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Calixarenes - The Third Generation of Supramolecules

Seiji Shinkai

Contribution from the Department of Organic Synthesis,
Faculty of Engineering, Kyushu University, Fukuoka 812,
Japan

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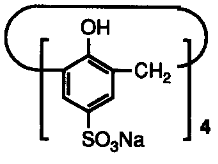
1. Introduction

Calixarenes are cavity-shaped cyclic molecules made up of phenol units linked via alkylidene groups. In spite of their attractive architecture, studies of host-guest chemistry related to calixarenes have been very limited.[1,2] This is in sharp contrast to cyclodextrins and crown ethers, which can form a variety of host-guest-type solution complexes. More recently, several groups have succeeded in demonstrating that calixarenes serve as an excellent "platform" to design the receptor site for the specific binding of guest atoms and molecules.[3-6] For example, Gustche[7] and we[8-12] have found that water-soluble calixarenes can form a variety of host-guest-type complexes with organic guests in water, and Ungaro,[13] McKervey,[14] and Chang[15] have found that calixaryl esters show high alkali metal ion affinity. These findings suggested that calixarenes have latent potential to be counted as the third generation of supramolecules, after cyclodextrins and crown ethers. In this article we review the basic characteristics of calixarenes, including the acidity of phenolic OH groups, conformational isomerism, and recognition properties.

2. Acidity Constants of the Phenolic OH Groups

It is known that the OH groups in calix[4]arenes form strong intramolecular hydrogen-bonds.[1-6] This affects the acid dissociation properties of these groups. We synthesized water-soluble **1** and carried out an acid-base titration, observing that the dissociation of the first proton (i.e. pK_{a1}) occurs at unusually low pH values.[16] This was supported by theoretical calculations[17] and photometric "titrations" of calix[4]arenes in organic solvents using picrate ion as an indicator,[18] but the precise determination of the pK_{a2}-pK_{a4} values was difficult, owing to the presence of inorganic salts.[16] To avoid this complication we prepared neutral **2** and **3** and obtained the pK_a values (in water for **2** and in 85.4 wt% ethanol for **3**) recorded in Table 1.[19] The results show that the dissociation of the first proton occurs at surprisingly low pH values (1.8-2.9), corresponding to a shift of about 8 pK units relative to phenol, whereas pK_{a2}-pK_{a4} appear at normal pH values or at higher pH regions than phenol.



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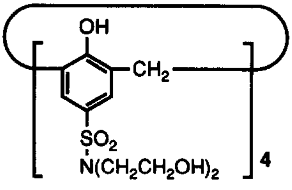

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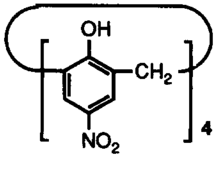

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Table 1. pK_a of OH groups in calix[4]arenes at 25 °C

Calixarene	Medium	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}
1[20]	Water	3.26	11.8	12.8	ca.14
1[22]	Water	3.34	11.5		
2[19]	Water	1.8	9.7	12.5	>14
3[19]	85.4 wt% EtOH	2.9	10.9	12.3	>14

More recently, the pK_a values for **1** were re-evaluated independently by three groups.[20-22] It was consistently found that the first dissociation occurs at very acidic pH values, whereas the residual three dissociations occur at relatively high pH (Table 1). Undissociated calix[4]arenes have a neat circular hydrogen-belt composed of four intramolecular hydrogen-bonds (Figure 1). This may suppress the dissociation of the first proton. However, the monodissociated species comprised of one oxide anion and three hydrogen-bonds is more stabilized by the strengthened intramolecular hydrogen-bonds. This causes the remarkable shift of pK_{a1} down to 3.3.

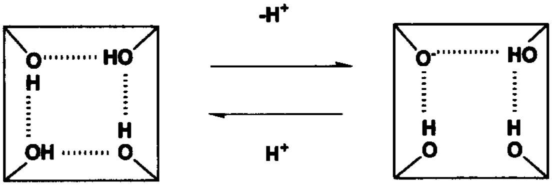


Figure 1. Schematic representation for the dissociation of the first proton

3. Conformational Isomerism

The ^1H NMR spectra of calix[4]arenes show a singlet resonance for the $ArCH_2Ar$ methylene protons at high temperature and a pair of doublets at low temperature.[1-5,23,24] The doublets coalesce to singlets at an intermediate temperature (T_c). This spectral behavior is ascribed to the interconversion between two mirror-image cone conformations which occurs at a rate comparable to that of the NMR time-scale (Figure 2).[23-25] The cone conformation *a priori* is stabilized by the intramolecular hydrogen-bonding interactions among OH groups. Thus, Gutsche and Bauer[23] found that the rate is speeded up (i.e. low T_c) in polar solvents which are capable of weakening the hydrogen-bonds, and estimated $\Delta G^{\neq}$ at T_c to be 10-16 kcal mol^{-1} by the Kurland-Rubin-Wise method[25]. Kämmerer *et al.*[27] and we[28,29] determined activation parameters by the computer-assisted simulation of the temperature-dependent NMR spectra. Activation parameters for calix[4]arene ring inversion showed large values of $\Delta H^{\neq}$ (11~17 kcal mol^{-1}) and relatively small values of $\Delta S^{\neq}$ (-10~2 e.u.), with an isokinetic temperature ß = 475 K.[28] The results indicate that the ring inversion process is mostly governed by the enthalpy term. It is also interesting to note that when the cavity of water-soluble calix[4]arenes includes guest molecules, the rate of ring inversion is significantly reduced.[29]

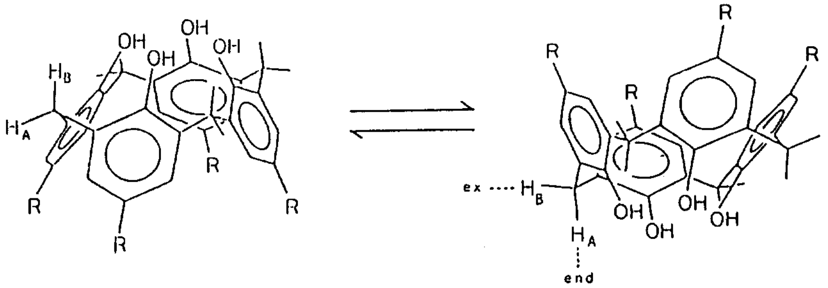
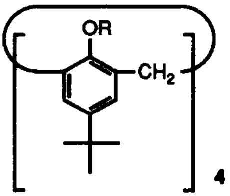
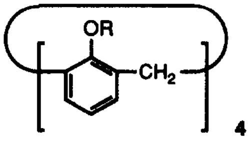


Figure 2. Ring inversion between mirror-image cone-cone conformations

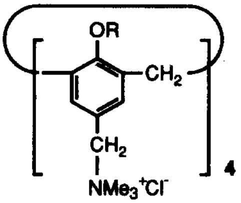
Among four possible conformers of calix[4]arenes, the cone is particularly stabilized by the intramolecular hydrogen-bonds. In tetra-O-methylated calix[4]arenes (**4Me**) without such interactions, in contrast, the cone is no longer a special conformation. Gutsche *et al.*[30] found that **4Me** predominantly exists in a partial-cone conformation but in its ^1H NMR spectrum there exist several additional peaks. These peaks were later assigned to three other conformers: the cone, 1,2-alternate, and 1,3-alternate; that is, **4Me** exists as a mixture of four interconvertible conformers.[31,32] In $CDCl_3$ at -25 °C, for example, **4Me** consists of cone (2%), partial-cone (92%), 1,2-alternate (5%), and 1,3-alternate (1%).[32b] These peaks coalesce at about 60 °C.[32b]



4R



5R



6R

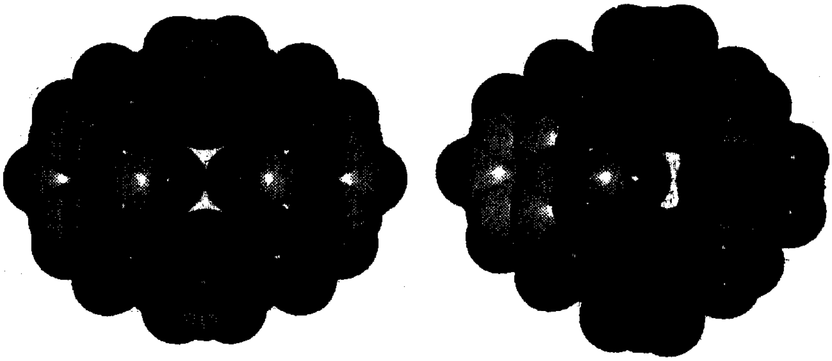
Calix[4]arenes actually consist of a 16-membered ring but involve only four stable and significant conformers. This peculiar characteristic of calix[4]arenes makes the computational approach to their conformational studies extremely simple and reliable.[17,33-38] We recently carried out combined NMR and molecular mechanics studies and found that the relative stabilities of **4Me** and **5Me** are reasonably explained by MM3 calculations.[38] The relative stabilities of the four conformers and the thermodynamic parameters for their interconversion for both **4Me** and **5Me** were determined by ^1H NMR spectroscopy. The relative stability for

5Me is in the order partial-cone (most stable) > cone > 1,2-alternate and 1,3-alternate (undetected) and that for **4Me** is in the order partial-cone (most stable) > cone > 1,2-alternate > 1,3-alternate (least stable). These orders are reproduced well by MM3 (Figure 3) in contrast to MM2.[17] In particular, the energy differences between partial-cones and cones computed by MM3 (0.27 kcal mol^{-1} for **5Me** and 1.50 kcal mol^{-1} for **4Me**) show good agreement with those determined by ^1H NMR spectroscopy (0.32±0.13 kcal mol^{-1} for **5Me** and 1.2±0.3 kcal mol^{-1} for **4Me**). Both the computational and the spectroscopic results suggest that the basic skeletons for cones, 1,2-alternates, and 1,3-alternates are relatively rigid (sharp potential energy surfaces) whereas that for partial-cones is more or less flexible (flattened potential energy surface). Thus, introduction of the *tert*-Bu groups into the *p*-positions destabilizes cones and 1,2-alternates because it is difficult to reduce the increased steric crowding by the conformational change. In 1,3-alternates the four phenol units are parallel, so that the tert-Bu groups would increase the steric crowding to a smaller extent. The basic skeleton for partial-cones changes significantly upon introduction of tert-Bu groups, indicating that the increased steric crowding is relaxed by the conformational change. This finding clearly explains why partial-cones frequently appear as the most stable conformer.[38] It is noteworthy that the optimized structure for cones adopts C_{2v} rather than C_{4v} symmetry.

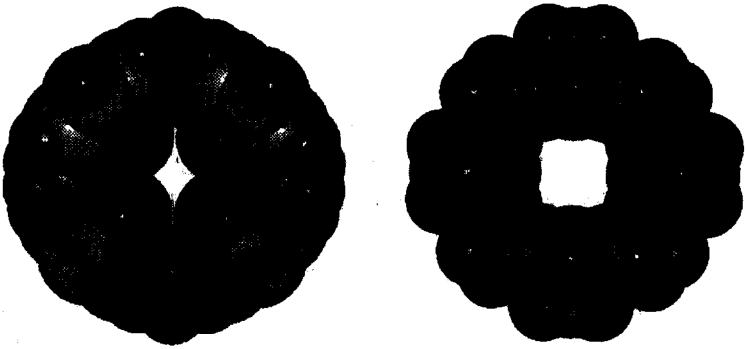
Strangely, we found that **6Me** and tetra-*O*-methylated **1** in water adopt a 1,3-alternate conformation, which has never been found as a major species in organic solvents.[39] The X-ray crystallographic study of Atwood and Bott[40] also shows that tetra-O-methylated **1** adopts a 1,3-alternate conformation in the solid state. Addition of THF or methanol to the aqueous solution gradually increased the proportion of the partial-cone.[39] The results suggest that the conformation of water-soluble calix[4]arenes balances the hydrophobic interactions and electrostatic repulsions, resulting in 1,3-alternates as the most stable conformers.

The conformer distribution (in particularly, the cone/partial-cone ratio) of **4Me** and **5Me** is sensitively affected by solvent effects.[34] This is fundamentally a result of the difference in the dipole moments: the cone (μ = 0.835 D) with four dipole moments orientating in the same direction behaves as a more polar molecule than the partial-cone (μ = 0.538 D) with one inverted dipole moment. Thus, the percentage of cone increases in polar solvents.[34] The concentration of cone can be increased by the addition of alkali metal salts such as $LiClO_4$ and $NaClO_4$.[34] For example, when $LiClO_4$ was added to a $CDCl_3$-CD_3CN (1:1 v/v) solution of **4Me**, an additional pair of doublets assignable to the $ArCH_2Ar$ methylene protons in the cone-**4Me**•Li^+ complex appeared. This equilibrium shift is attributed to an interaction of Li^+ with four methoxy oxygens in cone-**4Me** (Figure 4).[34] We also found that addition of organic ammonium cations induces the shift of a cone/partial-cone equilibrium of **5Me** to the cone (Figure 4).[40] Since the ^1H NMR signals of N^+CH_3 and

N^+CH_2 move to higher magnetic field, these ammonium cations are included in the benzene cavity through the cation-π interaction and the four benzene rings as π-bases favorably adopt a cone conformation.



Cone **Partial-cone**



1,2-Alternate **1,3-Alternate**

Figure 3. Optimized space-filling structures for four conformers in **5Me** (top views from the side of the lower rim)

When calix[4]arenes are tetra-*O*-ethylated in the presence of NaH, the product (e.g., **4Et**) has a partial-cone conformation.[32] It was at one time believed that the ethyl group is bulky enough to inhibit ring inversion by oxygen-through-the-annulus rotation. In fact, the ^1H NMR spectrum is hardly affected by temperature change. We noticed, however, that when **4Et** is heated above 100 °C, slow isomerization (mainly to 1,2-alternate) takes place.[32a] This means that the ethyl groups can still rotate through the calix[4]arene annulus, although the activation energy is quite high (*ca.* 28 kcal mol^{-1}).[32a] In contrast, **4Pr** and **4Bu**, prepared by the reaction of *p*-tert-butylcalix[4]arene and RBr, resulted in a cone and a partial-cone conformer in an approximately 1:1 ratio.[32] Isomerization of these conformers did not take place even above 100 °C, indicating that the n-propyl group is the smallest alkyl group which can inhibit the oxygen-through-the-annulus rotation.[32] Thus, one can discretely isolate four conformationally-immobile isomers from **4Pr**.[32]

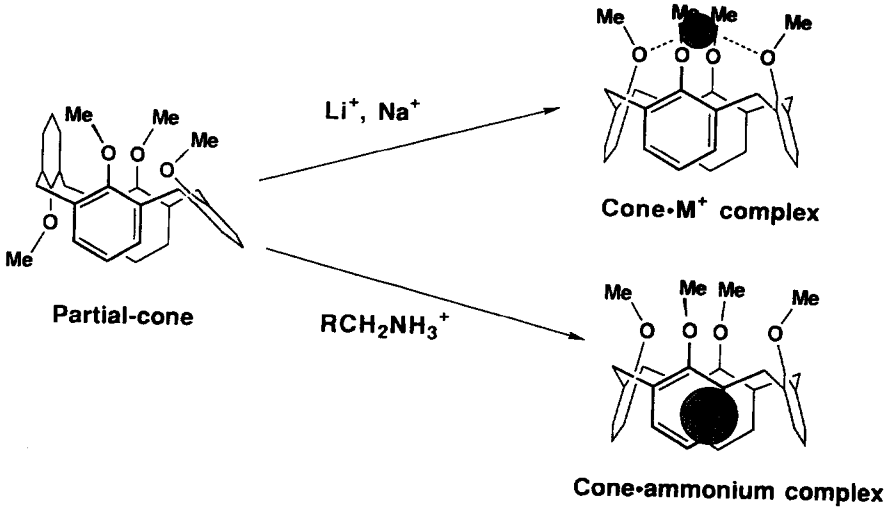


Figure 4. Inclusion of metal cation in an oxygen cavity and of ammonium cation in a π-base cavity. The binding of Li^+ and Na^+ is almost unaffected by *p*-substituents, whereas that of the ammonium cation is strongly suppressed by *p*-tert-butyl groups.

NaH has frequently been used as base in the tetra-*O*-alkylation of calix[4]arenes.[1-5,30] We tested alkali carbonates (Na_2CO_3, K_2CO_3, and Cs_2CO_3) as base.[32,41,42] The reaction of *p*-*tert*-butylcalix[4]arene and *n*-PrBr in DMF in the presence of Na_2CO_3 and K_2CO_3 did not yield **4Pr** even in the presence of excess *n*-PrBr. The product was identified to be **7H**$^{\alpha}$**Pr**$^{\alpha}$**H**$^{\alpha}$**Pr**$^{\alpha}$*. In the presence of Cs_2CO_3 (10 equiv.), on the other hand, the tetra-*O*-propylation reaction proceeded smoothly and gave no cone, 24% partial-cone, 9% 1,2-alternate, and 67% 1,3-alternate.[32] When $Ba(OH)_2$ or CaH was used as base, *O*-propylation stopped selectively at the tri-*O*-substituted stage and the product (**7HPrPrPr**) was 100% cone (i.e. **7H**$^{\alpha}$**Pr**$^{\alpha}$**Pr**$^{\alpha}$**Pr**$^{\alpha}$).[32,43] These results indicate that conformer distribution in *O*-alkylated calix[4]arenes is profoundly governed by metal template effects. In conclusion, the metal template effects are summarized as follows: cone results when the metal (e.g. Na^+ Ba^{2+}, or Ca^{2+}) can act as a template, whereas 1,3-alternate results when the metal (e.g. Cs^+) cannot act as a template.[32]

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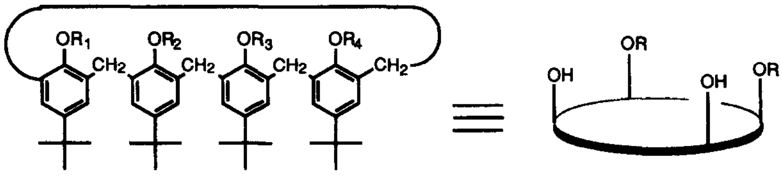
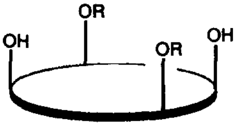
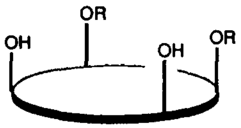
* To distinguish conformational isomers, we use α and β (for example, $\alpha\alpha\alpha\alpha$ for cone and $\alpha\beta\alpha\beta$ for 1,3-alternate) as used in the nomenclature for porphyrin atropisomers.



$7R_1{}^{\alpha}R_2{}^{\alpha}R_3{}^{\alpha}R_4{}^{\alpha}$



distal ($7H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}$)



proximal ($7H^{\alpha}H^{\alpha}R^{\alpha}R^{\alpha}$)

Di-*O*-alkylated calix[4]arenes comprise two regioisomers, distal and proximal. We[32,41,44] and others[45,46] have found that the reaction of alkyl halides with *p*-*tert*-butylcalix[4]arene in the presence of K_2CO_3 (2 equiv.) yields only distal (**7H$^{\alpha}$R$^{\alpha}$H$^{\alpha}$R$^{\alpha}$**) isomers. In contrast, Reinhoudt *et al.*[47] and Pappalardo *et al.*[48] reported that *O*-benzylation or *O*-(2-pyridyl)-methylation yields proximal (**7H$^{\alpha}$H$^{\alpha}$R$^{\alpha}$R$^{\alpha}$**) isomers as major products. To understand this controversial problem, we investigated the mechanistic basis of the distal *vs.* proximal regioselectivity through detailed product analyses.[44] Judging from the pK_a values of calix[4]arenes,[19-22] the OH groups are only partly dissociated in the presence of K_2CO_3 (weak base). In *O*-benzylation, the distal *vs.* proximal ratio is determined when the second benzyl group enters. As shown in Figure 5, species A, which has a phenoxide anion with two hydrogen bonds, should exist in preference to species B, which has a phenoxide anion with only one hydrogen bond. On the other hand, species B should be more reactive than species A as a nucleophile. The high distal selectivity supports the view that the difference in the nucleophilicity is small and the selectivity is mainly governed by the equilibrium shift to species A. In contrast, *O*-benzylation (2 equiv. benzyl bromide) in the presence of excess NaH (strong base) yielded distal and proximal isomers in a 1:2 ratio.[44] Mono-*O*-benzyl-*p*-tert-butylcalix[4]arene has one distal-forming phenoxide anion and two proximal-forming phenoxide anions. Thus, the regioselectivity is reasonably explained by the reaction mechanism occurring according to the probability. It was also found that distal isomer is more reactive than proximal isomer for further *O*-alkylation, resulting in the apparent proximal selectivity at the disubstituted stage.[44]

Examination of the reaction route by a stepwise method (i.e. the reaction with n-PrBr was initiated from **7H$^{\alpha}$Pr$^{\alpha}$H$^{\alpha}$Pr$^{\alpha}$**, **7H$^{\alpha}$H$^{\alpha}$Pr$^{\alpha}$Pr$^{\alpha}$**, or **7H$^{\alpha}$Pr$^{\alpha}$Pr$^{\alpha}$Pr$^{\alpha}$** and the conformer distribution was examined by HPLC and ^1H NMR) established that when NaH (containing a template metal ion) is used as base, tetra-*O*-propylation proceeds according to Figure 6: that is, the rotation of each phenol unit is suppressed, taking place only to the smallest extent.[32,42] In contrast, when Cs_2CO_3 (containing a nontemplate metal ion) is used as base, the rotation of phenol units frequently occurs eventually, giving the 1,2-alternate conformer which is not detected in the NaH system (Figure 7).[32,42]

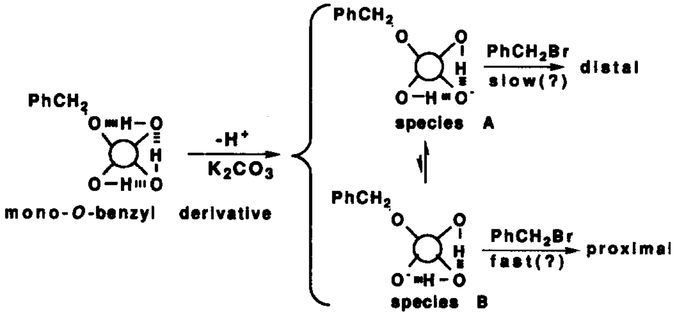


Figure 5. Distal *vs.* proximal selectivity in the presence of K_2CO_3.

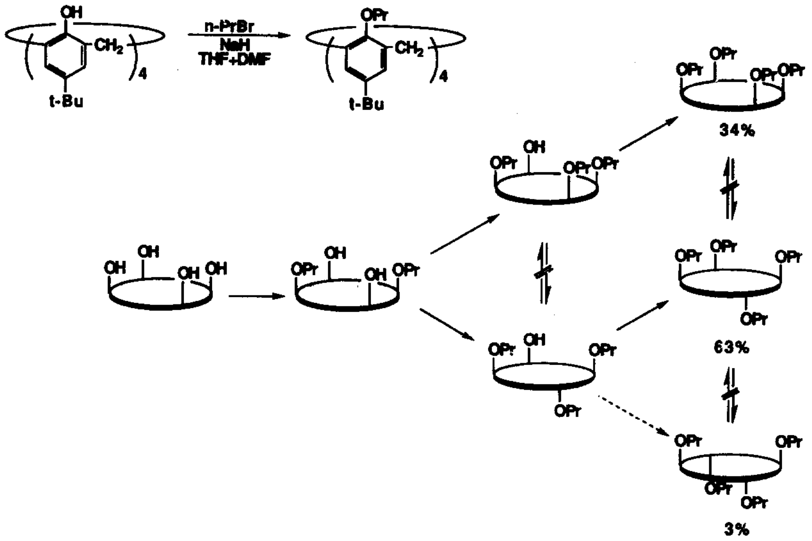


Figure 6. Reaction route for *O*-propylation in the presence of NaH. At the disubstituted stage, $7H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$ must also be taken into account. The possible trisubstituted products from $7H^{\alpha}H^{\alpha}Pr^{\alpha}Pr^{\alpha}$ are $7H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\alpha}$ and $7H^{\alpha}Pr^{\alpha}Pr^{\alpha}Pr^{\beta}$.

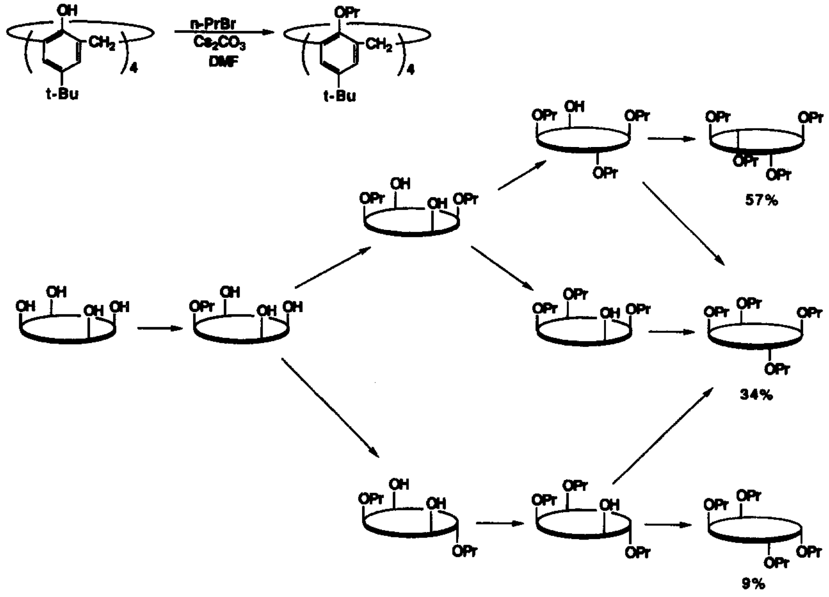


Figure 7. Reaction route for *O*-propylation in the presence of Cs_2CO_3

4. Syntheses of All Possible Conformers of Calix[4]arenes

Attempts directed toward exploitation of new synthetic methods for calix[4]arene-based conformers have been reported by the groups of Gutsche,[49,50] Ungaro,[51] Reinhoudt,[31] and Pappalardo.[52] However, these reports include only case-by-case discussions and there was no systematic review on calix[4]arene-based conformers. We thus planned to synthesize all possible conformers derivable from calix[4]arene.[32,53] As mentioned above, we have found that in *p*-tert-butylcalix[4]arene (**7H$_4$**) the n-propyl group (Pr) is bulky enough to inhibit the rotation. Basically, four different conformers can exist in conformationally-immobilized calix[4]arenes: they are cone, partial-cone, 1,2-alternate, and 1,3-alternate. As shown in Table 2, these four conformers can exist in di-, tri-, and tetra-*O*-propylated derivatives (**7H$_2$Pr$_2$**, **7HPr$_3$**, and **7Pr$_4$** respectively). Furthermore, two different regio-isomers (distal and proximal) exist at the **7H$_2$Pr$_2$** level. The total number of possible homologs is 23 (including cone-**7H$_4$** and cone-**7HPr$_3$**). In principle it could be extremely difficult to synthesize all possible conformers listed in Table 2. As described in this paper, however, we found that the OH group in the unmodified phenol unit can rotate through the calix[4]arene ring (even the OH group in **7HPr$_3$**).[53] This means that the position of the OH group in these conformers is determined as a consequence of the thermodynamic control. As summarized in Table 3, several conformers thus become equivalent to each other after the oxygen-through-the annulus rotation of the OH group. Hence, the number of conformers is reduced to 13 (including cone-**7H$_4$** and cone-**7H$_3$Pr**: Table 4).

Table 2. Conformational isomers possible in **7R$_4$** and its *O*-alkylated derivatives

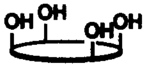
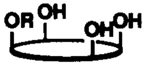
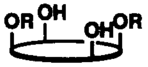
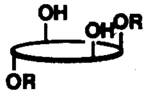
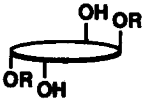
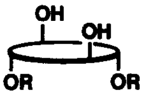
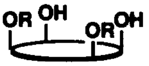
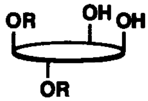
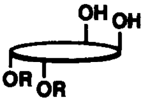
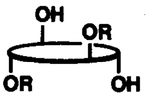
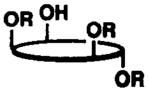
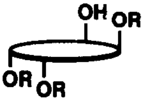
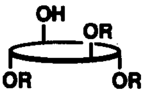
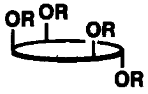
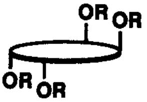
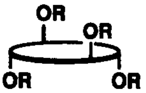
Calixarene	Conformation			
	Cone	Partial-cone	1,2-Alternate	1,3-Alternate
7H$_4$	 $7H^{\alpha}H^{\alpha}H^{\alpha}H^{\alpha}$			
7H$_3$R	 $7H^{\alpha}H^{\alpha}H^{\alpha}R^{\alpha}$			
distal-**7H$_2$R$_2$**	 $7H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}$	 $7H^{\alpha}R^{\alpha}H^{\alpha}R^{\beta}$ $7H^{\alpha}R^{\alpha}H^{\beta}R^{\alpha}$	 $7H^{\alpha}R^{\alpha}H^{\beta}R^{\beta}$	 $7H^{\alpha}R^{\beta}H^{\alpha}R^{\beta}$
proximal-**7H$_2$R$_2$**	 $7H^{\alpha}H^{\alpha}R^{\alpha}R^{\alpha}$	 $7H^{\alpha}H^{\alpha}R^{\alpha}R^{\beta}$ $7H^{\alpha}H^{\beta}R^{\alpha}R^{\alpha}$	 $7H^{\alpha}H^{\alpha}R^{\beta}R^{\beta}$ $7H^{\alpha}H^{\beta}R^{\beta}R^{\alpha}$	 $7H^{\alpha}H^{\beta}R^{\alpha}R^{\beta}$
7HR$_3$	 $7H^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$	 $7H^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$ $7H^{\alpha}R^{\alpha}R^{\beta}R^{\alpha}$ $7H^{\beta}R^{\alpha}R^{\alpha}R^{\alpha}$	 $7H^{\alpha}R^{\alpha}R^{\beta}R^{\beta}$	 $7H^{\alpha}R^{\beta}R^{\alpha}R^{\beta}$
7R$_4$	 $7R^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$	 $7R^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$	 $7R^{\alpha}R^{\alpha}R^{\beta}R^{\beta}$	 $7R^{\alpha}R^{\beta}R^{\alpha}R^{\beta}$

Table 3. Conformational isomers which become equivalent after the rotation of the OH group

Calixarene	Basic conformation		Equivalent conformation	
distal-$\mathbf{7H_2R_2}$	$\mathbf{7H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}}$	=	$\mathbf{7H^{\alpha}R^{\alpha}H^{\beta}R^{\alpha}}$	$\mathbf{7H^{\alpha}R^{\beta}H^{\alpha}R^{\beta}}$
	$\mathbf{7H^{\alpha}R^{\alpha}H^{\alpha}R^{\beta}}$	=	$\mathbf{7H^{\alpha}R^{\alpha}H^{\beta}R^{\beta}}$	
proximal-$\mathbf{7H_2R_2}$	$\mathbf{7H^{\alpha}H^{\alpha}R^{\alpha}R^{\alpha}}$	=	$\mathbf{7H^{\alpha}H^{\beta}R^{\alpha}R^{\alpha}}$	$\mathbf{7H^{\alpha}H^{\alpha}R^{\beta}R^{\beta}}$
	$\mathbf{7H^{\alpha}H^{\beta}R^{\alpha}R^{\beta}}$	=	$\mathbf{7H^{\alpha}H^{\alpha}R^{\alpha}R^{\beta}}$	$\mathbf{7H^{\alpha}H^{\beta}R^{\beta}R^{\alpha}}$
$\mathbf{7HR_3}$	$\mathbf{7H^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}}$	=	$\mathbf{7H^{\alpha}R^{\alpha}R^{\beta}R^{\beta}}$	
	$\mathbf{7H^{\alpha}R^{\alpha}R^{\beta}R^{\alpha}}$	=	$\mathbf{7H^{\alpha}R^{\beta}R^{\alpha}R^{\beta}}$	
	$\mathbf{7H^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}}$	=	$\mathbf{7H^{\beta}R^{\alpha}R^{\alpha}R^{\alpha}}$	

Table 4. Basic conformational isomers remaining after the rotation of the OH group

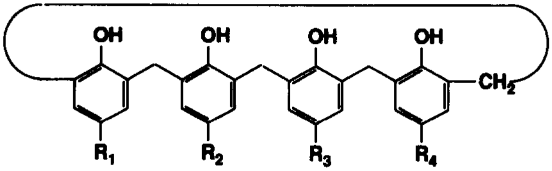
Calixarene	Conformation			
	Cone	Partial-cone	1,2-Alternate	1,3-Alternate
$\mathbf{7H_4}$	$\mathbf{7H^{\alpha}H^{\alpha}H^{\alpha}H^{\alpha}}$			
$\mathbf{7H_3R}$	$\mathbf{7H^{\alpha}H^{\alpha}H^{\alpha}R^{\alpha}}$			
distal-$\mathbf{7H_2R_2}$	$\mathbf{7H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}}$	$\mathbf{7H^{\alpha}R^{\alpha}H^{\alpha}R^{\beta}}$		
proximal-$\mathbf{7H_2R_2}$	$\mathbf{7H^{\alpha}H^{\alpha}R^{\alpha}R^{\alpha}}$			$\mathbf{7H^{\alpha}H^{\beta}R^{\alpha}R^{\beta}}$
$\mathbf{7HR_3}$	$\mathbf{7H^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}}$	$\mathbf{7H^{\alpha}R^{\alpha}R^{\beta}R^{\alpha}}$ $\mathbf{7H^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}}$		
$\mathbf{7R_4}$	$\mathbf{7R^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}}$	$\mathbf{7R^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}}$	$\mathbf{7R^{\alpha}R^{\alpha}R^{\beta}R^{\beta}}$	$\mathbf{7R^{\alpha}R^{\beta}R^{\alpha}R^{\beta}}$

We have found several versatile methods for the syntheses of new conformers[32,53]: (i) mono-*O*-alkylated *p*-tert-butylcalix[4]arenes ($\mathbf{7H_3R}$) can be synthesized in toluene by control of the $\mathbf{7H_4}$/RX (alkyl halide) ratio; (ii) the reaction of $\mathbf{7H_4}$ and RX in the presence of M_2CO_3 (M = Na or K) selectively yields $\mathbf{7H^{\alpha}R^{\alpha}H^{\alpha}R^{\alpha}}$; (iii) the reaction in the presence of Cs_2CO_3 yields either $\mathbf{7HR_3}$ or $\mathbf{7R_4}$ (depending on a $1H_4$/RX ratio), the product being the mixture of partial cone, 1,2-alternate, and 1,3-alternate; (iv) the reaction in the presence of $Ba(OH)_2$ affords only cone-$\mathbf{7HR_3}$; (v) a benzyl group is useful for protection of the OH group. With a combination of these strategies we can now synthesize all of the possible conformers listed in Table 4.

5. Chiral Calixarenes

Of particular interest in the chemistry of cyclodextrins is their ability to sustain asymmetric inclusion and catalysis owing to the presence of the chiral cavity made up of D-glucose units. It therefore seems to us that to introduce some asymmetric factors into calixarenes is an attractive and creative possibility. An expeditious method to make calixarenes chiral is to introduce optically-active groups.[12b,54-56] We have found that guest inclusion in chiral water-soluble calixarenes induces asymmetric deformation of calixarene rings, which can sensitively be monitored by the change in circular dichroism (CD) spectroscopy.[12b,25,55]

More interesting from a stereochemical viewpoint are chiral calix[4]arenes which lack symmetry because of the presence of ring substituents. Thus idea was first proposed by Böhmer *et al.*,[57-59] who synthesized calix[4]arenes (**8**) which have four different substituents at the *para* positions. Similarly, Vicens *et al.*[60] reported **9**, which has no plane of symmetry because of the *m*-methyl group. It is quite interesting that introduction of only one methyl group makes the calix[4]arene chiral. In these compounds, however, racemization through ring inversion occurs on the NMR time-scale and therefore optical resolution is impossible. We considered how we might suppress the ring inversion and optically resolve the racemates.



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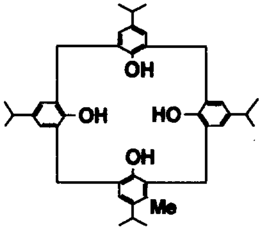

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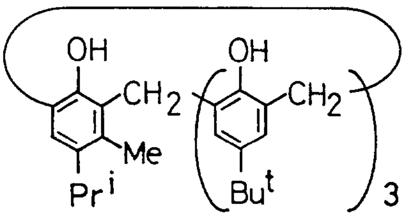
We had already established that the *n*-propyl group is bulky enough to suppress ring inversion of calix[4]arenes.[32] When compound **10** was directly tetra-*O*-propylated with PrBr in the presence of NaH, we obtained a mixture of conformers (at least 6 spots were detected by TLC).[61] Isolation of a pair of racemates from this mixture in reasonable yield would be almost impossible. After much trial and error we finally found that when $Ba(OH)_2$ is used as base, *O*-propylation results in formation of only a tri-*O*-substituted cone isomer (**11**), which can readily be converted into a tetra-*O*-substituted cone-isomer (**12**).[61] Conformationally-immobile racemic cone-**12** was optically resolved by HPLC on a chiral packed column.[61] This is the first example of successful optical resolution of an asymmetrically substituted calix[4]arene.



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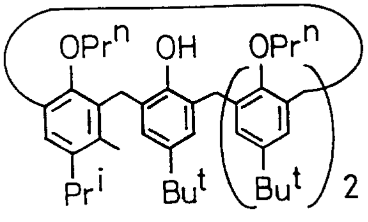

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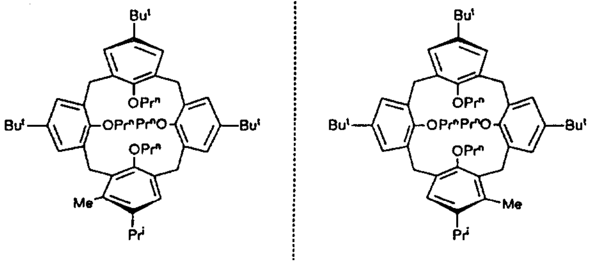

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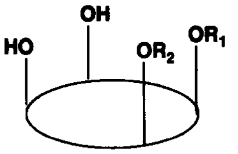
More recently, we found that substituent-based asymmetry in calix[4]arenes is readily realized by introduction of different substituents into OH groups.[62-65] To eliminate a plane of symmetry, at least three different substituents should be arranged in an asymmetric manner. One can count the unmodified OH group as one substituent, so that plane asymmetry is realized if two different substituents are introduced in an asymmetric manner (i.e. in proximal positions: e.g. **13**).[62-64] Even though the substituents are the same, they can serve as different substituents when one of them is inverted and immobilized (e.g. **14**).[63,64] Thus, the numbers of optically-active isomers derivable from calix[4]arene are 24 for tetra-*O*-substituted calix[4]arenes, 10 for tri-*O*-substituted calix[4]arenes, 3 for di-*O*-substituted calix[4]arenes, and 0 for mono-*O*-substituted calix[4]arenes.[64] We have already synthesized and optically resolved several chiral tetra-, tri-, and di-*O*-substituted calix[4]arenes.[64] The results remind us of stereo-isomerism in sugar molecules and show the versatility of calix[4]arene as a building-block for the design of chiral molecules.



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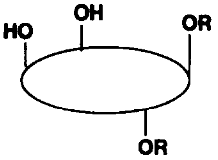
Chiral calix[4]arene with two different substituents



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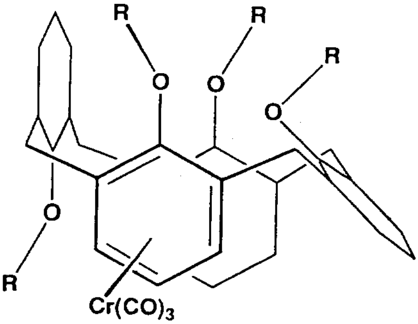
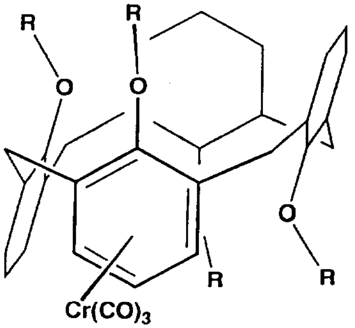
Chiral calix[4]arene with one kind of substituent

We recently developed a new synthetic method for the introduction of functional groups into benzene nuclei in calix[4]arenes *via* tricarbonylchromium complexes.[66,67] It is known that tricarbonylchromium [$Cr(CO)_3$] forms stable η^6-arene complexes and the complexed benzene ring becomes activated thereby. We thus expect that the functional group would be selectively introduced into the reactive benzene unit complexed with $Cr(CO)_3$. We have found that several functional groups such as Me and CHO can be selectively introduced by lithiation with n-BuLi followed by reaction with MeI and DMF, respectively.[67] Interestingly, 1:1 complexes with partial-cone-**5Pr** (**15**) and 1,2-alternate-**5Pr** (**16**) have no plane of symmetry. The ^{1}H NMR spectra of these complexes in the presence of a chiral shift reagent, Pirkle's reagent; showed signals split into pairs.[66] This indicates that the complexes consist of a pair of racemates. These are novel examples of ring-originating optical isomers which may serve as new building-blocks for asymmetric syntheses.



Partial-cone-5Pr(15)

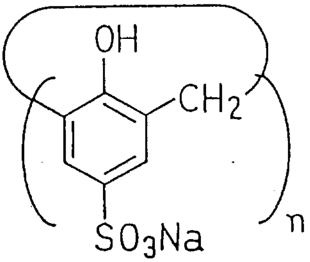


1,2-Alternate-5Pr(16)

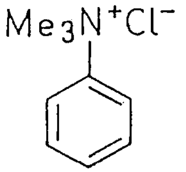
6. Inclusion of Organic Guest Molecules

As mentioned in the Introduction, inclusion of organic guest molecules in water-soluble calixarenes can arise because of the action of hydrophobic forces[6-12,25] and in a few cases guest selectivity on the basis of the cavity size has been observed.[9,10] As described by Gutsche[7], however, guest-binding to calixarene cavities occurs rather nonselectively because of flexibility and conformational isomerism.

The interaction of **17$_n$** with ammonium-type cations was studied in D_2O by the NMR method to estimate the hole-size selectivity possibly operating in these water-soluble calixarenes.[8,68] Although the NMR method is more complicated than other spectroscopic methods, it is applicable to a variety of guest molecules and provides many types of useful information. The guest molecules employed were **18** and **19**. The chemical shifts of **18** and **19** moved to higher magnetic field with increasing calixarene concentrations.[8] This indicates that they are included in the calixarene cavity composed of benzene rings. It was found on the basis of a molar ratio method that **17$_4$** and **17$_6$** form 1:1 complexes with these guest molecules, whereas **17$_8$** forms 1:2 complexes. These findings support the view that calixarenes **17$_n$** are capable of molecular recognition on the basis of the ring size. Examination of the thermodynamic parameters for the association process (determined at pD 7.3: Table 5) established that the complexation with **17$_4$** ($\Delta S < 0$) is mainly due to the electrostatic force, whereas that with **17$_6$** and **17$_8$** ($\Delta S > 0$) is due to the hydrophobic force.[8]



17$_n$



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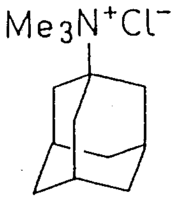

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Table 5. Association constants K at 25 °C (M^{-1}) and thermodynamic parameters ΔH (kcal mol^{-1}) and ΔS (cal mol^{-1} deg^{-1})[a] for the interaction of **18** and **19** with **17$_n$**.

Guest	Parameter	**17$_4$**	**17$_6$**	**17$_8$**	
				1:1	1:2
	K	5600	550	5200	4600
18	ΔH	-6.2	-0.25	0.0	0.0
	ΔS	-3.6	11.7	17.0	16.7
	K	21000	1000	19000	17000
19	ΔH	-5.7	-0.15	0.0	0.0
	ΔS	0.65	13.3	19.6	19.3

[a] D_2O, 25 °C pD 7.3 with 0.1 M phosphate buffer.

The $\Delta S > 0$ values observed for **17$_6$** and **17$_8$** are reasonably understandable because the main driving-force for complexation operating in an aqueous system is the hydrophobic force. However, the $\Delta S < 0$ value observed for 17_4 has remained inexplicable for a long period. It implies that the driving-force for inclusion in 17_4 is not the hydrophobic force but some "electrostatic force", even in aqueous solution. More recently, we noticed that the ^1H NMR spectrum for the $17_4 \cdot 18$ complex measured at pD 0.4 is quite different from that determined at pD 7.3[68] (the thermodynamic parameters were determined at pD 7.3). At pD 0.4 only the proton signals for the benzene protons shift to higher magnetic field, indicating that the benzene ring resides in the cavity, whereas at pD 7.3 both signals for the benzene protons and N^+CH_3 protons shift to higher magnetic field, indicating that both the benzene ring and the trimethylammonium moiety are included in the cavity.[68] The only possible change induced by the variation in pD is the dissociation of the OH groups. Thus, the difference can be accounted for by the change in the electron density in the benzene π-systems induced by the dissociation of the OH group: that is, in the acidic pH region the benzene ring is predominantly included because of the hydrophobic interaction, whereas in the neutral pH region the OH group is dissociated and the trimethylammonium moiety is included with the aid of the *cation-π interaction*. This means that under this pD condition the *cation-π interaction* can compete effectively with the hydrophobic interaction (Figure 8). This binding mode explains satisfactorily the $\Delta S < 0$ value observed at pD 7.3.[8] In this connection, it is interesting to note that in the crystal structure of *p*-tert-butylcalix[4]arene mono-cesium salt the metal atom resides in the cavity composed of benzene π-systems.[69] The driving-force for this inclusion is also attributable to the *cation-π interaction*.

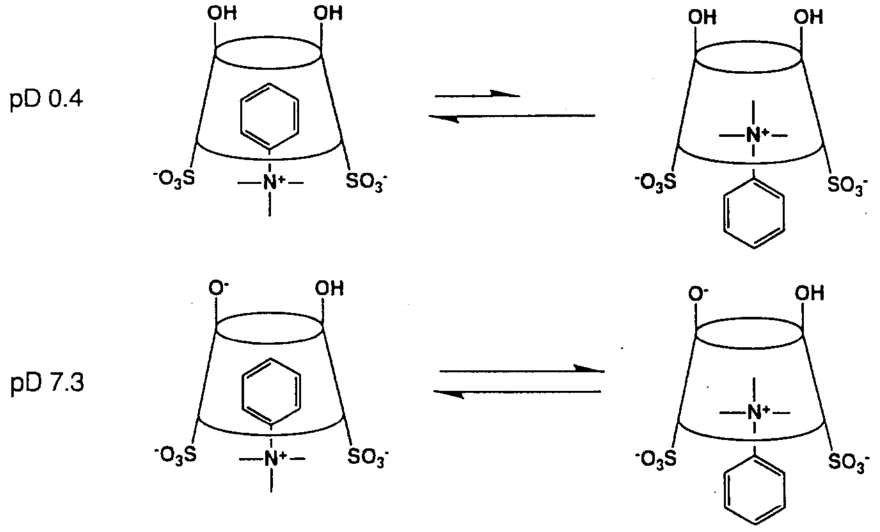
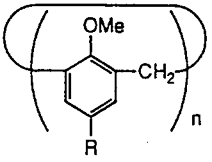
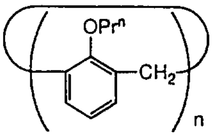


Figure 8. Complexation of 17_4 with **18** in acidic and neutral pD solutions

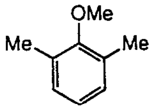
The foregoing findings tempted us to investigate *cation-π intractions*[70,71] in a calixarene family more in detail. We employed $\mathbf{20_nR}$, $\mathbf{21_n}$, and **22** (as an acyclic reference compound) as host molecules and **23** and **24** as cationic guest molecules in a study of their inclusion properties in $CDCl_3$ by ^1H NMR spectroscopy.[72] When **23** was used as a guest molecule, a significant up-field shift was observed only for the CH_3N^+ and CH_2N^+ protons. This trend is similar to that reported by Schneider *et al.*[73] for resorcinol tetramers. This reveals that the trimethylammonium head group is predominantly included in the calixarene cavity.[72] Among $\mathbf{20_nH}$, the magnitude of the up-field shifts appeared in the order $\mathbf{20_6H} > \mathbf{20_8H} > \mathbf{20_4H}$, indicating that calix[6]arenes can provide a π-base cavity, the size of which fits the size of the trimethylammonium cation (Figure 9).[72] On the other hand, $\mathbf{20_6Bu^t}$, with tert-butyl groups at the *p*-positions, and **22** scarcely interacted with **23**. In $CDCl_3:CD_3CN = 10:1$ v/v at -50 °C, $\mathbf{20_4H}$ exists as a mixture of cone (31%) and partial-cone (69%). Addition of **24** (1.0 equiv) increased the fraction of cone-$\mathbf{20_4H}$ to 67% and the chemical shifts for cone-$\mathbf{20_4H}$ were affected by added **24** while those for partial-cone-$\mathbf{20_4H}$ were not.[72] These results clearly indicate that the cation is favorably included in the cone-shaped cavity. This conclusion is further corroborated from the chemical shift change in conformationally-immobile $\mathbf{21_n}$: among four conformers of $\mathbf{21_n}$ a significant up-field shift was observed only for cone-$\mathbf{21_n}$.[72] In conclusion, we learned that a significant *cation-π interaction* is observable only when the π-base cavity for cation inclusion is "pre-organized", like an oxygen cavity for metal cation inclusion in a crown ether family.



$\mathbf{20_nR}$



$\mathbf{21_n}$



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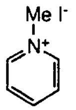
$CH_3(CH2)_7N^+(CH_3)_3\ Br^-$

23



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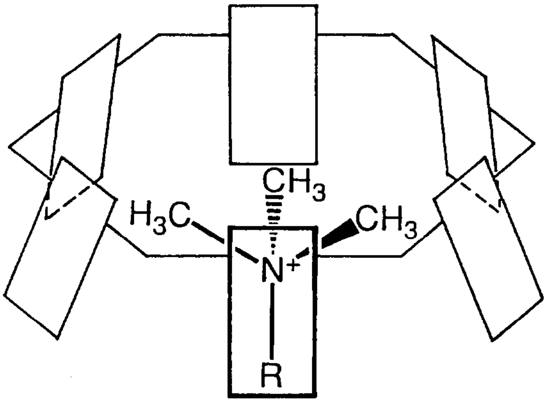
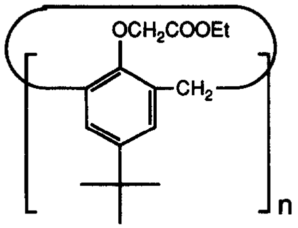


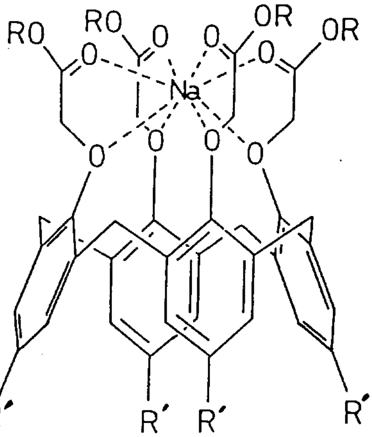
Figure 9. Inclusion of a trimethylammonium cation in the π-base cavity of calix[6]arene

7. Metal Inclusion Properties: Design of Chromogenic Calixarenes

It has been shown that calix[4]aryl esters **25_4** exhibit remarkably high selectivity toward Na$^+$.[13-15,74] This is attributable to the inner size of the ionophoric cavity composed of four OCH$_2$C=O groups, which is comparable with the ion size of Na$^+$, and to the cone conformation which is firmly constructed on the rigid calix[4]arene platform. In contrast, calix[6]aryl esters exhibit broad ion selectivity, although the highest selectivity is for K$^+$.[13-15,74] Probably, the broad ion selectivity is related to the flexibility remaining in the calix[6]arene framework.



25_n



25_4•Na$^+$ complex(R=Et, R'=*tert*-Bu)

We noticed that compounds **25_n** form stable monolayers at the air-water interface and the metal response therein is quite different from that in solution.[75]

As shown in Figure 10a, **25**$_4$ and **25**$_6$ form condensed monolayers: their molecular areas are 1.16 nm^2 for **25**$_4$ and 2.06 nm^2 for **25**$_6$.[75] These values are in accord with the areas of the larger sides (upper rims) of cone-shaped calix[n]arenes. In the π-A curve for **25**$_8$, on the other hand, the pressure increases gradually from 3.94 nm^2, with a break point at 18 mN m^{-1}.[75] The curve is reasonably explained by the flexibility and the pressure-induced conformational change in calix[8]arene. These monolayers "respond" to alkali metal cations. As shown in Figure 10b, the monolayer of **25**$_4$ is much expanded on aqueous NaCl but not on aqueous KCl.[75] This is what we could expect from the high Na^+ selectivity of **25**$_4$. In contrast, the monolayer of **25**$_6$ is expanded on aqueous KCl but not on aqueous NaCl. As mentioned above, **25**$_6$ shows high affinity towards K^+ but also binds Na^+.[13-15,74] The monolayer response of **25**$_6$ for K^+ is very sharp. We thus rationalize the discrepancy in the ion selectivity between the homogeneous solution and the air-water interface as follows: in the solution system the ring flexibility which allows **25**$_6$ to bind metal cations according to an induced-fit manner still remains, whereas in the monolayer system the conformation of **25**$_6$ is confined to cone, which leads to the high K^+ selectivity.

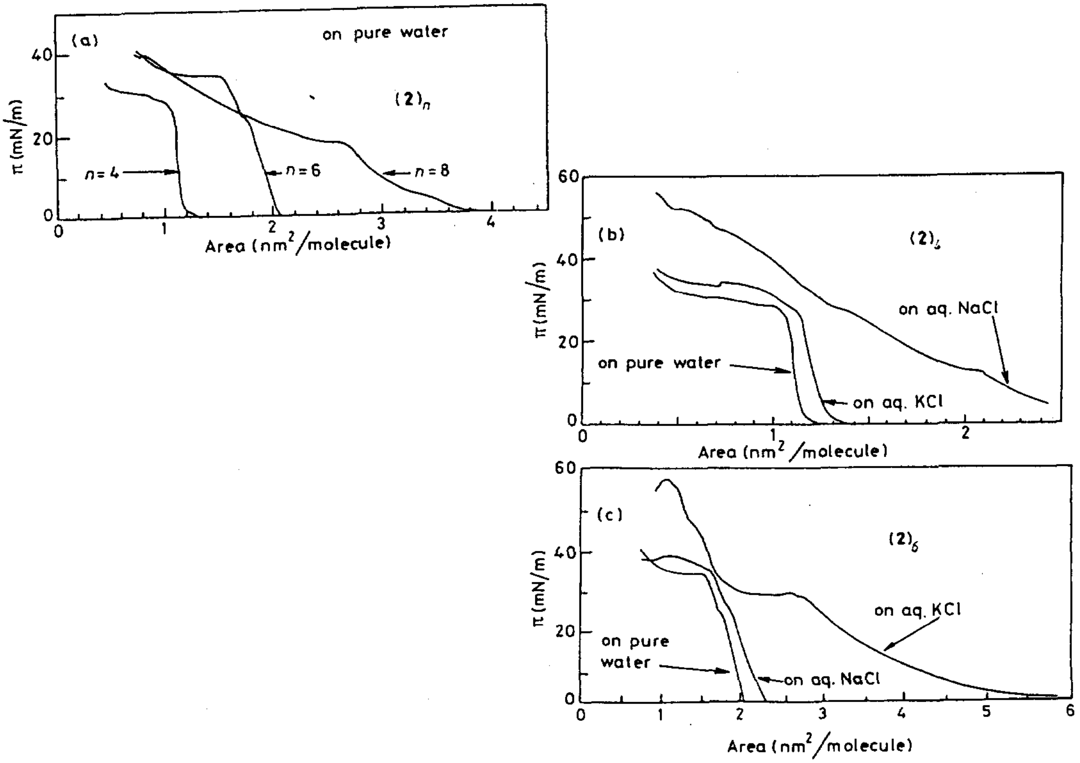
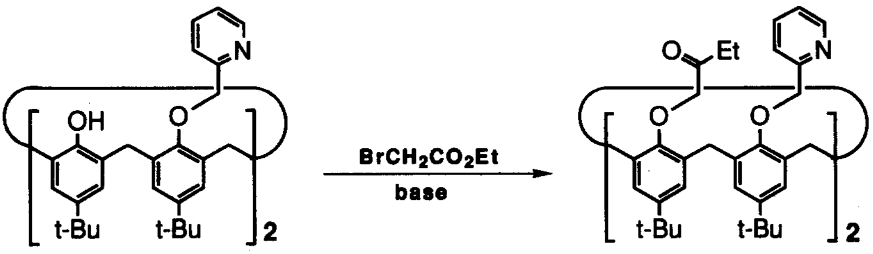


Figure 10. Surface presure-area (π-A) curves of **25**$_n$

Cone-$\mathbf{25_4}$ with a cone conformation was synthesized by the reaction of *p-tert*-butylcalix[4]arene and ethyl bromoacetate in the presence of NaH.[13-15,74] It is known, however, that tetra-*O*-alkylation of *p*-tert-butylcalix[4]arene in the presence of NaH yields a mixture of conformational isomers.[31,32,41,42,53] Why does the reaction of *p*-tert-butylcalix[4]arene and ethyl bromoacetate yield only cone-$\mathbf{25_4}$? Examination of the metal template effect on the conformer distribution established that when the metal cation present in the base used serves as a template, the cone conformer results predominantly.[32,41,53] Hence, Na^+ in NaH should serve as an efficient template ion to yield cone conformers. We considered that if one could synthesize ionophoric calix[4]arenes (such as $\mathbf{25_4}$) other than cone, they should show different metal affinity and metal selectivity and further extend calixarene-based receptor chemistry. We synthesized **27** by the reaction of **26** and ethyl bromoacetate in DMF in the presence of K_2CO_3.[76-78] The purpose of this study was to synthesize versatile calixarene-based ligands for transition metal ions. We found three spots on the TLC plate: the product was a mixture of cone-**27** (HPLC yield 79%), partial-cone-**27** (16%), and 1,3-alternate-**27** (5%).[76-78] When Cs_2CO_3 was used instead of K_2CO_3, we obtained cone-**27** (HPLC yield 0%), partial-cone-**27** (69%), and 1,3-alternate-**27** (31%) (Table 6). These results indicate that ionophoric calix[4]arenes other than cone can be synthesized by the use of nontemplate metal ions. The solvent extraction data indicated that cone-**27** shows strong ion affinity compared with $\mathbf{25_4}$ and binds not only Na^+ but Li^+.[76,77] On the other hand, partial-cone-**27** and 1,3-alternate-**27** show K^+ selectivity. X-Ray crystallographic studies[32,78] indicated that the distance between two pyridines in partial-cone and 1,3-alternate is longer than that in cone, providing larger ionophoric cavities suitable for the binding of K^+. This means that the metal selectivity of ionophoric calix[n]arenes can be changed not only by change in the ring size but also by conformational change.



26 **27**

We also found that a similar metal template effect governs the conformer distribution of $\mathbf{25_4}$.[41,79] As shown in Table 7, one can realize a change from 100% cone selectivity in the presence of Na_2CO_3 to 100% partial-cone selectivity in the presence of Cs_2CO_3 in acetone solvent.[79] 1,2-Alternate-**25**$_4$ and 1,3-alternate-**25**$_4$ were also synthesized by a protection-deprotection method using a benzyl group.[79] Cone-**25**$_4$ showed Na^+ selectivity whereas other three conformers showed K^+ selectivity, indicating that the ionophoric cavity of cone-**25**$_4$ is smaller than those of the other three conformers.[79]

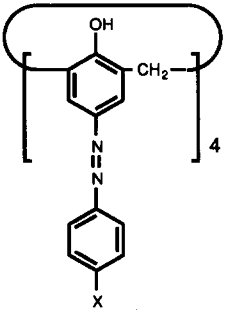
Table 6. Conformer distribution for the reaction of **26** and ethyl bromoacetate[79]

Solvent	Base	Distribution of **27**		
		Cone	Partial-cone	1,3-alternate
DMF	Li_2CO_3	100	0	0
DMF	K_2CO_3	79	16	5
DMF	Cs_2CO_3	0	69	31
Acetone	Li_2CO_3	100	0	0
Acetone	K_2CO_3	0	100	0
Acetone	Cs_2CO_3	0	37	63

Table 7. Conformer distribution for the reaction of *p-tert*-butylcalix[4]arene and ethyl bromoacetate[79]

Solvent	Base	Distribution of **25**$_4$		
		Cone	Partial-cone	1,3-Alternate
THF	NaH	100	0	0
DMF	Li_2CO_3	100	0	0
DMF	Na_2CO_3	88	12	0
DMF	K_2CO_3	84	16	0
DMF	Cs_2CO_3	27	73	0
Acetone	Na_2CO_3	100	0	0
Acetone	K_2CO_3	96	3	0
Acetone	Cs_2CO_3	0	100	0

Metal-binding events are usually estimated either by two-phase solvent-extraction or by ^1H NMR measurements. If they can be detected by more convenient methods, they not only simplify the estimation of the ion selectivity but also lead to the exploitation of new ion sensing systems. The basic concept has been demonstrated to some extent by so-called "chromogenic crown ethers". We thus tried to design "chromogenic calixarenes".[43,80-83] To "color" calix[n]arenes we introduced diazo groups into calix[4]arene. Diazo coupling with benzenediazonium ions in THF in the presence of pyridine afforded the tetrasubstituted calix[4]arenes (**28**) as the main products together with small amounts of mono-, di-, and tri-substituted calix[4]arenes, even in the presence of unchanged calix[4]arene.[80,82] This means that diazo coupling proceeds in an autoaccelerative manner. As a result of intramolecular hydrogen-bonding interactions, introduction of electron-withdrawing groups such as *p*-phenylazo would lower the pK_a of the OH groups not only in the substituted phenol unit but also in the neighboring phenol units. This situation facilitates the dissociation of the residual OH groups and diazo coupling occurs autoacceleratively. The products were obtained as new chromogenic calixarenes, in which the dissociation of the OH group to give new absorption maxima at 553 and 665 nm occurs only on the addition of Li^+.[82]



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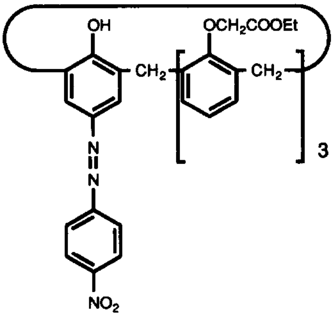

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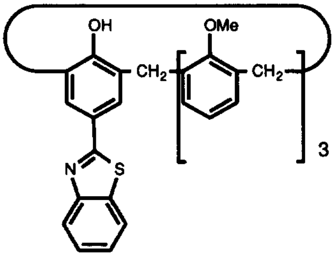

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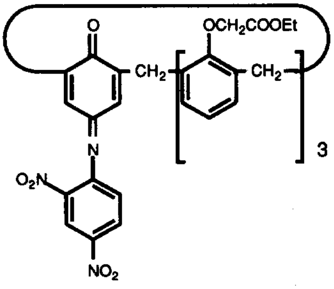

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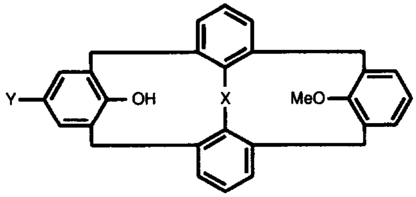
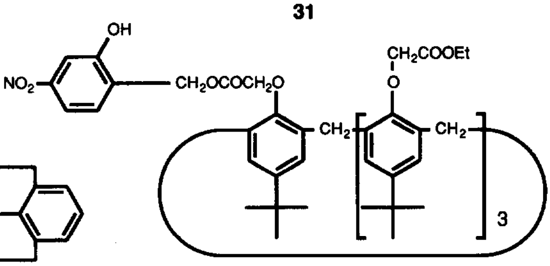


X = $OCH_2(CH_2OCH_2)_3CH_2O$
Y = 2,4-dinitrophenyl

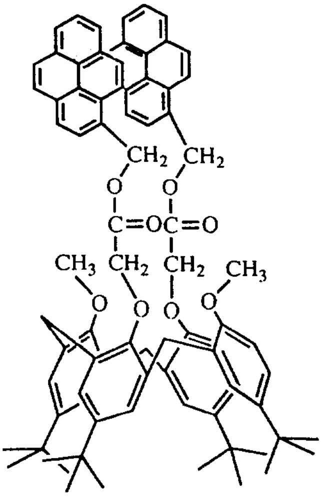
32



33

Based on a similar molecular design principle, we synthesized **29** and **30**. In **29**, an ionophoric cavity composed of three $OCH_2C=O$ groups is located near a dissociable phenol unit.[43] In **30**, an ionophoric cavity composed of three ether groups is located near a fluorogenic phenol unit.[83] Both compounds showed "perfect" Li^+ selectivity.[43,83] Compounds **31-33** are chromogenic calix[4]arenes designed on a similar basis.[84-86]

In cases where chromogenic calixarenes contain the dissociation group as a metal-binding reporter, one has to carefully adjust the pH of the medium: the OH group, for example, should not be dissociated before the metal-binding event, whereas it should be readily dissociated on metal-binding. This special requirement restricts the application range of chromophoric calixarenes. In 1991, we designed a new fluorogenic calix[4]arene **34**.[87] The fluorescence properties of **34** were very interesting: strong excimer emission (*ca.* 480 nm) was observed in the absence of metal cations, and with increasing metal concentration (Li^+, Na^+, or K^+) monomer emission (*ca.* 380 nm) increased.[87] The log K_{ass} values determined from the fluorescence change at 25 °C in diethyl ether were 4.73 for LiSCN, 5.34 for NaSCN, and 4.06 for KSCN.[87] ^1H NMR spectroscopy showed that added metal cations change the conformation of **34** from partial-cone to cone. Also, the ester carbonyls turned to the exo-annulus direction to reduce electrostatic repulsion rotate to the endo-annulus direction to coordinate to the bound metal cation. These two metal-induced molecular motions induce a drastic change in the distance between the two pyrene groups and the intensity of excimer emission is weaker. Thus, one can achieve metal sensing under a wide pH range. It was also shown that the fluorescence intensities of **34** change in response to certain carboxylic acids which are bound to the ionophoric cavity by hydrogen-bonding interactions.[88] In 1992, Jin *et al.*[89] reported compound **35**, which selectively responded to Na^+. In this compound, ring inversion of phenol units is inhibited, so that the *exo*-to-*endo*-annulus rotation of the ester groups is the main driving-force for the change in the monomer/excimer emission ratio. More recently, we designed compound **36** bearing pyrene (as a flluorophore) and nitrobenzene (as a quencher) near the ionophoric cavity.[90] In the absence of metal cations fluorescence is efficiently quenched by the intramolecular nitrobenzene. In the presence of Na^+ the quenching efficiency becomes low because of the separation of the fluorophore and the quencher, and the fluorescence intensity is dramatically enhanced.[90]



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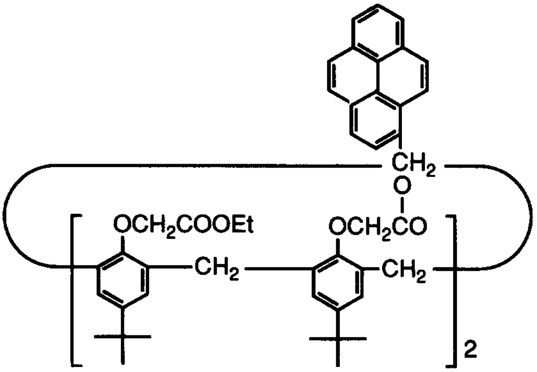

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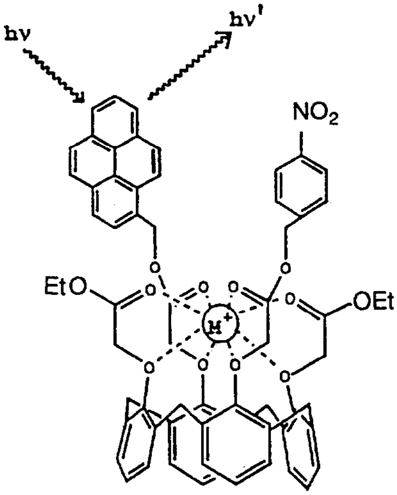
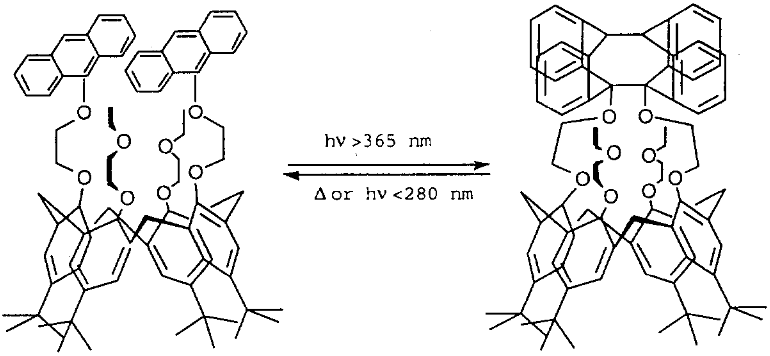


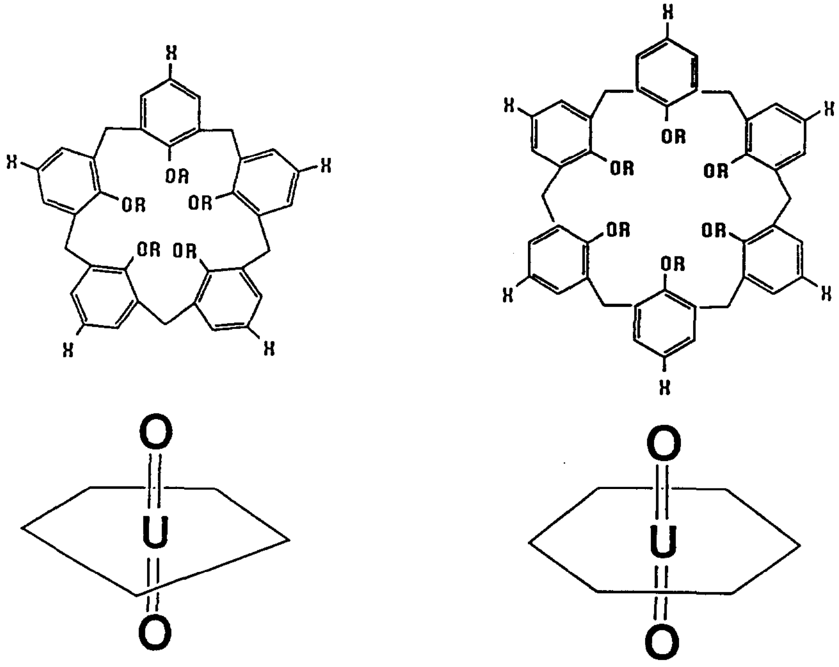
36·M+ complex

Ionophoric cavities constructed on the lower rim of calix[4]arenes show high Na^+ selectivity. It occurred to us that if one can "close" the cavity after the metal-binding event, the rate of the dissociation process would be suppressed and, eventually, the kinetically-stable metal complex would result. In crown ether chemistry photo-dimerization of anthracenes has been utilized for the design of light-responsive "switched-on" crown ethers.[91,92] We introduced two anthracenes near the metal-binding site of calix[4]arene.[93,94] Compound **37** itself showed poor ion affinity and poor ion selectivity, whereas the photochemically produced isomer **37'** with a closed ionophoric cavity showed much improved ion affinity and sharp Na$^+$ selectivity.[94] Although **37'** did not form a kinetically-stable complex with Na$^+$, the ^{1}H and ^{23}Na NMR spectra established that the association-dissociation rate for **37'** is much slower than that for **37**.[94]



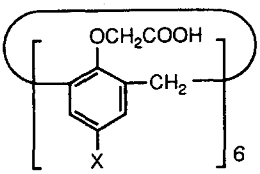
37 **37'**

In 1986, we found that certain calix[5]arenes and calix[6]arenes have not only high, record-breaking stability constants (log K_{uranyl} = 18.4-19.2) but also an unusually high selectivity for UO$_2^{2+}$ ($K_{\text{uranyl}} / K_{\text{Mn}^+}$ = 10^{12}-12^{17}).[93,94] The high affinity was rationalized in terms of "coordination-geometry selectivity": the pentamers and the hexamers can provide suitable arrangements of ligand groups on the edge of calixarenes required for pseudoplanar penta- and hexacoordination of UO$_2^{2+}$ complexes (Figure 11).[94] To improve further the UO$_2^{2+}$ affinity of **38** as a superuranophile, we synthesized **39** bearing hydroxamate groups, which are known to have high UO$_2^{2+}$ affinity.[95,96] The extractability (Ex%) and selectivity were compared in a two-phase (water-chloroform) solvent-extraction system. Ex% for **39** increased from pH 2 and saturation was reached at around pH 5, where 100% UO$_2^{2+}$ extraction occurred.[96] Since the pK_a values for hydroxamic acids are 8-9, the apparent pK_a shift caused by UO$_2^{2+}$ complexation amounts to 6-7 pK units. Extraction of UO$_2^{2+}$ from aqueous carbonate solution established that **39** in the organic phase can fully compete with CO$_3^{2-}$ in the aqueous phase for UO$_2^{2+}$, whereas **38** cannot.[96] We also found that the selectivity of **39** is superior to **38**: the Ex% values for **39** was scarcely affected by the addition of competing metal cations.[96] These results indicate that immobilization of uranophilic hydroxamate groups on the hexagonal calix[6]arene platform results in an excellent superuranophile. More recently, Ohto *et al.*[97] found that $\mathbf{40}_n$ (n=4 and 6) are useful for selective extraction of rare-earth metal ions.



R = H , CH_2COOH
X = H , ^{t}Bu , SO_3Na

Figure 11. Pseudoplanar penta- and hexacoordination structures of UO_2^{2+} complexes.



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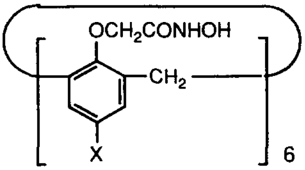

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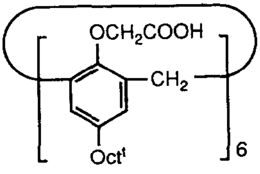
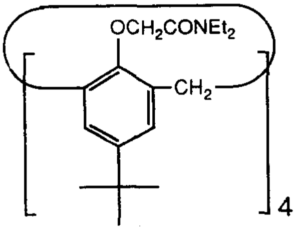


40$_n$



41

The luminescence properties of lanthanide ions have been of much interest because of their potential use as probes and labels for a variety of chemical and biological applications.[100-103] To design an excellent emitting system one has to take two prerequisites into consideration, viz. (i) lanthanide ions must be shielded from solvent molecules through encapsulation in the ligand, and (ii) the ligand must have the lowest excited state sufficiently high for the energy-transfer to lanthanide ions.[98,99] Subbatini *et al.*[100] found that Tb^{3+} and Eu^{3+} are strongly encapsulated in **41** and the **41**•Tb^{3+} complex exhibits a remarkably high luminescence quantum yield (ø 0.2). They proposed that **41** possesses the $3\pi\pi^*$ level from which the energy-transfer to Tb^{3+} can take place.[100,102] This result implies that **41** is an ideal ligand for energy-transfer luminescence of Tb^{3+}, but is useful only for Tb^{3+}. In fact, the luminescence quantum yield for the **41**•Eu^{3+} complex is extremely low (ø 2×10^{-4}).[100] It thus occurred to us that if one could introduce an appropriate sensitizer near the metal-binding site of calix[4]arene, one might be able to transfer the excited-state energy from the sensitizer to encapsulated lanthanide ions. After trial-and-error experiments, we finally discovered that **42**, bearing a diphenyl group as a sensitizer, is useful for luminescence of Tb^{3+} (ø 0.27) and Eu^{3+} (ø 0.06).[104] We consider that, as shown in Figure 12, the excited-state energy is transferred to Eu^{3+} from the diphenyl sensitizer. This concept should eventually become useful to excite any lanthanide ions by appropriate selection of the sensitizer.

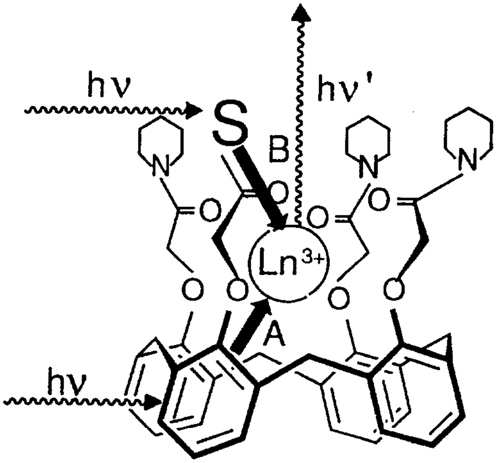
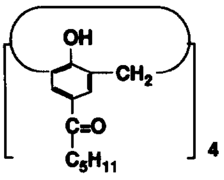


Figure 12. Energy-transfer luminescence in **42** (where S is a diphenyl sensitizer): path A is allowed only for Tb^{3+}, whereas path B is allowed for Tb^{3+} and Eu^{3+}.

8. Self-Assembly of Calixarenes

In previous studies on calixarene chemistry, central concerns have been related to the stereochemistry and molecular recognition properties of one calixarene molecule. On the other hand, when calixarenes aggregate, the assemblies may provide stereochemical and molecular recognition properties somewhat different from those of the isolated molecules. One example of such assembly systems is the monolayer of **25**$_6$ as described above, in which K$^+$ selectivity is markedly enhanced.[75]

We synthesized calix[n]arenes (n=4, 6, and 8) bearing long *p*-acyl or *p*-alkyl groups.[105] Among these, **43** showed a curious phase transition behavior: on raising the temperature it changed as crystal A → (95 °C) → liquid → crystal B → (194 °C) → liquid.[105] When the final liquid was cooled, it gave crystal B. Crystal A was reproduced only when crystal A was recrystallized from benzene. It was found on the basis of solid state ^{13}C NMR spectra that crystal A and crystal B adopt a cone and a partial-cone conformation respectively.[105] To the best of our knowledge, this is the only case where an unmodified calix[4]arene adopts a conformation other than cone. Calix[4]arenes adopt the cone conformation because of strong intramolecular hydrogen-bonding interactions. To isomerize to other conformers, one or two hydrogen bonds must be cleaved. Conceivably, above 95 °C the stabilization due to hydrogen-bonds becomes less effective because of vigorous molecular motion, and thus a cone isomer can isomerize to a more flexible partial-cone conformer.



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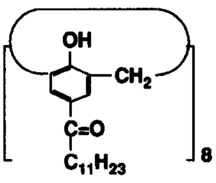

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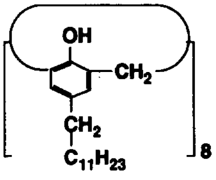
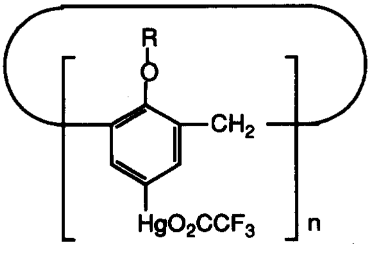


45

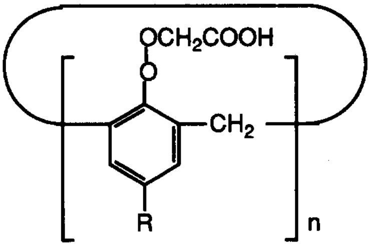
In the course of the above study,[105] we observed a curious phenomenon, namely that recrystallization of **44** from certain organic solvents (e.g. toluene, CCl_4, CS_2, *n*-hexane, etc.) results in the formation of gels.[105,106] The sol-gel phase transition temperatures (*T*g) were in the range 20-40 °C.[106,107] The change occurring at the phase transition temperature was directly observable using an optical microscope: below *T*g a fibrillar network (diameter *ca.* 1 μm) appeared, whereas above *T*g it "melted" down.[106] Spectroscopic studies established that the prerequisites for the formation of stable organic gels are (i) intermolecular C=O••••HO hydrogen-bonding interaction to form a three-dimensional network, and (ii) a moderate affinity with solvent molecules.[106,107] This is the first example of macrocycle-based organic gelators.

It is known that calix[n]arenes and their ester derivatives produce stable monolayers at the air-water interface.[75,108-110] While *p*-octadecylphenol forms a monolayer on water with the limiting area of 24.3 Å^2/molecule, *p*-

octadecylcalix[4]arene forms a stable monolayer only at the alkaline subphase with 1.03 nm^2/molecule.[108] *p*-tert-Butylcalix[6]arene forms a stable monolayer having a limiting area of 2.60 nm^2/molecule.[109] These cross sections roughly correspond to the upper edge of calix[4]arenes with a cone conformation. Regen *et al.*[110] prepared monolayers from mercurated O-alkoxycalix[n]arenes (**46**$_n$). Water evaporation studies revealed that calix[n]arene-based monolayers maintain a porous structure that offers little resistance to permeation of water molecules, compared to the densely packed aliphatic monolayer of surfactants.[110] We also found that compounds **47**$_n$ (n = 4 and 6) form stable monolayers at the air-water interface.[111] At pH 2.8 the limiting areas are 1.15 nm^2/molecule for **47**$_4$ and 1.72 nm^2/molecule for **47**$_6$. The collapse pressure of **47**$_4$ increases from 21 mN m^{-1} in the absence of $NaClO_4$ to 32 mN m^{-1} in the presence of 0.1 M $NaClO_4$.[111] This supports the view that **47**$_4$ can bind Na^+ at the monolayer. They respond specifically to transition metal cations.[111]

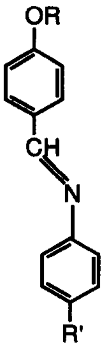


46$_n$



47$_n$

It is known that compounds **48** act as liquid crystals which have the K → N phase transition temperature at around room temperature. The skeleton of **48** can be readily introduced into calix[n]arenes via *p*-formylcalix[n]arenes **49**.[112] Among 12 products **50**$_n$**C**$_m$ (n = 4, 6, and 8; m = 8, 12, 14, and 16), only **50**$_8$**C**$_{16}$ showed the liquid crystal phase at 20-55 °C.[112] Other calix[n]arenes were glassy solids and melted over a broad range.[112] These compounds showed "flow-birefringence (FB)" under crossed Nicol prisms. In particular, **50**$_4$**C**$_{12}$ showed stable FB over a wide temperature range (10-40 °C).[112] When two glass plates sandwiching viscous **50**$_4$**C**$_{12}$ were slid under crossed Nicol prisms, the whole sample shone. When two glass plates were turned concentric-circularly, a dark cross appeared in a white background. This pattern implies that **50**$_4$**C**$_{12}$ orientates in a concentric circular manner. These results indicate that amorphous and mesomorphic compounds derived from calix[n]arenes possess a number of unique and potentially important properties for the development of optical storage and display devices.



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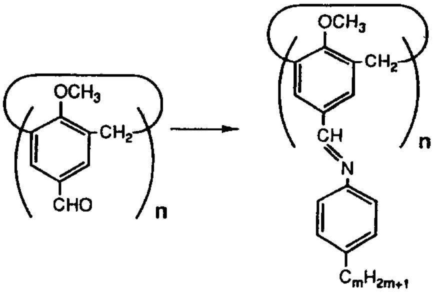

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50_nC_m

9. Conclusions

In the history of host-guest chemistry during the last two decades, the chemistry of cyclodextrins and crown ethers has been of central interest. Why have these two types of macrocycle attracted extensive attention for such a long time?: because (i) systematic change in the ring size is possible; (ii) large-scale preparation is possible; (iii) cyclodextrins can recognize organic guest molecules and crown ethers can recognize metal and ammonium guest ions, etc.[25] These characteristics allow us to classify cyclodextrins and crown ethers as "supramolecules". As surveyed in this review article, calixarenes undoubtedly possess the potential to be classified as the "third supramolecule", because they can recognize not only metal cations but also organic molecules; large-scale preparation is extremely easy, optically-active isomers can be synthesized, and selectivities are generally superior because of the rigid ring structures. We believe that further extension of calixarene chemistry will provide new fields of chemistry associated with molecular recognition, ion sensing, liquid crystals, display devices, energy conversion systems, etc.

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