EMMI Intensive Programme "Design, Synthesis and Validation of Imaging Probes", - 2011

2011 September 26, Monday

Gd(III) complexes: the importance of kinetic and thermodynamic stability

*Imre Tóth, University of Debrecen, Hungary*
Content

Introduction

Equilibrium

- Stability constants
- Conditional stability constants
- Simultaneous/competitive equilibria
- Data bases, modelling
- Measuring of stability constants of LnMC
- Case studies

Kinetics

- Rate of chemical reactions
- Formation of metal complexes
- Formation of Ln-complexes
- Dissociation of Ln-complexes
- Case studies
## Introduction

### Intensive Programme “Design, Synthesis and Validation of Imaging Probes” schedule - 2011

<table>
<thead>
<tr>
<th>Monday</th>
<th>September 19</th>
<th>Tuesday</th>
<th>September 20</th>
<th>Wednesday</th>
<th>September 21</th>
<th>Thursday</th>
<th>September 22</th>
<th>Friday</th>
<th>September 23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AM</strong></td>
<td>9h00 - 10h00</td>
<td>9h00 - 10h00</td>
<td>9h00 - 10h00</td>
<td>9h00 - 10h00</td>
<td>9h00 - 10h00</td>
<td>9h00 - 10h00</td>
<td>9h00 - 10h00</td>
<td>9h00 - 10h00</td>
<td></td>
</tr>
<tr>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td>Welcome and IP Introduction</td>
<td></td>
</tr>
<tr>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td></td>
</tr>
<tr>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td></td>
</tr>
<tr>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td>Silvia Alme</td>
<td></td>
</tr>
<tr>
<td><strong>PM</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td></td>
</tr>
<tr>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td>Optical Imaging probes</td>
<td></td>
</tr>
<tr>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td></td>
</tr>
<tr>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td>PET and SPECT radiochemistry: Selected examples of Labelling of Macromolecules</td>
<td></td>
</tr>
<tr>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td>Francesco Colbe</td>
<td></td>
</tr>
</tbody>
</table>

### Monday, September 18

<table>
<thead>
<tr>
<th>AM</th>
<th>9h00 - 10h00</th>
<th>9h00 - 10h00</th>
<th>9h00 - 10h00</th>
<th>9h00 - 10h00</th>
<th>9h00 - 10h00</th>
<th>9h00 - 10h00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorsten Oppermann</td>
<td>Thorsten Oppermann</td>
<td>Thorsten Oppermann</td>
<td>Thorsten Oppermann</td>
<td>Thorsten Oppermann</td>
<td>Thorsten Oppermann</td>
<td>Thorsten Oppermann</td>
</tr>
<tr>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
<td><strong>1h00 - 12h00</strong></td>
</tr>
<tr>
<td>Irene Tom</td>
<td>Irene Tom</td>
<td>Irene Tom</td>
<td>Irene Tom</td>
<td>Irene Tom</td>
<td>Irene Tom</td>
<td>Irene Tom</td>
</tr>
<tr>
<td><strong>PM</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
<td><strong>14h00 - 15h30</strong></td>
</tr>
<tr>
<td>Design of Imaging Probes</td>
<td>Design of Imaging Probes</td>
<td>Design of Imaging Probes</td>
<td>Design of Imaging Probes</td>
<td>Design of Imaging Probes</td>
<td>Design of Imaging Probes</td>
<td>Design of Imaging Probes</td>
</tr>
<tr>
<td>Alessandro Barge</td>
<td>Alessandro Barge</td>
<td>Alessandro Barge</td>
<td>Alessandro Barge</td>
<td>Alessandro Barge</td>
<td>Alessandro Barge</td>
<td>Alessandro Barge</td>
</tr>
<tr>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
<td><strong>16h00 - 17h30</strong></td>
</tr>
<tr>
<td>Ligand synthesis part I</td>
<td>Ligand synthesis part I</td>
<td>Ligand synthesis part I</td>
<td>Ligand synthesis part I</td>
<td>Ligand synthesis part I</td>
<td>Ligand synthesis part I</td>
<td>Ligand synthesis part I</td>
</tr>
<tr>
<td>Giovanni del Cembra</td>
<td>Giovanni del Cembra</td>
<td>Giovanni del Cembra</td>
<td>Giovanni del Cembra</td>
<td>Giovanni del Cembra</td>
<td>Giovanni del Cembra</td>
<td>Giovanni del Cembra</td>
</tr>
</tbody>
</table>

### Theoretical session

- Practical session

**Accordo numero:** 20114-IT2-E2A-082709
Coordination chemistry: basic principles

**Step-vice formation of complexes:**

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

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

**Stepvice constants**

Overall reaction

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

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

**Overall stability constants**

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

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

\[
\beta_n = \frac{[ML_n]}{[M(H_2O)_n][L]^n}
\]
Groups of complexes

a/ parent complexes: only one ligand \( MA, MA_2, MA_3, \ldots \) \( MA_N \) (\( N \): coordination number)

b/ mixed-ligand complexes: two or several ligands

\[
M + A + B \rightleftharpoons MAB \quad \text{or} \quad MA_2 + MB_2 \rightleftharpoons 2 \ MAB
\]

c/ protonated complexes: protonation of the non-coordinated donors of the ligand

\[
M + H_nA \rightleftharpoons M(AH) + n-1 \ H^+
\]
Groups of complexes

d/ deprotonated complexes: de-protonation and coordination of the ligand

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

– for example alcoholate, amid-group)
– deprotonation of coordinated water

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

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

A is a bridging ligand with one or two donor group(s)
Coordination chemistry: basic principles

**Influence of the charge of the metal ions on stability:**

- +3 ions have higher stability compared to +2

- +2 cations in the 3d transition metal block follow the Irving-Williams series:
  
  Mn(II) < Fe(II) < Co(II) < Ni(II) < Cu(II) > Zn(II)

  (i.e. it does not follow the change in size)
# Hard – soft theory of Lewis acids and bases

## Coordination chemistry

<table>
<thead>
<tr>
<th>hard acids (metal ions)</th>
<th>hard bases (ligands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H⁺, Na⁺, K⁺</td>
<td>O-donor ligands:</td>
</tr>
<tr>
<td>Mg²⁺, Ca²⁺, Mn²⁺, VO²⁺</td>
<td>H₂O, CO₃²⁻, NO₃⁻, PO₄³⁻,</td>
</tr>
<tr>
<td>Al³⁺, Co³⁺, Cr³⁺, Ga³⁺, Fe³⁺, Ln³⁺, Th⁴⁺ etc.</td>
<td>ROPO₃²⁻, (RO)₂PO₃⁻,</td>
</tr>
<tr>
<td></td>
<td>CH₃COO⁻, OH⁻, RO⁻, R₂O,</td>
</tr>
<tr>
<td></td>
<td>crown ethers</td>
</tr>
<tr>
<td></td>
<td>N-donor ligands:</td>
</tr>
<tr>
<td></td>
<td>NH₃, N₂H₄, RNH₂,</td>
</tr>
<tr>
<td></td>
<td>F⁻, Cl⁻</td>
</tr>
</tbody>
</table>
# Coordination chemistry of transition metals

<table>
<thead>
<tr>
<th>Borderline acids (metal ions)</th>
<th>Borderline bases (ligands)</th>
</tr>
</thead>
</table>
| Fe$^{2+}$, Ni$^{2+}$, Zn$^{2+}$, Co$^{2+}$, Cu$^{2+}$, Pb$^{2+}$, Sn$^{2+}$, Ru$^{2+}$, Au$^{3+}$, Tl$^+$ | Br$^-$, SO$_3^{2-}$,  
*N*-donor ligands: NO$_2^-$, N$_3^-$, N$_2$,  
\[\text{C}_{6}\text{H}_5-\text{NH}_2\text{; }\text{C}_{5}\text{H}_4\text{N}\] |
| **soft acids (metal ions)** | **soft bases (ligands)** |
| Cu$^+$, Au$^+$, Tl$^{3+}$, Ag$^+$, Hg$_2^{2+}$, Pt$^{2+}$, (Pb$^{2+}$), Hg$^{2+}$, (Cd$^{2+}$), Pd$^{2+}$, (Pt$^{4+}$) | S-donor ligands:  
S$^{2-}$, 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$^-$ |
Coordination chemistry: basic principles

Influence of the ligand on the stability of complexes
- hard-soft character of donor atoms
- charge
- denticity
- overall basicity
- chelate effect (entropy contribution)
  - chelate ring size (5 is preferred)
- macrocycle effect/encapsulating ligands
  - cavity size
  - rigidity of the MC
Mathing the size of the metal ion and the cavity

<table>
<thead>
<tr>
<th>Property</th>
<th>Mn</th>
<th>Cu</th>
<th>Ga</th>
<th>In</th>
<th>Gd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionic radius $M^{III}$ or $M^{II}$ (CN=6) (pm)</td>
<td>58 (ls)</td>
<td>73</td>
<td>62</td>
<td>80</td>
<td>93,8</td>
</tr>
<tr>
<td>64,5 (hs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coordination Number</td>
<td>II – 6(7)</td>
<td>II – 6(4)</td>
<td>III – 6</td>
<td>III – 8(9)</td>
<td>III – 8(9)</td>
</tr>
</tbody>
</table>
Properties of some $Y^{3+}$ complexes formed with DTPA type ligands

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$\Sigma \log K_i^H$ ($\log K_1^H$)</th>
<th>$\log K_{YL}$</th>
<th>$k_D^*$ ($s^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHX-A</td>
<td>32.92 (12.3)</td>
<td>24.7</td>
<td>0.462</td>
</tr>
<tr>
<td>CHX-B</td>
<td>31.47 (12.3)</td>
<td>24.4</td>
<td>0.047</td>
</tr>
<tr>
<td>1B4M</td>
<td>30.39 (11.31)</td>
<td>22.5</td>
<td>6.62</td>
</tr>
<tr>
<td>1B3M</td>
<td>30.60 (11.46)</td>
<td>22.5</td>
<td>13.5</td>
</tr>
<tr>
<td>2B</td>
<td>29.24 (10.75)</td>
<td>21.7</td>
<td>41.8</td>
</tr>
<tr>
<td>1B</td>
<td>29.18 (11.16)</td>
<td>21.5</td>
<td>37.4</td>
</tr>
<tr>
<td>CHX-DTPA</td>
<td>32.27 (12.3)</td>
<td>24.2</td>
<td>0.75</td>
</tr>
<tr>
<td>DTPA</td>
<td>28.00 (10.48)</td>
<td>22.4</td>
<td>144</td>
</tr>
</tbody>
</table>

* The rates of acid catalyzed dissociation were measured with the use of ArIII ([YL]=10^{-5} mol/dm$^3$ and [AAIII]=10^{-5} mol/dm$^3$).

Some general requirements to the complexes to be used in medicine

- Good water solubility (easy to administer)
- Low osmolality and preferably no (or negative) charge
- Non-toxicity
- High thermodynamic stability and kinetic inertness
- Possible quick complex formation
- Organ specificity (when injected the media concentrates in area(s) required or bifunctional ligands)
- The production of the ligand and the complex should be cost effective.
Clinically approved, commercially available Gd-based contrast agents (q=1)

GdDTPA$^{2-}$ Magnavist
GdDTPA-BMA Omniscan
GdDOTA$^-$ Dotarem
GdHP-DO3A ProHance
GdDO3A-Butrol Gadovist

GdDTPA-EOB$^{2-}$ Eovist
GdBOPTA$^{2-}$ Multihance
GdDTPA-BMEA Optimark
MS-325 Vasovist
<table>
<thead>
<tr>
<th>Name</th>
<th>Acronym</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Gadopentetate dimeglumine Megavist®</th>
<th>Gadobenate dimeglumine OptiMARK®</th>
<th>Gadobenate dimeglumine MultiHance®</th>
<th>Gadodextran acid disodium salt Primovist®</th>
<th>MS325 Gadofosveset trisodium salt Vasovist®</th>
<th>Gadodiamide Dotarem®</th>
<th>Gadocacetic acid ProHance®</th>
<th>Gadodiamide Gadomeridol</th>
<th>Gadobutrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company</td>
<td>Bayer-Schering</td>
<td>GE-Healthcare</td>
<td>Covidien</td>
<td>Bracco</td>
<td>Bayer-Schering</td>
<td>Bayer-Schering</td>
<td>Bayer-Schering</td>
<td>Bayer-Schering</td>
<td>Guerbet</td>
<td>Bracco</td>
<td>Bayer-Schering</td>
<td>Guerbet</td>
</tr>
<tr>
<td>Chemical structure</td>
<td>Open-chain</td>
<td>Open-chain</td>
<td>Open-chain</td>
<td>Open-chain</td>
<td>Open-chain</td>
<td>Open-chain</td>
<td>Open-chain</td>
<td>Open-chain</td>
<td>Macrocyclic</td>
<td>Iotic</td>
<td>Macrocyclic</td>
<td>Macrocyclic</td>
</tr>
<tr>
<td>Charge</td>
<td>Di-ionic</td>
<td>Nonoic</td>
<td>Nonoic</td>
<td>Di-ionic</td>
<td>Nonoic</td>
<td>Tri-ionic</td>
<td>Nonoic</td>
<td>Nonoic</td>
<td>Nononic</td>
<td>Nononic</td>
<td>Nononic</td>
<td>Nononic</td>
</tr>
<tr>
<td>Dissociated particles per molecule</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Log P in BuOH/H2O</td>
<td>−3.16</td>
<td>−2.13</td>
<td>ND</td>
<td>−2.33</td>
<td>−2.11</td>
<td>−2.11</td>
<td>−2.87</td>
<td>−1.98</td>
<td>−2</td>
<td>−2</td>
<td>−2</td>
<td>−2</td>
</tr>
<tr>
<td>Concentration (M)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.25</td>
<td>0.25</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Standard dose (nmol/kg)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.025</td>
<td>0.03</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Osmolarity at 37°C (mOsm/kg H2O)</td>
<td>1969</td>
<td>789</td>
<td>11.10</td>
<td>1970</td>
<td>688</td>
<td>825</td>
<td>1330</td>
<td>630</td>
<td>1603</td>
<td>1603</td>
<td>1603</td>
<td>1603</td>
</tr>
<tr>
<td>Osmotic load&lt;sup&gt;b&lt;/sup&gt; (mOsm/l)</td>
<td>2</td>
<td>0.67</td>
<td>0.67</td>
<td>2</td>
<td>0.5</td>
<td>0.8</td>
<td>1.33</td>
<td>0.67</td>
<td>0.67</td>
<td>0.67</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>Relaxivity (r1/r2) mM&lt;sup&gt;−1&lt;/sup&gt;s&lt;sup&gt;−1&lt;/sup&gt; at 37°C, 1.5 T in water&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.3/3.9</td>
<td>3.3/3.9</td>
<td>3.64/4.1</td>
<td>3.84/4.4</td>
<td>4.6/5.3</td>
<td>5.0/5.9</td>
<td>3.0/3.5</td>
<td>2.9/3.4</td>
<td>3.3/3.9</td>
<td>3.3/3.9</td>
<td>3.3/3.9</td>
<td>3.3/3.9</td>
</tr>
<tr>
<td>Viscosity (mPas) at 37°C</td>
<td>2.9</td>
<td>1.4</td>
<td>2.0</td>
<td>5.3</td>
<td>1.19</td>
<td>2.1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.0</td>
<td>1.3</td>
<td>4.96</td>
<td>4.96</td>
<td>4.96</td>
<td>4.96</td>
</tr>
<tr>
<td>Formulation</td>
<td>Free DTPA 0.2% (1 mmol/l)</td>
<td>Ca-DTPA-BMA (Na&lt;sup&gt;+&lt;/sup&gt; salt 5%) (25 mmol/l)</td>
<td>Ca-DTPA-BMEA (Na&lt;sup&gt;+&lt;/sup&gt; salt 5%) (50 mmol/l)</td>
<td>No formulation</td>
<td>Ca-EOB-DTPA (trisodium salt)</td>
<td>Fosvista ligand (0.225 mmol/l)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>No formulation</td>
<td>[Ca-HP-DOTA]&lt;sub&gt;2&lt;/sub&gt; (Ca&lt;sup&gt;2+&lt;/sup&gt; salt 0.1% (0.5 mmol/l)</td>
<td>Ca BT-DOTA (Na&lt;sup&gt;+&lt;/sup&gt; salt 1 mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log K&lt;sub&gt;part&lt;/sub&gt;</td>
<td>22.1</td>
<td>16.9</td>
<td>16.6</td>
<td>22.6</td>
<td>22.46</td>
<td>22.1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>25.6&lt;sup&gt;f&lt;/sup&gt;</td>
<td>23.8</td>
<td>21.8</td>
<td>21.8</td>
<td>21.8</td>
<td>21.8</td>
</tr>
<tr>
<td>Log K&lt;sub&gt;cond&lt;/sub&gt;</td>
<td>17.7</td>
<td>14.9</td>
<td>15.0</td>
<td>18.4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>18.7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>18.9&lt;sup&gt;f&lt;/sup&gt;</td>
<td>19.3&lt;sup&gt;f&lt;/sup&gt;</td>
<td>17.1</td>
<td>14.7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>14.7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>14.7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>14.7&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Dose for liver imaging: 0.05 mmol/kg

<sup>b</sup>Osmotic load = d(mOsm/l) / d(mOsm/kg H<sub>2</sub>O)<sup>c</sup> number dissociated ions values are calculated on the assumption that the agents distribute homogeneously in the interstitial space (10.5 l for a patient weighing 70 kg)

<sup>c</sup>Guerbet measurement on commercial solution; Inaccuracy on relaxometric measurement: ±0.3 mM<sup>−1</sup>s<sup>−1</sup> (for relaxivity measurements)

<sup>d</sup>(concentration not disclosed)

<sup>e</sup>Steiger-Hartmann et al. (2006)

<sup>f</sup>Carovan et al. (2001)

<sup>g</sup>Moreau et al. (2004) and Guerbet calculations

<sup>h</sup>Uggeri et al. (1995)

<sup>i</sup>Schmitz-Willich et al. (1999)

<sup>j</sup>Bellia et al. (2003)
Coupled equilibria (simultaneous equilibria)

Redox reaction:
- oxidation: \( M^{(x+1)+} \rightarrow M^{(x-1)+} \)
- reduction: \( A^{(y-1)-} \rightarrow A^{(y+1)+} \)

Complexation: \([ML_n] \rightleftharpoons nL \leftarrow [M^*A_m] \leftarrow [M_yA_{x+1}]^{y-}\)

Precipitation: \( M^{x+} + A^{y-} \rightleftharpoons M_yA_x \)

Acid-base r.
- M(OH)\(^{(x-1)+}\) + H\(^+\)
- HA + OH\(^-\)

„cation-hydrolysis” anion protonation
Conditional stability constants

There is a definite need to consider the “side reactions” of the metal ion and the ligand

The most important parameter (in clean systems) is pH:
- $H^+$ could protonate the (weak base) ligand
- $OH^-$ could form hydroxo-complexes/hydroxide precipitate with the metal ion

Endogenous metal ions and ligands in “real systems”: almost unlimited number of competitors
- One cannot calculate conditional constants by hand
- Model calculations need suitable data ($\log\beta_{ML}$, $\log\beta_{HL}$, $pL$ (solubility product), $pH$, $pE$, temperature
- (Could be good for planning experiments also!)
Modelling

(Stability Constants Databases - NIST and IUPAC)
Modelling
Modelling

You can click on one of the metal groups in the side panel or, for individual metal ions, type the name/s of metal ions in the edit box below the panel (e.g. Cu, Ni, Ag). Click on Search to see all matching metals in the list below.

List contains 2 metals for name: Cu++

Click below to record the list as your 'Own Metal Group' which can then be recalled by clicking in the panel above.

Groups of Metals:
- Hydrogen / Deuterium
- Any Metal Ion
- Alkaline Metals
- Lanthanides
- Own Metal Group
- Alkaline Earths
Modelling

Current specifications are:
2 ligands: Hididine, Thiolididine
2 metals: Cu++, Cu+++ 
(no references specified)
(no experimental details specified)

The list for these specifications will contain 81 experiments.
Table of experiment data:

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Method of Medium</th>
<th>Temperature</th>
<th>Ionic Strength</th>
<th>Recip. Flaps</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KNO₃ Calibration</td>
<td>25°C</td>
<td>0.10 M</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NaClO₂ Calibration</td>
<td>37°C</td>
<td>0.15 M</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Modelling
Modelling
Modelling

Metal ion, Reference and Ligand (continued)

C_{6}H_{5}N_{3}O_{2} Histidine HL CAS: 71-00-1
2-Amino-3-(4-imidazolyl)propanoic acid H_{2}NCH(CH_{2}C_{6}H_{5}N)COOH
Ligand Classes: biological amino acids / azoles (5 mem rings)

Data

| K_{1}[ML]/[H][L] | K_{2}[ML]/[ML] | K_{3}[ML]/[ML][L] |

Method: Glass Electrode Medium: NaNO_{3}
Temperature: 25°C Ionic Strength: 0.10M Calibration: Activity

Constants (lg values):

- K_{1} = 10.66
- K_{2} = 8.30
- K_{3} = 18.96

ΔG (K_{1} = 10.66) = -8.85
ΔG (K_{2} = 8.30) = -47.38
ΔG (K_{3} = 18.96) = -109.22

β(CuAL) = 18.08
β(CuH-1AL) = 7.22
β(CuH) = 14.98

HA is glycol-DL-leucine.

Data for TERNARY Complexes
Modelling
Modelling

The matrix and the constants are defined by selected components and the equilibrium reaction being considered!
Modelling

Diagram:

Y-axis:
- Fractions for:
  - Cu $^{2+}$

Diagram type:
- Fraction

Parameters:
- Ionic strength = 0.0

Concentrations:
- Total conc. of Cu $^{2+}$ = 0.05
- Total conc. of His $^{2+}$ = 0.1
- pH varied from 2.0 to 10.0

Save as defaults
Modelling

Distribution curves for the major species (e.g. >10 %)
Modelling

Log c – pH showing „all species”. Numerical values are also calculated.
Measuring of stability constants

**Step-vice formation of complexes:**

\[ \text{M} + \text{L} \rightleftharpoons \text{ML} \]

\[ K_1 = \frac{[\text{ML}]}{[\text{M}][\text{L}]} \]

Mass balance equations + measuring at least one equilibrium concentration

\[ T_M = [\text{M}] + [\text{ML}] \]
\[ T_L = [\text{L}] + [\text{ML}] \]

Several standard methods are known in case of fast equilibration and moderate stability: \([\text{M}] / [\text{ML}] \sim 1 \ (0.1 – 10)\) adjusted by the experimental conditions (pH, concentrations of components etc)

- pH-potentiometric titration (\(2 < \text{pH} > 12\))
- UV-VIS spectrophotometry
- multinuclear NMR spectroscopy
- 1H-NMR relaxometry
- microcalorimetry

Serious limitations in case of slow equilibration and very large stability
Measuring of (moderate) stability constants by pH-potentiometry: H⁺ competition

\[ M^{n+} + H_xL \rightleftharpoons ML + xH^+ \]

Fast formation and dissociation

Slow formation and dissociation

The stability of various complex species can be obtained simultaneously.

(\( \log K_{ML}, \log K^{H}_{ML:L}, \log K^{H}_{ML(OH)} \), \( \log K_{M2L} \) and \( \log K_{ML2} \))

The protonation constant of the complexes have to be determined in a separate (direct) titration

(\( \log K_{ML}^H, \log K_{ML:L}^H, \log K_{ML(OH)}^H \) and \( \log K_{ML(OH)}^H \))

In most of the cases the stability constants of the ML complexes can be calculated.

The titration data is usually fitted with the use of the following softwares:

- PSEQUAD
- SUPERQUAD
- HYPERQUAD
- OPIUM
Determination of (high) stability constants: proton + metal ion or ligand competition

\[
M^{n+} + H_yA + H_xL \rightleftharpoons ML + MA + x+yH^+
\]

\[
M^{n+} + Y^{z+} + H_xL \rightleftharpoons ML + YL + xH^+
\]

**Direct titration** when the ligand or the metal exchange reaction is fast

**“Out-of-cell”** technique when the ligand or the metal exchange reaction is slow

**pH-potentiometric titration**

Large number of protonation and stability constants must be known ion order to be able to calculate the one that is under question.

\[
\log K^{H}_{H_jA}, \log K^{H}_{H_jL}, \log K^{H}_{MA}, \log K^{H}_{MA(OH)_j}, \log K^{H}_{H_jL}, \log K^{Y}_{YL}, \log K^{H}_{YH_jL}, \log K^{H}_{YL(OH)_j}
\]

**UV-VIS spectrophotometry**

- Fast formation and dissociation: direct titration
- Slow formation and dissociation: “out of cell” method (metal or ligand exchange) formation

\[
A = 1 \cdot \varepsilon_{ML} \cdot c_{ML} + 1 \cdot \varepsilon_{MA} \cdot c_{MA} \quad \text{ligand exchange}
\]

\[
A = 1 \cdot \varepsilon_{ML} \cdot c_{ML} + 1 \cdot \varepsilon_{YL} \cdot c_{YL} \quad \text{metal exchange}
\]

Even larger number of constants must be obtained very precisely.

\[
\log K^{H}_{H_jA}, \log K^{H}_{H_jL}, \log K^{H}_{MA}, \log K^{H}_{MA(OH)_j}, \log K^{H}_{H_jL}, \log K^{Y}_{YL}, \log K^{H}_{YH_jL}, \log K^{H}_{YL(OH)_j}
\]

\[\varepsilon_{ML}, \varepsilon_{MHL}, \varepsilon_{ML(OH)}, \varepsilon_{MA}, \varepsilon_{MHA}, \varepsilon_{MA(OH)}\]

\[\varepsilon_{ML}, \varepsilon_{MHL}, \varepsilon_{ML(OH)}, \varepsilon_{YL}, \varepsilon_{YHL}, \varepsilon_{YL(OH)},\]
Speciation of $\text{Zn}^{2+}$-PCTA3Am - $\text{H}^+$ system

$\text{Zn}^{2+}\text{PCTA3Am}$

$\text{Zn(PCTA3Am)H}_1$
Competiton of PCT3Am and BIMP ligands for Zn$^{2+}$ ions

Species | log$\beta$
---|---
HPCTA3Am | 9.53
H$_2$PCTA3Am | 13.73
HBIMP | 9.33
H$_2$BIMP | 15.83
H$_3$BIMP | 18.36
H$_4$BIMP | 20.36
H$_5$BIMP | 21.78
ZnPCTA3Am | 14.74
ZnPCTA3AmH$_{-1}$ | 5.90
ZnPCTA3AmH$_{-2}$ | -5.54
ZnBIMP | 15.94
ZnBIMP | 18.08
ZnBIMP | 20.04
Zn2BIMP | 17.55
OH- | -13.815

VS.

H$_2$N\text{-}C\text{-}O\text{-}N\_\text{H}_2

HOOC\text{-}N\_\text{H}_2\text{-}C\_\text{O}-\text{NH}_2

HOOC\text{-}N\_\text{H}_2\text{-}C\_\text{O}-\text{NH}_2\text{-}C\_\text{O}\text{-}COOH
Zn – BIMP – PCTA3Am competition reaction followed by pH-potentiometry  \([\text{Zn}^{2+}] = [\text{PCTA3Am}] = 2 \text{ mM} \]
\([\text{BIMP}] = 4 \text{ mM} ([\text{HCl}]=0.2188 \text{ M}).\)
Competiton of PCT3Am and BIMP ligands for Cu$^{2+}$ ions

Cu – BIMP – PCTA3Am competition reaction

1. [Cu(PCTA3Am)] (4 mM); 2-8. [Cu(PCTA3Am)(BIMP)] (2. 0.5 mM; 3. 1.0 mM; 4. 1.5 mM; 5. 2.0 mM; 6. 2.5 mM; 7. 3.0 mM; 8. 3.5 mM BIMP) 9. [Cu(BIMP)] (4 mM)
Optimal Ln-complexes from thermodynamic point of view

- **High (as high as possible) thermodynamic stability**

  Tuning stability (as high as possible) playing with
  - quality and number of donor atoms
  - structure of ligand (open chain or MC)
  - basicity
  - rigidity etc

  One can not forget other requirements as effectiveness, inertness, price etc.
Kinetics: basic principles (Ions in Solution by J. Burgess, Ellis Horwood Ltd. Chichester, 1988).

\[
A + B \xrightleftharpoons[k_b]{k_f} C + D \quad K = \frac{k_f}{k_b}
\]

Table 8.1 — Thermodynamic and kinetic data relating to cyanide exchange at cyano-complexes of transition metals

<table>
<thead>
<tr>
<th>Complex</th>
<th>log_{10}\beta_a</th>
<th>Mean $\Delta f(M-CN)$ (kJ mol$^{-1}$)</th>
<th>$k$ (*CN$^-$ exchange) (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Mn(CN)$_6$]$_4^-$</td>
<td>0</td>
<td>0</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>[V(CN)$_6$]$_4^-$</td>
<td>0</td>
<td>0</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>[Co(CN)$_6$]$_3^-$</td>
<td>10</td>
<td>-43</td>
<td>&gt; $10^{-2}$</td>
</tr>
<tr>
<td>[Cr(CN)$_6$]$^{3-}$</td>
<td>0</td>
<td>0</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>[Mn(CN)$_6$]$_3^-$</td>
<td>0</td>
<td>0</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>[Ni(CN)$_6$]$_3^-$</td>
<td>31</td>
<td>-45</td>
<td>$2 \times 10^{-4}$</td>
</tr>
<tr>
<td>[Cr(CN)$_6$]$_3^-$</td>
<td>0</td>
<td>0</td>
<td>$3 \times 10^{-7}$</td>
</tr>
<tr>
<td>[Fe(CN)$_6$]$_3^-$</td>
<td>34</td>
<td>-60</td>
<td>&lt; $10^{-6}$</td>
</tr>
<tr>
<td>[Pt(CN)$_6$]$_3^-$</td>
<td>35</td>
<td>-96</td>
<td>$1.2 \times 10^{-2}$</td>
</tr>
<tr>
<td>[Pd(CN)$_6$]$_2^-$</td>
<td>42</td>
<td>-60</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>[Fe(CN)$_6$]$_3^3-$</td>
<td>44</td>
<td>-49</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>[Co(CN)$_6$]$_3^3-$</td>
<td>64</td>
<td>-60</td>
<td>&lt; $10^{-6}$</td>
</tr>
</tbody>
</table>
Water exchange

Stable vs. unstable (thermodynamics)
Inert vs. labile (kinetics)

Gd(III) complexes: the importance of kinetic and thermodynamic stability

Should be as:
Gd(III) complexes: the importance of kinetic inertness and thermodynamic stability
Solvent exchange

### Table 9.3 — Activation entropies as a guide to solvent exchange mechanisms

<table>
<thead>
<tr>
<th>Cation</th>
<th>Solvent</th>
<th>$\Delta S^*$ (J K$^{-1}$ mol$^{-1}$)</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be$^{2+}$</td>
<td>TMU</td>
<td>+16</td>
<td>dissociative</td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>-32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMP</td>
<td>-54</td>
<td></td>
</tr>
<tr>
<td>Al$^{3+}$</td>
<td>water</td>
<td>+42</td>
<td>dissociative</td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>+22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMP</td>
<td>+37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMF</td>
<td>+43</td>
<td></td>
</tr>
<tr>
<td>Ga$^{3+}$</td>
<td>water</td>
<td>+30</td>
<td>dissociative</td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>+4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMF</td>
<td>+46</td>
<td></td>
</tr>
<tr>
<td>In$^{3+}$</td>
<td>water</td>
<td>-96</td>
<td>associative</td>
</tr>
<tr>
<td></td>
<td>TMP</td>
<td>-113</td>
<td></td>
</tr>
<tr>
<td>Sc$^{3+}$</td>
<td>TMP</td>
<td>-126</td>
<td>associative</td>
</tr>
<tr>
<td></td>
<td>DMA</td>
<td>-132</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMU</td>
<td>+48</td>
<td>dissociative</td>
</tr>
<tr>
<td>Tm$^{3+}$</td>
<td>DMF</td>
<td>+10</td>
<td>dissociative</td>
</tr>
<tr>
<td>Cr$^{3+}$</td>
<td>DMSO</td>
<td>-49</td>
<td>associative</td>
</tr>
<tr>
<td></td>
<td>DMF</td>
<td>-42</td>
<td></td>
</tr>
<tr>
<td>Fe$^{3+}$</td>
<td>water</td>
<td>-54</td>
<td>associative</td>
</tr>
<tr>
<td></td>
<td>MeOH</td>
<td>-31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>-43</td>
<td></td>
</tr>
<tr>
<td>Pd$^{2+}$</td>
<td>water</td>
<td>-24</td>
<td>associative</td>
</tr>
</tbody>
</table>

*Solvent abbreviations as Table 9.3, plus: DMA dimethylacetamide; DMF dimethylformamide.*

determined for exchange of a coordinating solvent in an appropriate diluent. The form
Mechanisms of solvent exchange (A. Merbach)
Kinetics and mechanisms: complex formation

10.1 BACKGROUND

The formation of a metal complex from a solvated metal ion and a ligand is, like solvent exchange, a special case of substitution (Fig. 10.1). It is a special case which is

SUBSTITUTION: GENERAL

\[ ML_3 L' + L'^- \rightarrow ML_2 L'^- + L' \]

c.g. \([Fe(CN)_{6}^3](NH_3)^- + py \rightarrow [Fe(CN)_{6}^3(py)]^- + NH_3 \]

SUBSTITUTION: SPECIFIC

Solvent exchange

\[ M_{S1}' + S \rightarrow MS_{S1}' + S^- \]

c.g. \([Al(OH)_{3}]^3 + OH_2 \rightarrow [Al(OH)_{3}(OH_2)]^3 + OH_2 \]

Complex formation

\[ MS_2' + L \rightarrow MS_1 L'^- + S^- \]

c.g. \([Ni(CH)_{3}]^3 + Br^- \rightarrow [Ni(OH)_{2}Br]^3 + OH_2 \]

Aquation or solvolysis

\[ ML_3 L' + S \rightarrow ML_2 S + L' \]

c.g. \([Co(NH)_{3}Cl]^3 + H_2O \rightarrow [Co(NH)_{3}(OH_2)]^2 + Cl^- \]

Ligand exchange

\[ ML_2 L'^- + L \rightarrow ML_2 L'^- + L \]

c.g. \([Fe(CN)_{6}^- + *CN^- \rightarrow [Fe(CN)_{6}(*CN)]^3^- + CN^- \]

Fig. 10.1 — Types of substitution reactions at complexes.
Sec. 10.2] The Eigen–Wilkins mechanism

$$M(OH)_2^{2-} + L \overset{k_\text{cat}}{\rightarrow} M(L)^{n-} \rightarrow M^{n-} - L$$

$$M(OH)_2^{2-} + L \overset{k_\text{cat}}{\rightarrow} M(OH)_2^{2-} + L \rightarrow M(OH)_2^{2-} + L^{n-} + H_2O.$$ 

General rate law:

$$+ \frac{d[ML^{n-}]}{dt} = k_1(L^0)k_0[L][ML^{n-}]$$

Under usual experimental conditions, $[M^{n-}] > [L]$:

$$+ \frac{d[ML^{n-}]}{dt} = k_1k_0[L][ML^{n-}]$$

Whence:

$$k_1 = k_0k_1$$

Fig. 10.3 — Complex formation: mechanism, equations, and kinetics.

$$k_{05} = \frac{4\pi N_A^2}{3000} e^{-\frac{2.1 e_1 a}{\epsilon kT}}$$

- a: 1000 kmol kg⁻¹ cm⁻¹
- 10⁻⁸ cm
- ion tőlét
- e: elektron tőlét: $1.6 \times 10^{-19}$
- c: chel. oldaló, 80 mm
- k: boltman

$$k_{05} = 0.3 \times e^{-\frac{2.1 e_1 a}{\epsilon kT}}$$

$1.1 + 1.2$ $k_{05} = 1.2$
Eigen-Wilkins mechanism: Ni$^{2+}$ complexes

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Measured $k_r$ ($M^{-1} s^{-1}$)</th>
<th>Estimated $K_{os}$ (molar scale)</th>
<th>Derived $k_r$ ($s^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$-Methylimidazole$^+$</td>
<td>0.23</td>
<td>0.02</td>
<td>12</td>
</tr>
<tr>
<td>Imidazole$^+$ H$^+$</td>
<td>0.3</td>
<td>0.02</td>
<td>15</td>
</tr>
<tr>
<td>Ammonia</td>
<td>5</td>
<td>0.15</td>
<td>33</td>
</tr>
<tr>
<td>Hydrogen fluoride</td>
<td>3</td>
<td>0.15</td>
<td>20</td>
</tr>
<tr>
<td>Imidazole</td>
<td>2.8–6.4</td>
<td>0.15</td>
<td>19–43</td>
</tr>
<tr>
<td>1,10-Phenanthroline</td>
<td>4.1</td>
<td>0.15</td>
<td>26</td>
</tr>
<tr>
<td>Diglycine</td>
<td>21</td>
<td>0.17</td>
<td>12</td>
</tr>
<tr>
<td>Fluoride$^-$</td>
<td>8</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Acetate$^-$</td>
<td>100</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Glycinate$^-$</td>
<td>20</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Oxalate H$^+$</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Oxalate$^2-$</td>
<td>75</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Malonate$^2-$</td>
<td>450</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>Methylphosphosphate$^2-$</td>
<td>290</td>
<td>40$^*$</td>
<td>7</td>
</tr>
<tr>
<td>Pyrophosphate$^3-$</td>
<td>2100</td>
<td>88</td>
<td>24</td>
</tr>
<tr>
<td>Tripolyphosphate$^4-$</td>
<td>6800</td>
<td>570</td>
<td>12</td>
</tr>
<tr>
<td>Cf. Water exchange</td>
<td></td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>

*In this favourable case $K_{os}$ was derived from the kinetic results.
SCS mechanism for bidentate ligands

Fig. 10.6—Details of the SCS mechanism for complex formation from solvent-metal ions and chelating ligands. The inset relating to $k_{rc}$ shows competition between ring closure and solvent return.

A $M^{2+}$: butadiene $\quad 2 \cdot 10^4 \text{s}^{-1}$

B $Ca^{2+}$: pyroantimonate $\quad 2 \cdot 10^6 \text{s}^{-1}$

C $Cu^{2+}$: propargylamine $\quad 1 \cdot 10^9 \text{s}^{-1}$

SCS
SCS mechanism for bidentate ligands

Table 10.7 — Kinetic data relating to the SCS (sterically controlled substitution) mechanism for formation of chelate complexes; all rate constants are in units of M⁻¹ s⁻¹, at 298.2 K in aqueous solution

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Cobalt(II) Water Exchange</th>
<th>Cobalt(II) Complex Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycinate⁻</td>
<td>2 x 10⁹</td>
<td>2 x 10⁶</td>
</tr>
<tr>
<td>α-Alaninate⁻</td>
<td>2 x 10⁹</td>
<td>2 x 10⁶</td>
</tr>
<tr>
<td>α-Aminobutyrate⁻</td>
<td>2.5 x 10⁹</td>
<td>2.5 x 10⁶</td>
</tr>
<tr>
<td>Iminodiacetate²⁻</td>
<td>1 x 10⁷</td>
<td>1 x 10⁷</td>
</tr>
</tbody>
</table>

5-membered rings:

- Glycinate⁻: 2 x 10⁹ M⁻¹ s⁻¹
- α-Alaninate⁻: 2 x 10⁹ M⁻¹ s⁻¹
- α-Aminobutyrate⁻: 2.5 x 10⁹ M⁻¹ s⁻¹
- Iminodiacetate²⁻: 1 x 10⁷ M⁻¹ s⁻¹

6-membered rings:

- β-Alaninate⁻: 1 x 10⁹ M⁻¹ s⁻¹
- β-Aminobutyrate⁻: 2 x 10⁹ M⁻¹ s⁻¹
- Iminodipropionate²⁻: 3 x 10⁹ M⁻¹ s⁻¹

Copper(II)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Copper(II) Water Exchange</th>
<th>Copper(II) Reaction with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>4 x 10⁹</td>
<td>2 to 20 x 10⁸ :</td>
</tr>
<tr>
<td>Pyridine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imidazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-membered-ring: α-Alaninate: 10 x 10⁸ M⁻¹ s⁻¹
6-membered-ring: β-Alaninate: 2 x 10⁸ M⁻¹ s⁻¹
7-membered-ring: L-Carnosine*: 3 x 10⁸ M⁻¹ s⁻¹

*L-Carnosine =

\[
\begin{align*}
&\text{HN} \\
&\text{NHCOCH₂CH₂NH₃}
\end{align*}
\]
Polydentate and macrocycle ligands

Sec. 10.4

Table 10.10 — Rate constants, \( k_r \) \( (M^{-1} \cdot s^{-1}) \), for formation of macrocyclic complexes from \( Cu^{2+} \)aq and tetrathianmacrocycles; in 80% methanol at 298.2 K

<table>
<thead>
<tr>
<th>Ligand (LLLL)</th>
<th>( k_r ) for ( Cu^{2+} )aq + LLLL</th>
<th>( k_r )</th>
<th>1 to 4 ( \times 10^4 )</th>
<th>0.12 ( \times 10^4 )</th>
<th>0.12 ( \times 10^4 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>deuteroporphyrin-2,4-disulphonic acid dimethyl ester</td>
<td>( R^1 = R^2 = SO_3H ) ( R^3 = R^4 = CH_2CH_2CO_2CH_3 )</td>
<td>4.3</td>
<td></td>
<td></td>
<td>4.3</td>
</tr>
<tr>
<td>haematoporphyrin IX</td>
<td>( R^1 = R^2 = CH(OH)CH_3 ) ( R^3 = R^4 = CH_2CH_2CO_2H )</td>
<td>( \sim 0.01 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>meso-tetraphenylporphine (5 derivatives)</td>
<td>0.001 to 0.02</td>
<td>0.001 to 0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Estimated.

Kinetics and mechanisms: complex formation

Table 10.11 — Rate constants for formation of copper(II) complexes of rigid macrocyclic ligands; in aqueous solution at 298.2 K

<table>
<thead>
<tr>
<th>Ligand (LLLL)</th>
<th>( k_r ) ( (M^{-1} \cdot s^{-1}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>'picket fence' porphyrin</td>
<td>5.6*</td>
</tr>
</tbody>
</table>

*First-order rate constant \( (s^{-1}) \) for intramolecular incorporation of \( Cu^{2+} \) into the porphyrin ring, i.e., for:

\[
 Cu^{2+} + L \rightarrow CuL^2+ \rightarrow CuL^4+ + 2H^+ 
\]

\( k_{eq} \sim 2 \times 10^4 \, M^{-1} \cdot s^{-1} \)
Effect of rigidity on rate constants (of the rate determining step)

---

**Table 10.15** — Effects of ligand rigidity on rate constants \((k \text{ (s}^{-1})\) for the slower stage

in the formation of 18-crown-6 complexes of Na\(^+\), in N,N-dimethylformamide

at 313 K

<table>
<thead>
<tr>
<th></th>
<th>(3.5 \times 10^6)</th>
<th>(2 \times 10^6)</th>
<th>&lt;(1 \times 10^6)</th>
</tr>
</thead>
</table>

*The fast first stage, involving initial bonding of the crown ether to the Na\(^+\), has \(k_f\) between 4 and \(6 \times 10^8\)

M\(^{-1}\) s\(^{-1}\) for these three ligands.

---

**Table 10.16** — Rate constants, \(k_f\) (M\(^{-1}\) s\(^{-1}\)), for formation of cryptates of alkali

metal cations; in methanol at 298.2 K

<table>
<thead>
<tr>
<th></th>
<th>[211]</th>
<th>[221]</th>
<th>[222]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li(^+)</td>
<td>(4.8 \times 10^4)</td>
<td>(1.8 \times 10^7)</td>
<td>(2.7 \times 10^8)</td>
</tr>
<tr>
<td>Na(^+)</td>
<td>(3.1 \times 10^6)</td>
<td>(1.7 \times 10^8)</td>
<td>(4.7 \times 10^8)</td>
</tr>
<tr>
<td>K(^+)</td>
<td>(3.8 \times 10^8)</td>
<td>(4.1 \times 10^8)</td>
<td>(7.6 \times 10^8)</td>
</tr>
<tr>
<td>Rb(^+)</td>
<td>(~5 \times 10^8)</td>
<td>(~9 \times 10^8)</td>
<td></td>
</tr>
<tr>
<td>Cs(^+)</td>
<td>(~5 \times 10^8)</td>
<td>(~9 \times 10^8)</td>
<td></td>
</tr>
</tbody>
</table>
Kinetic studies on Ln(III)-ligand systems

Type of the ligand:

- **open chain**
  - Formation:
    - too fast (pH>2)
  - Metal exchange:
  - Dissociation:
    - too fast (pH<2)

- **macrocyclic**
  - Formation:
    - too slow (pH=1-3)
    - measurable (pH=3-7)
  - Metal exchange:
    - fast (pH > 7)
  - Dissociation:
    - measurable (pH=3-7)
    - in the presence of large [LnL] excess
    - slow (pH>1)
    - measurable (pH<1)

**Methods:**

- **fast**
  - Stopped-flow (UV-VIS)
  - Rapid mixing unit (UV-VIS)
- **intermediate**
  - UV-VIS
  - Luminescence
  - Relaxometry
- **slow**
  - UV-VIS
  - NMR (relaxometry)

**Detection:**

- on the metal ion:
  - UV-VIS (Ce$^{3+}$ and Eu$^{3+}$)
  - Relaxometry (Gd$^{3+}$)
- on the ligand:
  - UV-VIS
  - NMR
Formation kinetics of the MC complexes

Two cases were observed:

a. Formation of Ln(III) complexes of simple DOTA-tetraamides (e.g. DOTAM, DTMA, …) which is a simple second order reaction between the Ln$^{3+}$ and the deprotonated ligand.

\[
\text{Ce}^{3+} + \text{DTMA} \rightleftharpoons [\text{Ce(DTMA)}^{3+}]
\]

For the DTMA ligand ($R_1 = -\text{CH}_3$, $R_2 = -\text{H}$)

- $\log K_1^H = 9.56$ and $\log K_2^H = 5.95$
- $\log K_{ML} = 12.68$ (Ce$^{3+}$) $\div 13.91$ (Yb$^{3+}$)

Formation of $[\text{Ce(DTMA)}^{3+}]$ as a function of time ($C_{\text{Ce}} = C_L = 5 \times 10^{-4}$ M in NMP buffer ($C_{\text{NMP}} = 2.5 \times 10^{-2}$ M) with pH = 5.26).
Formation kinetics of the complexes

Dependence of the formation rates on the Ln$^{3+}$ ion concentration:

\[ v = \frac{d[LnL]}{dt} = k_{obs}[L]_t \]

\[ v = k_0[M][L] + k_1[M][HL] + k_2[M][H_2L] \]

\[ k_{obs} = \frac{[M](k_0 + k_1 K_1^H[H^+] + k_2 K_1^H K_2^H[H^+]^2)}{1 + K_1^H[H^+] + K_1^H K_2^H[H^+]^2} \]

Since the fitting returned negative values for \( k_1 \) and \( k_2 \) the reaction of HL and H$_2$L were neglected

\[ k_{obs} = \frac{k_0[M]}{1 + K_1^H[H^+] + K_1^H K_2^H[H^+]^2} \]
b. Formation of Ln(III) complexes of macrocyclic ligands bearing negatively charged side arms (e.g. DOTA, DOTP, DOTA-4Gly, DOTA-4AMP …) proceeds via the formation of stable intermediates (protonated complexes).

\[ \text{Ce}^{3+} + H_x\text{DOTA} \rightleftharpoons [\text{Ce}(H_2\text{DOTA})^+] + (x-2)H^+ \rightarrow [\text{Ce}(H\text{DOTA})]^- + [\text{Ce}(\text{DOTA})]^+ -H^+ \]

For the DOTA log \(K_1^H = 12.6\), log \(K_2^H = 9.70\), log \(K_3^H = 4.5\)¹ and log \(K_4^H = 4.14\)

\(\log K_{\text{ML}} = 23.0\ (\text{Ce}^{3+}) \div 24.1\ (\text{Yb}^{3+})\)

Formation of \([\text{Ce}(\text{DOTA})]^-\) as a function of time (\(C_{\text{Ce}} = C_L = 5\times10^{-4}\ M\) in NMP buffer (\(C_{\text{NMP}} = 5.0\times10^{-2}\ M\)) with pH = 4.39).

Own memories from the last century

Kinetics of Formation and Dissociation of Lanthanide(III)–DOTA Complexes

Éva Tóth, Ernő Brücher,* István Lázár, and Imre Tóth

Department of Inorganic and Analytical Chemistry, Lajos Kossuth University,
Debrecen H-4010, Hungary
\[
\text{Ln}^{3+} + \text{H}_2\text{DOTA} \rightleftharpoons \text{Ln(} \text{H}_2\text{DOTA})^+ + (i - 2)\text{H}^+ \quad (3)
\]

\[
\text{Ln(} \text{H}_2\text{DOTA})^+ \overset{\text{slow}}{\rightarrow} \text{Ln(} \text{HDOTA}) \overset{\text{slow}}{\rightarrow} \text{Ln(} \text{DOTA})^- \quad (4)
\]

---

4074 *Inorganic Chemistry, Vol. 33, No. 18, 1994*

---

**Figure 4.** $^1$H-NMR spectra of DOTA in the presence of Gd$^{3+}$. $\text{DOTA} = 0.02 \text{ M}; \nu_D = 3.8; c_{\text{DOTA}} = 0 (1), 5 \times 10^{-5} \text{ M (2), } 1 \times 10^{-4} \text{ M (3), } 3 \times 10^{-4} \text{ M (4), } 1 \times 10^{-3} \text{ M (5), and } 2 \times 10^{-3} \text{ M (6). } \delta(\text{acetate CH}_3) = 4.5 \text{ ppm, } \delta(\text{ring CH}_3) = 3.6 \text{ ppm.}$
Why do macrocyclic ligands form complexes with metal ions slowly?

H$_2$DOTA$^{2-}$ (pre-organized) $\xrightarrow{\text{fast}}$ Intermediate Ln(H$_2$DOTA)$^{+}$

slow step, requires deprotonation and rearrangement

Ln(DOTA)$^{-}$ formed
Approximate half-lives of the intermediates

At pH = 4.4 in 0.001 M solution of CeL

[Ce(CDTA)]⁻ \( t_{1/2} < 0.1 \text{ sec.} \)

[Ce(DOTA)]⁻ \( t_{1/2} \approx 12 \min. \)

[Ce(DOTMA)]⁻ \( t_{1/2} > 100 \h. \)

[Ce(DOTA-4AMP)]⁵⁻ thermodynamically practically stable under these conditions
Formation kinetics of the complexes

\[
\frac{d[LnL]_t}{dt} = k_{obs}[L]_t
\]

\[
k_{obs} = \frac{k_r K_{Ln}[Ln^{3+}]}{1 + K_{Ln}[Ln^{3+}]}
\]

\[
k_r = \frac{k_H}{[H^+]} = k_{OH}[OH^-]
\]

\(k_{obs}\) vs. \([Ln^{3+}]\rightarrow\) saturation curve !!!

\(K_{Ln}\) is the conditional stability constant of the accumulating intermediate, \(LnH_yL\), and \(k_r\) is the formation constant at the given pH.
Dissociation of the complexes

\[ \text{Ln}^3+ + \text{HL} \xrightleftharpoons[k_{L_nLH}]{k_{L_nLH}} \text{LnLH} \tag{2} \]

\[ \text{Ln}^3+ + \text{H}_2\text{L} \xrightleftharpoons[k^H_{L_nLH}]{k^H_{L_nLH}} \text{LnL} \tag{3} \]

\[ \frac{d[\text{LnL}]}{dt} = k_d[\text{LnL}]_t \]

\[ [\text{LnL}]_t = [\text{LnL}] + [\text{LnHL}] + [\text{LnHL}][H^+] + [\text{LLnL}^\ast] + [\text{LnLM}] \]

\[ \frac{d[\text{LnL}]}{dt} = k_d[\text{LnL}]_t = k_{L_nL}[\text{LnL}] + k_{L_nLH}[\text{LnHL}] + k^H_{L_nLH}[\text{LnHL}][H^+] + k_{L_nL^\ast}[\text{L}^\ast\text{LnL}] + k_{L_nLM}[\text{LnLM}] \]
Tuning the kinetic inertness of the complexes by making the ligands more rigid

\[
\text{Ln(OXAAZA)} + M^{2+} \rightleftharpoons M(\text{OXAAZA}) + \text{Ln}^{3+}
\]

\[k_d = k_0 + k_1[H^+]
\]
Tuning the kinetic inertness of the complexes by making the ligands more rigid

$$\text{Gd}(\text{p-NO}_2\text{-Bz-OXAAZA}) + \text{Zn}^{2+} \rightleftharpoons \text{Zn}(\text{p-NO}_2\text{-Bz-OXAAZA}) + \text{Gd}^{3+}$$

$$k_d = k_0 + k_1[H^+]$$

$$k_{obs} \times 10^7 (s^{-1})$$

$C_{\text{HCl}} \times 10^5 (\text{mol/dm}^3)$
Tuning the kinetic inertness of the complexes by making the ligands more rigid

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Ln$^{3+}$</th>
<th>Ce$^{3+}$</th>
<th>Eu$^{3+}$ or Gd$^{3+}$</th>
<th>Yb$^{3+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXAAZA</td>
<td>$k_0$ s$^{-1}$</td>
<td>(5.9±0.4)$\times$10$^{-7}$</td>
<td>(1.4±0.3)$\times$10$^{-7}$</td>
<td>(2.0±1.2)$\times$10$^{-7}$</td>
</tr>
<tr>
<td></td>
<td>$k_1$ M$^{-1}$s$^{-1}$</td>
<td>(0.22±0.01)</td>
<td>(1.19±0.06)$\times$10$^{-2}$</td>
<td>(4.05±0.08)$\times$10$^{-2}$</td>
</tr>
<tr>
<td>p-NO$_2$-Bz-OXAAZA</td>
<td>$k_0$ s$^{-1}$</td>
<td>-</td>
<td>(6.1±0.7)$\times$10$^{-8}$</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>$k_1$ M$^{-1}$s$^{-1}$</td>
<td>-</td>
<td>(3.7±0.4)$\times$10$^{-3}$</td>
<td>-</td>
</tr>
<tr>
<td>DTPA$^i$</td>
<td>$k_0$ s$^{-1}$</td>
<td>-</td>
<td>not detected</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>$k_1$ M$^{-1}$s$^{-1}$</td>
<td>-</td>
<td>0.58</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>$k_2$ M$^{-2}$s$^{-1}$</td>
<td>-</td>
<td>9.7$\times$10$^{-4}$</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>$k_3$ M$^{-1}$s$^{-1}$ (k$^{3}<em>{Eu}$, k$^{3}</em>{Cu}$ and k$^{3}_{Zn}$)</td>
<td>-</td>
<td>4.9$\times$10$^{-4}$, 0.93 and 5.6$\times$10$^{-2}$</td>
<td>-</td>
</tr>
</tbody>
</table>

Optimal Ln-complexes from kinetic point of view

- Possible quick complex formation

Engineering point of view (i.e. cheaper for Gd), but essential for some short lived radioisotopes

Easy(er) characterisation of the complex, good for students...

- Non-toxicity, i.e. high thermodynamic stability and kinetic inertness (i.e. slow dissociation)

Ideal case: no any dissociation of LnMC before the complete excretion
Some useful references


Three series of “Topics Current Chemistry” books were dedicated to the chemistry of contrast agents: Vol. 221, and 252


6. Review journals like:
   Chemical Society Reviews: [http://www.rsc.org/publishing/journals/cs/article.asp](http://www.rsc.org/publishing/journals/cs/article.asp)
   Chemical Reviews: [http://pubs.acs.org/journal/chreay](http://pubs.acs.org/journal/chreay)
   Coordination Chemistry Reviews: [http://www.elsevier.com/wps/find/journaldescription.cws_home/500845/description#description](http://www.elsevier.com/wps/find/journaldescription.cws_home/500845/description#description)
An expert is a man who has made all the mistakes which can be made in a very narrow field.

Bohr and Einstein debating quantum theory at Ehrenfest's home in Leiden (December 1925).
Acknowledgement

Torino, Italy
Silvio Aime, Enzo Terreno and Dario Longo
Debrecen, Hungary
Ernő Brücher
Gyula Tircsó
Erika Ádom
Zsolt Baranyai
Tamara Kócs

The authors thank the Hungarian Scientific Research Found (K-84291) and the TÁMOP 4.2.1./B-09/1/KONV-2010-0007 project implemented through the New Hungary Development Plan, co-financed by the European Social Fund and the European Regional Development Fund for financial support of this work. Part of the research was performed within the framework of the EU COST Action D38 “Metal-Based Systems for Molecular Imaging Applications”.