Bioinorganic Chemistry

What is bioinorganic chemistry?

- Intersection of classical inorganic chemistry and biology
  - Study of natural occurring inorganic elements in living systems
  - Study of metals introduced as probes or drugs
- Why is it important?
  - There are many metals that are essential to life.

Periodic table of life

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac															

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

Essential elements for humans (daily requirement: 25 mg)

Presumably essential elements

- Symptoms of deficiency: Mg (muscle cramps), Fe (animea), Mn (infertility)
- Toxic effects in case of high doses (therapeutic width)
- Occurrence of non essential elements (e.g. Rb: 1.1 g / 70 kg) and of contaminations (e.g. Hg)

Need for Metal Ions

- Metal ions must be obtained for growth and

Table 3.1 Approximate Elemental Composition of a Typical 70kg Human

Bulk elements and mineral ions

Oxygen	44 kg	Phosphorus	680 g
Carbon	12.6 kg	Potassium	250 g
Hydrogen	6.6 kg	Chlorine	115 g
Nitrogen	1.8 kg	Sulfur	100 g
Calcium	1.7 kg	Sodium	70 g
		Magnesium	42 g

Trace and ultra-trace elements

Iron	5000 mg	Barium	21 mg
Silicon	3000 mg	Molybdenum	14 mg
Zinc	1750 mg	Boron	14 mg
Rubidium	360 mg	Arsenic	~3 mg
Copper	280 mg	Cobalt	~3 mg
Strontium	280 mg	Chromium	~3 mg
Bromine	140 mg	Nickel	~3 mg
Tin	140 mg	Selenium	~2 mg
Manganese	70 mg	Lithium	~2 mg
Iodine	70 mg	Vanadium	~2 mg
Aluminum	35 mg		
Lead	35 mg		

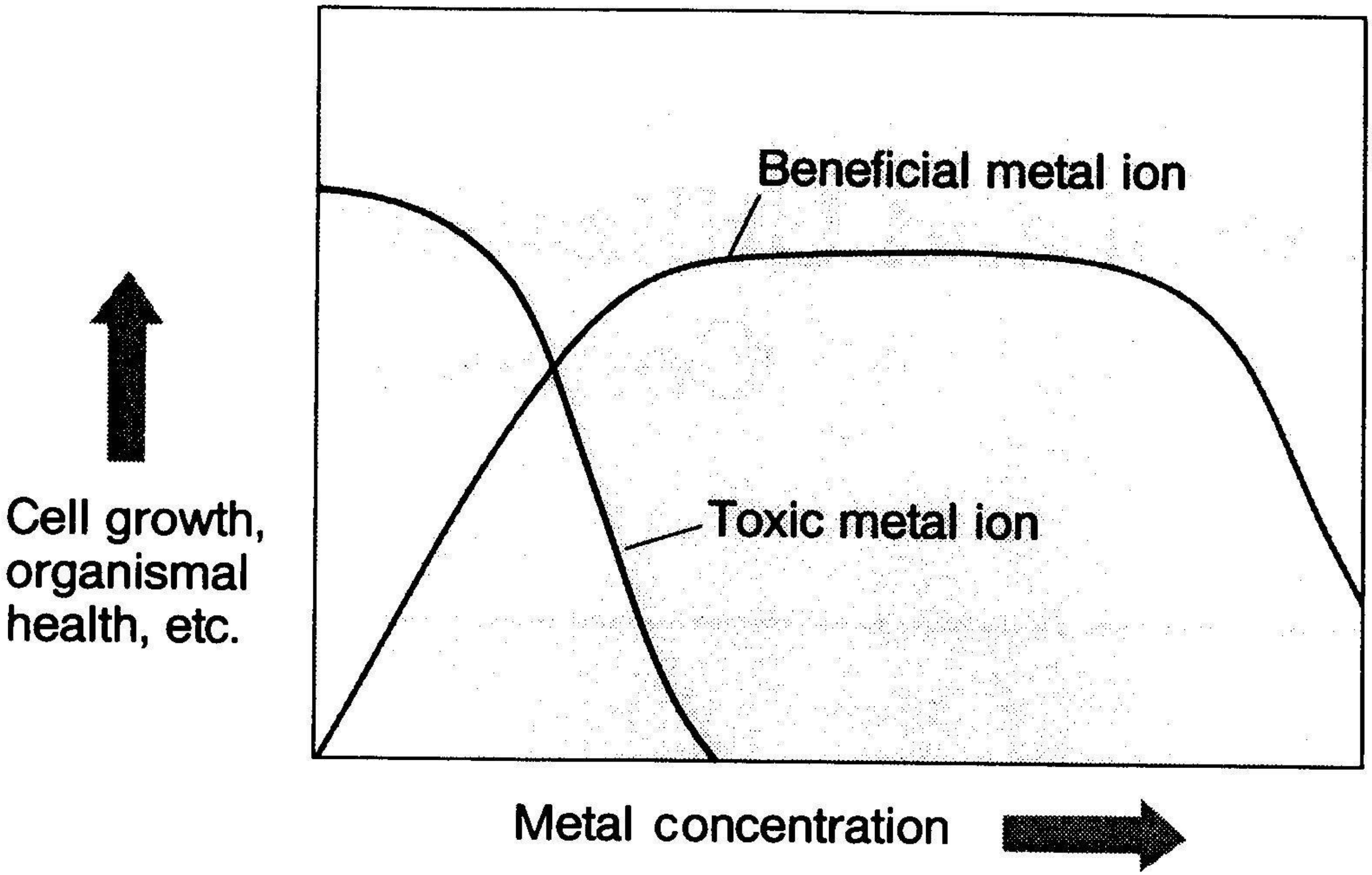
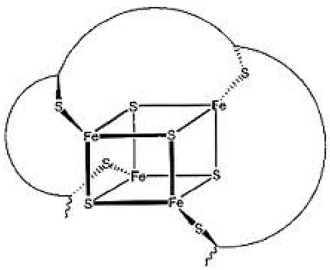


Figure 6.1
Representation of the concentration dependence of the toxic and beneficial effects of metal ions.

Roles of Metals in Biology

1. Metalloproteins
   - Dioxygen transport
     - Hemoglobin and hemocyanin
   - Electron transfer
     - iron-sulfur clusters, blue-copper proteins, and cytochromes
   - Structure
     - zinc finger proteins
       - nucleic acid-binding domains which regulate gene expression



Roles of Metals in Biology

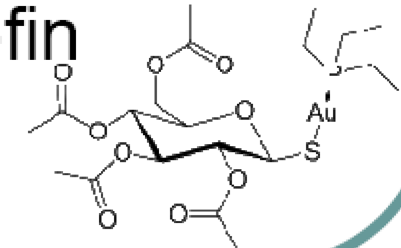
2. Metalloenzymes
   - Hydrolytic enzymes
     - Catalyze addition or removal of H or O in a substrate
   - Two-electron redox enzymes
     - Catalyze redox activity of substrate (e.g. removal O atoms from substrate)
   - Multielectron pair redox enzymes
     - $2H_2O \rightarrow O_2 + 4H^+ + 4e^-$

Roles of Metals in Biology

3. Cellular Communication
   - Cellular triggers
     - Na^+ flux across a cell membrane triggers neuron firing
     - Ca^{2+} has influence on muscle activity
   - Regulation of gene expression
     - Possible function of Zn^{2+} in zinc-finger proteins

Roles of Metals in Biology

4. Nucleic Acid Interactions
5. Ion Transport and Storage
6. Metals in Medicine
    - Diagnostic and therapeutic drugs
        - Historical: Hg^{2+} syphylis, Mg^{2+} for intestinal disorders, and Fe^{2+} for anemia
        - Current: cisplatin and auranofin

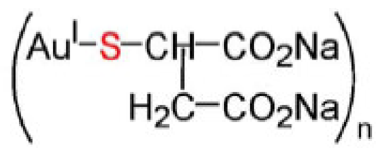


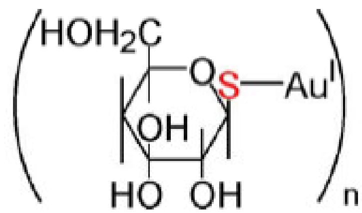
Application of metals in medicine

- Li^+: Treatment of depression (Li_2CO_3, low doses)
- Gd^{3+}: Contrast agent (NMR)
- $BaSO_4$: Contrast agent (radiography)
- ^{99}mTc: radio diagnostics (thyroid)

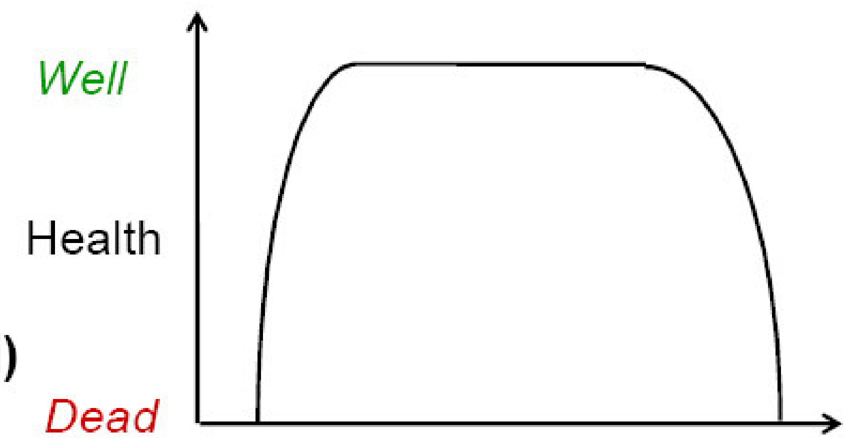
Technetium-99m or *99mTc* ("m" indicates that this is a metastable nuclear isomer) is used in radioactive isotope medical tests

- Au(I): Rheumatism



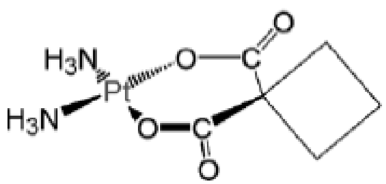


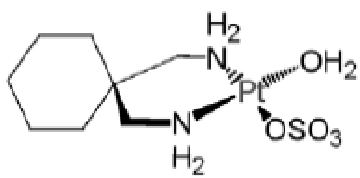
- Sb(III): Eczema
- Bi(III): Gastric ulcer
- Cd: Carboanhydrase (Thalassiosira weissflogii)

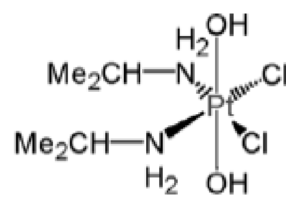


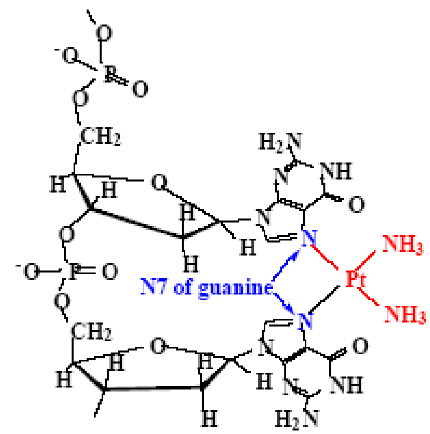
Application of metals in medicine

- Pt(II): Cisplatin (*cis*-[Pt(NH_3)$_2$Cl$_2$]), chemotherapy (inhibition of cell division, not cell growth)







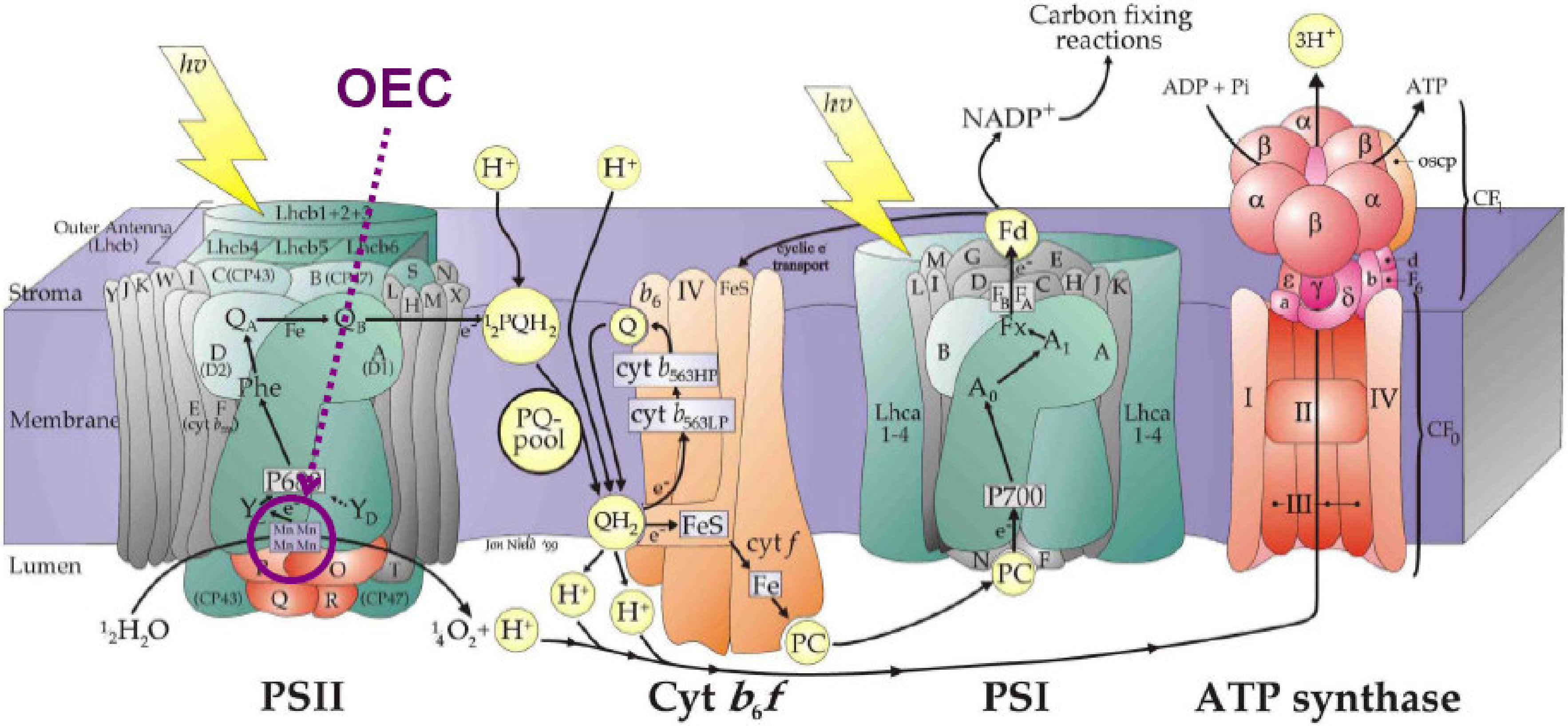


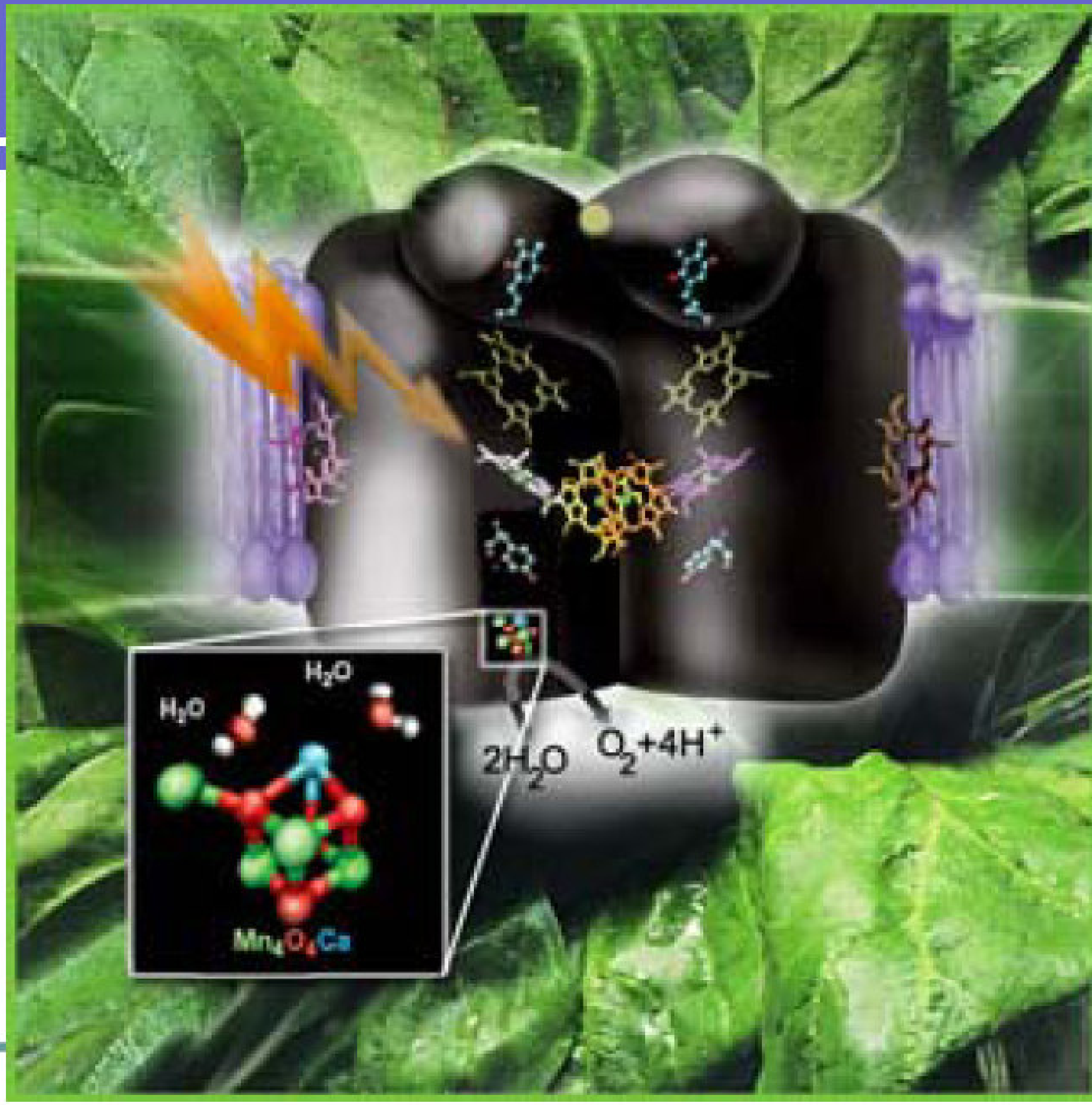
- Filamentous growth of bacteria

Oxygen Evolving Complex (OEC) in Photosystem II (PSII)

- Component of photosynthesis in all green plants
- Active site contains
  - 4 Mn atoms with oxo bridges
  - Ca^{2+} ions
  - Overall cluster structure is unknown
- Catalyzes rxn: $2H_2O \rightarrow O_2 + 4H^+ + 4e^-$
  - This manganese complex produced all the oxygen in the world!
- Energy from light drives this thermodynamically uphill process

Components of Photosynthesis





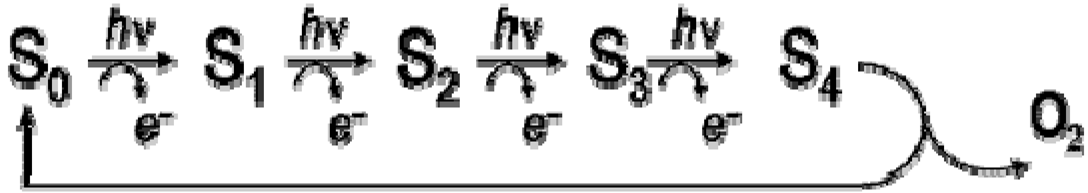
H₂O
H₂O
Mn₄O₄Ca
2H₂O
O₂+4H⁺

Function of the Photosystems

- In PSII, energy captured from light is used to split water into oxygen molecules and hydrogen ions, freeing electrons in the process.
  - $2H_2O \rightarrow O_2 + 4H^+ + 4e^-$
- The electrons are transported to PSI (photosystem I) then to the Calvin cycle
  - $CO_2 \rightarrow$ sugar

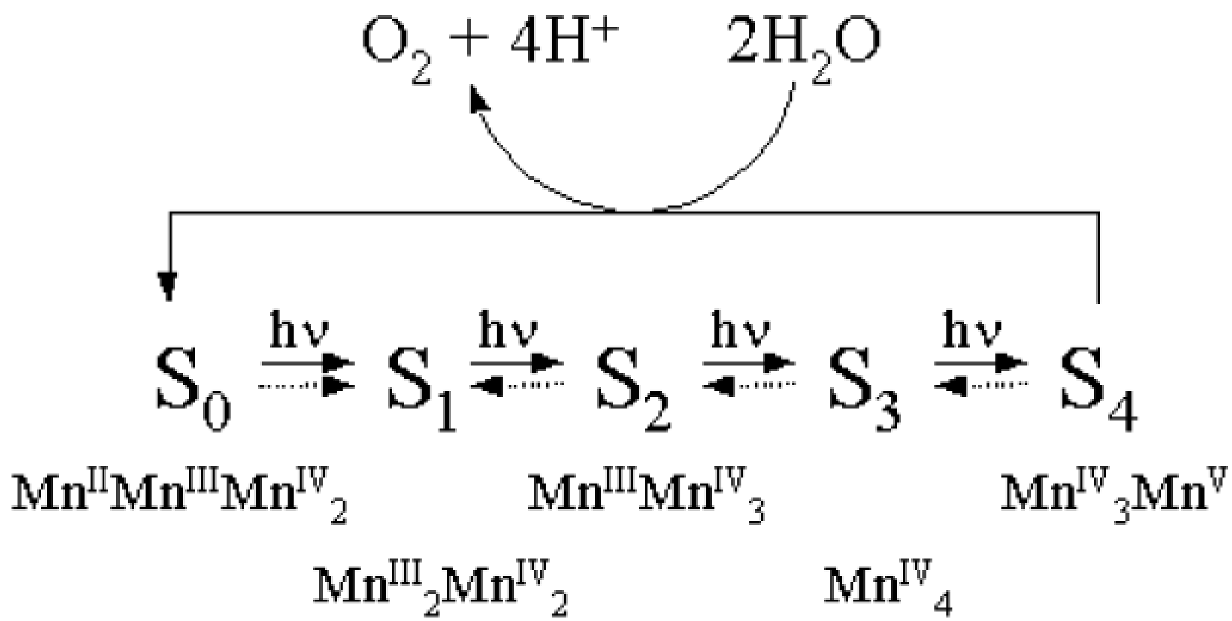
Mn Cluster

- Proceeds thru multiple oxidation states of Mn atoms (stable at 2^+, 3^+, 4^+ and 5^+) known as S-states.
- Each photon can access next highest state until S_4 is reached, O_2 is released and the cycle begins again
- Exact mechanism and structure still being studied



Proposed Oxidation States

- 4 total photons (hν) required for activity

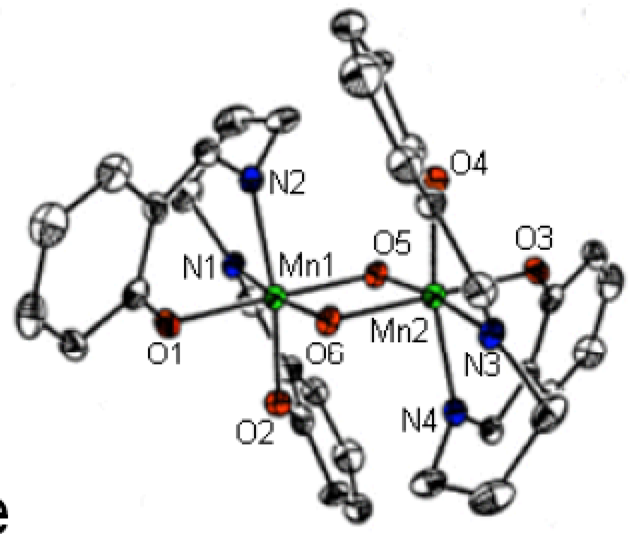


Small Model Systems

- Many small inorganic model complexes have been developed to model these mixed-valent Mn centers.
- Various goals
  - Give an insight into the high-valent Mn chemistry in aqueous media
  - Understand preference and structural requirements for oxidation states
  - Duplicate reactivity

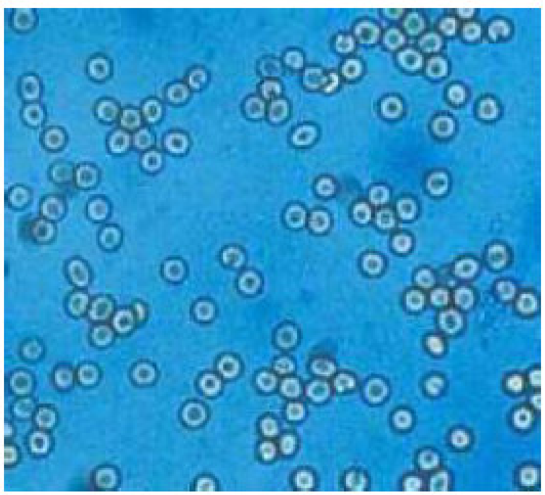
From Univ. of Michigan, V. Pecoraro's Group

- $[Mn^{IV}(salpn)(\mu\text{-}O)]_2$ structurally resembles the OEC Mn-cluster
  - Mn-Mn distance (2.7 Å) is equal to the distance deduced for the the lower S-states
  - Contains bis-oxo bridges like the proposed structure

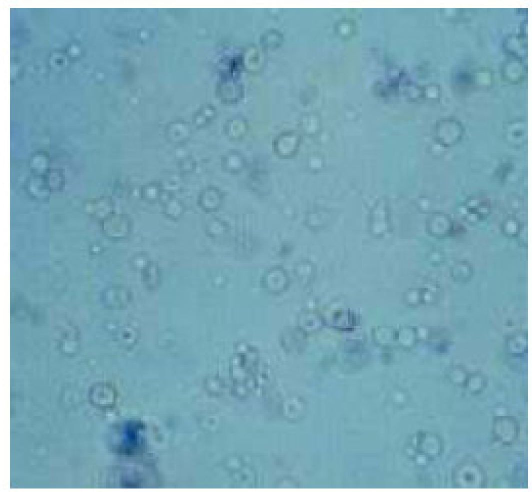


Hemoglobin

- O_2 transporter for all vertebrates
  - dioxygen removed from the air in lungs and delivered to Myoglobin in tissues (e.g. muscles)
  - dependent upon Fe.



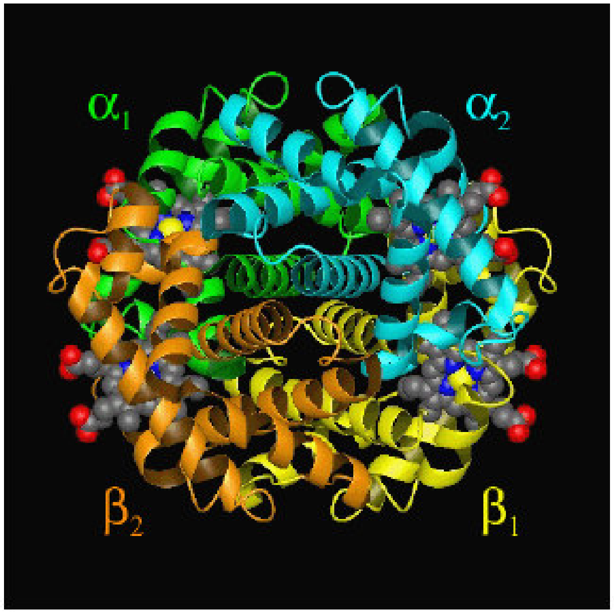
Oxygenated



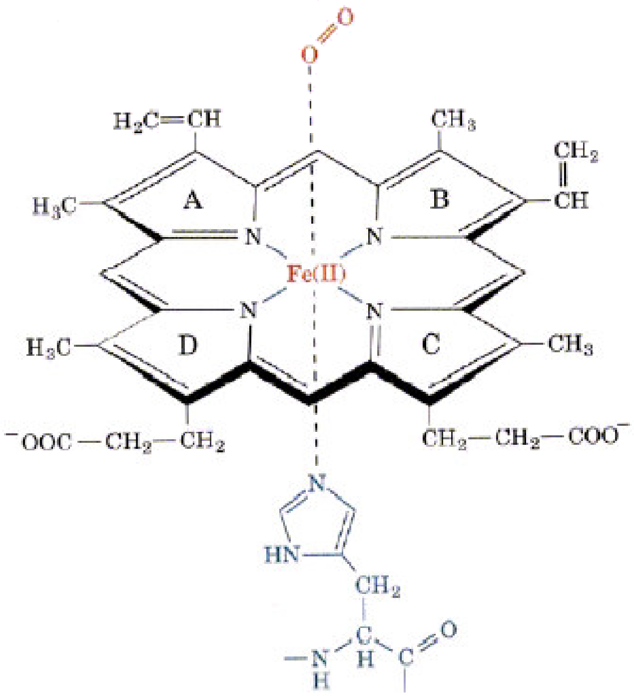
Poorly oxygenated

Structure of Hemoglobin

- Multisubunit protein, 2 α and 2 β peptides

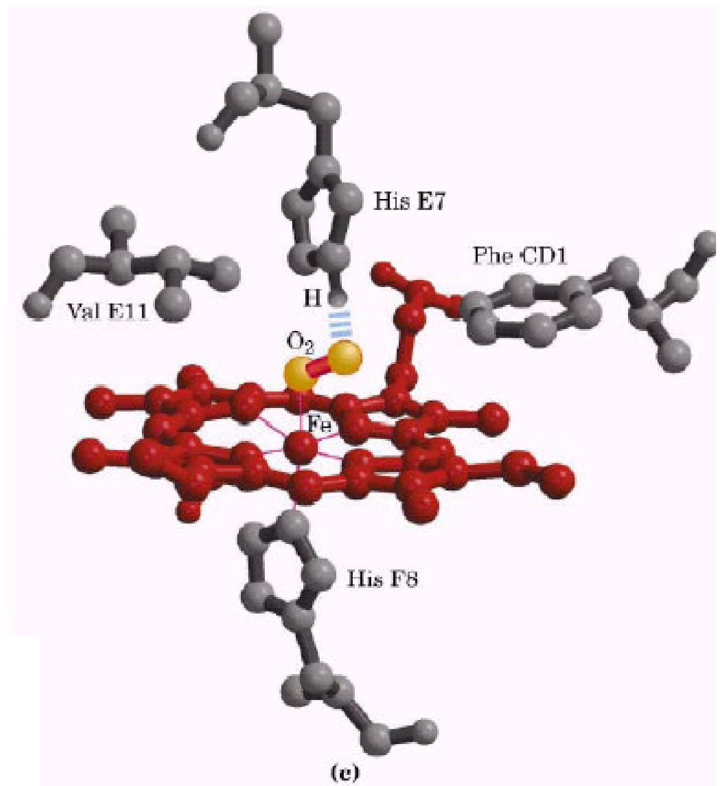


- 4 Iron-porphyrin rings, each can bind 1 O_2



Visualizing O_2 Binding

- O_2 approaches and binds to Fe^{2+} (ferrous)
- Electron transfer oxidizes Fe to 3+ (ferric)
- A distal histadine residue forms a H-bond to the bound O_2

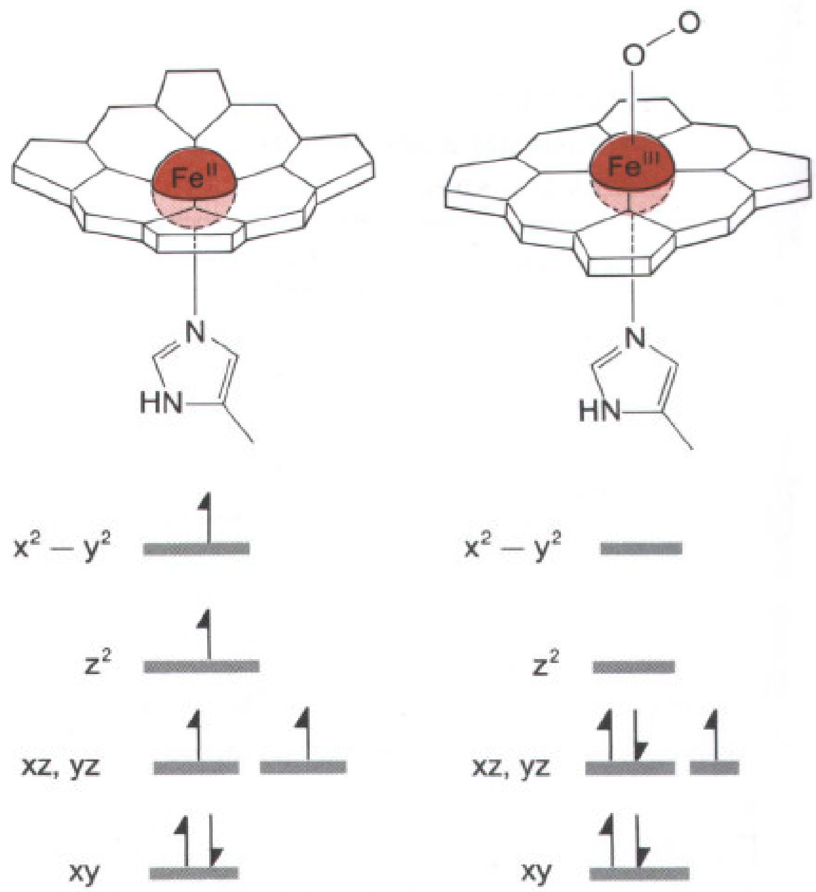


Iron Function in Hemoglobin

- Iron oxidized from 2+ (deoxy) to 3+ (oxy)
- The electronic configuration of the metal dictates O_2 binding
  - Deoxy form: high spin Fe^{2+} "bends" porphyrin ring to have a shortened Fe-N(his) bond.
  - Oxy form: after binding O_2, the low spin Fe^{3+}-N(his) bond lengthens, the porphyrin ring becomes more planar, and the Fe moves further into the plane
- Quaternary structure of the protein also changes thru deoxy-oxy cycle

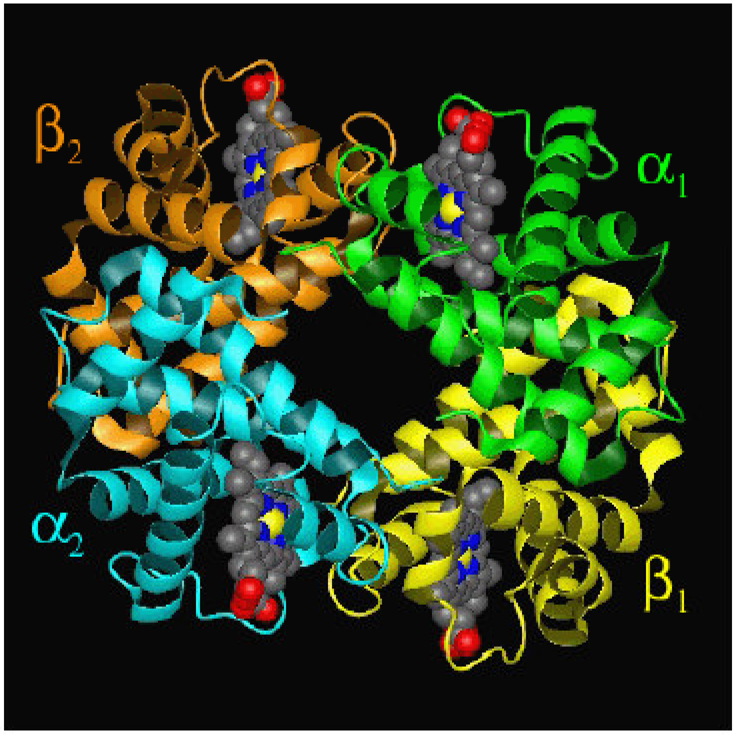
Electronic changes in Fe upon binding of O_2

- $Fe^{2+} \rightarrow Fe^{3+}$
- hs $\rightarrow$ ls
- Porphyrin ring becomes more planar
- Lengthening of Fe-N(his) bond anchoring heme

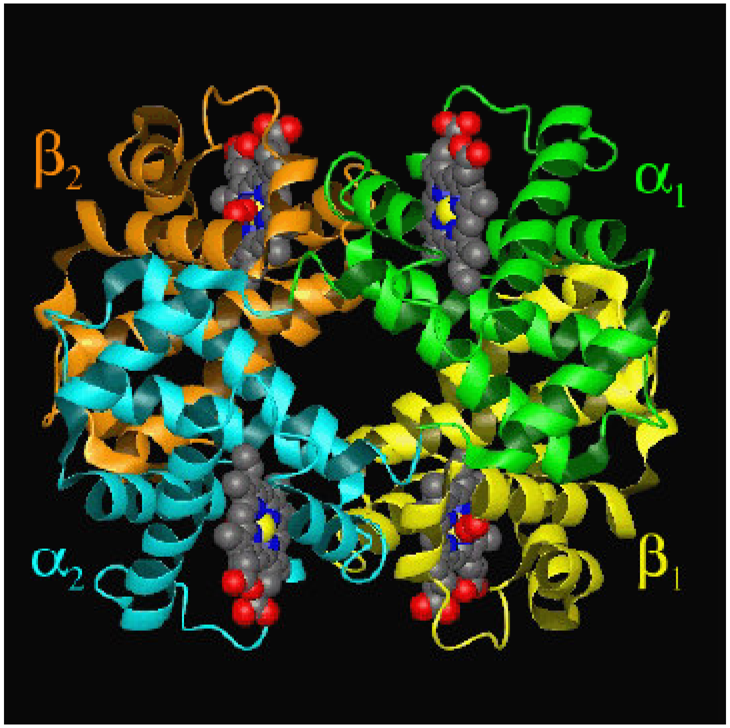


Quaternary structure changes upon binding of O_2 *(top view)*

Deoxy

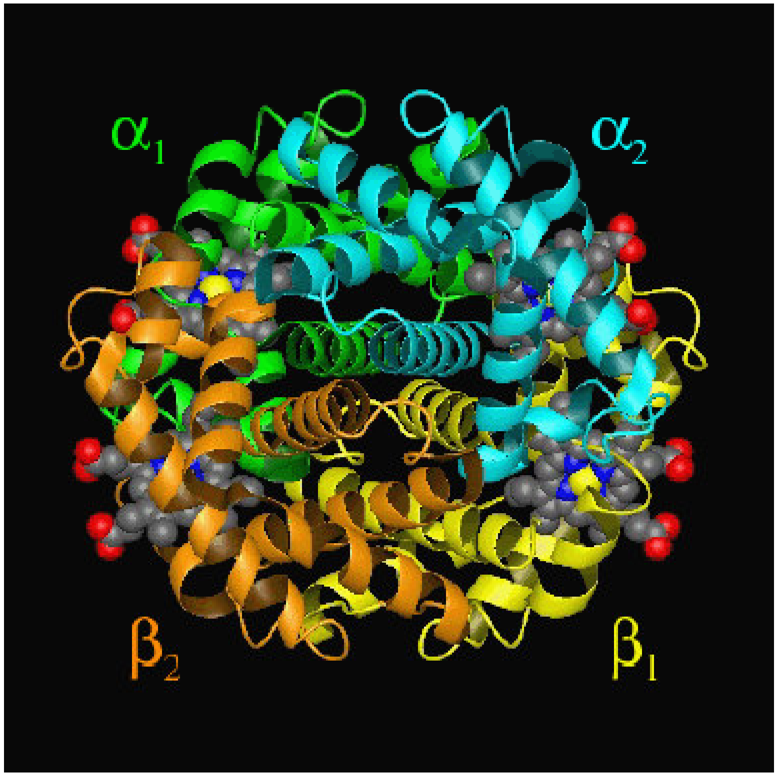


Oxy *(red O_2 on hemes)*

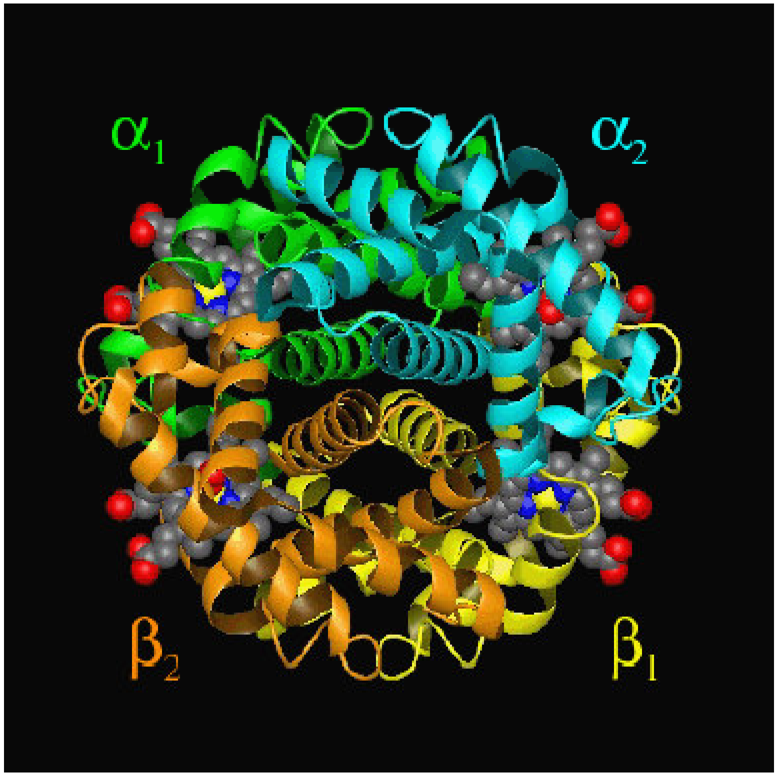


Quaternary structure changes upon binding of O_2 *(side view)*

Deoxy

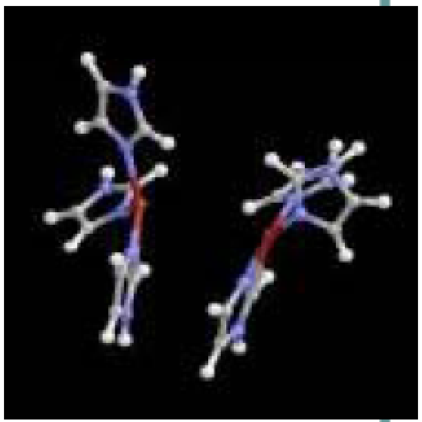


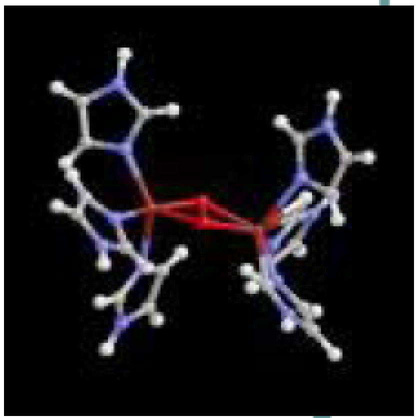
Oxy



Hemocyanin

- Very large oxygen transport protein (4x the size of Hb, >400,000 amu)
- Found only in arthropods and mollusks (e.g. lobsters and crabs)
- No heme group
- Deoxy form is colorless
- Two Cu^{1+} (d^9) atoms anchored by histadine residues are oxidized to Cu^{2+} upon binding O_2

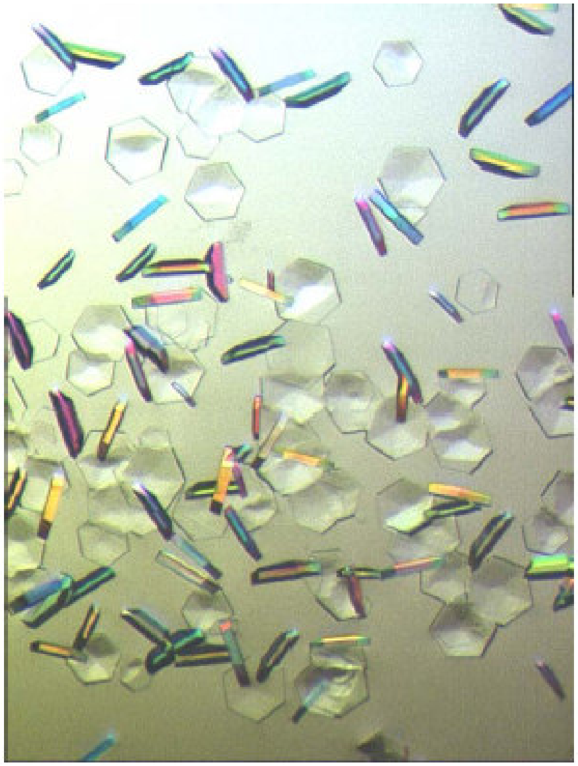




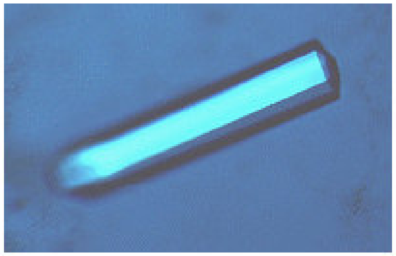
Physical Methods

- Protein X-ray Crystallography
  - When a single ordered crystal can be grown, X-ray diffraction can be used to determine the exact molecular structure of the protein
  - Actually identifies the position of each atom by measuring how the crystal diffracts X-rays
  - Very time consuming, may require months or years to determine structure
  - Resulting structure will bring much insight into the function and mechanism of the protein

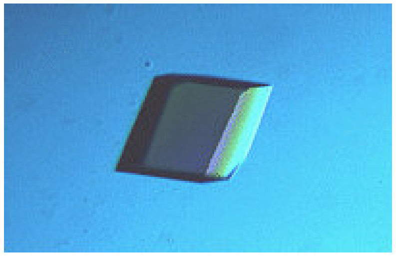
Example Protein Crystals



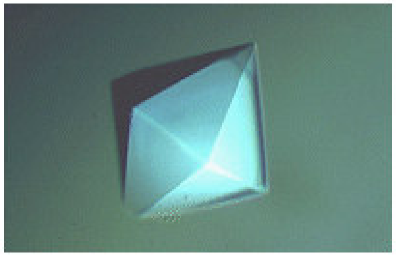
Hexagonal protein crystals of glycosol hydrolase.



hexagonal rod



trigonal



hexagonal bipyramid

Physical Methods

- Electron Paramagnetic Resonance, EPR
  - Samples with unpaired electrons yield unique EPR signatures; ideal for metalloproteins with metals (e.g. Cu^{2+} and Fe^{3+})
  - Useful in determining metal coordination environments and oxidation states
    - Can distinguish between high and low spin Fe^{3+}
    - Signal intensity can be followed to measure protein purification steps

Physical Methods

- Vibrational Spectroscopy
  - Molecular vibrations of proteins are very complex (100's of atoms, complex structure)
  - Resonance Raman (rR) spectroscopy can be used to identify molecular vibrations coupled to electronic transtions
  - In hemoglobin, by monitoring the O=O stretching frequency, rR can identify when the protein is in the deoxy or oxy form.

Summary

- Bioinorganic chemistry is everywhere!
- Transition metals have fundamental roles in biological processes
  - Hemoglobin ($Fe^{2+} \rightarrow Fe^{3+}$)
  - Hemocyanin ($2\ Cu^{1+} \rightarrow 2\ Cu^{2+}$)
  - OEC (4 Mn of varying oxidation states)
- Various physical methods are used to study bioinorganic systems
  - Including X-ray crystallography, EPR, and vibrational spectroscopy