Novel Cavity Design Using Calix[*n*]arene Skeletons: Toward Molecular Recognition and Metal Binding

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Contents

I. Introduction

Calixarenes are macrocyclic molecules, like crown ethers and cyclodextrins.[1−7] Calixarenes made up of phenol and methylene units have many conformational isomers because of two possible rotational modes of the phenol unit: the oxygen-through-the-annulus rotation and the para-substituent-through-the-annulus rotation (Figure 1). The conformational isomers thus yielded afford a great number of unique cavities with the different size and the different shape. Recently, a number of strategies have been exploited by which not only the conformation of calix[4]arenes, but also those of calix[6]arenes and calix[8]arenes, can be immobilized. This means that our group can now design various calixarene-based receptors that show high selectivity for guest molecules and metal cations. In this review article, our group describe novel strategies for cavity design using calix[*n*]arene skeletons, strategies that are intended to allow complexation of specific molecular targets or metal ions.

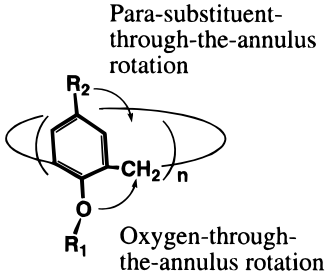

Figure 1. Two different modes for inversion of the phenyl unit.

II. Stereochemistry of Calixarenes

1. Conformers of Calix[4]arenes

Calix[4]arenes are cyclic tetramers made up of phenol and aldehyde units. Although each phenol unit can rotate according to the oxygen-through-the-annulus rotation mechanism, they favorably adopt a cone conformation because of the stabilization by intramolecular hydrogen-bonding interactions among OH groups.[8−10] Therefore, the *p-tert*-butylcalix[4]arene (**1**) adopts C_{4v} symmetry and has a π-basic cavity in the upper rim. In the crystalline state several kinds of solvent molecules are included in this cavity (toluene, acetonitrile, *etc.*).[11−13] In tetra-*O*-alkylated calix[4]arenes (**2**) the cone conformation is

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Seiji Shinkai was born in 1944 in Fukuoka, Japan, and received his Ph.D. in 1972 from Kyushu University, where he became a lecture soon afterwards. After postdoctoral work at the University of California, Santa Barbara, with Thomas C. Bruce, he joined Kyushu University in 1975 and became full professor there in 1988. He also worked at the director of Shinkai Chemirecognics Project (a government-owned project under the Japanese Research Development Corporation (JRDC)) (1990–1995). Currently he is also the director of Chemotransfiguration Project (JRDC). His interests focus on host–guest chemistry, molecular recognition, liquid crystals, and enzyme models.

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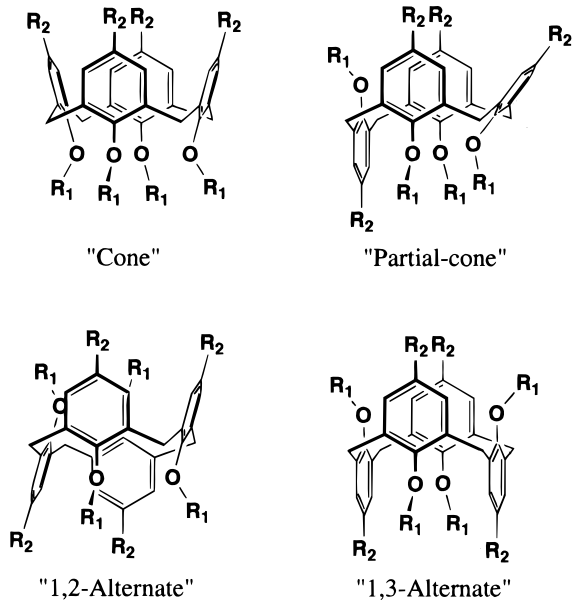
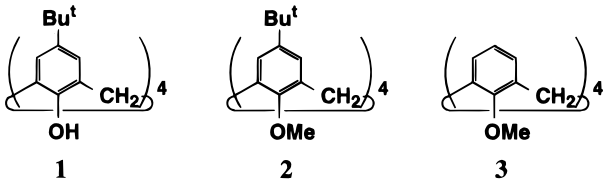


Figure 2. Four stable conformation of calix[4]arenes.

not necessarily stabilized because of the absence of such intramolecular hydrogen-bonding interactions.[1−7,14−20] Thus, one must take four different conformational isomers into account: they are "cone", "partial-cone", "1,2-alternate", and "1,3-alternate" (Figure 2).[1−7]

The conformational isomerism in tetra-*O*-methylcalix[4]arenes (**2**) is profoundly influenced by solvent, bound metal cations, and bound cationic guest molecules.[23−25] For example, a cone−partial-cone equilibrium in **2** is affected by the solvent polarity:[22] cone% linearly increases with the increase in the solvent-polarity parameter, $E_T(30)$. This is explained by a polar character of cone-**2** over partial-cone-**2**.



When $LiClO_4$ or $NaClO_4$ was added into $CDCl_3$/CD_3OD (4:1 v/v), new ^1H NMR peaks appeared that were assignable to cone-**2**·M^+ and partial-cone-**2**·M^+.[22] On the other hand, the spectra of partial-cone-**2** and 1,3-alternate-**2** were affected by addition of $KClO_4$ or $AgClO_4$. Ag^+ (and probably, K^+ also) is bound to the upper rim through the interaction with one or two oxygens and two benzene rings in these conformers (as shown in Figure 3).

Ungaro, Reinhoudt, *et al.*[26] reported that at −50 °C the ratio between cone, partial-cone, and 1,3-alternate conformations of calixcrown **4a** is 87:7:7, but in acetonitrile the most stable conformation of the **4a**·KPic complex is the 1,3-alternate (80%) and the partial-cone (20%) is next. On the other hand, in the case of **4b**·KPic the 1,3-alternate conformation is not detected, and the partial-cone and cone are present. The structure of **4b**·RbPic has been clarified by X-ray crystallographic analysis and the *p-tert*-butylcalixarene moiety has a conformation between

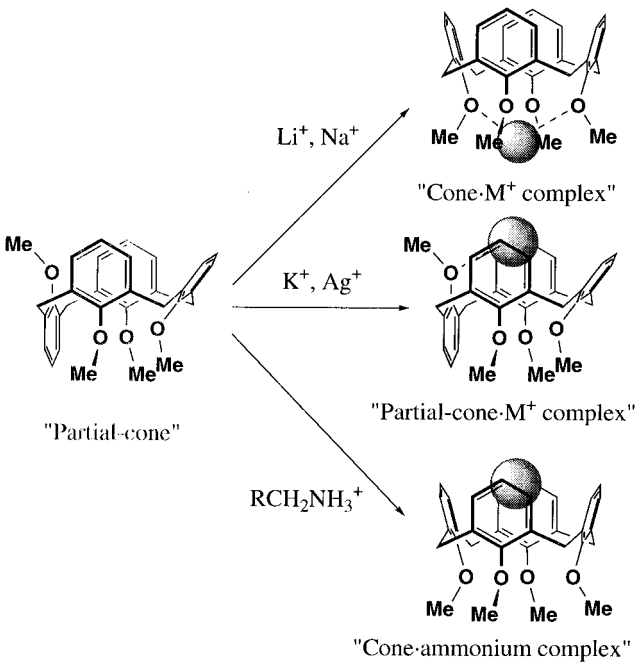
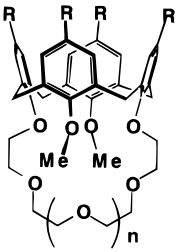


Figure 3. Inclusion of metal cation and of ammonium cation.

a cone and a partial-cone (*i.e.*, "flattened" partial-cone). On the other hand, when cesium picrate (CsPic) was added into CD_3CN solvent, new peaks appeared in ^1H NMR spectra, which were assignable to the 1,3-alternate-**5**·Cs^+.[27] The structure of **5**·CsPic has also been clarified by X-ray crystallographic analysis and the calixarene moiety has a 1,3-alternate conformation. These results indicate that conformer stability is affected by the size of bound metal cations.



4a R = H, n = 1
4b R = *tert*-Bu, n = 1
5 R = H, n = 2

A calix[4]arene **3** includes ammonium ions in the cone cavity that is composed of four benzene rings.[24] These cationic guest molecules are included in the π-basic cavities of **3** owing to the cation−π interaction. In $CDCl_3/CD_3CN$ (10:1 v/v) at −50 °C, **3** exists as a mixture of cone (31%) and partial-cone (69%). Addition of *N*-methylpyridinium iodide increases the fraction of cone-**3** up to 67%. It was observed that the chemical shifts for cone-**3** are significantly influenced by added *N*-methylpyridinium iodide, whereas those for partial-cone-**3** are not. The results clearly indicate that the cationic guest is selectively included in the cone cavity and that the preorganization of benzene rings is indispensable to the appearance of the "cation−π interaction".

2. Immobilization of Calix[4]arene Conformations

Tetra-O-alkylated Calix[4]arenes

The four conformers of **6** can be prepared from the reaction of **1** with *n*-PrI.[25] These conformers were heated in 1,1,2,2-tetrachloroethane at the reflux temperature (147 °C) for 12 h, but isomerization of these conformers did not take place. The same result was obtained when the solution was refluxed for 3 days. Thus, the *n*-propyl group is bulky enough to inhibit the oxygen-through-the-annulus rotation and, therefore, tetra-*O*-propylation can result in conformationally immobile calix[4]arenes.

Computational studies predicted that even tetra-*O*-alkylated cone-calix[4]arenes do not adopt regular C_{4v} symmetry but C_{2v} symmetry with a "pinched" conformation (Figure 4).[28,29] In the ^{1}H NMR spectra of **6** at room temperature, however, the four phenyl units appear equivalent.[25,30−32] Hence, if the computational prediction is correct, it follows that the rate of $C_{2v}-C_{2v}$ interconversion is faster than the NMR time scale. The sole exceptional example is cone-**7** or cone-**8**; the ^{1}H NMR study of cone-**7** shows that the C_{2v}-symmetrical conformation with two nonequivalent phenyl units is observable even at 4 °C.[33,34] In this example, however, the $C_{2v}-C_{2v}$ exchange rate is slowed by the intramolecular hydrogen bonds between the carboxylic acid groups.[33] It was not clear, therefore, if conventional tetra-*O*-alkylated cone-calix[4]arenes really adopt C_2 symmetry in solution.

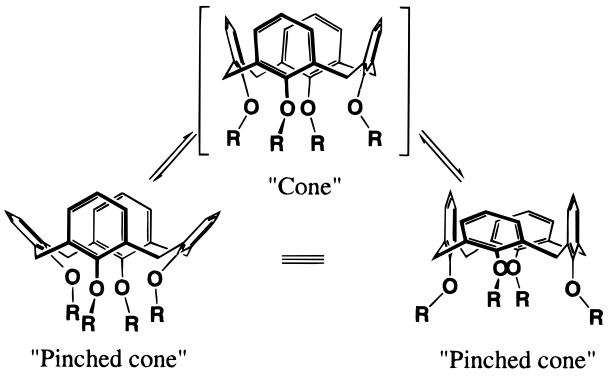
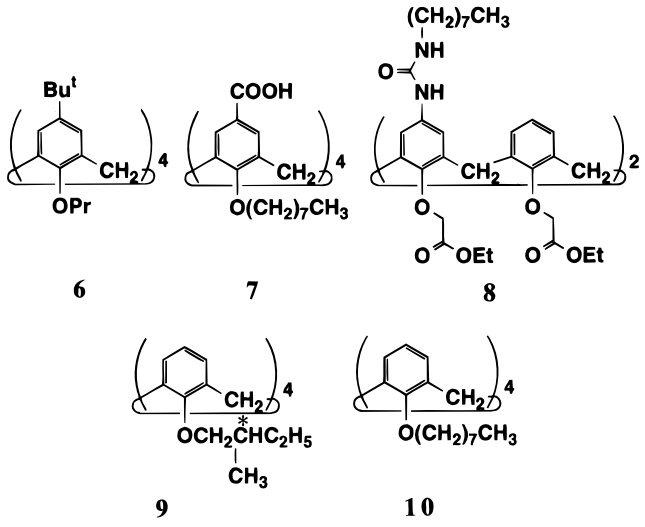


Figure 4. $C_{2v}-C_{2v}$ interconversion of tetraalkoxycalix[4]-arene in the cone conformer.

To find unequivocal evidence for C_2 symmetry the ^{1}H NMR spectra were measured at temperatures ranging from room temperature to −85 °C.[35] In the temperature-dependent ^{1}H NMR spectra of cone-**9** with (*S*)-2-methylbutyl groups, the signal for the *m*- and *p*-ArH protons appears as a singlet (*m*-ArH and *p*-ArH are overlapped accidentally) at 30 °C, whereas both *m*- and *p*-ArH give two peaks at −85 °C. The coalescence temperature (T_c) appears at −70 °C. The results clearly support the view that cone-**9** has C_2 symmetry in which two of the distal phenyl units are upright while the other two distal phenyl units are flattened and they interconvert in the NMR time scale. Ungaro *et al.*[36] also concluded that cone-**10** gives the coalescence temperature (T_c) at −57 °C and has a $C_{2v}-C_{2v}$ exchange. The slow exchange rate is probably due to the steric crowding on the lower rim.



The ^{1}H NMR spectrum of cone-**9** changes significantly on addition of Ag^+.[35] In cone-**9** a large downfield shift is observed for *m*-ArH and *p*-ArH, whereas the shift of the OCH_2 protons is relatively small. The result supports the view that Ag^+ resides in the π-basic upper rim cavity but not in the oxygenic lower rim cavity. Here, it is interesting to know whether Ag^+ bound to the π-basic upper rim cavity influences the rate of $C_{2v}-C_{2v}$ interconversion. The T_c in the absence of Ag^+ is −85 °C, whereas that in the presence of Ag^+ is −60 °C. The result implies that bound Ag^+ can really suppress the rate of $C_{2v}-C_{2v}$ interconversion.

In cone-**11**·$AgCF_3SO_3$ complex (Figure 5), Ag^+ ion is included in the π-basic benzene cavity at the upper rim but not in the oxygenic cavity at the lower rim (supported from the X-ray crystallographic data).[35] The four benzene rings are arranged in C_2 symmetry, the two distal benzene rings being flattened and the residual two benzene rings standing upright. These results show that the cone conformer can be preorganized for the binding of Ag^+ in solution.

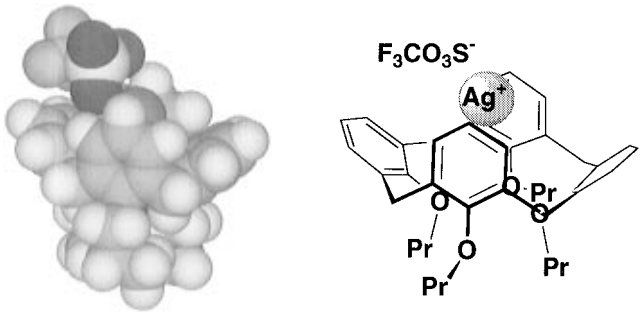


Figure 5. X-ray structure of the cone-**11**·$AgCF_3SO_3$ complex.

The inclusion ability of **11** was estimated with the use of **12** as a guest molecule.[24] Among four conformers the significant upfield shift was observed only for cone-**11**. Further evidence for inclusion of **12** in the cone-**11** was obtained from the NOE study (Figure 6). One can thus conclude that this cationic

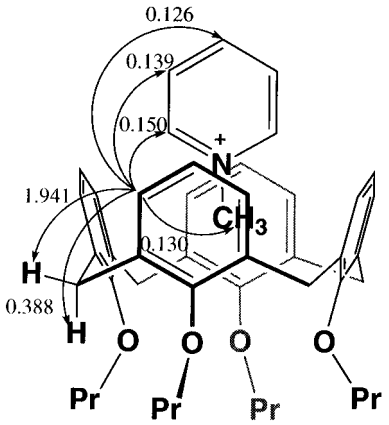
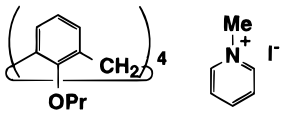


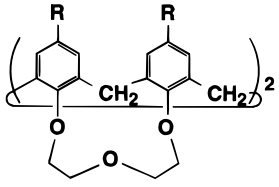
Figure 6. NOE peak intensities with respect to the *m*-ArH protons in cone-**11**.

guest molecule is included in the π-basic cavity of calix[4]arenes owing to the "cation$-\pi$ interaction".[27,36]



11 **12**

As mentioned above, tetra-*O*-alkylated cone-calix[4]arenes do not adopt regular C_{4v} symmetry but C_{2v} symmetry with a "pinched" cone conformation. Expecting that this residual mobility may affect the molecular recognition properties of calix[4]arenes, Ungaro *et al.*[37] tried to further rigidify calix[4]arene by functionalization of the lower rim. Complexation of nitromethane and malononitrile with *p-tert*-butylcalix[4]arene biscrown-3 (**13**) was studied by ^{1}H NMR spectroscopy. By adding variable amounts of the guest to a solution of the host in CCl_4, a significant upfield shift of the signal assignable to the CH protons of the guest can be observed. These shifts clearly show an interaction of the acidic protons of the guest with the electrons of the calixarene cavity. The X-ray crystal structure of the *p*-cyclohexylcalix[4]arene biscrown-3 (**14**)$-$nitromethane 1:1 complex shows that the host exists in a distorted cone cavity. In the solid state the nitromethane guest molecule lies inside the cavity and orients its N$-$$CH_3$ bond along the axis of the cone with CH_3 group faced on the aromatic nuclei of the host.



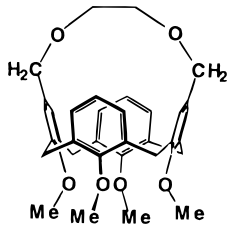
13 R = *tert*-Bu
14 R = cyclohexyl

As stated above, tetra-*O*-alkylated cone-calix[4]-arenes can bind the guest molecules or metal ions. Do the other three conformers, except for the cone conformer, have any ionophilic ability? Two-phase solvent extraction and determination of association constants by ^{1}H NMR spectroscopy for alkali metal cations established that 1,3-alternate- and partial-cone-**11** show an affinity higher than the cone-**11** for certain metal cations.[38] Detailed examination with ^{1}H NMR spectroscopy presented unambiguous evidence that in the 1,3-alternate-**11** the metal cation is bound asymmetrically to one of two metal-binding sites composed of phenolic oxygens in the inverted phenyl units and two benzene rings in the distal phenyl units. These metal-binding modes were rationalized in terms of the participation of "cation$-\pi$ interactions".

Bridged Calix[4]arenes

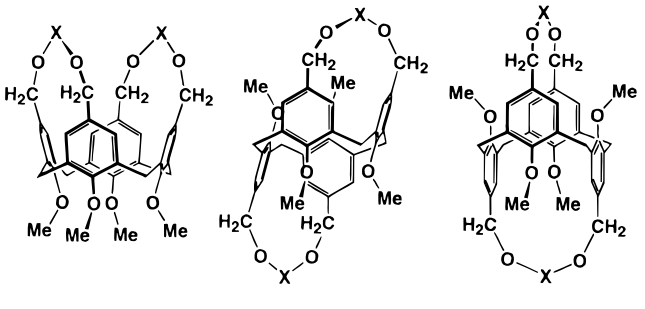
In the last decade, several articles have been devoted to the study of the upper rim cross-link.[39,40] In this section, our group are concerned with new methods other than *O*-substitution that immobilize the calix[4]arene conformation by cross-linking the upper rim.[41,42]

Reinhoudt *et al.*[41] reported calix[4]crowns **15** having a crown ether bridge at the upper rim. The ^{1}H NMR spectrum reveals that in solution **15** exists as a mixture of two conformations, *viz.*, the partial-cone and the cone (ratio partial-cone/cone = 4.0).



15

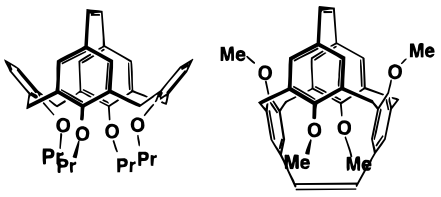
Compounds **16** and **17**, having double bridges at the upper rim, were isolated as two (1,2-alternate and 1,3-alternate) and three conformers (cone, 1,2-alternate, and 1,3-alternate), respectively.[45] To determine the three conformers of **16** and **17** isomerize, they were heated in $CDCl_2CDCl_2$ at 100 °C for 12 h. Analysis by ^{1}H NMR spectroscopy and HPLC established that they do not isomerize. One can conclude, therefore, that although compounds **2** are conformationally mobile, "stapled" **16** and **17** are conformationally immobile. Because of the presence of the



16; X =  **17**; X = 

asymmetric bridge unit, this "staple reaction" results in a *syn* isomer and an *anti* isomer, the latter isomer being classified as an inherently chiral calix[4]-

arene.[42,43] Compounds **18** and **19** also have conformation immobilized by cross-linking on the upper rim and can provide unique cavities.[44,45]



"Cone" "1,3-Alternate"

18 **19**

3. Stable Conformations of Dihydroxy-, Amino-, or Mercaptocalix[4]arenes

For the parent *p-tert*-butylcalix[4]arene (**1**), crystallographic and solution data both indicate that the most preferable conformation is the cone. On the other hand, calixarenes without OH groups or with other substituents such as hydrogen,[46−51] amino,[52,53] or mercapto[47,54−56] can exist in other conformations.

Biali,[46,48,50,51] Reinhoudt,[47] McMurry,[49] and coworkers reported the preparation of various dehydroxylated calix[4]arenes. As shown in Figure 7,

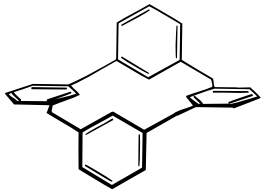
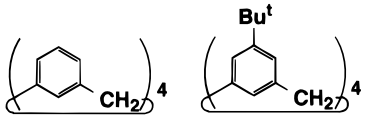
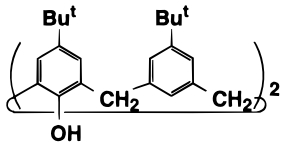


Figure 7. Calix[4]arene **20** in the chair conformation.

calix[4]arene **20** has none of the four conformations discussed above, but instead has an unusual chairlike conformation with two aromatic rings lying in a plane and the two other aromatic rings at right angles. When they pack together in the crystal, the individual molecules stack up like slightly offset chairs. Similar conformations were observed for **21** and **22**. These compounds, however, exist in a 1,2-alternate conformation with C_i symmetry in the crystal.



20 **21**



22

From *p-tert*-butylcalix[4]arene bis(diethyl phosphate) ester, diamino-*p-tert*-butylcalix[4]arene was synthesized in liquid ammonia cosolvent in the presence of KNH_2.[52] In $CDCl_3$ at −30 °C, **23** gives a pair of doublets for the $ArCH_2Ar$ protons.[53] This result indicates that **23** adopts a regular cone conformation. With rising temperature the peaks broaden and finally coalesce into one peak at 13 °C. This indicates that the rate of ring inversion of **23** is much faster than that of **1**. The difference is attributed to the loss of the cyclic hydrogen-bonding belt among OH groups or to the weak acidity of the NH_2 protons (in comparison to that of the OH proton).[53]

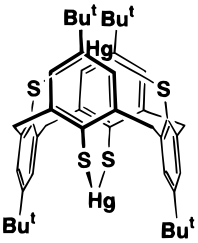
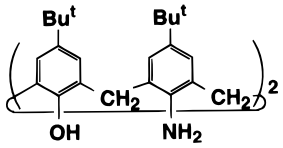


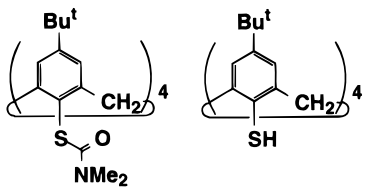
Figure 8. Conformation of **25**·2Hg^{2+} complex.



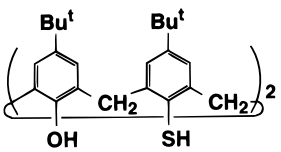
23

Gutsche *et al.*[54] succeeded in converting **1** to a tetramercaptocalix[4]arene derivative (**24**). The structure of compound **24** was determined to be a 1,2-alternate conformer by X-ray crystallography. On the other hand, the $ArCH_2Ar$ methylene protons in the ^1H NMR spectrum of **25** obtained from **24** (1,2-alternate conformer) showed a singlet. This can arise either from a rapidly interconverting set of cone conformers or from a 1,3-alternate conformer. That the latter is more likely is indicated by the invariance of the ^1H NMR spectrum down to −60 °C and by the X-ray crystallographic structure that shows **25** to be in the 1,3-alternate conformation in the solid state. This result has been rationalized by noting that replacement of all four OH groups in **1** with bulky SH moieties should makes **25** sterically more crowded favoring the 1,3-alternate conformation.

When mercuric acetate and **25** are mixed in 1:1 and 2:1 metal:ligand ratios in THF, rapid formation of the 1:1 and 2:1 complexes of Hg^{2+} occurs; they are isolated as pale-yellow crystalline solids.[56] The structure of the dimercury complex of **25** was investigated by X-ray study. From the precise structure determination ultimately performed on the true 2:1 complex (Figure 8), it has become apparent that two Hg^{2+} ions are indeed well encapsulated, with strong digonal binding, between two thiolate sulfur atoms.



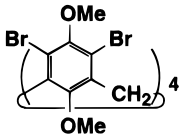
24 **25**



26

The structure of *p-tert*-butyl-1,3-dihydroxy-2,4-dimercaptocalix[4]arene **26**, which has two SH groups, was determined to be a cone conformation in the solid state by X-ray analysis.[57] On the other hand, the structure of the **26**·Hg^{2+} complex was found to be a 1,3-alternate conformation in the solid state.

Compound **27** was found to exist as the partial-cone conformer in solution (by ^{1}H NMR in $CDCl_3$).[58] Although the molecular mechanics simulation suggested that the partial-cone and the 1,3-alternate structures are of nearly equal energy (±5 kJ mol^{-1}), an attempt to generate the 1,3-alternate by heating **27** at reflux temperature in diphenyl ether solution (260 °C) was unsuccessful. This demonstrates that the mobility generally observed for conventional calix[4]arenes is effectively suppressed by substitution with bromine.



27

4. Immobilization of Calix[6]arene Conformations

Calix[6]arenes possess a cavity larger than calix[4]arenes and are probably more suitable to molecular recognition. However, the attempts to apply calix[6]arenes as hosts to specific molecular recognition[59−61] have so far been unsuccessful because of their large conformational freedom. Therefore, the understanding of their conformational and dynamic properties is very important. Calix[6]arenes possess eight possible conformational isomers: "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" (Figure 9). Gutsche *et al.*[59] thus commented reluctantly that "the calix[6]arenes are rather flexible and further insight into their mode of action must await the construction of more rigid and conformationally-defined analogs".

Hexa-O-alkylated Calix[6]arenes

Over the past few years, a considerable number of articles have been devoted to the studies of the conformations of calix[6]arenes in organic solvents.[55,62−66] The temperature-dependent ^{1}H NMR spectrum of the hexa-*O*-methyl ether of *p-tert*-butylcalix[6]arene (**29**) showed a pattern of sharp singlets down to −60 °C, indicating that **29** is conformationally mobile even at this low temperature.[62] On the other hand, the ^{1}H NMR spectrum of **30** is well resolved at room temperature, indicating that this derivative is considerably less conformationally flexible than the methyl ether derivative. The spectral data for **30** are commensurate with the 1,2,3-alternate conformation. As the temperature is increased above room temperature, the ^{1}H NMR spectrum of **30** becomes less well resolved, passing through a coalescence point at 61 °C and then sharpening to a spectrum of singlet resonances at 100 °C. The free-energy barrier for this conformational inversion is calculated to be 16.1 kcal mol^{-1}. It is postulated that when very bulky groups such as

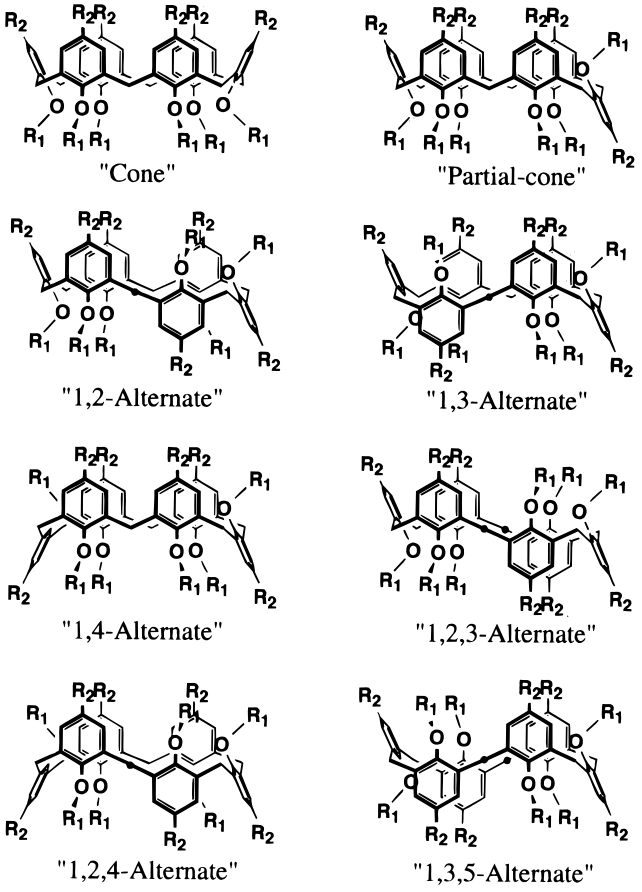
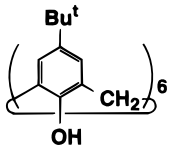


Figure 9. Eight possible conformation of calix[6]arenes.

trimethylsilyl are attached to oxygens in a calix[6]-arene, the preferred pathway for conformational inversion involves the rotation of the aryl rings in a direction that results in the para-substituent-through-the-annulus rotation.



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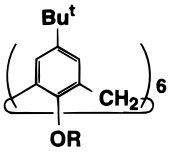
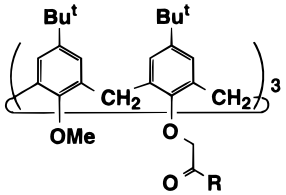


29 R = Me
30 R = $SiMe_3$

Ungaro *et al.* reported that unexpected compounds have comparatively stable cone conformations. The two ligands **31b** and **32** show ^{1}H and ^{13}C NMR spectra in accord with a cone structure.[67] The high



31a R = OBu^t
31b R = OEt
32 R = NEt_2

field shift of the methoxy groups, which absorb at around 2.2 ppm, indicates that these groups point inside the apolar cavity of the calix, experiencing

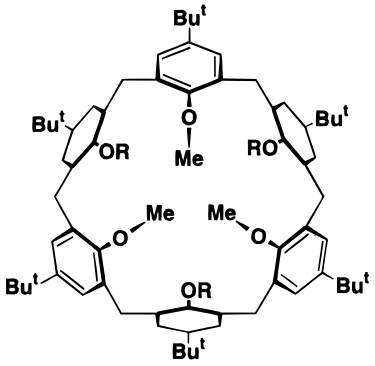
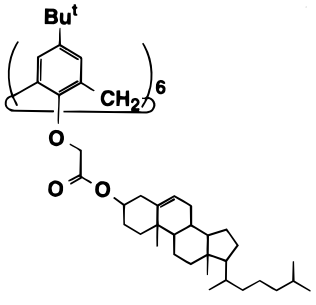


Figure 10. Conformation of compound **31** (R = CH_2-$CONEt_2$, or CH_2COOEt; flattened cone).

shielding by the π cloud of the aromatic rings. Therefore, the structure of compounds **31b** and **32** resembles a flattened cone structure (Figure 10). The spectra remain unchanged between 70 and −70 °C, indicating that the cone structure for compounds **31b** and **32** is stable in this temperature range. However, 2D EXSY data indicate that **31b** is not conformationally immobilized but that the rate of ring inversion is just slower than the NMR time scale.[68] The two ligands **31b** and **32** are not particularly effective in complexing alkali metal picrates in $CDCl_3$ (K_{ass} < 10^5 M^{-1}), whereas the triamide **32** complexes guanidinium ion very strongly (K_{ass} > 10^7 M^{-1}).[67]

To obtain evidence for the *tert*-butyl-through-the-annulus rotation in calix[6]arenes, the following experiement was carried out. The cholesteryl groups, which cannot pass through the cavity because of the bulkiness, were introduced into the OH groups in **28**.[69] At 30 °C, the $ArCH_2Ar$ methylene protons and the OCH_2CO methylene protons in **33** showed sharp peaks with a similar splitting pattern, indicating that **33** also adopts a 1,2,3-alternate conformation. At 130 °C, both methylene protons appeared as a broad singlet resonance. Since the oxygen-through-the-annulus rotation is sterically impossible, the spectral change unequivocally shows that the para-substituent-through-the-annulus rotation is operative in **33**; that is, the *tert*-butyl group can pass through the cavity. This conclusion clearly indicates that the conformation of calix[6]arenes cannot be immobilized as long as the *tert*-butyl group is used as a *para*-substituent.



33

Conformations of Calix[6]arene·Metal Complexes

It is known that **34** tends to adopt a 1,2,3-alternate conformation in the absence of metal cations. When the molar ratio between **34** and Na^+ is equal to 1.6, the ^1H NMR spectrum (at 25 °C) is very broad.[70] At

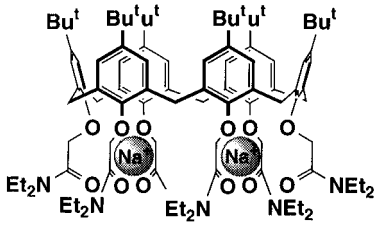
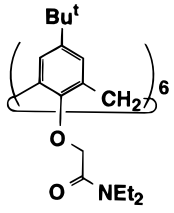


Figure 11. Schematic representation of the 1:2 complex of hexaamide calix[6]arene **34** and Na^+Pic^-.

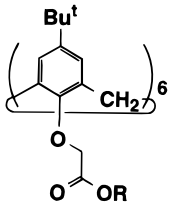
−25 °C it sharpens, showing only separate signals, and Ungaro *et al.*[70] assigned the signals to the free ligand and the 1:2 complex, respectively. Moreover, because the ^1H NMR spectrum of the 1:2 complex of **34** and Na^+ shows a very simple and symmetrical pattern, they concluded that the complexed ligand is in the cone conformation (Figure 11). Our group considered, however, that the true complex structure may be more complicated. The only direct evidence for the presence of two alkali metal ions per **34** was obtained from mass spectrometry.[70,71] It is necessary to study whether the complex of **34** and Na^+ is a 1:2 ratio, and whether the conformation of ligand **34** in the complex is in the cone conformation in solution.

The ^1H NMR spectrum of the 1:2 complex of hexaamide **34** with K^+ shows a more complex pattern than observed for 1:2 **34** plus Na^+, which rules out the formation of a cone structure for the complexed ligand.[70] This means that the binding mode for the large potassium cation is different from that for the sodium cation.



34

It is also known that **36** tends to adopt a 1,2,3-alternate conformation in the absence of metal cations, whereas it changes to a regular cone conformation with C_6 symmetry upon K^+ complexation.[68,69] This conformational change has been detected in by ^1H NMR spectra. The similar splitting pattern is also observed for the **36**·Cs^+ complex, indicating that the calix[6]arene skeleton in this complex also retains C_6 symmetry.[72] On the other hand, when K^+ is bound to **35**, the ^1H NMR spectrum becomes very compli-



35 R = Et
36 R = *tert*-Bu

cated: the ArH proton splits into three peaks, and both the $ArCH_2Ar$ protons and the $ArOCH_2$ protons give three pairs of doublets. In addition, the Et

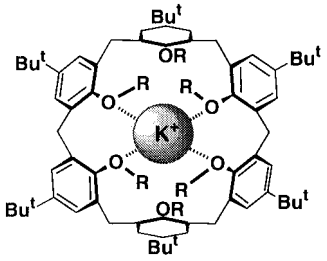


Figure 12. Proposed structure for the **35**·K^+ complex.

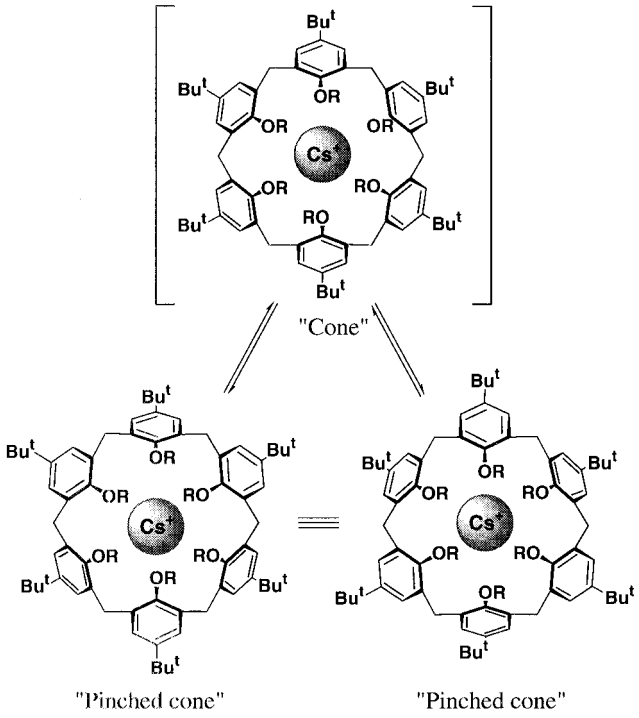


Figure 13. Proposed structure for the **35**·Cs^+ complex (C_{3v}−C_{3v} interconversion).

protons split into a 2:4 ratio, 2H at higher magnetic field and 4H at lower magnetic field. The splitting pattern suggests that the **35**·K^+ complex adopts a distorted cone with a lozenge-shaped ring in which two distal phenyl units are equivalent but inclined to one direction (Figure 12). The 2:4 splitting pattern of the Et protons suggests that 1,2,4,5-phenyl units are more flattened and strongly interact with K^+ while remaining 3,6-phenyl units relatively stand up and only weakly interact with K^+. When Cs^+ is bound to **35**, the ^{1}H NMR spectrum at 30 °C is consistent with a regular cone conformation (a pair of doublets for the $ArCH_2Ar$ protons), but it becomes more complicated at low temperature. At −30 °C peaks are split into two sets with a 1:1 ratio. The finding suggests that the **35**·Cs^+ complex adopts C_{3v} symmetry and 1,3,5-phenyl units and 2,4,6-phenyl units are interconverting in the NMR time scale (Figure 13). This situation is similar to calix[4]-arenes, which seem C_4 symmetrical from the ^{1}H NMR spectra at room temperature but actually are undergoing to C_{2v}−C_{2v} interconversion. Hence, it seems reasonable to consider that the "flattened" three alternate phenyl units interact with Cs^+ strongly, while the "standing up" three alternate phenyl units interact with Cs^+ weakly.

Doubly Bridged Calix[6]arenes

Cross-linking reagents (for example bis(bromomethyl) reagents) are useful not only as regioselective protecting groups of calix[6]arenes, but also as restricting groups of the conformational freedom. Gutsche,[73,74] Ungaro,[75] Okazaki,[76−78] Lüning,[79,80] and coworkers synthesized 1,4-bridged calix[6]arenes. Taking advantage of the earlier observation[75] that 1,4-diethers of calix[6]arenes are produced when a potassium base is used, *p-tert*-butylcalix[6]arene (**28**) is converted in fair to good yield (40−75%) to the 1,4-bridged ethers **37**−**39** by treatment with the appropriate bis(arylmethyl)halide in the presence of $KOSiMe_3$. The ^{1}H NMR spectrum of compound **37** shows singlets for OH, ArH of the bridging phenyl, and benzyl CH_2 protons; two pairs of very closely spaced doublets (2:1 ratio) for ArH of the calixarene phenyls; two sets of pairs of doublets (2:1 ratio) for calixarene CH_2 protons; and two singlets (2:1 ratio) for *p-tert*-butyl protons. A survey of the possible conformations for substituted calix[6]arenes[81] indicates that there is only one disubstituted calix[6]-arene that clearly possesses two sets of pairs of doublets (2:1 ratio) arising from the methylene resonances, *viz.* a 1,4-disubstituted calix[6]arene with the cone conformation. A 1,4-disubstituted calix[6]arene with the 1,4-alternate conformation might also possess two sets of pairs of doublets (2:1 ratio), but more likely would have only one pair of doublets along with a singlet (1:2 ratio). Therefore, the cone conformation is chosen as the more likely one for the bridged compounds **32**−**34**. This stands in contrast to the 1,2,4,5-tetraaroylates, which in an earlier investigation[81] were shown to exist in a 1,2,3-alternate conformation. It also stands in contrast to the 1,2,4,5-tetrakis(2-pyridylmethoxy)calix[6]arene, which is stated to exist in a 1,2,4-alternate conformation.[82]

Treatment of the bridged ring compounds **37** and **39** with MeI and NaH affords the corresponding tetramethyl ethers, **40** (from **37**) and **41** (from **39**), each isolable as a single compound.[73] The ^{1}H NMR of the tetramethoxy anthrylene-bridged compound **41** is quite similar to that of its precursor **39**, indicating that the starting material and the product have the same conformation; for example, both possess two sets of pairs of doublets for the calixarene methylene protons, which is commensurate with the cone conformation shown in Figure 14. The ^{1}H NMR spectrum of **40**, however, is quite different from that of

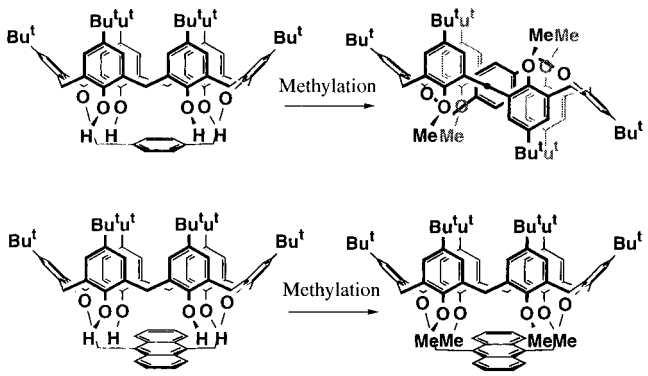
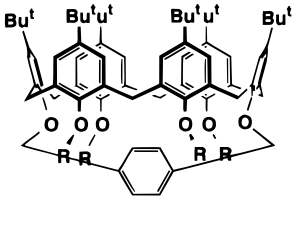


Figure 14. Methylation of the 1,4-bridged calix[6]arenes.

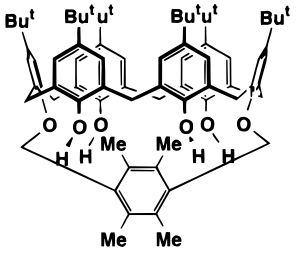
its precursor **37**. The ArH resonances of the bridged phenyl rings move upfield from 7.80 to 4.25 ppm, and the resonance of the CH_2 protons of the bridging moiety moves upfield from 5.15 to 4.57 ppm. The pattern for the calixarene CH_2 protons changes to a pair of doublets and a singlet (2:1 ratio); *viz.*, this pattern is commensurate with the 1,2,3-alternate conformation, as shown in Figure 14. A 1,4-disubstituted calix[6]arene with the 1,3,5-alternate conformation might also possess a pair of doublets and a singlet (2:1 ratio) but more likely would have only two singlets (2:1 ratio). Thus, the ^{1}H NMR spectrum of **40** appears to demand the same conformation as that adopted by 1,2,4,5-tetraaroylates of calix[6]-arenes. This rationale seems unlikely in the present case because this conformation requires the bridging moiety to be threaded through the annulus of the macrocyclic ring system. Such a conformation can be viewed as a rotaxane-type molecule (*i.e.*, an axle threads through a ring) in which the two ends of the axle are bonded to the ring (*i.e.*, a "self-anchored rotaxane"). The conformational difference in the bridged compounds **37**−**39** can be interpreted as the result of the relative size of the bridging moieties. Phenylene, the smallest of the bridges, should be the one most easily accommodated by the annulus; anthrylene the largest of the bridges, should be the one least easily accommodated; durylene, intermediate in size, is less easily accommodated than phenylene but more easily than anthrylene.

Okazaki *et al.*[76,77] reported that tetramethyl ether **42a** adopts a 1,2,3-alternate conformation with the central bromide functionality pointing into the cavity, as revealed by X-ray crystallographic analysis. On the other hand, the ^{1}H NMR spectrum of **42a** at room temperature shows complex and broadened signals. At high temperature above 120 °C, the signals are resolved and at 140 °C are observed as two *tert*-butyl resonances (ratio 2:1), a singlet for OMe protons, two pairs of doublets for $ArCH_2Ar$ methylenes (ration 1:2), and a singlet for $ArCH_2O$ methylenes. This spectral pattern indicates that at high temperature **42a** undergoes the flipping motion of the anisolic rings with the OMe groups passing through the annulus, which results in the equivalence of these rings in the NMR time scale. On the other hand, tetra-*O*-benzyl ether **42b** no longer rotates and results in two conformational isomers (cone and 1,2,3-alternate conformations).[78]

When the 1,3-phenyl units in calix[6]arene are bridged by a 4-methoxy-*m*-xylenyl unit, the product **43** is chiral, providing a compound suitable for testing the configurational stability.[83] The optical resolution of **43** was carried out with chiral column chromatography. Because of the high separation factor, it was possible to recover **43a** (first fraction) in 50% yield and 100% ee and **43b** (second fraction) in 49% yield and 99% ee. The CD spectra of two enantiomers are reciprocal to one another. Compound **43** was heated in various solvents for 12 h, and the racemization process was followed by an HPLC method. From the HPLC analysis of these solutions, it was confirmed that the racemization does not take place in any solvent. The finding unequivocally establishes that



37 R = H
40 R = Me



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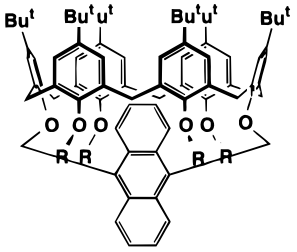
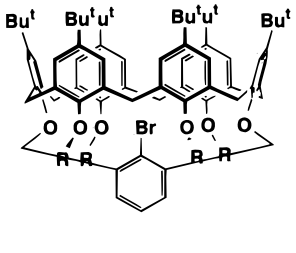


39 R = H
41 R = Me



42a R = Me
42b R = CH_2Ph

the ring inversion in **43** is inhibited (as shown in Figure 15). This is the first experimental evidence

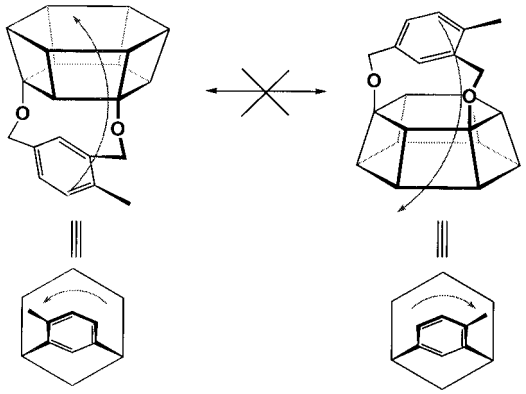
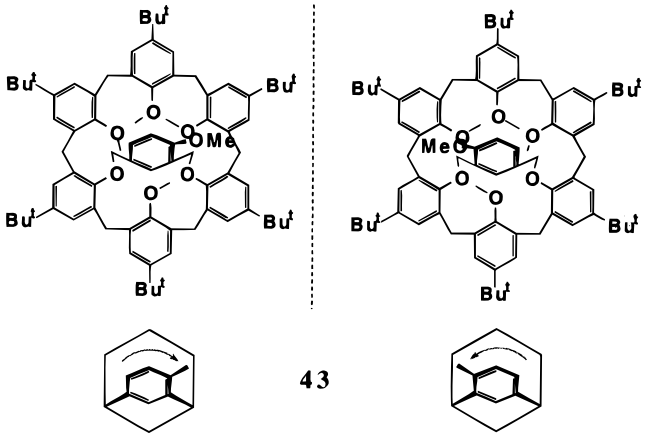


Figure 15. Schematic representation of a racemization due to a ring inversion in **43**.

that the calix[6]arene ring is truly immobilized on the laboratory time scale.



43

Multiply Bridged Calix[6]arenes

Multiple bridging of calix[6]arenes is expected to be more effective to limit the conformational mobility than double bridging. Several multiply bridged calix-

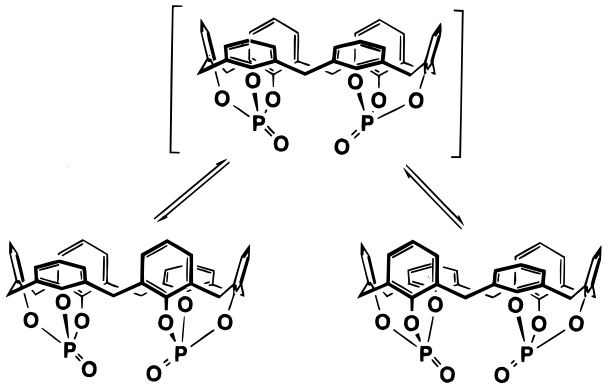
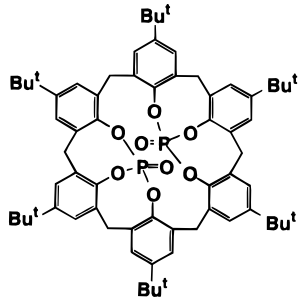


Figure 16. Flattened cone−flattened cone interconversion of **44** in a cone conformation. *tert*-Butyl groups are omitted for clarity.

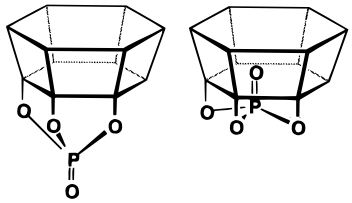
[6]arenes were synthesized and their conformational properties have been investigated.

The multiply bridged system **44** can be viewed as having two subunits, each formed by three proximal phenolic oxygens bridged by a phosphorus atom.[84,85] The compound displays a single singlet in the ^{31}P NMR spectrum. The ^{1}H NMR spectrum of the compound in $CD_3C_6D_5$ at 22 °C displays one sharp and two broad *tert*-butyl signals and two sharp and four broad doublets in the methylene region. Lowering the temperature results in sharpening of the broad signals, and six sharp doublets and three sharp singlets are observed at −23 °C for the methylene and *tert*-butyl groups, respectively. In principle, several stereoisomers are possible for this molecule depending on the conformation of the three rings attached to the phosphorus [toward the cavity (*endo*) **45** or away from it (*exo*) **46**] and on the mutual orientation of the two subunits (cone or 1,2,3-alternate conformation). The low-temperature NMR pattern is compatible only with a structure of C_2 symmetry in which the C_2 axis is perpendicular to the main macrocyclic plane, and therefore both subunits must be *syn* and the two P−O moieties must be both *endo* or *exo*. X-ray diffraction data of a single crystal of **44** grown in MeCN shows that the calixarene crystallizes in a conformation of approximate C_2 symmetry with five MeCN molecules. Both subunits exist in a conformation in which two rings are twisted with regard to the macrocyclic plane while the third ring is nearly coplanar to it (a "flattened cone"). The two "flattened cone" subunits of the macrocycle are *syn* to each other with the P−O bonds *exo* oriented (Figure 16).[86]

Conformational immobilization was attained by capping calix[6]aryl 1,3,5-tricarboxylic acid chloride with C_3-symmetrical triol.[87] The temperature-dependent ^{1}H NMR spectra of **47** was measured. At 40 °C a pair of doublets appeared, indicating that **47** adopts a cone conformation. The spectral pattern scarcely changed up to 110 °C. This implies that the rate of ring inversion, even if it occurs, is much slower than that of the NMR time scale. In **31a** which showed the similar temperature dependence, the rotation of the phenyl groups was evidenced by 2D EXSY in ^{1}H NMR spectroscopy: that is, the exchange between H_{ax} and H_{eq} in the $ArCH_2Ar$ methylene protons was clearly observed. To **47** the similar

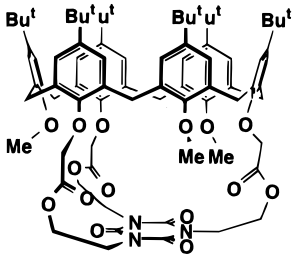


44



45 (*exo*) **46** (*endo*)

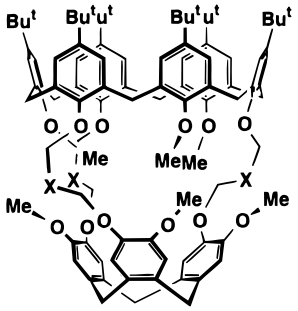
method was applied (NOESYTP with Time Proportional Phase Increment). Over the range 40−110 °C the correlation arising from the exchange between H_{ax} and H_{eq} was not observed. The result unequivocally indicates that **47** is firmly immobilized in a cone conformation; that is, flip−flop-type inversion of the "basket" cannot take place. It is known that **31a** binds guanidinium ion because of hole-size selectivity and C_3-symmetrical complementarity. It was considered that the capped, C_3-symmetrical cavity in **47** should bind guanidinium ion more strongly and via a kinetically slower process. Upon addition of guanidinium ion the ^{1}H NMR spectrum of **47** separated into two components assignable to the complex and free **47**, whereas that of **31b** did not separate but only displayed a change in the chemical shifts. This finding shows that the rates for the association and the dissociation of **47** and guanidinium ion are much slower than those for **31b**. The association constant (K_{ass}) for **47** was directly estimated from the ratio of the integral intensities to be 2300 M^{-1}. On the other hand, the K_{ass} for **48b** was determined from a plot of δ_H *vs* [guanidinium ion] to be 880 M^{-1}. The K_{ass} for **47** in which the functional groups for the guest binding are preorganized is larger by a factor of 3 than that for **31b**.



47

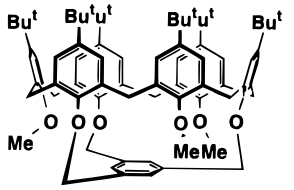
Reinhoudt *et al.*[88] prepared cryptocalix[6]arenes, which contain both a calix[6]arene and a cyclotriveratrylene unit. The ^{1}H NMR spectra of **48a**−**g** show two signals for the *tert*-butyl groups, two AB systems for the methylene bridges of the calix[6]arene skel-

eton and one AB system for the methylene bridges of the cyclotriveratrylene moiety. The methoxy groups of the calix[6]arene moiety are deeply embedded in the calix[6]arene annulus, as can be concluded from the large upfield shift of the signals by the ring currents of the aromatic rings. These features, together with the symmetry of the aromatic region, clearly prove the C_3 symmetry of these molecules. In order to investigate the dynamics of **48a**−**g**, variable temperature ^{1}H NMR spectra were recorded. The low-temperature ^{1}H NMR spectra of **48c**, **48d**, and **48f** clearly showed the existence of a minor conformer (B, partial-cone conformation) beside the major C_3 conformer (A, cone conformation), whose resonances coalesced upon raising the temperature. The upfield shift of one *tert*-butyl group of the minor conformer (B) indicates that one anisole moiety has rotated in such a way that its *tert*-butyl group is located in the cavity and is subjected to the ring current of the cyclotriveratrylene (CTV) aromatic system.



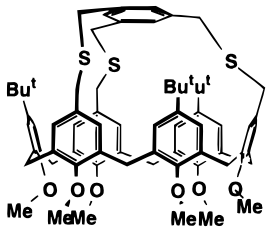
48 **a**; X = — **b**; X = CH_2
c; X = $(CH_2)_2$ **d**; X = $(CH_2)_3$
e; X = $(CH_2)_4$ **f**; X = CH_2OCH_2
g; X = $(CH_2OCH_2)_2$

In **49** direct evidence for immobilization is also obtained from 2D EXSY.[89] The result reveals that **49** is immobilized in a cone conformation, and that flip−flop-type ring inversion does not take place under the usual measurement conditions. Compound **49** possesses a capsulelike closed cavity. The study using ^{1}H NMR spectroscopy shows that **49** is capable of including Ag^+, Cs^+, RNH_3^+, *etc*.



49

A calix[6]arene (**50**) C_3 symmetrically capped at the upper rim was also reported.[90] Dynamic ^{1}H NMR spectra of calixarene **50** were measured in CD_2Cl_2 (below 20 °C) or in $CDCl_2CDCl_2$ (above 20 °C). Between −60 and 120 °C (in $CDCl_2CDCl_2$) **50** showed no chemical exchange but only positive NOE spectra between the two kinds of methylene protons. One can conclude, therefore, that there is no exchange in these protons, that is, no flipping motion occurs in the linked benzene rings of calix[6]arene **50**. As shown above, the capped calix[6]arene **50** has a rigid



50

C_3-symmetrical cavity composed of π-rich benzene rings. Therefore, such a cavity can act as a preorganized host molecule for inclusion of trimethylammonium ions by cation−π interactions. Nonbridged calix[6]arene **29** was used as a reference compound. The ^{1}H NMR spectra of **50** or **29** in the presence of trimethylammonium iodide ($PhNMe_3I$) were measured in CD_2Cl_2. The peak signals for $PhNMe_3I$ included in **50** appeared separately from those for free $PhNMe_3I$, indicating that the complexation−decomplexation velocity is slower than the NMR time scale. In contrast, addition of **29** did not result in separate $PhNMe_3I$ proton signals but only induced upfield shifts. At 0 °C, for example, the association constant (K_{ass}) for **50** is greater by a factor of 5.4 than that for **29**. The conformational immobilization of **50** results in preorganization suitable for complexation with ammonium ions such as $PhNMe_3I$ by cation−π interactions.

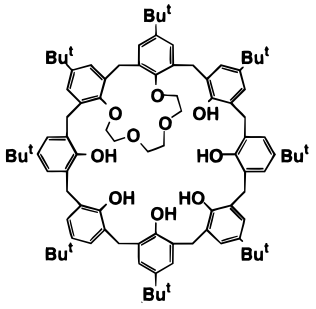
5. Immobilization of Calix[8]arene Conformations

The cavities of calix[8]arenes are large enough to capture various organic compounds. Calix[8]arenes can include ammonium ions,[24] fullerenes (C_{60}),[91−93] *etc*. In molecular design, however, our group frequently meet difficulties such as the regioselective synthesis of *O*-alkylation products and the restriction of immobilization of the conformational freedom. In the last few years, several articles have been devoted to regioselective *O*-alkylation[94−96] and conformation−immobilization of calix[8]arenes.

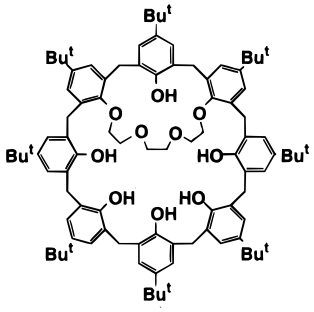
Bridged Calix[8]arenes

Recently, Neri *et al.*[97−99] reported that direct alkylation of *p*-*tert*-butylcalix[8]arene with oligo(ethylene glycol ditosylate)s affords calix[8]crowns with a bridging pattern dependent on the nature of the base used. 1,2-Calix[8]crown (**51**) was obtained when KH, K_2CO_3, or Cs_2CO_3 was used. 1,3-Calix[8]crown (**52**), and 1,4-calix[8]crown (**53**) were predominantly produced when K_2CO_3 or NaH was used, whereas 1,5-calix[8]crown (**54**) was predominantly produced when Cs_2CO_3 was used.[97] In ^{1}H NMR spectroscopy **51**−**54** gave broad signals. These results show that the monobridged calix[8]arenes are hampered by conformational mobility. Doubly crowned calix[8]arenes **55a** and **56a** were also synthesized.[98] The structure of the 1,5:3,7-calix[8]-biscrown-5 **56a** was assigned by ^{1}H NMR spectroscopy. The different resonances of the two crown bridges have to be ascribed to their different orientations with respect to the four benzylic substituents and, indeed, in the debenzylated com-

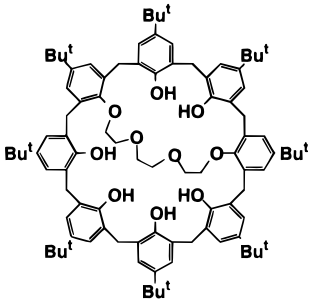
pound **56b**, which is conformationally mobile, they became completely equivalent.



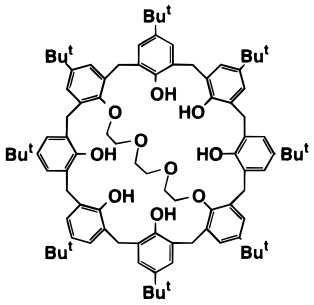
51



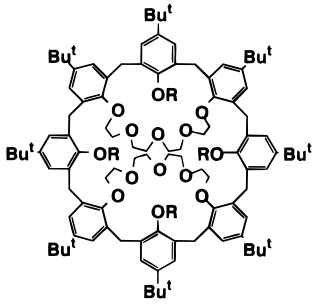
52



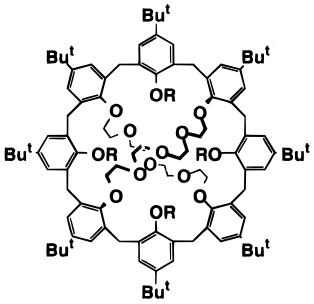
53



54

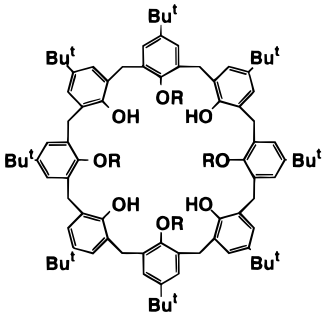


55a R = *p*-$CH_2C_6H_4Bu^t$
55b R = H

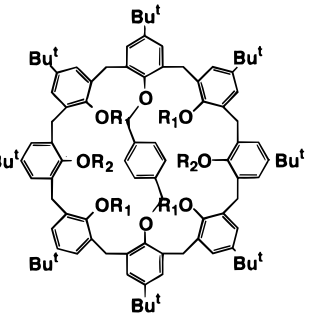


56a R = *p*-$CH_2C_6H_4Bu^t$
56b R = H

With the aim of the immobilization of the calix[8]arene conformation, the intramolecularly bridged calix[8]arenes **58** were synthesized by using more rigid bridging reagents.[100] In the ^{1}H NMR spectrum of the resulting compound, four *tert*-butyl signals (three *tert*-BuAr and one *tert*-$BuOCOCH_2$) were observed in a 1:2:1:2 ratio, indicative of a structure possessing two orthogonal twofold elements symmetry. This inference was substantiated by the presence in the methylene region of a pair of AB systems assignable to the methylenes of two $ArCH_2$-Ar groups in the calixarene rings, and three singlets of the same intensity attributable to the oxymethylenes of bridging and pendant groups and to the bromomethylenes of pendant groups. The presence of two AB systems for the bridging methylenes of the macrocycle in the ^{1}H NMR spectrum of **58** was the first evidence for a drastically reduced conformational mobility upon bridging. Dynamic NMR studies on **58** in $(CD_3)_2SO$ showed no hint of coalescence for these signals even at 117 °C, indicating the absence of conformational interconversion. Instead, an apparent coalescence at aound 67 °C was observed for the AB system of OCH_2CO protons. Cooling in $CDCl_3$ resulted in broadening of all the signals but no signal separation was observed down to −53 °C. These results can be interpreted by an assumption that a symmetrical averaged conformation, present above −23 °C, is frozen in an asymmetrical structure.

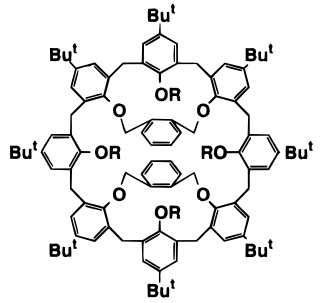


57a R = $CH_2CO_2Bu^t$
57b R = *p*-$CH_2C_6H_4Bu^t$
57c R = H

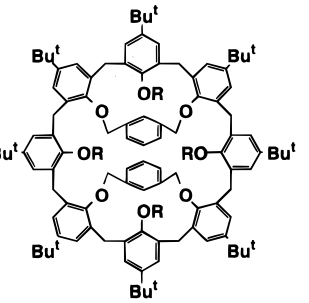


58 R_1 = $CH_2CO_2Bu^t$
R_2 = *p*-$CH_2C_6H_4CH_2Br$

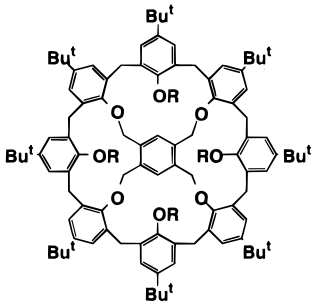
Meanwhile the high yields obtained in the 1,3-intrabridging with a *m*-xylene unit indicate that the aromatic rings at positions 1 and 3 are very close to each other, thus suggesting the possible formation of shorter bridges with *o*-xylene units.[88] In fact, the reaction of **57a** and **57b** with 1,2-bis(bromomethyl)-benzene afforded, respectively, **59a** and **59b** both in 98% yield, indicating that the *ortho* spacer is as well suited as the *meta* one. These two doubly bridged calix[8]arene derivatives have NMR spectral features in the 0.5−5.2 ppm region very similar to those of compounds **60a** and **60b**, indicating the same 1,3: 5,7-doublybridged structure. The reaction of **57a** with 1.2 equiv of 1,2,4,5-tetrakis(bromomethyl)benzene under the same conditions afforded the desired 1,3,5,7-bridged derivative **61** in 41% yield.[101]



59a R = $CH_2CO_2Bu^t$
59b R = *p*-$CH_2C_6H_4Bu^t$



60a R = $CH_2CO_2Bu^t$
60b R = *p*-$CH_2C_6H_4Bu^t$



61

The reaction of *p*-*tert*-butylcalix[8]arene (**57c**) with tetramethoxy-*p*-(chloromethyl)calix[4]arene (**62**) in the presence of CsF and NaI in refluxing acetone

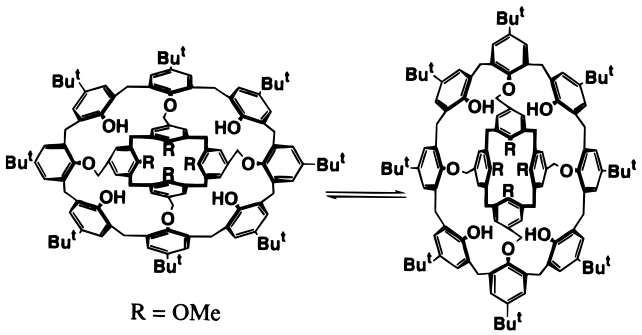
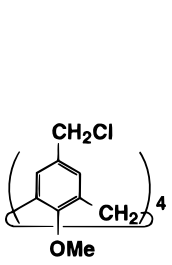


Figure 17. Conformation interconversion of calix[8]arene **63**.

under high dilution conditions gave a capped calix[8]arene **63** in 30% yield.[102] The ^{1}H NMR spectrum of **63** in $(CD_3)_2SO$ at 97 °C gives the two AX quartets of the methylene bridges of the calix[4]- and the calix[8]-arene units and therefore supports C_4 symmetry. The ^{1}H NMR spectrum of **63** in $CDCl_2CDCl_2$ at 57 °C is more complex. The most important feature of this spectrum is the presence of two signals for each group of protons belonging to the calix[4]arene unit, which is in agreement with C_{2v} symmetry. In particular, the two aromatic signals indicate a flattened cone conformation for this unit, in which the protons of one pair of aromatic nuclei are shielded by the anisotropic effect of the other pair. As a consequence of this particular conformational preference of the capping unit, the calix[8]arene macrocycle assumes a more elongated, elliptical conformation. On this basis the symmetry observed in $(CD_3)_2SO$ at high temperature can be explained as a fast exchange between two elliptical structures (Figure 17).



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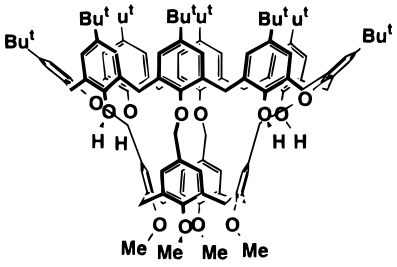


63

In a 1,5:3,7-doubly bridged calix[8]arene **64a** the central cavity is composed of eight phenolic oxygens.[103,104] This structure is basically classified into D_{2d}-symmetry. Four of the phenolic oxygens (1,3,5,7-bridged oxygens) adopt a tetrahedral arrangement and residual 2,4,6,8-oxygens (unmodified OH's) adopt a square-planar arrangement (Figure 18). Compounds **64b** and **64c** were synthesized from **64a**.

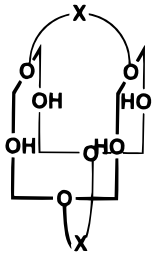
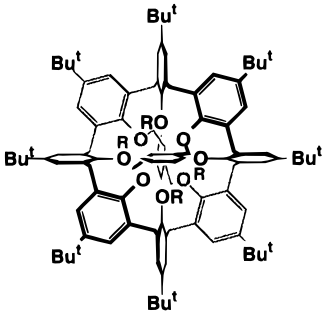


Figure 18. Schematic representation for the oxygen arrangement in **64a**.

Association constants (K_{ass}) for various metal ions were obtained from ^{1}H NMR spectroscopy. In THF-d_8/$CDCl_3$ (5:1 v/v) at 30 °C signals for the **64b**·M^+ complex (M^+ = K^+, Rb^+, and Cs^+; added as their tetraphenyl borate salts) appeared separately from those of free **64b**. The K_{ass} values were determined directly by comparing the integral intensities of these peaks: K_{ass} (M^{-1}) = 150 for K^+, 720 for Rb^+, and 5200 for Cs^+. On the other hand, the ^{1}H NMR spectrum of **64b** was scarcely affected by Na^+. Similarly, the ^{1}H NMR spectrum of the Cs^+ complex was scarcely changed by addition of an excess amount of other alkali metal cations (Na^+, K^+, and Rb^+), indicating that these metal cations are incapable of substituting Cs^+ bound to the **64b** cavity. These results establish the high Cs^+ affinity and the high Cs^+/Na^+ selectivity of **64b**.



64a R = H
64b R = Me
64c R = Et

III. Selectivity Changes and Reading-Out of Recognition Events

1. Selectivity Changes Induced by Conformational Changes of Calix[4]arenes

In compound **65**, two (anthryloxy)ethyl groups and two ethoxyethyl groups compose an "open" ionophoric cavity, whereas the cavity can be "closed" by photoirradiation.[105,106] The results of two-phase solvent extraction showed that **65** ("closed") has the high selectivity toward Na^+ (Figure 19). The increase in

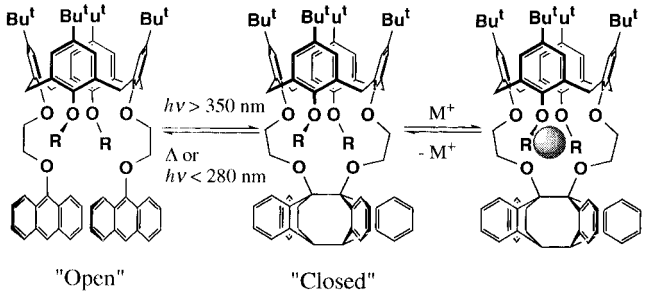
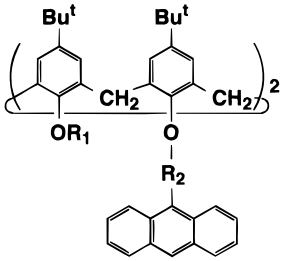


Figure 19. "Open" and "closed" ionopholic cavities of compound **65** (R = CH_2CH_2OEt).

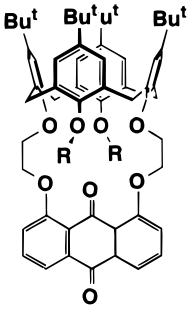
Ex % compared to **65** suggests that the ionophoric cavity is more preorganized for the size of Na^+ ion by photocycloaddition. On the other hand, in

compound **66** the Ex % for Na^+ was drastically reduced from 40.8% (**66**; "open") to 4.9% (dimeric **66**; "closed").[107]



65 $R_1 = CH_2CH_2OEt$
$R_2 = CH_2CH_2O$
66 $R_1 = CH_2COOEt$
$R_2 = CH_2COOCH_2$

Dougherty *et al.*[108] reported three examples of redox-switched calix[4]arenes having a basic structure **67**. Cyclic voltammetry was employed to evalu-



67a R = Me
67b $R = CH_2COOEt$
67c $R = CH_2CONEt_2$

ate the binding enhancements towards alkali-metal cations on one-electron reduction of the ionophores. The relationship $\log (K^*/K) = F(E_p - E_p°)/2.303RT$ was used to relate the ratio of binding constants of the ligand in the neutral (K) and reduced state (K^*) to the shift in peak potential in the presence of the metal cation, added as their perchlorates, relative to that observed in the presence of the tetrabutylammonium perchlorate supporting electrolyte alone ($E_p°$). Values of $\log (K^*/K)$ were calculated from the peak shifts of the first reduction waves. The binding enhancements for **67a** are high for Li^+, Na^+, and K^+ ($\log (K^*/K) = 7.0$, 5.6, and 3.2 in MeCN at 20 °C, respectively).

Calix[4]arene (**68**) has a hydrogen-bonding receptor site near an ionophoric site.[109] The possible communication between two sites is supported by ^1H NMR measurements. The δ_{NH} (−50 °C) for **68** appeared at 10.21 ppm, much lower magnetic field than the δ_{NH} for the monomeric analogue (at 9.79 ppm). Since hydrogen bonding causes OH and NH protons to shift to lower magnetic field, the NMR data imply that the NH protons in **68** are subject to the intramolecular hydrogen bonding. At −50 °C, the addition of $NaClO_4$ gave new signals for the **68**·Na^+ complex, at lower magnetic field from those for free **68**. The upfield shift for the **68**·Na^+ complex suggests

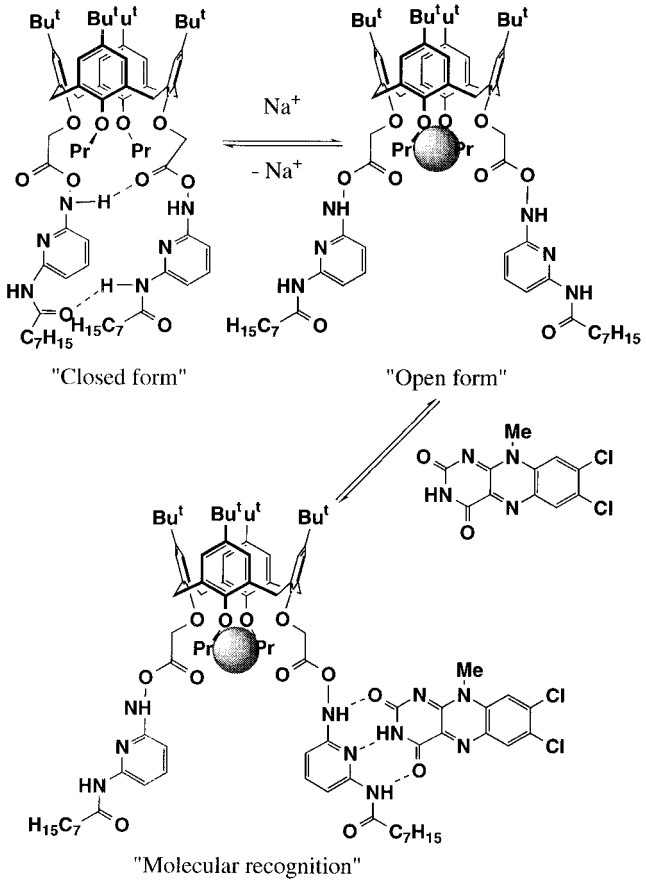
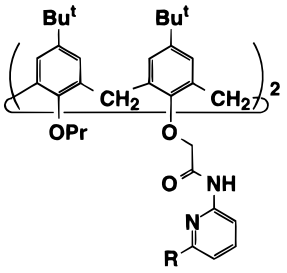


Figure 20. Conformational change from a "closed form" to an "open form" upon the guest binding.

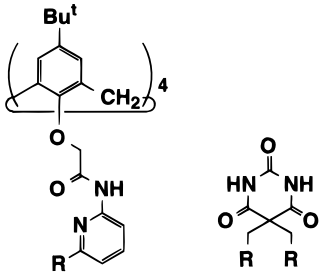
that the intramolecular hydrogen bonds are partly disrupted. When γ-butyrolactam (BL, specific guest for **68**) was added, only the NH signal for **68**·Na^+ complex moved to lower magnetic field (at 11.3 ppm). The results substantiate a view that a "closed" receptor site in **68** is switched by the metal binding to an "open" receptor site (as in Figure 20). It is known that in calix[4]aryl tetraesters and tetraamides the four carbonyls are turned outward to reduce electrostatic repulsion among carbonyl oxygens, whereas bound Na^+ induces the carbonyls to point inward, to bind the Na^+ ion. In **68**, this carbonyl movement disrupts intramolecular hydrogen bonds, so that the carbonyl groups can coordinate to Na^+ ion. In other words, a "closed" NHPy receptor site can be activated to an "open" receptor site by a metal switch. For compound **69** a similar phenomenon was observed.

Interaction of compound **69** or **70** with dimethyl- or dioctylbarbituric acid (**71a**,**b**) was studied with the aid of ^1H NMR spectroscopy in $CDCl_3$ or $CDCl_3/CD_3CN$ solution.[110,111] Derivative **69** possesses characteristic singlets of NH protons at 9.03 and 10.07 ppm, which are influenced neither by a change in the concentration nor by the presence of the barbituric acid derivative. On the other hand, addition of 1 equiv of $NaClO_4$ causes a dramatically high-field shift of NH signals, to 8.31 and 9.14 ppm, respectively. The low δ_H values for the NH protons can be explained by the presence of intramolecular hydrogen bonds in **69**, which are stronger than six theoretically possible intermolecular hydrogen bonds

between **69** and **71**. After addition of cations, these intramolecular hydrogen bonds are disrupted because of the change in the conformation. This new conformation is suitable for intermolecular hydrogen-bonding interactions and addition of **71** results in the low-field shift of both NH signals, indicating the presence of three hydrogen bonds. Light scattering was used to determine the molecular mass of self-assembled species. While an equimolar mixture of $NaClO_4$ and **70** (20 °C) exhibited the average size of diameter 1.8 nm, after addition of 2 equiv of **71a** the diameter increased up to 6.8−7.4 nm. In the presence of Na^+ the hydrogen-bonding sites in **70** (the same situation is in **69**) are exposed to the medium and then **70** (or **69**) and **71a** create oligomeric clusters.



68 R = H
69 R = $NHCOC_7H_{15}$

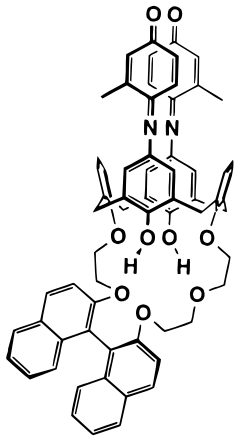


70 R = $NHCOC_7H_{15}$ **71a** R = H
71b R = C_7H_{15}

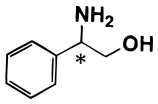
2. Reading-Out of Complexation Processes by Color Changes of Calix[4]arene

Recently, great attention has been given to the development of optical sensors for the selective determination of clinically important metals or molecules. Various "chromogenic calixarenes" have been suggested in recent years by taking advantage of easy attachment of chromogenic groups in the upper rim or the lower rim.[112−124]

Kubo *et al.*[124] reported that the spectral shift of a chromogenic calixarene is greater for one enantiomer of the guest molecules than for the other. Compound **72** gave a red solution in ethanol. When (*R*)-phenylglycinol ((*R*)-**73**) was added in this solution, the solution color changed to blue-violet, resulting from the spectral shift (23 nm) in the band originally at 515.5 nm and the appearance of a new absorption band at 650 nm. On the other hand, when the enantiomer (*S*)-**73** was added, the red color remained. These results indicate that distinction between enantiomers can be successfully achieved by the naked eye.



72



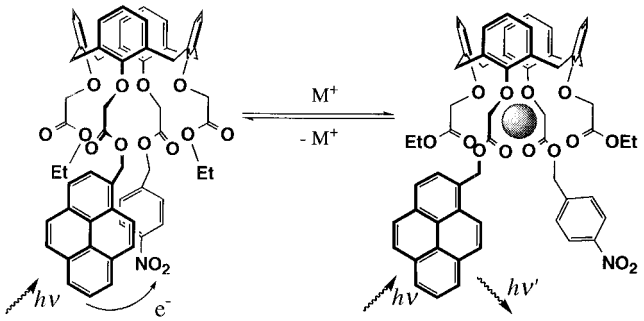
73

3. Reading-Out of Complexation Processes by Conformational Changes of Calix[4]arenes

Metal-binding events are usually estimated either by two-phase solvent extraction or by ^1H NMR measurements. Detection of metal binding by more convenient methods would simplify the estimation of the ion selectivity and lead to the exploitation of new ion-sensing systems. The basic concept has been demonstrated to some extent by so-called "chromogenic crown ethers". Several investigators have reviewed "chromogenic calixarenes".[112−124] Here, our discussion is limited to "chromogenic calixarenes" and their underlying created by conformational changes.

Compound **74** has two pyrene moieties as fluorophores.[125] From plots of $I_{excimer}$ against $[M^+]$ it is concluded that **74** forms 1:1 complexes with Li^+, Na^+, and K^+ (the spectral change was too small to estimate the complexation with Cs^+): log K_{ass} = 4.73 for LiSCN, 5.34 for NaSCN, and 4.06 for KSCN (at 25 °C in diethyl ether). It is known that the cone: partial-cone ratio in **74** increases when Li^+ or Na^+ is added. The increase in cone-**74** may be ascribed to metal−MeO interactions, like metal−crown interactions, which selectively stabilize the cone conformation. The increase in the relative peak intensity of the monomer emission [I_m (%) = 100 × $I_{monomer}$/($I_{monomer}$ + $I_{excimer}$)] on the addition of alkali metal cations may also be explained by the increase in cone-**74**. In addition, the cone-**74**·M^+ complex may have a I_m (%) value larger than that of the "free" cone-**74**, if the bound metal cation interferes with the interaction of the two pyrene moieties.

Koyama *et al.*[126] also provided the fluorescent Na^+ sensor by employing a calix[4]arene. From the data for Na^+ and K^+ titrations, monitored via fluorescence spectra, the dissociation constants for Na^+ and K^+ complexes of **75** were determined to be 3.7 × 10^{-5} and 5.7 × 10^{-3} M, respectively. The Na^+/K^+ selectivity, as measured by the ratio of the dissociation

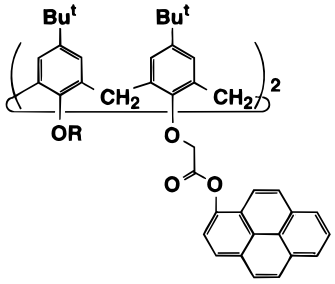


"Free **76**" weakly fluorescent

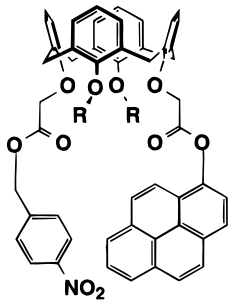
"**76**·metal complex" strongly fluorescent

Figure 21. Schematic representation of the metal-induced distance change between pyrene and nitrobenzene in **76**.

constants, amounts to 154. The affinity of **75** for Li^+ was too low to be determined accurately by fluorescence titration, and the dissociation constant was roughly estimated to be greater than 100 mM. A similar result was obtained for compound **76** bearing pyrene (as a fluorophore) and nitrobenzene (as a quencher) near the ionophoric cavity.[127] This system utilizes conformational changs similar to those of **74** or **75** (Figure 21).



74 R = Me
75 R = CH_2COOEt

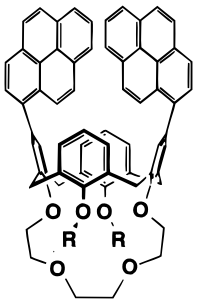


76 R = CH_2COOEt

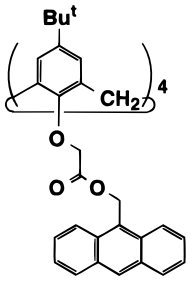
In compound **77**, bearing an ionophoric cavity on the lower rim and two pyrene groups on the upper rim, the absorption spectral change was induced by the addition of $NaClO_4$.[128,129] A similar spectral change was observed for the addition of $LiClO_4$. Association constants (K_{ass}) were determined from plots of A_{350} *vs* [$MClO_4$]: log K_{ass} = 4.65 for $LiClO_4$ and 5.16 for $NaClO_4$. In contrast, the addition of $KClO_4$ (up to [K^+]/[**77**] = 30) scarcely changed the absorption spectrum. The ionophoric cavity in **77** was designed to accommodate Li^+ or Na^+, but to be too small for K^+, which results in the record-breaking Na^+/K^+ selectivity of more than 10^5-fold. It is clearly seen that with increasing $NaClO_4$ concentration, monomer emission (390 nm) increases while excimer emission (480 nm) decreases.

Diamond and McKervey[130−132] reported spectroscopic study of **78** and **79**, focusing on the photophysical behavior of the four anthracene moieties in **78** and the four 3-hydroxy-4-nitrobenzyl moieties in **79**. These compounds may be useful as the chromogenic ligands for Li^+ and Na^+.

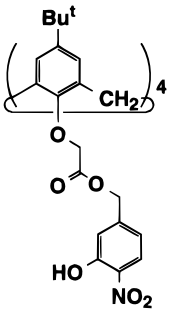
Calix[*n*]aryl esters **80** and **81** bearing two stable N−O• radicals on the lower rim were synthesized in



77 R = Et



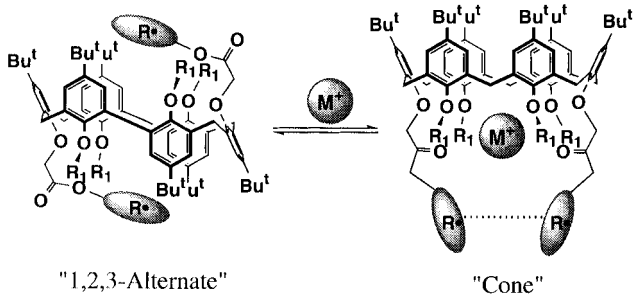
78



79

an effort to detect ion chelation via EPR.[133] The EPR spectra gave a quintet resonance both in the absence and the presence of Na^+. This result indicates that the exchange interaction (EI) among paramagnetic species occurs in **80**, regardless of the absence or the presence of Na^+. Although the spectral shape is somewhat different (particularly at low temperatures), no essential difference in EI is caused by the Na^+-induced rotation of the carbonyl groups. As demonstrated by monomer *vs* excimer emission in a pyrene-functionalized calix[4]aryl ester, the distance between two R• groups is shortened in the presence of Na^+.[133] However, this distance change is obviously not sufficient to affect EI between two N−O• radicals.

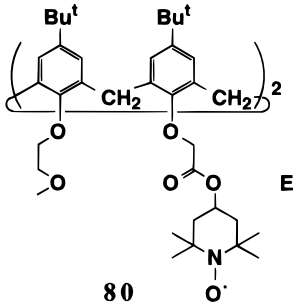
It was expected that a greater distance change would be realized in a metal-induced 1,2,3-alternate-to-cone conformational change in **81**.[133] Examination of CPK molecular models suggests that the distance between the two radicals in 1,2,3-alternate-**81** is larger than that in the cone-**81** complex. Compound **81** gave a triplet resonance, indicating that the distance between two radical groups occupying the distal *anti*-position in the 1,2,3-alternate conformation is too far away to enjoy EI. On the other hand, when the **81** conformation is converted to cone through metal cation complexation, an unsymmetrical quintet resonance is observed. This result clearly indicates that metal complexation can change the distance between two radical groups from the EI-free distance to the EI distance (Figure 22). The clearest



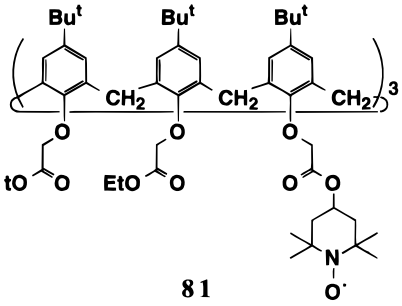
"1,2,3-Alternate" "Cone"

Figure 22. Schematic representation of the metal-induced distance change between radical groups (R•) in **81**. In 1,2,3-alternate-**81**, the radical-carrying phenyl units do not necessarily occupy the central position in a 1,2,3 (or 4,5,6) array. However, even though they occupy the verge position in the array, they are still in *anti* position.

splitting (*i.e.*, largest EI) was observed for Rb^+, and the next for K^+.



80



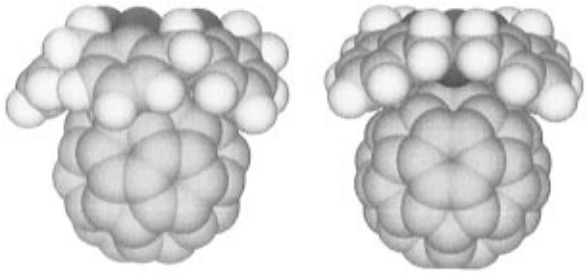
81

4. Reading-Out of Complexation Processes by Color Changes of Guests

As stated above, chromogenic calixarenes were prepared for the sensing of colorless guests. In limited systems, it is not necessary to synthesize chromogenic calixarenes because the guest itself absorbs in visible region, (*e.g.*, picrate salts).[134,135]

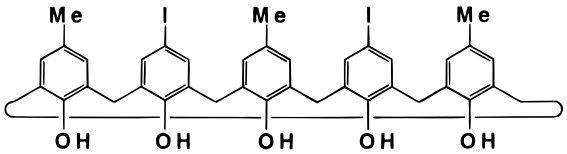
Our group[91,93] and Atwood *et al.*[92] discovered that *p-tert*-butylcalix[8]arene selectively includes C_{60} in carbon soot and forms a precipitate with 1:1 stoichiometry. Raston *et al.*[136] predicted by the use of molecular mechanics that the 1:1 *p-tert*-butyl-calix-[8]arene complex of C_{60} is micelle like, with a trimeric aggregate of fullerenes surrounded by three host molecules. This complexation has become a very useful method for obtaining pure C_{60} in large quantity and with high purity.[137] It has been believed that the origin of selective inclusion stems from the conformity of the C_{60} size with the calix[8]arene cavity. However, when this complex was solubilized (*e.g.*, by heating or using good solvents), it was dissociated into each component, and no spectroscopic indication of complex formation could be found.[93,138] This means that this complex exists only in the solid state. Inclusion complexes of C_{60} are obtained in an aqueous system with cyclodextrins and water-soluble calixarenes.[139−141] However, C_{60} has a practical solubility only in certain organic solvents; therefore, it seems more useful for C_{60} to be treated in organic solvents; for example, for further derivatization and functionalization.

Fukazawa[142] and our group [143] discovered that several calixarenes can include C_{60} in toluene solution. A color change (purple → pale yellow) was observed in an organic solution of C_{60} upon addition of the calix[5]arene (**82**).[142] In toluene the association constant for C_{60} was determined to be 2120 ± 110 M^{-1}. In addition, the calix[5]arenes (**83**), the homooxacalix[3]arenes (**84**), and calix[6]arenes (**28**) can include C_{60}[143] (Figure 23).

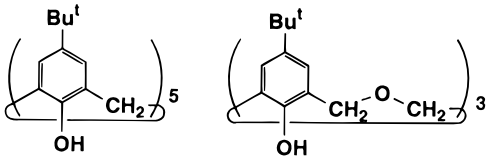


83 **84**

Figure 23. Possible interactions of **83** and **84** with C_{60}. Compounds **83** and **84** are energy minimized with MM3-(92). *tert*-Butyl groups are omitted for clarity of calculation.



82



83 **84**

More recently, Raston, Smith, *et al.* reported that in the pores of silica calix[*n*]arenes ($n = 4, 6, 8$) form supramolecular complexes with C_{60}.[144] Upon addition of toluene solution of calix[*n*]arene, the magenta color of silica-containing C_{60} changed to brown-yellow, reflecting by the appearance of a broad new band at ~450 nm. This spectral change is consistent with the formation of aggregates of C_{60}, most likely as part of micelle like structures with the cores surrounded by host molecules, in the pores of silica.

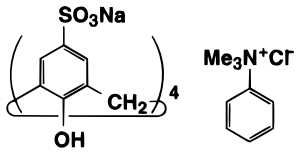
IV. Control of the Guest Mobility in Calixarenes

1. Intramolecular Mobility of Guests

Recently, the development of molecular devices has attracted much interest with regard to miniaturization of electronic components. Among these devices, many groups refer to the importance of molecular switches.[145−150] Molecular switches should ideally be able to respond sensitively and reversibly to external triggers. Here, our group describe several calixarenes that may act as novel molecular switches.

The ^1H and ^{13}C NMR spectra of a complex formed from tetrasodium *p*-sulfonatocalix[4]arene (**85**) and trimethylanilinium chloride (**86**) in D_2O showed that **86** is bound to the cavity of cone-shaped **85**.[151] In the absence of **85** the chemical shifts of **86** are scarcely affected by the pD of the medium. In the presence of **85**, in contrast, the chemical shifts become pD dependent: all resonance peaks move to a higher magnetic field, indicating that **86** is included

in the cavity of **85** and affected by the ring current of the aromatic components. Each chemical shift



85 **86**

reveals that in acidic aqueous solution the peaks assignable to aromatic protons specifically shift to higher magnetic field in the specific order *p*-H > *m*-H > *o*-H > N^+-CH_3, whereas in neutral aqueous solution both ammoniomethyl and aromatic protons shift nonspecifically to higher magnetic field. The results suggest that in acidic aqueous solution the phenyl moiety is selectively bound to the calixarene cavity, whereas in neutral aqueous solution both the ammoniomethyl and the phenyl moiety are nonselectively bound to the calixarene cavity (Figure 24).

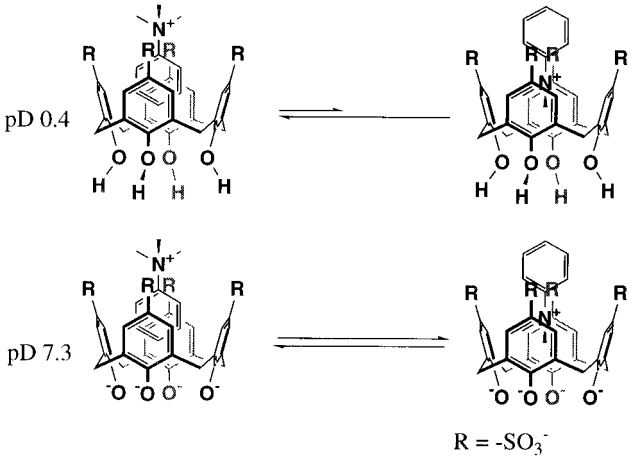


Figure 24. Complexation of **85** with **86** in acidic and neutral pD solutions.

Reinhoudt *et al.*[152−154] reported the first carceplex constructed from a calix[4]arene unit and a resorcinol unit (**87**), which has C_{4v} symmetry. This carceplex, containing one molecule of *N*,*N*-dimethylformamide (DMF) inside the cavity was isolated in 27% yield as a byproduct in the synthesis of an organic molecule with a rigid cavity of nanometer dimensions. Cooling of the sample causes the ^{1}H NMR signals of the bound guest molecule to decoalesce at 0 °C. At temperatures below −30 °C the broad signals are split into two sets, one of two small, equally intense singlets at −1.3 and −1.8 ppm, flanked by the larger singlets of the other at −0.9 and −2.2 ppm also with equal intensity. 2D EXSY experiments revealed that the large singlet at −0.9 ppm shows exchange with the small singlet at −1.3 ppm, while the other large singlet at −2.2 ppm exchanges with the small singlet at −1.8 ppm. Apparently, calix[4]arene−carceplex **87** switches between two isomeric states **A** and **B** in which the DMA molecule occupies the different orientation inside the cavity of **87** (Figure 25). The structures of **A** and **B** were determined by NOESY experiments. The two isomers (carceromers) **A** and **B**, which are not equally abundant (ΔG = 0.7 kcal mol^{-1} at −60 °C in $CDCl_3$), show a fast exchange on

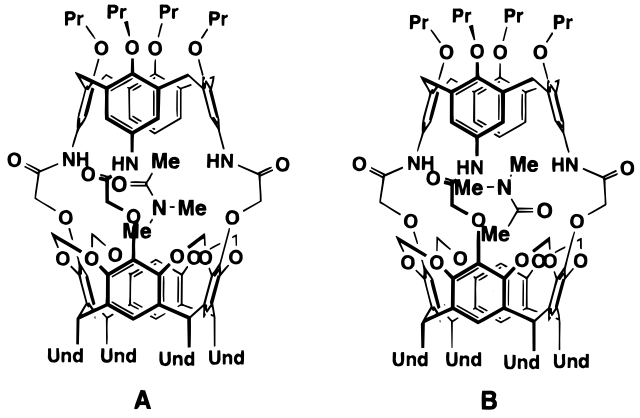
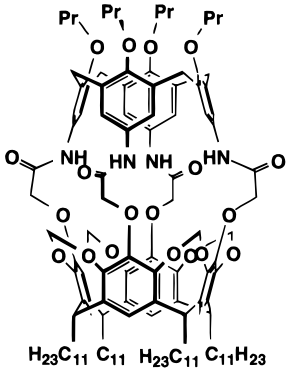


Figure 25. Two isomeric states **A** and **B** in which the DMA molecule occupies different orientations inside the cavity of **87**.

the ^{1}H NMR time scale above room temperature, but give rise to separate signals below −30 °C.



87

A series of biscalix[4]arenes (**88** or **89**) possessing two metal binding sites were synthesized, each of which contains four ester or four ether groups.[155−157] It was spectrometrically detected by temperature-dependent ^{1}H NMR spectroscopy that alkali metal cations such as Na^+ or K^+ "vibrates" between two metal binding sites in the NMR time scale (Figure 26). When one metal cation is bound to a ditopic ionophore [*e.g.*, bis(crown ether) and biscalix[4]-arene], it is believed that the metal cation jumps between the two binding sites. This phenomenon is interesting in relation to the behavior of metal cations

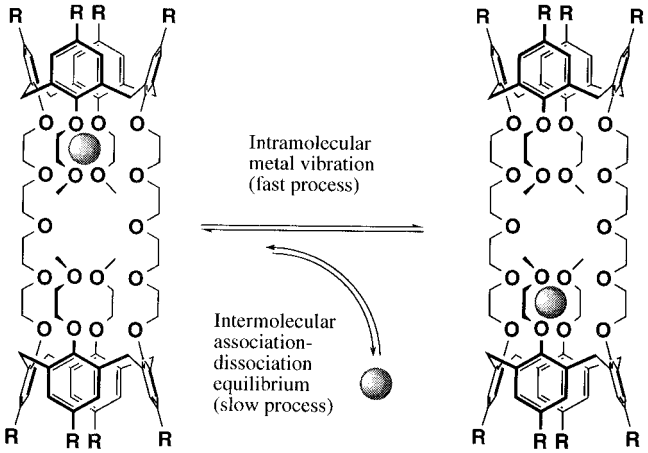
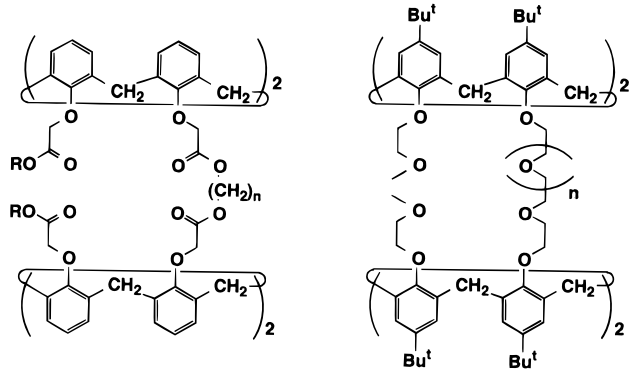


Figure 26. Intra- and intermolecular metal exchange processes in **89**.

moving in an ion channel. This process may be monitored by the measurement of the temperature-dependent NMR spectra if the rate is comparable to the NMR time scale. In artificial ditopic ionophores, however, the intermolecular exchange process frequently overlaps with the intramolecular exchange process, and therefore the discrimination becomes difficult. In the present system, however, our group could successfully discriminate between these two processes by ^{1}H NMR spectroscopy.



88a n = 2 R = Et or *tert*-Bu
88b n = 3 R = Et
88c n = 5 R = Et
88d n = 10 R = Et

89a n = 1
89b n = 2
89c n = 3

1,3-Alternate conformers can possess two independent ionophoric sites on either side of the cavity.[131] In the ^{1}H NMR spectra of 1,3-alternate-**90** in the presence of Ag^+, the signals for the complex and those for free 1,3-alternate-**90** are decoalesced at −50 °C and coalesced at 0 °C. This coalescence at 0 °C arises from intermolecular metal exchange ($T_{c,inter}$). In the ^{1}H NMR spectra below −50 °C, the signals arising from the 1,3-alternate-**90**·Ag^+ complex gradually broaden and eventually separate into pairs. This finding presents unequivocal evidence for hopping of Ag^+ between the two binding sites in 1,3-alternate-**90**. The coalescence temperature for this metal exchange process ($T_{c,intra}$) is estimated to be −70 °C. Differences in the concentration dependences of the two coalescence temperatures clearly show that $T_{c,inter}$ reflects a concentration-dependent, intermolecular event, whereas the second coalescence temperature ($T_{c,intra}$) reflects a concentration-independent, intramolecular event. These results show that Ag^+ alternates intramoleculary between two binding sites through the π-basic hole of 1,3-alternate calix[4]-arenes (**90**) (Figure 27). In 1,3-alternate calix[4]-biscrown **91**, the cation tunneling phenomenon across

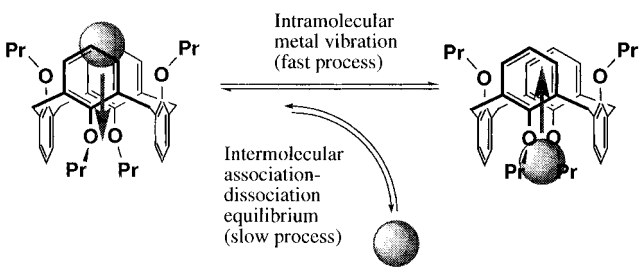
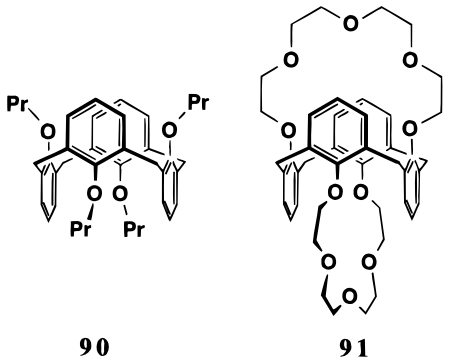


Figure 27. Schematic representation of the metal tunneling through a π-basic tube of a 1,3-alternate-**90**.

the calix[4]arene cavity was detectable with ^{1}H NMR spectroscopy even at room temperature.[159]



90 **91**

1,3-Alternate-**92** also has two binding sites, but the binding abilities of these sites are different.[158] The ^{1}H NMR spectrum of the 1,3-alternate-**92**·Ag^+ complex at −85 °C showed that 8.1% of the Ag^+ resides in the cavity composed of two PrO groups and two benzene rings, and 91.9% of the Ag^+ resides in the cavity composed of two $EtOCH_2CH_2O$ groups and two benzene rings (Figure 28). This implies that the

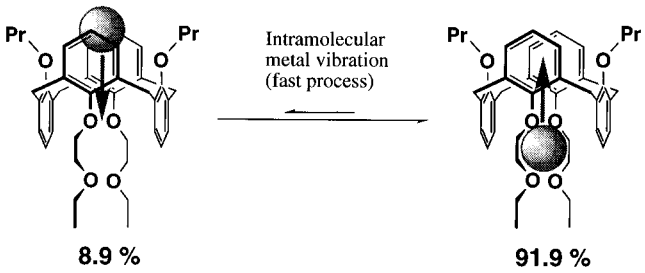
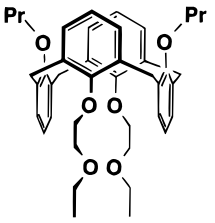


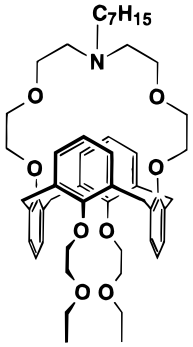
Figure 28. Different existence ratio of Ag^+ in the two different cavities of **92**.

latter cavity possesses an ionophoricity 10 times stronger than the former cavity.



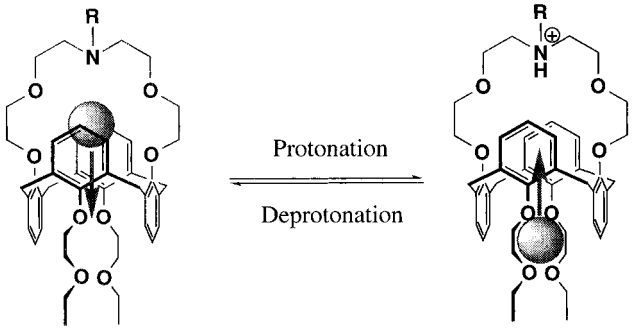
92

A 1,3-alternate calix[4]arene (**93**) bearing a nitrogen-containing crown cap at one side and a bis(ethoxyethoxy) group at the other side has been synthesized.[160] ^{1}H NMR spectroscopic studies showed that Ag^+ is bound to the crown-capped side (log K_{ass} = 9.78; CD_2Cl_2/CD_3OD = 4:1 v/v, 30 °C) and the dissociation of Ag^+ from this cavity is very slow. When the nitrogen atom in the crown ring is protonated with trifluoroacetic acid, Ag^+ is pushed out to the bis(ethoxyethoxy) side through a π-basic tube of the 1,3-alternate calix[4]arene. The dissociation of the complex from the bis(ethoxyethoxy) side occurs relatively fast. On the other hand, when the nitrogen·H^+ in the crown ring is deprotonated with Li_2CO_3 and diazabicycloundecene, Ag^+ is sucked back to the crown-capped side through the π-basic tube



93

(Figure 29). These chemically switchable actions imitate the function of a "syringe", using the π-basic tube as a pipet and the crown ring as a rubber cap.



R = $(CH_2)_5CH_3$

Figure 29. Schematic representation of a reversible metal pumping in a microscopic "molecular syringe" **93** designed from 1,3-alternate calix[4]arene.

2. Intermolecular Mobility of Guests

It is known that metal exchange in conventional crown ethers and calix[*n*]arenes occurs at rates comparable to or faster than the NMR time scale. In certain macrocycles with a closed ionopholic cavity, such as spherands and cavitands, in contrast, the metal exchange occurs more slowly than the human time scale.[161−163] In a mesitylene-capped calix[6]-arene (**49**) and doubly bridged calix[8]arenes (**64b** and **64c**), both CPK models and theoretical energy minimization suggested a closed inner cavity delineated by oxygen atoms and π-basic benzene rings, the size of which is comparable with Cs^+. Surprisingly, the time course of the Cs^+ complexation process could be followed spectrophotometrically by the absorption maximum of the Cs^+ complexes (390 nm) in THF.[164] Firstly, a Cs^+Pic^- solution (3 mL) in a quartz cuvette was equilibrated to the desired temperature and then a calix[*n*]arene solution (30 μL) was quickly injected from a microsyringe. After shaking for a few seconds, the absorbance change was monitored spectrophotometrically. This operation required a dead time of *ca.* ~5 s. The typical time dependences are shown in Figure 30. In contrast, a hexakis(ethoxycarbonylmethoxy) derivative of *p-tert*-butylcalix[6]arene of *p-tert*-butylcalix[8]arene, used as reference compound, gave a time-independent, constant absorbance after 5 s; that is, the reaction with Cs^+Pic^- was completed in 5 s in these compounds. In compounds **49**, **64b**, and **64c**, it was found that the Cs^+ exchange

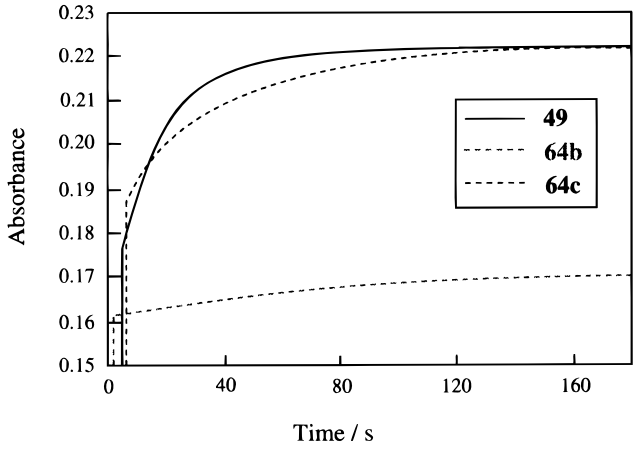
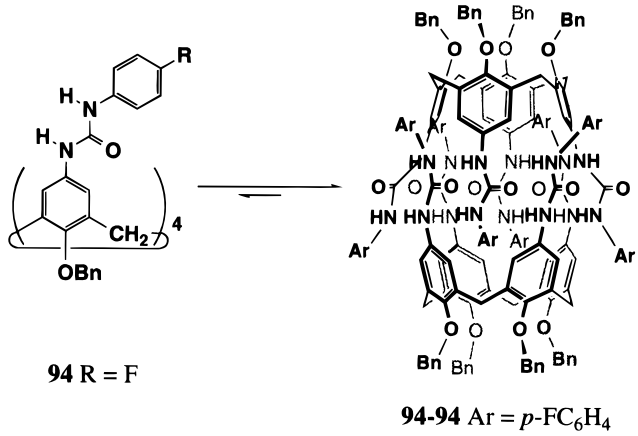


Figure 30. Time dependence of the 390 nm band: $[Cs^+Pic^-] = 1.00 \times 10^{-5}$ M, [calixarene] = 1.00×10^{-4} M, THF 10 °C.



94 R = F

94-94 Ar = *p*-FC_6H_4

Figure 31. The dimerization of the urea-substituted calix-[4]arene through the formation of intermolecular hydrogen bonds. Bn = benzyl.

rates are slow enough to be followed by the conventional spectroscopic method.

Recently, our group,[165] Rebek,[166−168] Böhmer,[169,170] and Reinhoudt[171] *et al.* reported several molecular capsules based on intermolecular hydrogen bonding. These capsules are formed with cavities large enough to include smaller guest molecules in a reversible manner.

Rebek *et al.*[166−168] reported that urea groups placed on the upper rim of the calix[4]arene permit dimerization to occur through a head-to-tail hydrogen bonding pattern (Figure 31). When excess benzene is added to the solution of the capsule **94**−**94**, a new singlet appears at 4.02 ppm and grows over the course of about 40 min.[168] Integration indicates an approximately 1:1 ratio of benzene to the capsule **94**−**94**, and the half-life for the uptake is about 8 min. Equilibrated solutions of benzene and the dimeric calixarene in *p*-xylene-d_{10} indicate an association constant of 230 M^{-1} for benzene encapsulation.

V. Conclusions

During the past decade, calix[n]arenes have become an increasingly important tool in host−guest chemistry. The unique molecular architecture has predetermined them for "catching" ions and/or neutral molecules in a well-defined manner. Further-

more, calix[*n*]arenes can be useful not only in pure "science", but also in various industrial applications (for example, isolation of C_{60}). In this review, our group demonstrated many examples in which calix[*n*]arene conformation is manipulated to promote molecular recognition and ion binding. Our group expect that calix[*n*]arenes having novel cavity shapes will be developed to include other guests in the cavity with high affinity and high selectivity.

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