DOUBLE CALIXARENES AND THEIR ANALYTICAL APPLICATIONS:

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ABSTRACT

The synthesis of various types of double calixarenes is reported. The complexation and extraction behaviors of these calixarenes are summarized.

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1. INTRODUCTION

Calixarenes have received special attention because of their ease of preparation and ability to undergo further synthetic elaboration. Calixarenes have a cavity that can bind guest molecules depending upon their size. Much work has been done to modify either the lower rim with phenolic hydroxy functions or the upper rim positions to create host molecules mainly for the complexation of simple cations, anions, and small molecules /1/.

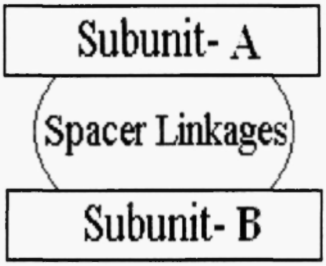
Calix[4]arene possesses the various conformers resulting from limited rotation about the σ bonds of the Ar-CH_2-Ar groups. In order precisely to recognize guest molecules, a rigid, conformationally defined calixarene is essential. Calix[4]arenes possess four possible basic conformations that are termed "cone", "partial cone", "1,2-alternate", and "1,3-alternate", respectively /2/.

However, this is not the case with calix[6]arene. Considering only the relative orientations (syn or anti) of the aromatic nuclei, there are eight possible conformations for calix[6]arenes, i.e. "cone", "partial cone", "1,2-alternate", "1,3-alternate", "1,4-alternate", "1,2,3-alternate", "1,2,4-alternate", and "1,3,5-alternate", and the number increases dramatically if the value of the angles that each aromatic nucleus makes with the average plane of the molecule is taken into account /2/.

The mobility of conformation of calix[6]arene has been reduced by bridging, including capping, of calix[6]arene. To freeze the conformation of calix[6]arene, another route is the bridging of two or capping of three or more phenolic rings. Here, the term "bridge" means that two phenolic rings are connected by a spacer, and "cap" means that the spacer links three or more phenolic rings of calix[6]arene, or the calixarene is linked by a spacer with triple or more linkage. The bridging or capping of calix[6]arene not only represents a potential method of freezing its conformation, but also constructs an interesting kind of host molecules with a special conformation, which possess good complexation ability /2/.

Researchers are also interested in one of the most useful building blocks for the construction of a complex molecule with an internal cavity capable of including large molecules. This goal requires a large cavity to hold the large molecules. Large molecules having internal cavities capable of including guest molecules are of great interest to workers. So, aiming at the elaboration of larger systems based on calixarenes units, organic chemists have been attracted to the design and production of double calixarenes /3/. Double calixarenes exhibit a potential to recognize and include larger species, such as neutral organic molecules and metal ions /4 a, b/.

This account deals with the synthesis, conformational behavior and complexing properties of double calixarenes. These double calixarenes can be represented as a receptor in which two calixarenes subunits are linked via different linkages [Fig 1].



Calixarene subunit A
Calixarene subunit B
where A=B or A≠B

Fig 1: Schematic representation of double calixarenes

2. SYNTHETIC STRATEGIES FOR DOUBLE CALIXARENES

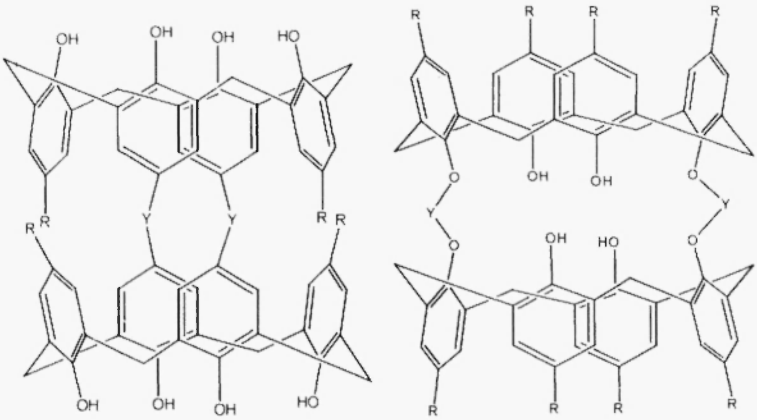
Double calix[4]arenes have been designed as a synthetic challenge as well as to provide the chemists with molecular receptors that present special properties due to their molecular ditopic structure.

Owing to the presence of two main arrays of reactive centers (the possible phenolic OH groups and the para positions on the phenyl ring), they can be arranged in three ways:

(i) "Head-to-head" linked where two calixarenes are linked by the para positions,

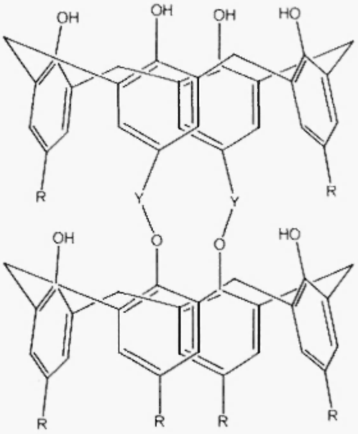
(ii) "Tail-to-tail"-linked where two calixarenes are linked by the phenolic oxygen, and

(iii) "Head-to-tail"-linked, which is a hybrid of the two preceding arrangements, as shown below **[Fig. 2]**.



(i)
"Head-to-Head"

(ii)
"Tail-to-Tail"



(iii)
"Head-to-Tail"

where Y= different types of linkages.

Fig. 2: Three different types of double calixarenes

Several double calixarenes were synthesized by the systematic reaction of calixarene with various types of spacers. Depending on the reaction conditions, such as the nature of the base, the structure of the reactant and the stoichiometry of the reactant, calixarenes with different topologies were isolated. The general synthetic scheme for double calixarenes is shown below [**Fig. 3**].

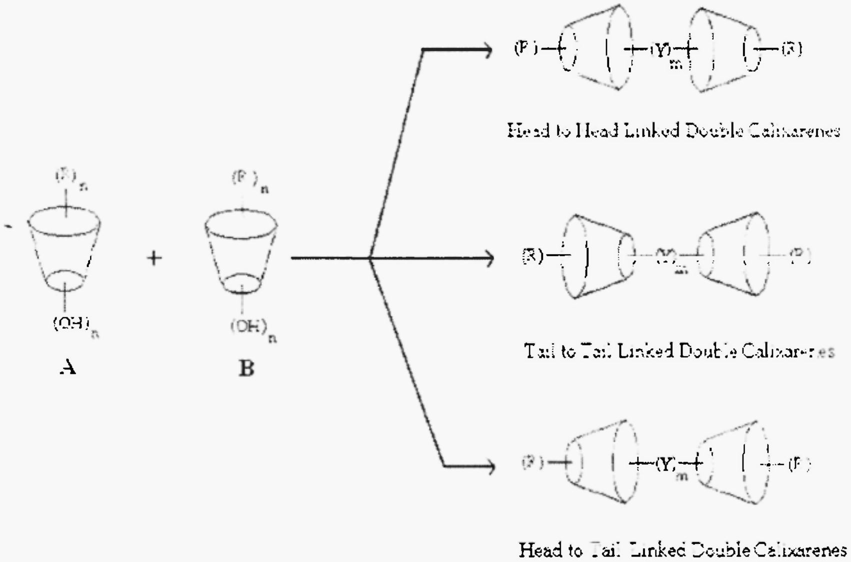


Fig. 3: Different synthetic pathways to synthesize double calixarenes.

Here, n = number of benzene rings in calixarene, i.e. 3, 4, 5, 6 or 8.
m = number of linkages between two calixarene subunits
Y = ether, amide, ester, imine, azo, alkene, and hydrogen bonding types of linkages
R = different types of alkyl groups and halogens.

Note: In some cases A = B and in some cases A ≠ B

The three types of double calixarenes; Head-to-Head, Tail-to-Tail and Head-to-Tail, are summarized below.

A) "Head-to-Head" Linked Double Calixarenes

The first double calix[4]arenes of the " Head-to-Head" type were synthesized by Bohmer *et al.* in 1989 /5/. In their study they reacted tetrabromomethylated diphenols with a linear trimer in refluxing dioxane in the presence of $TiCl_4$ to give double calix[4]arenes with one alkyl chain [X = CH_3-C-CH_3, $(CH_2)_5$, $(CH_2)_8$, $(CH_2)_{12}$] connecting the p-positions. The linkage by two opposite and four aliphatic chains created double calix[4]arene with a fixed cone conformation and an extorted cavity.

^{1}H-NMR studies showed that the addition of p-xylylenediamine to a $CDCl_3$ solution of the double calix[4]arene, mono linked with $(CH_2)_8$, proved strong electrostatic interaction in the hydrophilic region at the hydroxy groups, involving amino-basic protons transfer from the phenol unit to the amino functions [Eq. 1]. This could probably be a change of the original conformation of the aliphatic chain of the double calixarene.

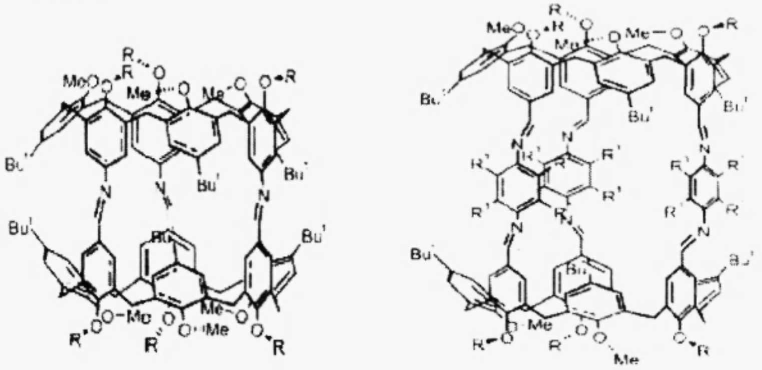
$$ArOH + NH_2R \longrightarrow ArO^- + NH^+_3R \longrightarrow ArO^- \cdots\cdots NH^+_3R \quad (1)$$

Another example of a double calixarene has also been reported by Arduini *et al.* in 1991 /6/. Their paper shows the direct selective upper rim 1,3-formylation of a conformationally rigid calix[4]arene with Cl_2CHOMe_2 and $SnCl_4$ in chloroform. The obtained diametrical bis (formyl) calix[4]arene was reduced by $NaBH_4$ in ethanol. The produced 1,3-bis (hydroxymethyl) derivative was further reacted with its ditosylates, prepared in situ in the presence of NaH in toluene 1,2-dimethoxyethane, to yield a double calix[4]arene in which the two opposite spacers are a benzyl ether linkage. Temperature-dependent ^{1}H-NMR experiments showed flexibilities in the ring and that "portals" are available for guest molecules of suitable size to enter the apolar cavity.

A very similar intermediate has been used by Vicens *et al.* for the synthesis of a double 1,3-dimetoxy-calix[4]arene, linked via the upper rims by two porphyrins /7/. The two calix[4]arene subunits were deduced to be in the cone conformation from observation of the AB system at δ 5.85 and δ 4.90 with J_{AB} = 12.4 Hz. The same 1,3- dimethoxy-bis (formyl) calix[4]arene intermediate was used for development of the Schiff-base double calixarene /3/.

Reinhoudt *et al.* reported the condensation of formyl calix[4]arene with amino calix[4]arene /8/, resulting in a Head-to-Head-linked double calix[4]arene Schiff base. This Schiff base possesses very high affinity to silver(I) ions which was proven by ^{1}H-NMR titration experiments, membrane transport experiments and CHEM-FET studies, confirming the selective transport and complexation of silver(I) ions in the presence of interfering ions.

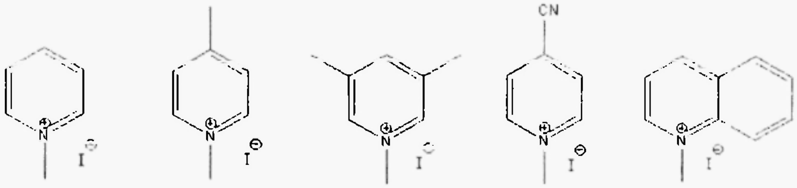
Upper rim covalently triply linked Schiff-base double calix[6]arenes have been synthesized by Arduini *et al.* /9/. The calix[6]arenes can be regarded as a new series of tripodal capped calix[6]arenes By reacting 37,39,41-trioctyloxy-11,23,35-tri-tert-butyl calix[6]arene (trialdehyde) with 37,39,41-trioctyloxy-38,40,42-tri-methoxy-5,17,29-triamino-11,23,35-tri-tert-butyl calix[6]arene (triamine) in refluxing toluene, (**X-1**) was obtained in 26% yield. Using 1,4-diaminobenzene instead of triamine, (**X-2**) was obtained in 50% or 40% yield. The internal cavities of these molecular cages exhibit different grades of accessibility toward a set of N-methyl – pyridinium cations [**Fig. 4**].



X-1 **X-2**

Fig. 4: Capped calix[6]arenes

Koji *et al.* /10/ determined the inclusion ability of biscalixarene with N-methyl pyridinium iodide (**I-a**) and analogs (**I-b**) to (**I-e**) [Fig 5]. The association constant (K_a) for inclusion of (**I-a**) to (**I-e**) reveals that the largest K_a was obtained for the complex of biscalixarene and N- methyl pyridinium iodide (**I-a**). This value in chloroform is 500-fold times greater than that of the complex of calix[4]arene and N-methyl pyridinium iodide. This significant enhancement in K_a is attributed to the cooperative action of the two π-basic cavities of the confronted cone-calix[4]arenes in the globular shaped biscalix[4]arene. The decreased K_a for (**I-b**) indicates that the introduction of an additional methyl group in (**I-a**) reduces the stability of the complex. No formation of complexes for (**I-c**) and (**I-e**) was observed.

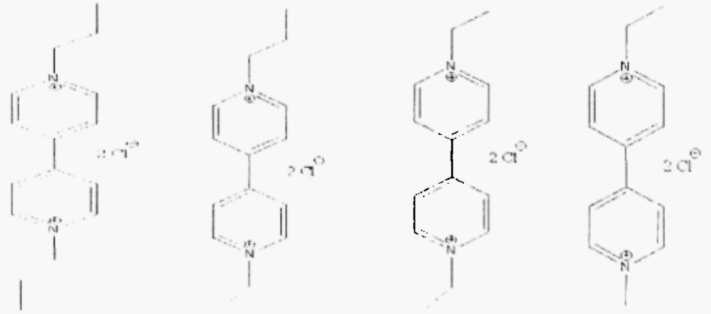


I-a **I-b** **I-c** **I-d** **I-e**

Fig. 5: Pyridinium iodide and its analogs

This study, indicating the importance of connecting the two calix[4]arenes with appropriate spacers and reducing the conformational freedom of host biscalix[4]arene, shows at the upper rims a strong inclusion ability for the cationic guest molecules due to the cooperative action of the cation π-interaction /10 a, b/.

Kim *et al.* /11/ carried out studies on viologen-type guest molecules entering the cavities of double calix[4]arene by ^{1}H NMR titration experiments. Viologens are formed by the diquaternizing of 4,4'-bipyridine to form 1,1'-disubstituted –4,4'-bipyridilium salts. Some viologen type guest molecules are shown below: **[Fig. 6]**

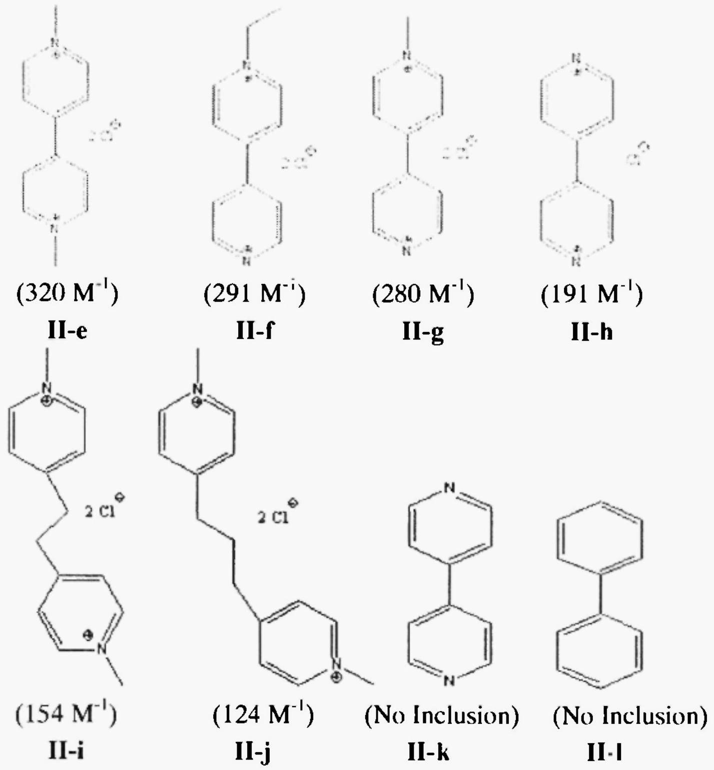


(No inclusion) **II-a**

(59 M^{-1}) **II-b**

(727 M^{-1}) **II-c**

(515 M^{-1}) **II-d**

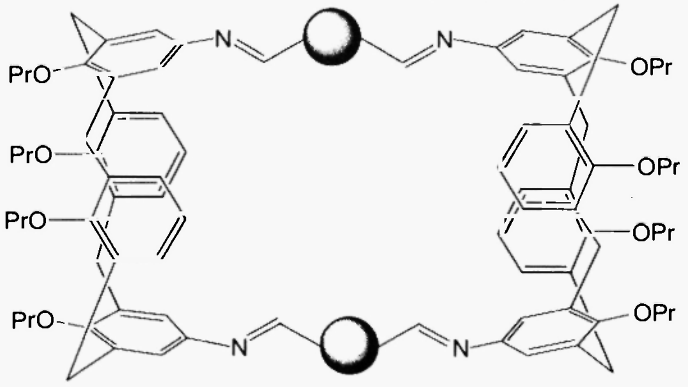


(320 M^{-1}) **II-e**　(291 M^{-1}) **II-f**　(280 M^{-1}) **II-g**　(191 M^{-1}) **II-h**

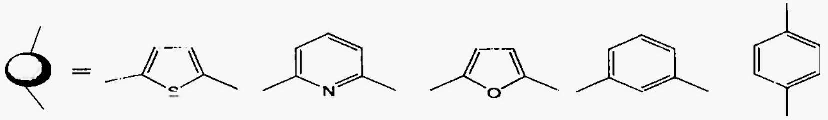
(154 M^{-1}) **II-i**　(124 M^{-1}) **II-j**　(No Inclusion) **II-k**　(No Inclusion) **II-l**

Fig. 6: Viologen type guest molecules and their associate constant with double calix[4]arene

They carried out the binding studies of double calix[4]arenes (**X-3**) to (**X-7**) and viologen-type guest molecules (**II-a**) to (**II-l**) [**Fig. 6**].



where,



X-3 **X-4** **X-5** **X-6** **X-7**

Fig. 7: Double calix Schiff bases with different types of heteroaromatic and aromatic linkages

When viologens (**II-b**) to (**II-j**) were added to the host solution, the signals of imine and aromatic protons in the double calix[4]arene (**X-3**) shifted down-field, whereas no change in the chemical shift values of (**X-3**) was detected when the compounds (**II-a**), (**II-k**), and (**II-l**) were added. Titration experiments with various viologen-type guest molecules clearly showed that a suitable size of the N-alkyl groups and the presence of the bipyridinium dication in viologens are essential for the inclusion to occur /11/.

The ^{1}H NMR spectra of double calix[4]arenes (**X-4**) to (**X-7**) remained unaltered upon the addition of any of the viologens (**II-c**), (**II-d**), (**II-i**), (**II-j**). This indicates that the hosts (**X-4**) to (**X-7**) have a low or no affinity towards viologens.

From these results, it can be concluded that the overall shape of the host molecules and the electron density of the aromatic linkers [thiophene, benzene, furan and pyridine] are important factors in the binding affinity with the viologen guests, because aromatic-aromatic interactions occur between the electron-deficient viologen moiety and the electron-rich thiophene aromatic linkers.

Shinkai *et al.* reported a calix[6]arene-based molecular capsule /12/ by reacting 5,11,17,23,29,35-hexakis (chloromethyl)- 37,38,39,40,41,42-hexamethyl-calix[6]arene with 5,11,17,23,29,35-hexakis (mercaptomethyl)-37,38,39,40,41,42-hexa-methoxycalix[6]arene in N-methyl formanilide/DMF solvents in the presence of Cs_2CO_3 and $NaBH_4$. This double-calix[6]arene molecular capsule is capable of "constrictive binding" of a guest molecule (N-methyl formanilide), which is a solvent and can be viewed as a hexapodous capped calix[6]arene in which each calix[6]arene plays the role of cap for the other one. No other hexapodous capped calix[6]arene is known.

A novel approach to the synthesis of double calixarene shows the dirhodium tetracarboxylate complex in which two calix[4]arene macrocycles, bridged at the upper rim by a Rh-Rh unit, serve as ligands and whose solid-solid structure shows an unusual coordination of a toluene molecule in the axial position at each rhodium atom /13/.

Stibor *et al.* reported novel biscalix[4]arene derivatives where two calixarene units are connected via one or two ureido bridges on the upper rim /14/. They also determined the complexation ability of this biscalix[4]arene derivative with two ureido bridges and another similar derivative with two ureido bridges, in which a cooperative effect of the two ureido units is possible. On the other hand, a similar derivative, with two amidic functions, does not exhibit any complexation ability towards selected anions (halides, benzoate).

Jorgensen *et al.* studied the binding ability of N,N'-bis-(4-nitrophenyl) tetrapropoxycalix[4]arene-5,17-dicarboxamide and doubly bridged biscalix[6]arene with benzene, naphthalene, anthracene, and pyrene as guest and related to the solvent-dependent conformations /1c/. Chemical-shift changes were observed at relatively high guest concentrations for the above calix[4]arene in chloroform, while in DMSO no significant chemical shift changes of calix[4]arene occurred on addition of an aromatic guest; the change in conformation due to DMSO could account for the lack of binding in this solvent. The dimer (i.e. the doubly bridged biscalix[4]arene) showed no significant chemical shift changes on addition of aromatic guest molecules; this can also be ascribed to the effect of DMSO on conformation and occlusion of the binding site.

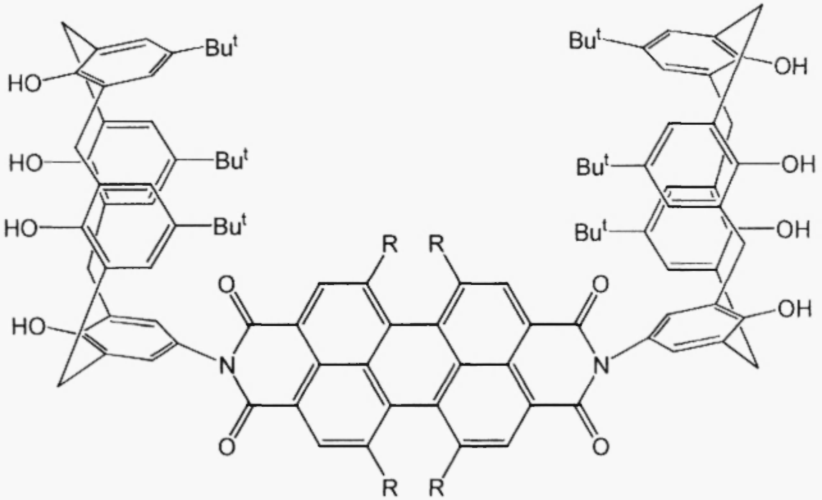
Neri *et al.* reported the first example of a bridgeless, head-to-head double calix[4]arene /15/, i.e. 5,5'-biscalix[4]arene, with a direct biphenyl-like para-para linkage. The alkylation of 5,5'-biscalix[4]arene with propyliodide and para-tert-butylbenzyl bromide in the presence of K_2CO_3, NaH and Cs_2CO_3 has been investigated /16-19/.

Neri *et al.* worked on an oxidative coupling reaction that effects the direct upper rim to upper rim attachment of a pair of calix[4]arenes, calix[6]arenes, or calix[8]arenes, respectively, to yield 5,5'-biscalix [4,6,or 8]arenes; these were then extended to 5,5'-biscalix[5]arene by Gutsche *et al.* /20/. They studied the complexation ability of 5,5'-biscalix[5]arene and calix[5]arene towards fullerenes, C_{60} and C_{70}. The x-ray crystallographic structure of the C_{60} complex reveals its clamshell-shaped architecture, presumably the result of a change in the conformation of biscalix[5]arene from anti (uncomplexed) to syn (complexed).

Gutsche and Wang also studied the complexation abilities of biscalix[n]arenes with fullerene (i.e.C_{60} and C_{70}) /21/. Here, biscalix[n]arenes, singly and doubly bridged at the upper rims with 2-butenyl or 2-methylenepropyl moieties, have been prepared by Tandem Claisen rearrangement of biscalix[n]arenes that are singly and doubly bridged via ether linkages at the lower rims with these same spanners. Gutsche *et al.* also published another example of doubly bridged bis calix[4]arene via diyne bridges /22/.

Silvio *et al.* reported a new dixanthylene double calix[6]arene, a mutual interconnection of two calix[6]arenes subunits by the formal incorporation of a dixanthylene core into a double calix[6]arene system /23/.

Another type of novel double calixarene has been published by Wurthner *et al.* in 2002 /24/. In their paper they have synthesized double calixarenes (**X-8**) and (**X-9**) by reacting bis-anhydrides and calixarene mono amine. They also reported the effect of photo-induced electron transfer by calixarene towards bis- anhydrides [**Fig. 8**].



where **X-8, R=H**

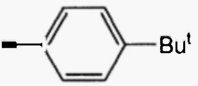
X-9=R


Fig. 8: Bis calix[4]arene connected via perylene-bis imide dye

Bis-, tris-, and hexakiscalix[4]arenes have been synthesized by using monohydroxy calixarene as starting material /25/. Another report also shows the synthesis of tail-to-tail-linked double calix[4]azacrown ether in the 1,3-alternate conformation /26/.

"Tail-To-Tail"-Linked Double Calixarenes

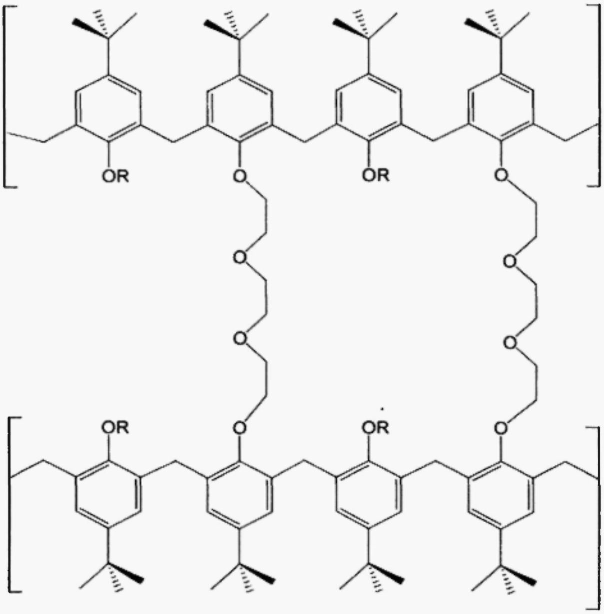
In 1990 Mc Kervey *et al.* reported the first tail-to-tail linked double calixarene /27/. They synthesized double calix[4]arenes with diamide or diester bridges. An ^{1}H NMR study on solutions of diamide derivative showed that kinetically stable complexes were formed in which both calix[4]arene moieties took up a Na^{+} ion.

In 1990, Kraft *et al.* proposed the building up of macrocyclic assemblies in which two calix[4]arene subunits are connected via two bridges between their respective oxygen atoms at the 1- and 3- positions. This goal was achieved by the use of difunctional reagents such as diacid chlorides, which are too rigid to make an intermolecular bridging of the calix[4]arene /28/. The addition of ethylenediamine or –diol to 1,3-diacyl chloride, obtained from the 1,3-diacid by action of SO_2Cl_2, led to double calix[4]arenes linked by two opposite ester or amide spacers. By changing the time of addition of the dichloride, the authors observed the formation of triple calix[4]arene /28/.

Vicens *et al.* reported another type of double calixarene in which the two calix[4]arene subunits are connected via glycolic chains /29/. The treatment of p-tert-butylcalix[4]arene or 1,3-dimethoxy-p-tert-butylcalix[4]arene with two equivalent yielded the corresponding double calix[4]arenes linked by two opposite glycolic chains [**Fig. 9**].

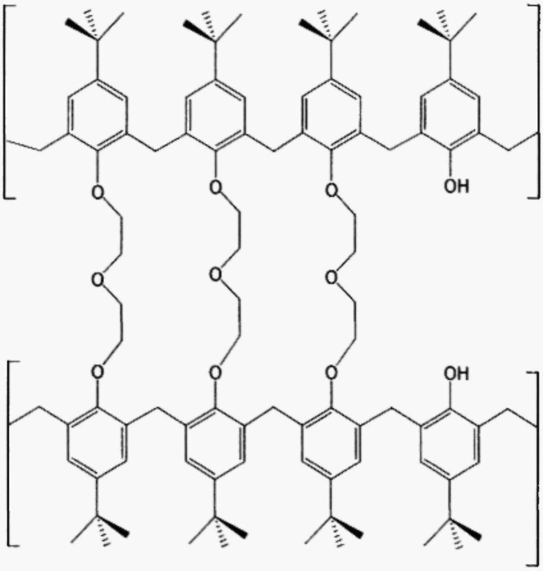
They also synthesized another compound in which they showed that the treatment of p-tert-butylcalix[4]arene with diethylene glycol ditosylates under very similar conditions yielded a double calix[4]arene triply bonded via the oxygen atoms by glycolic chains /30/. In this case the preferred formation of a double calix[4]arene is due to the shortness of the diethylene glycolic chain [**Fig. 10**].

Shinkai *et al.* published a similar type of double calix[4]arene linked with two tetraglycolic chains, possessing monoglycol and tert-butyl groups at their lower and upper rims, respectively /31, 32/. It was shown to be a ditopic ionophore in which Na^{+} or K^{+} vibrates between the two metal-binding sites in the NMR time scale.



X-10, R= H. **X-11,** R=CH_3.

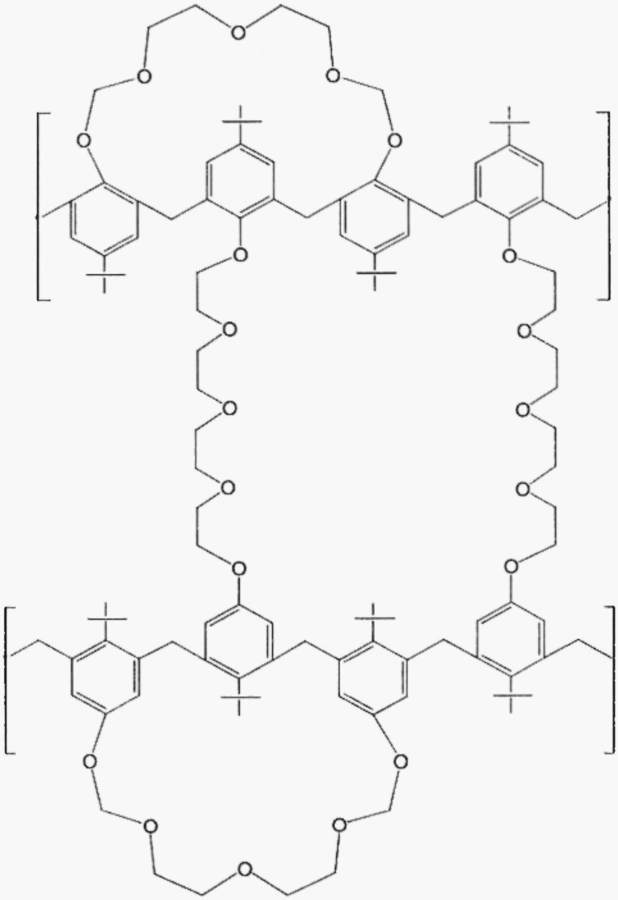
Fig. 9: Double calixarene connected via glycolic chains



X-12

Fig. 10: Double calixarene connected via diethylene glycolic chains

This approach has been enlarged to a double calix[4]crown ether. The first example of a double p-tert-butylcalix[4]crown ether was reported by Asfari *et al.* /33/. A double calix[4]crown was formed by changing the stoichiometry of the reactant p-tert-butylcalix[4]arene, which was treated with excess tetraethylene glycol ditosylates to yield a double p-tert-butylcalix[4]-biscrown-5, in which each calixarene unit is in the 1,3-alternate conformation and 1,3-capped by a tetraethylene glycolic chain [**Fig. 11**]. By ^{1}H-NMR experiments, the double calix[4]crown ether ligand was shown to form 1:1 complexes with potassium and rubidium picrates in the solid state and in solution in deuteriated chloroform /33/.

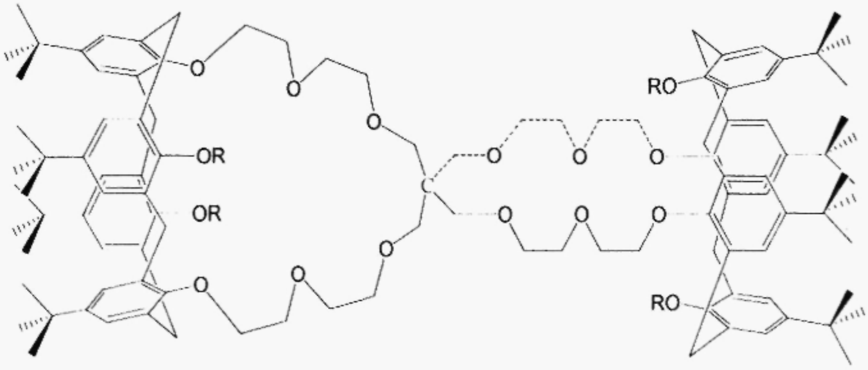


X-13

Fig. 11: Double calix[4]crown ether connected via tetraethylene glycolic chain

As a consequence of the preceding work double calixcrowns were prepared by Pappalardo *et al.* using 4,6,10,12,16,18,22,24,25,26,27,28-dodecamethyl-5,11,17,23-tetrahydroxycalix[4]arene or mesitol-derived calix[4]arene, which is in a fixed 1,3-alternate conformation and presents two sets of extra-annular hydroxy groups suitable for double bridging as described for double calixcrowns /34/. The reaction of mesitol-derived calix[4]arene with appropriate oligoethylene glycol ditosylates in acetonitrile in the presence of potassium carbonate gave, in addition to the expected double calix[4]crowns, doubly crowned calix[4]arenes /35/. The formation of the double calix[4]crown compared to the doubly crowned calix[4]arenes was attributed to the shortness of diethylene glycolic chain or the more rigid polyethral chain due to the presence of a hydroquinone unit.

Chen *et al.* reported a novel type of double calixcrown, spiro-biscalix[4]crown, in which two calix[4]arene subunits were linked via a spiro C-atom incorporated into poly(oxyethylene) chains /36/ [**Fig. 12**].



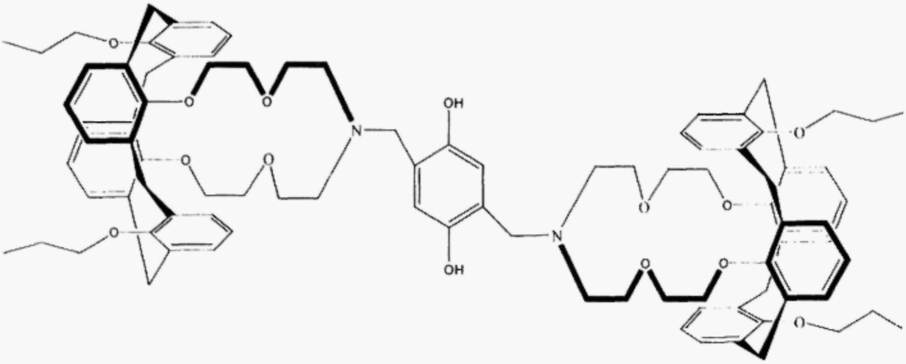
X-14, R = H.

X-15, R = CH_3.

Fig. 12: Spiro-biscalix[4]crown

They studied the complexation abilities of a double calixcrown: spiro-biscalix[4]crowns and p-tert-butylcalix[4]crown-5 toward Li^+, Na^+, K^+, NH_4^+, n-prNH_3^+, $Me_2NH_2^+$, $Et_2NH_2^+$ alkali metal picrate salts.

Another approach to double calix[4]crown ether has been extended to a bis calix[4]aza crown ether by Kim *et al.* /37/. In this paper the authors showed the synthesis of calix[4]aza crown by reacting 25,27-bis-(1-propyloxy)calix[4]arene and paraformaldehyde in the presence of 1,4 hydroquinone in benzene as a solvent. This reaction resulted in bis calix[4]aza crown ether [**Fig. 13**].



X-16

Fig. 13: Bis calix[4]aza crown ether

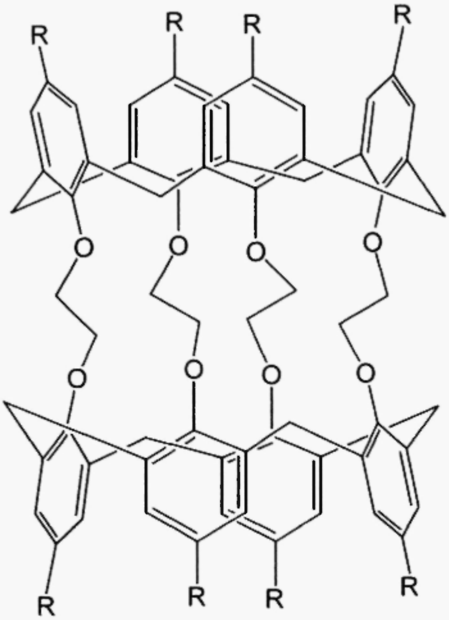
In this case of a bis calix[4]aza crown ether, the distance between OH and nitrogen is too large so they cannot form an intramolecular hydrogen bond, implying that the nitrogen atom can freely participate in the metal ion complexation. Kim *et al.* continued work on bis calix[4]azacrown /38/.

Raston *et al.* reported the first example of an unsymmetrical fused calixarene, derived by linking p-tert-butylcalix[4]arene with p-tert-butyl[n]arenes (n=5,8) via ethylene linkages /39/. Their efforts were directed towards the investigation of inclusion properties of these receptors and derivatization of these novel classes of bridged calixarenes.

Adopting the same approach of synthesizing unsymmetrical fused calixarene, Pappalardo *et al.* reported mixed triple and double calixarenes obtained from base-catalyzed condensation of p-tertbutyl calix[5]arene with tetrakis[2-(tosyloxy)ethoxy-p-tertbutyl calix[4]arene] /40/.

A new class of cryptand-type ionophore, the calix[4]tube, based on a bis calix[4]arene scaffold, was explored by Beer *et al.* /41/ [**Fig. 14**].

In their earlier studies they synthesized thia calix[4]tube by reacting the tetra tosylate derivative of the corresponding tetra alchohol calix[4]arene with tert-butyl thia calix[4]arene in the presence of K_2CO_3 /42/. They also reported the synthesis of a quadruply linked bis-tert-butyl calix[4]tube, and they also studied the complexation properties of these calix[4]tubes, finding that the linkages are steriochemically mobile and can change their conformation according to the situations /43 – 45/.



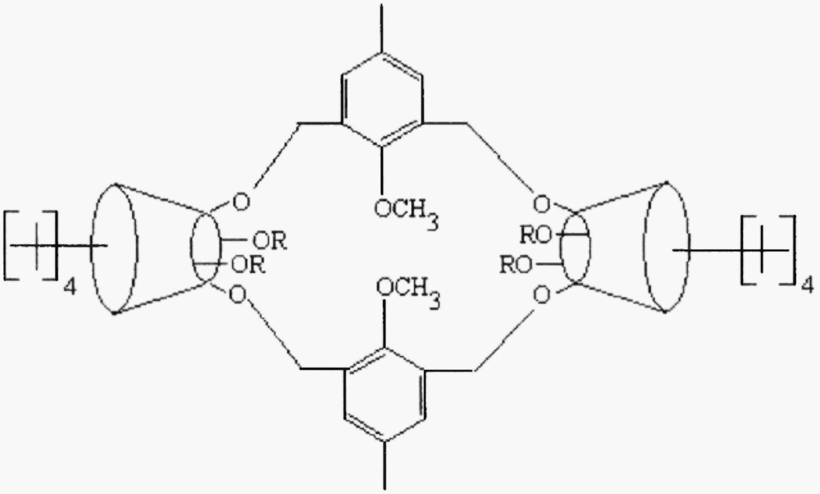
where R= Bu^t.

X-17

Fig. 14: Bis calix[4]tube

Le Gac *et al.* also reported a calix[6]tube with nitrogen as a ligand backbone /46/. They reacted N-protected calix[6]tris-amine with tris-tosylated calix[6]arene under basic conditions in anhydrous DMF. They also studied the effect of Cs^{2+} ions as a templating agent. Gonzalez *et al.* synthesized a series of bis calix[4]arene derivatives linked through the phenolic oxygens with the help of a single aliphatic chain /47/.

Zhong *et al.* also published a double calixarene in which they used aromatic segments as a spacer /48/. They reacted p-tert butyl calix[4]arene and 2,6-bis(bromethyl)-4-methylanisole at refluxing temperature for three days under basic conditions. The resulting product was methylated with excess methyl tosylate to yield a fully methylated bridged double calix[4]arene. This fully methylated bridged double calix[4]arene possesses higher binding ability toward Li^+, Na^+, and K^+ than that of a partially methylated bridged double calix[4]arene **[Fig. 15]**.



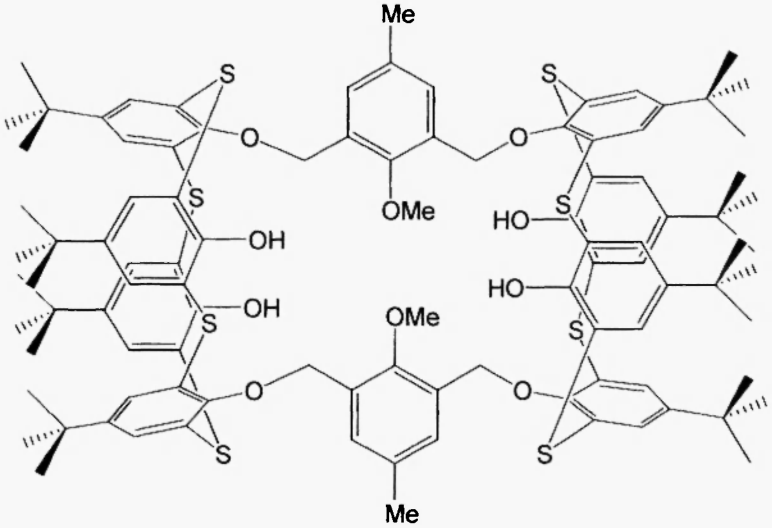
X-18, R = H.
X-19, R = CH_3

Fig. 15: Double calixarene connected via aromatic spacer

Jin *et al.* synthesized double thiacalix[4]arene by reacting p-tert-butylthiacalix[4]arene and 2,6' bis (bromomethyl)-4-methylanisole in the presence of Na_2CO_3 as a base under argon /49/ **[Fig. 16]**.

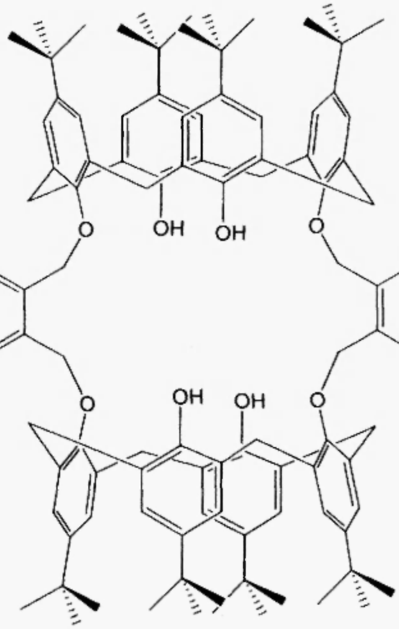
Vicens *et al.* published a paper in 2002 where they also utilized an aromatic spacer for the synthesis of bis calixarene /50/. They reacted p-tertbutyl calix[4]arene and α, α' dibromo-o-xylene in acetonitrile under basic conditions to obtain bis calix[4]arene with an o-xylene linkage **[Fig. 17]**.

This approach was then etended to Schiff-base biscalix[4]arenes. The first bridge calixarene Schiff base was reported by Zhang *et al.* /51/. They synthesized a double calixarene Schiff base by reacting 25, 27-N-N'-di-((2-ethoxy)benzyl)bu tylenediimine-p-tert-butyl-calix[4]arene and terephthal-aldehyde at 2:2 in ethanol medium at refluxing temperature for 12 hrs **[Fig. 18]**.



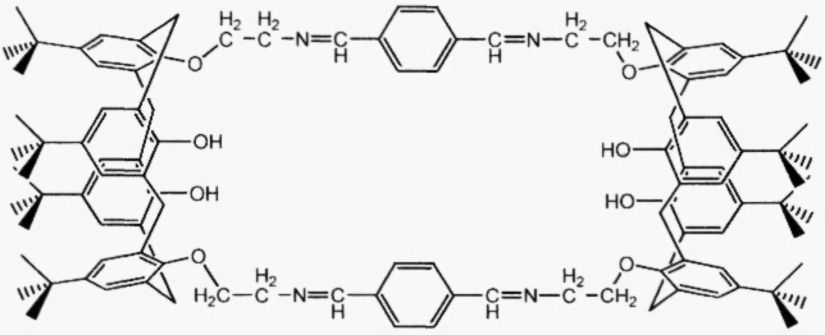
X-20

Fig. 16: Double thiacalix[4]arene connected aromatic spacer



X-21

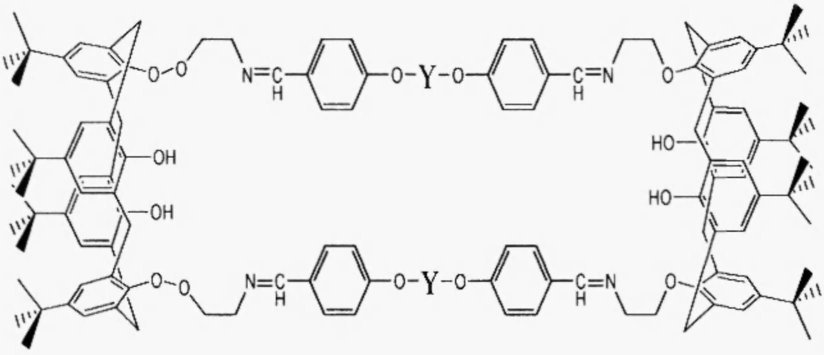
Fig 17: Bis calix[4]arene connected via o-xylene



X-22

Fig. 18: Schiff base biscalix[4]arene

Yuan *et al.* /52/ used the same pathway to synthesize a double calixarene Schiff base. They published a paper where they reacted aromatic dialdehyde derivatives having different spacers with 25,27-di(aminoethoxy)-4-tert-butylcalix[4]arene in refluxing ethanol medium. The reaction time depended on the dialdehyde taken. The effects of the spacer on the reaction time were also studied [**Fig. 19**].

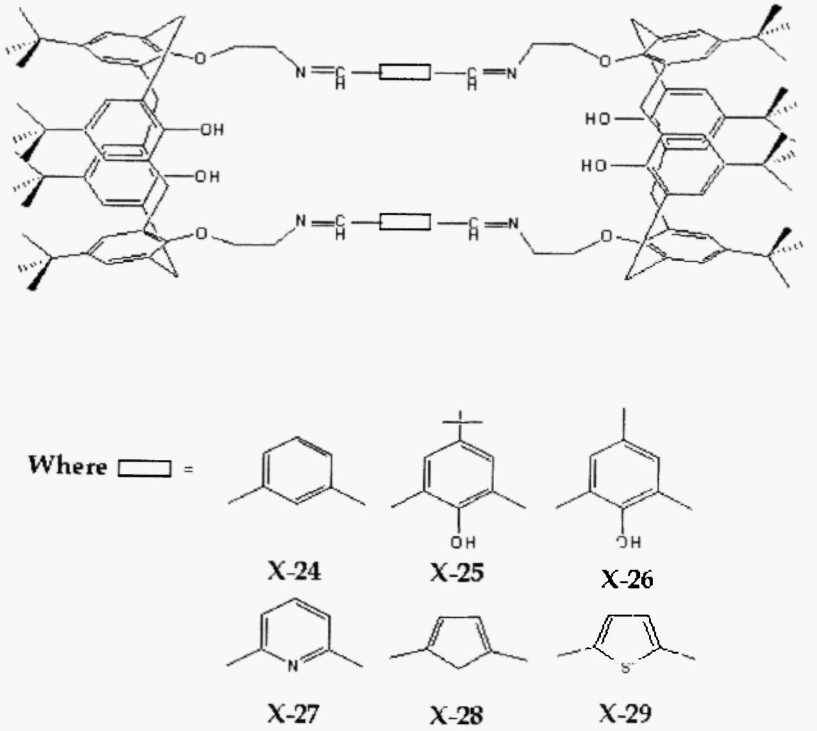


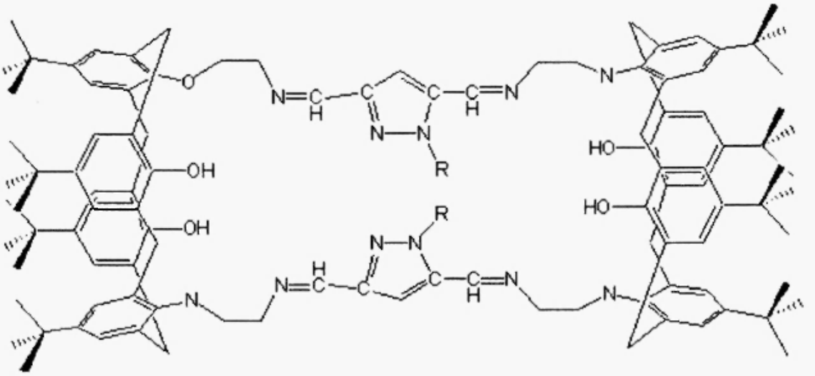
X-23

where Y= different aliphatic and aromatic spacers.

Fig. 19: Double calix[4]arene Derivatives connected via Schiff base linkages

The use of a diamine derivative for synthesis of double calixarene Schiff base has been explored by Kumar *et al.* /53 a/. In this paper they obtained a double calixarene Schiff base from 25,27-di(aminoethoxy)-4-tert-butylcalix[4]arene and different aromatic & heteroaromatic dialdehyde derivatives. The reaction method was 2:2 dipodal condensations [**Fig. 20**]. The same group also published a paper in which they used thiophene and pyrazole as heteroaromatic spacers /53 b/.

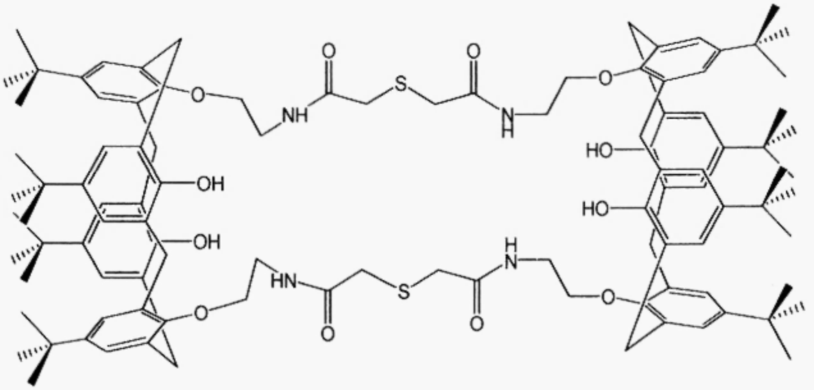




Where X-30 = $-CH_3$,
X-31 = $-H$,
X-32 = $-PhCH_3$,
X-33 = $-CH_3(CH_2)_4CH_2$

Fig. 20: Double calix[4]arene Schiff base connected via heteroaromatic and aromatic spacer

Francisco *et al.* reported a double calix[4]arene, in which two calixarene subunits connected by thiourea and an amide-sulfur spacer have been synthesized /54/. Here the bis calix[4]arene was obtained by reacting the bis(acetylthio) derivative of p-tert butyl calix[4]arene and the dichloroacetamide derivative of p-tert butyl calix[4]arene [**Fig. 21**].



X-34

Fig. 21: Double calix[4]arene connected via amide-sulfur groups

Reinhoudt *et al.* published a paper in which they synthesized double calixarene with two linkages and two aromatic segments /55/. They also studied the effect of the nature of the bridge on the formation of mono and biscalix[4]arenes. They conclude that rigidity is one of the major factors for the formation of bis calixarene.

Stang *et al.* published a novel type of bis calixarene in 1997 /56/. They reacted a calix[4]arene Pt (II) chloride complex /57/ with excess AgOTf in dichloro methane solvent, which resulted in a bis triflate complex. This complex interacted with a bis heteroaryliodonium salt /58/ to give a novel hybrid bis calixarene-iodonium-Pt molecular square in good yield.

In the search for molecular machines Asfari *et al.* published a novel type of double calixarene in which the condensation of dibromomethyl derivative of calix[4]-bis-crown with naptho poly ether diol was carried out under high dilution conditions /59/.

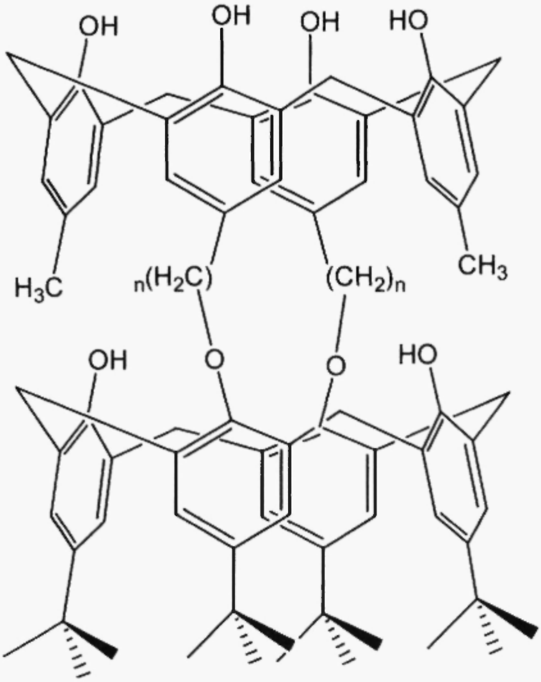
McKervey *et al.* used $RuCl_2(CHPh)(PCy_3)_2$ for the syntheasis of biscalix(4)arene linked by alkenyl bridges /60/.

C) "Head-To-Tail" Linked Double Calixarenes

Bohmer *et al.* reported the first calixarene of the "Head-to-Tail" type in which both calixarenes had the same orientation /61/. In contrast to compounds of head-to-head-linked double calixarenes or tail-to-tail-linked double calixarenes, in which the dipole moments of the calix(4) arene units cancel one another out, the dipole moments in head-to tail-linked double calixarenes add up. This may be of significance for the potential application of similar compounds in areas such as nonlinear optics /62/. They reacted a diphenol derivative of p-tert butyl calix[6]arene with bis bromo methylated p-cresol in glacial acetic acid in the presence of zinc acetate [**Fig. 22**].

D) Miscellaneous

Rebek *et al.* found that intermolecular hydrogen bonding through dimerization can be used to drive the conformational equilibrium exclusively to the cone conformation /63/. They reported that an urea group placed on the upper rim of the calix(4) arene permits dimerization to occur through a head-to-tail hydrogen bonding pattern to give molecular capsules /64-67/.



X-35

Fig. 22: Head-to-tail linked double calixarene

A novel homo oxacalix[3]arene based dimeric capsule cross-linked by a Pd(II)-pyridine interaction has been reported by Shinkai *et al.* /68, 69/ This dimeric capsule has been shown to include C_{60} fullerene in the three-dimensional cavity.

Fukazawa *et al.* also reported a different type of bis calixarene in which the bis calixarene has a bipyridine subunit /70/. They found that, while complexation with a transition metal ion occurs, the bis calixarene changes its conformation followed by generation of a deep cavity. This cavity has been evaluated by the authors for its binding properties towards fullerenes.

3. APPLICATIONS OF DOUBLE CALIXARENES

Double calixarenes possess greater complexation abilities than normal calixarenes due to their extendable cavity. It has also been noted that synthesizing a double or a bis calixarene acutely freezes the conformational mobilization which leads the molecules towards a stable complexation with a high association constant. The literature survey has shown that the head-to-head-linked double calixarenes generally possess an inclusion ability for the cationic guest molecule due to cooperative action of the cation-π interaction, and the tail-to-tail-linked double calixarenes generally possess extractability or complexation ability towards various metal ions.

This means design of double calixarene based receptors that show high selectivity for guest molecules and metal cations. Double calixarenes lend themselves well to many applications, such as the following.

i) Cation Complexation.
ii) Anion Reorganization.
iii) Organic Neutral and Charged Molecular Reorganization.
iv) Redox Active Ionophore.
v) Ion Selective Electrodes.
vi) Ditopic receptors.
vii) Functional Material or as Reaction Medium
viii) Miscellaneous.

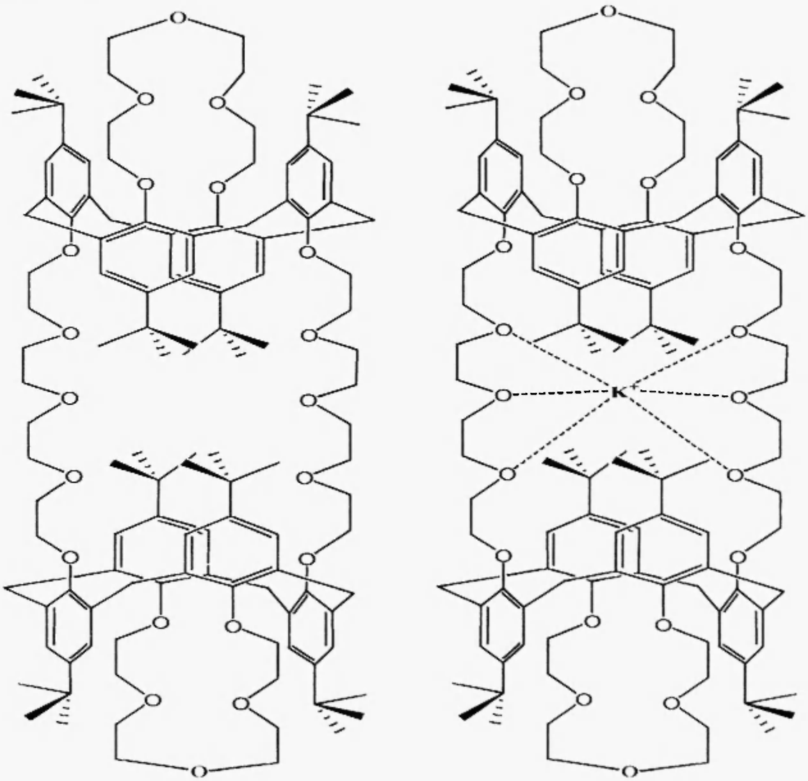
i) Cation Complexation

Double or multiple calixarenes have been prepared as an example of higher order molecular architectures with new high-level host properties /71, 72/, such as allostery and cooperativeness /73/. These compounds are highly selective receptors for alkali, alkaline earth, lanthanides, and transition metal ions. The selective recognition and extraction of alkali metals is currently an area of great interest. Alkali metal ions, such as Na^+ and K^+, are found in human organisms and are of importance in ion channels and ion pumps. The great importance of the cations mentioned is also evident from the fact that disorders in the metabolism of these ions can severely affect the state of health. Radioactive cesium ion is found in nuclear waste solutions.

Alkali and Alkaline Earth Metals

Solvent extraction of a metal cation by calix[n]arene was first investigated by Izatt *et al.*, where the calixarene showed selectivity towards Cs^+ /74/. Asfari *et al.* /33/ reported a double calix[4]biscrown-5 in which the two calix[4]crown-5 are crowned, constraining the calixarenic units into the 1,3-alternate conformation. Selectivity of complexation was observed for K^+

and Rb^+, the cation being located in the central cavity of the tritopic receptor **[Fig. 23]**.



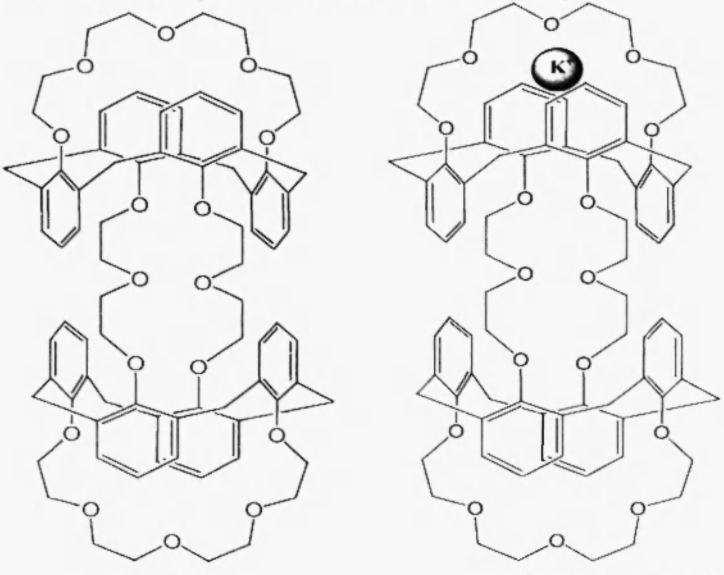
X-36 **K^+ complex of X-36**

Fig. 23

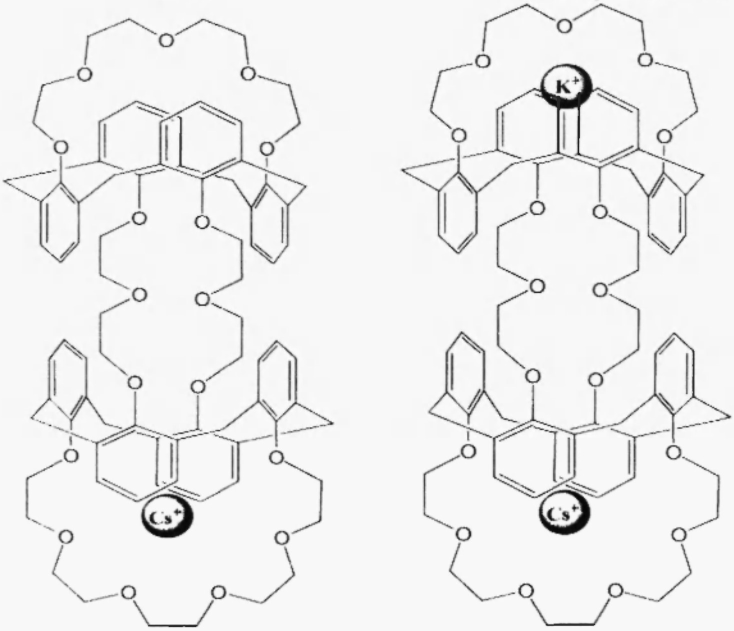
From the above figure it can be seen that double calix[4]crown ether forms 1:1 complexes with potassium picrate in the solid state and in solution in deuteriated chloroform.

Vicens *et al.* /75/ also studied the binding properties of polytopic receptors, double- and multi-1,3-alternate-calixcrowns, with alkali metal cations. ^{1}H NMR studies suggested that out of these double and multi-1,3-alternate-calixcrowns, (i) compounds containing a crown-5 loop showed better extraction properties for K^+ and Rb^+ because of their suitable cavity size (ii) compounds containing crown-6 loop were showing better extraction properties for Cs^+; and (iii) compounds having a hybrid structure, containing both crown-5 and crown-6 units, were good extractants for three cations K^+,

Rb^+ and Cs^+ in almost the same percentage range. This hybrid structure forms a heterobinuclear complex with K^+ and Cs^+ /76/ [**Fig. 24**].



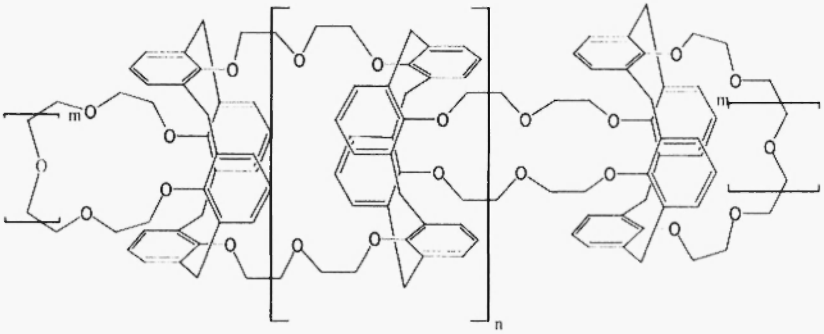
X-37 **K^+ Complex of X-37**



Cs^+ Complex, X-38 **K^+ and Cs^+ Complex, X-38**

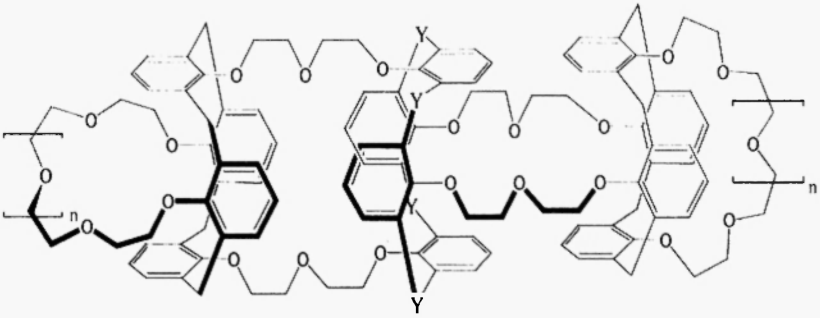
Fig. 24

In this case, the electrostatic interactions between the oxygen donor atoms of the crown ether ring and the metal cation play a major role in entrapping ther metal ion, while the cation-π interaction plays a minor role. In the case of tri-, tetra-, and pentameric calix[4]tubes, the metal-ion could not shuttle because the calix linkages (spacers) between the calix[4]crown-5 or between the calix[4]crown-6 stoppers did not contribute to cation complexation. This suggests that the end of calixcrown stoppers is the only site for binding of cations. In the case of 1,3-alternate calix-thia-calix[4]crown trimers, bearing crown-5 and crown-6, the Cs^+ and K^+ ions prefer to be encapsulated in the trimeric thiacalix[4]crown-6 and crown-5, respectively. On the contrary, the Ag^+ ion was entrapped in the central thiacalix spacer as a 1:1 complex, as confirmed by ^1H NMR spectroscopy. Variable-temperature ^1H NMR studies on trimeric thiacalix-calix[4]crown-6 encapsulation of the silver ion revealed that the Ag^+ ion oscillates through the central thiacalix spacer with the aid of cation-π interactions /77/ **[Fig 25]**.



X-39
tri-, tetra-, and pentameric calix[4]tube

where n = 1, 2 and 3
m = 1 and 2.



X- 40

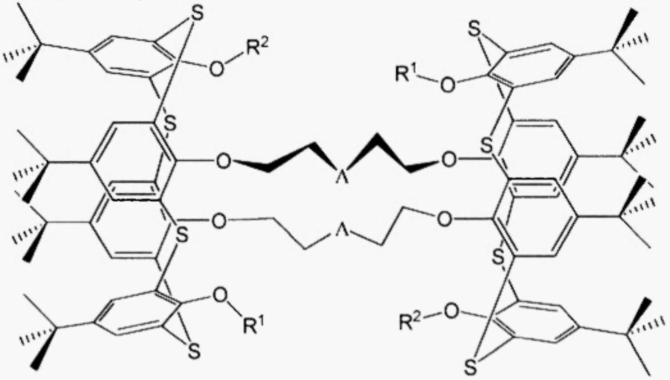
thia calix[4]crowntube

where n = l and 2

Y = CH_2 and S.

Fig. 25

In the case of partially alkylated double thiacalix[4]arenes [**Fig. 26**; **X-41** to **43**,], the extractabilities of compound (**X-43**) showed significant changes under strong basic conditions at pH 12. The K^+ and Rb^+ extraction capacity of the conic ligand (**X-43**) increased to 56 and 58%, respectively, indicating the formation of phenolate anions stabilizing the complexed cations by additional ion-pair interactions. In contrast, the counterpart (**X-42**) extracted none of the cations, since its phenolate salts precipitated from the biphasic system /78/ [**Fig. 26**].



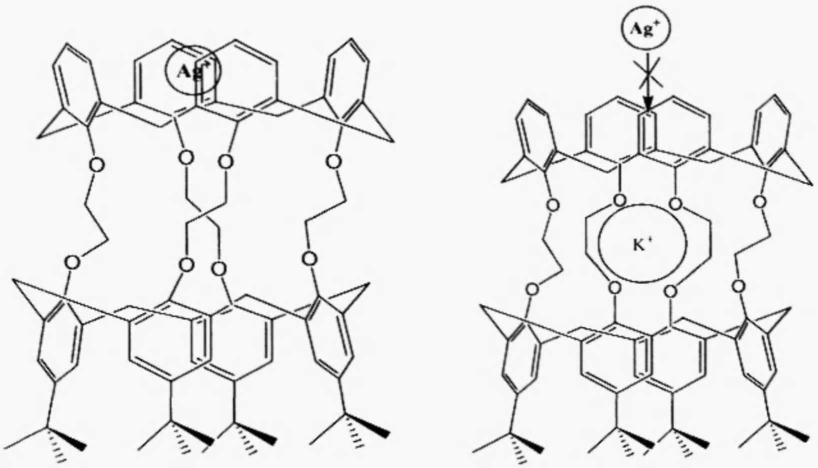
where **X-41**; (R^1= Me, R^2 = H, A= O)

X-42; (R^1 = Pr, R^2 = H, A = O)

X-43; (R^1 = Bn, R^2 = H, A = O)

Fig. 26: Alkylated double thiacalix[4]arenes

Stibor *et al.* /79/ reported a bis-calix[4]arene ditopic hard/soft receptor for K^+/Ag^+. This bis-calix[4]arene, bearing a tert-butylated and de-tert-butylated calix[4]arene unit, connected by four ethylenoxy bridges, adopts the pinched cone conformation (C_{2v} symmetry) and, hence, is suitably pre-organized for Ag^+ ion complexation. X-ray crystallography showed that the silver cation is sandwiched by the two distal co-planner phenyl rings of the de-tert-butylated part of the molecule, possessing a η^1-binding mode of aromatic units (cation-π interactions), and two electrostatic interactions with triflate oxygens **[Fig. 27; X-44]**; complexation of the K^+ cation into the central cavity created by the bridging moieties leads to a change in conformation (C_{4v} symmetry) and, hence, complete loss of complexation ability towards the Ag^+ cation **[Fig. 27; X-45]**

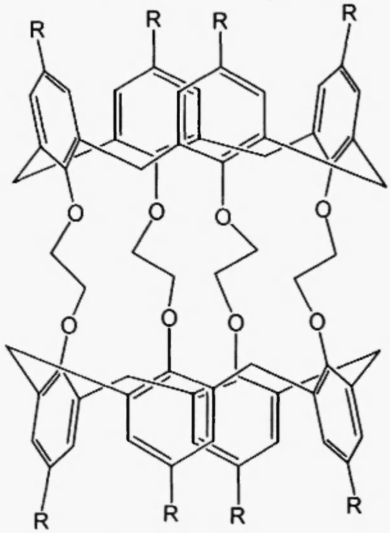


X-44: Complexation mode for Ag^+

X-45:The presence of K^+ prevents further complexation

Fig. 27: Complexation of an Ag^+ cation.

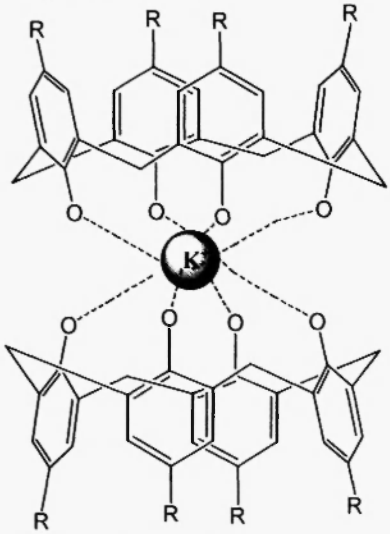
Calix[4]tube type double calixarenes include the use of oligo ethyl ether bridges. In the case of the oligo ethyl ether bridges, a cage-like central core is present, which is capable of binding metal ions, and has been implied in biomimetic cation transport through the cell membrane. Beer *et al.* /80/ have carried out molecular dynamic simulation on a calix[4]tube **[Fig. 28; X-46 to 48]** with different alkali ions. Double calixarene **(X-46)** displayed good selectivity towards the potassium cations over all alkali metals compared to other double calixarenes **[Fig. 29]**. Molecular modeling studies show that the calixarene tube is highly selective for K$^+$ because the ion enters into a tube from the upper rim of one calix[4]arene and forms an intermediate complex interacting with the aromatic rings and then proceeds to the center of the tube. It was reasoned that this is due to the presence of various groups, like tert-butyl, H or bulky tert octyl groups in the upper rim. For the structure (**X-47**), the bulky tert octyl groups interlock in the conformation and thus prevent any change in conformation. For the structure (**X-48**), the lack of an alkyl group at the top of the phenyl rings deprives the cage of any impetus for changing its conformation. Thus, it can be concluded that with the structure having tert butyl group, the tert butyl group plays an important role in the change in conformation. They conclude that smaller metal ions enter and leave the tube quickly, while for ions larger than potassium the ion remains in the intermediate position close to the aromatic rings and does not proceed to the center, unless the temperature is raised significantly /43/.



where **X-46**; R= R'= t-Bu
X-47; R= R'= t-octyl
X-48; R= R'= H

Double calix[4]arene connected via oligo ethyl ether bridge

Fig. 28



K$^+$ complex of **X-46**

Fig. 29

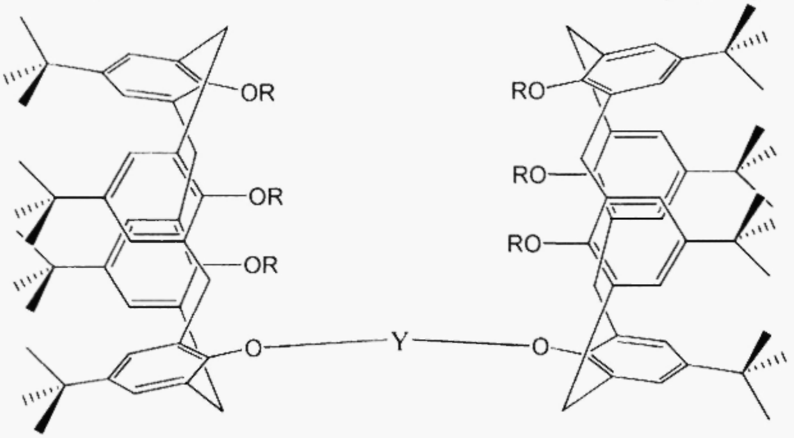
Yuanyin *et al.* suggested that examination of the CPK molecular models reveals that the spirobiscalix[4]crowns are highly preorganized for binding Li$^+$, Na$^+$, K$^+$ alkali metal cations /36/.

In the two-phase extraction, biscalix[4]aza crown ether /37/ can selectively encapsulate the Mg^{2+}ion at a certain pH, compared to other alkali earth metal cations, due to the additional coordinate phenoxide anion in an organic medium. They also conclude that the selectivity of this azacrown is attributed to the fact that the Mg^{+} ions encapsulate by cation-π interaction with size fit phenomena.

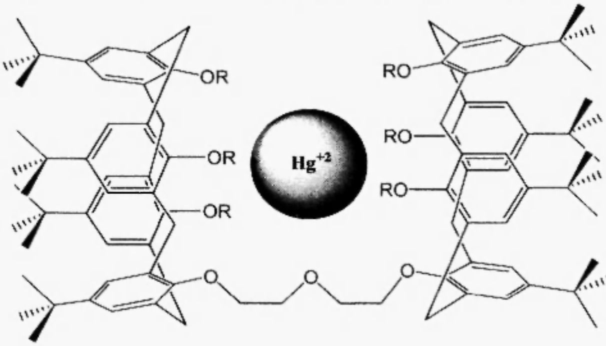
Nabeshima *et al.* published a novel host which shows homotropic and negative allostery for alkali metal ion recognition /81, 82/. It is constructed by utilizing a biscalix[4]arene skeleton bearing biphenyls and ester moieties. As the ionic radius of the guest increases, recognition of the second guest is suppressed more effectively. A larger ion changes the structure of the first binding site more drastically to cause a conformational change that is unfavorable to the guest binding of the second site.

Transition Metals

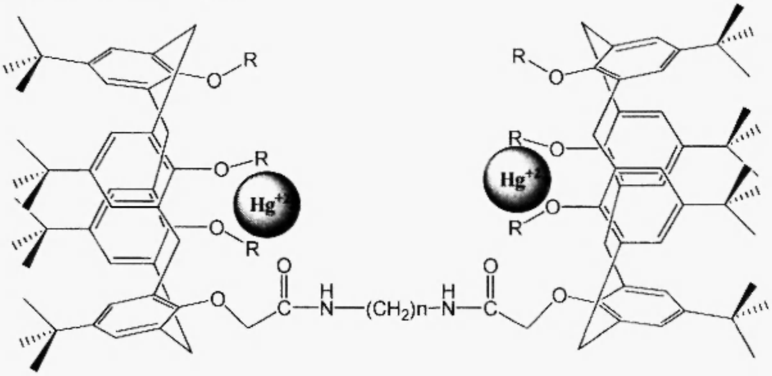
Yilmaz *et al.* /83,84/ studied complexation abilities of ionophoric biscalix[4]arene nitriles [**Fig. 30; X-49** to **52**] towards selected transition metal cations, such as Cu^{2+}, Co^{2+}, Cd^{2+}, Ni^{2+}, Hg^{2+} by liquid-liquid extraction. These nitrile derivatives of four different bridged biscalix[4]arenas (**X-49** to **52**) showed good selectivity towards Hg^{2+} cations, because according to the hard-soft acid-base principle, introduced by Pearson /85/, the -CN group is a soft base and shows a stronger affinity toward soft basic metal cations than toward hard metal cations. Here, in the cage of (**X-50**), the metal ion is probably held between two cone conformational calix moieties, while (**X-51**) and (**X-52**) have two metal ions held in each cone conformation [**Fig. 30**].



where **X-49**, Y = CH_2COCH_2, R = CH_2CN
X-50, Y = $CH_2CH_2OCH_2CH_2$, R = CH_2CN
X-51, Y = $CH_2CONH(CH_2)_2NHCOCH_2$; R = CH_2CN
X-52, Y = $CH_2CONH (CH_2)_8NHCOCH_2$; R = CH_2CN



X-50; where R = CH_2CN

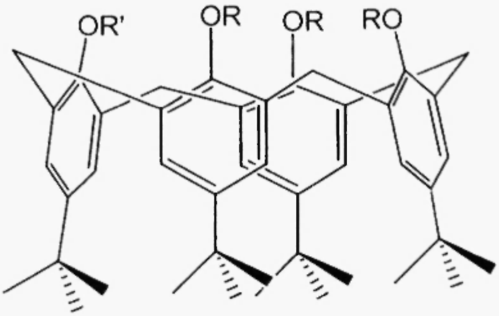


X-51; where n = 2 and R = CH_2CN
X-52; where n = 8 and R = CH_2CN

Fig. 30: Proposed structure of the complexes of Hg^{2+} formed with the different extractants

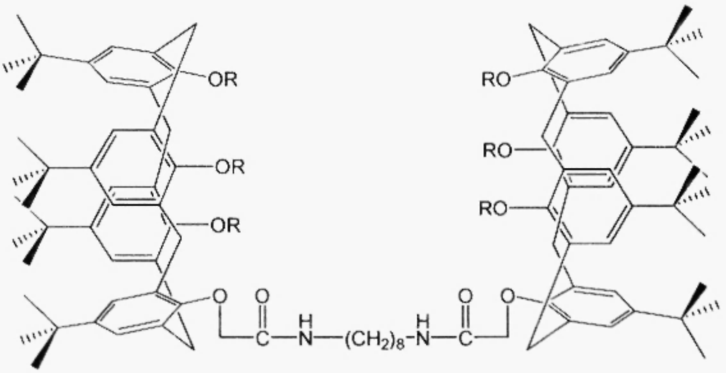
They also studied the complexation abilities of the two biscalix[4]arenes [**Fig. 31; X-53** & **X-54**] with ligating ester and ketone groups in the cone conformation towards transition (Ag^{2+}, $Hg^{2+}Cu^{2+}$, Ni^{2+} Co^{2+},Cd^{2+}) metal ions /86/. They found that the ester derivative (**X-53**) showed a higher affinity toward transition metals than alkali metal cations, while the ketone derivative

(**X-54**) extracts both alkali and transition metal cations effectively. This suggests that the ketonic groups are the efficient groups in this phase transfer. They also concluded that both biscalix[4]arenes (**X-53**) and (**X-54**) were better extractants than their monomeric analog (**X-55**) **[Fig. 31]**.



where R = H
R' = H

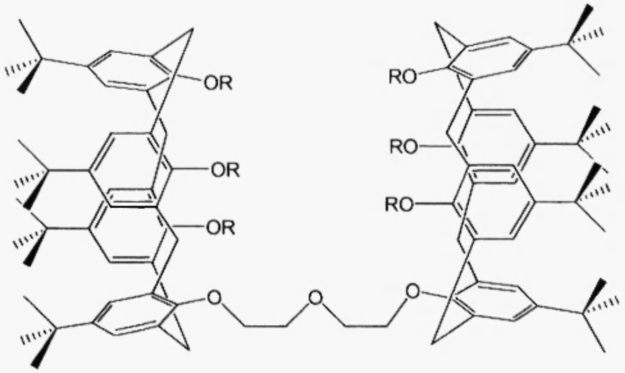
Monomer X-55



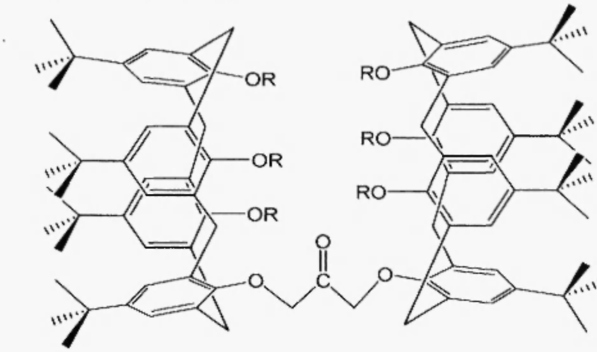
where **X-53**, R= $CH_2COOC_2H_5$
X-54, R= CH_2COCH_3

Fig. 31: Bis Calix[4]arene with ester and ketone groups as ligating sites

In 2001, Memon *et al.* studied the complexation properties of chemically modified biscalix[4]arenes /87/, **[Fig. 32, X-56** to **59]** towards transition metal cations /88/; like Ni^{2+}, Cu^{2+}, Co^{2+}, Cd^{2+} and Hg^{2+}.



where X-56; R = $CH_2COOC_2H_5$
X-57; R= CH_2COCH_3



where X-58; R = $CH_2COOC_2H_5$
X-59; R= CH_2COCH_3

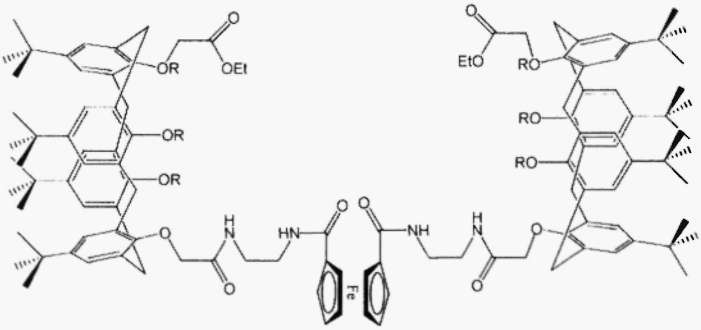
Fig. 32: The ester and ketone biscalixarene derivatives

According to this paper, the ester and ketone biscalixarene derivatives (**X-56**) and (**X-57**) with an ether bridges are better extractants for all metals compared to their monomeric analogues; but no significant difference in extraction ability were found between (**X-56**) and (**X-57**) and their dimeric homologues (**X-58**) and (**X-59**) that have ketone bridges [**Fig. 32**]. Comparing extraction results, it was observed that biscalixarene (**X-56**) and (**X-58**) extracted almost all the metal ions in the extraction studies, whereas the compounds (**X-57**) and (**X-59**) were particularly selective for Hg^{2+}. Thus, these ligands display high selectivity that depends on different factors, such as the conformation, polarizability, and the nature of the substituents on the lower rim of the biscalixarene. Almost all the extractants showed extraordinary affinity toward Hg^{2+}. These results are in agreement with the theory of "hard and soft acid - basis" introduced by Pearson in 1975 /85/.

Kumar *et al.* also published a series of novel bisthiacalix[4]arenes with diimine linkages of different aromatic or heteroaromatic dialdehydes. The structure of one of the bisthiacalixarene was analyzed by X-ray crystallography. These molecules quantitatively extract silver ion from the aqueous into the organic phase under neutral conditions /89/.

Lanthanides and Actinides:

Beer *et al.* /90/ reported that ferrocene-bridged biscalixarenes [**Fig. 33; X-60** to **62**] were observed by ES-MS to bind lanthanide ions in a 1:1 stoichiometry. Electrochemical methods show that all ligands undergo significant anodic potential shifts of their ferrocene redox center in the presence of lanthanide ions. It has been observed that monomeric ferrocene calixarene ligands undergo shifts of up to 60 mV and ferrocene-bridged biscalixarenes containing ester amide co-ordination functionalities undergo much greater potential shifts, typically 200 mV, on the addition of one equivalent of lanthanide ion.



where **X-60,** n = 1.
X-61, n = 2.
X-62, n = 3.

Fig. 33: Ferrocene-bridged biscalixarenes

Beer *et al.* /91/ synthesized new chelating biscarboxylate calix[4]arenes that possess binding and extraction capabilities towards uranyl. They were initially explored by ^{1}H-NMR. In a 8:2 deuteriated chloroform-methanol solvent mixture, the addition of $UO_2(OAc)_2$ $(H_2O)_2$ to biscalix [4]arene produced substantial downfield shifts of the carboxylate ortho-related benzylic and meta-related aromatic protons (+0.32 and +0.25 ppm, respectively), which is indicative of a conformational rearrangement consistent with the opening of the binding cavity **[Fig. 34]**.

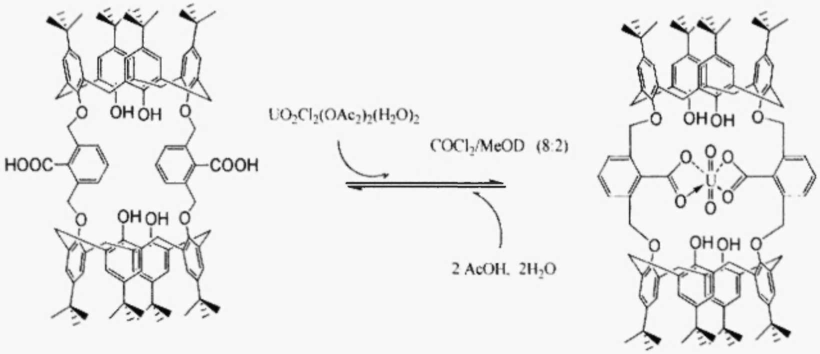


Fig. 34: Uranyl binding by bis calix[4]arene

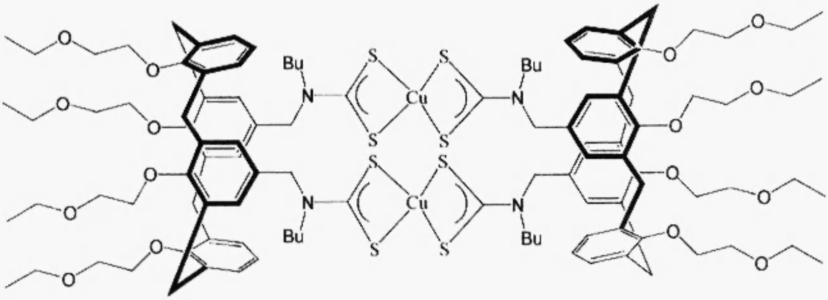
Group II A Metals

Thallium cation complexation by calix[4]tube **[Fig. 28; X-47]** has been investigated by a combination of ^{205}Tl, ^{1}H NMR and ES-MS demonstrating the solution of a di-thallium complex in which the cations are held in the calix[4]arene cavities /92/.

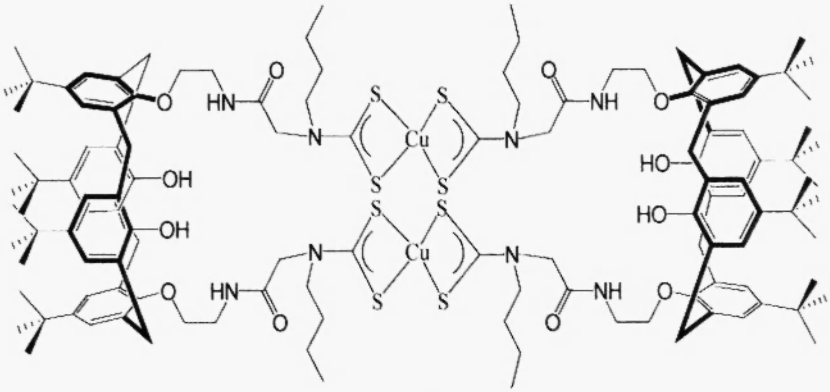
ii) Anion Recognition

Selective complexation of anions is more demanding than that of cations due to many reasons, such as size, charge density, polarizability, solvation energy and pH-dependent acid-base equilibrium /93/. The anion plays a fundamental role in a wide range of chemical and biological processes, and numerous efforts have been devoted to the development of a-biotic receptors for anion species, but they are still very limited. Urea derivatives have been utilized successfully as neutral host compounds for the various anion guests through hydrogen bonding /94/. Recently, for the development of cation calixtubes, a number of dimeric compounds of calix[4]arene biscrown structure were synthesized and their cation binding properties were investigated /95/. However, there are very few reports on anion recognition by biscalix[4]arenes.

The bimetallic copper^{II} bis(calixarene) complexes (**X-63**) and (**X-64**) can electrochemically sense carboxylate and dihydrogen phosphate anionic guests /96,97/ **[Fig. 35]**.



X-63



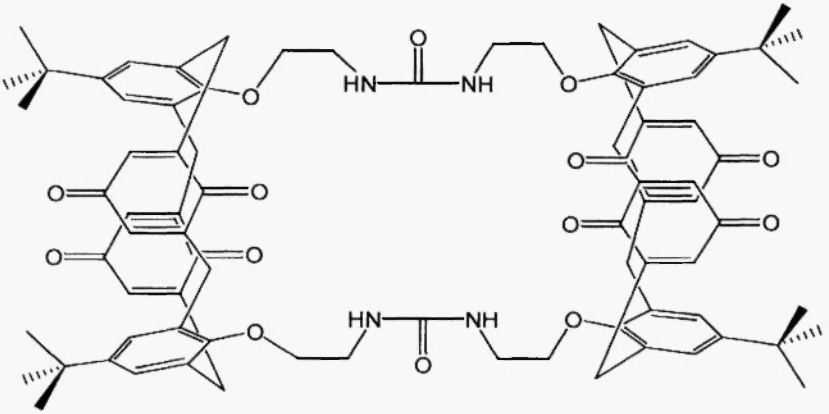
X-64

Fig. 35: Bimetallic copper^{II} bis(calixarene) complexes

Nam *et al.* /93/ have reported calixtubse based on a bis-calixarene scaffold for an anion **[Fig. 36]**.

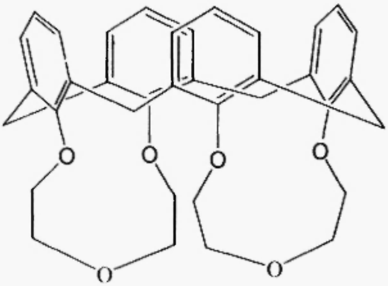
iii) Organic Neutral and Charged Molecular Reorganization

In several types of biscalixarene derivatives covalently bridged by various fundamental linkages have been reported /98, 99/. The covalent bridging of the two fixed cone conformation of calix[4]arene was realized as shown in **[Fig. 37; X-67 to 69]**. It also leads to a significant improvement in the binding properties. The association constant of 1:1 complexes with the two quaternary ammonium ions **(III-a)** and **(III-b)** are increased by one order of magnitude compared to the host **(X-66)**for instance from $33M^{-1}$ of **X-66/ III-b** to 1407 M^{-1} of **X-68/ III-b**, $CDCl_3$ /100/. This binding property can be changed by modifying the bridge length and rigidity **[Fig. 37]**.

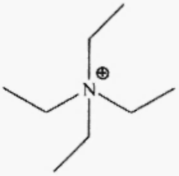


X-65

Fig. 36: Urea linked calix[4]tube



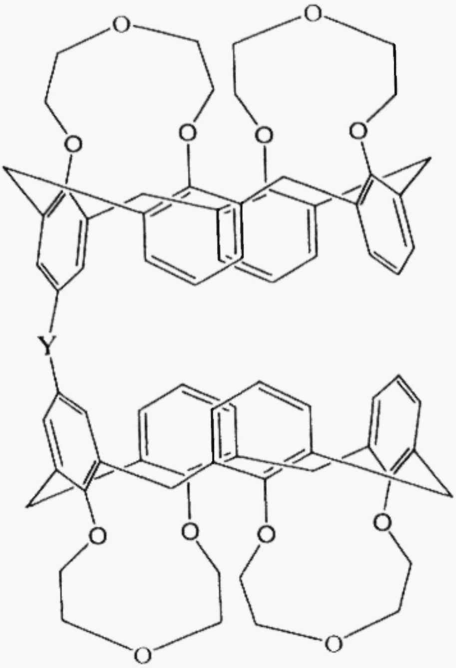
Monomer host X-66



III-a

III-b

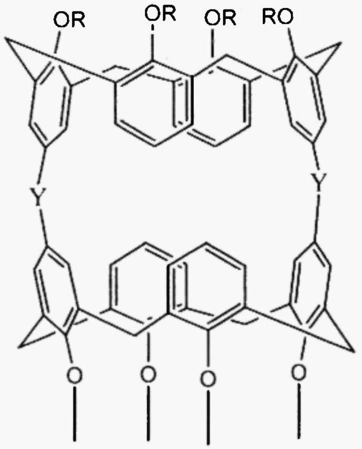
Quaternary ammonium ions



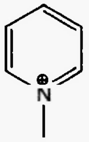
where **X-67**; Y= CH2
X-68; Y = -C=C-
X-69; Y = N=N

Fig. 37: Covalently bridged biscalixarene derivatives

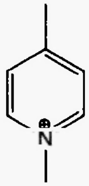
The two spacers on the upper rim make the capsule **[Fig. 38]**, formed by two calix[4]arenes. This molecular capsule formed complexes with the iminium ions (**IV-a**) and (**IV-b**) in $CDCl_3$ solution /101/. By replacing the propyl groups in this compound by hydrogen, the π-basicity of the aromatic cavity is increased /102/; consequently, the association constant with I is increased to 5×10^6 M^{-1}.



Molecular capsule formed by two spacers
where **X-70**, R = Pr
Y = OCH_2 **Fig. 38**



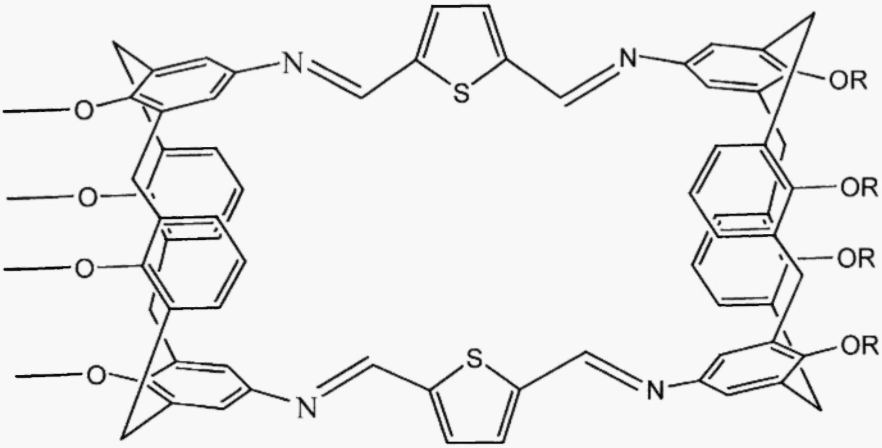
IV-a



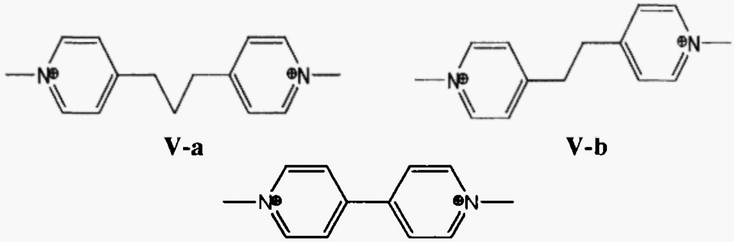
IV-b

Iminium ions

The above biscalix[4]arene with two different spacers, i.e. thiophenoimine linkages, yielded new biscalix[4]arenes /103/ which formed complexes with (**V-a**), (**V-b**), and (**V-c**) iminium ions in $CDCl_3/CD_3CN$ 2:1, exhibiting association constants between 700 and $100M^{-1}$ **[Fig. 39]**.



Bis calix[4]arene connected via thiophenoimine linkages spacers
where, R = Pr **X-71**



V-a **V-b**

V-c

Iminium Ions

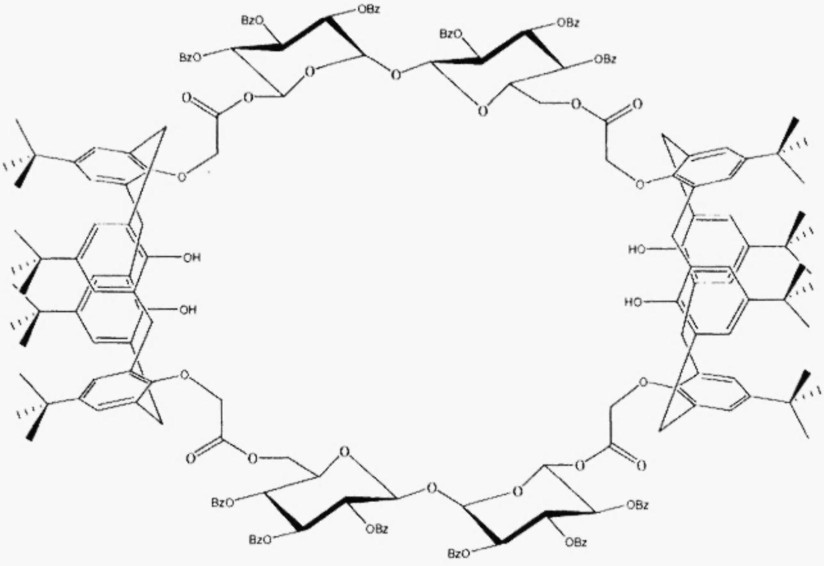
Fig. 39

Pappalardo *et al.* also published ^{1}H NMR complexation studies of tail-to-tail linked bis-calix[5]arenes. These calixarene subunits were connected by a rigid p-xylyl spacer. The complexation studies of this biscalixarene with alkyldiammonium ions (i.e. 1,10-decanediammonium ions)have been carried out. The studies showed that they form polycapsular assemblies (polycaps) via iterative inclusion processes /104/.

The implantation of biologically active molecules that can bind complementary neutral species is a much less investigated topic in supramolecular chemistry. In order to explore the amphiphatic properties of calixsugars as host for ions and neutral molecules, Dondoni *et al.* /105/ designed more rigid structures, in which a cavity is formed by bridging two 1, 3-distal lower rim sites of a calix[4]arene molecule with an oligosaccharide or by assembling biscalix[4]arene systems through lower rim-lower rim carbohydrate linkages. This double calixsugar showed selective reception properties toward imidazole **[Fig. 40]**.

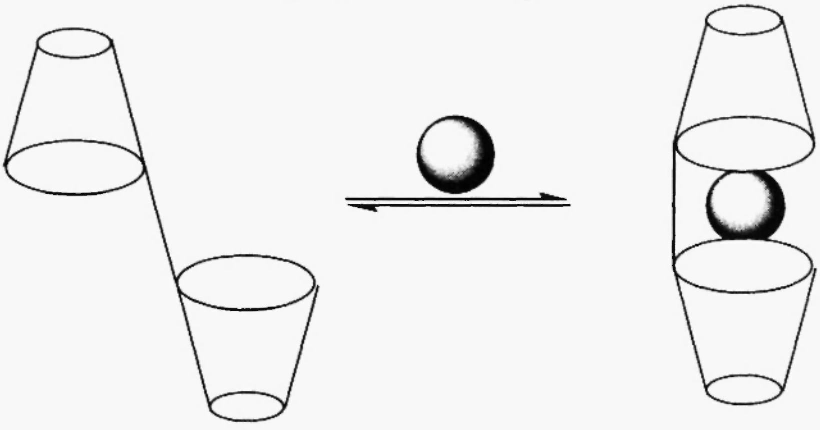
Gutsche *et al.* /20/ reported a good example of conformational complexation. They synthesized 5, 5'-biscalix[5]arene, which was initially in a anti conformation. But while encapsulating fullerenes, its conformation was arranged to syn to form a suitable cavity for fullerenes **[Fig. 41]**.

Fukazawa *et al.* /106/ demonstrated the first example of highly selective detection of fullerene using double-calixarene sensors produced by the combination of the supramolecular concept and the luminescence technique.



X-72

Fig. 40: Double calixsugar



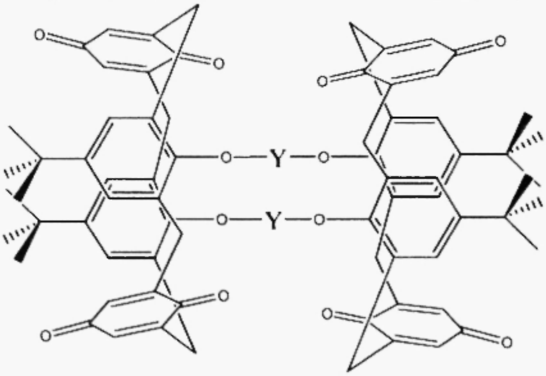
Anti-conformation of 5,5'-biscalix[5]arene

Syn-conformation of complex 5,5'- biscalix[5]arene and fullerenes

Fig. 41: Conformational conversion of anti-5,5'-biscalix[5]arene to syn-5,5'-biscalix[5]arene

iv) Redox Active Ionophores

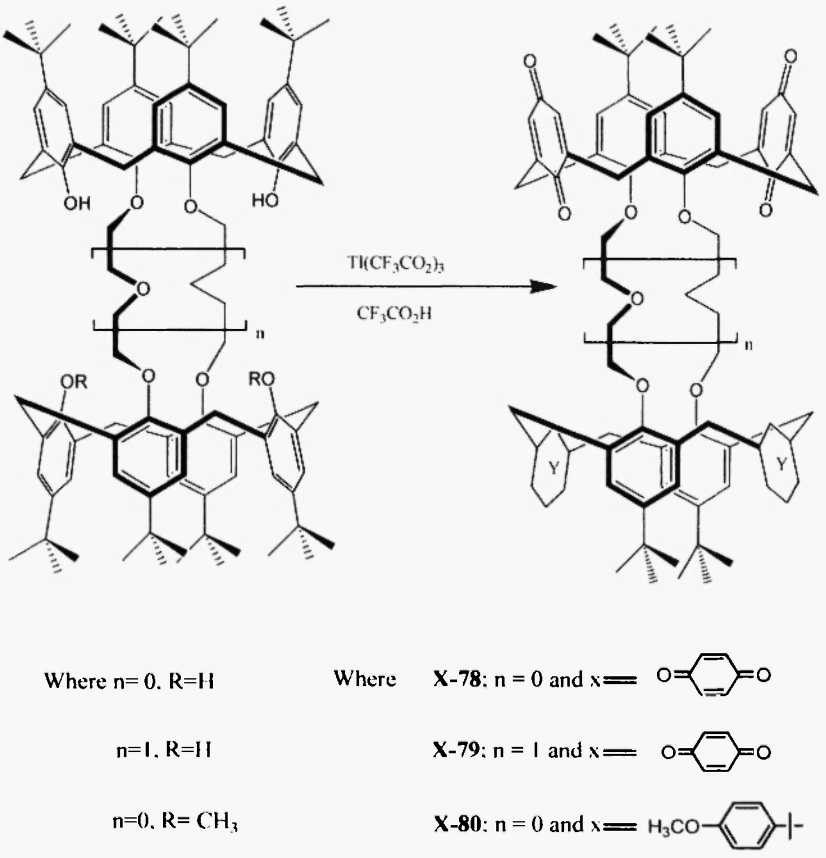
The development of molecular receptors designed to selectively recognize and sense charged or neutral guest species of biological and environmental importance is a highly topical research field for monitoring radioactive cesium in nuclear waste solutions and the potential use of rubidium isotopes in radiopharmaceutical reagents. Beer *et al.* /107/ synthesized a new class of redox-active ionophores comprised of two calix[4]diquinone moieties connected through either alkylene or pyridylene linkages. Spectroscopic and electrochemical investigations, X-ray crystal structure analyses, and molecular modeling studies show that butylenes and propylenes (**X-75**) and (**X-74**) linked members of this family of redox-active receptors exhibit remarkable selectivity for cesium and rubidium cations. In this case, the cation is bound by eight ion dipole interactions from the quinone and phenol oxygen atoms. Presumably sodium is too small to be bound efficiently in this large cavity /108/. The length and nature of the bridging spacer units between the two calix[4]diquinone moieties critically dictate the selectivity and strength of binding for first group metal cations /109/ **[Fig. 42]**.



where **X-73**; Y= C_2H_4 [Ethylene]
X-74; Y = C_3H_6 [Propylene]
X-75; Y = C_4H_8 [Butylene]
X-76; Y = C_5H_{10} [Pentylene]
X-77; Y = Py $(CH_2)_2$ [2,6-Di(Methylene)-pyridyl]

Fig. 42: Bis calix[4]diquinone receptors

Tuntulani *et al.* /110/ synthesized biscalix[4]quinones connected by ethylene bridges, which exhibit interesting electrochemical properties and show a promising ability to sense Na^+. They also synthesized bis(calix[4]diquinone) **[Fig. 43; X-78 & 79]** and double calix[4]diquinone **[Fig. 43; X-80]** and studied their complexation abilities with alkali metal ions, such as Li^+, Na^+, K^+, and Cs^+ by ^{1}H NMR titration. /111/ They found that the receptors (**X-78**) can selectively form 1:1 complexes with Na^+; the ligand (**X-79**) prefers to form 1:1 complexes with K^+ and Cs^+, while the receptors (**X-80**) retained the cone conformation of the calix[4]arene unit upon binding K^+ but it changed the conformation when complexing with Li^+ and Na^+ . Thus, the receptor (**X-80**) showed an electrochemically switched binding property toward Na^+ and K^+. In this case the polarizing ability of the $-OCH_3$ group can stabilize softer K^+.



Where n= 0. R=H

n=1. R=H

n=0. R= CH_3

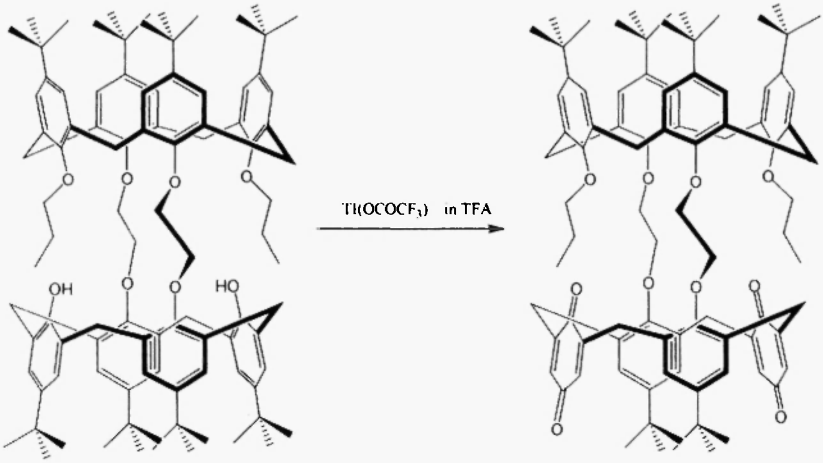
Where **X-78**: n = 0 and x=

X-79: n = 1 and x=

X-80: n = 0 and x=

Fig. 43: Double calix[4]diquinone

Beer *et al.* oxidized calix[4]semitube with Tl[OCOCF$_3$]$_3$ in TFA [trifluoro acetic acid] which resulted in the novel redox-active ionophore calix[4]semitube diquinone. This receptor displays a remarkable selective preference for potassium cations over all other first group metal cations. This receptor also exhibits substantial electrochemical recognition effects towards sodium and potassium cations /112/ **[Fig. 44]**.



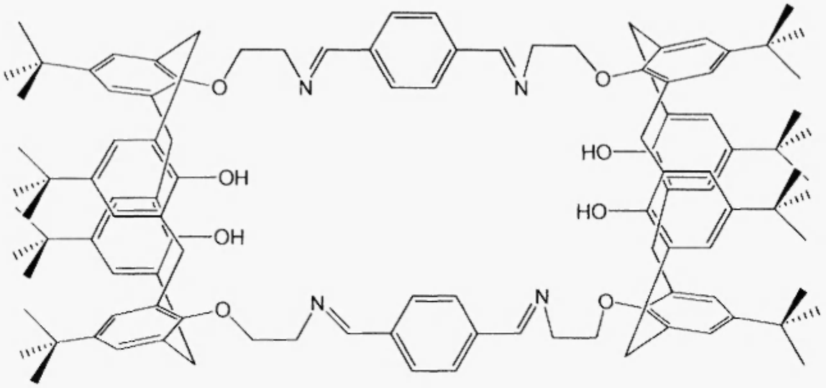
X-81 **Calix[4]semitube diquinone**

Fig. 44

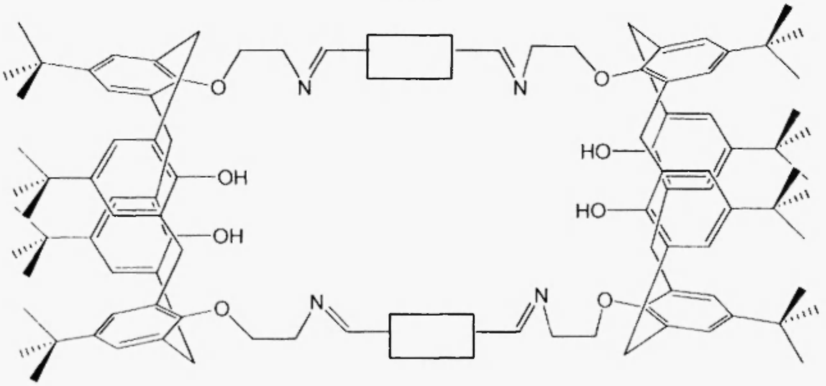
Marc *et al.* reported the first bis-calix[4]arene bridged by an electro active tetrathiafulvalene (TTF) unit /113/.

v) Ion-Selective Electrodes

Ion-selective electrodes, incorporating a macrocycle compound as an ionophore ligand, are well documented for many metal cations /114-118/. A potentiometric detector based on ion selective electrode has been studied particularly for fast, accurate, responsible and selective determination of various metal ions. This ion selective electrode can offer specificity, sensitivity, good response time, good precision, simplicity and reproducibility. This method allows direct online detection of a concentration of selected species without any pretreatment. Calixarene derivatives showed good binding abilities towards Cs$^+$, Cu^{2+}, Cd^{2+} and Pb^{2+} /119,120/. Kumar *et al.* /121, 122/ reported a few ion-selective electrodes based on biscalix[4]arene and having an imine linkage. They synthesized biscalix[4]arenes connected by various imine linkages, for example, **[Fig. 45; X-82 & 83]**. The selective response of electrodes towards Ag$^+$ can be explained by the electrostatic interaction between the metal ion and the four highly pre-organized soft binding sites surrounded by etheral oxygen atoms, and by a better fit of the cation.



X-82



X-83

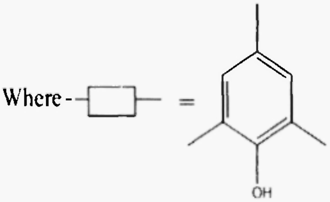
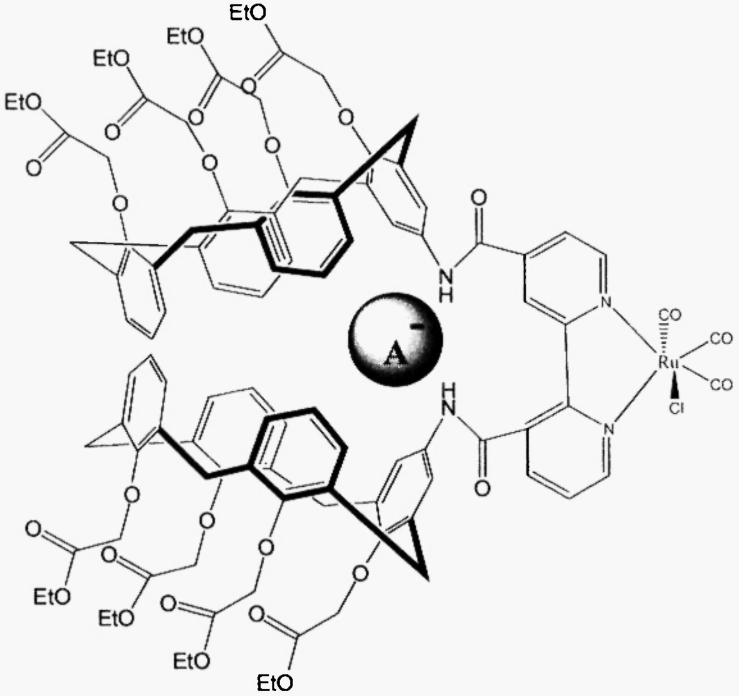


Fig. 45: Bis calix[4]arenes connected via imine linkages

vi) Ditopic Receptors

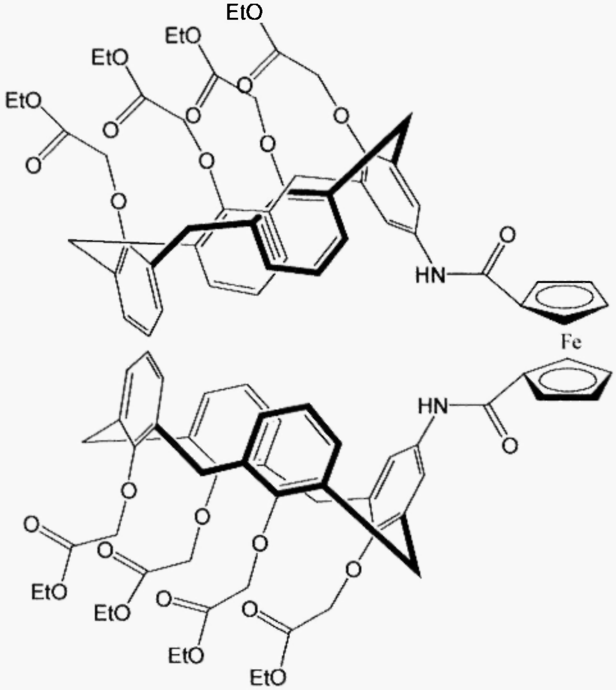
The design of new ditopic ligands for the simultaneous complexation of anionic and cationic guest species is a new exciting area of coordination chemistry, and is of significant relevance to the selective extraction and/or transportation of metal salts across lipophilic membranes. Beer *et al.* /123/ reported the synthesis of new heteroditopic bis(calix[4]arene)rhenium(I)bi-pyridyl receptors, which display positive cooperative upper rim binding of the iodide anion via lower rim complexation of alkali metal cations **[Fig. 46]**.



X-84

Fig. 46: Heteroditopic bis(calix[4]arene)rhenium(I)bi-pyridyl receptors

They also reported a heteroditopic bis[calix[4]arene] ferrocene receptor. It has been shown to bind a variety of anions like iodide and bromide on the upper rim and alkali metal cations on the lower rim. They found that the selectivity and strength of anion binding depends on the nature of the bridging group, with a ferrocene-containing receptor binding much more weakly than its rhenium (I) bipyridyl analogue **[Fig. 47]**.



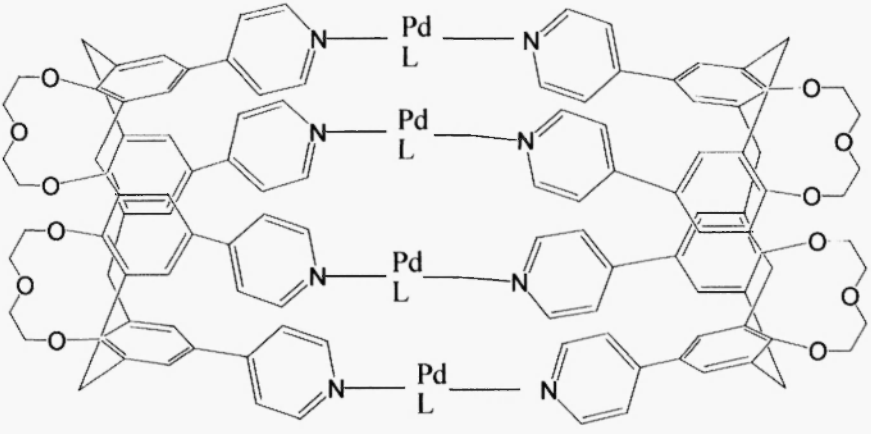
X-85

Fig. 47: Heteroditopic bis[calix[4]arene] ferrocene receptor

vii) As Functional Material or as Reaction Medium:

Hydrogen bonding is known as the important interaction for formation of DNA double helices and maintenance of higher-order protein structure. It is also essential in terms of molecular recognition and functional design of synthetic receptors and gel matrices. The molecular capsules, formed by hydrogen bonding built between carboxylic groups and pyridine groups, have been of great interest; tetra urea derivatives of calix[4]arne exist in nonpolar solvents as dimeric molecular capsules held together by a belt of 16 hydrogen bonds and their interiors are large enough to accommodate molecular guests./124,125/

Coordinate bonding, along with hydrogen bonding, is one of the important interactions for the formation of molecular assemblies. In recent years, coordinate bonding of Pd(I) or Pt(II) complexes has mostly been employed for construction of the desired capsule.



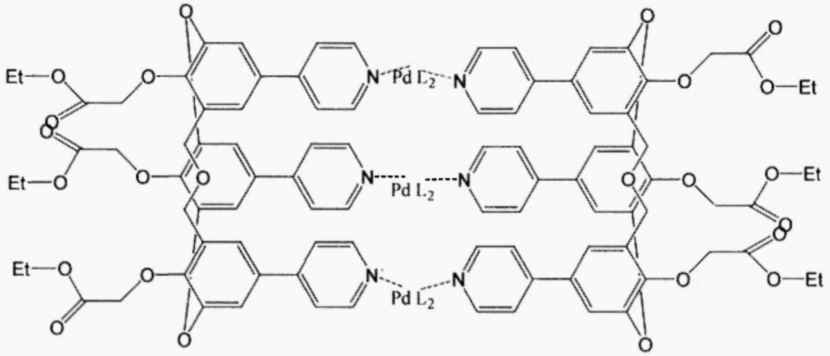
X-86

Fig. 48: Molecular capsule based on co-ordinate bonding

As shown in **Fig. 48**, the fixed cis configuration in Pd(II) and Pt(II) complexes is very useful in capsule formation, and the desired capsule can be readily obtained by adding the appropriate molecular equivalents /126, 127/.

Shinkai *et al.* /128/ reported that, when homooxa calix[3]arene and cis-Pd(II) complex are mixed at a molar ratio of 2:3, highly symmetric capsule molecules can be obtained capable of inclusion of fullerene C_{60}; the selectivity of fullerene C_{60} versus fullerene C_{70} is nearly perfect /129, 130/.

They also designed novel chiral molecular capsules based on a self assembled homooxacalix[3]arene dimer. The design of such chiral molecular capsules is more difficult, but they should show more important and more interesting recognition properties from the points of view of practical applications and combinatorial chemistry /131, 132/. This type of molecular capsule was constructed by dimerization of pyridine-containing homooxacalix[3]aryl esters, utilizing a Pd^{II} – pyridine interaction when Li^+ ions were bound to the ionophoric lower rims. These molecular capsules are twisted into triply bridged helical structures and chiral $R^*NH_3^+$ guests included in the cavity, and they induce a change in the right-handed versus left-handed ratio, resulting in high chiral induction [**Fig. 49**]. This means that this molecular capsule shows a novel chiral twisting motion and is readily controllable by the inclusion of chiral guest molecules /133/.



X-87

Molecular capsule based on homo oxacalix[3]arene

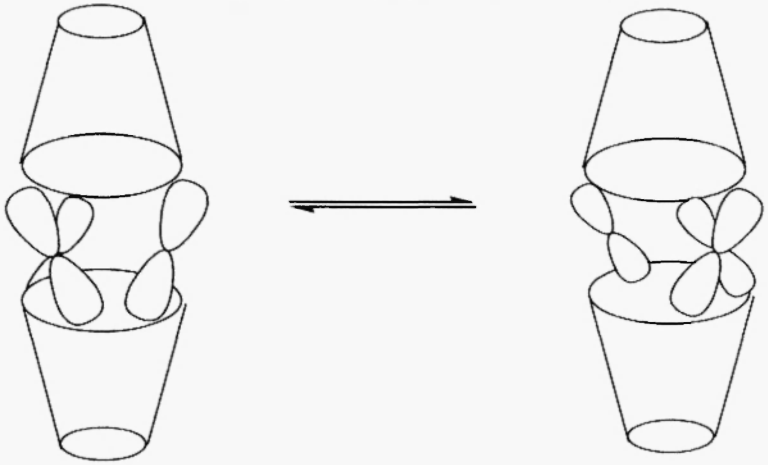
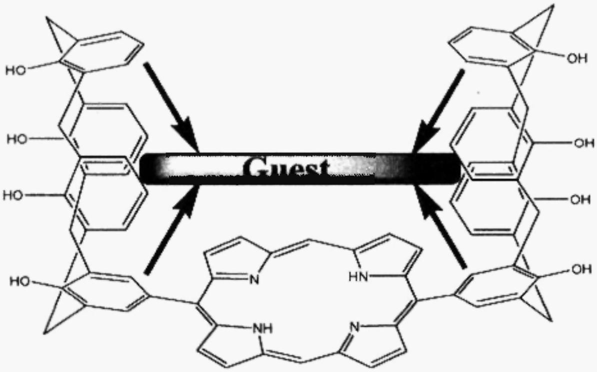


Fig. 49

viii) Miscellaneous

Lang *et al.* /134/ synthesized novel porphyrin-based biscalix[4]arenes. Porphyrin is known to be one of the "support pillars" of supramolecular chemistry, having suitable photoactive and electroactive properties for building of artificial molecular devices. Therefore, porphyrins with directly linked calixarenes could form attractive receptors possessing multipoint recognition ability towards no- covalently bound guest molecules.

The advantage of this porphyrin based biscalix[4]arene receptor is strengthening of the porphyrin-guest interaction by the cation-π and π- π attractive contributions from both calix[4]arene subunits **[Fig. 50]**.



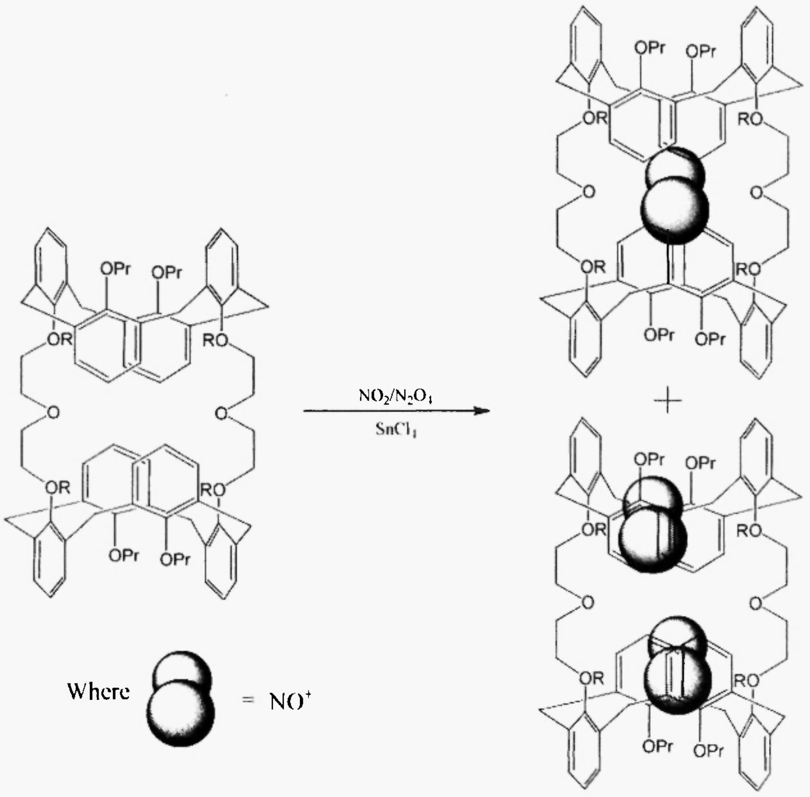
X-88

Fig. 50: Porphyrin-based biscalix[4]arene

For entrapment and conversion of NO_2/N_2O_4 gases, Rudkevich *et al.* synthesized a 1,3-alternate biscalix[4]arene tube. Exposure of this biscalix[4]arene tube to NO_2/N_2O_4 in chlorinated solvents results in rapid encapsulation of nitrosonium (NO^+) cations in its interior /135/ **[Fig. 51]**.

4. FUTURE PROSPECTS AND CONCLUSION

Double or multiple calixarenes have the potential to encapsulate larger neutral or charged species. There are a number of recent reports on these double calixarenes and fullerene encapsulation /20,106/. Compared to the conventional calixarenes, the double or multiple calixarenes have a larger cavity with promising ligating sites and are a targeted area of recent developments. More interesting properties of these types of molecules are numerous possibilities of structural modification, which enables us to explore new directions in the field of applied chemistry, like amide-based liquid-crystal double calixarenes [136]. Hydrogen-bonded multiple or double calixarenes, called molecular capsules, also form a potential application site in current co-ordination chemistry.



X-89

Fig. 51: Mononitrosonium complex and dinitrosonium complex of biscalix[4]arene tube.

To conclude, it can be said that there are a number of reports on synthetic strategies and analytical application of simple calixarenes, but the area of double and multiple calixarenes are still an unknown direction in calixarene chemistry. Double or multiple calixarenes also have an enormous amount of possibilities for design and synthesis of molecular platforms on which the new generation of molecular receptors depends.

5. REFERENCES

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