Outline

- Introduction to Bioinorganic Chemistry
- Biometals and common oxidation states
- Biological ligands
- Metal Binding Sites in Biological Systems
- Hemoglobin and Myoglobin

History

• Bulk inorganic elements long been known to be essential

• Blood known to contain iron since 17th century

• Need for Zinc, 1896

•Bioinorganic chemistry developed as a field after 1960

•First inorganic biochemistry symposium in 1970

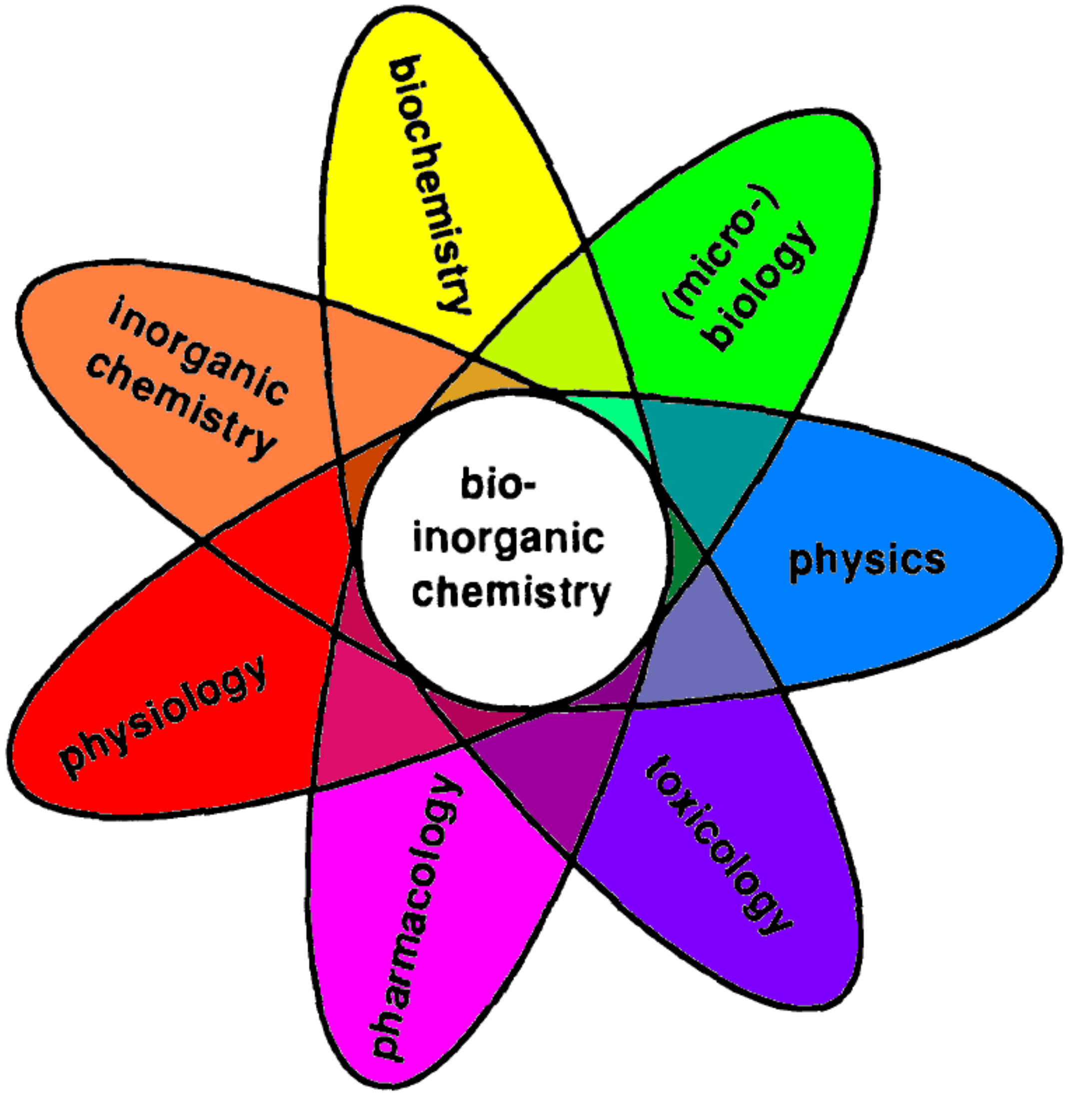
•SBIC (Society of Biological Inorganic Chemistry) formed in 1995

Average elemental composition of a human body (adult, 70 kg)

element	symbol	mass	year of discovery as an essential element
oxygen	O	45500	
carbon	C	12600	
hydrogen	H	7000	
nitrogen	N	2100	
calcium	Ca	1050	
phosphorus	P	700	
sulfur	S	175	
potassium	K	140	
chlorine	Cl	105	
sodium	Na	105	
magnesium	Mg	35	
iron	Fe	4.2	17^{th} Century
zinc	Zn	2.3	1896
silicon	Si	1.4	1972
rubidium[a]	Rb	1.1	
fluorine	F	0.8	1931
zirconium[a]	Zr	0.3	
bromide[b]	Br	0.2	
strontium[a]	Sr	0.14	
copper	Cu	0.11	1925
aluminum[a]	Al	0.10	
lead[b]	Pb	0.08	
antimony[a]	Sb	0.07	
cadmium[b]	Cd	0.03	(1977)
tin[b]	Sn	0.03	(1970)
iodine	I	0.03	1820
manganese	Mn	0.02	1931
vanadium[b]	V	0.02	(1971)
selenium	Se	0.02	1957
barium[a]	Ba	0.02	
arsenic[b]	As	0.01	1975
boron[b]	B	0.01	
nickel[b]	Ni	0.01	(1971)
chromium	Cr	0.005	1959
cobalt	Co	0.003	1935
molybdenum	Mo	<0.005	1953
lithium[b]	Li	0.002	

[a] **Not Essential** [b] Essentiality Uncertain

An Interdisciplinary Research Field



Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*, Wiley, New York, **1994**.

Who's Who in Bioinorganic Chemistry

GORDON RESEARCH CONFERENCES
FOUR POINTS SHERATON HARBORTOWN
METALS IN BIOLOGY
Chair: Alison Butler
January 18-23, 2004

Who’s Who in Bioinorganic Chemistry

Harry Gray—electron transport
Steve Lippard—cis platin
Liz Theil—iron storage
Alison Butler—Vanadium in the sea
Ken Raymond—siderophores, imaging agents
Mike Maroney—Nickel containing enzymes
Bob Scott—Nickel containing enzymes
Val Culotta—Copper transport
Ed Stiefel—nitrogenase/Valdez oil spill
Dick Schrock--nitrogenase
Dick Holm—iron sulfur clusters
Yi Lu—artificial enzymes
Eckard Munck—iron sulfur clusters

Element Abundance

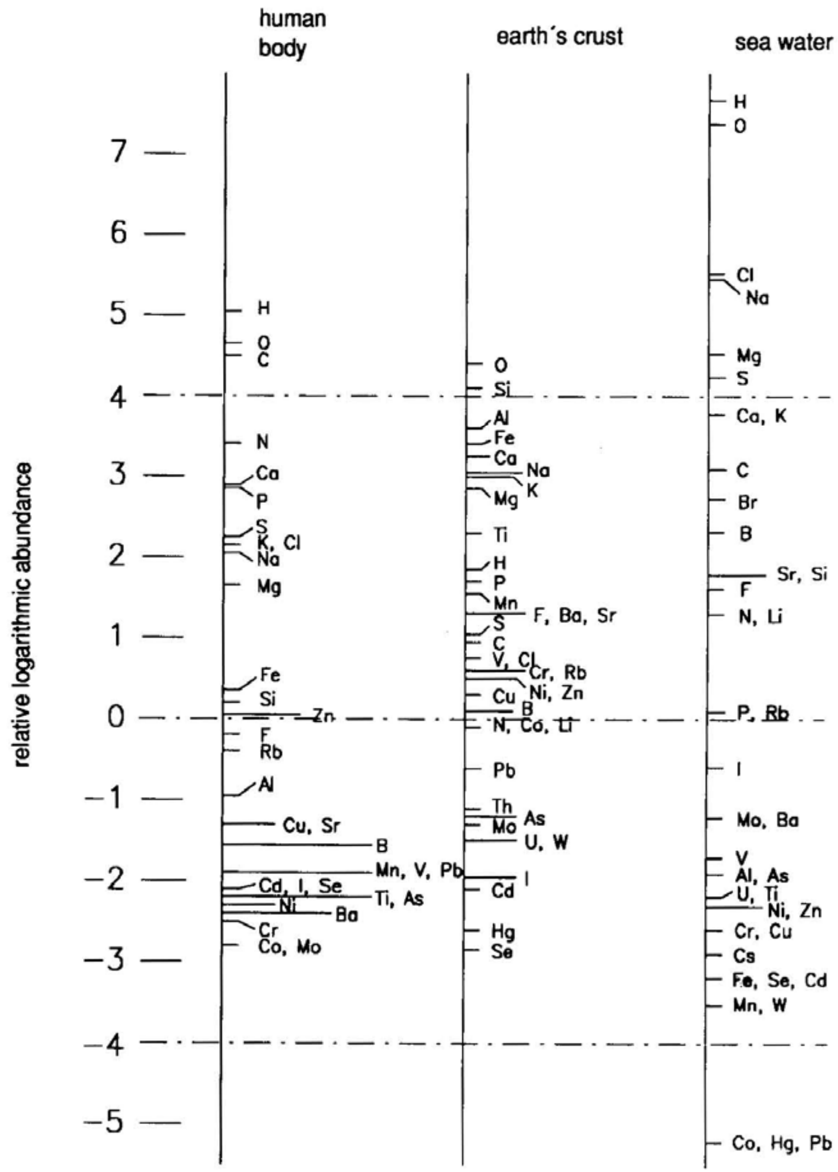


Figure 2.2
Logarithmic diagrams of relative molar concentrations of the elements in different environments (arbitrary units) (data from [1] and [4])

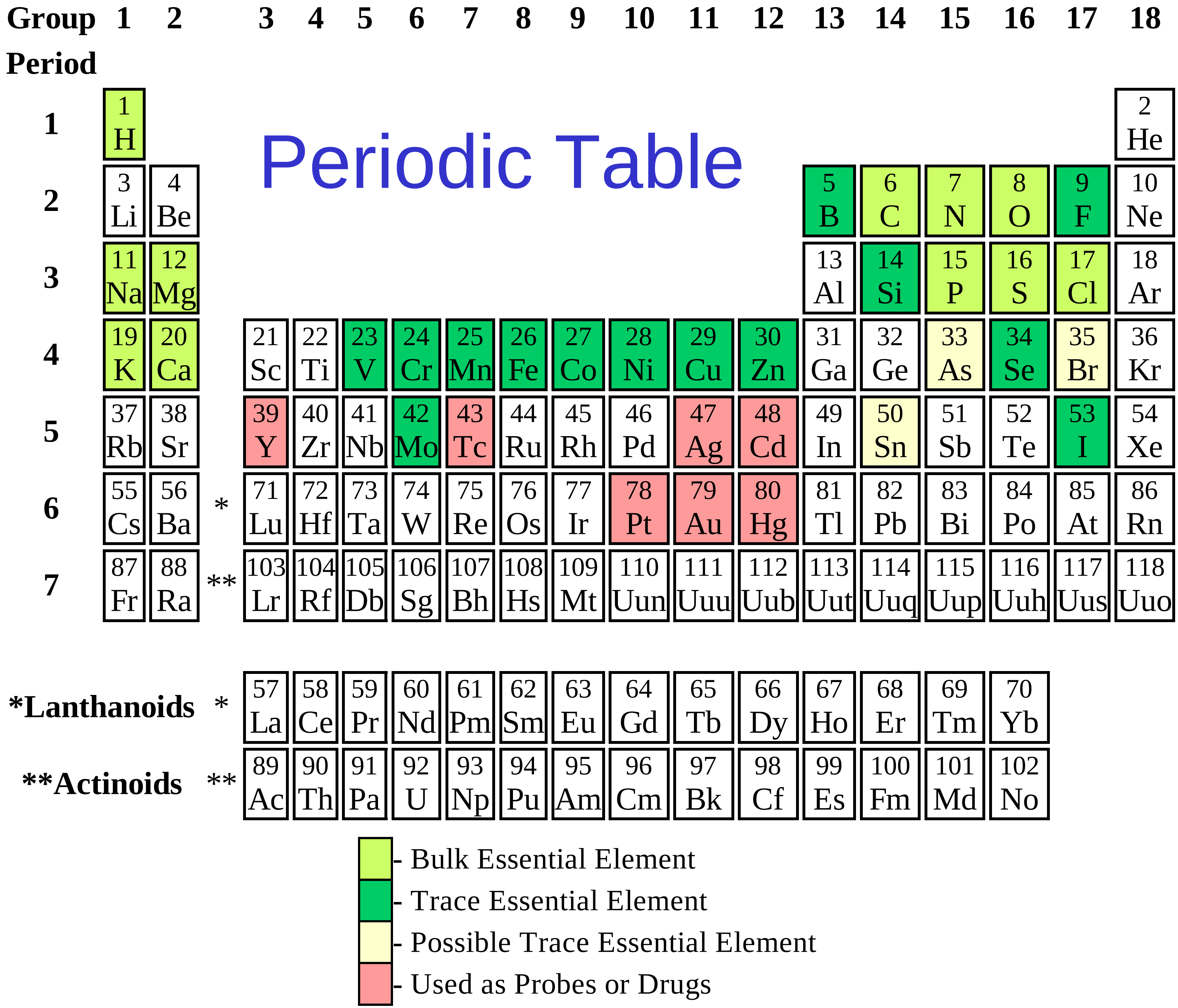
Element	Sea Water (M) x 10^{-8}	Human Plasma (M) x 10^{-8}
Fe	0.005-2	2230
Zn	8.0	1720
Cu	1.0	1650
Mo	10	1000
V	4.0	17.7
Mn	0.7	10.9
Cr	0.4	5.5
Ni	0.5	4.4
Co	0.7	0.0025

Bertini, I.; Gray, H. B.; Lippard, S. J.; Valentine, J. S. Bioinorganic Chemistry; University Science Books: Sausalito, CA, 1994.

Functions of Metals in Mammals

- Structure
  - Hard material – bone and teeth
  - Cell membranes
  - DNA and RNA structure
  - Protein, including enzyme conformation
- Charge carriers
  - Na^+, K^+, Ca^{2+}
- Electron transfer (Redox rxns)
  - Fe, Cu, Mn, Mo, Ni, Co
- Metabolism
  - Degradation of organic molecules
- Activation of small molecules
  - O_2, CO_2

Adapted from Bioinorganic Notes - Lindahl



Periodic Table
Group 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Period
1 1 H 2 He
2 3 Li 4 Be 5 B 6 C 7 N 8 O 9 F 10 Ne
3 11 Na 12 Mg 13 Al 14 Si 15 P 16 S 17 Cl 18 Ar
4 19 K 20 Ca 21 Sc 22 Ti 23 V 24 Cr 25 Mn 26 Fe 27 Co 28 Ni 29 Cu 30 Zn 31 Ga 32 Ge 33 As 34 Se 35 Br 36 Kr
5 37 Rb 38 Sr 39 Y 40 Zr 41 Nb 42 Mo 43 Tc 44 Ru 45 Rh 46 Pd 47 Ag 48 Cd 49 In 50 Sn 51 Sb 52 Te 53 I 54 Xe
6 55 Cs 56 Ba * 71 Lu 72 Hf 73 Ta 74 W 75 Re 76 Os 77 Ir 78 Pt 79 Au 80 Hg 81 Tl 82 Pb 83 Bi 84 Po 85 At 86 Rn
7 87 Fr 88 Ra ** 103 Lr 104 Rf 105 Db 106 Sg 107 Bh 108 Hs 109 Mt 110 Uun 111 Uuu 112 Uub 113 Uut 114 Uuq 115 Uup 116 Uuh 117 Uus 118 Uuo
*Lanthanoids * 57 La 58 Ce 59 Pr 60 Nd 61 Pm 62 Sm 63 Eu 64 Gd 65 Tb 66 Dy 67 Ho 68 Er 69 Tm 70 Yb
**Actinoids ** 89 Ac 90 Th 91 Pa 92 U 93 Np 94 Pu 95 Am 96 Cm 97 Bk 98 Cf 99 Es 100 Fm 101 Md 102 No
- Bulk Essential Element
- Trace Essential Element
- Possible Trace Essential Element
- Used as Probes or Drugs

Function in Biology and Affects of Metal Deficiency in Humans

Elemental Composition of the Adult Human Body

Bulk or Constituent Elements:

H, O, C, N, Ca, P, Na, K, S, Cl

Trace Elements:

Mg, Si, F, Fe, Zn, B, Rb, Sr, Br, Cu

Ultra Micro Trace Elements:

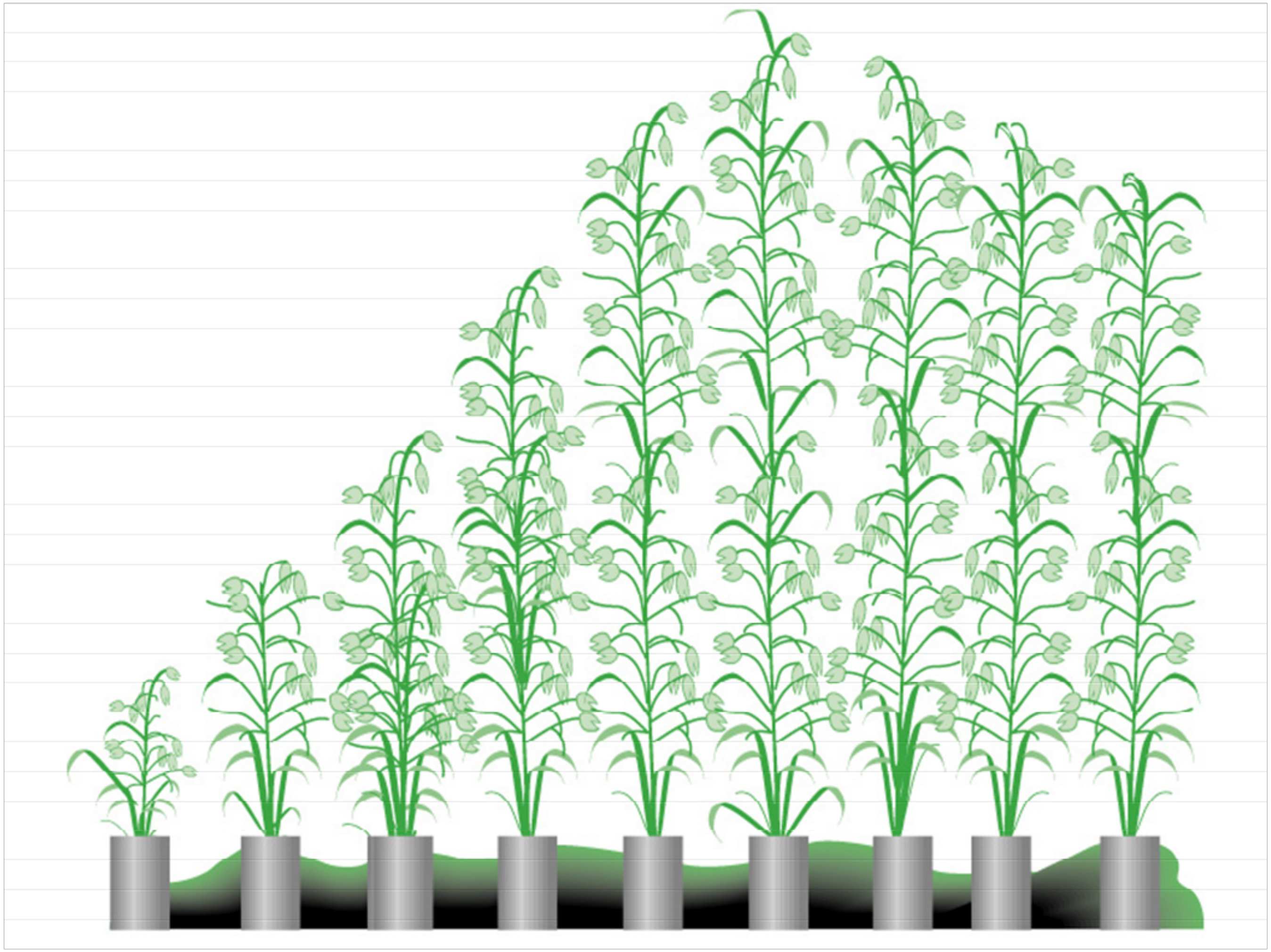
V, Li, Se, Mn, Ba, Ge, As, Ni, Mo, Cd, I, Sn, Cr, Pb, Co

Metal	*Function*	*Typical deficiency symptoms*
Sodium	Charge carrier; osmotic balance	
Potassium	Charge carrier; osmotic balance	
Magnesium	Structure; hydrolase; isomerase	muscle cramps
Calcium	Structure; trigger; charge carrier	retarded skeletal growth
Vanadium	Nitrogen fixation; oxidase	
Chromium	Unknown, possible involvement in glucose tolerance	diabetes symptoms
Molybdenum	Nitrogen fixation; oxidase; oxo transfer	retardation of cellular growth; propensity for caries
Tungsten	Dehydrogenase	
Manganese	Photosynthesis; oxidase; structure	infertility; impaired skeletal growth
Iron	Oxidase; dioxygen transport and storage; electron transfer; nitrogen fixation	anemia; disorders of the immune system
Cobalt	Oxidase; alkyl group transfer	pernicious anemia
Nickel	Hydrogenase; hydrolase	growth depression; dermatitis
Copper	Oxidase; dioxygen transport; electron transfer	artery weakness; liver disorders; secondary anemia
Zinc	Structure; hydrolase	skin damage; stunted growth; retarded sexual maturation

1) Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life. An Introduction and Guide*; John Wiley and Sons, Inc.: New York, 1994.

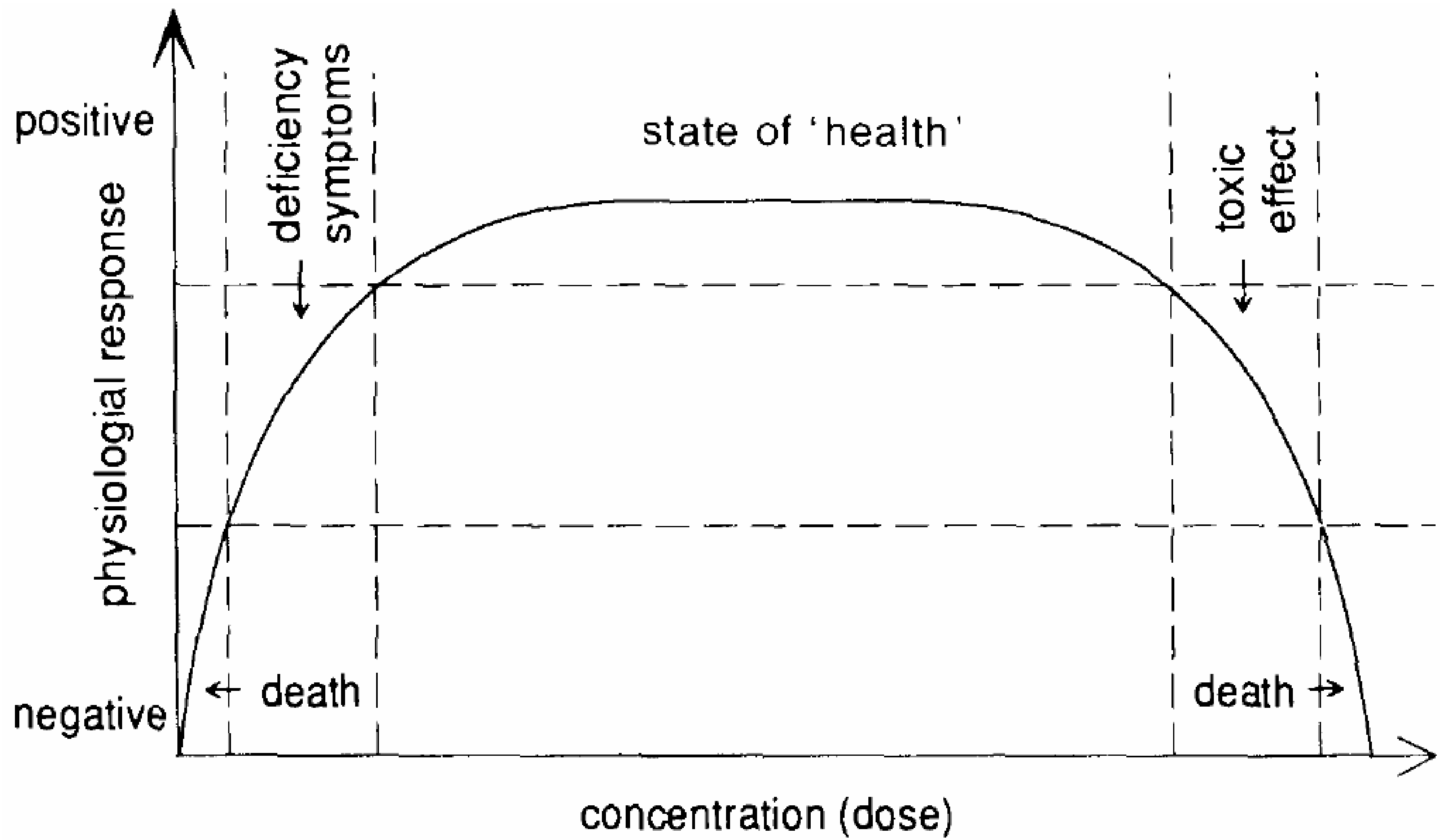
2) Lippard, S. J.; Berg, J. M. *Principles of Bioinorganic Chemistry*; University Science Books: Mill Valley, CA, 1994.

All things can be poisons



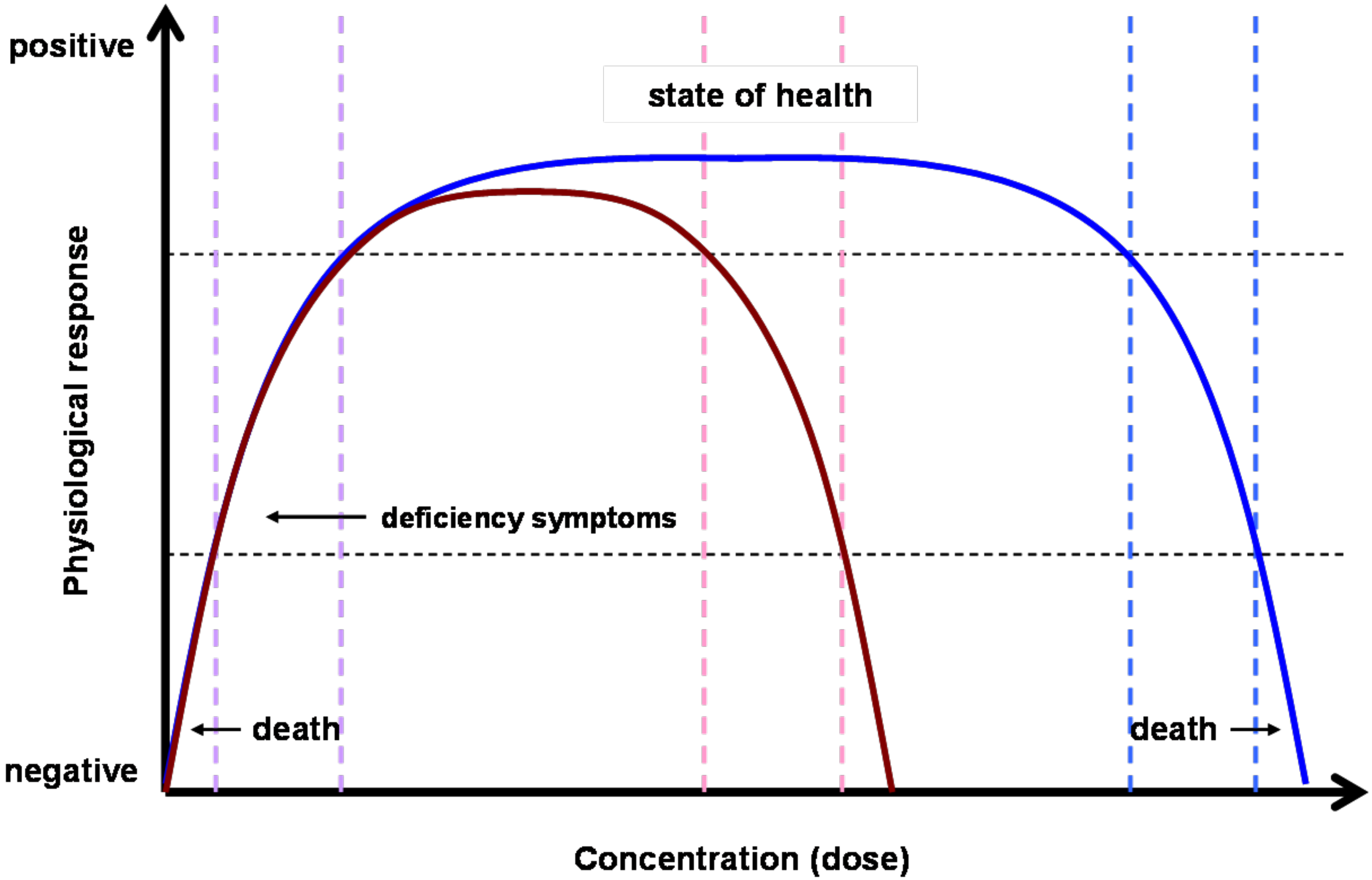
It depends on: dosage, individual health, and way of administration

Essential Element Dosage and Physiological Response: Metal Homeostasis

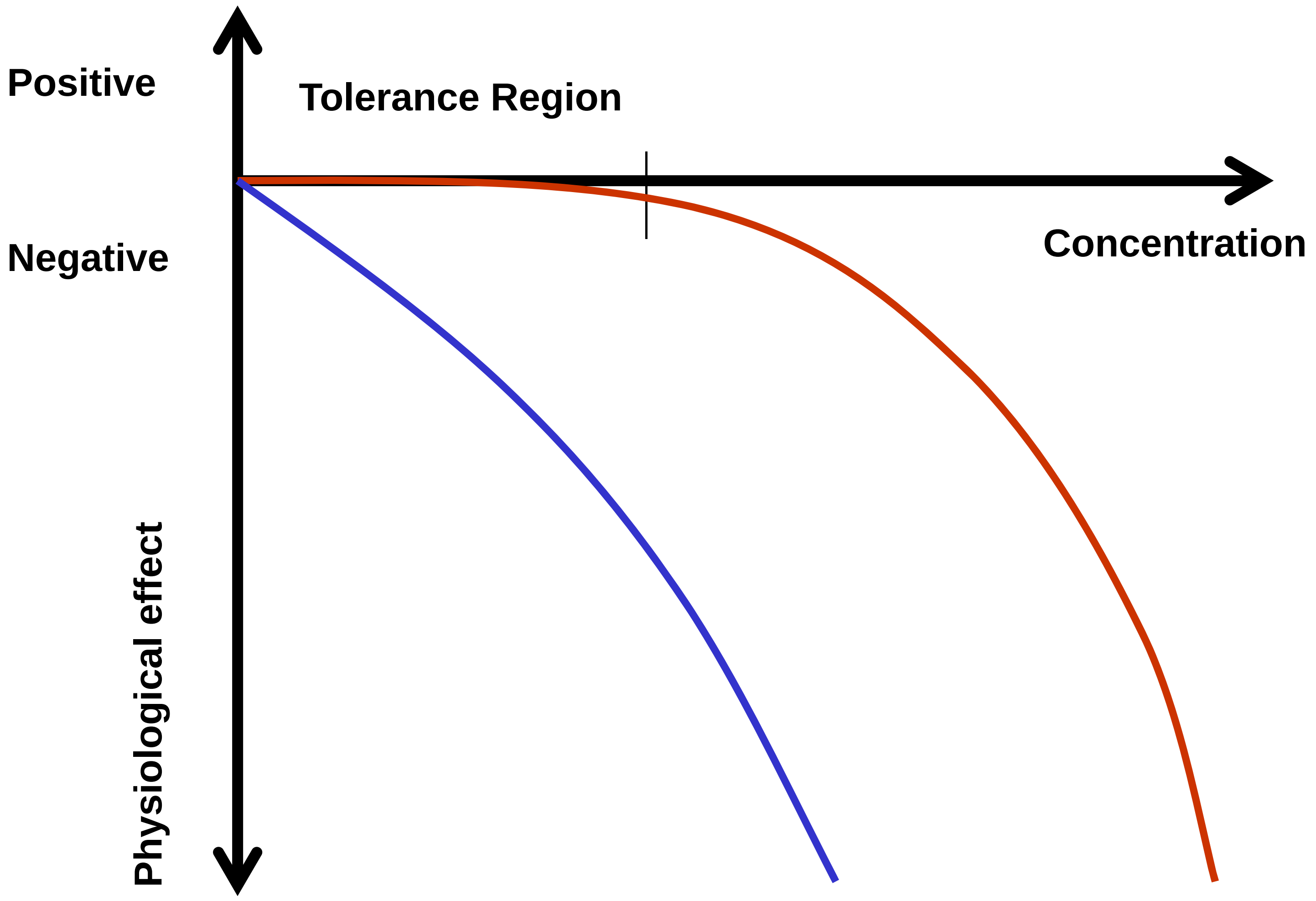


Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*, Wiley, New York, **1994**.

Dose Response: Essential Elements



Dose Response: Non-essential Elements



Recommended Daily Allowances for Inorganic Elements in the Human Body

Fe was the first essential transition metal discovered (17th century)
Zn → 1896
The rest followed in the 1900s

inorganic constituents	recommended daily allowances (in mg) adult[a]	infant[b]
K	2000 – 5500	530
Na	1100 – 3300	260
Ca	800 – 1200	420
Mg	300 – 400	60
Zn	15	5
Fe	10 – 20	7.0
Mn	2.0 – 5	1.3
Cu	1.5 – 3	1.0
Mo	0.075 – 0.250	0.06
Cr	0.05 – 0.2	0.04
Co	ca. 0.2 (vitamin B_{12})	0.001

Adapted from J. Chem. Ed. (1985), Vol. 62, No. 11, pp 917.
Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*, Wiley, New York, **1994**.

Outline—Lectures 1-3

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- Biometals and common oxidation states
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Transition Elements Relevent to Bioinorganic Chemistry: The Biometals

V, Mn, Fe, Co, Ni, Cu, Zn, Mo, W

First Row Transition Metals

Sc^{2+}	Ti^{2+}	V^{2+}	Cr^{2+}	Mn^{2+}	Fe^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
d^1	d^2	d^3	d^4	d^5	d^6	d^7	d^8	d^9	d^{10}

Oxidation States:

V = 2+, 3+, 4+, and 5+

Mn = 2+ (common), 3+ (common), 4+ (strong oxidant), 5+ (rare, very strong oxidant)

Fe = 2+ (common), 3+ (common), 4+ (rare, strong oxidant)

Co = 1+ (strong reductant), 2+ (common), 3+

Ni = 1+ (strong reductant), 2+ (common), 3+

Cu = 1+ (common), 2+ (common)

Zn = 2+ (common)

Mo = 3+, 4+, 5+, 6+

W = 4+, 5+, 6+

Adapted from Bioinorganic Notes - Lindahl

Common Properties of the Biometals

Vanadium

- 2+ to 5+ oxidation states are common
- 4+ is stable oxidation state
- 2+ and 3+ are reducing
- 5+ is slightly oxidizing
- O and N ligands are common

Common Properties of the Biometals

Manganese

- Wide range of stable oxidation states (from the strong reductant Mn^0 to the strong oxidant Mn^{7+})
- Prefers hard donor ligands such as oxygen
- **No** S donors
- CN = 4 – 6 are known

Adapted from Bioinorganic Notes - Lindahl

Common Properties of the Biometals

Iron

- 2+ and 3+ oxidation states are common
- 4+ and 5+ are implicated as intermediates
- Binds hard and soft donor ligands (O, N, S ligands)
- Tetrahedral geometry with S ligands (Fe_4S_4 clusters)
- 5 – 6 coordinate with O, N ligands (Heme)
- Flexible geometries

Adapted from Bioinorganic Notes - Lindahl

Common Properties of the Biometals

Cobalt

- 2+ is the most stable oxidation state
- 1+ (good nucleophile and reductant) and 3+ (strong oxidant) are accessible
- Prefers N donor ligands
- CN varies with oxidation state:
  - Co^{1+} = 4 coordinate
  - Co^{2+} = 5 coordinate
  - Co^{3+} = 6 coordinate

Adapted from Bioinorganic Notes - Lindahl

Common Properties of the Biometals

Nickel

- 2+ = d^8 is the most stable and prevalent
- 1+ (good nucleophile and reductant) and 3+ (good oxidant) are accessible
- Binds both hard and soft donors
- CN and geometry varies with oxidation state:
  - Ni^{1+} = 4 coordinate
  - Ni^{2+} = 4 coordinate, square planar
  - Ni^{3+} = 6 coordinate, distorted octahedral

Adapted from Bioinorganic Notes - Lindahl

Common Properties of the Biometals

Copper

- 2+ and 1+ oxidation states are common
- Binds both hard and soft donors
- CN and geometry varies with oxidation state:
  - Cu^{2+} = 4-6 coordinate, square planar, distorted octahedral
  - Cu^{1+} = 2-4 coordinate, linear, trigonal planar, tetrahedral
- Cu^{2+} geometries are distorted due to Jahn Teller effects

Adapted from Bioinorganic Notes - Lindahl

Common Properties of the Biometals

Zinc

- 2+ is the only accessible oxidation state (d^{10})
- Binds both hard and soft donors
- Tetrahedral geometry preferred, NOT square planar
- 5-6 CN are accessible
- Good Lewis acid because high charge/radius ratio

Common Properties of the Biometals

Molybdenum

- 4+, 5+ and 6+ oxidation states are most common
- Prefers O and S ligands
- Mo=O units are common

Adapted from Bioinorganic Notes - Lindahl

Common Properties of the Biometals

Tungsten

- 4+, 5+ and 6+ oxidation states are most common
- Prefers O and S ligands
- W=O units are common
- Lower redox potentials than corresponding Mo complexes

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Biological Ligands

Ligand	Name / Abbrev.
Cl^-	chloro
CN^-	cyano
CO	carbonyl
NO	nitric oxide
N_2	dinitrogen
H^-	hydrido
H_2	dihydrogen
O^{2-}	oxo
O_2	dioxygen
O_2^-	superoxo
O_2^{2-}	peroxo
OH_2	aqua
OH^-	hydroxo
S^{2-}	sulfido
RS^-	thiolato
RCO_2^-	carboxylate
PO_4^{3-}	phosphate

Adapted from Bioinorganic Notes - Lindahl

Classification of Ligands:

Hard/Soft Lewis bases

All are 2-electron Sigma donors—and IN ADDITION

Some are pi donors (typically hard):

Cl^-, OH^-, OR^-

Some are pi acceptors (typically soft):

CO, CN^-, NO^+ , aromatic ring-N

Some bind through a bonded pair

Side-on

through electrons in a pi bond: **N_2**

through electrons in a sigma bond: **H_2**

Back-bonding from Metal stabilizes side-on bonding

Table 2.1
Hard-soft acid-base classification of metal ions and ligands important to bioinorganic chemistry

Metals			Ligands		
Hard					
H^+	Mn^{2+}	Cr^{3+}	H_2O	CO_3^{2-}	NH_3
Na^+	Al^{3+}	Co^{3+}	OH^-	NO_3^-	RNH_2
K^+	Ga^{3+}	Fe^{3+}	$CH_3CO_2^-$	ROH	N_2H_4
Mg^{2+}	Ca^{2+}	Tl^{3+}	PO_4^{3-}	R_2O	RO^-
			$ROPO_3^{2-}$	$(RO)_2PO_2^-$	Cl^-
Borderline					
Fe^{2+}	Ni^{2+}	Zn^{2+}	NO_2^-		
Co^{2+}	Cu^{2+}		N_2		
			SO_3^{2-}		
			Br^-		
			N_3^-		
Soft					
Cu^+	Pt^{2+}	Pt^{4+}	R_2S	R_3P	
Au^+	Tl^+	Hg^{2+}	RS^-	CN^-	
Cd^{2+}	Pb^{2+}		RSH	RNC	
			$(RS)_2PO_2^-$	$(RO)_2P(O)S^-$	
			SCN^-	CO	
			H^-	R^-	

Biological Ligands

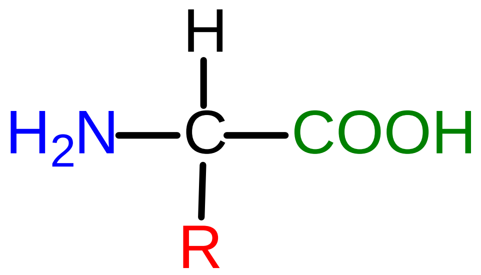
Ligand	Name / Abbrev.
Cl^-	chloro
CN^-	cyano
CO	carbonyl
NO	nitric oxide
N_2	dinitrogen
H^-	hydrido
H_2	dihydrogen
O^{2-}	oxo
O_2	dioxygen
O_2^-	superoxo
O_2^{2-}	peroxo
OH_2	aqua
OH^-	hydroxo
S^{2-}	sulfido
RS^-	thiolato

Common N, S, O – donors to metals come from amino acid residues in proteins

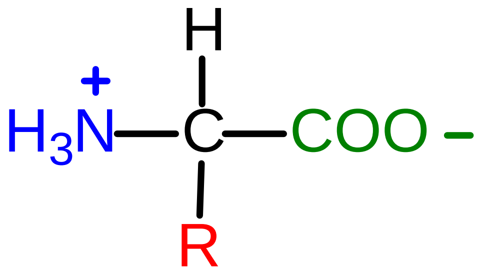
What do these look like??

Adapted from Bioinorganic Notes - Lindahl

Amino Acids



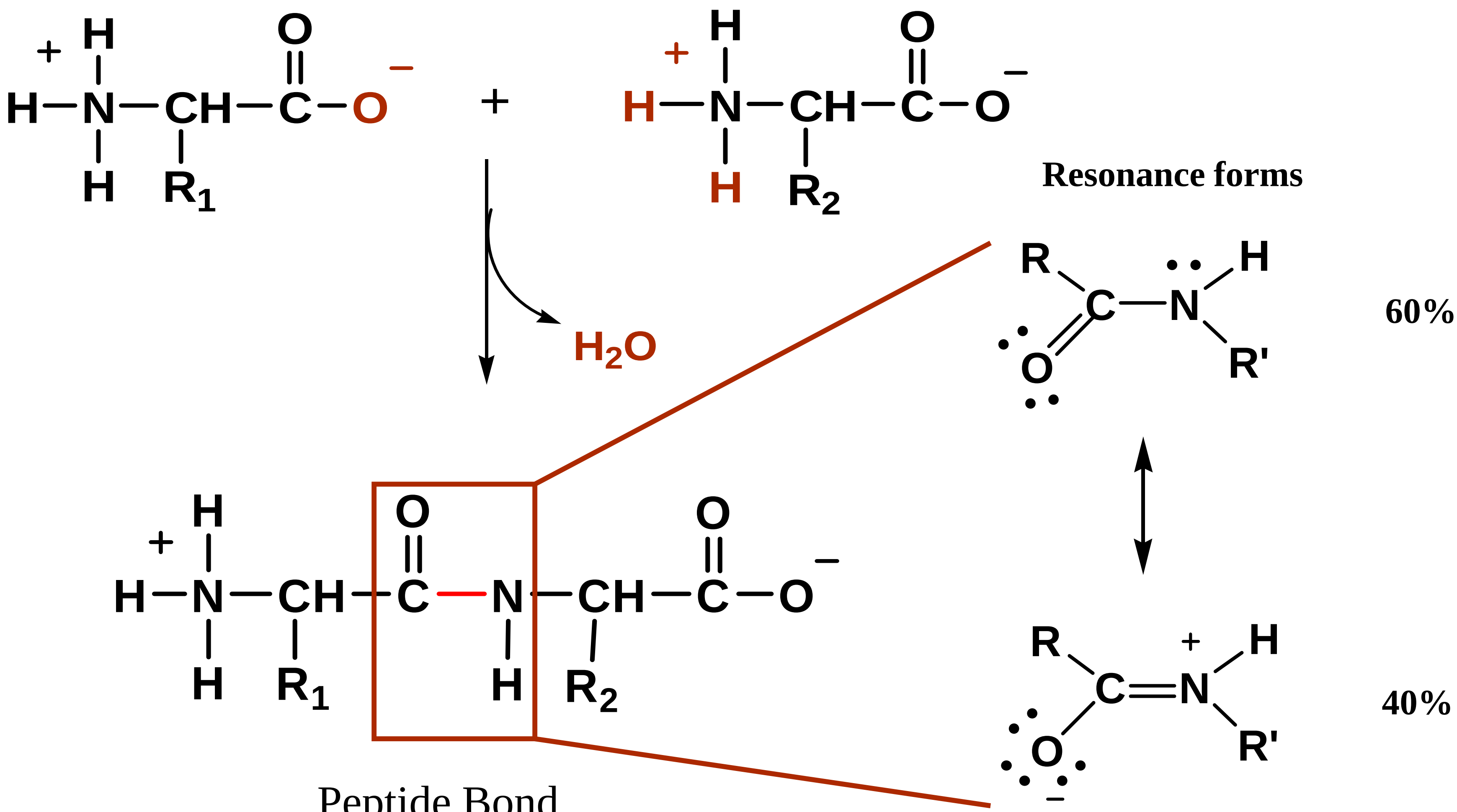
General Structure



Zwitterionic Amino Acid
Physiological pH

- Contain amine and carboxyl groups
- About 22 different R groups
- pK_a for the –COOH group is 2
- pK_a for the $–NH_3^+$ group is 10
- At physiological pH (~7.4), the amino acids exists as zwitterions

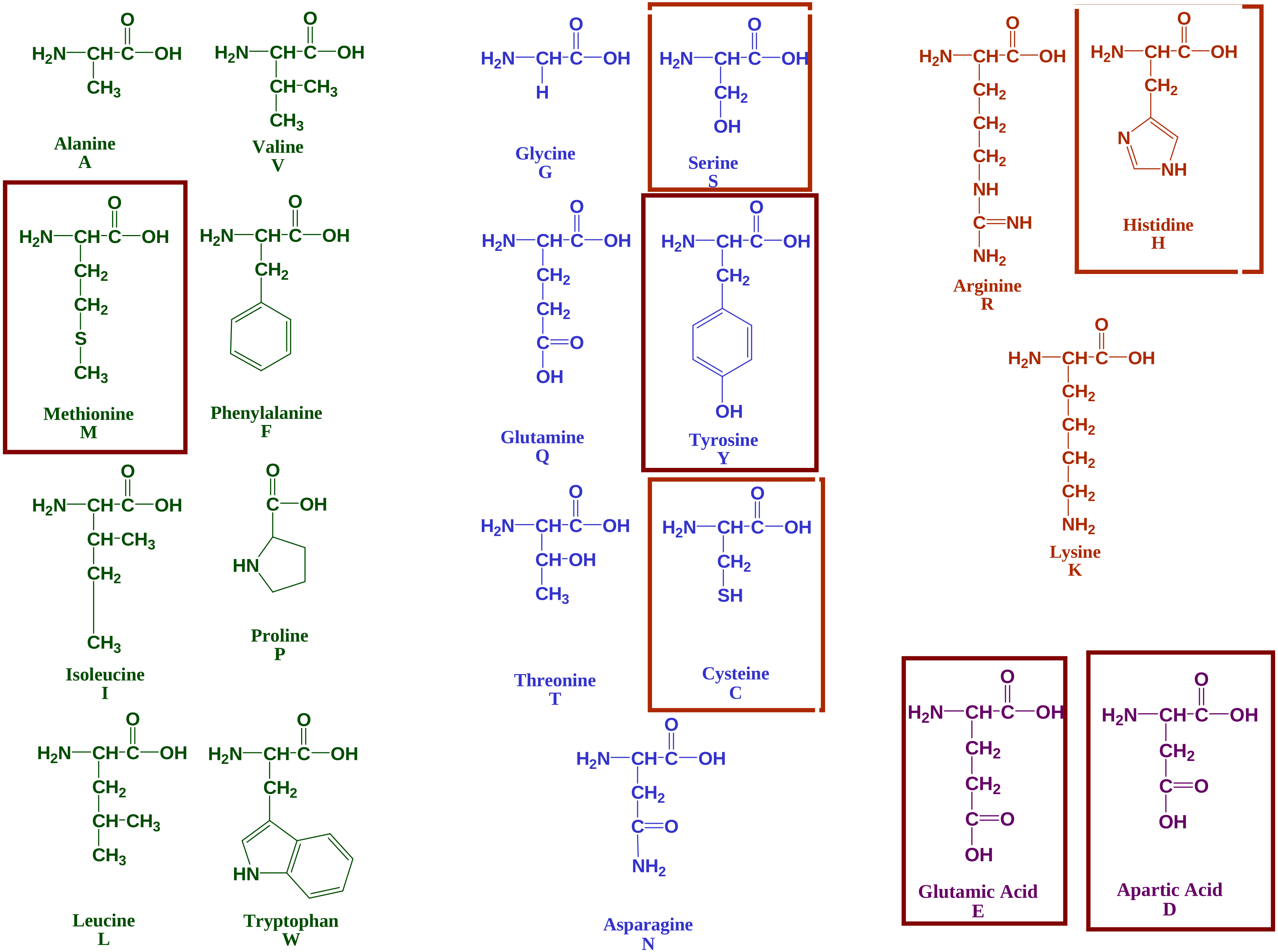
Fundamentals of Peptide Formation: Condensation Reaction



Peptide Bond

Sigel, H.; Martin, R.B. *Chem. Rev.* **1982**, *82*, 385-426.

Library of Ligands: Amino Acids



Amino Acid Building Blocks: Four levels of Protein Structure

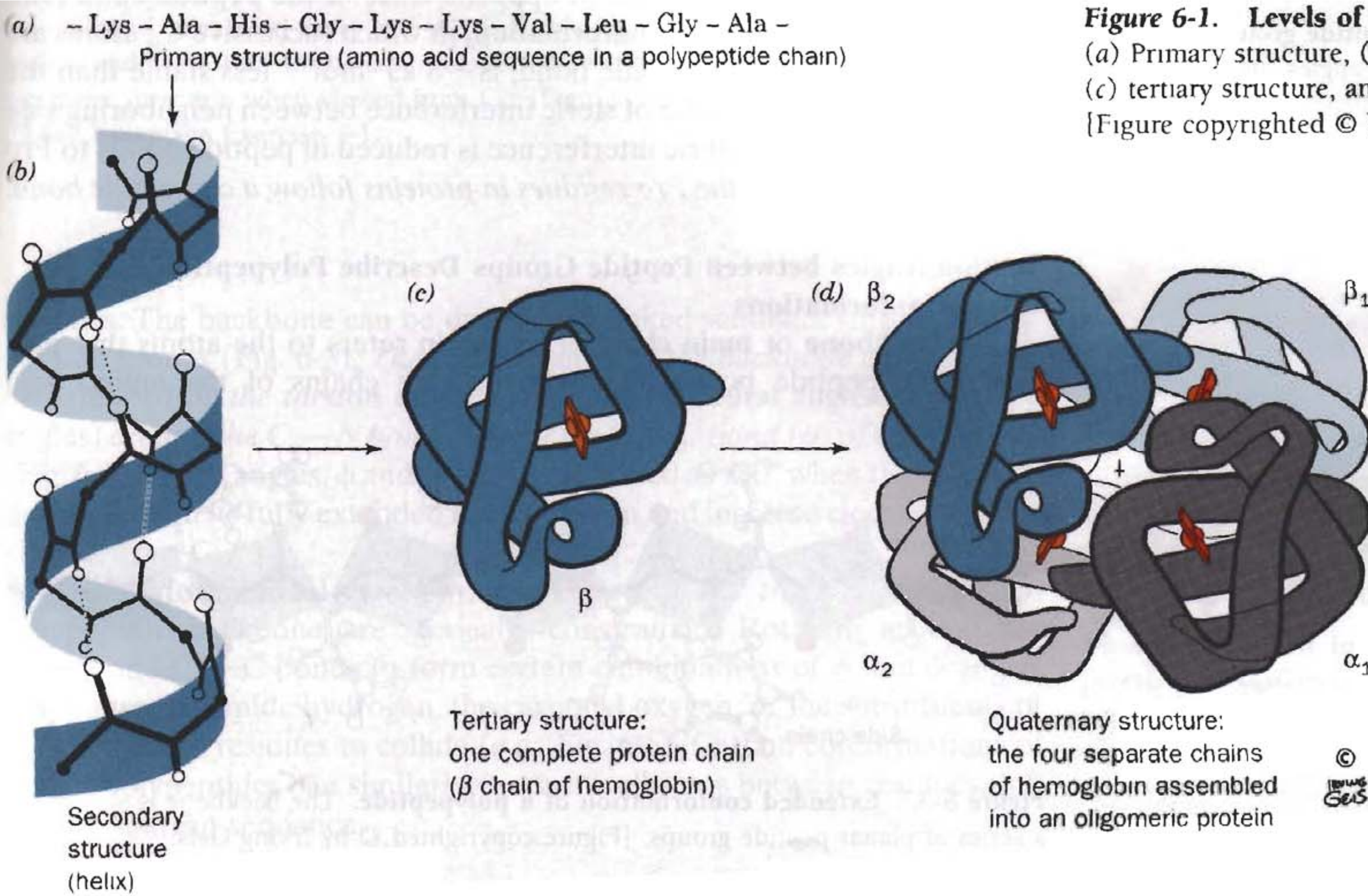


Figure 6-1. **Levels of protein structure.** (*a*) Primary structure, (*b*) secondary structure, (*c*) tertiary structure, and (*d*) quaternary structure. [Figure copyrighted © by Irving Geis.]

Where do the metals come in to play?

Voet, D.; Voet, J. G.; Pratt, C. W. *Fundamentals of Biochemistry*, John Wiley and Sons, New York, **2002**.

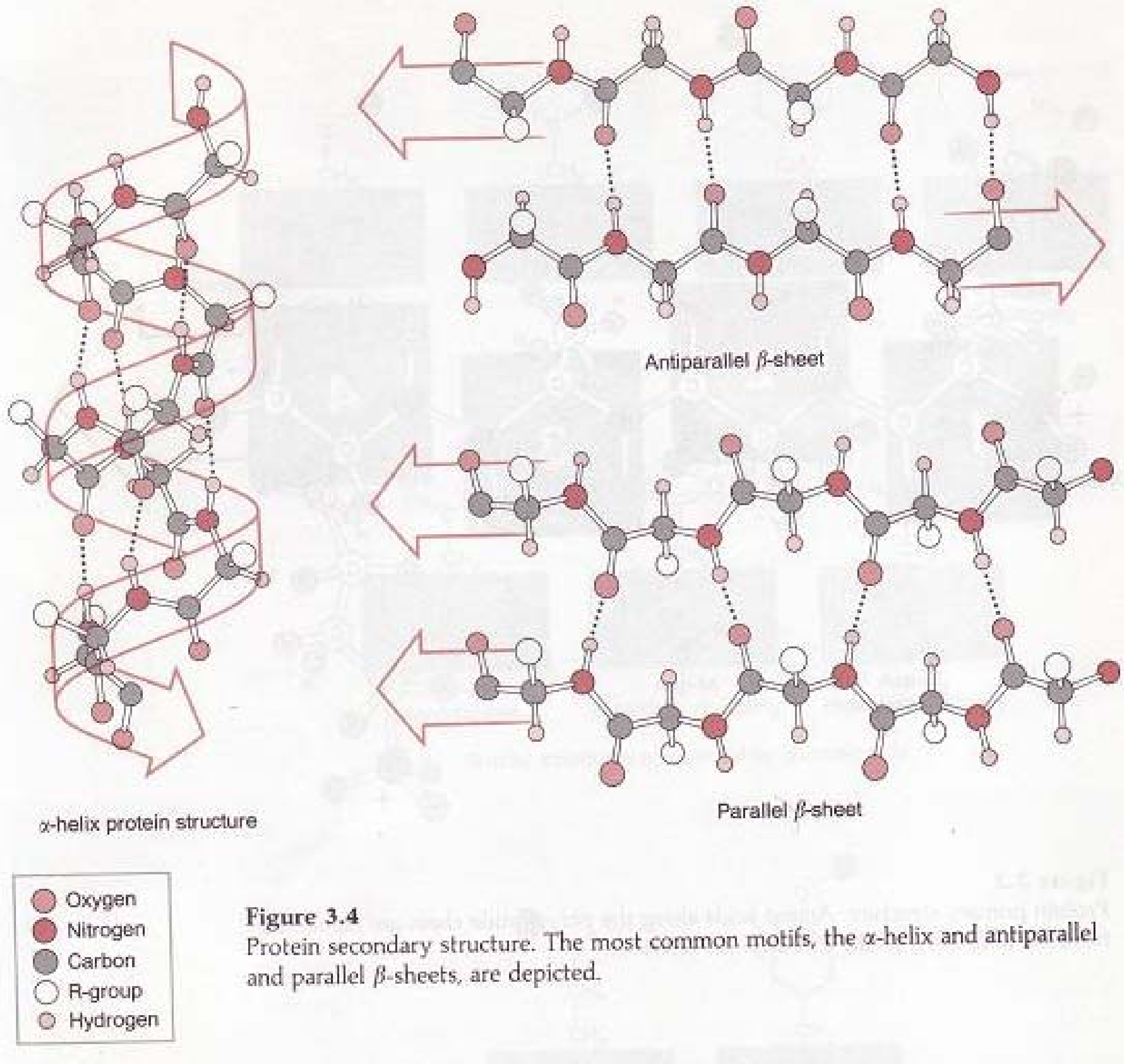


Figure 3.4
Protein secondary structure. The most common motifs, the α-helix and antiparallel and parallel β-sheets, are depicted.

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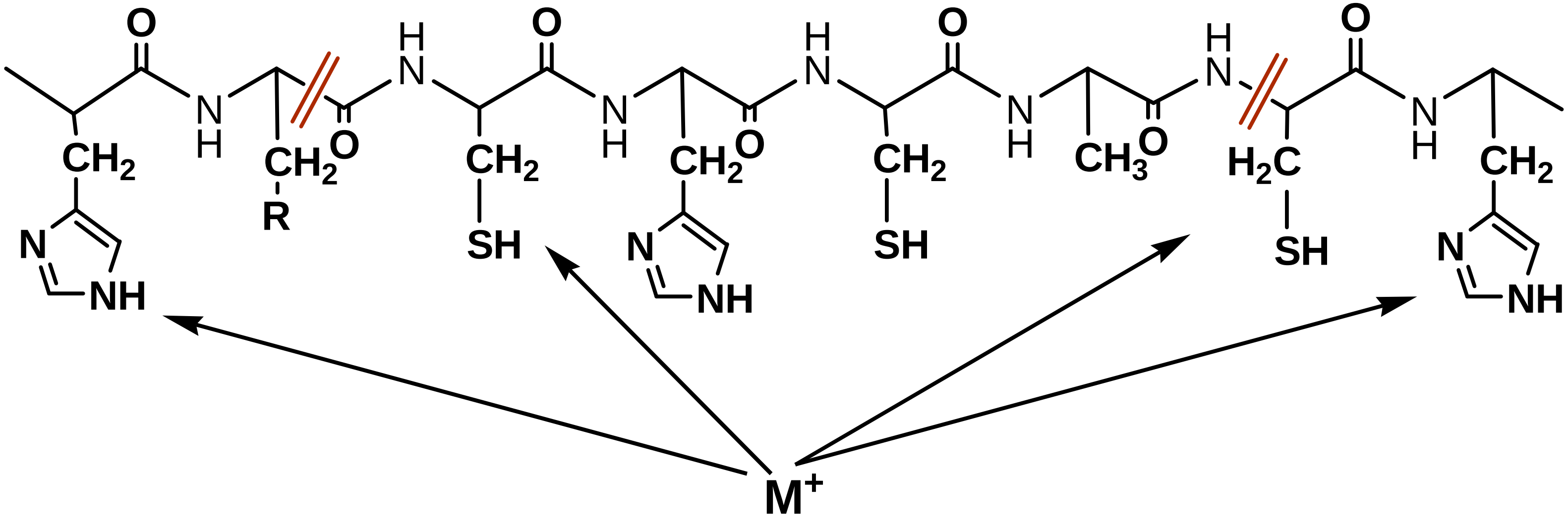
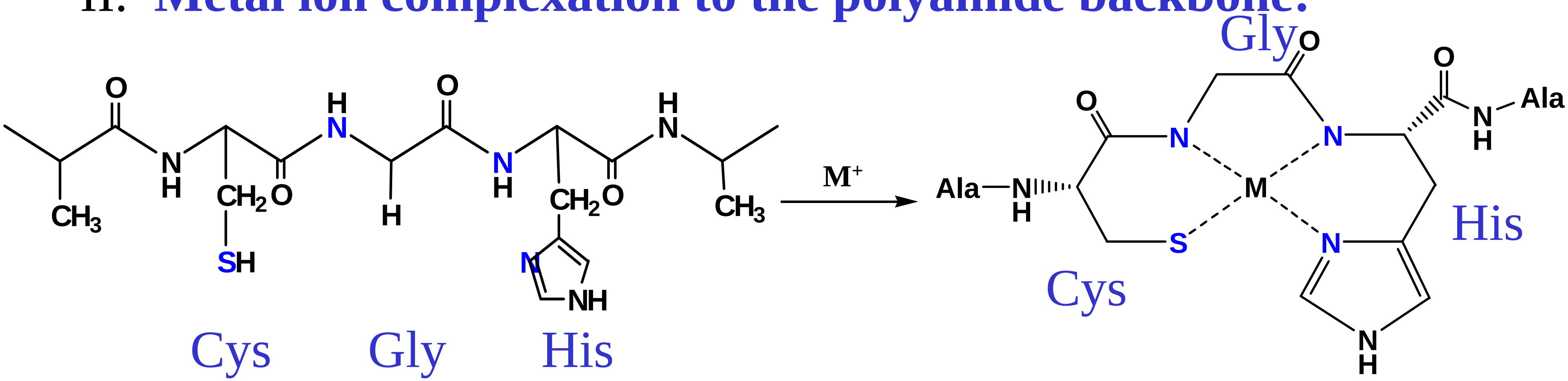
Metal Ion Complexation by Peptides

I. Metal Ligation by side-chain residues: from two to many amino acid units apart

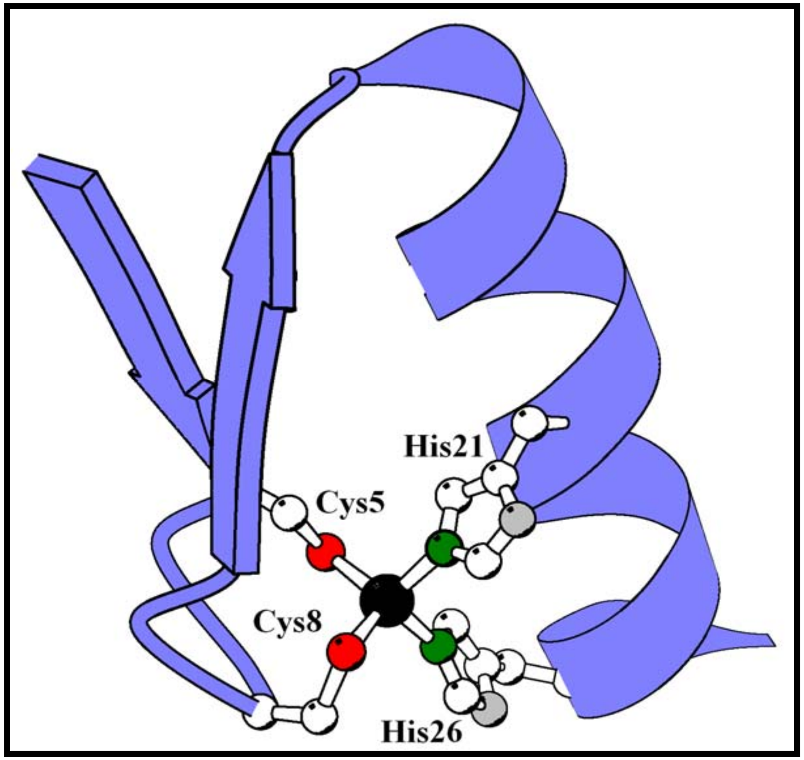


II. Metal ion complexation to the polyamide backbone:



The Two Classes of Peptide Ligands in Metalloproteins

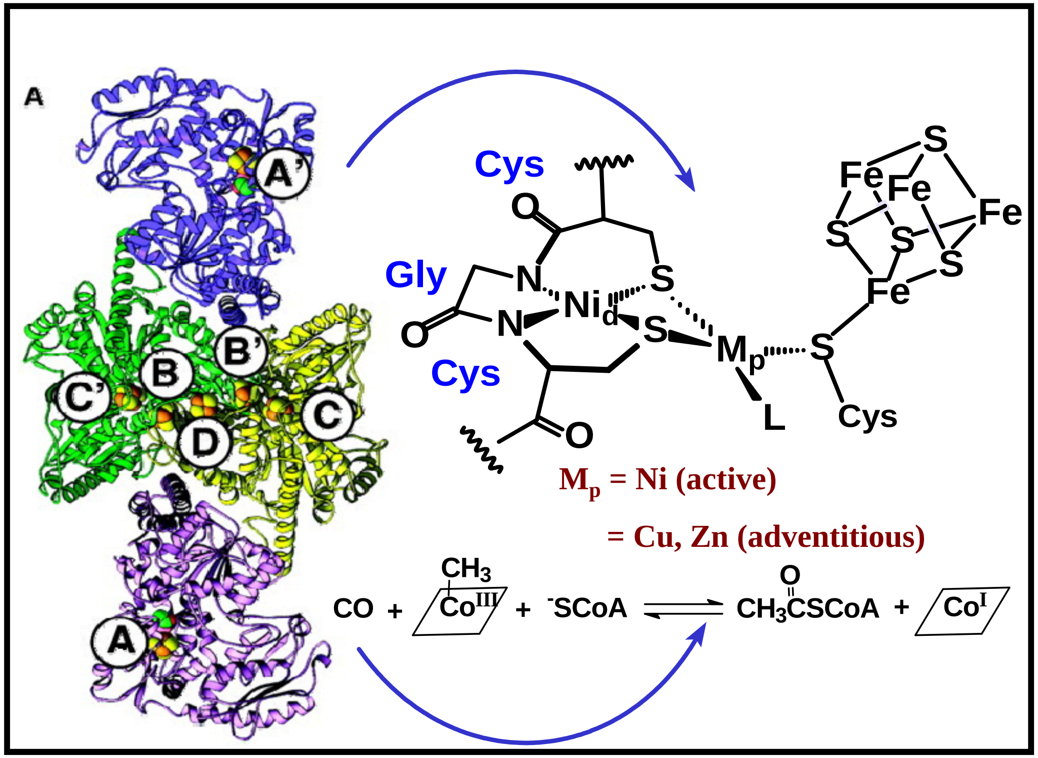
I. Binding to side chain residues



Cys_5XXCys_8~~~~$His_{21}XXXXHis_{26}$

Zinc Finger

II. Binding to deprotonated peptides



~~~~Cys_{595}-Gly_{596}-Cys_{597}~~~~

Acetyl CoA Synthase A-cluster

Metalloprotein vs. Metalloenzyme?

I. Berg, J.M.; Godwin, H.A. *Annu. Rev. Biophys. Biomol. Struct.* **1997**, *26*, 357-371.
II. Drennan, C.L.; et *al. Science*. **2002,** *298*, 567-572.
II. Fontecilla-Camps, J.C.; Lindahl, P.A.; *et al. Nature Structural Biology*. **2003**, 10, 271-279.
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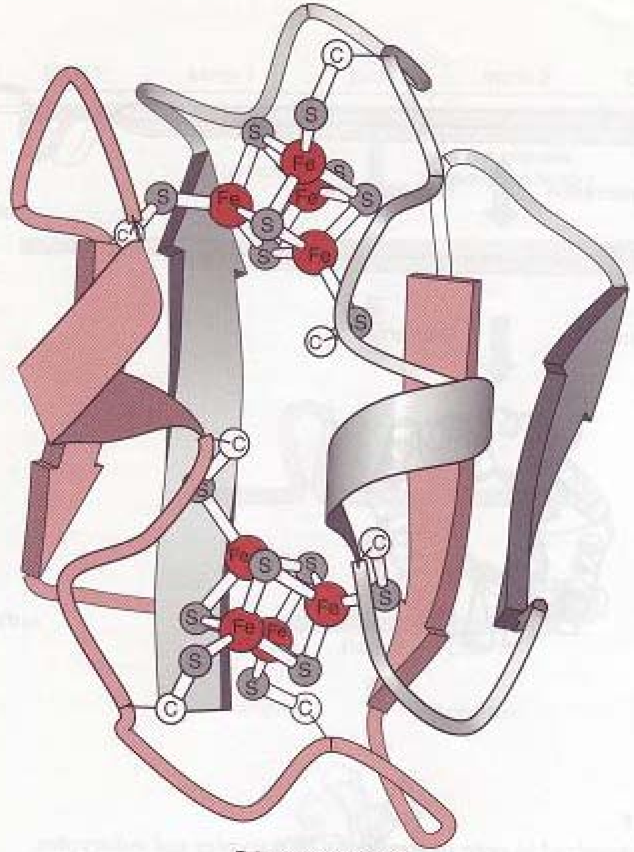
The capture of a 4Fe4S cube by 4 cysteine sulfurs in a ferridoxin protein.

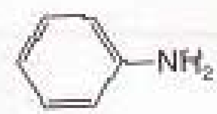


Primary structure

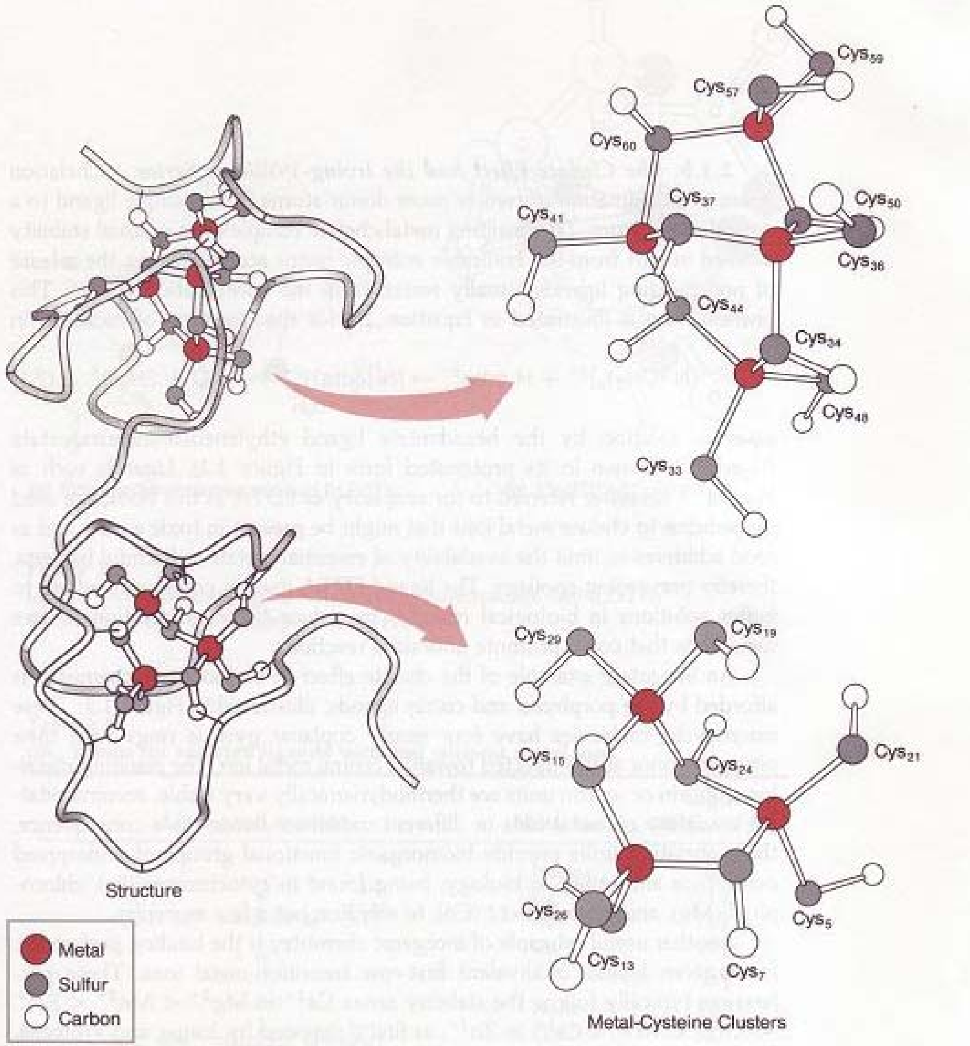
AYVINDSC_8 IAC_{11} GAC_{14} KPEC_{18} PVNIQQGSI
YAIDADSC_{35} IDC_{38}GSC_{41} ASVC_{45} PVGAPNPED

Figure 3.6
Primary and tertiary structures of an eight-iron ferredoxin. Although the primary structure includes two separate CXXCXXCXXXC sequences, each of the Fe_4S_4 cubes is bonded to cysteine residues from both cys-rich sequences.

Table 2.1
Hard-soft acid-base classification of metal ions and ligands important to bioinorganic chemistry

	Metals	Ligands
Hard		
	H^+, Na^+, K^+, Mg^{2+}, Mn^{2+}, Al^{3+}, Ga^{3+}, Ca^{2+}, Cr^{3+}, Co^{3+}, Fe^{3+}, Tl^{3+}	H_2O, OH^-, $CH_3CO_2^-$, PO_4^{3-}, $ROPO_3^{2-}$, CO_3^{2-}, NO_3^-, ROH, R_2O, $(RO)_2PO_2^-$, NH_3, RNH_2, N_2H_4, RO^-, Cl^-
Borderline		
	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}	NO_2^-, N_3, SO_3^{2-}, Br^-, N_3^-,  
Soft		
	Cu^+, Au^+, Cd^{2+}, Pt^{2+}, Tl^+, Pb^{2+}, Pt^{4+}, Hg^{2+}	R_2S, RS^-, RSH, $(RS)_2PO_2^-$, SCN^-, H^-, R_3P, CN^-, RNC, $(RO)_2P(O)S^-$, CO, R^-

Sulfur in thiolates or as sulfide bridges between Metals as in Metallo-thionen, a natural toxic metal scavenger



Amino acid sequence

CH_3CONH–Met Asp Pro Asn **Cys** Ser **Cys** Ala Thr Asp Gly Ser **Cys** Ser **Cys** Ala Gly Ser **Cys** Lys **Cys** Lys Gln **Cys** Lys **Cys** Thr Ser Cys Lys-Lys Ser **Cys Cys** Ser **Cys Cys** Pro Val Gly **Cys** Ala Lys **Cys** Ser Gln Gly **Cys** Ile **Cys** Lys Glu Ala Ser Asp Lys **Cys** Ser **Cys Cys** Ala-COO^-

Figure 2.1
Amino acid sequence and three-dimensional structure of metallothionein and its tetrametallic (top) and trimetallic (bottom) clusters.

About 40 % of metalloproteins

are metalloenzymes

Enzymes

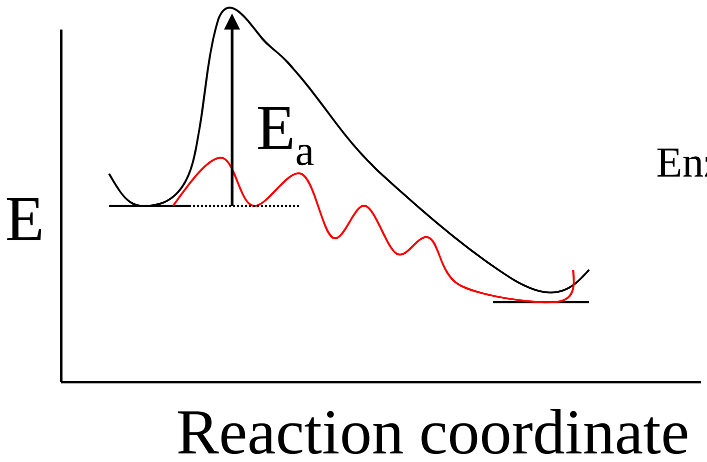
- Proteins serve different functions in cells, including catalysts, transport agents, and as structural supports.

- **Enzyme** = protein that catalyze reaction(s)

- Catalysts don’t change ΔG_o, they DO change the rate by lowering the energy of transition states.

- **Enzyme Mechanism** = series of steps through which catalysis is achieved.

- **Active Site** = where substrates bind and products are released.

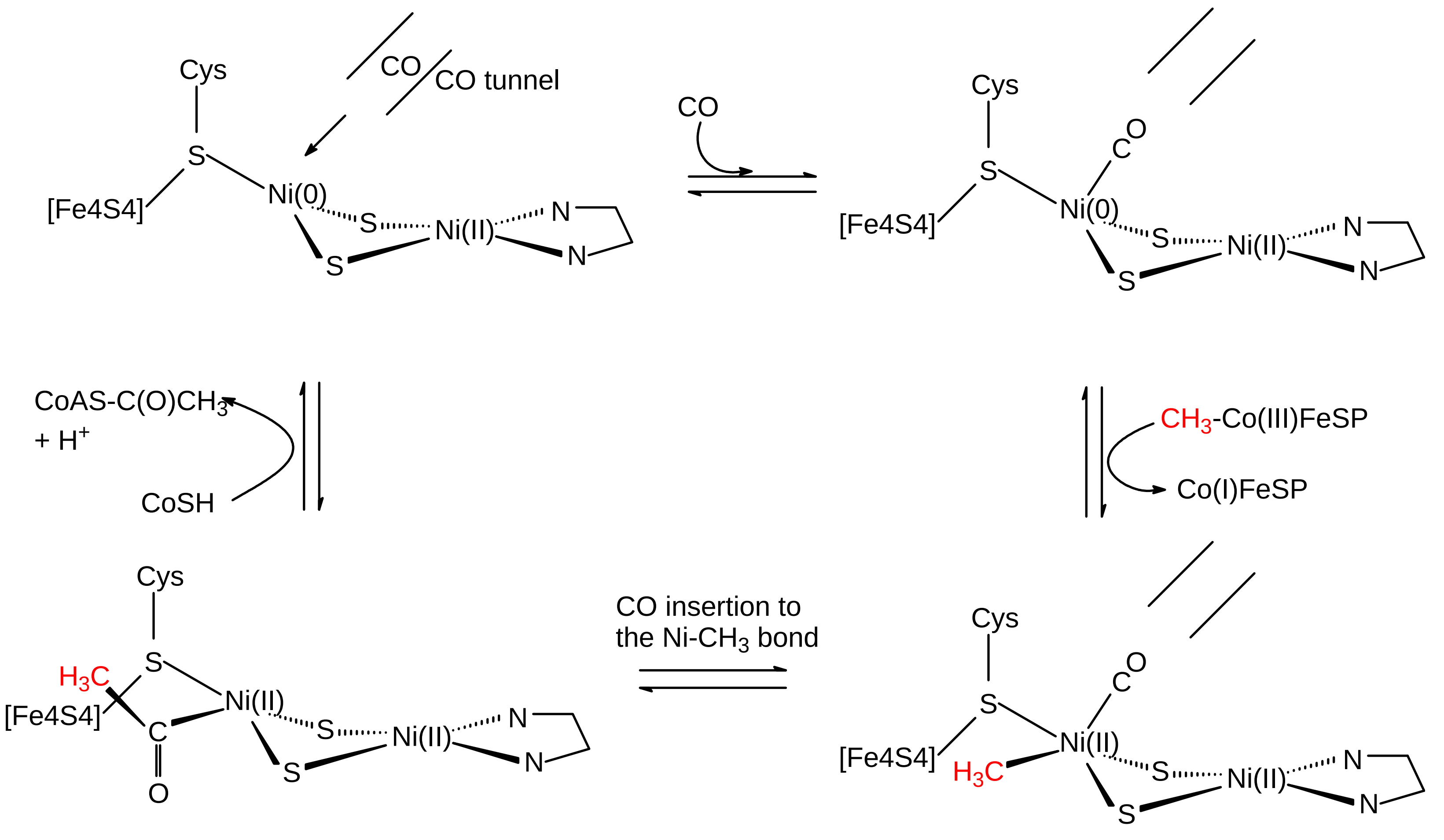


Enzymes affect **only Kinetics!!**

Rules for Constructing Catalytic Mechanisms

1. All substrates must be used in the mechanism.
2. All products must be released during the mechanism.
3. The catalyst must return to its original state at the end of the cycle.
4. A mechanism will be separated into fundamental steps.
5. Each step can only include 1 or 2 molecules.
6. Each step must be chemically reasonable.

A sample catalytic mechanism: ACS



Why does biology utilize transition metals?

- Transition Metals are extremely good catalytic active sites in enzymes, because they:
  - are stable in a variety of geometries and CN
  - have multiple coordination sites
  - Are stable in a variety of oxidation states
  - Are able to change the reactivity of ligands
  - Have “weak” coordinate bonds (where needed)
  - Are capable of stabilizing intermediates

Why does it matter what ligands are attached to the metal ?

- Tune Redox Properties
- Assist in stabilization of multiple oxidation states of transition metals
- Lability/Stability

Transition Metals Relevant to Bioinorganic Chemistry

- V, Mn, Fe, Co, Ni, Cu, Zn, Mo, & W

Amino Acid Residues Commonly Used as Ligands in Metalloenzymes

- Cysteine, Histidine, Aspartic Acid, Glutamic Acid, Methionine, Tyrosine, Serine, & Lysine

Enzymes Classified by Metal Centers: a few examples

- **Fe**
  - Hemes: Hemoglobin/Myoglobin, Cytochrome C, Cytochrome P450, Cytochrome C Oxidase
  - Binuclear Fe-Oxo: Hemerythrin, Methane Monoxygenase (MMO), Ribonucleotide Reductase
  - Iron Sulfur Clusters: Rubredoxin, (Fe_2S_2, Fe_3S_4, and Fe_4S_4) Feredoxins, Aconitase, Sulfite Reductase
- **Co**
  - Cobalamins: Cyanocobalamin (Vit. B12), Methylcobalamin (Coenzyme B12), Ribonucleotide Reductase, Methionine Synthase
- **Cu**
  - Others: Plastocyanin, CuZn SOD, Galactose Oxidase, Hemocyanin, Ascorbate Oxidase
- **Ni**
  - NiFe Hydrogenase, Acetyl CoA Synthase/ Carbon Monoxide Dehydrogenase (ACS/CODH), Coenzyme F430 Methyl Reductase, Urease
- **Mn**
  - Mn Cluster of Photosystem II
- **Mo**
  - Nitrogenase, DMSO Reductase, Sulfite Oxidase
- **W**
  - Aldehyde Ferrodoxin Oxidoreductase
- **Zn**
  - Carbonic Anhydrase, Alcohol Dehydrogenase, Zinc Fingers
- **V**
  - Haloperoxidase

Metals in Medicine

Metal-based drugs

Element	*Compound*	*Uses*	*Trade names/comments*
Approved agents (mostly US or worldwide):			
Li	Li_2CO_3	Manic depression	Camcolit; Cibalith-S; Lithane (of many)
Fe	$[Fe(NO)(CN)_5]^{2-}$	Vasodilation	Nipride. For acute shock. NO release
Ga	$Ga(NO_3)_3$	Hypercalcemia of malignancy	Ganite. Possible anticancer agent. In clinical trials for use in lymphomas
As	As_2O_3	Anticancer agent	Trisenox. Use in acute promyelocytic leukemia
Ag	$AgNO_3$	Disinfectant	Neonatal conjunctivitis
	Ag(sulfadiazene)	Antibacterial	Flamazine; Silvadene; treatment of burns. 1% cream
Sb	Sb^{III}(tartarate)	Antiparasitic, leishmaniasis	Tartar Emetic Stibophen; Astiban
Pt	*cis*-$[Pt(amine)_2X_2]$	Anticancer agents	Platinol; Paraplatin; Eloxatine Testicular, ovarian, colon cancers
Au	$Au(PEt_3)$(acetylthioglucose)	Rheumatoid arthritis	Ridaura. Orally active
Bi	Bi(sugar) polymers	Antiulcer; antacid	Pepto-Bismol; Ranitidine Bismutrex; De-Nol
Hg	Hg-organic compounds	Antibacterial	Thiomersal; mercurochrome (amongst many)
		Antifungal	Slow release of Hg^{2+}
Agents in clinical trials:			
Pt	Polynuclear Pt^{IV} species	Anticancer agents	BBR3464, Satraplatin, AMD-473
			Expands spectrum of activity of cisplatin; overcomes resistance; oral activity?
Mn	Mn chelates	Anticancer agents	SOD mimics
Ru	*trans*-$[RuCl_4(Me_2SO)(Im)]^-$	Anticancer agent	NAMI-A; antiangiogenic?
V	$VO(maltate)_2$	Type II diabetes	BMOV; insulin mimetic
Ln	$Ln(CO_3)_3$	Hyperphosphatemia	Fosrenol; phosphate binder

[a] Principal uses as medicinal agents. Other "trivial" or topical uses as ointments; antacids and skin desiccants for individual elements (especially Zn, Mg, and Al) may be found throughout.[14]

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Cinnabar: HgS

Medicinal use

Despite its toxicity, cinnabar has historically been used in traditional Chinese medicine, where it is called *zhūshā* (朱砂).

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

Metal-based diagnostics

Imaging Agents: Gd for MRI;
Tc-99m for heart

Metal-based therapeutics

Anti-cancer Agents: cis Platin
Ferrocifen

Vasodilation Agents: NO-releasing agents

Other small molecule releasing agents:
Carbon Monoxide Releasing Agents

Your big project: **Powerpoint Presentation**
On topic of your choice—well, sorta.
Chosen from Metals in Biology or
Metals in Medicine – Select your topic from
The list, dates will be assigned by The management.

CHEM 489-503 – Metals in Biology and Medicine

Topics for Presentations

From M. in Bio.

•Iron-Sulfur Clusters
•Nitrogenase
•Zinc Enzymes – Carboxypeptidase; Carbonic Anhydrase
•Zinc Finger Proteins
•Carbon Monoxide Dehydrogenase and Acetyl CoA Synthase: Nature suggests organometallic catalysis
•Hydrogenases --Organometallics in Nature
•Vitamin B-12 – Metal-carbon bonds
•Photosystem II (Science, 2004, 303, 1831) and the Oxygen-Evolving Complex
•Copper Proteins and Copper-Related Disorders (Wilson's, Menke's, Lou Gehrig's) Similarities and Differences to Iron
•Copper Enzymes –
Cu-Amine Oxidase
Hemocyanine – Model Compounds
•Mn, Mo, W Enzymes
•Non-heme Iron Enzymes
•Iron-Management – Ferritin and Siderophores

From M. in Med.

1M) Cis-Platin Anti-Cancer
2M) Gold Anti-Arthritis
3M) Imaging Agents (Gd or Tc or Both)
4M/B) Vanadium in medicine or biology or both
5M) Ferrocifen Anti Cancer
6M) NO Releasing Agents (NORA) – what they are and what they do
7M) CO Releasing Materials (CORM)

Here is the plan:

- Choose a topic. You can work in pairs or individually. Send 1^{st}, 2^{nd} and 3^{rd} choices to MYD (marcetta@mail.chem.tamu.edu)
- Presentation date will be set by MYD—cannot be changed
- Research by first going to classic text book like Lippard and Berg
- Research secondly by going to key journal articles.
- Present abstract, outline and sketch of slides to MYD 2 weeks prior to presentation
- You should expect to need about 20 – 25 slides per presentation
- You should identify fundamental inorganic chemistry that is at basis of your topic.
- Members of the audience will prepare questions addressing the fundamental inorganic chemistry and lead discussions on the topic.