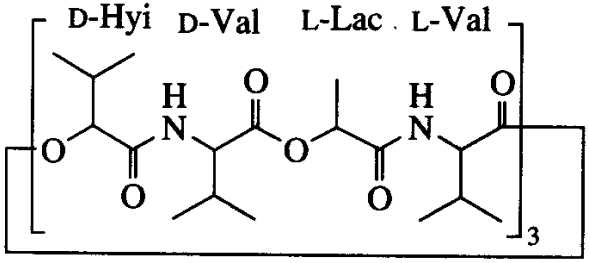
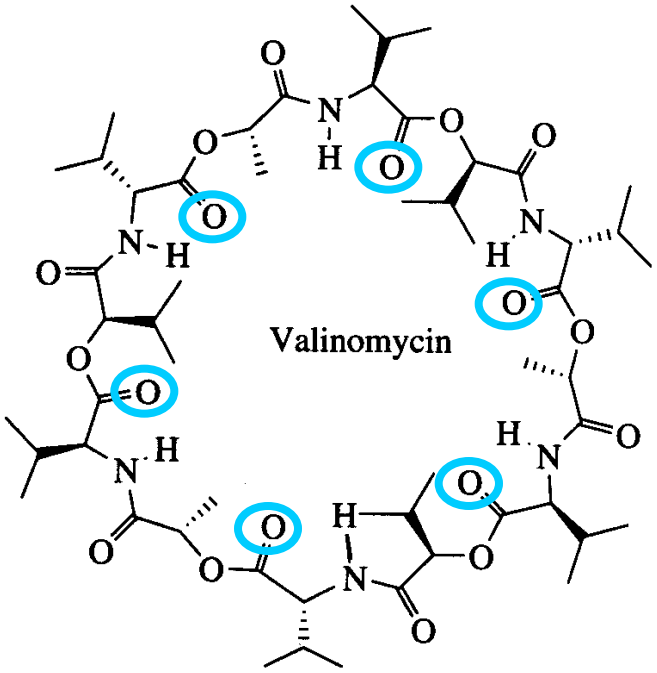
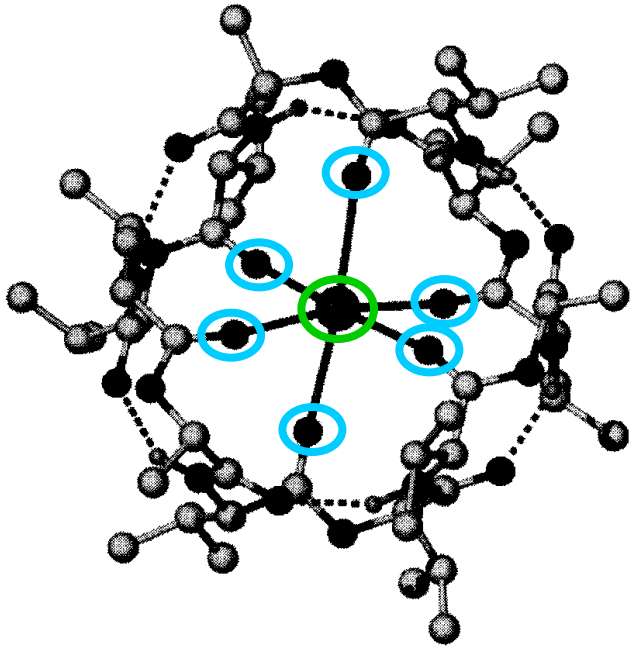
Cations and anions are ubiquitous in biological and chemical systems and their efficient and selective recognition is one of the main goals of Supramolecular Chemistry. As a matter of fact, research in this field started with Pressman's 1964 discovery[1] that valinomycin and other natural antibiotics increase the permeability of lipid bilayer membranes through the selective binding of potassium ion, and with Pedersen's finding[2] 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[3-7] and anion[8,9] complexation and sensing. More recently, a special role in ion

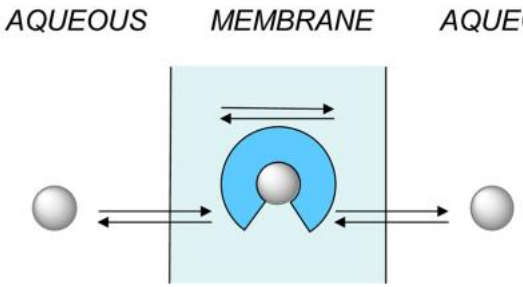

D-Hyi
D-Val
L-Lac
L-Val
3

=


Valinomycin



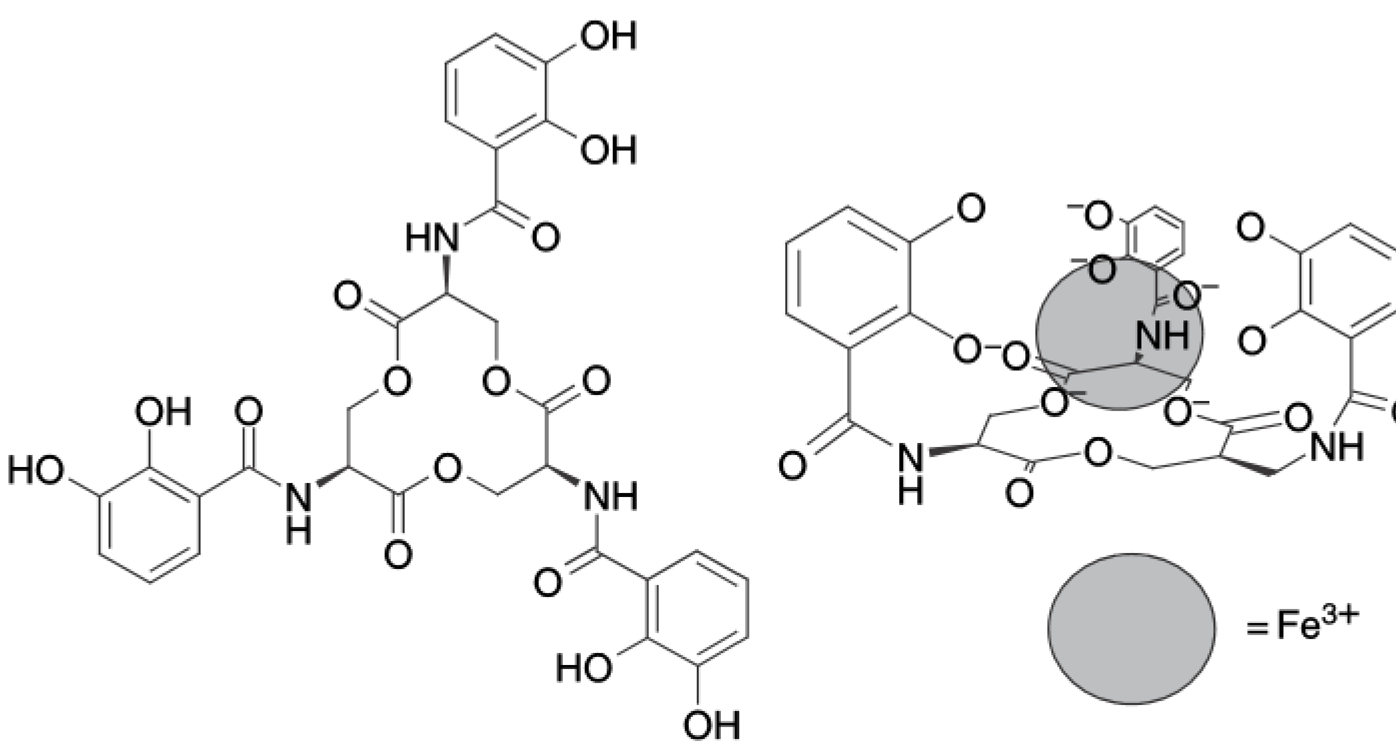

K+


AQUEOUS
MEMBRANE
AQUEOUS

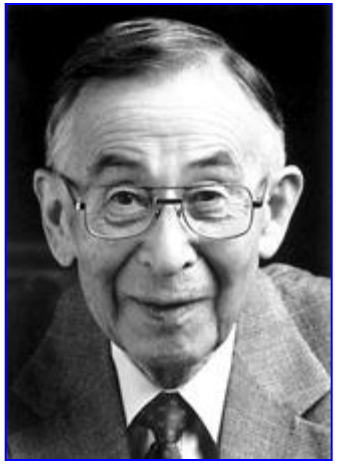
$K_{K+}/K_{Na+} = 10^5$

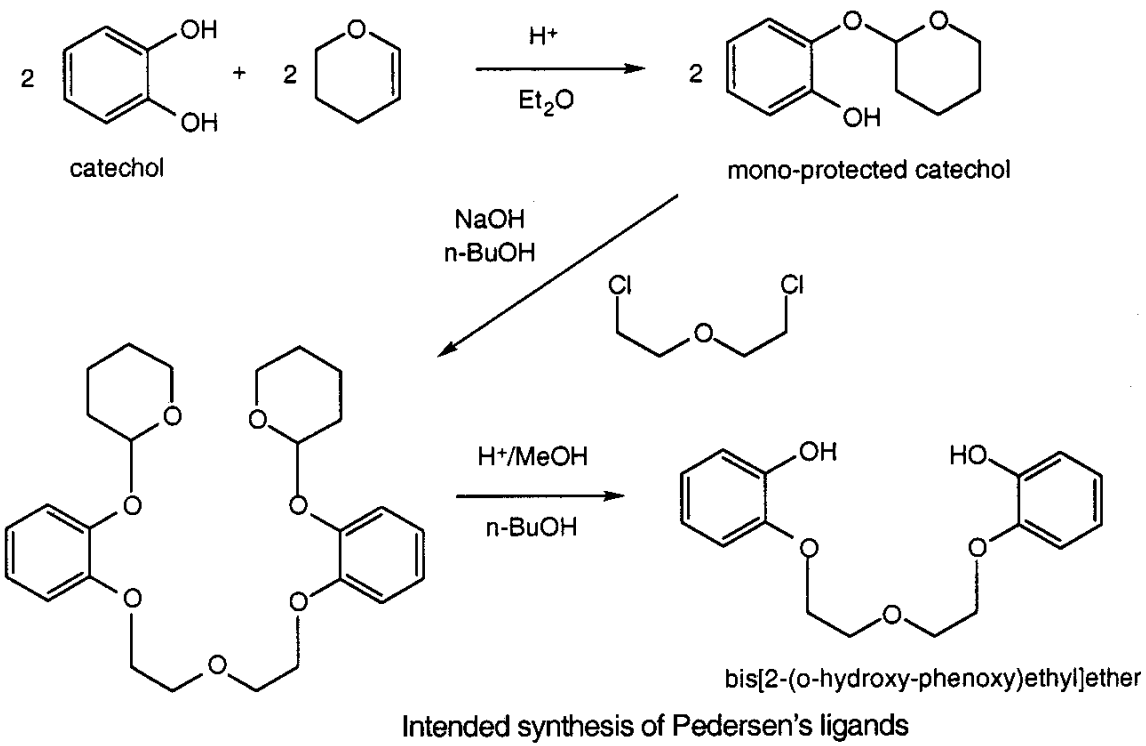
Another important natural cation-binding process is the detection and bioaccumulation of the trace element Fe^{III}. The majority of iron found in nature is 'tied up' within a number of enzymes and proteins that are involved either in iron storage or transport. Fe^{III} is virtually insoluble under physiological conditions; the solubility of $[Fe(H_2O)_6]^{3+}$ is $10^{-18}\ M^{-1}$. For optimum growth to occur, microbes require iron concentrations in the micromolar range. When a cell becomes iron-deficient, the organism produces low-molecular-weight organic compounds, called siderophores (from the Greek, meaning 'iron carriers'). The latter are a class of naturally occurring, low-molecular-weight compounds that are ferric-ion-specific chelating agents, utilised by many microbes. Siderophores are unique ligands that selectively bind Fe^{III} Ka > 1030 M^{-1} and are able to transport the iron across the cell membrane.

Many siderophores are three-armed podands that contain hydroxamates or catechol moieties which bind to the metal ion. Siderophore iron(III) complexes are high-spin and are highly thermodynamically stable. The iron(III) ion is totally enveloped by the catechol arms in a six-coordinate geometry, only the Δ enantiomer is recognized by cell receptors.

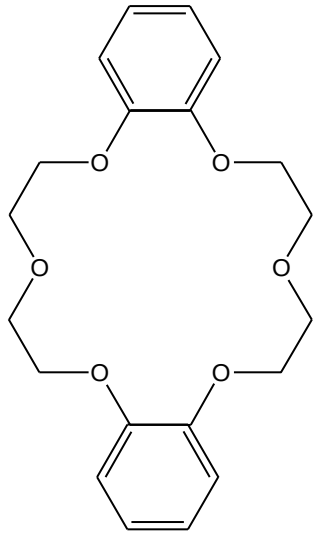


PEDERSEN (Nobel 1987), mutlidentate ligands for vanadium and copper (Dupont, anni ‘60)





Intended synthesis of Pedersen’s ligands



dibenzo[18]crown-6 – side product

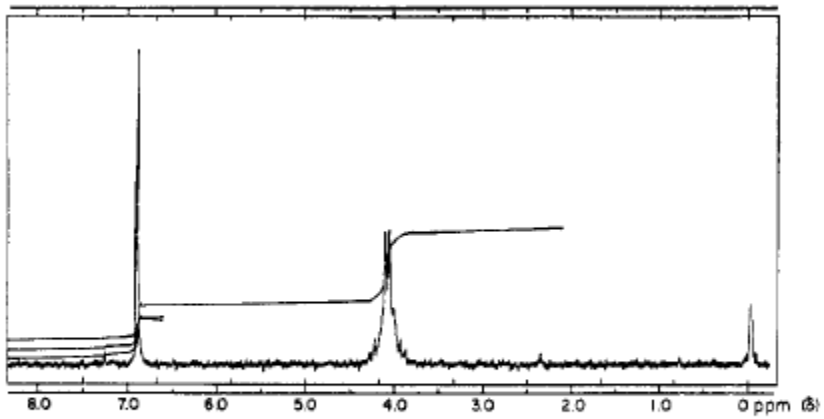


Figure 2. Nmr spectrum of dibenzo-18-crown-6 (XXVII): (upper) multiplet, 4.11 ppm downfield from TMS, area ratio 2.2; (lower) singlet, 6.92 ppm downfield from TMS, area ratio 1.0.

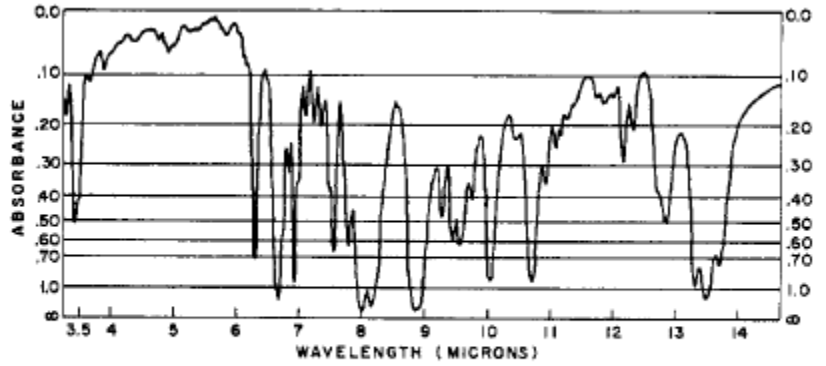


Figure 4. Infrared spectrum of dibenzo-18-crown-6 (XXVIII), KBr pellet.

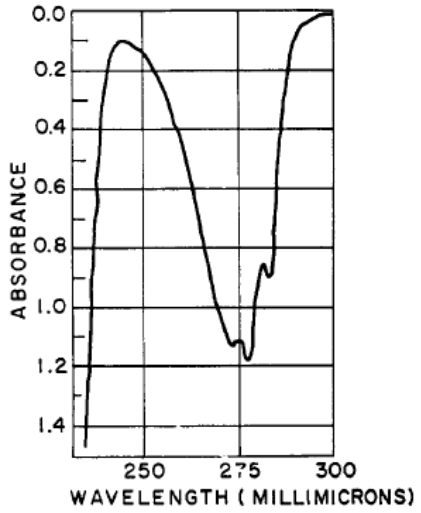


Figure 7. Ultraviolet spectrum of dibenzo-18-crown-6 (XXVIII) in cyclohexane, concentration 0.000255 mole/l., cell path 1 cm; λ_{max} 274 (ϵ 4400), 278 (ϵ 4700), and 283 (ϵ 3600).

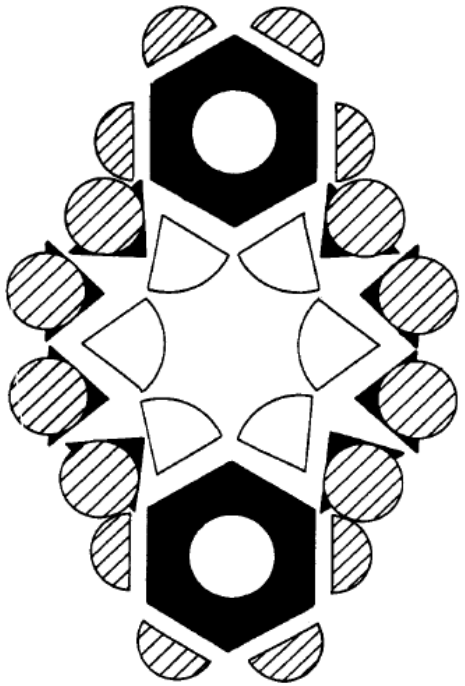
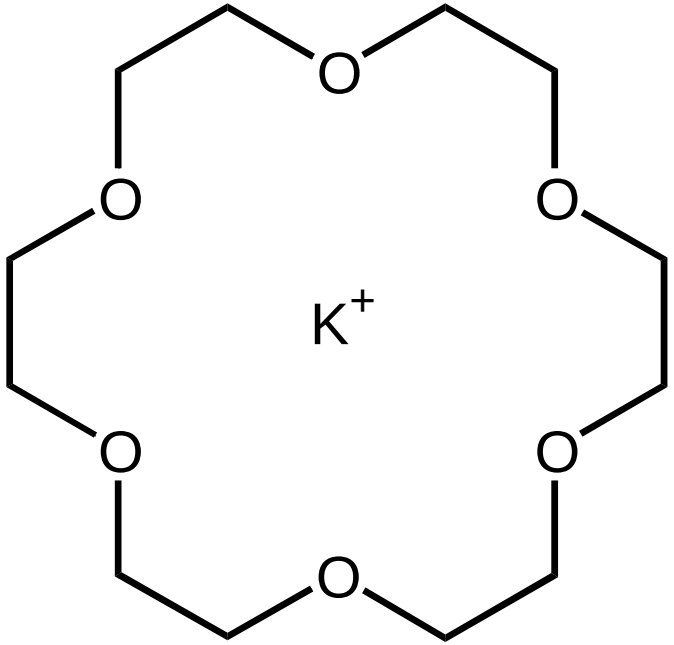


Figure 9. Courtauld model of dibenzo-18-crown-6 (XXVIII).

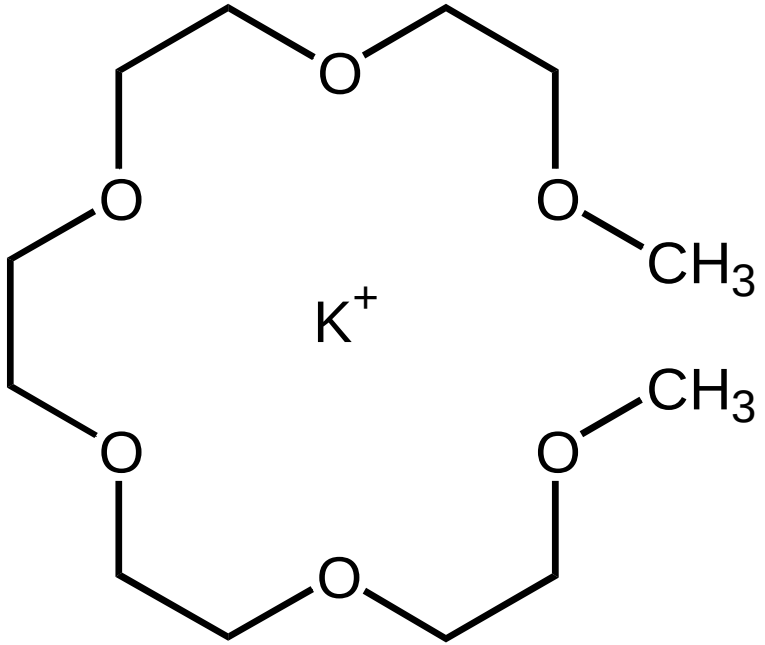
CROWN ETHERS

[18]crown-6

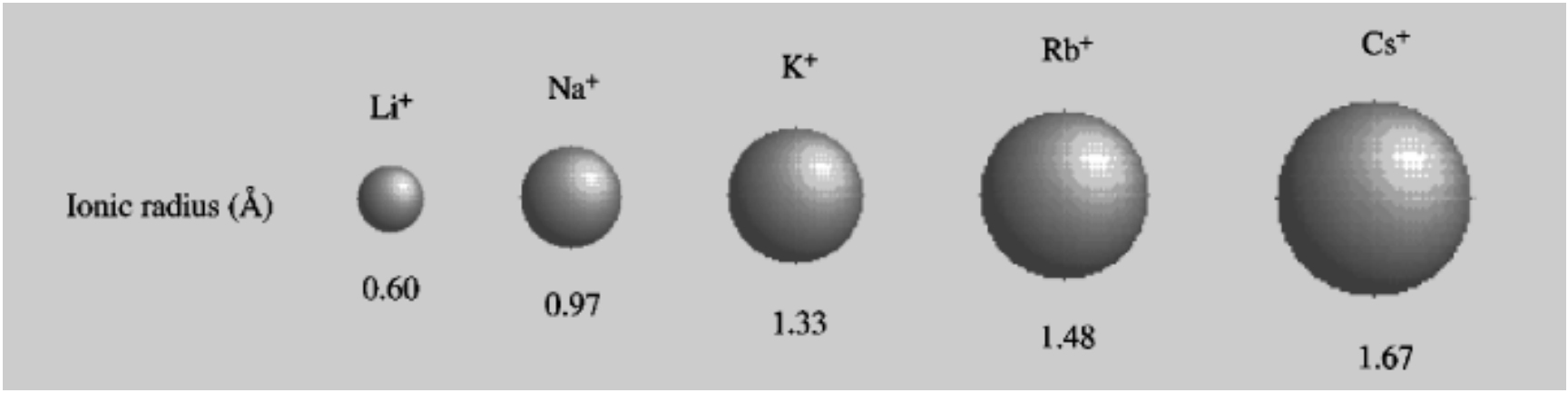


log K = 6.08

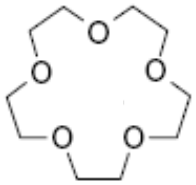
Pentaetylenglicol dimeylether



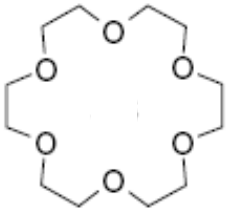
log K = 2.3



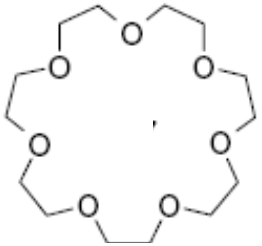
OPTIMAL SPATIAL FIT or SIZE-MATCH



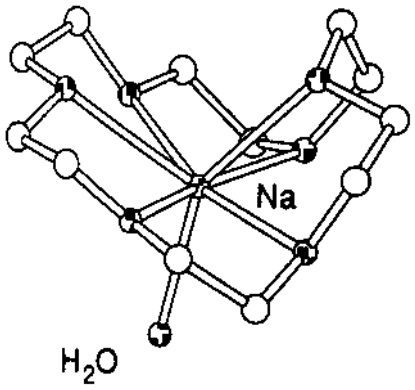
[15]crown-5
Complementary to Na^+

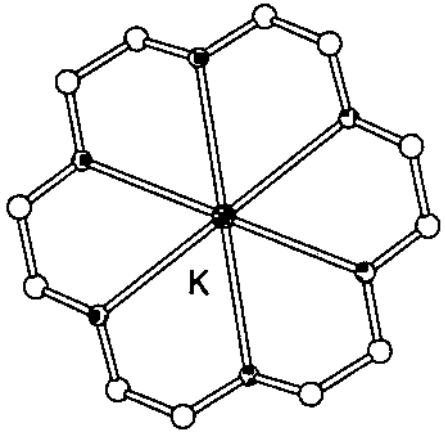


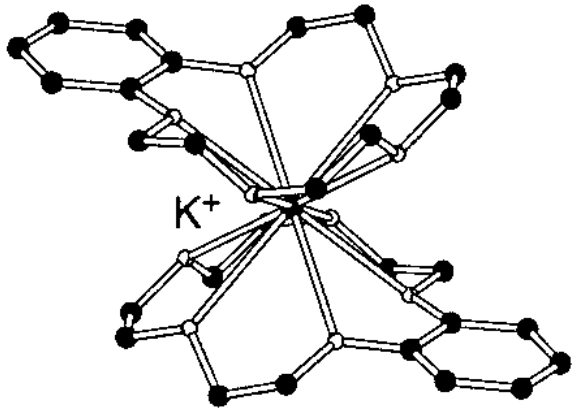
[18]crown-6
Complementary to K^+



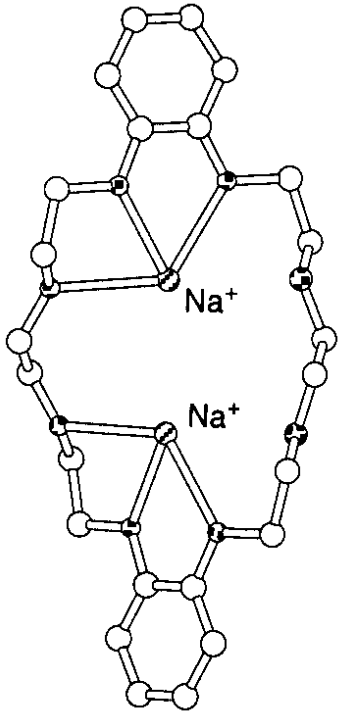
[21]crown-7
Complementary to Cs^+





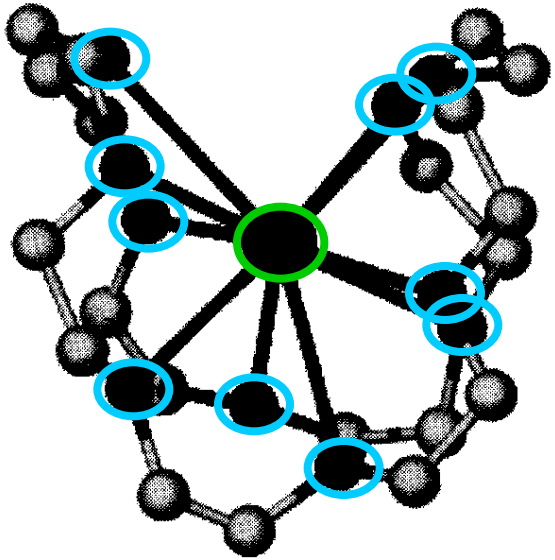


The crystal structure of two benzo-15-crown-5 molecules forming a 'sandwich complex' with a potassium cation



The crystal structure of $2Na^+$–[24]crown-8

[30]crown-10



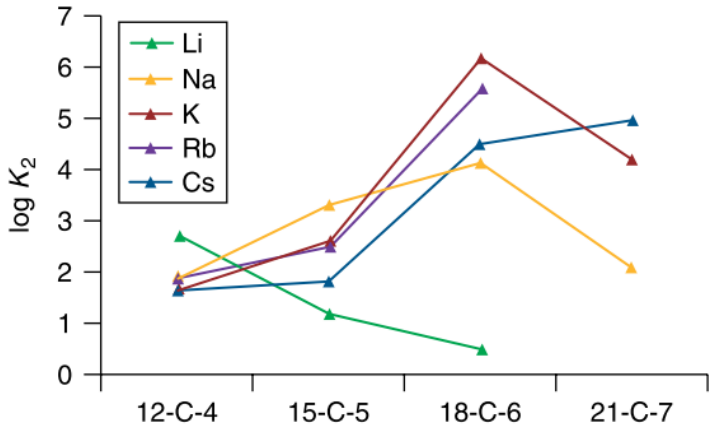
Thermodynamic selectivity: ratio of the binding constant for one guest over another:

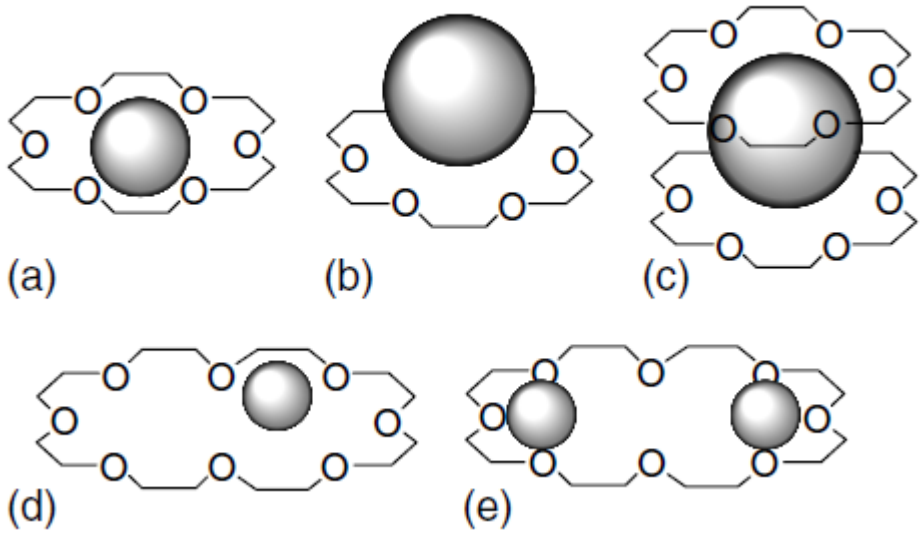
$$H + G_1 \rightleftharpoons [HG_1] \qquad K_1$$
$$H + G_2 \rightleftharpoons [HG_2] \qquad K_2$$

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

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


log K_2
7
6
5
4
3
2
1
0
Li
Na
K
Rb
Cs
12-C-4
15-C-5
18-C-6
21-C-7


(a)
(b)
(c)
(d)
(e)

SELECTIVITY

Nature of the donor atoms (O vs N similar VdW radius: hard/soft acid-base theory);

Number and orientation of the donor atoms (more important for transition metal cations than for alkaly, alkaly earth or REM);

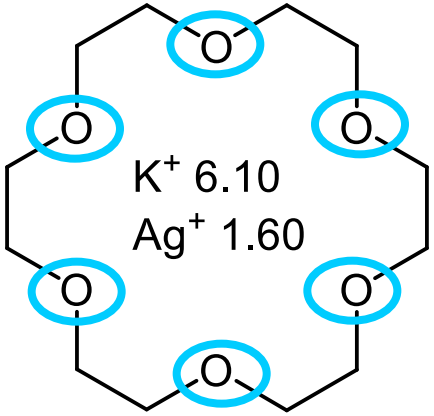
Electrostatic charge of the cation: for similar sizes a higher charge density correspond to a higher hydration energy (*cfr* Ca^{2+} vs Na^{+});

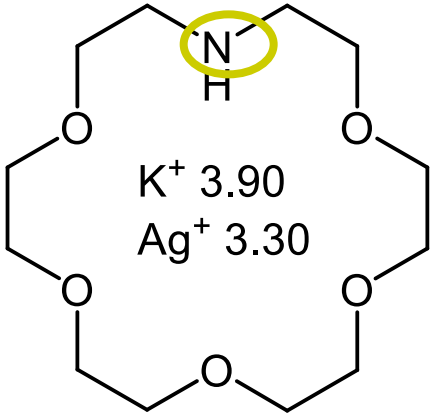
Solvation energy of the Host and the Guest;

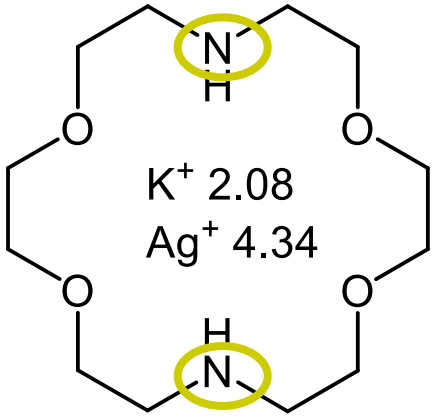
Solvent– competition for donor atoms dipoles/dielectric constant/ hydrogen bonds/coordination ability;

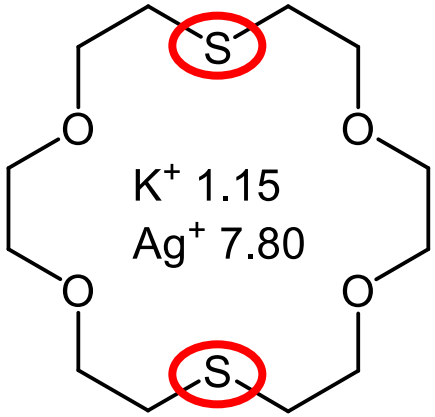
Nature of the counterion(s);

Kinetic of Complexation.



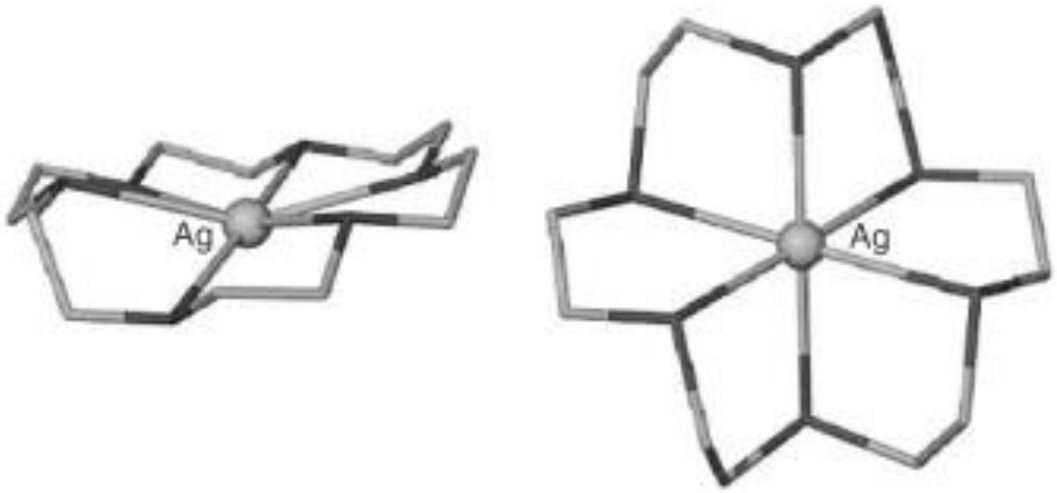




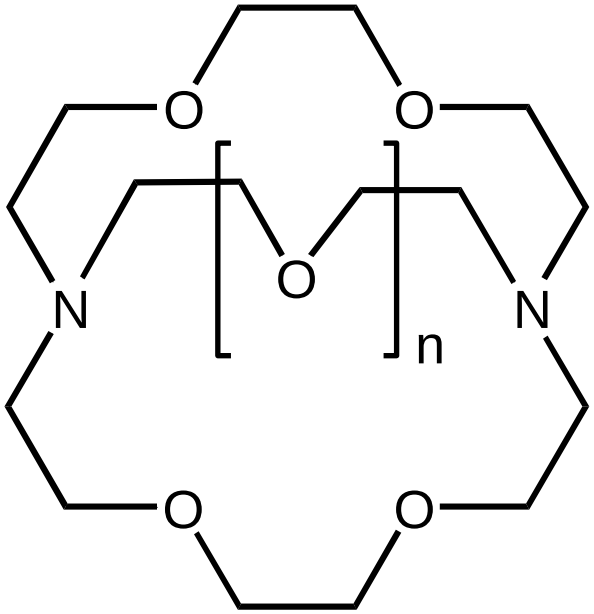


Aza-crown

Tio-crown



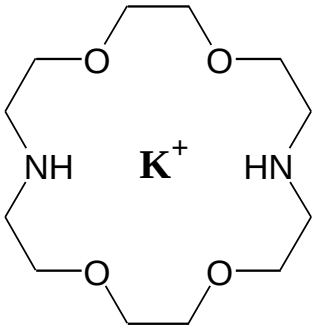
LEHN (Nobel 1987), extension of monocyclic receptors to bicyclic ones
CORANDS → CRIPTANDS, 1960's)



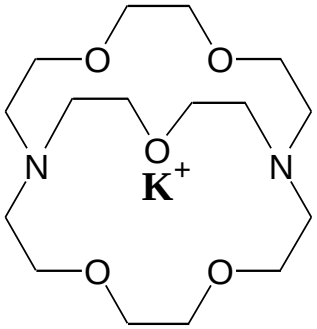
Na^+

n = 1, criptando [2,2,1]
n = 2, criptando [2,2,2]

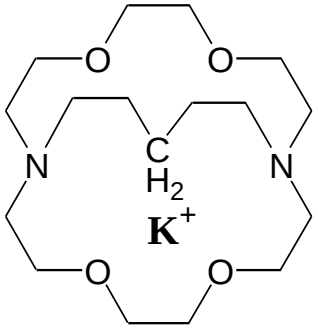
K^+



logK = 2.0



logK = 7.0



logK = 5.4

SELECTIVITY

Size-match o optimal-fit (progressively more important with with incresing degree of pre-organization: distance between the donor atoms dipoles and the guest.

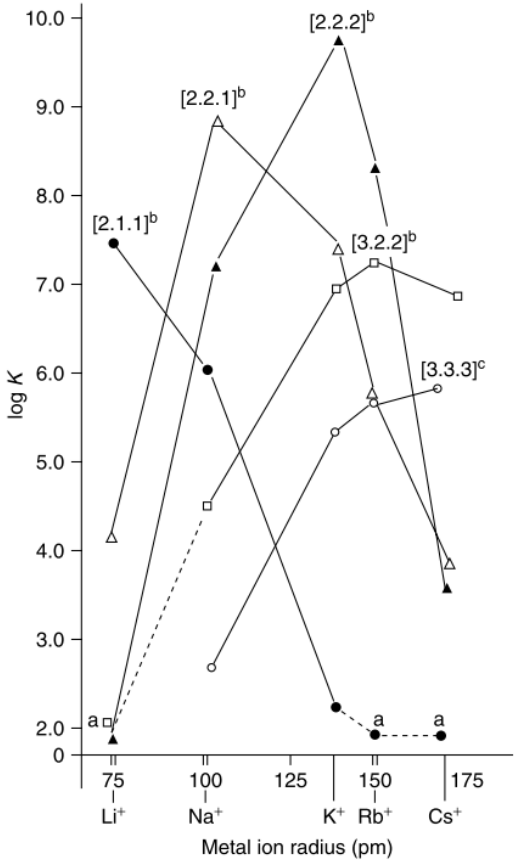
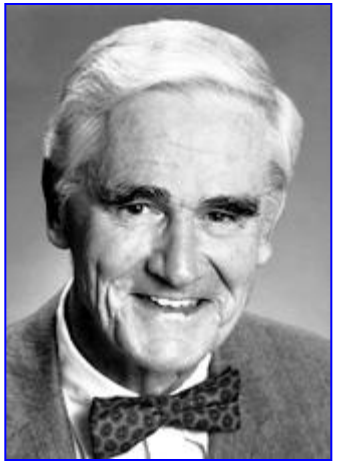
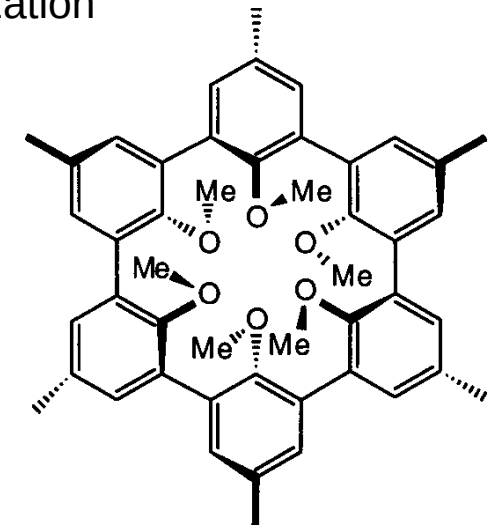


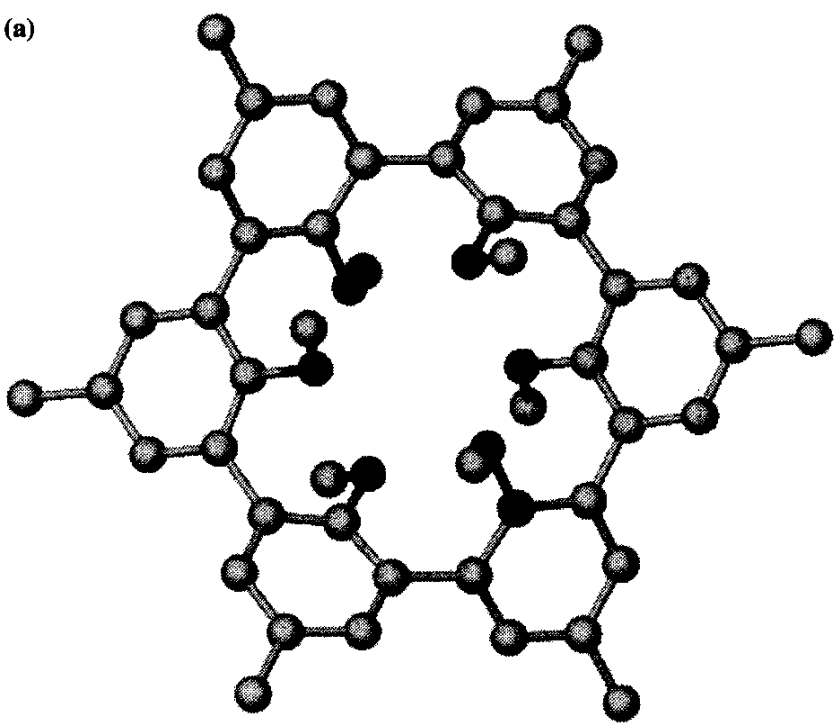
Figure 2 Selectivity of cryptands among alkali metal cations (a, value reported <2.0; b, in 95% CH_3OH; c, in methanol).

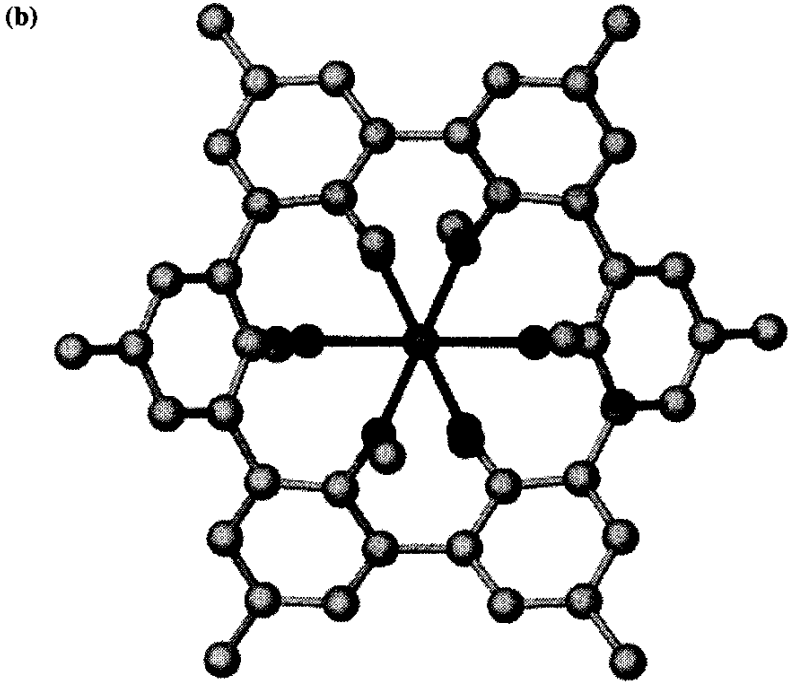
CRAM (Nobel 1987) - preoganization



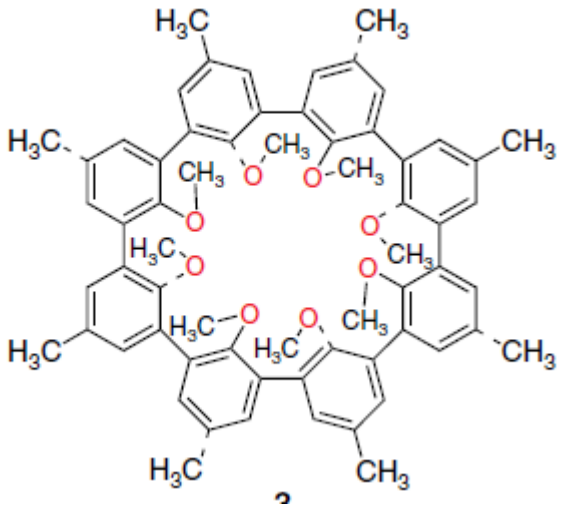


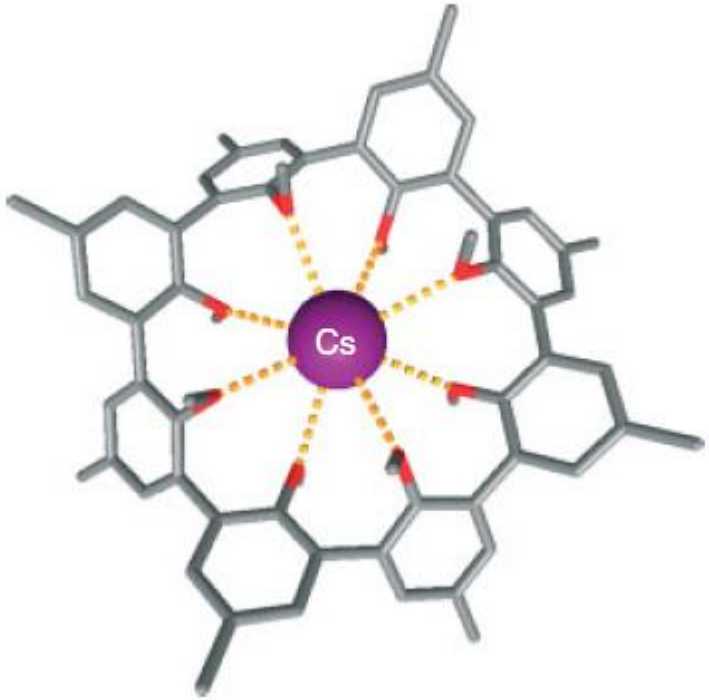
SPHERANDS - (*p*-METYLANISOL)

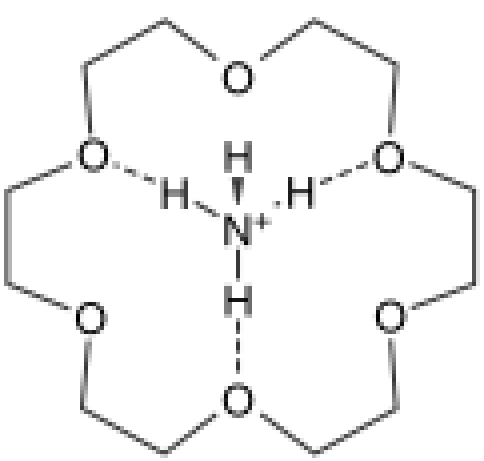




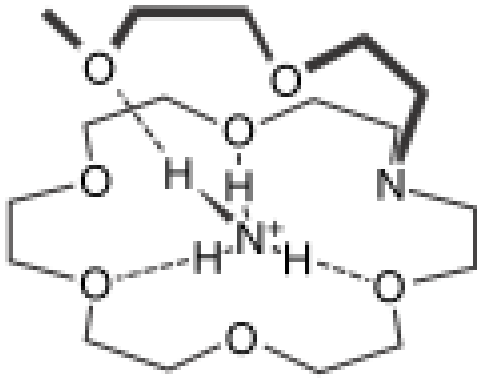
X-ray crystal structures of **(a)** free spherand **(3.30)** and **(b)** its Li^+ complex (after Trueblood *et al.* 1981).


H3C
CH3
H3C
CH3
CH3
O
CH3
O
CH3
O
H3C
O
O
CH3
O
H3C
O
O
CH3
H3C
O
H3C
CH3
CH3
H3C
CH3


Cs



log K = 4.35



2.23·NH_4^+

log K = 4.75

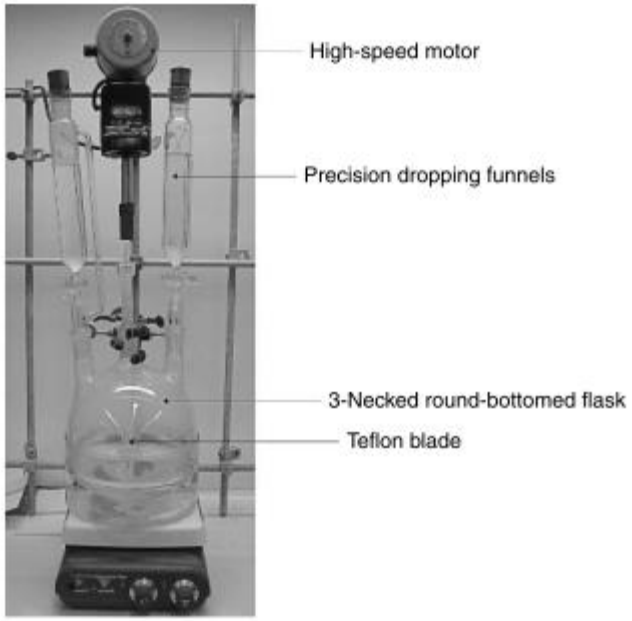
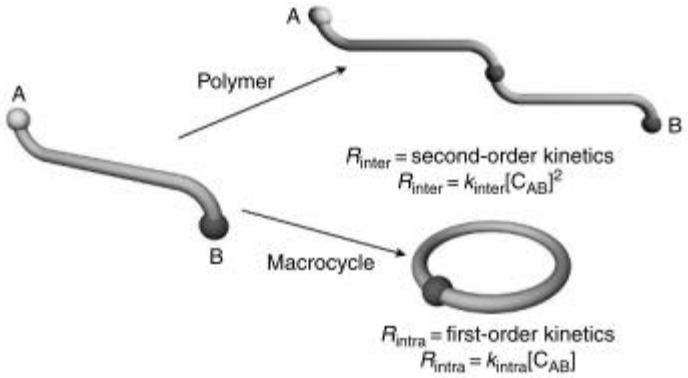
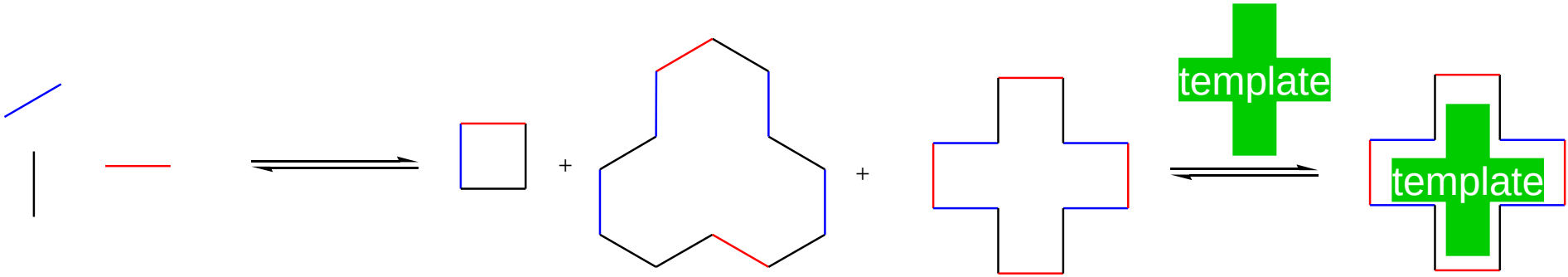
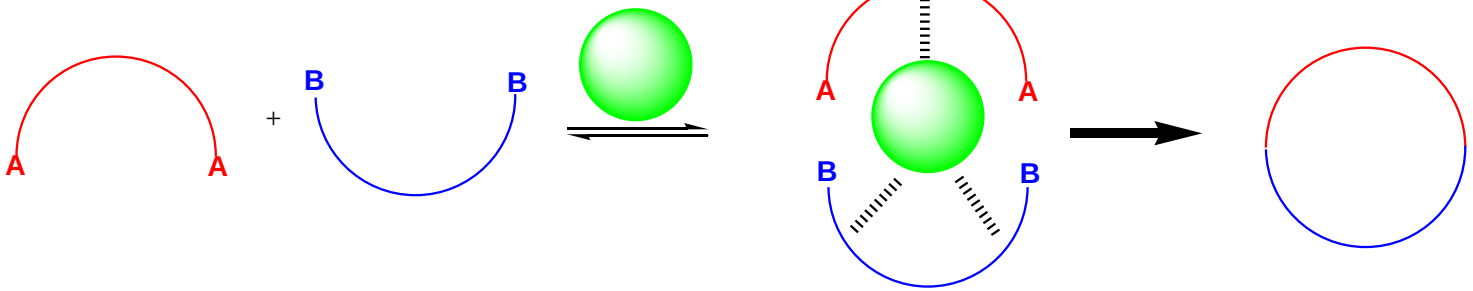
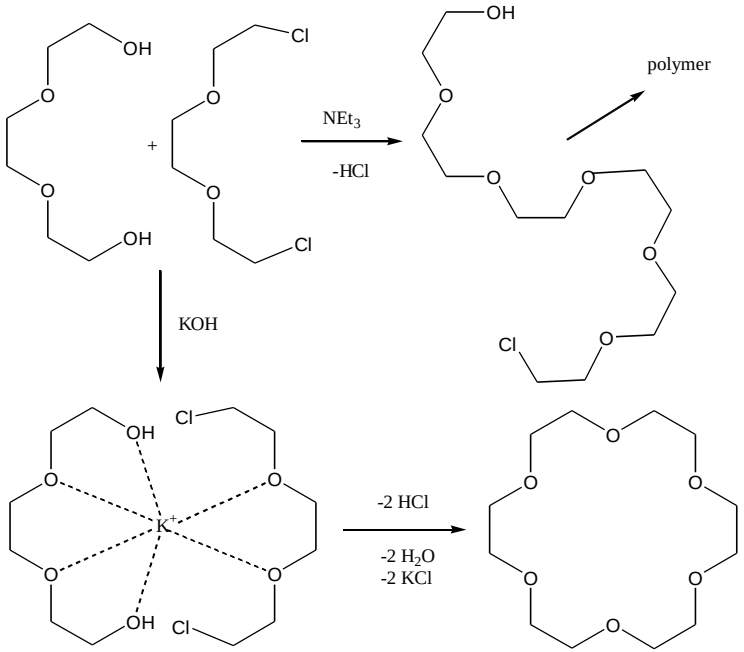


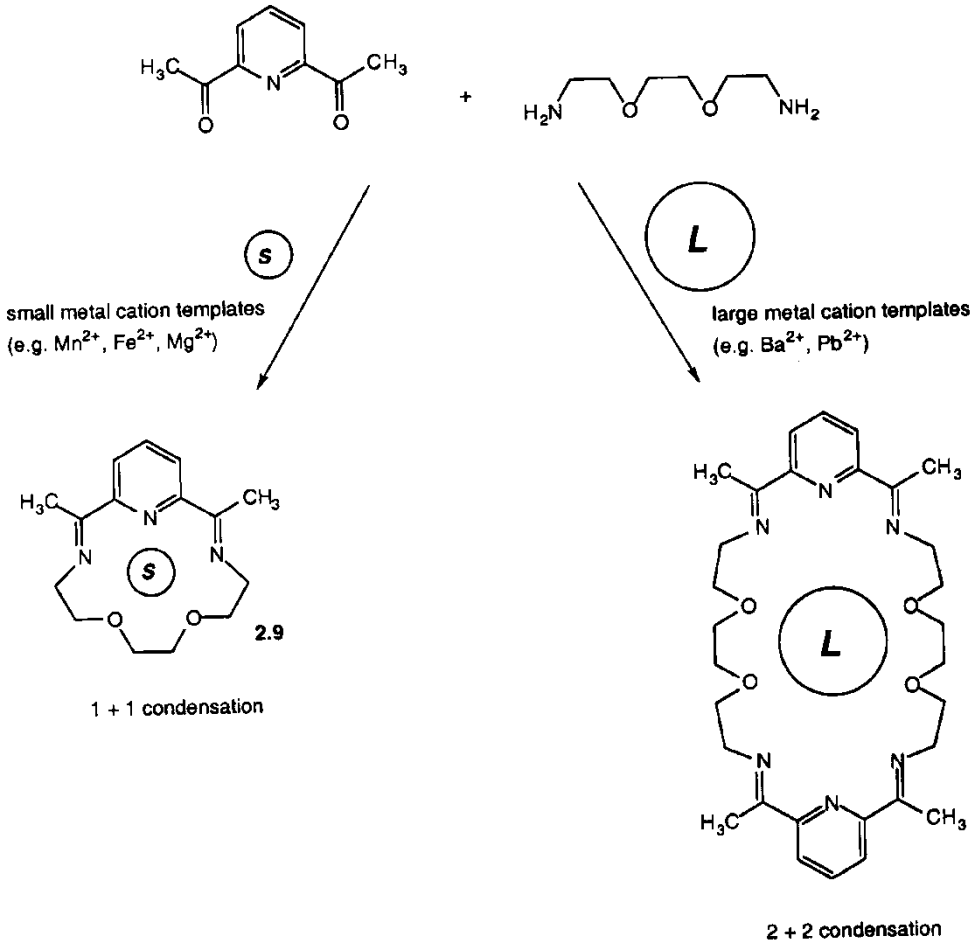
Figure 2.1 Typical apparatus used for high-dilution synthesis.

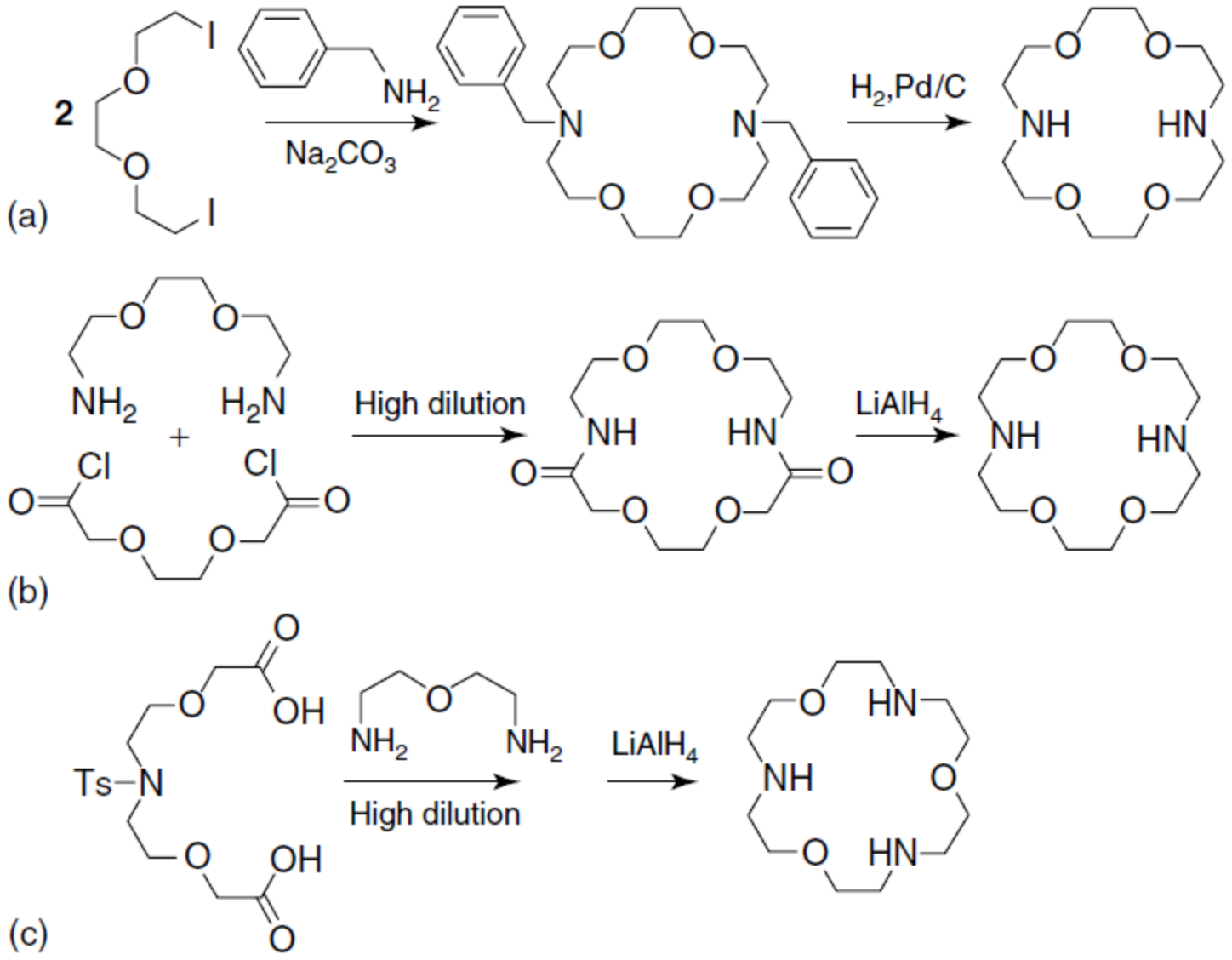



template
template

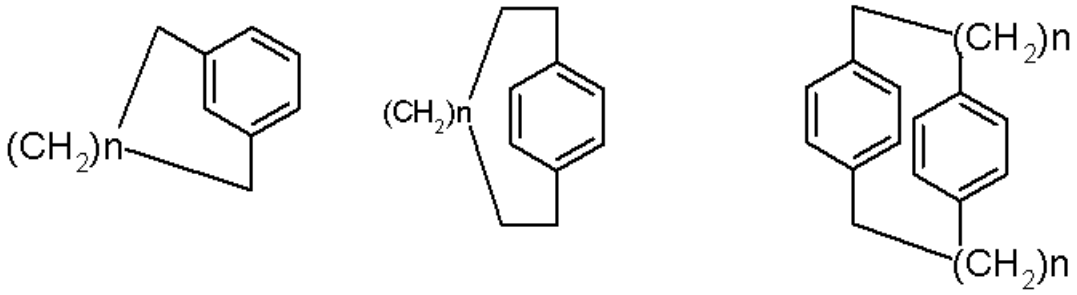

A
A
B
B
A
A
B
B


OH
Cl
NEt3
-HCl
polymer
KOH
-2 HCl
-2 H2O
-2 KCl

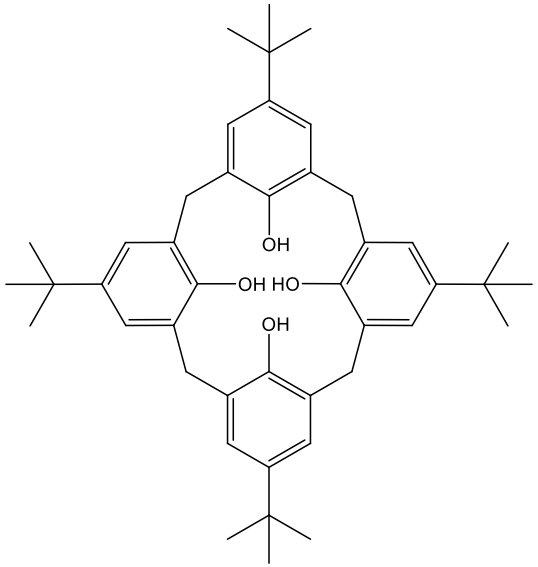

H3C
CH3
H2N
NH2
S
L
small metal cation templates
(e.g. Mn2+, Fe2+, Mg2+)
large metal cation templates
(e.g. Ba2+, Pb2+)
2.9
1 + 1 condensation
2 + 2 condensation


(a)
2
I
O
O
I
NH2
Na2CO3
N
N
O
O
O
O
H2,Pd/C
NH
HN
O
O
O
O
(b)
NH2
H2N
+
Cl
Cl
O
O
O
O
O
O
High dilution
NH
HN
O
O
O
O
O
O
LiAlH4
NH
HN
O
O
O
O
(c)
Ts
N
O
OH
O
OH
O
O
NH2
O
NH2
High dilution
LiAlH4
O
HN
NH
O
O
HN

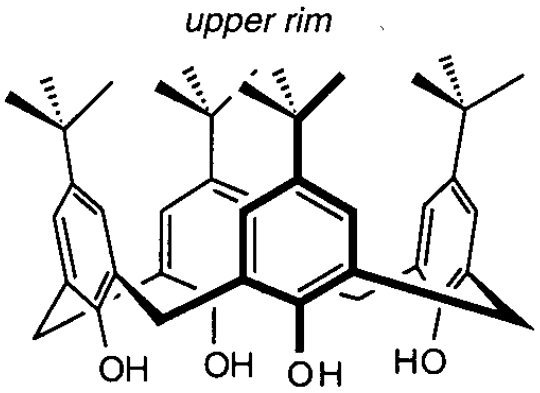
CICLOPHANES



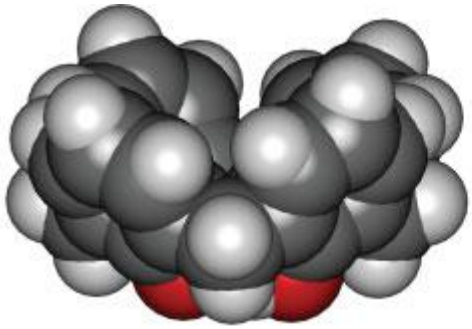
Calix[n]arenes

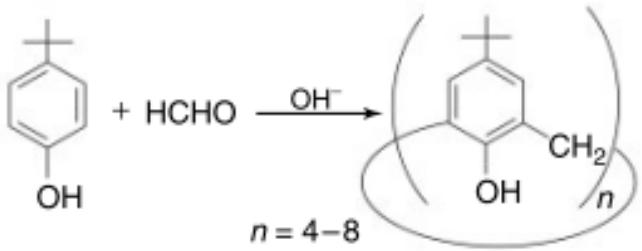


Calix[n]arenes

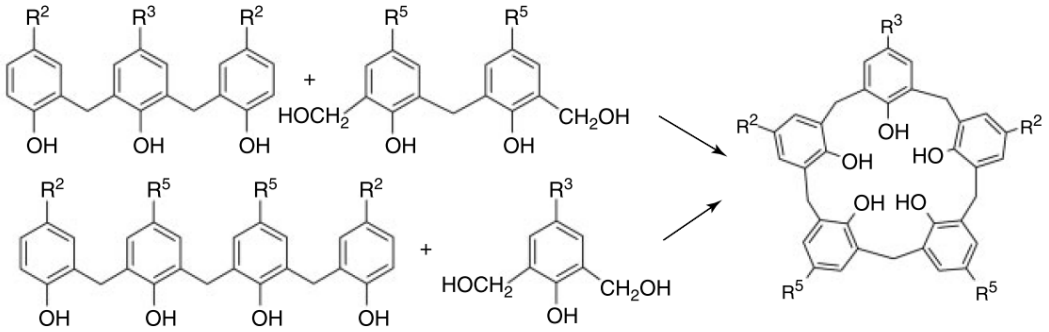


p-tert-Butylcalix[4]arene.

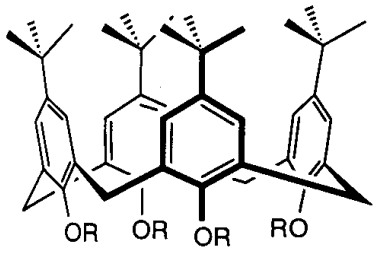




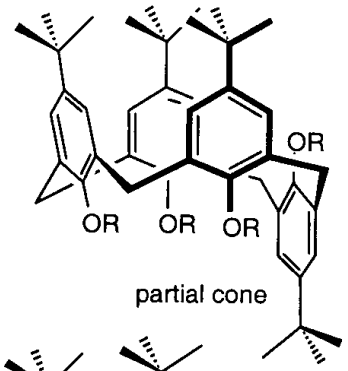
3+2 Fragment condensation



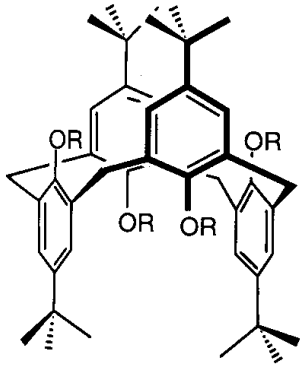
4+1 Fragment condensation



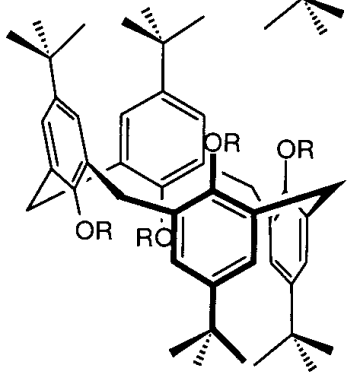
cone



partial cone

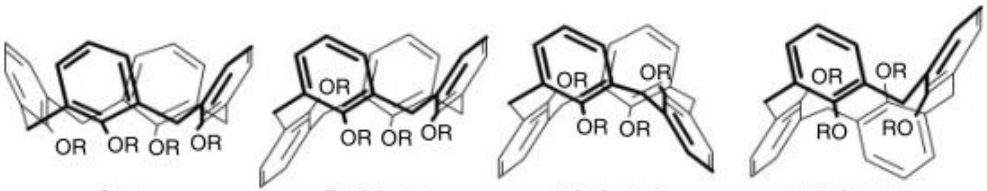


1,3-alternate



1,2-alternate

Conformations adopted by calix[4]arenes.



Cone | Partial cone | 1,3-alternate | 1,2-alternate

u, u, u, u | u, u, u, d | u, d, u, d | u, u, d, d

Calixarenes, which are [1$_n$]metacyclophanes comprising phenolic and methylene units,[1] 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 ^{1}H NMR measurements of several calix[4]arenes[2–4] 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^{-1}. The con-

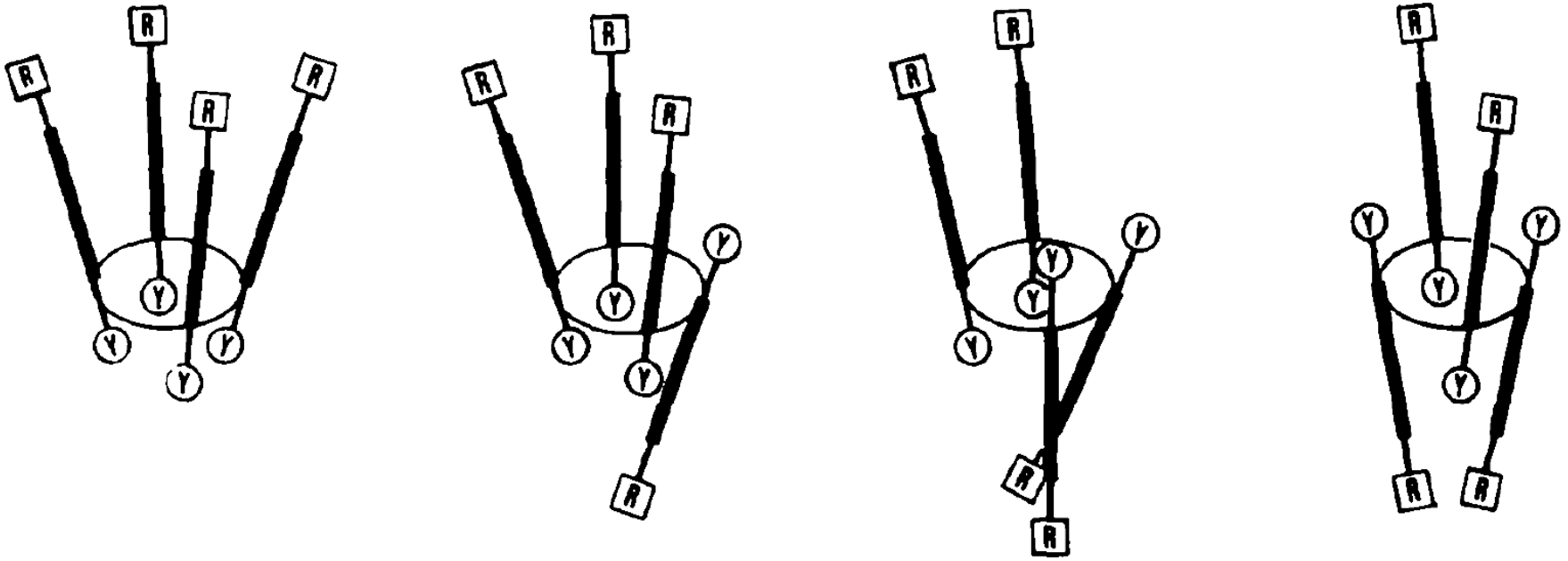
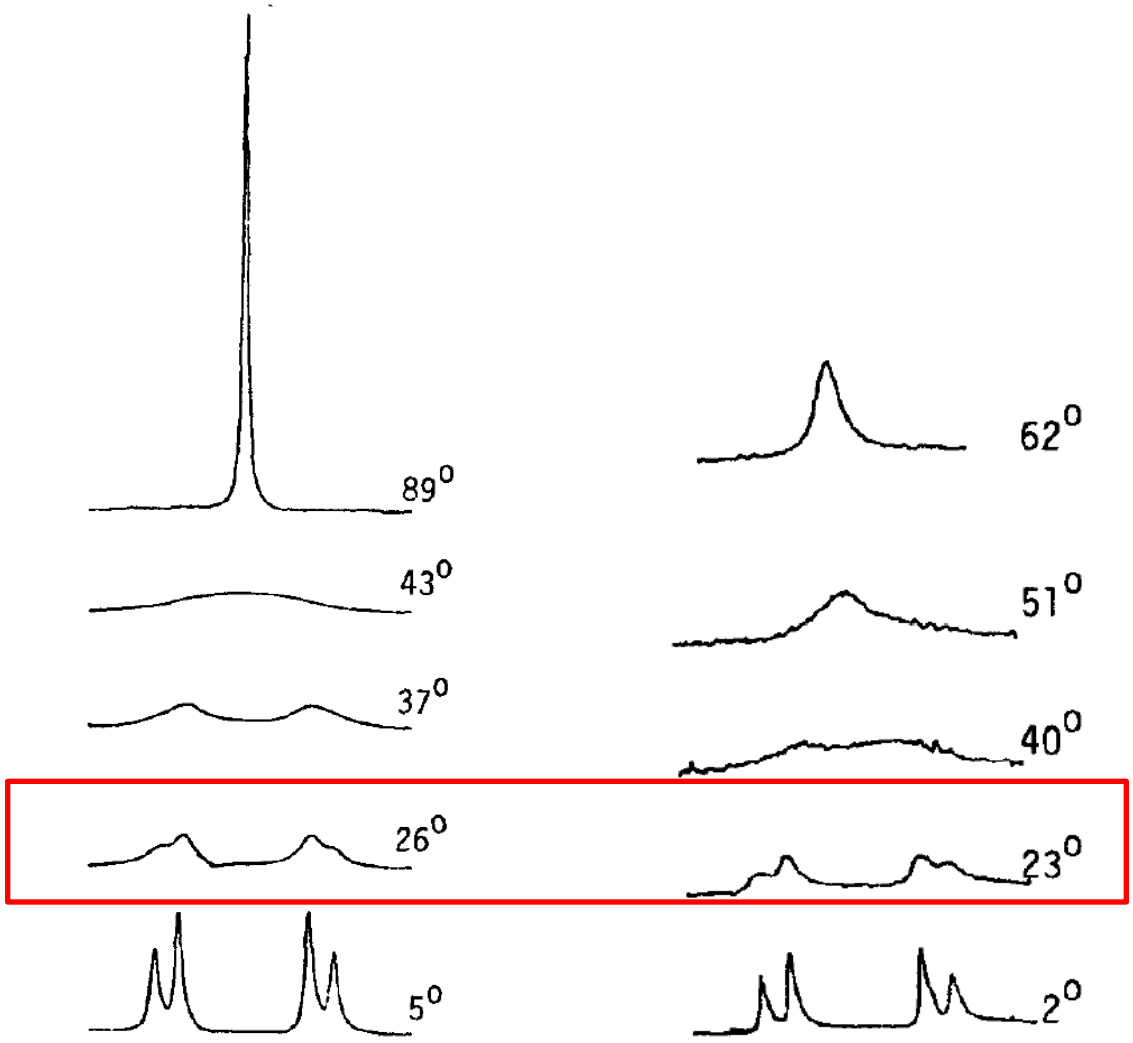
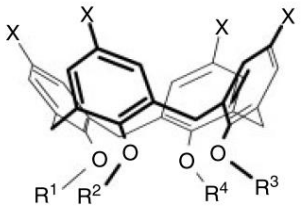


Fig. 1. Conformations of the calix[4]arenes.

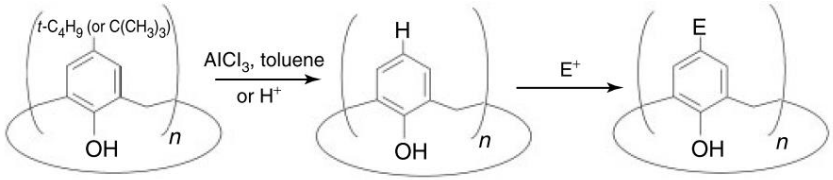


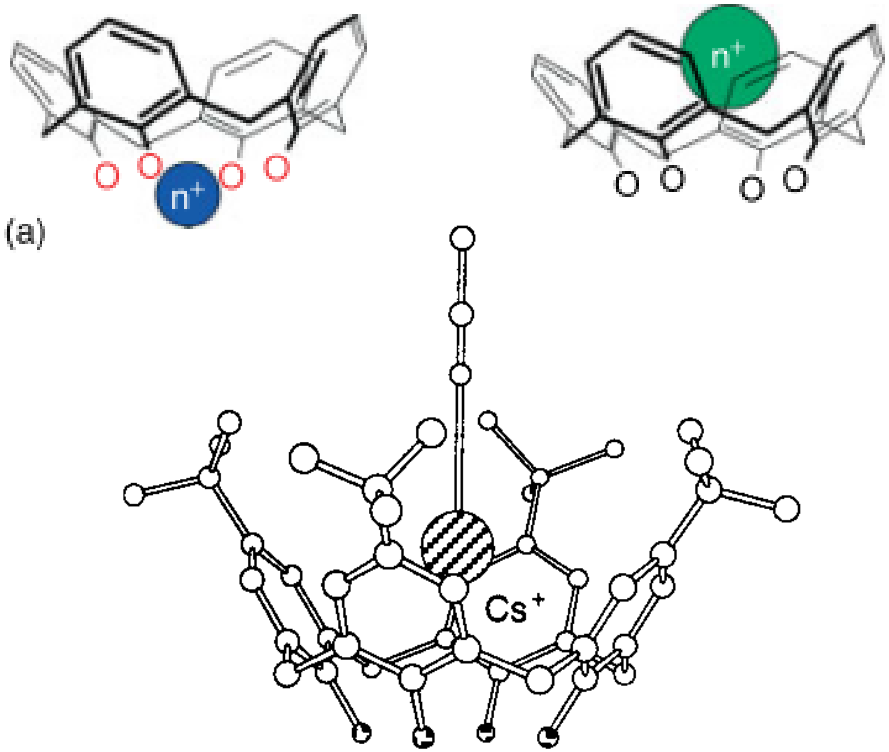
1-A. *p-tert*-butylcalix[4]-arene in bromobenzene-d_5

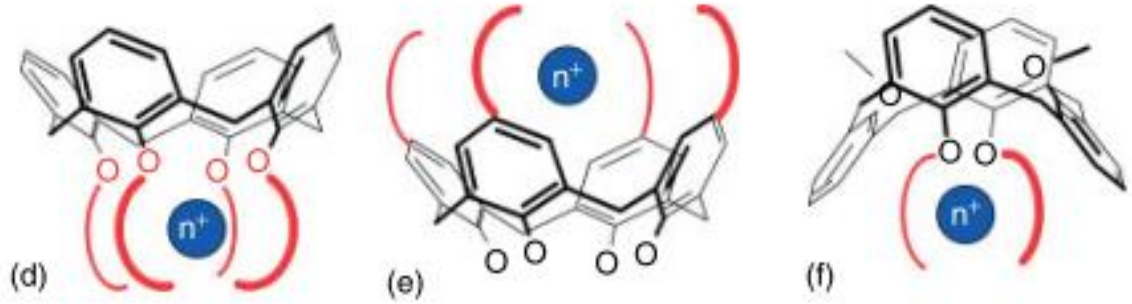
1-C. *p-tert*-butylcalix[4]-arene in $CDCl_3$

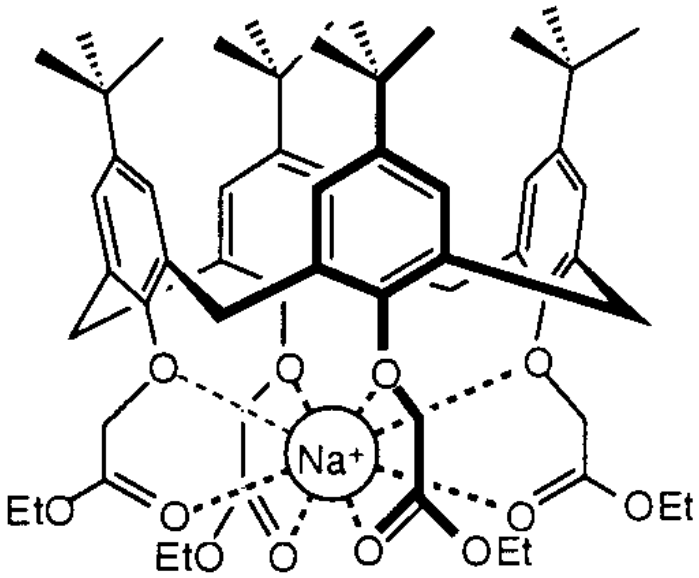


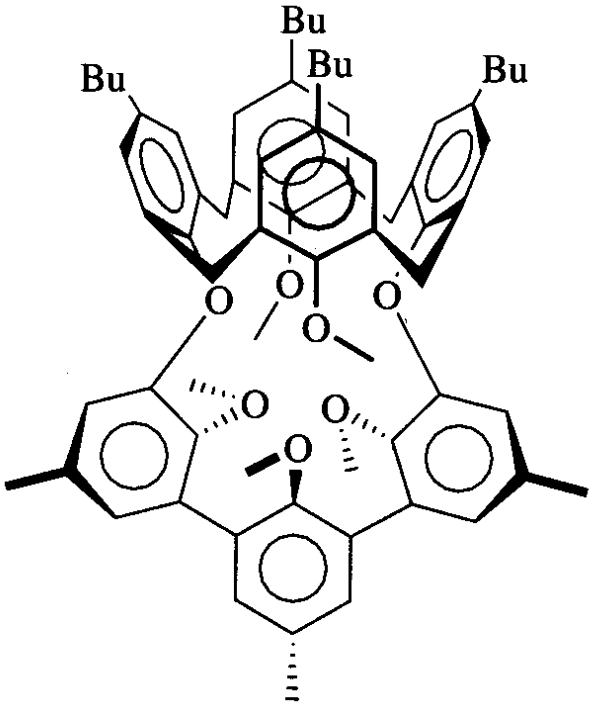
2a: R^1-R^4 = alkyl
2b: R^1, R^2 = alkyl, R^3, R^4 = OH
2c: R^1, R^3 = alkyl, R^2, R^4 = OH
2d: R^1 = alkyl, R^2–R^4 = OH
2e: R^1–R^3 = alkyl, R^4 = OH



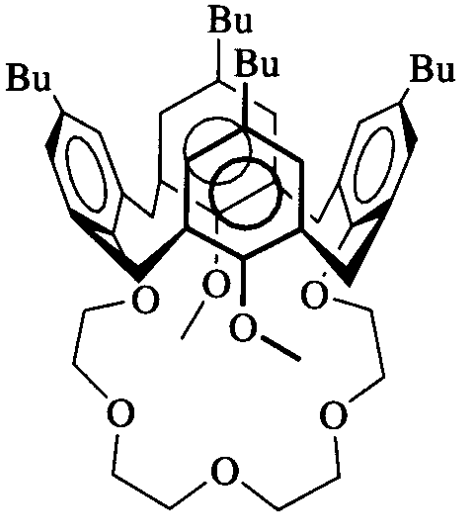



(d)
n+
(e)
n+
(f)
n+

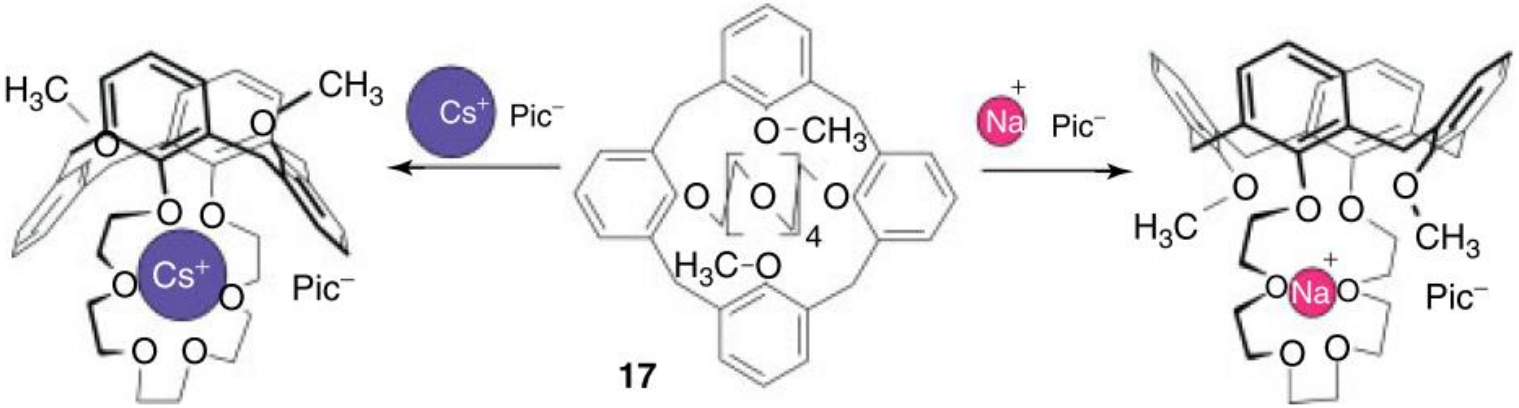

Na+
EtO
EtO
OEt
OEt



Calix-spherand



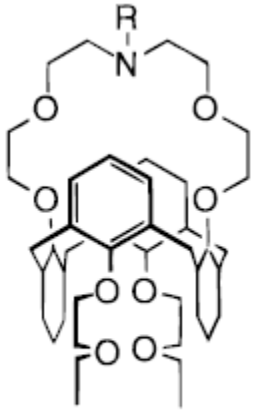
Calix-crown



J. Org. Chem. **1997**, *62,* 3568−3574

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*



R=$CH_2(CH_2)_4CH_3$

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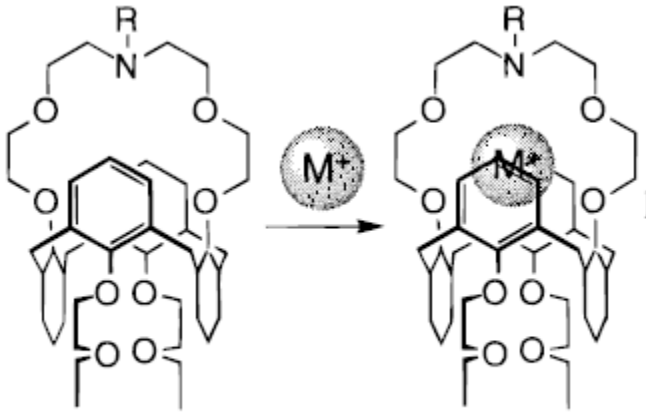

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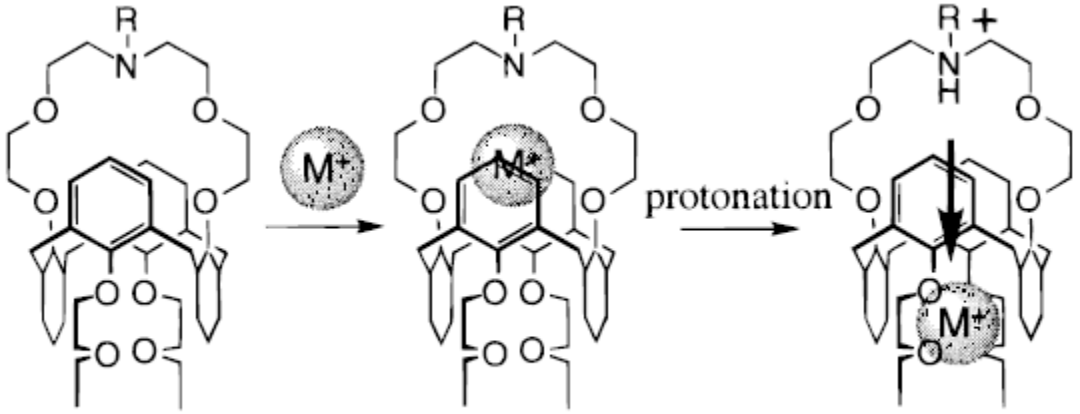
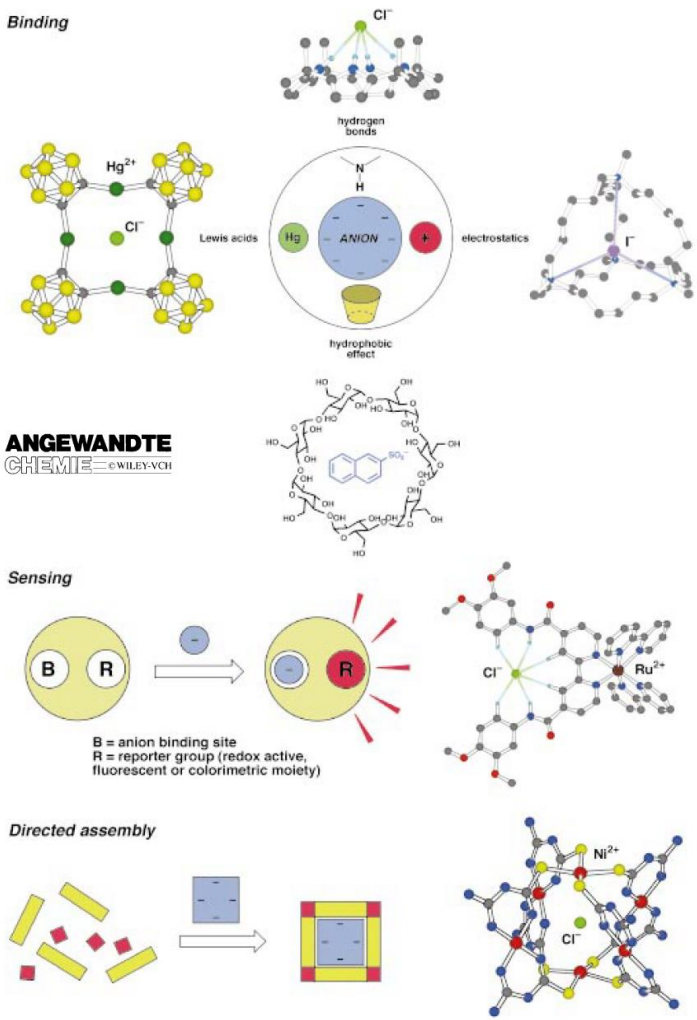


Anion Recognition and Sensing: The State of the Art and Future Perspectives

Paul D. Beer* and Philip A. Gale*

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



N. H. Evans and P. D. Beer

DOI: 10.1002/anie.201309937

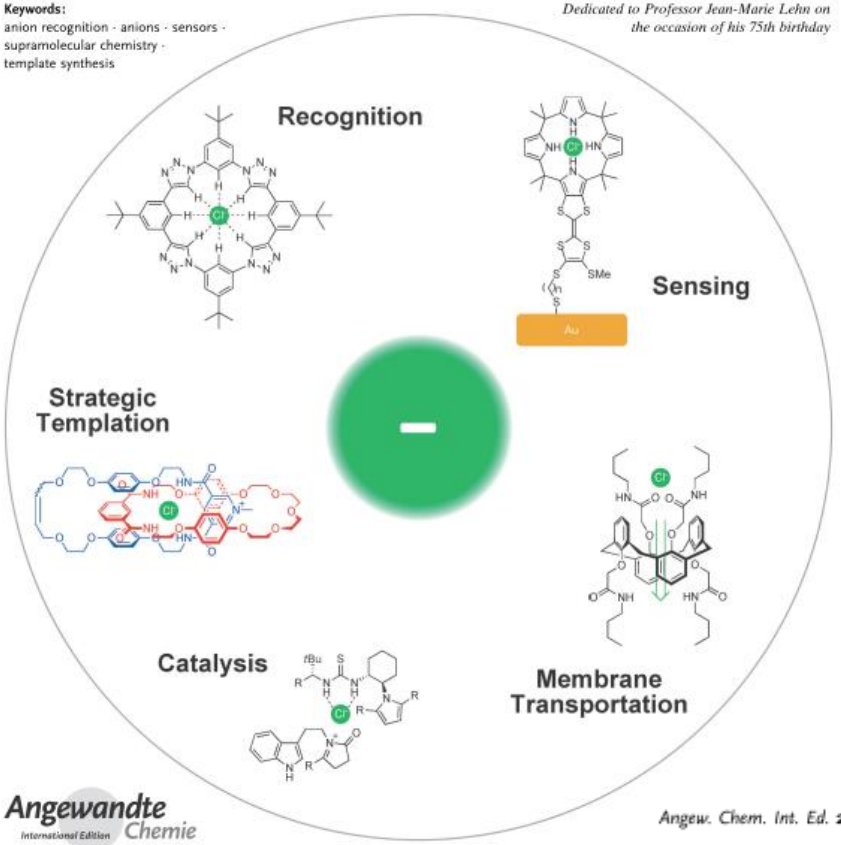
Supramolecular Chemistry of Anions

Advances in Anion Supramolecular Chemistry: From Recognition to Chemical Applications

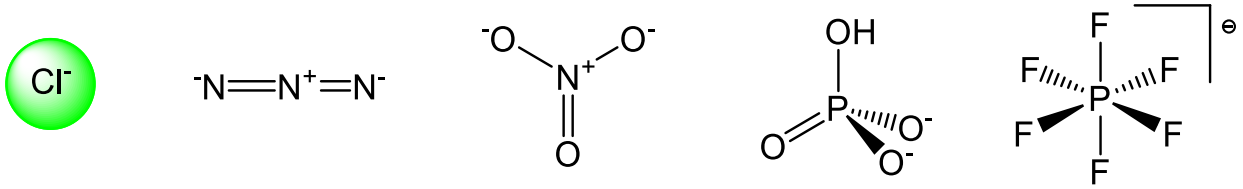
Nicholas H. Evans and Paul D. Beer**

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 - $r(F^-) \approx rK^+$
- large diversity of shapes and geometries (spherical, linear, trigonal, tetrahedral…)



- high free energies of hydration

$\Delta_r G°_{hydr}(F^-) = -465$ kJ.mol^{-1} $\Delta_r G°_{hydr}(K^+) = -295$ kJ.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

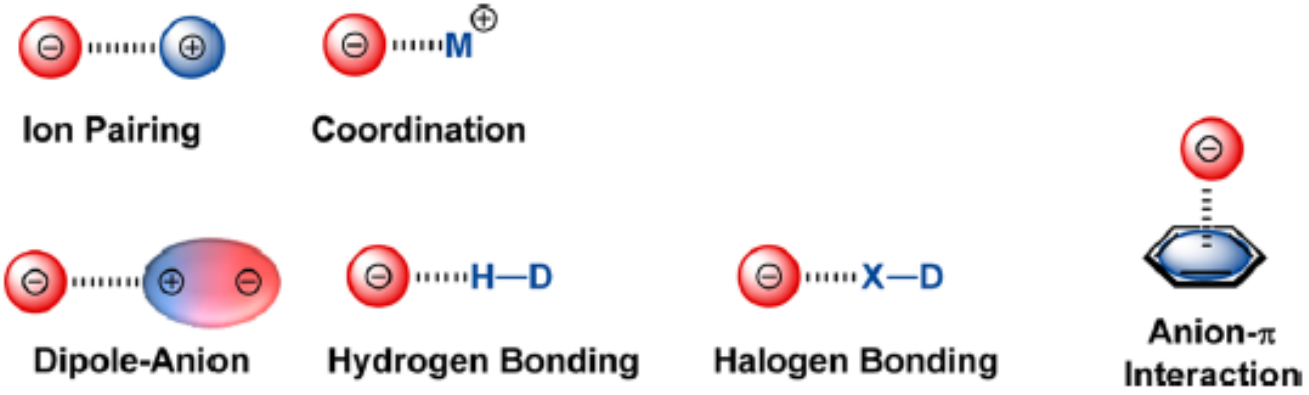
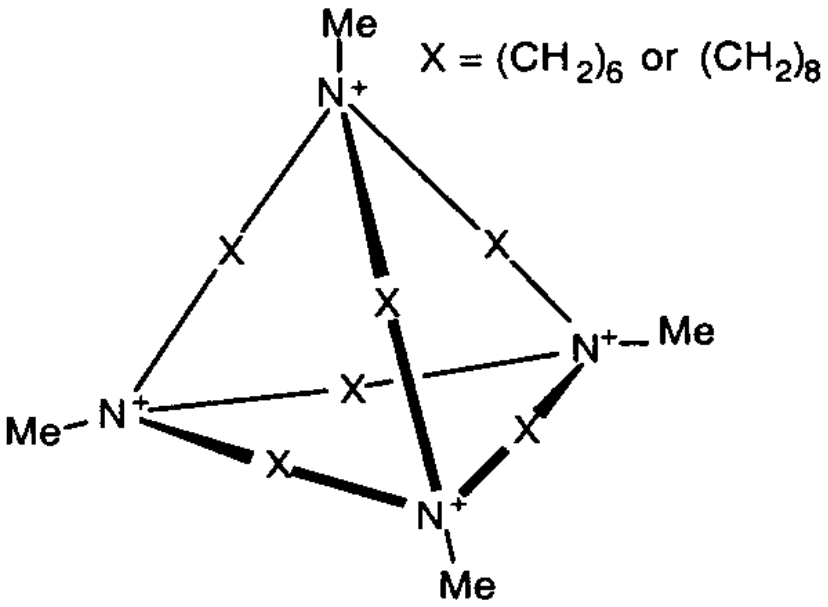


Figure 1. Representation of different interactions found in anion sensing and recognition.

Cationic Hosts



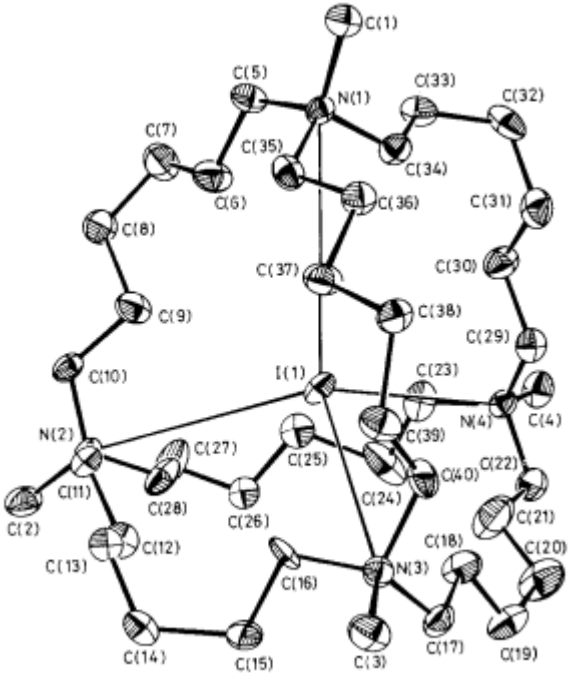
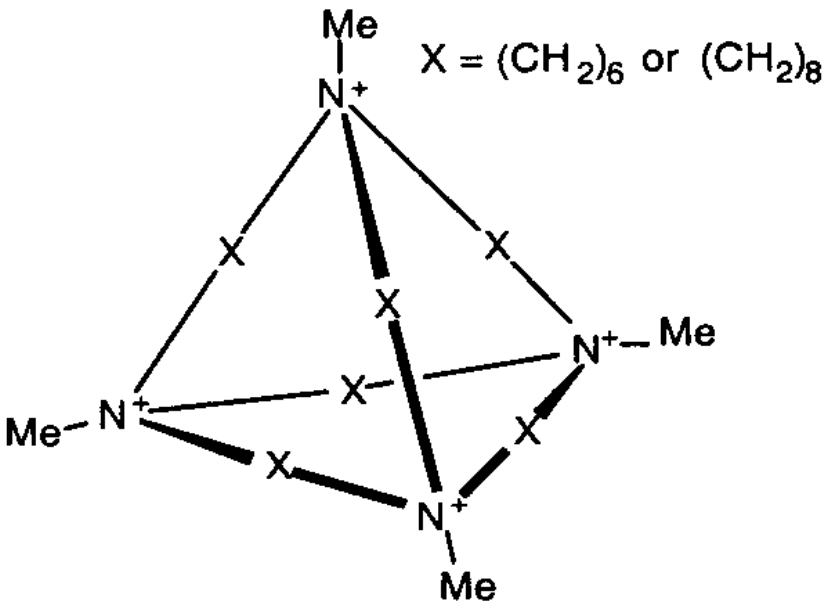


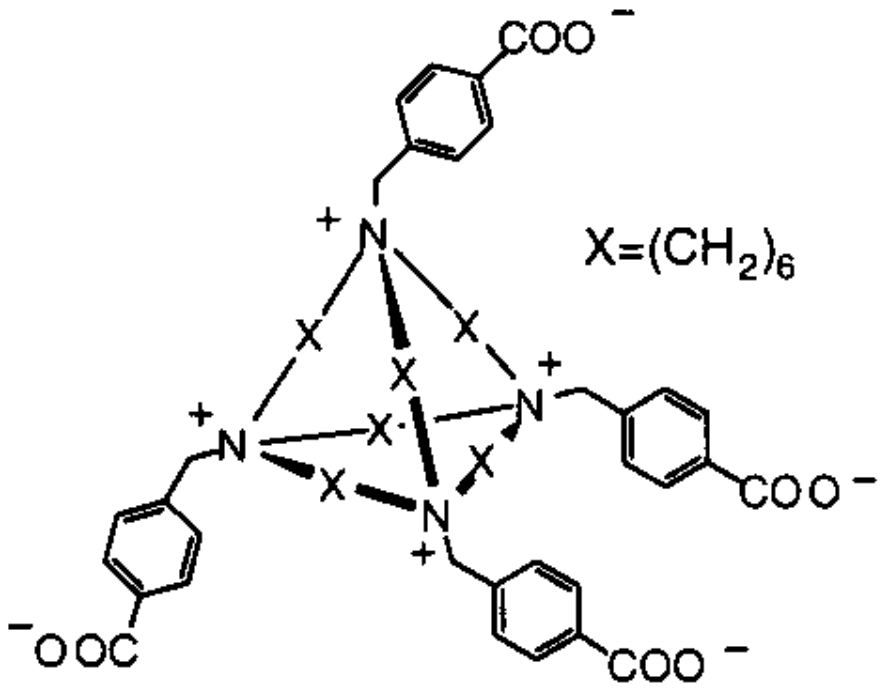
Figure 2. The X-ray crystal structure of the iodide complex of receptor **1**

Schmidtchen

Cationic receptors



Zwitter-ionic receptors

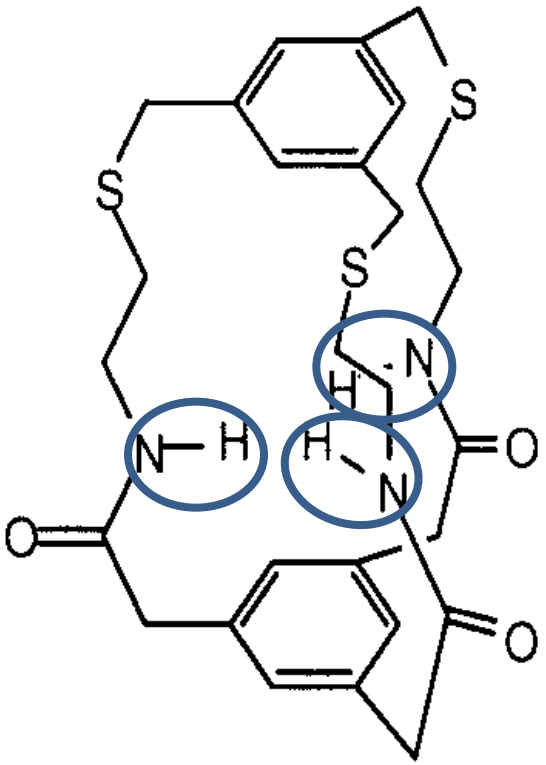


K(Br$^-$) = 1020 (H_2O)

K (Br $^-$) = 2150 (H_2O)

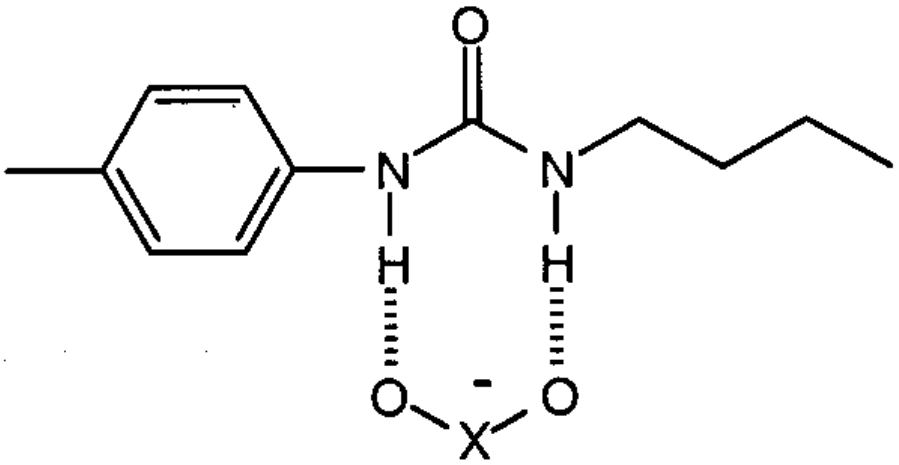
Selectivity <<

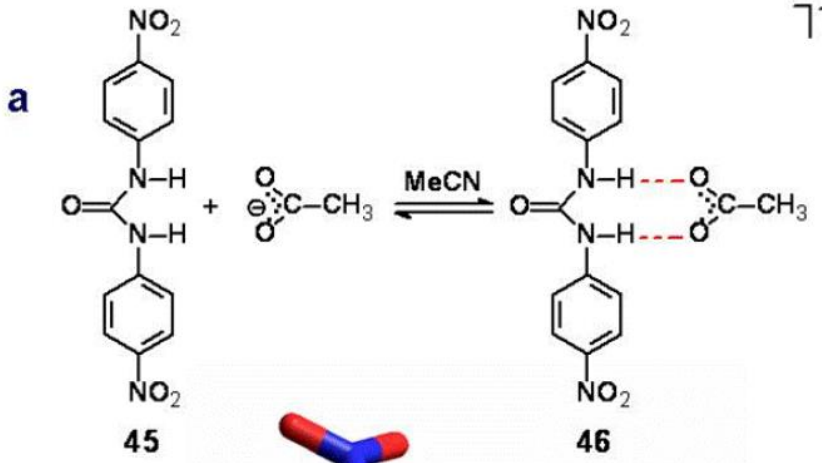
K(Br $^-$) = 1020 K(I $^-$) = 500 K(Cl$^-$) = 50

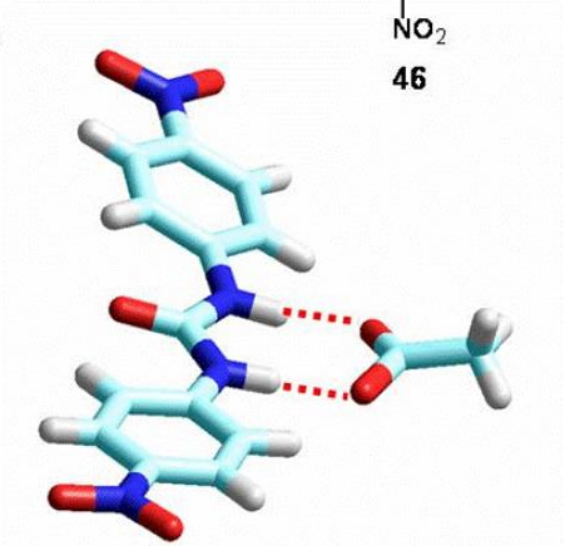


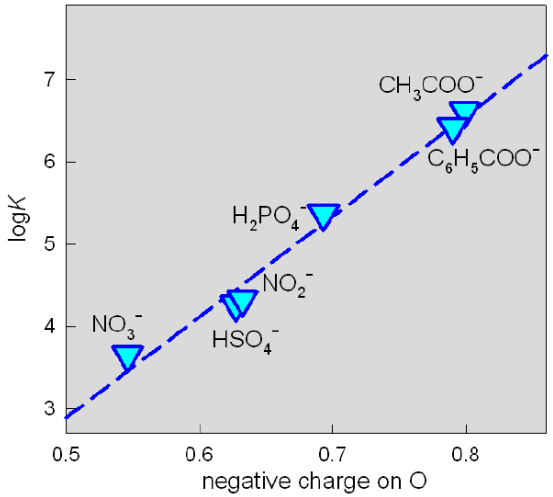
Hydrogen bonding receptor for fluoride anions.

Pascal

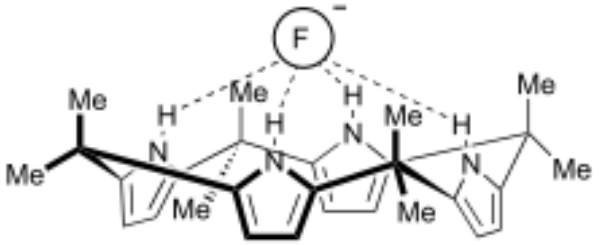


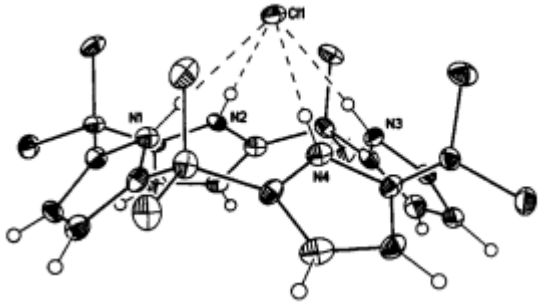

a
NO2
N–H
N–H
NO2
MeCN
C–CH3
45
46


b

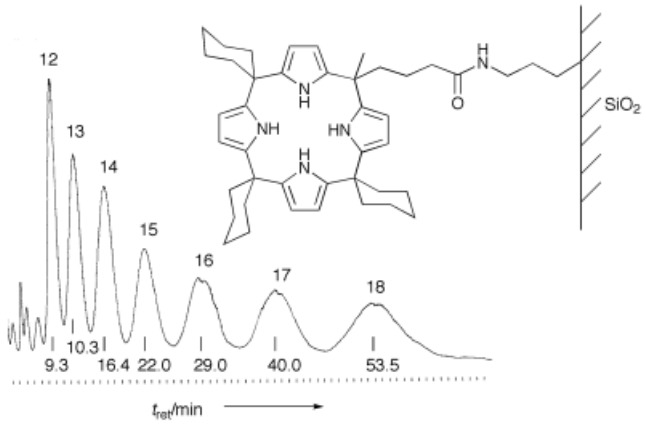

logK
negative charge on O
CH3COO-
C6H5COO-
H2PO4-
NO2-
HSO4-
NO3-
3
4
5
6
7
0.5
0.6
0.7
0.8

Fabrizzi

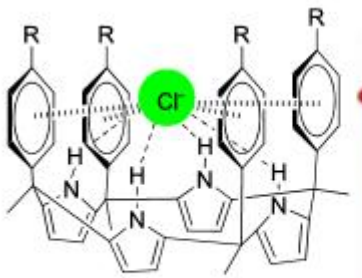




Sessler

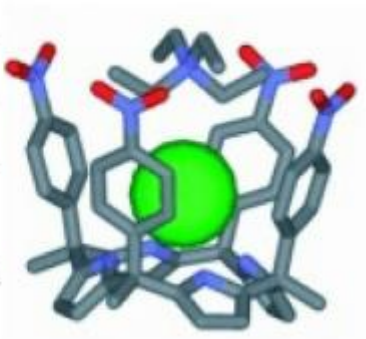


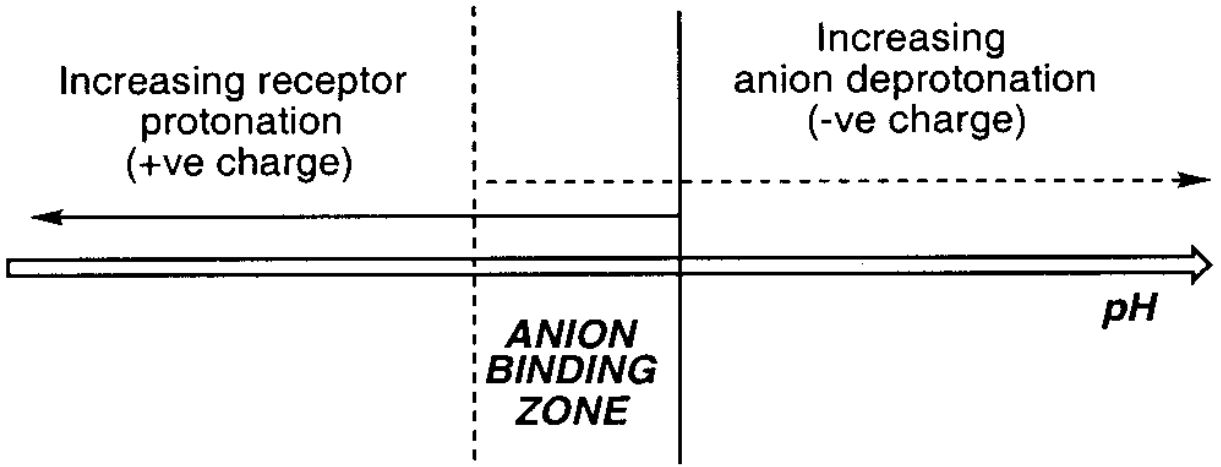
HPLC Separation of oligonuclotides of different lenght



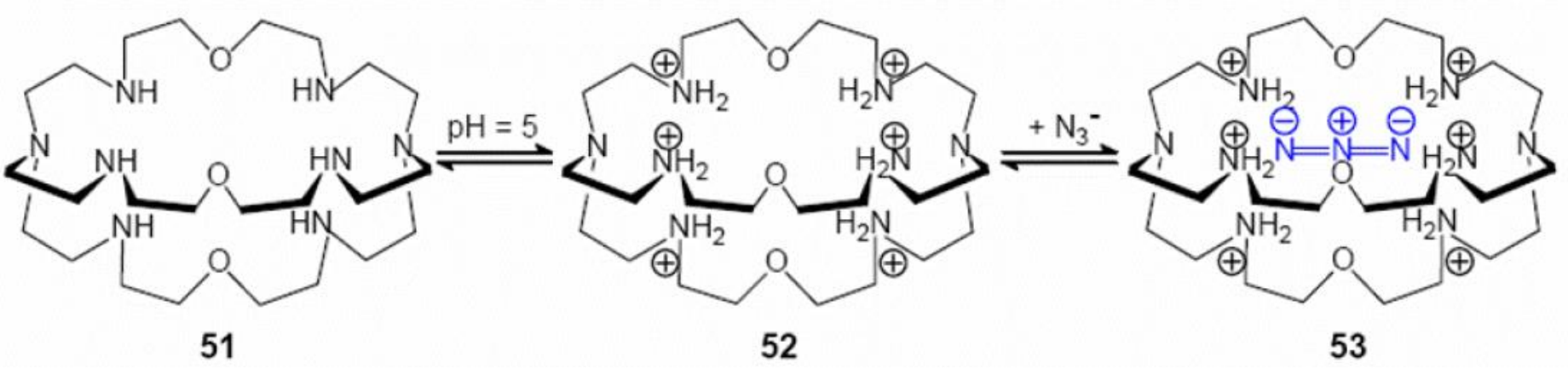
R = H, OMe, Br, CN, NO_2

57

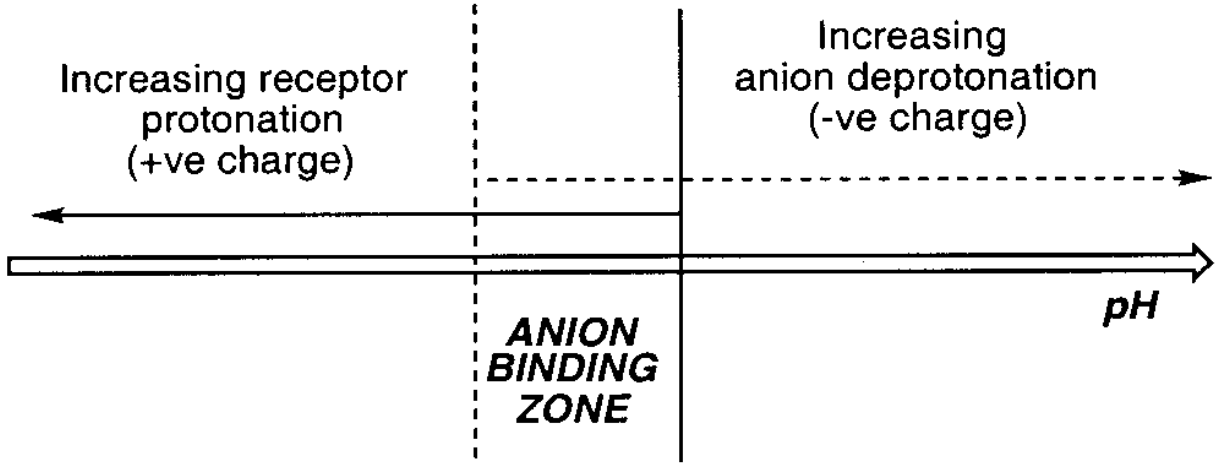




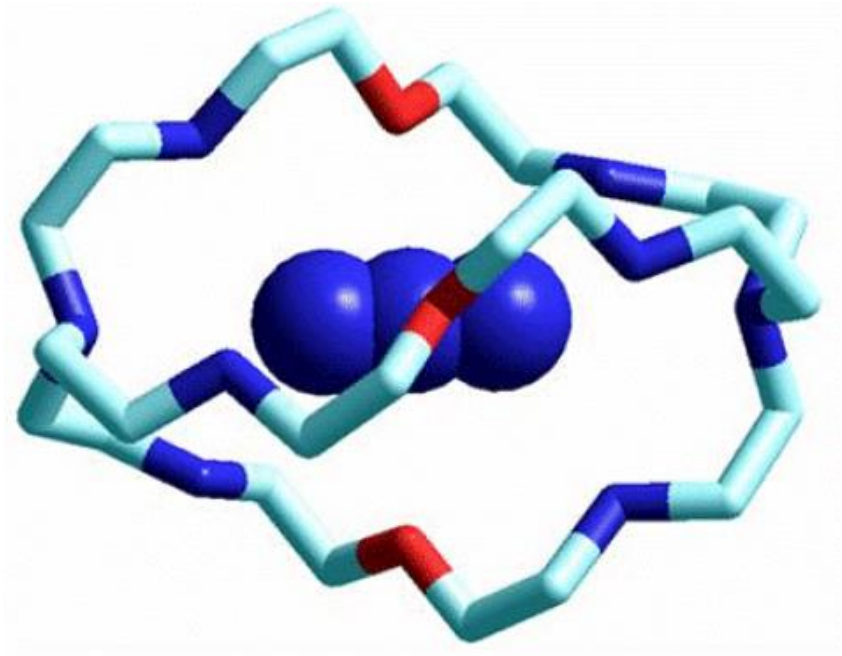
Balance between host protonation and guest deprotonation.

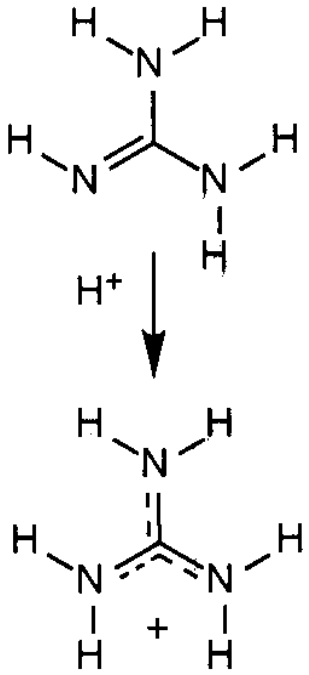


poliazamacrocycles

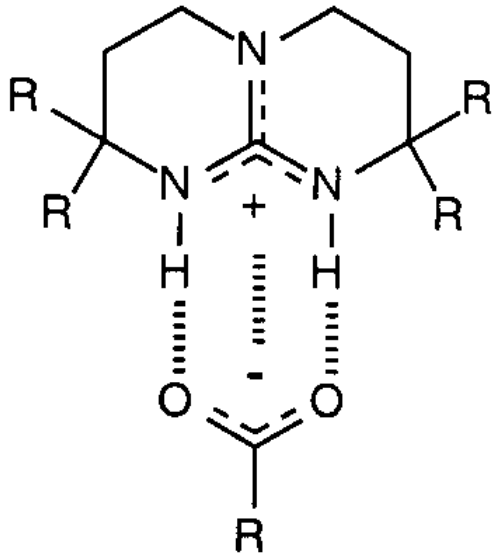


Balance between host protonation and guest deprotonation.

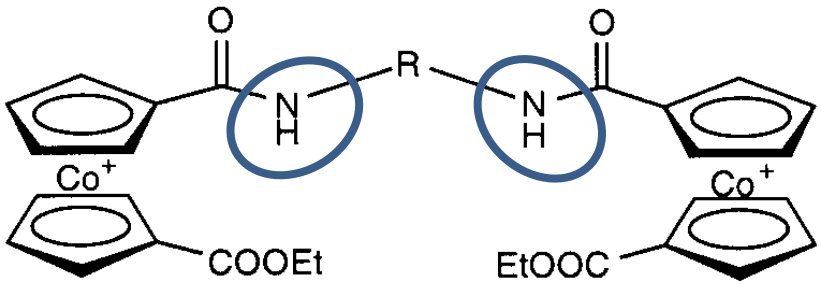




pKa = 13.6

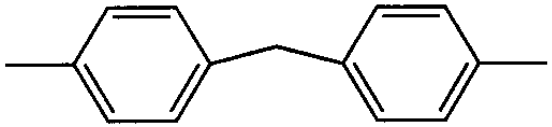


Bicyclic guanidinium is preorganized and complementary for binding bidentate anions.



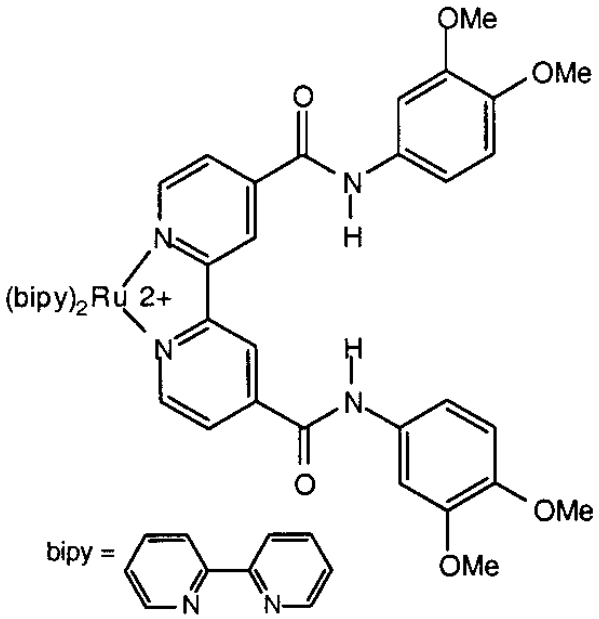
—R— =

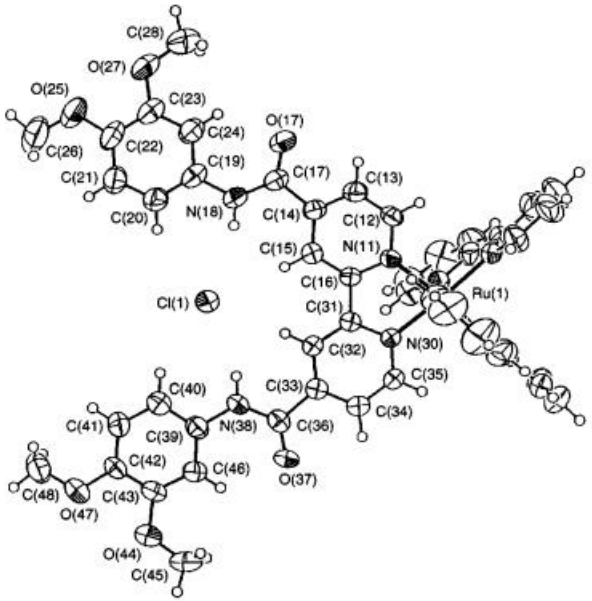
Binds 1 Cl⁻



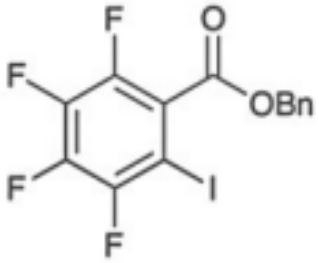
Binds 2 Cl⁻

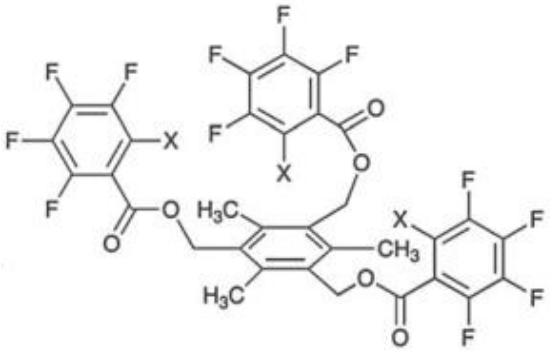
Cobaltocenium based anion receptors have easily tunable binding sites.



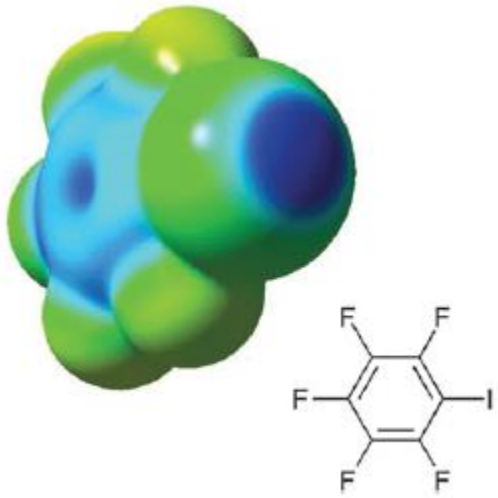


Beer

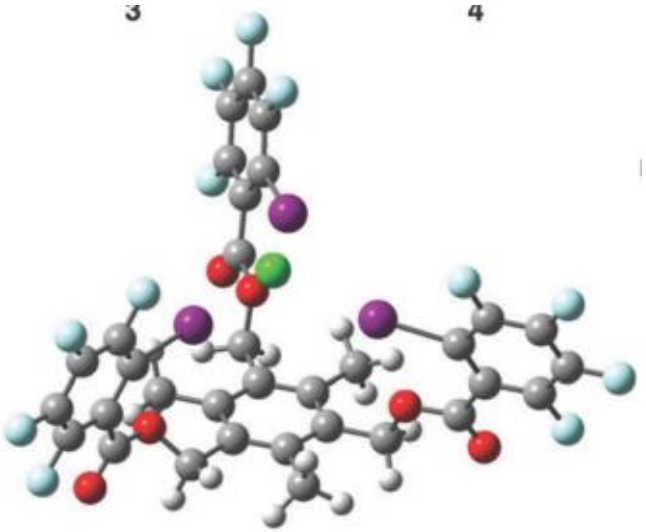




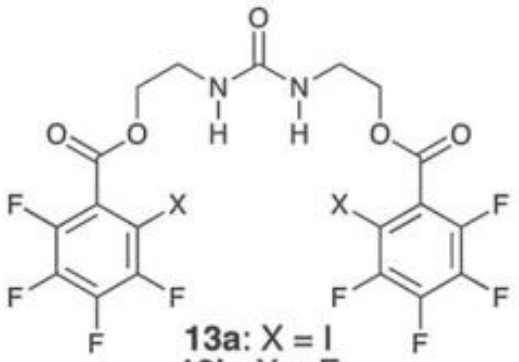
ortho-substituted iodotetrafluroroarenes on to trimethylbenzene scaffold



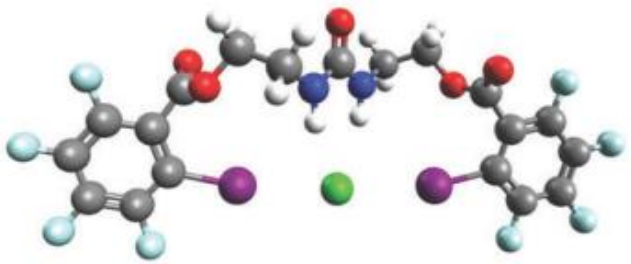
In acetone: $Cl^- > Br^- > I^-$



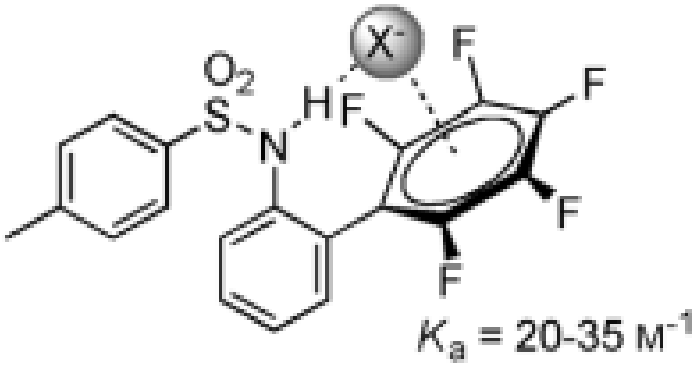
Taylor



13a: X = I
13b: X = F

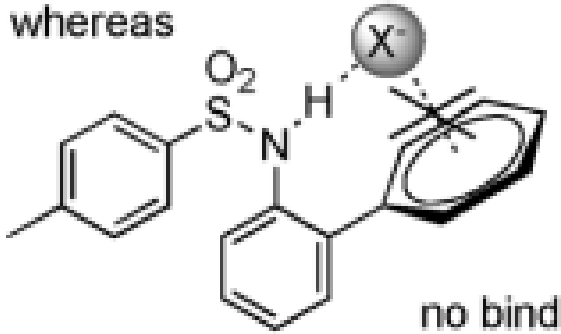


(a)



K_a = 20-35 M^{-1}

whereas



no binding

Berryman

(a)

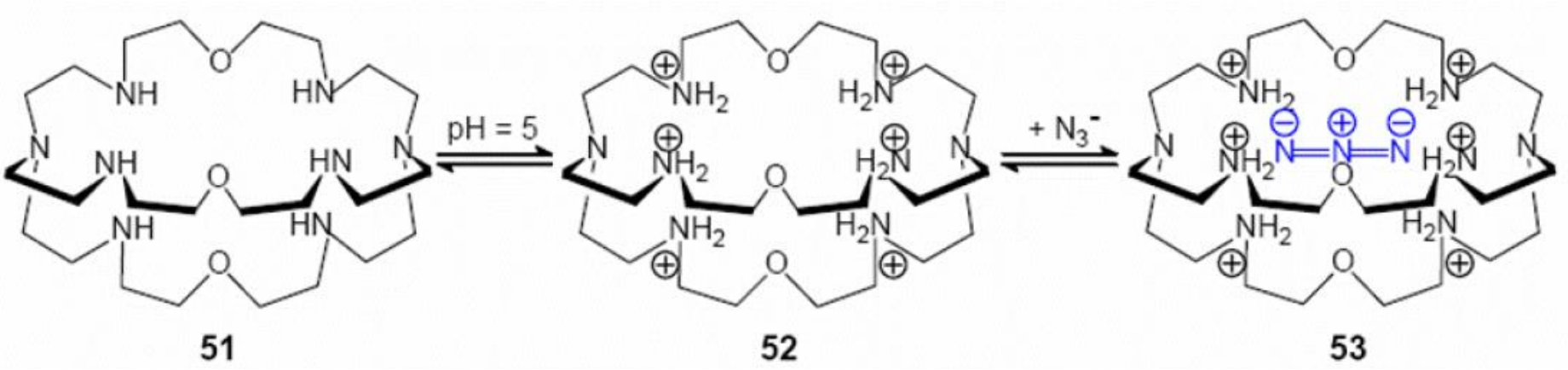
A cascade complex.

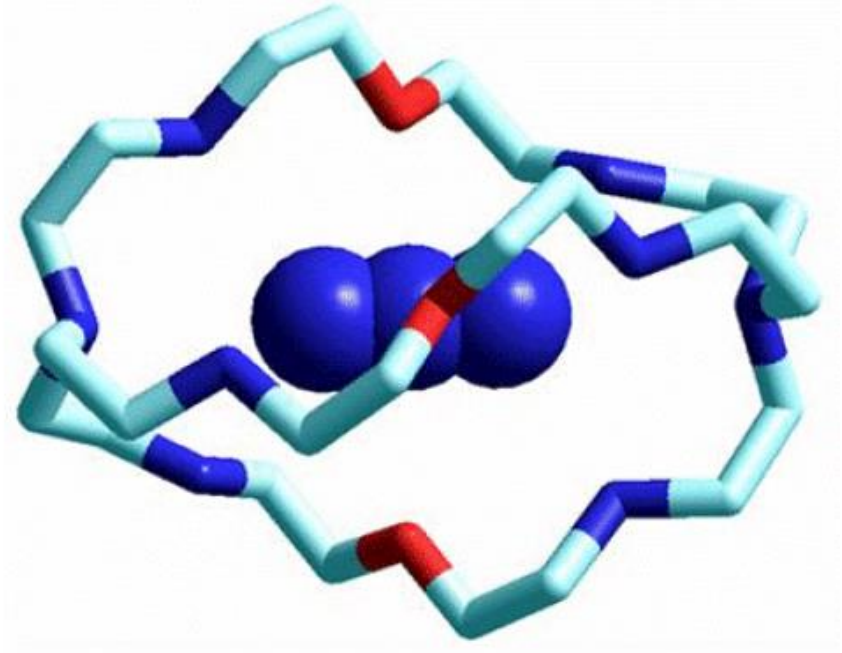
(b)

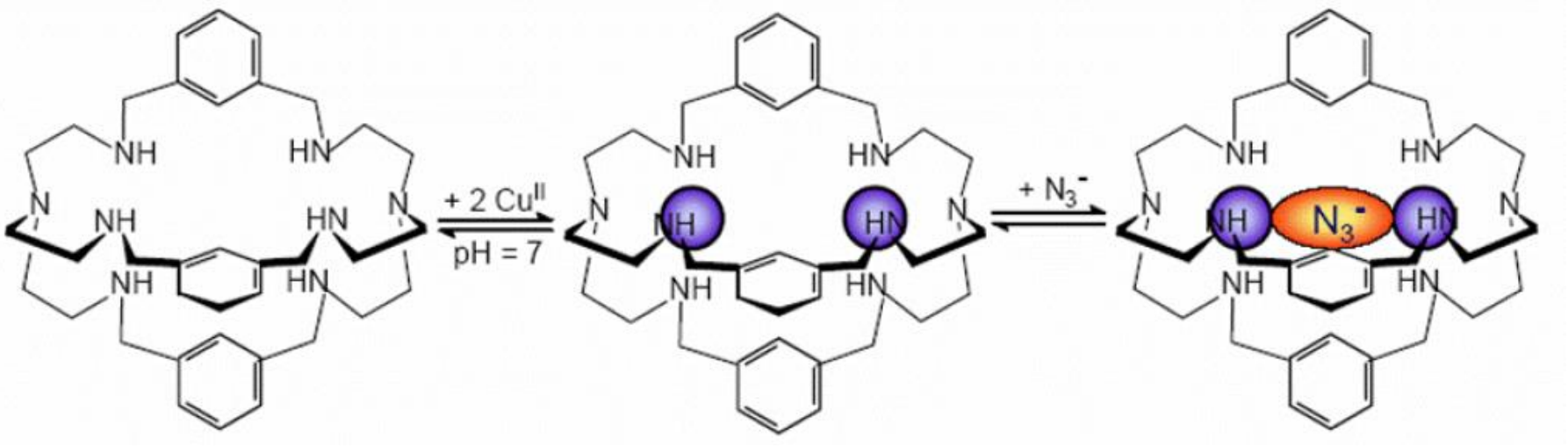
Receptor with individual cation and anion recognition sites.

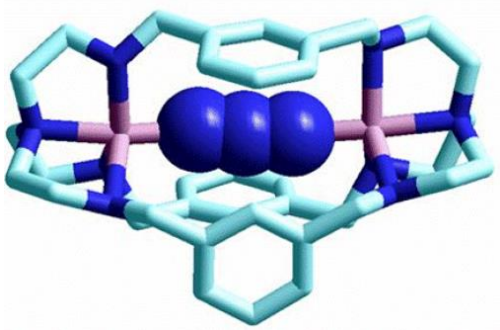
(c)

Receptor for zwitterionic guests.

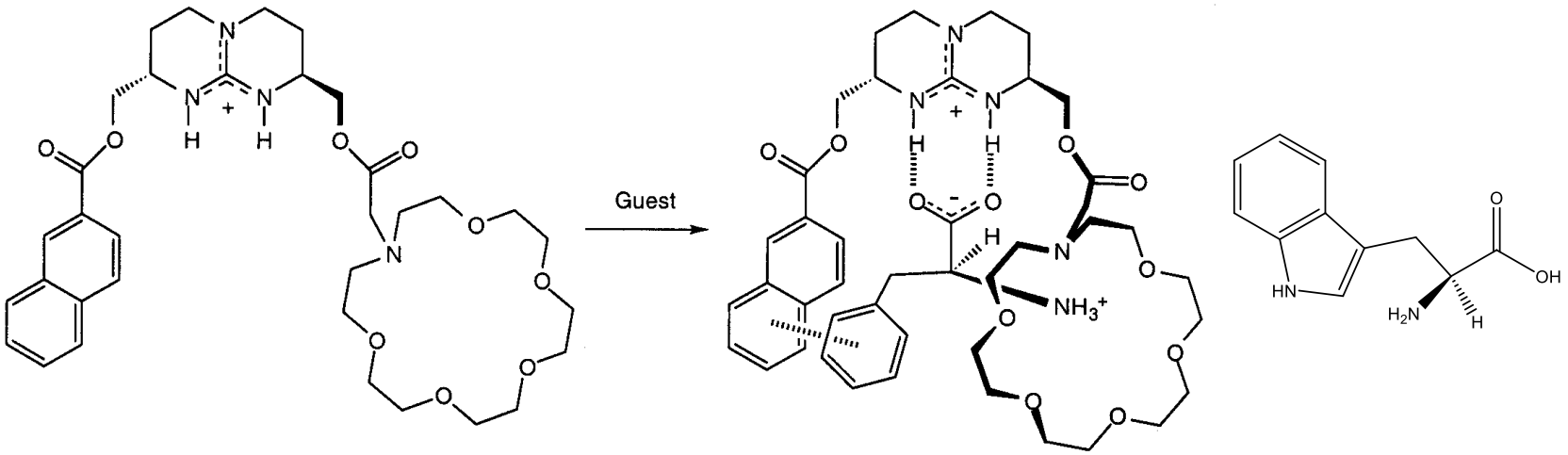

pH = 5
+ N_3^-
51
52
53




NH
HN
N
NH
HN
N
NH
HN
+ 2 Cu^II
pH = 7
+ N3^-
N3^-



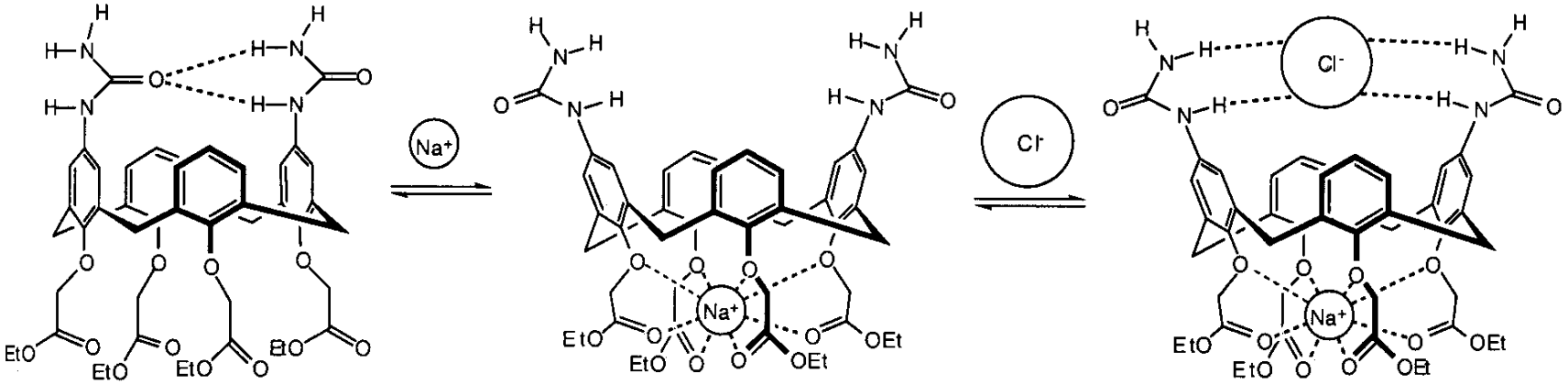
Extraction of aa's with aromatic side chains (Phe, Trp) in CH_2Cl_2



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*



The addition of Bu_4NCl and Bu_4NBr to a 5 mM solution of the **2a**·Na^+ complex results in a clear downfield shift of the ^1H NMR signals of the urea hydrogens, indicating complexation of the anionic guests through hydrogen bonding.[6] In con-

Addition of an excess of **2** or **5a,b** to a solution of the salt complexes gives two sets of distinctly separate signals for the complex and the free receptor in the ^1H NMR spectrum. This means that the cation and anion are always complexed to the same molecule and that calix[4]arenes with only a cation or an anion are not present.

The strong complexation of the NaX salts indicates the strong preference of the receptors for Na^+ ions. Only partial complexation of KX salts is observed, in agreement with the weaker binding of K^+ ions by calix[4]arene tetra(ethyl esters).[7] No complexation of Cs^+ salts is observed, apparently because the Cs^+ ion is too large to fit in the cavity. Although the solubility of the free salts in chloroform is very low and decreases in the order MI > MBr > MCl, the preferential extraction of chloride salts indicates the higher affinity of the urea binding sites for Cl^- ions over Br^- and I^- ions.

Addition of NaCl or NaBr to a chloroform solution of calix[4]arene **7**, which lacks an anion binding site, did not result in any complexation of Na^+ ions. Addition of NaCl and NaBr to a chloroform solution of calix[4]arene **6**, which lacks the cation binding site, did not result in complexation of Cl^- or Br^- ions. The addition of NaCl or NaBr to a 1:1 mixture of **6** and **7** in $CDCl_3$ did not result in the complexation of Na^+ and Cl^- or Br^- ions. This shows clearly that both the cation binding site and the anion binding site are necessary for the complexation of NaCl or NaBr and that these must be within the same calix[4]arene skeleton.

The Structure of the Potassium Channel: Molecular Basis of K^+ Conduction and Selectivity

Declan A. Doyle, João Morais Cabral, Richard A. Pfuetzner, Anling Kuo, Jacqueline M. Gulbis, Steven L. Cohen, Brian T. Chait, Roderick MacKinnon*

Science **280**, 69 (1998);
DOI: 10.1126/science.280.5360.69

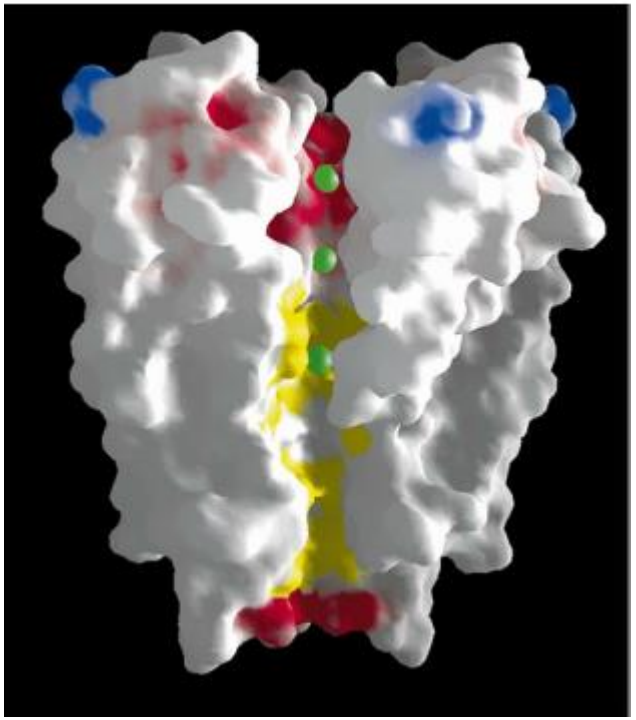
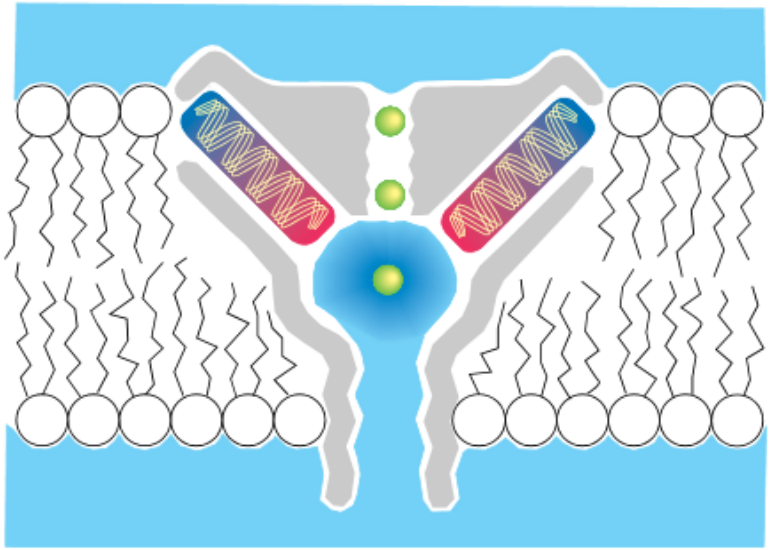


Fig. 7. Two mechanisms by which the K^+ channel stabilizes a cation in the middle of the membrane. First, a large aqueous cavity stabilizes an ion (green) in the otherwise hydrophobic membrane interior. Second, oriented helices point their partial negative charge (carboxyl end, red) towards the cavity where a cation is located.



http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2003/

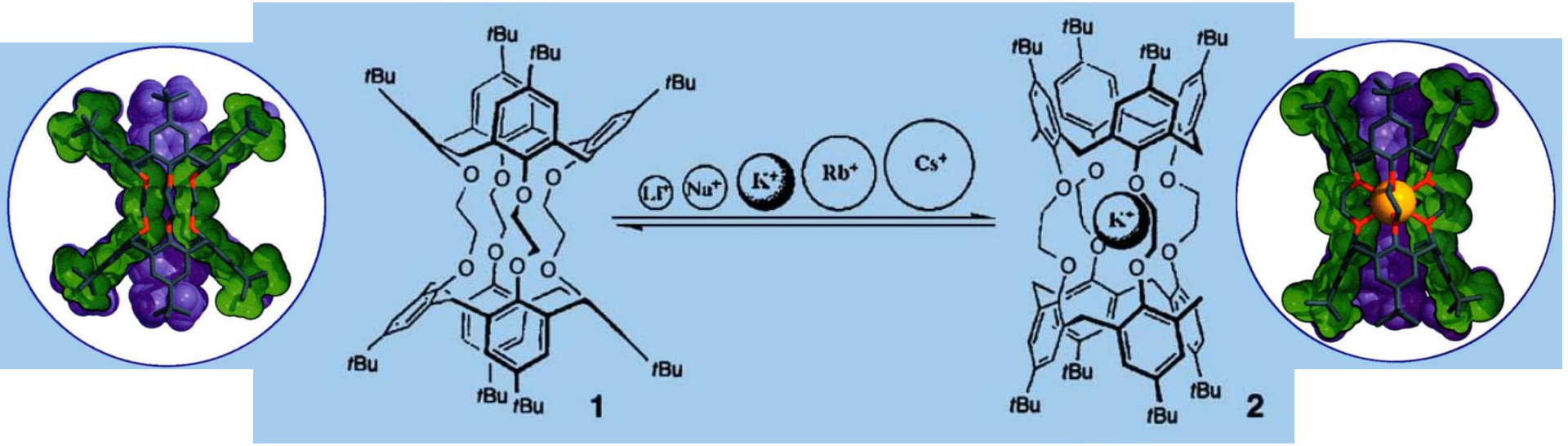
Peter Agre **Roderick MacKinnon**

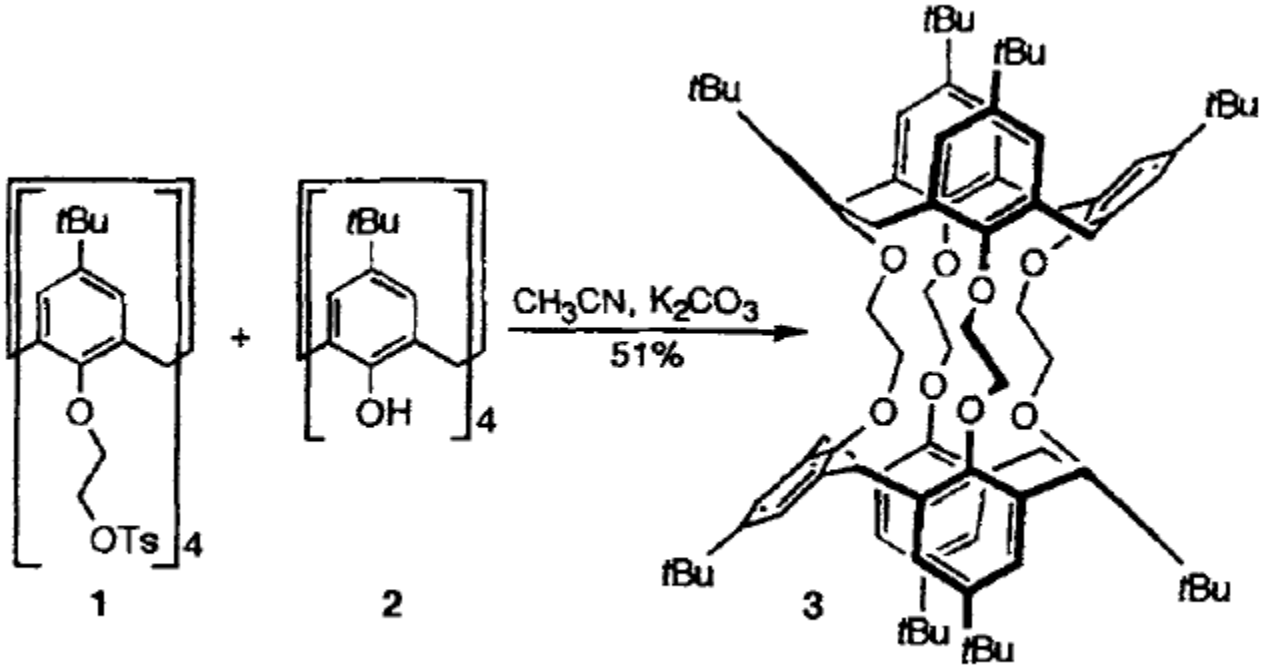
The Nobel Prize in Chemistry 2003 was awarded *"for discoveries concerning channels in cell membranes"* jointly with one half to Peter Agre *"for the discovery of water channels"* and with one half to Roderick MacKinnon *"for structural and mechanistic studies of ion channels"*.

Calix[4]tube: A Tubular Receptor with Remarkable Potassium Ion Selectivity**

Philippe Schmitt, Paul D. Beer,* Michael G. B. Drew, and Paul D. Sheen

Angew. Chem. Int. Ed. Engl. **1997**, *36*, 1840





Scheme 1. Synthesis of the calix[4]tube **3**.

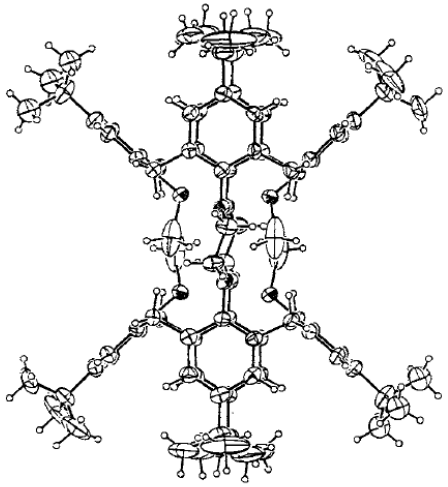


Figure 1. Crystal structure of the centrosymmetric calix[4]tube **3** in $3 \cdot 2.5\,C_6H_6$, with ellipsoids at 30% probability. Hydrogen atoms are included with small arbitrary radii. The benzene solvent molecules are not shown.

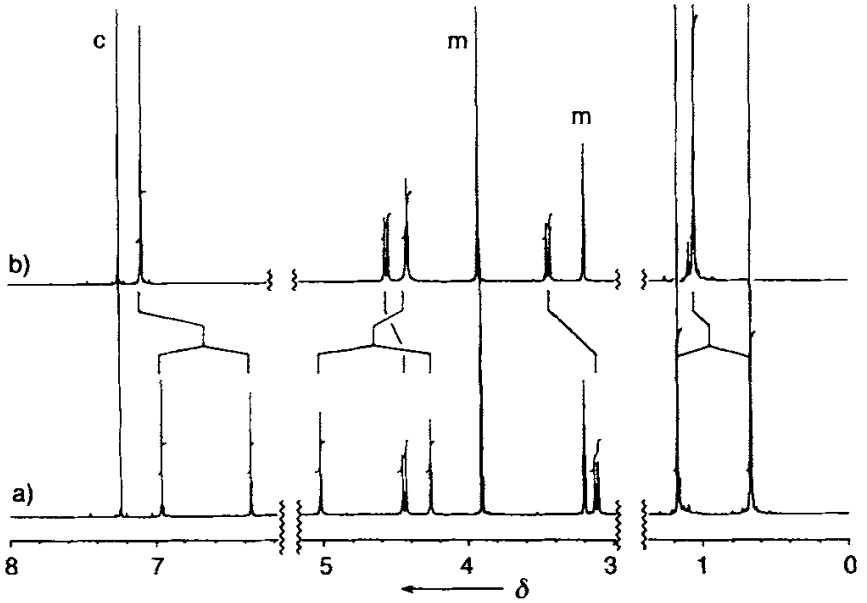


Figure 2. ^1H NMR spectrum of **3** [500 MHz, $CDCl_3/CD_3OD$ 4/1 (v/v)]: a) pure, b) with 10 equivalents of solid potassium iodide (c, m: solvent peaks corresponding to chloroform and methanol, respectively).

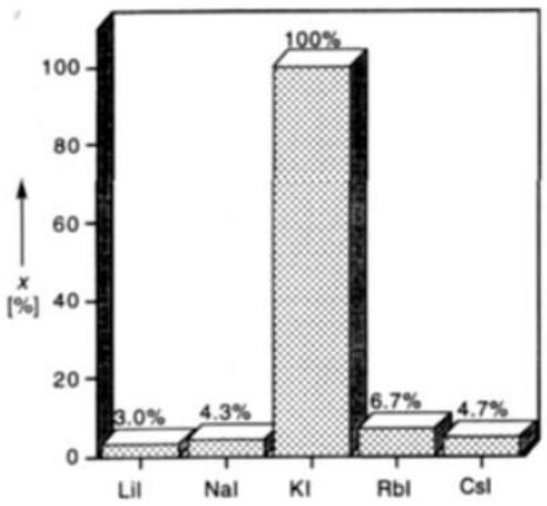


Figure 3. Uptake of alkali metal ions by **3** after treating its chloroform-methanol solution (4/1, [**3**] = 1 mM) with 10 equivalents of alkali metal iodide. The complexation ratio x was determined by integration of the ^{1}H NMR spectra after the samples had been left to stand for 90 h. In the case of KI, equilibrium was reached within an hour.

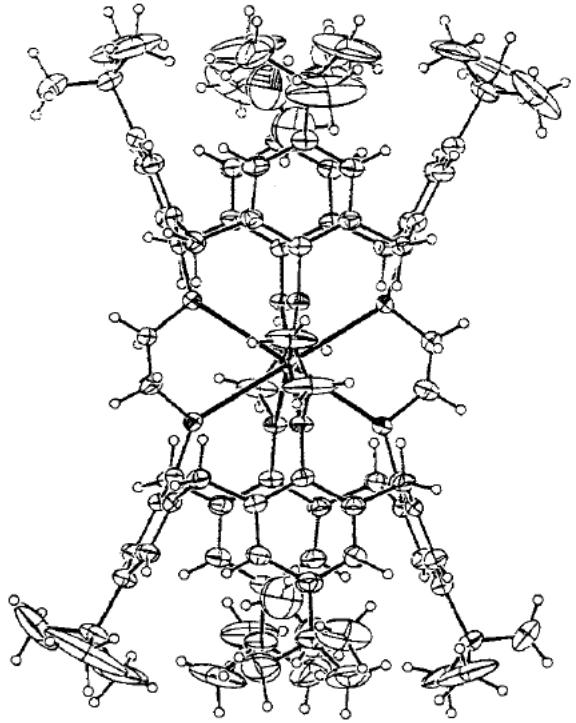
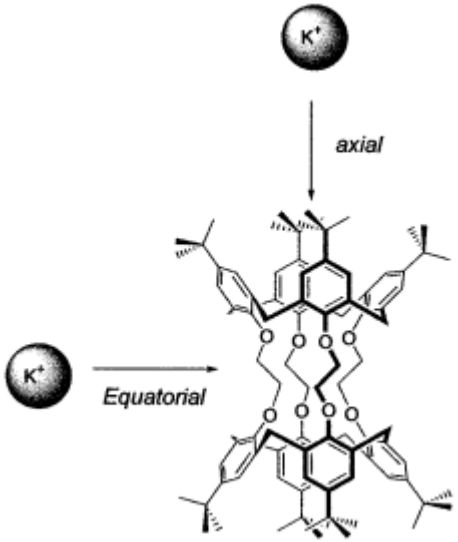
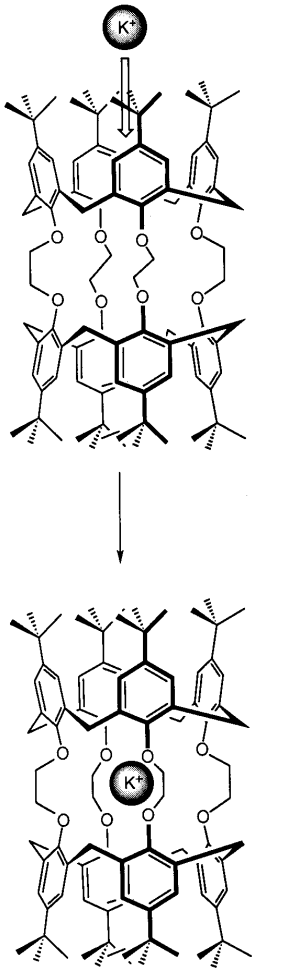


Figure 4. Structure of the K^+ complex **4** of the calix[4]tube **3** in crystals of **4**·I·3 $CHCl_3$·4 CH_3OH·H_2O. A potassium ion is located in the center of **3**, and two methanol molecules in the cone cavities. Ellipsoids are drawn at 30% probability. Hydrogen atoms are included with small arbitrary radii. The chloroform and water solvent molecules are not shown.

Calix-tubes





Potassium encapsulation in calix[4]tube