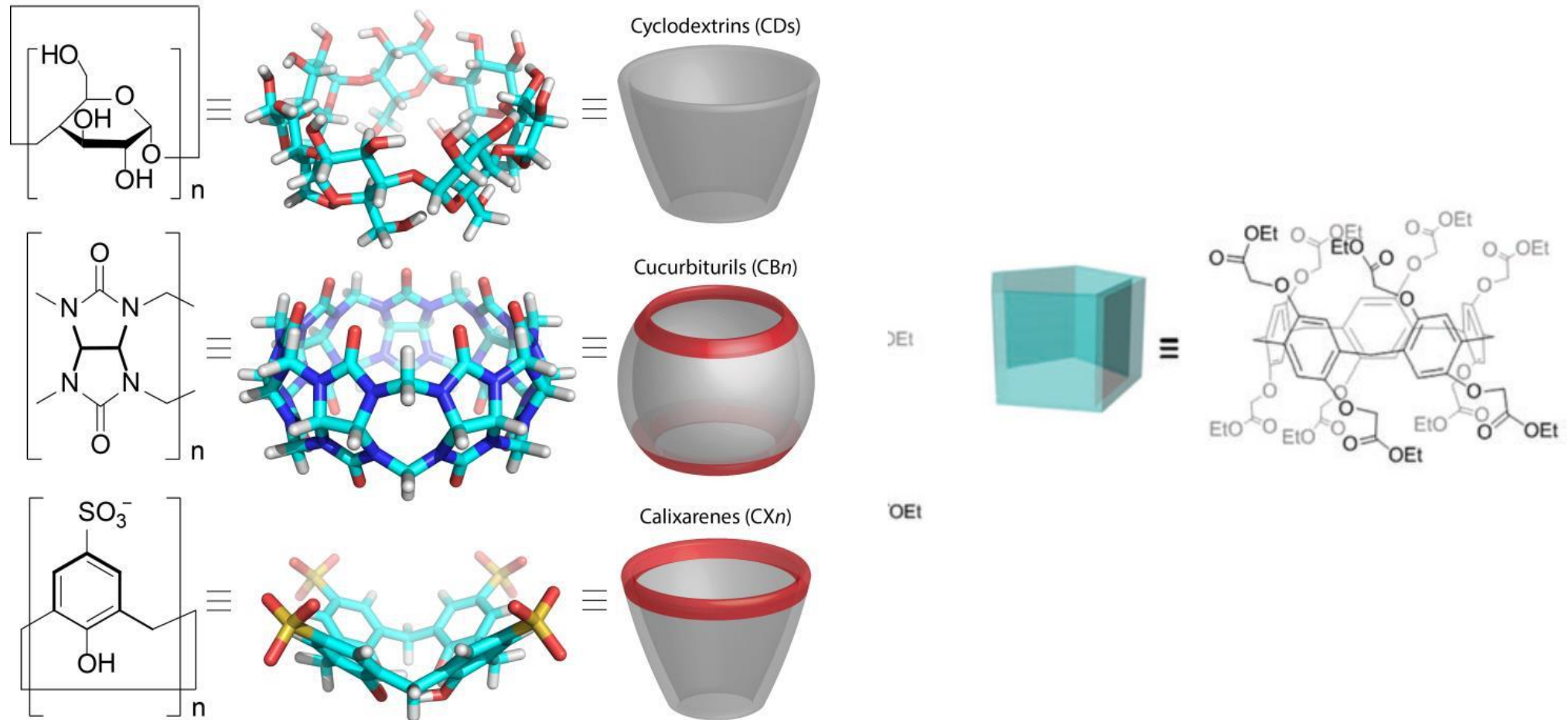


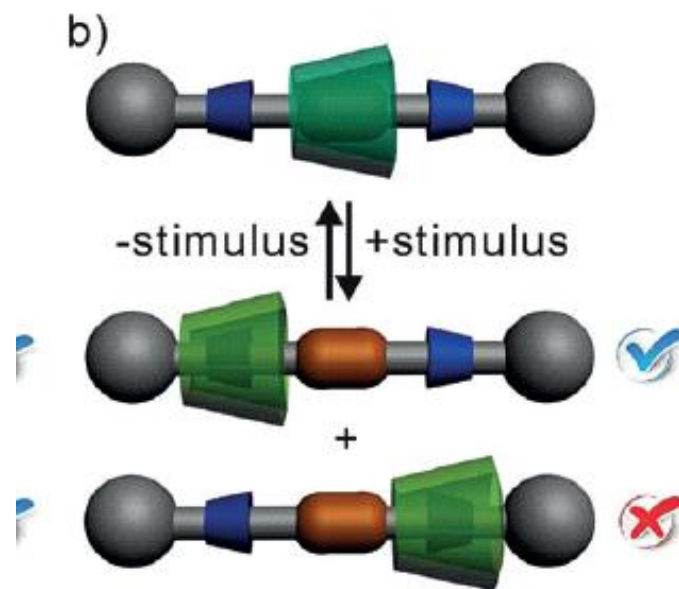
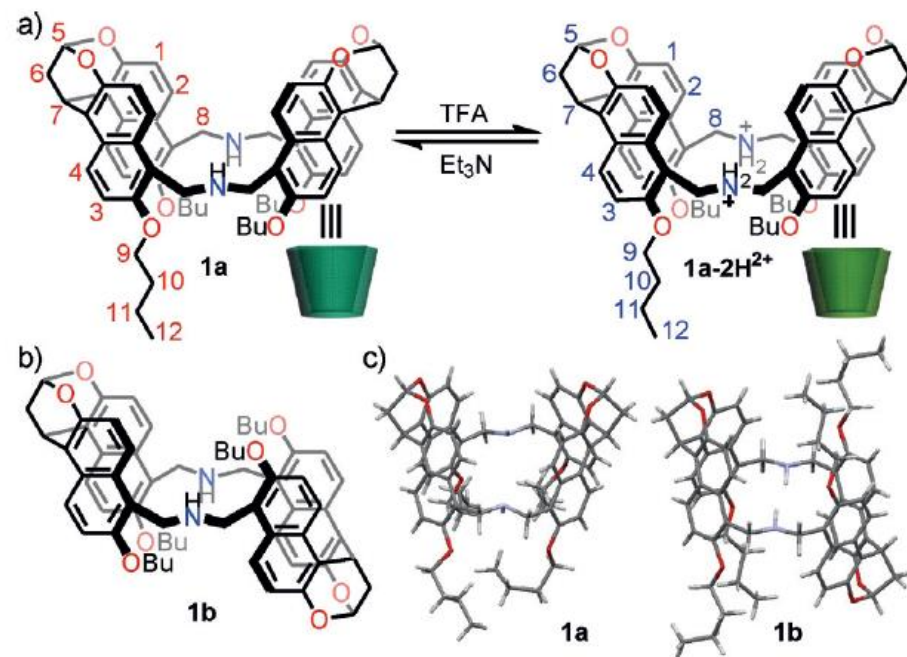
Lezione 9

- Macro cicli con cavità: i calixareni

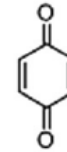
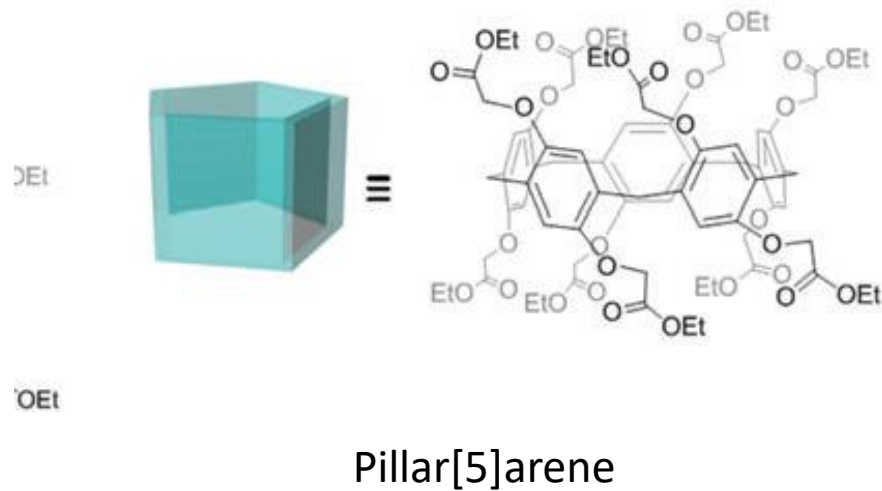
macrocyclic hosts with cavities: calix[n]arenes, cyclodextrins, cucurbiturils, pillar[n]arenes



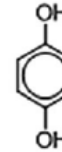
New cavitands...



Pillar(n)arenes



(A)



(B)

Hydroquinones, the building blocks of pillar[n]arenes, play a pivotal role in electron transfer processes. Quinones such as co-factors are responsible for the electron transport systems that facilitate the transfer of electrons to stimulate transmembrane electrochemical proton gradients in cells, driving the production of adenosine triphosphate (ATP).

Pillar[n]arenes are useful scaffolds for the design of various interesting supramolecular systems including liquid crystalline materials, cyclic dimers, chemosensors, supramolecular polymers, drug delivery systems, trans-membrane channels, cell glue, selective adsorption of porous materials, molecular recognition and nanotubes

Ion channels

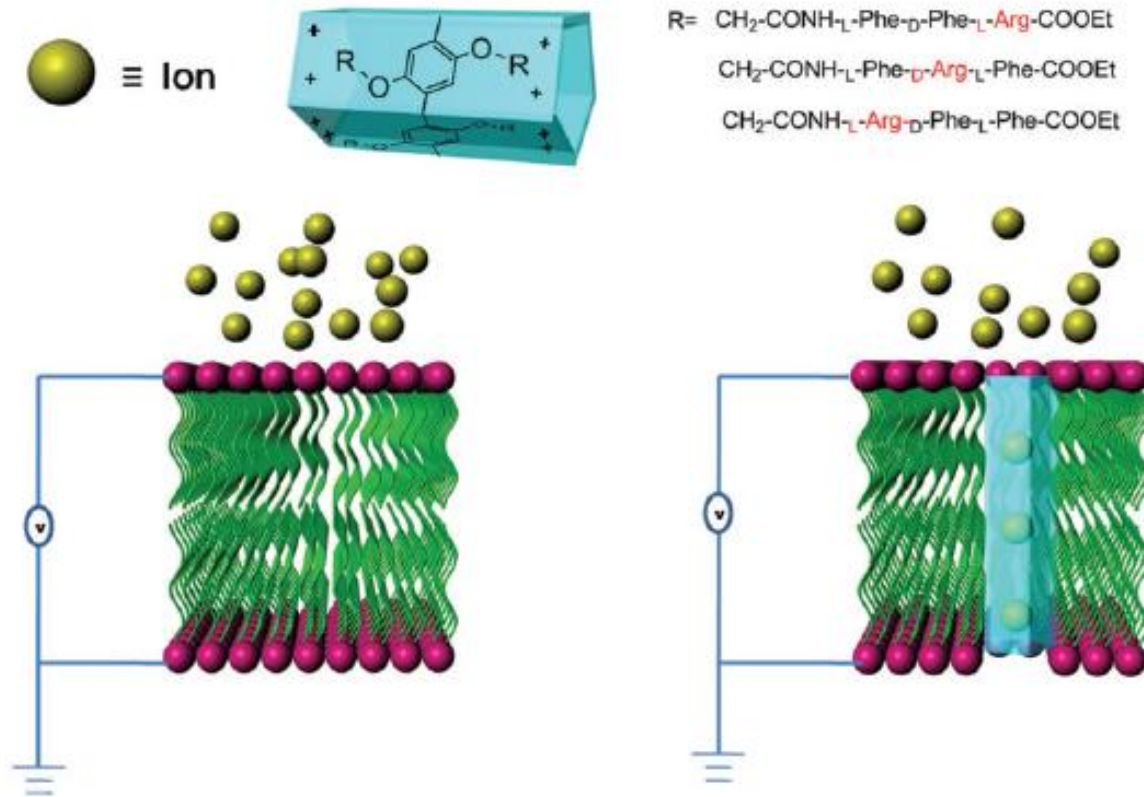
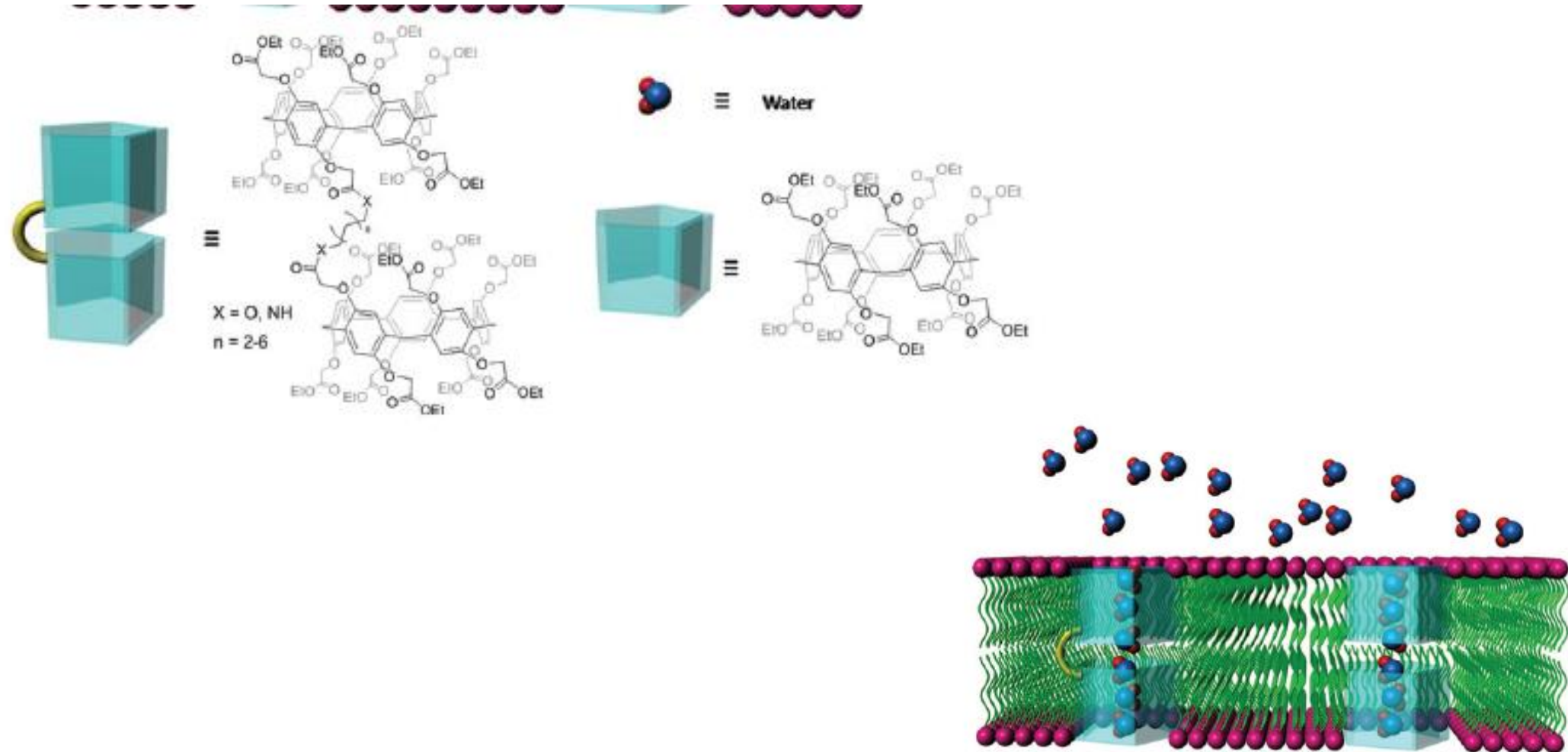


Fig. 4 Schematic representation of the artificial voltage-gated ion channel prepared by the incorporation of positively charged Arg units to pillar[5]arene side chains. Cation transport through the ion channel is regulated by voltage-dependent reversible insertion of the artificial ion channel in the lipid bilayer.

Pillar(5) arenes to build water channels



Calix[4]arene-based ion channels

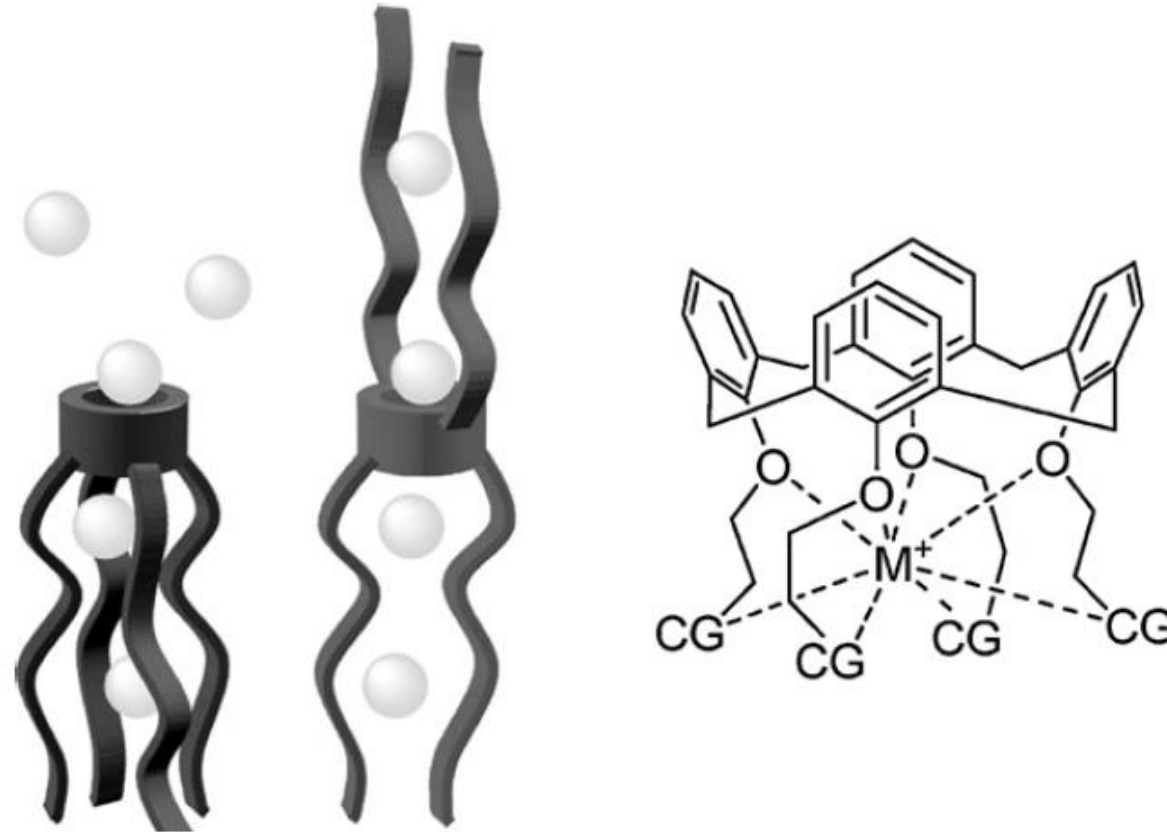
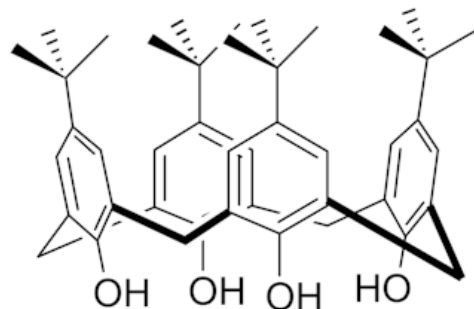


Fig. 3. Two possibilities of how calixarenes can span phospholipid bilayers (left, image reprinted with permission from Ref. [15]) and most common binding motif of calixarene based ion channels (right, CG = coordinating group).

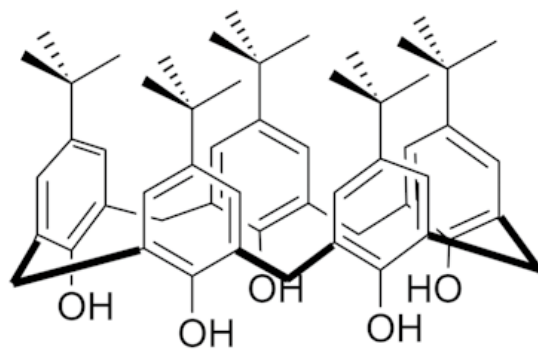
The calixarenes

The tert-butyl calix[4]arene

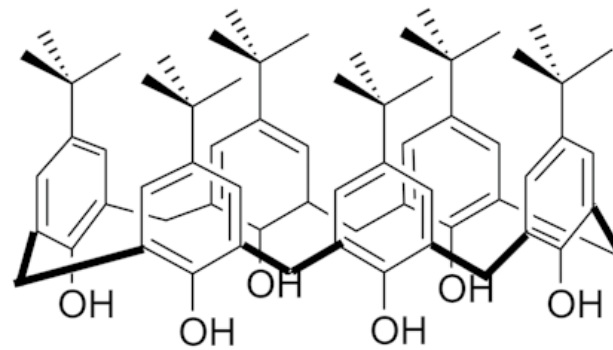


Calix[4]arene

T. David Gutsche:
number in square brackets =
phenol units

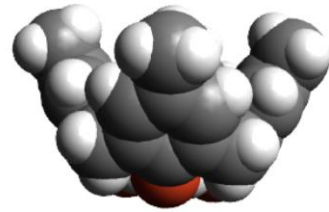


Calix[5]arene



Calix[6]arene

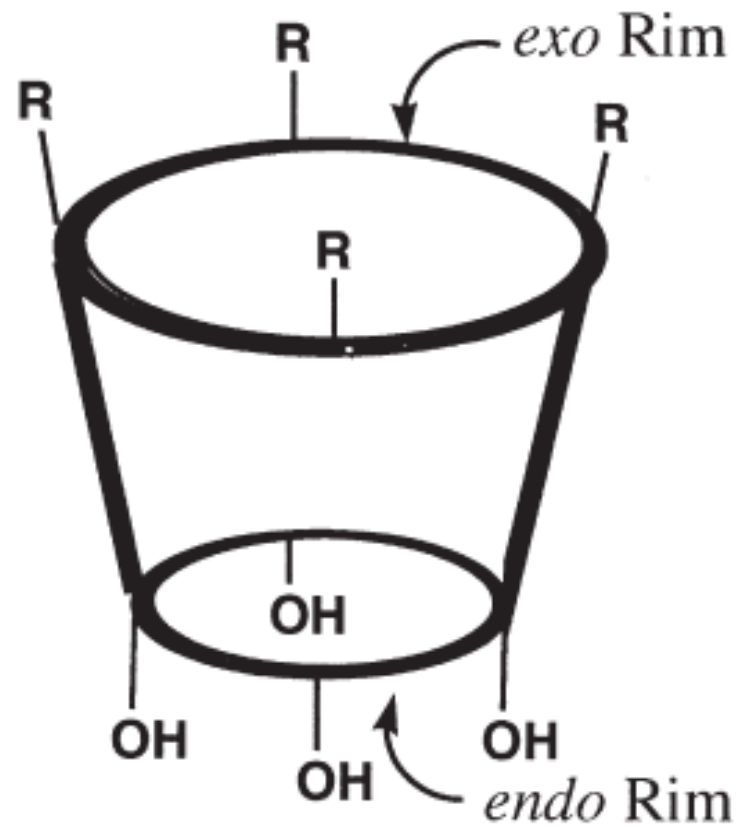
The cup shape



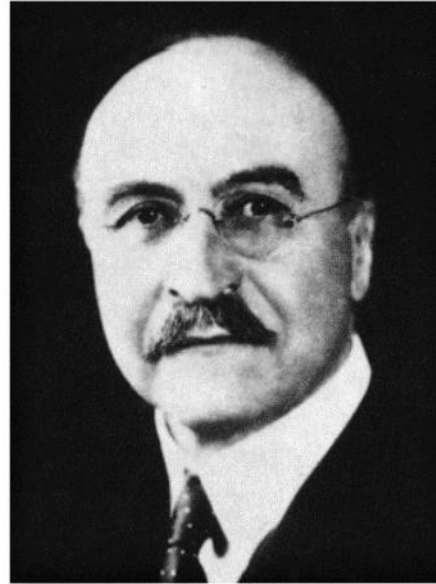
The smaller members of the family adopt a cone-shaped structure, hence the name calix[n]arene coined by Gutsche, from the Greek “calix” meaning vase, where n denotes the number of phenolic residues.

Such a bowl shape results in the formation of a hydrophobic, electron-rich cavity, which is well-suited to the formation of inclusion complexes, particularly cations.

Upper(exo) and lower (endo) rims



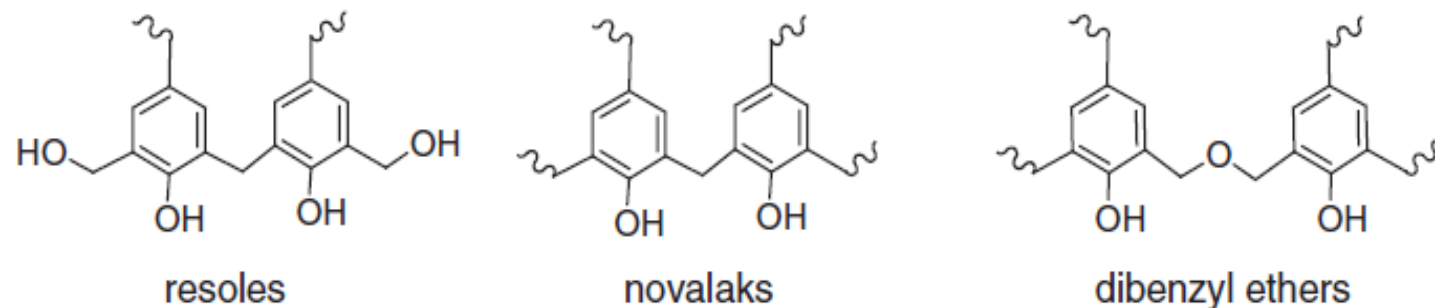
The synthesis



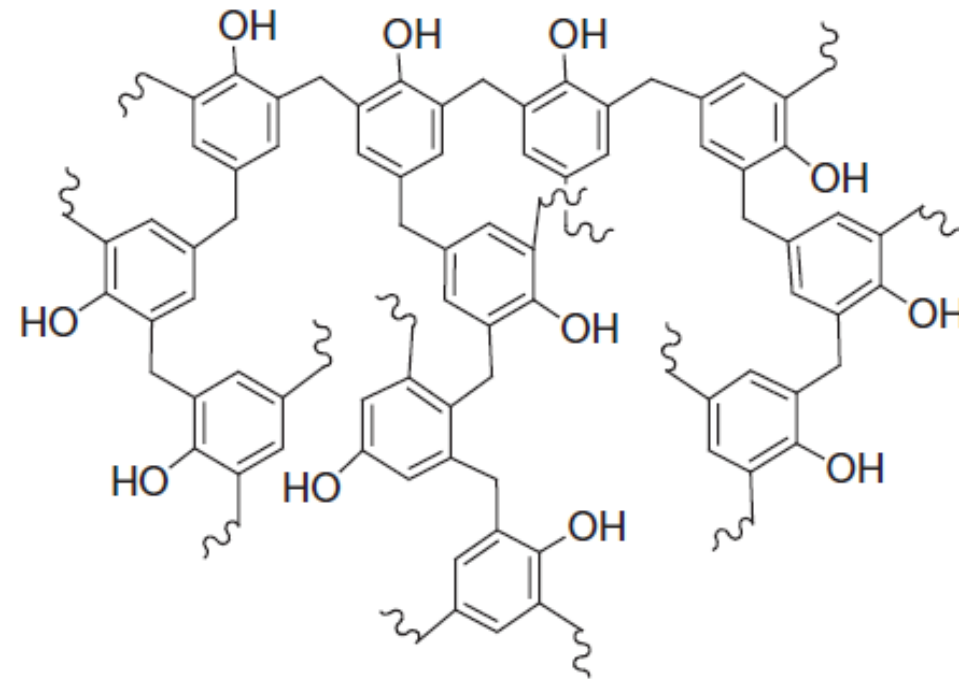
Leo Baekeland

- 1902: Leo Baekeland synthesized an interesting resin from phenol + formaldehyde in the presence of carefully controlled quantity of base, this highly cross-linked polymer was called “bakelite”.
- **The bakelite patent is the beginning of modern plastics.**

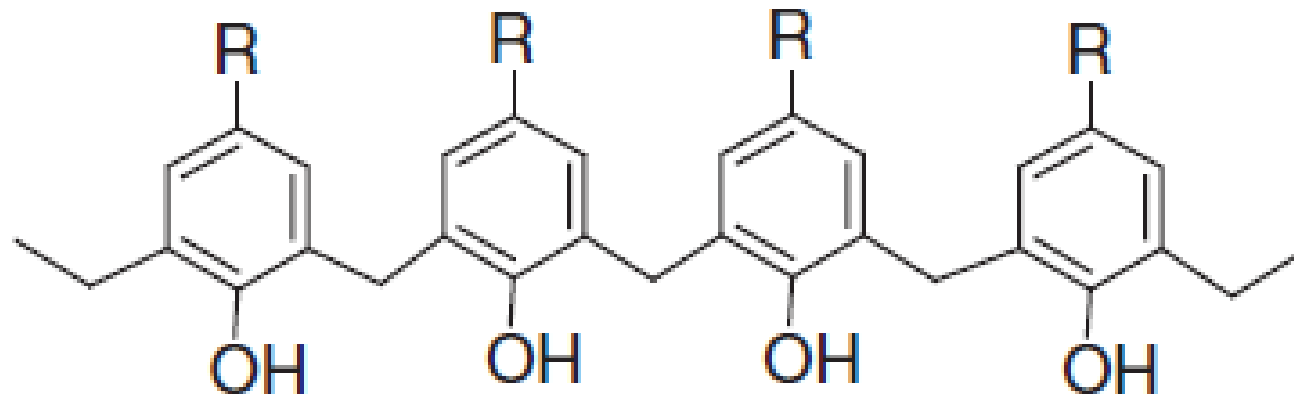
vollständig im Dunklen". Today, almost a century later we continue to be at least somewhat in the dark about the precise details of the Bakelites. The progress that has been made and the problems that remain unresolved are recounted in a variety of books and articles.¹⁴ As had already been realized by Baeyer in 1872, however, it is CH_2 and CH_2OCH_2 groups that are the most likely linkages between pairs of aromatic rings in a formaldehyde-phenol condensation product. Thus, the dominant structural diaryl moieties in a typical resin are those shown in Plate 1-6; *viz.* resoles, novolaks and dibenzyl ethers.

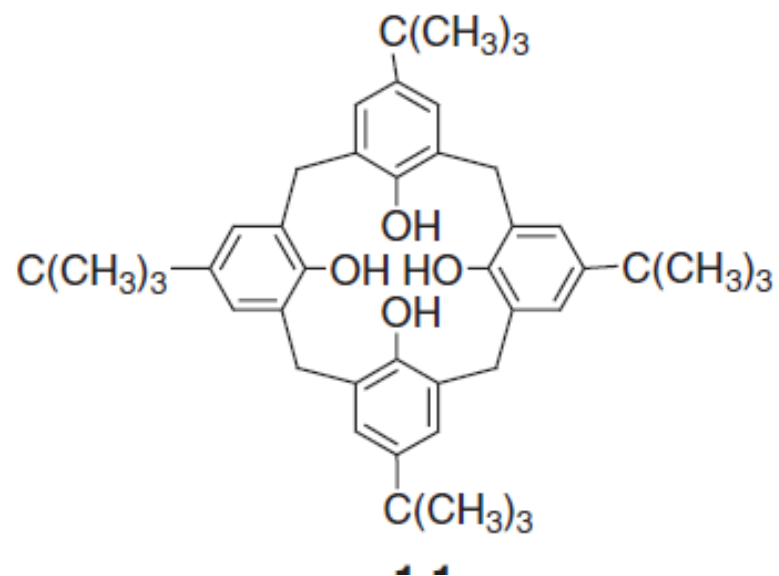


Whereas phenol reacts at both the ortho- and para- positions to form a highly cross-linked polymer in which almost all of the phenolic units are attached to three other phenolic residues.



a para-substituted phenol can react only at the two ortho-positions, thereby reducing the cross-linking possibilities.

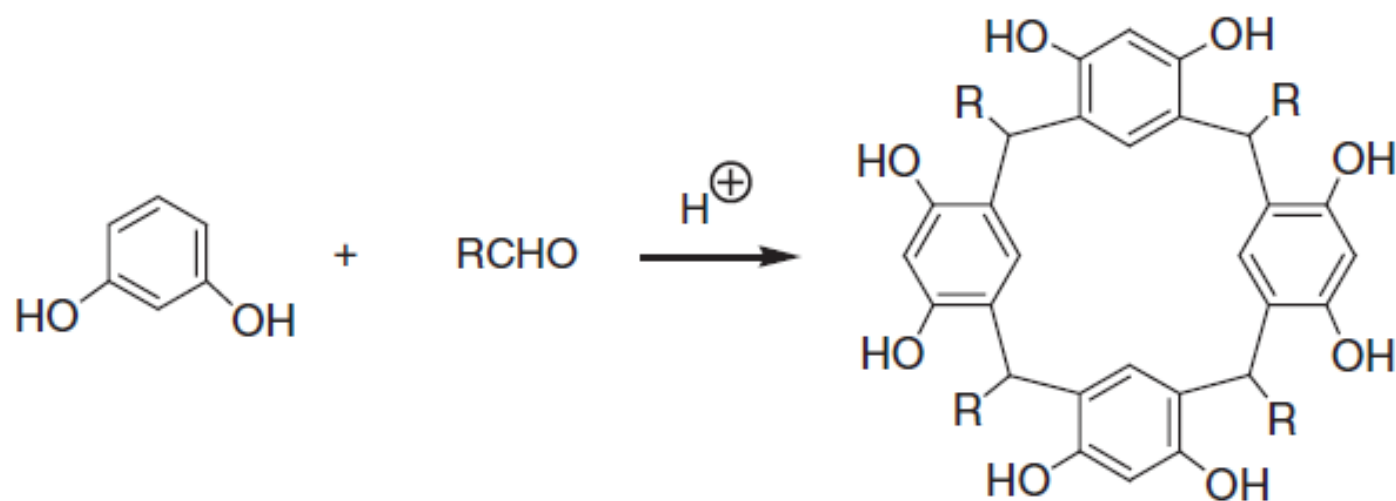




- 1942, as a part of the bakelite process, Alois Zinke (Univ. of Graz, Austria) isolated a cyclic product from the reaction of p-tertBu phenol with CH_2O : this was the p-tertButylcalix[4]arene contaminated with other high-MW products.
- In 1956 the p-tertButylcalix[4]arene was synthesized stepwise and its structure was then confirmed
- 1955 John Cornforth: conformers of calix[4]arene

The resorcinarenes

Resorcinol was among the reactants that Baeyer used in his investigations with phenols and aldehydes, and he discovered that it reacts with aldehydes such as acetaldehyde and benzaldehyde under acidic conditions to produce crystalline, high-melting compounds. Niederl and Vogel isolated solid, high melting condensation products from the reaction of resorcinol and aldehydes (e.g. acetaldehyde, propionaldehyde, isovaleraldehyde) and concluded, primarily on the basis of molecular weight determinations, that the products are best represented as cyclic tetramers (Figure). In contrast to the Zinke calixarenes in which four OH groups are intraannular (also designated as “endo-annular”), the eight OH groups in the Niederl octols are extraannular (also designated as “exo-annular”).



Calix[4]arene: proof of the structure

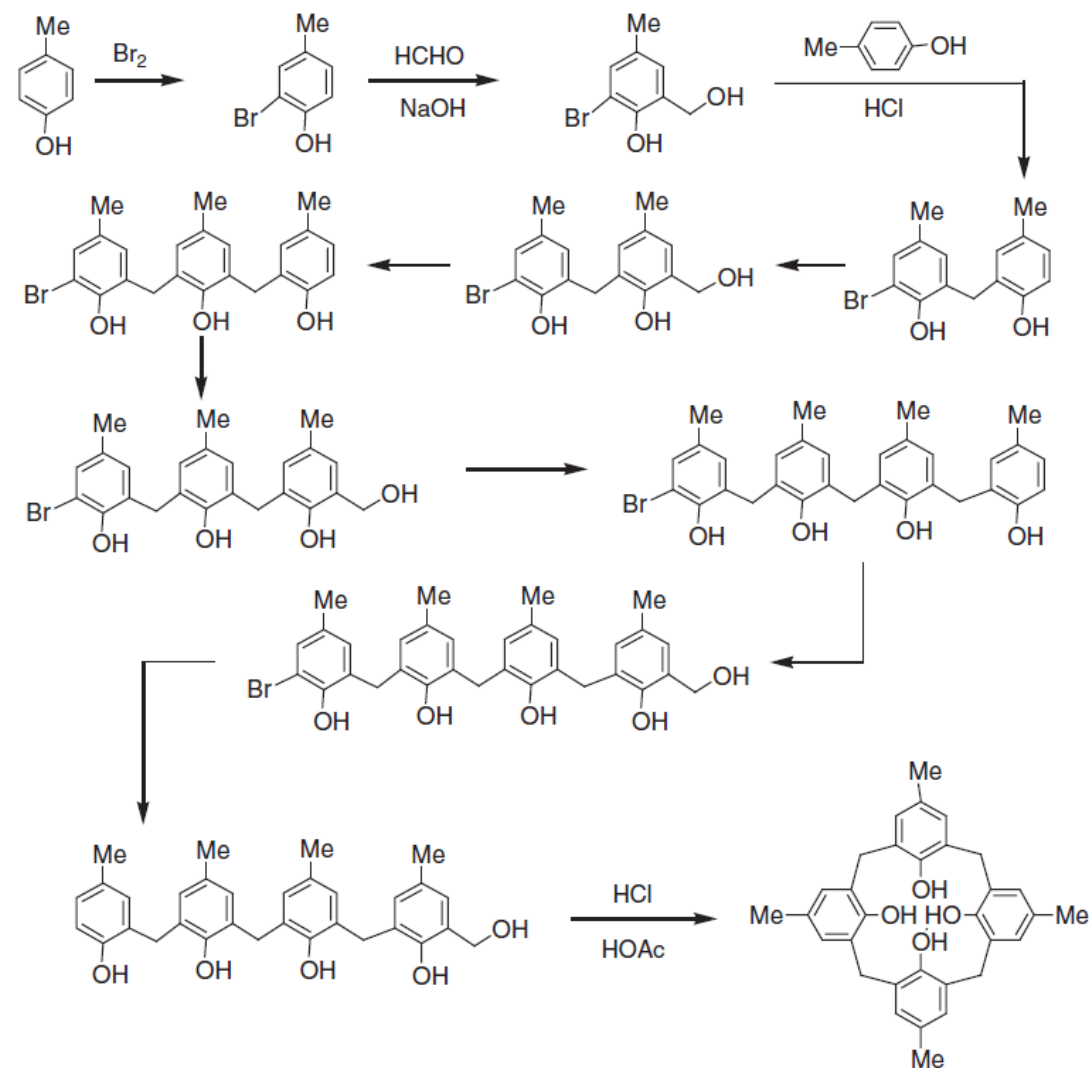
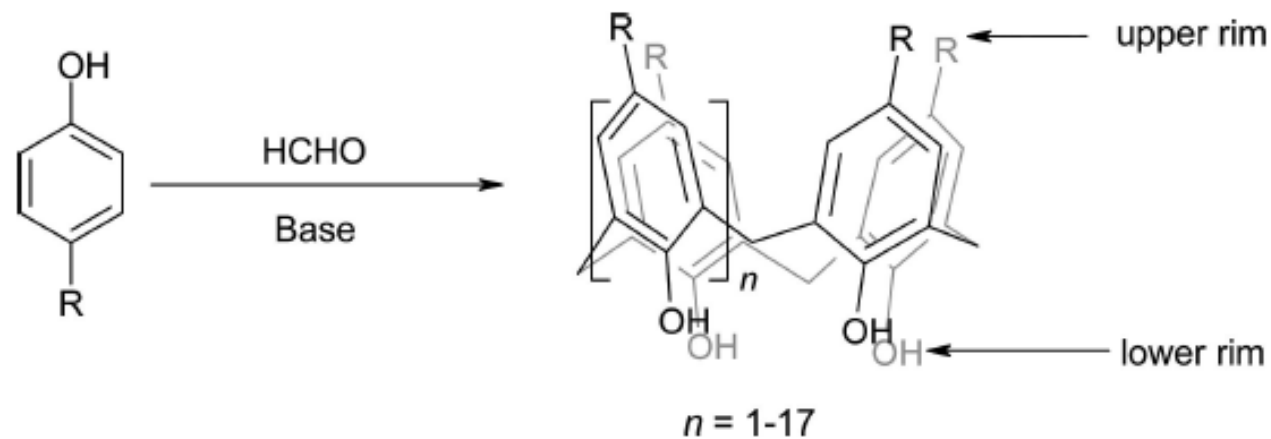


Figure 1.1 Hayes and Hunter stepwise synthesis of a calix[4]arene.

**Scheme 1. Formation and Nomenclature of Calix[*n*]arenes
(R = Alkyl)**

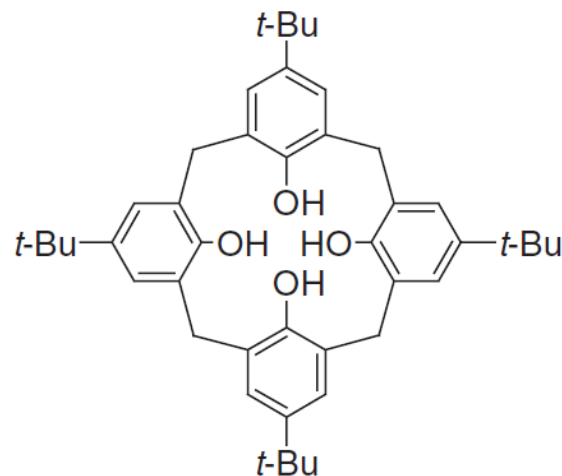


The condensation of formaldehyde with p-alkylphenols under alkaline conditions, a reaction dating back to the days of Baeyer and Zinke, affords initially linear polyphenols, which, once a certain temperature is achieved, yield cyclic oligomeric phenolic compounds.

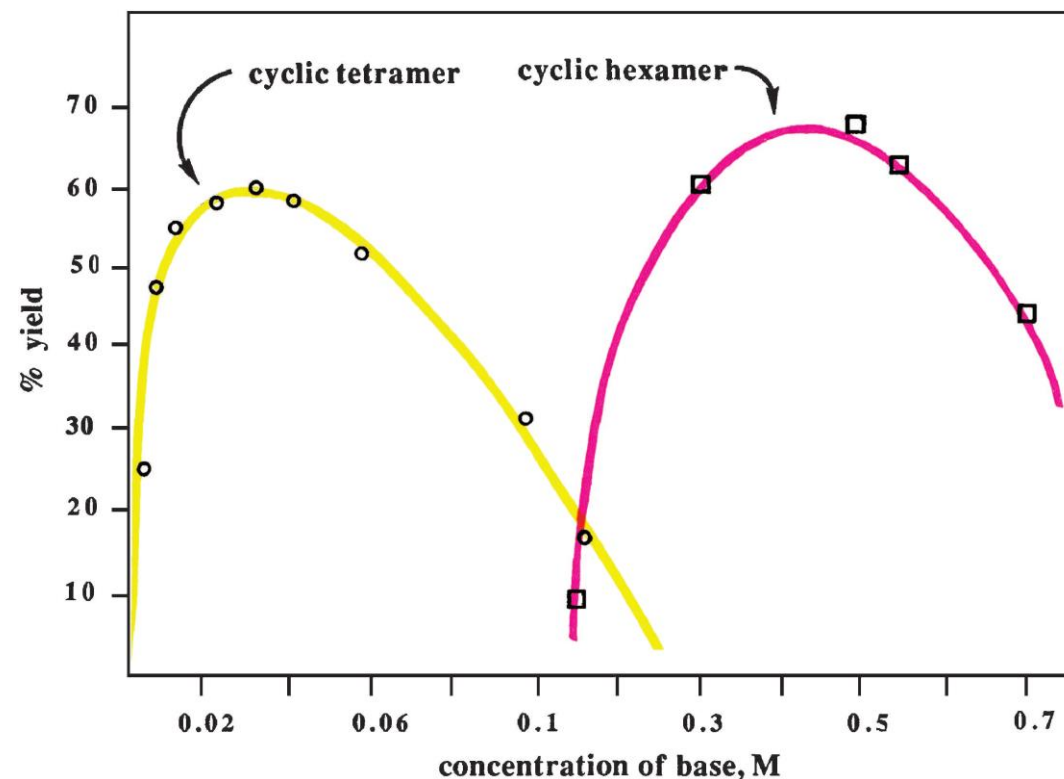
One-step, multigram synthetic procedures have now been developed, which by varying either the temperature or amount of base used in the preparation, readily afford the tetrameric, hexameric, and octameric phenolic ring systems, bridged by methylene (-CH₂-) spacers

Synthesis of *p*-tertbutylcalix[4] arenes

Modified Zinke–Cornforth Procedure (Synthesis of *p*-tert-butylcalix[4]arene).⁴ A mixture of *p*-tert-butylphenol, 37% formaldehyde and an amount of NaOH corresponding to 0.045 equivalents with respect to the phenol is heated for 2 hrs at 110–120 °C to produce a thick viscous mass called the “precursor”. The “precursor” is then heated in refluxing diphenyl ether for 2 hrs, the reaction mixture is cooled, and the crude product is separated by filtration and recrystallized from toluene to give *ca.* 50% yield of glistening white rhombs with mp. 342–344 °C.



p-tert-Butylcalix[4]arene

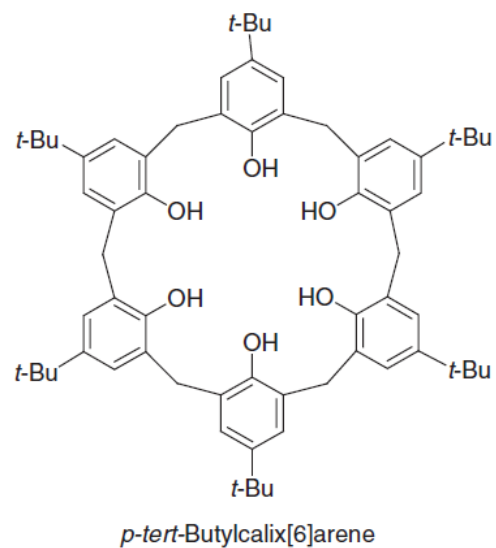


That there is an optimum amount of NaOH for producing the calix[4]arene is indicated by the data in Figure 2.1, which show that the yield of cyclic tetramer reaches a maximum at 0.03–0.04 equivalents of base and falls off on either side of this range. With less base the yield falls to zero, and with more base it again falls as the product increasingly becomes the cyclic hexamer.

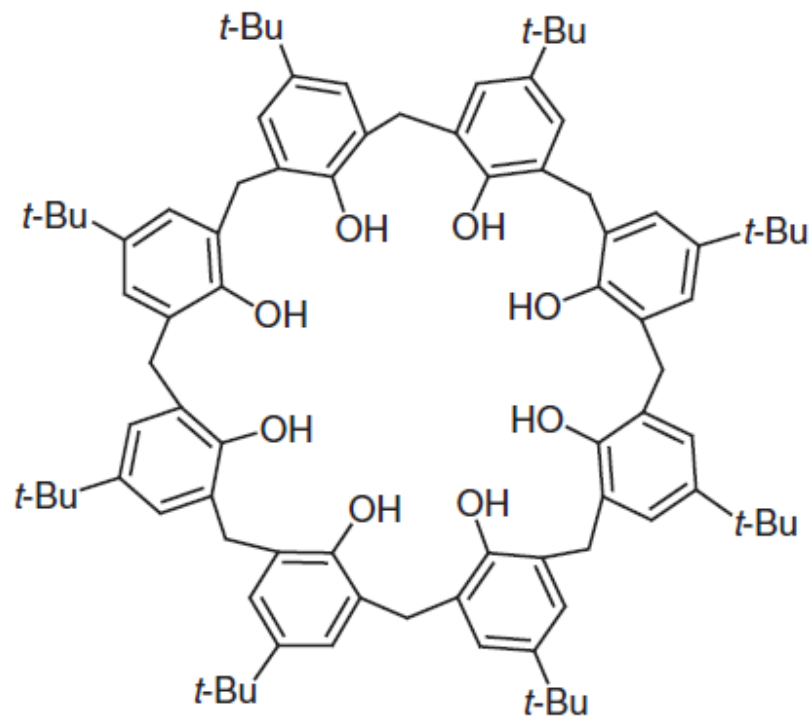
While the amount of base that is used in the cyclooligomerization process affects the outcome in a profound fashion, the cation that accompanies the basic anion also has a sometimes significant though smaller effect,⁷ as follows: (a) LiOH is usually, but not always, an inferior base for the cyclooligomerization, (b) NaOH tends to give somewhat higher yields of cyclic octamer in the Petrolite Procedure and (c) KOH, RbOH and CsOH tend to give somewhat higher yields of cyclic hexamer in the Modified Petrolite Procedure as described below

Modified Petrolite Procedure (Synthesis of *p*-tert-Butylcalix[6]arene).

A mixture of *p*-tert-butylphenol, 38% of formaldehyde and an amount of KOH corresponding to 0.34 equivalents with respect to the phenol is heated for 2 hrs to yield a light yellow, taffy-like “precursor”, which is then added to xylene and refluxed for 3 hrs. Filtration of the cooled reaction mixture yields a crude product that is neutralized and then recrystallized from chloroform-methanol to give an 80–85% yield of a white powder with mp 380–381 °C.



*Standard Petrolite Procedure (Synthesis of *p*-tert-butylcalix[8]arene).*¹⁰ A slurry of xylene containing *p*-tert-butylphenol, paraformaldehyde and an amount of NaOH corresponding to 0.03 equivalents with respect to the phenol is refluxed for 4 hrs. The cooled reaction mixture is filtered, and the crude product is recrystallized from chloroform to give 60–65% of glistening crystals, which quickly change to a white powder with mp 411–412 °C (after several recrystallizations samples with mp as high as 418–420 °C can be obtained).



p-tert-Butylcalix[8]arene

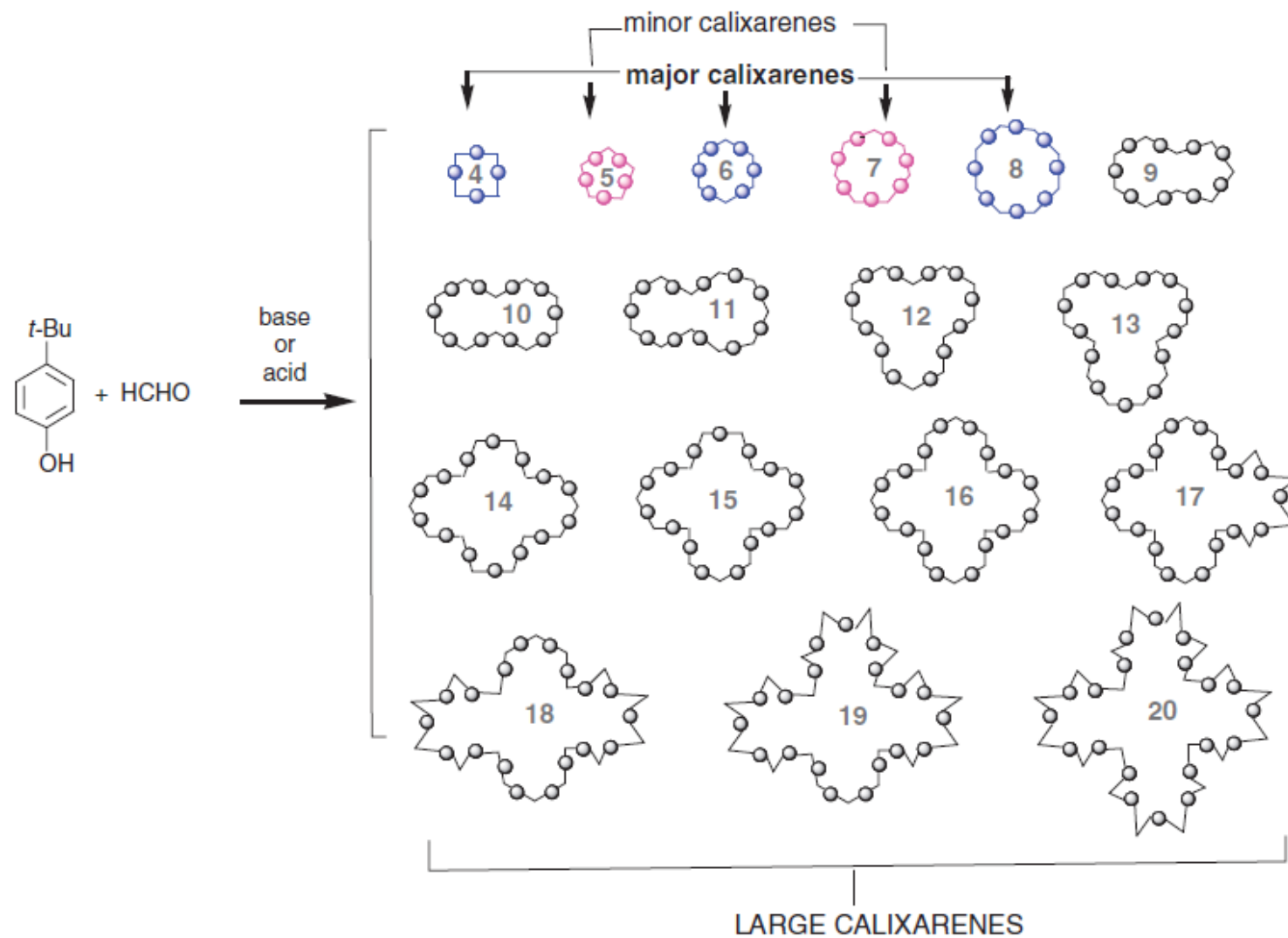
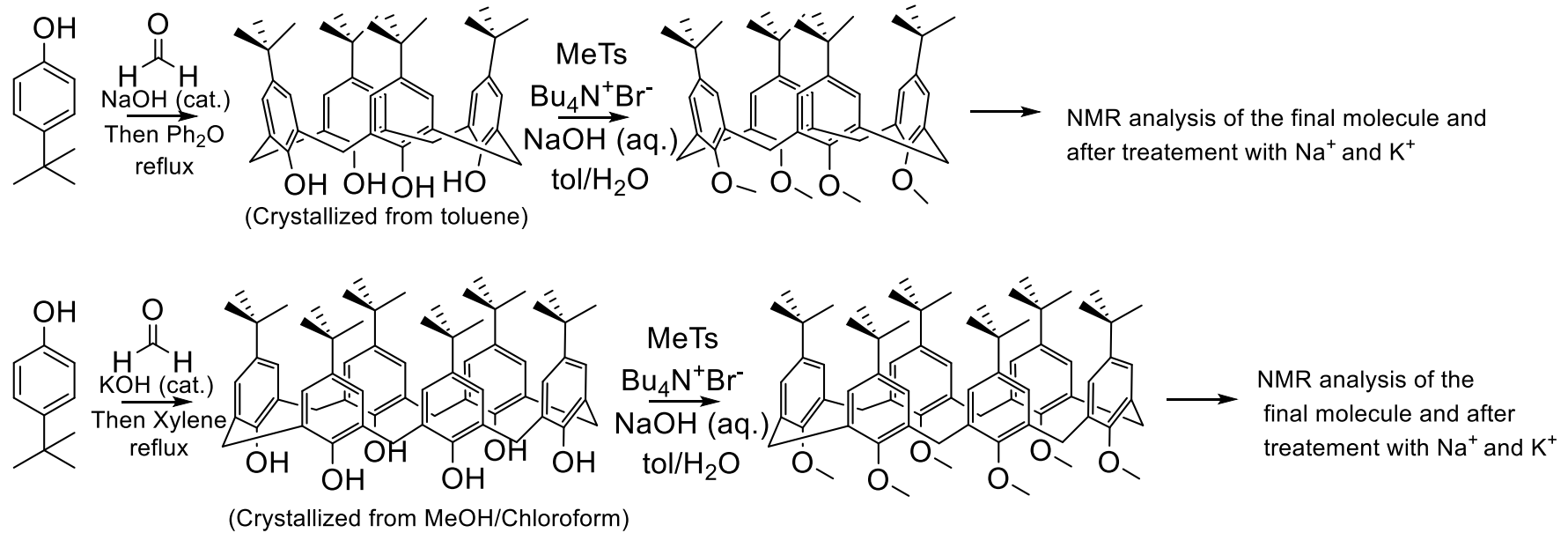


Figure 2.2 The extended calixarene family.

Laboratory: synthesis of tertbutyl-calix[4] and [6]arenes



^{13}C NMR spectra (symmetry)

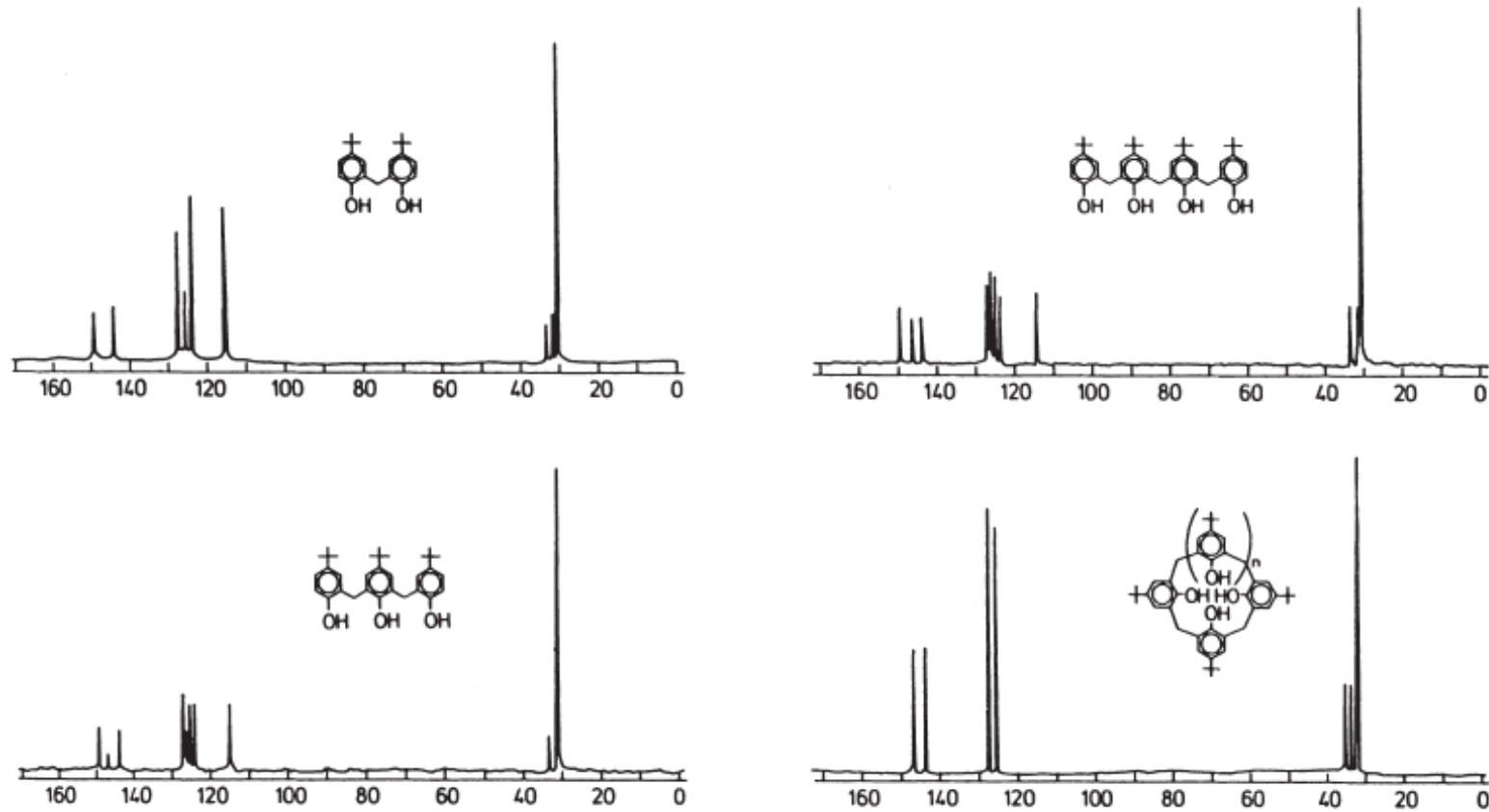
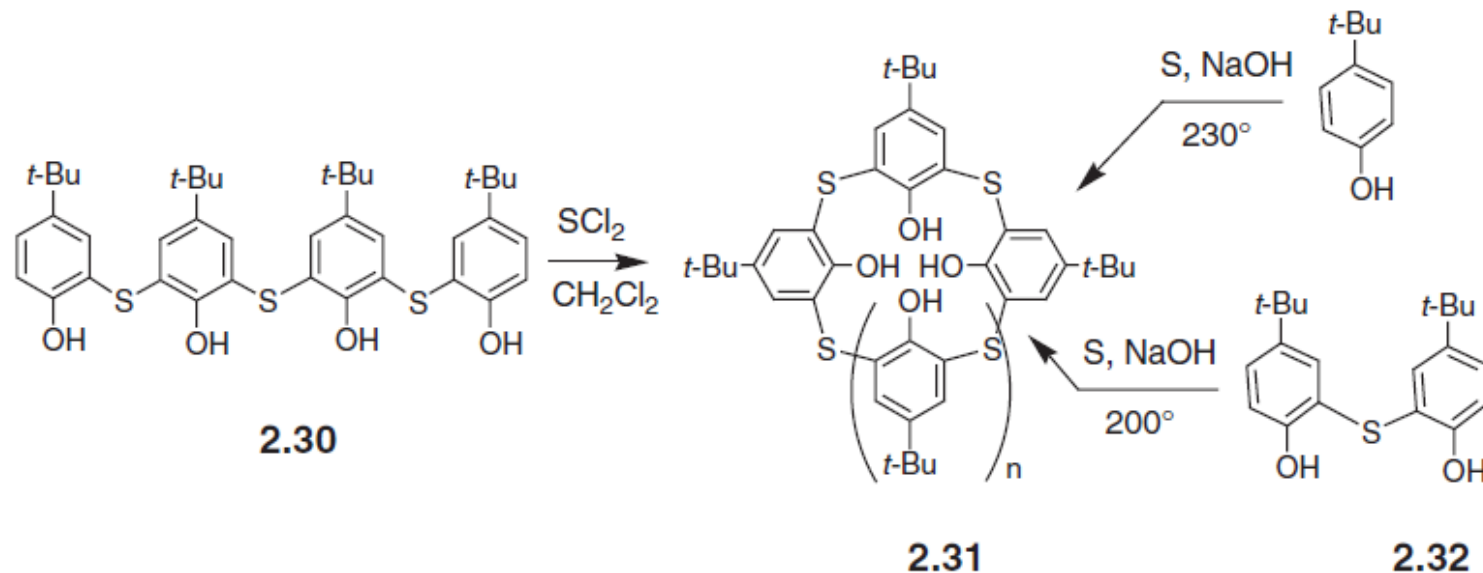
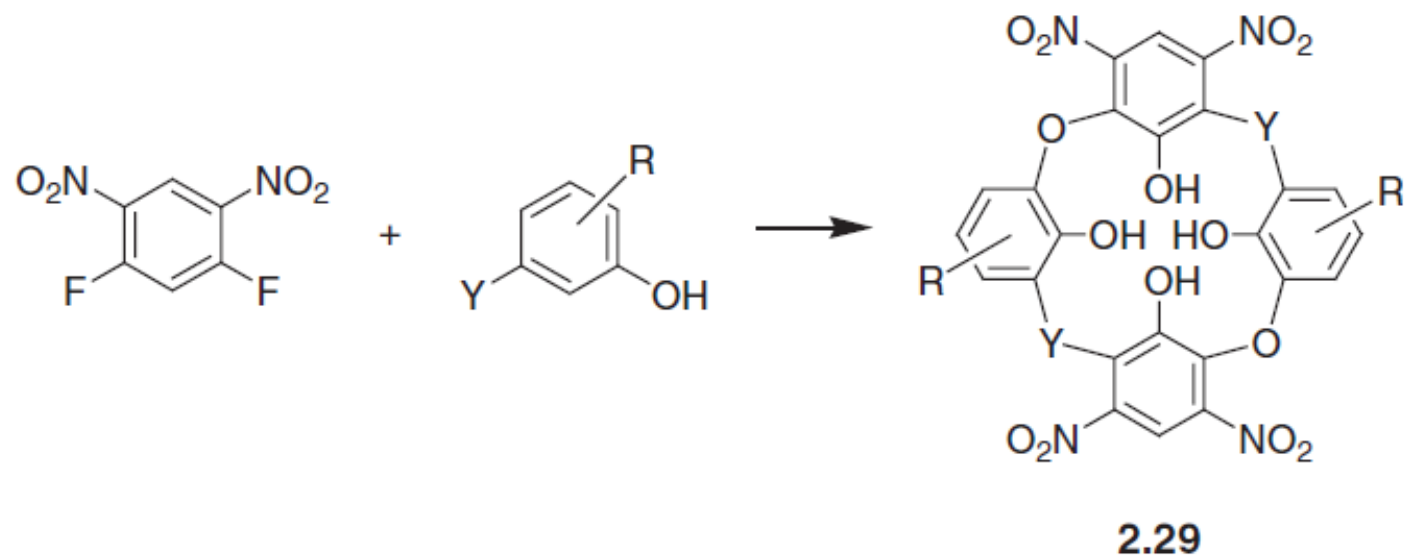


Figure 1.4 ^{13}C NMR spectra of linear oligomers and cyclic tetramer from *p*-tert-butylphenol.

The synthetic methodology has also been adapted to allow for the incorporation of bridging groups other than methylene, such as dimethyleneoxa (-CH₂OCH₂-), thia (-S-), and aza [-CH₂N(R)CH₂-] bridged calixarenes,⁶ and these additional donors can provide extra binding sites.



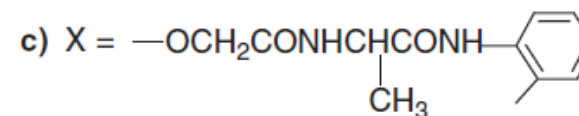
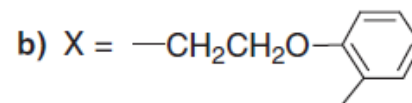
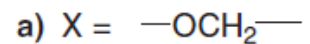
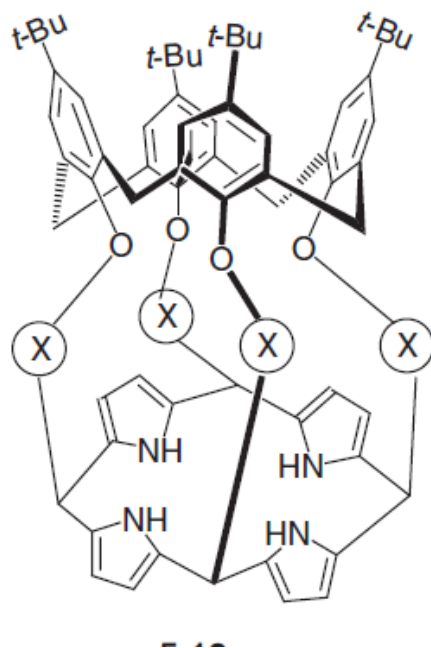
Aza- and oxacalixarenes



Katz and coworkers who have prepared 2.29 (Y=O, R=OH, CO₂Me, alkyl, CHO) in yields of 75–92%. In like fashion the 2,14-diaza-8,20-dioxazarene 2.29 (Y=NH) is produced by condensation with m-aminophenols (Y=NH₂).

From the synthetic point of view:

- **The chemical functionalization of upper and lower rims allowed:**
- Switch from cations to anions guests
- Large organic molecules as guests
- Other properties: sensors, capsules, polymers, machines, devices, drugs, other biological properties



The parent calixarenes are able to bind metals in various positions as illustrated in Figure 1, while the introduction of the aforementioned donor linker groups can lead to further bonding at the metal; for example, thia type bridges can bind in a κ^3 mode via sulfur and two oxygen atoms.

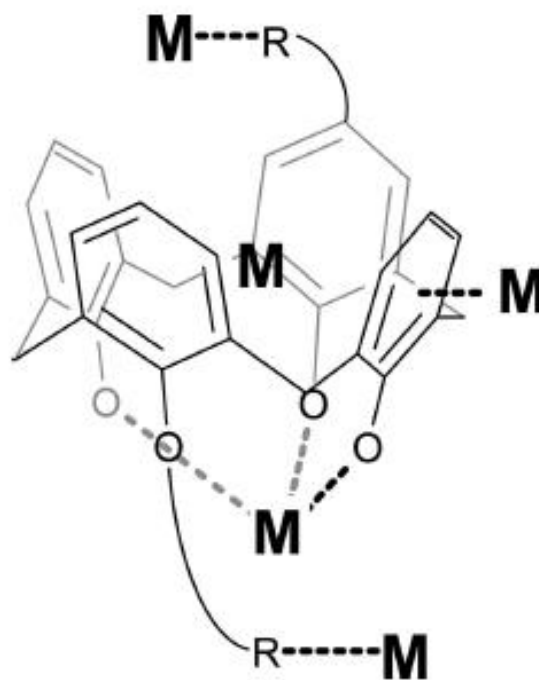
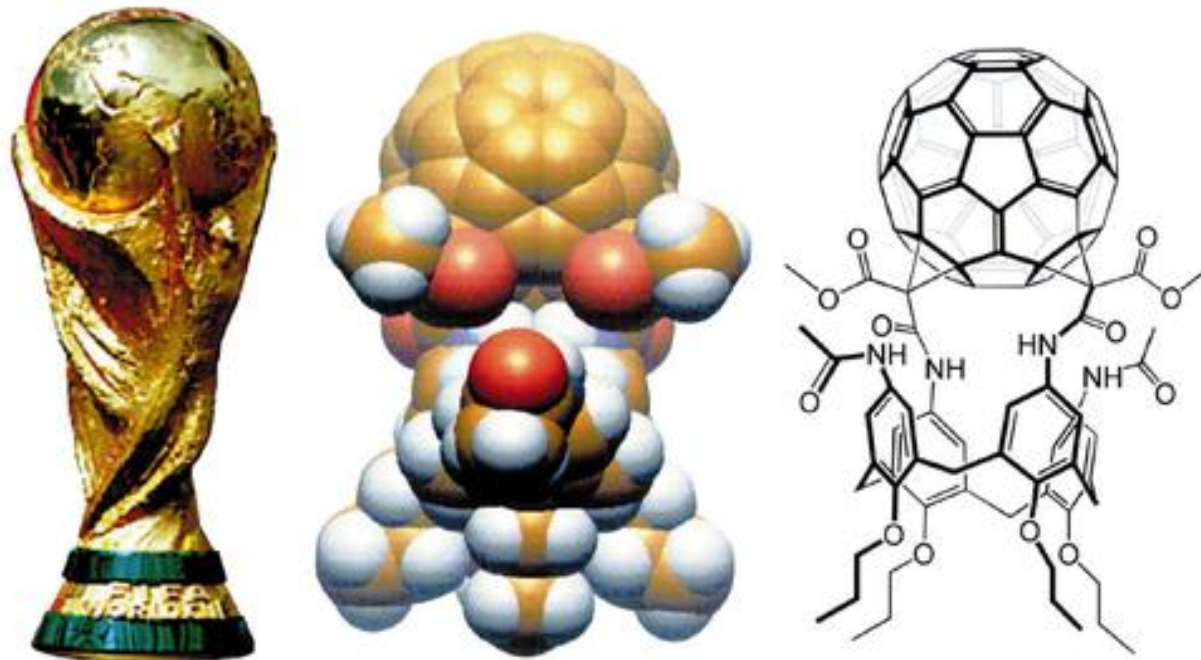


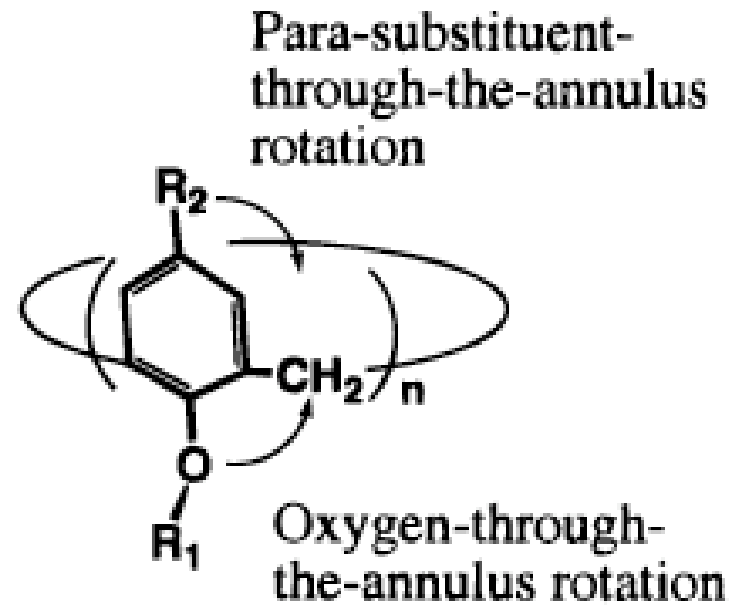
Figure 1. Potential metal binding sites in a calix[4]arene ligand system (R = assorted functionality).^{13–21}

Fullerene calix[4]arene conjugate

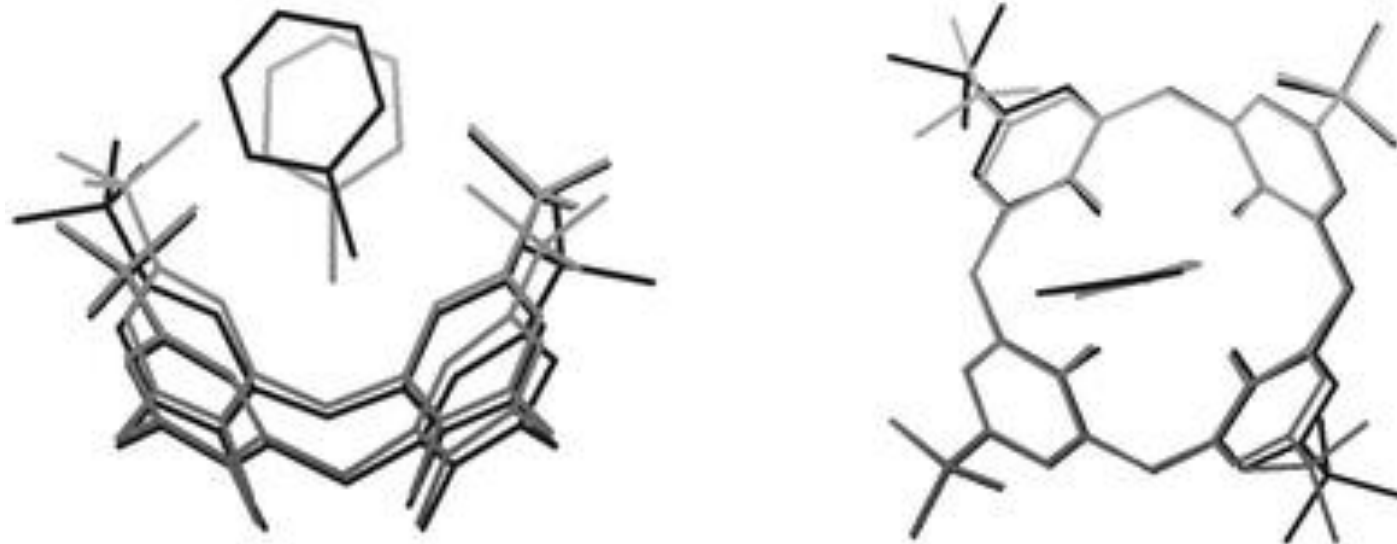


Relazione di forma tra la coppa del mondo di calcio (sinistra) e il coniugato fullerene-calix[4]arene nel modello a palle (centro) e rappresentazione schematica (destra).

Conformations



Calixarenes made up of phenol and methylene units have many conformational isomers because of two possible rotational modes of the phenol unit: the oxygen-through-the annulus rotation and the para-substituent-through the-annulus rotation (Figure 1).



Although each phenol unit can rotate according to the oxygen-through-the annulus rotation mechanism, **they favorably adopt a cone conformation because of the stabilization by intramolecular hydrogen-bonding interactions among OH groups.**

Therefore, the p-tert-butylcalix[4]-arene (1) adopts C_{4v} symmetry and has a π -basic cavity in the upper rim.

In the crystalline state several kinds of solvent molecules are included in this cavity (toluene, acetonitrile, etc.).

Shinkai

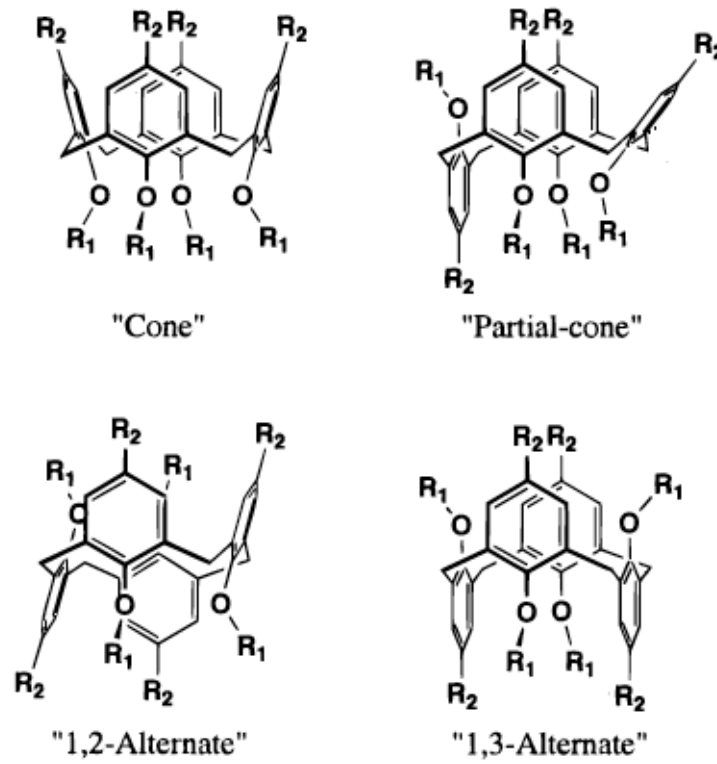
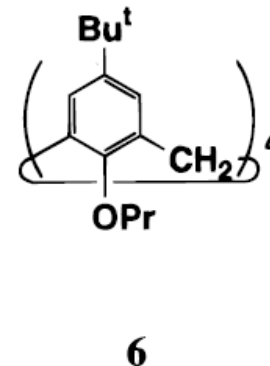
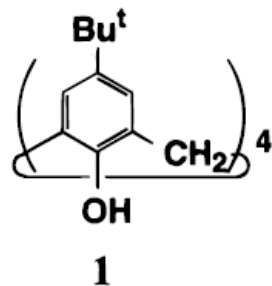


Figure 2. Four stable conformation of calix[4]arenes.

In tetra-O alkylated calix[4]arenes the cone conformation is not necessarily stabilized because of the absence of such intramolecular hydrogen-bonding interactions.

Thus, one must take four different conformational isomers into account: they are “cone”, “partial-cone”, “1,2-alternate”, and “1,3-alternate”

But tBu and O-propyl groups are enough to block conformers interconversion



The four conformers of 6 can be prepared from the reaction of 1 with n-PrI.

These conformers were heated in 1,1,2,2-tetrachloroethane at the reflux temperature (147 °C) for 12 h, but isomerization of these conformers did not take place.

The same result was obtained when the solution was refluxed for 3 days. Thus, the n-propyl group is bulky enough to inhibit the oxygen-through-the-annulus rotation and, therefore, tetra-O-propylation can result in conformationally immobile calix[4]arenes.

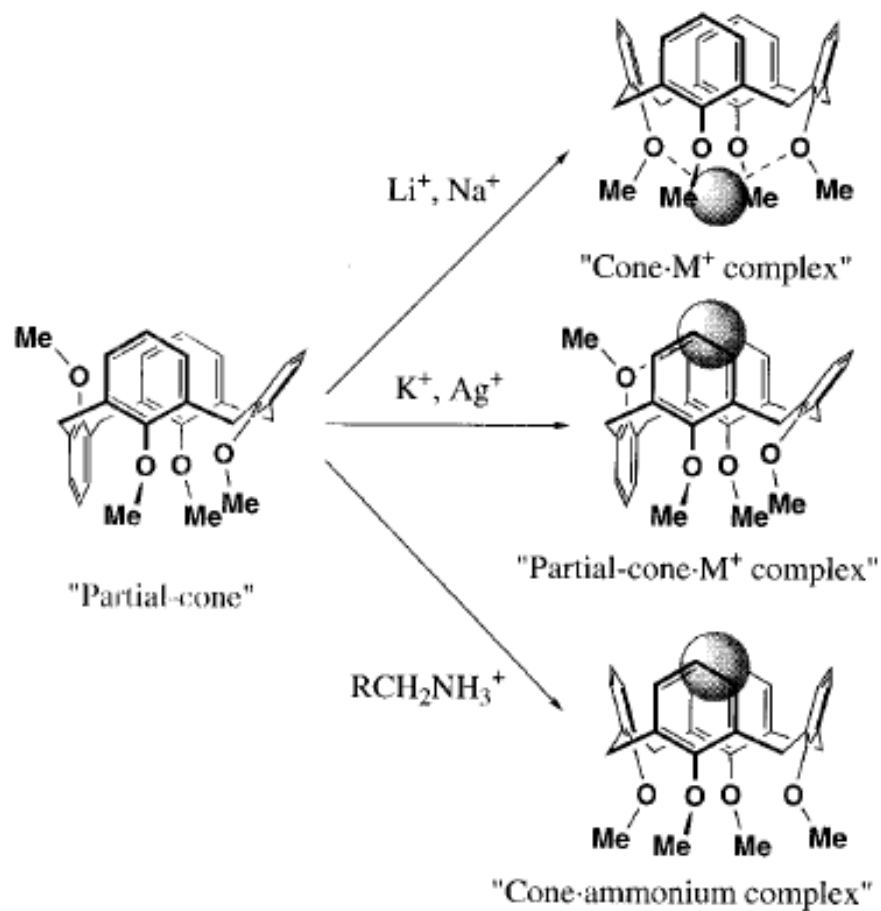


Figure 3. Inclusion of metal cation and of ammonium cation.

The conformational isomerism in tetra-O-methylcalix[4]arenes is profoundly influenced by solvent, bound metal cations, and bound cationic guest molecules.

When LiClO_4 or NaClO_4 was added into $\text{CDCl}_3 / \text{CD}_3\text{OD}$ (4:1 v/v), new ^1H NMR peaks appeared that were assignable to cone- 2M^+ and partial-cone- 2M^+ .

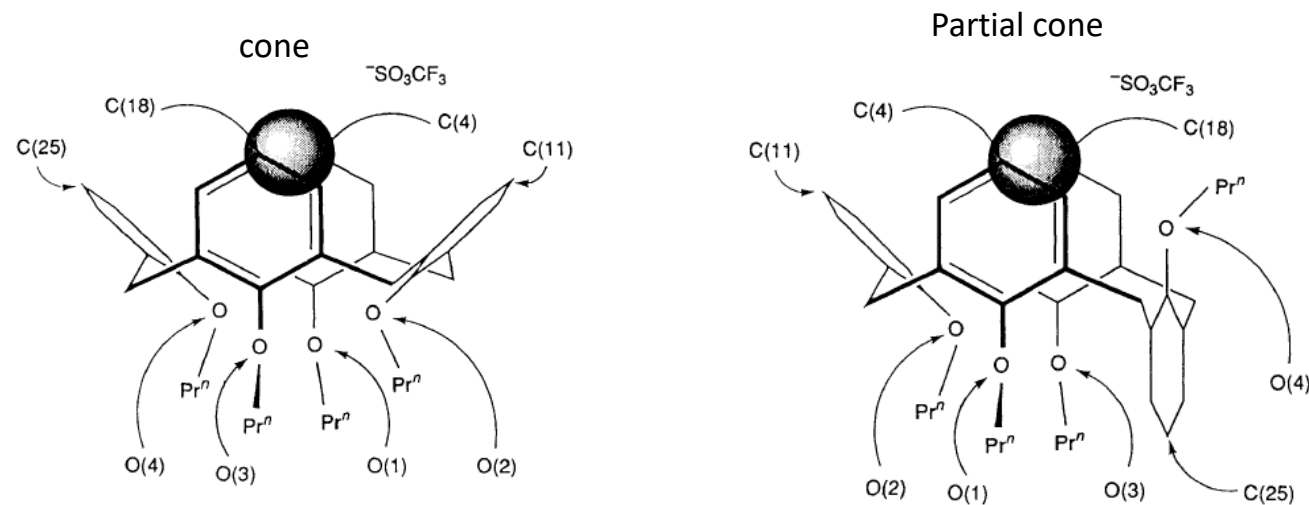
On the other hand, the spectra of partialcone-2 and 1,3-alternate-2 were affected by addition of KClO_4 or AgClO_4 . Ag^+ (and probably, K^+ also) is bound to the upper rim through the interaction with one or two oxygens and two benzene rings in these conformers.

These cationic guest molecules are included in the π -basic cavities of 3 owing to the cation- π interaction.

Lezione 11

- Calixarenes and applications

Complexation of Ag⁺



- K⁺ and Ag⁺ bind to oxygens but also establish cation-aromatic interactions, crystal structure of Ag⁺ bound to a cone and a partial cone conformation

NMR Spectroscopic and X-Ray Crystallographic Studies of Calix[4]arene-Ag⁺ Complexes. Influence of Bound Ag⁺ on C_{2v}-C_{2v} Interconversion in *cone*-Calix[4]arenes

Atsushi Ikeda,^a Hirohisa Tsuzuki^b and Seiji Shinkai^{*,a}

^a Department of Chemical Science and Technology, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan

^b Center of Advanced Instrumental Analysis, Kyushu University, Kasuga, Fukuoka 816, Japan

The Ag⁺ complexes of conformationally immobilized tetra-*O*-propylcalix[4]arene with a cone or a partial-cone conformation (*cone-2Prⁿ* or *partial-cone-2Prⁿ*, respectively) have been successfully analysed by X-ray crystallography. In both complexes Ag⁺ was bound to the upper rim cavity, sandwiched by the two *para* carbons in the distal phenyl units. The findings provide clear evidence for π-base participation. In particular, the basic calix[4]arene skeleton in *partial-cone-2Prⁿ*·Ag⁺ is almost the same as that in *partial-cone-2Prⁿ* itself. This establishes that *partial-cone-2R* possesses two distal benzene rings ideally preorganized for Ag⁺-binding. ¹H NMR spectroscopic studies for the Ag⁺ complexes in solution indicated that Ag⁺ is bound to the same site as that in the solid state. In conformationally mobile **2Me**, which exists in solution in equilibrium between *cone* and *partial-cone*, Ag⁺ induced a shift of the equilibrium to *partial-cone* to form the *partial-cone-2Me*·Ag⁺ complex. This is ascribed to the ideal preorganization in *partial-cone-2R* for the Ag⁺-binding. These results are of great significance for an understanding of π-base participation in the metal-binding events and have important implications on the cation-π interaction in biological systems.

NMR

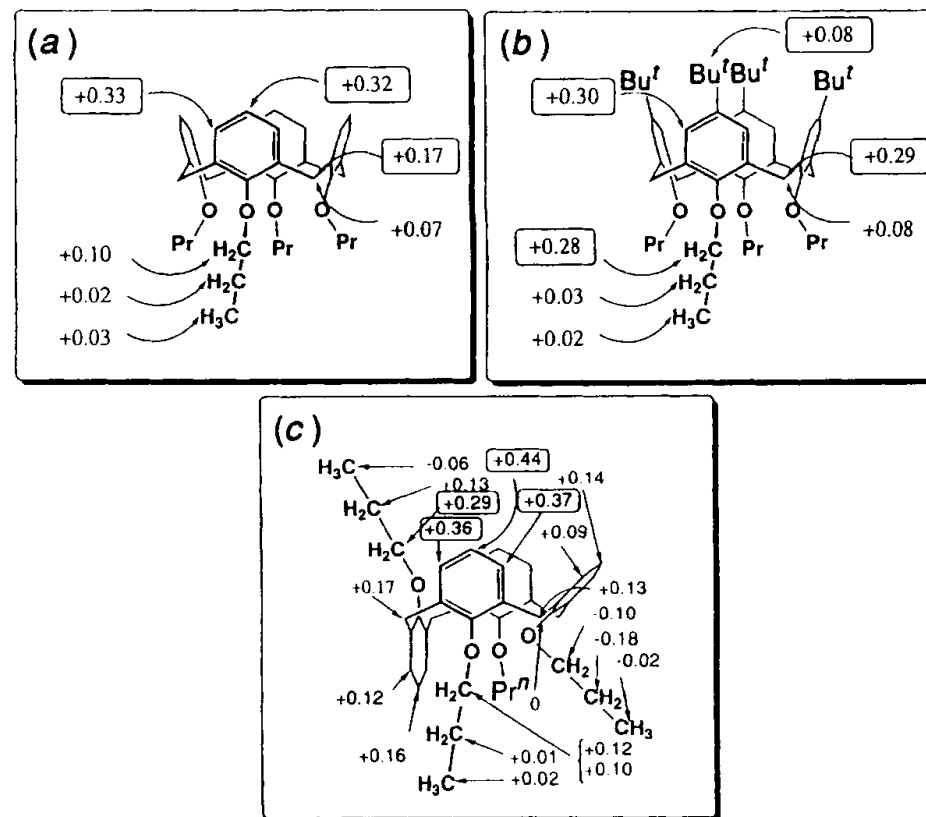


Fig. 3 Chemical shift changes induced by Ag^+ addition in CDCl_3 : $\text{CD}_3\text{OD} = 4:1$ v/v at 25°C : (calix[4]arene) = 1.0×10^{-2} mol dm^{-3} , $[\text{AgCF}_3\text{SO}_3] = 1.0 \times 10^{-1}$ mol dm^{-3} ; + denotes the down-field shift and - denotes the up-field shift

Inclusion of organic cations

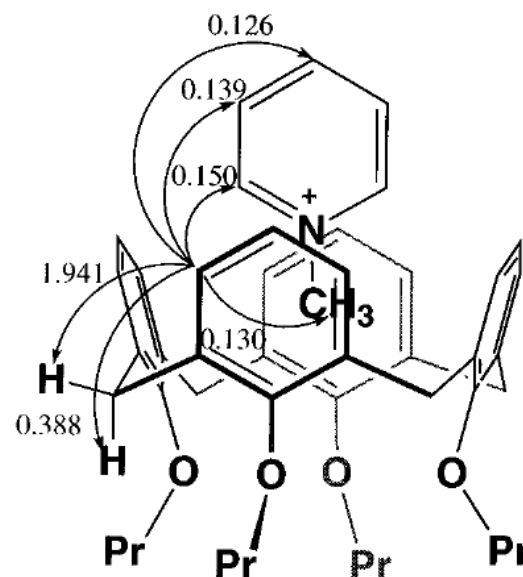


Figure 6. NOE peak intensities with respect to the *m*-ArH protons in cone-11.

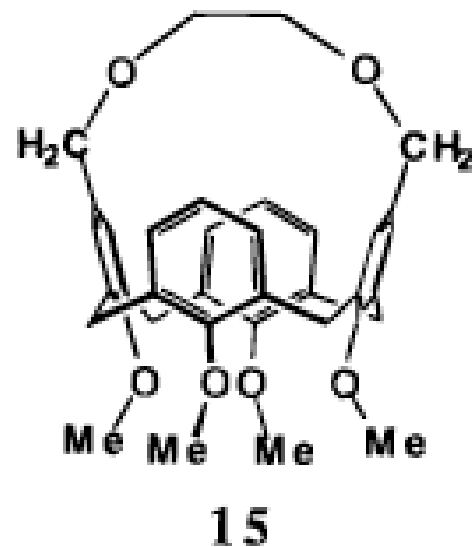
guest molecule is included in the π -basic cavity of calix[4]arenes owing to the “cation- π interaction”.

This growth in calixarene coordination chemistry has in turn led to an increasing number of reports concerning the use of calix[n]arenes as ancillary ligands in the metalcontaining components of catalysts in a variety of transformations.

For example, Floriani recognized that for the calix[4]arene ligand system, the four oxygen donors preorganized in a quasi-planar geometry offered an ideal opportunity for modeling oxo surfaces and heterogeneous Catalysts.

The conformational flexibility, presence of cavities, and ability to coordinate simultaneously numerous metal centers are proving extremely good attributes, although it should be emphasized that the bulk of the work carried out to date (and reported herein) has been conducted on the easily prepared, and hence comparatively cheap, calix[4]arene system, which upon metalation tends to retain the cone conformation, binding to only one metal center.

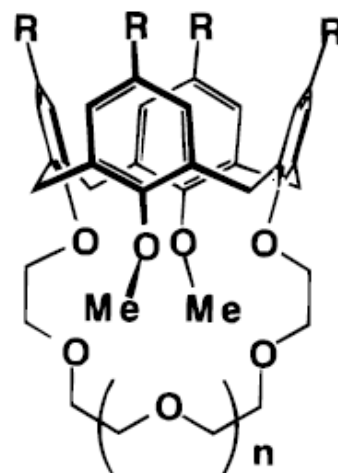
Bridged Calix[4]arenes



Reinhoudt et al. reported calix[4]crowns **15** having a crown ether bridge at the upper rim.

The ^1H NMR spectrum reveals that in solution **15** exists as a mixture of two conformations, viz., the partial-cone and the cone (ratio partial-cone/cone) 4.0).

Calixcrowns

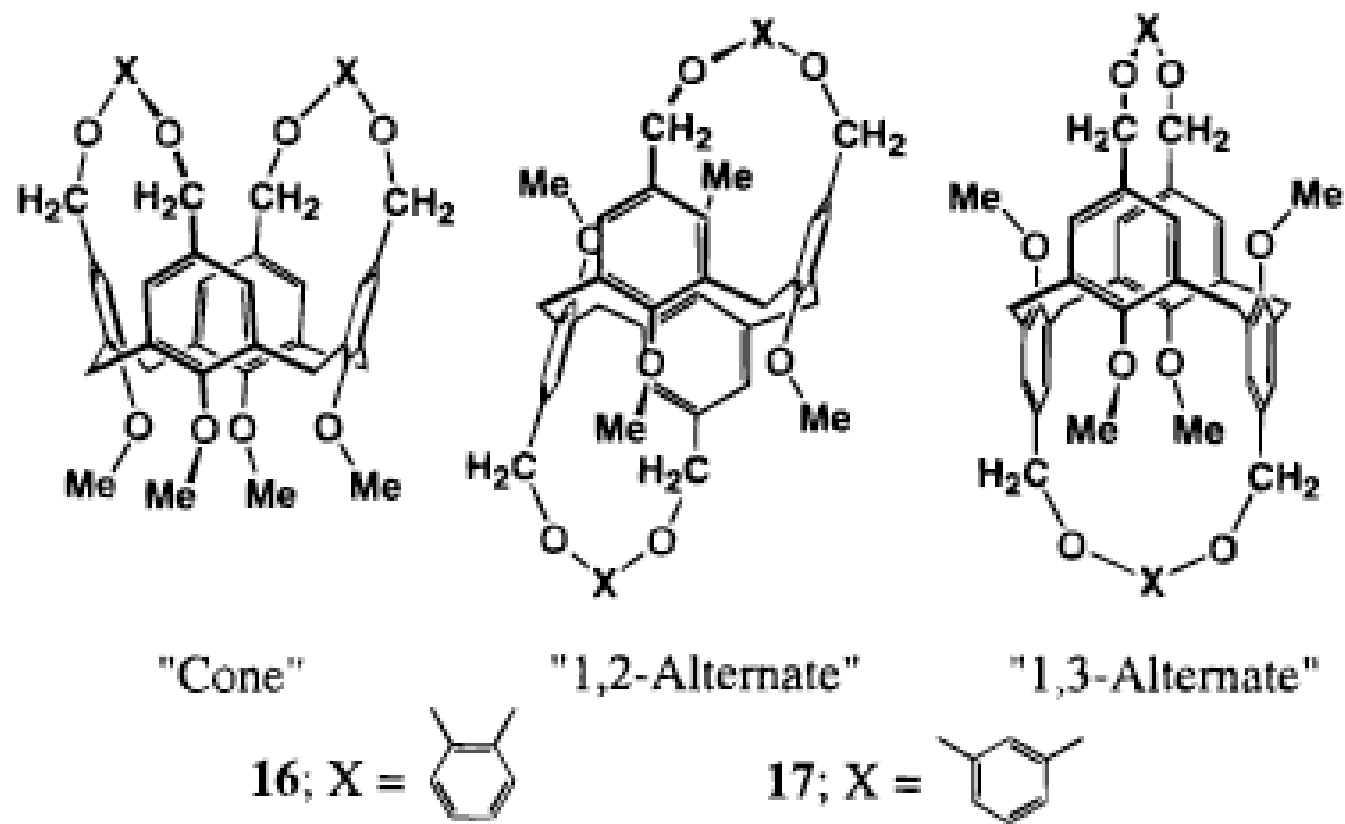


4a R = H, n = 1

4b R = *tert*-Bu, n = 1

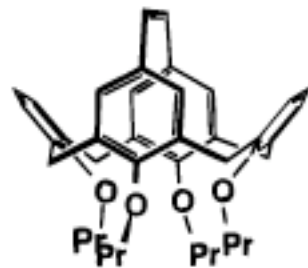
5 R = H, n = 2

Ungaro, Reinhoudt, *et al.*²⁶ reported that at -50°C the ratio between cone, partial-cone, and 1,3-alternate conformations of calixcrown **4a** is 87:7:7, but in acetonitrile the most stable conformation of the **4a**-K picrate complex is the 1,3-alternate (80%) and the partial-cone (20%) is next



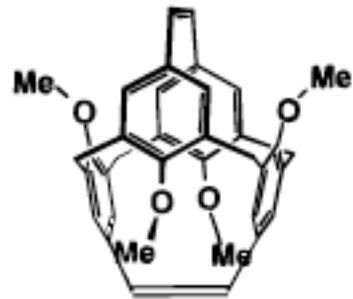
Compounds 16 and 17, having double bridges at the upper rim, were isolated as two (1,2-alternate and 1,3-alternate) and three conformers (cone, 1,2-alternate, and 1,3-alternate), respectively.

Calix[4]arenes immobilized in one conformation



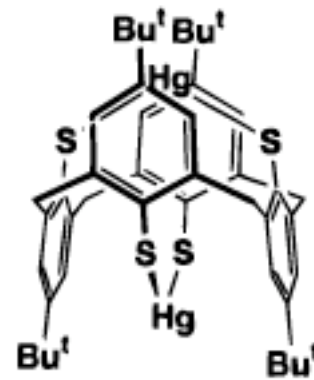
"Cone"

18

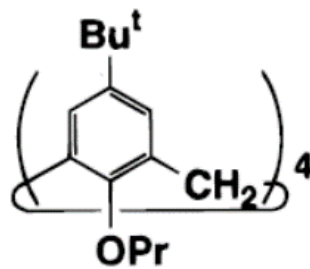


"1,3-Alternate"

19

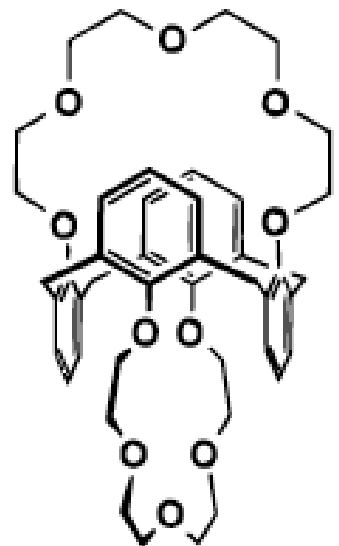


Conformation of 25·2Hg²⁺ complex.

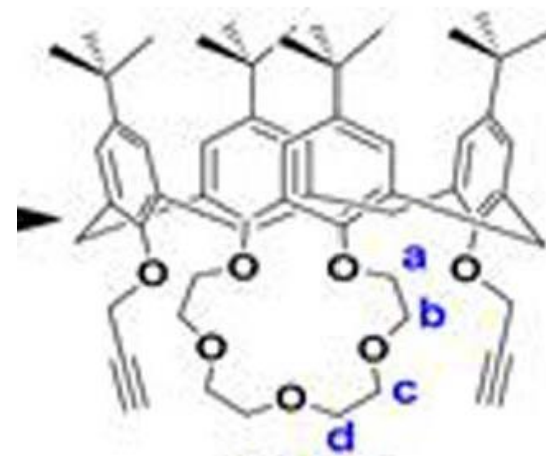


6

Crown calixarenes blocked in 1,3-alternate conformation



91



Calixcrown make a family of calixarenes that exhibit a superior recognition of organic molecules and metal ions via the cooperation of both the calixarene and crown moieties

Calix[6] arenes

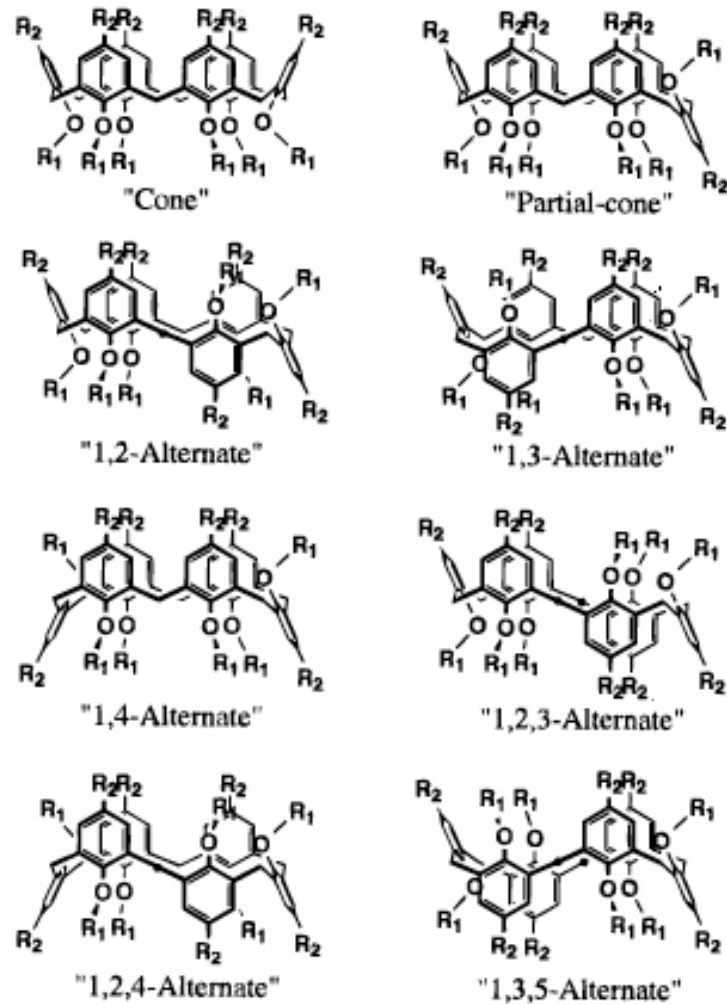


Figure 9. Eight possible conformation of calix[6]arenes.

Calix[6]arenes possess a cavity larger than calix- [4]arenes and are probably more suitable to molecular recognition.

However, the attempts to apply calix[6]arenes as hosts to specific molecular recognition have so far been unsuccessful because of their large conformational freedom.

Complexes of calix[6]arenes

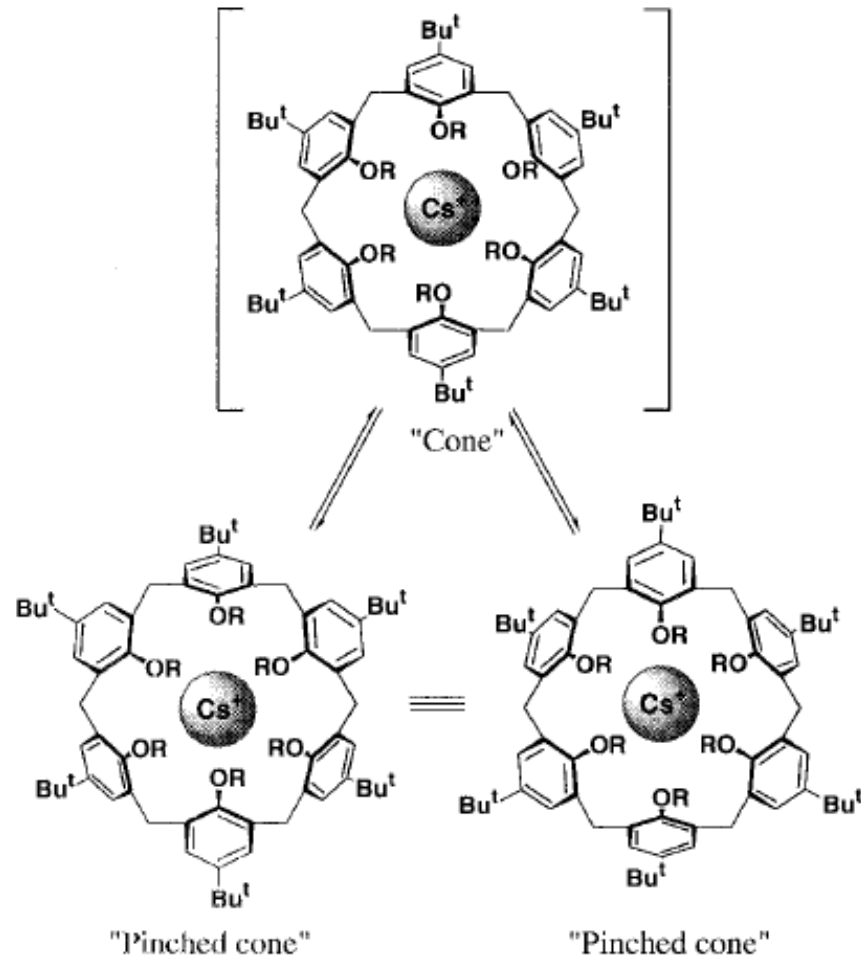
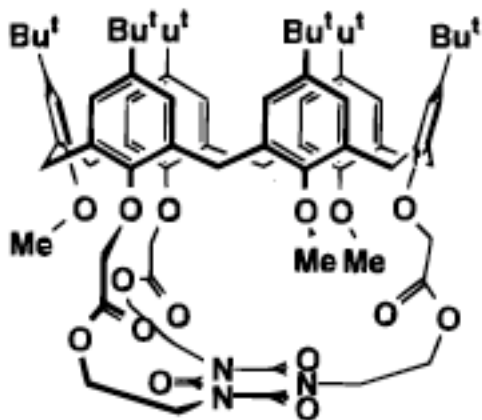
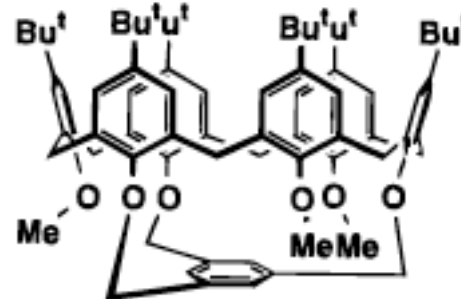


Figure 13. Proposed structure for the 35·Cs⁺ complex (C_{3v} - C_{3v} interconversion).

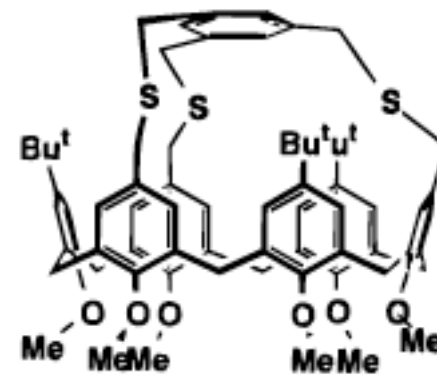
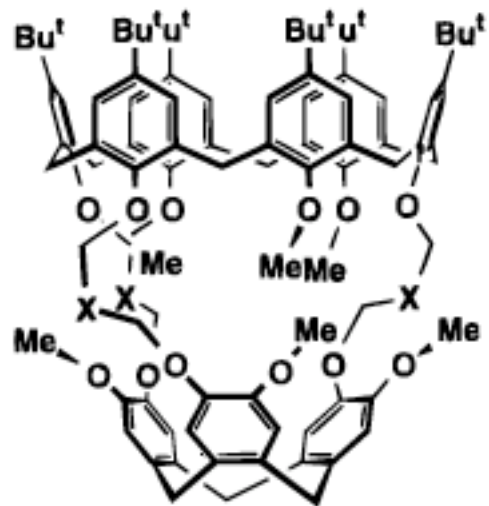
Blocking cali[6]arenes conformations



47

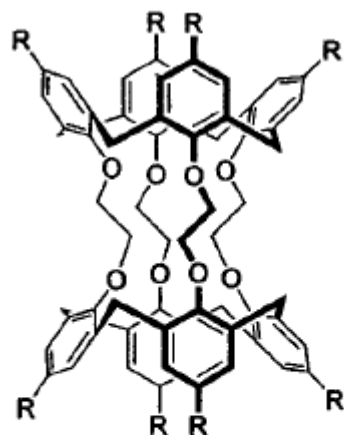


49



50

A calix-based cryptand: the calix[4]tube



Symmetric

- 1 R = *t*-Bu
- 2 R = *t*-Oct
- 3 R = H

Calix[4]tubes: A New Class of Potassium-Selective Ionophore

Susan E. Matthews,[†] Phillipe Schmitt,[†] Vitor Felix,^{‡,§} Michael G. B. Drew,[‡] and Paul D. Beer^{*,†}

Contribution from the Inorganic Chemistry Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford OX1 3QR, U.K., and Department of Chemistry, University of Reading, Whiteknights, Reading, Berkshire RG6 6AD, U.K.

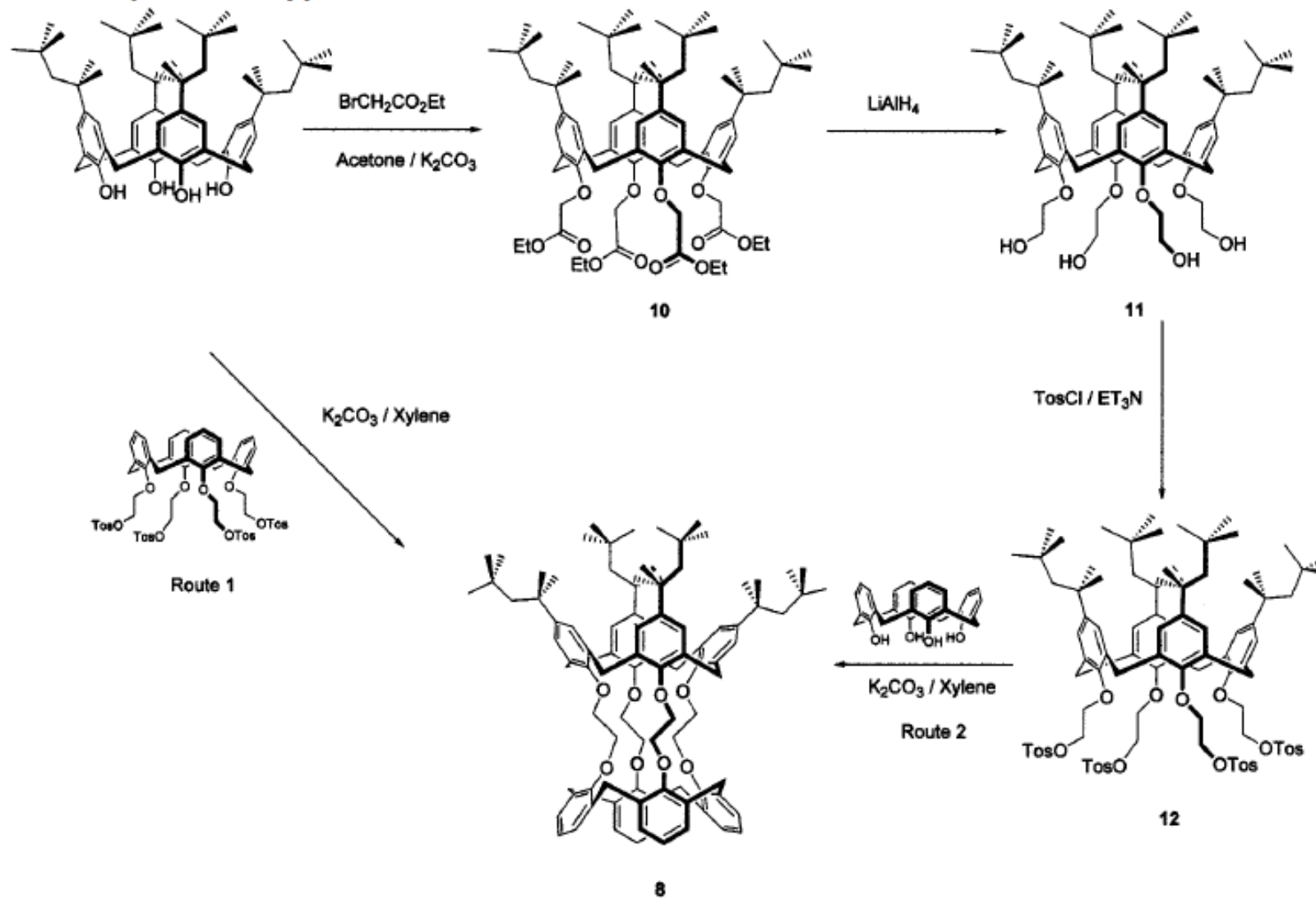
Received July 30, 2001

A new class of cryptand-like ionophore based on a bis calix[4]arene structure has been developed.

These molecules proved highly selective for complexation of potassium over all group I metal cations and barium.

Synthesis

Scheme 1. Synthesis of Calix[4]tube 8



Symmetrization of ^1H NMR spectrum

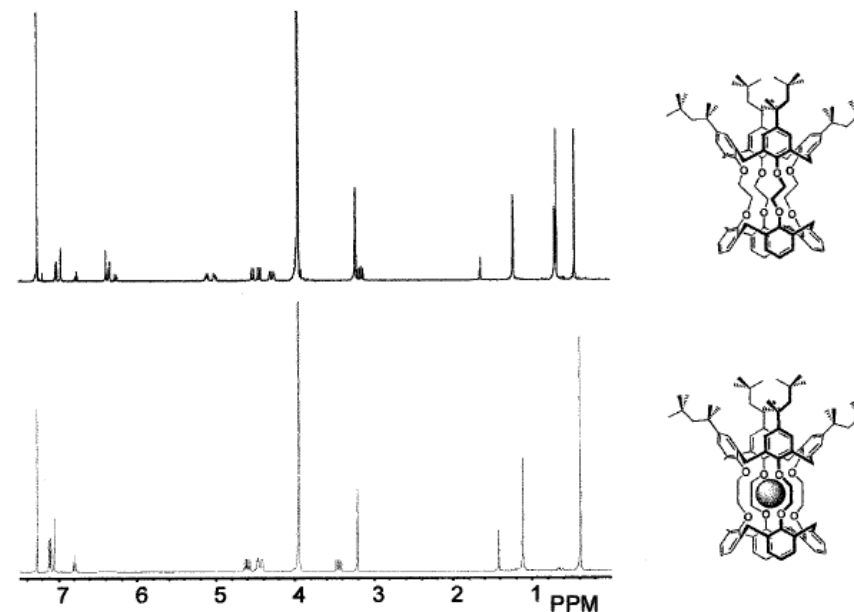
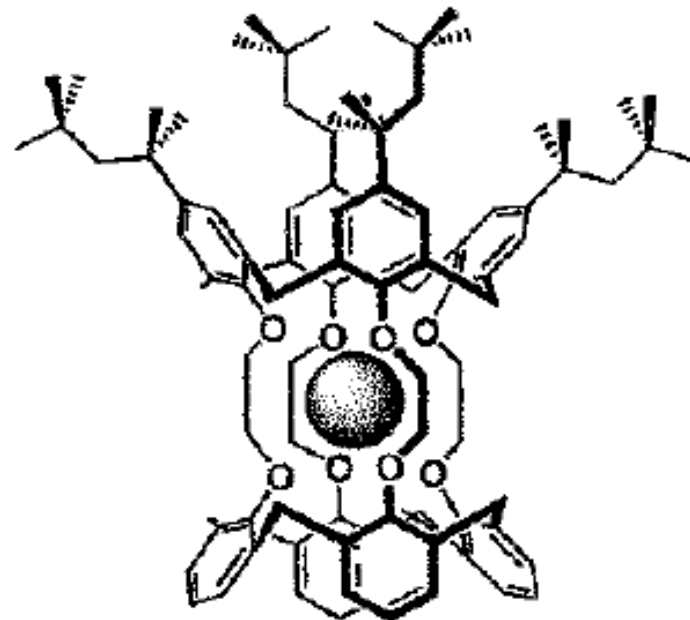
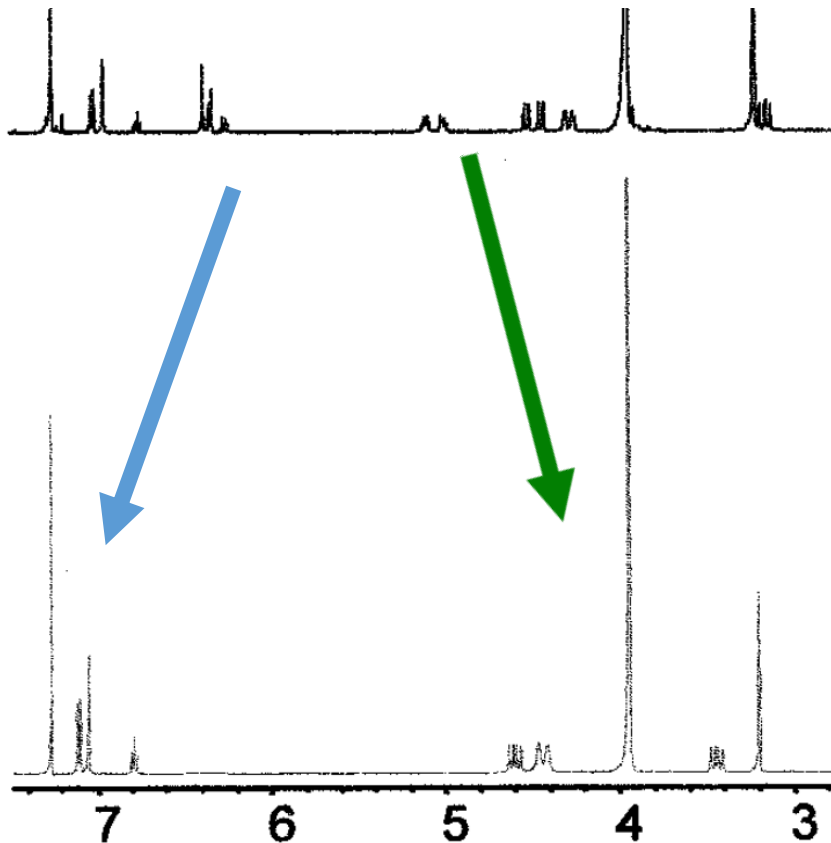


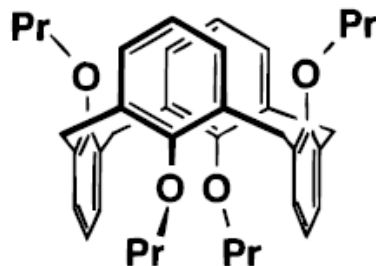
Figure 5. ^1H NMR of 8 in chloroform/methanol (4:1): (a) absence of K^+ ; (b) after 4 days in the presence of 20 equiv of KI.

Initial qualitative experiments demonstrated that on complexation with an excess of potassium iodide in chloroform/ methanol (4:1) new signals due to a calix[4] tube-cation complex can be observed (Figure 5b). In this case, the spectra simplify to give single peaks for all residues confirming that, once the cation is complexed, the tube adopts a time-averaged C_4 structure in which all aryl residues are equivalent, as observed in the solid state.



The downfield shift of all calix[4]arene protons on complexation (between 0.22 and 0.92 ppm) in combination with the upfield shift within the ethylene unit (0.23 ppm) is consistent with a displacement of the electron density to the equatorial plane due to the complexed positively charged cation

Calixarenes as molecular devices (switches, syringes)

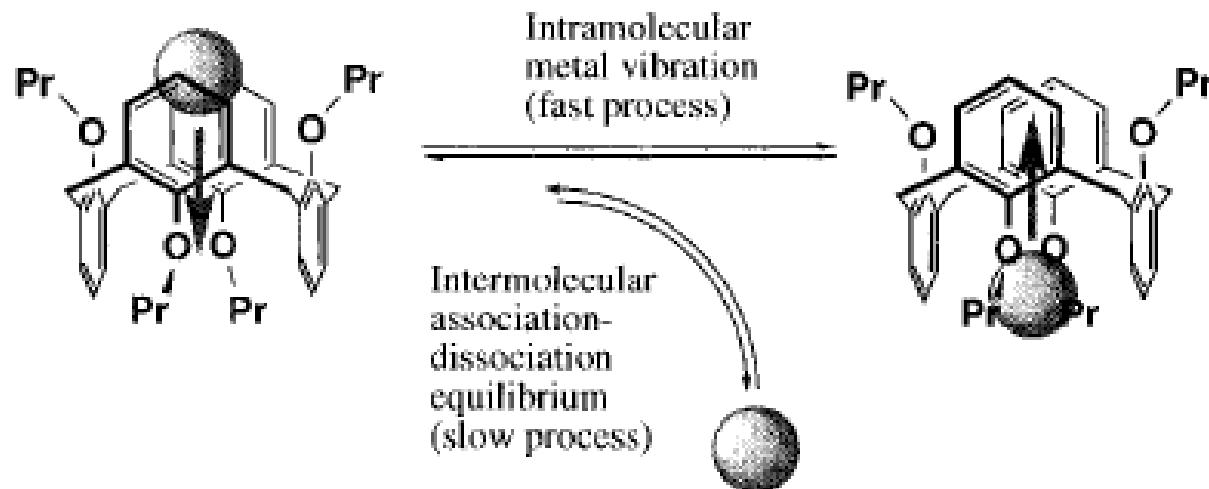


90

- 1,3-Alternate conformers can possess two independent ionophoric sites on either side of the cavity. In the ^1H NMR spectra of 1,3-alternate-calix in the presence of Ag^+ , the signals for the complex and those for free 1,3-alternate-90 are decoalesced at $-50\text{ }^\circ\text{C}$ and coalesced at $0\text{ }^\circ\text{C}$. This coalescence at $0\text{ }^\circ\text{C}$ arises from intermolecular metal exchange ($T_{c,\text{inter}}$).

Calixarenes as molecular devices

1,3-Alternate conformers can possess two independent ionophoric sites on either side of the cavity. In the ^1H NMR spectra of 1,3-alternate-calix in the presence of Ag^+ , the signals for the complex and those for free 1,3-alternate-90 are decoalesced at $-50\text{ }^\circ\text{C}$ and coalesced at $0\text{ }^\circ\text{C}$. This coalescence at $0\text{ }^\circ\text{C}$ arises from intermolecular metal exchange ($T_{c,\text{inter}}$).



Metal tunneling

This metal-binding mode is considered to be an example for the participation of the “cation- π interaction”. Dynamic ^1H NMR spectroscopy at low temperature showed that the metal cation alternates intramolecularly between the two cavity edges through a π -basic hole of 1,3-alternate calix[4]arenes

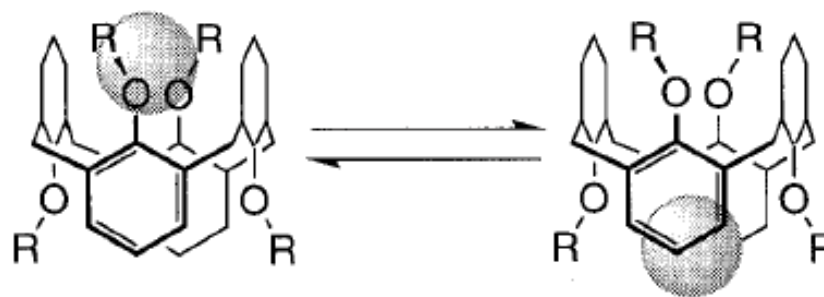
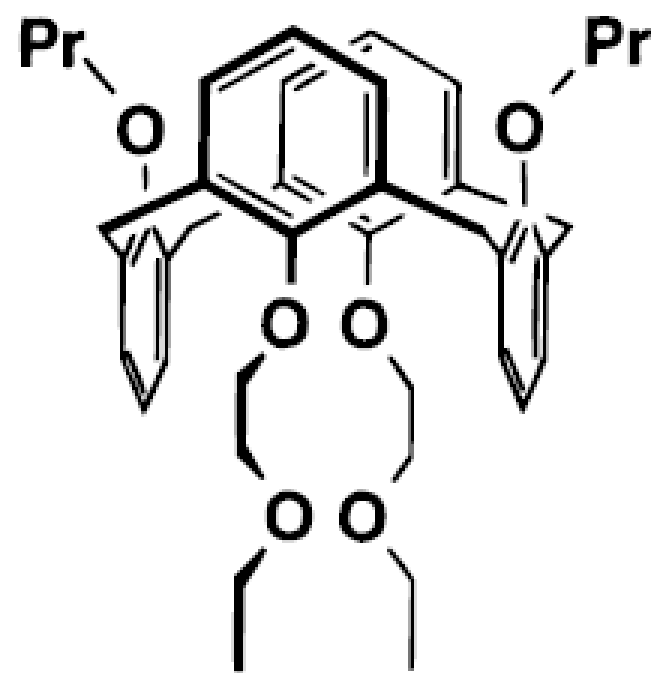


Figure 1. Schematic representation of the metal-tunneling through a π -basic tube of 1,3-alternate calix[4]arene.



92

1,3-Alternate-92 also has two binding sites, but the binding abilities of these sites are different.

The ^1H NMR spectrum of the 1,3-alternate-92% Ag^+ complex at $-85\text{ }^\circ\text{C}$ showed that 8.1% of the Ag^+ resides in the cavity composed of two PrO groups and two benzene rings, and 91.9% of the Ag^+ resides in the cavity composed of two $\text{EtOCH}_2\text{CH}_2\text{O}$ groups and two benzene rings.

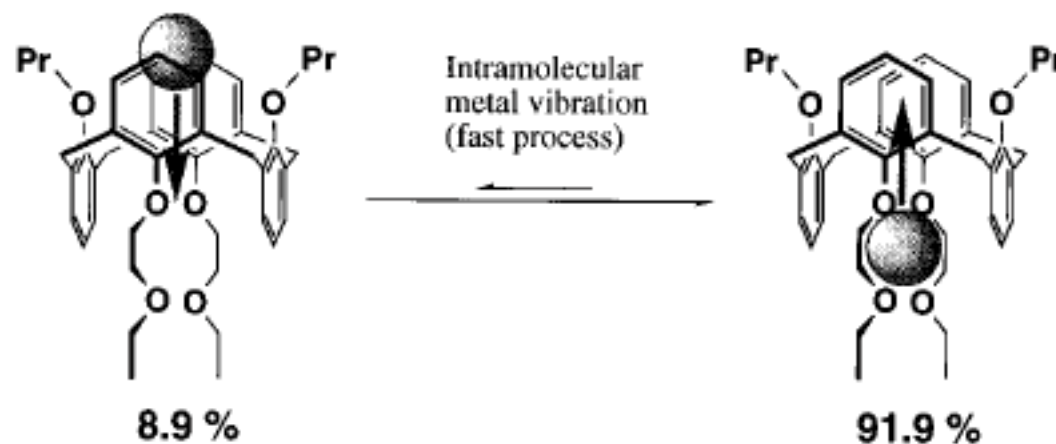


Figure 28. Different existence ratio of Ag^+ in the two different cavities of 92.

Control of guest mobility in calixarenes

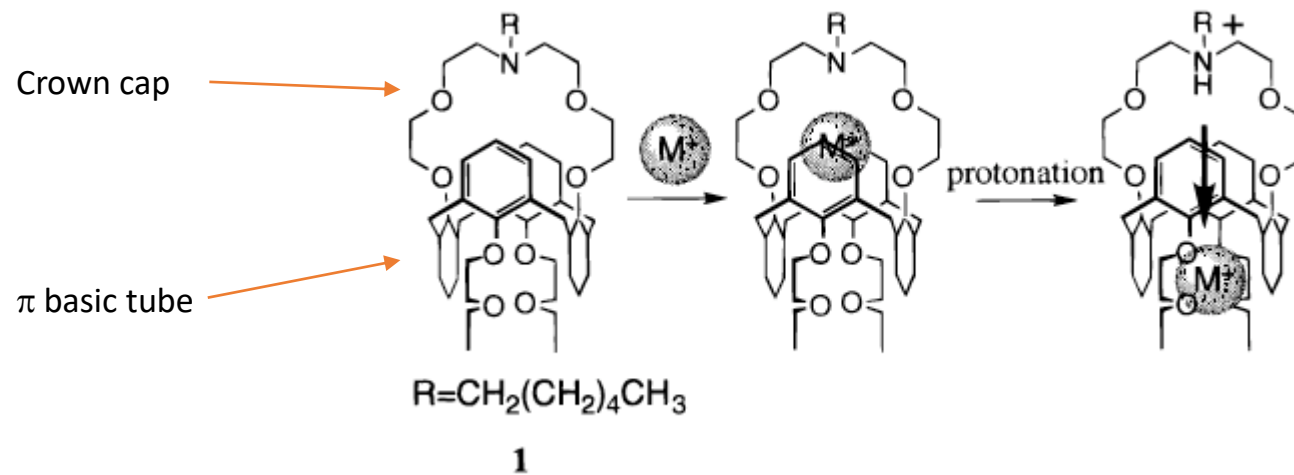
Calixarenes as molecular devices

Molecular Design of a “Molecular Syringe” Mimic for Metal Cations Using a 1,3-Alternate Calix[4]arene Cavity

Atsushi Ikeda, Takanobu Tsudera, and Seiji Shinkai*

*Department of Chemical Science & Technology, Faculty of Engineering, Kyushu University,
Fukuoka 812, Japan*

Received October 31, 1996[®]



This progress has enabled us to selectively synthesize and isolate four possible calix-[4]arene conformers: that is, cone, partial-cone, 1,2-alternate, and 1,3-alternate.

By applying these advanced synthetic methods, one can now design various ionophoric calix[4]arenes which show various metal selectivities.

We recently found that in certain 1,3-alternate conformers of calix[4]arene the metal cation is bound nonsymmetrically to one of two cavity edges.

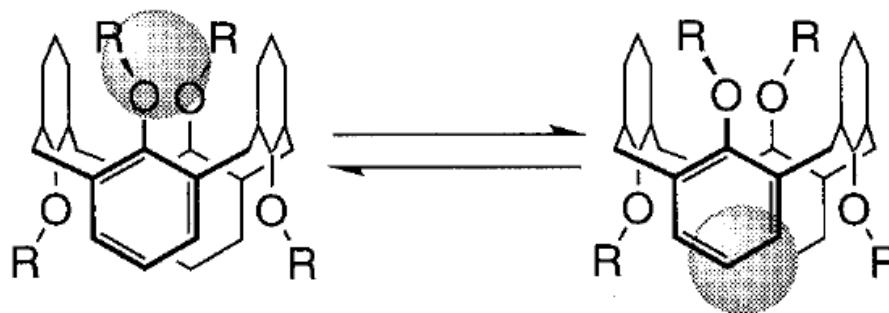


Figure 1. Schematic representation of the metal-tunneling through a π -basic tube of 1,3-alternate calix[4]arene.

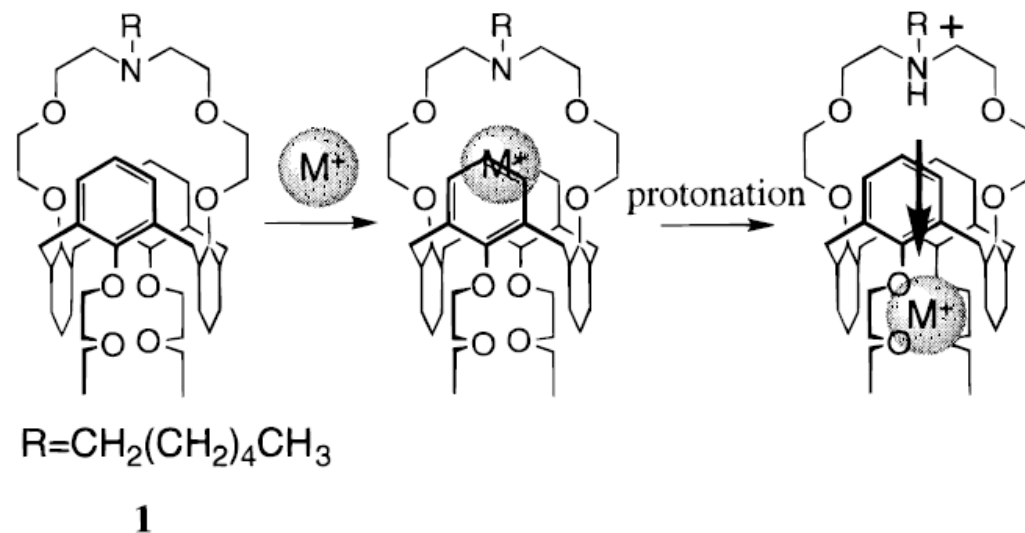
Since one cavity edge is composed of two phenolic oxygens and two benzene rings, this metal-binding mode is considered to be an example for the participation of the “cation- π interaction”.

Dynamic ^1H NMR spectroscopy at low temperature showed that the metal cation alternates intramolecularly between the two cavity edges through a π -basic hole of 1,3-alternate calix[4]arenes.

Remember the cation- π interaction in potassium channels....

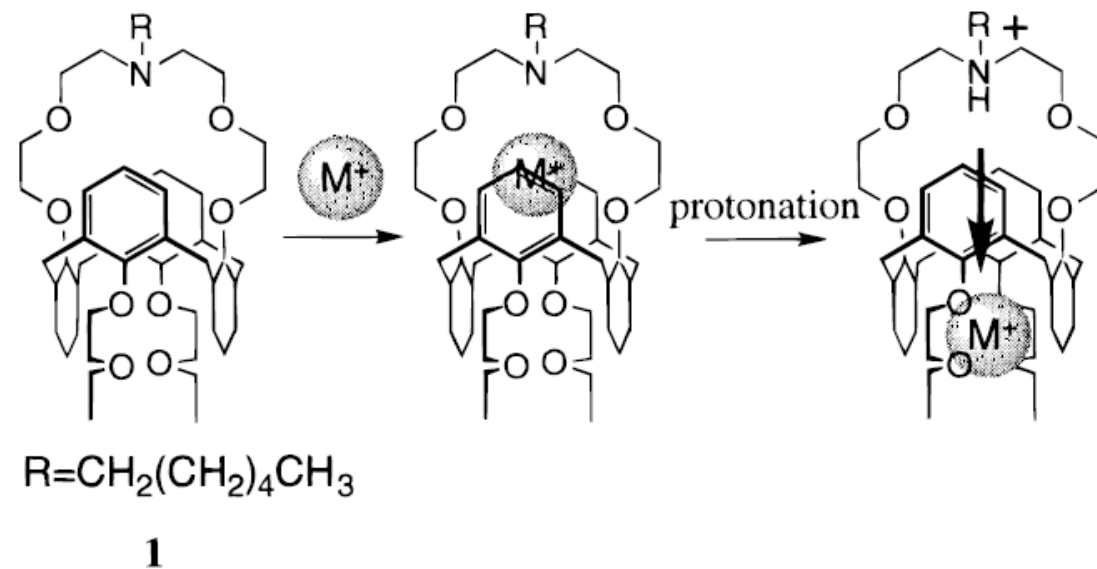
To the best of our knowledge, this is the first direct evidence for metal cation-tunneling across an aromatic cavity and has important implications with regard to the metal cation- π interaction expected for metal transport through ion channels, metal inclusion in fullerenes, intercalation of metal cations into graphites

The concept and the design of the molecular syringe



Here, it occurred to us that it might be possible to design a mechanochemical “molecular syringe” for metal cations from a 1,3-alternate calix[4]crown, using the π -basic tube as a “pipette” and the crown-ring as a “rubber cap”.

We thus synthesized a chemically-switchable compound 1.



Judging from the relative cation-binding ability of two calix[4]arene edges, the crown-capped side should bind metal cations more strongly than the bis(ethoxyethoxy) side. When the nitrogen atom in the crown ring is protonated, the metal cation would be pushed out through the π -basic cavity to the bis(ethoxyethoxy) side because of electrostatic repulsion.

A “Molecular Syringe” Mimic for Metal Cations

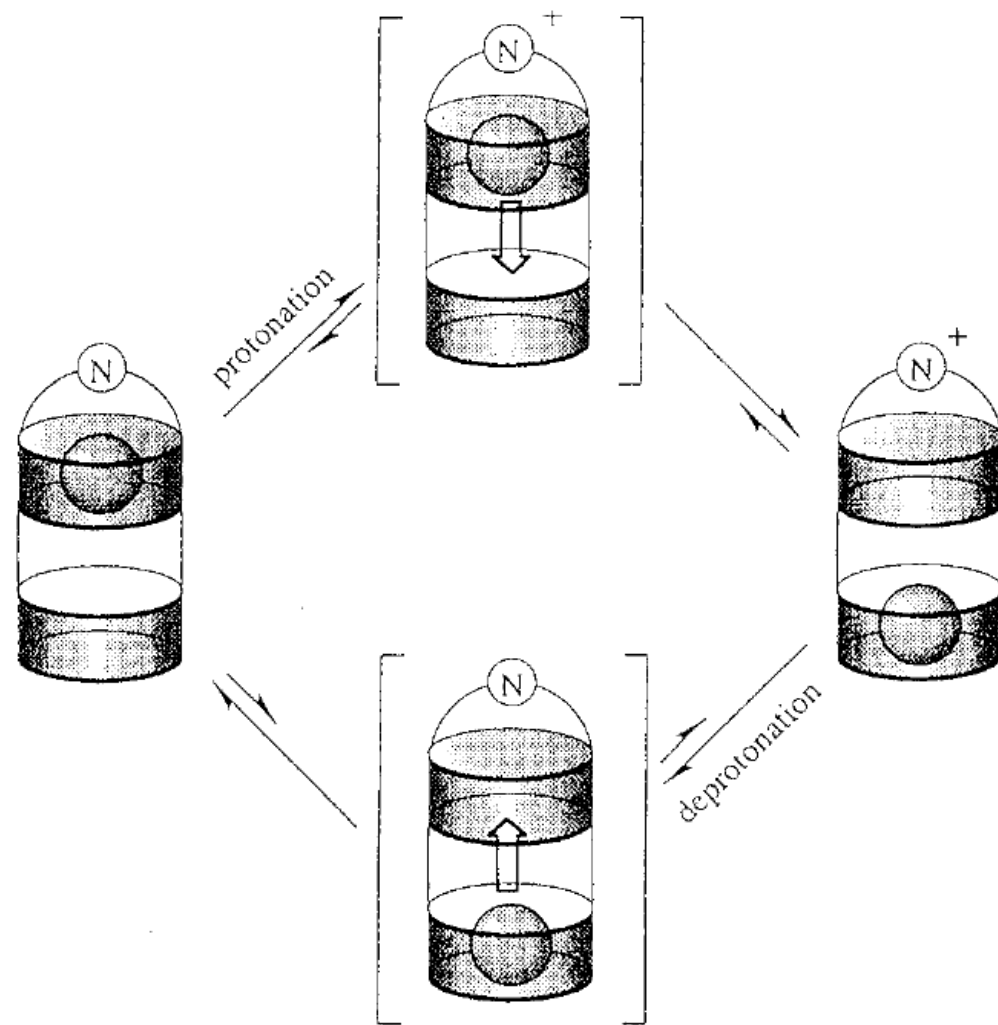
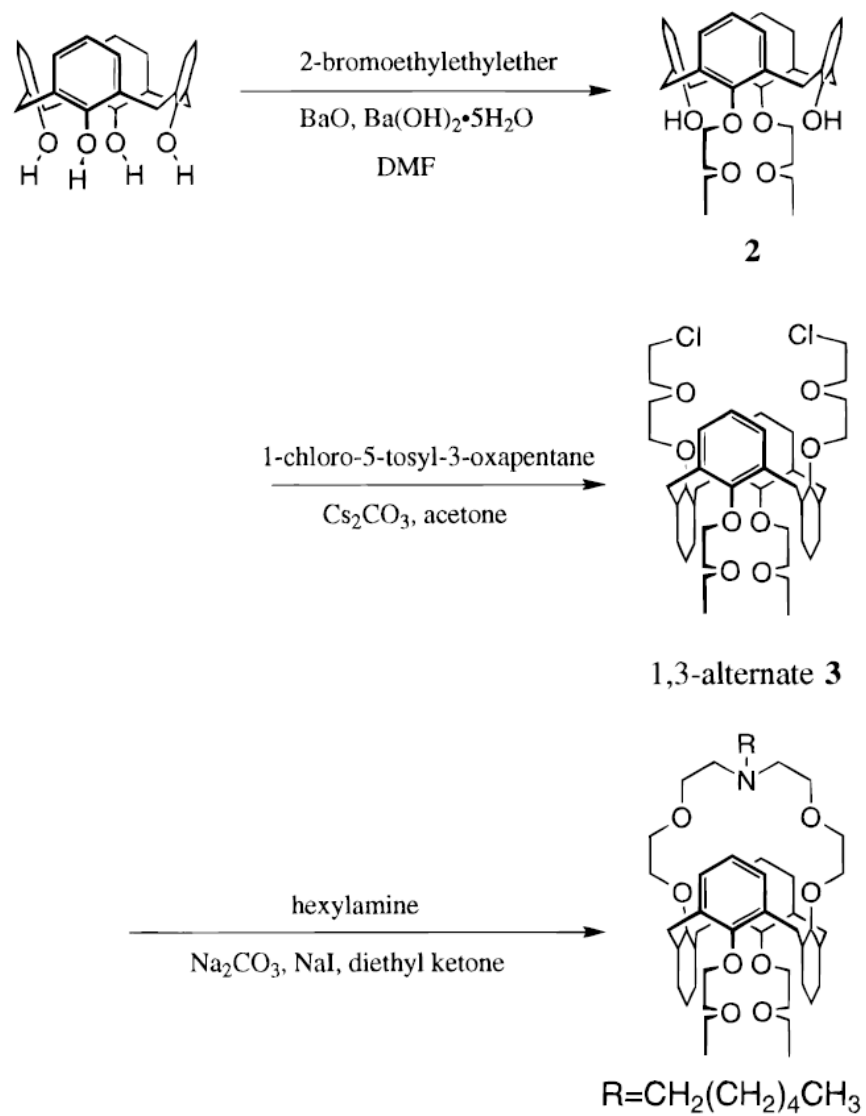


Figure 8. Schematic representation of a reversible metal pumping in a microscopic “molecular syringe” **1** designed from 1,3-alternate calix[4]arene.

The synthesis

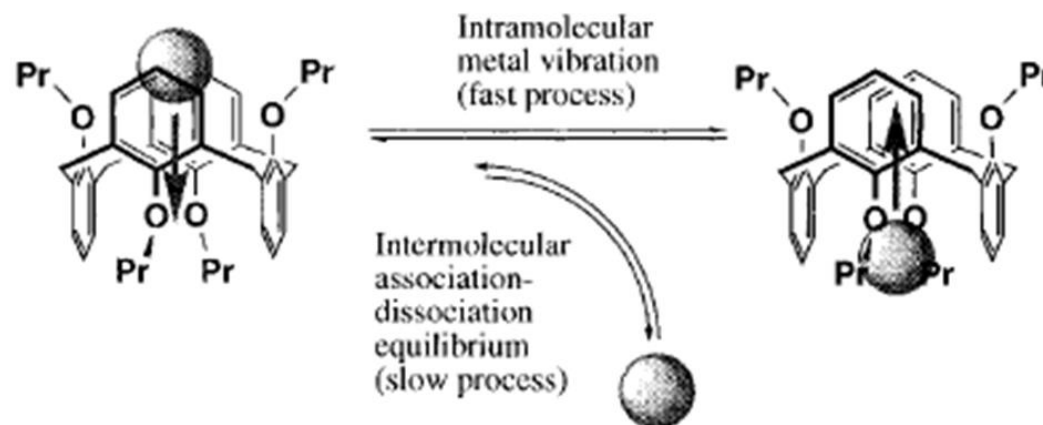
Scheme 1



The dynamic $^1\text{H-NMR}$ studies

For complexation studies, we chose Ag^+ which is known to form stable complexes with 1,3-alternate calix[4]arenes and possesses a metal-tunneling rate comparable with the NMR time-scale.

In previous examples of 1,3-alternate calix[4]arene- M^+ complexes, the coalescence temperature for the intermolecular metal exchange ($T_{c,\text{inter}}$) was always higher than that for the intramolecular metal-tunneling ($T_{c,\text{intra}}$). This result implied that the metal cation bound to the calix[4]arene edge tended to move intramolecularly to another edge rather than to dissociate intermolecularly into the solvent.



The $T_{c,intra}$ (intramolecular coalescence)

As the measurement temperature was lowered the peaks coalesced at $-20\text{ }^{\circ}\text{C}$ and then split into pairs again.

To corroborate that this coalescence is assignable to the $T_{c,intra}$, we examined the influence of the Ag^+ concentration on the coalescence temperature because the $T_{c,inter}$ reflects an intermolecular event and therefore is concentration-dependent whereas the $T_{c,intra}$ reflects an intramolecular event and therefore is concentration-independent

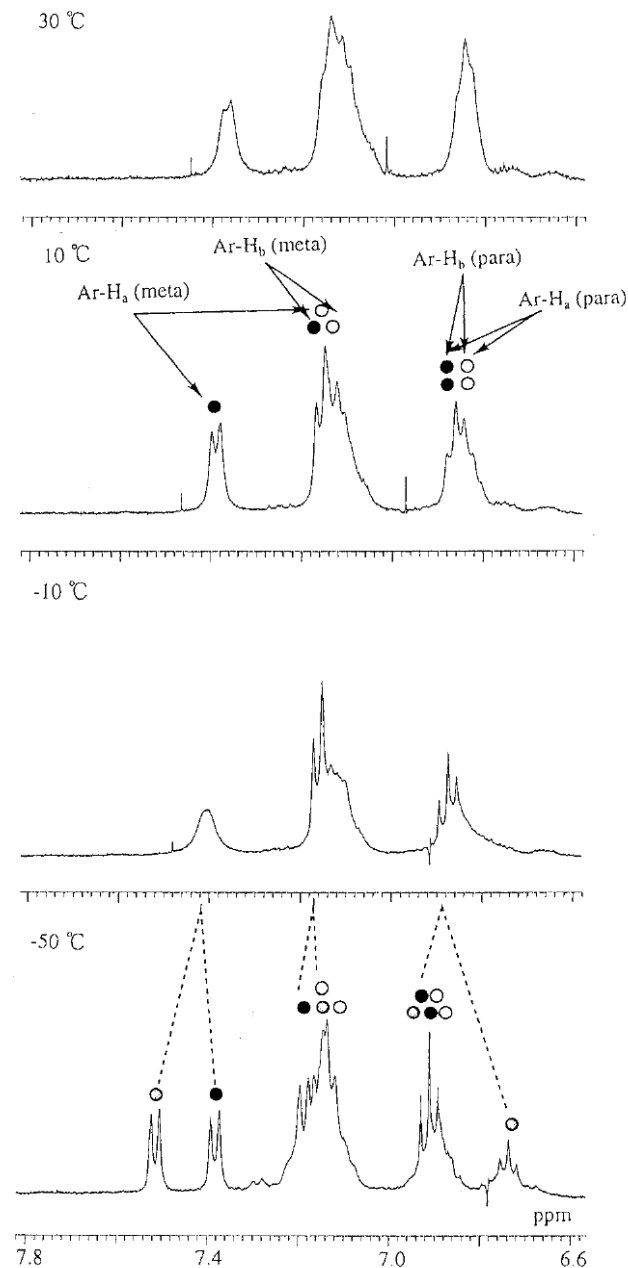


Figure 2. Partial ^1H NMR spectra of a 1-Ag^+ system: 400 MHz, $\text{CD}_2\text{Cl}_2:\text{CD}_3\text{OD} = 4:1$ v/v, $[1] = 5.00$ mM, $[\text{CF}_3\text{SO}_3\text{Ag}] = 2.50$ mM. Ar-H_a and Ar-H_b denote the aromatic protons at crown-capped side and those at bis(ethoxyethoxy) side, respectively.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

A 1,3-alternate calix[4]arene bearing a nitrogen-containing crown cap at one side and a bis- (ethoxyethoxy) group at another side has been synthesized.

^1H NMR spectroscopic studies showed that Ag^+ is bound to the crown-capped side ($\log K_{\text{ass}} = 9.78$; $\text{CD}_2\text{Cl}_2:\text{CD}_3\text{OD}$) 4:1 v/v, 30 °C), and the dissociation of Ag^+ from this cavity is very slow.

When the nitrogen atom in the crown ring is protonated with trifluoroacetic acid, Ag^+ is pushed out to the bis(ethoxyethoxy) side through a π -basic tube of the 1,3-alternate calix[4]arene. The dissociation of the complex from the bis(ethoxyethoxy) side occurs relatively fast. On the other hand, when the nitrogen- H^+ in the crown ring is deprotonated with Li_2CO_3 and diazabicycloundecene, Ag^+ is sucked back to the crown-capped side through the π -basic tube.

These chemically-switchable actions well imitate the function of a “syringe”, using the π -basic tube as a pipette and the crown ring as a rubber cap. We believe that this prototype of a “molecular syringe” is a novel molecular architecture for the action of metal cations.