

Chemistry 476

Bioinorganic Chemistry

Bioinorganic Chemistry

- True Hybrid Discipline drawing from Biochemistry, Inorganic, Physical
- Three Basic Approaches
 - *Biochemical* isolation and properties of biomolecules
 - *Synthetic inorganic* build small molecule models for metals in biomolecules
 - *Physical inorganic* use spectroscopy to study intact metalloproteins and models, theoretical modeling

Elements used in Biology

Group	1	2											13	14	15	16	17	18																																																																																																	
1	H																	He																																																																																																	
2	Li	Be											B	C	N	O	F	Ne																																																																																																	
3	Na	Mg	3	4	5	6	7	8	9	10	11	12	Al	Si	P	S	Cl	Ar																																																																																																	
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr																																																																																																	
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe																																																																																																	
6	Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn																																																																																																	
7	Fr	Ra		Rf	Db	Sg	Bh	Hs	Mt																																																																																																										
			8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120

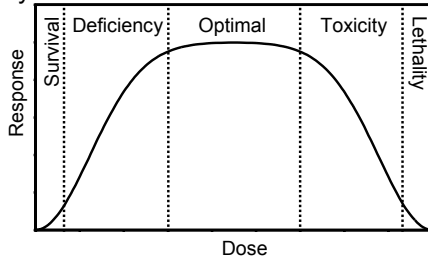
- Bulk Elements Essential Ultratrace Elements
 Essential Trace Elements Role Uncertain

Concept of Essentiality

- Criteria for Essential Elements
 - Physiological deficiency appears when element removed from diet
 - Deficiency is relieved by addition of one element
 - Element associated with a specific biochemical function
- Not all Elements are Essential for all Organisms

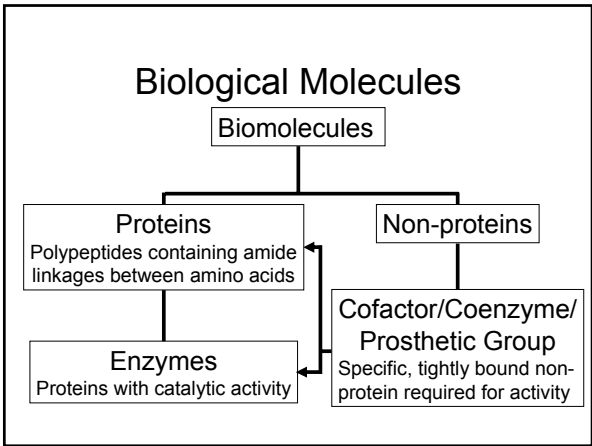
Concept of Essentiality

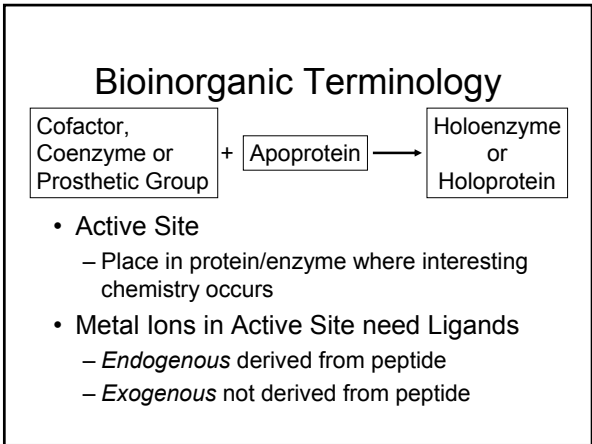
- General Response of a Biological System to an Element

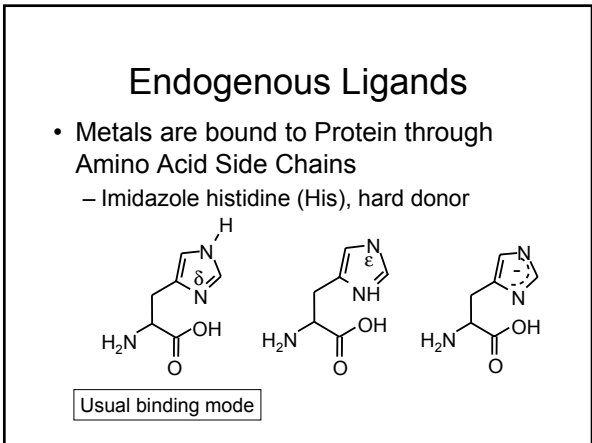


Availability of Elements

- Distribution of Elements in Living Organisms Generally follows Abundance in Seawater
- Bulk Elements are Available in Water-Soluble Forms
- Trace and Ultratrace Elements usually have Solubility Problems
 - Evolution of uptake mechanisms

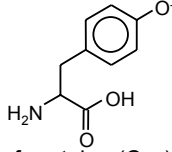




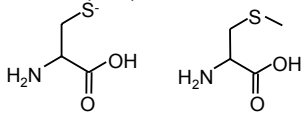


Endogenous Ligands

– Phenolate of tyrosine (Tyr), hard

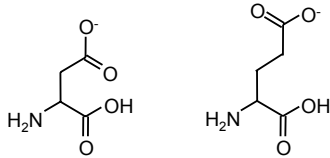


– Thiolate of cysteine (Cys) and thioether of methionine (Met), soft



Endogenous Ligands

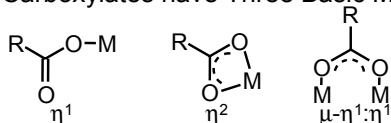
– Carboxylate of aspartic (Asp) and glutamic acids (Glu), hard



Bind η^1 or η^2 through side chain oxygens, but in γ -Glu and β -Asp other carboxylate used.

Binding Modes of Endogenous Ligands

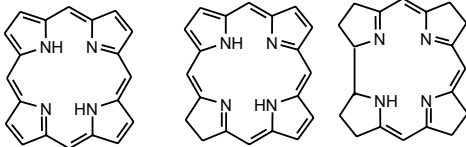
- Histidine usually η^1 through δ -N
 - Can be μ - η^2 if both N are deprotonated
- Tyrosine, Cysteine either η^1 or μ - η^2
- Methionine always η^1
- Carboxylates have Three Basic Modes



Common Exogenous Ligands

- Ligands not Integrated into Active Site Structure
 - Water-derived (H_2O , OH^-)
 - Oxygen-derived (O_2 , O_2^- , O_2^{2-} , HO_2^-)
 - Neutral species (CO , NO)
 - Halides and other charged species (Cl^- , PO_4^{3-})
- Ligands Integrated into the Active Site Structure (sometimes called Endogenous)
 - Water-derived (H_2O , OH^- , O^{2-})
 - “Inorganic sulfur” a.k.a. sulfide (S^{2-})

Tetrapyrrole Ligands



Porphin (unsubstituted)
Porphyrin (substituted)

Chlorin

Corrin

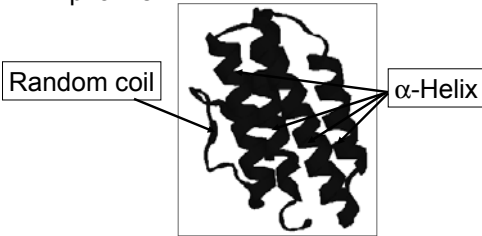
Usually covalently linked to protein as a coenzyme/prosthetic group (along with a metal). Other structures are known.

Polypeptide Structure

- *Primary Structure*
 - Amino acid sequence of polypeptide
- *Secondary Structure*
 - Three dimensional structures arising from interactions within and between polypeptide chains
- *Tertiary Structure*
 - Further three dimensional ordering of secondary structure
 - Overall protein structure

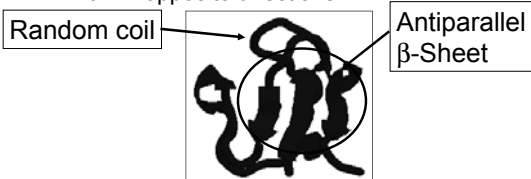
Secondary Structures

- Random Coil
 - No specific ordering
- Alpha Helix



Secondary Structures

- Beta Sheet
 - *Parallel* adjacent polypeptide strands run in same direction
 - *Antiparallel* adjacent polypeptide strands run in opposite directions



Practical Biochemistry

- Proteins are Fragile so require special Handling
 - Cold (4 °C)
 - Buffered solutions
- Purification by Recrystallization usually not possible
 - Columns (size exclusion)
 - Dialysis
 - Size-selective filtration (pressure, centrifuge)

Probes of Metal Sites in Metallobiomolecules

- Electronic Spectroscopy
 - Absorbance/CD
- Vibrational Spectroscopy
 - Raman
- Magnetic Measurements
 - EPR/MCD/magnetic susceptibility/nMR
- X-Ray Methods
 - Crystallography
 - EXAFS

Review of Spectroscopy

- For a Transition to be *Allowed* the Transition Moment Integral must be Nonzero: $\langle \psi_e | \hat{M} | \psi_g \rangle \neq 0$

- It is Equivalent to show that the Following is True: $\Gamma_e \times \Gamma_M \times \Gamma_g \subset A_{1(g)}$

- Transition Moment Operator can be written:

$$\hat{M} = \hat{M}(\text{electric dipole}) + \hat{M}(\text{magnetic dipole}) + \dots$$

Review of Spectroscopy

$6A_{1g}$ ← Orbital component of wavefunction
 Multiplicity (2S + 1) Molecular term symbol

- For Electronic Transitions separate Spin and Orbital Parts of Wavefunctions
 - Magnetic and electric dipole operators don't affect spin
 - So write

$$\langle S_e | S_g \rangle \langle \phi_e | \hat{M} | \phi_g \rangle \neq 0$$

Review of Spectroscopy

$$\langle S_e | S_g \rangle \langle \phi_e | \hat{M} | \phi_g \rangle \neq 0$$

- To be Non-zero $S_e = S_g$ ($\Delta S = 0$ for Transition)
 - If $\Delta S = 0$ *spin allowed*
 - If $\Delta S \neq 0$ *spin forbidden*
- For the Orbital Component need Transformation Properties of
 - Electric dipole operator (x, y, z) \Rightarrow Absorption
 - Magnetic dipole operator (R_x, R_y, R_z) \Rightarrow CD

Review of Spectroscopy

- In T_d is the ${}^6A_1 \rightarrow {}^4T_2$ d-d transition electric dipole allowed?

Different spin states, so $\Delta S \neq 0$ and spin forbidden

But what about the orbital part?

T_d	E	$8C_3$	$3C_2$	$6S_4$	$6\sigma_d$
A_1	1	1	1	1	1
T_2	3	0	-1	-1	1
T_2	3	0	-1	-1	1
$T_2 \times T_2 \times A_1$	9	0	1	1	1

Review of Spectroscopy

Reduce the reducible representation using Great Orthogonality Theorem

$$a_i = \frac{1}{h} \sum_{\text{symmetry operations}} \chi_j \chi_i$$

T_d	E	$8C_3$	$3C_2$	$6S_4$	$6\sigma_d$
A_1	1	1	1	1	1
$T_2 \times T_2 \times A_1$	9	0	1	1	1

$$a_{A_1} = \frac{1}{24} [(1)(1)(9) + (8)(1)(0) + (3)(1)(1) + (6)(1)(1) + (6)(1)(1)]$$

$$a_{A_1} = 1$$

Ligand Field Transitions

- Move Electrons Among d Orbitals
 - Occur $\sim 4000 - \sim 30000 \text{ cm}^{-1}$
- In Symmetries with g/u, all d-d Transitions are Laporté (Symmetry) Forbidden with Electric Dipole
- Spin Forbidden, Parity Forbidden
 - $\epsilon = 0.01 - 1 \text{ M}^{-1} \text{ cm}^{-1}$
- Spin Allowed, Parity Forbidden
 - $\epsilon = \sim 10 \text{ M}^{-1} \text{ cm}^{-1}$

Allowed Transitions

- Charge Transfer
 - Ligand to metal charge transfer
 - Metal to ligand charge transfer
- Intraligand Transitions
 - Moving electrons between orbitals on ligand
- *Usually* Intense ($\epsilon > 10000 \text{ M}^{-1} \text{ cm}^{-1}$)
 - Spin allowed
 - Excited states have “u” symmetry

Increasing Intensity of Forbidden Transitions

- Low Symmetry
 - Removes Laporté problem
 - Mixes orbitals
 - Does not affect spin
 - Spin and Laporté forbidden, ϵ to ~ 10
 - Spin allowed/Laporté forbidden, ϵ to ~ 100
- Vibronic Coupling
 - Dynamic symmetry lowering
 - Very small increase in ϵ

Increasing Intensity of Forbidden Transitions

- Mixing of Forbidden Transition with an Allowed Transition
 - Best when transitions have same symmetry and are close in energy
 - Spin-orbit coupling
 - Spin and Laporté forbidden ϵ to ~ 20
 - Spin allowed/Laporté forbidden ϵ to ~ 1000

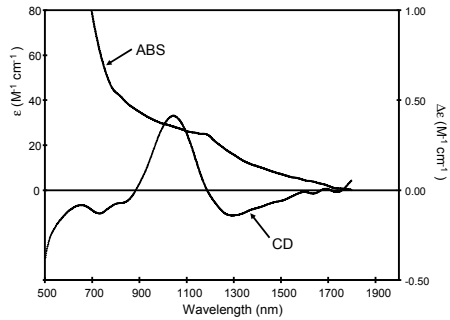
Circular Dichroism Spectroscopy

- Differential Absorption of Left and Right Circularly Polarized Light
 - Signal = $\epsilon_{\text{left}} - \epsilon_{\text{right}}$ (sign)
 - Magnetic dipole dominated (R_x, R_y, R_z)
- Compound must be Optically Active
 - CD spectra of enantiomers have same transitions, but opposite sign
 - Metal centers are not optically active, but protein is (induced CD)

Advantages of CD

- Probes only Metal Ions bound to Protein
- Different Selection Rule
 - Transitions weak in absorbance may be strong in CD
- Sign Differences allow Resolution of Closely Separated Transitions
- UV CD Spectrum sensitive to Secondary Structure of Protein

Comparison of CD and Absorbance



Polarization of Absorption Bands

- High Symmetries: All Components of Electric and Magnetic Operators transform Together
- Lower Symmetries: they don't
 - Example: in D_{4h} z transforms as a_{2u} and x,y transforms as e_u
- Absorption depends on Orientation of Molecule and Light
 - Single crystal polarized spectroscopy

Vibrational Spectroscopy

- IR Spectroscopy of Proteins not Useful
 - Water vibrations
 - Many allowed transitions of protein backbone and functional groups
 - Relatively broad lines
- Raman Spectroscopy better
 - Different selection rule
 - Relatively narrow lines
