Course Name: **Supramolecular & Photoinorganic Chemistry**

Paper Number: **101**

Section: **B**

Course Instructor: **Prof. Rajeev Gupta**

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Part – 1

Part I : General Background & Cation Binding

1. Alkali Metal Cations in Biochemistry
2. Sodium-Potassium Pump
3. Membrane Transport
4. Ionophores
5. Valinomycin and Nonactin
6. Enniatins
7. The Crown Ethers
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15. Cryptands
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21. Nomenclature of Cation Binding Macrocycles
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25. High Dilution Synthesis
26. Pre-organization
27. Complementarity
28. Complexation of Organic Cations
29. Binding of Ammonium Cations by Corands

Source / Materials:

1. Steed, J. W.; Atwood, J. L., *Supramolecular Chemistry, Second Edition,* John Wiley & Sons Ltd: West Sussex, U. K., 2009.
2. Cragg, P. J., *Supramolecular Chemistry: From Biological Inspiration to Biomedical Applications,* Springer: Dordrecht, 2010.
3. Lehn, J. M., *Supramolecular Chemistry: Concepts & Perspectives*; Wiley-VCH: Weinheim, 1995.

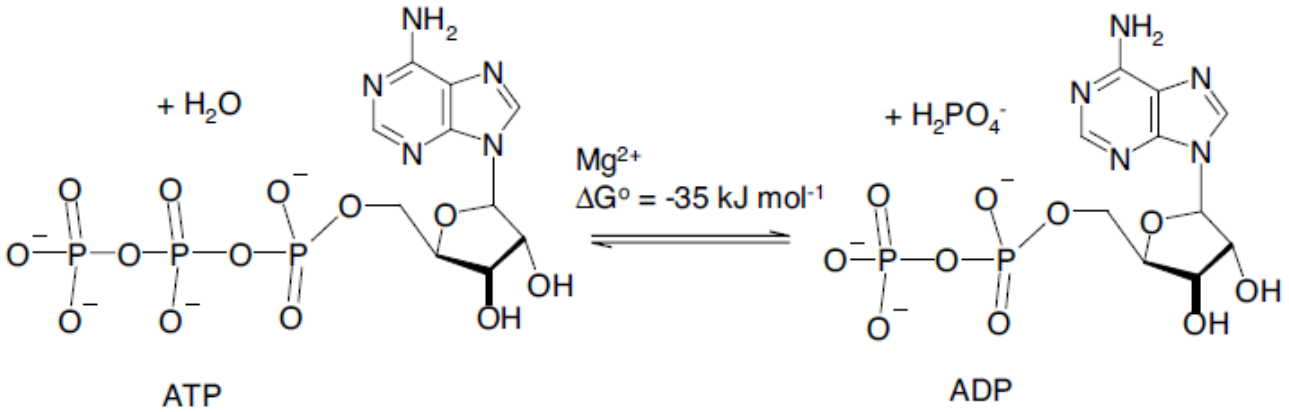
Alkali Metal Cations in Biochemistry

Membrane Potenial:

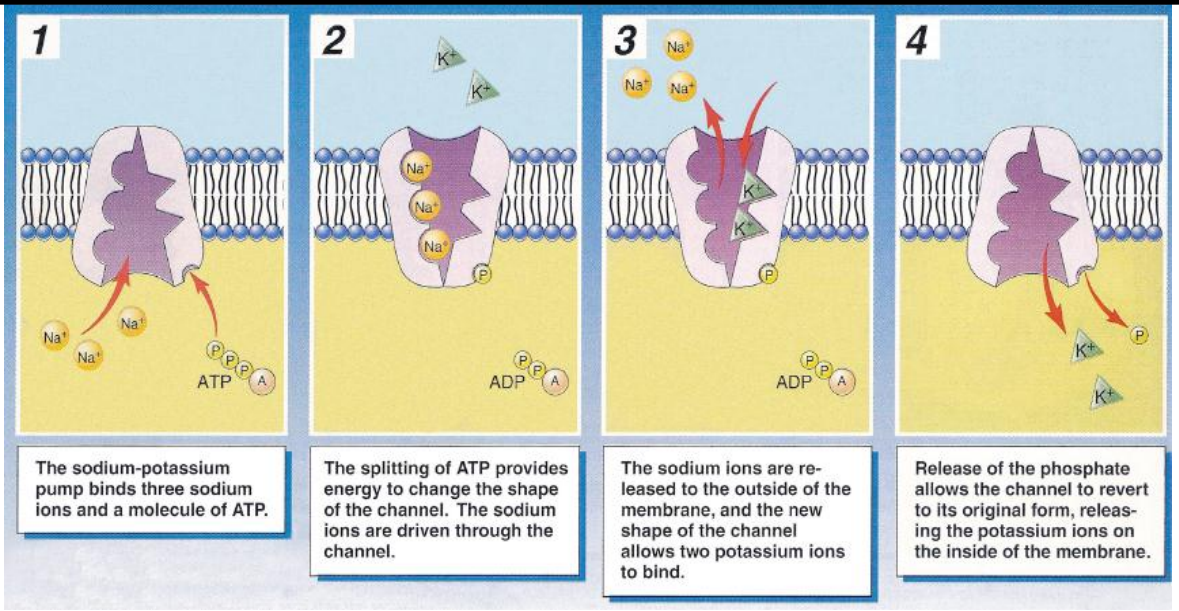
❖Energy is vital to life and is used in respiration, a process by which energy from food is transformed and stored as the chemical bond energy of ATP (adenosine triphosphate).

❖Strictly, ATP has a 4 ionic charge, balanced by alkaline and alkaline earth metal cations. ATP is capable of long-term energy storage and is transported to any areas where energy is needed to drive endergonic (energy-consuming) reactions such as muscle contraction.

❖The energy is released from ATP by a class of enzymes called ATPases, of which Na^+/K^+-ATPase is perhaps the most important example. One mole of ATP releases 35 kJ of energv.



Sodium-Potassium Pump



❖The Na^+/K^+-ATPase enzyme is an example of a ***transmembrane*** enzyme.

❖The enzyme scavenges Na^+ from the inside of the cell and transports it to the outside, against the prevailing concentration gradient. Simultaneously, K^+ is transported into the cell.

❖Thus, in the intracellular fluid there is a high concentration of K^+; outside there is a high concentration of Na^+.

❖ This uneven distribution of alkali metal cations across the cell membrane is very important and necessary feature and results in a transmembrane electrical potential, rather like a battery.

Membrane Transport

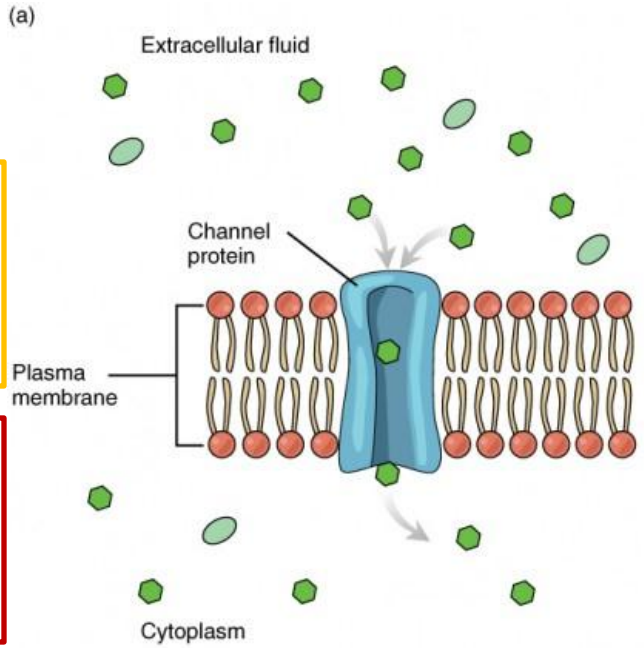
So how does an alkali metal get from the inside of the cell to the outside?

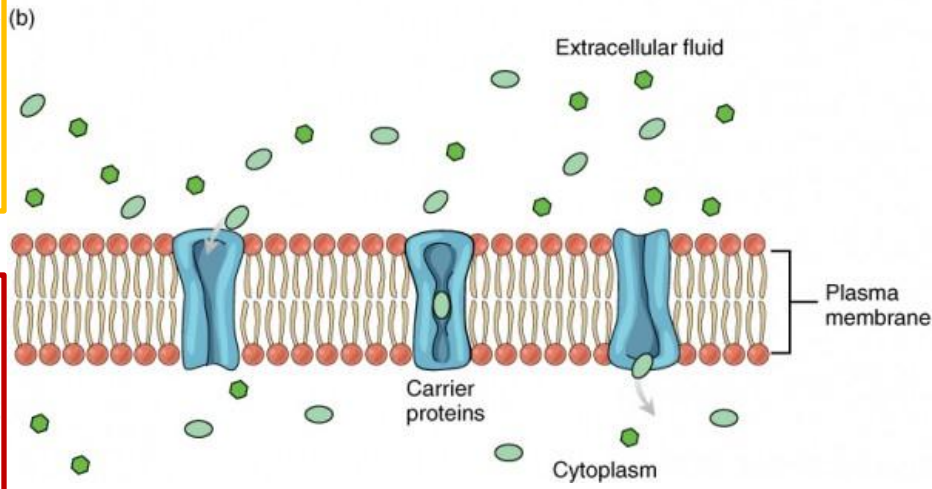
A cell membrane consists of hydrophilic phosphate head groups attached to a long lipid tail and is thus an example of an amphiphile.

In the body's aqueous environment, the hydrophilic head groups are attracted to the surrounding medium while the organic tail is repelled and this results in a bilayer arrangement .

Na^+ and K^+ cations are not at all lipophilic. They cannot effectively diffuse through the cell wall unless something makes them lipophilic or a non-lipophilic pathway is created for them.

There are two main possible methods of such passive cation transport along a concentration gradient: **(a) transport by some kind of lipophilic carrier, (b) controlled passage through a hydrophilic channel in the membrane.**

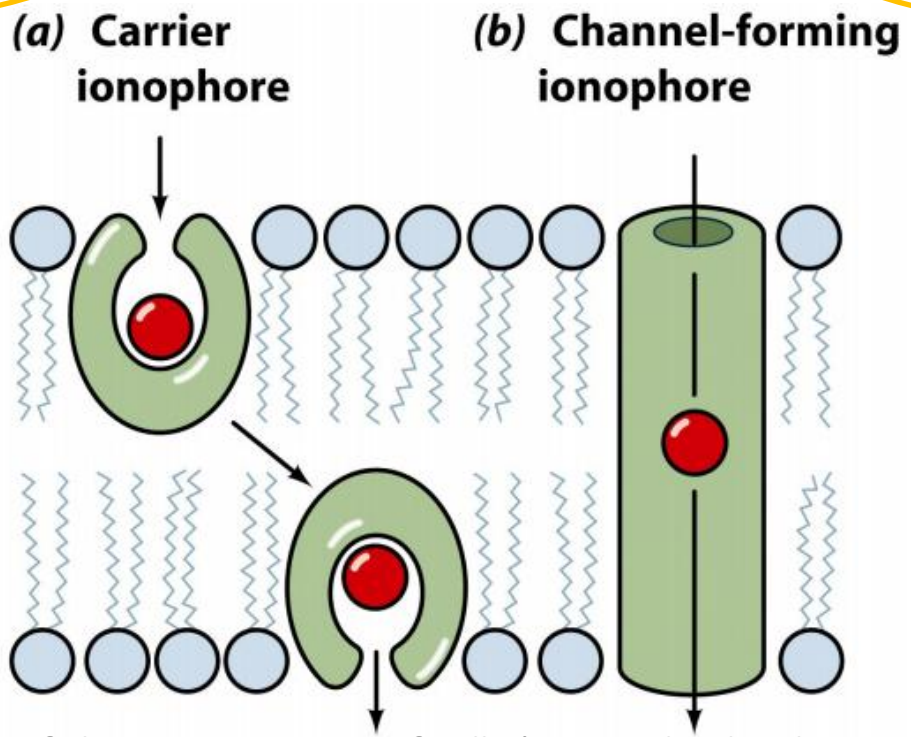




Ionophores

The carrier ligand required for metal ions transport which is selective to the metal cation and shields it from the lipophilic region of the membrane is called **ionophore.**

*The natural products **valinomycin** and **nonactin** are among* the best known.



Valinomycin and Nonactin

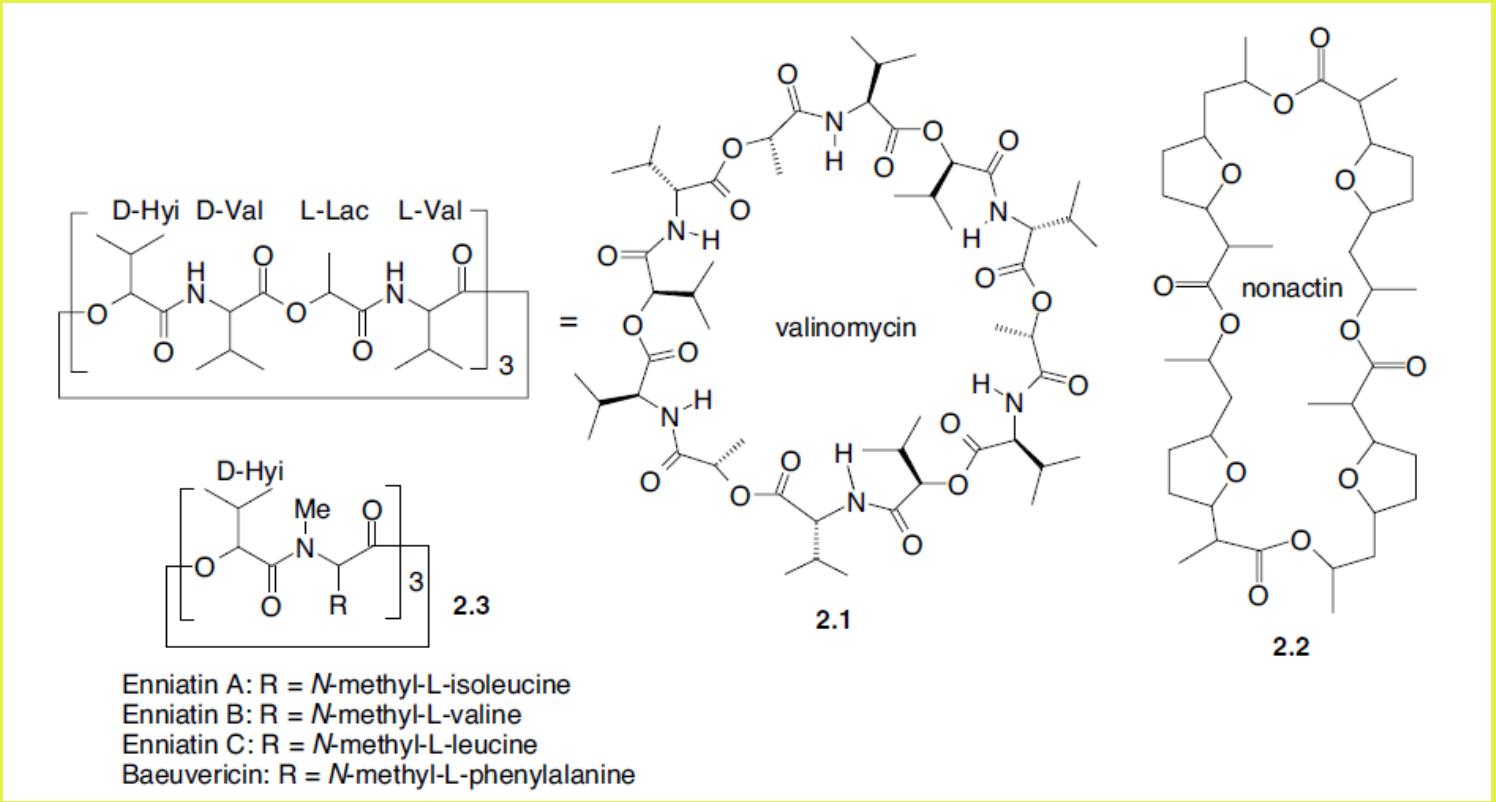
Valinomycin helps to catalyse the exchange of K^+ and H^+ across the membrane of mitochondria within cell. *Chemically, valinomycin* is a cyclic depsipeptide made up of a threefold repetition of four amino acid residues: L-valine (Val), D-hydroxyisovaleric acid (Hyi), D-valine and L-lactic acid (Lac)

Hydrogen bonding of type N–H…OC to both ester and amide carbonyl groups plays an important role in the conformation of valinomycin, where it helps the peptide chain wrap around the metal cation, contributing to its degree of preorganisation and stabilising the bound conformation.

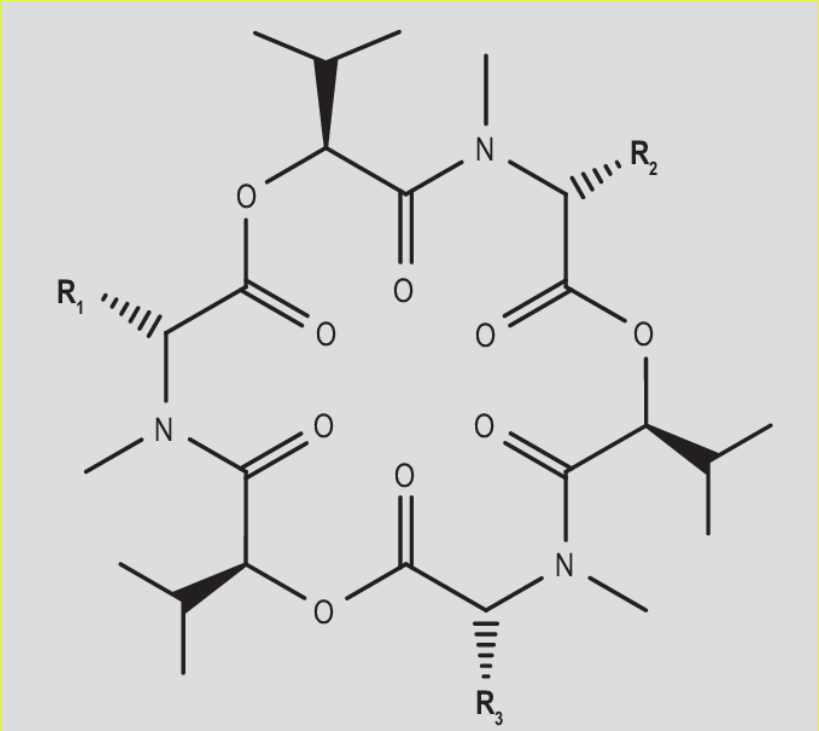
Valinomycin and nonactin are both selective for K^+ because they are able to fold in on themselves in order to produce an approximately octahedral array of hard (*i.e. non-polarisable, according to the hard and soft acids and bases (HSAB)* theory; carbonyl oxygen atom donors exactly suited to fit an ion of the size of K^+. Rubidium and caesium are too large, whereas the ionophore cannot contract tightly enough to bind to Na^+.

The interaction of the hydrophilic carbonyl oxygen atoms with the central K ion causes the lipophilic *iso-propyl groups to point outwards thus exposing a primarily hydrocarbon* coated outer sheath to the surrounding medium

The remaining amide functionalities act to ‘zip up’ the molecule *via intramolecular hydrogen bonds, ensuring the K ion is encased entirely in a lipophilic* exterior as it crosses the membrane. Both valinomycin and nonactin are potent antibiotics because of their ability to perturb transmembrane ionic balance in bacteria.



Enniatins



i-pr

sec-but

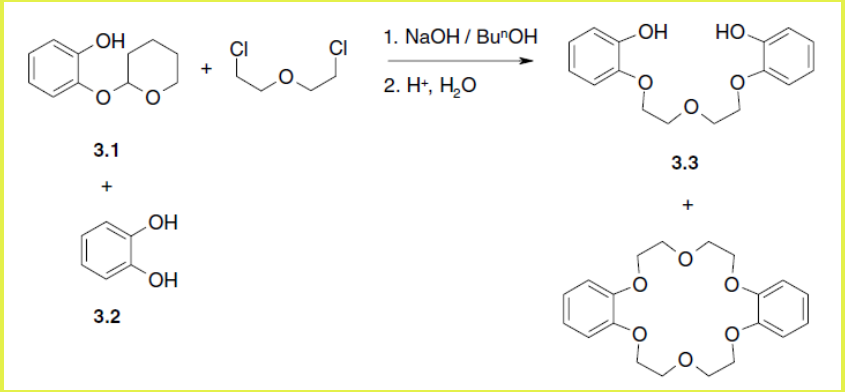
	R_1	R_2	R_3
enniatin A	*sec*-but	*sec*-but	*sec*-but
enniatin A1	*i*-pr	*sec*-but	*sec*-but
enniatin B	*i*-pr	*i*-pr	*i*-pr
enniatin B1	*i*-pr	*i*-pr	*sec*-but

Related closely to valinomycin are the **enniatins** which are made up of only half the number of amino acid binding units. The enniatins transport alkali metal cations and alkaline earth metal ions, although they are much less selective than valinomycin. Many of the ionophores bind strongly to K^+ while only monesin actually binds Na^+ with any selectivity.

The Crown Ethers

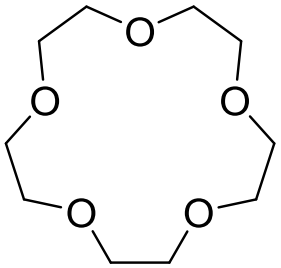
The **crown ethers** are among the simplest and most appealing macrocyclic ligands, and are present in supramolecular chemistry as hosts for both metallic and organic cations.They consist simply of a cyclic array of ether oxygen atoms linked by organic spacers, typically —CH2CH2— groups.

While the metal binding ability of uni-dentate ethers such as the common solvent diethyl ether is very poor, the crown ethers are much more effective by virtue of the chelate effect and the partial pre-organisation arising from their macrocyclic structure Pedersen's initial synthesis of the first crown ether, dibenzo[18]crown-6 was accidental.

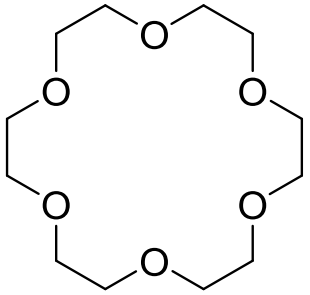


The compound dissolved sparingly in methanol, but its solubility was enhanced significantly on addition of alkali metal salts. Pedersen soon synthesized the compound in much better yield. He found that it dissolved inorganic salts like $KMnO_4$ in organic solvents such as benzene to give it a purple colouration (this was termed 'purple benzene').

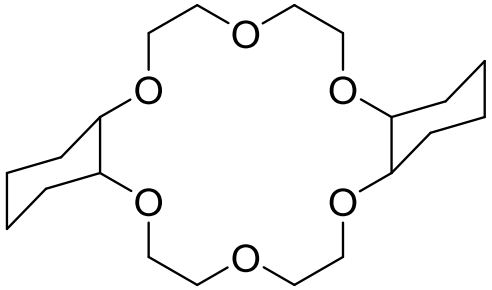
Examples of Crown Ethers



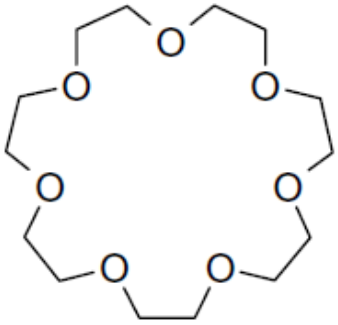
[15]crown-5



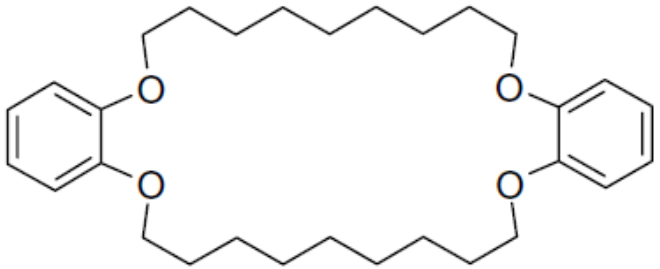
[18]-crown-6



Dicyclohexyl[18]crown-6



[21]crown-7



Dibenzo[26]crown-4

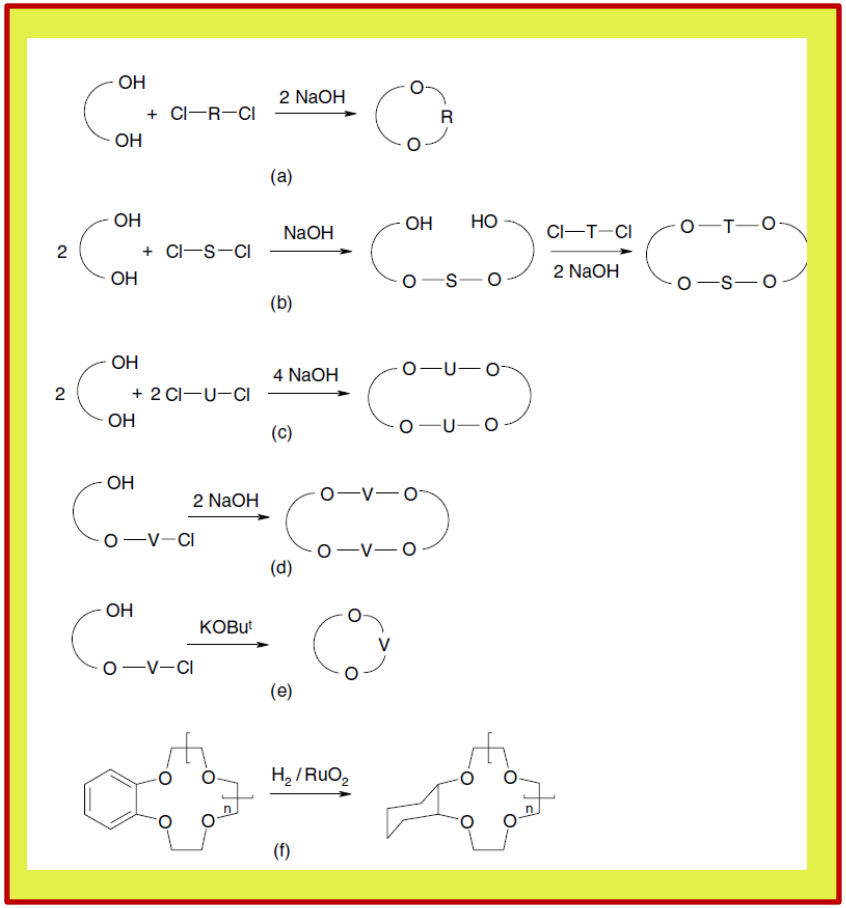
Synthesis of Crown Ethers

Pedersen described a total of six different methods of crown ether synthesis in his original work. Most new crown ethers are prepared by either method (a) or (b).

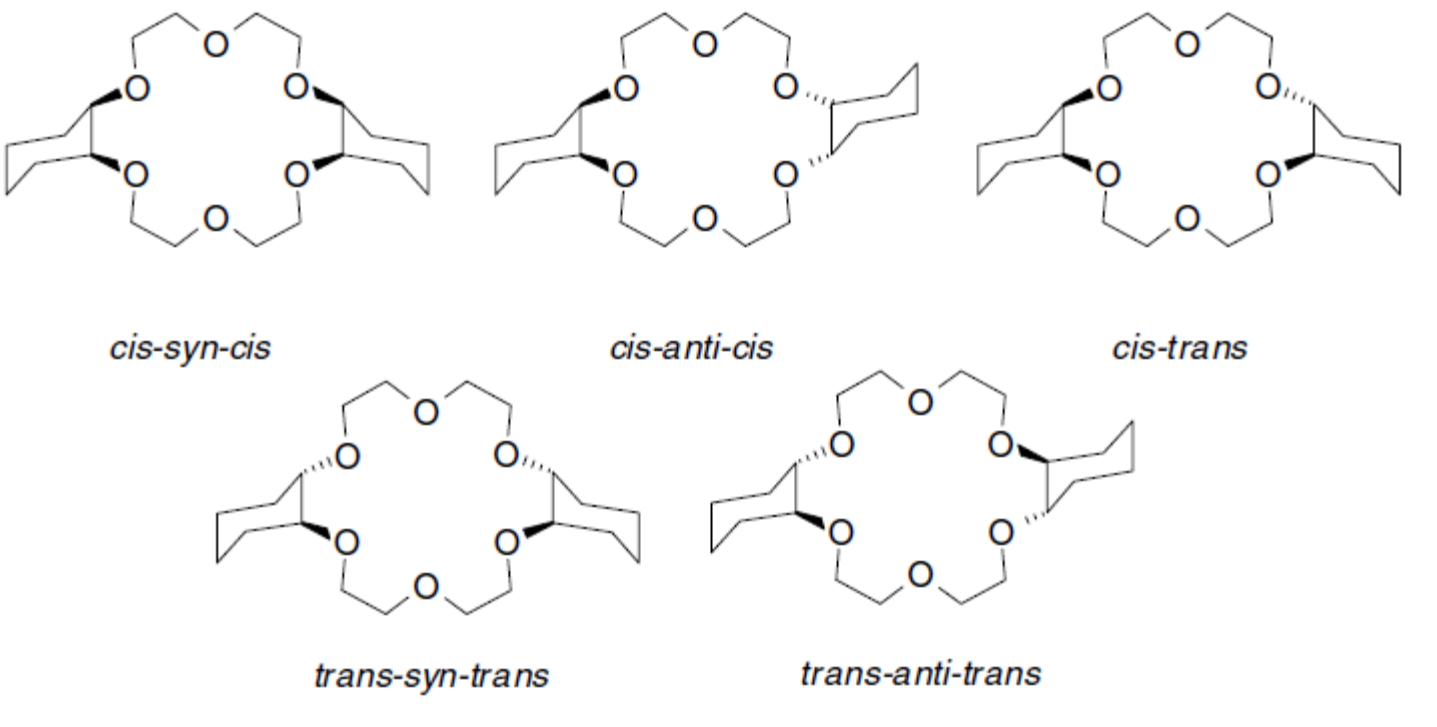
Method (c) led to the original preparation of dibenzo[18]crown-6. In fact, dibenzo[18]crown-6 may be prepared in much better yield (about 80%) *via method (b).*

The method shown in scheme (d) was used by Pedersen only for the preparation of macrocycle.

Method (e) (intramolecular cyclisation) is not a particularly viable one in general terms because of the non-availability of the starting materials and usually poor yields.

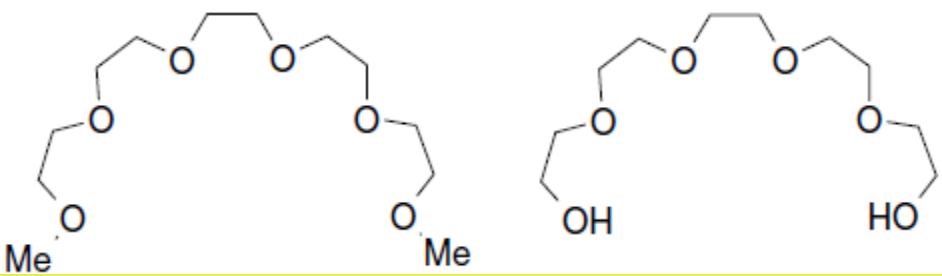


Method (f) is a catalytic reduction to produce saturated cyclohexyl rings from the correspondingarenes. In the case of dibenzo[18]crown-6 this can, in principle, result in up to fi ve isomers of dicyclohexyl[18]crown-6



Podands

Acyclic hosts with pendant binding sites are termed **podands**. *The simplest podands are simply acyclic* analogues of the crown ethers such as pentaethyleneglycol dimethylether analogous to [18]crown-6, or its di-ol analogue.



Podand hosts generally exhibit less cation affinity than their cyclic analogues, as a result of their lack of preorganisation, but they may adopt similar wrapping conformations to the crown ethers in the presence of suitable metal cations, such as the highly charged lanthanoids.

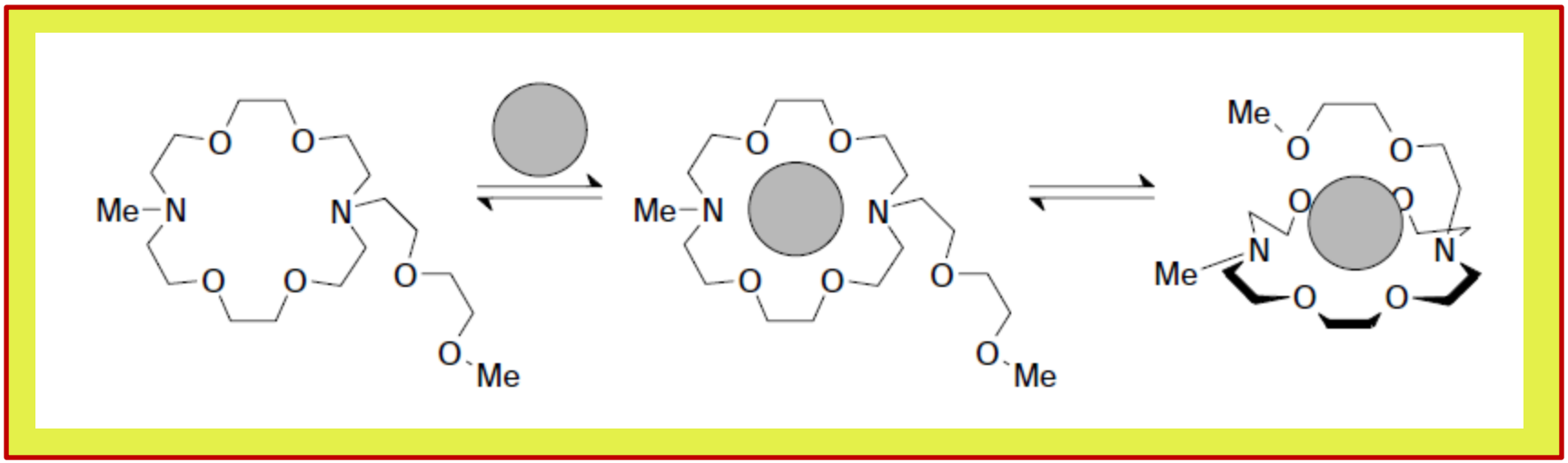
The extra flexibility of podand hosts, however, also allows them to engage in multiple bridging and helical binding modes. Also, the aliphatic chains contribute greatly to the lipophilicity of the compound, hence its membrane transport ability. One of the problems with podands is their high degree of flexibility, allowing them to adopt non-binding open conformations.

If the podand is terminated by a rigid functionality (*e.g. aryl,* ester, amide), binding is enhanced by the extra degree of organisation given to the podand host by the rigidifying endgroup.

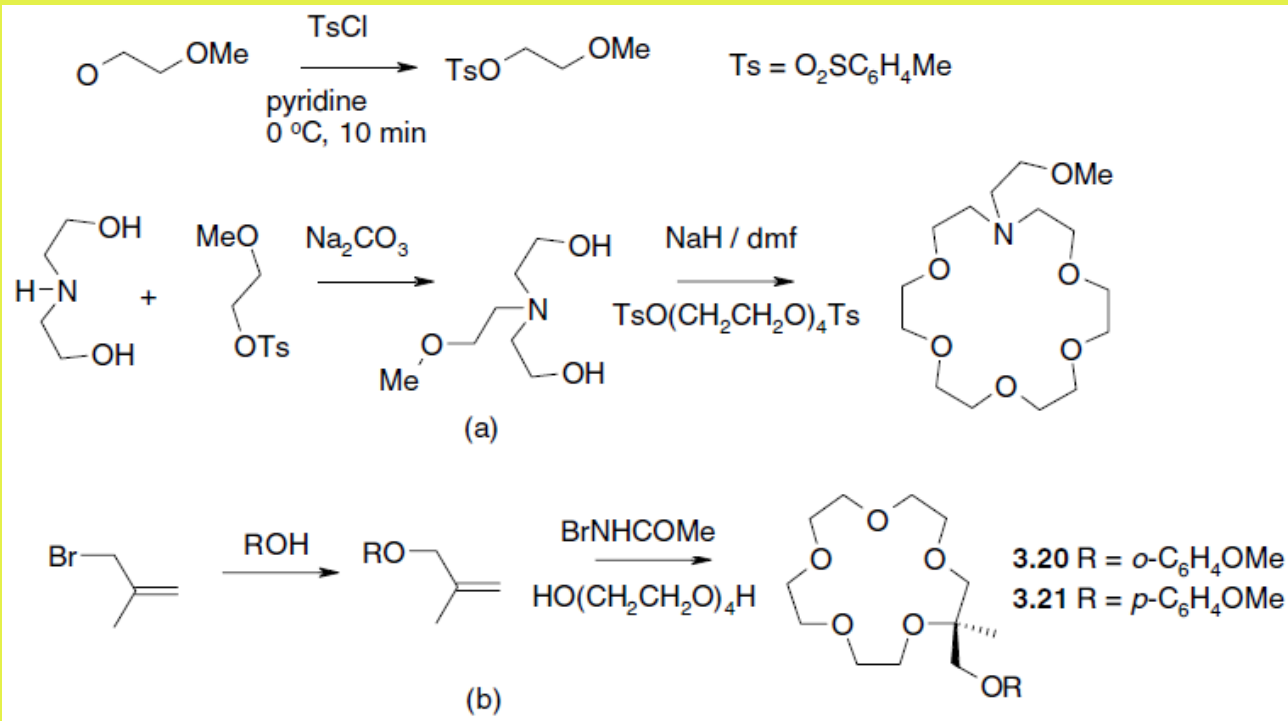
Lariat Ethers

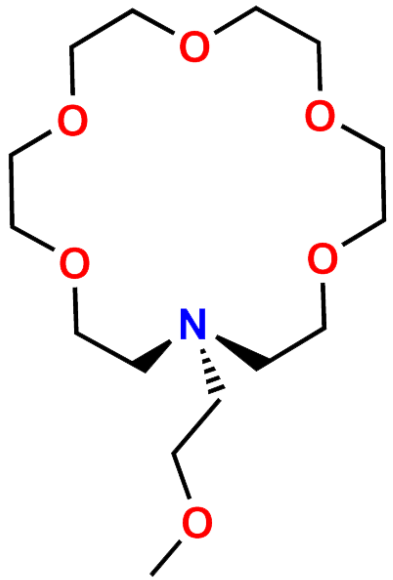
The term '**lariat ether**' refers to a crown ether or similar macrocyclic derivative with one or more accompanying appendages designed to enhance metal cation complexation ability by giving some three-dimensionality to the binding.

The compounds may be regarded as a crown type macrocycle with a podand side-arm. The name comes from the Spanish *la reata, meaning* '**the rope**'. They combine the higher rigidity and preorganisation of macrocyclic compounds with the additional stability and flexibility (which leads to fast cation binding kinetics) of podand complexation.



Synthesis of Lariat Ethers

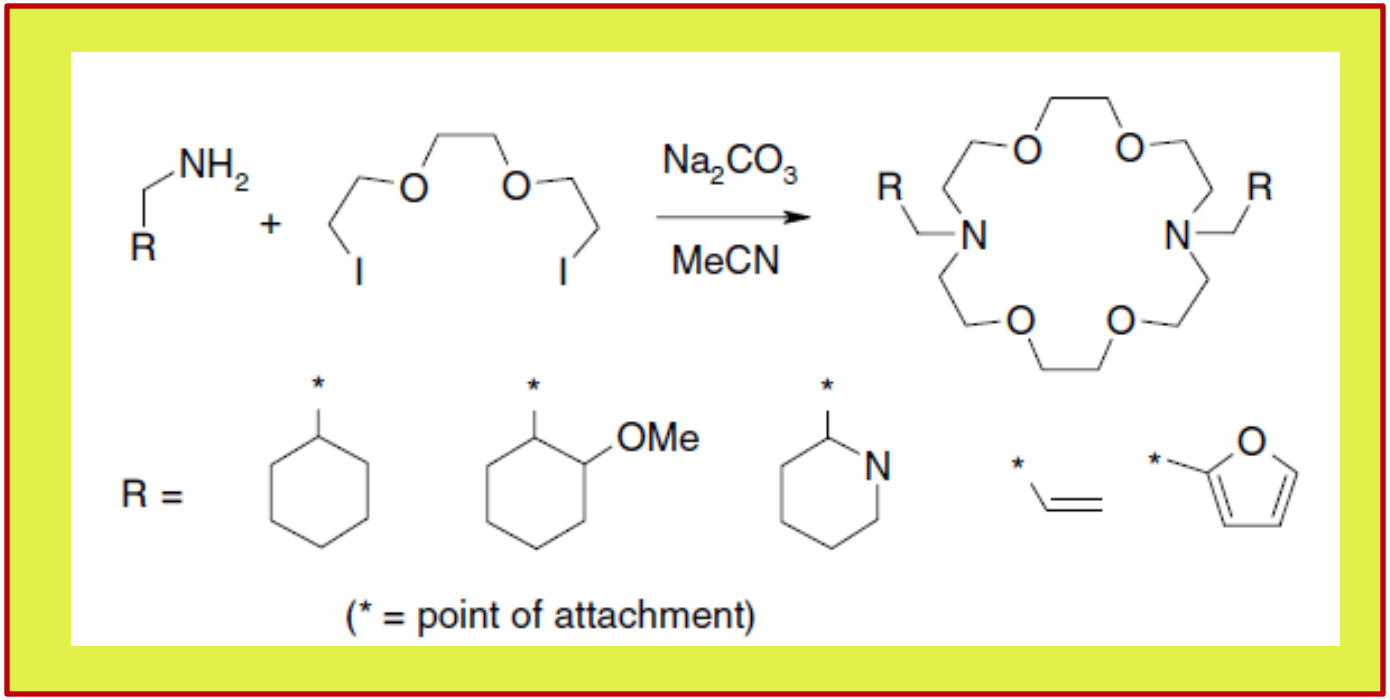




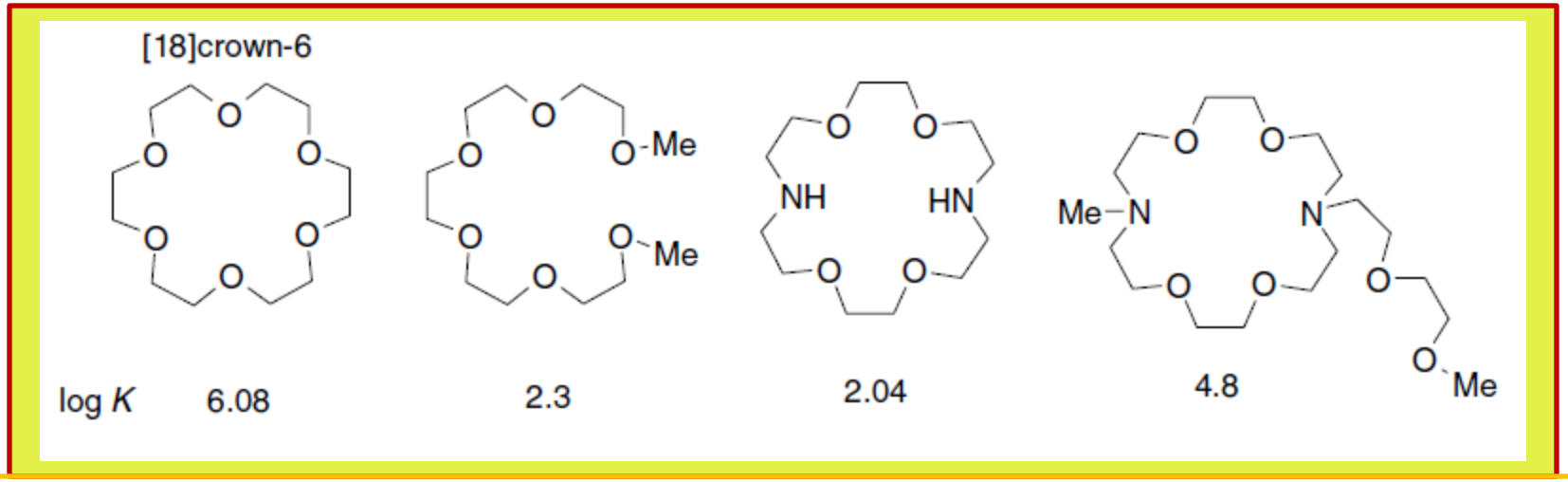
The synthesis proceeds under kinetic control, using the metal ion to organise the reactants. This is referred to as the ***kinetic template effect.***

Bibracchial Lariat Ethers

The lariat ether concept may be readily extended to produce so-called bibracchial lariat ether (BiBLE) hosts, which have two podand side-arms, thus displaying even more three-dimensional binding coverage of the metal ion guest's surface.



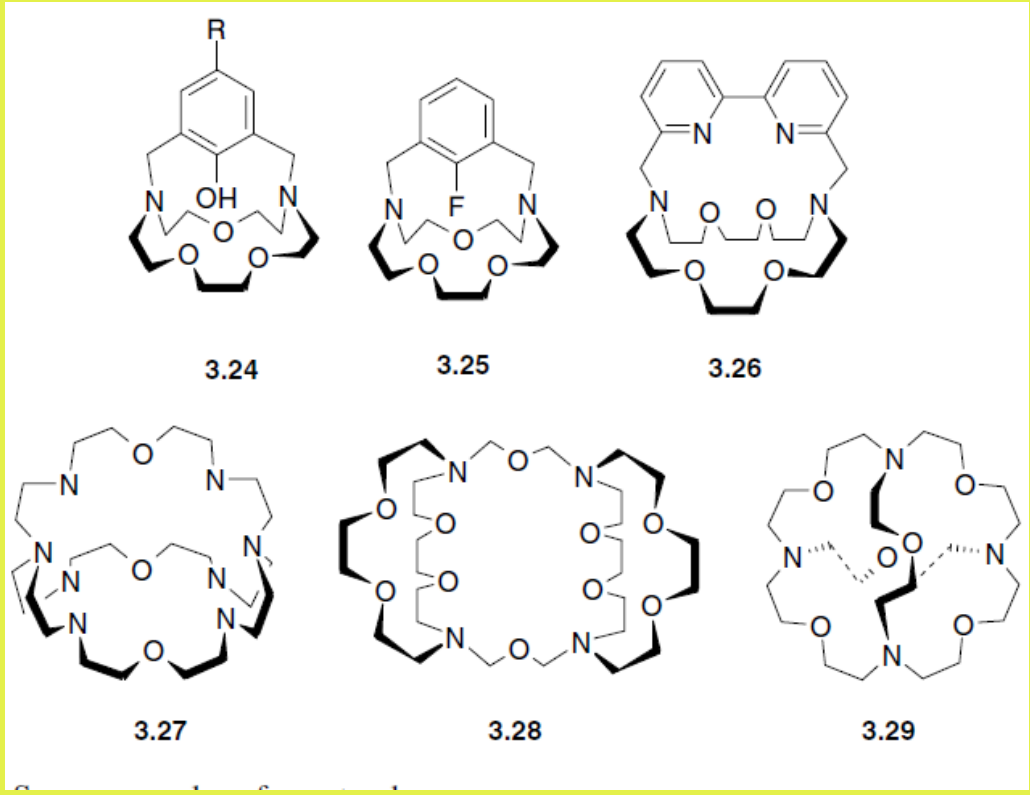
Comparison of Binding Constants

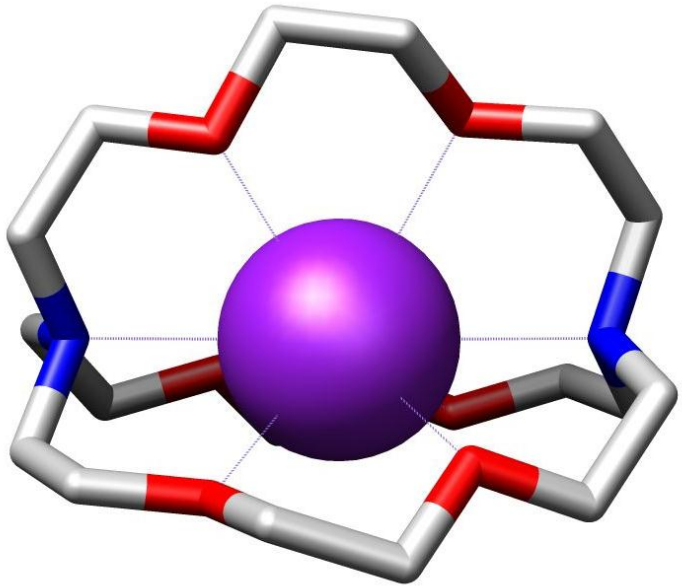


A comparison between the binding ability of some simple podand, crown and lariat ether compounds is shown above. Clearly [18]crown-6 is a much more effective ligand for K^+ than the podand pentaethyleneglycol dimethylether. At first sight, the lariat ether seems to lie somewhat in between the binding ability of the cyclic and acyclic compounds. However, the affinity for K^+ is also regulated by the character of the donor atoms. A more direct comparison between the aza-crowns (crown ethers with some oxygen atoms replaced with NH functionalities) suggests that it is the three-dimensional binding by the lariat ether that is the more effective of the two, although the greater amine basicity in last one also enhances the binding constant.

The Cryptands

Crypt from the Greek *kruptos meaning* ***'hidden'****.* The first and most important member of the series is [2.2.2]cryptand**.** It is based on a similar sized ring to [18]crown-6, this host also exhibits selectivity for K^+ over the other alkali metals. The binding of K^+ by [2.2.2]cryptand in methanol is 10^4 times stronger than its crown analogue. Similarly, [2.2.1]cryptand is selective for Na^+. The key to the dramatically enhanced metal cation binding ability of cryptands over crown ethers is the preorganised, three-dimensional nature of their cavity, which enables spherical recognition of the M ion to take place.



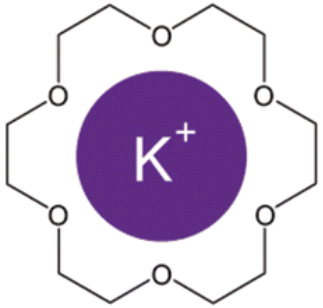


Prof. Rajeev Gupta, Department of Chemistry, University of Delhi (Supramolecular Chemistry Paper No. 101 Section - B)

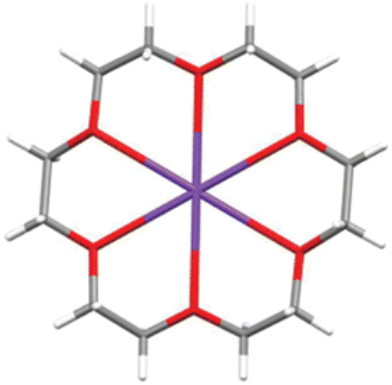
Size Selective Binding of Corands

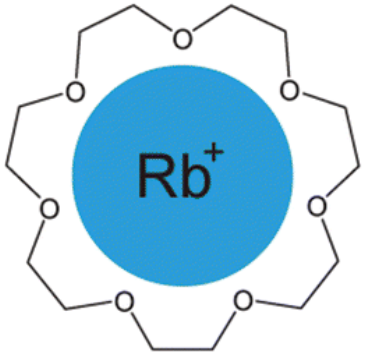
12-Crown-4

15-Crown-5

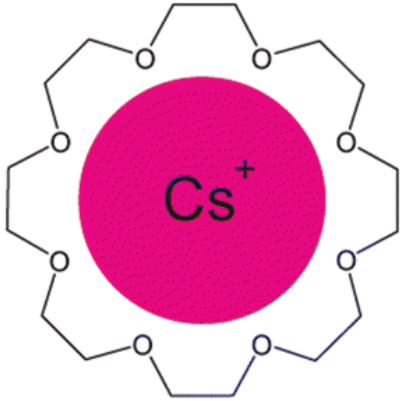


18-Crown-6

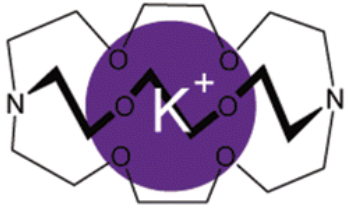




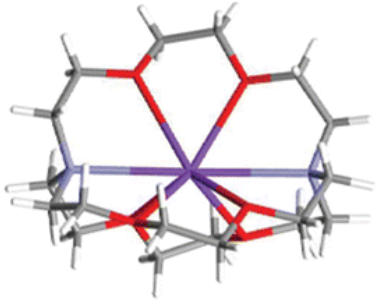
21-Crown-7



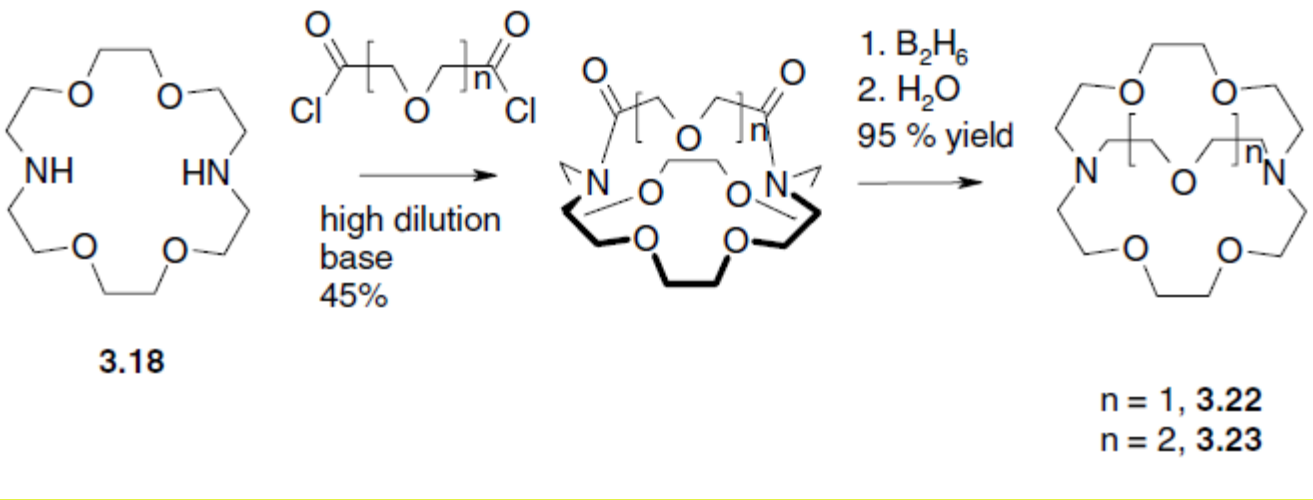
24-Crown-8



Cryptand



High Dilution Synthesis

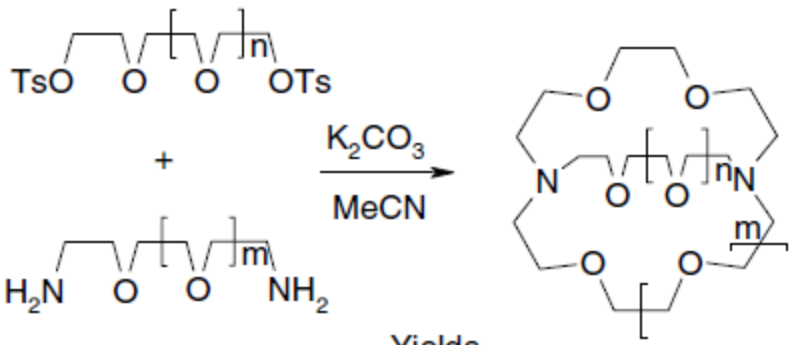


High-dilution syntheses do not readily enable large quantities of material to be prepared, and often involve many steps, particularly the final reductive decarbonylation with diborane. Since the early work of Lehn, a wide variety of synthetic procedures has been developed to prepare an enormous range of cryptands of varying degrees of sophistication, including chiral species and those containing three different bridges. Many of these follow a stepwise approach, which may be summarised as follows:

(i) building up two linear chains possessing suitable reactive groups at each chain end;
(ii) cyclisation reaction of these two chains leading to a corand (crown ether-like
(iii) macrocycle); addition of a third chain to the corand to give a macrobicyclic compound.

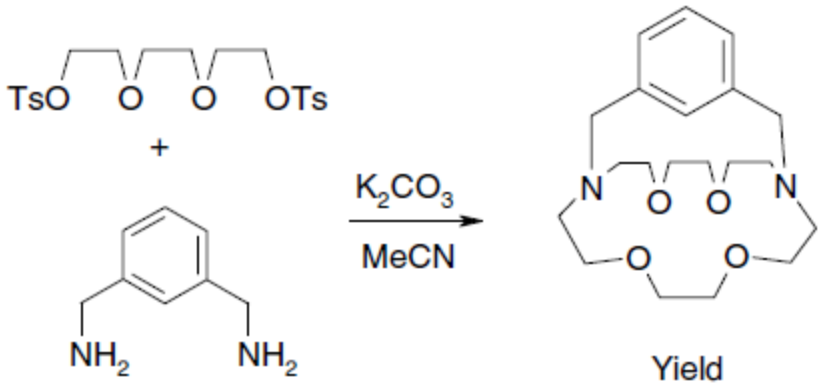
Simple Template Synthesis

Because of the length and tedium of such approaches, much simpler routes, often taking advantage of the template effect have been devised, which can be remarkably effective.



Yields
m = n = 1, 36 %
m = 1, n = 2, 50 %
m = 2, n = 2, 40 %

(a)

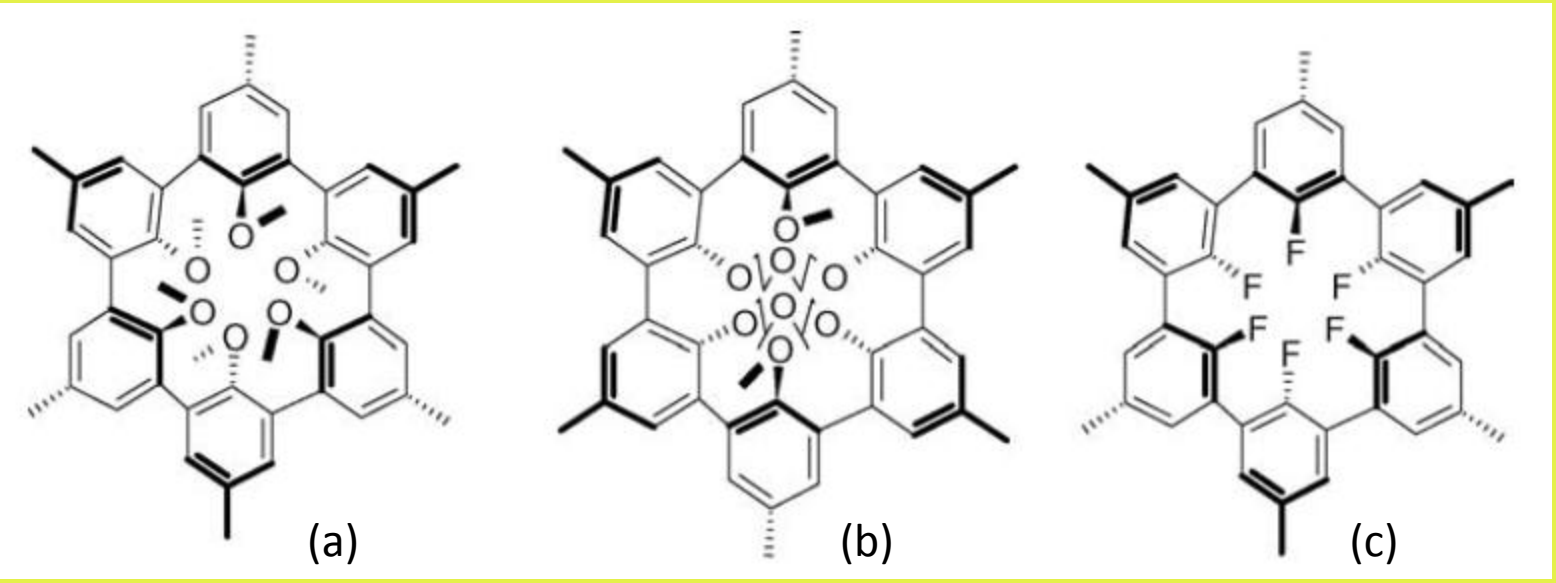


Yield
25 %

(b)

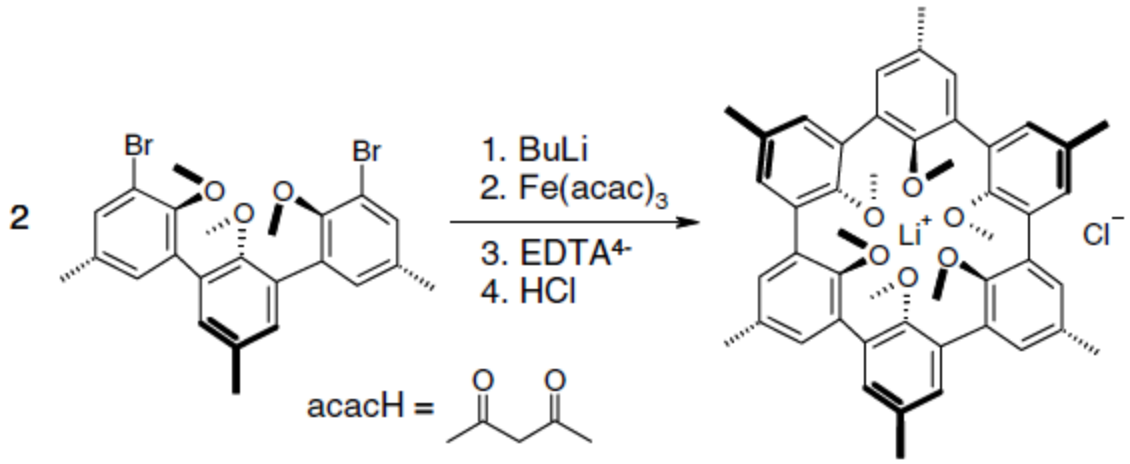
The Spherands

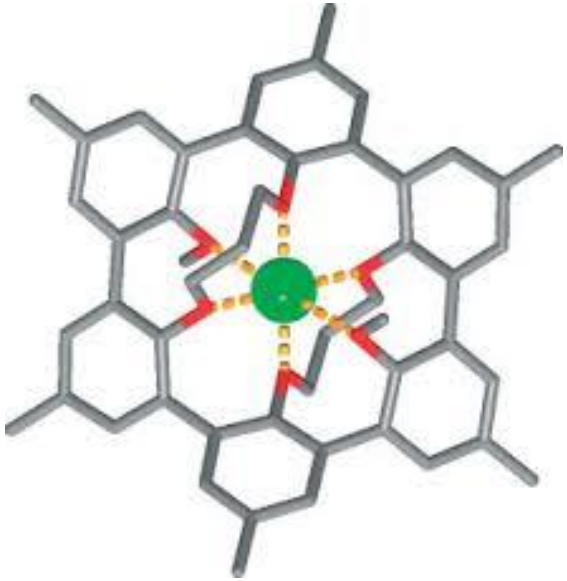
Rigid host which had donor sites that were forced to converge on a central binding pocket even before the addition of a metal cationthen strong binding and excellent selectivities between cations should be observed.



In the case of compound**,** three of the aryl rings are pointing upwards (out of the page) and three downwards. This results in the anisyl oxygen atoms being fixed in a nearly perfect octahedral array, while the p-methyl and anisyl methyl groups present a lipophilic surface to the solvent. This host **(a)** selectively binds small cations such as Li^+ and to a lesser extent, Na^+, in its cavity. Indeed, **(a)** is one of the strongest complexants known for Li^+.

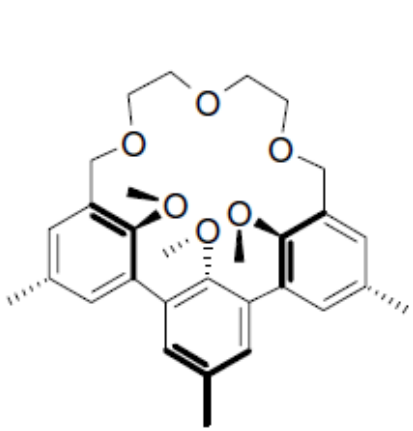
Synthesis of Spherands





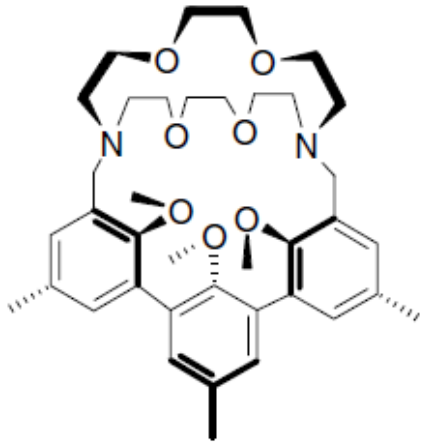
In order to achieve the final cyclisation step in the spherand syntheses, a new synthetic ring-closure procedure was developed (acac=acetylacetonato, $CH(COMe)_2^-$). The aryl lithium compound produced by action of butyl lithium is oxidised by the Fe(III) complex to give an aryl biradical, which then undergoes a template cyclisation about the Li ion

Cross-fertilisation between the crown ethers (more generally, corands), cryptands, spherands and podands has produced an enormous range of hybrid hosts such as cryptaspherands and hemispherands, many exhibiting all the useful features of the parent materials



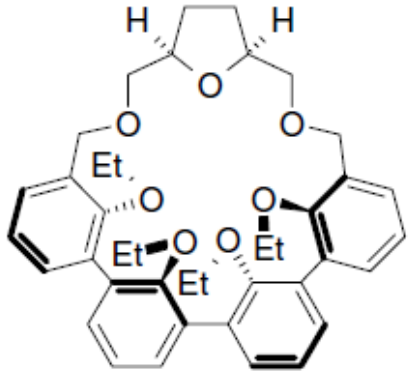
hemispherand

3.37



cryptaspherand

3.38



hemispherand

3.39

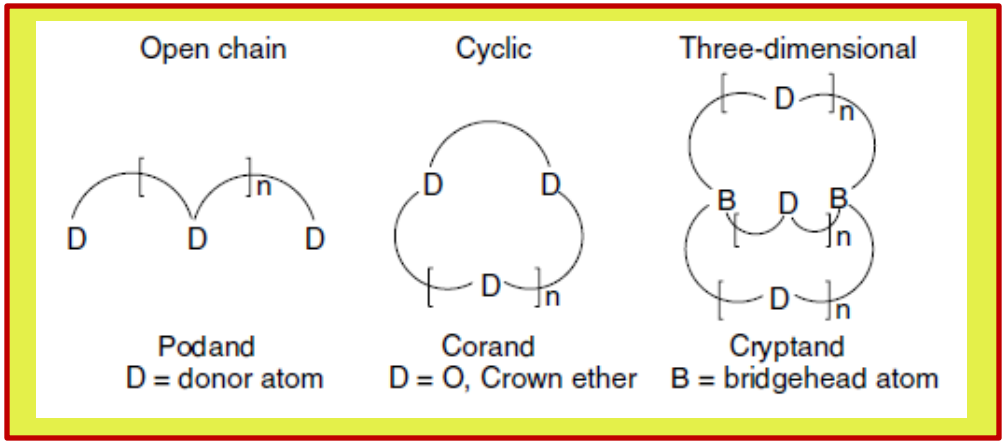
Nomenclature of Cation Binding Macrocycles

❖The first number in the crown name designates the number of atoms in the ring (usually given in square brackets).

❖The second number gives the number of oxygen (or other donor) atoms. Substituents are denoted with a prefix such as benzo-, dicyclohexano- *etc.*

❖For example, dibenzo[18]crown-6 is a crown ether with an 18-membered macrocyclic ring containing six oxygen atoms with two benzo substituents.

A more generalised system was developed by Vögtle and Weber and later modified by Cram in which any monocyclic system such as a the crown ether is termed a corand (originally coronand). Open chain molecules are called podands; bicyclic or oligocyclic systems are termed cryptands; and rigid, p-methylanisole-based systems are given the name spherand.



Selectivity of Cation Complexation

The thermodynamic selectivity of a given host for a particular cation represents the ratio between the host's affinity for a given metal *and other guest cations.* Strong but selective binding is the basis of molecular recognition. Thus a successful host exhibits a strong affinity for one particular guest and a much lower affinity for other cations.

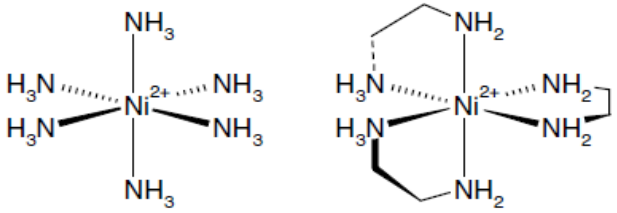
The selectivity is governed by an enormous number of factors, some of the most important of which are listed below:

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

Cooperativity and Chelate Effect

When two or more binding sites (A and B) on a host cooperate in a fashion to bind to a guest the phenomenon is termed as **cooperativity**. If the overall stability of the complex is greater than the sum of the energies of the interaction of the guest with binding groups A and B individually then the result is ***positive cooperativity***. While, if unfavourable steric or electronic effects arising from the linking of A and B together into one host cause the overall binding free energy for the complex to be less than the sum of its parts then the phenomenon is termed ***negative cooperativity***. Binding site cooperativity in a supramolecular host-guest interaction is simply a generalisation of the ***chelate effect***.

$$[Ni(NH_3)_6]^{2+} + 3NH_2CH_2CH_2NH_2 \xrightarrow{\log K = 8.76} [Ni(NH_2CH_2CH_2NH_2)_3]^{2+} + 6NH_3$$

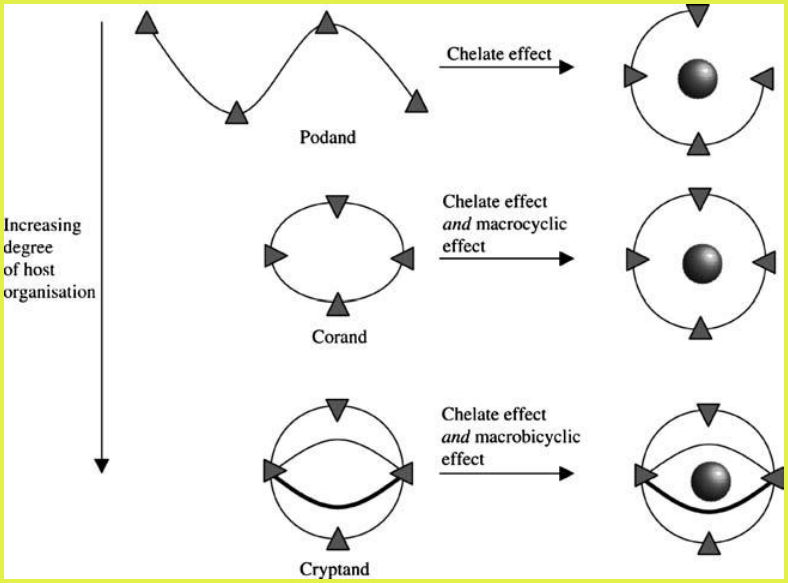


$[Ni(NH_3)_6]^{2+}$ $[Ni(en)_3]^{2+}$

The special stability of chelate complexes in solution may be traced to both thermodynamic and kinetic effects. Thermodynamically, reaction of a metal with a chelating ligand results in an increase of the number of free particles (four on the left-hand side of above equation, seven on the right) and hence a favourable entropy contribution (ΔS_o) *to the overall free energy of the reaction* (ΔG_o), *given by* $\Delta G_o \ \Delta H_o - T\Delta S_o$.

The hosts in these species are usually **macrocyclic** (large ring) ligands that chelate their guests, again *via a number of binding sites. Such compounds are stabilised additionally* by what is traditionally termed the *macrocyclic effect.* The macrocyclic effect makes cyclic hosts such as *corands (e.g. crown* ethers) up to a factor of 104 times more stable than closely related acyclic *podands with the same type* of binding sites. The enthalpic term arises from the fact that macrocyclic hosts are frequently less strongly solvated than their acyclic analogues.

This is because they simply present less solvent-accessible surface area. As a result there are fewer solvent–ligand bonds to break than in the extended, acyclic case. Entropically, macrocycles are less conformationally fl exible and so lose fewer degrees of freedom upon complexation. In general, the relative importance of the entropic and enthaplic terms varies according to the system studied although the enthalpy is frequently dominant as a result of additional factors such as lone pair repulsions.



Prof. Rajeev Gupta, Department of Chemistry, University of Delhi (Supramolecular Chemistry Paper No. 101 Section - B)

The Template Effect

Exchanging K_2CO_3 for an organic base such as triethylamine in the synthesis of [18]crown-6 does result in the formation of predominantly polymeric product.

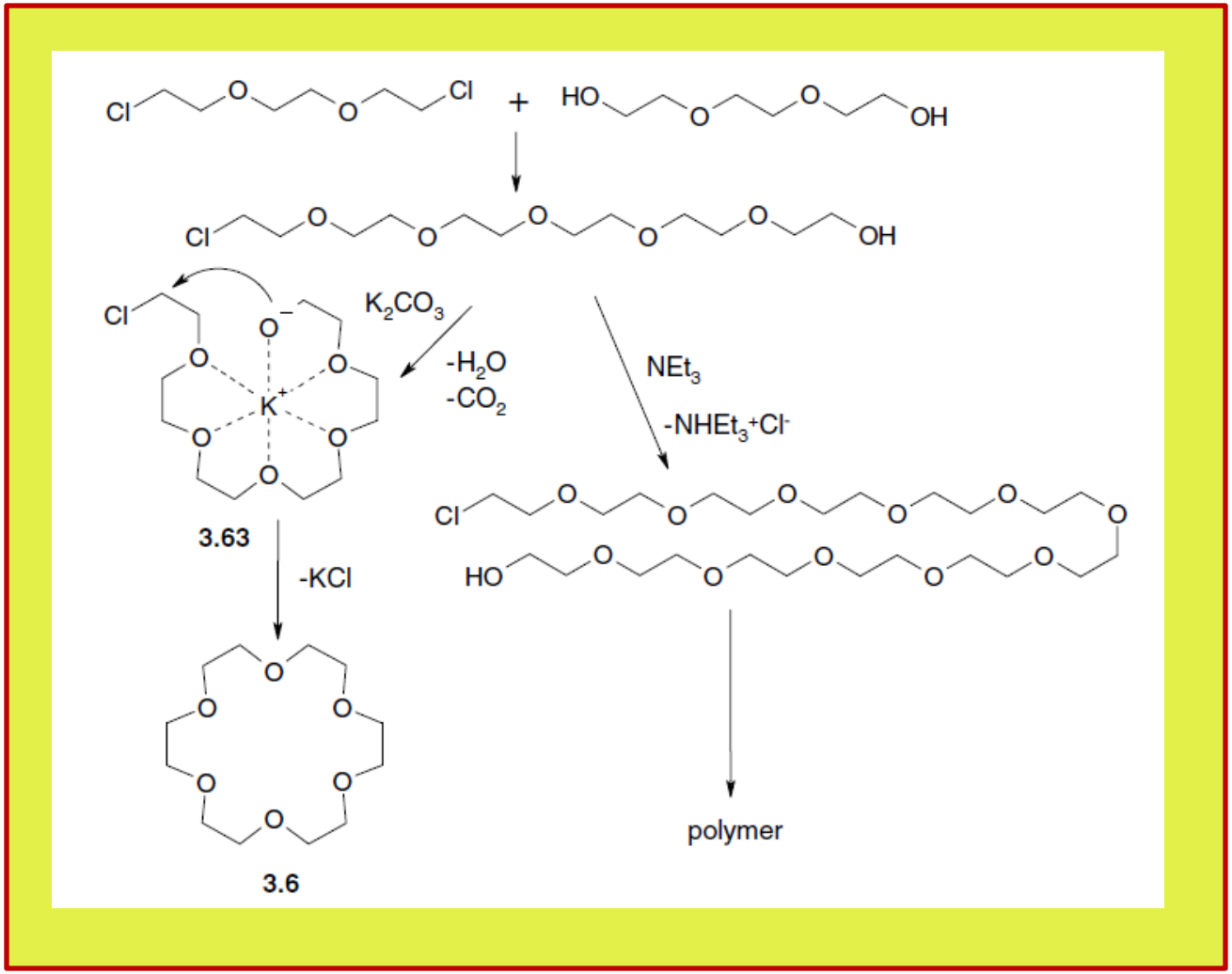
This crucial difference between the behaviour of the two classes of base lies in the ability of the K ion to organise the reactants about itself to give a reaction intermediate that is preorganised to form a cyclic product.

The functional groups —OH and —Cl are brought into close proximity to one another by coordination to the potassium cation (*via the chelate effect)* and cyclise readily.

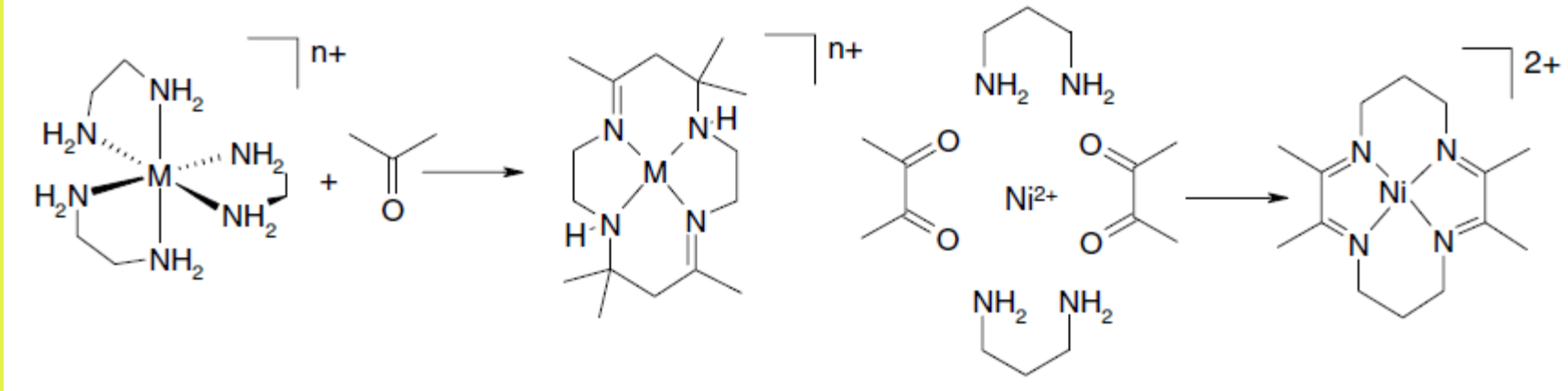
The organic base is unable to bring about the formation of this intermediate and the reaction takes an intermolecular, rather than intramolecular, pathway.

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.*

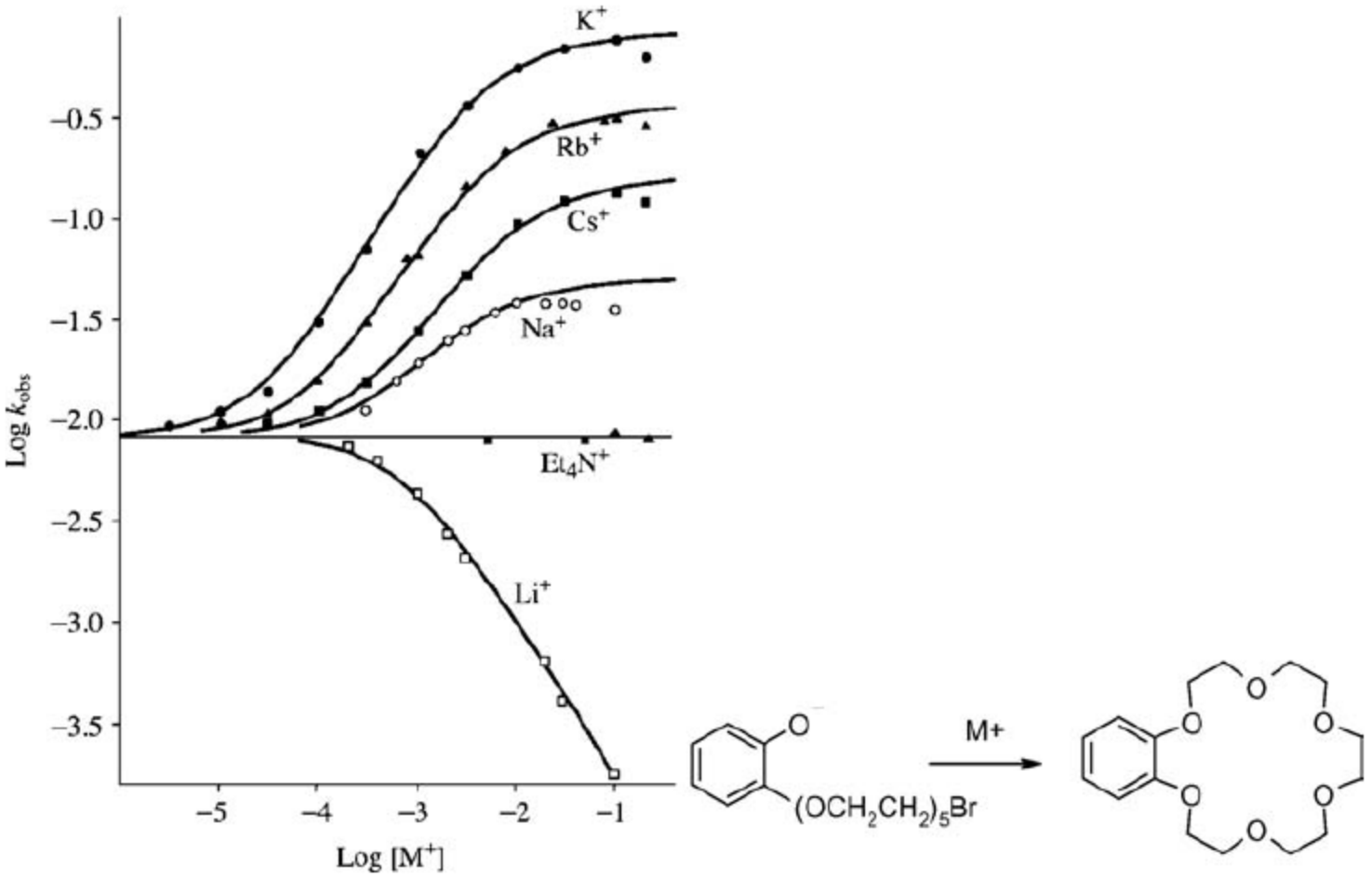
In fact, this is a form of catalysis in which the metal cation acts *to* stabilise the cyclic intermediate, thus dramatically increasing the rate of formation of the cyclic product. The template effect is thus a kinetic effect and the macrocycle is a kinetic product.



In discussing the kinetic template effect, it is important to distinguish it from another effect termed the ***thermodynamic template effect***. The kinetic template effect involves the actual formation of ligands about the metal centre. On the other hand, the thermodynamic template effect concerns the ability of a metal cation to pick out a ligand complementary to it from an equilibrating mixture of products, thus driving the equilibrium over to the product thus stabilized. One of the first examples of the thermodynamic template effect concerns the condensation of acetone with *tris(ethylenediamine)nickel(II) salts.*



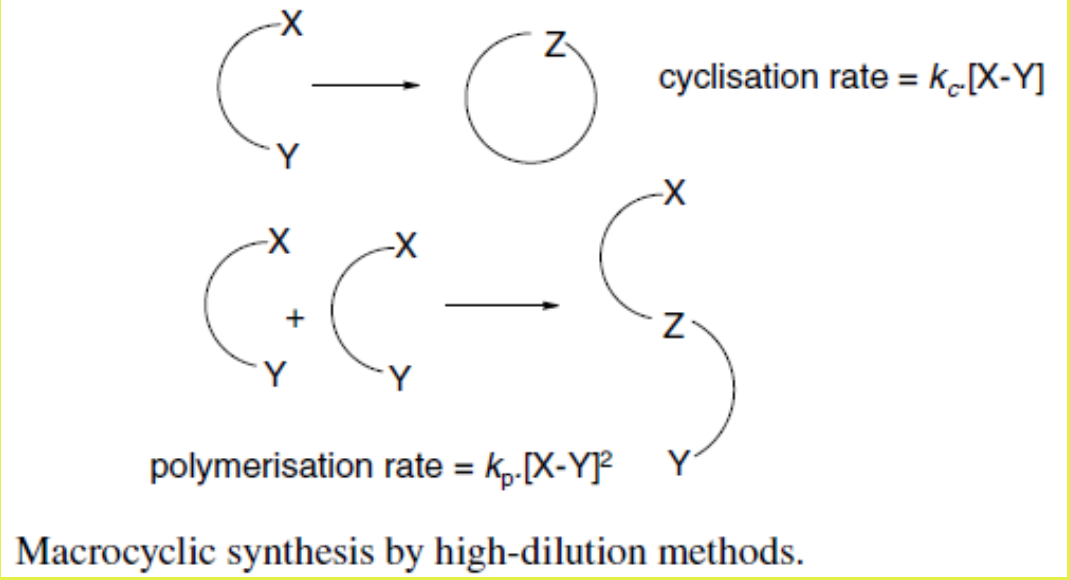
Thermodynamic template synthesis of two tetrazamacrocycles



Kinetic studies of the template effects of metal ions on cyclisation to form benzo[18]crown-6

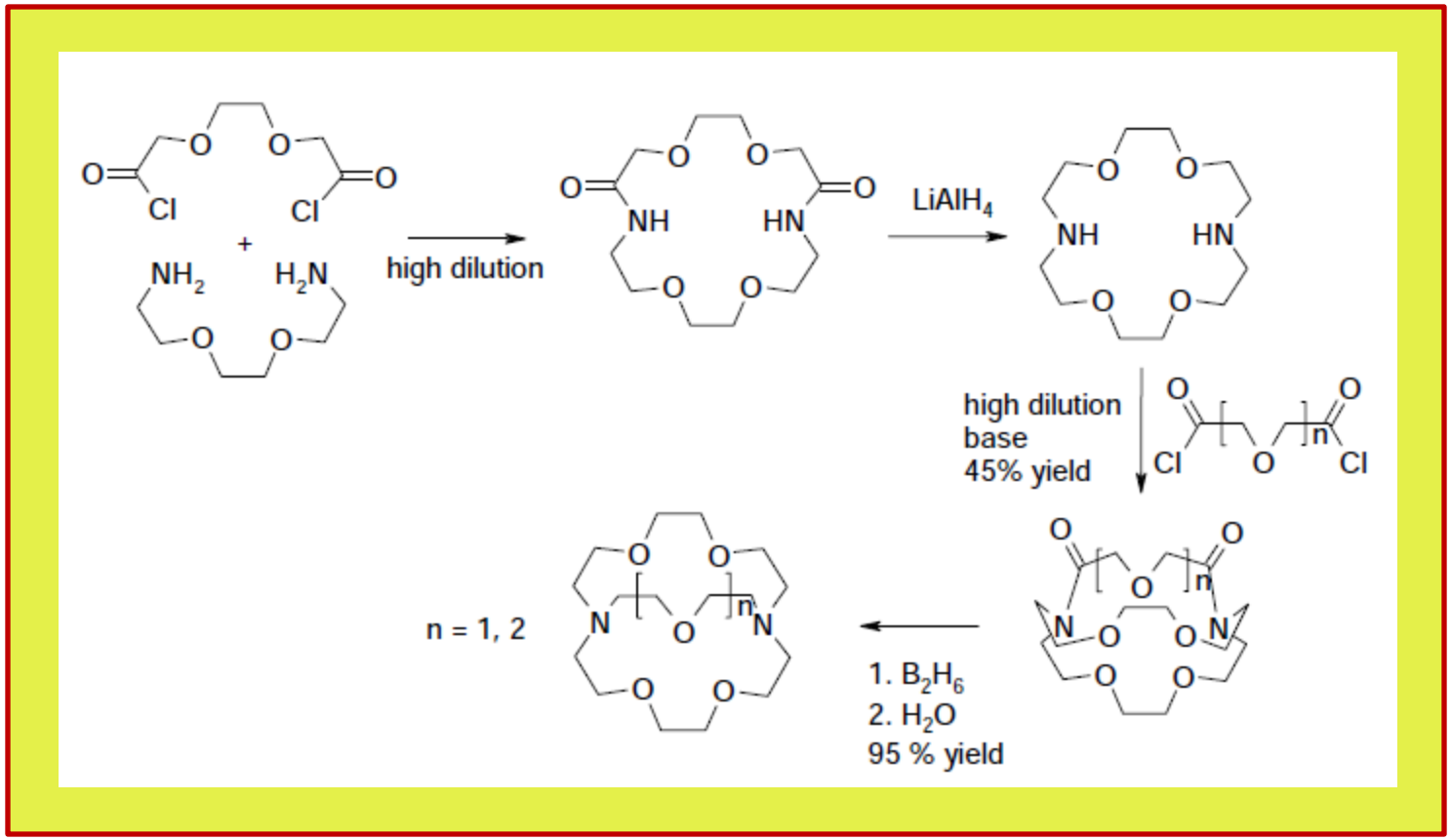
High Dilution Synthesis

In the absence of a suitable template, the synthesis of macrocyclic ligands is much more difficult and high-dilution conditions must be employed. By '**high dilution**', we mean that small quantities of reactants are used in a large volume of solvent. A typical apparatus for carrying out this kind of procedure is shown in Figure 3.46. Reactants are added dropwise at a very slow rate from each of the dropping reservoirs (this may be done automatically with an electronically controlled syringe pump) and mixed in the large round-bottomed flask at the bottom.

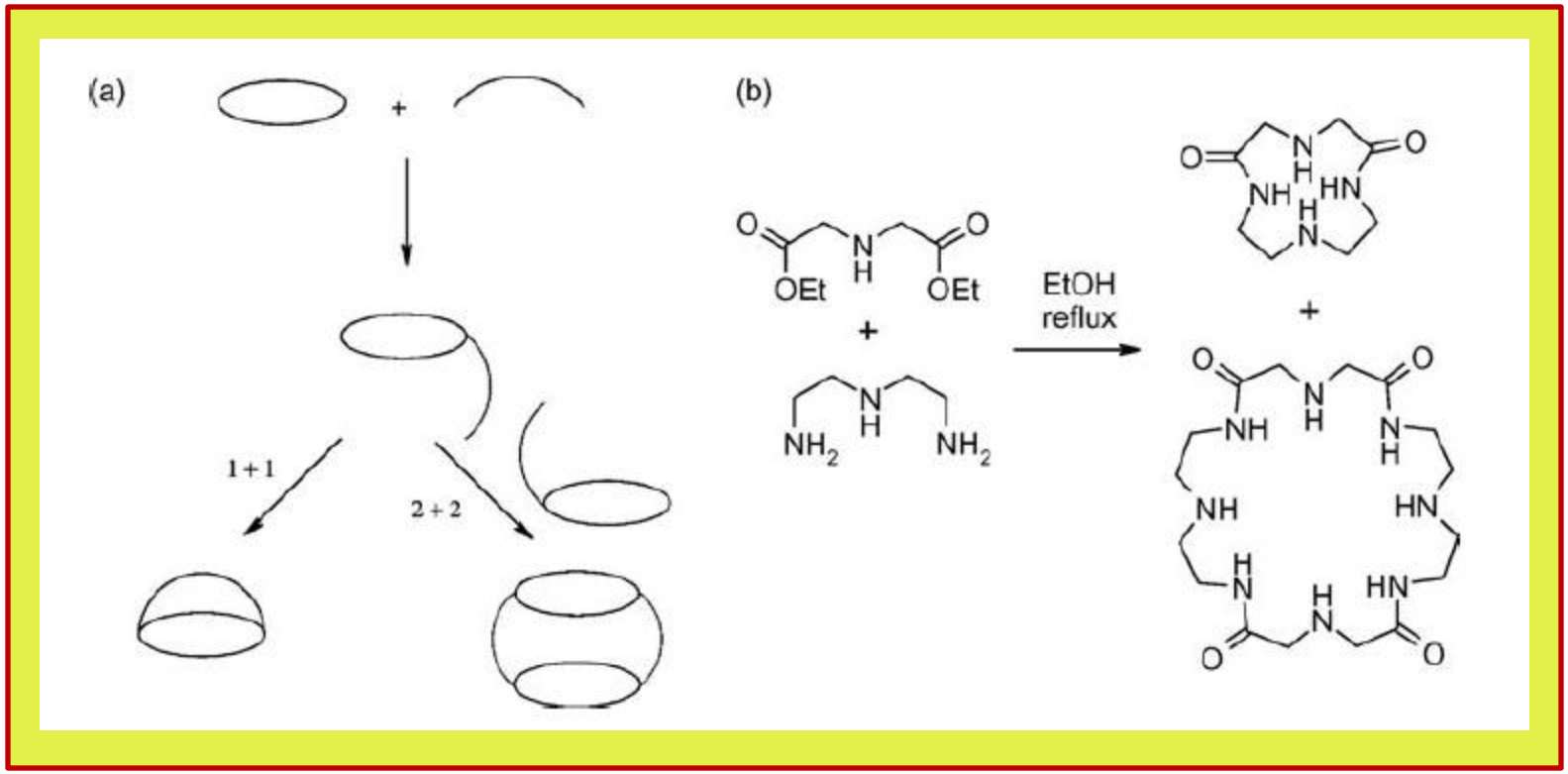


Macrocyclic synthesis by high-dilution methods.

High-dilution conditions have been used in a large number of macrocyclic and macrobicyclic syntheses, including many of the original cryptand preparations. In particular, the reaction of an amine with an acid chloride occurs suffi ciently rapidly as a result of the electron withdrawing and resonance stabilisation effect of the carbonyl groups. Its use in the high-dilution synthesis of a simple azacrown is shown below.

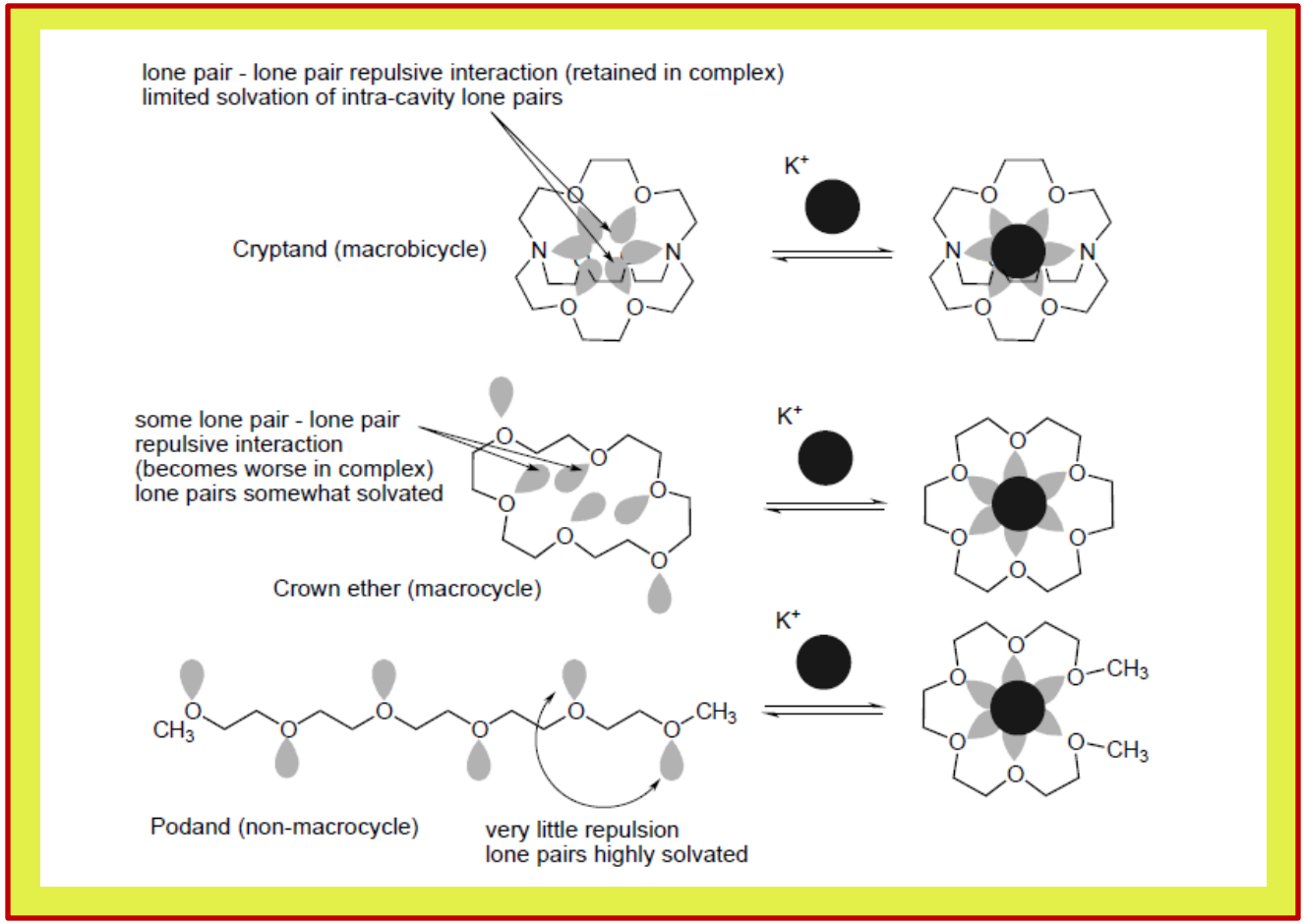


A wide variety of particularly interesting cryptands, especially containing larger cavities, have been synthesised by combined intra- and intermolecular reactions. The most common of these is the [2+2] cyclococondensation reaction in crown ether or cryptand synthesis, in which, often by accident, two pairs of reactants come together to make a macrobicycle or macrotricycle instead of a [1+1] reaction (a). Generally [2+2] cyclococondensation reactions result from situations in which the conditions of the reaction (rate and concentration) are balanced between polymerisation and cyclisation, or in circumstances where the [1+1] cyclisation product is sterically strained or otherwise disfavoured. An example (b) is the simultaneous formation of tetraoxo[24]ane-N_8 along with the monomer dioxo[12]ane-N_4



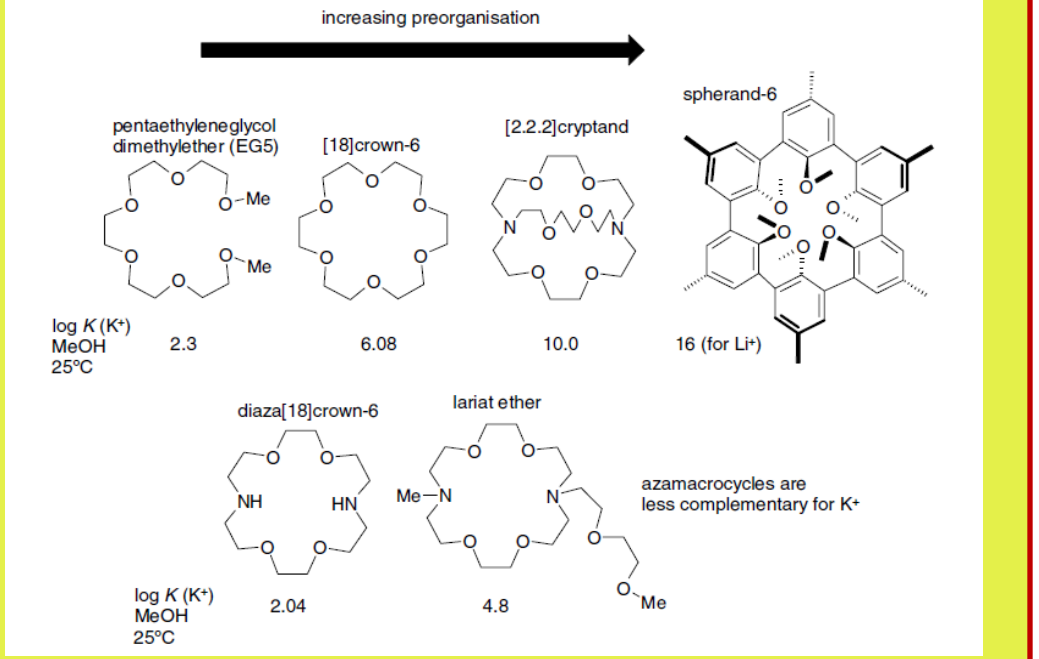
Preorganisation

If a host molecule does not undergo a significant conformational change upon guest binding, it is ***preorganised***. *Host* ***preorganisation*** is a key concept because it represents a major enhancement to the overall free energy of guest complexation.



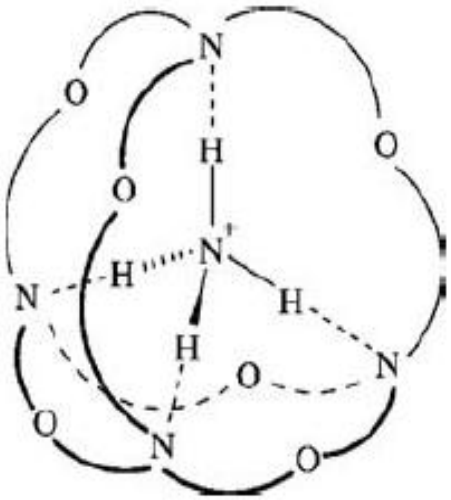
Complementarity

In addition to the degree of host preorganisation, the other principal factor in determining the affinity of a host for a guest is ***complementarity***. In order to bind, a host must have binding sites that are of the correct electronic character (polarity, hydrogen bond donor/acceptor ability, hardness or softness *etc.) to* complement those of the guest. Furthermore, those binding sites must be spaced out on the host in such a way as to make it possible for them to interact with the guest in the binding conformation of the host molecule. If a host fulfi ls these criteria, it is said to be *complementary.* The principle of ***complementarity*** has been summed up by Donald Cram: 'To complex, hosts must have binding sites which cooperatively contact and attract binding sites of guests without generating strong nonbonded repulsions.'



Complexation of Organic Cations

Non-metal cations can also interact with corands and cryptands as in the tetrahedral recognition of the ammonium cation (NH_4) by the 'soccer ball' cryptand**.** While this recognition only occurs *via hydrogen bonding* (N—H … N type), the effect on the ammonium ion is such as to increase its pKa value by six units, thus the cryptate is a million times less likely to deprotonate than its uncomplexed analogue.



Tetrahedral recognition of NH_4^+ by the 'soccer ball' cryptand

Binding of Ammonium Cations by Corands

The binding of ammonium and alkyl ammonium cations by [18]crown-6 and C-backbone substituted derivatives proceeds *via three N—H … O hydrogen bonds to give a perching complex, although* [18]crown-6 binds K^+ more strongly than NH^{4+}, a reflection of the relatively hard character of the ether oxygen atoms. The analogous triaza corand [18]ane-O_3N_3 and it trimethyl analogue form a sterically nearly identical triple array of N—H … N hydrogen bonds and is selective for alkyl ammonium ions over K^+, although this may be a reflection of the decrease in K^+ affinity as much as increase in affinity for the ammonium species.

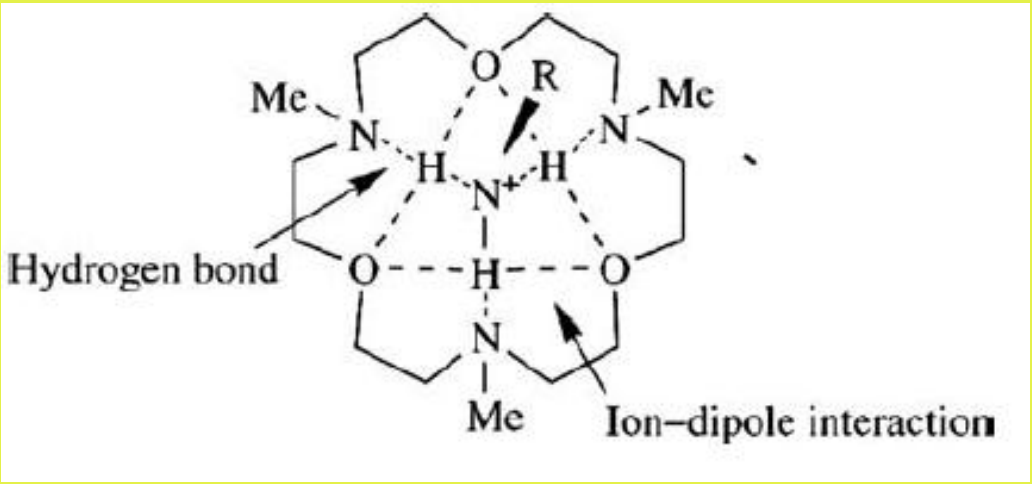


Table given below shows the complexation free energies for various ammonium ions with three corand receptors. It is immediately apparent that NH^{4+} is bound more strongly than either of its alkylated analogues, and methylammonium is bound more strongly than *t-butylammonium, with a particularly* large difference between NH^{4+} and $CH_3NH_3^+$ complexes of 3.95 and 3.96 (10 kJ mol1).

Table Complexation free energies for corand receptors with ammonium ions.

	$-\Delta G^\circ$ (kJ mol^{-1})		
Host	NH_4^+	$CH_3NH_3^+$	$(CH_3)_3CNH_3^+$
3.94	43.9	37.7	34.7
3.95	39.7	31.4	28.9
3.96	37.2	28.9	26.8

This difference suggests that steric effects may be important in all hosts. This low affi nity is attributed to unfavourable steric interactions between the methyl groups of the host with those of the guest.