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Conformational Analysis of *p-tert*-Butylcalix[4]arene Derivatives with *trans*-Alkyl Substituents on Opposite Methylene Bridges: Destabilization of the Cone Form by Axial Alkyl Substituents

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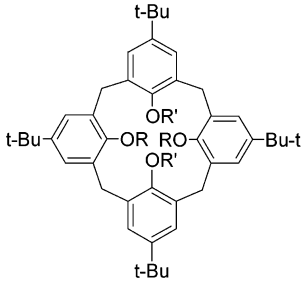
The stereochemistry of calix[4]arenes substituted by a pair of identical alkyl substituents in a trans fashion at two distal bridges is analyzed. MM3 calculations suggest that increasing the bulk of the alkyl group at the bridges destabilizes those conformations possessing an axial disposition of the substituent. In contrast to the 1,3-dimethyl ether of *p-tert*-butylcalix[4]arene, which adopts a cone conformation, solution NMR data indicate that the 1,2-alternate conformation is preferred in the dimethyl ether derivatives **5b** (alkyl = *i*-Pr) and **5c** (alkyl = *t*-Bu). In the derivative substituted by the less bulky methyl substituent (**5a**), both the cone and 1,2-alternate forms coexist in $CDCl_3$. Increasing the polarity of the solvent increases the relative population of the cone form of **5a** and **5b**. The steric destabilization ensuing from the presence of the axial substituent is so large in the cone conformation of **5c** that the 1,2-alternate conformer is the major form even in polar solvents. The cone → 1,2-alternate interconversion barrier of **5a** is 18.2 kcal mol^{-1}, indicating that the presence of an axial methyl group both destabilizes the cone conformation and decreases its rigidity.

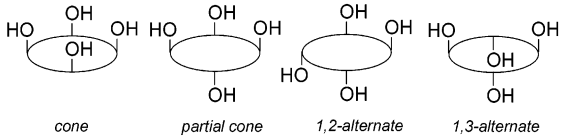
Introduction

The calixarenes are conformationally flexible macrocycles possessing a central [1_n] metacyclophane scaffold.[1] These synthetic hosts are usually obtained by base-catalyzed condensation of a *p*-alkylphenol with formaldehyde. The conformation of the parent *p-tert*-butylcalix[4]arene (**1**) and its derivatives is commonly analyzed in terms of four basic conformations (cone, partial cone, 1,2-alternate, and 1,3-alternate; Scheme 1), arising from the different possible "up" or "down" arrangements of the phenol rings. Usually the number and nature of the intramolecular hydrogen bonds present and the bulk of the intra-annular substituents determine the preferred conformation and the relative rigidity of the macrocyclic ring. Calixarene **1** adopts a cone conformation stabilized by a circular array of hydrogen bonds, which undergoes a cone-to-cone inversion process with a barrier of 15.7 kcal mol^{-1} (in $CDCl_3$).[2]



1 R = R' = H
2 R = H, R' = Me
3 R = R' = Me

SCHEME 1



Recently, we have described a synthetic scheme for the preparation of calixarenes substituted at two methylene groups in a trans fashion.[3−5] When these derivatives

* Corresponding author.

(1) (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1. (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.

(2) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

(3) (a) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (b) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136. (c) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3634.

(4) For the synthesis and conformation of calixarenes *cis*-substituted at two distal methylenes, see: (a) Grüttner, C.; Böhmer, V.; Vogt, W.; Thondorf, I.; Biali, S. E.; Grynszpan, F. *Tetrahedron Lett.* **1994**, *35*, 6267. (b) Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938.

(5) For other examples of the use of the fragment condensation method for the preparation of calixarenes substituted at the bridges, see: (a) Tabatabai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657. (c) Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, *36*, 2311, (d) Biali, S. E.; Böhmer, V.; Columbus, I.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I. *J. Chem. Soc., Perkin Trans 2* **1998**, 2261. (e) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037. (f) Tsue, H.; Enyo, K.; Hirao, K. *Org. Lett.* **2000**, *2*, 3071.

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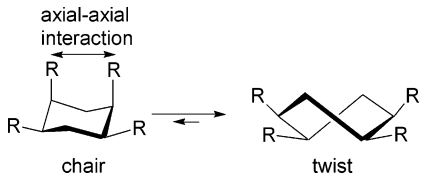
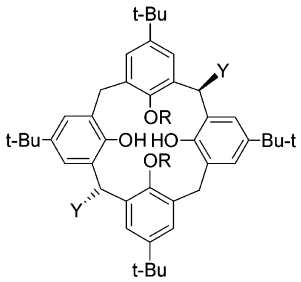
SCHEME 2

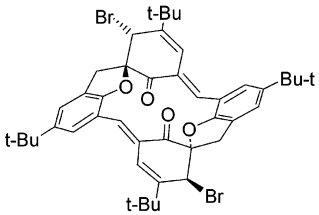


adopt the cone conformation, one substituent is located in an axial and one in an equatorial position (see below). In principle, a sufficiently bulky axial substituent could alter the intrinsic conformational preferences of the central ring, as observed in some alkyl-substituted cyclohexane systems. In such cyclohexane derivatives, a 1,3-diaxial interaction between alkyl substituents is strongly repulsive, and if the substituents are sufficiently bulky (e.g., R = cyclohexyl), this interaction can destabilize the chair conformation, rendering the twist form the lowest energy conformation (Scheme 2).[6] The present work was conducted to test whether the preference of a calixarene for the cone conformation can be modified by the presence of a pair of trans alkyl substituents at distal methylene bridges.[7]

Results and Discussion

Preparation, Conformation, and Rotational Barrier of the *trans*-di-*tert*-Butylcalixarene Derivative 4c. Calixarenes **4a** and **4b** possessing a pair of methyl or isopropyl groups at distal bridges in a trans arrangement were prepared as described previously via addition of RMgX/CuCN to the spirodiene derivative **6**.[3c,8,9] Under the reaction conditions, addition of the organocopper reagents to the exocyclic double bonds of the spirodiene takes place, followed by reduction of the spiro bonds, yielding in one step the trans-substituted derivative. Although the steric demands of a *t*-Bu group are larger than those on an isopropyl group, reaction of **6** with *t*-BuLi/CuCN proceeded readily, affording **4c**.

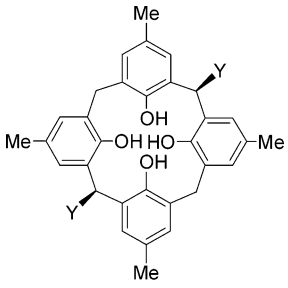




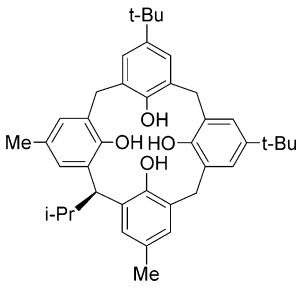
6

4a R = H, Y = Me **5a** R = Me, Y = Me
4b R = H Y = *i*-Pr **5b** R = Me, Y = *i*-Pr
4c R = H, Y = *t*-Bu **5c** R = Me, Y = *t*-Bu

The ^{1}H NMR spectrum pattern of **4c** in $CDCl_3$ was similar to those of **4a** and **4b**[3c] and consistent with the presence of a cone conformation. Two separate singlets were observed (at 4.54 and 3.74 ppm), which could be assigned to the axial and equatorial methine protons. The pair of methylene protons signals ($\Delta\nu$ = 288.3 at 400 MHz) coalesced at 342.3 K, affording a cone-to-cone inversion barrier of 15.7 kcal mol^{-1}.[10] This barrier is lower than the one determined by the diisopropyl derivative **4b** (17.6 kcal mol^{-1}). A similar trend in rotational barriers was previously observed for the series of *cis*-dialkyl derivatives **7a**−**7d**, where the barrier of **7d** was



7a Y = Me
7b Y = Et
7c Y = i-Pr
7d Y = t-Bu



8

lower than the one of **7c** (the compound with the largest barrier of the series).[4b] The lower barrier of **4c** suggests that the formal replacement of the two isopropyl groups of **4b** by *tert*-butyl groups destabilizes more the ground state (the cone conformation) than the rotational transition state of the cone-to-cone inversion process.

Axial, Equatorial, and Isoclinal Positions of the [1$_4$] Metacyclophane Scaffold. The two symmetry-nonequivalent methylene protons (or positions) in the cone conformation of **1** are usually designated as "axial" and "equatorial" by analogy to the nomenclature used for the protons of the chair conformation of cyclohexane.[11] These terms can be applied to the methylene protons present in other conformations of a calix[4]arene provided that the two phenol rings connected to the methylene group are oriented syn. In such a case, the methylene protons located proximal or distal to the OH group can be designated as "axial" and "equatorial", respectively, since their steric surroundings are very similar to those present in the axial and equatorial positions of the cone conformation (Scheme 3). If the methylene is connected to two rings oriented anti, the positions of its protons can be designated as "isoclinal" (Scheme 3)[12] by analogy to the term utilized for the pairs of geminal protons that are exchanged by a C_2 axis in the twist form of cyclohexane.[13]

(6) See, for example: Golan, O.; Biali, S. E. *J. Org. Chem.* **1999**, *64*, 6505. For a computational study of the chair/twist boat energy gap of polyalkylcyclohexanes, see: Weiser, J.; Golan, O.; Fitjer, L.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 8277.

(7) Oxidized thiacalixarenes adopt in the crystal a 1,3-alternate conformations in which the OH groups are hydrogen-bonded to the sulfone or sulfoxide groups at the bridges. See: Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1999**, *40*, 1129. Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Chem. Commun.* **1998**, 1345.

(8) For a recent review on spirodienone calixarene derivatives, see: Biali, S. E. *Synlett*; **2003**, 1.

(9) Calixarenes possessing identical substituents at distal methylene groups but differing in their cis or trans arrangement (e.g., trans **4a** and its cis from) are diastereomers and not different conformers of the same molecule. Their mutual interconversion requires cleavage of at least one σ bond.

(10) The exchange rate at the coalescence temperature was calculated using the Kurland−Wise equation: Kurland, R. J.; Rubin, M. B.; Wise, W. B. *J. Chem. Phys.* **1964**, *40*, 2426.

(11) See, for example: Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335.

(12) Biali, S. E.; Böhmer, V.; Brenn, J.; Frings, M.; Thondorf, I.; Vogt, W.; Wöhnert, J. *J. Org. Chem.* **1997**, *62*, 8350.

(13) See: Kellie, G. M.; Riddell, F. G. *Top. Stereochem.* **1974**, *8*, 225.

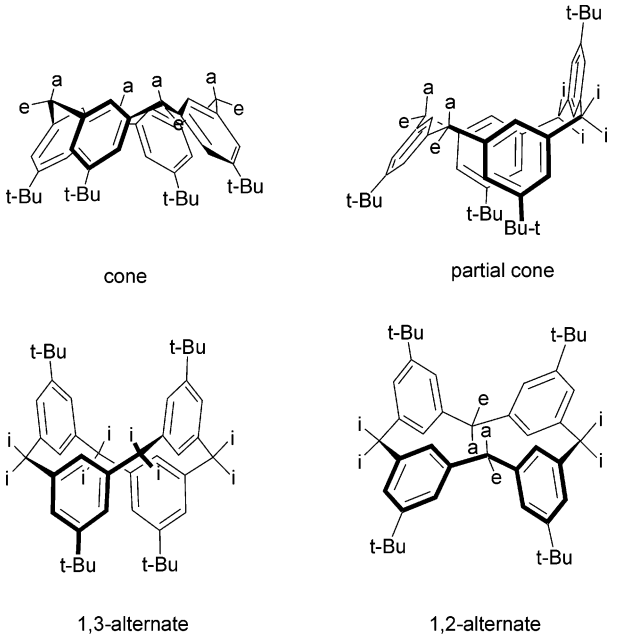
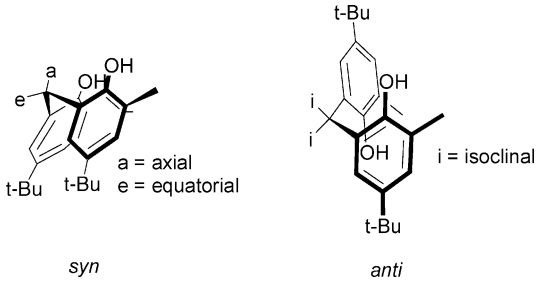


FIGURE 1. Axial (a), equatorial (e), and isoclinal (i) positions of the different up−down conformations of a calix[4]arene. The intraannular OH groups are omitted for clarity.

In the 1,2-alternate and partial cone conformations both axial/equatorial and isoclinal positions are present (Figure 1). In the parent **1**, the isoclinal protons within a given methylene group in the 1,3-alternate or 1,2-alternate conformations are symmetry-equivalent, since they are exchanged by the C_2 axis bisecting these methylene groups. However, in the partial cone form the two isoclinal protons within a methylene group are symmetry-nonequivalent, and the terms iso I and iso II were used to differentiate between the two.[12]

SCHEME 3



Possible Conformations of 4a−c. In the following discussion we will restrict ourselves to conformations arising from the different possible arrangements (equatorial, axial, or isoclinal) of a pair of identical trans alkyl groups at two distal bridges within each of the four basic up−down forms. In the case of the isopropyl substituent, additional conformers arise resulting from the gauche or anti arrangement of the isopropyl group. Solution NMR data indicate that **7c** and **8** adopt a cone conformation with an anti arrangement of the isopropyl groups (located at equatorial positions), and according to molecular mechanics calculations, this arrangement is the lowest in energy.[4b] A similar anti arrangement of both the axial and equatorial isopropyl groups was found for **4b**.[3c]

The cone forms of compounds **4a−c** exist as a single achiral form (C_s symmetry) with one substituent located in an axial and one in an equatorial position while a

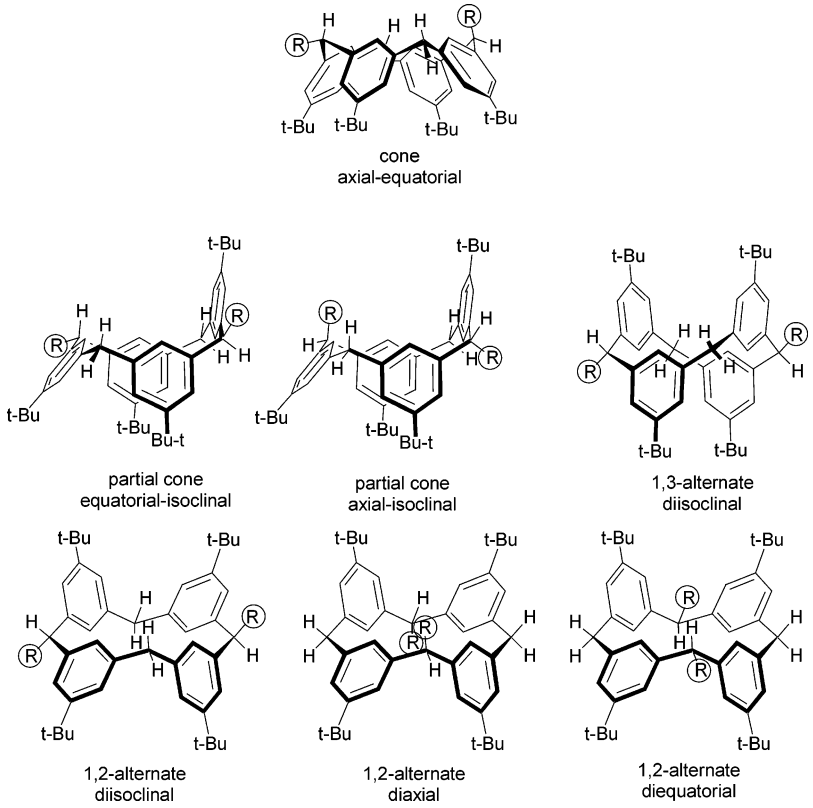


FIGURE 2. Possible conformations of a calix[4]arene functionalized at two distal methylene groups by identical substituents in a trans fashion. The phenolic OH groups are omitted for clarity.

TABLE 1. Calculated (MM3) Steric Energies (in kcal mol^{-1}) of Conformations of 1 and 4a−c[a]

	cone	partial cone	1,3-alternate	1,2-alternate
1	18.19	24.23	29.15	25.66
	(0.0)	(6.0)	(11.0)	(7.4)
4a	22.43	26.00 (eq−iso)[b] 28.25 (ax−iso)[d]	30.17	26.94 (iso−iso)[c] 27.13 (eq−eq)[e] 33.13 (ax−ax)[f]
	(0.0)	(3.6)	(7.7)	(4.5)
4b	28.01	32.65 (eq−iso)[b] 35.77 (ax−iso)[d]	37.62	39.08 (iso−iso)[c] 31.71 (eq−eq)[e] 39.11 (ax−ax)[f]
	(0.0)	(4.6)	(9.6)	(3.7)
4c	44.91	45.99 (eq−iso)[b] 51.20 (ax−iso)[d]	49.91	52.71 (iso−iso)[c] 46.40 (eq−eq)[e] 58.71 (ax−ax)[f]
	(0.0)	(1.1)	(5.0)	(1.3)

[a] Numbers in parentheses are energies differences between the lowest calculated conformer of a given up−down form and the global minimum. [b] Equatorial−isoclinal form. [c] Diisoclinal form. [d] Axial−isoclinal form. [e] Diequatorial form. [f] Diaxial form.

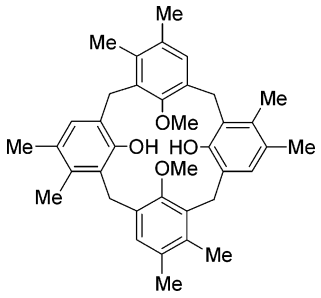
single disposition of substituents (diisoclinal, C_{2h} symmetry) is possible for the 1,3-alternate form. Three different achiral (C_{2h} symmetry) dispositions of the alkyl substituents are possible for the 1,2-alternate form (diisoclinal, diaxial, or diequatorial; Figure 2). For the partial cone form, two chiral diastereomeric conformations exist differing in the arrangement of substituents on the bridges (axial−isoclinal or equatorial−isoclinal). As shown in Figure 2, the axial disposition of a substituent in the cone form can be avoided by adopting (for example) the 1,2-alternate conformation, which allows locating both alkyl groups in equatorial positions. Although somewhat counterintuitive, this can be rationalized, since a pair of diequatorial positions (or substituents) is in a cis disposition in the cone form, whereas diequatorial positions in the 1,2-alternate form are trans to each other. *A pair of trans substituents can be arranged at diequatorial positions in the 1,2-alternate form, while only if the substituents are cis they can be located at diequatorial positions of the cone form*.

Molecular Mechanics Calculations. To assess the relative energies of the different up−down arrangements of the forms of **4a**−**c** and the conformational preferences of a pair of trans substituents within each of the forms, we resorted to molecular mechanics calculations (MM3 program[14] as implemented in Alchemy 2000).[15] According to the calculations (Table 1), the energy gap between the cone conformation and the other forms decreases with the increase in the bulk of the substituent, but even in the case of the bulkier *t*-Bu substituent, the cone form is still the lowest energy form, as observed experimentally. In the partial cone conformation the equatorial−isoclinal disposition of substituents is of lower energy than the axial−isoclinal arrangement.

Within the 1,2-alternate conformer, the diaxial arrangement of alkyl substituents corresponds to the highest energy form. Although both the diequatorial and diisoclinal arrangements are of similar energies for **4a**, when the bulk of the alkyl substituent increases, there is a clear preference for the diequatorial arrangement over the diisoclinal one in the 1,2-alternate form.

To summarize, the calculations suggest that within a given up−down form, if possible, a substituent will tend to avoid the axial position. The destabilization of the cone conformation relative to the other up−down forms is probably due to the steric repulsions involving the axial substituent.

Energy Gap between the up−down Forms of Tetrahydroxycalixarene and its 1,3-Dimethyl Ether Derivative. The 1,3-dimethyl ether derivative **2** adopts in solution a cone conformation.[11,16,17] X-ray analysis of **2** indicated that in the crystal the molecule adopts a pinched cone conformation with the anisyl rings oriented nearly perpendicular to the mean macrocyclic ring.[18,19] The system is more rigid than the parent **1** and no coalescence of the diastereotopic methylene groups could be observed up to 125 °C.[18] Molecular mechanics calculations predict a cone-to-cone barrier of 30.3 kcal mol^{-1} for the de-*tert*-butylated derivative of **2**,[20] whereas racemization studies of the chiral dimethyl ether derivative **9** provided a barrier of $\Delta G^{\ddagger} = 23.3$ kcal mol^{-1}.[21]



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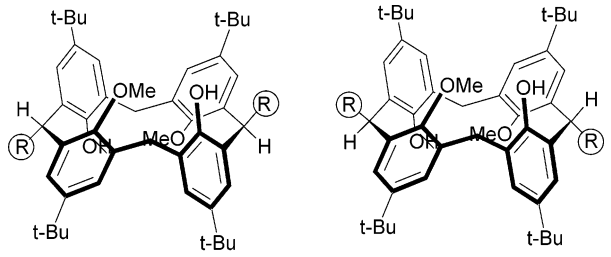
The stabilization of the cone form relative to the other up−down conformers is smaller in the dimethyl ether derivative **2** than in the parent tetrahydroxycalix[4]arene **1**. For example, whereas the energy gap between the cone and the 1,2-alternate conformer was calculated for **1**[18,22] by the AMBER and MM3 force fields as 11.8−7.5 kcal mol^{-1}, calculations conducted on the *p*-Me analogue of **2** predict a 1.9 (TRIPOS) and 3.5 (MM2) kcal mol^{-1} energy gap between the two forms.[23] The smaller energy gap can be ascribed in part to the hydrogen-bonding pattern of the conformers. Whereas the cone and 1,2-alternate form

(14) Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.
(15) *Alchemy 2000*; Tripos Inc.: St. Louis, MO 63144.
(16) (a) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409. (b) Groenen, L. C.; Steinwender, E.; Lutz, B. T. G.; van der Maas, J. H.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1893.
(17) It has been suggested (ref 16b) on the basis of spectroscopic data that the cone conformation of **2** is more "symmetrical" (all rings having similar tilt angles) in CS_2 than in CCl_4, as a result of the inclusion of the former in the calix cavity.
(18) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.
(19) 25,27-dimethoxythiacalix[4]arene also adopts a cone conformation in $CDCl_3$, but in the crystal the conformation is the 1,2-alternate. See: Lhoták, P.; Kaplánek, L.; Stibor, I.; Lang, J.; Dvořákova, H.; Hrabal, R.; Sýkora, J. *Tetrahedron Lett.* **2000**, *41*, 9339.
(20) Van Hoorn, W. P.; Morshuis, M. G. H.; van Veggel, F. C. J. M.; Reinhoudt, D. M. *J. Phys. Chem. A* **1998**, *102*, 1130.
(21) Kusano, T.; Tabatabai, M.; Okamoto, Y.; Böhmer, V. *J. Am. Chem. Soc.* **1999**, *121*, 3789.
(22) (a) Harada, T.; Ohseto, F.; Shinkai, S. *Tetrahedron* **1994**, *50*, 13377. (b) Thondorf, I.; Brenn, J. *J. Mol. Struct. (THEOCHEM)* **1997**, *398*−*399*, 307. (c) Lipkowitz, K. B.; Pearl, G. *J. Org. Chem.* **1993**, *58*, 6729. See also: Harada, T.; Rudzinski, J. M.; Ōsawa, E.; Shinkai, S. *Tetrahedron* **1993**, *49*, 5941.
(23) Thondorf, I.; Hillig, G.; Brandt, W.; Brenn, J.; Barth, A.; Böhmer, V. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2259.

SCHEME 4



of **1** differ in the number of hydrogen bonds (four and two, respectively), in **2** both forms possess an identical number of hydrogen bonds (two). On the basis of the smaller intrinsic energy gap between the forms, we examined next the effect of an axial substituent on the conformational preferences of the central scaffold of **2**.

Synthesis of the Dimethoxy Ether Derivatives. Methylation of two distal OH groups of **4a** was accomplished using the conditions developed for **1** (MeI, MeCN, K_2CO_3).[24] Preliminary experiments indicated that under the same reaction conditions the four OH groups of **4b** are methylated. However, methylation of **4b** could be stopped at the dialkylated stage (i.e., **5b**) using dimethyl sulfate/10% aq NaOH and a phase transfer catalyst. A similar procedure was used for the distal dimethylation of **4c**.

Possible Conformation of the Dimethyl Ether Derivatives 5a−c. The replacement of two distal OH protons by methyl groups may further decrease the symmetry of each of the conformations depicted in Figure 2. The substituted carbons at the methylene bridges are now attached to four different groups and possess opposite configurations (a meso compound). For the distal dimethyl ethers **5a−c**, only the 1,2-alternate form possesses a center of symmetry (C_i point group), while irrespective of the disposition of the trans methylene substituents, the cone, partial cone, and 1,3-alternate forms are chiral conformations lacking any symmetry (C_1 point group). Four different partial cone forms exist, differing in the relative orientations (syn or anti) of the anisyl rings and/or the axial−isoclinal or equatorial−isoclinal disposition of the substituents. Four different arrangements of the alkyl substituents are possible in the 1,2-alternate conformation. In addition to the diequatorial and diaxial forms, two different diisoclinal forms are possible, depending on whether the substituent is oriented syn to either a phenol- or anisole-substituted ring (Scheme 4).

Solution Conformation of the Dimethyl Ethers 5a−c. In contrast to **2**, where the ^{1}H NMR spectrum in $CDCl_3$ is consistent with a single cone conformation,[17] the ^{1}H NMR spectrum of **5a** in the same solvent indicates the presence of two conformers in a ca. 1:1 ratio. One conformer displayed a signal pattern consistent with a species possessing C_i symmetry (e.g., a single MeO signal, two signals for the *t*-Bu groups), which is only compatible with a 1,2-alternate disposition of the rings, while the second conformer possessed C_1 symmetry (displaying inter alia two MeO and four *t*-Bu signals). The two methylene protons in the C_i form (readily identified by their mutual coupling constant) possessed rather similar chemical shifts. This suggests that the two protons are located at the isoclinal positions of the 1,2-alternate form, since only in these positions the two protons are expected to be surrounded by similar (albeit not identical) environments (each of the protons is in proximity to a OH or OMe group), therefore possessing rather similar chemical shifts. By exclusion, the disposition of the alkyl groups at the bridges must be either at the remaining axial or equatorial positions. Since the methyl groups and two neighboring aromatic protons displayed NOE cross-peaks in the ROESY spectrum, it can be concluded that the alkyl substituents are located at the equatorial positions of the bridges.

The assignment of the second conformer as the cone form was achieved by 2D NMR spectroscopy (COSY and ROESY spectra). To simplify the spectra, the studies were conducted in DMF-d_7, since the relative population of the cone form is the largest in that solvent (see below). NOE cross-peaks were observed between pairs of aromatic protons located ortho to a given bridge and the equatorial group at that bridge (i.e., a proton for the unsubstituted bridges and a proton or alkyl for the substituted ones). These NOE interactions indicate that all pairs of vicinal rings are oriented in a mutual syn arrangement, i.e., the conformation adopted is the cone.

In contrast to **5a**, the ^{1}H NMR spectra of **5b** and **5c** in $CDCl_3$ indicated the presence of essentially a single conformer in solution. The observed NMR signal patterns (e.g., a single OMe signal, a single pair of methylene signals possessing similar chemical shifts) were consistent only with a structure possessing C_i symmetry, i.e., with the 1,2-alternate conformation with the alkyl groups located at either diequatorial or diaxial positions. Since the maximal attainable symmetry of **5b** is C_i, in all conformations no mirror symmetry plane can bisect the two substituted bridges and in all conformations the two geminal methyls within a given isopropyl group are diastereotopic. The large coupling constant present between the methine protons of the bridges and the isopropyl groups (^3J = 11.3 Hz) indicated that similarly to the parent **4b**, the isopropyl groups are oriented anti. This conformational assignment is also suggested by the NOE data. Each of the two diastereotopic methyls of the isopropyl groups displayed NOE interactions with a different aromatic group, in agreement with an equatorial disposition of the isopropyl groups. The similar chemical shifts observed by the methylene protons of the bridges of **5a−c** suggest that also in the case of **5c** the alkyl substituents are located at diequatorial positions of the 1,2-alternate form.

The nearly identical population of the cone and 1,2-alternate forms of **5a** in $CDCl_3$ and the near exclusive presence of the 1,2-alternate conformation in **5c** are a manifestation of the steric destabilization of the cone form as a result of the presence of a bulky axial substituent.

Solvent Effect on the Cone/1,2-Alternate Equilibrium. The cone/partial cone conformational equilibrium of the tetramethoxycalix[4]arene **3** is strongly influenced by the solvent polarity. In general, the population of the

(24) See for example: (a) Van Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639. (b) Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, *47*, 2221.

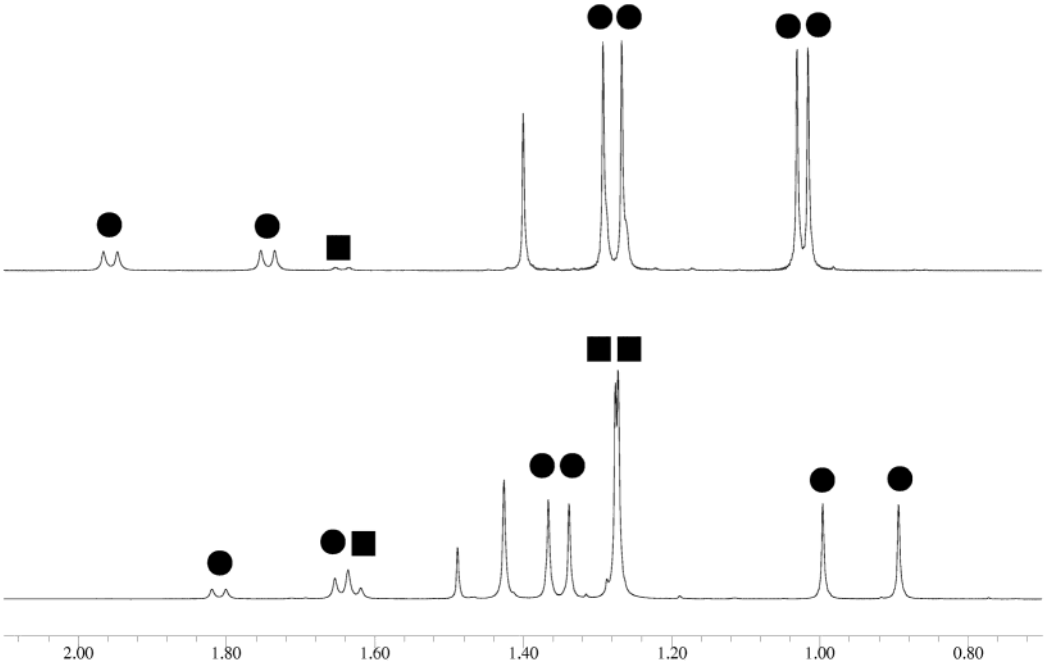


FIGURE 3. 400 MHz ^{1}H NMR spectrum of **5a** at room temperature (*tert*-butyl and methyl region). Top: in DMF-d_7. Bottom: in $CDCl_3$. Circles and squares denote signals of the cone and 1,2-alternate conformers, respectively. Both the cone and 1,2-alternate forms are significantly populated in $CDCl_3$, while in DMF-d_7 the preferred conformer is the cone.

TABLE 2. Relative Population of the Cone and 1,2-Alternate Conformations of 5a−c in Different Solvents at Room Temperature

compd	solvent	cone: 1,2-alternate ratio	compd	solvent	cone: 1,2-alternate ratio
5a	$CDCl_3$	1.03	**5b**	$CDCl_3$	<0.06[a]
	THF	1.3[b]		C_6D_6	<0.06[a]
	C_6D_6	1.5		CD_3CN	4.5
	$C_6D_5NO_2$	3.4		DMF-d_7	3.3[b]
	pyridine-d_5	3.8	**5c**	$CDCl_3$	<0.06[a]
	CD_3CN	4.7		toluene-d_8	<0.06[a]
	DMSO-d_6	5.1		THF	<0.06[a]
	DMF-d_7	9.4		DMF-d_7	<0.06[a]

[a] No signals corresponding to the cone conformation were detected in the ^{1}H NMR spectrum. [b] Small signals, which most likely correspond to an additional low populated conformer, were also observed.

cone form (the most polar form due to the arrangement of the four C−O dipoles in the same direction) relative to the partial cone form increases with the solvent polarity.[25]

In the case of **5a**, it could be expected that the solvent polarity should influence the cone/1,2-alternate ratio. Whereas the cone form is relatively polar due to the disposition of the C−O dipoles, the 1,2-alternate with its inversion center must possess a zero dipole moment. However, in contrast to **3**, both the cone and 1,2-alternate conformations possess two intramolecular hydrogen bonds, and the solvent may influence the conformational equilibria not only by dipolar interactions but also via the preferred formation of intermolecular hydrogen bonds with one of the conformers. As shown in Table 2, in the hydrogen-bond-accepting polar solvents (i.e., DMSO-d_6 and DMF-d_7), the cone form is stabilized relative to the 1,2-alternate form (Figure 3).[26] Similarly for **5b**, although the cone form is intrinsically less stable than the 1,2-alternate form, it is the major form in polar solvents such as CD_3CN (Table 2). For **5c**, the steric repulsion of the axial substituent in the cone form is so large that this interaction cannot be compensated by the polar solvent and the preferred conformation is the 1,2-alternate, irrespective of the solvent polarity.

Rotational Barrier. When the dimethoxy derivative adopts exclusively the 1,2-alternate conformation (as in the case of **5c**), the rotational barrier of the process involving passage of the rings through the macrocyclic annulus cannot be monitored by NMR, since no topomerization is involved. In addition, in all conformations no rotational process whatsoever can exchange between pairs of diastereotopic methylene groups at the bridges (for **5a**−**c**) or pairs of diastereotopic methyl groups within an isopropyl group (for **5b**), and therefore these groups cannot serve as probes for detecting a ring inversion process. This is in clear contrast to the cone conformation where the rotational process can be detected, for example, from the exchange of axial and equatorial alkyl groups.[27]

The ^{1}H NMR spectra of **5a** at various temperatures were determined in DMF-d_7. This solvent was chosen since it possesses a relatively high boiling point and there is a large population of the cone form of **5a**. Since the exchange involved two different conformers (cone and 1,2-alternate) differing in their relative population, to extract the rate of exchange and conformational ratio at each temperature we resorted to total line shape simulations

(25) Iwamoto, K.; Ikeda, A.; Araki, K.; Harada, T.; Shinkai, S. *Tetrahedron* **1993**, *49*, 9937. See also: van Hoorn W. P.; Briels, W. J.; van Duynhoven, J. P. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem*. **1998**, *63*, 1299.

(26) The conformational ratio was determined by integration of the signals of the two forms in the ^{1}H NMR spectrum.

(27) A cone-to-cone inversion process results in the enantiomerization of a given chiral cone conformation

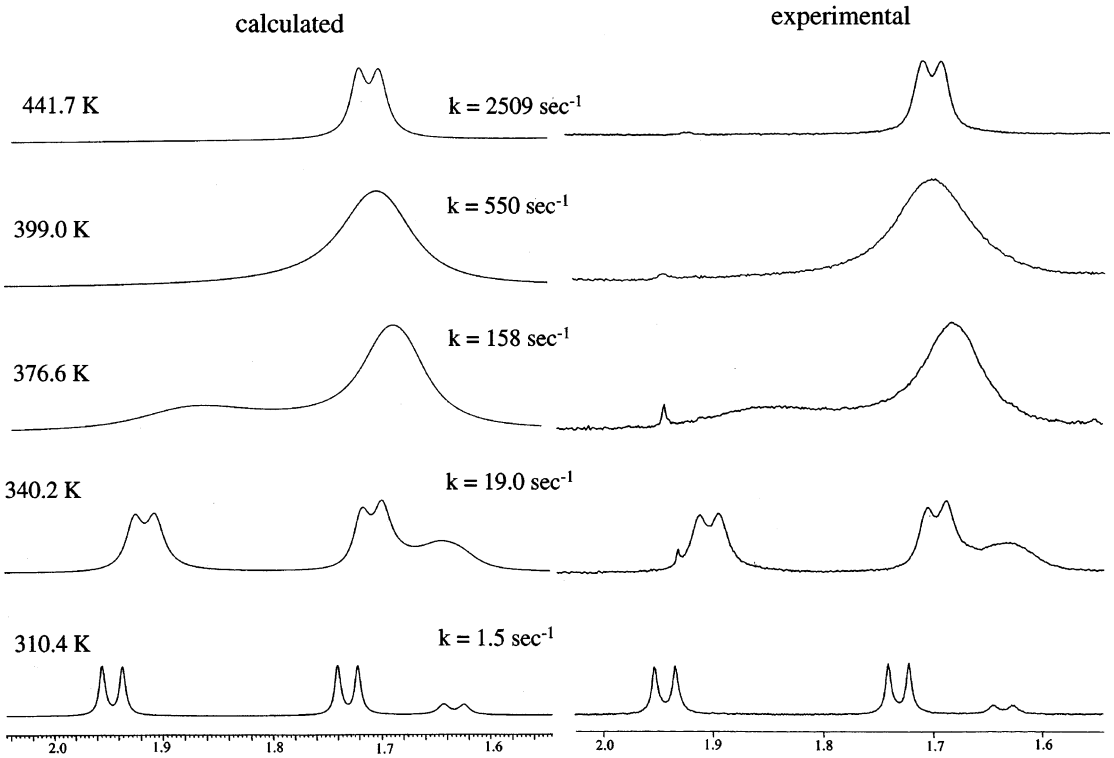


FIGURE 4. Calculated (left) and simulated (right) 400 MHz ^{1}H NMR spectra of **5a** in DMF-d_7 (methyl region) at different temperatures. The small signal at 1.64 ppm (in the spectrum at 310.4 K) corresponds to the 1,2-alternate form, while the pair of doublets at 1.73 and 1.94 ppm belong to the cone form.

(gNMR program).[28] An excellent match between the experimental and simulated spectra was obtained by assuming that the topomerization of the cone conformation proceeds via the 1,2-alternate form (Figure 4). According to the simulations, the equilibrium constant between the cone and 1,2-alternate form decreases from 7.8 at 298 K to 2.6 at 340 K. From the exchange rate obtained in the simulation of the experimental spectrum at 359.7 K (a temperature in which according to the simulations the populations of the cone and 1,2-alternate conformers are nearly identical), a barrier of 18.2 kcal mol^{-1} was determined for the cone → 1,2-alternate interconversion of **5a**.

Influence of the Axial Substituent on the Topomerization Barrier. The decrease in the cone/1,2-alternate energy gap of **5a** and its lower rotational barrier relative to the barrier determined for **9** suggest that the presence of an axial methyl in the cone conformation of **5a** both sterically destabilizes the cone conformation relative to the 1,2-alternate and, by raising the ground-state energy, decreases the rigidity of the conformation.

Conclusions

The preferred conformation and the rigidity of calix[4]arene derivatives may be altered by the presence of a bulky substituent at the bridges. As observed for cyclohexane systems, increasing the bulk of the alkyl substituent destabilizes those conformations possessing an axial disposition of a substituent. The steric destabilization decreases the barrier of the process involving rotation through the annulus of the aryl rings.

(28) *gNMR v4.1.0*; Cherwell Scientific Publishing: Oxford, UK.

Experimental Section

MM3 Calculations. Calculations were performed with the MM3 force field as implemented in the Alchemy 2000 program. All conformers were optimized with the full-matrix Newton−Raphson method and were characterized as minima by frequency calculations.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,-14-di-*tert*-butylcalix[4]arene (trans isomer, 4c). Into 100 mL of dry THF at 0 °C were added under an inert atmosphere 0.46 g (5 mmol) CuCN and 7.5 mL of a 1.4 M *tert*-butyllithium solution in pentane (10.5 mmol). The mixture was stirred until a clear solution was obtained. After addition of 1 g of the spirodiene **6** (1.25 mmol), the mixture was stirred for 3 h, and during this time it was allowed to reach room temperature. After quenching with water and extraction of the aqueous phase with CH_2Cl_2, the combined organic phase was evaporated and the residue recrystallyzed from $CHCl_3$/MeOH. Further purification was achieved by chromatography (silica, eluent 2:1 CH_2Cl_2/hexane) yielding 0.32 g (34%) **4c**: mp 268 °C. ^{1}H NMR (400.133 MHz $CDCl_3$, rt) δ 10.2 (br s, 4H), 7.39 (s, 2H), 7.14 (s, 2H), 6.94 (s 2H), 6.89 (s, 2H), 4.54 (s, 1H), 4.23 (d, J = 14.0 Hz, 2H), 3.74 (s, 1H), 3.50 (d, J = 14.1 Hz, 2H), 1.24 (s, 9H), 1.23 (s, 18H), 1.18 (s, 18H), 1.14 (s, 9H) ppm; ^{13}C NMR (100.1 MHz, $CDCl_3$, rt) δ 147.6, 147.1, 143.7, 143.3, 131.2, 131.1, 128.6, 127.9, 126.7, 124.7, 123.8, 69.2, 44.2, 36.7, 35.7, 34.0, 33.8, 33.1, 31.5, 31.4, 31.1, 30.6 ppm; CI MS (+DCI) m/z 761.4 (MH^+).

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxy-2,14-dimethylcalix[4]arene (trans isomer, 5a). To a solution of 1.3 g (1.9 mmol) of the calixarene **4a** in 50 mL of MeCN was added 0.15 g of K_2CO_3 and the mixture was refluxed for 30 min. MeI (1.5 mL, 0.024 mol) was added and the mixture was refluxed for 40 additional hours. The solvent

was evaporated and the residue was dissolved in dichloromethane and washed several times with aq HCl (1 M). After evaporation of the solvent, the residue was recrystallized from $CHCl_3$/MeOH, yielding 0.55 g of product. The compound was further purified by chromatography (eluent, 2:1 CH_2Cl_2:hexane) yielding 0.38 g (28%) **5a**: mp 218 °C; ^{1}H NMR (400.133 MHz, DMF-d_7, rt) major conformer (cone) δ 8.21 (s, 1H), 8.15 (br s, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.12 (overlapped d, 2H), 4.93 (q, J = 7.5 Hz, 1H), 4.23 (d, J = 12.9 Hz, 1H), 4.22 (partially hidden q, J = 7.8 Hz, 1H), 4.22 (d, J = 12.9 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.60 (d, J = 13.0 Hz, 1H), 3.59 (d, J = 12.9 Hz, 1H), 1.96 (d, J = 7.5 Hz, 3H), 1.74 (d, J = 7.5 Hz, 3H), 1.29 (s, 9H), 1.27 (s, 9H), 1.03 (s, 9H), 1.02 (s, 9H) ppm; ^{13}C NMR (100.1 MHz, DMF-d_7, rt) δ 158.5, 157.1, 156.9, 156.0, 153.0, 152.7, 147.4, 146.9, 143.7, 141.0, 139.9, 137.9, 137.8, 137.1, 133.7, 133.2, 132.8, 132.4, 131.7, 130.9, 135.0, 128.7, 126.2, 69.2, 69.0, 53.3, 37.3, 37.1, 37.0, 36.9, 36.8, 36.6, 36.2, 24.6, 23.4 ppm; CI MS (+DCI) m/z 705.4 (MH^+); ^{1}H NMR (400.133 MHz THF-d_8, rt) minor conformer (1,2-alternate) δ 7.23 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 4.34 (q, J = 6.9 Hz, 1H), 3.94 (d, J = 15.0 Hz, 1H), 3.86 (s, 3H), 3.74 (d, J = 14.9 Hz, 1H), 1.59 (d, J = 7.3 Hz, 3H), 1.26 (s, 9H), 1.24 (s, 9H).

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxy-2,14-diisopropylcalix[4]arene (trans isomer, 5b). To a solution of 0.5 g of the calixarene **4b** in 100 mL of CH_2Cl_2 were added 0.4 g of NBu_4^+ Br^-, 2 mL of dimethyl sulfate, and 10 mL of 10% aq NaOH, and the mixture was refluxed overnight with stirring. After phase separation, the organic phase was washed and evaporated. The residue was recrystallized from $CHCl_3$/MeOH and further purified by chromatography (silica, eluent, 3:1 CH_2Cl_2:hexane) yielding 0.28 g (54%) **5b**: mp 287 °C; ^{1}H NMR (400.133 MHz $CDCl_3$, rt) major conformer (1,2-alternate) δ 7.33 (d, J = 2.1 Hz, 2H), 7.14 (d, J = 2.2 Hz, 2H), 7.03 (d, J = 2.0 Hz, 2H), 6.96 (d, J = 1.9 Hz, 2H), 6.43 (s, 2H), 4.07 (d, J = 17.0 Hz, 2H,), 3.89 (d, J = 17.0 Hz, 2H), 3.76 (d, J = 11.3 Hz, 2H), 3.28 (s, 6H), 2.70 (2H, m), 1.33 (s, 18H), 1.27 (s, 18H), 0.94 (d, J = 6.4 Hz, 6H), 0.85 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100.1 MHz, $CDCl_3$, rt), major conformer (1,2-alternate) δ 152.8, 150.3, 147.3, 142.3, 136.7, 132.5, 131.7, 126.9, 124.6, 123.9, 121.7, 121.1, 60.4, 43.8, 39.2, 34.4, 34.0, 31.6, 31.5, 30.1, 22.1, 21.5 ppm. CI MS (+DCI) m/z 761.4 (MH^+); ^{1}H NMR (400.133 MHz CD_3CN, rt) major conformer (cone) δ 8.42 (s, 1H), 7.88 (s, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.20 (overlapped d, 3H), 7.15 (overlapped d, 2H), 7.09 (d, J = 2.5 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 4.41 (d, J = 12.6 Hz, 1H), 4.37 (d, J = 12.3 Hz, 1H), 4.13 (d, J = 13.0 Hz, 1H), 4.12 (s, 3H), 3.97 (s, 3H), 3.45 (d, J = 11.9 Hz, 1H), 3.40 (d, J = 12.7 Hz, 1H), 3.34 (d, J = 12.3 Hz, 1H), 3.27 (m, 1H), 2.85 (m, 1H), 1.19 (s, 9H), 1.18 (s, 9H), 1.17 (s, 9H), 1.16 (s, 9H), 1.00 (d, J = 5.0 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H), 0.80 (d, J = 6.3 Hz, 3H).

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxy-2,14-di-*tert*-butylcalix[4]arene (trans isomer) 5c. A 0.25 g (3.3 mmol) sample of the calixarene **4c** was dissolved in 50 mL of CH_2Cl_2 together with 0.2 g of NBu_4^+ Br^-, 1 mL of dimethyl sulfate, and 5 mL of a 5% aq NaOH solution, and the mixture was refluxed overnight under stirring. After phase separation, the organic phase was washed several times with water and evaporated. The residue was recrystallized from $CHCl_3$/MeOH; further purification was achieved by chromatography (silica, eluent 2:1 CH_2Cl_2:petroleum ether) yielding 80 mg (31%) **5c**: mp 307 °C; ^{1}H NMR (400.133 MHz, CD_3Cl, rt) (1,2-alternate) δ 7.65 (d, J = 2.2 Hz, 2H), 7.23 (d, J = 2.2 Hz, 2H), 7.10 (d, J = 2.1 Hz, 2H), 6.96 (d, J = 2.2 Hz, 2H), 5.32 (s, 2H), 4.32 (s, 2H), 3.98 (d, J = 16.1 Hz, 2H), 3.89 (d, J = 16.1 Hz, 2H), 3.20 (s, 6H), 1.34 (s, 18H), 1.22 (s, 18H), 1.14 (s, 18H); ^{13}C NMR (100.1 MHz, $CDCl_3$, rt) (1,2-alternate) δ 153.9, 150.3, 146.0, 141.4, 137.3, 132.2, 131.2, 127.5, 124.9, 124.8, 124.5, 124.3, 60.3, 44.5, 38.2, 35.0, 34.3, 33.8, 31.5, 31.5, 30.4; CI MS (+DCI) m/z 789.5 (MH^+).

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Supporting Information Available: Final calculated coordinates of conformers of **1** and **4a**−**c** and ^{1}H NMR spectra of compounds **4c** and **5a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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