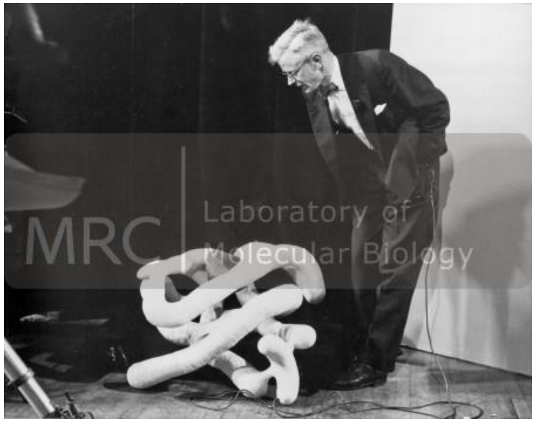
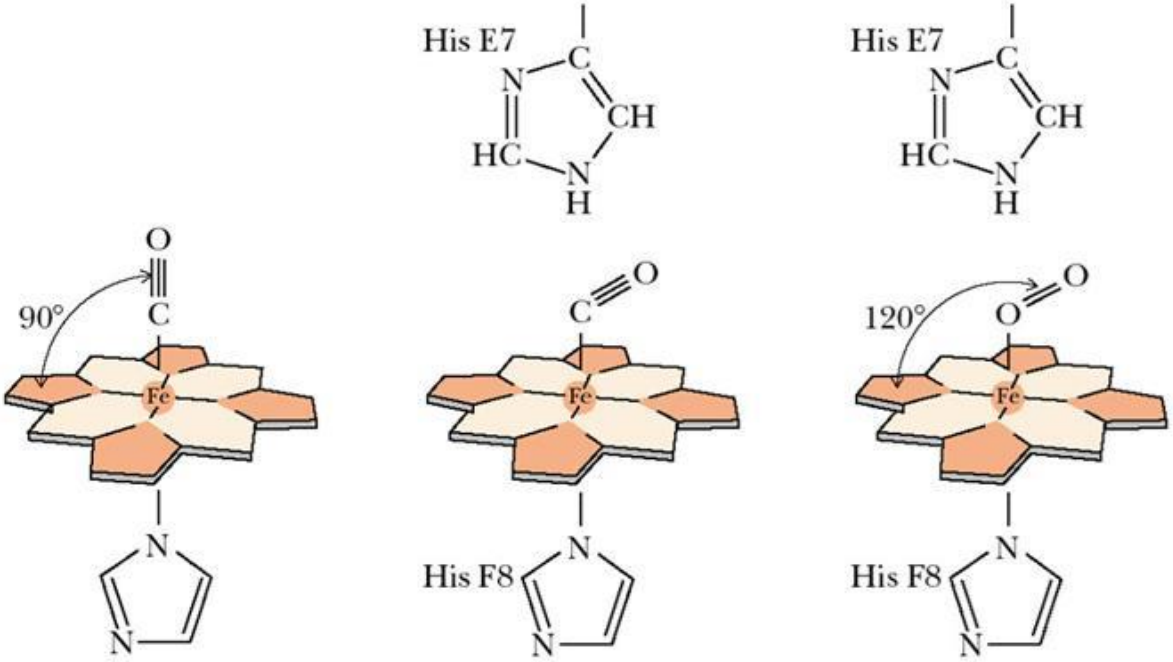
Pregunta: Qué es esto?



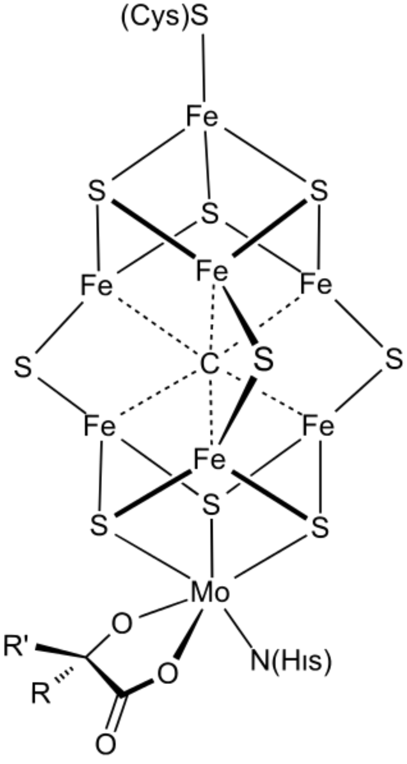


Química de Coordinación

UNAM Mayo 16, 2017

peter.kroneck@uni-konstanz.de
https://www.researchgate.net/profile/Peter_Kroneck

Iones metálicos en sistemas vivos - Metaloenzimas y metaloproteínas



$$N_2 + 8H^+ + 16\ Mg^{2+}\text{-ATP} + 8e^-$$

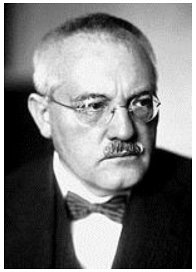
$$\downarrow$$

$$2NH_3 + H_2 + 16\ Mg^{2+}\text{-ADP} + 16\ P$$

N_2 Fixation

http://en.wikipedia.org/wiki/Nitrogenase

F. Haber



R. Bosch

Trayendo Química Inorgánica a Vida...

Biochemistry

Biogeochemistry

Physiology

Molecular Biology

Biophysics

Química de Coordinación Bioinorgánica

Microbiology

Environmental Chemistry

Spectroscopy

Structural Biology

Catalysis

Physical Chemistry

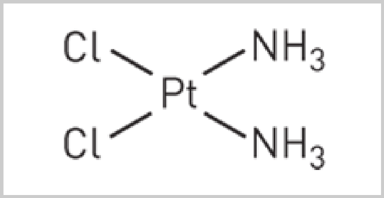
Medical Chemistry/Toxicology

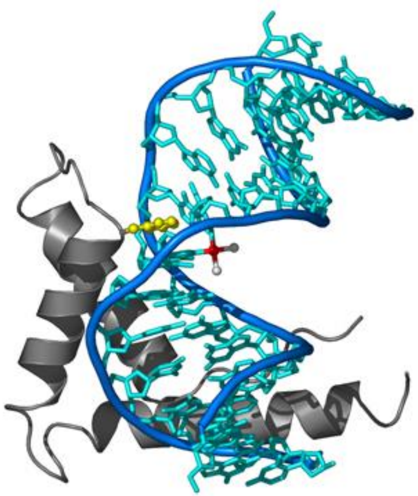
Metales y Vida: la Química de Coordinación de la Naturaleza

“El uso de metales para tratar dolencias humanas se remonta al menos al quinto siglo a. de J.C., y el estudio y la imitación de metales en la biología son un sujeto vibrante hoy”

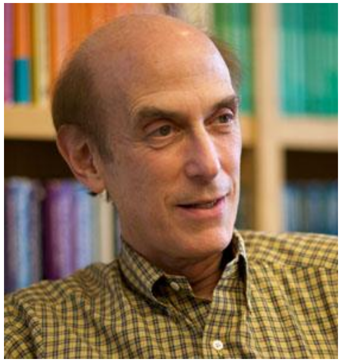
Stephen Lippard, J Am Chem Soc (2010), 132, 141689-14693

B. Rosenberg et al., (1965) Nature, 205, 698 - 699





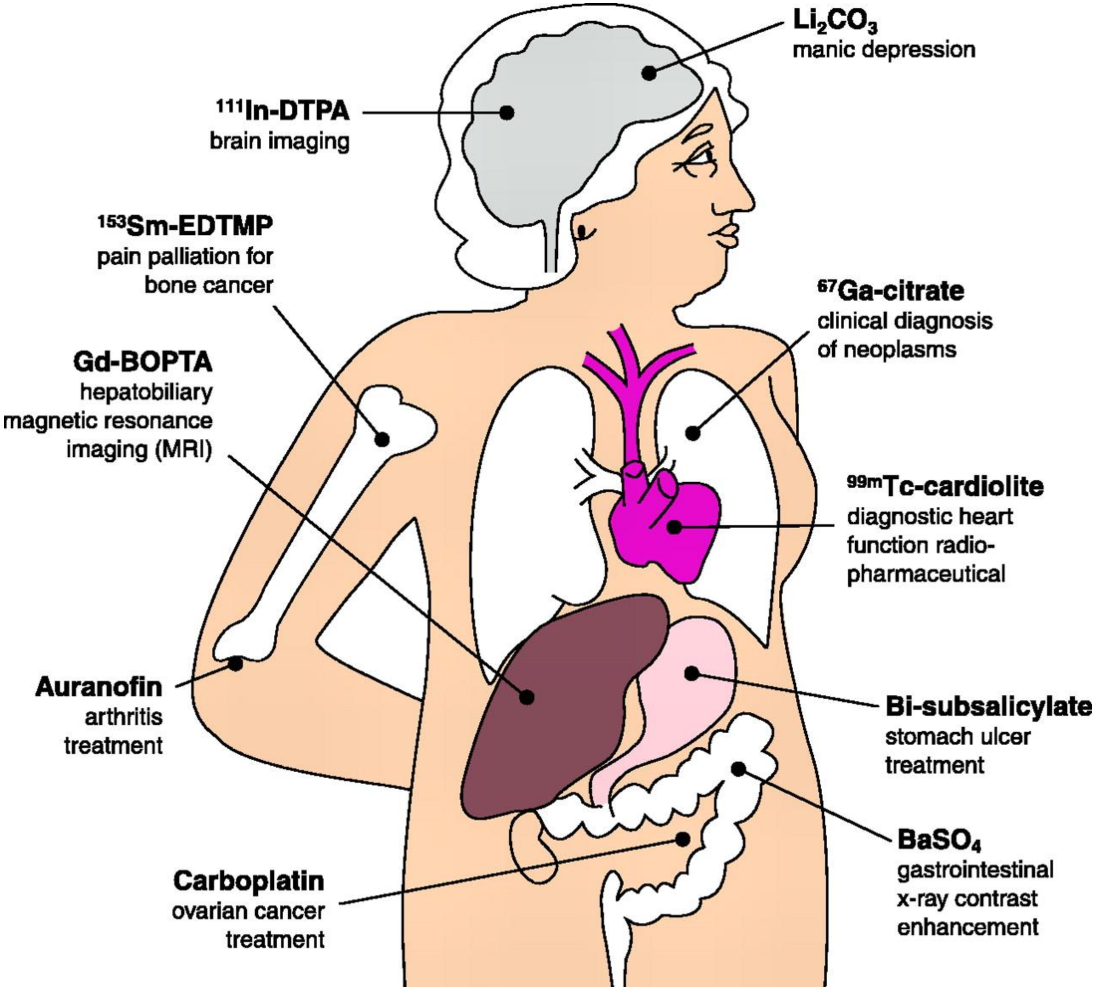
Cisplatin-DNA adduct bound to HMGB1. Cisplatin shown as red and white spheres; DNA is shown in blue; HMBG1 shown as grey cartoon with intercalated phenylalanine shown as yellow spheres. Image credits: Michael S. McCormick.



Metales en Medicina – Aplicaciones

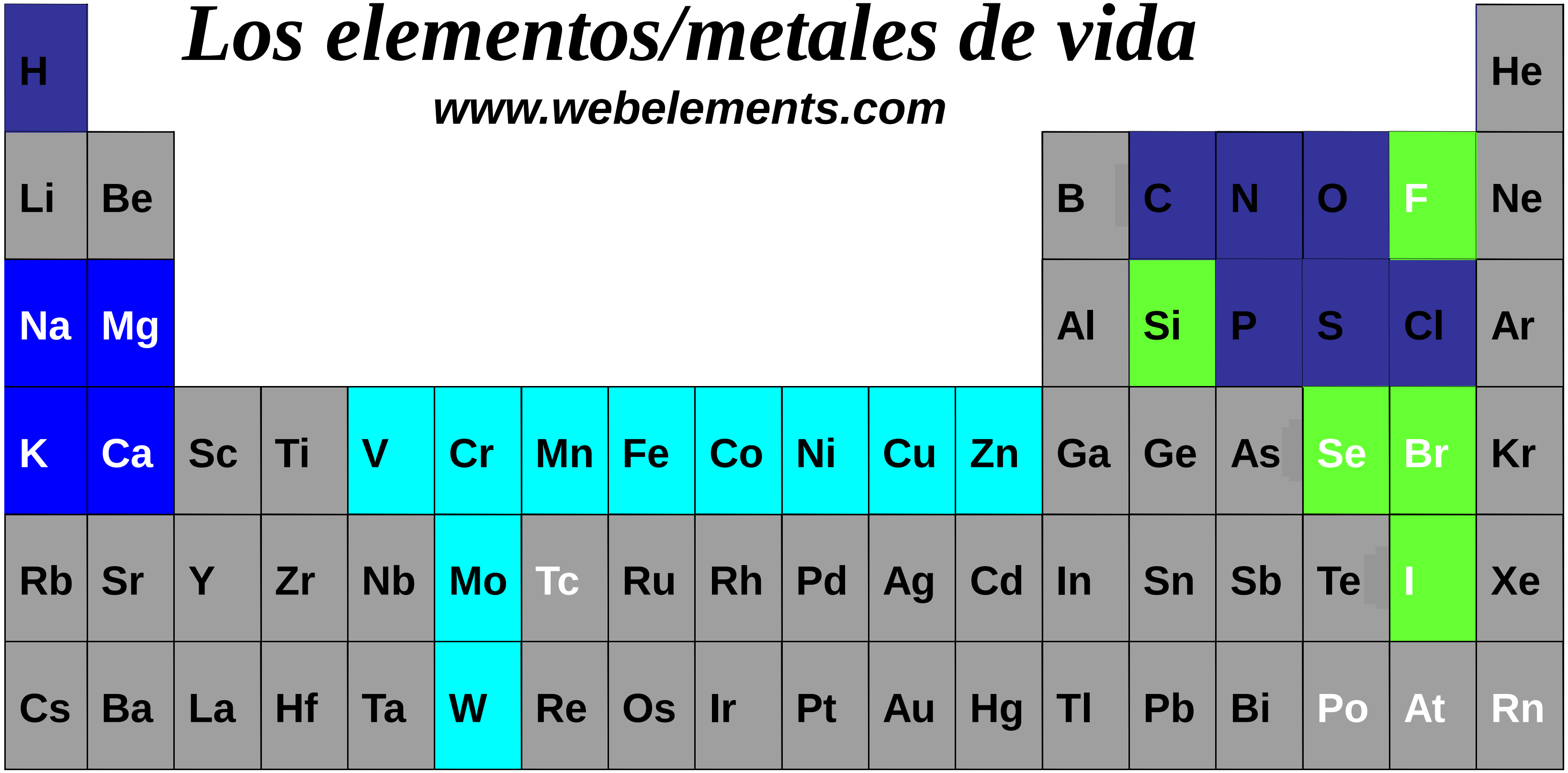
"Uno de los desafíos de diseñar medicinas basadas en el metal es equilibrar la toxicidad potencial de una formulación activa con el impacto positivo sustancial de estos recursos terapéuticos y diagnósticos cada vez más comunes"

K.H. Thompson, C. Orvig (2003) Science 300, 936-939



Los elementos/metales de vida

www.webelements.com



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

Ca: 1.2 kg
K: 150 g
Na: 70 g
Mg: 20-30 g

Essential Transition Metals
Fe: 4.5 g
Zn: 2.3 g
Cu: 72 mg
Mo: 9 mg

Los metales de transición están bajo el control estricto dentro de la célula viva; por lo general ligado a proteínas, péptidos u otras moléculas.
En la QUÍMICA: COMPLEJO DE METAL DE TRANSICIÓN

Bibliografia Basica y Complementaria

J.J.R. Fraústo da Silva, R.J.P. Williams, 2001
The Biological Chemistry of the Elements, Oxford University Press

R. R. Crichton, 2008 y 2012
Biological Inorganic Chemistry, Elsevier

Chemical Reviews, 1996; 2004; 2014
Special Issues on Bioinorganic Enzymology

Inorganic Electronic Structure and Spectroscopy, 1999 (advanced book)
(eds E.I. Solomon, A.B.P. Lever), John Wiley & Sons, LTD

Sitios Web Importantes

http://www.rcsb.org/pdb/home/home.do

comprehensive database of all published protein structures

http://www.brenda-enzymes.org/

comprehensive enzyme database including information on metal requirements

http://www.webelements.com

periodic table of the elements including useful information on each element

PDB Database

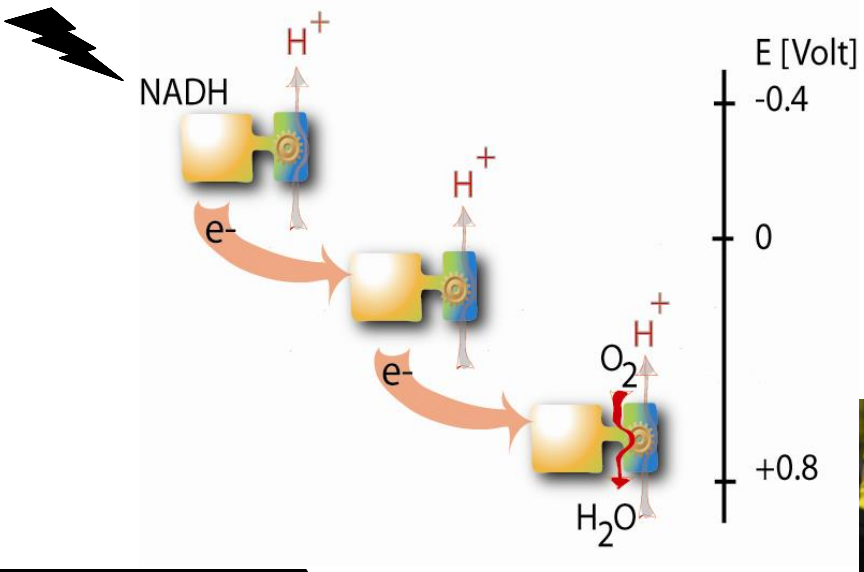
- **PDB = Protein Data Bank: http://www.rcsb.org/pdb/home.do; type in the search field the PDB number**

- **1A70 (for Ferredoxin)**

Por qué investigan metales en la biología?

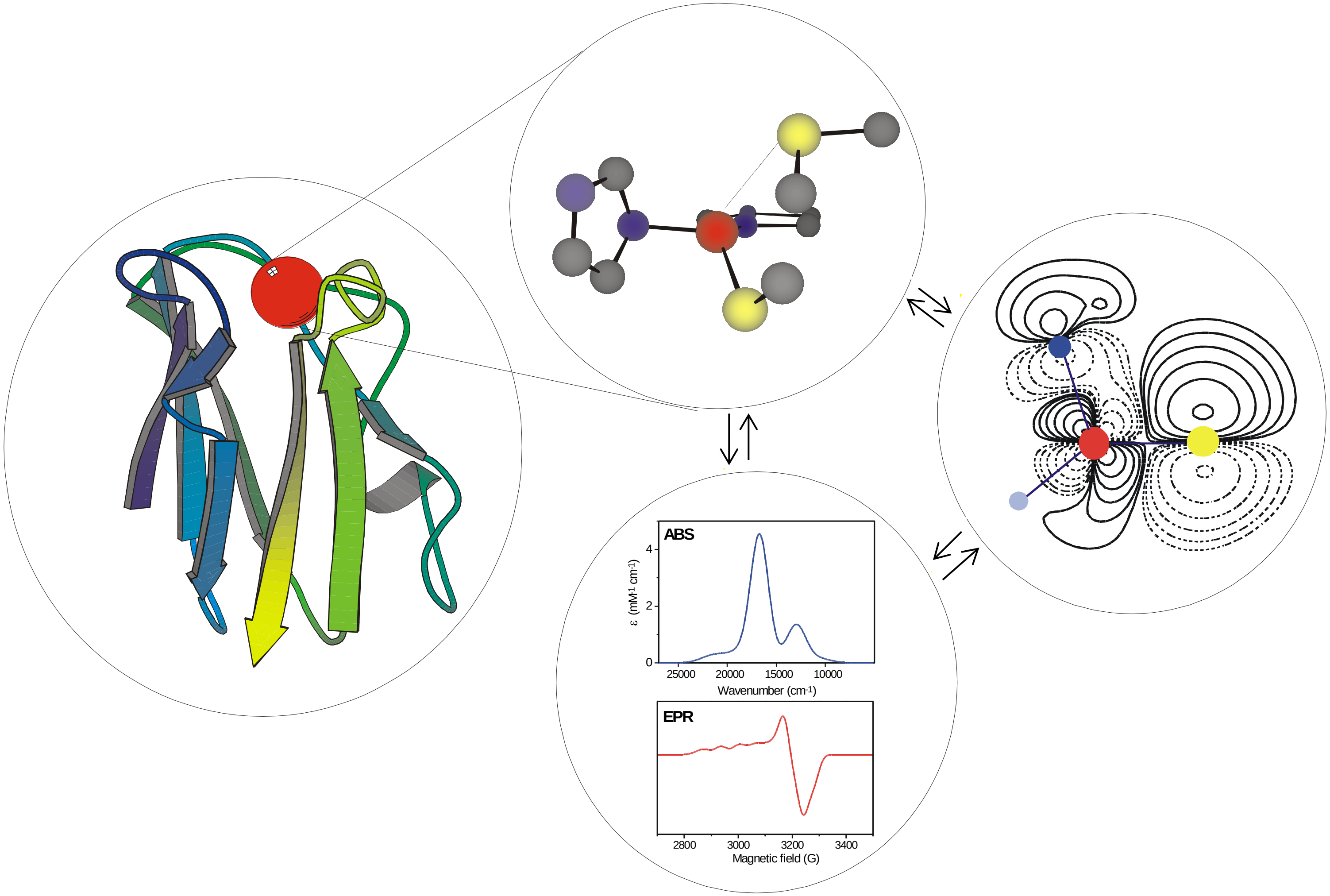
- **Hay apenas cualquier proceso importante en la naturaleza que no depende de un ión metálico; ~ 1/3 de las proteínas del genoma humano dependen de iones metálicos**
- **Dos ejemplos importantes:**
- **Catálisis ácida y baja (Zn)**
- **Química de redox – transferencia de protones y electrones, conservación de la energía (Fe,Cu)**

Transferencia de H^+ y e^-
Conservación de energía de hoy: reducción $O_2 \rightarrow H_2O$



$$\boxed{\Delta G^{o\prime} = -nF\Delta E^{o\prime}}$$

Objetivo:
Estructura 3D y Electrónica - Función - Mecanismo



Por qué (transición) iones de metal ?

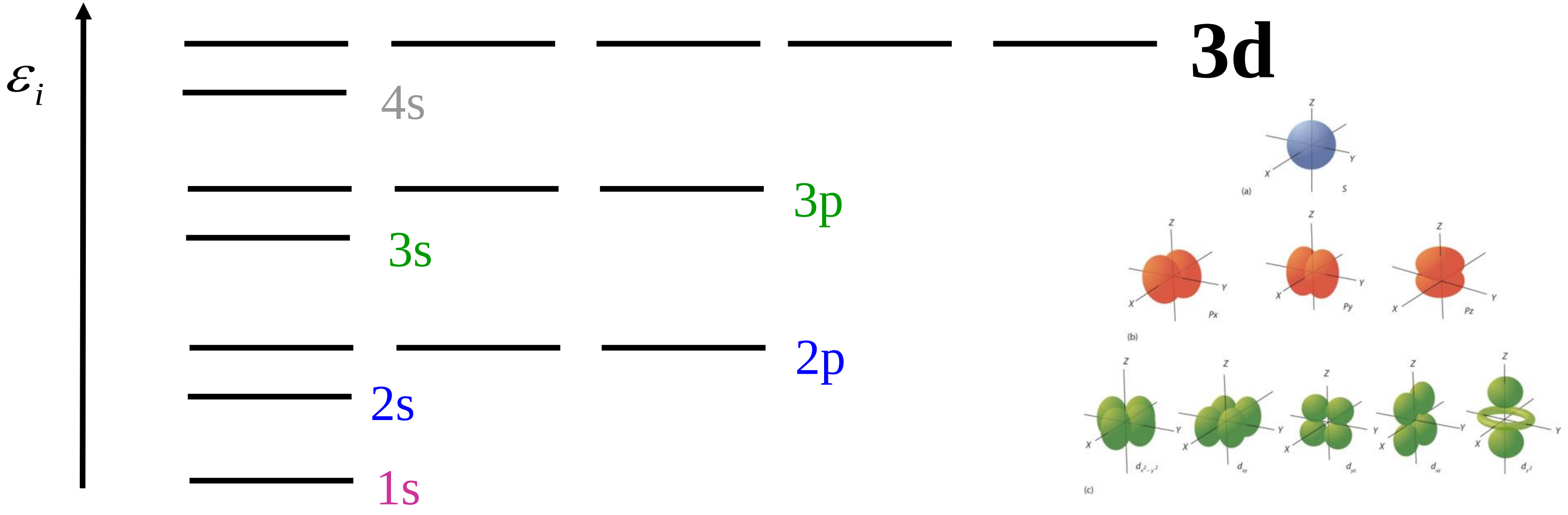
- **<u>Positively Charged</u>**
  - **Lewis Acids**
  - **Stabilization of Anions**
- **<u>Loosely Bound Electrons</u>**
  - **Redox Active**
  - **Multiple Redox States**
  - **Easily tunable Redox Potential**
- **<u>Redox/Acid Base Chemistry</u>**

- **<u>Open Shell Systems</u>**
  - **No Problems with Spin Restriction**
- **<u>Stereochemically Flexible</u>**
  - **Large Variety of Structures.**
  - **Little Reorganization**
  - **Facile Ligand Addition/Dissociation**
- **<u>Facilitate Reactions of Bound Ligands</u>**

Periodic Table - Electrons

www.webelements.com

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
					Mo												
					W												



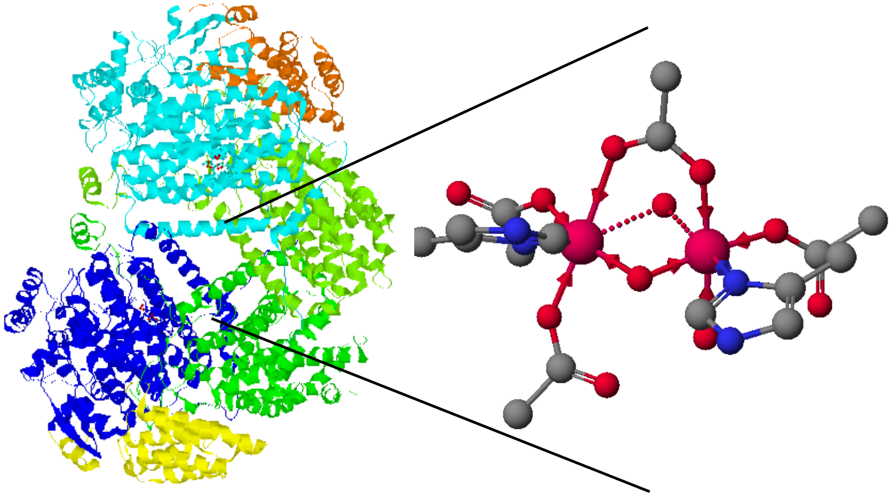
Propiedades básicas de un complejo de la proteína metálico

Chem. Rev. 96, 2239-2314 (1996) RH Holm, P Kennepohl, E I Solomon, Structural and Functional Aspects of Metal Sites in Biology

Prot-L| --------M

δ- δ+

strong attraction

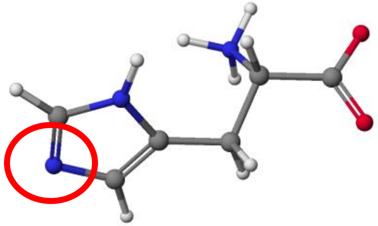


$CH_4 + O_2 + 2e^- + 2H^+ \rightarrow CH_3OH + H_2O$

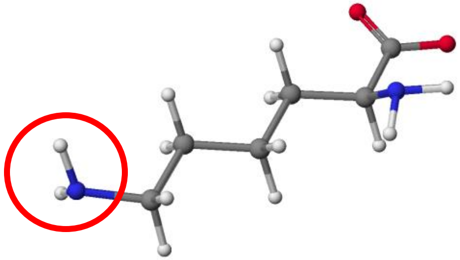
Química en el Centro Catalítico (Sitio activo) de la Enzima de Hierro Metano Monooxigenasa

Ligantes en proteínas – residuos del aminoácido

N

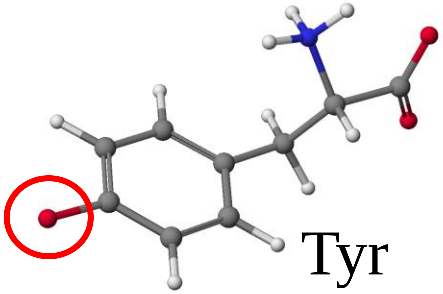


His

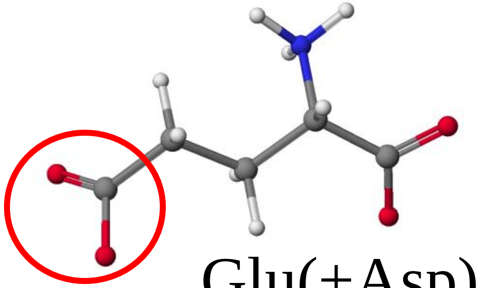


Lys

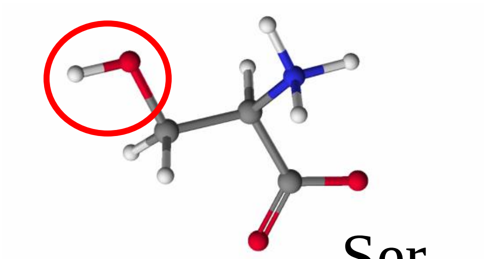
O



Tyr

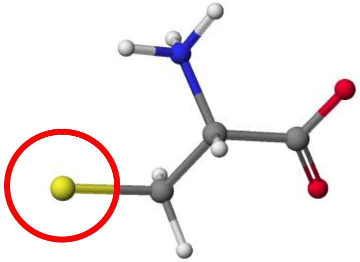


Glu(+Asp)

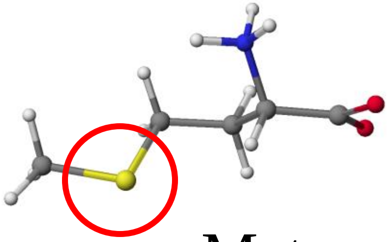


Ser

S

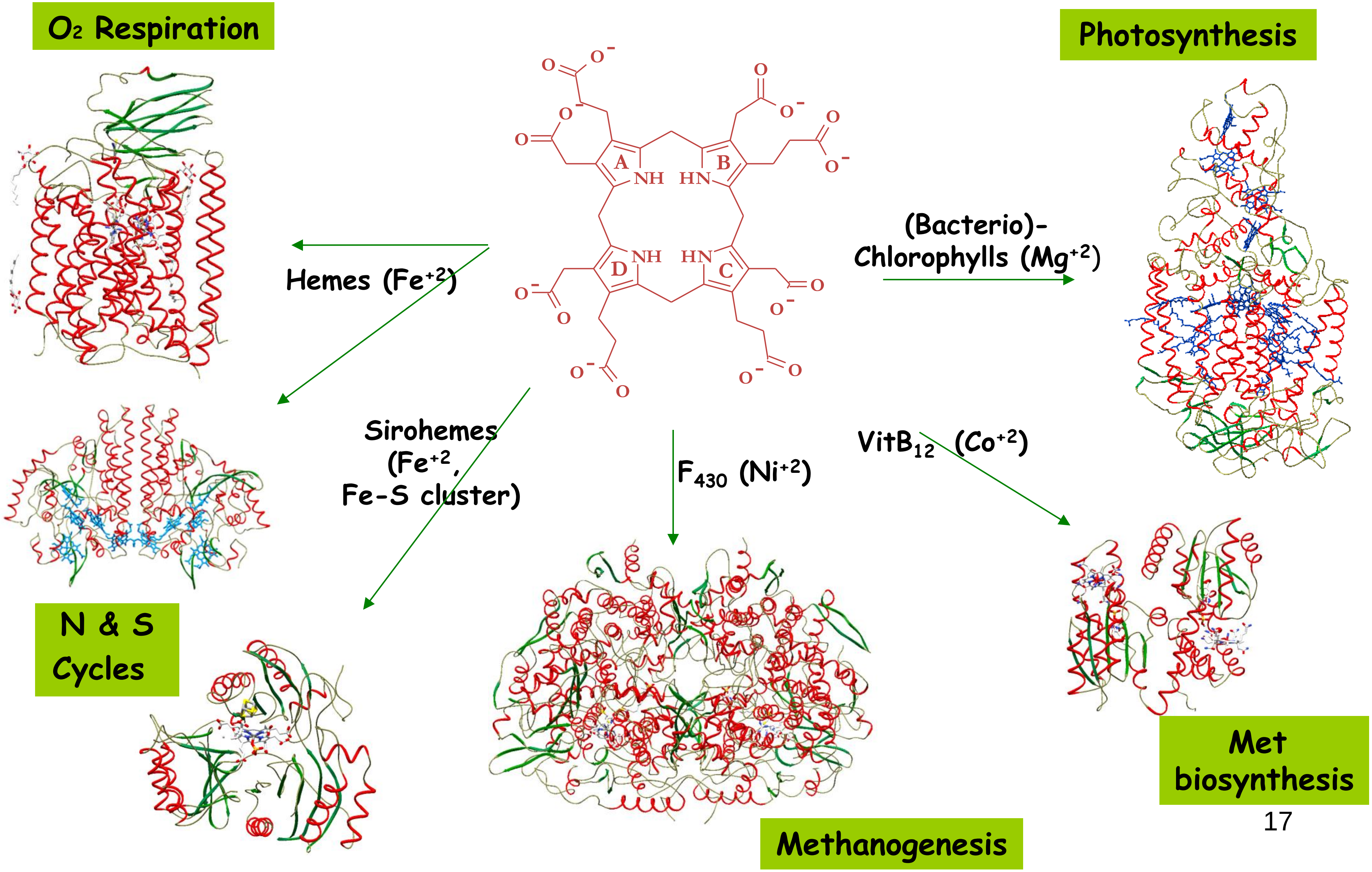


Cys



Met

Tetrapirrol está compuesto por 4 unidades de pirrol (porfirinas y ftalocianinas; clorofila, citocromos, pigmentos biliares y vitaminas)



O_2 Respiration

Photosynthesis

Hemes (Fe^{+2})

(Bacterio)-
Chlorophylls (Mg^{+2})

Sirohemes
(Fe^{+2},
Fe-S cluster)

F_{430} (Ni^{+2})

$VitB_{12}$ (Co^{+2})

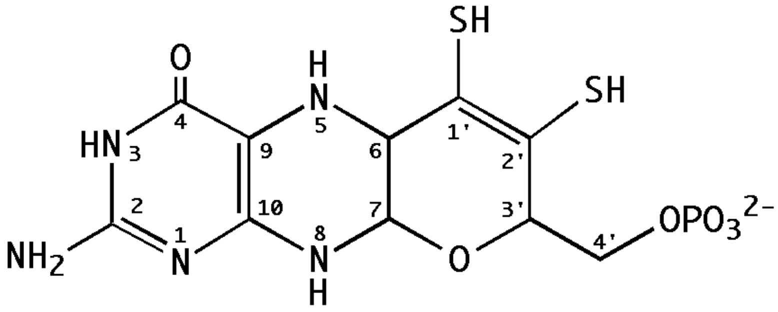
N & S Cycles

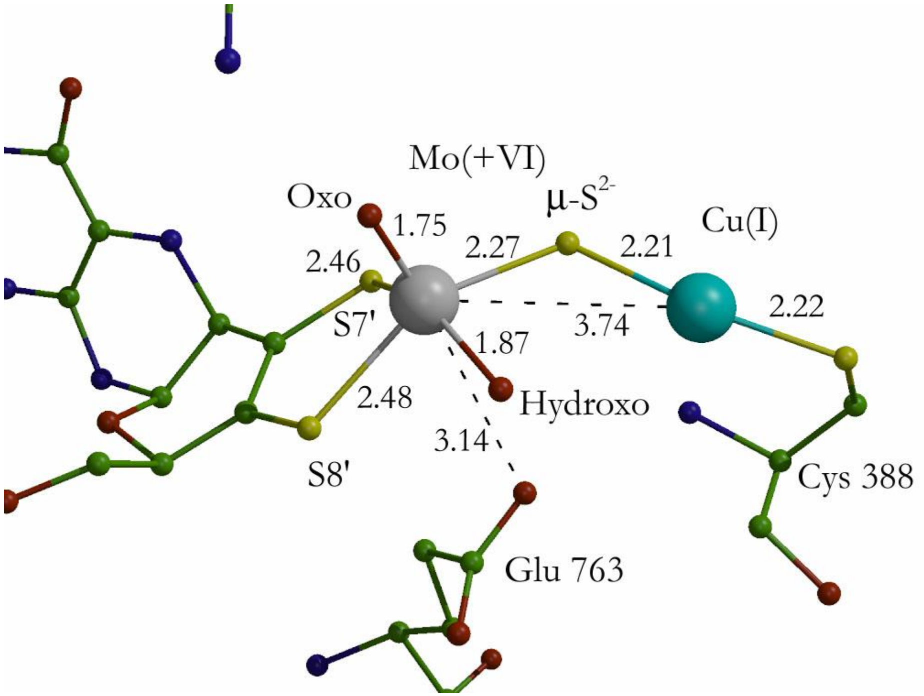
Met biosynthesis

Methanogenesis

Molybdopterin, un ligante que liga el Mo y el W

JOURNAL of BIOLOGICAL CHEMISTRY (2009) Vol. 284, p. e10, N Kresge, R D Simoni, R L Hill: The Discovery and Characterization of Molybdopterin - the Work of K. V. Rajagopalan





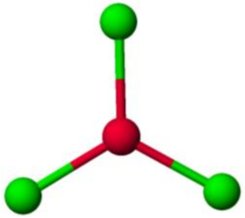
Mo-S-Cu Cluster in CO Dehydrogenase from *Oligotropha carboxidovorans* :

$CO + H_2O \rightarrow CO_2 + 2\,H^+ + 2e^-$

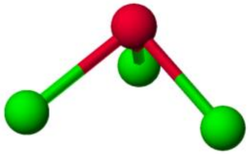
H Dobbek et al., Proceedings National Academy of Sciences/USA, 99, 15971-15976 (2002)

Geometría – Número de Coordinación

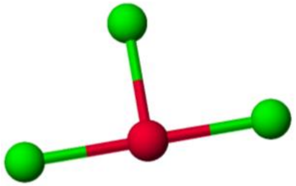
3



Trigonal

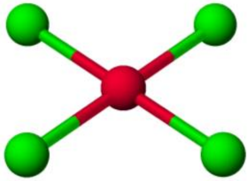


Trigonal pyramidal

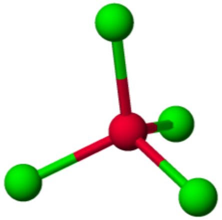


T-shape

4

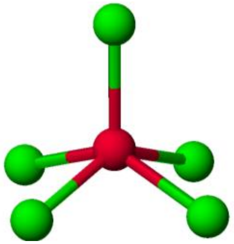


Square planar

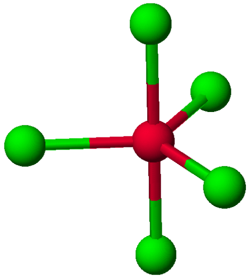


Tetrahedral

5

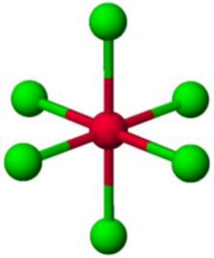


Square pyramidal



Trigonal bipyramidal

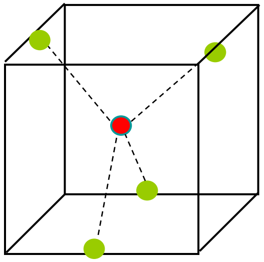
6



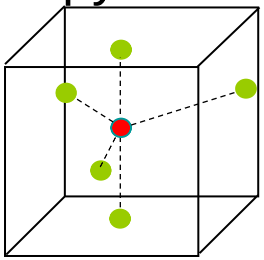
Octahedral

Geometría es importante: Proteínas de Hierro

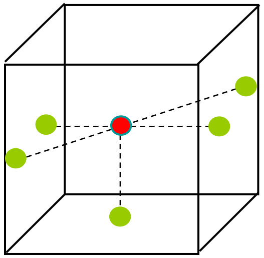
Tetrahedron



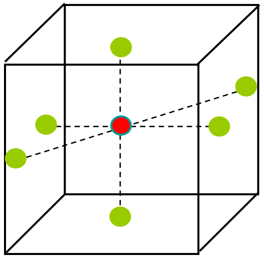
Trigonal Bipyramide

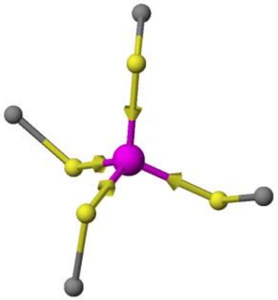


Tetragonal Pyramide

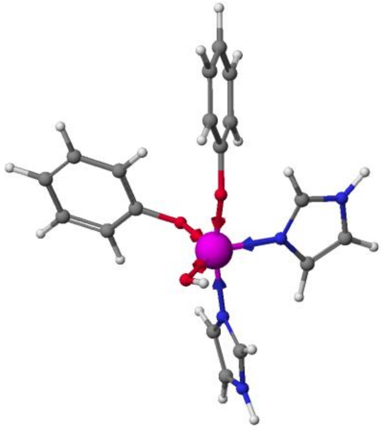


Octahedron

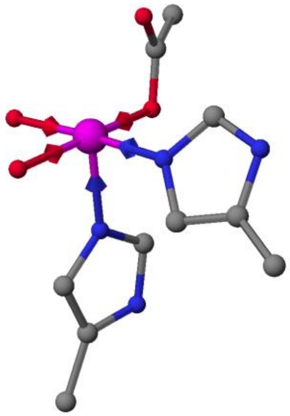




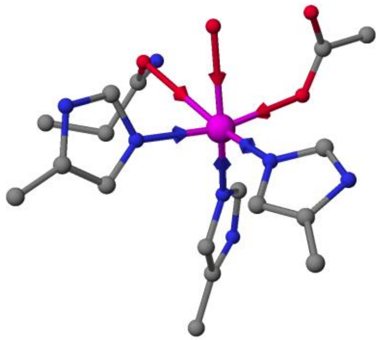
Rubredoxin



3,4-Protocatechoate Dioxygenase



Tyrosine Hydroxylase



Lipoxygenase

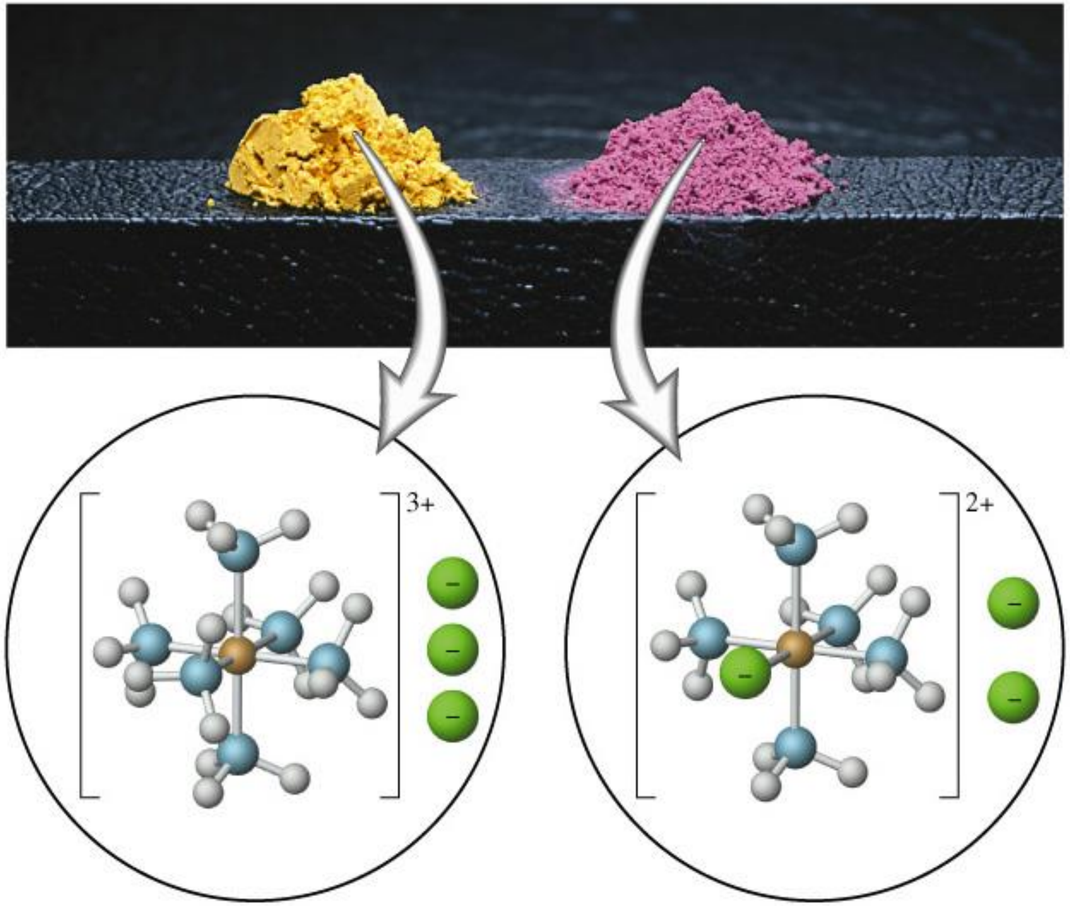
El Solomon, *et al.* (**2000**), Chem. Rev., *100*, 235–350

Color y Magnetismo

Alfred Werner
University of Zürich/CH
Nobel Prize in Inorganic Chemistry, 1913

$Co[(NH_3)_6]Cl_3$

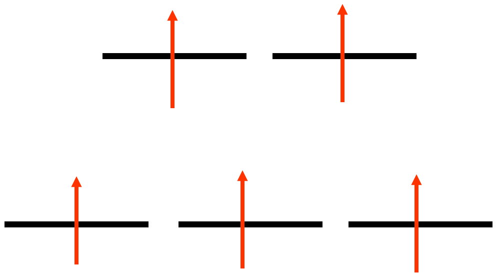
$Co[(NH_3)_5Cl]Cl_2$



Color y Magnetismo

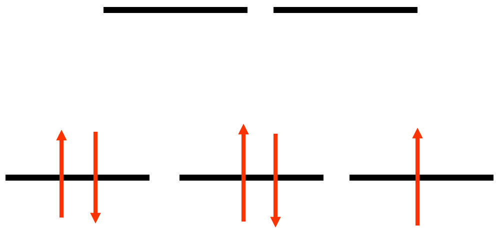
Estados de spin variables de centros metálicos

For a d^5 configuration, Fe(III)



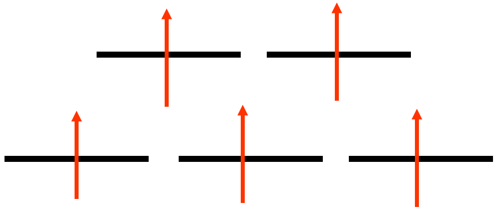
High-Spin, S= 5/2

OR



Low-Spin, S= 1/2

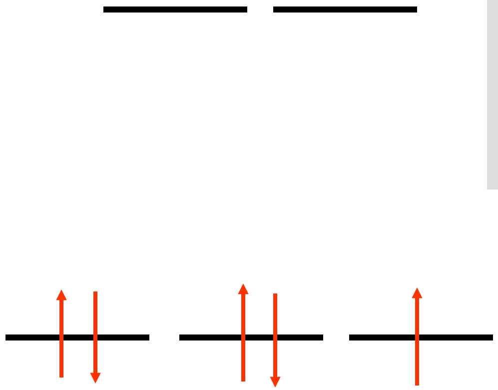
Depending on the METAL ION ENVIRONMENT, balance of Crystal Field Splitting, 10Dq and Spin-Pairing Energy, P



10Dq < P

Weak Field

High Spin

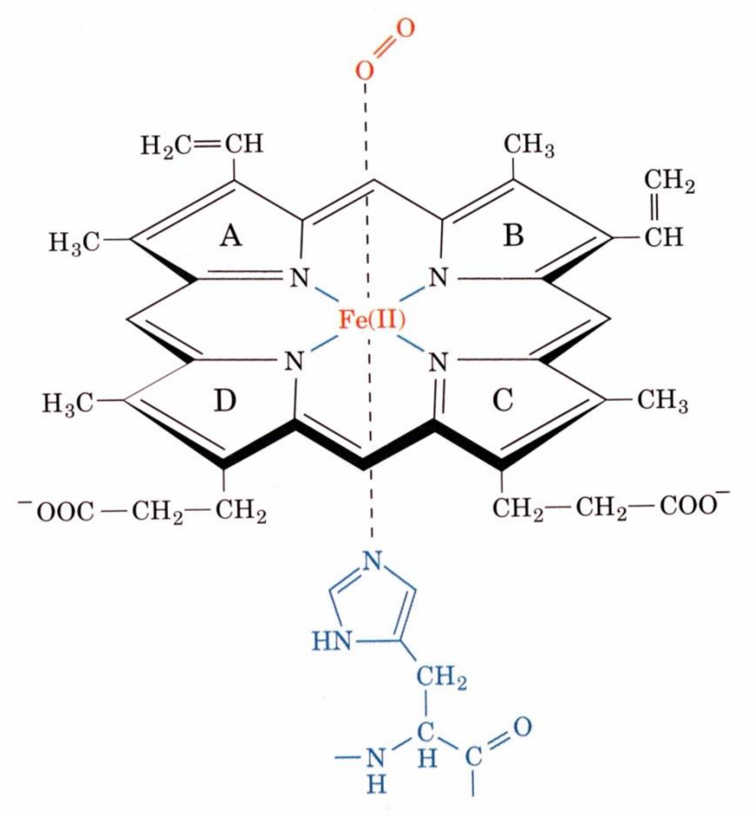


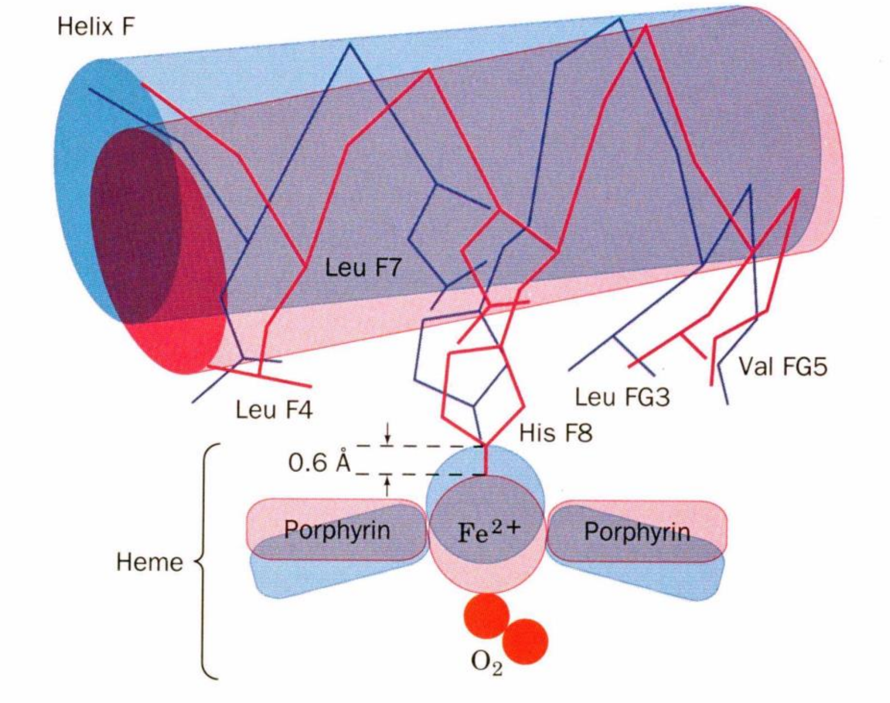
10Dq > P

Strong Field

Low-Spin

Encuadernación reversible de O_2 Myoglobin y Hemoglobin





El hierro debe estar en la oxidación estado Fe (II); Fe(II) high-spin → Fe(II) low-spin.

Metales – Funciones biológicas

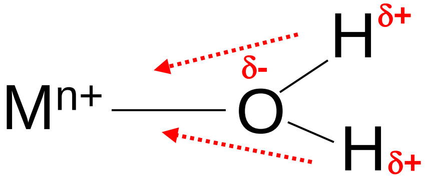
Metal (Ion)	Function, Enzymes
Na	Charge Carrier, Osmolysis/equilibrium
K	Charge Carrier, Osmolysis/equilibrium
Mg	Structure, ATP/ThDP Binding, Photosynthesis,...
Ca	Structure, Signaling, Charge Carrier
V	Nitrogen Fixation, Haloperoxidases, O_2 Carrier
Cr	***Unknown! (glucose metabolism ???)***
Mo	Nitrogen Fixation, Oxidoreductase, O-Transfer
W	Oxidoreductases, Acetylene Hydratase
Mn	Photosynthesis, Oxidases, Structure,...
Fe	Oxidoreductases, O_2 Transport + Activation,e^--Transfer,...
Co	Oxidoreductases, Vitamin B_{12} (Alkyl Group Transfer)
Ni	Hydrogenase, CO Dehydrogenase, Hydrolases, Urease
Cu	Oxidoreductases, O_2 Transport, e^- -Transfer
Zn	Structure, Hydrolases, Acid-Base Catalysis...

Estados de la oxidación de metales en biología

Metal	Valence state (Electron configuration)
Na	Na(I)
K	K(I)
Mg	Mg(II)
Ca	Ca(II)
V	V(V)=(d^0), V(IV)=(d^1), V(III)=(d^2)
Cr	Cr(III)=(d^3),Cr(IV)=(d^2),Cr(V)=(d^1)
Mo	Mo(III)=(d^3),Mo(IV)=(d^2),Mo(V)=(d^1), Mo(VI)=(d^0)
W	W(IV)=(d^2) ,W(V) =(d^1), W(VI)=(d^0)
Mn	Mn(V)=(d^2),Mn(IV) =(d^3),Mn(III) =(d^4),Mn(II) =(d^5)
Fe	Fe(V)=(d^3), Fe(IV)=(d^4),Fe(III)=(d^5),Fe(II)=(d^6), Fe(I)?=(d^7)
Co	Co(III)=(d^6), Co(II)=(d^7), Co(I)=(d^8)
Ni	Ni(III)=(d^7), Ni(II)=(d^8), Ni(I)=(d^9)
Cu	Cu(III)=(d^8), Cu(II)=(d^9), Cu(I)=(d^{10})
Zn	Zn(II) =(d^{10})

Exogenous Ligantes

	Ligand	pK_a
Acid/base	$H_2O/OH^-/O^{2-}$	14,~34
	HCO_3^-/CO_3^{2-}	10.3
	HPO_4^{2-}/PO_4^{3-}	12.7
	$H_3C\text{-}COO^-/H_3C\text{-}COOH$	4.7
	HO_2^- /H_2O_2	11.6
	NH_3 /NH_4^+	9.3
	N_3^- /N_3H	4.8
	F^-, Cl^- Br^-, I^-/XH	3.5, -7, -9, -11
Neutral	O_2, CO, NO, RNC	

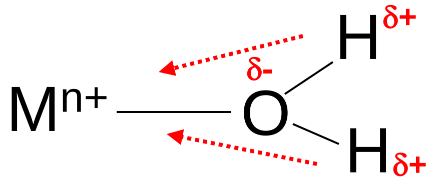


Modulación de pK_a

$$H_2O + M^{n+} \underset{+H^+}{\overset{-H^+}{\rightleftarrows}} HO^- \text{-}M^{n+}$$

Metal	pK_a
none	14.0
Ca^{2+}	13.4
Mn^{2+}	11.1
Cu^{2+}	10.7
Zn^{2+}	10.0

4 orders of magnitude !



Control cinético

$$[M^{n+}(H_2O)_m] \underset{+H_2O}{\overset{-H_2O}{\rightleftarrows}} [M^{n+}(H_2O)_{m-1}]$$

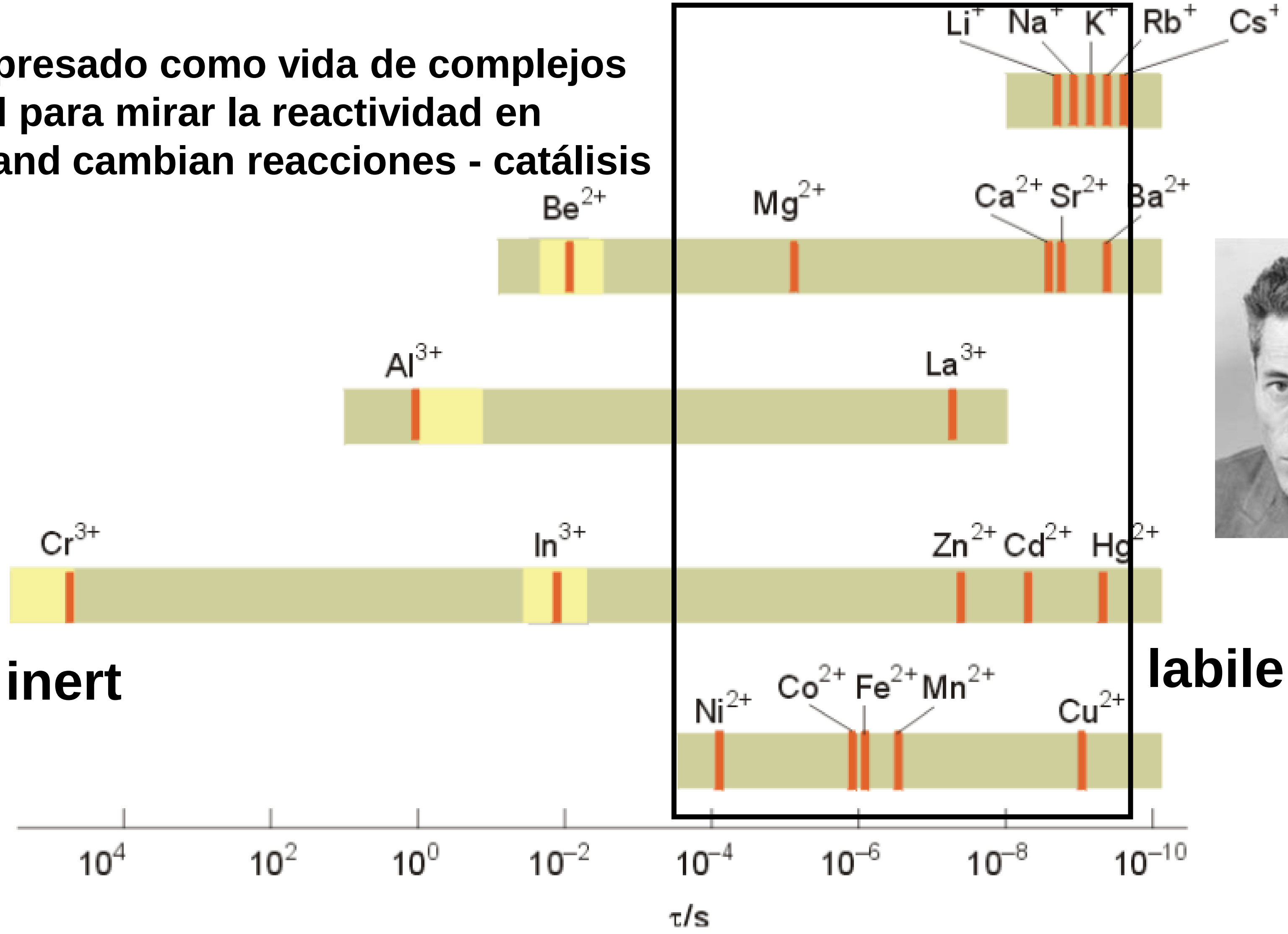
Metal	k (s^{-1})
K^+	$1x10^9$
Ca^{2+}	$3x10^8$
Mn^{2+}	$2x10^7$
Fe^{2+}	$4x10^6$
Co^{2+}	$3x10^6$
Ni^{2+}	$4x10^4$
Fe^{3+}	$2x10^2$
Co^{3+}	$<10^{-6}$

15 orders of magnitude!

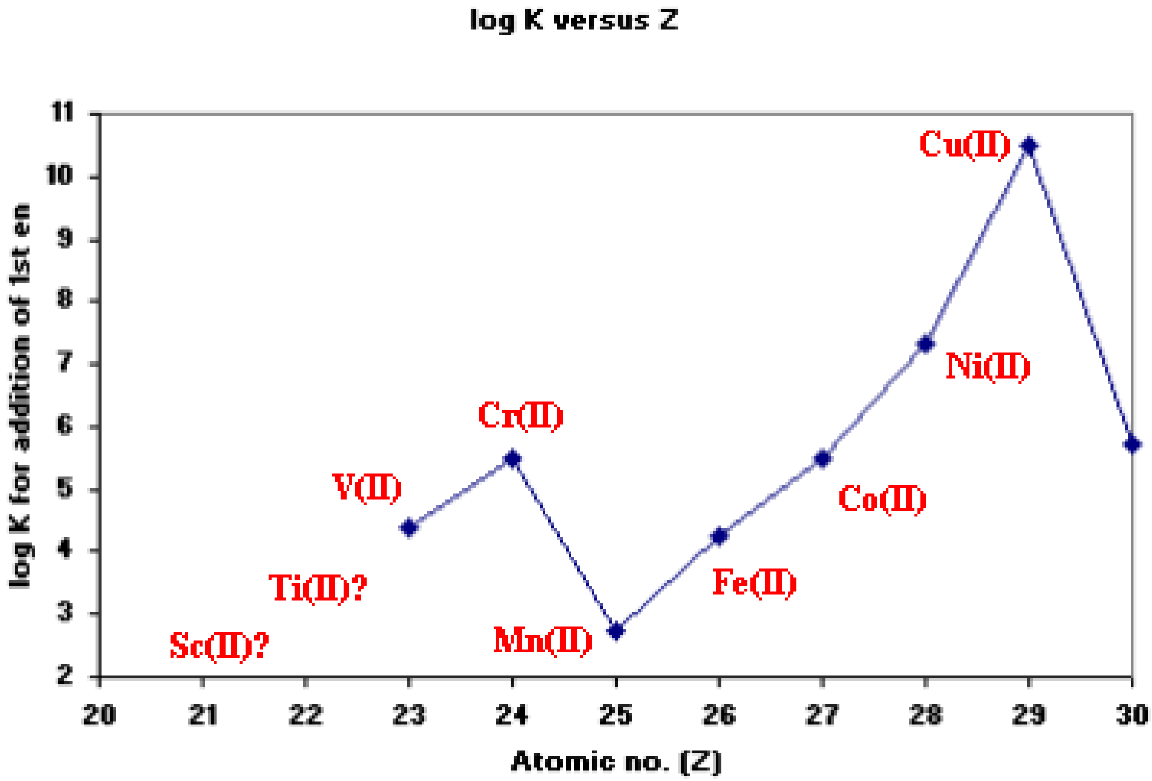
Velocidades de cambio de H_2O

M. Eigen, Nobel Prize Lecture 1967

Expresado como vida de complejos
Útil para mirar la reactividad en
ligand cambian reacciones - catálisis

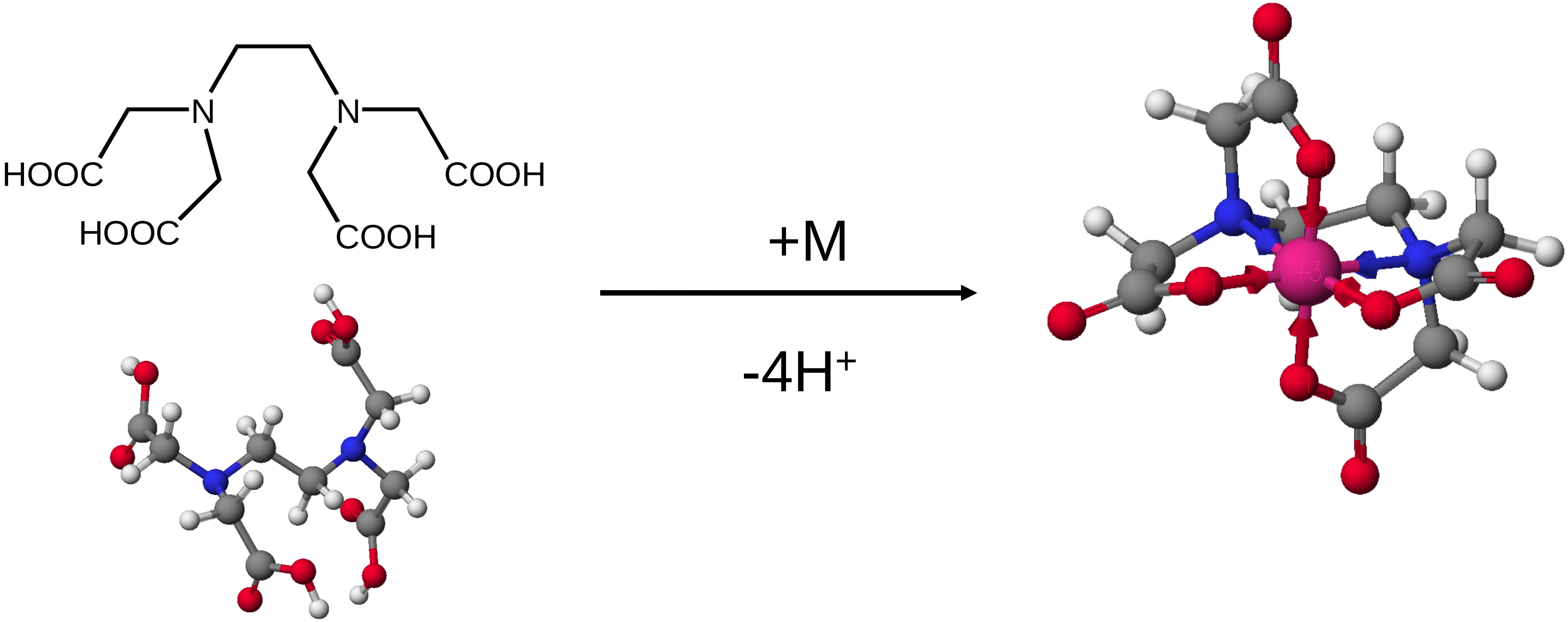


Estabilidad de complejos del iónes metálicos
Irving-Williams Series



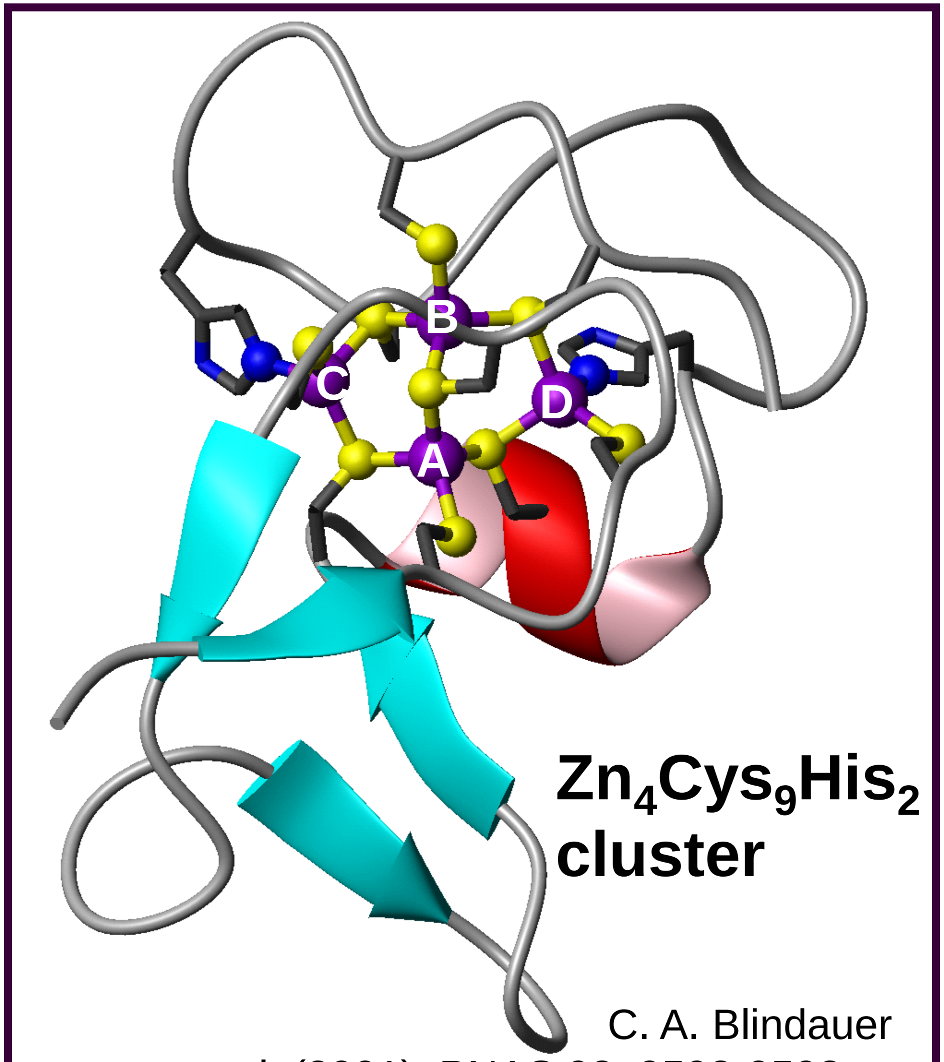
Stability order for high-spin divalent metal ion complexes: Maximum at Cu(II), Minimum at Mn(II)

Strong chelating ligand: EDTA



Hexadentate Ligand => strong complexing agent; can be applied to remove metal ions from biological samples (proteins, nucleic acids).

Protein Chelate: Bacterial Metallothionein (MT)

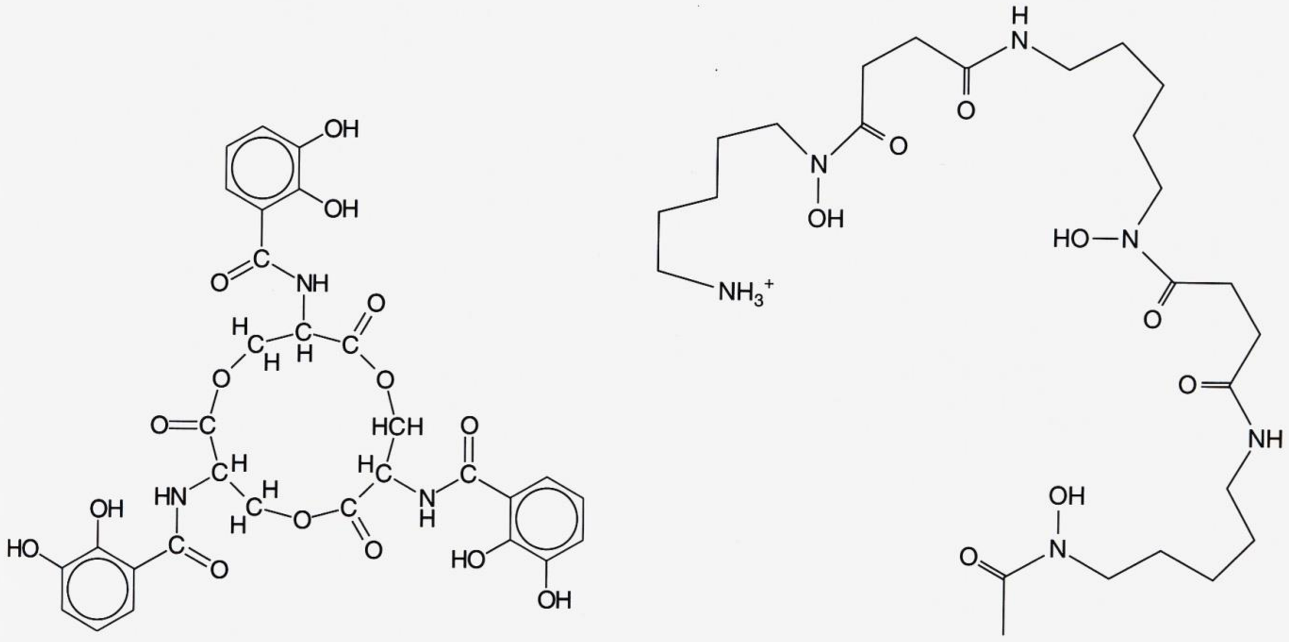


$Zn_4Cys_9His_2$ cluster

C. A. Blindauer et al. (2001) PNAS 98, 9593-9598.

- **55 amino acids**
- **One domain**
- **Not only Cys, but also 2 His**
- **Cluster similar to mammalian MT: Essentially a distorted piece of mineral (ZnS)**

Biological Chelate: Siderophores



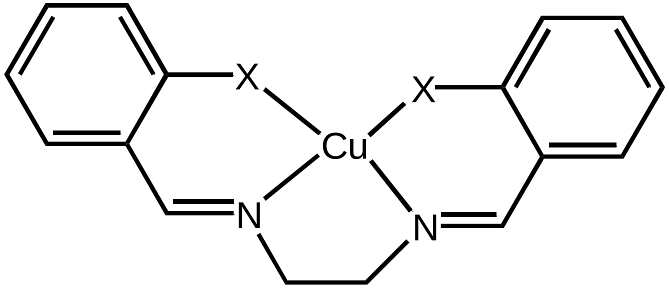
(a) Enterobactin

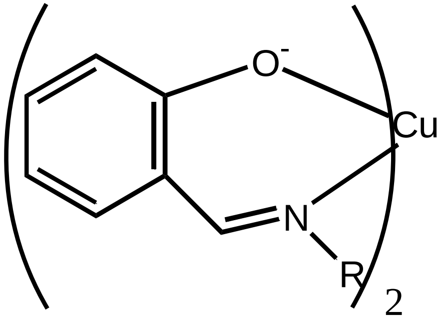
(b) Desferrioxamin

Extremely stable complex of Enterobactin/Fe^{3+} K~ 10^{49}

Release of Fe through a) degradation of ligand, or b) protonation and reduction to Fe^{2+} which binds much weaker to the siderophore.

Modulación de Potenciales de Redox





X=O^-: $E_{1/2}$ = -1.21 V

X=S^-: $E_{1/2}$ = - 0.83 V

R=CH_3 : $E_{1/2}$ = -0.90 V

R=C_2H_5 : $E_{1/2}$ = -0.86 V

R=*i*-Pr : $E_{1/2}$ = -0.74 V

R=*t*-Bu : $E_{1/2}$ = -0.66 V

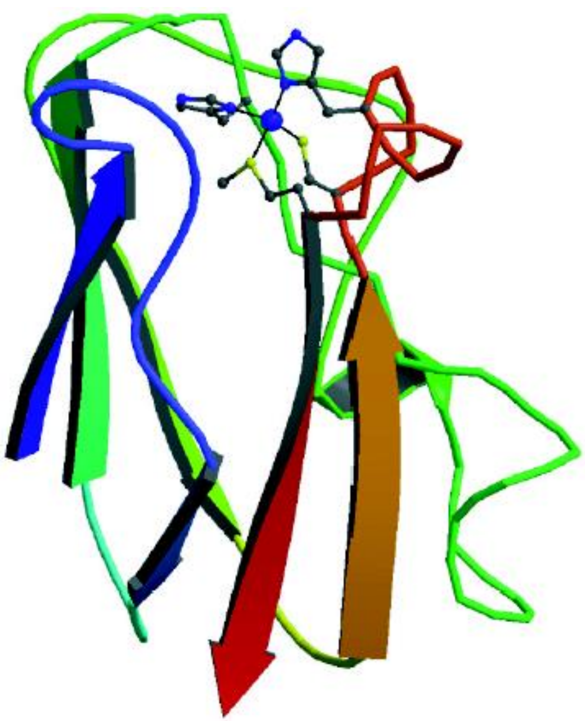
- **RS^- stabilizes Cu(I) state**
- **Positive Potential**
- **El obstáculo de Steric fuerza la geometría tetrahedral, stabilizes Cu(I)**

Metal Site 1: Blue Cu Site (Plastocyanin)

Function: Electron Transfer/Photosynthesis

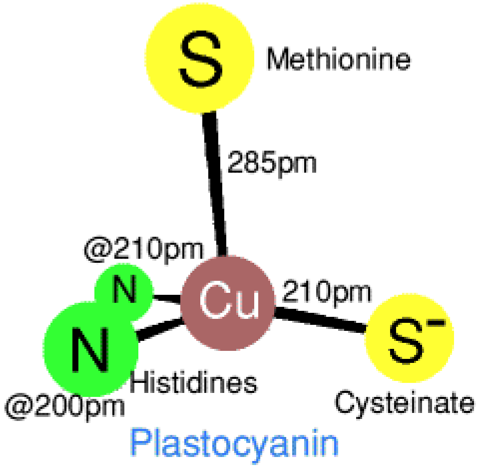
Covalent Cu-Cys π-bond is mainly responsible for its unique properties

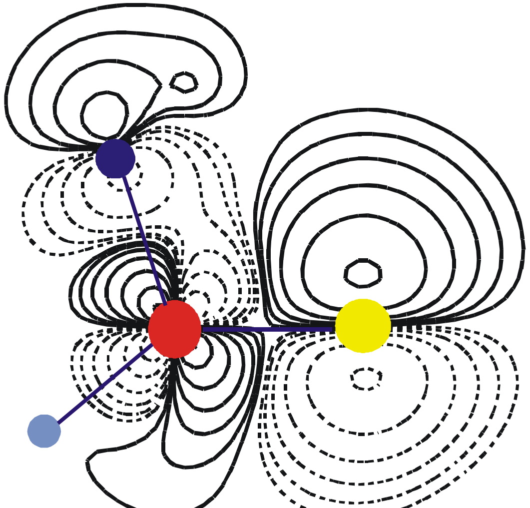
EI Solomon, Inorg. Chem. 2006, **45**, 8012-8025



PDB Code: 1PLC

HC Freeman, 1978



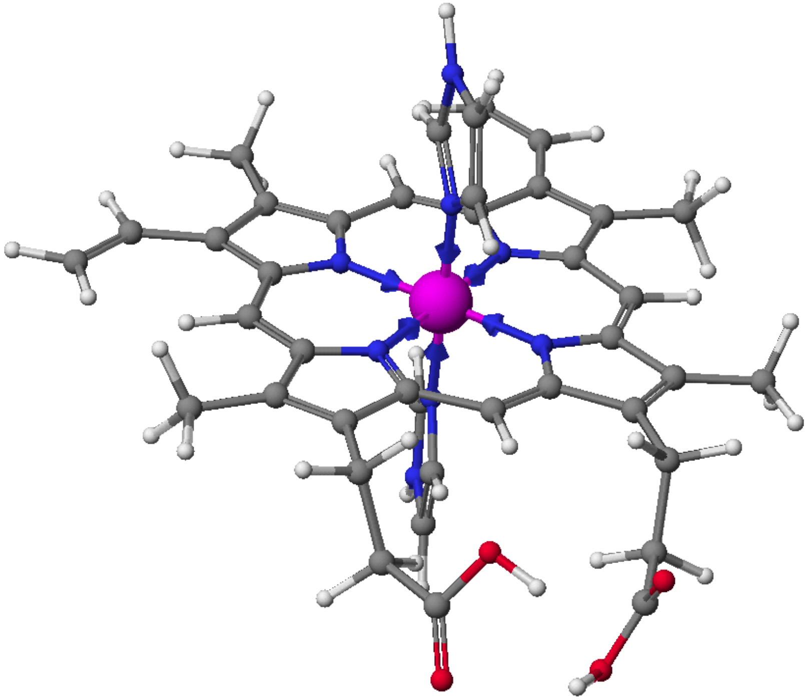


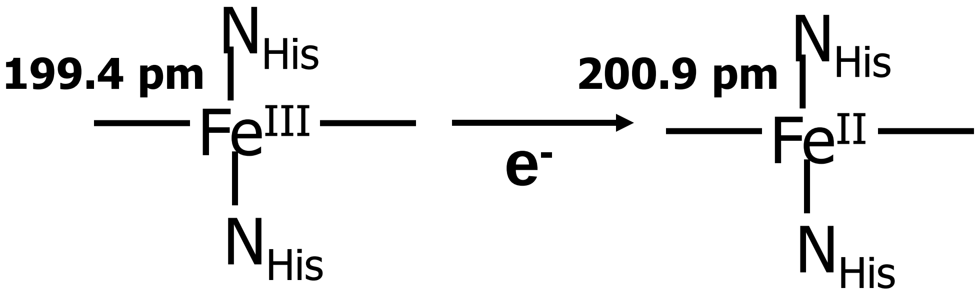
41% Cu 38-45% S

Cu(II) Spin-Distribution

Metal site 2: Heme Fe

Function: Electron Transfer/Respiration





Reorganization energy $\propto \Sigma(\Delta R_{ML})^2$

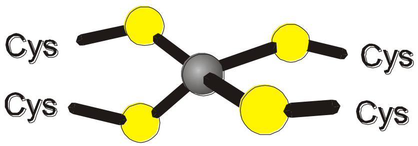
In Cytochromes ≤ 4-5 kcal/mol

Sigfridsson, E.; Olsson, M.H.M.; Ryde, U. (**2001**) *J. Phys. Chem. B*, 105, 5546

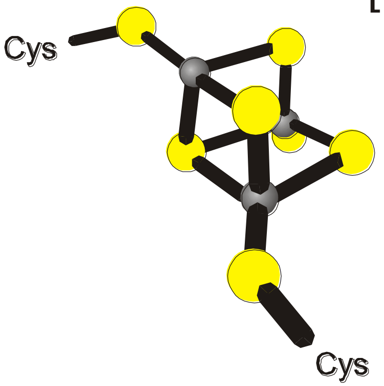
Metal Site 3: Iron – Sulfur centers (FeS)

Function: Electron Transfer and Catalysis

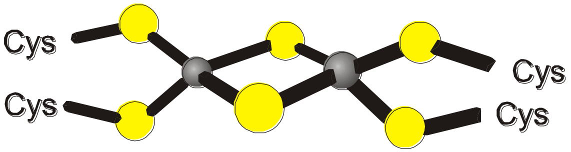
Rubredoxin



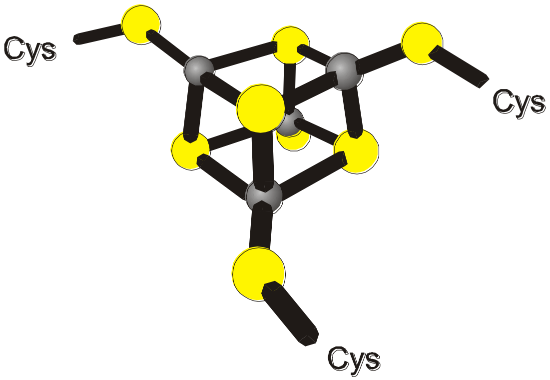
[3Fe-4S]



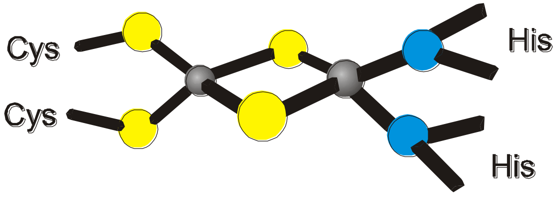
[2Fe-2S] Ferredoxin



[4Fe-4S]

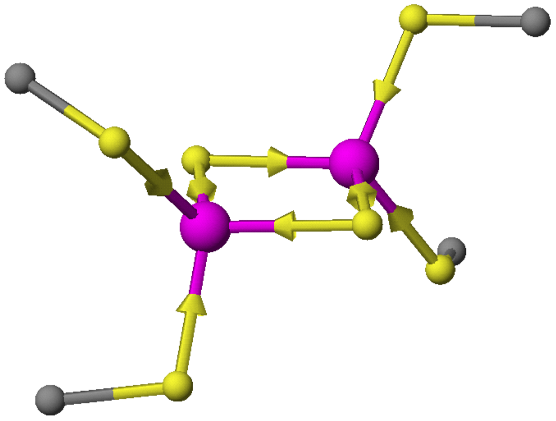


[2Fe-2S] Rieske center



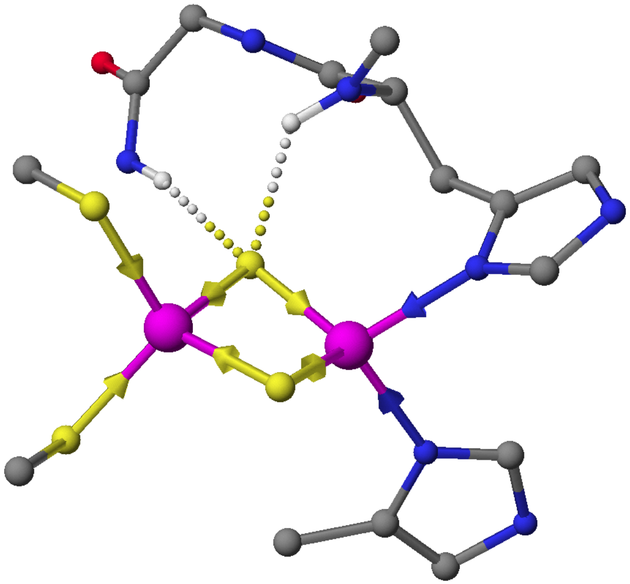
Modulación de potenciales de redox
(H bridges)

2Fe-2S Ferredoxin



$E^{0'} \sim -400$ mV

2Fe-2S Rieske



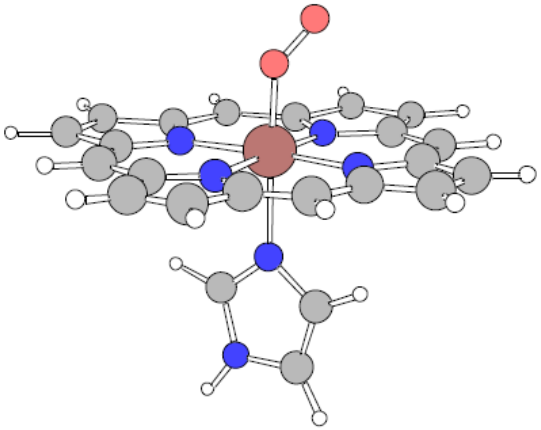
$E^{0'} \sim +280$ mV

(+150 mV without H bridges)

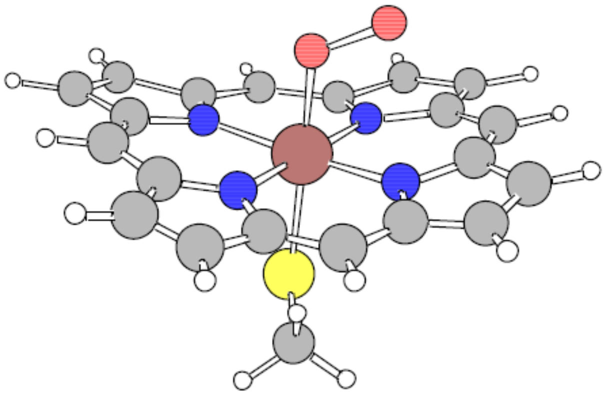
(a) Stephens, P.J.; Jollie, D.R.; Warshel, A. (**1996**) *Chem. Rev.*, 96, 2491
(b) Link, T.A. (**1999**) *Adv. Inorg. Chem.*, 47, 83

Trans-Effect - Modulación de reactividad

A ligand X *trans* to a second ligand Y can influence the stability of the M-Y bond. With X being a strong Lewis base, the M-Y bond will be weakened



Myoglobin
Axial Histidine
O_2 Transport



Cytochrome P450
Axial Cysteine
O_2 Activation

$$RH + O_2 + 2H^+ + 2e- \rightarrow R\text{-}OH + H_2O$$

Proteínas modulan las Propiedades de Iones Metálicos

Coordination number

- The lower the higher the Lewis acidity

Coordination geometry

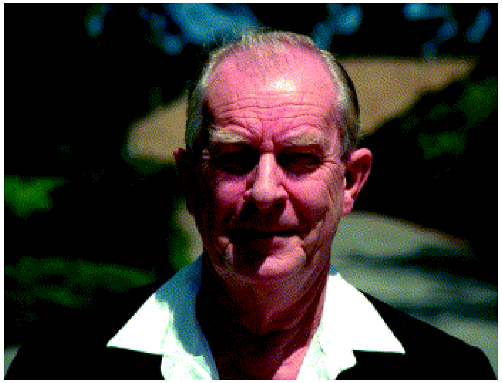
- Proteins can dictate distortion
- Distortion can change reactivity of metal ion

Weak interactions - Second Shell Effects

- Hydrogen bonds to bound ligands
- Hydrophobic residues: dielectric constant can change stability of metal-ligand bonds

Take Home Message

Las propiedades estructurales y funcionales de iones metálicos en sistemas biológicos pueden ser entendidas combinando los principios de la Química de Coordinación (Química inorgánica) con el conocimiento del ambiente único creado por biomoléculas.



Bo G. Malmström, Göteborg, 1927-2000