418 Chem.

Bioinorganic Chemistry

Part II. Transport and Storage of Metal Ions

b. Iron

Outline- Part II b

- The chemistry of iron
- The biological role of Fe
- Ferritin, the cellular Fe store
- Oxygen transport
  - Myoglobin
  - Hemoglobin

Oxidation states of Fe

Fe, Z=26, $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^6$

- The chemistry of iron is dominated by the +2 and +3 oxidation states.
- They form complex ions with selected ligands, usually of an octahedral shape, and a few tetrahedral iron(III) complexes exist.
- Fe(III) is stabilized by negatively charged ligands.
- Fe(II) is favored by neutral ligands which allow some charge delocalization in π-orbitals.

Fe^{3+} complexes

- At low pH, hydrolysis occurs (it is a complicated process and mixture, especially in presence of coordinating anions).

- Fe(III) salts dissolve in water producing high acidity, and the hexaquo ion predominates at very low pH ~0 **(pale-violet)**

- At pH 2-3 color becomes **yellow** due to hydrolyzed species.

Fe^{3+} complexes

- At pH > 2-3 colloidal gels form $\Rightarrow$ **reddish-brown** precipitate of hydrous iron(III) oxide

- Hydrous iron(III) oxide: Iron (III) oxide-hydroxide or ferric oxyhydroxide

- Fe(III) form complexes with a variety of ligands, but has a marked preference to O-donor ligands

Fe^{2+} complexes

- $[Fe(H_2O)_6]^{2+}$ ion is **pale green**
- No hydrolysis in acidic solutions
- Fe(II) forms complexes with a variety of ligands.
- These complexes are less stable than those with Fe(III) (smaller cationic charge)

The Fe(III)/Fe(II) couple

$Fe^{3+} + e \leftrightarrow Fe^{2+}$

- The standard reduction potential E value for the couple involving the simple aquated ions shows that:

➢ The $Fe^{II}(aq)$ is thermodynamically stable with respect to hydrogen.

➢ $Fe^{III}(aq)$ is spontaneously reduced by hydrogen gas.

➢ $Fe^{II}(aq)$ is oxidized to $Fe^{III}(aq)$ by atmospheric oxygen under certain circumstances.

➢ Oxidation is slow in acidic solutions

The Fe(III)/Fe(II) couple

$Fe^{3+} + e \leftrightarrow Fe^{2+}$

- When E decreases as the alkalinity of a solution increases , the precipitation of Fe(III) species occurs.

- When the alkalinity of a solution increases, the pH of the solution also increases. This is because alkaline substances, such as NaOH and KOH, produce OH- ions when dissolved in water. OH- ions react with H+ ions to form water

- Fe(II) solutions are not stable with respect to areal oxidation.

Which oxidation state of iron you think will be best utilized in biological systems? Why?

- Fe^{2+} (ferrous ion): it is the most stable and soluble form of iron
- Allows it to readily participate in biological processes such as oxygen transport, electron transfer, and enzyme catalysis.

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The Biological role of iron

- Iron is an essential element in our diet and is needed for the production of hemoglobin.
- The iron atom in the hemoglobin molecule helps coordinate of the oxygen molecule and hence the transportation of oxygen around the body to the cells of all the tissues.
- Iron deficiency causes anemia.
- Plants require iron for the synthesis of chlorophyll.

Selective transport and storage of iron

- Iron is essential for almost all life forms, and is difficult to obtain.
- Any excess presents a serious toxic risk.
- Nature has at least two problems in dealing with this element:

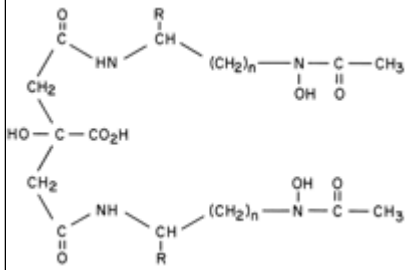
➢ The first is the insolubility of Fe(III) (the stable oxidation state found in most minerals). As the pH increases, hydrolysis, polymerization, and precipitation of hydrated forms of the oxide occur.

➢ The second problem is the toxicity of 'free-Fe' species, particularly through the generation of OH radicals.

Selective transport and storage of iron

In biological systems, Fe:

- Uptake into organisms involves special ligands known as siderophores (iron carriers/special ligands).



Citrate hydroxamate siderophore

- Transport in the circulating fluids of higher organisms requires a protein called transferrin
- Is stored as ferritin.

Siderophores: "iron carrier" are small, high-affinity iron-chelating compounds secreted by microorganisms such as bacteria and fungi and serving to transport iron across cell membranes.

Siderophores are amongst the strongest soluble Fe^{3+} binding agents known.

Why does iron uptake into organisms involve special ligands?

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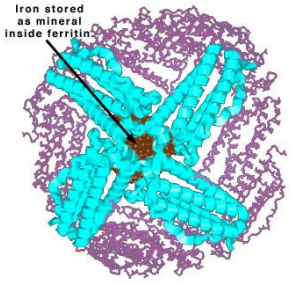


Ferritin

- Ferritin is the principal store of non-heam Fe in animals (most Fe is occupied in heamoglobin and myoglobin)
- It occurs in all types of organism (in mammals in spleen and in blood).
- Ferritins have two components:

- a 'mineral' core that contains up to 4500 Fe atoms (mammalian ferritin).
- and a protein shell (apoferritin).

Ferritin

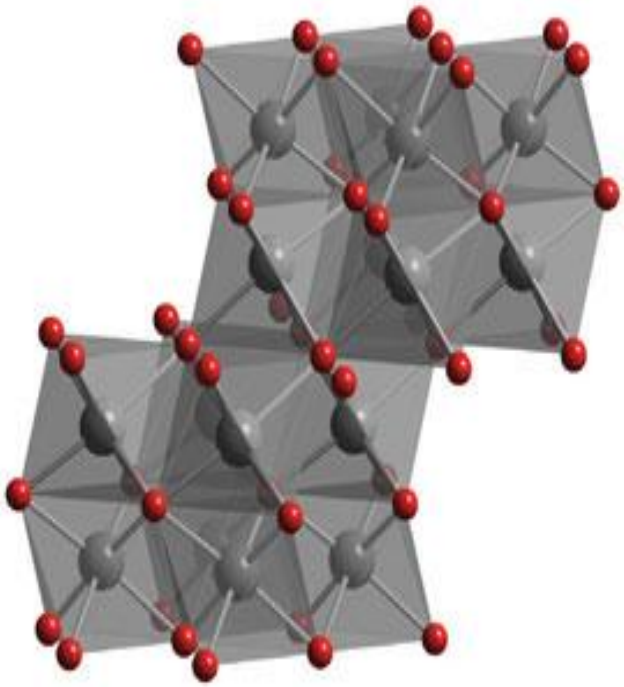
The mineral core is composed of:

- hydrated Fe(III) oxide (ferrihydrite)
- varying amounts of phosphate, which helps anchor it to the internal surface.

- The structure resembles that of the mineral ferrihydrite, $5Fe_2O_3.9H_2O$, which is insoluble and Fe must be mobilized.

Ferritin

Ferrihydrite: ($5Fe_2O_3.9H_2O$)



Based on an hcp array of O^{2-} and OH^- with Fe(III) layered in both the octahedral and tetrahedral sites.

Ferritin

- The proposed mechanism for the reversible incorporation of Fe in ferritin involves:

Transport in and out as Fe(II), perhaps as the Fe^{2+} ion, which is soluble at neutral pH, but more likely with some type of 'chaperone' complex.

molecular chaperones are proteins that assist the conformational folding or unfolding of large proteins or macromolecular protein complexes

Ferritin

Oxidation of Fe(II) to Fe(III) involves two steps:

- In the first step, O_2 coordinates to the Fe(II) center. In the second step, an electron is transferred from the Fe(II) center to O_2, forming Fe(III) and H_2O_2:

$$2\ Fe(II) + O_2 + 2H^+ \rightarrow 2\ Fe(III) + H_2O_2$$

- The mechanism by which Fe is released almost certainly involves its reduction back from Fe(III) to the more mobile Fe(II).

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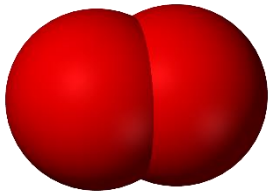


Dioxygen

- As the waste product of photosynthesis, O_2 is a biogenic substance, one that comes from solar energy capture by living organisms.

- For example, plants use sunlight to make sugar (food) and release oxygen (O_2) as a waste product (byproduct). This oxygen is a **biogenic substance**, meaning living organisms made it.

- The requirement for O_2 needs special systems for transporting and storing it.

Dioxygen

- There is difficulty in supplying O_2 to buried tissue, and achieving sufficiently high concentration in aqueous environments which was overcame by:

Metalloproteinase known as **O_2 carriers**

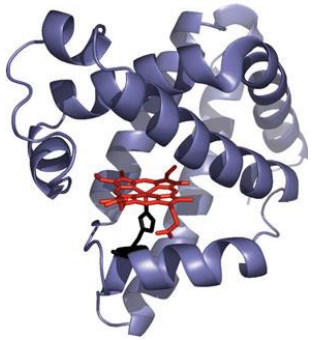
- In mammals and most other animals and plants, these special proteins (myoglobin and heamoglobin) contain an Fe porphyrin cofactor.

Dioxygen

- Some lower invertebrates use an alternative type of Fe protein, heamerythrin, which contains a dinuclear Fe site.

- Some primitive animals such (e.g. molluscs and arthropods) use a Cu protein called heamocyanin.

What does the word heam (heme) mean?



Myoglobin

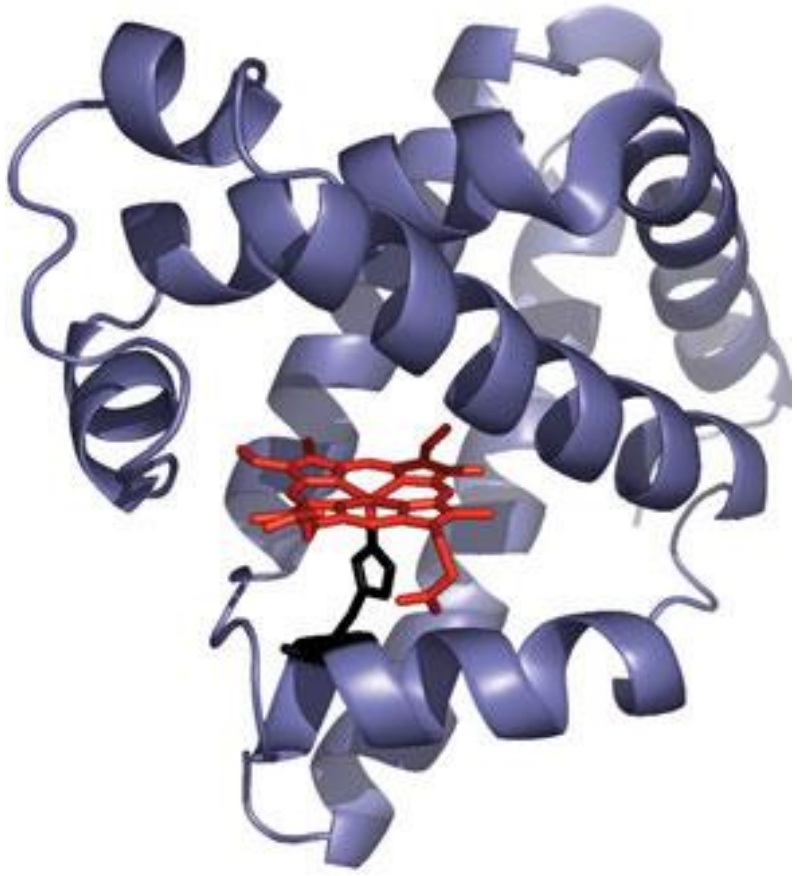
Is an Fe^{2+} protein that coordinates O_2 reversibly and controls its concentration in tissue.

- In mammals, O_2 (by respiration) is:
  - carried in the bloodstream by heamoglobin
  - and is stored in the tissues in myoglobin.

Myoglobin

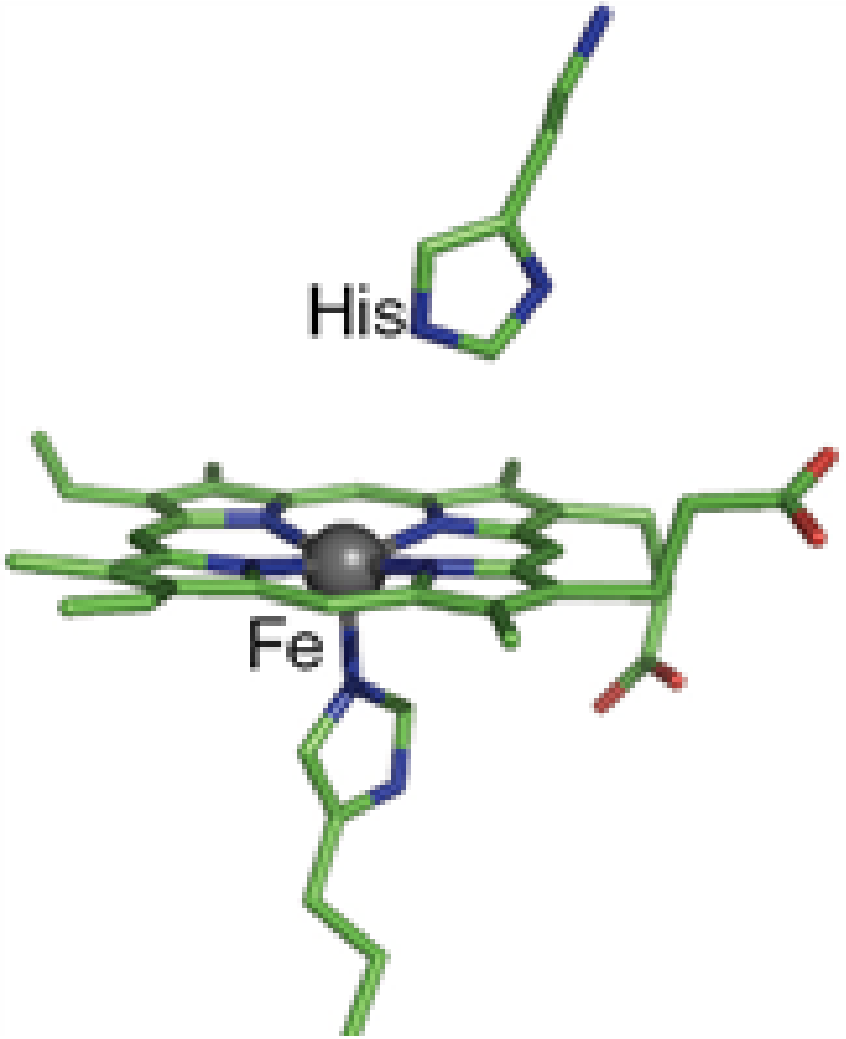
- Structure:

➢ The molecule contains several regions with the single Fe porphyrin group (heam group) located in a cleft between two helices.



Myoglobin

- Fe is coordinated to four N-donor atoms in the porphyrin ring.
- The fifth ligand to the Fe is provided by a histidine-N.
- The sixth position is the site at which O_2 is coordinated.



Myoglobin

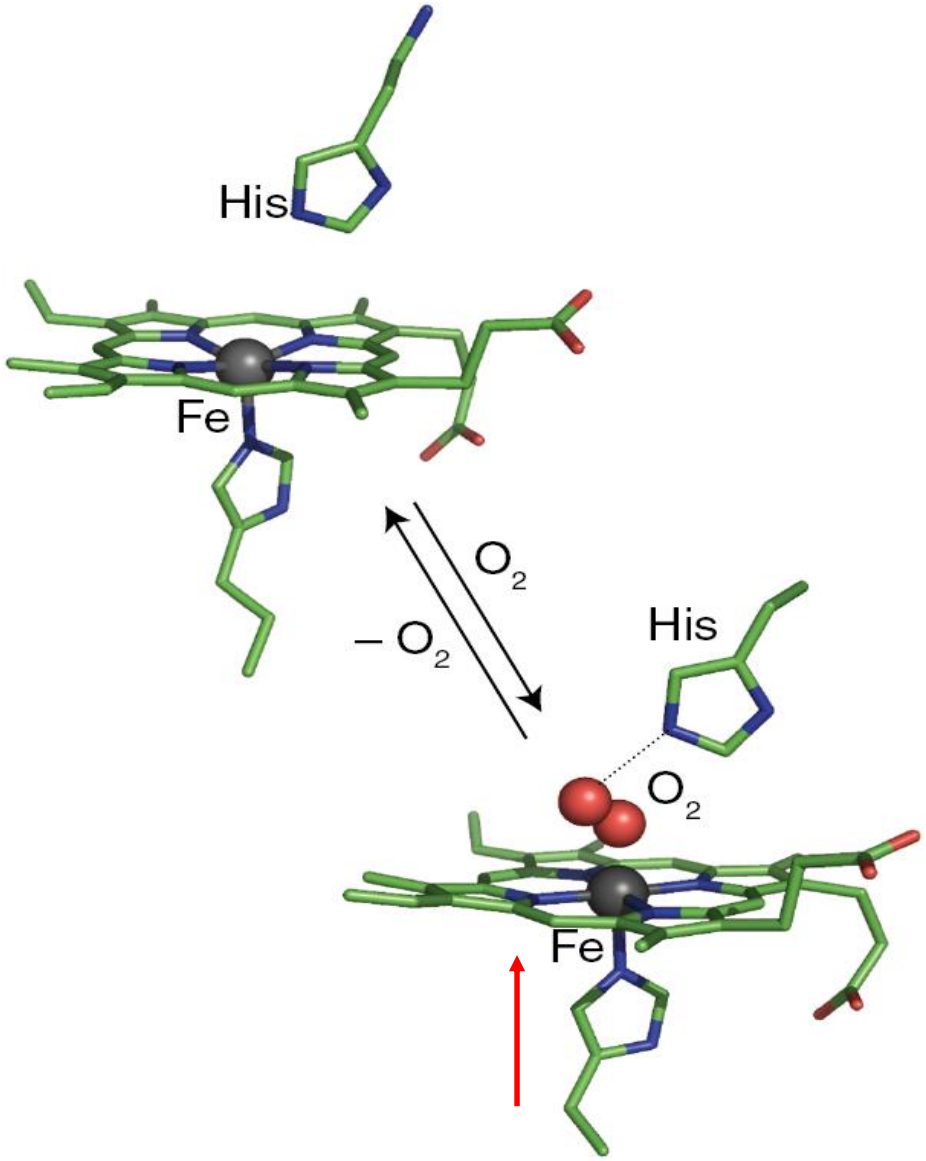
- Deoxymyoglobin is 5-coordinate, high-spin, and Fe^{2+} lies above the ring plane.
- When O_2 binds it is coordinated end-on to the Fe atom.
- The unbound end of O_2 is fastened by a hydrogen bond to the imidazole-NH.
- The coordination of O_2 (a strong-field π-acceptor) causes the Fe(II) to switch from high spin ($t_{2g}^4 e_g^2$) to low-spin (t_{2g}^6)

Myoglobin

- Coordination by O_2 causes the Fe to:

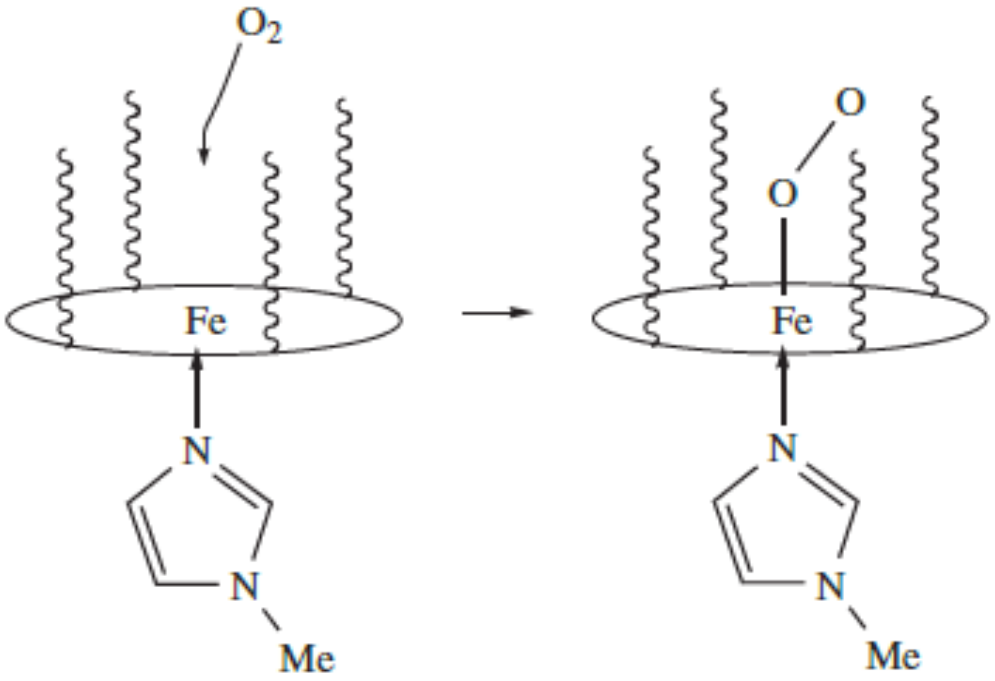
➢ Become low spin (smaller radius).

➢ Move into the plane of the porphyrin ring accordingly.



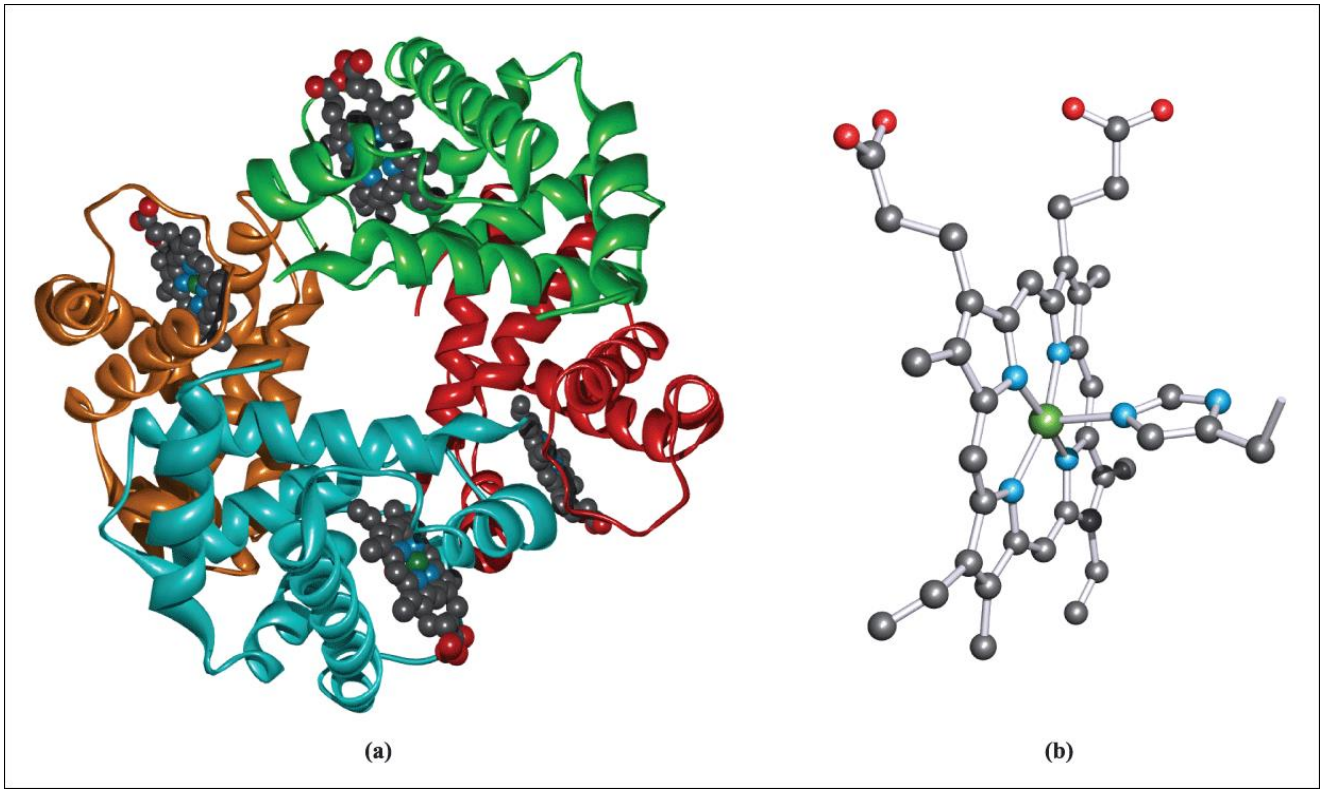
Myoglobin

- Interaction between iron centers is prevented by a so-called ‘picket-fence’ porphyrin.



Hemoglobin

Hemoglobin consists of a tetramer of myoglobin-like subunits with four Fe sites that bind O_2 cooperatively.



Hemoglobin

Although each of the four units in heamoglobin contains a heam group, the four groups do not operate independently of each other, and binding (and release) of O_2 is a cooperative process:

- As the tetramer binds successive O_2 molecules, the affinity of the 'vacant' heam groups for O_2 increases such that the affinity for the fourth site is ~ 300 times that of the first heam unit.

Hemoglobin

- When O_2 is released from hemoglobin to myoglobin, the loss of the first O_2 molecule triggers the release of the remaining three.

- Myoglobin does not exhibit this cooperative effect since it comprises only one protein chain.

Construct a comparison between haemoglobin and myoglobin.

Video links

- https://www.youtube.com/watch?v=Qv-KExGKAYw
- https://www.youtube.com/watch?v=0qT_D2UNSVc

Toxicity of CO and CN^-

Carbon monoxide:

- CO is small enough to fit into the protein cavity and form such strong bonds with the iron that the process is *irreversible*.
- High concentrations of CO rapidly use up the body's limited supply of hemoglobin molecules, and prevent them from binding to oxygen.
- Hemoglobin's binding affinity for CO is 200 times greater than for O_2.

Toxicity of CO and CN^-

Cyanide ion:

- Once cyanide is taken into the blood stream the majority (92-99%) is found bound to hemoglobin in red blood cells.

- Then CN^- is taken to the body's tissues where it binds to an enzyme called *cytochrome oxidase* and stops cells from being able to use oxygen.

Toxicity od CO and CN^-

Different mechanisms:

- Cyanide dissociates from hemoglobin faster than carbon monoxide and much slower than the dissociation rate constants for oxygen.

- Because of the extremely low affinity of CN^- ligand for the ferrous heam iron, the dissociation occurs.

Why?