Lecture XXVII: Molecular Recognition. Cation Recognition

1. Binding principles and characteristics

2. Cation binding
   - Crown ethers
   - Cryptands
   - Spherands

3. Binding principles and characterization

Let's assume $A + B$ associate into $A\cdot B$

$$A + B \xrightleftharpoons[k_1]{k_{-1}} A\cdot B$$

$$K_{eq} = \frac{[A\cdot B]}{[A][B]} = 10^5; \text{ for example}$$

Then, if $[AJ_0] = [BJ_0] = 1M \Rightarrow [ABJ] = K_{eq}\left([AJ_0] - [ABJ]\right)^2$

$$[ABJ] = K_{eq}\left([AJ_0] - [ABJ]\right)^2$$

$$K_{eq}[ABJ]^2 + (-2[AJ_0]K_{eq} - 1)[ABJ] + K_{eq}[AJ_0]^2 = 0$$

Quadratic equation

$$X = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

$$[ABJ] = \frac{2[AJ_0]K_{eq} - 1 \pm \sqrt{4[AJ_0]^2K_{eq}^2 + 4[AJ_0]K_{eq} + 1 - 4K_{eq}[AJ_0]^2}}{2K_{eq}}$$

$$[ABJ] = \frac{2 \times 10^5 - 1 \pm \sqrt{4 \times 10^{10} + 4 \times 10^5 + 1 - 4 \times 10^{10}}}{2 \times 10^5} = 0.996845 \pm 99.7\% \text{ bound}$$

But what if $[AJ_0] = [BJ_0] = 10^{-3} \text{ M}$

$$[ABJ] = \frac{2 \times 10^2 + 1 \pm \sqrt{4 \times 10^2 + 1}}{2 \times 10^5} = \frac{201 \pm 20.02}{200000} = 0.11\% \text{ bound}$$

With dilution, supramolecular complexes fall apart! Same applies to increasing temperature.

How do we quantify binding and establish $K_{eq}$?
- NMR
- UV
- Isothermal titration calorimetry (ITC)
**Cation binding - important in:**

- Mining
- Biology
- Medicine (ME, Gd³⁺)

- Environmental applications etc.

We will survey several classes of cation binders, with different operating principles behind them:

**2-A Crown ethers**, developed in 1960s by Charles Pederson (DuPont, Nobel Prize 1987)

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12-c-4
\[ \log k(\text{Li}^+) = \frac{1}{2} \log k(\text{Na}^+) = \log k(\text{K}^+) = \]

15-c-5, selective for Na⁺

18-c-6, selective for K⁺
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\[ \log k(\text{K}^+) = 6.10, \text{Na}^+ = 4.32, \text{Cs}^+ = 4.62 \]
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\text{dibenzo-18-crown-6}
\text{total # of ring atoms} \rightarrow L > \# of oxygens
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\text{Various crown ethers sites have been synthesized}
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15-c-5, selective for Na⁺
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18-c-6, selective for K⁺
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21-c-7, selective for Cs⁺
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Interesting structures can be formed in cases of mismatches:

\[ \text{[Image of molecular structures]} \]

\( K^+ (\text{benzol5-C-5})_2 \) since it cannot fit into a single ring.

Oxygen is a hard donor, so replacing it with softer N or S increases the affinity for transition metals:

- \( \log K (K^+) = 6.10 \)
- \( \log K (Ag^+) = 1.60 \)
- \( \log K (K^+) = 3.90 \)
- \( \log K (Ag^+) = 3.30 \)
- \( \log K (K^+) = 2.04 \)
- \( \log K (Ag^+) = 7.80 \)

18-C-6 also binds primary amino acids well on account of their symmetry.

Do all these molecules have to be cyclic? In principle no, but it would be better:

Better, 3D binding cavity:

\[ \text{[Image of molecular structures]} \]

binding conformation is unfavorable entropically and enthalpically:

MACROCYCLIC EFFECT!

30 cavity is also more selective \( K^+/Na^+ \sim 10^3 \), and only \( 10^2 \) for 18-C-6.

MACROCYCLIC EFFECT!
Spherands - preorganization effects (Donald Crow, UCLA, Nobel Prize 1987)

Crown ethers still have a lot of conformational flexibility, which means that they pay some entropic cost for complexation. Rigid, preorganized ligands should be stronger binders but are trickier to design.


Binding of organic ammonium salts

 Mostly based on derivatives of crown ethers, but more complex:

X = CO$_2$\(^-\)

- lateral discrimination $R_1$ vs $R_2$
- central discrimination $RMH_3$\(^+\) vs $RMH_2$\(^+\),

Ditopic receptors:

Selectivity, depending on $R$:

- $R = \text{none}$
- $R = (CH_2)_5$ Lehn
- $R = (CH_2)_7$
- $R = (CH_2)_9$

NEXT TIME, we will look at applications of cation binding.