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# "Cone" - "Partial-cone" Isomerism in Tetramethoxycalix[4]arenes. Influence of Solvent Polarity and Metal Ions

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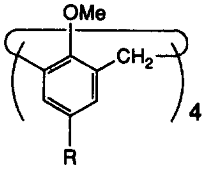
**Abstract:** It was found that the "cone" - "partial-cone" equilibrium in 25,26,27,28-tetramethoxycalix[4]arene derivatives is sensitively affected by the solvent polarity: the cone% increases with the increase in the solvent polarity. The novel finding was rationalized in terms of the difference in the dipole moment: cone conformers with four dipole moments orientating into the same direction are more polar than partial-cone conformers with one inverted phenyl unit and therefore are more stabilized in polar solvents. Alkali metal cations such as $Li^+$ and $Na^+$ strongly interact with four methoxy oxygens, resulting in the shift of the equilibrium to cone.

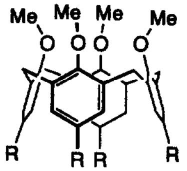
## Introduction

Calixarenes are cyclic oligomers made up of phenol units. Although each phenol unit can rotate according to the oxygen-through-the-annulus rotation mechanism, they favorably adopt a "cone" conformation because of the stabilization by intramolecular hydrogen-bonding interactions among OH groups.[1-4] In tetra-*O*-alkyl derivatives, on the other hand, the "cone" conformation is not necessarily stabilized because of the absence of such intramolecular hydrogen-bonding interactions.[5-8] Thus, one must take four different conformational isomers into account: they are "cone", "partial-cone", "1,2-alternate", and "1,3-alternate".[1-9] The relative stability of these four conformational isomers were estimated by a computational method.[10,11] In the course of our studies on the conformational isomerism of 25,26,27,28-tetramethoxycalix[4]arenes (**1R**), we unexpectedly found a novel phenomenon that the conformer distribution changes sensitively in response to solvent polarity.[12] To obtain further insights into this phenomenon we prepared four **1R**'s and examined the influence of solvent polarity and added metal ions on the conformational isomerism.

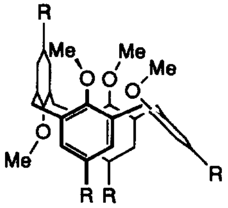
## Results and Discussion



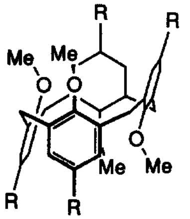
**1R**



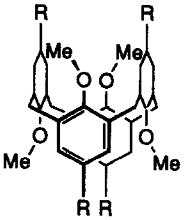
cone



partial-cone



1,2-alternate



1,3-alternate

**Theoretical Calculations of Dipole Moments and MM3 Optimized Structures.** Previously, we unexpectedly found that a cone - partial-cone equilibrium in **1Bu**$^t$ is sensitively affected by the solvent polarity.[12] The *p-tert*-butylanisole unit has a fairly strong dipole arising from the ether linkage.[12] In the cone conformation, four dipoles are enforced to orientate into the same direction whereas in the partial-cone conformation one dipole is reverted. The difference suggests that cone behaves as a polar molecule whereas partial-cone behaves as a less polar molecule and that cone is more stabilized in polar solvents than partial-cone.

In order to reconfirm the above hypothesis, we estimated the dipole moment of four conformers by a computational method (Table 1). Both AM1 and MM3 predict that the dipole moment of four conformers is in the order of cone > partial-cone > 1,2-alternate > 1,3-alternate. It is seen from Table 1 that the dipole moments for cone-**1H** and cone-**1Bu**$^t$ are not so large (note that the dipole moment of anisole is 1.35 D[13]). As shown in Figure 1, the dipole moment inherent to the ether linkages in cone-calix[4]arenes is turned to the endo-annulus direction. Since these calix[4]arenes adopt $C_{2v}$ symmetry,[11] the horizontal components are offset each other and only the perpendicular components remain. This structural characteristic well explains the small dipole moment for cone-**1H** and cone-**1Bu**$^t$. In cone conformers, introduction of electron-withdrawing substituents such as Br and CN to the *p*-position increases the dipole moment. In particular, the dipole moment for cone-**1CN** is very large (estimated to be 12.656 D by AM1).

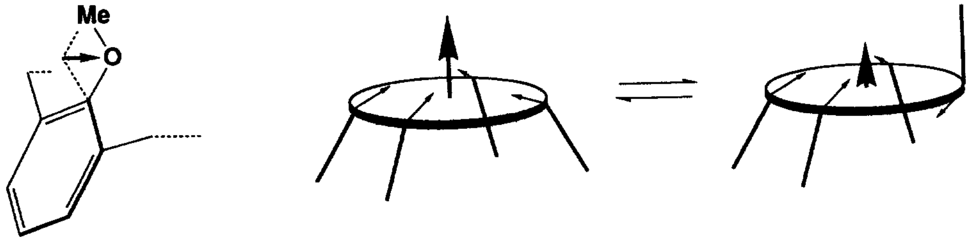


**Figure 1.** Dipole moments for cone and partial cone.

In partial-cone, one phenyl unit is inverted and one dipole in the remaining three phenyl units is used to offset the dipole of the inverted phenyl unit. From this structural characteristic one can expect that the dipole moment in partial-cone arises from the two remaining phenyl units and is approximately half of that in cone. As shown in Table 1, the dipole moments for cone-**1H**, cone-**1Br** and cone-**1CN** are exactly 52-54% of those for cone counterparts. Strangely, we noticed that in **1Bu$^t$** the dipole moment for partial-cone is 62-76% of that for cone. This can be explained in two ways: that is, the dipole moment for cone-**1Bu$^t$** is relatively too small or the dipole moment for partial-cone-**1Bu$^t$** is relatively too large. Examination of MM3-optimized structures for **1H** and **1Bu$^t$** manifests that the structure for cone-**1Bu$^t$** is scarcely different from cone-**1H** whereas that for partial-cone-**1Bu$^t$** is significantly different from partial-cone-**1H**: by introduction of *tert*-Bu groups two phenyl units proximal to the inverted phenyl unit are flattened and a phenyl unit distal to the inverted phenyl unit stands up.[11] The structural difference allows us to conclude that the dipole moment for partial-cone-**1Bu$^t$** is unusually large. This problem will be discussed again later.

On the other hand, 1,2-alternate and 1,3-alternate possess high symmetry such as $C_{2h}$ or $D_{2d}$ and the dipole moments are efficiently offset. These conformers are thus classified into apolar molecules.

**Influence of *p*-Substituents and Solvent Polarity.** It is known that the concentration of each isomer can be easily evaluated by a $^1$H NMR method because they give different splitting patterns for the $ArCH_2Ar$ protons: a pair of doublets for "cone", two pairs of doublets for "partial-cone", a pair of doublets plus a singlet peak for "1,2-alternate" and a single peak for "1,3-alternate".[1-6,14] The conformer distributions determined at -25 °C (at this temperature the peaks for each isomer appear discretely) are summarized in Table 2. Since 1,2-alternate and 1,3-alternate are observed only for **1Bu$^t$**, we mainly discuss the conformer distribution of cone against partial-cone.

**Table 1.** Theoretical calculations of dipole moments and MM3 calculated energies (relative energy) for optimized structures

| Computation tool | Calix[4]arene | Dipole moment (D) | | | |
|---|---|---|---|---|---|
| | | Cone | Partial-cone | 1,2-Alternate | 1,3-Alternate |
| AM1 | **1Bu$^t$** | 0.602 | 0.459 | 0.003 | 0.005 |
| | **1H** | 1.462 | 0.788 | 0.008 | 0.003 |
| | **1Br** | 6.406 | 3.303 | 0.008 | 0.006 |
| | **1CN** | 12.656 | 6.536 | 0.010 | 0.008 |
| MM3 | **1Bu$^t$** | 0.858 | 0.528 | 0.000 | 0.000 |
| | **1H** | 1.920 | 1.004 | 0.014 | 0.000 |
| | **1Br** | 9.055 | 4.833 | 0.000 | 0.000 |

| | | Relative energy (kcal)[a] | | | |
|---|---|---|---|---|---|
| | | Cone | Partial-cone | 1,2-Alternate | 1,3-Alternate |
| MM3 | **1Bu$^t$** | 42.59 | 41.28 | 47.69 | 43.14 |
| | **1H** | 32.52 | 32.26 | 36.34 | 33.35 |
| | **1Br** | 13.51 | 11.48 | 17.08 | 11.10 |

[a] The values in Reference 11 were obtained by using MM3(89) while the values in this table were obtained by using MM3(92). The calculation of **1CN** by MM3 is impossible at present because of deficiency of the parameters.

**Table 2.** Conformer distribution (%) at -25 °C

| Solvent | Calix[4]arene | Cone | Partial-cone | 1,2-Alternate | 1,3-Alternate |
|---|---|---|---|---|---|
| Toluene-$d_8$ | **1Bu$^t$** | 18.9 | 75.9 | 3.7 | 1.5 |
| $CDCl_3$ | **1Bu$^t$** | 2.0 | 92.0 | 5.0 | 1.0 |
| | **1H** | 29.6 | 70.4 | 0 | 0 |
| | **1Br** | 18.7 | 81.3 | 0 | 0 |
| | **1CN** | 6.3 | 93.7 | 0 | 0 |
| $CDCl_3$:$CD_3CN$ = 9:1[a] | **1Bu$^t$** | 17.6 | 65.0 | 6.1 | 11.3 |
| | **1H** | 34.0 | 66.0 | 0 | 0 |
| | **1Br** | 22.1 | 77.9 | 0 | 0 |
| | **1CN** | 9.8 | 90.2 | 0 | 0 |
| $CDCl_3$:$CD_3CN$ = 2:1[a] | **1Bu$^t$** | 26.9 | 61.3 | 3.4 | 8.4 |
| | **1H** | 37.0 | 63.0 | 0 | 0 |
| | **1Br** | 22.6 | 77.4 | 0 | 0 |
| | **1CN** | 9.4 | 90.6 | 0 | 0 |
| $CDCl_3$:$CD_3CN$ = 1:1[a] | **1Bu$^t$** | 32.3 | 62.6 | 3.6 | 1.5 |
| | **1H** | 37.3 | 62.7 | 0 | 0 |
| | **1Br** | 23.6 | 76.4 | 0 | 0 |
| | **1CN** | 8.5 | 91.5 | 0 | 0 |
| $CDCl_3$:$CD_3CN$ = 1:4[a] | **1Bu$^t$** | 38.7 | 58.5 | 2.5 | 0.3 |
| | **1H** | 38.3 | 61.7 | 0 | 0 |
| | **1Br** | 23.7 | 76.3 | 0 | 0 |
| | **1CN** | 7.9 | 92.1 | 0 | 0 |
| $CDCl_3$:DMF-$d_7$ = 1:4[a] | **1Bu$^t$** | 28.3 | 63.0 | 1.0 | 7.7 |
| | **1H** | 35.5 | 64.5 | 0 | 0 |
| | **1Br** | 23.7 | 76.3 | 0 | 0 |

[a] In vol / vol.

It is seen from Table 2 that except **1Bu$^t$**, introduction of electron-withdrawing substituents such as Br and CN leads to the decrease in cone% and the increase in partial-cone%. Conceivably, the strong dipole moments in *p*-bromoanisole and *p*-cyanoanisole units tend to repulse each other and the cone conformation is destabilized. This induces the rotation of a phenyl unit to increase partial-cone%. To efficiently reduce such repulsion, 1,2-alternate or 1,3-alternate should be more advantageous. It is known that the basic calix[4]arene skeletons of these conformers are less stable than those of cone and partial-cone.[10,11] The fact that 1,2-alternate and 1,3-alternate cannot be detected for **1H**, **1Br** and **1CN** supports the view that the reduction of dipole-moment repulsion by the rotation is not enough to sufficiently compensate the destabilization energy arising from the ring deformation.

In Figure 2 we plotted cone% against the solvent composition ($CDCl_3$ - $CD_3CN$). As expected from their dipole-moment values, cone% increases with increasing $CD_3CN$ concentration: that is, cone is more stabilized in polar solvents. We first expected that the largest change in the cone - partial-cone ratio would be observed for **1CN** because it shows the largest difference in the dipole moment between cone and partial-cone. In fact, however, the cone% of **1CN** is less sensitive to solvent polarity than that of **1H**.

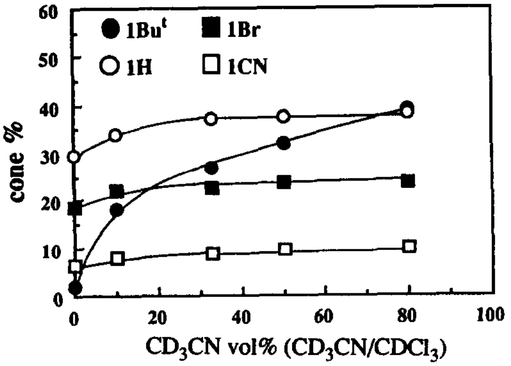


**Figure 2.** Plots of cone% vs. $CD_3CN$ vol% in $CD_3CN$-$CDCl_3$

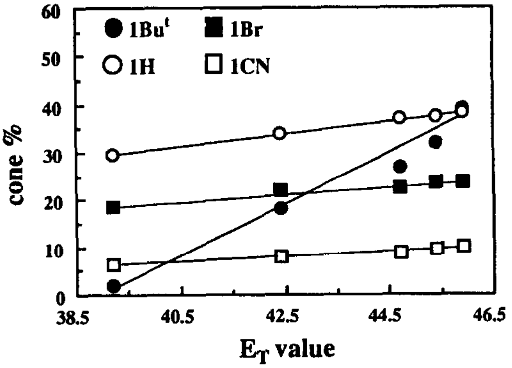


**Figure 3.** Plots of cone% vs. $E_T(30)$.

In Figure 3 we plotted cone% against a solvent-polarity parameter, $E_T(30)$. The $E_T(30)$ values for mixed solvents were determined in this laboratory. All plots showed a good linear relationship ($r > 0.96$), indicating that the cone- partial-cone equilibrium is governed by the solvent polarity. From the least-squares computation of the plots we determined the slope: they are 5.08 for **1Bu**$^t$, 1.24 for **1H**, 0.72 for **1Br** and 0.49 for **1CN**. As mentioned above, the difference in the dipole-moment values between cone-**1Bu**$^t$ and partial-cone-**1Bu**$^t$ is relatively small. Nevertheless, the above result indicates that the cone - partial-cone equilibrium for **1Bu**$^t$ is most sensitive. As a summary of the foregoing results we can conclude that **1Bu**$^t$ is classified as an exceptional molecule because (i) the cone - partial-cone equilibrium is exceptionally sensitive to the solvent polarity and (ii) four conformers are observable for **1Bu**$^t$ whereas only cone and partial-cone are observed for other tetramethoxycalix[4]arenes.[5,8,11] Previously, Reinhoudt *et al.*[8] considered that 1,2-alternate is not a particularly unstable conformation because this is also observed for **1Bu**$^t$. The present study manifests, however, that in general, 1,2-alternate conformers are "exceptionally" unstable (as the computational studies predict[10,11]) and only in **1Bu**$^t$ the 1,2-alternate conformer emerges "exceptionally". Here, an essential query arises as to why **1Bu**$^t$ is exceptional. The computational studies show that **1Bu**$^t$ is not particularly different from other **1R** molecules.[10,11] Through past investigations on molecular recognition by calix[4]arenes we have noticed a special characteristic of **1Bu**$^t$. For example, **1H** forms a complex with $RNMe_3^+$ through a cation-$\pi$ interaction and a charge-transfer complex with tetracyanoethylene whereas **1Bu**$^t$ forms these complexes only weakly.[15,16] These results can be reasonably understood if the bulky *tert*-butyl groups interfere with the interaction of guest molecules with the calix[4]arene $\pi$-systems. Provided that this concept is allowed to be extended to solvation more generally, it follows that cone with a $\pi$-base cavity and partial-cone with a partial $\pi$-

base cavity are more stabilized by inclusion of solvent molecules.[17] Since such a contribution is expected to **1Bu$^t$** only to a smaller extent, cone and partial-cone of **1Bu$^t$** are relatively destabilized to allow the appearance of 1,2-alternate and 1,3-alternate without a π-base cavity.

**Influence of Alkali Metal Cations on the Cone - Partial-cone Equilibrium.** In $^1$H NMR spectrum of **1Bu$^t$** in $CDCl_3$:$CD_3CN$ = 9:1 v/v, one can detect the presence of four conformers: cone (14%), partial-cone (79%), 1,2-alternate (5%) and 1,3-alternate (2%) (see Table 3). When $LiClO_4$ or $NaClO_4$ was added, new peaks appeared which were assignable to the cone-**1Bu$^t$**•$M^+$ complex (Figure 4). On the other hand, the spectrum was scarcely affected by the addition of $KClO_4$. The findings indicate that to bind alkali metal cations four oxygens must be arranged in the same side of the cone-shaped platform and the ionophoric cavity thus composed is comparable with the size of $Li^+$ or $Na^+$. From the integral intensity the association constant for cone-**1Bu$^t$** ($K_{cone}$) was estimated to be log $K_{cone}$ = 4.3 for $Li^+$ and 5.3 for $Na^+$. Under the same conditions we obtained $K_{cone}$ for **1H**: log $K_{cone}$ = 4.0 for $Li^+$ and 4.6 for $Na^+$.

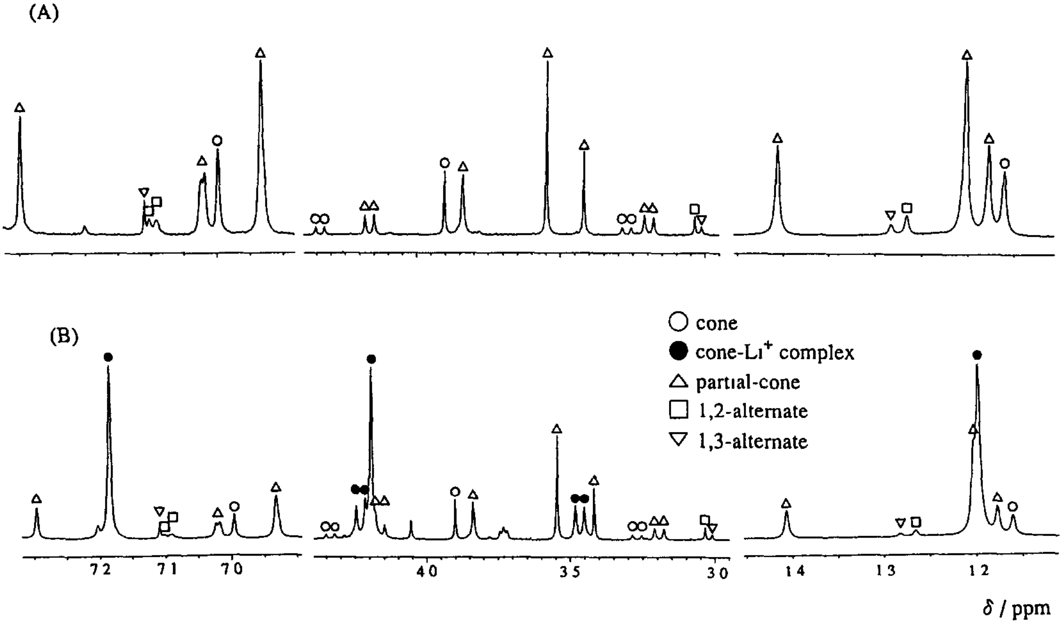


**Figure 4.** Partial $^1$H NMR spectra of (A) **1Bu$^t$** (1.0 mM) and (B) **1Bu$^t$** + $LiClO_4$ (1.0 mM each): -50 °C, 400 MHz, $CDCl_3$:$CD_3CN$ = 9:1 v/v.

When $CDCl_3$:$CD_3OD$ (4:1 v/v) was used as solvent, not only cone-**1Bu$^t$** but also partial-cone-**1Bu$^t$** interacted, although weakly, with $Li^+$ and $Na^+$ (Table 3). To specify the metal-binding site we compared the $^1$H NMR spectra in the presence of $Li^+$ or $Na^+$ with those in the absence of metal cations. As illustrated in Figure 5, the protons in four methyl groups in cone-**1Bu$^t$** and those in three methyl groups on the lower rim in partial-cone-**1Bu$^t$** shift to lower magnetic field. The results support the view that these metal cations are bound to the ionophoric cavities composed on the lower rim. It is interesting to note that in partial-cone-**1Bu$^t$** the δ for the Me protons in the inserted phenyl unit shift to higher magnetic field. Probably, the metal-binding to the lower

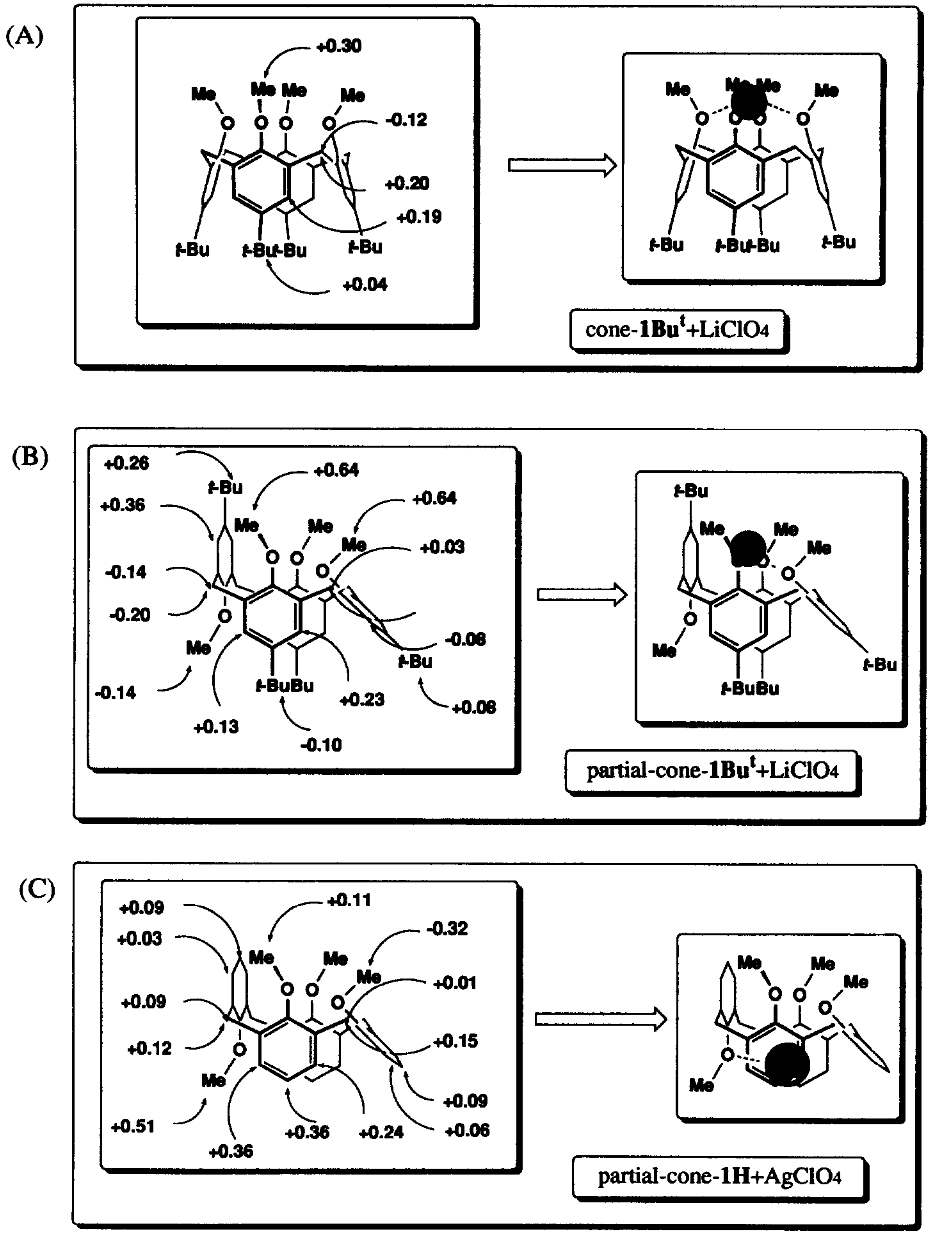


**Figure 5.** Chemical shift changes induced by metal cations: (A) cone-**1Bu$^t$** + $LiClO_4$ in $CDCl_3$:$CD_3OD$ (4:1 v/v), (B) partial-cone-**1Bu$^t$** + $LiClO_4$ in $CDCl_3$:$CD_3OD$ (4:1 v/v), (C) partial-cone-**1H** + $AgClO_4$ in $CDCl_3$:$CD_3OD$ (4:1 v/v). The concentrations of **1Bu$^t$** and metal salts are all 1.0 mM. The changes induced by $Na^+$ are similar to those induced by $Li^+$ whereas the changes induced by $K^+$ are similar to those induced by $Ag^+$.

rim repulse the inverted phenyl ring and consequently the Me protons move into the cavity in which they undergo the shielding effect.

**Table 3.** Conformer distribution and metal complexation of **1Bu**$^t$ and **1H** at -50 °C[a]

| Calixarene | Solvent[b] | Conformer (%)[c] | | | | Metal salt[d] | log K[e] |
|---|---|---|---|---|---|---|---|
| | | cone | p.c. | 1,2 | 1,3 | | |
| **1Bu**$^t$ | A | 14 | 79 | 5 | 2 | None | - |
| **1Bu**$^t$ | A | 64(57) | 33 | 2 | 1 | $LiClO_4$ | 3.6(4.3) |
| **1Bu**$^t$ | A | 85(82) | 14 | 1 | 0 | $NaClO_4$ | 4.4(5.3) |
| **1Bu**$^t$ | A | 14 | 79 | 5 | 2 | $KClO_4$ | - |
| **1Bu**$^t$ | B | 7(7) | 86(6) | 5 | 2 | $LiClO_4$ | 2.2 |
| **1Bu**$^t$ | B | 31(31) | 65(7) | 3 | 1 | $NaClO_4$ | 3.0 |
| **1Bu**$^t$ | B | 0 | 82(12) | 5 | 14(12) | KPic | 2.6 |
| **1Bu**$^t$ | B | 0 | 47(16) | 41(39) | 13(12) | $AgCF_3SO_3$ | 3.8 |
| **1H** | A | 32 | 68 | 0 | 0 | None | - |
| **1H** | A | 70(57) | 30 | 0 | 0 | $LiClO_4$ | 3.5(4.0) |
| **1H** | A | 82(74) | 18 | 0 | 0 | $NaClO_4$ | 4.1(4.6) |
| **1H** | A | 31 | 69 | 0 | 0 | $KClO_4$ | - |

[a] The concentrations of **1Bu**$^t$, **1H** and metal salts are all 1.0 mM.
[b] A is $CDCl_3$:$CD_3CN$ (9:1 v/v). B is $CDCl_3$:$CD_3OD$ (4:1 v/v). [c] The number in the parenthesis indicates the percentage of the conformer present as the metal complex. [d] Potassium picrate (KPic) and $AgCF_3SO_3$ were used because of the poor solubility of their perchlorate salts. [e] Association constants are defined as [total metal complexes] / [metal salt] [total calixarene conformers]. The number in the parenthesis is defined as [cone•$M^+$] /[metal salt] [cone].

Examination with CPK molecular models teaches us that $K^+$ ion is too large to be bound to the lower rim. As shown in Table 3, $K^+$ is bound to partial-cone-**1Bu**$^t$. How does partial-cone-**1Bu**$^t$ trap $K^+$ ion? We found that $Ag^+$ is efficiently bound to partial-cone-**1Bu**$^t$ and the $^1H$ NMR spectral changes induced by $Ag^+$ is very similar to those induced by $K^+$: that is, the δ values for the Me protons in the inverted phenyl unit and the aromatic protons in the three ordinary phenyl units move to lower magnetic field as shown in Figure 5 for the partial-cone-**1H**•$Ag^+$ complex. Previously, we unexpectedly found that 1,3-alternate conformers of calix[4]arenes have the exceptionally high affinity with $Ag^+$ and the moderate affinity with $K^+$.[18] Since the 1,3-alternate conformers have within molecule two cavities composed of two benzene rings and two oxygens, we proposed the significant contribution of the cation-π interaction. A similar trend was observed in $^1H$ NMR spectral changes for the $Ag^+$ complex with partial-cone-**1Bu**$^t$. Hence, we consider that $Ag^+$ (and probably, $K^+$ also) is bound to the upper rim through the interaction with one oxygen and three benzene rings (as in Figure 5).

## Concluding Remarks

The present study demonstrated that the conformational isomerism in **1R** is profoundly influenced by the solvent effect and the bound metal cations. The results suggest several potential applications of this class of calix[4]arenes: that is, (i) **1R** would serve as a novel solvent-polarity parameter, (ii) if the appropriate reporter group which is sensitive to the conformational change is added,[19] **1R** would be useful for the metal sensing and (iii) since there are only four significant conformers in spite of the 16-membered macrocycle and the X-ray data are available, **1R** would be useful for the computational approach to the solvent effect and dipole moment effect. Further studies are currently continued in these laboratories.

## Experimental

### Materials

The preparations of 25,26,27,28-tetramethoxycalix[4]arene (**1H**) and 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene (**1Bu$^t$**) were described previously.[7,11]

**5,11,17,23-Tetrabromo-25,26,27,28-tetramethoxycalix[4]arene (1Br).** This compound was synthesized from **1H** in a manner similar to Gutsche's method[20]: mp 268-269 °C, yield 61% (lit.[15] 269-270 °C, 82%). The compound was identified by a $^1$H NMR spectral method and elemental analysis.

**5,11,17,23-Tetracyano-25,26,27,28-tetramethoxycalix[4]arene (1CN).** **1Br** (2.0 g, 2.5 mmol) in 1-methyl-2-pyrrolidone (70 ml) was treated with CuCN (2.02 g, 22.6 mmol) for 3 h at the reflux temperature under a nitrogen stream. A 3 M HCl aqueous solution (100 ml) containing $FeCl_3 \cdot 6H_2O$ (3.40 g, 16.5 mmol) was added and the mixture was stirred for 1 h at 80 °C. The precipitate was recovered by filtration and finally recrystallized from toluene: mp 327-329 °C (lit.[20] 327-329 °C), yield 41%; IR (Nujol) $\nu_{CN}$ 2222 cm$^{-1}$. The $^1$H NMR spectrum ($CDCl_3$, 25 °C) showed that **1CN** exists as a mixture of cone and partial-cone: δ for cone-**1CN** 3.30 and 4.35 ($ArCH_2Ar$, d each, 4H each), 3.87 ($OCH_3$, s, 12H), 7.09 (ArH, s, 8H); δ for partial-cone-**1CN** 3.08, 3.77 and 3.85 ($OCH_3$, s each, 1H, 2H and 1H), 3.22, 3.53, 3.67 and 4.04 ($ArCH_2Ar$, d each, 2H each), 6.71, 7.27, 7.49 and 7.62 (ArH, d, d, s and s, 2H each). Anal. Calcd for $C_{36}H_{28}N_4O_4 \cdot 0.3H_2O$: C, 73.78; H, 4.92; N, 9.56%. Found: C, 73.78; H, 4.72; N, 9.41%.

### Spectral Measurements

The apparatus used for the $^1$H NMR measurements was a JEOL GSX-400 (400 MHz) unless otherwise stated.

### Theoretical Calculations

Methods of theoretical calculations were described previously.[11] In this reference the calculations were performed by using MM3(89) and a full matrix Newton-Raphson method was applied only to **1H**. In the present study using MM3(92) a full matrix Newton-Raphson method was also applied to **1Bu$^t$** and **1Br**.

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