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Conformational Isomers of the Trimethyl Ethers of Monodeoxycalix[4]arenes

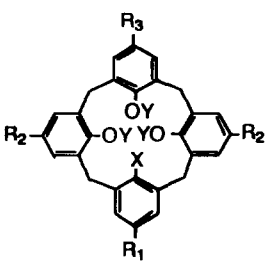
Yoshimasa Fukazawa,* Kousaku Yoshimura, Shigeru Sasaki, Masumi Yamazaki, and Toshiya Okajima

Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-Hiroshima 739, Japan

Abstract: The conformational analysis of title compounds using X-ray crystallographic analysis and molecular mechanics calculations is presented. The (u,u,d) conformer is the most stable among three possible forms. Solvent polarity plays a significant role in its conformational dynamic equilibrium. In the most stable form, the orientation of the methoxyl group of the inverted anisole ring is inside a cavity created by the remaining three aromatic rings as was found in the structure of one of the derivatives in its crystalline state. This cavity filling inward orientation of the alkoxyl group is quite a characteristic feature for the trimethyl ethers of the monodeoxycalix[4]arenes.

INTRODUCTION

Calix[4]arenes (**1**) are macrocyclic molecules composed of four phenols and four methylene units.[1] The conformations of these compounds have been discussed in terms of four structures: cone, partial cone, 1,2-alternate and 1,3-alternate.[2] It is well established that calix[4]arenes exist exclusively in the cone conformation.[3] The intramolecular cyclic hydrogen bonding due to the four phenolic OH groups of the cone is believed to be responsible for this preference. Difference of conformational energies between the cone and the partial cone is probably significantly large because the isolation of the latter structure has never been reported. Thus the stability of the conformers is closely related to the extent of the intramolecular hydrogen bond.[4] Conformational analysis of calix[4]arenes with partially broken hydrogen bonds should be quite interesting to shed light on the relationship between the extent of hydrogen bonds and the stability of the conformers. Conversion of a calix[4]arene to an ether derivative is a simple method to break the hydrogen bonds, and partial depletion of hydroxyl groups is another way to break these bonds. This type of compound (**2**) was reported recently.[5]



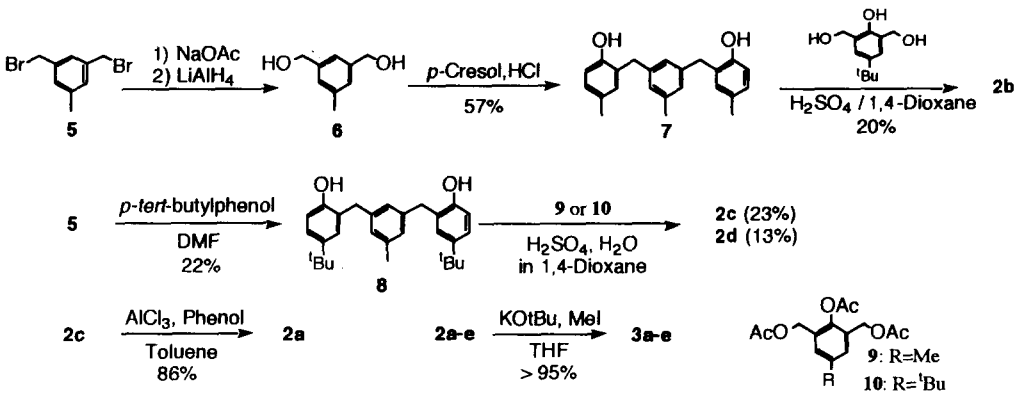
	X	Y	R_1	R_2	R_3
1	OH	H			
2a	H	H	Me	H	Me
2b	H	H	Me	Me	tBu
2c	H	H	Me	tBu	Me
2d	H	H	Me	tBu	tBu
2e	H	H	tBu	tBu	tBu
3a	H	Me	Me	H	Me
3b	H	Me	Me	Me	tBu
3c	H	Me	Me	tBu	Me
3d	H	Me	Me	tBu	tBu
3e	H	Me	tBu	tBu	tBu
4	OMe	Me	tBu	tBu	tBu

In monoalkyl ether of a calix[4]arene a cone structure was found to be exclusive among the four conformers.[3a] In this structure three out of four cyclic hydrogen bonds of the calix[4]arene were retained. The situation became slightly complicated in polyalkyl ethers. In 1,2-dialkyl ether two structures, a cone and a partial cone were found in solution;[6] both have the same number of intramolecular hydrogen bonds and hence are almost isoenergetic. On the other hand, a cone structure is an exclusive conformer in 1,3-dialkyl ether.[7] In the cone structure of this ether both of the two hydroxyl groups can form a hydrogen bond on either side of the adjacent alkoxyl groups and a rapid flip-flop motion of the OH group makes this structure more stable than any other. In a trialkyl ether ^{1}H-NMR spectrum can be explained in terms of a cone conformation,[3a] in which both the phenol and diametrical alkoxybenzene are flattened and the other two rings are nearly parallel.[7]

Substitution of all the phenolic protons of a calix[4]arene by a bulky alkyl group generally leads to conformationally rigid products.[8] However, when the substituent is small such as a methyl group, the resulting methyl ether is no longer rigid and any anisole ring can rotate via oxygen-through-the-annule to give a mixture of the four possible conformers.[9] The conformational distribution and hence the thermodynamic stability of the four structures is influenced by various factors, the solvent effect known to be the most important. The polarity[10] and the molecular size[6b] of a solvent are claimed to be two major influential factors since the four conformers have different dipole moments and some have cavities in which a small solvent molecule can be included. To learn how these factors influence the conformational distribution of the trimethyl ethers of monodeoxycalix[4]arenes, we synthesized various compounds with different upper rim substituents. In these compounds one anisole ring is replaced by a lesser polar benzene ring to change the dipole moment of the conformers. Moreover, the cavity size of the cone can be modified by the number of bulky upper rim substituents. Here, we report the results of a detailed study on the conformational preference of various derivatives of trimethyl ethers of monodeoxycalix[4]arene by ^{1}H-NMR spectroscopy, molecular mechanics calculation and X-ray crystallographic analyses.

RESULTS AND DISCUSSION

Trimethyl ethers of monodeoxycalix[4]arenes To prepare monodeoxycalix[4]arenes with various upper rim substituents we selected a stepwise synthetic route similar to that developed by Böhmer.[11] Partial bromination of mesitylene using NBS gave 3,5-bis(bromomethyl)toluene (**5**). Replacement of bromines of **5** by acetoxyl groups followed by $LiAlH_4$ reduction gave 3,5-bis(hydroxymethyl)toluene (**6**). Acid treatment of **6** with *p*-methylphenol gave 3,5-bis(2-hydroxy-5-methylbenzyl)toluene (**7**). Condensation of **7** with 4-*tert*-butyl-2,6-bis(hydroxymethyl)phenol in acidic dioxane gave monodeoxycalix[4]arene (**2b**). Variation of upper rim substituents was carried out by a similar route. 3,5-Bis(5-*tert*-butyl-2-hydroxybenzyl)toluene (**8**) was obtained by coupling reaction of **5** with *p*-*tert*-butylphenol in DMF. Acid treatment of **8** with 2,6-bis(acetoxymethyl)-4-alkylphenols (**9** and **10**) in aqueous dioxane gave monodeoxycalix[4]arenes (**2c** and



Scheme 1. Synthesis of **3a-e**

2d). **2c** was converted in good yield to dimethyl derivative (**2a**) by treatment with an excess amount of phenol in the presence of $AlCl_3$. Tetra-*t*-butyl derivative (**2e**) was prepared by the reported procedure.[5a,b] Methylation of monodeoxycalix[4]arenes by methyl iodide in the presence of KO^tBu gave desired trimethyl ethers (**3a-3e**) in quantitative yield.

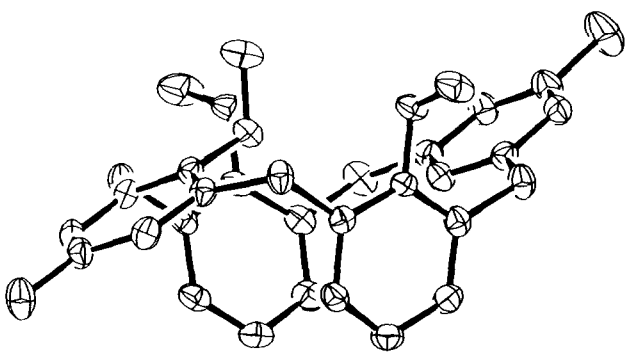


Figure 1. ORTEP drawing of the molecular structure of **3a.**

X-Ray Crystallography The molecular structure of the trimethyl ether **3a** was determined by an X-ray crystallographic analysis of a single crystal of this compound. The ORTEP drawing of this molecule is shown in Figure 1. As is clearly seen, it is in the partial cone conformation with the three methoxyl groups on the same face of the 16-membered carbocycle. The deoxy ring has inverted orientation. All methyl groups point outward. The dihedral angles between the four phenyl rings and the mean plane of the methylene groups (canting angle[12]) are 99.4°, 36.0°, 102.2°, and -32.5°. These values are quite different from those observed in a partial cone of tetramethyl ether of a calix[4]arene (**4**)[7,8b]: those are 88.3°, 35.3°,

84.8°, and -88.0°, respectively. Partial cone structures are rather common in calix[4]arene tetraalkyl ethers.[13] In these structures the inverted ring and two proximal alkoxybenzene rings are usually parallel with each other and diametrical alkoxybenzene of the inverted ring leans outwards significantly. Again, all α-carbon of the alkoxyl groups point outward. On the other hand, in **3a** the inverted benzene and the diametrical *p*-methyl anisole ring are almost parallel with each other. The other anisole rings of **3a** are not parallel but lean inward so as to widen the O - O distance of the two alkoxyl groups. This movement of the two ring squeezes a cavity composed by the three methoxybenzene rings. If some *p*-alkyl substituents are present on the two diametrical anisole rings, steric repulsion between the two *p*-substituents prevents these rings from inclining toward each other. Hence, this prominent inward bending of the anisole rings is due to van der Waals attractive interaction of two diametrically oriented anisole rings.

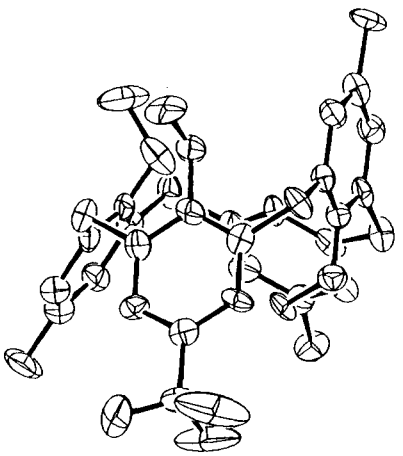


Figure 2. ORTEP drawing of the molecular structure of **3b**.

The molecular structure of compound **3b** is also in a partial cone form in crystal. In sharp contrast with **3a**, the inverted ring of **3b** is not the deoxy ring but one of the two *p*-methyl anisole rings. The canting angles of the four aromatic rings are 42.8° (deoxy ring), 58.5° (*p*-methyl anisole), 76.1° (*p-tert*-butyl anisole) , and -88.1° (inverted *p*-methyl anisole). These values are rather similar to those found in the partial cone of **4** (*vide supra*). However, there is a prominent difference between the two partial cones and that difference is the orientation of the methoxyl group of the inverted rings. Although the methoxyl group in **4** points outward from its cavity, that of **3b** points inward to the cavity formed by the three aromatic rings. Since the partial cone of **4** has a narrow cavity because of the parallel arrangement of the two diametrical anisole rings, the methyl group of the inverted anisole ring cannot reside in the cavity and hence points outward in the crystal. The inward orientation of the methoxyl group is thus quite characteristic for monodeoxy derivative. In this structure the deoxy aromatic ring inclines outward, thus widening the cavity. This can be explained by freedom of movement of the aromatic rings. In the deoxy ring there is less severe inner annular steric repulsion, and hence greater freedom of movement than the other rings. The wide cavity

for the methyl group is formed by the outward inclination of the deoxy ring. The methoxyl group can then have the cavity filling orientation through a self-complexation[14] process.

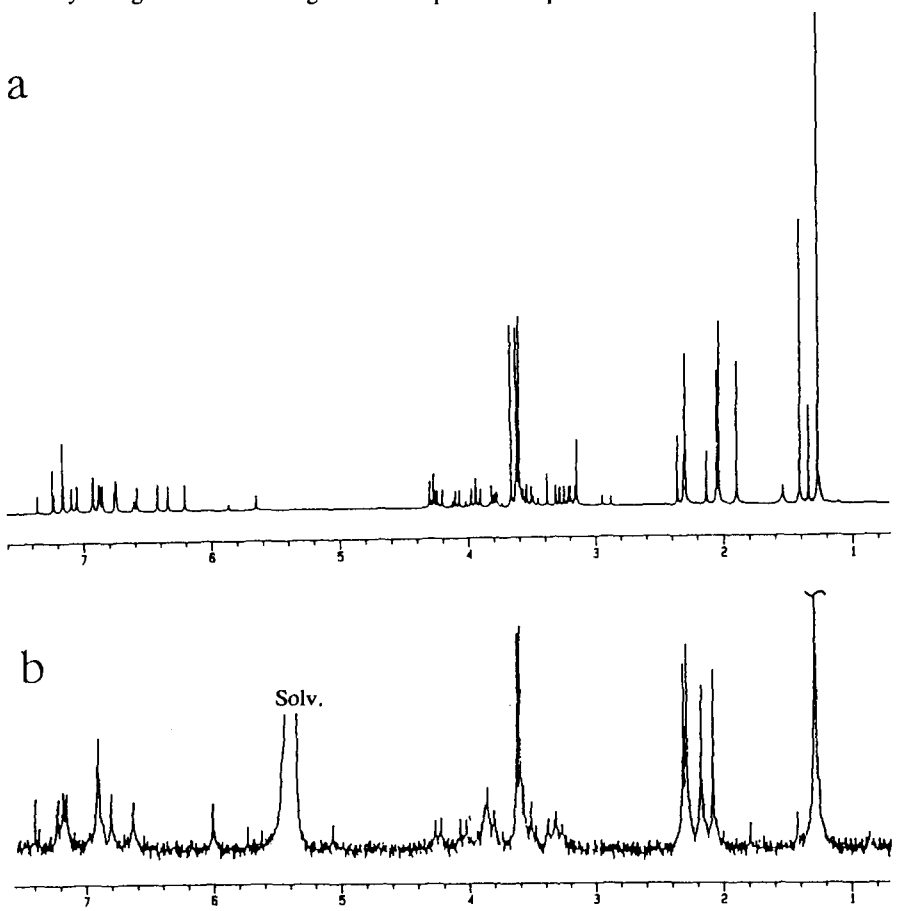


Figure 3. a) ^{1}H-NMR spectra of **3b** in $CDCl_3$ at 27°C. b) ^{1}H-NMR spectra of **3b** dissolved in pre-cooled solvent of CD_2Cl_2 at -80° C.

Conformational distribution in $CDCl_3$ Solution In the ^{1}H-NMR spectrum of the trimethyl ether **3b** in $CDCl_3$ there are three signals due to the *tert*-butyl group of different intensities at 1.26, 1.35 and 1.42 ppm at room temperature. The ^{1}H-NMR spectra in CCl_4 and CD_2Cl_2 show the same characteristic signals indicating three conformers are present in the solution. These three signals coalesced at around 130° C in DMSO-d_6. The observed coalescence temperature of **3b** is significantly higher than that of **4**[2b] suggesting higher activation energy for the conformational interconversion process. From this experiment it is clear that the three conformers are interconvertible with each other by rotating the aromatic rings through the average plane of the four methylene groups. The barrier to rotation is about 20 kcal/mol in DMSO-d_6. The other

signals due to methoxyl groups and the para substituted methyls in $CDCl_3$ at room temperature show a complex pattern which prevents straightforward assignment of the three conformers. Since **3b** has lower symmetry than **4**, it is very difficult to identify the three conformers using the chemical shift and splitting pattern criteria[15] found in calix[4]arenes.

We applied our newly developed technique to find a single conformer of the crystalline state in solution.[16] When crystals of **3b** were dissolved in pre-cooled solvent of CD_2Cl_2 at -80° C, they gave the ^{1}H-NMR spectrum of the simple signal pattern (Figure 3). In this spectrum only one intense singlet due to the *tert*-butyl group was observed indicating that there is only one conformer in solution at that temperature. There are three singlets (between 2.10 - 2.40 ppm) assignable to methyl groups of the para substituent. Though two of the three methoxyl signals appeared at the normal absorption region one signal shifted significantly to the upfield (~2.1 ppm). This signal splitting pattern is compatible with the structure found in its crystalline state. Although we are unable to obtain any direct information on the orientation of the deoxy ring, the presence of the upfield shifted methoxyl signal is indicative of the partial cone of the crystalline state even in solution. This further indicates that the self-complexation type cavity filling orientation of the methoxyl group of the inverted anisole ring is still a stable structure in solution. With rising the temperature, signals due to the other conformers appeared and gradually increased in intensity.

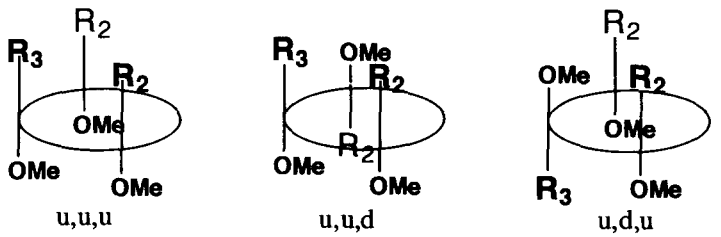


Figure 4. Conformations of the trimethyl ethers of monodeoxycalix[4]arene.

From this experiment we found that it is very difficult to identify the orientation of the deoxy ring in solution. Hence we applied the "u" (up) and "d" (down) notation of the orientation of three anisole rings which was proposed by Gutsche in his study of conformational properties of calix[6]arenes.[17] The structure found in the pre-cooled solution is thus designated as a (u,u,d); the other two structures should be (u,u,u) and (u,d,u). These conformers can be distinguished by the NMR signal splitting pattern; for example, the number of singlets and the intensity of their methoxyl groups are shown in Table 1.

Table 1. Number of singlets and their intensity of methoxyl groups for **3**.

	u,u,u	u,u,d	u,d,u
Number of singlets	2	3	2
Intensity	2 : 1	1 : 1 : 1	2 : 1

Identification of the other conformers was successfully carried out by magnetization transfer experiments of the known methoxyl signals of the (u,u,d) conformer. With irradiation of the upfield shifted methoxyl signal which is assigned to the inverted terminal anisole, three singlets (3.15, 3.60, and 3.67 ppm) were inverted (negative intensity). Since the conformational interconversion at room temperature is rapid, the irradiated conformer changed to other conformers and corresponding methoxyl signals had negative intensity. One of the signals (3.60 ppm) was assigned to the methoxyl of the diametrical anisole within the same (u,u,d) conformer, suggesting the rapid interconversion of the (u,u,d) conformer to its mirror image (d,u,u) at ambient temperature. The other two inverted signals were assigned to the terminal anisole rings of the (u,u,u) and (u,d,u) conformers. A similar irradiation experiment on the central methoxyl signals of the (u,u,d) gave the assignment of the corresponding methoxyl signal of both the (u,u,u) and (u,d,u) forms. Chemical shift criteria of the methoxyl signals are helpful for the assignment of the conformer (Table 2); in (u,u,u) form the two chemical shifts should be similar (3.67 and 3.61 ppm), but those of the (u,d,u) form should be greatly different (3.15 and 3.39 ppm). From the intensity ratio of each signal we can estimate the relative population of the three conformers in 5 : 3 : 1 of (u,u,d) : (u,u,u) : (u,d,u).

Table 2. Chemical shift of methoxyl groups (ppm) for **3**.

	u,u,u	u,u,d	u,d,u
3a	3.70,3.66	3.65,3.61,2.17	3.51,3.18
	2 : 1	1 : 1 : 1	1 : 2
3b	3.67,3.61	3.63,3.60,2.06	3.39,3.15
	2 : 1	1 : 1 : 1	1 : 2
3c	3.77,3.72	3.68,3.55,2.16	3.55,3.06
	1 : 2	1 : 1 : 1	1 : 2
3d	3.81,3.71	3.65,3.56,2.01	3.55,3.01
	1 : 2	1 : 1 : 1	1 : 2
3e	3.80,3.72	3.62,3.56,2.03	3.55,3.02
	1 : 2	1 : 1 : 1	1 : 2

Similar NMR analysis gave the population of the three conformers in solution for all the trimethyl ethers of monodeoxycalix[4]arenes (**3a** - **3e**). The results are summarized in Table 3. The unsymmetrical (u,u,d) conformer was the most stable in each case. The above mentioned characteristic upfield shift of methoxyl signal of the terminal inverted anisole ring is found in every (u,u,d) conformer. The self-complexation type cavity filling orientation of the methoxyl group of the inverted anisole ring is still valid even in the smallest cavity size compound (**3a**, *vide supra*). It is noteworthy that in **3a** the most stable structure in solution is not the same conformer found in the crystalline state. The (u,u,u) conformer is the second populating structure in both **3a** and **3b**. On the other hand, the same conformer is the least stable in the poly *tert*-butyl derivatives (**3c** - **3e**). Thus the relative stability of the (u,u,u) conformer is dependent on the number of bulky upper rim substituents.

Table 3. The ratio of conformers (%) in various solvents determined by ^{1}H-NMR analysis.

	$CDCl_3$			CCl_4			CS_2		
	u,u,u	u,u,d	u,d,u	u,u,u	u,u,d	u,d,u	u,u,u	u,u,d	u,d,u
3a	38	45	17	42	42	16	35	56	9
3b	30	57	13	49	40	11	40	49	11
3c	5	74	21	8	76	16	9	79	12
3d	6	73	21	11	72	17	10	78	12
3e	7	72	21	16	63	21	10	76	14

Molecular mechanics calculation To gain insight into the potential energy of these conformers we examined the calculated relative stabilities of all the possible structures for these compounds. In this study we applied molecular mechanics calculation to get the structure and the relative energy of these conformers. A number of studies have been carried out to predict the most stable conformer of calix[4]arene and its alkyl ethers using molecular mechanics calculation.[3c,5c,7,9,18,19] The most stable predicted conformer for tetramethyl ether of calix[4]arenes differs depending on method: 1,3-alternate by MM2 and AMBER force fields, partial cone by QUANTA/CHARMm, and AM1 (MOPAC6), cone by AM1 (AMPAC).[12] On the other hand, Shinkai and his co-workers have reported successful prediction of not only the most stable form but also the correct order of the relative stabilities of the four conformers of **4** (partial cone > cone > 1,2-alternate >1,3-alternate) by MM3 force field.[19] Hence, we applied MM3 force field in the original version.

In the case of **3** we have to consider two orientations of the deoxy ring for the three conformers found in solution. The orientation of the deoxy ring is also expressed by "u" and "d" notation, but with an underline. Inward orientation of the methoxyl group of an anisole ring as was found for the molecular structure of **3b** in its crystalline state should also be taken into consideration. Inside orientation of the methoxyl group is expressed as "i" (inside) by subscript, but outside orientation is not shown explicitly, thus the molecular structure of **3b** in the crystalline state is expressed as (u,u,d_i,$\underline{u}$). In **3b**, (u,u,d_i,$\underline{u}$) conformer is calculated to be more stable than (u,u,d,$\underline{u}$) conformer. The relative steric energy differences of the calculated structures are summarized in Table 4.

The calculations disclosed that the most stable conformer is (u,u,u,$\underline{u}$) in **3a** followed, in order of decreasing stability, by (u,u,u,$\underline{d}$), (u,u,d,$\underline{u}$), (u,u,d_i,$\underline{u}$), (u,d,u,$\underline{u}$), (u,d,u,$\underline{d}$), (u,d_i,u,$\underline{u}$), (u_i,d,u,$\underline{d}$), (u,u,d,$\underline{d}$), and (u,d_i,u,$\underline{d}$) conformations. The calculated structures of these conformers are shown in Figure 4. When the number of bulky substituents is increased the order of stability changes from compound to compound, but the most stable and the least stable conformers are always (u,u,u,$\underline{u}$) and (u,d_i,u,$\underline{d}$), respectively, except in the case of **3e**.

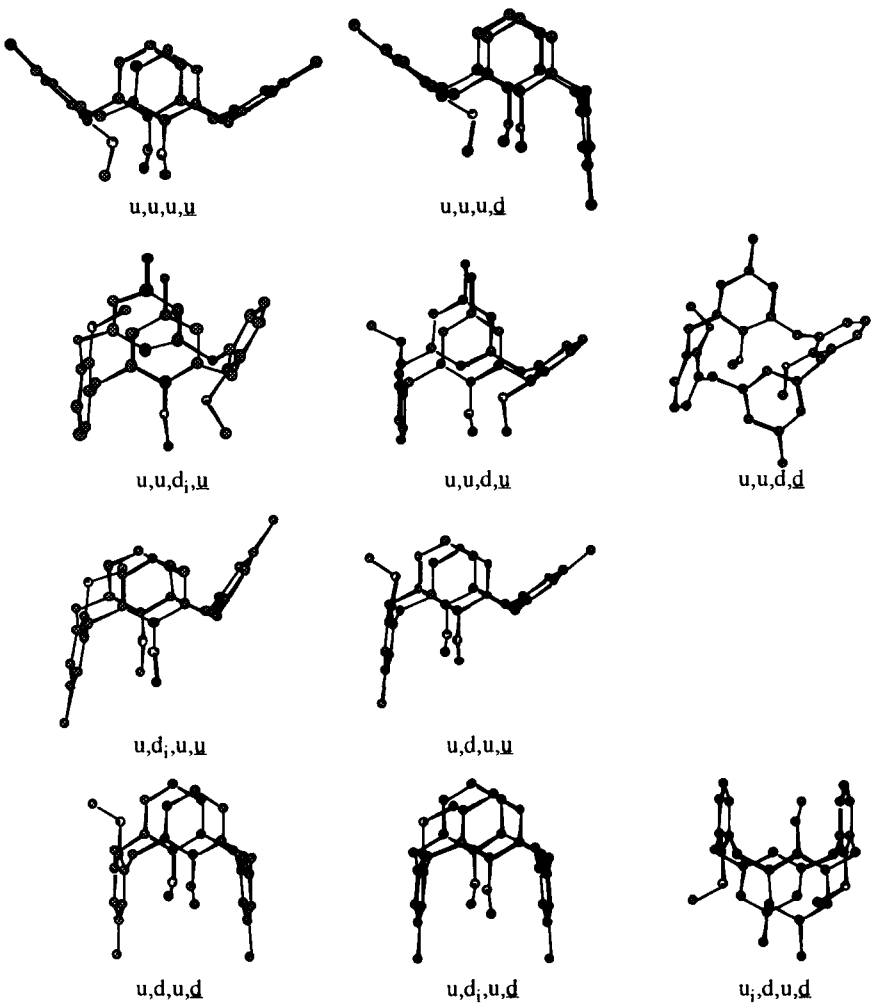


Figure 5. The structure of each conformer of **3a** calculated by MM3(92).

Within the two (u,u,u) forms, the cone type "u" isomer is always more stable than the partial cone type "d" isomer. The energy difference of the two forms increases with increase in the number of bulky substituents. Large energy differences of the two forms in **3c**, **3d** and **3e** are experimentally supported by the chemical shifts of the methoxyl signals for these compounds (Table 2). In the (u,u,u,d) forms the methoxyl group of the central anisole ring is placed just above the diametrical inverted benzene ring and thus it is in the magnetic shielding cone of the latter. If the population of the (u,u,u,d) form is large, the NMR signal for the central methoxyl group should shift upfield significantly and the signals for **3a** and **3b** shift to a higher magnetic field than the other signals. The signals of the central anisole for **3c**, **3d** and **3e** appeared

in a lower field than the others, in which the energy differences between the two forms, (u,u,u,u) and (u,u,u,d) are large enough (0.7 ~ 0.9 kcal), and hence there is a smaller contribution of the latter conformers.

Table 4. The relative steric energy differences (kcal/mol) for **3** calculated by MM3(92).

	3a,Bu=0	**3b**,Bu=1	**3c**,Bu=2	**3d**,Bu=3	**3e**,Bu=4
u,u,u,u	0.0	0.0	0.0	0.0	0.0
u,u,u,d	0.1	0.3	0.7	0.9	0.9
u,u,d_i,u	0.3	0.2	0.6	0.6	1.1
u,u,d,u	0.2	1.7	2.6	2.1	3.2
u,u,d,d	3.3	2.7	5.0	4.8	5.8
u,d_i,u,u	1.7	1.1	3.0	3.0	2.8
u,d,u,u	0.7	0.8	5.5	5.7	5.6
u,d,u,d	1.2	0.0	1.5	0.9	1.1
u,d_i,u,d	4.7	4.2	5.9	5.4	5.4
u_i,d,u,d	3.0	2.4	3.3	3.6	4.1

Although a similar tendency is found in the (u,u,d) forms the energy difference between the two forms is much larger in these conformers. In the (u,u,d,u) form two orientations for the methoxyl group of the inverted anisole are possible. The inward orientation is always more stable than the outward except **3a**. The energy difference of the two orientations is fairly large (1.5 ~ 2.1 kcal). This large energy difference and hence negligible contribution of the conformer for the outward orientation is compatible with the observed NMR chemical shifts of these compounds, in which one of the three methoxyl signals shows a large upfield shift. The deoxy ring has a greater freedom of movement than the other rings because of the less severe inner annular steric repulsion, and a wide cavity for methyl group can thus be formed by the outward inclination of the deoxy ring. The canting angles of the deoxy ring in these cavity filling conformers are 39.7°, 43.9°, 39.7°, 38.9°, and 39.5° for **3a**, **3b**, **3c**, **3d**, and **3e**, respectively. The methoxyl group can then have the cavity filling orientation through the self-complexation process. The inward orientation of the alkoxyl group is thus quite a characteristic feature for the trimethyl ethers of the monodeoxy calix[4]arene.

In contrast to the above two cases, five conformers should be taken into consideration for the (u,d,u) form. They are the two pairs of the (u,d,u,u) and (u,d,u,d) with respective "i" and "o" orientations of the inverted anisole rings and (u_i,d,u,d). The lowest energy conformer of these five forms is (u,d,u,d) except **3a**. Since the (u,d,u,d) conformer corresponds to the 1,3-alternate for the calix[4]arenes and its four aromatic rings are almost parallel to each other, the space composed of the two diametrical rings is not wide. The inward orientation of the methoxyl group in this form thus has higher energy than the outward. Actually, steric repulsion between the methoxyl group and two buttressing walls makes the two aromatic rings bend outward. In the (u,d_i,u,d) form the outward bending of the two anisoles causes the movement of the two anisole oxygens toward each other. This repulsive interaction can be reduced if one of the outward

bending rings has no sterically bulky methoxyl group as was found for the smaller destabilization energy in the (u_i,d,u,d) form than the (u,d_i,u,d). The ability to have a wider space by the greater freedom of movement for the deoxy rings can be supported further in these cases. The (u,d,u,d) form is the most stable conformer among the five conformers of these compounds except for **3a**. The second most stable conformation of the poly *tert*-butyl compounds, **3c**, **3d**, and **3e** is the (u,d_i,u,u) form, and its energy difference from the most stable form is larger than 1.5 kcal. The corresponding energy difference is smaller in **3b** and the contribution of the inside methyl conformer is slightly larger than the poly *tert*-butyl compounds. Increase of the contribution of the inside methyl conformer is shown by the chemical shift of the methoxyl signals for these compounds. The compound **3b** has upfield shifted signal (3.39 ppm) due to the central methoxyl group than do those of the poly *tert*-butyl compounds (3.55 ppm), supporting the more appreciable contribution of the inside methyl conformer for **3b** than the other compounds.

Table 5. The calculated population (MM3) of each conformer.

	3a,Bu=0	**3b**,Bu=1	**3c**,Bu=2	**3d**,Bu=3	**3e**,Bu=4
u,u,u,u	24	24	52	50	62
u,u,u,d	20	15	16	16	14
u,u,d_i,u	20	24	26	26	14
u,u,d,u	24	2	1	1	0
u,u,d,d	0	0	0	0	0
u,d_i,u,u	1	4	0	0	1
u,d,u,u	7	6	0	0	0
u,d,u,d	3	24	4	4	10
u,d_i,u,d	0	0	0	0	0
u_i,d,u,d	0	0	0	0	0

The population of these conformers for each compound was estimated from the steric energy where the contribution of symmetry of the structure is taken into account in estimating its entropy. The population of the three structures, (u,u,u), (u,u,d), and (u,d,u) in the gas phase is thus obtained by summation of the contribution of each conformer in these three forms (Table 5). Although the calculation showed that the population of the three forms for **3a** is close to the observed one, it deviates significantly from the observed one with the increase in number of bulky substituents. The most stable conformer is the cone type (u,u,u) in each compound. When the number of bulky substituents increased the population of the (u,u,u) increased gradually, and hence the calculation cannot reproduce the observed sudden decrease of the conformer between **3b** and **3c**.

Solvent dependent conformational distribution The conformational distribution of the trimethyl ethers of monodeoxycalix[4]arenes (**3a** - **3e**) is influenced by the solvent in which they are dissolved. Table

3 summarizes relative populations of trimethyl ethers **3** in different solvents. The population of the three conformers in CS_2 and CCl_4 is very similar for each compound, but it is slightly different in $CDCl_3$. The (u,u,d) form is the most stable conformer for every compound in every solvent except **3b** in CCl_4. Though the (u,u,d) is not the most stable form in the gas phase, its preference in solution can be explained by the calculated dipole moment. Since the (u,u,d) has the largest dipole moment among the three it is quite reasonable to find it the most populating conformer in solution. The (u,u,d_i,u) form, the most stable among the three (u,u,d) conformers is responsible for the largest dipole moment (1.9 D). The (u,u,u) form is the second most stable conformer of **3a** and **3b** for every solvent except CCl_4, but it is the least populating form for the poly *tert*-butyl compounds, **3c**, **3d**, and **3e** in every solvent. The population of the (u,u,u) form for the latter three compounds is smallest in $CDCl_3$ but it increased slightly in less polar solvents. Increase in the population of the (u,u,u) form in CS_2, the smallest molecular size solvent among the three could not be observed. Since the cavity size of the cone form in the former two compounds is quite small because of the small upper rim substituent, inclusion of a solvent molecule in the cone cavity is rather difficult. If the solvent inclusion, as was proposed in a methyl ether of calix[4]arene, is operative, the population of the (u,u,u) forms in the poly *tert*-butyl compounds should be higher because their cavity sizes are larger than the former two and are stabilized significantly by the van der Waals interaction between the cavity wall and the included solvent.

Although the molecular size of the two solvents (CS_2 and CCl_4) is significantly different, their polarity parameters (E_T30) are very similar (32.5 for CS_2 and 32.6 for CCl_4). Chloroform has the largest solvent polarity parameter, and hence the least polar conformer reduce its population in this solvent. Thus, these results suggest that the solvent polarity plays a significant role in the stability of the conformers in solution.

CONCLUSION

In this study conformational isomers of the trimethyl ethers of monodeoxycalix[4]arene with various numbers of *tert*-butyl group were elucidated in solution with the aid of molecular mechanics calculation and X-ray crystallographic analysis. The (u,u,d) conformer is the most stable among the three possible forms. The orientation of the methoxyl group for the inverted anisole ring of the (u,u,d) form in crystal of **3b** is inside a cavity composed of the remaining three aromatic rings. This cavity filling conformation is also found in solution not only for **3b** but for all the compounds studied. The conformational population of the three forms is solvent dependent. Polarity of the solvent plays an important role in the conformational equilibrium. Identification of a set of NMR signals due to the conformer in its crystalline state from the complex signals of dynamically equilibrating multiple conformers can be made by simple dissolution of a crystalline compound into a precooled solvent, and is found to be an efficient method for the analysis of a multiple conformational problem.

EXPERIMENTAL SECTION

General Methods. All reagents and chemicals were reagent grade and obtained from commercial suppliers and used without further purification unless otherwise noted. All solvents were purified according to standard laboratory techniques prior to use. Solvents used for chromatography were not distilled. Reactions under water- or air-sensitive conditions were performed under dry N_2 or Ar, in dry solvents. Synthetic workups were usually conducted in air. Solvents was evaporated by a rotary evaporator under water aspirator vacuum. Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. Flash column chromatographic separations were performed in air on Merck silica gel 60 (230-400 mesh). Reactions were monitored by thin-layer chromatography (TLC) using E. Merck silica gel plates. Compounds are visualized by illumination with UV light (254 nm) and spraying with EtOH solution of *p*-anisaldehyde, followed by heating. Hitachi 260-10S spectrometer was used to record IR spectra, with solid samples ground with KBr and pressed into pellets. Mass spectra (HRMS) were obtained on a Jeol JMS-SX102A spectrometer. Mass spectral data are reported m/z with the molecular ion designated as M^+.

NMR Spectroscopy: ^{1}H-NMR spectra were recorded on either 270 MHz on a Jeol JNM-EX270 and 400 MHz on a Jeol JNM-EX400 NMR spectrometer, at 291 K operated in pulsed Fourier transform mode and locked on solvent deuterium. The chemical shifts were referenced to an internal reference tetramethylsilane (TMS) at 0.00 ppm and downfield shifts are given a positive sign. Deuterio-chloroform ($CDCl_3$) was used at room temperature. Coupling constants (*J*) are reported in hertz (Hz). Spectral data are reported as follows: chemical shift (multiplicity, coupling constants, and number of protons). Variable-temperature ^{1}H-NMR spectra were recorded on a Jeol JNM-EX270 NMR spectrometer using Cu-Constantan variable temperature controller.

X-Ray Structure Determinations of compounds 3a and 3b: Crystallographic data for both **3a** and **3b** are presented in Table 6. All crystal structures were determined and refined using the same procedures. Data were collected on a Mac Science MXC18, fully automated four-circle diffractiometer using graphite monochromated MoKα radiation (λ = 0.71073 Å). A scan speed of 4.0°/min was employed. All intensity measurements were made at room temperature. Crystal decomposition was monitored throughout data collection and no significant variation in intensity was observed. Data with [|Fo|>3σ(|Fo|)] were considered observed. The structures were solved by direct methods using SHELXS program and the remaining atoms were located in the initial E synthesis. After several cycles of refinement of non-hydrogen atoms with anisotropic temperature factors, hydrogen atoms were located from the difference Fourier map and included in the further calculations. Full matrix least-squares refinement with all atoms led to convergence with R and R_W values as shown in the Table 6. All the calculations were done on a Titan-750 computer using the Crystan-G program package.

Table 6. Crystallographic Parameters for **3a** and **3b**.

	3a	**3b**
formula	$C_{33}H_{34}O_3$	$C_{38}H_{44}O_3$
crystal habit	prism	prism
color	colorless	colorless
molecular weight	478.60	548.80
crystal size, mm	0.60*0.40*0.30	0.35*0.30*0.20
crystal system	Monoclinic	Monoclinic
space group	$P2_1/a$	$P2_1/n$
cell parameters		
a, Å	18.513 (4)	21.210 (3)
b, Å	20.180 (4)	15.462 (2)
c, Å	7.109 (2)	9.854 (2)
β, deg	92.29 (2)	101.61 (2)
V, Å^3	2653.7 (9)	3215.1 (8)
Z	4	4
$d$calc, g/cm^3	1.20	1.13
reflections measured	$\pm h,k,l$	$\pm h,k,l$
unique reflections	6094	5780
reflections used (F>3.00(σ(F)))	2908	2334
no. of variables	428	503
R	0.082	0.106
R_W	0.052	0.069

Synthetic Procedure

3,5-bis(2-hydroxy-5-methylbenzyl)toluene 7: A mixture of 3,5-bis(hydroxymethyl)toluene[20] (8.75 g, 57.5 mmol) and conc.HCl (4 mL) in *p*-cresol (150 mL) was stirred at 80 °C for 2 h. *p*-Cresol was removed by distillation under reduced pressure (0.9 mmHg). The residue was purified by column chromatography on silica gel (eluting with benzene) to give a trimer (**7**, 10.8 g, 57%) as pale yellow oil.
5: IR ($CHCl_3$) 3600, 2925, 1726, 1600, 1502, 1261, 1176, 817 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 6.55-7.00 (9H, m), 4.6-5.4 (2H, bs), 3.85 (4H, s), 2.2 (9H, s); HRMS m/z 332.1790 (M^+), calcd for $C_{23}H_{24}O_2$ 332.1776.

3,5-bis(5-*tert*-butyl-2-hydroxybenzyl)toluene 8: A mixture of 3,5-bis(bromomethyl)toluene[20] (5.0 g, 18.0 mmol) and *p-tert*-butylphenol (27.0 g, 180 mmol) in DMF (20 mL) was refluxed for 14 h. DMF and *p-tert*-butylphenol were removed by distillation under reduced pressure (30 mmHg), and the residue was purified by column chromatography on silica gel (eluting with hexane:AcOEt (8:2)). The crude product was further purified by recrystallization from hexane-CH_2Cl_2 to give a trimer (**8**, 1.6 g, 22%) as colorless prisms.

6: mp 106-107 °C; IR (KBr) 3245, 2955, 1598, 1508, 1436, 1361, 1242, 1183, 827 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.2-6.8 (m, 9H), 4.57 (s, 2H), 3.91 (s, 4H), 2.25 (s, 2H), 1.27 (s, 18H); HRMS m/z 416.2716 (M^+), calcd for $C_{29}H_{36}O_2$ 416.2715.

26,27,28-trihydroxy-5,17-dimethylcalix[4]arene 2a: To a solution of **2b**[5c] (170 mg, 0.32 mmol) and phenol (170 mg, 1.9 mmol) in toluene (6 mL) was added $AlCl_3$ (300 mg, 2.3 mmol). After being stirred at room temperature for 2 h, the reaction was quenched with water. The mixture was extracted with AcOEt and washed with 0.2 N HCl and then with brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The remained solid was washed with MeOH to give **2a** (120 mg, 86%) as colorless powder.

2a: mp 179-180 °C; IR (KBr) 3320, 2915, 1597, 1468, 1454, 1246, 753 cm^{-1}; ^{1}H-NMR ($CDCl_3$-Acetone-d_6) 9.2 (bs, 3H), 7.61 (s, 1H), 7.05 (d, J= 7.5 Hz, 4H), 6.94 (s, 2H), 6.88 (s, 2H), 6.62 (t, J= 7.5 Hz, 2H), 3.88 (s, 4H), 3.86 (s, 4H), 2.14 (s, 3H), 2.09 (s, 3H); HRMS m/z 436.2061(M^+), calcd for $C_{30}H_{28}O_3$ 436.2038.

17-*tert*-butyl-26,27,28-trihydroxy-5,11,23-trimethylcalix[4]arene 2b: A solution of trimer 7 (179 mg, 0.54 mmol) and 4-*tert*-butyl-2,6-bis(hydroxymethyl)phenol[21] (113 mg, 0.54 mmol) in dioxane (25 mL) was added dropwise for 5 h into a solution of sulfonic acid (2 mL) in dioxane (50 mL) using dropping funnel under reflux condition. The reaction mixture was allowed to stir at reflux temperature for additional 12 h and then neutralized with aqueous $NaHCO_3$. After evaporation, the reaction mixture was extracted with AcOEt and washed with brine. The organic layer was dried over Na_2SO_4, and solvent was evaporated. The residue was purified by column chromatography on silica gel (eluting with hexane:AcOEt (8:2)) to give **2b** (53.8 mg, 20%) as colorless prisms.

2b: mp 240-241 °C; IR (KBr) 3200, 2955, 1600, 1483, 1450, 1200, 689 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.07 (s, 2H), 6.93 (bs, 1H), 6.87 (bs, 2H), 6.83 (d, J = 2.4 Hz, 2H), 6.60 (s, 2H), 3.83 (s, 4H), 3.81 (s, 4H), 2.30 (s, 3H), 2.17 (s, 6H), 1.26 (s, 9H); HRMS m/z 506.2837 (M^+), calcd for $C_{35}H_{38}O_3$ 506.2821.

11,23-di-*tert*-butyl-26,27,28-trihydroxy-5,17-dimethylcalix[4]arene 2c: A solution of trimer **8** (1.13 g, 2.71 mmol) and 2,6-bis(acetoxymethyl)-4-methylphenol[22] (1.47 g, 5.5 mmol) in dioxane (50 mL) was added dropwise using dropping funnel into a mixture of sulfonic acid (3 mL) and water (20 mL) in dioxane (180 mL) under reflux condition for 5 h. After the addition, the mixture was refluxed for 12 h and neutralized with $NaHCO_3$. After evaporation, the reaction mixture was extracted with AcOEt, and washed with brine. The organic layer was dried over Na_2SO_4, and solvent was evaporated. The product was purified by column chromatography on silica gel (eluting with hexane:AcOEt (8:2)), then further purified by GPLC (eluting with $CHCl_3$) to give **2c** (343 mg, 23%) as colorless powder.

2c: mp 210-215 °C; IR (KBr) 3240, 2940, 1601, 1484, 1194 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.15 (s, 1H), 7.08 (s, 4H), 6.87 (s, 2H), 6.81 (s, 2H), 3.83 (s, 4H), 3.82 (s, 4H), 2.21 (s, 3H), 2.13 (s, 3H), 1.27 (s, 18H); HRMS m/z 548.3260 (M^+), calcd for $C_{38}H_{44}O_3$ 548.3290.

11,17,23-tri-*tert*-butyl-26,27,28-trihydroxy-5-methylcalix[4]arene 2d: The compound **2d** was prepared from **8** (1.50 g, 3.60 mmol), 2,6-bis(acetoxymethyl)-4-*tert*-butylphenol[23] (5.4 g, 16 mmol), H_2SO_4 (3 mL), H_2O (20 mL), and dioxane (180 mL) according to general procedure described for **2c**.

Workup and chromatography on silica gel (eluting with hexane:AcOEt (8:2)) and GPLC (eluting with $CHCl_3$) gave **2d** (280 mg, 13%) as colorless powder.

2d: mp 194-196 °C; IR (KBr) 3330, 2960, 1601, 1485, 1366, 1207, 882 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.9 (bs, 2H), 7.25 (s, 4H), 7.01 (s, 2H), 6.95 (s,2H), 6.67 (s, 1H), 3.85 (s, 4H), 3.84 (s, 4H), 2.18 (s, 3H), 1.12 (s, 27H); HRMS m/z 590.3727 (M^+), calcd for $C_{41}H_{50}O_3$ 590.3760.

26,27,28-trimethoxy-5,17-dimethylcalix[4]arene 3a: To a solution of **2a** (51 mg, 0.11 mmol) in THF (6 mL) was added KO^{t}Bu (50 mg, 0.46 mmol) and then, after being stirred for 2 h, MeI (0.25 mL). After being stirred at room temperature overnight, AcOEt (50 mL) was added and washed by brine (3 times). The organic layer was dried over Na_2SO_4, and solvent was evaporated. The product was purified by column chromatography on silica gel (eluting with CH_2Cl_2) to give trimethyl ether **3a** (10.8 g, 57%) as colorless prisms.

3a: mp 179-180 °C; IR (KBr) 2920, 1600, 1465, 1229, 1082, 1012 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.30-6.34 (m, 9H), 4.32-3.23 (m, 8H), 3.65 (s, 3H), 3.61 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H); HRMS m/z 478.2520 (M^+), calcd for $C_{38}H_{44}O_3$ 478.2508.

17-*tert*-butyl-26,27,28-trimethoxy-5,11,23-trimethylcalix[4]arene 3b: Compound **3b** was prepared from **2b** (99 mg, 0.20 mmol), KO^{t}Bu (107 mg, 1.0 mmol), and MeI (0.5 mL) in THF (12 mL) according to general procedure described for **3a**. Workup and recrystallization from n-hexane gave **3b** (118 mg, 100%) as colorless prisms.

3b: mp 199-201 °C; IR (KBr) 2930, 1599, 1471, 1229, 1135, 1019, 862 cm^{-1}; ^{1}H-NMR (CD_2Cl_2) 7.21 (s, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.91 (s, 3H), 6.80 (s, 1H), 6.62 (s, 1H), 6.02 (s,1H), 4.27-3.28 (m, 8H), 3.63 (s, 3H), 3.60 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H), 1.29 (s, 9H); HRMS m/z 548.3324 (M^+), calcd for $C_{38}H_{44}O_3$ 548.3290.

11,23-di-*tert*-butyl-26,27,28-trimethoxy-5,17-dimethylcalix[4]arene 3c: Compound **3c** was prepared from **2c** (40 mg, 0.073 mmol), KO^{t}Bu (50 mg, 0.4 mmol), and MeI (1 mL) in THF (3 mL) according to general procedure described for **3a**. Workup and chromatography on silica gel (eluting with hexane:AcOEt 8:2) gave **3c** (41 mg, 95%) as colorless powder.

3c: mp 140-143 °C; IR (KBr) 2960, 1602, 1477, 1208, 1109, 1019 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.34-6.48 (m, 9H), 4.26-3.19 (m, 8H), 3.67 (s, 3H), 3.55 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 1.35 (s, 9H), 1.18 (s, 9H); HRMS m/z 590.3780 (M^+), calcd for $C_{41}H_{50}O_3$ 590.3760.

11,17,23-tri-*tert*-butyl-26,27,28-trimethoxy-5-methylcalix[4]arene 3d: Compound **3d** was prepared from **2d** (40 mg, 0.068 mmol), KO^{t}Bu (50 mg, 0.4 mmol), and MeI (0.5 mL) in THF (2 mL) according to general procedure described for **3a**. Workup and chromatography on silica gel (eluting with CH_2Cl_2) gave **3d** (42 mg, 98%) as colorless powder.

3d: mp 94-98 °C; IR (KBr) 2955, 1603, 1485, 1374, 1209, 1123, 1020, 871 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.32-6.36 (m, 9H), 4.34-3.24 (m, 8H), 3.65 (s, 3H), 3.56 (s, 3H), 2.32 (s, 3H), 2.02 (s, 3H), 1.33 (s, 9H), 1.27 (s, 9H), 1.12 (s, 9H); HRMS m/z 632.4235 (M^+), calcd for $C_{44}H_{56}O_3$ 632.4229.

5,11,17,23-tetra-*tert*-butyl-26,27,28-trimethoxycalix[4]arene 3e: The compound **3e** was prepared from **2e** (40 mg, 0.063 mmol), KO^{t}Bu (50 mg, 0.4 mmol), and MeI (0.5 mL) in THF (3 mL)

according to general procedure described for **3a**. Workup and chromatography on silica gel (eluting with hexane:AcOEt (8:2)) gave **3e** (41 mg, 95%) as colorless powder.

3e: mp 101-104 °C; IR (KBr) 2955, 1595, 1480, 1365, 1208, 1121, 1019, 872 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.29 (d, J = 2.4 Hz, 1H), 7.16 (s, 2H), 7.08 (s, 2H), 6.97 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.30 (s, 1H), 4.35-3.24 (m, 8H), 3.62 (s, 3H), 3.56 (s, 3H), 2.03 (s, 3H), 1.34 (s, 9H), 1.31 (s, 9H), 1.29 (s, 9H), 1.09 (s, 9H); HRMS m/z 674.4725 (M^+), calcd for $C_{47}H_{62}O_3$ 674.4699.

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