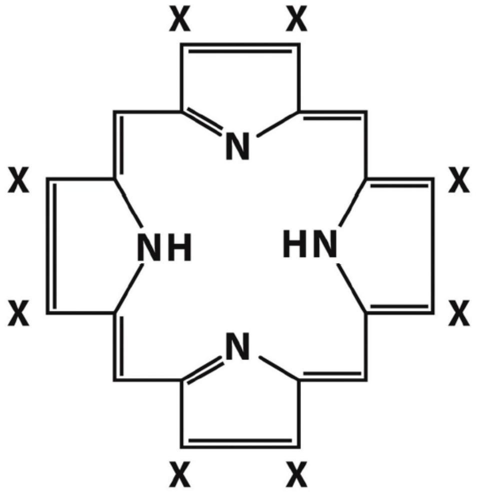


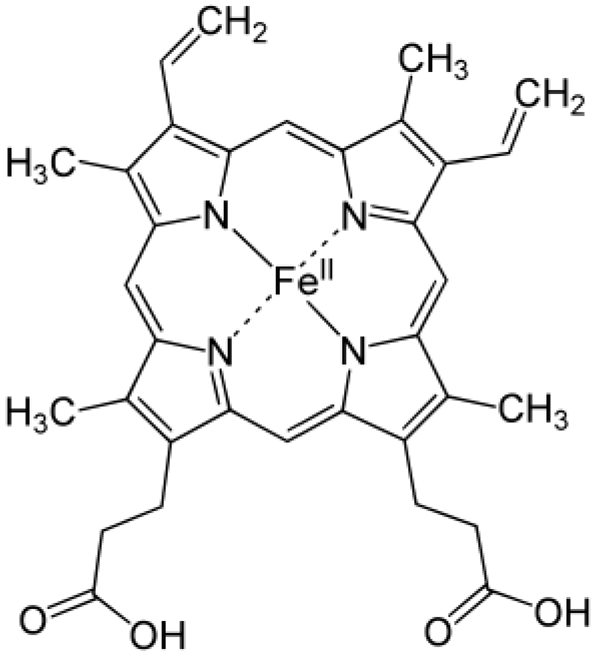
- Heme is a complex of an iron (Fe) ion coordinated to a large, planar, cyclic organic molecule known as a porphyrin ring.
- The most well-known heme-containing protein is hemoglobin, which is responsible for oxygen transport in vertebrates.



Porphyrin ring

A porphyrin ring forms the base structure of heme (with different hemes differing at X)





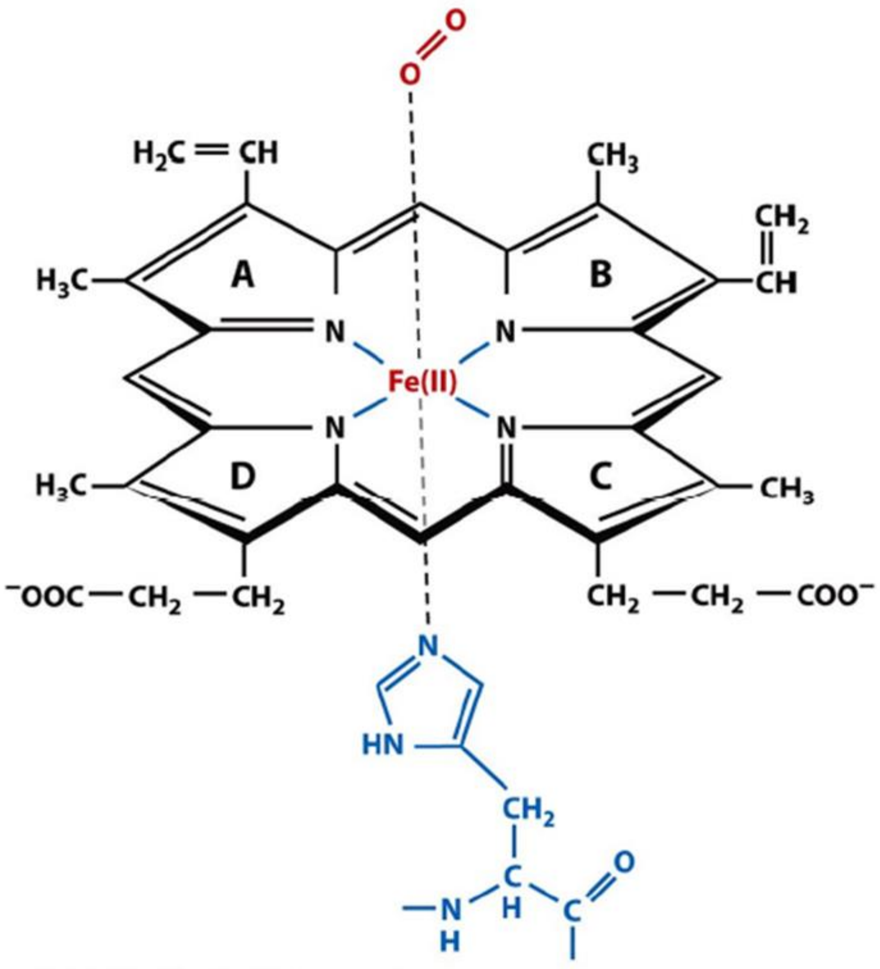
The heme of myoglobin and hemoglobin is a protoporphyrin IX with a bound Fe^{2+}

- Heme prosthetic groups are essential for the function of hemoproteins, and they can be classified into different types based on the specific protein they are associated with. The two main types of heme prosthetic groups are:

1. **Heme A:** Found in cytochrome c oxidase, an enzyme involved in the electron transport chain of aerobic respiration.
2. **Heme B:** This is the most common type of heme and is found in proteins such as hemoglobin, myoglobin, and cytochromes.

Haemoglobin and Myoglobin

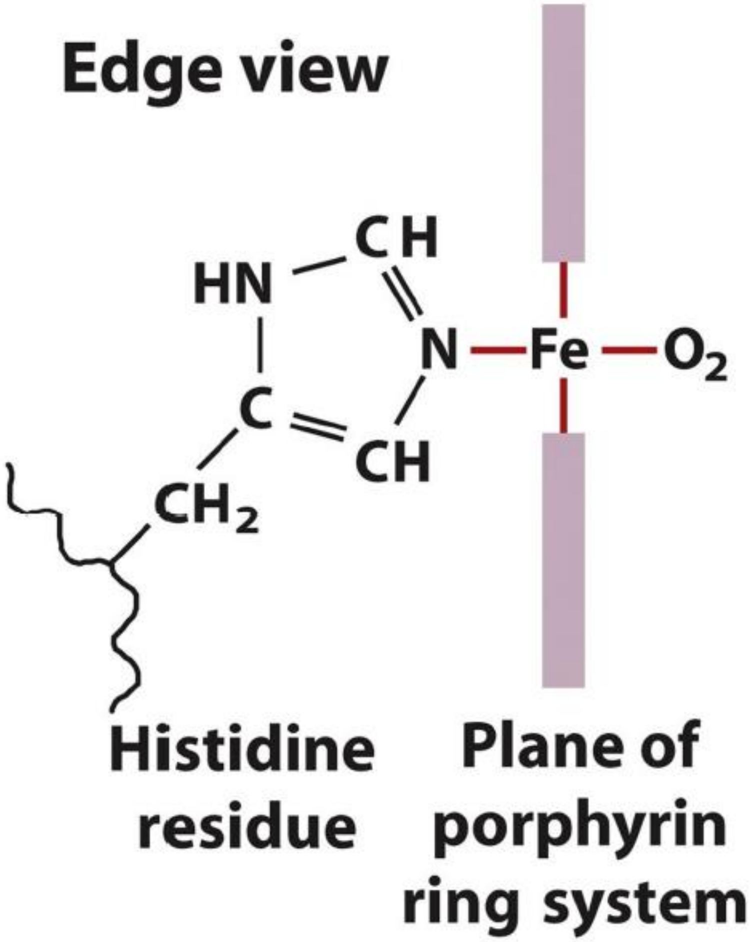
- Both Haemoglobin and Myoglobin are metal porphyrins which contain the “heme” group in their structure.
- The heme group consists of an iron atom which is coordinated to four nitrogen atoms of porphyrin ring



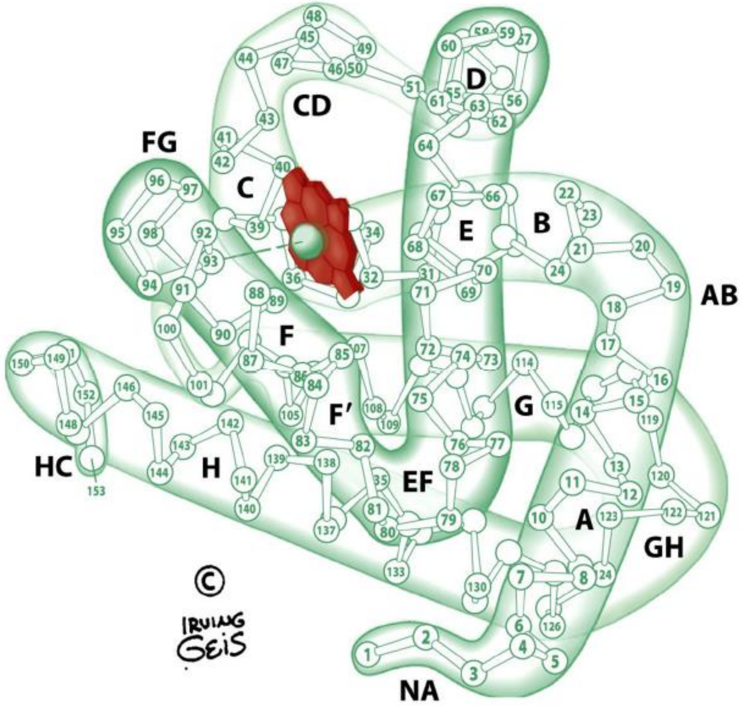
Hemoglobin is present in red blood cells and is responsible for transporting oxygen from the lungs to tissues throughout the body, while myoglobin is found in muscles and is involved in oxygen storage and release.

Myoglobin

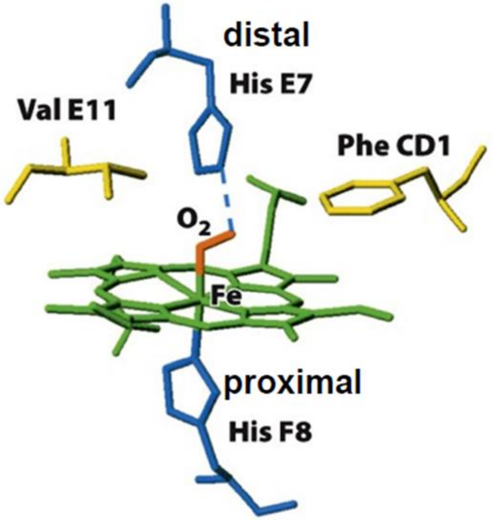
- Myoglobin is a protein of molecular weight of about 17000 with the protein chain containing 153 amino acid residues folded about the single heme group.
- . Myoglobin and hemoglobin are both part of the globin family; a family of heme-containing globular polypeptides with eight α -helices in their protein fold. Myoglobin contains only one subunit of globin, while hemoglobin has four subunits.

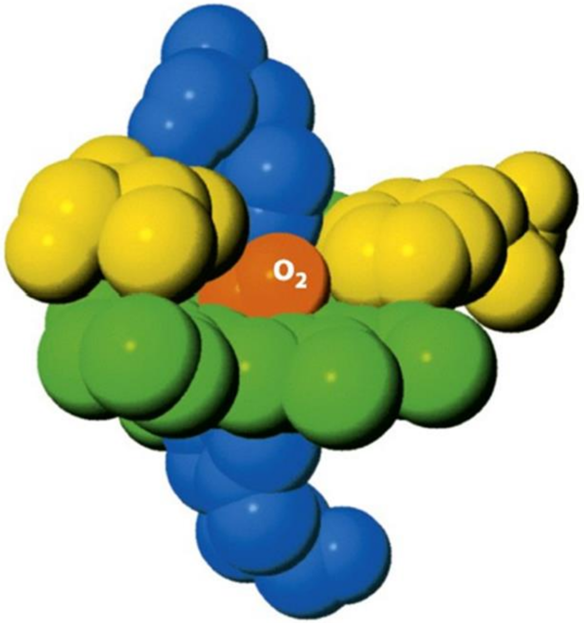


Myoglobin is a single-subunit, α-helical protein, with a heme cofactor that binds O_2



Heme is held in place by the proximal His and by hydrophobic residues





- The iron (Fe)-containing heme group allows myoglobin to reversibly bind to O2. Heme is a large, aromatic porphyrin ring with four pyrrole nitrogens bound to a ferrous (Fe(II)) ion at the center in the high spin state.

- The nitrogens from the porphyrin ring and a Histidine imidazole serve as ligands for the Fe(II) metal center. The heme Fe is bound to the myoglobin polypeptide through the proximal histidine residue.

- The iron ion has six coordination sites: four equitorial sites are occupied by pyrole nitrogens of heme, and one axial site is occupied by a proximal histidine residue. The remaining axial coordination site is available for binding a O2 molecule

Oxygen binding changes the position of the iron ion

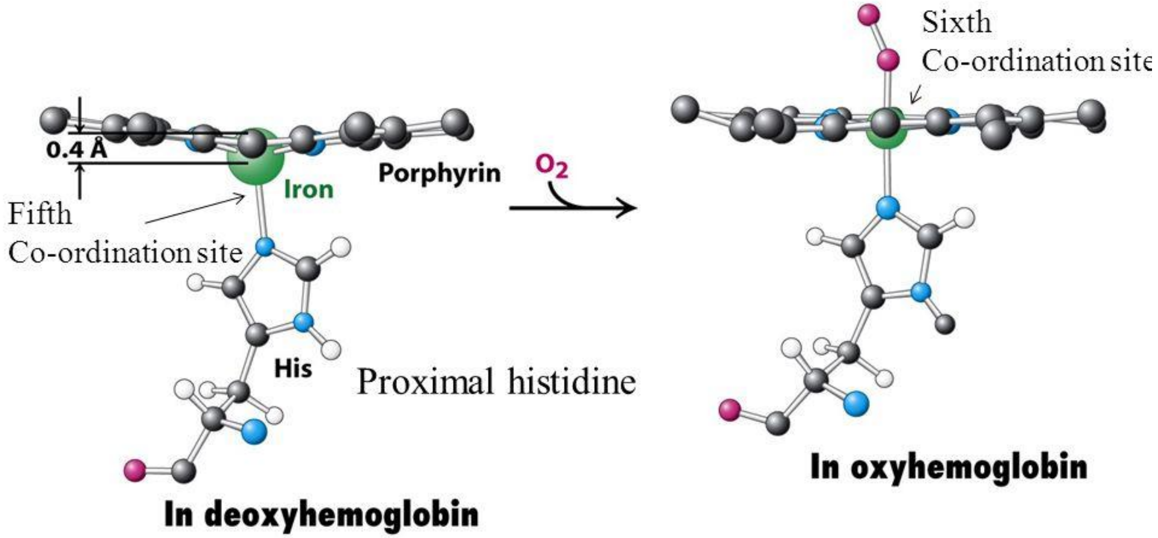


Figure 7-2
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- Iron (II) is d^6 when in high spin has a radius of 92 pm in a pseudo-octahedral environment and the iron atom is not fit into the hole of the porhyrin ring.
- The iron (II) atom thus lies 42 pm above the plane of the porphyrin ring .
- When a dioxygen molecule binds to the iron atom it becomes low spin d6 .
- The ionic radius of low spin iron(II) with coordination number six is only 75pm , in contrast with 92 pm in the high spin iron.
- Here the iron atom shrinks upon spin paring and drops into the hole of the prohyrin ring.
- All the ligands are able to approach the iron atom more closely including the proximal histidine

Oxygen binding changes the position of the iron ion

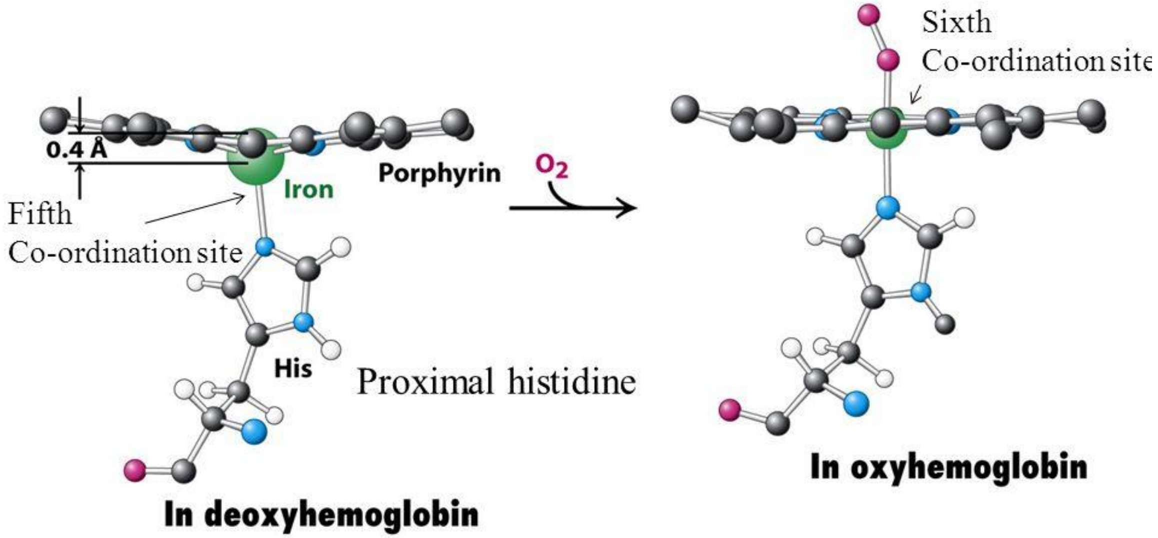

Figure 7-2
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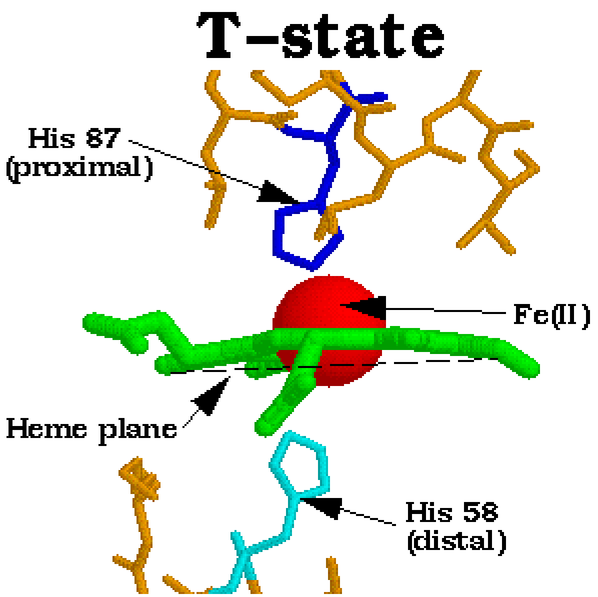
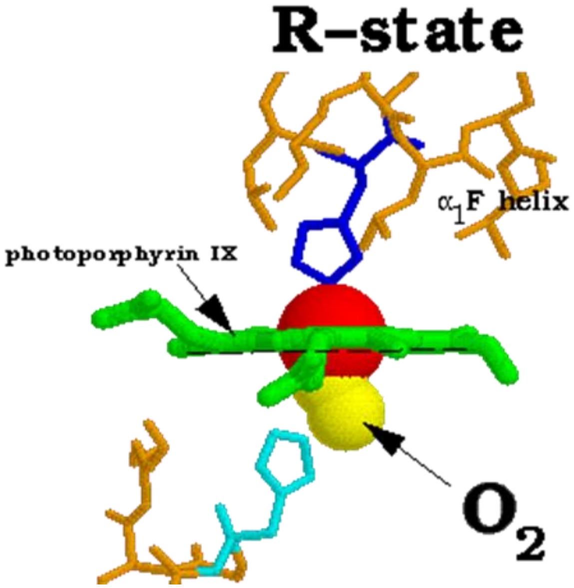
Hemoglobin

- Hemoglobin is considered as an approximate tetramer of myoglobin.
- It has a molecular weight of 64,500 and contains four heme groups bonded to four protein chains.
- Two of the chains labelled beta have 146 amino acid and other two alpha have 141 amino acids.
- Upon oxygenation of hemoglobin two of the heme groups move about 100 pm towards each other while two others separate by about 700 pm.
- The quaternary structure exhibited by the deoxy from is called the Tense (T) state, and the oxy form the Relaxed (R) state.

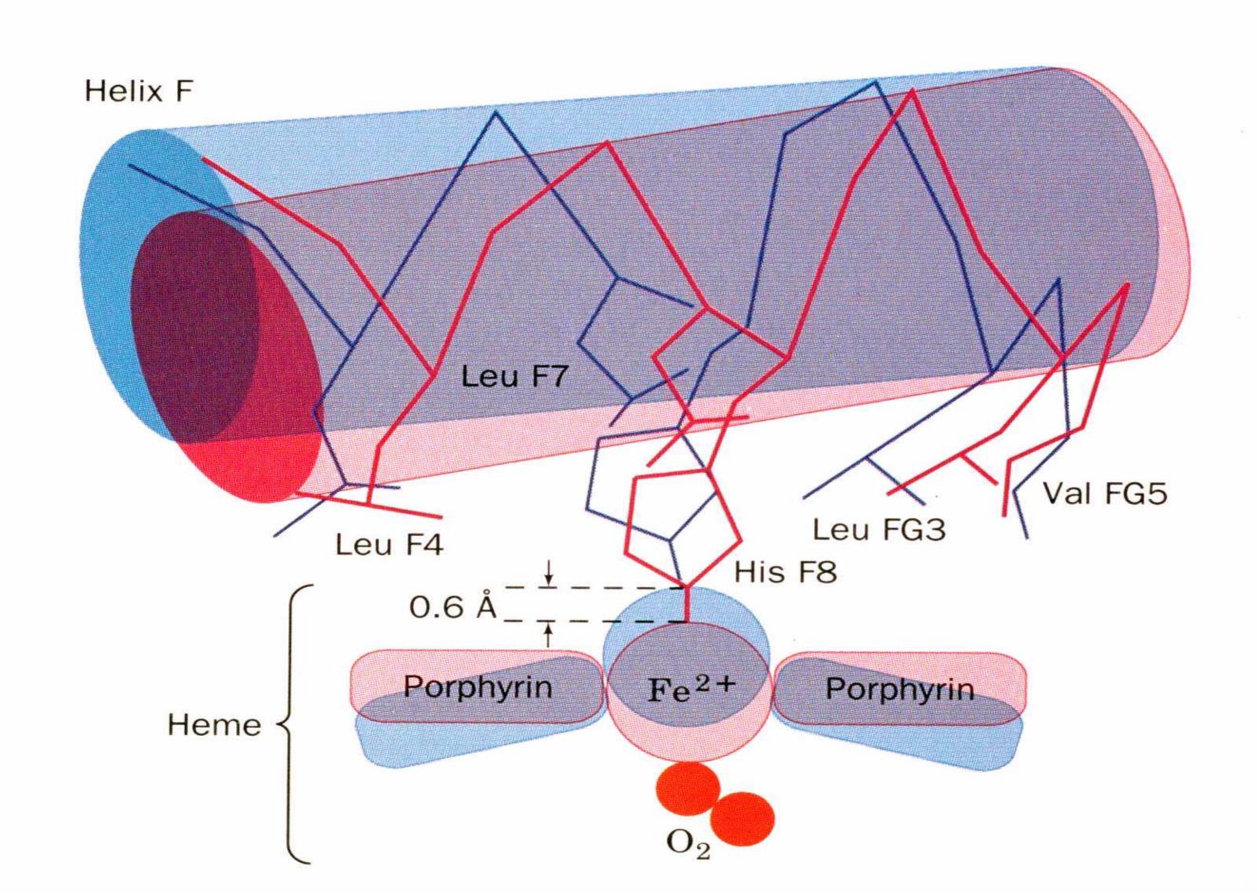


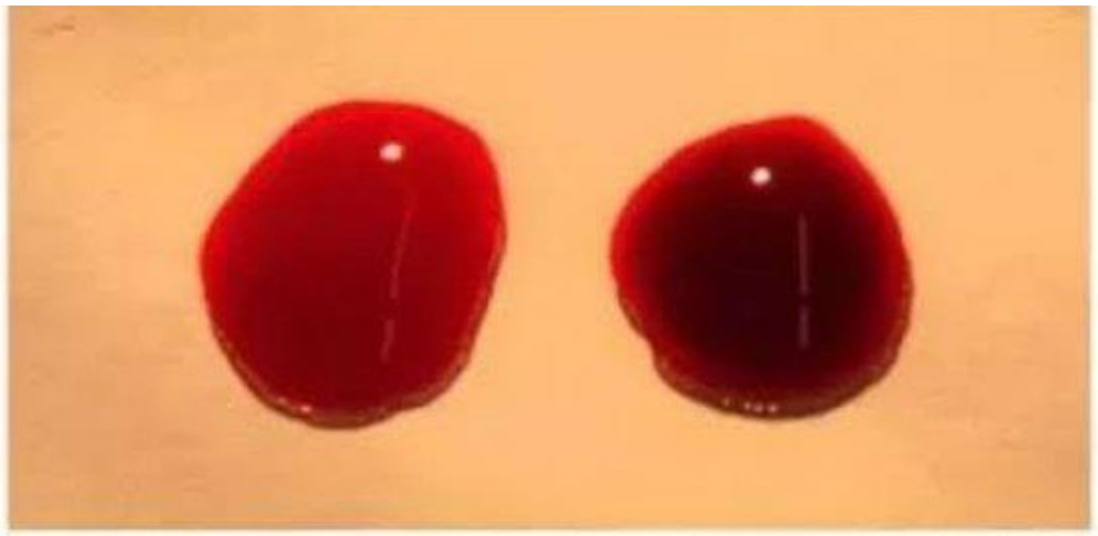


- The interaction between a dioxygen molecule and a heme group can effect the position of the protein chain attached to it.
- Which in turns effects the other protein chains through hydrogen bonds etc., and eventually and tertiary and quaternary structure of the protein. This accounts for the cooperativity of the heme groups in haemoglobin. This is called Perutz mechanism.
- The key or tigger in the Perutz mechanism is the high spin Fe(II) atom in a dioxygen free heme.
- The radius of high spin Fe2+ is too large to fit within the plane of the four porphyrin nitrogen atoms.

This molecule also is also responsible for the color of blood. Oxygenated blood is a bright red because hemoglobin absorbs green light of wavelengths 540-542 nm, and thus it results in a bright red colored solution.

Deoxygenated blood, however, is darker in color because it absorbs a more yellow/green color of wavelength 554 nm, and thus produces a darker color of red.

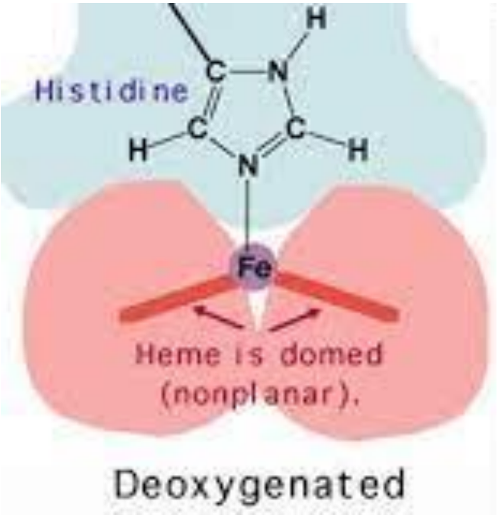


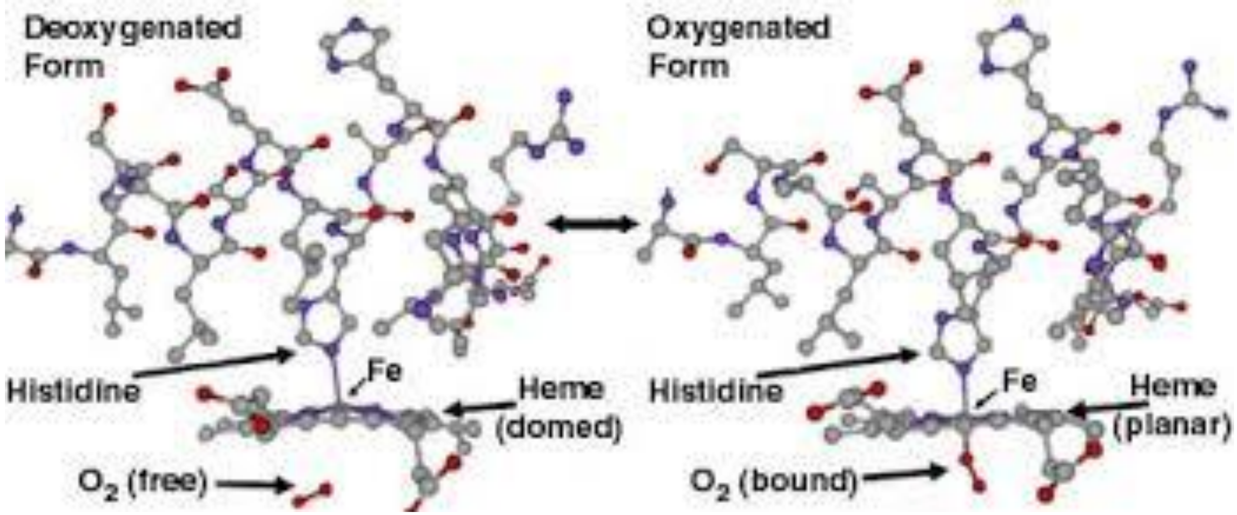


Oxygenated blood: Bright red

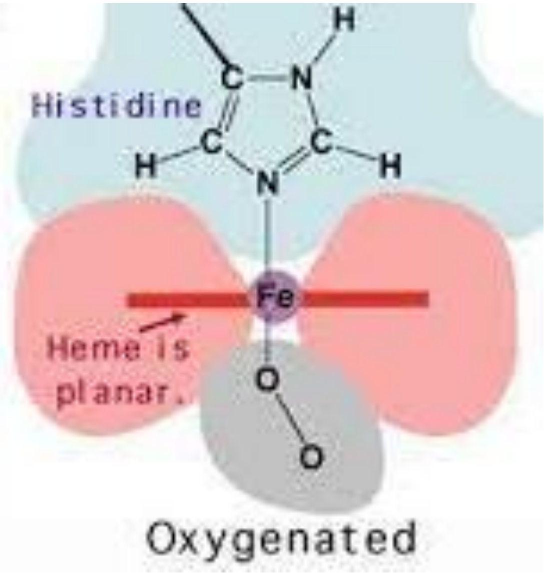
Deoxygenated blood: Deep red-purple

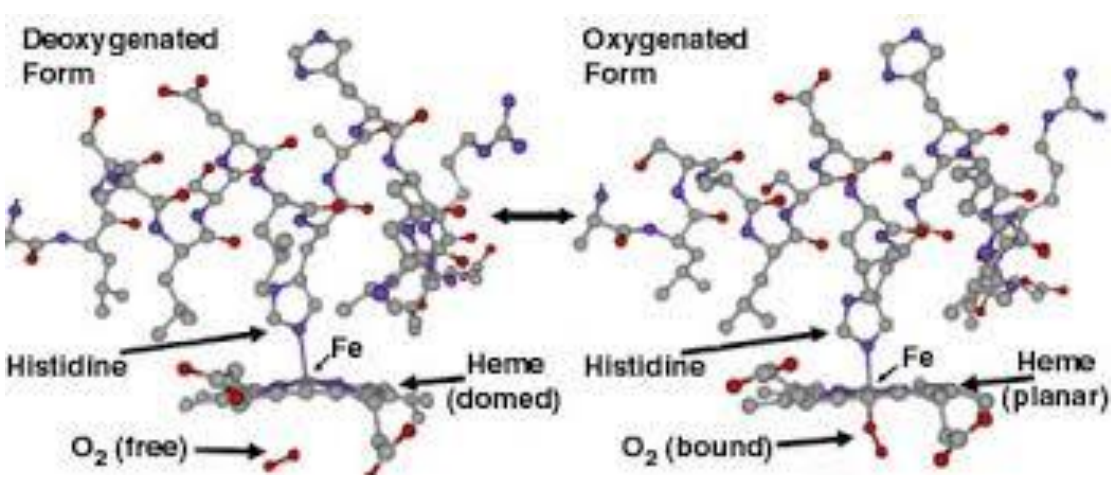
- The iron atom is thus forced to sit above the center of the heme group with the Fe-N porphyrin distance of about 206 pm.
- The heme group is domed upward towards the proximal histadine Fe-Nprox distance of about 215 pm.





- The coordination of the dioxygen molecule as the sixth ligand causes spin paring to take place on the iron atom.
- Since the radius of the low spin Fe(II) is about 17 pm smaller than high spin Fe(II) it should fit into the porphyrin hole.





Cooperative binding of O_2

An important feature of hemoglobin is a cooperative binding of oxygen to each subunit due to conformational changes upon oxygen binding to the heme iron.

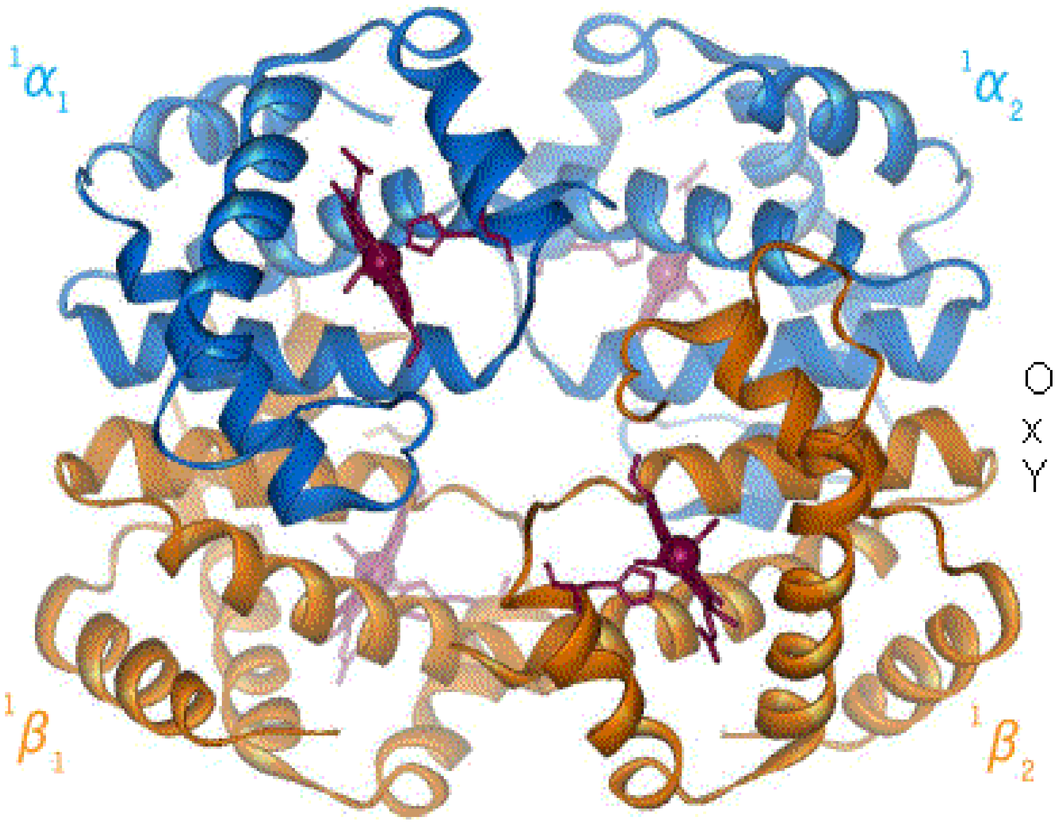
Hemoglobin exists in both the T-state (tense state) and the R-state (relaxed). The T-state has lower affinity for dioxygen due to the tilting of the proximal histidine and steric hindrance of the O_2 coordination site.

Steric hindrance makes it difficult for oxygen molecule to enter the site and bind to Fe.

When an oxygen binds to one subunit of hemoglobin, the iron shifts into the plane of the porphoryn ring, and tugs on the proximal histidine.

This causes the proximal histidine ring to be pulled toward the plane of the prosthetic group, decreasing the tilt of the histidine, causing a shift in the tertiary structure of that subunit, and displacing residues that were providing steric hiderance of the oxygen binding site.

These conformational changes in one subunit cause similar changes to the tertiary structures of adjacent subunits, in turn decreasing steric and electrostatic constraints in those adjacent units. The result is adoption of the R-state and a subsequent increase in oxygen affinity to the other subunits.



When the inorganic iron ion is bound to only five coordination sites the iron (II) lies 0.4 Å outside of the porphyrin ring.

When the oxygen binds to the iron core the iron becomes smaller as it becomes low-spin because electrons are pulled closer to the Fe core or are transfered to the dioxygen molecule due to backbonding.

The low spin iron and is able to fit in the plane of the porphyrin ring.

As oxygen binds to one monomer of hemoglobin, the tetramer's conformation shifts from the T (tense) state to the R (relaxed) state. This shift promotes the binding of oxygen to the remaining three monomers' heme groups, thus saturating the hemoglobin molecule with oxygen.

In the tetrameric form of normal adult hemoglobin, the binding of oxygen is, thus, a cooperativity process.
The binding affinity of hemoglobin for oxygen is increased by the oxygen saturation of the molecule, with the first molecules of oxygen bound influencing the shape of the binding sites for the next ones, in a way favorable for binding.

This positive cooperative binding is achieved through steric conformational changes of the hemoglobin protein complex as discussed above; i.e., when one subunit protein in hemoglobin becomes oxygenated, a conformational or structural change in the whole complex is initiated, causing the other subunits to gain an increased affinity for oxygen.

As a consequence, the oxygen binding curve of hemoglobin is sigmoidal , or *S*-shaped.

The Bohr Effect

Higher pH i.e. lower [H^+] promotes tighter binding of oxygen to hemoglobin

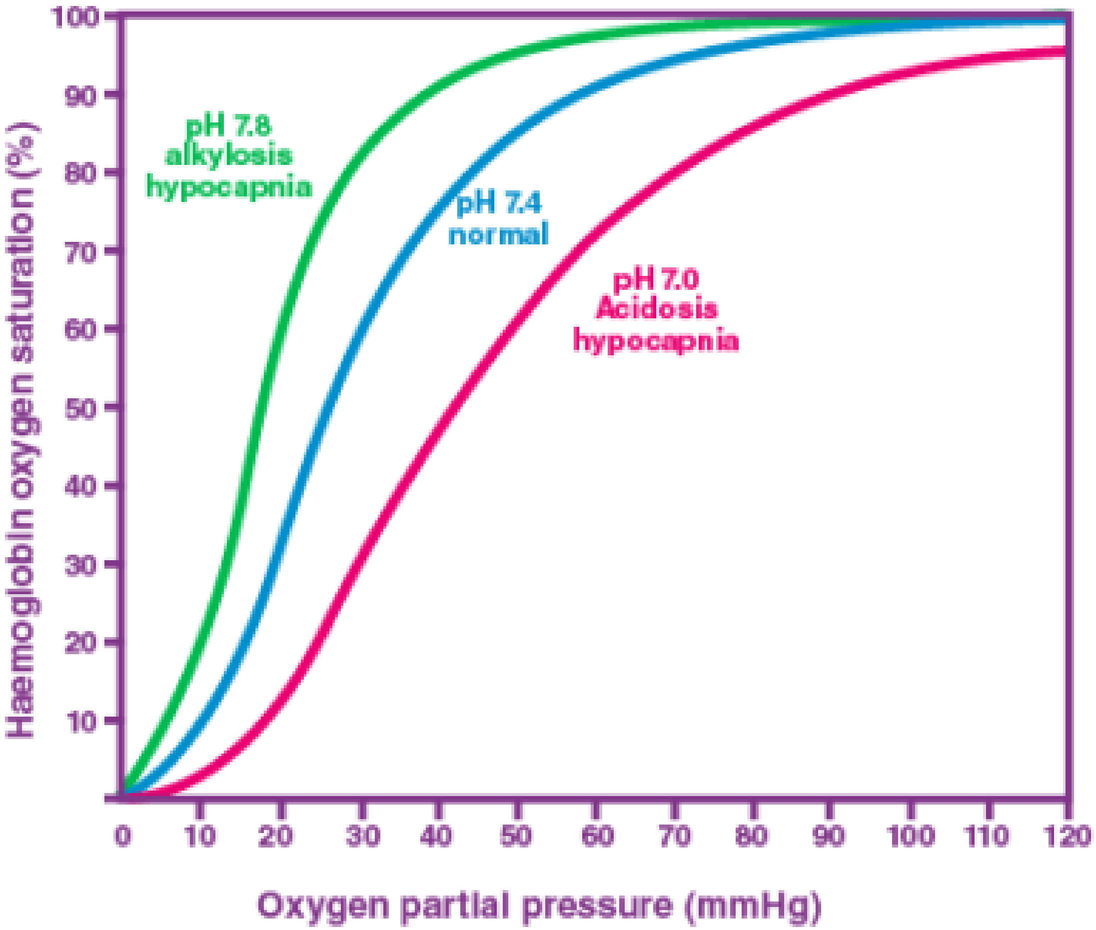
and

Lower pH i.e. higher [H+] permits the easier release of oxygen from hemoglobin

$$\mathrm{Hb}(\mathrm{O}_2)_n\mathrm{H}_x + \mathrm{O}_2 \Leftrightarrow \mathrm{Hb}(\mathrm{O}_2)_{n+1} + x\mathrm{H}^+$$

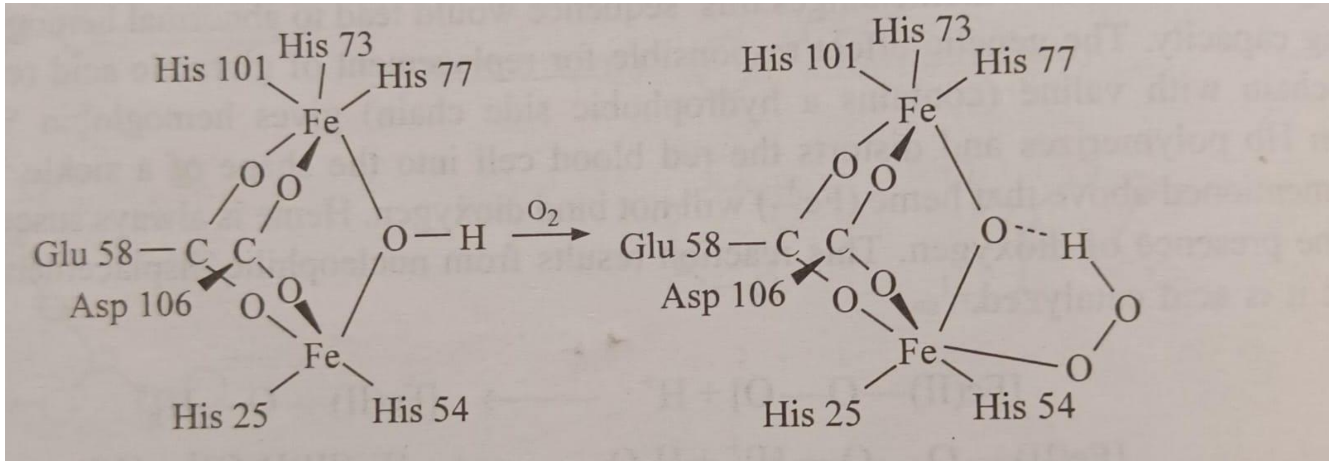
Where n = 0, 1, 2, 3 and $x \cong 0.6$ A shift in the equilibrium will influence the amount of oxygen binding. Bohr protons

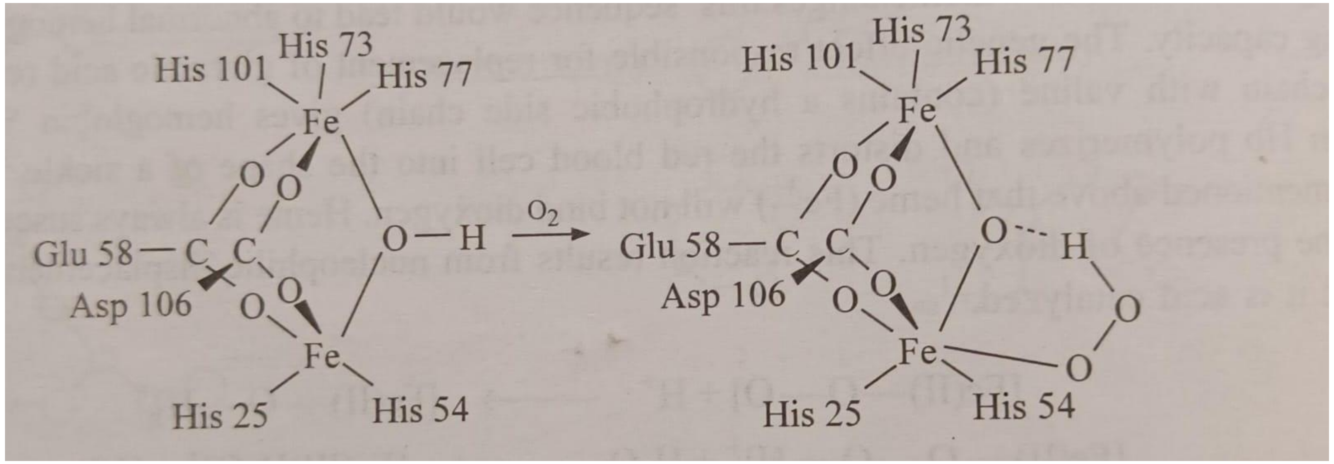
According to Bohr's effect, the affinity of oxygen with haemoglobin depends on the pH of blood.
As the concentration of carbon dioxide is less near lungs the haemoglobin binds with oxygen on higher rate as the pH of blood is on higher side it reaches towards tissue the concentration starts to increase and pH decreases its affinity towards oxygen also decreases.
It was given by Christian Bohr in 1904.



Hemerythrin

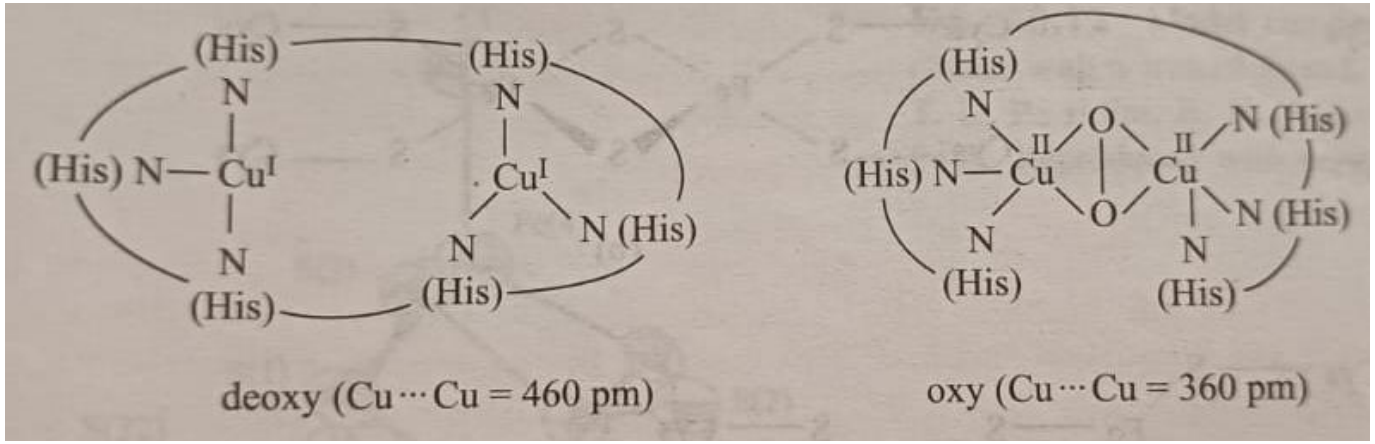
- Hemerythrin is a nonheme, dioxygen-binding pigment utilized by four phyla of marine invertebrates.
- Its chief interest to the chemist lies in the similarities to and differences from hemoglobin and myoglobin.
- Hemerythrin contains iron(II) which binds oxygen reversibly, but when oxidized to methemerythrin (Fe^{3+}) it does not bind dioxygen.





- Mossbauer data indicate that the two iron (III) atoms are in different environments in oxyhemerythrin.
- The two iron atoms in hemerythrin are bound the imidazole rings of five histidine residues and the carboxylates of an aspartic acid and a glutamic acid. In addition, the complex contains an oxygen atom bridging between the two iron atoms.
- In deoxyhemerythrin, the bridge is a hydroxyl group, while in met- and oxyhemerythrin, the bridge is a μ-oxo atom.
- Oxyhemerthrin is diamagnetic, indicating spin coupling of the odd electrons on the two iron(III) atoms.

Hemocyanine


deoxy (Cu···Cu = 460 pm) oxy (Cu···Cu = 360 pm)

- Hemocyanin, a copper-containing protein chemically unlike hemoglobin, is found Mollusca and Arthropoda.
- Hemocyanin is blue in colour when oxygenated and colourless when oxygen is removed.
- The gross molecular structures of the hemocyanins in the two phyla are quite different , though both bind dioxygen cooperatively
- Spectroscopic evidence indicates that the di-oxygen binding centres are similar..
- The dioxygen binding site appears to be a pair of copper atoms, each bound by three histadine ligands,
- The copper is in the +1 oxidation state in the deoxy form and +2 in the oxy form.
- Hemocyanin name simply means “blue blood”.