Bulk and trace elements

– bulk elements:  C, H, O, N, S, P
– maintaining the osmotic pressure body fluids
  Na, K, Ca, Mg, Cl

– essential trace elements:
  F, I, Se, Si, Sn (main group elements)
  Fe, Zn, Cu, Mn, Mo, Co, V, Ni (transition metals)

– potential trace elements:  B, Ti, As, Pb, Cd, W, ....
– toxic elements
### Average abundance of trace elements (70 kg individual)

<table>
<thead>
<tr>
<th>Organic elements</th>
<th>element</th>
<th>weight (g)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>45550</td>
<td>65.1</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>12590</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>6780</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1815</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>680</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>100</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>
### Average amount of trace elements (70 kg individual)

<table>
<thead>
<tr>
<th>Bulk elements</th>
<th>Ca</th>
<th>1700</th>
<th>2.42</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K</td>
<td>250</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>115</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Na</td>
<td>70</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Mg</td>
<td>42</td>
<td>0.06</td>
</tr>
<tr>
<td>Trace elements</td>
<td>Fe</td>
<td>4.2-4.6</td>
<td>0.007</td>
</tr>
<tr>
<td>(&lt;100 mg/body kg)</td>
<td>Zn</td>
<td>2-4</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Cu</td>
<td>80-120 mg</td>
<td>0.00014</td>
</tr>
<tr>
<td></td>
<td>Mn</td>
<td>12-20 mg</td>
<td>0.00003</td>
</tr>
<tr>
<td></td>
<td>Mo</td>
<td>4 mg</td>
<td>0.00001</td>
</tr>
</tbody>
</table>
Trace elements

1. The abundance of elements in different living organisms is in a given concentration range.

2. The decreasing of abundance of elements causes physiological changes (diseases).

3. Administration of missing trace elements improve the physiological condition.

   They take part in the metabolism.

4. The elements have defined biochemical functions.
Trace elements

- Survival
- Deficiency
- Optimal (therapeutic width)
- Toxicity
- Lethal

Trace elements shown in µg/day and mg/day:
- Selenium (Se) 10 - 200 µg/day
- Fluorine (F) 2 - 10 mg/day

Survival is optimal, deficiency is toxic, and lethality is indicated by the lethal values.
Roles of trace elements

1. Transport of biological small molecules
   - pl. O$_2$-transport: hemoglobin (Fe), hemocianin (Cu)
   - O$_2$-storage: mioglobin (Fe)

2. Activation of molecules: metalloenzymes, enzymes activated by metal ions
   a) catalysing of redox processes (Fe, Cu, Mn, Co, Mo, Ni)
      - biological oxidation, reduction of substrate
   b) catalysing of acid-base processes (Zn)
Roles of trace elements

3. Secunder conformation of macromolecules
   – determination of conformation of enzymes
   – determination of conformation of proteins, nucleic acids

4. Metabolism of microelements
   – uptaking, transport, storage of trace elements
Experimental methods for study of biological systems

- UV-visible (UV) spectroscopy (excited electron $\rightarrow$ groundstate)
- Electron spin resonance spectroscopy (ESR) (interaction between unpaired electron and magnetic field)
- Nuclear magnetic resonance spectroscopy (NMR)
- X-ray diffraction (study of solid crystals)
- Mössbauer spectroscopy (study of iron-, tin-complexes)
- Molecule modelling (computational modelling)
**Abundance of trace elements in a caveman and today (ppm)**

<table>
<thead>
<tr>
<th>element</th>
<th>caveman</th>
<th>today</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe</td>
<td>60</td>
<td>60</td>
<td>1,0</td>
</tr>
<tr>
<td>Zn</td>
<td>33</td>
<td>33</td>
<td>1,0</td>
</tr>
<tr>
<td>Cu</td>
<td>1,0</td>
<td>1,2</td>
<td>1,2</td>
</tr>
<tr>
<td>Mo</td>
<td>0,1</td>
<td>0,1</td>
<td>1,0</td>
</tr>
<tr>
<td>Co</td>
<td>0,03</td>
<td>0,03</td>
<td>1,0</td>
</tr>
<tr>
<td>B</td>
<td>0,3</td>
<td>0,7</td>
<td>2,3</td>
</tr>
<tr>
<td>Al</td>
<td>0,4</td>
<td>0,9</td>
<td>2,3</td>
</tr>
<tr>
<td>Ti</td>
<td>0,4</td>
<td>0,4</td>
<td>1,0</td>
</tr>
<tr>
<td>Cd</td>
<td>0,001</td>
<td>0,7</td>
<td>700</td>
</tr>
<tr>
<td>Hg</td>
<td>&lt;0,001</td>
<td>0,19</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>Pb</td>
<td>0,01</td>
<td>1,7</td>
<td>170</td>
</tr>
</tbody>
</table>
### Composition of Earth crust and see water (ppm)

<table>
<thead>
<tr>
<th>element</th>
<th>earth crust</th>
<th>see water</th>
<th>see/earth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>28300</td>
<td>10050</td>
<td>0.37</td>
</tr>
<tr>
<td>Cl</td>
<td>130</td>
<td>190000</td>
<td>146</td>
</tr>
<tr>
<td>Al</td>
<td>81300</td>
<td>0.01</td>
<td>~10⁻⁷</td>
</tr>
<tr>
<td>Si</td>
<td>277000</td>
<td>3.0</td>
<td>~10⁻⁵</td>
</tr>
<tr>
<td>Ti</td>
<td>4400</td>
<td>0.001</td>
<td>~10⁻⁷</td>
</tr>
<tr>
<td>Cr</td>
<td>100</td>
<td>0.0005</td>
<td>~10⁻⁶</td>
</tr>
<tr>
<td>Mo</td>
<td>1.5</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Ln</td>
<td>1-100</td>
<td>~10⁻⁷</td>
<td>~10⁻⁸</td>
</tr>
<tr>
<td>Cu</td>
<td>55</td>
<td>0.003</td>
<td>5.10⁻⁷</td>
</tr>
</tbody>
</table>
- circumstances of life origin
- chemical factors
  (complex formation ability, solubility, reversibility of bound, hard-soft acid-base properties)

The origin of life

Chemical evolution: formation of simple and more complicate organic molecules from elements
Prebiological evolution: formation of living cells from group of complicate organic compounds
Biological evolution: the development of living world
Coordination chemistry of metal ions

**Complex formation processes:**

\[ M(H_2O)_n + L \rightleftharpoons ML(H_2O)_{n-1} + H_2O \]

\[ ML_{n-1}(H_2O) + L \rightleftharpoons ML_n + H_2O \]

\[ M(H_2O)_n + nL \rightleftharpoons ML_n + nH_2O \]

\[ \beta_n = K_1 \cdot K_2 \cdot \ldots \cdot K_n \]

\[ K_1 = \frac{[ML(H_2O)_{n-1}]}{[M(H_2O)_n][L]} \]

\[ K_n = \frac{[ML_n]}{[ML_{n-1}(H_2O)][L]} \]

\[ \beta_n = \frac{[ML_n]}{[M(H_2O)_n][L]^n} \]
Complex formation processes

General equilibrium

\[ pM + qA + rB + sH \rightleftharpoons M_pA_qB_rH_s \]

\[ \beta_{pqrs} = \frac{[M_pA_qB_rH_s]}{[M]^p[A]^q[B]^r[H]^s} \]

M: metal ion (oxidation number: 1-3 (4)) or oxoanion
A, B: ligands
Coordination chemistry of metal ions

Types of coordination compounds

a/ parent complexes: complex formed with one ligand:
   MA, MA₂, MA₃ .... MAₙ (N: coordination number)

b/ mixed ligand complexes: complex formed with two or more ligands:
   \[ M + A + B \rightleftharpoons MAB \] or
   \[ MA₂ + MB₂ \rightleftharpoons 2MAB \]

c/ protonated complexes: the non-coordinated donor groups of ligands are protonated
   \[ M + H_nA \rightleftharpoons M(AH) + n–1 H^+ \]
Coordination chemistry of metal ions

**Types of coordination compounds**

d/ deprotonated complexes:

\[ M + A \rightleftharpoons M(AH_{-1}) + H^+ \]

– deprotonation and coordination of ligands (e.g.: alcoholic group, amide group

– deprotonation of coordinated water molecule

\[ MA(H_2O)_n \rightleftharpoons MA(H_2O)_{n-1}(OH) + H^+ \]

c/ polynuclear complexes: \( nM + mA \rightleftharpoons M_nA_m \)

(A: bridge ligand or ligand containing more donor atoms)
Coordination chemistry of metal ions

Reactions of metal complexes
1. Substitution of ligands

\[ MA + B \rightleftharpoons MB + A \]

in solution:

\[ M(H_2O)_n + nA \rightleftharpoons MA_n + nH_2O \]

thermodinamic aspect: stable, instable complexes (\( \lg \beta \))

kinetic aspect: labile (fast exchange), inert (slow exchange)

Biological importance:

\[ MXY + L \rightleftharpoons MXL + Y \]

(X - polifunktional macromolecule, Y – small molecule)

e.g.: Zn-carboxypeptidase, Fe-mioglobin
## Coordination chemistry of metal ions

### Reactions of metal complexes

2. Redox reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Oxidation Potential (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe(III)/Fe(II)</td>
<td>( \varepsilon (\text{oxidated form}) )</td>
</tr>
<tr>
<td></td>
<td>( \varepsilon_0 )</td>
</tr>
<tr>
<td></td>
<td>( \varepsilon (\text{reduced form}) )</td>
</tr>
<tr>
<td>H₂O</td>
<td>+0.77</td>
</tr>
<tr>
<td>OH⁻</td>
<td>-0.56</td>
</tr>
<tr>
<td>Oxalate</td>
<td>+0.02</td>
</tr>
<tr>
<td>CN⁻</td>
<td>+0.22</td>
</tr>
<tr>
<td>Bipiridine</td>
<td>+0.96</td>
</tr>
<tr>
<td>Fenantroline</td>
<td>+1.10</td>
</tr>
<tr>
<td>Cu(II)/Cu(I)</td>
<td>( \varepsilon (\text{V}) )</td>
</tr>
<tr>
<td>H₂O</td>
<td>+0.17</td>
</tr>
<tr>
<td>Glycine</td>
<td>-0.16</td>
</tr>
<tr>
<td>Oxalate</td>
<td>+0.02</td>
</tr>
<tr>
<td>CN⁻</td>
<td>+0.22</td>
</tr>
<tr>
<td>Bipiridine</td>
<td>+0.96</td>
</tr>
<tr>
<td>Fenantroline</td>
<td>+1.10</td>
</tr>
<tr>
<td>Imidazole</td>
<td>+0.35</td>
</tr>
<tr>
<td>CN⁻</td>
<td>+1.10</td>
</tr>
</tbody>
</table>

For example, Fe(III)/Fe(II) undergoes a redox reaction with a change in oxidation potential from +0.77 V to -0.56 V when water is involved, and from +0.02 V to +0.96 V when bipiridine is involved.
Factors influenced stability of complexes:

- **Type and charge of metal ion**
  - the complex of metal ion with +3 oxidation state is more stable
  - the stability of complexes of 3d elements with +2 oxidation state follow the Irving-Williams series
    
    \[
    \text{Mn(II)} < \text{Fe(II)} < \text{Co(II)} < \text{Ni(II)} < \text{Cu(II)} > \text{Zn(II)}
    \]

    (related to the decrease in ionic radii)
Coordination chemistry of metal ions

Factors influenced stability of complexes:
• Type of metal ions and ligands
  - hard metal ions (Lewis-acids) form stable complexes with ligands containing hard donor atoms (F, O)
  - soft metal ions (Lewis-acids) form stable complexes with ligands containing soft donor atoms (I, S)

• Type of ligands
  - formation of chelate rings (five- or six-membered ring) → enhance the stability of complexes: chelate effect
Potential donor atoms in biological systems

- Hard-soft acid-base groups of metal ions and ligands

<table>
<thead>
<tr>
<th>hard acids (metal ions)</th>
<th>hard bases (ligands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(^+), Na(^+), K(^+)</td>
<td>Oxigen containing ligands:</td>
</tr>
<tr>
<td>Mg(^{2+}), Ca(^{2+}), Mn(^{2+}), VO(^{2+})</td>
<td>H(_2)O, CO(_3)^{2-}, NO(_3)^{-}, PO(_4)^{3-},</td>
</tr>
<tr>
<td>Al(^{3+}), Co(^{3+}), Cr(^{3+}), Ga(^{3+}), Fe(^{3+}), Tl(^{3+}), Ln(^{3+}), MoO(^{3+})</td>
<td>ROPO(_3)^{2-}, (RO)(_2)PO(_3)^{-}, CH(_3)COO(^{-}), OH(^{-}), RO(^{-}), R(_2)O, crownethers</td>
</tr>
<tr>
<td></td>
<td>Nitrogen containing ligands:</td>
</tr>
<tr>
<td></td>
<td>NH(_3), N(_2)H(_4), RNH(_2), Cl(^{-})</td>
</tr>
</tbody>
</table>
### Potential donor atoms in biological systems

<table>
<thead>
<tr>
<th>intermediate acids (metal ions)</th>
<th>intermediate bases (ligands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe$^{2+}$, Ni$^{2+}$, Zn$^{2+}$, Co$^{2+}$, Cu$^{2+}$, Pb$^{2+}$, Sn$^{2+}$, Ru$^{2+}$, Au$^{3+}$</td>
<td>Br$^-$, SO$_3^{2-}$, <em>Nitrogen containing ligands</em>: NO$_2^-$, N$_3^-$, N$_2$,</td>
</tr>
<tr>
<td></td>
<td><img src="" alt="NH$_2$" /> <img src="" alt="N" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>soft acids (metal ions)</th>
<th>soft bases (ligands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu$^+$, Au$^+$, Ti$^+$, Ag$^+$, Hg$^{2+}$, Pt$^{2+}$, Pb$^{2+}$, Hg$^{2+}$, Cd$^{2+}$, Pd$^{2+}$, Pt$^{4+}$</td>
<td><em>Sulphur containing ligands</em>: RSH, RS$^-$, R$_2$S, S$_2$O$_3^{2-}$, R$_3$P, (RS)$_2$PO$_2^-$, (RO)$_2$P(O)S$^-$, RNC, CN$^-$, CO, R$^-$, H$^-$, I$^-$</td>
</tr>
</tbody>
</table>
The most important ligands in biological systems

- amino acid, peptide, protein
- nucleic acid base, nucleoside, nucleotide
- porfirins
- polyphenols, carbohydrates, glycerides

**Metal complexes of amino acids and peptides**

- $\text{-COO}^-$-coordination: $\text{Na}^+$, $\text{Ca}^{2+}$, $\text{Al}^{3+}$
- $\text{-NH}_2$-coordination: $\text{Ag}^+$, $\text{Hg}^{2+}$
- ($\text{NH}_2$,COO$^-$) coordination: $\text{M}^{2+}$ ($\text{M}^+$, $\text{M}^{3+}$) transition metal ions
coordination is influenced:
• by $R_1$-$R_n$ sidechain
• pl: Asp, Glu – carboxylate group,
• His – imidazole ring,
• Cys – SH-group
Nucleic acids and their components

nucleic base: N-donors
phosphate: O-donors
soft metal ions
hard metal ions
Metalloporphyrines

Order of stabilities
Mg(II) < Zn(II) < Cu(II) < Fe(II) < Ni(II) < Pd(II) < Pt(II)

N = 4 (Ni(II), Pt(II), Pd(II)) – all coordination sites are occupied
N = 6 (Fe(II), Co(II), Mg(II), Zn(II)) – axial coordination site

\[ M^{2+} + H_2P \rightleftharpoons MP + 2 H^+ \]
Complexes of alkali metal ions

No stable complexes with “normal” ligands

**Crown ethers**: macrocyclic polyethers

- 18-crown-6
- Dibenzo-crown-6
Complexes of alkali metal ions

cryptand e.g. 2,2,2

Li$^+$ complex of 12-crown-4
Factors influencing the stability of alkali complexes

a) the size of cavity

\[ \lg \beta_{\text{Na}(l)} = 2.2 \text{ (methanol)} \]
\[ \lg \beta_{\text{K}(l)} = 1.3 \text{ (methanol)} \]

\[ \lg \beta_{\text{Na}(l)} = 4.1 \text{ (methanol)} \]
\[ \lg \beta_{\text{K}(l)} = 5.9 \text{ (methanol)} \]

\[ \text{K}^+ \succ \text{Rb}^+ \succ \text{Cs}^+ \succ \text{Na}^+ \succ \text{Li}^+ \]
Factors influenced the stability of alkali complexes

a) the size of cavity

<table>
<thead>
<tr>
<th>(vizben)</th>
<th>$\text{lg} \beta_{\text{Li(I)}}$</th>
<th>$\text{lg} \beta_{\text{Na(I)}}$</th>
<th>$\text{lg} \beta_{\text{K(I)}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m=0$, $n=1$</td>
<td>5.3</td>
<td>2.8</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>$m=1$, $n=0$</td>
<td>2.5</td>
<td>5.4</td>
<td>3.9</td>
</tr>
<tr>
<td>$m=n=1$</td>
<td>&lt;2.0</td>
<td>3.9</td>
<td>5.4</td>
</tr>
<tr>
<td>$m=1$, $n=2$</td>
<td>&lt;2.0</td>
<td>1.65</td>
<td>2.2</td>
</tr>
<tr>
<td>$m=2$, $n=1$</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>$m=n=2$</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
</tr>
</tbody>
</table>
Factors influenced the stability of alkali complexes

c) number of binding side

\[
\begin{align*}
\lg \beta_{Na(I)} &= 6.95 \\
\lg \beta_{K(I)} &= 9.45
\end{align*}
\]

methanol/water = 95/5
Factors influenced the stability of alkali complexes

d) type of binding side

\[ \lg \beta_{Na(I)} = 4.3 \ (\text{methanol}) \]
\[ \lg \beta_{K(I)} = 6.1 \ (\text{methanol}) \]

\[ \lg \beta_{Na(I)} = 3.7 \ (\text{methanol}) \]
\[ \lg \beta_{K(I)} = 5.3 \ (\text{methanol}) \]
Factors influenced the stability of alkali complexes

d) type of binding side

\[
\begin{align*}
\log \beta_{Na(I)} &= 3.9 \text{ (water)} \\
\log \beta_{K(I)} &= 5.4 \text{ (water)}
\end{align*}
\]

\[
\begin{align*}
\log \beta_{Na(I)} &= 2.5 \text{ (water)} \\
\log \beta_{K(I)} &= 2.6 \text{ (water)}
\end{align*}
\]
Selectivity of ligands

Importance

• specific chelators (diagnostic, therapy)
• phasetransfer: transport of KMnO₄ in organic phase
Complexes of alkali earth metals

O-donor ligands are preferred
- crown ethers, macrocyclic
- edta

\[
\text{HOOC-}\hspace{1cm}N-\text{CH}_2-\text{CH}_2-N\hspace{1cm}\text{COOH}
\]

\[
\text{HOOC-}\hspace{1cm}N-\text{CH}_2-\text{CH}_2-N\hspace{1cm}\text{COOH}
\]

\[
\text{HOOC-}\hspace{1cm}N-\text{CH}_2-\text{CH}_2-N\hspace{1cm}\text{COOH}
\]
Alkali and alkali earth metal ions: 
biological roles

Abundance in human body
• cca 1 % of body (trace elements < 0,01 %)
• e.g. 170 g potassium/ 70 kg, 1000-1250 g Ca, 26 g Mg

• bulk elements: C, H, O, N, S, P
  Na, K, Ca, Mg, Cl
Alkali and alkali earth metal ions: biological roles

**Distribution** (mmol/1000 g)

<table>
<thead>
<tr>
<th></th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Mg²⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood cell</td>
<td>11.0</td>
<td>92.0</td>
<td>2.5</td>
<td>0.1</td>
</tr>
<tr>
<td>blood plasma</td>
<td>152.0</td>
<td>5.0</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Calamary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracellular fluid of neuron</td>
<td>49.0</td>
<td>410.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracellular fluid of neuron</td>
<td>440.0</td>
<td>22.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Alkali and alkali earth metal ions: biological roles

Membrantransport processes
Alkali and alkali earth metal ions: biological roles

Membranterransport processes

*Transport across the membrane*

**Diffusion:** non-selective, in direction of concentration gradient

**Facilitated passive transport:** by means of carriers (ionophors) energy is not required

**Active transport:** in opposite direction of concentration gradient, energy is required energy source: hydrolysis of ATP
Alkali and alkali earth metal ions: biological roles

Membrantransport processes

*Transport across the membrane*
Membrane transport processes

*Transport across the membrane*

**Diffusion:** non-selective, in direction of concentration gradient

**Facilitated passive transport:** by means of carriers (ionophors) energy is not required

**Active transport:** in opposite direction of concentration gradient, energy is required energy source: hydrolysis of ATP

Alkali and alkali earth metal ions: biological roles
Alkali and alkali earth metal ions: biological roles

Transport across the membrane

Membrantransport processes

PASSIVE TRANSPORT

ACTIVE TRANSPORT

transported molecule
channel protein
carrier protein

lipid bilayer
simple diffusion
channel-mediated
carrier-mediated

concentration gradient

ENERGY
Alkali and alkali earth metal ions: biological roles

Membrantransport processes

*Passiv transport*

Ligands: carrier ionophors: e.g. Valinomicin
Chanel ionophors
e.g. *Gramicidin A*
Alkali and alkali earth metal ions: biological roles

Membrantransport processes

Transport across the membrane

Diffusion: non-selective, in direction of concentration gradient

Facilitated passive transport: by means of carriers (ionophors) energy is not required

Active transport: in opposite direction of concentration gradient, energy is required

energy source: hydrolysis of ATP
Alkali and alkali earth metal ions: biological roles

Membrantransport processes

*Transport across the membrane*

![Diagram showing transport processes across a membrane](image)
Alkali and alkali earth metal ions: biological roles

Biological roles
Na\(^{+}\), K\(^{+}\):
- maintaining of osmotic pressure of cells
- take part in acid-base processes
- regulation of membrane potentials
- K\(^{+}\): take part in determination of conformation of biomolecules, in activation of enzymes, in synthesis of acetilcoline
- Na\(^{+}\): take part in activation of enzymes, in secondary active transport
Biological roles of alkali metals

$\text{Na}^+, \text{K}^+: \text{regulation of membrane potentials}$
Biological roles of alkali metals

$\text{Na}^+\text{, }\text{K}^+$: regulation of membrane potentials
Basic Neural Processes
Biological roles of alkali earth metals

$\text{Ca}^{2+}$:

- regulation the processes of nerve transmission
- regulation the muscle contraction
- regulation electrolyte balance
- blood coagulation
- building up bones and theeths
Biological roles of alkali earth metals

$\text{Ca}^{2+}$: regulation the processes of nerve transmission
Ca$^{2+}$: muscle contraction

- **ATTACHED**
  - Myosin head attached to actin filament.
  - ATP binding.

- **RELEASED**
  - Myosin head detached from actin filament.
  - ATP hydrolysis.

- **COCKED**
  - Myosin head in position for attachment.
  - ADP and Pi released.

- **FORCE-GENERATING**
  - ADP and Pi regeneration.

- **ADP**
  - ADP regeneration for next cycle.

- **P$_1$**
  - Phosphate released.
Ca$^{2+}$-binding proteins
• trigger proteins: e.g.: calmodulin

Buffer proteins: pl. calbindin
• Ca-storage proteins: calreticulin, calsequestrin
• blood coagulation: prothrombin
• building up bones: osteocalcin: Ca$_5$(PO$_4$)$_3$OH
Biological roles of alkali earth metals

Ca$^{2+}$-binding proteins: blood coagulation - protrombin

10.29 ábra. a) Gla oldaláncok az alvadási faktorok N-terminális szakaszán tömörülnek, néha egymás mellett, párosával; b) A K-vitamin-függő alvadási faktort Ca-hid kapcsolja a trombocita membrán foszfolipidiejéhez.
Biological roles of alkali earth metals

Mg$^{2+}$:
• activation of enzymes, determination of conformation of proteins
• take part in hydrolysis of ATP, universal source of energy → metabolism of energy
• building up of bones
• part of chlorophyll (photosynthesis)
Biological roles of alkali earth metals

Mg\(^{2+}\) - photosynthesis

\[ 6 \text{CO}_2 + 6 \text{H}_2\text{O} = \text{C}_6\text{H}_{12}\text{O}_6 + 6 \text{O}_2 \]

Two photosystem

I. reduction of CO\(_2\) (dark reaction)

\[
\text{CO}_2 + \text{NADPH} + \text{H}^+ + \text{ATP} \rightarrow \text{C}_6\text{H}_{12}\text{O}_6 \\
+ \text{ADP} + \text{P}_i + \text{NADP}^+ 
\]

II. photolysis of water (light reaction)

\[
\text{H}_2\text{O} + \text{NADP}^+ + \text{P}_i + \text{ADP} \xrightarrow{\text{light}} \text{O}_2 + \text{NADPH} + \text{H}^+ + \text{ATP} 
\]
Biological roles of alkali earth metals

$\text{Mg}^{2+}$ - photosynthesis

Chlorophyll $a$: $R = \text{--CH}_3$

Chlorophyll $b$: $R = \text{--C} = \text{O}$
Biological roles of alkali earth metals

Mg$^{2+}$ - photosynthesis

$^{90}$Sr – radioactive, $t_{1/2} = 28$ year, can be built up in bones

BaSO$_4$ – contrast compound (X-ray)
Complexes of iron(II)

Complexes:
• in solution: \( [\text{Fe(H}_2\text{O})_6]^{2+} \) (octahedral, pale green)
• easy oxidation to iron(III) (in basic solution)
• redoxpotential of Fe(III)/Fe(II) is changed by formation of complexes

\[
\begin{align*}
\text{Fe}^{3+}/\text{Fe}^{2+} & : \\
\text{CN}^- & +0,36 \text{ V} \\
\text{H}_2\text{O} & +0,77 \text{ V} \\
\text{Phen} & +1,12 \text{ V}
\end{align*}
\]
Complexes of iron(II)

Complexes:
• intermediate (hard/soft) acid: binding to O-, N- and S-donor-atoms
  • most important ligands: aromatic nitrogen donors in chelatable position
    • bipiridine, fenantroline, porphyrins
  • usually octahedral complexes (some tetrahedral complexes)
Complexes of iron(III)

Complexes:
• in solution: \([\text{Fe(H}_2\text{O)}_6]^3+\) (pale violet)
• stable complexes in acid and basic pH range
• characteristic reaction: hydrolysis
  \[
  \text{pH} > 1: \quad [\text{Fe(H}_2\text{O)}_6]^3+ + \text{H}_2\text{O} \leftrightarrow [\text{Fe(H}_2\text{O)}_5(\text{OH})]^2+ + \text{H}_3\text{O}^+ \\
  K_s = 1,8 \cdot 10^{-3}
  \]
• Dimerization → structure with oxo bridges (yellow)
  \((\text{H}_2\text{O})_5\text{Fe–O–Fe(H}_2\text{O)}_5)^{4+}\)
Complexes of iron(III)

Complexes:
pH > 2: polynuclear structures, mixed hydroxo complexes $\rightarrow$ Fe(OH)$_3$ precipitation

• usually octahedral complexes
• hard acid:
• binding to $F^-$ and O-donors containing ligands
• $[\text{Fe(SCN)}_4]^- + 6 F^- \rightleftharpoons [\text{FeF}_6]^{3-} + 4 \text{SCN}^-$

intensive red colorless
Biological role of iron

- Human body: cca. 4 g iron (~3 g in hemoglobin)
- Uptaking of iron: 1 mg/day
Biological role of iron

Iron proteins

Hem proteins
- oxygen transport, storage
  - hemoglobin
  - myoglobin
- electron transfer
  - cytochromes
- oxidases, oxygenases
  - cytochrome c oxidase

Non-hem proteins
- iron transport
- iron storage
  - transferrin
  - ferritin
Myoglobin (oxygen storage)

Globin: contains 153 amino acids
Hem: Fe-porphyrin

Hem is bound to globin protein via iron ion (without covalent bound)

5. coordination side:
imidazole N
Hemoglobin (oxygen transport)

It contains 4 globin units.

Fe(II) + O$_2$: iron ion passes to porphyrin ring.
Hemoglobin (oxygen transport)

uptaking of oxygen: high partial pressure of oxygen
giving down of oxygen: low partial pressure of oxygen

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}^+
\]
Hemerythrin

– oxygen transporter in molluscs
– 4 part, one part contain two iron, it binds one $O_2$
Cytochromes

• transfer electrons (redox proteins and enzymes)
• insert oxygen atoms or dioxygen into organic substrates or catalyse other important organic reaction
• coordination number: 5 or 6
• interaction between protein and hem moiety: covalent or van der Waals bound
Cytochrome C

provide electrons via following reaction:

\[ \text{Fe}^{2+} \rightleftharpoons \text{Fe}^{3+} + e^- \]
Cytochromes

Cytochrome P450

- part of monooxygenase enzymes
- activation of dioxygen molecule

\[
RH + O_2 + 2 \, e^- + 2 \, H^+ \rightarrow ROH + H_2O
\]

- 5. coordination side: cysteine S
- 6. coordination side: H_2O
Cytochrome P450
Catalase

– catalysing the disproportion of $\text{H}_2\text{O}_2$

\[ 2 \text{H}_2\text{O}_2 \rightarrow 2 \text{H}_2\text{O} + \text{O}_2 \]

– it contains four same units

– 5. coordination side: tyrosine $\text{O}^-$

– mechanism:
Catalase
Iron-sulphur proteins

- Tetrahedral geometry of iron
- Iron binding to inorganic and organic sulphur donors (Cys) $\text{S}$
- one $e^-$-pass

- reduced ferredoxin $\overset{-e^-}{\leftrightarrow}$ oxidized ferredoxin
- unusually low redox potential: $-0.05 - -0.49 \text{ V} \rightarrow$ they behave as a reduction agents

- rubredoxin: $[\text{1Fe}]^{3+}(\text{RS}^-)_4 (-0.06 \text{ V})$
- ferredoxins: $[\text{2Fe-2S}]^{2+}(\text{RS}^-)_4 (-0.3 - -0.4 \text{ V})$
  $[\text{4Fe-4S}]^{2+}(\text{RS}^-)_4 (-0.4 \text{ V})$
- HIPIP: $[\text{4Fe-4S}]^{2+}(\text{RS}^-)_4 (0.35 \text{ V})$
Iron-sulphur protein (HIPIP)
Iron-sulphur proteins
Transport of iron

Transferrin:
Transport: iron(III) form, at neutral pH
Structure: $M \sim 80,000$, 0.15% iron

two structural units:
  one unit: 2 iron(III) + protein


**Transport of iron**

Siderophores:
iron transporter in microorganisms

---

hydroxamate-type
- e.g. ferrichrom

 catecholate-type
- e.g. enterobactin
Storage of iron

Ferritin
It contains 24 protein units (~175 amino acids/unit)
4500 iron atoms/ferritin (25 %)
iron micelle (7 nm diameter): \((\text{FeOOH})_8\cdot\text{FeO}\cdot\text{H}_2\text{PO}_4\)
uptaking: iron(II) form, it is followed by oxidation to iron(III)

Hemosiderin
storage of excess of iron
cca. 45 % iron
Biological role of copper

- Essential for every living organisms
- 80-120 mg / 70 kg body
- uptaking: 1,5-3,0 mg/day, < 10 mg
- toxicity: > 15 mg
- diseases caused by copper:
  - excess of copper: Wilson disease
  - missing of copper: Menke’s disease
Biological role of copper

Functions of copper proteins

• Oxygen transport, storage: hemocyanin (mollusc)

• Catalysing of redox processes
  oxidases (blue-copper oxydase), oxygenases, superoxide dismutase

• Copper transport, storage: ceruloplasmin, metallothionein
Biological role of copper

Superoxide dismutase (SOD)

$$2 \text{O}_2^- + 2 \text{H}^+ \xrightarrow{\text{SOD}} \text{H}_2\text{O}_2 + \text{O}_2$$
Biological role of copper

Superoxide dismutase (SOD)

**Zn:** regulation of structure

**Cu:** takes part in redox processes

Reactions:

\[ \text{Cu}^{2+}(\text{His}^-)\text{Zn}^{2+} + \text{O}_2^- + \text{H}^+ \rightarrow \text{Cu}^+ + (\text{HisH})\text{Zn}^{2+} + \text{O}_2 \]

\[ \text{Cu}^+ + \text{O}_2^- + \text{H}^+ + (\text{HisH})\text{Zn}^{2+} \rightarrow \text{Cu}^{2+}(\text{His}^-)\text{Zn}^{2+} + \text{H}_2\text{O}_2 \]
Biological role of copper

Ceruplasmine:
1005 amino acid (single protein chain), 6 copper

Function:
• oxidase
• ferrioxidase: \( \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} \)
• transport of copper
• metabolism of copper → missing of ceruloplasmine → Wilson disease, Menke’s disease
Biological role of zinc

The second most abundant trace element
The least toxic element
Essential for every living organism
2-4 g zinc / 70 kg body

Zinc metalloproteins
1940 – first zinc enzyme: carbonic anhydrase
1985 – 100 zinc containing enzymes
1995 – 300 enzymes + > 100 zinc containing proteins

Role of zinc:
• active centrum (catalysing of acid-base processes)
• regulating of structure
Carboanhydrase

• Process:
  \[ \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}^+ \]
  \( k = 3 \cdot 10^{-2} \text{ s}^{-1} \), with enzyme: \( k = 6 \cdot 10^5 \text{ s}^{-1} \)

• Zn: tetrahedral geometry,

• coordination: 3 histidine + 1 H$_2$O

• Zn – H$_2$O → Zn-OH$^-$ → interact with CO$_2$

Carboxypeptidase A

• Process: hydrolysis of peptide bound at C-termini

• 1 Zn + 307 amino acids (M ~ 34.000)

• coordination: 2 histidine + 1 glutamate COO$^-$ + 1 H$_2$O
Carboanhydrase

His 64
Thr 199
Glu 106
Glu 117
His 96
H_2O
His 94
His 119
Gln 92
Zn^{2+}
Carboxypeptidase A
Zinc fingers

• Metalloproteins, which take part in the DNA transcription
• Zn: regulation of structure
• 9-10 zinc ions,
• $\text{Zn}^{2+}$: tetrahedral geometry (His N, Cys S) \rightarrow
the conformation is similar to a finger
Zinc fingers
Pharmaceutical application of metals

Administration of trace elements
• treatment of deficiency diseases

Remove of toxic elements
• treatment of toxicity of heavy metals

Important aspects:
• metal complexes of chelatable or macrocyclic ligands have high stability
• neither ligands nor complex are not toxic
• ligand is selective
Pharmaceutical application of metals

Metal complexes in therapy

Anticancer pharmaceuticals, medicines: cisplatin complexes

\[
\begin{align*}
\text{cisplatin} & : & H_3N & \text{Pt} & H_3N \\
\text{carboplatin} & : & H_3N & \text{Pt} & O & C & O & C
\end{align*}
\]
Pharmaceutical application of metals

Mechanism of cisplatin

\[ \text{H}_3\text{N}(\text{II})\cdot\text{Cl} \quad \text{hydrolysis} \quad \text{H}_3\text{N}(\text{II})\cdot\text{Cl} \]

\[ \text{Pt} \quad \text{Pt} \]

\[ \text{H}_3\text{N} \quad \text{H}_3\text{N} \]

\[ \text{G} \quad \text{G} \]

\[ \text{DNA} \]

\[ \text{NH}_3 \quad \text{H}_3\text{N} \quad \text{Pt(II)} \quad \text{Guanin (DNA)} \]

\[ \text{Cl} \]
Pharmaceutical application of metals

Metal complexes in therapy

Lithium: maniac depression: \( \text{Li}_2\text{CO}_3 \)
Vanadium: insulin mimic (oral) pharmaceuticals

- bis(picolinato)oxovanadium(IV)
- bis(maltolato)oxovanadium(IV)
Pharmaceutical application of metals

Metal complexes in therapy
- Bismuth: gastric ulcer: Bi(NO$_3)_3$
- zinc: treatment of ulcers
Pharmaceutical application of metals

Metal complexes in therapy
• gold: rheumatoid arthritis

Myochrysine

Solganol

Allochrysine
Pharmaceutical application of metals

Metal complexes in therapy
silver: treatment of infection

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{S} \quad \text{N} \\
\text{O} & \quad \text{H} \quad \text{N} \quad \text{O} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

sulfadiazin
Pharmaceutical application of metals

Contrast compounds

• X-ray contrast:
  heavy metal salts: e.g.: \( \text{BaSO}_4 \)
  organic iodine compounds

• NMR tomography: Gd-polycarboxylate complexes
Pharmaceutical application of metals

Contrast compounds

- NMR tomography: Gd-polycarboxylate complexes

![Chemical structures of DTPA (Magnevist) and DOTA (Dotaterm)]

DTPA - Magnevist
DOTA - Dotaterm
Pharmaceutical application of metals

Radioactive isotopes
Diagnosis
• > 80 %, $^{99m}$Tc, γ-ray ($t_{1/2}(γ) = 6$ hours, $t_{1/2}(β) = 212000$ years)

Therapy
• outer ray source
• Injection: $^{186}$Re, $^{188}$Re