Annelated Calixarenes Composed of Calix[4]arenes with Hydroxy Groups in the *Endo* and *Exo* Position

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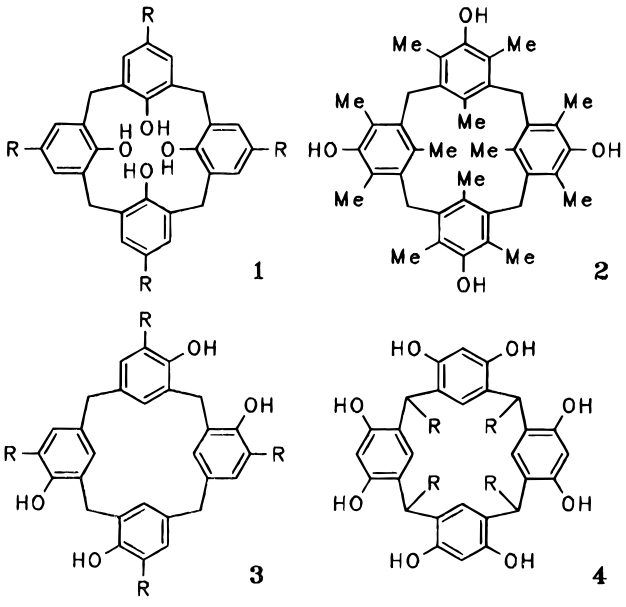
Various phenol-derived calix[4]arenes (**3**) bearing four hydroxy groups in the *exo* position have been prepared by uncatalyzed condensation of suitable dimers or tetramers with formaldehyde in xylene in yields up to 44%. The tetra-*tert*-butyl compound (**3a**) has been shown by X-ray analysis to adopt a regular cone conformation (nearly identical in shape with the *endo* isomer) with two intramolecular O−H···O hydrogen bonds, while the corresponding dimer (**6c**) prefers a conformation (not possible in the calixarene) with two intramolecular O−H···π(arene) interactions. Condensation of *exo*-calix[4]arenes **3f**,**g** with free ortho positions (easily available by debutylation) with bisbromomethylated dimers gave annelated double (**9**) and triple (**10**) calixarenes consisting of *endo*- and *exo*-calix[4]arene substructures in yields up to 24% and 10%, respectively. Molecular dynamics calculations suggest that the *exo*-calixarene part in **9** is less mobile than the entirely flexible **3**, while the *endo*-calixarene part shows a higher mobility than usual. A complete interconversion cone → cone is impossible, however, which enables the construction of inherently chiral molecules.

The name calixarenes initially was coined by Gutsche for the cyclic condensation products (**1**) which are obtained by condensation of *p*-alkyl (mainly *tert*-butyl) phenols and formaldehyde under alkaline conditions.[1] It seems reasonable, however, and justified especially by various modifications and derivatives of **1** to use the name calixarenes also in a more general sense for the basic skeleton of 1_n-metacyclophanes.[2] With respect to the macrocyclic ring system, the hydroxy groups in **1** are in the *endo* position. However, each of the aromatic units in a metacyclophane also has three *exo* positions, and various macrocyclic molecules of the calixarene-type (1_n-metacyclophane type respectively) bearing *exo*-hydroxy groups, like **2**[3] or **3**,[4] have been synthesized meanwhile, among them also compounds with hydroquinone units[5] or resorcinol units.[6] Here resorcarenes[7] (**4**), cyclic tetramers obtained from resorcinol and aldehydes other than formaldehyde under acidic conditions, deserve special mention.[1,8]



Calix[4]arenes of type **1** may be synthesized by condensation of suitable dimers with bisbromomethylated dimers,[9] a strategy which enables also the synthesis of compounds bearing different substituents in the para position. If in this reaction a calix[4]arene of type **3** with free ortho positions is used as the dimer, larger molecules with annelated calix[4]arene structures are accessible.[4]

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(1) For a recent review on calixarenes, see: Böhmer, V. *Angew. Chem.* **1995**, *107*, 785−818; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745.

(2) Compounds **1** would be then hydroxycalixarenes, a name which, however, is to be used only when a distinction from "non-hydroxy" calixarenes is necessary.

(3) Pappalardo, S.; Ferguson, G.; Gallagher, J. F. *J. Org. Chem.* **1992**, *57*, 7102−7109.

(4) Böhmer, V.; Dörrenbächer, R.; Vogt, W.; Zetta, L. *Tetrahedron Lett.* **1992**, *33*, 769−772.

(5) See for instance: (a) Morita, Y.; Agawa, T.; Nomura, E.; Taniguchi, H. *J. Org. Chem.* **1992**, *57*, 3658−3662. (b) Reddy, P. A.; Gutsche, C. D. *J. Org. Chem.* **1993**, *58*, 3245−3251. (c) Casnati, A.; Comelli, E.; Fabbi, M.; Bocchi, V.; Mori, G.; Ugozzoli, F.; Manotti Lanfredi, A. M.; Pochini, A.; Ungaro, R. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 384−392.

(6) For a calix[5]arene with resorcinol units linked via their 2- and 6-positions, see: Tabatabai, M.; Vogt, W.; Böhmer, V.; Ferguson, G.; Paulus, E. F. *Supramol. Chem.* **1995**, *4*, 147−152.

(7) Various names have been used for these cyclic tetramers among which "resorcarenes" is shortest.

(8) (a) For a review on resorcarenes, see: Timmermann, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron*, in press. (b) For the first resorc[6]arenes obtained from 2-alkyl resorcinols and formaldehyde, see: Konishi, H.; Ohata, K.; Morikawa, O.; Kobayashi, K. *J. Chem. Soc., Chem. Commun.* **1995**, 309−310.

(9) Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.* **1987**, 896−897.

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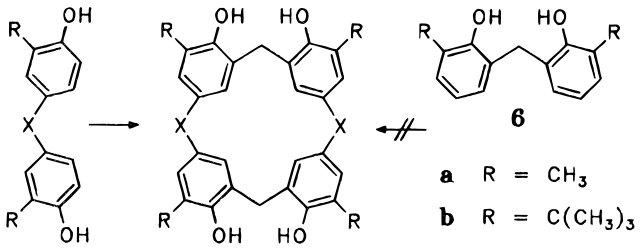
Scheme 1



5 **3** **6**

a R = CH_3
b R = $C(CH_3)_3$

a X = $-CH_2-$ R = $C(CH_3)_3$
b X = $-CH_2-$ R = CH_3
c X = $CH_3-\overset{CH_3}{\overset{|}{C}}-CH_3$ R = $C(CH_3)_3$
d X = $CH_3-\overset{(CH_2)_5-CH_3}{\overset{|}{C}}-CH_3$ R = $C(CH_3)_3$

We report here on a more detailed study of the synthesis of calixarenes **3** and of such larger systems.

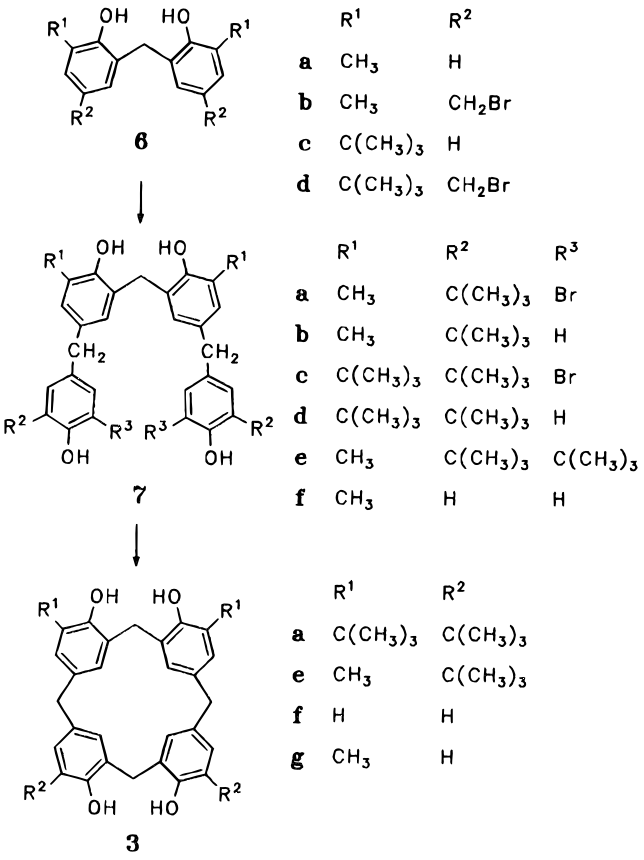
Syntheses

Symmetrically substituted calixarenes **3** are readily prepared by condensation of suitable para-linked dimers **5** with formaldehyde in aprotic solvents like xylene at 175 °C in an autoclave, the first example (**3c**) being reported by Chasar[10] in 1985 (Scheme 1).

The driving force for the formation of the macrocycle without high dilution conditions is obviously the formation of intramolecular OH···OH hydrogen bonds in **3**. Thus, no cyclic material is obtained with dioxane as solvent, and the yield is distinctly lower also for **3b** (6%) than for **3a** (38%) where the directing influence exerted by the bulky *tert*-butyl groups on the OH groups favors such hydrogen bonds. (**3f** is detected only in traces if the synthesis is tried with 4,4′-methylenediphenol which has no ortho substituents. This may be caused, however, by the formation of polymeric material by further condensation of **3f**.) Finally, no calix[4]arene is formed if instead of **5a**,**b** the isomeric compounds **6** are used. Here an intramolecular hydrogen bond already exists in the dimer and is not formed during the macrocyclization. If dimers **5** with a substituted bridge are used, the yield of **3** obviously decreases with increasing size of these substituents: **3a** (38%), **3c** (20%), and **3d** (13%, mixture of the two diastereomers). This could be interpreted in terms of a steric hindrance of the cyclic conformation necessary for the final cyclization step. Weaker hydrogen bonds, expressed by an OH signal at 5.2 ppm in **3d**, in comparison to the signal at 6.3 ppm for **3a** point in the same direction.

Calix[4]arenes of type **3** having different substituents R^1/R^2 are available as outlined in Scheme 2. Although this synthesis has been carried out to date only for $R^1 = CH_3$ or *t*-Bu and R^2 = *t*-Bu, there is, in principle, also the possibility of having other substituents and even two different residues $R^1/R^{1'}$ since the synthesis of various dimers **6** is possible in a definite way, using for instance halogen to protect the para positions. (The symmetrically substituted dimers **6a**,**c** are obtained more easily by

Scheme 2



6

	R^1	R^2
a	CH_3	H
b	CH_3	CH_2Br
c	$C(CH_3)_3$	H
d	$C(CH_3)_3$	CH_2Br

7

	R^1	R^2	R^3
a	CH_3	$C(CH_3)_3$	Br
b	CH_3	$C(CH_3)_3$	H
c	$C(CH_3)_3$	$C(CH_3)_3$	Br
d	$C(CH_3)_3$	$C(CH_3)_3$	H
e	CH_3	$C(CH_3)_3$	$C(CH_3)_3$
f	CH_3	H	H

3

	R^1	R^2
a	$C(CH_3)_3$	$C(CH_3)_3$
e	CH_3	$C(CH_3)_3$
f	H	H
g	CH_3	H

direct condensation of the *o*-alkylphenols in apolar, aprotic media.[11]) Bromomethylation of **6a** (60−70% of **6b**), condensation of **6b** with excess 2-bromo-6-*tert*-butylphenol (70−75% of **7a**), and dehalogenation of **7a** (hydrogenation in alkaline solution) leads in well-known steps to **7b** (75−80%). Condensation of **7b** with formaldehyde gives here the calix[4]arene **3e** in 43% yield. In a similar way **3a** was prepared starting from **6c**, via **6d** (86%), **7c** (72%), and **7d** (69%). The yield of 44% in the final cyclization step is (not unexpectedly) higher than that in the direct condensation of the corresponding **5**, since no intermolecular connection of phenolic units is necessary.

Transbutylation ($AlCl_3$, toluene) of **3a** and **3e** gives the unsubstituted calix[4]arene **3f** with four and the dimethylcalix[4]arene **3g** with two reactive ortho positions, which are used as starting material for the preparation of annelated calixarenes.

The calix[4]arenes **3f**,**g** can be regarded as methylene-bridged phenolic dimers (2,2′-methylenediphenols) connected via their para positions (4-positions) by an additional bridge. Consequently they can be incorporated into calix[4]arene systems with *endo*-OH groups by condensation with bisbromomethylated dimers **8** according to the well-established "2 + 2" strategy[9] (Scheme 3).

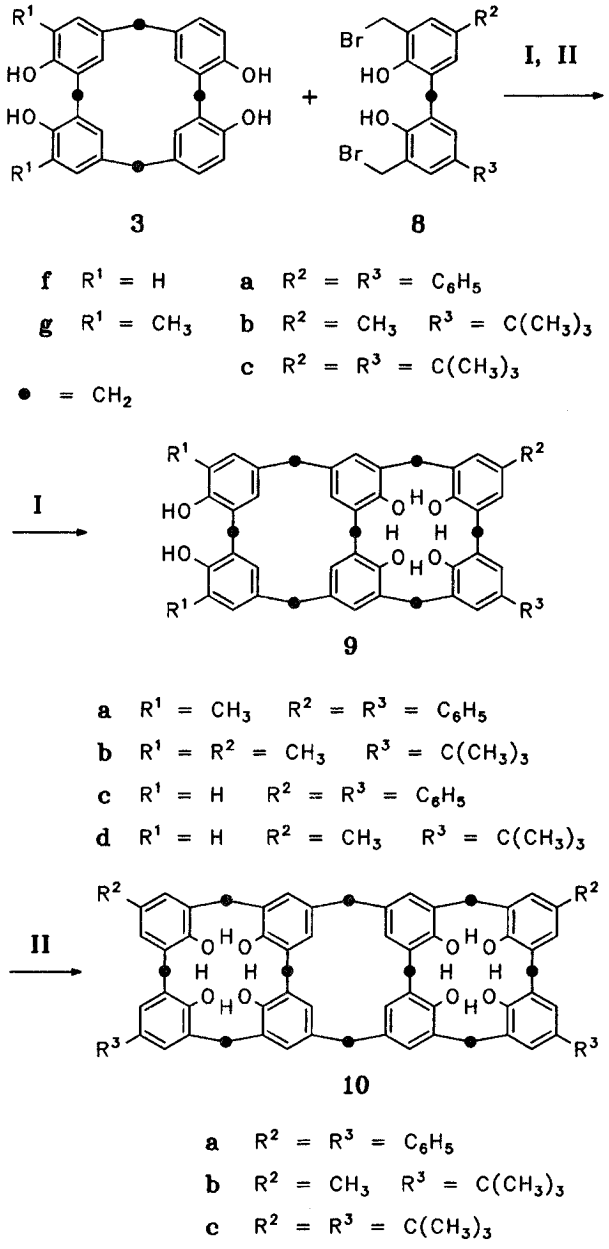
Compounds **9a**,**b** are thus obtained in 24% yield if a 1.5-fold amount of **8a**,**b** is used. Such an excess, which accounts for side reactions like the formation of quinone methides and their di- and trimerization,[12] cannot be used with **3f**, which has four reactive ortho positions. This may be one reason for the lower yield (8%) observed for

(10) (a) Chasar, D. W. *J. Org. Chem.* **1985**, *50*, 545−547. (b) Recently the BF_3·OEt_2-catalyzed condensation of **6a** with paraformaldehyde in CH_2Cl_2 has been reported to yield **3a** in 30% yield, while only linear oligomers have been obtained from **6b**: Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, *36*, 2311−2314.

(11) Casiraghi, G.; Casnati, G.; Pochini, A.; Puglia, G.; Ungaro, R.; Sartori, G. *Synthesis* **1981**, *2*, 143−146.

(12) E.g., Bavoux, C.; Perrin, M.; Goldmann, H.; Böhmer, V. *J. Chem. Soc., Perkin Trans. 2* **1989**, 2059−2063.

Scheme 3



compound **9c** under stoichiometric conditions. Seven percent of **10a** was obtained, on the other hand, with a 2.6-fold amount of **8a**. However, all the factors determining the yield are not yet understood, since **9d** (8%) *and* **10b** (mixture of the two isomers, 10%) were isolated when a 1.7-fold amount of **8b** was applied. A 1.5-fold amount of **8c** leads to 6% of **10c** as the only identifiable product. It should be noted that in all condensations with **3f** the newly formed calix[4]arene has the four OH groups in the *endo* position. A structure with two *endo*- and two *exo*-OH groups was never observed. This may be due to a template effect exerted by $TiCl_4$ (one Ti being bound to three adjacent oxygen atoms/functions) as discussed earlier.[13]

The annelated double calix[4]arenes **9** can be regarded as calix[6]arenes with an additional methylene bridge between opposite phenolic units (and compounds **10** correspondingly as doubly methylene bridged calix[8]arenes) and should be available therefore from an appropriate calix[6]arene by condensation with formaldehyde.

Calix[6]arene **11a**, for instance, having two OH groups in the *endo* and four OH groups in the *exo* position, would be such a precursor for **9a**. **11a** can be obtained by debutylation of **11b**, which in turn was obtained by condensation of **7b** with **8a** in dioxane in the presence of $TiCl_4$ in 7% yield. Under analogous conditions **11a** could be prepared by direct condensation of **7f** with **8a** in 13% yield. This difference in yield can be understood, assuming again a Ti-templated arrangement of the oxygen functions of rings C−F in a calix[4]arene-like fashion which is hindered in **11b** by the two *tert*-butyl groups. Such a template effect in the synthesis of **11** is further corroborated by the fact that the calix[6]arene **12** with six *endo*-OH groups from a linear tetramer of *tert*-butylphenol and **8b** is formed with only 3%. Although **9a** could not be obtained from **11a** and formaldehyde, the compounds **11** are interesting, since they represent the first calix[6]arenes with OH groups not only in the *endo* but also in the *exo* position.[8b]

Tetraester derivatives of calix[4]arenes, easily obtained by etherification with bromoacetates, form strong complexes with Na^+ ions, which are kinetically stable on the NMR time scale.[14] The hexaether ester obtained from **11a** and ethyl bromoacetate could arrange four arms in a similar way around a Na^+ ion if the basic calixarene skeleton assumes a conformation similar to that of **9a**. No complexation of NaSCN could be detected however in $CDCl_3$ by ^1H NMR, which means that the coordination around a Na^+ cation is not sufficient to impart a conelike conformation to the phenolic units C−F.

Conformation

(a) Crystalline State. Single crystals suitable for X-ray analysis were obtained for **3a** by recrystallization from acetonitrile/acetone (1:1). Although numerous crystal structures of calix[4]arenes of type **1** have been published,[15] including examples for OH-depleted compounds,[16] this is the first structure determination for an *exo*-calix[4]arene of type **3**.[17]

Molecule **3a** has crystallographic *mm* symmetry, as shown in Figure 1, with an acetonitrile molecule enclathrated in the calix cup; the shortest C···C contact is 3.752(3) Å between the acetonitrile methyl C22 and the *endo* aromatic carbon C5. The calixarene assumes a regular cone conformation, stabilized (see later) by pairs of intramolecular OH···O hydrogen bonds. This is not very

(13) Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811−6817.

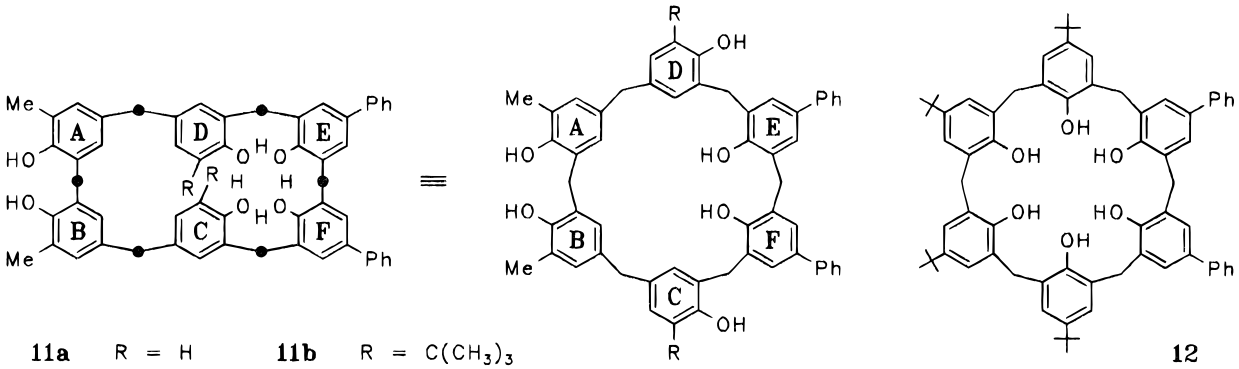
(14) (a) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681−8691. (b) For the X-ray structure of a similar complex, showing the arrangement of the ligating groups, see: Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, G.; Ugozzoli, F. *J. Incl. Phenom.* **1988**, *6*, 119−134.

(15) See for instance: (a) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005−1007. (b) Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans 2* **1983** 1773−1779. (c) Ehlinger, N.; Lecocq, S.; Perrin, R.; Perrin, M. *Supramol. Chem.* **1993**, *2*, 77−82. (d) Rantsordas, S.; Perrin, M.; Gharnati, F.; Lecocq, S.; Vogt, W.; Fey, W.; Böhmer, V. *J. Incl. Phenom.* **1990**, *9*, 145−152. (e) Gharnati, F.; Perrin, M.; Rantsordas, S.; Goldmann, H.; Böhmer, V. *J. Cryst. Spectr. Res.* **1991**, *21*, 69−74. (f) Atwood, J. L.; Orr, G. W.; Bott, S. G.; Robinson, K. D. *Angew. Chem.* **1993**, *105*, 1114−1115. (g) Juneja, R. K.; Robinson, K. D.; Johnson, C. P.; Atwood, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3818−3819.

(16) (a) Grynszpan, F.; Goren, Z.; Biali, S. B. *J. Org. Chem.* **1991**, *56*, 532−536. (b) For the basic 1_4-metacyclophane, see: McMurry, J. E.; Phelan, J. C. *Tetrahedron Lett.* **1991**, *32*, 5655−5658.

(17) The X-ray structure of **2** which assumes the 1,3-alternate conformation is reported in ref 3.

Chart 1



11a R = H **11b** R = $C(CH_3)_3$ **12**

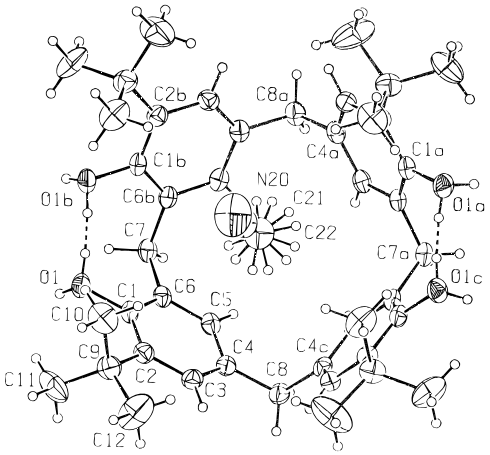


Figure 1. View looking into the cavity of **3a** in the crystalline state showing our numbering scheme and the acetonitrile in the calixarene cavity. Ellipsoids are drawn at the 30% probability level. The molecule has *mm* crystallographic symmetry. The hydroxyl H atoms are equally disordered over two sites; the acetonitrile molecule also has *mm* symmetry and its hydrogens are totally disordered.

surprising, although a 1,2-alternate conformation found for instance in a 1,3-OH-depleted calix[4]arene would allow also two intramolecular hydrogen bonds. Entirely surprising, however, is the fact that the conformation of the carbon framework of **3a** is practically identical to that of the isomeric *tert*-butylcalix[4]arene (**1**, R = *t*-Bu)[15a] which has crystallographic 4-fold symmetry. The unique aromatic ring in **3a** is inclined at 123.7(1)° to the plane of the four CH_2 groups; the corresponding angle in **1** (R = *t*-Bu) is 123.0°. The conformational similarity of **3a** and **1** (R = *t*-Bu) is further demonstrated by the fact that fitting of the cyclophane skeleton of both compounds is possible with a rms value of 0.071 Å, even although a toluene molecule is included in the cavity of **1** (R = *t*-Bu) while acetonitrile is included in **3a**.

The packing of **1** (R = *t-Bu*) and **3a** in the solid state is quite different. In **1** (R = *t*-Bu) there is a cyclic array of *intra*molecular hydrogen bonds and the toluene in the calix cup is disordered about a 4-fold axis; *inter*molecular contacts are of the van der Waals type. Compound **3a** has its hydroxy H atoms equally disordered over two sites, and in each molecule there are pairs of *intra*molecular O−H···O bonds (across crystallographic mirror planes) with O···O 2.657(3) Å. The molecules are then linked by pairs of *inter*molecular O−H···O hydrogen bonds (O···O 2.712(3) Å) about inversion centers to form infinite zig-zag ribbons as shown in Figure 2, which extend along the *ab* cell diagonal.

Single crystals were also obtained from **6c**, which is representative of a structural motif that is present (twice) in calix[4]arene **3a**. Surprisingly molecule **6c** forms neither intra- nor intermolecular O−H···O hydrogen bonds between the two hydroxy groups, as has been found in other X-ray structures published on phenolic dimers[18a−c] or linear oligomers[18] of this type. Molecule **6c** has no crystallographically imposed symmetry but has approximate 2-fold symmetry, with the 2-fold axis passing through the central methylene carbon. The OH groups found here are not *syn* as in **3a** but are oriented *anti* with respect to a plane through the methylene carbon and the two adjacent aromatic carbon atoms. Both hydroxys are involved in O−H···π(arene) interactions, as shown in Figure 3, with the hydroxy H atoms directed toward the phenyl carbons of the adjacent rings and O1···C22 2.987(1) and O2···C12 2.959(2) Å. Intermolecular contacts are of the van der Waals type with no unusual interactions.

A conformation analogous to **6c** (stabilized by a pair of OH···π(arene) hydrogen bonds) was found for 2,2-bis-(2-hydroxy-3-*tert*-butyl-5-methylphenyl)propane in the crystalline state;[19] this conformation effectively maximizes the intramolecular O···C(methyl) separations. Our structure analysis of **6c** (which is devoid of methyl groups

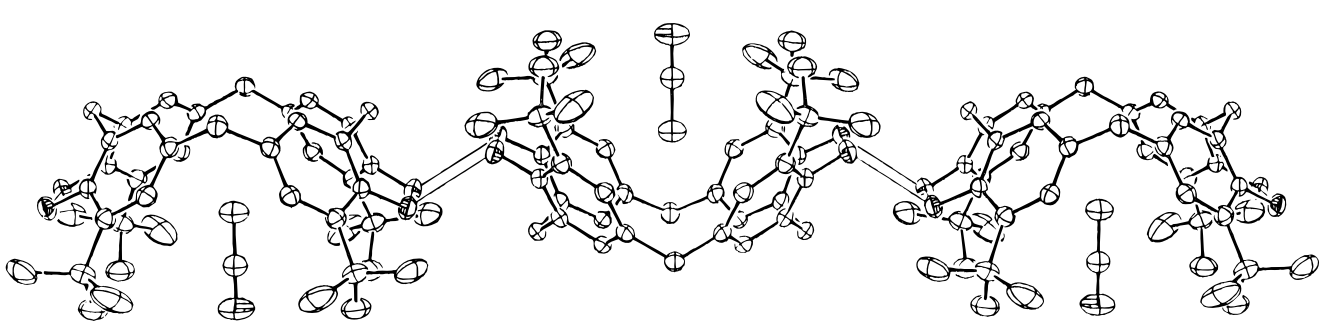


Figure 2. View showing part of the zig-zag hydrogen-bonded ribbon in **3a**·CH_3CN. Hydrogen atoms are omitted for clarity.

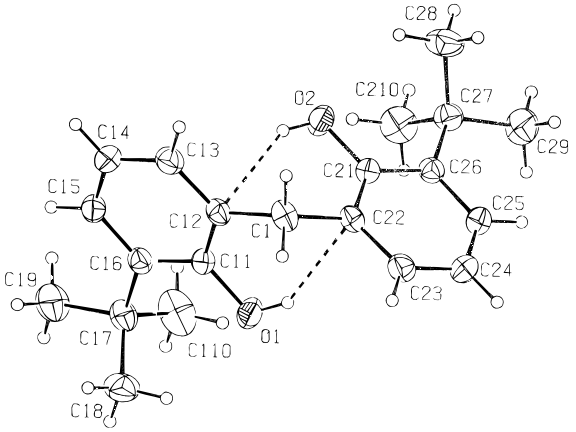


Figure 3. Molecular conformation of **6c** in the crystalline state, showing the O−H···π hydrogen bonding and our numbering scheme. Thermal ellipsoids are at the 30% probability level.

at the central C atom) shows that achieving this C···O separation is most probably not the main reason for adopting this conformation. Probably in dimers with two *o*-*tert*-butyl groups two intramolecular OH···π(arene) give better stabilization than a combination of intra- and intermolecular OH···O hydrogen bonds as found in linear dimers and oligomers having at least one ortho position unsubstituted.[18] Only when the formation of OH···π-(arene) hydrogen bonds is precluded for other reasons, as in the calixarene **3a**, does OH···O hydrogen bonding become energetically attractive. We are presently studying additional molecules of the **6c** type with more and less substitution to provide more examples of competitive hydrogen bonding.

If a conformational arrangement as in **6c**, which is different from that in the calixarene molecule, would be favored in compounds **7b**,**d**, it is hard to see why a cyclization should be favored over the polycondensation. Thus, as in other areas of calixarene synthesis, further work is necessary to elucidate entirely all the factors determining the outcome of the cyclization reaction.

Unfortunately suitable crystals for X-ray analysis could not yet be obtained for the annelated calixarenes **9** and **10**.

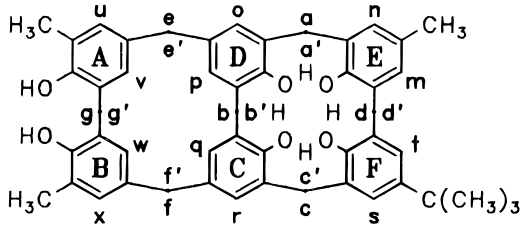
(b) Solution. Calixarenes **1** assume a cone conformation in solution; however a mutual conversion of opposite cone conformations is possible on a time scale corresponding to the ^{1}H NMR time scale. Thus, methylene protons are found as a singlet at high temperature and as a pair of doublets at low temperature.[1] In contrast, the *exo*-calixarenes **3** are flexible, showing a singlet for the protons of each of the different methylene groups. No significant change which could be interpreted as conformational freezing is observed upon cooling to −70 °C. This difference in flexibility arises from the absence of intraannular substituents and also from the weaker stabilization of two extraannular hydrogen bonds in comparison to the complete array of four intraannular hydrogen bonds in **1**.

(18) (a) Casiraghi, G.; Cornia, M.; Sartori, G.; Bocchi, V.; Casnati, G.; Andreetti, G. D. *Makromol. Chem.* **1982**, *183*, 2611−2633. (b) Casiraghi, G.; Cornia, M.; Ricci, G.; Balduzzi, G.; Casnati, G.; Andreetti, G. D. *Makromol. Chem.* **1983**, *184*, 1363−1378. (c) Casiraghi, G.; Cornia, M.; Ricci, G.; Casnati, G.; Andreetti, G. D.; Zetta, L. *Macromolecules* **1984**, *17*, 19−28. (d) Paulus, E.; Böhmer, V. *Makromol. Chem.* **1984**, *185*, 1921−1935.

(19) Hardy, A. D. U.; MacNicol, D. D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1140−1142.

Four pairs of doublets (ratio 1:1:1:2) and a singlet (for 4H) are found for the methylene protons of the annelated double calixarenes **9a** and **9c**, showing that the molecule has the expected symmetry plane. No principal change of this pattern is observed over a wide temperature range (checked for **9c** from 293 to 353 K in pyridine-d_5 and from 293 to 193 K in CD_2Cl_2) which means that these molecules are not flexible enough for *all pairs* of diastereotopic methylene protons to change places. A signal at 10.3 ppm for four OH groups indicates that the *endo*-calix[4]arene part of the molecule assumes as usual a cone conformation, stabilized by intramolecular hydrogen bonds, which is confirmed further by NOEs observed between aromatic protons of adjacent phenolic units. No entirely convincing argument for a certain conformation of the *exo*-calix[4]arene part can be given at the moment. As discussed earlier for **9a**, some results are in favor of a 1,2-alternate conformation but a rapid equilibrium between 1,2-alternate and cone cannot be ruled out.

As an additional example, the ^{1}H NMR spectrum of **9b** (in CD_2Cl_2) is discussed in some detail below. Due to the difference of R^2 and R^3, no symmetry plane exists and **9b** (as well as **9d**) is chiral. Three signals are found for the methyl groups (2.11, 2.14, and 2.18 ppm), which is best understood by a cone conformation of *both* calix[4]-arene systems by which the methyl groups of A and B are opposed to the methyl and *tert*-butyl group in E and F. With a 1,2-alternate conformation of ABCD, these groups would point in opposite directions, making the difference between A and B less understandable. Two signals for the OH groups at A and B (6.35 and 6.38 ppm weak intramolecular H-bonding) suggest the same.



9b

All seven methylene groups are different in **9b**. For a−d typical doublets (geminal coupling) for an *endo*-calix-[4]arene in the cone conformation (confirmed also by the OH signal at 9.98 ppm) are found in CD_2Cl_2 with axial protons at 4.09 (b′), 4.17, 4.186, and 4.191 ppm and equatorial protons at 3.26 (b), 3.43, 3.44, and 3.47 ppm, where the slight high-field shift for b is remarkable and could be due to shielding by A and B in the 1,2-alternate conformation. Protons g/g′ are less separated (3.89, 3.54 ppm), an argument against a fixed cone conformation of ABCD, while e,e′ (pseudosinglet at 3.71 ppm) and f,f′ (3.72, 3.65 ppm) are nearly identical. Doublets (*m* coupling) are found for the aromatic protons s, t, o, r, p, and q (7.06, 7.04, 6.95, 6.93, 6.55, 6.53 ppm) where the high-field shift for p/q again indicates shielding by A and B. The other aromatic protons n, m, u, v, w, and x appear as pseudosinglets at 6.83 (3H), 6.78 (1H), and 6.76 (2H) ppm. Thus, all these results, which are partly in favor of a cone and partly in favor of a 1,2-alternate conformation of ABCD, are probably best understood in terms of a flexible *exo*-calixarene part.

The chirality of **9d** was also demonstrated by doubling of the signals for the methyl and *tert*-butyl groups in the presence of Pirkle's reagent, which shows again that the

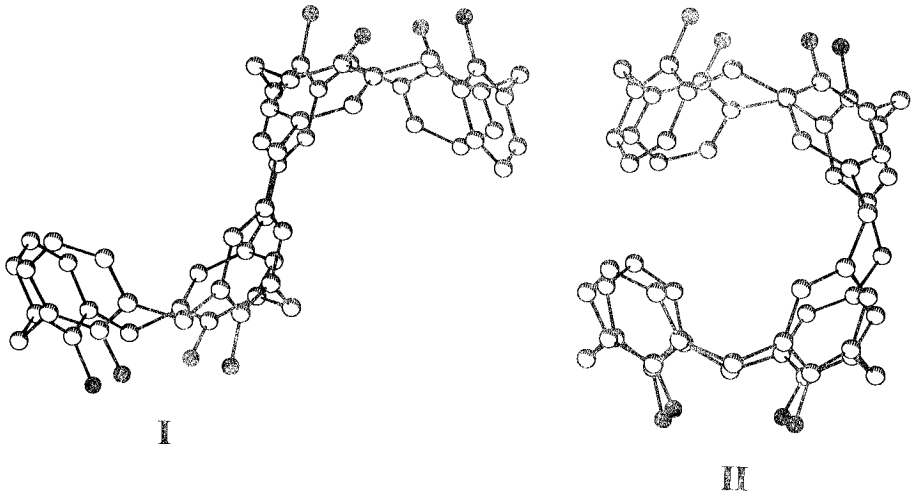


Figure 4. Possible conformational isomers of annelated triple calix[4]arenes of type **10** (substituents and hydrogen atoms omitted for clarity). I: cone/1,2-alternate/cone. II: cone/cone/cone (not possible for large substituents R^1, R^2). In both isomers the *endo*-calixarene systems can (in principle) be converted to 1,2-alternate, while a mutual interconversion of both isomers is impossible.

molecule exists in the form of enantiomers stable on the NMR time scale. This means that a diphenylmethane unit which belongs to two calix[4]arene substructures cannot change its configuration.

The triple calix[4]arenes **10a** and **10c** possess a highly symmetrical conformation, as demonstrated by the ^{1}H NMR spectrum of **10c**. One singlet for the *tert*-butyl groups (1.22 ppm) and for the OH groups (10.55 ppm, cone conformation!), four doublets (*m* coupling) for aromatic protons (7.11, 7.07, 6.90, 6.58 ppm), and a singlet (3.78 ppm, 4H) and three pairs of doublets in the ratio 1:2:1 (geminal coupling, 4.31, 4.25 (4H), 4.08, 3.54, 3.50 (4H), 3.26 ppm) for the methylene protons are compatible with a conformation with overall C_{2h} symmetry (I), in which the two *endo*-calix[4]arenes are in the cone and the *exo*-calixarene in the middle of the molecule has an 1,2-alternate conformation (Figure 4).

Although an all-cone conformation with C_{2v} symmetry (II) would have diastereotopic protons also at the methylene groups in the middle of the molecule, it cannot be strictly ruled out by the observed singlet, since these protons most probably would be isochronous. However, such a conformation is sterically impossible for **10a** and highly unlikely for **10c**, since the phenyl or *tert*-butyl residues would point toward each other. The high-field shift of one Ar-H doublet and one pair of Ar-CH_2-Ar doublets may be interpreted again in favor of I where the 1,2-alternate conformation of the *exo*-calixarene in the middle brings these protons in the shielding region of the adjacent cone conformations. From the results obtained with **9**, it follows that an interconversion of I and II is impossible.

The triple calix[4]arene **10b** is obtained as a hitherto inseparable mixture of two regioisomers, which, assuming the cone−1,2-alternate−cone arrangement of the calix[4]arene substructures, have C_s and C_i (= S_2) symmetry. Interestingly the signals of the methyl and *tert*-butyl groups of both isomers (their integration leads to a ratio of 1:1) are better separated in pyridine-d_5 ($\Delta\delta$ = 0.12 ppm) than in $CDCl_3$ ($\Delta\delta$ = 0.01 ppm), which solvent differentiates better the various methylene groups.

It has been found for *endo*-calixarenes and their derivatives that the ^{13}C NMR signals of the methylene carbons are diagnostic for the mutual arrangement of the adjacent phenolic units,[20] allowing thus for determination of the conformation. Table 1 contains these values for the *exo*-calix[4]arenes **3** and the double and triple calixarenes **9** and **10**. They demonstrate that similar conclusions cannot be drawn in the present cases, since the configurational factors are superimposed by constitutional ones.

Table 1. Chemical Shifts (δ, $CDCl_3$) for Methylene Carbon Atoms

3a	3e	9a	9b	9c	9d	10a	10c
40.86	40.27[b]	39.45	39.54	39.33	39.44	39.54	39.48
34.30	34.22	32.29	34.09	32.28	34.10	32.46	34.10
		32.08	32.33	32.09	32.33	32.25	32.81
		31.57	32.25	31.61	32.25	29.69	31.68
3f[a]	**3g**[a]	30.83	31.89	30.83	31.90		
			31.68		31.73		
41.19	41.18[b]						
30.83	31.51						

[a] Acetone-d_6. [b] Two signals superimposed.

(c) Computational Studies. In order to evaluate the possible conformations of *exo*-calixarenes, we performed an extensive conformational search of **3f** as a model compound. For this, the RANDOMSEARCH procedure of the SYBYL[21] program was used. All dihedral angles around the aryl−methylene bonds were defined as rotable and randomly perturbed followed by energy minimization using the TRIPOS force field.[22] From this approach 31 conformers were obtained which served as starting structures for subsequent minimizations using the TRIPOS force field with decreased termination criteria and the MM3(92) force field[23] for means of comparison. The 19 (TRIPOS) and 17 (MM3) unique conformers obtained in this way were then classified by analogy to the main conformations of the parent *endo*-calix[4]arene's cone (2/2 conformers with TRIPOS/MM3), partial cone (10/5), 1,2-alternate (4/6), and 1,3-alternate (2/4) (a boat-like conformation was found in addition with

(20) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372−3376.
(21) Sybyl (versions 5.4, 5.5, and 6.0), Tripos Associates, Inc., St. Louis, MO 63144.
(22) Clark, M.; Cramer, R. D.; van Opdenbosch, N. *J. Comput. Chem.* **1989**, *10*, 982−1012.
(23) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am Chem. Soc.* **1989**, *111*, 8551−8556. (b) Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am Chem. Soc.* **1990**, *112*, 8293−8307.

Table 2. Relative Energies of the Lowest Energy Conformers of the *exo*-Calixarene 3f Obtained by Using the TRIPOS and the MM3 Force Fields

energy in kcal/mol	conformation			
	cone	1,2-alt	partl cone	1,3-alt
		TRIPOS		
E_{bond}	4.45	4.73	3.71	4.19
E_{vdw}	−9.76	−9.16	−9.49	−10.43
E_{elec}	−8.54	−8.58	−6.37	−3.64
E_{total}	−13.85	−13.27	−12.16	−9.88
E_{rel}	**0.00**	**0.58**	**1.69**	**3.97**
		MM3		
E_{bond}	−18.55	−15.94	−16.76	−16.57
E_{vdw}	16.56	17.90	19.43	22.06
E_{elec}	15.55	14.10	14.26	15.49
E_{total}	13.56	16.05	16.92	20.97
E_{rel}	**0.00**	**2.49**	**3.36**	**7.41**

the TRIPOS force field). These single conformers are energetically different, mainly because of the differing torsion angles around the methylene bridges, but also because different orientations of the OH groups lead to different numbers of intramolecular hydrogen bonds.

The following discussion is restricted to the most stable conformers of each main conformation. Their relative energies obtained with the two force fields are given in Table 2.

With both methods the same energetical order cone > 1,2-alternate > partial cone > 1,3-alternate was obtained; however, the energy differences between the conformers differ considerably both with respect to the whole energy range and to the energy differences between the conformers. Whereas for the TRIPOS force field the energy differences between the conformers result mainly from the electrostatic term and hence from the number of possible intramolecular hydrogen bonds, the MM3 energy differences are due to both the bonding (essentially the torsional term) and the van der Waals interactions. This leads to a similar energy of the cone and 1,2-alternate conformer within the TRIPOS force field resulting mainly from the same number of hydrogen bonds whereas within the MM3 force field the larger steric strain of the 1,2-alternate conformer results in a larger energy difference.

The geometries of the energetically most stable conformers obtained with the TRIPOS force field correspond to those known from the various crystal structures of *endo*-calix[4]arenes. However, the partial cone and the 1,2-alternate conformer obtained with the MM3 force field are characterized by the fact that the four methylene carbons do not lie in a plane. Instead of using a single mean plane, the spatial situation can be described by two "reference planes" of two triangles formed by the methylene carbons, as was proposed by Harada et al.[24] for some 1,2-alternate conformers of OH-depleted calixarenes. These planes form dihedral angles of 147° and 128° in the partial cone and 1,2-alternate conformation, respectively. The "conventional" partial cone and 1,2-alternate conformers are less stable by 0.4 and 3.2 kcal mol^{-1}, respectively.

Additionally, with the TRIPOS force field a boat-like structure was found where two phenolic rings are nearly perpendicular whereas the other two lie in the mean plane of the methylene carbons. However, the relative energy of this conformer was 4.7 kcal mol^{-1} higher than that of the most stable conformer.

We compared the most stable cone conformers of **3f** with the crystal structure of **3a** by fitting of the metacyclophane framework which led to rms values of 0.204 Å (TRIPOS conformer) and 0.426 Å (MM3 conformer). The reason for these rather large deviations is the C_2 symmetry of the calculated structures whereas the crystal structure exhibits a (noncrystallographic) C_4 symmetry of the metacyclophane skeleton. This is not unexpected since in the crystal the C_4 symmetry is favored by incorporation of an acetonitrile molecule in the cavity of the calixarene whereas the calculations of the isolated molecule in vacuo neglect this effect.

Furthermore, we studied the conformational possibilities of the annelated calixarenes **9** by using the entirely unsubstituted compound ($R^1 = R^2 = R^3 = H$) as a model (details of this study will shortly be submitted for publication). This "naked" annelated calixarene was again subjected to the RANDOMSEARCH procedure followed by subsequent energy minimization using the two force fields. Both methods yielded two, energetically nearly equal, low-energy conformers, namely, a structure showing the cone conformation for both the *exo*- and the *endo*-calixarene part ($E_{TRIPOS} = -25.44$ kcal mol^{-1}, $E_{MM3} = 14.9$ kcal mol^{-1}) and a structure consisting of a cone conformation in the *endo*-calixarene and a 1,2-alternate conformation in the *exo*-calixarene part ($E_{TRIPOS} = -25.07$ kcal mol^{-1}, $E_{MM3} = 16.96$ kcal mol^{-1}). These calculations indicate that both conformers, having the maximum number of intramolecular hydrogen bonds, may be present under experimental conditions.

To study the conformational flexibility and the possibilities of interconversion of the annelated calixarene, we performed a molecular dynamics simulation of **9** ($R^1 = R^2 = R^3 = H$) and compared it with the corresponding simulations of **1** ($R = CH_3$) and **3f**. The results of the MD runs are shown in Figure 5.

At the conditions chosen for the MD run the *endo*-calixarene **1** shows only the $C_{2v} \rightarrow C_{2v}$ pseudorotation whereas for **3f** nonstop interconversions between the four main conformations take place without any significant preference of a single conformation. In contrast, in the annelated calixarene there is a dynamic interplay between the *exo*- and the *endo*-calixarene part, that is, the flexibility of the *endo*-calixarene part is enhanced and the flexibility of the *exo*-calixarene part is diminished when compared to the isolated molecules. As a result, the presence of the cone, partial cone, and 1,2-alternate conformation can clearly be distinguished for both parts.

Experimental Section

(a) Computational Studies. For the computational studies the SYBYL 6.1 software including the RANDOMSEARCH module and the TRIPOS force field as well as the MM3(92) force field were run on both a SGI Crimson Elan and an IBM RISC/6000 workstation.

For the random conformational search procedure, a maximum of 10 000 cycles with an energy cutoff of 10 kcal mol^{-1} and rms gradient of 0.01 kcal mol^{-1} $Å^{-1}$ was chosen. The optimizations with the TRIPOS force field were performed using some modified parameters[25] with a distance-dependant dielectric with $e = 1$ until the rms energy gradient was less than 0.001 kcal mol^{-1} $Å^{-1}$ using the Powell minimizer included in the SYBYL/MAXIMIN2 routine. The Gasteiger−Hückel method[26] was applied for the calculation of the partial charge

(24) (a) Harada, T.; Rudzinski, J. M.; Osawa, E.; Shinkai, S. *Tetrahedron* **1993**, *49*, 5941−5954. (b) Harada, T.; Ohseto, F.; Shinkai, S. *Tetrahedron* **1994**, *50*, 13377−13394.

(25) Thondorf, I.; Hillig, G.; Brandt, W.; Brenn, J.; Barth, A.; Böhmer, V. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2259−2267.

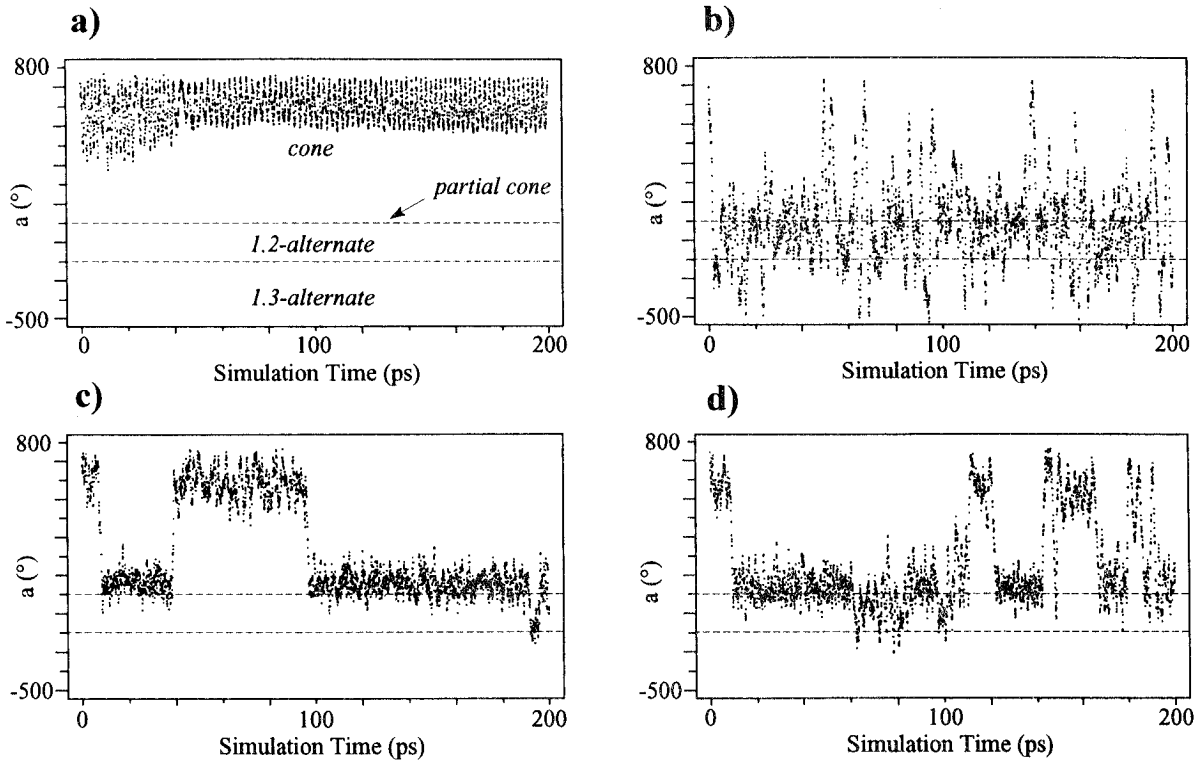


Figure 5. Molecular dynamics simulation for (a) **1** (R = CH_3), (b) **3f**, (c) **9** *endo* part, (d) **9** *exo* part. The values *a* on the ordinate, characterizing the conformation,[25] are obtained for each snapshot conformer from the torsion angles at the methylene bridges as

$$a = [(|\Sigma\varphi_i| + |\Sigma\chi_i|) - \Sigma|\varphi_i + \chi_i|]$$

The following values of *a* are characteristic for the four main conformations: cone, about 400 to 800°; partial cone, around 0°; 1,2-alternate, 0 to −200°; and 1,3-alternate, −200 to −500°.

distribution of the molecules. For the MM3 optimizations the full-matrix Newton−Raphson method was used.

The molecular dynamics simulations were done with the MD module of SYBYL. For each molecule a 200 ps dynamics run at 300 K using a time step of 1 fs and a snapshot every 50 fs was performed. All bonds involving hydrogens were constrained by the SHAKE option; starting velocities were chosen randomly. A constant dielectric of $e = 4$ was applied.

(b) X-ray Analyses of 3a and 6c.[27] Details of the crystal data, data collection, structure solution, and refinement are concisely summarized in Table 3. Diffraction data were corrected for Lorentz and polarization effects using NRCVAX;[28] no absorption correction was required. The structures were solved with SHELXS86.[29] In both **3a** and **6c** the hydroxy H atoms were clearly located in difference maps before constrained refinement with the AFIX-147 option in SHELXL93.[30] The unique hydroxy H atom in the asymmetric unit of **3a** was equally disordered over two sites. The acetonitrile molecule in **3a** is at the junction of two mirror planes, and the hydrogens are necessarily disordered. A difference map section in the expected locus of these H atoms showed a disk of density; these H atoms were allowed for with a suitably disordered model. The C−C molecular dimensions in **3a** and **6c** are entirely in accord with expected values and are unexceptional.

Figures 1 to 3 were produced with the aid of ORTEP[31] (as implemented in PLATON[32] and NRCVAX[28]) and with PLUTON.[33]

(c) Syntheses. Starting materials were commercially available or prepared according to the literature prescriptions indicated. Dehydrogenation reactions were carried out with Raney nickel (Fa. Merck, Darmstadt), 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 ASTH), as stationary phase. The eluent is indicated for the individual case.

As is often found with calixarenes, the elemental analyses deviate sometimes significantly from the values calculated for the pure compounds. This may be caused, especially in the case of low carbon values, by included solvent which is difficult to remove. As shown below for the *exo*-calixarenes **3**, the experimental values may be matched by the assumption of a certain fraction of the solvent used for recrystallization, although this has only been exactly proved for **3a** by X-ray analysis. Such an adjustment frequently found in publications is especially problematic if solvent mixtures (also petroleum ether) have been used, and we therefore do not calculate such arbitrary values for the double and triple calixarenes **9** and **10**. All compounds are carefully characterized, however, by NMR spectra and by their mass spectra.

5,11,17,23-Tetra-*tert*-butyl-4,12,16,24-tetrahydroxycalix[4]arene (3a). A solution of **5a**[34] (10 g, 32 mmol) and paraformaldehyde (1.2 g, 40 mmol) in 200 mL of xylene

(26) (a) Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, *36*, 3219−3226. (b) Marsili, M.; Gasteiger, J. *Croat. Chem. Acta* **1980**, *53*, 601−614.

(27) The atomic coordinates for all the X-ray structures of **3a** and **6a** have been deposited 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.

(28) Gabe, E. J.; Le Page, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384−387.

(29) Sheldrick. G. M. Shelxs86. Program for the solution of crystal structures, 1986, University of Göttingen, Germany.

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(31) Johnson, C. K. ORTEP−A Fortran Thermal Ellipsoid Plot Program, Technical Report ORNL-5138, 1976, Oak Ridge National Laboratory, Oak Ridge, TN.

(32) Spek. A. L. Platon Molecular Geometry Program, 1994, July 1994 version, University of Utrecht, Utrecht, Holland.

(33) Spek. A. L. Pluton Molecular Graphics Program, 1994, July 1994 version, University of Utrecht, Utrecht, Holland.

Table 3. Summary of Crystal Data, Data Collection, Structure Solution, and Refinement Details

	3a	6a
	(a) Crystal Data	
formula	$C_{44}H_{56}O_4 \cdot CH_3CN$	$C_{21}H_{28}O_2$
molar mass	689.94	312.43
color, habit	colorless, plate	colorless, block
crystal size, mm	0.39 × 0.30 × 0.10	0.40 × 0.39 × 0.39
crystal system	tetragonal	triclinic
a, Å	16.1990(14)	9.3773(12)
b, Å	16.1990(14)	10.5053(14)
c, Å	15.9570(13)	11.0439(11)
α, deg	90	106.971(10)
β, deg	90	101.022(10)
γ, deg	90	107.371(10)
V, Å^3	4187.2(6)	945.8(2)
space group	$P4_2/ncm$	$P\bar{1}$
Z	4	2
molecular symmetry	*mm*	none
F(000)	1496	340
d_{calc}, g cm^{-3}	1.094	1.097
μ, mm^{-1}	0.068	0.069
	(b) Data Acquisition[a]	
temp, K	294(1)	294(1)
unit-cell reflcns (*θ*-range, deg)	25 (8.9 13.8)	25 (17.8 24.2)
max *θ* (deg) for reflcns	26.9	27.0
hkl range of reflcns	0 20; 0 14; 0 20	−11 11; 0 13; −14 13
variation in three standrd reflcns	1.6%	1.0%
reflcns measd	4663	4117
unique reflcns	2405	4117
R_{int}	0.011	
reflcns with $I > 2\sigma(I)$	1069	3026
	(c) Structure Solution and Refinement[b]	
refinement on	F^2	F^2
solution method	SHELXS86	SHELXS86
H-atom treatment	riding	riding
no. of variables in L.S.	126	208
k in $w = 1/(\sigma^2F_o^2 + k)$ $[P = (F_o^2 + 2F_c^2)/3]$	$(0.0777P)^2$	$(0.0699P)^2 + 0.0621P$
R, R_w, gof	0.051, 0.149, 0.93	0.041, 0.132, 1.12
density range in final Δ-map, e Å^{-3}	−0.144, 0.207	−0.148, 0.217
final shift, error ratio	−0.003	−0.004
sec. extnct type	SHELXL	SHELXL
sec. extnct corrctn	0.0016(4)	0.078(7)

[a] Data collection on an Enraf Nonius CAD4 diffractometer with graphite-monochromatized Mo Kα radiation ($\lambda = 0.7107$ Å). [b] All calculations were done on a Silicon Graphics 4D-35TG computer system with the NRCVAX system of programs (Gabe, E. J.; Le Page, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384−389) and with SHELXL-93 (Sheldrick, G. M., 1993) for refinement with all data on F^2.

was heated to 175 °C for 16 h in an autoclave. The solvent was removed and the residue extracted into acetonitrile, giving a yellow product which was recrystallized from acetone/acetonitrile: yield 3.98 g (38%); mp 278−282 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (d, J = 1.9 Hz, 4H), 6.81 (d, J = 1.8 Hz, 4H), 6.33 (4H), 3.81 (4H), 3.79 (4H), 1.41 (36H); MS(EI), *m/z* 648.5 (M^+, calcd 648.9). Anal. Calcd for $C_{44}H_{56}O_4 \cdot CH_3CN$: C, 80.08; H, 8.62. Found: C, 79.90; H, 8.69.

5,11,17,23-Tetra-*tert*-butyl-8,20-dihexyl-8,20-dimethyl-4,12,16,24-tetrahydroxycalix[4]arene (3d). A solution of **5d** (2.87 g, 7 mmol; prepared by acid-catalyzed condensation of 2-*tert*-butylphenol and octanone-2) and paraformaldehyde (0.27 g, 9 mmol) in 200 mL of xylene was heated to 180 °C for 15 h. After removal of the solvent, the remaining oil was purified by flash chromatography ($CHCl_3$ as eluent), giving 1.4 g of an orange oil which was recrystallized from petroleum ether at −18 °C to give a white solid: yield 0.38 g (13%); mp 107−111 °C; ^{1}H NMR ($CDCl_3$) δ 7.18 (d, J = 1.8 Hz, 4H), 6.36 (d, J = 1.8 Hz, 4H), 5.22 (2H), 5.20 (2H), 3.67 (4H), 1.94−1.86 (m, 4H), 1.50 (4H), 1.42 (36H), 1.22 (14H), 1.15−1.00 (m, 4H), 0.88−0.82 (m, 6H); MS(FD), *m/z* 846.6 (M^+, calcd 845.3). Anal. Calcd for $C_{58}H_{84}O_4$: C, 82.41; H, 10.02. Found: C, 81.56; H, 9.98.

5,23-Di-*tert*-butyl-4,12,16,24-tetrahydroxy-11,17-dimethylcalix[4]arene (3e). 7b (6.0 g, 10.8 mmol) was dissolved in 220 mL of xylene, paraformaldehyde (0.4 g, 13.4 mmol) was added, and the mixture was kept for 16 h at 180 °C in an autoclave. The solvent was removed, the remaining brown oil was dissolved in 200 mL of CH_2Cl_2, silica (50 g) was added, and the solvent was removed to adsorb the oil on the silica. The product was extracted with CH_2Cl_2 (Soxhlet). Removal of the solvent and recrystallization from $CHCl_3$ gave a pale brown solid: yield 2.9 g (47%); mp 240−243 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (d, J = 2.0 Hz, 2H), 6.90 (d, J = 2.0 Hz, 2H), 6.84 (d, J = 1.9 Hz, 2H), 6.61 (d, J = 2.0 Hz, 2H), 6.30 (2H), 6.28 (2H), 3.84 (2H), 3.78 (4H), 3.69 (2H), 2.21 (6H), 1.40 (18H); MS(FD), *m/z* 564.4 (M^+, calcd 564.7). Anal. Calcd for $C_{38}H_{44}O_4 \cdot 0.25CHCl_3$: C, 77.26; H, 7.50. Found: C, 77.63; H, 7.90.

4,12,16,24-Tetrahydroxycalix[4]arene (3f). 3a (6 g, 9.2 mmol) was dissolved in 500 mL of toluene, $AlCl_3$ (5.9 g, 44.4 mmol) was added, and the mixture was kept for 3 h at 50 °C under argon. The volume was then reduced to 50 mL and the mixture poured into water. The product was precipitated by acidification with hydrochloric acid, recrystallized from methanol, and dried at 100 °C *in vacuo*: yield 2.8 g (71%); mp 350−357 °C; ^{1}H NMR (acetone-d_6) δ 8.50 (4H), 6.96 (m, 8H), 6.72 (m, 4H), 3.81 (4H), 3.70 (4H); MS(EI), *m/z* 424.2 (M^+, calcd 424.5). Anal. Calcd for $C_{28}H_{24}O_4$: C, 79.23; H, 5.70. Found: C, 79.36; H, 5.78.

4,12,16,24-Tetrahydroxy-5,23-dimethylcalix[4]arene (3g). 3e (2.9 g, 5.1 mmol) was dissolved in 200 mL of toluene, $AlCl_3$ (1.8 g, 13.5 mmol) was added, and the mixture was heated to 50 °C for 3 h. After cooling, the mixture was poured into 200 mL of water and the toluene removed by distillation. Hydrochloric acid was added and the crude product filtered off. Extraction with boiling methanol gave a white solid residue: yield 1.78 g (77%); mp 346−349 °C; ^{1}H NMR ($CDCl_3$) δ 8.62 (br, 2H), 8.12 (br, 2H), 6.96 (3H), 6.92 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 1.9 Hz, 2H), 6.84 (2H), 6.71 (d, J = 7.8 Hz, 2H), 3.97 (2H), 3.78 (2H), 3.66 (4H), 2.14 (6H); MS(FD), *m/z* 452.2 (M^+, calcd 452.5). Anal. Calcd for $C_{30}H_{28}O_4 \cdot 0.5CH_3OH$: C, 78.18; H, 6.45. Found: C, 78.13; H, 6.43.

4,4′-Bis(bromomethyl)-6,6′-dimethyl-2,2′-methanediyldiphenol (6b). Gaseous HBr was bubbled through an ice-cooled suspension of **6a**[35] (15 g, 65.7 mmol) and paraformaldehyde (7 g, 0.233 mol) in 60 mL of acetic acid to obtain a clear, usually red solution. After 16 h at room temperature a grey solid was filtered off, washed with petroleum ether, and dried over KOH: yield 20 g (73.5%); mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.15 (d, J = 2.1 Hz, 2H), 7.02 (d, J = 1.8 Hz, 2H), 6.25 (br, 2H), 4.43 (4H), 3.87 (2H), 2.21 (6H); MS(EI), *m/z* 414 (M^+, calcd 414.4). Anal. Calcd for $C_{17}H_{18}Br_2O_2$: C, 49.30; H, 4.38. Found: C, 49.31; H, 4.50.

4,4′-Bis(bromomethyl)-6,6′-di-*tert*-butyl-2,2′-methanediyldiphenol (6d) was synthesized as described for **6b**, starting with **6c**[36] (20 g, 64 mmol). **6d:** yield 27.5 g (86%); mp 134 °C; ^{1}H NMR ($CDCl_3$) δ 7.18 (4H), 4.46 (4H), 3.89 (2H), 1.40 (18H).

6,6′-Dimethyl-4,4′-bis(3-bromo-4-hydroxy-5-*tert*-butylbenzyl)-2,2′-methanediyldiphenol (7a). A mixture of **6b** (6 g, 14.5 mmol), 2-bromo-6-*tert*-butylphenol (30 g, 0.131 mol), and $ZnCO_3$ (1.7 g, 3.1 mmol) was kept at 60 °C for 16 h. The mixture was taken into 100 mL of $CHCl_3$ and filtered, and the solvent was removed. The product was isolated by column chromatography as the second component. **7a:** yield 5.9 g (58%); ^{1}H NMR ($CDCl_3$) δ 7.07 (d, J = 2.0 Hz, 2H), 7.01 (d, J = 1.9 Hz, 2H), 6.91 (d , J = 1.9 Hz, 2H), 6.76 (d, J = 1.8 Hz, 2H), 6.00 (2H), 5.65 (2H), 3.85 (2H), 3.73 (4H), 2.17 (6H), 1.35 (18H); MS(FD), *m/z* 710.9 (M^+, calcd 710.5).

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4,4′-Bis(3-*tert*-butyl-4-hydroxybenzyl)-6,6′-dimethyl-2,2′-methanediyldiphenol (7b). Raney nickel (10 g) was added to a solution of **7a** (10 g, 14 mmol) and KOH (5 g, 87.8 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 absorption was completed. The catalyst was removed by filtration and washed with methanol, and the washings were combined with the filtrate. Acidification with dilute hydrochloric acid gave a red oil which was separated and recrystallized from petroleum ether to give a grey solid: yield 5.3 g (68%); mp 146−149 °C; ^{1}H NMR ($CDCl_3$) δ 7.04 (d, J = 2.0 Hz, 2H), 6.94 (d, J = 1.8 Hz, 2H), 6.79 (m, 4H), 6.53 (d, J = 8.0 Hz, 2H), 4.70 (br, 4H), 3.84 (2H), 3.77 (4H), 2.16 (6H), 1.39 (18H); MS(FD), *m*/*z* 552.8 (M^+, calcd 552.7). Anal. Calcd for $C_{37}H_{44}O_4$: C, 80.40; H, 8.02. Found: C, 79.86; H, 7.90.

4,4′-Bis(3-bromo-5-*tert*-butyl-4-hydroxybenzyl)-6,6′-di-*tert*-butyl-2,2′-methanediyldiphenol (7c). A mixture of **6d** (4 g, 8 mmol) and 2-bromo-6-*tert*-butylphenol (20 g, 87 mmol) was heated to 80 °C for 8 h. The excess of 2-bromo-6-*tert*-butylphenol was removed by steam distillation, and the remaining solid was recrystallized several times from petroleum ether: yield 4.6 g (72%); mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 7.14 (d, J = 2.0 Hz, 2H), 7.02 (d, J = 1.8 Hz, 2H), 6.95 (d, J = 1.9 Hz, 2H), 6.89 (d, J = 1.8 Hz, 2H), 5.82 (2H), 5.66 (2H), 3.86 (2H), 3.77 (4H), 1.358 (18H), 1.355 (18H).

6,6′-Di-*tert*-butyl-4,4′-bis(3-*tert*-butyl-4-hydroxybenzyl)-2,2′-methanediyldiphenol (7d) was synthesized as described for **7b**, starting with **7c** (4 g, 5 mmol). **7d:** yield 2.21 g (69%); mp 89 °C; ^{1}H NMR ($CDCl_3$) δ 7.1 (d, J = 2.1 Hz, 2H), 6.97 (d, J = 2.0 Hz, 2H), 6.90 (d, J = 1.8 Hz, 2H), 6.78−6.83 (dd, J = 7.9 Hz, J = 2.1 Hz, 4H), 6.56 (2H), 6.52 (2H), 3.85 (2H), 3.79 (4H), 1.38 (18H), 1.35 (18H).

4,4′-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)-6,6′-dimethyl-2,2′-methanediyldiphenol (7e). A mixture of **6b** (14 g, 33.8 mmol), 2,6-di-*tert*-butylphenol (46 g, 0.223 mol), and $ZnCO_3$ (4 g, 7.3 mmol) was heated to 60 °C for 16 h under argon. Petroleum ether (300 mL) was added, and the solution was filtered to remove inorganic materials. Silica (50 g) was added and the solvent evaporated. In a Soxhlet apparature first the excess of 2,6-di-*tert*-butylphenol was extracted with *n*-hexane and then the product with $CHCl_3$. A total of 15.5 g (69%) of **7e** was obtained as a yellow oil solidifying as a glassy foam when dried in vacuum. It was used without further purification.

6,6′-Dimethyl-4,4′-bis(4-hydroxybenzyl)-2,2′-methanediyldiphenol (7f). A mixture of $AlCl_3$ (13 g, 98 mmol), phenol (9.6 g, 0.102 mol), and **7e** (15.5 g, 23 mmol) in 450 mL of toluene was stirred at 0 °C for 1 h under argon and then at room temperature for 9 h. The mixture was poured into 500 mL of HCl−water and extracted with diethyl ether. The organic phase was dried with $MgSO_4$ and the phenol removed with boiling petroleum ether (80−100 °C). After evaporation of the solvent the product was purified by flash chromatography with 4:1 $CHCl_3$/acetone (R_f = 0.34) and recrystallized from CH_2Cl_2: yield 3.0 g (50%); mp 168−169 °C; ^{1}H NMR (acetone-d_6) δ 8.15 (2H), 7.93 (2H), 7.03−6.94 (m, 6H), 6.77−6.72 (m, 6H), 3.86 (2H), 3.70 (4H), 2.17 (6H); MS(EI), *m*/*z* 440.3 (M^+, calcd 440.5).

6,6′-Bis(bromomethyl)-4-*tert*-butyl-4′-methyl-2,2′-methanediyldiphenol (8b) was synthesized as described for **6b**, starting with 4-*tert*-butyl-4′-methyl-2,2′-methanediyldiphenol (15 g, 55.5 mmol; obtained by dehalogenation of 6′-bromo-4-*tert*-butyl-4′-methyl-2,2′-methanediyldiphenol[37]). **8b:** yield 6.0 g (24%); mp 126−128 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 1.7 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 6.50 (br, 2H), 4.54 (2H), 4.52 (2H), 3.90 (2H), 2.22 (3H), 1.27 (9H); MS(EI), *m*/*z* 456 (M^+, calcd 456.2). Anal. Calcd for $C_{20}H_{24}O_2Br_2$: C, 52.65; H, 5.30. Found: C, 52.47; H, 5.39.

Double Calixarene 9a. $TiCl_4$ (4.93 g, 26 mmol) was added to a warm solution (60 °C) of **3g** (2 g, 4.4 mmol) and **8a**[9] (2.37 g, 4.4 mmol) in 500 mL of dioxane, and the mixture was refluxed for 5 days under argon. Additional portions of **8a** (1 g and 0.5 g) were added after 72 and 96 h, respectively. The solvent was removed, and the residue was taken into 200 mL of ethyl acetate and adsorbed onto 50 g of silica by evaporation of the solvent. Extraction with ethyl acetate (Soxhlet) gave a crude product which was purified by flash chromatography (4:1 $CHCl_3$/acetone) to give a brownish oil. Further purification by precipitation from $CHCl_3$ with petroleum ether and recrystallization from $CHCl_3$/petroleum ether gave 0.893 g (24%): mp >470 °C; ^{1}H NMR ($CDCl_3$) δ 10.32 (4H), 7.45 (d, J = 1.8 Hz, 2H), 7.41 (d, J = 1.6 Hz, 4H), 7.34 (2H), 7.30 (m, 6H), 6.97 (d, J = 1.8 Hz, 2H), 6.80 (d, J = 1.8 Hz, 4H), 6.45 (2H), 6.38 (d, J = 1.8 Hz, 2H), 4.38 (d, J = 14.8 Hz, 1H), 4.30 (d, J = 14.1 Hz, 2H), 4.11 (d, J = 13.8 Hz, 1H), 4.07 (d, J = 13.9 Hz, 1H), 3.75 (4H), 3.67 (d, J = 14.2 Hz, 1H), 3.58 (d, J = 14.0 Hz, 2H), 3.45 (d, J = 14.0 Hz, 1H), 3.20 (d, J = 13.9 Hz, 1H), 2.20 (6H); MS(FD), *m*/*z* 828.6 (M^+, calcd 828.9). Anal. Calcd for $C_{56}H_{48}O_6$: C, 82.33; H, 5.92. Found: C, 70.39; H, 5.58.

Double Calixarene 9b. A mixture of **3g** (2 g, 4.4 mmol) and **8b** (2 g, 4.4 mmol) was heated in 500 mL of dioxane to 50 °C. $TiCl_4$ (4.93 g, 26 mmol) was added and the mixture refluxed. After 3 days an additional quantity of **8b** (1 g, 2.2 mmol) was added and the mixture refluxed for an additional 2 days. The solvent was then removed and the remaining oil adsorbed onto 50 g of silica and extracted with ethyl acetate as described above. The extract was purified by flash chromatography with 27:1 $CHCl_3$/acetone and the product finally recrystallized from $CHCl_3$/acetone: yield 772 mg (24%); mp >300 °C; ^{1}H NMR ($CDCl_3$) δ 10.24 (4H), 7.07 (d, J = 2.3 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 1.8 Hz), 6.83 (2H), 6.81 (2H), 6.77 (1H), 6.44 + 6.43 (3H), 6.34 (d, J = 1.7 Hz, 1H), 6.32 (d, J = 1.7 Hz, 1H), 4.22 (d, J = 13.8 Hz, 1H), 4.21 (d, J = 13.9 Hz, 1H), 4.19 (d, J = 13.6 Hz, 1H), 4.12 (d, J = 13.9 Hz, 1H), 4.07 (d, J = 13.7 Hz, 1H), 3.76 (2H), 3.75 (d, J = 13.7 Hz, 1H), 3.69 (d, J = 13.7 Hz, 1H), 3.49 (d, J = 14.5 Hz, 1H), 3.47 (d, J = 14.0 Hz, 1H), 3.45 (d, J = 14.3 Hz, 1H), 3.43 (d, J = 13.9 Hz, 1H), 3.16 (d, J = 13.8 Hz, 1H), 2.22 (3H), 2.19 (3H), 2.12 (3H), 1.24 (9H); MS(FD), *m*/*z* 746.8 (M^+, calcd 746.9).

Double Calixarene 9c and Triple Calixarene 10a. $TiCl_4$ (4 g, 21 mmol) was added to a solution of **3f** (1.5 g, 3.5 mmol) and **8a** (1.9 g, 3.5 mmol) in 500 mL of dioxane at 60 °C. The mixture was then refluxed for 2 weeks. During this time two additional portions of **8a** (0.8 g, 1.47 mmol each) were added. The solvent was removed and the residue dissolved in 200 mL of ethyl acetate and adsorbed on 50 g of silica by removing the solvent again. Extraction with ethyl acetate (Soxhlet) gave a crude product which was further purified by flash chromatography (4:1 chloroform/acetone). The triple calixarene **10a** (R_f = 0.98) was eluted first followed by fractions containing the double calixarene **9c** (R_f = 0.85). Further purification by flash chromatography (27:1 $CHCl_3$/acetone) gave pure **9c** (R_f = 0.63) and **10a** (R_f = 0.98), which were finally recrystallized from $CHCl_3$/methanol: yield **9c**, 224 mg (8%), mp >470 °C; **10a**, 8 mg (0.2%), mp >470 °C.

When a larger amount of **8a** (1.9 g + 3 × 1.0 g) was used, **10a** was the main product: yield **9c**, 16 mg (0.4%); **10a**, 288 mg (7%).

9c: ^{1}H NMR ($CDCl_3$) δ 10.33 (4H), 7.45 (dd, J = 7.1 Hz, J = 1.3 Hz, 4H), 7.38 (d, J = 6.5 Hz, 4H), 7.31 (d, J = 2.0 Hz, 2H), 7.30 (d, J = 2.2 Hz, 2H), 7.28 (m, 2H), 6.99 (d, J = 7 Hz, 2H), 6.95 (d, J = 1.9 Hz, 2H), 6.92 (dd, J = 8.1 Hz, J = 2.0 Hz, 2H), 6.80 (d, J = 8.1 Hz, 2H), 6.28 (d, J = 1.6 Hz, 2H), 4.62 (d, J = 14.0 Hz, 1H), 4.31 (d, J = 14.0 Hz, 2H), 4.13 (d, J = 14.4 Hz, 1H), 4.10 (d, J = 14.3 Hz, 1H), 3.81 (4H), 3.69 (d, J = 14.1 Hz, 1H), 3.59 (d, J = 14.0 Hz, 2H), 3.43 (d, J = 14.0 Hz, 1H), 3.17 (d, J = 13.9 Hz, 1H); MS(FD), *m*/*z* 800.2 (M^+, calcd 800.3). Anal. Calcd for $C_{55}H_{44}O_6$: C, 82.48; H, 5.30. Found: C, 75.41; H, 5.36.

10a: ^{1}H NMR ($CDCl_3$) δ 10.45 (8H), 7.42 (dd, J = 1.3 Hz, J = 7.8 Hz, 8H), 7.34 (t, J = 7.2 Hz, 8H), 7.33 (d, J = 2.3 Hz, 4H), 7.30 (d, J = 2.3 Hz, 4H), 7.28−7.26 (m, 4H), 6.94 (d, J = 1.9 Hz, 4H), 6.58 (d, J = 1.7 Hz, 4H), 4.41 (d, J = 14.0 Hz, 2H), 4.30 (d, J = 13.9 Hz, 4H), 4.03 (d, J = 13.8 Hz, 2H), 3.78 (4H), 3.70 (d, J = 13.7 Hz, 2H), 3.58 (d, J = 14.1 Hz, 4H), 3.25

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(d, J = 13.8 Hz, 2H); MS(FD), m/z 1178.1 (M^+, calcd 1177.3). Anal. Calcd for $C_{82}H_{64}O_8$: C, 83.65; H, 5.48. Found: C, 73.39; H, 5.49.

Double Calixarene 9d and Triple Calixarene 10b. $TiCl_4$ (4 g, 21 mmol) was added to a solution of **3f** (2 g, 4.7 mmol) and **8b** (3.84 g, 8 mmol) in 500 mL of dioxane at 70 °C and the mixture refluxed for 7 days under an argon atmosphere. After 2 days **8b** (1 g) was added again and after an additional 3 days another portion of 0.5 g was added. The solvent was removed, and the residue was taken up in 200 mL of ethyl acetate and adsorbed on 50 g of silica as described above. Extraction with ethyl acetate (Soxhlet) gave a black oil which was purified first by flash chromatography with 4:1 $CHCl_3$/acetone followed by flash chromatography of the crude fractions using 27:1 $CHCl_3$/acetone to give the pure products. **9d**: 0.227 g (8.2%), R_f = 0.47, mp 347−349 °C. **10b**: 0.504 g (10%), R_f = 0.93, mp >470 °C. **9d**: ^{1}H NMR ($CDCl_3$) δ 10.26 (4H), 7.26 (2H), 7.09 (d, J = 2.3 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 1.9 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 1.9 Hz, 2H), 6.88 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 1.2 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.28 (dd, J = 8.4 Hz, J = 1.5 Hz, 2H), 4.24 (d, J = 13.5 Hz, 1H), 4.22 (d, J = 13.9 Hz, 1H), 4.21 (d, J = 12.5 Hz, 1H), 4.14 (d, J = 14.0 Hz, 1H), 4.07 (d, J = 13.8 Hz, 1H), 3.82 (d, J = 16.1 Hz, 1H), 3.81 (2H), 3.74 (d, J = 16.6 Hz, 1H), 3.48 (d, J = 13.9 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 3.44 (d, J = 13.5 Hz, 1H), 3.15 (d, J = 13.9 Hz, 1H), 2.14 (3H), 1.25 (9H); MS(FD), m/z 718.5 (M^+, calcd 718.8). Anal. Calcd for $C_{48}H_{46}O_6$: C, 80.20; H, 6.45. Found: C, 74.92; H, 7.39.

10b: ^{1}H NMR ($CDCl_3$) δ 10.45 (8H), 7.12−7.09 (m, 4H), 6.91 (d, J = 1.9 Hz, 2H), 6.88 (d, J = 1.8 Hz, 2H), 6.86−6.84 (m, 4H), 6.61 (d, J = 1.8 Hz, 1H), 6.60 (d, J = 1.8 Hz, 1H), 6.55 (d, J = 1.8 Hz, 1H), 6.54 (d, J = 1.7 Hz, 1H), 4.27 (d, J = 13.8 Hz, 2H), 4.25 (d, J = 13.4 Hz, 1H), 4.24 (d, J = 13.8 Hz, 1H), 4.23 (d, J = 13.9 Hz, 1H), 4.21 (d, J = 13.4 Hz, 1H), 4.07 (d, J = 13.8 Hz, 2H), 3.78 (d, J = 13.9 Hz, 2H), 3.77 (1H), 3.74 (1H), 3.50 (d, J = 14.0 Hz, 1H), 3.49 (d, J = 14.0 Hz, 3H), 3.45 (d, J = 14.0 Hz, 1H), 3.44 (d, J = 14.0 Hz, 1H), 3.27 (d, J = 13.9 Hz, 2H), 2.13 (3H) 2.12 (3H), 1.244 (9H), 1.238 (9H); ^{1}H NMR (pyridine-d_5) δ 8.55 (8H), 7.46 (2H), 7.45 (2H), 7.15 (2H), 7.11 (2H), 7.00 (1H), 6.87 (1H), 6.70 (1H), 6.60 (1H), 6.49 (1H) 6.40 (1H), 6.08 (1H), 5.93 (1H), 6.43 (d, J = 16.6 Hz, 2H), 4.48 (d, J = 16.6 Hz, 4H), 4.26 (d, J = 13.8 Hz, 2H), 3.76 (d, J = 13.3 Hz, 2H), 3.70 (d, J = 13 Hz, 2H), 3.61 (2H), 3.51 (d, J = 14.2 Hz, 2H), 3.48 (d, J = 13.3 Hz, 2H), 3.07 (d, J = 13.5 Hz, 1H), 3.04 (d, J = 13.4 Hz, 1H), 1.91 (3H) 1.79 (3H), 1.31 (9H), 1.20 (9H); MS(FD), m/z 1013.2 (M^+, calcd 1013.2). Anal. Calcd for $C_{68}H_{68}O_8$: C, 80.60; H, 6.76. Found: C, 71.10; H, 6.28.

Triple Calixarene 10c. A mixture of **3f** (2 g, 4.7 mmol) and **8c** (2.34 g, 4.7 mmol) in 500 mL of dioxane was heated to 50 °C, $TiCl_4$ (4 g, 21 mmol) was added, and the mixture was heated to reflux. The next day additional **8c** (1 g, 2 mmol) was added and the mixture refluxed for 6 days. The solvent was removed, and the remaining oil was dissolved in 200 mL of ethyl acetate, adsorbed onto 50 g of silica, and extracted with ethyl acetate to give a dark red oil which was purified by flash chromatography (27:1 $CHCl_3$/acetone) and finally by recrystallization from $CHCl_3$/methanol. **10c:** yield 331 mg (6%); mp 411−414 °C; ^{1}H NMR ($CDCl_3$) δ 10.55 (8H), 7.11 (d, J = 2.4 Hz, 4H), 7.07 (d, J = 2.6 Hz, 4H), 6.90 (d, J = 1.8 Hz, 4H), 6.58 (d, J = 1.9 Hz, 4H), 4.31 (d, J = 13.6 Hz, 2H), 4.25 (d, J = 13.8 Hz, 4H), 4.08 (d, J = 13.8 Hz, 2H), 3.78 (4H), 3.54 (d, J = 13.9 Hz, 2H), 3.50 (d, J = 14.0 Hz, 4H), 3.26 (d, J = 13.9 Hz, 2H), 1.22 (36H); MS(FD), m/z 1098.4 (M^+, calcd 1097.4). Anal. Calcd for $C_{74}H_{80}O_8$: C, 80.99; H, 6.85. Found: C, 73.20; H, 7.02.

16,24,28,36,41,42-Hexahydroxy-23,29-dimethyl-5,11-diphenylcalix[6]arene (11a). 7f (3.28 g, 7.5 mmol) and **8a** (4 g, 7.5 mmol) were dissolved in 500 mL of dioxane under argon. At a temperature of 50 °C $TiCl_4$ (6 g, 31.5 mmol) was added and the mixture refluxed for 48 h. The solvent was removed and the remainder adsorbed onto 50 g of silica as described above. The product was extracted with ethyl acetate, purified by flash chromatography (4:1 $CHCl_3$/acetone), and recrystallized from $CHCl_3$/petroleum ether: yield 810 mg (13%); mp 318−320 °C; ^{1}H NMR ($CDCl_3$) δ 9.86 (2H), 8.38 (2H), 7.47−7.45 (m, 4H), 7.41−7.35 (m, 8H), 7.31−7.26 (m, 2H), 7.05 (d, J = 2.0 Hz, 2H), 6.83 (d, J = 1.5 Hz, 2H), 6.78 (d, J = 8.3 Hz, 2H), 6.67 (d, J = 1.8 Hz, 2H), 6.43 (2H), 6.34 (dd , J = 8.4 Hz, J = 1.70 Hz, 2H), 4.00 (2H), 3.87 (4H), 3.73 (6H), 2.20 (6H); MS(FD), m/z 816.7 (M^+, calcd 816.9).

16,24,28,36,41,42-Hexakis[(ethoxycarbonyl)methoxy]-23,29-dimethyl-5,11-diphenylcalix[6]arene. A mixture of **11a** (300 mg, 0.37 mmol), ethyl bromoacetate (736 mg, 4.4 mol), K_2CO_3 (617 mg, 4.4 mol), and 24 mL of acetonitrile was refluxed for 16 h. The solvent was removed and the remainder dissolved in 50 mL of CH_2Cl_2 and three times washed with water. Removal of the solvent and recrystallization from hot ethanol gave a colorless solid: yield 440 mg (90%); mp 78−80 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 2H), 7.28 −7.19 (m, 10H), 7.09 (d, J = 2.2 Hz, 2H), 6.79 (dd, J = 8.3 Hz, J = 1.9 Hz, 2H), 6.73 (d, J = 1.6 Hz, 2H), 6.59 (d, J = 8,3 Hz, 2H), 6.54 (d, J = 1.1 Hz, 4H), 4.57 (4H), 4.48 (4H), 4.28−4.10 (m, 22H), 3.87 (2H), 3.34 (4H), 2.11 (6H), 1.27 (t, J = 7.2 Hz, 6H), 1.22 (t, J = 7.5 Hz, 6H), 1.18 (t, J = 7.5 Hz, 6H); MS(FD), m/z 1332.8 (M^+, calcd 1333.5).

5,23-Di-*tert*-butyl-4,12,16,24,36,37-hexahydroxy-11,17-dimethyl-29,35-diphenylcalix[6]arene (11b). A mixture of **7b** (2.76 g, 5 mmol) and **8a** (3.69 g, 6.9 mmol) in 500 mL of dioxane was heated to 40 °C under argon. $TiCl_4$ (2.31 mL, 21 mmol) was added and the mixture then refluxed for 3 days. **8a** (1 g) was added and the reaction continued for 24 h. The solvent was removed and the remainder adsorbed onto 50 g of silica. The product was extracted with ethyl acetate and then purified by flash chromatography (27:1 $CHCl_3$/acetone). Final recrystallization from $CHCl_3$/petroleum ether gave 331 mg (7.2%): mp 310−312 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (br, 2H), 7.42−7.32 (m, 10H), 7.12 (d, J = 2.0 Hz, 2H), 6.92 (d, J = 1.8 Hz, 2H), 6.87 (d, J = 1.5 Hz, 2H), 6.79 (d, J = 1.7 Hz, 2H), 6.72 (d, J = 1.4 Hz, 2H), 6.00 (br, 2H), 5.25 (br, 2H), 4.02 (2H), 3.93 (4H), 3.76 (2H), 3.74 (4H), 2.13(6H), 1.39 (18H); MS(FD), m/z 928.7 (M^+, calcd 929.2).

5,11,17,23-Tetra-*tert*-butyl-37,38,39,40,41,42-hexahydroxy-29,35-diphenylcalix[6]arene (12). A solution of 6,6′-bis(5-*tert*-butyl-2-hydroxybenzyl)-4,4′-di-*tert*-butyl-2,2′-methanediyldiphenol[38] (3.18 g, 5 mmol) and **8a** (2.69 g, 5 mmol) in 500 mL of dioxane was heated to 60 °C under an argon atmosphere. $TiCl_4$ (2.31 mL, 21 mmol) was added and the reaction refluxed for 4 days. **8a** (1 g) was added again and the reaction continued for 3 days. The solvent was removed and the remainder adsorbed onto 50 g of silica. The product was extracted with ethyl acetate, purified by flash chromatography with $CHCl_3$ (R_f = 0.96), and recrystallized from $CHCl_3$/petroleum ether: yield 120 mg (3%); mp 340−343 °C; ^{1}H NMR ($CDCl_3$) δ 10.64 (br, 2H), 10.52 (br, 4H), 7.48 (d, J = 7.5 Hz, 4H), 7.47 (t, J = 7.5 Hz, 6H), 7.36 (2H), 7.28 (t, J = 7.3 Hz, 2H), 7.16 (8H), 4,1 (br, 12H), 1.259 (18H), 1.255 (18H); MS(FD), m/z 1012.8 (M^+, calcd 1013.3).

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Supporting Information Available: ^{13}C NMR spectral data of 23 compounds (5 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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