Conformation, Inversion Barrier, and Solvent-Induced Conformational Shift in *Exo*- and *Endo*/*Exo*-Calix[4]arenes

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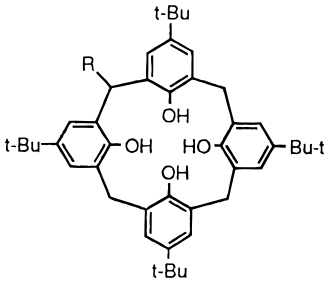
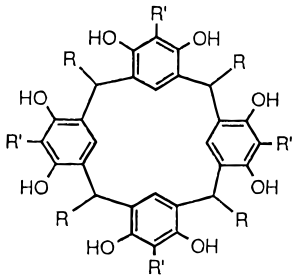
Calixarenes **4a** and **4b** having hydroxyl groups in *endo* and *exo* positions and the ethanediyl-bridged *exo*-calixarene **5a** were synthesized by a stepwise strategy. Single-crystal X-ray structures were obtained for **4a** and for the *exo*-calixarene **3d**, showing the molecules to exist in the 1,2-alternate conformation which is also found for **4a,b** in solution. The inversion barriers of **4a** and **4b** (10.3 and 10.8 kcal mol^{-1}) are similar to that determined for the *endo*-dihydroxycalixarene **12**, indicating that the additional intramolecular hydrogen bond between the *exo* OH groups does not decrease the flexibility of the molecule. In $CDCl_3$ solution *exo*-calixarene **5a** adopts a 1,2-alternate conformation with the methyl group at the bridge located in an axial position, while in DMSO-d_6 the conformation adopted is the partial cone. Similar solvent-induced conformational shifts were found for the *exo*-calixarenes **3b** and **3d**. MM3 calculations predict that the cone form is the lowest energy conformation of **4** and the *exo*-calixarenes **3** and **5**. The calculations suggest that the conformational preferences of the methyl group at the bridge for either the axial or equatorial positions are in large part determined by the repulsive steric interactions with the hydroxyl groups. The inversion barrier of **4b** is satisfactorily reproduced by calculations, which indicate that the rotation of the *exo* rings is less energetically demanding than the rotation of the *endo* rings.

Introduction

In recent years, two types of [1_4] metacyclophane derivatives have been intensively studied as potential molecular hosts: the calix[4]arenes[1] (e.g., *p-tert*-butylcalix-[4]arene, **1a**) and the resorcarenes[2] (**2a**). The calixarenes possess an array of OH groups located at the *intra*annular (*endo*) positions of the macrocyclic ring. These groups are involved in a circular array of hydrogen bonds in which each hydroxyl group serves both as a donor and as an acceptor. In the resorcarenes the hydroxyl groups are present in *extra*annular (*exo*) positions of the macrocycle, and therefore these and related compounds possessing a similar disposition of the hydroxyls may be designated by the general term "*exo*-calixarenes" as opposed to the "conventional" *endo*-calixarenes.[3−5] Although intramolecular hydrogen bonds may be formed between adjacent OH groups, no circular array of hydrogen bonds is possible in resorcarenes. The *all-cis* resorcarenes and the alkanediyl derivatives of **1a** (e.g., **1b**) adopt cone conformations, but they differ in the conformational preferences of the alkyl groups: the alkanediyl group of **1b** prefers the equatorial position,[6,7] while a tetraaxial disposition of the alkyl substituents is exclusively found in *all-cis*-**2a**.[8]



1a R = H
1b R = alkyl



2a R = alkyl, R' =H
2b R = H, R'=alkyl

Recently, resorcarenes with unsubstituted methylene bridges (**2b**) were reported by Konishi and Morikawa.[9] Although both **1a** and **2b** adopt cone conformations which are held by four intramolecular hydrogen bonds between the OH groups, the cone-to-cone inversion barrier of **1a** and **2b** (R′ = C_6H_{13}) in $CDCl_3$ differ by 3.7 kcal mol^{-1}, being $\Delta G_c^{\ddagger} = 15.7$[10] and 12.0 kcal mol^{-1}, respectively.[9,11]

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(1) For reviews on calixarenes see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (d) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1.

(2) For a recent review see: Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663.

(3) Böhmer, V.; Dörrenbächer, R.; Frings, M.; Heydenreich, M.; de Paoli, D.; Vogt, W.; Ferguson, G.; Thondorf, I. *J. Org. Chem.* **1996**, *61*, 549.

(4) (a) Böhmer, V.; Dörrenbächer, R.; Vogt, W.; Zetta, L. *Tetrahedron Lett.* **1992**, *33*, 769. (b) Thondorf, I.; Brenn, J.; Brandt, W.; Böhmer, V. *Tetrahedron Lett.* **1995**, *36*, 6665. (c) Böhmer, V.; Ferguson, G.; Frings, M. *Acta Crystallogr. C* **1997**, *C53*, 1293.

(5) (a) Sartori, G.; Porta, C.; Bigi, F.; Maggi, R.; Peri, F.; Marzi, E.; Lanfranchi, M.; Pellingheli, M. A. *Tetrahedron* **1997**, *53*, 3287. (b) Sorrell, T. N.; Yuan, H. *J. Org. Chem.* **1997**, *62*, 1899.

(6) 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.

(7) For other studies of alkanediyl calix[4]arene derivatives see: Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657.

(8) See for example: Abis, L.; Dalcanale, E.; Du vosel, A.; Spera, S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2075; Mann, G.; Hennig, I.; Weinelt, F.; Müller, K.; Meusinger, R.; Zahn, G.; Lippmann, T. *Supramol. Chem.* **1994**, *3*, 101.

(9) Konishi, H.; Morikawa, O. *J. Chem. Soc., Chem. Commun.* **1993**, 34.

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

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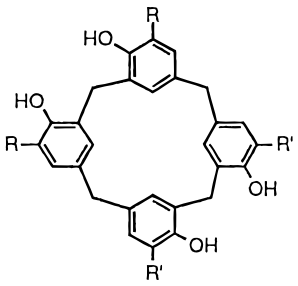
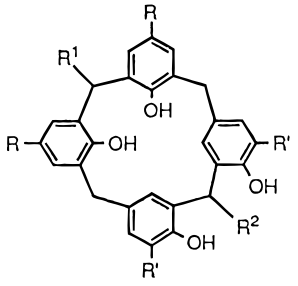
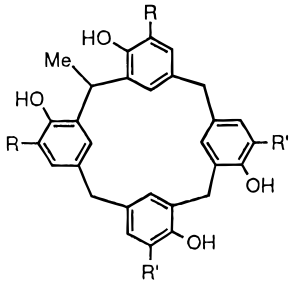
The preparation of *exo*-calixarenes possessing only four *exo* hydroxyl groups (**3**) was recently described.[3−5,12] X-ray diffraction studies of **3a**·CH_3CN and **3a**·CH_2Cl_2 indicate that the *exo*-calixarene exists in a cone conformation[3,5a] whereas **3c** and a bis(dioxamethylene) derivative exist in the crystal in a 1,2-alternate conformation.[4c,5b] In solution all the *exo*-calixarenes **3** were found to be flexible on the NMR time scale, even at −70 °C, and since the dynamic processes could not be frozen, the solution conformation could not be unambiguously determined.[3] MM3 calculations suggest a ring inversion barrier as low as 6.7 kcal mol^{-1} for **3c**.[4b]



3a R = R′ = t-Bu
3b R = Me, R′ = t-Bu
3c R = R′ = H
3d R = Me, R′ = H
3e R = R′ = Me



4a R= Me, R′ = t-Bu, $R^1 = R^2$ = H
4b R = R′ = t-Bu, $R^1 = R^2$ = H
4c R = R′ = Me, $R^1 = R^2$ = H
4d R = R′ = R^2 = Me, R^1 = H
4e R = R′ = R^1 = Me, R^2 = H

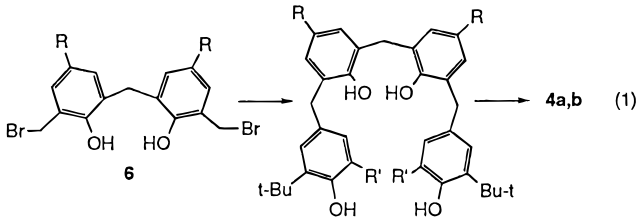


5a R = Me, R′ = t-Bu
5b R = R′ = Me
5c R = R′ = t-Bu

In this paper we extend our conformational studies on *exo*-calixarenes **3** to calixarenes possessing both *endo* and *exo* hydroxyl groups (**4a** and **4b**) and to the ethane-1,1-diyl *exo*-calixarene **5a**. Both structural modifications desymmetrize the calixarene scaffold and may decrease its flexibility, thus facilitating the determination of the preferred conformation by NMR methods.

Results and Discussion

Synthesis. The *exo*/*endo*-calixarenes **4a** and **4b** were prepared in a stepwise manner summarized in eq 1 which is similar to the synthesis of **3b**.[3] Condensation of the bis-bromomethylated dimers **6** with an excess of 2-bromo-6-*tert*-butylphenol led to the linear tetramers **7** in 60−65% yield. In this step a stoichiometric amount of $ZnCO_3$ was applied, which not only provides a mild Lewis acid, but completely traps the HBr developed thus preventing debutylation. Debromination was achieved by hydrogenation in alkaline solution (Raney-nickel, rt, normal pressure) to yield 70−85% of **8**, having two free *ortho*-positions in the terminal *o*-*tert*-butylphenol unit. Their condensation with paraformaldehyde in xylene at 175 °C (autoclave) led to the calixarenes **4a,b** which were obtained in 37 and 20% yield, respectively, after simple recrystallization.



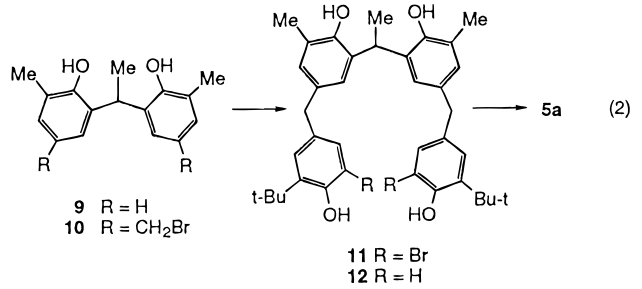
6

a R = Me
b R = t-Bu

7 R′ = Br
8 R′ = H

4a,b (1)

Starting with the ethanediyl-bridged dimer **9**, the analogous reaction sequence (eq 2) of bromomethylation (55% of **10**), condensation (50% of **11**), and debromination (90% of **12**) furnished a linear tetramer which upon cyclization with paraformaldehyde gave calix[4]arene **5a** in 38%.



9 R = H
10 R = CH_2Br

11 R = Br
12 R = H

5a (2)

Conformational Description of 3 and 4. For *endo*-calixarenes (e.g., **1**) usually four basic conformations are discussed (cone, partial cone ("paco"), 1,2-alternate ("1,2-alt"), and 1,3-alternate ("1,3-alt"))[1] while for the resorcarenes additional conformations are considered.[2] Notably, although the four aryl rings of **3a,c,e** are identical, two distinct 1,2-alt forms exist in which pairs of rings with either convergent ("1,2-alt(conv)") or divergent ("1,2-alt(div)") OH groups are oriented in a syn fashion. Only in the 1,2-alt(conv) form are OH···OH intramolecular hydrogen bonds possible. Two different paco forms exist for **4** in which either an *endo* or *exo* ring is oriented anti to the rest of the rings.[13] These forms will be dubbed "paco(*endo*)" and "paco(*exo*)", respectively.

[1^4] metacyclophanes (e.g., **1**) adopting a cone conformation possess methylene protons located in positions commonly denominated, by analogy with the chair form of cyclohexane, as axial or equatorial.[1] For simplicity, we propose that in all conformations where two adjacent rings are oriented syn (i.e., both rings pointing "up" or "down") the protons on the bridging methylene which are proximal or distal to the *endo* positions will be denoted

(11) The authors in ref 9 concluded that the energy gap between the rotational barriers of **1a** and **2b** (R′ = *n*-C_6H_{13}) is 4.4 kcal mol^{-1}. This estimation was based on the value determined for **1a** (16.4 kcal mol^{-1}) by simulation of the temperature-dependent NMR (Araki, S.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 581). However, the latter barrier is most likely incorrect, the correct value being the one determined by the coalescence approximation (15.7 kcal mol^{-1}).[10] See: Van Gelder, J. M.; Brenn, J.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, *62*, 3511.

(12) Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, *36*, 2311.

(13) For identification purposes, the aryl rings of **4** possessing *endo* or *exo* hydroxyl groups will be denoted *endo*- and *exo* rings, respectively, while the *tert*-butyl and Me substituted rings of **5a** will be dubbed *tert*-butylphenol and cresol rings.

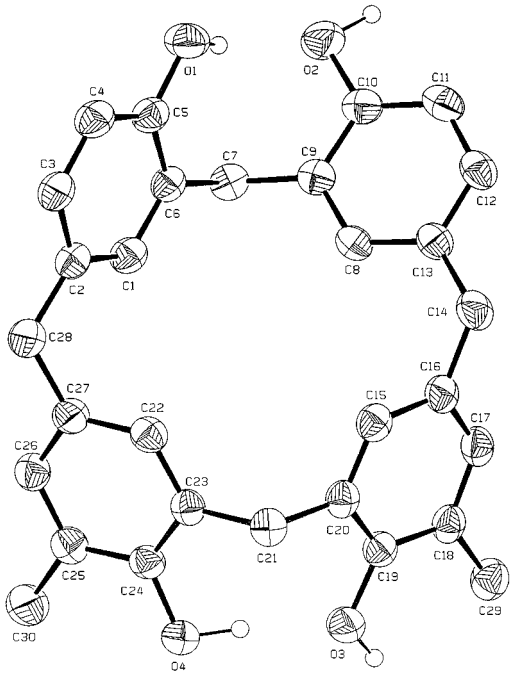


Figure 1. Crystal structure of the *exo*-calixarene **3d**.

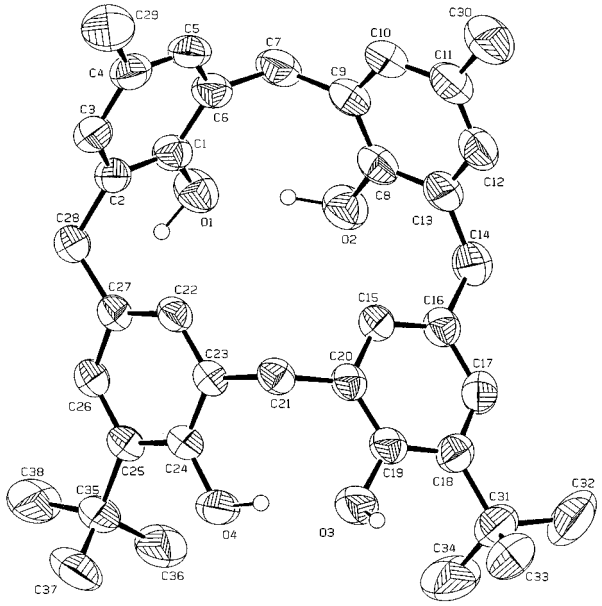


Figure 2. Molecular structure of calix[4]arene **4a**.

"axial" and "equatorial". If the two rings are oriented anti, we suggest for these protons, by analogy to the twist-boat conformation of cyclohexane, the term "isoclinal".[14] The paco and 1,2-alt forms possess two kinds of methylene groups, with axial/equatorial or isoclinal positions available for substituents. In the paco form the isoclinal positions within a methylene group are not symmetry equivalent. In this case the isoclinal positions pointing away or toward the unique ring oriented anti to the rest of the rings will be denominated "iso I" and "iso II", respectively.

X-ray Crystallography. Single crystals of **3d** and **4a** were obtained by slow evaporation of solutions in acetonitrile, a solvent which often favors a cone conformation due to its tendency to be included into the molecular cavity. However, in contrast to **3a**,[3] both calixarenes assume a 1,2-alt conformation (Figures 1−3).[15] Equivalent rings are in syn arrangement in both cases, which means that the skeletal symmetry plane bisecting the methylene carbons C7 and C21 is roughly found in the crystal.

As found in **3c**[4c] the methylene carbon atoms show deviations up to 0.8 Å from their mean plane, which therefore cannot be taken as a reference plane for the description of the molecular conformation. The deviation can be characterized by the interplanar angle of two triangles formed by the methylene carbons, and these triangles can be used then as reference planes for the inclination of the adjacent phenolic rings. Alternatively the molecular conformation can be described by the torsion angles around the Ar−CH_2−Ar bonds. This way, proposed by Ugozzoli and Andreetti[16] is unambiguous but less pictorial. Both values are collected in Table 1.

In both molecules the usual "reference plane" of the methylene carbons is folded nearly to the same extent. Somewhat stronger differences can be seen in the inclination of the phenolic rings where differences up to 43° in **3d** (rings C(1−6) and C(8−13)) and up to 32° in **4a** (rings C(15−20) and C(22−27)) are found. The folding of the molecule leads even to a change in the sequence of the signs of the torsion angles which is (+−,−+,−+,−−) for **3d** and (+−,+−,−+,−−) for **4a** (both notations are equivalent) while (+−,++,−+,−−) is reported for a "regular 1,2-alternate" conformation.

The 1,2-alt conformation allows intramolecular hydrogen bonds between the adjacent OH groups (O1···O2 = 2.744 and O3···O4 = 2.748 Å for **4a**). A molecule of acetonitrile is included in the crystal lattice of **4a**, weakly hydrogen bonded by one of the *endo* OH groups (O1···N = 2.878 Å), but this is the only intermolecular hydrogen bond formed in this case. For **3d** only the distance O3···O4 = 2.756 Å is in agreement with an intramolecular hydrogen bond, while O1···O2 = 2.935 Å is even longer than the intermolecular contacts O1···O3′ = 2.842 and O2···O4′ = 2.758 Å. The packing shown in Figure 4 suggests, however, that the molecules are arranged into sheets linked together by infinite chains of intra- and intermolecular hydrogen bonds (isodromic hydrogen bonds) in which a given molecule is involved at both sides. Similar arrangements were found for some dimers[17a−c] (as well as linear trimers[17a,c] and tetramers[17d]). The packing differs from the arrangement found for **3a** and **3c** where cyclic arrays of intra- and intermolecular hydrogen bonds (including the solvent in the case of **3c**) lead to infinite ribbons of calixarene molecules.[3,4c]

Conformation of 4a and 4b in Solution. The determination of the conformation and rotational barrier of calixarenes **4a** and **4b** is of interest since they share structural features with both the *endo*-calixarenes and the *exo*-calixarenes. The 181 K NMR spectrum of **4a** in CD_2Cl_2 is in agreement with a preferred conformation or average structure in which a mirror plane bisects the

(14) The term "isoclinal" is commonly used in the twist-boat conformation of cyclohexane for the positions at the methylene groups bisected by the C_2 axis. See: Kellie, G. M.; Riddell, F. G. *Top. Stereochem.* **1974**, *8*, 225.

(15) A preliminary X-ray diffraction study indicates that *exo*-calixarene **4b** also adopts a 1,2-alternate conformation in the crystal.

(16) Ugozzoli, F.; Andreetti, G. D. *J. Incl. Phenom.* **1992**, *13*, 337.

(17) (a) Casiraghi, G.; Cornia, M.; Sartori, G.; Bocchi, V.; Casnati, G.; Andreetti, G. D. *Makromol. Chem.* **1982**, *183*, 2611. (b) Casiraghi, G.; Cornia, M.; Ricci, G.; Balduzzi, G.; Casnati, G.; Andreetti, G. D. *Makromol. Chem.* **1983**, *184*, 1363. (c) Casiraghi, G.; Cornia, M.; Ricci, G.; Casnati, G.; Andreetti, G. D.; Zetta, L. *Macromolecules* **1984**, *17*, 19. (d) Paulus, E.; Böhmer, V. *Makromol. Chem.* **1984**, *185*, 1921.

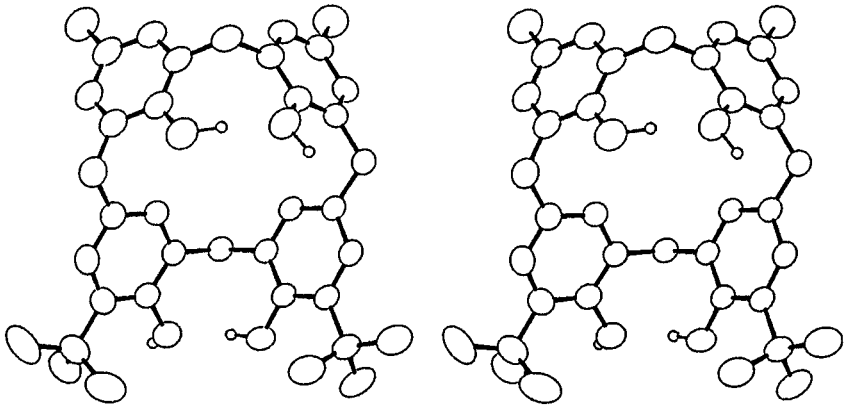


Figure 3. Stereoview of the crystal conformation of **4a**.

Table 1. Conformational Parameters of Molecules 3d and 4a (in degrees)[a]

	3d	4a
Interplanar Angles		
C(7,28,21)−C(7,14,21)	148.4	144.6
C(14,7,28)−C(14,21,28)	145.3	140.8
C(14,7,28)−C(1−6)	105.0	121.2
C(14,7,28)−C(8−13)	147.7	125.8
C(14,21,28)−C(15−20)	130.5	142.4
C(14,21,28)−C(22−27)	130.9	110.5
Torsion Angles		
C5−C6−C7−C9	73.3	86.0
C6−C7−C9−C10	−109.3	−88.3
C12−C13−C14−C16	−156.2	92.5
C13−C14−C16−C17	96.4	−161.5
C19−C20−C21−C23	−90.5	−102.9
C20−C21−C23−C24	92.8	77.6
C26−C27−C28−C2	−123.5	−164.1
C27−C28−C2−C3	−155.7	−106.2

[a] For the interplanar angles only absolute values are given, while the sign of the torsion angles follows the usual convention.

two methylene bridges connecting two *exo* or *endo* rings. The NMR signals were assigned by COSY and NOESY spectra. The *endo* and *exo* OH groups show similar chemical shifts (6.88 and 6.46 ppm). The protons within the two methylene groups connecting identical rings are diastereotopic and display large chemical shift differences ($\Delta\delta$ 0.61 and 0.85 ppm), suggesting that pairs of *endo* or *exo* rings adopt syn arrangements. The signals at 3.44 and 4.05 ppm were assigned to the equatorial and axial protons of the methylene group connecting the two *endo* rings on the basis of their NOE's with an aromatic proton and with the OH protons of the *endo* ring, respectively. This assignment is in agreement with the general observation that in calix[4]arenes **1** the equatorial protons resonate at a higher field than the axial ones.[18] However, according to the NOE data in the methylene group connecting the *exo* rings the equatorial methylene proton resonates at a lower field (3.89 ppm) than the axial one (3.04 ppm). These shifts are easy to rationalize. In a syn arrangement of the *exo* rings the equatorial methylene proton will be in close proximity to the OH group, and is located in a steric environment similar to the axial protons of a "classic" *endo*-calix[4]arene and vice versa, the axial proton of this methylene is in a similar environment to the equatorial protons of an *endo*-calixarene. Thus, it could be generally expected that whenever a methylene group connects two *exo* rings existing

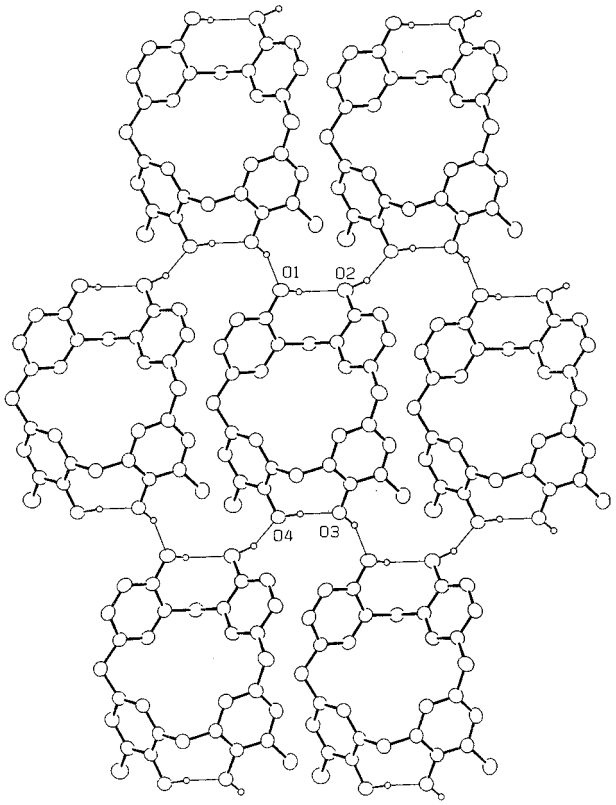


Figure 4. Section of the crystal lattice showing the chains of intra- and intermolecular hydrogen bonding array of *exo*-calixarene **3d**.

in a syn arrangement, the equatorial proton will resonate at a lower field than the axial one.

The presence of a mirror plane bisecting two methylene bridges, the nonequivalence of the protons within each methylene bridge as well as their large chemical shift difference, and the NOE interactions, are all consistent with either a 1,2-alt or a cone conformation. However, the NMR data seem to fit better a 1,2-alt conformation, in particular, the relatively high field resonance of the *intra*annular aromatic protons (6.11 ppm) which indicates that these protons are shielded by the ring current of a neighboring ring, as expected for a 1,2-alt form.[19] We therefore conclude that *the 1,2-alt form is the major conformer of* ***4a*** *in* CD_2Cl_2 *solution*. Increasing the

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

(19) A cross-peak between the *extra*annular aromatic protons of the *endo* and *exo* rings which would unambiguously indicate the presence of a cone conformation was not detected.

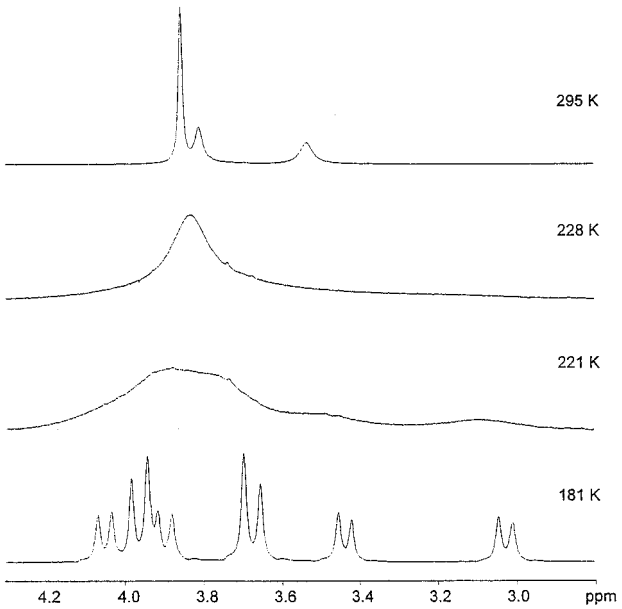
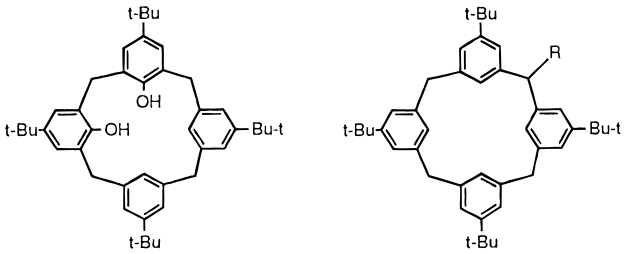


Figure 5. 400 MHz ^{1}H NMR spectra of the methylene region of **4a** in CD_2Cl_2 at different temperatures.

temperature resulted in a downfield shift of the *intra*annular aromatic protons, which may indicate an increased population of a second conformation (most likely, a cone form) in fast equilibrium with the 1,2-alt form. The NMR spectrum of **4b** (CD_2Cl_2, 187 K) is similar to that of **4a**, but the NOESY spectrum suggests that in addition to the major 1,2-alt conformer, the cone conformer is also present.



Rotational Barrier. To determine the rotational barrier of **4a**, its ^{1}H NMR spectra were recorded in CD_2Cl_2 in the 181−295 K temperature range. Upon raising the temperature, the three pairs of methylene doublets coalesced into three singlets in a 2:1:1 ratio (Figure 5). These findings can be explained by a dynamic process involving the (stepwise) passage of the four rings through the macrocyclic cavity which results in the mutual exchange between the axial and equatorial protons. On the basis of the chemical shift differences under slow exchange (113.0, 245.6, and 348.7 Hz), the mutual coupling constants (17.0, 13.8, and 14.3 Hz, respectively), and the coalescence temperatures (221, 221, and 229 K, respectively), a barrier of 10.3 ± 0.1 kcal mol^{-1} was calculated.[20] Similarly, from the coalescence of the methylene protons of **4b** ($\Delta\delta = 116.7$ Hz, $J = 16.9$ Hz, $T_c = 231$ K) an inversion barrier of 10.8 kcal mol^{-1} was determined for **4b** in CD_2Cl_2. The barriers for **4a** and **4b** in CD_2Cl_2 are similar to that found for **13** in $CDCl_2F$ (10.6 kcal mol^{-1})[21] which indicates that the presence of the additional *extra*annular hydrogen bond in **4** does not reduce the conformational mobility of the system.

Static and Dynamic Stereochemistry of the Ethanediyl *exo*-Calixarene 5a. The low inversion barrier of the *exo*-calixarenes **3** precluded the unambiguous experimental determination of their preferred conformation by NMR since the protons within the methylene groups remained isochronous even at the lowest temperature studied. However, if one methylene proton of **3** is replaced by an alkyl group, in the resulting system (e.g., **5a**) the protons within the methylene groups are also diastereotopic under fast ring inversion conditions. Thus, it should be possible to obtain more detailed conformational information from the NMR spectra in solution. A priori it is not clear whether the preference of the alkanediyl groups of **2a** for the axial positions applies also for the ethanediyl *exo*-calixarene **5a**.

Conformation of 5a in $CDCl_3$. The ^{1}H NMR spectrum of **5a** in $CDCl_3$ at 250 K displays single singlets for the methyl and *t*-Bu groups, as well as four aromatic signals and four methylene doublets. This is in agreement with a structure in which a mirror plane bisects the bridges connecting identical rings. The NMR pattern can be rationalized either in terms of a mirror symmetric conformation (e.g., 1,2-alt or cone) or an asymmetric structure in which a fast rotational process (even at 250 K) renders the pairs of cresol and *tert*-butylphenol rings symmetry equivalent.[13] The large chemical shift difference observed between the equatorial and axial methylene protons connecting the two *tert*-butylphenol rings (0.66 ppm) suggests that both rings exist in a syn arrangement. Similarly, as indicated by NOE studies at 250 and 298 K, the two cresol rings exist in a syn arrangement. This can be rationalized, since these arrangements allow an intramolecular hydrogen bond between OH groups facing each other across a methylene bridge. Since the *extra*annular aromatic protons of the cresol and *tert*-butylphenol rings (which resonate at 6.81 and 7.01 ppm, respectively) display NOE interactions with a different proton of the methylene groups which bridge both rings, it can be concluded that the solution conformation in $CDCl_3$ is the 1,2-alternate.[22]

In the low-temperature NOESY spectrum, the OH signal of the cresol ring shows a cross-peak with the methine signal. This suggests that the latter proton is located in an equatorial position. This assumption is confirmed by a cross-peak between the signal at 7.07 ppm (the *intra*annular proton of a cresol ring) and the methyl group attached to the bridge. It can be concluded that, as observed for the resorcarenes, *the methyl group at the bridge prefers an axial position*. The equatorial conformation is most likely destabilized by the steric interactions between the alkyl group and the *exo* oxygens of the neighboring rings.

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

(21) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 11.

(22) The relative orientation of the two pairs of rings could be derived in principle by examining the chemical shifts of the protons of the methylene groups connecting a cresol with a *tert*-butylphenol ring. In the *endo*-calixarenes small and large chemical shift differences for the protons of a given methylene group can be taken as an indication of an anti or syn orientation of the neighboring rings, respectively. However, it is unlikely that a similar behavior will be observed for the methylene protons between the *tert*-butylphenol and the cresol rings, since in the syn and in the anti arrangements both protons are expected to be located in rather similar chemical environments.

Axial/Equatorial Interconversion. In principle, a ring inversion process in which all rings pass through the macrocyclic annulus should interconvert the preferred 1,2-alt conformation with the methyl group located in an axial position (1,2-alt(ax)) with a diastereomeric 1,2-alternate conformation in which the methyl group is located in an equatorial position (1,2-alt(eq)). The ^{1}H NMR spectra of **5a** were recorded in the 220−290 K temperature range ($CDCl_3$) and down to 190 K (CD_2Cl_2). No line broadening, indicating a dynamic exchange process with a second less populated conformation (a hidden partner), was found.[23] This suggests that the equilibrium is so strongly biased toward one conformer that no line broadening can be experimentally observed, and/or that the rotational barrier is so low that even at 190 K the compound is rapidly undergoing a dynamic process.

Conformation of 5a in DMSO-d_6. Since the relative stabilities of the conformations of **5a** are probably determined by the intramolecular hydrogen bonds, we examined the influence of a strong hydrogen bond-accepting solvent (DMSO-d_6) on the conformation of the system. The COSY and NOESY NMR spectra of **5a** in DMSO-d_6 were recorded at rt and at 338 K, taking advantage of the better resolution obtained at this slightly elevated temperature. The main differences of the ^{1}H NMR spectra in DMSO in comparison to $CDCl_3$ are as follows: (i) The *intra*annular protons on the cresol rings are shifted upfield by 0.39 ppm. (ii) The protons on the methylene bridge connecting two *tert*-butylphenol rings which displayed substantially different chemical shifts in $CDCl_3$ ($\Delta\delta$ = 0.66 and 0.59 ppm at 250 K and rt, respectively) display in DMSO rather similar chemical shifts ($\Delta\delta$ = 0.13 and 0.17 ppm at rt and 338 K) in agreement with an anti orientation of the rings. (iii) The two OH signals are shifted downfield in DMSO (7.95 and 8.14 ppm), suggesting hydrogen bonding with the solvent molecules.

Conformational information was extracted from the NOESY spectrum which suggests that both *o*-cresol rings are in a syn arrangement, with the Me substituent of the bridge located in the axial position. The two *extra*annular aromatic protons on the different rings display strong cross-peaks with the methylene proton at 3.55 ppm. In addition NOE interactions were observed for the *intra*annular and the OH protons of the *tert*-butylphenol ring and both protons of the methylene group connecting the two *tert*-butylphenol rings. This is in agreement with a preferred paco conformation with a *tert*-butylphenol ring pointing in the opposite direction than the rest of the rings. This indicates that *changing the solvent from $CDCl_3$ to DMSO results in a conformational change from 1,2-alt to paco* and that DMSO disrupts selectively the syn arrangement of the two *tert*-butylphenol rings.[24] The similar chemical shift observed for both OH signals in DMSO suggests that all OH groups are hydrogen bonded to the solvent. In the case of the *tert*-butylphenol rings, the conformation changes from syn to anti since the latter arrangement facilitates the association of both OH groups with the solvent molecules. However, the anti arrangement is destabilized for the *o*-cresol rings by the steric interactions between the methyl at the bridge and one OH group and the two rings retain their mutual syn arrangement, even if they are no longer intramolecularly hydrogen bonded.[25]

Raising the temperature of a DMSO-d_6 solution of **5a** resulted in changes in the methylene region. Notably, the chemical shift difference ($\Delta\delta$) between the protons on the methylene connecting the two *tert*-butylphenol rings increased with the temperature ($\Delta\delta$: 0.13 (rt), 0.164 (338 K), 0.219 (383 K)). This may indicate that a second conformation in which the *tert*-butylphenol rings are syn, is in fast equilibrium with the preferred partial cone conformation, the population of the second form increasing with the temperature.

Solvent-Induced Conformational Shift in *exo*-Calixarenes. To determine whether the solvent effect observed for **5a** is due to the presence of the ethanediyl group or if it is an intrinsic property of the *exo*-calixarene skeleton, we examined also the NMR spectra of the *exo*-calixarenes **3b** and **3d**. Cooling a solution of **3b** in $CDCl_2F$[26] down to 140 K did not result in decoalescence of the methylene signals, although some broadening due to the increased viscosity was observed. Assuming that the chemical shift difference between the protons of the methylene group connecting the *tert*-butylphenol rings is 230 Hz (this is the chemical shift difference observed for the corresponding protons in **5a**), an upper limit of $\Delta G_c^{\ddagger} < 6.6$ kcal mol^{-1} can be estimated for the barrier of ring inversion. Since this low barrier precludes the determination of the slow-exchange spectrum, the relative orientation of the rings with respect to their adjacent methylene protons could not be determined directly. NOESY spectra were recorded for **3b** in $CDCl_3$ and DMSO-d_6 while the poor solubility of **3d** in $CDCl_3$ prevented conformational studies in that solvent. The NOESY spectra of **3b** in $CDCl_3$ displayed cross-peaks between the proton pairs "a"/"d", "a"/"c", "b"/"c" (for the notation "a"−"d" see Figure 6). Assuming that in this solvent the OH groups are intramolecularly hydrogen bonded (thus inducing syn arrangements of two pairs of neighboring rings), the NOE can be interpreted as indicating the presence of both the cone and the 1,2-alt(conv) conformations.

NOE cross-peaks were observed between the signal pairs "a"/"d", "a"/"c", "b"/"c", "b"/Me and "d"/R for both **3b** and **3d** in DMSO-d_6 (Figure 6). Although there are several ways to rationalize the observed pattern,[27] the similarity of the chemical shifts observed in the NMR spectra of **5b**, **3b**, and **3d** in DMSO-d_6 suggests that the compounds adopt similar conformations. The similar spectra and the NOE observed indicate that in DMSO-d_6 both **3b** and **3d** exist as a mixture of all possible partial cone conformations which are in fast exchange on the NMR time scale. The solvent-induced conformational shift observed for **5a** seems to be present also in the *exo*-calixarenes **3b** and **3d**.

Molecular Mechanics Calculations. A comprehensive search of the conformational space of several *exo*-

(23) Anet, F. A. L.; Basus, V. J. *J. Magn. Reson.* **1978**, *32*, 339. For papers using this method see for example: Adams, S. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 1602; Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839. For a recent example of the use of this technique for measuring rotational barriers of conformational biased calixarene systems see ref 6.

(24) Solvent effects affect the conformational stability of substituted resorcarenes. See for example: Shivanuk, A. N.; Pirozhenko, V. V.; Kalchenko, V. I.; Markovsky, L. N. *J. Chem. Res.* **1995**, 374.

(25) The partial cone conformation of **5a** is chiral, and a dynamic process fast at the NMR time scale and resulting in enantiomerization must be assumed. The observed NOE should correspond to the average of the NOE present in the two enantiomeric conformations.

(26) Siegel, J. S.; Anet, F. A. L. *J. Org. Chem.* **1988**, *53*, 2629.

(27) For example, an additional explanation for the cross-peaks would be that **3b** and **3d** exist in DMSO-d_6 as a mixture of 1,2- and 1,3-alt conformations.

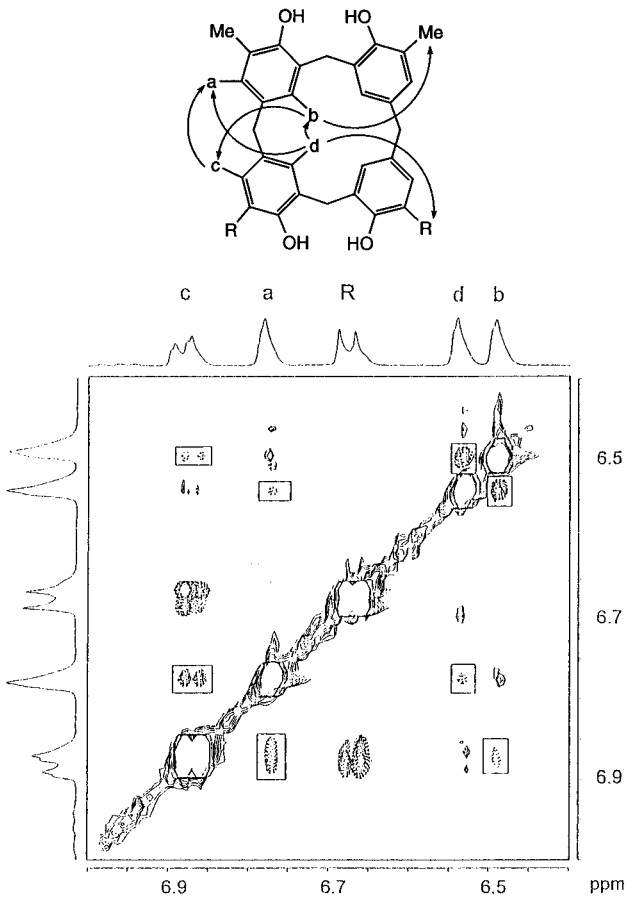


Figure 6. Top: schematic representation of the NOE interactions observed in the NOESY spectra of **3b** (R = t-Bu) and **3d** (R = H) in DMSO-d_6. Bottom: 400 MHz ^{1}H NMR NOESY spectrum (aromatic region) of **3d** in DMSO-d_6.

and *endo*/*exo*-calixarenes was accomplished using a random search method based on the MM3 force field[28,29] which was specially adapted to calixarenes (see Experimental Section). Selected calixarenes were also calculated with the stochastic search routine included in MM3.[30] Tables 2 and 3 list the relative energies of the most stable structures of each conformation obtained from this approach.

(i) Unsubstituted *exo*-Calix[4]arenes. From a structural point of view, **1a** and the [1$_4$] metacyclophane **14a** represent two limiting cases in calixarene chemistry. As shown by force field calculations, the stability and rigidity of the cone conformer of **1a** are largely determined by the circular hydrogen bonding scheme and the bulk of the *intra*annular substituents. In contrast, **14a** exhibits neither a pronounced energetical preference for a single conformer nor a substantial rotational barrier.[31,32] A priori, it could be expected that the formation of two *extra*annular hydrogen bonds in **3** should stabilize the cone and the 1,2-alt(conv) conformers. Indeed, the calculations indicate that these two forms are lower in energy than the other conformers. However, in contrast to the NMR and X-ray data, the computations favor the cone over the 1,2-alt structure. In general, the energy range between the basic conformations of **3** is narrower than in **1a** but wider than in **14a**. The calculated structure of the lowest energy 1,2-alt conformer of **3d** is very similar to that found in the crystal structure while the structures of the cone and the 1,3-alt forms closely resemble those found in various crystal structures of *endo*-calix[4]arenes.[33] The most stable cone conformers assume a "pinched" shape which is somewhat lower in energy (0.3−0.7 kcal mol^{-1}) than a cone structure possessing nearly C_4 symmetry. In the 1,2-alt and paco forms of **3** the methylene carbons do not lie in a common plane but adopt a folded arrangement.

The results of the calculations for **4a**−**c** listed in Table 2 reveal that the cone and 1,2-alt(conv) possess the lowest energies followed by a paco form, a relative stability which parallels the number of possible hydrogen bonds. The energy gaps between the cone and the 1,2-alt or paco conformers are smaller than those found in **3**, which probably is the result of the destabilization of the *cone* conformation by *intra*annular OH groups which cannot form a complete cyclic array of hydrogen bonds. Furthermore, the paco(*exo*) form is 0.7 to 1.1 kcal mol^{-1} lower in energy than the paco(*endo*). This suggests that in the context of the force field the hydrogen bond between *endo* rings is somewhat stronger than the one between *exo* rings. The geometric shapes of the lowest energy conformers of **4a**−**c** resemble closely those described above

Table 2. Relative Energies (in kcal mol^{-1}) for the Low Energy Conformers of Several Calix[4]arene Systems

compd	cone	partial cone		1,2-alt		1,3-alt
				conv[a]	div[a]	
1a	0.0	6.0		7.7		11.3
3a	0.0	3.2		3.2	4.8	7.1
3b	0.0	3.3/2.7[b]		2.2	4.6	7.5
3d	0.0	3.3/3.2		2.2	5.7	7.3
3e	0.0	3.3		2.2	5.6	7.5
		endo	*exo*			
4a	0.0	2.4	1.5	0.5	4.8	5.9
4b	0.0	2.8	1.7	1.0	5.8	6.1
4c	0.0	2.3	1.6	0.4	5.6	6.6
14a	0.0	1.2		3.2		1.8

[a] The terms converging (conv) and diverging (div) denote that adjacent hydroxyl groups are in a syn and anti orientation, respectively. [b] Two different partial cone forms exist in which the cresol and *tert*-butylphenol ring, respectively, assume an *anti* orientation.

Table 3. Relative Energies (in kcal mol^{-1}) for the Low Energy Conformers of Ethanediyl-Substituted Calix[4]arenes

	cone		partial cone			1,2-alt			
compd	ax	eq	ax	eq	iso[a]	ax	eq	iso	1,3-alt
4d	0.0	2.3	2.2	4.5	4.1	0.1	2.5	4.1	7.9
4e	2.6	0.0	4.5	1.9	1.9	3.3	0.4	4.9	6.3
5a	0.0	2.9	2.7	5.5	5.2	1.6	5.0	4.4	7.5
5b	0.0	2.6	3.3	6.0	5.3	1.7	4.9	5.3	8.6
5c	0.0	3.3	3.2	6.6	5.3	2.9	6.3	4.3	7.3
14b	0.0	0.3	0.5	1.0	0.3	0.9	1.8	1.0	0.9

[a] Two different orientations exist for the methyl substituent at the bridge in the partial cone conformation (paco(iso I) and paco(iso II)); values given here are for the lower energy conformer.

(28) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293.

(29) MM3(92) is available from the Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405.

(30) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

(31) Thondorf, I.; Brenn, J. *J. Mol. Struct. (THEOCHEM)* **1997**, *398*−*399*, 307.

(32) Harada, T.; Ohseto, F.; Shinkai, S. *Tetrahedron* **1994**, *50*, 13377.

(33) E.g., the cone structure of tris(25,26,27,28-tetrahydroxycalix[4]arene)acetone clathrate (Ungaro, R.; Pochini, A.; Andreetti, G. D.; Sangermano, V. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1979) and the 1,3-alt conformation of 25,27-bis(allyloxy)-26,28-bis(benzoyloxy)calix[4]arene (Georgiev, E. M.; Mague, J. T.; Roundhill, D. M. *Supramolecular Chemistry* **1993**, *2*, 53).

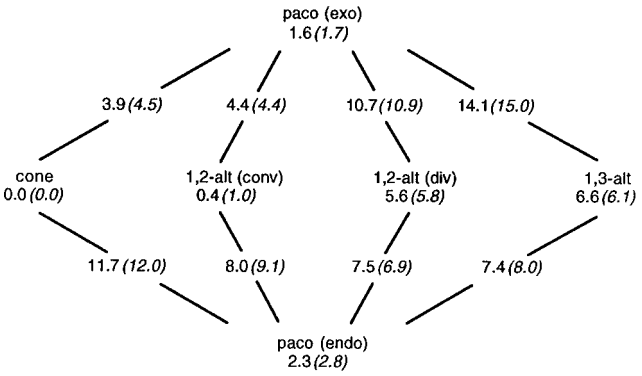


Figure 7. Possible interconversion pathways and rotational barriers (in kcal mol^{-1}, relative to the lowest energy cone structure) for **4c** and (in parentheses) for **4b**.

for the *exo*-calixarenes **3**, with the exception of the paco-(*endo*) form which exhibits a nearly planar arrangement of the methylene carbon atoms.

The pathways of ring inversion of *exo*/*endo*-calixarenes were studied using the coordinate driver method.[31] To characterize the influence of the *extra*annular alkyl groups on the heights of the rotational barriers, **4b** and **4c** were chosen as examples (Figure 7). The complete inversion of the calixarene scaffold leading to the topomerization of the methylene protons of the cone conformer necessarily requires the rotation of all four rings through the macrocyclic annulus. In general, the rotational barriers of the *endo* rings are higher than those of the *exo* rings, probably because the passage of the *intra*annular hydroxyl through the interior of the macrocycle is sterically more demanding than the passage of a hydrogen. The lowest energy pathway for the interconversion of the cone into the paco(*endo*) form involves the steps: cone → paco(*exo*) → 1,2-alt(conv) → paco(*endo*). A single ring rotation may transform the paco(*endo*) into a (topomerized) cone* form, with a barrier of 11.7 kcal mol^{-1} (for **4c**). However, a lower energy topomerization pathway is available since the paco(*endo*) form may topomerize via the 1,2-alt(div) conformation (i.e., paco(*endo*) → 1,2-alt(div) → paco(*endo*)*). The topomerization of the cone form can then be achieved by reversal of the first three steps (paco(*endo*)* → 1,2-alt(conv)* → paco(*exo*)* → cone*). The overall energy barriers for this process are 9.1 and 8.0 kcal mol^{-1} for **4b** and **4c**, respectively, and are in reasonable agreement with the experimental value of $\Delta G^{\ddagger}$ of 10.8 kcal mol^{-1} determined for **4b**.[34] The calculated values are higher than those obtained for the metacyclophane **14a** (4.4 kcal mol^{-1})[31] and the *exo*-calixarene **3c** (6.7 kcal mol^{-1})[4b] but lower than for **1a** (13.7 kcal mol^{-1}).[31]

(ii) Ethanediyl Bridged *exo*-Calix[4]arenes. By analogy to the 1,1-alkanediyl-calixarenes **1b** and resorcarenes **2a** it could be expected that the hydroxyl groups of the correspondingly substituted *exo*- and *exo*/*endo*-calixarenes should influence the axial/equatorial conformational preference of the alkyl group. To test whether the calixarene scaffold itself influences the orientation of a 1,1-ethanediyl group we performed molecular mechanics calculations on the [1_4] metacyclophane **14b**. The relative energies listed in Table 3 indicate, however, that neither a single conformation of the macrocyclic skeleton is energetically dominating nor the axial or equatorial arrangement of the methyl substituent is markedly preferred.

In the calixarene series **5a**−**c** the *extra*annular hydroxyl groups "direct" the substituent into an axial position which is, for a given conformation of the calix skeleton, approximately 3 kcal mol^{-1} lower in energy than the equatorial one. The calculations favor the cone over the 1,2-alt conformation in contrast to the NMR data which indicate that **5a** adopts in $CDCl_3$ solution a 1,2-alt arrangement with an axial disposition of the methyl substituent.

Two 1,1-ethanediyl derivatives of **4** (**4d** and **4e**) were examined. The calculations predict that the substituent will assume an axial arrangement if proximal to two *exo* rings and an equatorial orientation if in the neighborhood of two *endo* rings. For a given conformation of the macrocyclic ring, the energy gaps between the forms are in the range 2.3−2.9 kcal mol^{-1}.

The possible pathways for the cone-to-cone inversion of **5c** (a process which interconverts the cone(ax) with the cone(eq) forms) were calculated assuming stepwise ring rotations (Figure 8). The cone(eq) and cone(ax) forms generate distinct paco conformations (paco(iso I) and paco(iso II), respectively). Nearly all the rotational barriers of a ring proximal to the alkanediyl group are higher than for a distal ring (e.g., paco(ax) → 1,2-alt(iso): 11.8 kcal mol^{-1} vs paco(ax) → 1,2-alt(ax): 7.7 kcal mol^{-1}). This is probably due to the repulsive steric interactions which exist between the *exo* hydroxyl of the rotating ring and the alkyl group in the transition state of the first process. However, in the case of the paco(iso) → 1,2-alt interconversions, the barriers for rotation of the adjacent rings are lower than those of the distal rings. Apparently, the folded structure of these conformations circumvents the repulsive interactions during the ring rotation. In addition, in the paco(iso I/II) → 1,2-alt(ax/eq) processes a hydrogen bond is formed in the transition state, whereas the rotation of the distal ring involves breaking of a hydrogen bond.

Starting from the cone(ax) form, the lowest energy pathway to the cone(eq) form involves the following sequence: cone(ax) → paco(iso II) → 1,2-alt(eq) → paco(eq) → cone(eq) conformations with an overall energy barrier of 9.5 kcal mol^{-1}. This barrier is about 3 kcal mol^{-1} higher than that we have calculated for the unsubstituted *exo*-calixarene **3c**[4b] which means that the methyl substituent does not strongly reduce the flexibility of the *exo*-calixarene. A previous DNMR study[6] has also shown that the incorporation of an alkanediyl bridge into **1** (e.g., **1b**) leads only to slightly higher barriers.

Conclusions. *Exo*-Calix[4]arenes **3** are flexible on the NMR time scale, as predicted by computational methods. This flexibility is not significantly reduced by an alkyl substituent at one of the bridges (like the methyl group in **5a**), although such a substituent seems to favor the axial position. Single-crystal X-ray analyses suggest a slight preference of the 1,2-alternate conformation over the cone conformation in the crystalline state for the examples studied so far. The 1,2-alternate conformation is predominant also in apolar solvents such as $CDCl_3$, while a polar, hydrogen bonding breaking solvent like DMSO-d_6 shifts the conformation toward partial cone. *Exo*-*endo*-calix[4]arenes **4** show analogous conformational preferences, but their inversion barrier is in a measurable region of 10−11 kcal mol^{-1}, a value to which the intramolecular hydrogen bond of the *exo*-hydroxy groups

(34) The calculated energies cannot be directly related to the experimentally determined values of $\Delta G^{\ddagger}$ since the entropy term $\Delta S^{\ddagger}$ is neglected in the computations.

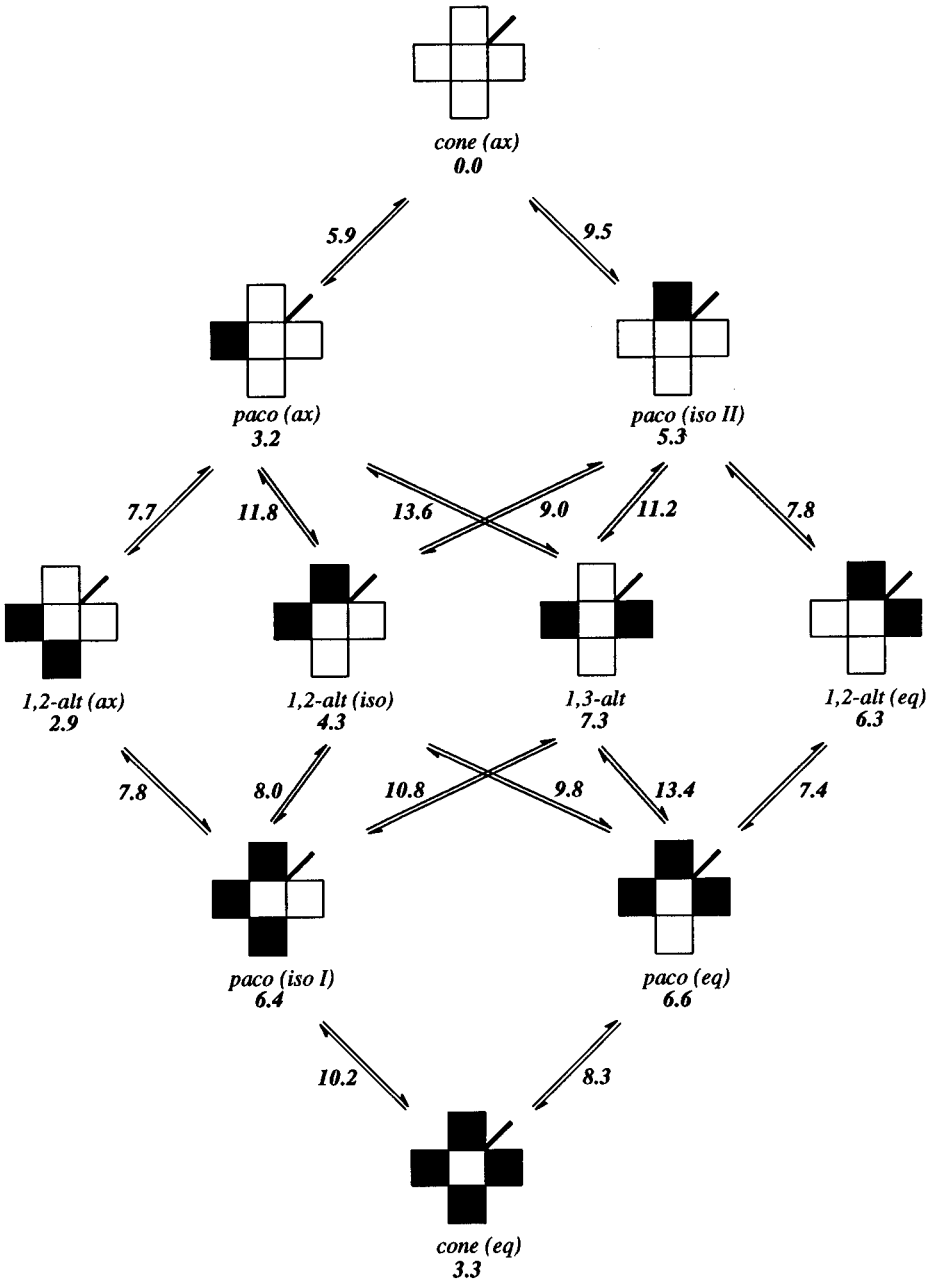


Figure 8. Pathways for the conformational interconversions of **5c**. All energies (in kcal mol^{-1}) are relative to the most stable cone(ax) conformation. The peripheral black and white squares represent rings pointing "up" or "down", respectively. Two different partial cone forms are possible in which the methyl is in an isoclinal position (paco(iso I) and paco(iso II), see text) while only a single 1,3-alt form exists.

does not significantly contribute. Molecular mechanics calculations predict for the methyl group at the bridge an axial position in **4d** and an equatorial position in **4e**. This tendency of alkyl substituents to avoid the neighborhood of the hydroxy groups may be used to steer the conformation in these types of calix[4]arenes.

Experimental Section

Molecular Mechanics Calculations. All calculations were done using the MM3(92) force field running on either SGI Crimson or IBM RISC 6000 workstations. Each compound was subjected to a comprehensive conformational search. Starting from a cone conformation of the corresponding calixarene, whose mean plane through the four methylene carbons was aligned in the *xy*-plane of the Cartesian coordinate system, possible orientations for all upper rim carbon atoms were generated independently from each other in the range -3 Å $\leq z \leq +3$ Å in steps of 0.5 Å, taking into account symmetry considerations. This was followed by partial minimization of the conformers under fixation of the corresponding *z*-coordinates. Using the "coordinate calculation options" of the MM3 force field, alkyl substituents were added, and their arrangement was optimized. The conformers were subsequently energetically minimized without any constraints using the block-diagonal Newton−Raphson method. The orientation of the hydroxyl groups was studied using a systematic search of the corresponding torsional angles in increments of 180°. Finally, all conformers were optimized using the full-matrix Newton−Raphson method.

For means of comparison, some compounds were calculated using the stochastic search option of the MM3 force field. To cover the entire conformational space different runs were started from each of the basic conformations. No significant differences with respect to low energy conformations were detected in the results of both methods.

The pathways of conformational interconversion were simulated starting from the energetically most stable conformation of a given compound. Ring inversions were performed by modification of the *z*-coordinate of the aromatic para-carbon in steps of 0.1 Å while two to four methylene carbon atoms were kept fixed in their *z*-coordinates. The energy minima and maxima were subsequently minimized with the option 6 and 7 of the MM3 force field, respectively, without any constraints.

Crystallography. The X-ray diffraction data were measured with a ENRAF−NONIUS CAD-4 computer-controlled diffractometer. Cu Kα (λ = 1.54178 Å) radiation with a graphite crystal monochromator in the incident beam was used. All crystallographic computing was done on a VAX 9000 computer using the TEXSAN structure analysis software.[35]

Crystallographic data: **3d**: $C_{30}H_{28}O_4$, space group $P\bar{1}$, a = 11.670(2) Å, b = 12.334(2) Å, c = 8.971(1) Å, α = 109.24(1)°, β = 108.84(1)°, γ = 97.35(2)°, V = 1113.4(4) Å^3, z = 2, ρ_{calc} = 1.35 g cm^{-3}, μ(Cu Kα) = 6.67 cm^{-1}, no. of unique reflections = 4115, no. of reflections with I ⩾ 3σ_I = 3600, R = 0.041, R_w = 0.069. **4**: $C_{38}H_{44}O_4$·CH_3CN, space group $P\bar{1}$, a = 13.541(2) Å, b = 15.337(4) Å, c = 9.240(3) Å, α = 95.01(3)°, β = 107.67(2)°, γ = 106.68(2)°, V = 1719.2(9) Å^3, z = 2, ρ_{calc} = 1.17 g cm^{-3}, μ(Cu Kα) = 5.51 cm^{-1}, no. of unique reflections = 6513, no. of reflections with I ⩾ 3σ_I = 4974, R = 0.044, R_w = 0.070.

Syntheses. Starting compounds were commercially available or prepared according to the literature. Dehydrogenation reactions were carried out with Raney-nickel (Merck), but other qualities can be used also according to our experience. Melting points above 300 °C were determined under argon using sealed capillary tubes. All melting points are uncorrected. All chromatographic separations were done using silica gel 60, particle size 0.040−0.063 mm (230−400 mesh), as stationary phase. The eluent is indicated for the individual case. All compounds were checked for purity by TLC (except the bromomethyl derivatives) and by ^{1}H NMR spectroscopy. Elemental analyses were performed only for the new calixarenes.

6,6′-Bis(bromomethyl)-4,4′-dimethyl-2,2′-methanediyldiphenol (6a). A mixture of 4,4′-dimethyl-2,2′-methanediyldiphenol[36] (2 g, 8.8 mmol) and paraformaldehyde (0.6 g, 20 mmol) was stirred in 20 mL of HBr−acetic acid for 5 h. After standing overnight, the product was filtered off and washed several times with petroleum ether. Yield: 1.2 g (34%); mp: 138 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.05 (br s, 2H), 6.95 (br s, 2H), 4.52 (s, 4H), 3.87 (s, 2H), 2.24 (s, 6H) ppm.

6,6′-Bis(bromomethyl)-4,4′-di-*tert*-butyl-2,2′-methanediyldiphenol (6b). A mixture of 4,4′-di-*tert*-butyl-2,2′-methanediyldiphenol[37] (5 g, 16 mmol) and paraformaldehyde (1.2 g, 40 mmol) was stirred in 80 mL of HBr−acetic acid for 5 h and then poured into water. The crude product was filtered off and several times recrystallized from *n*-hexane at −18 °C. Yield: 4.5 g (56%); mp: 152−153 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.29 (d, J = 2.4 Hz, 2H), 7.12 (d, J = 2.4 Hz, 2H), 6.56 (s, 2H), 4.55 (s, 4H), 3.93 (s, 2H), 1.26 (s, 18H) ppm.

6,6′-Bis(3-bromo-4-hydroxy-5-*tert*-butylbenzyl)-4,4′-dimethyl-2,2′-methanediyldiphenol (7a). A mixture of **6a** (6.0 g, 14.5 mmol), 2-bromo-6-*tert*-butylphenol (30 g, 0.131 mol), and $ZnCO_3$ (4 g, 30 mmol) was kept at 60 °C for 16 h. The mixture was treated with 100 mL of $CHCl_3$ and filtered, and the solvent was evaporated. The product was isolated by column chromatography (toluene) as the second eluted compound. A complete separation of the 2-bromo-*tert*-butylphenol proved to be difficult in this case, and a crude product was used for the debromination, after which o-*tert*-butylphenol was easier to remove. Yield of crude **7a**: 5.8 g (57%); mp: 76 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.11 (br s, 2H), 7.08 (br s, 2H), 6.98 (br s, 2H), 6.75 (br s, 2H), 5.80 (br, 2H), 5.70 (s, 2H), 3.85 (s, 2H), 3.83 (s, 4H), 2.24 (s, 6H), 1.36 (s, 18H) ppm. MS(FD), m/z 710.4 (M^+).

6,6′-Bis(3-bromo-4-hydroxy-5-*tert*-butylbenzyl)-4,4′-di-*tert*-butyl-2,2′-methanediyldiphenol (7b) was obtained analogously from 6,6′-bis(bromomethyl)-4,4′-di-*tert*-butyl-2,2′-methanediyldiphenol (**6b**). Yield: 67%; mp: 94−95 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.23 (d, J = 2.5 Hz, 2H), 7.15 (d, J = 1.9 Hz, 2H), 7.11 (d, J = 1.5 Hz, 2H), 6.98 (d, J = 2.2 Hz, 2H), 5.93 (s, 2H), 5.72 (s, 2H), 3.91 (s, 4H), 3.87 (s, 2H), 1.37 (s, 18H), 1.28 (s, 18H) ppm. MS(FD), m/z 794.5 (M^+).

6,6′-Bis(3-*tert*-butyl-4-hydroxybenzyl)-4,4′-dimethyl-2,2′-methanediyldiphenol (8a). Raney-nickel (10 g) was added to a mixture of **7a** (3.2 g, 4.5 mmol) and KOH (2.5 g, 40 mmol) in 200 mL of methanol. The flask was flushed with hydrogen three times and the mixture stirred at room temperature under a hydrogen atmosphere until the hydrogen uptake was complete. The catalyst was removed by filtration and washed with methanol and the washings combined with the filtrate. Acidification with dilute HCl precipitated a crude product which was recrystallized from petroleum ether to give a white solid. Yield: 2.14 g (86%); mp: 97−98 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15 (br s, 2H), 7.00 (br s, 2H), 6.83 (br s, 2H), 6.79 (br s, 2H) 6.49 (d, J = 8.0 Hz), 6.04 (s, 2H), 4.91 (s, 2H), 3.88 (s, 4H), 3.83 (s, 2H), 2.25 (s, 6H), 1.39 (s, 18H) ppm. MS(FD), m/z 552.8 (M^+).

6,6′-Bis(3-*tert*-butyl-4-hydroxybenzyl)-4,4′-di-*tert*-butyl-2,2′-methanediyldiphenol (8b) was obtained analogously from **7b**. Yield: 70%; mp: 104 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.18 (d, J = 2.4 Hz, 2H), 7.14 (d, J = 2.0 Hz, 2H), 6.96 (d, J = 2.4 Hz, 2H), 6.81 (dd, J = 6.0, 2.0 Hz, 2H), 6.55 (d, J = 8.0 Hz, 2H), 6.01 (s, 2H, OH), 4.76 (s, 2H, OH), 3.89 (s, 2H), 3.87 (s, 4H), 1.38 (s, 18H), 1.26 (s, 18H) ppm. MS(FD), m/z 636.7 (M^+).

5,23-Di-*tert*-butyl-11,17-dimethyl-4,24,26,27-tetrahydroxycalix[4]arene (4a). A mixture of **8a** (3.0 g, 5.4 mmol) and paraformaldehyde (0.18 g, 6 mmol) in 150 mL of xylene was heated to 175 °C for 16 h in an autoclave. The solvent was removed by evaporation and the residue recrystallized from acetonitrile to give pale white crystals. Yield 1.15 g (37%); mp: 315−319 °C; ^{1}H NMR (CD_2Cl_2, 400 MHz, 181 K) δ 7.10 (br s, 2H, ArH), 7.02 (br s, 2H, ArH), 6.88 (s, 2H, OH), 6.78 (br s, 2H, ArH), 6.40 (s, 2H, OH), 6.11 (br s, 2H, ArH), 4.05 (d, J = 13.7 Hz, 1H, CH_2), 3.96 (d, J = 17.0 Hz, 2H, CH_2), 3.89 (d, J = 14.3 Hz, 1H, CH_2), 3.67 (d, J = 17.0 Hz, 2H, CH_2), 3.44 (d, J = 13.8 Hz, 1H, CH_2), 3.04 (d, J = 14.3 Hz, 1H, CH_2), 2.18 (s, 6H, Me), 1.27 (s, 18 H, *t*-Bu). ^{1}H NMR (CD_2Cl_2, 400 MHz, RT) δ 7.10 (d, J = 1.9 Hz, 2H, ArH), 7.07 (d, J = 2.1 Hz, 2H, ArH), 6.81 (d, J = 1.8 Hz, 2H, ArH), 6.46 (s, 2H, OH), 6.31 (s, 2H, OH), 6.30 (d, J = 2.1 Hz, 2H, ArH), 3.86 (s, 4H, CH_2), 3.83 (s, 2H, CH_2), 3.56 (s, 2H, CH_2), 2.24 (s, 6H, Me), 1.38 (s, 18H, *t*-Bu) ppm. MS(FD), m/z 564.6 (M^+). Anal. Calcd for $C_{38}H_{44}O_4$: C, 80.82; H, 7.85. Found: C, 80.88; H, 7.93.

5,11,17,23-Tetra-*tert*-butyl-4,24,26,27-tetrahydroxycalix[4]arene (4b) was obtained analogously from **4a**. Yield: 20%; mp: 360−364 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.32 (br, 2H), 7.10 (br, 2H), 7.02 (br, 2H), 6.56 (s, 2H), 6.44 (br, 2H), 6.40 (s, 2H), 3.96 (s, 4H), 3.91 (s, 2H), 3.64 (s, 2H), 1.41 (s, 18H), 1.31 (s, 18H). MS(FD), m/z 649.0 (M^+). Anal. Calcd for $C_{44}H_{56}O_4$·1.5 CH_3CN: C, 79.45; H, 8.58. Found: C, 79.26; H, 8.88. CH_3CN could not be removed by drying in high vacuum at 50 °C in this case, as shown also by the ^{1}H NMR spectrum.

6,6′-Dimethyl-4,4′-bis-(bromomethyl)-2,2′-ethanediyldiphenol (10). A mixture of 6,6′-dimethyl-2,2′-ethanediyldiphenol (**9**, 4.0 g, 16.5 mmol) and paraformaldehyde (1.0 g, 34 mmol) was stirred with 80 mL of a 33% solution of HBr in acetic acid until complete dissolution was achieved. After standing overnight the precipitate was filtered off and washed several times with cold acetic acid. Yield: 4.02 g (57%); mp: 172 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.17 (d, J = 2.0 Hz, 2H), 7.04 (d, J = 1.8 Hz, 2H), 4.55 (q, J = 7.1 Hz, 1H), 4.45 (s, 4H), 2.19 (s, 6H), 1.64 (d, J = 7.1 Hz, 3H).

6,6′-Dimethyl-4,4′-bis(3-bromo-4-hydroxy-5-*tert*-butylbenzyl)-2,2′-ethanediyldiphenol (11) was prepared from **10** as described above for **7**. The product was isolated by column chromatography ($CHCl_3$) as the second eluted compound. Yield: 51%; mp: 87 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.07 (d, J = 1.9 Hz, 2H), 7.01 (d, J = 1.8 Hz, 2H), 6.97 (d, J = 1.7, 2H), 6.75 (br s, 2H), 5.65 (s, 2H), 5.56 (s, 2H), 4.51 (q, J = 7.1 Hz,

(35) The authors have deposited atomic coordinates for the structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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1H), 3.76 (s, 4H), 2.16 (s, 6H), 1.59 (d, J = 7.1 Hz, 3H), 1.35 (s, 18H). MS(FD), m/z 724.3 (M^+).

6,6′-Dimethyl-4,4′-bis(3-*tert*-butyl-4-hydroxybenzyl)-2,2′-ethanediyldiphenol (12) was obtained from **11** as described above for **8**. Yield: 88%; mp: 98 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 7.06 (d, J = 1.8 Hz, 2H), 6.98 (d, J = 1.3 Hz, 2H), 6.78 (dd, J = 1.9, 7.0 Hz, 2H), 6.52 (d, J = 7.9 Hz, 2H), 5.56 (s, 2H), 4.67 (s, 2H), 4.50 (q, J = 7.1 Hz, 1H), 3.78 (s, 4H), 2.15 (s, 6H), 1.59 (d, J = 7.1 Hz, 3H), 1.37 (s, 18H). MS(FD), m/z 566.9 (M^+).

11,17-Di-*tert*-butyl-2,5,23-trimethyl-4,12,16,24-tetrahydroxycalix[4]arene (5a). A mixture of **11** (1.0 g, 1.76 mmol) and paraformaldehyde (60 mg, 2 mmol) in xylene (150 mL) was heated to 180 °C in an autoclave for 5 days. The solvent was removed and the remaining oil dissolved in a small amount of xylene. After standing for 2 days, the crude product was filtered and recrystallized from xylene. Yield: 390 mg (38%); mp: 269−272 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 250 K) δ 7.07 (s, 2H, ArH), 7.01 (s, 2H, ArH), 6.81 (s, 2H, ArH), 6.65 (s, 2H, OH), 6.48 (s, 2H, OH), 6.39 (s, 2H, ArH), 4.74 (q, 1H, J = 6.5 Hz, CH), 3.94 (d, 1H, J = 14.1 Hz, CH_2), 3.84 (d, 2H, J = 16.1 Hz, CH_2), 3.78 (d, 2H, J = 15.8 Hz, CH_2), 3.28 (d, 1H, J = 14.2 Hz, CH_2), 2.04 (s, 6H, Me), 1.59 (d, 3H, J = 6.5 Hz, Me), 1.36 (s, 18H, t-Bu). ^{1}H NMR ($CDCl_3$, 400 MHz, RT) δ 6.99 (s, 2H, ArH), 6.95 (s, 2H, ArH), 6.81 (s, 2H, ArH), 6.50 (s, 2H, ArH), 4.69 (q, 1H, J = 7.1 Hz, CH), 3.96 (d, 1H, J = 14.4 Hz, CH_2), 3.83 (d, 2H, J = 15.7 Hz, CH_2), 3.74 (d, 2H, J = 15.4 Hz, CH_2), 3.37 (d, 1H, J = 14.4 Hz, CH_2), 2.21 (s, 6H, Me), 1.54 (d, 3H, J = 7.1 Hz, Me), 1.39 (s, 18H, t-Bu). ^{1}H NMR (DMSO-d_6, 338 K) δ 8.14 (s, 2H, OH), 7.95 (s, 2H, OH), 6.92 (d, J = 2.0 Hz, 2H, ArH), 6.76 (2H, ArH), 6.68 (d, J = 1.8 Hz, 2H, ArH), 6.56 (d, J = 2.0 Hz, 2H, ArH), 4.67 (q, J = 7.2 Hz, 1H, CH), 3.88 (d, J = 15.6 Hz, 1H, CH_2), 3.71 (d, J = 15.6 Hz, 1H, CH_2), 3.64 (d, J = 14.4 Hz, 2H, CH_2), 3.55 (d, J = 14.5 Hz, 2H, CH_2), 2.11 (s, 6H, Me), 1.39 (d, J = 7.2 Hz, 3H, Me), 1.37 (s, 18H, t-Bu) ppm. MS(FD), m/z 578.5 (M^+). Anal. Calcd for $C_{39}H_{46}O_4$: C, 80.92; H, 8.02. Found: C, 80.79; H, 8.04.

The *exo*-calixarenes **3b** and **3d** showed the following spectroscopic data:

3b: ^{1}H NMR (DMSO-d_6, 318 K) δ 8.32 (2H, OH), 8.27 (2H, OH), 6.91 (2H, ArH), 6.79 (2H, ArH), 6.57 (2H, ArH), 6.56 (2H, ArH), 3.74 (s, 2H, CH_2), 3.74 (s, 2H, CH_2), 3.58 (s, 4H, CH_2), 2.13 (s, 6H, Me), 1.34 (s, 18H, t-Bu). ^{1}H NMR ($CDCl_3$, 400 MHz, RT) δ 6.99 (br s, 2H, ArH), 6.88 (br s, 2H, ArH), 6.84 (br s, 2H, ArH), 6.61 (br s, 2H, ArH), 3.83 (s, 2H, CH_2), 3.78 (s, 4H, CH_2), 3.69 (s, 2H, CH_2), 2.21 (s, 6H, Me), 1.40 (s, 18H, t-Bu) ppm.

3d: ^{1}H NMR (DMSO-d_6, 400 MHz, 318 K). δ 8.94 (2H, OH), 8.30 (2H, OH), 6.88 (dd, ^4J = 2.1 Hz, ^3J = 8.1 Hz, 2H, ArH), 6.78 (d, J = 1.7 Hz, 2H, ArH), 6.69 (d, J = 8.1 Hz, 2H, ArH), 6.55 (d, J = 2.0 Hz, 2H, ArH), 6.50 (d, J = 1.8 Hz, 2H, ArH), 3.71 (s, 2H, CH_2), 3.67 (s, 2H, CH_2), 3.54 (s, 4H, CH_2), 2.12 (s, 6H, Me) ppm. The NMR data of **3d** previously described[3] were obtained in acetone-d_6 and not in $CDCl_3$ as reported.

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Supporting Information Available: ^{1}H NMR spectra of calixarenes **4a**, **4b**, and **5a** and of compounds not characterized by elemental analyses (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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