Chelate chemistry for molecular imaging

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Take home lessons: What you should learn from today's lecture

• Choose the proper ligand for a particular metal ion. Why is this important?
• Macrocyclic ligands versus acyclic ligands: pros & cons
• Which is more important for metal chelate applications in vivo? Thermodynamics or kinetics

Ligands versus Chelates

A ligand is defined as any anion or organic molecule that donates a pair of electrons to a metal ion.

Multidentate ligands bind to a metal ion by displacing solvent molecules (often water) to form a ML complex

• Multidentate ligands are called chelating agents (claw)
• The resulting ML complexes are called chelates

Typical chelates

 Gadolinium DTPA

Fe(EDTA)

Some common ligands used for chelating metal ions

Macrocyclic ligands

Acyclic ligands

Bifunctional ligands are widely used to attach a ligand to a targeting moiety ⇒ bifunctional chelates (BFC)

Question: So, with all these choices, how does one choose the best ligand or bifunctional ligand for your particular molecular imaging application?

Answer: It depends!

• On size matching of metal ion and ligand cavity
• Thermodynamics (how stable does the chelate need to be?)
• Kinetics of ML complex formation
• Charge on resulting chelate; perhaps it needs to be charged or neutral
Some common radionuclides and ligands used in molecular imaging

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Most common metal ion</th>
<th>Most common ligand(s)</th>
<th>Ligand characteristics (coord #, donor types)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Gd^{3+}</td>
<td>DOTA-like, DTPA-like</td>
<td>8-coordinate, needs one water site, prefers &quot;hard&quot; donor atoms</td>
</tr>
<tr>
<td>PET</td>
<td>^{64}Cu^{2+}</td>
<td>cyclen, DOTA, TETA, bridged TETA, NOTA</td>
<td>Prefer N donors, only 4 coordinate necessary</td>
</tr>
<tr>
<td>PET</td>
<td>^{68}Ga^{3+}</td>
<td>DOTA, NOTA</td>
<td>Prefer octahedral and &quot;hard&quot; donor atoms</td>
</tr>
<tr>
<td>PET</td>
<td>^{86}Y^{3+}</td>
<td>DOTA-like</td>
<td>Similar to Gd^{3+}</td>
</tr>
<tr>
<td>PET</td>
<td>^{89}Zr^{2+}</td>
<td>Desferrioxamine-like</td>
<td>&quot;Hard&quot; oxygen donors</td>
</tr>
<tr>
<td>SPECT</td>
<td>^{99m}Tc^{2+}</td>
<td>Methoxyisobutylisonitrile (Sestamibi)</td>
<td>N donor atoms</td>
</tr>
<tr>
<td>SPECT</td>
<td>^{111}In^{3+}</td>
<td>DTPA-like</td>
<td>8-coordinate, somewhat &quot;softer&quot; ion</td>
</tr>
</tbody>
</table>

Factors to consider in the design of ligands for various metal ions

- Selection of ligand donor atoms
- HSAB principles, matching coordination numbers
- Role of ligand architecture (cyclic versus acyclic)
- Limited to size-match selectivity
- Kinetics of ML complex formation & dissociation
  - Ligands with flexible backbone structures form complexes more quickly but also dissociate faster
  - Macroyclic ligands form complexes more slowly but also dissociate more slowly

Hard-Soft Acid-Base Principles (HSAB)

Ligand donor types (from softest to hardest): P < S < N < O < F

For 3d transition metal ions:

1) M^{2+} ions get smaller and harder from left to right (increasing nuclear charge)
   
   Ti^{2+} (86 pm) > V^{2+} (79 pm) > Cr^{2+} (73 pm) > Mn^{2+} (67 pm) > Fe^{2+} (61 pm)

2) M (softer) < M^{2+} (intermediate) < M^{3+} (harder)

As one progresses down a series (3d → 4d → 5d) for ions of the same charge

- hardest
- hardest
- intermediate
- intermediate
- softest
- softest

Some basic definitions: thermodynamic constants, kinetic constants, pKa's and basicity

\[ K_{\text{cond}} = \frac{[L\text{HL}]}{[L][HL]} \]

\[ K_{\text{st}} = \frac{[LN]}{[L^{3+}][L]} \]

Thermodynamic ML stability constant (most basic site)

Size does matter!

64^{2+} (4f^7) ionic radius ~1.0Å \[ \log K_{\text{st}} = 24.7 \]

68^{3+} (3d^10) ionic radius ~0.6Å \[ \log K_{\text{st}} = 31 \]

Thermodynamic Stability Constant Determinations:

Potentiometry is considered the "gold standard"
Correlation of $k_{f,HL}$, $k_{d,HL}$ and log $K_{ML}$ with the first protonation constant of the ligand (log $K_{HL}$)

$$
\log K_{ML} = \log K_{HL} - \log K_{HL}^f - \log K_{HL}^d + \log K_{HL}^i
$$

Importance of kinetics: rates of ML formation

$$
\text{Ln}^{3+} + \text{HL} \xrightarrow{k_{f,HL}} \text{LnL} + \text{H}^+
$$

Why do macrocyclic ligands form complexes with metal ions so slowly?


Ligand charge also plays a role

$$
\log K_{ML} \quad 24.7^* \quad 20.1^b \quad 27.2^c \quad 28.8^d
$$

Log $K_{ST}$ vs $\Sigma pK_a$'s for a series of GdL complexes


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Correlation of $k_f, H_L$ with the first protonation constant of the ligand ($\log K_{HL}$)


Comparison of bifunctional chelates for $^{64}$Cu$^{2+}$-antibody imaging


Increased backbone rigidity improves the kinetic stability of complexes


Are LnDOTA-tetraamide complexes safe for in vivo use?


Take home lessons:

- Why it is important to choose the proper ligand for a particular metal ion for molecular imaging:
  - Ligand size and donor type should match the characteristics of the metal ion
- Macrocyclic ligands versus acyclic ligands:
  - Macrocyclic ligands form more stable ML chelates but they also form more slowly (this kinetic barrier may be important in radiolabeling of antibodies which cannot be heated)
- Which is more important for metal chelate applications in vivo?
  - Thermodynamic is more important in vivo applications

Thanks

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