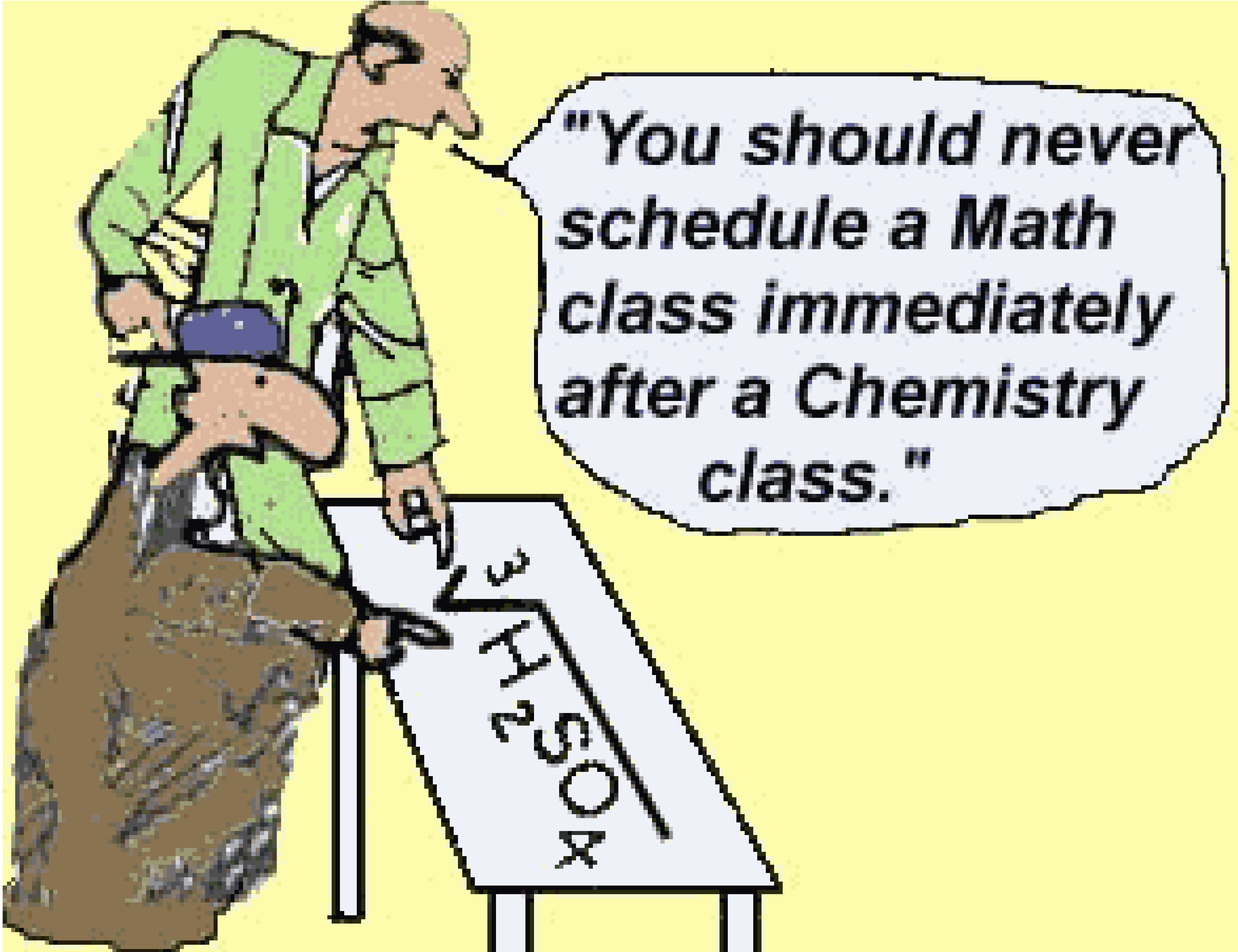

"You should never schedule a Math class immediately after a Chemistry class."

# Inorganic Chemistry in Biology

**Or**

# Biological Inorganic Chemistry

**Or**

# Bioinorganic Chemistry

# Two Main Avenues of Study

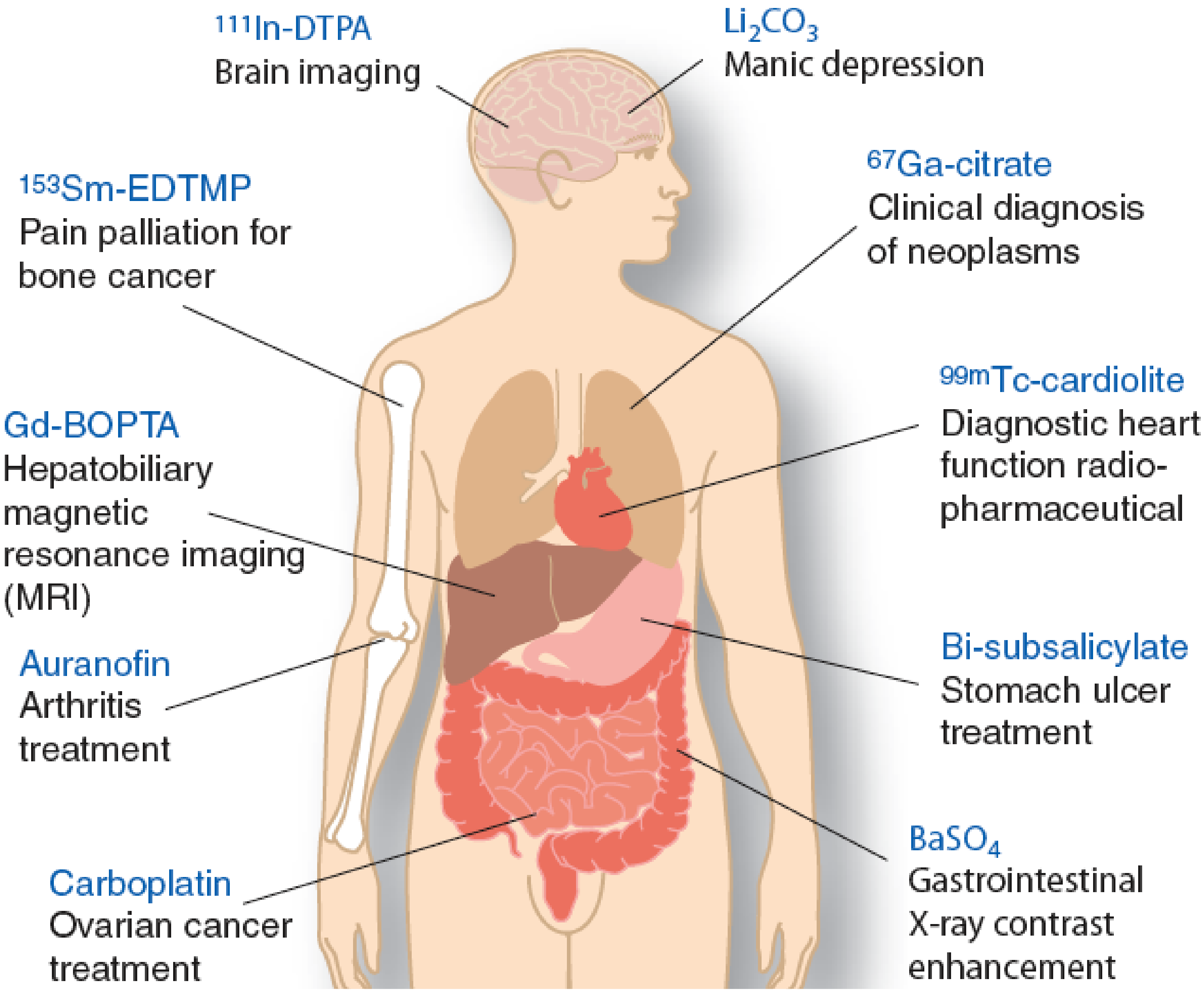
- Understand the roles of naturally occurring inorganic elements in biology. By weight, > 50% of living matter is inorganic. Metal ions at the core of biomolecules control many key life processes.

- Use metals as probes and drugs

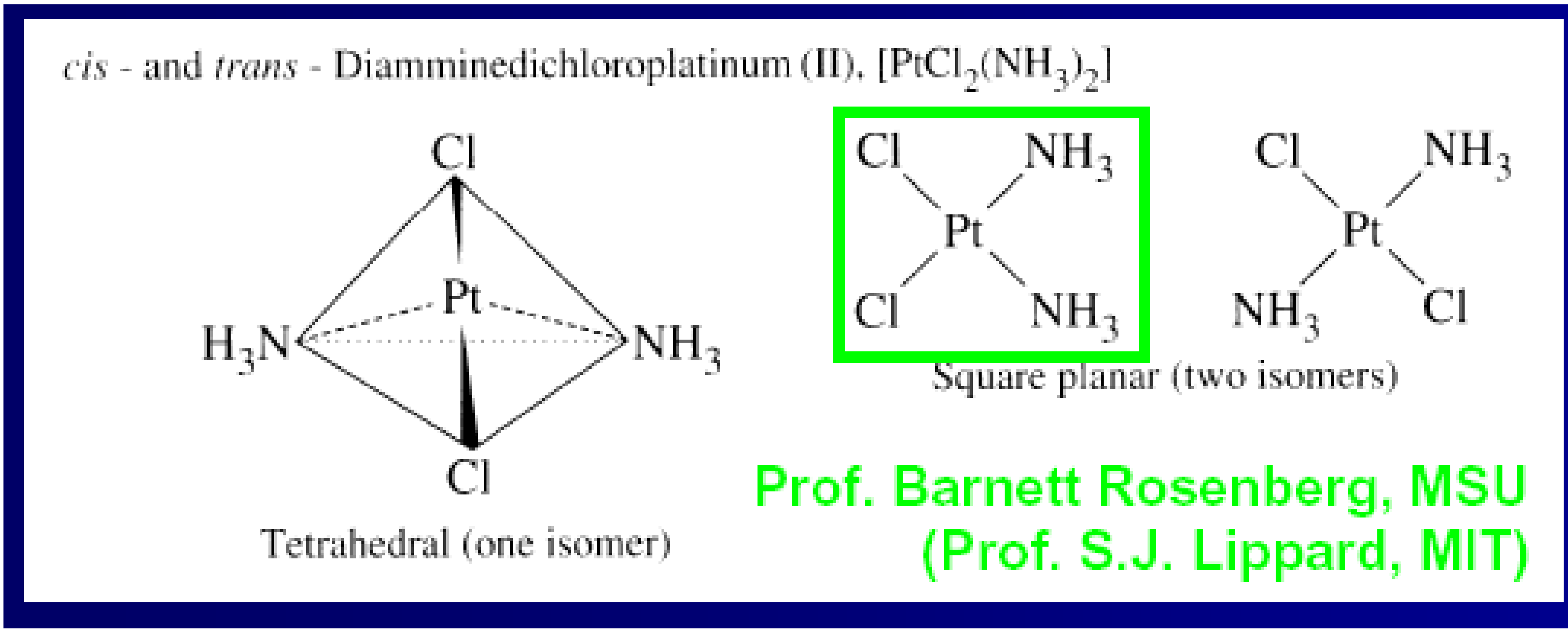
Examples:

Cisplatin, auranofin as pharmaceuticals
Cardiolyte ($^{99m}Tc$) and Gd, imaging agents
$MoS_4^{2-}$, Wilson's disease; cancer??

# Medicinal Inorganic Compounds

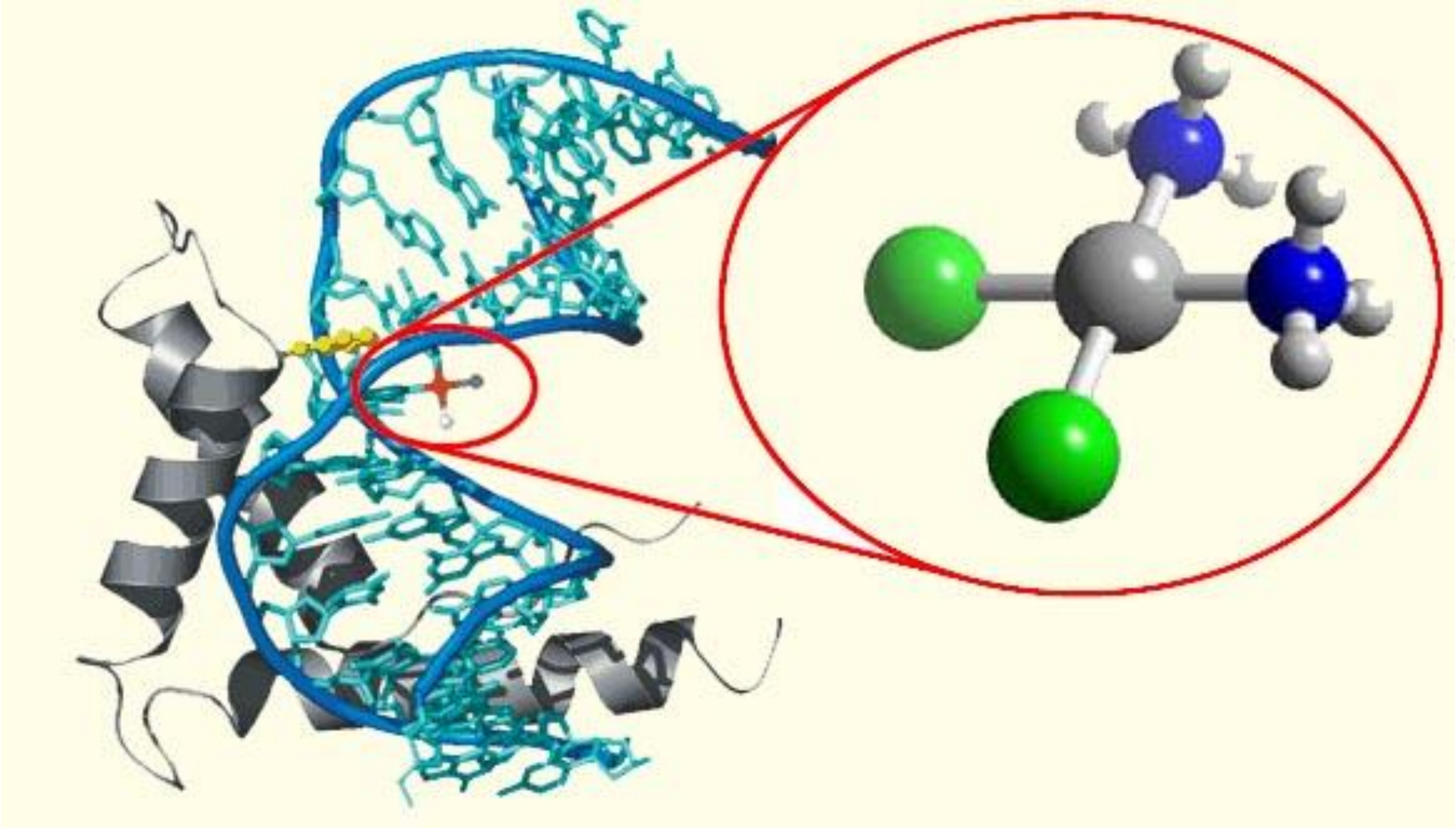



# Cis- vs. Trans- Platin isomers: Serendipity in Chemistry Is a boon to cancer patients



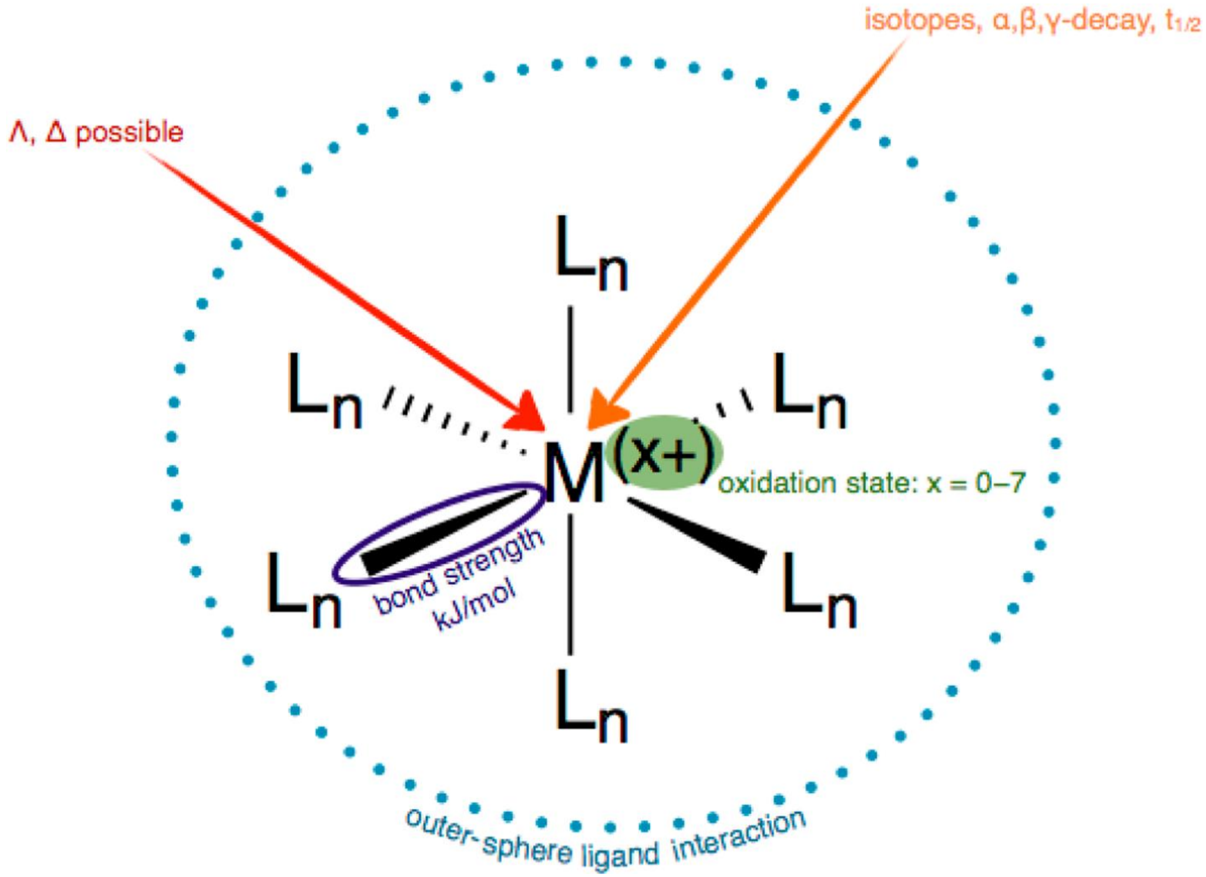

Prof. Barnett Rosenberg, MSU
(Prof. S.J. Lippard, MIT)

**Cisplatin** acts by cross-linking DNA in several different ways, making it impossible for rapidly dividing cells to duplicate their DNA for mitosis. The damaged DNA sets off DNA repair mechanisms, which activate apoptosis when repair proves impossible. The trans-isomer **does not** have this pharmacological effect.



**Anticancer activity of the Cis-Platin is based its cross-linking with DNA and inhibiting to copy the DNA by enzymes**

# How does one design inorganic drugs?




**It all depends on coordination chemistry principles & the interaction of the compound with biomolecules or cells or tissue or organs**

# Bioinorganic Chemistry

A study of the **structural and functional aspects of metal bound species**, such as proteins and nucleic acids in **biological systems**

- metal ion transport and storage
- metallohydrolase enzymes (peptidases)
- metal-containing electron transfer proteins
- oxygen transport and activation proteins
- oxidation and hydroxylation (oxidases)
- hydrogenases and transferases
- enzymes involved in nitrogen metabolism pathways

# Chemical elements essential for various forms of life: Categorization

(i) Bulk elements: C, H, N, O, P, S

(ii) Macrominerals and ions: Na, K, Mg, Ca, Cl, $PO_4^{3-}$, $SO_4^{2-}$

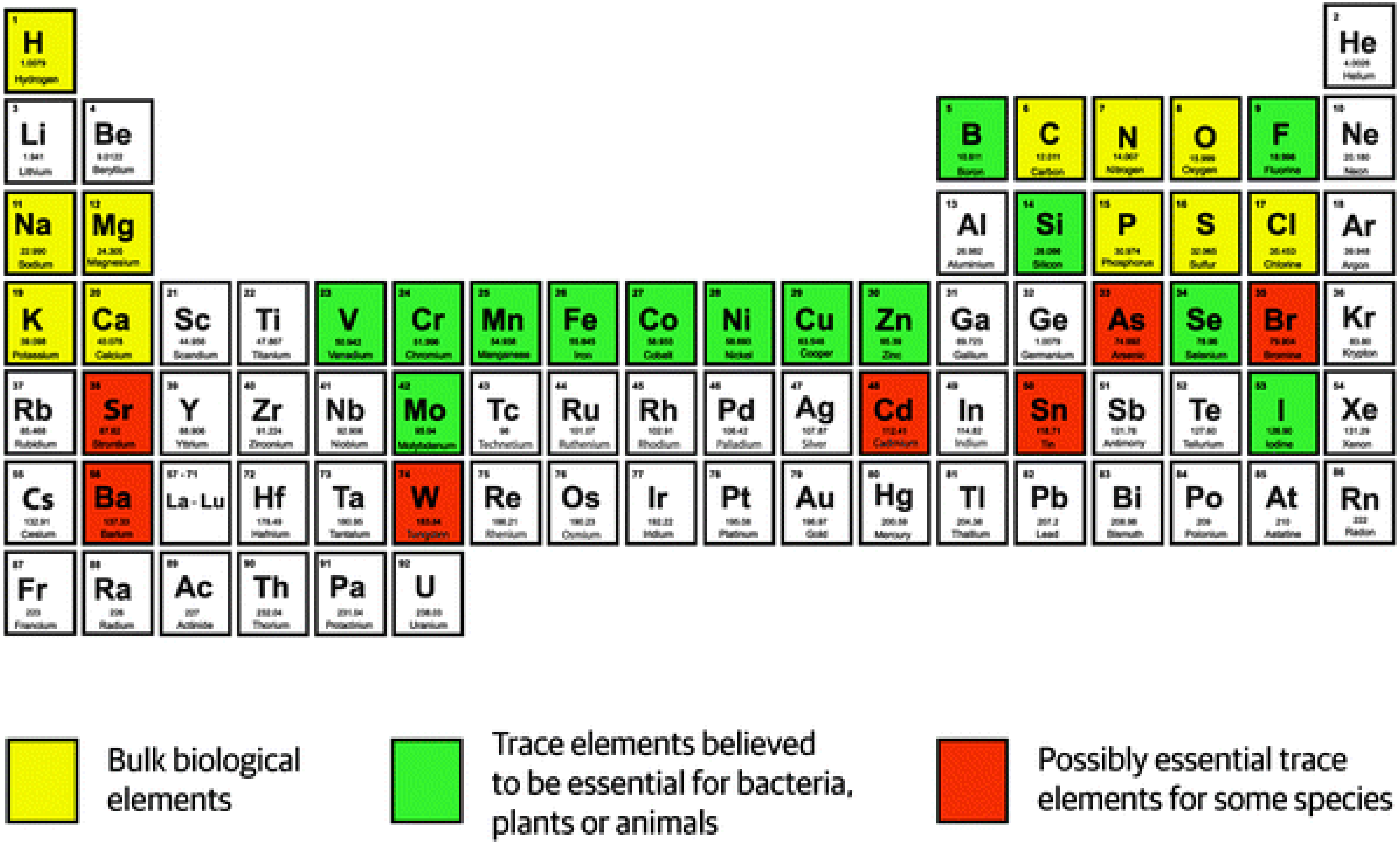
(iii) Trace elements: Fe, Zn, Cu

(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

# Periodic Table Relevant to Life



# Criteria for ESSENTIALITY of Elements in Life

- Should be present in the **tissues** of different animals at comparable concentrations

- A specific **biochemical function** (structural or catalytic or regulatory type) should be associated with that element

- Physiological **deficiency** appears when the element is removed from a purified diet

- The deficiency can be relieved by the **addition** of that element

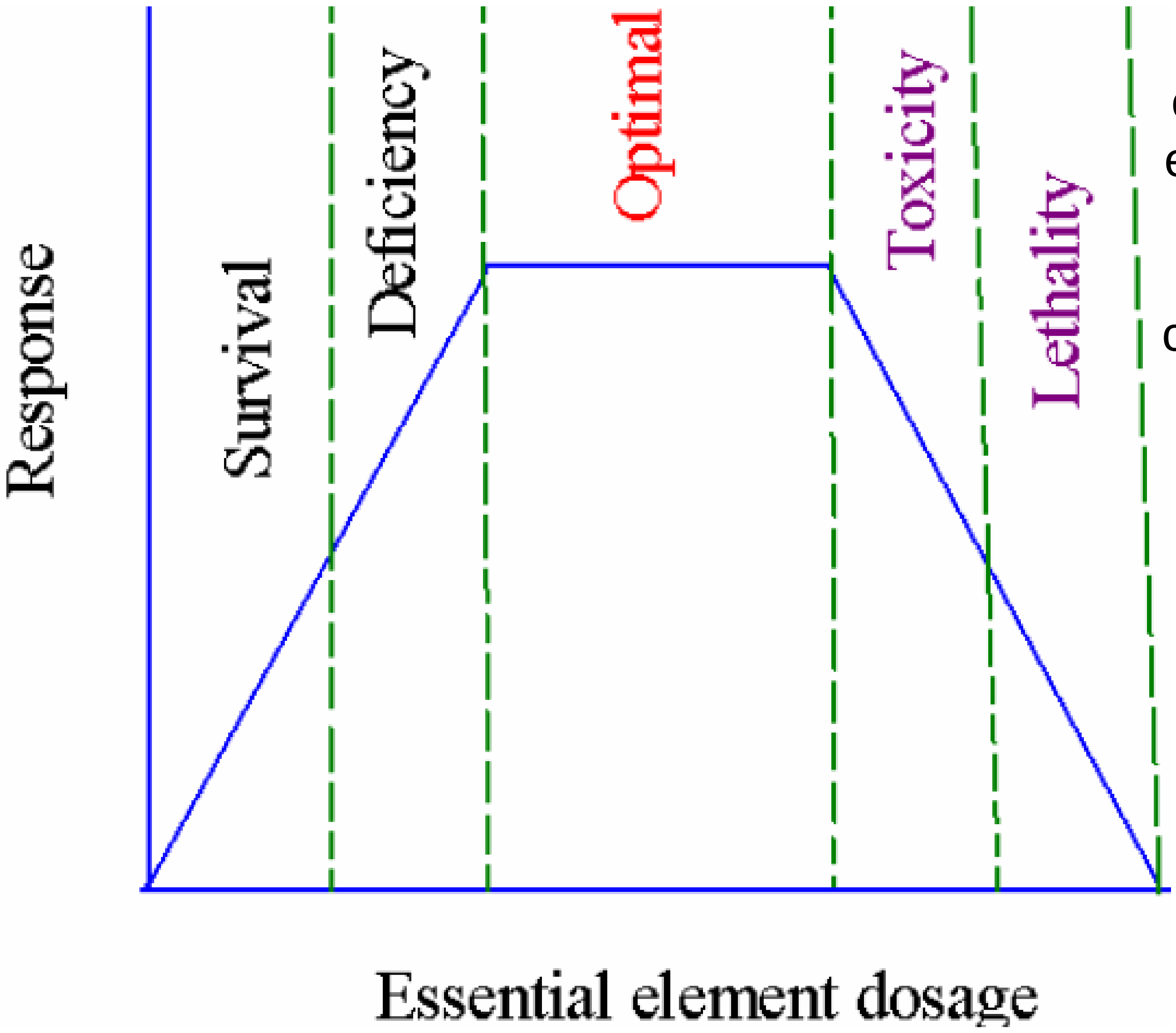
# How nature has chosen these elements?

# Criteria for the selection of elements

**Elemental abundance is not ONLY the determining factor**

- Solubility of the element
- Charge type/Oxidation state
- Ionic Radius
- Ligating atoms
- Preferential coordination geometry
- Spin-pairing stabilization
- Kinetic reactivity and other controls
- Thermodynamic aspects
- Chemical reactivity

# Essential Element of life: Dose – Response Curve

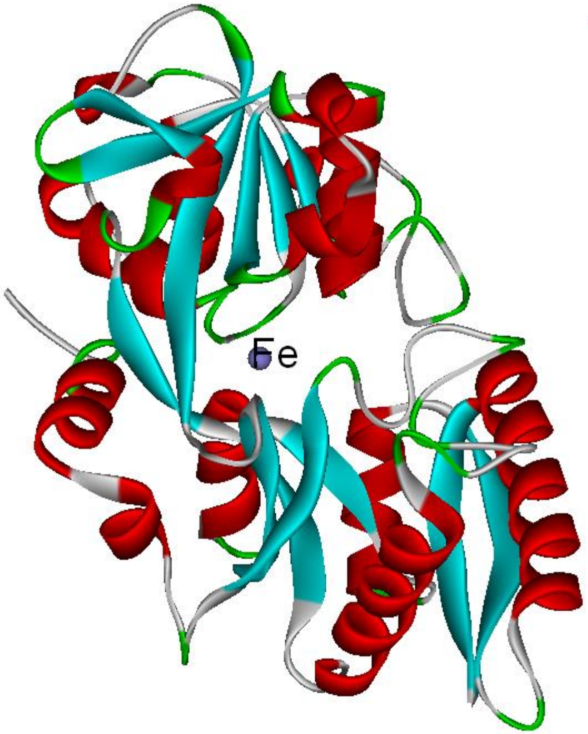


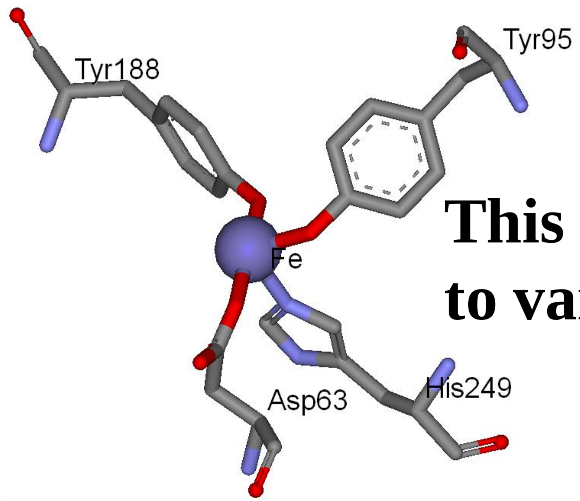

The Dose – Response curve is similar for all the essential elements of life.

Only the dosage will change from one element to the other.

# Structure of human serum transferrin –

## Coordination about Fe



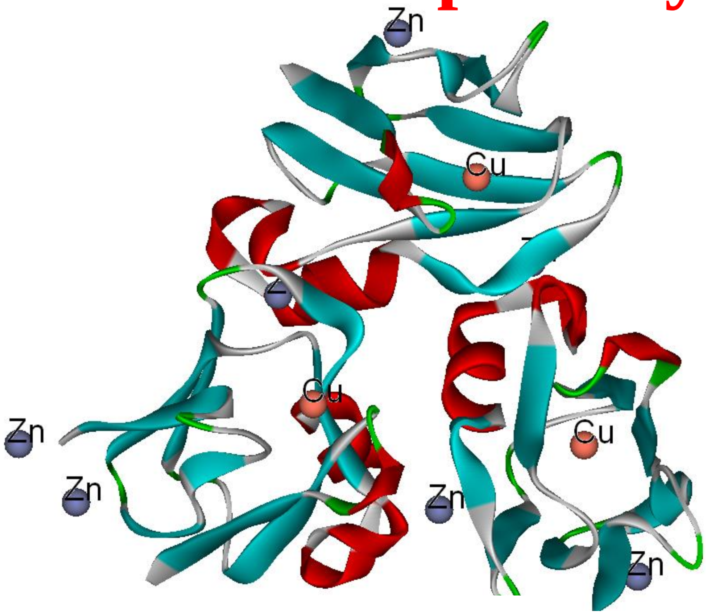

**This protein transports iron ions to various organs of the body.**

**Picks up iron from the storage protein, viz., ferritin, goes through the blood and delivers at the organ tissue.**

**During pick up and delivery iron is in +2; and during transport and storage it is in +3.**

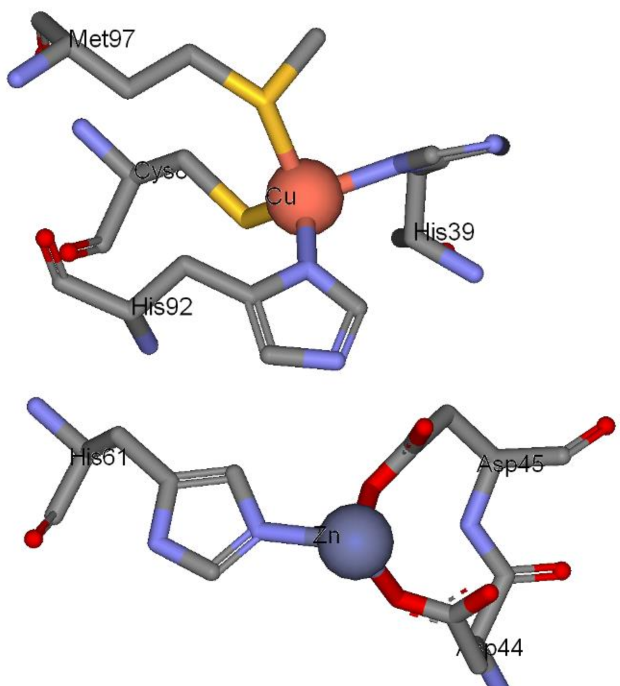
HUMAN SERUM TRANSFERRIN pdb code:1a8e

# Structure of plastocyanin – Coordination about Cu & Zn




This is an **electron transfer enzyme.**

This enzyme is able to function since **Cu** can undergo oxidation states of **+1** and **+2** easily and their inter-conversion through this protein is facile.



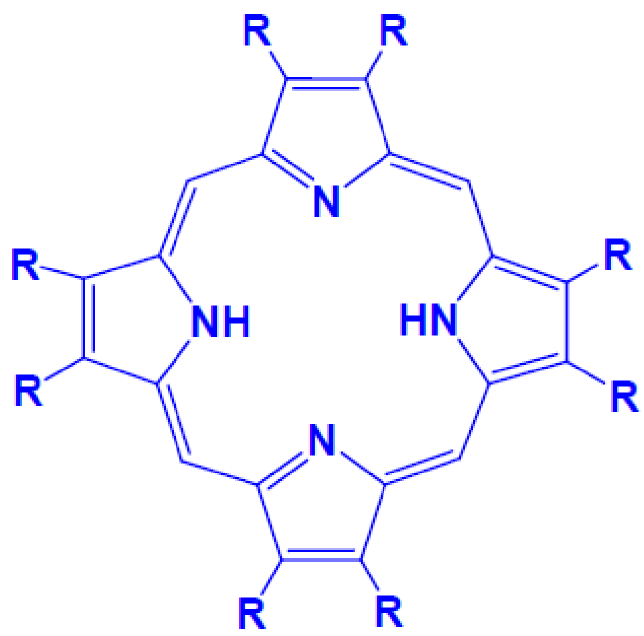

## What is $Zn^{2+}$ doing?

**In this enzyme, the $Zn^{2+}$ stabilizes the protein structure that is required for the function or catalysis.**

PLASTOCYANIN-pdb code:2w88

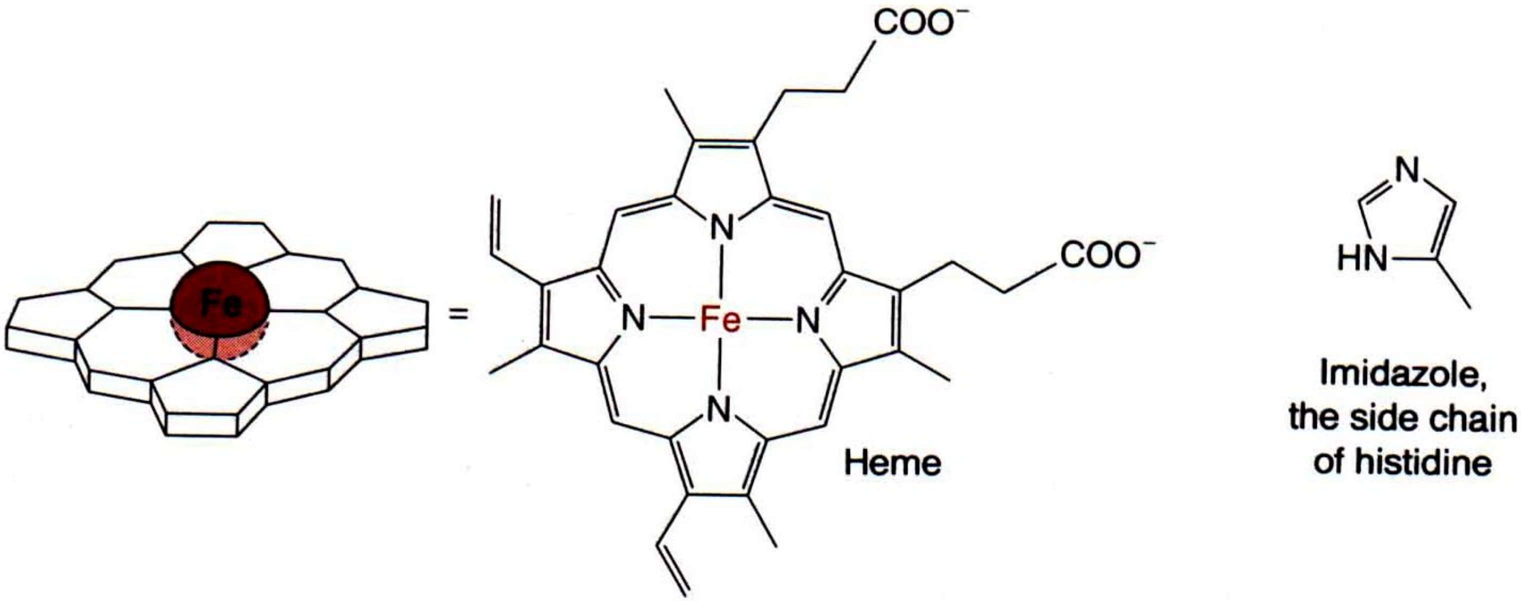
# *Porphyrins*

**Porphyrins are tetrapyrrole macrocycles with conjugated double bonds and various groups attached to the perimeter**



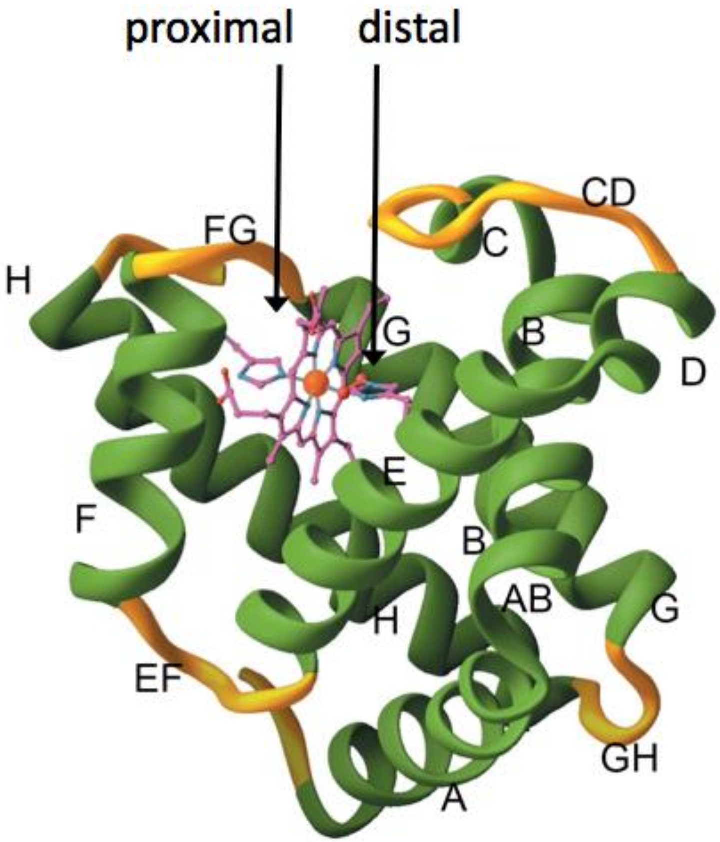

**variation of substituents facilitates the tuning of electron-donating and electron-withdrawing ability of the ligand**

# The Heme Group; the Defining E xample of a Bioinorganic Chip

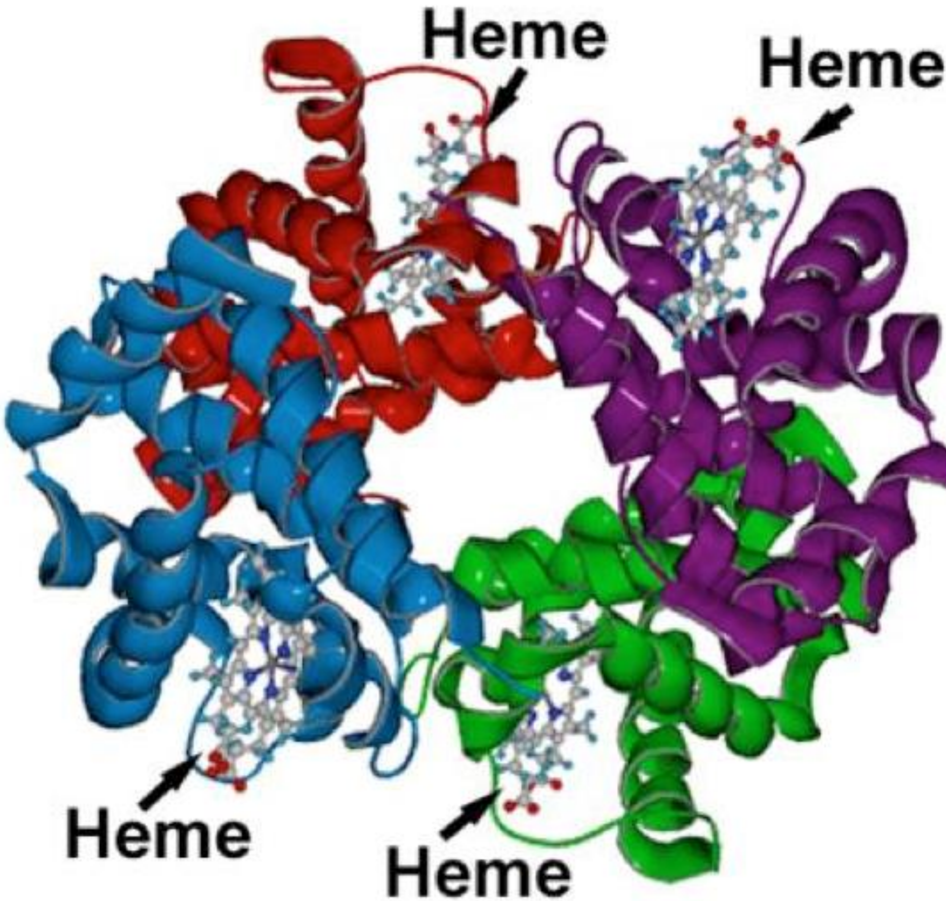



**Peripheral carboxylates and axial ligands matter!**

# Structures of Mb and Hb




V&V p 244 Fig. 8-39b Ribbon Structure of Myoglobin




www.animalscience.ucdavis.edu

**Oxygenated Myoglobin**

**monomeric**

**Hemoglobin**

**Tetrameric**

**Myoglobin – $O_2$ storage; Hemoglobin – $O_2$ transport**

| **Property** | **Hemoglobin** | **Myoglobin** | **H** |
|---|---|---|---|
| metal | Fe | Fe | |
| $M^{n+}$ ox state for deoxy | II | II | |
| Metal:$O_2$ | Fe:$O_2$ | Fe:$O_2$ | |
| Color deoxy | red-purple | red-purple | |
| Color oxy | red | red | |
| Metal coor motif | porphyrin | porphyrin | |
| Molecular weight (Da) | 65,000 | 16,700 | |
| # of subunits | 4 | 1 | |

Hemoglobin is tetramer of the Myoglobin structure. But functionally differs and acts as a transport protein due to **COOPERATIVITY**

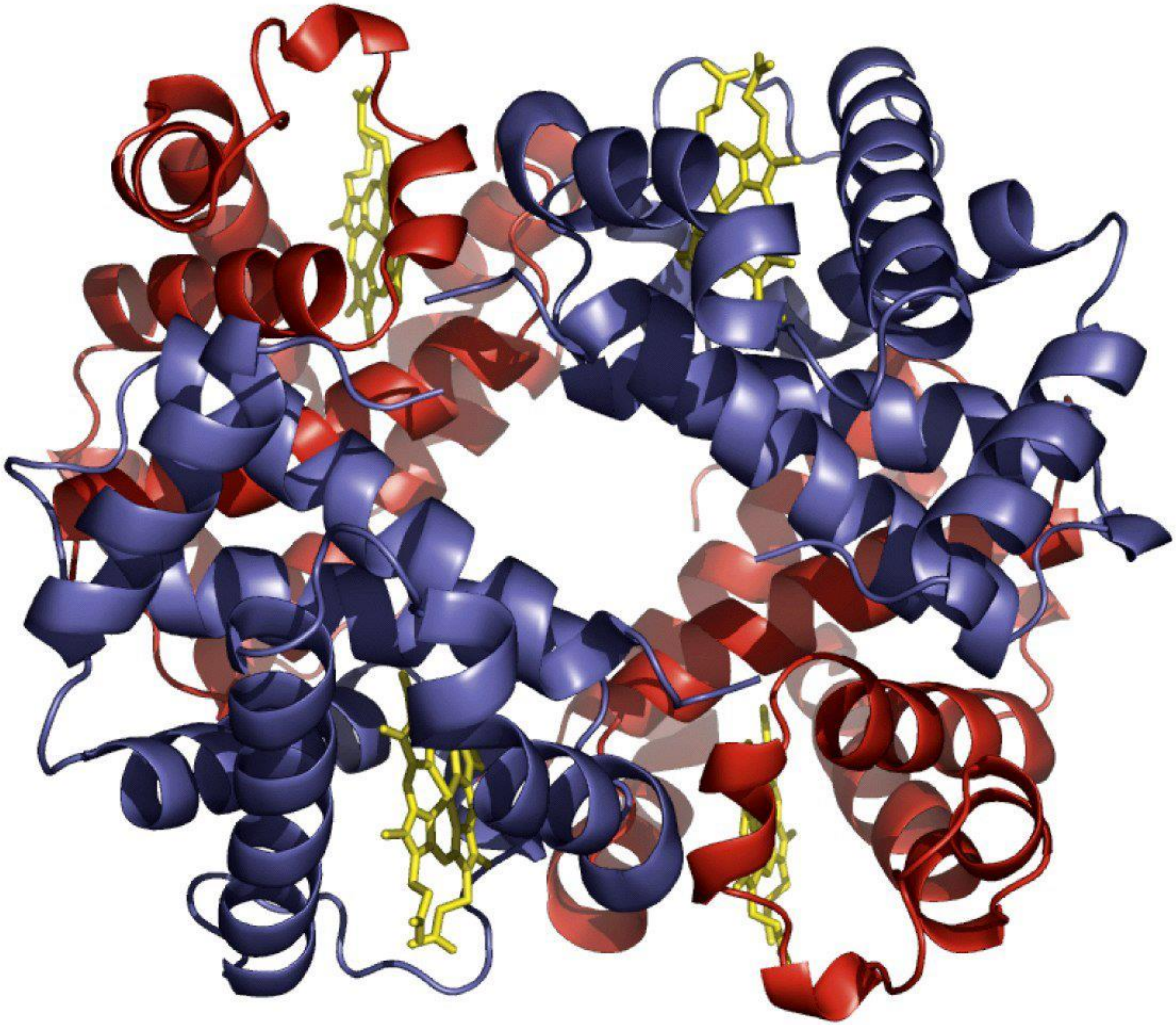


**Figure 26-16**
***Shriver & Atkins Inorganic Chemistry, Fourth Edition***

# Biochemistry of myoglobin and hemoglobin

## Oxygenation kinetics

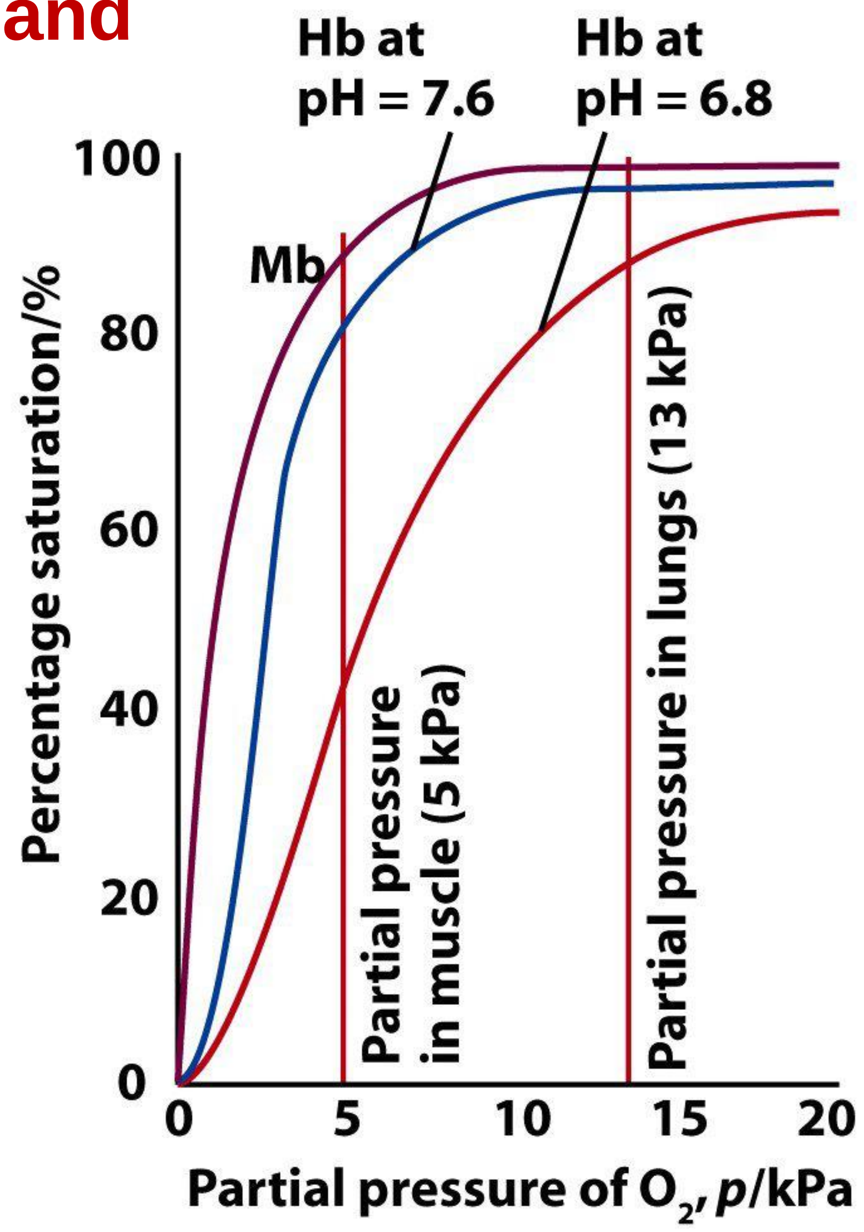



Figure 26-17
*Shriver & Atkins Inorganic Chemistry, Fourth Edition*

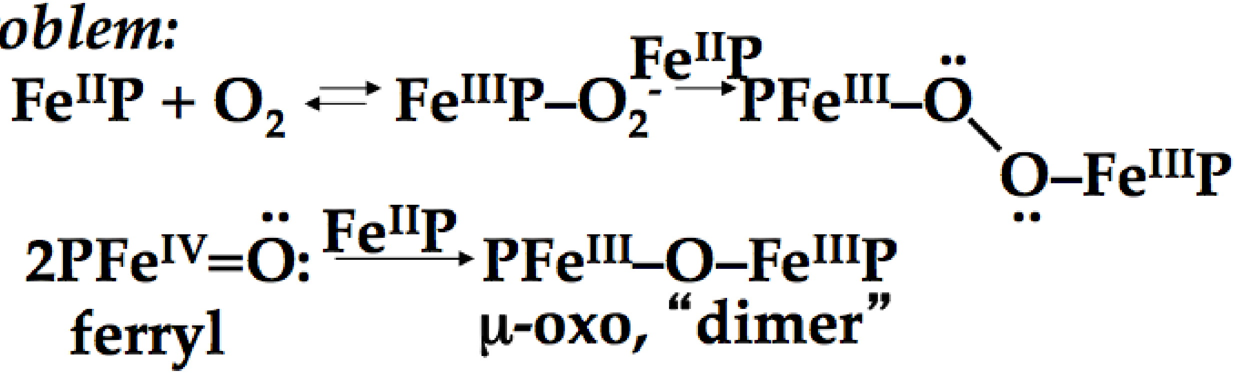
# Role of the protein in case of hemoglobin

## Binding pocket of $O_2$ in protein:

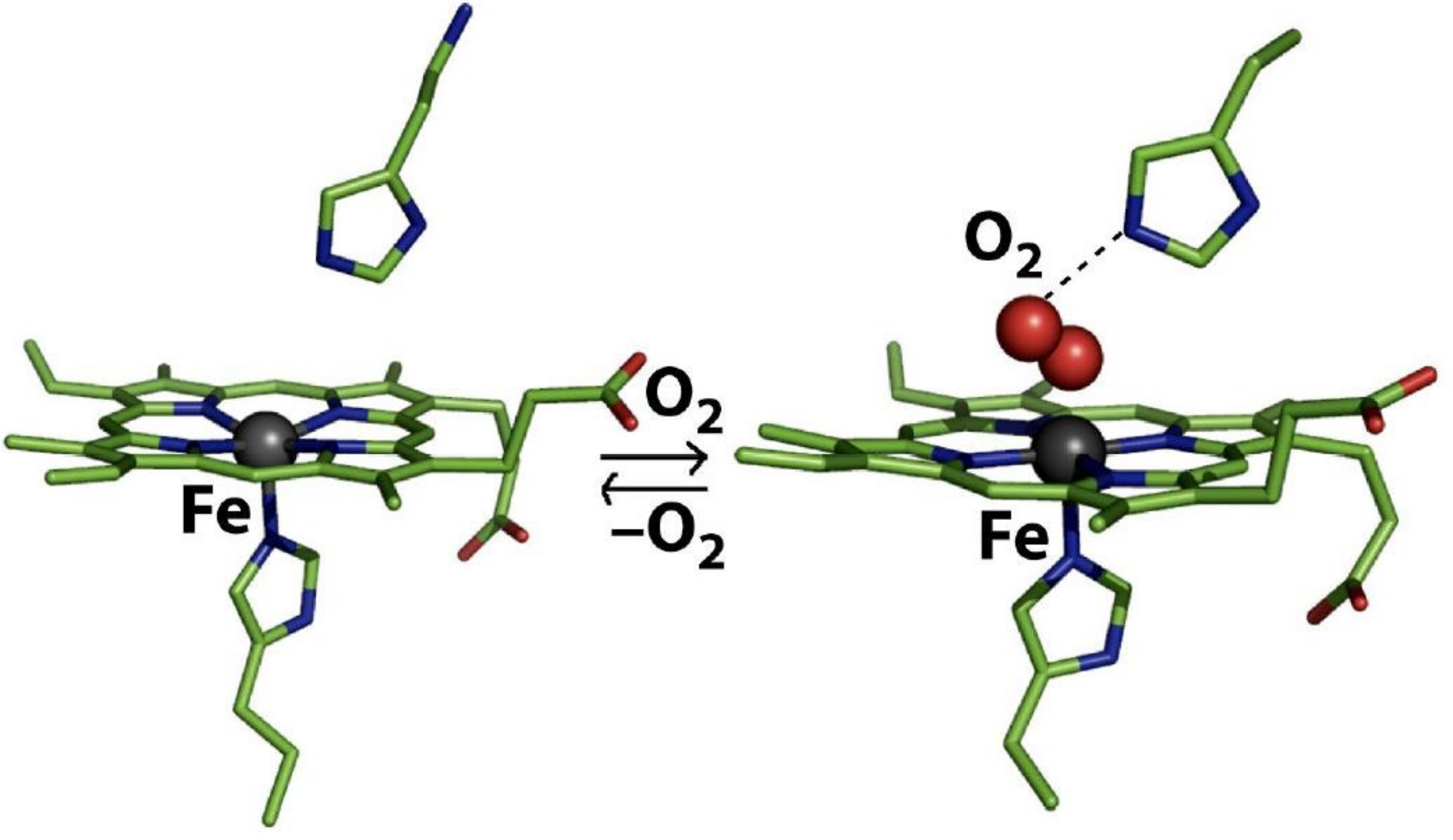
- Prevent 2-e reduction
- Prevent μ-oxo dimer formation
- Stabilizing PFe(II)…$O_2$ complex
- Bent $O_2$ geometry
- Binding of CO vs. $O_2$

## Thermodynamics vs. Kinetics -- Role of the protein

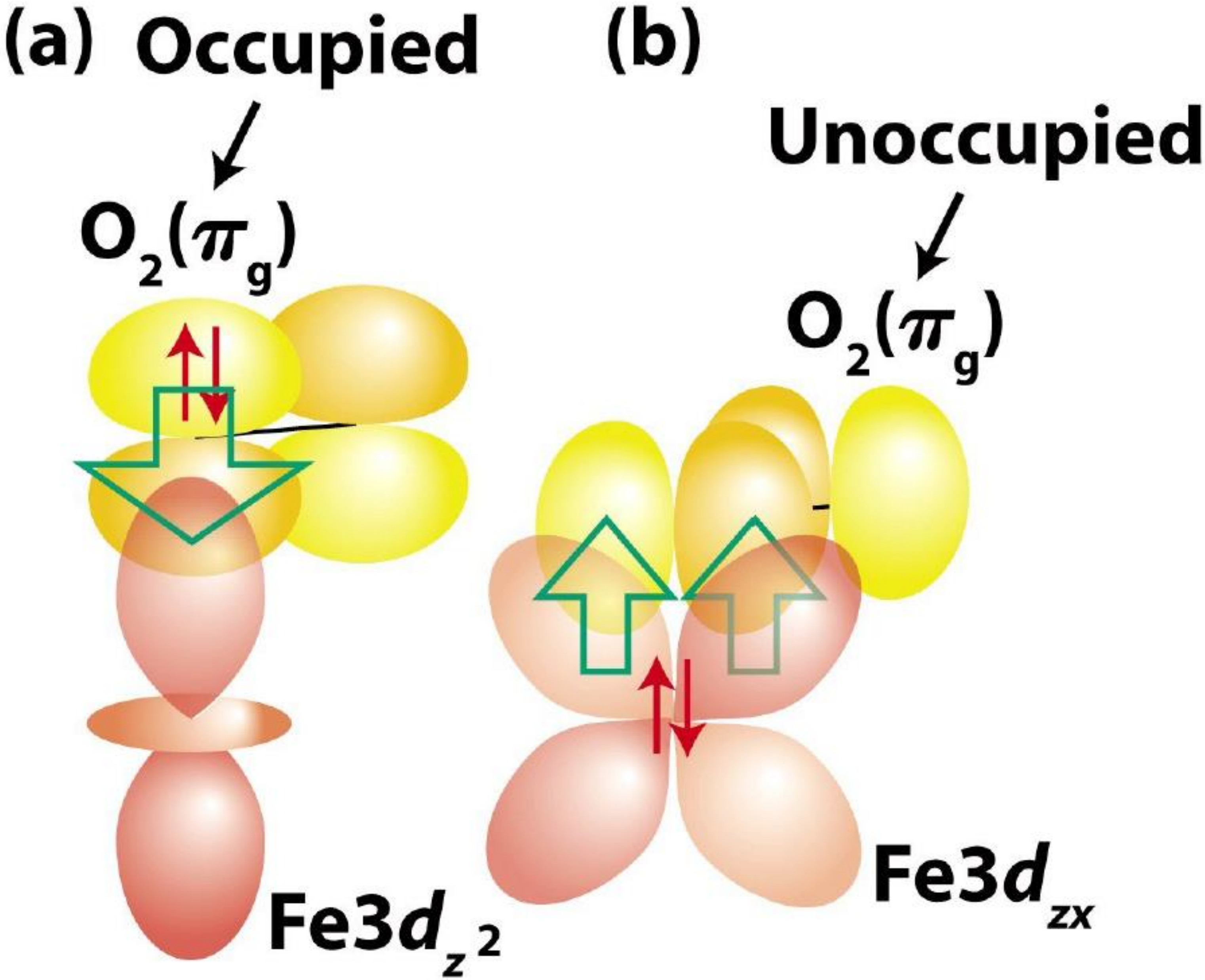
*The problem:*



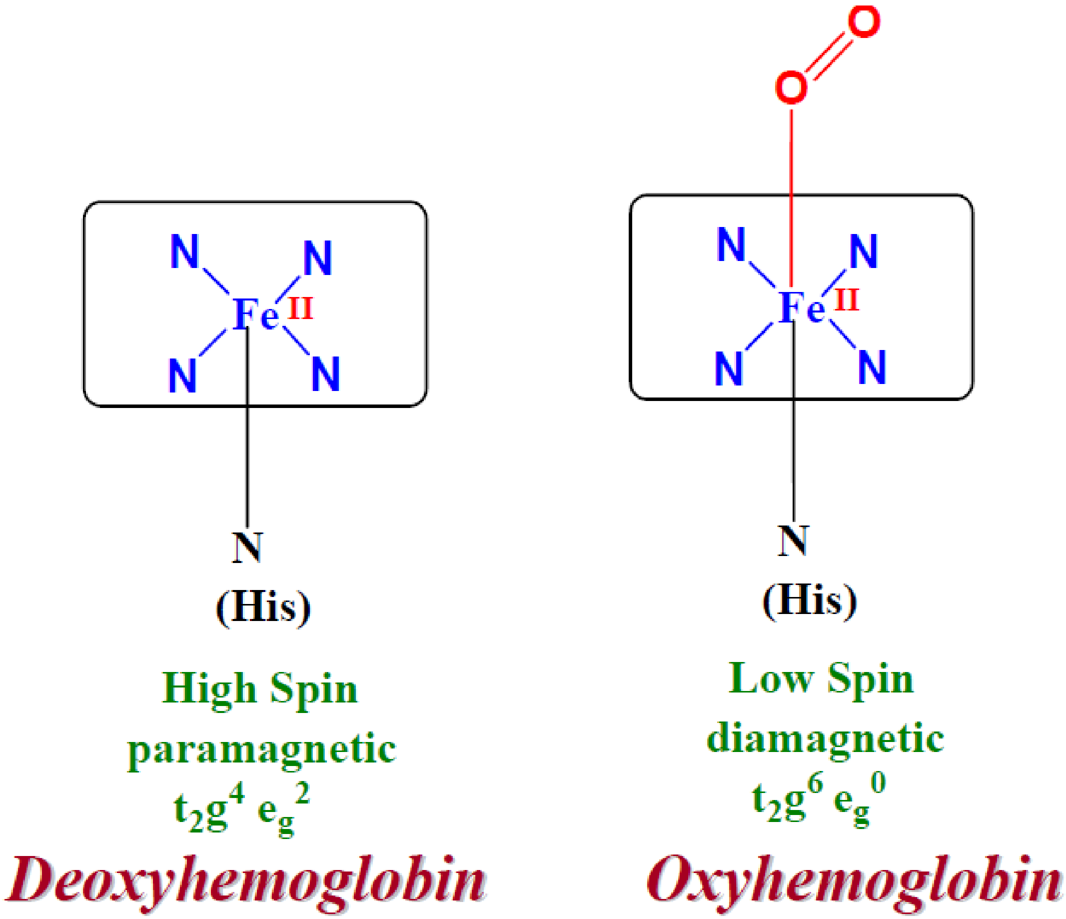
# Selectivity of $O_2$ over CO by Hemoglobin



# Nature of $O_2$ bonding to iron center in Hemoglobin



# Oxy- and de-oxy forms of Hemoglobin




*Deoxyhemoglobin* is the form of hemoglobin without the bound oxygen. The oxyhemoglobin has significantly lower absorption (660 nm) than deoxyhemoglobin (940 nm). This difference is used for measurement of the amount of oxygen in patient's blood by pulse oximeter.

# What happens when $O_2$ binds to Hemoglobin

The size of $Fe^{2+}$ increase by 28% on going from

Low spin (oxyhemoglobin) (0.61 Å)

↓ to

High spin (Deoxyhemoglobin) (0.78 Å)

The $Fe^{2+}$ in deoxyhemoglobin is too large to fit in the ring and is situated (0.7-0.8)A° above the ring

Thus, presence of $O_2$ changes the electronic arrangement of $Fe^{2+}$ and distorts the shape of the complex

The globular protein prevents the irreversible oxidation of Fe(II) to Fe(III)

# Cooperativity in $O_2$ binding and release in Hemoglobin

When $O_2$ binds to one sub-unit → $Fe^{2+}$ contracts, moves into plane of porphyrin ring

↓

moves the histidine attached to it → triggers conformational changes in the globin chain

↓

translated through H-bond network → Enhances the ability of other three units to bind $O_2$

↓

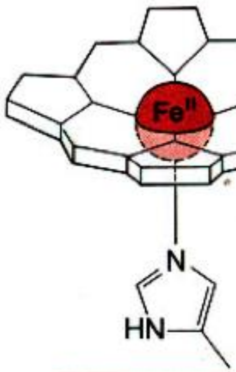
***This phenomenon is called cooperative effect***

*In a similar way when the blood reaches the muscle, only one $O_2$ is released, the others are released even more easily due to the cooperative effect in reverse*

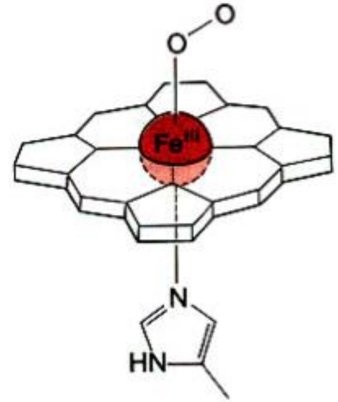
**Not for exam**

**Slides 30-44**

# Respiration - Three $O_2$ Carriers in Biology

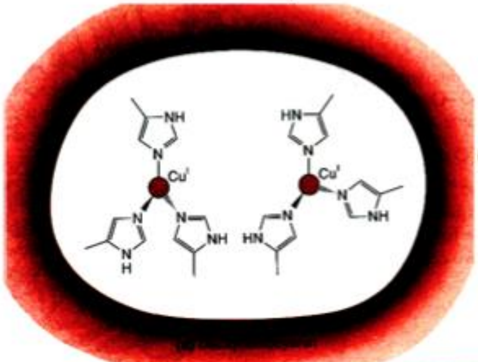



deoxyHb, Mb

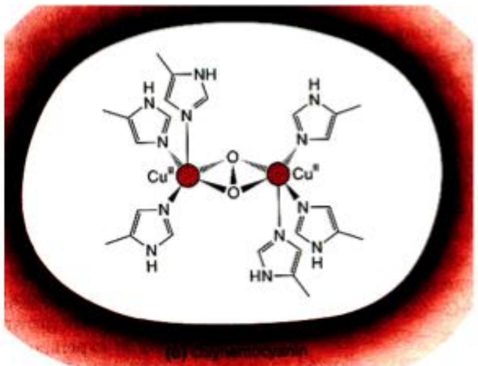



oxyHb, Mb

Red



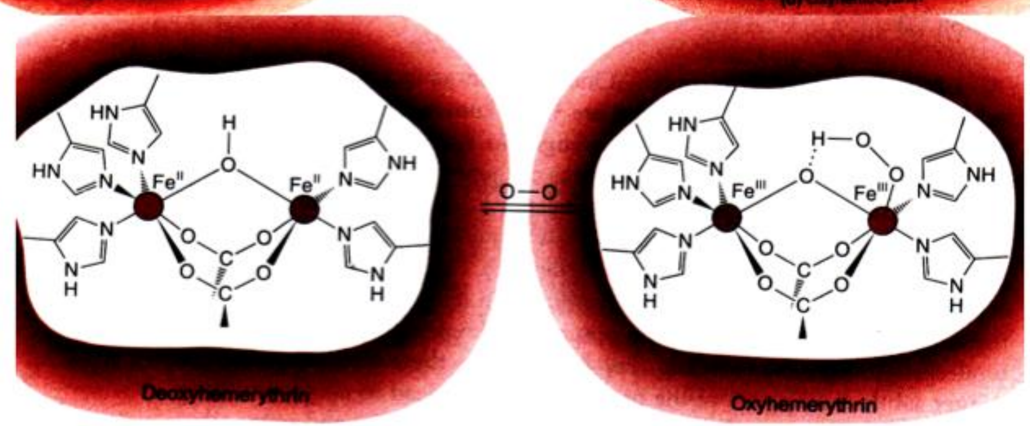
deoxyHc



oxyHc

Blue

deoxyHr



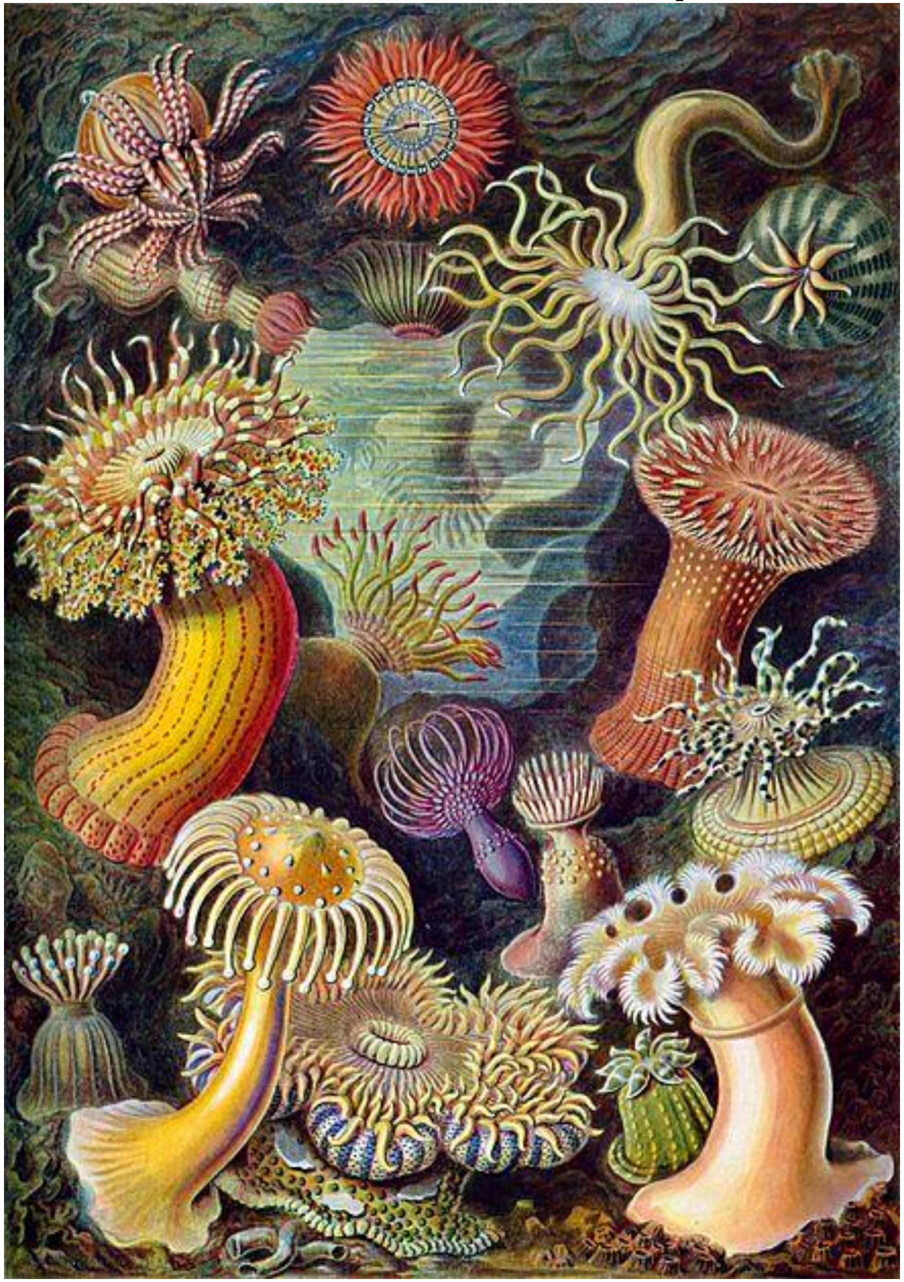

oxyHr

violet-pink

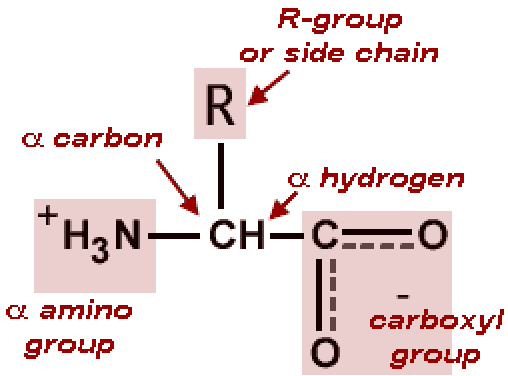
# Mollusca and Arthropoda

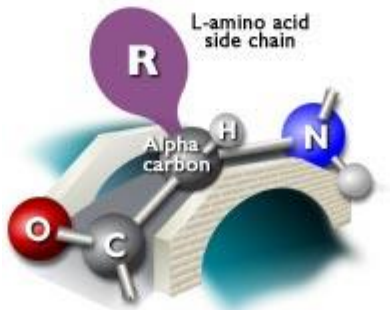
**Hemocyanin, Hc**

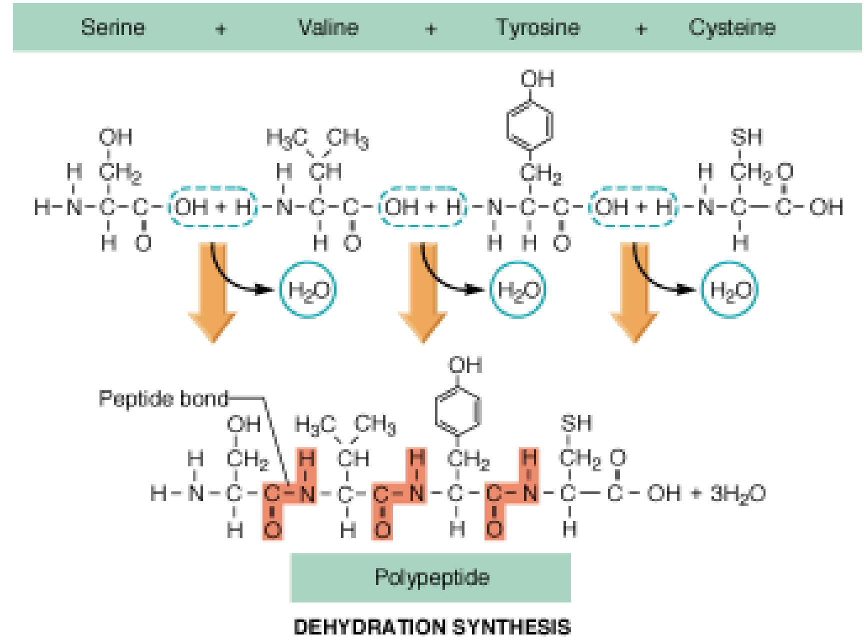
# marine invertebrate (Hemerythin, Hr)

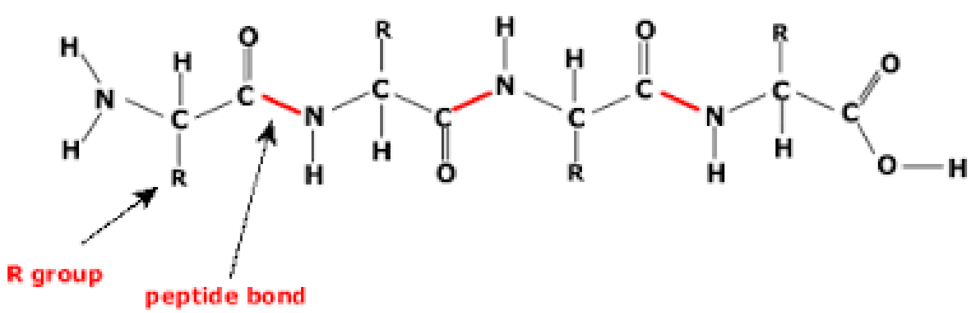


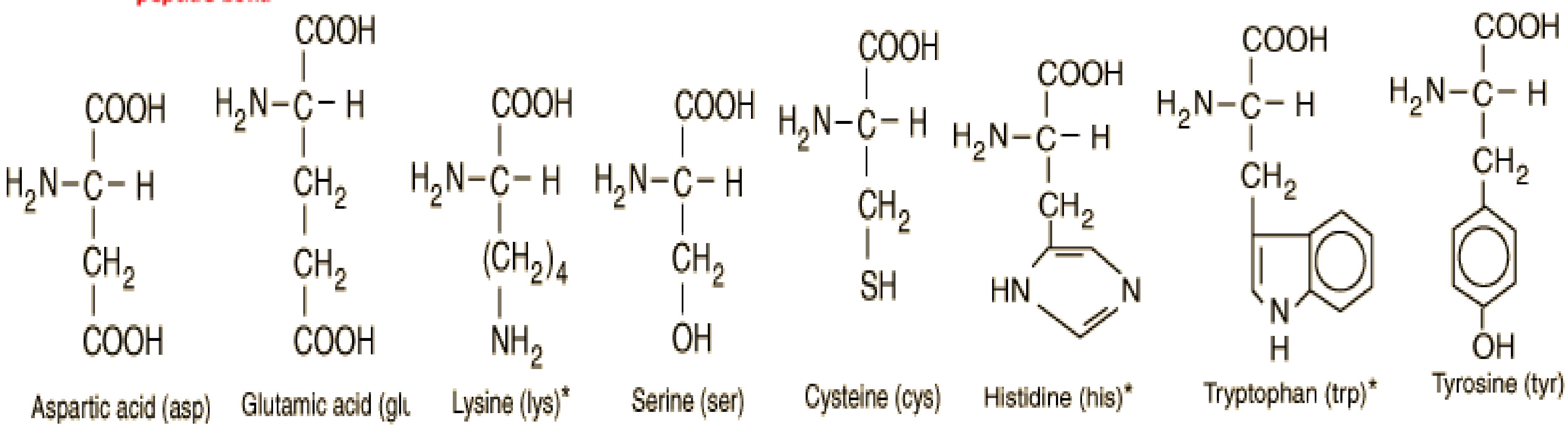
# Amino acids, peptides & proteins



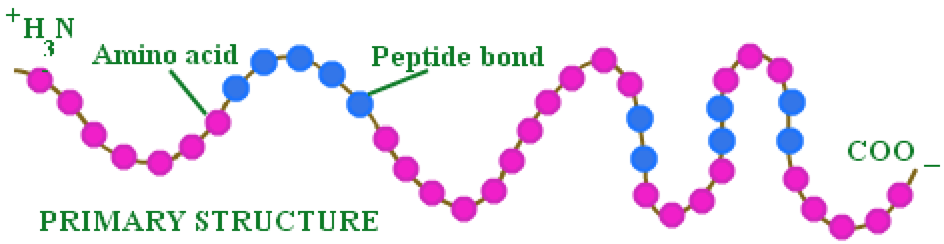



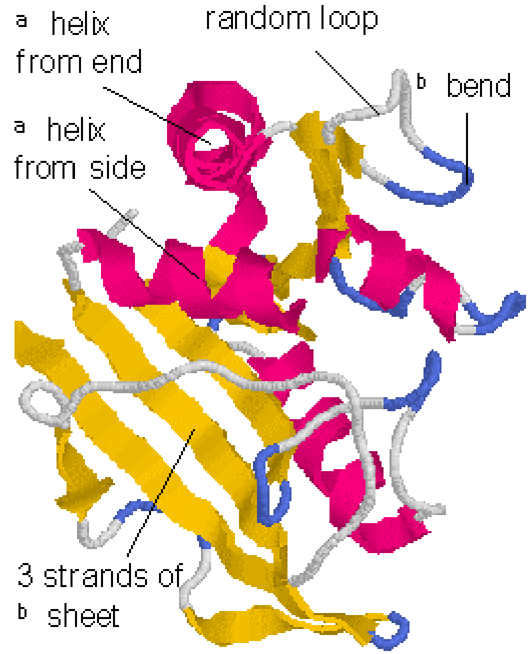



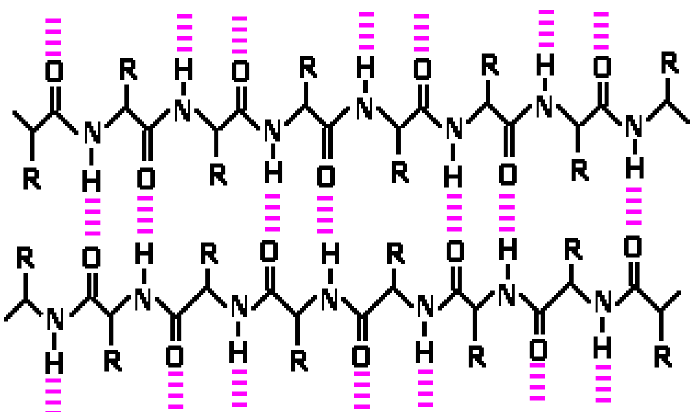



# Protein → Metalloproteins → Metalloenzymes



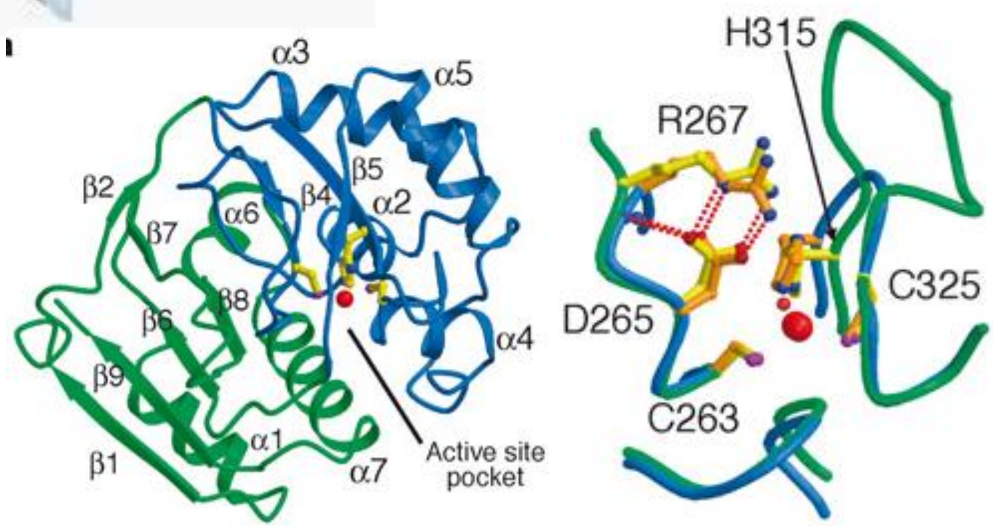




skeletal formula showing hydrogen bonding holding together polypeptide chains in beta-sheets of protein

(c) doc b



## *Active Site and Enzyme-Substrate (ES) Complex*

**The active site of an enzyme is the region that binds the substrate and contributes the amino acid residues that directly participates in the (reactivity) *making and breaking of chemical bonds***

## Generalizations

**1) Enzymes are usually very large compared to the substrate**

**Only a small portion is involved in ES complex**

**Rest is involved in the reaction control and maintaining the structure & conformation required**

**2) The substrate is bound by relatively weak forces**

**$\Delta G_{E\text{-}S}$ complex = (12 to 36) KJ mol$^{-1}$**

**(strength of a covalent bond is upto ~ 450 KJ mol$^{-1}$)**

**3) Active sites are mostly designed to exclude $H_2O$. Few water ligation are possible and are useful.**

**Surrounded with non-polar amino acids to create a hydrophobic environment**
**Essential for substrate binding and product formation (Catalysis) at least in some cases**

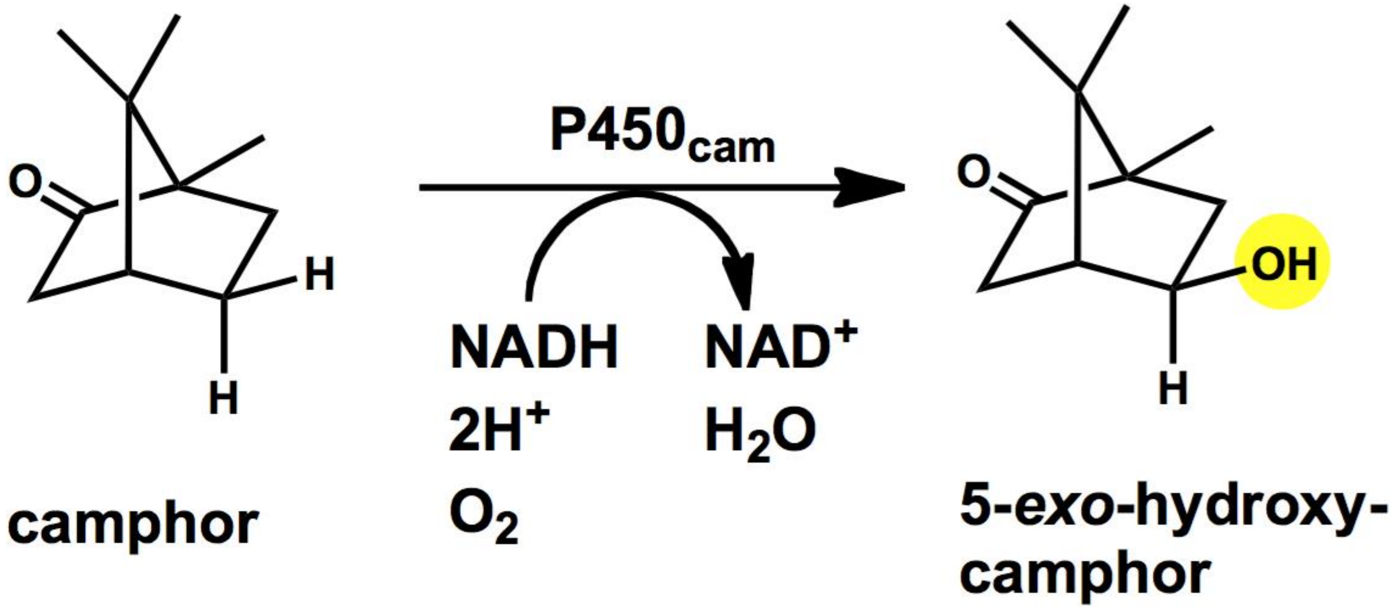
## *Specificity*

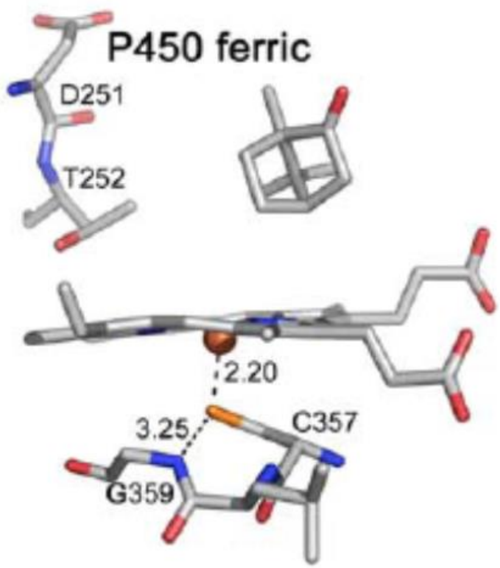
**Active site provides specificity for its particular substrate**

**Substrate has a matching shape to fit into the active site (Lock and Key mechanism)**

**Formation of Enzyme-Substrate Complex and its transformations are thus crucial to the product formation**

# Cytochrome P-450 in oxidizing camphor specifically at C-5



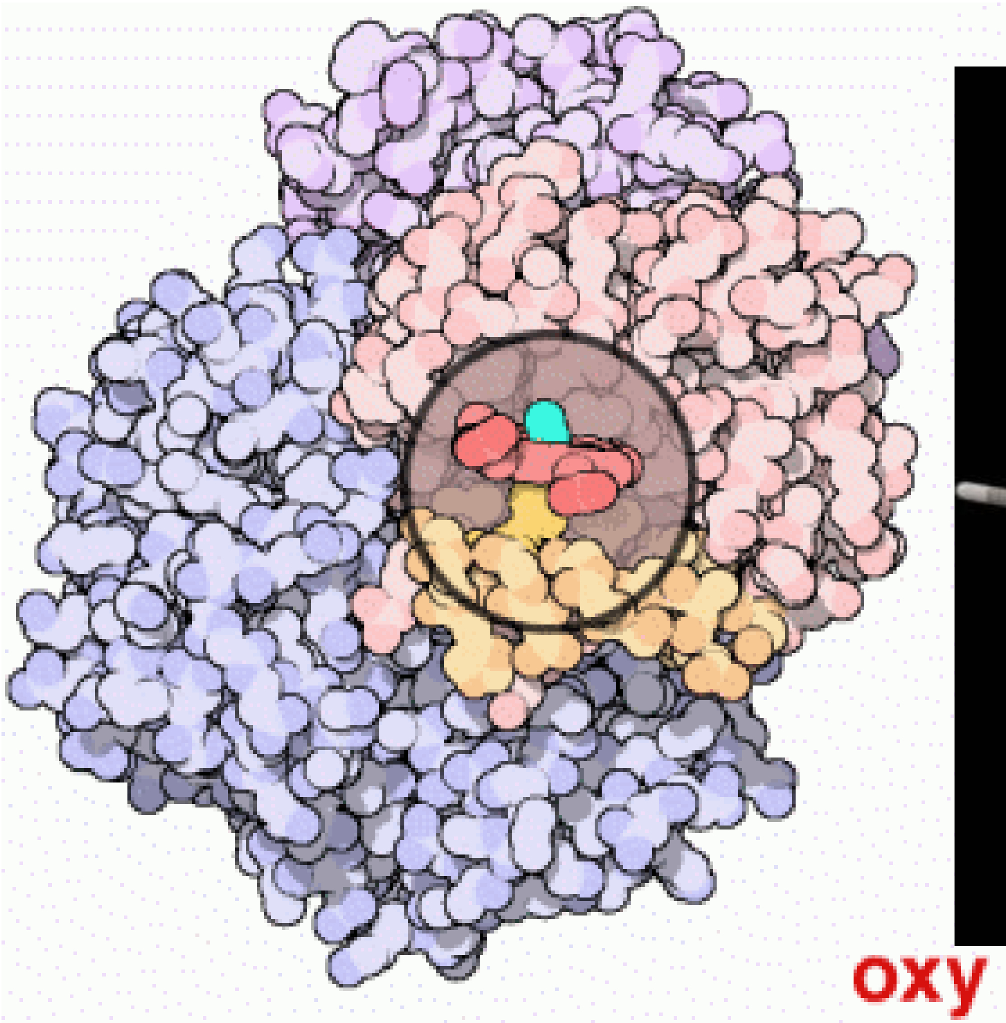



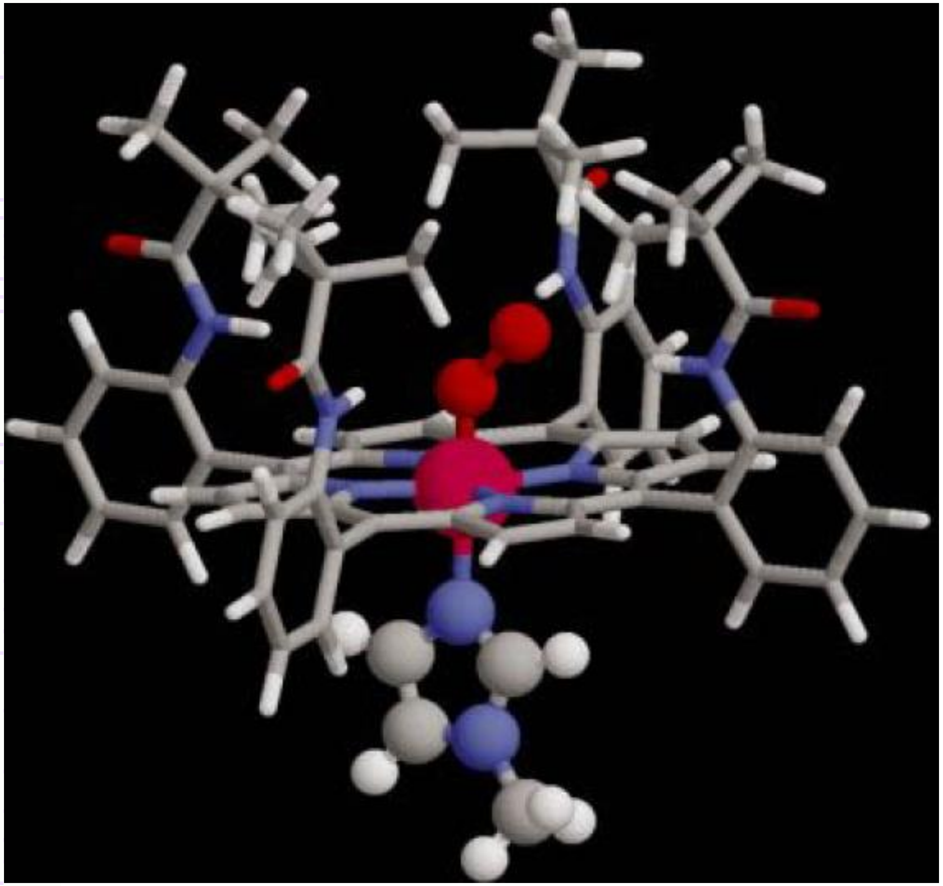

Structure of substrate-bound $P450_{cam}$

Note location of camphor substrate & distal Thr-252, Asp-251

Hersleth *et. al. J. Inorg. Biochem.* **2006**, *100*, 460-476.

# Protein burried oxy-from of hemoglobin vs. synthetic picket fence porphyrin: A comparison

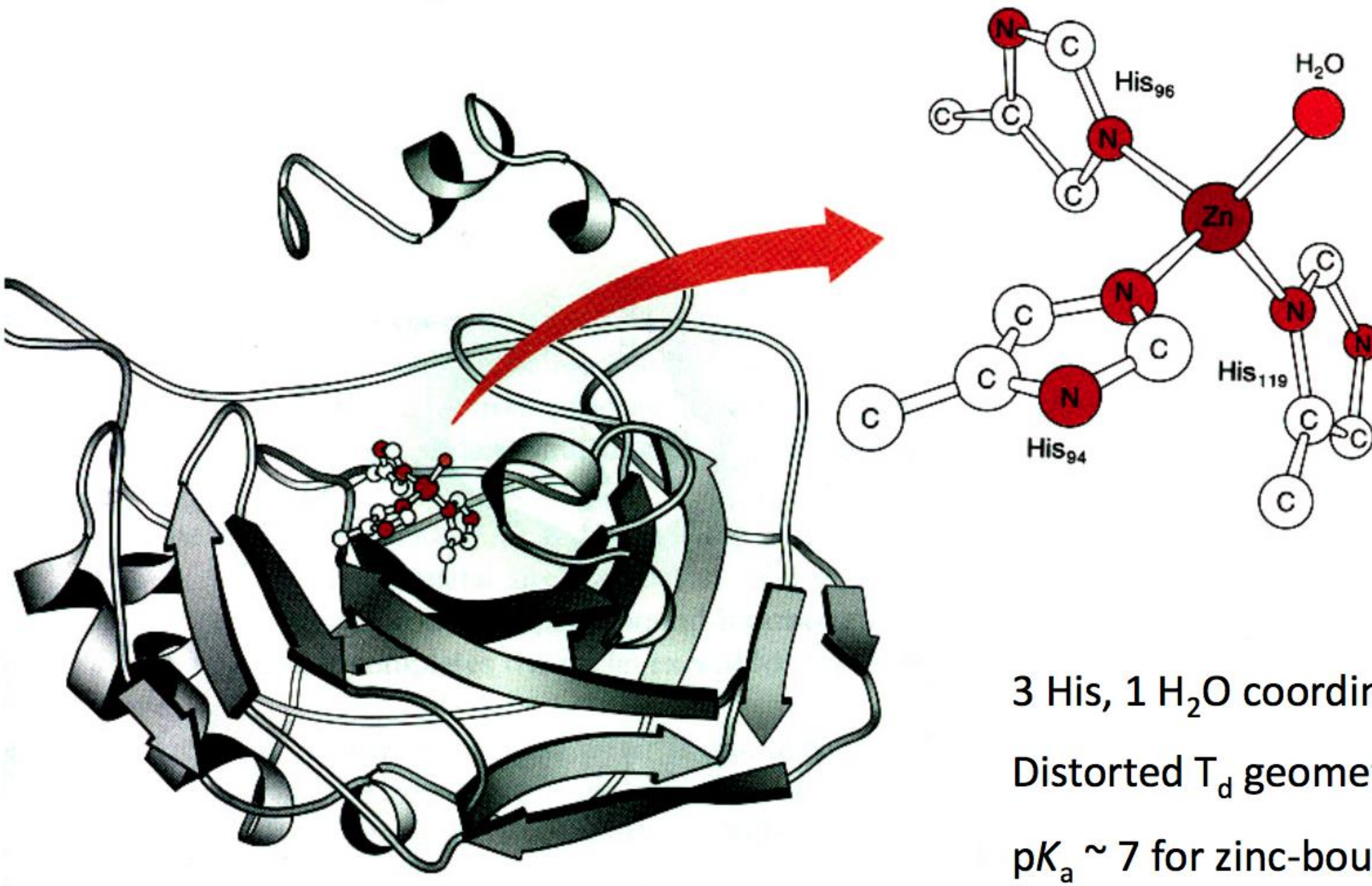


# 1. Carbonic Anhydrase: Mononuclear Zinc Lyase

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$$

Rates: no enzyme, $10^{-2}\ s^{-1}$; enzyme, $10^{6}\ s^{-1}$



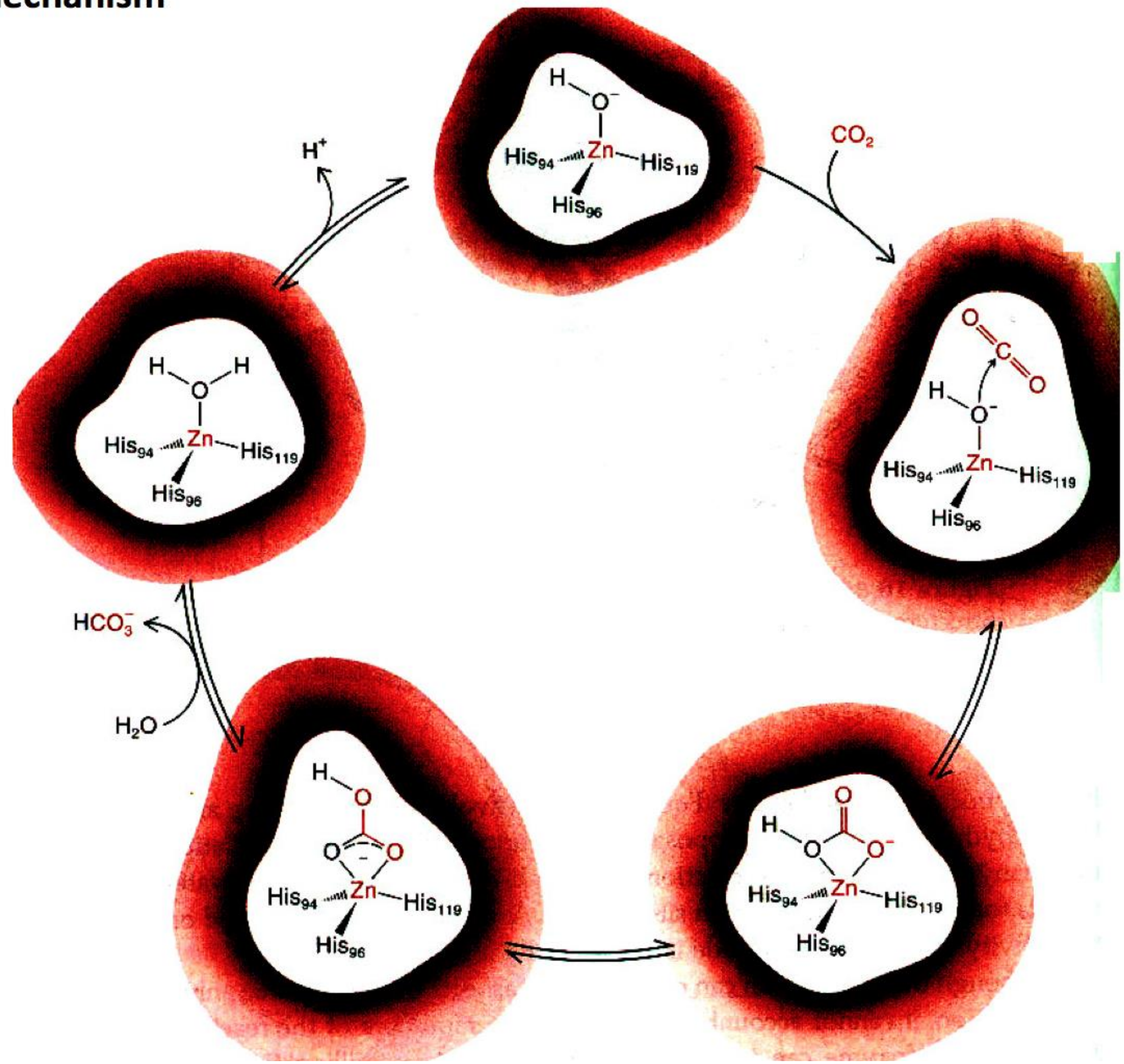

3 His, 1 $H_2O$ coordinate Zn(II)

Distorted $T_d$ geometry

p$K_a$ ~ 7 for zinc-bound $H_2O$

## 1. Carbonic Anhydrase: Mononuclear Zinc Lyase

**Proposed mechanism**



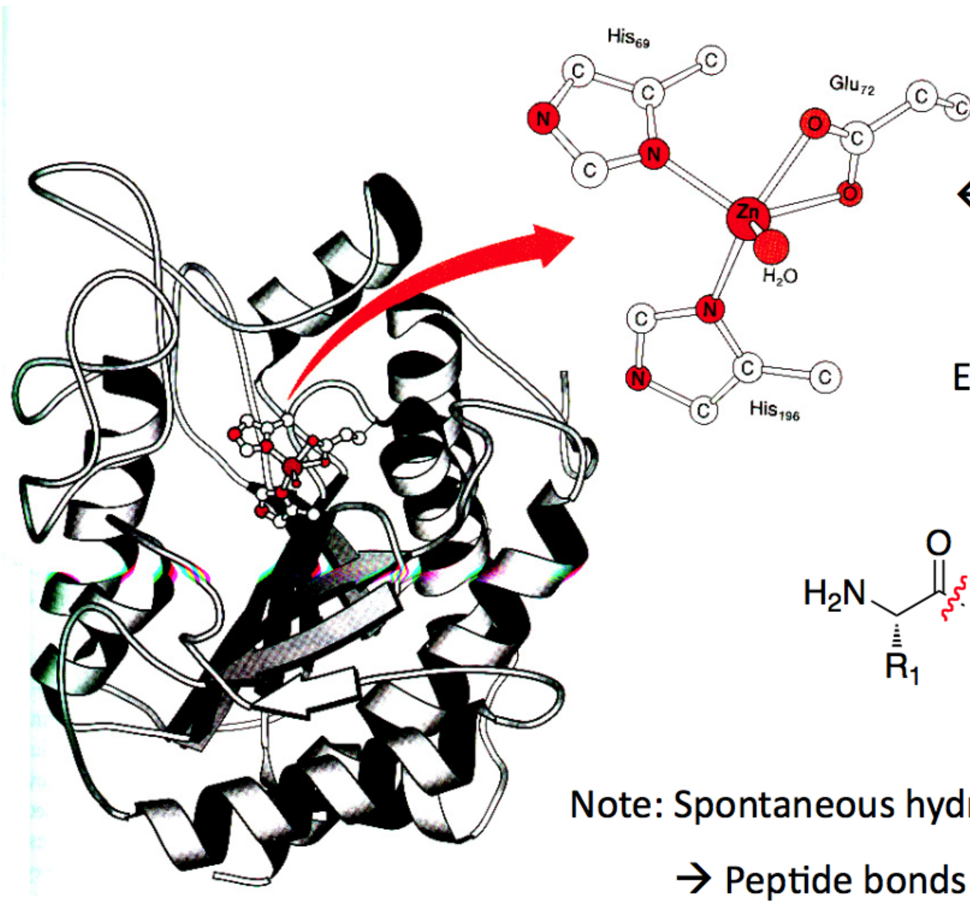

# Liver Alcohol Dehydrogenase: Mononuclear Zinc Oxidoreductase

# 3. Carboxypeptidase A: Mononuclear Zn(II) Hydrolase

Carboxypeptidase A is a **metalloprotease** that hydrolyzes C-terminal peptide bonds

35 kDa, **pentacoordinate zinc** in the absence of substrate or inhibitor

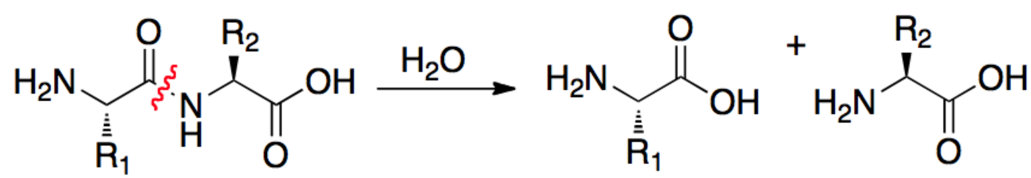
**Glu$_{77}$** undergoes **carboxylate shift** with substrate/inhibitor coordination → bi- to monodentate




← Bidentate Glu$_{77}$

Ex. Hydrolysis of 2-mer peptide

(aromatic & branched sidechains preferred)




Note: Spontaneous hydrolysis a pH 7 → $k = 3 \times 10^{-9}$ sec$^{-1}$

→ Peptide bonds are very stable under physiological conditions!

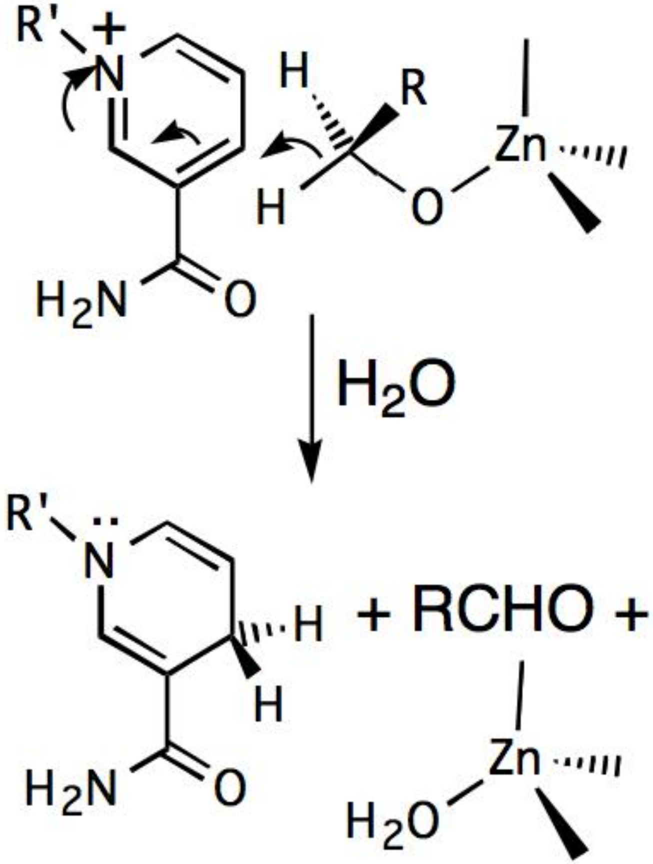
Protease action irreversible thermodynamically → activity controlled in cell

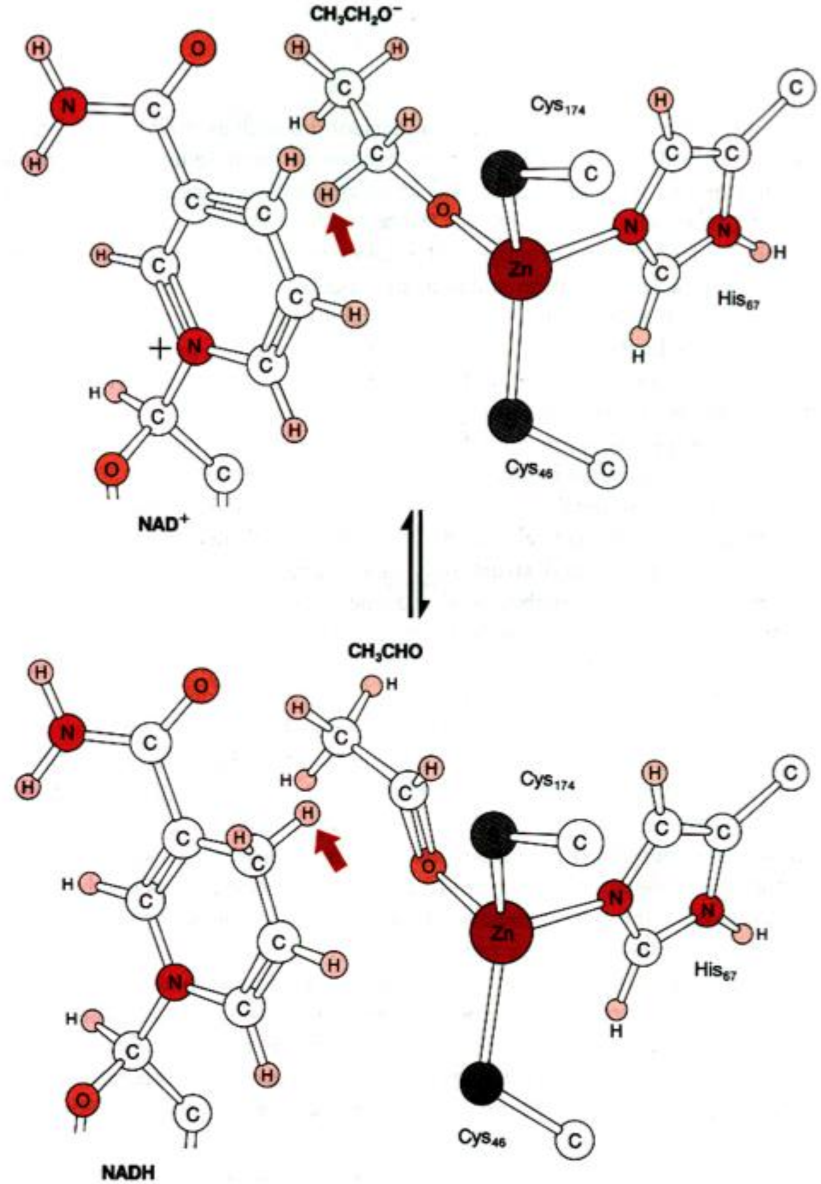
# 2. Liver Alcohol Dehydrogenase: Mononuclear Zinc Oxidoreductase

**Details of hydride transfer to $NAD^+$**

After $H^-$ transfer, aldehyde product & NADH dissociate

## Hydride Transfer Mechanism



Cisplatin was approved by the FDA for the treatment of genitourinary tumors in 1978.

Since then, Michigan State has collected over $160 million in royalties from cisplatin and a related drug, carboplatin, which was approved by the FDA in 1989 for the treatment of ovarian cancers.

"Testicular cancer went from a disease that normally killed about 80% of the patients, to one which is close to 95% curable. This is probably the most exciting development in the treatment of cancers that we have had in the past 20 years. It is now the treatment of first choice in ovarian, bladder, and osteogenic sarcoma [bone] cancers as well."

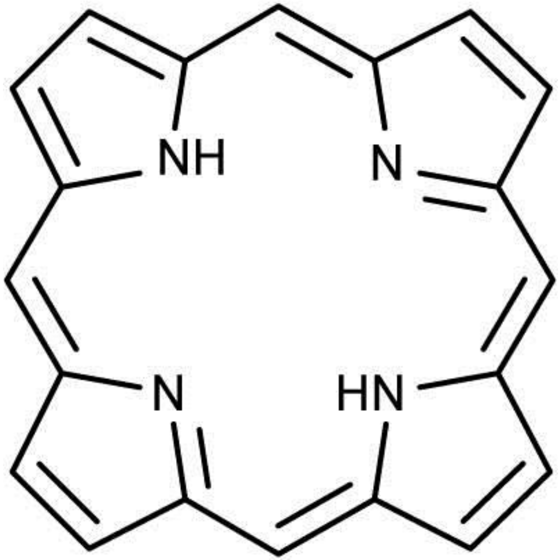
—Barnett Rosenberg, who led the research group that discovered cisplatin, commenting on the impact of cisplatin in cancer chemotherapy

# Tutorial

**Q1. What are storage and transport proteins? Draw the structure of porphin.**

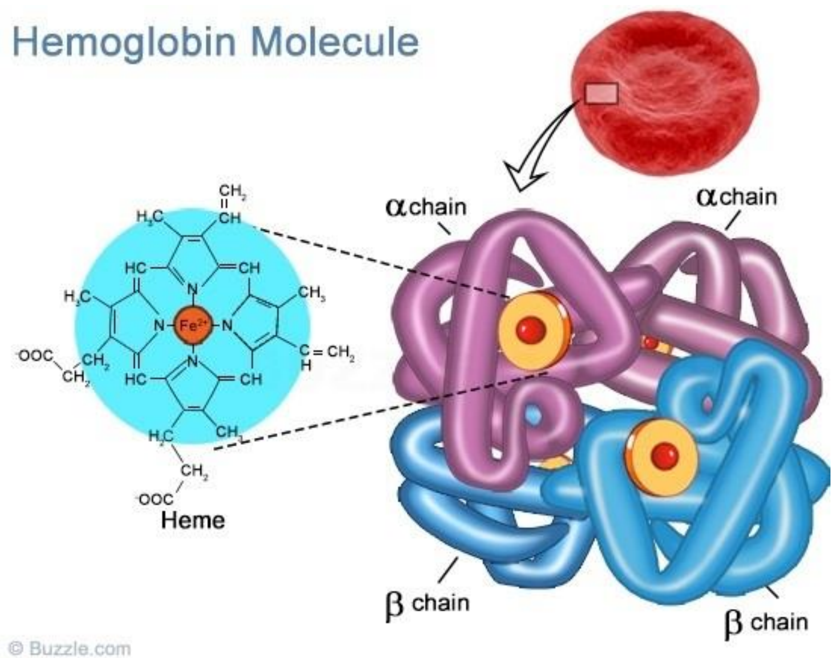
**Storage proteins** are biological reserves of metal ions and amino acids, used by organisms. They are found in plant seeds, egg whites, and milk. Ferritin is an example of a **storage protein** that stores iron. Iron is a component of heme, which is contained in the transport **protein** hemoglobin and in cytochromes.

**Porphin**



# Q02. Why $CN^-$ ion toxic to human?

$CN^-$ Binds with Fe(II) very strongly and the reaction is irreversible

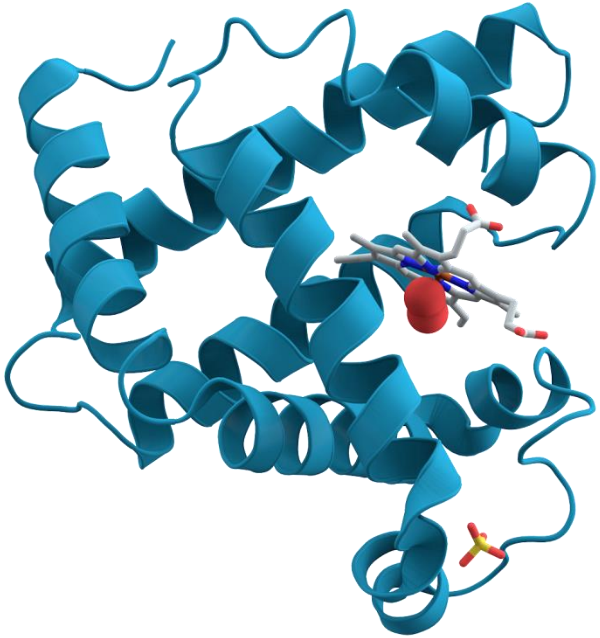



- Hemoglobin is actually Iron porphyrine complex: Hence once it binds with $CN^-$ . $O_2$ carrying process get affected hence it is toxic to human body

- Also activity of Cytochrome get inhibited

**Q03. What is the role of globular protein in oxygen transport?**

**Globular proteins**, or spheroproteins, are spherical ("globe-like") **proteins** and are one of the common **protein** types (the others being fibrous, disordered and membrane **proteins**).



**The globular protein generates a hydrophobic pocket and Prevents Fe(II)-$O_2$ complex from solvation and also stops formation of Fe-$O_2$-Fe etc.**

# Q04. What is "cooperative effect"?

**Co-ordination of one $O_2$ leads to conformational changes in the protein chain leading to facilitate co-ordination of $O_2$ by other 3-sub-unit**

***Cooperativity***

When $O_2$ binds to one sub-unit → $Fe^{2+}$ contracts, moves into plane of porphyrin ring → moves the histidine attached to it → triggers conformational changes in the globin chain → translated through H-bond network → Enhances the ability of other three units to bind $O_2$ → *This phenomenon is called cooperative effect*

*In a similar way when the blood reaches the muscle, only one $O_2$ is released, the others are released even more easily due to the cooperative effect in reverse*

**Q05. Why are all the oxygen carriers that contain iron and porphyrins found inside the cells?**

**The inside cell environment is reducing and sustains Fe(II) whereas outside the cell the $O_2$ concentration is high thus increasing the probability of the oxidation of Fe(II) ions to Fe(III)**

**Q06. Why is the size of high spin Fe(II) is larger than the low spin Fe(II)?**

**High spin Fe(II) has $e_g^2$ whereas low spin Fe(II) has $e_g^0$.**

**That is when the $e_g$ is empty, all the six ligands can approach the metal ion much more closely, thus leading to a reduction in the effective ionic radius. When the configurationis H.S. $e_g^2$, the approach of all the six ligands is hindered because of the repulsion between the ligands and metal $e_g$ electrons, thus leading, to an enhancement of the metal ionic radius**

**Q07. What prevents synthetic iron porphyrins from functioning as $O_2$ carriers?**

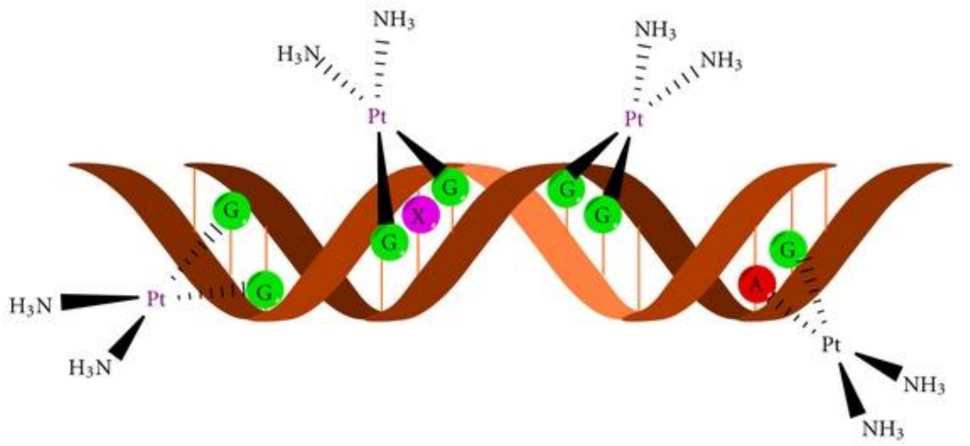
**Synthetic Fe-porphyrins easily form DIMER**

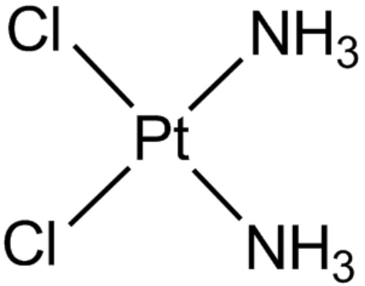
**Q08. Why is CO toxic to $O_2$ binding proteins?**

**CO Binds with Fe(II) very strongly and hence it block the metal co-ordination site prevented the oxygen transportation. That is why in presence of CO, $O_2$ can not be distributed to the cell and tissues**

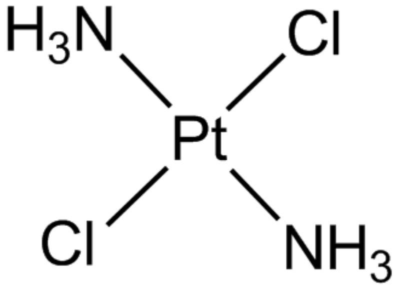
**Q09. While the cis-platin is potent anticancer agent, its trans-isomer is not. Why?**

**The *cis*-platin forms an adduct with DNA that is stable and prevents the copying, while the *trans*- does not.**




*cis*-Platin




*trans*-Platin

**Q10. Are you convinced with the statement that the coordination complexes are capable of acting as drugs for various health disorders. How & Why?**

The literature shows plethora of coordination complexes develope to suit as drugs for a variety of health disorders, such as, anti bacterial, anti viral, anti-diabetic, anti cancer, anti parasitic, anti HIV, and so on and so forth.

All this is possible since the diversity in the generation of coordination complexes arises from change of metal ion & its oxidation state; change of the ligand and its bonding strength; ligand exchange reactivity variations; outer sphere interactions with the biological molecules or systems, etc.

I have many

**CHEMISTRY JOKES**

I'm just afraid they won't get a good reaction


तेरे दिमाग़ मे
Chemical
लोचा है