Pergamon

Tetrahedron, Vol. 53, No. 38, pp. 13037-13052, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00827-2

Stepwise Synthesis and Structural Characterization of Calix[4]- and Calix[5]arenes Bearing a Functionalized Arm on the Methylene Bridge.

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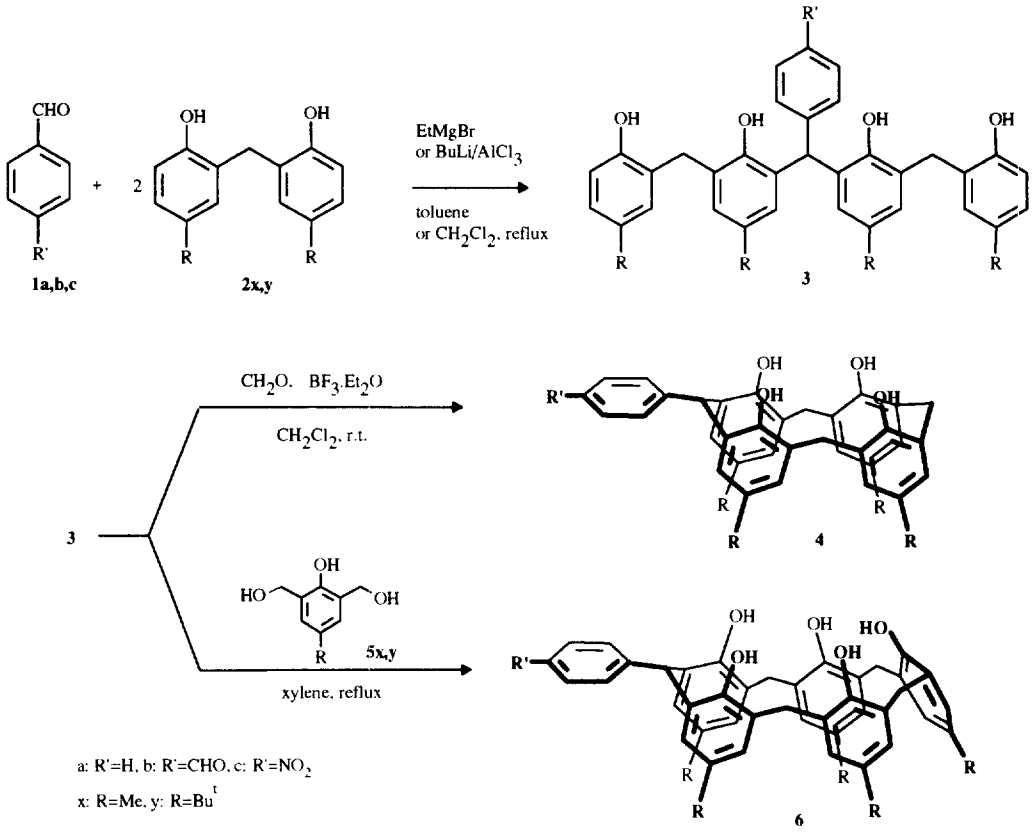
Abstract: Calix[4]arenes **4** and calix[5]arenes **6** functionalized at the methylene bridge are synthesized starting from benzaldehydes **1**, diphenylmethanes **2** and formaldehyde or 2,6-dihydroxymethylphenols **5** respectively. ^{1}H NMR analyses of macrocycles **4** and **6** as well as crystal structure of the calix[5]arene **6by** are reported. © 1997 Elsevier Science Ltd.

Introduction

Calixarenes are well-known cyclic oligomers derived from phenols and formaldehyde which have found extensive use in the complexation of ions[1] as well as neutral molecules.[2] These compounds can, in principle, be chemically modified at the three reacting sites: the hydroxy groups, the aromatic rings and the methylene bridges.[3] While the functionalization of the macrocycles at both rims has been extensively studied and described in a series of papers and books,[1a,b] the introduction of new functionalized arms at the methylene bridges has been only recently investigated by V. Böhmer et al.[4]

In conjunction with our ongoing program aimed at the construction of new classes of phenolic macrocycles, we have developed a synthetic strategy where easily accessible 2,2'-dihydroxytriphenylmethanes were utilized as building blocks to synthesize calix[4]arenes bearing two aryl groups on the diametrical methylene bridges.[5] In the present paper we show the synthesis and structural characterization of calix[4]- and calix[5]arenes carrying one aryl substituent on a methylene bridge (Scheme).



Scheme

Results and Discussion

The starting compounds **2x,y** utilized in the present study were synthesized in 80-85% yield by condensation of convenient phenols (2-*tert*-butyl-4-methylphenol or 2,4-di-*tert*-butylphenol) and formaldehyde[6] followed by $AlCl_3$-promoted de-*tert*-butylation.[7] Compounds **3** were successively prepared starting from **2** and the selected aromatic aldehyde **1** following the procedure previously reported for the general synthesis of 2,2'-dihydroxytriphenylmethanes.[8] A mixture of the bis-bromomagnesium derivative of **2x** and benzaldehyde **1a** in dry toluene (molar ratio 2:1) was heated at reflux for 15 hours affording **3ax** in 60% yield after normal work up. A modified procedure was utilized to prepare the other compounds **3**. Thus, solid $AlCl_3$ was added to a slurry of dilithium salt of **2** in dry toluene followed by terephthalaldehyde **1b** or *para*-nitrobenzaldehyde **1c** (molar ratio 2:1). After heating at reflux for 8 hours, compounds **3bx**, **3by** and **3cy** were obtained in 50,[9] 40 and 32 % yields, respectively.

Next, we studied the possibility of utilizing compounds **3** as linear synthons for the preparation of calixarenes **4** and **6** by reaction with formaldehyde or 2,6-dihydroxymethyl-4-alkylphenol **5x,y**,[10] respectively.

Compound **3ax** was utilized as the model reagent to study the cyclization process. After some experiments with different Lewis acids and solvents, compound **4ax** was obtained in 25% yield by reacting **3ax** with paraformaldehyde at room temperature in CH_2Cl_2 solution in the presence of $BF_3{\cdot}Et_2O$. Moreover, refluxing an equimolecular amount of **3ax** and **5x** in dry xylene without any catalyst, **6ax** was obtained in 28% yield after chromatographic separation. Upon applying these procedures to **3bx**, **3by** and **3cy**, different macrocycles **4** and **6** were accessible in moderate yields (Table).

Table. Synthesis of various calix[4]- and calix[5]arenes.

Entry	R'	R	Compound	Yield (%)*
1	H	Me	**4ax**	25
2	CHO	Me	**4bx**	18
3	CHO	Bu^t	**4by**	8
4	H	Me	**6ax**	28
5	CHO	Me	**6bx**	24
6	CHO	Bu^t	**6by**	19
7	NO_2	Bu^t	**6cy**	18

* Yields are referred to the steps **3**→**4** or **3**→**6**.

All attempts to synthesize compound **4cy** were unsuccessful, being the calix[8]arene **7cy** obtained as the sole cyclic compound (32% yield). Calix[8]arene **7by** was isolated as by-product (4% yield) from the reaction of **3by** and formaldehyde (Fig. 1).

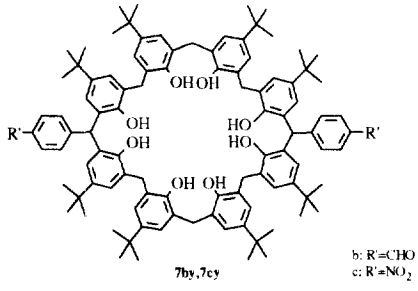


Figure 1

^{1}H NMR studies were undertaken in order to investigate the conformational mobility of calix[4]- and calix[5]arenes synthesized. The presence of the substituent at the methylene bridge reduces the macrocycle symmetry, affecting the signal multiplicity and the number of the distinguishable conformers. The spectra of

calix[4]arenes **4** recorded at low temperature show the presence of two diastereomeric cone-conformations (Fig. 2).

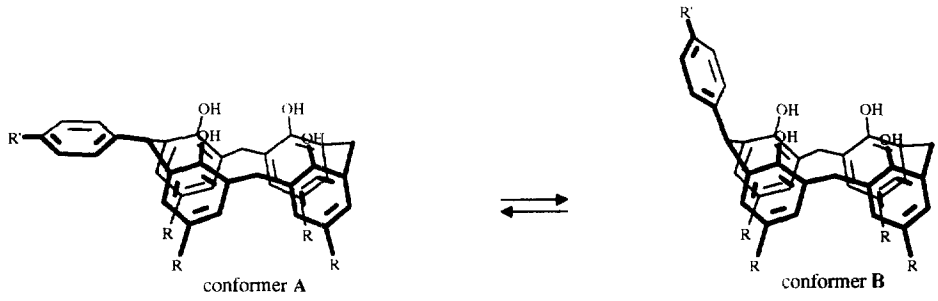


Figure 2. Conformational equilibrium for calix[4]arenes **4**.

The hydroxylic proton signals are at low field, at δ>9 ppm, in spectra recorded at different temperatures (from 218 K to 333 K), indicating a cone conformation, the only one with isodromic hydrogen bonding that accounts for such a deshielding of the hydroxylic protons. Moreover, the spectrum of compound **4ax** recorded at 263 K ($CDCl_3$, 400 MHz) shows, for example, the expected doublets for geminal protons of methylene bridges. In particular the axial hydrogens give two doublets at 4.22 and 4.21 ppm (in a 2 : 1 ratio) and two doublets at 4.16 and 4.12 ppm (in a 2 : 1 ratio) for the methylene bridges near and opposite to the methine bridge of conformers **A** and **B**, respectively. The corresponding equatorial hydrogens give doublets overlapping around 3.4 ppm. The integration of the methine singlets at 6.10 and 5.29 ppm indicates an **A** : **B** ratio of 1.5 : 1. The barriers to conformational cone to cone ring interconversion determined by variable temperature experiments in $CDCl_3$[11] are 14.5 Kcal/mol for **4ax** and for **4bx** (coalescence temperatures of methine singlets) and 14.9 Kcal/mol for **4by** (coalescence temperature of formyl singlets) as expected for typical calix[4]arenes.[12] It is interesting to note the non-equivalence of geminal protons at high temperature, in

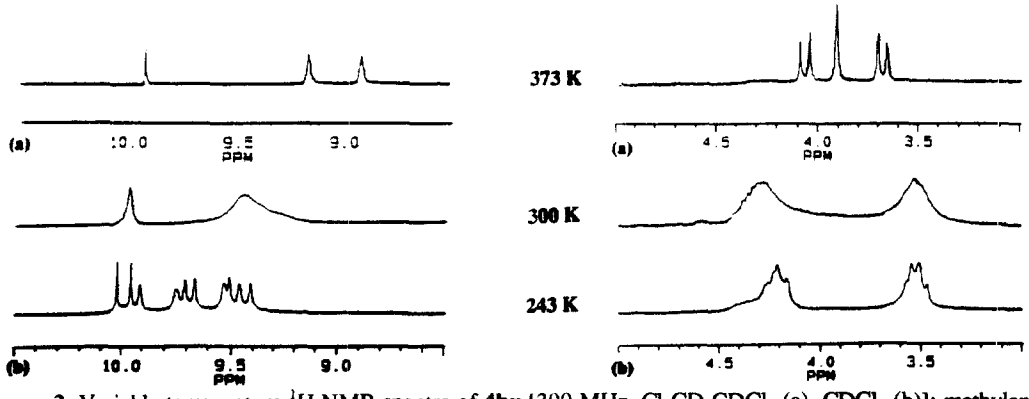


Figure 3. Variable temperature ^1H NMR spectra of **4by** [300 MHz, Cl_2CD-$CDCl_2$ (a), $CDCl_3$ (b)]: methylene region (on the right) and hydroxylic region (on the left).

fast exchange conditions, as previously reported for quite similar compounds.[4b,c] As reported in Fig. 3 (right), the spectrum of compound **4by** at 373 K shows well resolved signals, revealing the diastereoisomeric relationship, for the geminal hydrogens of the methylene group near the methine one (two doublets at δ 4.07 and 3.68 ppm, J = 13.6 Hz), whereas the methylene bridge in the opposite position appears as a singlet at δ 3.91 ppm, probably due to the long distance from the aryl substituent.[13] It is interesting to observe the dependence of the **4by** OH signal on the temperature (Fig. 3, left). At fast interconversion (373 K in Cl_2CD-$CDCl_2$) two peaks are present at δ = 8.92 and 9.16 ppm, attributable to the hydroxy groups near and far from the alkylidene bridge. As expected, on lowering the temperature the signal number is increased, but surprisingly eight peaks are evident at 243 K (δ 9.5-10.0 ppm in $CDCl_3$). The presence of one peak for each hydroxy group of the two isomers allows us to suppose a very strong isodromic hydrogen bond that results in the non-equivalence of the hydroxy groups near as well as far from the substituted bridge. In the spectra of compounds **4** recorded at low temperature, the methine bridge singlets are respectively at δ 6.10 and 5.29 (**4ax**), 6.13 and 5.30 (**4bx**), 6.23 and 5.51 ppm (**4by**) for the diastereomeric conformers **A** and **B**. The assignment of the methine signals of calixarene **4by** was made on the basis of a 2D-NOESY experiment carried out in $CDCl_3$ at 218 K.[14] The correlation between the singlet at δ 6.23 ppm and the OH signals at δ 9.48 ppm indicates that the methine proton occupies an axial position (isomer **A** in Fig. 2). Moreover the correlation between the singlet at δ 5.51 ppm and the phenolic aromatic hydrogens confirms the equatorial position of the methine proton in isomer **B**. The absence of a cross-peak between the methine signals due to chemical exchange ensures that at this temperature the interconversion is blocked.

The calix[5]arenes **6** synthesized showed a conformational dependence on the temperature similar to that described above for calix[4]arenes. At 380 K ($Cl_2CDCDCl_2$), the fast diastereomeric cone interconversion of **6by**, for example, gives the expected pattern of signals due to the two different methylene bridges: two doublets at δ 4.07 and 4.01 ppm for axial hydrogens and two doublets at δ 3.52 and 3.47 ppm for equatorial protons (Fig. 4). Decreasing the temperature, the methylene region gives again the same pattern at 200 K in CD_2Cl_2, showing a typical behaviour due to "exchange with a hidden partner";[15] a careful examination of the spectrum revealed the presence of signals due to the diastereomeric conformations **A** and **B** of calixarene **6by** (Fig. 5).

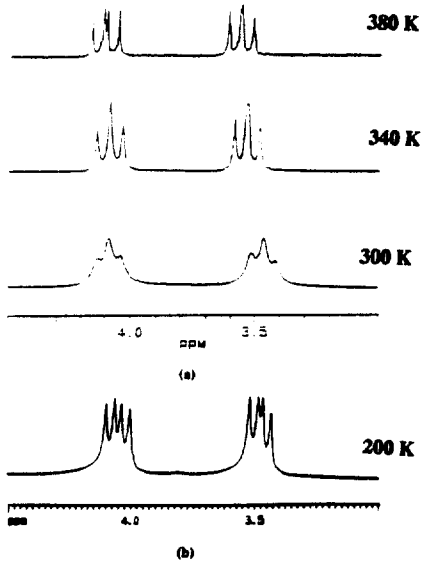


Figure 4. Variable temperature ^1H NMR spectra of **6by**, methylene region: a) 300 MHz, Cl_2CD-$CDCl_2$ and b) 400 MHz, CD_2Cl_2.

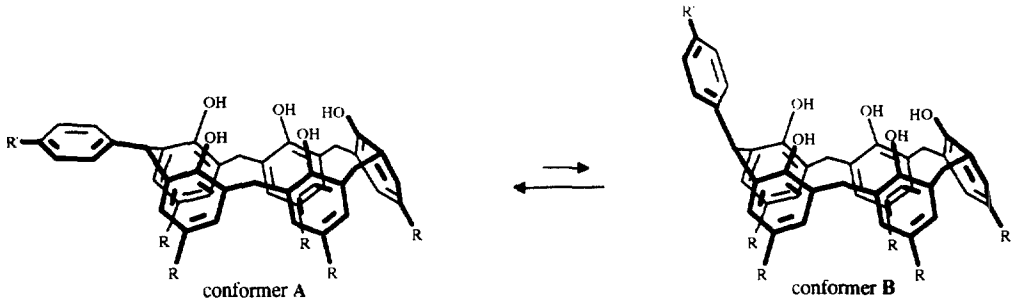


Figure 5. Conformational equilibrium for calix[5]arenes **6**.

It was quite surprising to observe that one isomer is strongly preferred (24 : 1 ratio for **6by** and 32 : 1 ratio for **6cy**). Indeed it was possible to see small signals belonging to the minor isomer, at δ 9.94 ppm for the formylic hydrogen, at δ 7.79 ppm for the more deshielded aromatic protons of the *para*-system and at δ 5.48 ppm for the methine bridge, partially overlapped with the solvent (Fig. 6a). The 2D-NOESY spectrum of **6by** recorded in CD_2Cl_2 at 200 K (Fig. 6b) was evidence that in the major isomer the aryl bridge substituent occupies the equatorial position. Indeed the cross peaks between the low field methine singlet at δ 6.09 ppm (**A**), and the hydroxy signals indicate an axial position for the methine hydrogen. Further the small singlet at δ 5.48 ppm (**B**) correlates with aromatic signal, as expected for equatorial methine.

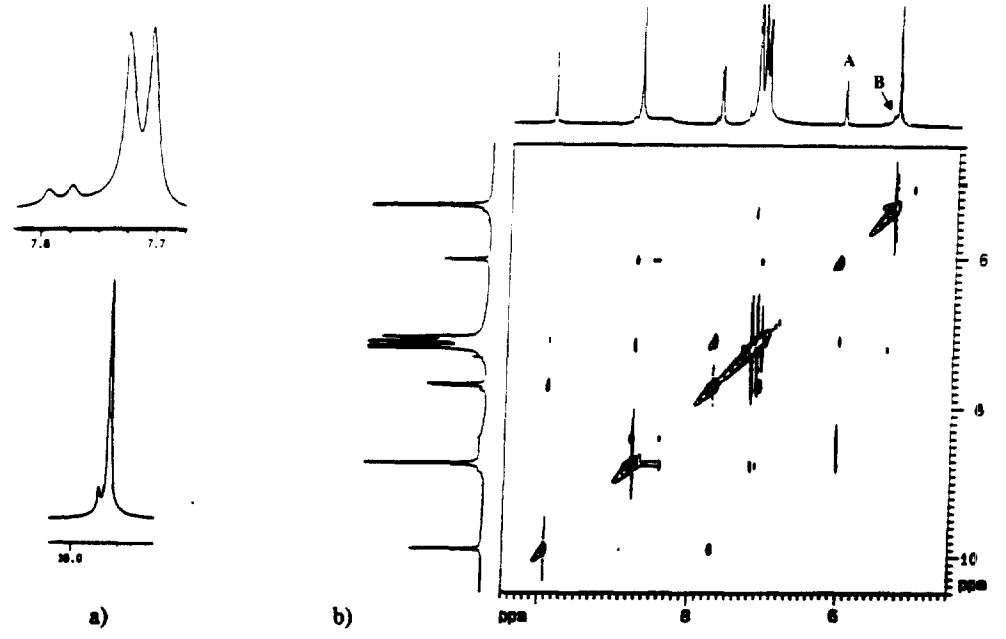


Figure 6. ^1H NMR (400 MHz, CD_2Cl_2) of **6by** at 200 K: a) parts of the 1D spectrum; b) 2D-NOESY map.

The study of the calix[5]arene **6cy** confirmed the dramatic preference for the isomer **A** bearing the aromatic substituent in equatorial position. A 2D-NOESY experiment in CD_2Cl_2 at 200 K revealed that the small signals at δ 5.49 and 8.22 ppm are due to the minor isomer **B**. It is noteworthy that the aromatic residue displays a distinct preference for the equatorial position on varying the macrocycle dimension. In calix[4]arenes the two diastereomeric cone conformations are about equally populated, in agreement with the calculated small energy differences reported in the literature.[4c] The unusual strong preference of the aromatic bridge substituent in occupying the equatorial position in calix[5]arenes is not easily explained and deserves further investigation. It is interesting to note that also in the solid state the calix[5]arene **6cy** adopts a cone conformation with the aryl group in the equatorial position (Fig.7). From variable temperature measurements we determined[16] the free energy barriers $\Delta G^{\neq}_{eq\rightarrow ax}$=13.5 Kcal/mol and $\Delta G^{\neq}_{ax\rightarrow eq}$ =12.2 Kcal/mol at 233 K for **6by** and $\Delta G^{\neq}_{eq\rightarrow ax}$ =13.2 Kcal/mol and $\Delta G^{\neq}_{ax\rightarrow eq}$ =12.0 Kcal/mol at 242 K for **6cy** (coalescence temperatures of the more deshielded *para*-system protons in CD_2Cl_2). Comparing the energy barriers for conformational cone to cone ring inversion of calix[4]- and calix[5]arenes we observe that, according to the usual intuition, the largest cycle is more mobile.

X-Ray Structural Analysis

Compound **6cy**, obtained as colourless crystals from a 1,1,2,2-tetrachloroethane-toluene solution, adopts an almost regular cone conformation in the solid state (Fig. 7), with the hydroxy O atoms almost coplanar (max dev. 0.062(7) Å for O1E). The hydrogen bonds that the five proximal hydroxy O atoms exchange show some variability in their strength (O1A...O1B 2.682(8), O1B...O1C 2.754(8), O1C...O1D 2.889(8), O1D...O1E 2.784(9), O1E...O1A 2.869(7) Å). The hydrophobic cavity is large enough to enclose a toluene molecule that is oriented parallel to the plane defined by the five hydroxy O atoms (23.6(6)°). The guest is found disordered in at least two positions with the methyl group not clearly located. The *para*-nitrophenyl substituent assumes the equatorial position and the steric hindrance gives rise to a narrowing of the methine bridge bond angle (C2E-C11E-C6A 110.0(6)°) which is substantially lower than those of the methylene ones (range 115.5(8)-120.0(7)°). A toluene and a 1,1,2,2-tetrachloroethane molecule are disordered outside the calix[5]arene cavity occupying the same site with an occupancy factor of 0.8 and 0.2, respectively.

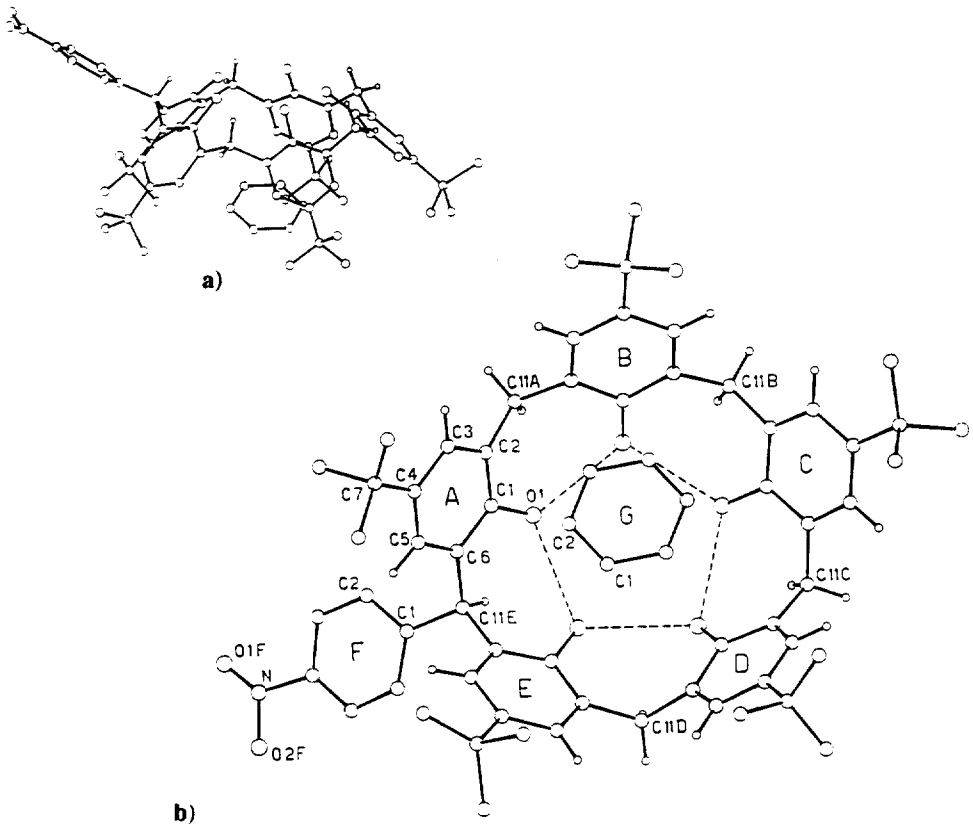


Figure 7. Molecular structure (seen from two different directions) of **6by** determined by single crystal X-ray analysis: a) perspective view, b) projection on the plane of the five hydroxy O atoms with labeling scheme. For clarity the atoms are drawn with arbitrary radii.

Experimental

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Nicolet PC5 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AMX400 spectrometer at 400 MHz and on a Bruker AC300 at 300 MHz. Chemical shifts are expressed in ppm relative to TMS as internal standard. Mass spectra were obtained on a Finnigan SSQ 710 instrument in CI mode at 70 eV. TLC analyses were performed on Merck 60 PF_{254} silica gel plates developed with hexane-ethyl acetate mixtures. CH_2Cl_2 was dried on 4Å molecular sieves. All the reagents were of commercial quality from freshly opened containers. Attempts to obtain satisfactory elemental analyses of calixarenes synthesized were unsuccessful, nevertheless we believe that the identity of compounds reported is correct.[17]

Synthesis of 2',2''-dihydroxy-3',3''-bis-(2'''-hydroxy-5'''-methylbenzyl)-5',5''-dimethyltriphenylmethane (**3ax**). *General Procedure.* A solution of ethyl bromide (3.82 g, 0.035 mol) in dry Et_2O (20 ml) was added dropwise to magnesium (0.72 g, 0.03 mol) in Et_2O (30 ml). When all magnesium had dissolved, a solution of 2,2'-dihydroxy-5,5'-dimethyldiphenylmethane **2x** (3.42 g, 0.015 mol) in dry Et_2O (50 ml) was added. The mixture was stirred for 30 min, then the solvent was distilled off under reduced pressure. Successively, dry toluene (100 ml) and benzaldehyde **1a** (0.8 g, 0.008 mol) were added and the reaction was refluxed with stirring for 15 h. After cooling, the reaction was quenched with 10% aqueous HCl solution (100 ml), then extracted with CH_2Cl_2 (3 x 70 ml). The combined extracts were dried (Na_2SO_4), the solvents were distilled off, and the residue was purified by flash-chromatography utilizing a hexane-ethyl acetate mixture (80 : 20) as eluent to give a white solid powder, mp 122-125°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (6 H, s, 2 CH_3), 2.23 (6 H, s, 2 CH_3), 3.76 (2 H, d, J=14.2 Hz, 2 x ½ CH_2), 3.86 (2 H, d, J=14.2 Hz, 2 x ½ CH_2), 5.85 (1 H, s, CH), 6.69 (2 H, d, J=8.1 Hz, 2 H-3'''), 6.79 (2 H, d, J=1.7 Hz, H-4' and H-4'' or H-6' and H-6''), 6.86 (2 H, dd, J=8.1 and 1.6 Hz, 2 H-4'''), 6.94 (2 H, d, J=1.7 Hz, H-6' and H-6'' or H-4' and H-4''), 7.06 (2 H, d, J=1.6 Hz, 2 H-6'''), 7.1-7.3 (5 H, m, 5 H-Ph), 7.5 (2 H, br s, 2 OH), 8.2 (2 H, br s, 2 OH); IR (KBr) 3325 (OH) cm^{-1}; MS *m/e* 545 (M^++1, 30%), 544 (M^+, 85), 466 (75), 316 (100).

Synthesis of triphenylmethanes **3bx**, **3by** and **3cy**. *General Procedure.* To a solution of diphenylmethane **2x** or **2y** (0.03 mol) in dry Et_2O (50 ml), a solution of BuLi (37.5 ml, 0.06 mol) in Et_2O (30 ml) was added under nitrogen. The mixture was stirred for 30 min, then the solvent was distilled off. Successively, dry CH_2Cl_2 (170 ml) and $AlCl_3$ (4.02 g, 0.03 mol) were added and the reaction was refluxed for 20 min. After cooling to r.t. a solution of aldehyde **1b** or **1c** (0.015 mol) in dry CH_2Cl_2 (30 ml) was added. The reaction mixture was refluxed with stirring for 8 h. After cooling, the reaction was quenched with 10% aqueous HCl solution (200 ml), then extracted with CH_2Cl_2 (3 x 100 ml). The combined extracts were dried (Na_2SO_4), the solvent was distilled off, and the residue was purified by flash-chromatography utilizing CH_2Cl_2 as eluent.

2',2''-Dihydroxy-3',3'''-bis-(2'''-hydroxy-5'''-methylbenzyl)-5',5''-dimethyl-4-formyltriphenylmethane (**3bx**): white solid, mp 100-102°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (6 H, s, 2 CH_3), 2.23 (6 H, s, 2 CH_3), 3.79 (4 H, s, 2 CH_2), 5.94 (1 H, s, CH), 6.66 (2 H, d, J=8.1 Hz, 2 H-3'''), 6.69 (2 H, d, J=1.9 Hz, H-4' and H-4'' or H-6' and H-6''), 6.84 (2 H, dd, J=8.1 and 1.6 Hz, 2 H-4'''), 6.98 (2 H, d, J=1.9 Hz, H-6' and H-6'' or H-4' and H-4''), 7.05 (2 H, d, J=1.6 Hz, 2 H-6'''), 7.29 (2 H, d, J=8.2 Hz, H-2 and H-6), 7.71 (2 H, d, J=8.2 Hz, H-3 and H-5), 8.1 (2 H, br s, 2 OH), 8.4 (2 H, br s, 2 OH), 9.90 (1 H, s, CHO); IR (KBr) 3320 (OH), 1680 (C=O) cm^{-1}; *m/e* 601 (M^++29, 10%), 572 (M^+, 18), 73 (39), 345 (100).

2',2''-Dihydroxy-3',3''-bis-(2'''-hydroxy-5'''-tert-butylbenzyl)-5',5''-di-tert-butyl-4-formyltriphenylmethane (**3by**): yellow solid, mp 107-109°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (18 H, s, 2 $(CH_3)_3C$), 1.26 (18 H, s, 2 $(CH_3)_3C$), 3.82 (2 H, d, J=14.1 Hz, 2 x ½ CH_2), 3.95 (2 H, d, J=14.1 Hz, 2 x ½ CH_2), 5.90 (1 H, s, CH), 6.80 (2 H, d, J=8.4 Hz, 2 H-3'''), 7.04 (2 H, d, J=2.3 Hz, H-4' and H-4'' or H-6 and H-6''), 7.10 (2 H, dd, J=8.4 and 2.3 Hz, 2 H-4'''), 7.16 (2 H, d, J=2.3 Hz, H-6' and H-6'' or H-4' and H-4''), 7.31 (2 H, d, J=2.3 Hz, H-6'''), 7.41 (2 H, d, J=8.2 Hz, H-2 and H-6), 7.80 (2 H, d, J=8.2 Hz, H-3 and H-5), 7.9 (2 H, br s, 2 OH), 9.0 (2 H, br s, 2 OH), 10.01 (1 H, s, CHO); IR (KBr) 3335 (OH), 1700 (C=O) cm^{-1}; MS *m/e* 741 (M^++1, 100%), 726 (22), 592 (17).

2',2''-Dihydroxy-3',3''-bis-(2'''-hydroxy-5'''-tert-butylbenzyl)-5',5''-di-tert-butyl-4-nitrotriphenylmethane (**3cy**): yellow solid, mp 93-95°C; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.18 (18 H, s, 2 $(CH_3)_3C$), 1.27 (18 H, s, 2 $(CH_3)_3C$), 3.84 (2 H, d, J=14.1 Hz, 2 x ½ CH_2), 3.94 (2 H, d, J=14.1 Hz, 2 x ½ CH_2), 5.90 (1 H, s, CH), 6.81 (2 H, d, J=8.4 Hz, 2 H-3'''), 7.03 (2 H, d, J=2.3 Hz, H-4' and H-4'' or H-6' and H-6''), 7.18 (2 H, dd, J=8.4 and 2.3 Hz, 2 H-4'''), 7.18 (2 H, d, J=2.3 Hz, H-6' and H-6'' or H-4' and H-4''), 7.32 (2 H, d, J=2.3 Hz, 2 H-6'''), 7.41 (2 H, d, J=8.6 Hz, H-2 and H-6), 7.9 (2 H, br s, 2 OH), 8.14 (2 H, d, J=8.6 Hz, H-3 and H-5), 9.0 (2 H, br s, 2 OH); IR (KBr) 3340 (OH), 1699 (N=O) cm^{-1}; MS *m/e* 758 (M^+, 100%).

Synthesis of calix[4]arenes **4**. *General Procedure*. The selected compound **3** (0.005 mol) was dissolved in dry CH_2Cl_2 under stirring, then $BF_3{\cdot}Et_2O$ (0.630 ml, 0.005 mol) was added under nitrogen. The reaction mixture was cooled to 0°C, paraformaldehyde (0.09 g, 0.003 mol) was added. The reaction was stirred until r.t. was reached, then paraformaldehyde (0.09 g, 0.003 mol) was added and the mixture was stirred for 3 h. The reaction was quenched with 10% aqueous HCl solution (100 ml), then extracted with CH_2Cl_2 (3 x 100 ml). The organic phase was dried (Na_2SO_4) and distilled off. The residue was chromatographed on silica gel plates with hexane-methylene chloride mixture (50 : 50) to give the products.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2-phenylcalix[4]arene (**4ax**) ([A] : [B] molar ratio = 1.5 : 1): white solid, mp dec. before melting; ^{1}H NMR ($CDCl_3$, 400 MHz, 293 K) δ 2.10, 2.15 and 2.19 (24 H, 3 s, 4 CH_3 [A] and 4 CH_3 [B]), 3.4 (6 H, br s, H-8eq, H-14eq and H-20eq [A] and H-8eq, H-14eq and H-20eq [B]), 4.2 (6 H, br s, H-8ax, H-14ax and H-20ax [A] and H-8ax, H-14ax and H-20ax [B]), 5.3 (1 H, br s, H-2 [B]), 6.1 (1 H, br s, H-2 [A]), 6.6-7.4 (26 H, m, 13 H-Ph [A] and 13 H-Ph [B]), 9.96 (8 H, s, 4 OH [A] and 4 OH [B]); ($CDCl_3$, 400 MHz, 263 K) δ 2.10 and 2.17 (12 H, 2 s, 2 CH_3 [A] and 2 CH_3 [B]), 2.15 and 2 20 (12 H, 2 s, 2 CH_3 [A] and 2 CH_3 [B]), 3.3-3.5 (6 H, m, H-8eq, H-14eq and H-20eq [A] and H-8eq, H-14eq and H-20eq [B]), 4.12 (1 H, d, J=13.7 Hz, H-14ax [B]), 4.16 (2 H, d, J=13.8 Hz, H-8ax and H-20ax [B]), 4.21 (1 H, d, J=13.7 Hz, H-14ax [A]), 4.22 (2 H, d, J=13.8 Hz, H-8ax and H-20ax [A]), 5.29 (1 H, s, H-2 [B]), 6.10

(1 H, s, H-2 [A]), 6.6-7.4 (26 H, m, 13 H-Ph [A] and 13 H-Ph [B]), 9.9 and 10.0 (8 H, 2 br s, 4 OH [A] and 4 OH [B]); IR (KBr) 3150 (OH) cm^{-1}; MS *m/e* 557 (M^++1, 100%).

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2-(4'-formylphenyl)calix[4]arene (**4bx**) ([A] : [B] molar ratio = 1 : 1): white solid, mp dec. before melting; ^1H NMR ($CDCl_3$, 400 MHz, 298 K) δ 2.16 (24 H, s, 4 CH_3 [A] and 4 CH_3 [B]), 3.5 (6 H, br s, H-8eq, H-14eq and H-20eq [A] and H-8eq, H-14eq and H-20eq [B]), 4.2 (6 H, br s, H-8ax, H-14ax and H-20ax [A] and H-8ax, H-14ax and H-20ax [B]), 5.3 (1 H, br s, H-2 [B]), 6.1 (1 H, br s, H-2 [A]), 6.6-7.1 (16 H, m, 8 H-Ph [A] and 8 H-Ph [B]), 7.5 (4 H, br s, H-2' and H-6' [A] and H-2' and H-6' [B]), 7.83 (4 H, d, J=7.9 Hz, H-3' and H-5' [A] and H-3' and H-5' [B]), 9.94 (8 H, s, 4 OH [A] and 4 OH [B]), 10.02 (2 H, s, CHO [A] and CHO [B]); ($CDCl_3$, 400 MHz, 273 K) δ 2.11, 2.15, 2.17 and 2.21 (24 H, 4 s, 4 CH_3 [A] and 4 CH_3 [B]), 3.37 and 3.43 (2 H, 2 d, J=13.8 Hz, H-14eq [A] and H-14eq [B]), 3.44 and 3.47 (4 H, 2 d, J=13.7 Hz, H-8eq and H-20eq [A] and H-8eq and H-20eq [B]), 4.12 and 4.21 (2 H, 2 d, J=13.8 Hz, H-14ax [A] and H-14ax [B]), 4.15 and 4.22 (4 H, d, J=13.7 Hz, H-8ax and H-20ax [A] and H-8ax and H-20ax [B]), 5.30 (1 H, s, H-2 [B]), 6.13 (1 H, s, H-2 [A]), 6.65, 6.72, 6.75, 6.83, 6.86, 6.88, 6.93 and 6.99 (16 H, 8 br s, 8 H-Ph [A] and 8 H-Ph [B]), 7.41 and 7.51 (4 H, 2 d, J=8.1 Hz, H-2' and H-6' [A] and H-2' and H-6' [B]), 7.82 and 7.86 (4 H, 2 d, J=8.1 Hz, H-3' and H-5' [A] and H-3' and H-5' [B]), 10.03 (10 H, s, 4 OH and CHO [A] and 4 OH and CHO [B]); IR (KBr) 3200 (OH), 1690 (C=O) cm^{-1}; MS *m/e* 584 (M^+, 10%), 478 (100).

25,26,27,28-Tetrahydroxy-5,11,17,23-tetra-tert-butyl-2-(4'-formylphenyl)calix[4]arene (**4by**) ([A] : [B] molar ratio = 1 : 1): white solid, mp 173-175°C; ^1H NMR ($CDCl_3$, 300 MHz, 300 K) δ 1.18, 1.26 and 1.31 (72 H, 3 br s, 4 $(CH_3)_3C$ [A] and 4 $(CH_3)_3C$ [B]), 3.5 (6 H, br s, H-8eq, H-14eq and H-20eq [A] and H-8eq, H-14eq and H-20eq [B]), 4.3 (6 H, br s, H-8ax, H-14ax and H-20ax [A] and H-8ax, H-14ax and H-20ax [B]), 5.5 (1 H, br s, H-2 [B]), 6.4 (1 H, br s, H-2 [A]), 7.0-7.4 (16 H, m, 8 H-Ph [A] and 8 H-Ph [B]), 7.5 (4 H, br s, H-2' and H-6' [A] and H-2' and H-6' [B]), 7.77 (4 H, d, J=7.3 Hz, H-3' and H-5' [A] and H-3' and H-5' [B]), 9.5 (8 H, br s, 4 OH [A] and 4 OH [B]), 9.97 (2 H, s, CHO [A] and CHO [B]); ($CDCl_3$, 300 MHz, 218 K) δ 1.14, 1.27, 1.31 and 1.32 (72 H, 4 s, 4 $(CH_3)_3C$ [A] and 4 $(CH_3)_3C$ [B]), 3.3-3.8 (6 H, m, H-8eq, H-14eq and H-20eq [A] and H-8eq, H-14eq and H-20eq [B]), 4.0-4.5 (6 H, m, H-8ax, H-14ax and H-20ax [A] and H-8ax, H-14ax and H-20ax [B]), 5.51 (1 H, s, H-2 [B]), 6.23 (1 H, s, H-2 [A]), 7.1 (2 H, br s, H-4 and H-24 [A]), 7.2 (2 H, br s, H-4 and H-24 [B]), 7.2-7.4 (12 H, m, 6 H-Ph [A] and 6 H-Ph [B]), 7.49 (2 H, d, J=7.7 Hz, H-2' and H-6' [B]), 7.58 (2 H, d, J=7.7 Hz, H-2' and H-6' [A]), 7.8-8.0 (4 H, m, H-3' and H-5' [A] and H-3' and H-5' [B]), 9.48, 9.59, 9.69 and 9.79 (4 H, 4 s, 4 OH [A]), 9.59, 9.67, 9.92 and 10.03 (4 H, 4 s, 4 OH [B]), 10.01 (1 H. s, CHO [B]), 10.08 (1 H, s, CHO [A]); ($Cl_2CDCDCl_2$, 300 MHz, 373 K) δ 1.19 and 1.31 (36 H, 2 s, 4 $(CH_3)_3C$), 3.68 (2 H, d, J=13.6 Hz, H-8 and H-20), 3.91 (2 H, s, 2 H-14), 4.07 (2 H, d, J=13.6 Hz, H-8 and H-20), 6.16 (1 H, s, H-2), 7.08 and 7.16 (4 H, 2 d, J=2.3 Hz, H-4, H-6, H-22 and H-24),

7.21 (4 H, s, H-10, H-12, H-16 and H-18), 744 (2 H, d, J=8.3 Hz, H-2' and H-6'), 7.71 (2 H, d, J=8.3 Hz, H-3' and H-5'), 8.92 (2 H, s, 2 OH), 9.16 (2 H, s, 2 OH), 9.92 (1 H, s, CHO); IR (KBr) 3238 (OH), 1704 (C=O) cm^{-1}; MS *m/e* 781 (M^++29, 10%), 753 (M^++1, 100).

Synthesis of calix[5]arenes **6**. *General Procedure.* A solution of triphenylmethane **3** (0.005 mol) and 2,6-dihydroxymethyl-4-alkylphenol **5x** and **5y** (0.006 mol) was refluxed in xylene for 8 h. After cooling, the solvent was distilled off and the residue was purified by flash-chromatography, using hexane-ethyl acetate mixture (85 : 15) as eluent.

31,32,33,34,35-Pentahydroxy-5,11,17,23,29-pentamethyl-2-phenylcalix[5]arene (**6ax**): white solid, mp 272-274°C; ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ 2.19 (6 H, s, 2 CH_3), 2.23 (6 H, s, 2 CH_3), 2.25 (3 H, s, CH_3), 3.49 (2 H, d, J=13.9 Hz, H-8eq and H-26eq or H-14eq and H-20eq), 3.54 (2 H, d, J=14.1 Hz, H-14eq and H-20eq or H-8eq and H-26eq), 4.00 (2 H, d, J=13.9 Hz, H-8ax and H-26ax or H-14ax and H-20ax), 4.04 (2 H, d, J=14.1 Hz, H-14ax and H-20ax or H-8ax and H-26ax), 5.96 (1 H, s, H-2), 6.8-7.3 (15 H, m, 15 H-Ph), 8.19 (2 H, s, 2 OH), 8.53 (1 H, s, OH), 8.60 (2 H, s, 2 OH); ($CDCl_3$, 400 MHz, 223 K) δ 2.21, 2.25 and 2.27 (15 H, 3 s, 5 CH_3), 3.48 (4 H, pseudo t, J=15.8 Hz, H-8eq, H-14eq, H-20eq and H-26eq), 4.10 (4 H, m, H-8ax, H-14ax, H-20ax and H-26ax), 6.02 (1 H, s, H-2), 6.8-7.4 (15 H, m, 15 H-Ph), 8.4 (2 H, br s, 2 OH), 8.8 (3 H, br s, 3 OH); IR (KBr) 3260 (OH) cm^{-1}; MS *m/e* 705 (M^++29, 35%), 677 (M^++1, 100).

31,32,33,34,35-Pentahydroxy-5,11,17,23,29-pentamethyl-2-(4'-formylphenyl)calix[5]arene (**6bx**): white solid, mp 191-193°C; ^{1}H NMR ($CDCl_3$, 300 MHz, 300 K) δ 2.20 (6 H, s, 2 CH_3), 2.23 (6 H, s, 2 CH_3), 2.24 (3 H, s, CH_3), 3.54 (4 H, pseudo t, J=13.8 Hz, H-8eq, H-14eq, H-20eq and H-26eq), 4.01 (4 H, pseudo t, J=13.8 Hz, H-8ax, H-14ax, H-20ax and H-26ax), 5.98 (1 H, s, H-2), 6.83 (2 H, s, H-4 and H-30), 6.98 and 7.03 (8 H, 2 s, 8 H-Ph), 7.25 (2 H, d, J=8.1 Hz, H-2' and H-6'), 7.76 (2 H, d, J=8.1 Hz, H-3' and H-5'), 8.24 (2 H, s, 2 OH), 8.5 (3 H, br s, 3 OH), 9.98 (1 H, s, CHO); ($CDCl_3$, 400 MHz, 230 K) δ 2.2 (6 H, br s, 2 CH_3), 2.23 (6 H, s, 2 CH_3), 2.25 (3 H, s, CH_3), 3.3-3.6 (4 H, m, H-8eq, H-14eq, H-20eq and H-26eq), 3.9-4.1 (4 H, m, H-8ax, H-14ax, H-20ax and H-26ax), 6.01 (1 H, s, H-2), 6.80 (2 H, s, H-4 and H-30), 7.00, 7.02 and 7.04 (8 H, 3 s, 8 H-Ph), 7.20 (2 H, d, J=8.1 Hz, H-2' and H-6'), 7.76 (2 H, d, J=8.1 Hz, H-3' and H-5'), 8.4 (2 H, br s, 2 OH), 8.6 (1 H, br s, OH), 8.7 (2 H, br s, 2 OH), 9.98 (1 H, s, CHO); IR (KBr) 3330 (OH), 1695 (C=O) cm^{-1}; MS *m/e* 733 (M^++29, 10%), 705 (M^++1, 100).

31,32,33,34,35-Pentahydroxy-5,11,17,23,29-penta-tert-butyl-2-(4'-formylphenyl)calix[5]arene (**6by**): white solid; mp dec. at 190°C; ^{1}H NMR ($Cl_2CDCDCl_2$, 300 MHz, 300 K) δ 1.10 (18 H, s, 2 $(CH_3)_3C$), 1.19 (18 H, s, 2 $(CH_3)_3C$), 1.20 (9 H, s, $(CH_3)_3C$), 3.47 (4 H, pseudo t, J=14.3 Hz, H-8eq, H-14eq, H-20eq and H-26eq), 4.09 (4 H, pseudo t, J=14.3 Hz, H-8ax, H-14ax, H-20ax and H-26ax), 5.98 (1 H, s, H-2), 7.04 (2 H, s,

H-4 and H-30), 7.1-7.2 (10 H, m, H-2', H-6' and 8 H-Ph), 7.67 (2 H, d, J=8.2 Hz, H-3' and H-5'), 8.1 (2 H, br s, 2 OH), 8.3 (1 H, br s, OH), 8.4 (2 H, br s, 2 OH), 9.90 (1 H, s, CHO); (CD_2Cl_2, 400 MHz, 200 K) δ 1.09 (18 H, s, 2 $(CH_3)_3C$), 1.17 (18 H, s, 2 $(CH_3)_3C$), 1.22 (9 H, s, $(CH_3)_3C$), 3.45 (2 H, d, J=14.0 Hz, H-8eq and H-26eq or H14eq and H-20eq), 3.50 (2 H, d, J=13.9 Hz, H-14eq and H-20eq or H-8eq and H-26eq), 4.03 (2 H, d, J=14.0 Hz, H-8ax and H-26ax or H14ax and H-20ax), 4.09 (2 H, d, J=13.9 Hz, H-14ax and H-20ax or H-8ax and H-26ax), 6.04 (1 H, s, H-2), 7.11 (2 H, d, J=8.2 Hz, H-2' and H-6'), 7.0-7.3 (10 H, m, 10 H-Ph), 7.71 (2 H, d, J=8.2 Hz, H-3' and H-5'), 8.76 (5 H, s, 5 OH), 9.92 (1 H, s, CHO); ($Cl_2CDCDCl_2$, 300 MHz, 360 K) δ 1.10 (18 H, s, 2 $(CH_3)_3C$), 1.19 (18 H, s, 2 $(CH_3)_3C$), 1.20 (9 H, s, $(CH_3)_3C$), 3.47 (2 H, d, J=14.1 Hz, H-8eq and H-26eq or H-14eq and H-20eq), 3.52 (2 H, d, J=14.2 Hz, H-14eq and H-20eq or H-8eq and H-26eq), 4.01 (2 H, d, J=14.1 Hz, H-8ax and H-26ax or H-14ax and H-20ax), 4.07 (2 H, d, J=14.2 Hz, H-14ax and H-20ax or H-8ax and H-26ax), 5.96 (1 H, s, H-2), 7.04 (2 H, d, J=2.4 Hz, H-4 and H-30), 7.1-7.2 (10 H, m, H-2', H-6' and 8 H-Ph), 7.63 (2 H, d, J=8.3 Hz, H-3' and H-5'), 8.0 (2 H, br s, 2 OH), 8.2 (3 H, br s, 3 OH), 9.89 (1 H, s, CHO); IR (KBr) 3310 (OH), 1676 (C=O) cm^{-1}; MS *m/e* 915 (M^++1, 100%).

31,32,33,34,35-Pentahydroxy-5,11,17,23,29-penta-tert-butyl-2-(4'-nitrophenyl)calix[5]arene (**6cy**): white solid, mp dec. at 167°C; ^1H NMR (CD_2Cl_2, 300 MHz, 300 K) δ 1.21 (18 H, s, 2 $(CH_3)_3C$), 1.28 (18 H, s, 2 $(CH_3)_3C$), 1.30 (9 H, s, $(CH_3)_3C$), 3.62 (4 H, pseudo t, J=15.2 Hz, H-8eq, H-14eq, H-20eq and H-26eq), 4.12 (4 H, pseudo t, J=15.2 Hz, H-8ax, H-14ax, H-20ax and H-26ax), 6.08 (1 H, s, H-2), 7.1-7.3 (12 H, m, H-2', H-6' and 10 H-Ph), 8.11 (2 H, d, J=8.9 Hz, H-3' and H-5'), 8.4 (2 H, br s, 2 OH), 8.5 (3 H, br s, 3 OH); (CD_2Cl_2, 400 MHz, 200 K) δ 1.20 (18 H, s, 2 $(CH_3)_3C$), 1.28 (18 H, s, 2 $(CH_3)_3C$), 1.32 (9 H, s, $(CH_3)_3C$), 3.56 (2 H, d, J=14.3 Hz, H-8eq and H-26eq or H-14eq and H-20eq), 3.60 (2 H, d, J=14.3 Hz, H-14eq and H-20eq or H-8eq and H-26eq), 4.13 (2 H, d, J=14.3 Hz, H-8ax and H-26ax or H-14ax and H-20ax), 4.19 (2 H, d, J=14.3 Hz, H-14ax and H-20ax or H-8ax and H-26ax), 6.14 (1 H, s, H-2), 7.15 (2 H, d, J=1.9 Hz, H-4 and H-30), 7.21 (2 H, d, J=8.8 Hz, H-2' and H-6'), 7.2-7.4 (8 H, m, 8 H-Ph), 8.13 (2 H, d, J=8.8 Hz, H-3' and H-5'), 8.86 (5 H, s, OH); ($Cl_2CDCDCl_2$, 300 MHz, 353 K) δ 1.16 (18 H, s, 2 $(CH_3)_3C$), 1.24 (18 H, s, 2 $(CH_3)_3C$), 1.25 (9 H, s, $(CH_3)_3C$), 3.55 (4 H, pseudo t, J=15.4 Hz, H-8eq, H-14eq, H-20eq and H-26eq), 4.08 (4 H, pseudo t, J=15.4 Hz, H-8ax, H-14ax, H-20ax and H-26ax), 5.99 (1 H, s, H-2), 7.07 (2 H, d, J=1.7 Hz, H-4 and H-30), 7.1-7.3 (10 H, m, H-2', H-6' and 8 H-Ph), 8.02 (2 H, d, J=8.7 Hz, H-3' and H-5'), 8.3 (5 H, br s, 5 OH); IR (KBr) 3324 (OH), 1604 (N=O) cm^{-1}; MS *m/e* 961 (M^++29, 18%), 933 (M^++1, 100).

49,50,51,52,53,54,55,56-Octahydroxy-5,11,17,23,29,35,41,47-octa-tert-butyl-2,26-bis(4'-formylphenyl) calix[8]arene (**7by**): white solid, mp dec. at 210°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (36 H, s, 4 $(CH_3)_3C$), 1.32 (36 H, s, 4 $(CH_3)_3C$), 3.4-3.6 (6 H, m, H-8eq, H-14eq, H-20eq, H-32eq, H-38eq and H-44eq), 4.3-4.5 (6 H, m, H-8ax, H-14ax, H-20ax, H-32ax, H-38ax and H-44ax), 6.38 (2 H, H-2 and H-26), 7.07 (4 H, s, 4 H-Ph), 7.18 (4 H, s, 4 H-Ph), 7.26 (8 H, s, 8 H-Ph), 7.48 (4 H, d, J=8.0 Hz, 2 H-2' and 2 H-

6'), 7.75 (4 H, d, J=8.0 Hz, 2 H-3' and 2 H-5'), 9.6 (4 H, br s, 4 OH), 9.8 (4 H, br s, 4 OH), 9.98 (2 H, s, CHO); IR (KBr) 3231 (OH), 1700 (C=O) cm^{-1}; MS *m/z* 1533 (M^++29, 10%), 1505 (M^++1, 100).

49,50,51,52,53,54,55,56-Octahydroxy-5,11,17,23,29,35,41,47-octa-tert-butyl-2,26-bis(4'-nitrophenyl) calix[8]arene (**7cy**): white solid, mp dec. at 240°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (36 H, s, 4 $(CH_3)_3C$), 1.32 (36 H, s, 4 $(CH_3)_3C$), 3.2-3.8 (6 H, m, H-8eq, H-14eq, H-20eq, H-32eq, H-38eq and H-44eq), 4.1-4.7 (6 H, m, H-8ax, H-14ax, H-20ax, H-32ax, H-38ax and H-44ax), 6.37 (2 H, H-2 and H-26), 7.03 (4 H, d, J=2.3 Hz, 4 H-Ph), 7.20 (4 H, d, J=2.3 Hz, 4 H-Ph), 7.2-7.4 (8 H, m, 8 H-Ph), 7.49 (4 H, d, J=8.7 Hz, 2 H-2' and 2 H-6'), 8.09 (4 H, d, J=8.7 Hz, 2 H-3' and 2 H-5'), 9.2 (2 H, br s, 2 OH), 9.4 (2 H, br s, 2 OH), 9.6 (2 H, br s, 2 OH), 9.8 (2 H, br s, 2 OH); IR (KBr) 3256 (OH), 1704 (N=O) cm^{-1}; MS *m/z* 1540 (M^+, 38%), 1094 (100).

X-ray Analysis and Structure Determination of 6cy·1.8$C_6H_5CH_3$·0.2$CHCl_2CHCl_2$. Unit cell parameters were determined from the θ values of 30 carefully centered reflections having 15°<θ<33°. Data were collected at room temperature (22°C) on a Siemens AED diffractometer, using the Ni-filtered Cu Kα radiation. All reflections with θ in the range 3-65° were measured; of 11711 independent reflections, 4287, having $I \geq 3\sigma(I)$, were considered observed and used in the analysis. The individual profiles were analyzed according to the technique of Lehmann and Larsen.[18] Intensities were corrected for Lorentz and polarization effects. No correction for absorption was applied. Only the observed reflections were used in the structure solution and refinement.

The structure was solved by direct methods (SIR92)[19] and Fourier methods and refined by full-matrix least-squares technique (SHELX-76)[20] first with isotropic thermal parameters and then anisotropically by blocked full-matrix least-squares in the last cycles for all non-hydrogen atoms, apart the *tert*-butyl carbon atoms and the solvent molecules. The methyl carbon atoms of the *tert*-butyl groups of the rings C and E were found to be disordered and distributed in two positions with equal occupancy factor. The H atoms of the calix[5]arene were placed at their geometrically calculated positions and refined "riding" (d C-H = 0.96 Å) on the corresponding carbon atoms with an overall refined isotropic thermal parameter. The hydroxy H atoms were not clearly located (probably disordered). The toluene and 1,1,2,2-tetrachloroethane molecules of solvation were found disordered and the methyl group of the toluene molecules was not located. In the final cycles of refinement better results were obtained with unit weights. The atomic scattering factors, corrected for the real and imaginary parts of anomalous dispersion, were taken from ref 21.

All calculations were carried out on the ENCORE 91 of the Centro di Studio per la Strutturistica Diffrattometrica del CNR, Parma, Italy. The programs PARST[22] and ORTEP[23] were also used.

Crystal Data. Molecular formula: $C_{61}H_{73}NO_7$·1.8$C_6H_5CH_3$·0.2$CHCl_2CHCl_2$; molecular weight: 1131.67; crystal system: monoclinic; space group: $P2_1/n$; diffractometer: Siemens AED; radiation: Nickel-filtered (Cu-

Kα, $\bar{\lambda}$=1.541838 Å); *a* = 18.158(3) Å, *b* = 17.399(3) Å, *c* = 22.974(5) Å, β = 108.68(2)°; V = 6876(2) Å^3; *Z* = 4; *D*calc. = 1.093 g cm^{-3}; *F(000)* = 2433.6; crystal dimensions: 0.28 x 0.35 x 0.45 mm; μ (Cu-Kα) = 8.15 cm^{-1}; scan speed: 3-12 °min^{-1}; scan width: 1.20 + 0.142 tan θ°; scan mode θ/2θ; 2θ range: 6-130°; standard reflection: one measured after 100 reflections; reflections measured: ±*h*, *k*, *l*; unique total data: 11711; unique observed data: 4287 [$I>3\sigma(I)$]; n. of variables: 611; maximum shift/error, final cycle: 0.59; max/min diff. peaks: 0.16/-0.10 goodness of fit: 2.43; $R = \Sigma||Fo|-|Fc||/\Sigma|Fo| = 0.1098$; $Rw = [\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2]^{1/2} = 0.0943$, (unit weights).

Supplementary Material Available

Hydrogen atom coordinates and isotropic thermal parameters, anisotropic thermal parameters for the non-hydrogen atoms, complete bond distances and angles, crystallographic data (11 pages), and listing of observed and calculated structure factors (26 pages) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Ordering information is given on any current masthead page.

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy and by the CNR ("Progetto Strategico Tecnologie Chimiche Innovative: Sottoprogetto A). The authors are grateful to the Centro Interfacoltà Misure (CIM) for the use of NMR and mass instruments.

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(*Received in UK* 15 *April* 1997; *accepted* 17 *July* 1997)