Review Artrcle

Bridged Calix[6]arenes

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Abstract

Bridging including capping of calix[6]arene is not only an important route to synthesize new host molecules, but also an efficient route to reduce the mobility of conformation of calix[6]arene. This article reviews the syntheses, conformations and complexation behavior of this kind of host molecules.

Introduction

Calixarenes are a class of host molecules with a three-dimensional cavity capable of accepting guest molecules. During the last decade, several excellent monographs, reviews and books have been published [1]. At present, the study of calix[4]arenes has approached maturity, much attention has been paid to the next member of calixarene family, calix[6]arene. In comparison with calix[4]arene composed of four phenolic units, calix[6]arene is constructed by six phenolic units, which results not only in more kinds of derivatives, but also in more conformation mobility than that of calix[4]arene.

Calixarenes possess a lot of conformers resulting from the limited free rotation about the σ bonds of the *Ar—CH$_2$—Ar* groups. In order to recognize guest molecules precisely, a rigid, conformationally-defined calixarene is essential. For calix[4]arenes, which possess four possible basic conformations, this task is easily realized by introducing substituents bulkier than ethyl onto the lower-rim of calix[4]arene. The four conformations of calix[4]arene are termed "cone", "partial cone", "1,2-alternate" and "1,3-alternate", respectively. However, this is not the case for calix[6]arene. The conformational interconversion in calix[6]arenes can occur not only via the oxygen through the annulus but also by the para-substituent through the annulus pathway, even in the case of *p-tert*-butyl derivatives. Thus, it is difficult to immobilize the conformation of calix[6]arene by introducing bulky substituents onto the lower-rim simply, even if the substituent is as bulky as cholesteryl group [2].

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. Theoretical calculations indicate that the parent calix[6]arene has up to 90 energy minima and its conformation stability is higher than that of *p-tert*-butylcalix[6]arene [3]. In 1993, Gutsche introduced a simplified conformational notation with general utility in the calixarene field to describe the conformations of calix[n]arenes [4a]. Take *p-tert*-butylcalix[6]arene for an example, the orientation of an aryl group of a calixarene ring is designated as "up" and "down" relative to the average plane of the molecule, as determined by its methylene groups, using the descriptors "**u**" (up) and "**d**" (down). Similarly, "**o**" (out), "**i**" (in), "**uo**" (up and out), "**ui**" (up and in), "**do**" (down and out) and "**di**" (down and in) are thus introduced to describe the calixarene conformations when the orientation of an aryl group is inclined close to 90° or within 45° from the perpendicular, respectively. Then the orientation of the aryl group occupying the *left-hand* position is listed firstly, the rest are listed in *clockwise sequence*. So a (**u, u, u, u, u, u**) and a (**u, u, u, d, d, d**) are adopted to describe the two *p-tert*-butylcalix[6]arene conformations: cone and 1,2,3-alternate conformation as shown in Figure 1, respectively.

To freeze the conformation of calix[6]arene another route is 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 linkages. Singly (mono), doubly and triply is related to the number of spacers. For example, doubly capped implies the occurrence of two spacers and each linking three. It should be noted that the term was used in the literature with various meaning. The bridging or capping of calix[6]arene not only represents a potential method to freeze its conformation, but also constructs an interesting kind of host molecules with special conformation. Sometimes the latter is more

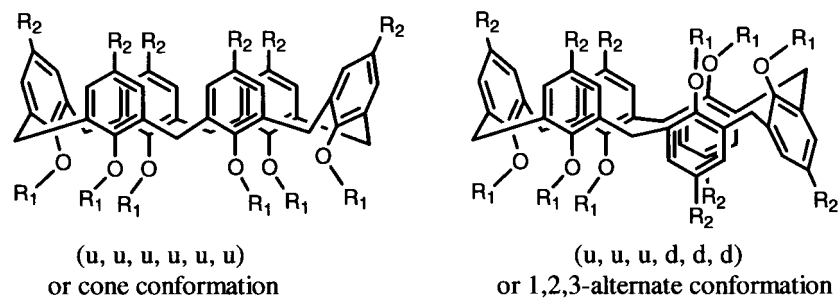* Author for correspondence: E-mail: yychen@whu.edu.cn

(u, u, u, u, u, u)
or cone conformation

(u, u, u, d, d, d)
or 1,2,3-alternate conformation

Figure 1. Nomenclature of conformers of calix[6]arene.

important. This article surveys the *status quo* and prospect of bridged calix[6]arenes, especially, our work in this field. We are sorry that some research achievements have not been included due to the length of the article.

Singly bridged calix[6]arenes

The first bridged calix[6]arene was reported as early as 1992 by Gutsche and co-workers [4b]. Treating A,D-*bis*(*p*-tolyloxy)calix[6]arene with succinyl chloride in the presence of triethylamine as a base, 5,11,17,23,29,35-hexa-*tert*-butyl-37,40-dihydroxy-39,42-succinyldioxy-38,41-*bis*-*p*-tolyloxycalix[6]arene was obtained in 55% yield after purification by column chromatography. A,B-bridged calix[6]arene was first synthesized by bridging *p-tert*-butylcalix[6]arene with ethyldichlorophosphate in low yield [5]. The first A,C-bridged calix[6]arene, 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetramethoxy-40,42-*m*-xylenyloxy calix[6]arene was synthesized by reacting corresponding calix[6]arene with α, α'-dibromo-*m*-xylene using Cs_2CO_3 as a base in 93% yield [6]. Among the singly bridged calix[6]arenes, much work was devoted to the A,D-bridged ones as they are easily prepared and can construct a special kind of reagent, concave reagents.

A,B-Bridged calix[6]arenes

Most of A,B-bridged calix[6]arenes were synthesized by selectively bridging calix[6]arene with bisfunctional reagents possessing short and rigid spacers such as phthaloyl, *o*-xylylene, methylene, ethylene etc. [7–9]. However, in the reaction of *p-tert*-butylcalix[6]arene with tetraethylene glycol ditosylate, A,B-bridged *p-tert*-butylcalix[6]crown-5 was formed as a by-product in the yield of 3% [10]. It is surprising that among the oligoethylene diglycol ditosylates used, A,D-bridged *p-tert*-butylcalix[6]crown-4 was formed as the main product as expected, A,D-bridged *p-tert*-butylcalix[6]crown-3 was also formed, although the yield is lower than that of the former, as tetraethylene glycol ditosylate has the longest chain among the ditosylates used, one may expect that the A,D-bridged *p-tert*-butylcalix[6]crown-5 be the main or sole product. But in fact, the major product isolated was A,C-bridged *p-tert*-butylcalix[6]crown-5 (19%), accompanied by an unexpected

minor product, i.e., A,B-bridged *p-tert*-butylcalix[6]crown-5 (3%), the first example of A,B-bridged calix[6]arene with long flexible spacer. Such a phenomenon seems difficult to explain.

When using oligoethylene glycol bischloroacetates instead of polyethylene glycol ditosylates, A,B-bridged *p-tert*-butylcalix[6]dioxocrowns **1** were the sole products being isolated [9]. The longer the spacer in bischloroacetates, the higher the yield. When the "n" is 0, 1, 2 and 3 in bischloroacetates, $ClCH_2COOCH_2(CH_2OCH_2)_nCH_2OCOCH_2Cl$, the A,B-bridged products were isolated in yields of 0%, 15%, 22% and 30%, respectively. It was postulated that in this reaction the real active species is the coordinated intermediate composed of oligoethylene glycol bischloroacetates and the potassium ion. The bischloroacetate plays a role of pseudo crown ether with the ether bonds and the oxygen atoms of the carbonyl group incorporated into the coordinated shell as shown in Scheme 1. In other words, a new kind of template effect that had never reported in the literature was occurring. Thus, the behavior of bischloroacetates in the presence of base is like a spacer-rigid reagent, such as α, α'-dibromo-*o*-xylene and the A,B-bridged calix[6]arenes were the only isolated products.

This hypothesis well explains that the yields of A,B-bridged *p-tert*-butylcalix[6]dioxocrown increase with the increase of the length of spacer. No A,B-bridged product formed by using ethylene glycol bischloroacetate as bridging reagent, and also, only in the case of using tetraethylene glycol ditosylate, A,B-bridged product was isolated as a by-product, because the formation of such an active intermediate needs enough number of oxygen atoms, and the oxygen atoms of the tetraethylene glycol ditosylate and diethylene glycol bischloroacetate just fit in with this condition. Furthermore, more oxygen atoms favor the formation of the intermediate, the coordination ability of oxygen atom in carbonyl group being stronger than that of ether oxygen atom. This methodology is also applicable successfully for the synthesis of 1,2-*p-tert*-butyl-calix[8]dioxocrowns [11].

A,C-Bridged calix[6]arenes

There were two known *m*-xylenyl A,C-bridged calix[6]arenes, 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetramethoxy-40,42-*m*-xylenyloxycalix[6]arene and 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetra-methoxy-40,42-*m*-(4'-methoxy-xylenyloxy)calix[6]arene [8b]. The latter work has attracted much attention as
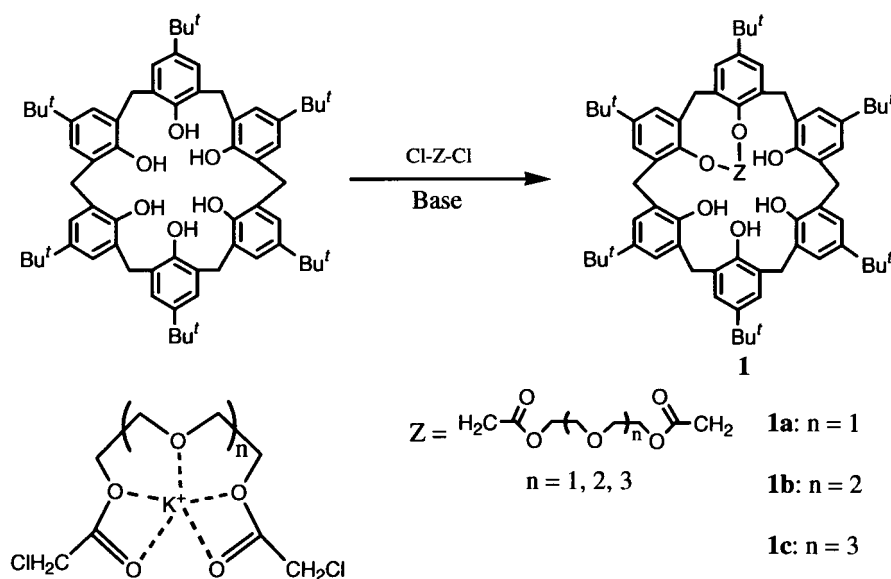
Scheme 1. *p-tert*-Butylcalix[6]-1,2-dioxocrowns.

providing a non-spectral methodology to obtain unambiguous evidence for the immobilization of the calix[6]arene ring. It was reported that the chiral 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetramethoxy-40,42-*m*-(4′-methoxyxylenyloxy)calix[6]arene doesn't racemize up to 100 °C. As the ring conversion is obligatorily accompanied by racemization, this finding means that no ring conversion occurs.

It should be noted that the above mentioned A,C-bridged calix[6]arenes were synthesized constrainedly by reacting α,α'-dibromo-*m*-xylene with tetrasubstituted calix[6]arene. If α,α'-dibromo-*m*-xylene reacted with unsubstituted calix[6]arene, i.e., *p-tert*-butylcalix[6]arene itself, only the A,D-bridged product was obtained. However, using pyridine-2,6-dicarboxylic acid dichloride instead of α,α'-dibromo-*m*-xylene, the A,C-bridged calix[6]arene could be obtained in 24% yield [12]. The first 1,3-bridged calix[6]arene possessing a long and flexible chain was prepared by reacting *p-tert*-butylcalix[6]arene with diethylene glycol ditosylate in 1999 [13]. 1,3-*p-tert*-Butylcalix[6]crown-4 and 1,3-*p-tert*-butylcalix[6]crown-5 have been also synthesized [10]. Some examples of A,C-bridged calix[6]arenes **2a–2f** are shown in Scheme 2.

Recently, we have found another route to synthesize A,C-bridged calix[6]arene selectively. Reacting N,N'-bis(chloroacetyl)ethylenediamine with *p-tert*-butylcalix[6]arene, **2d** (n = 2) was obtained in 35% yield [14a]. Using other N,N'-bis(chloroacetyl)alkylenediamine instead of N,N'-bis(chloroacetyl)ethylenediamine has got success also. The longer the alkylene spacer in the diamide, the lower the yield. When the alkylene spacer extends to hexanediyl, the yield of **2e** was down to 17% [14b]. It is interesting to see that compounds **2d** exist in cone conformation, while **2e** adopts 1,2,3-alternate conformation as shown in Figure 2.
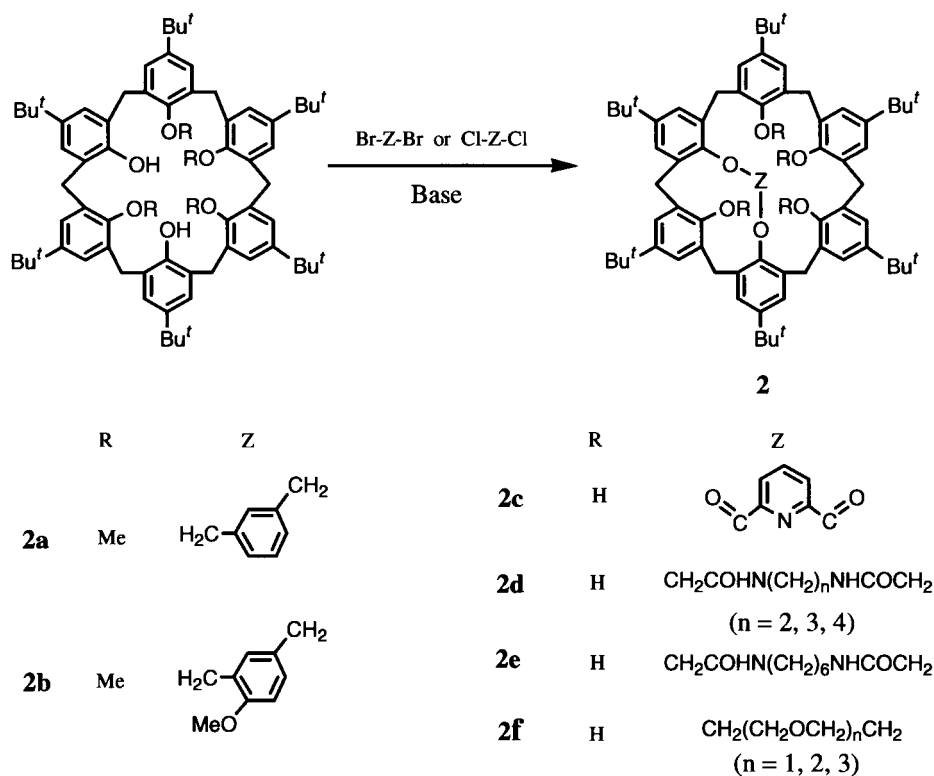
It is known that the ring inversion is often suppressed in the cone conformation of A,C-bridged calix[6]arene due to

destabilization of the transition state, compound **2e** provides an example of an A,C-bridged calix[6]arene adopting the 1,2,3-alternate conformation. This can be attributed to the aforementioned rule being broken when the length of spacer is long enough.
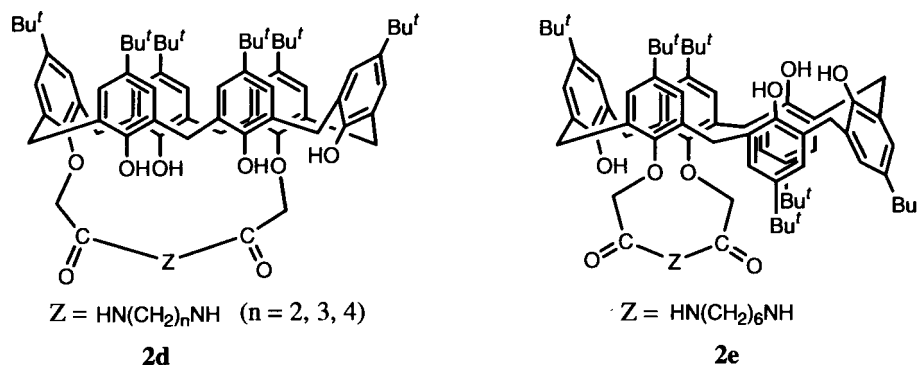
A,D-Bridged calix[6]arenes

In 1992, Gutsche and co-workers synthesized a series of lower-rim A,D-bridged *p-tert*-butylcalix[6]arenes from 1,4-*bis*(*p*-methylbenzyl)ether of *p-tert*-butylcalix[6]arene using diacid chlorides ranging from succinyl to suberoyl including terephthaloyl as a bridging reagent and Et$_3$N as a base [4b]. They also obtained A,D-bridged calix[6]arenes from *p-tert*-butylcalix[6]arene or *p*-H-calix[6]arene with a series of *bis*-halomethyl-aryl compounds in the presence of KOSiMe$_3$ directly. The products can be further converted to tetraetherified products. When Ar is anthrylene the conformation (u,u,u,u,u,u or cone) of the starting reactant remains unchanged, but when Ar is phenylene the conformation changes from original cone to 1,2,3-alternate one (u,u,d,d,d,u), in which the bridging moiety to be threaded through the annulus of the macrocyclic ring system, and can be viewed as a self-anchored rotaxane; when Ar is duryl, a mixture of conformers is obtained. It is obvious that in the latter two cases, the conformation of starting materials did not immobilize (see Figure 3).

Otsuka and co-workers prepared lower-rim A,D-bridged *p-tert*-butylcalix[6]arenes *via* condensation of *p-tert*-butylcalix[6]arene with α,α'-dibromo-*m*-xylene in the presence of NaH in DMF [6] or 1,3-*bis*(bromomethyl)-4-methoxybenzene in the presence of Cs$_2$CO$_3$ in acetone [8]. Since then, a lot of A,D-bridged *p-tert*-butylcalix[6]arenes were prepared by treatment with rigid bifunctional reagents, including a series of *bis*-halomethylaryl compounds [4a], 1,3-*bis*(bromomethyl)-2-bromobenzene [15a], 2,6-*bis*(bromomethyl)-4-alkyloxypyridine etc. [12, 16] (Scheme 3). Most of the bridged ones adopt defined con-

Br-Z-Br or Cl-Z-Cl

Base

2

	R	Z		R	Z
2a	Me		**2c**	H	
2b	Me		**2d**	H	CH$_2$COHN(CH$_2$)$_n$NHCOCH$_2$ (n = 2, 3, 4)
			2e	H	CH$_2$COHN(CH$_2$)$_6$NHCOCH$_2$
			2f	H	CH$_2$(CH$_2$OCH$_2$)$_n$CH$_2$ (n = 1, 2, 3)

Scheme 2. Some examples of A,C-bridged calix[6]arenes.

Z = HN(CH$_2$)$_n$NH (n = 2, 3, 4)

2d

Z = HN(CH$_2$)$_6$NH

2e

Figure 2. Conformations of diamide-bridged *p-tert*-butylcalix[6]arenes.

formations, in general, cone conformation. After further methylation of the residual phenolic hydroxyl, the cone conformation may convert to corresponding 1,2,3-alternate isomers in general [3, 15].

Calix[6]-1,4-crowns

Calixcrowns are a family of macropolycyclic molecules in which the subunits of calixarene and crown ethers are combined through the bridging of phenolic oxygen of calixarene by polyoxyethylene chains. As calixcrowns possess well preorganized structures and more rigid binding sites in comparison with calixarene and crown ethers, they would exhibit superior recognition ability toward alkali metal ions. The first member of this family, *p-tert*-butyl-calix[4]crown-5, was reported by Alfieri *et al.* as early as 1983 [17a] and the first example of calix[6]crowns was reported in 1995 by Ungaro and co-workers [17b]. They synthesized calix[6]crowns by refluxing *p-tert*-butylcalix[6]arene

or calix[6]arene with flexible tetraethylene glycol ditosylate in the presence of *t*-BuOK in benzene. After etherifying with *N*, *N*-diethylchloroacetamide, the *p-tert*-butylcalix[6]crown-5 in 1,2,3-alternate conformation converted to full etherified product but in cone conformation (Figure 4). These results are just contrary to that of using rigid bridging spacers reported by Saiki [15]. The full etherified product **4b** exhibits high complexation ability towards tetraethylamonium cation.

It is well known that some of the calix[4]crowns exhibit outstanding recognition abilities towards cations. How about calix[6]crowns? No other calix[6]crowns have been known up to 1999. Thus, we decided to synthesize other calix[6]-1,4-crowns, as well as calix[6]-1,2- and 1,3-crowns. In the presence of large excess Na$_2$CO$_3$ (50 equivalent per mole *p-tert*-butylcalix[6]arene) in acetonitrile, the lower-rim-1,3-crowned calix[6]-crown-3 was obtained in 41% yield [13]. Using K$_2$CO$_3$ instead of Na$_2$CO$_3$, a series of calix[6]crowns
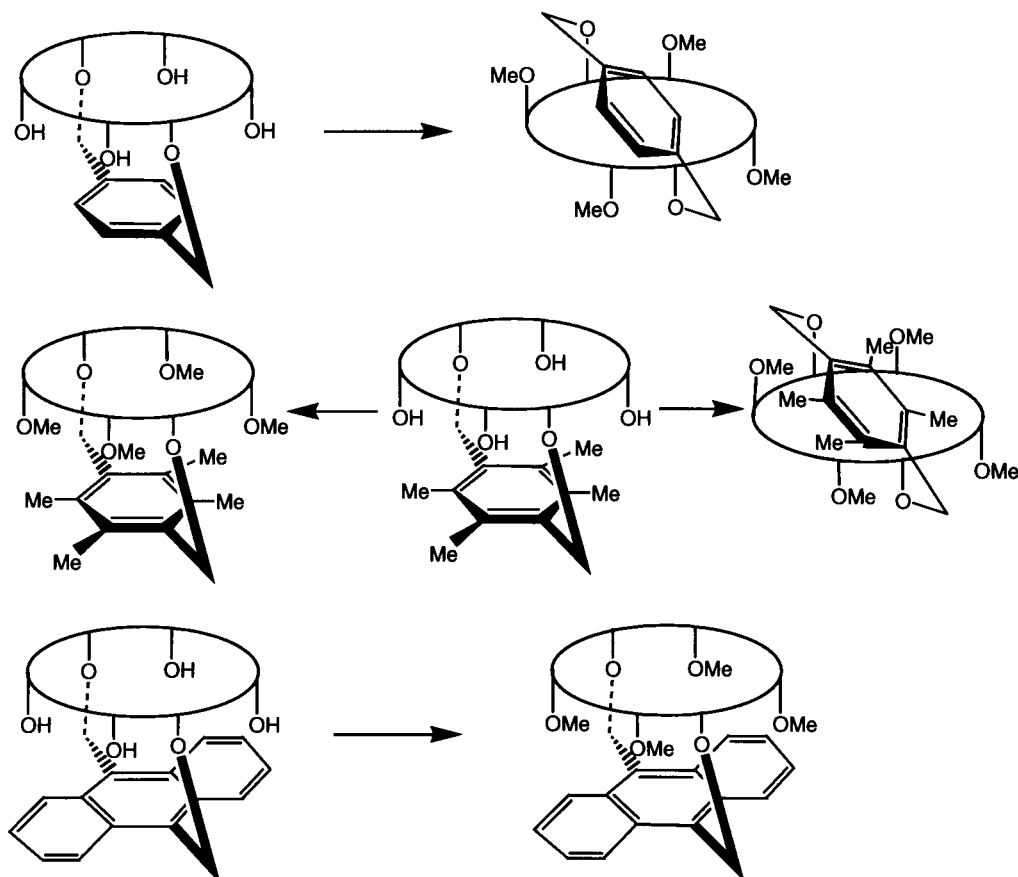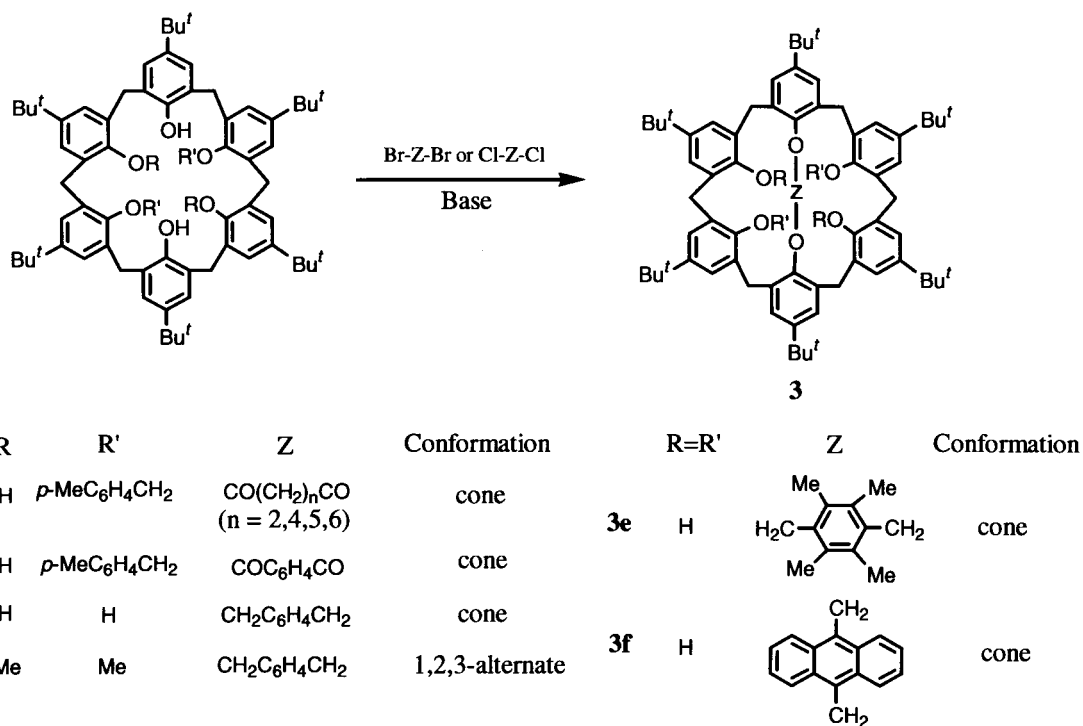
Figure 3. Conformations of A,D-bridged *p-tert*-butylcalix[6]arenes before and after exhaustive methylation.

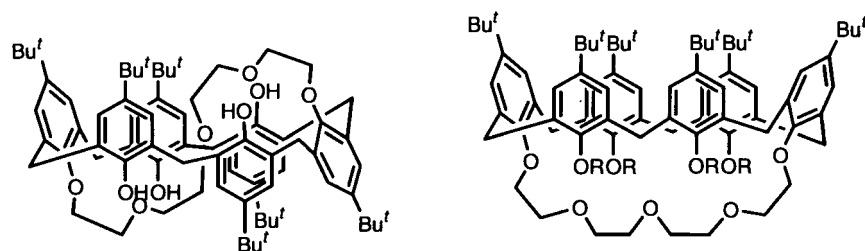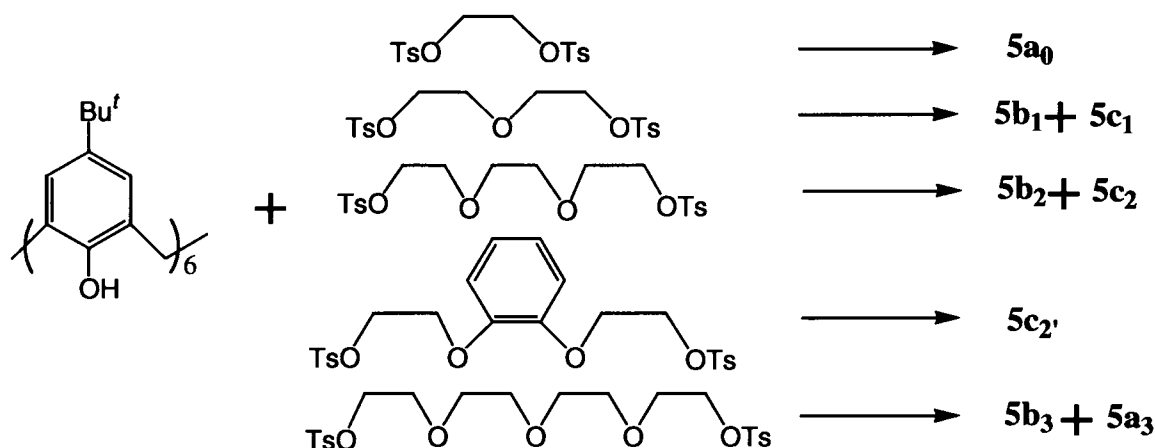*Scheme 3.* Some examples of A,D-monobridged calix[6]arenes.

Figure 4. Conformations of *p-tert*-butylcalix[6]-crown-5 and its etherified product.

Scheme 4. Synthesis of calix[6]crowns. Abbreviations: a, 1,2-bridged; b, 1,3-bridged; c, 1,4-bridged; 0, –CH$_2$CH$_2$–; 1, crown-3; 2, crown-4; 2′, benzocrown-4; 3, crown-5.

have been obtained by reacting *p-tert*-butylcalix[6]arene with ethylene glycol ditosylate and oligoethylene glycol ditosylates [10]. The synthetic scheme is shown below (Scheme 4).

It is worth noting that the conformations of 1,4-calix[6]crowns are very sensitive to the length of the spacer. *p-tert*-Butylcalix[6]-1,4-crown-3 adopts a rather special flattened (o,o,o,o,o,o) conformation and possesses remarkable steric strain (Figure 5). It cannot be further functionalized in the presence of either strong base or weak base and most of it decomposed to *p-tert*-butylcalix[6]arene. *p-tert*-Butylcalix[6]-1,4-crown-4 exists in cone conformation, and *p-tert*-butylcalix[6]-1,4-crown-5 adopts a 1,2,3-alternate conformation [17b].

Functionalization of the above-mentioned calix[6]crowns may produce a series of new host molecules. In fact, we have synthesized a series of A,D-bridged *p-tert*-butylcalix[6]crown-4 tetraesters, tetraamides, and tetraacids, they all exist in cone conformations (see Scheme 5) [18]. The percentage extractions of these compounds toward some picrate salts from water into CH$_2$Cl$_2$ are shown in Table 1. Among them, A,D-bridged *p-tert*-butyl-calix[6]crown-4 tetraethylester **6-2b** and A,D-bridged *p-tert*-butyl-calix[6]benzocrown-4 tetramethylester **6-3a** show high selectivity towards Li$^+$, Na$^+$ ion, respectively. The high selectivity may be due to the cooperation of the appropriate structure of the polyoxyethylene spacer and the appropriate alkyl chain in the ester moiety that can create an appropriate size of cavity and thus improve complexation selectivity. It was concluded that the ion selectivity is very sensitive to the structure of polyethylene spacer and the alkyl

Table 1. Percentage extraction (E%) of picrate salts from water into CHCl$_3$ at 20 °C

Host	E%			
	Li$^+$	Na$^+$	K$^+$	Cs$^+$
6-1a	2.6	6.5	4.5	/
6-1b	1.2	3.9	4.1	/
6-2a	53.1	46.0	27.4	12.3
6-2b	**34.5**	1.3	<1	<1
6-3a	1.4	**35.9**	<1	<1
6-3b	44.7	32.4	14.6	8.6
6-4a	36.7	34.5	3.4	/
6-4b	23.6	17.9	8.7	/
6-5a	47.0	38.9	21.2	/
6-5b	33.7	23.9	15.5	/
6-0 Me	1.7	10.3	29.1	/
6-0 Et	11.4	50.1	85.9	/

6-0 Me *p-tert*-butylcalix[6]arene hexaacetic acid hexamethyl ester.
6-0 Et *p-tert*-butylcalix[6]arene hexaacetic acid hexaethyl ester.

in the ester moiety. This implies that more host molecules with high selectivity toward special guest molecules can be constructed by incorporating appropriate functional groups to calix[6]crowns. The calix[6]arene-based lithium-selective ionophore was never reported before.

With the aid of 3-glycidyloxypropyltrimethoxysilane as a bridging agent, a novel type of the A,D-bridged *p-tert*-butylcalix[6]-1,4-crown-4 coated capillary has been prepared and used in open-tubular capillary electrochromatography successfully [19]. The calix[6]crown-coated capil-
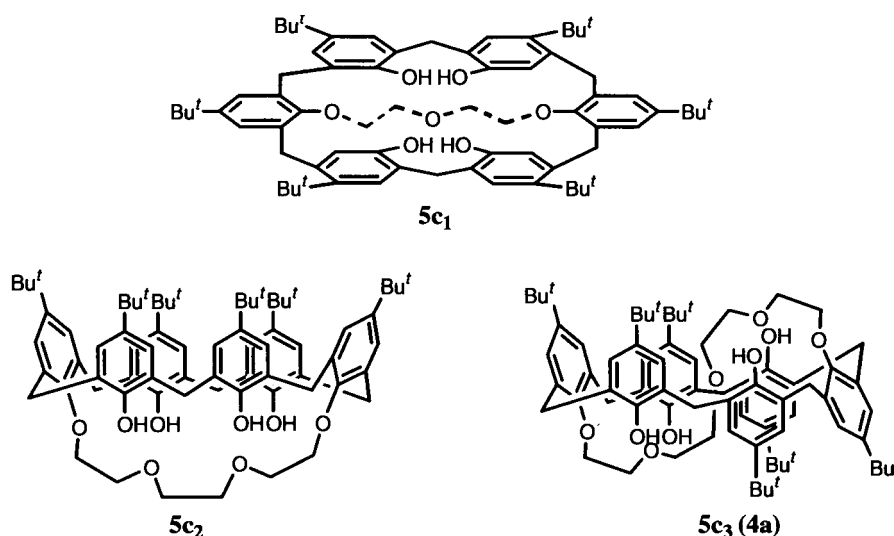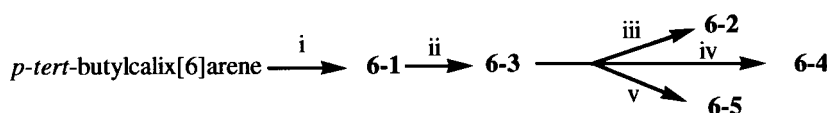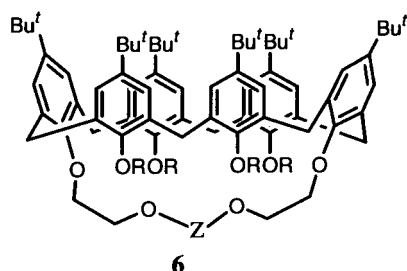
Figure 5. Conformations of p-tert-butylcalix[6]-1,4-crowns.

i. TsOCH₂CH₂OZOCH₂CH₂OTs; ii. BrCH₂COOEt; iii. MeOH; iv. H₂NCH₂CH₂OH; v. NaOH/EtOH.

6-1 R =H (**5c₂** or **5c₂'**)
6-2 R =CH₂COOMe
6-3 R =CH₂COOEt
6-4 R =CH₂CONHCH₂CH₂OH
6-5 R =CH₂COOH
a) Z= CH₂CH₂; b) Z= o-phenylene

Scheme 5. Synthesis of A-D-bridged p-tert-butylcalix[6]crown-4.

lary has shown improved separations of isomeric nitrophenols, dihydroxybenzenes, and toluidines in comparison with uncoated one. The special selectivity for phenolic compounds and toluidines indicates that there are to a certain extent host-guest interactions between solutes and the calix[6]crown coating.

Two A,D-bridged p-tert-butylcalix[6]crown-4 organosilicone resins were synthesized from p-tert-butylcalix[6]-1,4-crown-4 via condensation with γ-glycidyloxypropyltrimethoxysilane or reacting p-tert-butylcalix[6]-1,4-crown-4 tetraacetate with γ-glycidyloxypropyltrimethoxysilane, followed by copolymerization with tetraethoxysilane via sol-gel process, respectively [20]. The former exhibited higher adsorption capacity toward alkali metal ions and lower adsorption capacity toward transition metal ions and heavy metal ions than that of the latter. The thermodynamic and dynamic parameters of the resins toward Hg^{2+} ion was deduced.

Concave reagents

It is well known that the high selectivity of an enzyme is mainly caused by the concave environment of the active site. As an enzyme mimics, concave reagents are constructed by combining the activities of functional group with concave topology. In other words, concave reagents are cavity-shaped molecules with an inwardly-directed functionality embedded in the concave position. The first examples of concave reagents based on calix[6]arenes were reported by Lüning [12] and Okazaki [21] in 1995, independently. By reacting 2,6-bis(bromomethyl)pyridine or its 4-methoxy derivative with p-tert-butylcalix[6]arene in THF/DMF (9:1) with NaH as a base at reflux temperature, **7a₁** or **7a₂** was obtained in 55% and 51% yields, respectively [12]. An aryl azide confined in a 1,4-bridged calix[6]arene **7b** was synthesized by reacting p-tert-butylcalix[6]arene with 2-azido-1,3-bis(bromomethyl)benzene under basic conditions in 86% yield, followed by exhaustive methylation [21]. 1,10-Phenanthroline bridged calix[6]arenas **7c** [22] and 1,4-benzoquinone bridged p-tert-butylcalix[6]arene **7d** are two other types of calix[6]arene-based concave reagents [23]. The latter was synthesized with difficulty via a multi-step synthetic procedure. Their structures are shown in Figure 6.

A number of their derivatives have been synthesized, their structures are shown in Figure 7.

Most of concave reagents can be easily prepared on a large scale from calix[6]arenes and α, α'-dibromo-m-
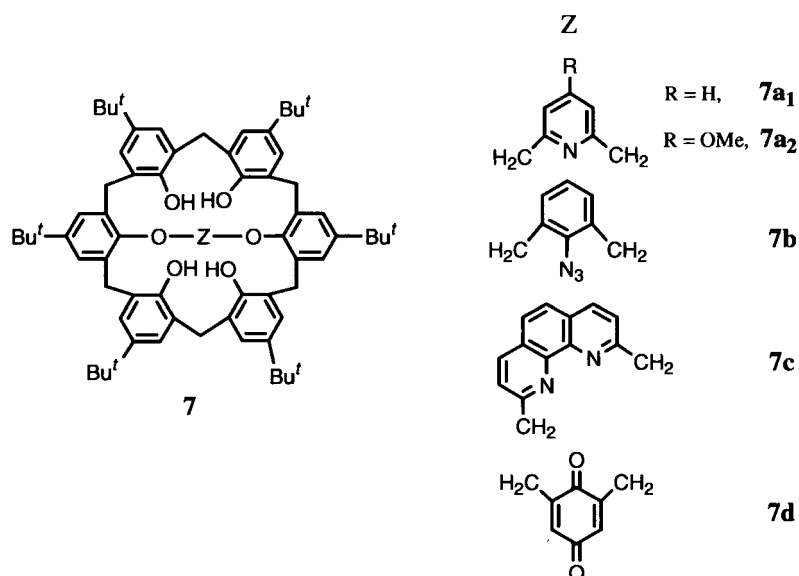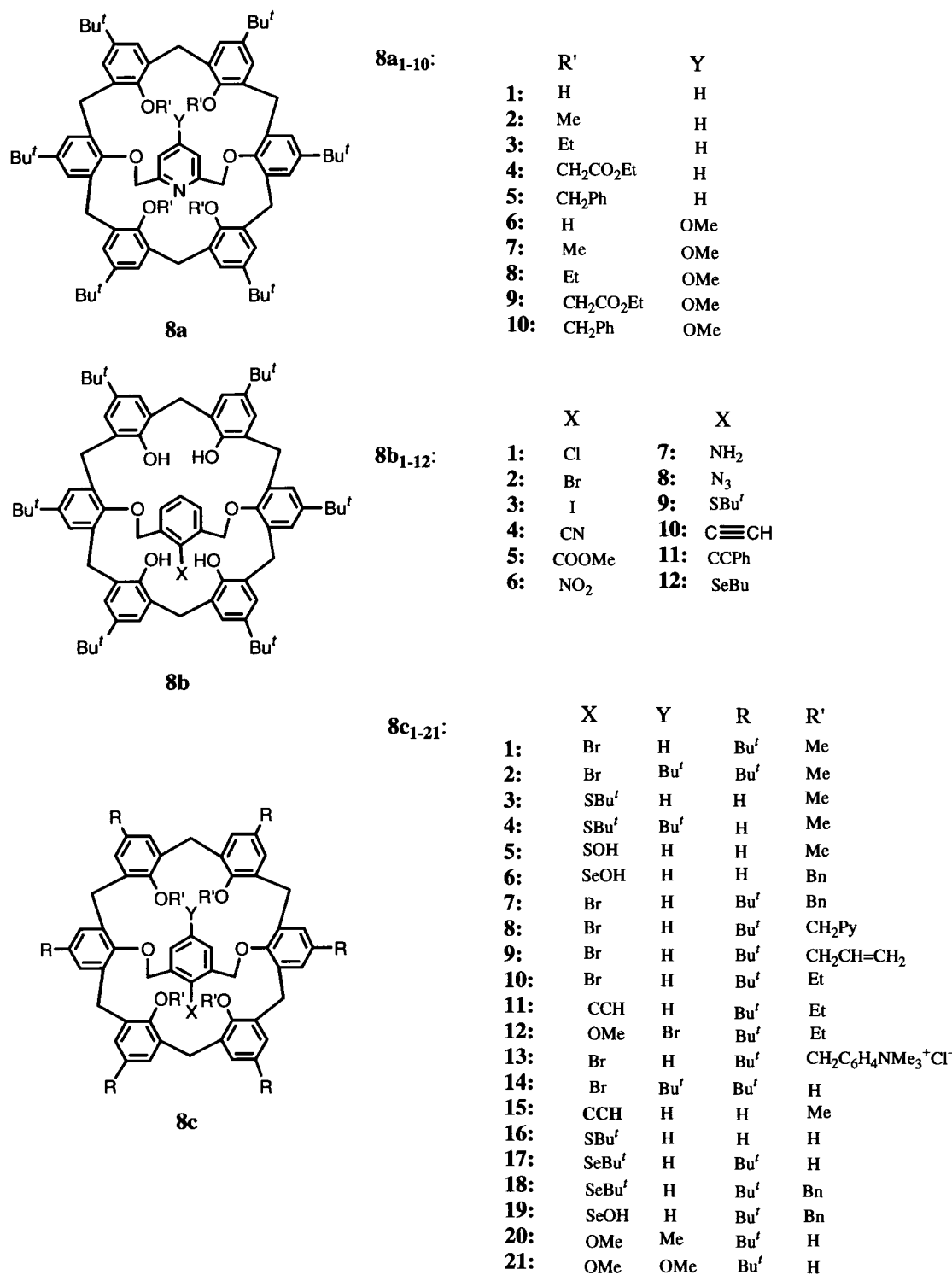
Figure 6. Representative examples of calix[6]arene-based concave reagents.

xylene derivatives or 2,6-dibromomethylpyridine derivatives simply. The yields were often fairly good to high. In general, concave reagents are in cone conformations [3, 29]. After exhaustive alkylation, the conformation of the tetraalkylated product was dependent on what kind of alkylating reagent being used. For exhaustive methylation, the methylated products have a tendency to adopt a 1,2,3-alternate conformation, at least, in the crystalline state [29]. As the upper-rim-through-the-annulus rotation is inhibited, conformation immobilization is considered to be possible by introducing bulky groups into the lower-rim so as to restrict the rotation from this side. In fact, if the incorporated groups are benzyl, or 4-pyridylmethyl, two conformational isomers were often obtained, and the two conformers are non-interconvertible. Benzylation of $8b_2$ afforded two conformational isomers in cone and 1,2,3-alternate conformation with yields of 58% and 16%, respectively [29]. The isomers could be isolated as pure products by chromatography and remained virtually unchanged up to 130 ° [15b]. This reveals that the rotation is still occurring in the original *m*-xylene bridged calix[6]arenes, but fully inhibited in the benzylated products. Pyridylmethylation of $8b_2$ gave similar results [27]. As the two isomers have similar thermodynamic stability, the predominant formation of the cone conformer is due to kinetic reasons [30]. Benzylation of the bridged calix[6]arene bearing a central SeBu group $8c_{17}$ also afforded two conformational isomers, although the yield of 1,2,3-alternate isomers is very low (4%) [29]. Incorporation of ethyl groups onto the lower-rim gave interesting results [26]. 2-Bromoxylylene bridged *p-tert*-butylcalix[6]arene tetraethyl ether $8c_{10}$ and $8c_{11}$ existed as a mixture of two inseparable conformers on the laboratory time-scale in solution, whereas $8c_{12}$ was found to exist in cone conformation in solution exclusively resulting in the thermodynamic stability of the cone conformer. It was concluded that the conformation mobility of this type of bridged calix[6]arenes can be finely modulated by appropriate capping of their lower-rim.

The concave reagents bearing unstable or reactive species such as sulfenic acids, selenenic acids etc. have attracted special attention. It is well known that sulfenic acids (R-SOH) play an important role as reactive intermediates in organosulfur chemistry and some enzymatic reactions. Usually they are very unstable because of facile self-condensation reactions leading to the corresponding thiosulfinates (RS(O)SR). Reacting *p*-H-calix[6]arene with *m*-dibromomethylphenyl *tert*-butylthioether in the presence of KOH gave $2'$-*tert*-butylthioxylylene bridged calix[6]arene **9b** in 92% yield (Scheme 6) [25c]. It was subjected to exhaustive methylation, followed by oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) to give the sulfoxide as a pair of inseparable conformers. Thermolysis of the sulfoxide in toluene at 80 °C afforded the sulfenic acid-containing calix[6]arene **9d** ($8c_5$) in 97% yield [31]. The sulfenic acid adopts 1,2,3-alternate conformation and exhibits high stability both in the crystalline state and in solution. It is stable toward air or moisture, and the thermal decomposition temperature is up to 182 °C as measured by DSC. The SOH functionality is directed into the cavity and surrounded by the calix[6]arene macrocycle from all sides, being effectively protected from self-condensation. Reacting it with methyl propiolate in chloroform at 50 °C for 16 h afforded corresponding addition product in 86% yield [31].

Stable selenenic acid bearing a bridged calix[6]arene framework was similarly synthesized. Bridging *p-tert*-butylcalix[6]arene with 2,6-dibromethylphenyl butyl selenide in the presence of KOH in THF/DMF afforded $2'$-butylseleno-*m*-xylylene bridged *p-tert*-butylcalix[6]arene $8b_{12}$ in 80% yield [25b]. After exhaustive benzylation and then oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA), followed by thermolysis in toluene gave the selenenic acid $8c_6$. The benzylated products are a mixture of conformers, which could be further separated by chromatography. The isolated yields of cone conformer and 1,2,3-alternate isomer were 4% and 59%, respectively. Both

8a₁₋₁₀:

	R'	Y
1:	H	H
2:	Me	H
3:	Et	H
4:	CH_2CO_2Et	H
5:	CH_2Ph	H
6:	H	OMe
7:	Me	OMe
8:	Et	OMe
9:	CH_2CO_2Et	OMe
10:	CH_2Ph	OMe

8a

8b₁₋₁₂:

	X		X
1:	Cl	7:	NH_2
2:	Br	8:	N_3
3:	I	9:	SBu^t
4:	CN	10:	$C{\equiv}CH$
5:	COOMe	11:	CCPh
6:	NO_2	12:	SeBu

8b

8c₁₋₂₁:

	X	Y	R	R'
1:	Br	H	Bu^t	Me
2:	Br	Bu^t	Bu^t	Me
3:	SBu^t	H	H	Me
4:	SBu^t	Bu^t	H	Me
5:	SOH	H	H	Me
6:	SeOH	H	H	Bn
7:	Br	H	Bu^t	Bn
8:	Br	H	Bu^t	CH_2Py
9:	Br	H	Bu^t	$CH_2CH{=}CH_2$
10:	Br	H	Bu^t	Et
11:	CCH	H	Bu^t	Et
12:	OMe	Br	Bu^t	Et
13:	Br	H	Bu^t	$CH_2C_6H_4NMe_3{}^+Cl^-$
14:	Br	Bu^t	Bu^t	H
15:	CCH	H	H	Me
16:	SBu^t	H	H	H
17:	$SeBu^t$	H	Bu^t	H
18:	$SeBu^t$	H	Bu^t	Bn
19:	SeOH	H	Bu^t	Bn
20:	OMe	Me	Bu^t	H
21:	OMe	OMe	Bu^t	H

8c

References: **8a** [16]; **8b** [24,25a,25b]; **8c** [25c,26, 27]; **8c₂₀** [28]

Figure 7. Concave reagents.

isomers could be converted to the target product by thermo-lysis and exhibited high thermal stability as expected [32]. However, they showed different reactivity towards a thiol. While the cone isomer reacted with BuSH at room temper-ature to give seleneryl sulfide (-SSeBu^t), the 1,2,3-alternate conformer underwent no reaction even at 50 °C. The results were explained as the cooperation of hydrogen bonding and steric environment of SeOH.

Finally, some conclusions can be made for the conform-ation and immobilization of conformation of monobridged calix[6]arenes. First, with the same bridge, A,C-bridged is more effective in immobilizing conformation than A,D-bridged, in turn, which is much effective than A,B-bridged. Second, the conformation of A,C-*m*-xylylene bridged *p*-*tert*-butylcalix[6]arene is well immobilized in cone con-formation, especially, *m*-xylylene derivative [6], but not
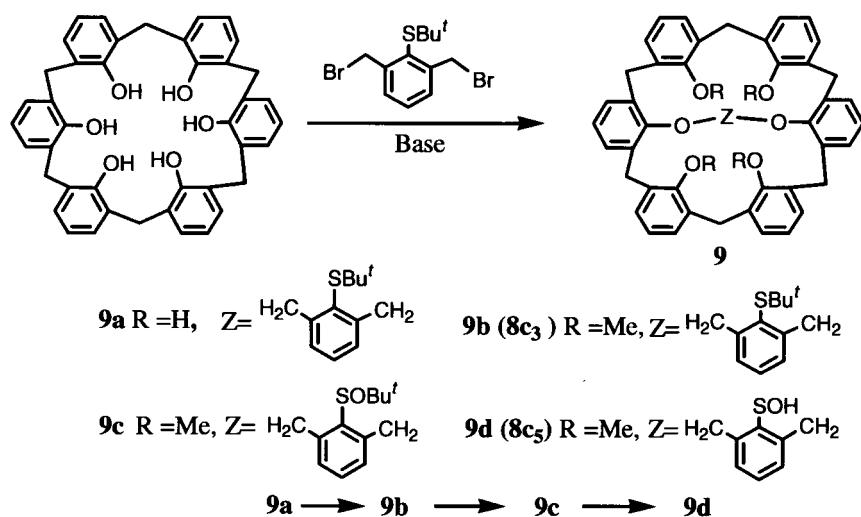
Scheme 6. Synthesis of a bridged calix[6]arene with a sulfenic acid functionality in the cavity.

including those with very long bridges. Third, the A,D-bridged *p-tert*-butylcalix[6]arenes with rigid spacers such as *m*-xylylene generally exist in cone conformation, but those with long flexible spacers preferably adopt 1,2,3-alternate one. Fourth, for A,D-bridged *p-tert*-butylcalix[6]arene, the stability of its conformation is related to the volume of the Ar in the bridge. If the volume is bulky enough as 1,10-phenanthroline (Z in **7c**, see Figure 6), its conformation may be immobilized in cone one, this is also the case for anthrylene group. Fifth, the conformation of exhaustive alkylated A,D-xylylene-bridged *p-tert*-butylcalix[6]arene depends on what kind of alkyl being incorporated, tetramethyl ether has a tendency to exist in 1,2,3-alternate conformation, and not immobilized, but tetrakis-benzyl ether, tetrakis-pyridylmethyl ether usually exists in a mixture of separable, stable steric isomers, cone and 1,2,3-alternate. What conformation will be adopted by tetraethyl ether is in a borderline case.

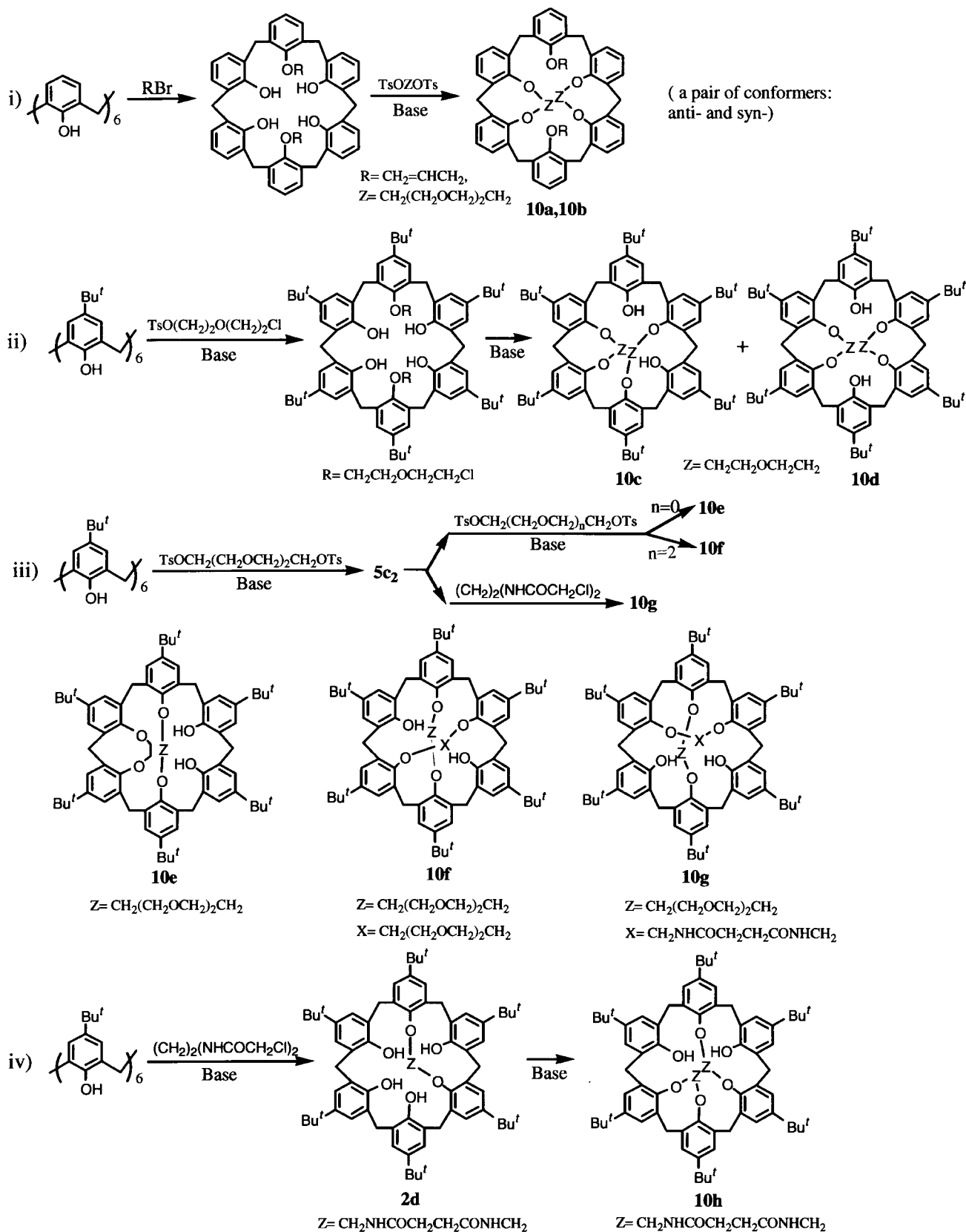**Doubly bridged calix[6]arenes**

In 1992, Roundhill *et al.* introduced ethyl phosphate substituents onto the lower-rim of calix[6]arene. A,B-Monobridged and A,B-D,E-doubly bridged products were obtained. In each case the ethyl phosphate group spans two adjacent positions on the lower-rim of the calix[6]arene [5].

It is well known that calixcrowns exhibited superior recognition ability toward alkali metal ions due to their well preorganized structure and more rigid binding sites in comparison with calixarenes and crown ethers. At present, the calix[4]crown chemistry is approaching maturity. Not only all types of calix[4]monocrowns but also all types of calix[4]biscrowns have been synthesized, and their recognition ability toward ions and molecules was extensively studied. In contrast, the calix[6]crown chemistry has been receiving little attention, though it is regarded as the next candidate for close scrutiny. The first calix[6]monocrowns were reported as late as 1995 by Ungaro *et al.* [17b]. As the calix[6]biscrowns have more sophisticated structures,

it is expected that they have the potential to be the next generation of host molecules and may enjoy the popularity and application rivaling that of calix[4]crowns. Very recently, we found that the calix[6]biscrowns could be synthesized by reacting *p-tert*-butylcalix[6]crown-4 **5c₂** or *p-tert*-butylcalix[6]benzocrown-4 **5c₂′** with triethylene glycol ditosylate in the presence of NaH as a base in DMF [33a]. After purification by column chromatography, the A,D-B,E doubly bridged *p-tert*-butylcalix[6]-1,4-2,5-biscrown-4 **10f** and *p-tert*-butylcalix[6]-1,4-crown-4-2,5-benzocrown-4 were isolated as white solids in 66% and 70% yield, respectively. The crystal structure and complexing properties of the *p-tert*-butylcalix[6]-1,4-2,5-biscrown-4 was also investigated [33b].

In the meantime, the synthesis and complexation properties of two calix[6]biscrowns were also reported by Blanda *et al.* [34]. Bridging 1,4-diallylated calix[6]arene with triethylene glycol ditosylate and NaH in THF/DMF (90/10), approximately equal amounts of stereoisomers of A,C-D,F doubly bridged 37,40-diallyloxy-38,42-39,41-biscrown-4-calix[6]arene (calix[6]-1,4-diallyloxy-2,6-3,5-biscrown-4) were isolated (15% and 11% for *anti*-isomer and syn-isomer, respectively). One isomer **10b** exists in (u,uo,do,d,do,uo) conformation, or 1,2,3-alternate conformation, and the other **10a** adopts cone conformation. Both conformers exhibited a strong preference for the larger cesium ion, and the Cs⁺/Na⁺ selectivity factor for cone one was found to be 1500, while that of 1,2,3-alternate one was only 140.

Ignoring the orientation of residual two phenolic rings with respect to the two bridges, there are eight possible positional isomers for doubly bridged calix[6]arenas, i.e., A,B-C,D; A,B-C,E; A,B-C,F; A,B-D,E; A,C-B,D; A,C-B,E; A,C-D,F; and A,D-B,E isomer. Depending on the relative orientation of two bridges, each isomer may exists in *syn* or *anti* conformation, although it is impossible for A,C-B,D; A,C-B,E; and A,D-B,F doubly bridged isomers due to steric exclusion between two bridges except one bridge is very long.

i) $\xrightarrow{\text{RBr}}$ $\xrightarrow[\text{Base}]{\text{TsOZOTs}}$

R= CH$_2$=CHCH$_2$,
Z= CH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$ **10a,10b**

(a pair of conformers:
anti- and syn-)

ii) $\xrightarrow[\text{Base}]{\text{TsO(CH}_2\text{)}_2\text{O(CH}_2\text{)}_2\text{Cl}}$ $\xrightarrow{\text{Base}}$ +

R= CH$_2$CH$_2$OCH$_2$CH$_2$Cl   **10c**   Z= CH$_2$CH$_2$OCH$_2$CH$_2$ **10d**

iii) $\xrightarrow[\text{Base}]{\text{TsOCH}_2\text{(CH}_2\text{OCH}_2\text{)}_2\text{CH}_2\text{OTs}}$ **5c$_2$**

$\xrightarrow[\text{Base}]{\text{TsOCH}_2\text{(CH}_2\text{OCH}_2\text{)}_n\text{CH}_2\text{OTs}}$ n=0 → **10e**   n=2 → **10f**

$\xrightarrow{\text{(CH}_2\text{)}_2\text{(NHCOCH}_2\text{Cl)}_2}$ **10g**

10e
Z= CH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$

10f
Z= CH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$
X= CH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$

10g
Z= CH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$
X= CH$_2$NHCOCH$_2$CH$_2$CONHCH$_2$

iv) $\xrightarrow[\text{Base}]{\text{(CH}_2\text{)}_2\text{(NHCOCH}_2\text{Cl)}_2}$ $\xrightarrow{\text{Base}}$

2d
Z= CH$_2$NHCOCH$_2$CH$_2$CONHCH$_2$

10h
Z= CH$_2$NHCOCH$_2$CH$_2$CONHCH$_2$

Scheme 7. Syntheses of some typical calix[6]biscrowns.

Table 2. Percent extraction (E%) of picrate from water into CHCl$_3$ at 25 °C

Host	E%							
	Li$^+$	Na$^+$	K$^+$	Cs$^+$	Cu^{2+}	Ni^{2+}	Hg^{2+}	Pd^{2+}
5c$_2$	2.6	6.5	4.5	10.2	1.2	1.6	0.2	0.4
10g	0.2	0.4	2.5	20.8	5.8	26.8	0.8	0.3
2d(n = 2)	5.3	1.2	0.9					
Ion radii (Å)	0.68	0.97	1.33	1.67	0.72	0.69	1.10	0.80

Reacting *p-tert*-butylcalix[6]-1,4-crown-4 with ethylene glycol ditosylate and polyethylene glycol ditosylates using NaH as a base in DMF, A,B-C,F doubly bridged *p-tert*-butylcalix[6]-2,3-ethylene-1,4-crown-4 **10c**, A,D-B,F doubly bridged *p-tert*-butylcalix[6]-1,4-crown-4-2,6-crown-3, *p-tert*-butylcalix[6]-1,4-crown-4-2,6-crown-5 were obtained in selective reaction conditions [35]. *p-tert*-Butylcalix[6]-2,3-ethylene-1,4-crown-4 **10c** exists in cone conformation, but the conformation of the latter two are uncertain because the (u,d,d,u,d,d) and (u,d,u,u,u,d) conformation gave same NMR data for methylene protons, though the former is more plausible.

1,4-*Bis*-(2-(2′-chloroethoxy)ethoxy)-*p-tert*-butylcalix[6]arene could be synthesized by the functionalization of *p-tert*-butylcalix[6]arene with (2-(2′-chloroethoxy)ethoxy tosylate in selected conditions. Refluxing the latter with NaH in benzene afforded A,C-D,F doubly bridged *p-tert*-butylcalix[6]-1,3-4,6-biscrown **10d** and A,B-C,E doubly bridged *p-tert*-butylcalix[6]-1,2-3,5-biscrown-3 **10c** in 25% and 17% yields, respectively. The former exists in 1,2,3-alternate (u,u,u,d,d,d) conformation and the latter adopts a self-anchored (u,u,u,u,d,u) conformation [36].

Reacting *p-tert*-butylcalix[6]-1,4-crown-4 with *N*, *N*′-*bis*(chloroacetyl)ethylenediamine in refluxing MeCN in the presence of Cs$_2$CO$_3$ as a base and KI afforded A,D-B,F doubly bridged *p-tert*-butylcalix[6]-1,4-crown-4-2,6-dioxo-diaza-crown-4 **10g** in 32% yield [37]. This compound belongs to the molecule bearing a hard and a soft binding site simultaneously. For alkali metal ions, it showed the largest extraction percentage toward the largest cesium ion, for transition metal ions, it showed the highest complexation ability toward the smallest nickel ion among the transition metal ions used (Table 2). In comparison with its complexation behavior with that of *p-tert*-butylcalix[6]-1,4-crown-4 **5c$_2$** with hard binding site and that of *p-tert*-butylcalix[6]-1,3-dioxo-diazacrown-4 **2d(n = 2)** with a soft binding site, it can concluded that the cesium ion was included into the hard binding site and the nickel ion was embedded into the soft binding site. This is an interesting evidence for existence of two binding sites with contrary complexation properties in one host molecule.

Doubly bridged calix[6]bisazacrown was also synthesized [14a]. A,B-C,E doubly bridged *p-tert*-butylcalix[6]-1,2-3,5-*bis*-dioxodiazacrown-3 could be obtained from *p-tert*-butylcalix[6]arene and *N*, *N*′-*bis*(chloroacetyl)ethyleneamine directly in 40% yield or by reacting *p-tert*-butylcalix[6]dioxodiazacrown-3 **2d** (n

= 2) with *N*, *N*′-*bis*(chloroacetyl)ethyleneamine in 67% yield, which is stable as a cone (u,u,u,u,u,u) conformation at ambient temperature. Some calix[6]biscrowns with defined conformations are shown in Figure 8.

No A,B-C,D type, A,C-B,D-type and A,B-D,E type of doubly bridged calix[6]biscrowns have been known up to date, though doubly ethyl phosphate bridged calix[6]arene may be counted as A,B-D,E doubly bridged calix[6]arene.

It is obvious that calix[6]biscrowns possess more plenty of conformations as compared with that of monobridged calix[6]arenes. Up to date, only the crystal structure of *p-tert*-butylcalix[6]-1,4-2,5-biscrown-4 **10g** and 1,2,3-alterate conformation of calix[6]-2,5-diallyloxy-1,3-4,6-biscrown-4 **10f** have been determined. As the orientation of the two residual phenolic rings is hard to be deduced from the NMR data, how to determine their conformation is still a problem. It is clear that the investigation on doubly bridged calix[6]arenes is far from maturity, including the synthetic methodology of new types of doubly bridged calix[6]arenes, the relationship between the structure and properties, and their conformation and application, etc. More effort should be devoted to doubly bridged calix[6]biscrowns.

Triply bridged calix[6]arenes

Little is known about triply bridged calix[6]arene. There were eight types of possible positional isomers of triply lower-rim bridged calix[6]arenes. Only two types of triply lower-rim bridged calix[6]arenes and one upper-rim triply bridged calix[6]arene are known. Pappalardo reported the synthesis and conformational characteristics of A,B-C,D-E,F trimethylene bridged *p-tert*-butylcalix[6]arene as early as 1992 [38]. By reacting *p-tert*-butylcalix[6]arene with a large excess of BrCH$_2$Cl in anhydrous DMF at room temperature in the presence of Cs$_2$CO$_3$, the triply bridged compound **11a** was obtained in 25–35% yield. It exists in a mixture of conformers and indicates a complete flexibility above 270 K [38]. Lüning prepared A,D-pyridinediyldimethyloxy-B,C-E,F dimethylenedioxy triply bridged calix[6]arene **11b** by treating 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetrahydroxy-40,42-pyridinediyldimethyloxycalix[6]arene **7a$_1$** or 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,41-tetrahydroxy-40,42-4′-methoxy-pyridinediyldimethoxycalix[6]arene **7a$_2$** with BrCH$_2$Cl in refluxing DMF in the presence of Cs$_2$CO$_3$ in 93% yield [16]. The third triply bridged calix[6]arene **11c** was synthesized by Shinkai and his
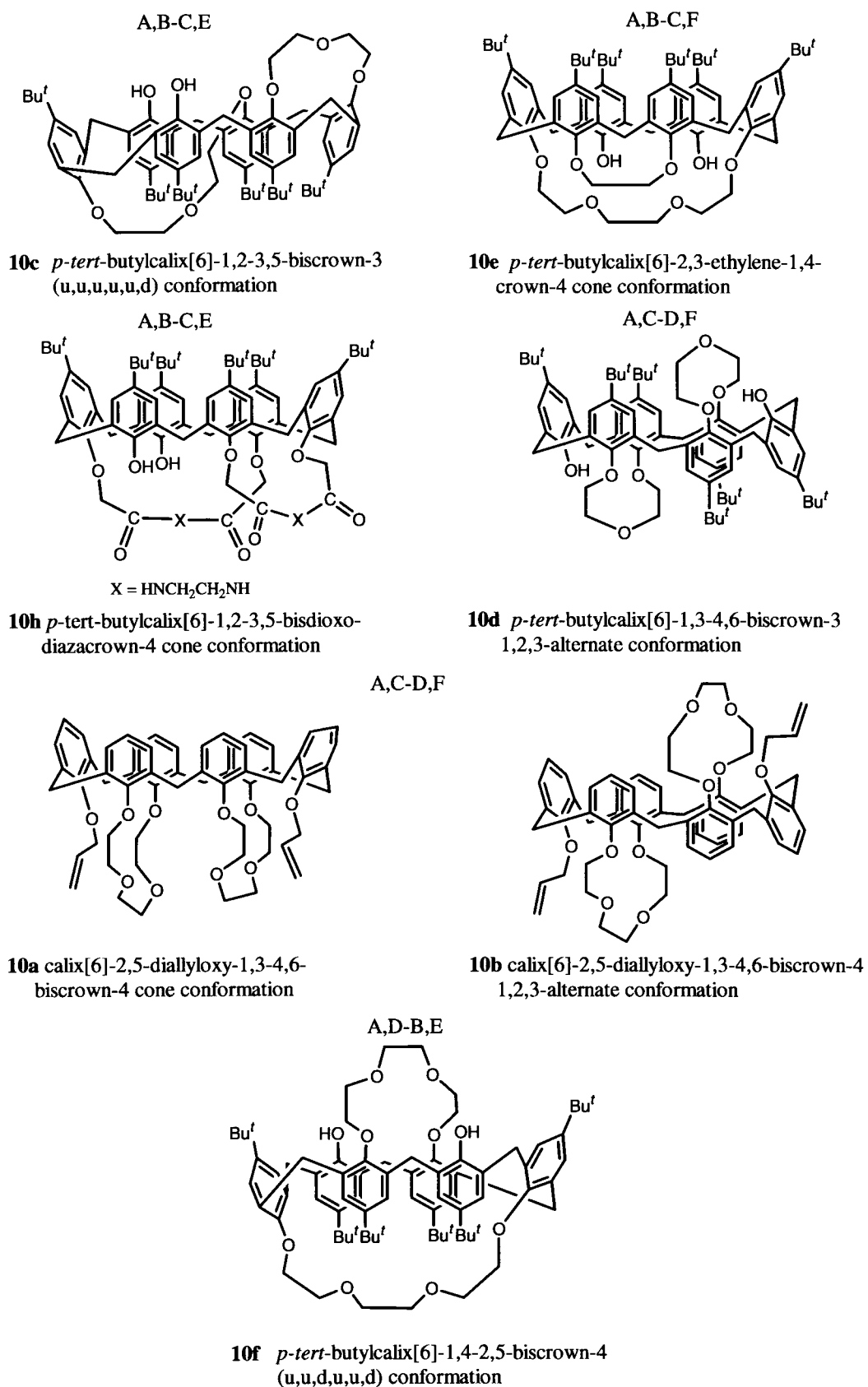
A,B-C,E

10c *p-tert*-butylcalix[6]-1,2-3,5-biscrown-3
(u,u,u,u,u,d) conformation

A,B-C,E

X = HNCH₂CH₂NH

10h *p*-tert-butylcalix[6]-1,2-3,5-bisdioxo-
diazacrown-4 cone conformation

A,C-D,F

10a calix[6]-2,5-diallyloxy-1,3-4,6-
biscrown-4 cone conformation

A,B-C,F

10e *p-tert*-butylcalix[6]-2,3-ethylene-1,4-
crown-4 cone conformation

A,C-D,F

10d *p-tert*-butylcalix[6]-1,3-4,6-biscrown-3
1,2,3-alternate conformation

10b calix[6]-2,5-diallyloxy-1,3-4,6-biscrown-4
1,2,3-alternate conformation

A,D-B,E

10f *p-tert*-butylcalix[6]-1,4-2,5-biscrown-4
(u,u,d,u,u,d) conformation

Figure 8. Calix[6]biscrowns with defined conformation.
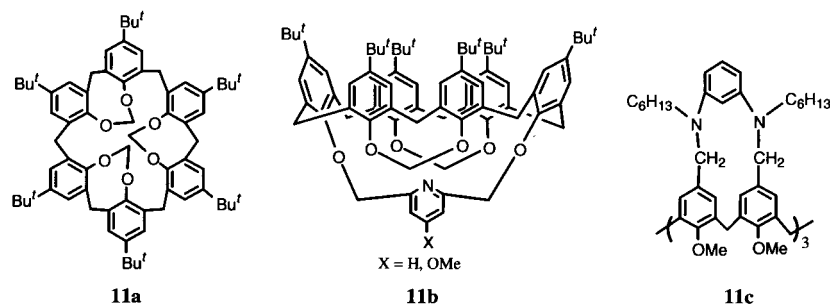
Figure 9. Triply bridged calix[6]arenes.

coworkers [39]. Reacting *p*-chloromethylcalix[6]arene hexamethylether (5,11,17,23,29,35-hexachloromethyl-37,38,39,40,41,42-hexamethoxycalix[6]arene) with *N*, *N'*-dihexyl-*m*-phenyldiamine in the presence of Cs_2CO_3 as a base, A,B-C,D-E,F-tri-*m*-phenylenedihexylaminomethyl bridged calix[6]arene hexamethyl ether **11c** was obtained in 9% yield. This is also the first upper-rim triply bridged calix[6]arene. **11c** is an effective capture agent for [60]fullerene in organic solution, the association constants is up to 1.1×10^2 dm^3 mol^{-1}. The structures of compound **11a**, **11b**, **11c** are shown in Figure 9.

Capped calix[6]arenes

Here the term "capped calixarene" 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 linkages. Singly, doubly and triply is related to the number of spacers. For example, "doubly capped" implies occurrence of two spacers and each linking three phenolic rings. It should be noted that the term was used in the literature with various meanings. For further distinction how many phenolic rings are linked, tripodal, tetrapterous etc. should be added beyond "bridged calixarene" or "capped calixarene".

Tripodal capped calix[6]arenes

There are three types of possible capped calix[6]arenes: A,B,C-, A,B,D- and A,C,E-capped calix[6]arene. A,C,E-Capped calix[6]arene, or symmetrical capped calix[6]arene, has attracted more attention than the others.

A,C,E-Capped calix[6]arenes (1,3,5-tripodal calix[6] cryptand, cryptocalix[6]arene)

In 1994, Reinhoudt *et al.* and Shinkai *et al.* put forward independently that capping is a key to suppress the ring inversion and control the structure of calix[6]arene in defined conformation, in general, cone conformation. Reinhoudt *et al.* synthesized C_3-symmetrical cryptocalix[6]arenes or calix[6]cryptands **12a$_1$-12a$_7$** by convalently three-point linking of a symmetrical trimethylated *p-tert*-butylcalix[6]arene with a variety of reactants in the presence of Cs_2CO_3 as a base in DMF at 60–80 °C followed by cyclization in glacial acetic acid [40]. A minor part of C_3-symmetrical cryptocalix[6]arene may convert to

Table 3. Association constants (Ka) of complexes of hosts with picrate salts in $CHCl_3$ saturated with water

Host	$K_a \times 10^{-5}$ (25 °C)			
	Li^+	Na^+	K^+	NH_4^+
12d	1.8	2.1	1.2	0.7
12e	20.3	18.1	8.1	2.9

its conformer isomer, in which one anisole moiety has rotated in such a way that its *tert*-butyl group is located in the cavity. Shinkai *et al.* reported that the synthesis of a conformationally-immobilized calix[6]arene **12b** by capping *p-tert*-butylcalix[6]arene 1,3,5-trimethyl ether 2,4,6-tricarboxylic acid chloride with a C_3-symmetrical triol, tris(2-hydroxyethyl)isocyanurate as a cap in 2.5% yield [41]. No ring inversion could be observed up to 110 °C by 2D EXSY in NMR spectra. In other words, the compound is firmly immobilized in a cone conformation and the flip-flop type inversion of the "basket" can not take place, at least, on the NMR time scale. This can be attributed to the more rigid linkages between calix[6]arene and cap in the latter [41]. In fact, in the more rigidly capped product **12c** which was prepared from 1,3,5-trialkylated calix[6]arenes and 1,3,5-tris(bromomethyl)benzene, the situation is entirely the same [6]. It should be mentioned that the yields of **12c** (R = Me) is surprisingly high: 91%. The authors considered that the high yield results in the C_3 symmetrical complementary and the similar size between the calix[6]arene cavity and the 1,3,5-tris(bromomethyl)benzene cap [6]. The compound possesses a closed ionophoric cavity: the upper hemisphere is closed by three *tert*-butyl groups of anisole units and the lower hemisphere is closed by a mesitylene cap and three anisole methoxy groups. Its structure is extremely rigidified and exhibits high selectivity toward Cs^+ ion [42].

A calix[6]arene C_3 symmetrically capped at the upper-rim **12g** was also prepared by reacting 37,38,39,40,41,42-hexamethoxy-11,23,35-tri-*tert*-butyl-5,17,29-tris(chloromethyl)calix[6]arene with 1,3,5-tris(mercaptomethyl)benzene in the presence of KOH in ethanol under high-dilution conditions in 28% yield [46]. Again, it was proved by dynamic ^{1}H NMR spectra that the flipping motion is entirely restricted. As it has a rigid C_3 symmetrical cavity composed of π-rich benzene rings, it

can act as a preorganized host molecule for inclusion of trimethylammonium ions by cation-π interactions.

The aforementioned capped calix[6]arenes all have a flat-topped cap, i.e., benzene ring or isocyanurate ring, no in- and out-stereoisomerism can be found in these compounds without bridgehead carbon atoms. If one adopts an appropriate tripodal capping reagent with a bridgehead carbon atom instead of the aforementioned capping reagents, a new type of calix[6]cryptand will be synthesized. We found this is the case [43]. Reacting 1,3,5-trimethylated *p-tert*-butylcalix[6]arene with 1,1,1-tris(tosyloxyethoxyethoxymethyl)propane in refluxing dioxane using NaH as a base under refluxing temperature, a pair of separable stabilized in- and out- calix[6]cryptands was obtained in 32.3% yield for **12d** and 21.7% yield for **12e**, respectively. It is interesting to note that the complexation ability toward alkali metal ions of in-isomer **12d** is lower than that of out-isomer (**12e**) due to steric hindrance.

The two isomers can not interconvert even heating at 280 °C indicating that they are real stereoisomers but not conformers (Figure 10), and also, the flip-flop type inversion can not take place at all. This paper not only described a new approach to capped calix[6]arene, but also provided the second non-spectral methodology to obtain unambiguous evidence for the ring immobilization in calix[6]arene with stereoisomers, after Shinkai's method [8b]. The in- and out-isomer **12d** and **12e** were mixed with OV-1701 (stationary phase, commercial name of methyl silicon oil containing 7% phenyl and 7% cyanopropyl groups) and used as stationary phases to coat fused-silica columns for capillary gas chromatography, respectively. The columns exhibited different selectivity for the separation of polycyclic positional isomers and polycyclic aromatic hydrocarbons, which can only be explained by the discrimination between their stereo structure [44].

A triethanolamine-derivative capped *p-tert*-butylcalix[6]arene **12f** was also reported [45a]. Reacting $(ClCH_2COOCH_2CH_2)_3N$ with *p-tert*-butylcalix[6]arene in acetone in the presence of K_2CO_3 and KI, compound **12f** was obtained in 25% yield. It adopts stabilized cone conformation and can form 1 : 3 or 1 : 4 complex with alkali metal ions. Its solid-state structure has been determined by X-ray diffraction analysis [45b]. Their conformations can be seen from Figure 10.

Recently, some upper-rim covalently triply linked double calix[6]arenes **13a** and **13b** have been synthesized by Arduini *et al.* [47]. The calix[6]arenes can be regarded as a new series of tripodal capped calix[6]arenes too. By reacting 37,39,41-trioctyloxy-38,40,42-trimethoxy-5,17,29-triformyl-11,23,35-tri-*tert*-butylcalix[6]arene (trialdehyde) with 37,39,41-trioctyloxy-38,40,42-trimethoxy-5,17,29-triamino-11,23,35-tri-*tert*-butylcalix[6]arene (triamine) in refluxing toluene, **13a** was obtained in 26% yield. The ^1H NMR data indicate that the linear imino bridges impose a flattened cone conformation to both subunits which thus create a cavity having the symmetry of a trigonal prism defined by the bridged aromatics and where the nuclei bearing the *tert*-butyl groups are tilted toward the outside. Using 1,4-

diaminobenzene or 2,3,4,5-tetramethyl-1,4-diaminobenzene instead of triamine, **13b** was obtained in 50% or 40% yield, respectively. The internal cavities of these molecular cages exhibit different grades of accessibility toward a set of *N*-methyl-pyridinium cations. Their conformations can be seen from Figure 11.

A,B,D-Capped calix[6]arenes
The aforementioned lower-rim A,C,E-capped calix[6]arenes all were prepared from 1,3,5-trimethylated *p-tert*-butylcalix[6]arene. No one investigated the reaction of capped reagent with *p-tert*-butylcalix[6]arene itself and didn't know what happens. We found that heating a mixture of *p-tert*-butylcalix[6]arene and 1,1,1-tris(tosyloxyethoxyethoxymethyl)propane in refluxing THF in the presence of K_2CO_3 as a base, a *p-tert*-calix[6]-1,4-crown ether with a side chain terminated by a tosyloxy group **14a** and an asymmetric capped calix[6]arene, A,B,D-tripodal calix[6]cryptand **14b** were obtained in 43% and 5% yields, respectively [48]. It is important to note that heating **14a** under reflux in the presence of K_2CO_3 gave a small amount of compound **14b**. Using tetrakis(tosyloxyethoxyethoxymethyl)methane instead of 1,1,1-tris(tosyloxyethoxyethoxymethyl)propane in benzene using *t*-BuOK as a base, an asymmetric double calix[6]arene **14c** was obtained in 16% yield. **14c** is composed of a *p-tert*-butylcalix[6]arene and a A,B,D-tripodal calix[6]cryptand. This type of double calix[6]arene was never reported before. The structures of the new capped calix[6]arenes are shown in Figure 12.
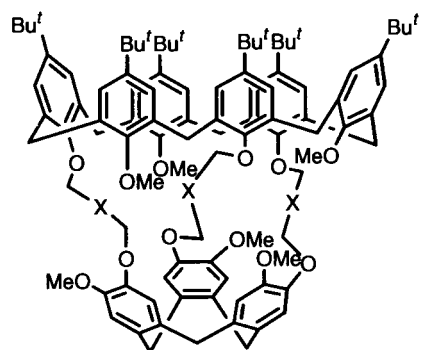
A,B,C-Capped calix[6]arenes
Although A,B,C-capped calix[6]arene has not been reported up to date, doubly A,B,C-capped calix[6]arene was known for a long time [49]. Reacting *p-tert*-butylcalix[6]arene with $ClPO(OEt)_2$, followed by heating the isolated product under vacuum to 330 °C afforded doubly capped *p-tert*-butylcalix[6]arene in 47% yield. The compound can be viewed as having two subunits, each formed by three proximal phenolic oxygen atoms capped by a phosphorus atom.

Depending on the mutual orientation of the two subunits, *syn* and *anti* conformers are possible. Another conformer based on the orientation of P=O moieties toward the cavity (*endo*) seems impossible as the P—O bond is too short. Phosphite doubly capped *p-tert*-butylcalix[6]arene was synthesized from *p-tert*-butylcalix[6]arene and PCl_3. A mixture of stereoisomers was obtained [50a] (Figure 13). The *syn* isomer could be separated in pure form, but this was not the case for *anti* isomer. The two isomers are noninterconvertible. The *syn* isomer was used to complex Pd, Pt etc. noble metal ions. The palladium complex exhibited activity in the copolymerization of carbon monooxide and ethylene [50b].
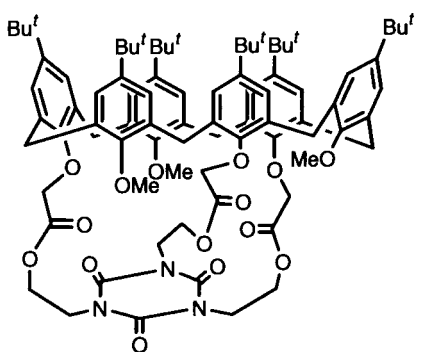
Tetrapterous capped calix[6]arene

Only one type of tetrapterous capped calix[6]arene has been known. Reacting 1,4-dialkylated calix[6]arene with 1,2,4,5-tetrakis(bromomethyl)benzene in the presence of Cs_2CO_3 in dilute solution, a series of four point capped calix[6]arene
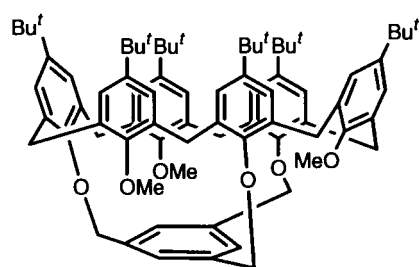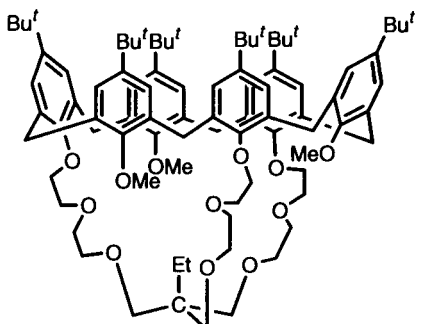
		X
12a₁₋₇:	**1:**	—
	2:	CH_2
	3:	$(CH_2)_2$
	4:	$(CH_2)_3$
	5:	$(CH_2)_4$
	6:	CH_2OCH_2
	7:	$(CH_2OCH_2)_2$

12a

12b

12c

12d
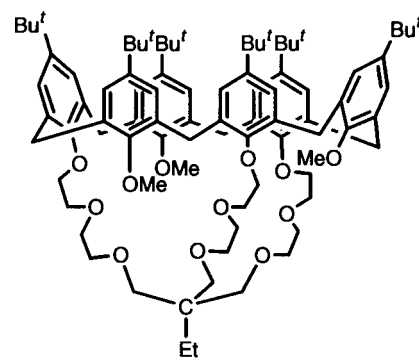
12e
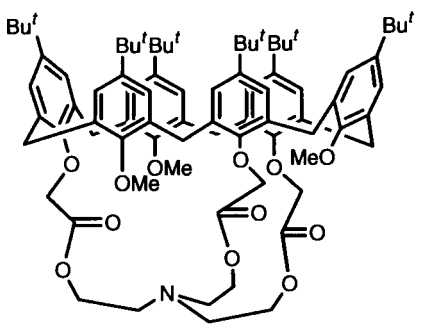
12f
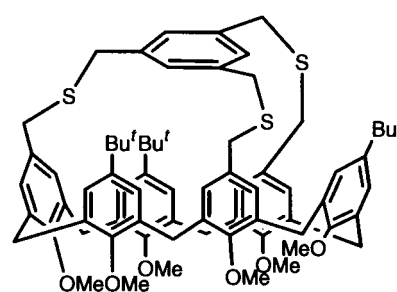
12g

Figure 10. C₃-Symmetrical capped calix[6]arenes.

R = C₈H₁₇

13a

R = C₈H₁₇, R' = H, CH₃

13b
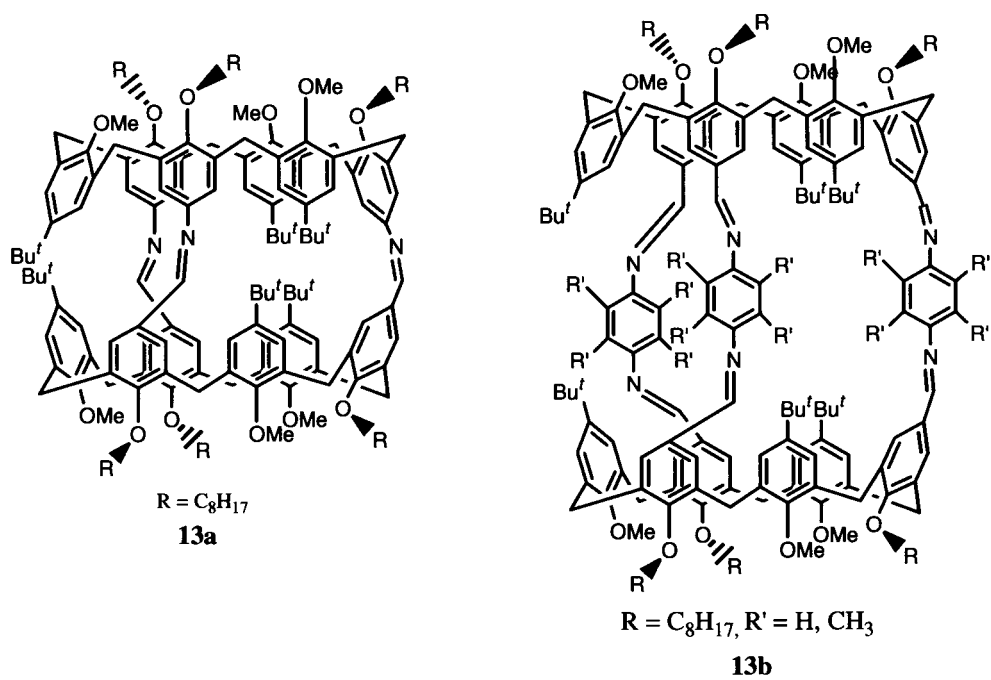
Figure 11. C$_3$-Symmetrical capped double calix[6]arenes.

14a

14b

14c
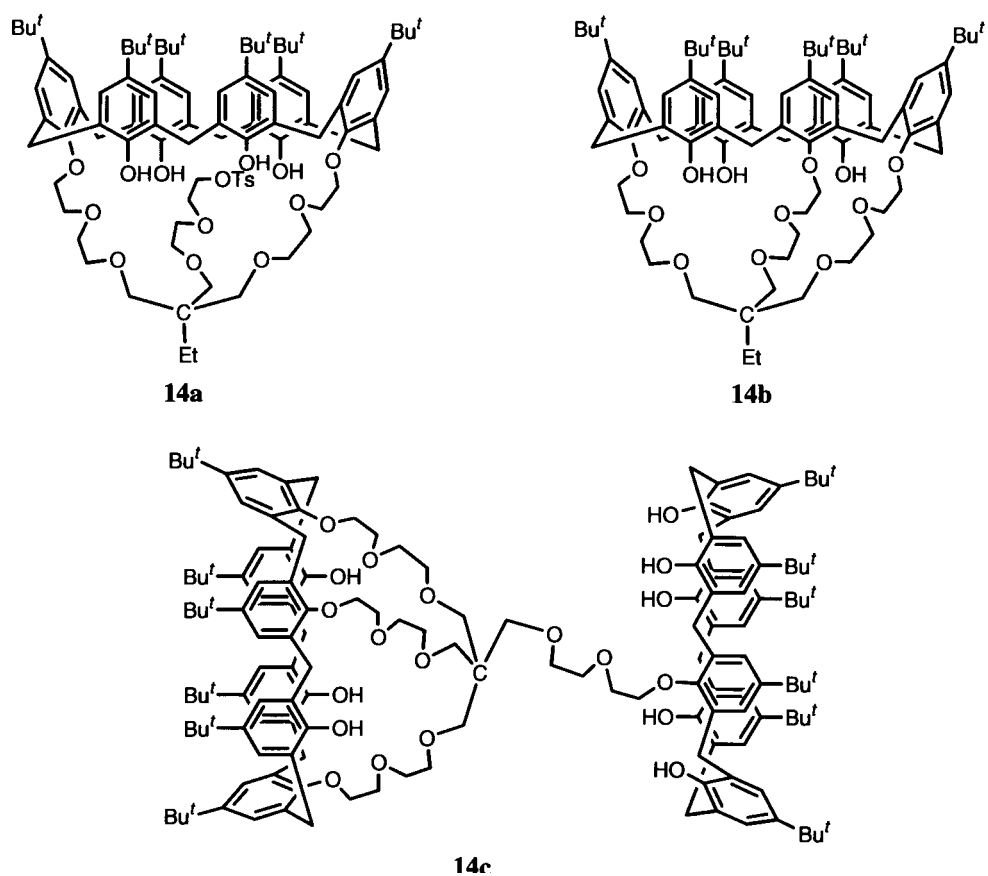
Figure 12. A,B,D-capped calix[6]arenes.

syn conformer of **15**

15a: X = P=O
15b: X = P

exo   *endo*   *syn* conformer   *anti* conformer
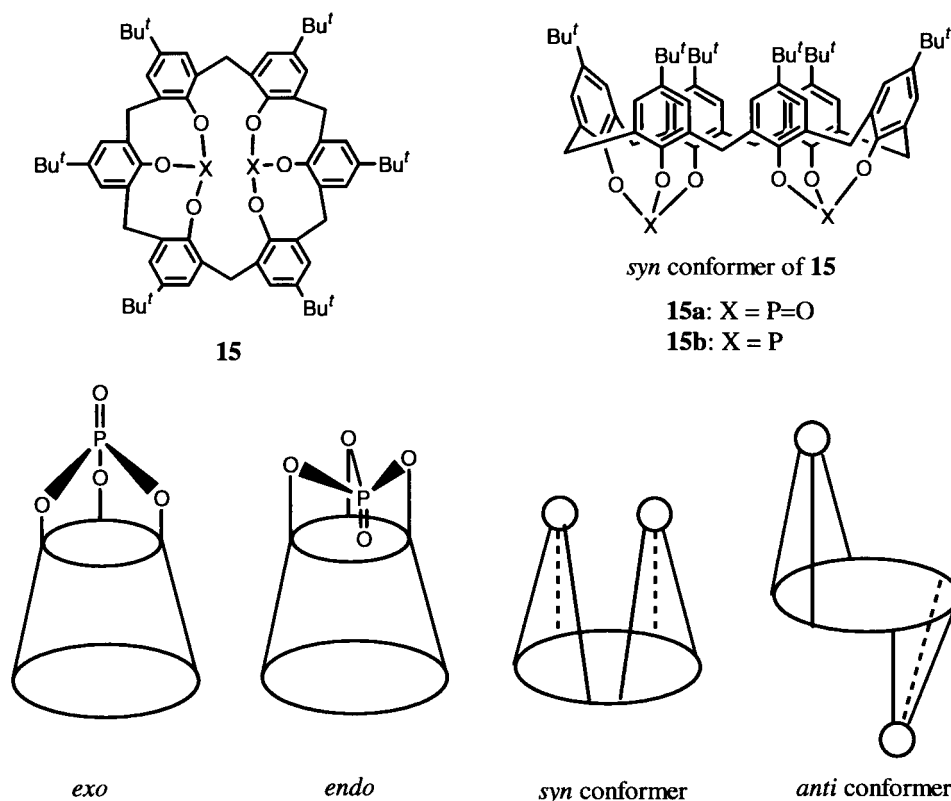
Figure 13. Phosphate and phosphite doubly capped *p-tert*-butylcalix[6]arenes.

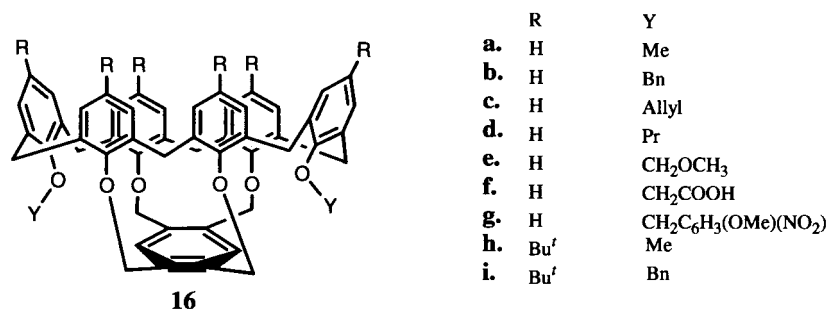|	R	Y
a.	H	Me
b.	H	Bn
c.	H	Allyl
d.	H	Pr
e.	H	CH_2OCH_3
f.	H	CH_2COOH
g.	H	$CH_2C_6H_3(OMe)(NO_2)$
h.	Bu^t	Me
i.	Bu^t	Bn

Figure 14. Tetrapterous capped calix[6]arene.

16 were obtained in high yield [51a,b] (Figure 14). The reaction proceeded without much difference regardless of the size of the R groups, suggesting that R groups were situated outward when the capping reaction took place. The tetrapterous capped calix[6]arenes exhibited high extraction selectivity toward Cs^+ among alkali metal ions. As the 1,3,5-trimethylated calix[6]arene was inevasible material for the preparation of A,C,E-capped calix[6]arene, and the reaction products of 1,3,5-trimethylation of calix[6]arene were difficult to separate, the authors believed that the preparation of tetrapterous capped calix[6]arene is relatively simple and selecting tetrapterous capped calix[6]arene instead of 1,3,5-capped calix[6]arene as a Cs^+ selective ionophore is a good choice. The ion binding properties of 1,3,5-capped calix[6]arenes and the tetrapterous capped calix[6]arenas were carefully investigated (Table 4).

A PVC membrane containing tetrapterous capped calix[6]arene as active component was also prepared [51c].

Table 4. Percentage extraction of alkali picrates into dichloromethane at 25 °C [51b]

Host	E%				
	Li^+	Na^+	K^+	Rb^+	Cs^+
16a	0	0	0	36	96
16b	0	0	0	36	97
16c	0	0	0	35	96
16d	0	0	0	14	74
16e	0	0	0	35	98
16f	0	0	0	0	0
16g	0	0	4	37	97
16h	0	0	8	35	96
6-0 Et	11	50	86	89	100
12c	0	0	5	8	77

6-0 Et *p-tert*-butylcalix[6]arene hexaacetic acid hexaethyl ester; **12c** see Figure 10.
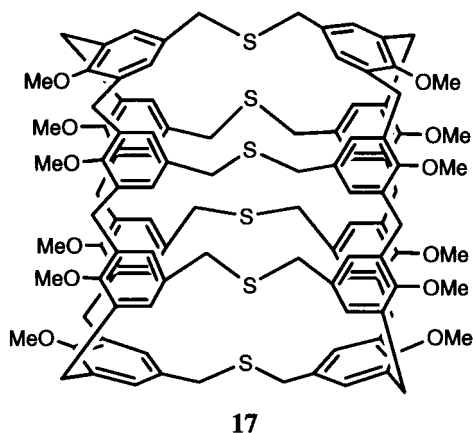
17

Figure 15. Hexapodous capped calix[6]arene.

Hexapodous capped calix[6]arene

As early as 1991, Shinkai synthesized a calix[6]arene-based molecular capsule [52]. By reacting 5,11,17,23,29,35-hexakis (chloromethy)-37,38,39,40,41,42-hexamethoxy-calix[6]arene with 5,11,17,23,29,35-hexakis(mercapto-methyl)-37,38,39,40,41,42-hexamethoxycalix[6]arene in *N*-methylformanilide/DMF mixed solvent in the presence of Cs_2CO_3 and $NaBH_4$, the molecular capsule **17** was obtained (Figure 15). The compound is capable of "constrictive binding" of a guest molecule (*N*-methylformanilide), and can be viewed as a hexapodous capped calix[6]arene in which each calix[6]arene plays a role of cap for the other. No other hexapodous capped calix[6]arene is known.

Summary

Remarkable progress has been made for bridged including capped calix[6]arenes. By carefully designing and selecting the bridging agent or capping agent and skilful use of solvents, bases, molar ratios of reactants etc., a series of new types of bridged including capped calix[6]arenes were synthesized and characterized, although this is far from maturity. It should be noted that some bridged calix[6]arenes possess new types of conformations other than cone or 1,2,3-alternate one and some bridged calix[6]arenes exhibit a potential to recognize and include larger species such as neutral organic molecules and cesium ions.

Acknowledgements

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