Inorganic compounds/complexes in medicine

Inorganic compounds in medicine!

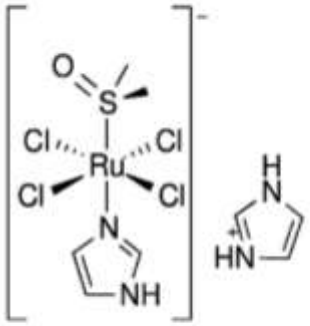
Element	Compound	Use
Ag	Silver sulphadiazine	Antibacterial
Al	$Al(OH)_3$	Antacid
As	Salvarsan, Melarsen, Tryparsamide	Antimicrobial
Au	Gold(I) thiolates	Antitumour
	Auranofin	Antiarthritic
	Au(I) diphosphine complexes	Antiviral
Ba	Barium sulphate	X-ray contrast
Bi	Bismuth subsalicylate, colloidal bismuth citrate, ranitidine bismuth citrate	Antacid, antiulcer
Br	Sodium bromide	Sedative
Cr	Chromium complexes	Antidiabetic
Cu	Copper histidine complex	Supplement for Menkes Disease treatment
Co	Coenzyme B_{12}	Supplement
Fe	Sodium nitroprusside	Vasodilator
	Fe(III) desferrioxamine chelates	Antimicrobial
Gd	Gd metallotexaphyrins	MRI contrast agent. PDT, Radiopharmaceuticals
Hg	Mereurochrome	Antiseptic
I	I_2	Antiseptic

Ag, As: antibacterial, antimicrobial; Au: Antiarthritis; V, Cr: antidiabetic; Co: Vit. B12 supplement; Hg, I: antiseptic; Mg: antacid; Pt, Ru, Ti: anticancer; Zn: antiviral; W: anti HIV; Gd: MRI contrast

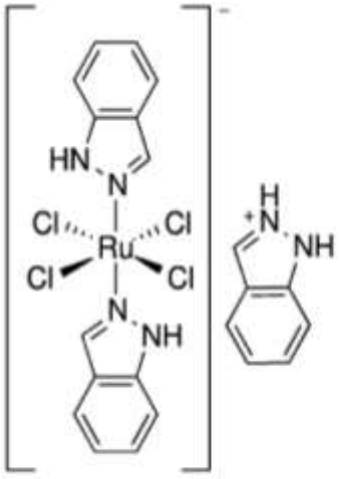
Inorganic compounds in medicine!

	$Na^{131}I$	Diagnosis of Thyroid
Li	Li_2CO_3	Manic depression
Lu	Lutetium complexes	PDT
Mg	MgO	Antacid, laxative
Mn	Mn-SOD complexes	Superoxide scavengers
		MRI contrast agent
Pt	Cisplatin, carboplatin	Anticancer
Ru	Ru(III) complexes	Anticancer
Sb	Pentostam, N-methylglucamine antimonate	Antileishmanial
Si	$Al_2(OH)_4Si_2O_5$	Antidiarrhoeal
Sn	Tin(IV) ethyl etiopurpurin	PDT
Tc	^{99m}Tc (V) propyleneamine oxime	Diagnostic imaging
Ti	Titanocene dichloride, bis(β-diketonato) Ti(IV)	Anticancer
V	bis(maltolato) oxovanodium(IV)	Antidiabetic
	bis(glycinato) oxovanodium (IV)	
	bis(methylpicolinato oxovanadium (IV)	
W	Polyoxometallates	Anti-HIV activity
Zn	ZnO	Skin ointment
	Zn(II)bicyclam complexes	Antiviral
	Zinc citrate	Supplement
Zr	Zr(IV) glycinato	Antiperspirant
Se	Ebselen :	Synthetic antioxidant
	(2-phenyl-1,2-benzisoselenazol-3(2H)-one	Anti-inflammatory
		neuroprotective agent
	Phenylaminoalkyl selenide:	Antihypertensive
	(4-hydroxy-α-methyl-phenyl-2-aminoethyl selenide)	
	Selenazofurin	Antineoplastic and antiviral a
	Selenotifen	Anti-allergic agent

Inorganic complexes as drugs for different diseases



NAMI-A



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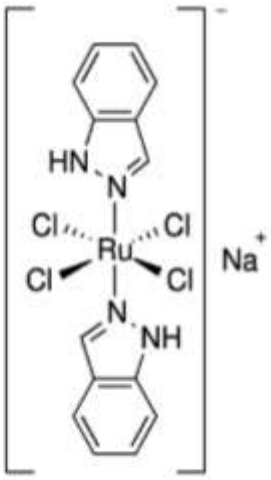

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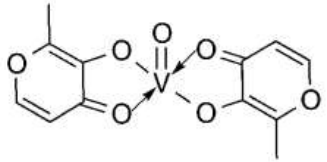
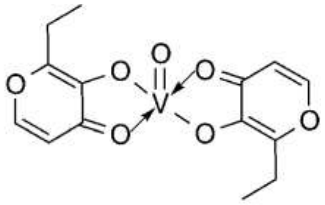


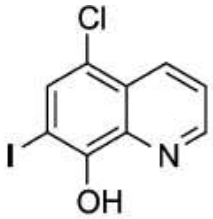
BMOV

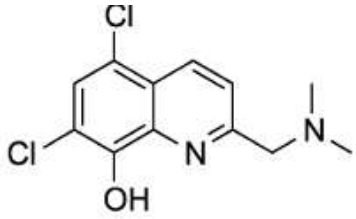


BEOV

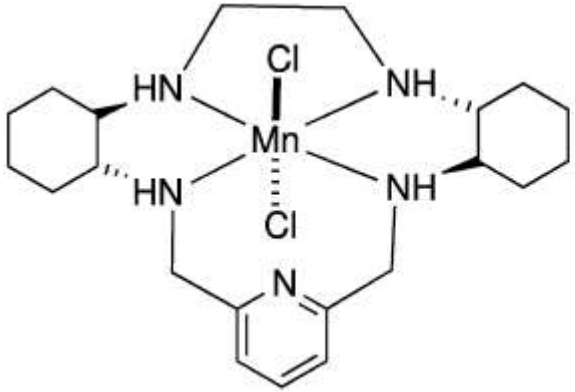
Anti-diabetic

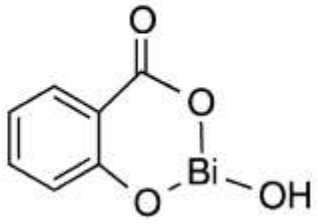
Ru-based anticancer drugs!





Metal chelators for Alzheimer disease

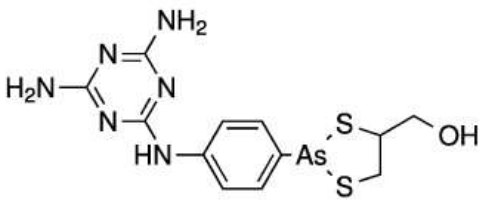




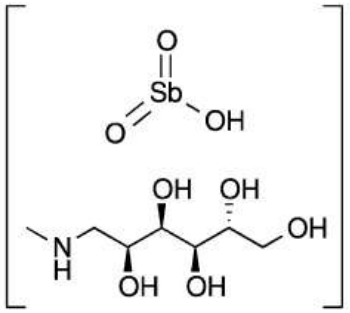
Gastro-intestinal problems

Anti-microbial & anti- parasitic drugs

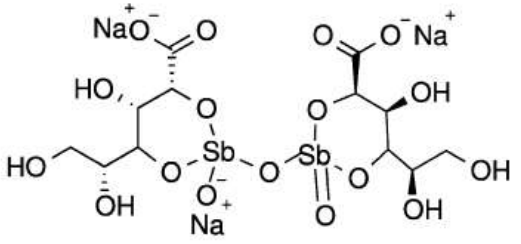
Approved



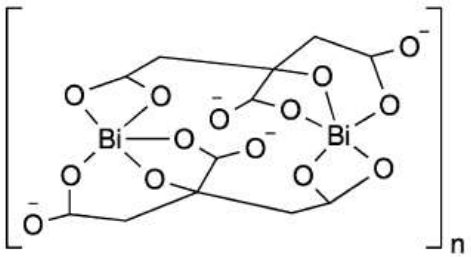
melarsoprol



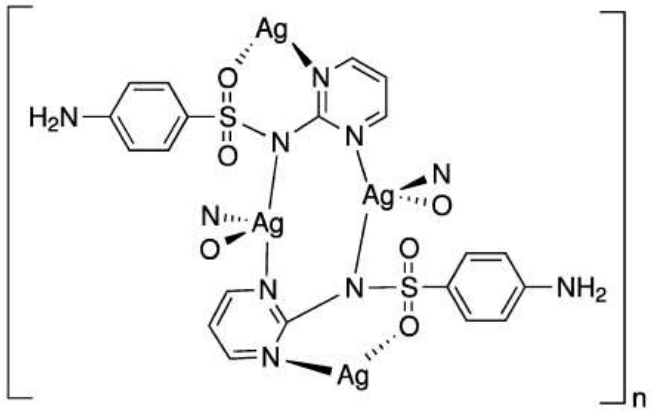
meglumine antimoniate



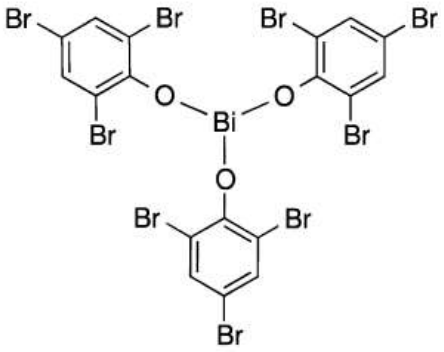
sodium stibugluconate



CBS

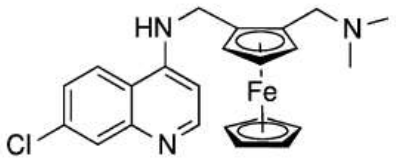


silver sulphadiazine



xeroform

Clinical trials



ferroquine

Platinum based anticancer drugs!

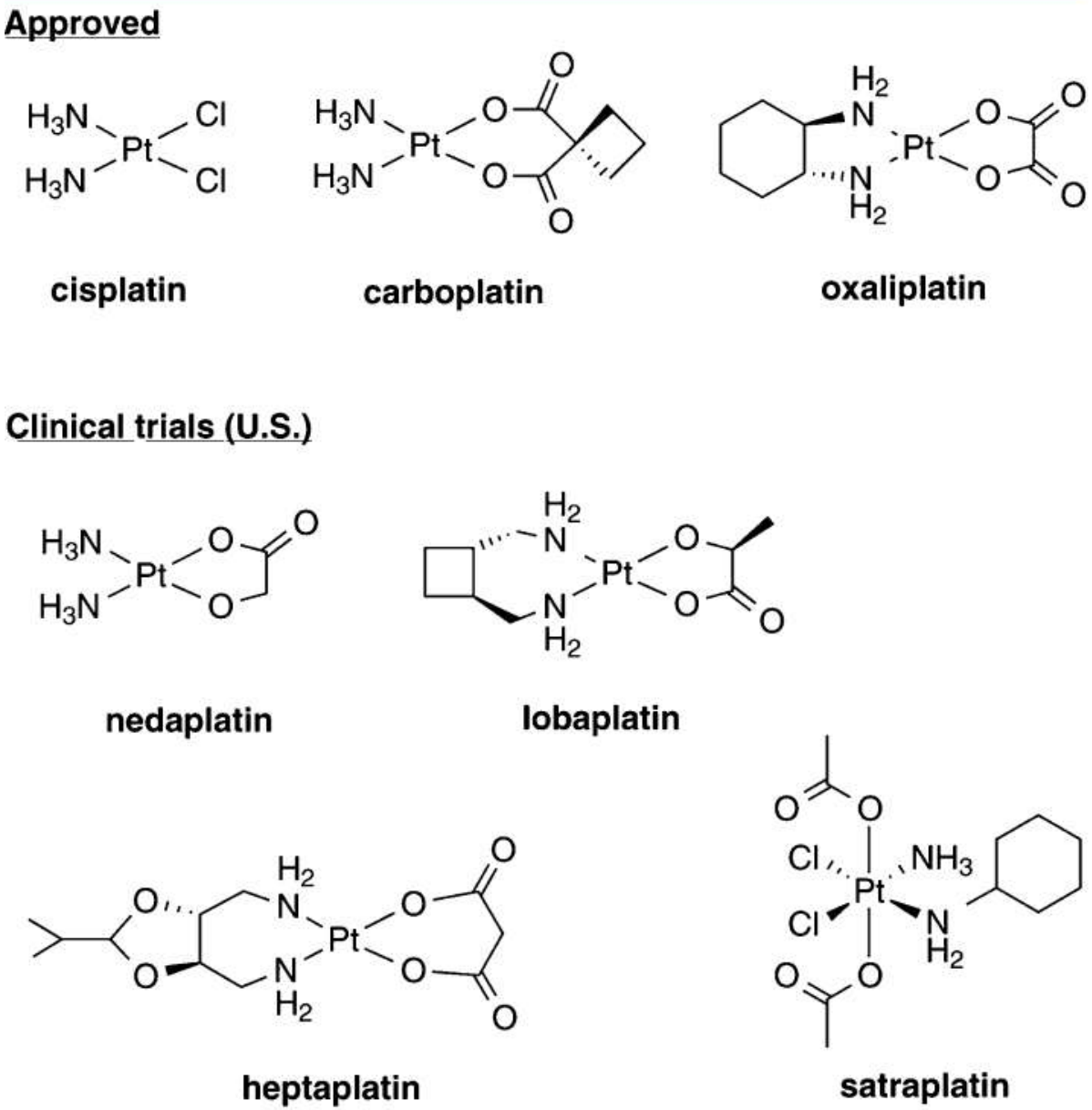
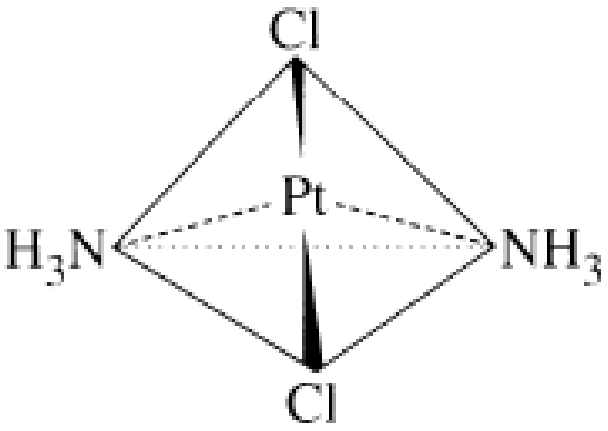


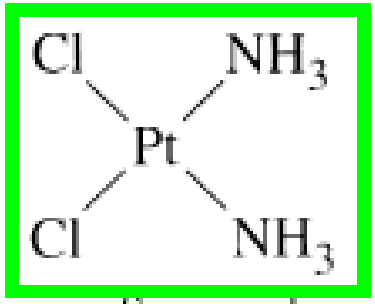
Figure 2. Anticancer platinum metallodrugs approved and in clinical trials in the U.S.

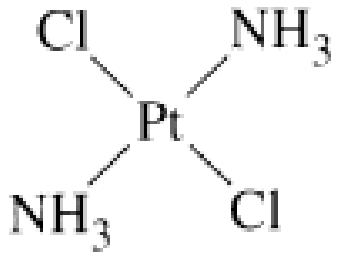
Cis- vs. Trans- Platin isomers: Serendipity in Chemistry Is a boon to cancer patients

cis - and *trans* - Diamminedichloroplatinum (II), $[PtCl_2(NH_3)_2]$



Tetrahedral (one isomer)

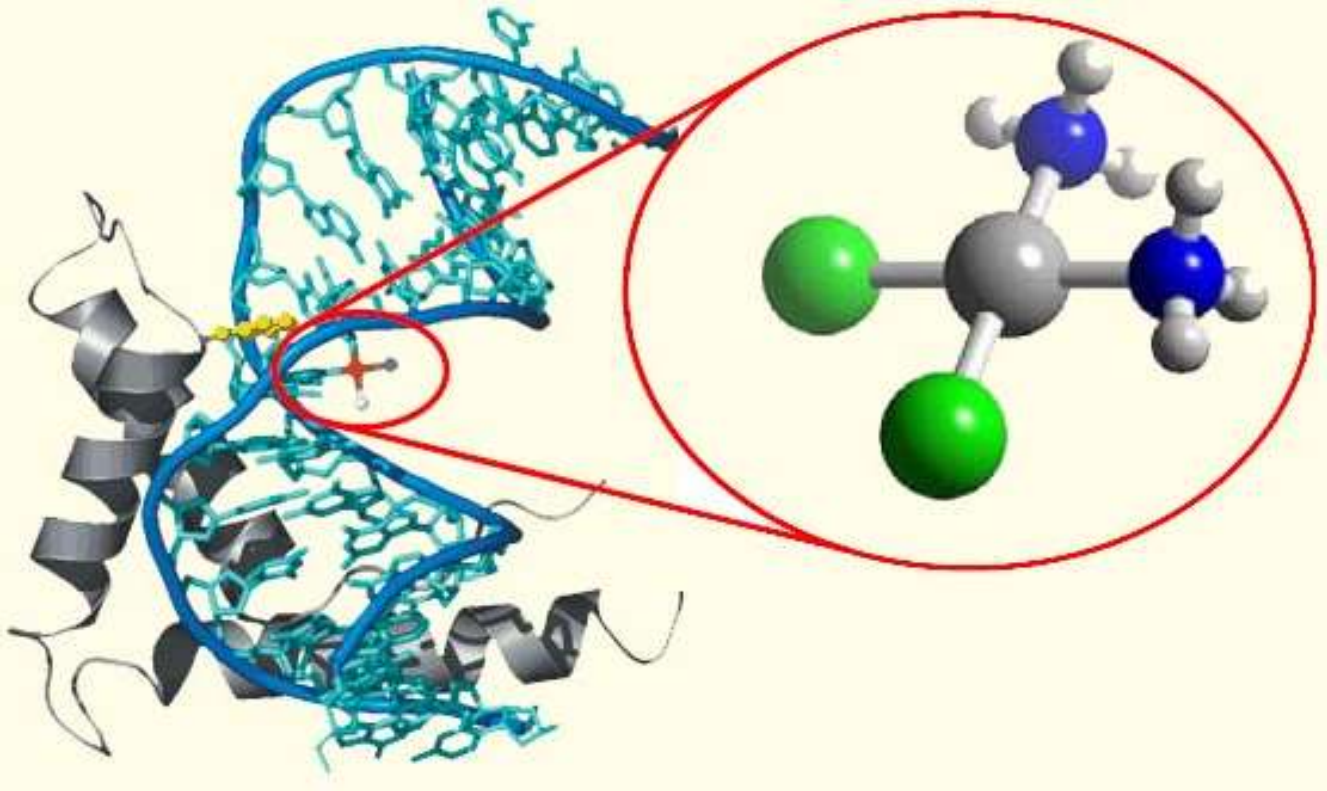




Square planar (two isomers)

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

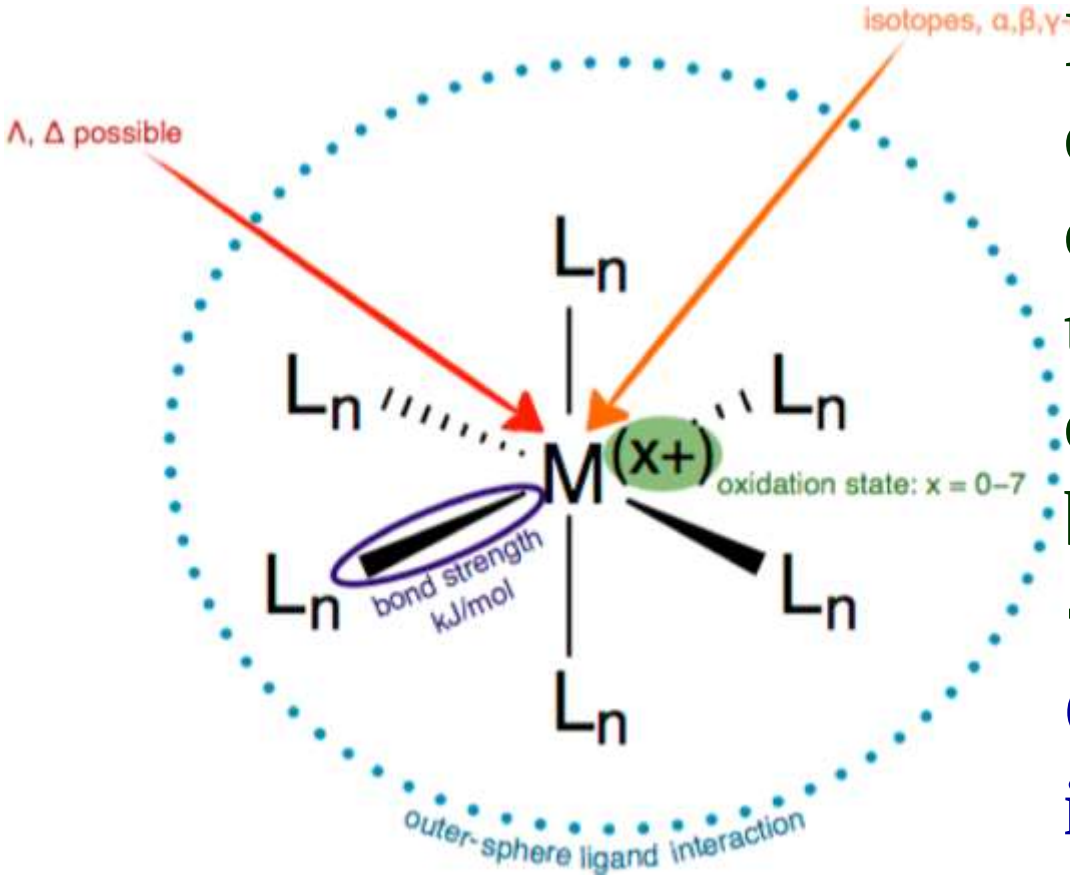
Cis-platin vs. trans-platin: anticancer activity



Anticancer activity of the Cis-Platin is based on its effective cross-linking with DNA and inhibiting to copy the DNA by enzymes and thereby prevents the cell division.

The damaged DNA sets off DNA repair mechanisms, which activate apoptosis when repair proves impossible. The trans-isomer does not have the paramacological effect.

How does one design an inorganic drug?



All the ligands need not be same. There can be mixed ligands in the complex. The complex could be either neutral or charged.

It all depends on coordination chemistry principles & the interaction of the compound with biomolecules → cells → tissue → organs. Complex should interact selectively with biomolecules either through outer sphere or inner sphere binding or reaction

Inorganic Chemistry in Biology

Or

Biological Inorganic Chemistry

Or

Bioinorganic Chemistry

Bioinorganic Chemistry

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

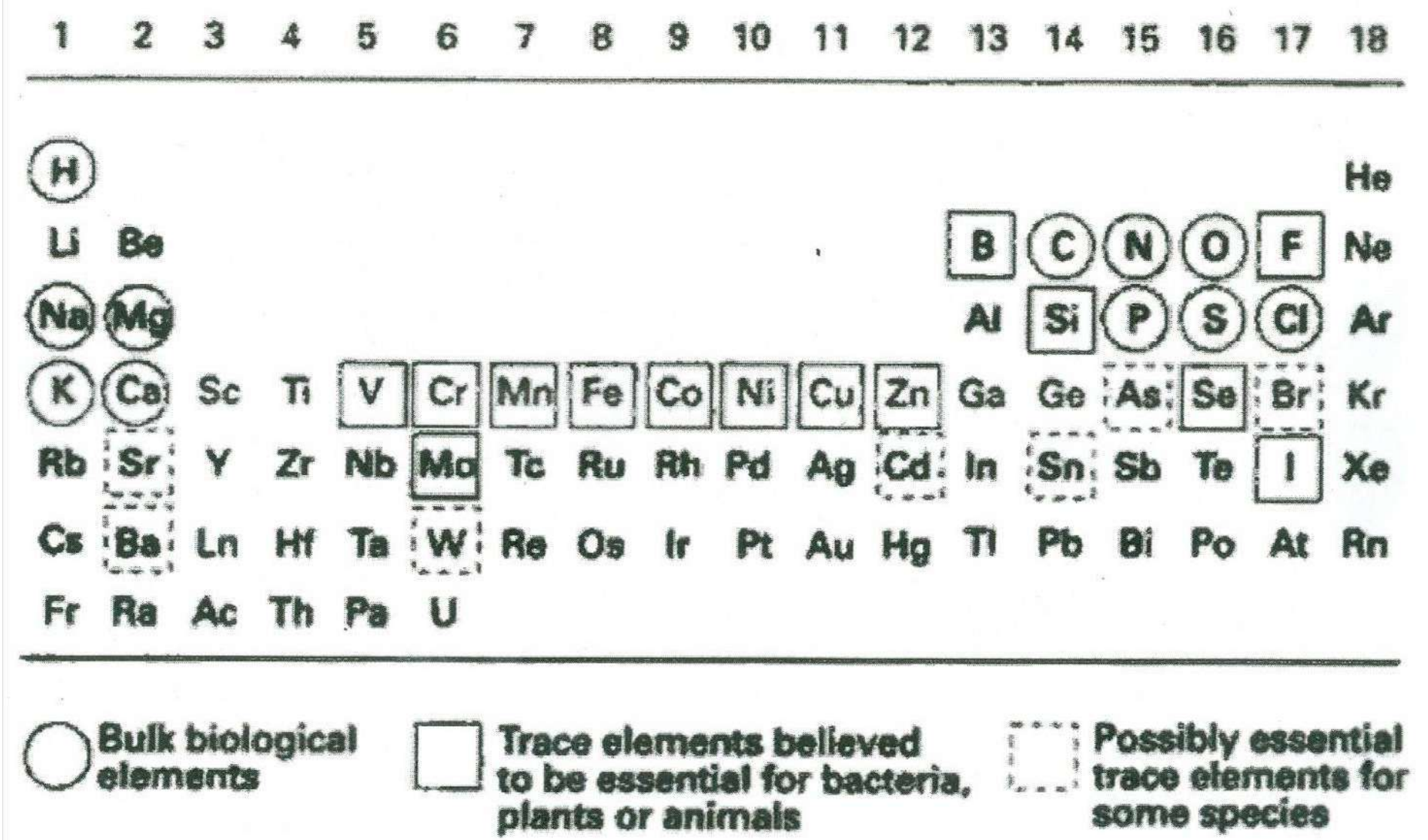
Few selected Functions of Metalloenzymes

- **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**

Which Elements are Relevant to Life?



Chemical elements essential for various forms of life: Categorization (no need of memorizing)

(i) **Bulk Elements: C, H, N, O, P, S (involved in making proteins and nucleic acids, etc.)**

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

(i)& (ii) together constitute >99% of human body weight

Critical elements of metalloenzymes (Essential):

(iv)Trace Elements: Fe, Zn, Cu (present in few grams in human body)

(v)Ultra-Trace Elements: (each of these present to only few to several milligrams in human body)

(a) Metals: Mn, Mo, Co, Cr, V, Ni, Cd, Pb, Li

(b) Non-metals: F, I, Se, Si, As, B

ESSENTIAL Element of Life: Criteria to be fulfilled

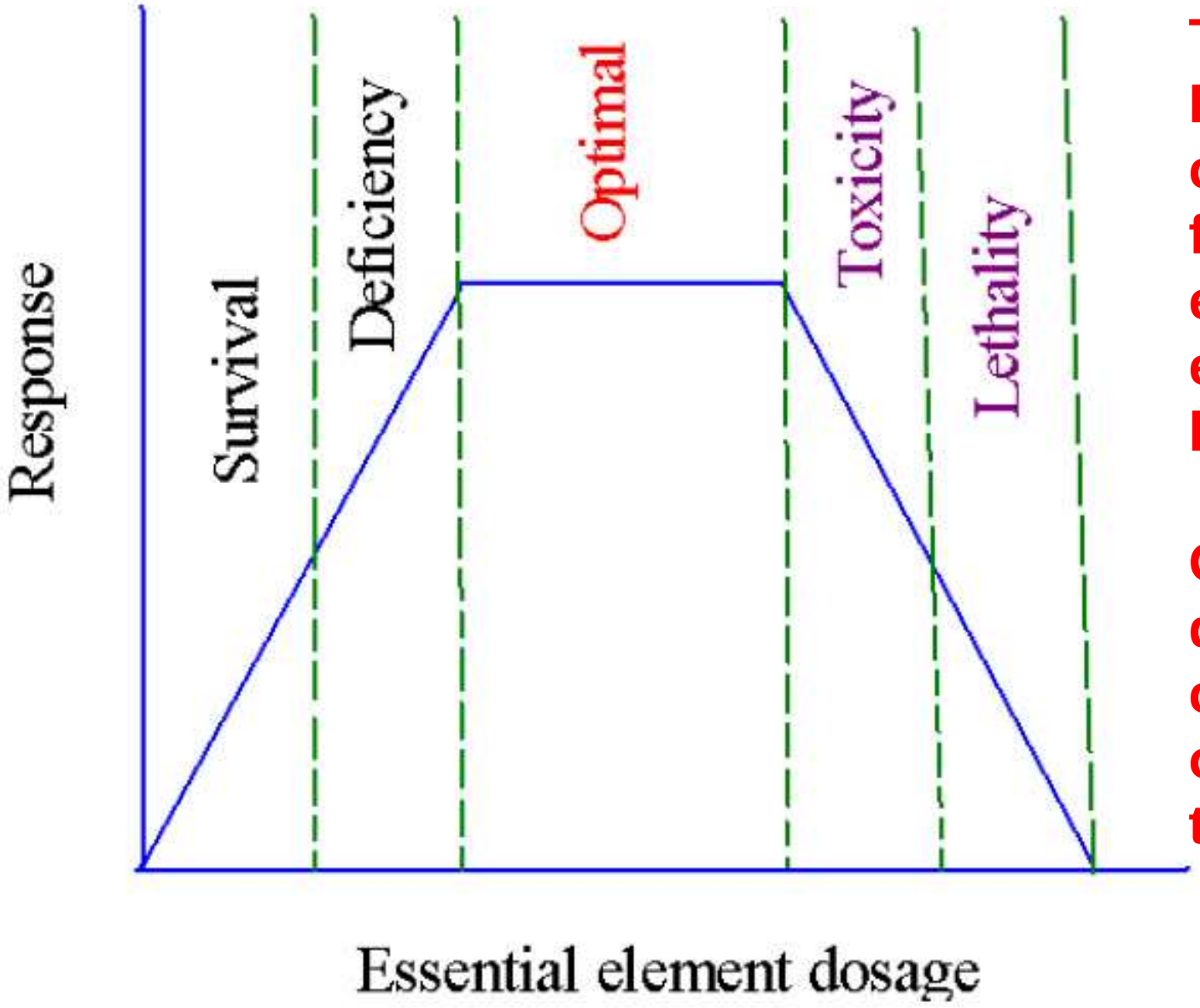
- **Should be present in the tissues of different animals at comparable concentrations**
- **A specific biochemical function (structural or catalytic or regulatory type) should be associated with that element**
- **Physiological deficiency appears when the element is removed from a purified diet**
- **The deficiency can be relieved by the addition of that element**

Why did nature choose these elements for life?

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 stablization**
- **Kinetic reactivity and other controls**
- **Thermodynamic aspects**
- **Chemical reactivity**

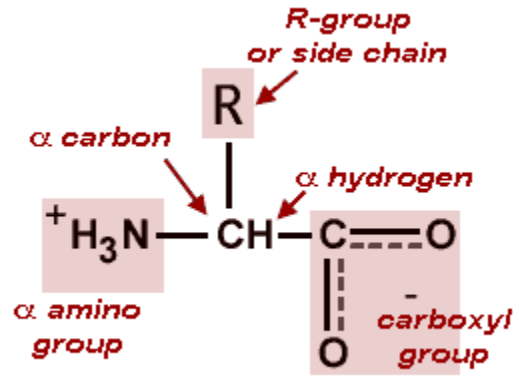
Essential Element of life: Dose – Response Curve

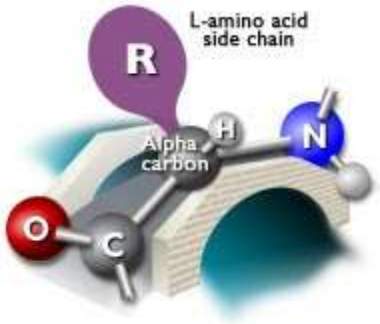


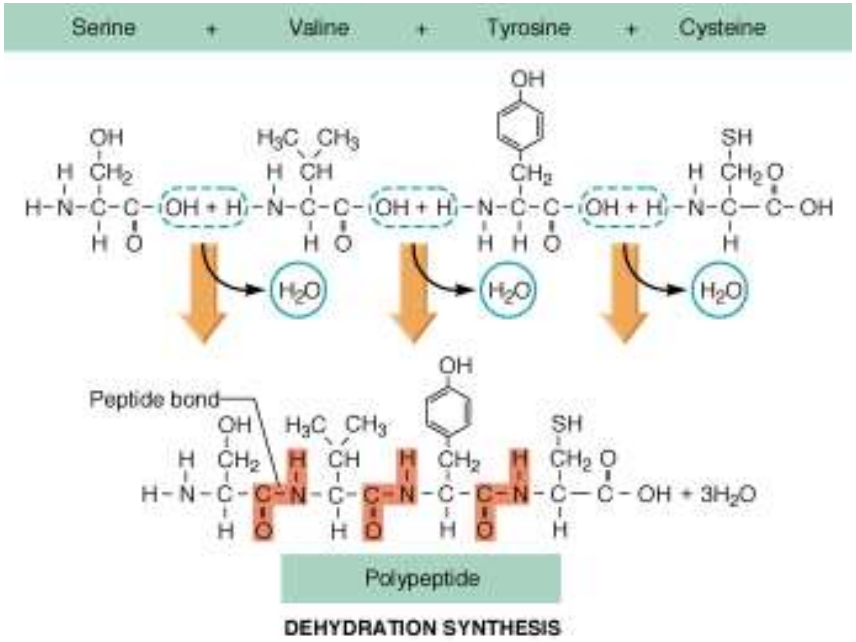
The Dose – Response curve is similar for all the essential elements of life.

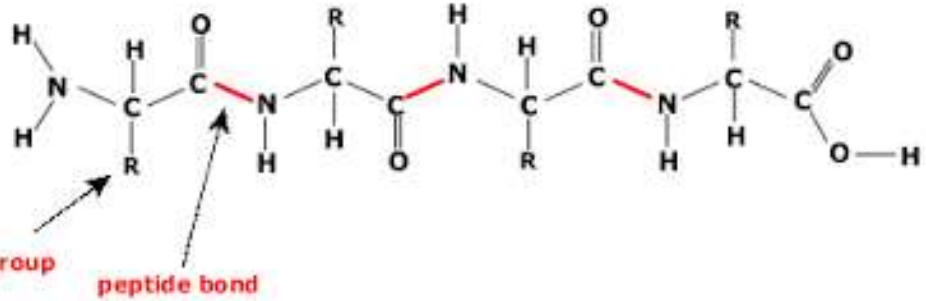
Only the dosage will change from one element to the other.

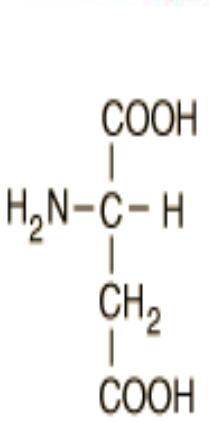
Amino acids, peptides & proteins



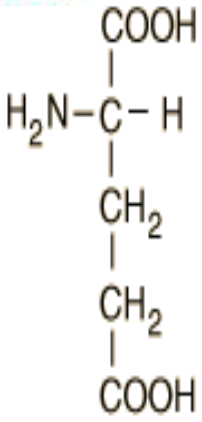




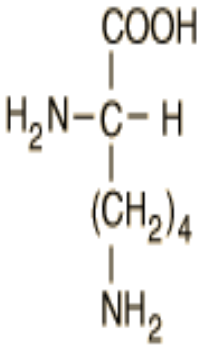




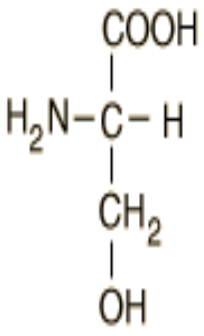
Aspartic acid (asp)



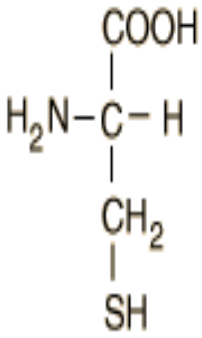
Glutamic acid (glu



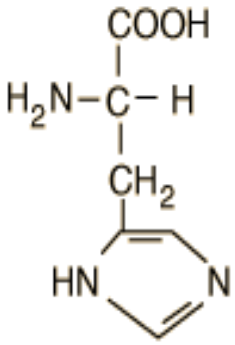
Lysine (lys)*



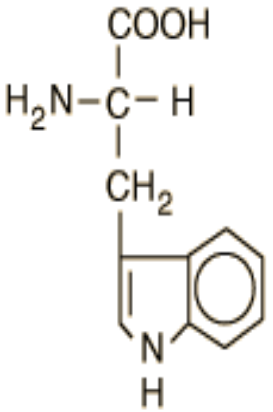
Serine (ser)



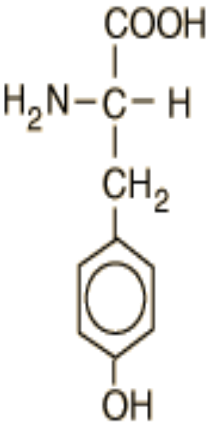
Cysteine (cys)



Histidine (his)*

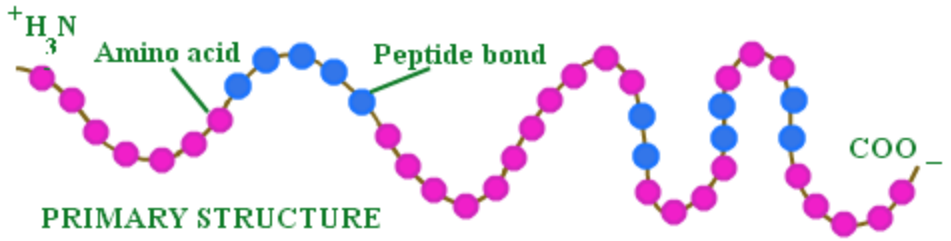


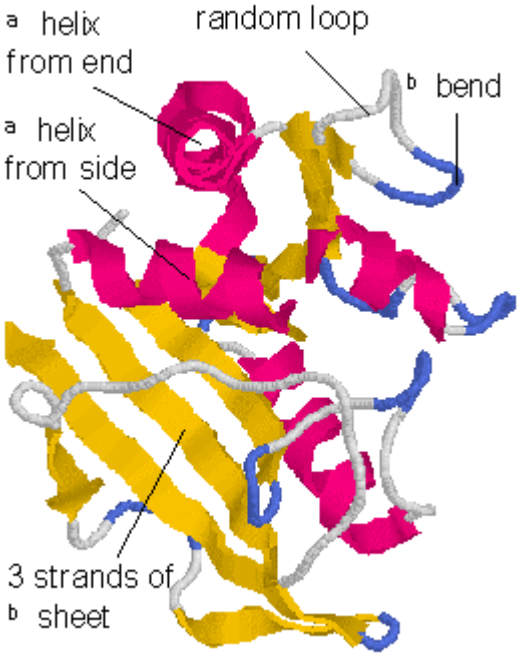
Tryptophan (trp)*

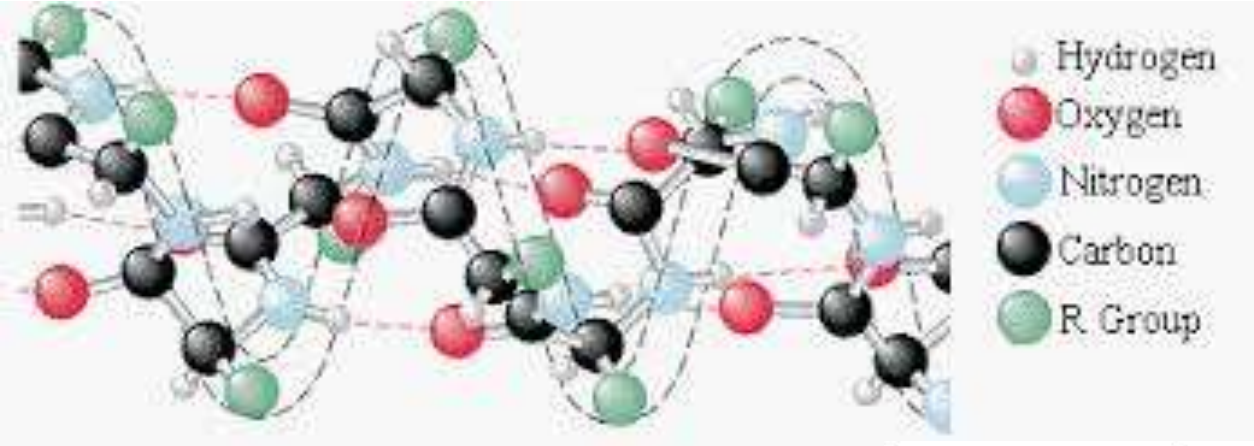


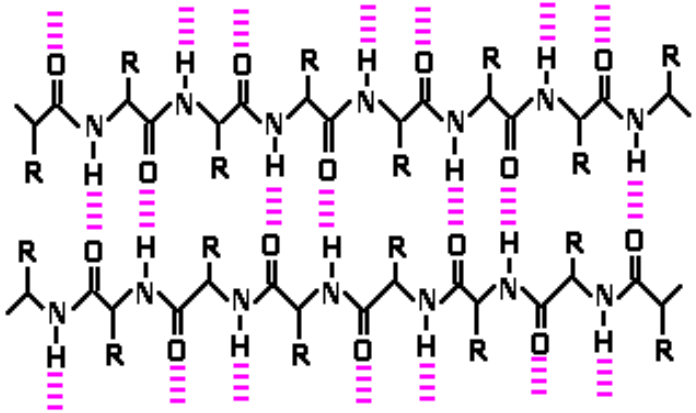
Tyrosine (tyr)

Protein → Metalloproteins →Metalloenzymes



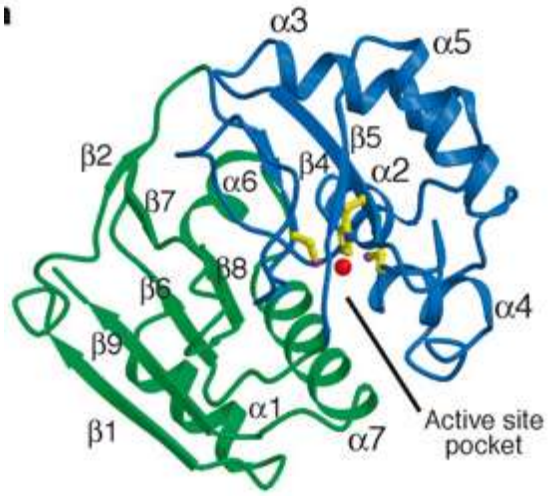


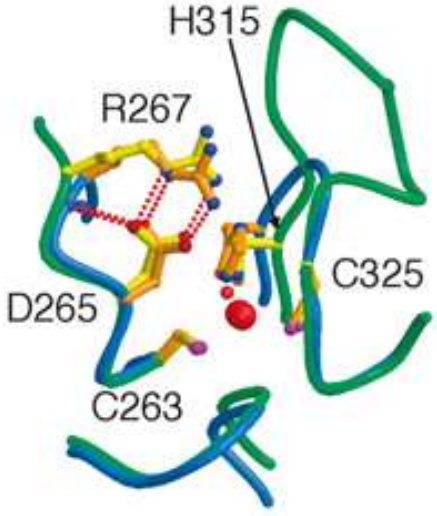




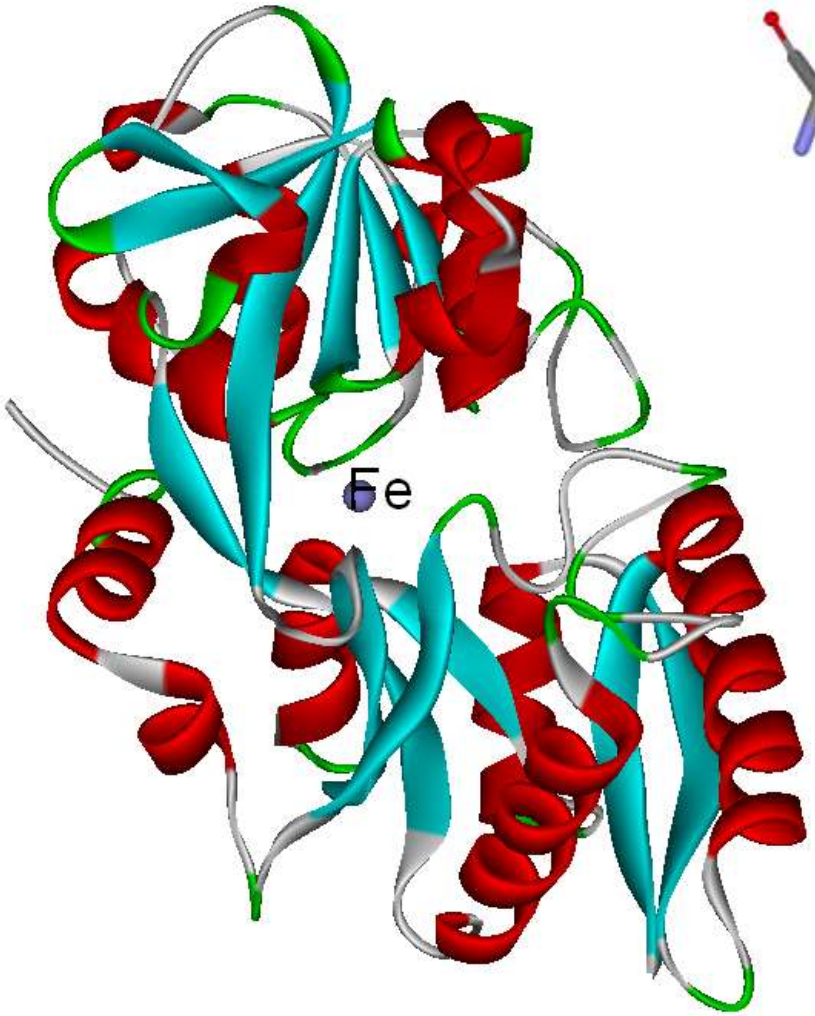
skeletal formula showing hydrogen bonding holding together polypeptide chains in beta-sheets of protein

(c) doc b

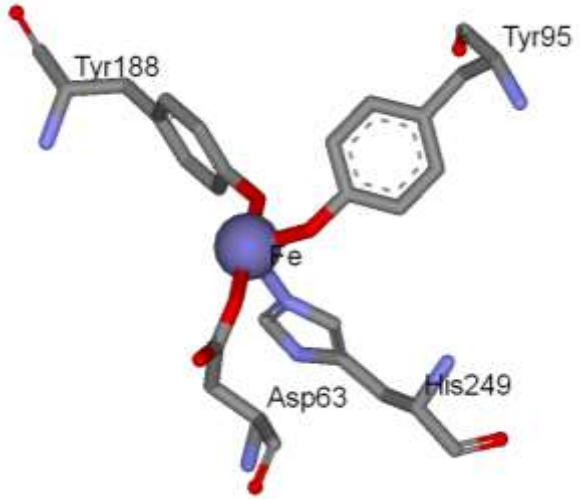




Structure of human serum transferrin – Coordination about Fe



HUMAN SERUM TRANSFERRIN
pdb code:1a8e

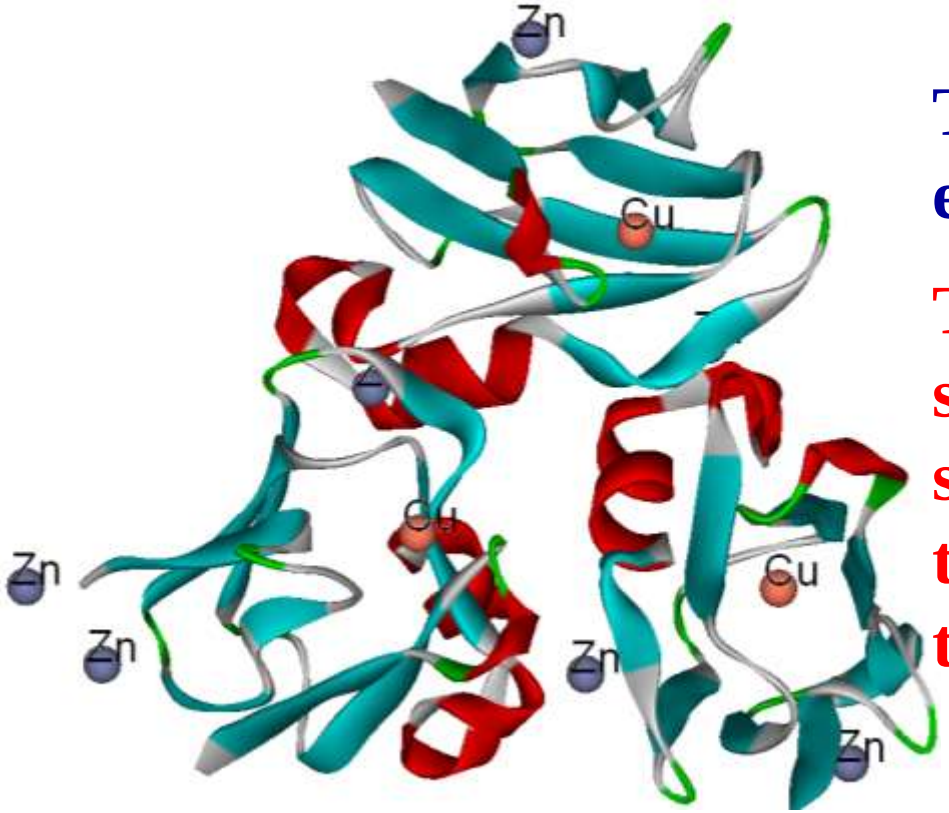


This protein transports iron ions to various organs of the body.

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

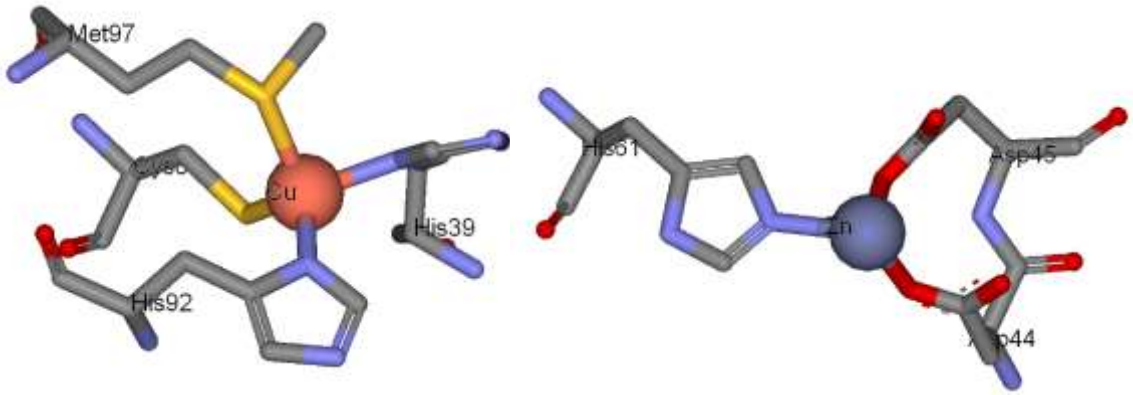
During pick up and delivery iron is in +2; and during transport and storage it is in +3.

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.



PLASTOCYANIN-pdb code:2w88

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

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. In a metalloenzyme, this is the metal ion bound region.*

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

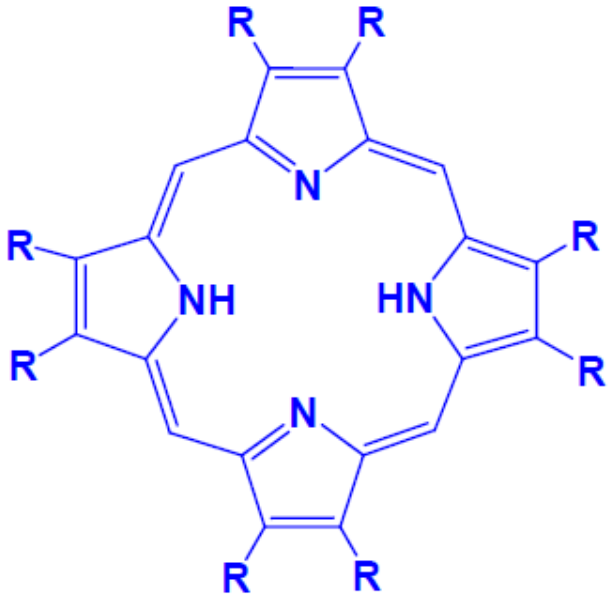
Active site provides specificity for its particular substrate

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

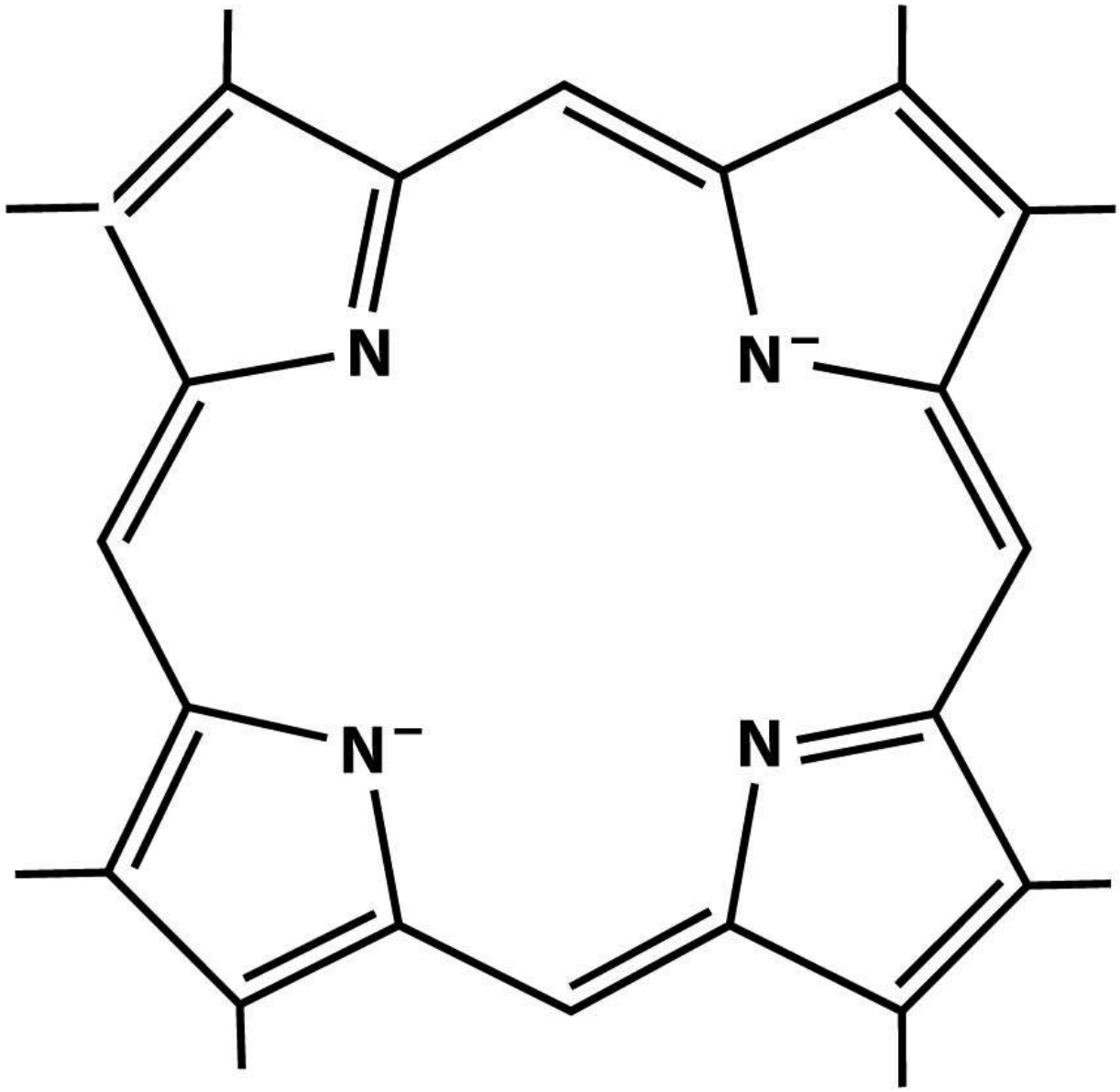
Formation of Enzyme-Substrate Complex and its transformations are thus crucial to the product formation

Porphyrins

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

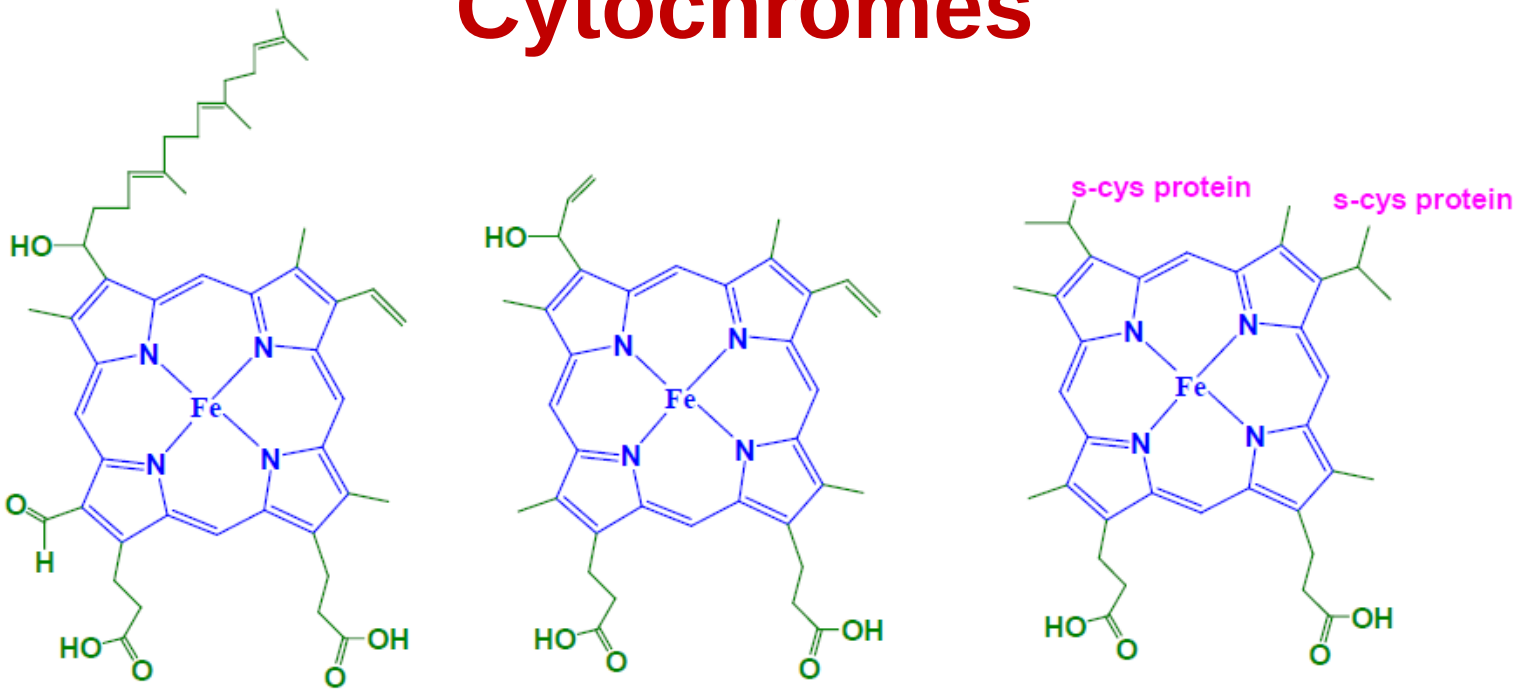


variation of substituents facilitates the tuning of electron-donating and electron-withdrawing ability of the ligand



8 Porphyrin^{2-}

Cytochromes



Substitutions affects the red-ox potential of the hemes

These are electron transfer proteins if both 5th and 6th coordinations are filled by the protein side chains.

These are oxygenases if only the 5th coordination is filled by the side chain and NOT ALL THE SIX (6) POSITIONS

Myoglobin – O_2 storage

Hemoglobin – O_2 transport

In hemoglobin there are four heme units.

Each unit has a molecular weight of 12,400.

Total molecular weight is 49,600 (~50 kDaltons)

Each unit is equivalent to myoglobin.

When four are connected together, the resultant acts as a hemoglobin and not as myoglobin

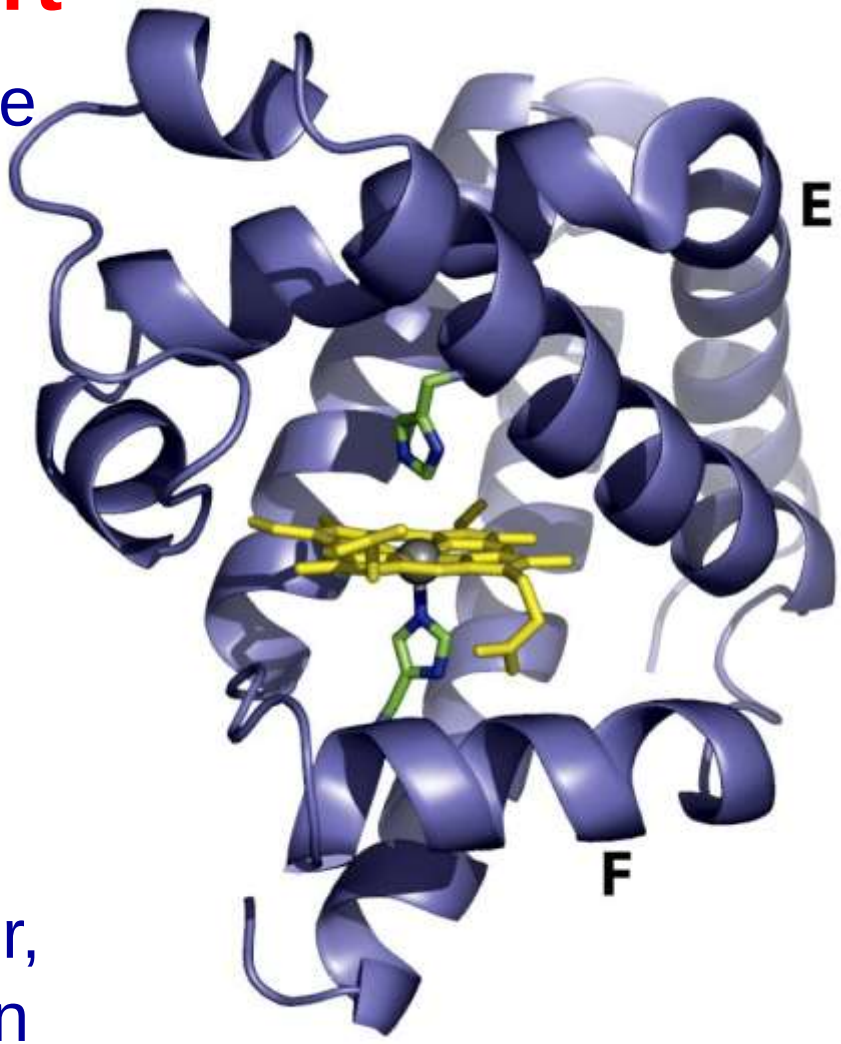


Figure 26-13
Shriver & Atkins Inorganic Chemistry, Fourth Edition

Hemoglobin is tetramer of the Myoglobin structure

But functionally differs and Acts as a Transport Protein due to COOPERATIVITY

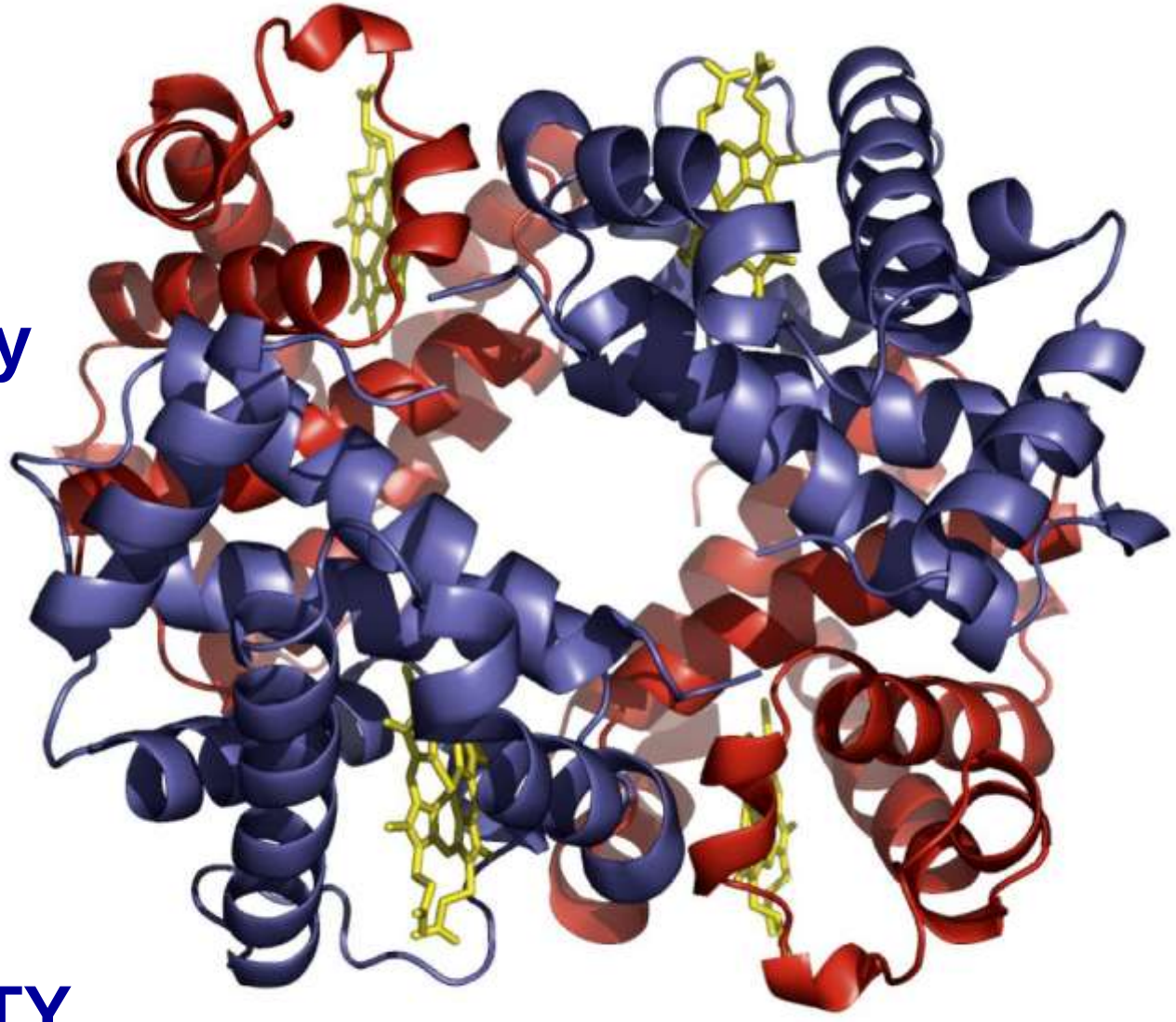


Figure 26-16
Shriver & Atkins Inorganic Chemistry, Fourth Edition

Biochemistry of myoglobin and hemoglobin

Oxygenation kinetics

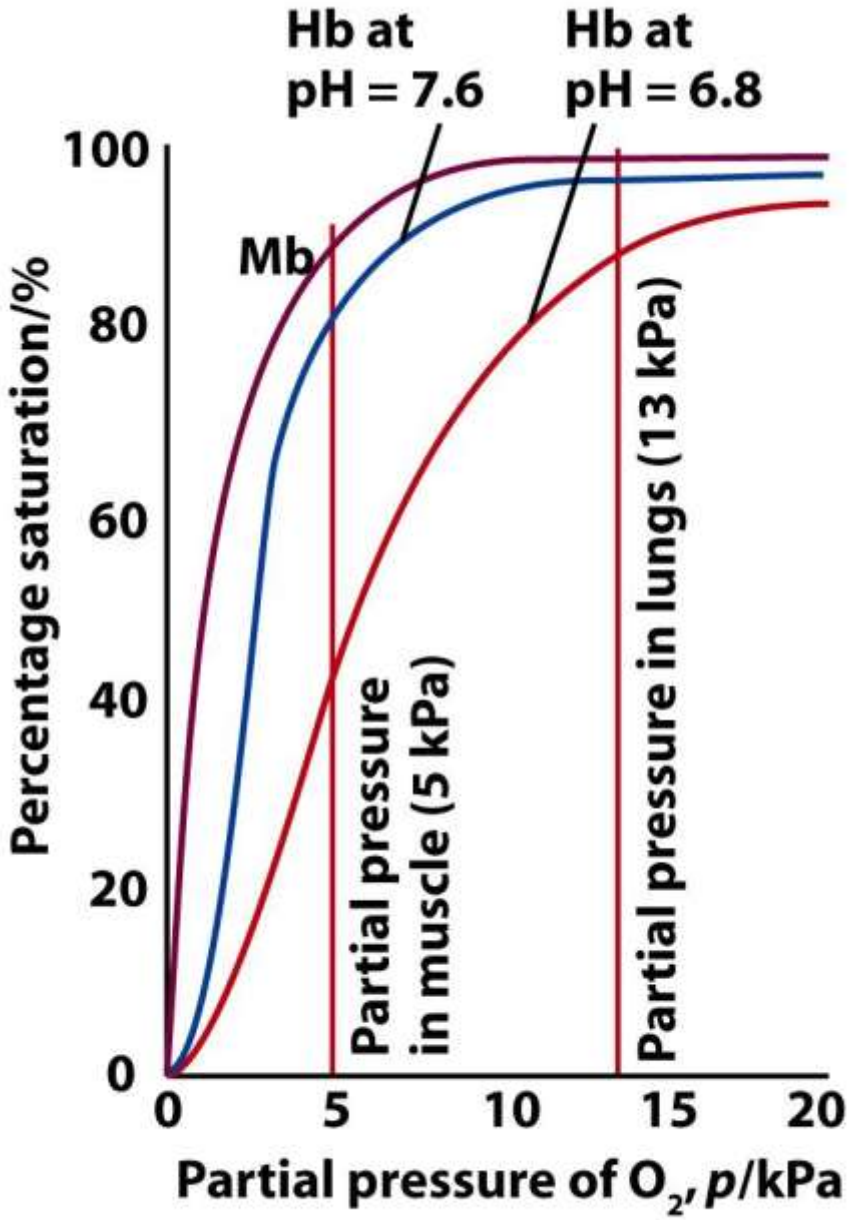


Figure 26-17
Shriver & Atkins Inorganic Chemistry, Fourth Edition

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

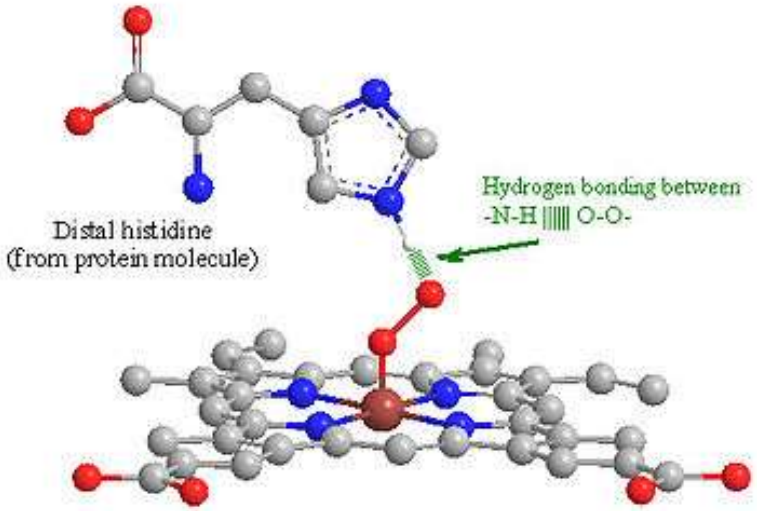
Binding of CO vs. O_2

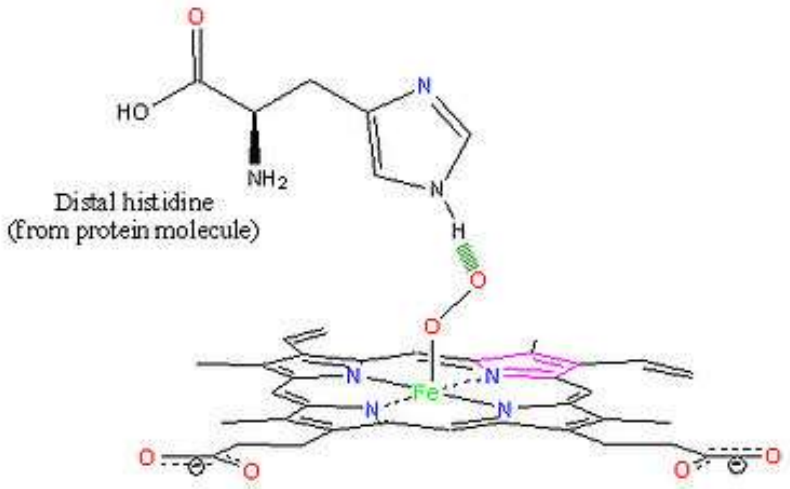
Thermodynamics vs. Kinetics -- Role of the protein

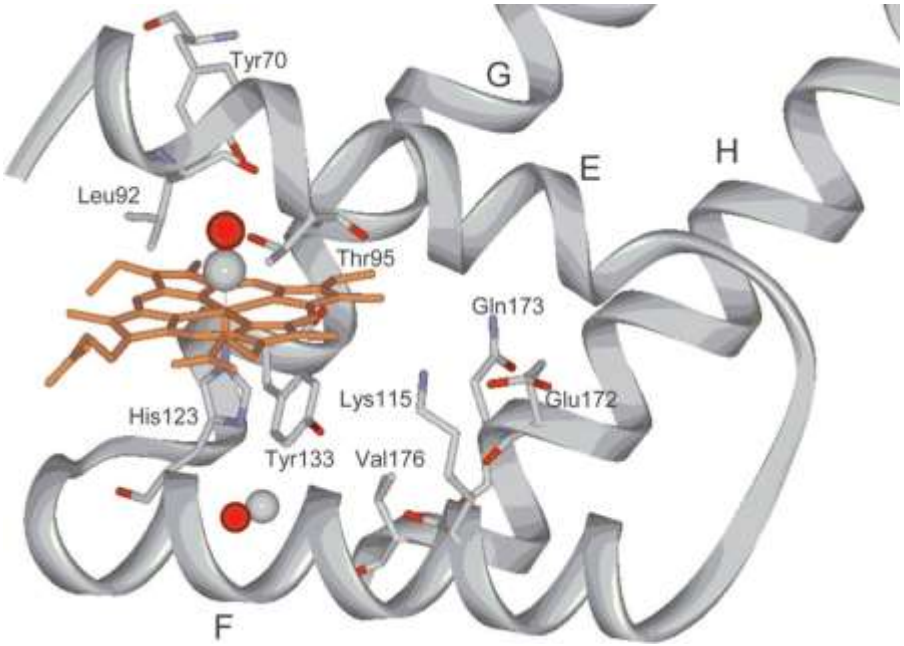
4 x PFe(II) + O_2 → 2 x PFe(III)-O-O-Fe(III)P

→ 2 x PFe(III)-O-Fe(III)P + O_2

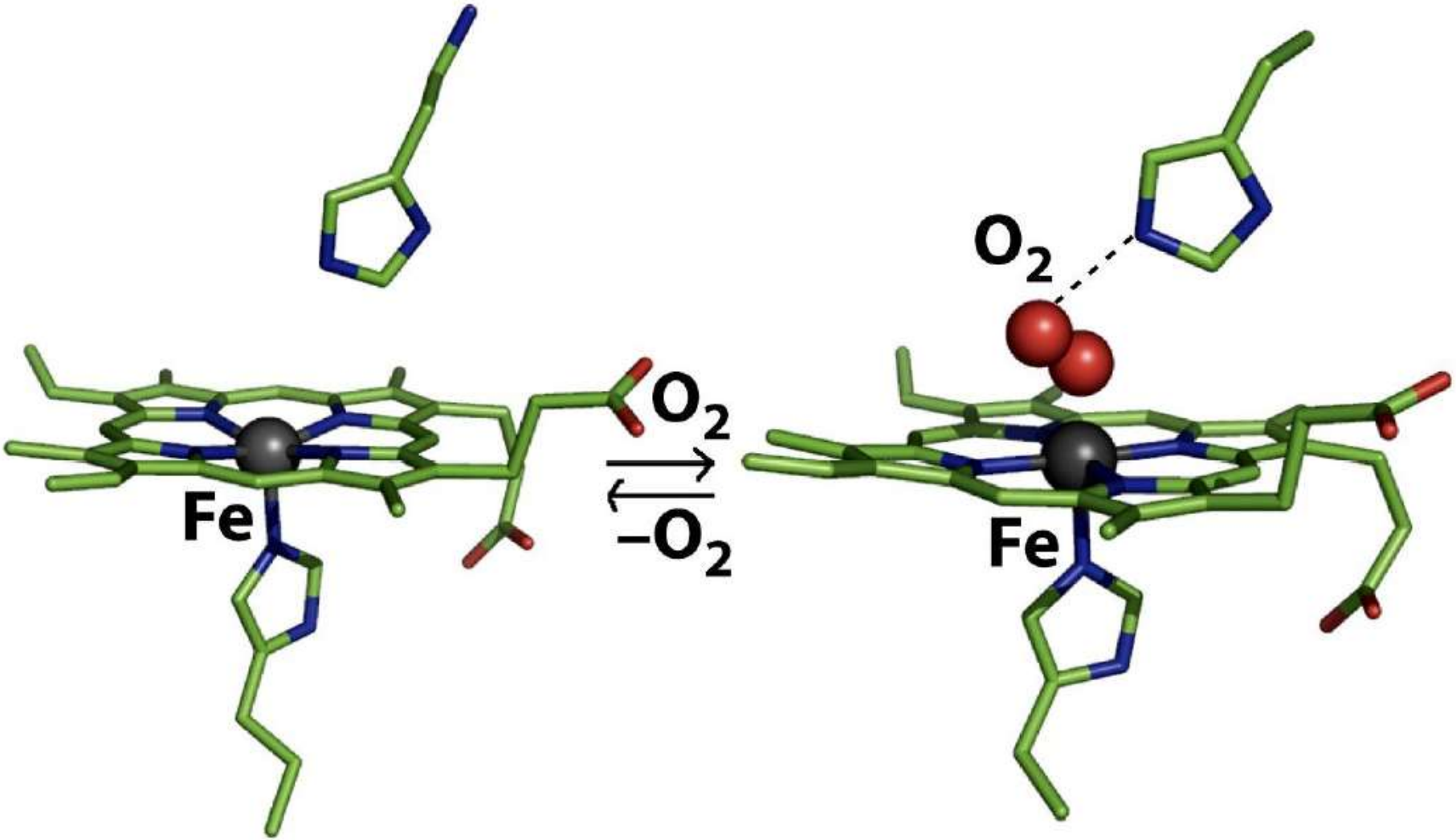
Oxy & carboxy myoglobin structures



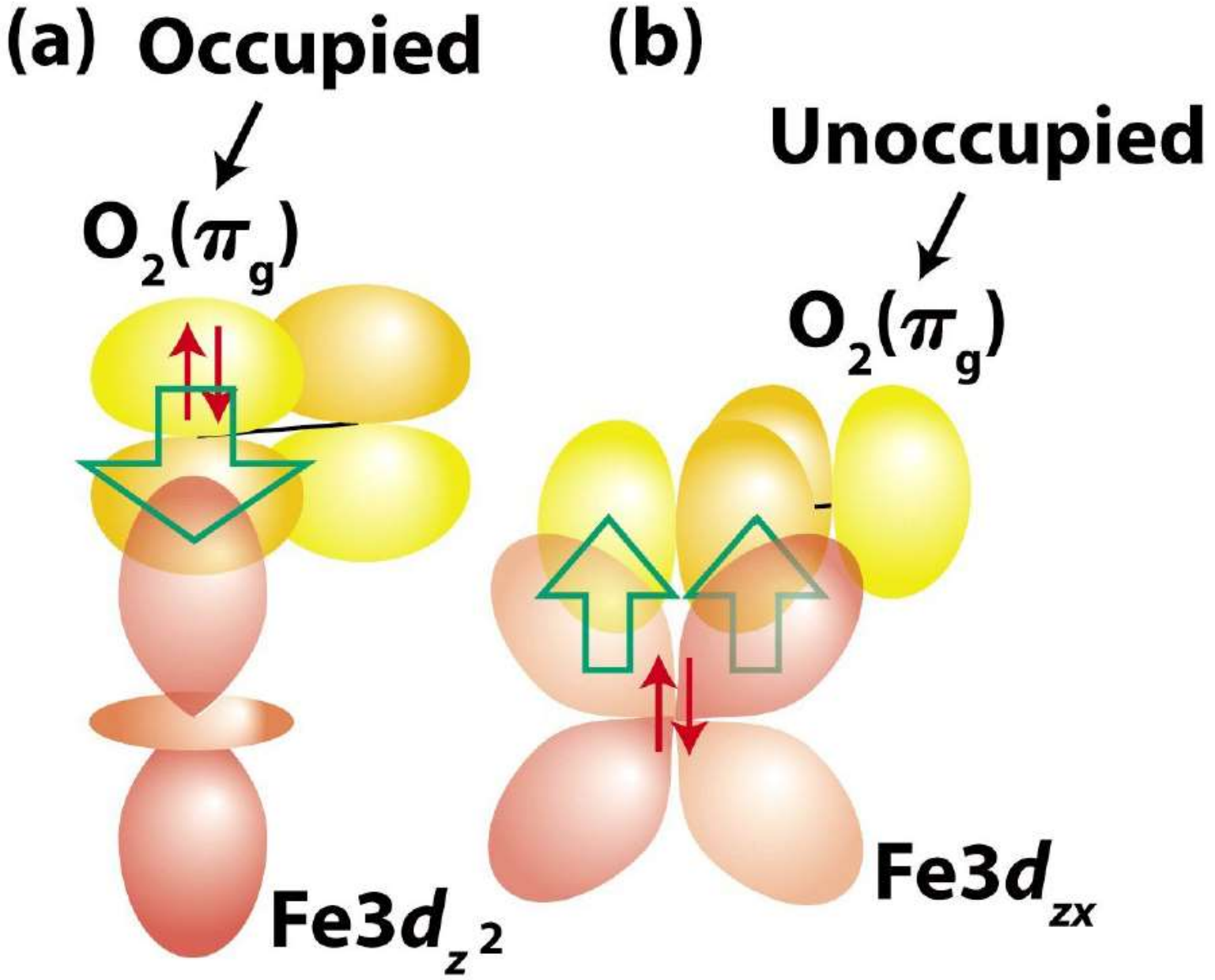




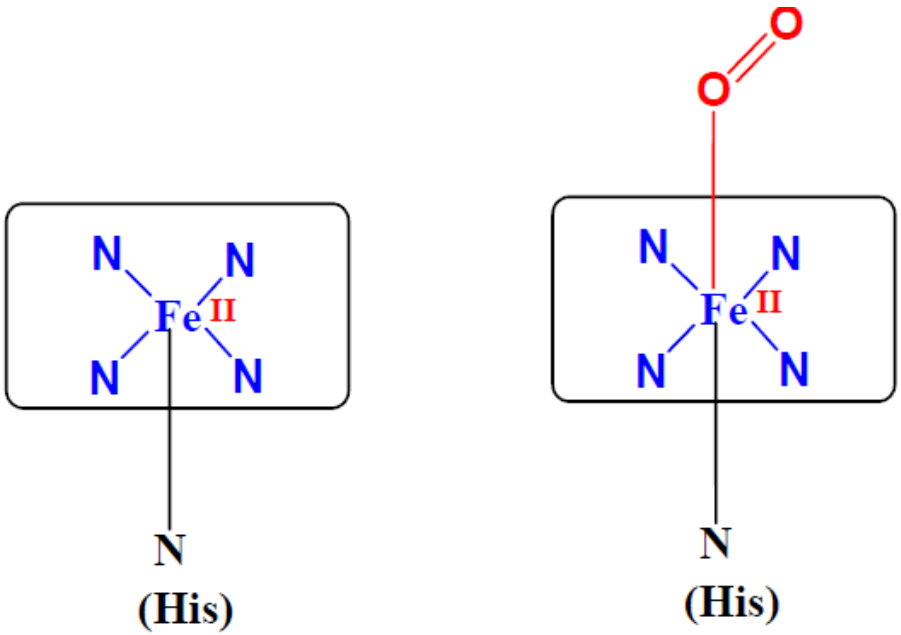
Selectivity of O_2 over CO by Hemoglobin



Nature of O_2 bonding to iron center in Hemoglobin



Oxy- and de-oxy forms of Hemoglobin



High Spin
paramagnetic
$t_2g^4\ e_g^2$

Deoxyhemoglobin

Low Spin
diamagnetic
$t_2g^6\ e_g^0$

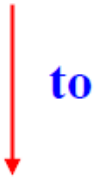
Oxyhemoglobin

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)



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

↓

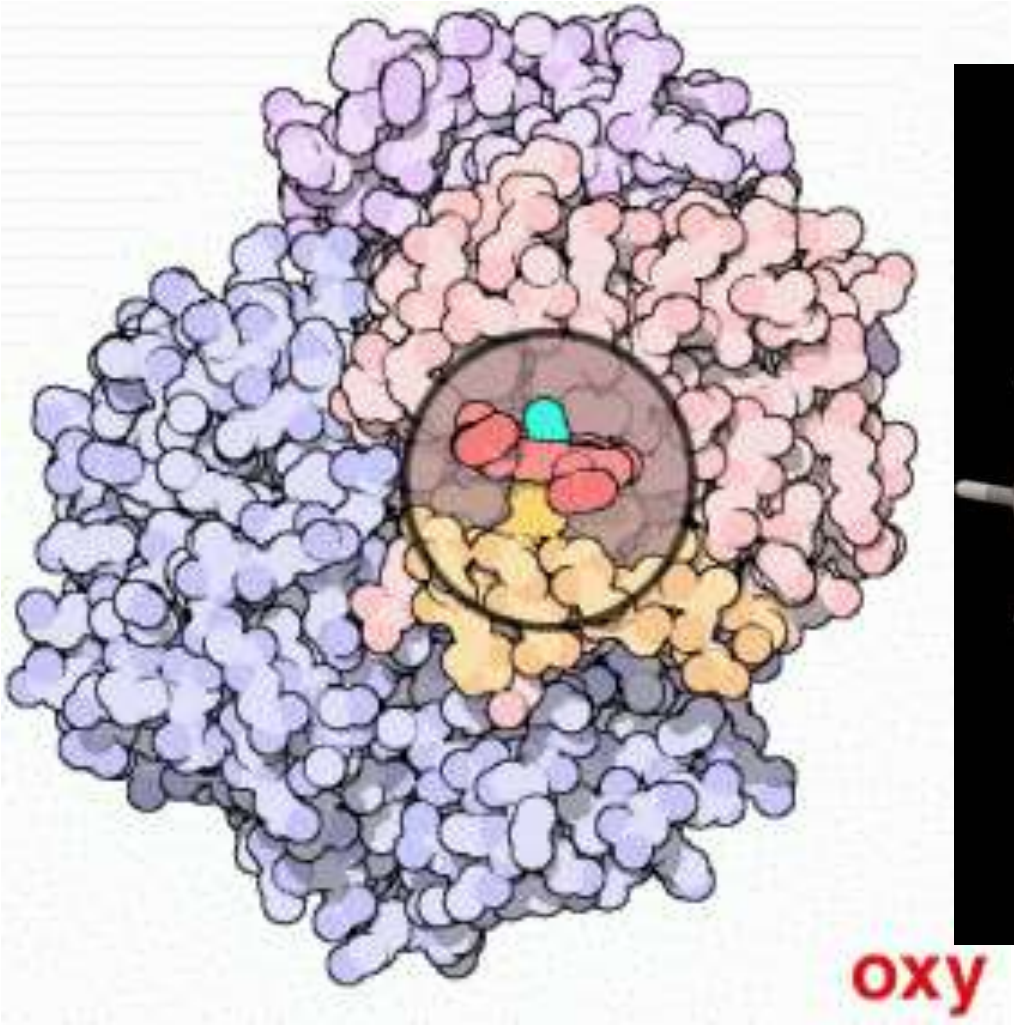
translated through H-bond network → Enhances the ability of other three units to bind O_2

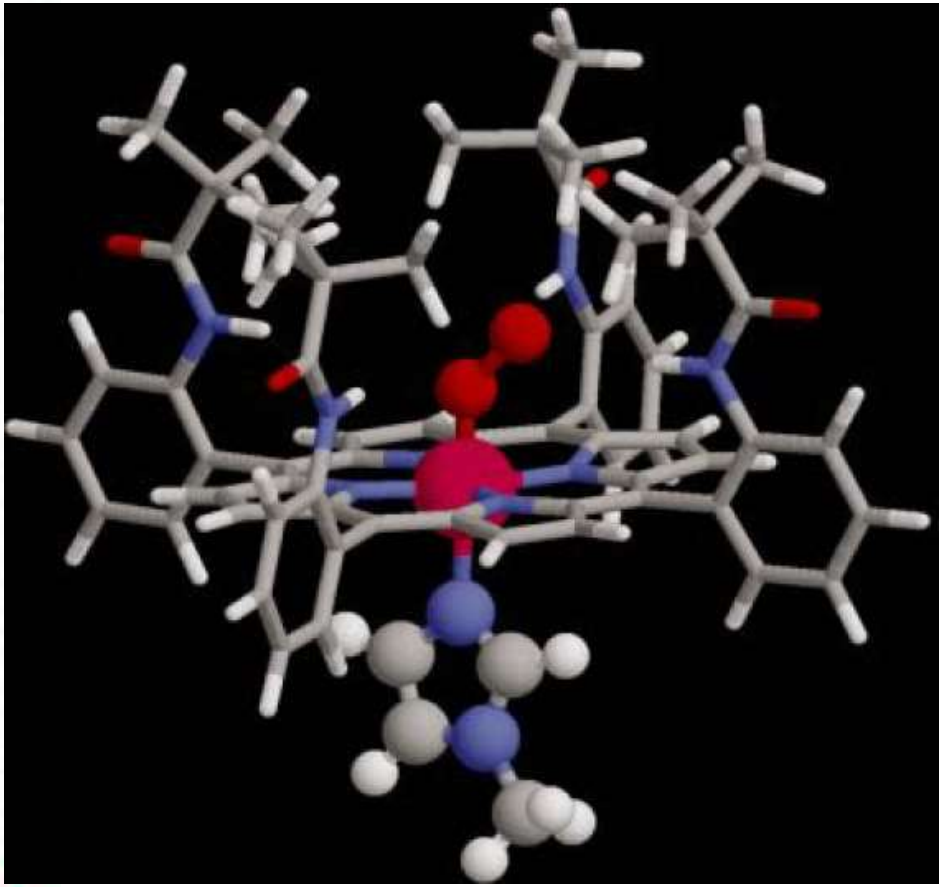
↓

This phenomenon is called cooperative effect

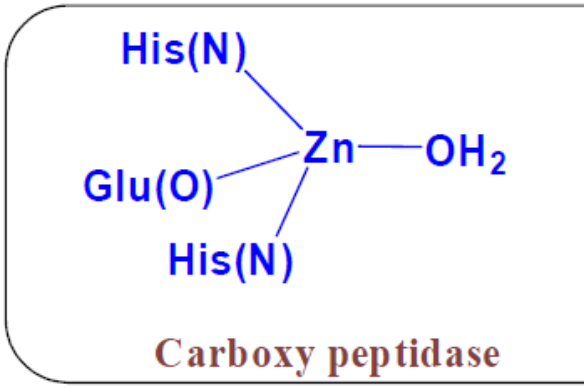
In a similar way when the blood reaches the muscle, only one O_2 is released, the others are released even more easily due to the cooperative effect in reverse

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



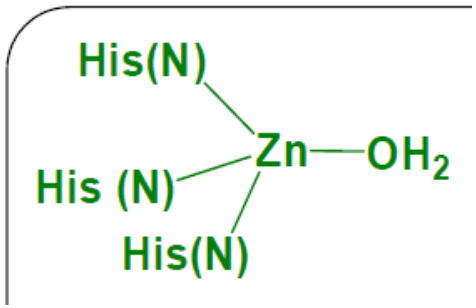


Active sites of some zinc based enzymes



Carboxy Peptidase

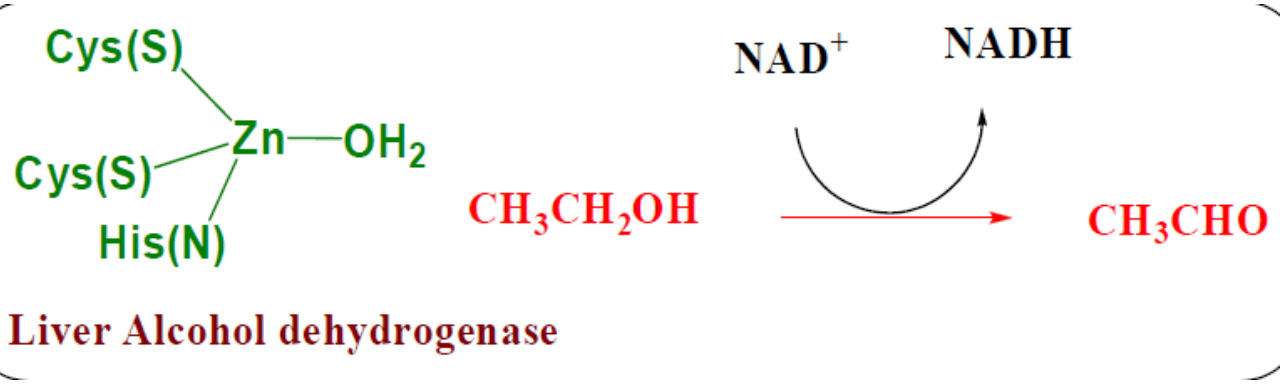
Peptide bonds of the proteins you consume are hydrolyzed, is known as peptide hydrolysis. This enzyme hydrolyzes the bonds from the terminal of the protein.



Carbonic Anhydrase

Removes CO_2 from blood and pH of the blood is maintained.

$H_2O + CO_2 \rightarrow \{H^+ + HCO_3^-\} H_2CO_3$

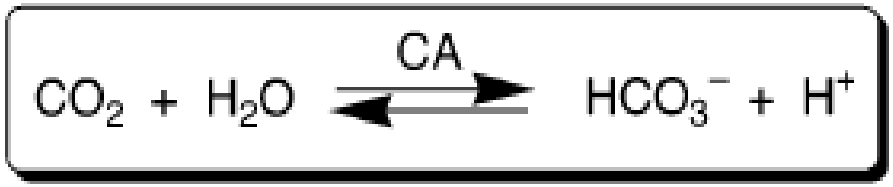


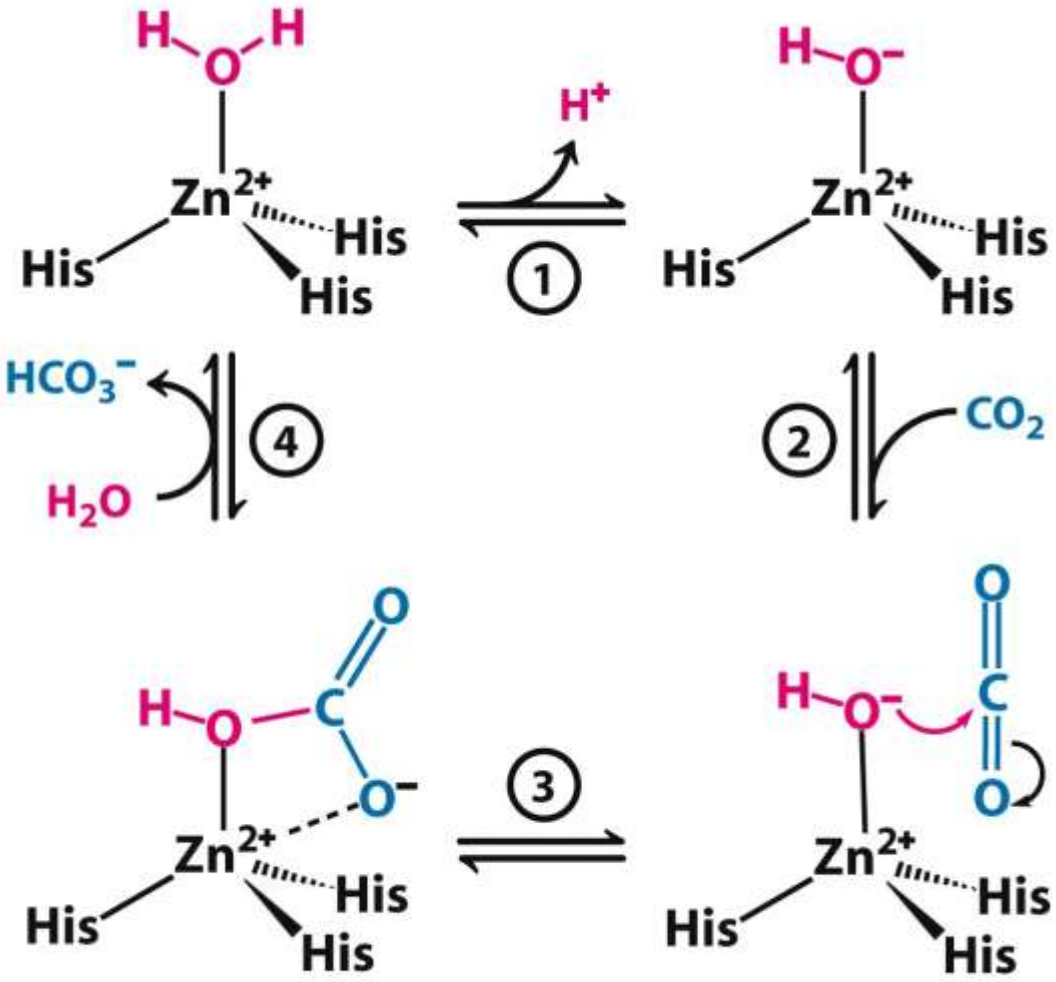
Liver Alcohol Dehydrogenase

This converts the alcohol present in the liver.

P.S.: Somebody who is not having this enzyme should not consume alcohol.

Carbonic anhydrase (CA) – Reactivity at the metal site

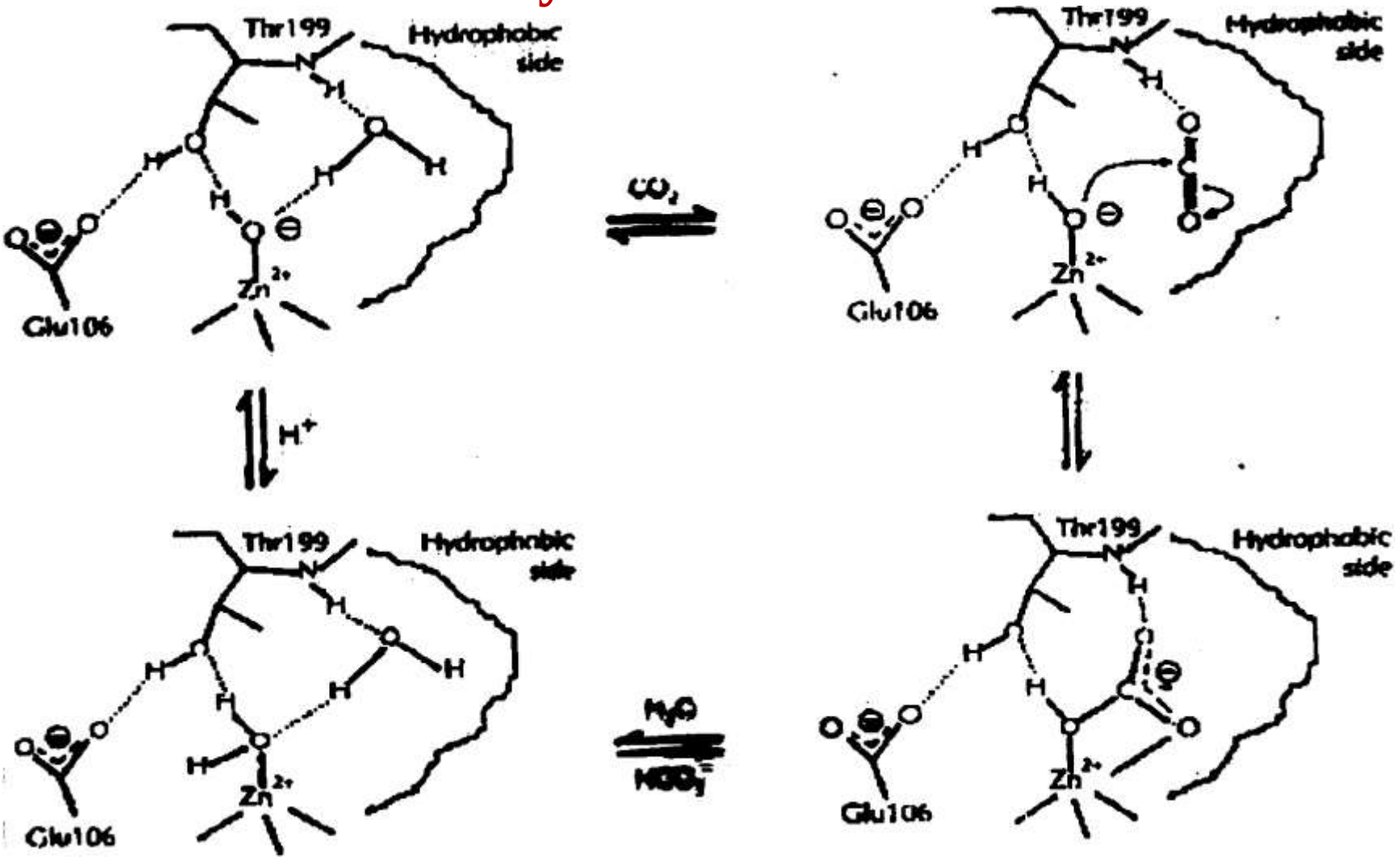




If this were to be the case, why protein is needed?

Figure 9.25
Biochemistry, Seventh Edition

Carbonic anhydrase – Role of Protein



For Substrate recognition; To bring selectivity in the reaction; To control reactant & product; To act in a catalytic manner

CH103 (Inorganic) – bioinorganic chemistry (tutorial)

Q01. What are storage and transport proteins? Draw the structure of porphin.
Q02. Why CN^- ion toxic to human?
Q03. What is the role of globular protein in oxygen transport?
Q04. What is "cooperative effect"?
Q05. Why are all the oxygen carriers that contain iron and porphyrins found inside the cells?
Q06. Why is the size of high spin Fe(II) is larger than the low spin Fe(II)?
Q07. What prevents synthetic iron porphyrins from functioning as O_2 carriers?
Q08. Why is CO toxic to O_2 binding proteins?
Q09. While the cis-platin is potent anticancer agent, its trans-isomer is not. Why?
Q10. Are you convinced with the statement that the coordination complexes are capable of acting as drugs for various health disorders. How & Why?