

CHEMISTRY

THEORY PAPER: Theoretical organic chemistry-II

(as per Model CBSGS curriculum)

M.Sc. (Prog.) Semester IV

Supramolecular chemistry

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TITLE:	Supramolecular Chemistry
Key words for Search:	Crown ethers, cryptands, cyclophanes, calixarenes, rotaxanes and cyclodextrins.

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Suggested Readings:

- ✚ Supramolecular Chemistry; Concepts and Perspectives, J. M. Lehn, VCH.
- ✚ Crown ethers and analogous compounds, M. Hiraoka, Elsevier, 1992. 30.
- ✚ Large ring compounds, J.A.Semlyen, Wiley-VCH, 1997. 31
- ✚ Bioorganic, Bioinorganic and Supramolecular chemistry, P.S. Kalsi and J.P. Kalsi. New Age International Publishers

Web-links:**Activities:**

- ✚ Tell your students to find structures of crown ethers, cryptands, cyclophanes, calixarenes, rotaxanes and cyclodextrin.

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SYLLABI OF THIS MODULE:**Supramolecular Chemistry**

- 2.3 Structures and properties of crown ethers, cryptands, cyclophanes, calixarenes, rotaxanes and cyclodextrins. Synthesis of crown ethers, cryptands and calixarenes.

Learning outcomes:

Upon completion of this course, student will be able to

1. Explain the structures of crown ethers, cryptands, cyclophanes, calixarenes, rotaxanes and cyclodextrins.
2. Explain the properties of crown ethers, cryptands, cyclophanes, calixarenes, rotaxanes and cyclodextrins.

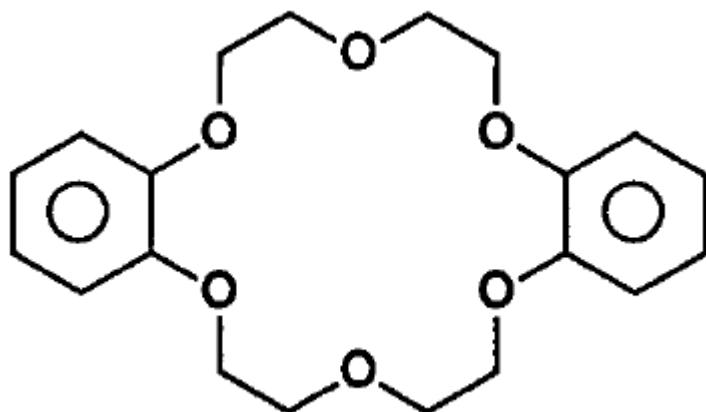


Introduction:

Crown Ether: Structure, properties and Synthesis

- Discovered by Pederson: New field of chemistry
- First identified crown ether dibenzo-18-crown-6 was not the target synthesis but incidence and unexpected byproduct with 0.4% yield
- During preparation of bis[2-(o-hydroxyphenoxy)ethyl] from 1-butanol bis(2-chloroethyl) ether and sodium salt of 2-(o-hydroxyphenoxy)tetrahydropyran contaminated with some catechol.

Structure: cyclic polyethers derived from repeating —OCH₂CH₂—units

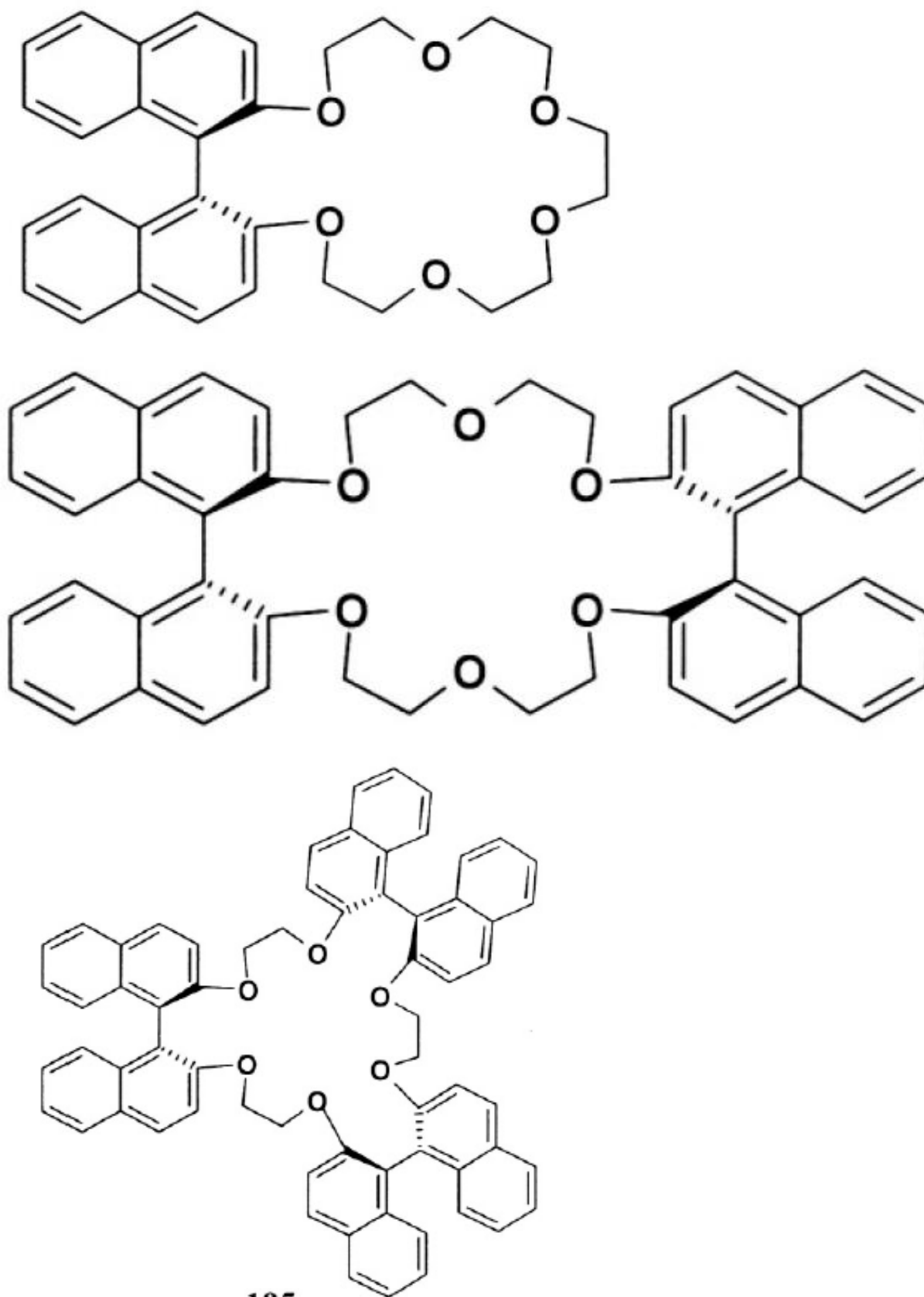


- The first oral announcement of the discovery of crown ethers and their unusual property of complexing alkali and alkaline earth metal salts was made at the Xth International Conference on Coordination Chemistry in Nikko, Japan, on September 15, 1967.
- Subsequently, the first short communication followed by the detailed report consists of 20 pages were published in the Journal of the American Chemical Society before the end of 1967.
- Furthermore, Pedersen reported the discovery of a series complex crystals and novel crown compounds, including macrocyclic polyether sulphides containing sulphur atoms in the ring structure.
- Pedersen named these macrocyclic polyethers with specific characteristics "crown ethers", because of their chemical structure as well as the fact that the shape of the complexes resembled a crown on a metal ion.

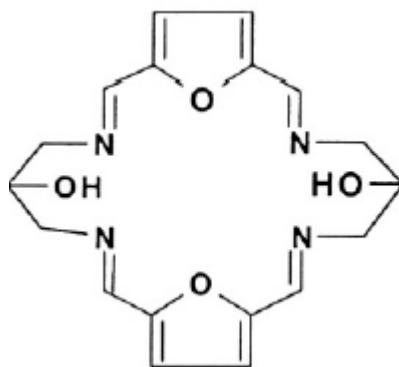
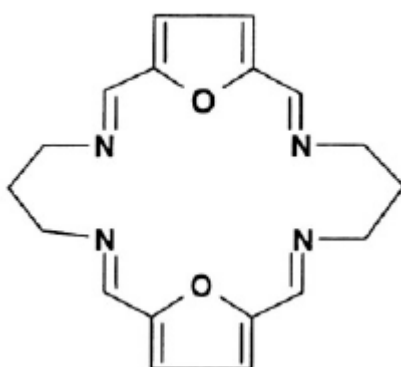
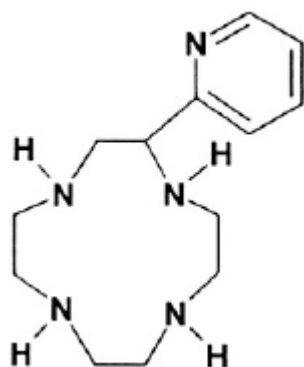
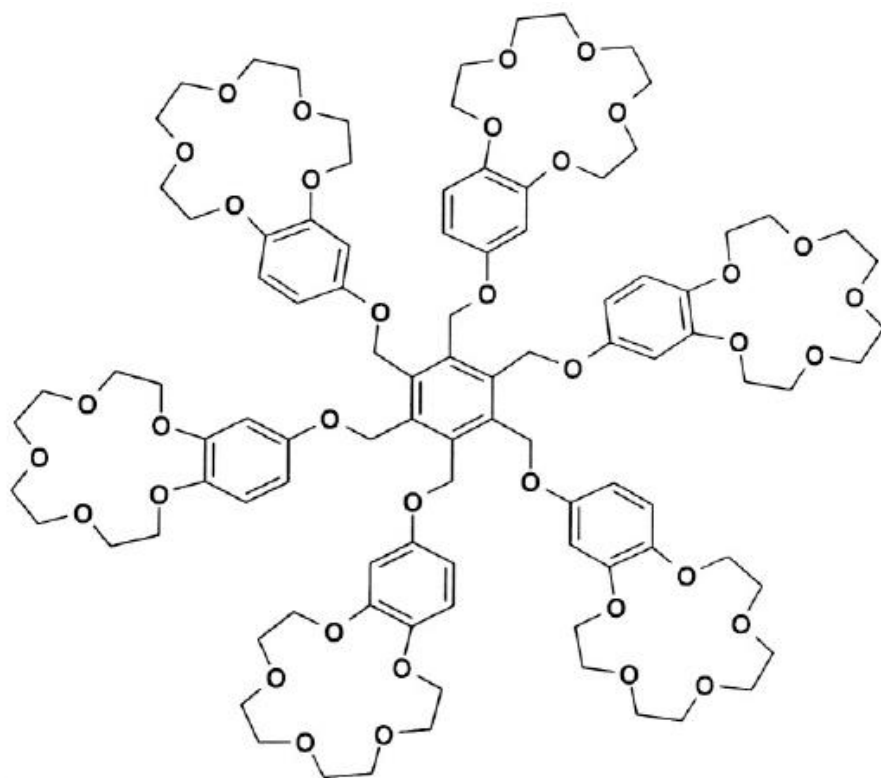
Classifications of crown ethers:

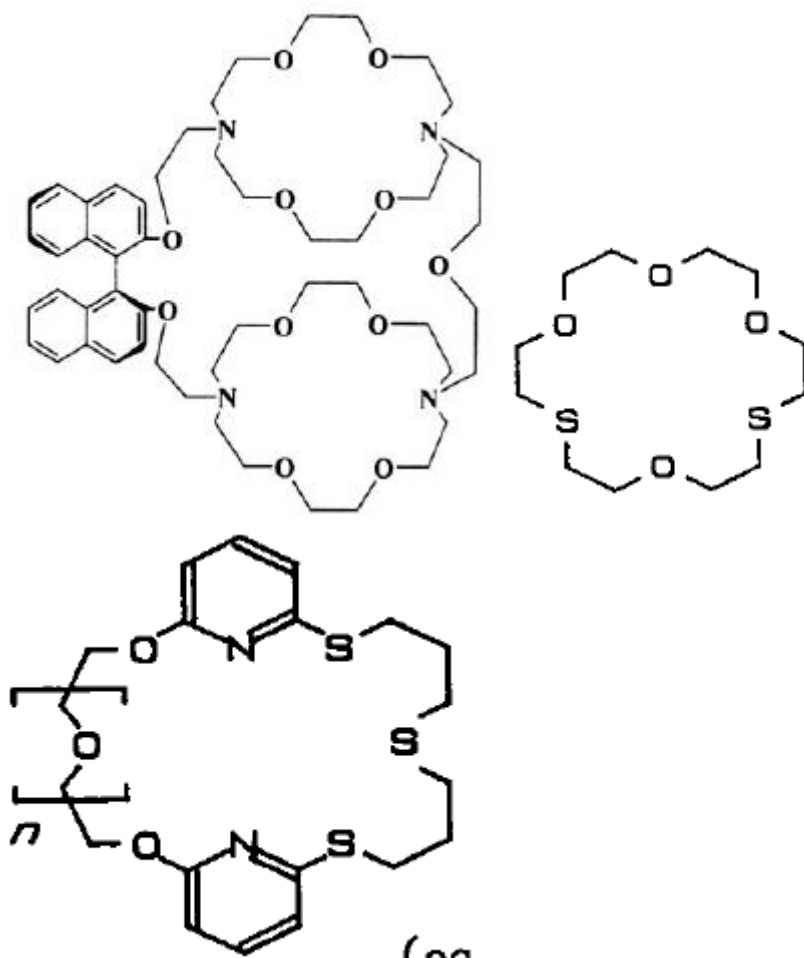
- Crown ethers are generally described as the macrocyclic compounds with hetero atoms such as O, N, S, P, or Se as the donor atoms in their ring structures.
- Sometimes crown ether termed multidentate macrocyclic compounds" or "macroheterocycles".
- Polyethers bearing oxygen atoms as the donor atoms are termed "crown ethers".
- Cyclic amino ethers in which N (NH, NR) replaces some of O donor atoms of a crown ether are known as "azacrown ethers"
- Cyclic polyether sulphides in which sulphur replaces some of the O donors are called "thiacrown ethers".
- Macrocyclic compounds with three kinds of donor atoms, O, N, and S, are called "azathiacrown ethers".
- Macrocyclic polyamines bearing only N atoms as donors are termed "azacrowns"

- Macrocyclic polysulphides bearing only S atoms as donors are labelled "thiacrowns".



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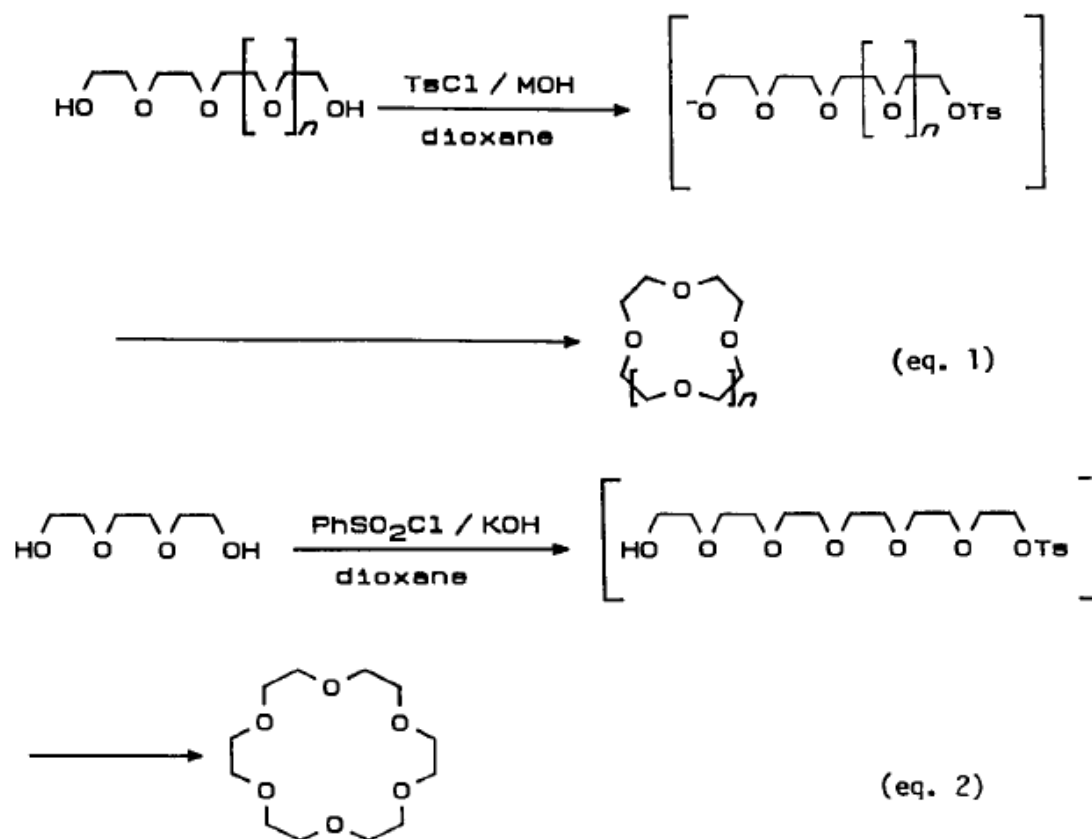
SYNTHESES OF CROWN COMPOUNDS

- Pederson, Cram and Lehn contributed enormously towards synthesis of crown compounds.
- Developed many novel macrocyclic host compounds and have clarified the relationship between structure and complexation properties.
- These findings have been systematized as the concept of host-guest chemistry.

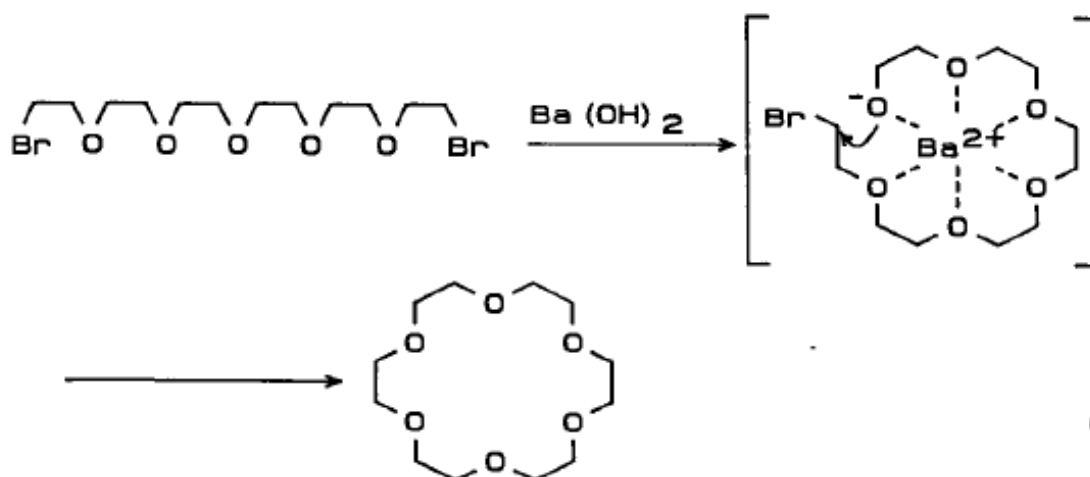
1) OXYGEN CROWN ETHERS

(a) Unsubstituted crown ethers

- Okahara and his coworkers developed one pot intramolecular cyclisation
- Oligoethylene glycol (penta- or hexaethylene glycol) was treated with arenesulphonyl or alkanesulphonyl chloride in alkali metal hydroxide furnished oligoethylene glycol monotosylate which subsequently intramolecularly cyclized to give the corresponding crown compound in a high yield

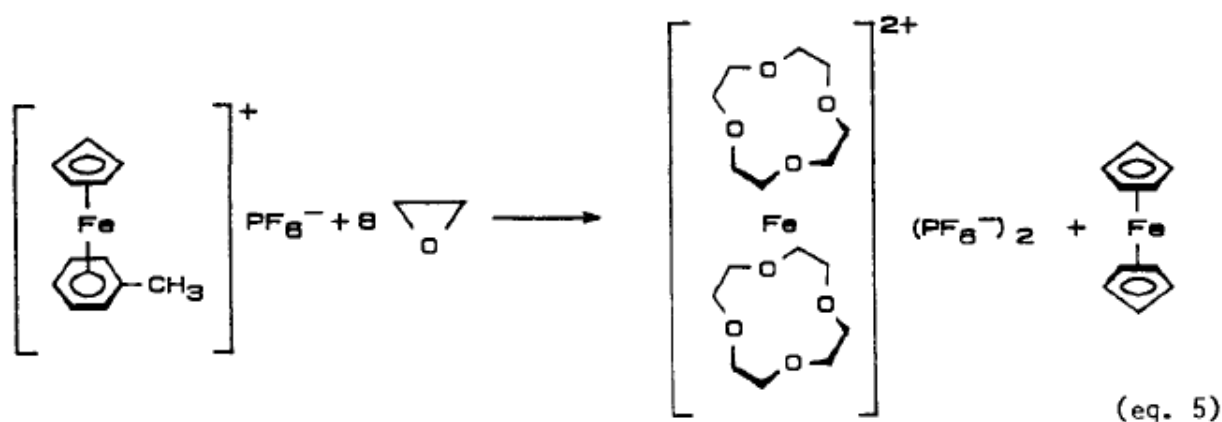


- In the case of **tri or tetraethylene glycol**, **dimerization occurred before the cyclization** reaction and gave 18-crown-6 or 24-crown-8, respectively (eq. 2)
- Mandolini and his coworkers reported that **hexaethylene glycol dibromide** was **treated with Ba(OH)₃** to give **18-crown-6** via the corresponding monobromide (eq.3).



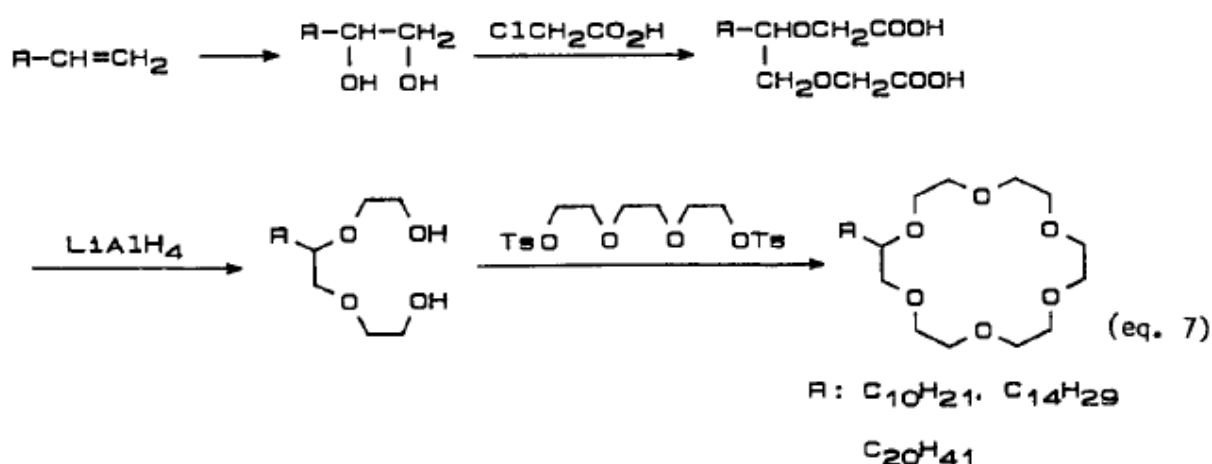
- Cyclooligomerization of ethylene oxide was reported by Dale and his coworkers.

- Meier and Rihs irradiated ethylene oxide in dichloromethane in the presence of cationic iron arene complex and obtained 12-crown-4 iron complex and the corresponding ferrocene.



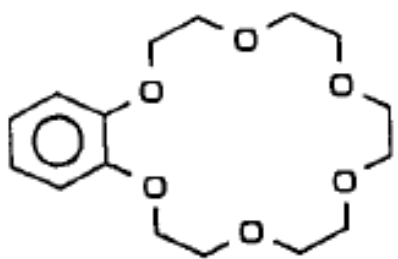
(b) Substituted crown ethers:

- Crown ethers with a **long chain alkyl group** are as **surface active agents**, and **crown ring is a hydrophilic** group and they work well as a **phase transfer catalyst**.
- The first synthesis of alkyl-substituted 18-crown-6 from olefin was published by Cinquini and Tundo.

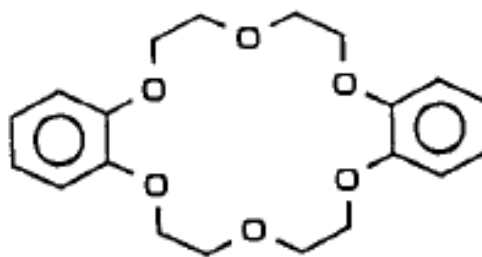


(c) Benzocrown ethers and related compounds:

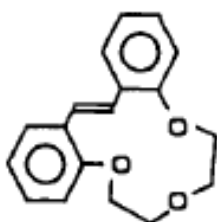
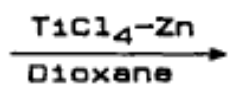
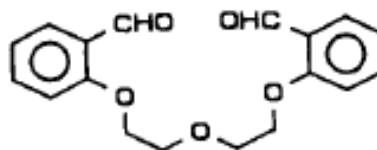
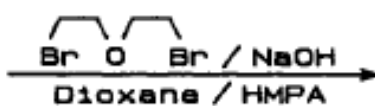
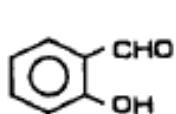
- Benzocrown ether (**10**) or dibenzocrown ether (**11**) was prepared by the intermolecular condensation reaction of catechol with oligoethylene glycol in the presence of an appropriate base in Pedersen's original work.



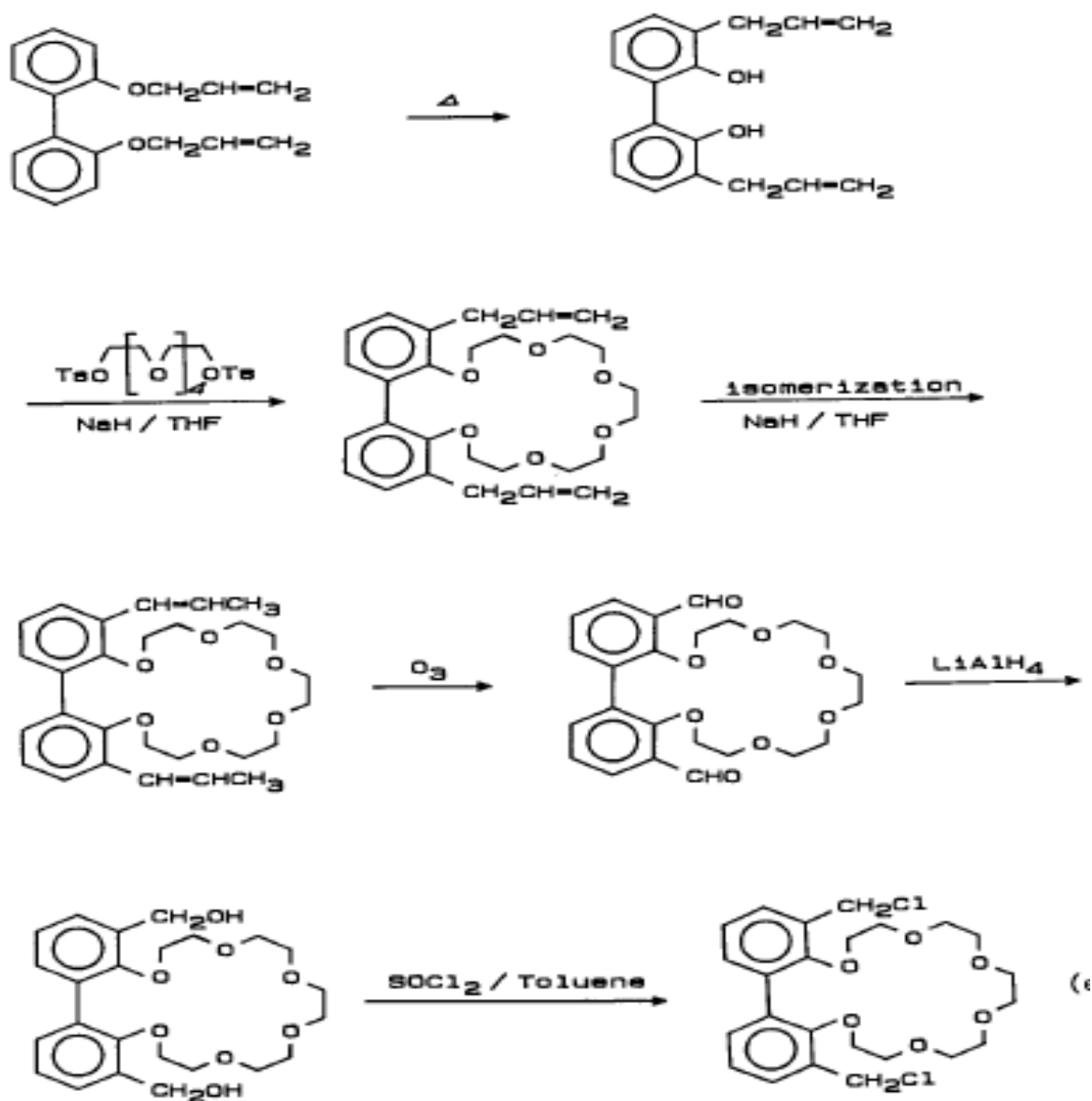
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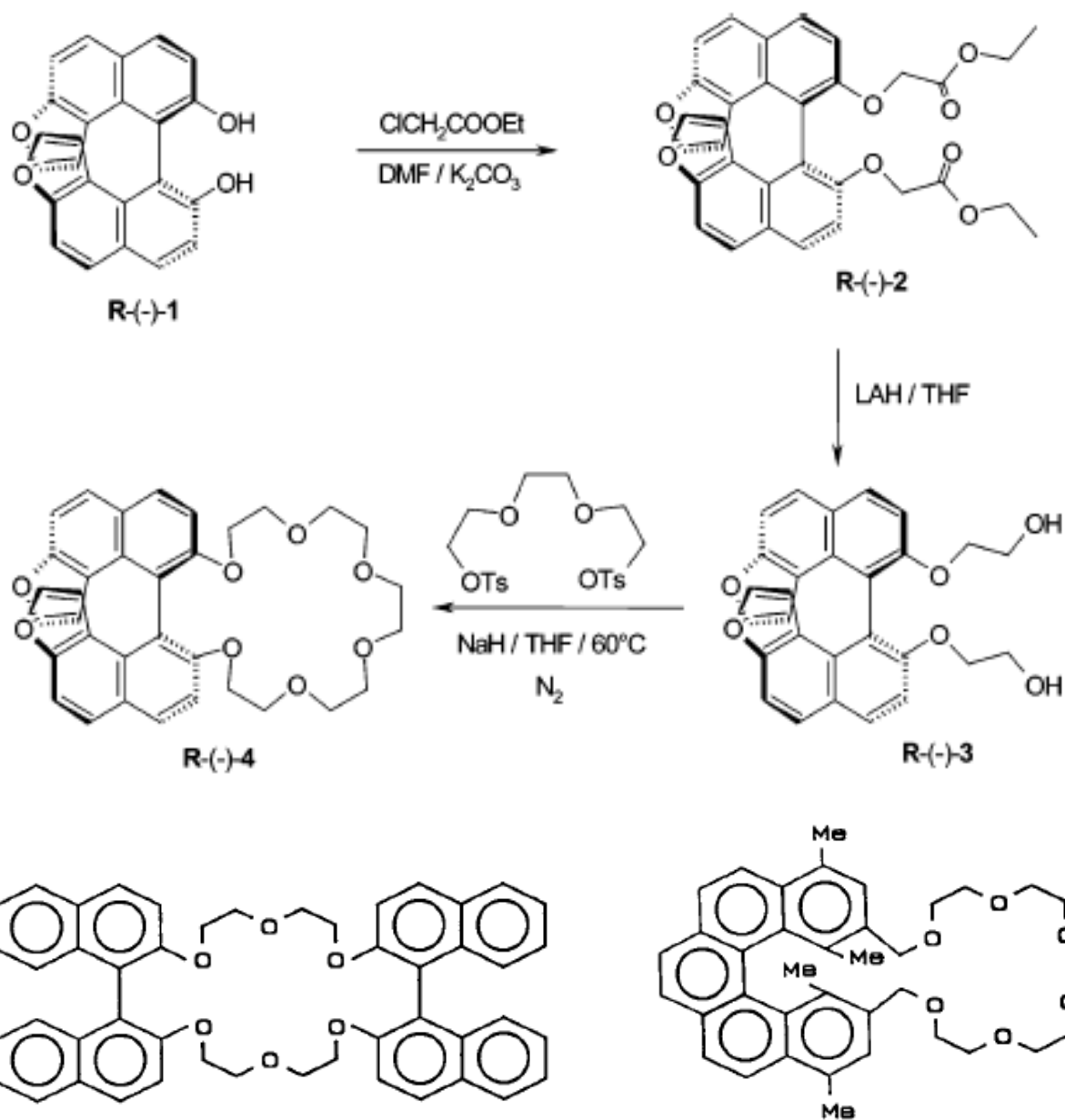
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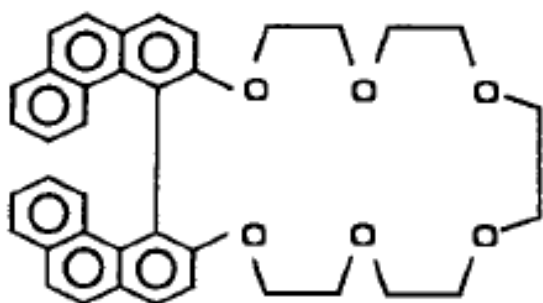
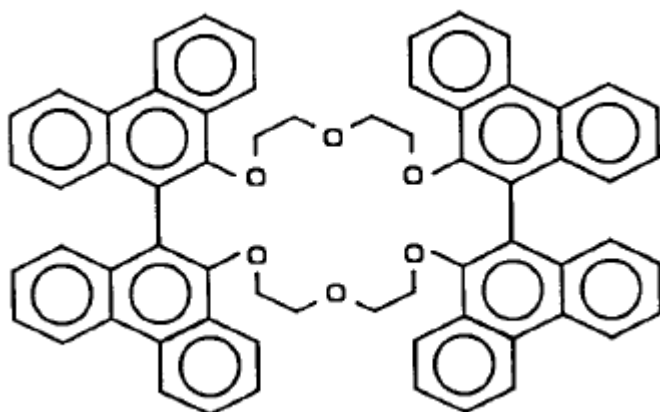
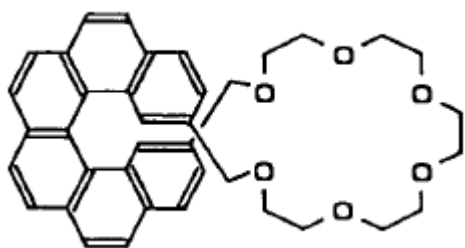


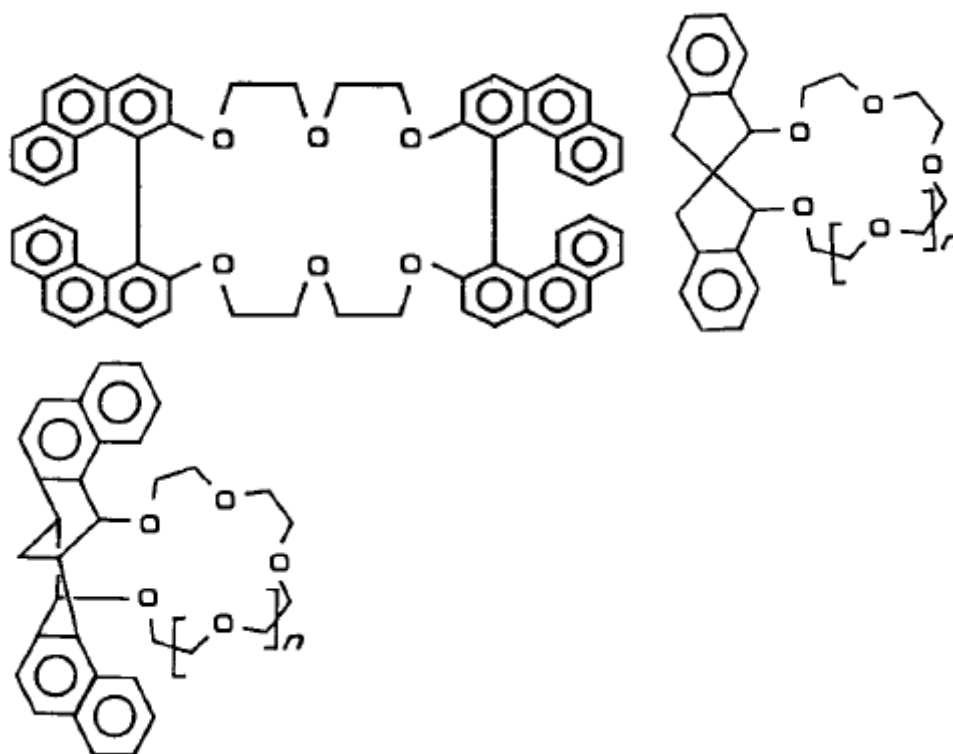
(eq. 19)



Synthesis of Chiral Furo-Fused BINOL Based Crown:

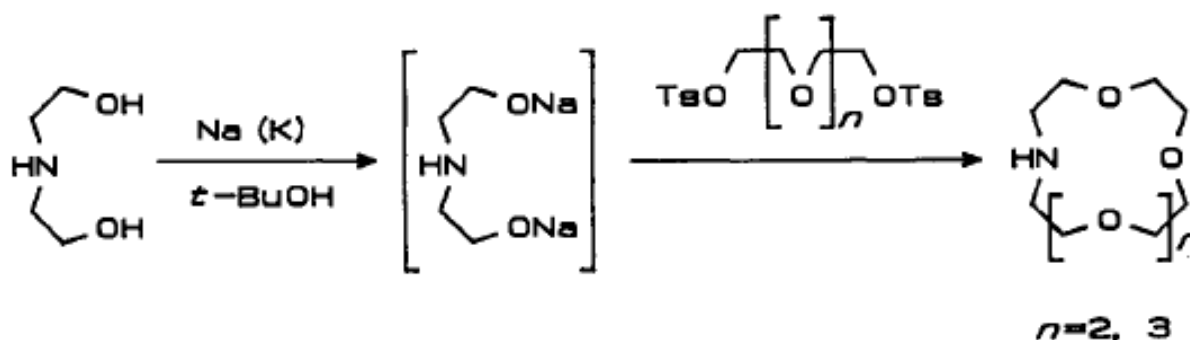




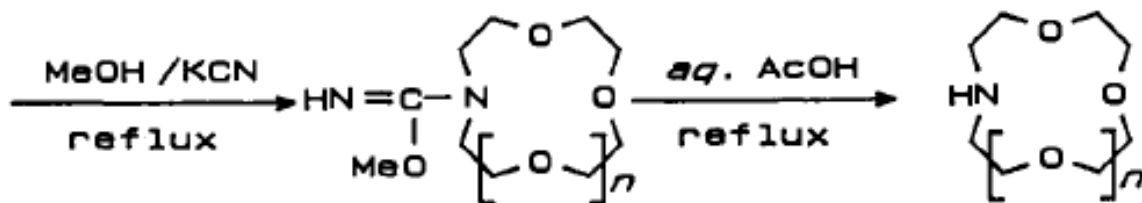
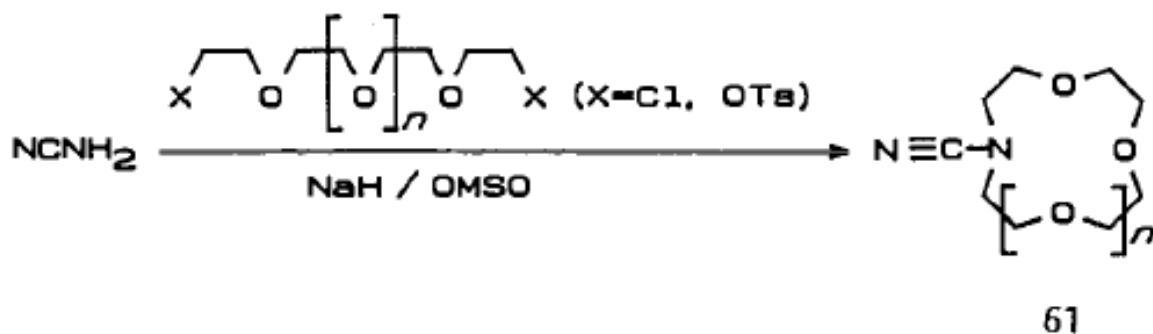


2. AZACROWN ETHERS

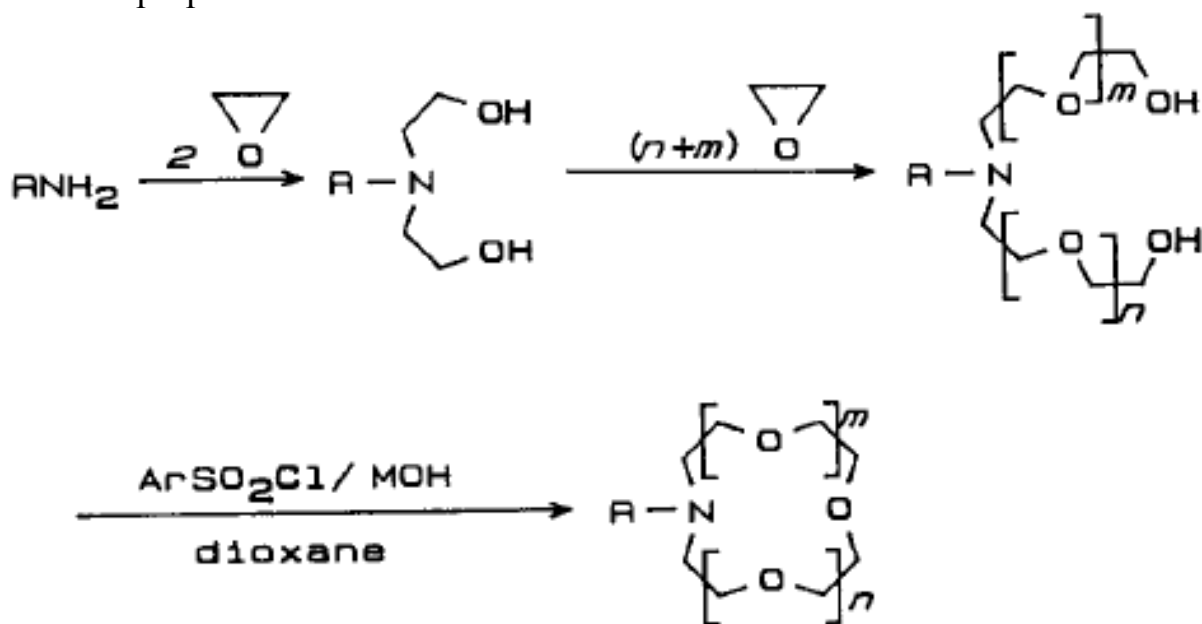
- Azacrown ethers are a series of crown compounds having more than one nitrogen atoms in the macrocyclic ring.
- Unsubstituted azacrown ethers are classified as reactive crown ethers because of the reactivity of the nitrogen atom.
- The **reaction of N-substituted diethanolamine** with an **appropriate oligoethylene glycol ditosylate** was the original method of synthesis of unsubstituted monoazacrown ethers.
- Treatment of ethanolamine in t-BuOM (M=Na, K) / t-BuOH system, an appropriate oligoethylene glycol ditosylate was furnished monoazacrown ether.

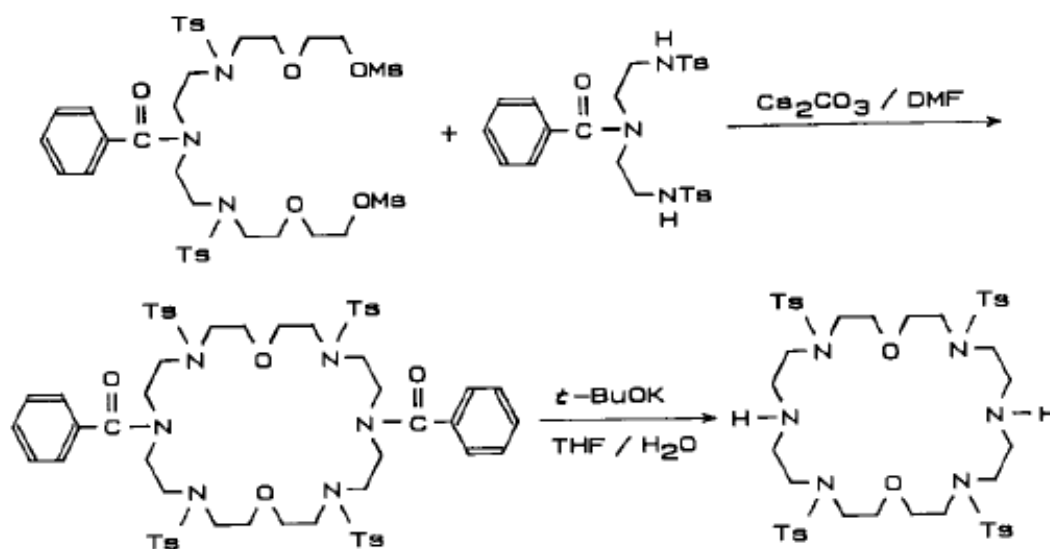
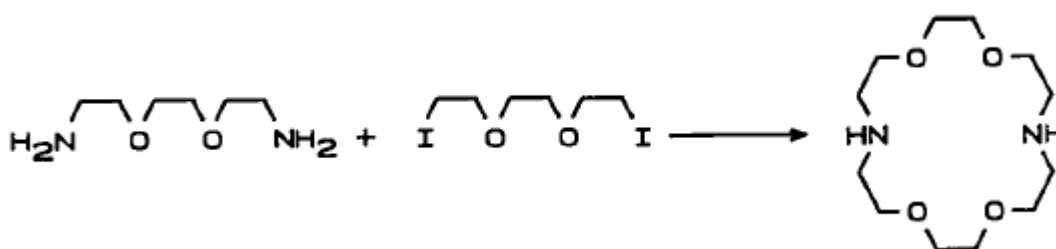
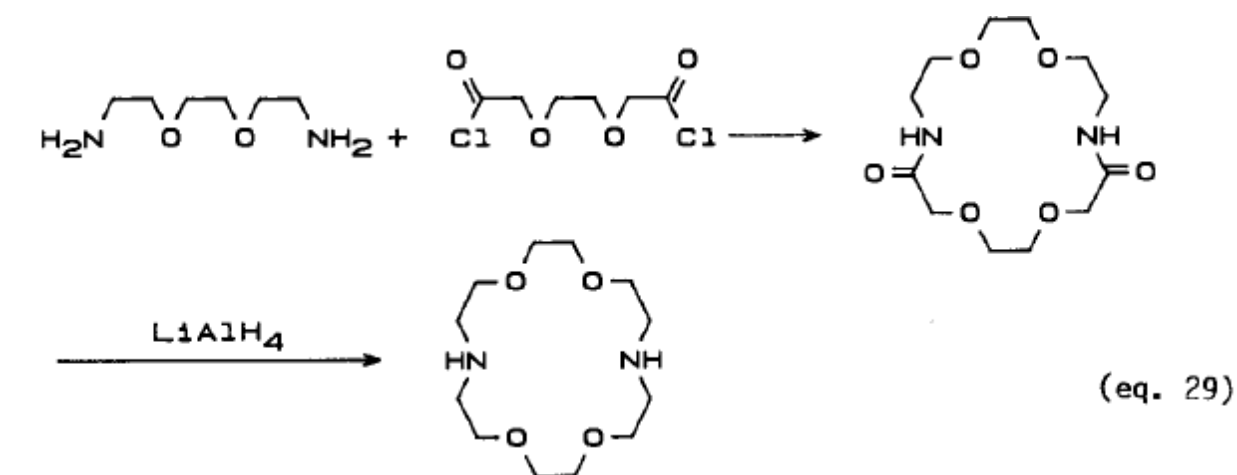


- The reaction of **dicyanamide with oligoethylene glycol di chloride or ditosylate** in the presence of **NaH** gave **N-cyanomonoazan crown ether (61)** followed by base-promoted methanol addition and hydrolysis.

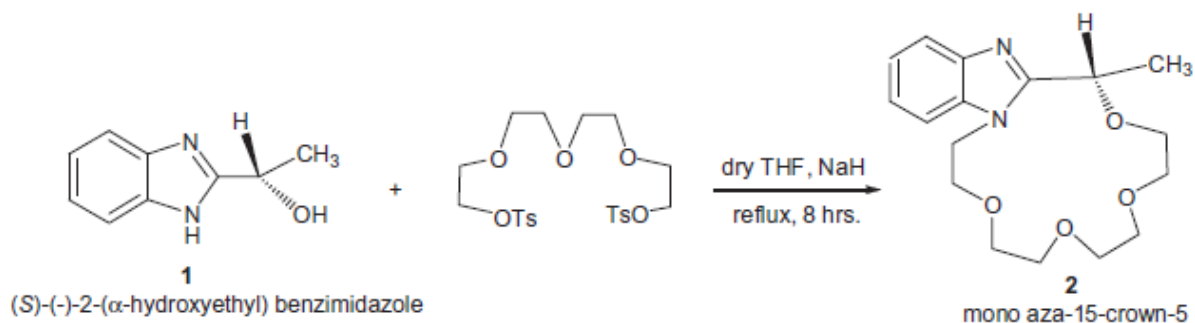


- **N-substituted monoazacrown ethers** are easily synthesized by the **intramolecular cyclization of the corresponding precursor**, obtained by the addition of 4-6 molar amounts of ethylene oxide to alkylamines . In particular, the derivative with a long-chain alkyl group displays interesting surface properties in addition to its complexation properties.

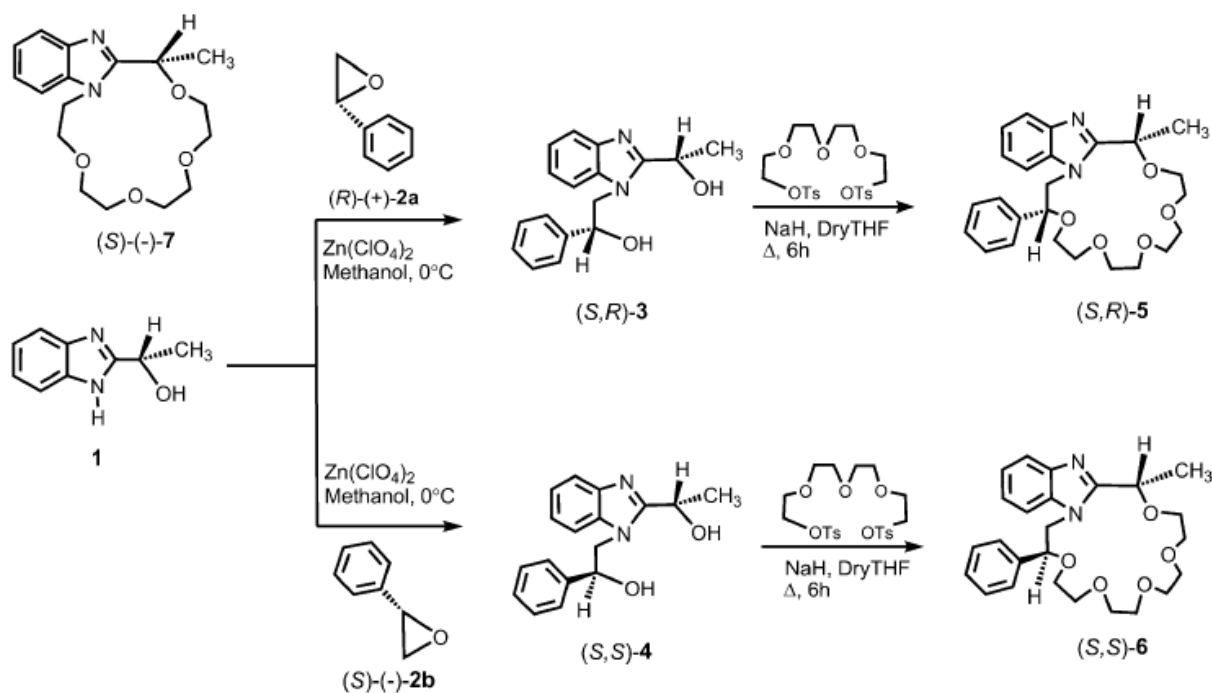




Synthesis of mono aza-15-crown-5

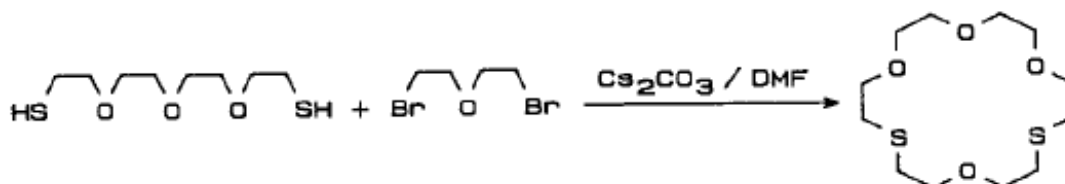


Synthesis of azacrowns (S,R)-5 and (S,S)-6.

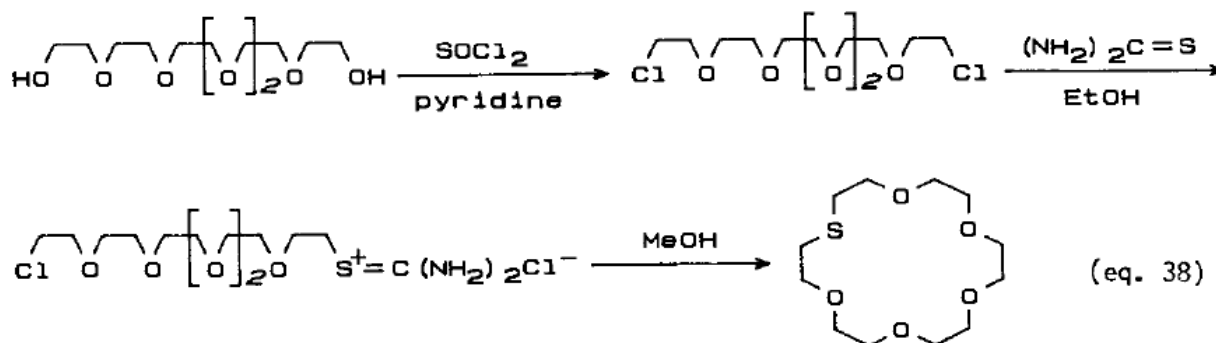


3. THIACROWN ETHERS:

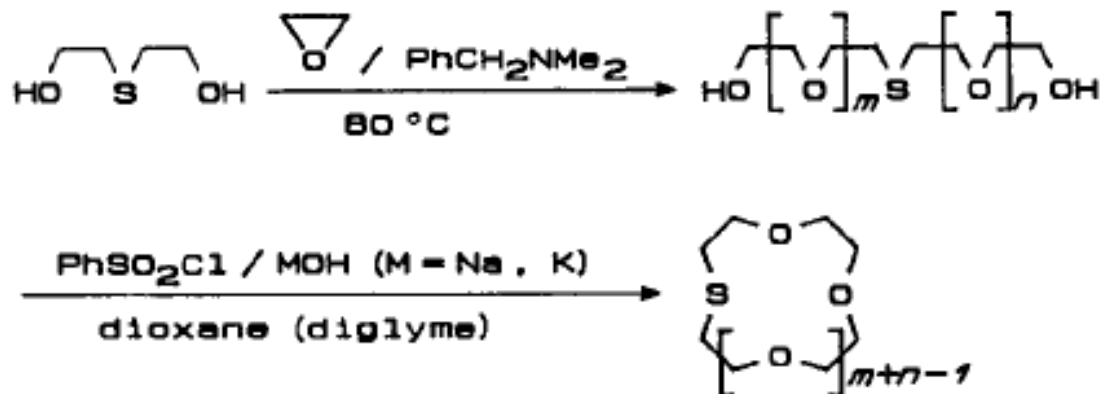
- Bradshaw and his coworkers had been published general synthetic procedures for thiacrown ethers, and these were modified by Buter and Kellogg who used the reaction of α,ω -dithiol with α,ω -dibromide in DMF in the presence of caesium carbonate to produce dithiacrown ethers.



- Kuwamura and his coworkers obtained monothia-18-crown-6 by the treatment of hexaethylene glycol dichloride with thiourea, followed by cyclization

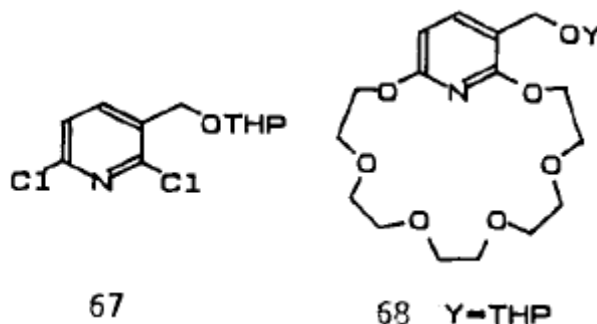


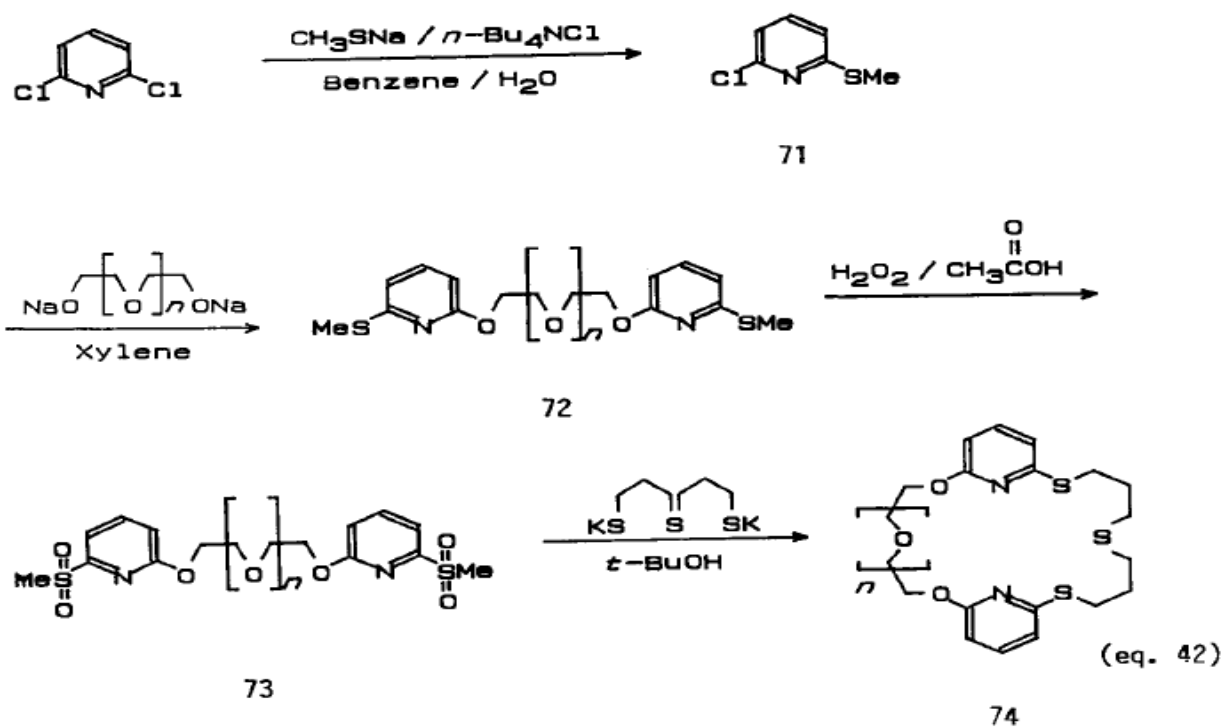
- Thiocrown ethers were prepared according to the intramolecular cyclization method.



4. CROWN ETHERS WITH A HETEROCYCLIC SUBUNIT

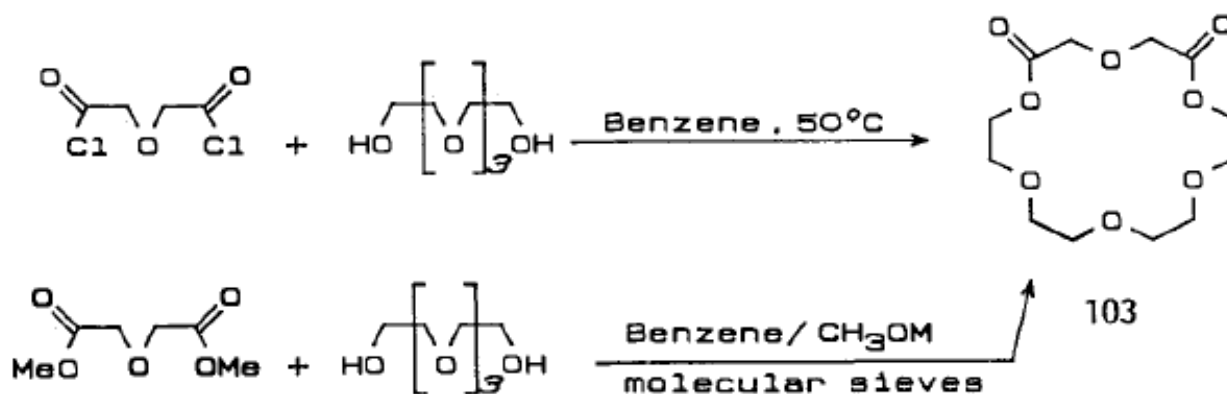
- Crown compounds having **heterocyclic subunits** would be **expected to possess a different complexation property** from normal crown ethers according to the specific coordination property of the hetero atom.
- The reaction of **3-substituted-2,6-dichloropyridine** (67) with **pentaethylene glycol** using **NaH** as the base gave the corresponding macrocyclic compound (68).



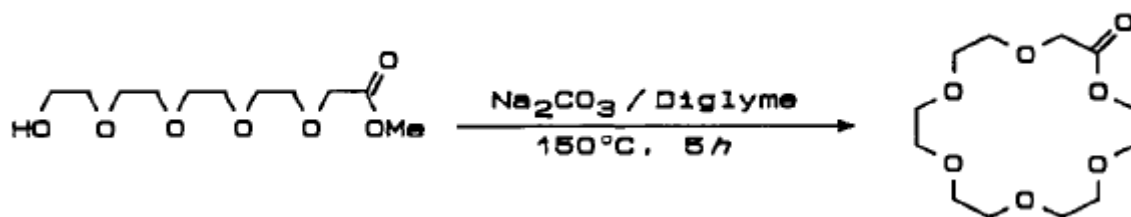


5. MACROCYCLIC POLYETHER LACTONES

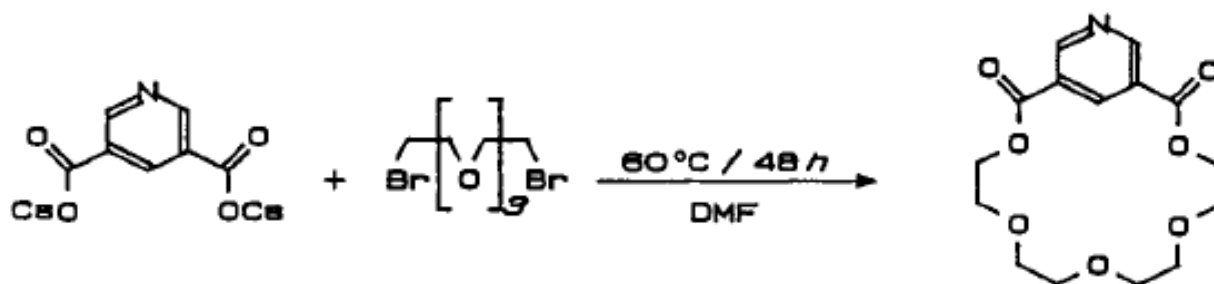
- Bradshaw and his coworkers prepared a variety of macrocyclic polyether-esters by stirring a mixture of diacid chloride and glycol.



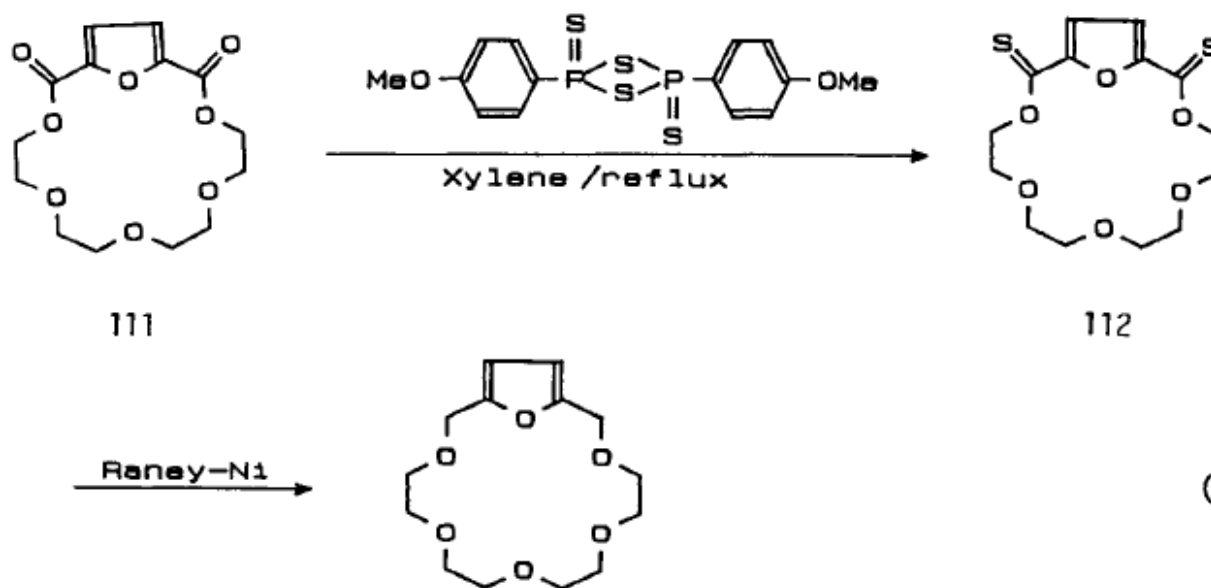
- Okahara and his coworkers utilized the transesterification method in the synthesis of monoester-type crown ethers.



- Kellogg and his coworkers prepared diester - type crown ethers by the [Hantzsch condensation](#)



- Bradshaw and his coworkers obtained the crown ether by the reduction of the **corresponding thioester**, which is **derived from the diester**, using Raney nickel.



CHARACTERISTICS/PROPERTIES OF CROWN COMPOUNDS

- It possesses **selective complexation/binding properties** towards **cations, anions, and neutral guest species**.
- It **vary widely in chemical composition** and **molecular size with specific varied cavity sizes**.
- They bind the cationic portion of alkali and alkaline earth metal salts, ammonium salts and ionic or polar organic compounds, such as thiourea, semicarbazide, diazonium salt and acetonitrile (guest), into the cavity of the crown ring (host).
- The **complex of crown ether** with a **guest** is formed by **ion-dipole interaction between the cation** and the negatively charged donor atoms in the ring structure of the cyclic polyether.
- The selectivity of crown ethers for a given cation is dependent
 - (a) **Relative size** of the cavity of the crown ring and the **diameter of the cation**.
 - (b) **Number of donor atoms** in the crown ring and the **topological effect**.
 - (c) The relationship between the "**hardness**" of the **cation and that of the donor atom**.
 - (d) **Charge number of the cation**.
- They offer various applications such as extraction, transport, and catalysis, based on their property of specific molecular recognition, some of which are of biological significance and often of practical interest.

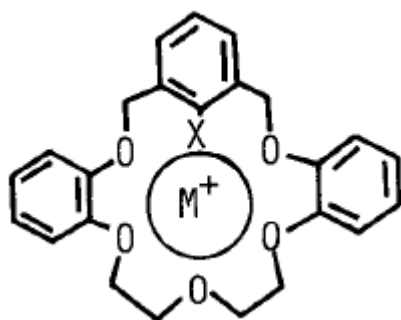
STRUCTURE AND BINDING OF NEW CROWN COMPOUNDS

- The cation binding properties of crown compounds are generally determined by
 - (1) correspondence of size of crown ring and guest ion;
 - (2) nature of host-guest interaction; and
 - (3) orientation in the ligation.
- These factors are generally considered in the design of any desired crown compound
- This section describes cation binding and the structure of novel crown-type compounds from the standpoint of host-guest chemistry and thermodynamic aspects and chemical functions.
- (a) **Structure and Binding of Monocyclic Crown Compounds**
 - While designing monocyclic crown compound, **first select the donor groups to be incorporated** in the crown structure, because **their nature predominantly controls selectivity and efficiency** in the host-guest complexation.
 - Many types of crown-type compounds have been designed with various chemical structures in the crown skeletons .

- Their **host-guest complexations** depend upon **interactions** including electrostatic force, metal coordination, hydrogen bonding, charge-transfer force, hydrophobic interaction, and so on.
- We must choose the molecular structure of the crown skeleton, because **multiple contacts between crown and guest depend on complementary location of their binding sites**.
- A **rigid crown ring offers** highly selective binding compare to flexible ring.

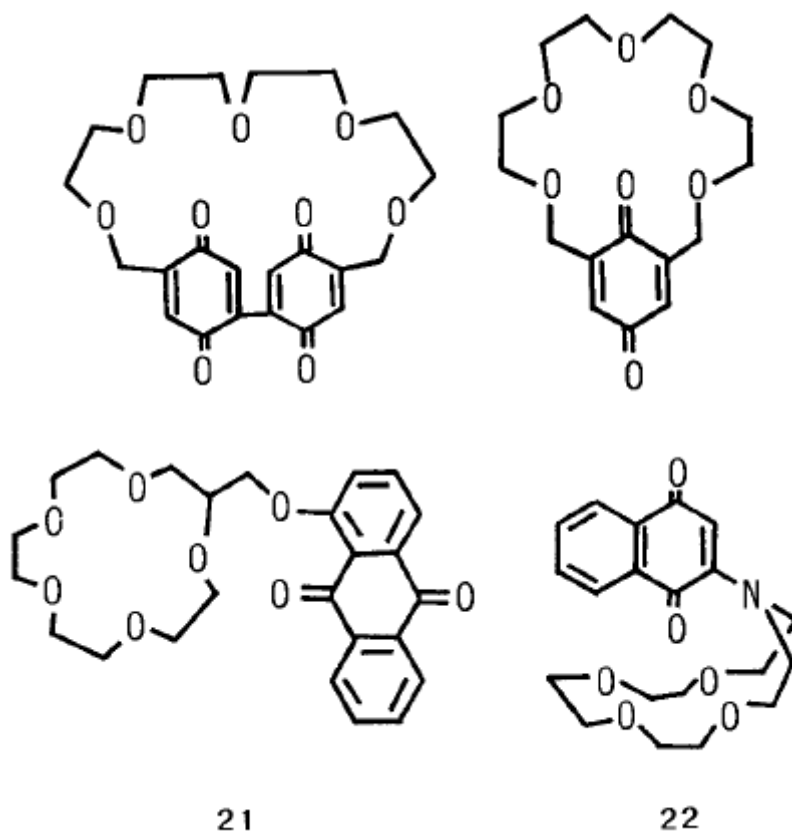
Monocyclic Crown Compounds for Binding Cations:

- **Powerful donor sites** (hetero-atoms and anionic) into the crown ring skeleton is the **most effective method** for **providing specific host-guest complexation**.
- Further, radical groups are also **demonstrated to be powerful donor sites** e.g. quinone, nitrobenzene, reducible group containing crown, a unique host-guest complex is electrochemically formed via **cation-radical interaction**. In such a complex, the **reduced radical species acts as a more effective** ligating donor than its neutral form.
- Thus, the **electrochemical process** can be effectively coupled with crown-guest interaction.



X: HETERO-ATOM,
ANIONIC DONOR,
RADICAL GROUP.

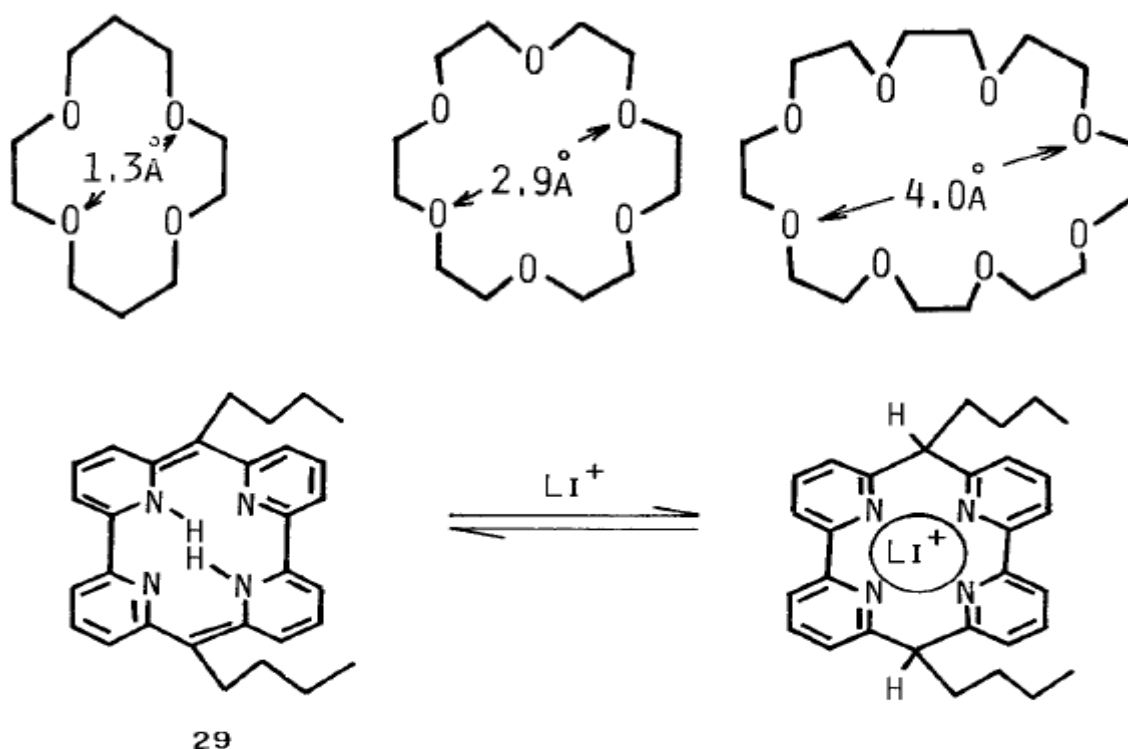
- Maruyama et al. prepared a variety of "quinonoid crown ethers" such as **19** by **oxidative C-C coupling cyclization** of polyether precursors.
- **Electrochemical studies clearly demonstrated** that the reduced quinone-incorporated crown compounds bound several guest cations about 10^3 - 10^4 times more strongly than the corresponding neutral forms.



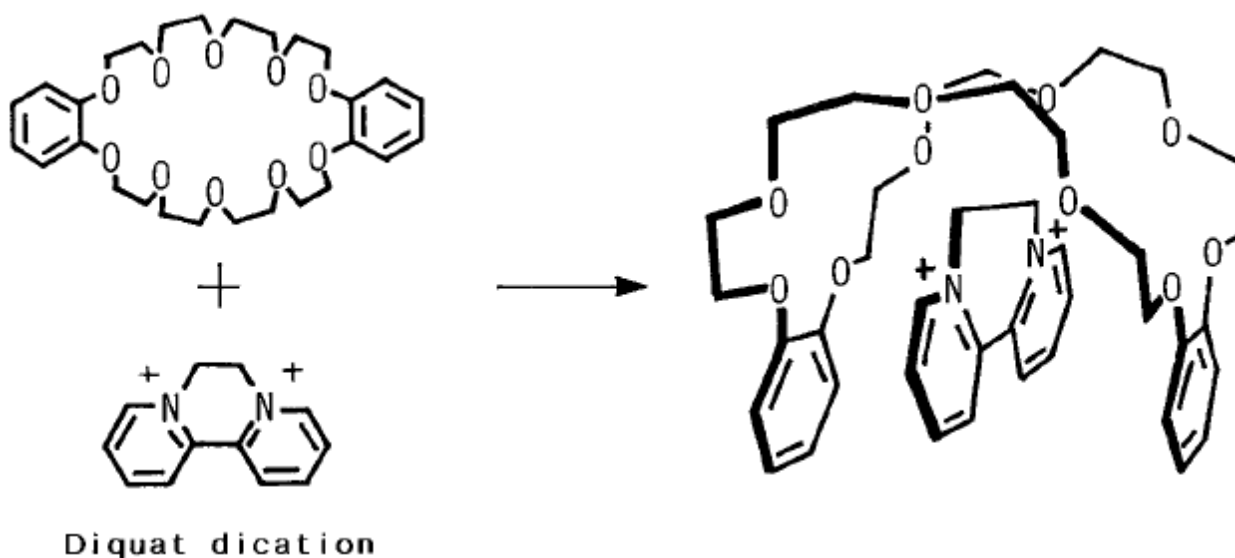
- Compound 20, 21, and 22 similarly showed electrochemically enhanced cation bindings, and direct evidence of coordination of the semiquinone radical to the guest cation was obtained using ESR spectroscopy.

Rigid and Flexible Crown Compounds for Binding Cations:

- The ring-size of the crown compound, limits the size of target guest cations, because multiple and complementary binding.
- Small and rigid crown compounds often show pronounced and strong selectivity for small cations such as Li^+ and Na^+ ions, while large and flexible crown compounds offer effective complexations with large and polyfunctional guest cations.

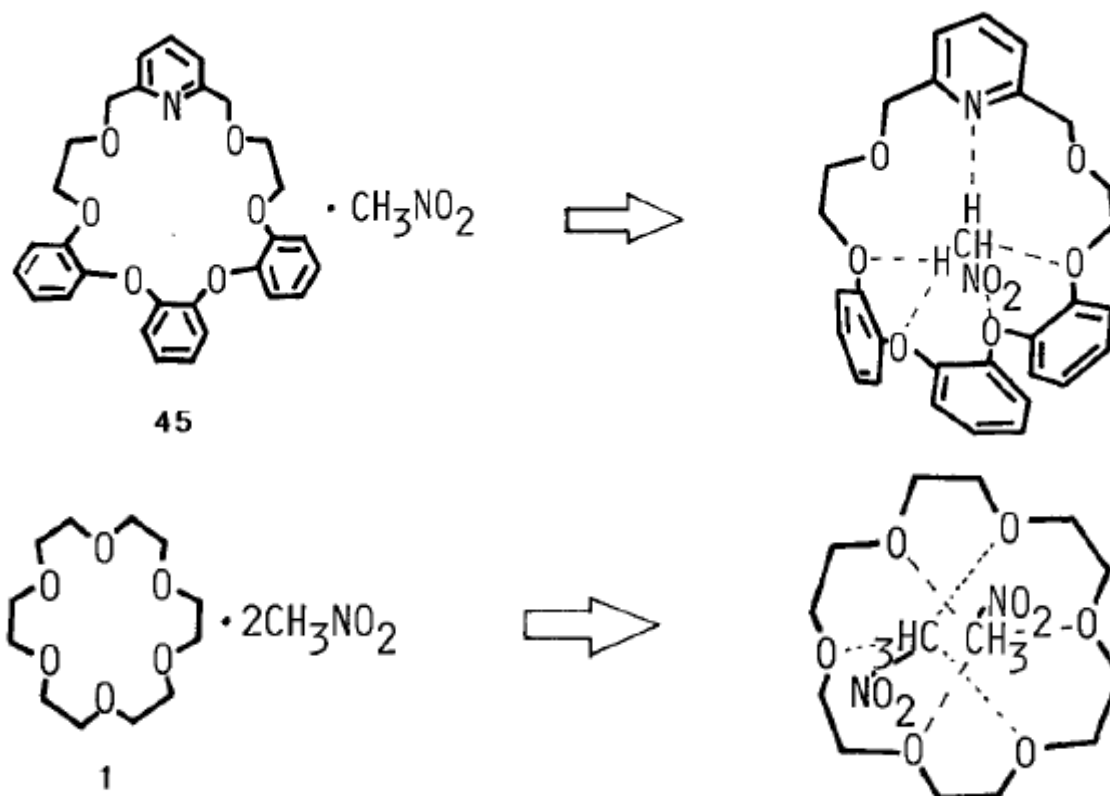


- Ogawa et al. developed a rigid crown-type compound **29** with Li ion selective binding over Na and K ion.
- For larger guest-bindings, further multiple contacts between binding sites of crown and guest species are necessary.
- Stoddart et al. revealed the significance of "charge-transfer interactions" between dibenzo-30-crown-10 and the bipyridium dication. This formed a 1:1 encapsulated complex.
- Geometrical overlap between the aromatic units of crown and guest is the major stabilizing force in complexation.



Crown Compounds for Binding Neutral Guest:

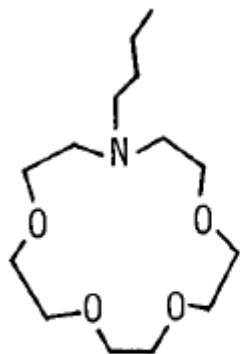
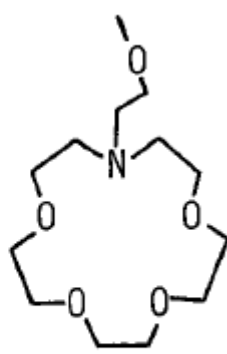
- Rapid progress is being made in the design of crown family useful for uncharged/neutral guest compounds. Some of these crown compounds have cavities lined with convergent hydrogen bonding sites.
- Weber et al. prepared a **21-membered crown compound 45** incorporating **2,6-bridged pyridine** and **three adjacent catechols** as characteristic binding groups.
- It formed a **1:1 complex with CH_3NO_2** , in which the **guest molecule was held by a system of hydrogen bonds** between the methyl terminal of the guest and pyridine-nitrogen and two oxygen pairs of the crown-ring.

**Structure and Binding of Armed Crown Compounds:**

- By introduction of additional ligating groups into a crown, a **three-dimensional complex** is formed, **dynamic binding** is assured, **specificity in guest binding** is increased, and **solubility** is changed.
- Dynamic, **three dimensional complexation is an essential feature of carriers in solvent** extraction, membrane transport, catalysis, and biological ion-carriers, "ionophores".
- E.g. Gokel, Okahara, and other investigators presented a series of single armed crown ethers, called "lariat ethers".
- **Altering the side-chain structure**, **adjusting the size of the crown ring**, and **varying the arrangement of the component hetero-atoms** make it

possible to control both **binding strength and selectivity for alkali and alkaline earth cations**.

- Gokel, Izatt, and their coworkers determined thermodynamic parameters for complexations between lariat ethers and alkali metal cations. Comparison of **51** with **50** reveals evidence of side-arm interactions with Na⁺, K⁺, and Ca ions. Since the log K value of crown **51** with K⁺ ion is 16-times larger than that of simple crown **50**.

**50****51**

Physical Properties of Crown ethers:

- Crown ethers of the ethylene oxide oligomer type (1 – 4) are colorless, odorless, viscous liquids or solids with a low melting point.
- They are strongly hygroscopic and readily soluble in most organic solvents and in water.
- Crown ethers with condensed aromatic rings (5 – 7) are colorless, barely hygroscopic, crystalline compounds. At room temperature they have poor solubility in water, alcohols, and many other common solvents. They are readily soluble only in halogenated hydrocarbons, pyridine, and formic acid.
- Crown ethers with alicyclic bridges (8, 9) have much better solubility in hydrocarbons and much poorer solubility in water than the ethylene oxide oligomers.
- The solubility of crown ethers increases markedly if salts are added, e.g., 25- fold for dibenzo-18-crown-6 in MeOH after addition of KF. The increase depends on the type of salt used. Conversely, presence of the crown ether increases the solubility of the salt.

Table 2. Physical properties of crown ethers

Compound no.	Trivial name	M_r	mp , °C	bp , °C	Ref.
1	12-crown-4	176.21	16 ^a	67 – 70 ^b	[34]
2	15-crown-5	220.27	–32 ^e , ^d	78 ^e	[26, 34]
3	18-crown-6	264.32	36.5 – 38	116 ^f	[27–30, 33, 35–37]
4	21-crown-7	308.37		oil	[38]
5	benzo-15-crown-5	268.31	79 – 79.5		[33]
6	dibenzo-18-crown-6	360.41	162.5 – 163.5	380	[1, 38]
7	dibenzo-24-crown-8	448.52	113 – 114		[1]
8	dicyclohexano-18-crown-6	372.50	36 – 56 ^g		[1, 39, 40]
9	dicyclohexano-24-crown-8	460.61	<26 ^g		[1]
10	diaza-15-crown-5	218.30	89 – 90		[41]
11	diaza-18-crown-6	262.35	115 – 116 ^e , ^h		[41]
12	diaza-21-crown-7	306.40	–10		[41]
13	dithia-18-crown-6	296.44	90 – 91		[42]
14	dithiadiaza-18-crown-6	294.48	47		[43, 44]
15	dibenzopyridino-18-crown-6	393.44	135 – 137		[45]

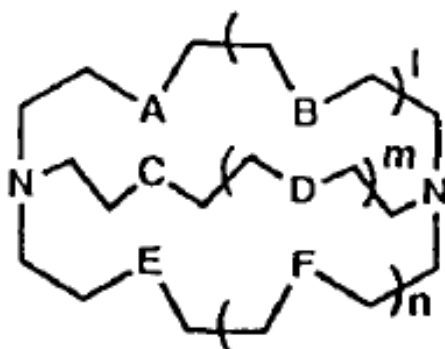
Chemical Properties of crown ether:

- Like simple dialkyl ethers, aliphatic and alicyclic crown ethers are chemically stable.
- Aromatic crown ethers react like anisole or veratrole, i.e., they can be halogenated or nitrated and they react with formaldehyde.
- Hydrolysis takes place only in special cases.
- Crown ethers are also thermally stable; dibenzo-18-crown-6 can be distilled at 38 °C without decomposition. With hydrogen ions and in the presence of Lewis acids (AlCl₃, TiCl₃), oxonium compounds are formed.
- The hetero derivatives (10 – 15) are usually more reactive than the classical crown ethers.
- Aza analogues are strong bases and react with acids to form salts.

Cryptands

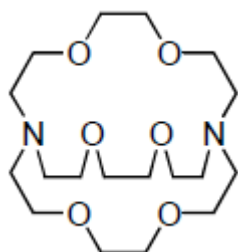
- Crown ethers and their derivatives are usually flexible molecules capable of accommodating a wide variety of guests, which is one of the reasons they can often display poor selectivity.
- It should also be noted that many of the crowns are restricted in the manner in which they can arrange themselves around a guest, possibly reducing potential binding interactions.
- Jean-Marie Lehn, who shared the Nobel Prize with Pedersen and Cram, investigated that a flexible molecule which could present donor atoms in a threedimensional array could potentially be capable of actually encapsulating a guest.

- Lehn and his coworkers first time discovered the cryptands, the cage-type bicyclic crown compounds, whose two bridgeheads consist of two N atoms.
- These compounds, with a three-dimensional framework, show higher complexing ability and selectivity toward a variety of cations in comparison with crown ether, which is regarded as a two-dimensional host.
- Cryptands form very strong complexes with a variety of metals and ammonium cations.
- Because of their strong complexing abilities, the cryptands are used for isotopic separations, for detoxifications, for the transport of cations, amines, and organic ammonium salts, as catalysts in certain organic or biochemical reactions, as photoactive compounds, and for separations of a variety of ions.

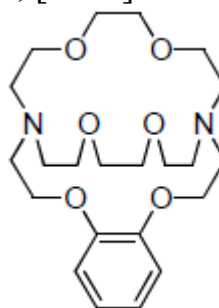


Nomenclature:

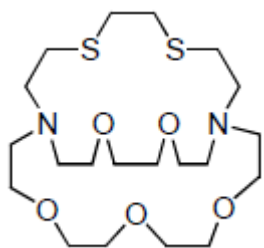
- Just as Pedersen did for the crown ethers, Lehn developed an abbreviated nomenclature system for cryptands to simplify the complicated IUPAC nomenclature.
- The number of heteroatoms, n, in each bridge are separated by periods and placed in square brackets, [n.n.n].



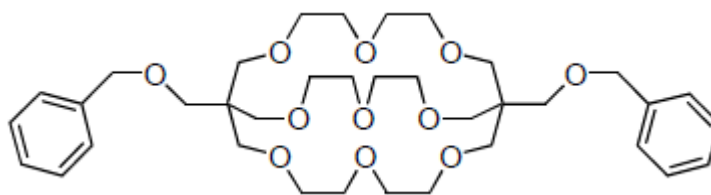
[2.2.2]-cryptand



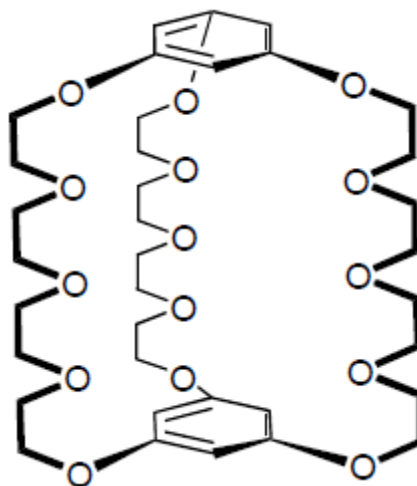
[2.2.2B]-cryptand



[3.2.2S]-cryptand



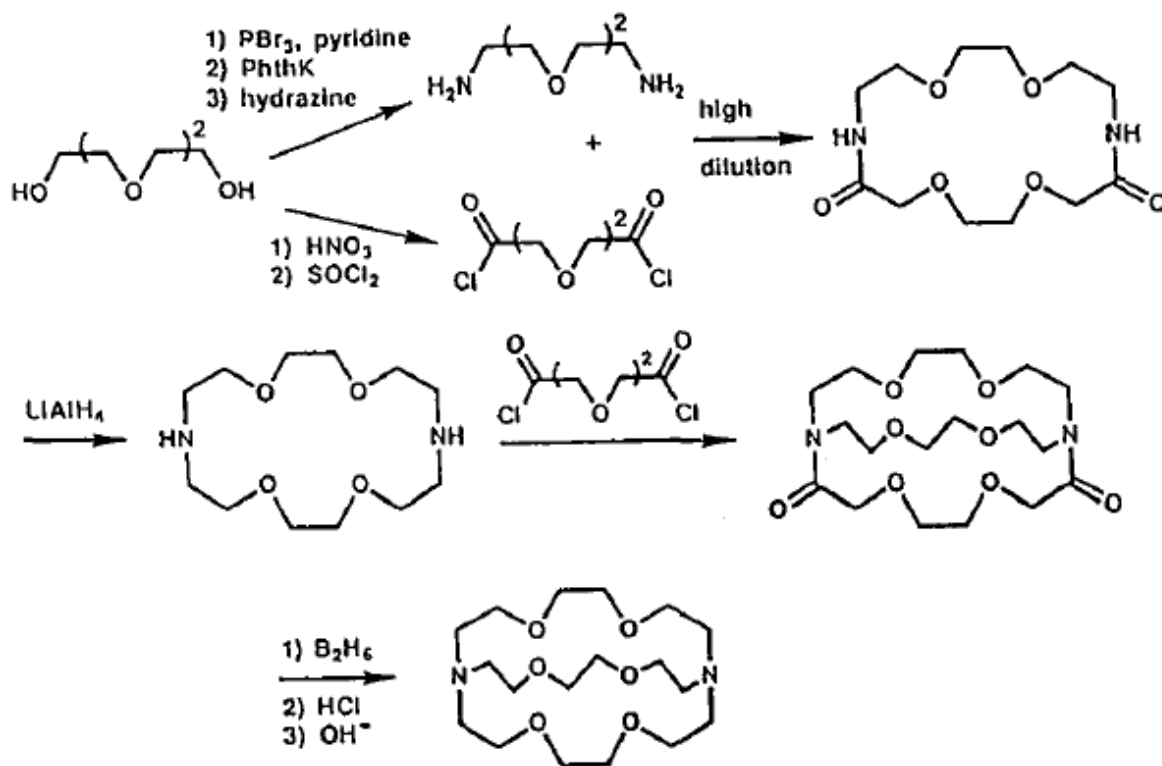
[3.3.3]-cryptand



[5.5.5]-cryptand

Synthesis of Cryptands

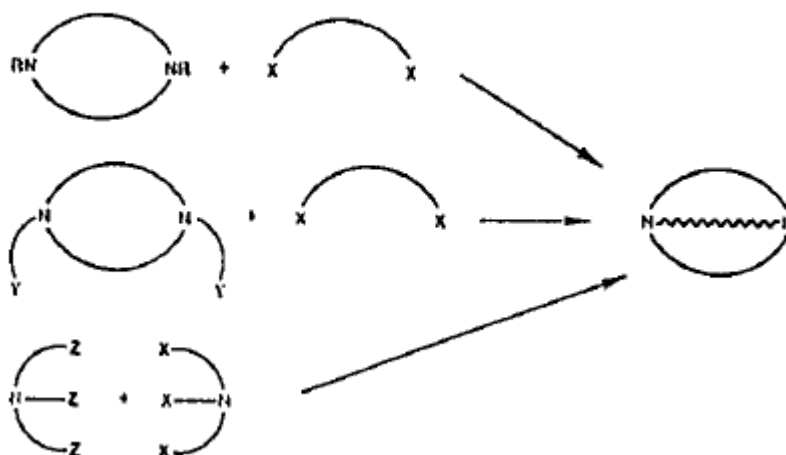
- Lehn and his coworkers first time described a new class of compounds, which they called cryptands, in 1969.

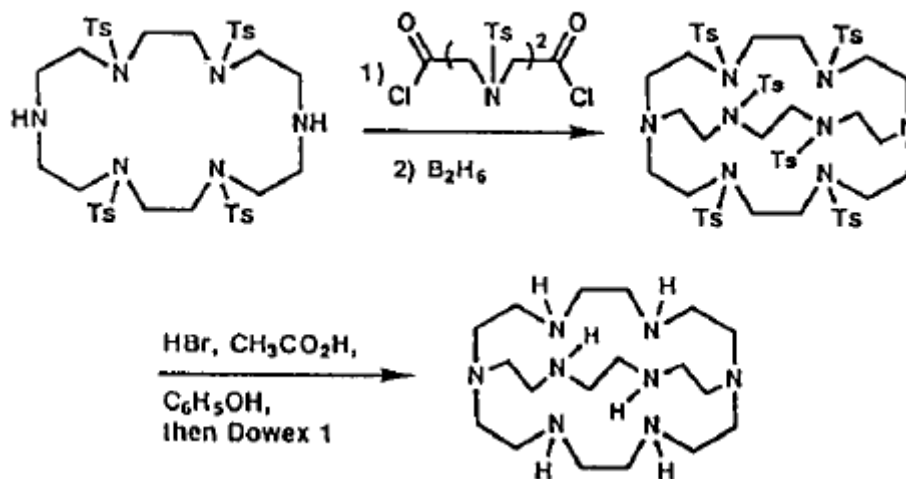


CRYPTAND SYNTHESIS BY 1:1 CYCLOCONDENSATIONS:

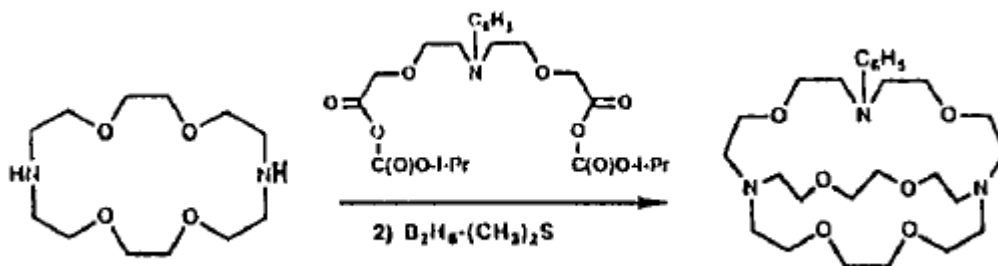
- The condensation of a diaza-crown ether and an activated diacid in the form of a diacid dichloride was the first method used to produce a cryptand.
- A peraza-cryptand was recently prepared by the 1:1 of a tetra-N-tosylated hexaaza-crown and di-N-tosylated diazadiacid dichloride.

1:1 Cyclocondensation

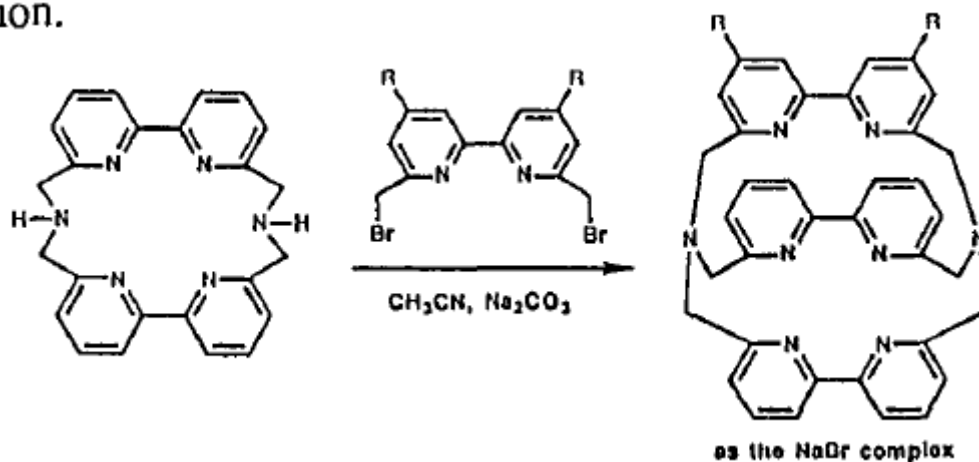




- Cryptands have also been prepared using the reactive **bis(2,4-dinitrophenyl)ester** or a **bis mixed anhydride** rather than the usual diacid dichloride in the ring closure step.



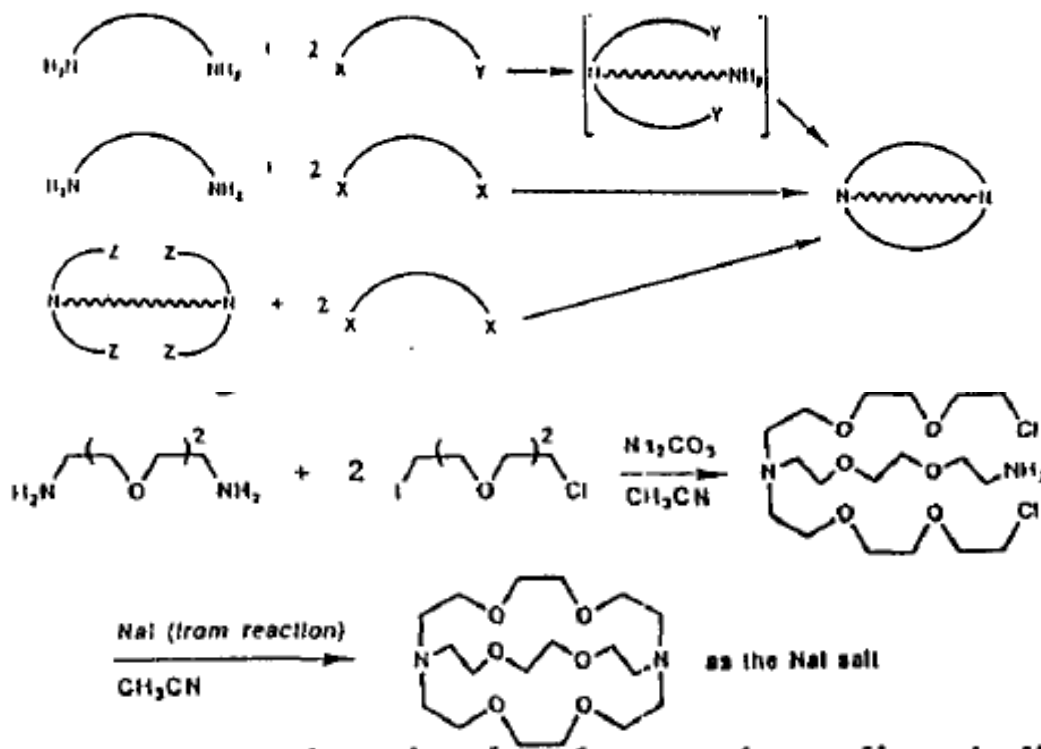
- The reactions of **bis(bromomethyl)-substituted aromatic compounds** [6,6-bis(bromomethyl)-2,2'-bipyridyl], with a **polyaza macrocycle** leads to the complexed cryptand in excellent yields (60-71 %).



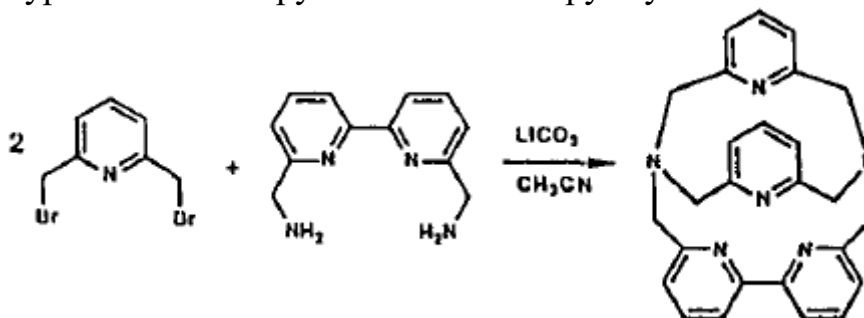
CRYPTAND SYNTHESSES BY 2:1 CYCLOCONDENSATIONS

- It is easy to imagine the synthesis of a cryptand from the reaction of **two molecules** of one reactant with **one molecule** of another.
- In this case, **four simultaneous C-N or C-O bonds must be formed**.
- [2.2.2] cryptand formed in the reaction of **2 molecules of 1,8-diiodo-3, 6-dioxaoctane** with **one molecule of the diamine** in the presence of K_2CO_3 , Cs_2CO_3 , or $MgCO_3$.

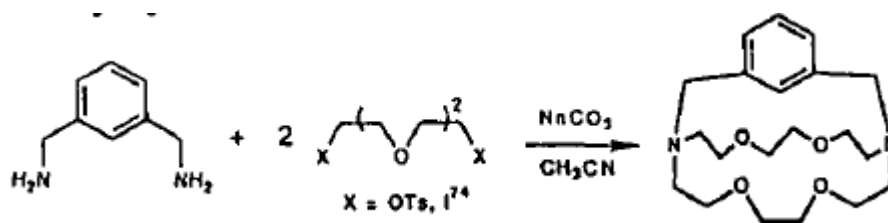
2:1 Cyclocondensation



- The reaction of 2 molecules of 2,6-bis(bromo-methyl)pyridine with 6,6'-bis(aminomethyl)-2,2'-bipyridyl in the presence of $LiCO_3$ gave a cryptand with two pyridine and one bipyridyl units in 48% yield.



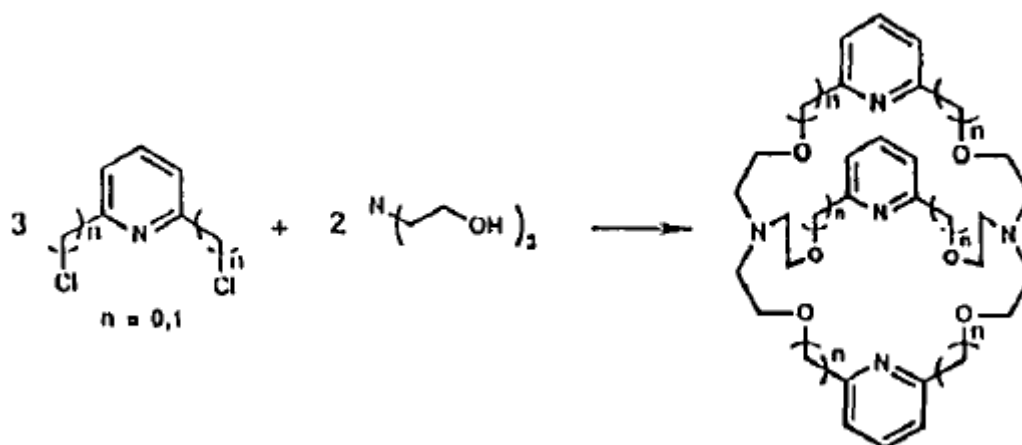
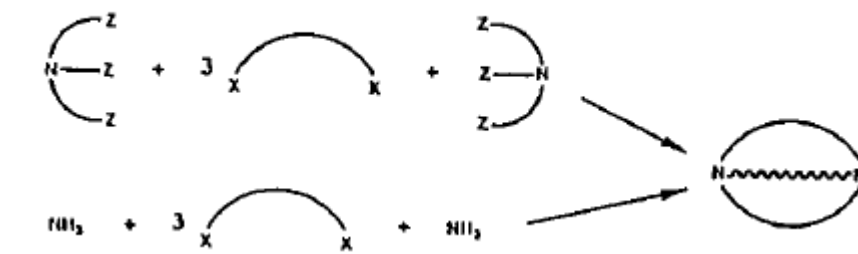
- A very attractive synthesis of a cryptand containing one benzene subcyclic unit in a 25% yield was reported recently by Pietraszkiwicz and co-workers for the reaction of one molecule 1,3-bis(aminomethyl)benzene with triethylene glycol ditosylate



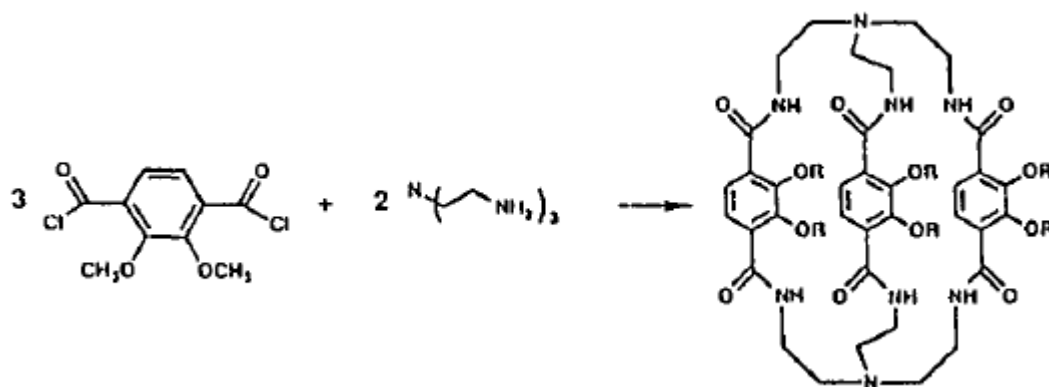
CRYPTAND SYNTHESIS BY 3:2 CYCLOCONDENSATION:

- Cyclocondensation of **3 molecules of a dihalide** (or diacid dichloride) with **2 molecules of a trialcohol or triamine** form cryptands wherein **six C-O or six C-N bonds are formed**.
- For example, cryptands were formed from triethanolamine and 2,6-bis(chloromethyl or 2-chloroethyl)pyridine.
- The reaction was carried out in xylene or DMF in the presence of NaH to give low yields of the products.

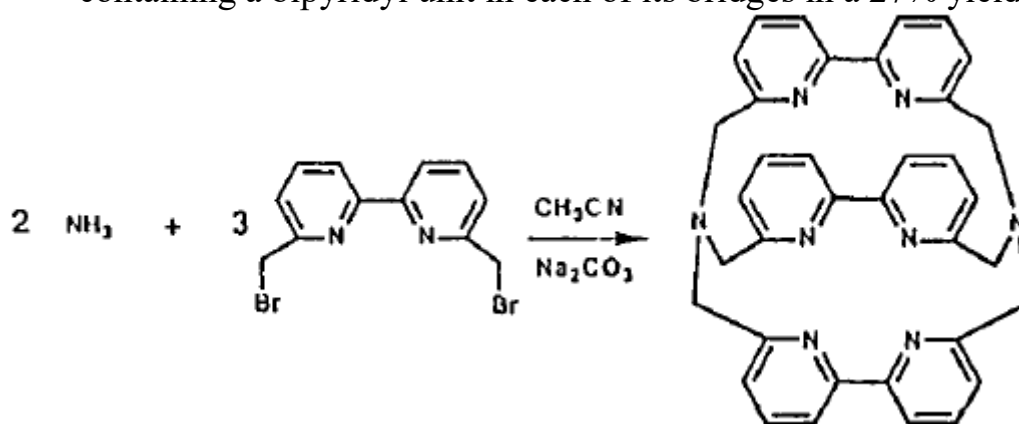
3:2 Cyclocondensation



- A high dilution 3:2 cyclocondensation of 2,3-dimethoxyterephthaloyl dichloride and tris(2-aminoethyl)amine gave the cryptand suitable for complexing ferric ions



- A simple macrobicyclization reaction of 2 molecules of ammonia with 3 molecules of 6,6'-bis(bromomethyl)-2,2'-bipyridyl gave a cryptand containing a bipyrindyl unit in each of its bridges in a 27% yield.



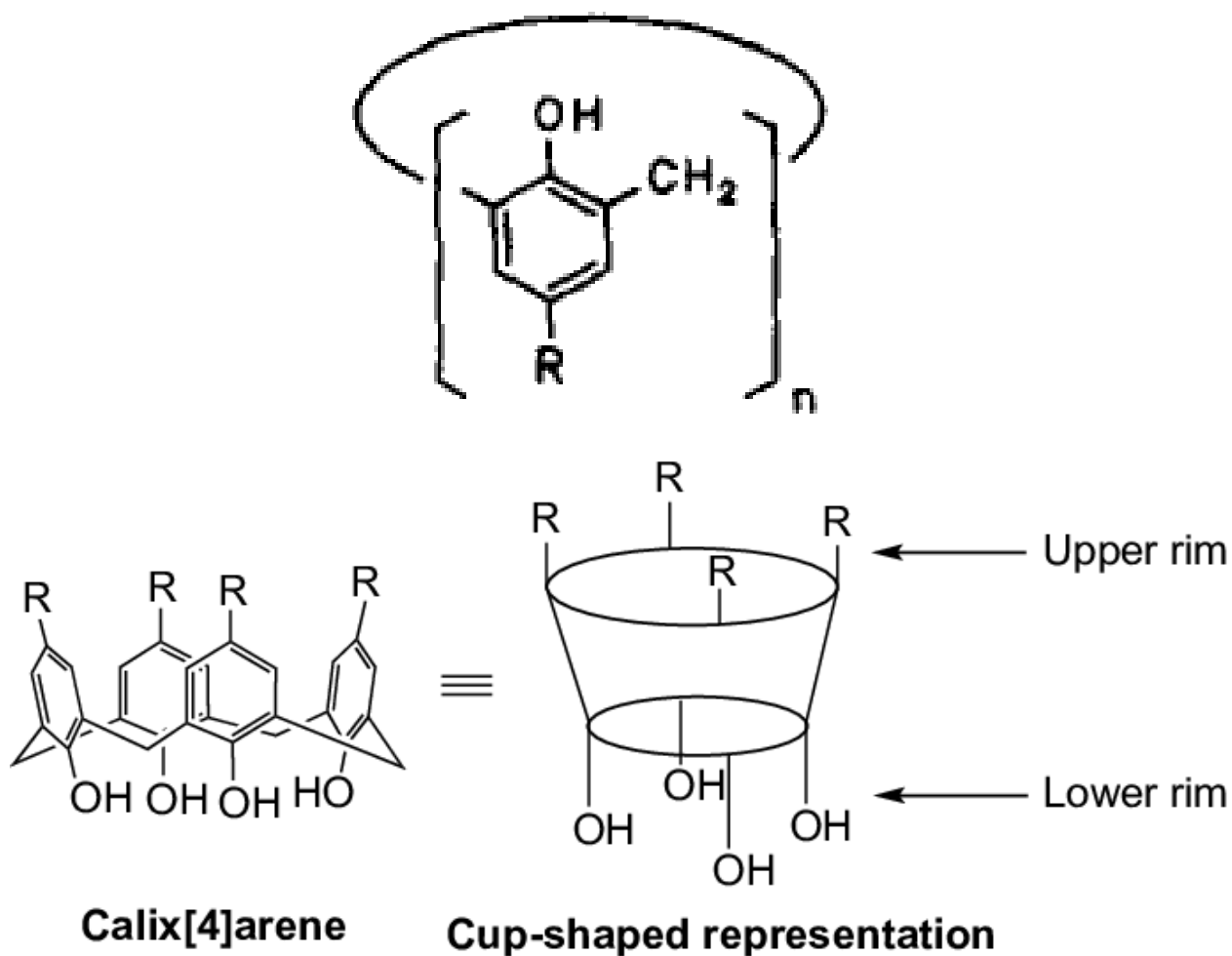
Properties of Cryptands:

- The cryptands have the same kind of properties as the crown ethers and the same uses.
- In general, they form much more strongly bound complexes and can be used to stabilize unusual ionic species. For example, it is possible to produce the negative Na^- ion in the compound $[(2,2,2)\text{-cryptand-Na}]^+ \text{Na}^-$, which is a gold-coloured crystalline substance stable at room temperature.

Calixarene

- The name calixarenes was introduced by Gutsche.
- It is a **macrocyclic or cyclic oligomer based on a hydroxyl alkylation product of phenols and aldehydes** i.e. cyclic oligomers are obtained from the condensation of formaldehyde with p-alkylphenols under alkaline conditions.
- The use of this word (“calix” means “beaker” in Latin and Greek) was suggested in particular by the shape of the tetramer, which can (and generally does) adopt a **bowl- or beaker like conformation** which indicates the possibility of the inclusion of “guest” molecules.

- Calixarene and resorcinarene macrocycles are renowned for their ability to form inclusion complexes or act as molecular scaffolds.
- Calixarenes and resorcinarenes have been successfully applied in a variety of roles such as catalysis (1), as selective ionophores (2) and chromatographic stationary phases (3).
- It has hydrophobic cavities that can hold smaller molecules or ions and belong to the class of cavitands known as host guest chemistry.



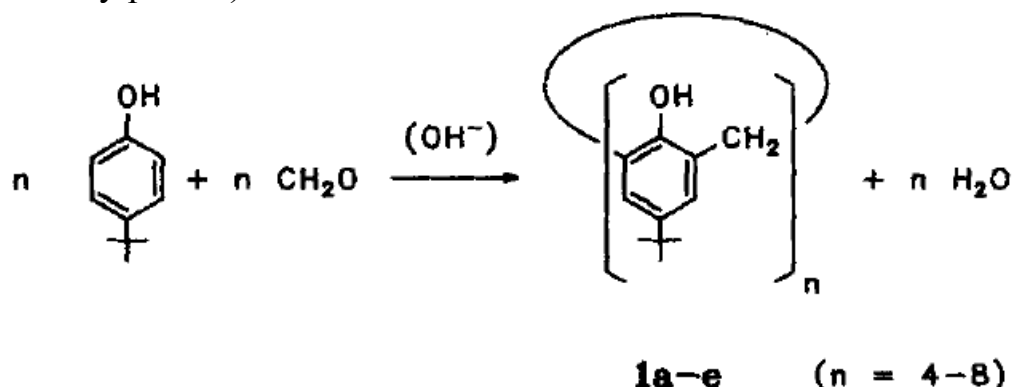
Synthesis of Calixarenes:

One pot procedure:

- Gutsche et al. developed the reaction conditions for the direct "one-pot synthesis" of calixarenes **1** with four, six, or eight tert-butylphenol units. Condensation of tert-butylphenol with formaldehyde under alkaline conditions (NaOH, KOH) leads in one step to the tetra-, hexa-, or octamer in yields (after recrystallization) of about 50, 85, and **63** %, respectively.
- The optimum amount of base for the formation of the tetramer and octamer appears to lie at about 0.03 mole NaOH per mole tert-

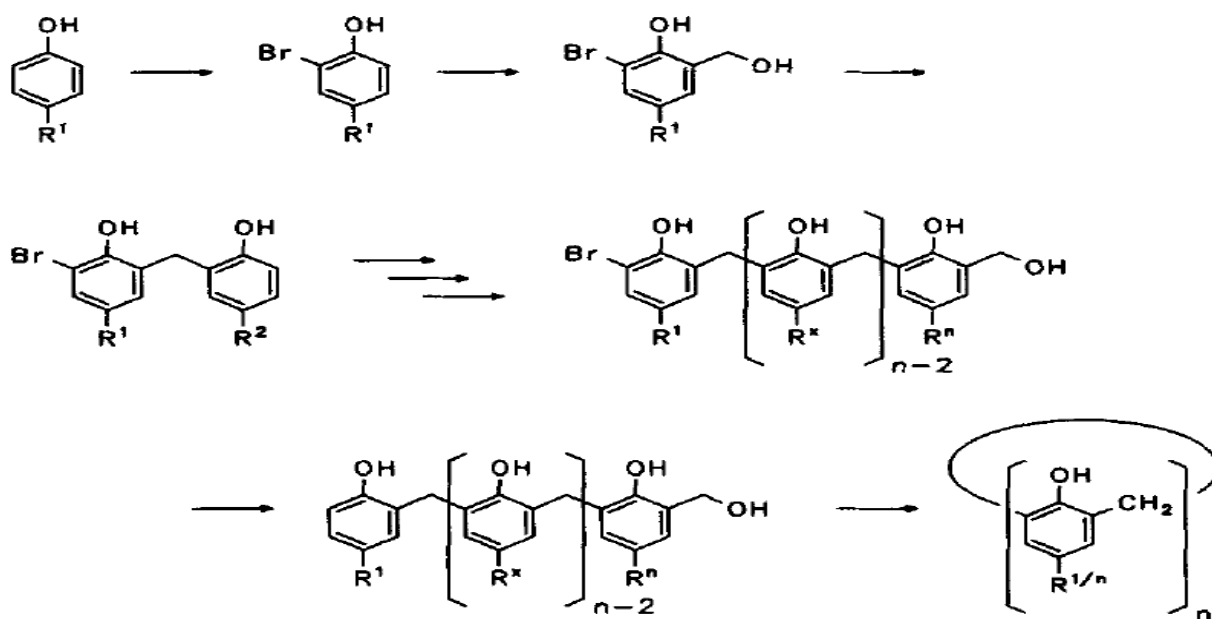
butylphenol, the tetramer requiring higher temperatures (diphenyl ether, reflux) than the octamer.

- Considerably larger amounts of base (0.4 mole KOH per mole tert-butylphenol) favor the formation of the hexamer.



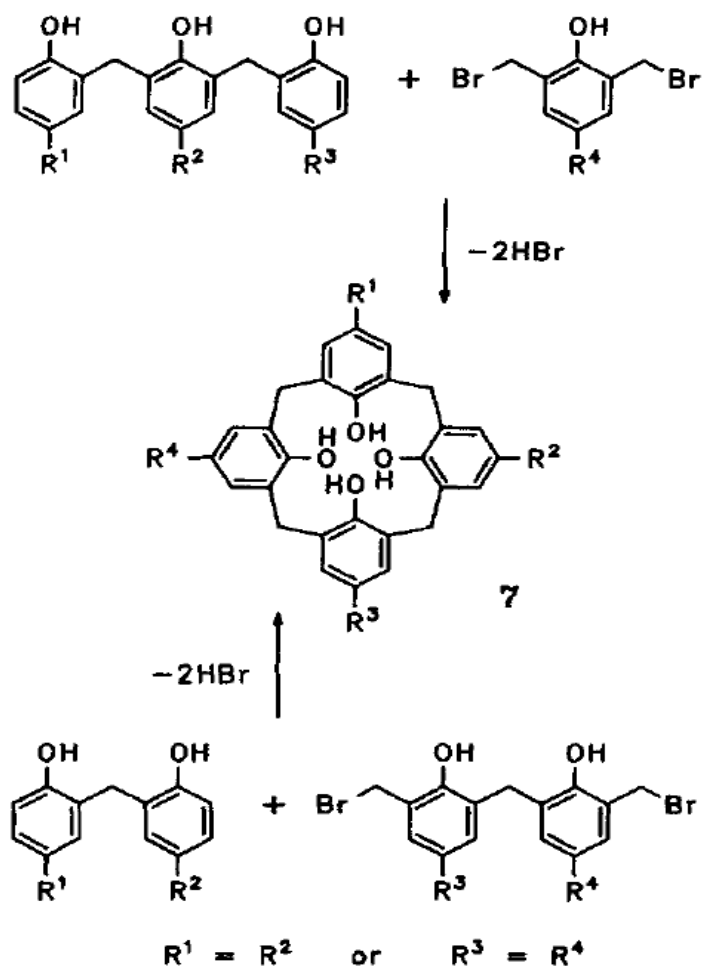
Stepwise Syntheses:

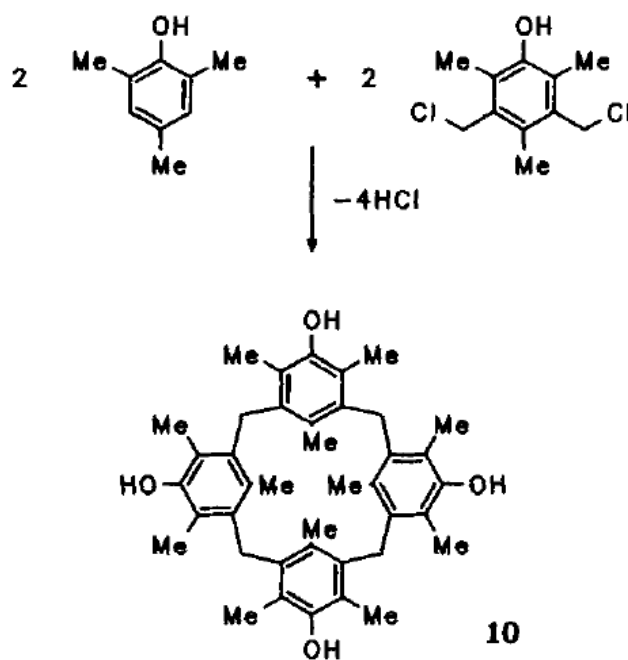
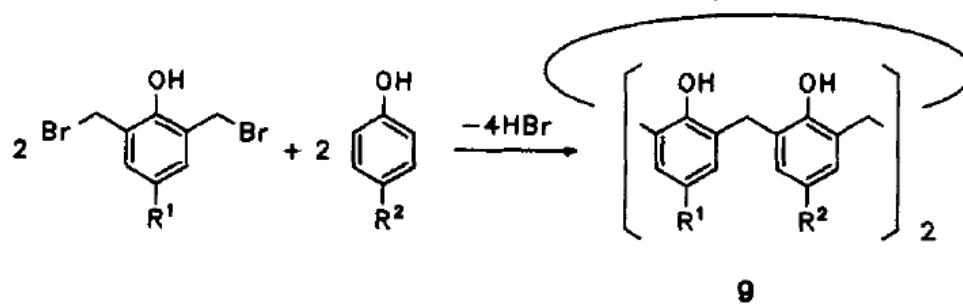
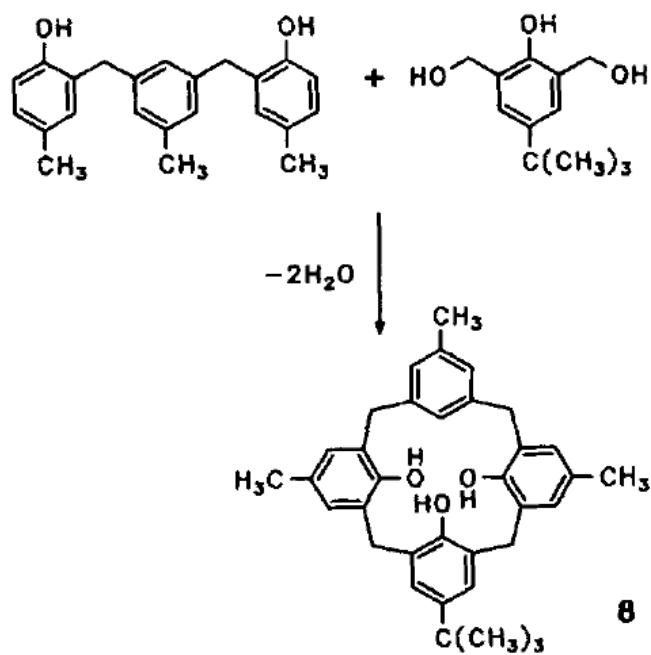
- The calixarenes obtained from a one-pot synthesis necessarily have the same substituent in all the p-positions.
- Calixarenes with different substituents can be obtained by the stepwise synthesis described by Hayes and Hunter and further optimized by Klmmerner, Happel et al.
- This stepwise synthesis starts from an o-bromo-p-alkylphenol and uses a series of alternating hydroxymethylation and condensation steps to build up a linear oligomer with a hydroxymethyl group at one end; this can then be cyclized under dilution conditions after the other o-position has been freed by dehalogenation.

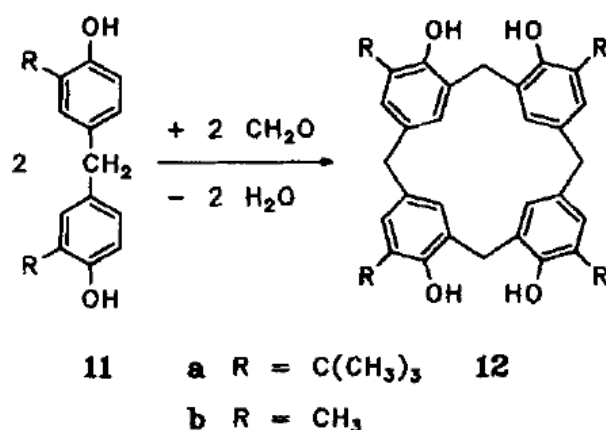


Fragment Condensation

- The last step in the stepwise synthesis involves the cyclization of *one* linear starting molecule in *one* intramolecular reaction step.
- It is also possible to prepare (in particular) calix[4]arenes from two (or more) fragments, further, the cyclization step is followed through one intermolecular condensation.
- Condensations using the 3 + 1 and “2 + 2” principles have been used for the synthesis of a range of calix[4]arenes **7**; substituents such as COOR, NO₂, N=N-Ph, and halogen can be present in the *p*-position.

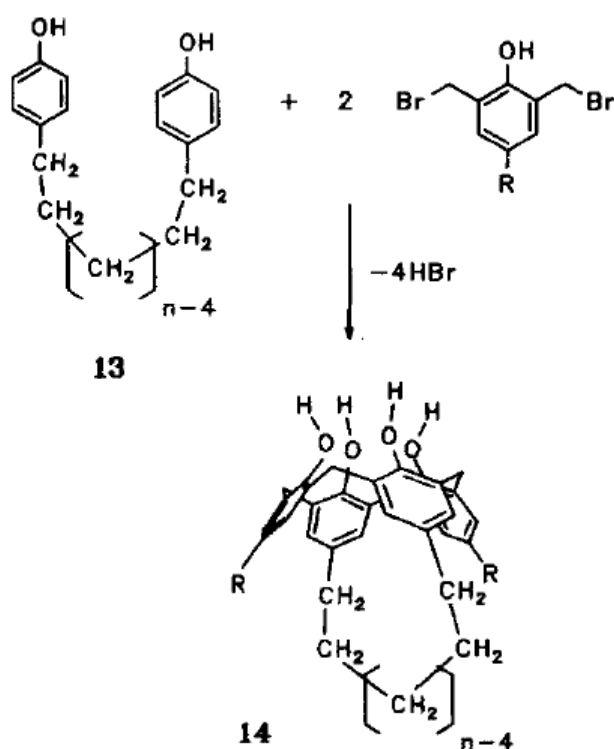


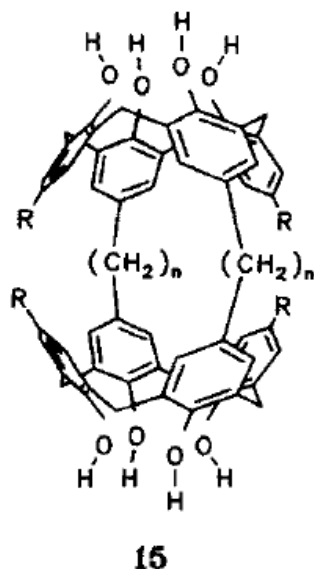




Bridged, Double, and Annelated Calixarenes:

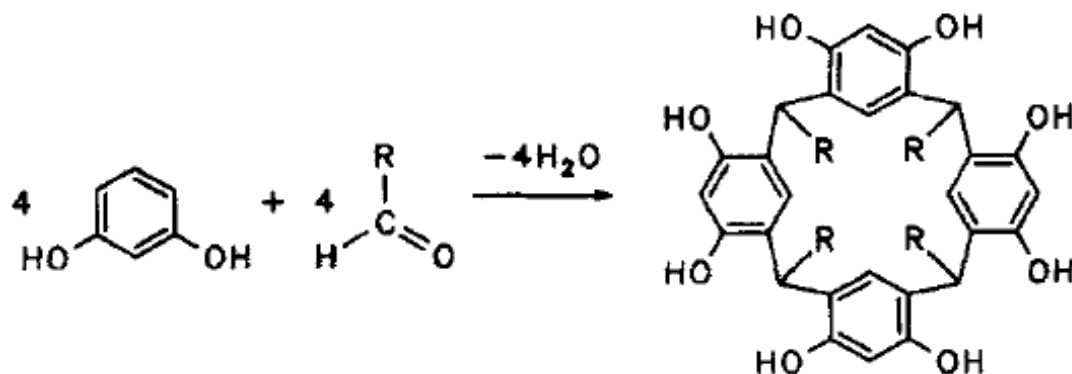
- *p*-linked diphenol **13** treated with two molecules of *o*-dibromomethylene phenol derivative to furnish the calix[4]arenes **14**.
- The synthesis of compounds **14**, yields up to 34%, for chain lengths $n = 5-16$ and the substituents R = Me, *t*Bu, alkyl, or cycloalkyl, phenyl, and chlorine.
- Further, byproduct calix[4]arenes such as **15** in which two calix[4]arene units are linked by two aliphatic bridges also obtained.





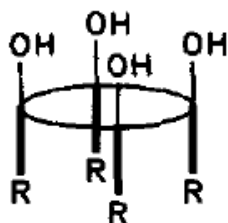
Resorc[4]arene

- Because of its greater reactivity resorcinol affords no defined condensation products with formaldehyde. Cyclic tetramers can be obtained by acid-catalyzed condensation with other less reactive aldehydes.

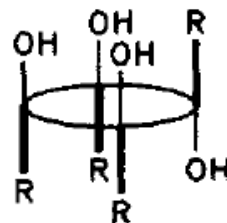


The Conformations of the Parent Compounds:

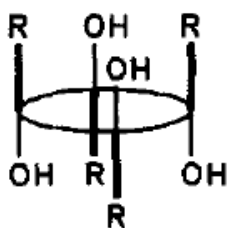
- Calixarenes lies in the variety of conformations due to free rotation about the sigma bonds of the Ar-CH₂-Ar groups.
- In the case of calix[4]arenes, relative orientation of phenol as shown in figure.
- Gutsche has introduced the terms cone, partial cone, 1,2 alternate and 1,3-alternate as the basis of conformations.
- They differ with respect to position of the phenolic OH groups (and the p-positions) with respect to the molecular plane (here easily defined by the C atoms of the methylene bridges).



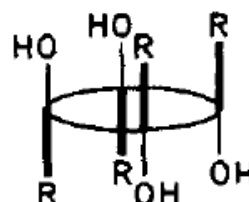
cone



partial cone



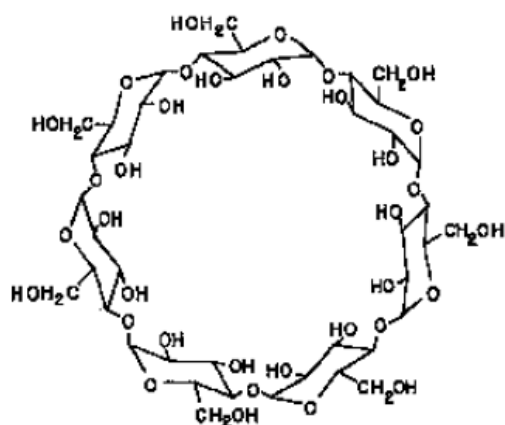
1,3-alternate



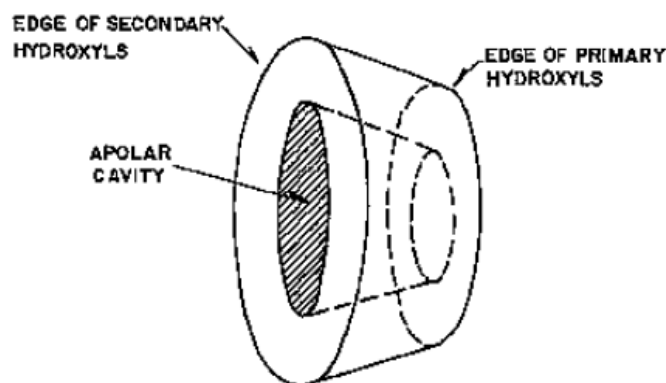
1,2-alternate

CYCLODEXTRINS

β -CYCLODEXTRIN



CHEMICAL STRUCTURE

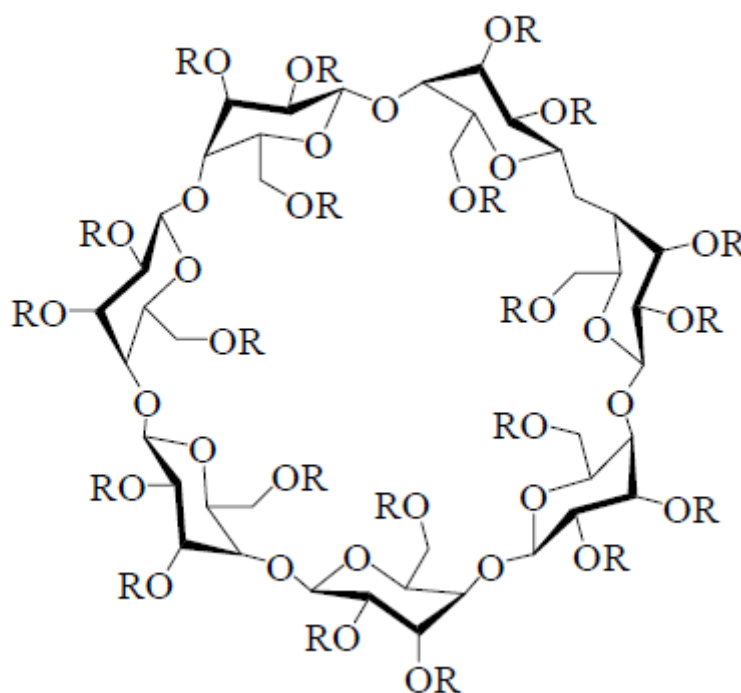


SCHEMATIC DRAWING OF THE CYCLODEXTRIN CYLINDER

Structure:

- Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose.
- These cyclic oligosaccharides consist of (α -1,4)-linked α -D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface.
- Due to the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders.

- The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge.
- The central cavity is lined by the skeletal carbons and ethereal oxygens of the glucose residues, which gives it a lipophilic character.
- Cyclodextrins are of three types: α -cyclodextrin, β -cyclodextrin and γ -cyclodextrin, referred to as first generation or parent cyclodextrins.
- The natural α -, β - and γ -cyclodextrin consist of six, seven, and eight glucopyranose units, respectively.
- The natural cyclodextrins, in particular β -cyclodextrin, are of limited aqueous solubility meaning that complexes resulting from interaction of lipophiles with these cyclodextrin can be of limited solubility resulting in precipitation of solid cyclodextrin complexes from water and other aqueous systems.
- In fact, the aqueous solubility of the natural cyclodextrins is much lower than that of comparable acyclic saccharides. This is thought to be due to relatively strong intermolecular hydrogen bonding in the crystal state.
- Cyclodextrin derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β - and γ -cyclodextrin, the randomly methylated β -cyclodextrin, sulfobutylether β -cyclodextrin, and the so-called branched cyclodextrins such as glucosyl- β -cyclodextrin.
- Beta-Cyclodextrin is the most accessible, the lowest-priced and generally the most useful.



Cyclodextrin	R = H or
β -Cyclodextrin	-H
2-Hydroxypropyl- β -cyclodextrin	-CH ₂ CHOHCH ₃
Sulfobutylether β -cyclodextrin sodium salt	-(CH ₂) ₄ SO ₃ ⁻ Na ⁺
Randomly methylated β -cyclodextrin	-CH ₃
Branched β -cyclodextrin	Glucosyl or maltosyl group

Properties:

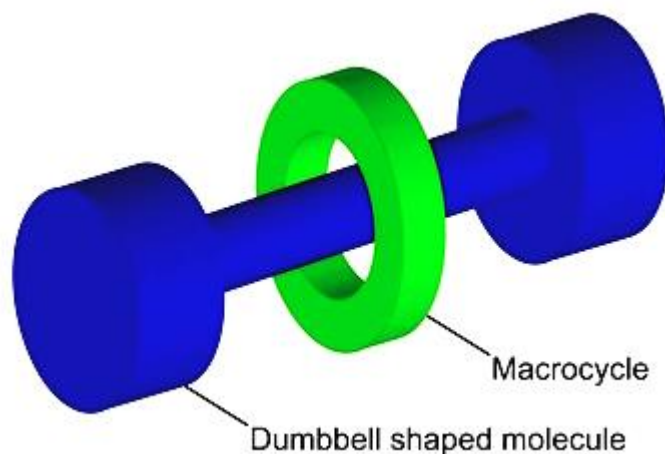
- The main properties of those cyclodextrins are given in Table 1
- Studies of cyclodextrins in solution are supported by a large number of crystal structure studies.
- Cyclodextrins crystallise in two main types of crystal packing, channel structures and cage structures, depending on the type of cyclodextrin and guest compound.

Table 1
Cyclodextrins properties

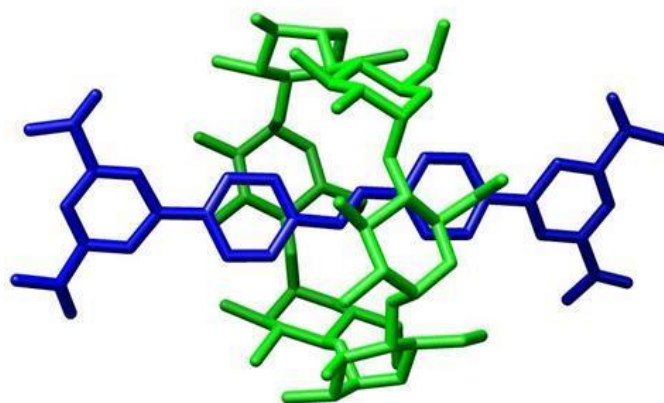
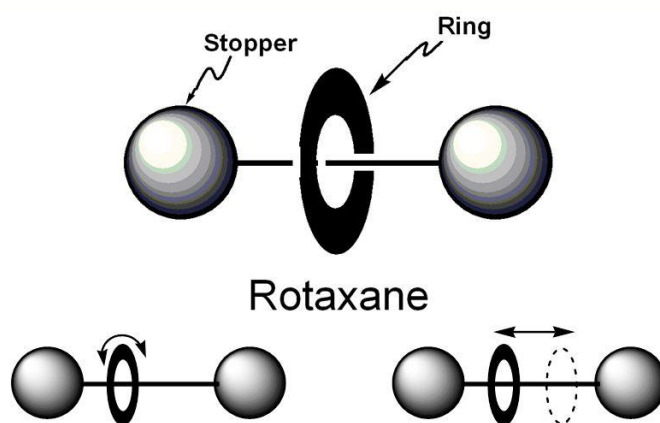
Property	α -Cyclodextrin	β -Cyclodextrin	γ -Cyclodextrin
Number of glucopyranose units	6	7	8
Molecular weight (g/mol)	972	1135	1297
Solubility in water at 25 °C (% w/v)	14.5	1.85	23.2
Outer diameter (Å)	14.6	15.4	17.5
Cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3
Height of torus (Å)	7.9	7.9	7.9
Cavity volume (Å ³)	174	262	427

- These crystal structures show that cyclodextrins in complexes adopt the expected 'round' structure with all glucopyranose units in the 4C1 chair conformation.
- α -cyclodextrin is the form in which the steric strain due to cyclization is least while γ -cyclodextrin is most strained.
- Depending on the substituent, the solubility of the cyclodextrin derivatives is usually different from that of their parent cyclodextrins.
- Cyclodextrins are frequently used as building blocks. Up to 20 substituents have been linked to β -cyclodextrin in a regioselective manner.

- The synthesis of uniform cyclodextrin derivatives requires regioselective reagents, optimisation of reaction conditions and a good separation of products.
- The most frequently studied reaction is an electrophilic attack at the OH-groups, the formation of ethers and esters by alkyl halides, epoxides, acyl derivatives, isocyanates, and by inorganic acid derivatives as sulphonic acid chloride cleavage of C–OH bonds has also been studied frequently, involving a nucleophilic attack by compounds such as azide ions, halide ions, thiols, thiourea, and amines; this requires activation of the oxygen atom by an electron-withdrawing group
- Because of their ability to link covalently or noncovalently specifically to other cyclodextrins, cyclodextrins can be used as building blocks for the construction of supramolecular complexes.
- Their ability to form inclusion complexes with organic host molecules offers possibilities to build supramolecular threads.



Structure of Rotaxane



The simplest rotaxane is based on threading of an axle molecule through the cavity of CDs with the assistance of noncovalent intermolecular attractive forces or one dumbbell-shaped molecule and one macrocycle are interlocked

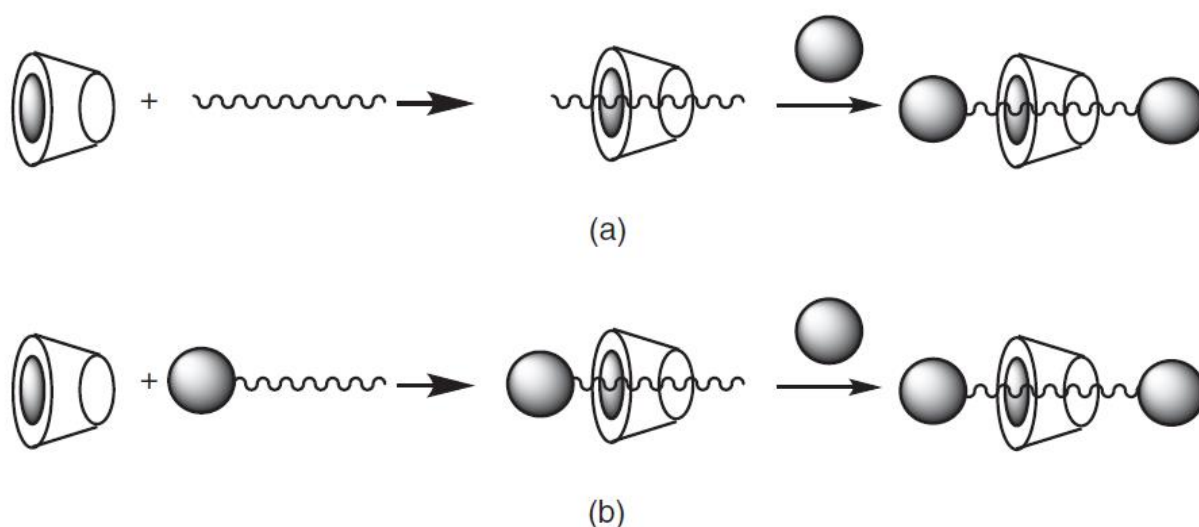


Figure Schematic synthesis of rotaxane via two methods, (a) synthesis of a pseudorotaxane and then reaction with bulky blocking group and (b) formation of an inclusion complex containing a guest molecule with one blocking agent at the end and reaction with another blocking agent.

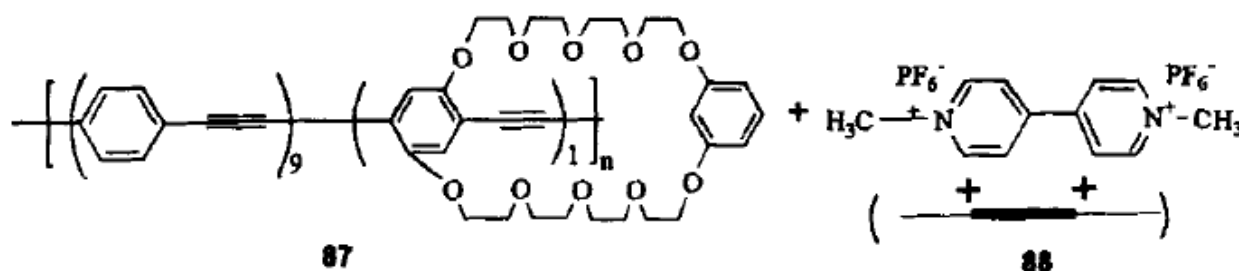
Properties of Rotaxane:

- The absorption spectra of [2]rotaxanes showed higher absorption than those of dumbbell-shaped molecules.
- The emission spectra of [2]rotaxanes showed higher emission than those of dumbbell-shaped molecules.

Polyrotaxanes:

Electronic Properties:

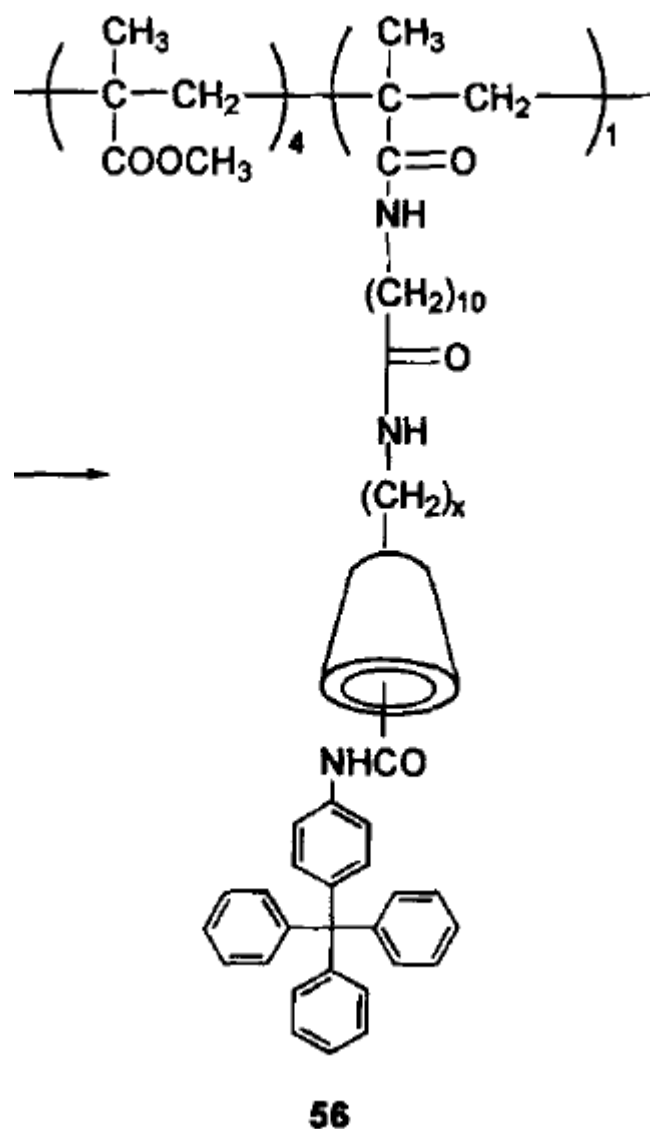
Phenyleneacetylene-derived polymeric cyclic **87** was investigated for its complexation with paraquat salts (e.g. **88**) in solution. It was found that the strong fluorescence of the polymer backbone was highly quenched by the formation of the polyrotaxane.



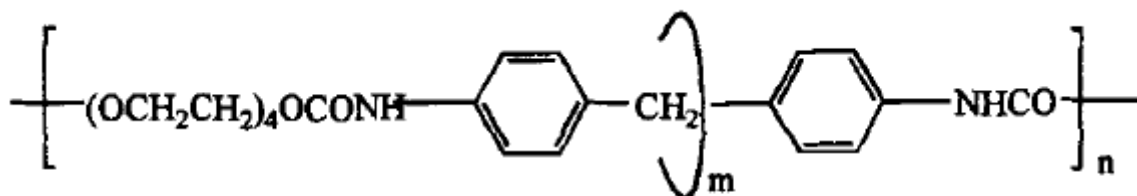
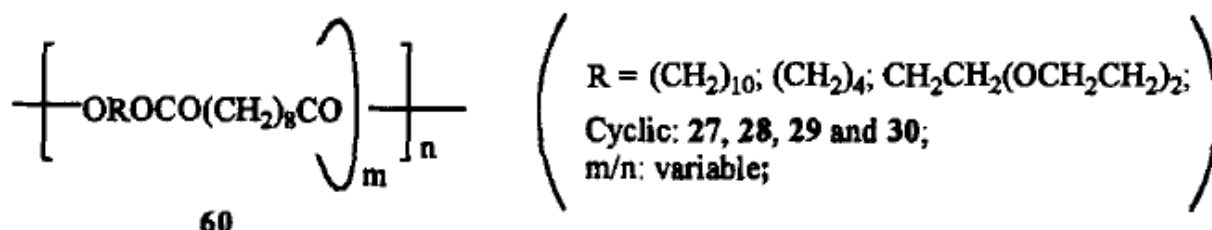
Solubility:

- The solubility of a polymer will be altered by threading of the cyclic to form a polyrotaxane. The change is related to the properties and structures of both components.
- Ritter and coworkers reported that CD-derived side-chain poly(methyl methacrylate rotaxane) **56** is soluble in ether, a poor solvent for the parent backbone.

- The solubility change is because of the **loss of intermolecular hydrogen bonding** between the pendant **NH** groups of the backbone as these NH groups are shielded by the threaded CD units.



- Threading crown ethers **onto poly(alkylene sebacate)s** increased the solubility of the **systems (60)** in **methanol and water**. This **enhancement is because of hydrogen bonding** of the crown ether with the hydroxy group of the solvents.
- Sufficient crown ether even made the **poly(urethane rotaxane)s 59** soluble in water.



59 (cyclic: 28, 29 and 30; m/n: variable)

Mechanical Properties

- Polyrotaxanes derived from self-assembly of a polyurethane bearing paraquat moieties had higher rubbery plateau moduli than the corresponding backbones. Thermal analysis revealed that the stability was enhanced by the formation of the polyrotaxanes.

Summary

- ✚ Catenanes are interlocked to each other while rotaxanes are linear molecules which treaded through a macrocyclic ring.
- ✚ The nomenclature assign through the number of rings which are interlocked to each other.
- ✚ The statistical and direct approach have been used for the synthesis of catenanes.
- ✚ The statistical approach have been used for the synthesis of rotaxanes.
- ✚ Catenanes and rotaxanes are synthesized by following the π - π stacking interactions.
- ✚ Hydrogen bonding also play important during the synthesis of Catenanes and rotaxanes.