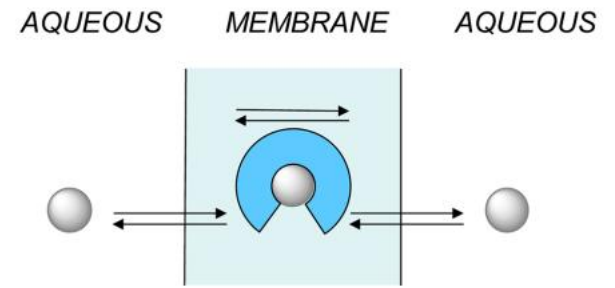
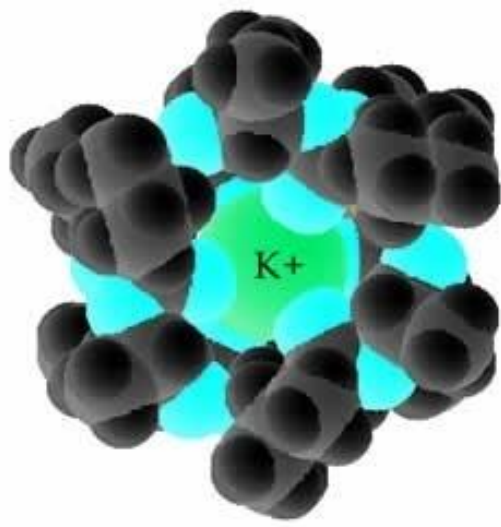
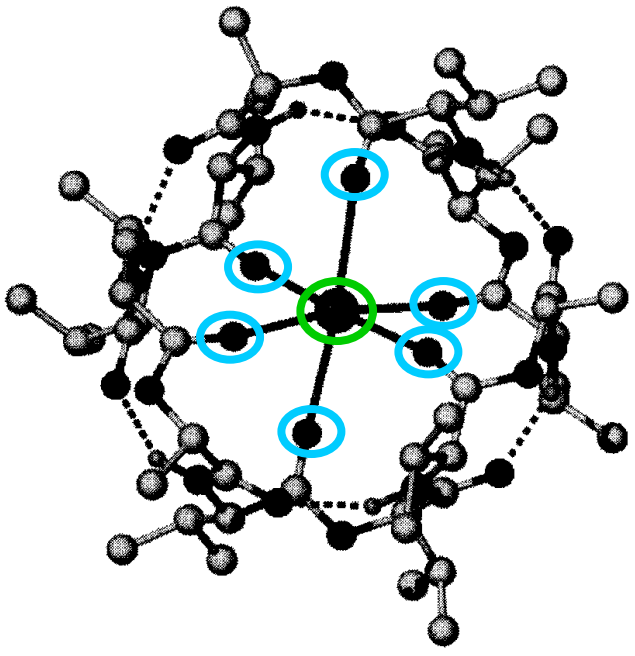
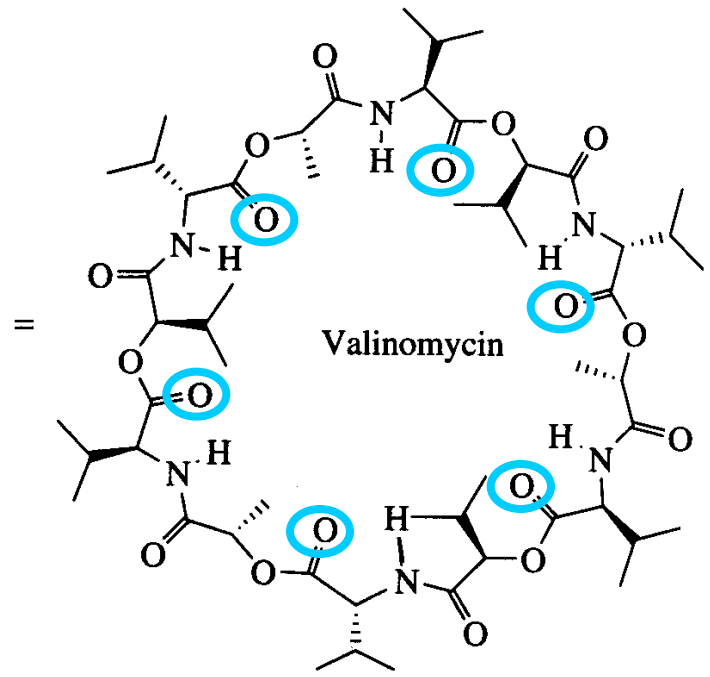
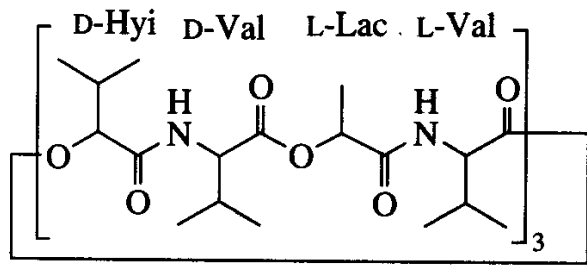


Cations and anions are ubiquitous in biological and chemical systems and their efficient and selective recognition is one of the main goals of Supramolecular Chemistry. As a matter of fact, research in this field started with Pressman's 1964 discovery<sup>1</sup> that valinomycin and other natural antibiotics increase the permeability of lipid bilayer membranes through the selective binding of potassium ion, and with Pedersen's finding<sup>2</sup> that macrocyclic polyethers (crowns) are able to complex salts of alkali metal ions and dissolve them in organic media. Since then, the topic of ion recognition by synthetic receptors has developed tremendously and is still quite fertile as testified to by the recent review articles and books concerning cation<sup>3-7</sup> and anion<sup>8,9</sup> complexation and sensing. More recently, a special role in ion



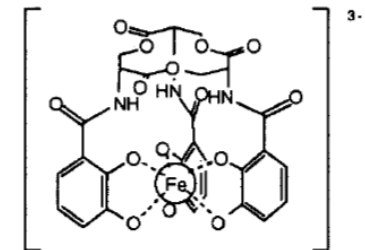
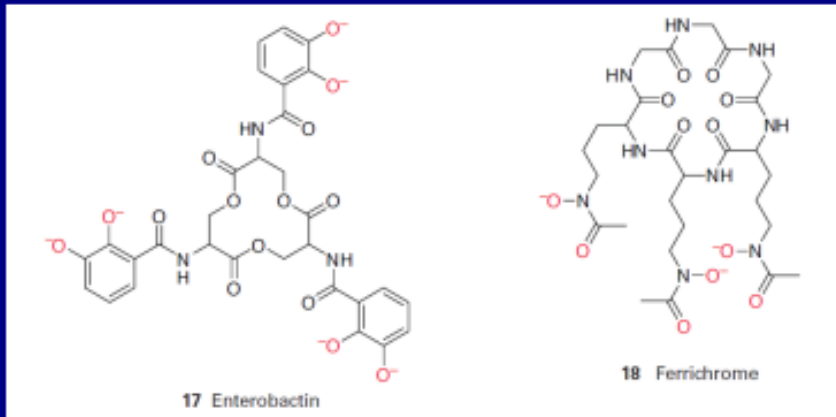
$$K_{K^+}/K_{Na^+} = 10^5$$

A pH fisiologico 7.4 la concentrazione di  $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$  - in equilibrio con  $\text{Fe}(\text{OH})_3$  - è circa  $10^{-18}\text{M}$ , mentre per le condizioni ottimali di crescita i micro-organismi richiedono una concentrazione intracellulare di circa  $10^{-7}\text{M}$

### Siderofori:

I siderofori sono piccoli leganti polidentati con O/N donatori che hanno grande affinità per lo ione hard Fe(III) (e scarsa per Fe(II)) e lo rendono solubile attraverso la formazione di complessi ottaedrici ad alto spin.

Oltre al complesso con citrato, vi sono siderofori basati su fenolati o catecolati come l'*enterobactina* (costante di associazione  $10^{52}$ ) e basati su idrossammati come l'esapeptide ciclico *ferrichrome* (3 glicine + 3 N-idrossil-L-ornitine).

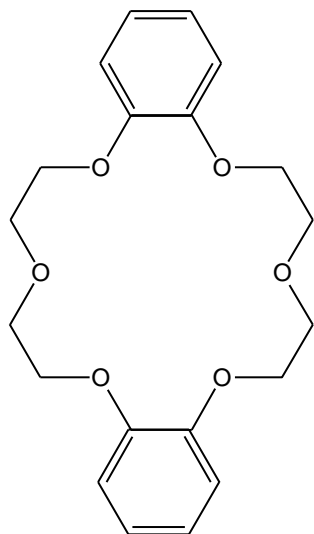
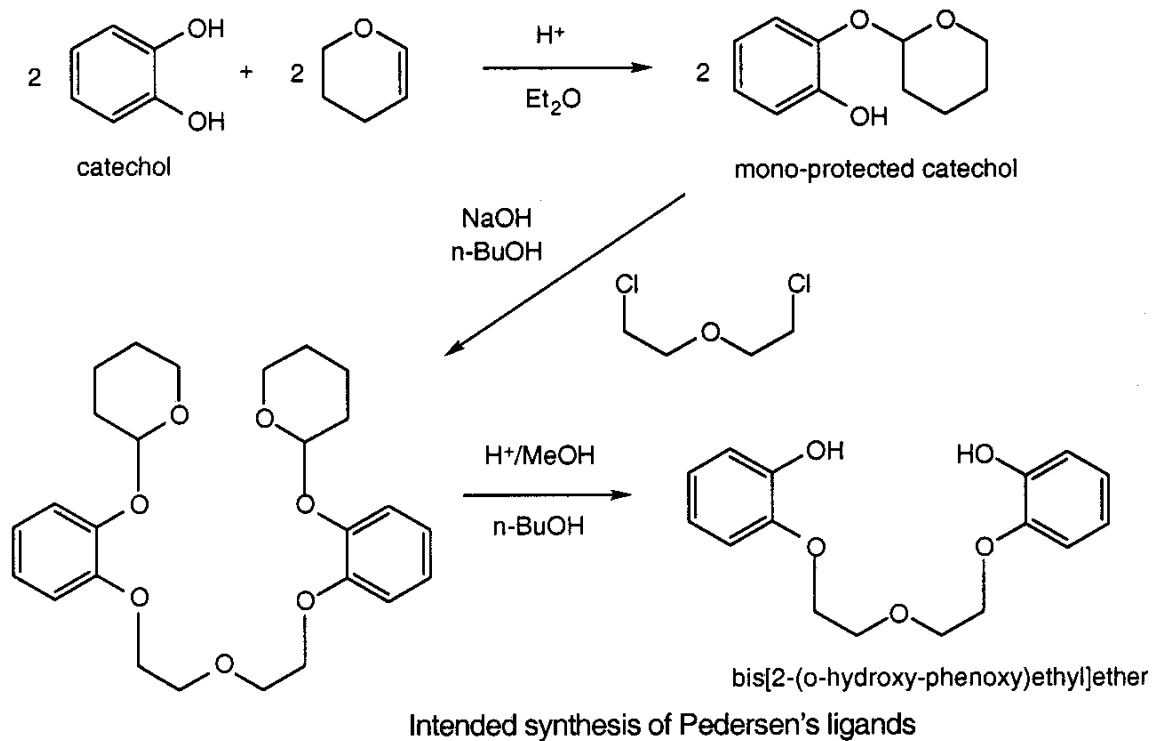
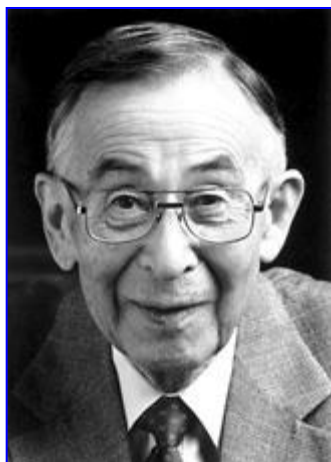


[enterobactin-Fe(III)]<sup>3-</sup> complex

L'enterobactina- $\text{Fe}^{\text{III}}$  complesso è anche chirale; la struttura del triestere ciclico, che è chirale in quanto ha tre carboni asimmetrici adiacenti agli azoti, impone la configurazione

$\Delta$  dei catecolati intorno al Fe(III); il suo enantiomero  $\Lambda$  coordina il ferro, ma non è in grado di rilasciarlo ai batteri perché non è riconosciuto dai recettori dell'enterobactina.

PEDERSEN (Nobel 1987), studio di leganti multi dentati per rame e vanadio (Dupont, anni '60)



dibenzo[18]crown-6 - sottoprodotto

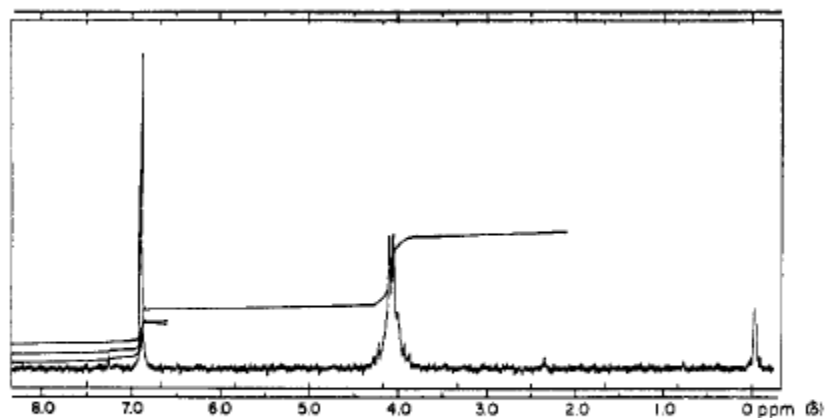


Figure 2. Nmr spectrum of dibenzo-18-crown-6 (XXVII): (upper) multiplet, 4.11 ppm downfield from TMS, area ratio 2.2; (lower) singlet, 6.92 ppm downfield from TMS, area ratio 1.0.

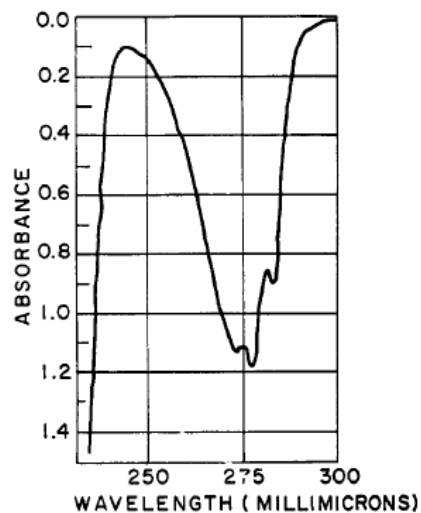


Figure 7. Ultraviolet spectrum of dibenzo-18-crown-6 (XXVII) in cyclohexane, concentration 0.000255 mole/l., cell path 1 cm;  $\lambda_{\max}$  274 ( $\epsilon$  4400), 278 ( $\epsilon$  4700), and 283 ( $\epsilon$  3600).

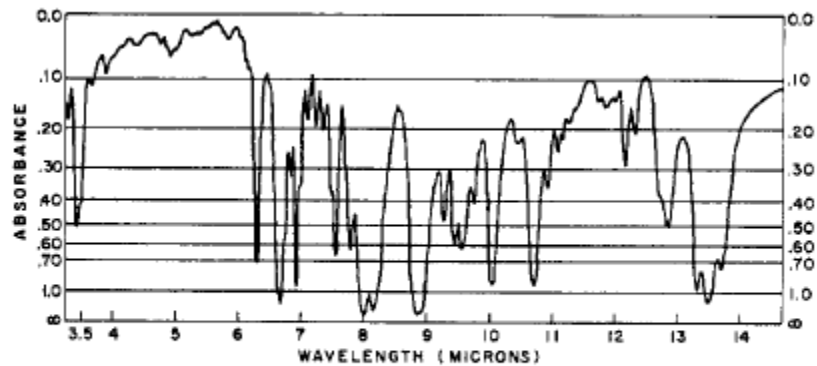


Figure 4. Infrared spectrum of dibenzo-18-crown-6 (XXVIII), KBr pellet.

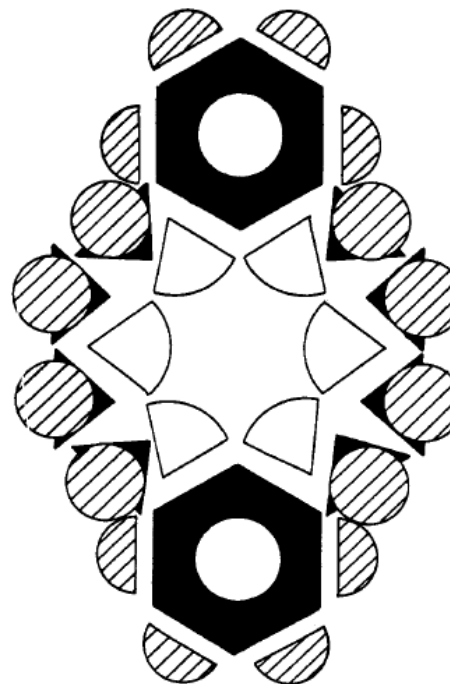
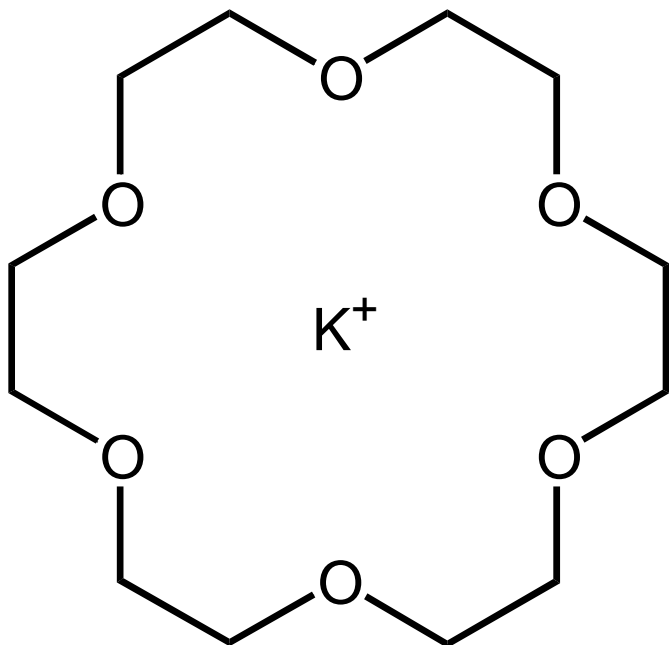


Figure 9. Courtauld model of dibenzo-18-crown-6 (XXVIII).

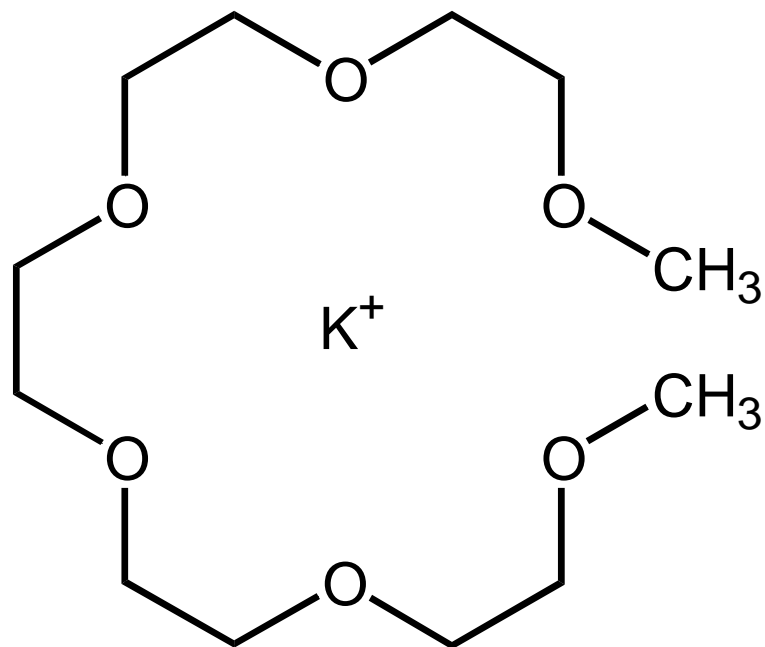
ETERI CORONA (Crown Ethers)  
(monocilci = CORANDI)

[18]crown-6

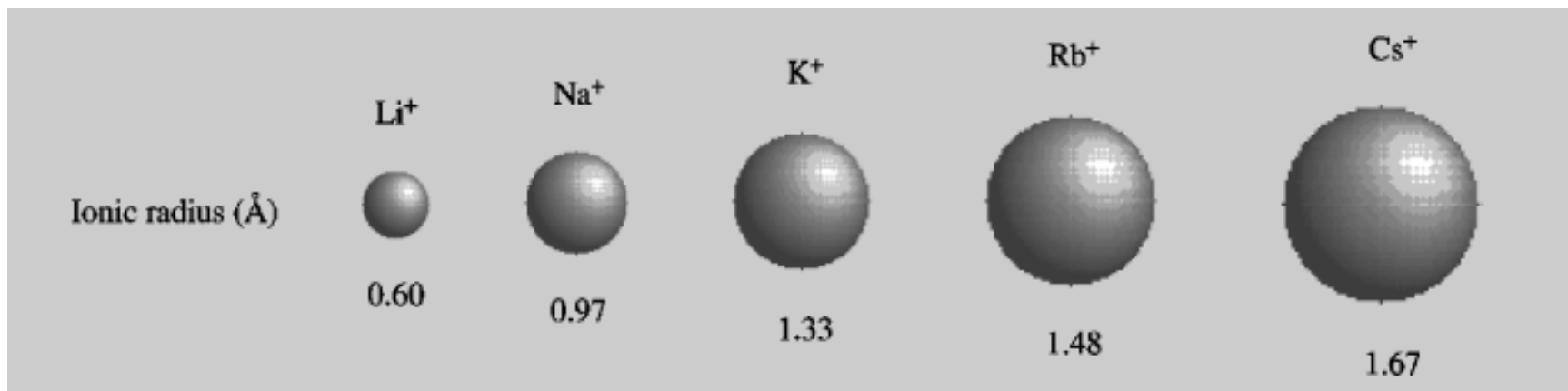


$\log K = 6.08$

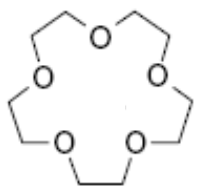
Pentametilene-glicol-dietilere



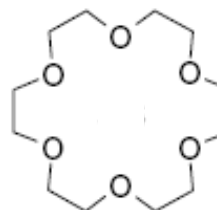
$\log K = 2.3$



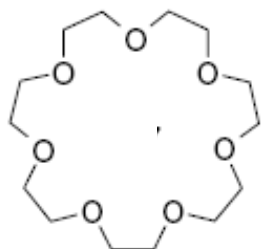
### OPTIMAL SPATIAL FIT or SIZE-MATCH



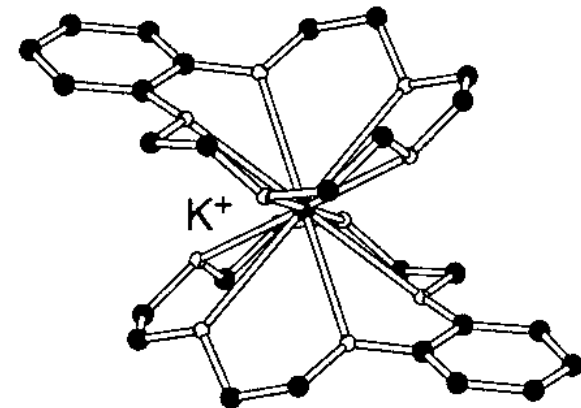
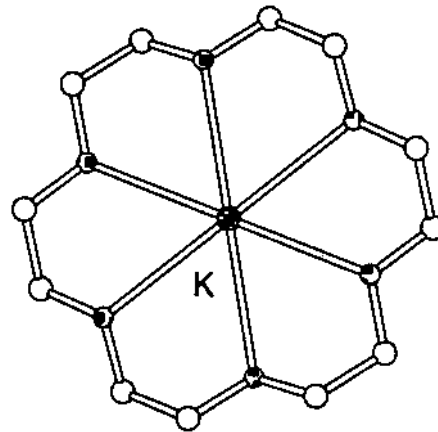
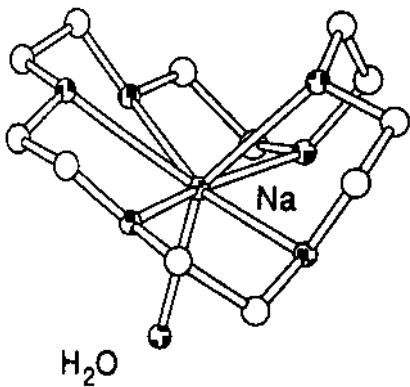
[15]crown-5  
Complementary to Na<sup>+</sup>



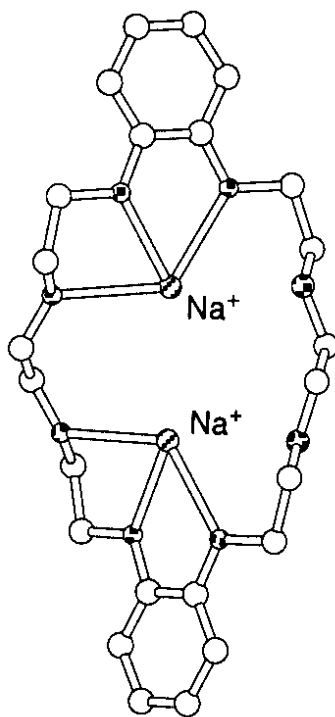
[18]crown-6  
Complementary to K<sup>+</sup>



[21]crown-7  
Complementary to Cs<sup>+</sup>

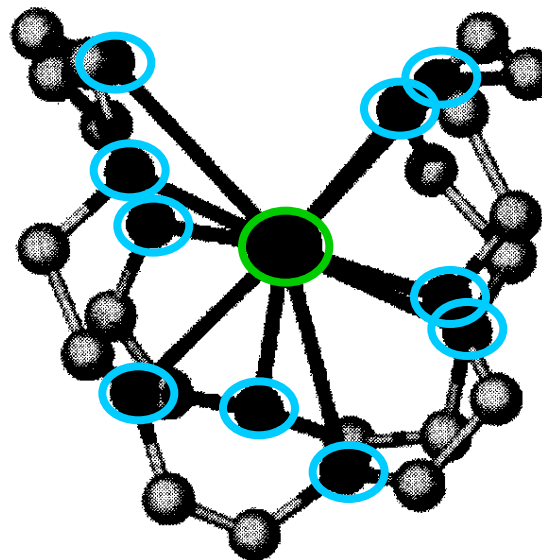


The crystal structure of two benzo-15-crown-5 molecules forming a 'sandwich complex' with a potassium cation



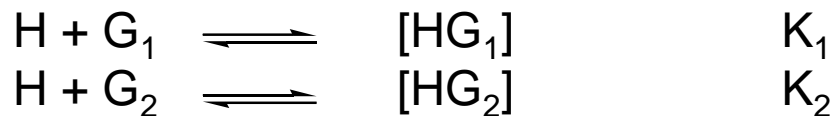
The crystal structure of  $2\text{Na}^+ - [24]\text{crown-8}$

[30]crown-10





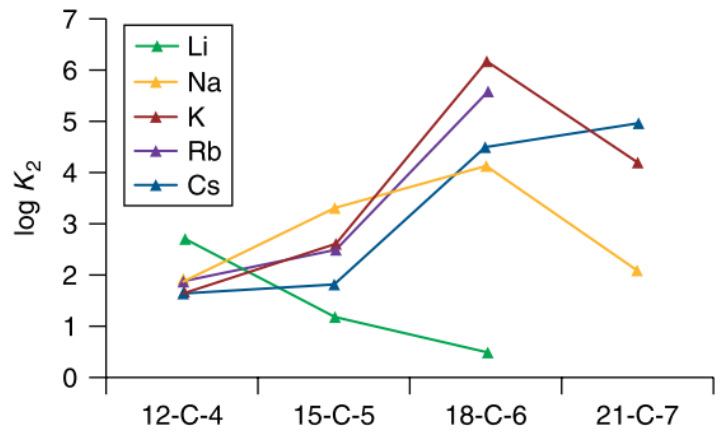
**Thermodynamic selectivity:** ratio of the binding constant for one guest over another:



$$\text{selectivity} = \frac{K_1}{K_2}$$

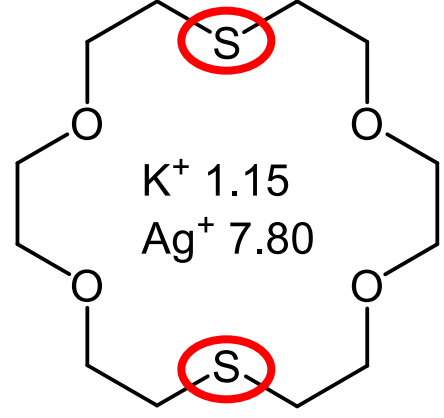
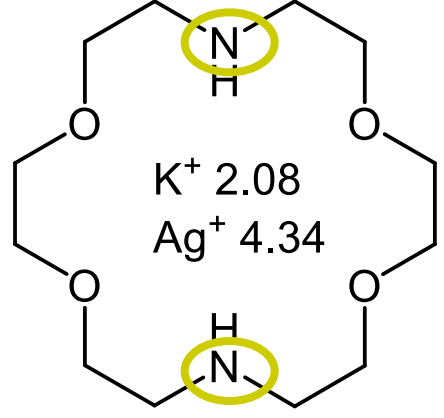
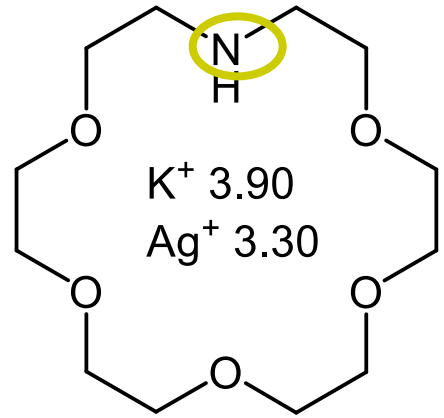
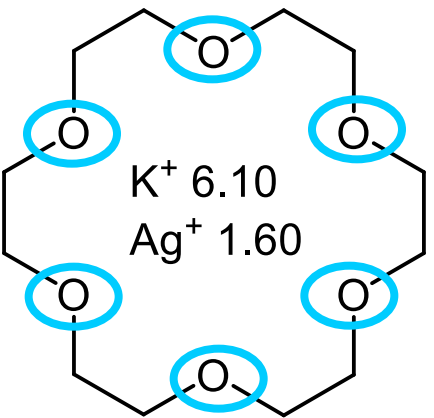
Needs to be calculated at equilibrium in the same conditions (**Temperature! Solvent!**)

Size-match o optimal-fit



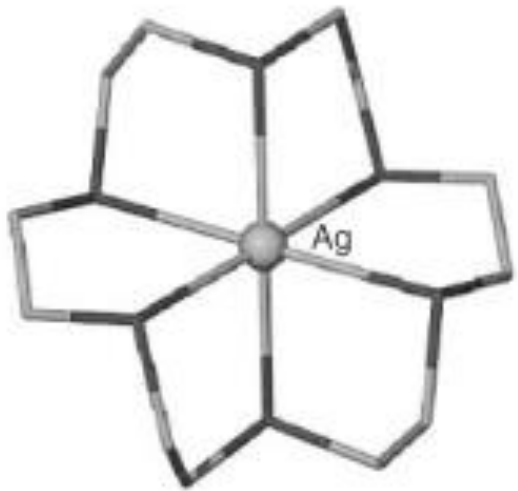
**Kinetic selectivity:** preference of a host for the fastest transformation of a substrate over another (Michaelis-Menten model)

- transport
- catalysis
- sensing and signaling



Aza-crown

Tio-crown



# Selettività

Natura degli atomi donatori (O vs N VdW radius simile: hard/soft acid-base theory)

Numero e orientazione degli atomi donatori (pesa di più per cationi di M transizione, che per alcalini; alcalinoterrosi e REM).

Carica elettrostatica dello ione: a parità di raggio ionico, carica maggiore può corrispondere a maggiore energia di idratazione (*cfr*  $\text{Ca}^{2+}$  vs  $\text{Na}^+$ );

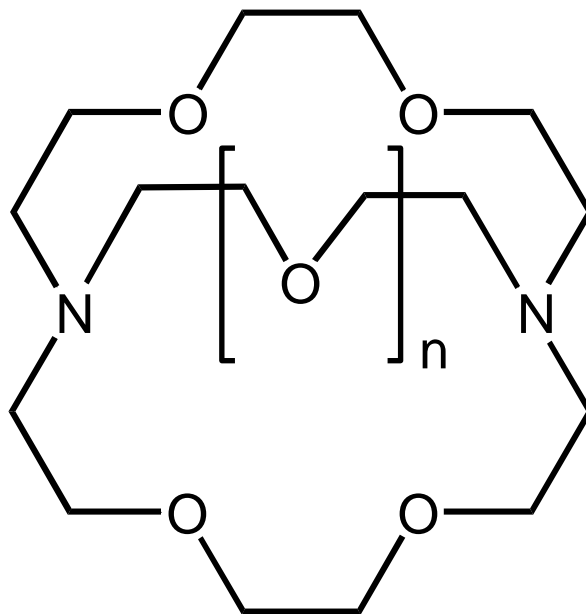
Energie libere di solvatazione dell'host e del catione

Solvente – competitivo per i dipoli/ costante dielettrica/ legami idrogeno/capacità coordinanti

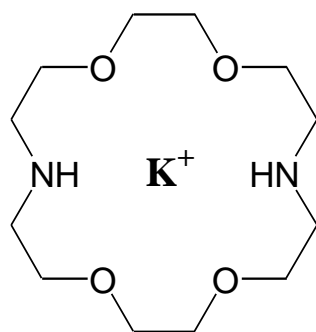
Natura del contro-ione (interazione con solvente/catione/solvatazione)

Cinetica di complessazione

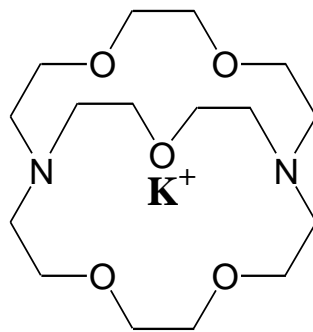
LEHN (Nobel 1987), estensione dei sistemi monociclici a sist. biciclici (CRIPTANDI, anni '60)



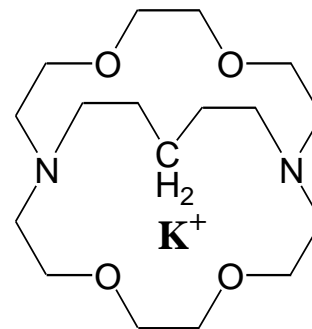
Na<sup>+</sup>  
n = 1, criptando [2,2,1]  
n = 2, criptando [2,2,2]  
K<sup>+</sup>



logK = 2.0



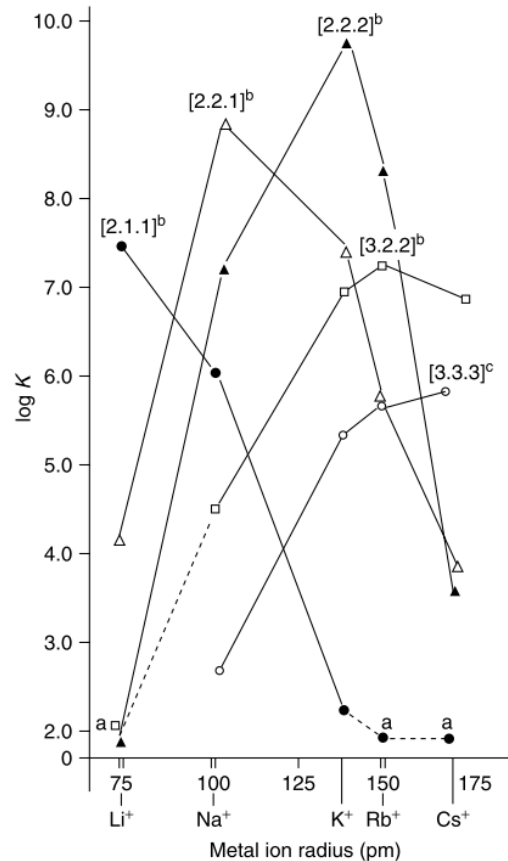
logK = 7.0



logK = 5.4

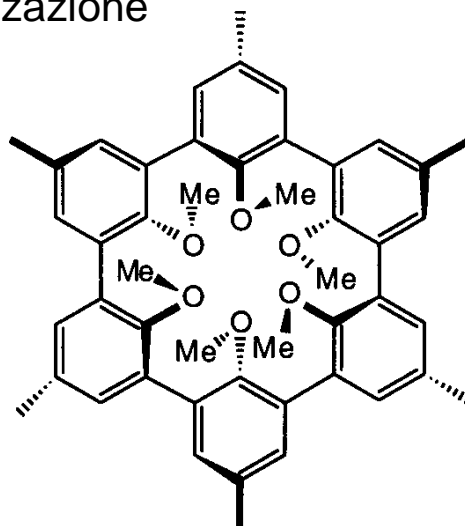
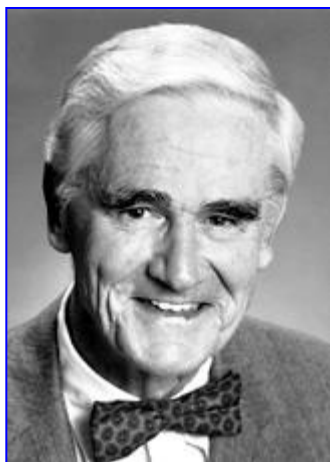
# Selettività

Size-match o optimal-fit (progressivamente più determinante aumentando la rigidità /preorganizzazione dell'Host) – distanza tra i dipoli del macrociclo e la carica ionica



**Figure 2** Selectivity of cryptands among alkali metal cations (a, value reported <2.0; b, in 95% CH<sub>3</sub>OH; c, in methanol).

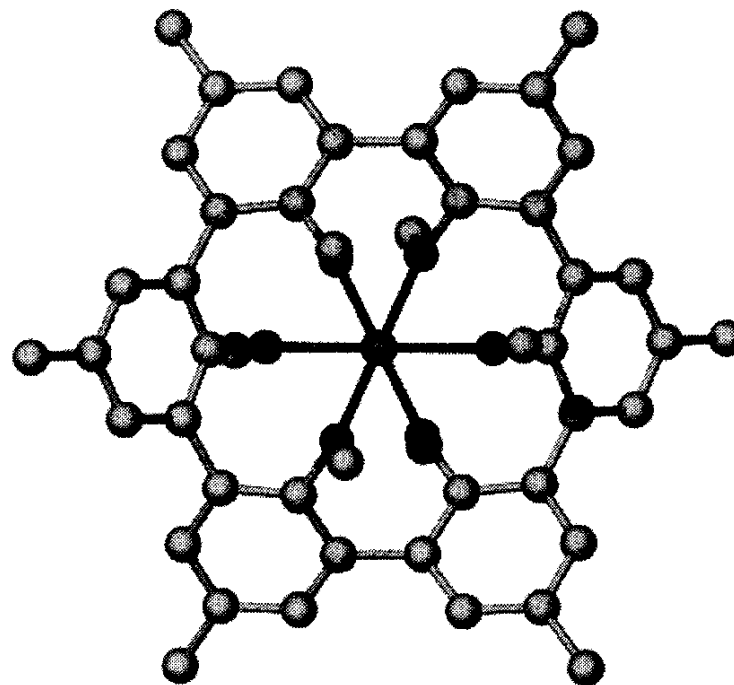
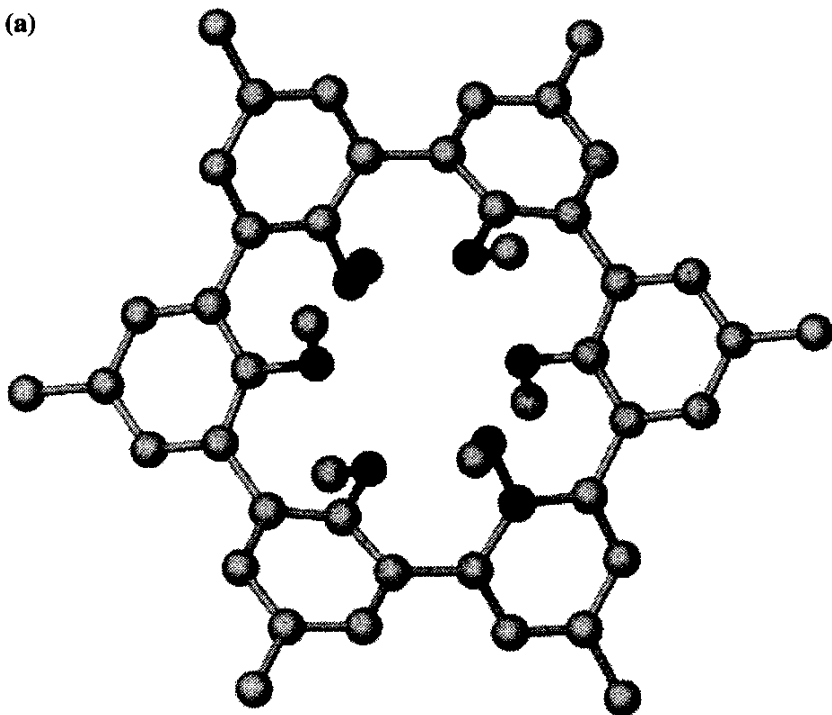
# CRAM (Nobel 1987) - preorganizzazione



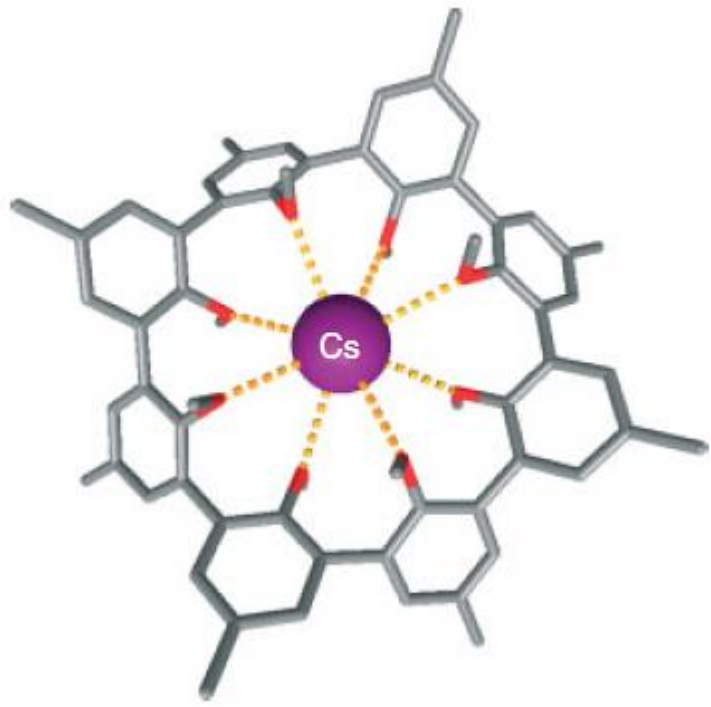
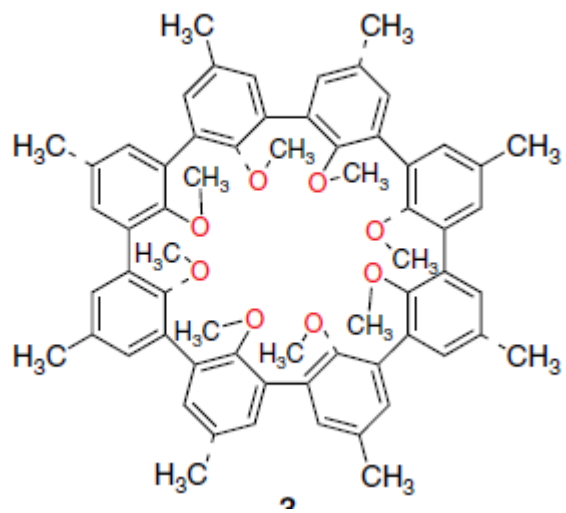
Sferandi  
(*p*-metilansolo)

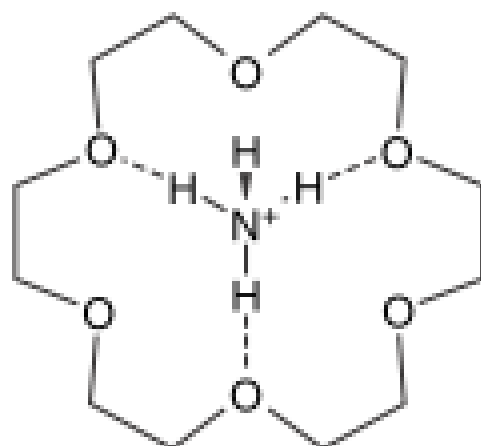
(b)

(a)

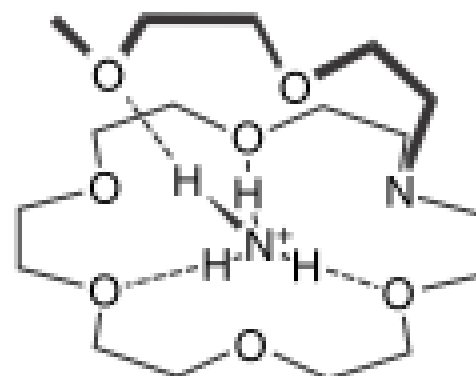


X-ray crystal structures of (a) free spherandi (3.30) and (b) its  $\text{Li}^+$  complex (after Trueblood *et al.* 1981).





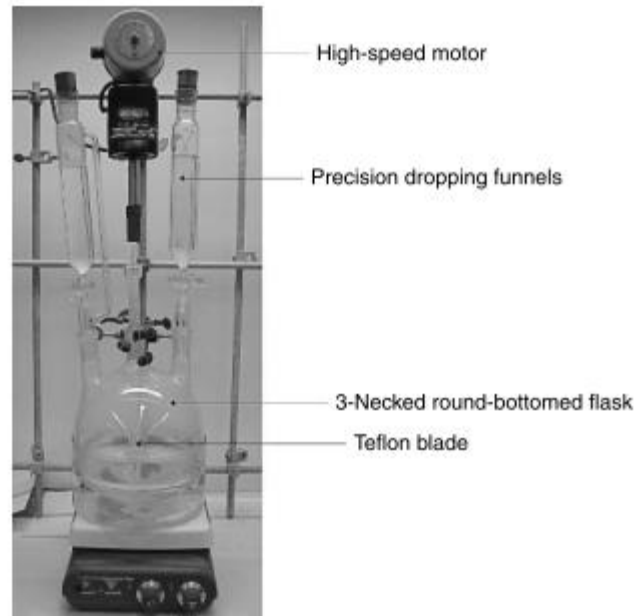
$\log K = 4.35$



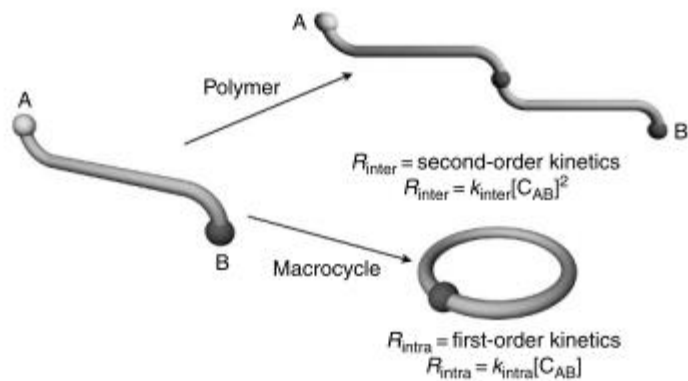
$2.23 \cdot \text{NH}_4^+$

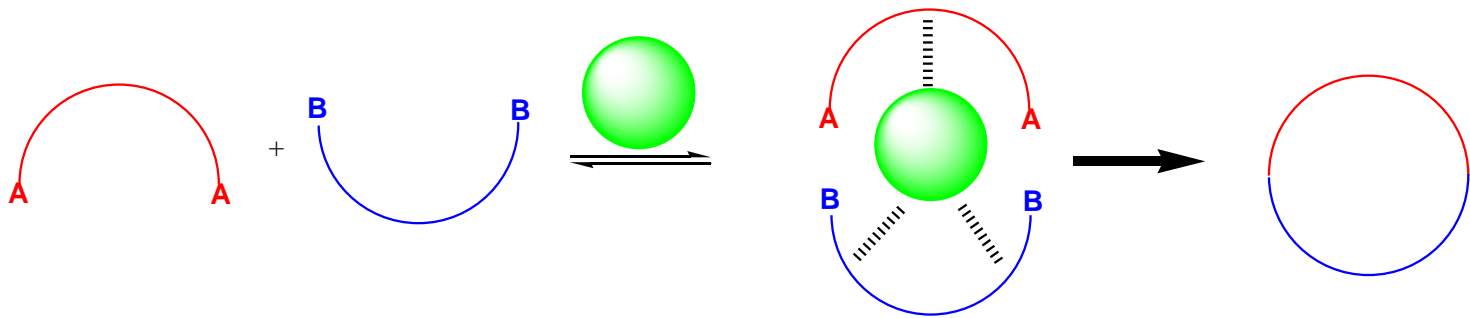
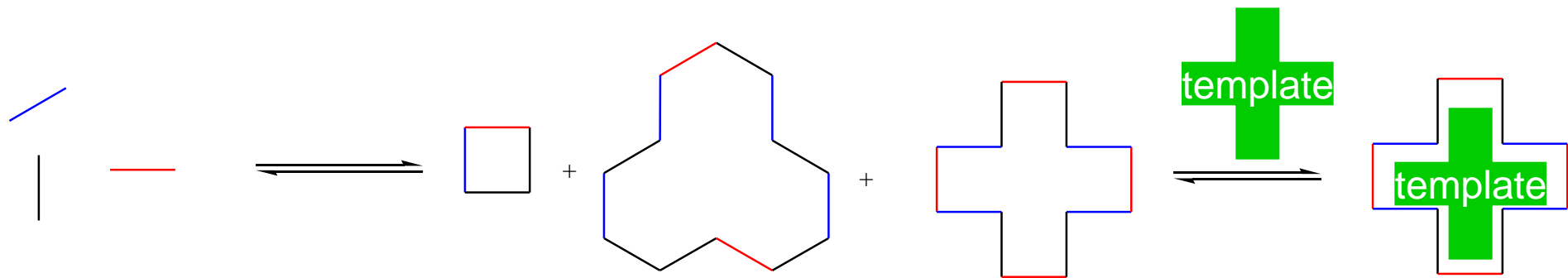
$\log K = 4.75$

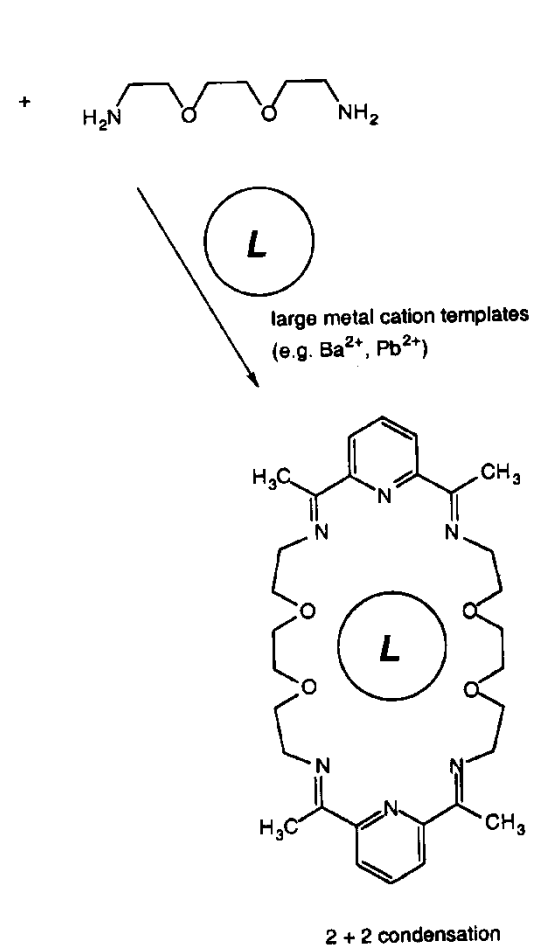
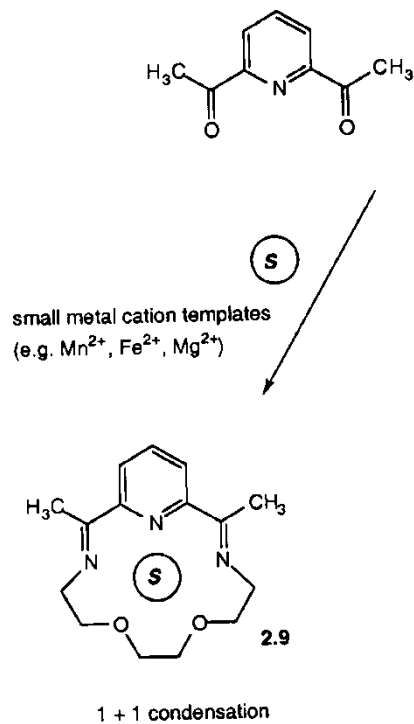
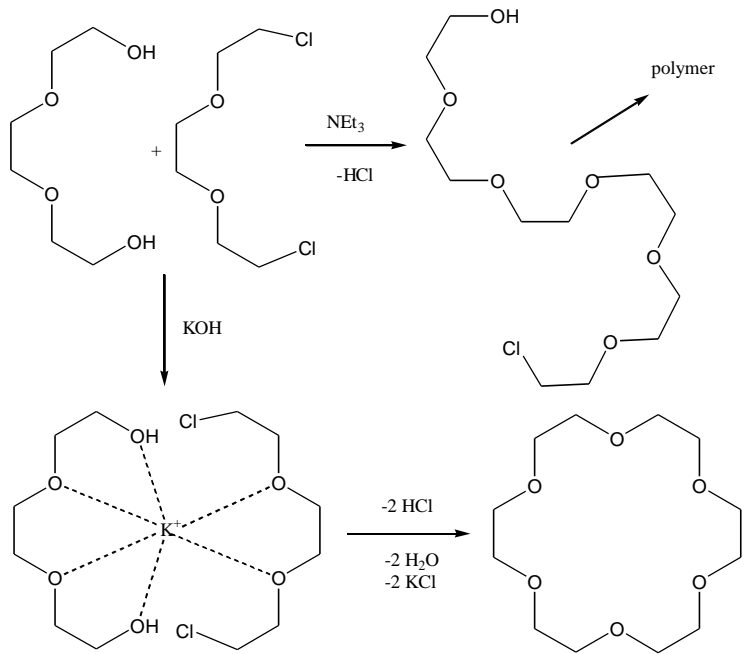


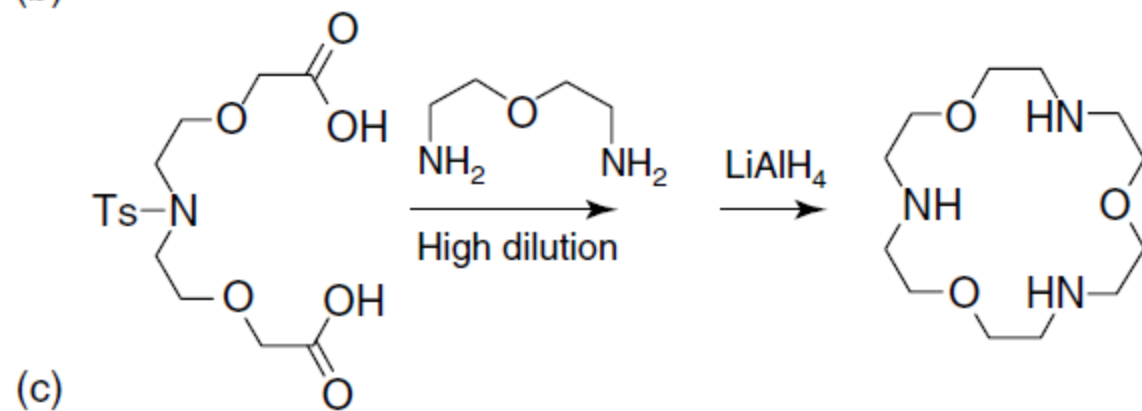
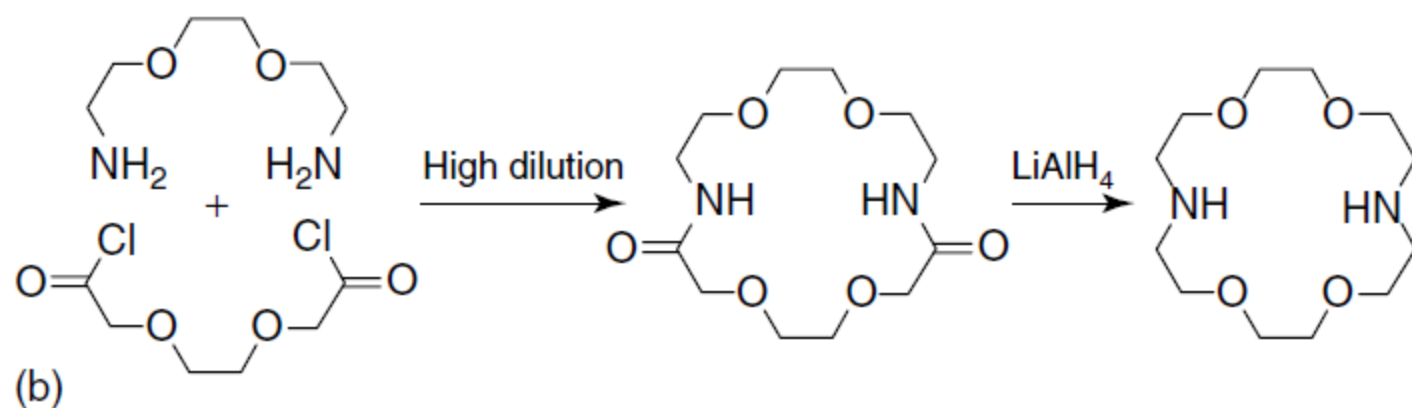
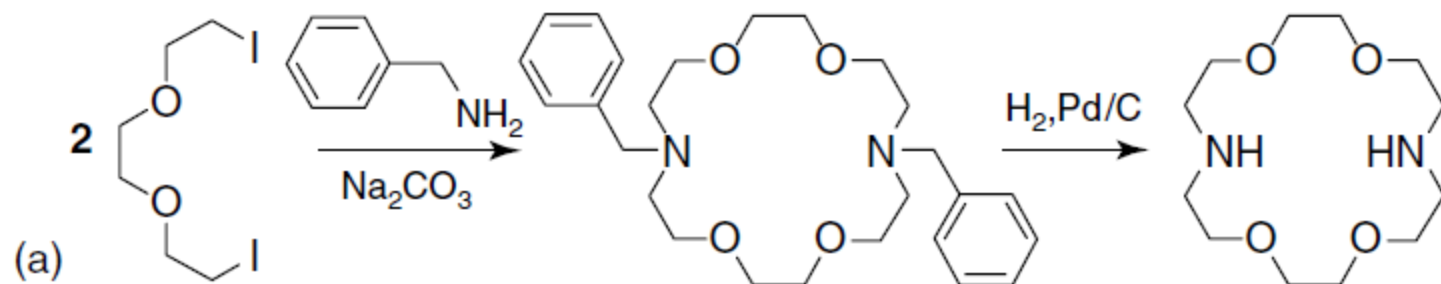


**Figure 2.1** Typical apparatus used for high-dilution synthesis.

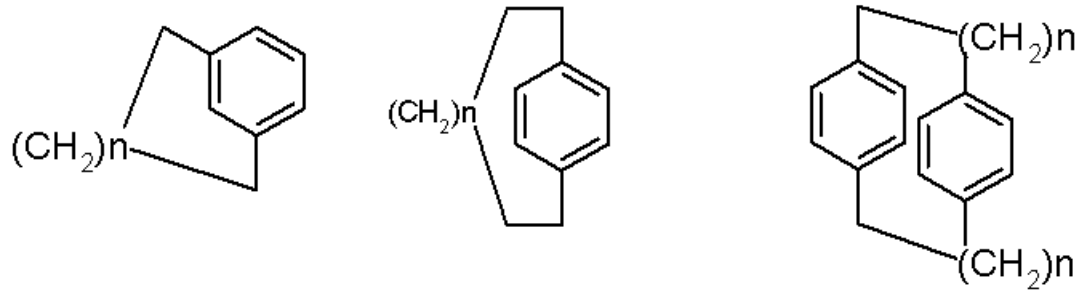




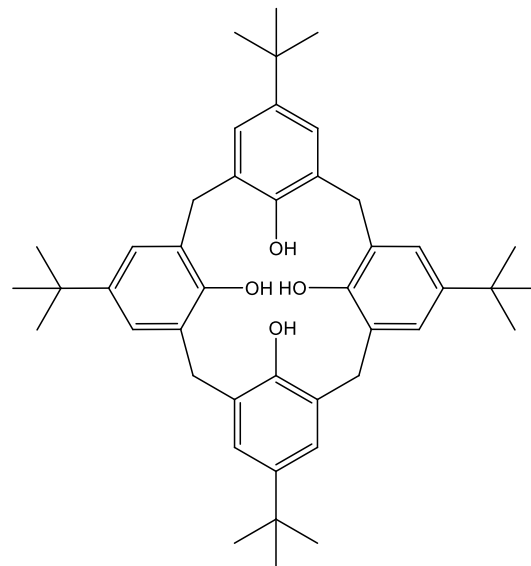




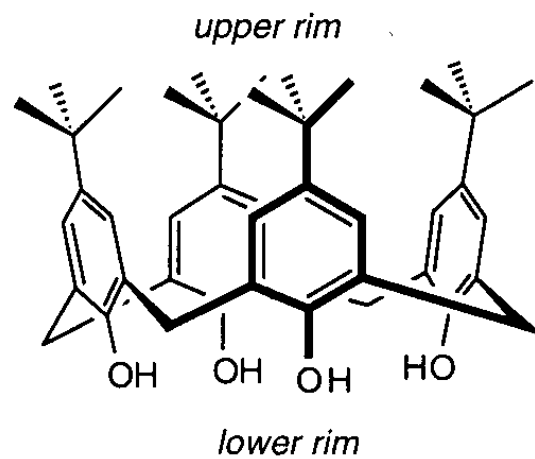
# Ciclofani



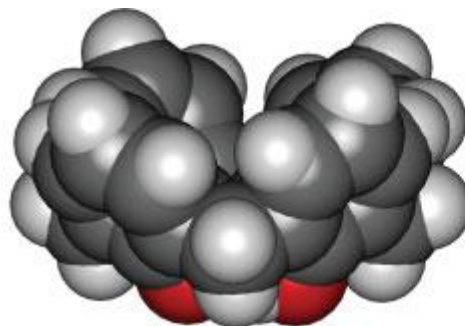
# Calix[n]areni

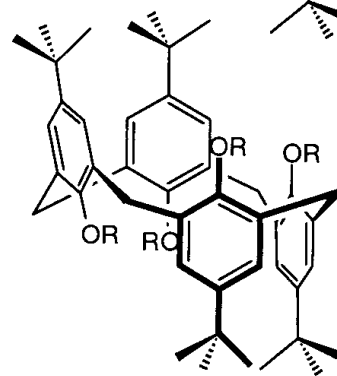
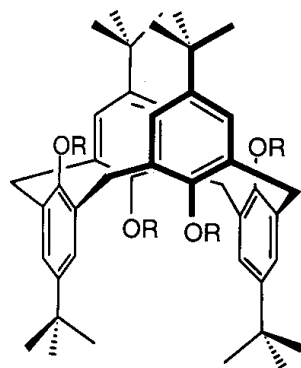
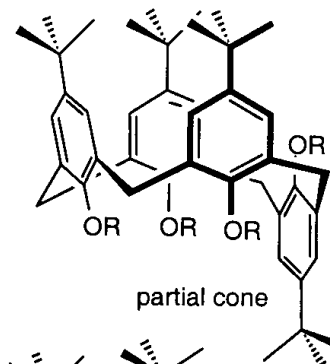
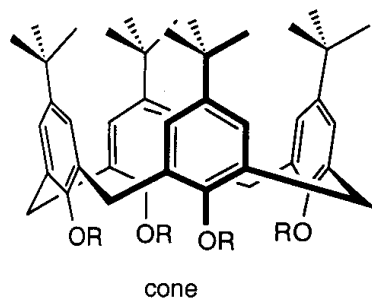


# Calix[n]areni

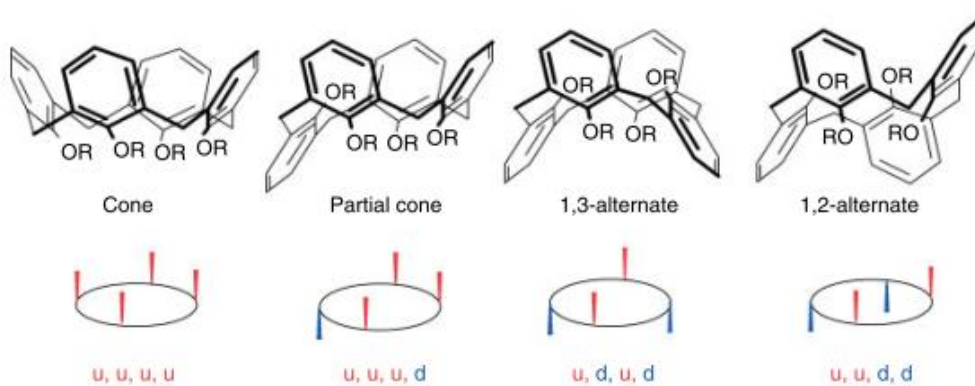


*p*-tert-Butylcalix[4]arene.



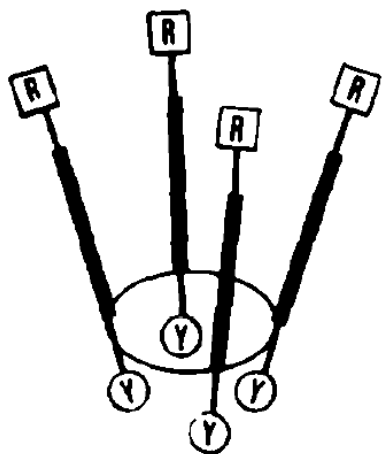


Conformations adopted by calix[4]arenes.

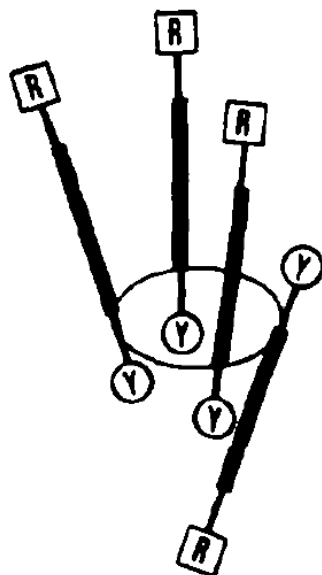


Calixarenes, which are [1<sub>n</sub>]metacyclophanes comprising phenolic and methylene units,<sup>1</sup> are conformationally flexible compounds. The smallest of the known calixarenes are the cyclic tetramers, designated as calix[4]arenes (1), for which four "up-down" conformations can be specified, viz cone (all "up"), partial cone (three "up" and one "down"), 1,2-alternate (two "up" and two "down"), and 1,3-alternate (two "up" and two "down"), as illustrated in Fig. 1. Dynamic <sup>1</sup>H NMR measurements of several calix[4]arenes<sup>2-4</sup> have shown that they exist preferentially in the cone conformation but are conformationally mobile at room temperature, interconverting at a rate of ca 100 sec<sup>-1</sup>. The con-

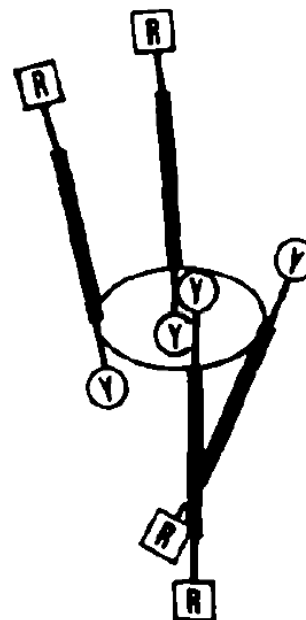




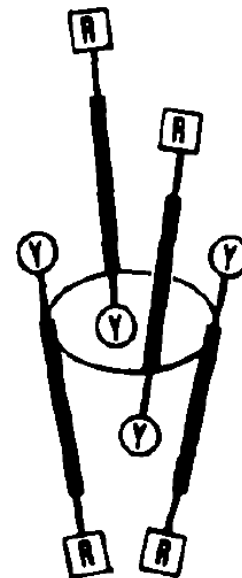
CONE



PARTIAL CONE

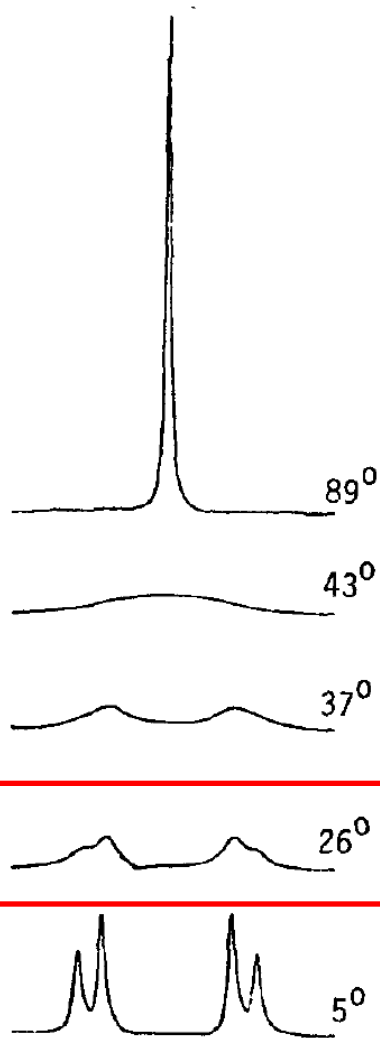


1,2 ALTERNATE

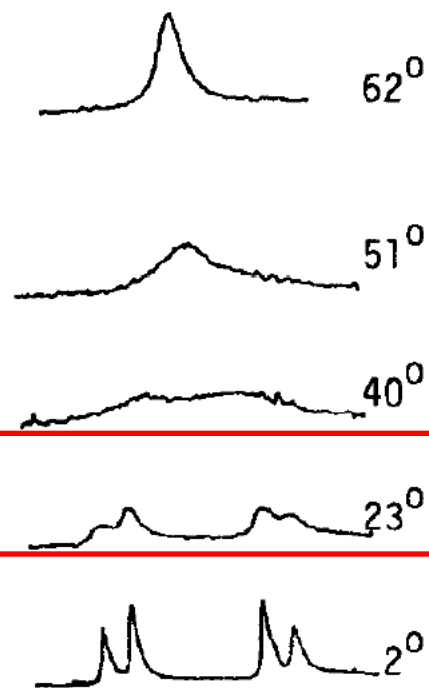


1,3 ALTERNATE

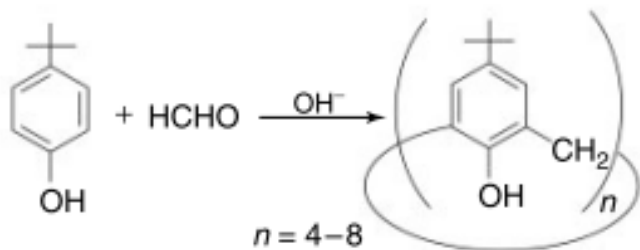
Fig. 1. Conformations of the calix[4]arenes.



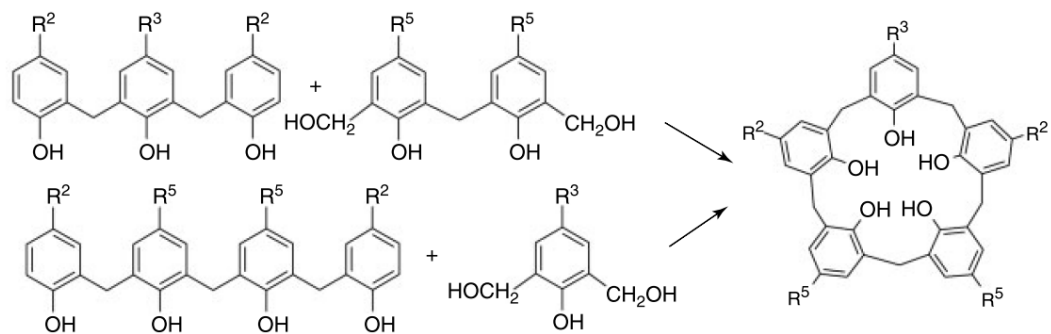
1-A. *p*-tert-butylcalix[4]arene in bromobenzene-d<sub>5</sub>



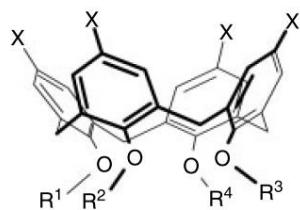
1-C. *p*-tert-butylcalix[4]arene in CDCl<sub>3</sub>



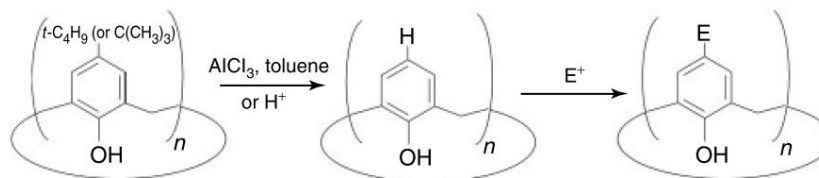
3+2 Fragment condensation

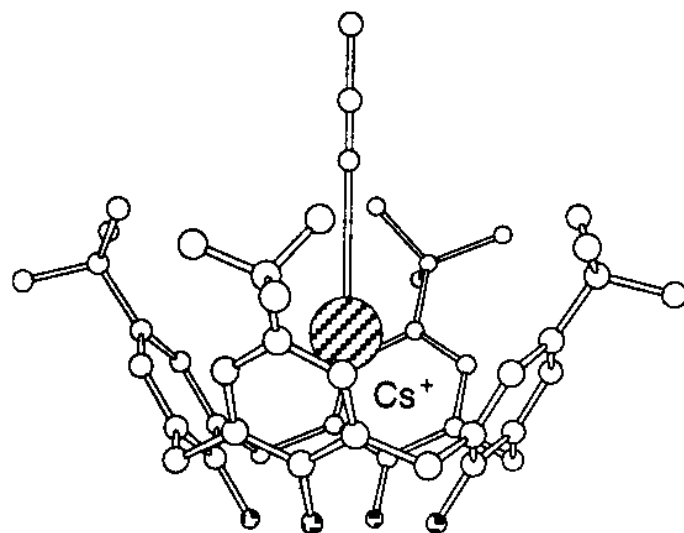
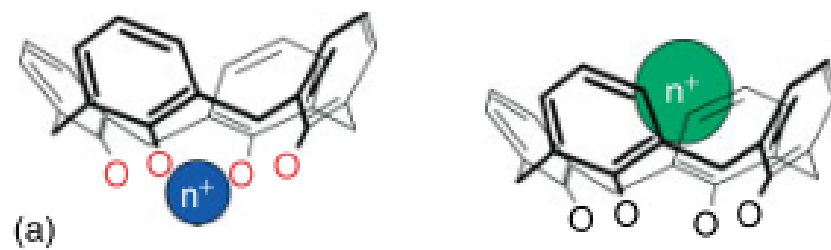


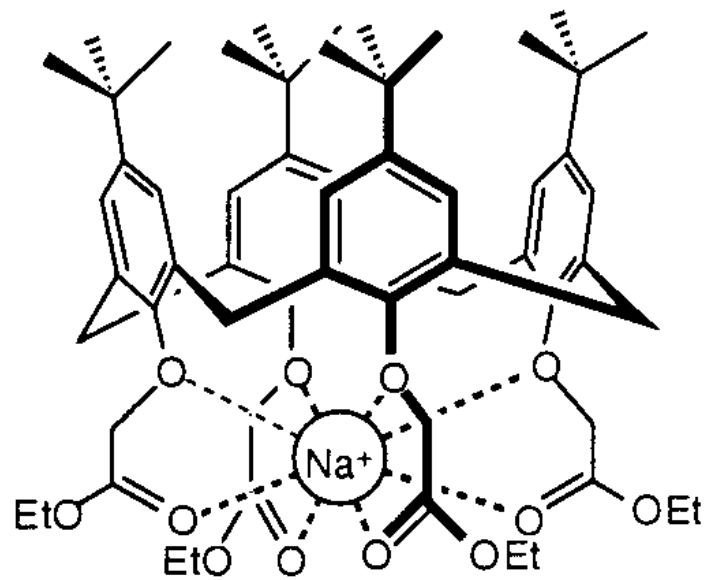
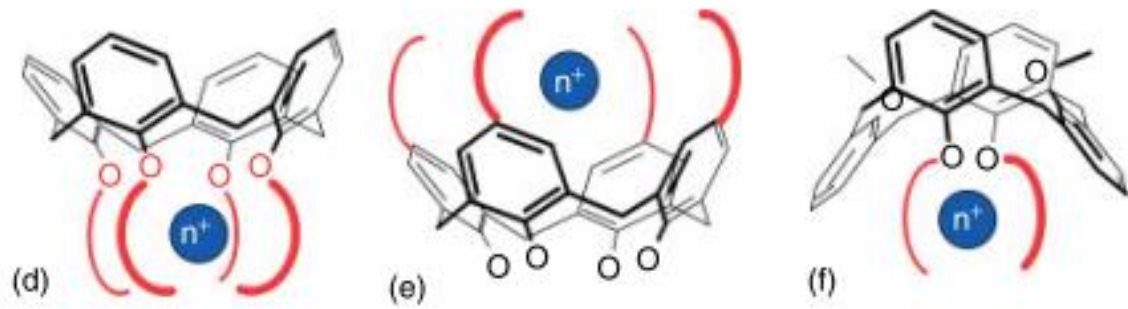
4+1 Fragment condensation

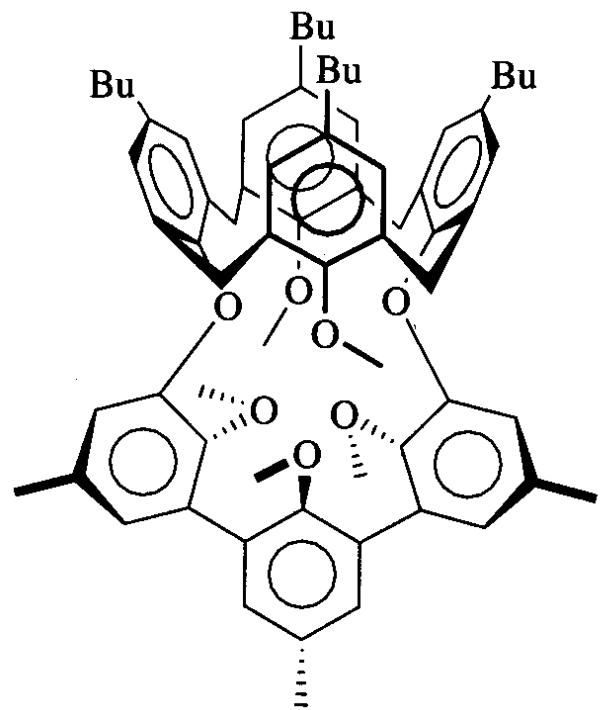


- 2a: R<sup>1</sup>-R<sup>4</sup> = alkyl
- 2b: R<sup>1</sup>, R<sup>2</sup> = alkyl, R<sup>3</sup>, R<sup>4</sup> = OH
- 2c: R<sup>1</sup>, R<sup>3</sup> = alkyl, R<sup>2</sup>, R<sup>4</sup> = OH
- 2d: R<sup>1</sup> = alkyl, R<sup>2</sup>-R<sup>4</sup> = OH
- 2e: R<sup>1</sup>-R<sup>3</sup> = alkyl, R<sup>4</sup> = OH

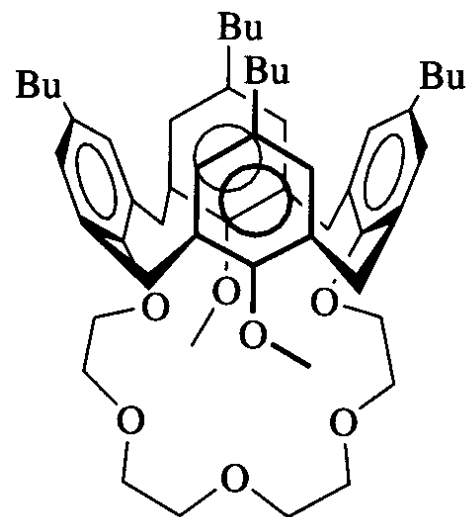




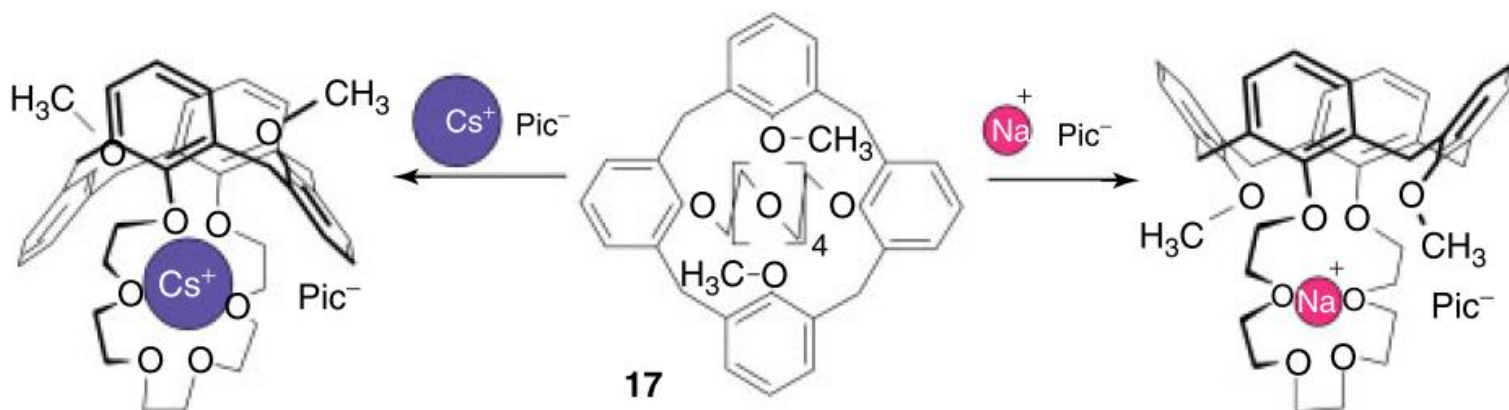




Calix-sferando

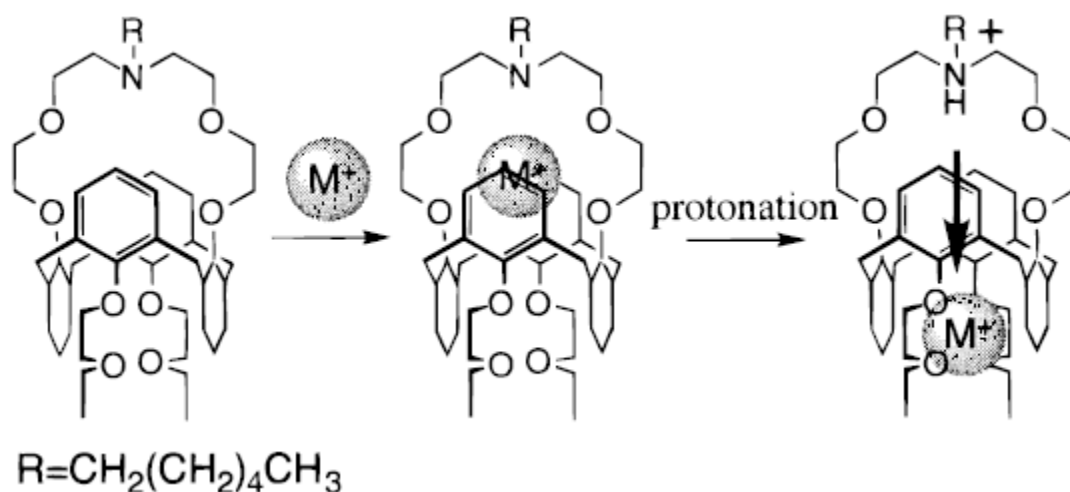


Calix-crown



# Molecular Design of a “Molecular Syringe” Mimic for Metal Cations Using a 1,3-Alternate Calix[4]arene Cavity

Atsushi Ikeda, Takanobu Tsudera, and Seiji Shinkai\*

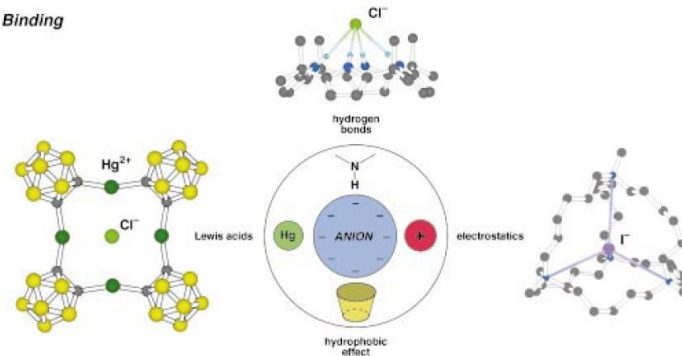


# Anion Recognition and Sensing: The State of the Art and Future Perspectives

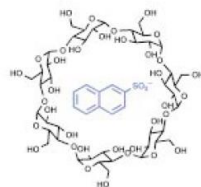
Paul D. Beer\* and Philip A. Gale\*

*Angew. Chem. Int. Ed.* 2011, 50, 1845–1848

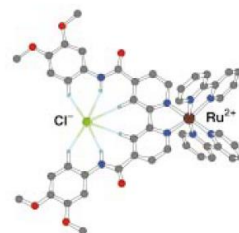
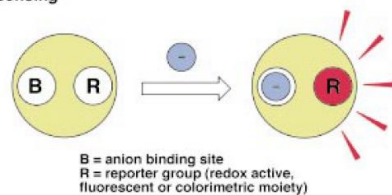
## Binding



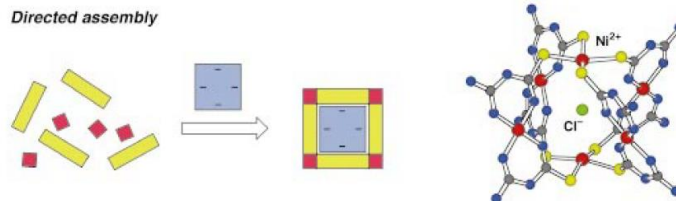
**ANGEWANDTE**  
**CHEMIE** = WILEY-VCH



## Sensing



## Directed assembly



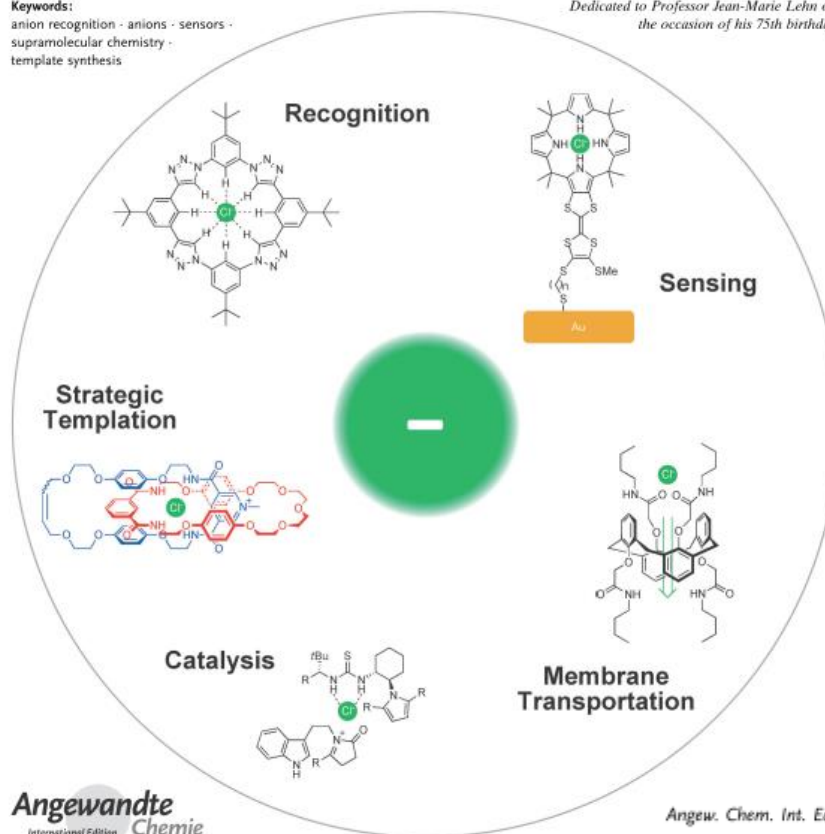


# Advances in Anion Supramolecular Chemistry: From Recognition to Chemical Applications

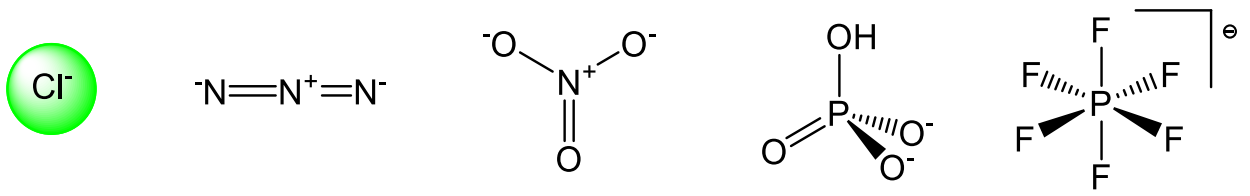
Nicholas H. Evans\* and Paul D. Beer\*

**Keywords:**  
anion recognition · anions · sensors ·  
supramolecular chemistry ·  
template synthesis

*Dedicated to Professor Jean-Marie Lehn on  
the occasion of his 75th birthday*



- anions are large and require receptors of bigger size than cations -  $r(\text{F}^-) \approx r\text{K}^+$
- large diversity of shapes and geometries (spherical, linear, trigonal, tetrahedral...)



- high free energies of hydration

$$\Delta_r G^\circ_{\text{hydr}}(\text{F}^-) = -465 \text{ kJ}\cdot\text{mol}^{-1} \qquad \Delta_r G^\circ_{\text{hydr}}(\text{K}^+) = -295 \text{ kJ}\cdot\text{mol}^{-1}$$

- anions are sensitive to pH (crucial for recognition on water)
- anions are coordinatively saturated : only weak interactions (H bond, electrostatic, Van der Waals), no strict coordination number
- Lewis bases

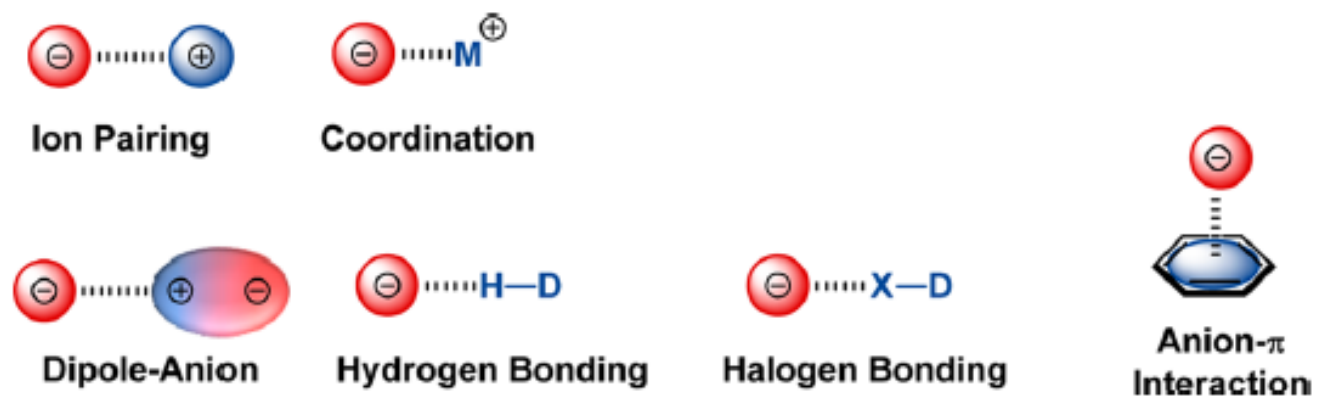


Figure 1. Representation of different interactions found in anion sensing and recognition.

Host cationici

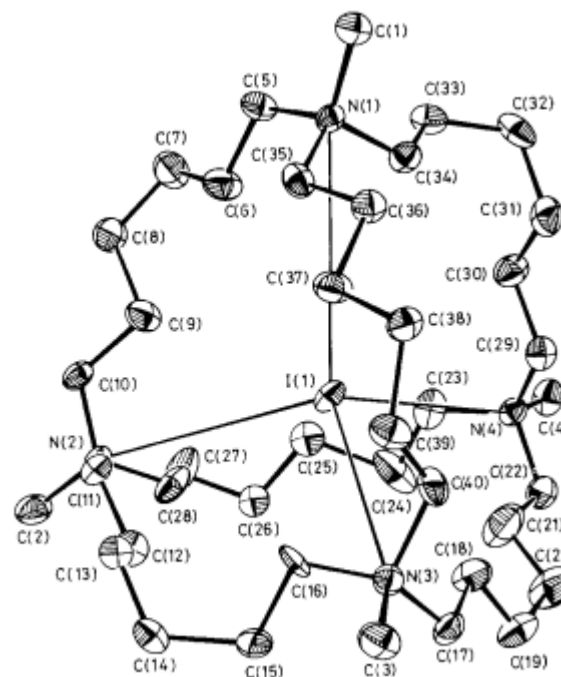
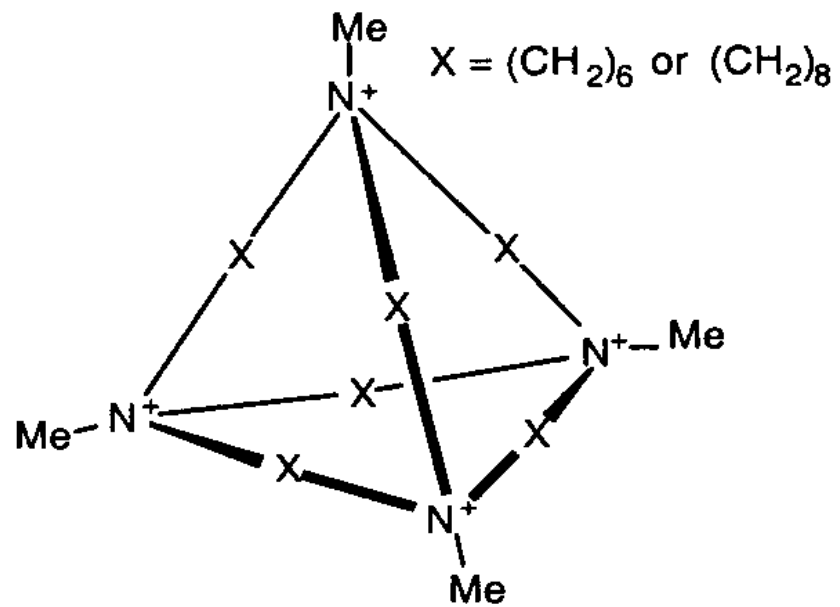
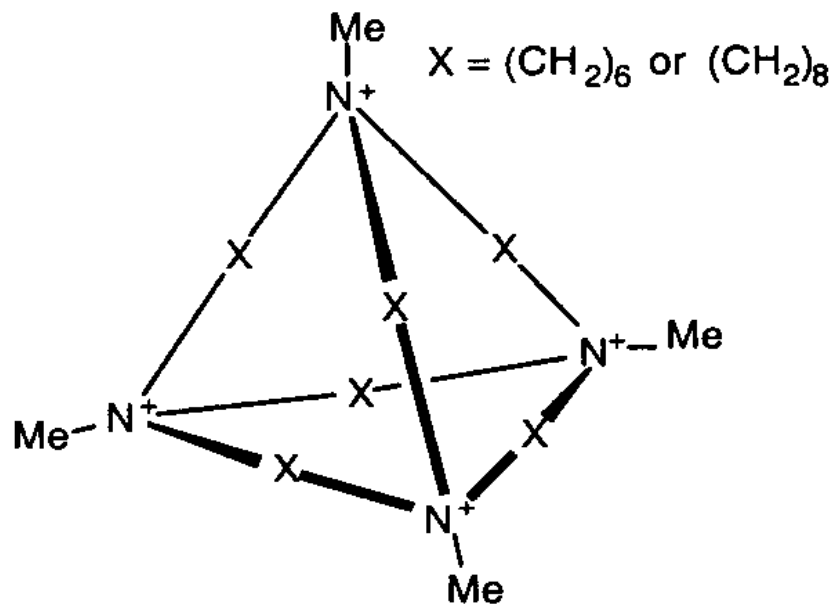


Figure 2. The X-ray crystal structure of the iodide complex of receptor 1

Host cationici

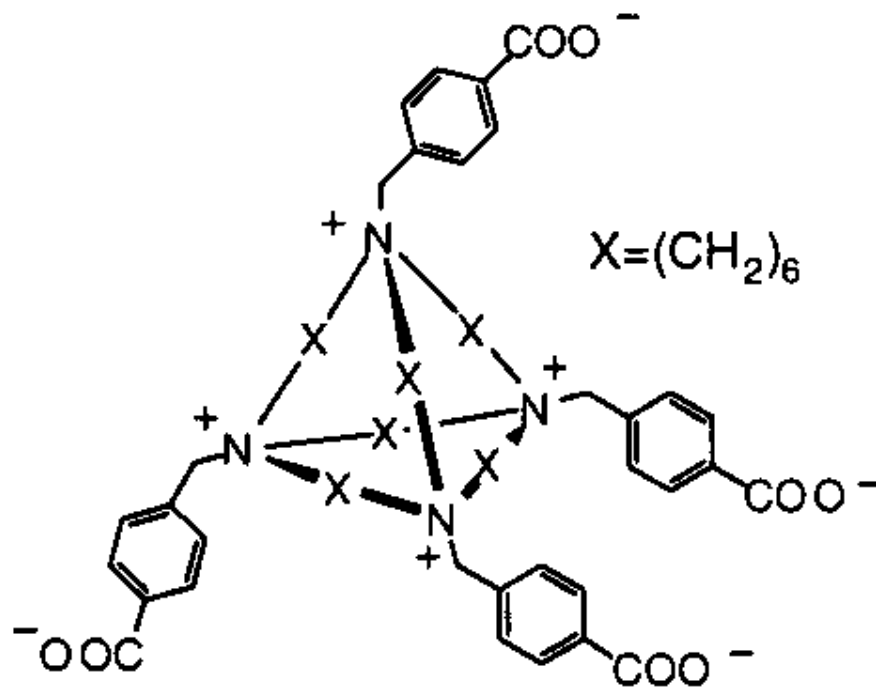


$K(\text{Br}^-) = 1020 \text{ (H}_2\text{O)}$

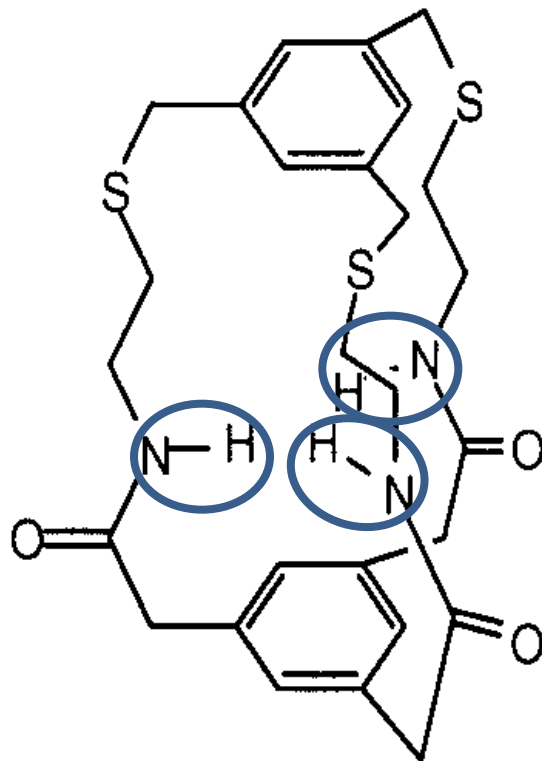
Selettività  $\ll$

$K(\text{Br}^-) = 1020 \text{ } K(\text{I}^-) = 500 \text{ } K(\text{Cl}^-) = 50$

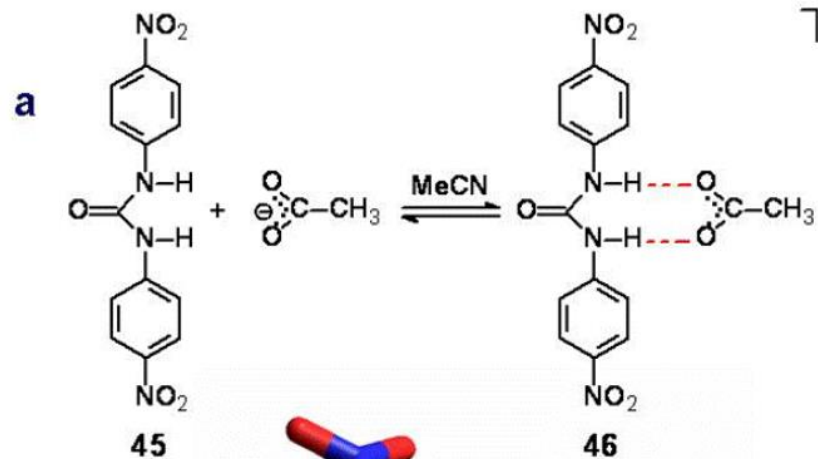
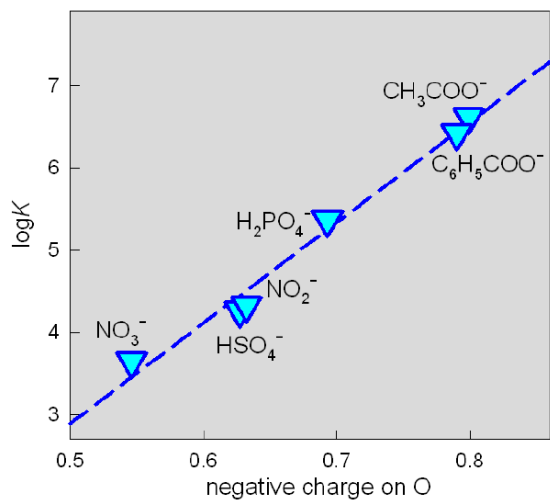
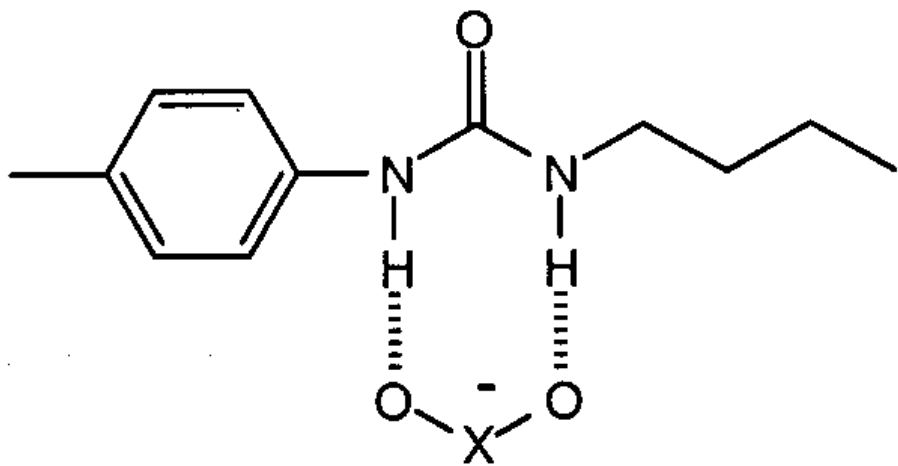
Host zwitter-ionici



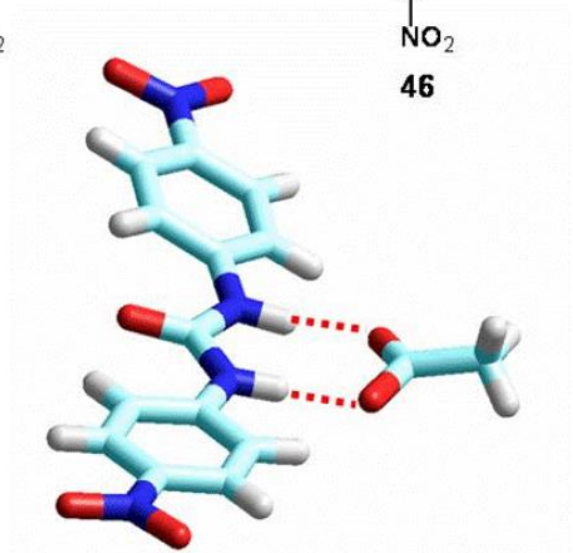
$K(\text{Br}^-) = 2150 \text{ (H}_2\text{O)}$

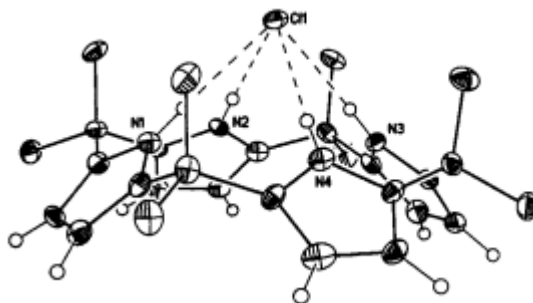
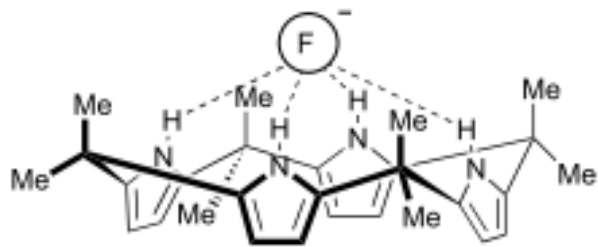


Hydrogen bonding receptor  
for fluoride anions.

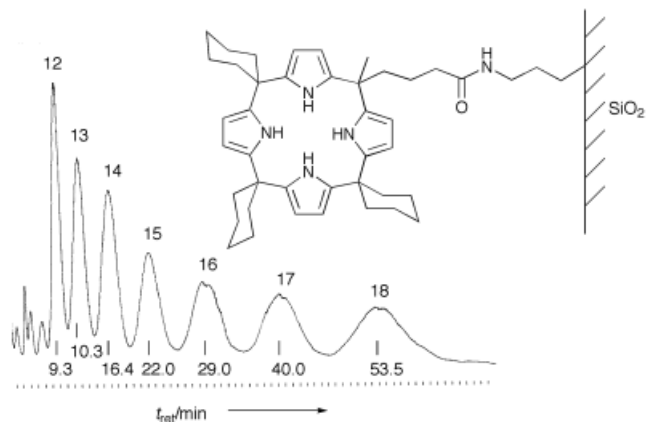


**b**

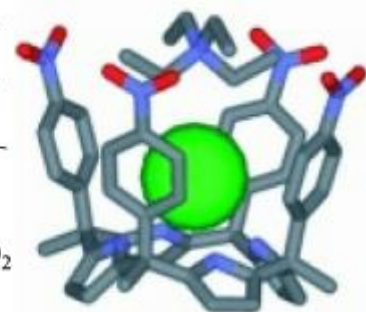
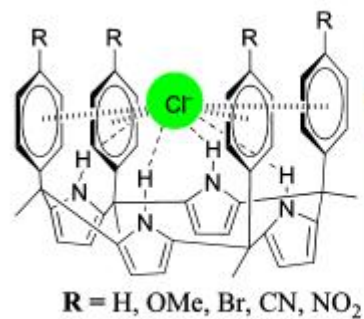




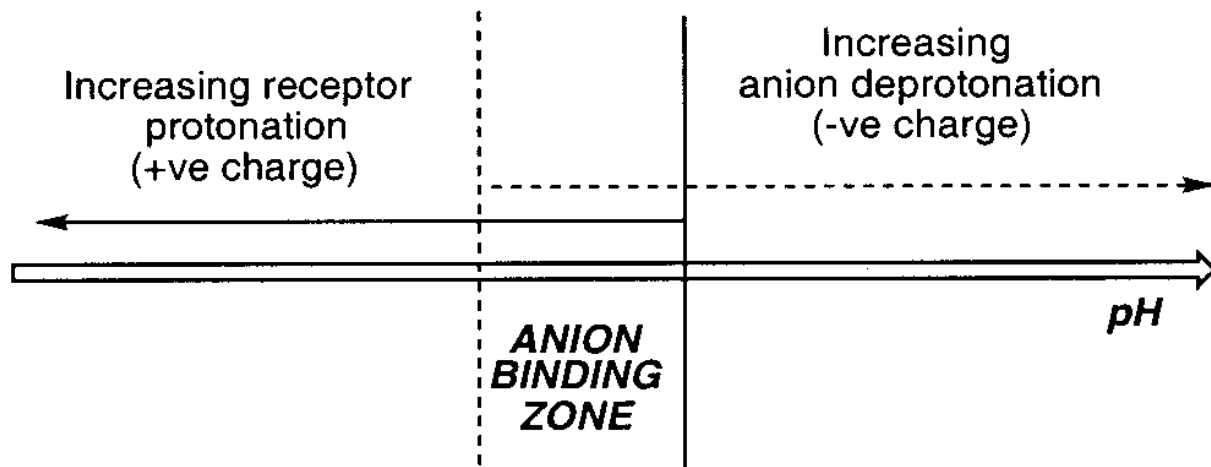
*Sessler*



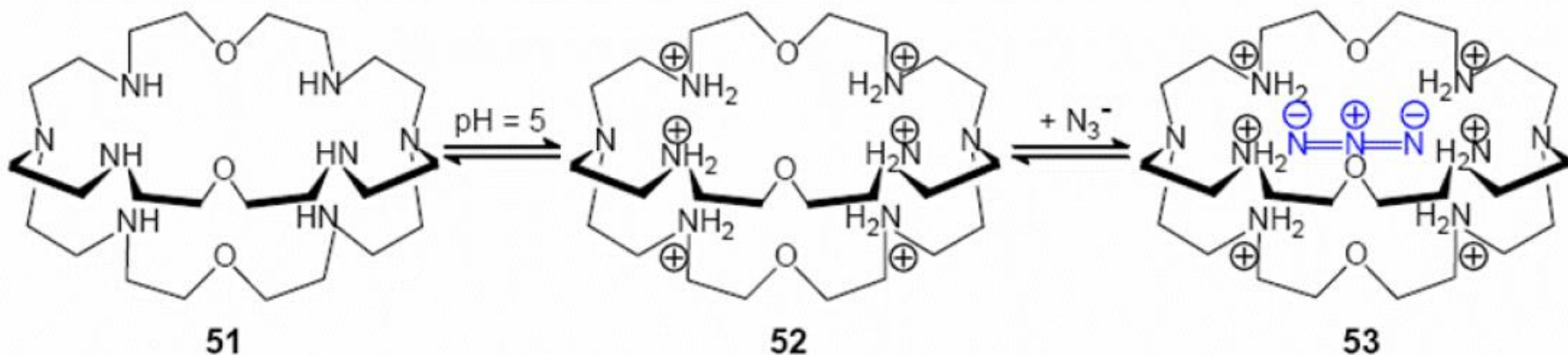
HPLC Separation of oligonucleotides of different length



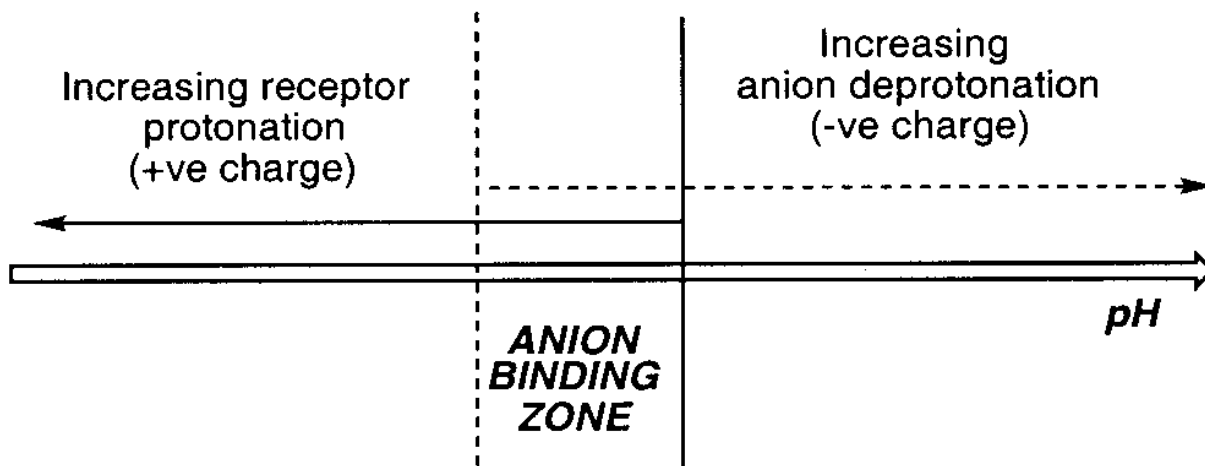




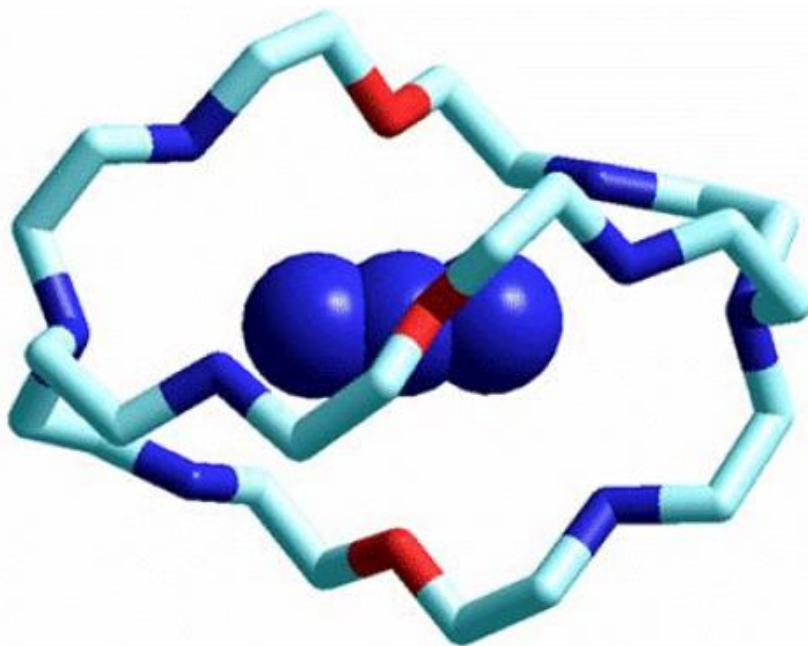
Balance between host protonation and guest deprotonation.

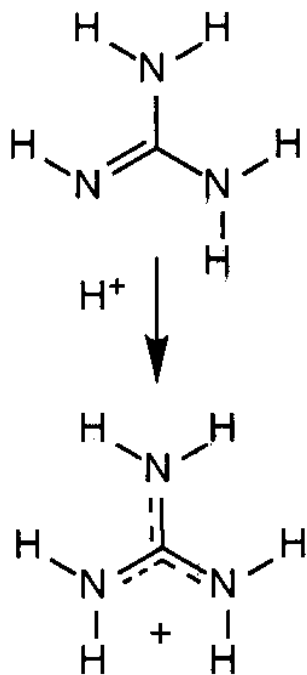


poliazamacrocicli

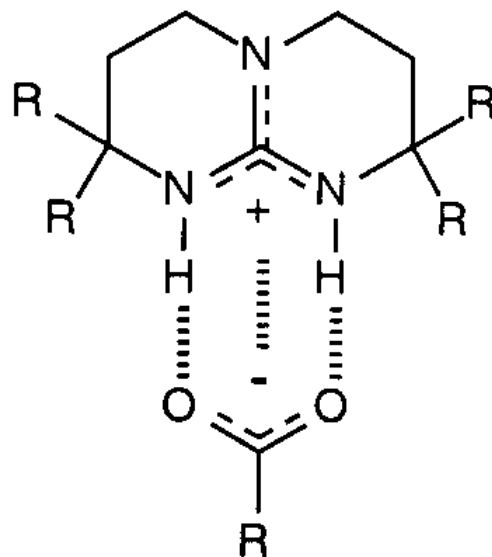


Balance between host protonation and guest deprotonation.

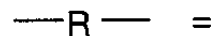
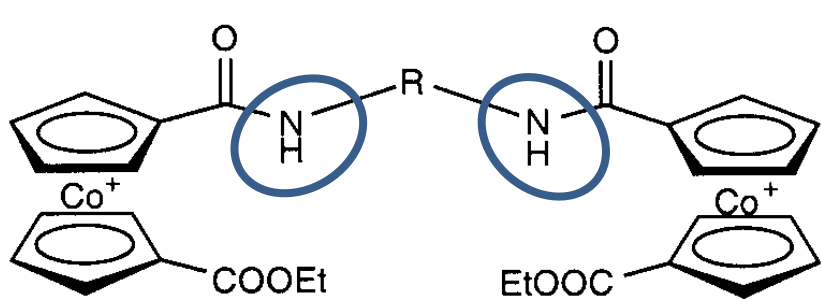




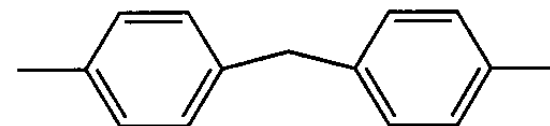
pKa = 13.6



Bicyclic guanidinium is preorganized and complementary for binding bidentate anions.

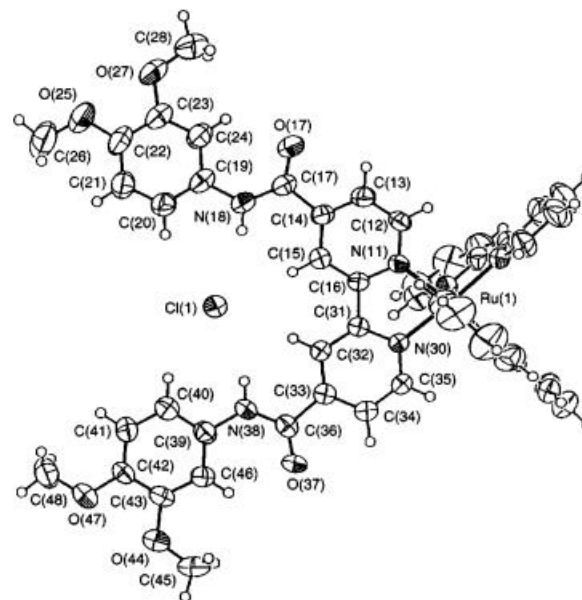
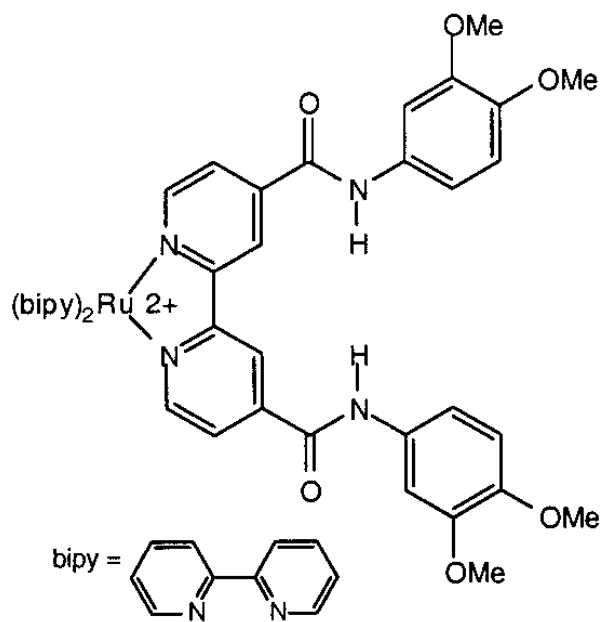


*Binds 1 Cl*

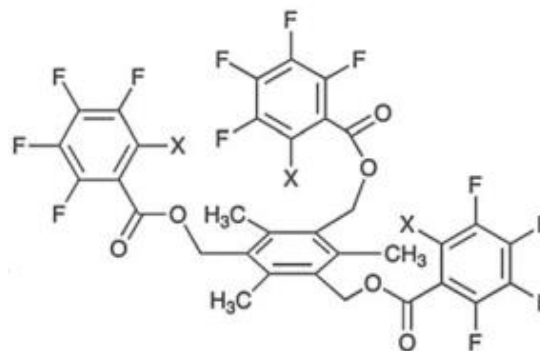
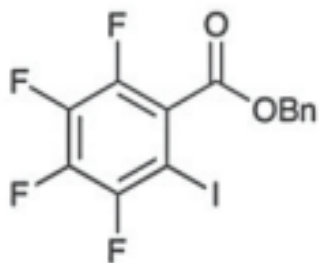


*Binds 2 Cl*

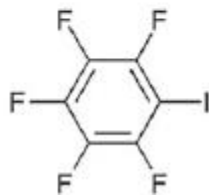
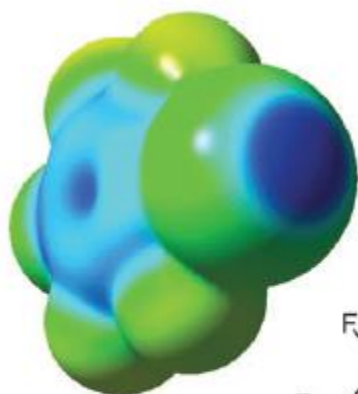
Cobaltocenium based anion receptors have easily tunable binding sites.



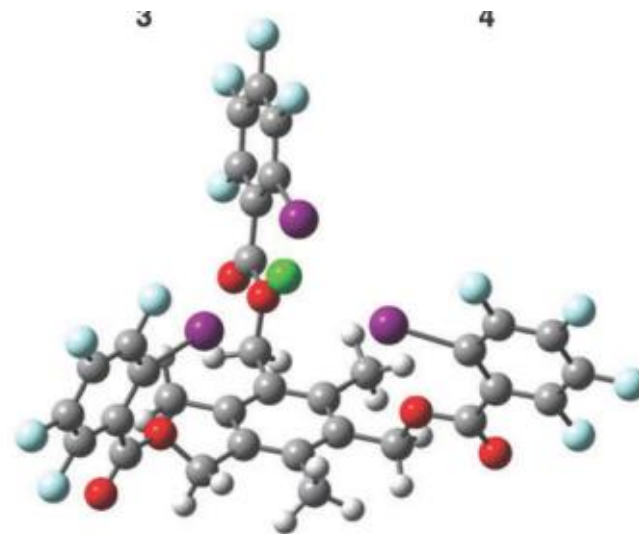
**Beer**



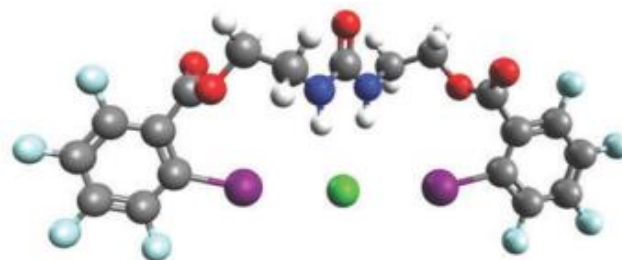
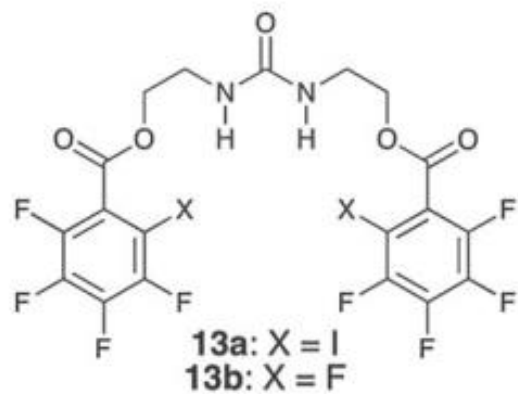
ortho-substituted iodotetrafluoroarenes on to trimethylbenzene scaffold



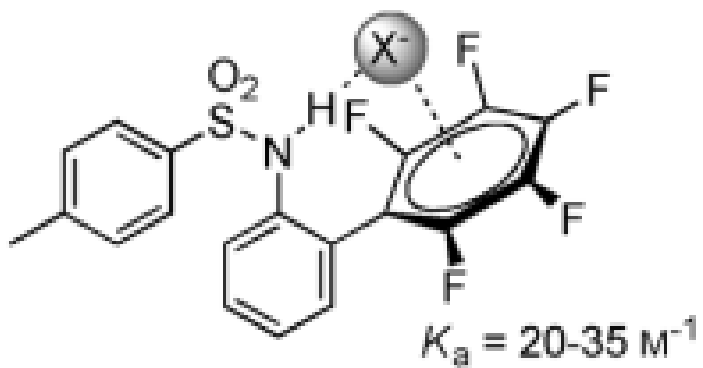
In acetone:  $\text{Cl}^- > \text{Br}^- > \text{I}^-$



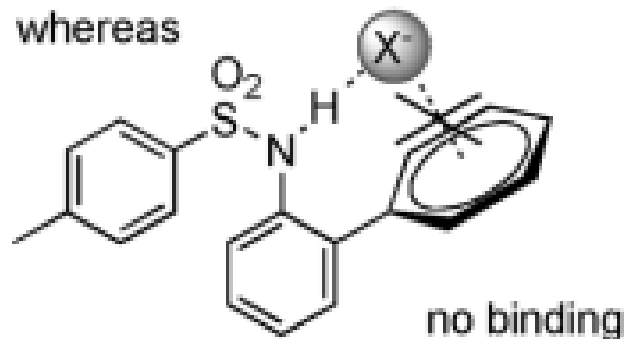
*Taylor*



(a)



whereas



**Berryman**



(a)

A cascade complex.



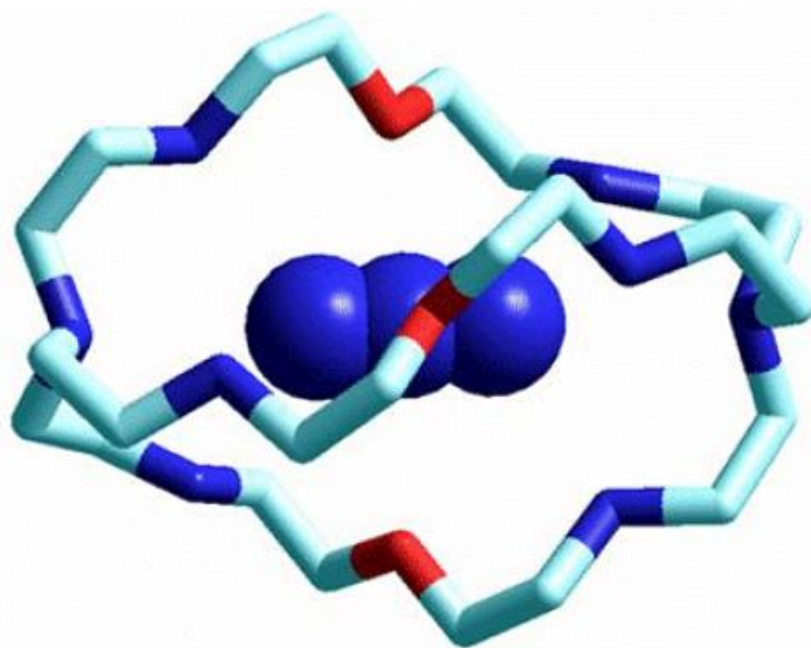
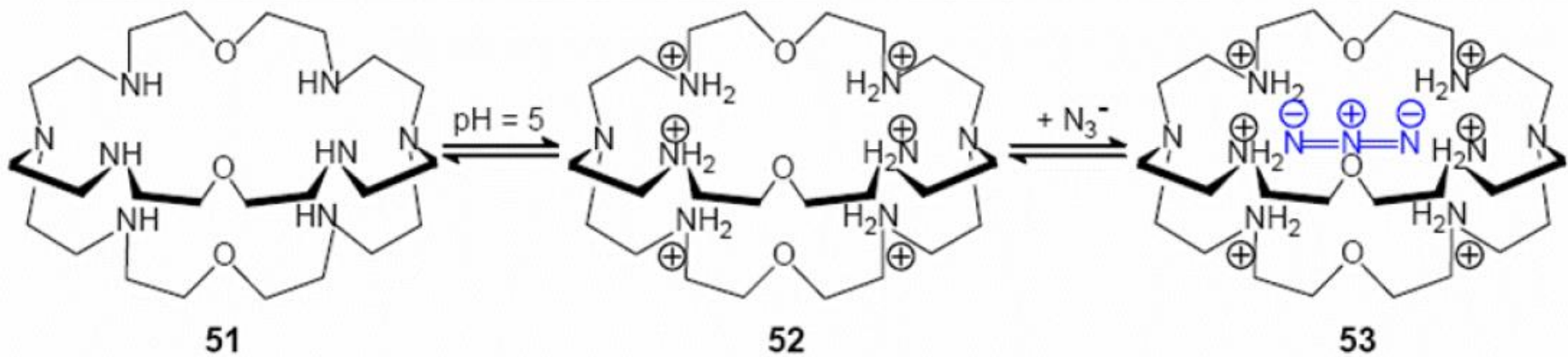
(b)

Receptor with individual  
cation and anion recognition sites.

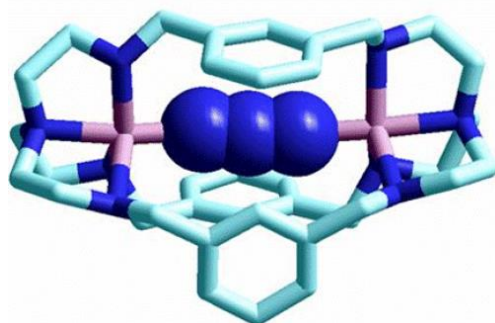
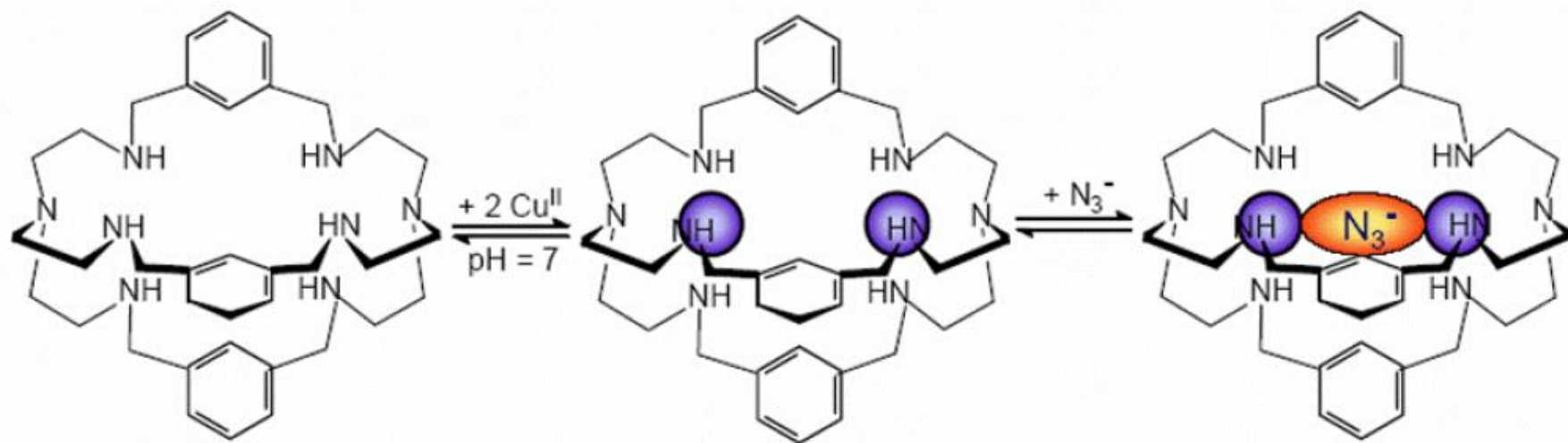


(c)

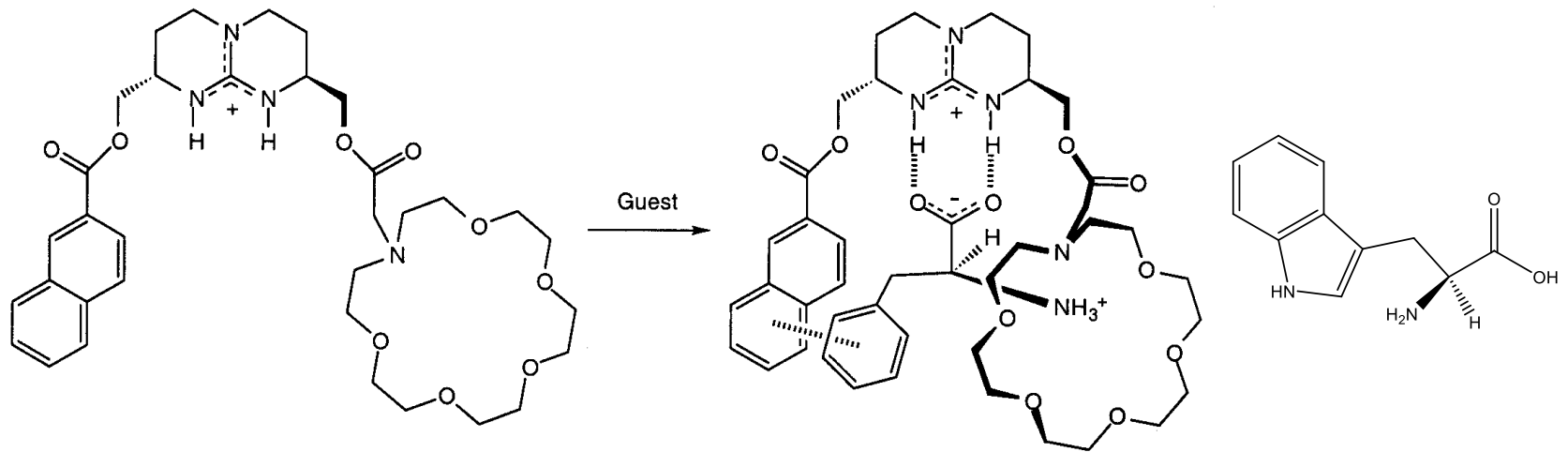
Receptor for zwitterionic  
guests.







# Estrazione di aa con catene laterali aromatiche (Phe, Trp) in $\text{CH}_2\text{Cl}_2$



Three point receptor

for the selective recognition and extraction of zwitterionic amino acids.

# Solubilization of NaX Salts in Chloroform by Bifunctional Receptors\*\*

Jurgen Scheerder, John P. M. van Duynhoven,  
Johan F. J. Engbersen, and David N. Reinhoudt\*

