Mie University
Department of Chemistry for Materials

General Principles and Selected Examples in Supramolecular Chemistry

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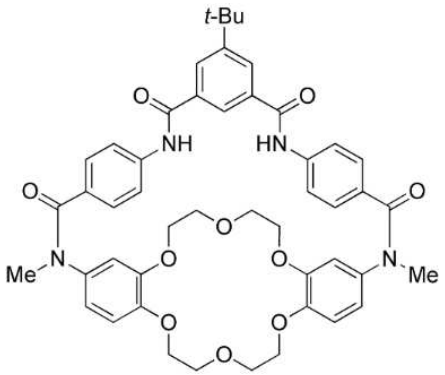
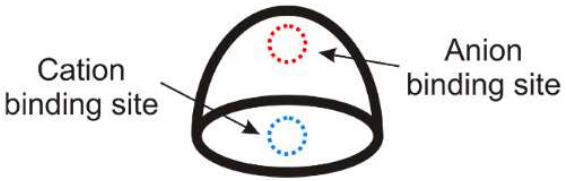
2. Solution host-guest chemistry

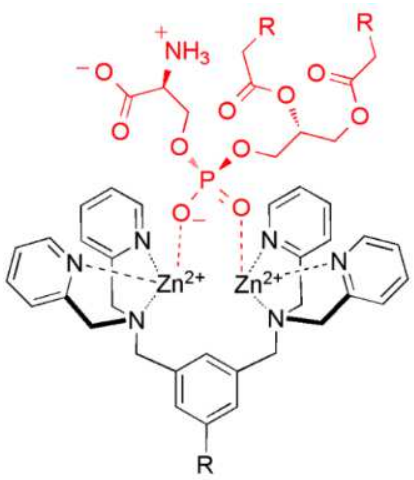
2.1 Introduction: guests in solution

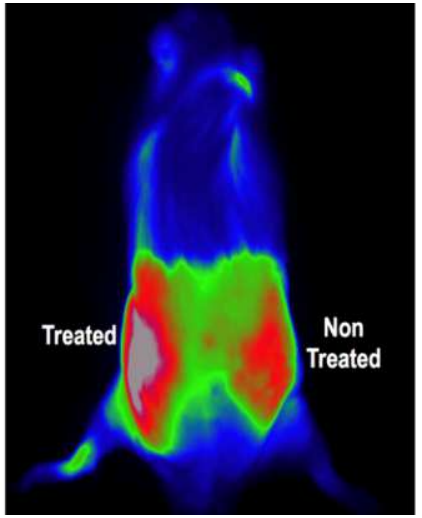
- The **host–guest chemistry of anions, cations and neutral-guest species in solution.**
- The electrostatic charge on any ion must be balanced by a corresponding counter-ion.
- Thus a 'cation' or 'anion' host is always a host for an **ion pair** (either contact or solvent-separated).
- The effect of the counter-ion is sometimes ignored or assumed to be negligible, particularly if weakly interacting counter-ions are used, such as NBu_4^+, PF_6^-, or $B(C_6H_3(CF_3)_2)_4^-$. However, there are a number of successful ion-pair binding hosts.





Macrocyclic receptor that binds solvent separated ion-pairs

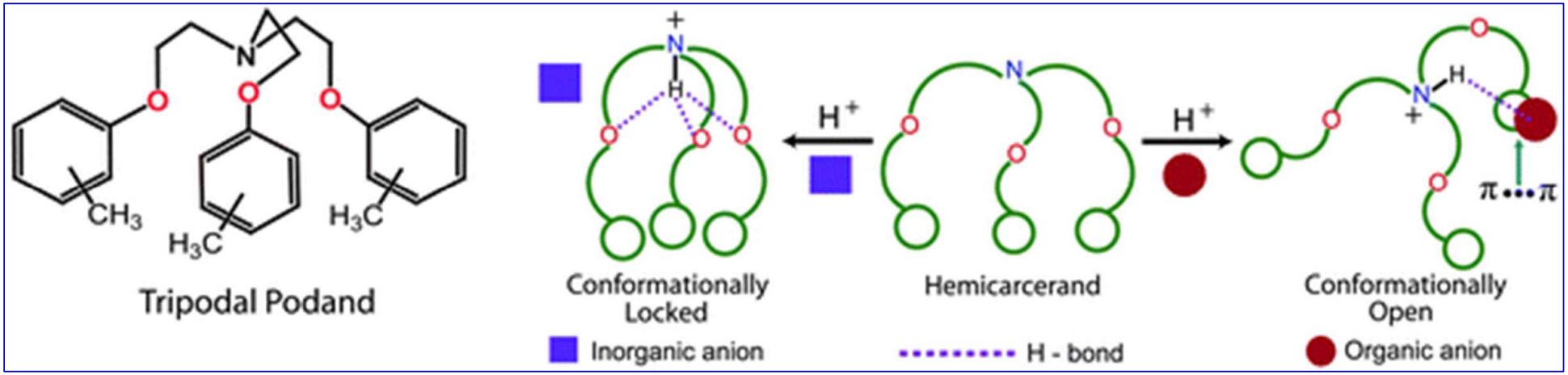




Association of ZnDPA probe with phosphatidylserine head group. False colored fluorescence image of a living rat bearing two tumors.

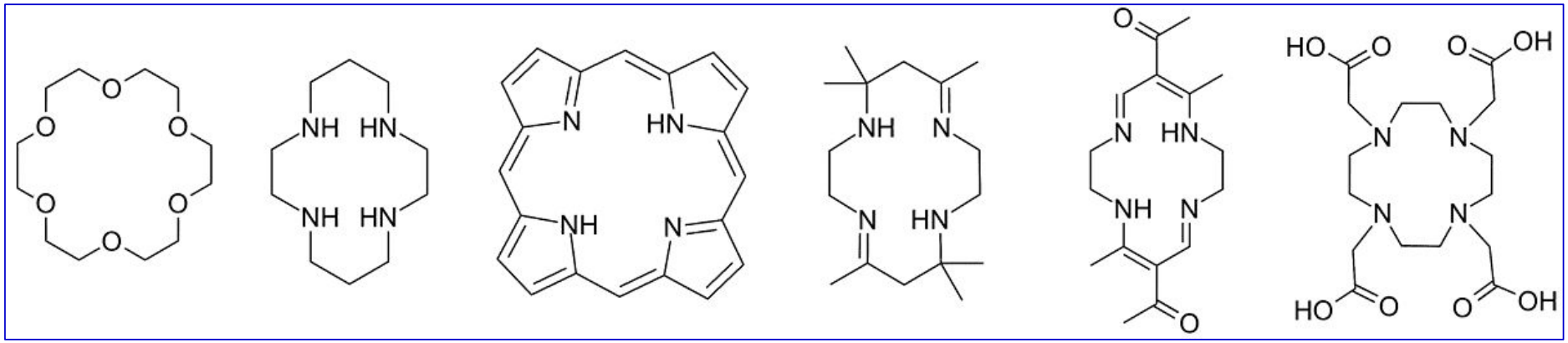
2.2 Macrocyclic versus acyclic hosts

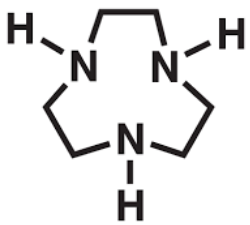
- Two major classes of host: acyclic (***podands***) and cyclic (***macrocycles, macrobicycles* or *macrotricycles***).
- **Podand**: An acyclic chain-like or branching host with a number of binding sites that are situated at intervals along the length of the molecule, or about a common spacer.
- **Podand:** Linear or branching chain species with two or more sets of guest-binding functional groups positioned on the spacer unit in such a way as to chelate a target guest species to maximise guest affinity (*cf*. *co-operativity*).
- Podands generally have a high degree of flexibility and on binding to a guest the conformational change that occurs to produce a stable host–guest complex, may result in *allosteric effects*.
- In general, host flexibility is of key importance, especially in biological systems, for example, in a protein's biochemical role (*cf*. *induced-fit model*)

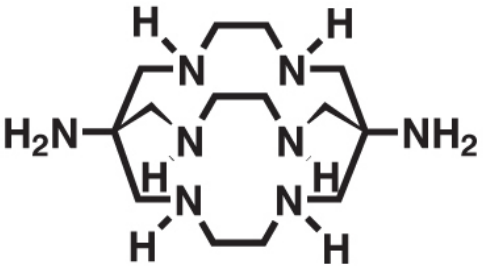


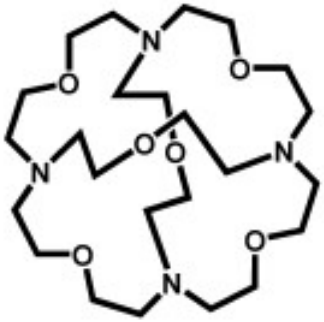
CrystEngComm, 2011,**13**, 1664

- **Cyclic receptors** have binding sites positioned in a closed-ring arrangement.
- **Cyclic systems** are more preorganised and hence form more thermodynamically stable complexes because less conformational change is required upon binding.
- **Macrocycle:** A cyclic molecule usually with nine or more atoms in the ring.
  In supramolecular chemistry containing a number of binding sites that are arranged around the closed system.



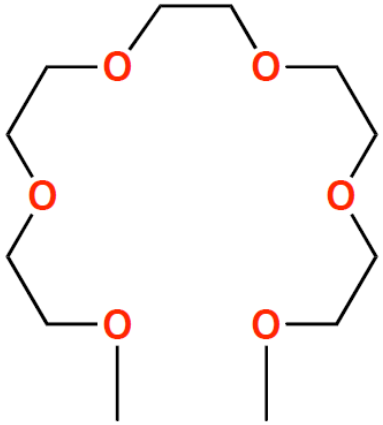




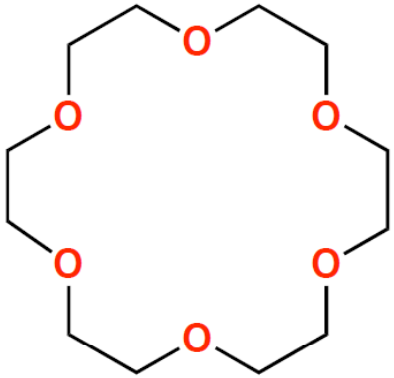


Increasing Organization

Decreased organization and increased conformational space.



Podand
Acyclic
File
logK_S = 2.0



Coronand
Macrocyclic
Cavity
logK_S = 6.08

Stability for the potassium complex in methanol

Increased organization and reduced conformational space.

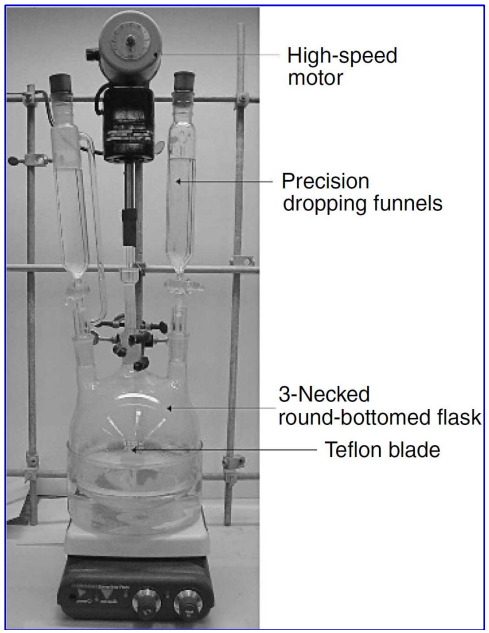
2.2.1 High-dilution synthesis

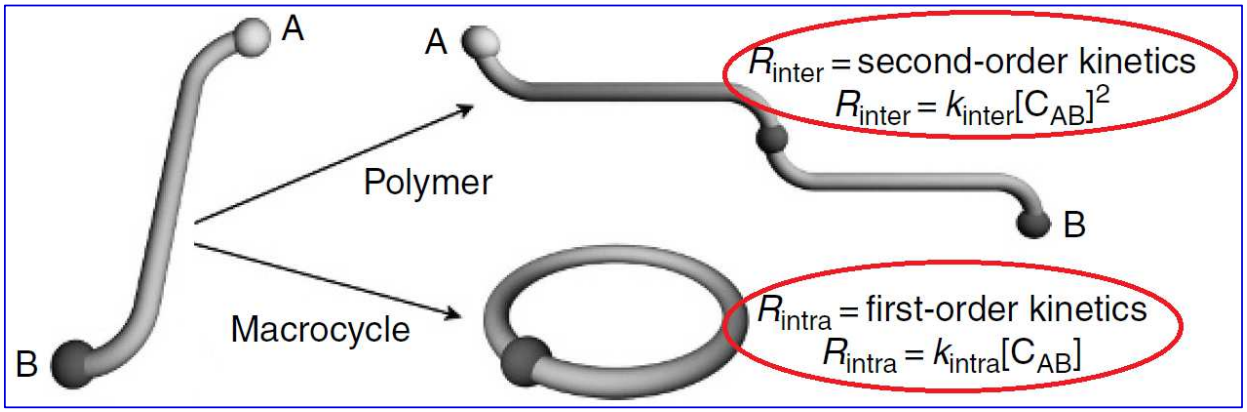
- Small quantities of reactants are mixed together at a controlled rate in a large volume of solvent.
- Why is macrocycle formation favoured when using this technique?

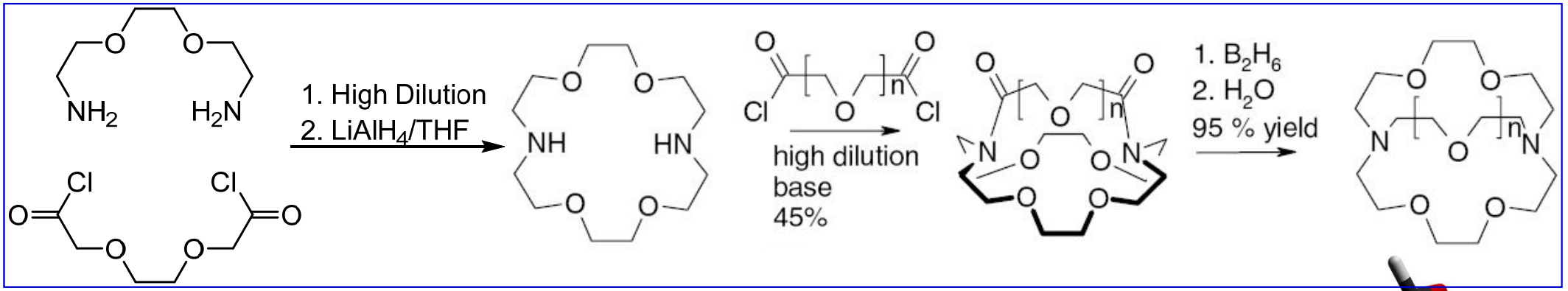
1. A low concentration of the 'open-strand' reactant has a greater chance of reacting with itself to form a closed-ring system than of reacting with another molecule to form a polymer.
2. ▸In terms of **reaction rate**, intramolecular ring closure is a **unimolecular process**
   – it has a rate that is **proportional to the concentration** of the reactant.

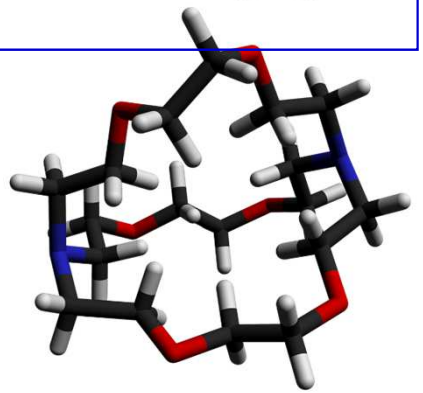
   ▸Intermolecular reaction leading ultimately to undesired polymer formation is a **bimolecular process** and its rate is **proportional to the square of the concentration** of a single reactant.

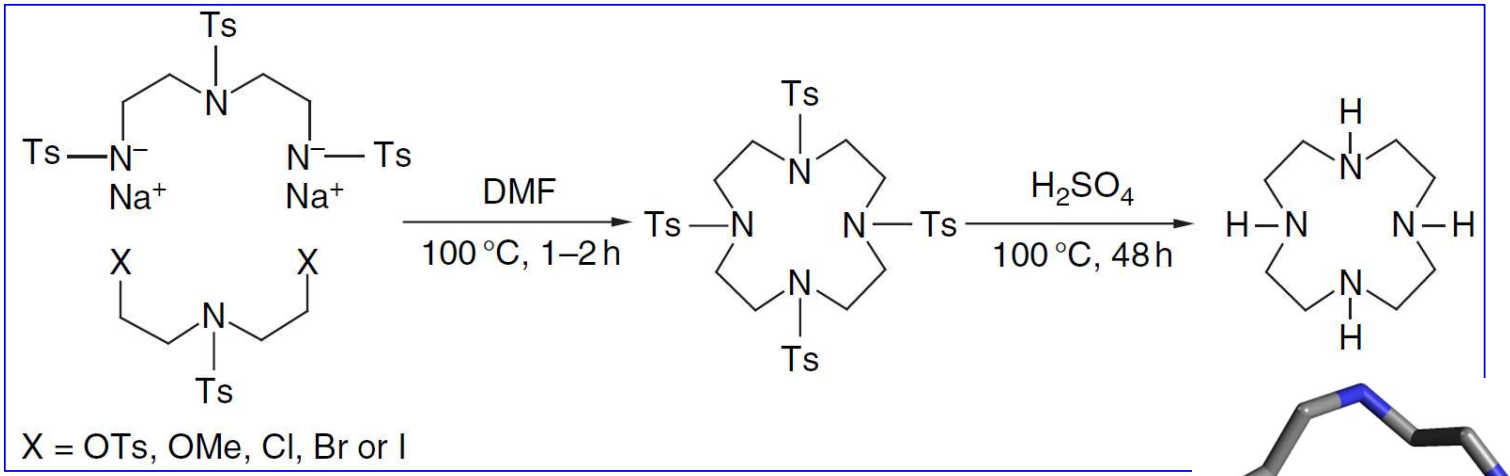
Therefore, high dilution favors an intramolecular reaction.

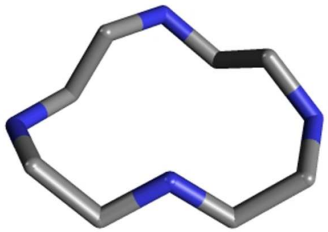





1. High Dilution
2. LiAlH4/THF
high dilution
base
45%
1. B2H6
2. H2O
95 % yield

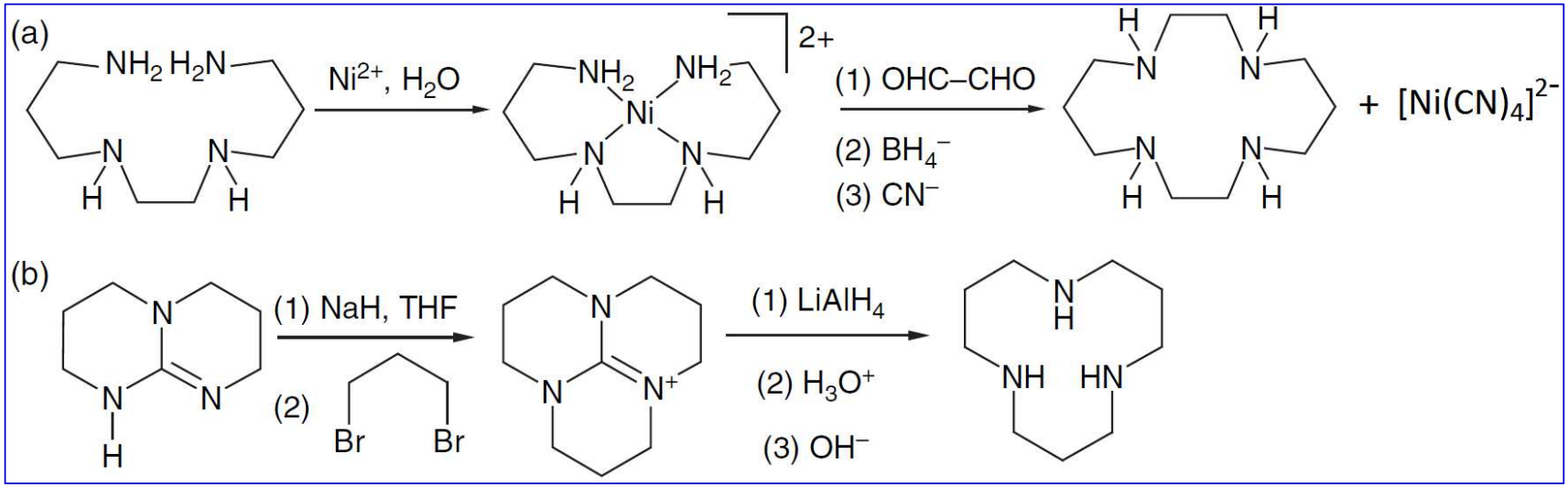



DMF
100 °C, 1–2 h
H2SO4
100 °C, 48 h
X = OTs, OMe, Cl, Br or I



2.2.2 Template synthesis

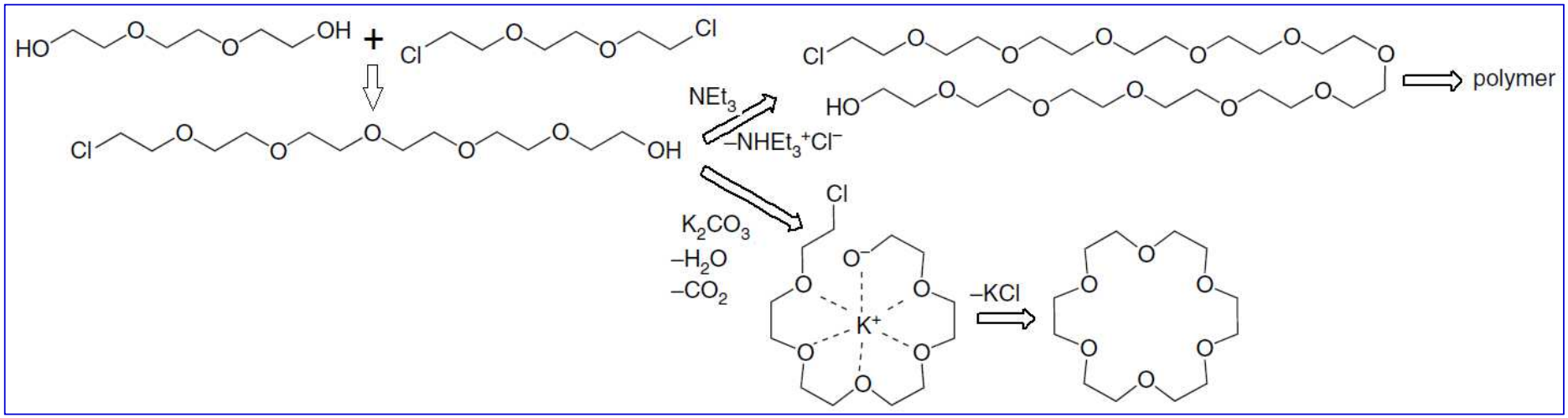
- ***Template effect***: the formation of macrocycles in preference to linear oligomers through the use of a template
  (Demonstration by the original synthesis of dibenzo[18]crown-6 by Pedersen in 1967.
  (C.J. Pedersen, *J. Am. Chem. Soc*, 1967, **89**, 7017)
- **(a) *Exo-templates*:** The synthesis by the use of external templates, such as metal ions → the most common
  The metal acts as a temporary centre and is removed in the final step
  (e.g. synthesis of cyclam).
- **(b) *Endo-template***: Ring expansion of a smaller ring system
  (e.g. as in the synthesis of 1,5,9-triazacyclododecane).



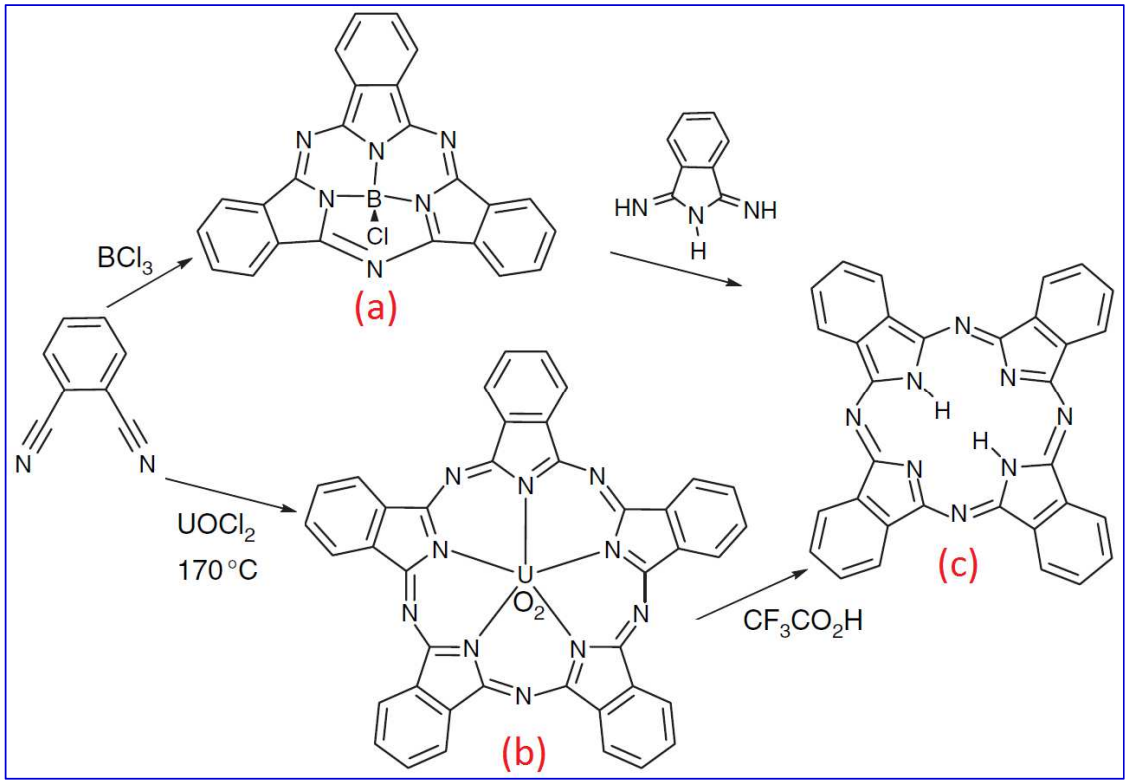
(a) exo-template effect; (b) endo-template effect.

❑ *Kinetic template effect*

- ▶ (e.g.) [18]crown-6
  triethylene glycol + 1,2-bis(2-chloroethoxy)ethane
  → two different bases (K_2CO_3 or NEt_3) are employed
  → K^+ ion act as an *exo*-template → cyclic product
- ▶ Product formation is irreversible and the reaction is kinetically controlled.
- ▶ The role of the template is to enhance the rate of formation of the cyclic product.



- ***Thermodynamic template effect***
  - Phthalocyanine
  - 1,2-dicyanobenzene + either BCl_3 or uranyl chloride
    - → two different-sized macrocycles
    - → Macrocycles **(a)** and **(b)** are themselves only stable when the template is still present.
      On the removal of the template,
      the normal phthalocyanine **(c)** is formed,
      which is highly stable.
- The binding of the template
  thermodynamically stabilises
  the most complementary product.
  (usually a macrocyclic compound)



❑ Disadvantage of the template effect

- ▶ Removing the template without destroying the product.
  This is not easy task and, in some cases, impossible.
- ▶ Effective demetallation strategies: depending on the stability of the metal–macrocycle complex

(e.g.) (1) Labile or weakly bound metal to the macrocycle (K^+ complexes of the crown ethers),

→ dissolve the complex in an organic solvent

→ washed with water to extract the metal salt

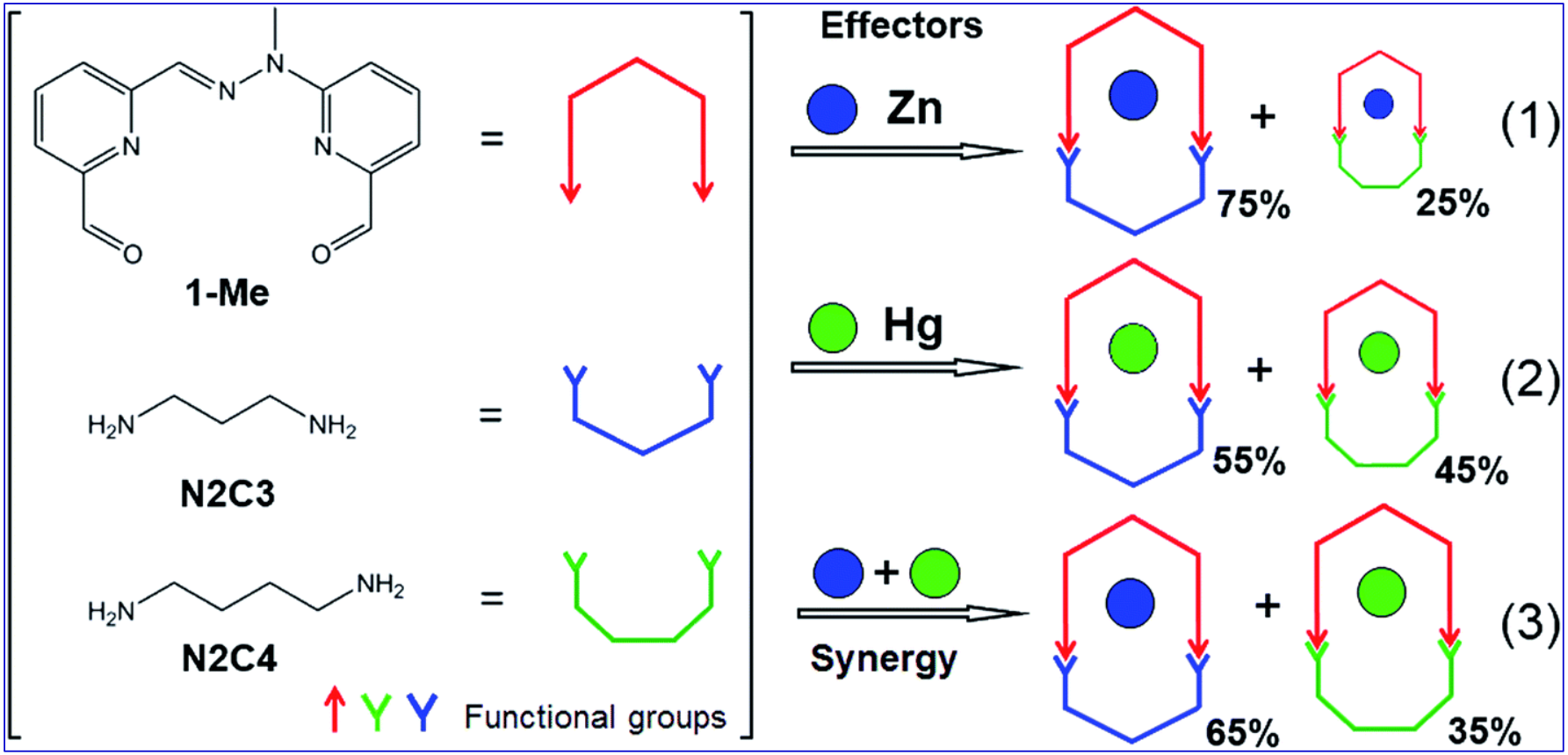
(2) Strong bound metal ion within the cavity

→ Demetallate by using strongly coordinating ligand (e.g. CN^-)

(3) Redox reactions

→ Inert configuration (e.g. low-spin Co^{3+}) change to a more labile configuration (e.g. Co^{2+})

→ easier demetallation



J-.M. Lehn, *Chem. Sci*., 2017, **8**, 2125-2130

2.3 Cation binding

Cations in Body Fluids

Cations (mmol/L)	Plasma	Interstitial	Intracellular
Na^+	142	139	14
K^+	4.2	4.0	140
Ca^{2+}	1.3	1.2	0
Mg^{2+}	0.8	0.7	20

2.3.1 Introduction

- Cation complexes play an essential role in many biological systems.
- Na^+, K^+, Mg^{2+}: critical to life.

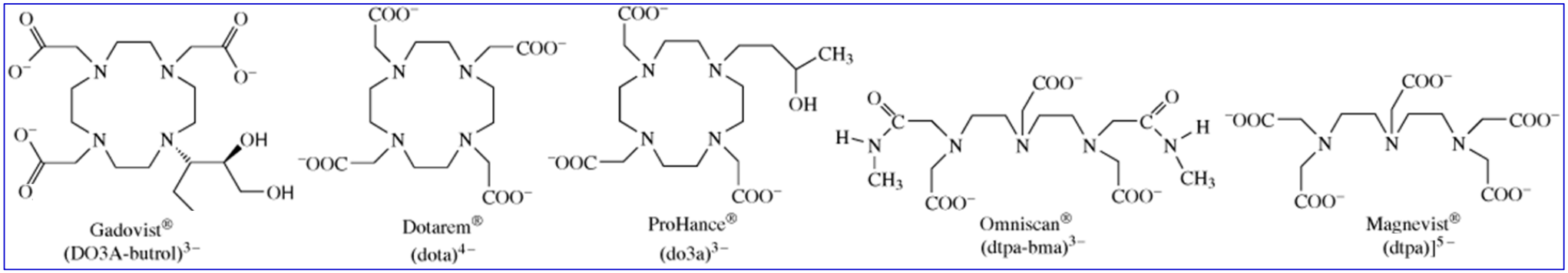
  Na^+: Important for membrane function, nerve impulses, muscle contraction, prevent blood clotting

  K^+: Membrane function, maintaining osmotic balance, cofactor in photosynthesis and respiration

  Ca^{2+}: Signal pathways, skeletal material, maintaining potential difference across membranes
- Toxic heavy metals (Pb^{2+}, Cd^{2+}, Hg^{2+}) are critical importance to remove due to environment problem
- Metal chelate ligands are also highly important in biomedical imaging and radiotherapy applications

  e.g. using ^{99}Tc and ^{60}Co, Zn
- In industrial perspective, extraction of more valuable metal ions from a mixture of species

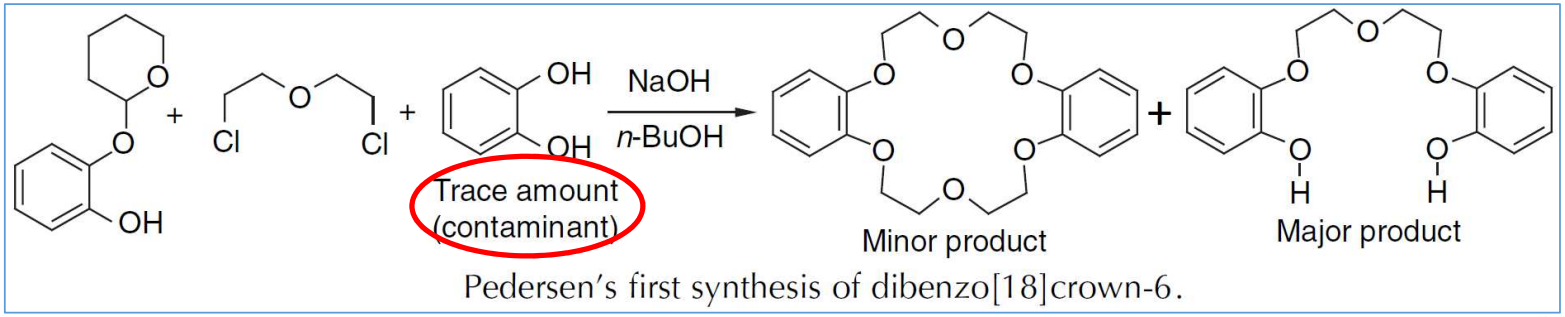
  e.g. Ag, Au, Pt



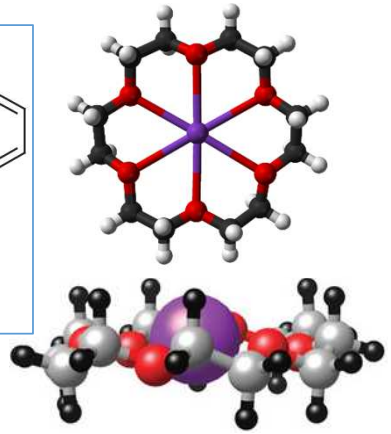
Ligands of Gd(III) complexes approved for clinical use as MRI contrast agents.

2.3.2 The early years

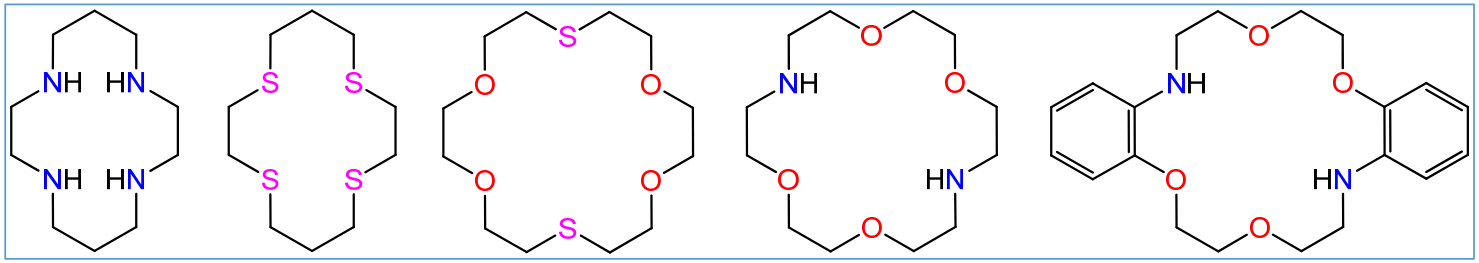
- Key step in the development of supramolecular chemistry
  → The discovery of **dibenzo[18]crown-6** (**Charles J. Pedersen**)
  → Side-product during the attempted preparation of a bis(phenol) derivative.
  → Fortuitous consequence of the presence of an alkali metal (the operation of the template effect)



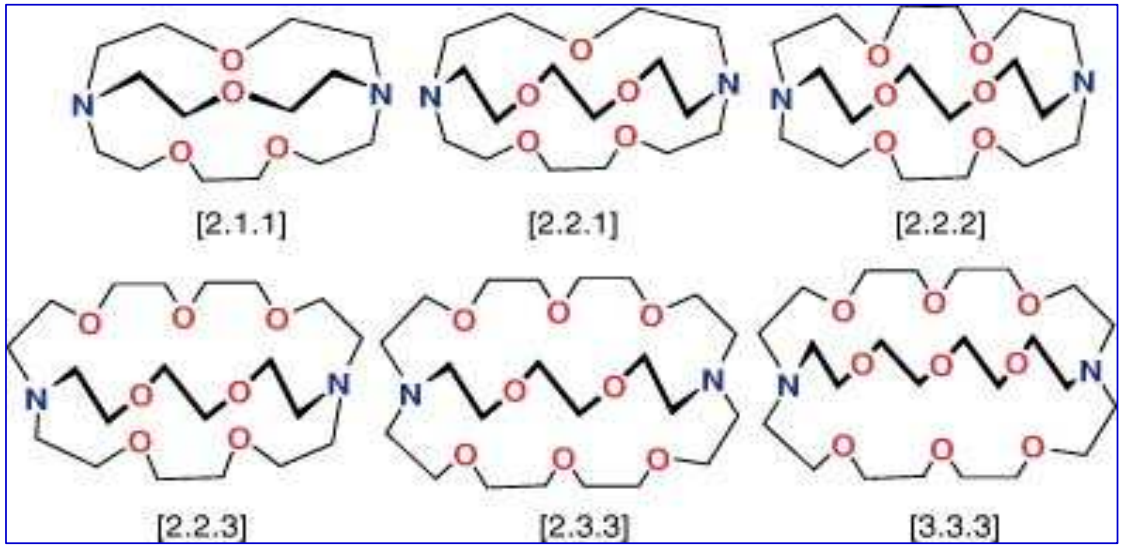
Pedersen's first synthesis of dibenzo[18]crown-6.

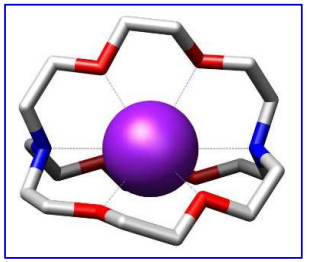


- Subsequent work: a wide variety of analogues
  Subsequent work: ***azacrowns***, ***thiacrowns***, **P,N-*containing corands***
- **The family of crown ethers and related heteroatom donor macrocycles: *corands***



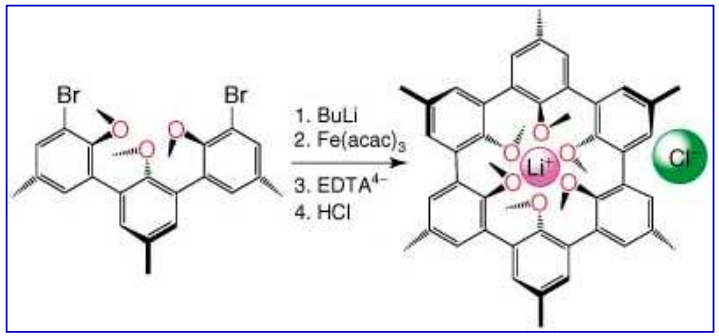
- Shortly after the original crown ether work,
  donor atoms within **three-dimensional array to completely encapsulate the ion** (**Jean-Marie Lehn**)
- Bicyclic systems named '**cryptands**', **[2.2.2]cryptand** (the first one)

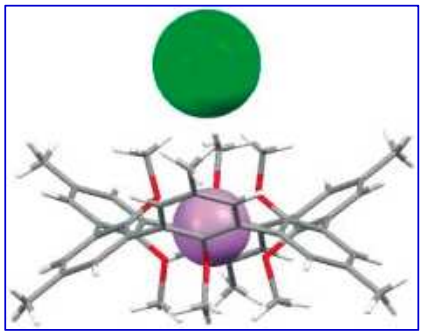




Simple bicyclic cryptands of increasing size.

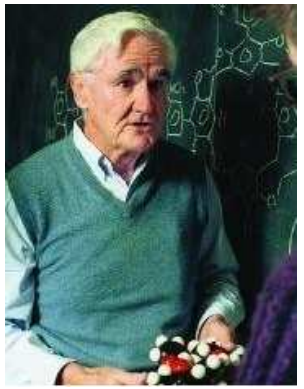
- Cyclic polyethers (***Spherands***): Rigidly preorganised in an octahedral array. (**Donald Cram**)
- Li^+-selective **spherand-6** (The best-known example)
- The work of Pedersen, Lehn and Cram:
  binding cation, anion and neutral species, sensing and catalysis.
  → the synthesis of self-assembled rotaxanes, catenanes and knots (Chapter 3).



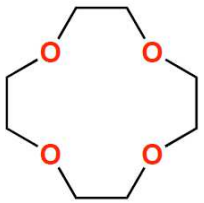


- **Cram, Pedersen** and **Lehn** shared the **Nobel Prize (1987)** for the development of Supramolecular Chemistry.

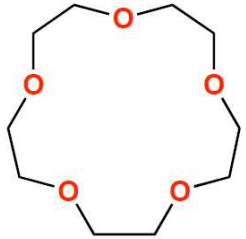




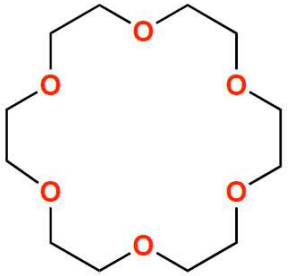
Cyclic polyethers (Crown ethers)



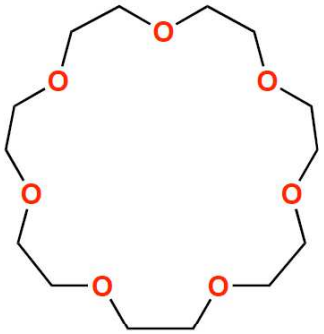
[12]O_4



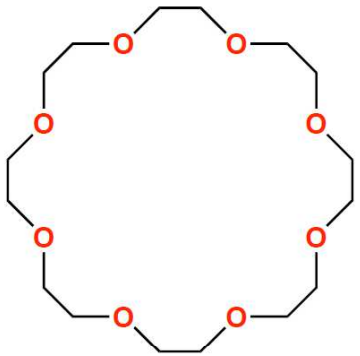
[15]O_5



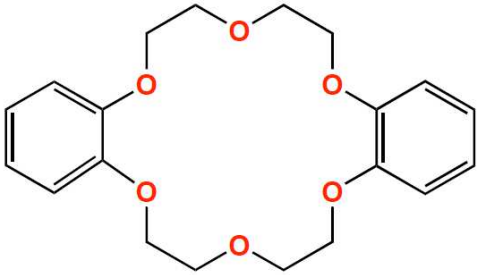
[18]O_6



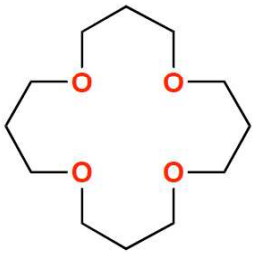
[21]O_7



[24]O_8



Dibenzo[18]O_6



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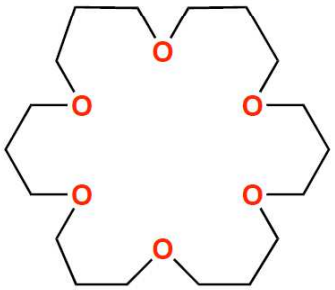
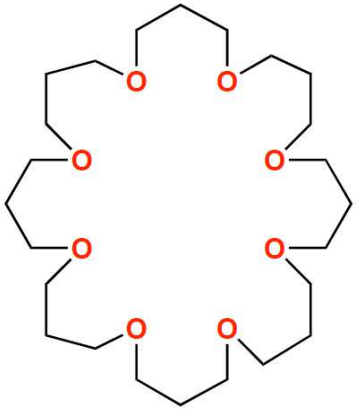
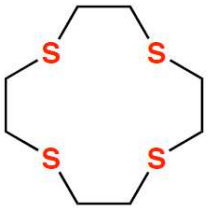


[24]O_6

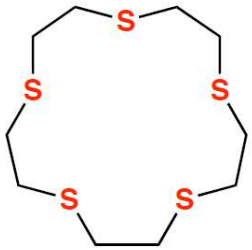


[32]O_8

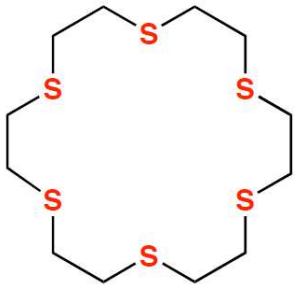
Cyclic polythioethers (Thioether crowns)



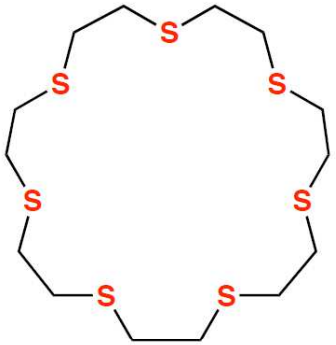
[12]S_4



[15]S_5



[18]S_6



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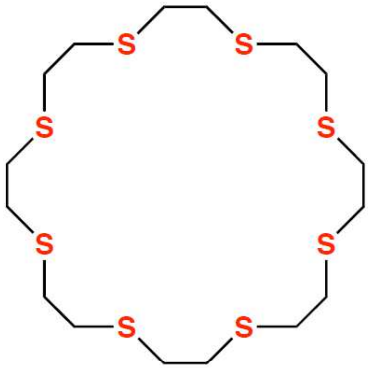
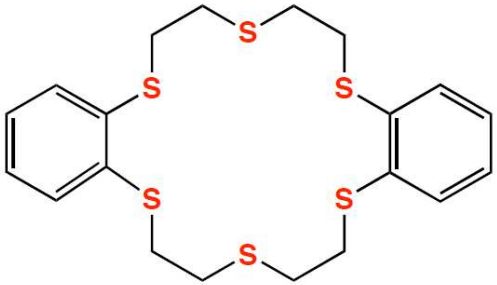
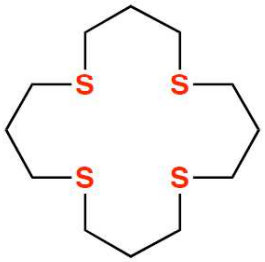


[24]S_8



Dibenzo[18]S_6



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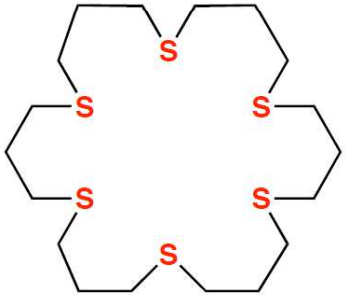

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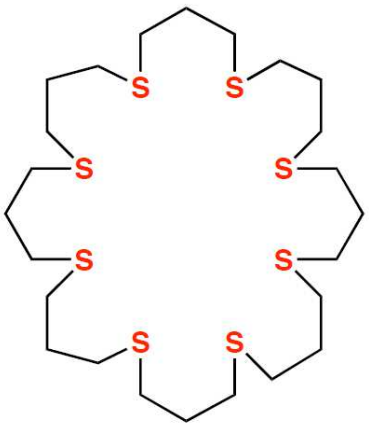
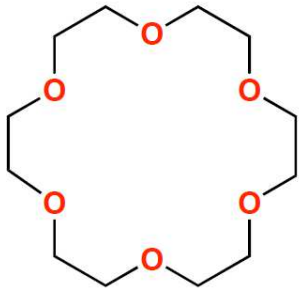


[32]S_8

Cyclic polyaaza-oxa-thia



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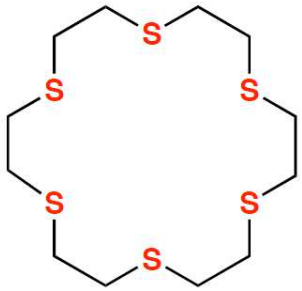

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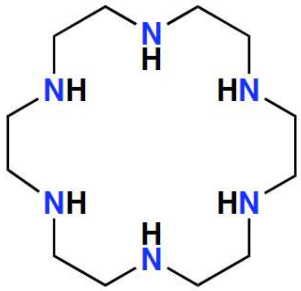

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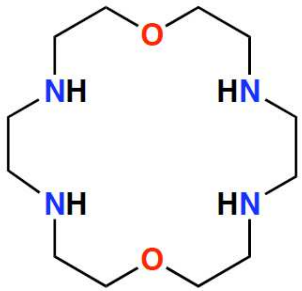

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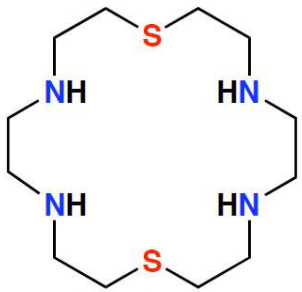

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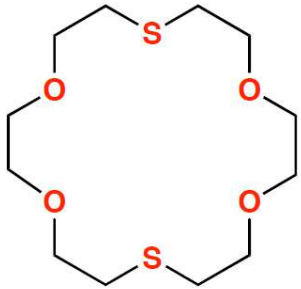

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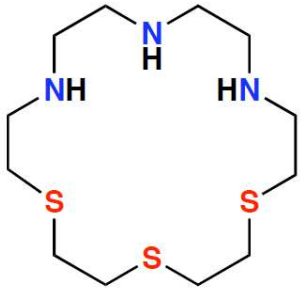

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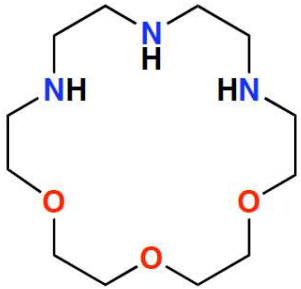

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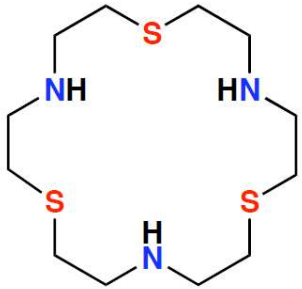
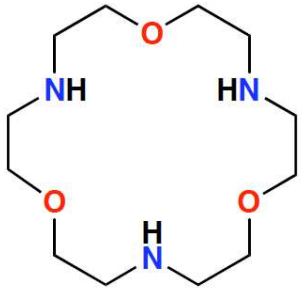


[18]S_3N_3



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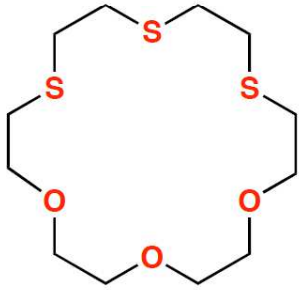

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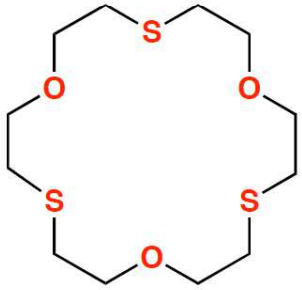

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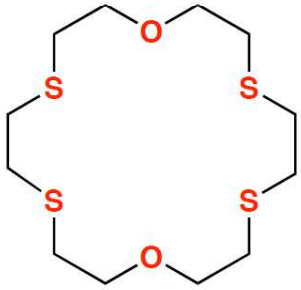

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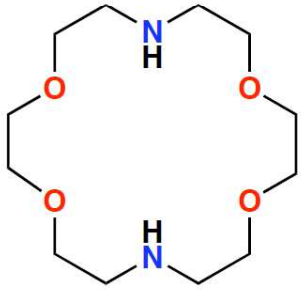

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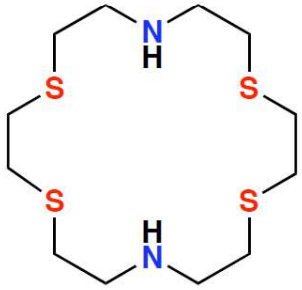
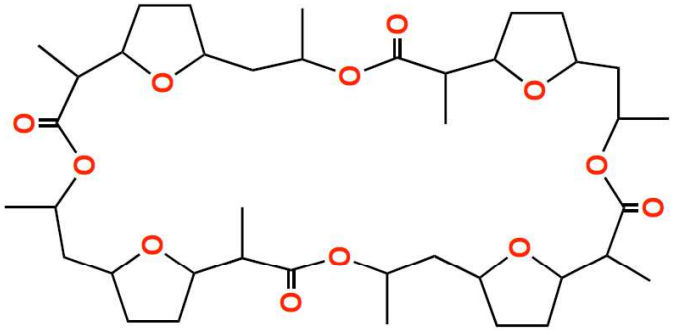
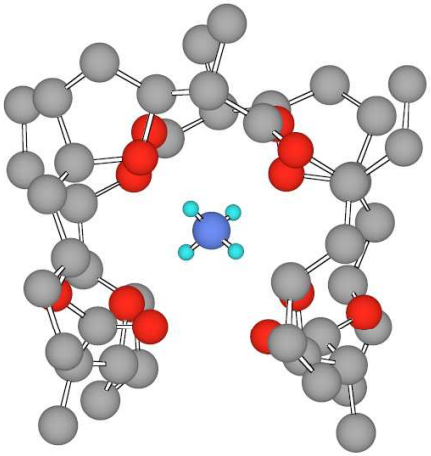


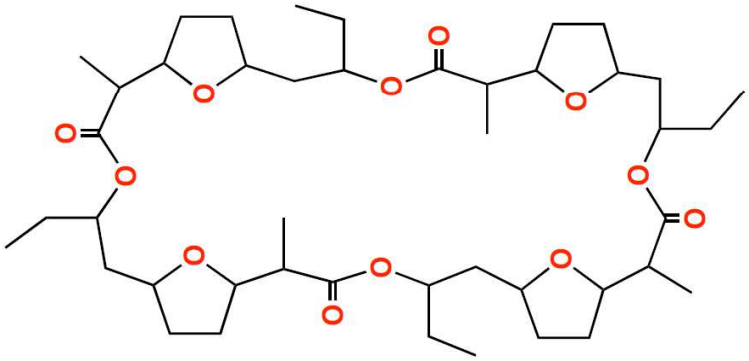
[18]S_4N_2

Complexation of ammonium by Antibiotics

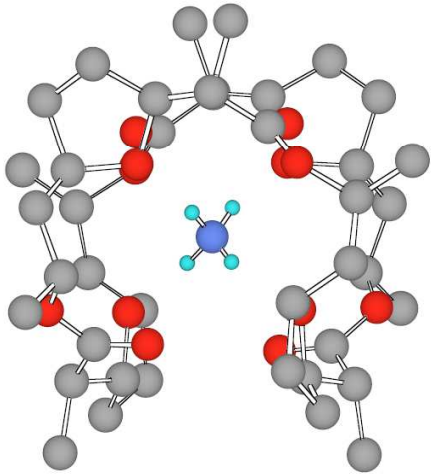


Nonactin



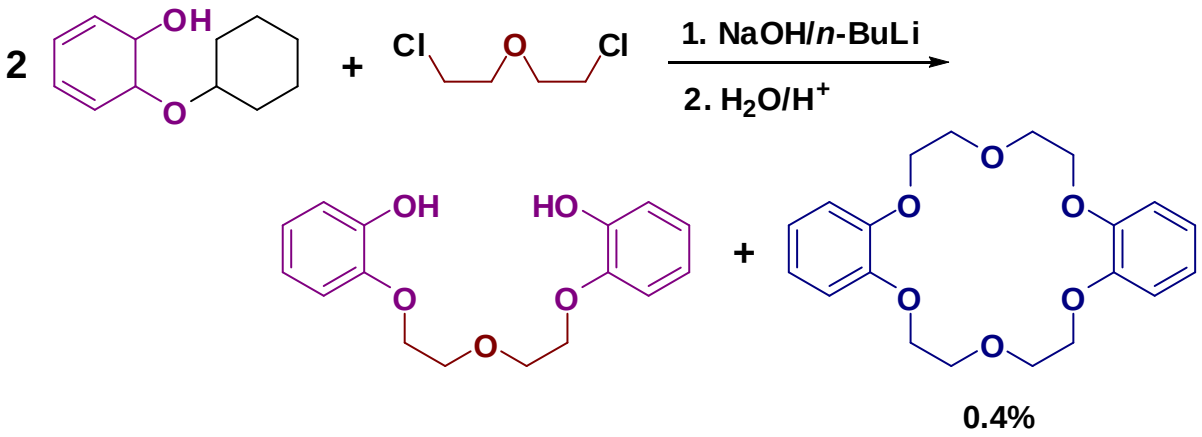


Tetranectin

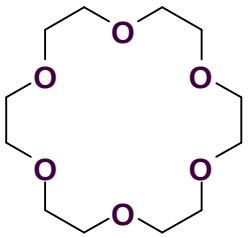


2.3.3 Crown ethers, lariat ethers and cryptands

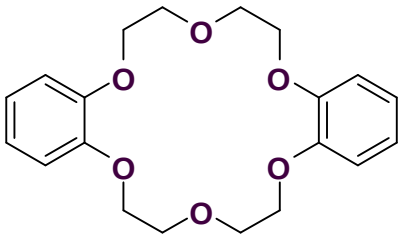
The Crown ethers (C. Pedersen)



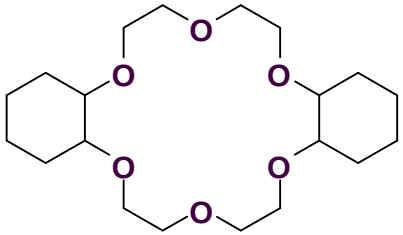
Charles J. Pedersen (1904-1989)
(The Nobel Prize in Chemistry, 1987)



[18] Crown-6
18C6



Dibenzo [18] Crown-6
DB18C6



Dicyclohexyl [18] Crown-6
DCH18C6

Cyclic Polyethers and Their Complexes with Metal Salts

C. J. Pedersen

Contribution No. 157 from E. I. du Pont de Nemours and Company, Inc., Elastomer Chemicals Department, Experimental Station, Wilmington, Delaware 19898. *Received April 13, 1967*

Abstract: Thirty-three cyclic polyethers, derived from aromatic vicinal diols and containing from 9 to 60 atoms including 3 to 20 oxygen atoms in the ring, have been synthesized. Some of these have been prepared in good yields without the use of a high-dilution technique. Fifteen of the compounds have been catalytically hydrogenated to the corresponding saturated cyclic polyethers. Many of those containing five to ten oxygen atoms form stable complexes with some or all of the cations of: Li, Na, NH_4, RNH_3, K, Rb, Cs, Ag(I), Au(I), Ca, Sr, Ba, Cd, Hg(I), Hg(II), La(III), Tl(I), Ce(III), and Pb(II). Many of these complexes can be isolated in the crystalline form depending on the anion. They appear to be salt–polyether complexes formed by ion–dipole interaction between the cation and the negatively charged oxygen atoms of the polyether ring. The stoichiometry of the complexes is one molecule of polyether per single ion regardless of the valence. Some of the polyethers, by complexing, solubilize inorganic compounds, such as potassium hydroxide and permanganate, in aromatic hydrocarbons.

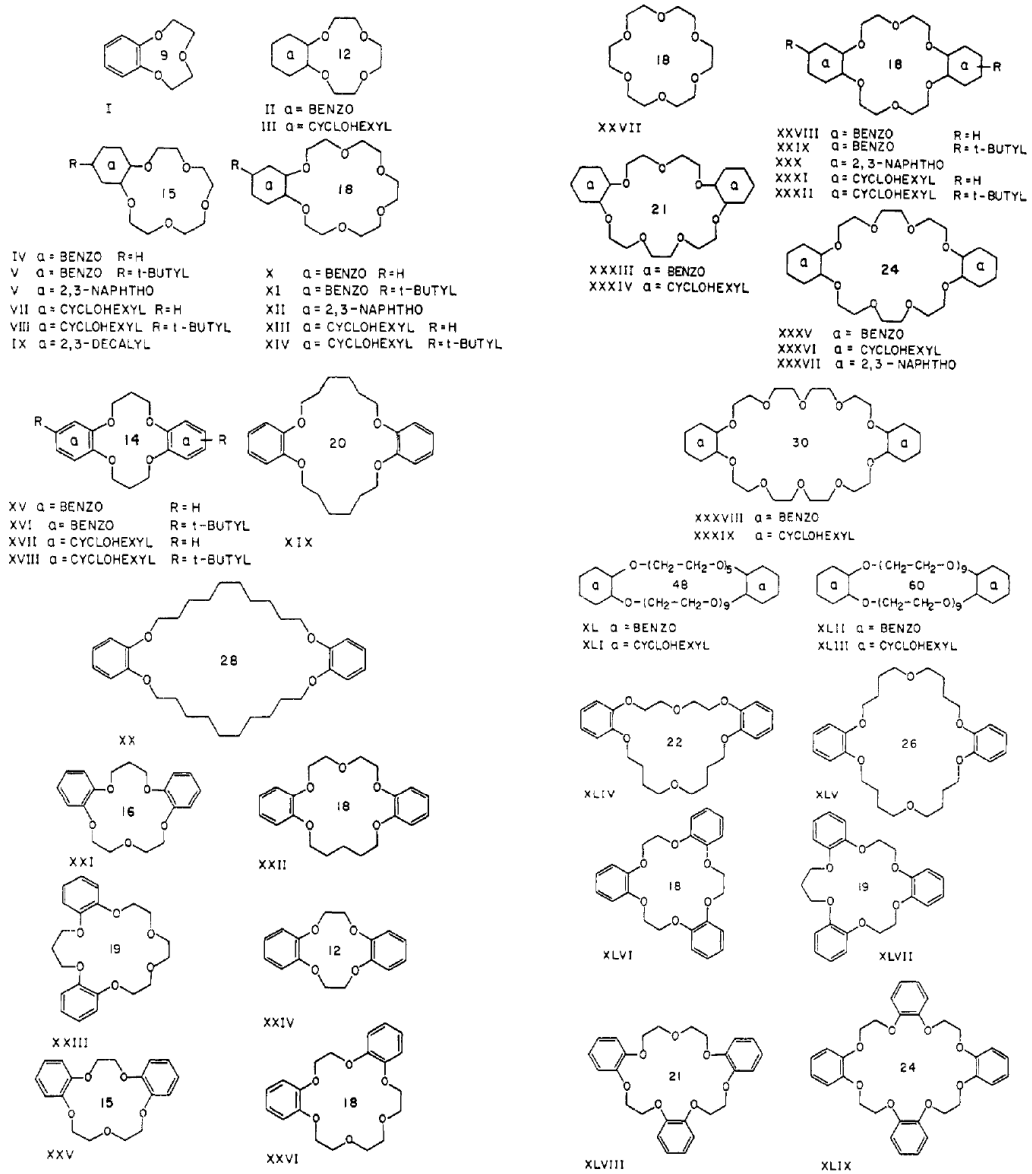
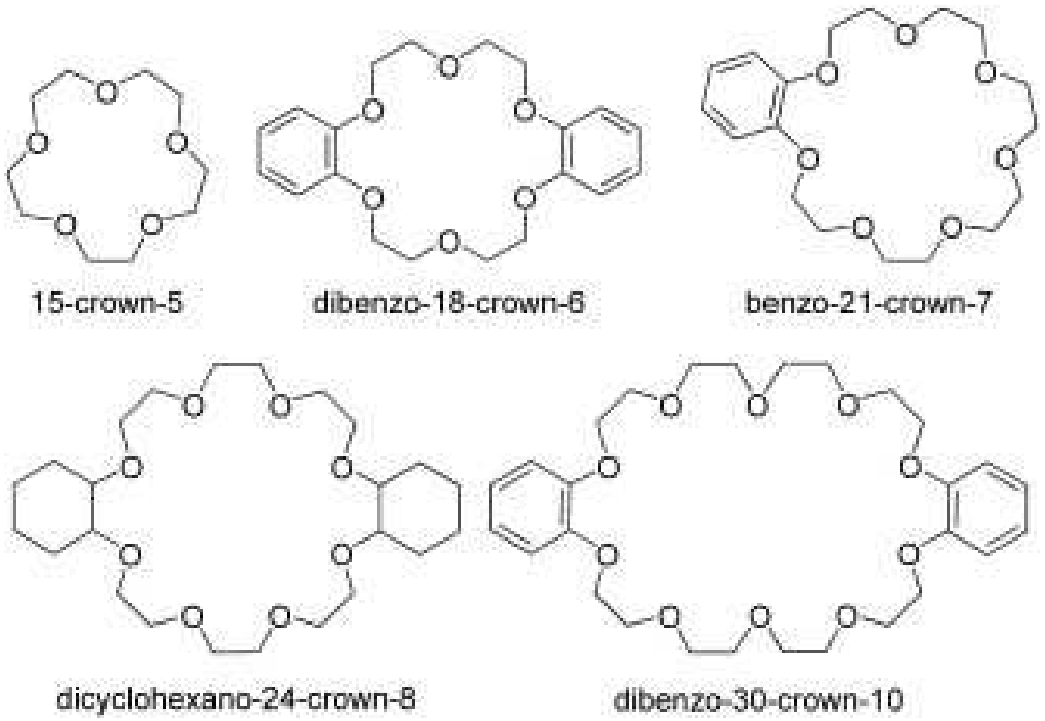
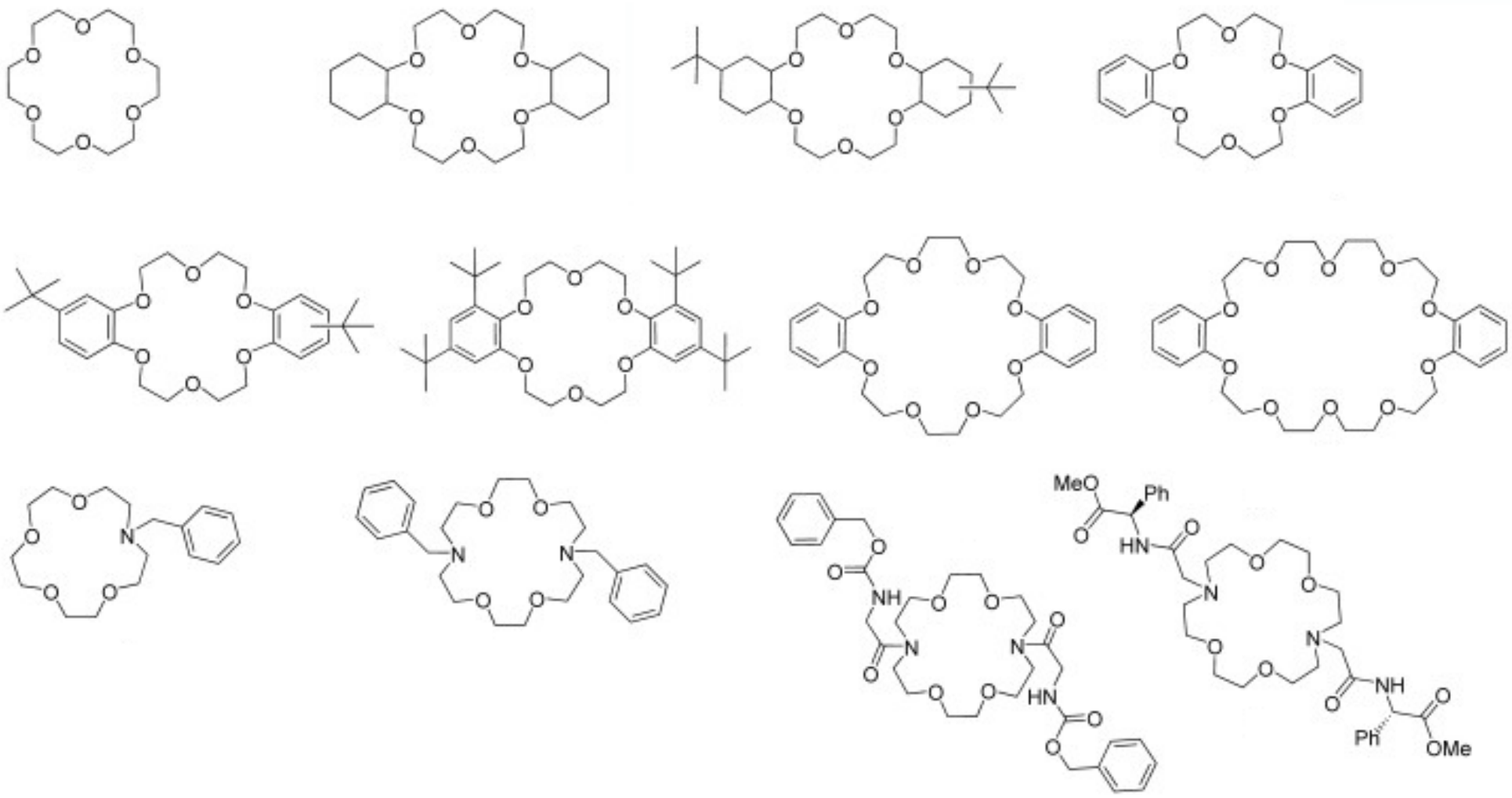
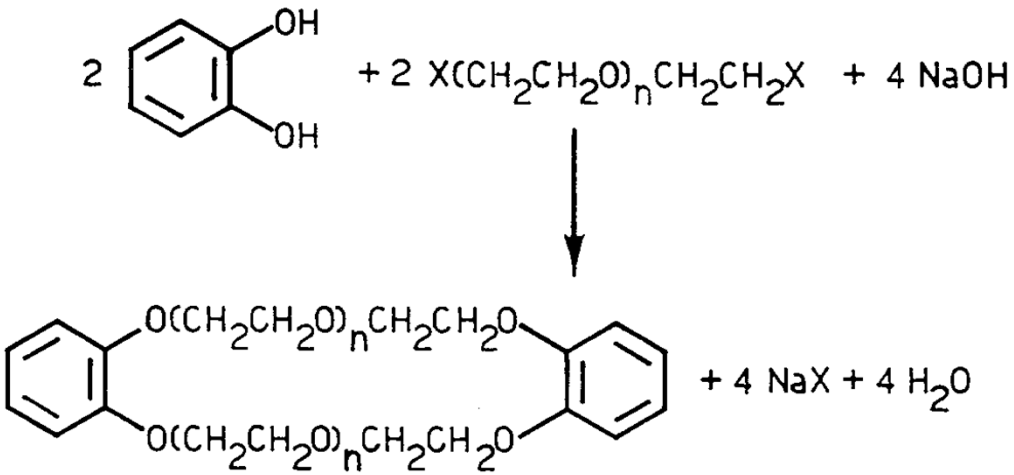


Figure 1. Structural formulas of cyclic polyethers.


15-crown-5
dibenzo-18-crown-6
benzo-21-crown-7
dicyclohexano-24-crown-8
dibenzo-30-crown-10

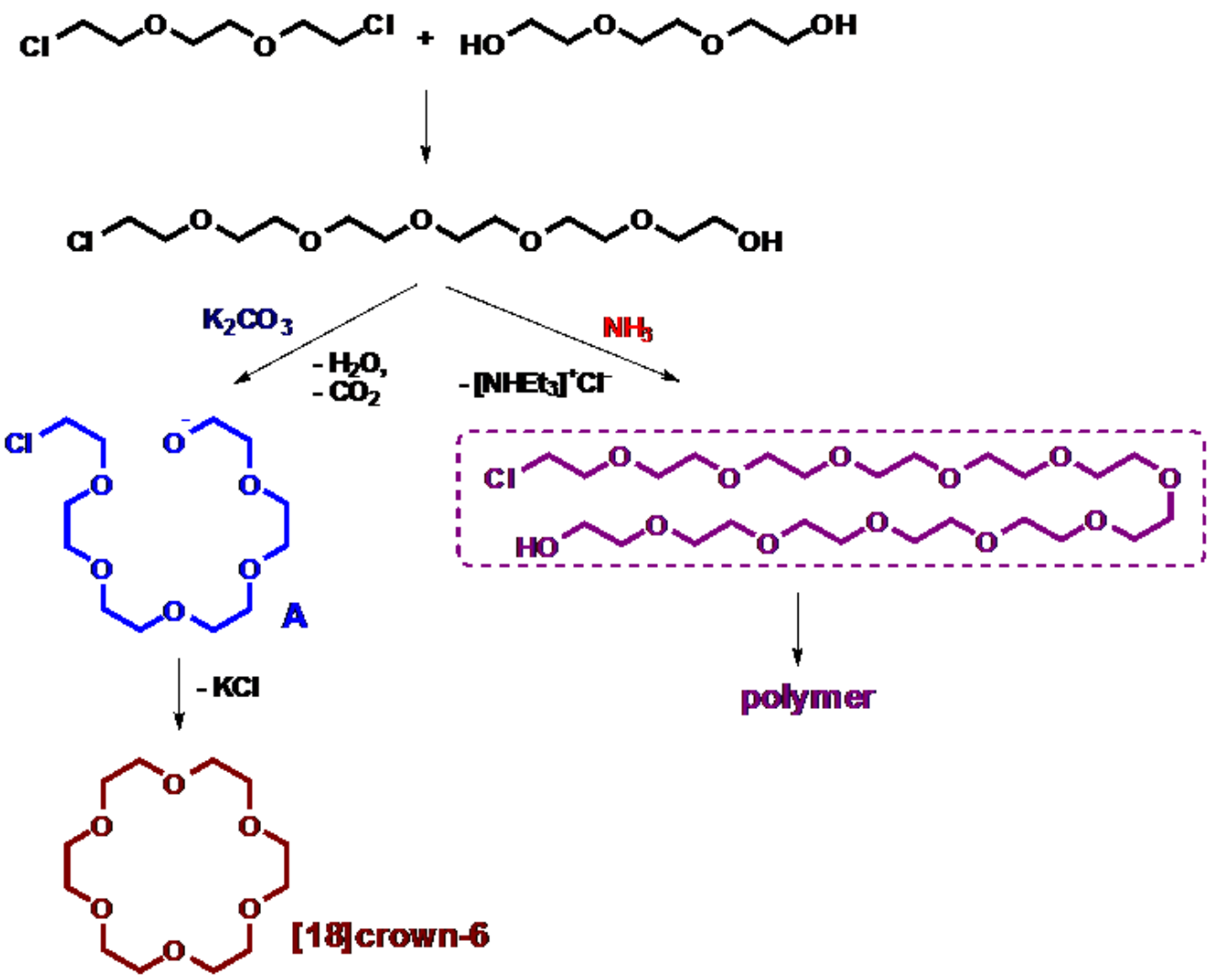

MeO
Ph
HN
NH
Ph
OMe

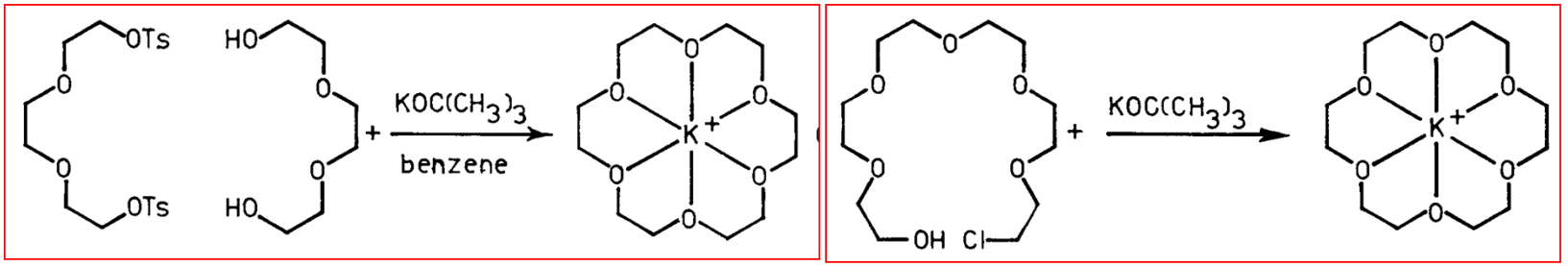
2.3.3.1 High Dilution Synthesis of Crowns



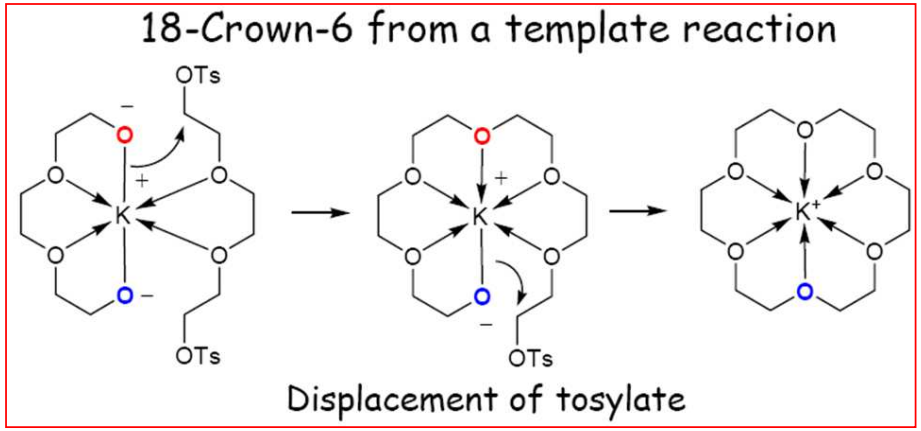
X = suitable leaving group such as Cl or OTosyl

2.3.3.2 Alternative Routes to 18-Crown-6




OTs
HO
KOC(CH3)3
benzene
OTs
HO
K+
OH
Cl
KOC(CH3)3
K+

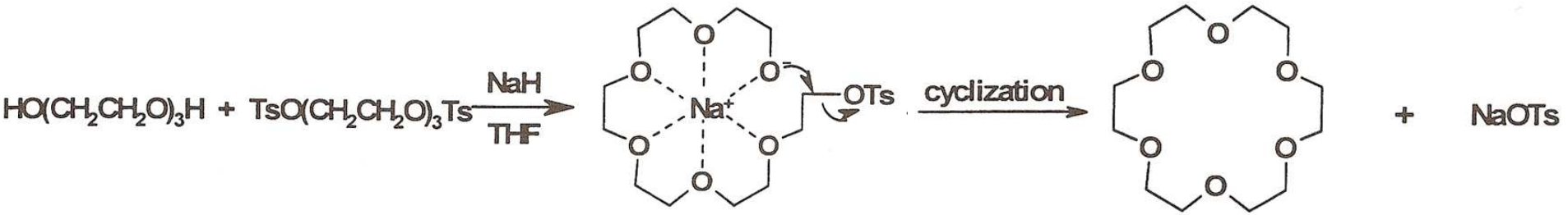
(REVISION)

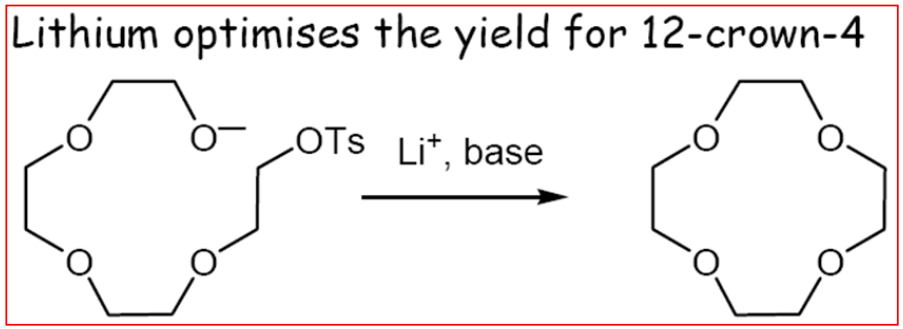

18-Crown-6 from a template reaction
OTs
OTs
K
OTs
K
K+
Displacement of tosylate

2.3.3.3 Template approach

Template approach

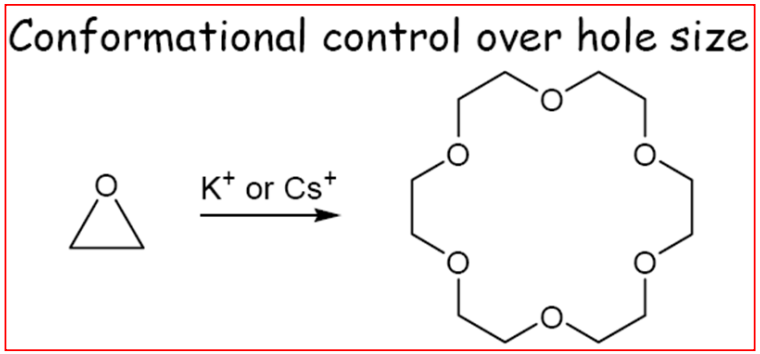
- In the template approach a template (normally a metal ion for polyethers) is used to preorganize the reactive end groups.
- In other words, the template used brings the two reactive groups close together to facilitate the cyclic structure formation.



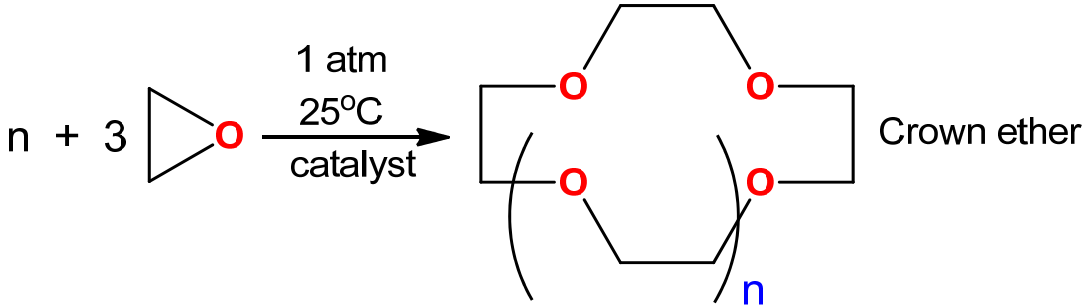


We will look at metal template effects again later in this lecture series.

Ethylene Oxide Oligomerisation

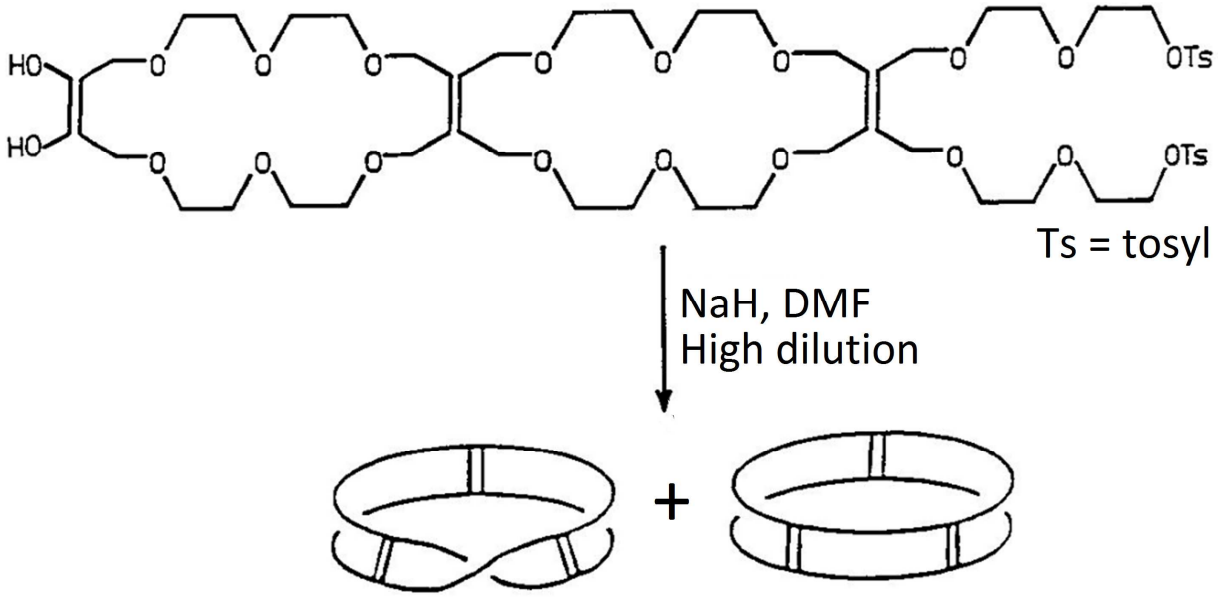


Product is very dependent on the metal catalyst employed

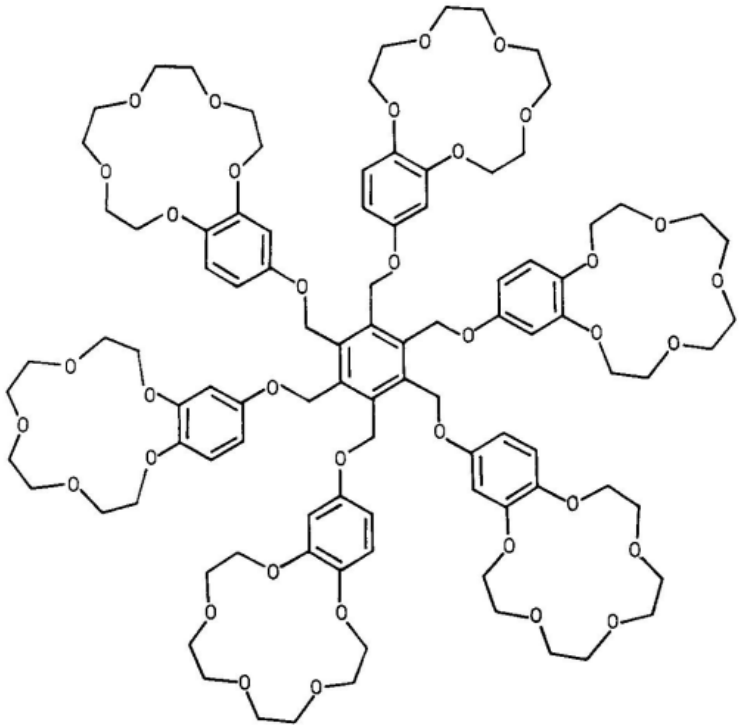


n	catalyst	Crown ether
3	$CsBF_4$	18-crown-6
2	$Cu(BF_4)_2$	15-crown-6
1	$Ca(BF_4)_2$	12-crown-4 (50%) + 18-crown-6 (50%)

Synthesis of ring structures

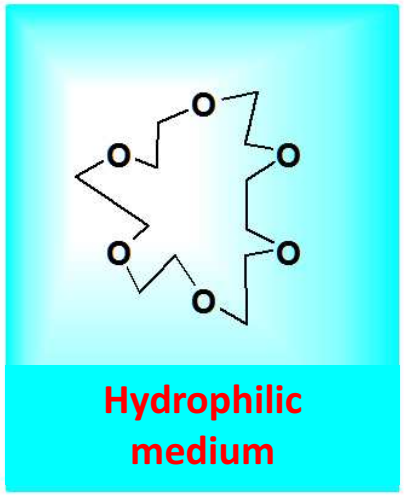


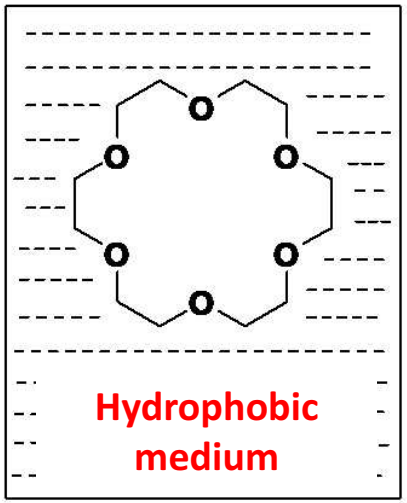
'Mobius strip' crowns

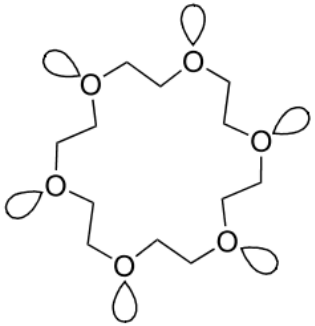


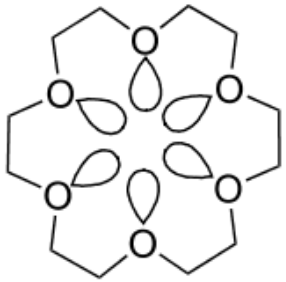
2.3.3.4 Polarity and Solubility

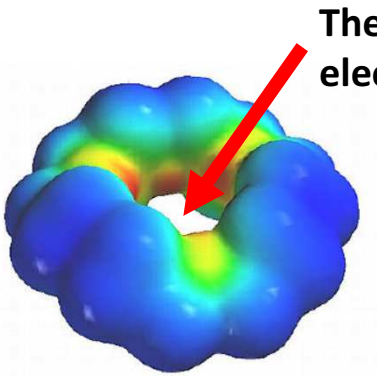
- O atoms: hydrophilic
- CH_2 fragments: hydrophobic or lipophilic
- Crown ether is soluble in most of organic solvents.











Electrostatic Interaction with metal ions in the cavity

Cation Complexes of Crown Ethers –Solubility Aspects

- Many simple crown ethers are moderately soluble in water.
- Marked changes in solubility often accompany complexation

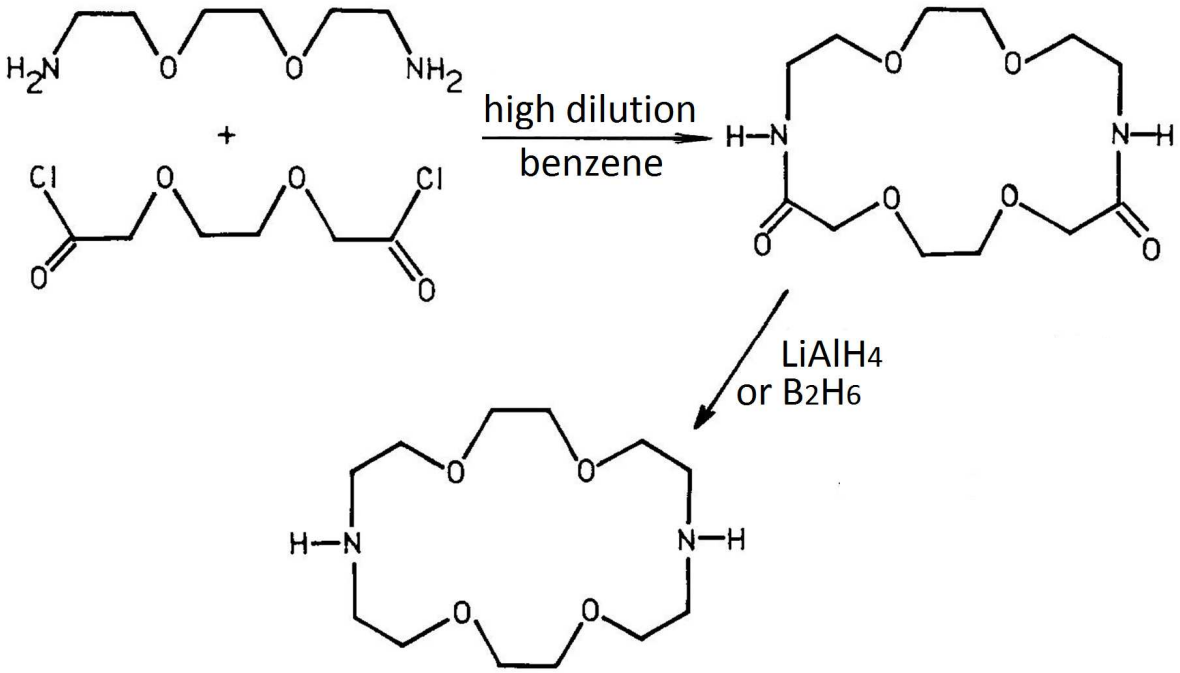
  – thus a crown in the presence of a metal salt may lead to an increase in the solubility of both.
- The solubility of 18-crown-6 in methanol is 1×10^{-3} mol dm^{-3}

  whereas the solubility of the KNCS complex is 100-fold greater.
- This has implications for the synthetic procedure for obtaining the metal complex.
- Surrounding a Lewis acid such as an alkali metal ion with a crown results in

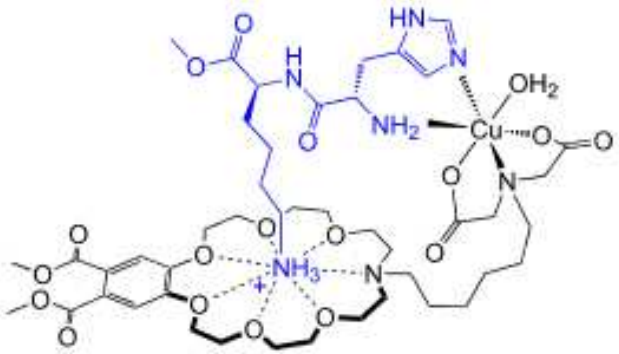
  an increase in the hydrophobic nature of the resulting cation

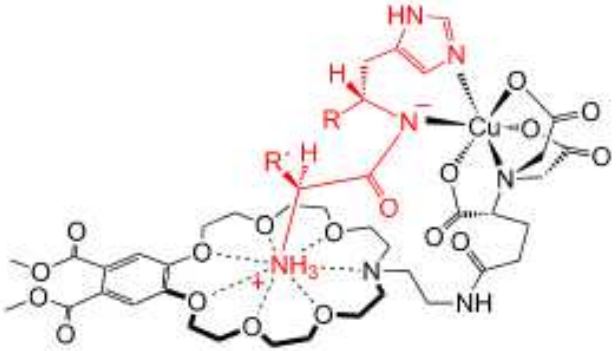
  – greater solubility of the ion-paired complex in non-polar organic solvents is the result.

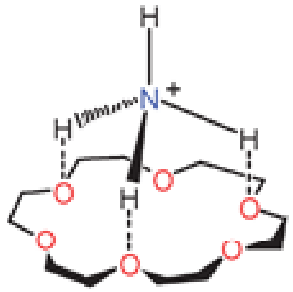
2.3.3.5 Elaborated crown ether ligand systems



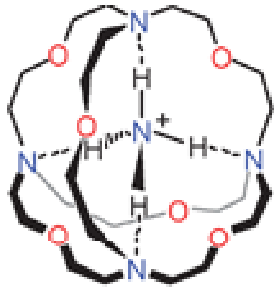
1,10-diaza-18-crown-6



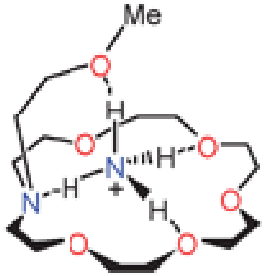




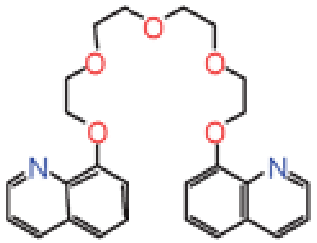
18-Crown-6·NH_4^+ complex (**1**)



Cryptand·NH_4^+ complex (**2**)

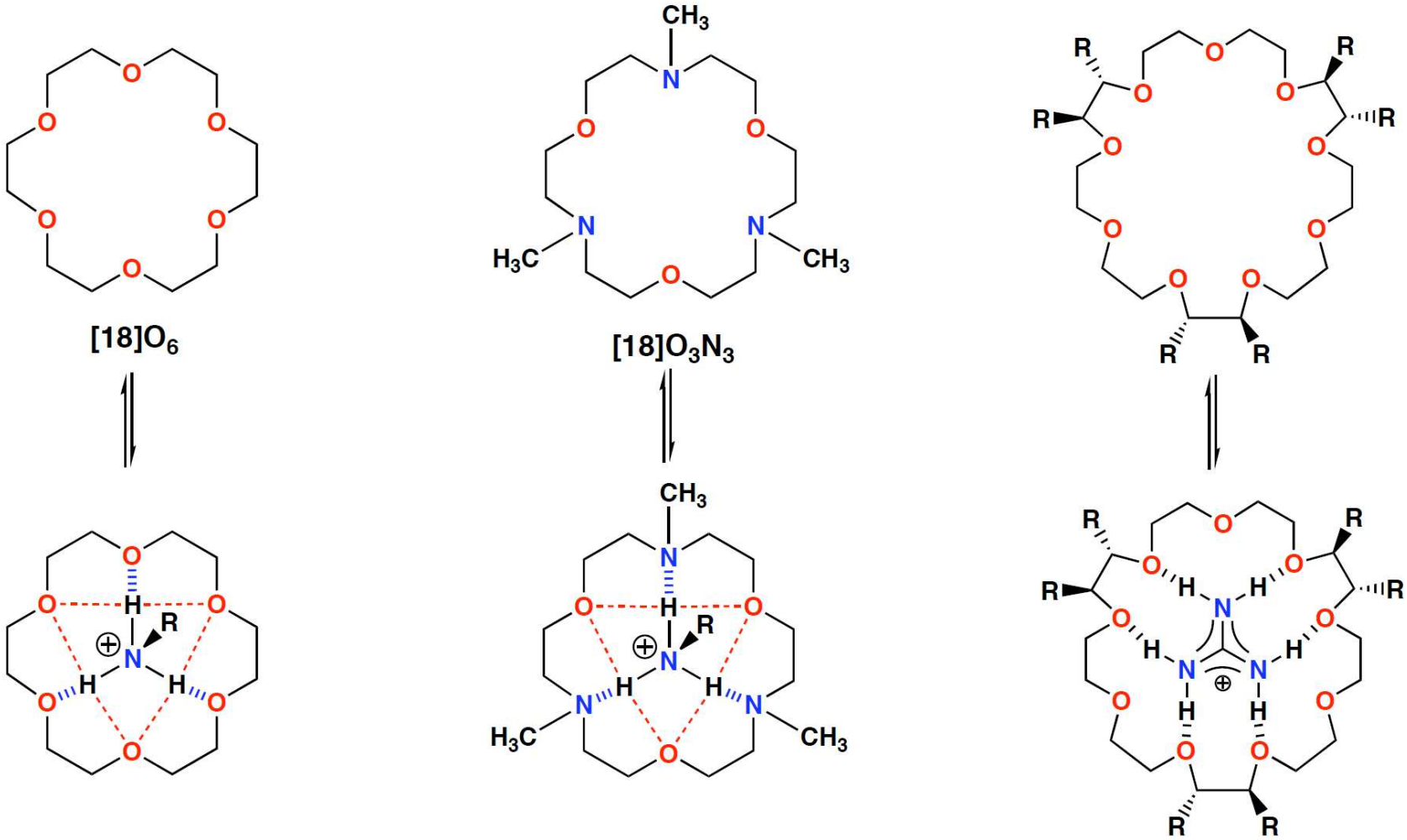


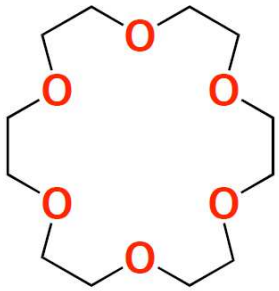
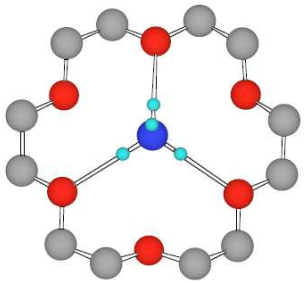
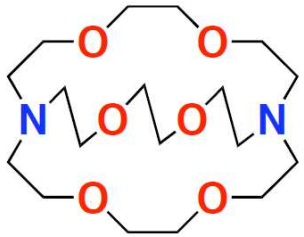
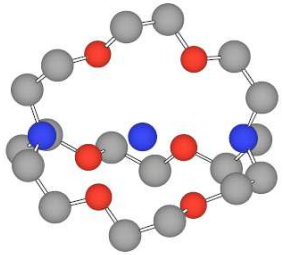
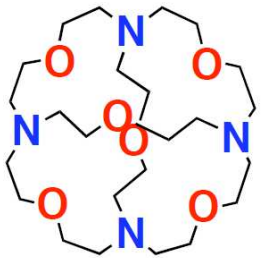
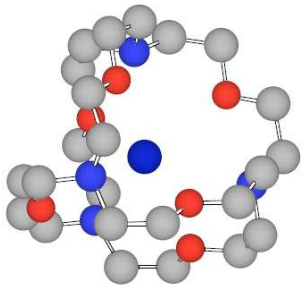
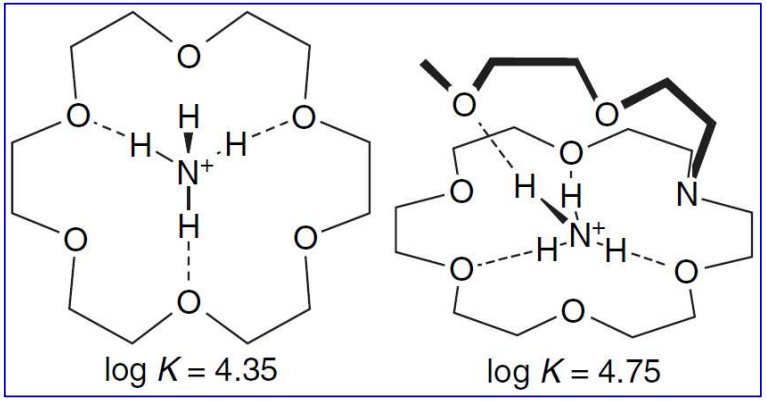
Lariat crown·NH_4^+ complex (**3**)



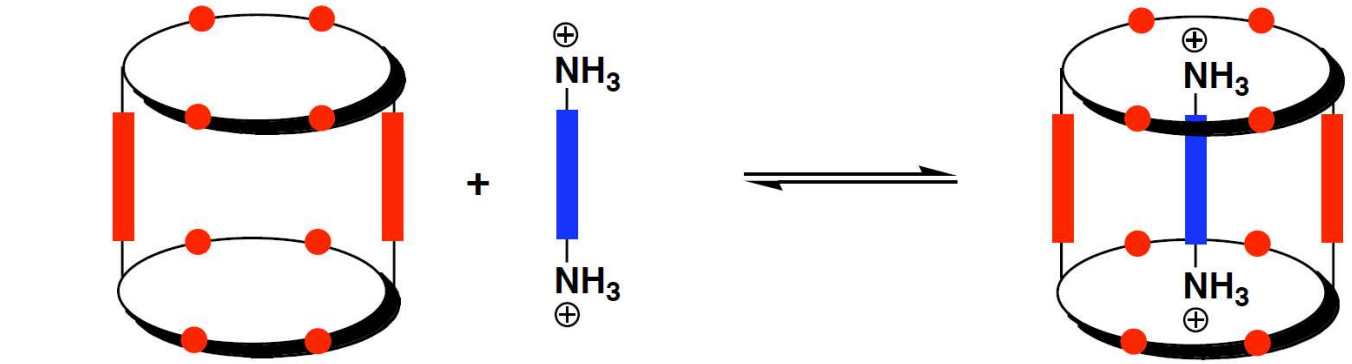
L

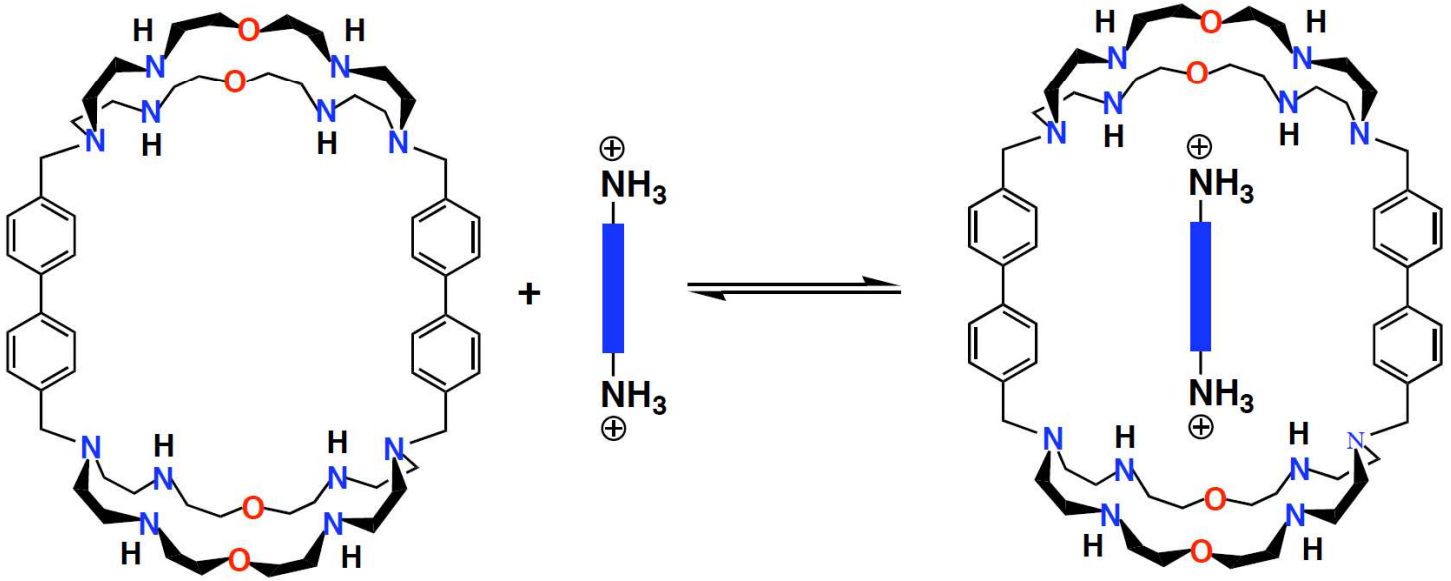
Establishment of H bonds with amines and ethers



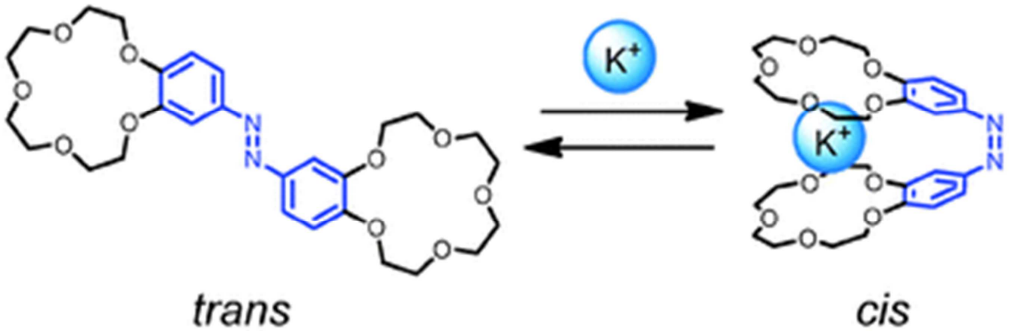







log K = 4.35
log K = 4.75

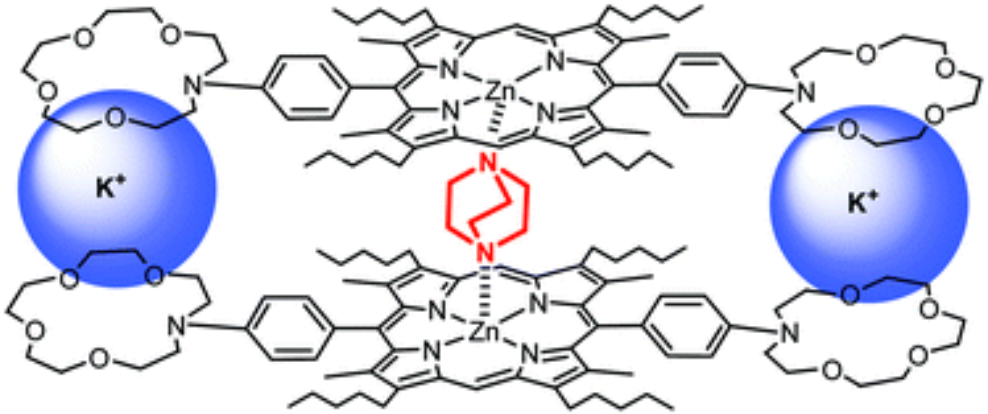
Linear recognition of diammonium

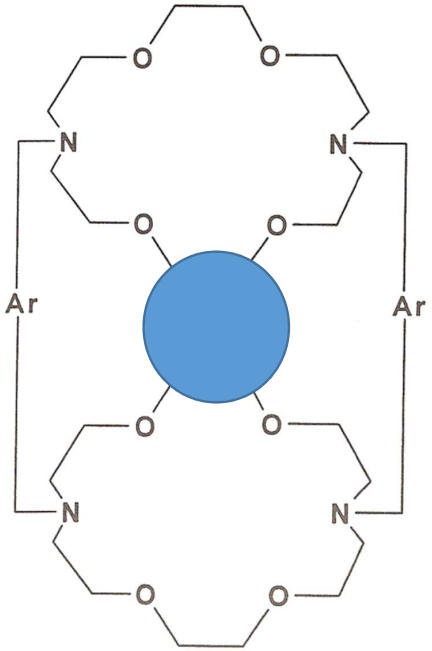


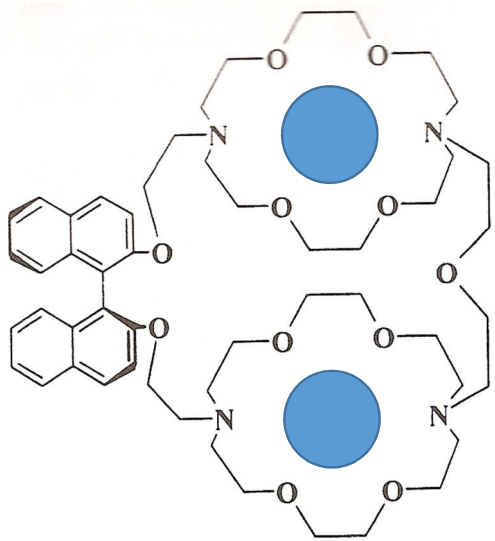


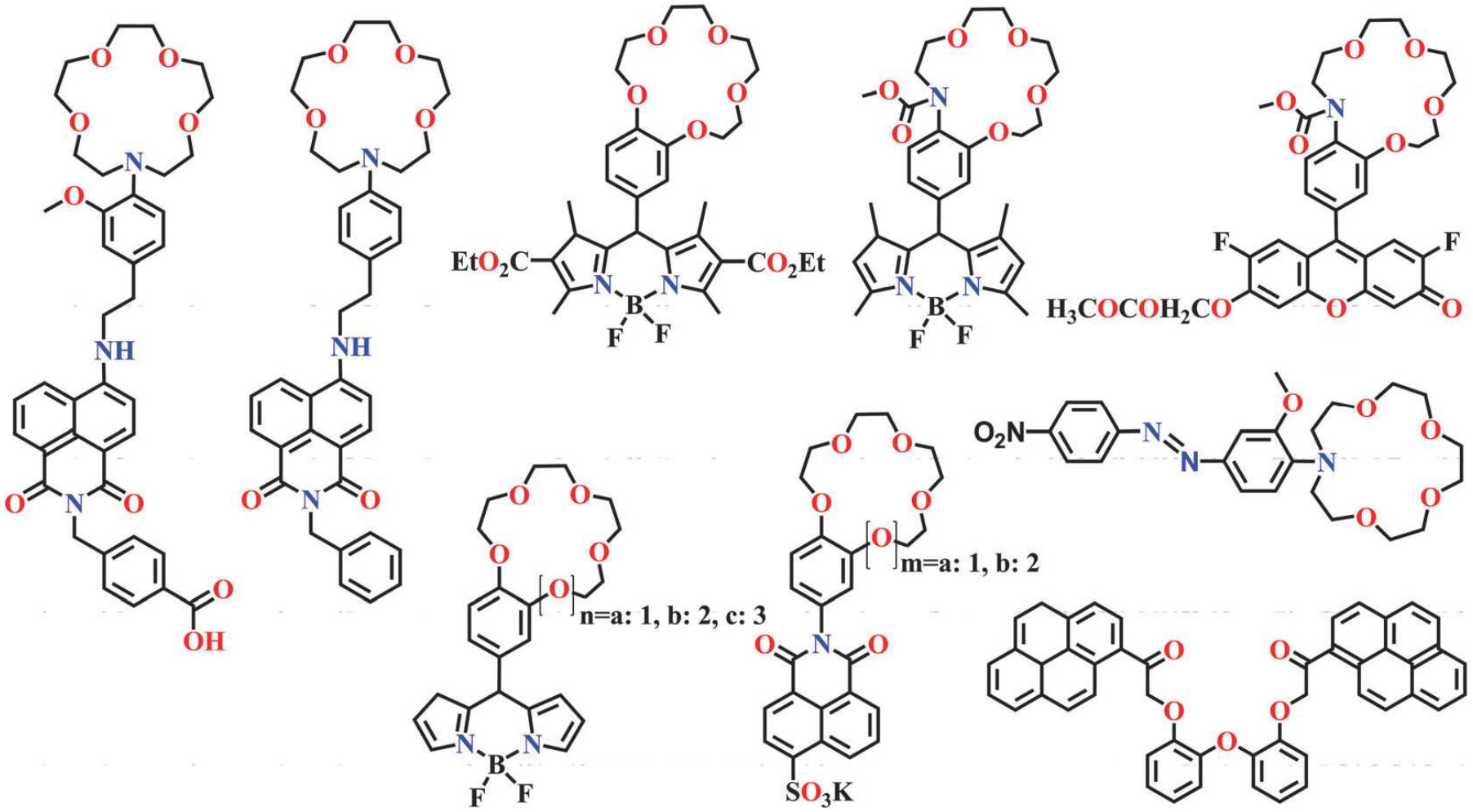
2.3.3.6 Binding of more than one cation or making a sandwich complex











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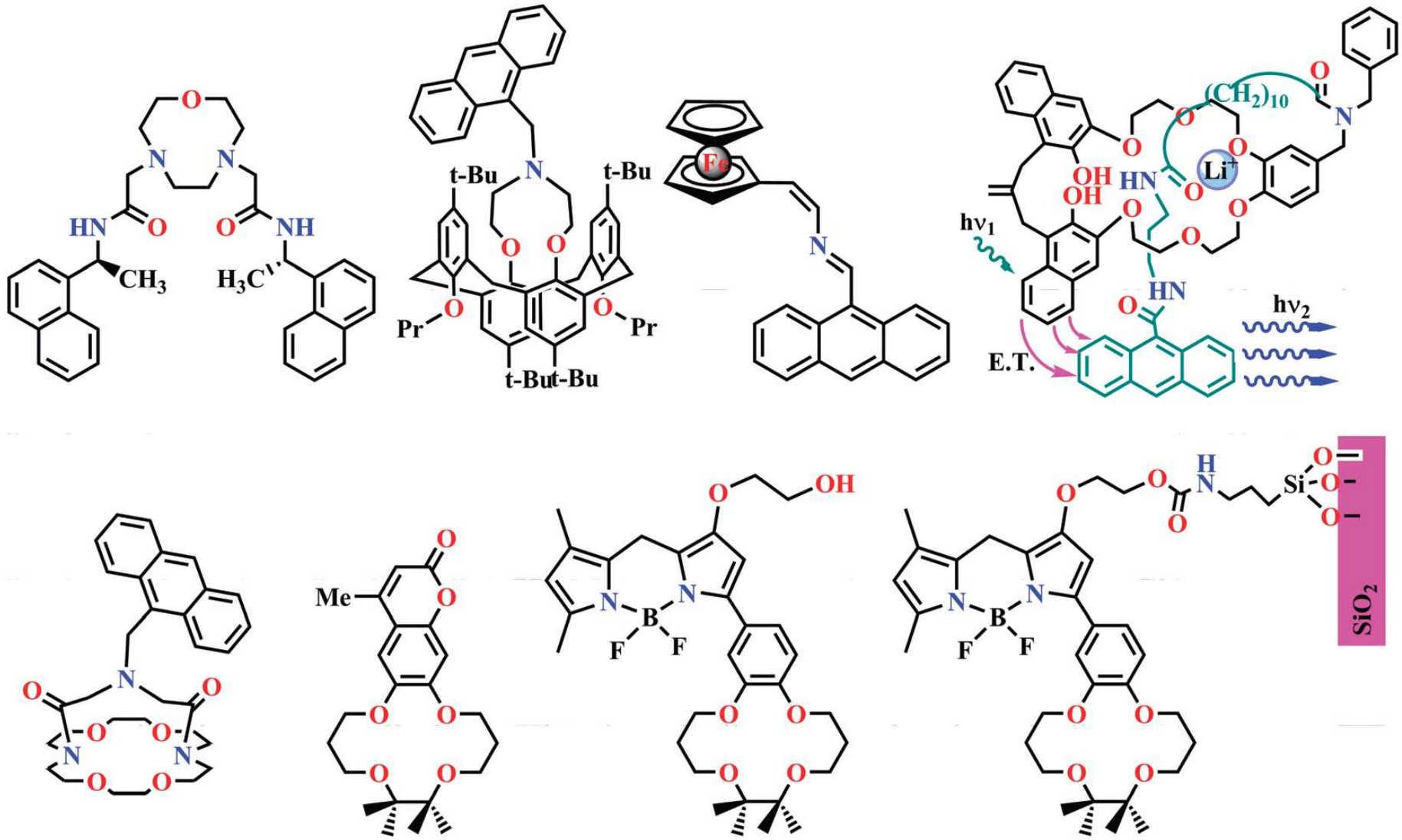
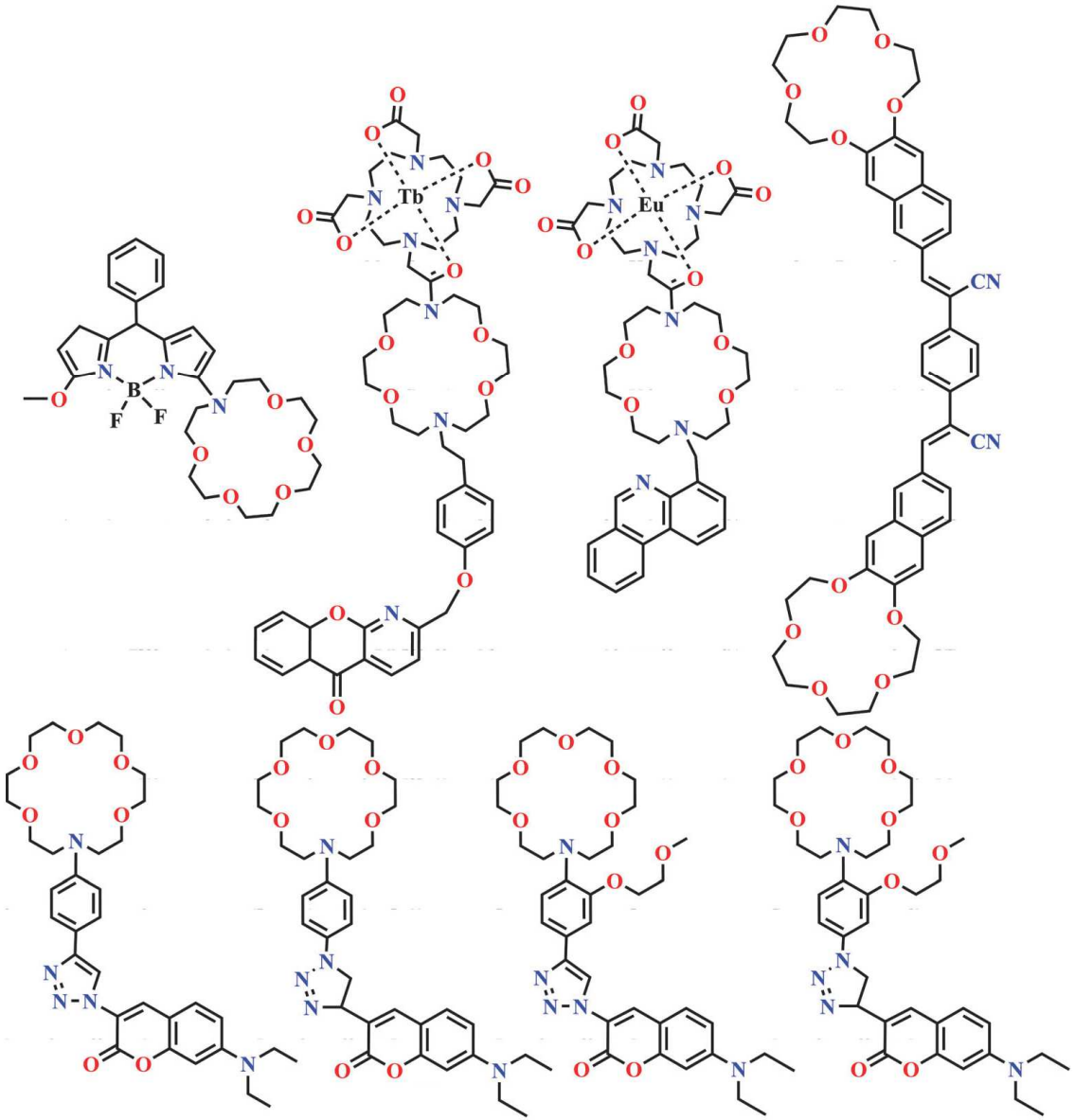
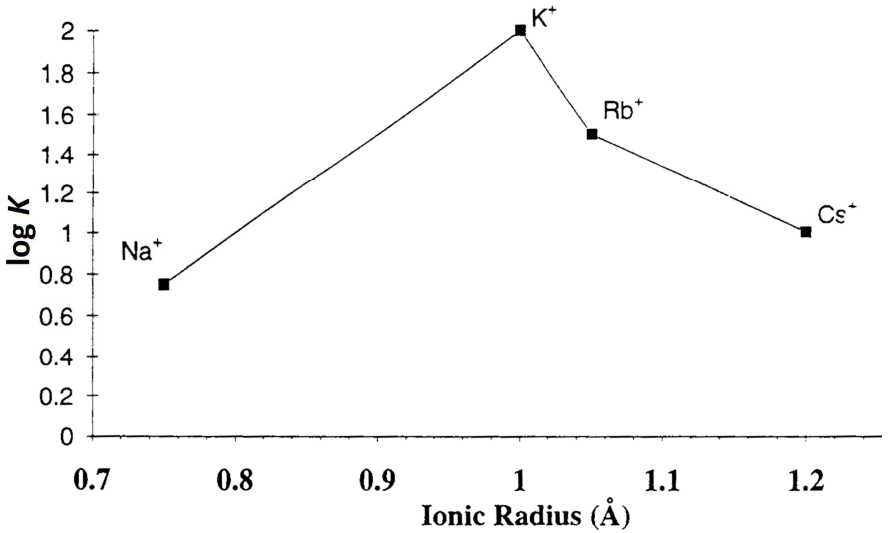

HN
O
O
NH
CH3
H3C
t-Bu
t-Bu
Pr
Pr
t-But-Bu
Fe
N
(CH2)10
Li+
OH
OH
hν1
hν2
E.T.
Me
OH
B
F
F
Si
SiO2


Tb
Eu
CN
CN

2.3.3.7 Crown ethers - Selectivity for Metal Ions

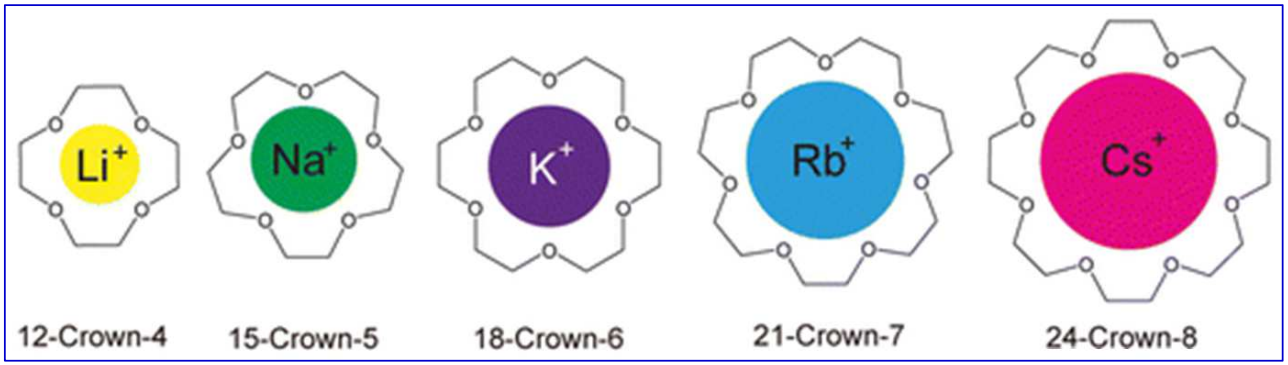
Comparison of the diameters of different alkali metal ions and crown ethers

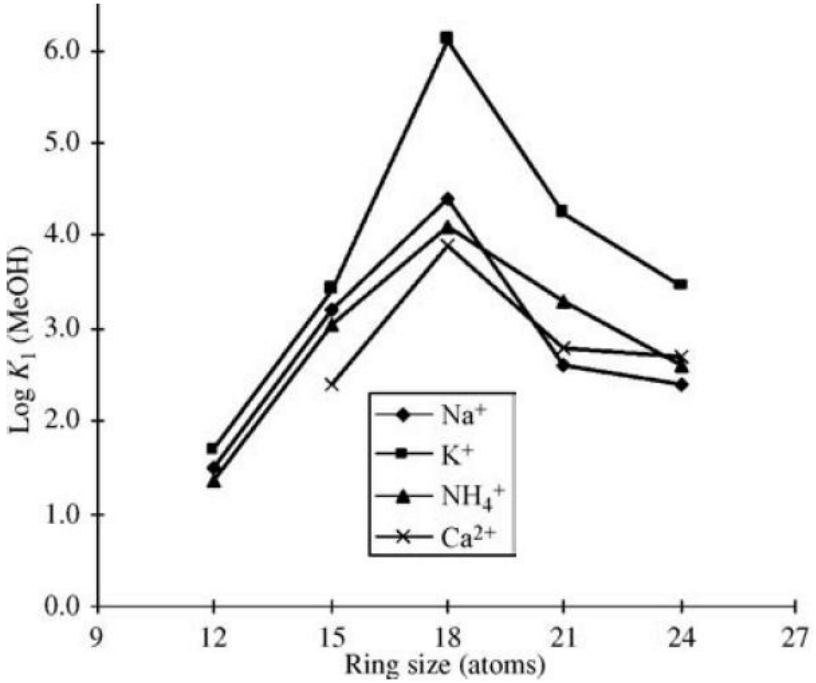
Cation	Diameter (Å)	Crown ether	Cavity diameter (Å)
Li^+	1.36	[12]crown-C4	1.20–1.50
Na^+	1.90	[15]crown-C5	1.70–2.20
K^+	2.66	[18]crown-C6	2.60–3.20
Cs^+	3.38	[21]crown-C7	3.40–4.30



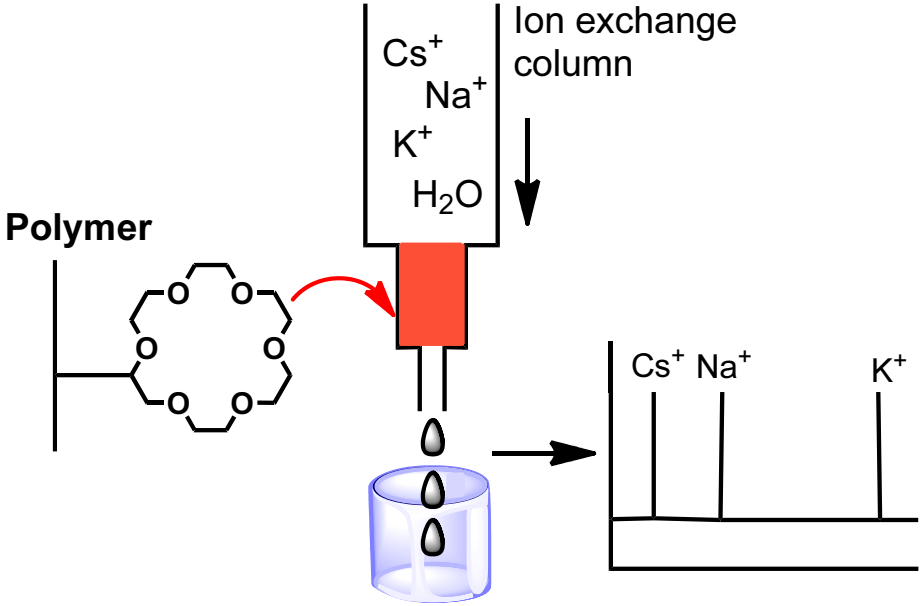
1:1 Complexes of 18-Crown-6 and the Alkali Metals

❑ **Initial propose**: an optimal spatial fit between crown ethers and particular cations.

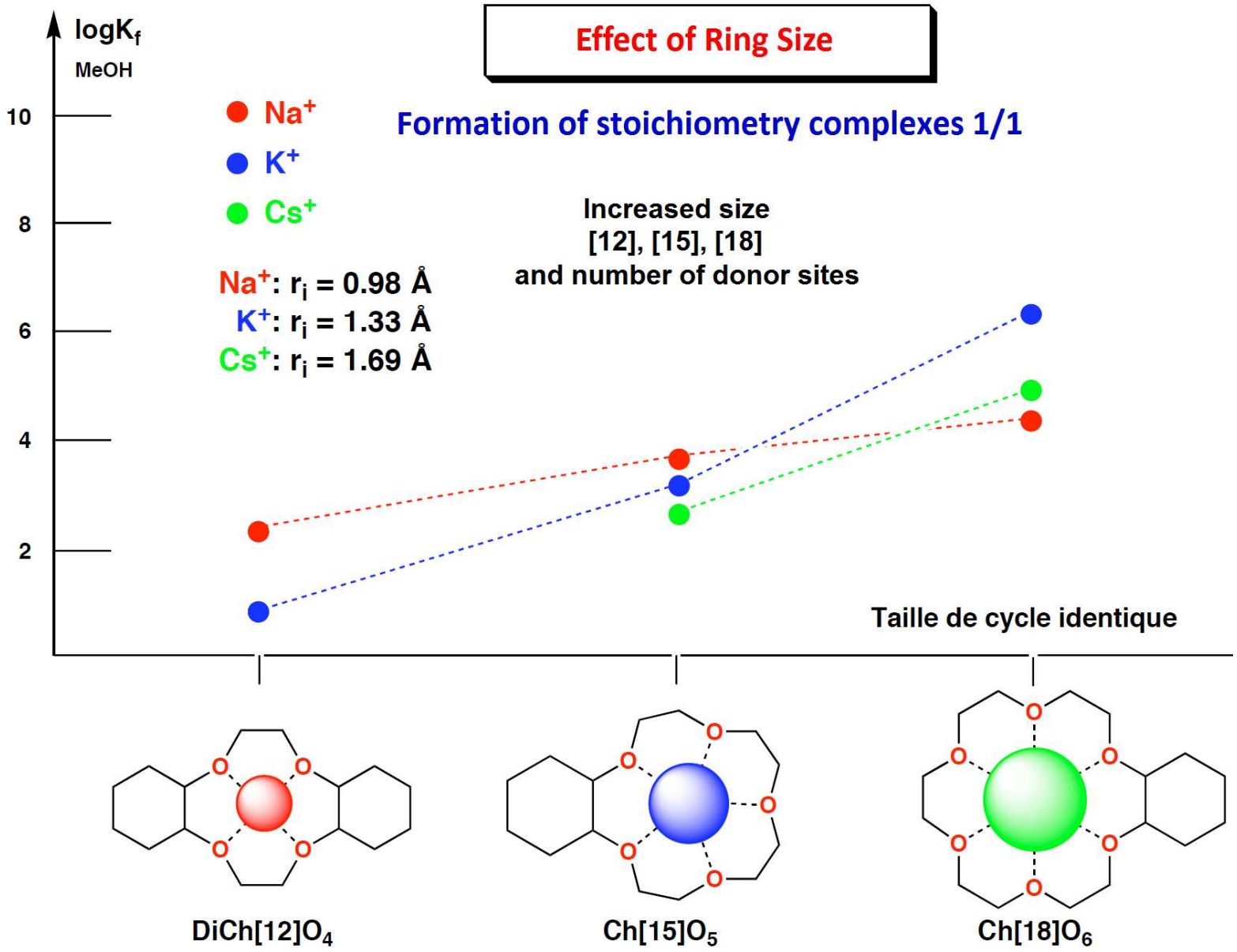




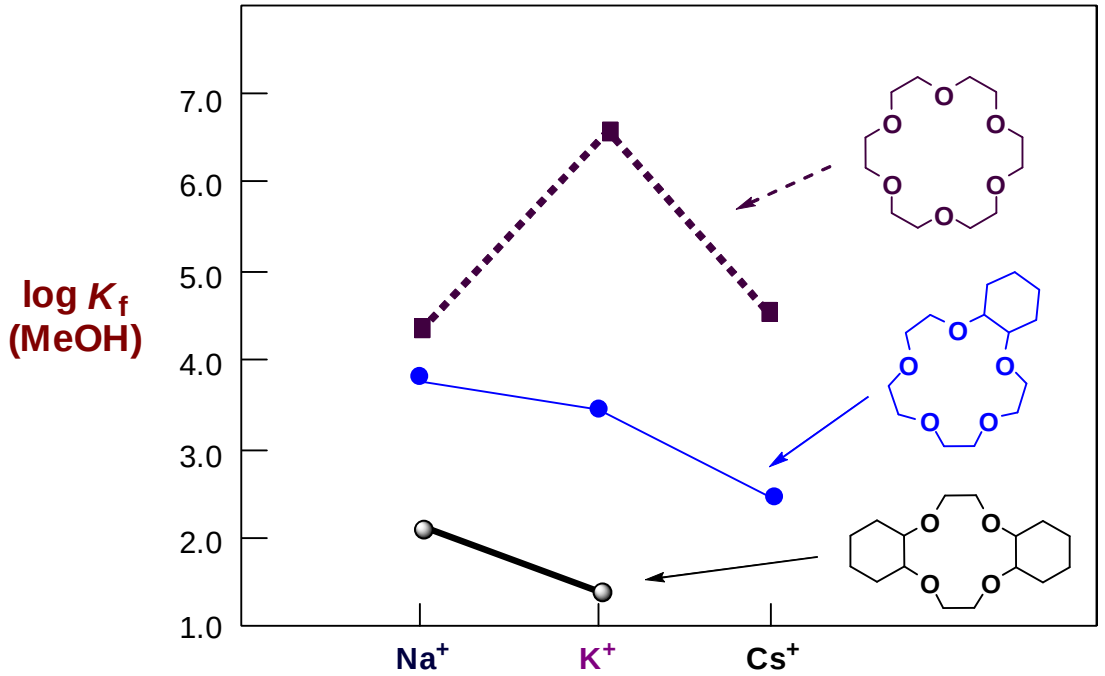
Binding constants obtained for
various cations and crown ethers (log *K*, methanol, 20 ^{O}C)



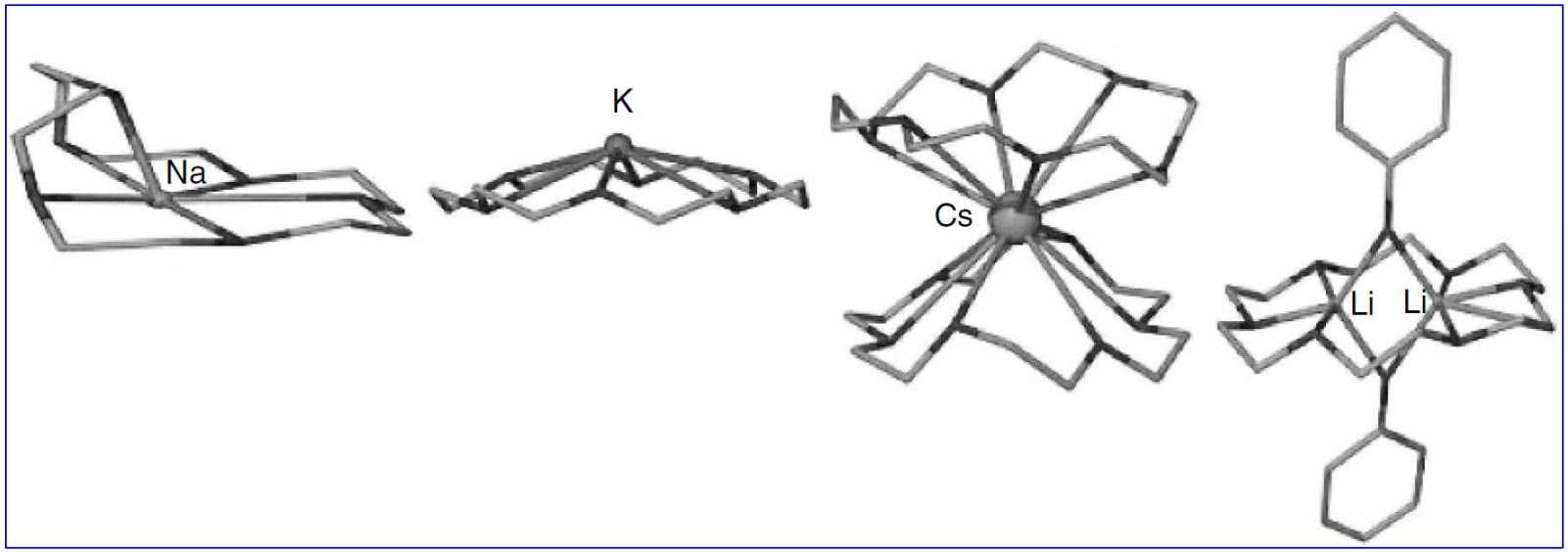
Selectivity of crown ether


Effect of Ring Size
Formation of stoichiometry complexes 1/1
logK$_f$
MeOH
10
8
6
4
2
Na$^+$
K$^+$
Cs$^+$
Na$^+$: r$_i$ = 0.98 Å
K$^+$: r$_i$ = 1.33 Å
Cs$^+$: r$_i$ = 1.69 Å
Increased size
[12], [15], [18]
and number of donor sites
Taille de cycle identique
DiCh[12]O$_4$
Ch[15]O$_5$
Ch[18]O$_6$

Binding topologies of the caton depending on the crown ring size

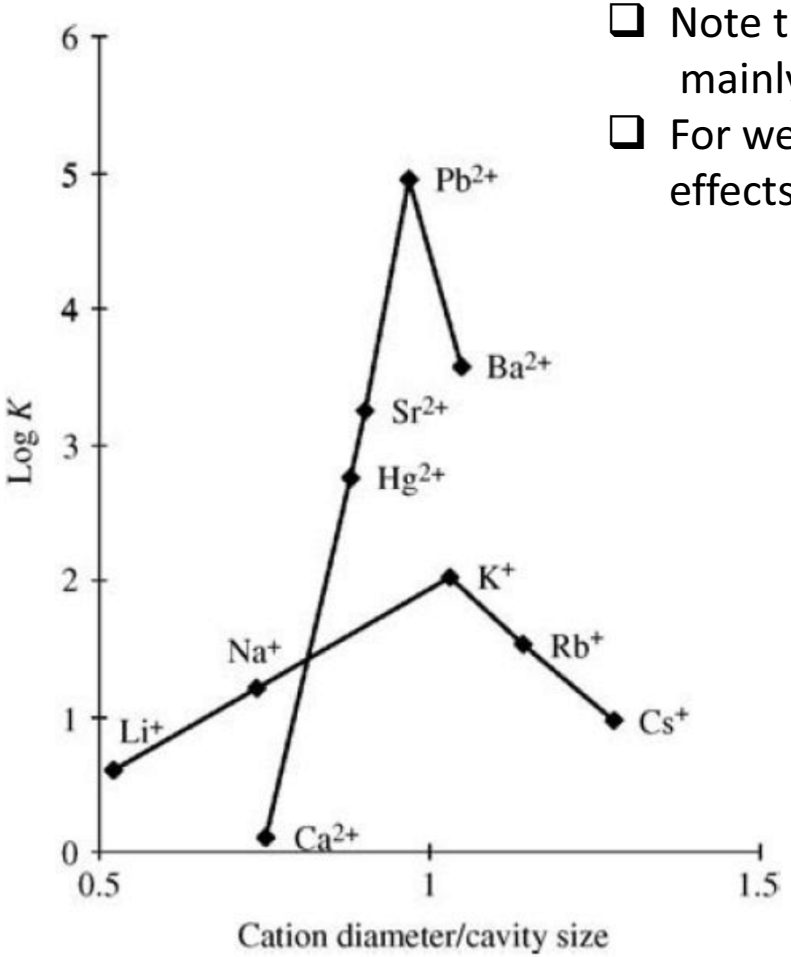


- **Complementarity** between the crown ether and guest by X-ray crystallography.
- The crown ethers are highly flexible molecules.
- There is some relationship between size-match and binding constants.



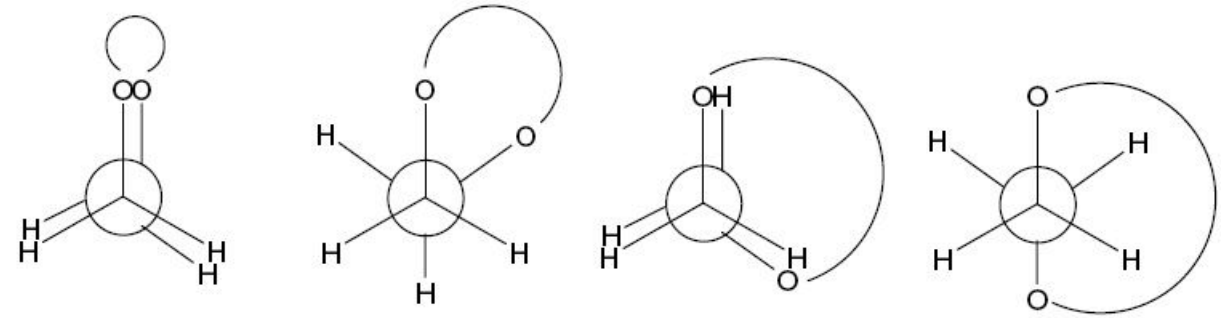
X-ray crystal structures of [18]crown-6 containing Na^+, K^+, Cs^+ and two Li^+ ions (phenolate salt).

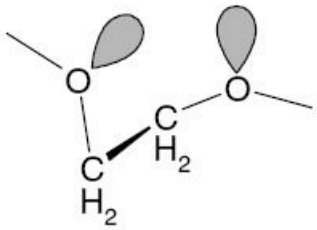
The effect of charge

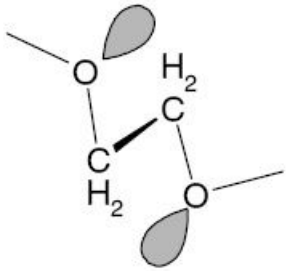


- Note that Ca^{2+} is bound only weakly by a large variety of crown ethers, mainly due to its small size and large hydration energy.
- For well-matched cations and cavities, in the absence of large hydration effects, the formal positive charge on the cation is a dominant factor.

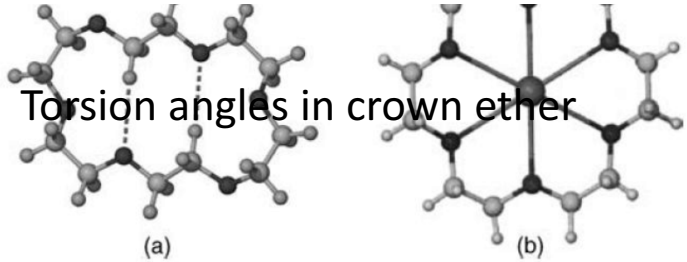
Conformational Characteristics of Crown Ethers





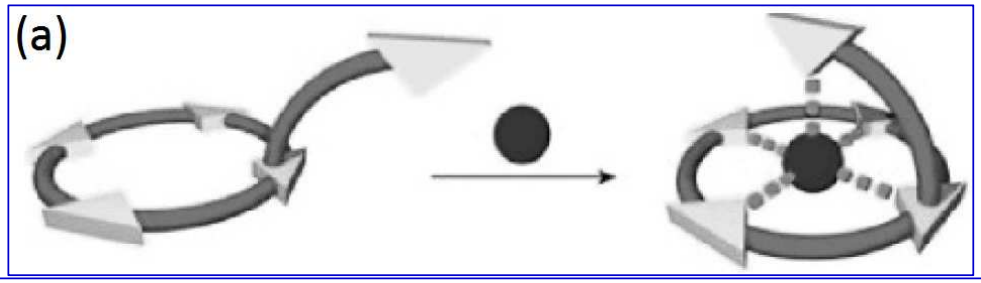


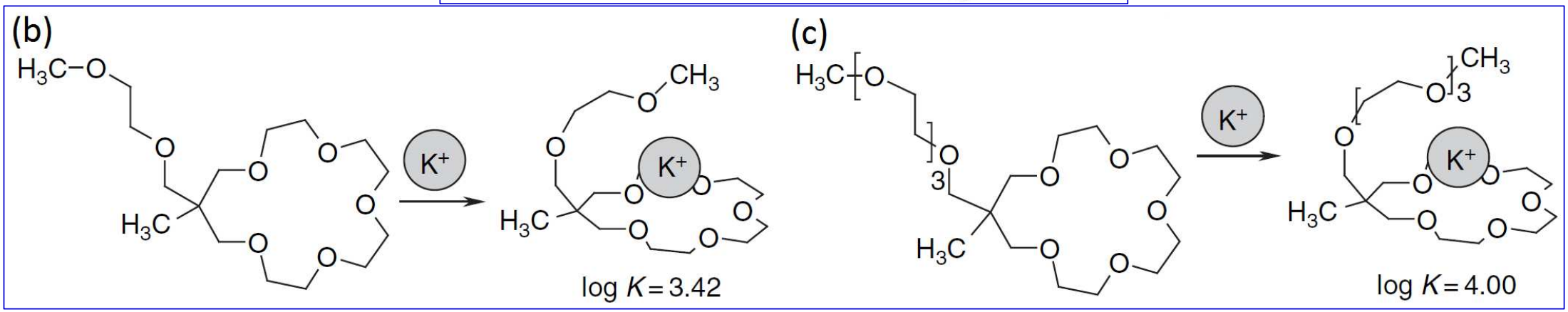
Torsion angles in crown ether



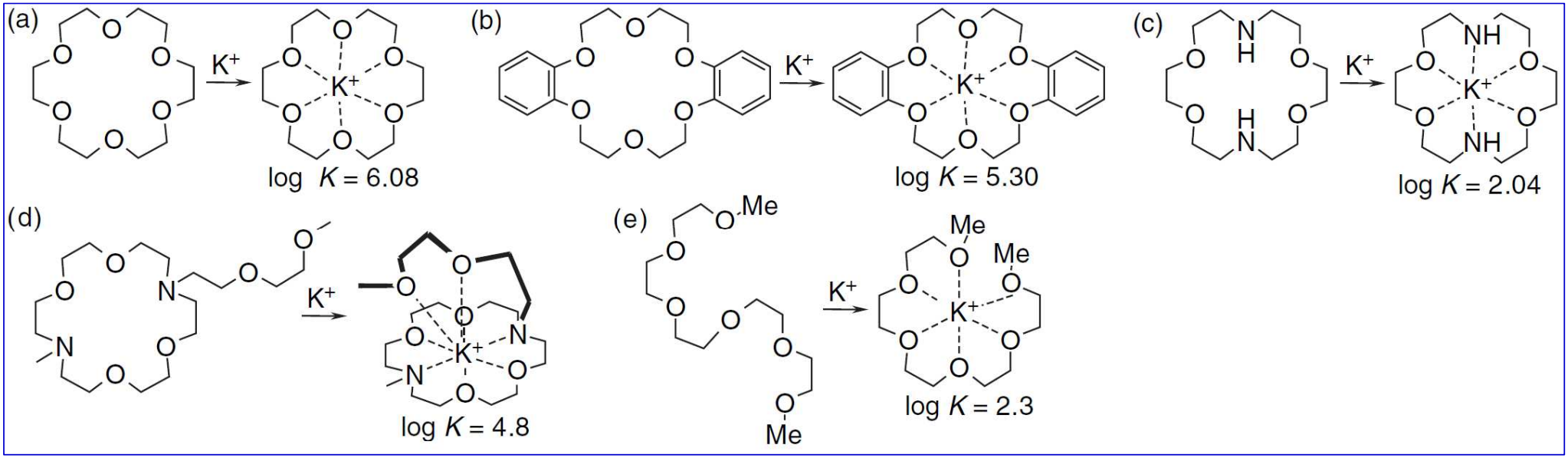
X-ray crystal structures of (a) free [18]crown-6 showing intramolecular CH···O hydrogen bonds with (b) the potassium complex of [18]crown-6.

- **Lariat ethers**
  Compounds that contain a single side arm attached to a macrocycle (often by the N atom)
- **The side arm**: flexible but contributes to the guest cation in a three-dimensional array (as cryptands), while stronger complexation than in podand systems.
- The *pseudo*-podand arm comes over the face of the macrocycle and binds to the cation that has been encapsulated within the host.





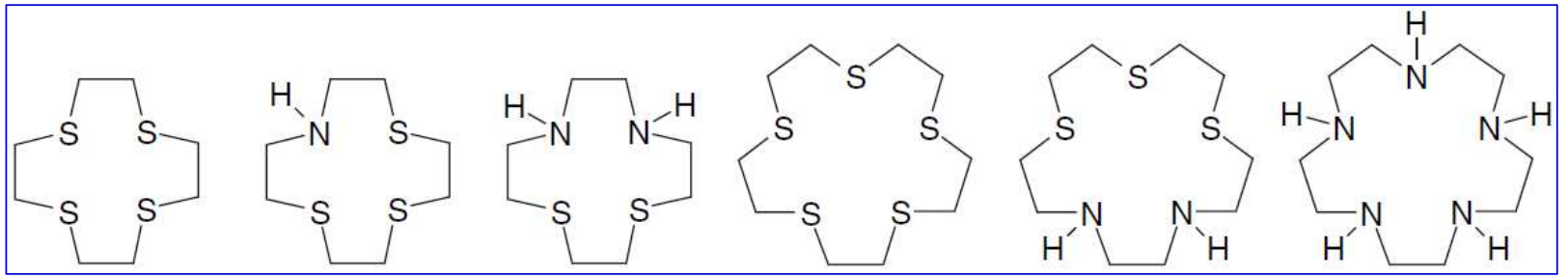
(a) one side armed macrocycle, (b) cation within the cavity and (c) a longer lariat side.

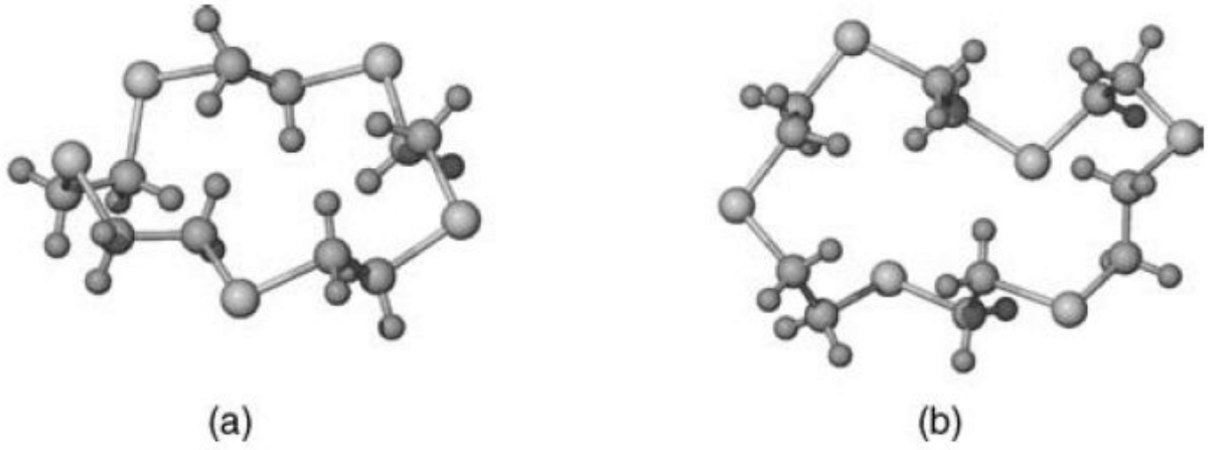


The binding constants (MeOH, 25 °C) of a potassium ion bound to: (a) [18]crown-6; (b) dibenzo[18]crown-6; (c) diaza[18]crown-6; (d) a lariat ether; (e) the podand pentaethyleneglycol.

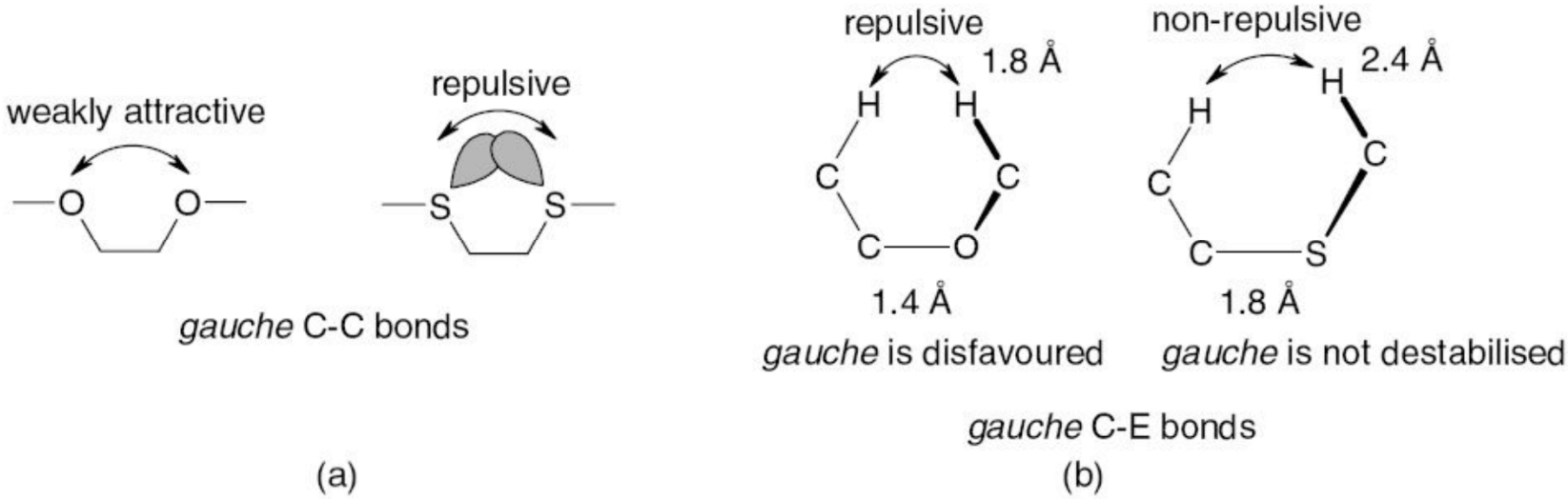
2.3.3.8 Heterocrown ethers

- ***Heterocrowns***: O, N and S are the three most common heteroatoms
- By selectively exchanging the type of atom within a crown ether scaffold for softer donor atoms there is a dramatic change in the selectivity of the host for softer metal cations.
- For example, Ag^+ is a large, polarisable, heavy-metal ion that forms more stable complexes with soft donor atoms, such as sulfur.

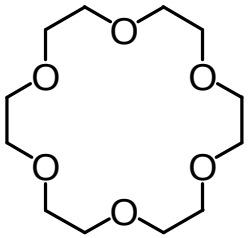


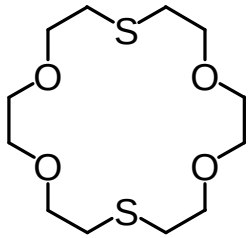


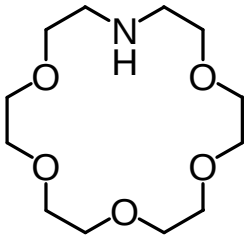
X-ray crystallographically-derived structures of (a) [15]ane-S5 and (b) [18]ane-S6.

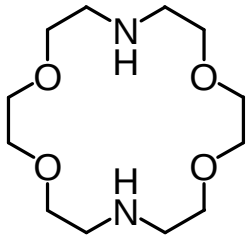


Influence of donor type on complexation behaviour (log*K* values)



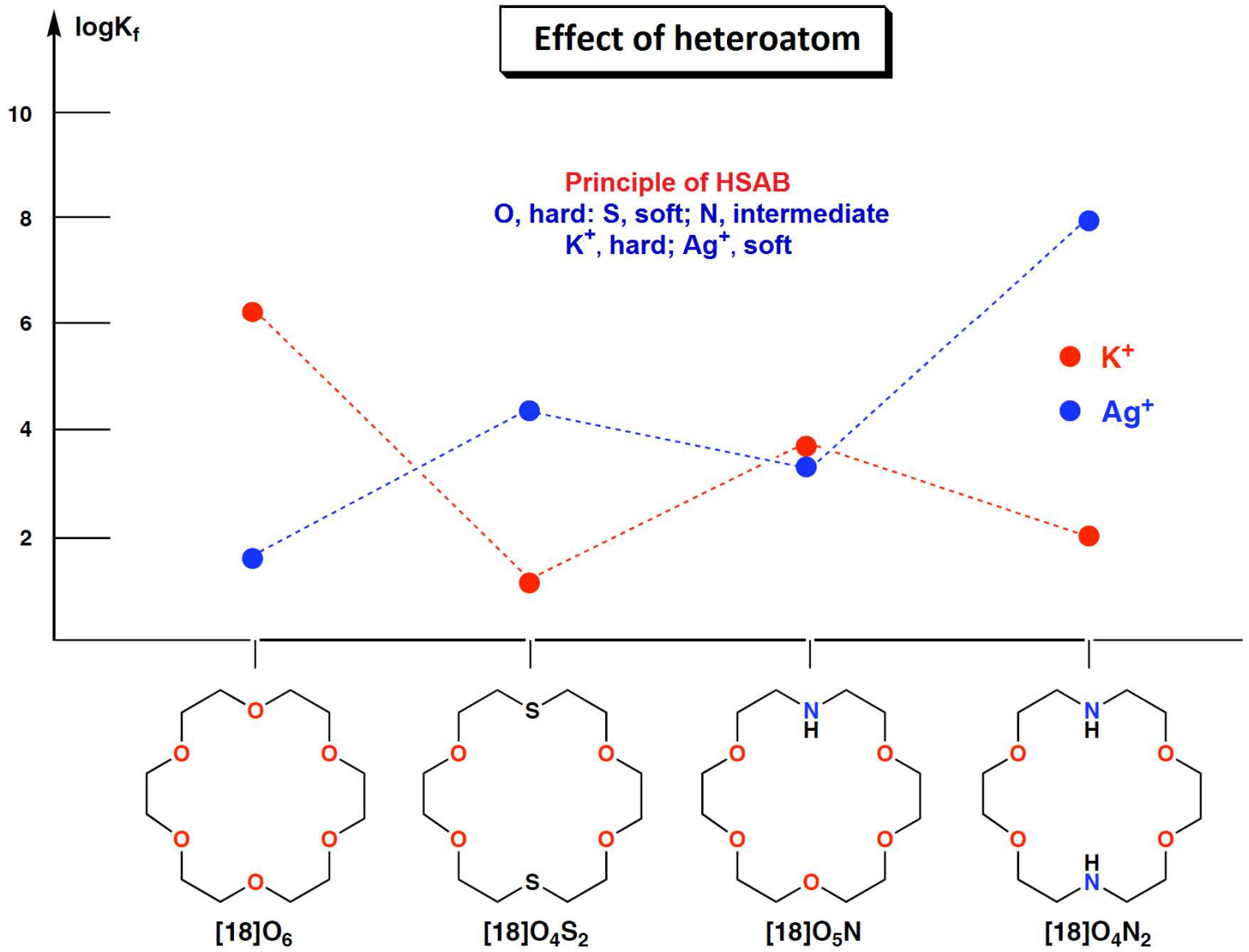






K^+ (a)	6.10	1.15	3.90	2.04
Ag^+ (b)	1.60	4.34	3.30	7.80

Note: radius of K^+ = 2.66 Å; radius of Ag^+ = 2.52Å. (a) measured in MeOH; (b) measured in H_2O


Effect of heteroatom
logK$_f$
10
8
6
4
2
Principle of HSAB
O, hard: S, soft; N, intermediate
K$^+$, hard; Ag$^+$, soft
K$^+$
Ag$^+$
[18]O$_6$
[18]O$_4$S$_2$
[18]O$_5$N
[18]O$_4$N$_2$

2.3.3.9 Some Applications of Crown Ethers

- Widely used as phase transfer reagents in organic chemistry –

  (ex) can dissolve $KMnO_4$ in benzene in the presence of 18-crown-6.

- Many uses in analytical chemistry –

  (ex) as the sensing reagent in ion selective electrodes.

- Commonly used in solvent extraction studies for the extraction of a wide range of cations –

  (ex) for removing radioactive Cs from nuclear wastes.

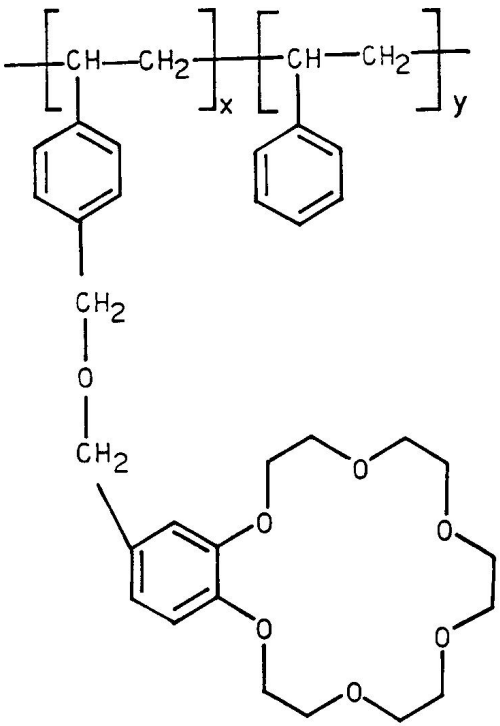
$$M^{m+}_{(aq)} + C_{(org)} + mA^-_{(aq)} \overset{K_{ex}}{\rightleftharpoons} (MCA_m)_{(org)}$$

$$\text{where} \quad K_{ex} = \frac{[MCA_m]_{(org)}}{[M^{m+}]_{(aq)}[C]_{(org)}[A^-]^m_{(aq)}}$$

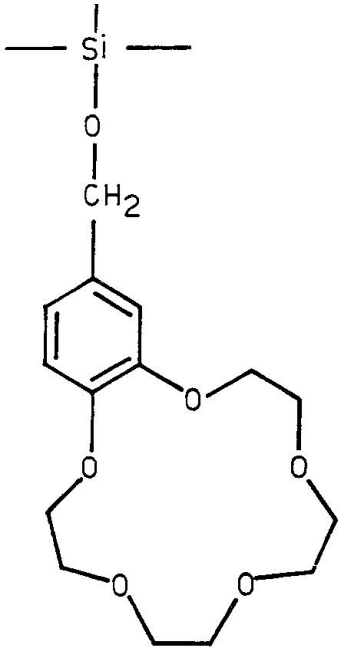
Solvent extraction studies

- This is a convenient means by which **complexation strength** can be compared.
- It requires a **metal picrate in water** in contact with an immiscible solvent such as $CHCl_3$ or $CDCl_3$ containing the crown ether.
- Optical or NMR methods are used to measure the picrate extracted which relates to the metal extracted.
- However, **the choice of solvents is limited** and any 'constants' calculated will vary with the conditions employed.

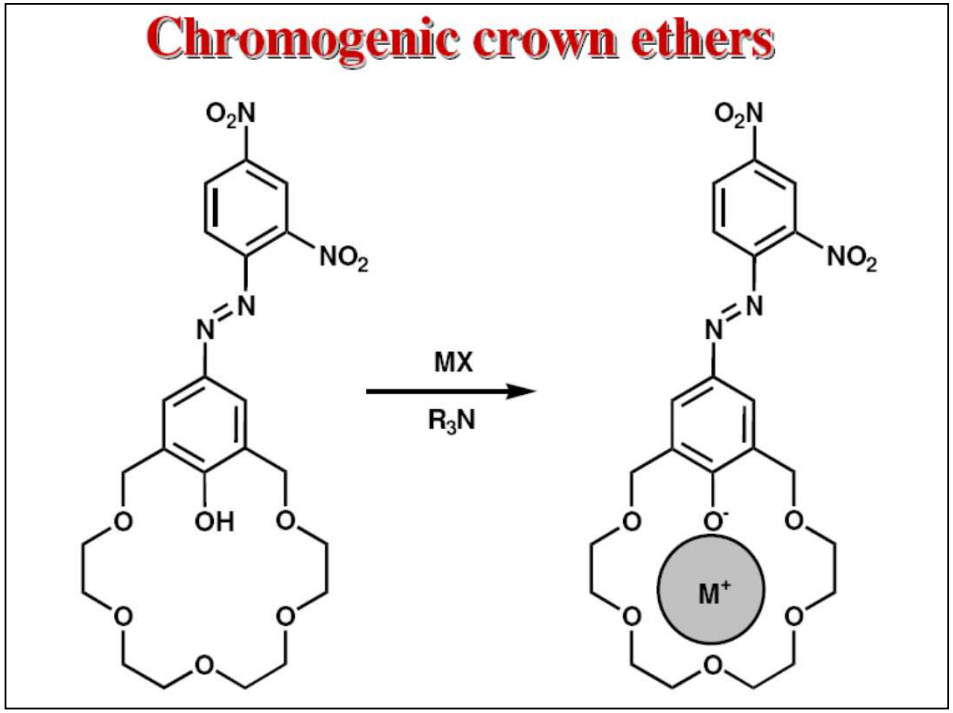
Polystyrene



Silica gel



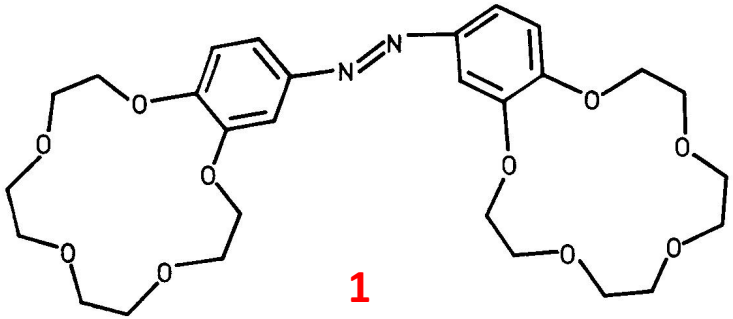
Chromogenic crown ethers



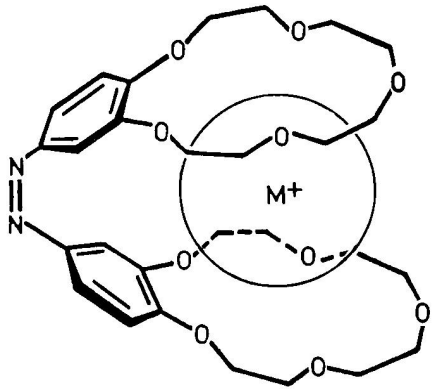
Marked colour change

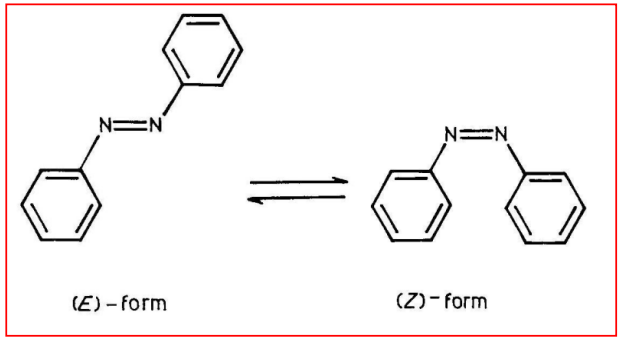
- Used in chromatography as 'ion-adsorption materials' when attached to solid supports such as chloromethylated polystyrene or silica gel.
- Such materials are available commercially.

Light induced control of coordination mode



1

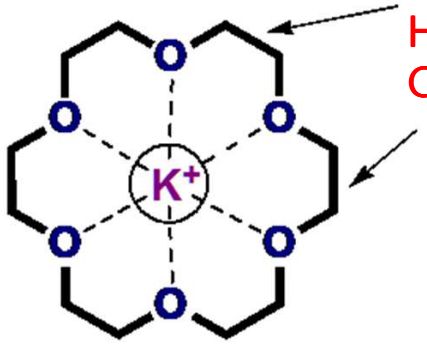




- An example of light-assisted membrane transport involves use of **1** as the carrier in a liquid membrane.
- Irradiation of the membrane alternatively with UV and visible light significantly increases the rate of K^+ and Rb^+ transport in the presence of picrate ion.
- This system also exhibits discrimination since the transport of K^+ is favoured over Rb^+.

2.3.3.10 Crown Ethers as Synthetic Reagent

- Crown ether dissolves ionic compounds in organic solvents, activates anions, and retains cations.
- Crown ether forms a coordination compound with the cation of an ionic compound and has the ability to mask the cation **(masking effect)** and activate the anion **(activation effect).**
- The anions are almost not solvated and become so-called **"naked"** state, and the activity of the anions becomes enormously high because of small volume of anion.



Hydrophobic outer-sphere.
Cation is coordinated and dissolved in organic solvent.

Application:

Nucleophilic substitution reaction, reaction involving carbon anion, C-C bond formation, addition reaction, elimination reaction, carbene formation, oxidation-reduction, rearrangement reaction, isomerization reaction, polymerization reaction

Preparation of akalide anion

- When a metal like Fe is used as a catalyst,
  an alkali metal reacts with ammonia to generate metal amide and hydrogen gas.

  $2\ M + 2\ NH_3 \rightarrow 2\ MNH_2 + H_2$
- In the absence of catalyst and impurities,
  the alkali metal is dissolved in the liquid ammonia without releasing hydrogen gas.
  When the liquid ammonia is evaporated, the metal is recovered.
- All alkali metals are dissolved in liquid ammonia and become a **bronze solution** in high concentration
  a **blue solution** in low concentration.
- The bronze solution conducts electricity to almost the metal level, and the blue solution conducts electricity a little better than the solution of the strong electrolyte.

- When Na metal is dissolved in liquid ammonia,

  $Na + NH_3\ (l) \rightarrow Na^+(NH_3)_n + e^-(NH_3)_m$

  ▶ **Metal electride** solution has a single electron by EPR.

  Solvated metal + solvated electron
- When the temperature is increased:

  $2\ [Na^+(NH_3)_n][e^-(NH_3)_m] + 2\ NH_3 \rightarrow 2\ NaNH_2 + H_2 + (n + m)NH_3$

❑ The following side reactions are also possible when metals are dissolved in liquid ammonia.

$M + e^- \rightarrow M^-$ (alkalide)

► This reaction is rare under normal conditions
since the electride ion is very strongly solvated by ammonia.

❑ The high affinity of alkali metal ions for crown ether and cryptand ligand
is a major driving force for the formation of cationic coordination compounds.

❑ Excess ligands make the formation of **electride** easier
because they convert all metals to coordination compounds.

Cs + excess [18]crown-6 $\rightarrow [Cs\{[18]crown\text{-}6)\}_2]^+ + e^-$

- When the metal: ligand ratio is adjusted to 2: 1, an alkalide anion can be formed.

  2 Na + [18]crown-6

  $\rightarrow$ $[Na\{[18]crown\text{-}6)\}]^+ + Na + e^-$

  $\rightarrow$ $[Na\{[18]crown\text{-}6)\}]^+ + \mathbf{Na^-}$

- Stability of akalide anion: $Na^- > K^- > Rb^- > Cs^-$

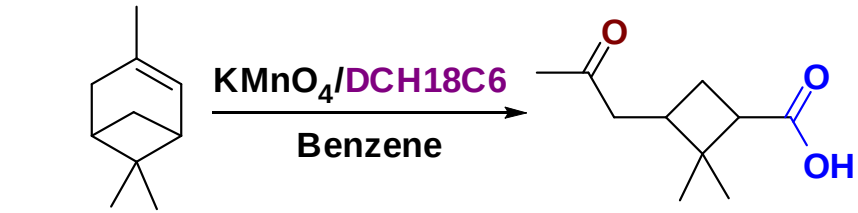
  Na + K + 18-crown-6 $\rightarrow$ $[\mathbf{K}(18\text{-crown-}6)]^+ + \mathbf{Na^-}$

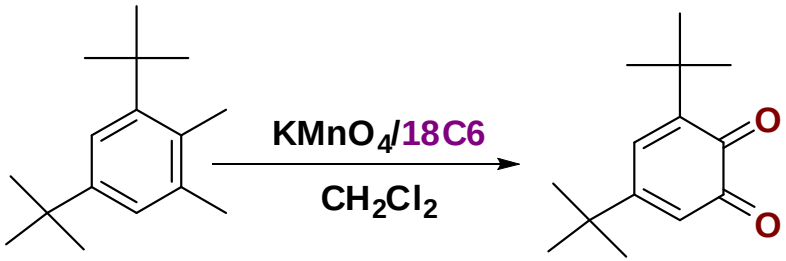
- Metal electride solution is excellent reducing agent.

  $Fe(CO)_5 + 2\ [\mathbf{Na^+/e^-}] \rightarrow Na_2[Fe(CO)_4] + CO(g)$

  $O_2 + [\mathbf{Li^+/e^-}] \rightarrow LiO_2 + [Li^+/e^-] \rightarrow Li_2O_2$

- ‘Purple benzene’ used in the oxidation reaction.
- Yield is nearly 100%

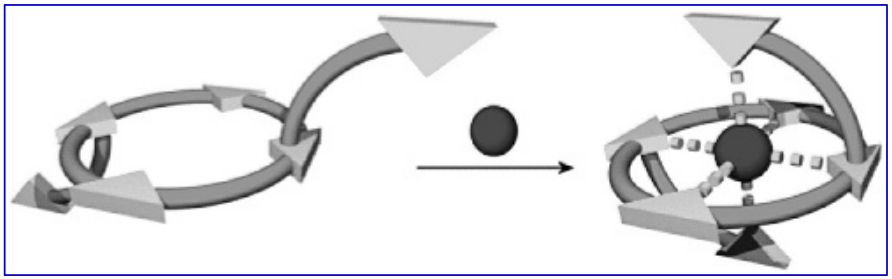


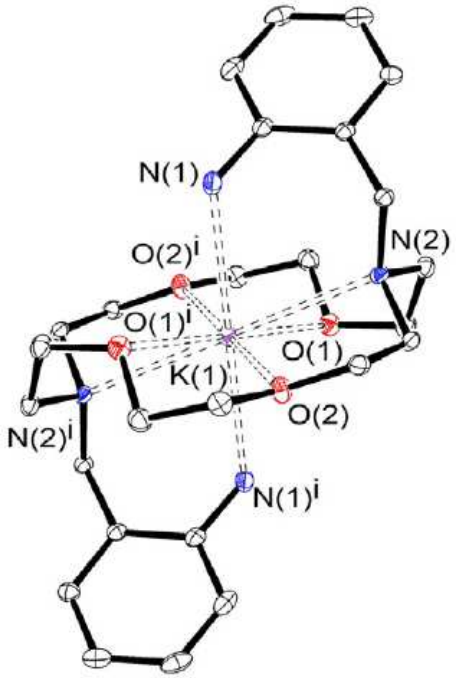


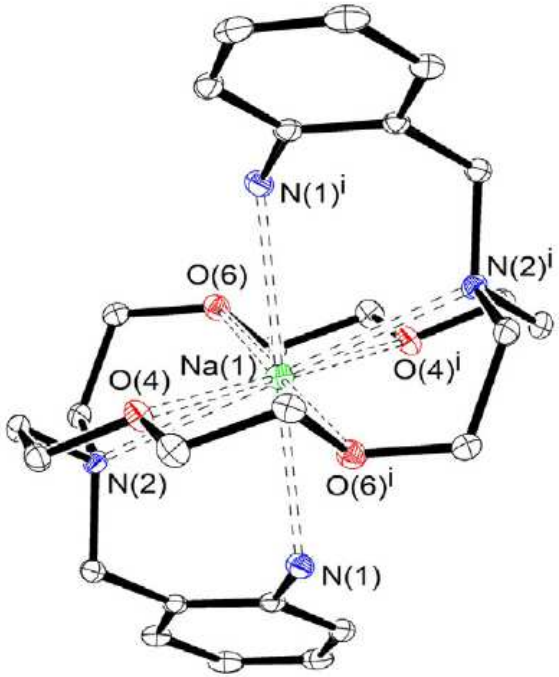
—CH_2	→	—C=O
—C–OH	→	—C=O
—C–OH	→	—COOH
—C–Cl	→	—CHO
—C–X	→	—C–OH
—C–X	→	—C–OO–C

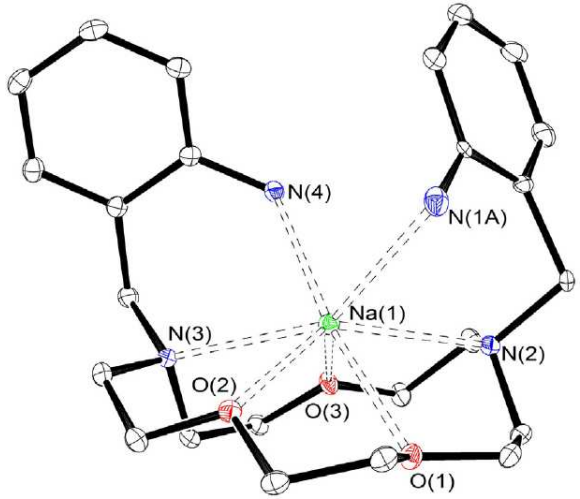
$KMnO_4$, KIO_4, K_2CrO_4, $KCrO_2Cl$, $Ca(OCl)_2$, KO_2

Bibracchial lariat ethers (BiBLEs)



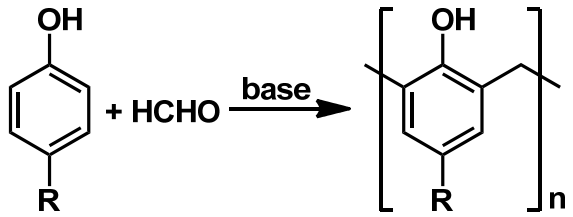




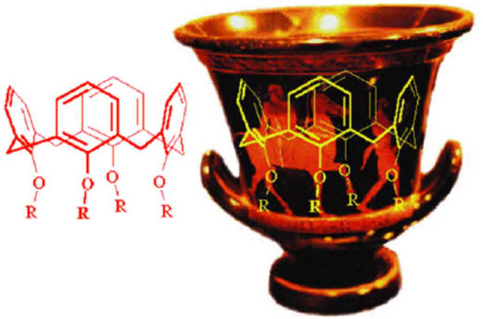


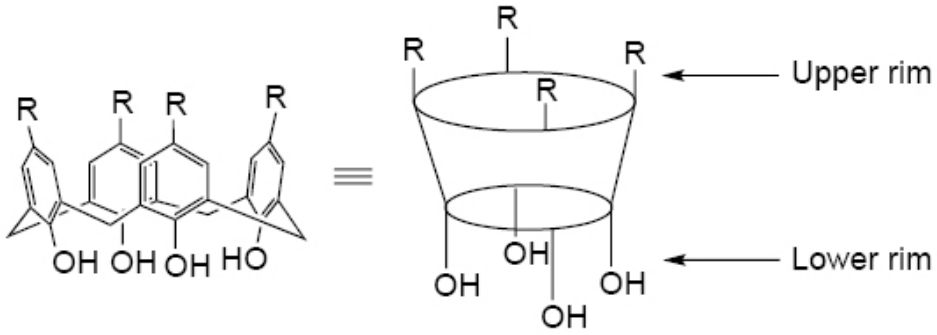
2.3.4 Calixarenes

- **Calixarenes**: cyclic hosts by the condensation reaction between a *p*-substituted phenol and HCHO.
- The name comes from a Greek vase, called a ***calix crater***.
- Varying thermal conditions and altering the ratio of reactants: n = 4–16
- n = 4 is the most common.

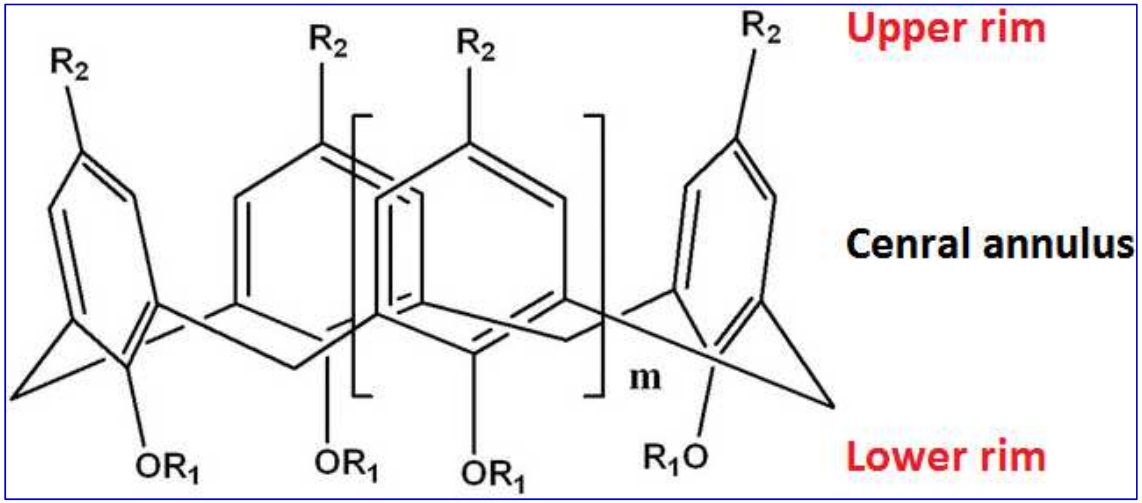


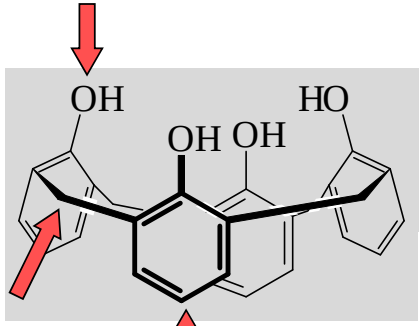
n = 4–16





- The calixarene framework is very versatile and many derivatives have been prepared by functionalising the groups on the ‘upper’ and ‘lower’ rims.
- By selectively changing the framework:
  Calixarene hosts cations, anions, neutral species or simultaneously combining different guests.



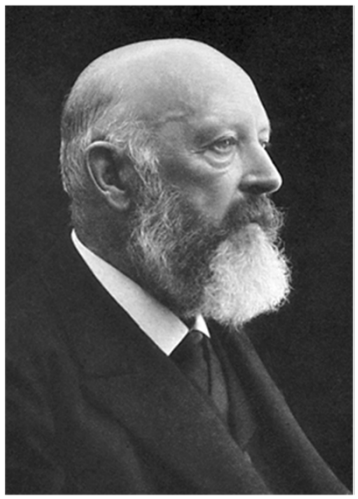


Hydrophilic site

Hydrophobic site

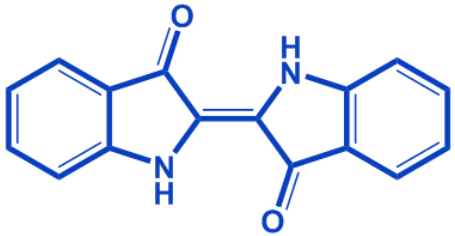
Functionalisation site

2.3.4.1 History of Calixarenes

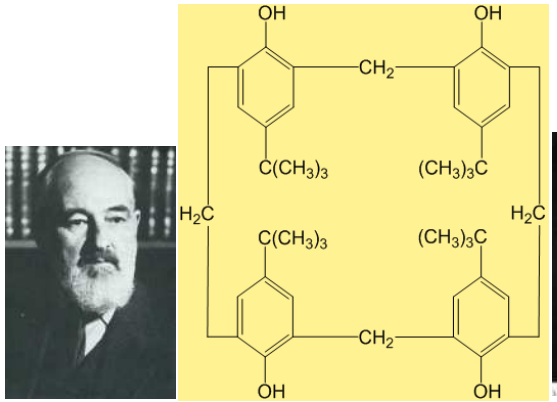


Johann Friedrich Wilhelm Adolf von Baeyer (1835-1917): German chemist

- ❑ He taught at Berlin and Strasbourg.
- ❑ Nobel Prize in Chemistry (1905)
- ❑ Discovery of the molecular structure of **indigo**



The original proposed structure



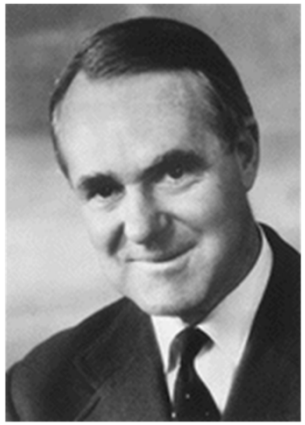
Alois Zinke
(1892-1963)

Erich Ziegler
(1912-1993)

Zur Kenntnis des Härtungsprozesses von Phenol-Formaldehyd-Harzen, X. Mitteilung
Chemische Berichte, **77**, 264-272 (1944)

In 1994, a special issue about the 50th anniversary
of the proposal of the macrocyclic structure of calixarenes was published in:
Journal of Inclusion Phenomena and Macrocyclic Chemistry, **19**, 3-15 (1994)

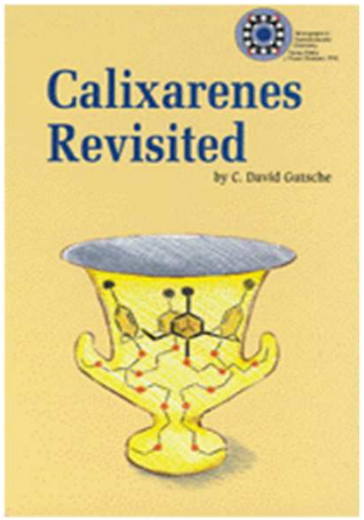
Thomas Kappe ***"The Early History of Calixarene Chemistry"***



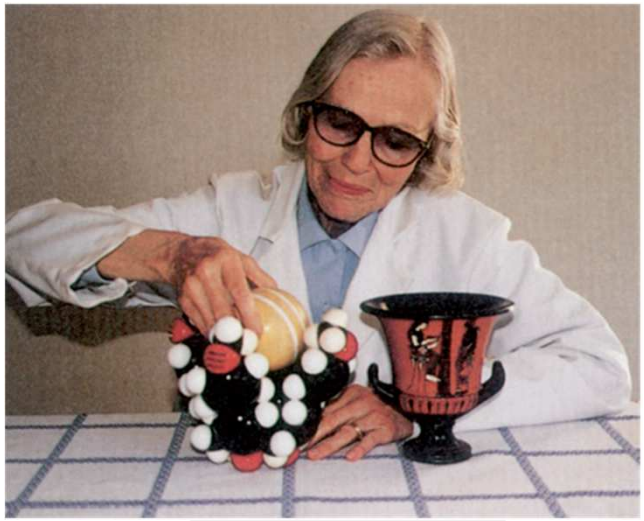
Sir John Warcup Cornforth (1917 -)

- Nobel Prize in Chemistry (1975)
- His work on the stereochemistry of enzyme-catalyzed reactions.
- Born in Sydney, University of Sydney from 16 yo,
  graduated with first-class honours and the University medal in 1937
- University of Sussex, Brighton, UK

Preliminary conformational assumptions
and use as pharmaceutics of calixarenes



C(arl) David Gutsche



Alice Gutsche

In 1981, C. D. Gutsche published the separation of calixarenes and the first book on their chemistry in 1989.

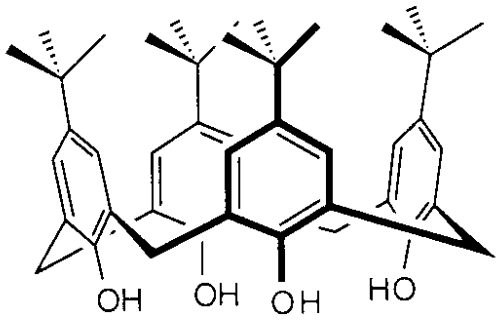
2.3.4.2 *P-tert*-Butylcalix[*n*]arene

Calix[n]arenes:

- A family of synthetic structure consisting of cyclic arrays of *n* phenol residues linked by methylene groups.
- Synthesised by base catalysed condensation of *p-tert*-butylphenol and formaldehyde.

- Altering the reaction condtions gives rise to different size calixar[*n*]enes.
- The cone conformation of *p-tert*-butylcalix[4]arene is stabilised by an array of hydrogen bonds between the phenolic OH groups on the lower rim.
- Deprotonated calixarenes are capable of binding alkali cations at the lower rim.
- Can readily append functional groups to the lower rim. The upper rim can also be modified.
- Cavity can also bind a substrate.
  (ex) toluene binds via CH- π interactions with aromatic rings of the cavity.

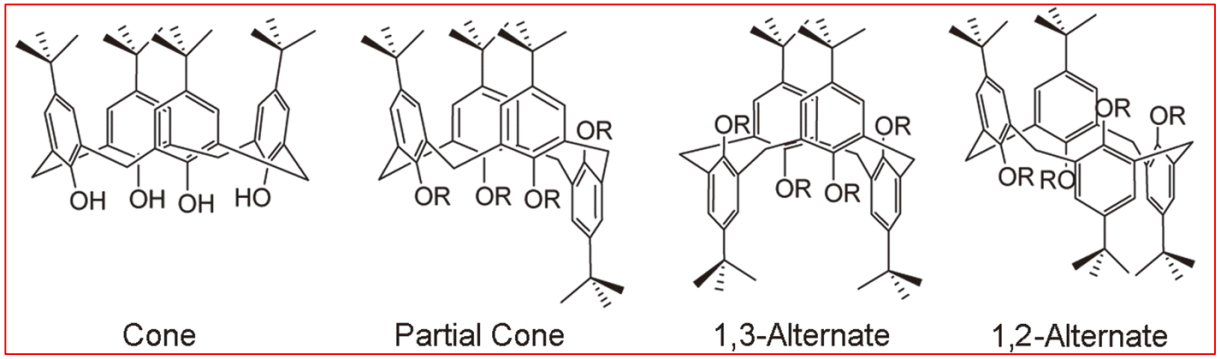
Upper rim



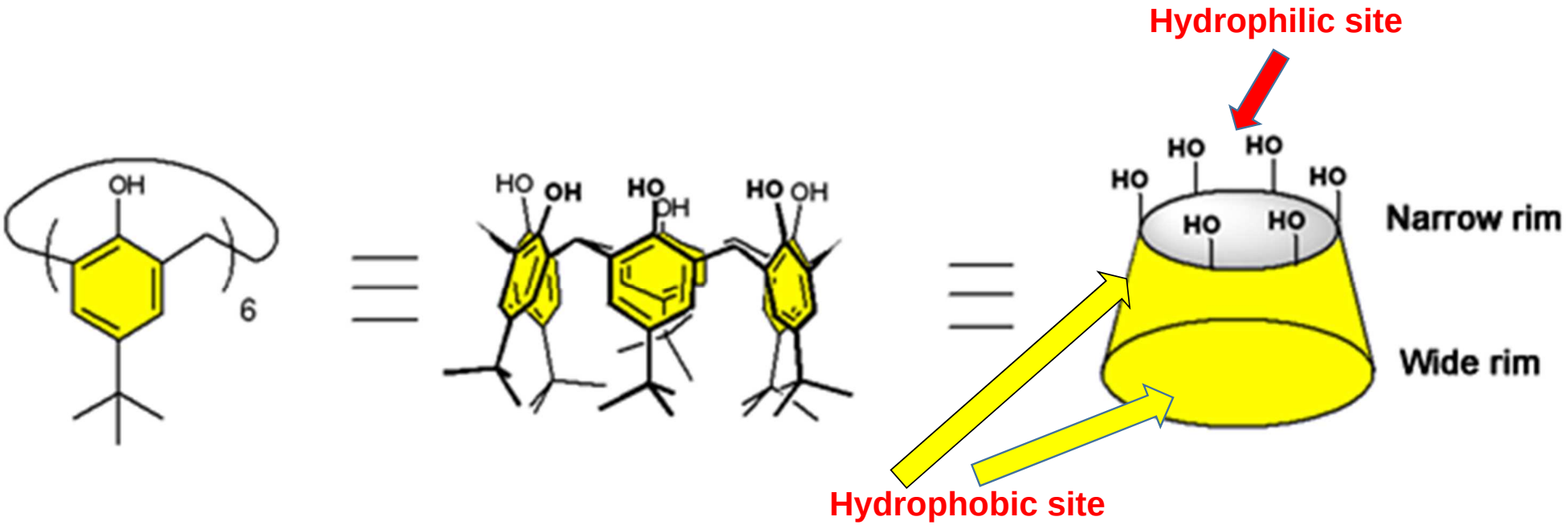
Lower rim

P-tert-Butylcalix[4]arene

- For calix[4]arenes with small -OR groups at the lower rim, conformations are interconvertible by rotations of the OR group through the annulus.
- The relative proportions of the different conformations in solution are solvent- and temperature-dependent.
- When **R = H**, the **cone conformer predominates**, by virtue of intramolecular hydrogen bonding between the lower rim phenol groups.
- Where **R = methyl** in $CDCl_3$ at 243 K, the preferred conformer is the **partial cone** (1 up, 3 down).
- The cone conformer displays the highest affinity for organic cations within its π-basic cavity.
- For efficient binding, it is necessary to immobilise the calix[4]arene in a cone conformation.
- Substitution of the lower rim phenolic hydrogens by groups of three carbons in length or longer is required for this immobilisation.
- The size of the -OR groups (feet) in these systems is such that the 'through the annulus rotation' of the OR group is not possible at room temperature, thereby preventing the interconversion between conformers.



Hydrophobic and hydrophilic molecules can interact with this receptor

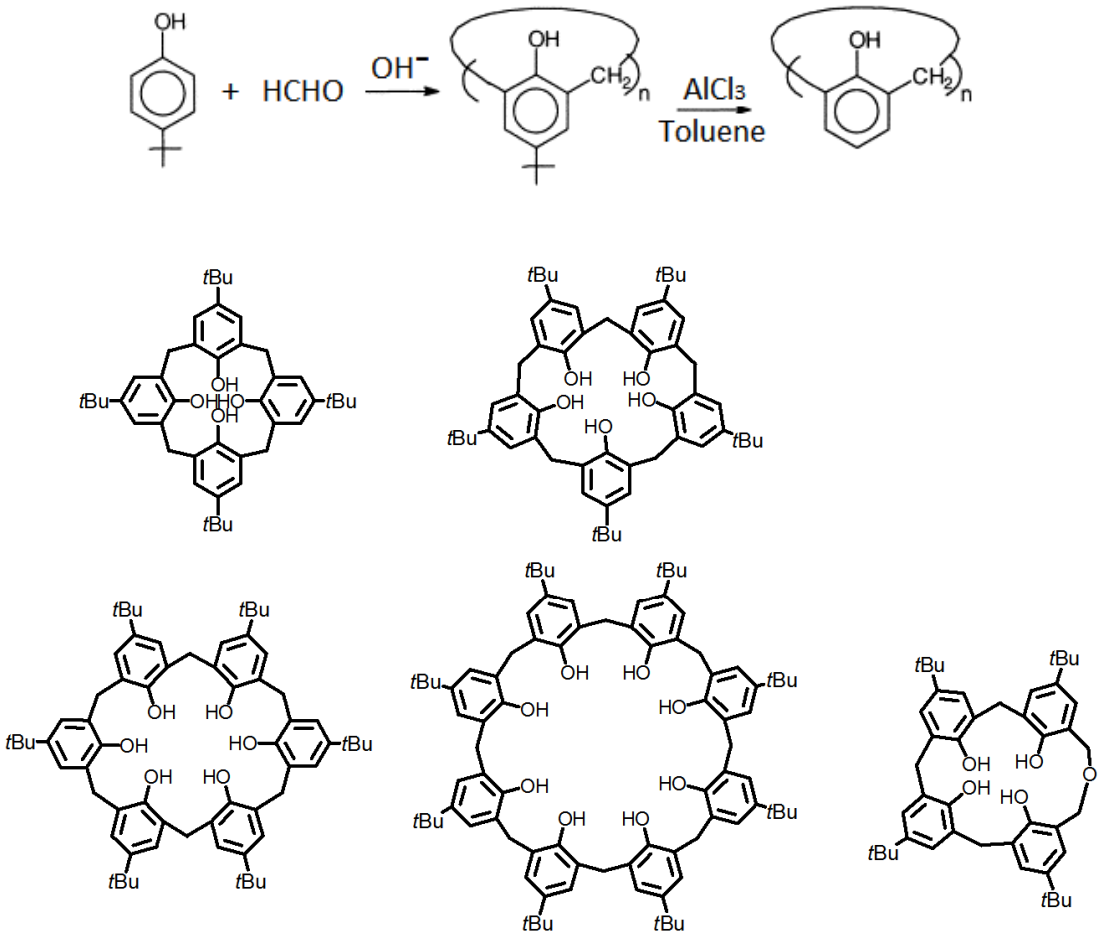


2.3.4.3 Applications and research fields

- supramolecular and host-guest reagents
- metallo-dendrimeric catalyzers
- liquid crystals
- red-ox and optical (light conversion and nonlinear optics)
- light-harvesting
- nanodevices
- carriers for drug delivery
- microbial antiadhesins
- sensitive analytical devices
- MRI contrast and EPR imaging agents in gene therapy
- and prior research

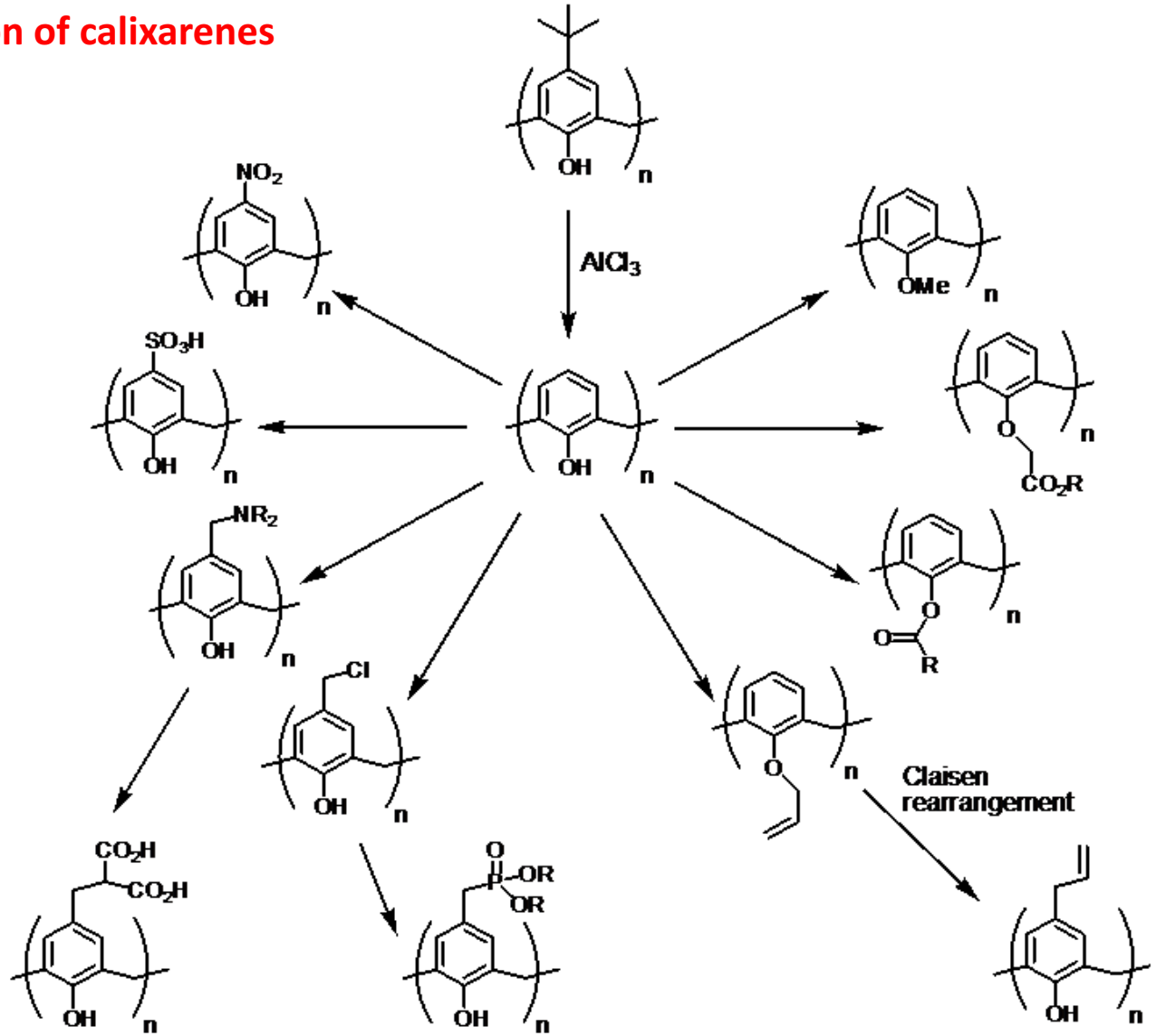
Not exhaustive

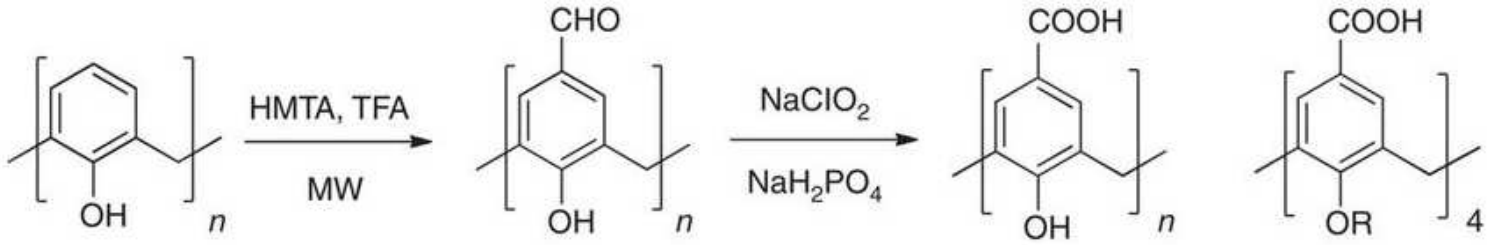
2.3.4.4 Synthesis

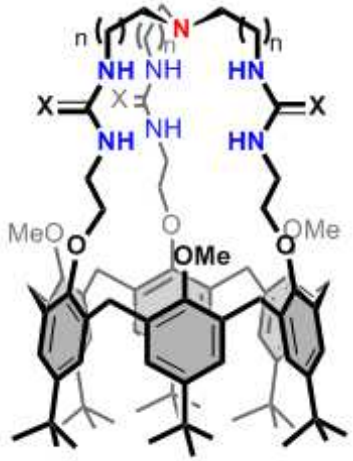


Products from the base catalyzed condensation of *p-tert*-butylphenol and formaldehyde

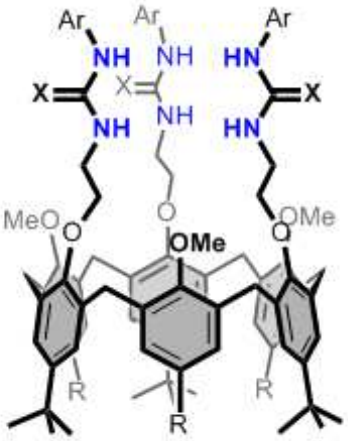
Functionalisation of calixarenes



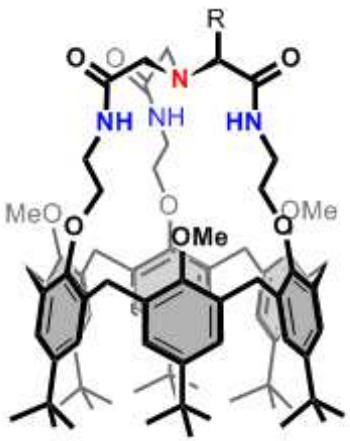




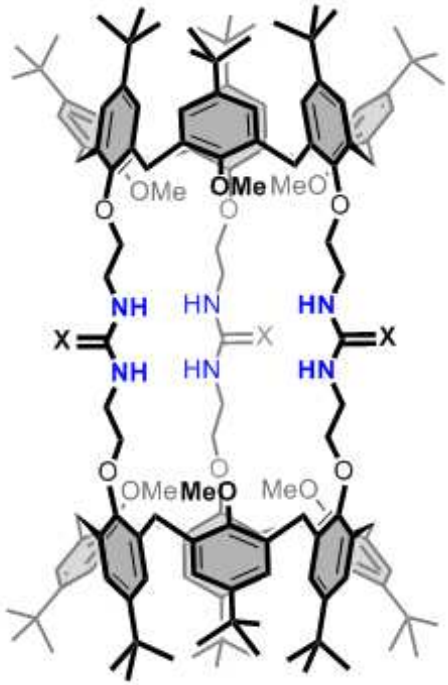
Calix[6]crypt-(thio)ureas



Calix[6]tris-(thio)ureas

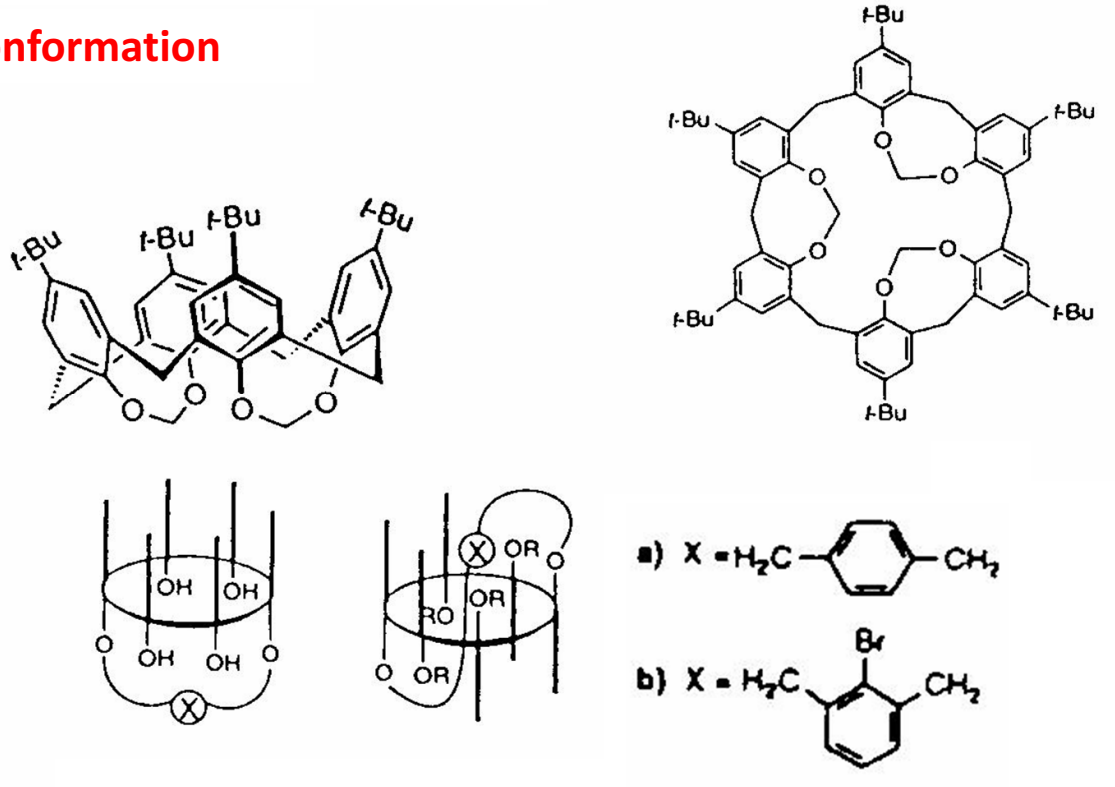


Calix[6]cryptamides

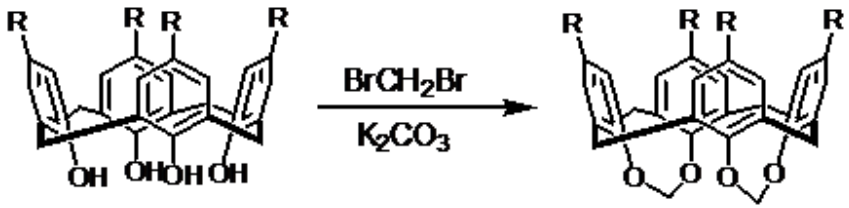


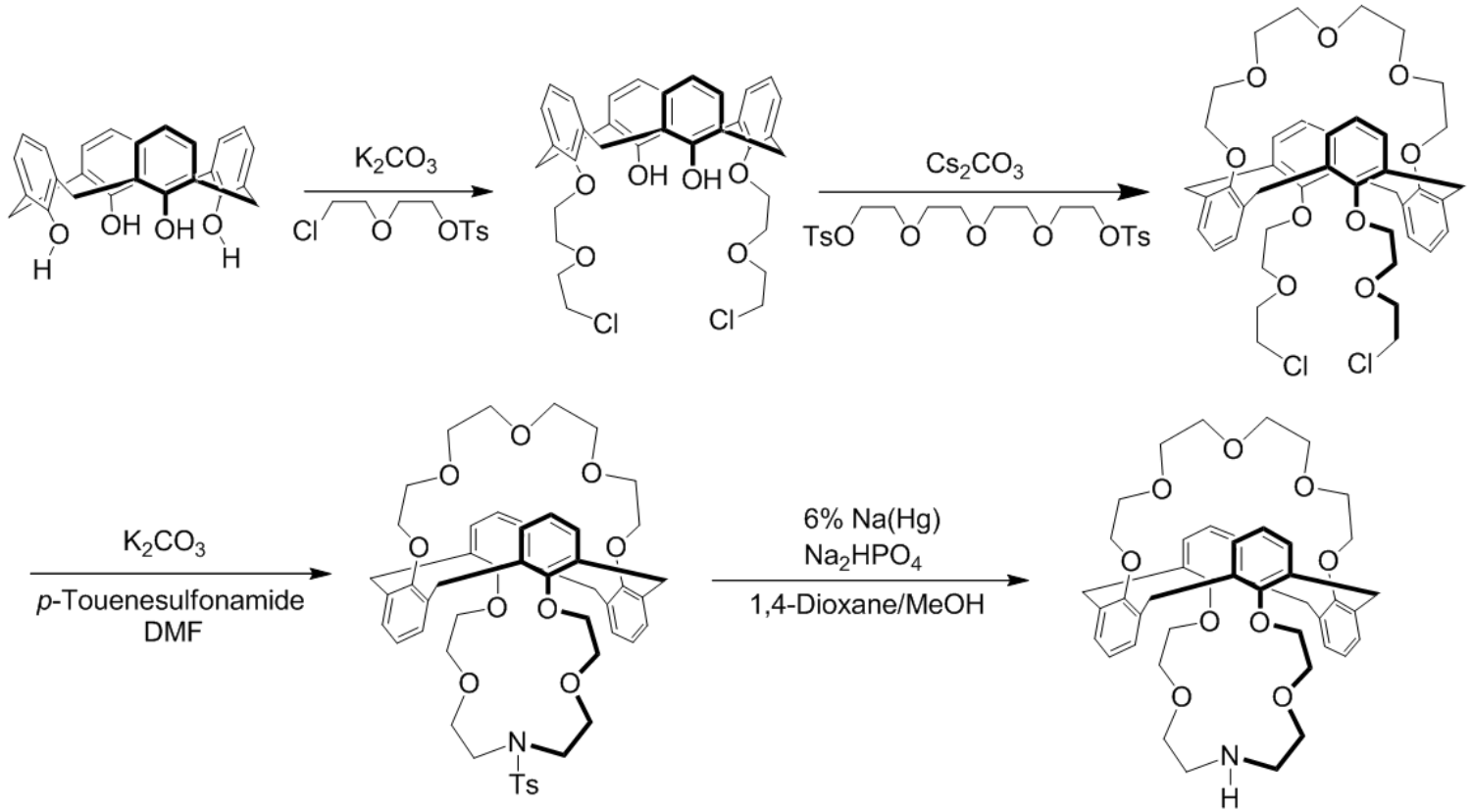
Bis-calix[6]tube-(thio)ureas

Constraining the conformation

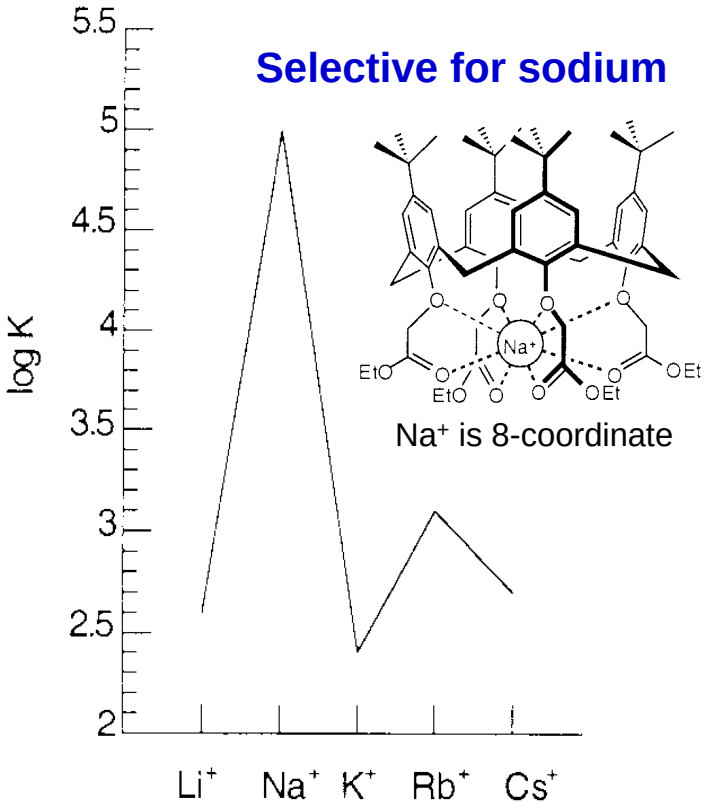


Formation of molecular basket

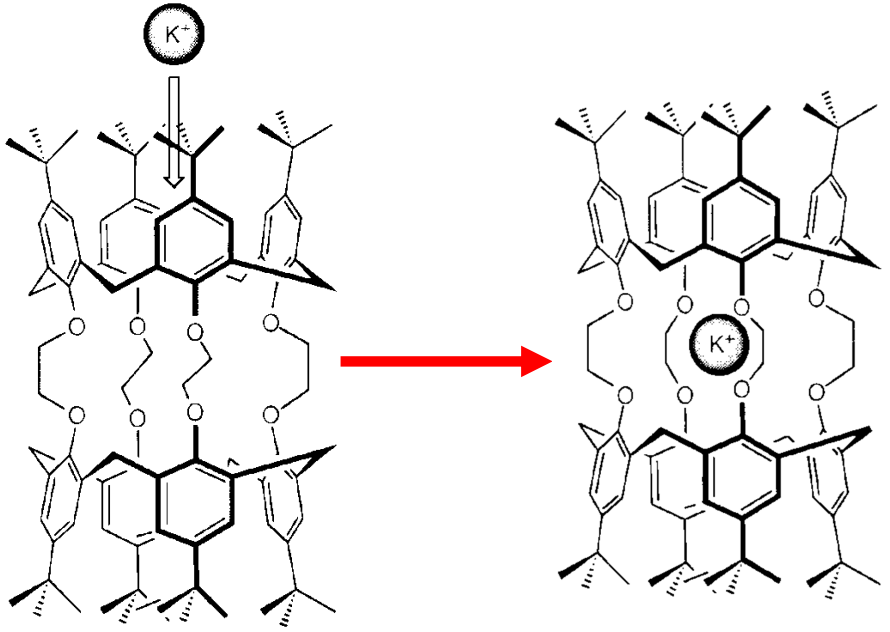



K2CO3
Cl O OTs
Cs2CO3
TsO O O O OTs
K2CO3
p-Touenesulfonamide
DMF
6% Na(Hg)
Na2HPO4
1,4-Dioxane/MeOH
OH
Cl
Ts
H

2.3.4.5 Alkali metal complex

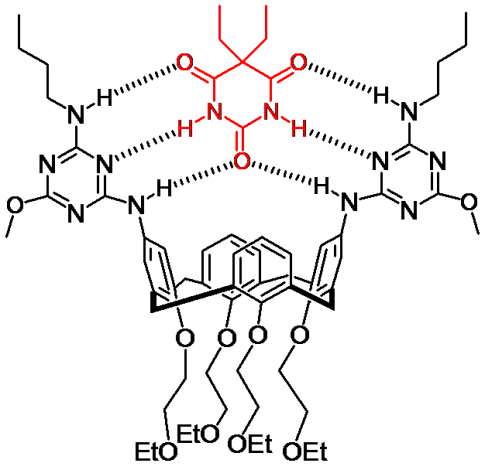


log*K* values for Group 1 metal cations of
p-*tert*-butylcalix[4]arene tetra ester in methanol

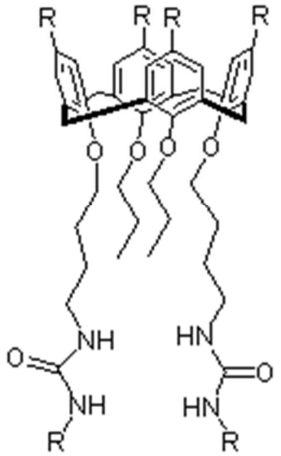


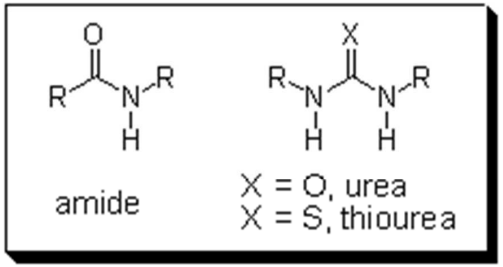
Potassium encapsulation in calix[4]tube

2.3.4.6 Receptor for natural molecule and anions



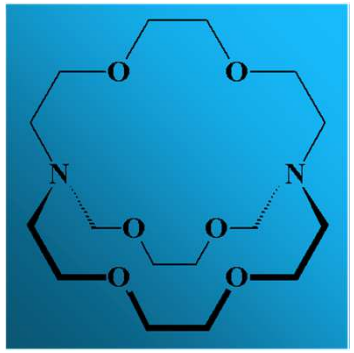
Amides, Ureas and Thioureas - hydrogen bonds only

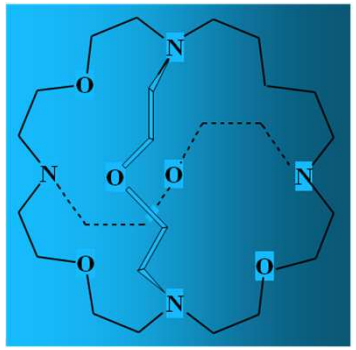




Anion	Radius(Å)	K (M^{-1})
Cl^-	1.81	7105
Br^-	1.95	2555
I^-	2.16	605
CN^-	1.82	1115

2.3.4.7 Recognition of cations



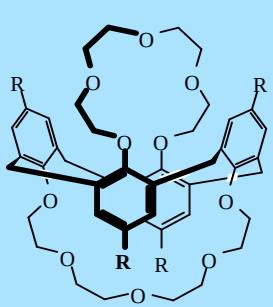


log*K*s (in H_2O)		
K^+	5.3	3.4
NH_4^+	4.5	6.1
Selectivity NH_4^+/K^+	0.8	2.7~500

J. Phys. Chem. 91, 6600(1987)

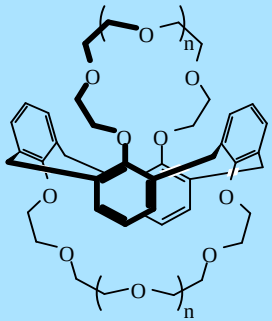
Cs/Na selectivities in Supported Liquid Membranes (SLM's)

Waste Treatment by SLM 's



R = i-Pr

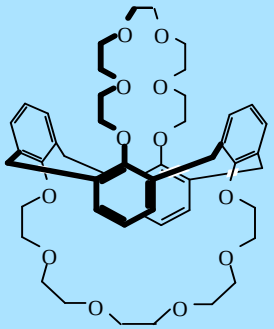
R = t-Bu



n = 1 **220**

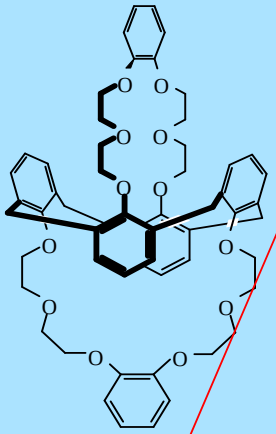
n = 2 **1500**

n = 3 **300**

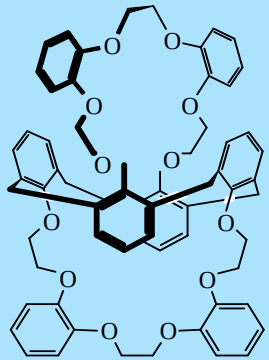


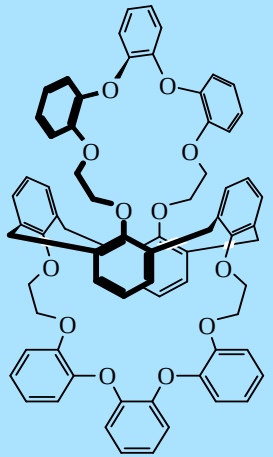
1500

$\alpha_{Cs/Na}$



19000





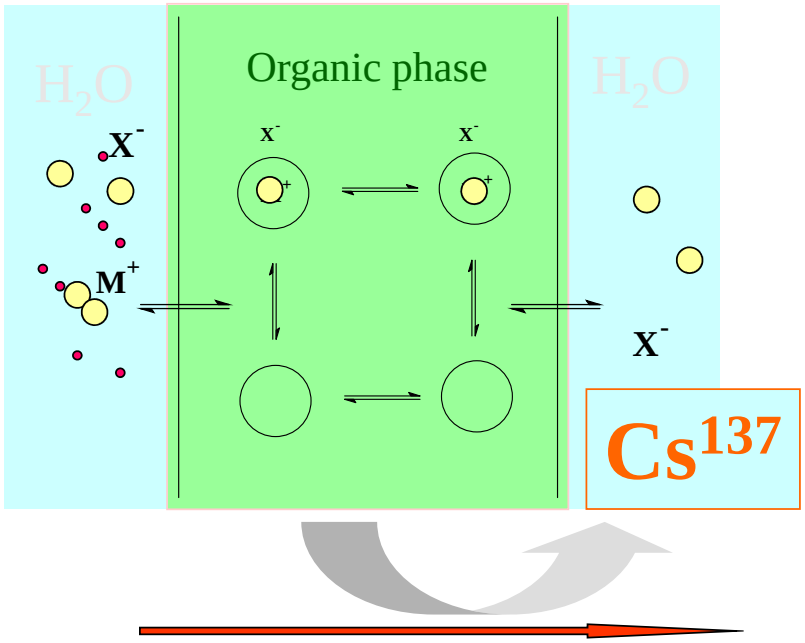
J. Incl. Phenom. 19, 399-408 (1994)

Waste treatment by SLM's

Need of high Cs/Na selectivity !!!

Na^{22}	3×10^{-10}
Mn^{54}	7×10^{-11}
Co^{60}	6×10^{-10}
Sr^{85}	2×10^{-11}
Cs^{137}	**3.5×10^{-9}**
Eu^{152}	1.5×10^{-9}
Np^{237}	2.5×10^{-4}
Pu^{239}	2.7×10^{-6}
Am^{241}	5.2×10^{-8}

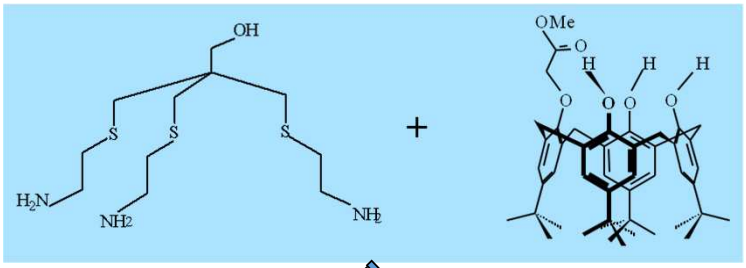
Concentration (mol. L^{-1})



Highly acidic medium

$NaNO_3$ **10 mol. L^{-1}**; HNO_3 **1 mol. L^{-1}**

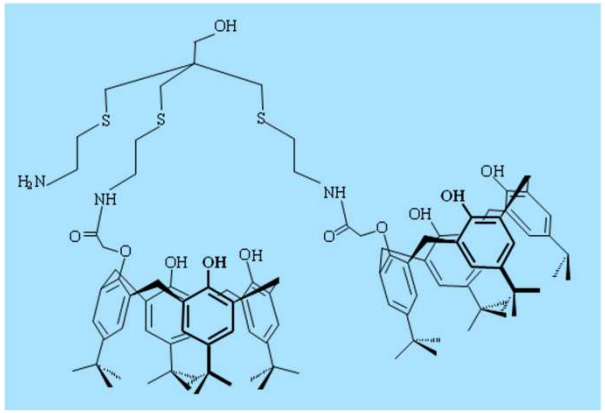
Preparation of di- and tricalix



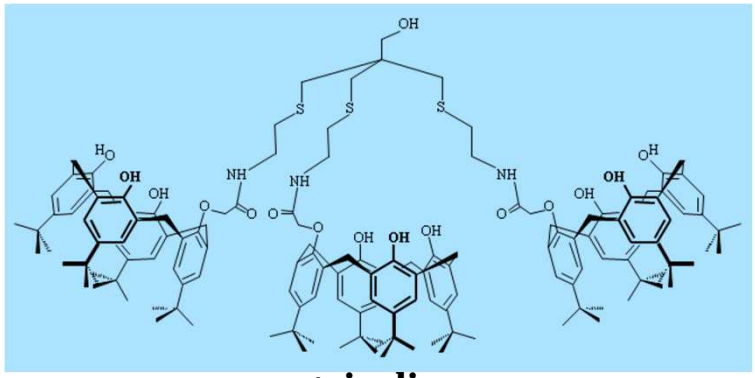
1 day

8 days

MeOH/Toluene



dicalix



tricalix

Supramolecular Chemistry, **17**, 323-330 (2005)

Extraction of metal picrate with dicalix and tricalix to CH_2Cl_2

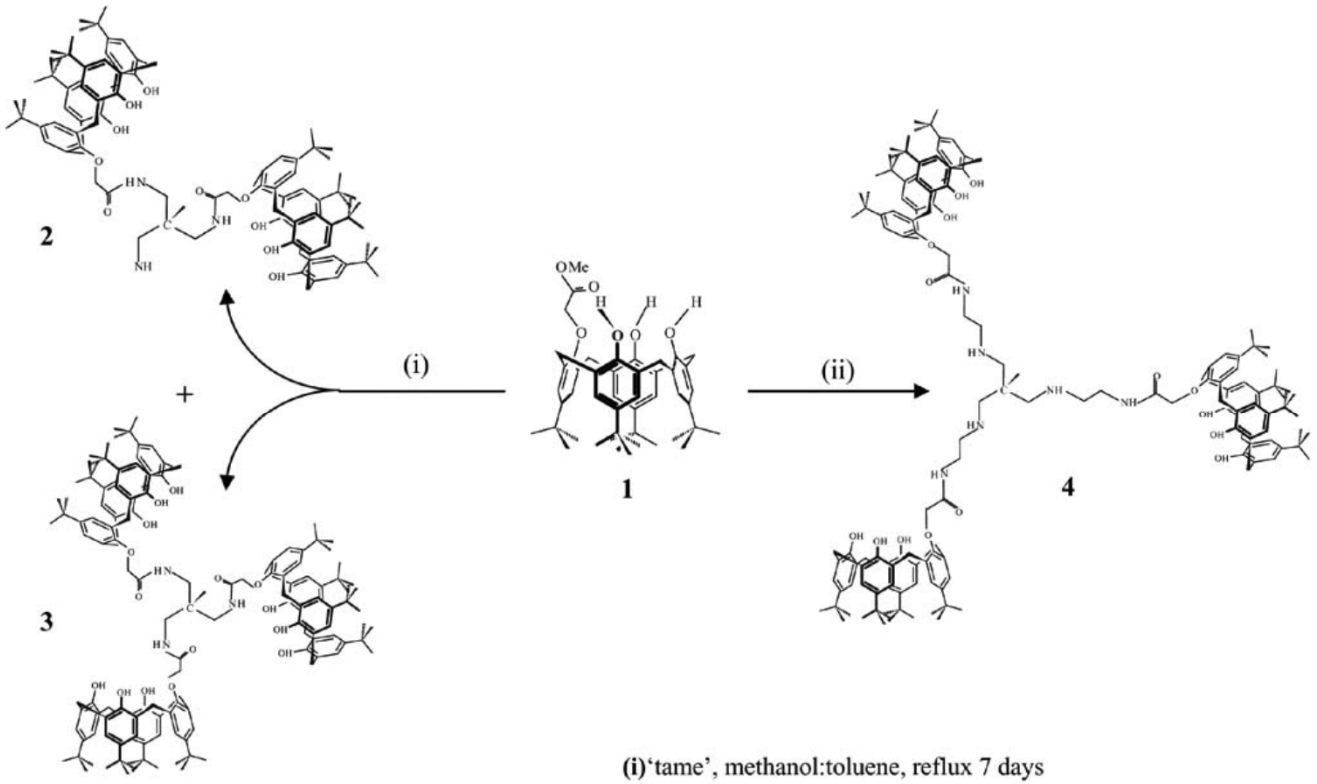
$$E\,(\%) = 100 \times \frac{A_0 - A}{A}$$

A : the absorbance of the water phase in the presence of the ligand
A_0: the absorbance without the ligand
Absorbance at 355 nm

$E\,(\%)$	dicalix	tricalix
Zn(II)	15.3	6.5
Co(III)	15.4	4.6

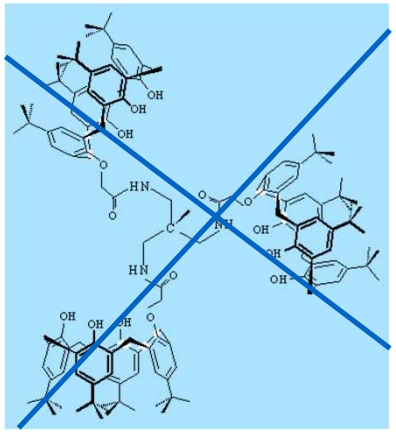
Free NH_2 group in involved in the complexation
by increasing the percentage of extraction

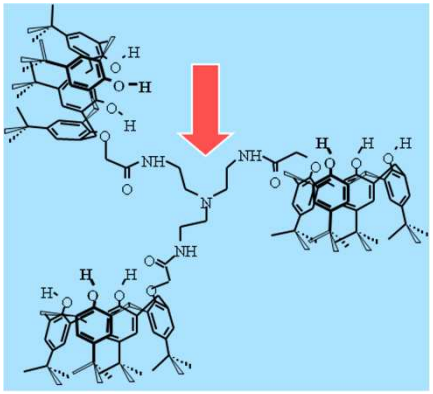
Calixarene-Based Hyperbranched Molecules

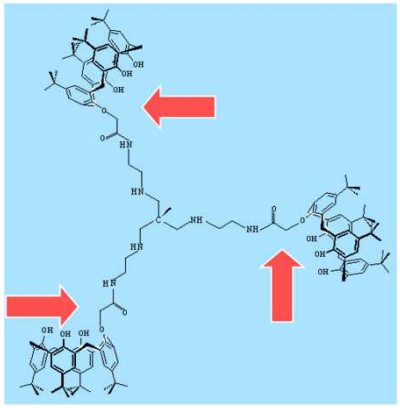


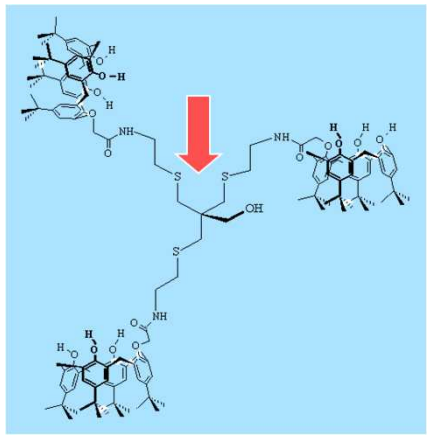
Letters in Organic Chemistry, **3**, 426-429 (2006)

$ZnPic_2$-complexation studies on tricalixes with various cores



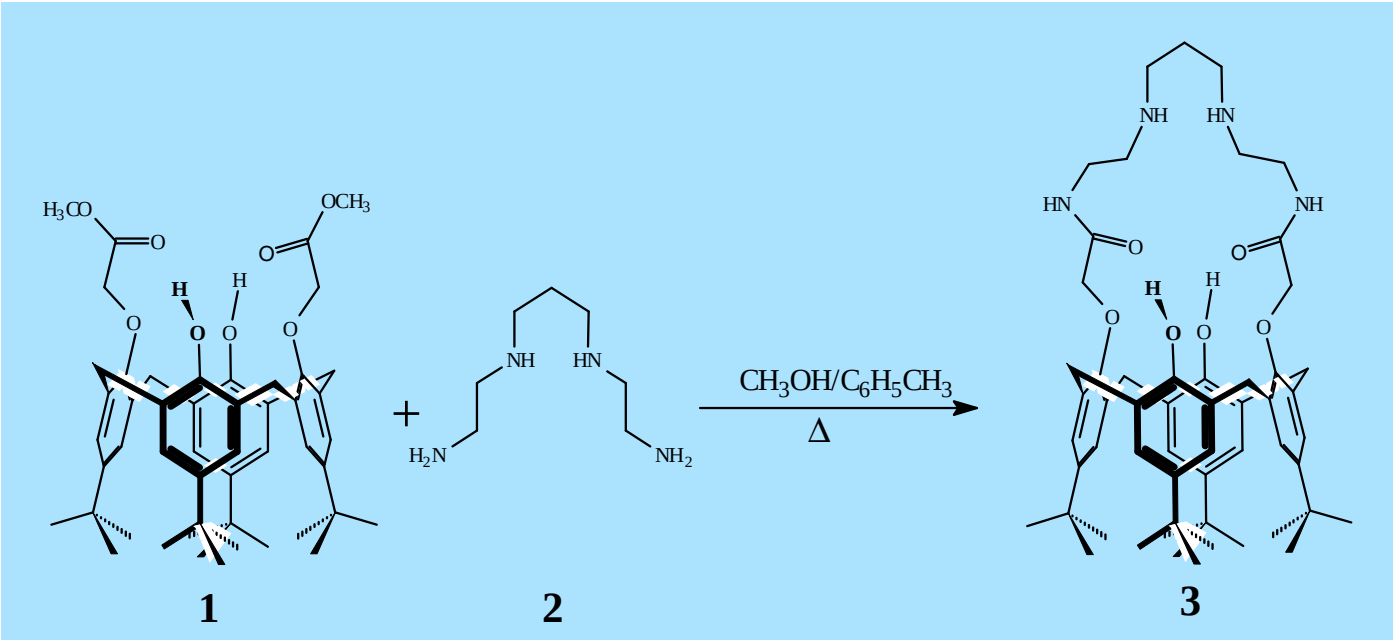






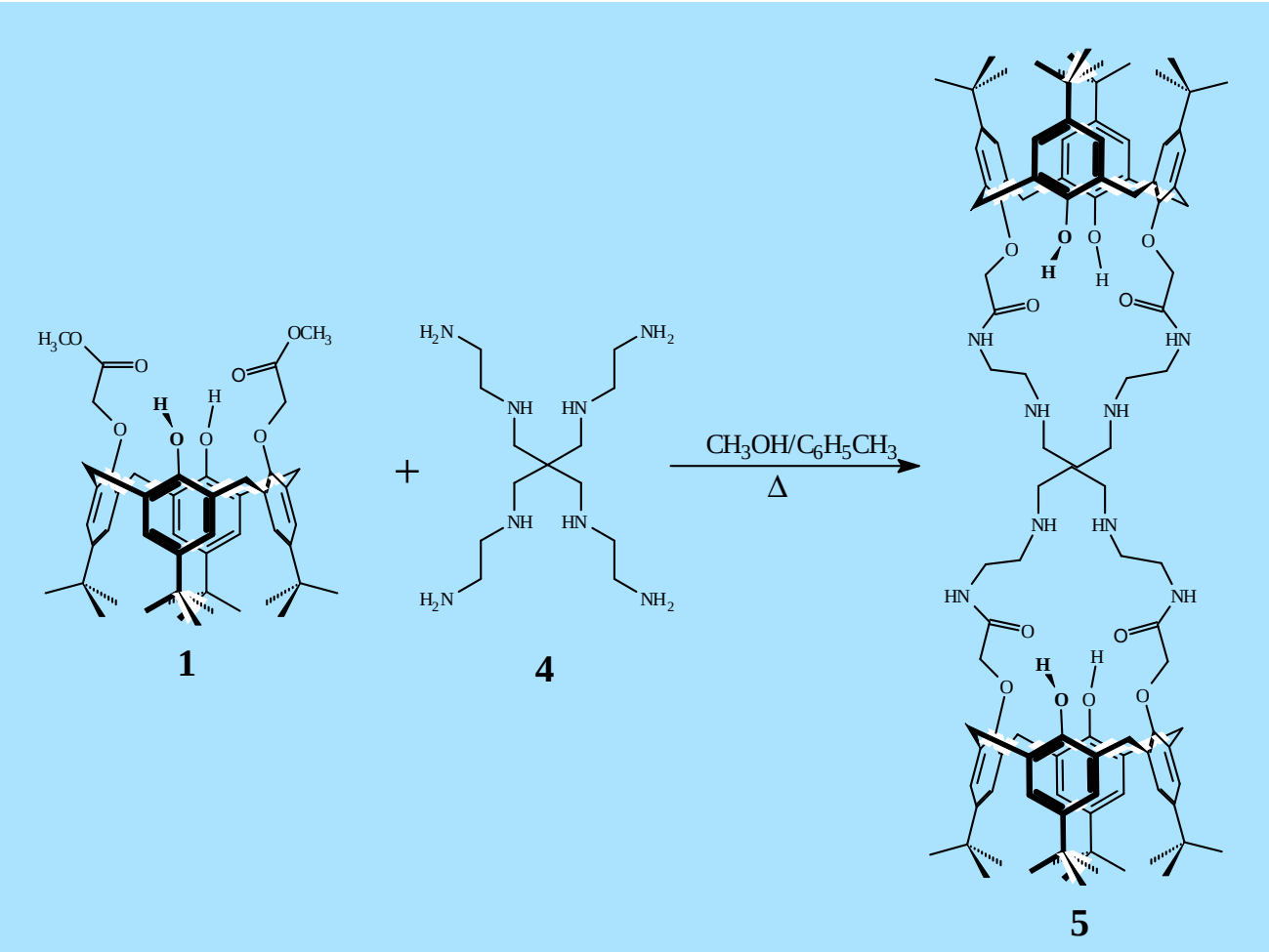
The tripodal cores can be used to arrange the calix units, the focal cores and the complexed metals

Calix[4]azacrown



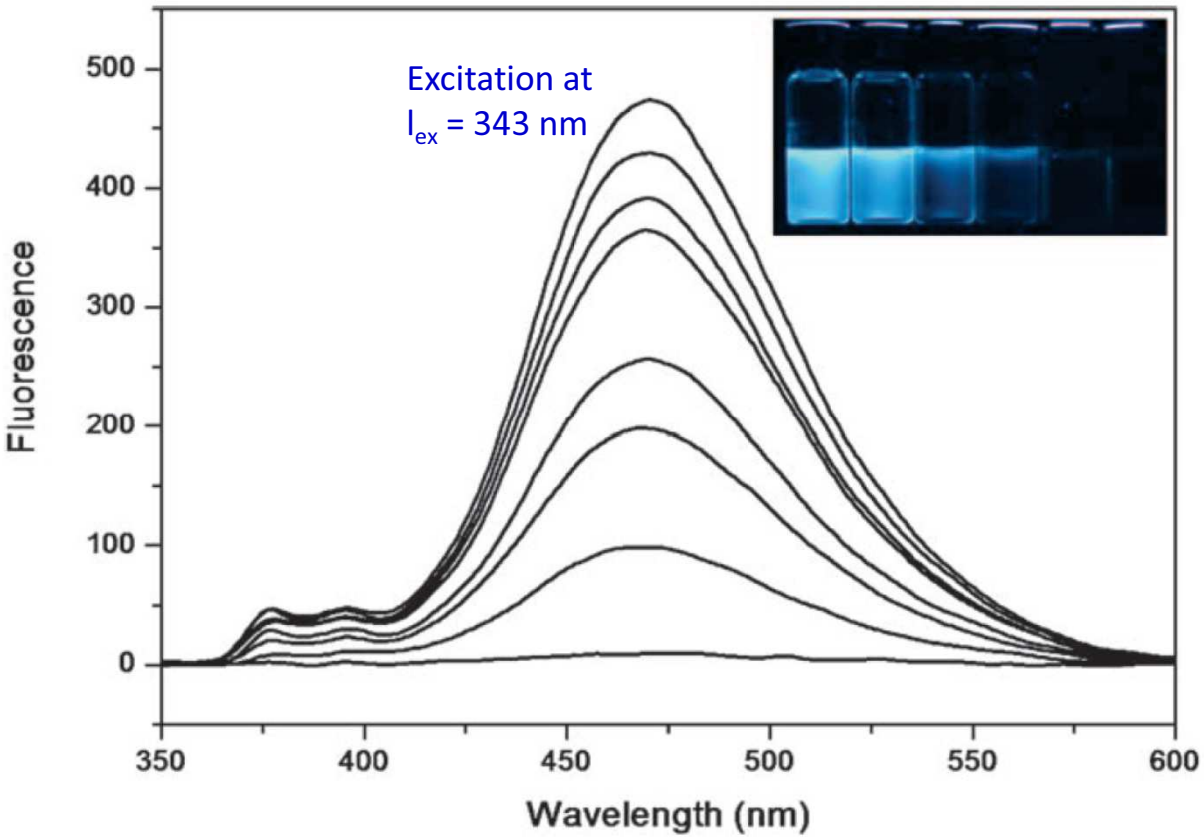
Tetrahedron Letters **50,** 540–543 (2009)

Spirobiscalix[4]azacrown

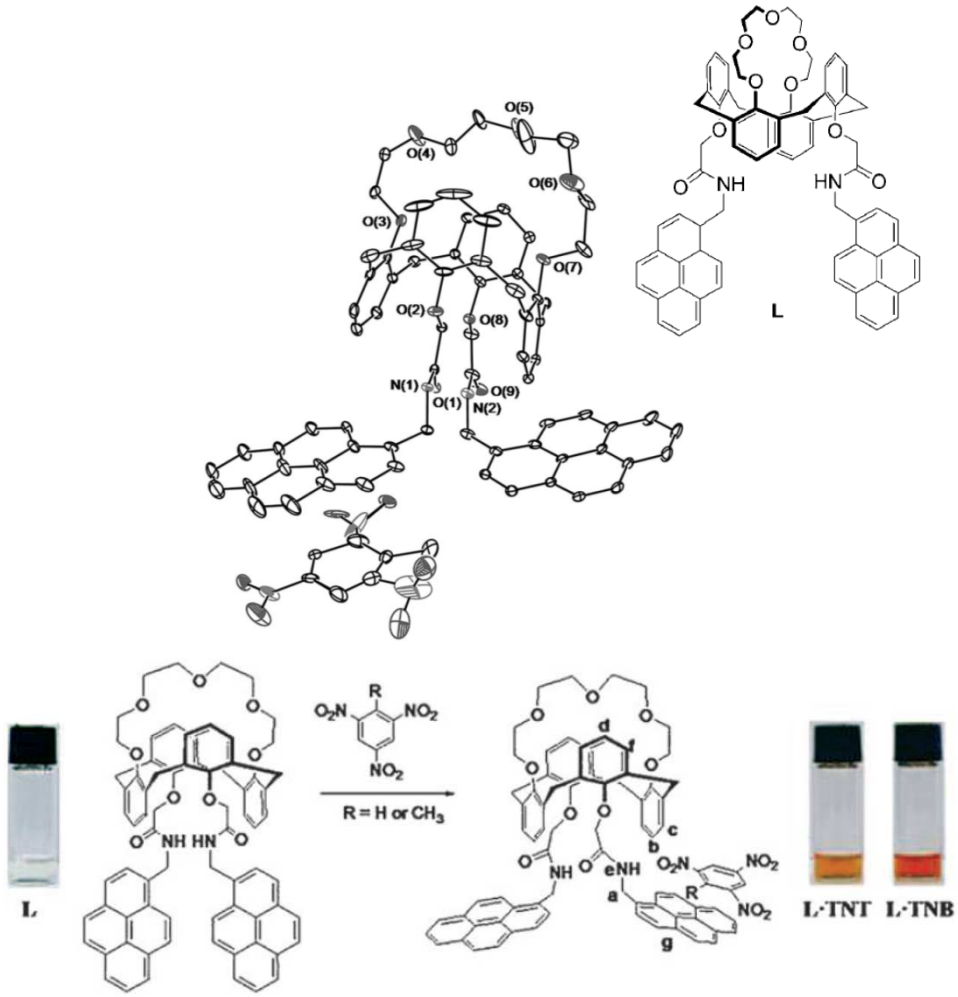


Tetrahedron Letters **50,** 540–543 (2009)

Fluorescence quenching and visual changes observed



TNT in CH_3CN
(from top to bottom and from left to right in the insert:
0, 1, 5, 10, 30, 50, 100, 300 equiv)

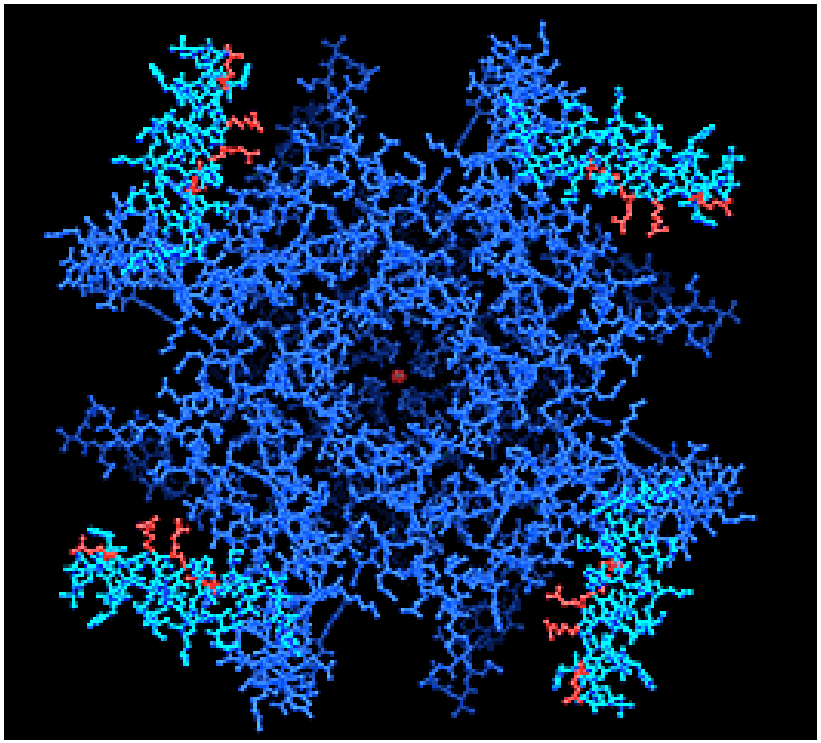


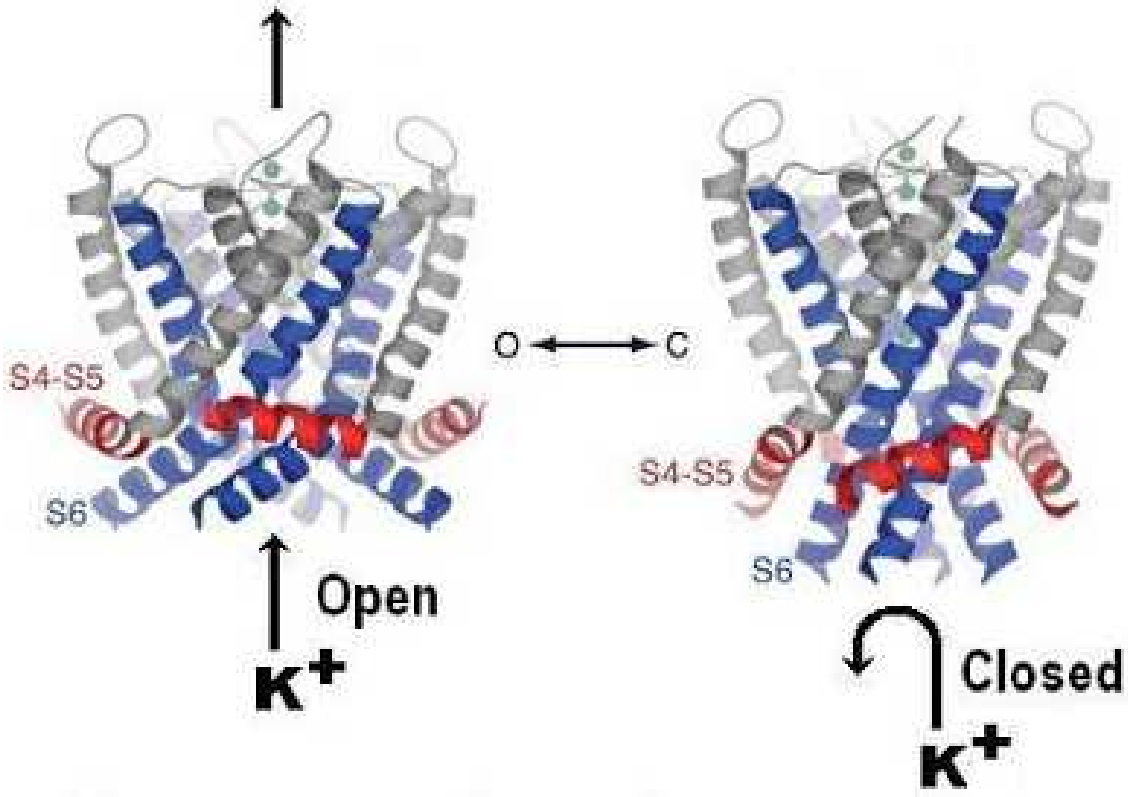
Crystal structure of complex L·TNT

Chem. Eur. J. **16**, 5895 – 5901 (2010)

2.3.5 Biological ligands: ion channels and siderphores

- Interest in modelling cation transport across biological cell membranes by ion channels is significant.
- X-ray crystal structure of biological K^+ and Cl^- channels (2003 Nobel Prize in Chemistry)

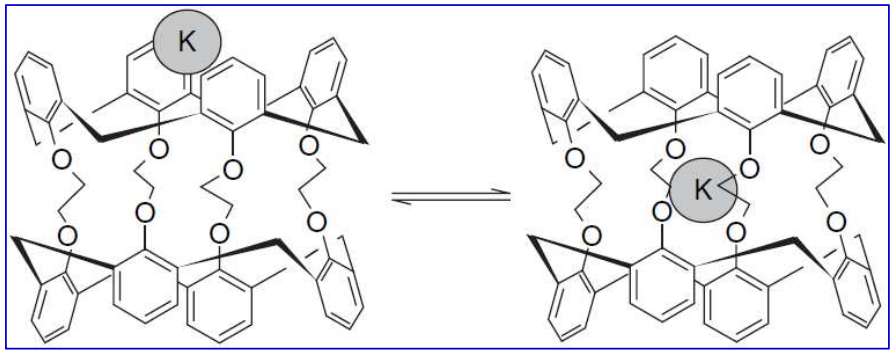


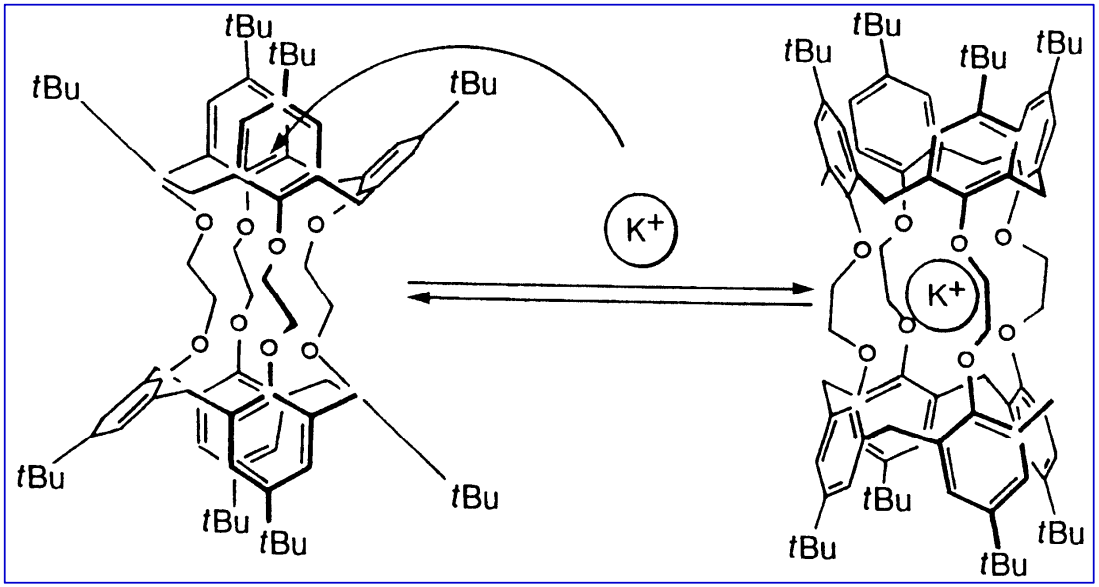


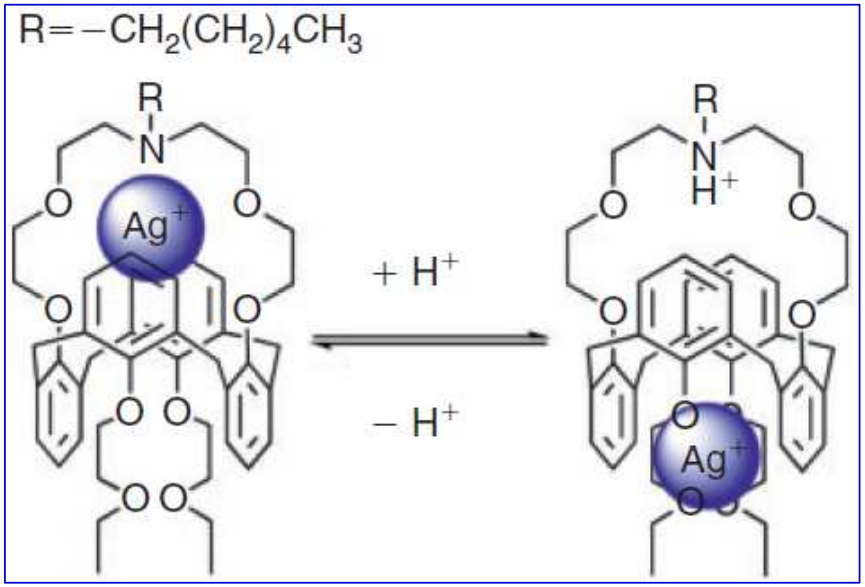
K+ channel in the open (left) and closed (right) conformations.

- A model calixarene system for a K^+-gated ion channel has been developed by coupling two calixarenes together with ethyleneoxy chains to give a bis(calixarene) 'tube'.
- This 'calixtube' selectively binds K^+ over any other alkali- or alkaline-earth metals;

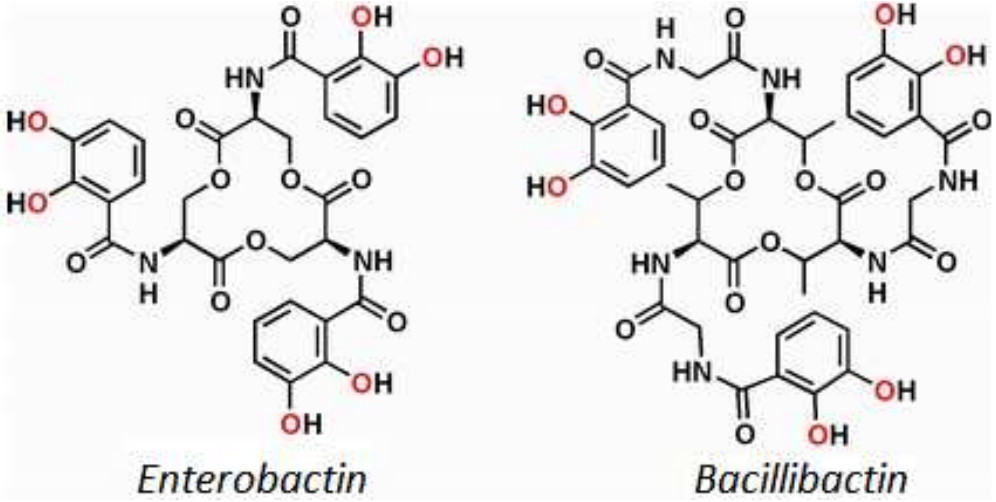
  $K = 4\times10^4\ M^{-1}$ in $CHCl_3/H_2O$



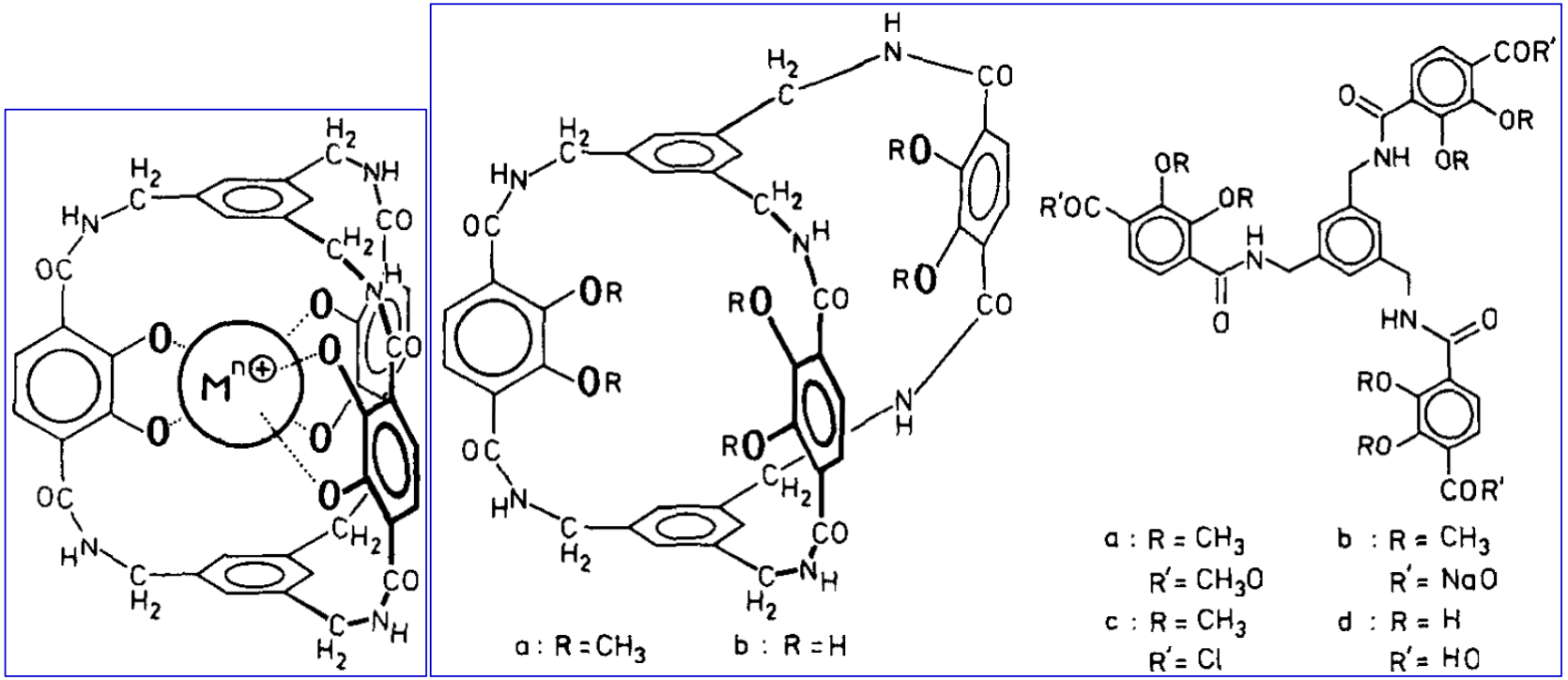




- Important natural cation-binding process: detection and bioaccumulation of the trace element Fe(III).
- When a cell becomes iron-deficient, the organism produces low-molecular-weight organic compounds, called ***siderophores*** (from the Greek, meaning 'iron carriers').
- Siderophores are unique ligands that selectively bind Fe(III) $K_a > 10^{30}$ M^{-1} and are able to transport the iron across the cell membrane.



Trilactone-based natural siderophores



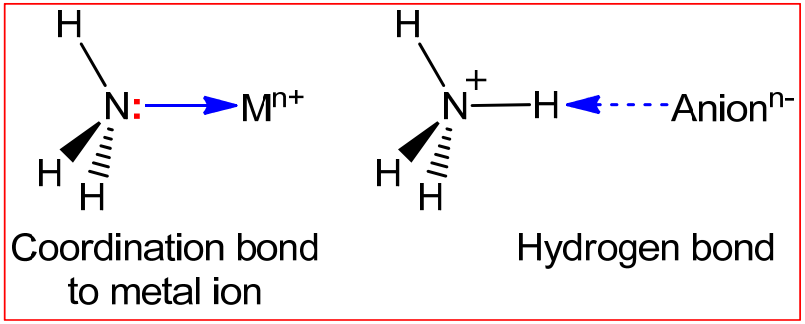
Artificial, macrobicyclic siderophores

Angew. Chem., Int. Ed. Engl. **23**, 714(1984)

2.4 Anion binding: 2.4.1 Introduction

- In contrast to cation binding, anion binding was relatively slow to develop.
- The design of cation and anion hosts uses the same criteria,
  i.e. specificity arising from the preorganised placement of complementary binding sites.

- Design of anion host: more challenging task due to the properties of anions.
  - Negative charge
  - Size and polarizability
  - Shape
  - pH Dependence
  - Solvation



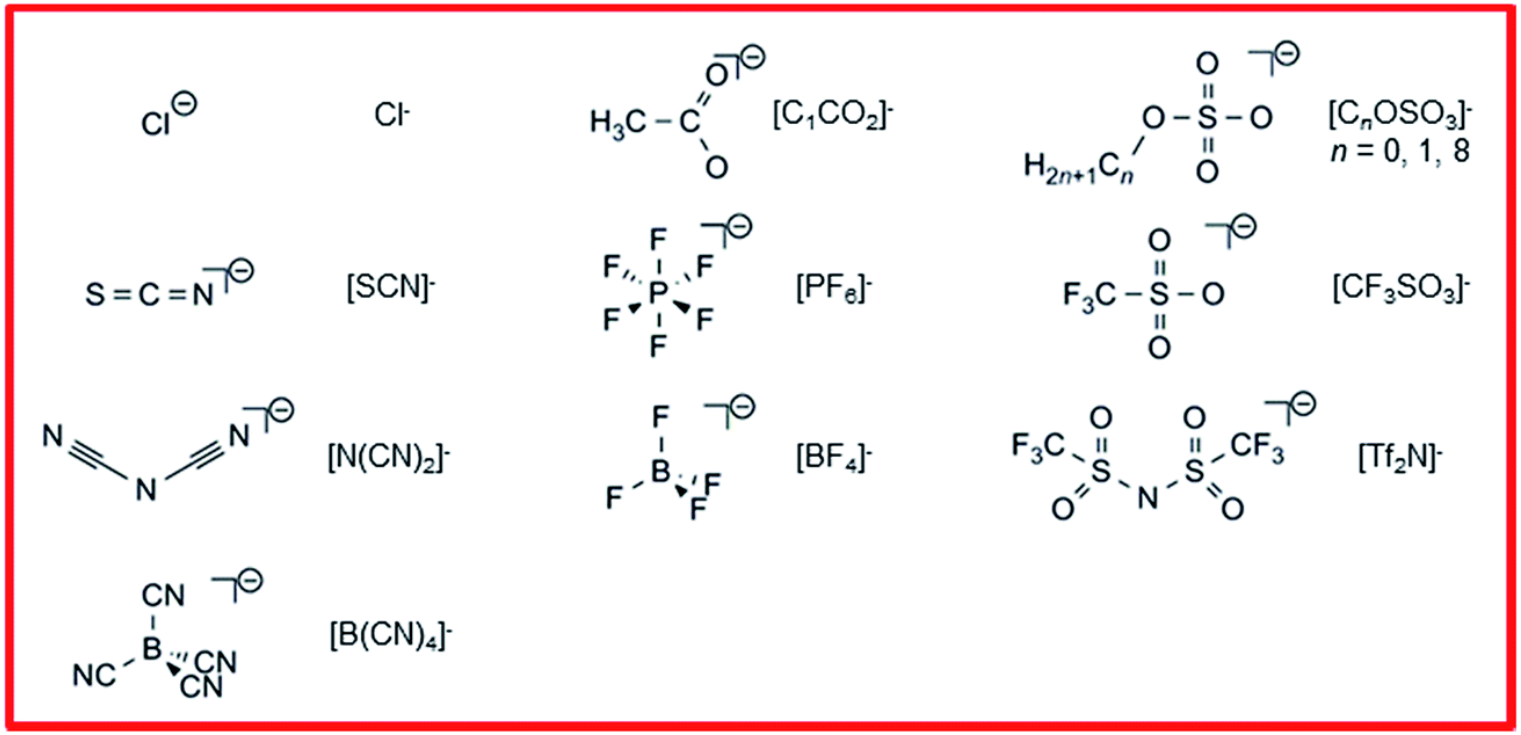
Ionic radii (Å)			
H^+	1.14	F^-	1.33
Li^+	0.60	Cl^-	1.81
Na^+	0.95	Br^-	1.96
K^+	1.33	I^-	2.20
Rb^+	1.48	O^{2-}	1.40
Cs^+	1.69	S^{2-}	1.84
NH_4^+	1.48		
Ba^{2+}	1.35		

- There are several structural similarity
  between transition metal and anion coordination chemistry.
  - Chelate effect
  - Sandwich
  - Similar coordination numbers and geometries

1. Anions come in many shapes and sizes.

- Generally larger than cations and therefore larger hosts are required to bind them.
- The smallest anion, F^-, has a radius approximately comparable to the radius of K^+.
- Generally, cations are spherical (except for organic cations, such as ammonium ions), but anions are found in various shapes.
  e.g. spherical (halides), linear SCN^-, planar NO_3^-, tetrahedral HPO_4^{2-} and octahedral PF_6^-.
- Biologically important anions (nucleotides and proteins) have much more complex shapes.

Shapes of Anions: Spherical, Linear, Trigonal planar, Tetrahedral, Octahedral.

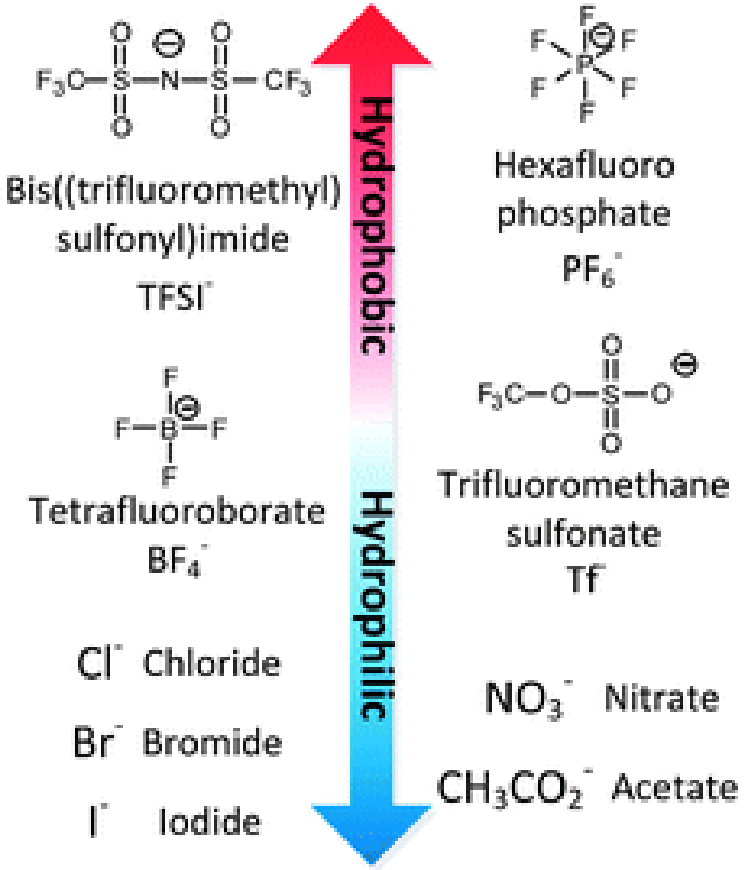


2. Anions have high free energies of solvation compared to cations of similar size
and hence hosts for anions experience more competition from the surrounding medium.
e.g. standard free energies of hydration,
G^{o}_{hydr} for F^{-} = −465 kJ mol^{-1} and G^{o}_{hydr} for K^{+} = −295 kJ mol^{-1}

3. Generally, most anions exist in a narrow pH window.
- This can be problematic for hosts.
- The host may not be fully protonated in the pH range where the anion is deprotonated.

4. Many anions are generally coordinatively saturated and they only bind *via* weak interactions,
such as hydrogen bonding and van der Waals interactions.

Hydrophobic and hydrophilic anions

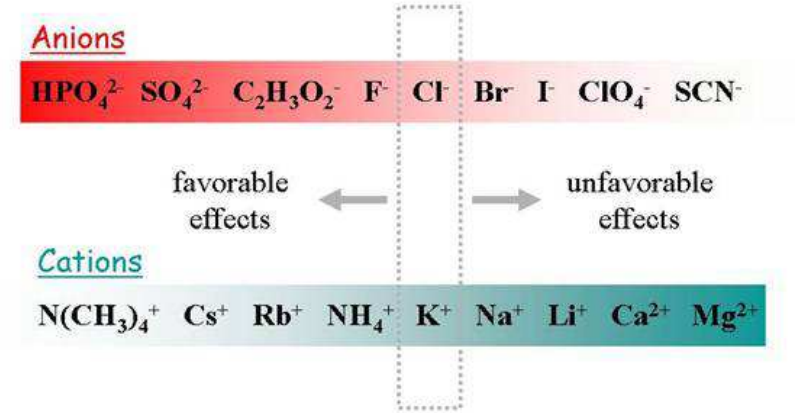


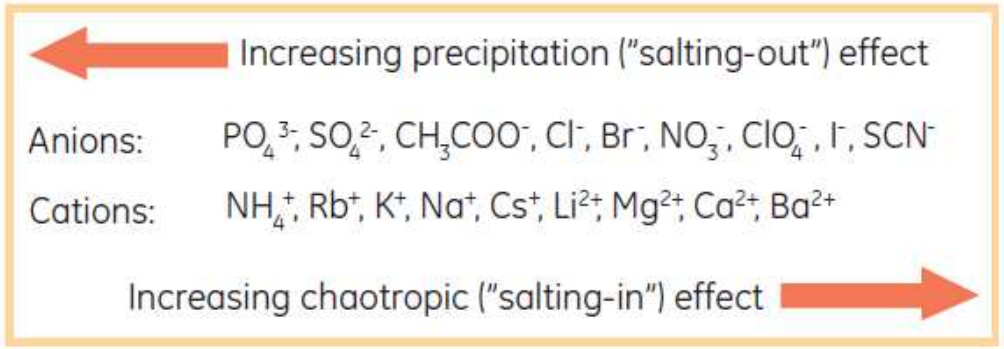
Anion	Name	pK_a
ClO_4^-	Perchlorate	-10
I^-	Iodide	-9.5
Br^-	Bromide	-9
Cl^-	Chloride	-6
ClO_3^-	Chlorate	-2.7
SCN^-	Thiocyanate	-1.9
NO_3^-	Nitrate	-1.3
Ph-SO_3^-	Phenylsulfonate	-1.0
p-CH_3-Ph-SO_3^-	Methyl phenylsulfonate	-1.0
$CH_3SO_3^-$	Methylsulfonate	-0.6
$CF_3CO_2^-$	Trifluoroacetate	-0.3

J. Am. Chem. Soc. 90, 319(1968)

Hofmeister series:

showing the effect of some anions and cations on protein precipitation.





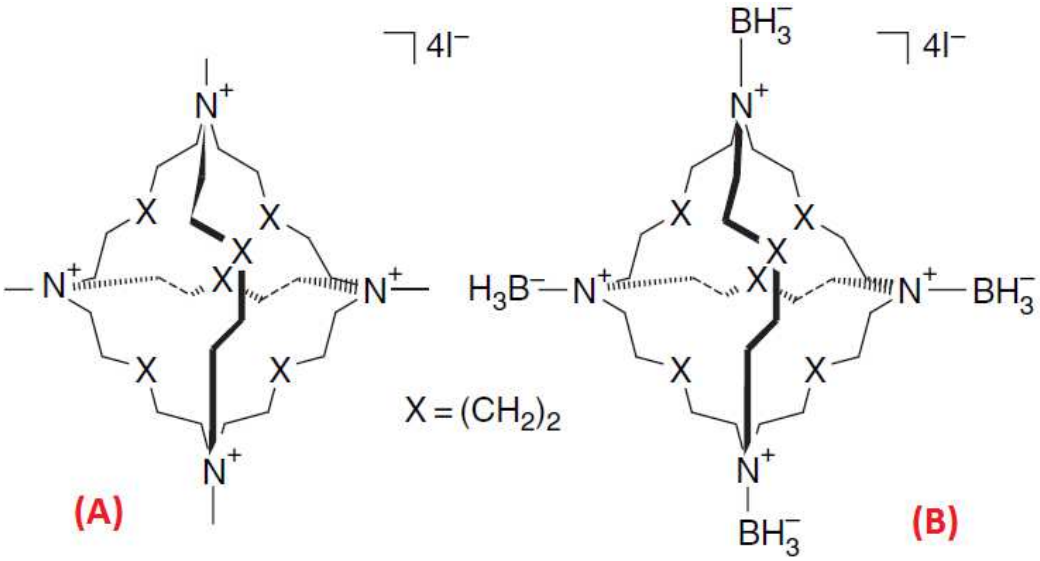
$Na_2SO_4 > K_2SO_4 > (NH_4)_2SO_4 > Na_2HPO_4 > NaCl > LiCl$ ..... $> KSCN$

Relative effects of some salts on protein precipitation.

2.4.2 Charged receptors

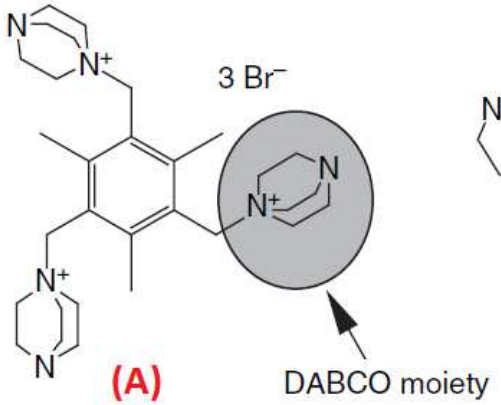
Electrostatic interactions

- Binding anions → design of a host containing positive electrostatic charge.
- Modulation of non-directional and non-selective nature of the electrostatic interactions
  → by functionalities such as hydrogen bond donors or acceptors.
- Electrostatic interactions are often the first interactions between the substrate and enzyme.
- Early work:
  - electrostatic interactions to tetrahedral tertiary ammonium cryptand (A) → **very effective host for I^-**
  - zwitterionic neutral cryptands containing BH_3 (B)

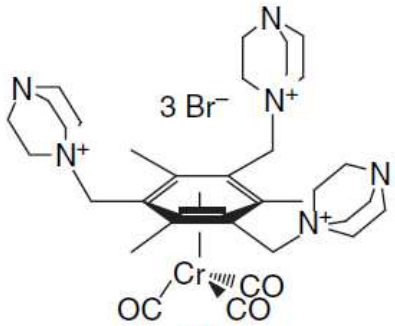


Selective host for NO_3^- and Br^-

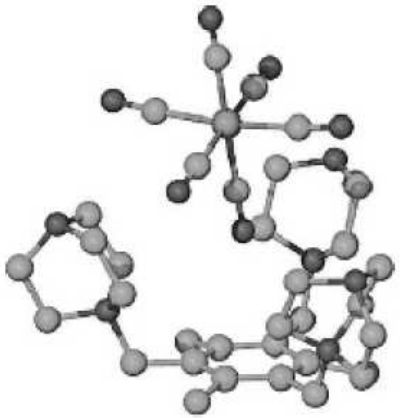
- A common building motif for anions → 1,4-diazabicyclo[2.2.2]octane (DABCO).
- Relatively unselective cationic host and binds large anions such as $FeCN_6^{3-}$.
- The simple DABCO-based podand (A) is flexible
  and not preorganised due to free rotation around the $-CH_2-$ groups.
- The free rotation can be controlled by the incorporation of a metal-containing moiety (B).



(A)

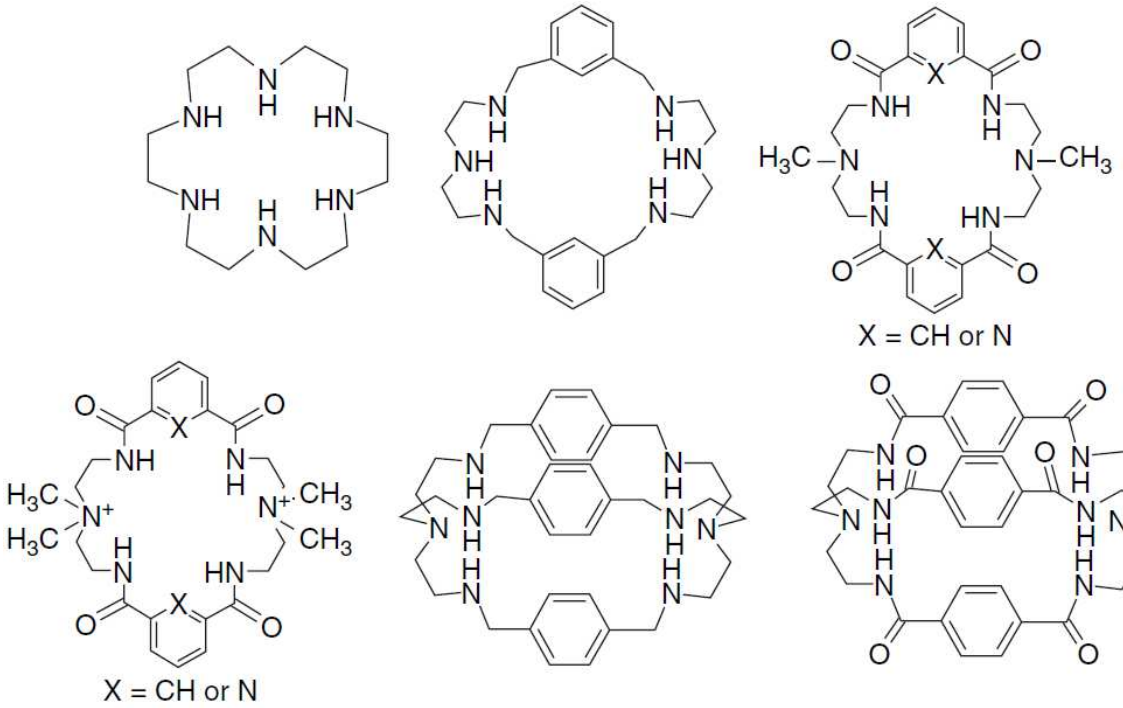


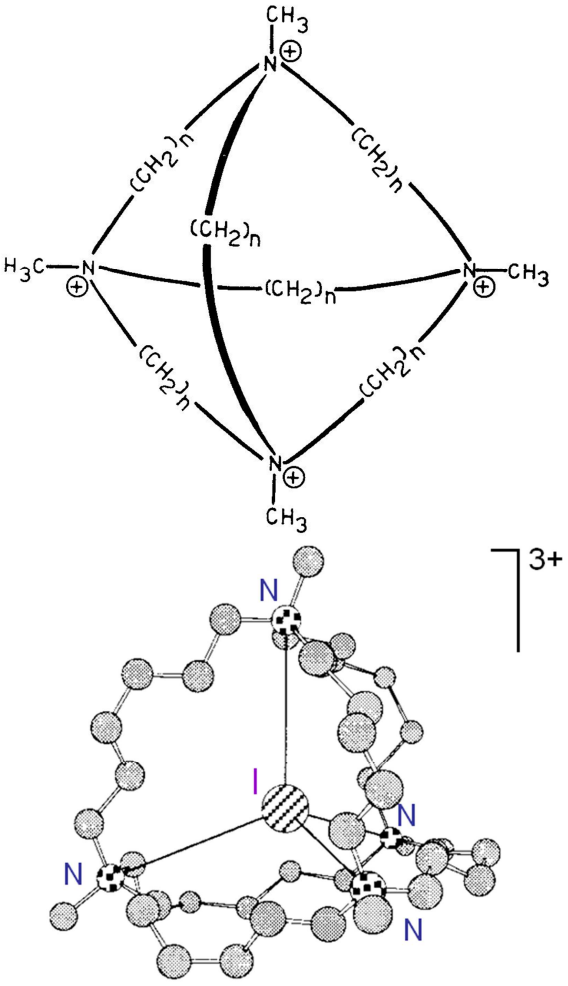
(B)



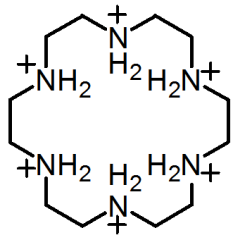
Electrostatic and hydrogen bonding interactions

- The most common class of anion binding:
  combination of electrostatic interactions and hydrogen bonding.
- Protonated nitrogen-containing macrocycles and macrobicycles (azacorands and cryptands).

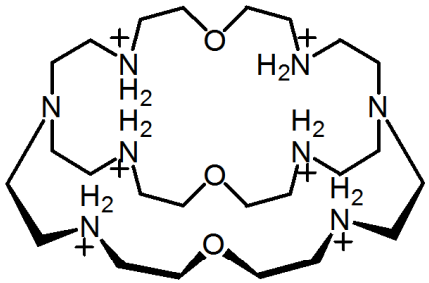




Aza-Crowns and Cryptands – Coordination of Anions

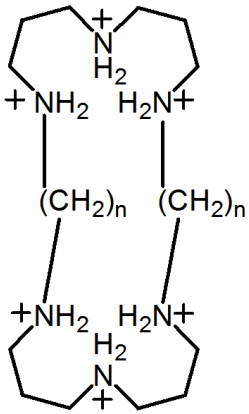


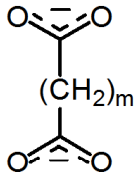
Hexacyclen
- selective for Cl^- over I^-



bis(tren)

Anion	F^-	Cl^-	Br^-	I^-	N_3^-
log*K*	4.19	3.0	2.6	2.15	4.30

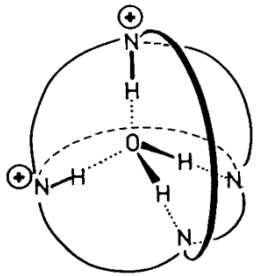




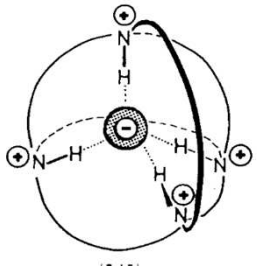
n = 7, 10
m = 1 - 8

Cage Host-Guest Systems

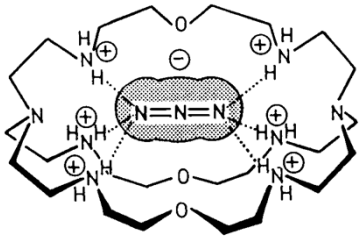
Neutral form binds ammonium



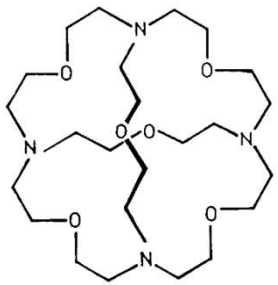
Diprotonated form binds water

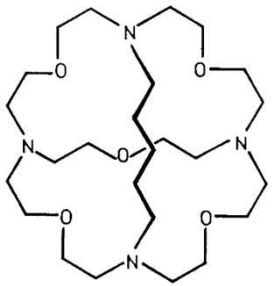


Tetraprotonatd form binds halide ions



Tailor-made for azide



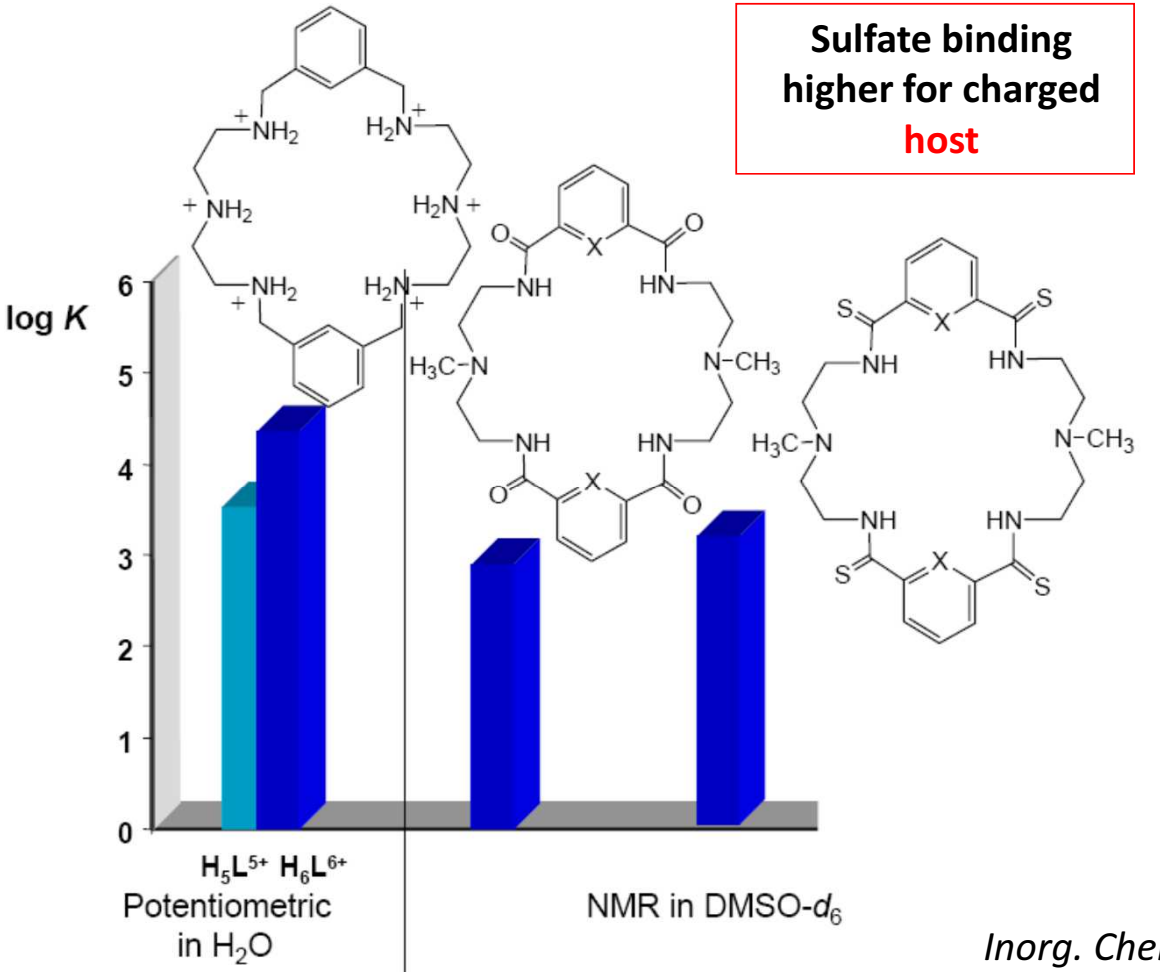


Both bind alkali metal ions

Sperical hosts able to bind cations, anions or neutral molecules

H Bonding - Sulfate

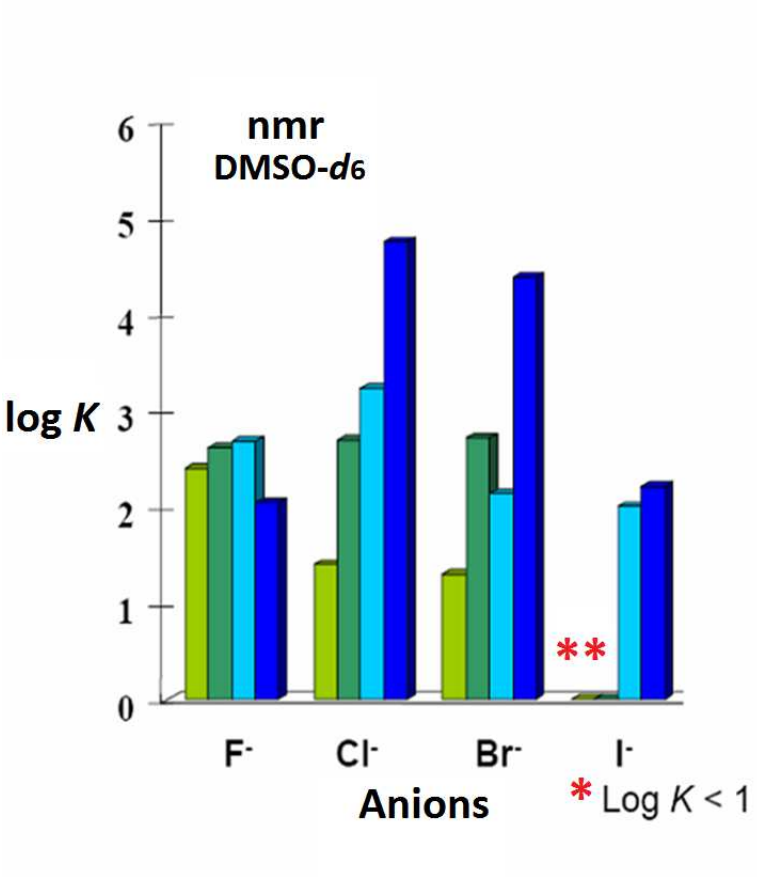
Sulfate binding higher for charged host

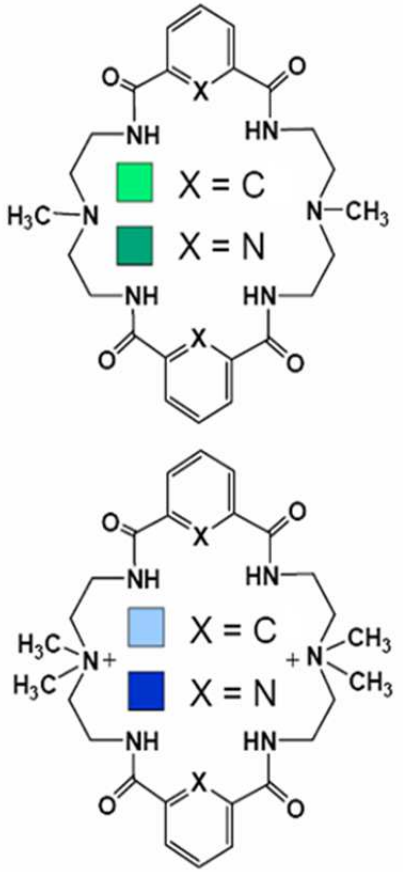


Inorg. Chem. 40, 4710(2001)
Inorg. Chem. 42, 5043(2003)

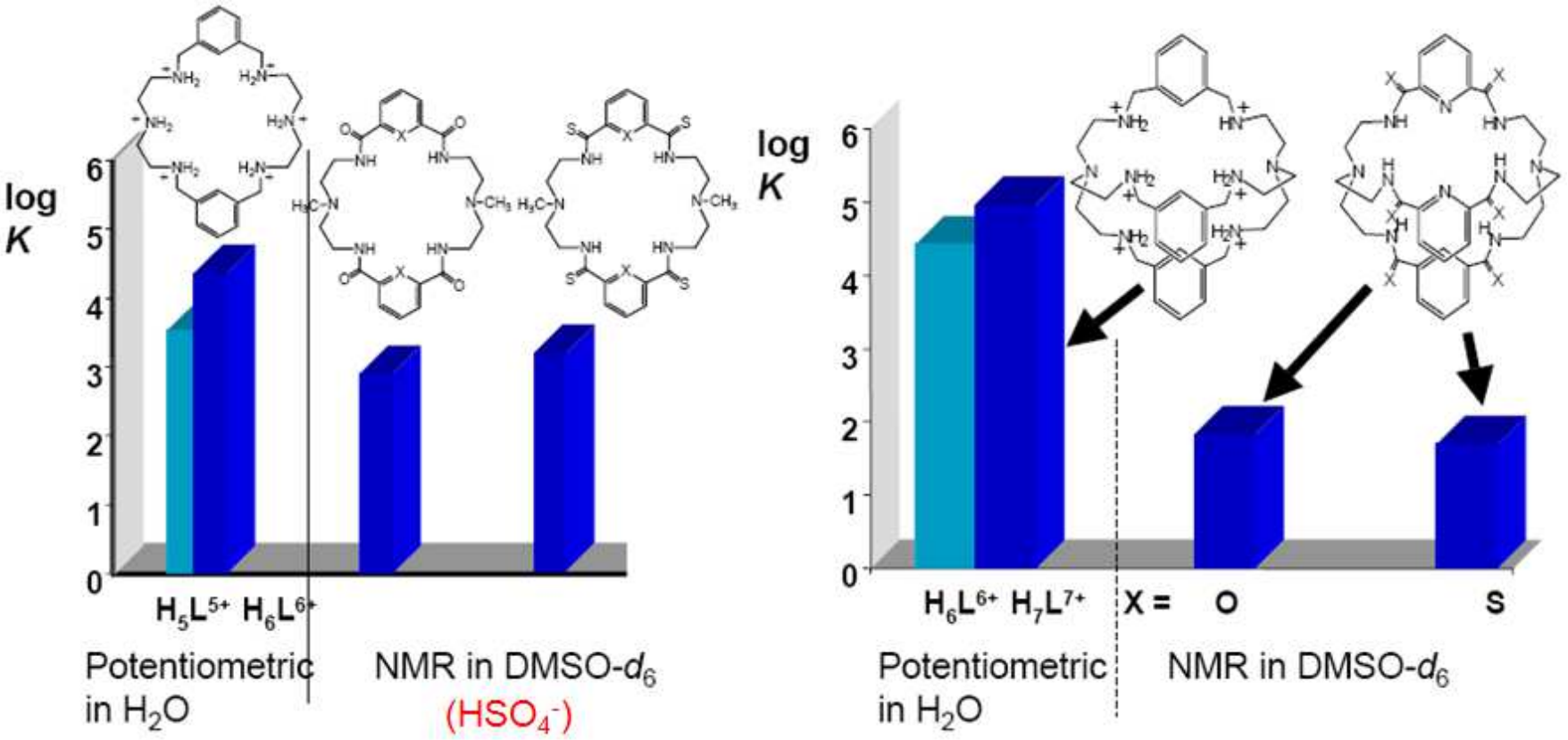
❑ Electrostatic Attraction

- ❑ Charged hosts clearly stronger binders of larger halides
  - – perhaps in part reflecting relative desolvation ease



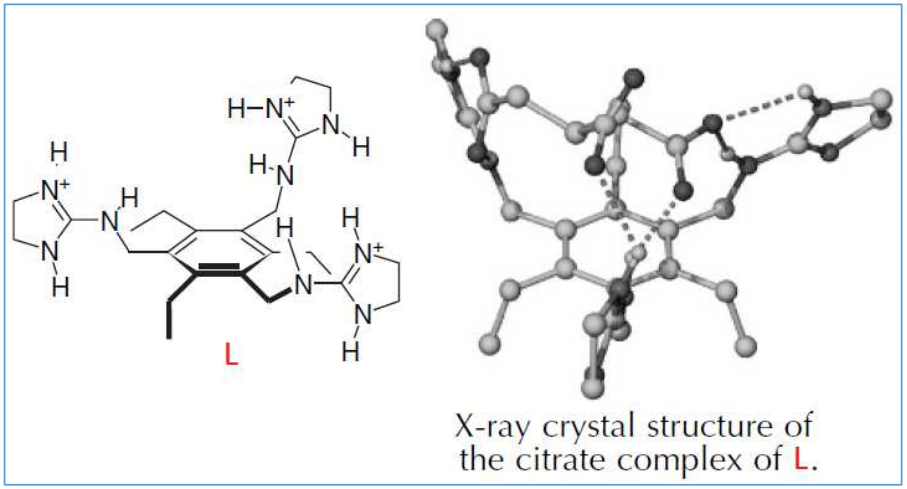


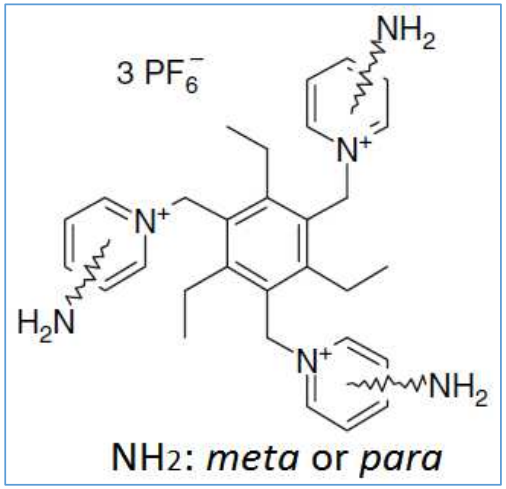
Amine *vs* Amide: Sulfate



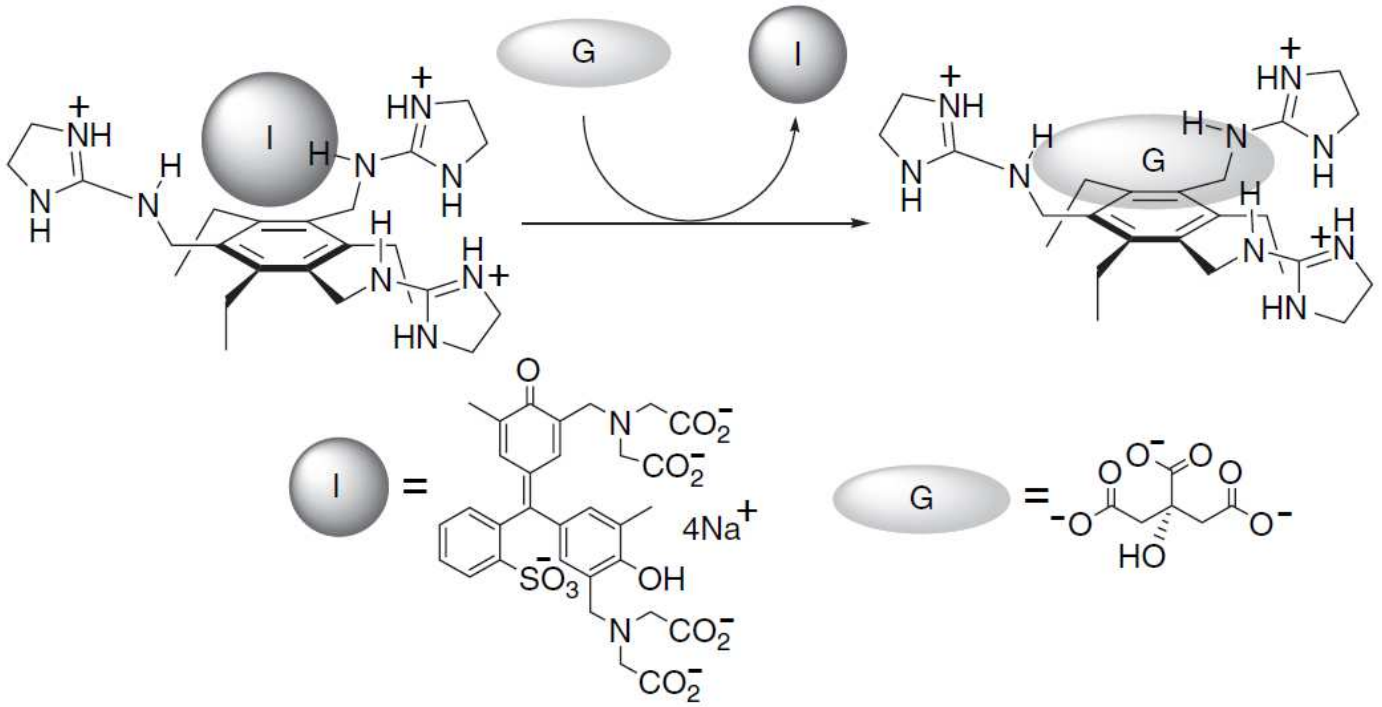
Log *K* values are higher when strong electrostatic interactions are present.

- The receptor of tripodal species which contains guanidinium functionalities.
  → hydrogen bonding with polycarboxylates (*ex*. citrate).
- The host–guest interaction is then enhanced by the positive charge on the guanidinium side arms.
- The role of the ethyl groups
  → preorganization of the podand arms into a '**3-up and 3-down**' arrangement.
  → producing an anion-chelating conformation with the guest by hydrogen bond.
- The energetic preference for alternation about a hexasubstituted aryl ring imparts ca. 15 kJ mol^{-1} additional binding energy to the complex.

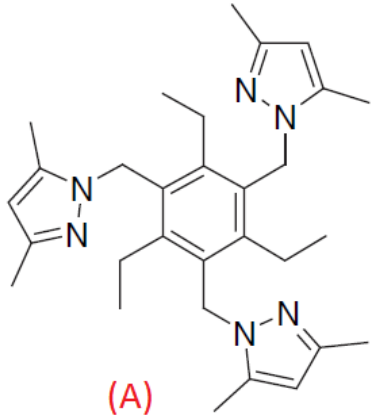




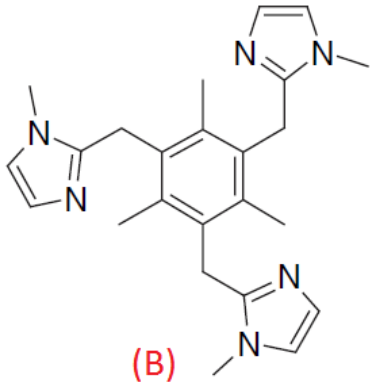
- Upon addition of a guest (ex. citrate anion), the indicator is displaced into free solution, changing λ_{max} due to the enhanced solvation of the indicator.
- The process is particularly effective when the indicator is chemically related to the target guest species.



- Compound (**A**): an effective host for the ammonium cation (NH_4^+).
- Compound (**B**): binds the anion $ZnCl_4^{2-}$ when triprotonated.
- When neutral, forms a complex with Ru^{2+}.



(A)

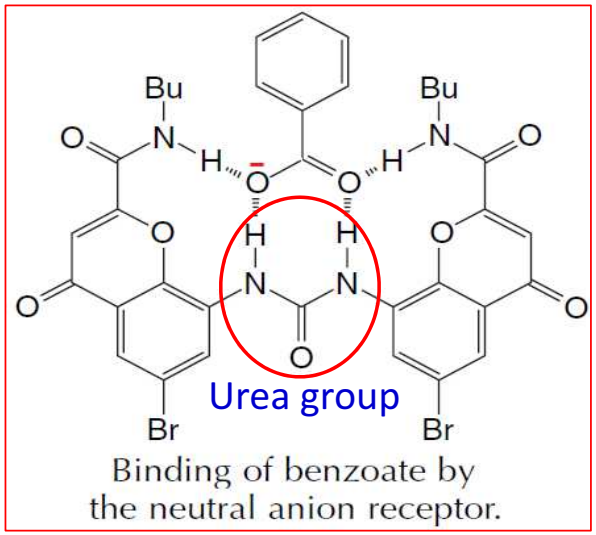


(B)

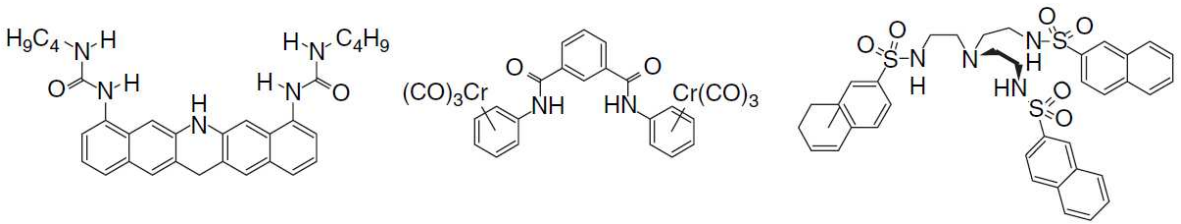
2.4.3 Neutral receptors

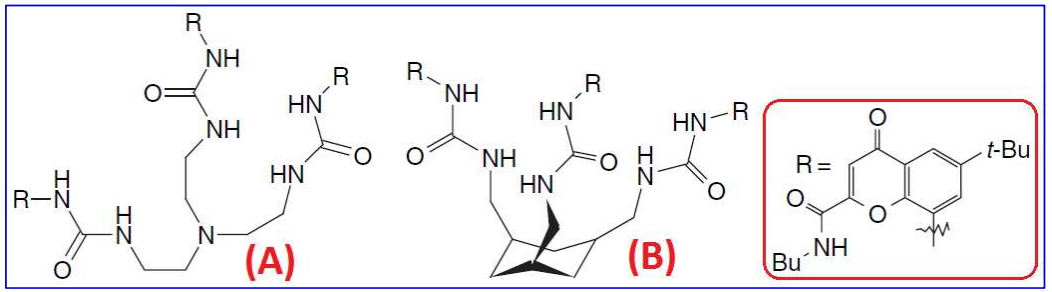
Hydrogen bonding interactions

- Neutral anion receptors incorporate strong, multiple hydrogen bond-donor groups (ex. urea)
- Urea group acts as both a binding site and the backbone of the dipodal system.
- The four hydrogen bond-donor NH groups can interact with oxo-anions.
- The binding constant for benzoate is high, at 15×10^4 M^{-1} in acetonitrile, hence suggesting a good match between the host and the guest.



Binding of benzoate by the neutral anion receptor.





- Receptors **(A)** and **(B)**: incorporated into membrane ion-selective electrodes.
  → Two hosts differ dramatically in the **degree of rigidity**, **preorganisation**, and the **size of the cavity**.
- More rigid **(B)** shows **Hofmeister-like selectivity**
  More flexible tris(2-aminoethylamine) derivative **(A)** proved to be distinctly **'anti-Hofmeister'**.
- Hofmeister series (1888) based on the ability of ions to 'salt-out' proteins and correlates the hydrophobic tendencies of various ions.

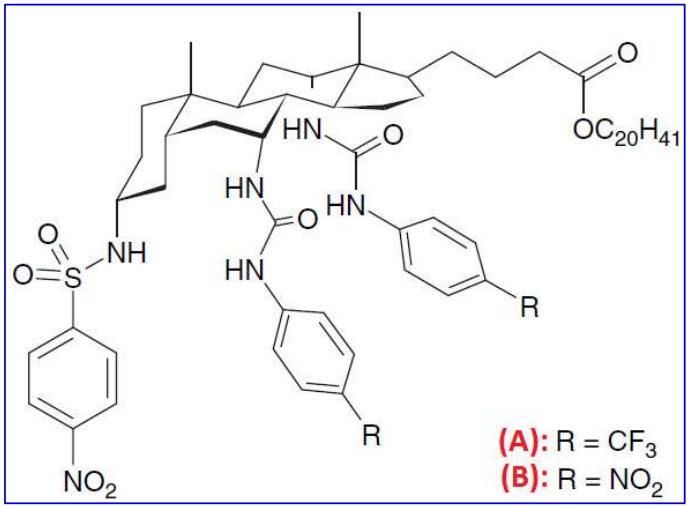
Hofmeister Series:

Strongly hydrated — Weakly hydrated

Anions: citrate^{3-} > SO_4^{2-} > HPO_4^{2-} > F^- > Cl^- > Br^- > I^- > NO_3^- ≈ ClO_4^-

Cations: Al^{3+} > Mg^{2+} > Ca^{2+} > H^+ > Na^+ > K^+ > Rb^+ > Cs^+ > NH_4^+ > $N(CH_3)_4^+$

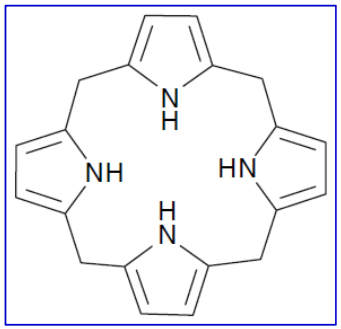
- ***Cholapods*** based on a cholesterol framework
  → 'second-generation' hosts: extremely powerful anion-chelating agents.
- Five acidic NH protons: a preorganised anion-binding conformation by the rigid cholesterol framework.
- The addition of electron-withdrawing $-CF_3$ and $-NO_2$ substituents
  increases the hydrogen bond acidity of the urea and sulfonamide groups.
  - **(B)**: binding constant for Cl^- of $6.60 \times 10^{10}\ M^{-1}$
    for thiourea analogue $1.03 \times 10^{11}\ M^{-1}$



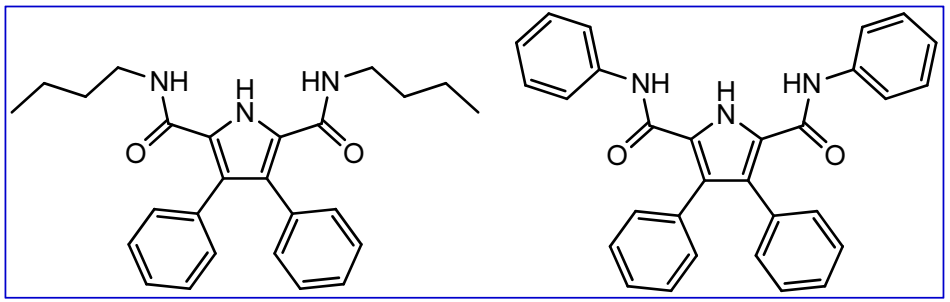
- Calix[4]pyrrole (**A**): generally adopt a 1,3-alternate conformation
  but undergo a conformational change on the addition of fluoride.

- One of the simplest classes of pyrrole-based molecular receptors (**B**)
  binds oxo-anions in polar organic solvents.
  - host **B1** binds benzoate 18 times more strongly than chloride in acetonitrile
  - host **B2** binds benzoate 51 times more strongly than chloride in a 0.5 % DMSO/H_2O mixture.
  - K_{assoc} of $H_2PO_4^-$ for **B1**, K_{assoc} = 357 M^{-1}
    for **B2**, K_{assoc} = 1,450 M^{-1}

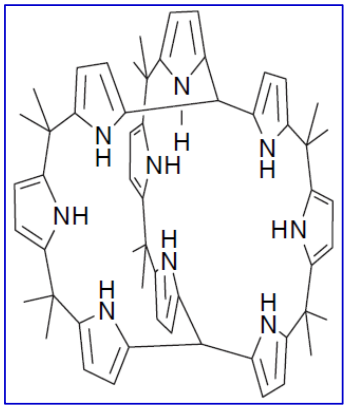
- Cryptand-like calixpyrrole (**C**) binds fluoride *via* six of the nine hydrogen atoms,
  forming a one-to-one host–guest complex in CH_2Cl_2/THF mixed solvent.



A



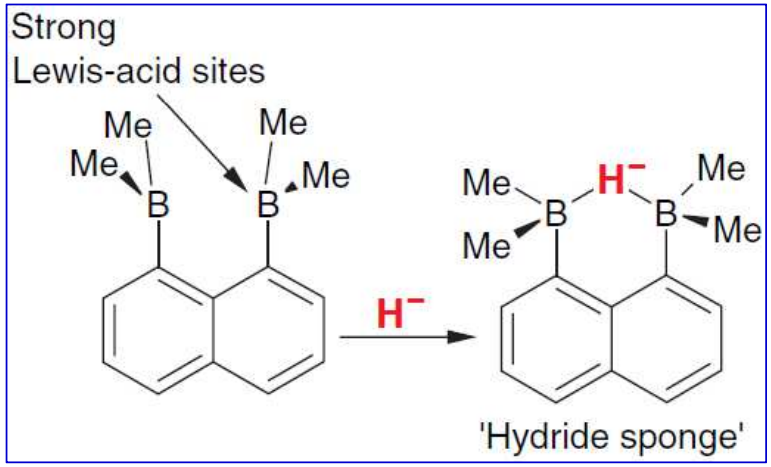
B1 **B2**

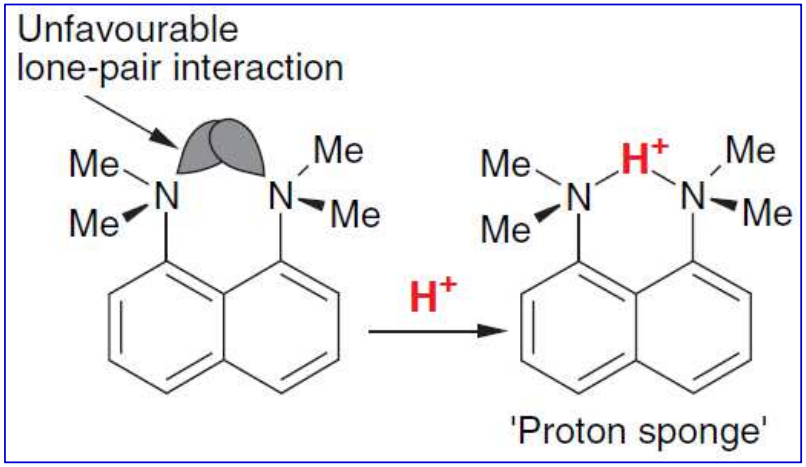


C

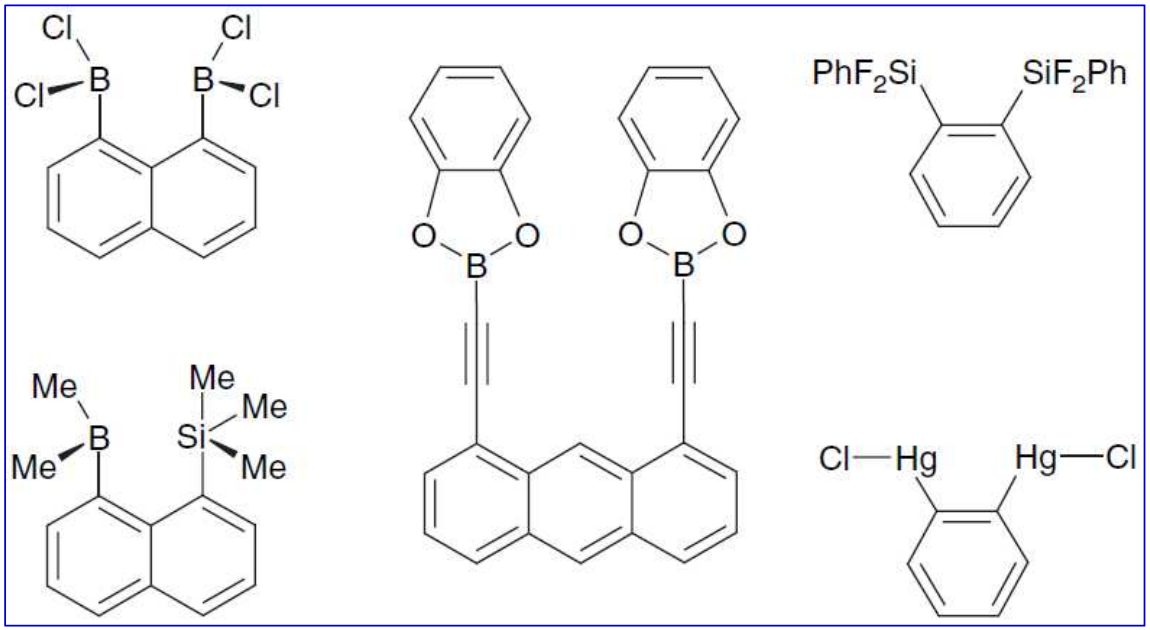
2.4.4 Lewis-acid receptors and anticrowns

- The earliest types of anion-binding Lewis-acidic receptors
  → rigidly preorganised '**hydride sponge**'
  → This is analogous to the H^+-binding '**proton sponge**'
- The electron-withdrawing naphthalene spacer makes the boron centres more electron deficient than aliphatic trialkylboranes, which also enhances the stability of the hydride complex.

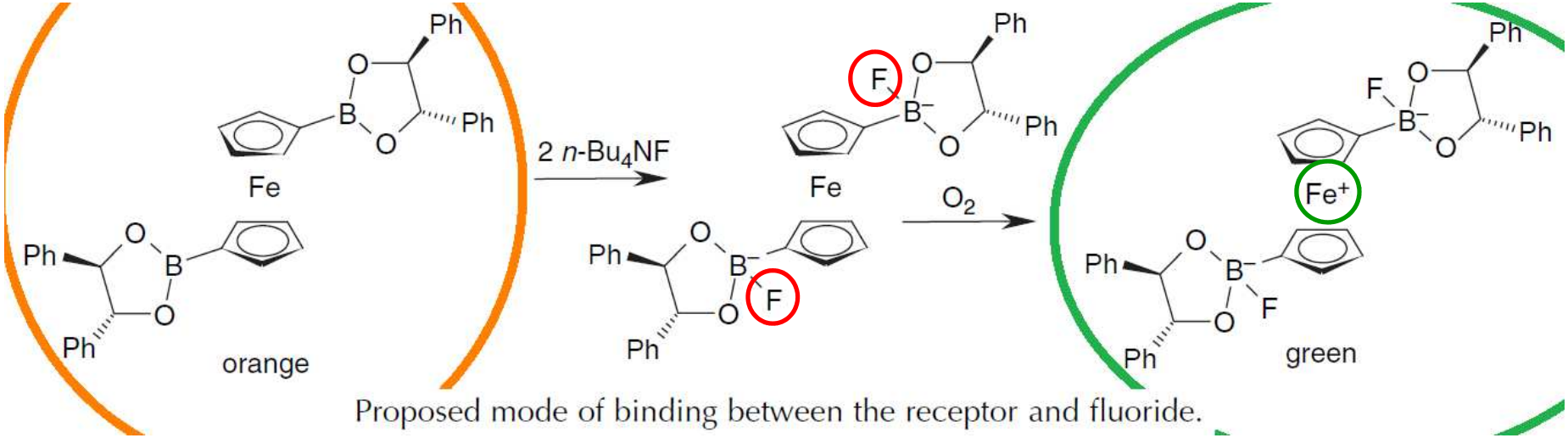




- Since the preparation of this simple receptor, there has been many Lewis-acid receptors for anion recognition in supramolecular chemistry.

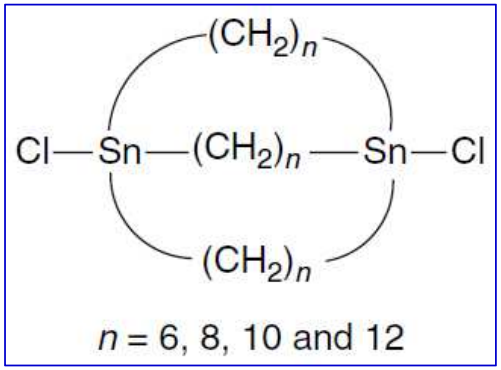


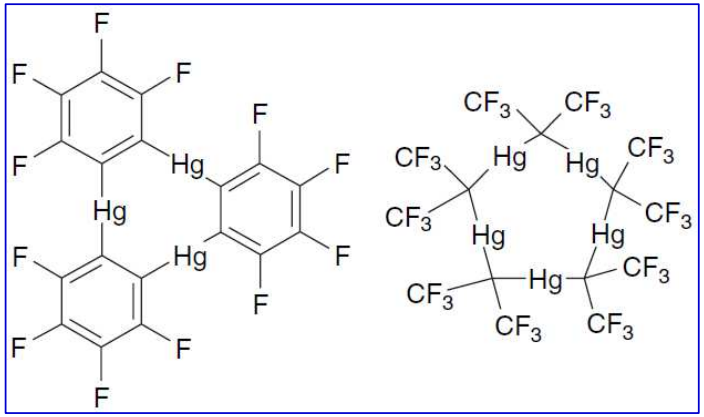
- Multidentate Lewis-acid host: colourimetric fluoride sensor.
- Reaction of the host with *n*-$Bu_4N^+F^-$ in $CHCl_3$ produces a marked colour change (orange to pale green) under aerobic conditions.
- No colour change under anaerobic conditions or with the addition of Cl^-, Br^-, I^-, BF_4^-, PF_6^-, $H_2PO_4^-$, HSO_4^{-2-}, NO_3^-, → selectivity for **F^-** alone.



Proposed mode of binding between the receptor and fluoride.

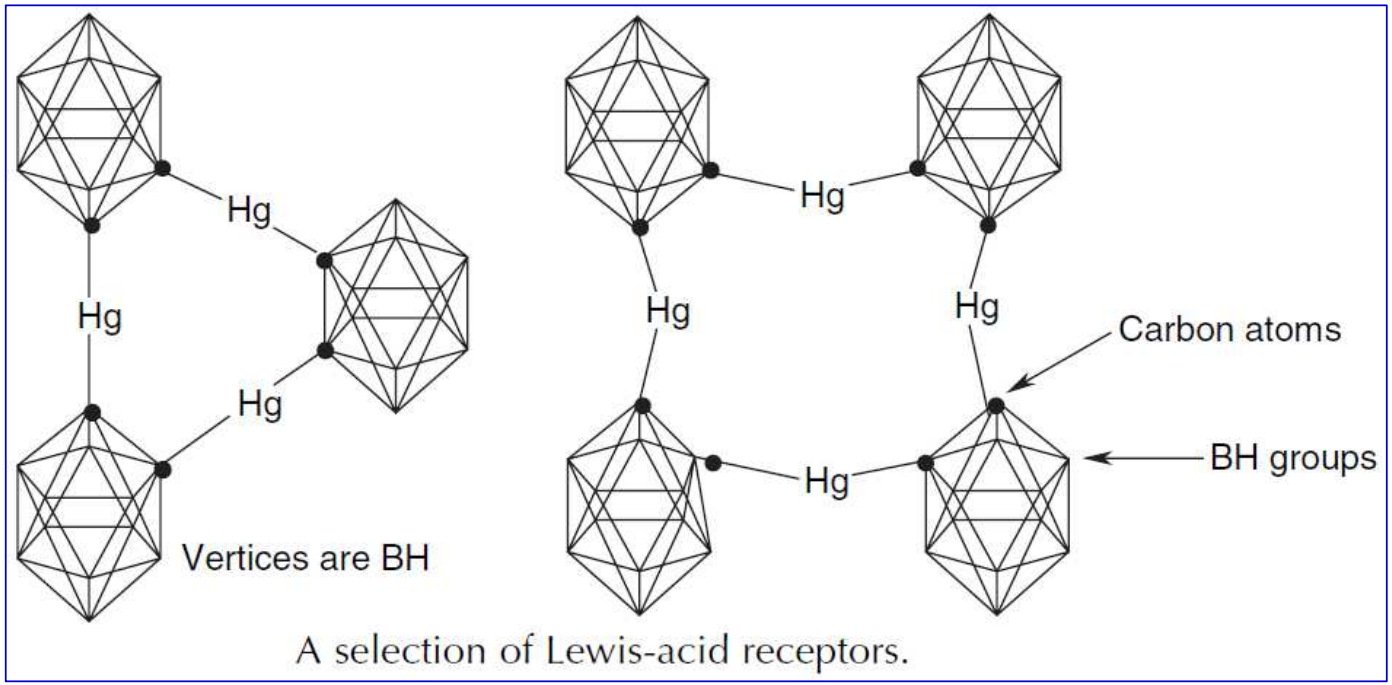
- ***Anticrowns:*** An interesting and unusual class of Lewis-acid receptors, which contain Lewis-acid centres (Si, Sn and Hg being the most common) incorporated into a macrocyclic ring system.
- The simple tin complexes $Cl_2Sn[(CH_2)_n]_3SnCl_2$ (n = 6, 8, 10, and 12) form with halide anions in CH_3CN.
- **F^-** coordinates to both the Lewis-acidic centres in the small n = 6 host, **Cl^-** only binds to a single Sn atom in the larger n = 8 homologue – the anion is too small to stretch across the larger cavity.
- To increase the binding affinity of anticrowns towards anionic species, electron withdrawing groups are attached to the scaffold.
  - ▸The fluorine atoms drastically increase the Lewis acidity of mercury atoms.





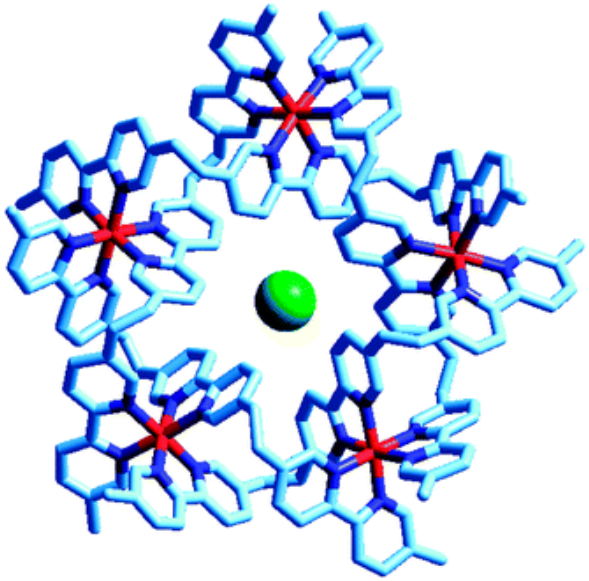
High affinity towards Cl^-, Br^-, I^- SCN− and BH_4^-.

- The best known of the anticrowns: **mercuracarborands**
- As with the fluorinated complexes, the carborane substituents act as elaborate electron-withdrawing groups and increase the Lewis acidity of the mercury(II) ions.



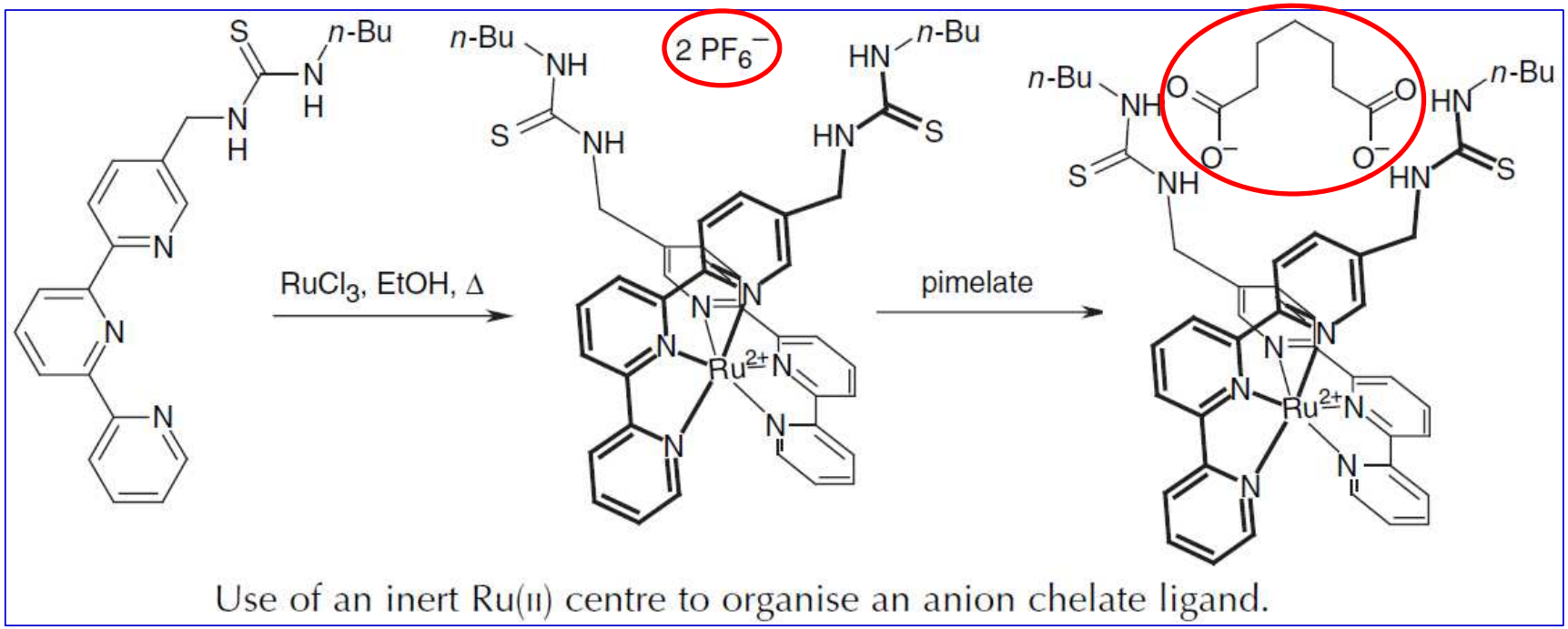
A selection of Lewis-acid receptors.

2.5 Metal-containing receptors



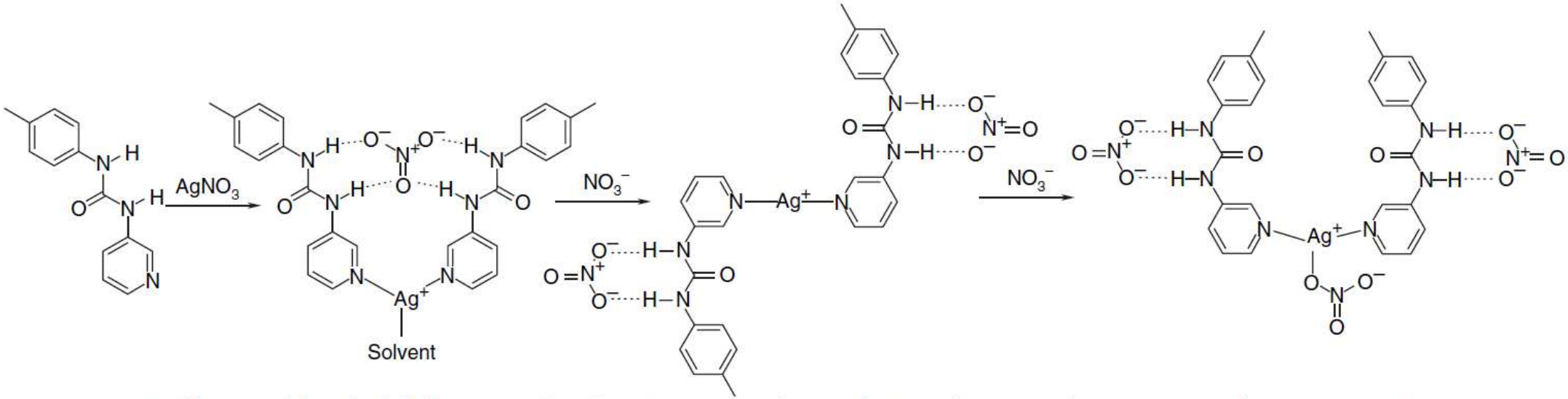
2.5.1 Metals as structural elements

- Further divided hosts with metals as structural elements:
  Inert and labile coordination complexes.
- **Inert complexes:**
  (ex). Two thiourea-derived terpyridyl ligands are held together
  by a relatively inert (low-spin d^6) Ru(II) centre



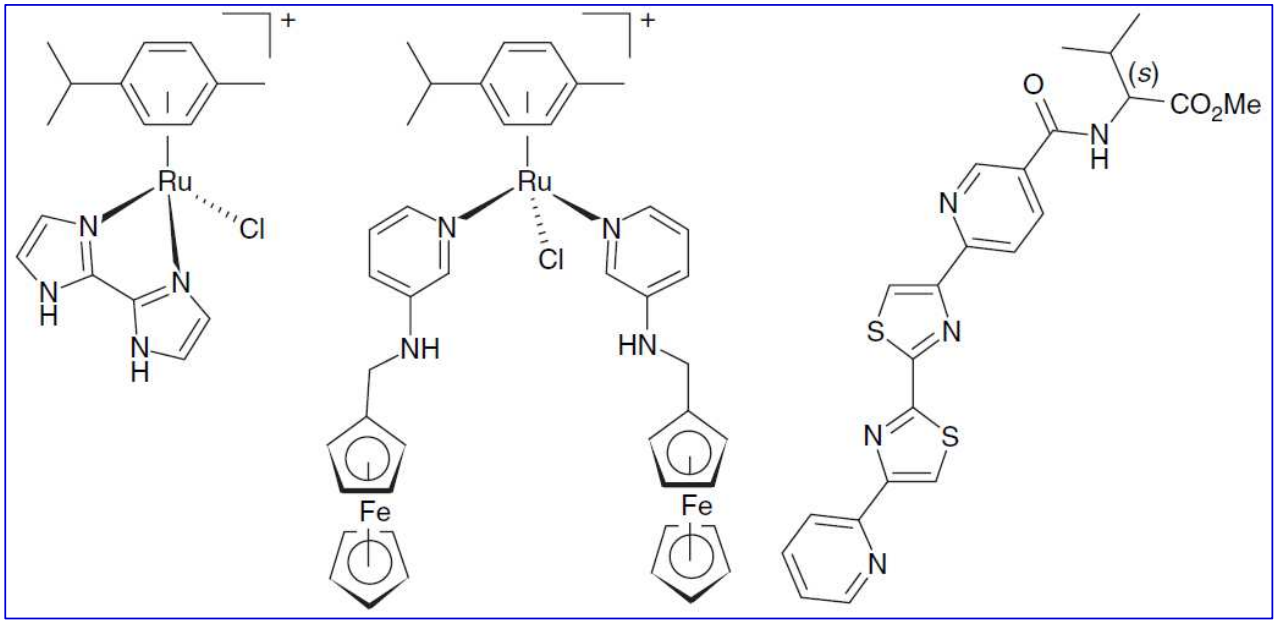
Use of an inert Ru(II) centre to organise an anion chelate ligand.

- **Labile complexes** are not true anion hosts.
  Instead, they fall into the category of self-assembly
  and are frequently templated by anions, cations or both.



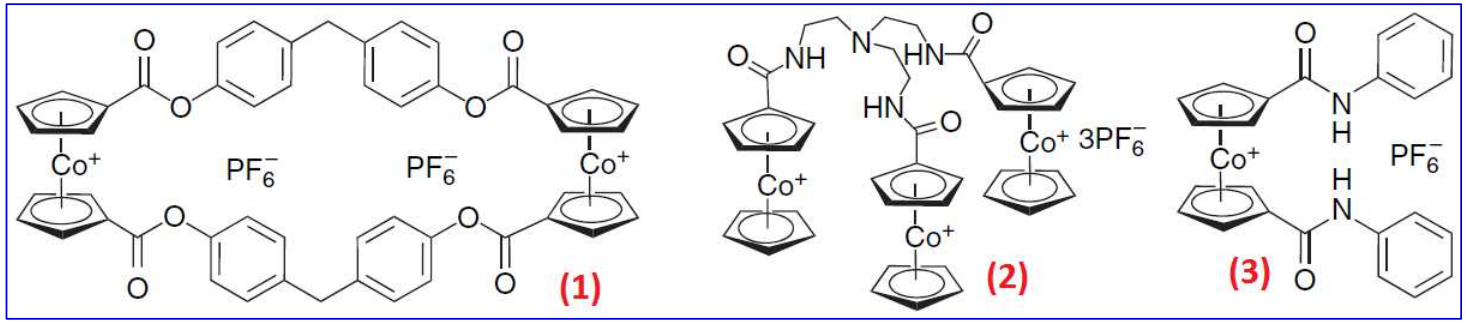
Self-assembly of a labile nitrate-binding Ag(I) complex and its evolution in the presence of excess nitrate.

- The boundary between labile and inert-complexes: the arene Ru(II) derivatives.



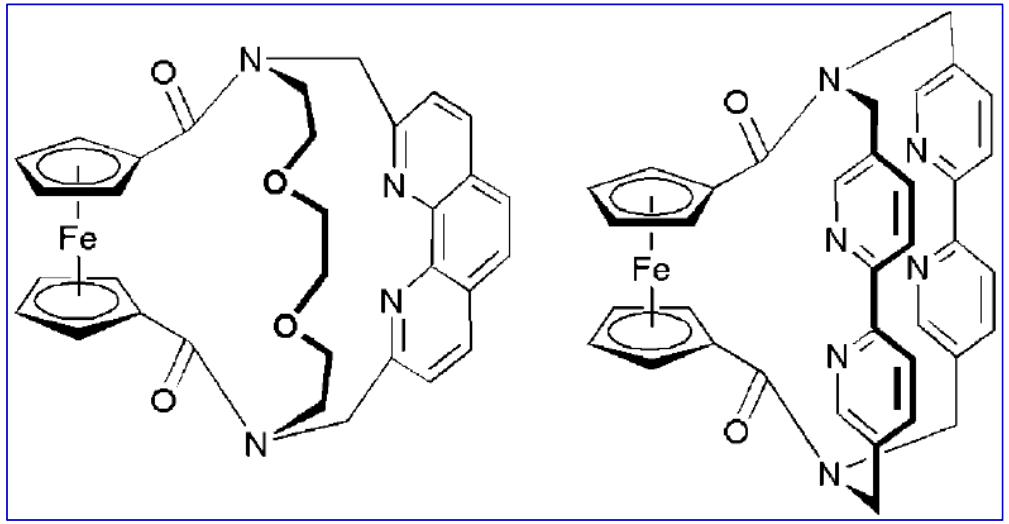
2.5.2 Metals as electrochemical sensing elements

- **Anion receptors containing redox-active groups** (ferrocene or cobaltocenium): popular research area.
  1. Cyclophane organometallic receptor (**1**)
  2. Tripodal receptor (**2**)
  3. Molecular cleft (**3**)

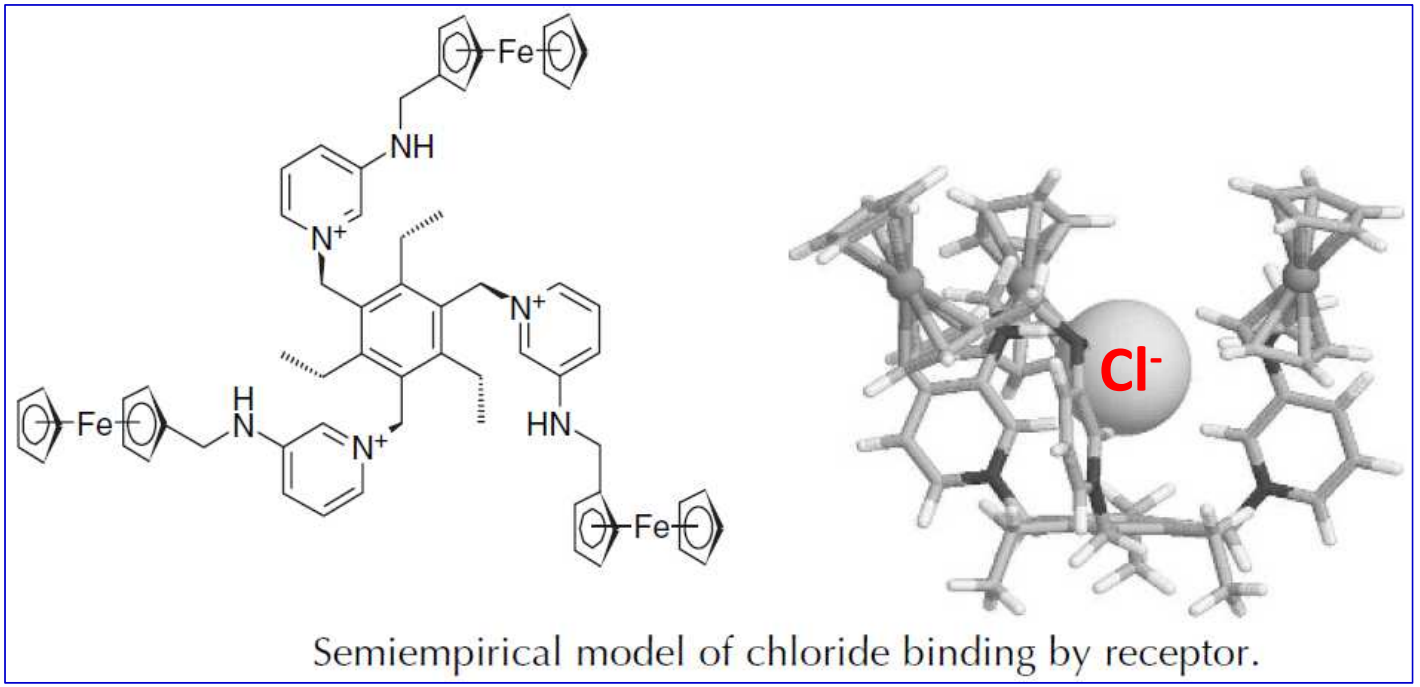


- Receptors **2** and **3** have an affinity for $H_2PO_4^-$ over Cl^- in CH_3CN.
  for **2**, K ($H_2PO_4^-$) = 1200 and K (Cl^-) = 100 M^{-1}
  for **3**, K ($H_2PO_4^-$) = 320 and K (Cl^-) = 35 M^{-1}
- The reason for the selectivity for $H_2PO_4^-$ over other anions is the basicity of $H_2PO_4^-$.

- **Redox-switchable cation-binding cryptands**
- Upon oxidation of the ferrocene moiety,
  guest cations are expelled from the cryptand cavity due to increased electrostatic repulsion.

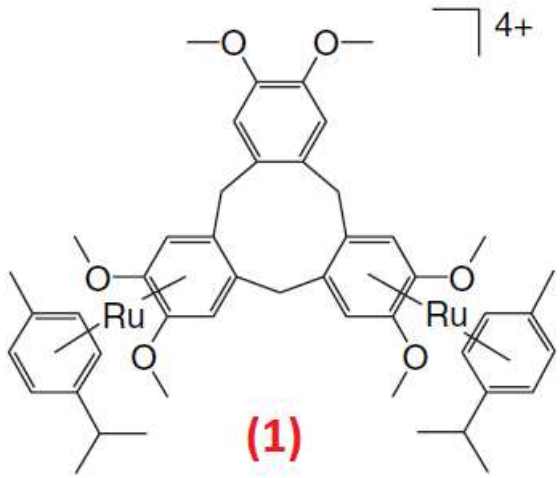


- Anion-binding hosts are often transformed into sensing systems by appending redox-active groups such as ferrocenyl units.
- (ex). the '**Venus' flytrap**' anion sensor was developed from the chloride binding tripodal host.
  ▸high affinity towards chloride (binding constants > 17,400 M^{-1} in CH_3Cl

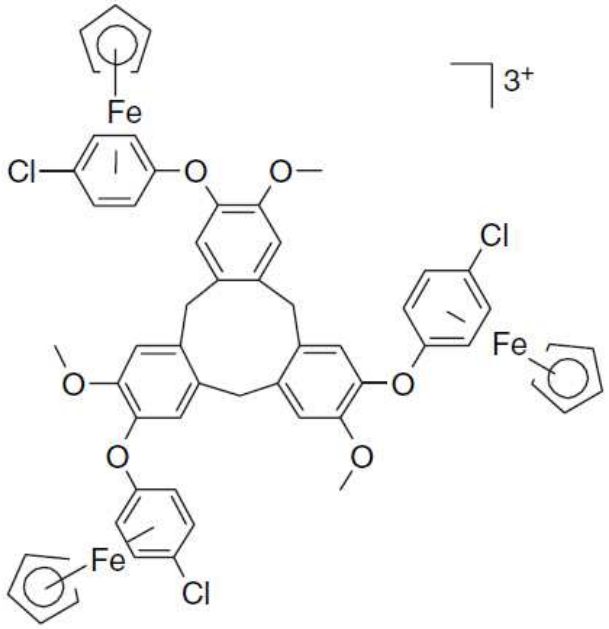


Semiempirical model of chloride binding by receptor.

- A number of organometallic bowl-shaped anion hosts have been prepared based on Ru(II), Rh(I), Rh(III) and Ir(III) -complexes of bowl-shaped macrocycles.



(1)



- Compound **(1)** binds large tetrahedral anions, such as $^{99}TcO_4^-$.
- Technetium-99 is a major uranium fission product and a long-lived -emitter.

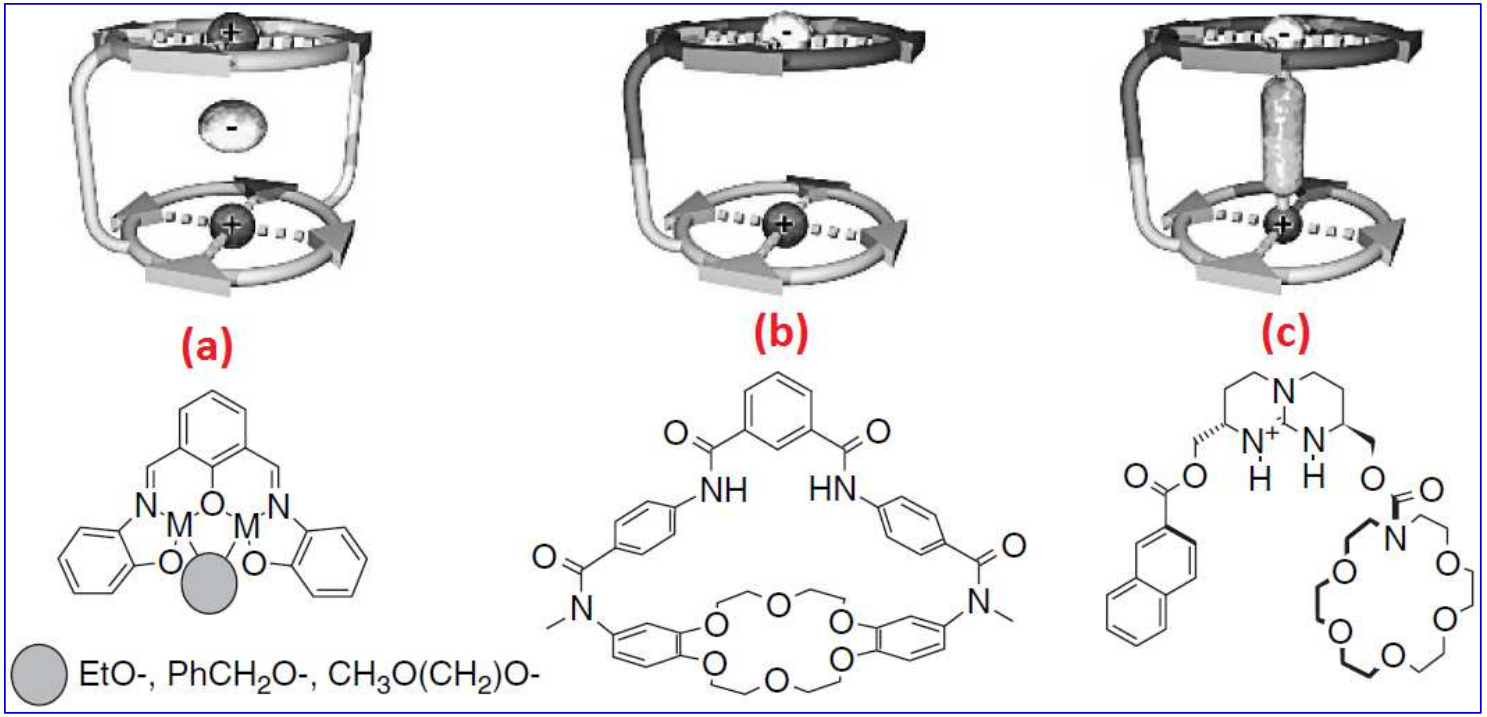
2.6 Simultaneous cation and anion receptors

- Three types of receptors that are used for simultaneous ion binding:

(a) Cascade receptors: binding one type of guest and use this as a new binding site for the counter-ion.

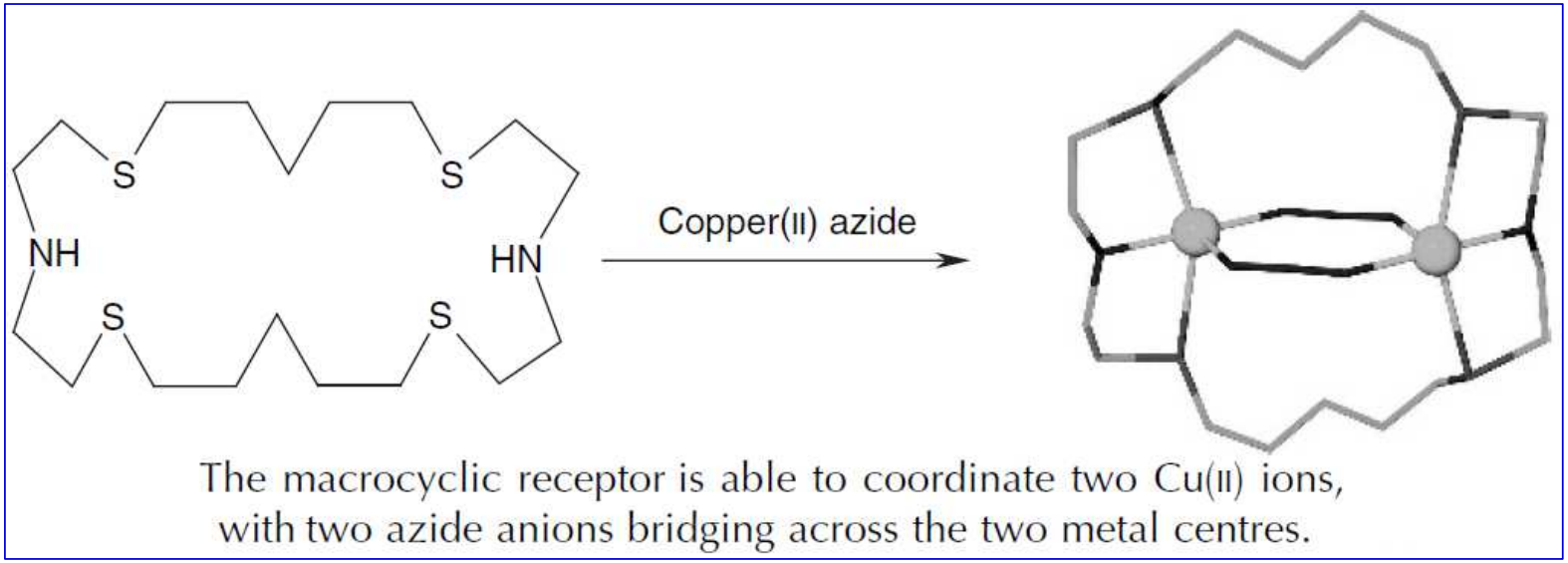
(b) Ditopic receptors: two distinct binding sites in the host.

(c) Zwitterion receptors: guests having both positive- and negative-charged regions in the same molecule.



2.6.1 Cascade receptors

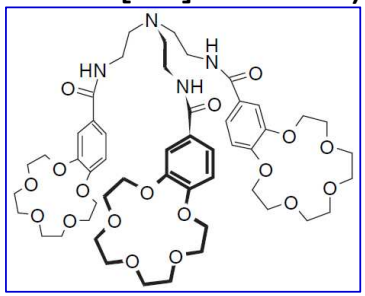
- ***Casacade complex:*** Typically, more than one metal ion (cation) coordinates to a particular ligand (often a Schiff base or macrocyclic heteroalkane) in a well-defined geometry and the anionic species then coordinates to the metal centre.
- Cascade receptors often find applications as models for enzyme-active sites.



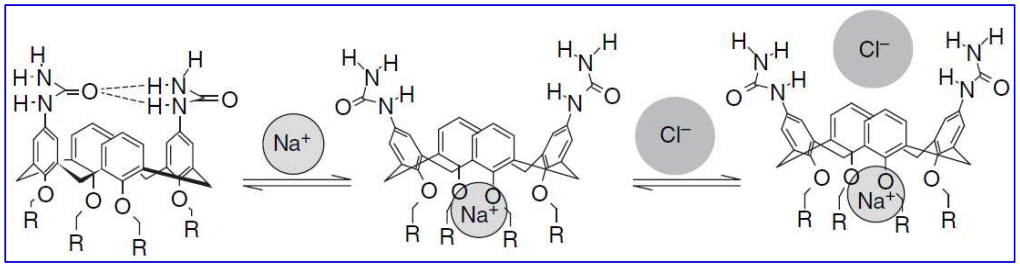
The macrocyclic receptor is able to coordinate two Cu(II) ions, with two azide anions bridging across the two metal centres.

2.6.2 Ditopic receptors

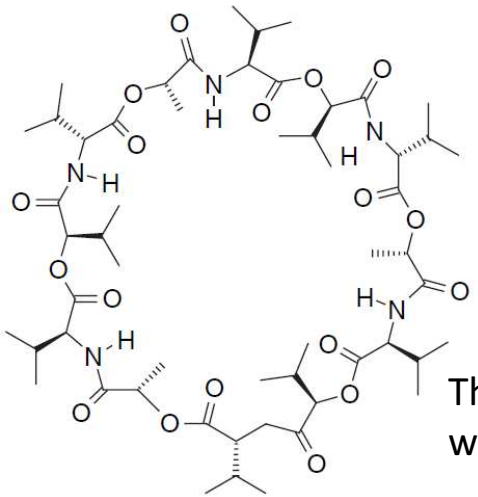
- **Ditopic ion-pair receptors** involve the binding of ion pairs, either as contact or separated ion pairs with a separate binding site.
- Binding both cations and anions often exhibit co-operative behavior. (ex. tripodal tris(amido-benzo[15]crown-5) receptor)



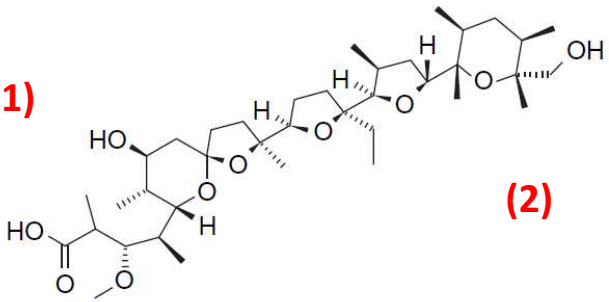
- Co-operative binding with Cl^-, I^- and ReO_4^- anions, in conjunction with Na^+ crown ether complex.
- Na^+ binding improves the receptor's affinity for ReO_4^- by a factor of 20 in comparison to Cl^- and I^-.



- The fixed conformation prevents anion binding.
- Upon the addition of a cation (ex. Na^+), the conformation of the calix[4]arene changes, so forcing the hydrogen bonding interactions to break, forming a cavity for anions (ex. Cl^- and Br^-) to sit within the upper rim.



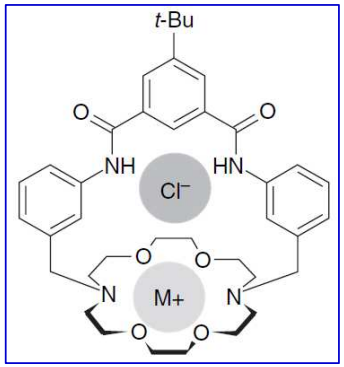
(1)

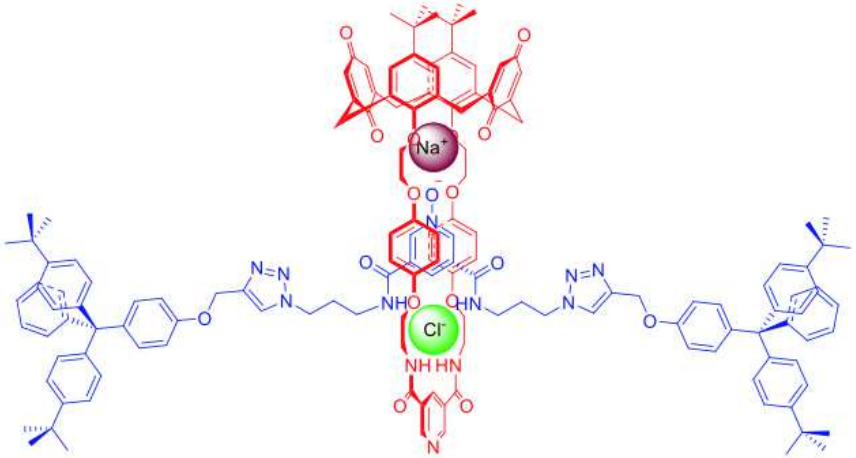


(2)

The biological receptors valinomycin (**1**) and monesin (**2**) which areable to transport cations across cell membranes.

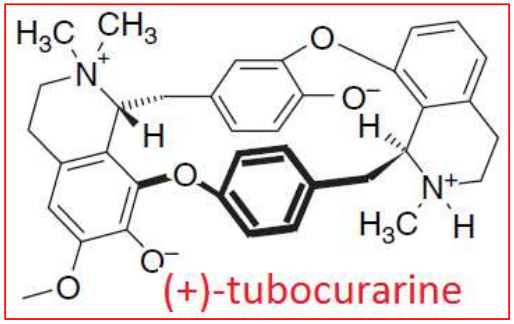
- In contrast to cation binding, there are very few synthetic examples of anion- or salt-binding synthetic receptors for transport of salts across cell membranes.
- One example is the very elegant ditopic receptor which binds both NaCl and KCl.

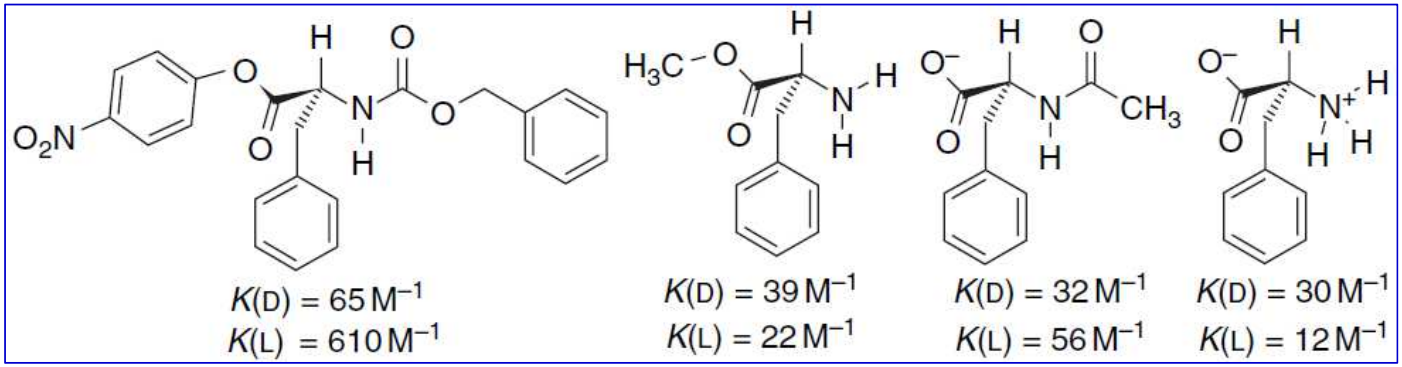




2.6.3 Zwitterion receptors

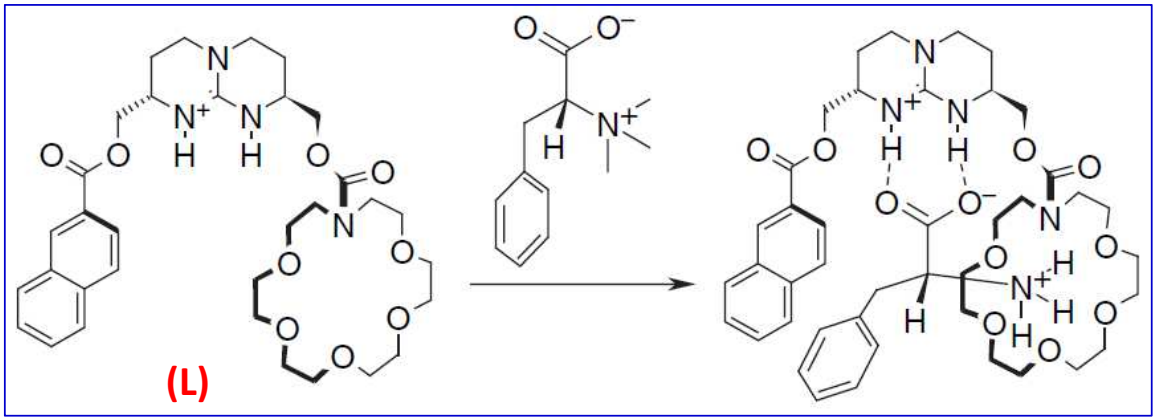
- The chiral macrocylic alkaloid (+)-turocurarine (**A**) at pH 9 is in a zwitterionic form, and binds various chiral amino acid derivatives with significant enantioselectivity.
- This selectivity is attributed to a balance in charge–charge interactions and the hydrophobic effect.
- The cavity is too small for the guest to sit inside and it places slightly above the hollow.



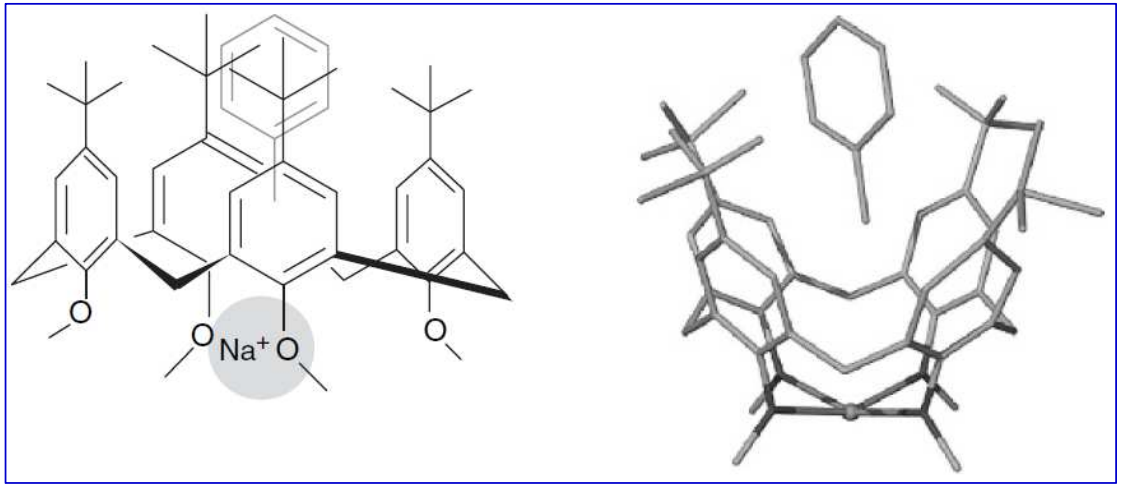


Chiral discrimination of amino acid derivatives by the zwitterions (+)- tubocurarine.

- The ditopic receptor **(L)** extracts amino acids from aqueous solution to dichloromethane.
- The ditopic receptor binds to typtophan *via* two sets of hydrogen bonding interactions and those between the ammonium ion and the crown ether.
- The complex is stabilised by π–π interactions between the aromatic side chains.



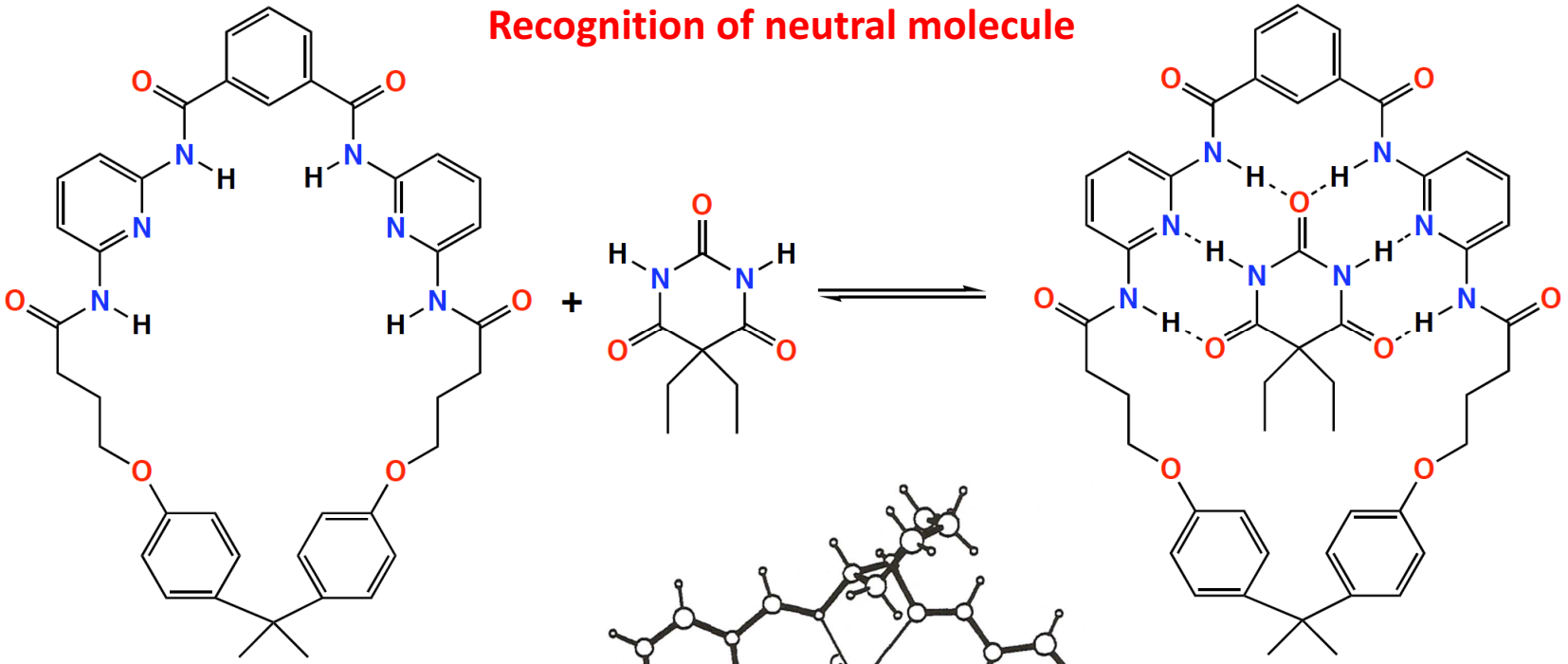
2.6.4 Cation and neutral simultaneous receptors

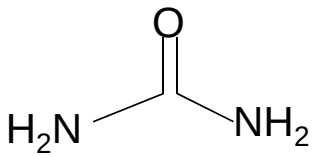


Simultaneous receptors binding **Na^+** and a single molecule of **toluene** within the cavity.

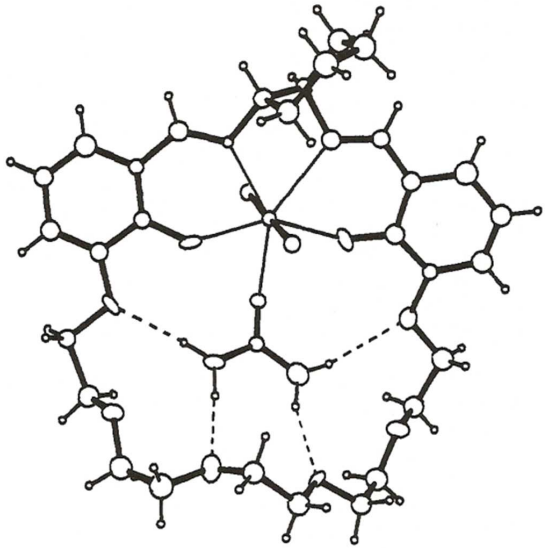
2.7 Neutral-molecule binding

Recognition of neutral molecule





Urea



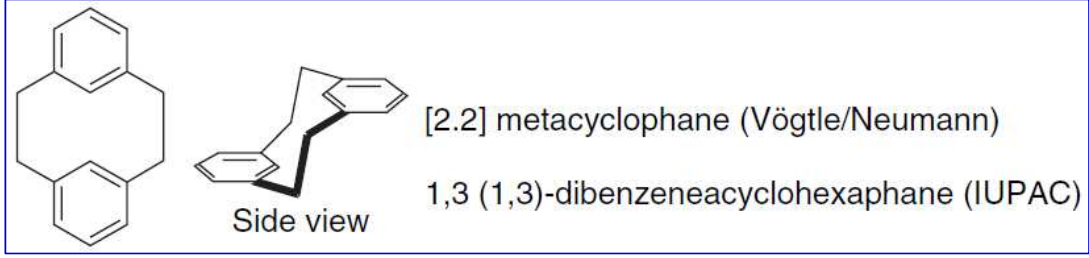
Urea complex

2.7.1 Cyclophane hosts

- In order to achieve neutral-molecule recognition,
  the host needs to either self-assemble around the neutral guest or it must be highly preorganised.

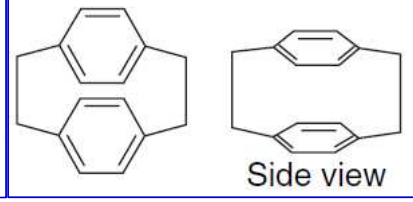
Cavitand: A molecular host that has an enforced concave surface, producing a cavity.

Caviplex: The term given to the complex between a cavitand and a guest molecule.



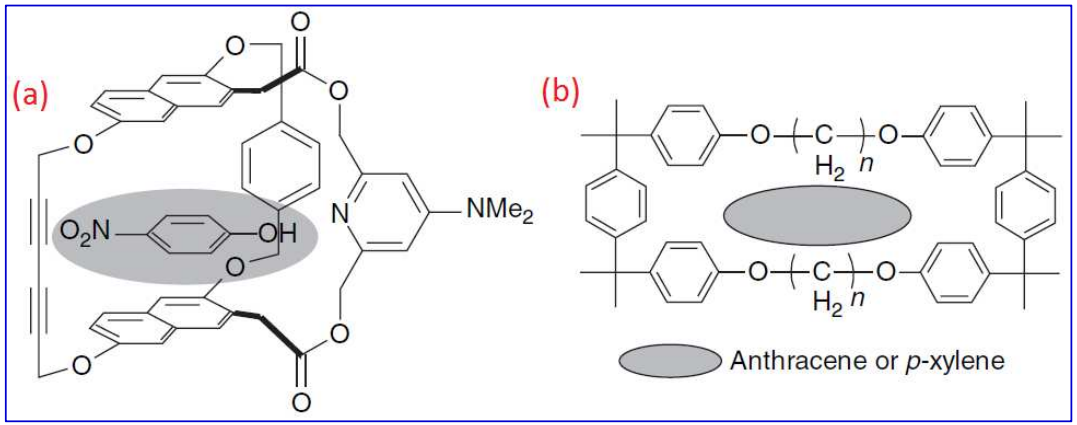
[2.2] metacyclophane (Vögtle/Neumann)

1,3 (1,3)-dibenzeneacyclohexaphane (IUPAC)



[2.2] paracyclophane (Vögtle/Neumann)

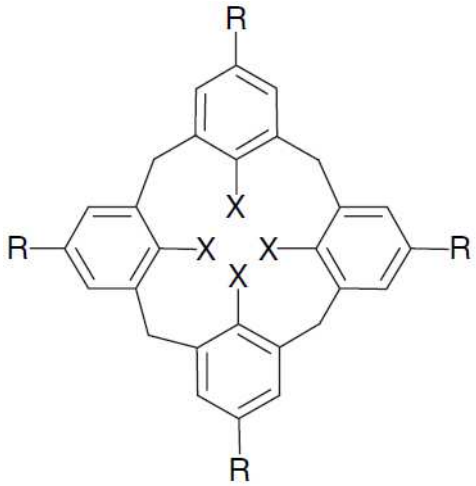
1,4 (1,4)-dibenzeneacyclohexaphane (IUPAC)



(a) *p*-Nitrophenol bound within the cavity of the cyclophane *via* π–π interactions

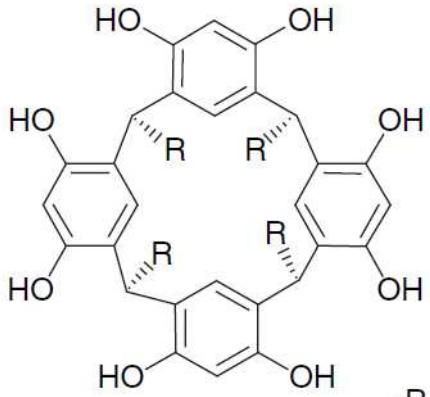
(b) Aromatic neutral guests bound *via* π–π interactions with the cyclophane

2.7.2 Calixarenes and resorcarenes



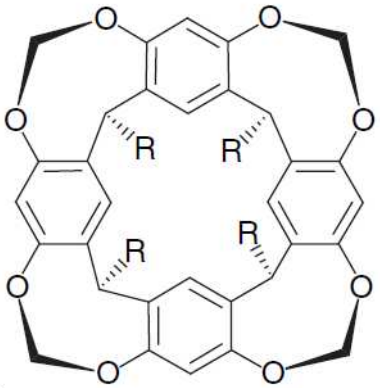
Calix[4]arene

X = OH
R = H, CH_3, *t*-Bu



Calix[4]resorcarene

R = alkyl



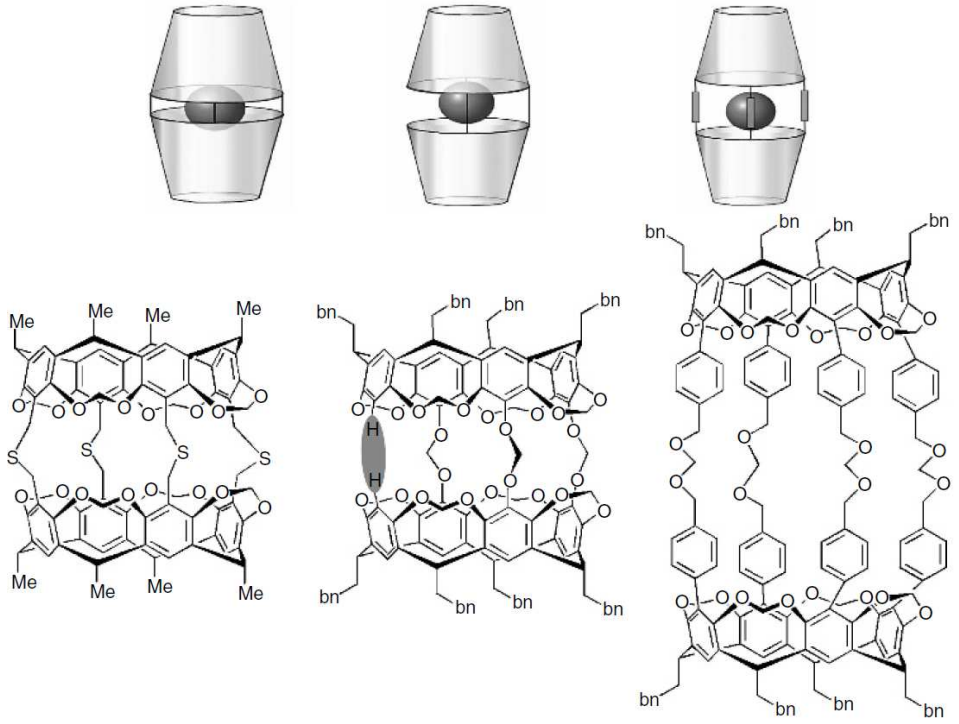
A bridged resorcarene

- Both calixarenes and resorcarenes bind a wide range of aromatic guest molecules, predominantly in a 1:1 stoichiometry in the solid state as clathrates.
- The complexes are generally stabilised by a range of weak interactions, such as C–H···π hydrogen bonds.

2.7.3 Carcerands and hemicarands

Carcerand: Two cavitands covalently linked together, resulting in a completely enclosed cavity. Guests are unable to escape.

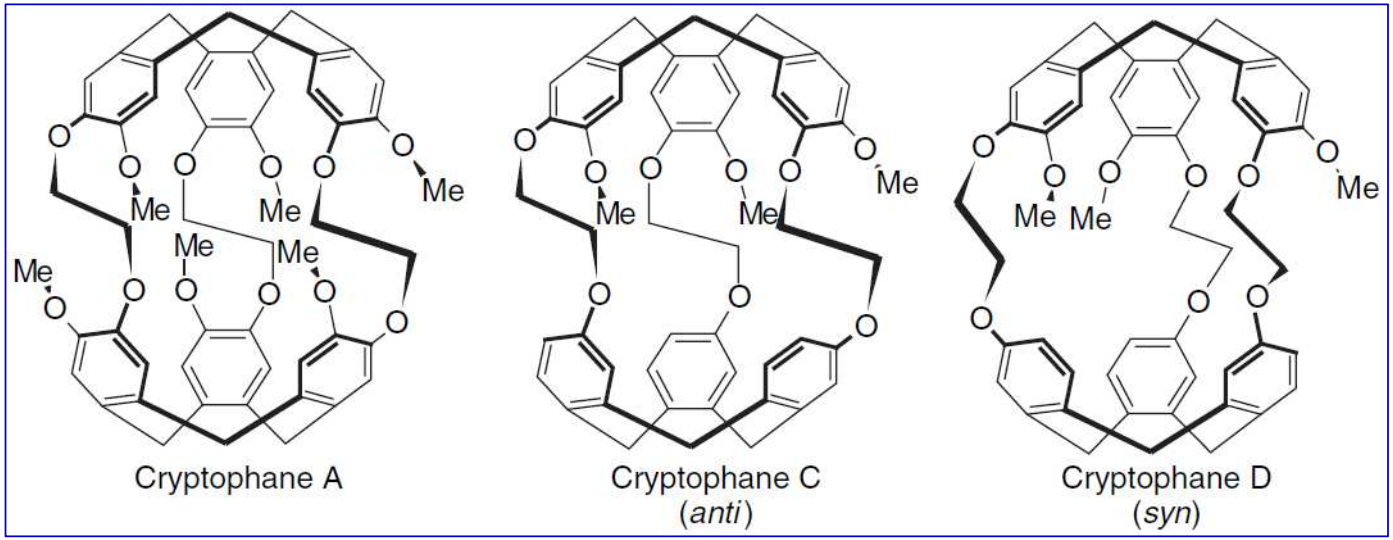
Hemicarcerand: Cavitands covalently linked together that either have a portal made by omitting one of the four bridging groups, or by making the bridging groups long enough to provide large holes.



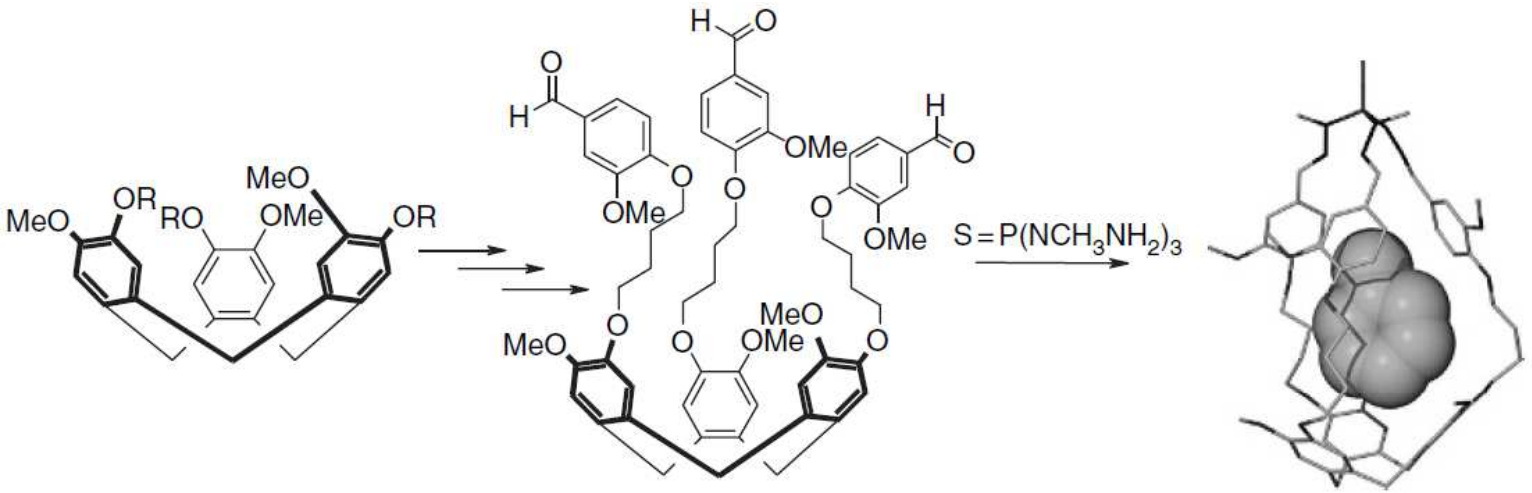
carcarand hemicarcarand hemicarcarand

2.7.4 Cryptophanes and hemicryptophanes

- ***Cryptophanes*** are related to hemicarcerands – composed of smaller and shallower cavitand bowls.
- The first cryptophane *via* a 'self-directed synthesis' (1981)
- This small cage is named, chronologically, **cryptophane-A**.
- Larger cryptophane by omitting OCH_3 groups: cryptophane-C and cryptophane-D (*anti* and *syn isomers*)
- The *anti*-diastereomer (cryptophane-C) binds guest molecules more effectively than the *syn*-diastereomer (cryptophane-D).



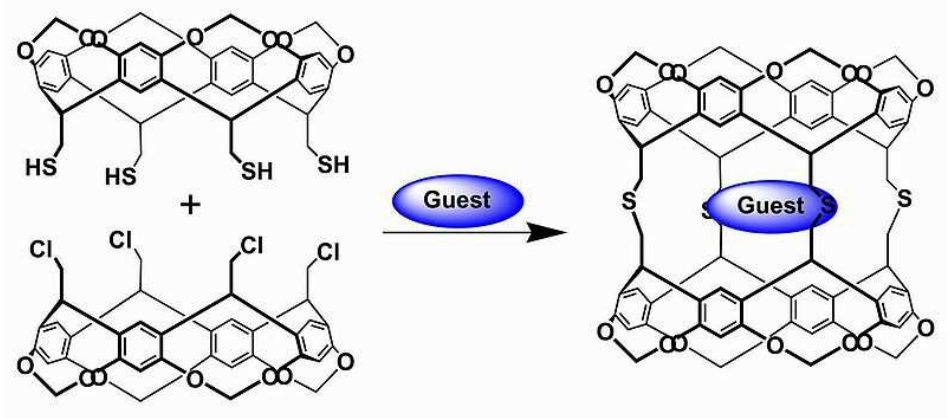
- Hemicryptophanes: only one bowl-shaped fragment



hemicryptophane

Synthesis of the hemicryptophane.

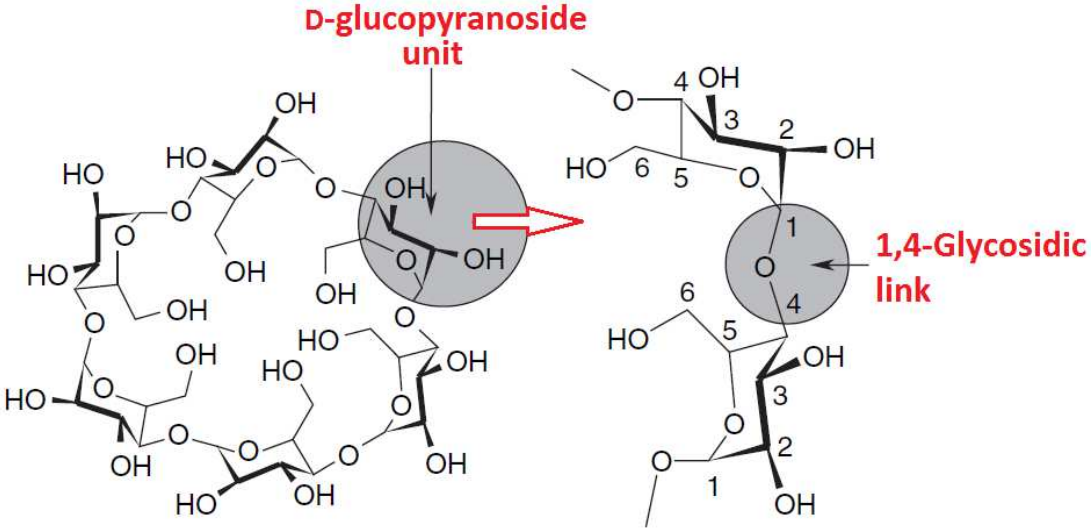
The X-ray crystal structure shows a toluene solvent molecule encapsulated within the host.

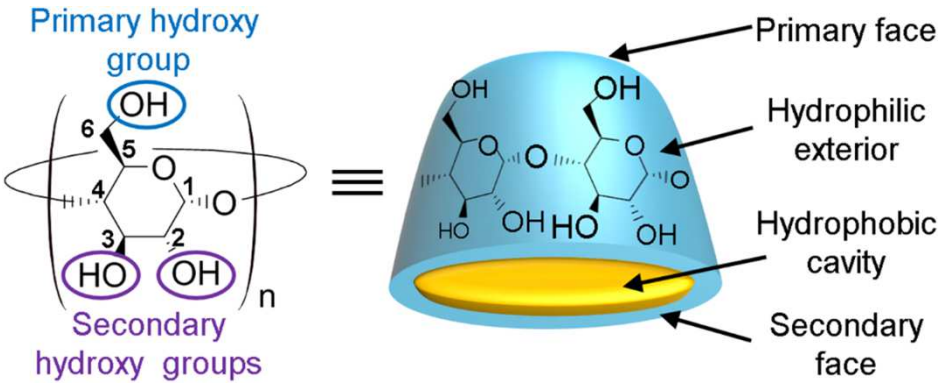


2.7.5 Cyclodextrins

Cyclodextrins

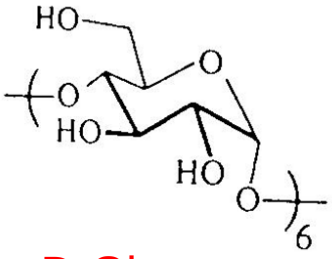
- semi-natural compounds – they are synthesised from starch *via* a simple enzymatic conversion
- cheap and environmentally friendly
- chiral and cyclic oligosaccharides that have molecule sized cavities.
- preorganised and bowl shape by an intramolecular hydrogen bonding network
- the most widely used receptors in host–guest inclusion chemistry
- broad range of applications and industrial production (> thousand tons per annum)
- application in food and cosmetics industries
- the pharmaceutical sector as stabilising agents and for the slow release of drugs
- effective complexing agents for a wide range of molecular guests



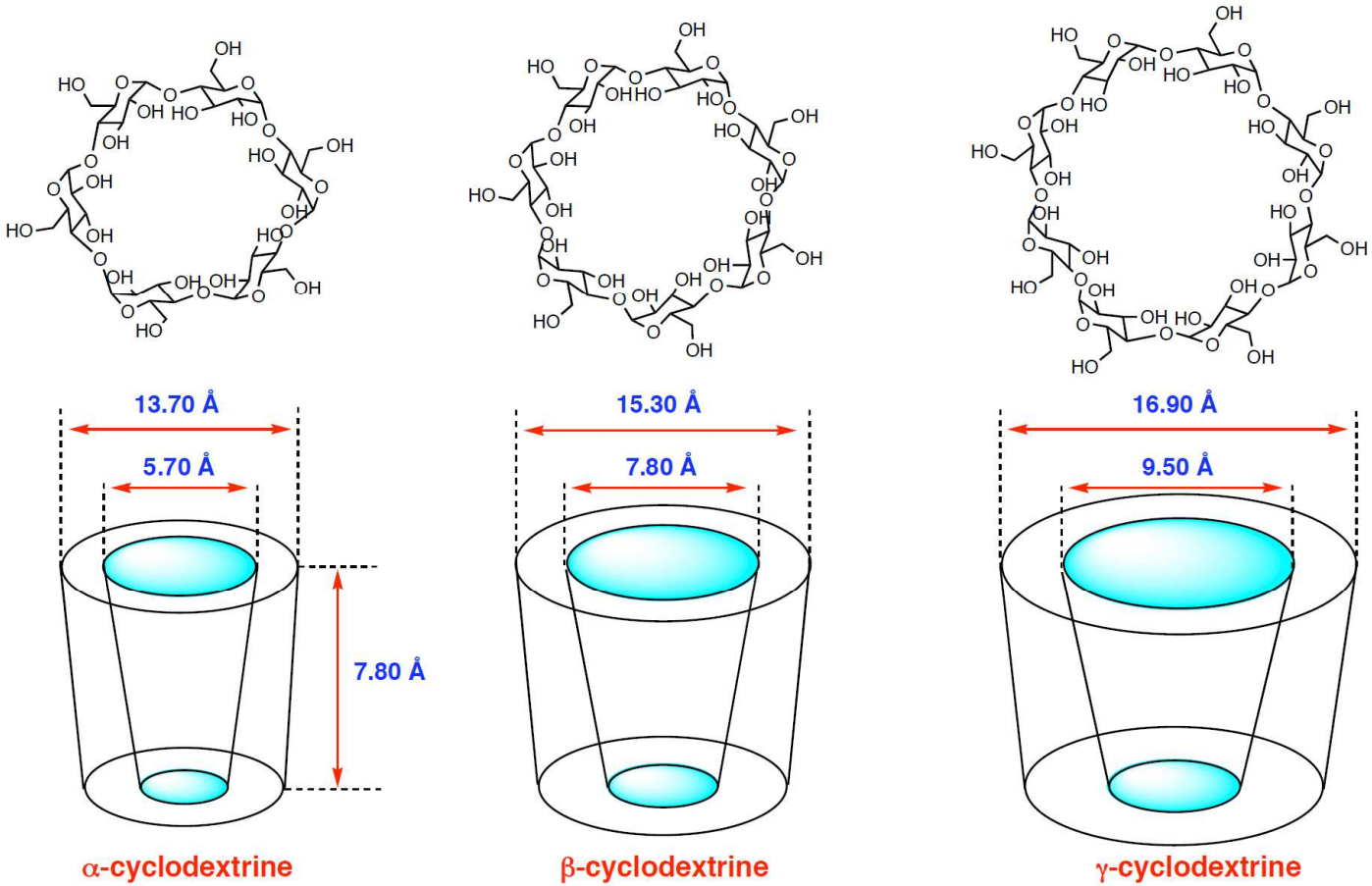


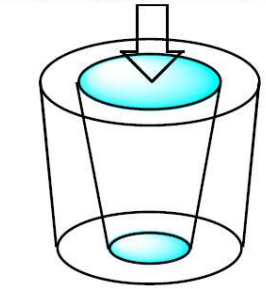
Cyclodextrin

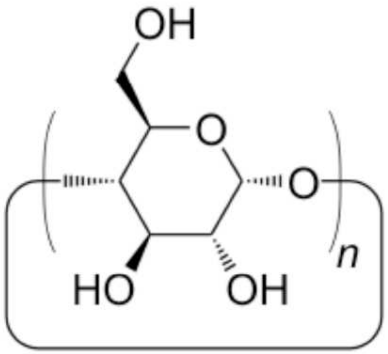
- Nomenclature is historical, and is generally accepted in industry.
- α– β–, and γ–cyclodextrin, consisting of six, seven and eight glucopyranose units.
- Smaller and larger ring systems:
  five units (pre-α-cyclodextrin), nine units (δ-cyclodextrin), ten units (ε-cyclodextrin)



D-Glucose





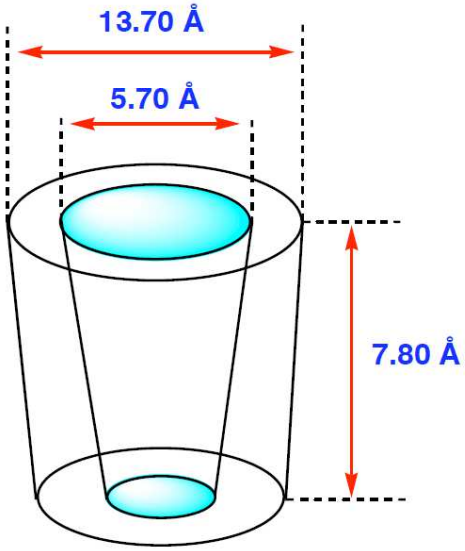


n = 6 : α-cyclodextrine

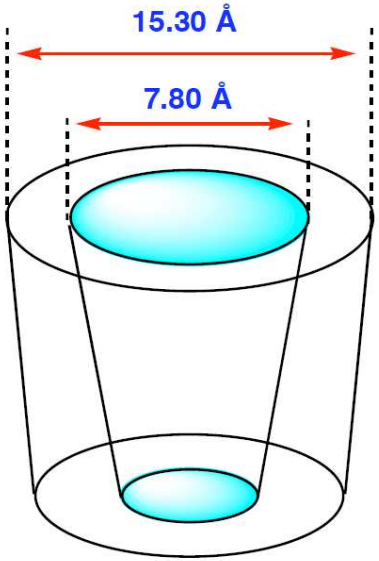
n = 7 : β-cyclodextrine

n = 8 : γ-cyclodextrine

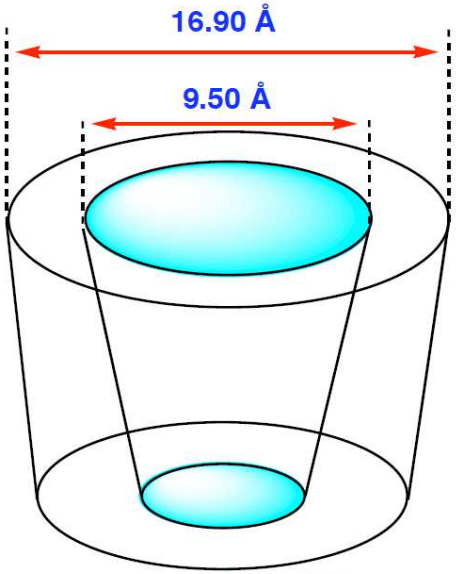
n = 9 : δ-cyclodextrine



α-cyclodextrine

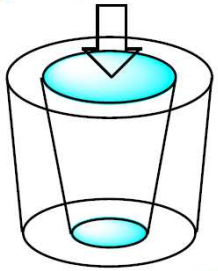


β-cyclodextrine



γ-cyclodextrine

Hydrophobic cavity



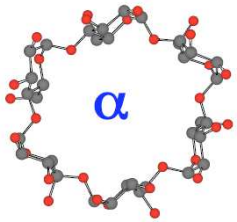
Secondary hydroxyl

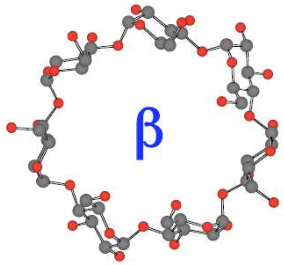
Primary hydroxyl

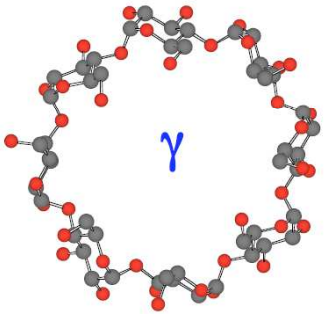
6 α-Cyclodextrine

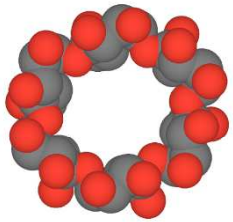
7 β-Cyclodextrine

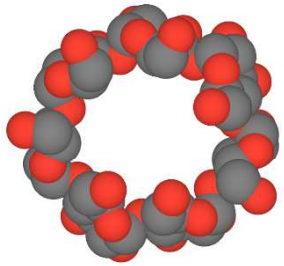
8 γ-Cyclodextrine

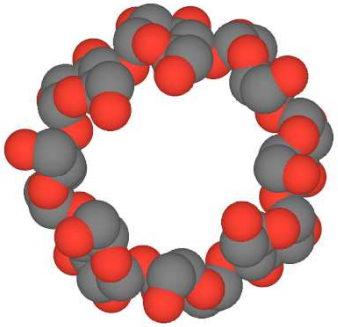


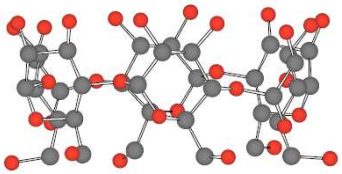


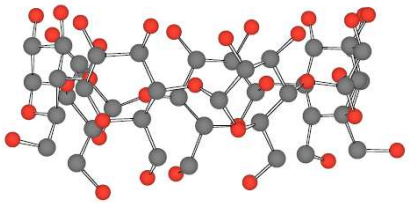


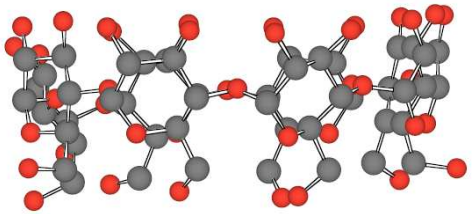




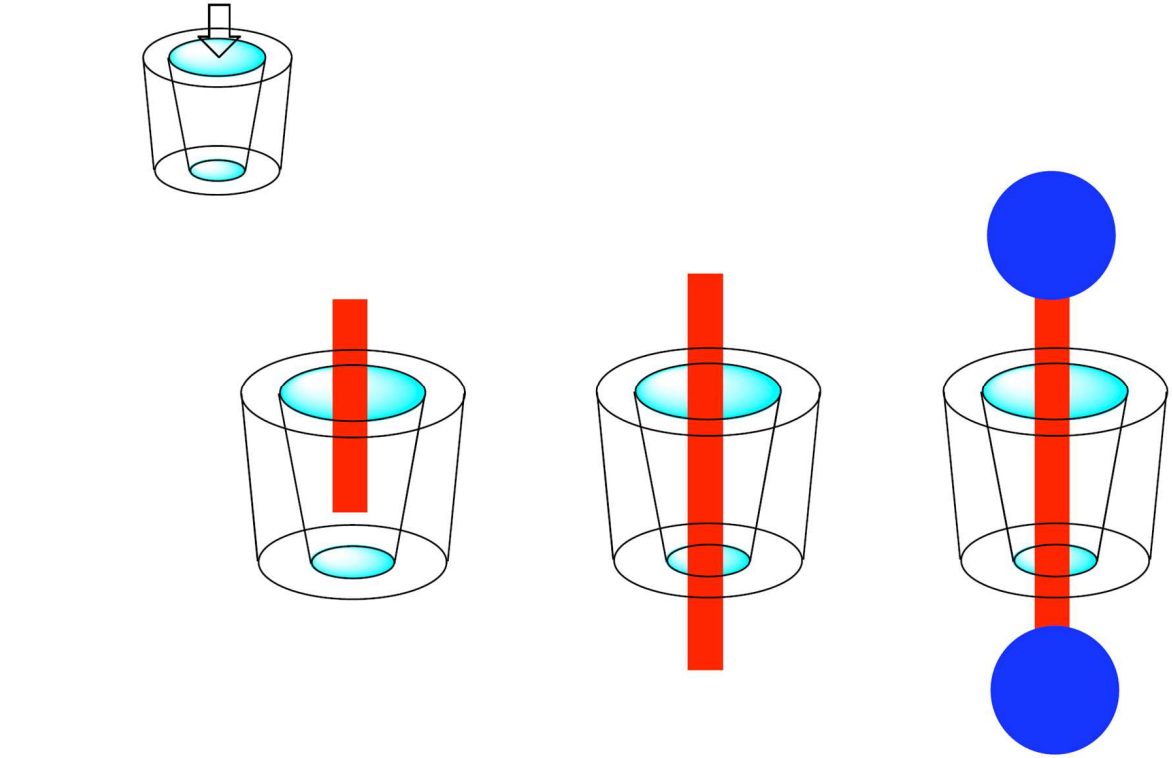


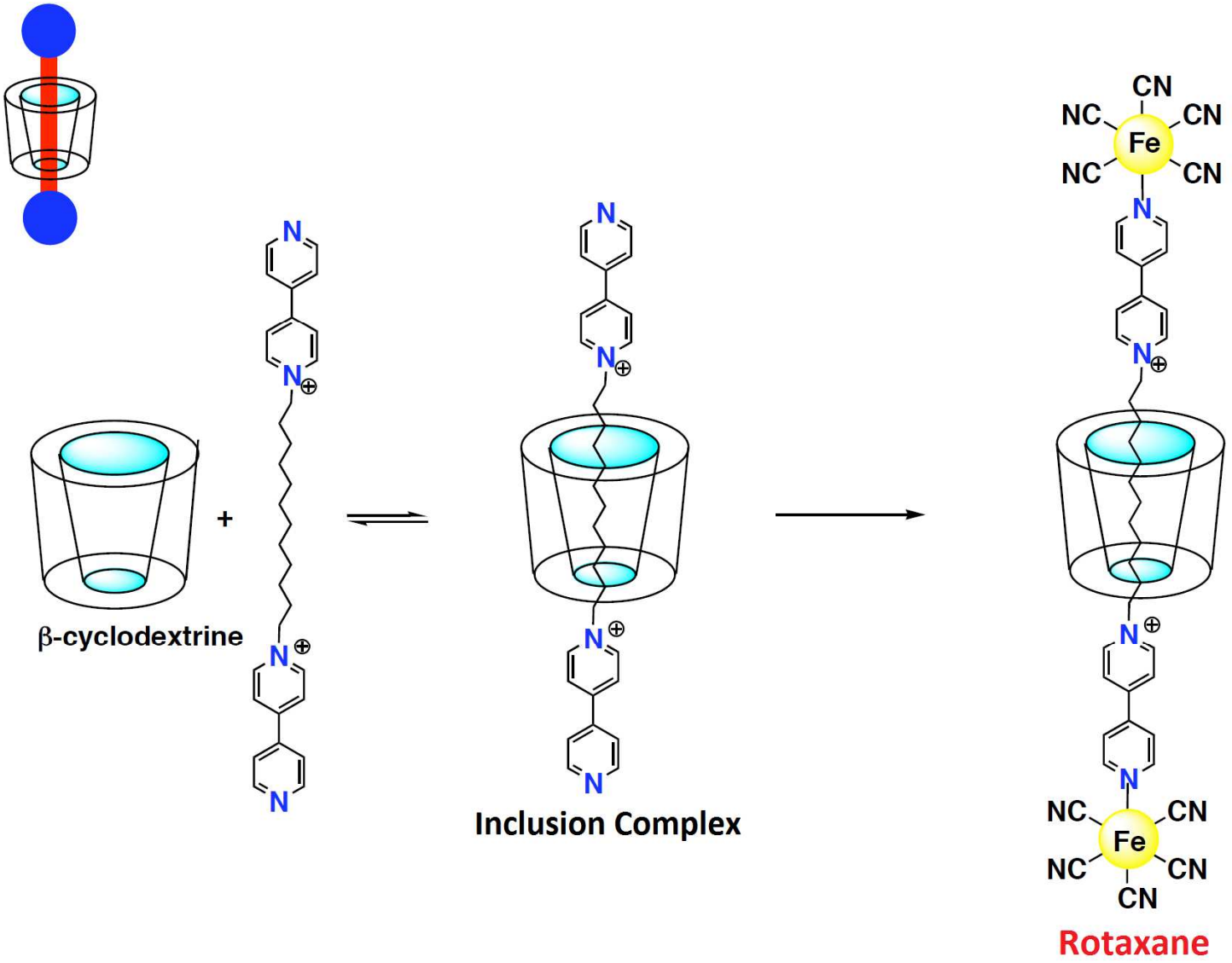


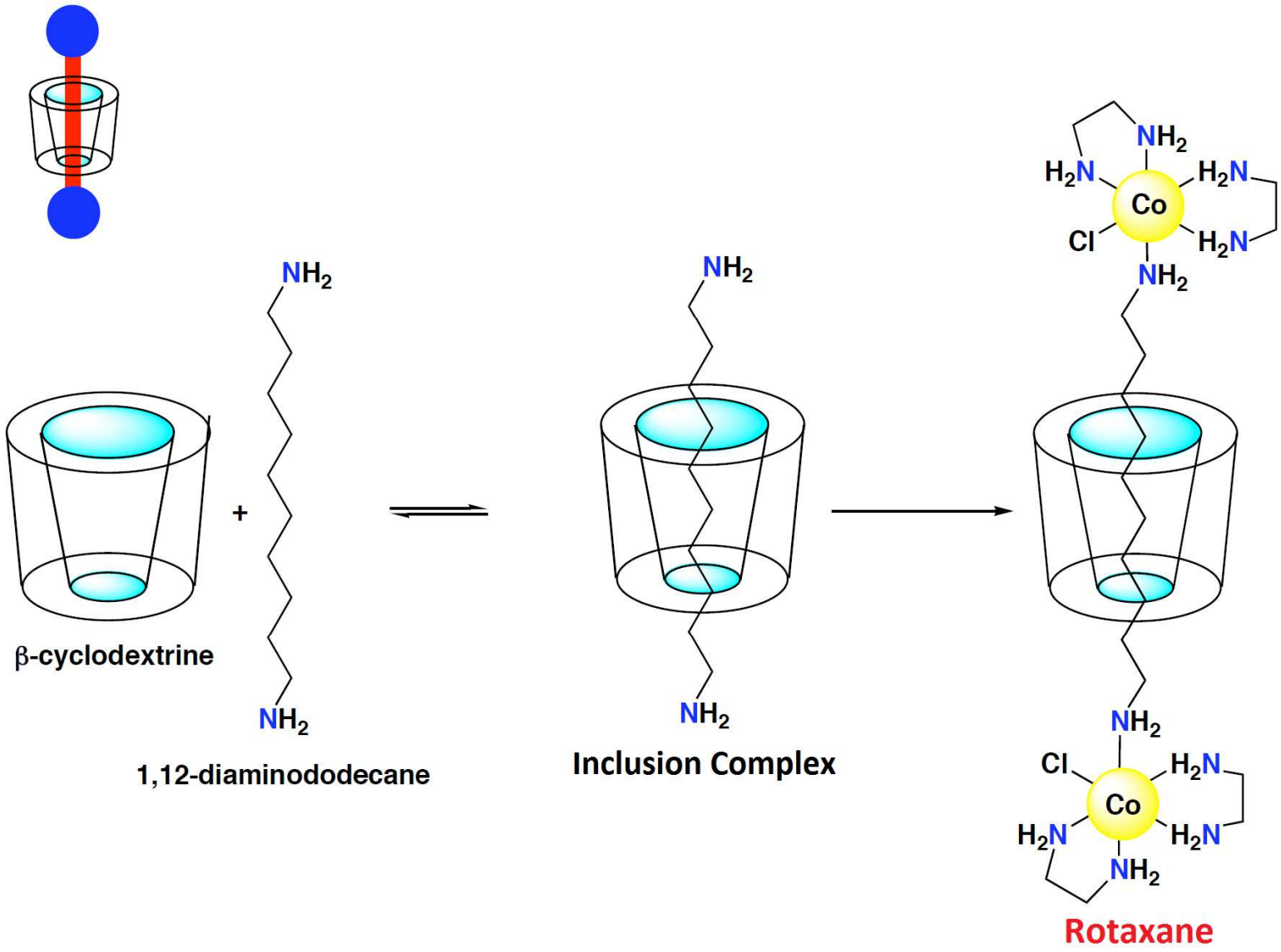




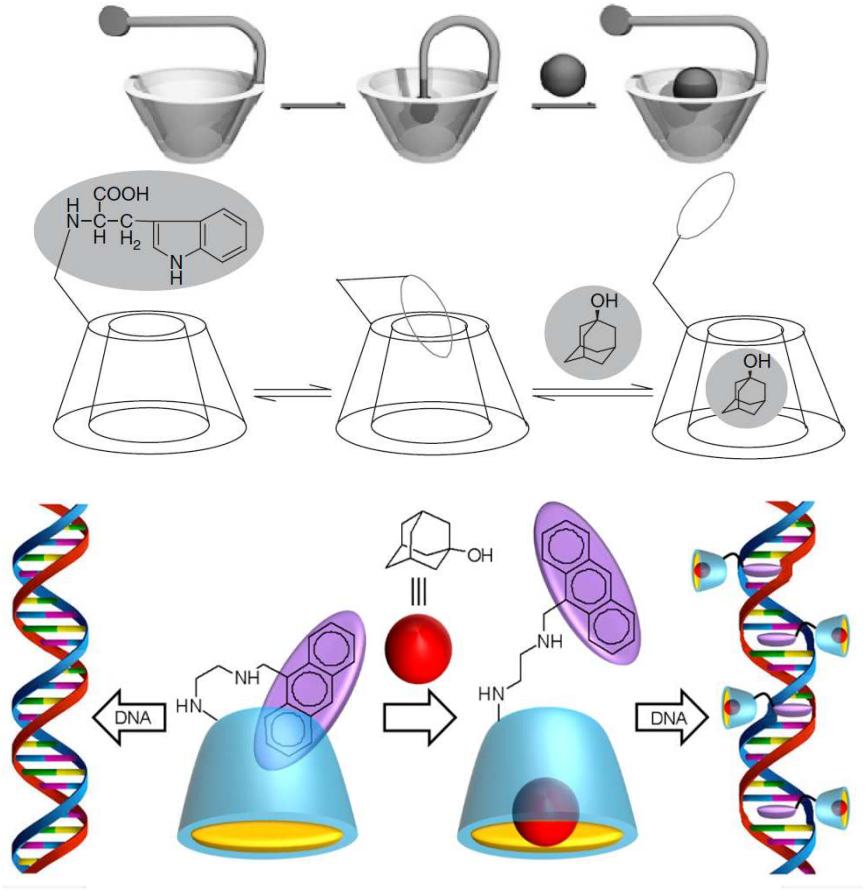
Hydrophobic cavity




β-cyclodextrine
+
Inclusion Complex
CN
NC
CN
Fe
NC
CN
N
N⊕
NC
CN
Fe
NC
CN
CN
Rotaxane


NH2
β-cyclodextrine
+
NH2
1,12-diaminododecane
NH2
NH2
Inclusion Complex
NH2
H2N
H2N
Co
Cl
H2N
NH2
NH2
Cl
H2N
Co
H2N
H2N
NH2
Rotaxane

- The fluorescent indole group of the L-tryptophane-derived lariat arm
  → encapsulation within the cavity of the cyclodextrin in aqueous solution by hydrophobic effects.
- On the addition of a guest,
  the lariat arm is displaced and the guest takes its place within the cavity.



2.8 Supramolecular catalysis and enzyme mimic

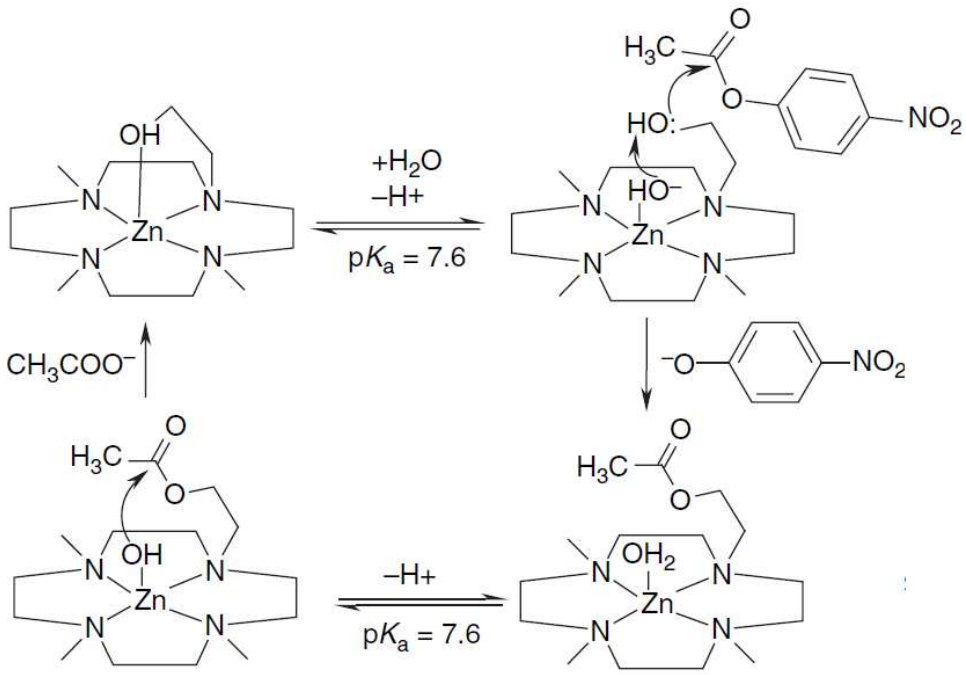
- How enzymes themselves catalyse reactions.
- One of the most important catalytic biological reactions is the hydrolysis of the amide linkage in a protein.
- For this to occur in nature, three things are required to happen.

  (1) enhancement in the rate of nucleophilic attack on the substrate

  (2) stabilisation of the intermediate

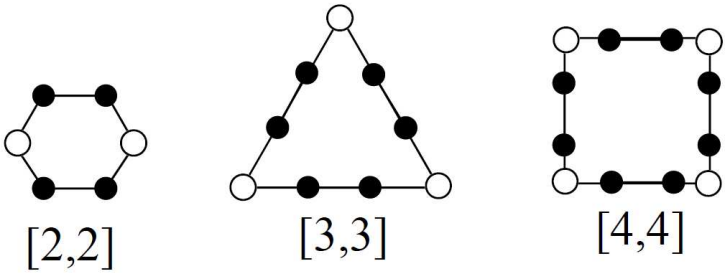
  (3) enhancement of the rate of leaving-group departure.

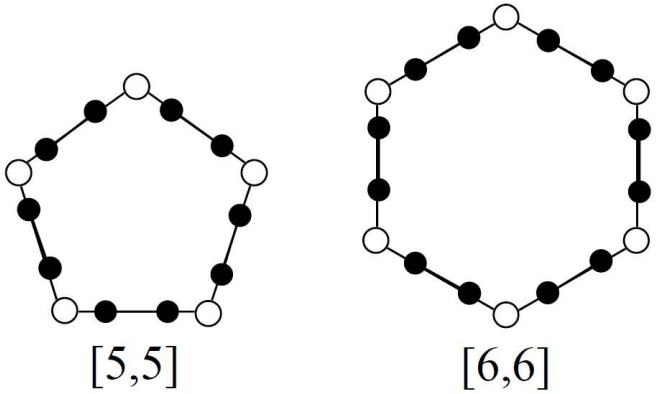
The Zn(II) complex mimics the *esterase* reaction.



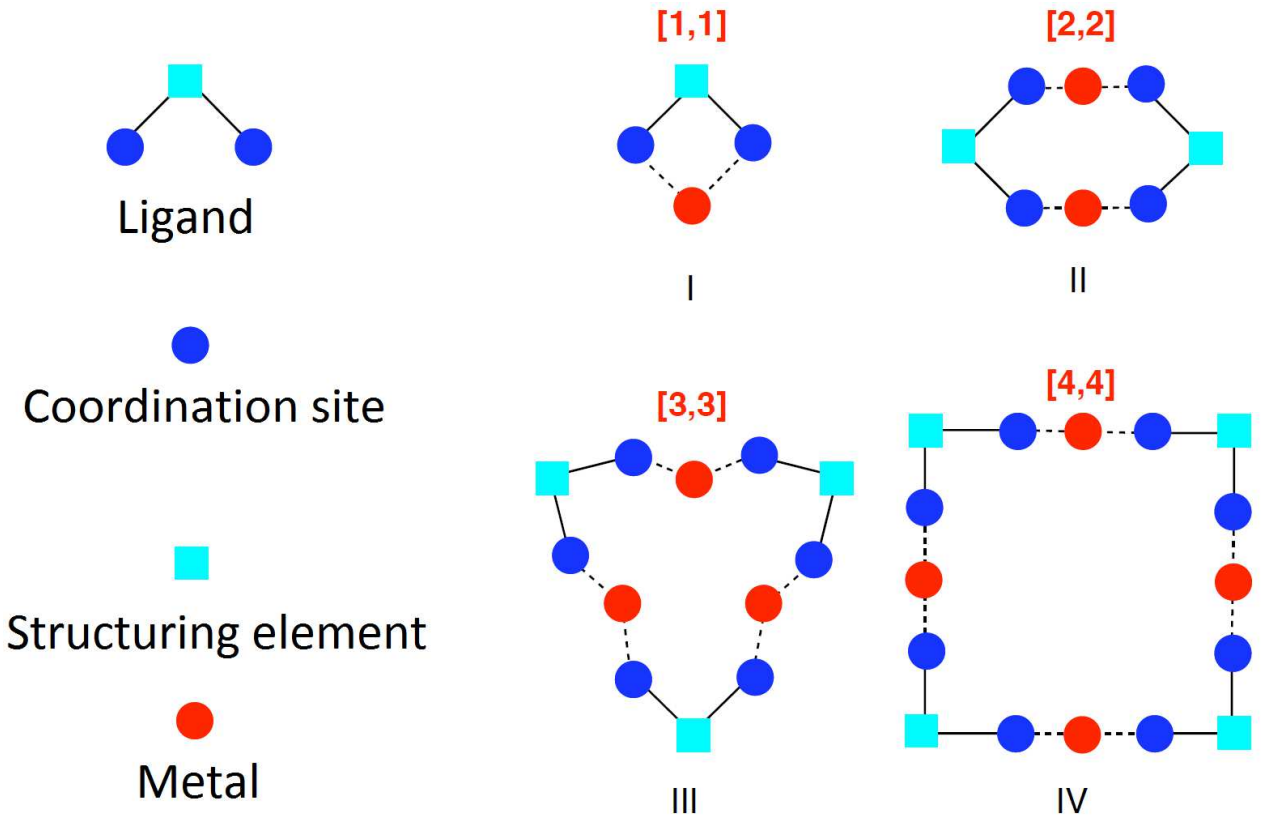
The catalytic cycle for the hydrolysis of 4-nitrophenyl acetate

2.9 Metallomacrocycles: Metal as a junction

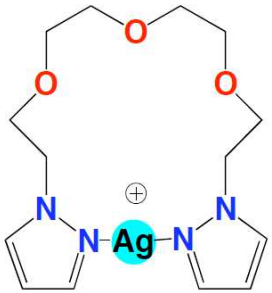


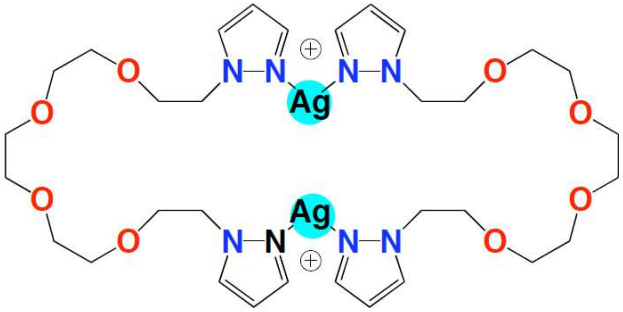


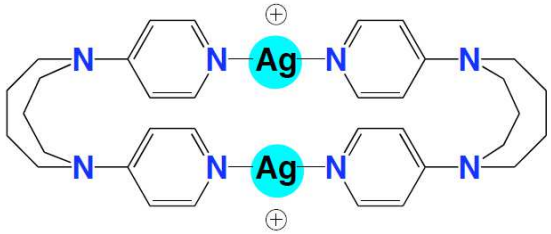
- A **metallamacrocycle** is a cyclic architecture containing organic fragments (ligands) and metal centers.
- The metal is contained in the cyclic structure (endocyclic).

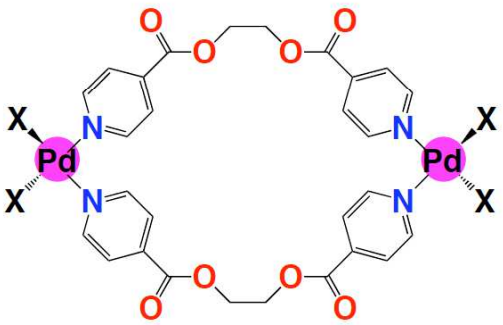


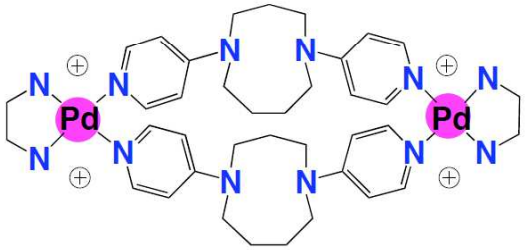
2.9.1 Examples of Metallomacrocycles

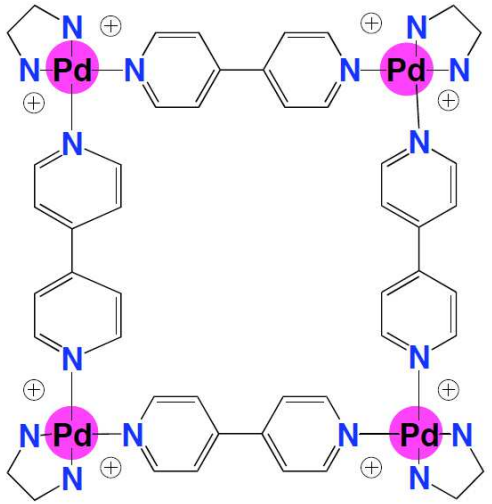












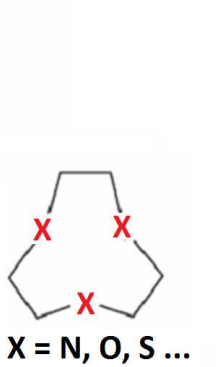
2.10 Macrocyclic Ligands & Their Metal Complexes

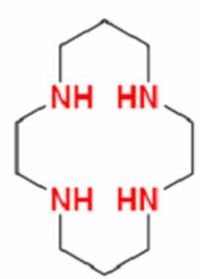
- **Macrocyclic effect:** Discovered in 1969.
- **Definition of IUPAC**: cyclic macromolecule or macromolecular ring part of a molecule.
- Macrocycle by organic chemists: A cyclic molecule containing seven or more atoms.
- **Macrocycle in coordination chemistry:** A cyclic molecule with three or more donor atoms capable of coordinating to a metal ion.

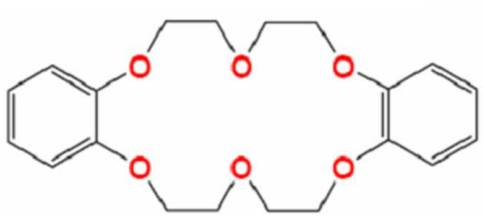
A natural window in Kalbarri National Park
Western Australia

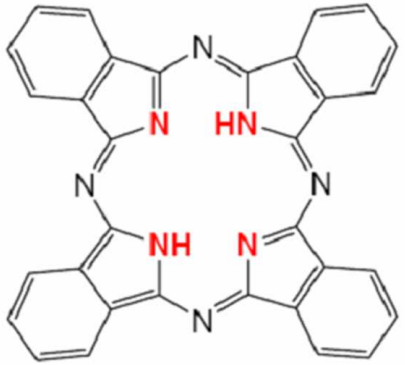
2.10.1 What is macrocyclic ligand?

- **Macrocyclic ligands:** Polydentate ligands containing the donor atoms incorporated to a cyclic backbone.
- Usual definition:
  A cyclic molecule containing at least **3 donors and 9 atoms**.
- Macrocycles with
  3 donors → 9- to 13-membered rings
  4 donors → 12- to 17-membered rings
  5 donors → 15- to 21-membered rings
  6 donors → 18- to 25-membered rings









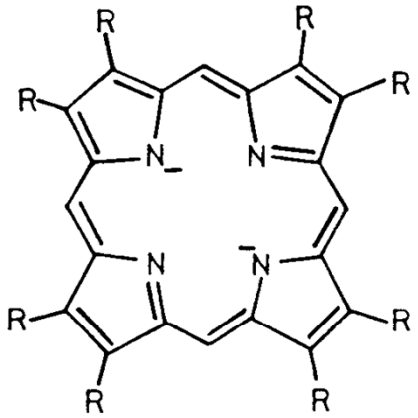
- Often exhibit unusual properties
- Found in several important biological systems

(ex)Fe-porphyrin – transport of O_2 in respiration

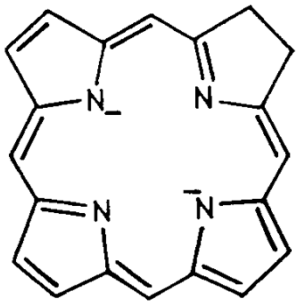
Mg-chlorin – in chlorophyll for photosynthesis

Co-corrin – in Vitamin B12

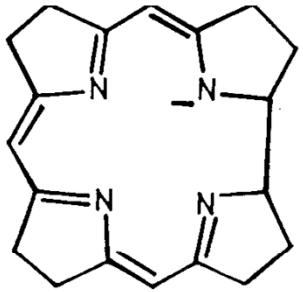
K-nonactin – K^+ transport



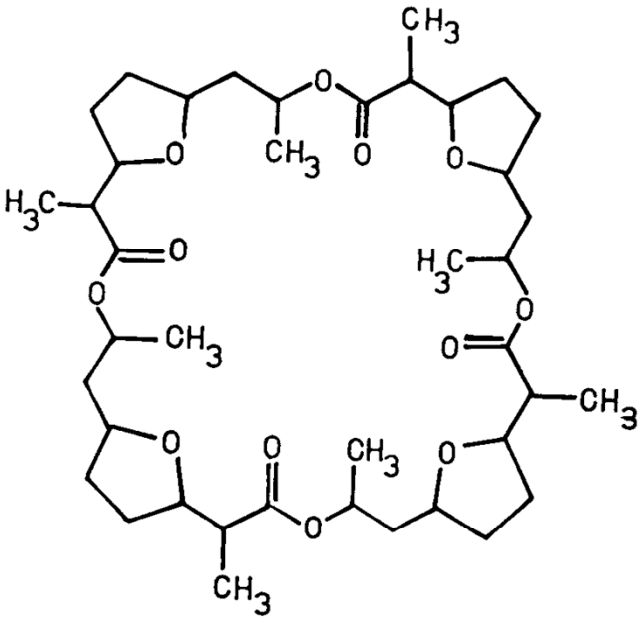
porphyrin



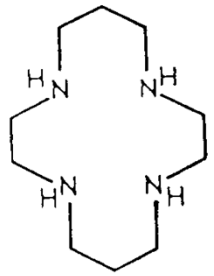
chlorin



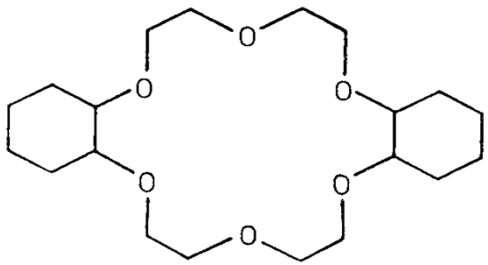
corrin

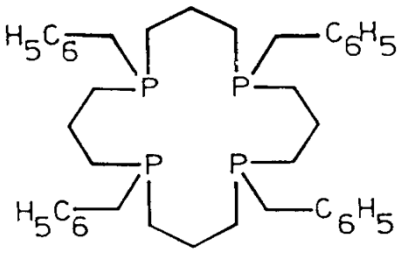


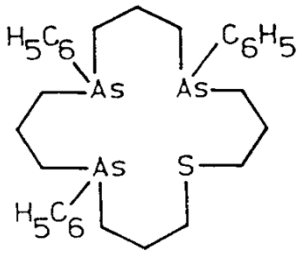
nonactin

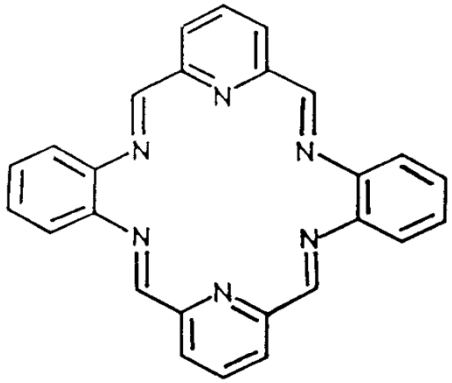


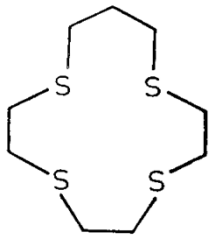
cyclam

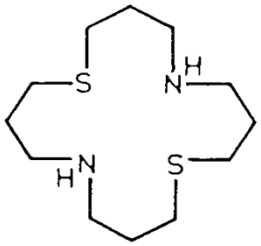


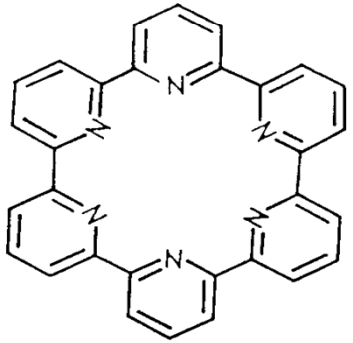


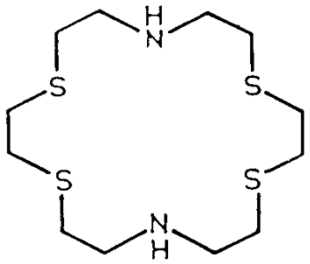


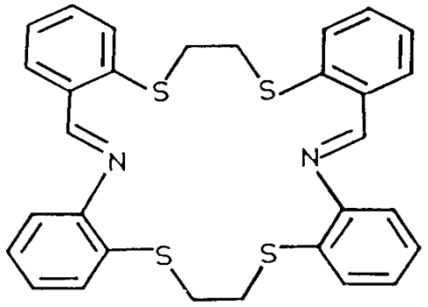










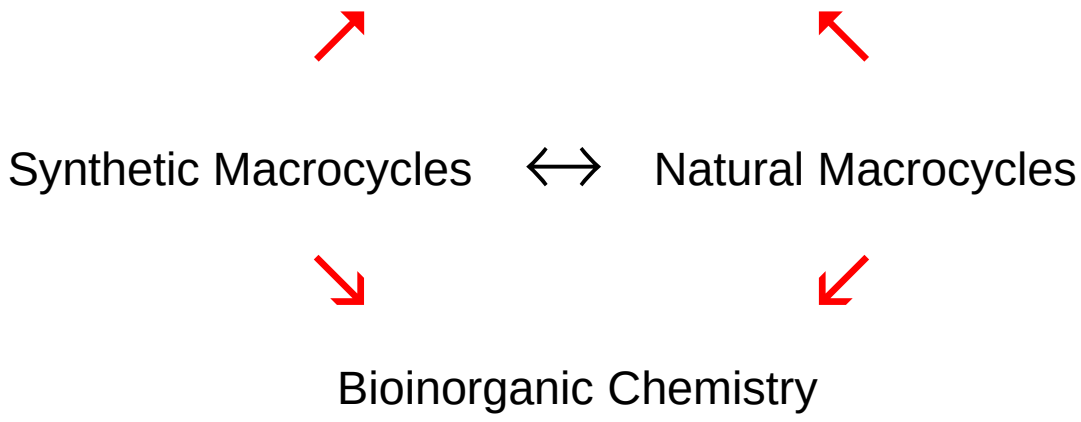


History of Macrocycles

Pre-1960 Synthetic Macrocyclic chemistry

(ex) mainly phthalocyanine and its derivatives

Post–1960 Macrocyclic Chemistry



Selectivity of Cation Complexation

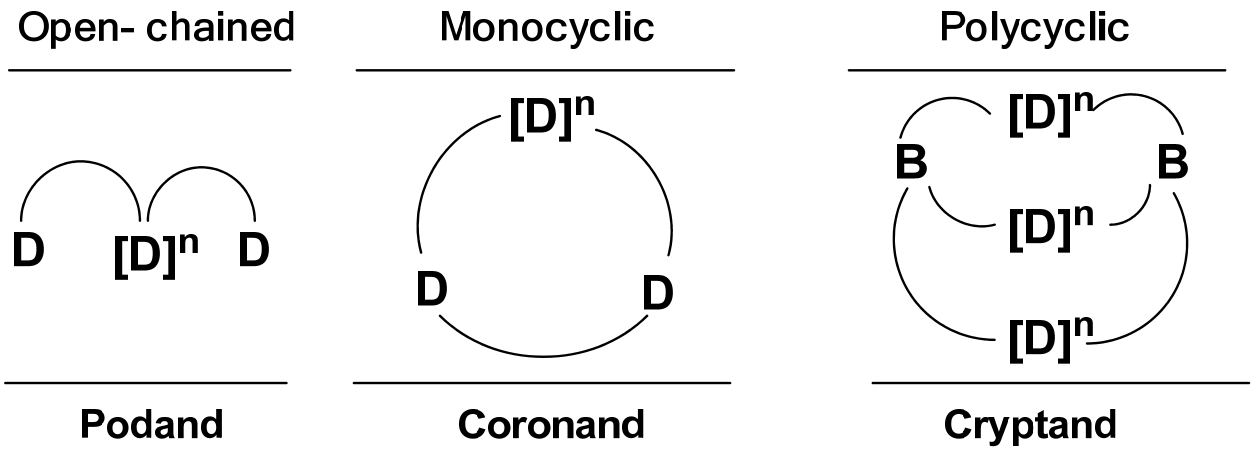
General considerations

- size complementarity between cation and host cavity
- electronic complementarity between the cation and host binding sites (*e.g.* HSAB)
- electrostatic charge
- solvent (polarity, hydrogen bonding and coordinating ability)
- degree of host preorganization
- enthalpic and entropic contributions to the cation–host interaction
- cation and host free energies of solvation
- nature of the counter-anion and its interactions with solvent and the cation
- cation binding kinetics
- chelate ring size and donor group orientation

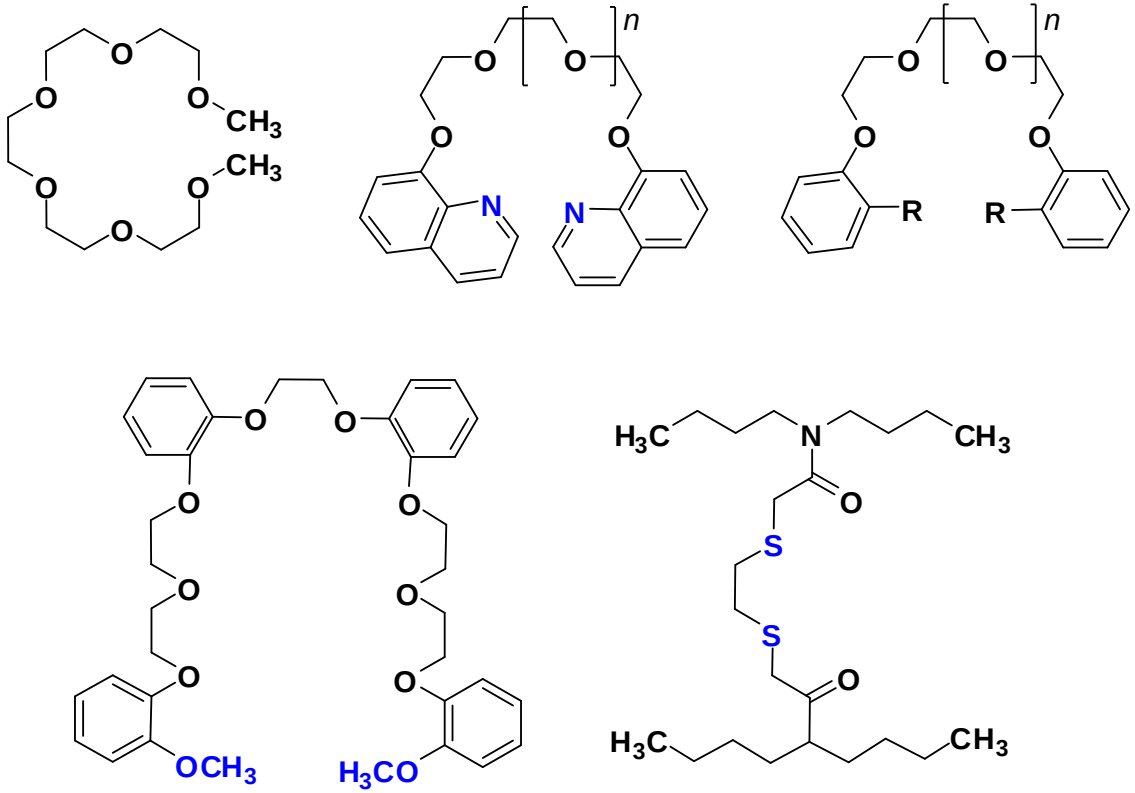
2.10.2 Different types of macrocycles

- **Neutral ligand**
  Open-chained ligand: **podand**
  Monocyclic ligand: **coronand**
  Polycyclic ligand: **cryptand**

- **Crown ether: coronand ligand** containing ethereal oxygen atoms



Open-chained ligand: **podand**



2.10.3 Macrocyclic Effect

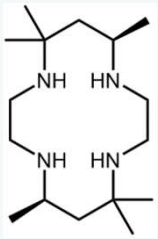
- Macrocyclic ligands give rise to metal complexes that are more **kinetically and thermodynamically stable** than their open-chain analogues.

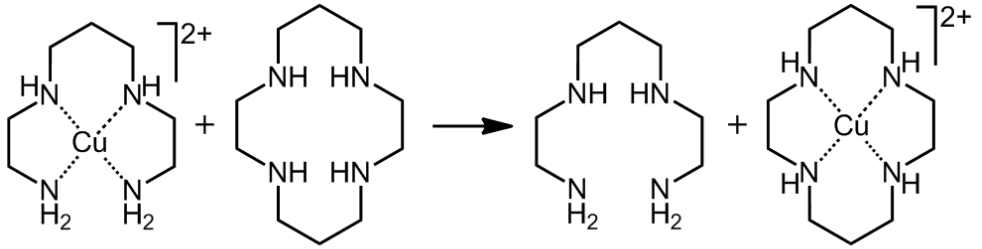
- Kinetic stability: the rate at which demetallation of the complex occurs.

- **Additional stability** of the macrocyclic system is usually considerably **greater** than the presence of an additional chelate ring.

Macrocyclic Effect

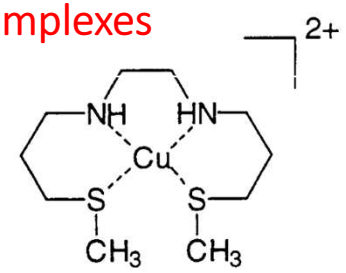
Thermodynamic stability data for Cu(II) complexes

Ligand	log *K*
$H_2N(CH_2)_2NH_2$ (en)	10.7
$H_2N(CH_2)_3NH_2$ (tn)	9.8
$H_2N(CH_2)_2NH(CH_2)_2NH_2$ (dien)	16.1
$H_2N(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$ (2,2,2-tet)	20.1
$H_2N(CH_2)_2NH(CH_2)_3NH(CH_2)_2NH_2$ (2,3,2-tet)	23.9
	28.0

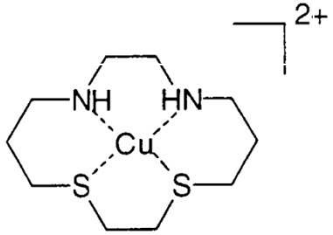


log *K* = 5.2

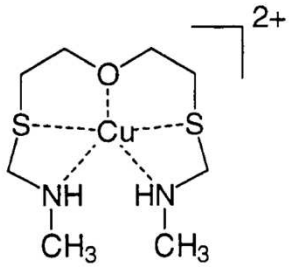
Stability Constants for Cu(II) Complexes



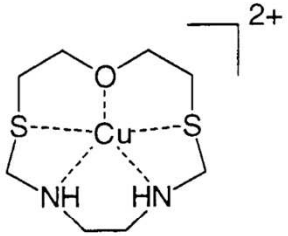
log K_{ML} = 11.4



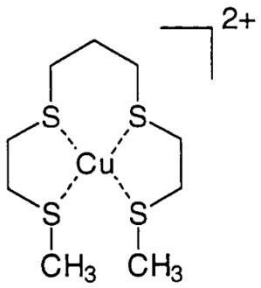
log K_{ML} = 16.0



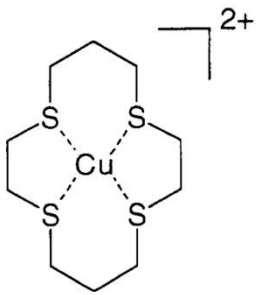
log K_{ML} = 9.2



log K_{ML} = 13.3



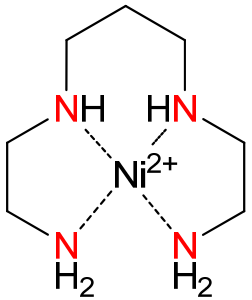
log K_{ML} = 9.2

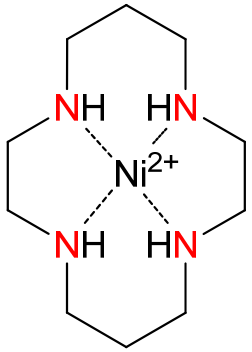


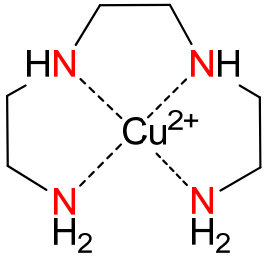
log K_{ML} = 13.3

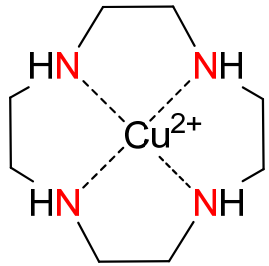
A macrocyclic ligand complex is more stable than its open chain analogue

Complex









Log K	**15.3**	**22.2**	**20.1**	**24.8**
ΔH (kJ/mol)	**-71**	**-130**	**-91**	**-71**
TΔS (kJ/mol)	**17**	**2.5**	**24**	**64**
ΔG (kJ/mol)	**-88**	**-132.5**	**-115**	**-139**

Thermodynamic considerations show that the effect depends on both enthalpy and entropy

- **Enthalpy:** The conformational nature of the ligand (the macrocycle may be locked in the conformation in which bonding occurs and therefore no energy needs to be spent on its rearrangement).
- **Entropy:** The change in solvation of both the metal center and ligand (as the complex forms, the solvent needs to rearrange, and this is an entropic factor, and is different for the cyclic and acyclic ligands)

- Origins of the effect:
  In the **simpliest** situation, one may compare
  the **formation of an open-chain ligand complex** and its cyclic analogue:

  $$\mathbf{M + L \rightarrow ML}\ (k_f)$$

- For both ligand types,
  the above process should be facile,
  although formation of the cyclic complex is expected to be somewhat slower.

- However, the **dissociation of the metal ion** from the macrocyclic complex (consider to be first order)
  is likely to be **much slower than for the open-chain analogue**:

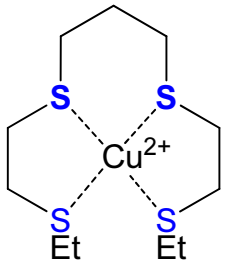
  $$\mathbf{ML \rightarrow M + L}\ (k_d)$$

- **At equilibrium:**

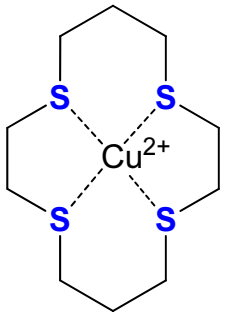
$$\mathrm{M} + \mathrm{L} \underset{k_d}{\overset{k_f}{\rightleftharpoons}} \mathrm{ML} \qquad K = k_f / k_d$$

  k_d **(first order)** of macrocyclic complex will be **smaller**
  while k_f **(second order)** will be approximately similar to the open-chain case
  hence ***K* will be enhanced**.

- The enhanced stability of a macrocyclic ligand complex may arise from its rate of dissociation being slow compared to its open chain analogue.



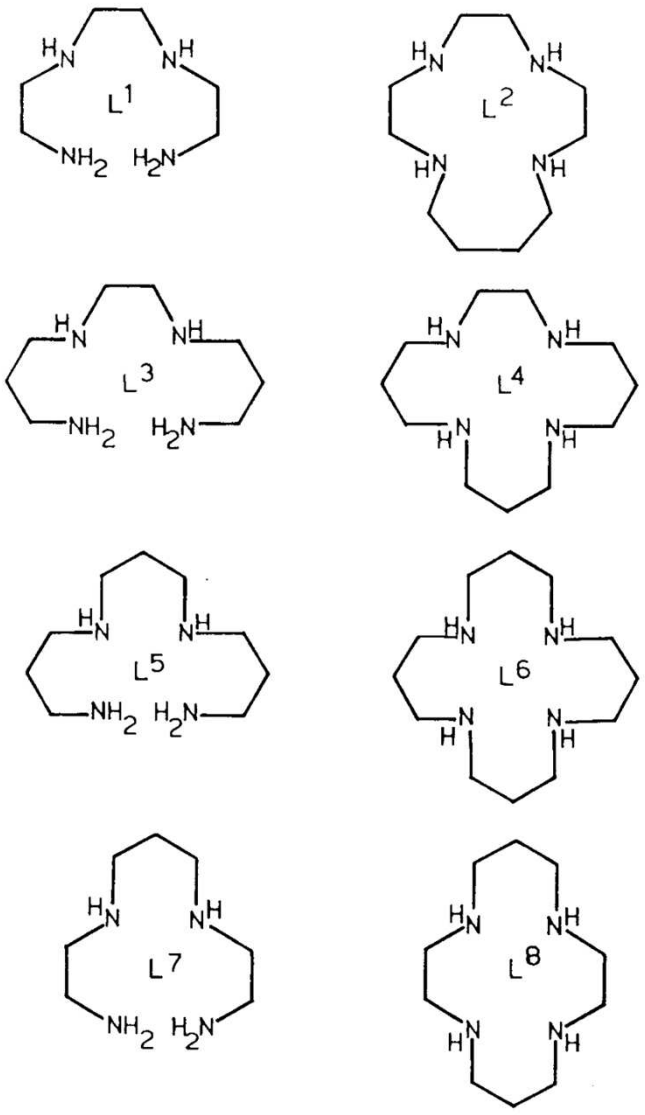
$K_f = 4.1 \times 10^5$; $K_d = 3 \times 10^4$; $K_f / K_d = 14$



$K_f = 2.8 \times 10^4$; $K_d = 9$; $K_f / K_d = 3100$

- In the sulphur complexes above, it is seen that the rate of dissociation of the macrocycle is very low: the macrocycle complex is **kinetically stabilised**, ie. it is relatively **inert**.

Comparative Thermodynamic Parameters



$$[NiL_{oc}]^{2+} + L_{mac}{}^{2+} \rightleftharpoons [NiL_{mac}]^{2+} + L_{oc}$$

oc = open chain; mac = macrocyclic

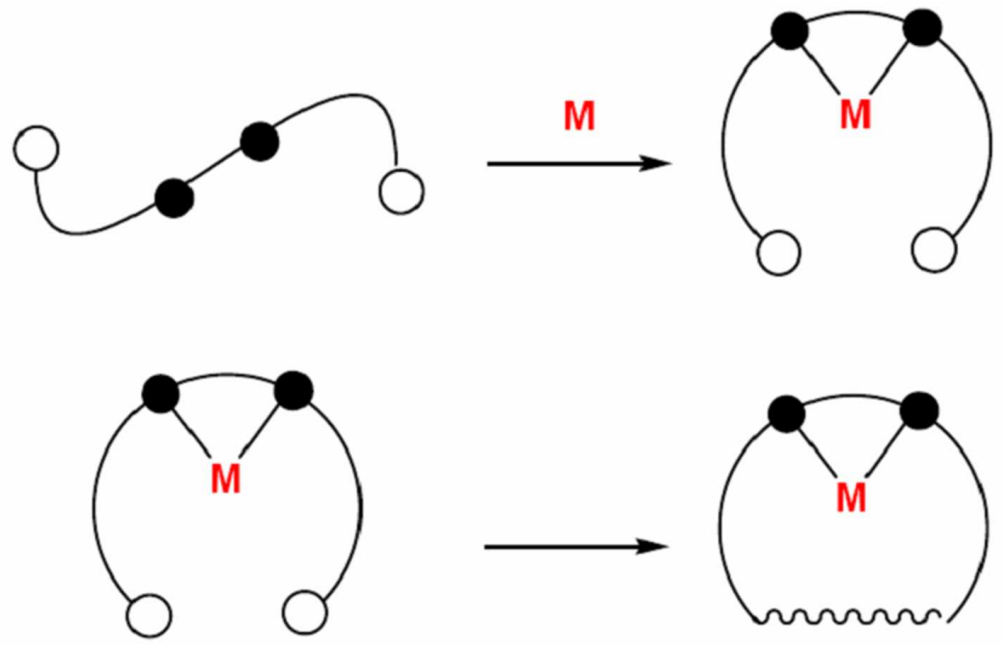
L_{oc}/L_{mac}	$\frac{-\Delta G}{kJ\ mol^{-1}}$	$\frac{\Delta H}{kJ\ mol^{-1}}$	$\frac{T\Delta S}{kJ\ mol^{-1}}$
L^1/L^2	2.43	5.1	7.4
L^3/L^4	21.05	5.3	26.4
L^5/L^6	15.69	3.5	19.2
L^7/L^8	33.67	−20.5	13.2

The entropy term associated with the macrocyclic effect tends to be favourable while the enthalpy term can be quite variable (and either favourable or unfavourable).

$$\Delta G = \Delta H - T\Delta S$$

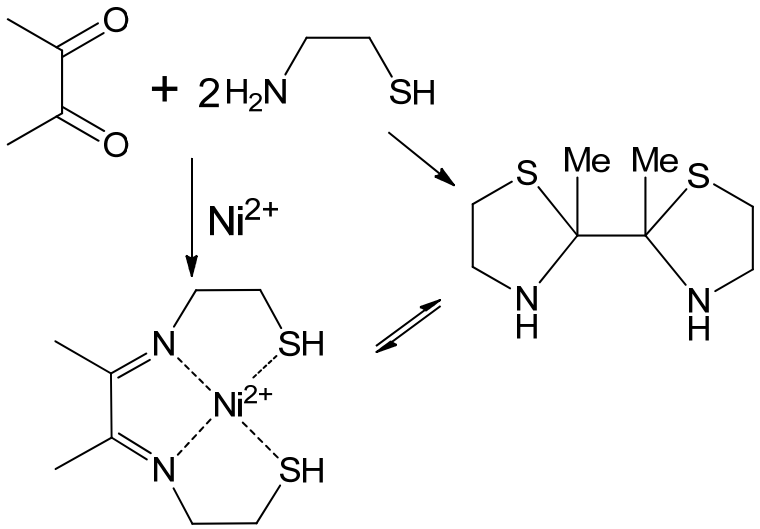
2.10.4 Template Effect

- A metal ion template reaction is favour of a specific macrocyclic compound.
- This means that **the presence of the metal is controlling the synthesis**: **template effect**
- The template effect is demonstrated in two ways, the **thermodynamic** and the **kinetic template effects**.



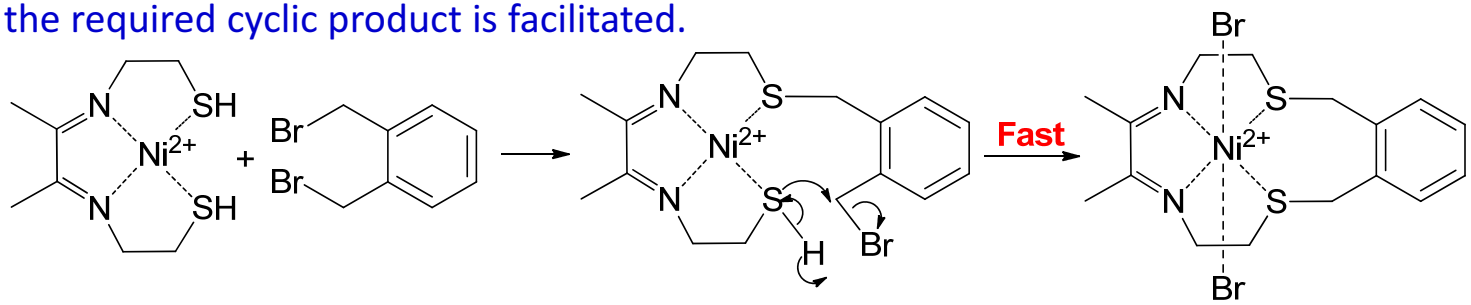
- Thermodynamic and kinetic template effect (D. Busch)
- **The thermodynamic template effect:** Formation of macrocycle is promoted as its metal complex.
- **The Kinetic template effect:** The metal ion directs the steric course of a condensation such that formation of the required cyclic product is facilitated.

- The **Equilibrium (or Thermodynamic) Template Effect**:
  Complexation to a metal ion stabilizes one component of a mixture, shifting the equilibrium in favour of production of a metal complex.
- Formation of the macrocycle is promoted as its metal complex.



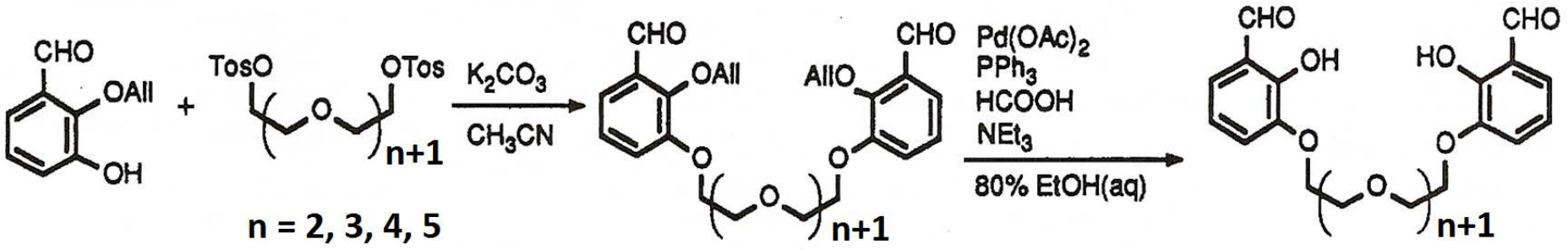
- The **Kinetic Template Effect**

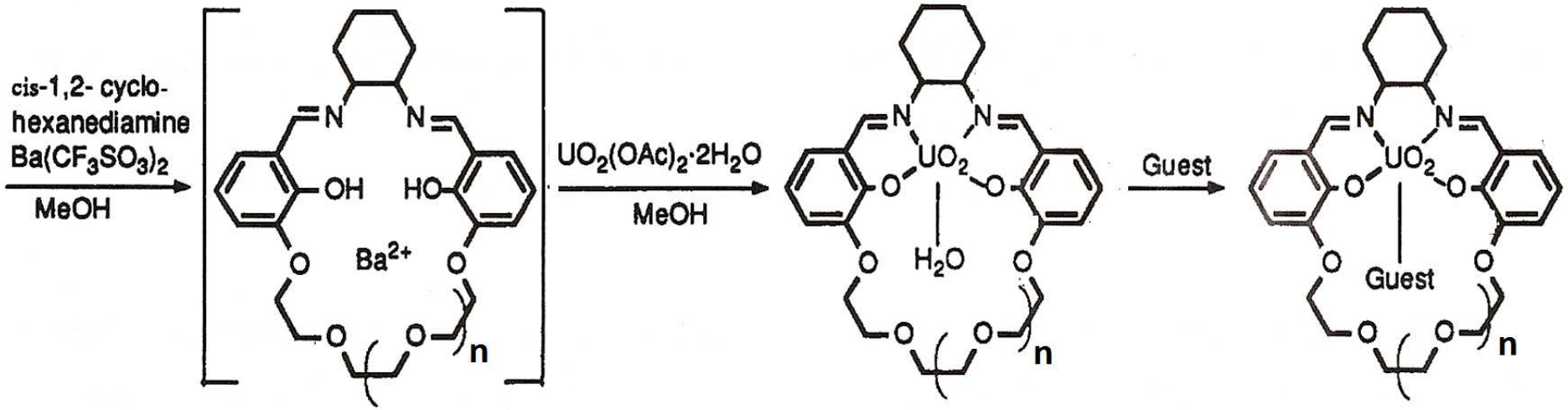
  The metal ion directs the steric course of a condensation such that formation of the required cyclic product is facilitated.



The favoured octahedral coordination about the metal center drives the reaction to give the cyclic product.

- Receptor site incorporated with metal ions
- Metal ion centers in the receptors can be used to complex neutral molecules, especially, if they have electron rich atoms (O, N etc.)
- Common metal ions used for such studies include Cu, UO_2 etc.





Ba^{2+} acts as a template for cyclization

2.10.5 Synthesis of Macrocycles

Macrocycle Synthesis	
/	¥
Direct	In situ
Conventional Organic reactions - Without metal ion	Reaction in presence of metal ion which acts as a template

❑ An aim of both template and direct syntheses is to maximize yields by choosing strategies which inhibit the formation of competing linear polymerization reactions.

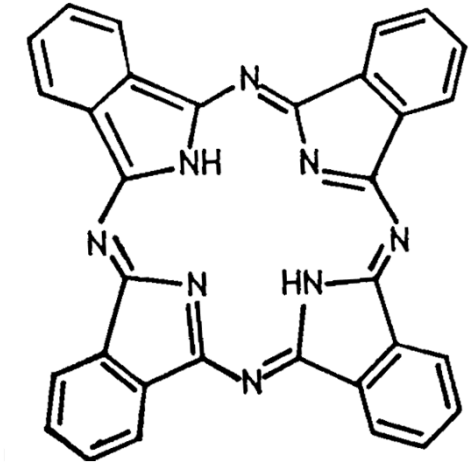
❑ **Direct Syntheses**

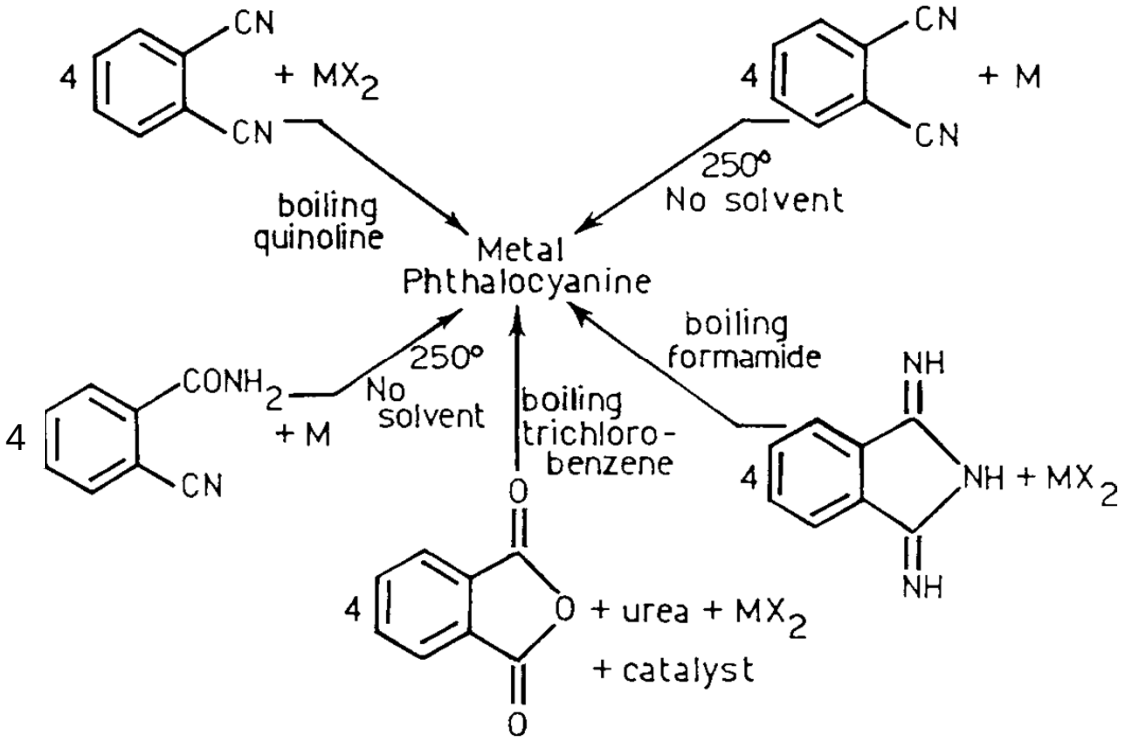
- Frequently performed under high dilution –
  favours self-condensation over linear polymerization.
- Special procedures developed for such reactions –
  slow addition of reagents to large reaction volumes using motor-driven burettes.

❑ Template Syntheses:

- Reactions often complicated multistep procedures – difficult to define precise role of metal.
- Very little research into specific reactions – much '*witchcraft*'!

Metal Phthalocyanine Synthesis

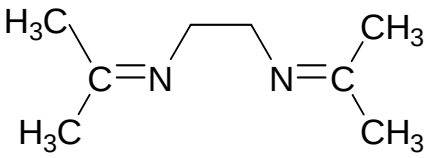




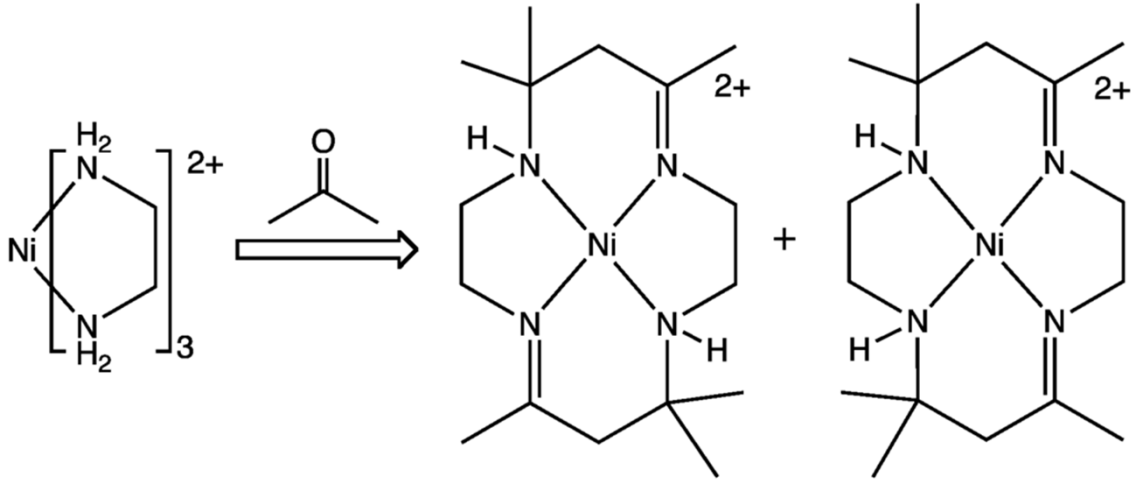
- Pre-1960 Synthetic macrocyclic chemistry mainly that of phthalocyanine and derivatives.
- Synthesized via metal template procedures.

Examples of typical *in situ* syntheses
The Curtis Macrocycle (1960)

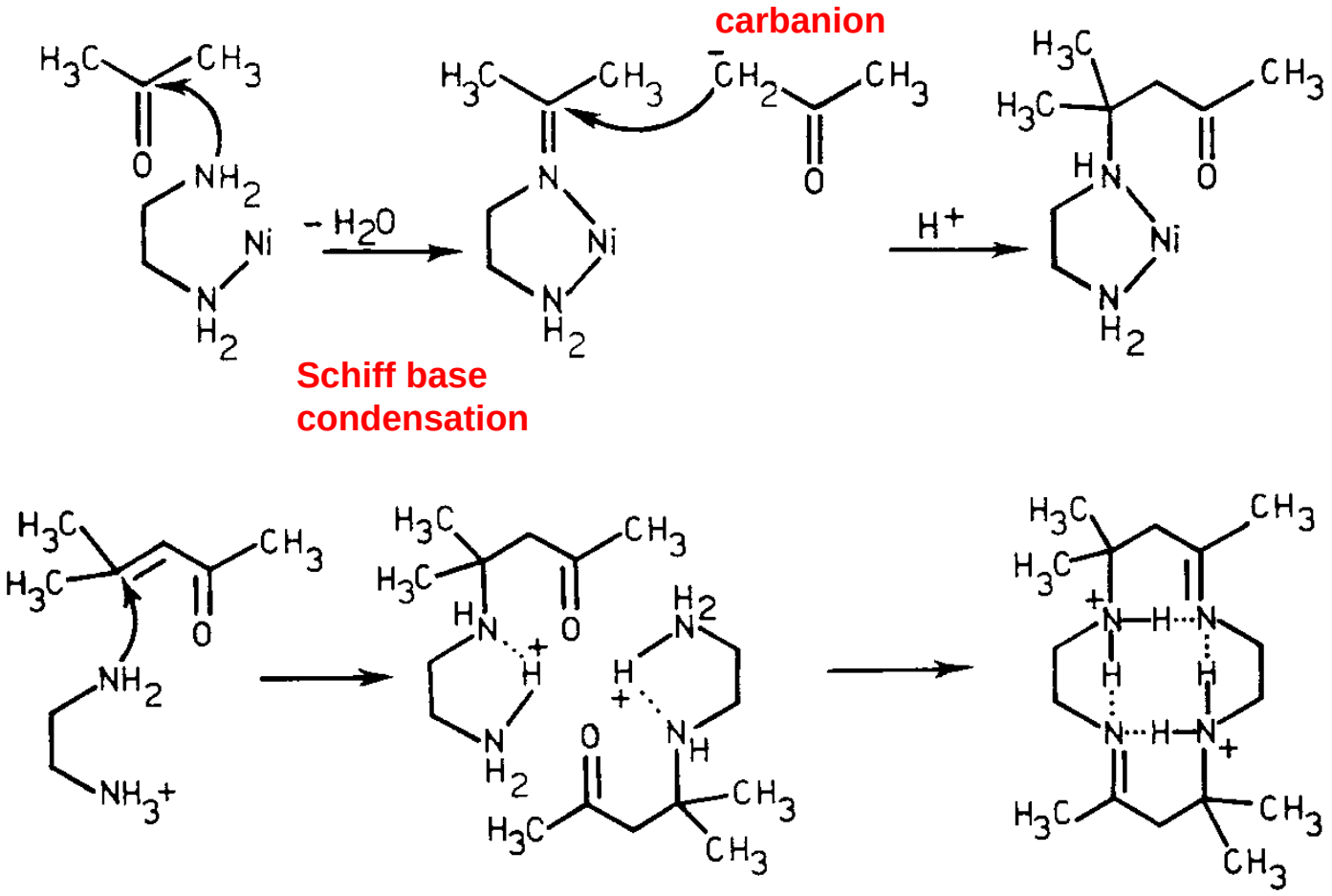
- Curtis investigated the reaction between dry acetone and $[Ni(en)_3]^{2+}$.
- Obtained a yellow crystalline product.
- Initially formulated as the Schiff base Ni(II) complex of type $[NiL_2]^{2+}$.



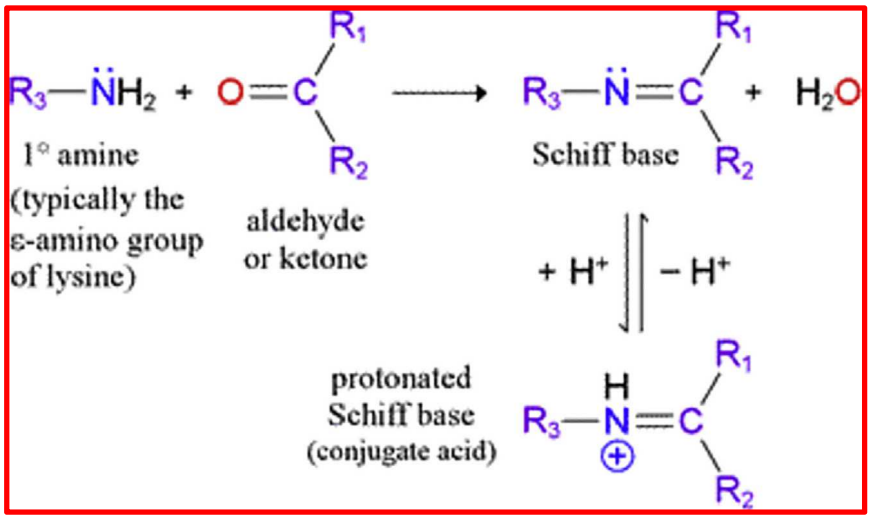
- Extreme stability did not fit this formulation.
- Correct formulation is a mixture of the isomeric complexes:



Prof. Neil Curtis
Victoria University of Wellington


carbanion
Schiff base
condensation

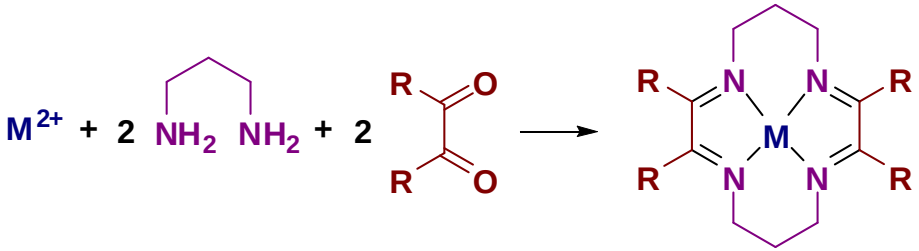
2.10.6 Template Synthesis



General scheme for formation of Schiff bases

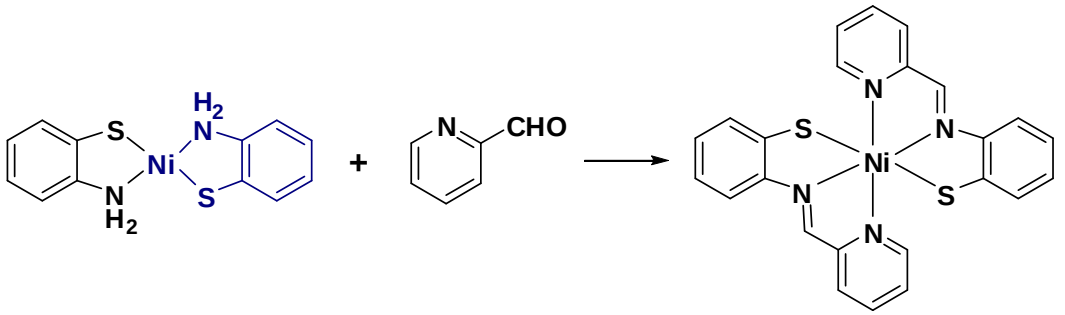
$(CH_3)_2C{=}O + H_2NCH_3 \rightarrow (CH_3)_2\mathbf{C{=}N}CH_3 + \mathbf{H_2O}$

Most condensation reactions proceed without metal ion, but the reaction rate is much faster in the presence of metal ion.

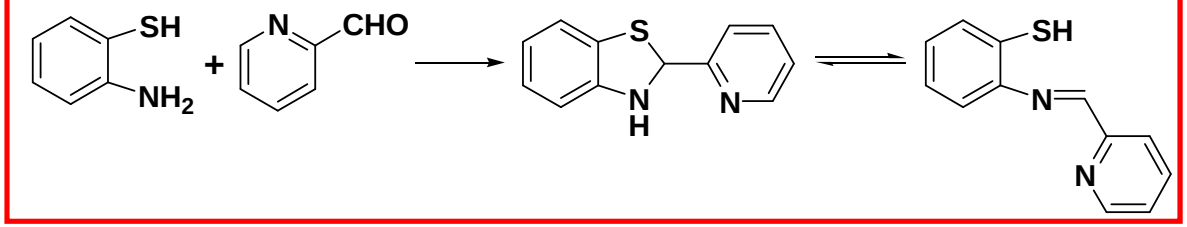


[M = Fe(II), Ni(II), Cu(II)]

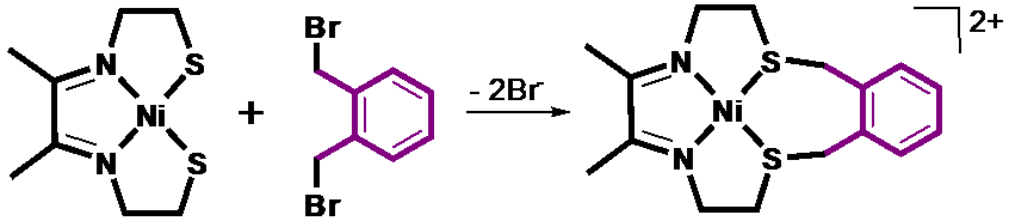
Synthesis of Ni-imine complex by Schiff-base condensation



In absence of Ni(II)



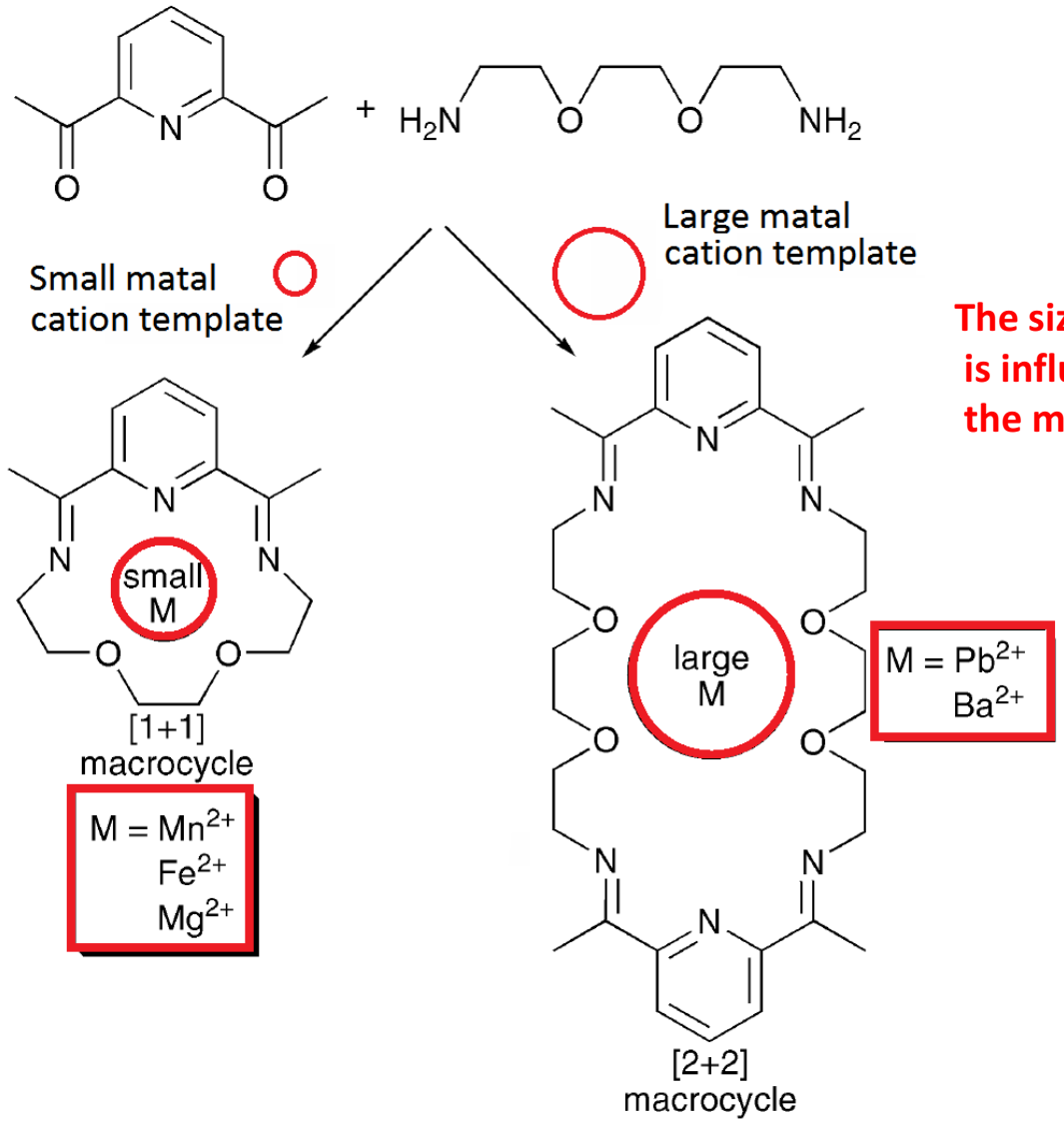
- Early template reaction: Dialkylation by nickel(II) ditholate
- **Polymer product in absence of Ni(II)**



Limit of template reaction

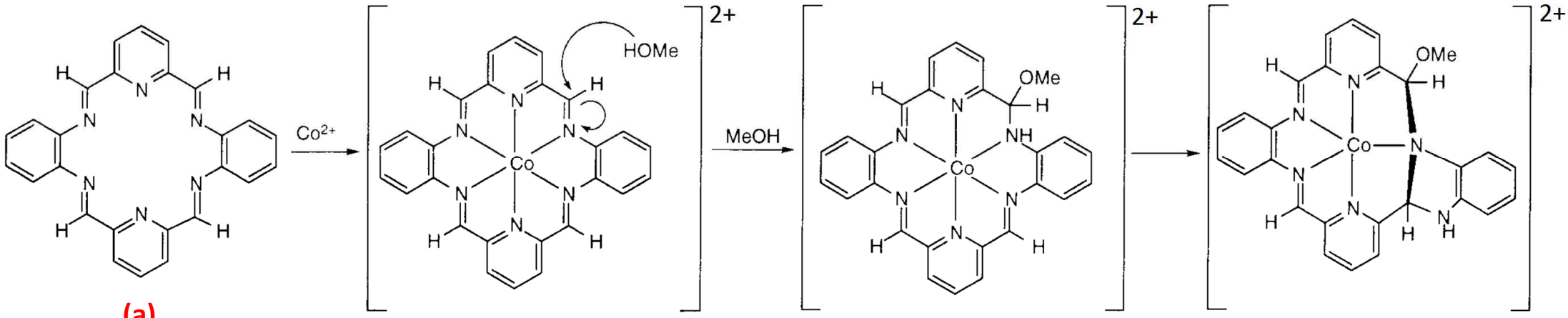
- Template synthesis is stoichiometric reaction
- Difficult demetalation from template product
- Template reaction may proceed without metal ion

2.10.7 Size Effect



The size of the macrocyclic product is influenced by the size of the metal cation template used

Hole-size Effects



(a)

Nucleophilic attack by oxygen of methanol

MeOH adds across double bond

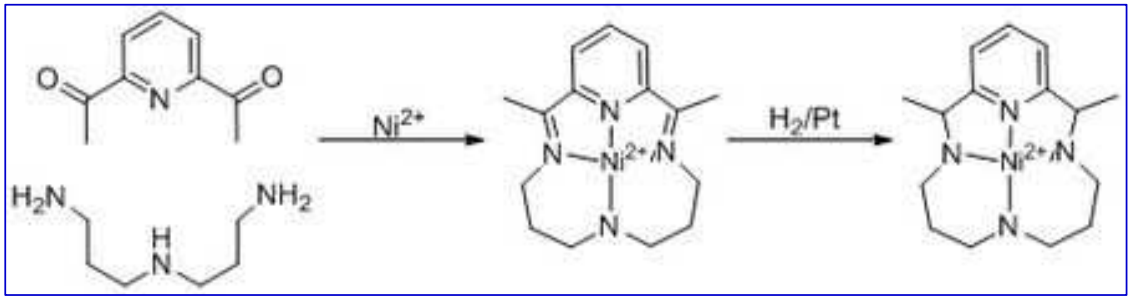
In some other systems the reaction stops at this stage

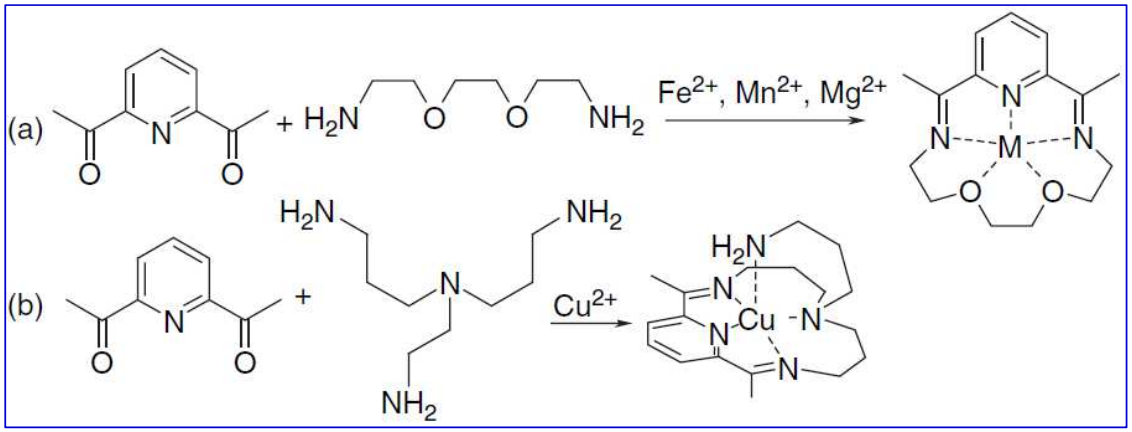
Heterocyclic ring closure

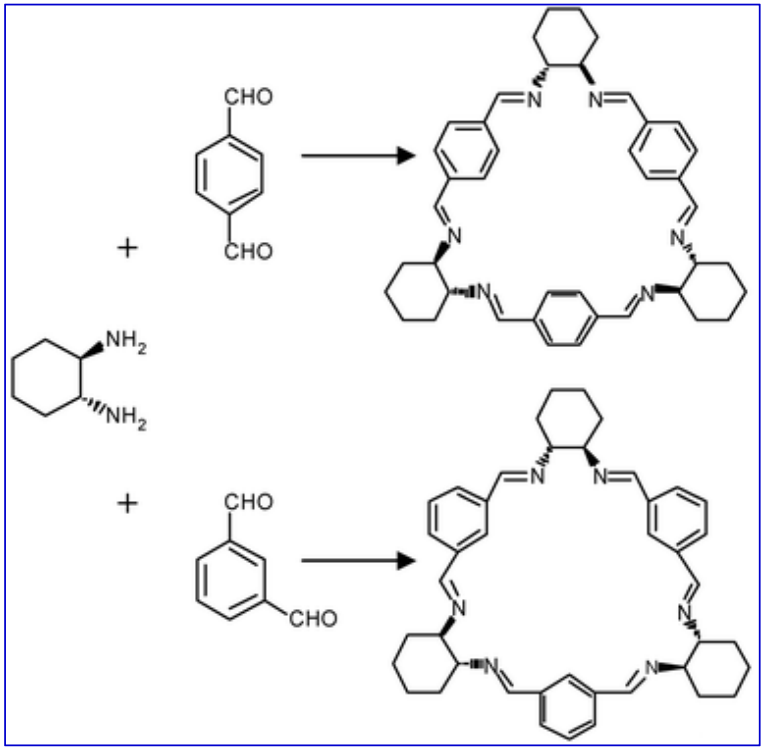
- A dramatic rearrangement that occurs when **(a)** is treated with Co(II) salts.
- The driving force in the formation of a macrocyclic cavity which can accommodate Co(II).

Schiff bases

- **Aliphatic imines** are unstable with respect to hydrolysis.
  (*i.e.* the formation of the Schiff base is reversible).
- Schiff base macrocycles are often reduced to the amine with a reducing agent, such as $NaBH_4$.
- **Aryl imines** are relatively stable due to the delocalisation of the electrons across the π-system.

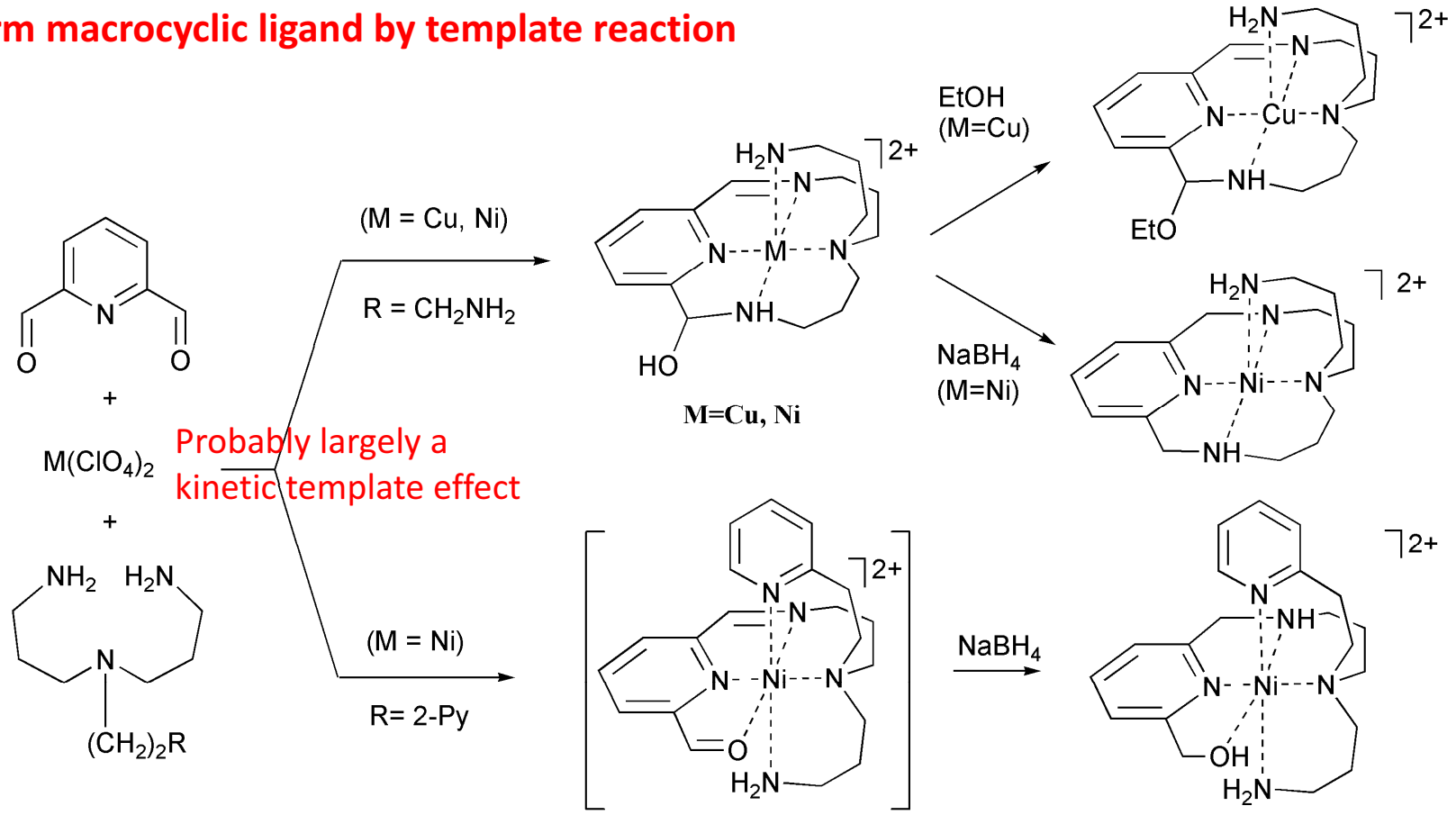




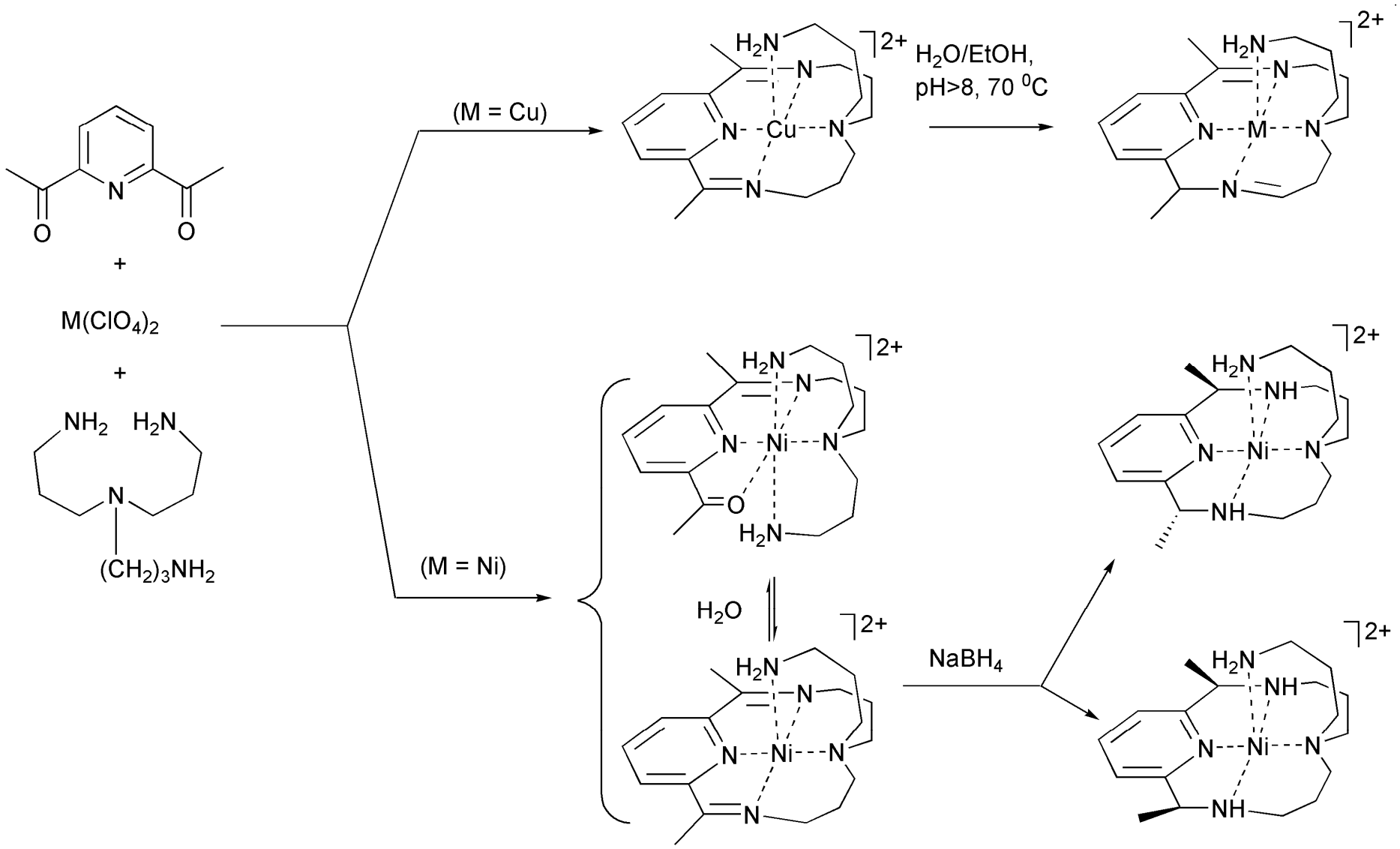


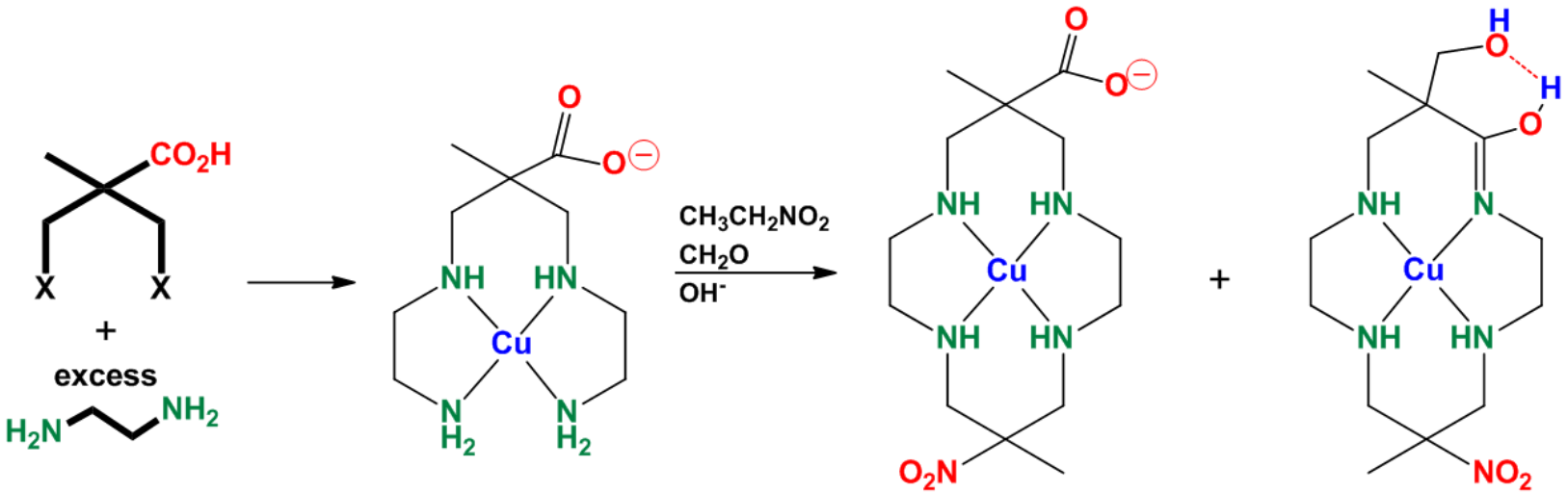
2.10.8 Pendant–Arm Macrocycles

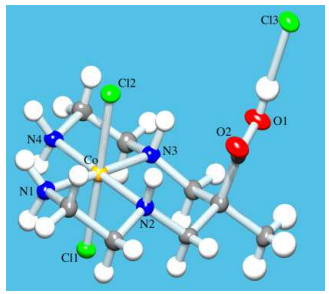
A pendant-arm macrocyclic ligand by template reaction

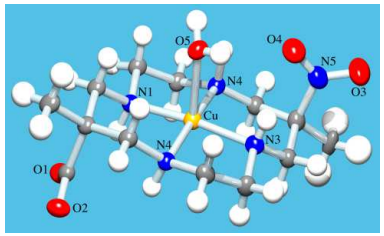


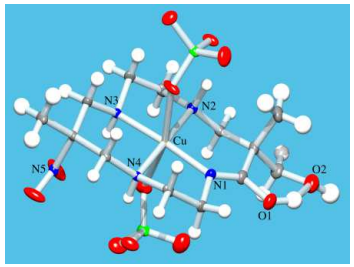
Dalton Trans. 4482(2003)


M(ClO4)2
(M = Cu)
(M = Ni)
H2O/EtOH,
pH>8, 70 0C
H2O
NaBH4
2+

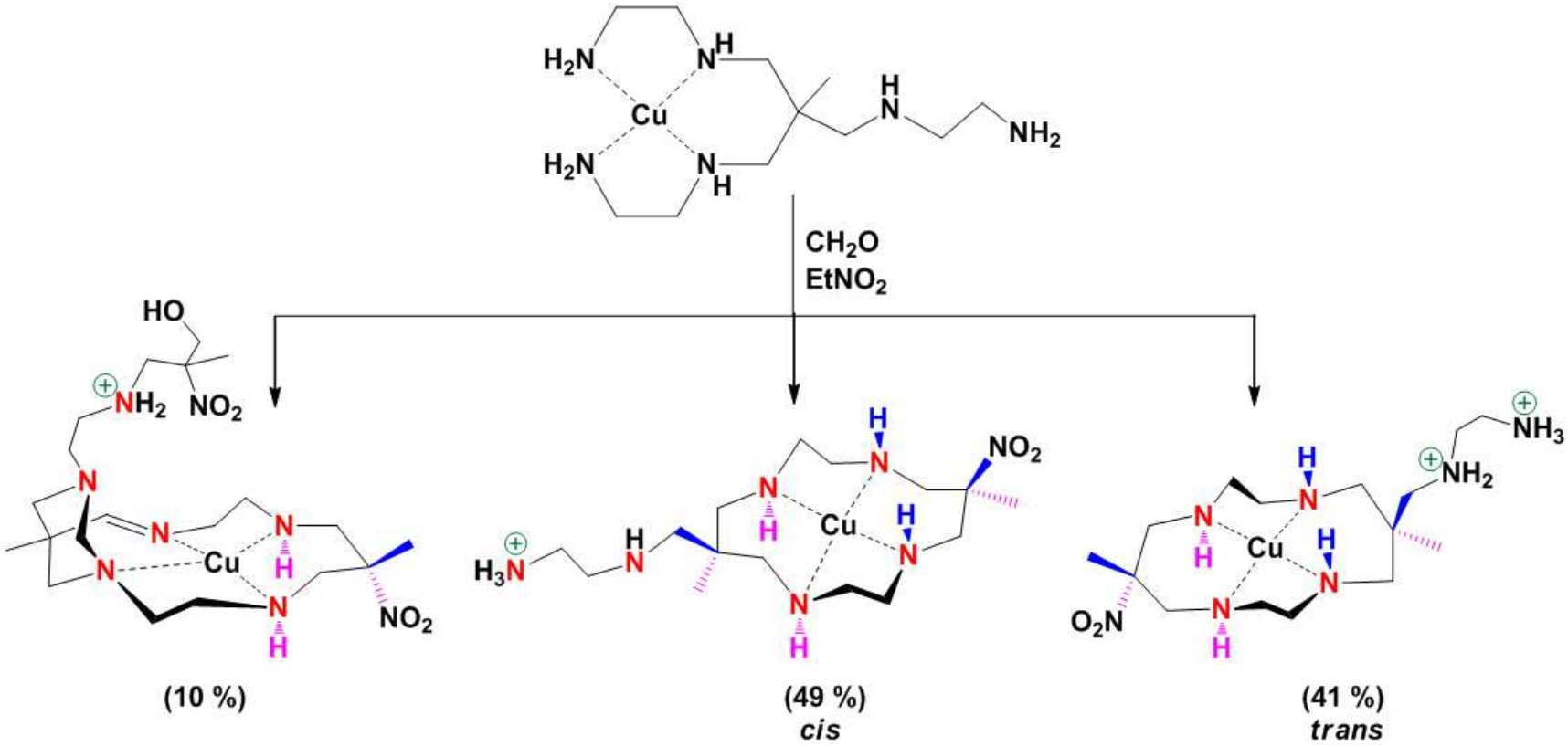






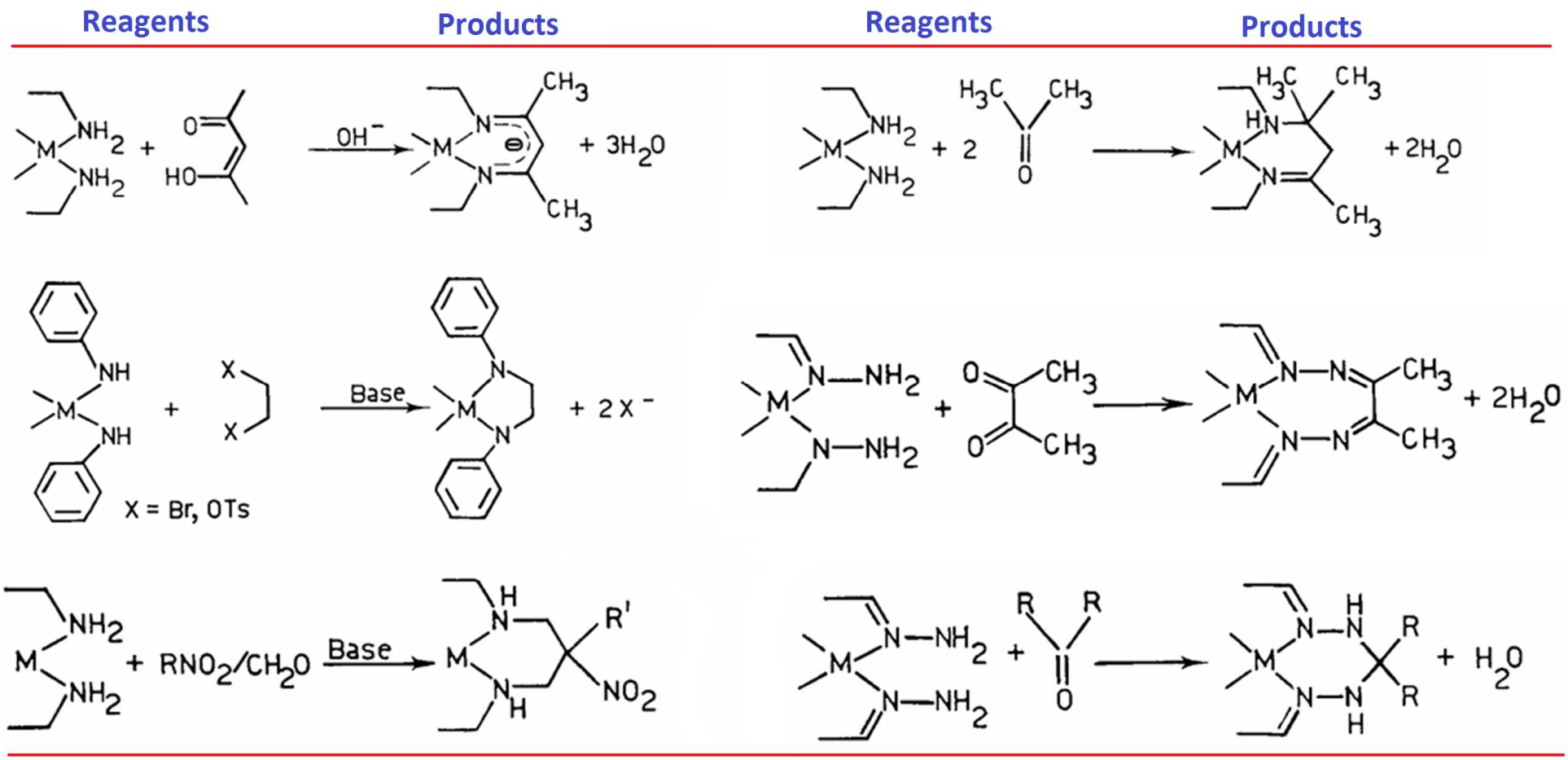


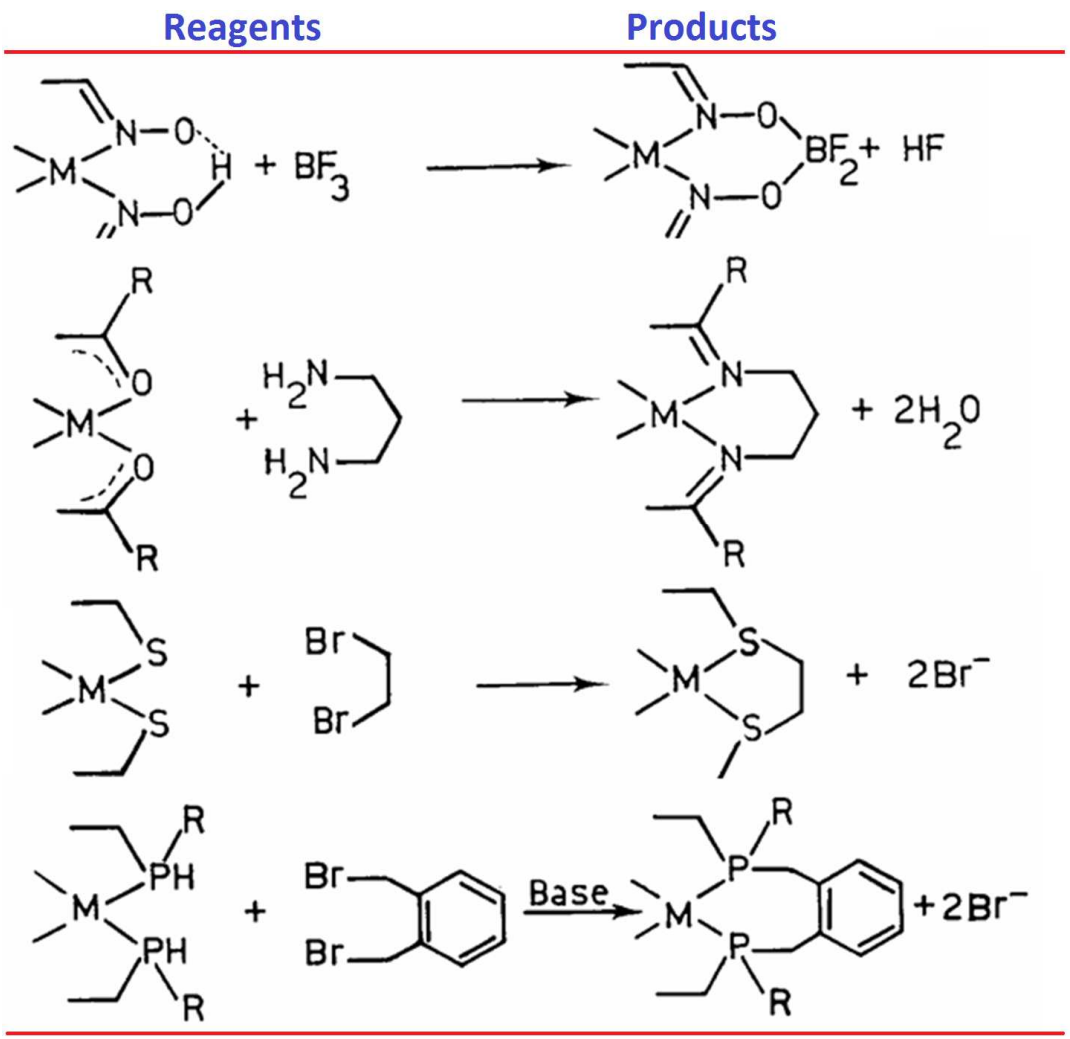
Inorg. Chem., 43, 1681(2004)



Eur. J. Inorg. Chem., 2913(2003)
Polyhedron, 23, 869(2004)

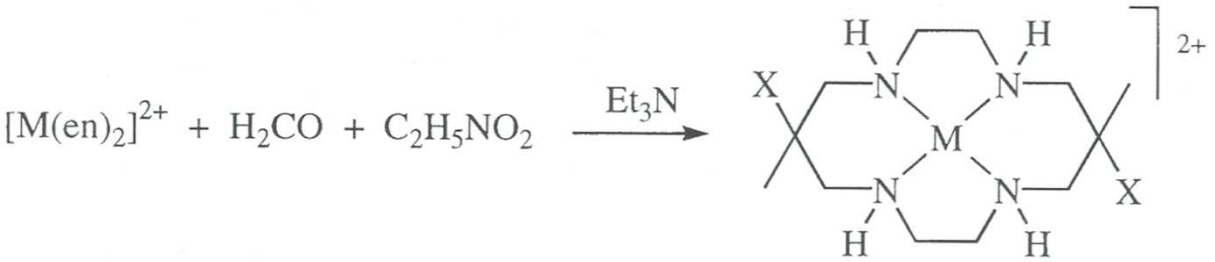
2.10.9 Representative *In Situ* Ring-Closing Reactions




Reagents
Products
+ BF3
BF2+ HF
+ 2H2O
+ 2Br−
Base
+2Br−

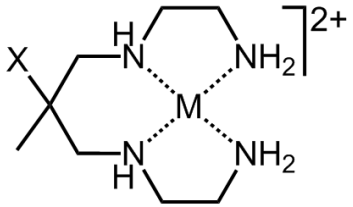
2.10.10 Saturated polyazamacrocyclic compounds

- Two geometric isomers are potentially possible: ***cis* (or *syn*)** and ***trans* (or *anti*)**.
- In case of Pd(II) and Cu(II), this reaction is stereoselective in that the ***anti* isomer is preferentially formed**.



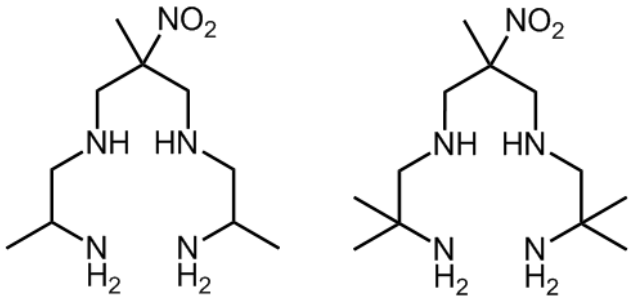
M = Ni, Cu, Pd: X = NO_2

- For Cu(II) and Pd(II), **the intermediate half-capped** may also be isolated, and can be chromatographically separated from competing species.

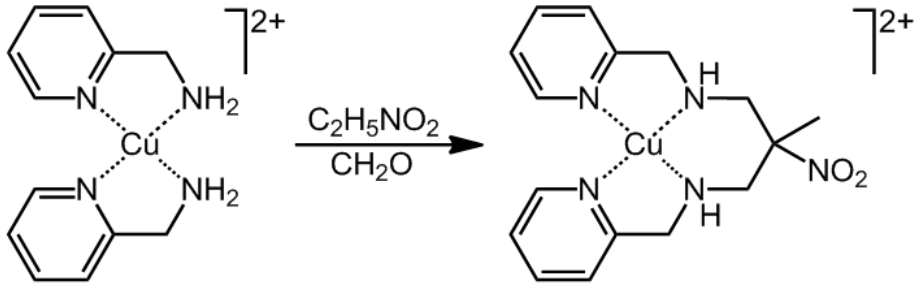


X = NO_2
M = Cu, Pd

- The influence of the consecutive introduction of one and then two methyl groups at one 1,2-diaminoethane carbon atom on Cu(II)-conducted **carbon acid-formaldehyde condensation reactions** has been studied.
- These reactions occur predominantly distant from the site of C-methylation, leading mainly to the **half-capped intermediates**.

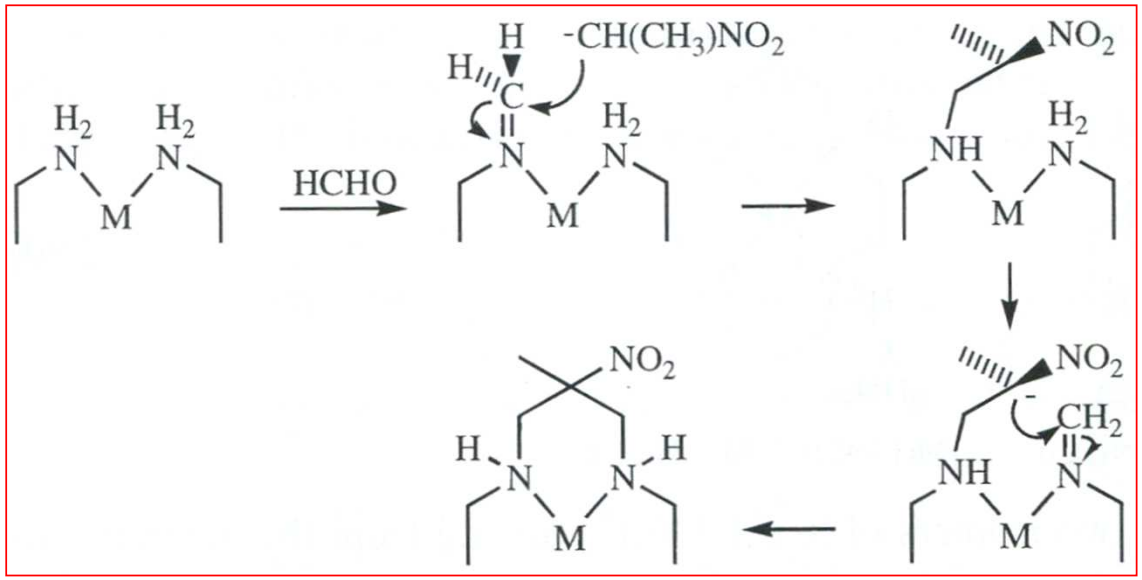


- On interaction of $[Cu(picolylamine)_2](ClO_4)_2$ with nitroethane and formaldehyde, condensation occurs **only at the terminal coordinated amino groups** as product.



2.10.11 Mechanism of Condensation Reaction

- The **condensation reaction of coordinated amines** with formaldehyde and nitroalkanes is believed to proceed through an **imine (or aminol) intermediate** sensitive to attack of the carbon acid conjugate base on the imine carbon atom.
- It should also be pointed out that the first condensation step involves **nucleophilic attack on an HCHO molecule** by a coordinated amido ligand arising from deprotonation of the metal-bound primary amine.



- Attempts to reduce the nitro group with Zn in aqueous HCl unexpectedly led to the isolation of NH_2-macrocycle in 90% yield.

2.10.12 Application of Aza-macrocycles

- **Tetrabenzyl[14]N_4 complexes (copper, gold, silver): antitumor active**
- **Paramagnetic complexes (Fe^{3+}, Gd^{3+} and Mn^{2+}): contrast agents in medicinal MRI**
- **Removal of heavy metals or radioactive elements**
- **Treatment of kidney stones**
- **Catalyst**
- **Sensor**
- **Chromatographic separation of metal ions**
- **Selective extraction of cations**
- **Antibacterial and antitumor agents**
- ***There may be many industrial applications……..***

2.10.13 Functionalised macrocycles are opening additional possibilities

- **Applications in analytical Chemistry**

  $Ca(DOTA)^{2-}$: probably the most stable among all such complexes ever reported

- **The strongest chelator for Gd(III)**

  Imaging agent for MRI

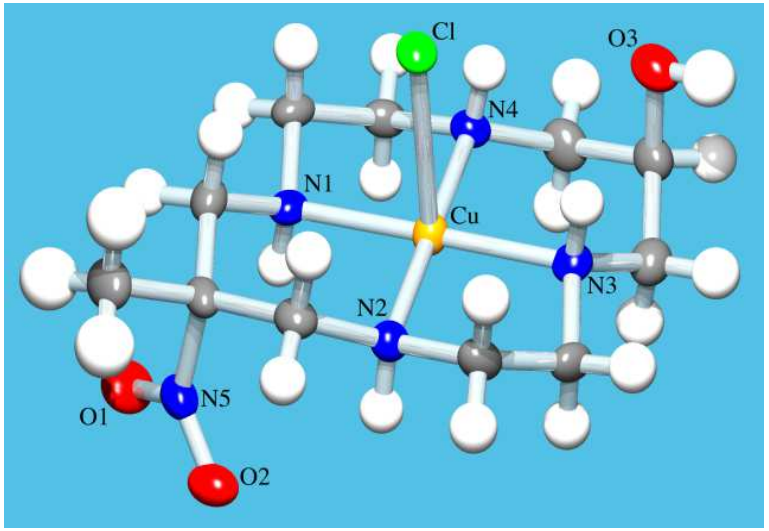
- **Functional group provide a suitable site for attachment of biomolecules**

  such as monoclonal antibodies.

- **Electroactive sensor**

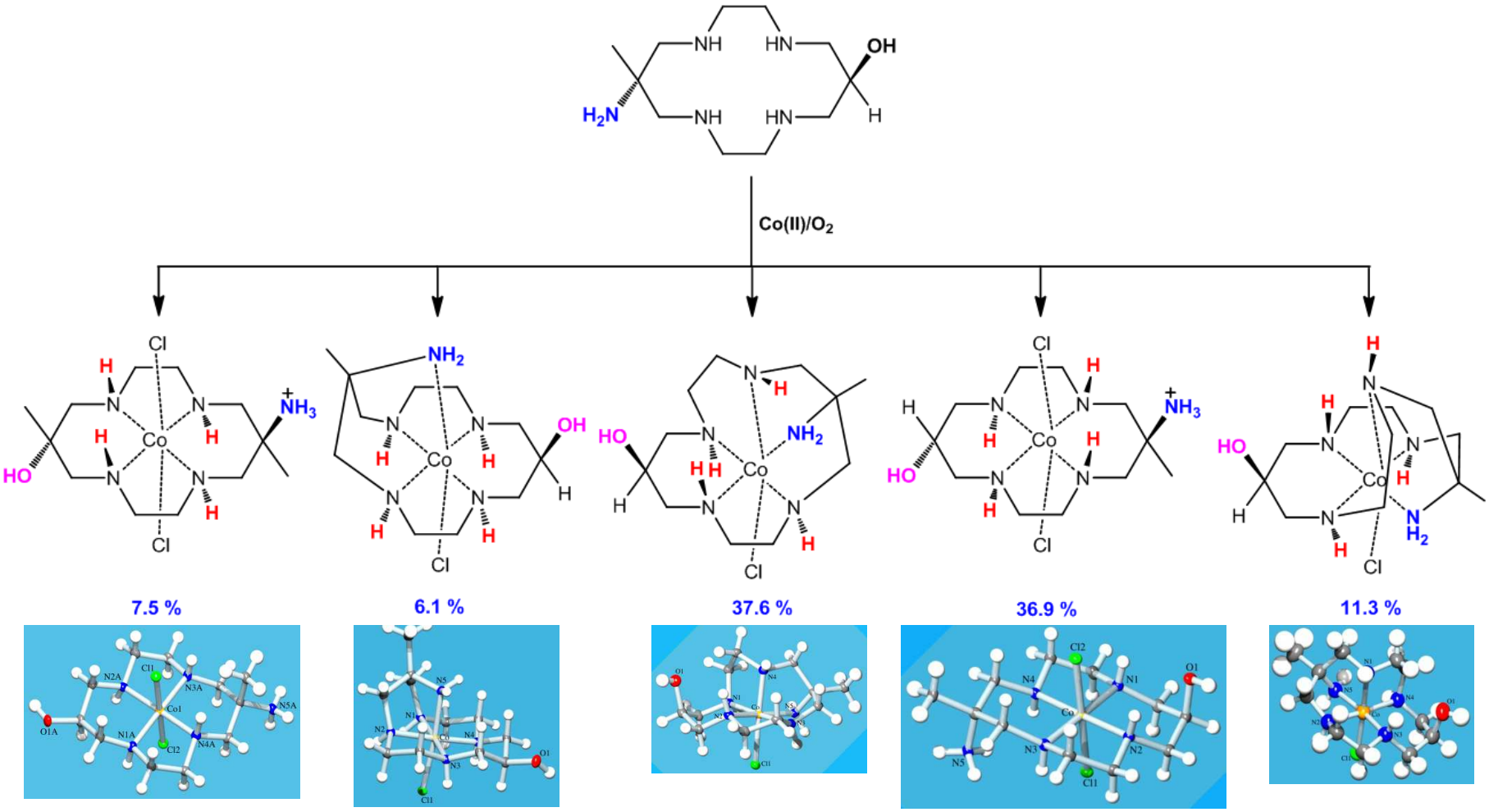
  Photoelectrochemical energy storage devices

- **Catalysts in redox processes**
- **Liquid crystals**
- **Highly charged detergents**
- **…….**



Inorg. Chem., 43, 1689(2004)

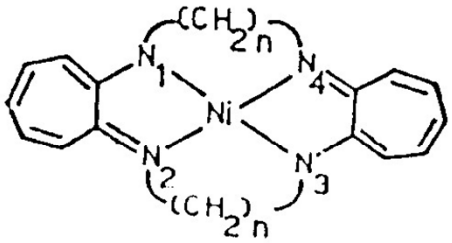
2.10.14 Stereochemistry of Co(III) Macrocycles



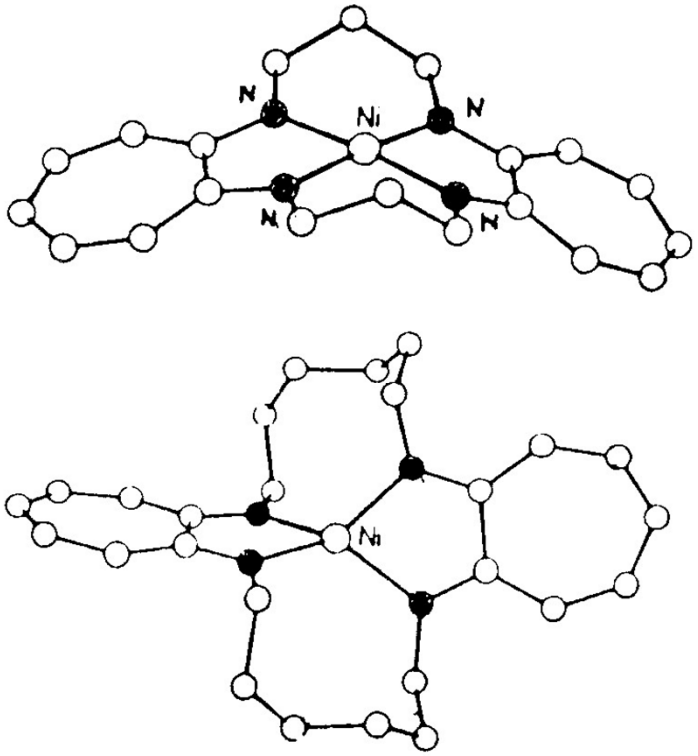
2.10.15 Steric constraints and less-common coordination geometries

- Induced ring strain on coordination may lead to less common coordination geometries.

  (ex): The Ni(II) complexes of the tropocoronands (Lippard *et al., 1983).*



85° between N_1, N_2 and N_3, N_4 chelate ring planes



- The 14-membered ring complex is planar,

  but a progressive distortion towards tetrahedral with increase in ring size:

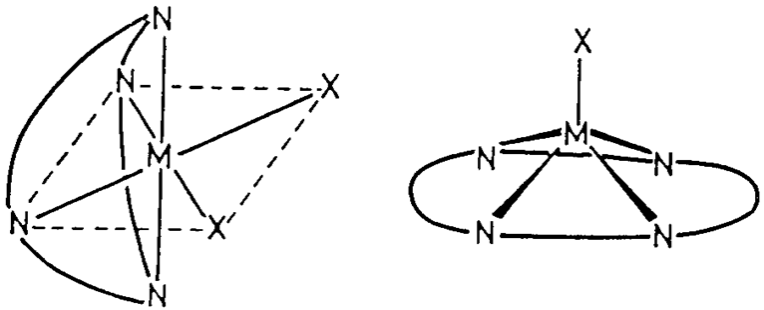
  - reflects steric crowding in large chelate rings.

- **In case macrocyclic hole is too small for the metal ion,**

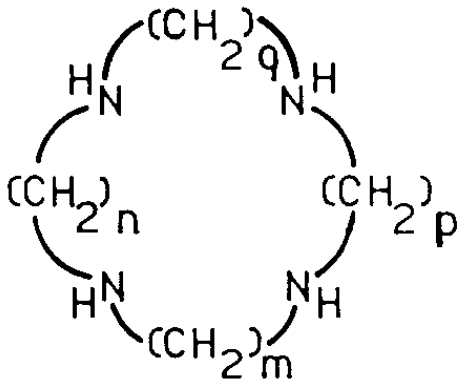
  either the macrocycle will fold

  or the metal ion will sit out of the donor plane

  (often with coordination of an axial ligand in the fifth position).

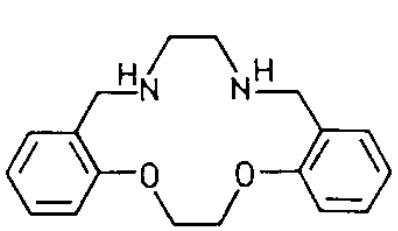


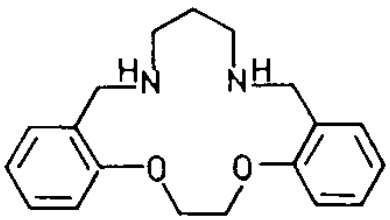
2.10.16 Macrocyclic Ring Size

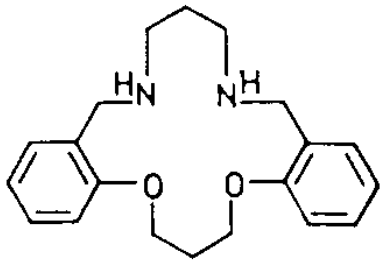


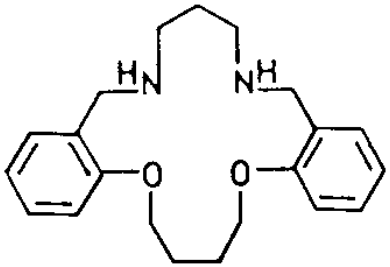
- **However**, ring expansions and contractions readily occur on coordination of such flexible macrocycles and differences in their radii more frequently change by around 0.05 Å for each stepwise increase in ring size.

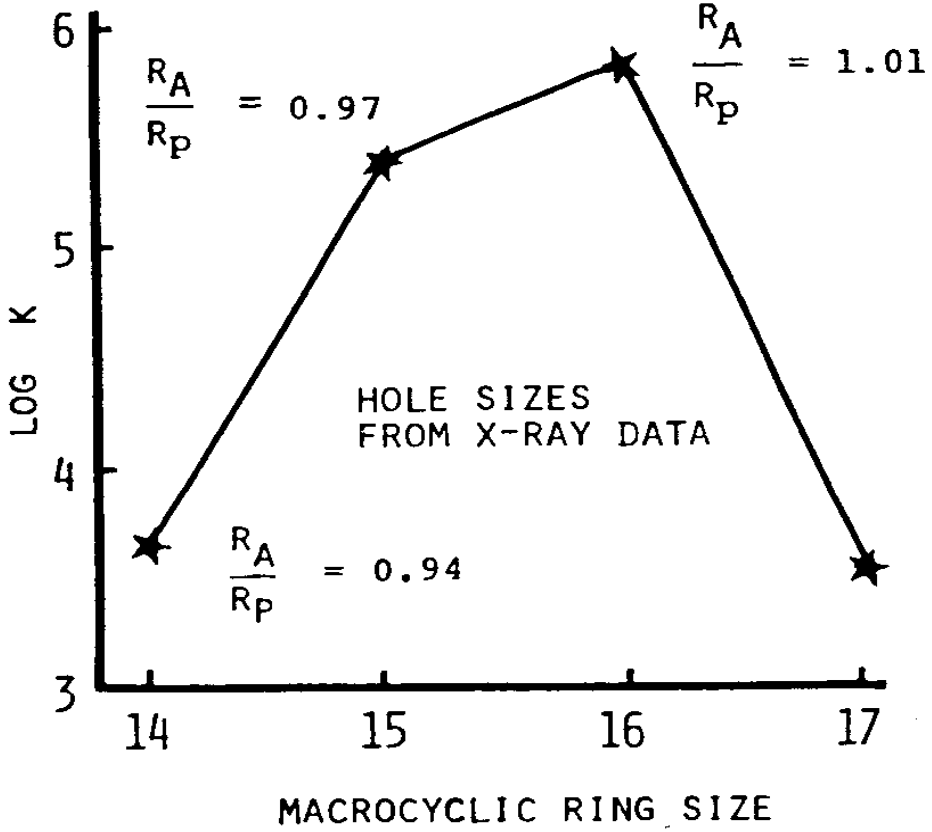
‘Goodness of fit’: Ni(II) complexes of 14- to 16-membered N_2O_2-macrocycles









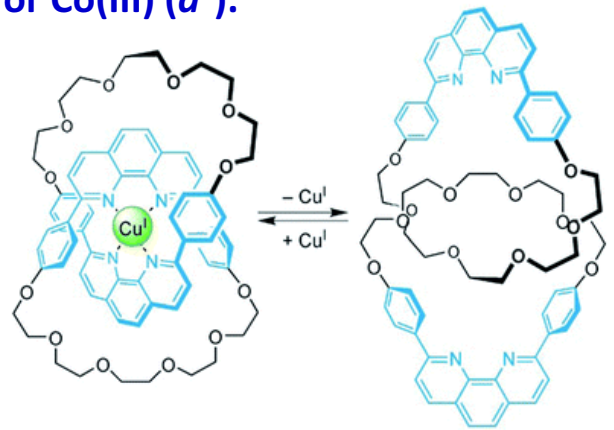


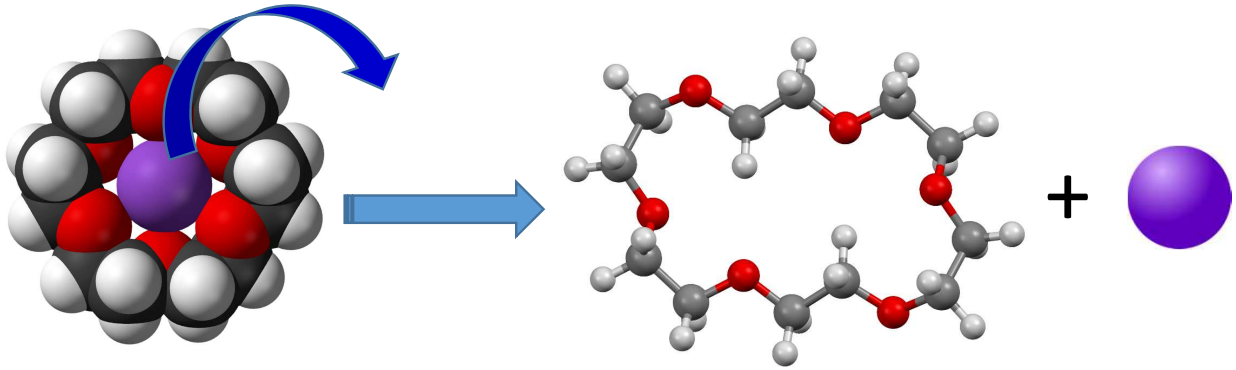
R_A = Apparent radius of the macrocyclic cavity

R_P = Pauling covalent radius for high-spin Ni(II)

2.10.17 Generation of free macrocycles from their metal complexes

- **Often the case when a kinetically inert metal centre is present such as Cr(III) (d^3) or Co(III) (d^6).**
- The addition of **excess acid** may lead to demetallation of the complex of an amine-containing macrocycle.
- Demetallation may be induced by addition of a **strongly competing ligand** to a solution of the macrocyclic complex [the cyanide ion or ethylenediaminetetraacetate **(edta)** are frequently used].
- In special cases, when the template ion is weakly coordinated, demetallation may be induced simply by **dissolution of the complex in a coordinating solvent** in which the free macrocycle has poor solubility.
- For some systems it has been found necessary to perform a **redox reaction** (**usually reduction**) on the complexed metal before it can be removed from the macrocycle.





2.10.18 Strategy of macrocycle synthesis

1. Macrocyclic ligand design, synthesis, and characterisation.
2. Metal complex synthesis and characterisation
3. Thermodynamic studies
4. Complementary kinetic studies
5. X-ray structural studies
6. Computer simulation studies
7. Assessment of factors promoting metal-ion specificity
8. Feedback of relevant data to (1) and, if appropriate, repetition of 1-8.

Three main parameters of tuning macrocycles for metal ion recognition

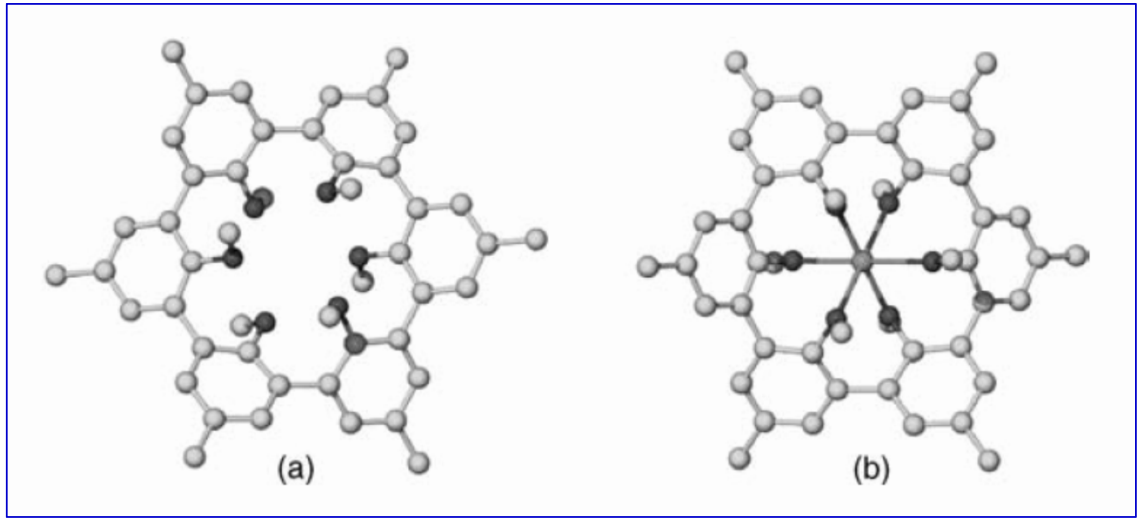
(1) Hole size variation, (2) Donor set variation, (3) Ring substituent variation

2.11 Spherands, hemispherands, cryptaspherands, heterocrowns and heterocryptands

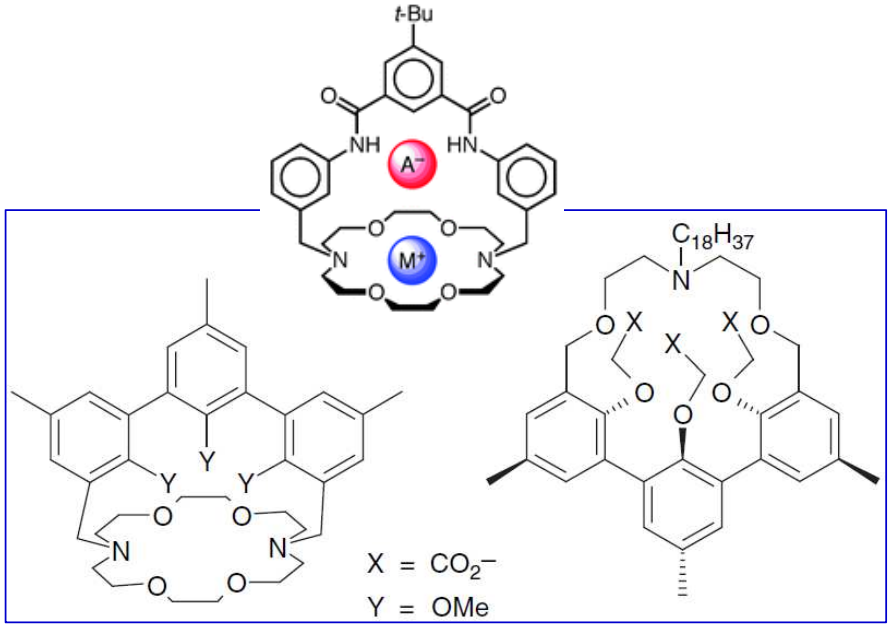
- ***Spherands*** are the most preorganised of the macrocyclic ligands and are very rigid.
- Binding constant of spherand-6 for Li^+ and Na^+ are in excess of 16 and 14 log units, respectively. Because of their extreme preorganization.
- Derivatives of spherands: hybrids of spherands with crown ethers, podands and cryptands

A general trend for $-\Delta G$

spherands > cryptaspherands > cryptands > hemispherands > corands > podands > solvents

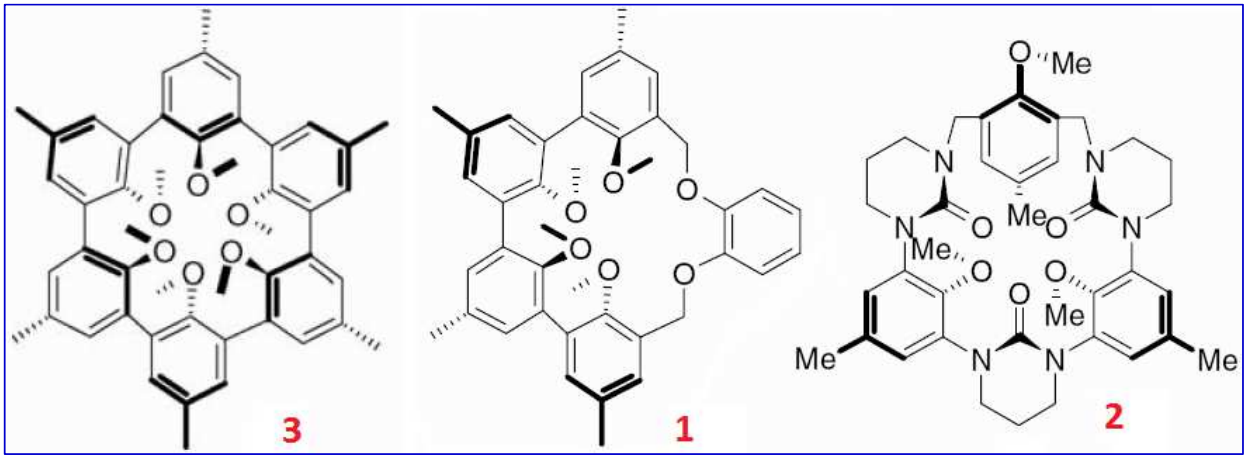


X-ray molecular structures of
(a) a free spherand and (b) its Li^+ spheraplex



hemispherands *cryptaspherands*

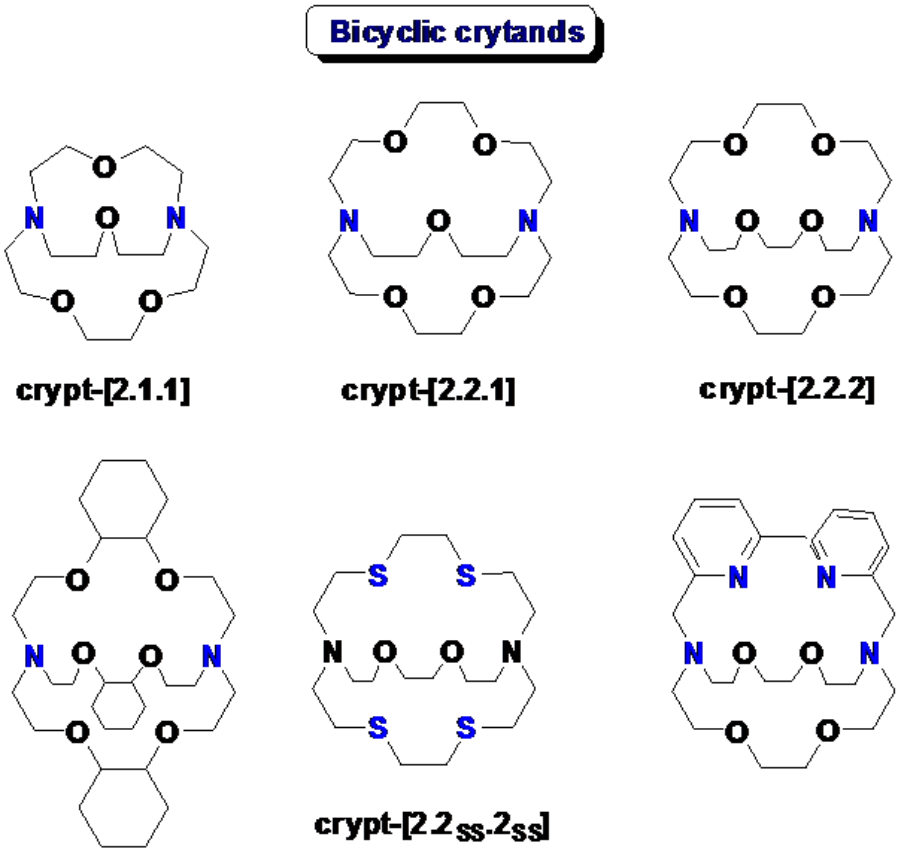
Complexation and decomplexation rate constants of picrate salts for representative compounds under standard conditions

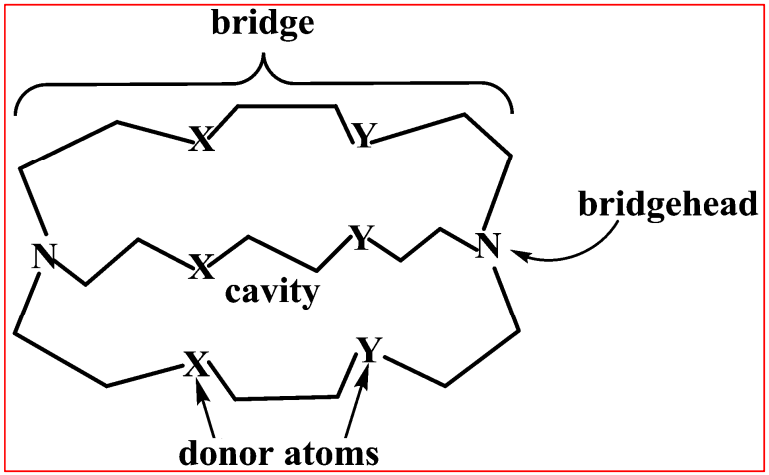


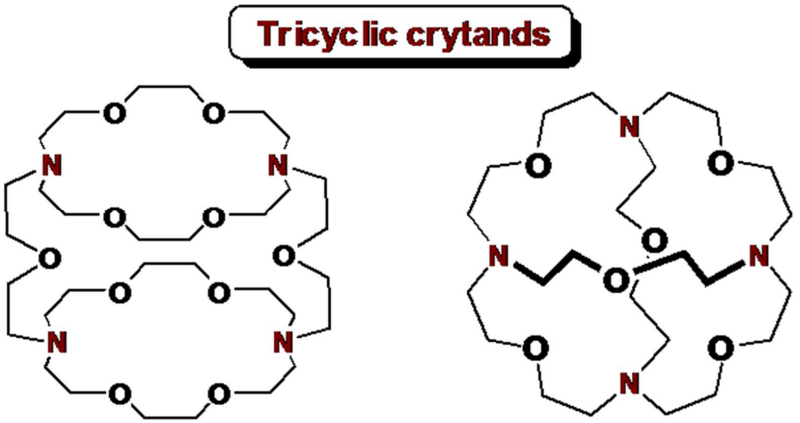
	3 capsular		**1** nesting		**2** perching	
Guest	k_1 ($M^{-1}\,s^{-1}$)	k_{-1} (s^{-1})	k_1 ($M^{-1}\,s^{-1}$)	k_{-1} (s^{-1})	k_1 ($M^{-1}\,s^{-1}$)	k_{-1} (s^{-1})
Li^+	8×10^4	$<10^{-12}$				
Na^+	4×10^5	2×10^{-7}				
K^+			2×10^9	14		
$(CH_3)_3CNH_3^+$					3×10^{12}	7×10^2

2.12 Cryptands

- Polycyclic compounds having cavity.
- **Cryptands** (Greek: *cryptos* = cave) first introduced by J.-M. Lehn.

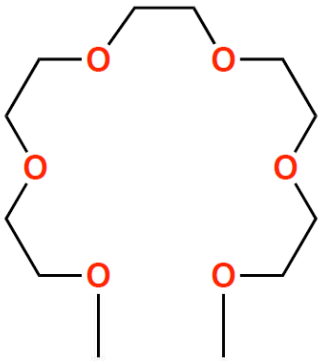




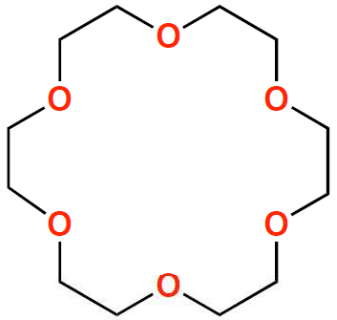


2.12.1 Macrobicyclic effect

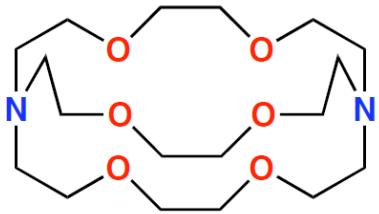
Decreased organization and increased conformational space



Podand
Acycle
logKs = 2.0



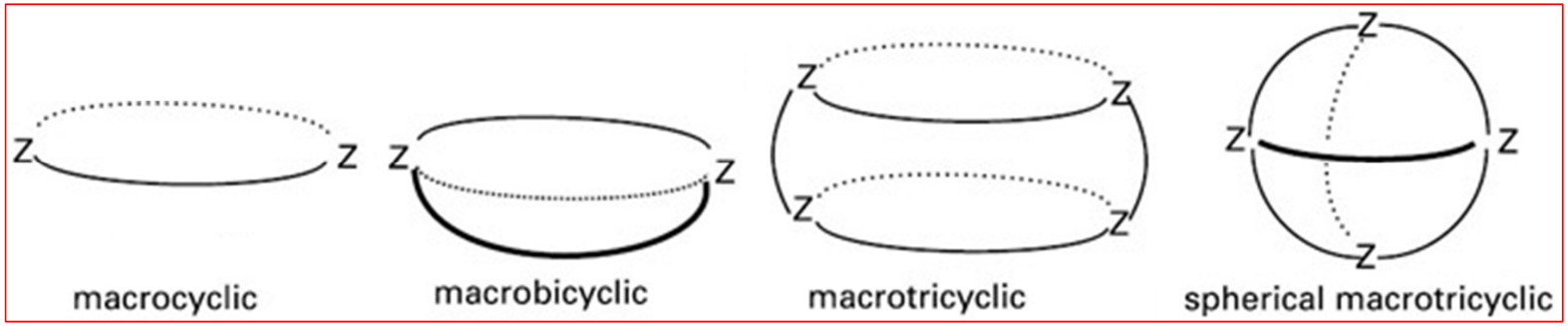
Coronand
Macrocycle
logKs = 6.08

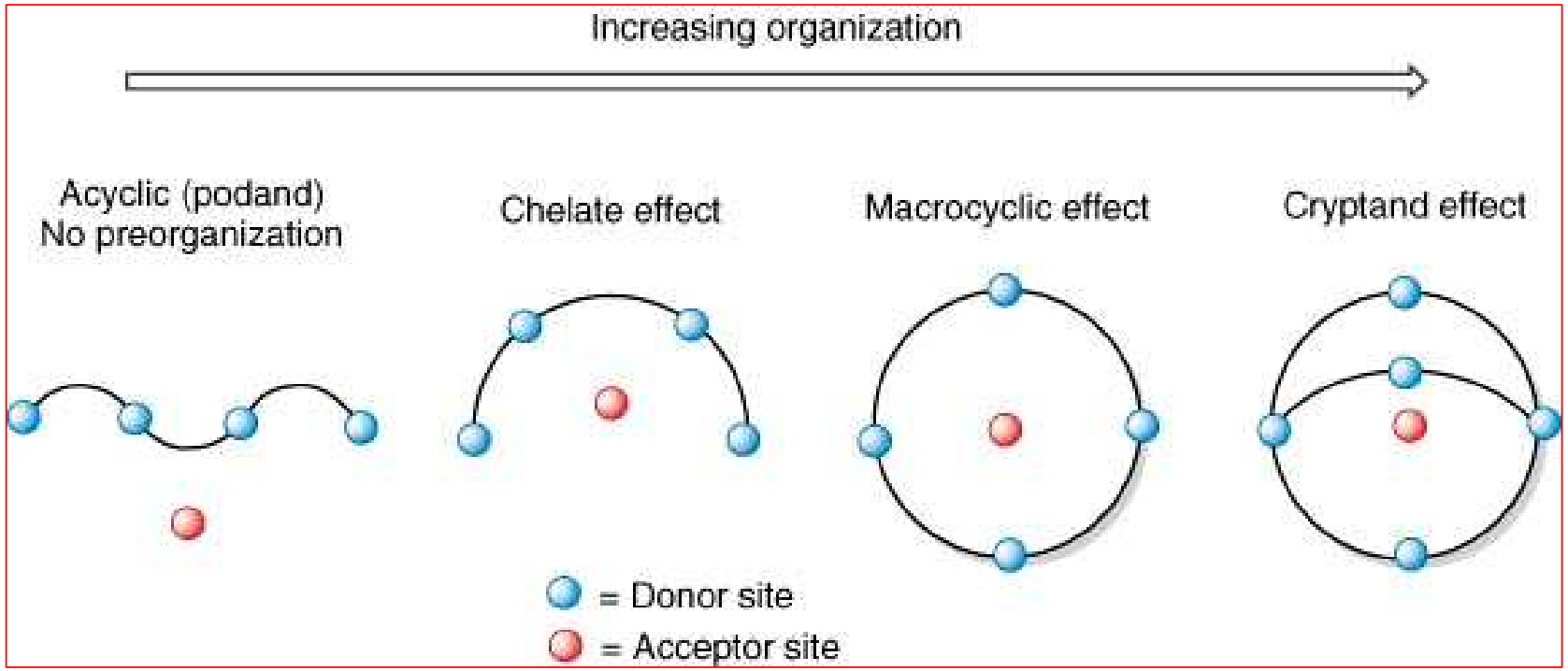


Cryptand
Microbicycle
logKs = 10.0

Stability for the potassium complex in methanol

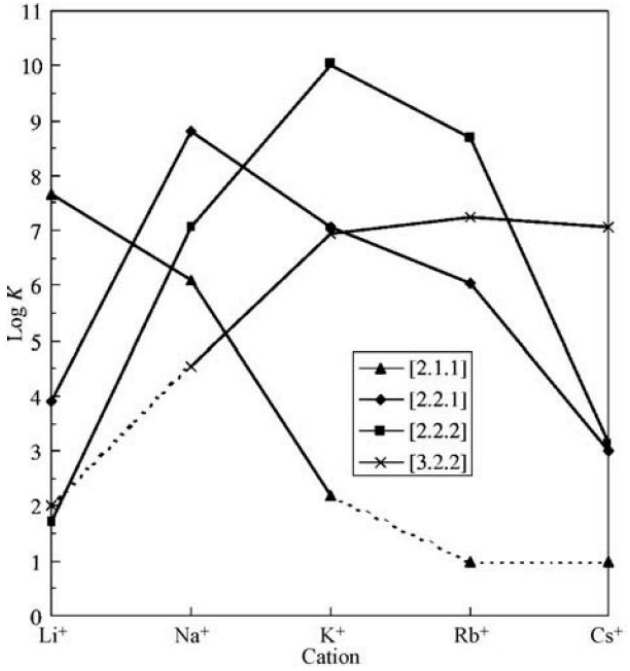
Increased organization and reduced conformational space

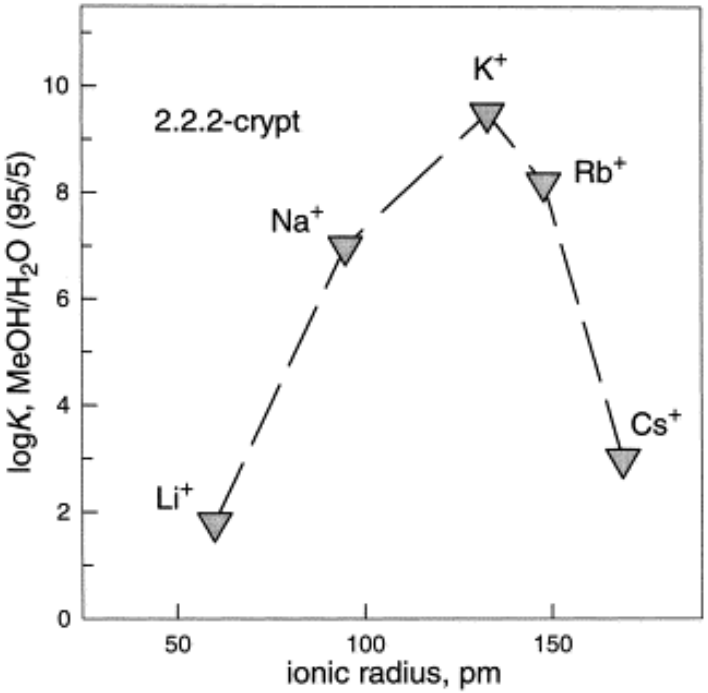

macrocyclic
macrobicyclic
macrotricyclic
spherical macrotricyclic

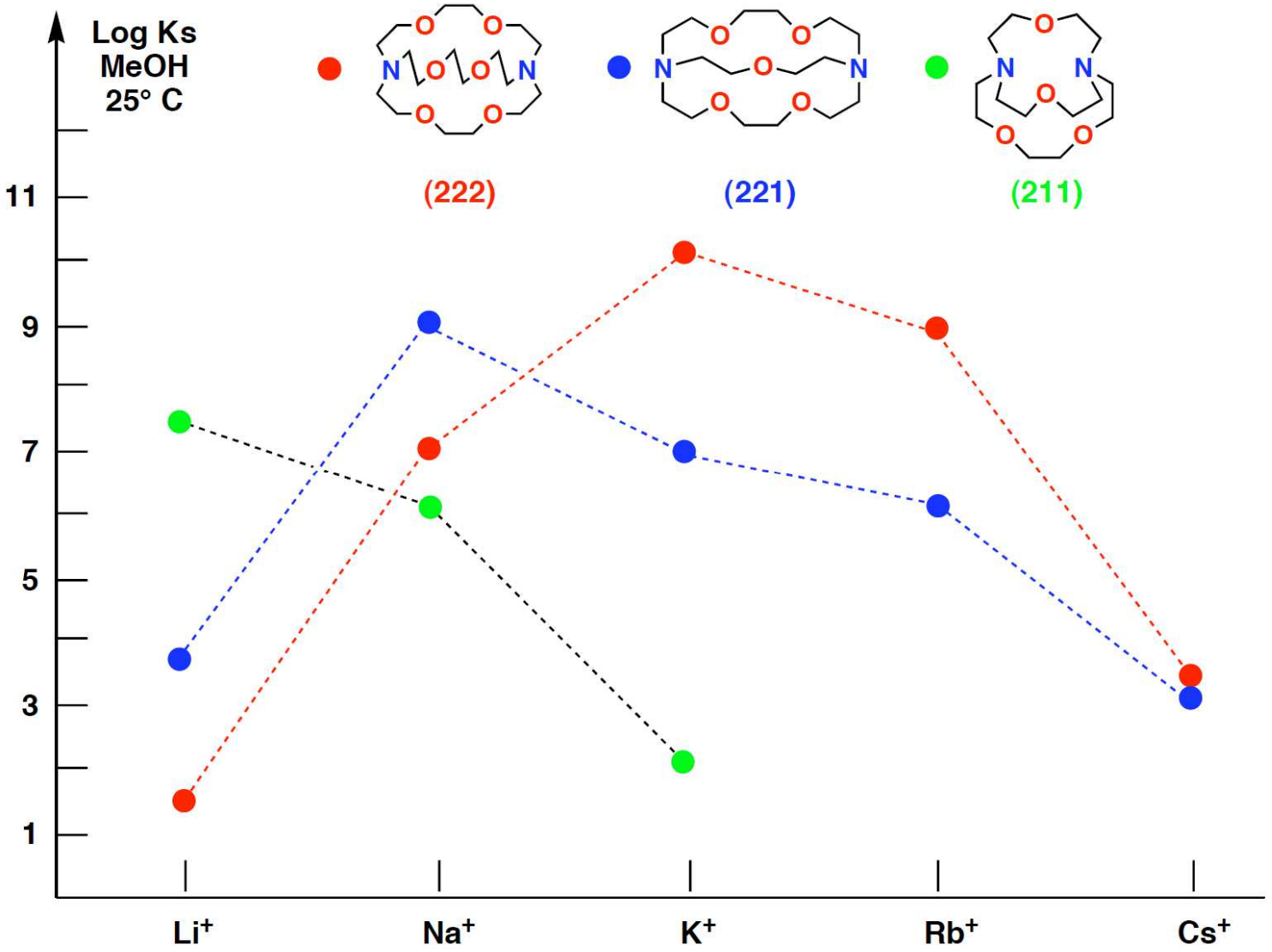

Increasing organization
Acyclic (podand)
No preorganization
Chelate effect
Macrocyclic effect
Cryptand effect
= Donor site
= Acceptor site

- Synthesis of cryptands → **high-dilution techniques**
- The cavity size of the [2.2.2]cryptand → similar to [18]crown-6 and a good host for K^+.
- The bicyclic structure → More preorganization, hence binding constant for K^+ >> [18]crown-6.

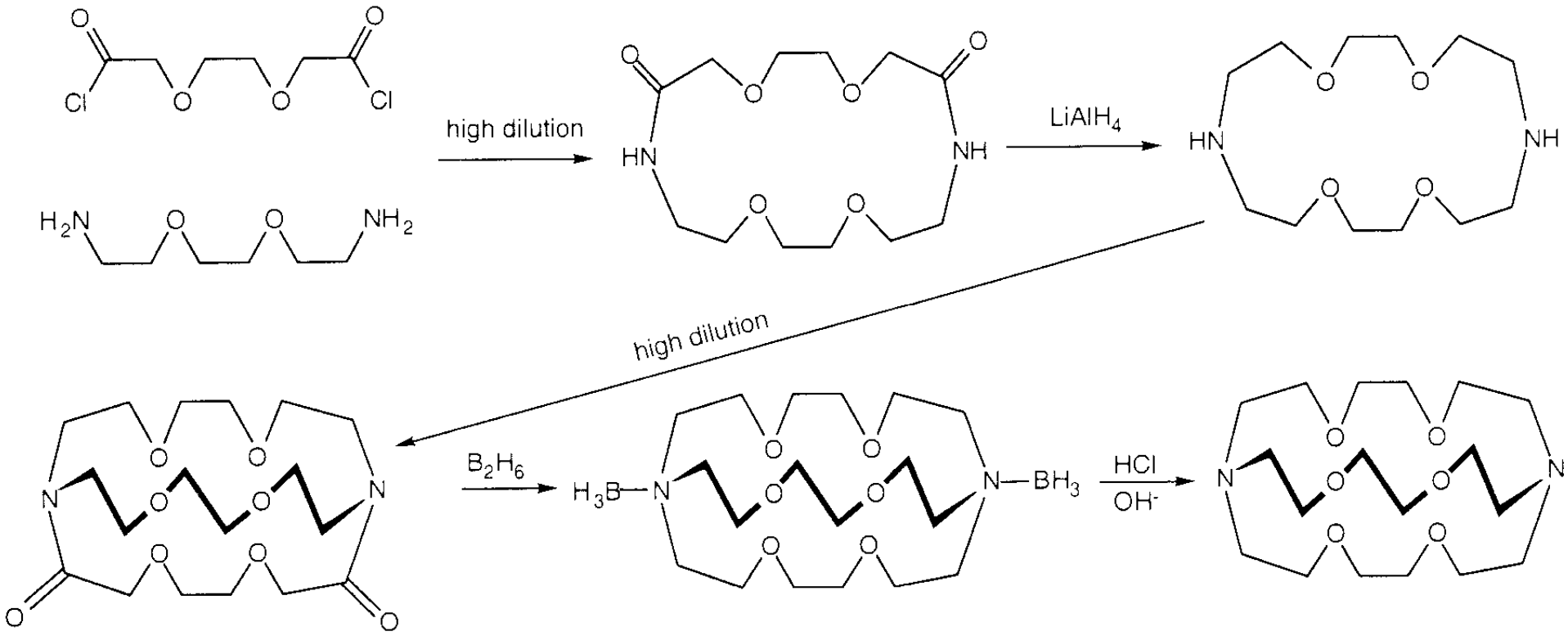
  Macrobicyclic effect
- (*e.g.)* the binding constant of the [2.2.2]cryptand for K^+ in MeOH is 10^4 times larger than [18]crown-6.
- The smaller cryptand, [2.2.1]cryptand, is selective for Na^+.
- Due to their lower flexibility and greater degree of preorganisation, cryptands display *peak selectivity*, in which binding constants are at a maximum for a particular metal ion.





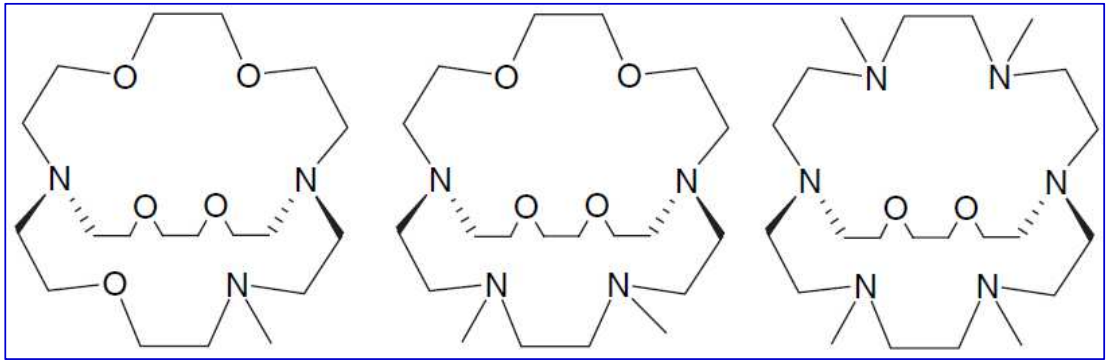

Log Ks
MeOH
25° C
11
9
7
5
3
1
(222)
(221)
(211)
Li+
Na+
K+
Rb+
Cs+

2.12.2 Synthesis of Cryptands

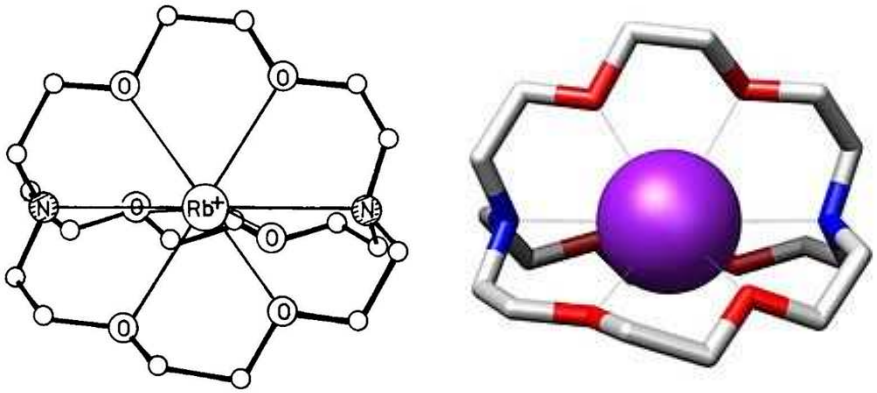


- Here a modified synthetic strategy is employed to incorporate the heteroatom
- The macrocycle is formed using a combination of two half units with a terminal heteroatom such as N, S etc. which are good nucleophiles.

2.12.3 Complexation of alkali metal ions by cryptands

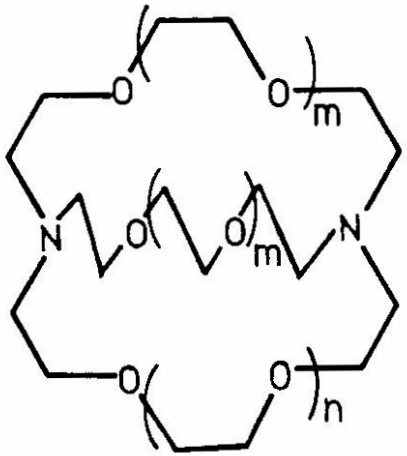


- K^+ forms a stable complex with the [2.2.2]cryptand.
- If one or more of the oxygen atoms are substituted with NMe functionalities, the **binding affinity for the K^+ ion** is **drastically reduced**.
- However, the corresponding affinity for softer metal ions, such as the Ag^+ ion, **increases**.



Crystal structure of Rubidium cryptate

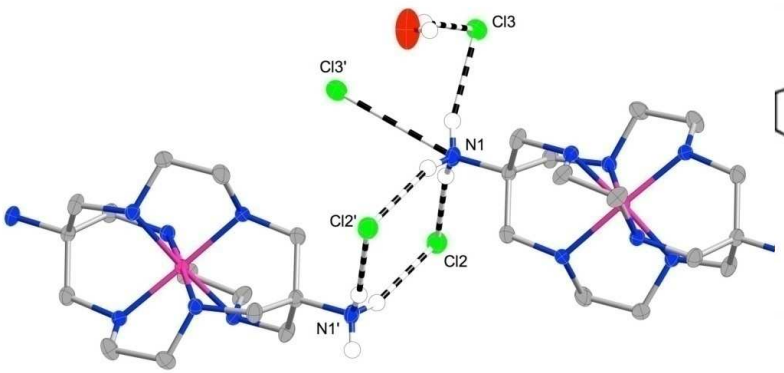
Cavity size of cryptands

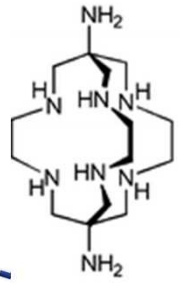


m	n	Abbreviation	Estimated cavity diameter (Å)
0	0	1.1.1	1·0
0	1	2.1.1	1·6
1	0	2.2.1	2·2
1	1	2.2.2	2·8
1	2	3.2.2	3·6
2	1	3.3.2	4·2
2	2	3.3.3	4·8

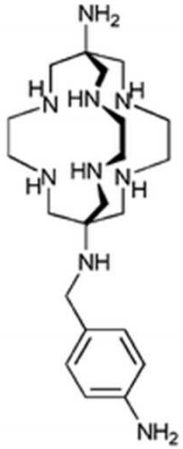
Substituting benzo groups for CH_2CH_2 groups results in a small reduction in the cavity size and a lower donating ability of the adjacent ether groups.

2.13 Cage Compounds (Azacryptands)

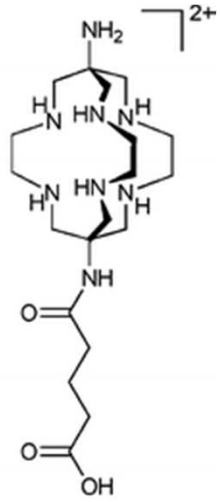




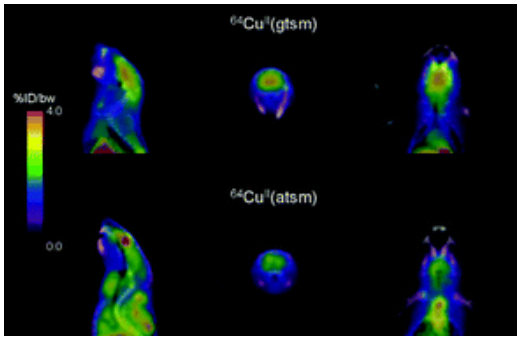
$(NH_2)_2$sar



SarAr



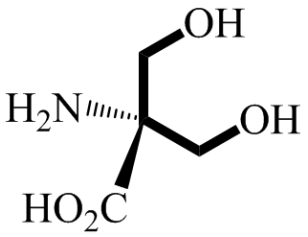
L^4



2.13.1 The Akabori reaction

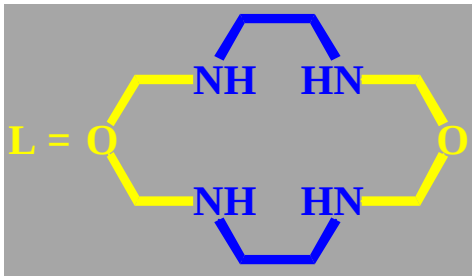
- **The Akabori reaction is a long-known exploitation of the reactions of a coordinated ligand.**

Glycine, Cu(II), HCHO, base ⇨⇨



- Of many attempts to fully understand the coordination chemistry involved, one provided results interesting in a very different domain.

$$[Co(en)_2gly]^{2+} + 6HCHO + OH^- \rightarrow [Co(L)(serCH_2OH)]^{2+}$$

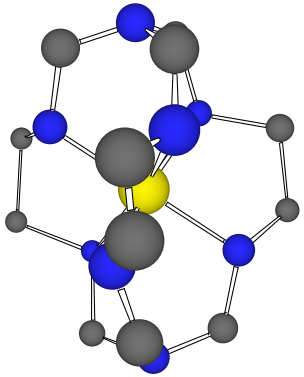


2.13.2 Sepulchrate and Sarcophagine

- **If a diprotic acid like water or nitroethane can turn up as a bridge to link two diamine units together, why shouldn't a triprotic acid like NH_3 or CH_3NO_2 give a bridgehead between three diamine units ?**
- It does !

  Which in fact first gave **"sepulchrate"** (NH_3 in place of CH_3NO_2),

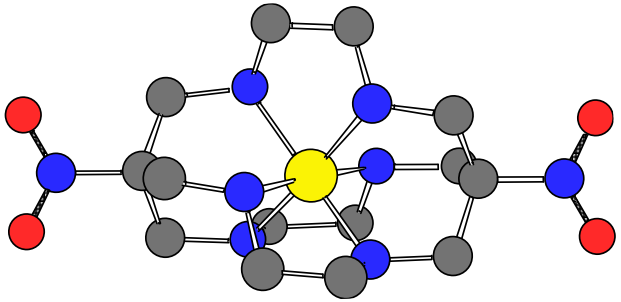
  only later **"sarcophagine"**, of course on Co(III) to give a cage ligand called dinitrosarcophagine (dinosar)



Sepulchrate (diazasarcophagine) on Co(III)

$[Co(sep)]^{3+}$ or $[Co(diazasar)]^{3+}$

J. Am. Chem. Soc. **1977**, *99*, 3181



Dinitro **sarcophagine** on Co(III)

$[Co(diNOsar)]^{3+}$

J. Am. Chem. Soc. **1982**, *104*, 6016; **1984**, *106*, 5478

Chem. Br. **1979**, *15*, 23; *Inorg. Synth*. **1980**, *20*, 85

2.13.3 What is Cage Chemistry?

- **An extension of simple macrocyclic chemistry.**

- **Synthesis, reaction, properties of large (macro), highly connected (polycyclic), concave, hollow ligands with a three dimensional framework of donor atoms capable of encapsulating metal ion.**

- **"Encapsulation"**

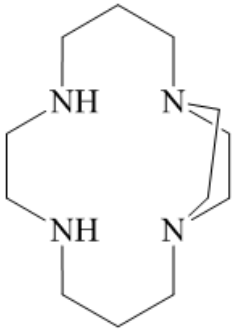
  Process which a single macropolycyclic ligand occupies all the coordination sites about a metal.

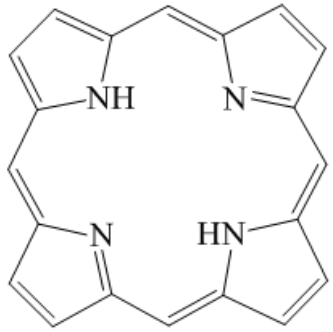
- **The consequence of encapsulation**

  Dramatic decrease in the rate of substitution at the metal ion centre

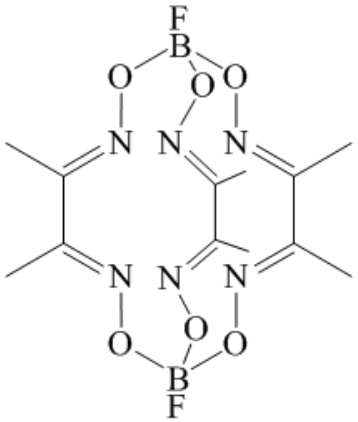
  and hence very high stability for the complex.

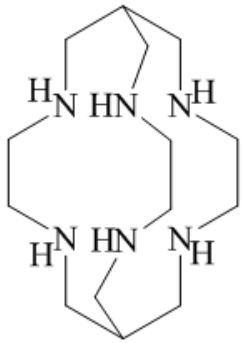
Some examples of cage and simple macrocyclic ligands

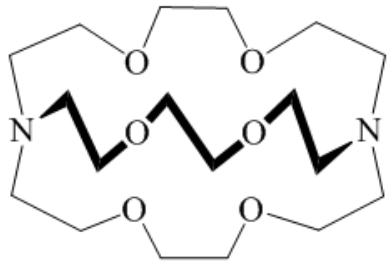




MACROCYCLES







CAGES

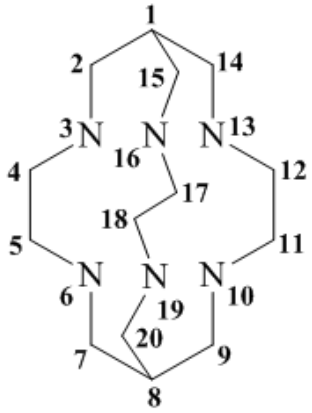
2.13.4 Some basic properties of cage amine complexes

1. Highly inert in several oxidation state
2. Chiral and resolvable
3. Selective in metal ion binding
4. Form complexes with various transition metals covering a wide range of potentials
5. Readily functionalised
6. Powerful metal chelating ability
7. Extraordinary thermodynamic and kinetic stability

   (The rate of loss of the metal ion from the cage is dramatically

   slower ($> 10^{10}$ fold) than for simple metal chelate complexes.)

2.13.5 Trivial nomenclature for polyamine cages



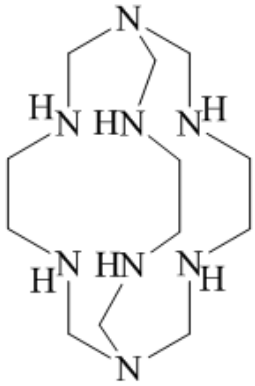
3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane

Sarcophagine (sar)

"Sarcophagus": A stone coffin or tomb

A vehicle for transport to the better worl.

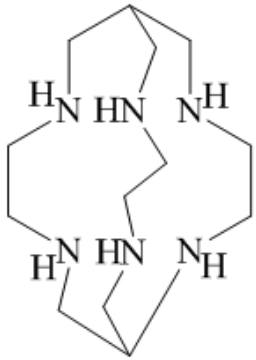
i.e. transport metal ions into a better world.



1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]icosane

Sepulchrate (sep)

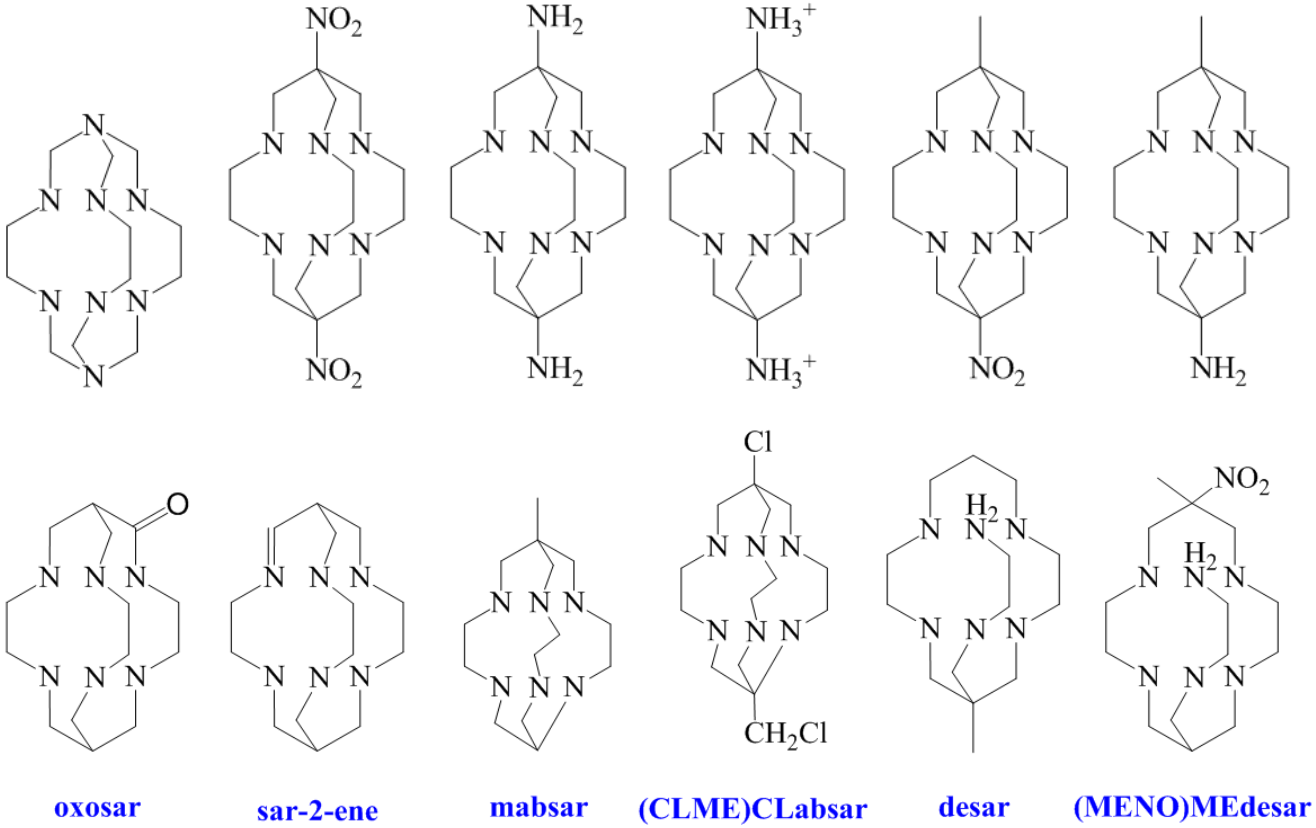
"Sepulcher": A burial place, tomb



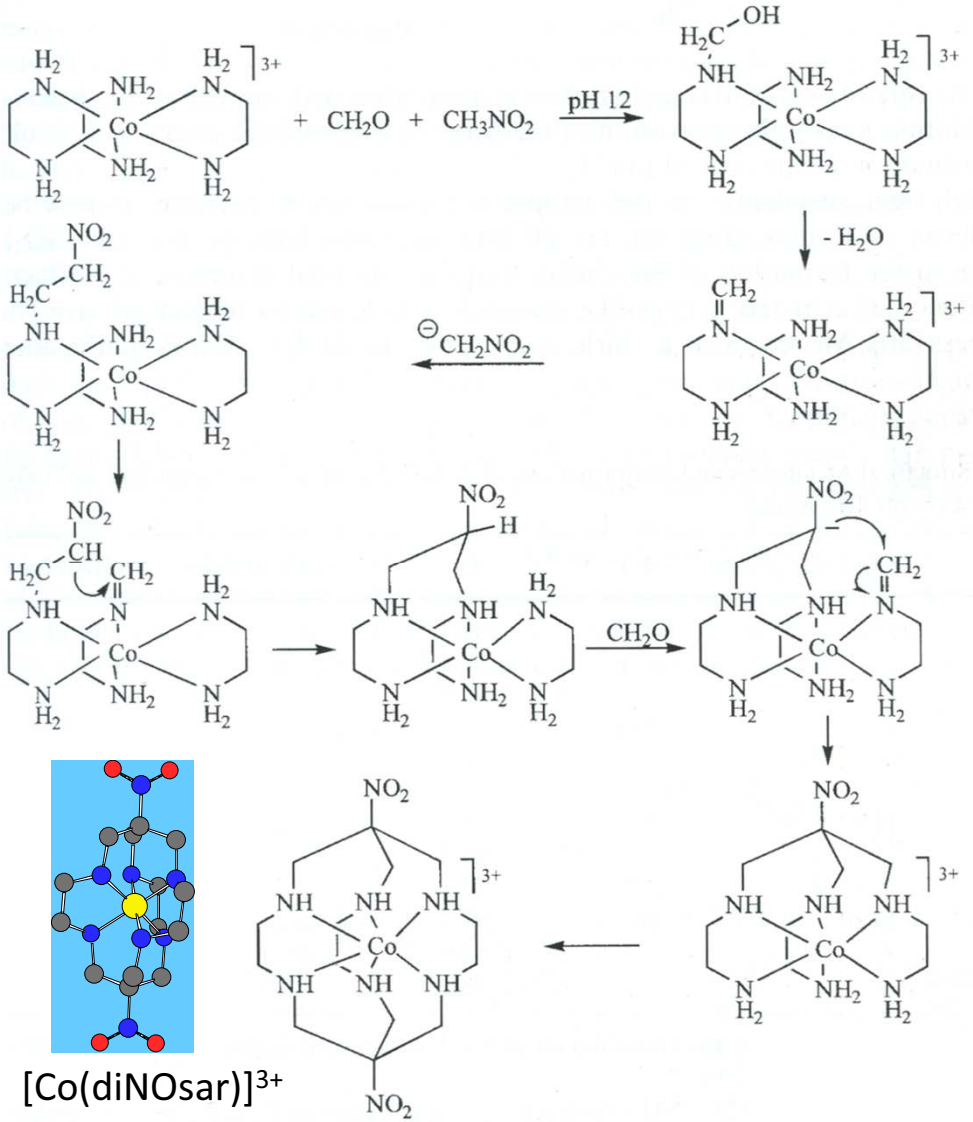
3,6,10,13,15,18-hexaazabicyclo[6.6.5]nonadecane

absar

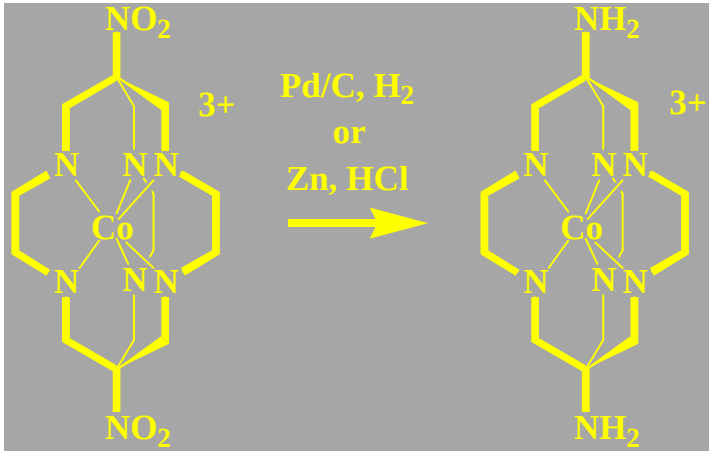
	Prefix	Group
1	AZA	
2	CA	-COO^-
3	AM	-NH_2
4	HA	-NHOH
5	MeAM	-$NHCH_3$
6	Me_2AM	-$N(CH_3)_2$
7	Me_3AM	-$N^+(CH_3)_3$
8	NO	-NO_2
9	ME	-CH_3
10	AA	-$NHCOCH_3$
11	BzIM	-$NCHC_6H_5$
12	CL	-Cl
13	CA	-COOH
14	EF	-$COOC_2H_5$
15	NI	-NO
16	HM	-CH_2OH
17	CN	-CN^-
18	HY	-H

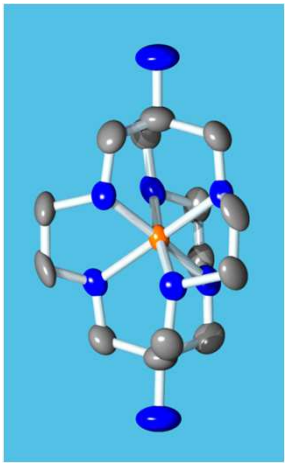


2.13.6 Template synthesis

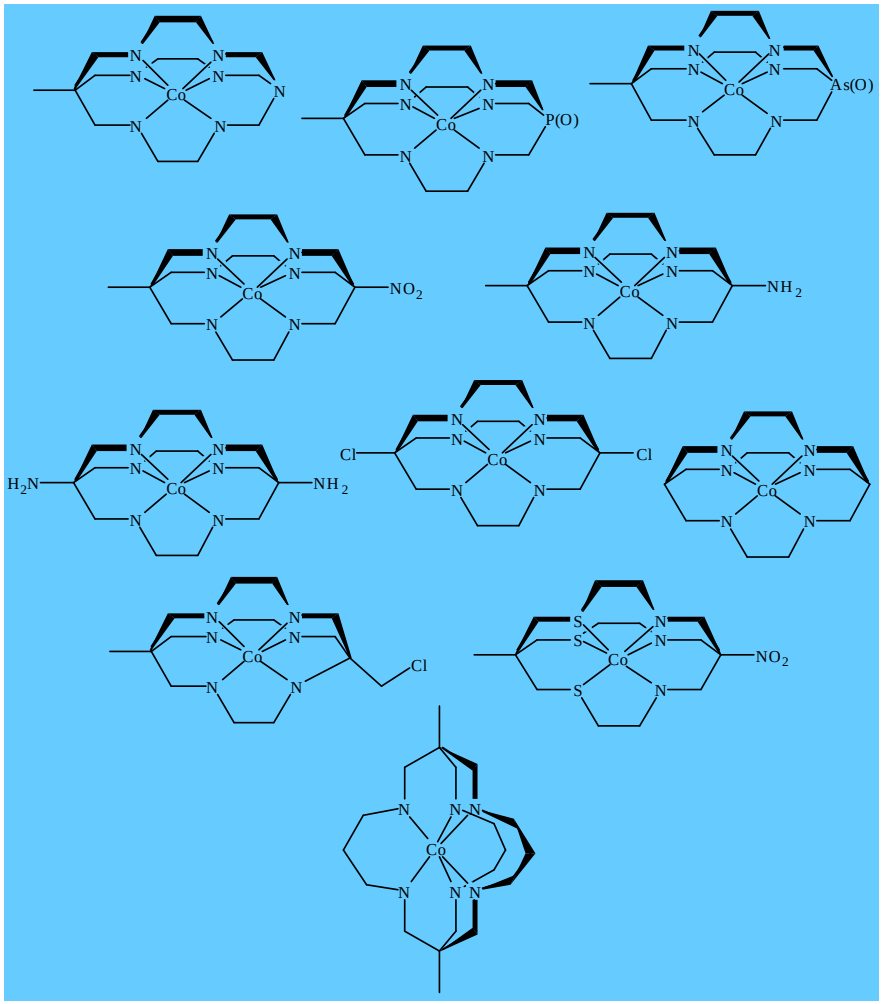


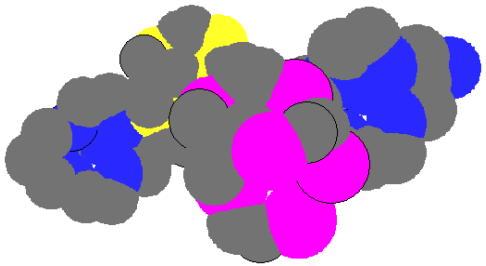
It remains the case that a template synthesis on Co(III) is the most efficient pathway to the ligand “dinosar” but,
even on Co(III), it can be transformed in many ways, perhaps simplest being the reduction to diaminosarcophagine, “diamsar”





Then came the offspring!



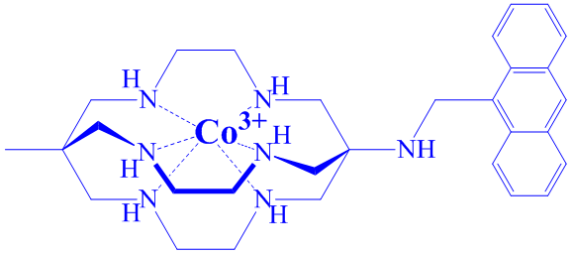


and many others !

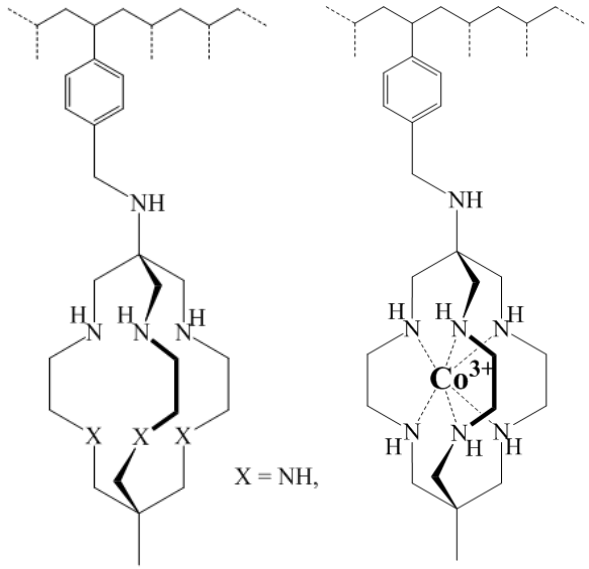
Chem. Eur. J. **2010**, *16*, 3166
Polym. Chem., **2010**, *1*, 207

2.13.7 Application of Cages

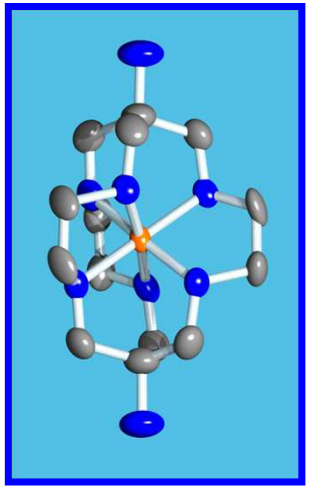
- Co(III) cages with paraffin chain are very stable and not absorbing through gut
  - Active against intestinal worm at the 1.0~0.1 mM level
  - Kill nematodes and tapeworms
- Cleavage agents of DNA
- Tying the cage to monoclonal antibodies and using ^{67}Cu as a nuclide to effect radiotherapy



- Removing metal ions at least the ppb level from water or even sodium salt solution
- Resource recovery
- Reagent purification and pollution control
- Optically active ion exchange resin
- Light battery
- Electrode or catalyst
- Electron transfer photosensitizer



- **High chemical stability** of cobalt cages allows Co(III)/Co(II) redox states to be cycled repeatedly without decomposition.
- Co(III) cage with N_3S_3 donors can be used as electron relay compounds for the photoinduced H_2 production.



$$S + h\nu \longrightarrow S^*$$

$$S^* + Co^{III}L \longrightarrow S^+ + Co^{II}L$$

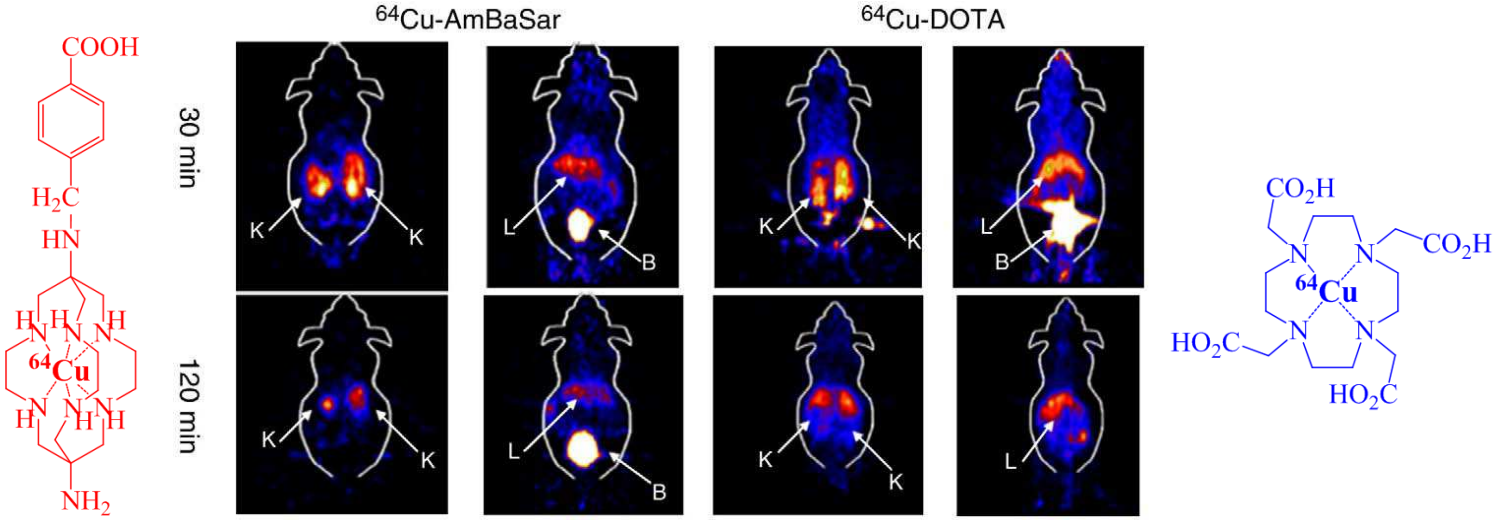
$$Co^{II}L + H^+ \xrightarrow{Pt/pva^{a}} \tfrac{1}{2}\,H_2 + Co^{III}L$$

$$Co^{II}L + S^+ \longrightarrow S + Co^{III}L$$

[a] Colloidal platinium dispersion on poly(vinyl alcohol).

Prog. Inorg. Chem., *51*, 251-331 (2003)

Some good can be done !



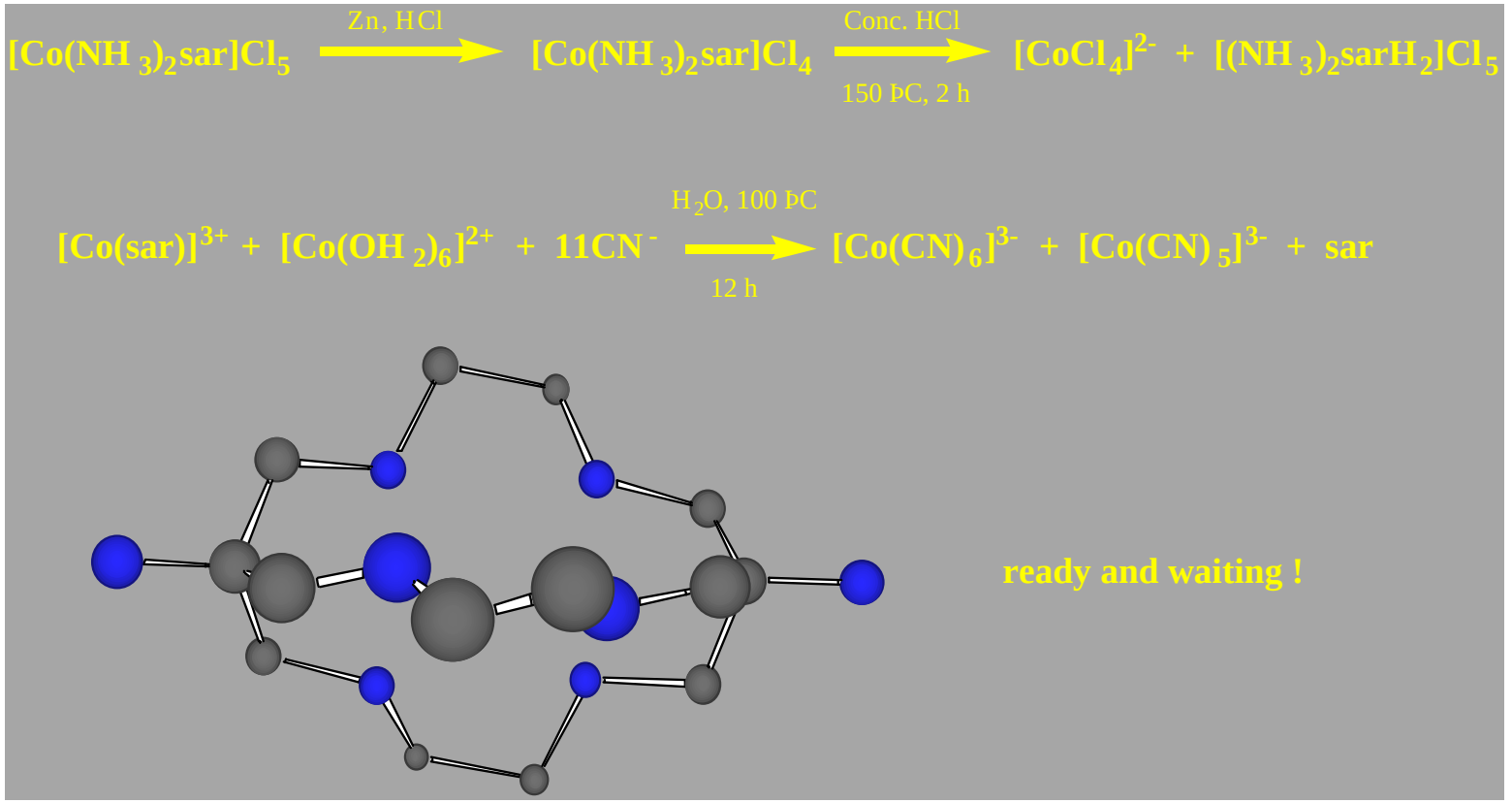
Coronal sections of a microPET study of Balb/c mouse after a single intravenous injection of ^{64}Cu-AmBaSar and ^{64}Cu-DOTA at 30 min and 2 h. K=Kidney; L=liver; B=bladder.

In vitro and *in vivo* evaluation of the AmBaSar demonstrated its promising potential for preparation of **^{64}Cu radiopharmaceuticals**.

Nuclear Medicine and Biology. **2009**, *36*, 277
Nuclear Medicine and Biology, **2010**, *37*, 57

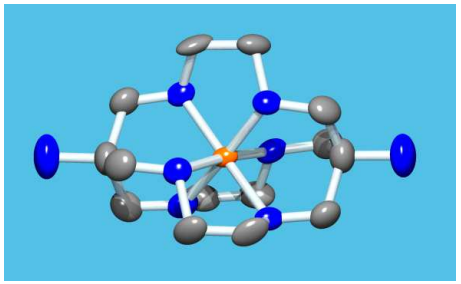
2.13 Demetalation

- **Some of these ligands can be easily stripped from Co(II)**



The ligands are flexible enough to accommodate coordination geometry ranging from near trigonal prismatic to almost exactly octahedral but the metal must have a six-coordinate ionic radius <0.8 Å.

And a ligand like “diAMsar” can accommodate many metal ions



H																He
Li	Be											B	C	N	O	F	Ne
Na	**Mg**											Al	Si	P	S	Cl	Ar
K	**Ca**	Sc	**Ti**	**V**	**Cr**	**Mn**	**Fe**	**Co**	**Ni**	**Cu**	**Zn**	**Ga**	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	**Ru**	**Rh**	Pd	**Ag**	**Cd**	**In**	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	**Re**	Os	**Ir**	**Pt**	**Au**	**Hg**	Tl	**Pb**	Bi	Po	At	Rn

The End