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Synthesis, Conformations and Inclusion Properties of Homocalix[3]arenes

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Abstract. A new type of host is introduced: homocalix[3]arenes containing three aromatic units. Phane synthesis leading to molecules which may be termed, in the most general sense, homocalix[3]arenes, are outlined in a brief overview. The design, synthesis, conformations and host properties of homocalix[3]arenes are described in detail.

Key words: phane synthesis, homocalix[3]arenes, conformations, ionophores, host properties, extraction.

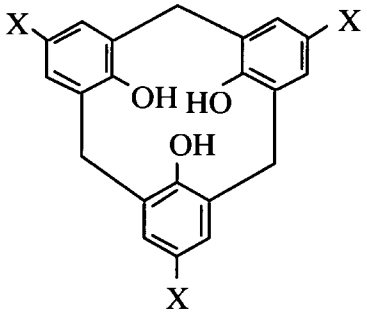
1. Introduction

Molecular recognition is a fundamental aspect of biological processes and particular interest has been focused on its understanding. One pathway to this understanding is the study of 'model' compounds, the products of 'supramolecular chemistry', wherein specific properties of biomolecules may be considered in isolation. The control of both functional groups and molecular stereochemistry in these synthetic molecules provides numerous insights into the relationship between structure and function, insights which are often obscure within the full complexity of the biological systems.

The calixarenes [1, 2] are a versatile group of 'host' molecules which have indeed been used to probe various aspects of enzyme functions [3]. The most important properties of calix[n]arenes are their easy derivatization in a well-defined manner and their unique molecular architecture suitable for complexation with ions and/or neutral molecules [4, 5]. This short review describes such a group of molecules, closely related to the calixarenes obtained through the synthesis which combine aspects of cyclophane and host-guest chemistry. It was defined as 'homocalixarenes'. Whereas calix[4]arenes contain a $[1_4]$MCP (MCP = metacyclophane) skeleton, the homocalix[3]arenes are $[n_3]$MCPs in which additional CH_2 groups or CH_2XCH_2 (X = O, NR, C=O etc.) are present in their bridges.

2. Synthesis

Although there has been an extensive study of calixarenes in the last decade [1–3], it is surprising that reports on the preparation of calix[3]arenes containing three benzene rings and characterization of their structure have been very limited. Although the first success of the condensation of 5,5′-dihalo-2,2′-dihydroxydiphenylmethane with 4-halo-2,6-bis(hydroxymethyl)phenol to afford a 69–90% yield of *p*-halocalix[3]arenes **1** was reported in 1982 by Moshfegh and coworkers [6], no further study has apparently followed it so far, which seems to be due to the much more strained structure of calix[3]arenes **1** than that of calix[4]arene **2** containing a larger ring.



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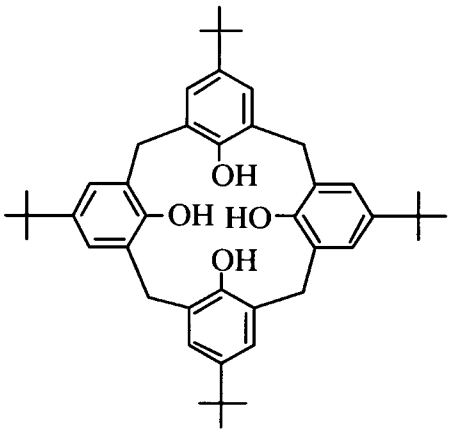

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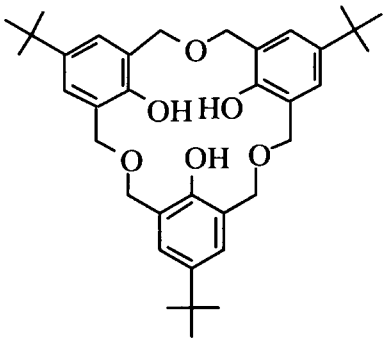
2.1. Synthesis of hexahomotrioxacalix[3]arenes

The interest which calixarenes have aroused in the last ten years [1–3] is due in the main to their ready availability. Multigram amounts can be obtained on a laboratory scale in a relatively simple manner starting from cheap starting materials. Hexahomotrioxacalix[3]arene **3** was initially reported to be formed in trace amounts during the base-catalyzed condensation of *p-tert*-butylphenol and formaldehyde to form phenolic resins [7]. Vicens and Gutsche [8, 9] reported that the dehydration of 2,6-bis(hydroxymethyl)phenol in refluxing xylene resulted in the direct "one-pot synthesis" of hexahomotrioxacalix[3]arene **3** along with other macrocyclic products. Gutsche and co-workers isolated a mixture of macrocycles which included **3** in 30% yield, and the mixture was reported to be separated by a simple recrystallization. Hampton [10] developed this condensation reaction by using acid catalyst, CH_3SO_3H, and applied it to a variety of substituted oxacalix[3]arenes.



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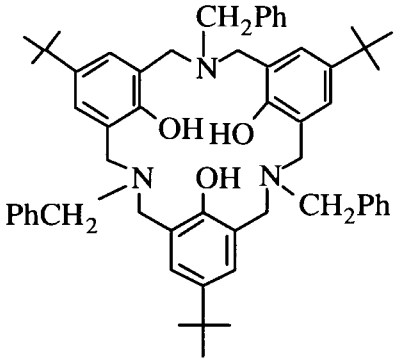

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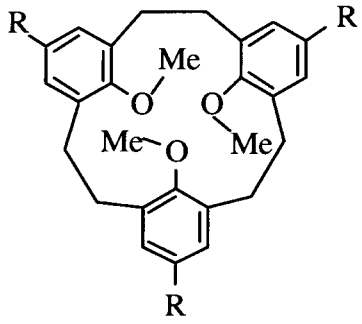
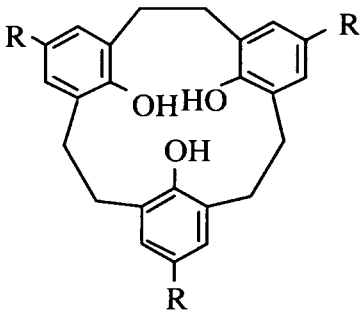
Recently, synthesis of oxacalixarene analogues (azacalixarenes) **4** based on condensation between benzylamine and 2,6-bis(hydroxymethyl)-4-alkylphenol have been described [11, 12].

2.2. SYNTHESIS OF [2_3]MCPS

Using a modified Wultz reaction, Jenny et al. [13] were able to obtain "oligomeric" [2_3]MCP containing three aromatic units from 1,3-bis(bromomethyl)benzene in 7.5% yield along with other cyclooligomers. Recently, "all-homocalix[3]arenes **5**", in which all the methylene bridges are replaced by ethylene bridges, have been obtained by Vögtle et al. [14] from bisbromomethylated anisoles by employing Müller-Röscheisen conditions of sodium tetraphenylethene in THF at −80°C [15]. Tashiro et al. [16] have synthesized similar compounds **6** via the corresponding CH_2-S-CH_2-bridged macrocycles using the sulfone extraction method known from cyclophane chemistry.



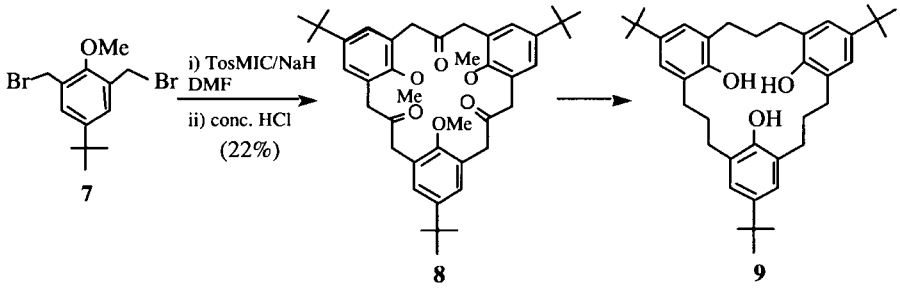
5 R = H, Me



6 R = H, t-Bu

2.3. SYNTHESIS OF [3_3]MCPS

Vögtle [17] reported the preparation of carbocyclic [3_3]MCPs using (*p*-tolylsulfonyl)methylisocyanide (TosMIC) [18] as the cyclization reagent, which was applied in a new cyclization procedure without phase-transfer conditions [19]. This strategy can be employed for the preparation of trihydroxy MCPs containing three benzene rings. We deveoped the convenient preparation of propane-bridged calixarene-analogous macrocyclic MCPs, [3_3] MCPs using the TosMIC method [20]. We have improved the addition procedure in Vögtle's method. Thus, to a suspension of NaH in DMF was dropped a solution of 2,6-bis(bromomethyl)-4-*tert*-butylanisole **7** and TosMIC in DMF at room temperature. This does not only improve the yield of the desired ketones but also makes the handling of the base (solid NaH) easier.

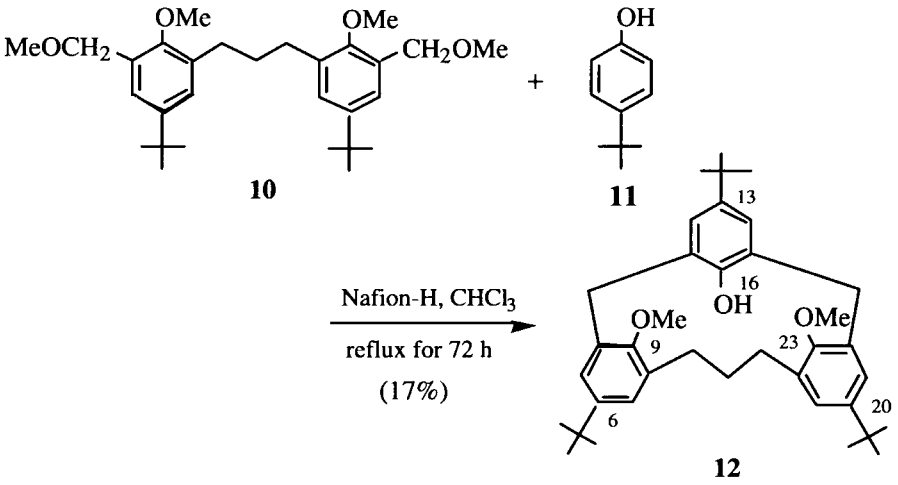


7 **8** **9**

Trihydroxy[3.3.3]MCP **9** was obtained in 76% yield by the Wolff-Kishner reduction of triketone **8** followed by demethylation with boron tribromide in dichloromethane.

2.4. SYNTHESIS OF ASYMMETRIC OR INCOMPLETE "HOMOCALIX[3]ARENES"

Hydroxy[3.1.1]MCP **12**, which is regarded as an asymmetric or incomplete "homocalix[3]arene" bearing a propane bridge, has been synthesized using Nafion-H catalyzed cyclobenzylation. The cyclobenzylation reaction of **10** with 4-*tert*-butylphenol **11** carried out in the presence of Nafion-H (solid perfluorinated resin-sulfonic acid) [21,22] under chloroform reflux for 72 h afforded the desired 6,13,20-tri-*tert*-butyl-16-hydroxy-9,23-dimethoxy[3.1.1]MCP **12** in 17% yield [23].



3. Conformations

3.1. THE CONFORMATIONS OF THE PARENT HOMOCALIX[3]ARENES

The calix[n]arenes show concentration-independent hydroxyl stretching bands in the 3200 cm^{-1} region of the infrared spectrum and a signal at δ = 9–10 in the ^{1}H-NMR spectrum, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes [1–3]. The IR spectra of homocalix[3]arenes **3** and **9** show the absorption of the hydroxyl stretching vibration around 3410 and 3452 cm^{-1}, respectively (Table I). The ^{1}H-NMR spectra (in $CDCl_3$) exhibit the signals for hydroxyl groups around δ = 8.5 and 7.13 ppm [9,20]. The υ_{OH} and δ_{OH} values in triols **3** and **9**, in which two hydroxyl groups are located in neighbouring positions, show slightly higher-frequencies and upper-field shifts, which imply that a weak hydrogen bond exists. These observations strongly suggest that the intramolecular hydrogen bonding among the hydroxyl groups between the diaryl propane units is weakened due to a distance longer than that between the diaryl methane units in the corresponding tetrahydroxy[1_4]MCP (calix[4]arene) (υ_{OH} = 3160 cm^{-1} and δ_{OH} = 10.2 ppm in $CDCl_3$) [1–3].

In comparison with the structural characteristics of calix[4]arenes whose cyclophane ring is composed of a 16-membered ring, triols **3** and **9** have a cavity composed of a 18-membered ring. Gutsche and his coworkers[9] have reported that the strong intramolecular hydrogen bond of calix[4]arene may fix the “cone” shape conformation. A conformational inversion has also been observed in this system; the value of the free energy of activation for inversion $\Delta G^{\neq}$ = 15.7 kcal/mol. The conformations of triols **3** and **9** have been evaluated by dynamic ^{1}H-NMR spectroscopy. The protons of the ArCH_2OCH_2Ar or Ar$CH_2CH_2CH_2$Ar methylene group each appear as a broad singlet even below −90 °C, and the rate of conformational ring flipping of triols is faster than the NMR time scale above this

Table I. Selected ^{1}H-NMR and IR spectral data for calix[4]arene **2**, homocalix[3]arenes **3** and **9**

Compounds	IR [KBr] υ_{OH} (cm^{-1})	^{1}H NMR δ [$CDCl_3$] OH (ppm)	Tc ($\Delta Gc^{\neq}$) [°C (kcal/mol)]
2	3160	10.2	52 (15.7)
3	3410	8.5	<−90
9	3452	7.13	<−90

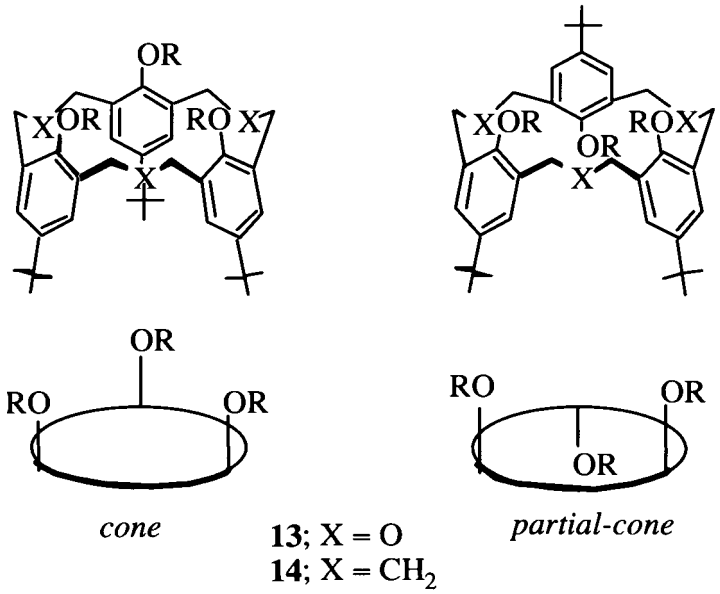


Figure 1. Two possible conformations of *O*-alkylated homocalix[3]arenes.

temperature. This indicates that the triols **3** and **9** are much more flexible than the calix[4]arene.

Suzuki and coworkers [24] have reported the crystal structure for triol **3** with cone conformation due to the intramolecular hydrogen bonding.

3.2. *O*-ALKYLATIONS OF HOMOCALIX[3]ARENES

When larger alkyl groups were introduced onto the phenolic oxygens of homocalix[3]arenes, which cannot pass each by oxygen-through-the-annulus rotation, there are only two possible conformations, “cone” and “partial-cone” in *O*-alkylation products in contrast to four possible conformations in calix[4]arenes. Thus, the conformational isomerism is much simpler than that of *O*-alkylated calix[4]arenes.

Table II. Influence of *O*-substituents on the oxygen-through-the-annulus rotation in hexahomotrioxacalix[3]arene **13** and [3_3]MCP **14**

O-substitutent	Homotrioxacalix[3]arene **13**	[3_3]MCP **14**
Me	Mobile ($Tc < -50$ °C)	Mobile ($Tc < -50$ °C)[a]
Et	Mobile ($Tc = 50$ °C)	Mobile ($Tc = 90$ °C)[b]
Pr	Mobile[c]	Immobile[b]
Bu	Immobile	Immobile[b]

[a] Solvent: $CDCl_3/CS_2 = 1/3$.
[b] Solvent: $CDBr_3/CDCl_3$ (3/1).
[c] The oxygen-through-the-annulus rotation is slower than the NMR time scale at 100 °C in $Cl_2CDCDCl_2$.

Homocalix[3]arenes were tri-*O*-alkylated with alkyl halides (RX: R = Et, Pr and Bu) in the presence of Cs_2CO_3 to predominantly yield partial-cone conformer. These findings support the view that when substituents are introduced into homocalix[3]arenes they prefer a partial-cone conformer to reduce steric crowding [25]. The proportion of cone conformer dramatically increased, and led to almost complete formation in the *O*-substitution of trihydroxy[3_3]MCP **9** with ethyl bromoacetate, when a stronger base was employed (e.g., NaH rather than Cs_2CO_3) [20]. The same result was obtained in the case of *O*-substitution with *N*,*N*-diethylchloroacetamide but not on *O*-alkylation with propyl bromide, which afforded only partial-cone conformer even in the presence of NaH. Only when the template metal can hold the ester or amide group(s) and the oxide group(s) on the same side of the homocalixarenes is the conformation immobilized to the cone.

Quite recently, regioselective synthesis of *O*-alkylated homocalixarenes has been established by a protection-deprotection method using the benzyl group as a protecting group. Thus we have succeeded in preparing all possible tri-*O*-alkylation products derived from hexahomotrioxacalix[3]arene in which two derivatives are chiral [26].

3.3. CONFORMATION OF *O*-ALKYL DERIVATIVES

Shinkai et al. [27] reported on the influence of *O*-substituents on the conformational isomerism of hexahomotrioxacalix[3]arene **3** in detail. Interconversion between conformers, which occurs by oxygen-through-the-annulus rotation, can be sterically allowed for methyl, ethyl, and propyl groups whereas it is inhibited for the butyl group. Similar properties were also observed for *O*-alkylated [3_3]MCPs **14** [20].

The influence of *O*-substituents on the oxygen-through-the-annulus rotation of *O*-alkylated [3_3]MCPs **14** is compared with that in the corresponding *O*-alkylated hexahomotrioxacalix[3]arene **13** in Table II [20].

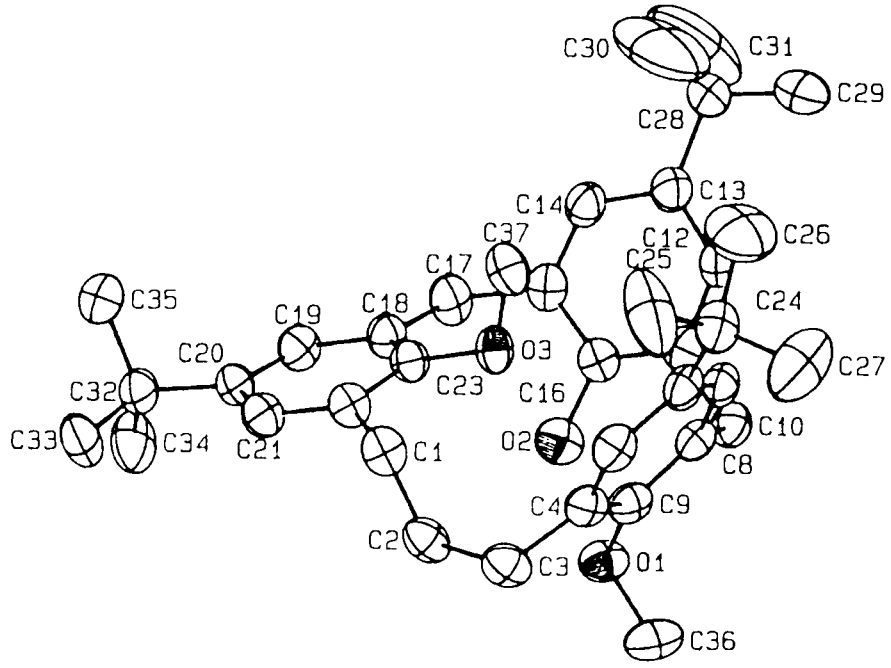


Figure 2. X-ray structure of hydroxy[3.1.1]MCP **12**.

In the hexahomotrioxacalix[3]arenes **13** the propyl group only introduces some steric hindrance and the rotation is inhibited only by the bulkier butyl group. In **14**, on the other hand, the propyl group is bulky enough to inhibit the rotation. The results consistently reveal that it is more difficult to inhibit the rotation in *O*-alkylated homotrioxacalix[3]arenes **13** than in **14**: in other words, the inner cavity of **14** is apparently smaller than that of *O*-alkylated homooxacalix[3]arenes **13** in spite of the difference in the bond distances between $C(sp^3)$-$C(sp^3)$, 1.53 Å and $C(sp^3)$-O, 1.43 Å. This finding is easily rationalized by the staggered conformation of the diarylpropane like [3.3]MCPs, which adopt a *syn*-conformation [28]. Hence the ring size of *O*-alkylated hexahomotrioxacalix[3]arenes is greater than that of *O*-alkylated [3_3]MCPs **14**. The ring of *O*-alkylated hexahomotrioxacalix[3]arenes **13** is more flexible than that of **14** because of three etheral linkages.

Recently, Kanters et al. [29] have reported that 27,28-diethoxy-*p*-*tert*-butylcalix[4]arene exhibited interconversion of equivalent partial cone conformers steered by intramolecular hydrogen bondings. However, due to the low energy barrier in the conformational process, this process has been frozen on the IR time scale, but not on the ^{1}H NMR time scale.

We have also demonstrated a novel “pendulum” type motion steered by intramolecular hydrogen bonding by the ^{1}H-NMR method, the first of its kind in the calixarene field [23]. Thus, the dimethoxy compound **12** is fixed to form an asymmetric “2-partial-cone” conformation at room temperature by the observation

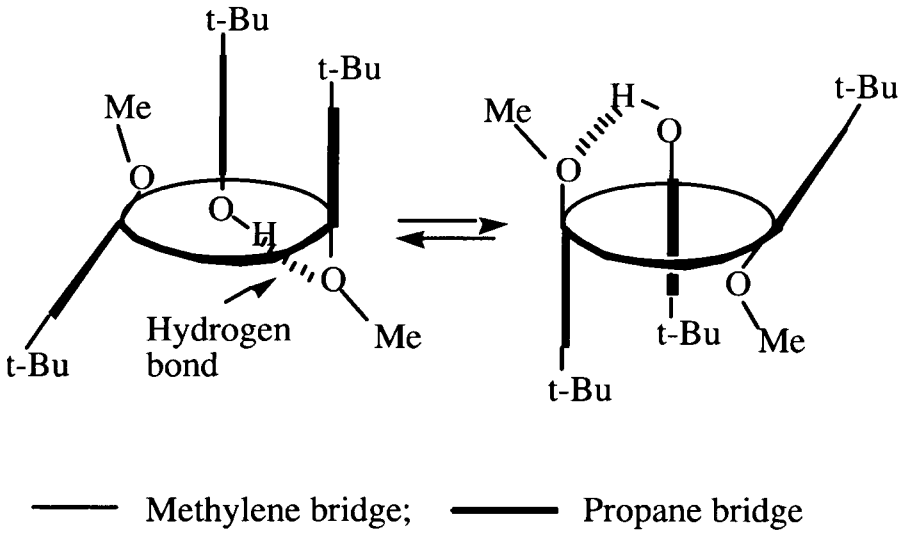


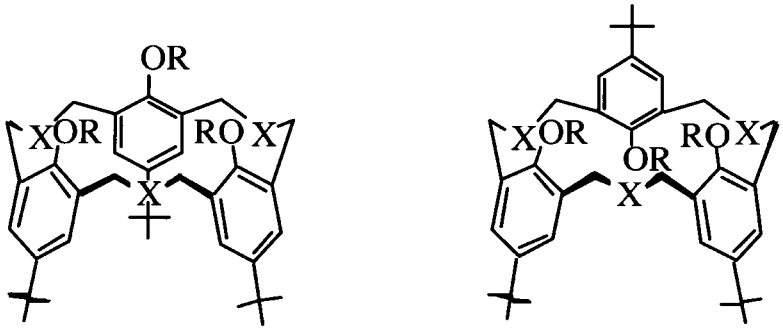
Figure 3. Schematic representation of the ring inversion of hydroxy[3.1.1]MCP **12**.

of two sets of doublets for the methylene protons. Thus, in this conformation the two methoxy groups in the compound point up and down with one of them folded into the π-cavity by two benzene rings and thus shielded greater upfield at δ 2.29. The crystal structure of **12** is shown in Figure 2. It is clear that one methoxy group is present between two aromatic rings that are forced towards each other as predicted from the ^{1}H NMR data. The distance between H (OH) and O_1 (OMe) is 2.05 (3) Å, which is a reasonable value for the intramolecular hydrogen bonding [H (OH)—O_3 (OMe) = 2.92 (3) Å]. Two possible structures could be drawn for this conformation based on the position of the OH group which could form a hydrogen bond with either of the methoxy oxygens like a "molecular pendulum". This phenomenon is shown in Figure 3.

4. Homocalix[3]arenes as Host Molecules

4.1. Complexation of metal ions

Two-phase solvent extraction established that *cone*-**13**Es_3 shows Na^+ selectivity, whereas *partial-cone*-**13**Es_3 shows K^+ selectivity [30], but lower complexation abilities than those for the corresponding calix[4]arene teraesters [31]. *cone*-**13**Am_3 showed very high affinity for alkali and alkaline earth metal cations [27]. Particularly, it formed stable complexes with alkaline earth metal cations



cone *partial-cone*

13 Es_3; X = O, R = CH_2COOEt
Am_3; X = O, R = CH_2CONEt_2

14 Es_3; X = CH_2, R = CH_2COOEt
Am_3; X = CH_2, R = CH_2CONEt_2

15; X = CH_2, R = Pic
16; X = CH_2, R = Bzl

which were scarcely bound to the tri-ester derivatives **13**Es_3. The difference is attributed to the much higher affinity of the amide carbonyl oxygen with alkaline earth metal cations than that of the ester carbonyl oxygen. The corresponding [3_3]MCPs **14** show similar inclusion properties for alkali metal cations, but slightly lower extractabilities than those for **13**. These findings suggest that the three oxygene atoms in the ethereal linkage are contributed to the complexation towards the metal cations, especially in the partial-cone conformer having encapsuled ionophilic cavities.

Although *cone*-(*cone*-**15**) and *partial-cone*-tris[(2-pyridylmethyl)oxy]MCP (*partial-cone*-**15**) hardly extracted either alkali metal cations or n-butylammonium cation under the experimental conditions, high extractability for Ag^+ was observed. The present extractabilities for Ag^+ (extraction%: 78% for *cone*-**15** and 76% for *partial-cone*-**15**) are superior than that of commercially available dibenzopyridino-18-crown-6 (extraction%: 65%) [32]. In contrast, the corresponding tris(benzyloxy) derivatives, *cone*-**16** and *partial-cone*-**16** hardly extracted Ag^+ cation under the same experimental conditions (extraction%: less than 1%). Therefore, the synergism of cyclophane moiety and two or three lower-rim side chains having pyridyl groups play an significant role on the complexation of tris[(2-pyridylmethyl)oxy] derivatives *cone*-**15** and *partial-cone*-**15** with Ag^+.

The conformational changes of pyridine moiety from the original outward orientation of the ring nitrogen to the inside orientation toward the cyclophane cavity was observed in the process of Ag^+ complexation. This result strongly suggests that the original C_3 and C_2-symmetry might remain after the metal cation complexation in *cone*-**15** and *partial-cone*-**15**, respectively.

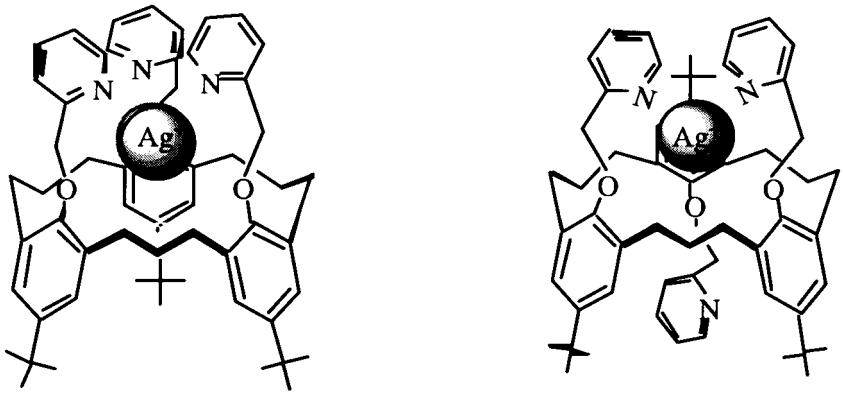


Figure 4. Binding mode of tris[(2-pyridylmethyl)oxy][3.3.3]MCPs *cone*-**15**, *partial-cone*-**15** and Ag^{+}.

4.2. COMPLEXATION OF ORGANIC MOLECULES

The development of ammonium ion recognition systems has been of concern because ammonium ions play important roles in both chemistry and biology [33]. For example, Lehn et al. [33d] reported that C_3 symmetric crown ethers bearing ester groups form very stable complexes with primary ammonium ions.

The triester and triamide of the hexahomotrioxacalix[3]arene **13** and [3_3]MCP **14** in the cone conformation exibit high affinity for ammonium ions in extraction experiments because of their threefold symmetry [20]. More recently, it has been reported that calix[n]arene derivatives with C_3 or C_6 symmetry can selectively bind ammonium ions [34]. Thus, Shinkai et al. [35] reported the construction of C_3 symmmetric pyrene functionalized hexahomotrioxacalix[3]arenes, which selectively recognize primary ammonium ions detected by an intramolecular eximer fluorescence change. This is a novel sensing system for primary ammonium ions. They developed the chiral recognition of optically active alkylammonium ions using functionalized homooxacalix[3]arene with a pseudo-C_2-symmetry [36].

Quite recently, Shinkai et al. [37] discovered that hexahomotrioxacalix[3]arene **3** interacts with C_{60} in toluene and isolated the 1 : 1 complex as a dark brown solid.

5. Conclusions

To summarize, in this paper we have presented the synthesis and conformations of homocalix[3]arenes. We have also demonstrated that the derivatives of the homocalix[3]arenes formed by alkylation with ethyl bromoacetate and *N,N*-diethylchloroacetamide give ionophores with promising complexation properties and interesting stereochemistry. A synthetic advance associated with the synthesis of homocalix[3]arenes, especially, [3_3]MCPs is that almost any binding site or functional group can be readily incorporated. Therefore, due to the ethereal linkages of the hexahomotrioxacalix[3]arenes, further functionalization, i.e., elec-

trophilic substitution on the aromatic ring, could lead to ring cleavage reactions. In contrast, the stability of multi-membered carbon skeletons is an advantage which permits the interconversion of functional groups without special regard to ring-opening side reactions. These multiple possibilities for structural modification enable the host structure to be optimised for metal cations, anions, and both neutral and charged organic guests. Many applications as analytical sensors can then be envisaged.

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