Bioinorganic Chemistry
What is bioinorganic chemistry?

- Intersection of classical inorganic chemistry and biology
  - Study of natural occurring inorganic elements in living systems
  - Study of metals introduced as probes or drugs

- Why is it important?
  - There are many metals that are essential to life.
### Periodic table of life

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>Li</th>
<th>Be</th>
<th></th>
<th>B</th>
<th>C</th>
<th>N</th>
<th>O</th>
<th>F</th>
<th>Ne</th>
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<tbody>
<tr>
<td>Na</td>
<td>Mg</td>
<td>Al</td>
<td>Si</td>
<td>P</td>
<td>S</td>
<td>Cl</td>
<td>Ar</td>
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<tr>
<td>K</td>
<td>Ca</td>
<td>Sc</td>
<td>Ti</td>
<td>V</td>
<td>Cr</td>
<td>Mn</td>
<td>Fe</td>
<td>Co</td>
<td>Ni</td>
<td>Cu</td>
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<td>Y</td>
<td>Zr</td>
<td>Nb</td>
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#### Essential elements for humans (daily requirement: 25 mg)

**Presumably essential elements**

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

- Metal ions must be obtained for growth and development.

Table 3.1  Approximate Elemental Composition of a Typical 70kg Human

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<th>Bulk elements and mineral ions</th>
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<td>Iron</td>
</tr>
<tr>
<td>Carbon</td>
<td>12.6 kg</td>
<td>Silicon</td>
</tr>
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<tr>
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Figure 6.1
Representation of the concentration dependence of the toxic and beneficial effects of metal ions.
Roles of Metals in Biology

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

2. Metalloenzymes
   - Hydrolytic enzymes
     - Catalyze addition or removal of H or O in a substrate
   - Two-electron redox enzymes
     - Catalyze redox activity of substrate (e.g. removal of O atoms from substrate)
   - Multielectron pair redox enzymes
     - \( 2\text{H}_2\text{O} \rightarrow \text{O}_2 + 4\text{H}^+ + 4\text{e}^- \)
3. Cellular Communication
   - Cellular triggers
     - $\text{Na}^+$ flux across a cell membrane triggers neuron firing
     - $\text{Ca}^{2+}$ has influence on muscle activity
   - Regulation of gene expression
     - Possible function of $\text{Zn}^{2+}$ in zinc-finger proteins
Roles of Metals in Biology

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

- Li\textsuperscript{+}: Treatment of depression (Li\textsubscript{2}CO\textsubscript{3}, low doses)
- Gd\textsuperscript{3+}: Contrast agent (NMR)
- BaSO\textsubscript{4}: Contrast agent (radiography)
- \textsuperscript{99m}Tc: radio diagnostics (thyroid)
  - Technetium-99m or 99m\textit{Tc} ("m" indicates that this is a metastable nuclear isomer) is used in radioactive isotope medical tests
- Au(I): Rheumatism

\[
Na_3\left[O_3S_2-Au^{I-S}_2O_3\right]\left(H_2C-CO_2Na\right)_n\left(HOH\right)_n
\]

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

\[
\text{Well} \quad \text{Health} \quad \text{Dead} \\
\text{Health} \quad \text{Concentration}
\]
Application of metals in medicine

- Pt(II): Cisplatin (cis-[Pt(NH$_3$)$_2$Cl$_2$]), chemotherapy (inhibition of cell division, not cell growth)

- Filamentous growth of bacteria
Oxygen Evolving Complex (OEC) in Photosystem II (PSII)

- Component of photosynthesis in all green plants
- Active site contains
  - 4 Mn atoms with oxo bridges
  - Ca$^{2+}$ ions
  - Overall cluster structure is unknown
- Catalyzes rxn: $2\text{H}_2\text{O} \rightarrow \text{O}_2 + 4\text{H}^+ + 4\text{e}^-$
  - This manganese complex produced all the oxygen in the world!
- Energy from light drives this thermodynamically uphill process
Components of Photosynthesis

PSII  OEC  PSI  ATP synthase
Function of the Photosystems

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

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

\[
\begin{array}{c}
S_0 \xrightarrow{h\nu} S_1 \xrightarrow{h\nu} S_2 \xrightarrow{h\nu} S_3 \xrightarrow{h\nu} S_4 \\
\uparrow e^- \quad \uparrow e^- \quad \uparrow e^- \quad \uparrow e^- \quad O_2
\end{array}
\]
4 total photons ($h\nu$) required for activity
Small Model Systems

- Many small inorganic model complexes have been developed to model these mixed-valent Mn centers.
- Various goals
  - Give an insight into the high-valent Mn chemistry in aqueous media
  - Understand preference and structural requirements for oxidation states
  - Duplicate reactivity
[Mn^{IV}(salpn)(\mu-O)]_2 structurally resembles the OEC Mn-cluster

- Mn-Mn distance (2.7 Å) is equal to the distance deduced for the lower S-states
- Contains bis-oxo bridges like the proposed structure
Hemoglobin

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

Oxygenated

Poorly oxygenated
Structure of Hemoglobin

- Multisubunit protein, 2 $\alpha$ and 2 $\beta$ peptides
- 4 Iron-porphyrin rings, each can bind 1 $O_2$
Visualizing $O_2$ Binding

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

- Iron oxidized from 2+ (deoxy) to 3+ (oxy)
- The electronic configuration of the metal dictates $O_2$ binding
  - Deoxy form: high spin $Fe^{2+}$ “bends” porphyrin ring to have a shortened Fe-N(his) bond.
  - Oxy form: after binding $O_2$, the low spin $Fe^{3+}$-N(his) bond lengthens, the porphyrin ring becomes more planar, and the Fe moves further into the plane.
- Quaternary structure of the protein also changes thru deoxy-oxy cycle
Electronic changes in Fe upon binding of O₂

- Fe^{2+} \rightarrow Fe^{3+}
- hs \rightarrow ls
- Porphyrin ring becomes more planar
- Lengthening of Fe-N(his) bond anchoring heme
Quaternary structure changes upon binding of $O_2$ (*top view*)

Deoxy  

Oxy (*red $O_2$ on hemes*)
Quaternary structure changes upon binding of O$_2$ (side view)
Hemocyanin

- Very large oxygen transport protein (4x the size of Hb, >400,000 amu)
- Found only in arthropods and mollusks (e.g., lobsters and crabs)
- No heme group
- Deoxy form is colorless
- Two Cu$^{1+}$ ($d^9$) atoms anchored by histidine residues are oxidized to Cu$^{2+}$ upon binding O$_2$
Physical Methods

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

Hexagonal protein crystals of glycosol hydrolase.
Physical Methods

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

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

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