Complexation of Cations, Anions, and Organic Substrates using Modified Cyclodextrins

Suhash Harwani
University of Iowa
DTSC - ECL
28 January 2009
Outline

• Background on cyclodextrins
• Inner-sphere coordination of Ln$^{\text{III}}$/An$^{\text{III}}$
  • Synthesis of acid cyclodextrin scaffolds
  • Binding with Ln$^{\text{III}}$
• Outer-sphere coordination of ClO$_4^-$, PO$_4^{3-}$, and SO$_4^{2-}$
  • Synthesis cyclodextrin scaffold
  • Binding studies via ESI-MS
  • Binding Mode
• Organic substrate binding
• Conclusions
Cyclodextrins

Cyclic molecules consisting of 6, 7, or 8 α-(1 → 4) linked D-glucose molecules named α, β, and γ-cyclodextrin

Cyclodextrin Properties

Physicochemical properties

- Hydrophobic interior
- Hydrogen-bonding lower and upper
- Cavity Size

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Cavity Diameter (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>4.7 – 5.3</td>
</tr>
<tr>
<td>β</td>
<td>6.0 – 6.5</td>
</tr>
<tr>
<td>γ</td>
<td>7.5 – 8.3</td>
</tr>
</tbody>
</table>

Llinares, J. M.; Powell, D.; Bowman-James, K. *Coor. Chem. Rev.* 2003, 240, 57-75
http://geoweb.princeton.edu/research/geochemistry/research/aqueous-sulfate.html
Modifying Cyclodextrin Properties

- Primary hydroxyls substituted

Per-6-modified

- Important Interactions for Binding
  - H-bonding
  - Electrostatic Interactions
  - Vander Waals Interactions
  - Outer- vs. Inner-sphere coordination

Mono-6'-modified

Created with novaPDF Printer (www.novaPDF.com). Please register to remove this message.
Outline

• Background on cyclodextrins
• Inner-sphere Coordination of Ln$^{\text{III}}$/An$^{\text{III}}$
  • Synthesis of acid cyclodextrin scaffolds
  • Binding with Ln$^{\text{III}}$
• Outer-sphere Coordination of ClO$_4^-$, PO$_4^{3-}$, and SO$_4^{2-}$
  • Synthesis cyclodextrin scaffold
  • Binding studies via ESI-MS
  • Binding Mode
• Organic substrate binding
Preorganization for Binding

- **Calix[n]arenes**
  - Carbamoylmethylphosphine oxide
- **Imperiali et al.** developed an EF-hand peptide
  - $K_d$ values (nM): 57 ($\text{Tb}^{3+}$), 71 ($\text{Dy}^{3+}$), 78 ($\text{Er}^{3+}$) up to 950 ($\text{Ce}^{3+}$) and 3500 ($\text{La}^{3+}$)
- **NHC for binding $\text{U}^{3+}$ vs $\text{Ce}^{3+}$**


Per-6-modified β-cyclodextrins

Increasing the Denticity of per-6-ethylenediamine-\(\beta\)-cyclodextrin

Increasing the Denticity of per-6-ethylenediamine-β-cyclodextrin

DTPA is metal chelating agent - effective at binding lanthanides

Mono-6-modified β-cyclodextrins
Mono-6-modified β-cyclodextrins

1. 1 eq. DTPA dianhydride
   DIEN
   DMSO, RT
   4-5h

2. 2-3 eq. NaOH
   1h
   34.2% yield

excess dansyl chloride

K₂CO₃
DMF, 70°C
18h
78.8% yield
Fluorescence of mono-6-ethylenediamine-dansyl-β-cyclodextrin

- $\lambda_{ex} = 355\text{nm}$
- $\lambda_{em} = 540-542\text{nm}$
- Unable to quench the fluorescence with Cu$^{2+}$ or D-glucose
- No FRET using between tryptophan or Tb$^{3+}$
  - Inclusion of dansyl moiety within the cavity
  - Distance greater than 10 Å between tryptophan or Tb$^{3+}$
Fluorescence Emission of Eu\textsuperscript{3+} with 10
Fluorescence Emission of Tb$^{3+}$ with 10

Fluorescence Emission of Tb$^{3+}$ Titrated with 15

![Diagram showing fluorescence emission of Tb$^{3+}$ titrated with 15 at different equivalents.](image)
ESI-MS Tb\(^{3+}\) with 10

[semi-anhydride \(15-3H^+ + Tb^{3+} + Na^+\)]\(^+\)
ESI-MS Gd$^{3+}$ with 10

[semi-anhydride $15\text{-}3\text{H}^+\text{+Gd}^{3+}\text{+Na}^+]^+$
Outline

• Background on cyclodextrins
• Inner-sphere Coordination of Ln$^{III}$/An$^{III}$
  • Synthesis of acid cyclodextrin scaffolds
  • Binding with Ln$^{III}$
• Outer-sphere Coordination of ClO$_4^-$, PO$_4^{3-}$, and SO$_4^{2-}$
  • Synthesis cyclodextrin scaffold
  • Binding studies via ESI-MS
  • Binding Mode
• Organic substrate binding
• Conclusions
Importance of Remediating Tetrahedral Anions

• Concentrations of tetrahedral oxyanions have been increasing in nature (mostly from fertilizers and factories)

• Perchlorate and pertechnetate have been shown compete with iodide uptake with the thyroid gland in mammals

• A major form technetium exists as as pertechnetate anion, $\text{TcO}_4^-$

Anion Receptors

- Phosphate Binding Protein (K_d ~ 0.8 µM)
- Tetraamine spermine in yeast

\[
\begin{align*}
&\text{H}_3\text{N} & \quad & \text{H} & \quad & \text{NH}_3^+ \\
&\text{N} & \quad & \text{H} & \quad & \text{NH}_3^+ \\
&\text{NH}_2 & \quad & \text{H} & \quad & \text{NH}_3^+ \\
&\text{NH}_2 & \quad & \text{H} & \quad & \text{NH}_3^+
\end{align*}
\]

- Additional anion receptors

\[
\text{Ar} = \text{Aryl groups}
\]

n=1, NO_3^- and Cl^-  
F^- (~2), SO_4^{2-} (~4.4), HPO_4^{2-} (~7.4)

Synthesis of modified Cyclodextrin

Goals with functionalization of the upper rim:

- Elongate the upper-cyclodextrin binding pocket
- Add hydrogen bonding acceptor-donor
- Create possible sites for electrostatic interaction

<table>
<thead>
<tr>
<th>*</th>
<th>Phosphate</th>
<th>Sulfate</th>
<th>Perchlorate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge/Size</td>
<td>0.63</td>
<td>0.43</td>
<td>0.21</td>
</tr>
<tr>
<td>Diameter (Å)</td>
<td>4.76</td>
<td>4.60</td>
<td>4.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Cavity Diameter (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>4.7 – 5.3</td>
</tr>
<tr>
<td>β</td>
<td>6.0 – 6.5</td>
</tr>
<tr>
<td>γ</td>
<td>7.5 – 8.3</td>
</tr>
</tbody>
</table>
Non-covalent Interactions via ESI-MS

• Soft-ionization technique
• Gas phase ESI-MS has been shown to resemble solution phase well
• Unambiguous stoichiometry of complexes formed

MS of α-cyclodextrin

![Mass Spectrum of α-cyclodextrin with peaks labeled for [+H+] and [+NH4+] at specific m/z values.]

Created with novaPDF Printer (www.novaPDF.com). Please register to remove this message.
MS α-cyclodextrin with LiClO$_4$ (1:7)
MS of α-cyclodextrin with KH₂PO₄ (1:7)
MS α-cyclodextrin with MgSO₄ (1:7)
MS of Cyclodextrin 14

\[ [M + 2H^+ + OH - EDA]^{2+}/2 \]

\[ [M + 3H^+]^{3+}/3 \]

\[ [M + 2H^+ + OH - EDA]^{3+}/3 \]

\[ [M + H^+ + OH - EDA]^+ \]

\[ [M + 2H^+ + OH - EDA]^{2+}/2 \]

\[ [M + 3H^+]^{3+}/3 \]

\[ [M + 2H^+ + OH - EDA]^{3+}/3 \]

\[ [M + H^+]^+ \]
MS 14 with ClO$_4^-$ (10:1)
MS 14 with ClO$_4^-$ (1:1)

\[
\frac{[M + 2H^+ - EDA + OH + ClO_4^-] + ClO_4^-}{2}
\]

\[\frac{[M + 3H^+ + ClO_4^-]}{2}\]

\[\frac{[M + 2H^+ - EDA + OH + ClO_4^-]}{2}\]

\[\frac{[M + 2H^+ + ClO_4^-]}{+}\]

\[\frac{[M + 2H^+ + ClO_4^-]}{+}\]
MS 14 with ClO$_4^-$ (1:5)
MS 14 with ClO$_4^-$ (1:10)
MS 14 with SO$_4^{2-}$ (10:1)
MS 14 with SO$_4^{2-}$ (1:1)
MS 14 with SO$_4^{2-}$ (1:5)
MS 14 with \( \text{SO}_4^{2-} \) (1:10)
MS 14 with PO$_4^{3-}$ (10:1)
MS 14 with PO$_4^{3-}$ (1:1)
MS 14 with PO$_4$$^3-$ (1:5)
MS 14 with $\text{PO}_4^{3-} \ (1:10)$
Calculation of K\textsubscript{d} from ESI-MS

\[
\% \text{Bound} = \frac{[G]_{\text{bound}}}{[H]_{\text{total}}} = \frac{[G]_0 - [G]}{[H]} = \frac{[G]_0 - K_d [HG][H]}{[H]} \quad \text{or}
\]

\[
K_d = \frac{[HG]}{[H]}
\]

\[
\% \text{Bound} = R^* \left( \frac{I_{HG}}{I_H + I_{HG}} \right)
\]

\[
R^* \left( \frac{I_{HG}}{I_H + I_{HG}} \right) = \frac{[G]_0 - R^* K_d (I_{HG} / I_H)}{[H]}\]

\[
\left( \frac{I_{HG}}{I_H + I_{HG}} \right) = \frac{[G]_0}{[H]} * R - K_d * \frac{I_{HG}}{I_H}
\]

Definitions

\[R = \text{response factor} = R' \ast n\]

\[[G]_0 = \text{Initial guest (tetrahedral anion) concentration} \]

\[[H]_0 = \text{Initial host (cyclodextrin) concentration} \]

\[[G] = \text{Amount of free guest (tetrahedral anion) present} \]

\[[H] = \text{Amount of free host (cyclodextrin) present} \]

\[I_{HG} = \text{Absolute intensity of HG complex} \]

\[I_H = \text{Absolute intensity of H} \]
### Binding with Cyclodextrin

<table>
<thead>
<tr>
<th>Anion</th>
<th>ClO$_4^-$</th>
<th>SO$_4^{2-}$</th>
<th>PO$_4^{3-}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge/Size Ratio</td>
<td>0.21</td>
<td>0.43</td>
<td>0.63</td>
</tr>
<tr>
<td>Log $K_a$</td>
<td>3.8 ± 0.02</td>
<td>3.62 ± 0.04</td>
<td>4.0 ± 0.02</td>
</tr>
<tr>
<td>$R',*$</td>
<td>-8</td>
<td>-1</td>
<td>-4</td>
</tr>
<tr>
<td>$n,*$</td>
<td>0.3</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>
Binding Modes

Anions can bind at numerous positions
- Interaction at upper rim through ethylenediamine arms
- Interaction at lower rim through hydroxyl groups
- Within the cavity (unlikely due to the hydrophobic nature of the cavity)

\[ X(n) = \text{Cl}(-1), \text{P}(3-), \text{S}(2-) \]
Proton $T_1$ Relaxation Times

$T_1$ Relaxation Values: Titration of 14 with LiClO$_4$

Definitions:

- $M_t = M_0 (1 - 2e^{-\tau/T_1})$
- $M_t$ = peak intensity at a specified $\tau$ value
- $M_0$ = peak intensity at full relaxation
- $\tau$ = delay time before the spectrum taken
- $T_1$ = $T_1$ relaxation value being calculated
Outline

• Background on cyclodextrins
• Inner-sphere Coordination of Ln^{III}/An^{III}
  • Synthesis of acid cyclodextrin scaffolds
  • Binding with Ln^{III}
• Outer-sphere Coordination of ClO_4^-, PO_4^{3-}, and SO_4^{2-}
  • Synthesis cyclodextrin scaffold
  • Binding studies *via* ESI-MS
  • Binding Mode
• **Organic substrate binding**
• Conclusions
Host-Guest Studies

2, 3-dihydroxyquinoxaline  
DHQ

2, 3-diaminonaphthalene  
DAN

$N$-(1-pyridyl-methyl)-2-amino-benzoic acid  
DJ-101
### Analysis of Titration Spectra

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cyclodextrin</th>
<th>$\log K_a$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAN</td>
<td>Native $\beta$</td>
<td>2.7 ± 0.1</td>
</tr>
<tr>
<td>DHQ</td>
<td>Native $\beta$</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>DJ-101</td>
<td>Native $\beta$</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td>DJ-101</td>
<td>Per-6-EDA-$\beta$ (3)</td>
<td>5.4 ± 0.1</td>
</tr>
</tbody>
</table>
Conclusions

• Cation Binding
  • Synthesis of novel per-6- and mono-6-modified β-cyclodextrins has been accomplished
  • The initial analysis indicates complexation by cyclodextrin 11 (DTPA modified) with Tb$^{3+}$, Eu$^{3+}$, and Gd$^{3+}$
  • Fluorescence and MS experiments indicate a 1:1 (Cyclodextrin/Ln$^{III}$) stoichiometry

• Anion Binding
  • Characterization of perchlorate, phosphate, and sulfate binding with native α-cyclodextrin and 14 using ESI-MS have been completed
  • Binding affinities determined, indicating a minor amount of discrimination
  • Binding modes analyzed through $T1$ calculations

• Organic Substrate Binding
  • Cyclodextrins incorporate DHQ, DAN, and DJ-101 into their hydrophobic cavities with modest association constants
Acknowledgements

- Professors Jason Telford and Sonya Franklin
- Telford Group Members (David, Nate, Heaweon, and Tony)
- Department of Chemistry at the University of Iowa
- Funding sources
  - PRF
  - University of Iowa GCSF