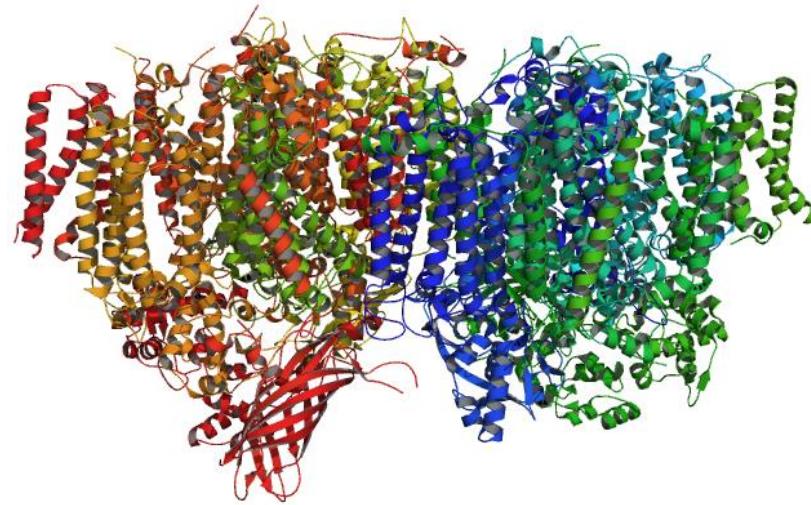
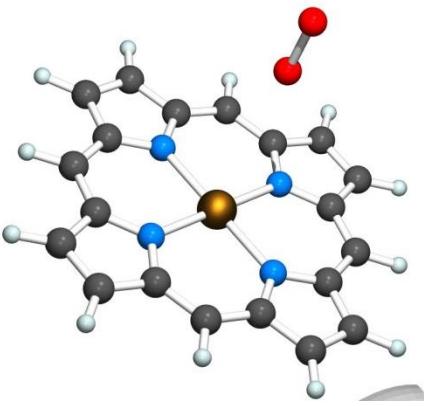
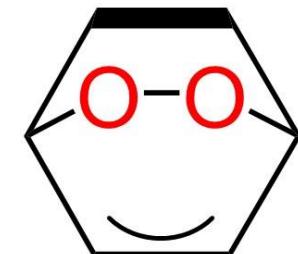


Bioinorganic Chemistry (BIC): CH316

I. Course Introduction & Overview: Coordination Chemistry ($M-L_{bio}$)



Dr. ($O_6S_4C_4Ar$) Lung Wa CHUNG(钟龙华)
(oscarchung@sustech.edu.cn)
Department of Chemistry



2022年春-生物无机...

群号: 300019856



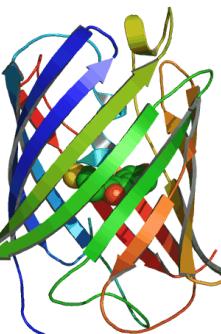
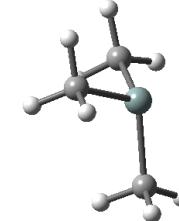
**Our Course
Material &
Discussion
Group**

My Quick Personal Profile



- **2000** The Hong Kong University of Science & Technology, B.Sc. (1st Hon.) & Academic Achievement Medal (GGA: A)
- **2006** The Hong Kong University of Science & Technology, Ph.D. (Supervisor: Prof. Yun-Dong Wu)

Computational Studies of Mechanism of Metal-Catalyzed Organic Reactions



- **2006-2013** Fukui Institute for Fundamental Chemistry, Kyoto University (Advisor: Prof. Keiji Morokuma, student of 2 Nobel Prize Winners: Profs. Fukui & Karplus)

Multi-Scale Simulations of Complex Systems



- **2013(Oct)** SUSTech

Multi-Scale **Simulations** of Complex Chemical, Biochemical & Biophysical Systems, including Bioinorganic (Fe (Heme), Co (B12), Ni, Cu, Zn)



**Computational (Bio-)Chemistry
(Virtual (Bio-)Chemical Reactions)**

Course Description

Bioinorganic Chemistry (or metals in biology): a *cross-discipline* course, covering *inorganic, organic and physical chemistry & biochemistry* (one of the most complex subjects in chemistry).

- Target to senior undergraduate students who develop a **strong background in inorganic chemistry & have interests in biological inorganic systems.**
- Introduce/outline basic & sometimes frontier (NOT COMPREHENSIVE & detailed) knowledge of bioinorganic chemistry, such as general **structures, functions (properties)** and **chemical reactions** of some representative bioinorganic systems.

References & Textbook

Textbook is NOT required; Lectures notes are the key for this course; **No need memorize many info., but know the key points & concepts!!**

1. “Biological Inorganic Chemistry”, Bertini, I.; Gray, H. B.; Stiefel, E. I., Valentine, J. S. Eds. University Science Book, 2007. (main)
2. “Biological Inorganic Chemistry: A New Introduction to Molecular Structure and Function”, (2nd Ed.) Robert R. Crichton. Elsevier, 2012. (main)
3. “Bioinorganic Chemistry: A Short Course”, (2nd Ed.) Roat-Malone, R. John Wiley & Sons, Inc., 2007.
4. “生物无机化学导论(第3版)” 计亮年, 毛宗万, 黄锦汪. 科学出版社2010. Or “生物无机化学” 郭子建, 孙为银2014.

Grading (Total: 100 %)

- A. One Quiz** (~40 mins: multiple-choice, and 1-2 mechanism or “metal-cluster” questions): **40%**
- B. Class Performance:** **10%**

Group project (~2 persons as a group):
choose to review **ANY** bioinorganic (**with metal(s)**) systems you like.

- C. Professional Essay** (~4 pages with ACS style & template): **30%**;

- D. Presentation** (~10-12 min): **20%**

- **30 Apr (11:59 pm)**: Proposal submission (tentative title & members) deadline (email to TA)
- **5 Jun (11:59 pm)**: Essay submission deadline (email to TA)

Tentative Lecture Outline (TBD)

| Week (dates) | Topics |
|----------------------------|---|
| 1 (18 Feb) | I. Introduction & Overview: Coordination Chemistry |
| 2 (25 Feb) | II. Metal Ions & Proteins: Binding, Folding Transport & Storage |
| 3-4 (4 & 11 Mar) | III. Hydrolytic Chemistry |
| 5-6 (18 & 25 Mar) | IV. Electron Transfer, Respiration & Photosynthesis |
| 7 (1 Apr) | V. Metals in Medicine |
| 7-9 (1, 8 & 15 Apr) | VI. Oxygen Metabolism |
| 10-12 (22 & 29 Apr; 6 May) | VII. Hydrogen, Carbon, & Nitrogen Metabolism |
| 12-14 (6, 13 & 20 May) | VIII. Metalloenzymes with Radical Intermediates |
| 14 (20 May) | Student Presentation |
| 15 (27 May) | Course Review & Quiz |
| 16 (5 Jun) | Essay Submission Deadline |

**What is
Bioinorganic
Chemistry?**

A rough definition:

Organic Chemistry: structure, properties, & reactions of organic molecules containing **carbon** (element; and usually with hydrogen).

Inorganic Chemistry: chemistry for all molecules (with all elements) **except organic** molecules.

Biochemistry: chemistry in biological system (living organisms).

Bioorganic Chemistry: organic molecules or reaction in biological system, e.g. DNA, glucose.

Bioinorganic Chemistry: **usually** focusing **metal-** containing molecules & their reactions in biological system, e.g. hemoglobin (Fe).

The Important Roles of BIC

Metals (+ biological (macro)molecules as a ligand (L_{bio}) and environment) play important roles in our lives and all living organisms.

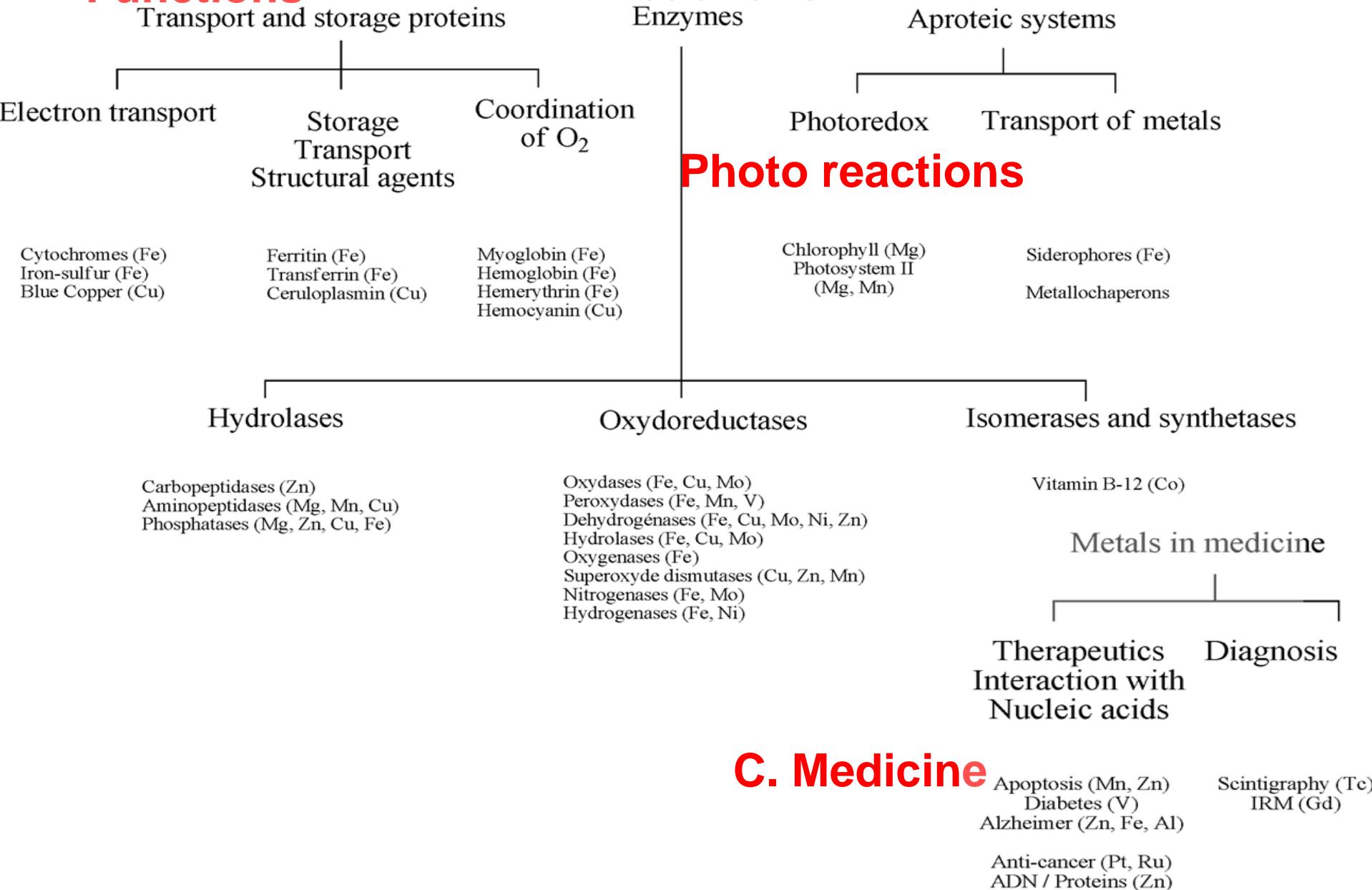
E.g. molecular **mechanisms of life** (O_2 transfer and storage), **photosynthesis**, N_2 **fixation**: **highly selective, efficient & regulated** processes and (sometimes challenging) reactions.

General roles (with $M-L_{bio}$):

- 1. Structures**: stability & folding/shape
- 2. Functions**: storage/transport of small molecules, pKa, electron-transfer, electrolytes
- 3. Chemical reactions**: various enzymatic reactions
- 4. Medicine**: e.g. anti-cancer drug cis-Platin (Pt)

A. Structures & Functions

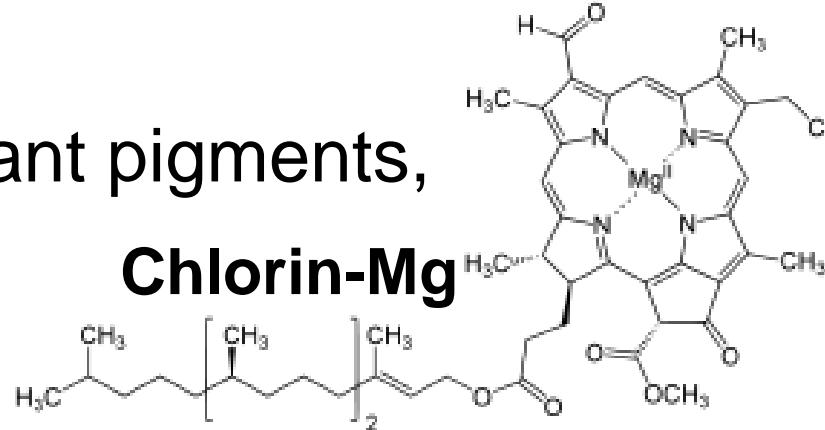
Overview



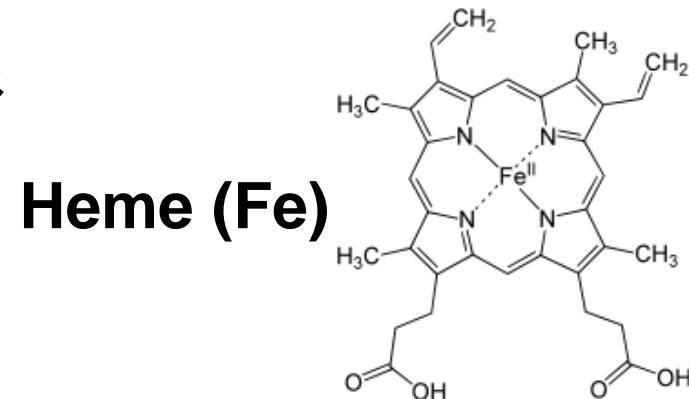


Strong BIC-relevant Nobel Prizes

1915: "for his researches on plant pigments, especially chlorophyll" (**Mg**)



1930: "for his researches into the constitution of haemin (heme) & chlorophyll and especially for his synthesis of haemin" (**Fe**)



1931: "for his discovery of the nature and mode of action of the respiratory enzyme" (Heme, **Fe**)

1946: "for his discovery that enzymes can be crystallized" (e.g. urease, **Ni**)

1955: "for his discoveries concerning the nature & mode of action of oxidation enzymes" (e.g. peroxidase, **Fe**)

1961: "for his research on the carbon dioxide assimilation in plants" (e.g. ribulose-1,5-bisphosphate carboxylase, **Mg**)

1962: "for their studies of the structures of globular proteins" (hemoglobin & myoglobin, **Fe**)

1964: "for her determinations by X-ray techniques of the structures of important biochemical substances" (B12, **Co**)

1978: "for the discovery of restriction enzymes..." (restriction endonuclease, e.g. **Mg**)

1988: "for their determination of the 3-dimensional structure of a photosynthetic reaction center" (**Mn, Ca**)

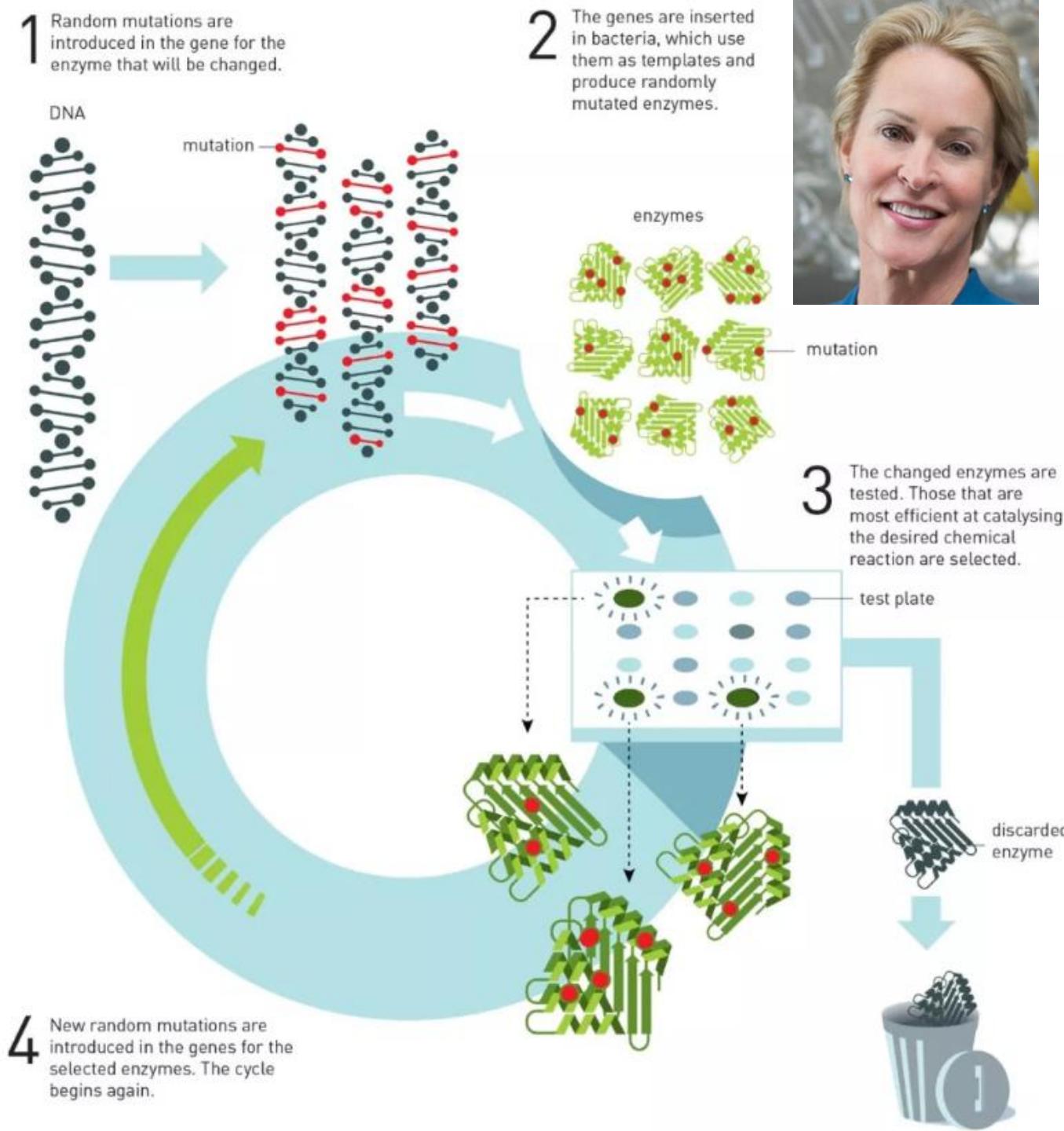
1989: "for their discovery of catalytic properties of RNA" (e.g. **Mg, Mn**)

1997: "for the first discovery of an ion-transporting enzyme, **Na⁺, K⁺-ATPase**"

2003: "for discoveries concerning channels in cell membranes [...] for structural and mechanistic studies of ion channels" (**K⁺**)

2018: "for the directed evolution of enzymes" (e.g. artificial heme enzymes, **Fe**)

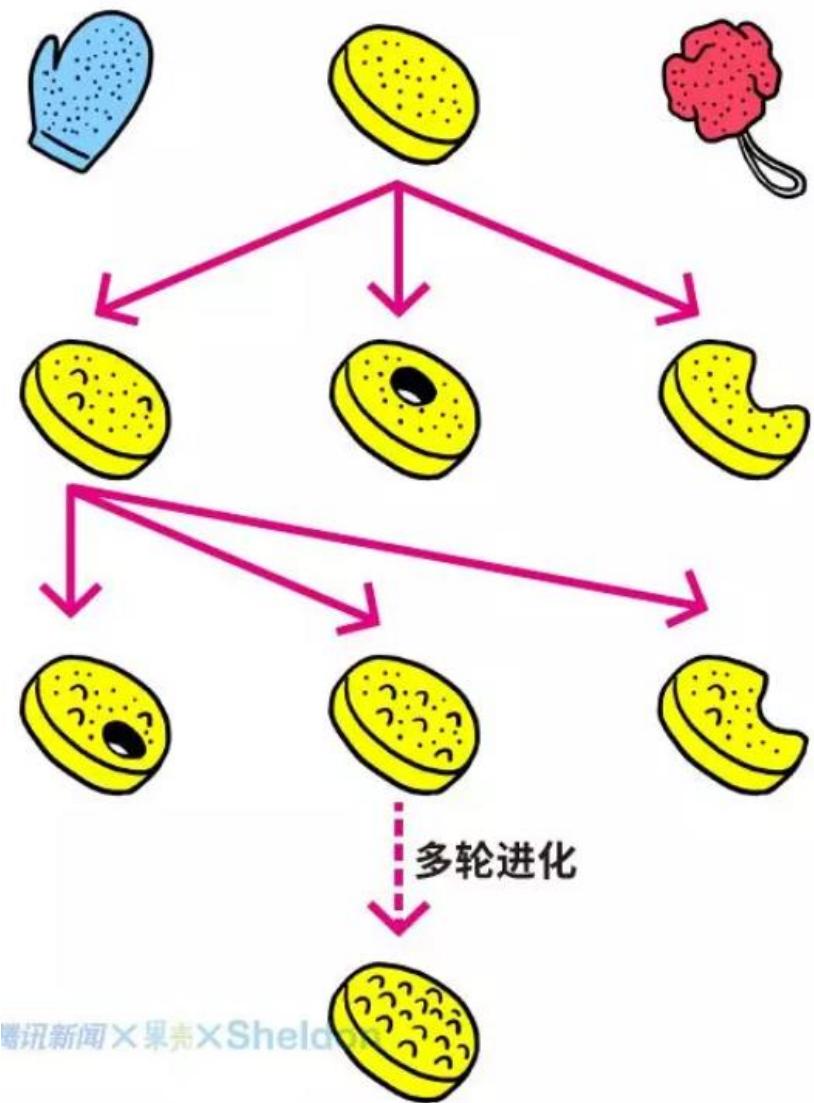
2018: Directed Evolution of New or Artificial Enzymes



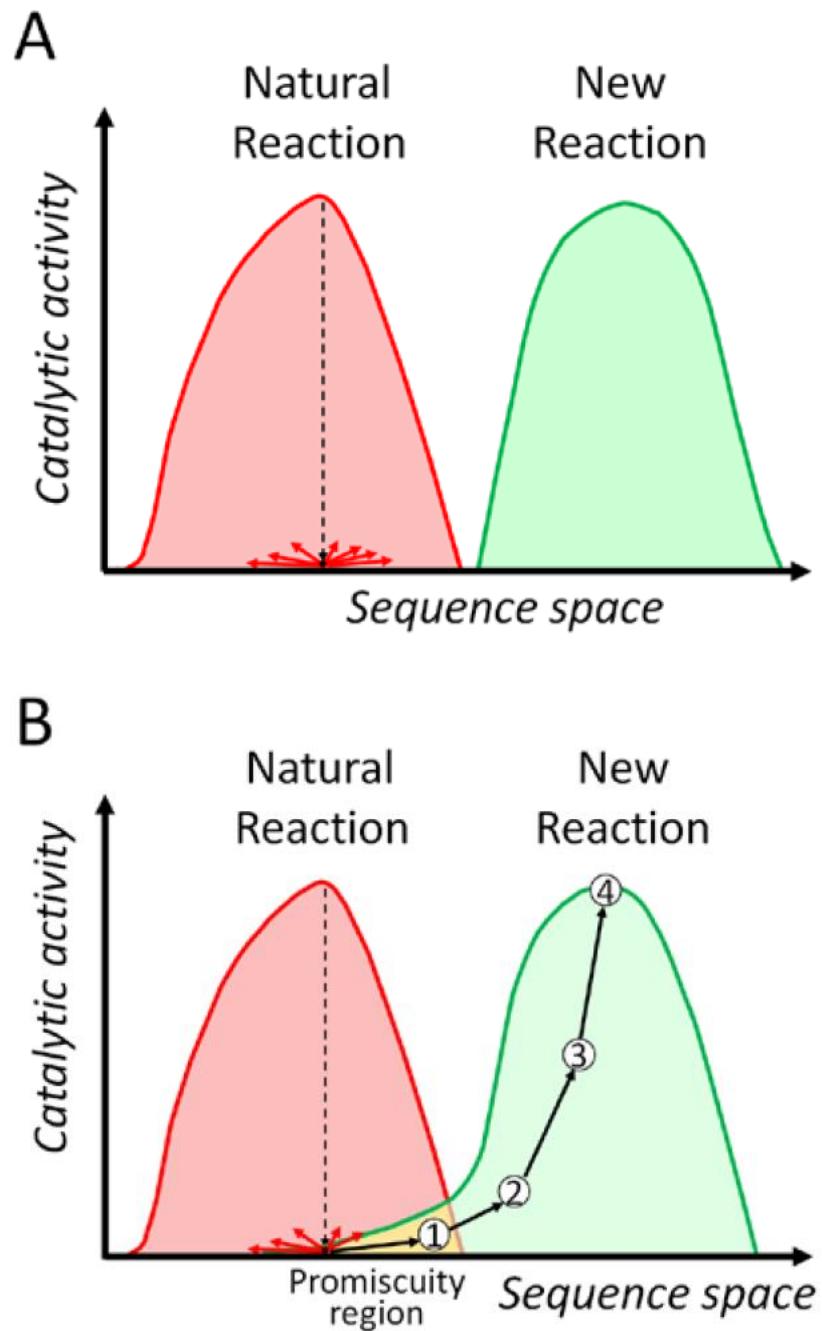
manufacture from biofuels to pharmaceuticals

genetic change & selection – to develop proteins that solve mankind's chemical problems

搓澡巾(蛋白酶)的定向进化

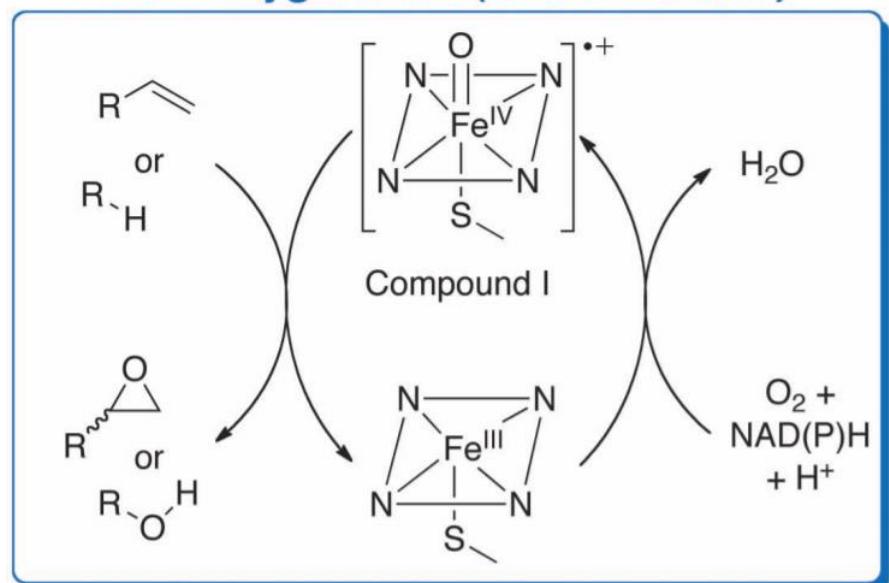


最好的搓澡巾(蛋白酶)

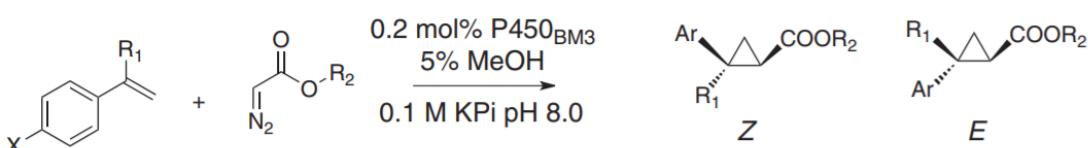
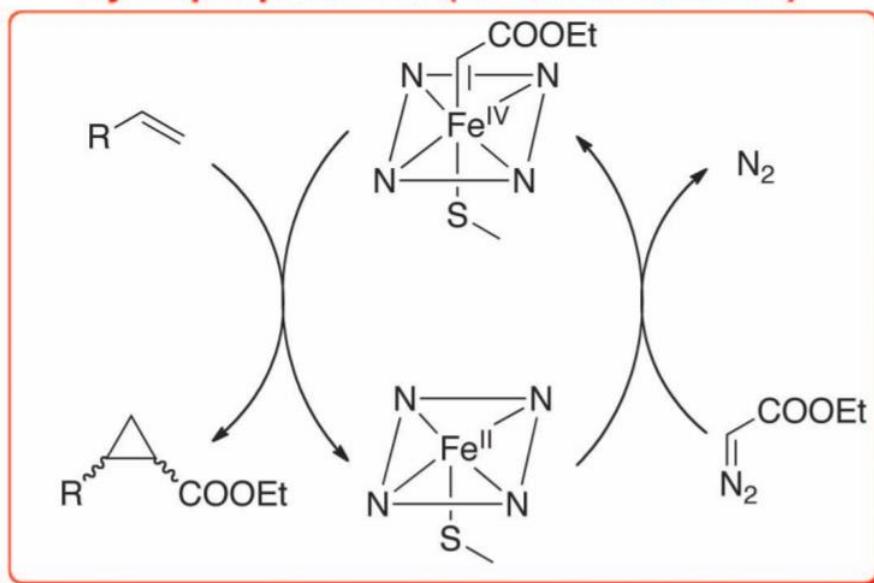


Olefin Cyclopropanation via Carbene Transfer Catalyzed by Engineered Cytochrome P450 Enzymes

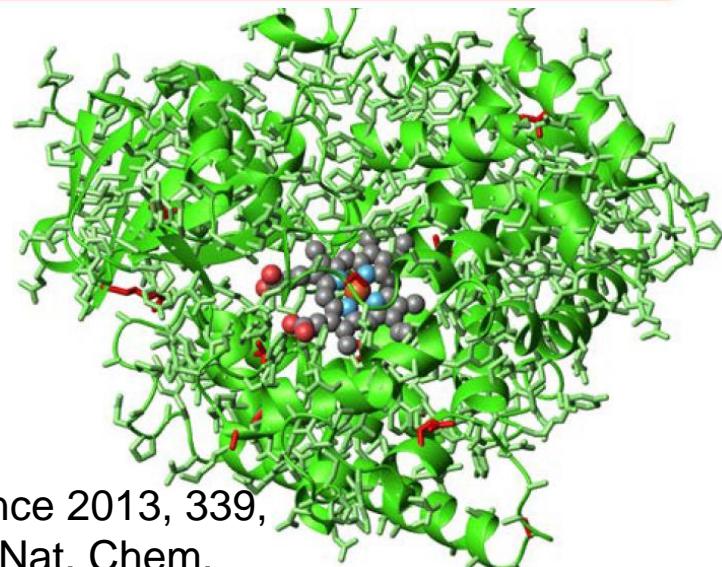
Monooxygenation (oxene transfer)



Cyclopropanation (carbene transfer)

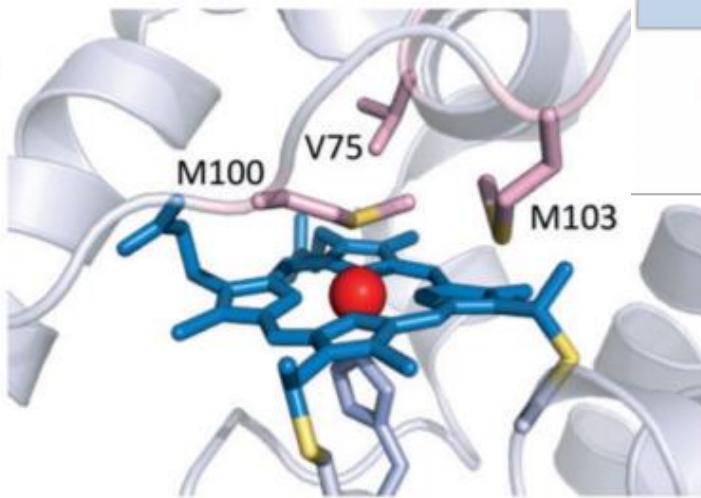
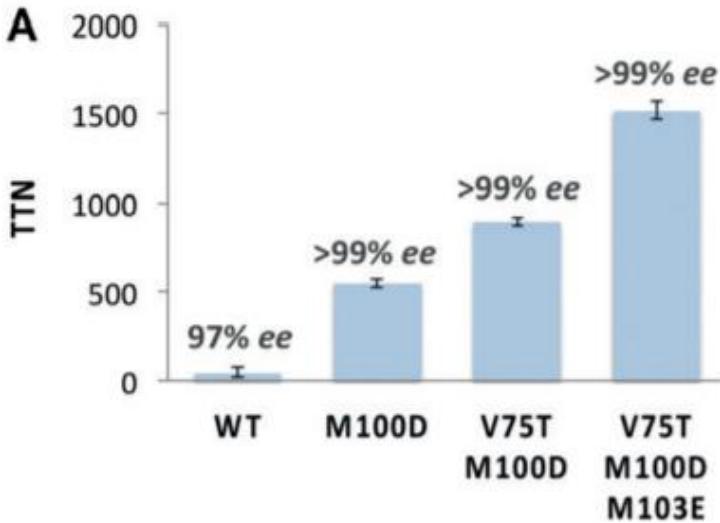


| Reagents | P450 catalyst | TTN | Z : E | %ee _Z | %ee _E |
|---|---------------|-----|---------|------------------|------------------|
| $\text{R}_1 = \text{H}, \text{X} = \text{Me}, \text{R}_2 = \text{Et}$ | BM3-CIS | 228 | 78 : 22 | -81 | N/A |
| $\text{R}_1 = \text{H}, \text{X} = \text{OMe}, \text{R}_2 = \text{Et}$ | H2-5-F10 | 364 | 11 : 89 | 38 | N/A |
| $\text{R}_1 = \text{H}, \text{X} = \text{CF}_3, \text{R}_2 = \text{Et}$ | 7-11D | 120 | 76 : 24 | 31 | 59 |
| $\text{R}_1 = \text{Me}, \text{X} = \text{H}, \text{R}_2 = \text{Et}$ | 7-11D | 157 | 41 : 49 | 42 | N/A |
| $\text{R}_1 = \text{H}, \text{X} = \text{H}, \text{R}_2 = t\text{-Bu}$ | H2A10 | 120 | 3 : 97 | N/A | N/A |

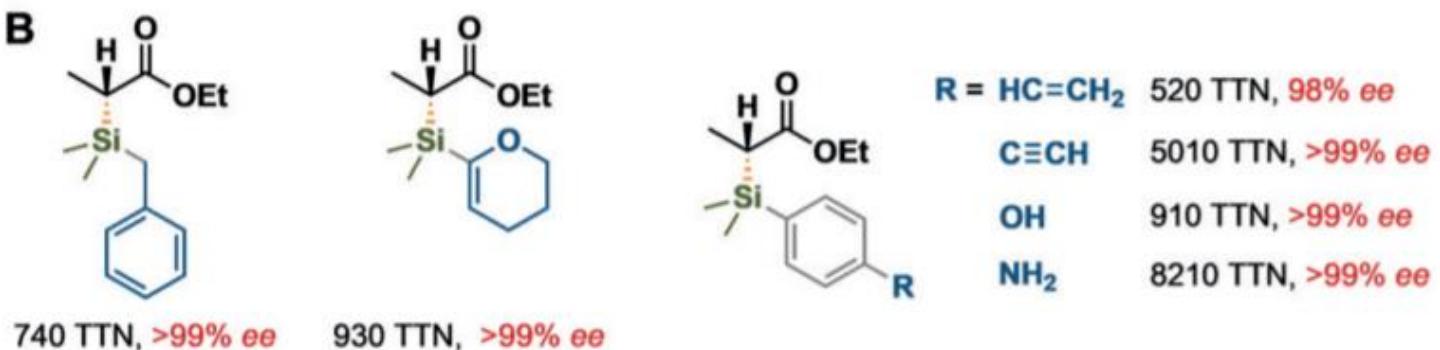
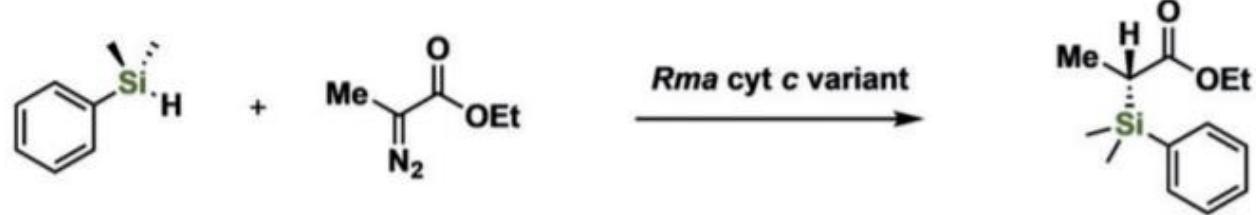


Science 2013, 339, 307; Nat. Chem. Biol. 2013, 9, 485

Directed evolution of cytochrome c for C–Si bond formation: Bringing silicon to life

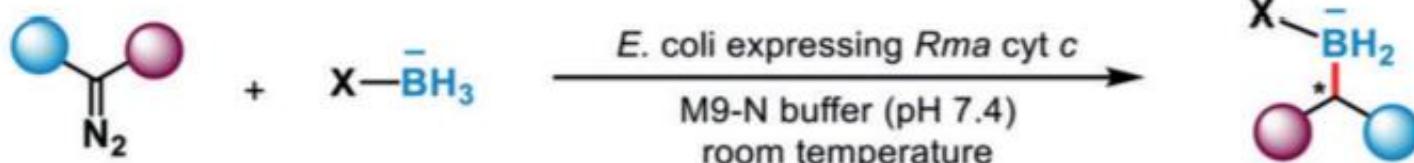


| catalyst | TTN | % ee |
|-----------------------|-----|------|
| None | 40 | - |
| Hemin | 20 | 0 |
| Hemin + BSA | 0 | 0 |
| Horse heart cyt c | <5 | <5 |
| Bovine heart cyt c | 6 | <5 |
| S. cerevisiae cyt c | <5 | <5 |
| R. marinus cyt c | 97 | 97 |
| H. thermophilus cyt c | 16 | <5 |
| R. globiformis cyt c | <5 | <5 |



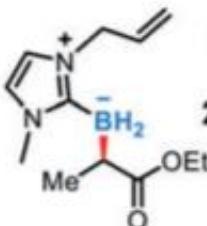
Science 2016,
354, 1048

Genetically programmed chiral organoborane synthesis



Rma cyt c V75R M100D M103T

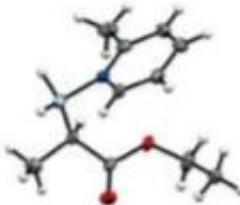
15300 TTN
96:4 er



100% selective for
B-H insertion
2580 TTN, > 99:1 er



≡



gram scale
synthesis
2910 TTN, 96:4 er

*Rma cyt c Y71C V75P
M89C M99C M100D*

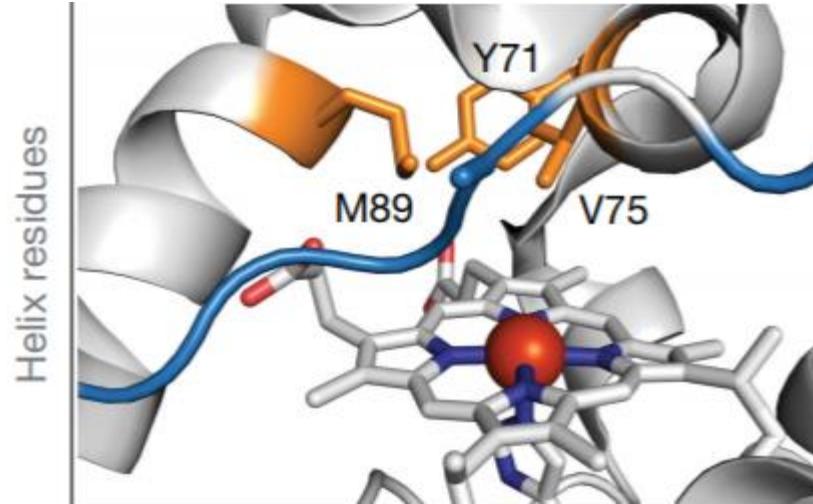
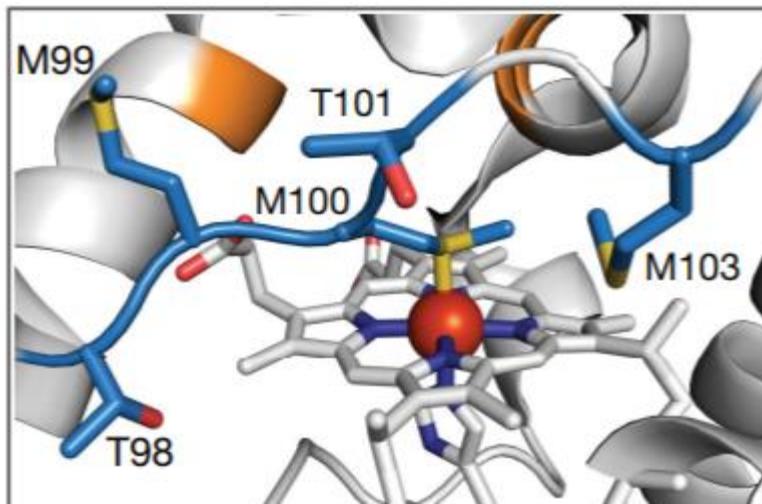
R-selective
1010 TTN
96:4 er

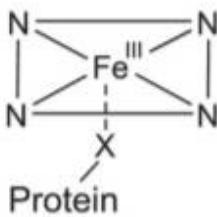


*Rma cyt c M89F T98V
M99L T101L M103F*
S-selective
1120 TTN
90:10 er

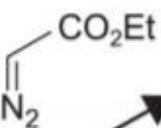


Nature 2017,
552, 132

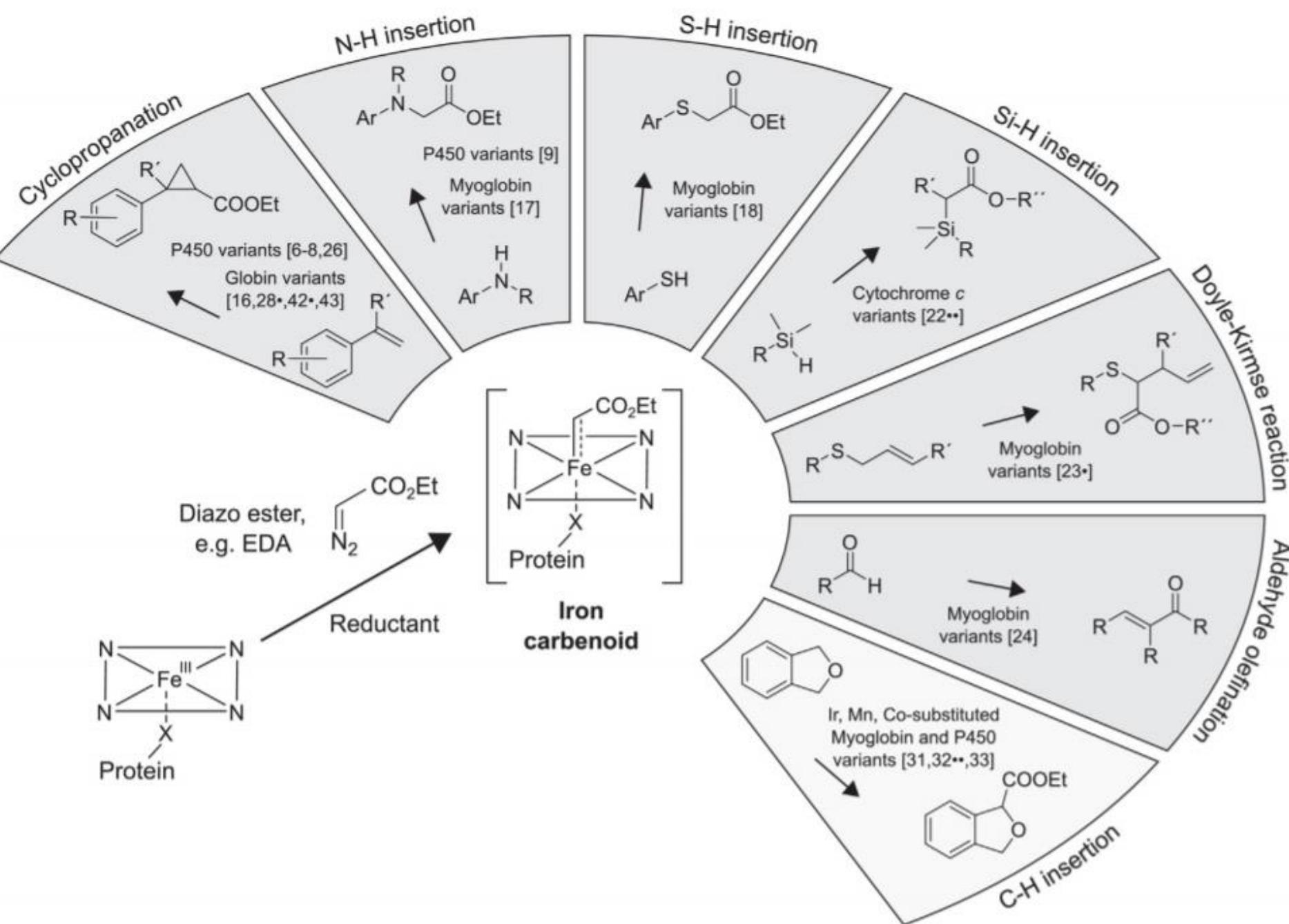
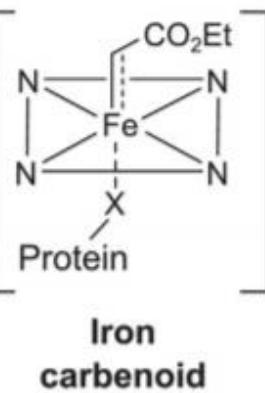


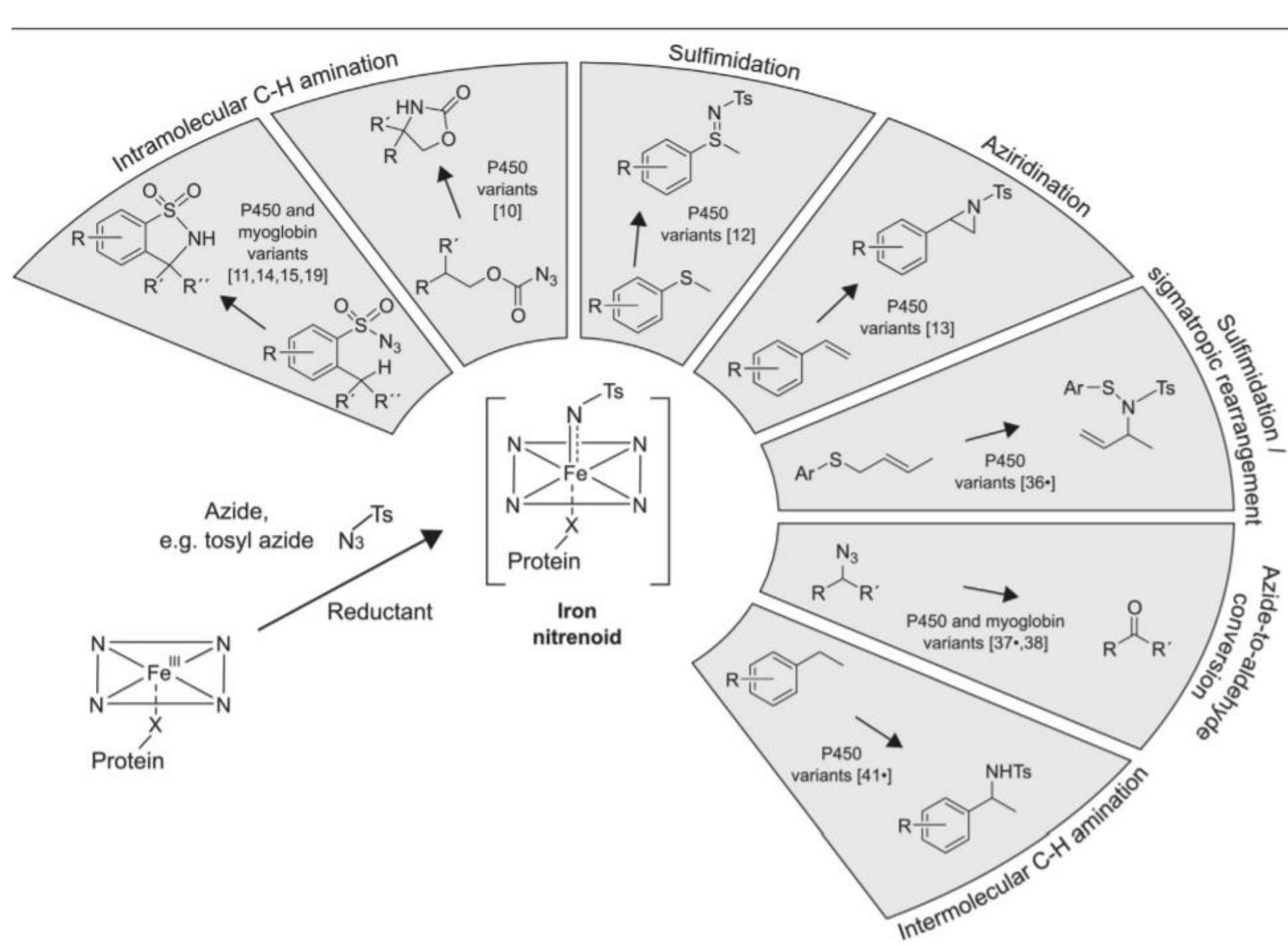


Diazo ester,
e.g. EDA

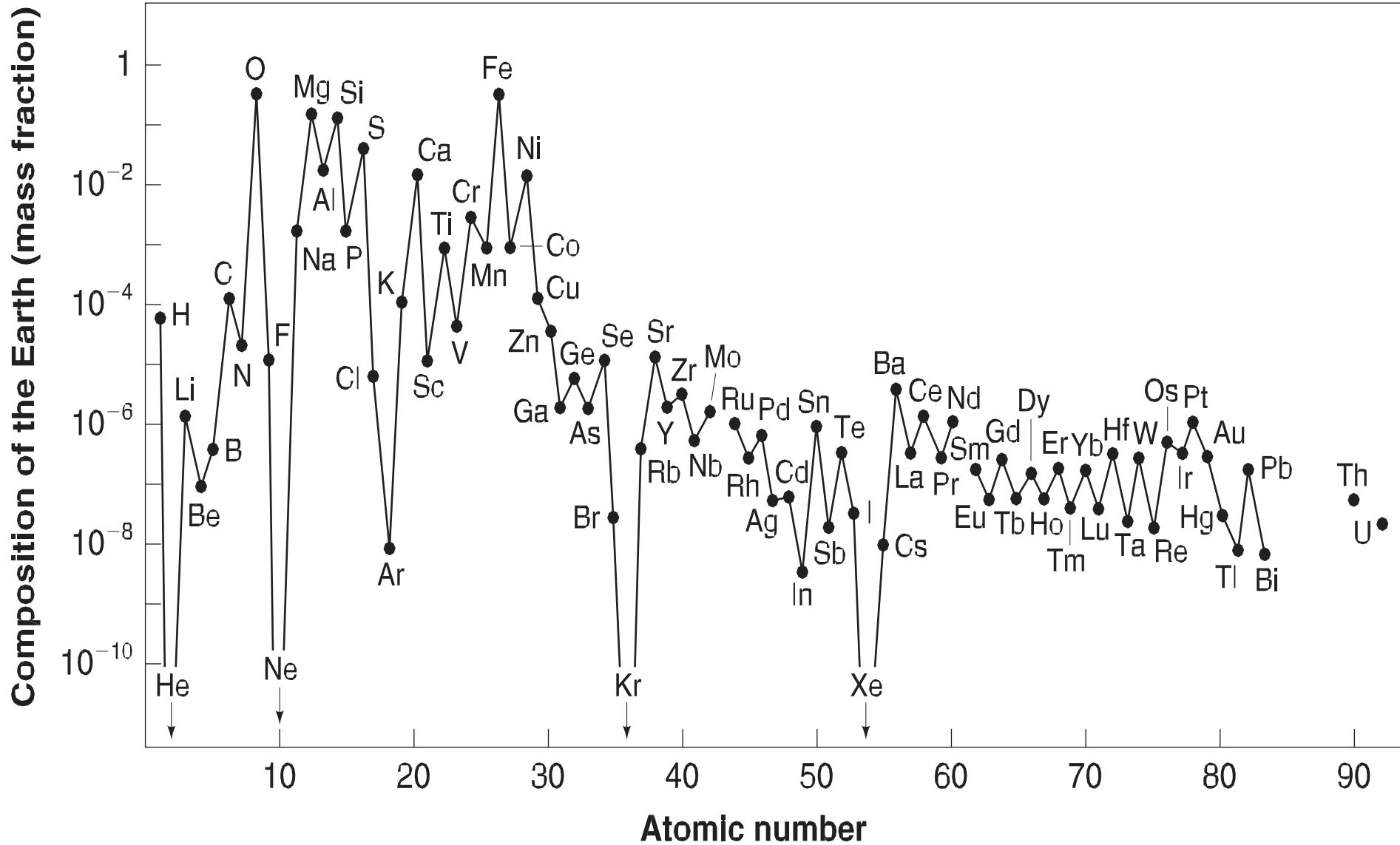


Reductant





The Abundance of Elements in the Earth



Biologically-relevant Elements

| | | | | | | | | | | | | | | | | | |
|--------|----------------|----------------|---|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| 1 | 1 H 1.0079 | 2 | 2 He 4.003 | | | | | | | | | | | | | | |
| 2 | 3 Li 6.941 | 4 Be 9.012 | 10 Ne 20.18 | | | | | | | | | | | | | | |
| 3 | 11 Na 22.99 | 12 Mg 24.30 | 18 Ar 39.95 | | | | | | | | | | | | | | |
| 4 | 19 K 39.10 | 20 Ca 40.08 | 36 Kr 83.80 | | | | | | | | | | | | | | |
| 5 | 37 Rb 85.47 | 38 Sr 87.62 | 54 Xe 131.3 | | | | | | | | | | | | | | |
| 6 | 55 Cs 132.9 | 56 Ba 137.3 | 85 At 222.0 | | | | | | | | | | | | | | |
| 7 | 87 Fr 223.0 | 88 Ra 226.0 | 86 Rn 210.0 | | | | | | | | | | | | | | |
| Period | 3 | 4 | 13 14 15 16 17 | | | | | | | | | | | | | | |
| | 21 Sc 44.96 | 22 Ti 47.87 | 23 V 50.94 | 24 Cr 52.00 | 25 Mn 54.94 | 26 Fe 55.85 | 27 Co 58.93 | 28 Ni 58.69 | 29 Cu 63.55 | 30 Zn 65.41 | 31 Ga 69.72 | 32 Ge 72.64 | 33 As 74.92 | 34 Se 78.96 | 35 Br 79.90 | 36 Kr 83.80 | |
| | 39 Y 88.91 | 40 Zr 91.22 | 41 Nb 92.91 | 42 Mo 95.94 | 43 Tc 97.91 | 44 Ru 101.1 | 45 Rh 102.9 | 46 Pd 106.4 | 47 Ag 107.9 | 48 Cd 112.4 | 49 In 114.8 | 50 Sn 118.7 | 51 Sb 121.8 | 52 Te 127.6 | 53 I 126.9 | 54 Xe 131.3 | |
| | 55 Cs 132.9 | 56 Ba 137.3 | 72 Hf 178.5 | 73 Ta 180.9 | 74 W 183.8 | 75 Re 186.2 | 76 Os 190.2 | 77 Ir 192.2 | 78 Pt 195.1 | 79 Au 197.0 | 80 Hg 200.6 | 81 Tl 204.4 | 82 Pb 207.2 | 83 Bi 209.0 | 84 Po 209.0 | 85 At 210.0 | 86 Rn 222.0 |
| | 87 Fr 223.0 | 88 Ra 226.0 | 104 Rf 105 Db 106 Sg 107 Bh 108 Hs 109 Mt 110 Ds 111 Rg 112 Uub | Transition metals | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|-------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|-----------------|
| Lanthanides | 57 La 138.9 | 58 Ce 140.1 | 59 Pr 140.9 | 60 Nd 144.2 | 61 Pm 145.0 | 62 Sm 150.4 | 63 Eu 152.0 | 64 Gd 157.2 | 65 Tb 158.9 | 66 Dy 162.5 | 67 Ho 164.9 | 68 Er 167.3 | 69 Tm 168.9 | 70 Yb 173.0 | 71 Lu 175.0 |
| Actinides | 89 Ac 227.0 | 90 Th 232.0 | 91 Pa 231.0 | 92 U 238.0 | 93 Np 237.0 | 94 Pu 244.0 | 95 Am 243.0 | 96 Cm 247.0 | 97 Bk 247.0 | 98 Cf 251.0 | 99 Es 252.1 | 100 Fm 257.1 | 101 Md 258.0 | 102 No 259.0 | 103 Lr 262.0 |

Bulk biological elements

Elements essential for a wide range of bacteria, plants and/or animals

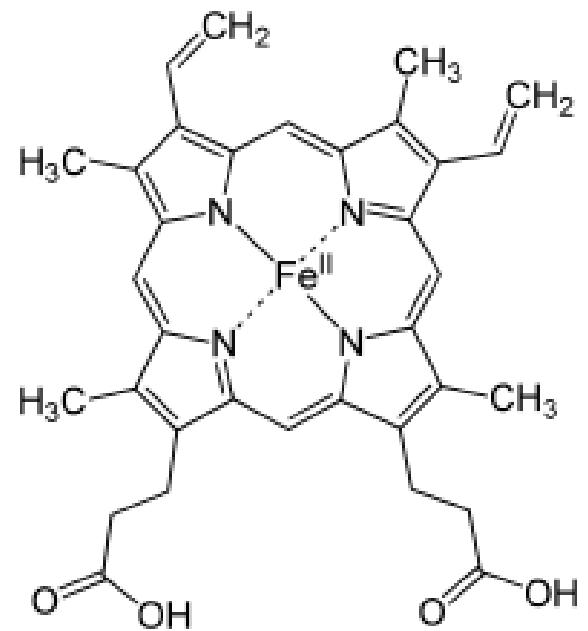
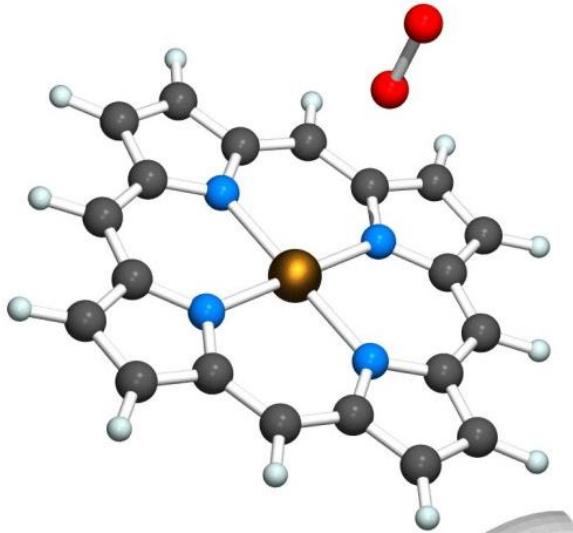
Elements essential or possibly essential for some species

Functional Roles of Biological Inorganic Elements

Elements involved in all life processes e.g.

1. Charge Balance and Electrolytic Conductivity:
Na, K, Cl
2. Structure and Templating: **Ca, Zn, Si, S**
3. Signaling: **Ca, NO**
4. Brønsted Acid–Base Buffering: **P, C**
5. Lewis Acid–Base Catalysis: **Zn, Fe, Ni, Mn**
6. Electron Transfer: **Fe, Cu**
7. Group Transfer (e.g., CH₃, O, S): **V, Fe, Co, Ni, Cu, Mo, W**
8. Redox Catalysis: **V, Mn, Fe, Co, Ni, Cu, W, S**
9. Energy Storage: **H, P, Na, K**
10. Biomineralization: **Ca, Mg, Fe**

Overview of Coordination Chemistry (M-L)



Thermodynamics of Metal-Ligand Complexation



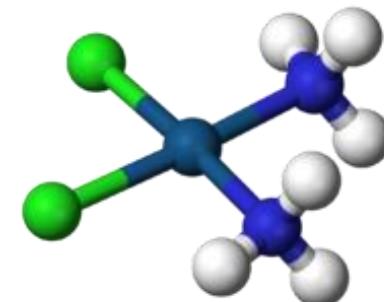
$$K_1 = \frac{[ML]}{[M][L]}$$



$$K_2 = \frac{[ML_2]}{[ML][L]}$$



$$K_3 = \frac{[ML_3]}{[ML_2][L]}$$



Cisplatin
 $\text{PtCl}_2(\text{NH}_3)_2$

Ligand (**L**) directly coordinates to the metal (**M**) to form its ***first coordination sphere***, e.g. $L = \text{H}_2\text{O}, \text{NH}_3$

K: equilibrium constant for the complexation (or so-called formation constant): **larger K value** \rightarrow **stronger M-L bond & more stable** metal-L complex.

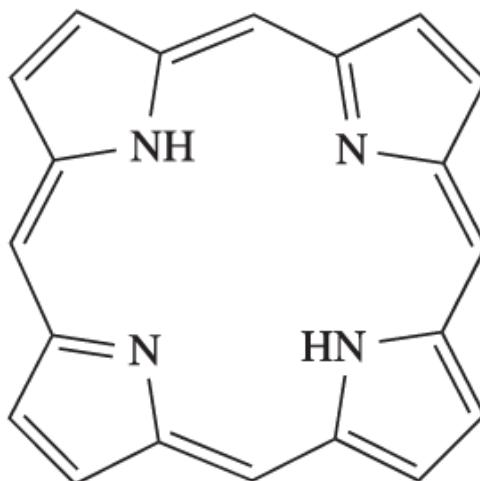
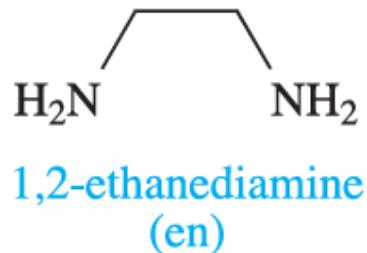
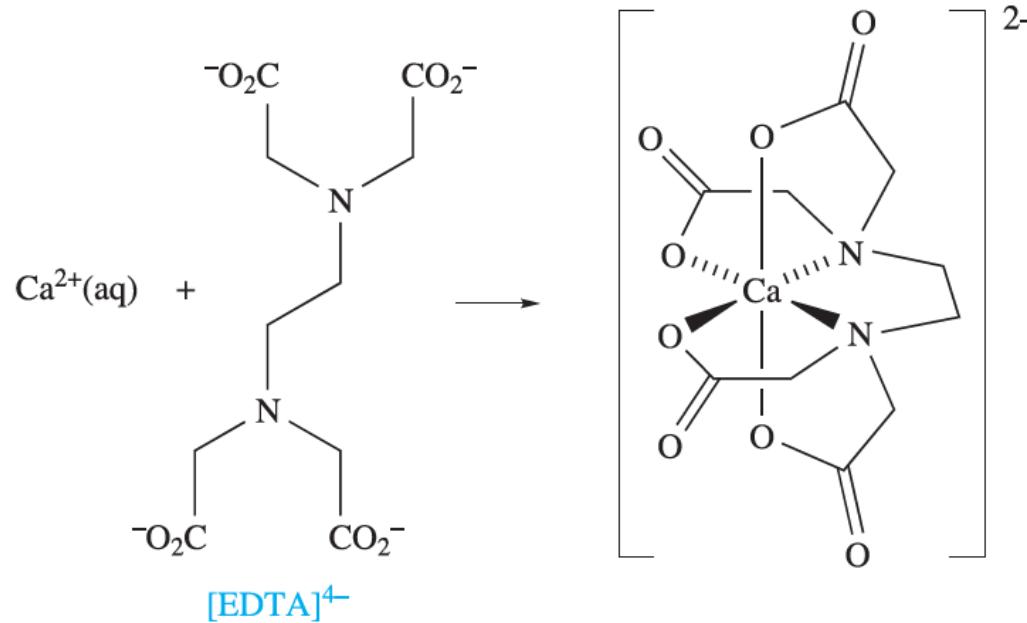
β : the overall formation constant: e.g.



$$\beta_3 = K_1 K_2 K_3$$

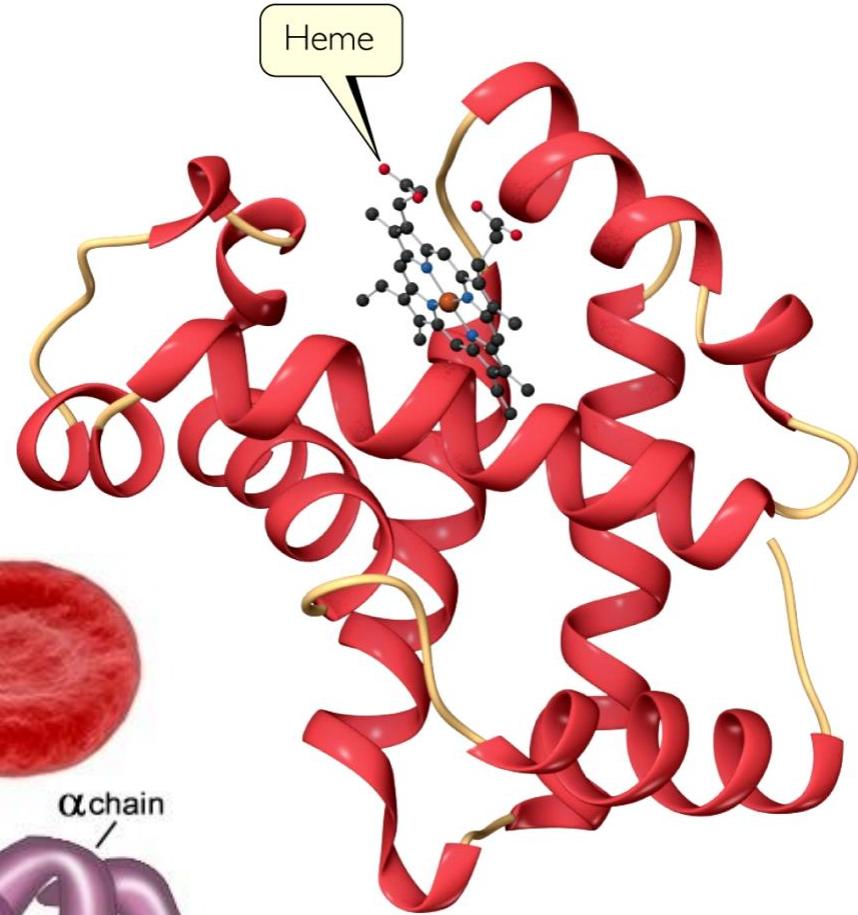
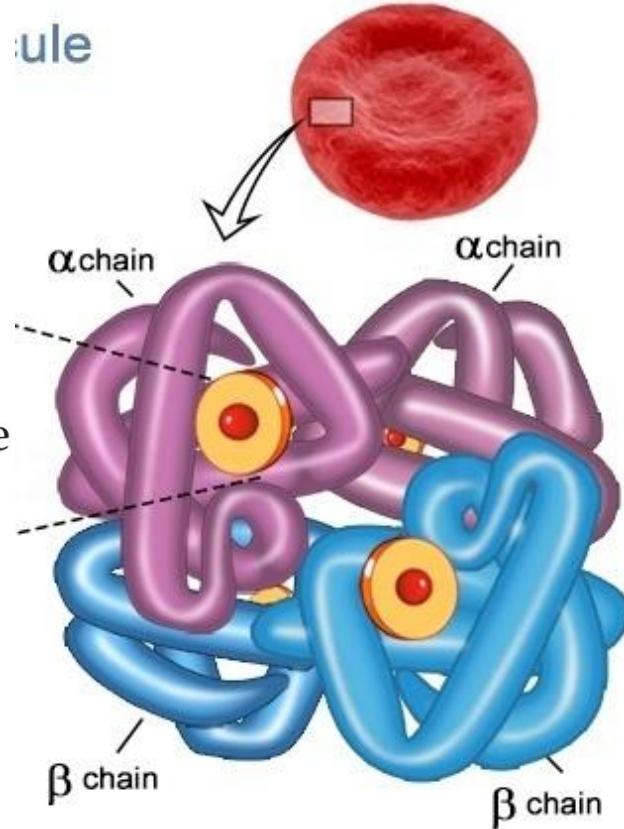
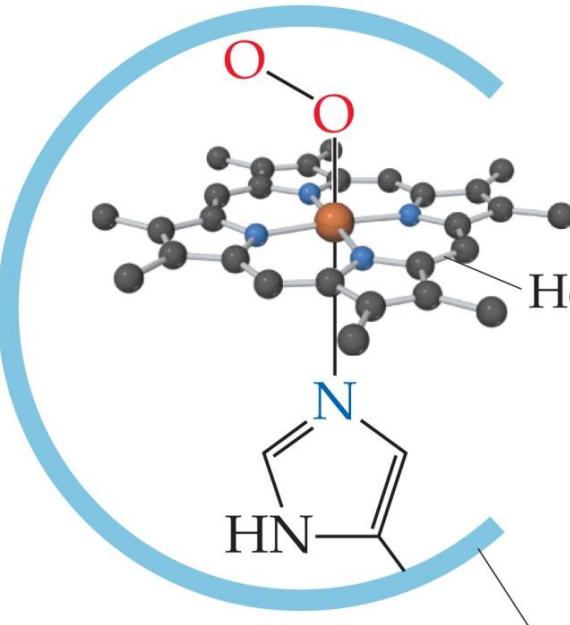
Chelate Effect

- Multidentate ligands can coordinate with the metal by forming more than **multiple M-L bonds** (e.g. EDTA = ethylenediamine-tetraacetic acid).

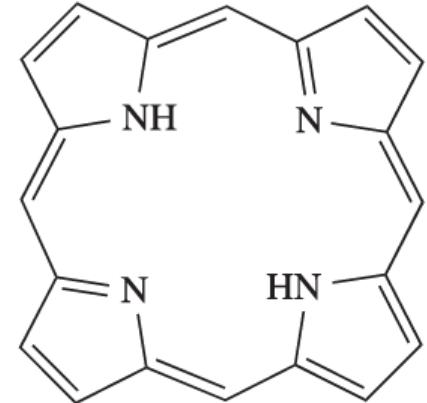


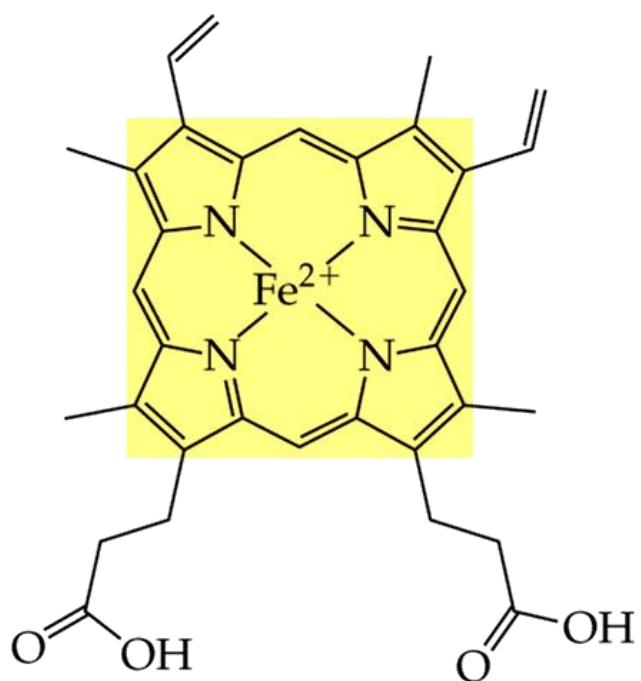
Porphyrin
(e.g. with Fe, Mg)

- Many **transition metals** (e.g. Fe, Cu, Co, Ni & Mn) are vital to human life.
 - Several of these are bound to chelating agents.

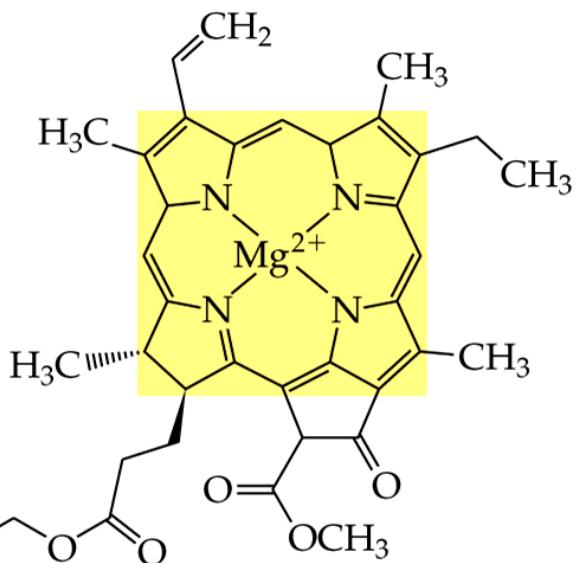


Hemoglobin

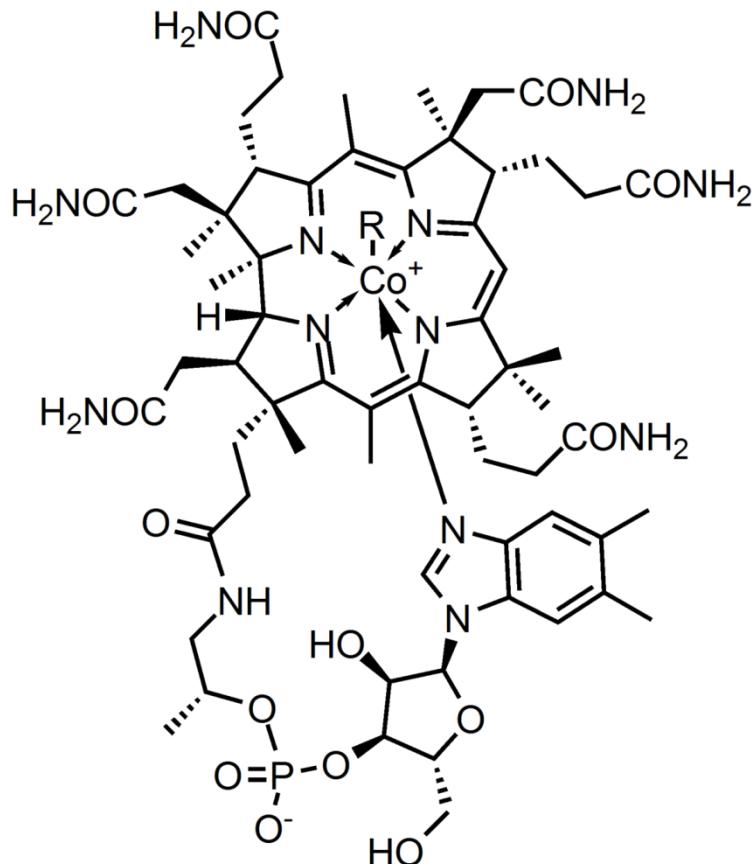




Heme b



Chlorophyll a



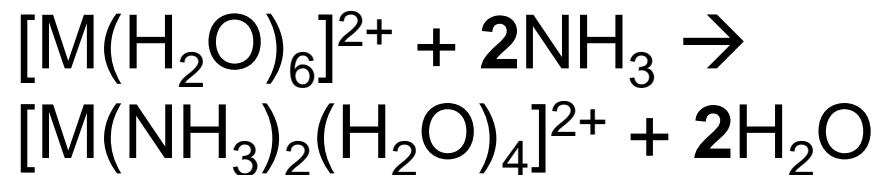
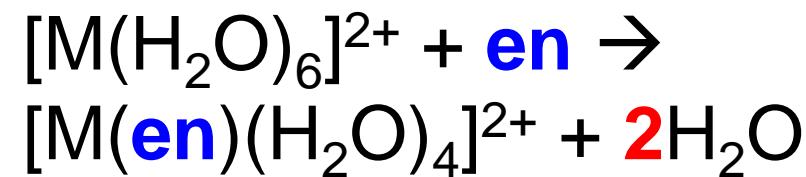
R = 5'-deoxyadenosyl, Me, OH, CN

Vitamin B12

| Reactants | Product | ΔH° (kJ/mol) | ΔS° (J/mol K) | ΔG° (kJ/mol) $\Delta H^\circ - T\Delta S^\circ$ | K |
|--|--|---------------------------|----------------------------|---|----------------------|
| $[\text{Cd}(\text{H}_2\text{O})_6]^{2+}$ | | | | | |
| 4 CH_3NH_2 | $[\text{Cd}(\text{CH}_3\text{NH}_2)_4(\text{H}_2\text{O})_2]^{2+}$ | -57.3 | -67.3 | -37.2 | 3.3×10^6 |
| 2 en | $[\text{Cd}(\text{en})_2(\text{H}_2\text{O})_2]^{2+}$ | -56.5 | +14.1 | -60.7 | 4.0×10^{10} |
| $[\text{Cd}(\text{H}_2\text{O})_6]^{2+}$ | | | | | |
| 2 NH_3 | $[\text{Cu}(\text{NH}_3)_2(\text{H}_2\text{O})_4]^{2+}$ | -46.4 | -8 | -43.9 | 4.5×10^7 |
| en | $[\text{Cu}(\text{en})(\text{H}_2\text{O})_4]^{2+}$ | -54.4 | +23 | -61.1 | 4.4×10^{10} |

2 molecules \rightarrow **3** molecules

3 molecules \rightarrow **3** molecules



- The metal complex with **multidentate** ligands are **much stable than** that with **monodentate** ligands \rightarrow **larger K** value.
- Chelate effect:** increase entropy by releasing more molecules ($\Delta G = \Delta H - T\Delta S$)

Hard and Soft **Acids** and **Bases** (HSAB) Concept

HSAB concept developed by Pearson (Lewis **Acids**: **Metals**; Lewis **Bases**: **Ligands**):

- Hard acids (**M**) tend to form complexes with hard bases (**L**) (ionic bonding mostly).
- Soft acids (**M**) tend to form complexes with soft bases (**L**) (covalent bonding mostly).

Hard: less polarizable (usually with *high charge (oxidation state) and/or small radius*)

Soft: more polarizable (usually with *low charge (oxidation state) and/or large radius*)

Discussion on how metals selectively coordinate with ligands of different biological systems in future

Ligands (Lewis bases)

Hard; class (a) F^- , Cl^- , H_2O , ROH , R_2O , $[\text{OH}]^-$, $[\text{RO}]^-$, $[\text{RCO}_2]^-$, $[\text{CO}_3]^{2-}$, $[\text{NO}_3]^-$, $[\text{PO}_4]^{3-}$, $[\text{SO}_4]^{2-}$, $[\text{ClO}_4]^-$, $[\text{ox}]^{2-}$, NH_3 , RNH_2

Soft; class (b) I^- , H^- , R^- , $[\text{CN}]^-$ (*C*-bound), CO (*C*-bound), RNC , RSH , R_2S , $[\text{RS}]^-$, $[\text{SCN}]^-$ (*S*-bound), R_3P , R_3As , R_3Sb , alkenes, arenes

Intermediate Br^- , $[\text{N}_3]^-$, py , $[\text{SCN}]^-$ (*N*-bound), ArNH_2 , $[\text{NO}_2]^-$, $[\text{SO}_3]^{2-}$

Metal centres (Lewis acids)

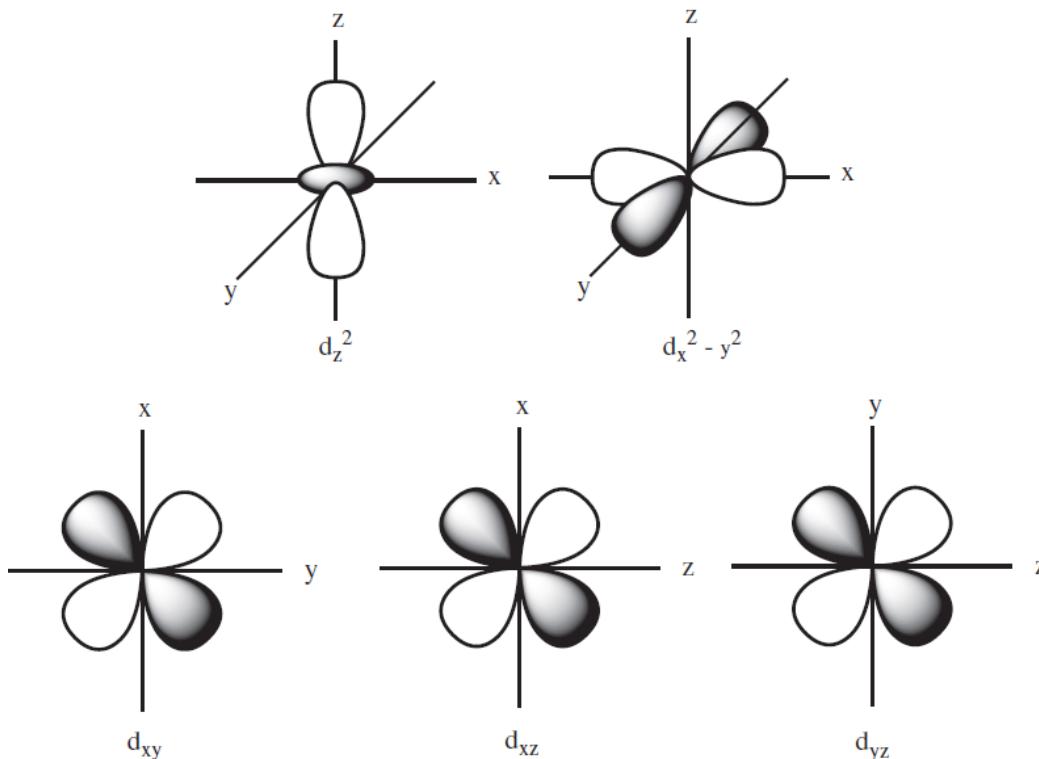
Hard; class (a) Li^+ , Na^+ , K^+ , Rb^+ , Be^{2+} , Mg^{2+} , Ca^{2+} , Sr^{2+} , Sn^{2+} , Mn^{2+} , Zn^{2+} , Al^{3+} , Ga^{3+} , In^{3+} , Sc^{3+} , Cr^{3+} , Fe^{3+} , Co^{3+} , Y^{3+} , Th^{4+} , Pu^{4+} , Ti^{4+} , Zr^{4+} , $[\text{VO}]^{2+}$, $[\text{VO}_2]^+$

Soft; class (b) Zero oxidation state metal centres, Tl^+ , Cu^+ , Ag^+ , Au^+ $[\text{Hg}_2]^{2+}$, Hg^{2+} , Cd^{2+} , Pd^{2+} , Pt^{2+} , Tl^{3+}

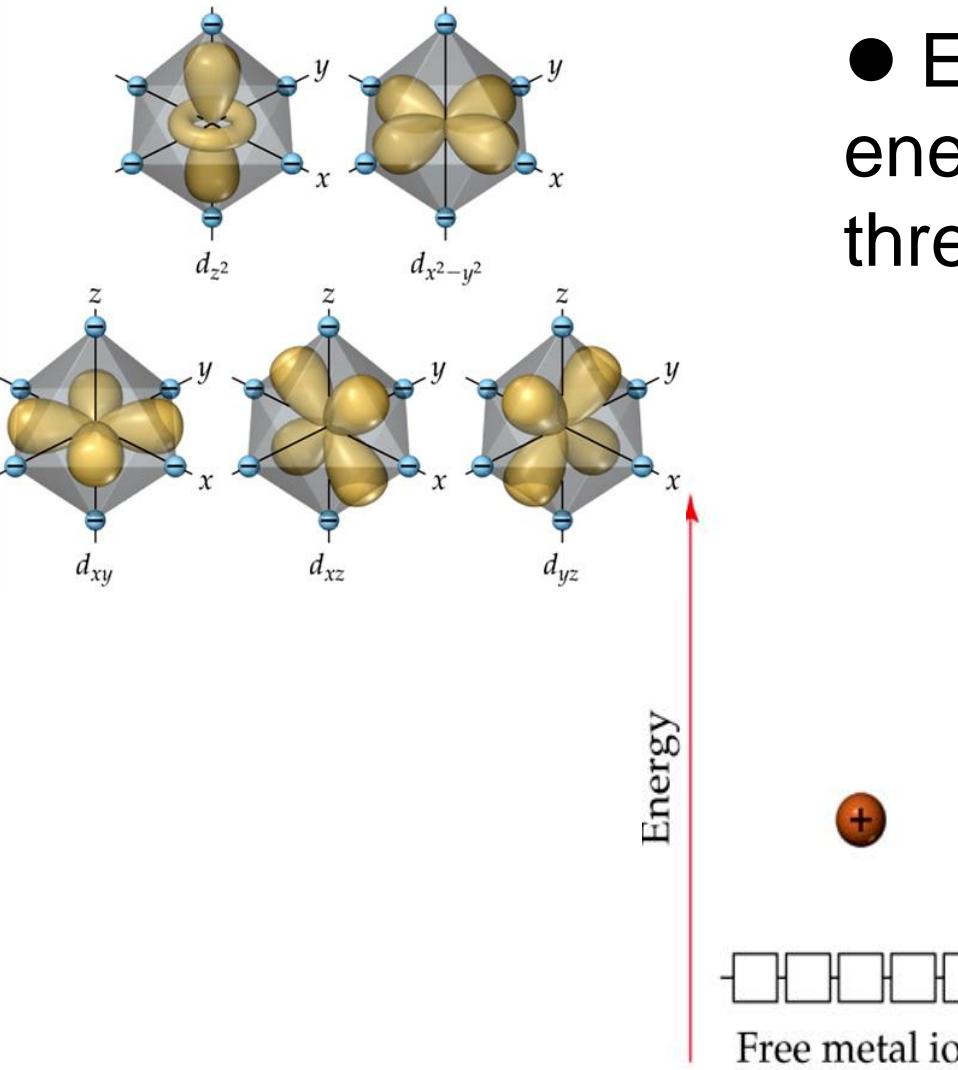
Intermediate Pb^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Os^{2+} , Ru^{3+} , Rh^{3+} , Ir^{3+}

Ligand-Field Theory

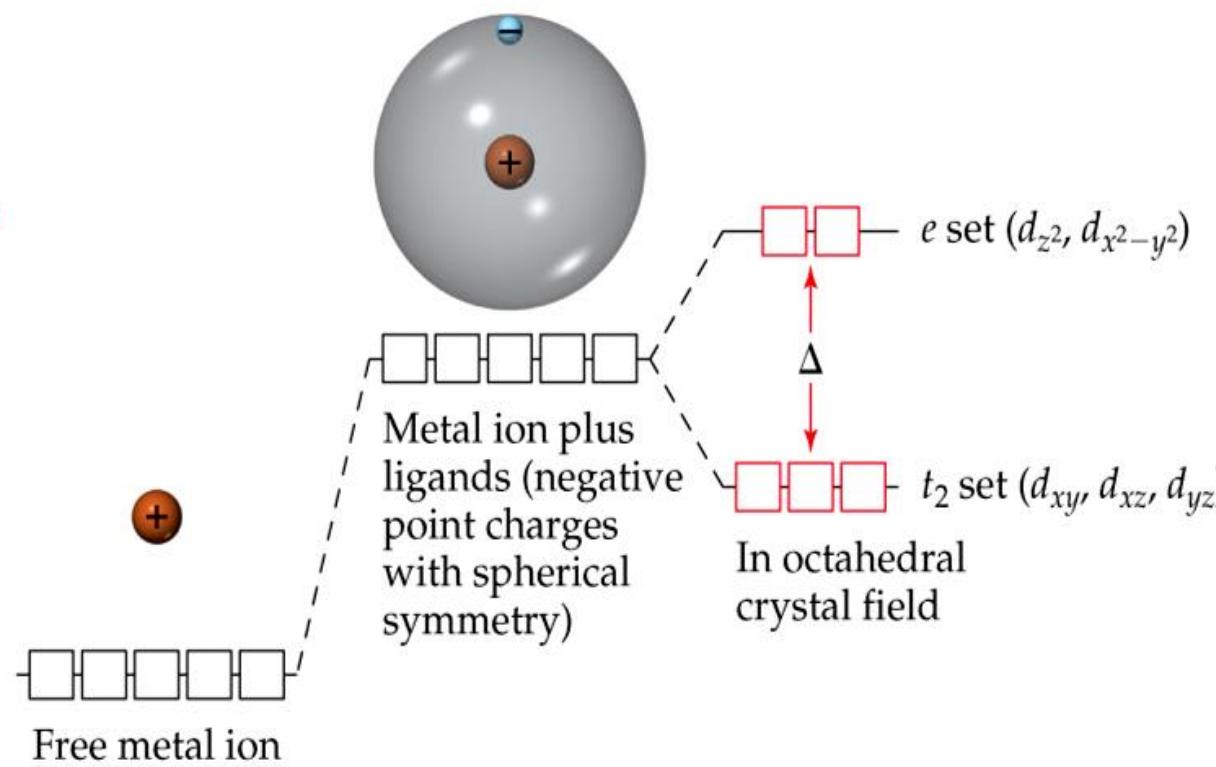
- Some properties (e.g. photo & magnetic) of transition metal complex depends on the *identities of the ligands* & on ***coordination number & geometry*** of the complex.
- Ligand-field theory: a simple theory to show the effect of *the ligands* on the properties of **transition metals**.



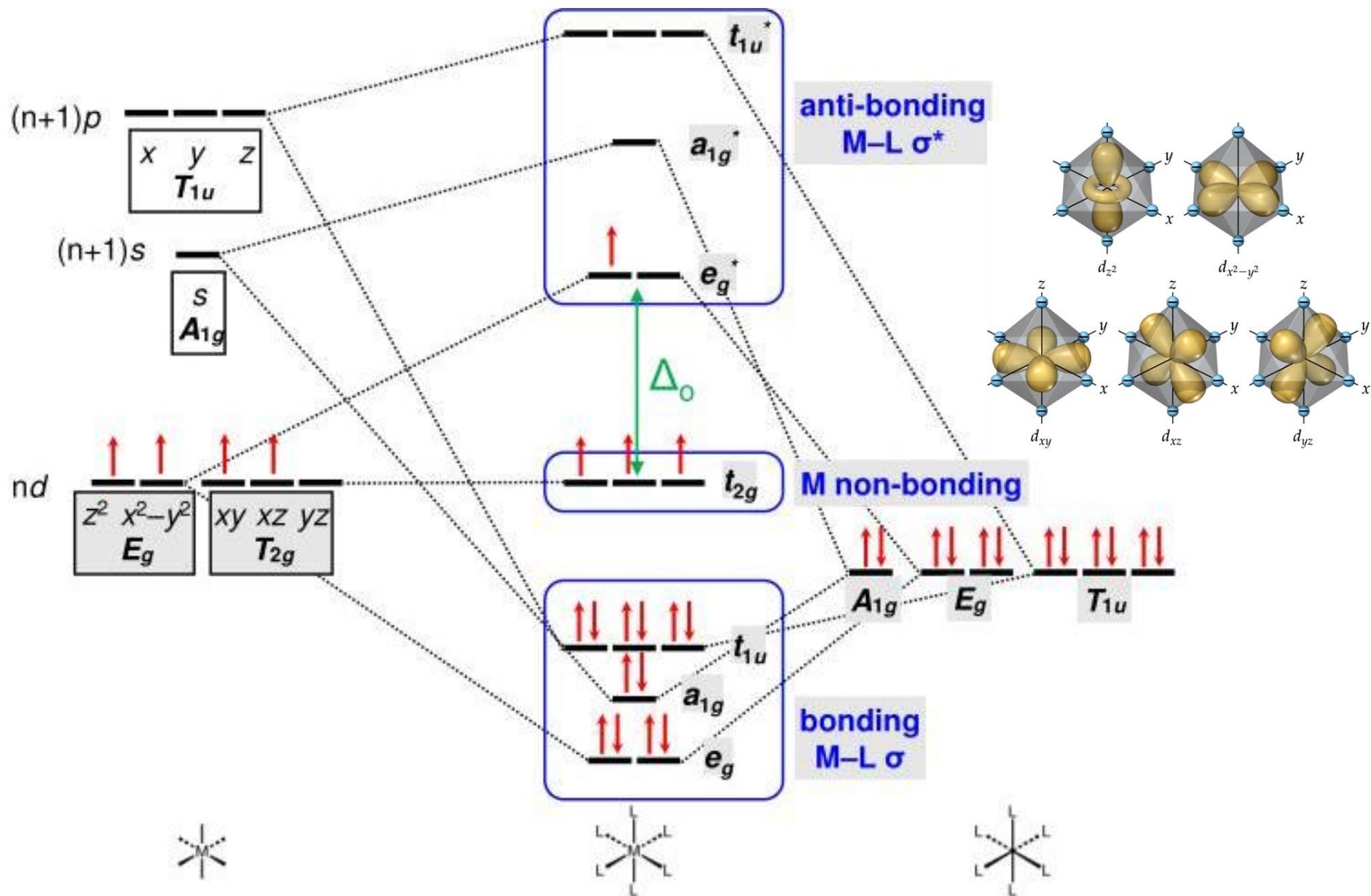
- Bonding electrons from a **ligand** can **raise an energy level of d orbitals** of the metal (electrostatic repulsion), if the ligand interacts with the orbital: **ligand field splitting (Δ)**, or ligand field stabilization energy (LFSE).



- Electron(s) gains stabilization energy, when residing in any three lower-energy orbitals (t_{2g}).

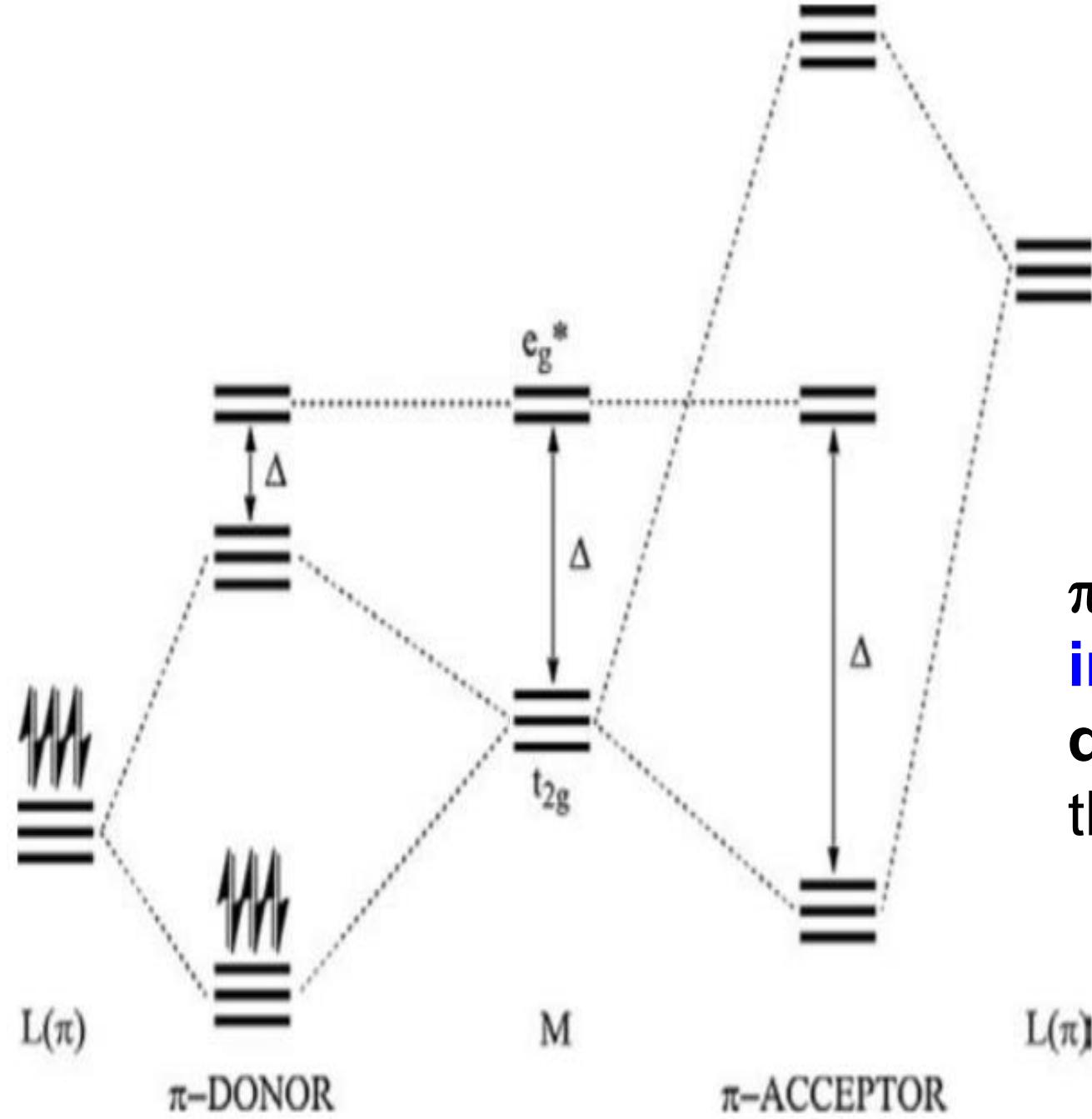


σ Effect in Octahedral MO



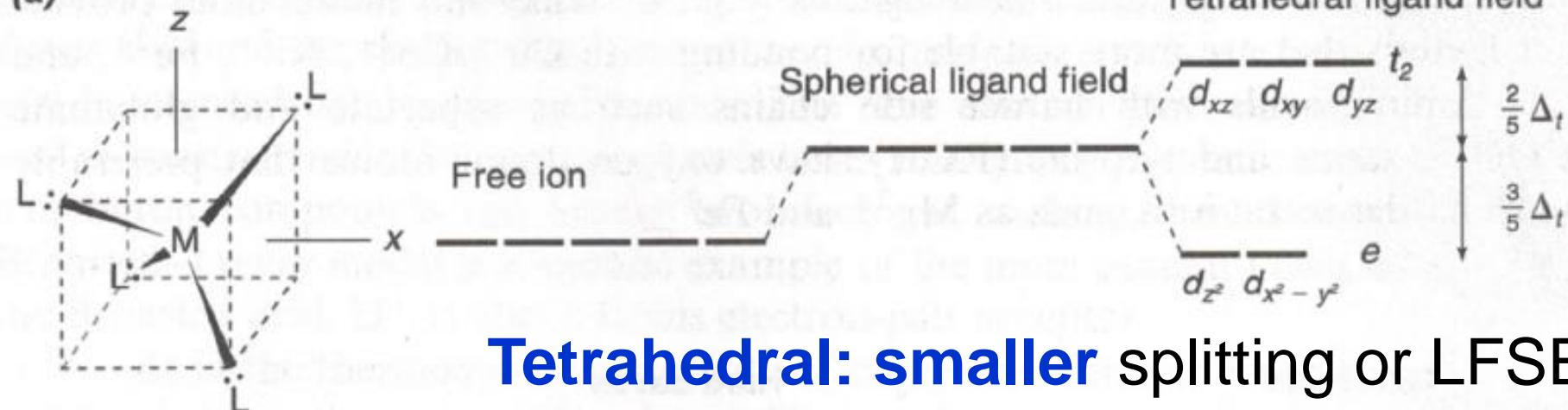
The stronger the M-L bonds, the **larger** the splitting.

π Effects in Octahedral MO



π -acceptor increases & π -donor decreases the splitting.

(a)



Tetrahedral ligand field

Spherical ligand field

Free ion

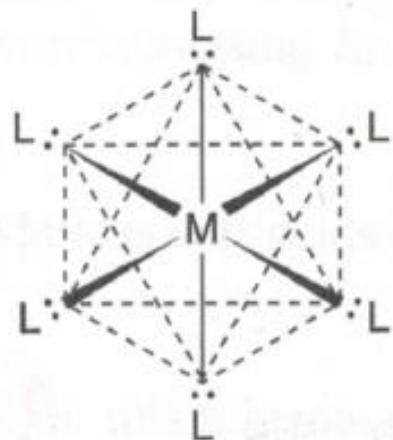
t_2
 d_{xz} d_{xy} d_{yz}

e
 d_{z^2} $d_{x^2-y^2}$

$$\frac{2}{5} \Delta_t$$
$$\frac{3}{5} \Delta_t$$

Tetrahedral: smaller splitting or LFSE

(b)



Octahedral ligand field

Spherical ligand field

Free ion

e_g
 d_{z^2} $d_{x^2-y^2}$

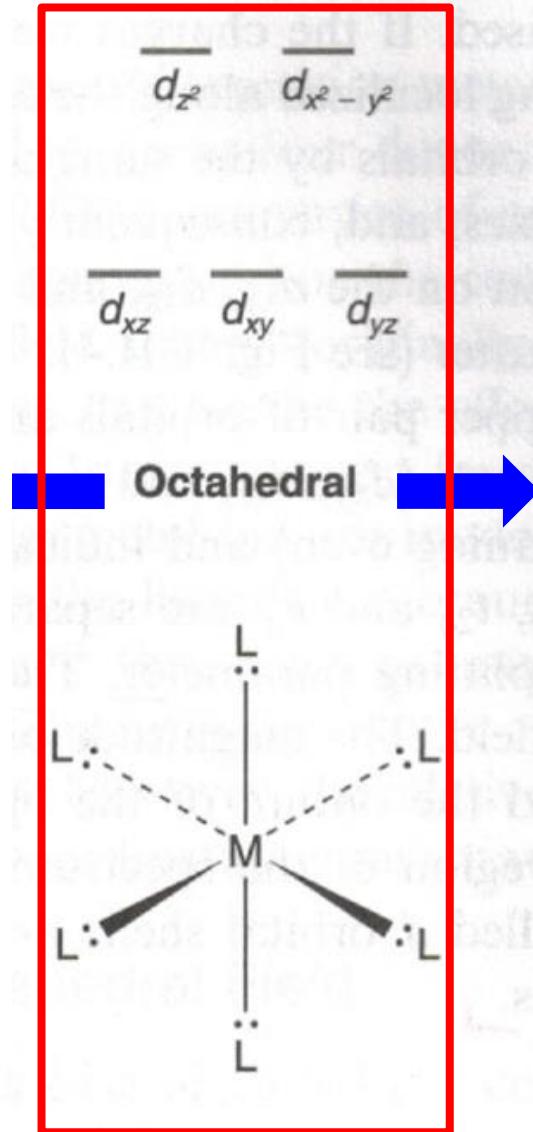
t_{2g}
 d_{xz} d_{xy} d_{yz}

$$\frac{3}{5} \Delta_o$$
$$\frac{2}{5} \Delta_o$$

Octahedron: larger splitting or LFSE

$$\Delta_t < \frac{1}{2} \Delta_o$$

Effect of the geometry on ligand field splitting



Destabilize Z-related orbitals

Stabilize Z-related orbitals

Spectrochemical series

For the same geometry and metal, ligand field splitting depends on the identities of the **ligand**:

Weak-field ligands

(**smaller** splitting)

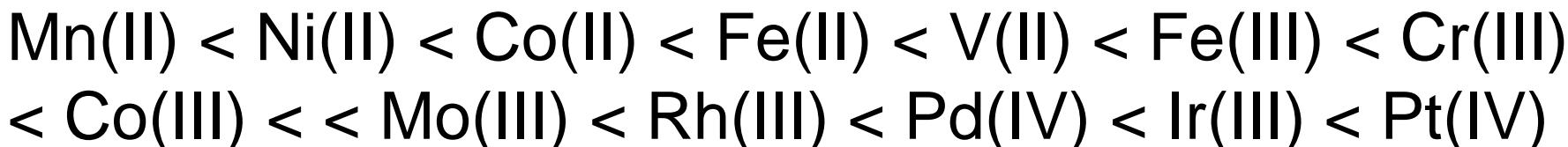


Strong-field ligands

(**larger** splitting)

Metal with higher oxidation number &/or down a group increases Δ (\rightarrow strong M-L σ bonding):

Weak-field



Strong-field



d⁴

d⁵

d⁶

d⁷

High Spin

Weak-field L: High spin



d⁴

d⁵

d⁶

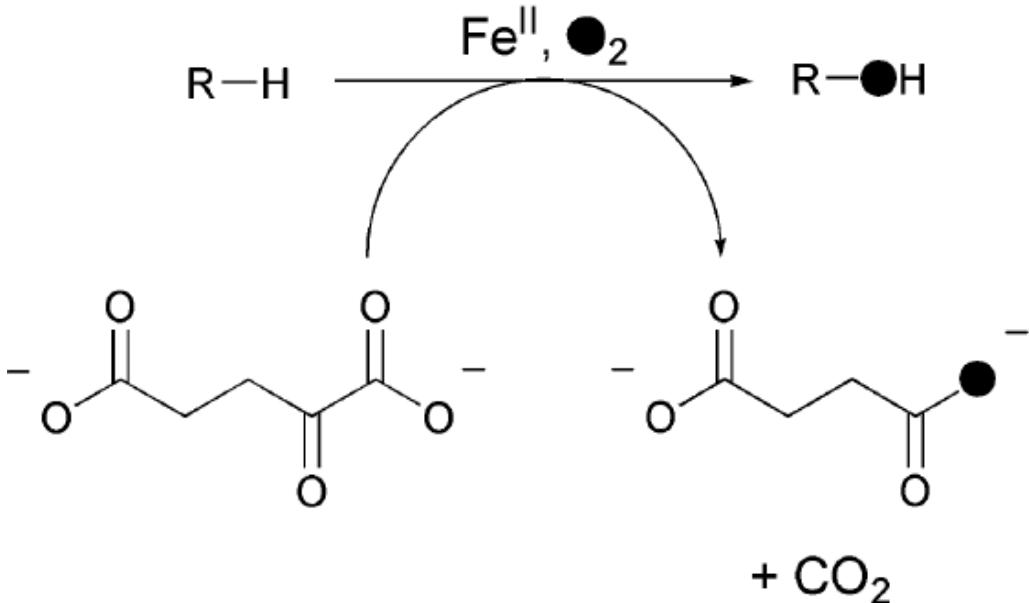
d⁷

Low Spin

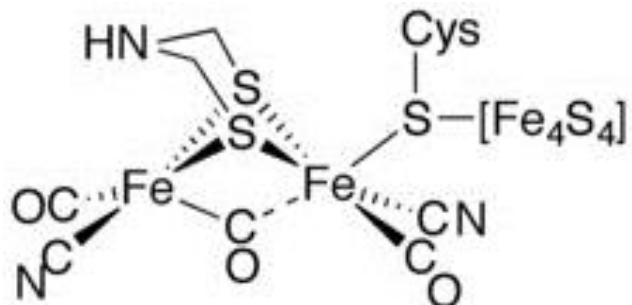
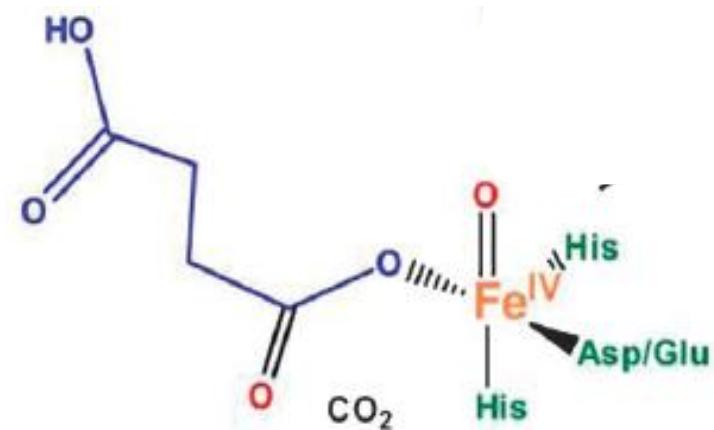
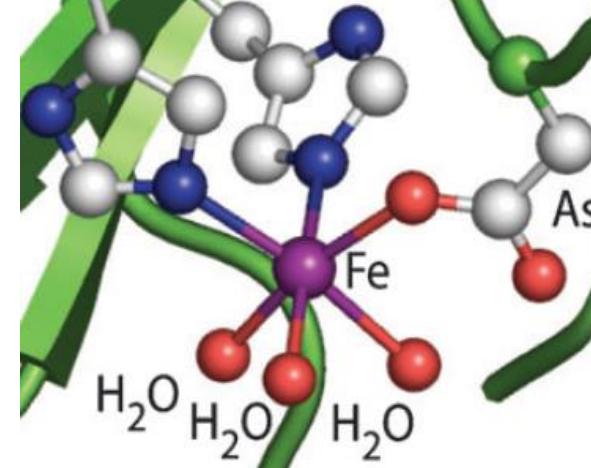
Strong-field L: Low spin

Electronic configuration (HS, LS → paramagnetic) of octahedral complexes depends on LFSE & pairing energy (e-e repulsion).

Tetrahedral complex (HS more or LS more)?



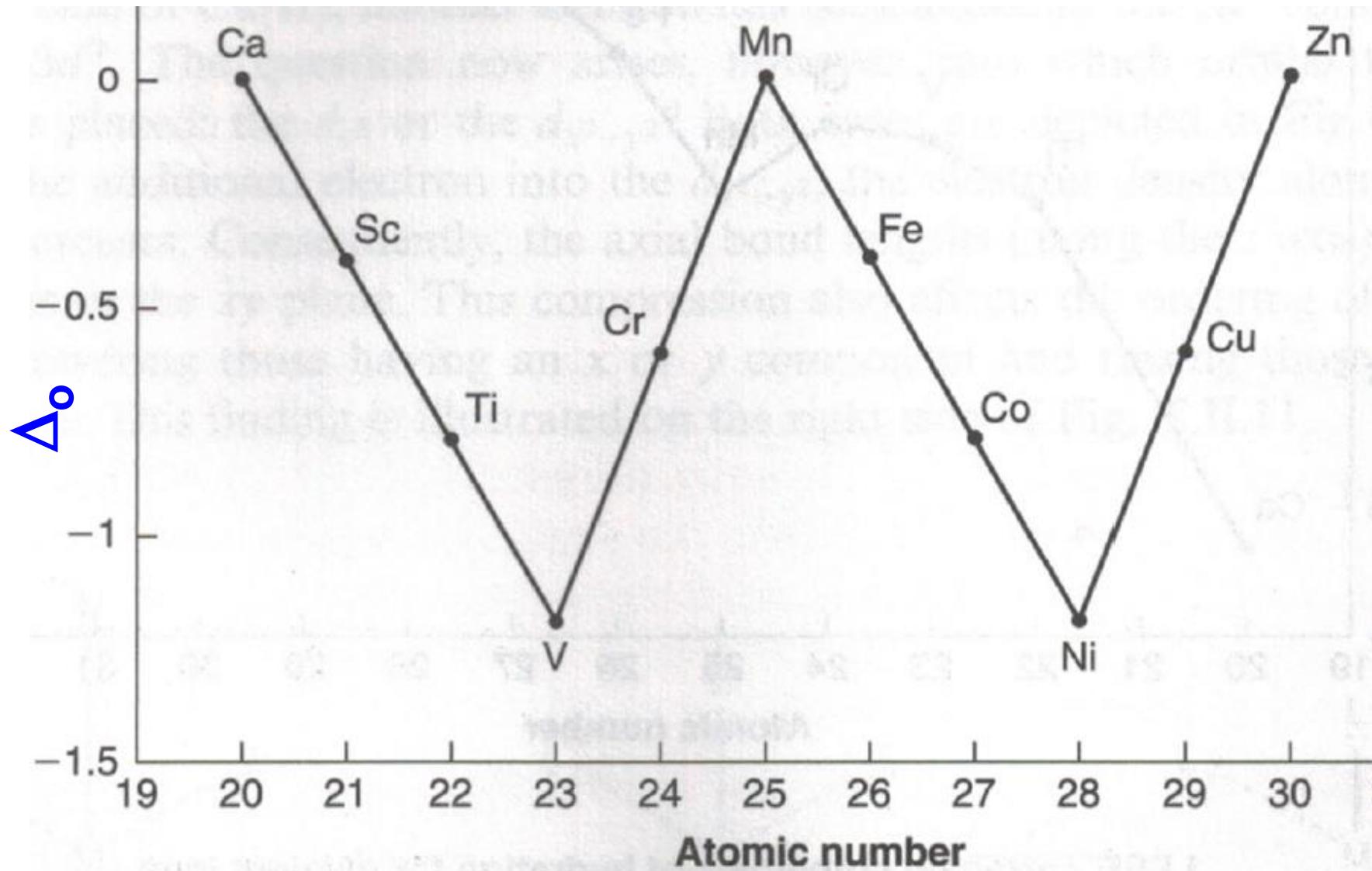
Non-heme Oxygenase: high-spin Fe(IV)-oxo



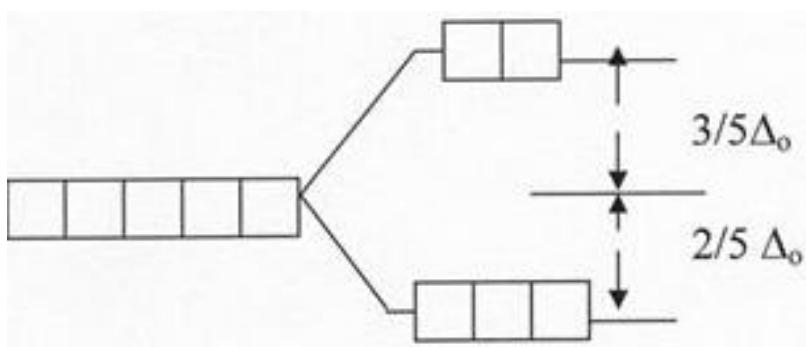
$[FeFe]H_2$ ase

Hydrogenase: low-spin Fe

LFSE (Δ_o) for High-spin M(II)

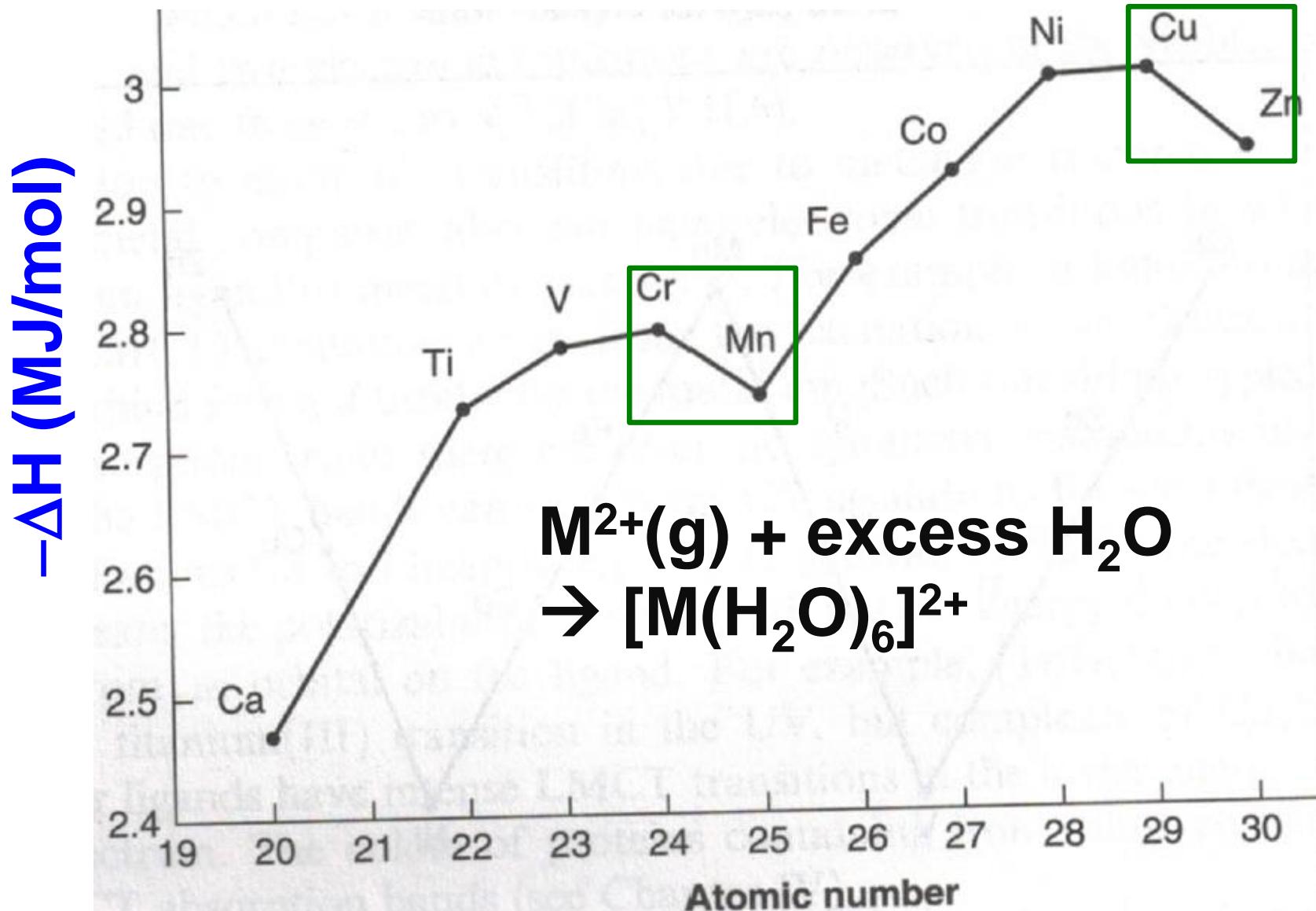


More electrons in t_{2g} orbitals or less electrons in e_g orbitals \rightarrow more LFSE in the octahedral complex.



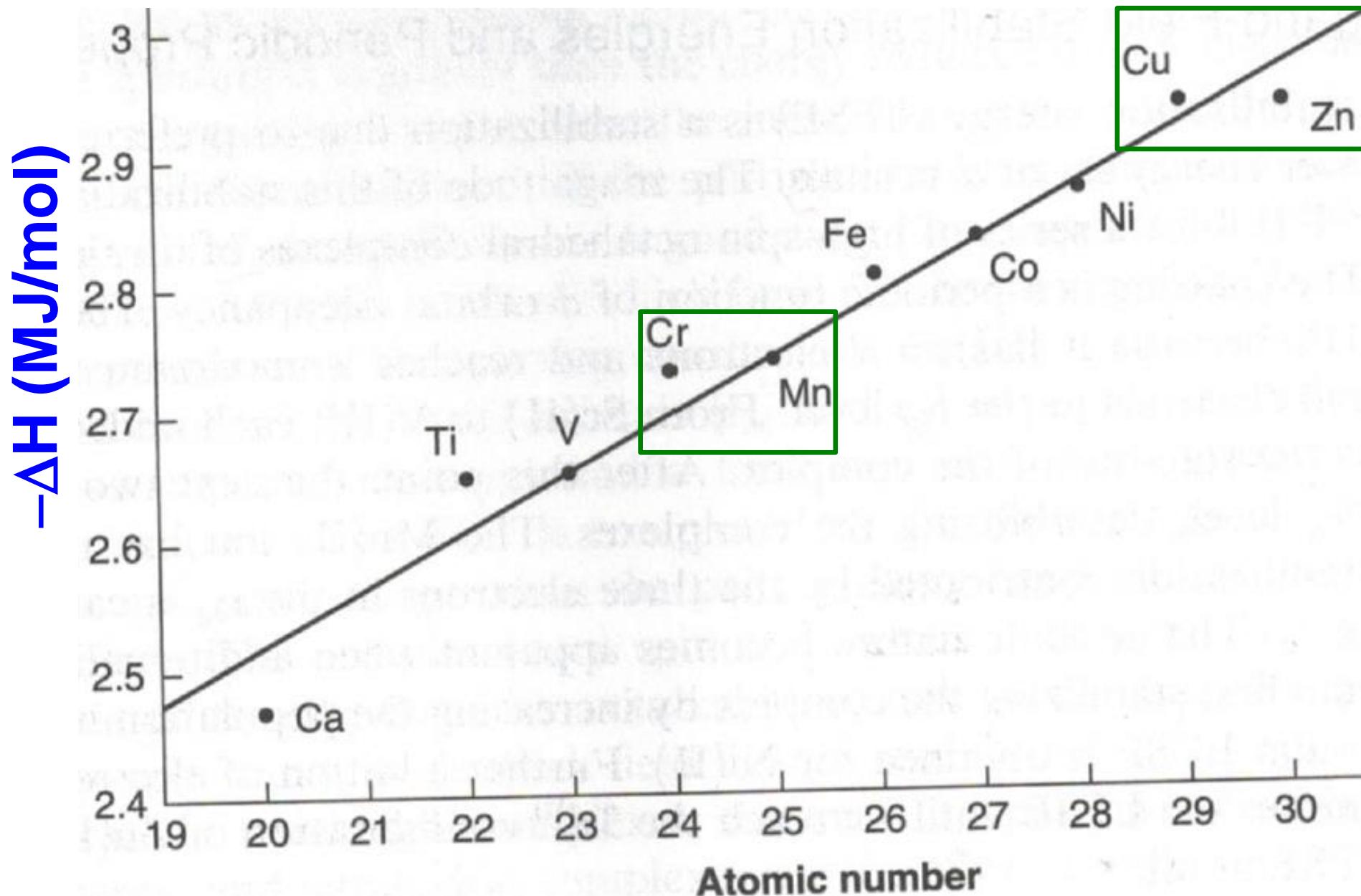
| High Spin | | Low Spin | |
|------------------|---------------------|------------------|---------------------|
| d^n | LFSE (Δ_0) | d^n | LFSE (Δ_0) |
| t_{2g}^1 | - 2/5 | t_{2g}^1 | - 2/5 |
| t_{2g}^2 | - 4/5 | t_{2g}^2 | - 4/5 |
| t_{2g}^3 | - 6/5 | t_{2g}^3 | - 6/5 |
| $t_{2g}^3 e_g^1$ | - 3/5 | t_{2g}^4 | - 8/5 |
| $t_{2g}^3 e_g^2$ | 0 | t_{2g}^5 | - 10/5 |
| $t_{2g}^4 e_g^2$ | - 2/5 | t_{2g}^6 | - 12/5 |
| $t_{2g}^5 e_g^2$ | - 4/5 | $t_{2g}^6 e_g^1$ | - 9/5 |
| $t_{2g}^5 e_g^2$ | - 6/5 | $t_{2g}^6 e_g^2$ | - 6/5 |
| $t_{2g}^6 e_g^3$ | - 3/5 | $t_{2g}^6 e_g^3$ | - 3/5 |
| $t_{2g}^6 e_g^4$ | 0 | $t_{2g}^6 e_g^4$ | 0 |

Enthalpies of hydration for High-spin M(II)

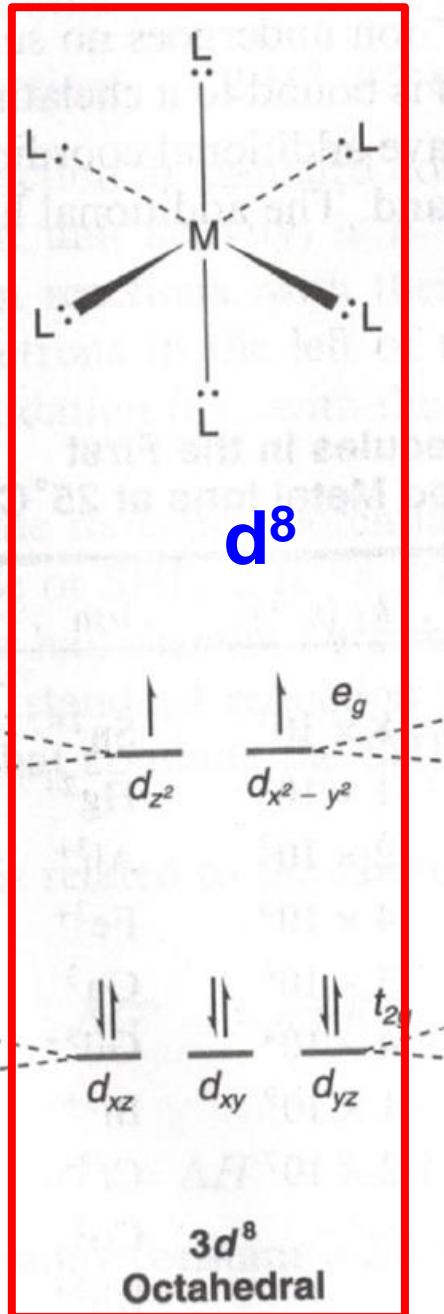


It depends on **LFSE & electrostatic interactions**

LFSE-corrected Enthalpies of hydration



Jahn-Teller Distortion: remove degeneracy (e.g. d⁹)



Kinetics of M-L Binding ($M-X + Y \rightarrow M-Y + X$)

Thermodynamics (K): STABLE vs. UNSTABLE

Kinetics (k): INERT vs. LABILE

Exchange rates for water molecules from the first coordination sphere of metal ions at 25°C

| Ion | $k_1, \text{ sec}^{-1}$ | Ion | $k_1, \text{ sec}^{-1}$ | Ion | $k_1, \text{ sec}^{-1}$ |
|------------------|-------------------------|------------------|-------------------------|------------------|-------------------------|
| Li^+ | 4×10^8 | V^{2+} | 8×10^1 | Sn^{2+} | $> 10^4$ |
| Na^+ | 7×10^8 | Cr^{2+} | 1×10^9 | Hg^{2+} | 4×10^8 |
| K^+ | 1×10^9 | Mn^{2+} | 2×10^7 | Al^{3+} | 1 |
| Be^{2+} | 8×10^2 | Fe^{2+} | 4×10^6 | Fe^{3+} | 2×10^2 |
| Mg^{2+} | 6×10^5 | Co^{2+} | 3×10^6 | Ga^{3+} | 4×10^2 |
| Ca^{2+} | 3×10^8 | Ni^{2+} | 4×10^4 | Gd^{3+} | 2×10^9 |
| Ba^{2+} | 2×10^9 | Cu^{2+} | 1×10^9 | Bi^{3+} | $> 10^4$ |
| | | Zn^{2+} | 2×10^7 | Cr^{3+} | 2×10^{-6} |
| | | | | Co^{3+} | $< 10^{-6}$ |
| | | | | Rh^{3+} | 6×10^{-9} |

Associative or dissociative mechanism for the ligand exchange

Correlations Between Ligand Binding, Mobility, Function of Some Biological Relevant Metal Ions

| Metal Ion | Binding | Mobility | Function |
|-------------------------------------|-----------------|--------------|----------------------------------|
| Na ⁺ , K ⁺ | Weak | High | Charge carriers |
| Mg ²⁺ , Ca ²⁺ | Moderate | Semi-mobile | Triggers, transfers structural |
| Zn ²⁺ | Moderate/Strong | Intermediate | Lewis acid, transfers structural |
| Co, Cu, Fe, Mn, Mo* | Strong | Low | Redox catalysts Oxygen chemistry |

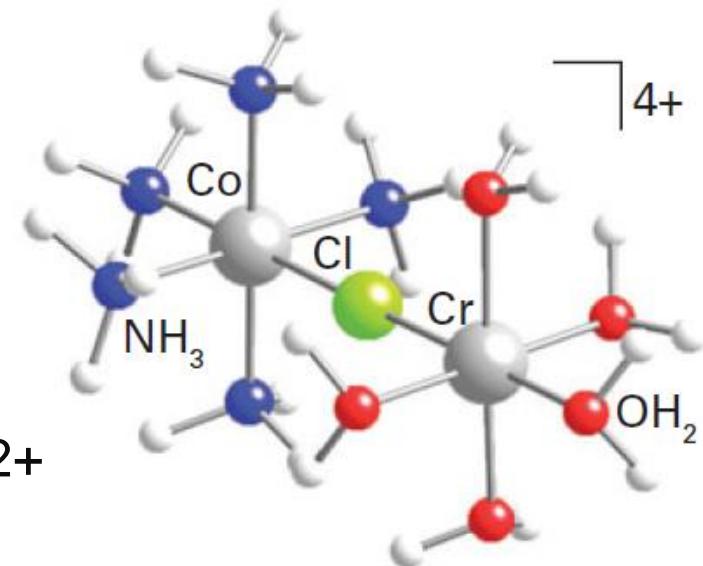
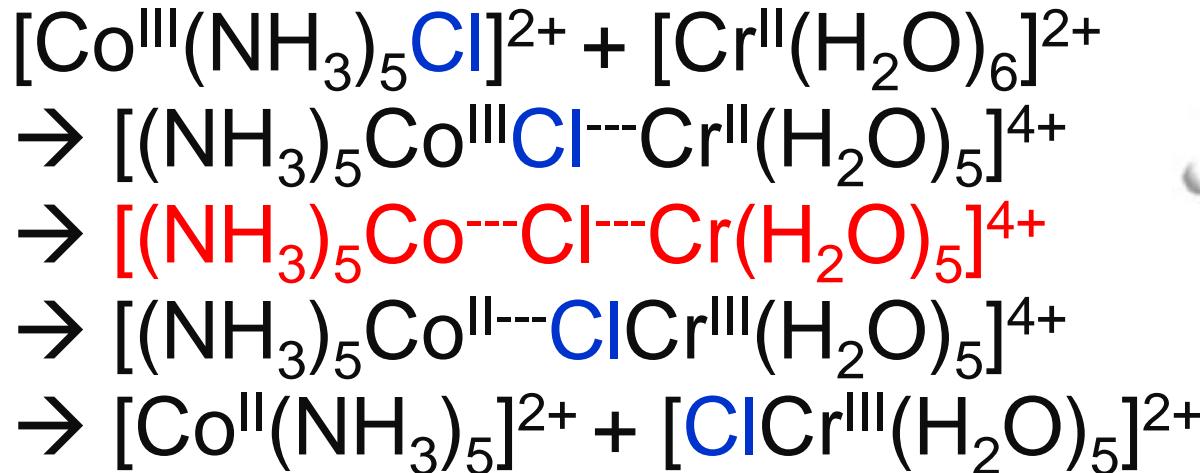
*Charge not given, since this varies with oxidation state

Labile metal complexes: important for metal exchange or update in biological systems

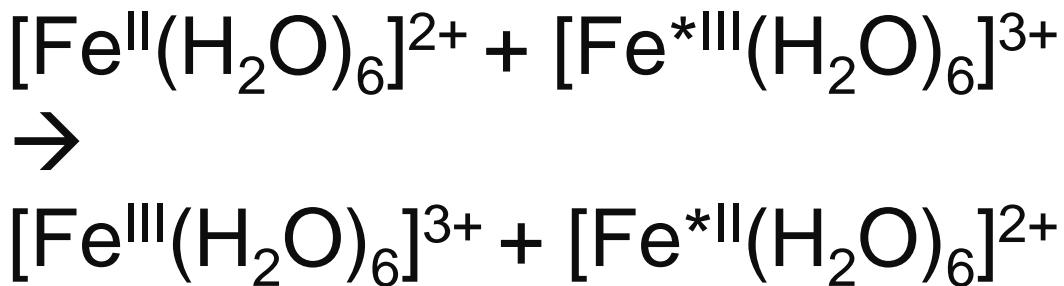
Electron Transfer/Redox Reaction

Electron transfer (ET): the most simplest form of redox reactions, & *quite common & important in bioinorganic chemistry*

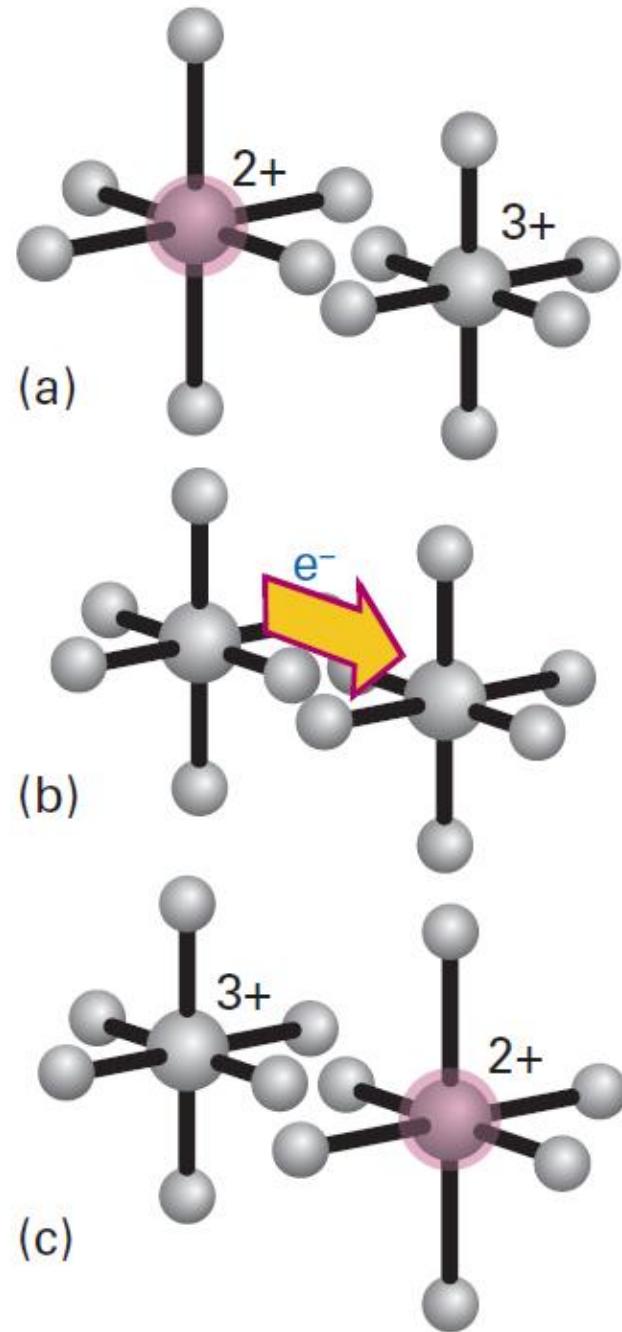
Inner-sphere mechanism: the coordination spheres of the metal complexes **share a ligand** (e.g. Cl) temporarily and **form a bridged transition state.**



Outer-sphere mechanism: the metal complexes come into contact **without** sharing a **bridging ligand** and the **electron tunnels** from one metal atom to the other.



Self-exchange reaction



Reduction potential range of redox centers in ET processes (Fe & Cu)

$\text{Fe}(\text{S-Cys})_4^{2+/3+}$ Rubredoxin

$[\text{2Fe-2S}]^{1+/2+}$ Ferredoxin

$[\text{2Fe-2S}]^{1+/2+}$ Rieske

$[\text{3Fe-4S}]^{0/1+}$ in $[\text{3Fe-4S}][\text{4Fe-4S}]$

$[\text{4Fe-4S}]^{2+/3+}$ HiPIP

$[\text{4Fe-4S}]^{1+/2}$ in $[\text{3Fe-4S}][\text{4Fe-4S}]$

$[\text{3Fe-4S}]^{0/1+}$ in $[\text{3Fe-4S}]$

Cytochrome c- class IV

$[\text{4Fe-4S}]^{1+/2}$ in $[\text{4Fe-4S}][\text{4Fe-4S}]$

Cytochrome c- class IIb

$[\text{4Fe-4S}]^{1+/2}$ in $[\text{4Fe-4S}]$

Cytochrome c- class IIa

Cytochrome f

Cytochrome c- class I

Cytochrome c- class III

Cu_A

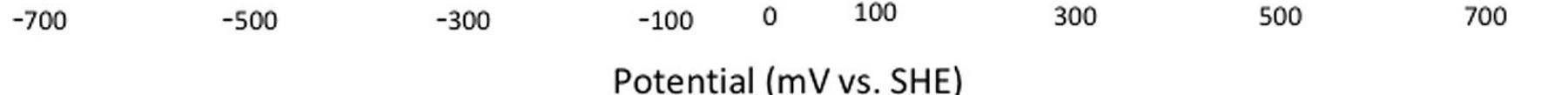
Blue copper in multi-copper oxidases

Cytochrome b except *A. Vinelandii* bacterio ferritin

A. Vinelandii bacterio ferritin

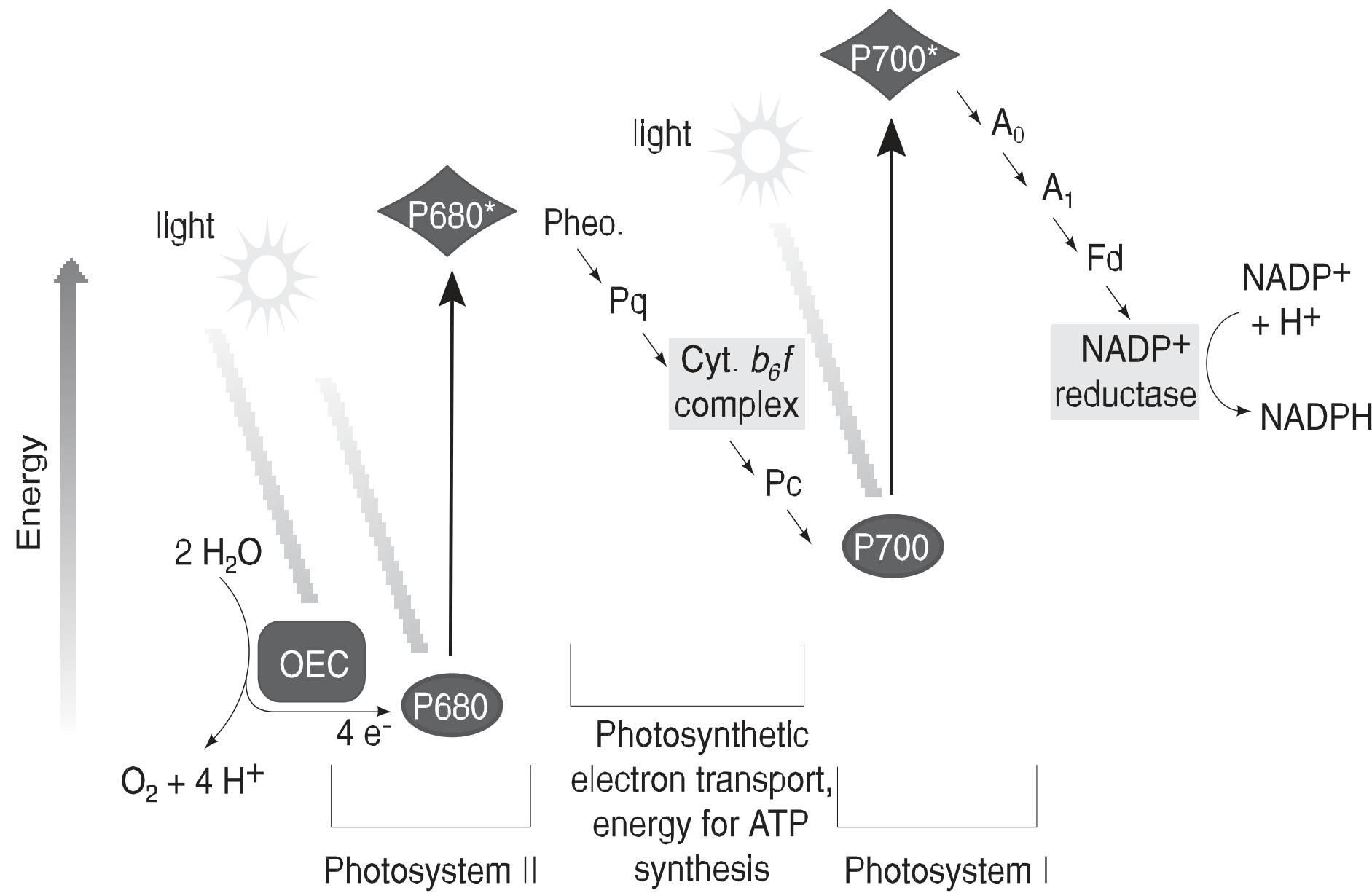
Blue copper (except Rusticyanin)

Rusticyanin



Liu et al. Chem. Rev.
2014, 114, 4366.

Electron Transfer in Photosynthesis

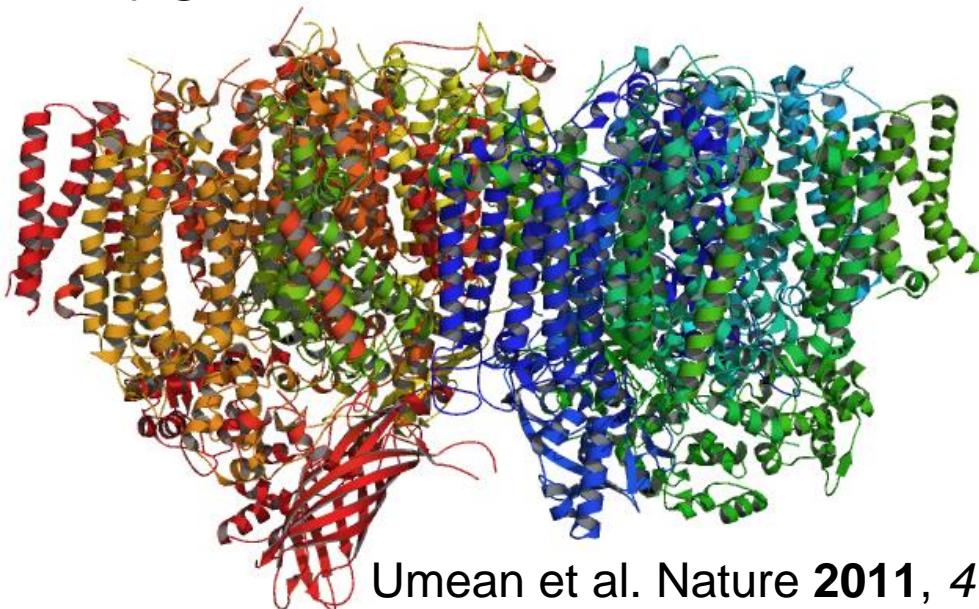


Quick Overview of Physical Methods for Observations and Characterization of Bioinorganic Systems

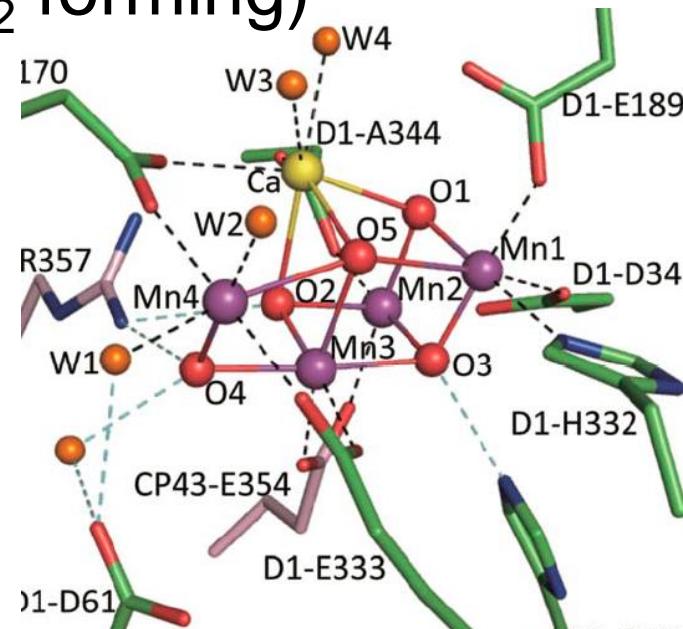
A professional reference book: Physical Methods in Bioinorganic Chemistry: Spectroscopy and Magnetism Ed. by L. Jr. Que, Univ Science Books; 2000

- **X-Ray Diffraction:** the best method to see 3D atomic structure clearly, mostly **static** structures (except time-resolved); challenging crystallization of flexible systems.
- **Electron Microscopy (EM):** 3D structure with medium resolution. **Cryo-EM** is a recent popular method to give a better resolution for large systems.

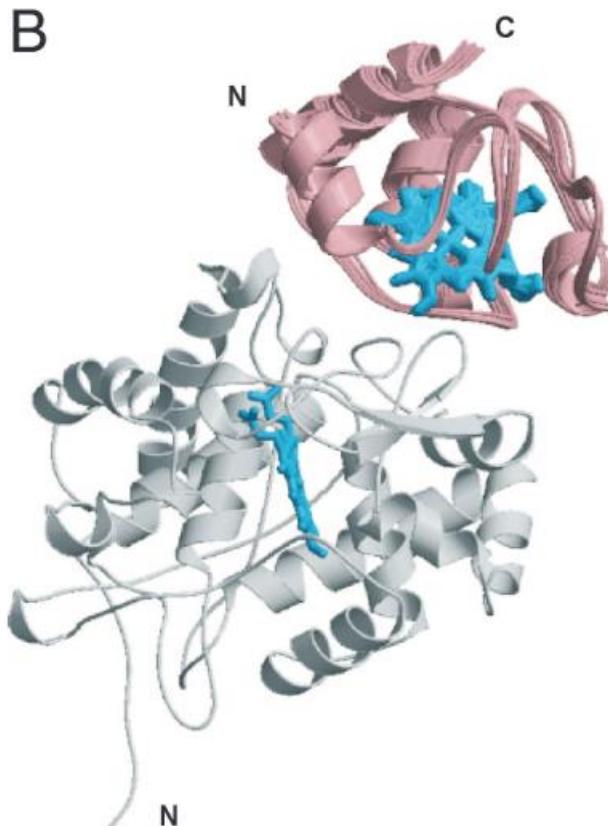
X-ray crystal structure of Photosystem II (**PSII**) with Oxygen Evolution Center (**OEC**, O₂ forming)



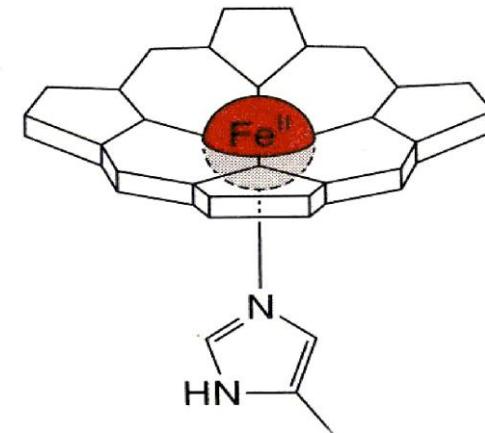
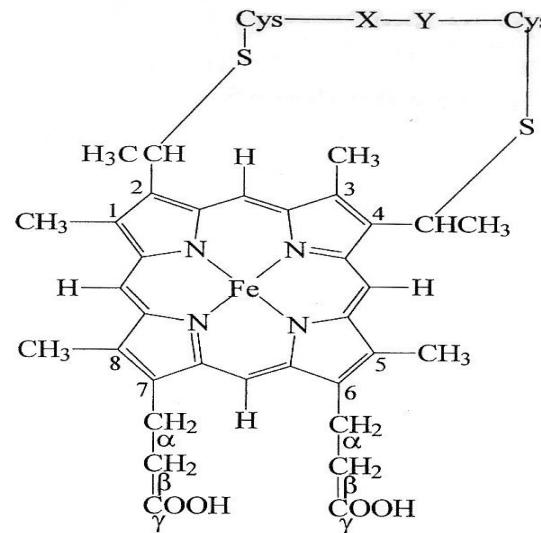
Umean et al. Nature 2011, 473, 55



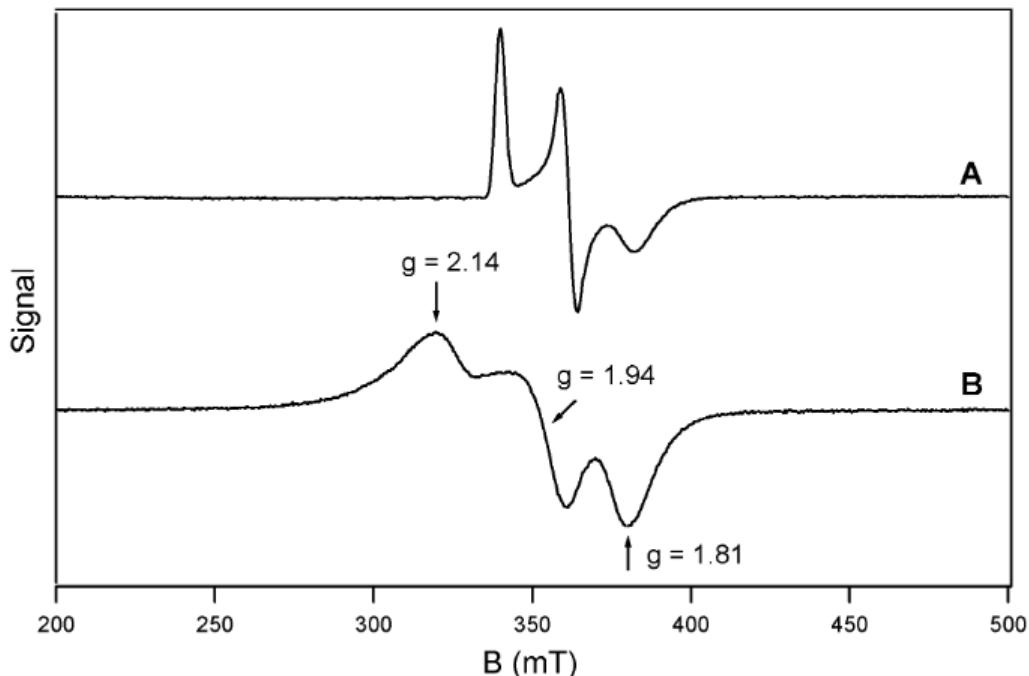
● (Paramagnetic) NMR: local structure/environment and dynamical properties; nuclear spin/electronic spin interaction; ^1H , ^{13}C , ^{15}N ; chemical shifts and line width; can work with small systems, hard to apply to large and complex systems.



Solution structure & dynamics of Cytochrome c by paramagnetic NMR



● Electron Paramagnetic Resonance (EPR): electronic properties (e.g. ground-state wave function) of paramagnetic species containing **unpaired electrons**; electronic spin/magnetic field interaction; hard to get detailed structures.



Active site of Rieske protein

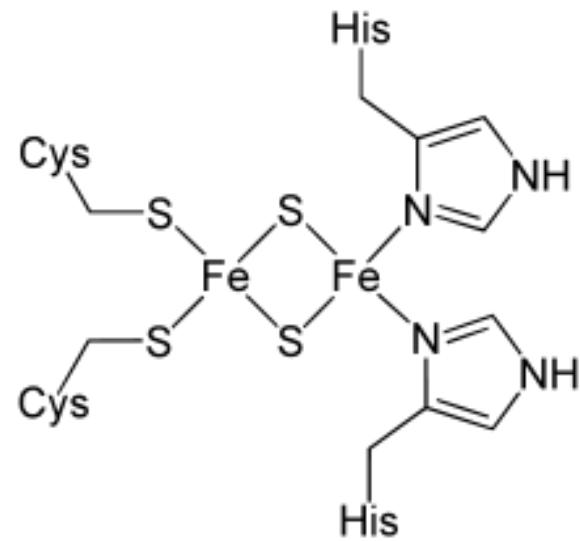
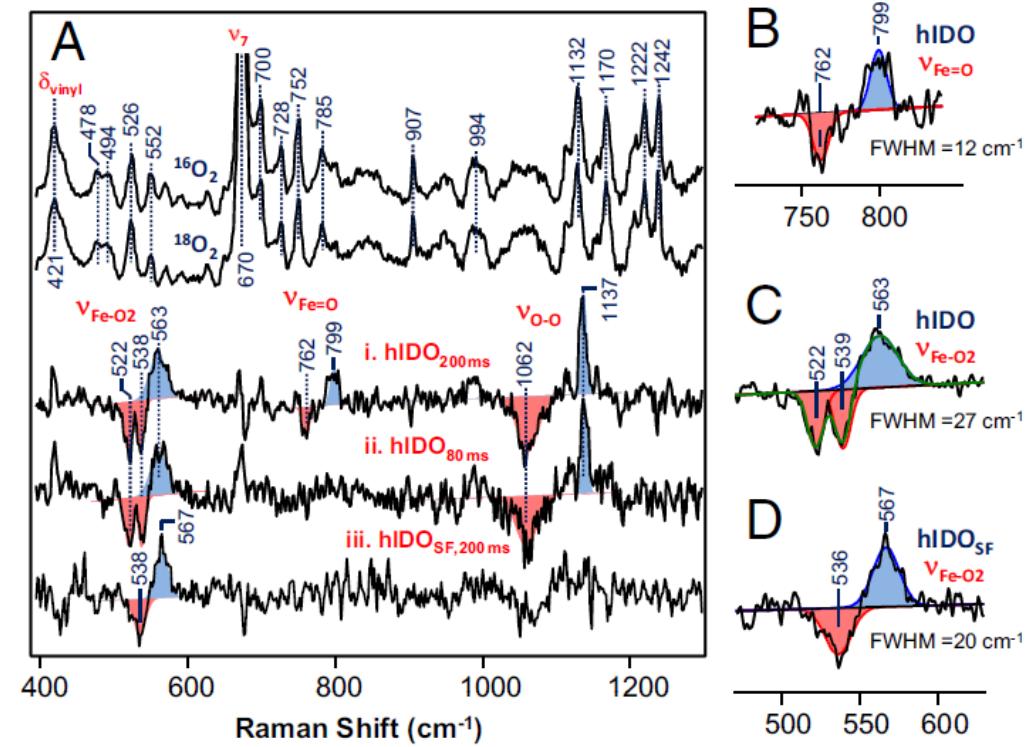


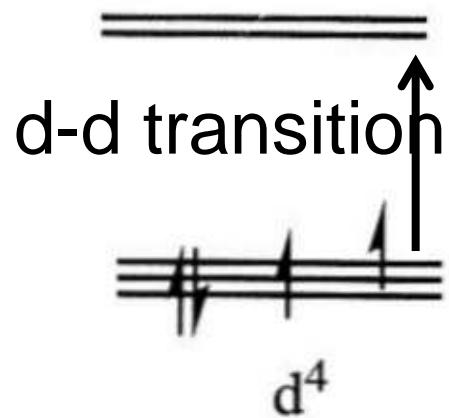
Figure 1. EPR spectra of *Tt* Rieske protein at pH 7 (A) and pH 14 (B). Conditions: $T = 18 \text{ K}$; 9.62 GHz; 0.2 mW (A) and 2 mW (B) microwave power, 1 mT modulation.

- **Mössbauer Spectroscopy:** identification of species with quadrupole coupling (e.g. ^{57}Fe (abundant ~2.2 %); **oxidation & spin states** & coordination environment of the iron metal; hard to get detailed structures.
- **IR & Resonance Raman (RR):** Vibrations/bonding of M-L bonds.



Resonance Raman of
indoleamine dioxygenase
(IDO, heme)

- UV-Visible Spectroscopy: electronic properties (ligand field): d-d transitions (very weak intensity); LMCT/MLCT (charge-transfer states).



Fingerprint of an heme protein (porphyrin $\pi \rightarrow \pi^*$): very intense Soret band (350 - 450 nm)

Absorption Spectra of indoleamine dioxygenase (IDO, heme)

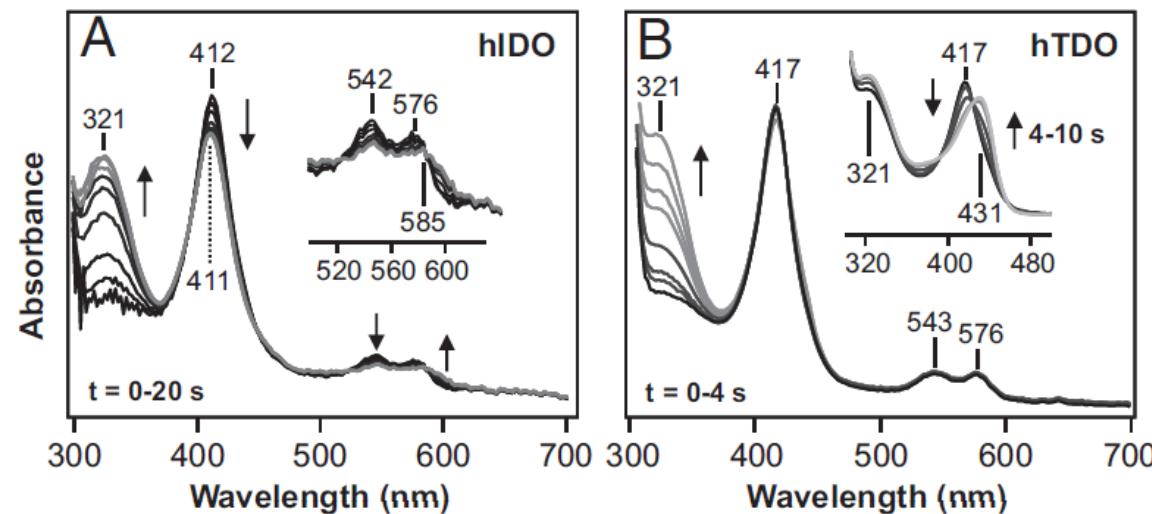
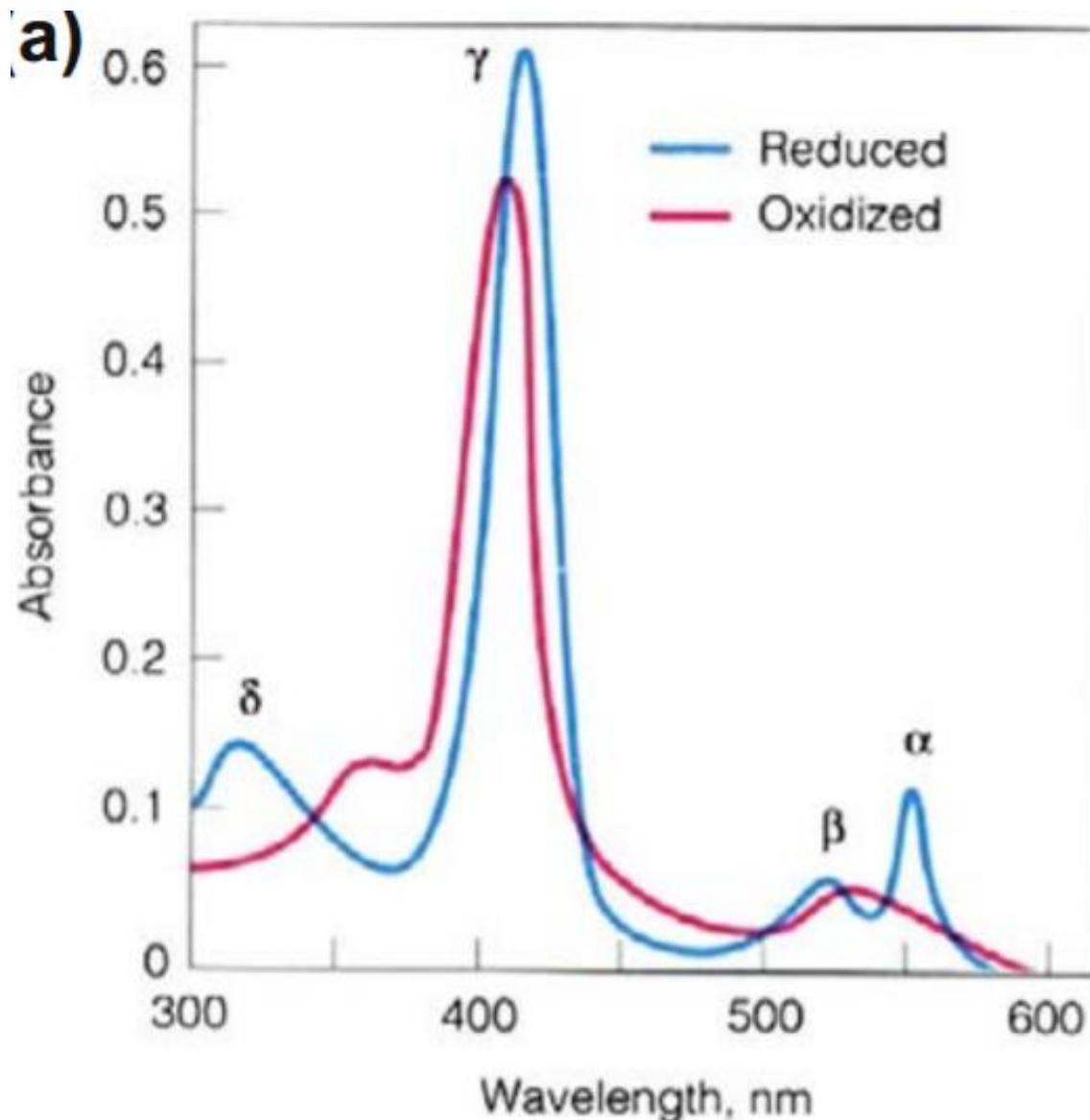


Fig. 1. Time-resolved absorption spectra obtained following the mixing of deoxy hIDO (A) or hTDO (B) with O_2 -containing buffer in the presence of L-Trp in a stopped-flow system. The time-dependent spectra in (A) and (B) were obtained in the 0 to 20 s and 0 to 4 s time window, respectively. The inset in (B) shows the data obtained in the 4 to 10 s time window. The associated kinetic traces are shown in Fig. 2. The inset in (A) shows the expanded view of the visible region of the spectra.

Visible absorption spectrum of Cytochrome c

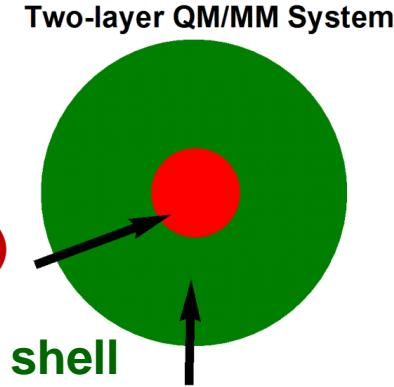


Cytochrome c

- **X-ray Absorption Technique, Extended X-ray Absorption Fine Structure (EXAFS):** the system with no single crystal; oxidation state & environment of the nucleus (identity of the ligands, M-L distance).
- **Cyclic Voltammetry:** characterization of redox.
- **Mass Spectroscopy:** info. of mass.
- **Computational CHEM, Quantum Mechanics + Classical Mechanics;** atomic structures (e.g. TS), energy, electronic structures.



Key part of the reaction by high-level QM method (accuracy)

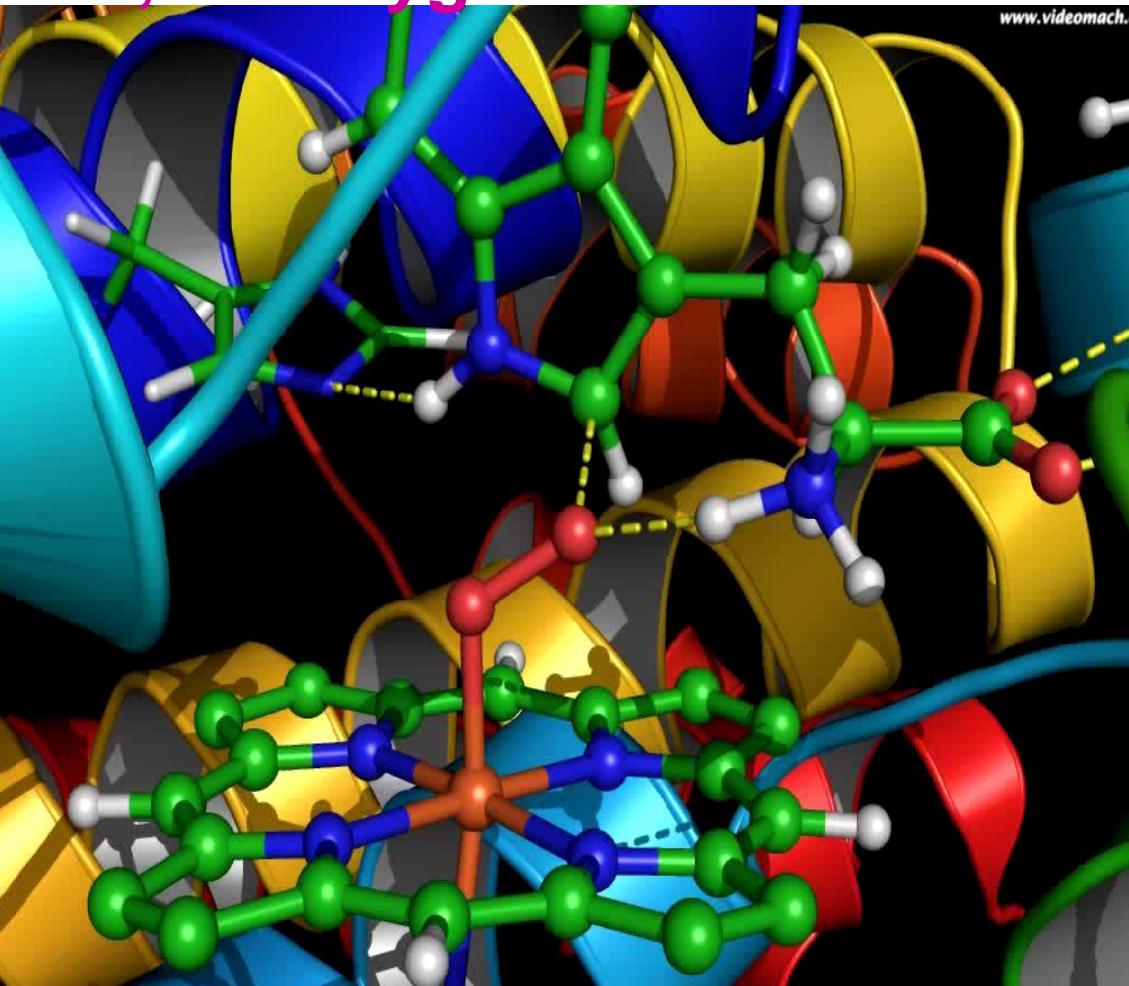
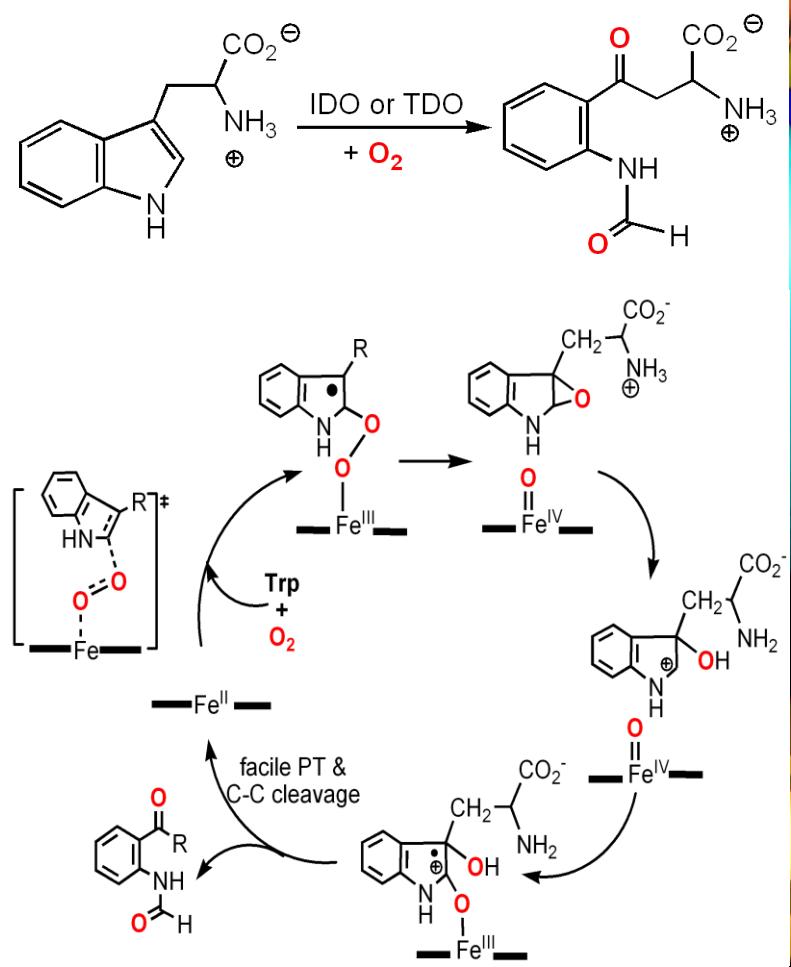


The large protein & water shell by low-level MM method (speed)

The Nobel Prize in Chemistry 2013

was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

QM/MM for Tryptophan 2,3-Dioxygenase



Chung, L. W.; Li, X.; Sugimoto, H.; Shiro, Y.; Morokuma, K.
JACS 2010, 132, 11993

Emma Curr. Opin. Chem. Biol. 2012, 60.

One of two very prescient and insightful computational papers from Chung *et al.* (see also [52]), which together present likely (as well as unlikely) mechanisms to guide experimental work. The computational data overall do not support base-catalyzed abstraction (subsequently confirmed experimentally [45**]), or the Criegee/dioxetane mechanisms previously proposed [8]; and they implicated both ferryl heme (subsequently identified experimentally [48**]), epoxide formation (suggested later [48**]), and ring opening of the epoxide (subsequently inferred from experimental work [53]).

| Method | Parameters | Information content |
|--|--|---|
| Magnetic susceptibility | Molecular g-value, axial and rhombic zero-field splitting, exchange interaction | Number of unpaired electrons/ground spin state; defines antiferromagnetic and ferromagnetic interactions; quantitates ground sublevel splittings |
| Mössbauer spectroscopy | Quadrupole coupling, isomer shift | For ^{57}Fe sites: oxidation and spin state; chemical environment |
| Electron paramagnetic resonance (EPR) | Quadrupole tensor, nuclear Zeeman splitting, g values, coupling constants, relaxation times | Usually for odd electron metal sites: probes ground-state wave function at high resolution |
| Electron-nuclear double resonance (ENDOR) | | Combines sensitivity of EPR and high resolution of NMR to probe ligand superhyperfine interactions |
| Nuclear magnetic resonance (NMR) | Chemical shift, nuclear coupling constants, relaxation times | For paramagnetic proteins: enhanced chemical shift resolution, contact and dipolar shifts, spin delocalisation, magnetic coupling from temperature dependence of shifts. |
| Vibrational spectroscopy (Raman and IR) | Energies (with isotope perturbation), intensities and polarisations | Identification of ligands coordinated to a metal centre |
| Electronic absorption spectroscopy (ABS) | Energies, intensities, and band shapes | Direct probe of ligand field and charge transfer excited states |
| Magnetic circular dichroism (MCD) | Same as ABS plus circular polarisation induced by applied magnetic field and magnetic susceptibility | Greater sensitivity than ABS in observing weak transitions and greater resolution due to differences in circular polarisation; complimentary selection rules aiding in assignment of electronic transitions |
| Circular dichroism (CD) | Same as ABS plus circular polarisation due to asymmetric nature of metal site | Allows detection of transitions not readily observable in absorption |
| Resonance Raman spectroscopy | Intensity profiles, depolarisation ratios | Allows study of chromophoric active sites in biological molecules at low concentration; can provide information on metal-ligand bonding |
| Extended X-ray absorption fine structure (EXAFS) | Energies, intensities, and polarisations | Identity of ligand atoms: distance of ligand atoms from metal: number of scattering ligands of a given type |
| X-ray diffraction | Atomic coordinates at a given resolution | Identity of ligands to metal centre (but distances more precise by EXAFS) |

Key Summary

Bioinorganic Chemistry: metal-containing molecules & their reactions in biological system. Many transition metals were found to involve in bioinorganic systems.

General Roles of the Metal(s): structures, functions, chemical reactions & medicine.

Thermodynamics & Kinetics of Metal-Ligand bond: depends on the identity of metals & ligands (e.g. HSAB, chelate effect, ligand effect); Various metal-ligand binding for various biological functions.

Combinations of Physical Methods: Observations & characterization of bioinorganic systems.

**Thank You for Your
Attention!
Any Questions?**