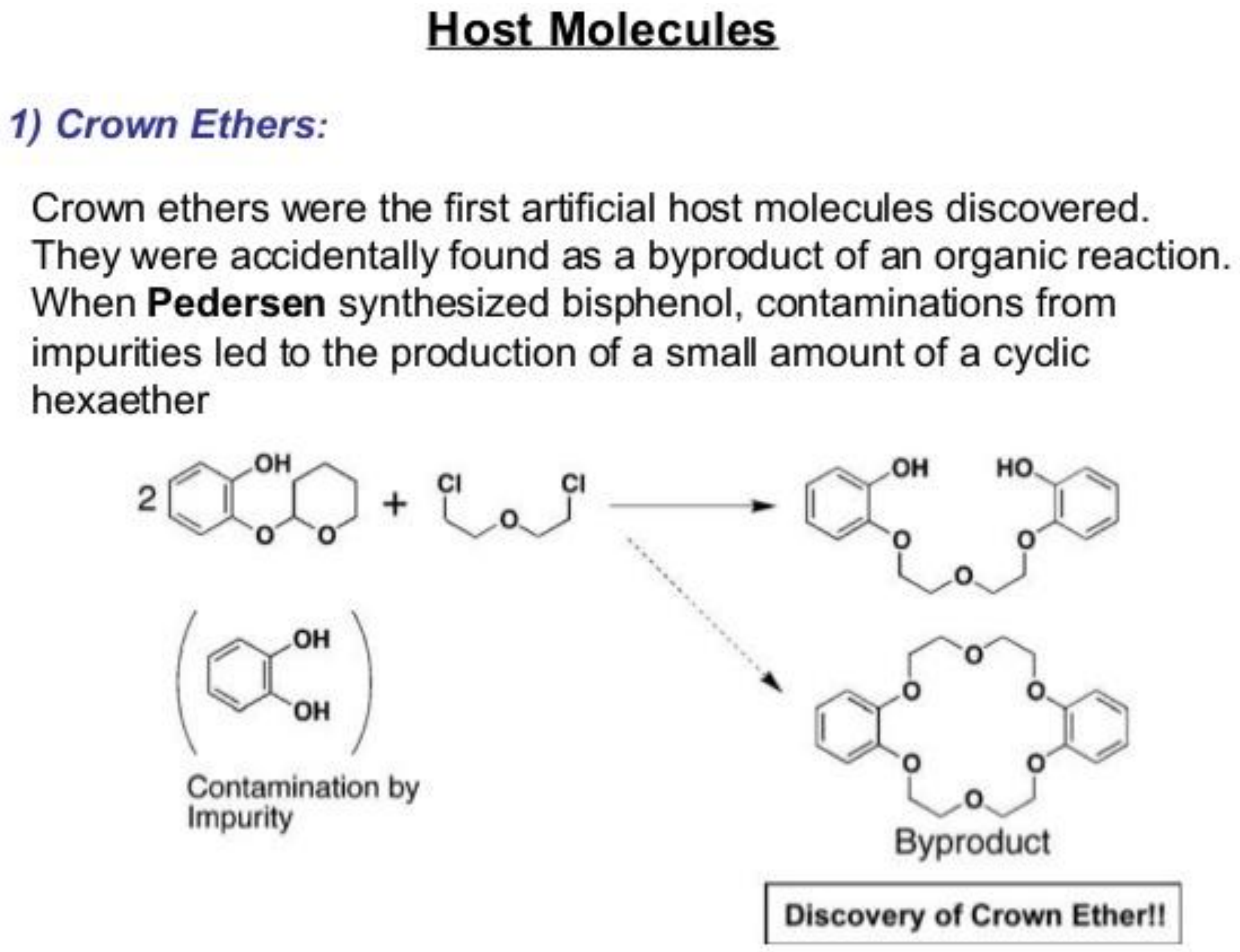
Lesson 4

- The crown ethers
- Cation selectivity
- Interlocked molecules with crown ethers

Crown ethers

- Charles Pedersen, Nobel prize in 1967
- Accidental synthesis of first crown ether (dibenzo[18]crown-6)
- Nomenclature: the first number in square brackets designates the number of atoms in the ring
- The second number the number of oxygen or other donor atoms (N, S)
- The prefix dibenzyl- dicyclohexil- indicate the other

First synthesis (serendipitous)



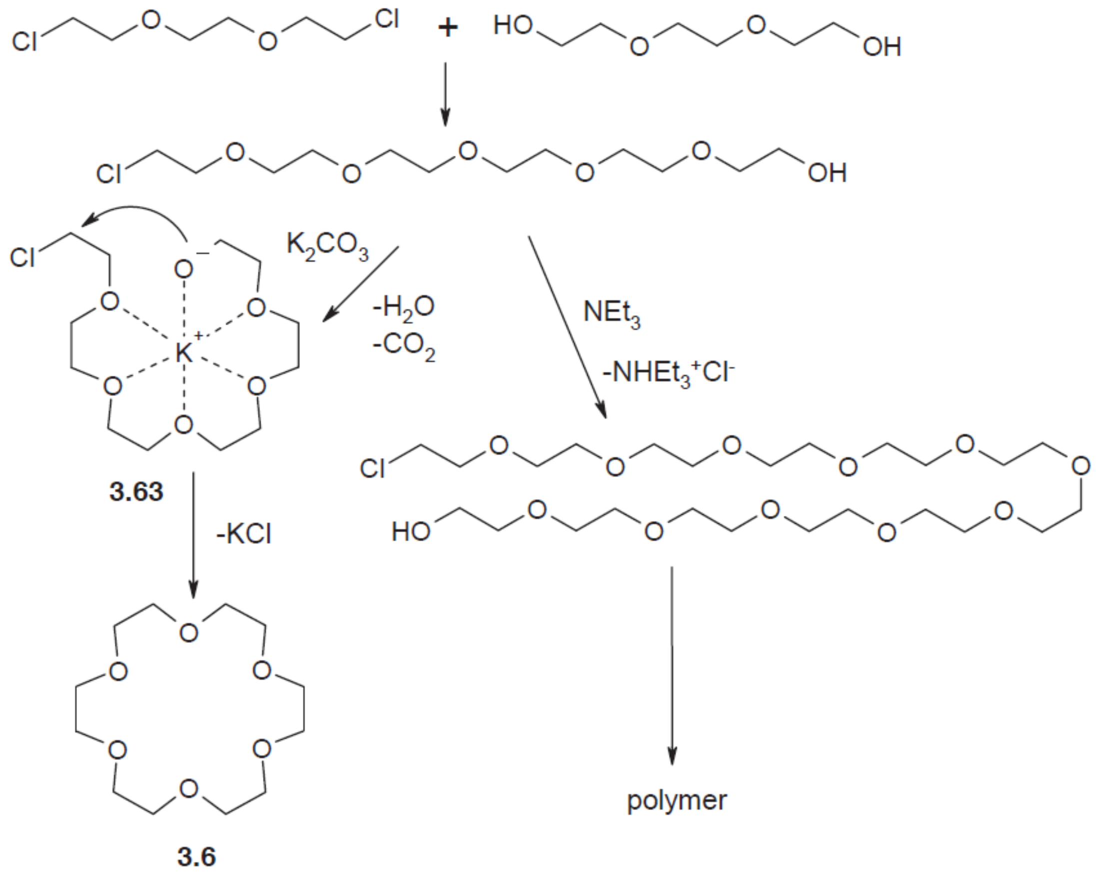
Host Molecules

1) Crown Ethers:

Crown ethers were the first artificial host molecules discovered. They were accidentally found as a byproduct of an organic reaction. When **Pedersen** synthesized bisphenol, contaminations from impurities led to the production of a small amount of a cyclic hexaether

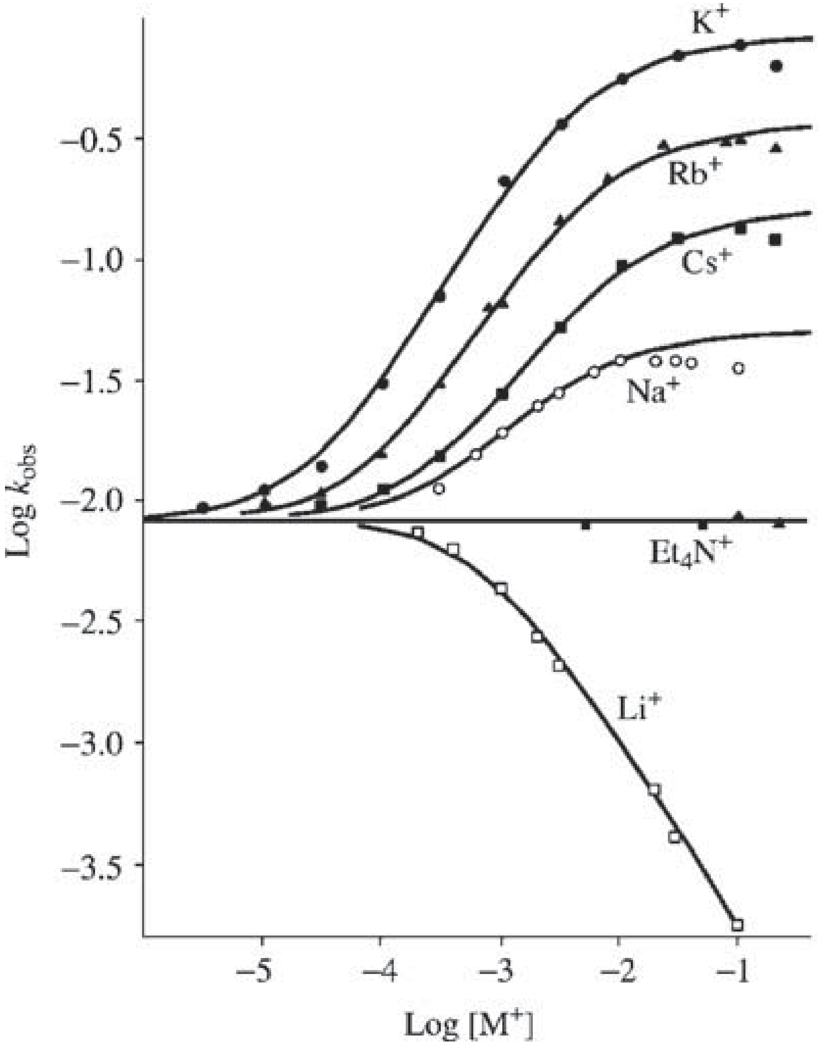
Synthesis: The Template Effect and High Dilution

- The fortuitous macrocycle dibenzo[18]crown-6 that gave birth to modern supramolecular chemistry might never have formed if the reaction had taken a different course, leading to polymeric (polycondensation) products.
- The conflicting possibilities are illustrated for the closely related [18]crown-6 in the Scheme



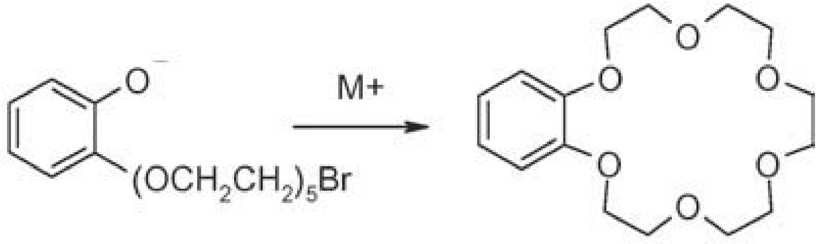
The kinetic template effect

- The K^+ ion is thought of as a template for the reaction, and the formation of macrocyclic compounds in this way is termed the template effect, or, more rigorously, the kinetic template effect. In fact, this is a form of catalysis in which the metal cation acts to stabilise the cyclic intermediate, thus dramatically increasing the rate of formation of the cyclic product.
- In simple terms, if we want to induce the formation of a host that is selective for an alkali metal about the size of K^+, we use K^+ as a pattern to induce its formation. Ù
- The template effect is used widely in macrocyclic synthesis, including the synthesis of macrobicyclic compounds, knots, interlocking rings (catenanes) and many other examples.

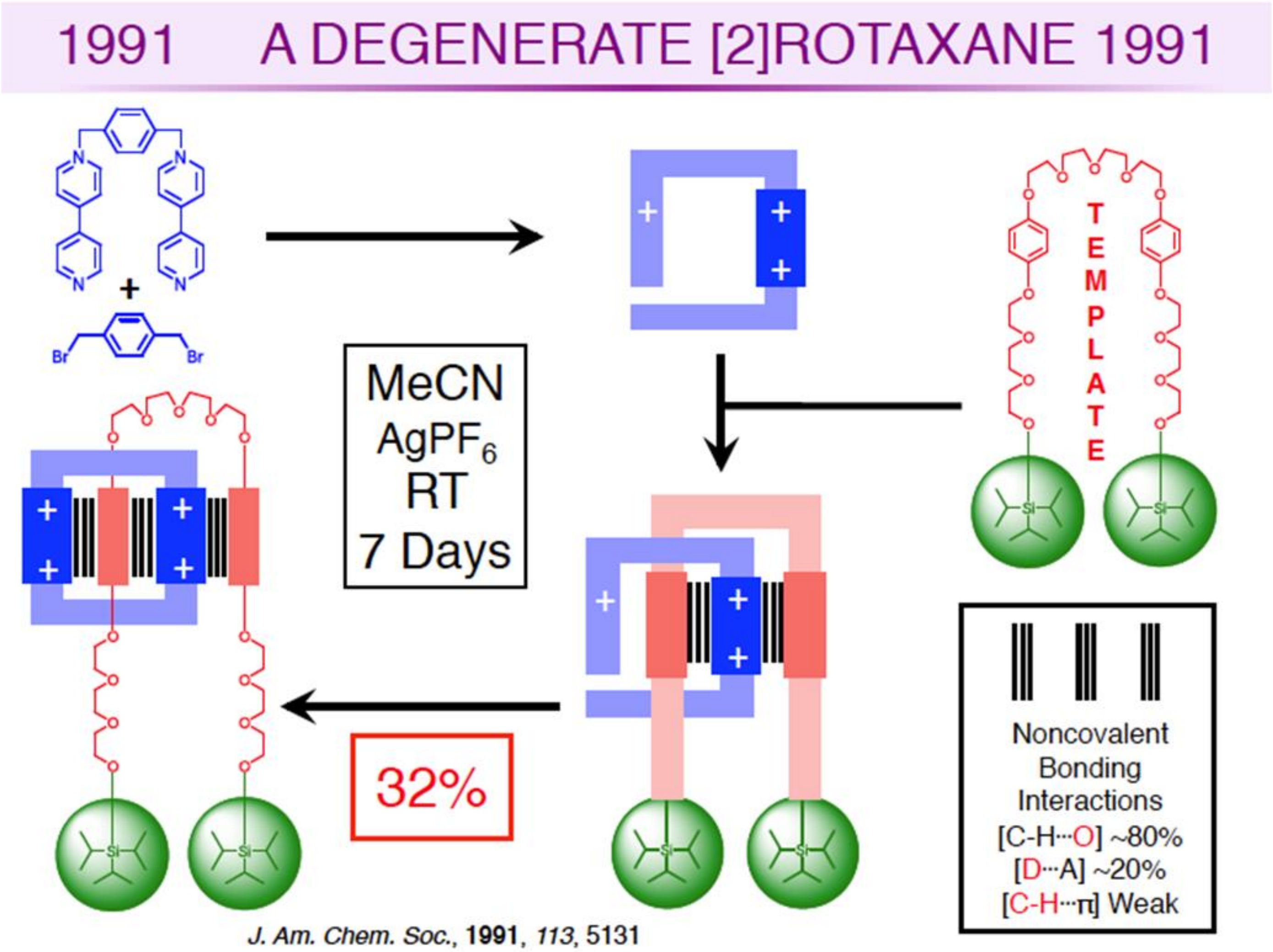


Results of kinetic studies of the template synthesis of benzo[18]crown-6 according to the reaction shown, as a function of the templating cation.

Clear rate enhancements (relative to the untemplated reaction in the presence of NEt4+) are seen with increasing concentration of all alkali metal ions except Li+, which tends to form very strongly bound ion pairs with the phenoxide ion, thus inhibiting its reactivity.

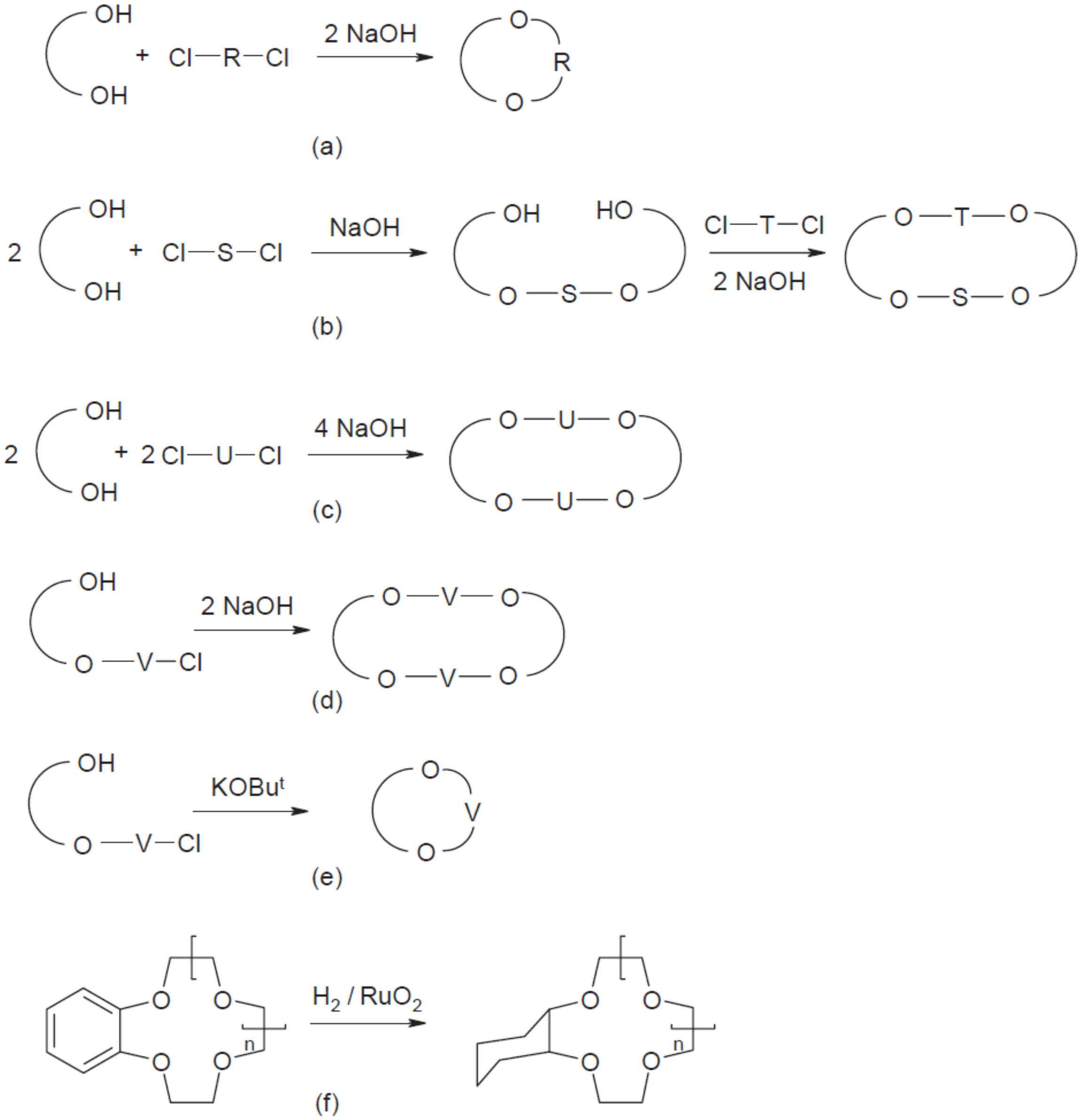


An interesting example of template-assisted synthesis of interlocked catenane (Stoddart, J Am Chem Soc 1991)



J. Am. Chem. Soc., **1991**, *113*, 5131

Synthesis strategies



heme 3.3 Methods for synthesising the crown ethers (R – V are organic linker groups).

Examples of crown ethers

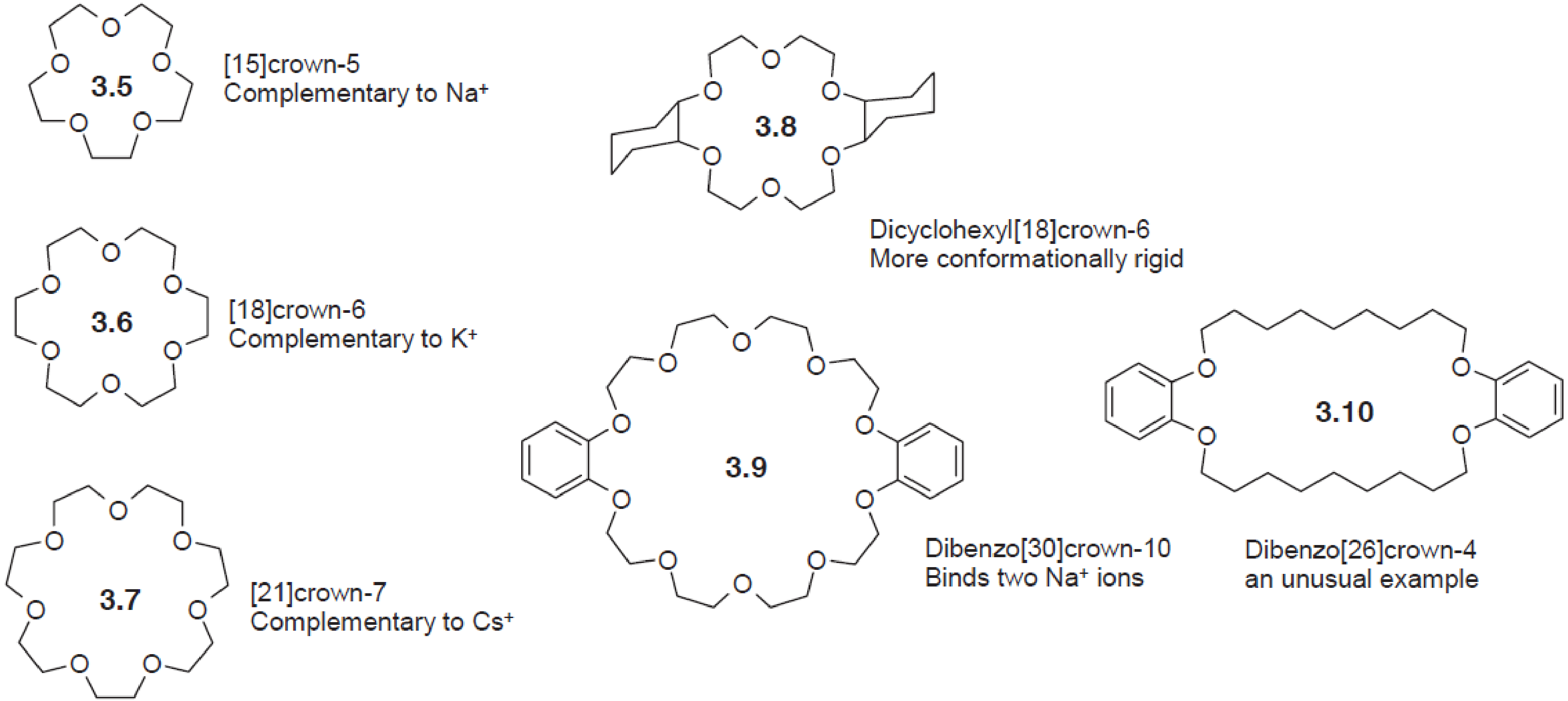
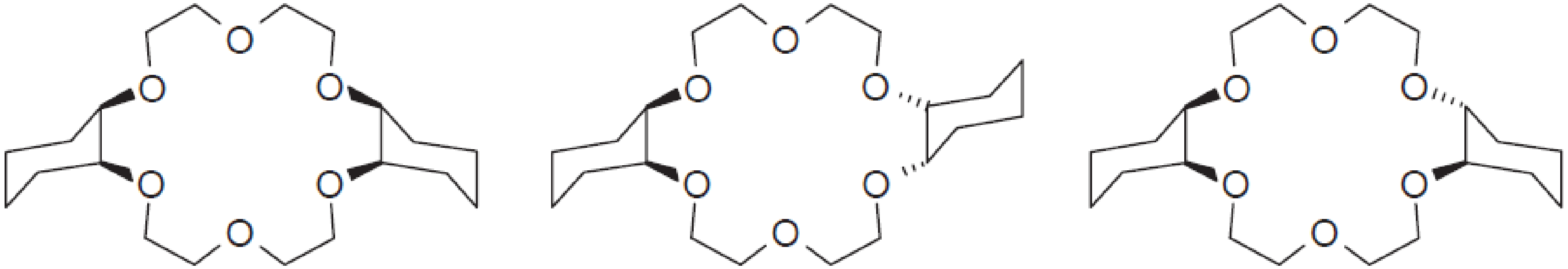
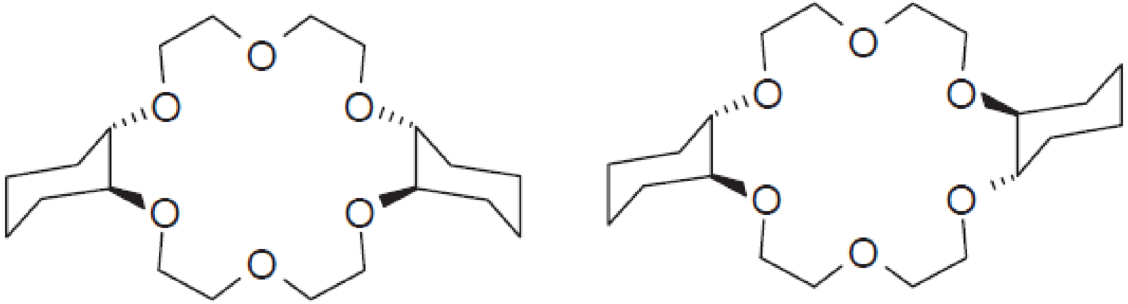


Figure 3.7 Some common crown ethers.

Stereoisomers



cis-syn-cis *cis-anti-cis* *cis-trans*



trans-syn-trans *trans-anti-trans*

Figure 3.8 Isomers of dicyclohexyl[18]crown-6.

Selectivity of cation complexation

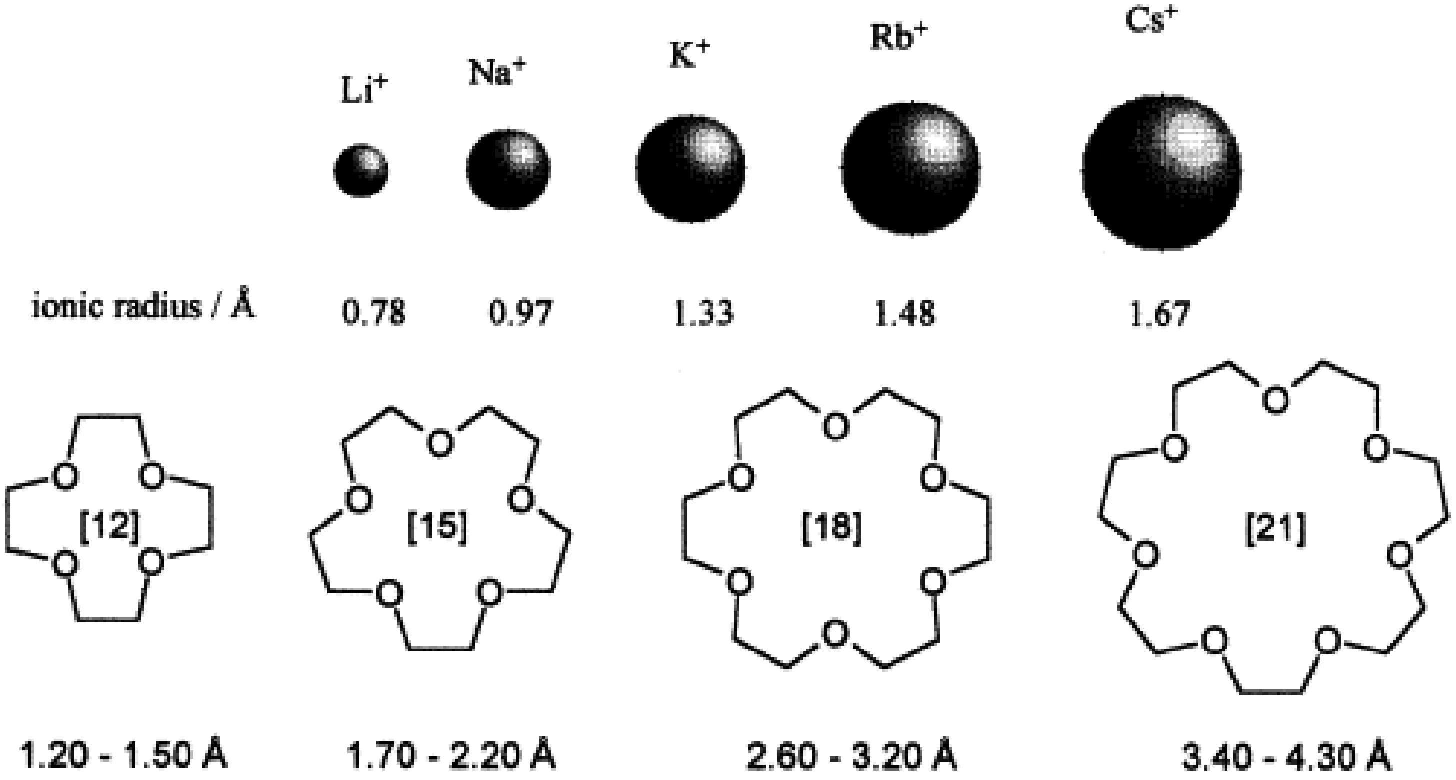
- Designing a synthetic host that will be highly selective for a given cation is a very complicated task because the selectivity is governed by an enormous number of factors, some of the most important of which are listed below:
- **size complementarity between cation and host cavity**;
- electronic complementarity between the cation and host binding sites (cf. HSAB, Section 3.1.2);
- electrostatic charge;
- solvent (polarity, hydrogen bonding and coordinating ability);
- degree of host preorganisation;
- 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; and
- **chelate ring size** and donor group orientation.

- Size match: the flexible [18]crown-6 is a good size to bind all cations, the optimum for K+
- Number of donor atoms: supramolecular interactions are additive: crown-6 better than crown-5 better than crown-4, plateau effect for rings of higher size
- Solvation of cation: solvation free energy K+ less than Na+ less than Ca++ (calcium is the worst guest because the largest hydration energy)
- Chelate ring size and ligand bite angle: small bite angle (60°) most suitable for larger ions (K+), larger bite angle (72°) better for smaller cations (Li+)

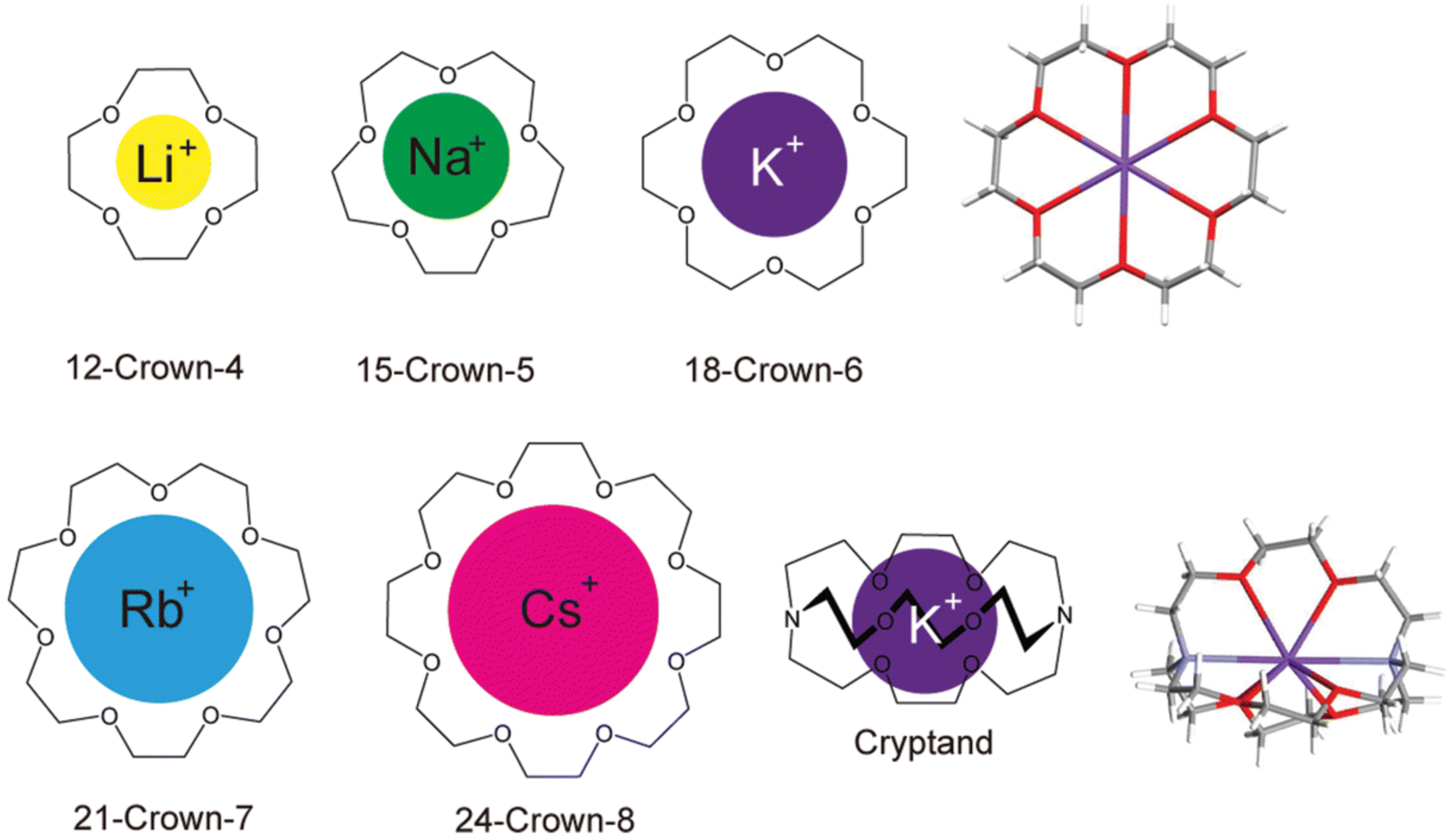
Size complementarity

radius

diameter



- Larger crown ethers have selectivity for larger ions (Rb+ and Cs+).



Size complementarity

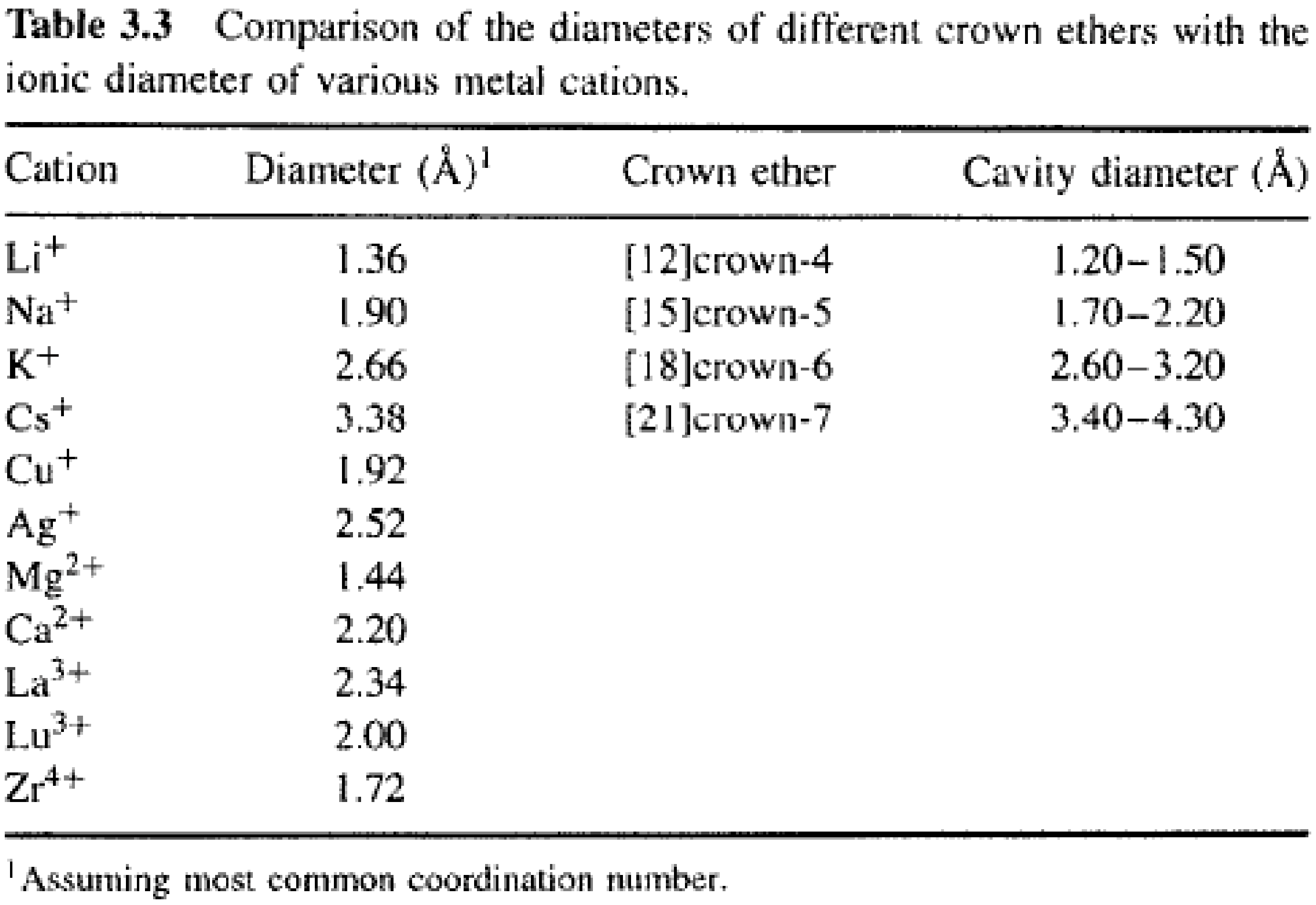
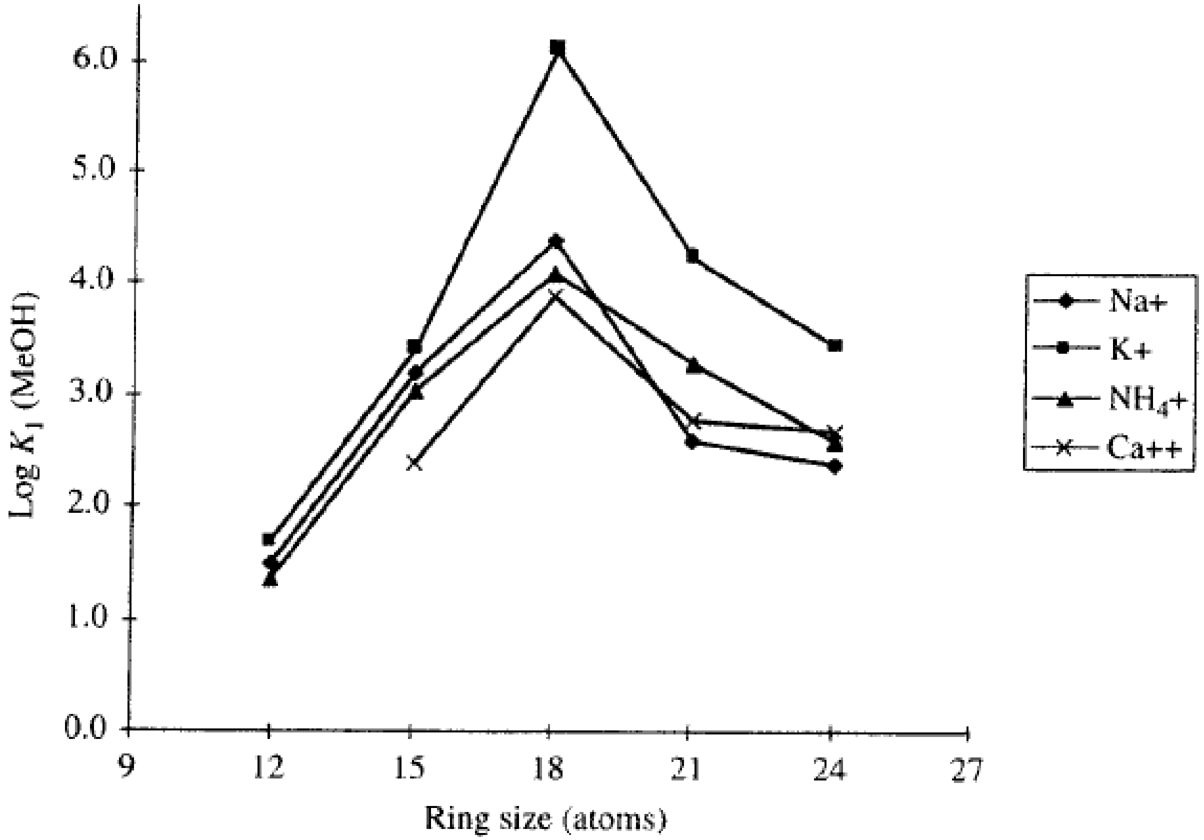


Table 3.3 Comparison of the diameters of different crown ethers with the ionic diameter of various metal cations.

Cation	Diameter (Å)[1]	Crown ether	Cavity diameter (Å)
Li^+	1.36	[12]crown-4	1.20–1.50
Na^+	1.90	[15]crown-5	1.70–2.20
K^+	2.66	[18]crown-6	2.60–3.20
Cs^+	3.38	[21]crown-7	3.40–4.30
Cu^+	1.92		
Ag^+	2.52		
Mg^{2+}	1.44		
Ca^{2+}	2.20		
La^{3+}	2.34		
Lu^{3+}	2.00		
Zr^{4+}	1.72		

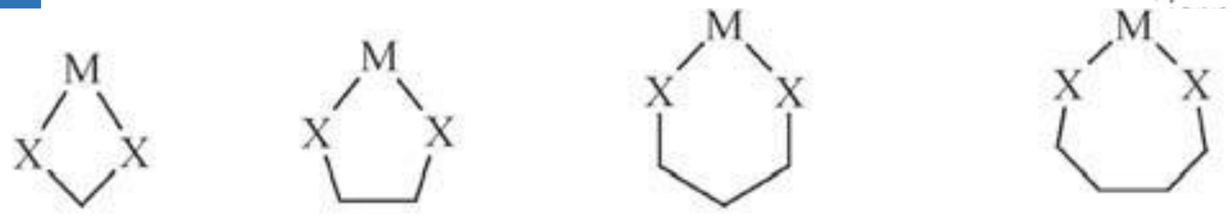
[1] Assuming most common coordination number.

- Variation of binding constants as a function of ring size: [18]crown-6 is the best ligand for all cations!!



chelate ring size

- The stabilisation afforded by the chelate effect is highly dependent on the size of the chelate ring. Five-membered rings, as in metal complexes of 1,2-diaminoethane, are often the most stable by far because they contain the least amount of ring strain, particularly for larger cations. Four membered rings (e.g. chelating acetate) are highly strained.



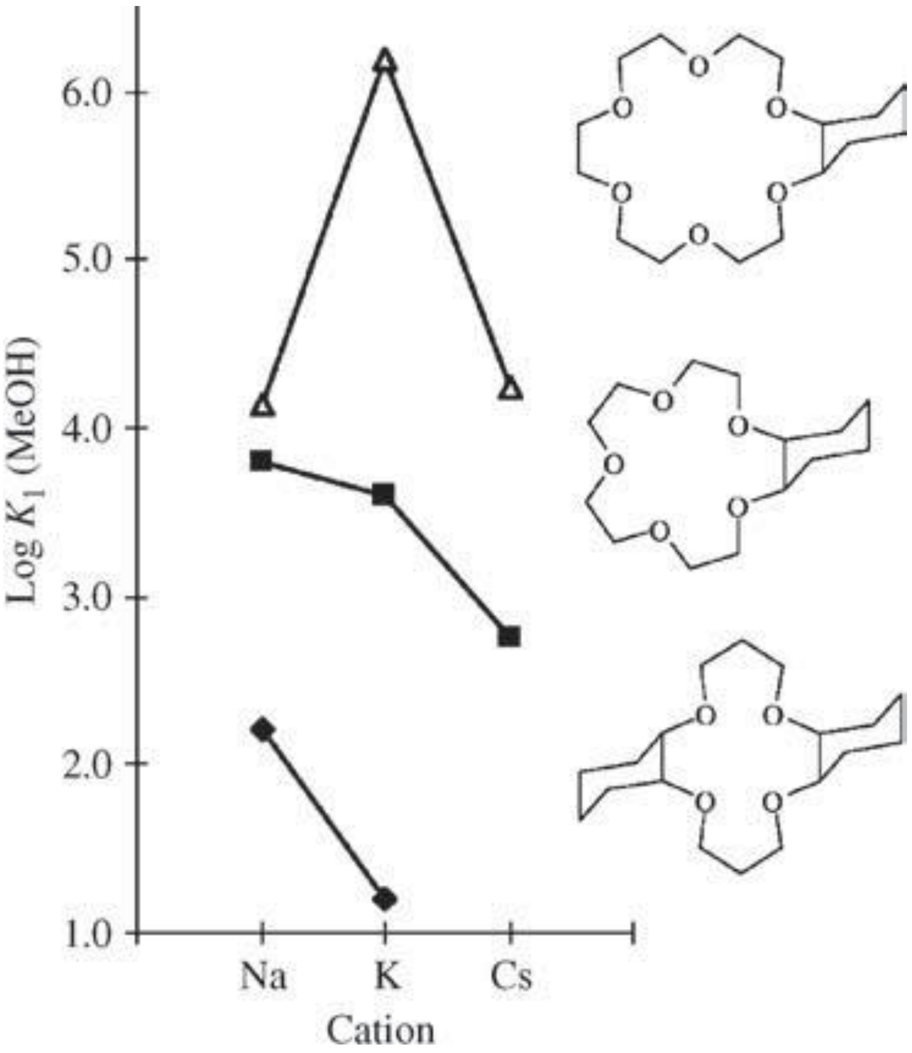
Strained ring Optimum geometry for larger cations Increasing flexibility–less entropically favourable

les for (a) two-carbon and (b) three-carbon linked crown ethers.

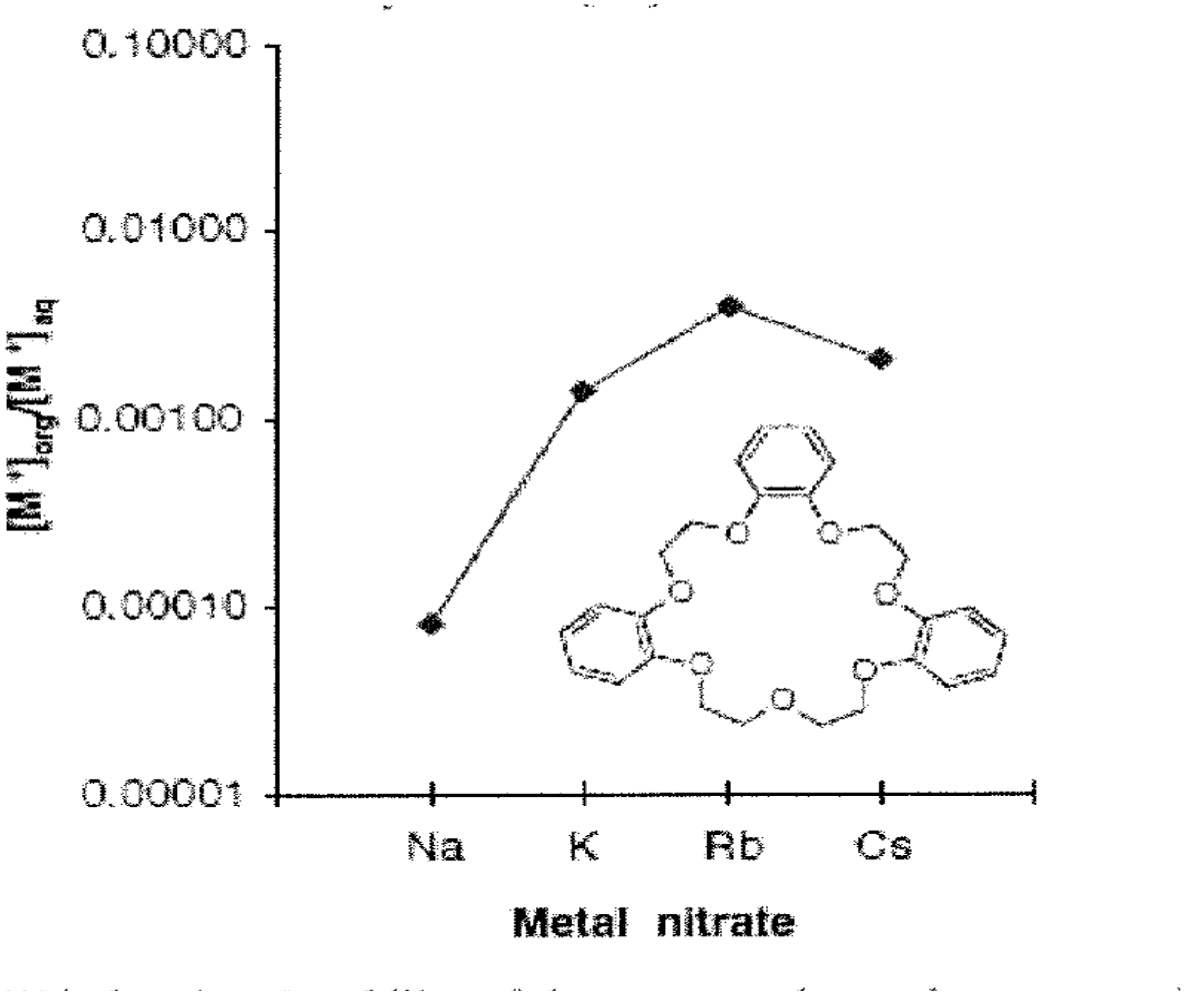
(a) Five-membered chelate ring, bite angle about 60°

(b) Six-membered chelate ring, bite angle about 60°

Variation of binding constants for hard alkali metal ions as a function of ionic radius and bite angle



Tribenzo[21]crown-7 selectivity for Rb+



Allosteric effect

In addition to cooperativity between two or more host binding sites in binding a single guest we can also recognise both **positive and negative cooperativity in the binding of multiple guests by a single host**, multiple ligands by a single metal or in multi-component self-assembly processes.

Cooperativity in cases where the binding of a first guest influences (particularly enhances) the affinity of a host for a second guest at a remote site is termed an allosteric effect.

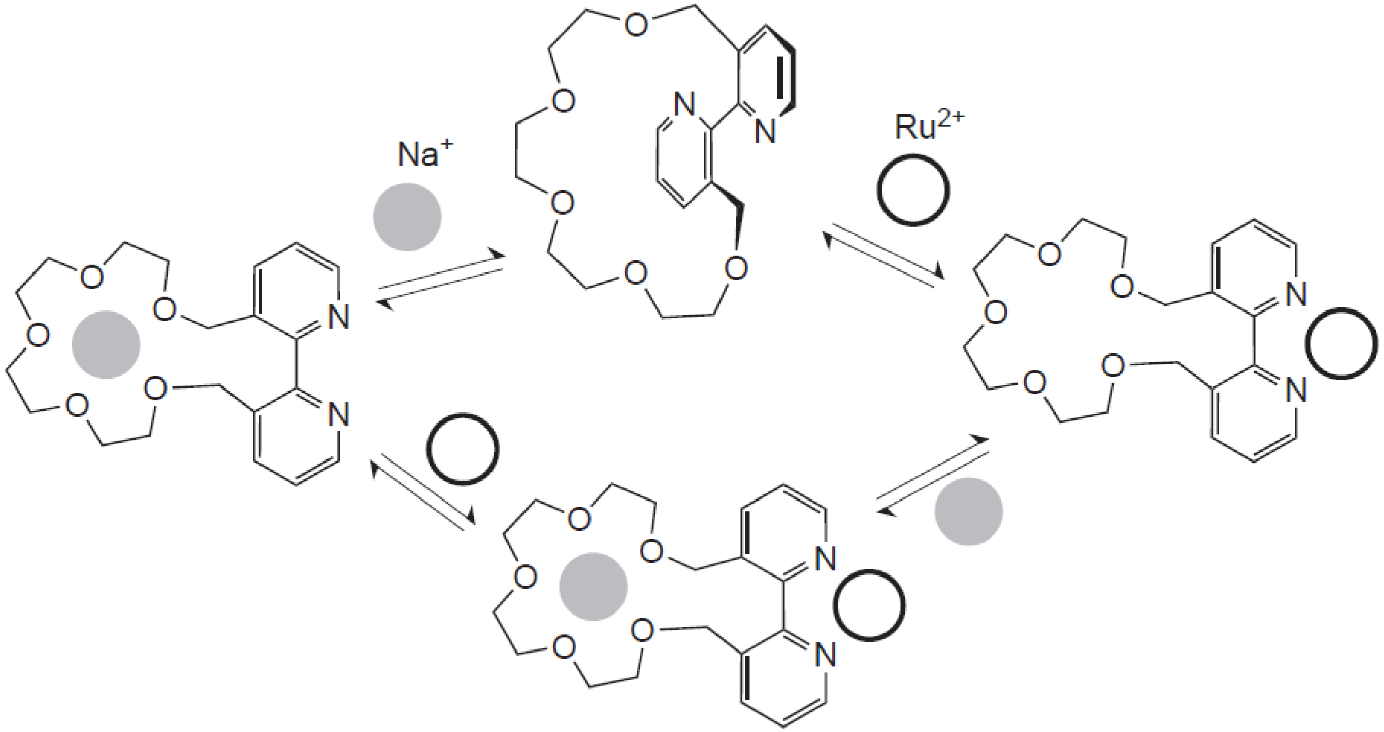
A good example is shown in the Scheme Cooperativity in cases where the binding of a first guest influences (particularly enhances) the affinity of a host for a second guest at a remote site is termed an *allosteric effect*. A good example is shown in figure.

Here a binding of Ru(II) to the bipyridyl portion of the host changes its conformation by rotation about the pyridyl-pyridyl bond to create a cavity suitable for chelating an alkali metal cation such as Na.

Similarly binding of Na to the polyether site predisposes (*preorganises*) the bipyridyl portion for Ru(II) binding.

Here a binding of Ru(II) to the bipyridyl portion of the host changes its conformation by rotation about the pyridyl-pyridyl bond to create a cavity suitable for chelating an alkali metal cation such as Na+. Similarly binding of Na+ to the polyether site Predisposes the bipyridyl portion for Ru(II) binding.

Allosteric effect



Scheme 1.2 Allosteric (cooperative) enhancement of Na^+ binding by preorganisation of the polyether binding site by Ru(II), and *vice versa*.[11]

C’è anche un effetto allosterico «negativo» per cui il binding di un guest provoca il rilascio di un guest già legato

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SUBJECT AREAS:
SUPRAMOLECULAR CHEMISTRY
SURFACE CHEMISTRY
SELF-ASSEMBLY

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Cation-Induced Pesticide Binding and Release by a Functionalized Calix[4]arene Molecular Host

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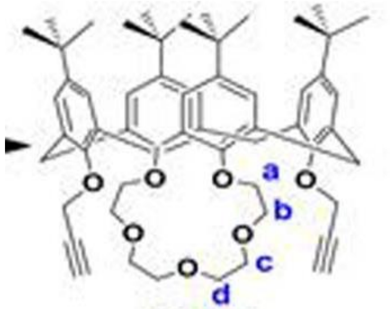
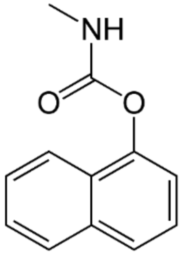
Ion-controlled switchable progress is very important in many biological behaviors. Here, we reported K^+-controlled switch, this switch system exhibited excellent carbaryl (G) binding/release by fluorescent (FL), ultraviolet-visible (UV) spectrums and ^{1}H NMR spectroscopy. More importantly, the K^+-controlled G binding/release switch based on C4C5 not only in the solution, but also on the surface, promising for the application for the pesticide controlled release.



C4C5



Carbaryl (G)

Carbaryl (G) is a pesticide which have naphthalene group can interact with calixarene through π-π stacking.
Crown ether was employed to selectively bind K^+ in aqueous solution.
It was known that 18C6 is a very strong sequestering agent for potassium ion, which has strong binding affinity toward K^+ . Therefore, we designed a wettable responsive switch based on K+-controlled calix-crown binding/release G.
All were shown in the figure 1b. As a consequence of its outstanding properties, the K+-controlled switch has formed attractive application in many fields, especially on a silicon surface.

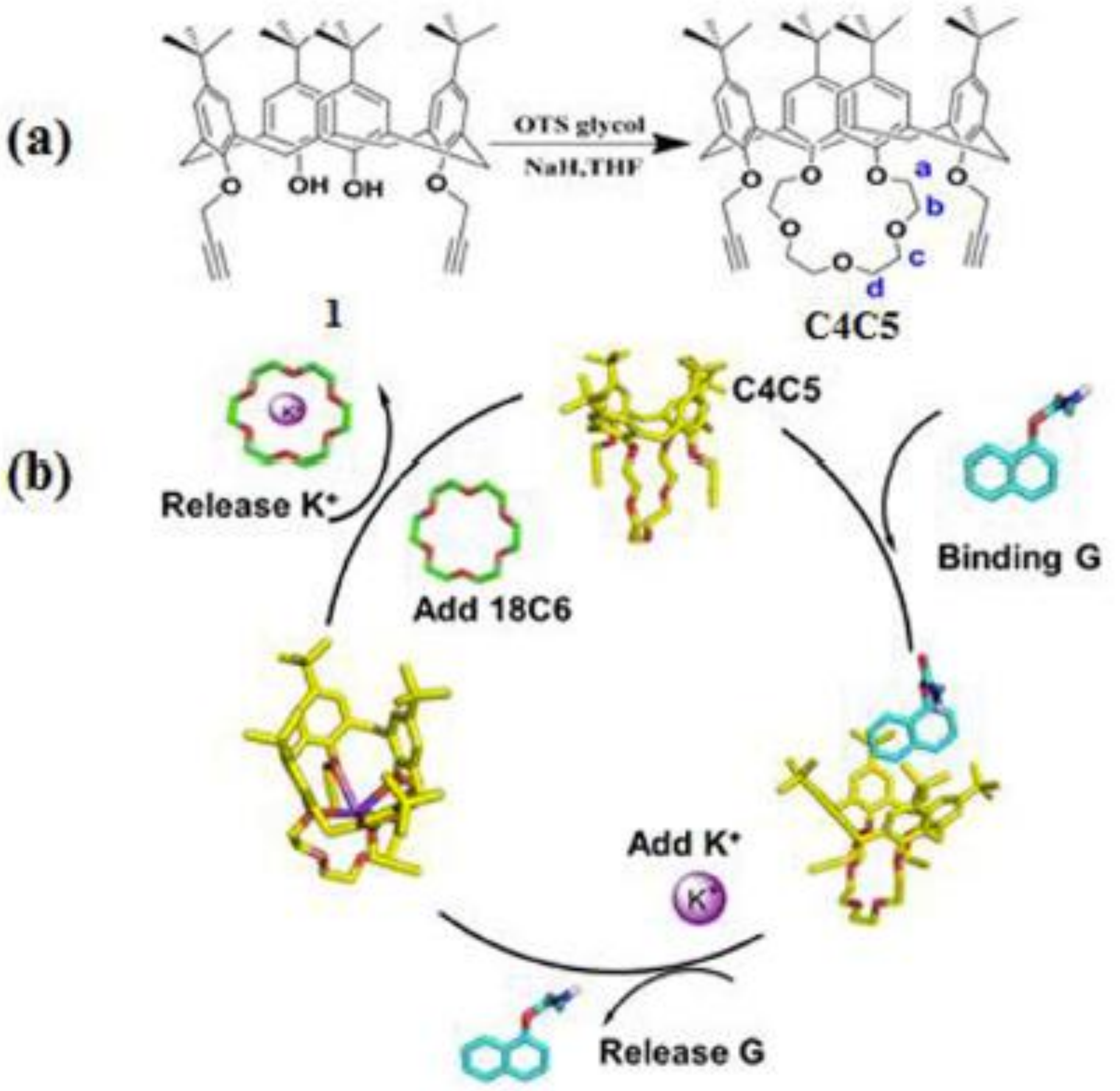
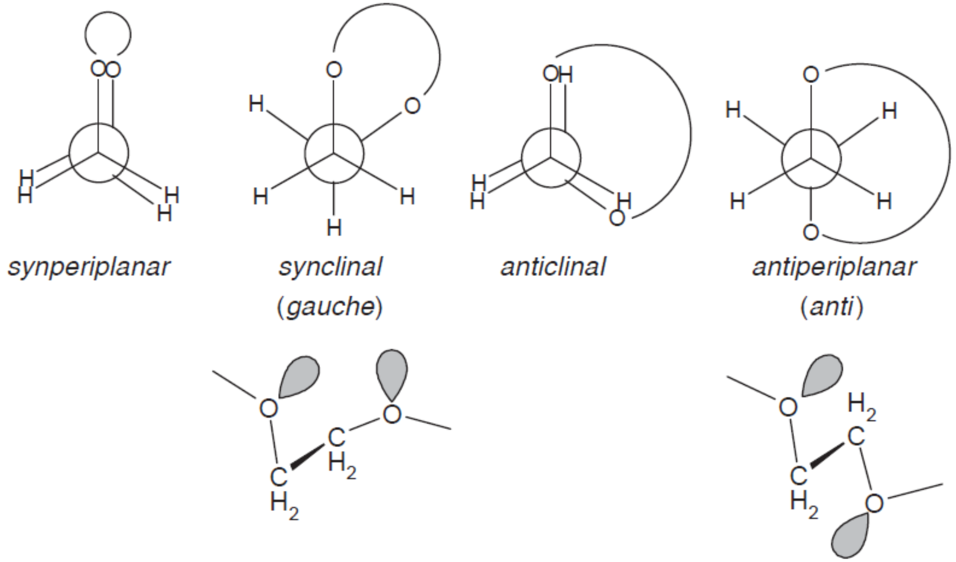
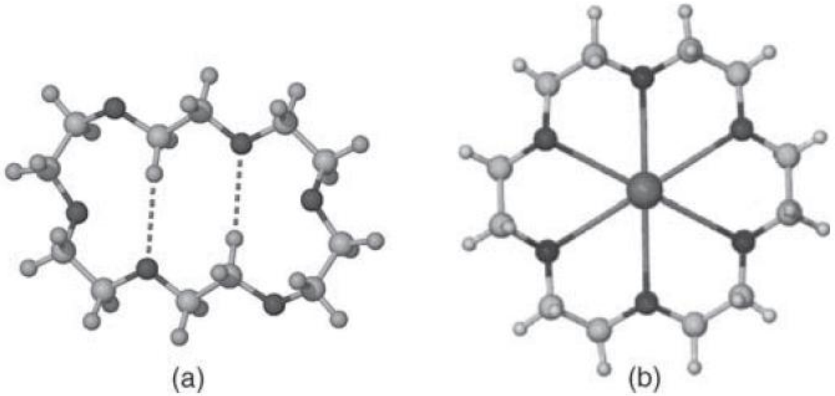


Figure 1 | (a) The synthesis of C4C5. (b) The scheme of K^+-controlled binding/release **G**.

Conformations of crown ethers

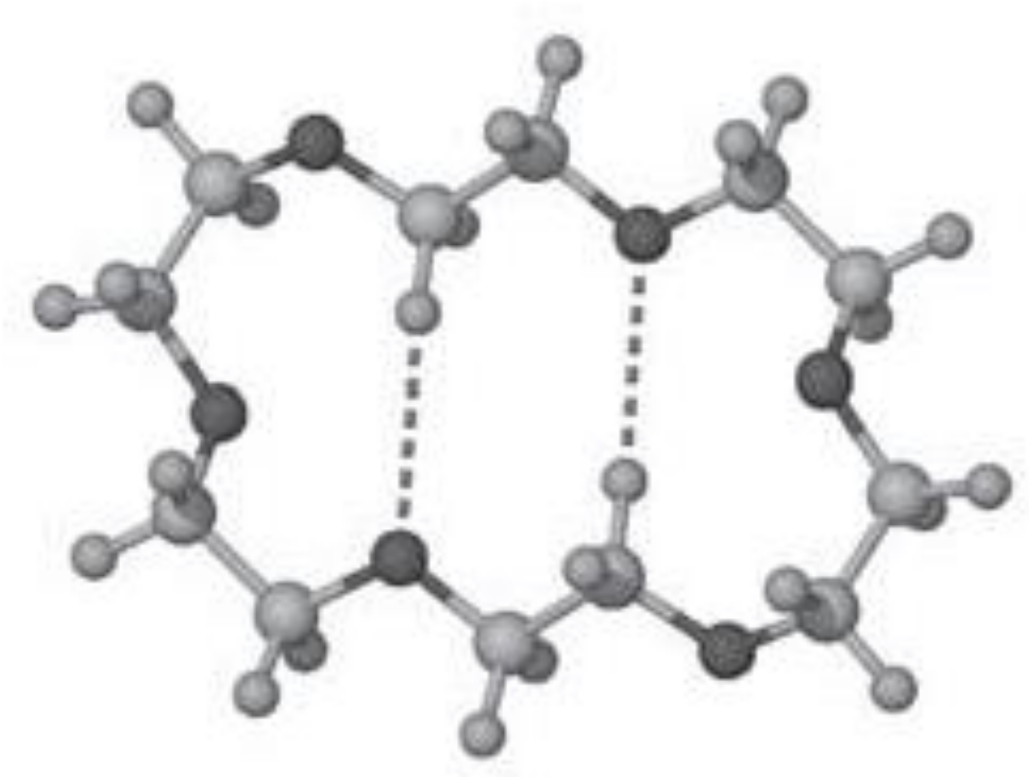
- In order to form a cyclic molecule a crown-type macrocycle must have eight gauche torsion angles (Figure). If those gauche angles occur at O–C–C–O bonds then the oxygen atoms will point into the centre of the ring and hence will be preorganised for metal ion binding.
- Conversely, if they occur at C–C–O–C bonds then the donor atoms will point out of the ring, reducing the degree of preorganisation. The conformation adopted by [18]crown-6 in the solid state derived by X-ray crystallographic measurements is shown in the Figure.





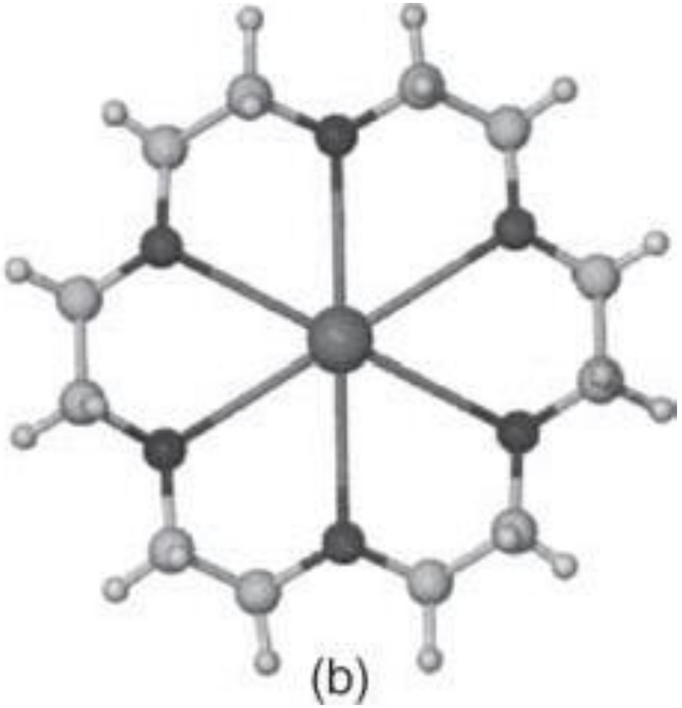
20 Comparison of the X-ray crystal structures of (a) free [18]crown-6 showing intramo-
H···O hydrogen bonds with (b) the potassium complex of [18]crown-6.

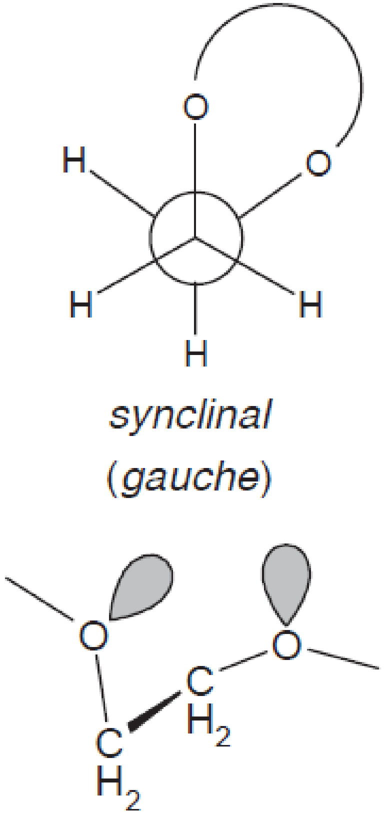
FREE [18]-crown-6



- Two of the oxygen atoms point out of the ring (allowing the formation of a pair of intramolecular CH···O hydrogen bonds) and the remainder are inside

[18]-crown-6 K^+ complex





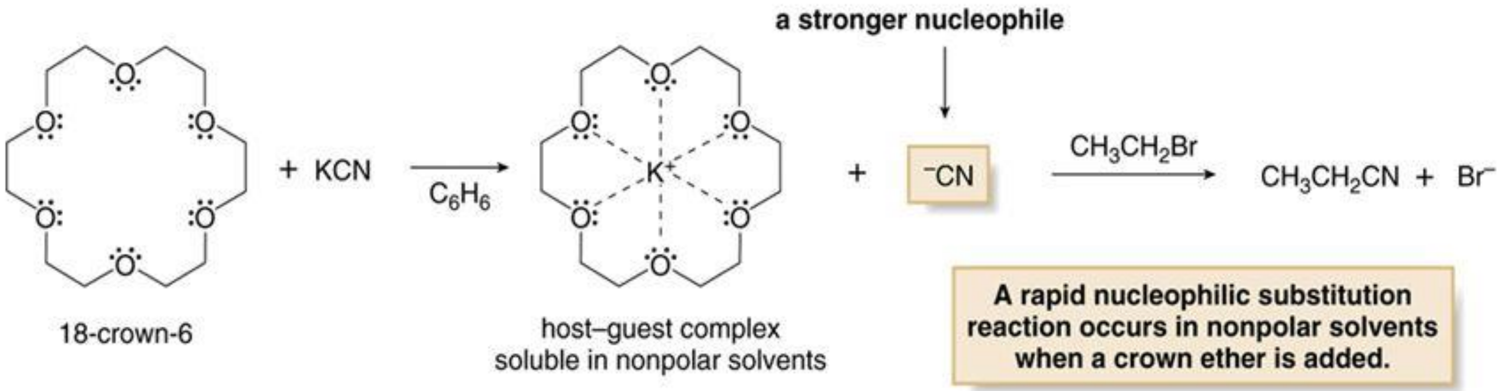
- Tutti gli ossigeni sinclinali (gauche)

Use of Crown Ethers

- The ability of crown ethers to complex cations can be exploited in nucleophilic substitution reactions.
- As the complexed cation goes into solution it carries the anion with it to maintain neutrality.
- The relatively unsolvated anion is extremely nucleophilic.

Figure 9.5

KCN is insoluble in nonpolar solvents alone, but with 18-crown-6:



18-crown-6

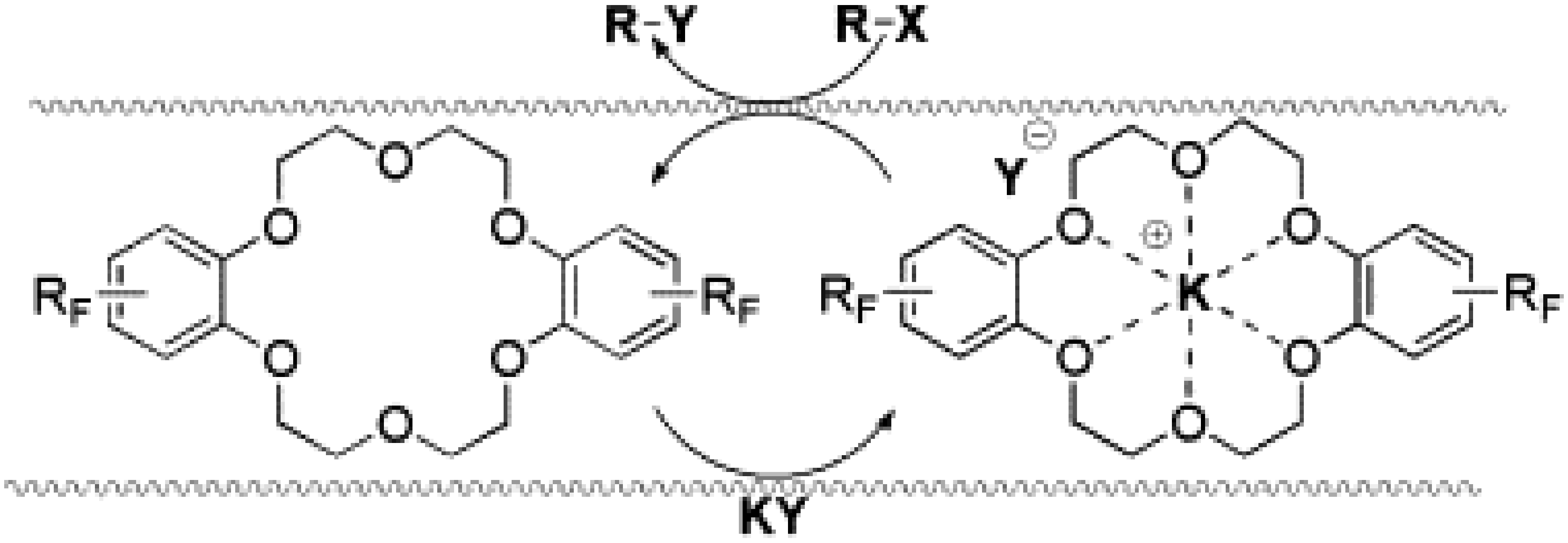
host–guest complex soluble in nonpolar solvents

a stronger nucleophile

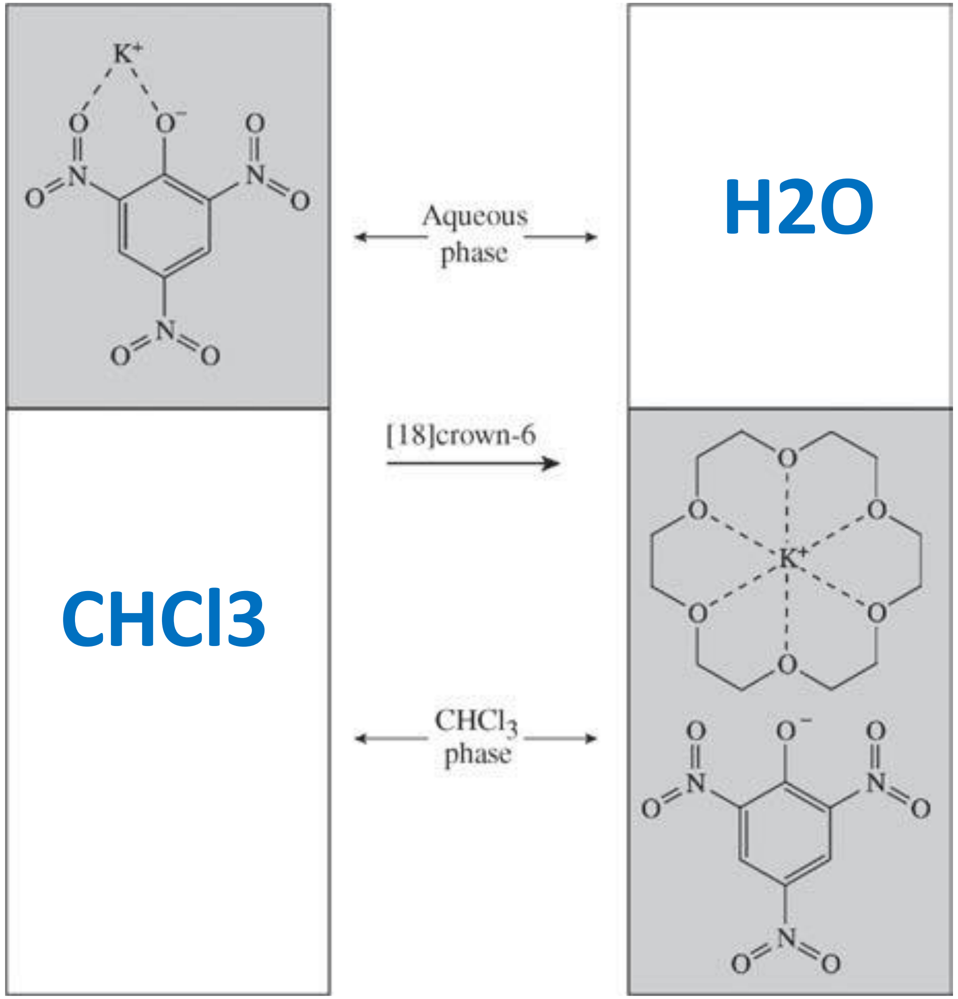
A rapid nucleophilic substitution reaction occurs in nonpolar solvents when a crown ether is added.

Phase transfer catalysis (PTC)

- Complexation of inorganic cations such as alkaline or alkaline earth metals by macrocyclic polyethers produces large, lipophilic cationic metal–macrocycle complexes that are readily soluble in nonpolar solvents such as benzene, toluene and haloalkanes.
- In order to maintain charge balance, the cationic complex has an associated counter anion. In an immiscible two-phase liquid system, such as a mixture of chloroform and water, the anion is necessarily pulled into the organic phase as the cationic complex crosses the phase boundary.
- After reaction the CE goes in the interphase and complexes another ion



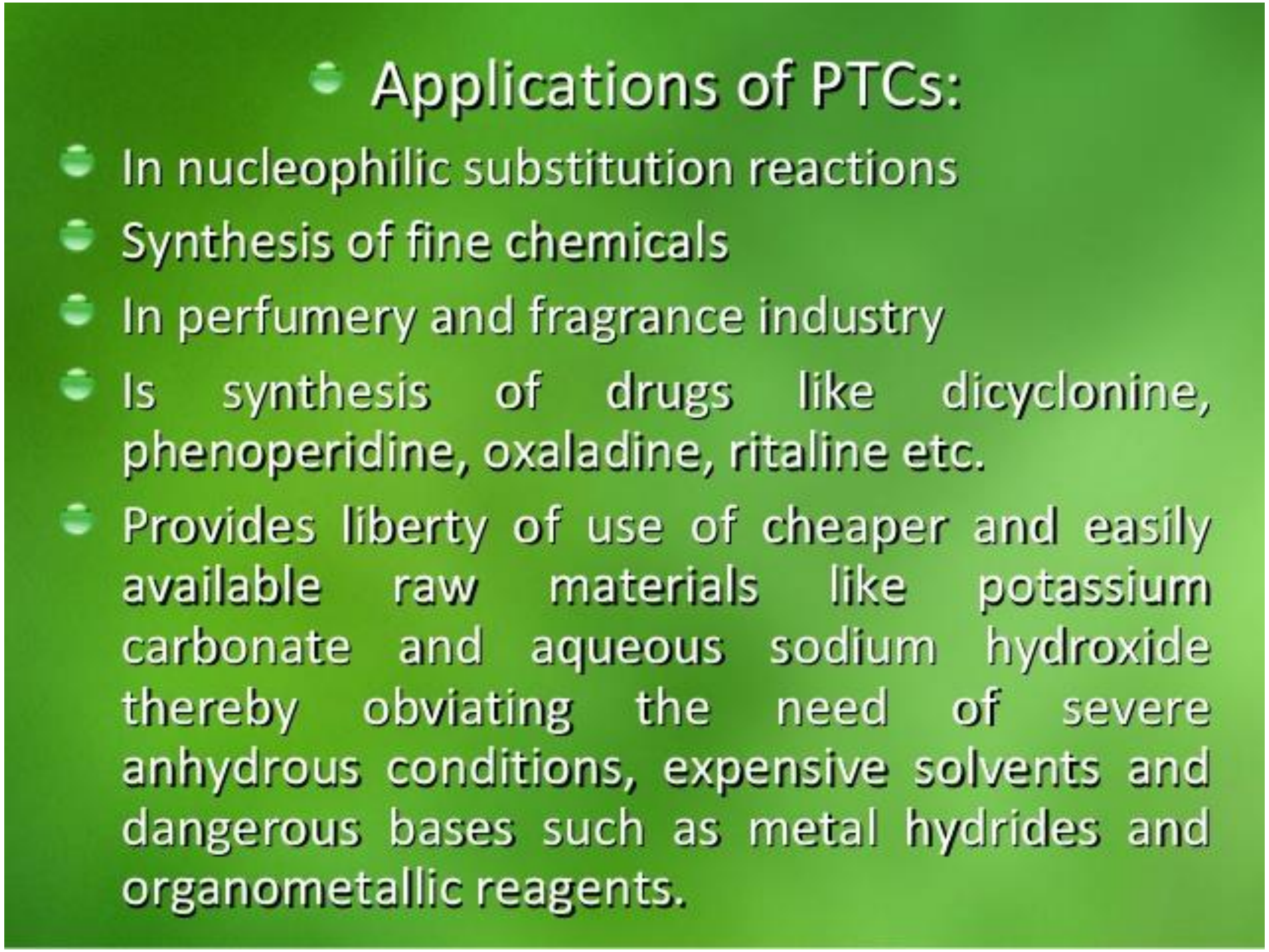
Picrate transport in organic phase by CE



Catalisi della sostituzione nucleofila

- Another intriguing aspect of reaction catalysis by macrocyclic cation hosts is the ‘naked anion’ effect. In a conventional anion reaction, such as an organic nucleophilic substitution, the activity of the anionic nucleophile is reduced by coordination or ion pairing with the cation (its counter ion).
- The activation energy for the reaction is thus increased by the amount of energy necessary to break the anion–cation association. In the presence of a crown ether or especially cryptand, the cation is sequestered within a lipophilic sheath, bringing about a large physical separation of anion and cation.

PTC is green!!!



Applications of PTCs:

- In nucleophilic substitution reactions
- Synthesis of fine chemicals
- In perfumery and fragrance industry
- Is synthesis of drugs like dicyclonine, phenoperidine, oxaladine, ritaline etc.
- Provides liberty of use of cheaper and easily available raw materials like potassium carbonate and aqueous sodium hydroxide thereby obviating the need of severe anhydrous conditions, expensive solvents and dangerous bases such as metal hydrides and organometallic reagents.

Nitrogen and sulfur analogues of crown ethers

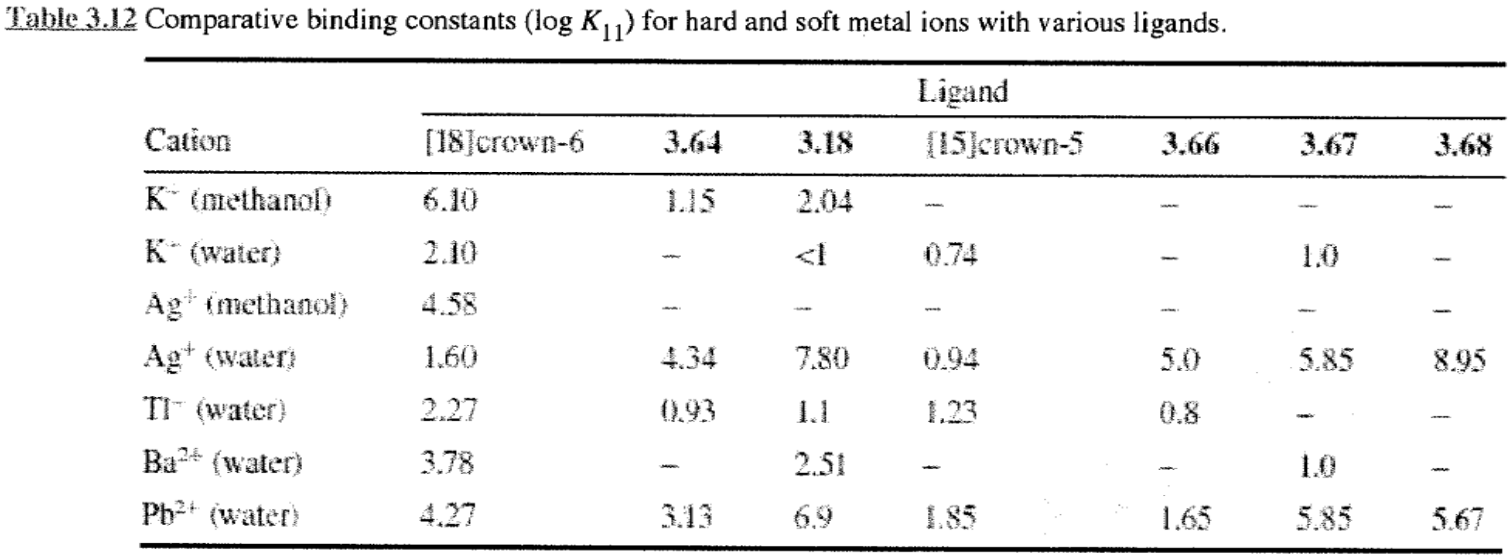
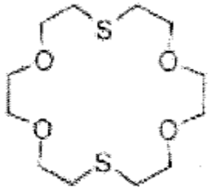
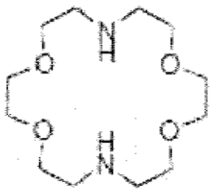


Table 3.12 Comparative binding constants (log K_{11}) for hard and soft metal ions with various ligands.

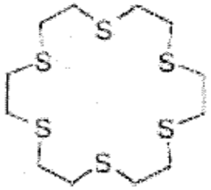
	Ligand						
Cation	[18]crown-6	**3.64**	**3.18**	[15]crown-5	**3.66**	**3.67**	**3.68**
K$^+$ (methanol)	6.10	1.15	2.04	–	–	–	–
K$^+$ (water)	2.10	–	<1	0.74	–	1.0	–
Ag$^+$ (methanol)	4.58	–	–	–	–	–	–
Ag$^+$ (water)	1.60	4.34	7.80	0.94	5.0	5.85	8.95
Tl$^+$ (water)	2.27	0.93	1.1	1.23	0.8	–	–
Ba^{2+} (water)	3.78	–	2.51	–	–	1.0	–
Pb^{2+} (water)	4.27	3.13	6.9	1.85	1.65	5.85	5.67



3.64



3.18



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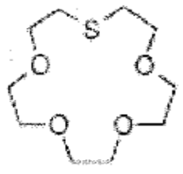

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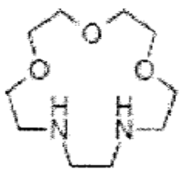

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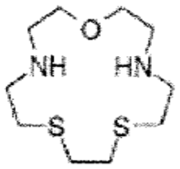
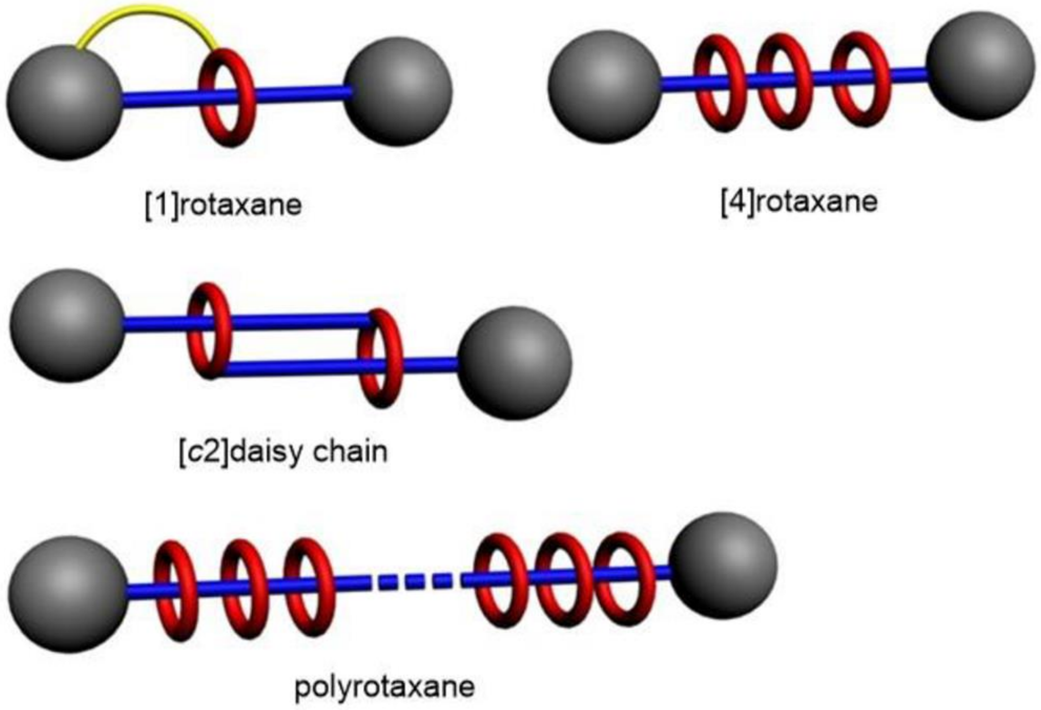
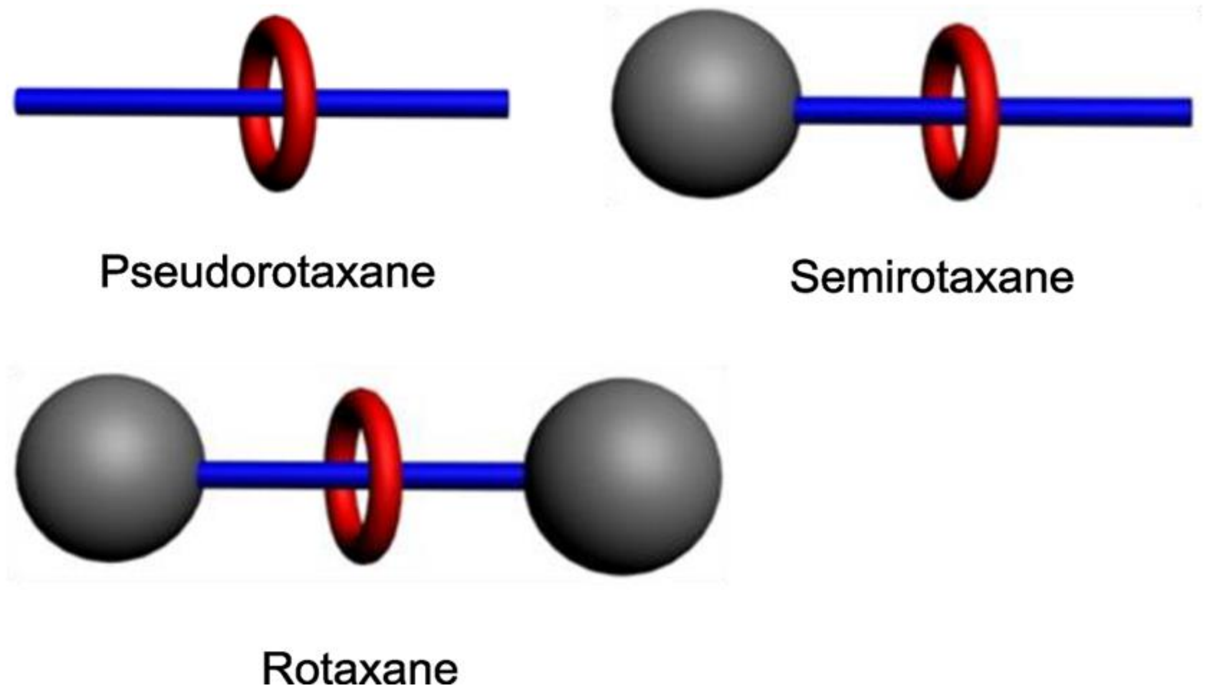


3.68

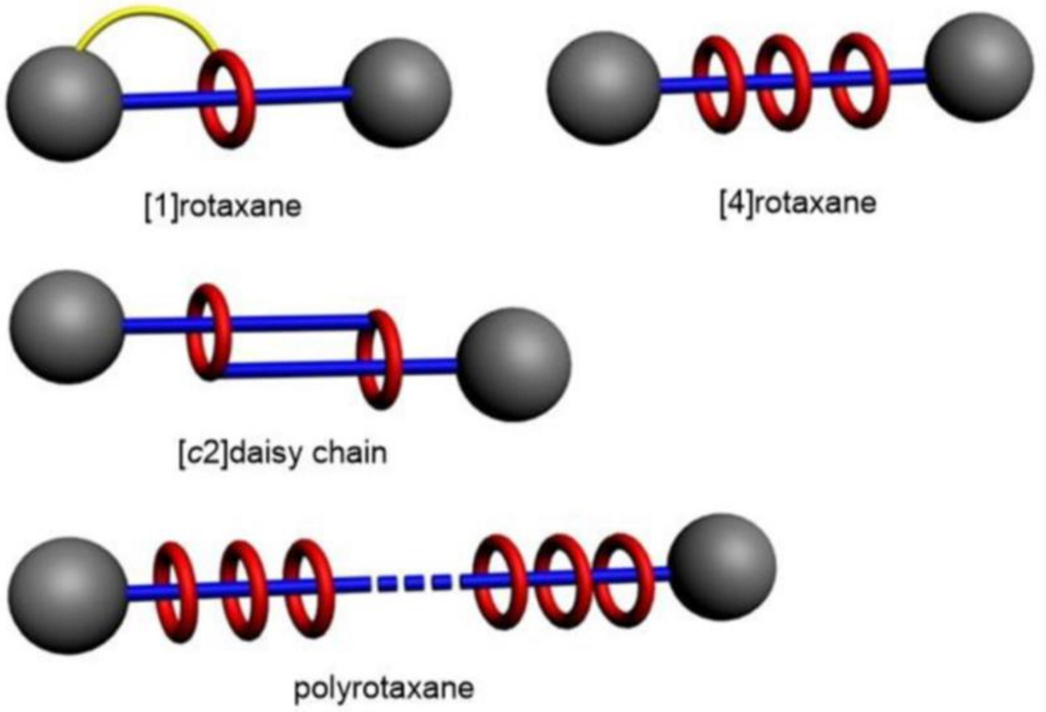
Crown ethers are used as rings (or wheels) in rotaxanes



"Rotaxane" is derived from the Latin words for "wheel" and "axle", and describes a compound that consists of a linear species (sometimes called the rodlike part or guest) and cyclic species (sometimes called the beadlike part or host) bound together in a threaded structure by noncovalent forces

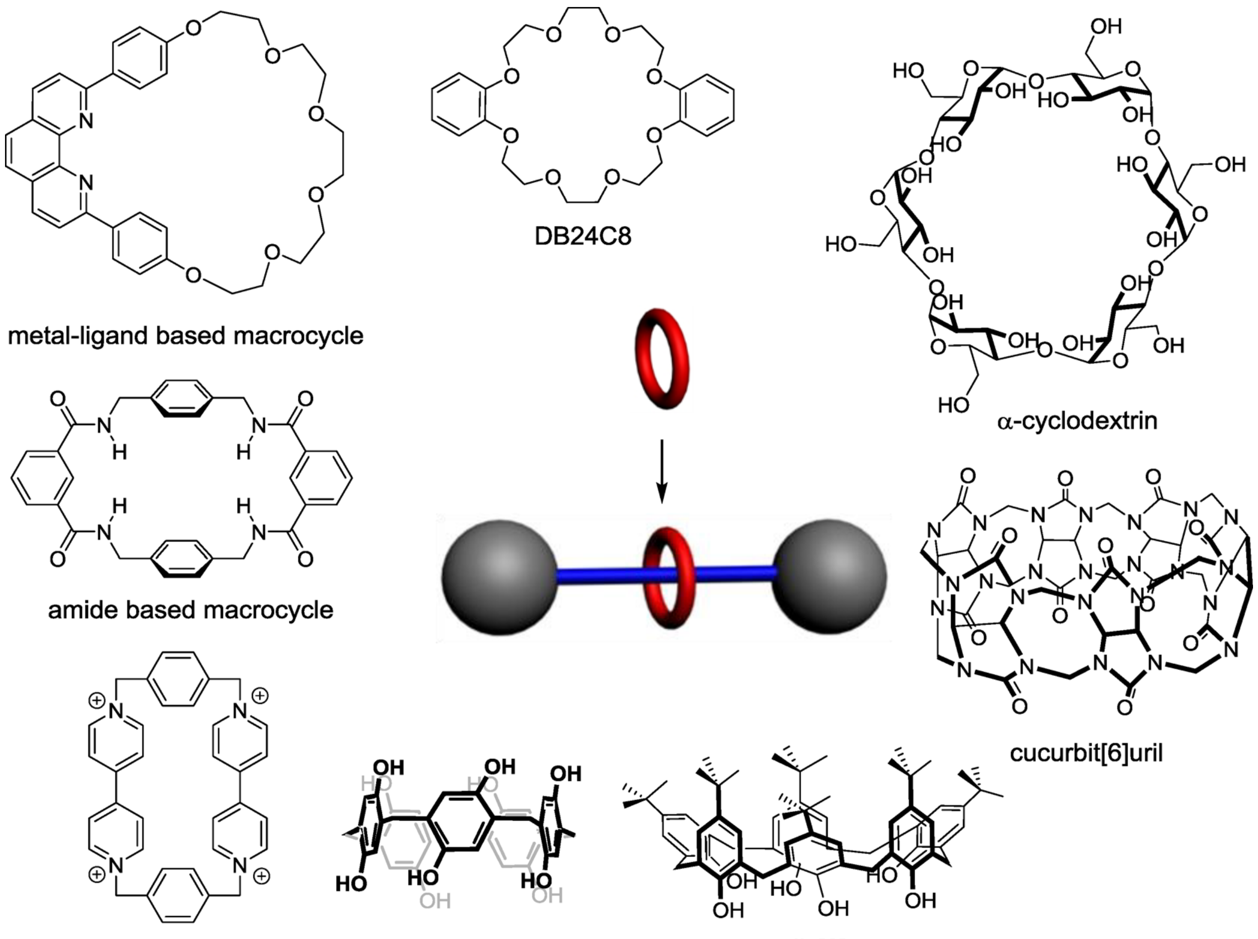


Cartoon representations of pseudorotaxane, semirotaxane, and rotaxane are shown in Figure. The gray balls here represent stoppers, which are bulky groups and can prevent dethreading of the cyclic component.



- Among different types of rotaxanes, daisy chains, because of their unique muscle-like mobility, have gained special attention

Rotaxanes «wheels»



metal-ligand based macrocycle

DB24C8

α-cyclodextrin

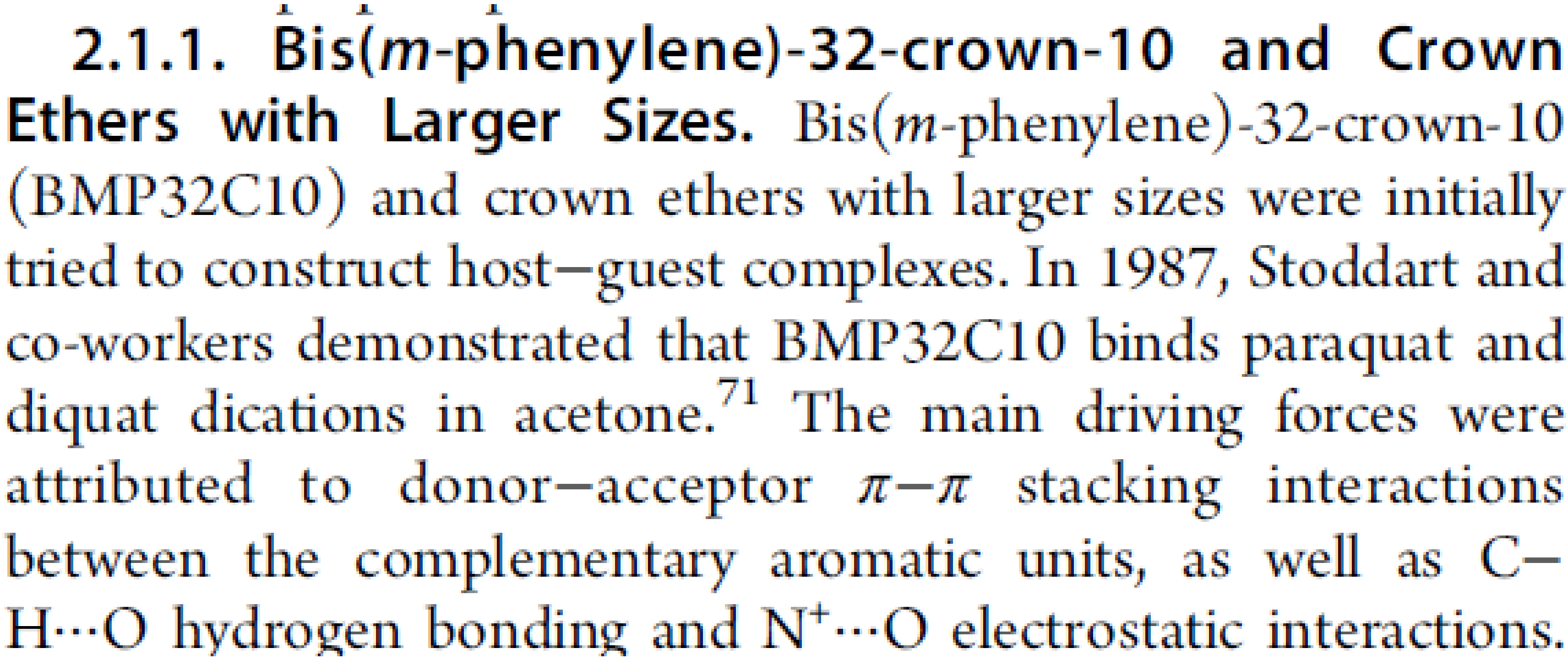
amide based macrocycle

cucurbit[6]uril

$CBPQT^{4+}$

pillar[5]arene

calix[6]arene



2.1.1. Bis(*m*-phenylene)-32-crown-10 and Crown Ethers with Larger Sizes. Bis(*m*-phenylene)-32-crown-10 (BMP32C10) and crown ethers with larger sizes were initially tried to construct host–guest complexes. In 1987, Stoddart and co-workers demonstrated that BMP32C10 binds paraquat and diquat dications in acetone.[71] The main driving forces were attributed to donor–acceptor $\pi-\pi$ stacking interactions between the complementary aromatic units, as well as C–H···O hydrogen bonding and N^+···O electrostatic interactions.