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*Accounts*

# Recent Topics on Functionalization and Recognition Ability of Calixarenes: The 'Third Host Molecule'

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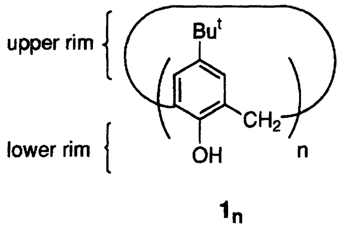
This review article covers recent topics of a calixarene family concerning their stereochemistry, complexation with metal ions and organic guests, and other topics. As stereochemistry of calixarenes, the restriction of flipping motions of the composed benzene units of calix[4]-, [5]-, [6]arenes is summarized. In Recognition of Calixarenes, the selective recognition of alkali metal cations utilizing calixcrowns is a main subject in metal cation recognition. Concerning with recognition of metal cations and organic molecules, the 'reading-out' systems of recognition phenomena are summarized. The complexation of calix[8]arene with fullerene, which was discovered as serendipity and will be very useful as a new fullerene purification method is also reported.

Calixarenes $\mathbf{1}_n$ are examples of $[1_n]$metacyclophanes which are composed of phenol and methylene bridge units (Chart 1). In the history of host–guest chemistry, calixarenes have attracted much interest because of their unique characters: (1) Calixarenes can be prepared from para-substituted phenols and formaldehyde which are commercially available at a reasonable price; the preparation affords calixarenes with the desired ring size selectively according to reaction conditions. (2) Calixarenes have cyclic phenolic hydroxyl groups which are useful for the building-up of the functionalized host molecules. (3) Calixarenes have several-sized $\pi$-rich cavities for including guest compounds. Table 1 shows the comparison of three representative host molecules, and calixarene has the advantage of complexation with both ionic and neutral guests compared with other two host molecules. Moreover, as described above, calixarene seems to be easy to derivatize to the more functionalized host molecules. These facts consistently suggest that host–guest chemistry using calixarene and their derivatives can develop the new area of supramoleculer chemistry.[1)] In this review article, we introduce recent topics concerning the stereochemistry of calixarenes, their complexation with metals and organic molecules, and other topics.



**1**$_n$

calix[n]arene

Chart 1.

## Stereochemistry of Calixarenes

**(1) Conformational Rigidification of Calixarenes.** It is reported that calixarenes change their conformations when they form complexes with guest molecules since calixarenes are composed of flexible benzene units.[2)] These results mean that calixarenes and their derivatives and classified as an 'induced-fit' type host molecule. If we can arrange the structure of calixarenes for the most suitable structure to complex with the specific guest molecules, we may obtain the most favorable receptors for the guest molecules (preorganization). Restrictions of conformational change have thus been investigated to obtain more finely preorganized host molecules. There seem to be two methods to restrict the flipping motion of

Table 1. Comparison of Three Representative Host Molecules

| | Cyclodextrin | Crown ether | Calixarene |
|---|---|---|---|
| Systematic change in the ring size | ○ | ○ | ○ |
| Large-scale preparation | ○ | ○ | ○ |
| Spectroscopic transparency | ○ | ○ | × |
| Neutrality under working conditions | ○ | ○ | △ |
| Optical-activity | ○ | △ | △ |
| Synthetic access to derivatives | △ | ○ | ○ |
| Functions as ionophores | × | ○ | ○ |
| Functions as cavity-shaped host | ○ | × | ○ |

○ denotes that the macrocycle already satisfies requirement; △ denotes that the requirement can be easily satisfied by simple modification; × denotes that it is especially difficult to satisfy the requirement.

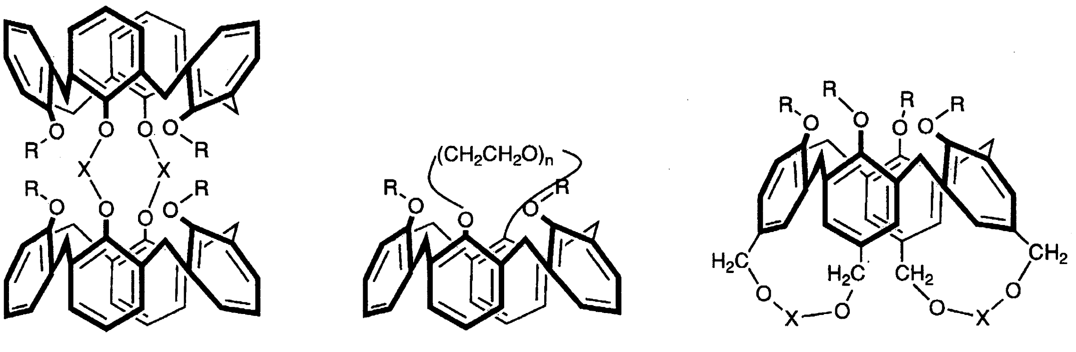


Chart 2.

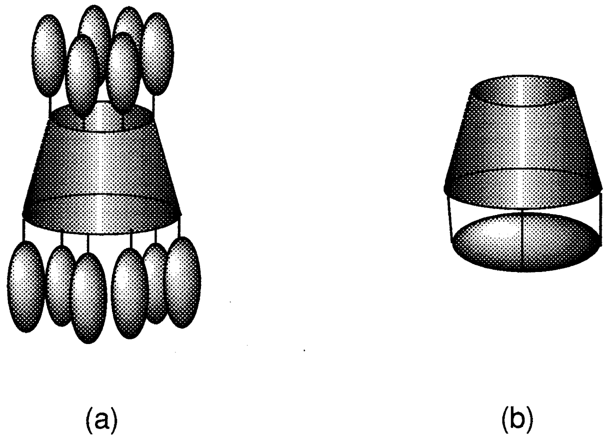
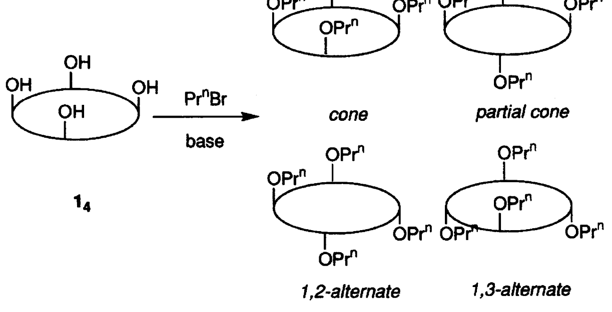

(a) (b)

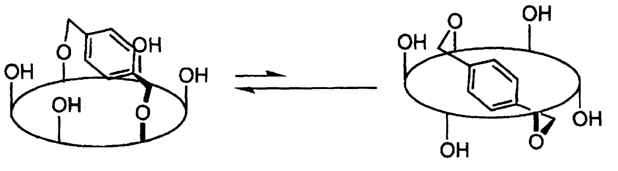
Fig. 1. Restriction of ring flipping: (a) To introduce bulky groups. (b) To bridge benzene rings intermolecularly or intramolecularly.



Scheme 1.

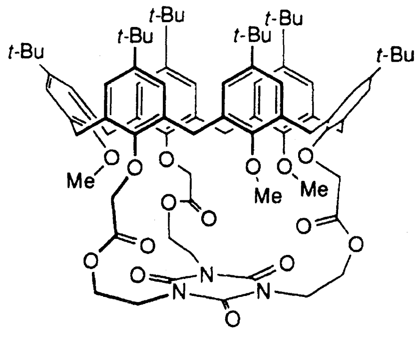
the benzene rings in calixarenes, as shown in Fig. 1: (1) To introduce bulky groups into both lower rim (hydroxyl group side) and upper rim (papa-position of hydroxyl groups). (2) To bridge each benzene ring intramolecularly or intermolecularly. For calix[4]arene, the para-substituent-through-the-annulus rotation is suppressed, so that alkoxy groups bulkier than ethoxyl group at lower rim are large enough to restrict the flipping motion.[3] According to this result, all possible conformers of tetraalkoxycalix[4]arene were synthesized (Scheme 1).[4] This synthetic method has enabled us to obtain the desired conformations of calix[4]arene derivatives according to molecular designs.

On the other hand, intra- and intermolecularly bridged calix[4]arenes whose flipping motion are restricted have also been reported.[5—8] 'Double calixarenes' **2**[6] composed of two intermolecularly bridged calixarene units are examples of conformationally frozen calix[4]arenes. 'Calixcrowns' **3**[7] are also classified as conformationally restricted calixarenes by bridging intramolecularly (Chart 2). Not only are their structures of interest but also their properties as host molecules. Synthesis of 'stapled' calix[4]arenes **4** whose neighboring benzene rings are bridged by 1,2- or 1,3-disubstituted benzenes at the upper rim was reported: In these stapled calix[4]arenes, conformational change is restricted, even though small methoxyl groups are attached to their lower rim.[8] To stiffen the conformation of calix[5]arene by introducing a bulky group into lower rim was also reported.[9]



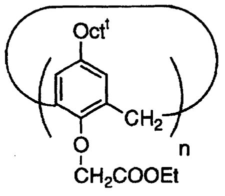
**5**

Fig. 2. Self-anchored rotaxanes **5**.



**7**

Chart 3.



**8**

Chart 4.

In the case of calix[6]arene, whose ring size is larger than calix[4]- and [5]arenes, a synthetic method to afford all possible methylated isomers of calix[6]arene at lower rim[10)] is presented; selective functionalizations of calix[6]arene at upper rim are also reported.[11)] However, bulky functional groups such as cholesteryl[12)] and *t*-butoxycarbonylmethyl group[13)] at lower rim can not restrict the flipping motion of calix[6]arene, because *t*-butyl groups at upper rim are not bulky enough to restrict the flipping motion from the upper rim side (i.e., the para-substituent-through-the-annulus rotation).[12)] To freeze the conformation of calix[6]arene, therefore, the intramolecular bridging of each benzene ring is considered to be a potential method. Gutsche and his co-workers reported that the bridging of two distal benzene rings of calix[6]arene by bifunctional aromatic rings at the lower rim affords self-anchored rotaxanes **5** (Fig. 2).[14)] This result shows that the intramolecular bridging of two benzene rings in calix[6]arene is not sufficient to freeze their conformation. We reported two types of 'capped' calix[6]arene: Capped by a tri-functional benzene ring **6**[15)] or an isocyanurate **7**[16)] at upper rim and lower rim, respectively (Chart 3). The flipping motion of benzene rings of these calix[6]arenes **6** and **7** are frozen due to steric hindrance of the capping functionalities: The direct evidence was obtained from their dynamic $^1$H NMR spectra and NOESY spectra. Hence, these capped calix[6]arenes are the first examples of the flipping-motion-restricted calix[6]arenes. Moreover, the wobble motion between the regular cone and the flattened cone, which is assigned as the stable conformer in tri-substituted calix[6]arene,[13)] was found in compound **6** (Figs. 3 and 4).[15)]

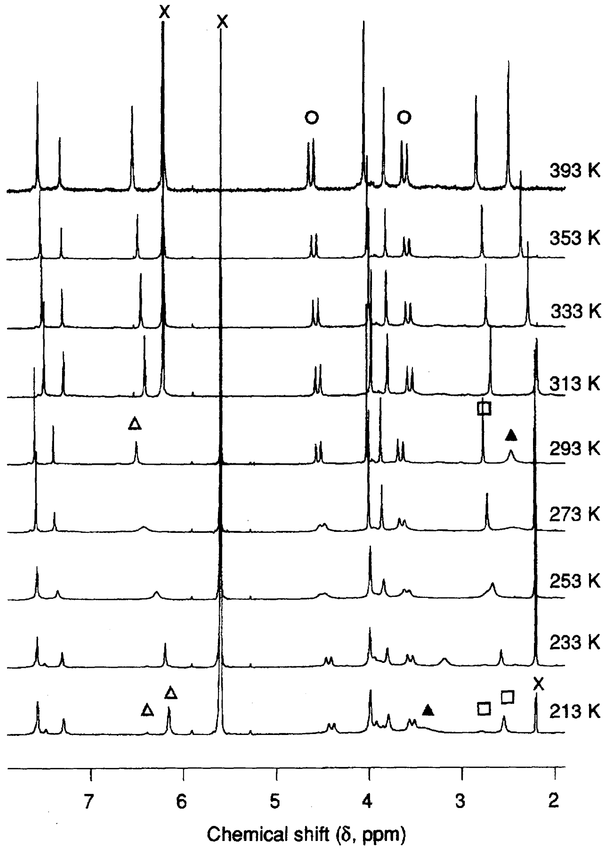
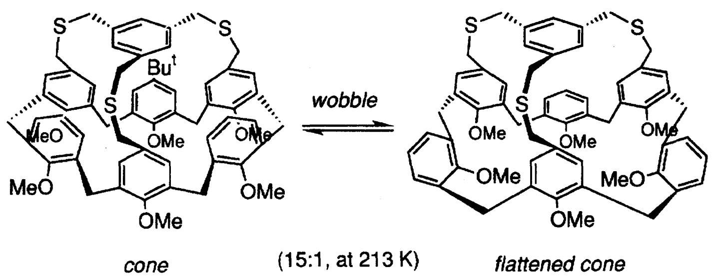


Fig. 3. Dynamic $^1$H NMR spectra of **6** (2.0 mol dm$^{-3}$) in $CD_2Cl_2$ (below 293 K) and $CDCl_2CDCl_2$ (above 293 K): (○) a pair of doublets for $ArCH_2Ar$, (△) ArH and (▲) OMe in the non-bridged phenyl units, and (□) OMe in the bridged phenyl units.

Recently, the positional selective functionalizations of calix[8]arene were reported.[17)] However, probably owing to its huge ring size and to complications in preparation of its derivatives, there is no report on conformational rigidification of calix[8]arene. This problem needs to be addressed in the future.

## Recognition of Calixarenes

**(1) Recognition of Metal Cations.** Alkali and alkaline earth metal ions play important roles not only in chemistry but also in biological systems. Recognition of such metal cations is one of the most interesting subjects in artificial host molecules. Many kinds of artificial receptors, such as crown ether derivatives for recogni-

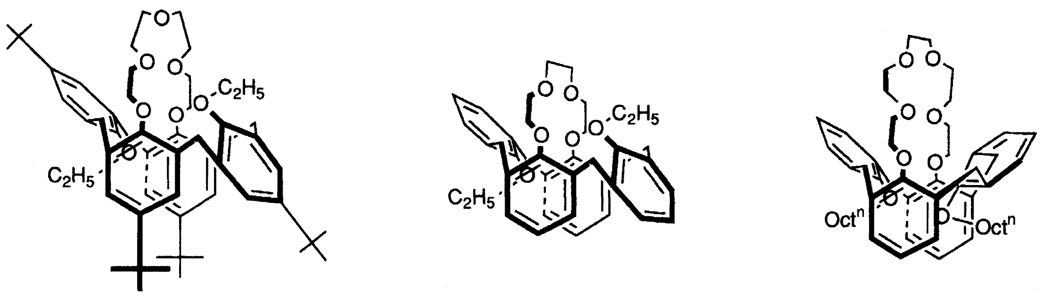


*cone* (15:1, at 213 K) *flattened cone*

**6**

(*tert*-Butyls are omitted for clarity)

Fig. 4. Conceivable motion of capped calix[6]arene **6**.



**9** **10** **11**

Chart 5.

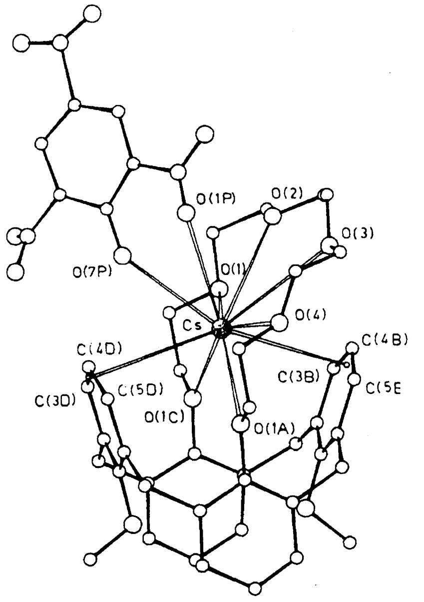


Fig. 5. X-Ray crystal structure of the complex of **11** and cesium picrate.

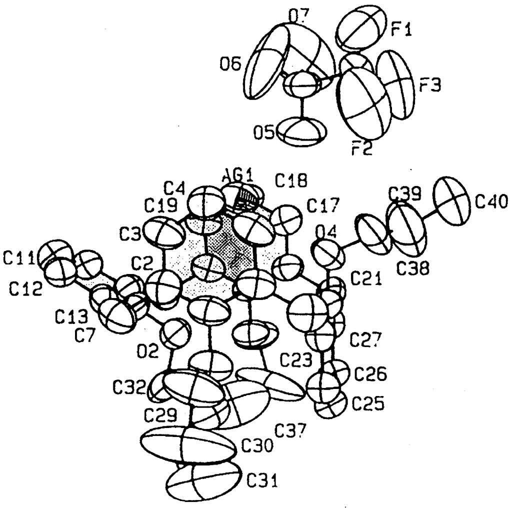
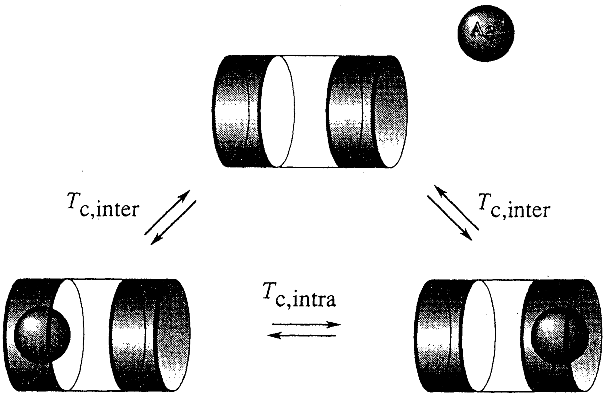


Fig. 6. X-Ray crystal structure of the complex of partial cone conformer of **12** and $AgCF_3SO_3$.

tion of alkali metal cations, have been prepared.[18] Also, there are many reports on recognition of alkali metal cations using calixarenes and their derivatives: However, although calixarenes have been used as a potential 'platform' for fixing binding sites, such binding sites in these calixarenes are not rigid enough to recognize metal cations strictly by only metal ion sizes.[1] After many turns and twists, the calix[4]arene based ionophore **8** achieved $10^{3.1}$ $Na^+/K^+$ selectivity (Chart 4).[19] Is there any strategy to break this selectivity? Valinomycin is produced by nature so as to selectively recognize $K^+$ in the presence of $Na^+$. It is known, however, that the highest selectivity is not for $K^+$ but for $Rb^+$.[20] This contrivance in nature teaches us that to discriminate larger $K^+$ from smaller $Na^+$ efficiently, the ionophoric cavity should be adjusted to a size slightly larger than $K^+$. According to this hypothesis, calixcrowns **9**,[7a)] **10**,[7b)] and **11**[21)] were prepared to design ionophores for $K^+/Na^+$, $Na^+/K^+$, and $Cs^+/Na^+$ selective electrodes (Chart 5). The selectivities of **9** and **10** are $K^+/Na^+=10^{4.07}$ and $Na^+/K^+=10^{5.3}$, respectively. Es-



Metal-Tunneling through a π-Basic Tube

Fig. 7. Schematic representation of the metal exchange in 1,3-alternate conformers of **12**.

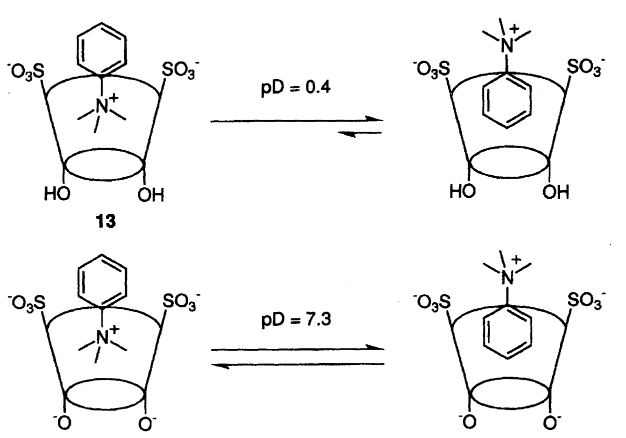
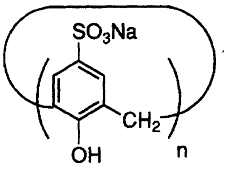


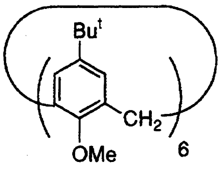
Fig. 8. Complexation of **13** with trimethylanilinium ions in acidic and neutral pD solution.



**13**: n = 4
**14**: n = 8

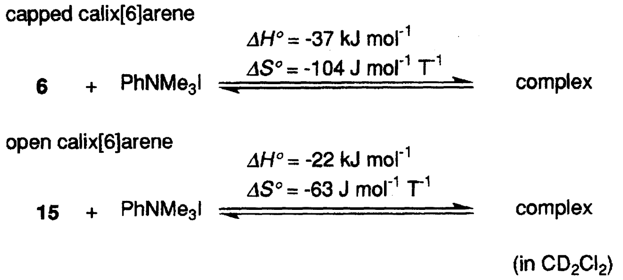
Chart 6.

pecially, the selectivity of **10** for $Na^+/K^+$ is higher by more than two orders of magnitude than the past data.[19] The selectivities of **9** for $K^+/Rb^+$ and **10** for $Na^+/Li^+$ are $10^{0.8}$ and $10^{2.4}$, respectively. These values mean that these selectivities $K^+/Na^+$ and $Na^+/K^+$ for **9** and **10** stem from the design of ionophores according to the hypothesis shown above. Since calixcrowns can only form 1 : 1 complexes with metal cations and the binding sites exist deeply in the cavity, this is the one of the reasons why such high selectivities are obtained. Furthermore, since $Rb^+$ and $Li^+$ ions are rarely found in nature, one can expect that these calixcrowns also useful for measuring $K^+$ or $Na^+$ ions in vivo. In calixcrown **11** with a longer bridge, more than 33000 times $Cs^+/Na^+$ selectivity was found in extraction of their picrate salts from aqueous phase to hexyl 2-nitrophenyl ether phase. Figure 5 shows X-ray crystallographic analysis of **11**·$Cs^+$ complex, interactions between $Cs^+$ and benzene rings are also observed.[21]

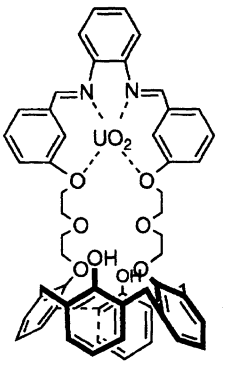


**15**

Chart 7.



Scheme 2.



**16**

Chart 8.

Recently, the structure of complexes of calix[4]arene derivatives with $Ag^+$ was determined by X-ray crystallographic analysis. Two distal benzene rings of partial-cone conformer **12** held the guest $Ag^+$, as shown in Fig. 6.[22] It is considered that this complex is stabilized by interactions between π-electrons of benzene rings and $Ag^+$, that is, cation-π interactions. Intramolecular tunneling of $Ag^+$ through the cavity of 1,3-alternate conformer of calix[4]arene is also observed in its dynamic $^1$H NMR: This was called "metal tunneling", as shown in Fig. 7.

**(2) Recognition of Organic Guest Molecules.** Calixarenes and their derivatives have cavities surrounded by benzene rings. When we introduce the functional groups such as sulfonate, phosphate, carboxylate, and trimethylammonium groups, which enhance solu-

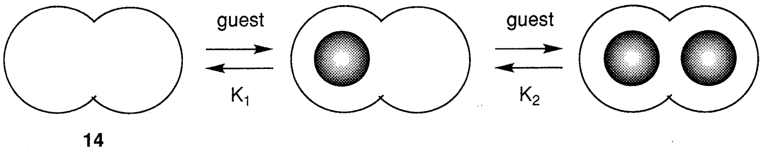


Fig. 9. Schematic representation of complexation of **14** and one and two molar of trimethylanilinium ions.

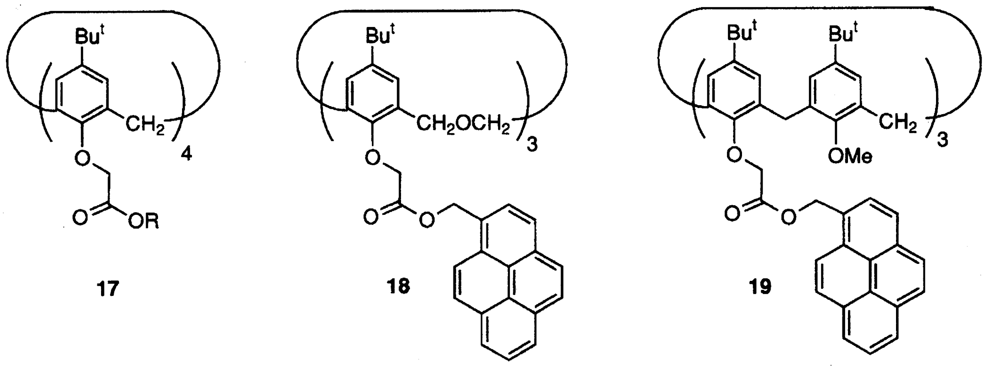


Chart 9.

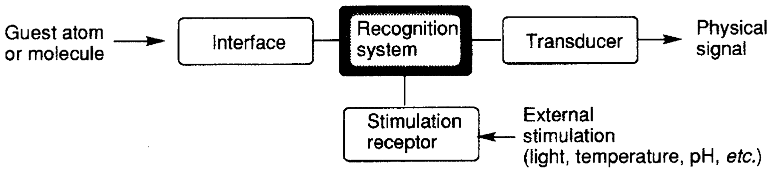


Fig. 10. Concept for 'reading-out' system of complexation.

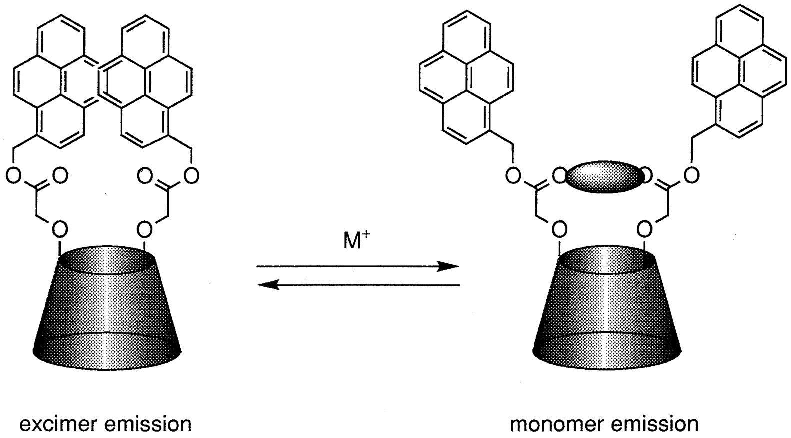


Fig. 11. Schematic representation of fluorometric sensing system of ammonium ions.

bility of calixarenes in aqueous media, water-soluble calixarenes may work as host molecules for organic guest molecules by use of their hydrophobic cavities as cyclodextrins do.[23—25] For example, the binding forms of water-soluble calix[4]arene **13** with trimethylanilinium ions change by pD (corresponds pH in $D_2O$) as shown in Fig. 8.[24] At pD=0.4 in acidic condition, phenolic hydroxyl groups are not dissociated; therefore, trimethylanilinium ions are included the cavity from the benzene moiety, which seems to be the most hydrophobic part of this molecule (Chart 6). On the other hand, in neutral condition (pD=7.3) one of phenolic hydroxy groups is dissociated, so that the basicity of benzene rings are increased, then trimethylanilinium ions can be included from the ammonium moiety in the cavity by cation–$\pi$ interactions. In the case of water-soluble calix[8]arene **14** which has a large cavity than other calixarenes, not only 1:1 complex but 1:2 complex with ammonium ions are formed (Fig. 9).[25] Inclusion of the large neutral molecule $C_{60}$ in **14** is also reported.[26]

On the other hand, as mentioned above, calixarenes have cavities surrounded by $\pi$-electrons so that one can expect that calixarenes form complexes with cations by cation–$\pi$ interactions, especially in non-polar media.[27]

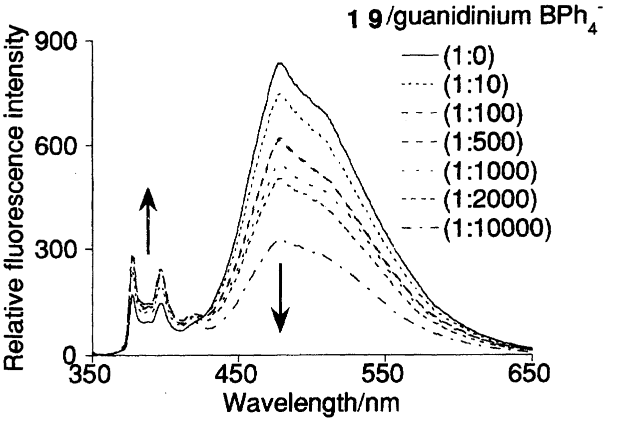


Fig. 12. Fluorescence change in **19** upon addition of guanidinium $BPh_4^-$ ([**19**]=$2\times10^{-6}$ mol dm$^{-3}$, 20 °C, in $CHCl_3$/THF (4 : 1 v/v), excitation 346 nm).

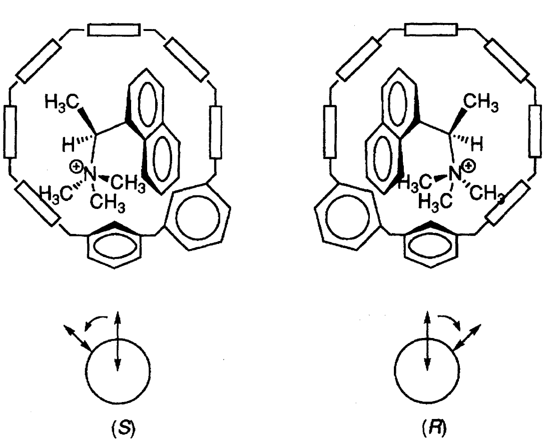


Fig. 13. Schematic representation of the complex of **14** and (*R*)- or (*S*)-1-(1-naphthyl)ethyltrimethylammonium ions viewed from the lower rim.

Recently, it was reported that cation-π interactions in complexation of hexamethoxycalix[6]arene **15** (Chart 7) with trimethylanilinium ions are enhanced by $C_3$-symmetrical capping of calix[6]arene **6** (Scheme 2).[15] The association constant *K* of **6** with trimethylanilinium ions is 60-fold larger than that of **15** at 200 K in $CD_2Cl_2$. This is the preorganization for complexing with $C_3$-symmetrical ammonium ion by building-up a rigid $C_3$-symmetrical π-rich cavity. Furthermore, the complexation and decomplexation velocities are slow enough to be observed by $^1$H NMR spectroscopy. This is the first example in which the complexation phenomena based on cation–π interactions can be demonstrated by NMR spectroscopy.

There are many reports on recognition of organic guest molecules such as primary ammonium ions by host molecules based on calixarenes.[28] For example, lower rim $C_3$-symmetrical capped calix[6]arene **7** is reported as a "preorganized receptor" for complexation of guanidinium ion.[16] Transport of urea by use of a complex of calix[4]arene with uranyl ion **16** is also reported (Chart 8).[29]

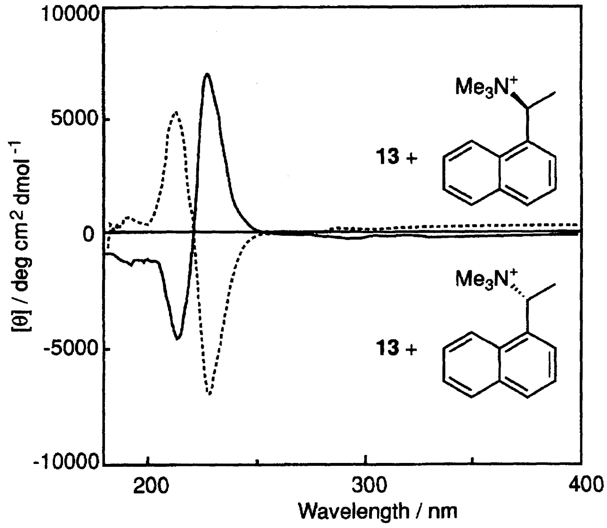


Fig. 14. ICD spectra of **14** (0.10 mmol dm$^{-3}$) in the presence of (*R*)- or (*S*)-1-(1-naphthyl)ethyltrimethylammonium iodide (0.10 mmol dm$^{-3}$) at 25 °C and pH 7.0.

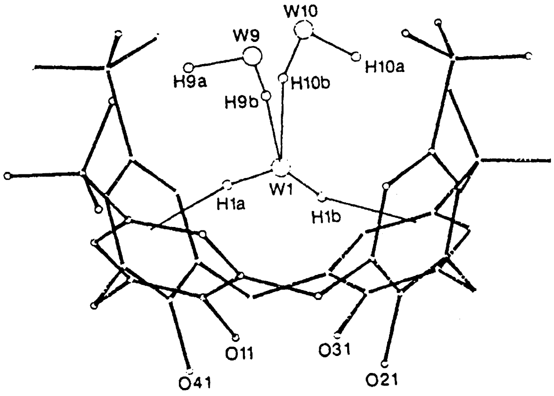
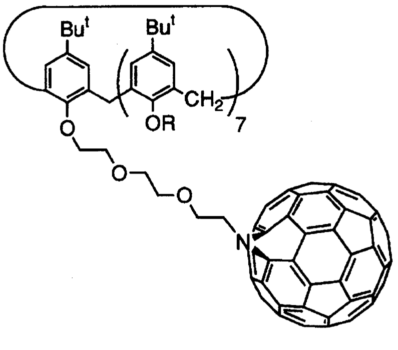


Fig. 15. X-Ray crystal structure of **13**·13.5 $H_2O$.

**(3) 'Reading-Out' of Complexation.** Recently, 'reading-out' systems for complexation phenomena were designed by use of functionalized calixarenes. These make it easier to monitor the binding event occuring at the recognition site. Figure 10 shows the concept for 'reading-out' system of recognition. The 'interface', which is built on the calixarene platform, selectively binds with the guest atom or molecule. Then the 'transducer' in the molecule changes the information of recognition from the 'interface' to the physical signal such as fluorescence change, color change, etc.

Calix[4]arene-tetraester derivative **17** is known to form a complex with alkali metal cations (Chart 9).[30] By use of this complexation, a fluorometric sensing system of alkali metal cations by use of pyrene or anthracene functionalized calix[4]arene-tetraester derivative is reported.[31] This system is based on included metal cations disturbing the intramolecular excimer formation of pyrenes or anthracenes (Fig. 11). By use of this system, fluorometric sensing for primary ammonium ions



**20**

Chart 10.

by $C_3$-symmetrical **18**[32] and for guanidinium ions by $C_3$-symmetrical **19** in the presence of ammonium ion[33] could be accomplished (Fig. 12).

It is reported that chiralities of chiral trimethylammonium ions and amino acid esters can be read-out by use of induced circular dicromism (ICD) of water-soluble calixarenes by complexation with these guest molecules in aqueous media.[34] Figure 13 shows conceivable structures of enantiomers of the complexes of water-soluble calix[8]arene and trimethylammonium ions. As shown in Fig. 13, the included chiral ammonium ions induce the chiral deformation of the calixarene ring: That is, benzene rings of calixarenes are arranged chirally. Then ICD spectra are observed in UV region even if the guest ammonium ions have very low absorption in the UV region (Fig. 14).

Reading-out of lithium ion,[35] calcium ion,[36] and uranyl ion[37] by color changes are also reported by use of the chromogenic calixarenes.

## Other Topics in Calixarene Chemistry

Buckminsterfullerene ($C_{60}$) has been attracting much attention because of its topological, physical, and chemical interests.[38] A severe limitation to this research is the cost for $C_{60}$, especially for its purification by column chromatography. Almost simultaneously, Atwood's group[39] and our group[40] found an epoch-making new purification method of $C_{60}$ by use of calix[8]arene which has enabled us to supply $C_{60}$ in more reasonable price. That is, a mixture of calix[8]arene and carbon soot containing 70—85% of $C_{60}$ in toluene forms green-yellow precipitates after being stirred for several hours. A suspension of the precipitates in chloroform affords $C_{60}$ as precipitates. Repeating this procedure for three times, $C_{60}$ can be obtained in 99.8% purity and 70% recovery.[40] This precipitate was confirmed to be a calix[8]arene·$C_{60}$ 1 : 1 complex by its elemental analysis. CP-MAS NMR studies of this complex show that $C_{60}$ exists in the calix[8]arene cavity in solid state.[40,41] Since the complex has not yet been found in solution state, it seems to be necessary for formation of this type of complex to include an irreversible process such as precipitation. The structure of the complex is still obscure, since the precipitate decomposes when it is solubilized in solution at high temperature. Very recently, 'calixfullerene' **20** (Chart 10), which is $C_{60}$ functionalized calix[8]arene and can form the intramolecular complex of $C_{60}$ into the calix[8]arene cavity, was synthesized to clarify the structure of the precipitate; its spectrometric properties were studied.[42] In the dynamic $^1$H NMR spectra of **20** in acetone-$d_6$/$CDCl_3$ (5 : 1), a new species assignable to a self-inclusion complex was observed.[43] This is the first example of inclusion of $C_{60}$ into the cavity of a host molecule in organic media.

Atwood's group found that calix[4]arene-tetrasulfonate **13** and $H_2O$ form a complex in solid state (Fig. 15).[44] The distance between the closest hydrogen atom of $H_2O$ molecule and the benzene ring is 2.38 Å. This value and direction shows hydrogen bonding between the hydrogen atom of $H_2O$ and a $\pi$-electron. This provides some evidence for XH–$\pi$ interactions, which are the important interactions found in biological systems.[45]

## Conclusions

In the past two decades, cyclodextrins and crown ethers have played 'leading roles' in host–guest chemistry. Cyclodextrins mainly include organic molecules, while crown ethers mainly bind metal cations and ammonium ions. As shown in this review, calixarenes and their derivatives can form selective complexes with both organic and inorganic guests. Furthermore, the artificial host molecules based on calixarenes can contribute to development not only of pure chemistry but also of material science and biology. Therefore, calixarenes can be called the "Third host molecules", following cyclodextrins and crown ethers (the first two host molecules).

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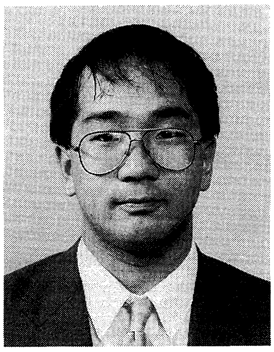

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