

Corso di Chimica Supramolecolare

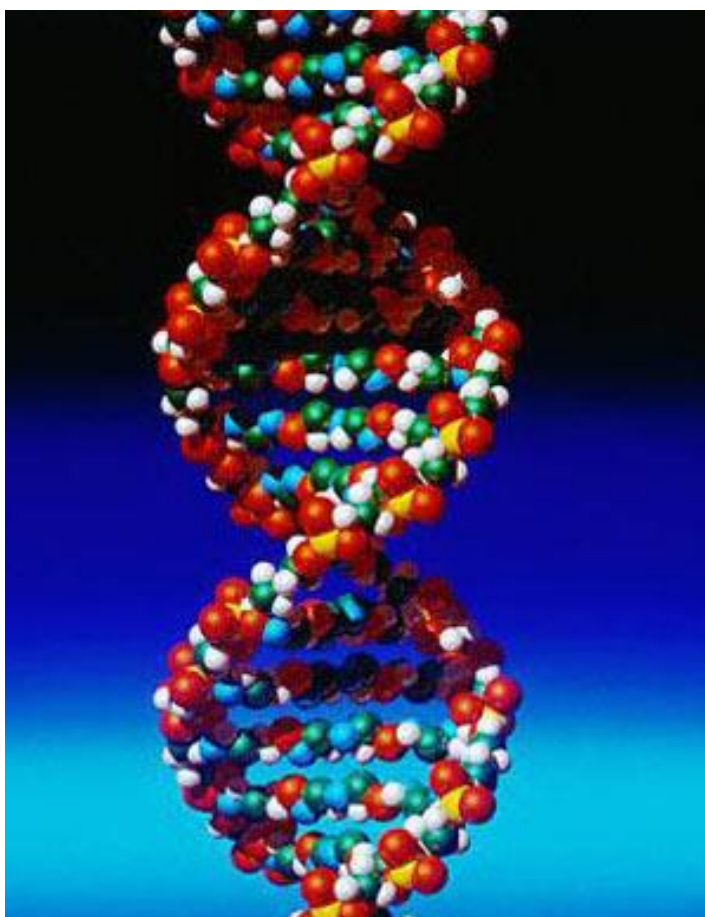
(LM in Chimica @units)

AA 2020/2021

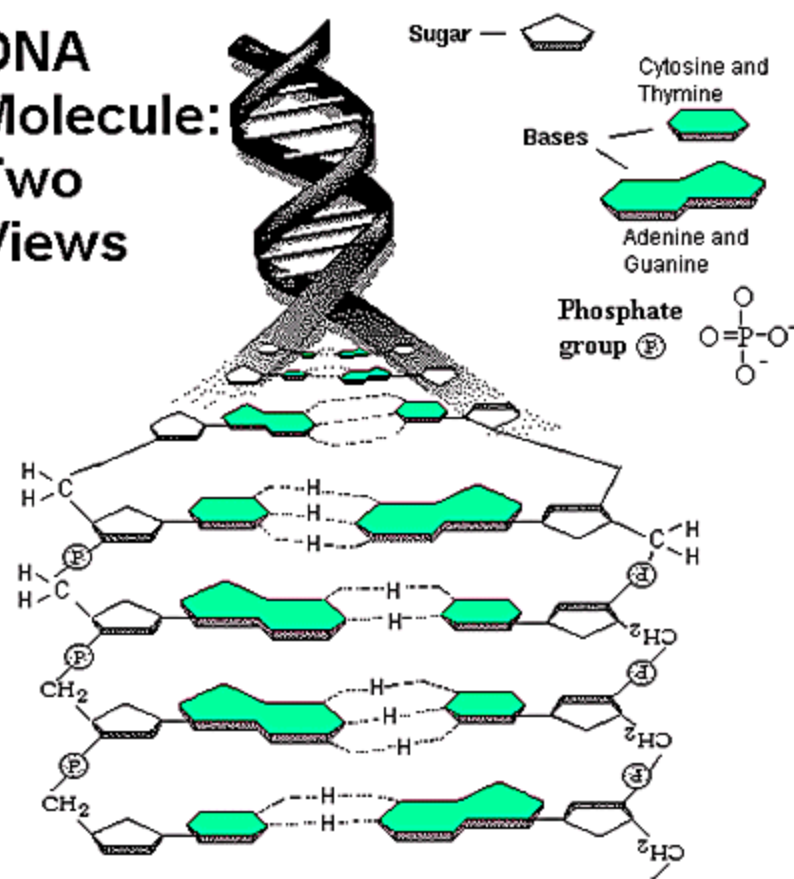
Prof. E. Iengo
eengo@units.it

The original inspiration: Supramolecular systems in Nature

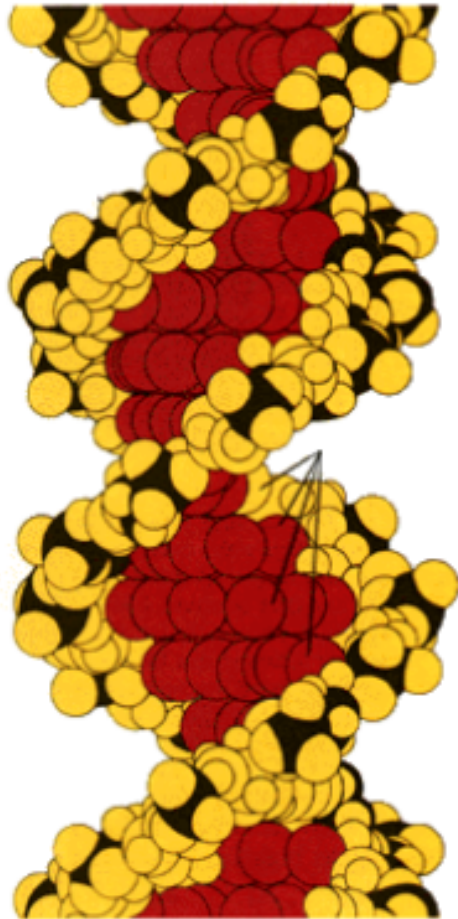
DNA



DNA
Molecule:
Two
Views



Information Storage



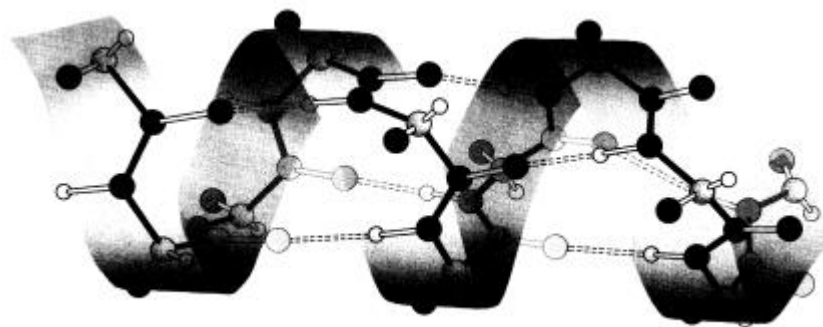
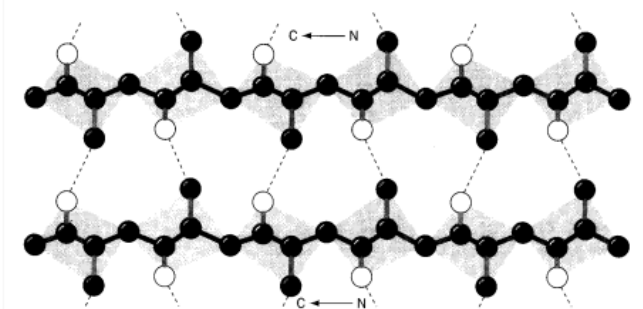
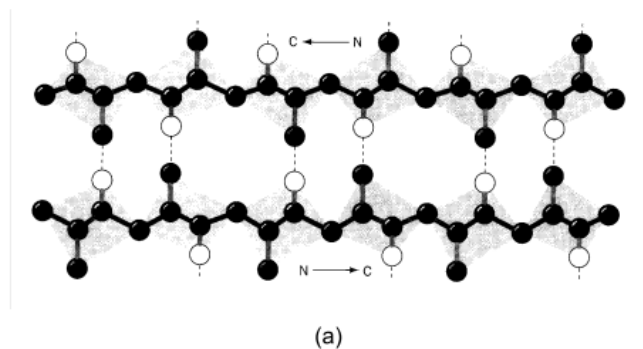
The ultimate supramolecular material?

- Encodes gigabytes of data
- Can Self-Replicate
- Built-in Error Correction
- Is the basis of life

Watson & Crick 1953

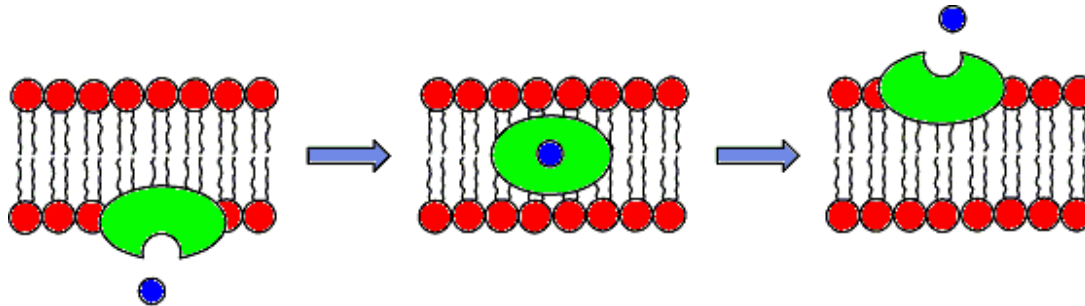
The original inspiration: Supramolecular systems in Nature

PROTEINS



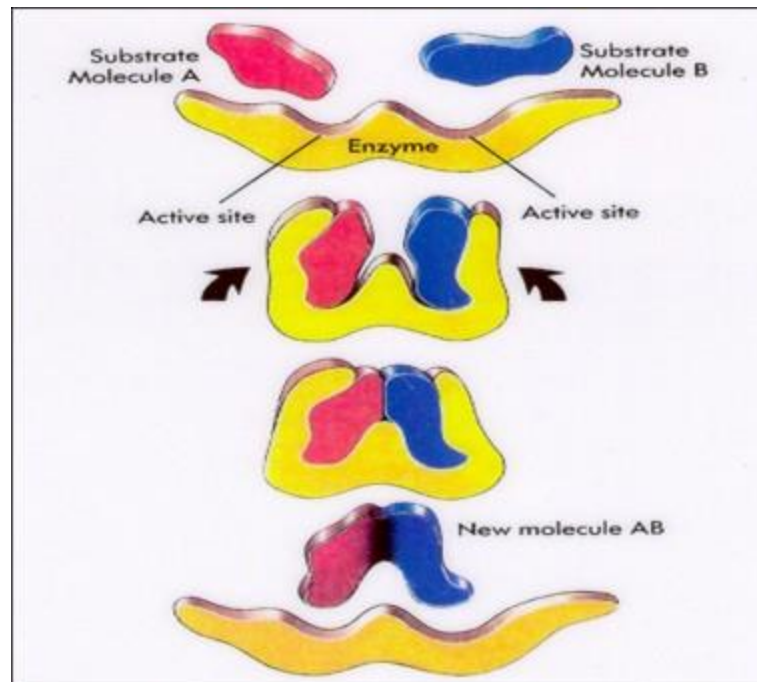
The original inspiration: Supramolecular systems in Nature

MEMBRANES and TRANSMEMBRANE CARRIERS



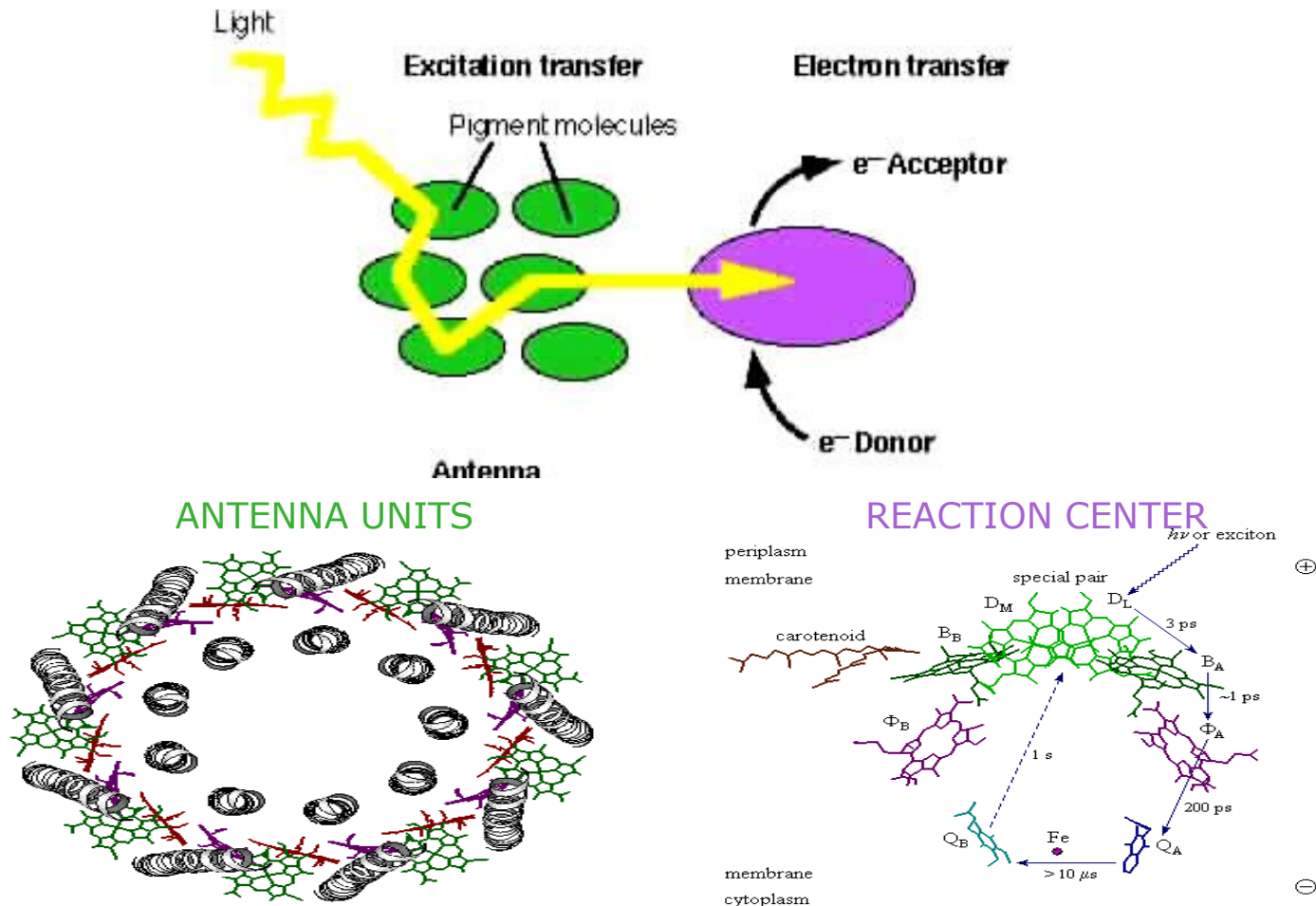
The original inspiration: Supramolecular systems in Nature

ENZYMES



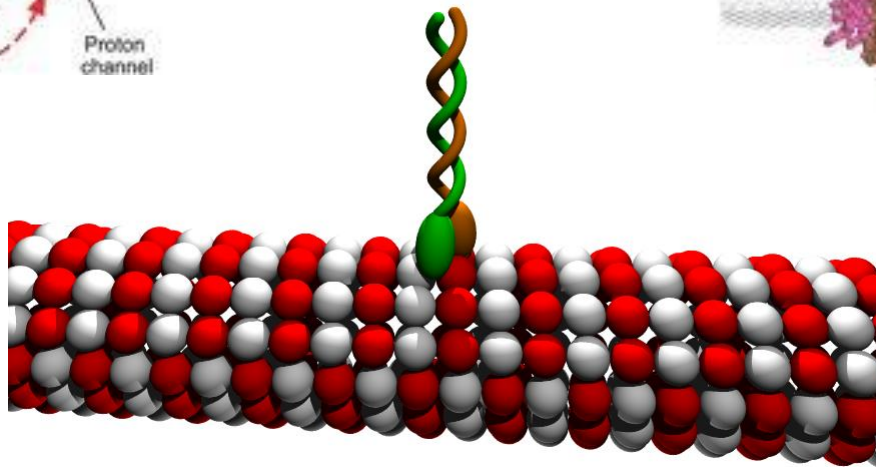
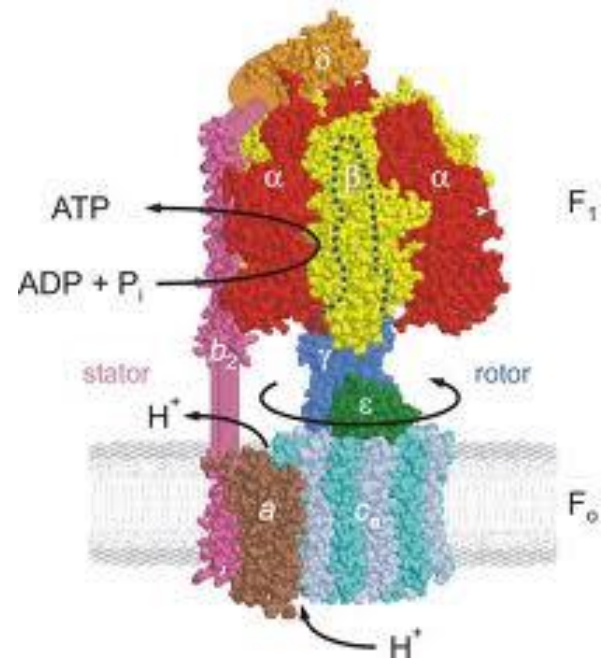
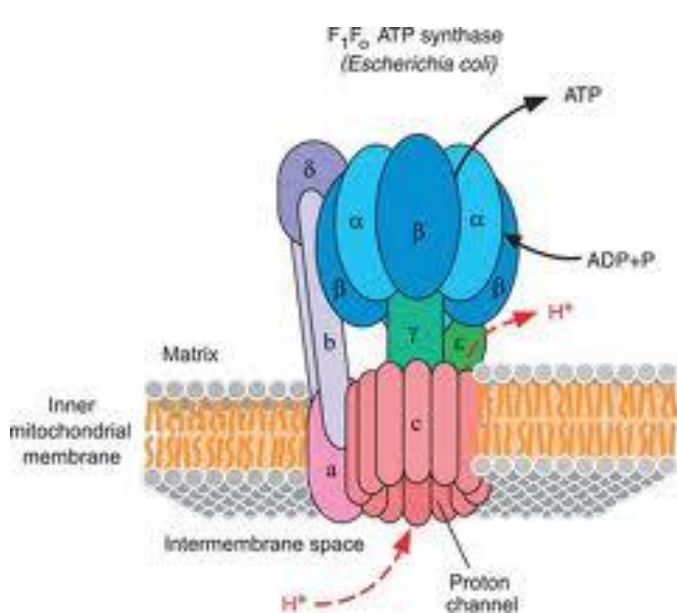
The original inspiration: Supramolecular systems in Nature

THE PHOTOSYNTHETIC APPARATUS



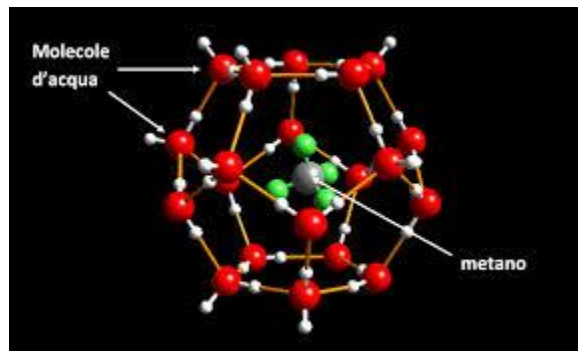
The original inspiration: Supramolecular systems in Nature

ATP Synthase and KINESIN



The original inspiration: Supramolecular systems in Nature

METHANE CLATHRATE (Siberian craters)



Supramolecular Chemistry - definitions

- the chemistry **beyond the molecules**: molecules are already formed
- the chemistry of molecular **assemblies** and of the **intermolecular bond**: association of molecules
- the chemistry of the **non covalent bond**: weak interactions

Bottom-up approach

Nano objects

Smart and functional materials

Supramolecular Chemistry - vocabulary

Host-Guest, Self-assembly, Supramolecular Assembly, Design, Control, Non covalent Interactions, Electrostatic Int., Anion- π Int., Solvent effects,...

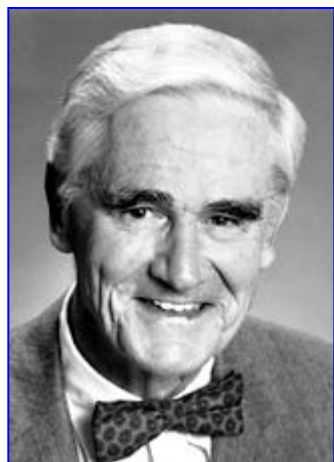
Molecular machines, containers, nanoscale flasks, nanoassemblies, supramolecular architectures, cages, transporters, molecular magnets, nanoparticles, nanoballs, channels, tubes,...

Macrocycles, Cucubiturils, Helicates, Rotaxanes, Catenanes, Dendrimers..

Functional and complex nanomaterials and devices (smart materials, MOFs, polymers, gels, SAMs..)

Imaging, Sensing, Recognition, Catalysis, Switching, ...

Nobel Prize in Chemistry, 1987



Donald J. Cram



Jean-Marie Lehn



Charles J. Pedersen

*«for their development and use of molecules with
structure-specific interactions of high selectivity»*

http://nobelprize.org/nobel_prizes/chemistry/laureates/1987/

The Nobel Prize in Chemistry, 2016



J-P. Sauvage



Sir J. F. Stoddart



B. L. Feringa

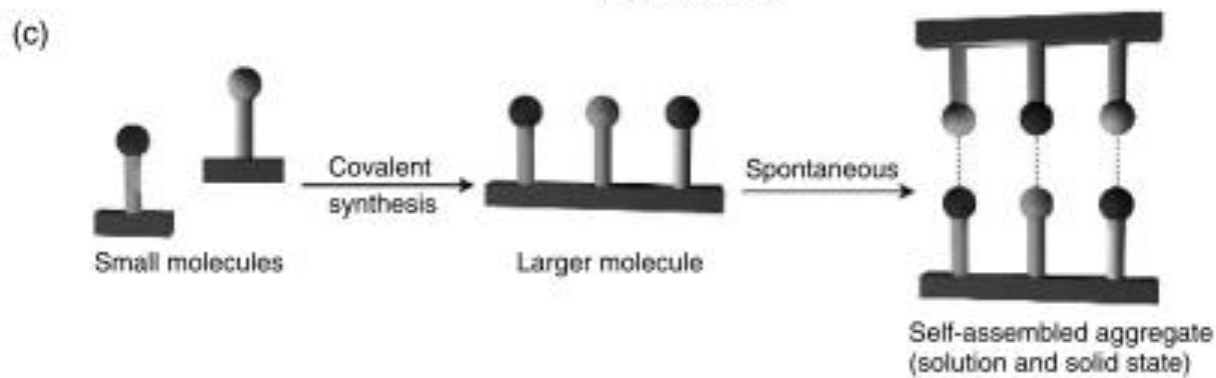
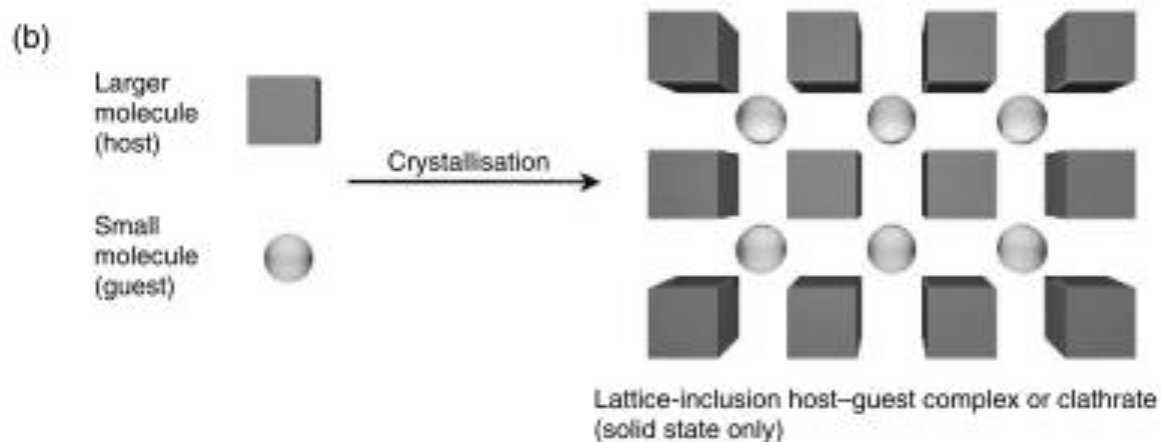
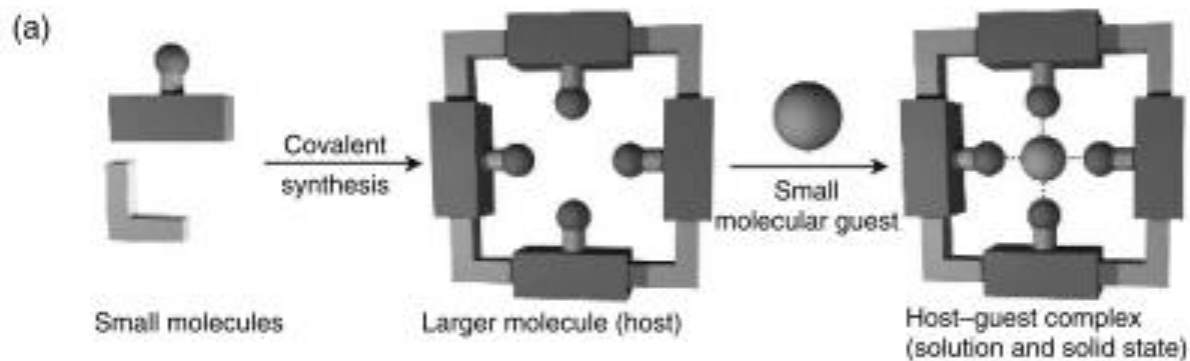
"for the design and synthesis of molecular machines"

https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2016/

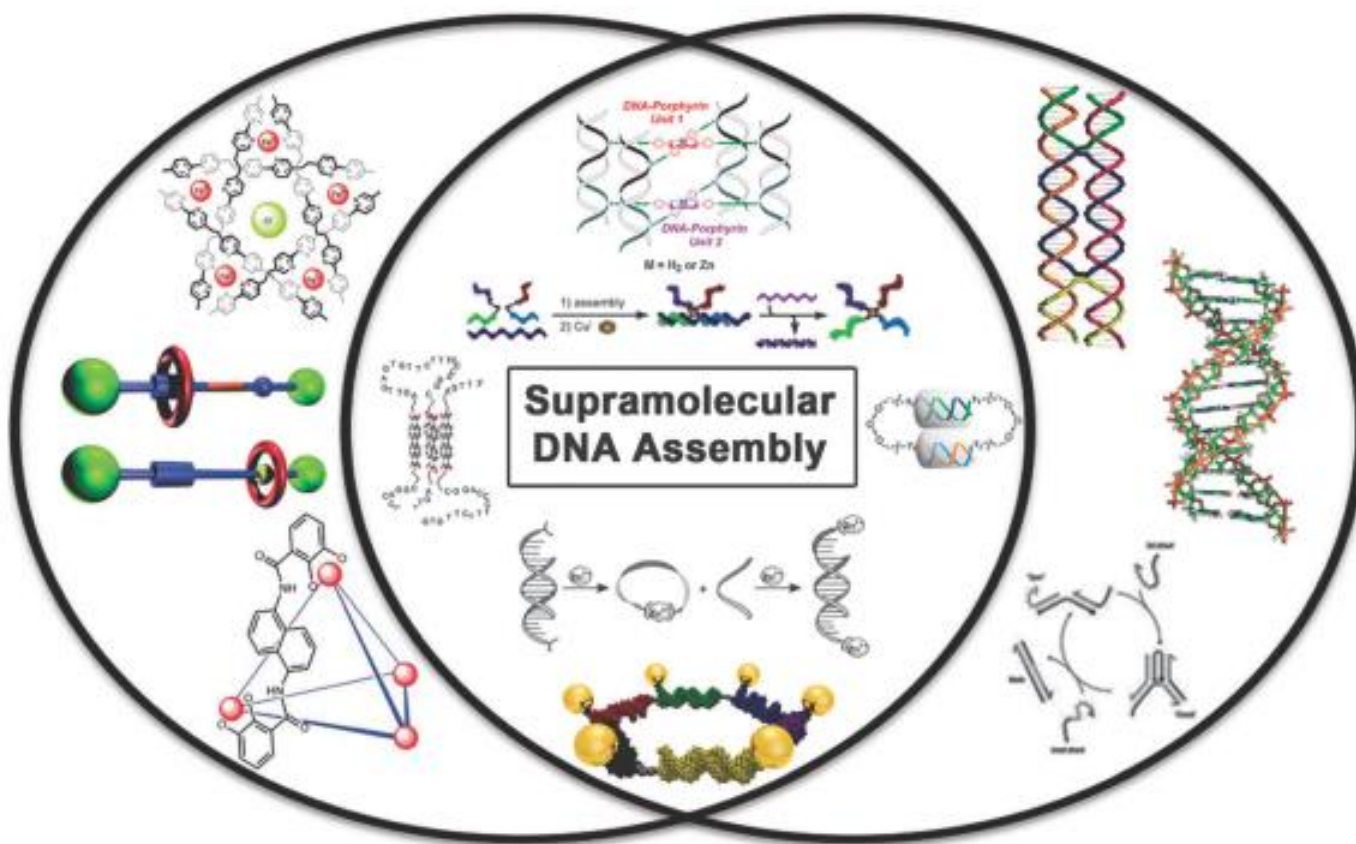
Chimica, il Nobel mancato



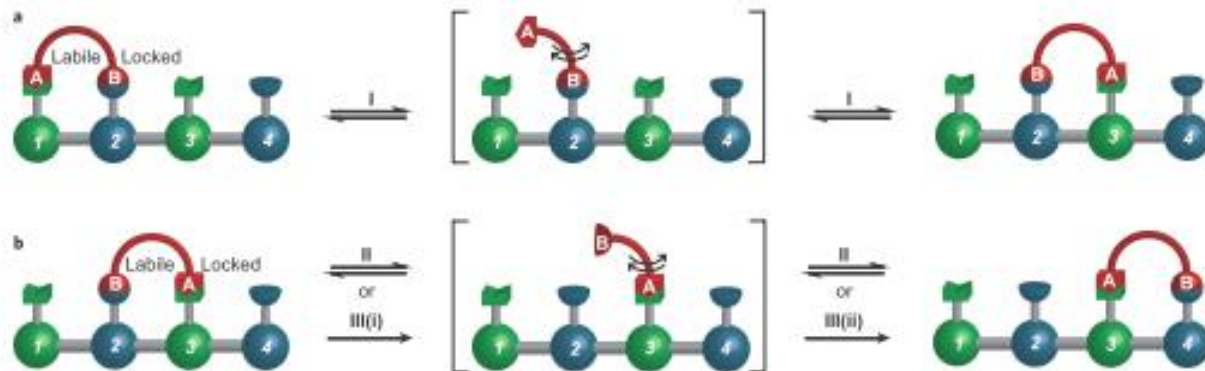
Prof. Vincenzo Balzani, docente emerito dell'Università di Bologna



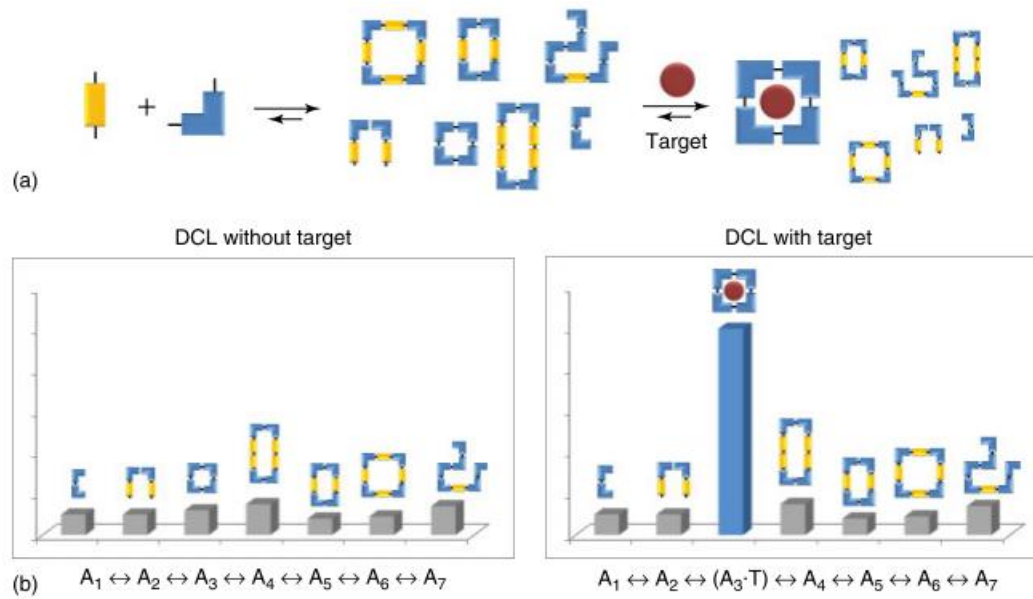
The bridge: Supramolecular ARTIFICIAL and NATURAL systems



A synthetic molecule that CAN WALK DOWN A TRACK



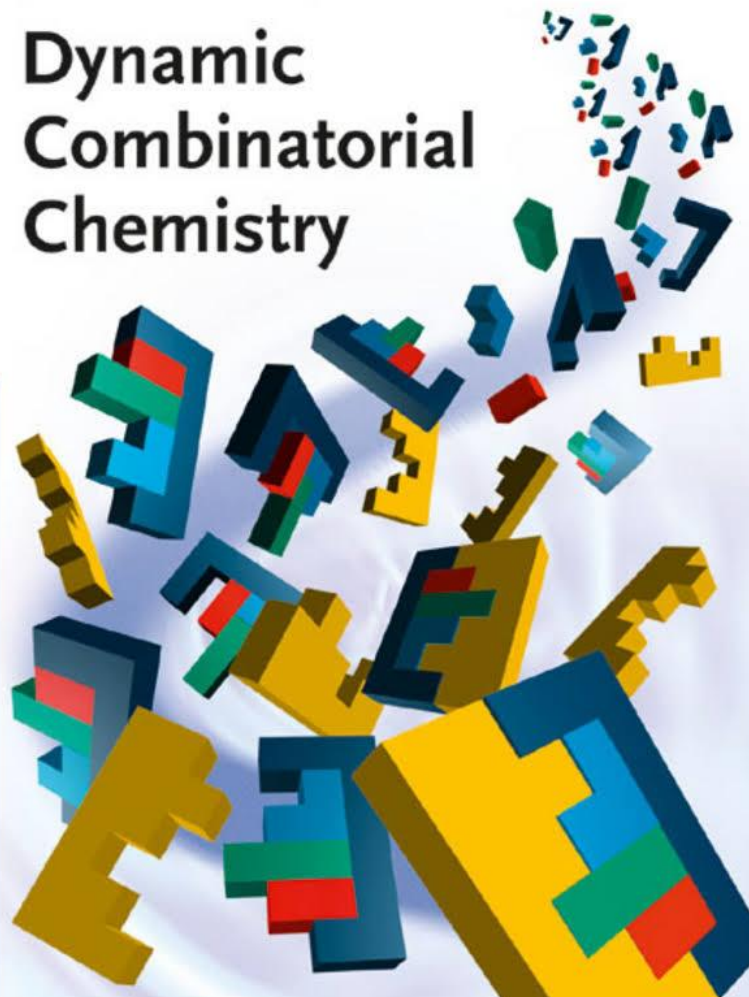
DYNAMIC COMBINATORIAL LIBRARIES

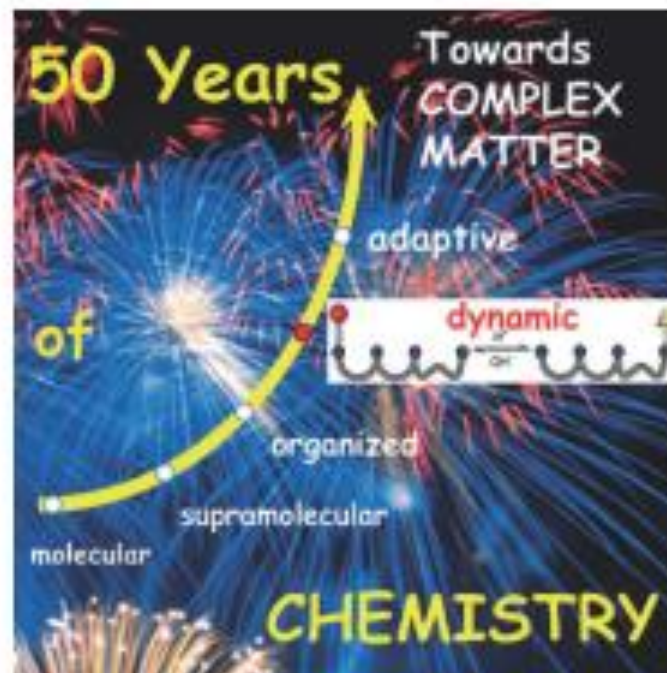


Edited by
Joost N.H. Reek and Sijbren Otto

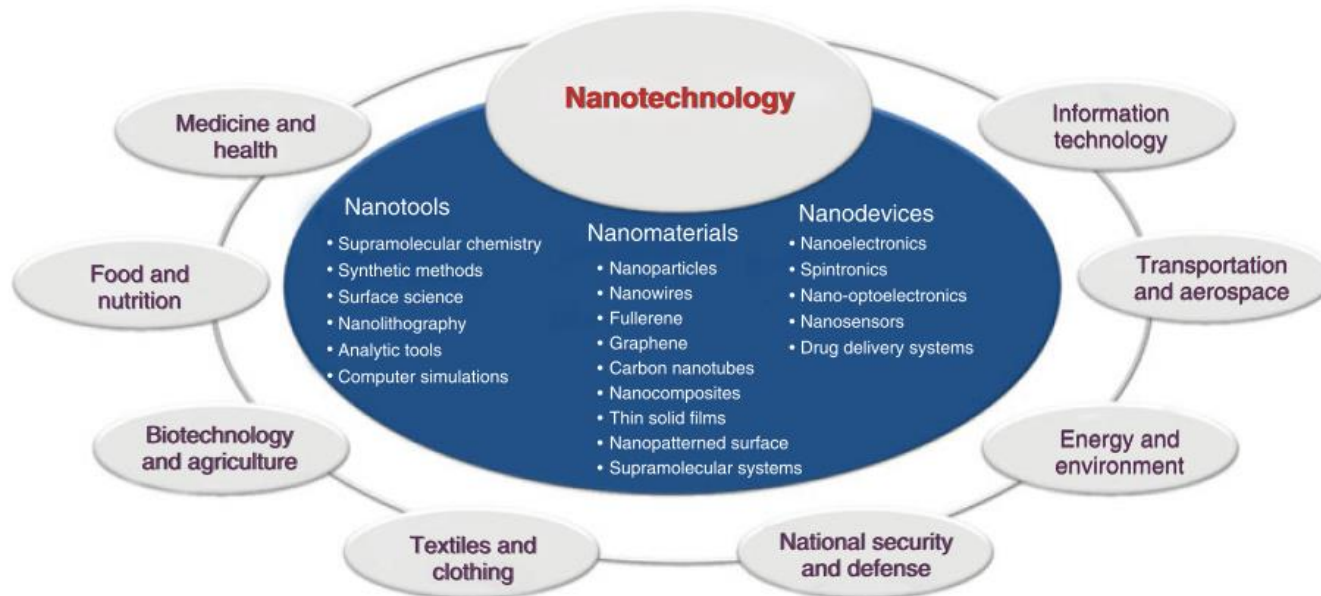
WILEY-VCH

Dynamic Combinatorial Chemistry

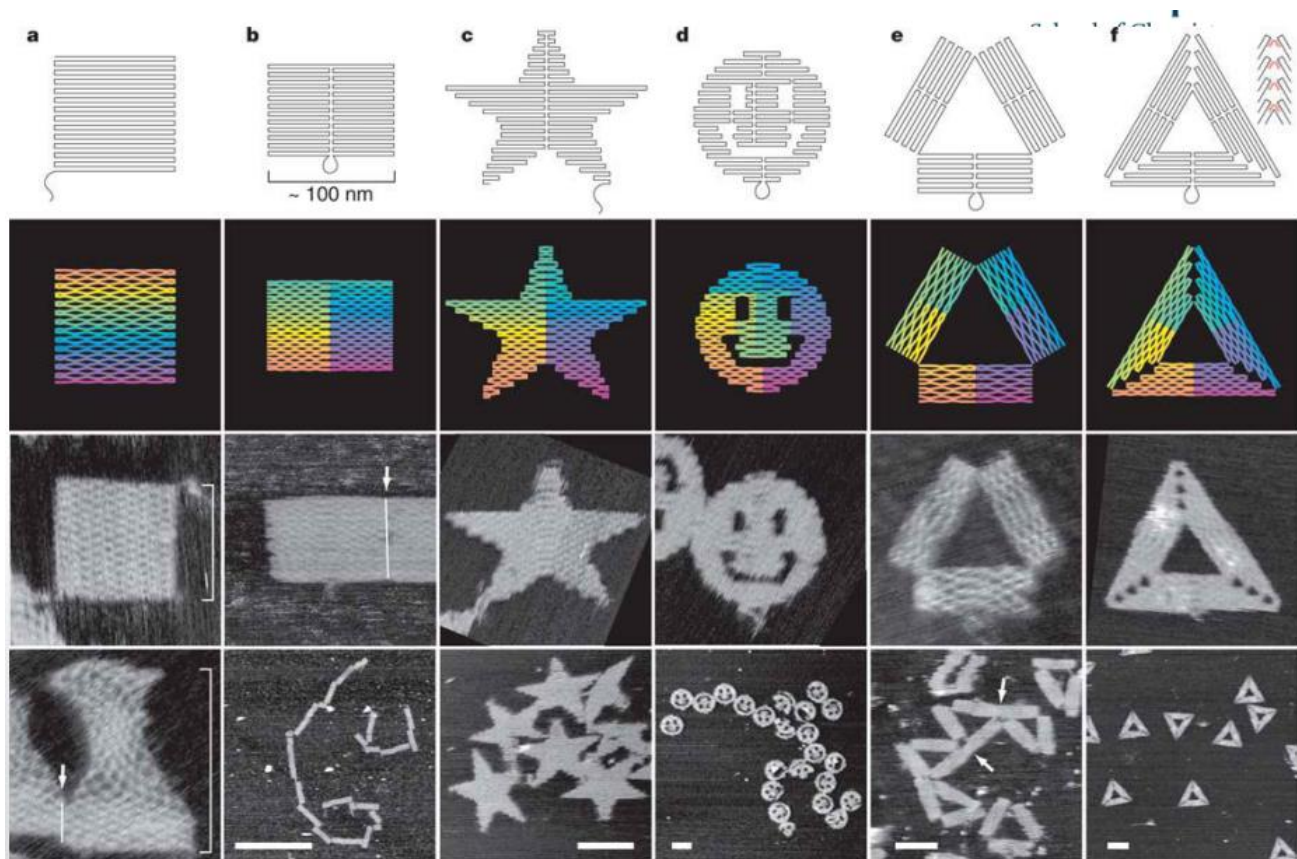




From Supramolecular Chemistry to Nanotechnology



Folding DNA to create NANOSCALE SHAPES AND PATTERNS



P.W. Rothemund, *Nature* **2006**

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2. J. W. Steed, J. L. Atwood *Supramolecular Chemistry*, J. Wiley & Sons, UK, **2000**.
3. J. W. Steed, D. R. Turner, K. J. Wallace *Core Concepts in Chemistry and Nanochemistry*, Wiley, Chichester, **2007**.
4. H.-J. Schneider, A. Yatsimirsky *Principles and Methods in Supramolecular Chemistry*, J. Wiley & Sons, UK, **2000**.
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6. V. Balzani, M. Venturi, A. Credi *Molecular Devices and Machines*, Wiley-VCH, Weinheim (Germany), **2003**.
7. P. J. Cragg *A Practical Guide to Supramolecular Chemistry*, J. Wiley & Sons, UK, **2005**.
8. C. A. Schalley (Ed.) *Analytical Methods in Supramolecular Chemistry*, Wiley VHC, Weinheim (Germany), **2007**.
9. P. W. N. M. Van Leeuwen *Supramolecular Catalysis*, Wiley-VCH, Weinheim (Germany), **2008**.
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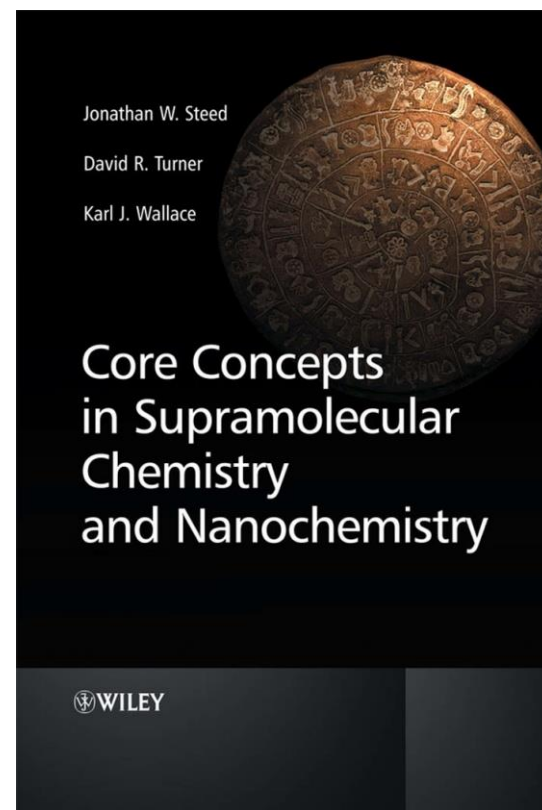
Jonathan W. Steed,
Durham University, UK

David R. Turner,
Monash University, Australia

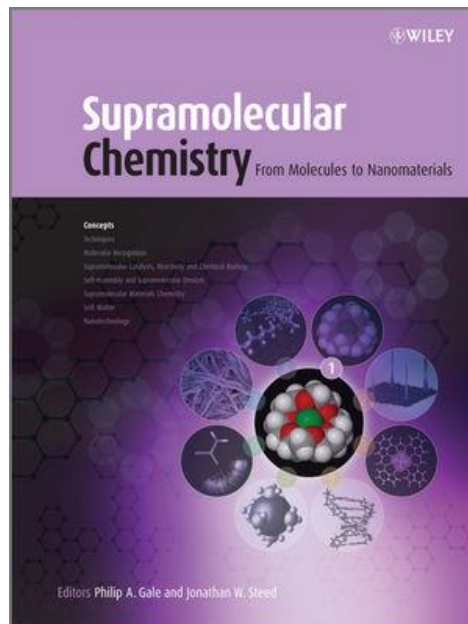
Karl J. Wallace,
University of Southern Mississippi, USA



John Wiley & Sons, Ltd



Bibliography



Supramolecular Chemistry: From Molecules to Nanomaterials, 8 Volume Set
[Jonathan W. Steed](#) (Editor-in-Chief), [Philip A. Gale](#) (Editor-in-Chief), Wiley.

Programma

Interazioni non covalenti

Recettori 1

cationi/anioni/molecole neutre

Metodi Analitici

Recettori 2

Cavitandi/Contenitori molecolari

- Covalenti
- Auto-assemblati (legami H, legami M, legami covalenti dinamici)
- Applicazioni: isolamento di intermedi instabili; reattività nello spazio confinato; catalisi

Programma

Chimica Topologica

Elicati/Catenani/Rotaxani/Nodi

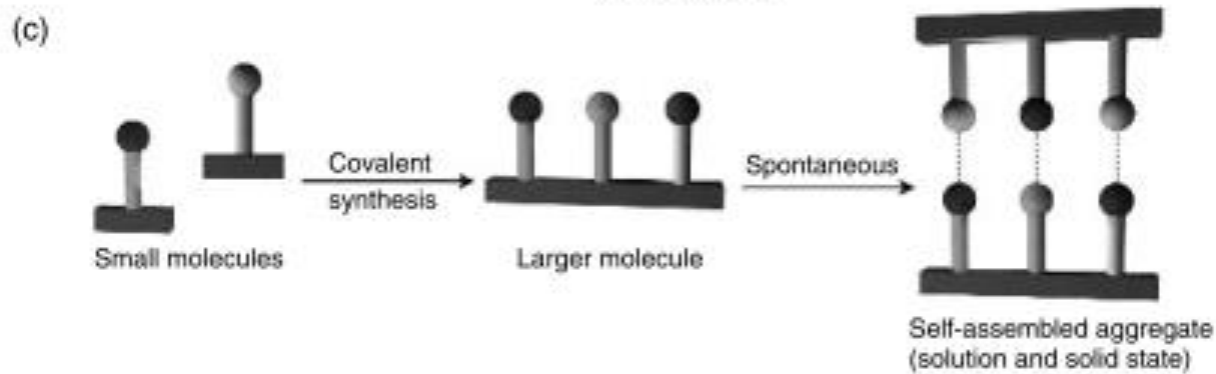
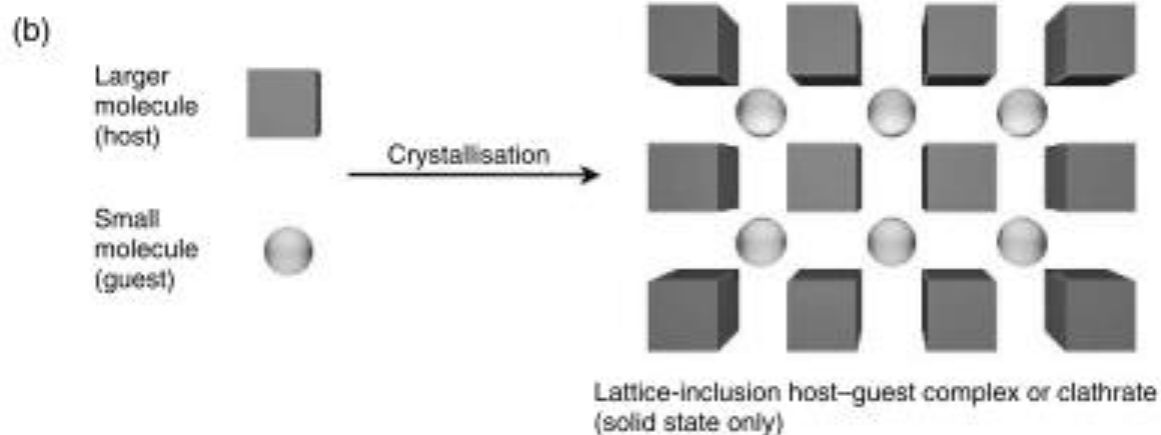
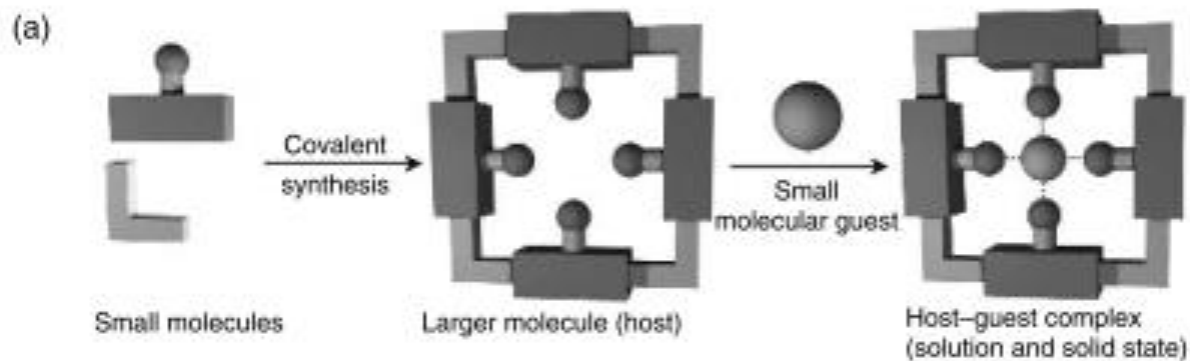
Dispositivi e Macchine molecolari

Determinazione delle Costanti di Associazione

(Prof. P. Tecilla 4h)

Dynamic Combinatorial Chemistry

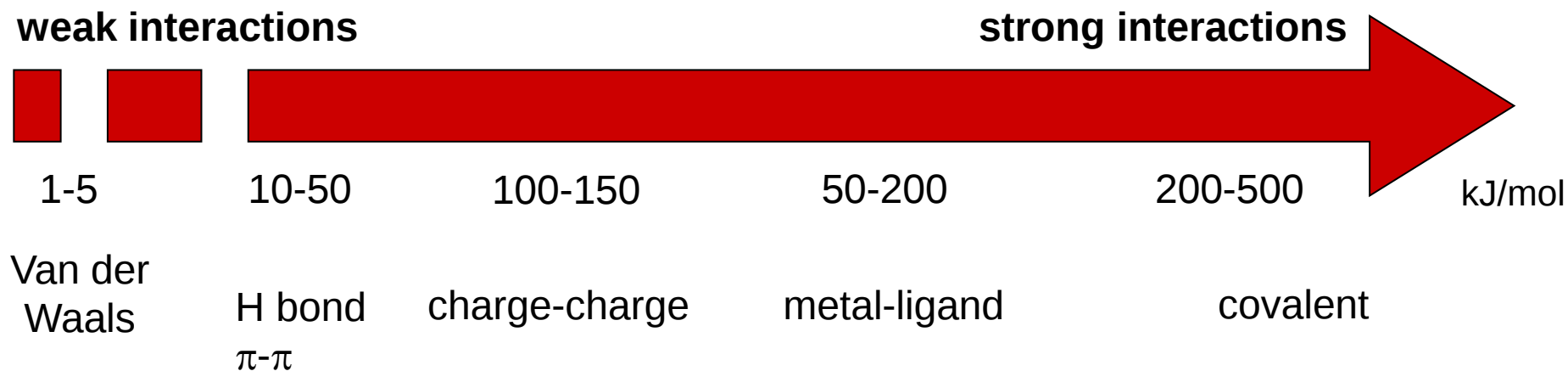
(Prof. P. Pengo 3h)



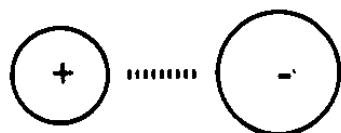
Weak (Reversible) Intermolecular Interactions

- Electrostatic
- π - π
- Cation- π / Anion- π /CH- π
- H Bonding
- Halogen Bonding
- Metal-Ligand Coordination
- Reversible Covalent Bonding
- Chelate Effect
- Macrocyclic Effect
- Hydrophobic Effect

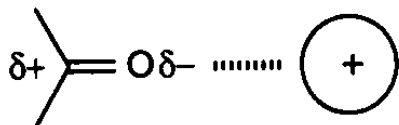
Weak Intermolecular Interactions



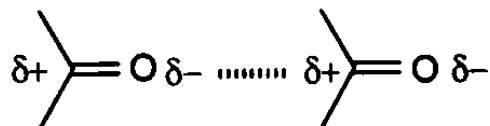
Electrostatic Interactions



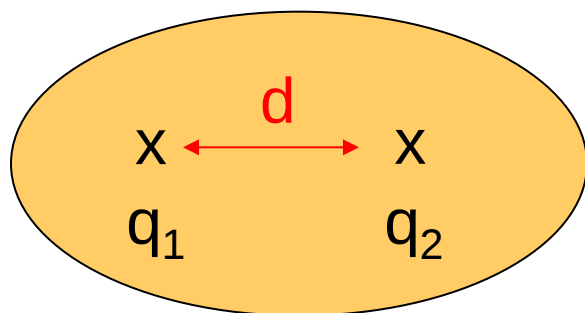
Charge-Charge Interactions 100-350 kJ/mol



Dipole-Charge Interactions 50-200 kJ/mol



Dipole-Dipole Interactions 5-50 kJ/mol



$$W = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{\epsilon d} \quad (\text{J})$$

vacuum
permittivity

dielectric constant
(nature of solvent)

$$\epsilon(\text{vacuum}) = 1$$

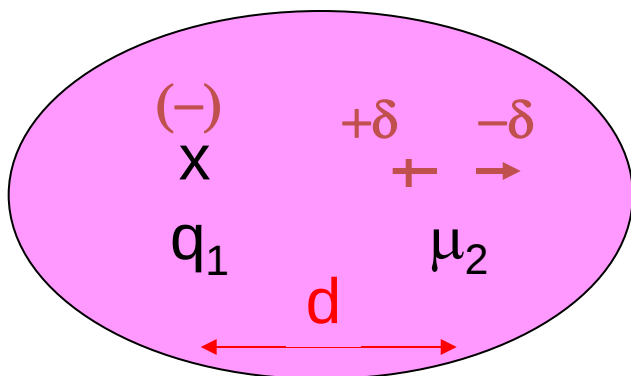
apolar medium $\Leftrightarrow \epsilon$ small (~ 2)
polar medium $\Leftrightarrow \epsilon$ big ($\text{H}_2\text{O} \sim 80$)

dielectric constant of the solvent

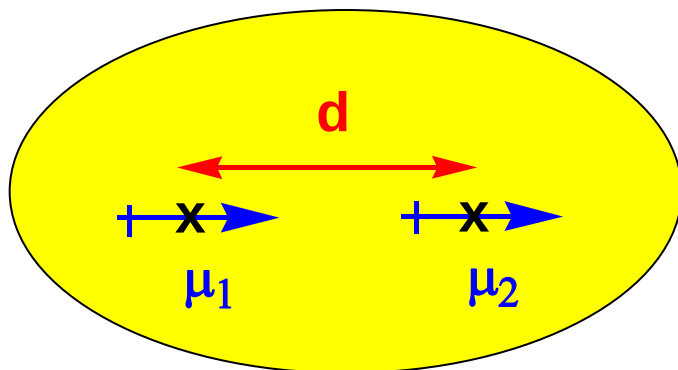
		ϵ	
Benzene		2,3	apolar ↓ polar
Acetone		20,7	
Ethanol		24,3	
water		78,5	

$$\epsilon = 78.5 \quad d = 0.5 \text{ nm} \Rightarrow W = 3.75 \text{ kJ.mol}^{-1}$$

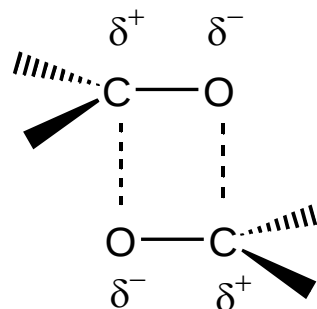
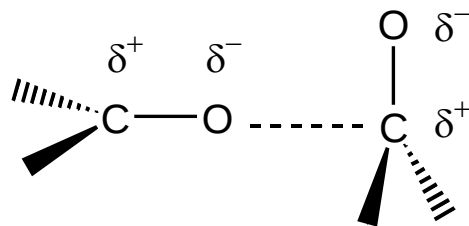
$$\epsilon = 2 \quad d = 0.5 \text{ nm} \Rightarrow W = 140 \text{ kJ.mol}^{-1}$$



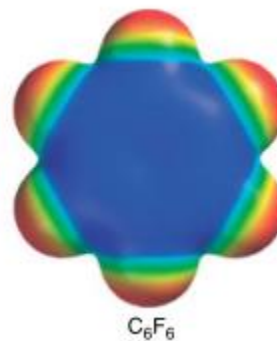
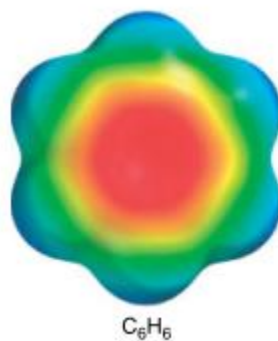
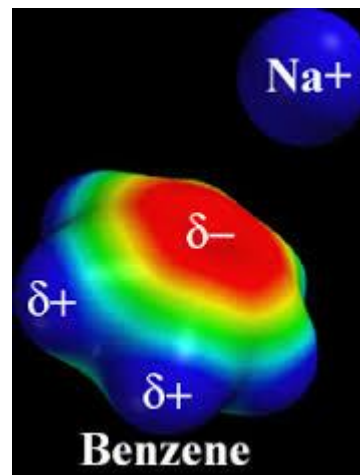
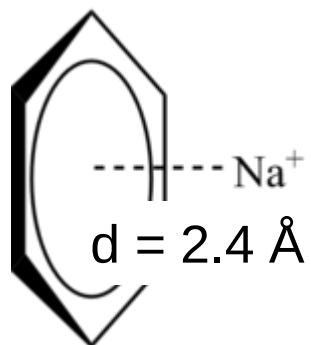
$$W = - C^{\text{te}} \times \frac{|q| \mu_2}{\epsilon d^2}$$



$$W = - C^{\text{te}} \frac{\mu_1 \mu_2}{\epsilon d^3}$$



Cation- π Interactions

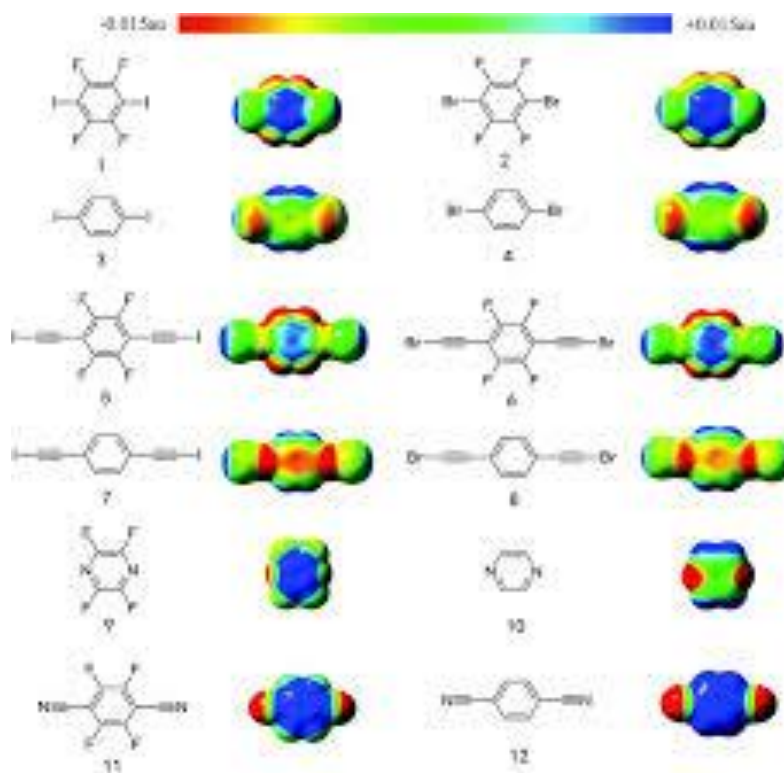


Anion- π Interactions

Proposed by three research groups of theoreticians independently in 2002 based on their theoretical calculations, anion- π interactions are defined as attractive interactions between negatively charged species and electron-deficient aromatic rings.

Typical anion- π interaction indicates the attraction of an anion species to the centroid of an aromatic ring.

In comparison to a plethora of theoretical calculations of anion- π interactions, experimental studies on these intriguing noncovalent bond interactions are limited.



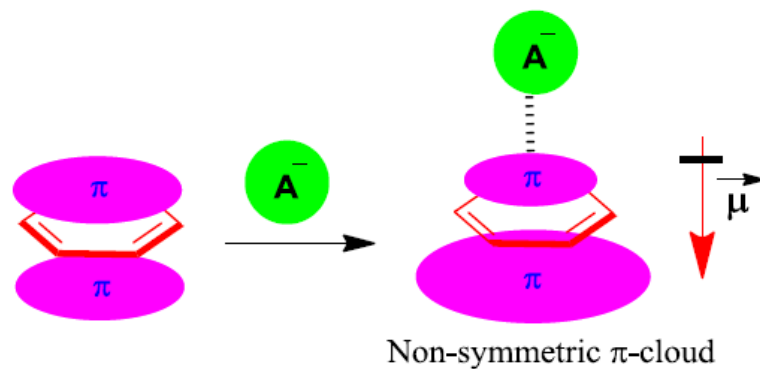


Fig. 1. Diagrammatic representation of “anion-induced dipole moment”.

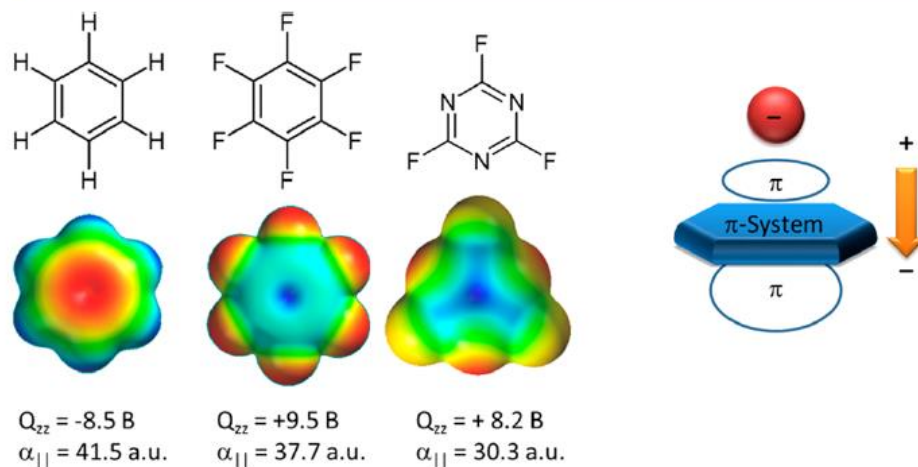


Figure 5. Structures and electron-density surfaces of selected arenes showing low electron density (blue region) in the aromatic core of C_6F_6 and $\text{C}_3\text{N}_3\text{F}_3$ (left). In addition the concept of “anion-induced dipole moment” is illustrated (right).⁸⁸

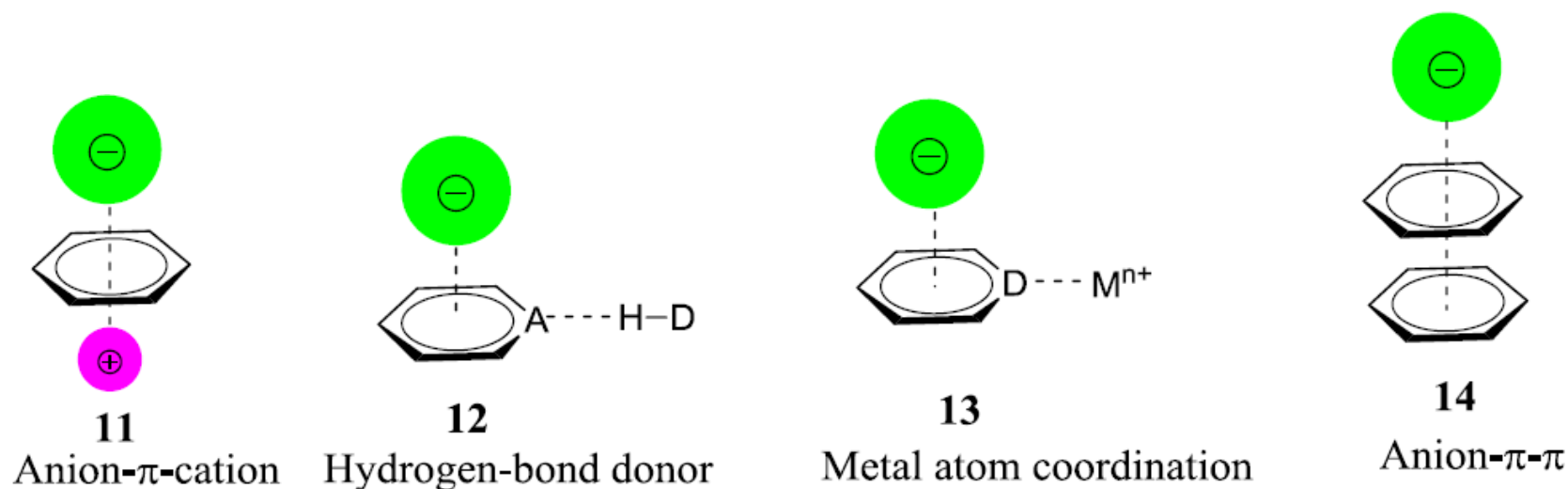


Fig. 4. Illustration of diverse factors affecting the strength of anion- π interactions.

Anion- π Interactions with Fluoroarenes

Michael Giese,^{*,†} Markus Albrecht,^{*,‡} and Kari Rissanen^{*,§}

DOI: 10.1021/acs.chemrev.5b00156

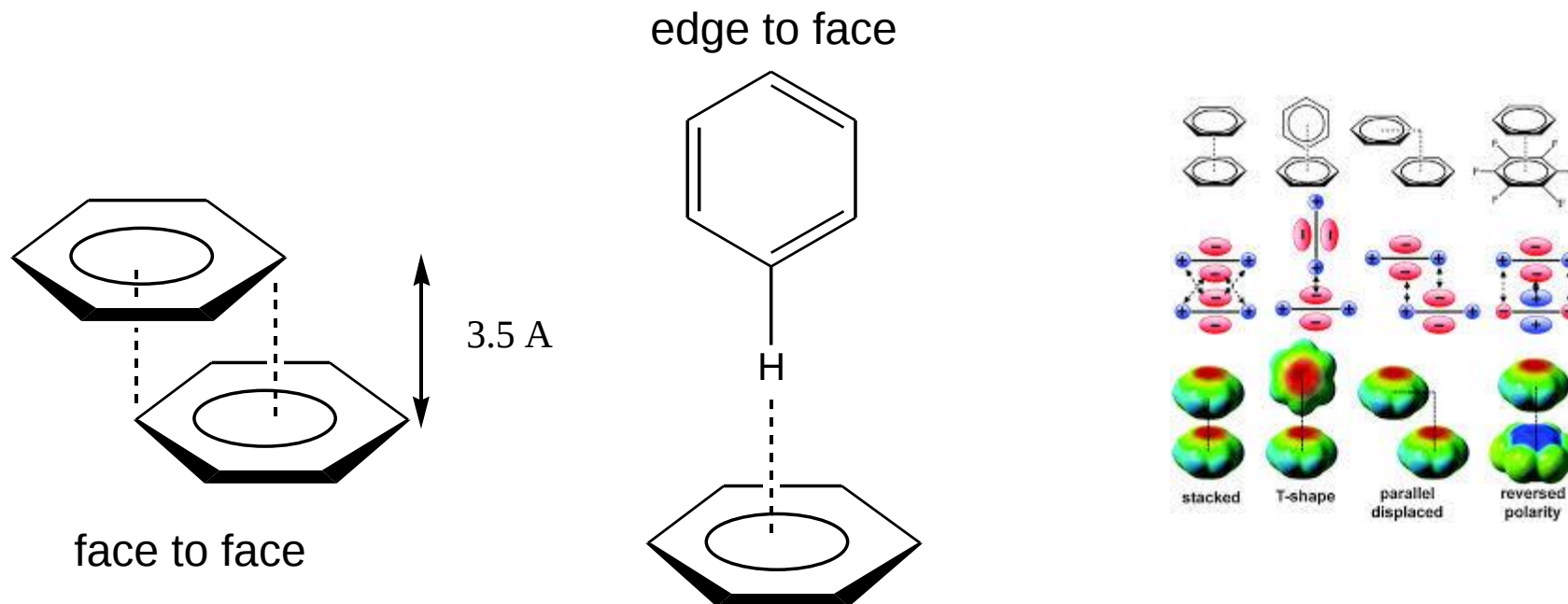
Chem. Rev. 2015, 115, 8867–8895

Emergence of anion- π interactions: The land of opportunity in supramolecular chemistry and beyond

Ishfaq Ahmad Rather, Shafieq Ahmad Wagay, Rashid Ali *

Coordination Chemistry Reviews 415 (2020) 213327

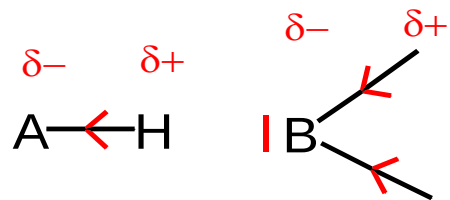
π - π Interactions up to 50 kJ/mol



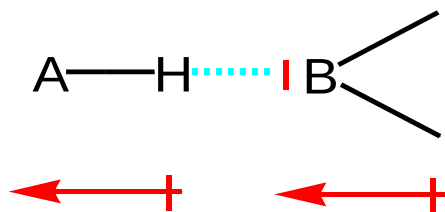
C.A. Hunter and J.K.M. Sanders, ***The Nature of π - π interactions***, *J. Am. Chem. Soc.*, **1990**, *112*, 5525;

E.-I. Kim, S. Paliwal and C.S. Wilcox, ***Measurements of molecular electrostatic field effects in edge-to-face aromatic interactions and CH- π interactions with implications for protein folding and molecular recognition***, *J. Am. Chem. Soc.*, **1998**, *120*, 11192.

H Bond 4-120 kJ/mol

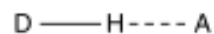


A, B electronegative or
electrondeficient atoms

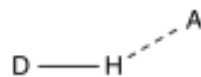


permanent dipoles

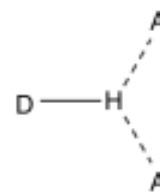
(a)



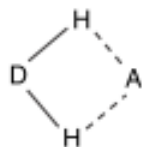
(b)



(c)



(d)



(e)



(f)

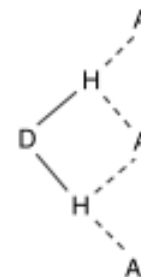


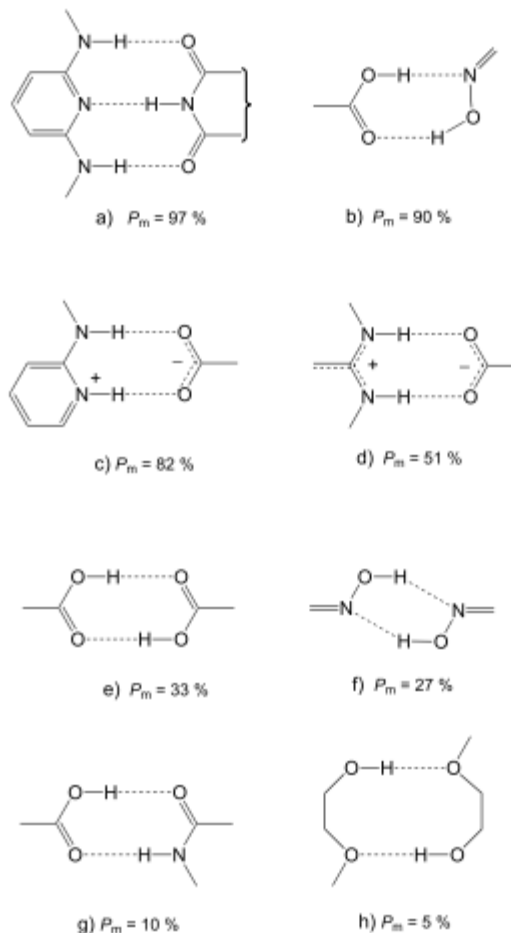
Table 1.5 Properties of hydrogen bonded interactions.

	Strong	Moderate	Weak
A–H...B interaction	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol ⁻¹)	60–120	16–60	<12
Bond lengths (Å)			
H...B	1.2–1.5	1.5–2.2	2.2–3.2
A...B	2.2–2.5	2.5–3.2	3.2–4.0
Bond angles (°)	175–180	130–180	90–150
Relative IR vibration shift (stretching symmetrical mode, cm ⁻¹)	25%	10–25%	<10%
¹ H NMR chemical shift downfield (ppm)	14–22	<14	?
Examples	Gas phase dimers with strong acids/bases Proton sponge HF complexes	Acids Alcohols Biological molecules	Minor components of bifurcated bonds C–H hydrogen bonds O–H... π hydrogen bonds

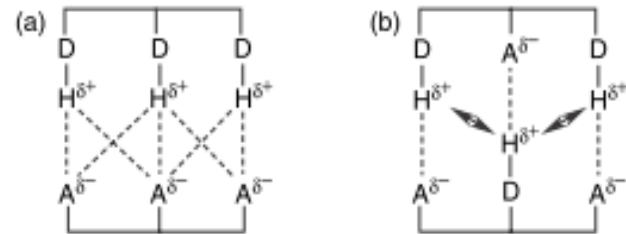
The Hydrogen Bond in the Solid State

Thomas Steiner*

Angew. Chem. Int. Ed. **2002**, *41*, 48–76



Scheme 17. Eight examples of intermolecular hydrogen bond motifs with their probability of formation (P_m) in crystals.^[122] Notice that P_m of the carboxy-oxime heterodimer (b) is much higher than that of the carboxylic acid (e) and oxime homodimers (f).

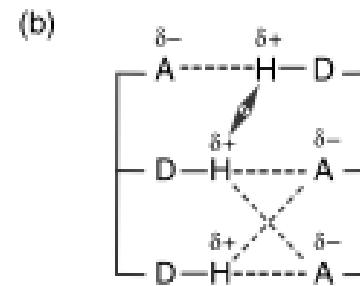
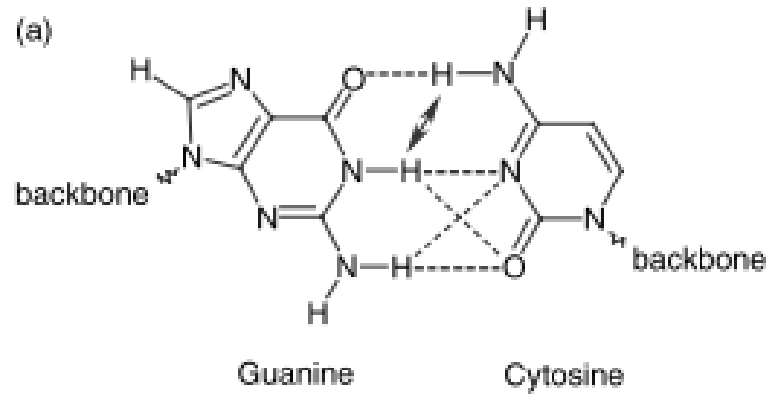


D Donor

A Acceptor

----- Attractive interaction

↔ Repulsive interaction



Halogen Bond

In 2009 the International Union of Pure and Applied Chemistry (IUPAC) started a project (project no. 2009-032-1-100) having the aim “ to take a comprehensive look at intermolecular interactions involving halogens as electrophilic species and classify them”

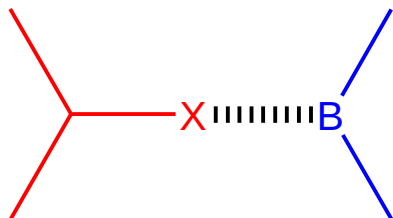
<http://www.halogenbonding.eu/>

<http://www.iupac.org/web/ins/2009-032-1-100>

An IUPAC recommendation defining these interactions as halogen bonds was issued in 2013 when the project was concluded: This definition states that

“ A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity. ”

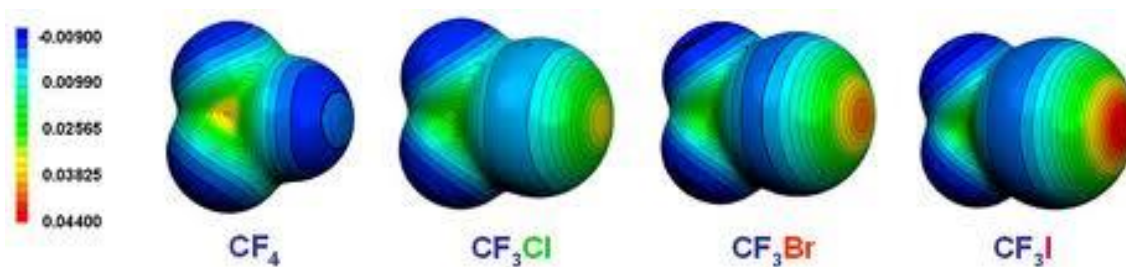
Halogen Bond



B : Lewis base (neutral or anionic)

X : electron-poor halogen atom

- Very directional (180° , but also other geometries)
- As strong as H-bond
- Often encountered in solid state, more rarely in solution



molecule	atom	bond producing a σ -hole
H ₃ C-F	F	C-F
H ₃ C-Cl	Cl	C-Cl
H ₃ C-Br	Br	C-Br
H ₃ C-I	I	C-I
F ₃ C-F	F	C-F
F ₃ C-Cl	Cl	C-Cl
F ₃ C-Br	Br	C-Br
F ₃ C-I	I	C-I
NC-F	F	C-F
NC-Cl	Cl	C-Cl
NC-Br	Br	C-Br
NC-I	I	C-I
Dihalogens		
F-F	F	F-F
Cl-Cl	Cl	Cl-Cl
Br-Br	Br	Br-Br
Focus on Bromine		
Br-C $\equiv$ C-Br	Br	C-Br
H ₃ Si-Br	Br	C-Br
F ₃ Si-Br	Br	Si-Br
H ₃ Ge-Br	Br	Ge-Br
H ₂ N-Br	Br	N-Br
F ₂ N-Br	Br	N-Br
H ₂ P-Br	Br	P-Br
F ₂ P-Br	Br	P-Br
HO-Br	Br	O-Br
FO-Br	Br	O-Br
HS-Br	Br	S-Br
FS-Br	Br	S-Br
F-Br	Br	F-Br
Cl-Br	Br	Cl-Br

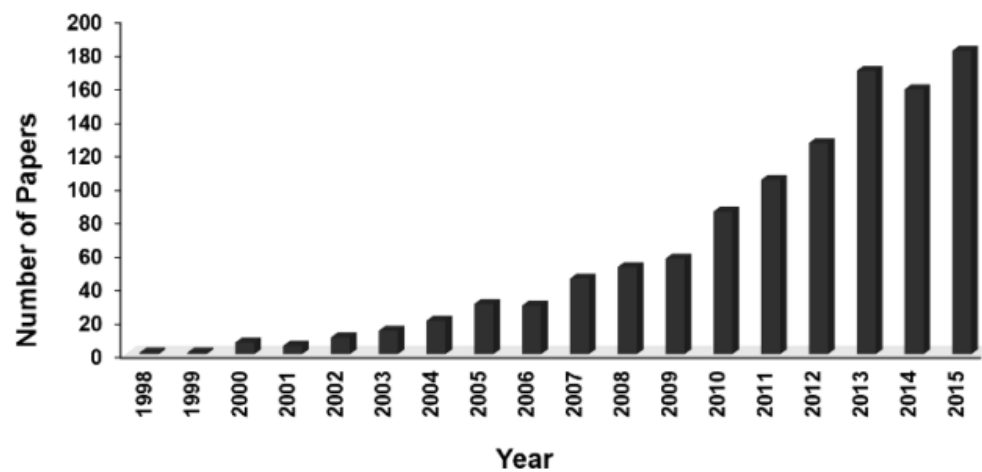


Figure 5. Number of papers per year having “halogen bonding” in the title and/or abstract (source SciFinder, search performed in November 2015).

The Halogen Bond

Gabriella Cavallo,[†] Pierangelo Metrangola,^{*,†,‡} Roberto Milani,[‡] Tullio Pilati,[†] Arri Priimagi,[§] Giuseppe Resnati,^{*,†} and Giancarlo Terraneo[†]

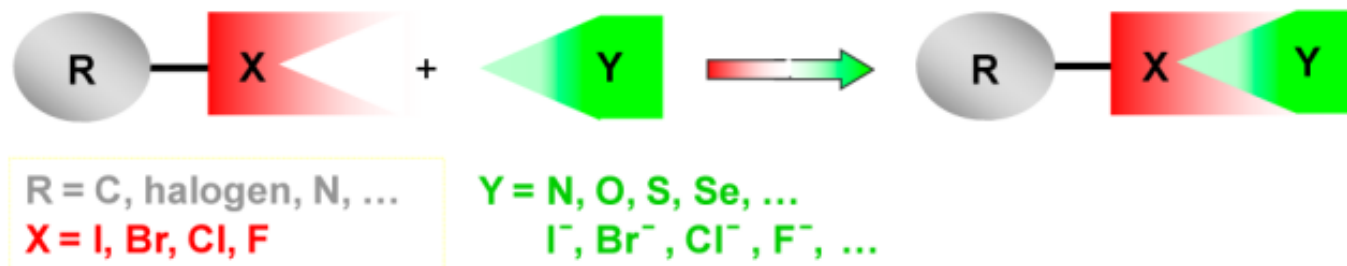


Figure 1. Schematic representation of the halogen bond.

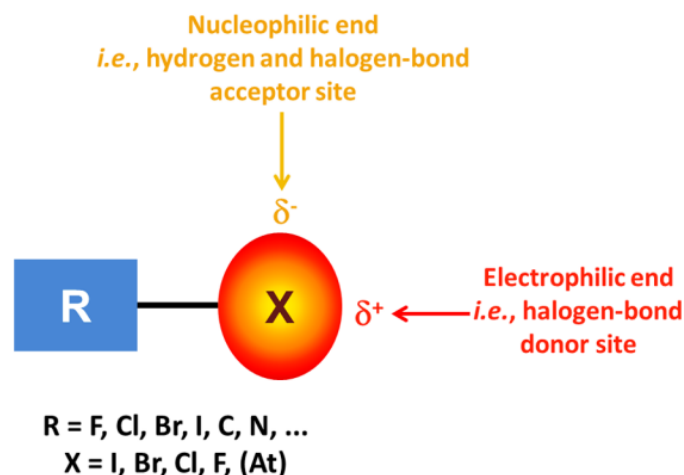
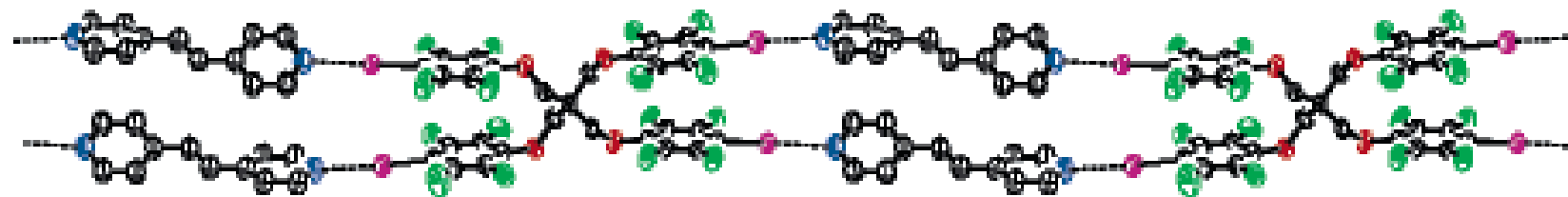
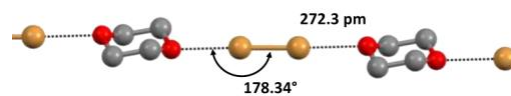
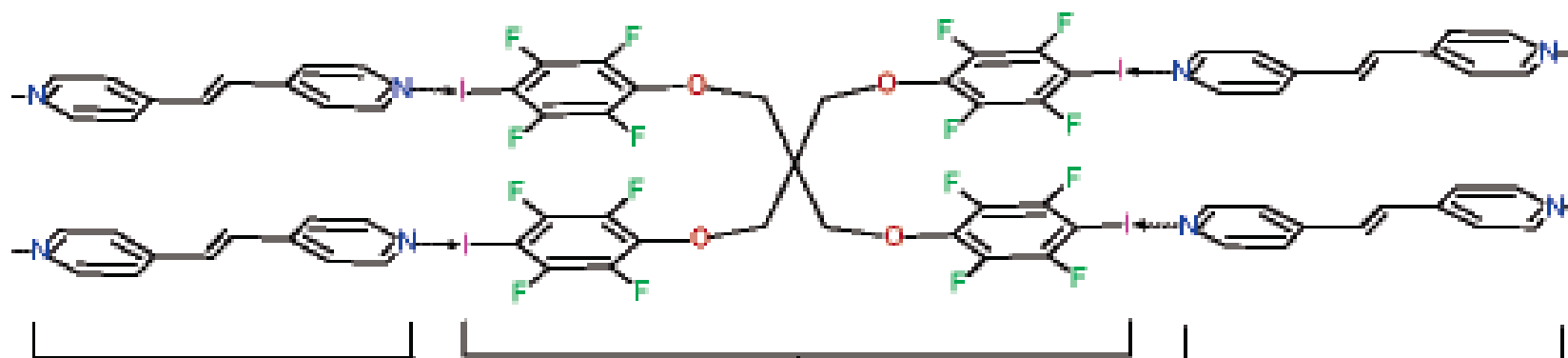


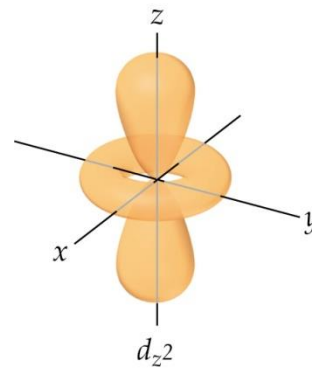
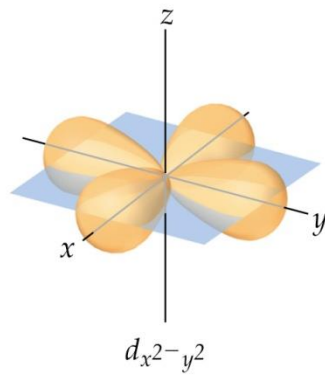
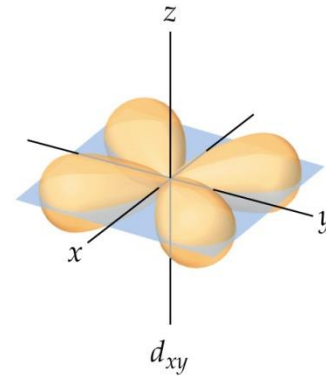
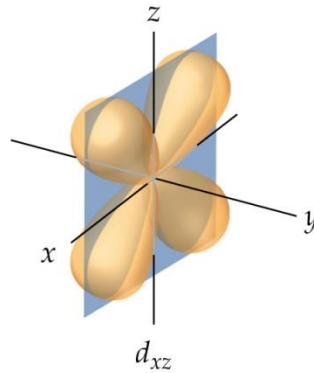
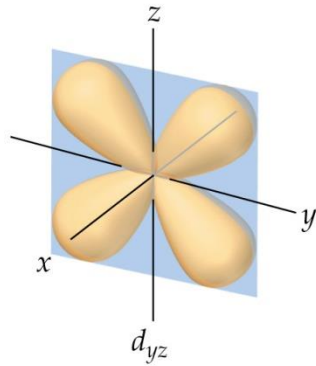
Figure 21. Schematic representation of the anisotropic distribution of the electron density around covalently bound halogen atoms and the pattern of the resulting interactions.



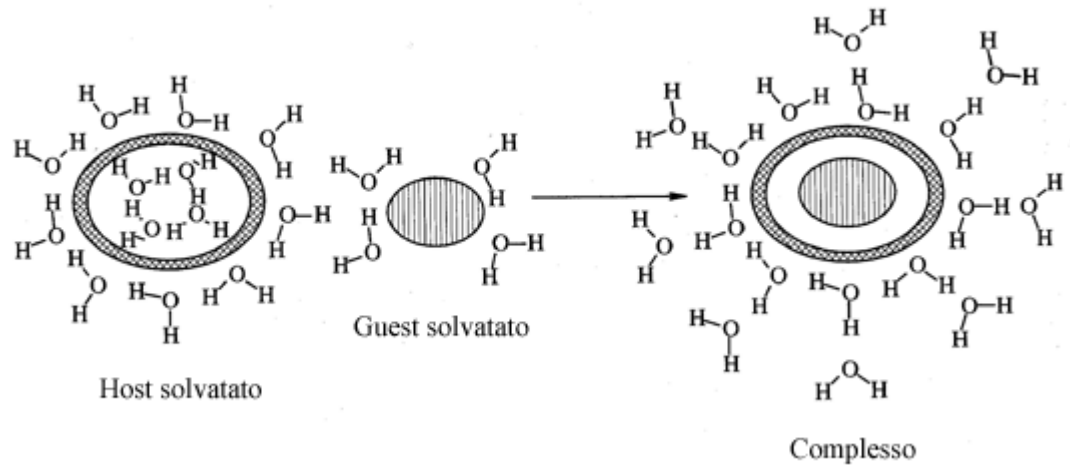
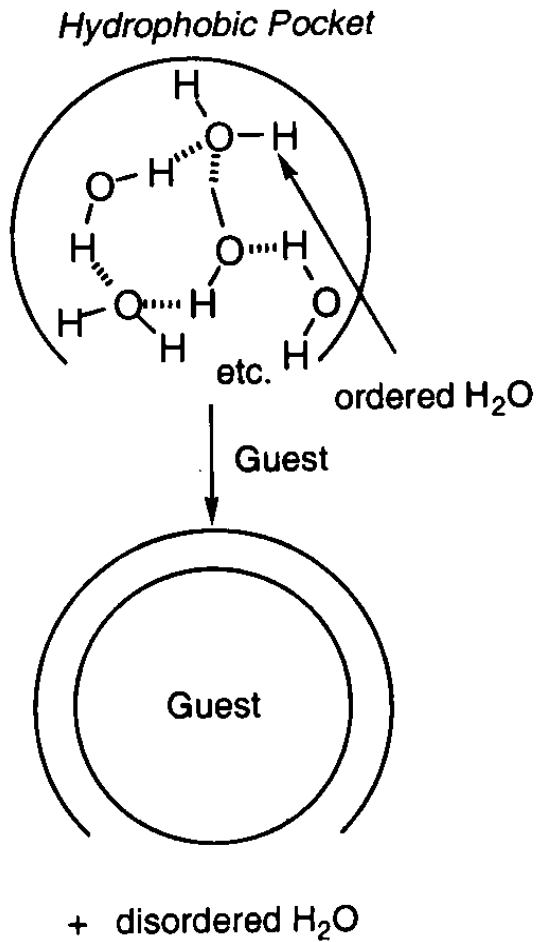
14



Metal-Ligand Interaction



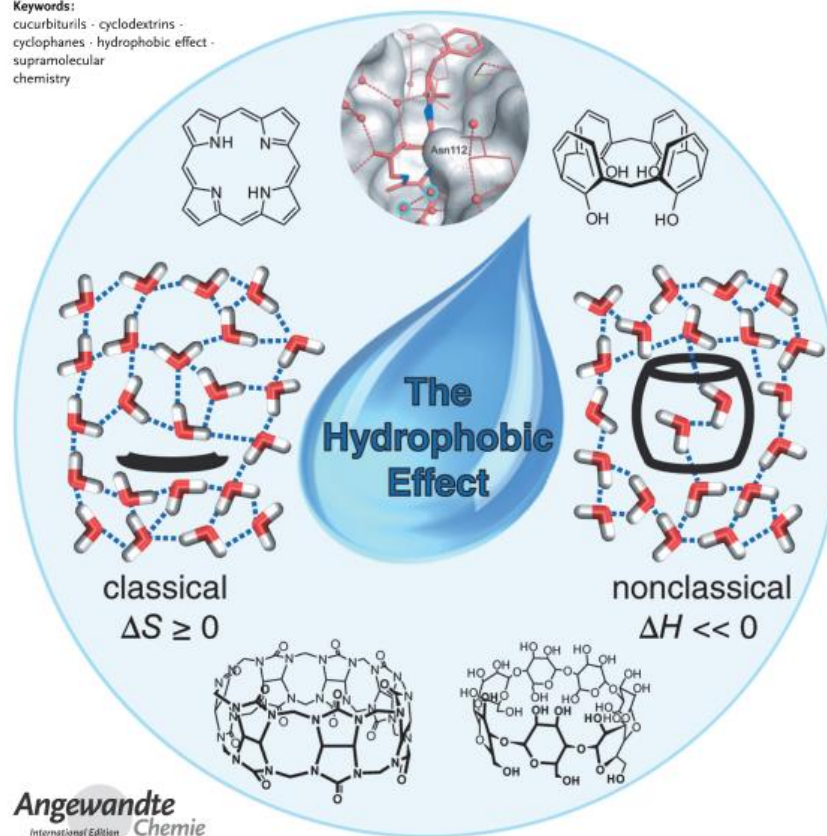
Hydrophobic Effect

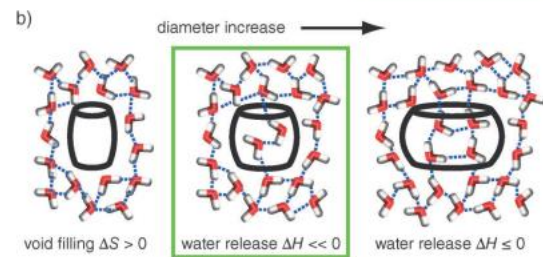
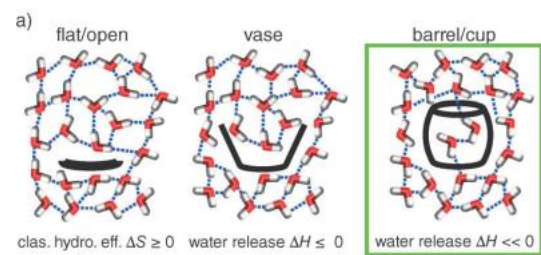


The Hydrophobic Effect Revisited—Studies with Supramolecular Complexes Imply High-Energy Water as a Noncovalent Driving Force

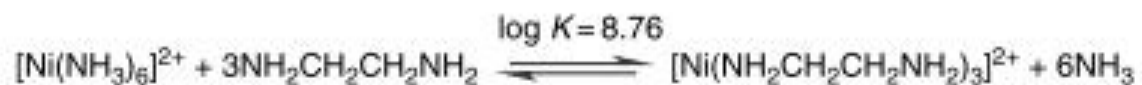
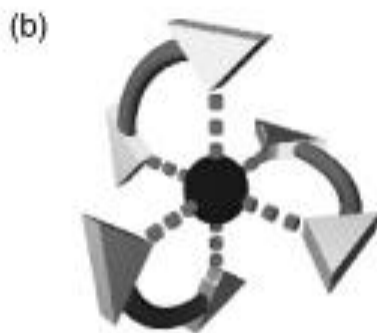
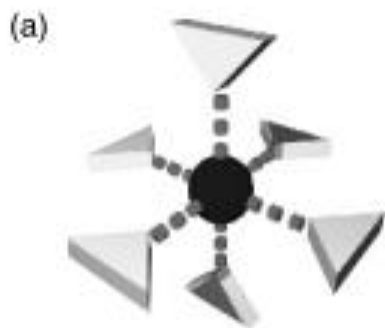
Frank Biedermann,* Werner M. Nau,* and Hans-Jörg Schneider*

Keywords:
cucurbiturils · cyclodextrins ·
cyclophanes · hydrophobic effect ·
supramolecular
chemistry

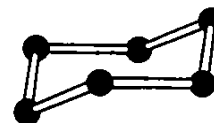




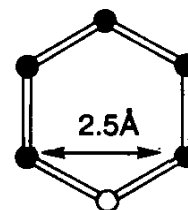
Chelate Effect



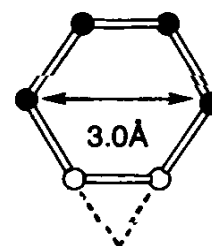
Chair form of cyclohexane



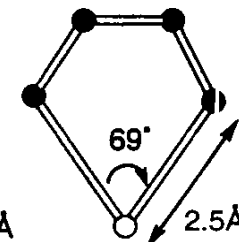
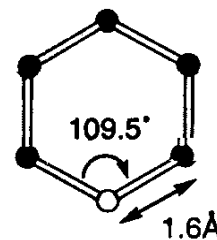
all C-C-C angles are 109.5°



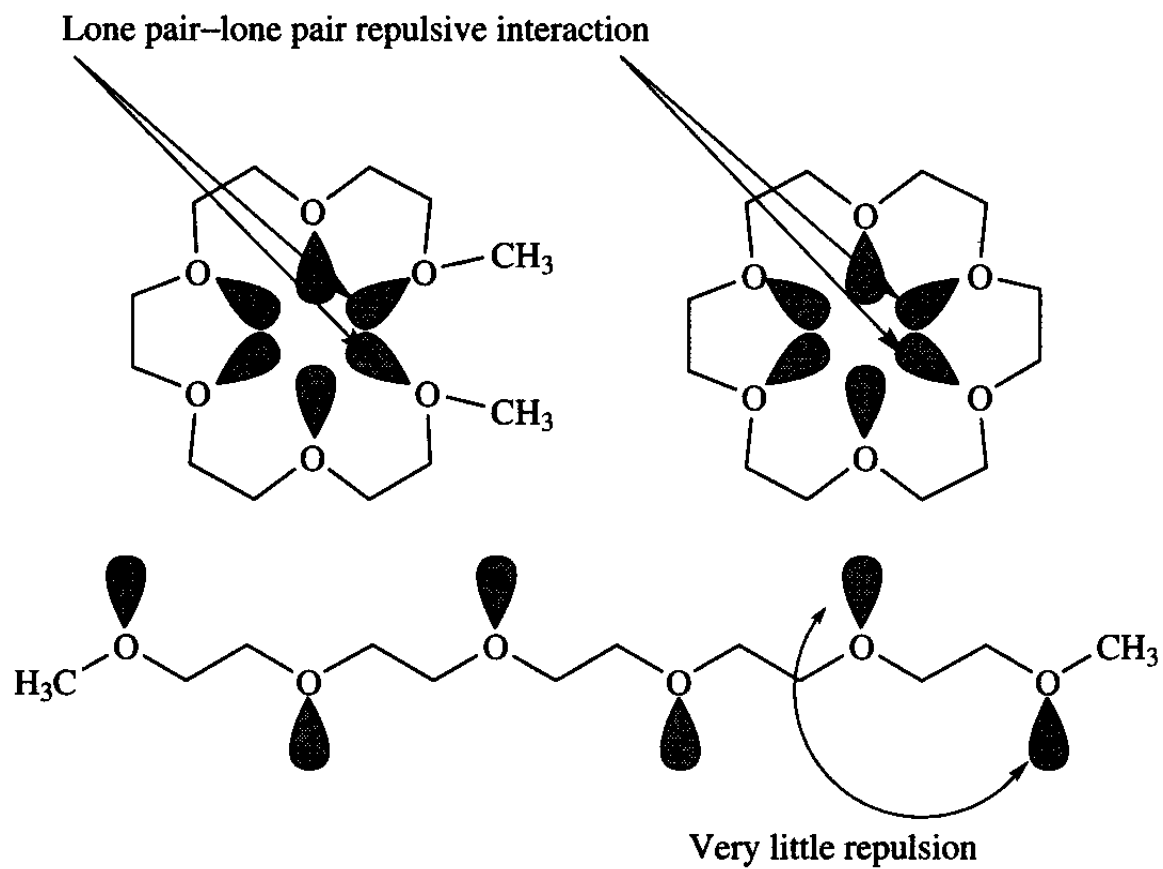
bite size in
six membered
rings



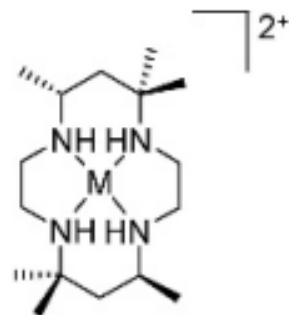
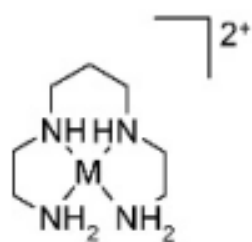
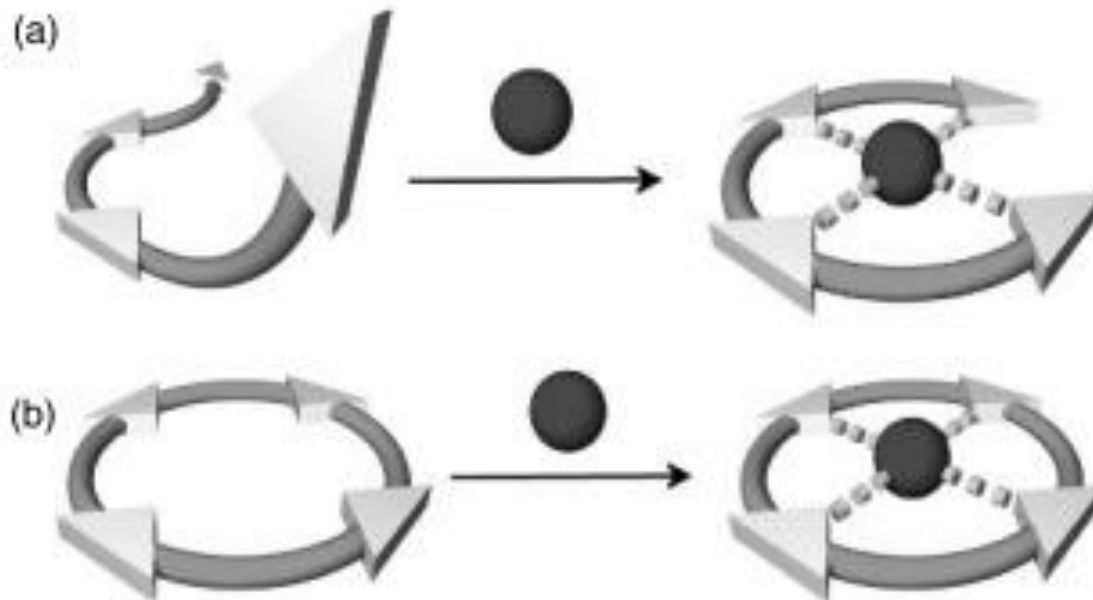
bite size in
five
membered rings



Macrocyclic Effect



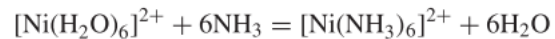
Macrocyclic Effect



M = Zn, Cu

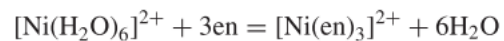
Stabilità: Sistema Ciclico 10^4 superiore Sistema Aciclico

Chelate and Macrocyclic Effects



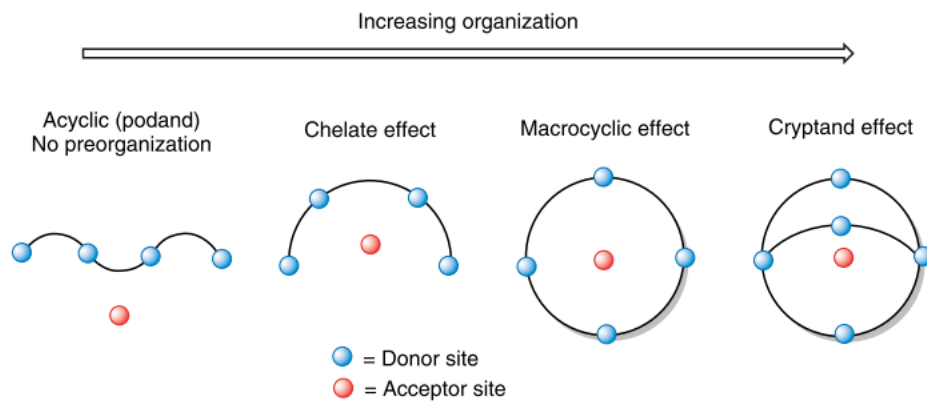
$$\beta \sim 10^9, \Delta G = -51.8 \text{ kJ mol}^{-1},$$

$$\Delta H = -100 \text{ kJ mol}^{-1}, \Delta S = -163 \text{ J mol}^{-1} \text{K}^{-1}$$



$$\beta \sim 10^{18}, \Delta G = -101.8 \text{ kJ mol}^{-1},$$

$$\Delta H = -117 \text{ kJ mol}^{-1}, \Delta S = -42 \text{ J mol}^{-1} \text{K}^{-1}$$



Recettori

cationi

anioni

molecole neutre

Metodi Analitici

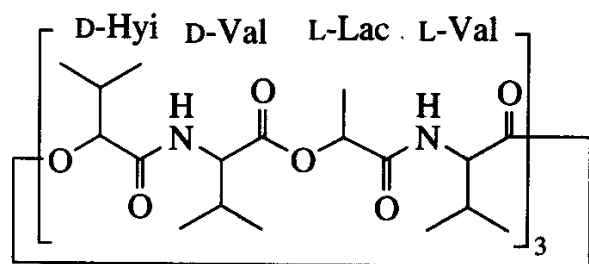
Cavitandi

Contenitori molecolari

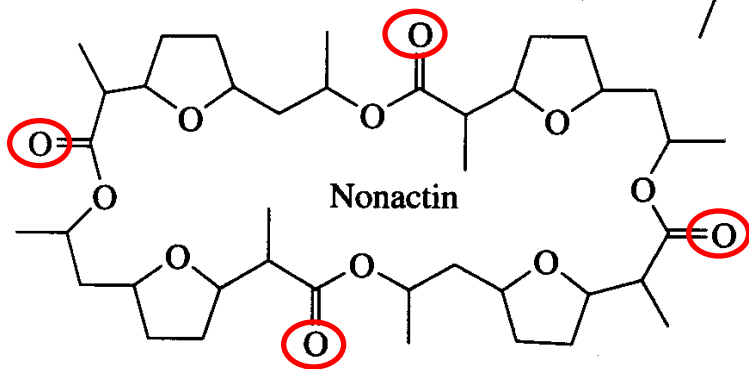
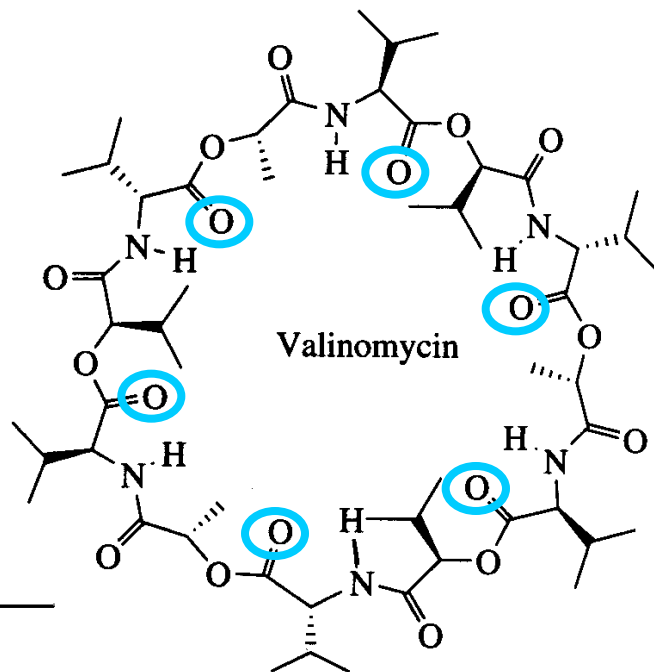
-covalenti

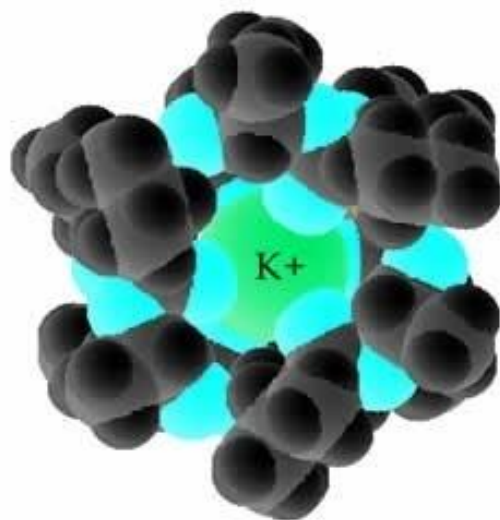
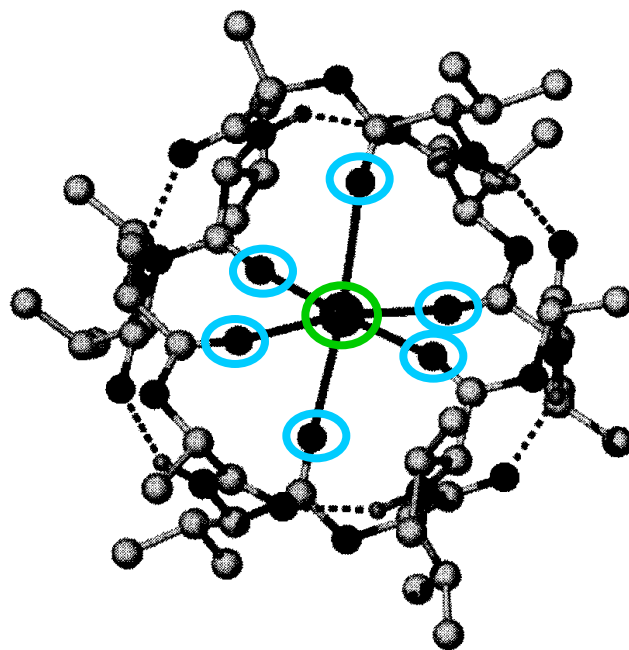
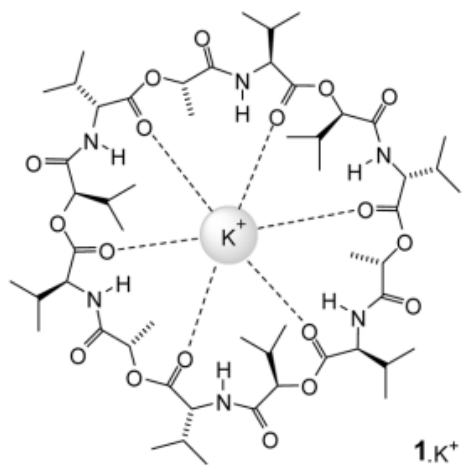
-auto-assemblati (legami idrogeno, legami di coordinazione,
legami covalenti dinamici)

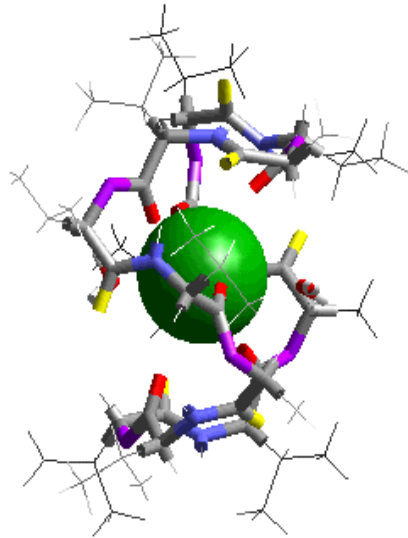
Cations and anions are ubiquitous in biological and chemical systems and their efficient and selective recognition is one of the main goals of Supramolecular Chemistry. As a matter of fact, research in this field started with Pressman's 1964 discovery¹ that valinomycin and other natural antibiotics increase the permeability of lipid bilayer membranes through the selective binding of potassium ion, and with Pedersen's finding² 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 cation³⁻⁷ and anion^{8,9} complexation and sensing. More recently, a special role in ion



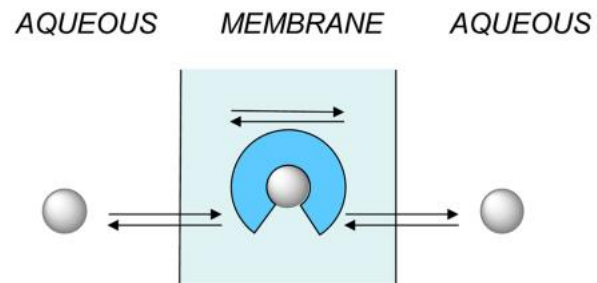
=







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

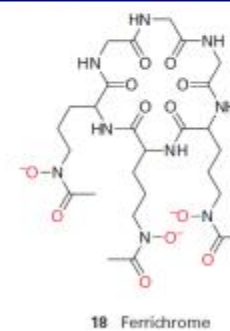
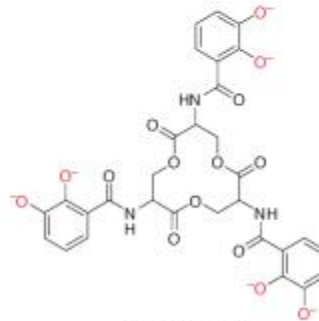


A pH fisiologico 7.4 la concentrazione di $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$ - in equilibrio con $\text{Fe}(\text{OH})_3$ - è circa 10^{-18}M , mentre per le condizioni ottimali di crescita i micro-organismi richiedono una concentrazione intracellulare di circa 10^{-7}M

Siderofori:

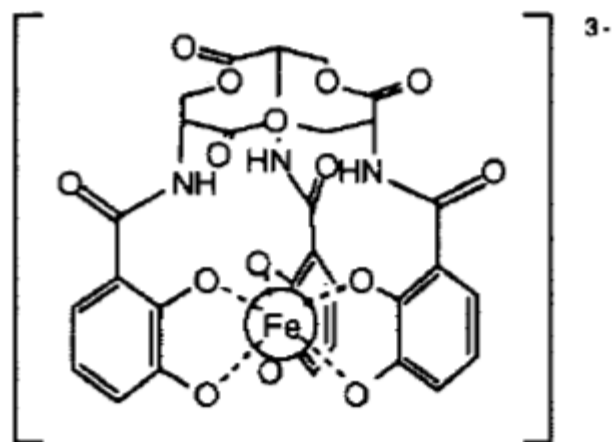
I siderofori sono piccoli leganti polidentati con O/N donatori che hanno grande affinità per lo ione hard $\text{Fe}(\text{III})$ (e scarsa per $\text{Fe}(\text{II})$) e lo rendono solubile attraverso la formazione di complessi ottaedrici ad alto spin.

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 *ferricromo* (3 glicine + 3 N-idrossil-l-ornitine).



L'enterobactina- Fe^{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

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



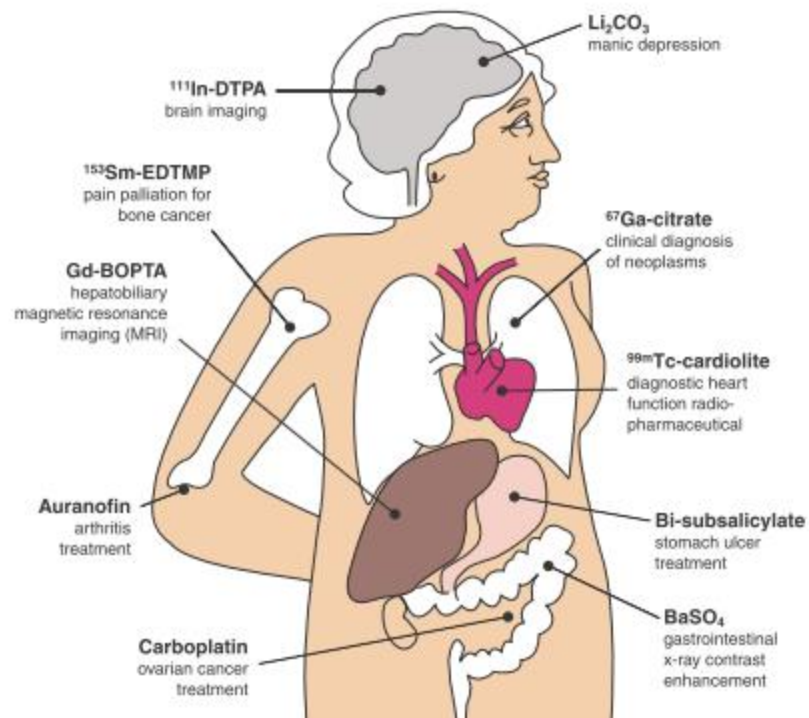
[enterobactin-Fe(III)]³⁻ complex

Boon and Bane of Metal Ions in Medicine

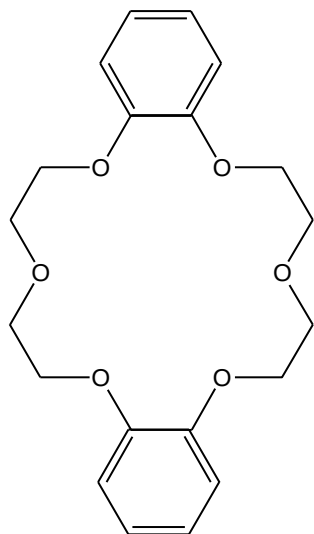
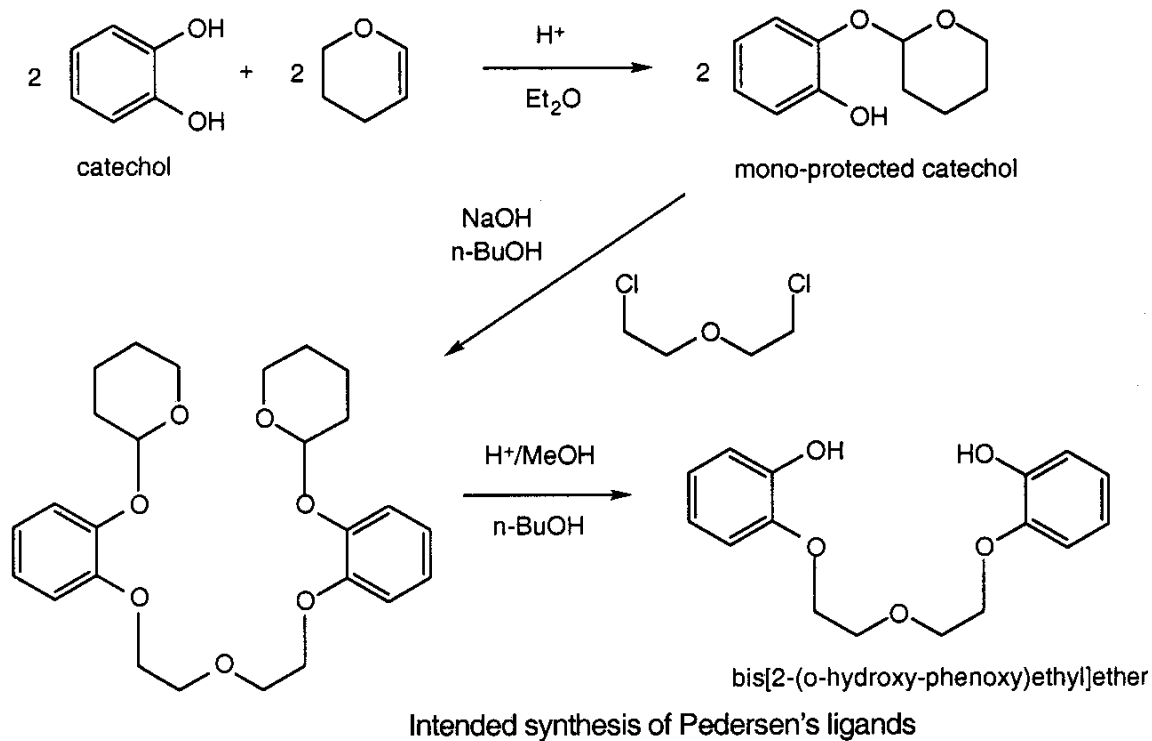
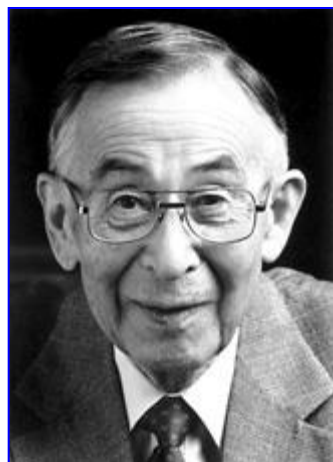
Katherine H. Thompson and Chris Orvig

Science **300**, 936 (2003);

DOI: 10.1126/science.1083004



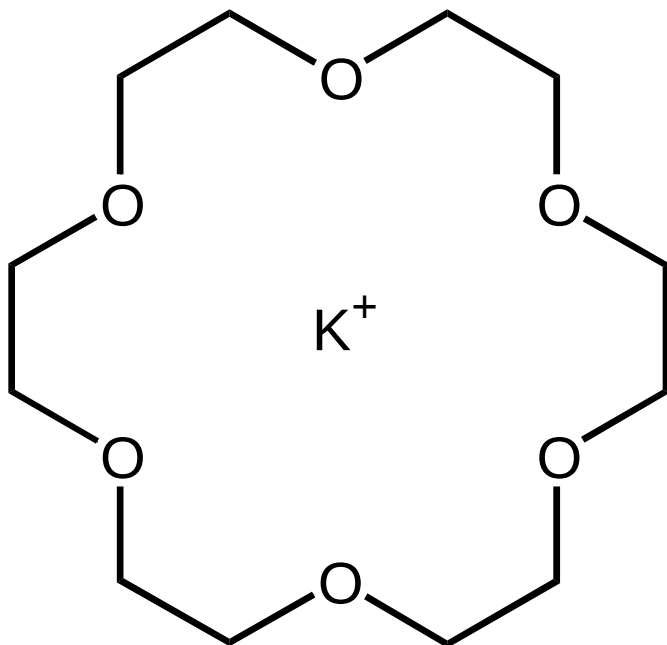
PEDERSEN (Nobel 1987), studio di leganti multi dentati per rame e vanadio (Dupont, anni '60)



dibenzo[18]crown-6 - sottoprodotto

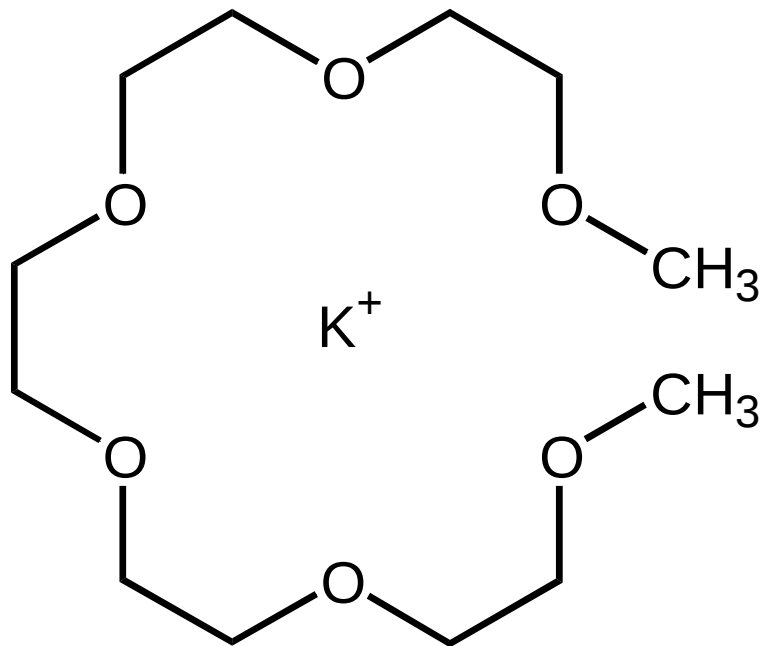
ETERI CORONA (Crown Ethers)
(monocilci = CORANDI)

[18]crown-6

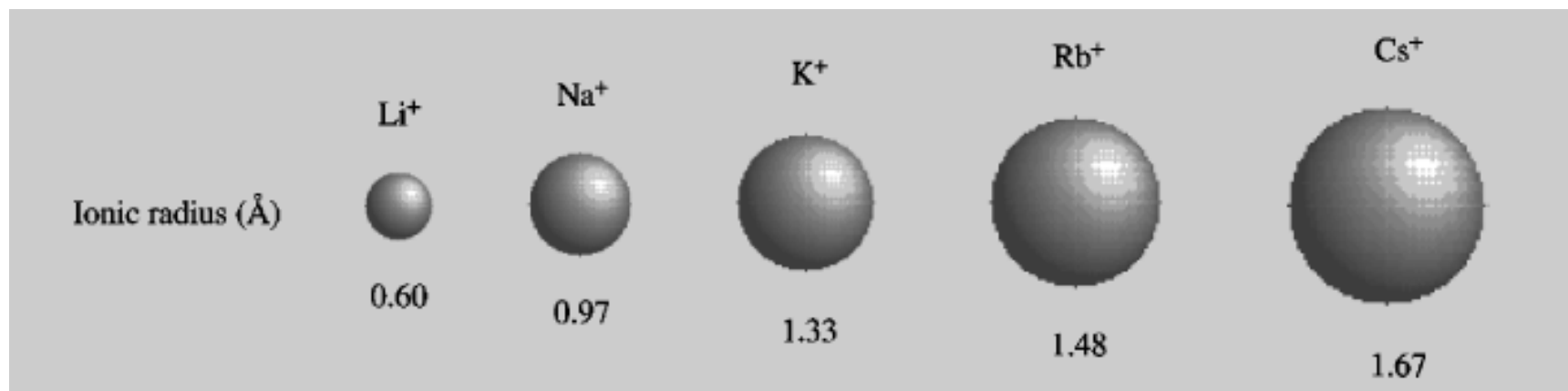


$\log K = 6.08$

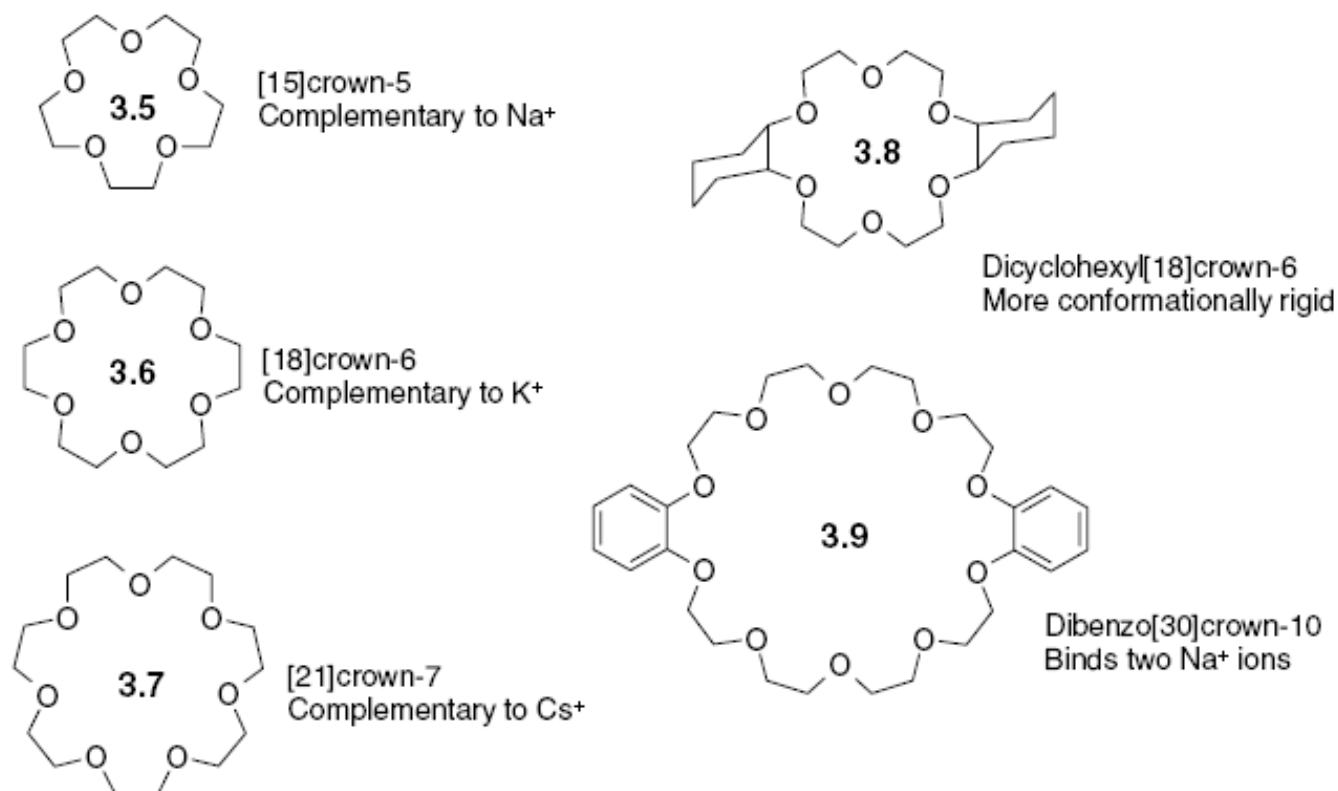
Pentametilenglicol-dietiletere

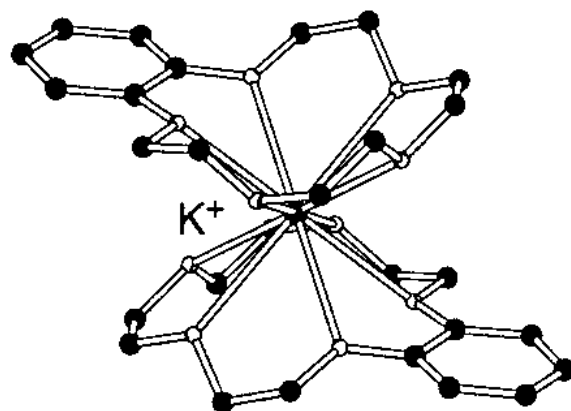
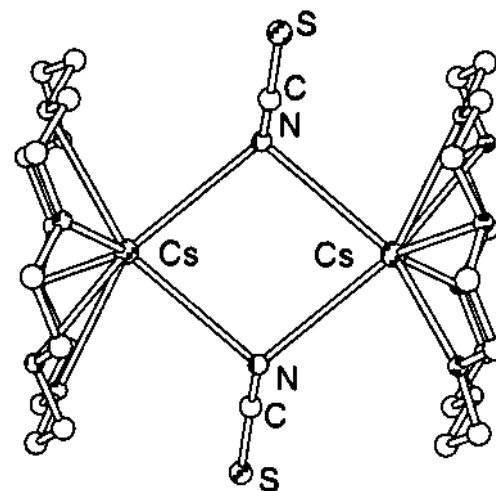
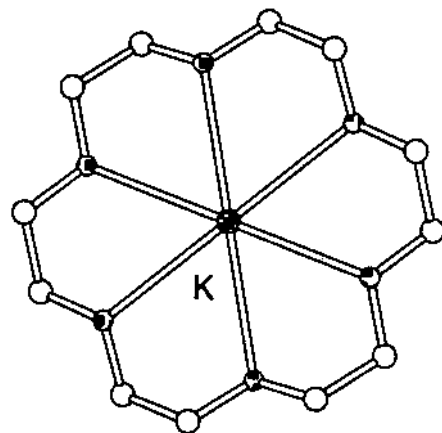
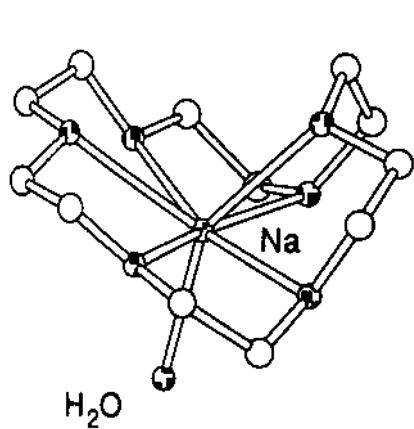


$\log K = 2.3$

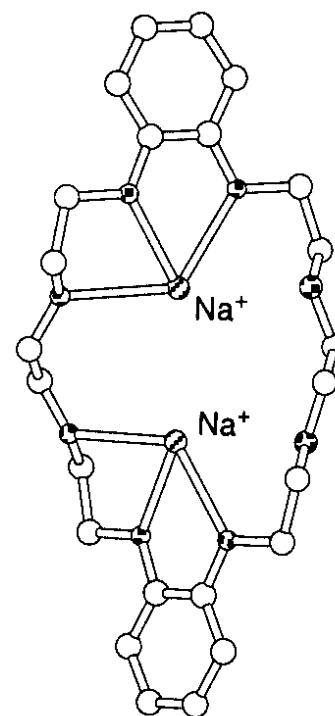


OPTIMAL SPATIAL FIT or SIZE-MATCH





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

a Cationi **hard** formano complessi in cui le interazioni coulombiane sono dominanti

b Cationi **soft** formano complessi in cui è dominante il legame covalente.

Ioni metallici di tipo **a** sono principalmente:

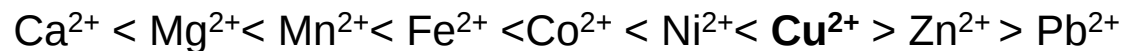
- ioni dei metalli alcalini e alcalino-terrosi
- ioni metallici leggeri e con elevata carica: Ti^{4+} , Fe^{3+} , Co^{3+} , Al^{3+}

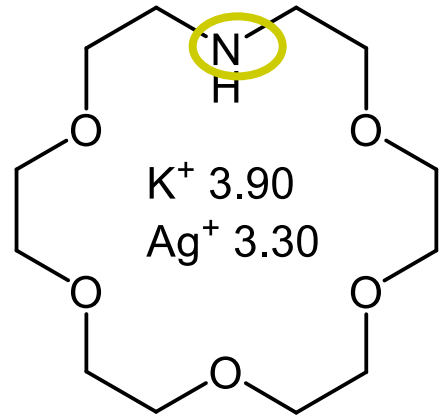
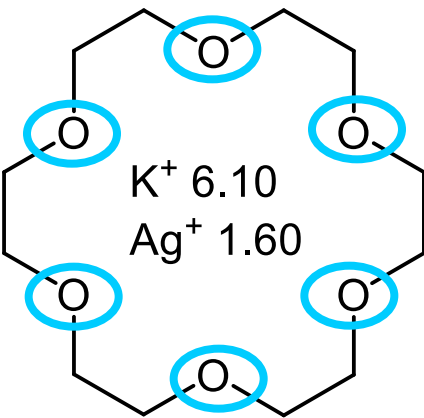
Ioni metallici di tipo **b** sono principalmente:

- ioni pesanti di metalli di transizione: Hg_2^{2+} , Hg^{2+} , Pt^{2+} , Pt^{4+} , Ag^+ , Cu^+
- ioni di metalli in bassi stati di ossidazione, ad es. nei metallo carbonili

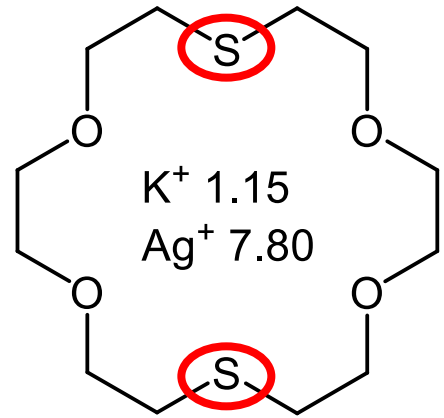
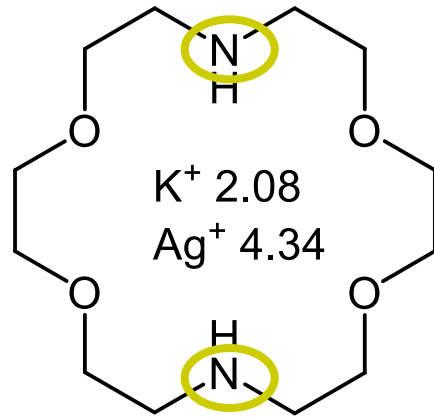
Alcuni ioni (Fe^{2+} ; Co^{2+} ; Ni^{2+} ; Cu^{2+} ; Zn^{2+} ; Pb^{2+}) formano complessi le cui stabilità non possono essere pronosticate sulla base della classificazione hard/soft: essi formano la classe *border-line*

La costante di stabilità dei complessi di questi ioni con un dato legante segue l'ordine, noto come serie di **Irving-Williams**:

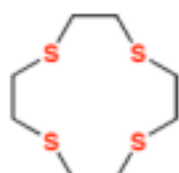




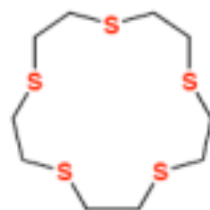
Aza-crown



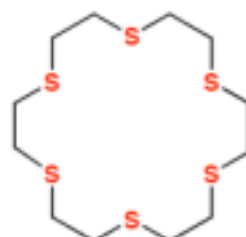
Tio-crown



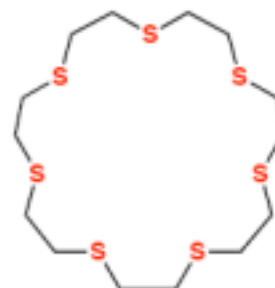
[12]S₄



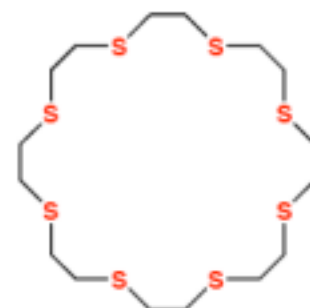
[15]S₅



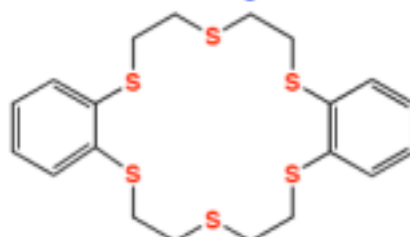
[18]S₆



S



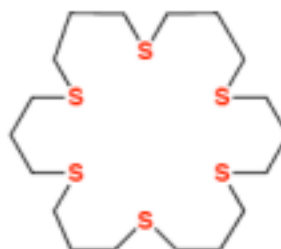
[24]S₈



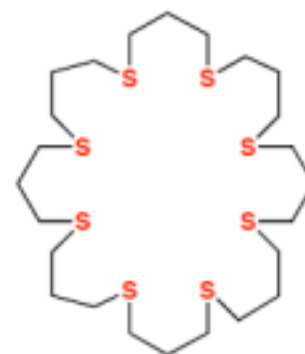
Dibenzo[18]S₆



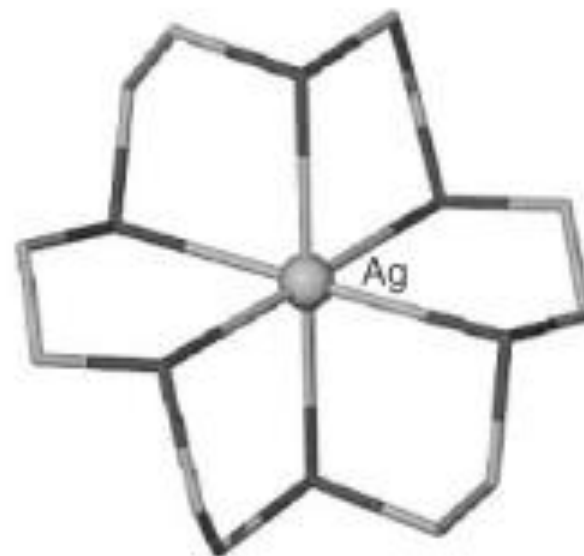
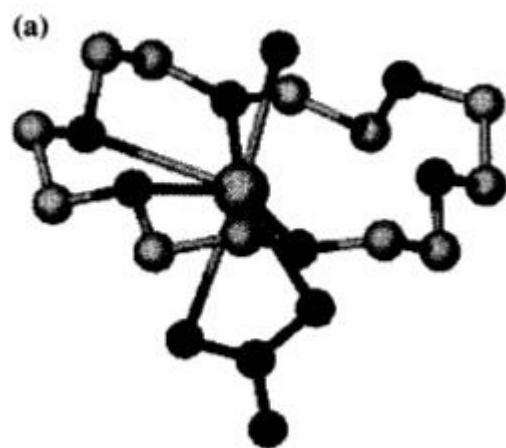
[16]S₄

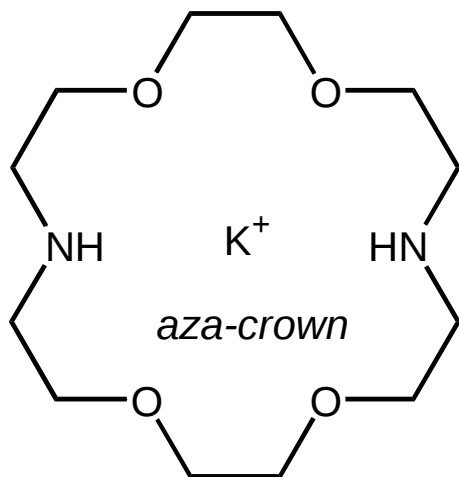


[24]S₆

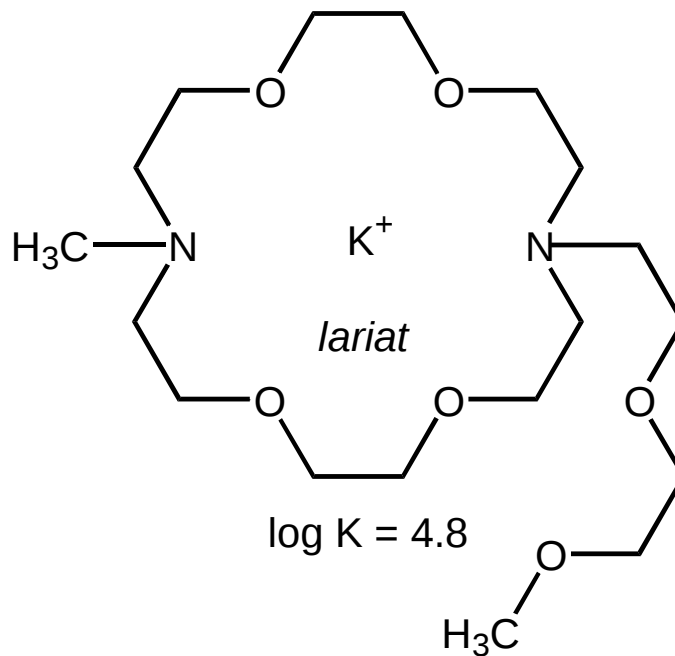


[32]S₈





$$\log K = 2.04$$



$$\log K = 4.8$$

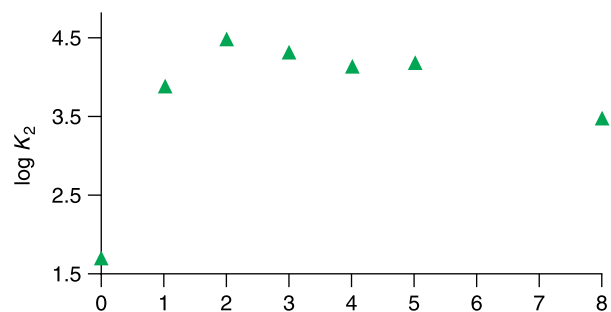
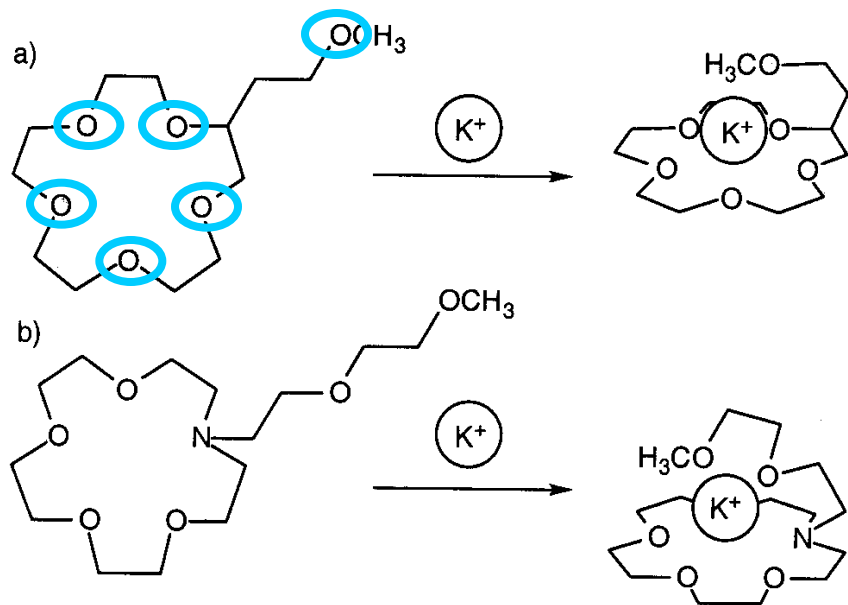


Figure 17 Na^+ complexation by aza-15-crown-5 lariat ethers with n oxygen donor atoms in the side arm ($n = 0-8$).⁵⁷

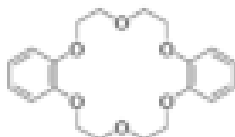
(a) Carbon and (b) nitrogen pivot lariat crown ethers binding potassium cations.



18-crown-6

274984-1G

78.40 euro



Dibenzo-18-crown-6

158399-2.5G

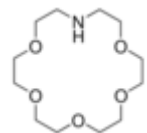
17.50 euro



15-crown-5

188832-1G

15.30 euro

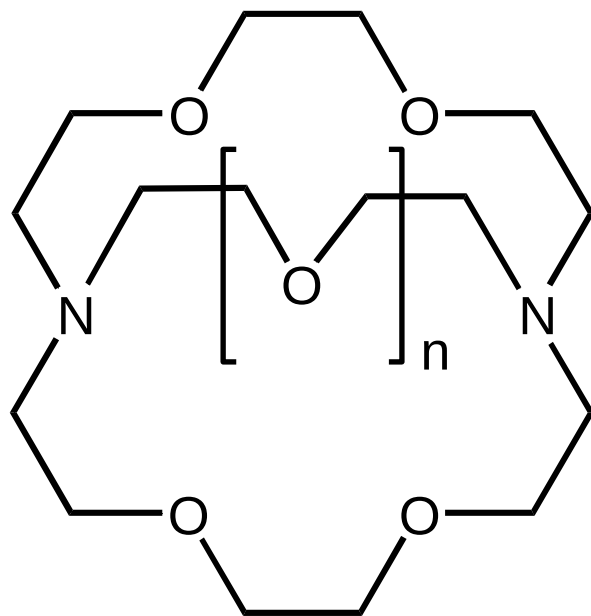


1-Aza-18-crown-6

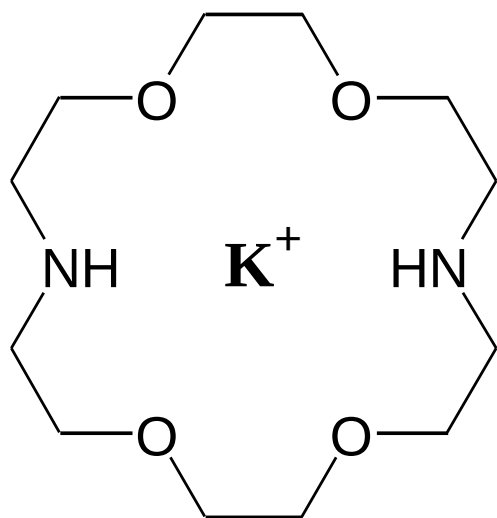
11382-1G

212.00 euro

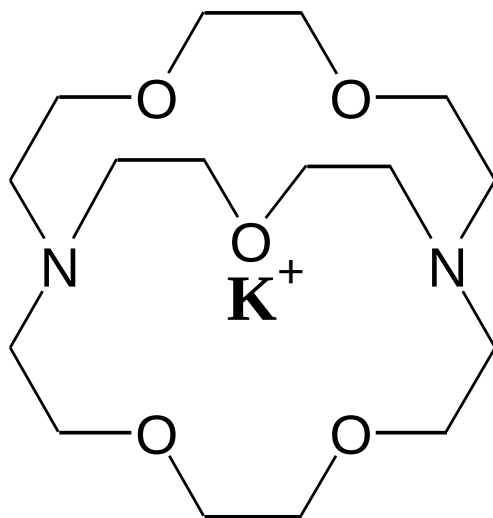
LEHN (Nobel 1987), estensione dei sistemi monociclici a sist. biciclici (CRIPTANDI, anni '60)



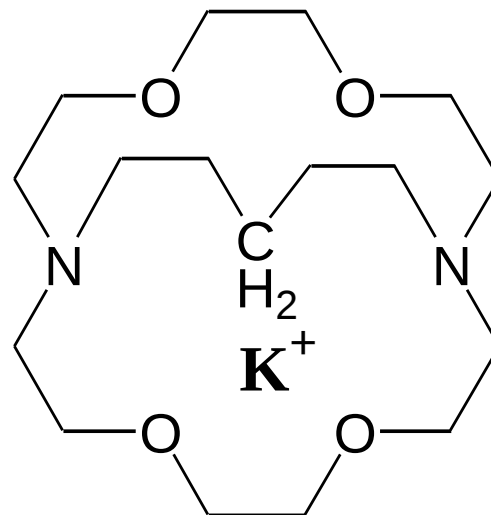
Na^+
 $n = 1$, criptando $[2,2,1]$
 $n = 2$, criptando $[2,2,2]$
 K^+



$\log K = 2.0$

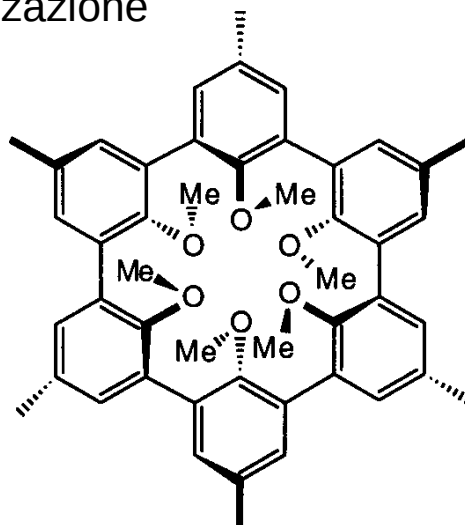
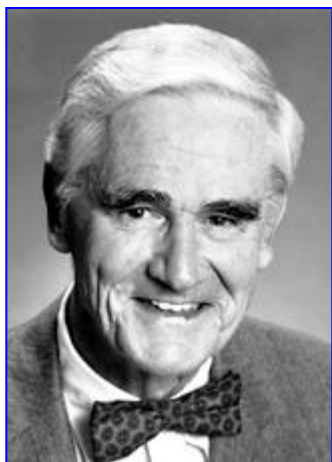


$\log K = 7.0$



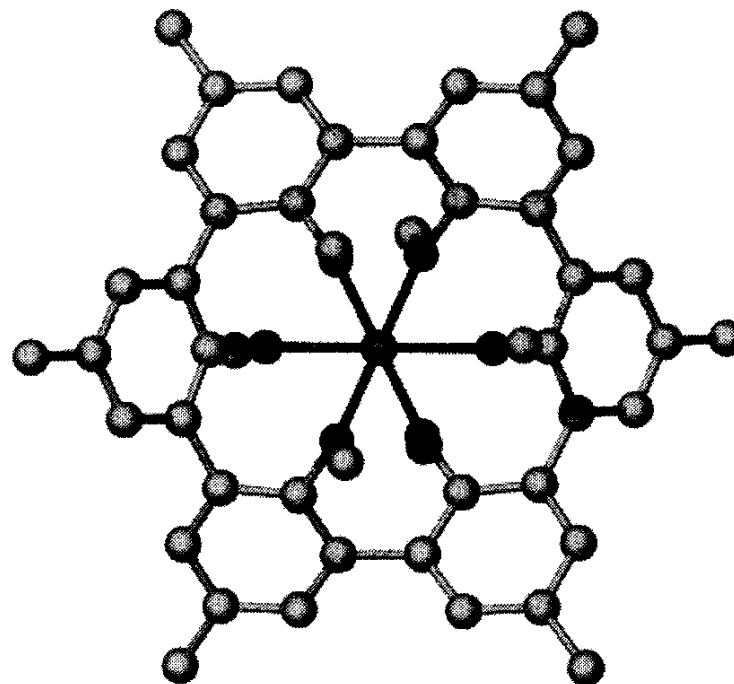
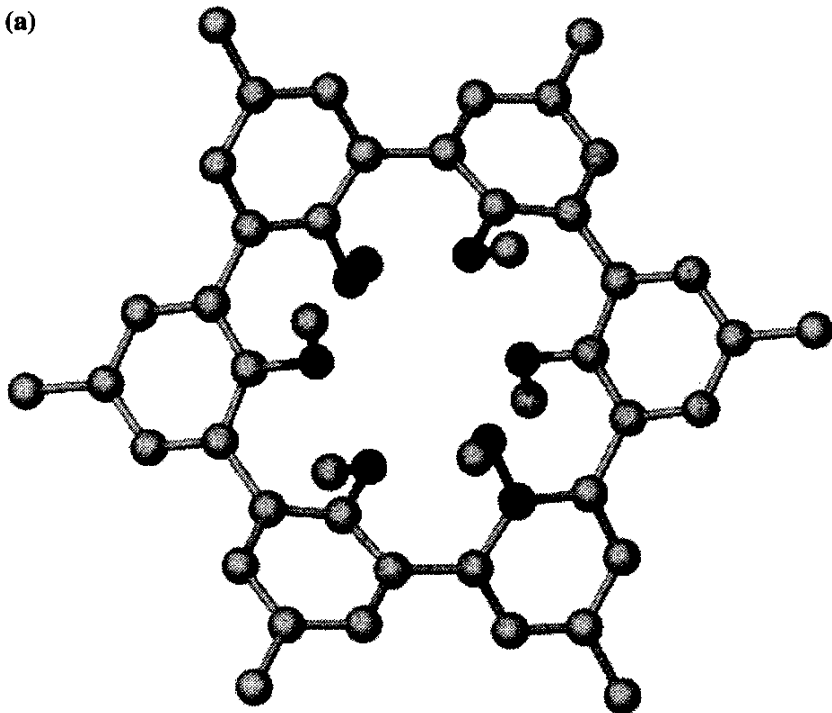
$\log K = 5.4$

CRAM (Nobel 1987) - preorganizzazione

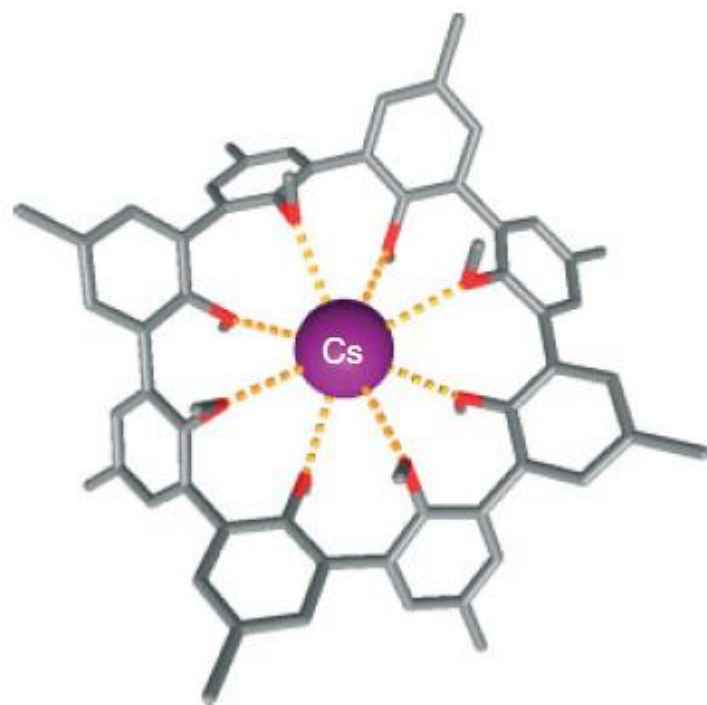
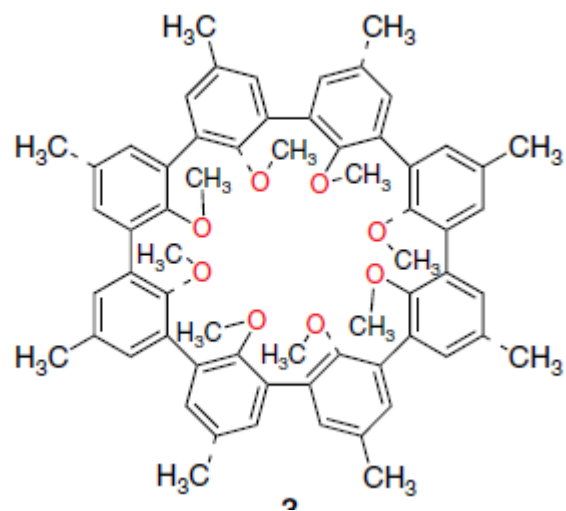


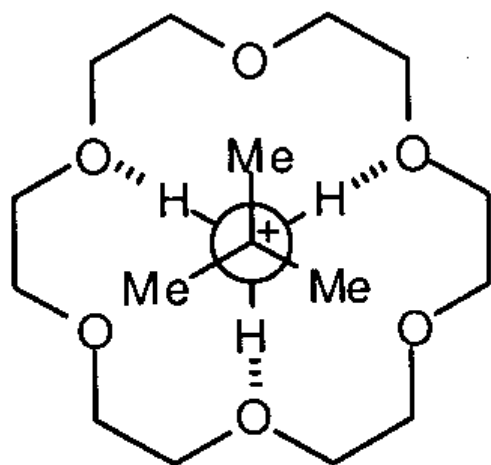
Sferandi
(*p*-metilanisolo)

(b)

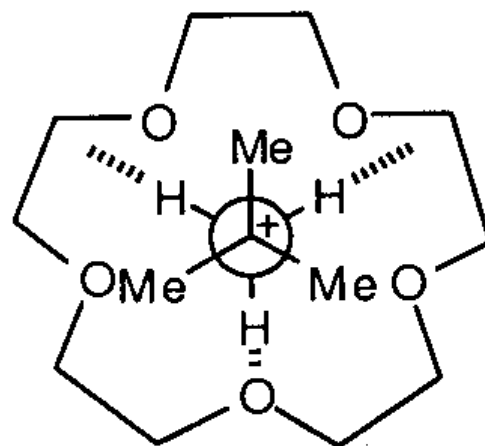


X-ray crystal structures of (a) free spherand (3.30) and (b) its Li^+ complex (after Trueblood *et al.* 1981).

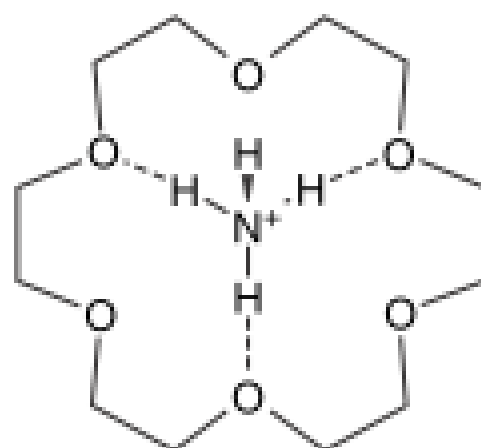




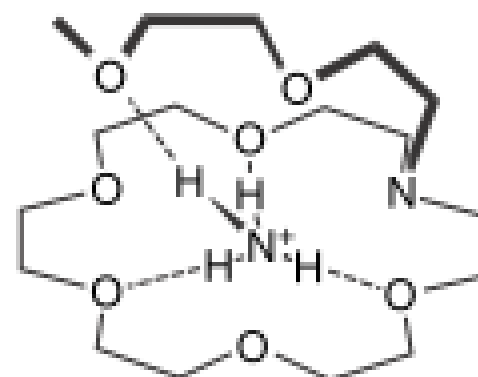
strong complex
ideal arrangement of hydrogen bond
donors and acceptors



weaker complex
mismatch in geometry of hydrogen bond
donors and acceptors

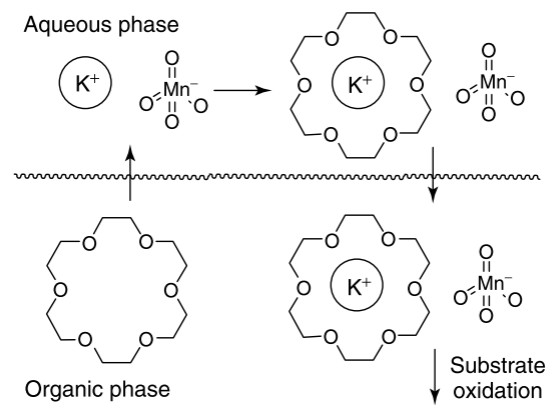


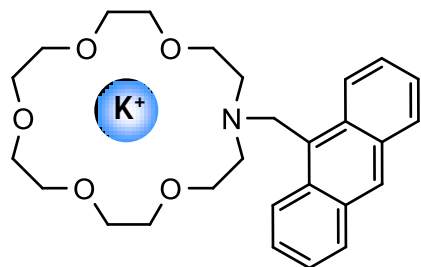
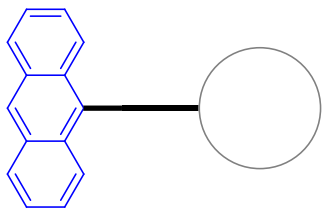
$\log K = 4.35$



2.23· NH_4^+

$\log K = 4.75$



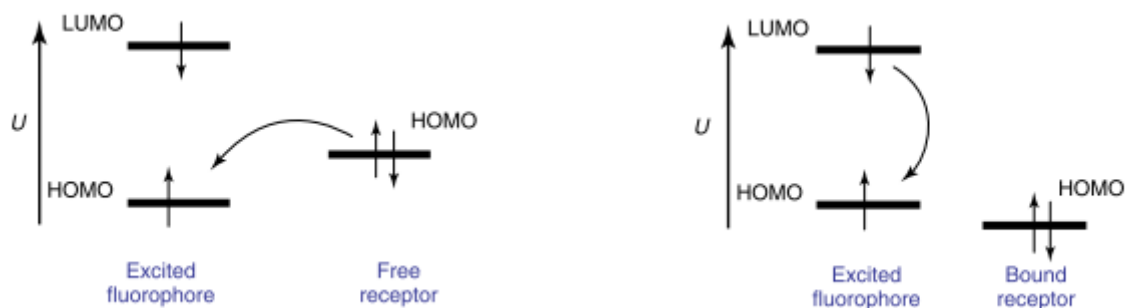
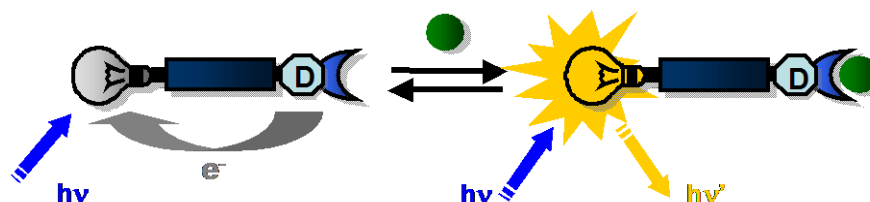


Silent substrates (analiti silenti):

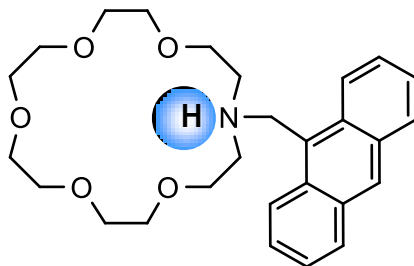
Meccanismo ON/OFF (PET) intrinseco al sensore
attivato dall'analita (ammina terziaria)

OFF in ASSENZA di analita

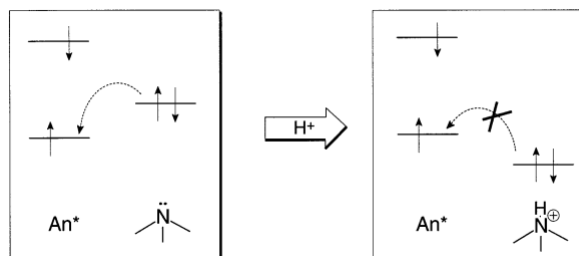
ON in presenza di analita



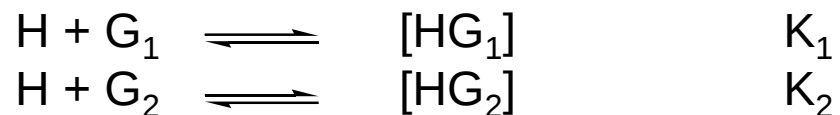
In soluzione acquosa attenzione al pH!



**Fluorescenza accesa anche in assenza di catione
se ammina protonata;
in presenza di catione l'ammina deve essere
deprotonata perché il sensore si accenda!**



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



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

Selectivity is a consequence of preorganization, complementarity...

Needs to be calculated at equilibrium in the same conditions

Temperature! Solvent!

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

- transport
- catalysis
- sensing and signaling

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* Ca^{2+} vs Na^{+});

Energie libere di solvatazione dell'host e del catione

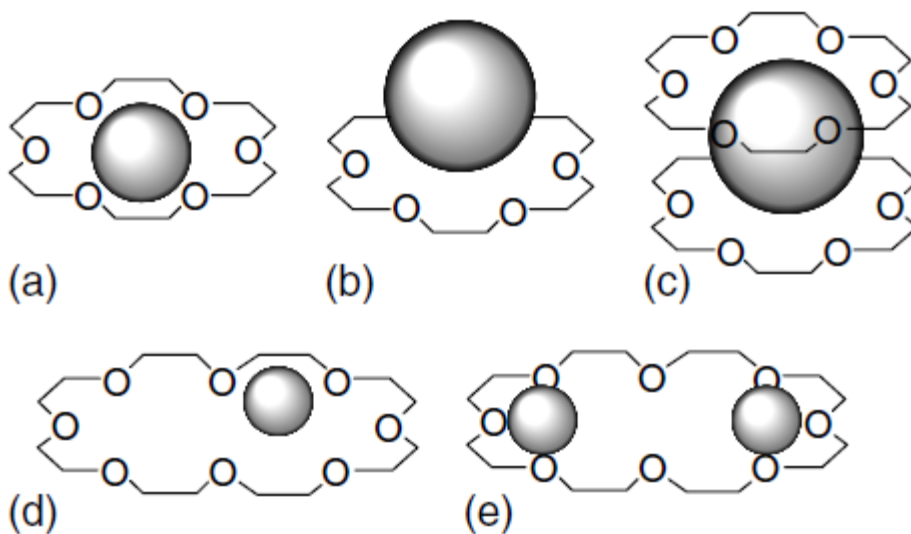
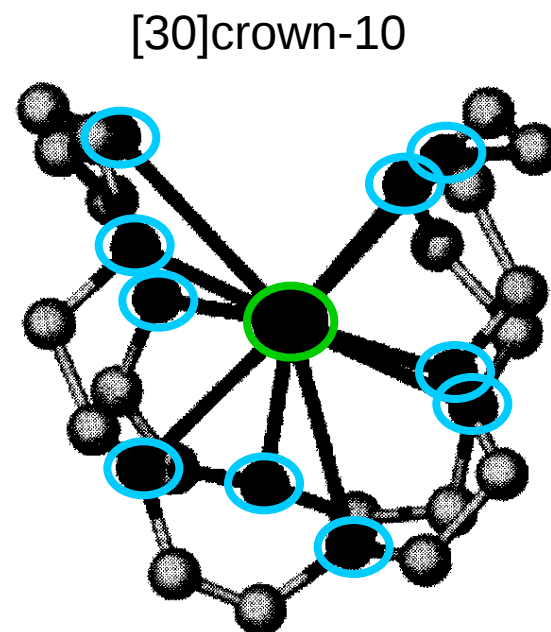
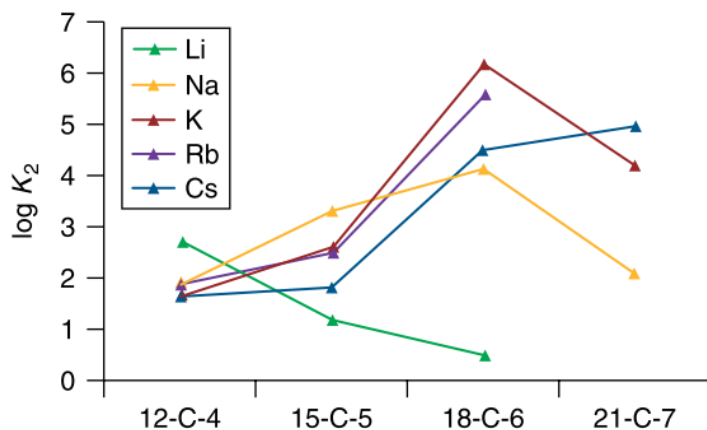
Solvente – competitivo per i dipoli/ costante dielettrica/ legami idrogeno/capacità coordinanti

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

Cinetica di complessazione

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



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

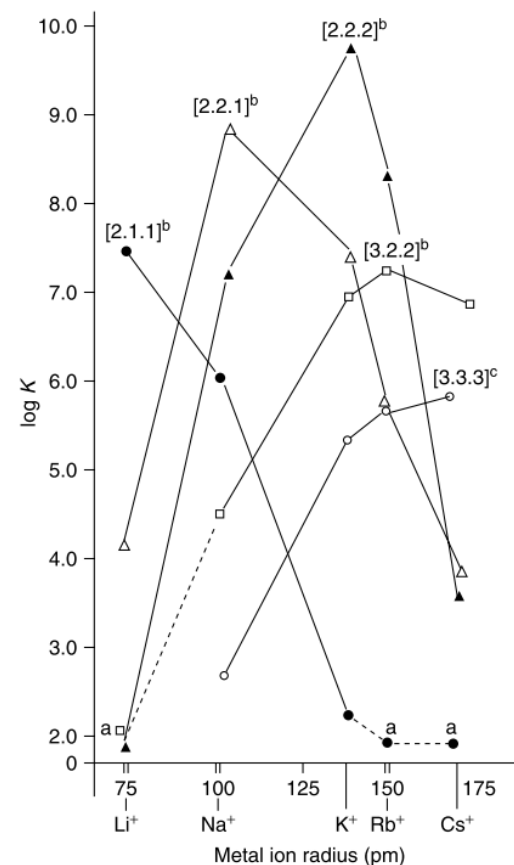
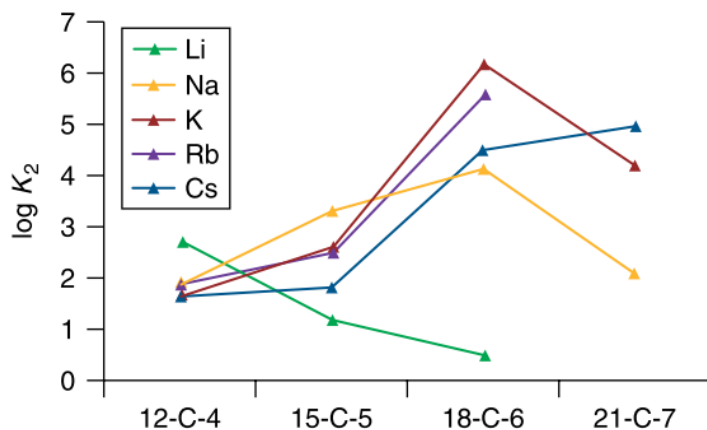
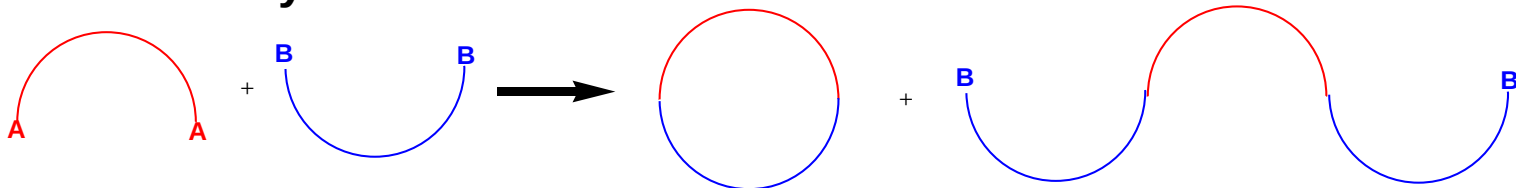


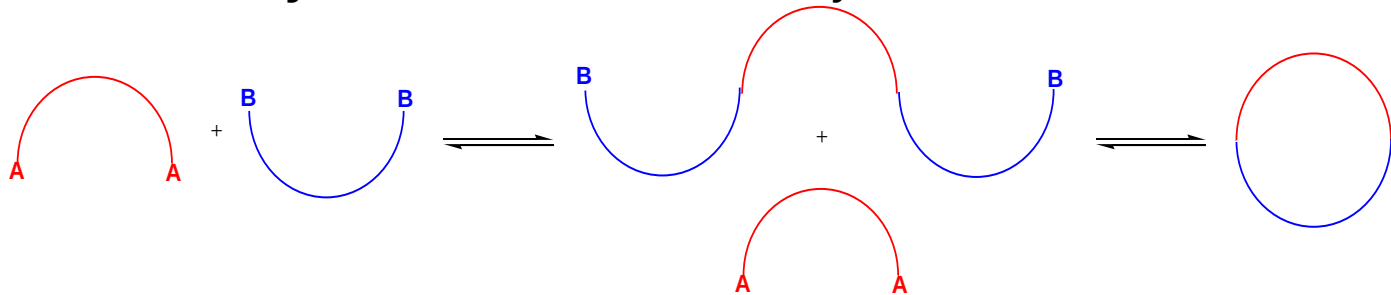
Figure 2 Selectivity of cryptands among alkali metal cations (a, value reported <2.0; b, in 95% CH₃OH; c, in methanol).

- **covalent synthesis** : under kinetic control



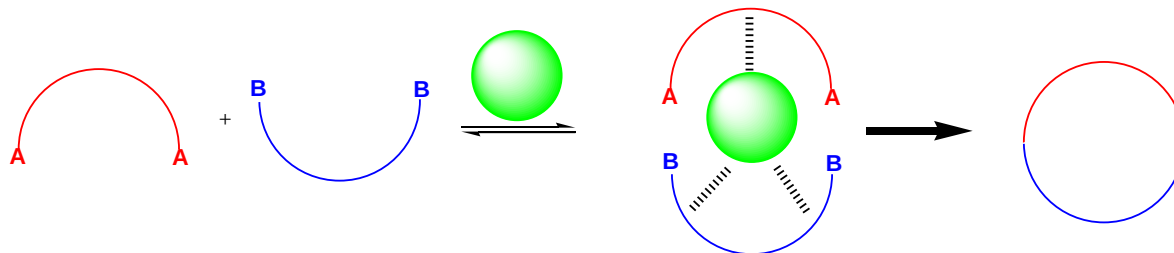
- classical organic chemistry. Irreversible bond formation
- highly stable molecules.
- not adapted to big molecules. low yield

- **non covalent synthesis** : under thermodynamic control



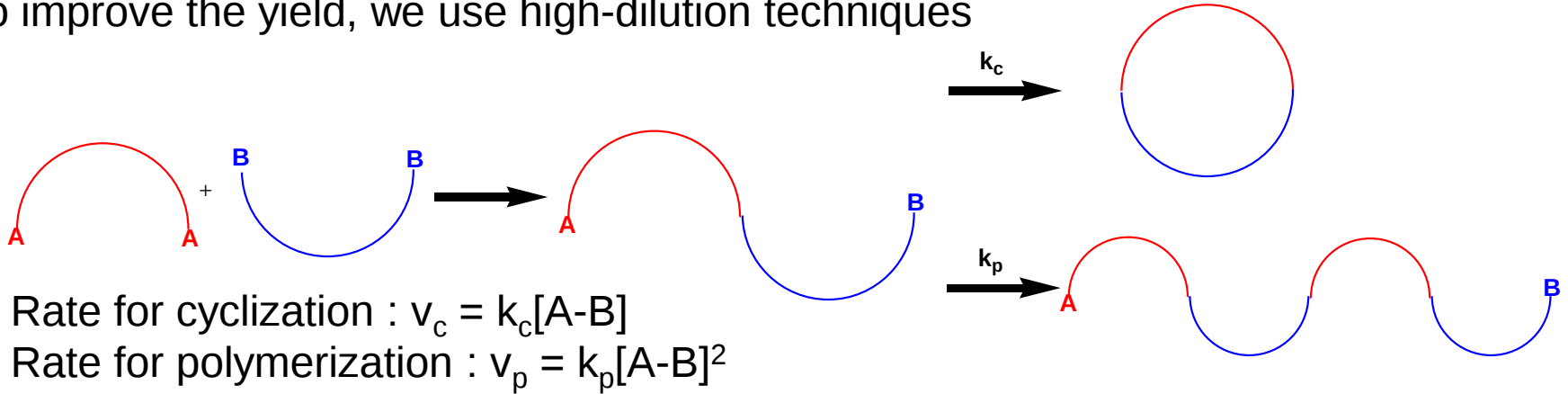
- thermodynamic directed synthesis. Reversible bond formation
- lower stability
- adapted to big molecules. high yield

- **a mix**



- take advantage of the two approaches

To improve the yield, we use high-dilution techniques



- the more dilute, the more cyclic product is formed
- the reaction has to be fast

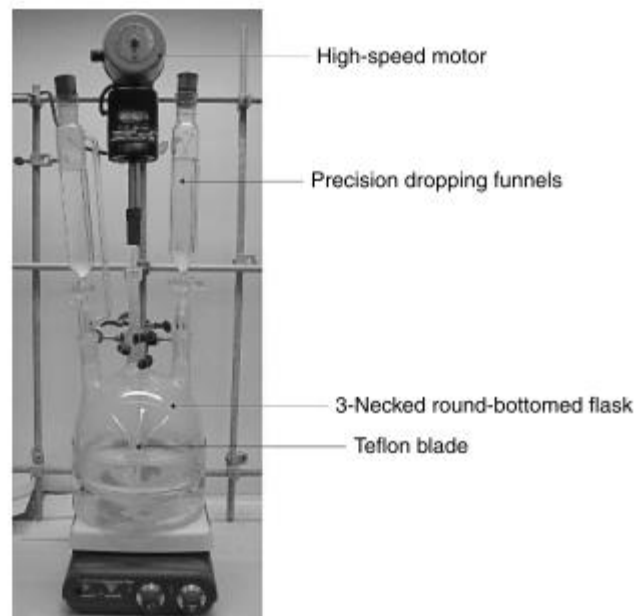
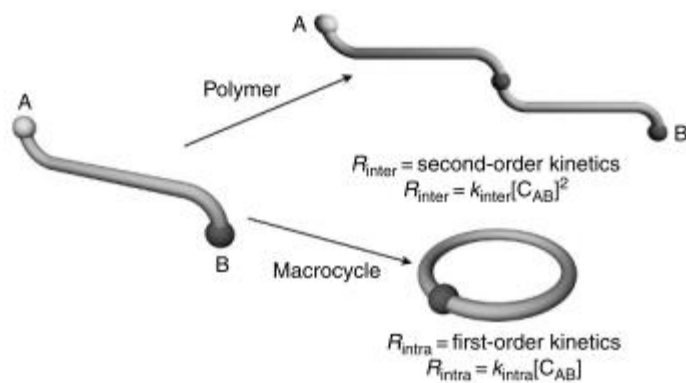
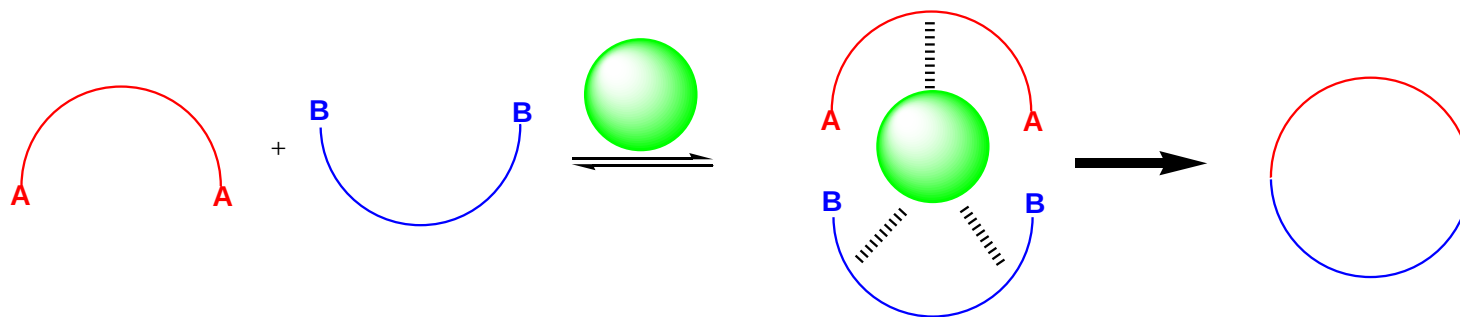
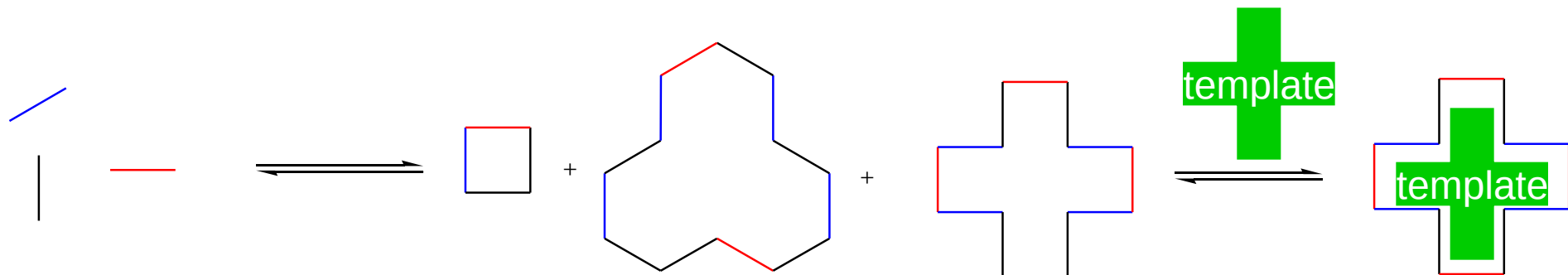
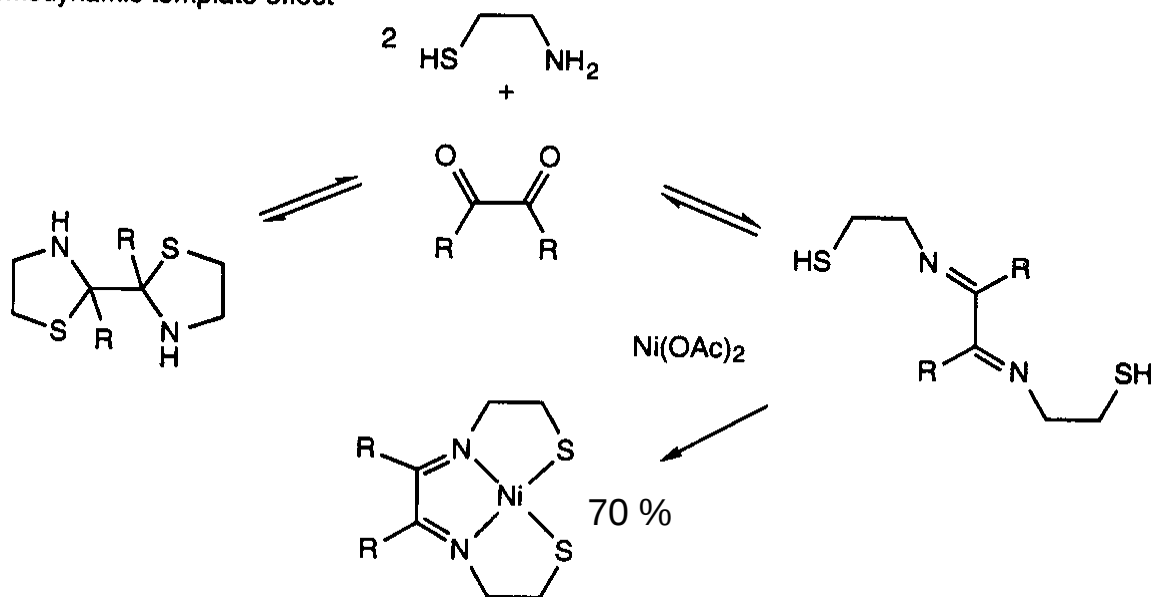


Figure 2.1 Typical apparatus used for high-dilution synthesis.

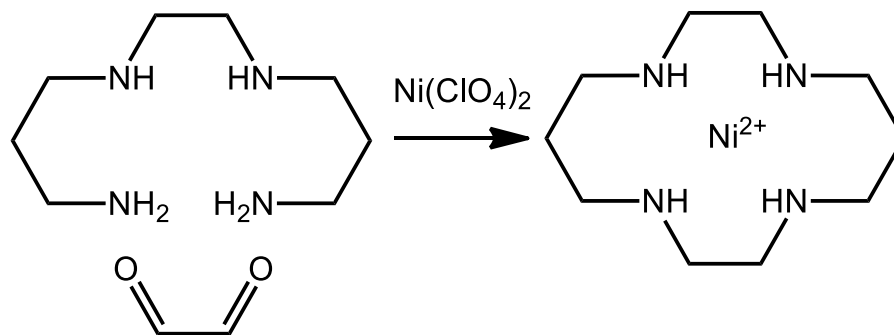




a) thermodynamic template effect



Effetto templato cinetico CYCLAM (base di Schiff)



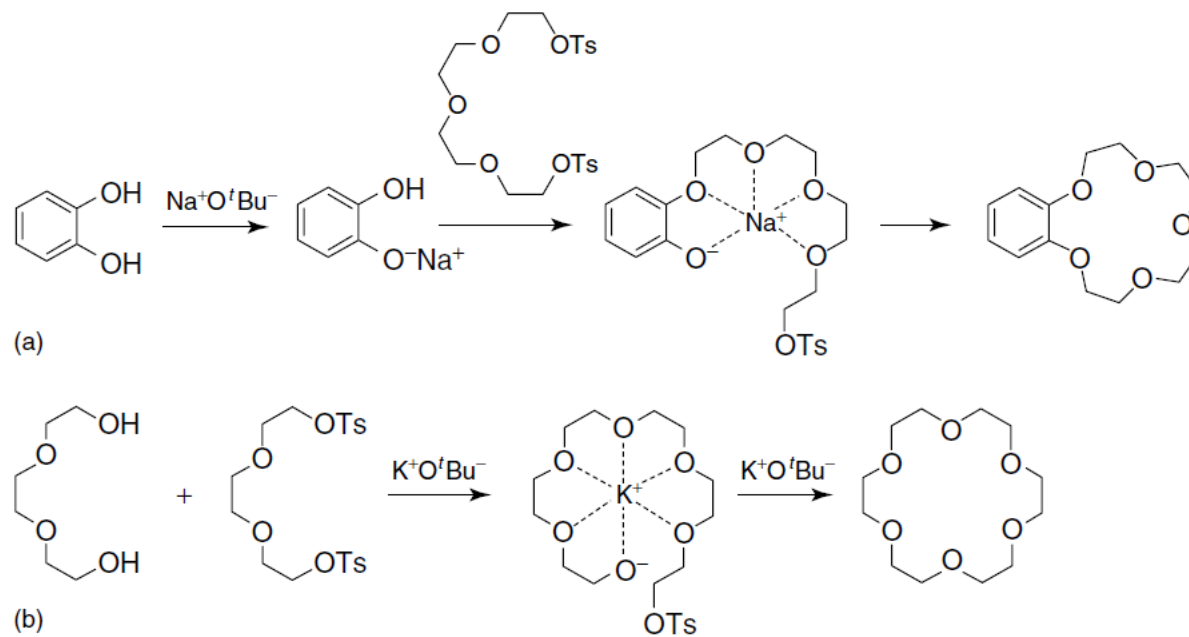
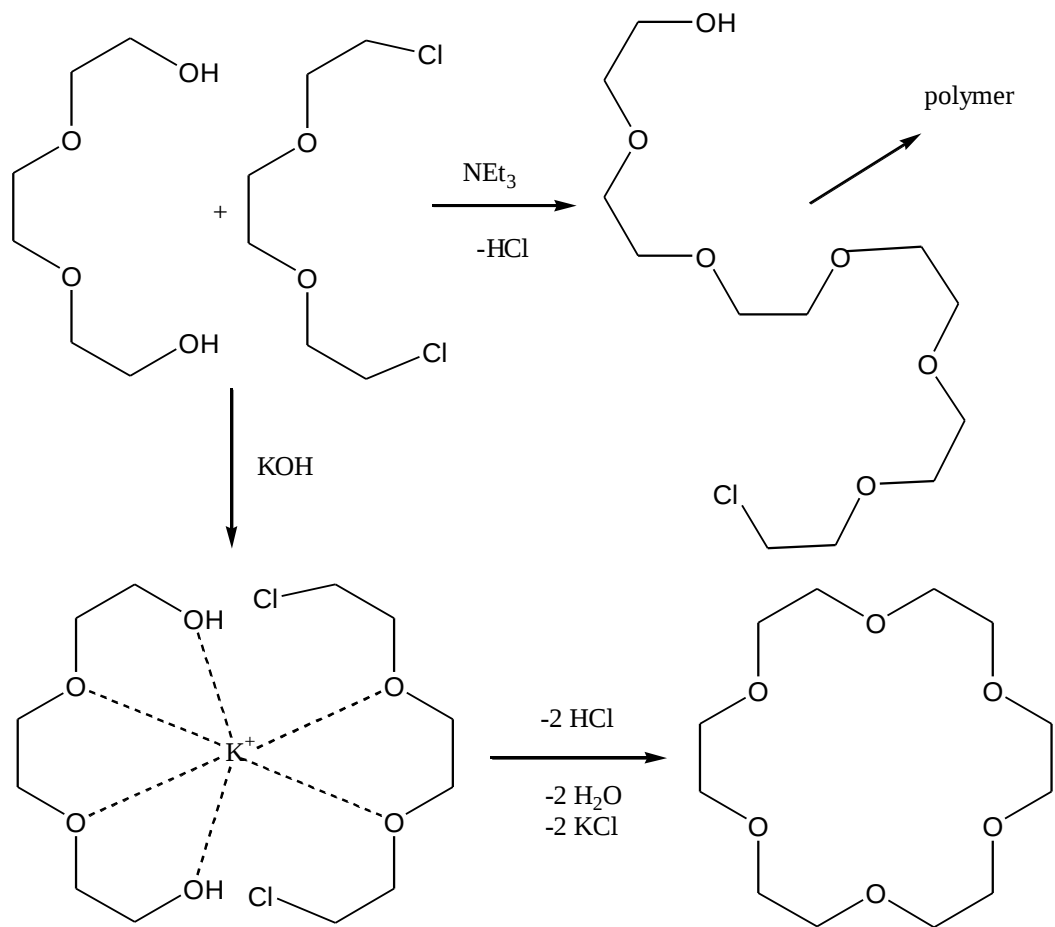
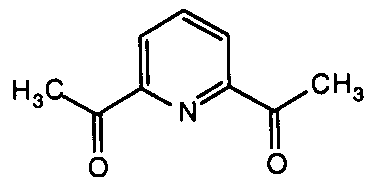


Figure 3 Template synthesis: (a) benzo-15-crown-5; (b) 18-crown-6.



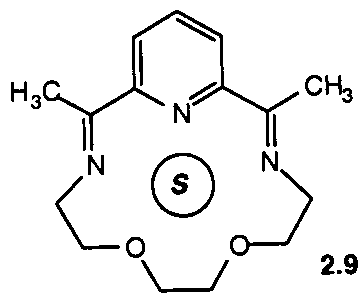


+



S

small metal cation templates
(e.g. Mn^{2+} , Fe^{2+} , Mg^{2+})

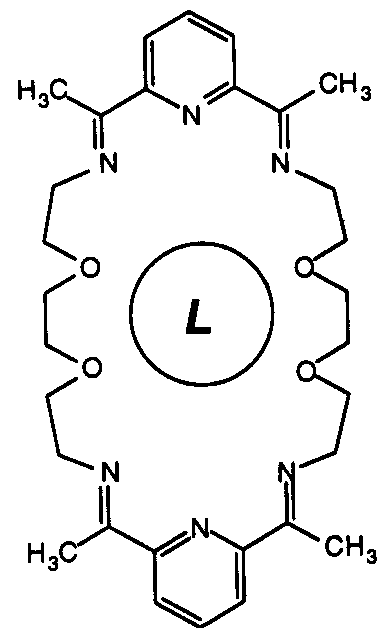


2.9

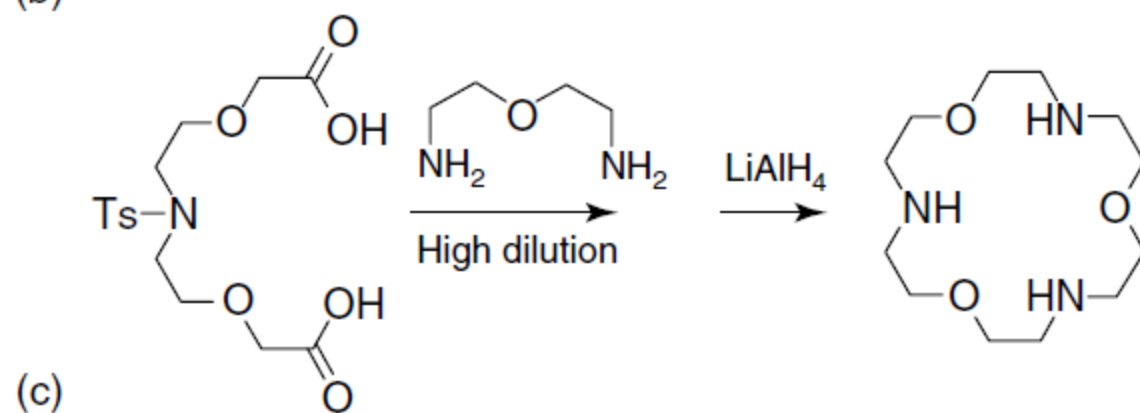
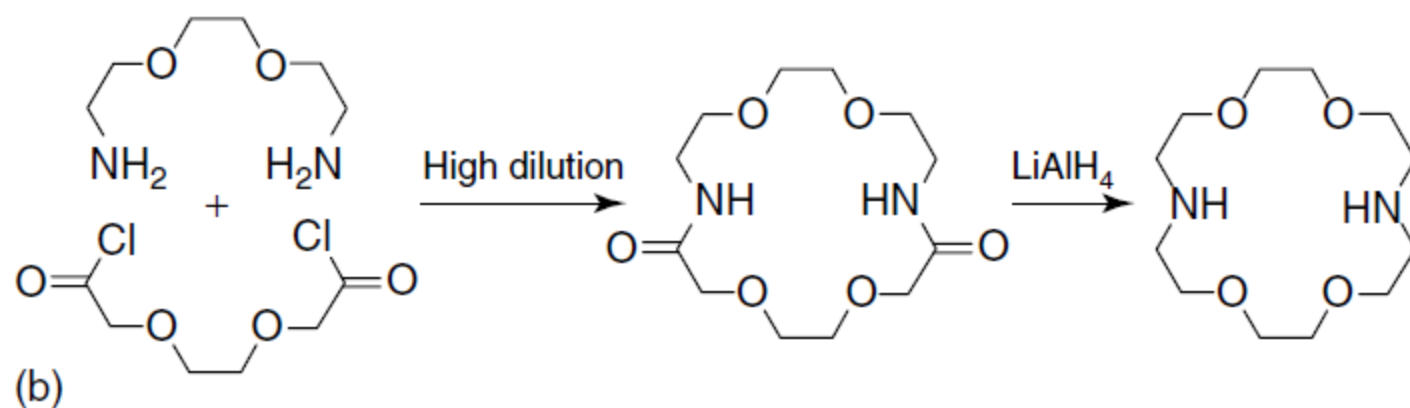
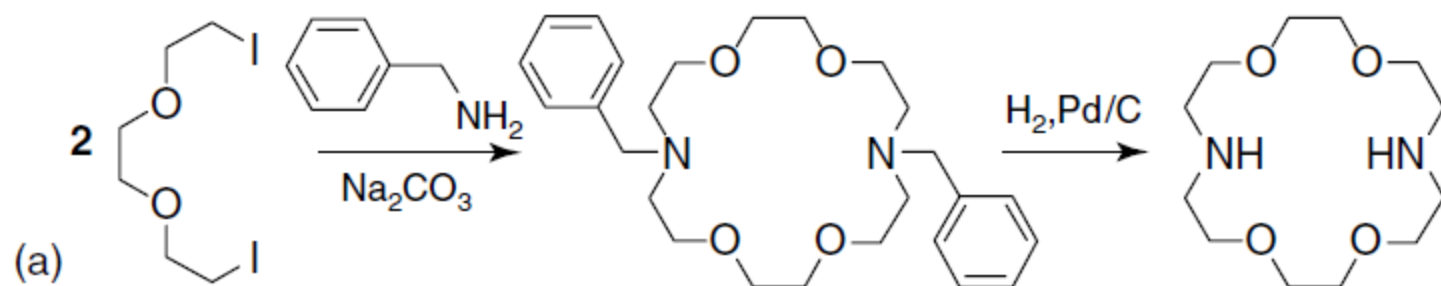
1 + 1 condensation

L

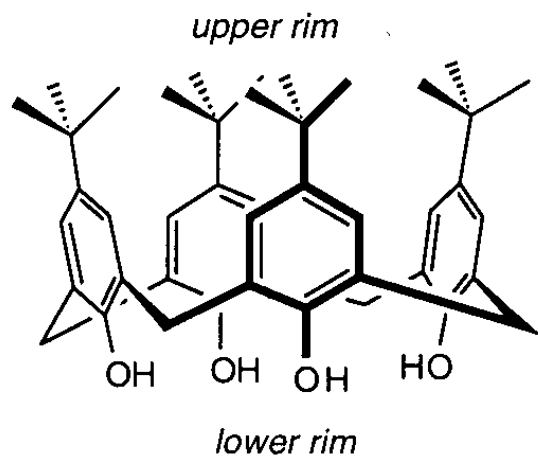
large metal cation templates
(e.g. Ba^{2+} , Pb^{2+})



2 + 2 condensation

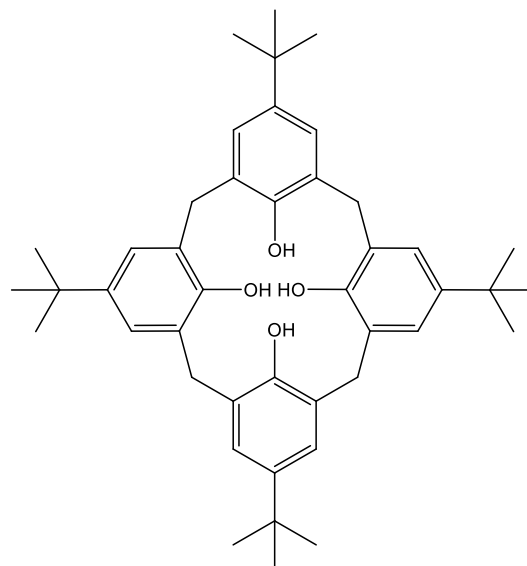
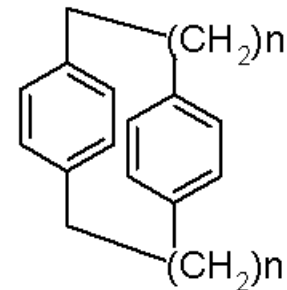
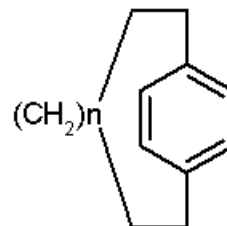
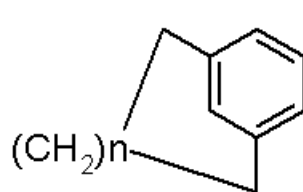


Calix[n]areni

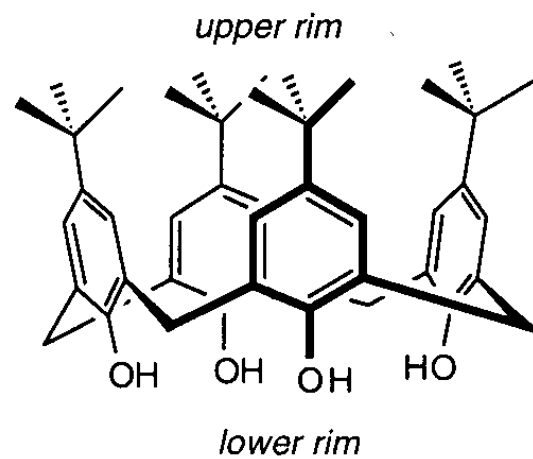
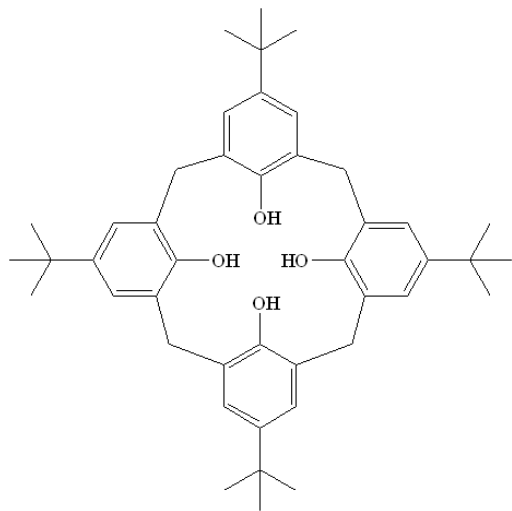


p-tert-Butylcalix[4]arene.

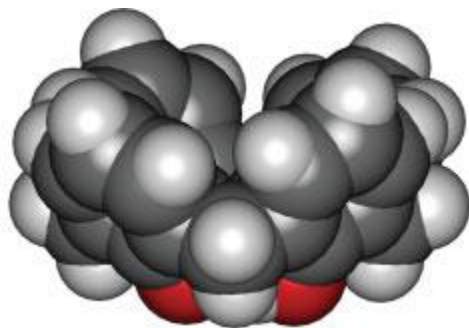
Ciclofani

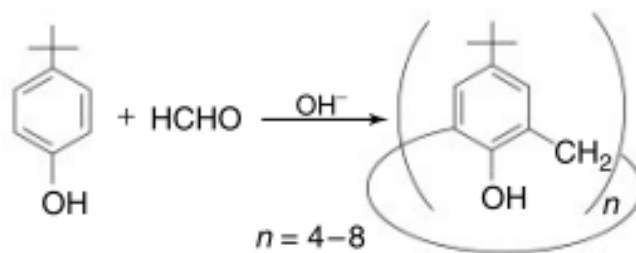


Calix[n]areni

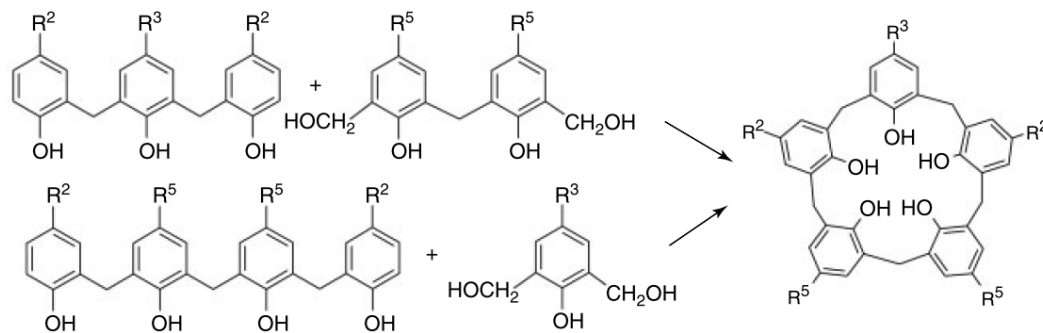


p-tert-Butylcalix[4]arene.

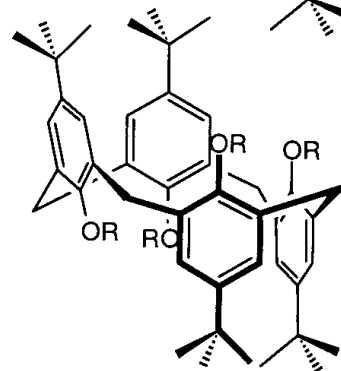
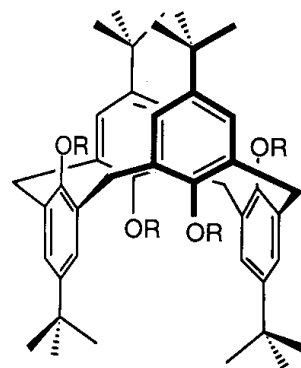
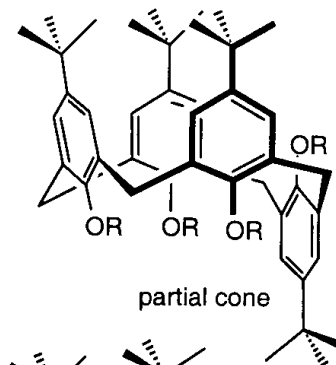
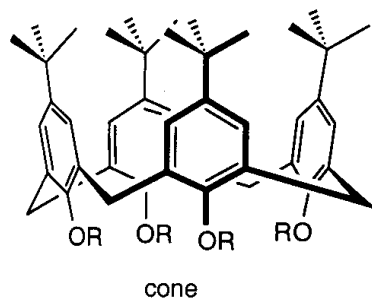




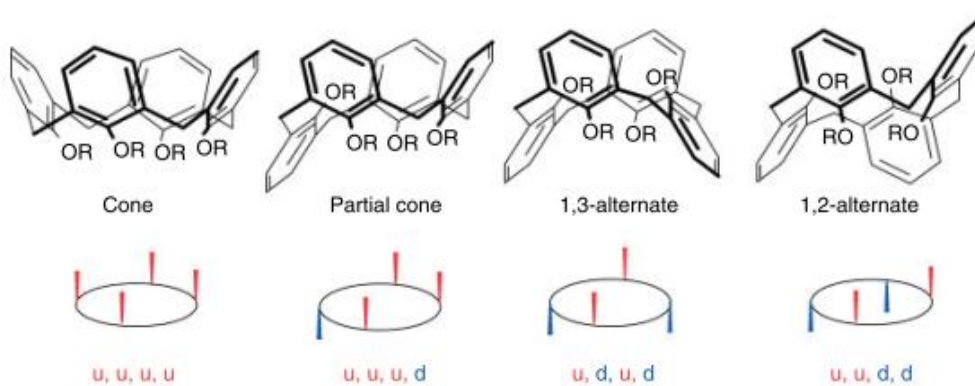
3+2 Fragment condensation



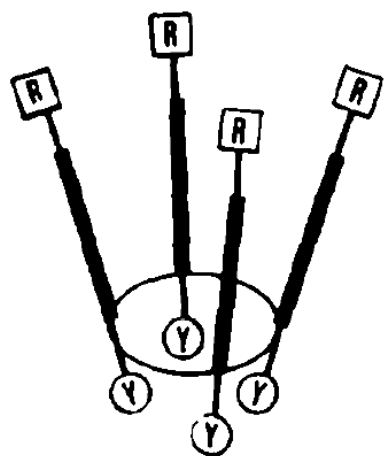
4+1 Fragment condensation



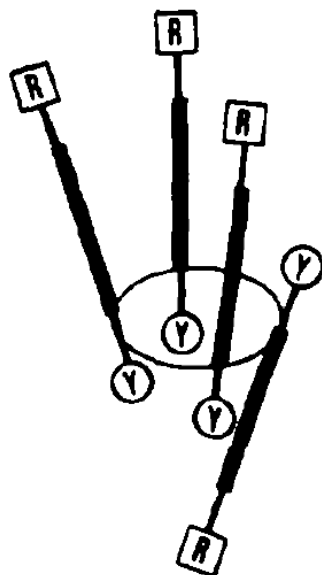
Conformations adopted by calix[4]arenes.



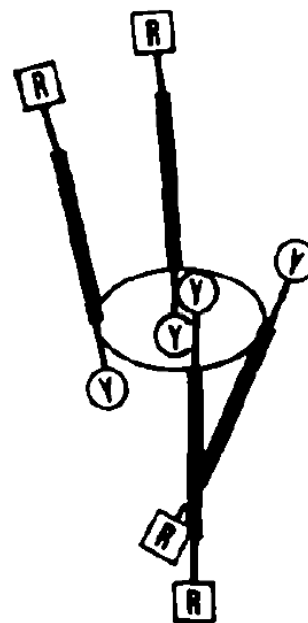
Calixarenes, which are [1_n]metacyclophanes comprising phenolic and methylene units,¹ are conformationally flexible compounds. The smallest of the known calixarenes are the cyclic tetramers, designated as calix[4]arenes (1), for which four "up-down" conformations can be specified, viz cone (all "up"), 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 ¹H NMR measurements of several calix[4]arenes²⁻⁴ 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-



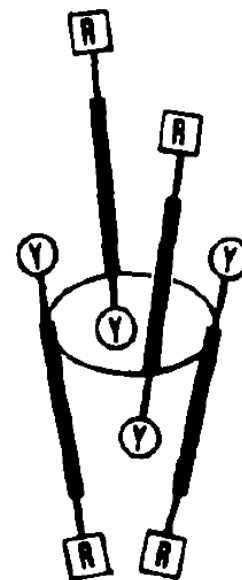
CONE



PARTIAL CONE

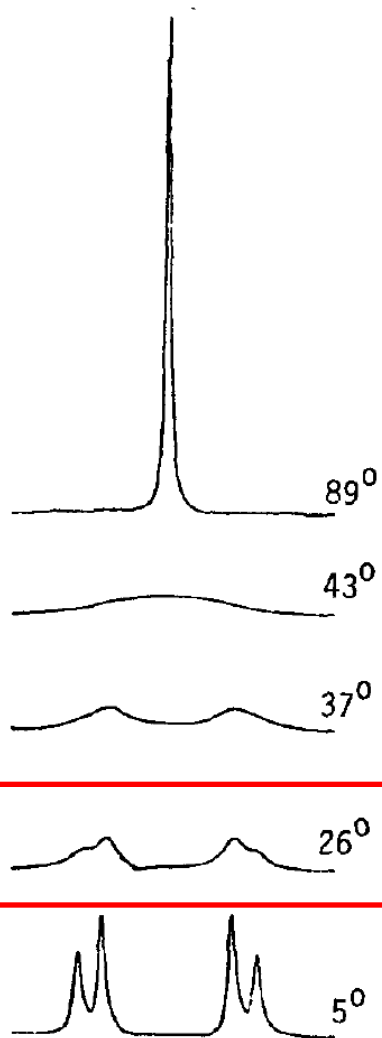


1,2 ALTERNATE

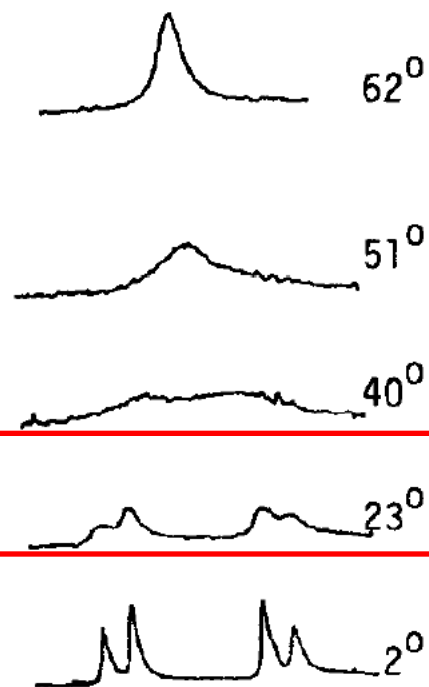


1,3 ALTERNATE

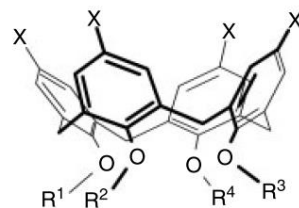
Fig. 1. Conformations of the calix[4]arenes.



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



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



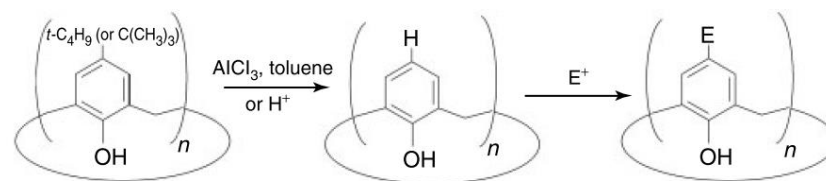
2a: R^1 - R^4 = alkyl

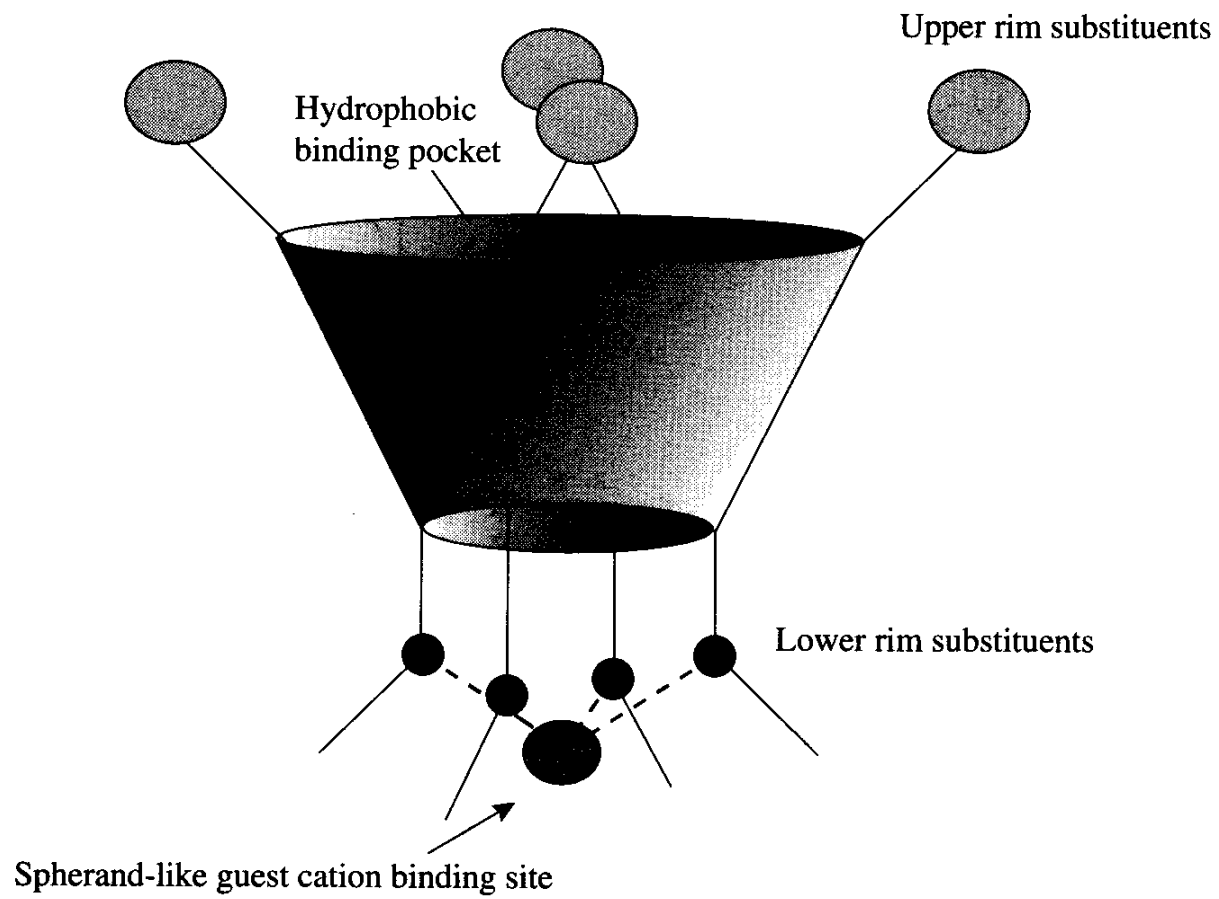
2b: R^1 , R^2 = alkyl, R^3 , R^4 = OH

2c: R^1 , R^3 = alkyl, R^2 , R^4 = OH

2d: R^1 = alkyl, R^2 - R^4 = OH

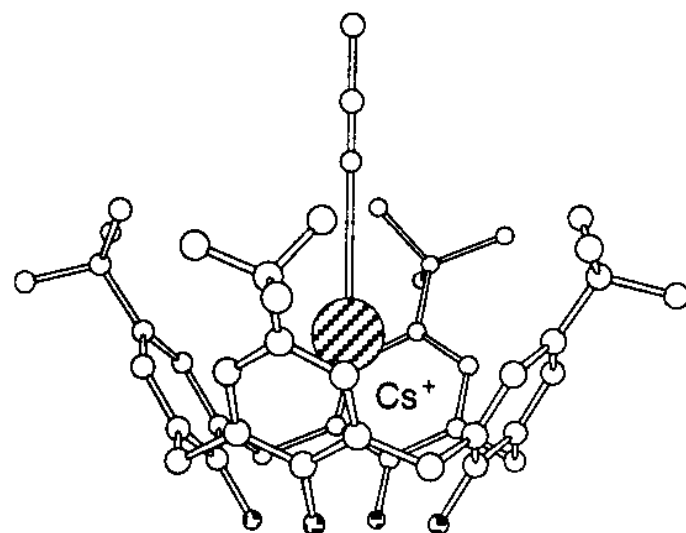
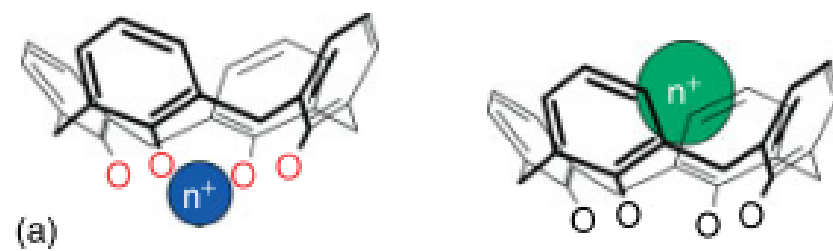
2e: R^1 - R^3 = alkyl, R^4 = OH

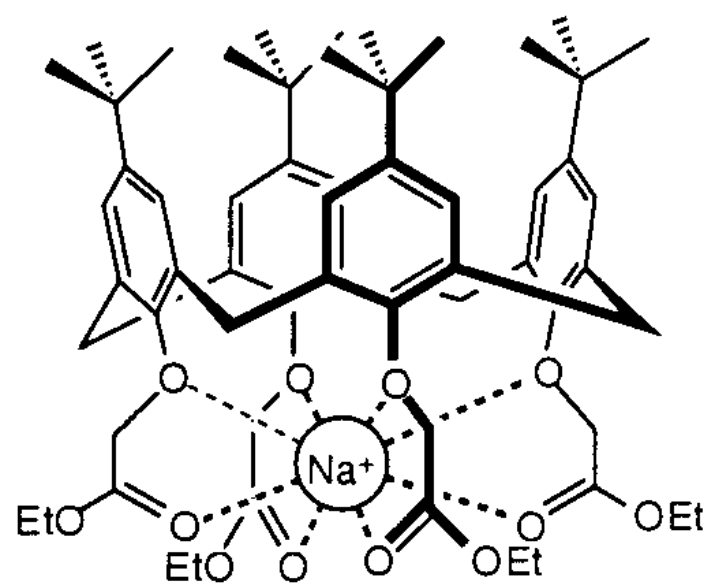
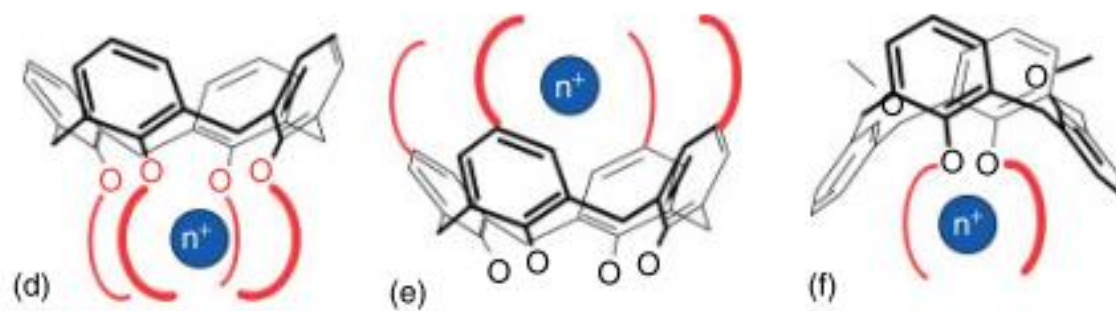


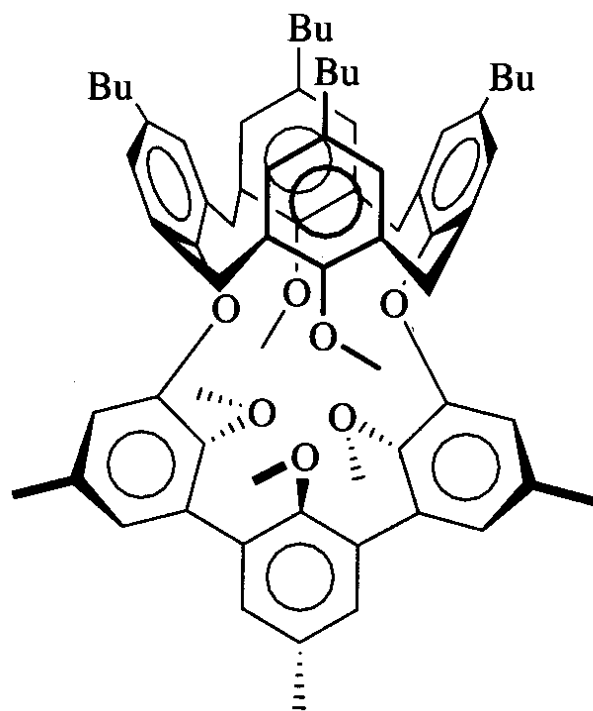


sons. Selective lower-rim (i.e., hydroxy) modification is increasingly important in modifying calixarene function,⁴ and this usually involves initial deprotonation; however, much current design is empirical. Comprehensive pK_a data would allow improved rationalization of modification methodology. In calixarene host–guest interactions,⁵ many guests are potential bases toward the calixarene; pK_a data would allow better assessment of the extent of ionic (e.g., ion-pair) vs dipolar (e.g., hydrogen-bonded) complexation. Calixarenes are increasingly being used as selective hosts for neutral and cationic guests, and the strength of binding is dependent on the protonation of the calixarene;⁶ reliable pK_a data will allow better design of such systems. Calixarenes show a complex and varied conformational chemistry;⁷ examination of pK_a data can provide information about conformational effects. Calixarene salts have been proposed as novel surfactants, and

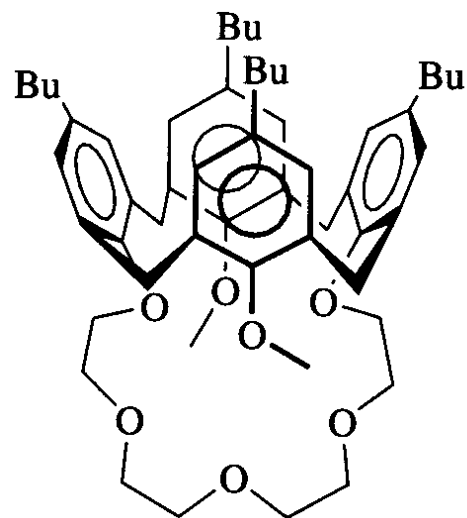
In conclusion, the recently established consistent scale of amine basicity in MeCN has been put to use to determine all accessible pK_a values for calix[4]arene, calix[6]arene, and calix[8]arene in MeCN. For mono-deprotonation, the dominant factor in calixarene acidity is the anion's ability to form internal hydrogen bonds that are not only numerous but also strong. For di-deprotonation, the ability to spatially separate the anions becomes important.



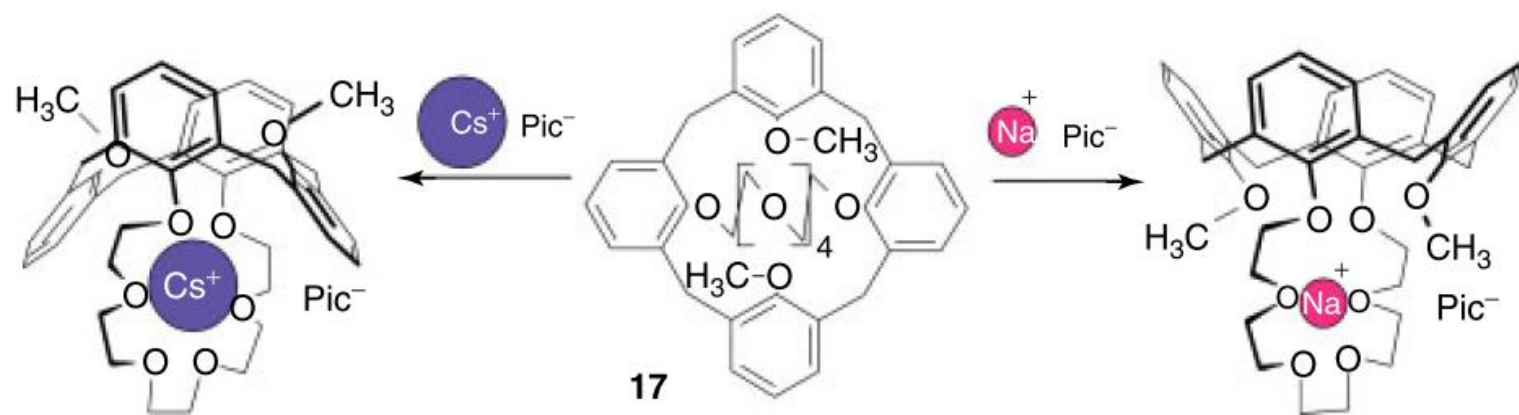




Calix-sferando



Calix-crown



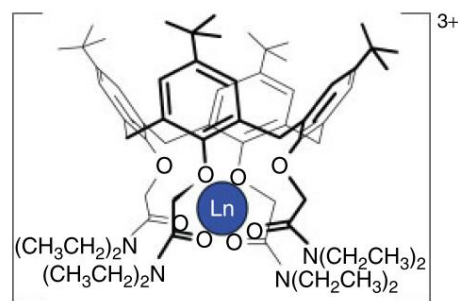
Macrocyclic Polyethers and Their Complexes^[*]**

By C. J. Pedersen and H. K. Frensdorff^[*]

Angew. Chem. internat. Edit. / Vol. 11 (1972) / No. 1

Discusso direttamente dal pdf dell'articolo

Ln^{3+} recognition
(treatment of radioactive waste/extraction- high
distribution coefficient even from very acidic water
solutions)



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*

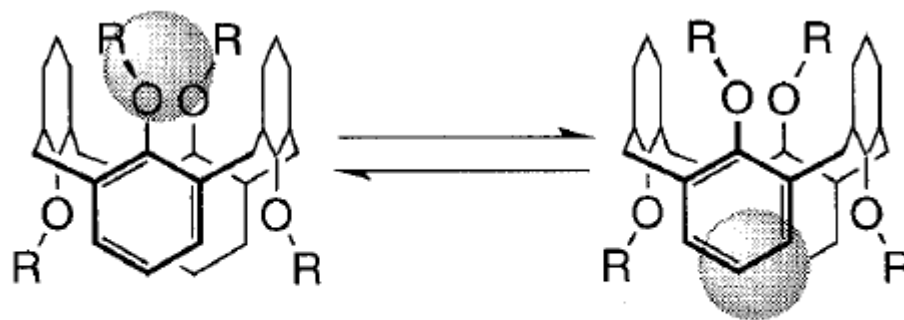
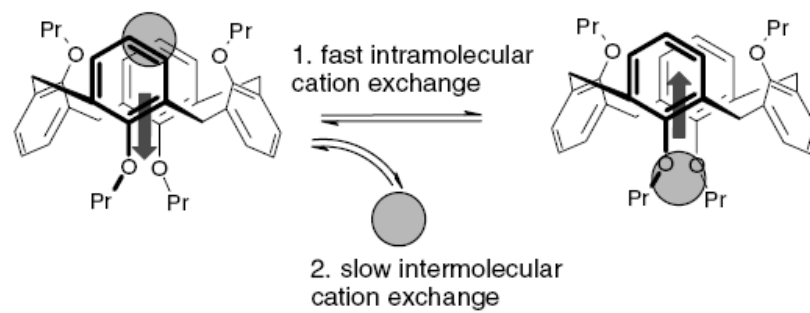


Figure 1. Schematic representation of the metal-tunneling through a π -basic tube of 1,3-alternate calix[4]arene.

Cation tunnelling



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*

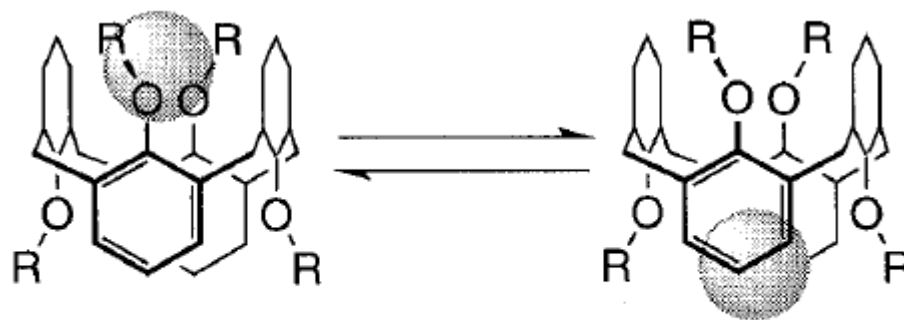
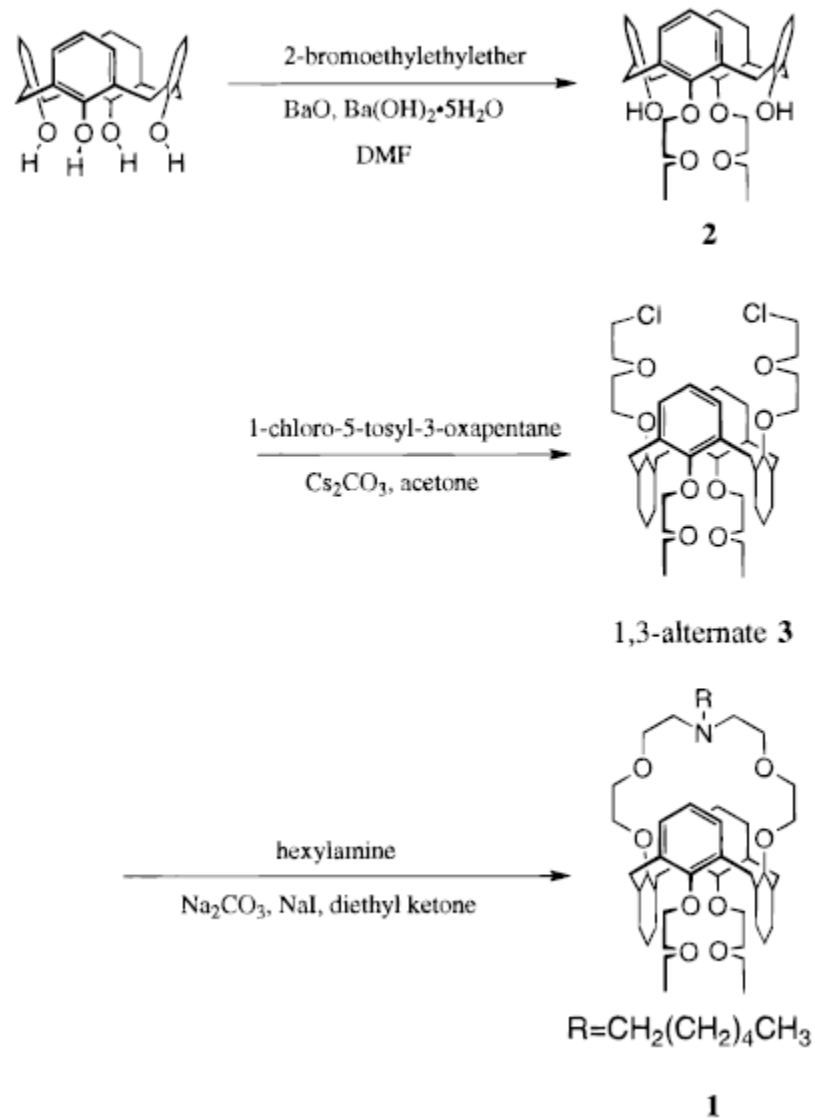


Figure 1. Schematic representation of the metal-tunneling through a π -basic tube of 1,3-alternate calix[4]arene.

Scheme 1



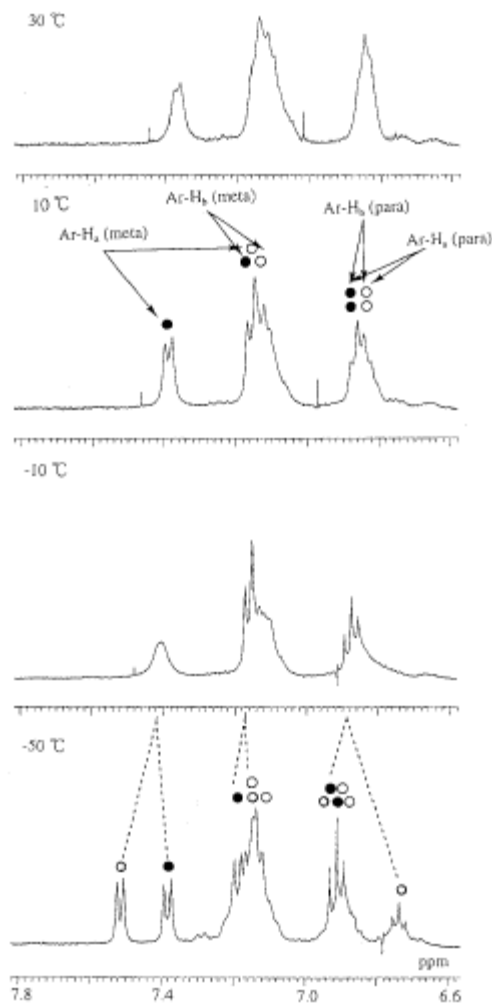


Figure 2. Partial ^1H NMR spectra of a 1-Ag^+ system: 400 MHz, $\text{CD}_2\text{Cl}_2\text{:CD}_3\text{OD} = 4\text{:}1$ v/v, $[1] = 5.00$ mM, $[\text{CF}_3\text{SO}_3\text{Ag}] = 2.50$ mM. Ar-H_a and Ar-H_b denote the aromatic protons at crown-capped side and those at bis(ethoxyethoxy) side, respectively. Open and solid (or shaded) circles denote the signals for free **1** and those for the 1-Ag^+ complex, respectively.

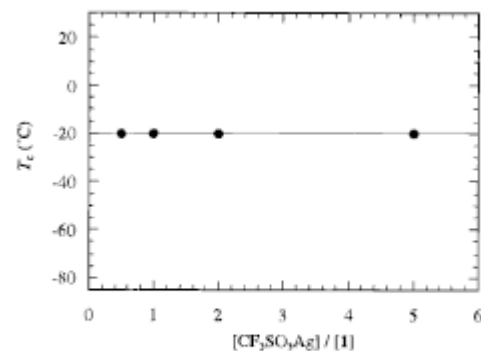


Figure 3. Concentration dependence of $T_{c(\text{free})}$: $[1] = 5.00$ mM, $\text{CD}_2\text{Cl}_2\text{:CD}_3\text{OD} = 4\text{:}1$ v/v. The concentration of **1** was maintained constant while the concentration of $\text{CF}_3\text{SO}_3\text{Ag}$ was varied.

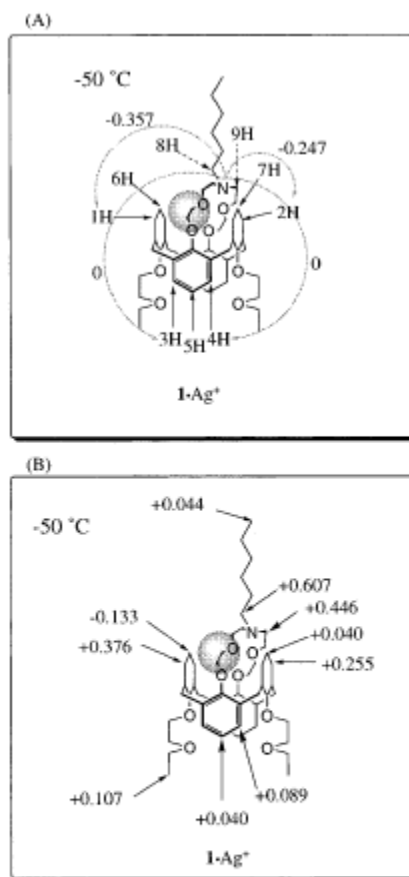


Figure 4. (A) Assignment of chemical shifts for selected protons in the 1-Ag⁺ complex by 2D COSY and NOE signal intensities with respect to 8-H and 9-H: -50 °C, CD₂Cl₂:CD₃OD = 4:1 v/v, [1] = 5.00 mM, [CF₃SO₃Ag] = 10.0 mM. (B) Changes in the ¹H NMR chemical shift of 1 induced by added Ag⁺: the measurement conditions are the same as A. A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (-) denotes a shift to higher magnetic field.



Figure 5. Schematic representation of a rope-jumping motion in the 1-Ag⁺ complex.

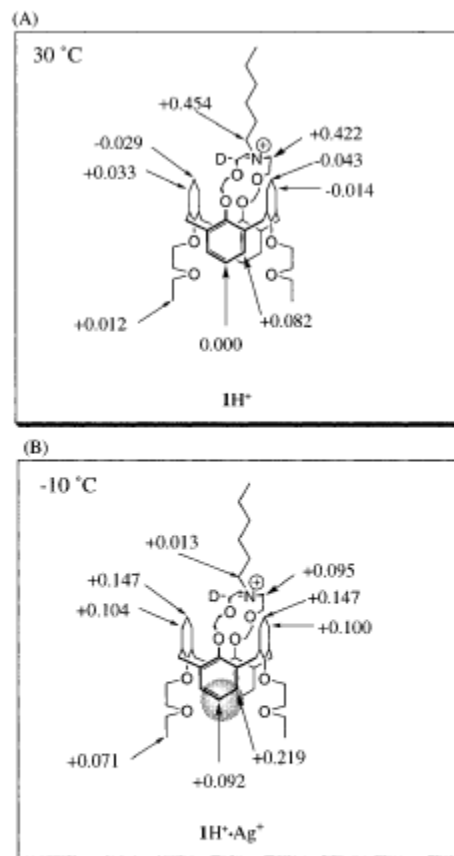


Figure 6. (A) Assignment of chemical shifts for selected protons in 1H⁺ and changes from those in 1:30 °C, [1] = 5.00 mM, [TFA-*d*] = 600 mM, CD₂Cl₂:CD₃OD = 4:1 v/v. (B) Changes in the ¹H NMR chemical shift of 1H⁺ induced by added Ag⁺ ([CF₃SO₃Ag] = 10.0 mM): the measurement conditions are the same as A. A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (−) denotes a shift to higher magnetic field.

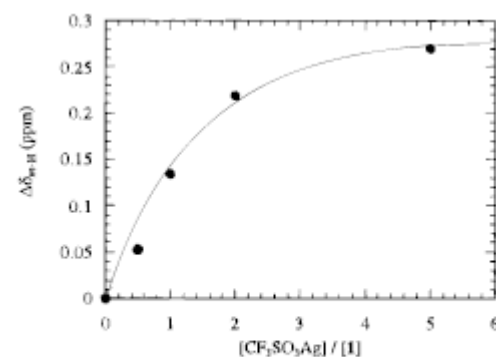


Figure 7. Chemical shift change in δ_{m-H} of 1H⁺ induced by added CF₃SO₃Ag: 30 °C, [1] = 5.00 mM, [TFA-*d*] = 600 mM, CD₂Cl₂:CD₃OD = 4:1 v/v.

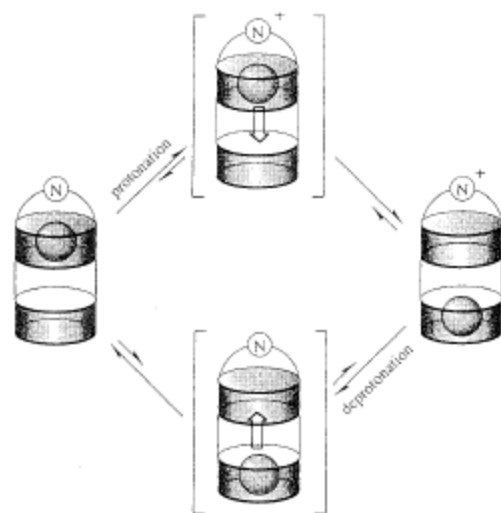
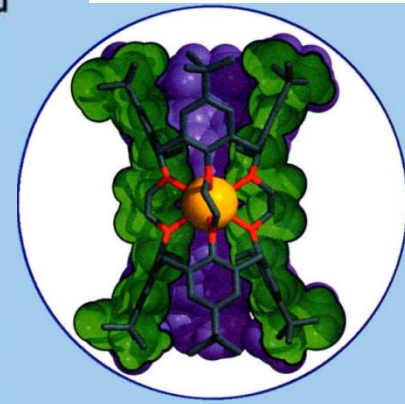
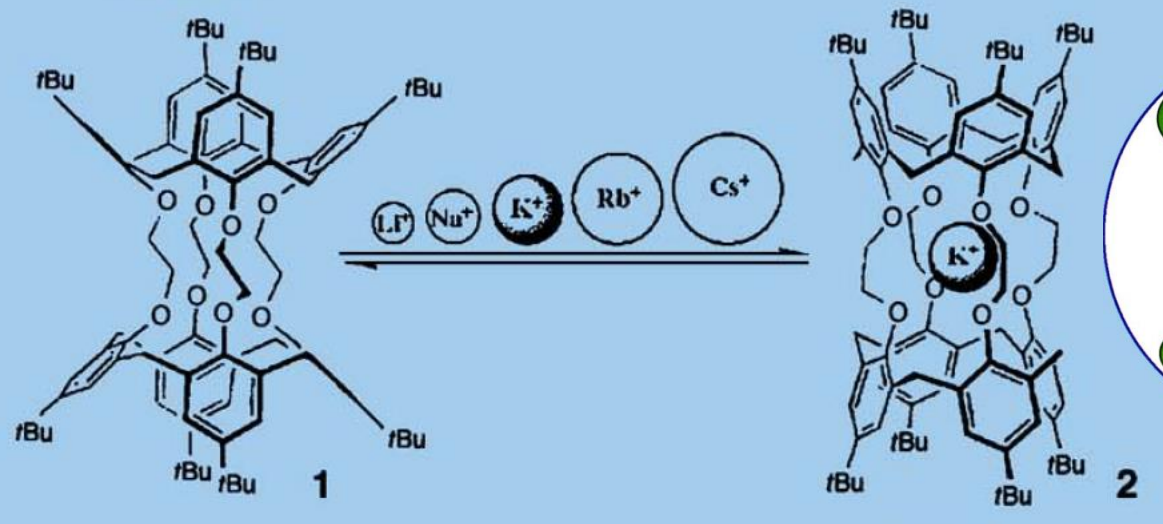
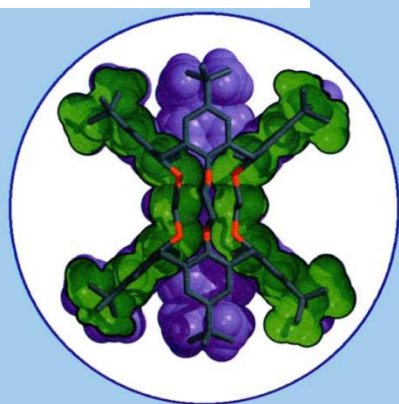


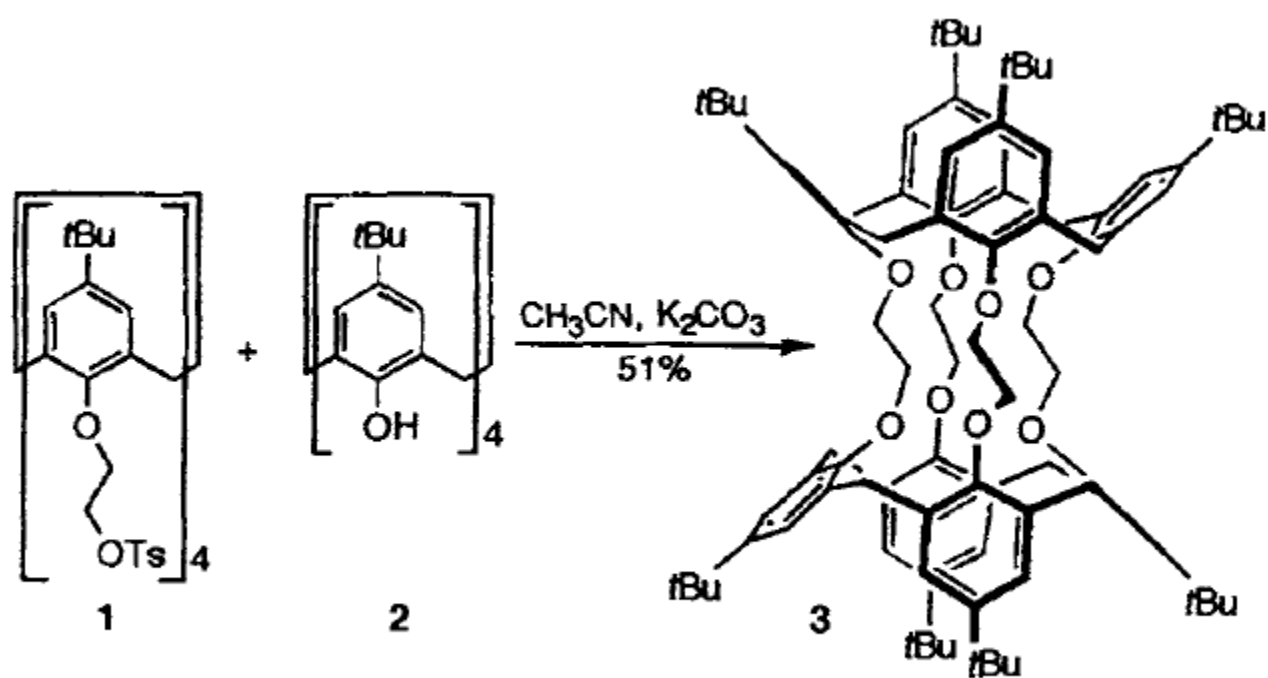
Figure 8. Schematic representation of a reversible metal pumping in a microscopic "molecular syringe" **1** designed from 1,3-alternate calix[4]arene.

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

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

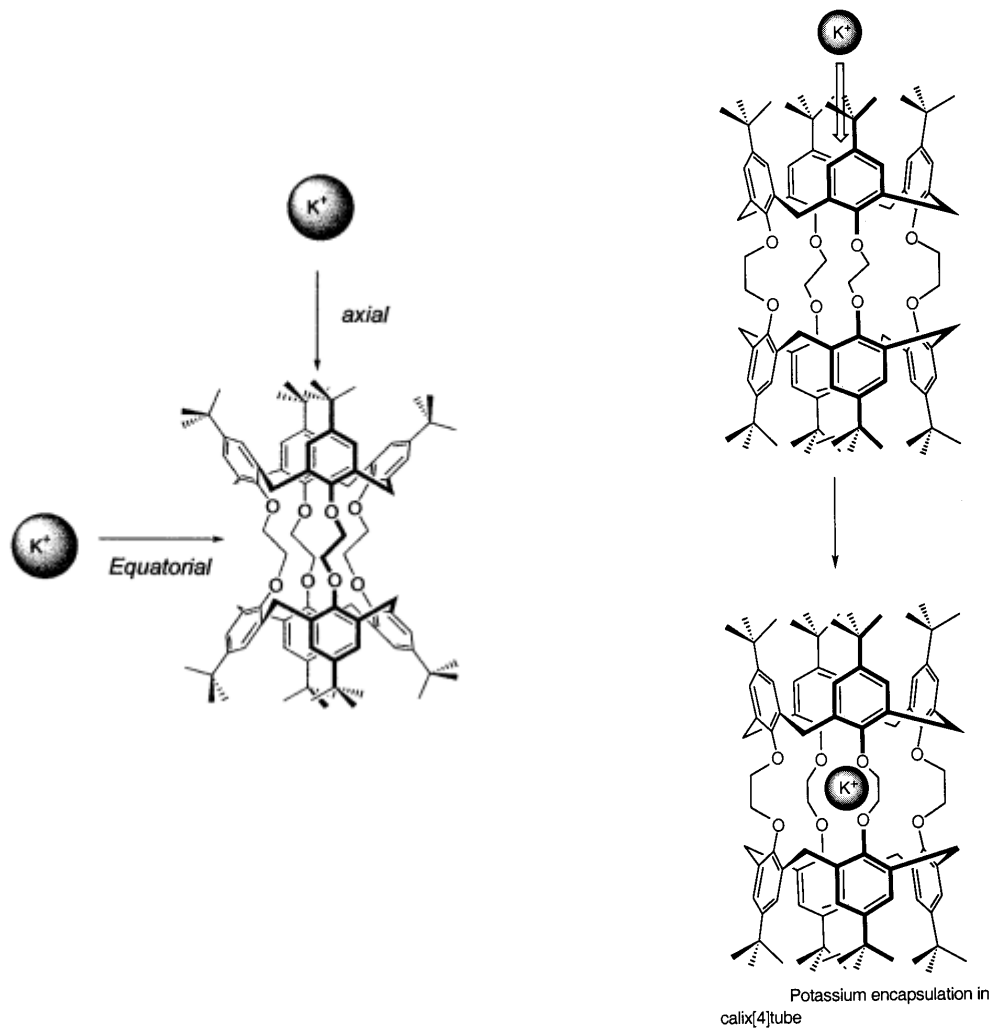
Angew. Chem. Int. Ed. Engl. **1997**, *36*, 1840





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

Calix-tubes



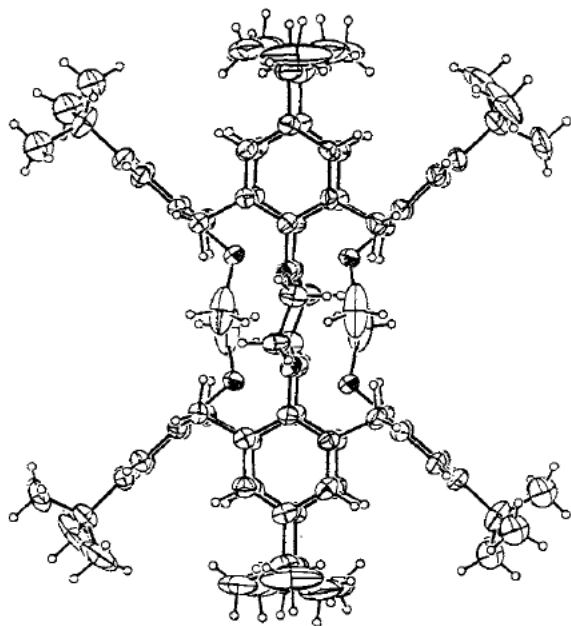


Figure 1. Crystal structure of the centrosymmetric calix[4]tube **3** in $3 \cdot 2.5 \text{ C}_6\text{H}_6$, with ellipsoids at 30% probability. Hydrogen atoms are included with small arbitrary radii. The benzene solvent molecules are not shown.

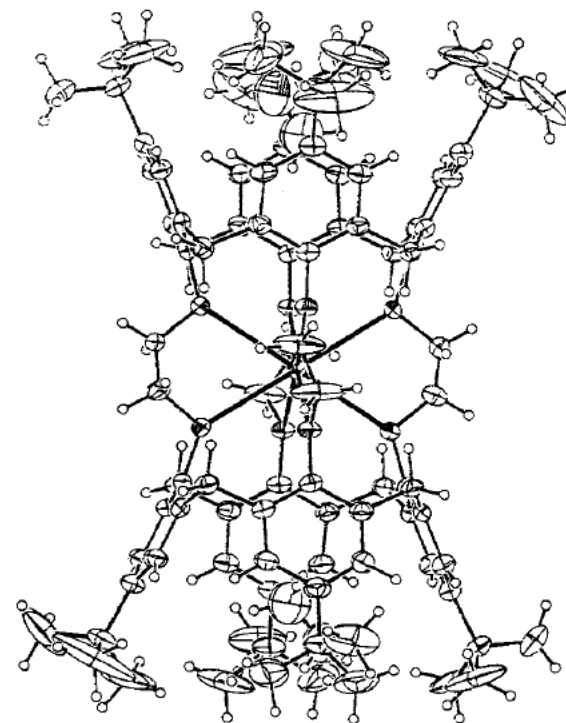


Figure 4. Structure of the K^+ complex **4** of the calix[4]tube **3** in crystals of $4 \cdot \text{I} \cdot 3 \text{ CHCl}_3 \cdot 4 \text{ CH}_3\text{OH} \cdot \text{H}_2\text{O}$. A potassium ion is located in the center of **3**, and two methanol molecules in the cone cavities. Ellipsoids are drawn at 30% probability. Hydrogen atoms are included with small arbitrary radii. The chloroform and water solvent molecules are not shown.

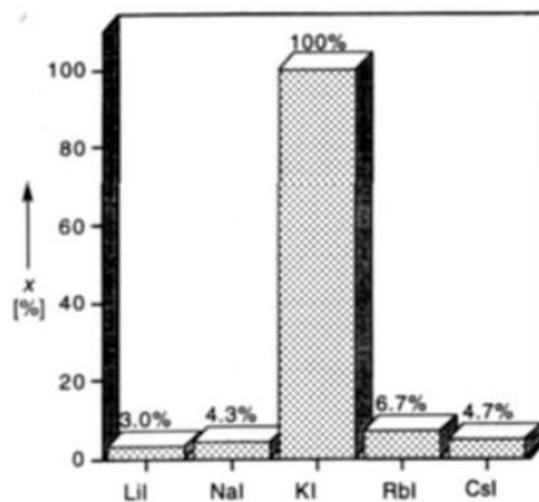


Figure 3. Uptake of alkali metal ions by **3** after treating its chloroform-methanol solution (4/1, $[3] = 1 \text{ mM}$) with 10 equivalents of alkali metal iodide. The complexation ratio x was determined by integration of the ^1H NMR spectra after the samples had been left to stand for 90 h. In the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

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"*.



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);

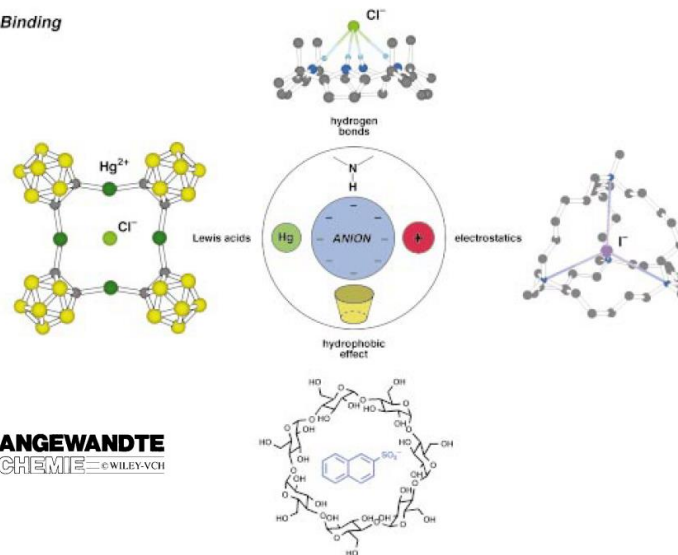
DOI: 10.1126/science.280.5360.69

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

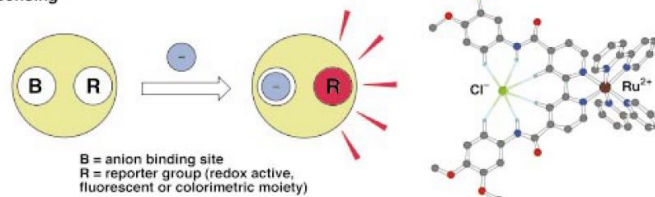
Paul D. Beer* and Philip A. Gale*

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

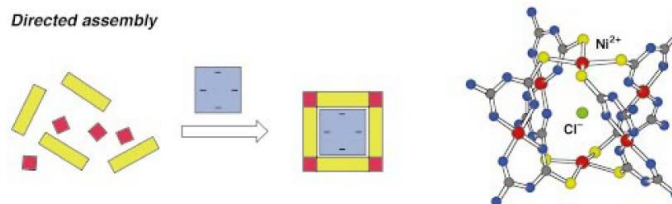
Binding



Sensing



Directed assembly



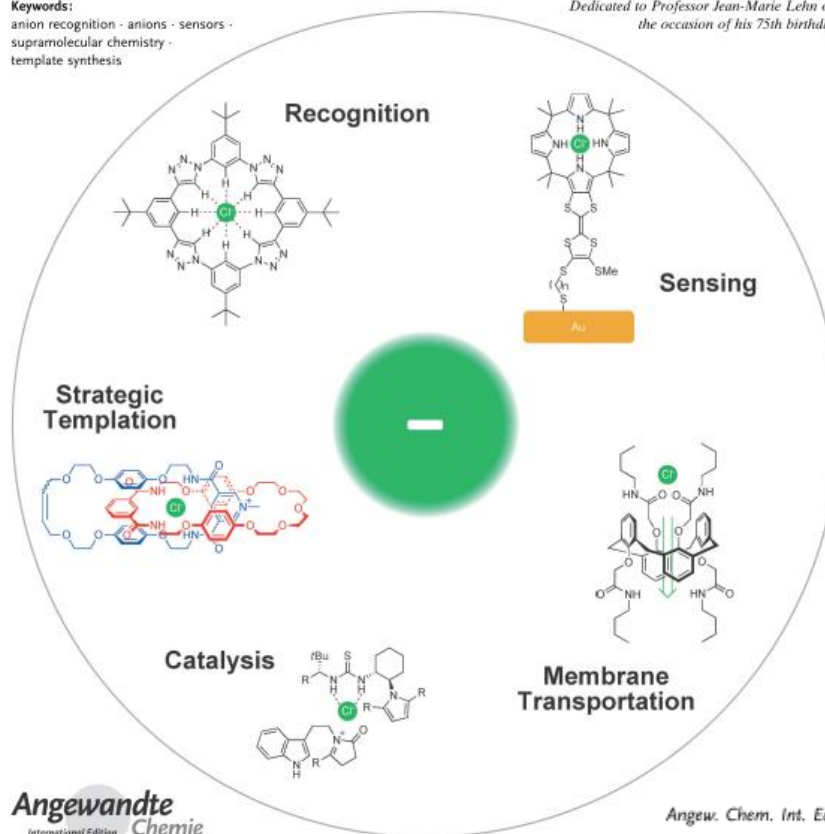
Advances in Anion Supramolecular Chemistry: From Recognition to Chemical Applications

Nicholas H. Evans* and Paul D. Beer*

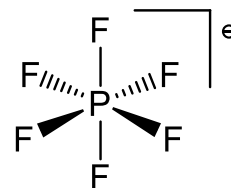
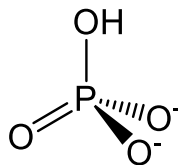
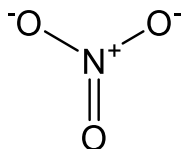
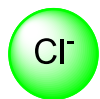
Keywords:

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

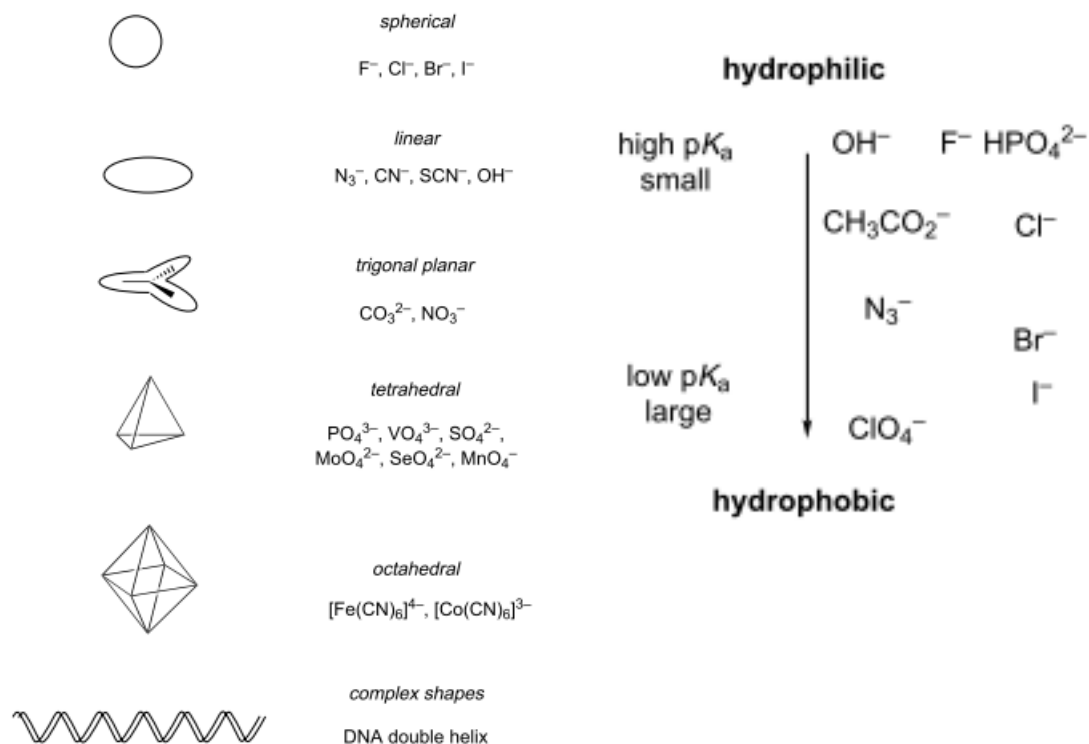
$$\Delta_r G^\circ_{\text{hydr}}(\text{F}^-) = -465 \text{ kJ.mol}^{-1}$$

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

- 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

Table 1. A comparison of the radii r of isoelectronic cations and anions in octahedral environments.^[7]

Cation	r [Å]	Anion	r [Å]
Na ⁺	1.16	F ⁻	1.19
K ⁺	1.52	Cl ⁻	1.67
Rb ⁺	1.66	Br ⁻	1.82
Cs ⁺	1.81	I ⁻	2.06



Host cationici

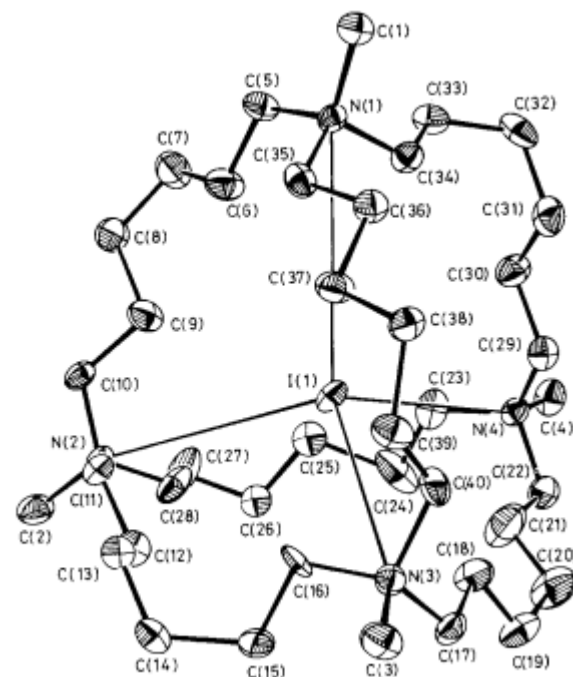
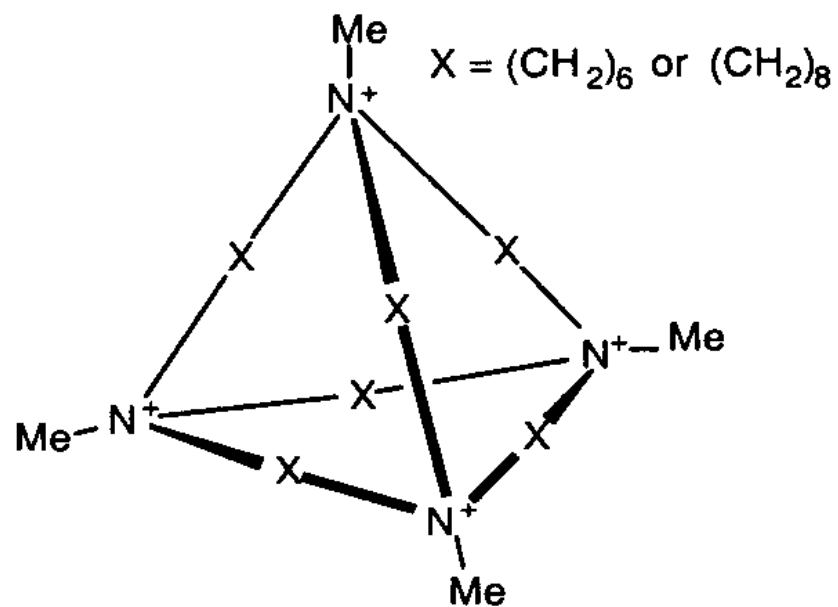
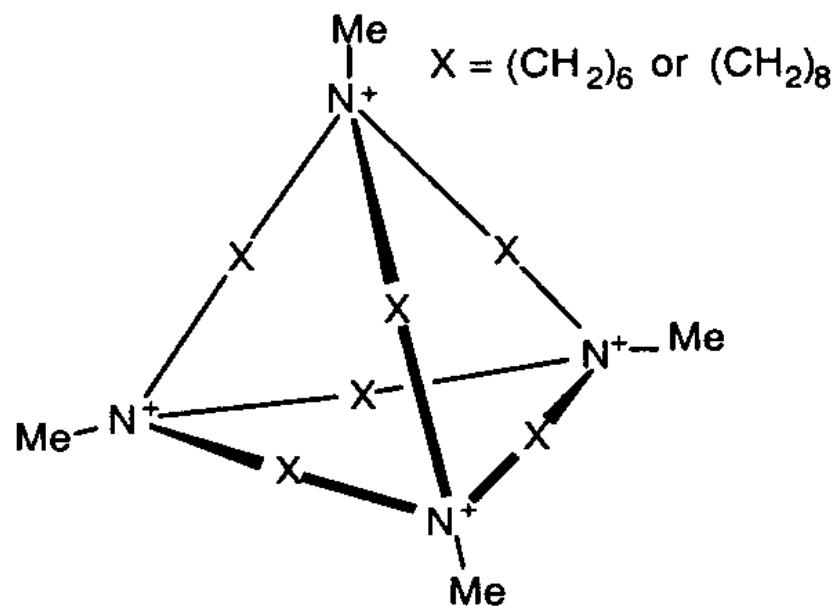


Figure 2. The X-ray crystal structure of the iodide complex of receptor **1**

Host cationici

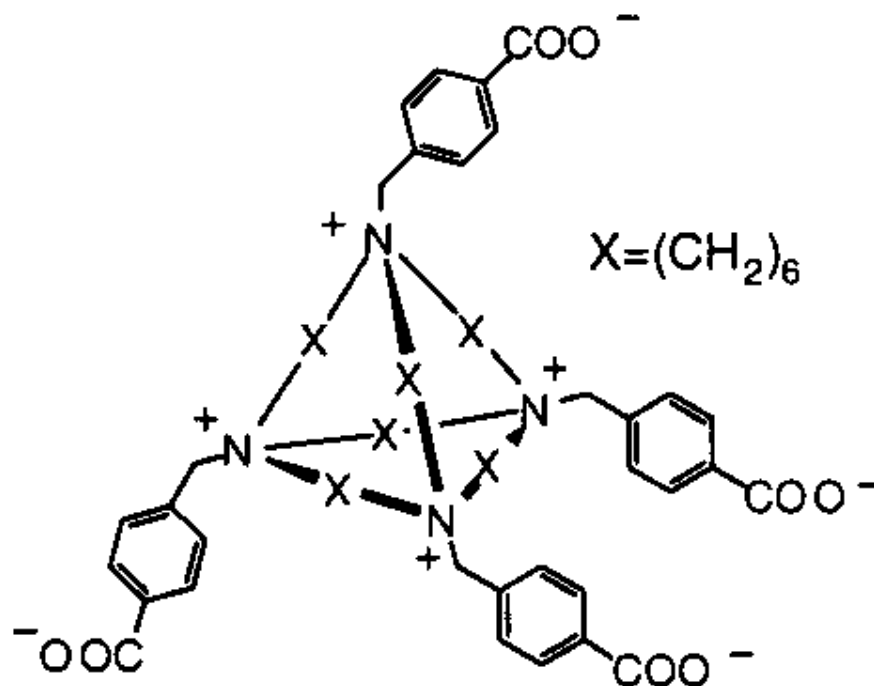


$K(\text{Br}^-) = 1020 \text{ (H}_2\text{O)}$

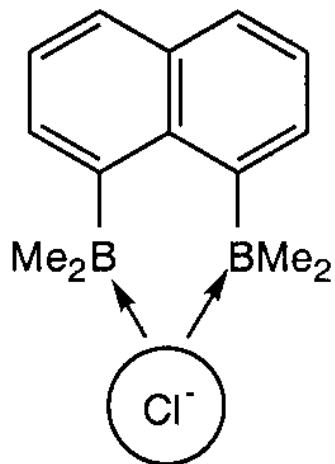
Selettività $\ll$

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

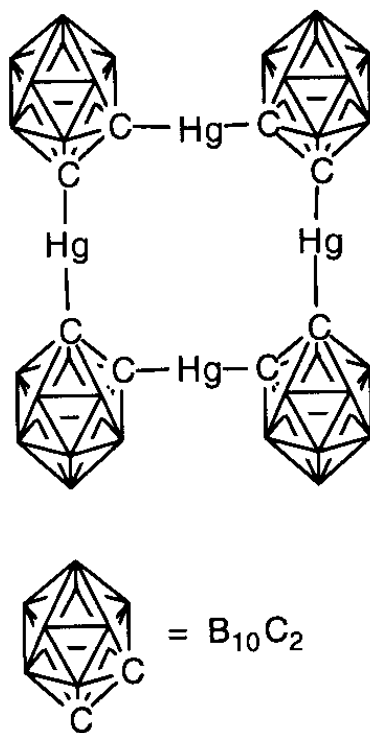
Host zwitter-ionici



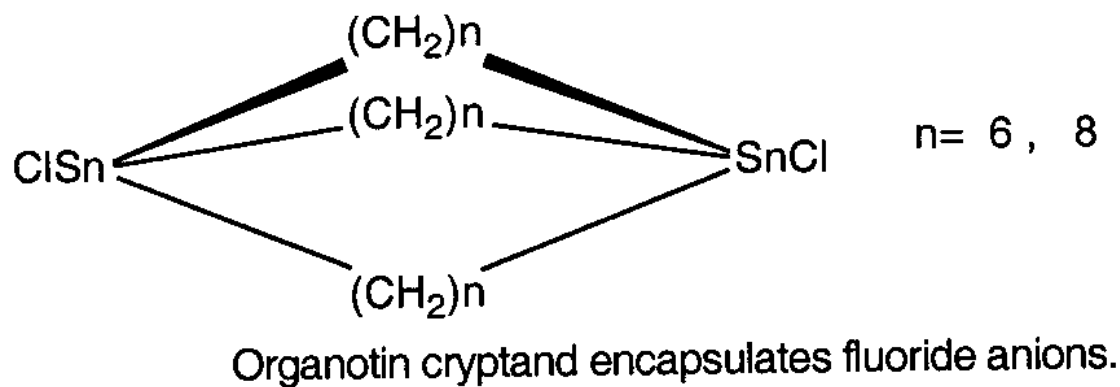
$K(\text{Br}^-) = 2150 \text{ (H}_2\text{O)}$



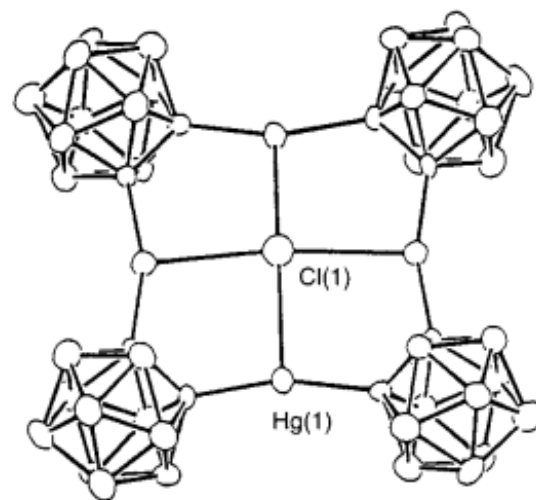
Organo-Boro



Organo-Hg(II)



Organo-Sn(IV)



Hawthorne

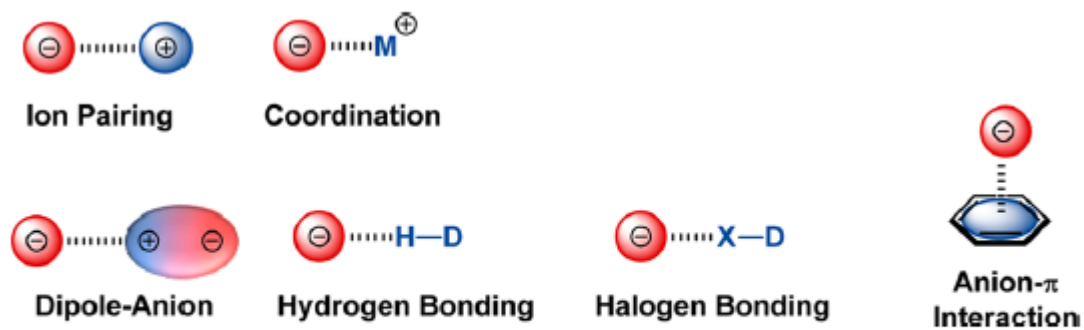
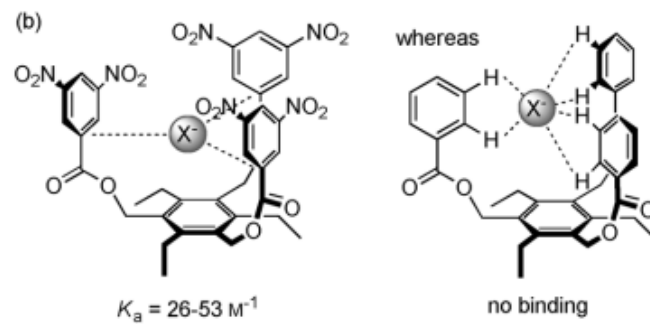
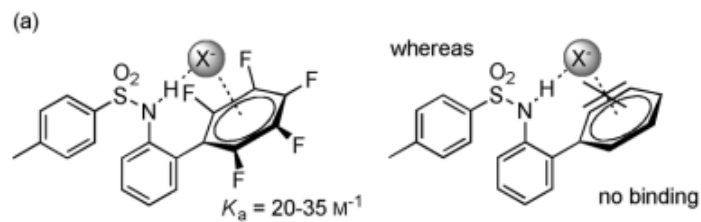
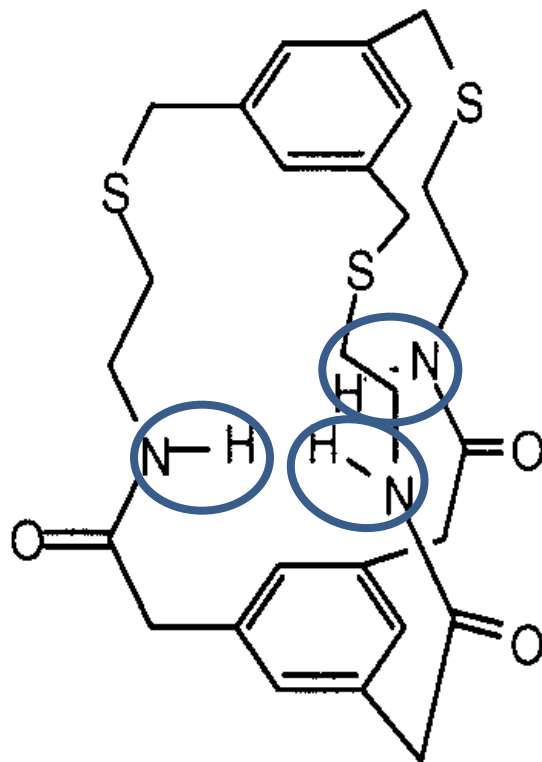
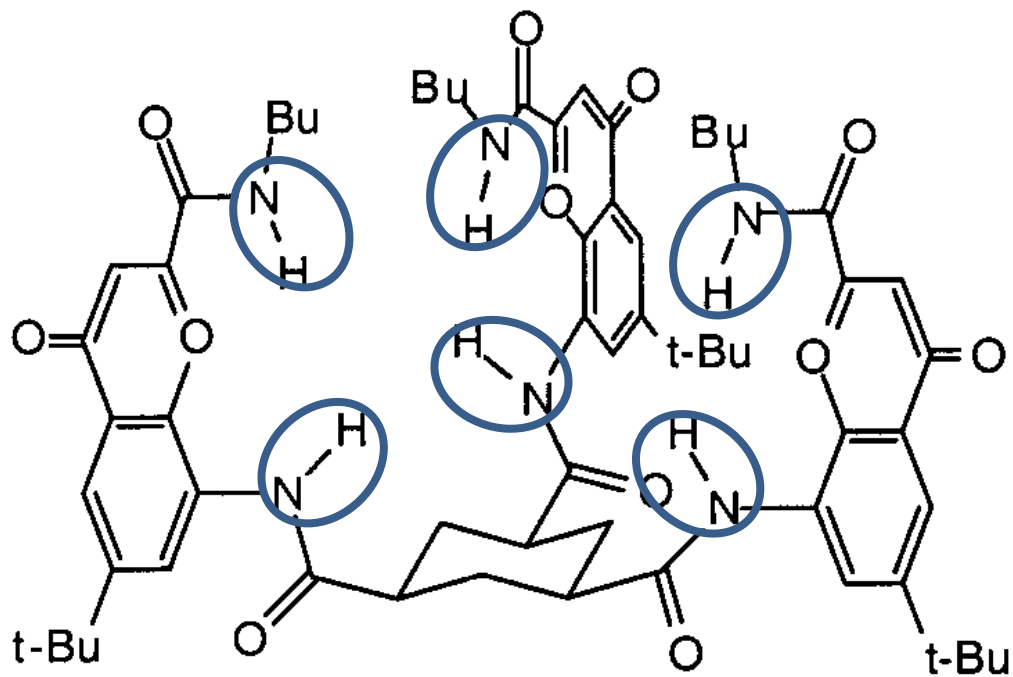
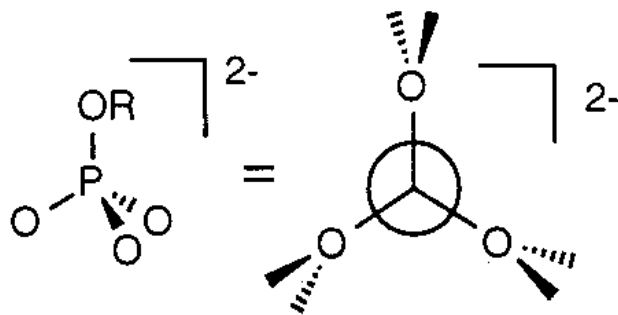


Figure 1. Representation of different interactions found in anion sensing and recognition.



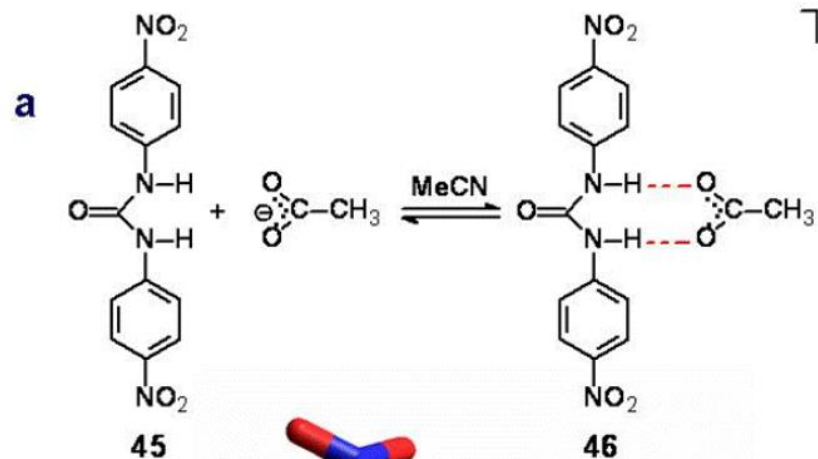
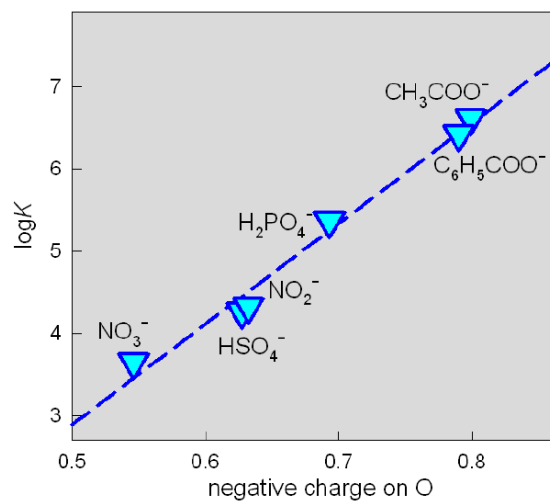
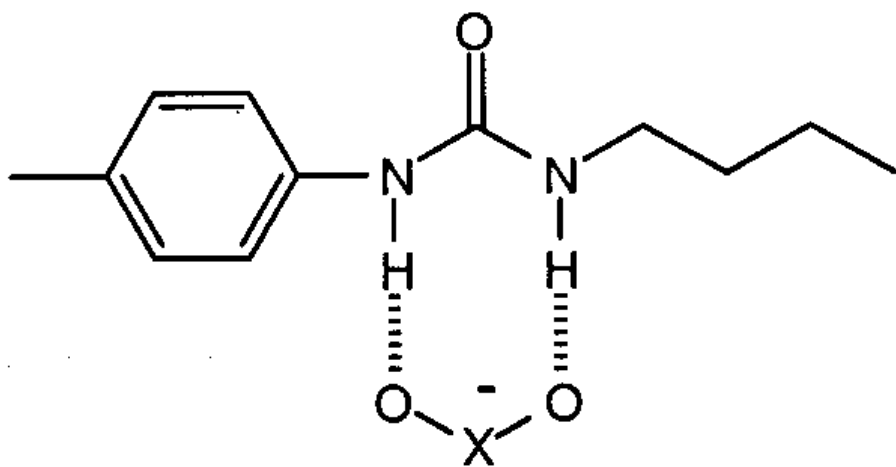


Hydrogen bonding receptor
for fluoride anions.

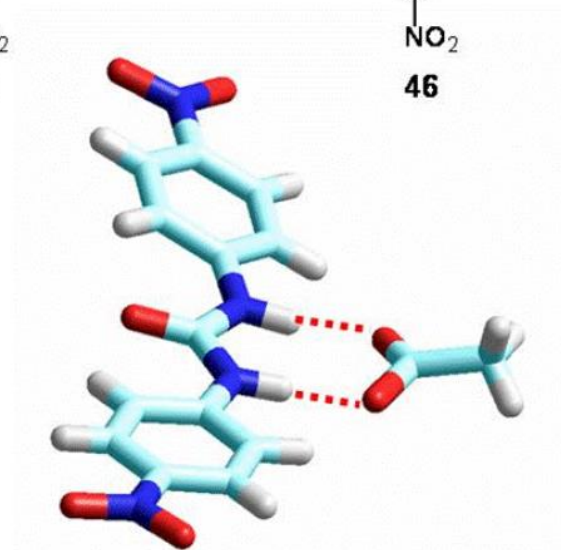


Trigonal receptors can bind phosphate anions strongly in competitive solvents.

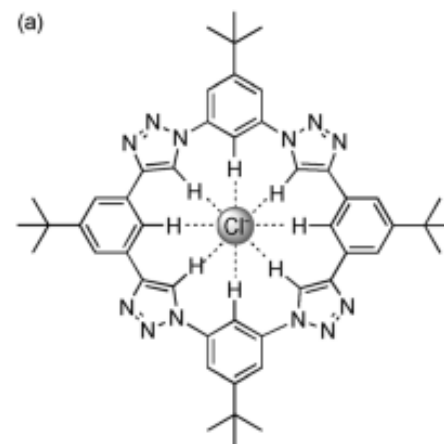
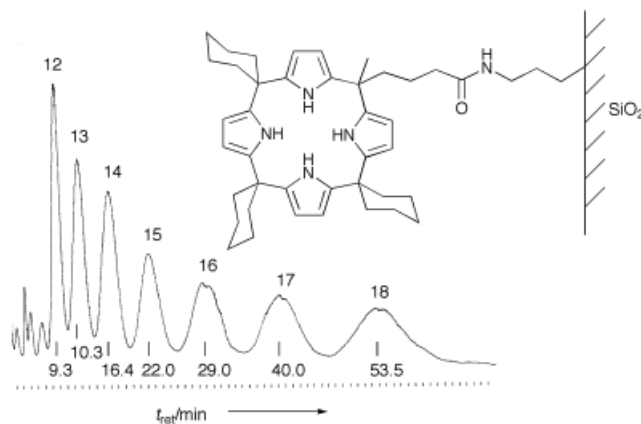
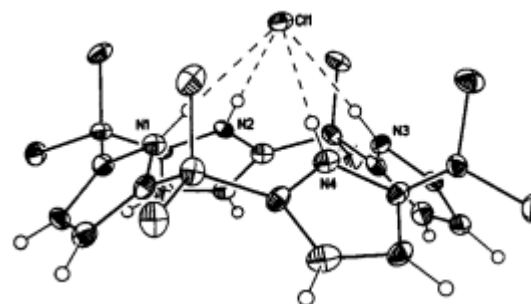
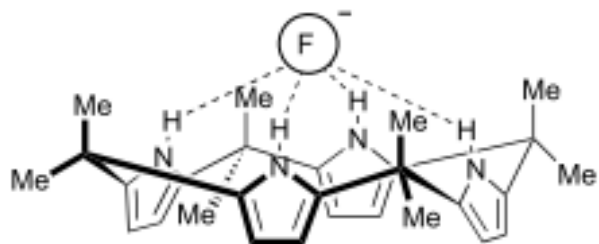
Raposo



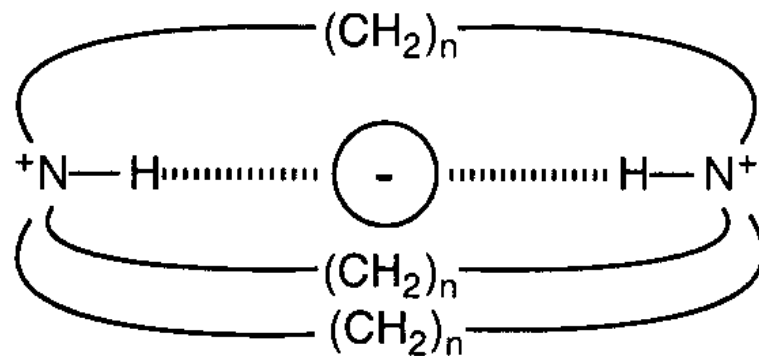
b



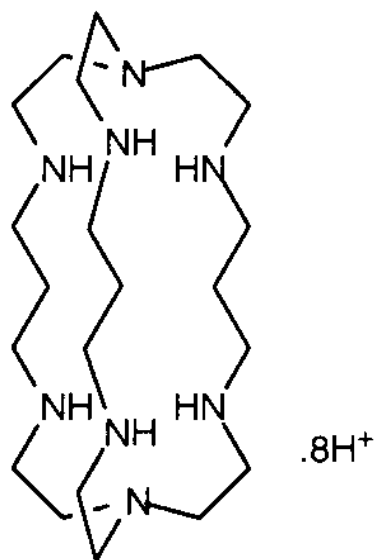
Fabrizzi



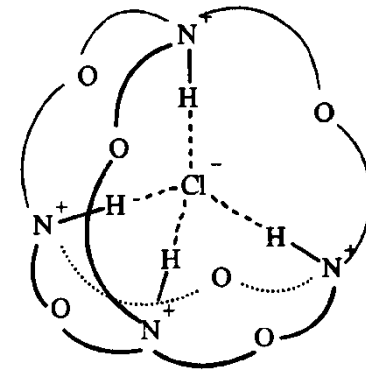
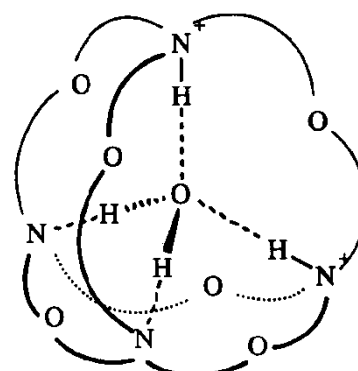
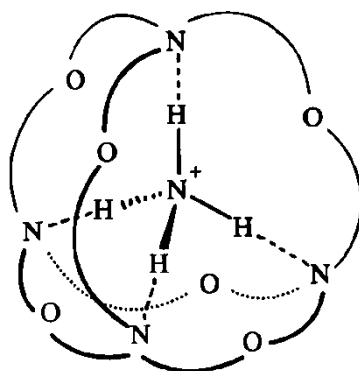
HPLC Separation of oligonucleotides of different length



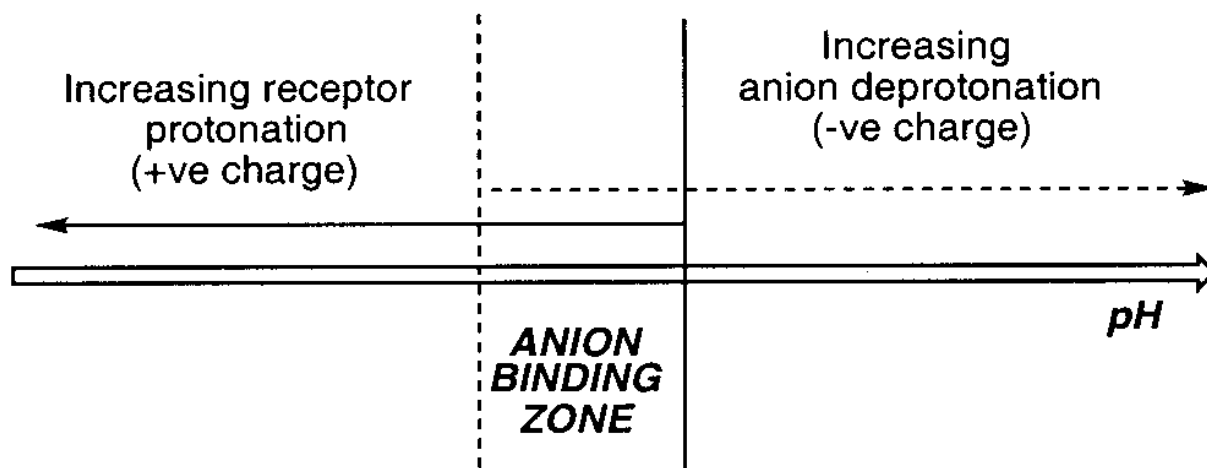
poliazamacrocicli



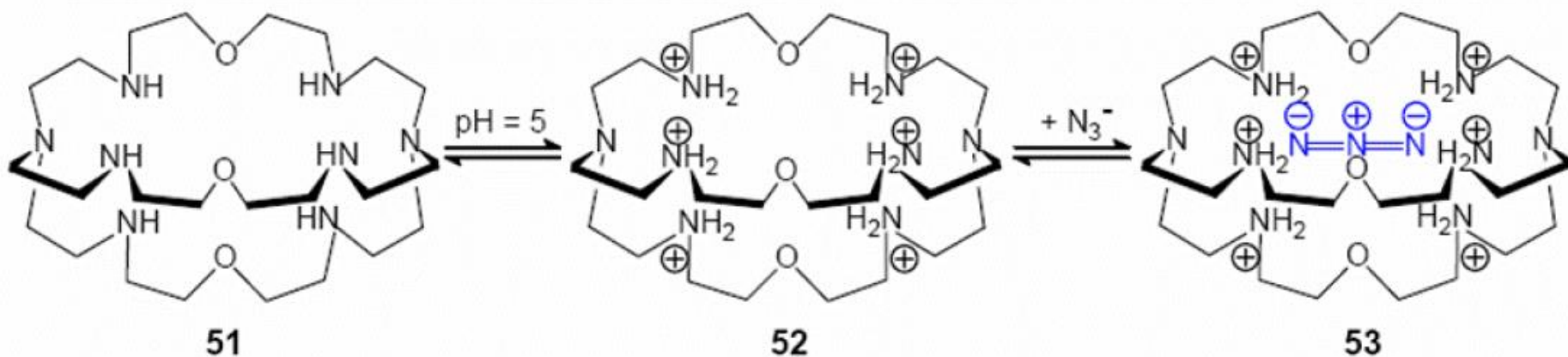
Receptors for anions.

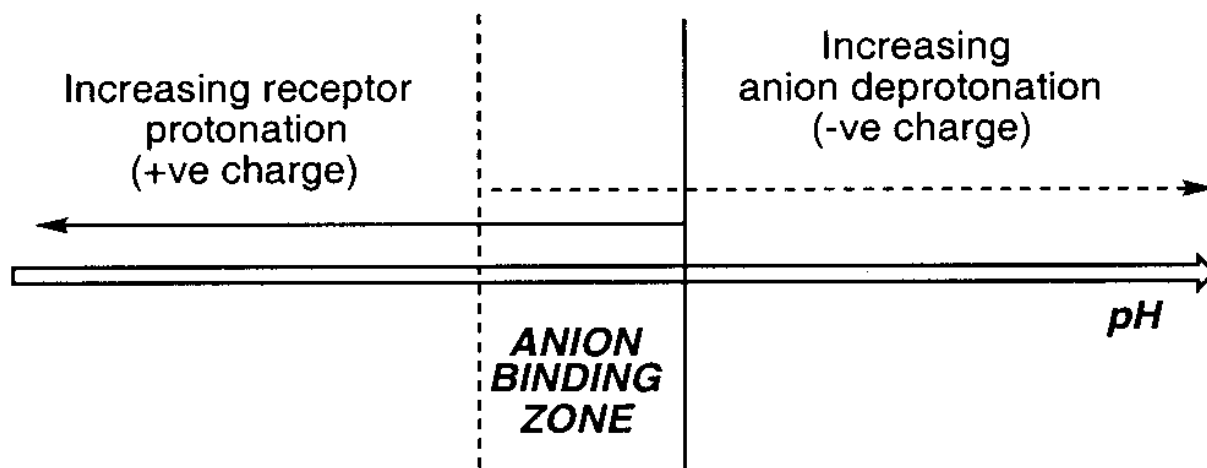


Lehn

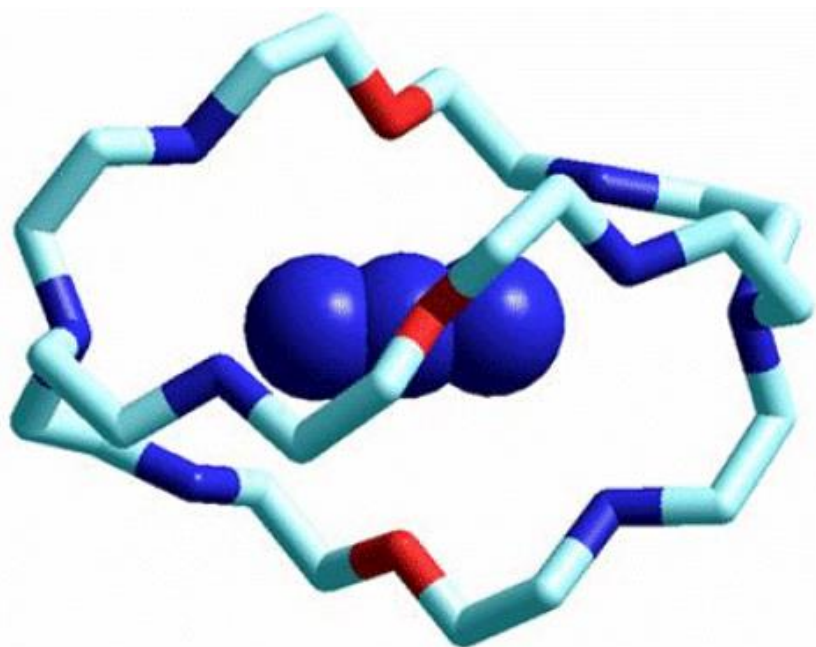


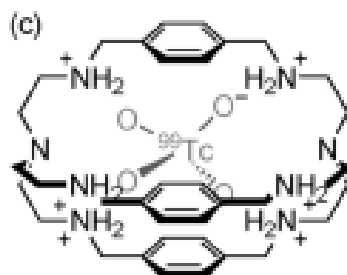
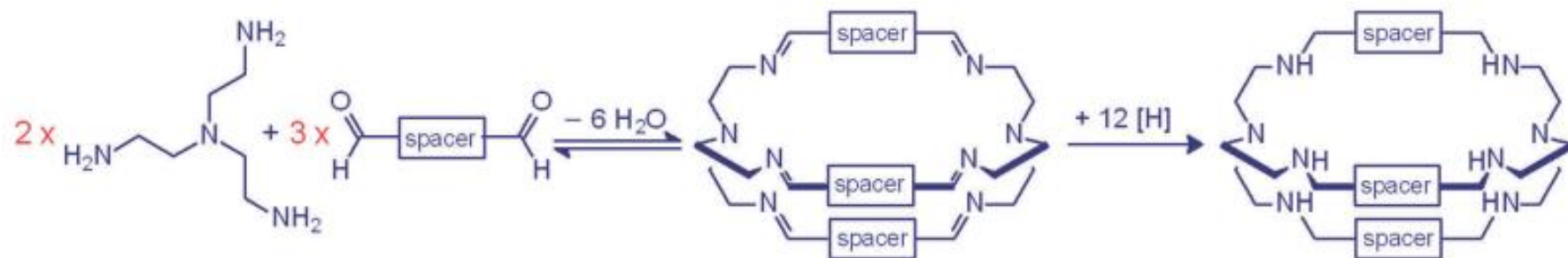
Balance between host protonation and guest deprotonation.

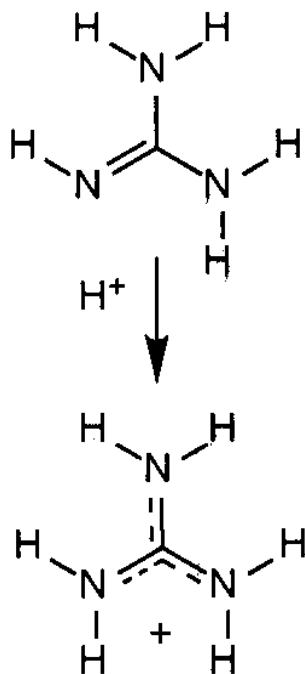




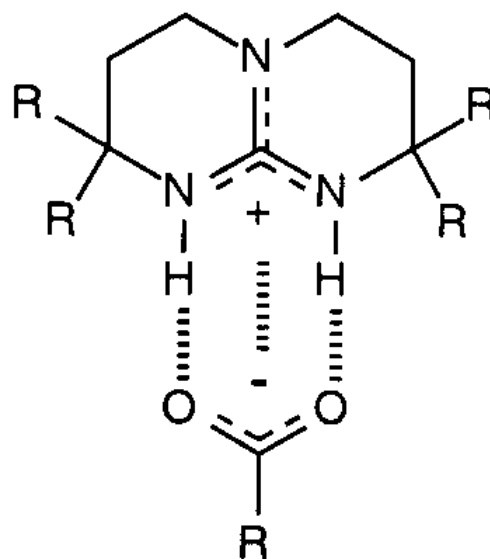
Balance between host protonation and guest deprotonation.



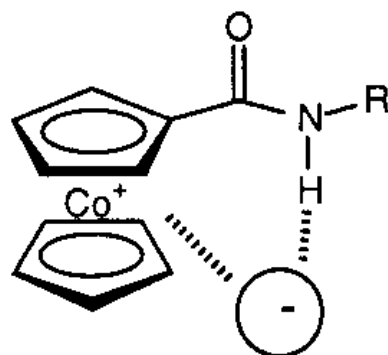




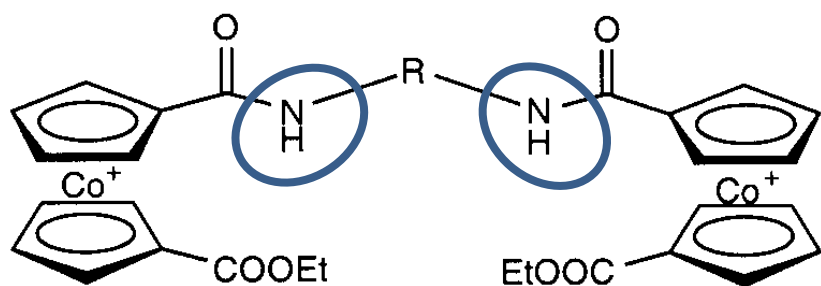
$pK_a = 13.6$



Bicyclic guanidinium is preorganized and complementary for binding bidentate anions.



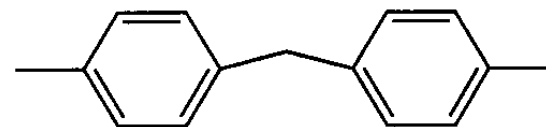
Amide functionalized
cobaltocenium binds anions.



—R— =



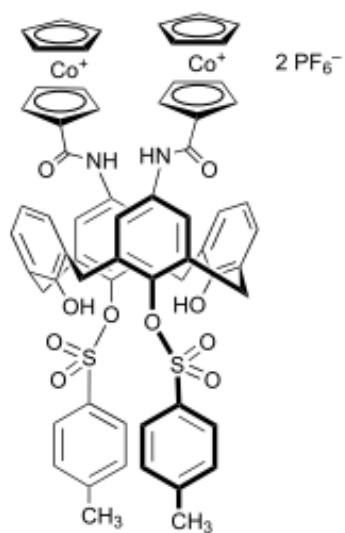
Binds 1 Cl⁻



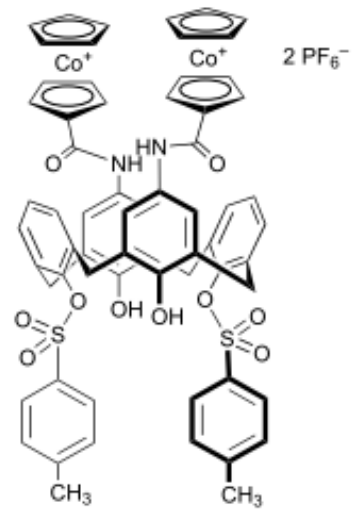
Binds 2 Cl⁻

Cobaltocenium based anion receptors have easily tunable binding sites.

Beer



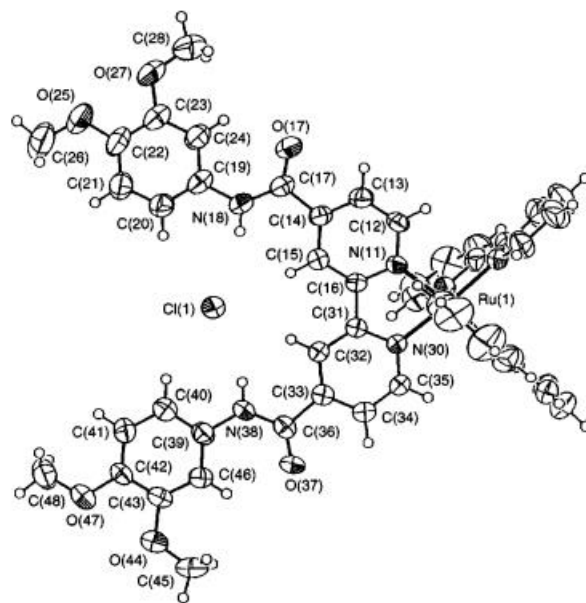
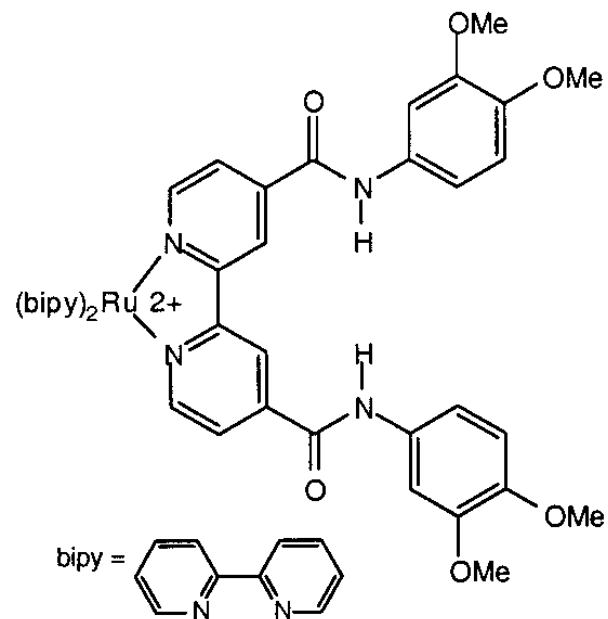
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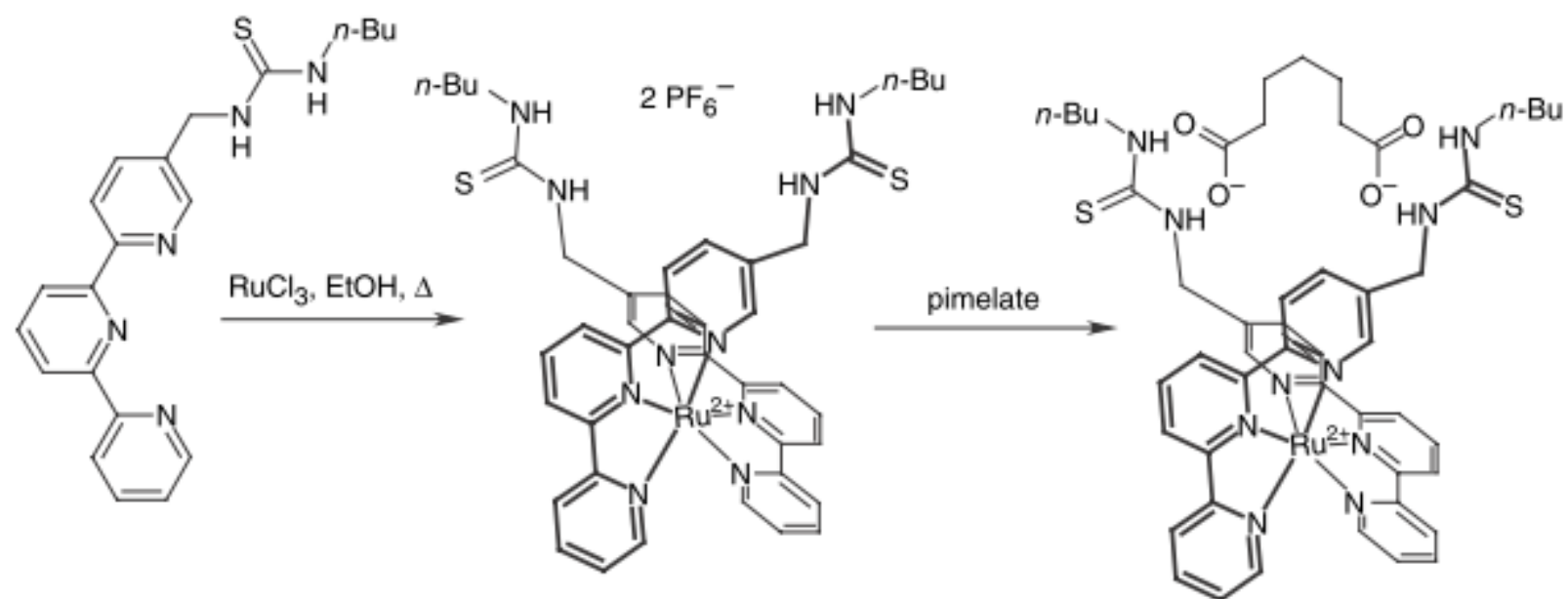
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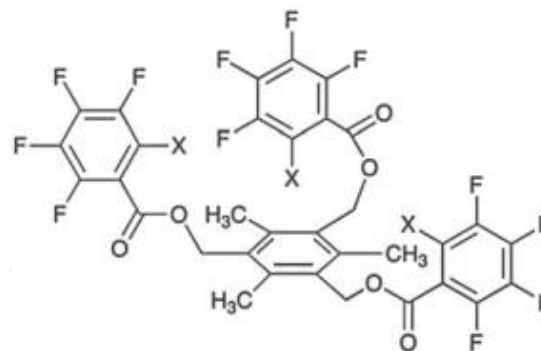
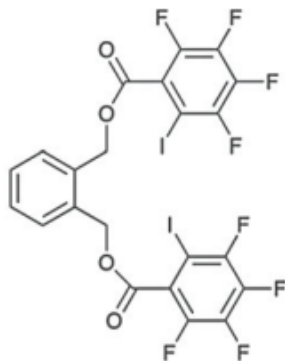
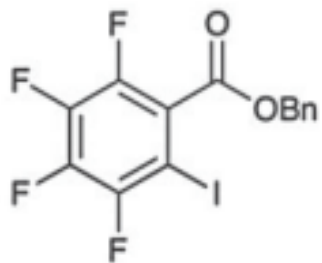
50: $\text{CH}_3\text{CO}_2^- \gg \text{H}_2\text{PO}_4^-$

51: $\text{H}_2\text{PO}_4^- \gg \text{CH}_3\text{CO}_2^-$

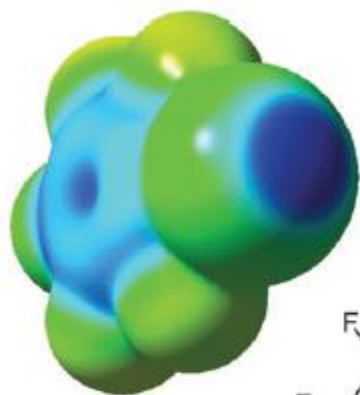


Beer

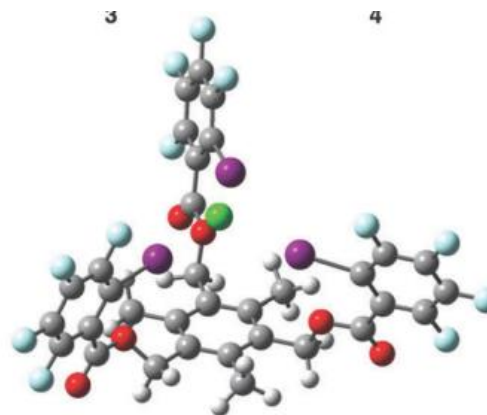




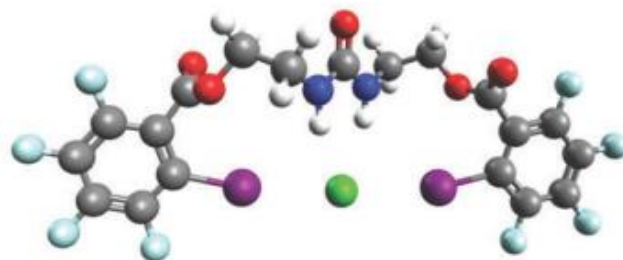
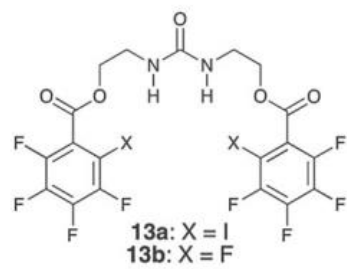
ortho-substituted iodotetrafluoroarenes on to trimethylbenzene scaffold



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



Taylor





(a)

A cascade complex.



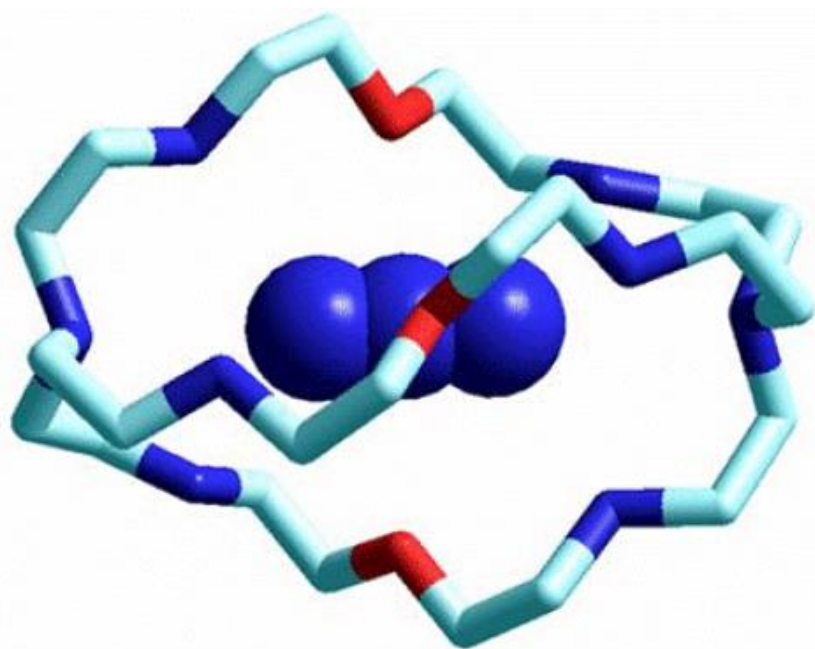
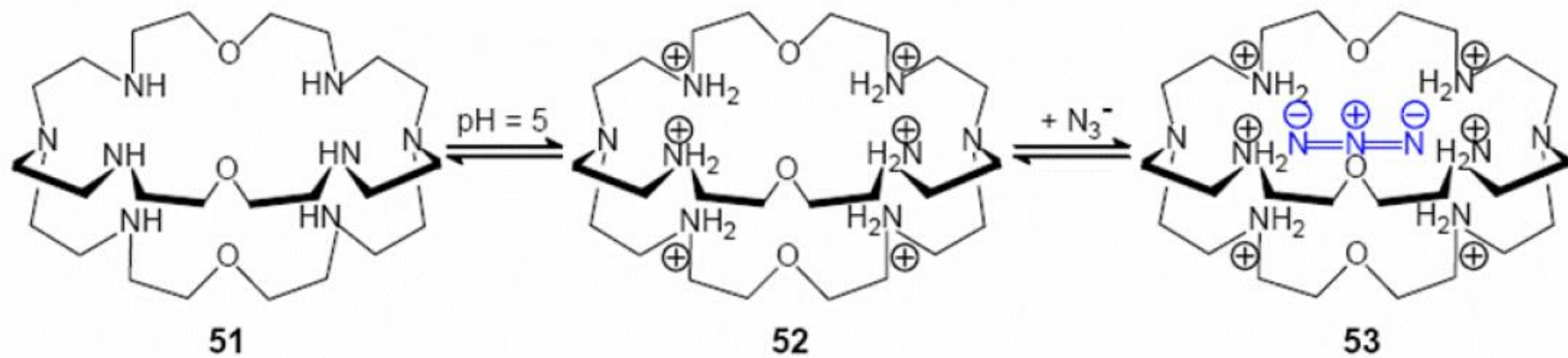
(b)

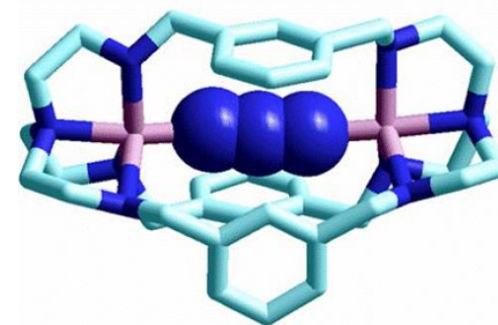
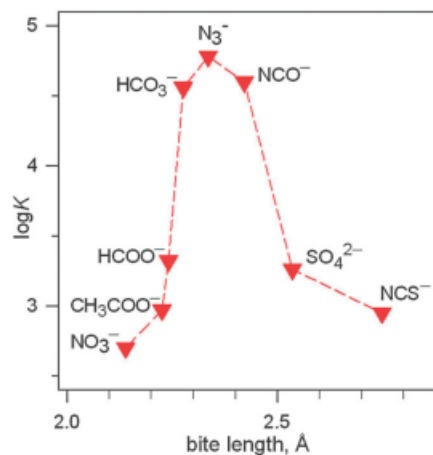
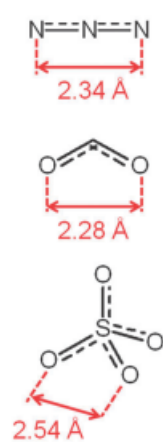
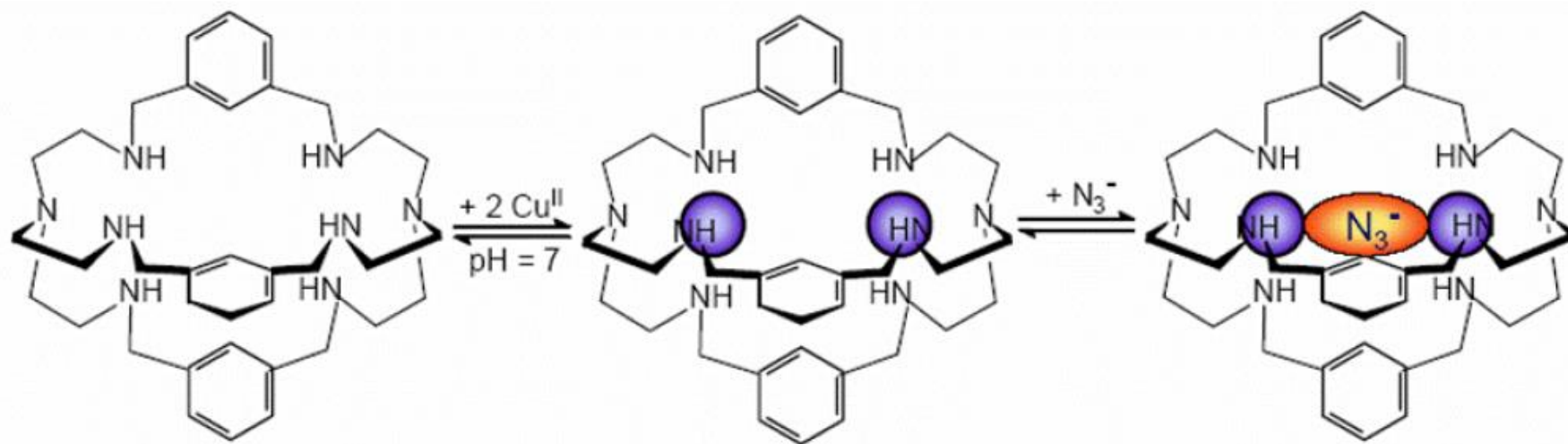
Receptor with individual
cation and anion recognition sites.



(c)

Receptor for zwitterionic
guests.





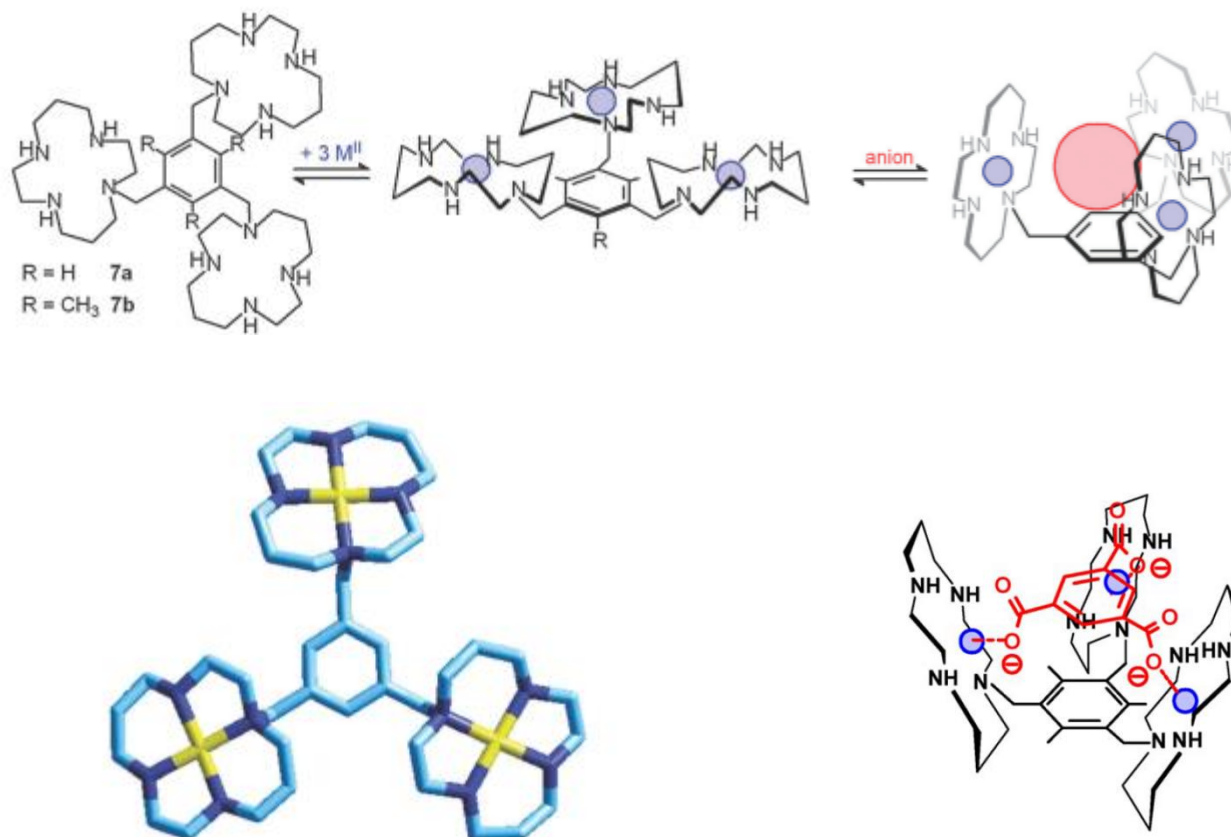
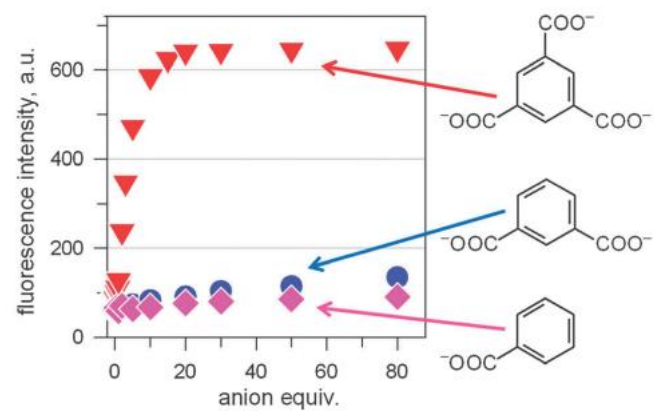
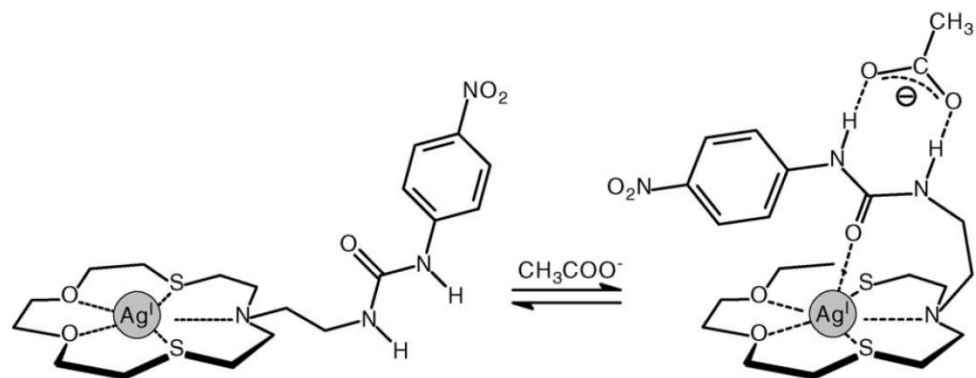
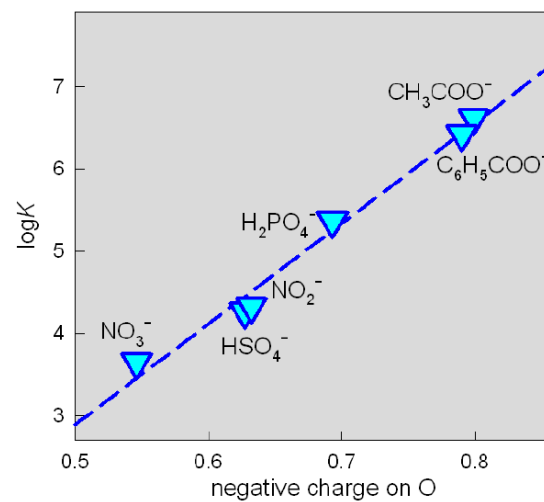
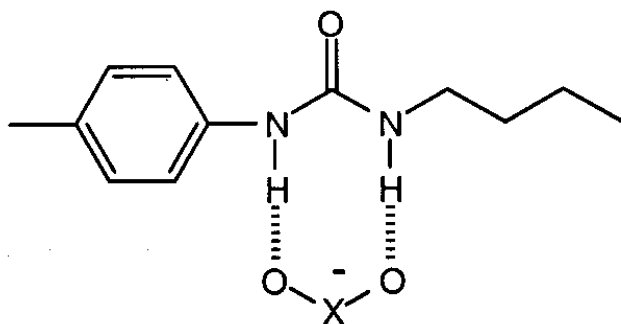


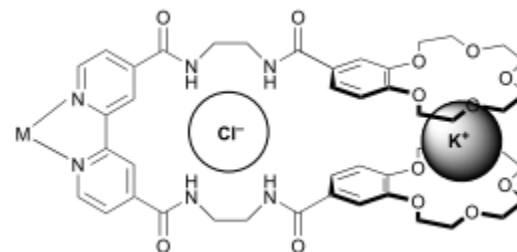
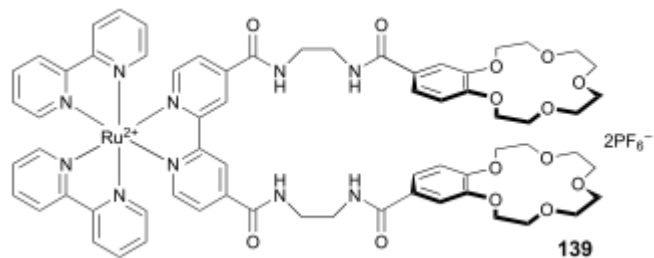
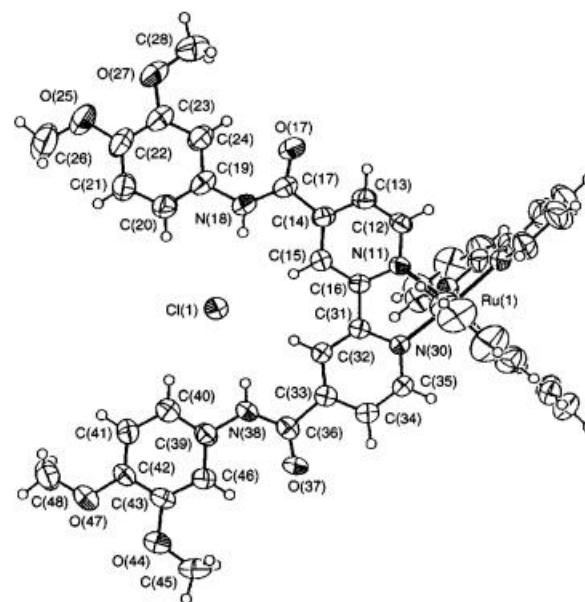
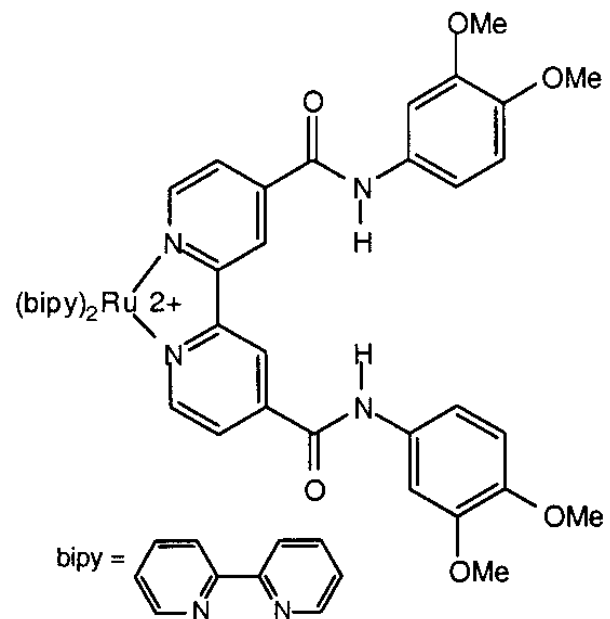
Fig. 25 The crystal structure of the complex salt $[Ni^II_3(7a)](ClO_4)_6 \cdot H_2O$.⁵⁸ Non-coordinating ClO_4^- ions and water molecule have been omitted for clarity, as well as hydrogen atoms. Each low-spin Ni^{II} centre shows a square coordination geometry.

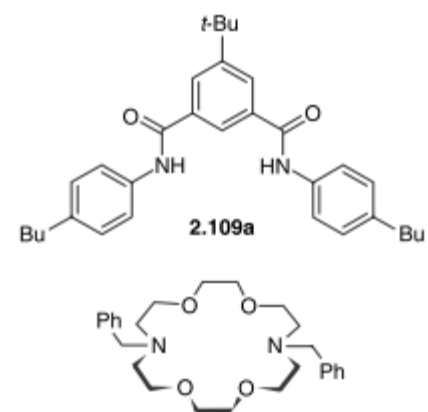
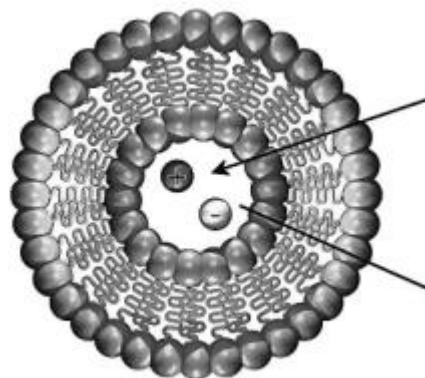
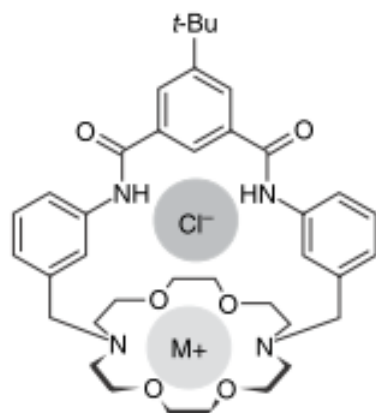


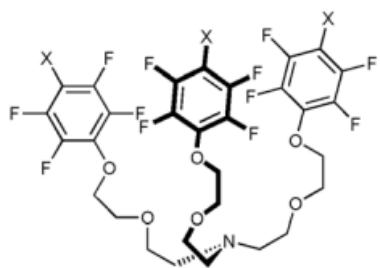


Scheme 4. Enhanced affinity of the urea subunit toward acetate, through coordination of the carbonyl oxygen atom to the proximate Ag^+ centre.

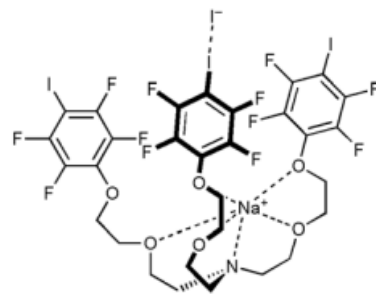








2a: X = I
2b: X = F



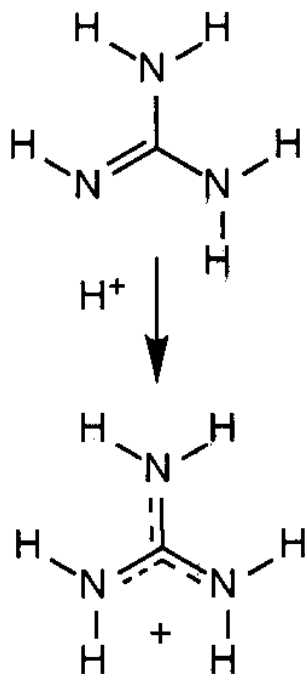
2a---NaI

$$K_a(\mathbf{2a} \cdots \text{NaI}) = 2.6 \times 10^5 \text{ M}^{-1}$$

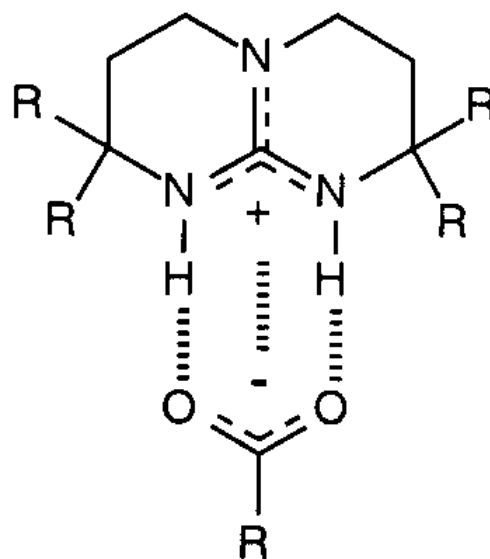
$$K_a(\mathbf{2b} \cdots \text{NaI}) = 1.3 \times 10^4 \text{ M}^{-1}$$

$$\Delta\Delta G_{\text{XB}} = 7 \text{ kJ/mol}$$



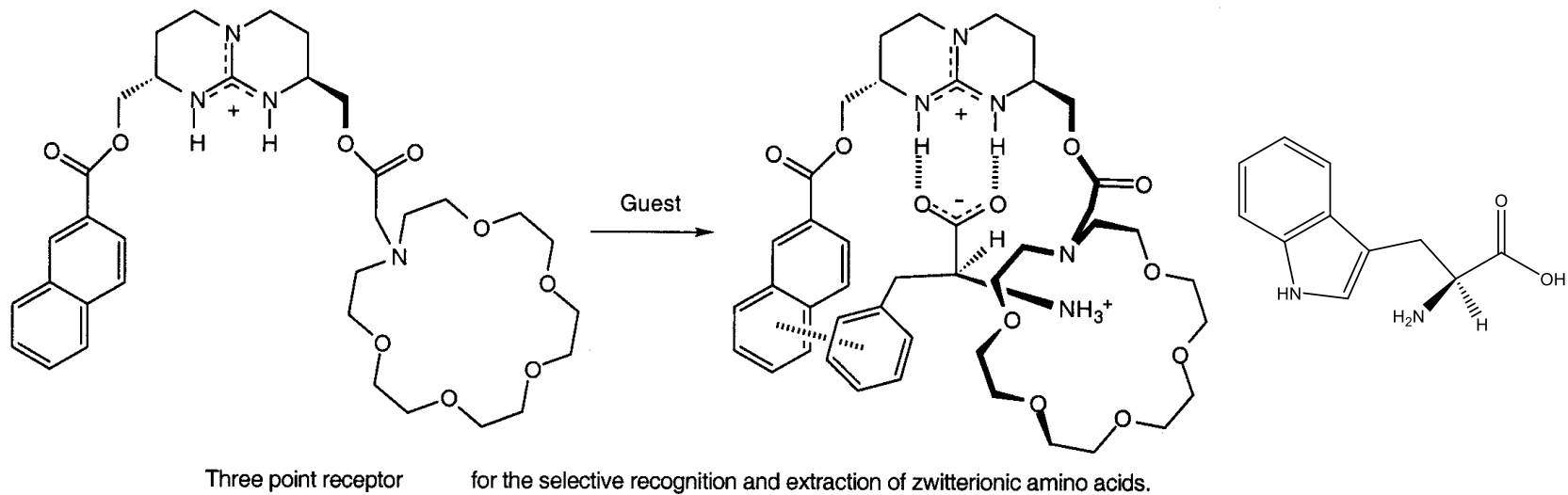


$pK_a = 13.6$



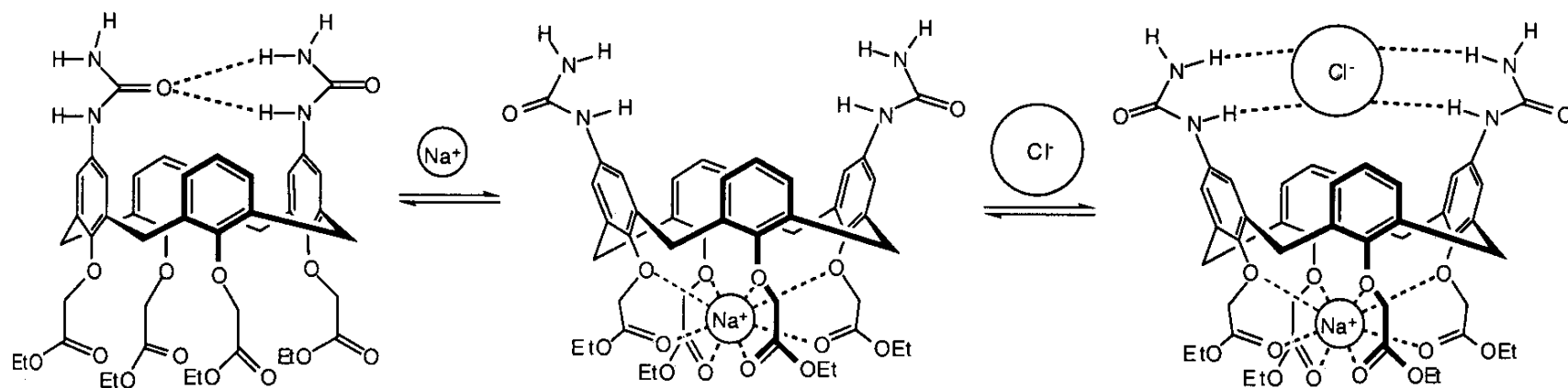
Bicyclic guanidinium is preorganized and complementary for binding bidentate anions.

Estrazione di aa con catene laterali aromatiche (Phe, Trp) in CH_2Cl_2



Solubilization of NaX Salts in Chloroform by Bifunctional Receptors**

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



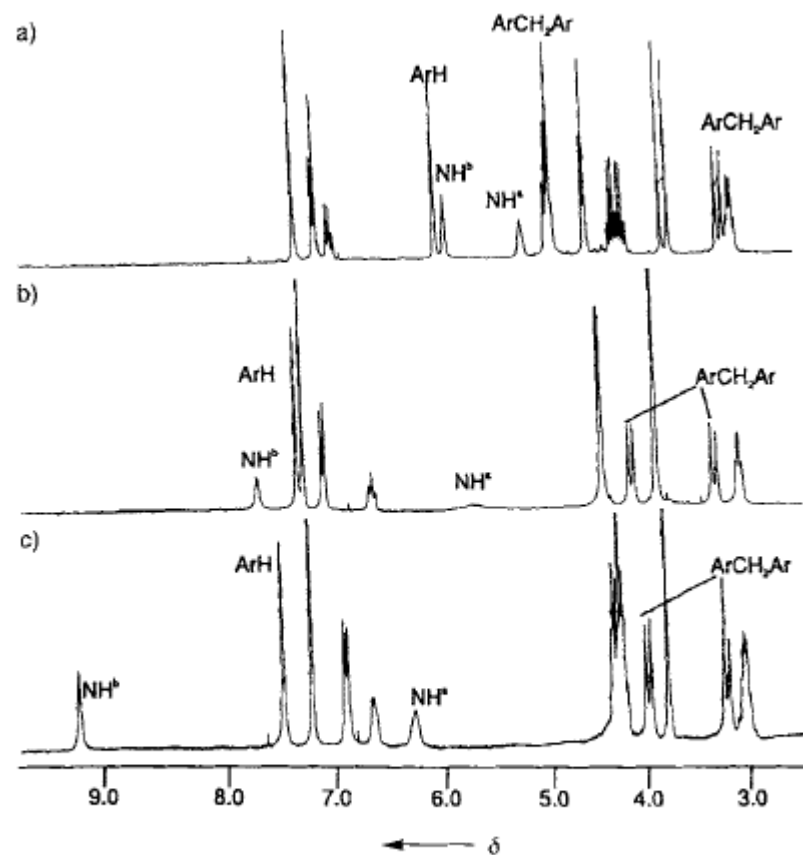
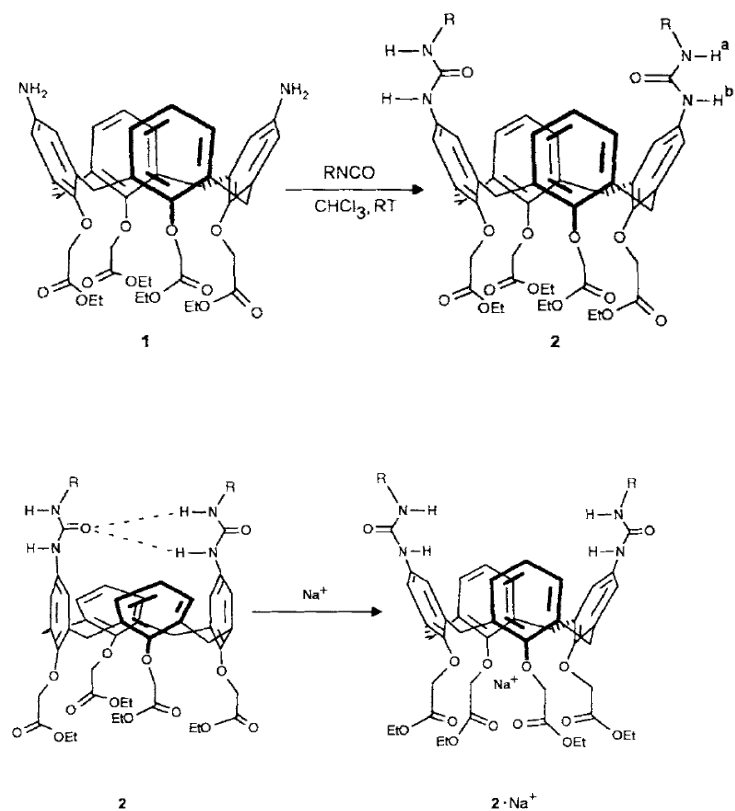
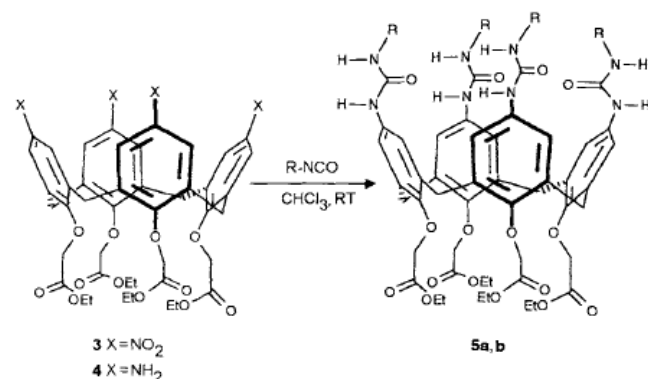


Fig. 1. ^1H NMR spectra of 2 (CDCl_3 , 5 mm). a) Uncomplexed, b) $[2 \cdot \text{Na}]\text{ClO}_4$, c) $[2 \cdot \text{NaCl}]$. For NH^a and NH^b see Scheme 1; for ArH and ArCH_2Ar see the text or ref. [14].



[14] NOESY experiments with **5a,b** reveal through-space connectivities between the aromatic hydrogens of the calix[4]arene skeleton and the NH⁺CH₂CH₂ and NH⁺CH₂CH₂ hydrogens of **5a** and the *tert*-butyl hydrogens of **5b**. These connectivities cannot result from through-space interactions within a single molecule since in the same molecule these hydrogens are not close enough [14a]. Consequently, these NOE connectivities must result from intermolecular interactions. Furthermore, the sign of the NOE connectivities is positive, suggesting that slow-tumbling entities with increased molecular mass (≥ 2000) are present

[14a]. Using the initial rate approximation [14b] and the distance between the equatorial and axial calix[4]arene bridging methylene hydrogens as a reference (1.79 Å) the cross relaxation constants (σ_{12}) for a two-spin system involving two atoms (1 and 2) were determined [14c]. The σ_{12} values are an indication of the degree of aggregation of the two atoms involved [14a]. The σ_{12} values for **5a** and **5b** are -0.7 and -0.2 , respectively. The negative σ_{12} values suggest the presence of species with a higher molecular mass. These results support the dimeric structure for **5a,b** proposed by Rebek [13]. a) D. Neuhaus, W. P. Wil-

[15] According to Shimizu and Rebek, Jr. the presence of two signals for the aromatic hydrogens of tetra(ureido)calix[4]arenes **5a,b** results from hindered rotation of the urea moieties around the aryl-urea bond due to hydrogen bonding in the dimer [13]. The fact that upon the complexation of Na⁺ by **5a,b** one signal for these hydrogens is present in the ¹H NMR spectra indicates that this hindered rotation is absent and that the dimer is no longer present.

Table 1. Percentage of MX complex formed with **2** and **5a,b** after L-S extraction [a].

	2			5a			5b		
	Na ⁺	K ⁺	Cs ⁺	Na ⁺	K ⁺	Cs ⁺	Na ⁺	K ⁺	Cs ⁺
Cl ⁻	100	~	-	100	29	-	100	30	-
Br ⁻	100	16	-	100	62	-	100	75	-
I ⁻	100	100	-	100	100	-	100	100	-

[a] The concentration of **2** and **5a,b** is 5 mM in CDCl₃. See also ref. [18].

[18] A 5 mM solution (0.5 mL) of **2** or **5a,b** in CDCl₃ was stirred with an excess of MX for 24 h. The organic layer was separated and the relative amount of complex formed was determined on basis of the intensities of the ¹H NMR signals for the bridging calix[4]arene methylene hydrogens of the complex and the free ligand.