Synthesis and Structural Characterization of Calix[4]arenes, Calix[6]arenes, and Calix[8]arenes with 3-Hydroxypropoxy or 2-Hydroxyethoxy Functional Groups Appended onto the Lower Rim

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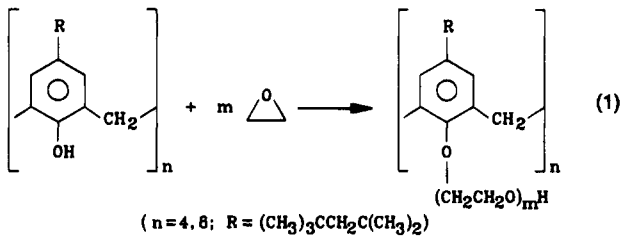
Received April 15, 1994[⊗]

The compound 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trihydroxy-38,40,42-trimethoxycalix[6]-arene, **1**, has been prepared by treating 5,11,17,23,29,35-hexa-*tert*-butylcalix[6]arene with potassium carbonate, followed by methyl *p*-toluenesulfonate. The analogous reaction with the unsubstituted calix[6]arene gives 37,38,39-trihydroxy-40,41,42-trimethoxycalix[6]arene, **2**. Treating **1** or 5,11,-17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene, **3**, with sodium hydride followed by allyl bromide gives 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-tris(allyloxy)-38,40,42-trimethoxycalix[6]arene, **4**, or 5,11,17,23-tetra-*tert*-butyl-25,27-bis(allyloxy)-26,28-dimethoxycalix-[4]arene, **5**, respectively. Compounds **4** and **5** react with BH_3, followed by H_2O_2 to give 5,11,17,-23,29,35-hexa-*tert*-butyl-37,39,41-tris(3-hydroxypropoxy)-38,40,42-trimethoxycalix[6]arene, **6**, and 5,11,17,23-tetra-*tert*-butyl-25,27-bis(3-hydroxypropoxy)-26,28-dimethoxycalix[4]arene, **7**, respectively. A general procedure for the synthesis of 2-hydroxyethoxy-substituted calixarenes involves reduction of the corresponding ethyl calixaryl acetates with $LiAlH_4$. The procedure has been used to synthesize 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(2-hydroxyethoxy)calixarene, **8**, 25,-26,27,28-tetra(2-hydroxyethoxy)calix[4]arene, **9**, 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,-42-hexakis(2-hydroxyethoxy)calix[6]arene, **10**, 37,38,39,40,41,42-hexa(2-hydroxyethoxy)calix[6]-arene, **11**, 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis(2-hydroxyethoxy)calix-[8]arene, **12**, and 49,50,51,52,53,54,55,56-octakis(2-hydroxyethoxy)calix[8]arene, **13**. Compounds **2**, **4**, **5**, **9**, and **10** have been characterized by X-ray crystallography. The conformations of the tetrols, hexols, and octols have been computationally explored using molecular mechanics calculations.

Introduction

Calixarenes are a family of macrocycles that can be prepared by condensation reactions between para-substituted phenols and formaldehyde.[1,2] Synthetic procedures have been developed for selectively obtaining these macrocycles with four, six, or eight phenolic residues in the ring in high yields.[3,4] The number of phenolic residues in the macrocycle is designated by the value of n (4, 6, or 8) in the term calix[n]arene. Calixarenes are synthesized using phenols that have an alkyl (usually a tertiary butyl) group substituent at the para position, but subsequent removal of these tertiary butyl groups can be achieved by the aluminum chloride-catalyzed de-tert-butylation.[5] Calixarenes with aliphatic ether alcohol functional groups appended to the lower rim were initially prepared by Cornforth et al. in a study directed at the synthesis of antituberculous surfactants. Their approach involved oxyethylation of the lower rim by treatment of the calixarene with different proportions of ethylene oxide under basic conditions (eq 1).[6-11]



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In this paper we report the synthesis and characterization of calix[4]arenes, calix[6]arenes, and calix[8]arenes having either 3-hydroxypropoxy or 2-hydroxyethoxy functionalities incorporated onto the lower rim. These compounds have been synthesized for a number of different reasons. One of these is to prepare calixarenes that have hydrophobic substituents on one rim and hydrophilic substituents on the other. Such compounds can potentially act as bilayers at cell surfaces. A second reason for preparing calixarenes having terminal OH functionalities is that these groups can be used in capping reactions for the synthesis of calixspherands. By changing the number of such functionalities and the chain length to the ether oxygens on the lower calixarene rim, both the cavity size and the range of possible capping

⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1994.

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0022-3263/94/1959-5990$04.50/0

reactions can be modified and changed. These alternative routes to that reported by Cornforth *et al.* have been developed because they avoid the necessity of controlling the oligomerization of ethylene oxide in the synthesis of the 2-hydroxyethoxy derivatives and also because the previously unreported 2-hydroxypropoxy derivatives can be readily synthesized. We have used two approaches that lead to changes in the number of methylene groups in the hydroxyalkoxy chain appended to the lower rim. The first method involves introducing allyloxy groups onto the hydroxylated sites, followed by hydroboration of the terminal position of the alkene. Subsequent oxidative hydrolysis of the borane gives the terminal 3-hydroxyethoxy group at the lower rim position. The second method involves reduction of the ethyl calixaryl acetate groups to 2-hydroxyethoxy functionalities with lithium aluminum hydride.[12] We have used molecular mechanics calculations to predict the preferred conformations for a series of substituted calix[*n*]arenes (n = 4, 6, 8) having 2-hydroxyethoxy groups attached to their lower rims and compared the calculated structures in two cases with crystallographically characterized compounds.

Experimental Section

All compounds used were of reagent purity and used as supplied. Dry THF was distilled from the ketyl prepared from sodium and benzophenone. The compound 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene, **3**, was prepared according to the published procedure. The ethyl calixarylacetates were prepared from the calixarene and ethyl bromoacetate according to the literature procedure.[12] Fast atom bombardment (FAB) mass spectra were obtained with the samples introduced in a *m*-nitrobenzyl alcohol matrix.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trihydroxy-38,40,42-trimethoxycalix[6]arene (1). A suspension of 5,11,17,23,29,35-hexa-*tert*-butylcalix[6]arene (1.080 g, 1.11 mmol), potassium carbonate (0.230 g, 1.67 mmol), and methyl *p*-toluenesulfonate (0.626 g, 3.36 mmol) in dry acetonitrile (25 mL) was refluxed for 24 h. The solution was cooled, and the solvent was removed under reduced pressure. The resulting solid was then washed with methyl alcohol (50 mL) and filtered. The solid was then dissolved in dichloromethane (50 mL), any insoluble material was filtered, and the solvent was removed under reduced pressure. The residue was submitted to flash chromatography using dichloromethane as the eluant. Yield: 0.281 g (25%). R_f: 0.25 (silica gel 200–400 mesh, CH_2Cl_2). Anal. Calcd for $C_{69}H_{90}O_6 \cdot CH_3OH$: C, 80.3; H, 9.04. Found: C, 80.0; H, 9.07. FAB mass spectrum: m/z 1015 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ 1.10 (s, 27H), δ 1.19 (s, 27H), δ 3.46 (s, 9H), δ 3.88 (s, 12H), δ 6.77 (s, 3H), δ 6.89 (s, 6H), δ 7.01 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 30.79, δ 31.19, δ 31.52, δ 33.88, δ 34.08, δ 61.04, δ 125.70, δ 126.64, δ 132.41, δ 142.35, δ 146.83, δ 149.81, δ 152.33. IR (KBr): ν(OH) 3345, 3522 cm^{-1}.

37,38,39-Trihydroxy-40,41,42-trimethoxycalix[6]-arene (2). A suspension of calix[6]arene (1.507 g, 2.37 mmol), potassium carbonate (5.888 g, 42.66 mmol), and methyl *p*-toluenesulfonate (1.326 g, 7.13 mmol) in acetone (60 mL) was refluxed for 24 h. The solution was cooled and filtered. The solvent was then removed under reduced pressure. The solid was dissolved in dichloromethane (80 mL) and then washed with hydrochloric acid (100 mL of 0.5 N) and water (100 mL). The organic layer was separated and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was flash chromatographed using dichloromethane as eluant. The compound was recrystallized from a mixture of chloroform and methanol. Yield: 0.386 g (24%). R_f: 0.45 (silica gel 200–400 mesh, CH_2Cl_2). Mp: 275 °C dec. Anal. Calcd for $C_{45}H_{42}O_6 \cdot 0.33\ CHCl_3$: C, 7.58; H, 5.94. Found: C, 75.6; H, 6.20. FAB mass spectrum: m/z 679 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ 3.29 (s, 3H), δ 3.77 (s, 4H), δ 3.86 (s, 4H), δ 3.98 (s, 6H), δ 4.05 (s, 4H), δ 6.90 (m, 18H), δ 7.58 (s, 1H), δ 8.42 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 30.56, δ 31.09, δ 31.53, δ 60.56, δ 61.79, δ 120.15, δ 120.33, δ 123.64, δ 125.12, δ 126.52, δ 126.94, δ 127.72, δ 128.62, δ 128.80, δ 128.81, δ 128.94, δ 129.16, δ 129.32, δ 132.94, δ 133.48, δ 134.39, δ 151.27, δ 151.67, δ 154.08, δ 156.71. IR (KBr): ν (OH) 3293 cm^{-1}.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-tris(allyloxy)-38,40,42-trimethoxycalix[6]arene (4). A solution of **1** (0.207 g, 0.204 mmol) in tetrahydrofuran (8 mL) was added to a suspension of sodium hydride (0.617 g, 20.57 mmol) in tetrahydrofuran (10 mL) and dimethyl formamide (2 mL). After the solution was stirred for 30 min, allyl bromide (1.80 mL, 20.80 mmol) was added and the reaction mixture refluxed for 2 h. The solution was cooled to room temperature, and the excess sodium hydride was carefully destroyed by the slow addition of water. The solvent was removed under reduced pressure. The residue was partitioned between chloroform (60 mL) and hydrochloric acid (30 mL of 1 N). The organic layer was washed with brine (30 mL) and then dried over magnesium sulfate. The solution was filtered and the solvent removed under reduced pressure. The residue was triturated with methanol to obtain the compound as a solid. This solid was then recrystallized from a mixture of chloroform and methanol. Yield: 0.190 g (82%). Mp: 246–248 °C. Anal. Calcd for $C_{78}H_{102}O_6$: C, 82.5; H, 9.05. Found: C, 82.4; H 9.05. FAB mass spectrum: m/z 1137. ^1H NMR ($CDCl_3$): δ 0.95 (s, 27H), δ 1.29 (s, 27H), δ 2.52 (s, 6H), δ 3.93 (s, 12H), δ 4.16 (d, 6H, ^3J(HH) = 5.47 Hz), δ 5.05 (dd, 3H, ^2J(HH) = 10.4 Hz, ^3J(HH) = 2.7 Hz), δ 5.23 (dd, 3H, ^2J(HH) = 17.1 Hz, ^3J(HH) = 2.7 Hz) δ 5.92 (m, 3H), δ 6.81 (s, 6H), δ 7.19 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 31.23, δ 31.94, δ 32.23, δ 34.71, δ 34.85, δ 60.00, δ 74.00, δ 117.77, δ 125.22, δ 127.99, δ 133.79, δ 134.33, δ 134.68, 146.27, δ 152.96, δ 155.01.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(allyloxy)-26,28-dimethoxycalix[4]arene (5). A solution of **3** (0.339 g, 0.501 mmol) in tetrahydrofuran (10 mL) was added to a suspension of sodium hydride (1.208 g, 40.26 mmol) in tetrahydrofuran (8 mL) and dimethyl formamide (2 mL). After stirring for 30 min, allyl bromide (4.3 mL, 49.68 mmol) was added, and the solution was refluxed for 2 h. The solution was then cooled, and the excess sodium hydride was slowly destroyed by the addition of water. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (100 mL). The chloroform solution was washed once with hydrochloric acid (50 mL of 1 N) and twice with water (50 mL each). The organic layer was dried over magnesium sulfate and then filtered. The solvent was removed until only 10 mL of solution remained. Methanol (150 mL) was then added, and the solid that precipitated was collected by vacuum filtration. This solid product was then recrystallized from a mixture of chloroform and methanol. Yield: 0.307 g (81%). Mp: 189–191 °C. Anal. Calcd for $C_{52}H_{68}O_4$: C, 82.5; H, 9.05. Found: C, 81.6; H, 9.08. FAB mass spectrum: m/z 757. ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H), δ 1.33 (s, 18H), δ 1.36 (s, 9H), δ 3.07 (d, 2H, J(HH) = 12.6 Hz), δ 3.13 (d, 2H, ^2J(HH) = 12.6 Hz), δ 3.19 (s, 3H), δ 3.71 (m, 4H), δ 3.93 (s, 3H), δ 4.06 (d, 2H, ^2J(HH) = 12.6 Hz), δ 4.33 (d, 2H, ^2J(HH) = 12.6 Hz), δ 5.35 (m, 4H,), δ 6.13 (m, 2H), δ 6.90 (m, 8H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 31.46, δ 31.65, δ 32.04, δ 32.14, δ 32.25, δ 34.21, δ 34.65, δ 38.59, δ 60.48, δ 61.04, δ 75.50, δ 117.14, δ 124.79, δ 125.47, δ 125.66, δ 126.38, δ 128.56, δ 132.68, δ 133.15, δ 133.81, δ 136.29, δ 136.46, δ 143.88, δ 145.77, δ 153.55, δ 155.68, δ 156.29.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-tris(3-hydroxypropoxy)-38,40,42-trimethoxycalix[6]arene (6). To a solution of **4** (0.343 g, 0.302 mmol) in tetrahydrofuran (5 mL) was added BH_3·THF (1 mL of a 1 M solution) dropwise over 15 min. The solution was stirred for 2 h and then refluxed for a further 1 h. The solution was cooled to 0 °C, and water (1.5 mL) was carefully added. After a sufficient quantity of a 3 M sodium hydroxide was added to bring the pH of the solution up to 8, H_2O_2 (1.5 mL of a 30% solution) was added dropwise over 15 min. The solution was stirred at room temperature for 1.5 h and then refluxed for a further 1 h. The

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solution was then allowed to cool to ambient temperature and poured into water (10 mL). The aqueous layer was then saturated with potassium carbonate and extracted with diethyl ether (three portions of 15 mL). The separate extracts were then combined and dried over magnesium sulfate. The solution was filtered and the solvent removed under reduced pressure. The residue was submitted to flash chromatography (3:1 mixture of hexane and ethyl acetate). Yield: 0.079 g (22%). Mp: 167–170 °C. Anal. Calcd for $C_{78}H_{108}O_9 \cdot 2H_2O$: C, 76.4; H, 9.20. Found: C, 76.3; H, 9.19. FAB mass spectrum: m/z 1175 $(M - CH_3)^+$. ^1H NMR ($CDCl_3$): δ 0.54 (brs, 9H), δ 1.08 (s, 18H), δ 1.17 (s, 9H), δ 1.32 (s, 18H), δ 1.46 (brs, 6H), δ 3.60 (br m, 33H), δ 6.42 (brs, 2H), δ 6.93 (brs, 8H), δ 7.18 (s, 2H), δ 7.22 (s, 2H), δ 7.68 (brs, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 31.02, δ 31.40, δ 31.55, δ 31.74, δ 31.99, δ 32.14, δ 32.20, δ 32.62, δ 34.38 ($C(CH_3)_3$), δ 34.76 ($C(CH_3)_3$), δ 34.83, δ 60.22, δ 61.31, δ 61.59, δ 71.79, δ 124.74, δ 125.51, δ 125.86, δ 126.12, δ 127.82, δ 128.11, δ 128.17, δ 133.00, δ 133.25, δ 133.59, δ 134.05, δ 134.14, δ 142.81, δ 145.82, δ 146.63, δ 147.06, δ 150.38, δ 153.37, δ 153.55, δ 153.93. IR (KBr): ν(OH) 3423 cm^{-1}.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(3-hydroxypropoxy)-26,28-dimethoxycalix[4]arene (7). To a solution of **5** (0.4106 g, 0.515 mmol) in tetrahydrofuran (4 mL) was added BH_3·THF (1.3 mL of a 1 M solution) dropwise over a period of 20 min. The solution was stirred for 4 h at room temperature and then cooled to 0 °C. Water was added slowly to destroy excess BH_3. The pH was raised to 8 by addition of a solution of 3 M sodium hydroxide, and then H_2O_2 (2 mL of a 30% solution) was added dropwise over 15 min. The solution was stirred for 2 h at ambient temperature and then refluxed for a further 1 h. The solution was then allowed to cool to ambient temperature and poured into water (10 mL). The aqueous phase was then saturated with potassium carbonate and extracted with diethyl ether (three portions of 15 mL). The combined extracts were then dried over magnesium sulfate. The solution was removed, and the residue was submitted to flash chromatography (3:1 mixture of hexane and ethyl acetate). Yield: 0.082 g (19%). R_f: 0.85 (silica gel 200–400 mesh, EtOAc/hexane). Mp: 244 °C. Anal. Calcd for $C_{52}H_{72}O_6 \cdot CH_3CO_2CH_2CH_3$: C, 77.5; H, 9.15. Found: C, 77.9; H, 9.15. FAB mass spectrum: m/z 792. ^1H NMR ($CDCl_3$) at −60 °C: δ 1.11 (s, 9H), δ 1.18 (s, 18H), δ 1.41 (s, 9H), δ 1.83 (m, 4H), δ 3.29 (d, 2H, J(HH) = 12.0 Hz), δ 3.67 (s, 3H), δ 3.69 (m, 4H), δ 3.86 (2H), δ 3.88 (s, 3H), δ 4.01 (m, 4H), δ 4.25 (d, 2H, J(HH) = 12.0 Hz), δ 4.36 (brm, 2H), δ 6.98 (s, 2H), δ 7.07 (s, 2H), δ 7.18 (s, 2H), δ 7.23 (s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) at −50 °C: δ 29.52, δ 31.43, δ 31.56, δ 31.61 , δ 34.17, δ 34.19, δ 34.28, δ 39.41, δ 59.84, δ 60.44, δ 63.05, δ 72.16, δ 125.31, δ 125.55, δ 126.64, δ 127.29, δ 133.21, δ 133.61, δ 133.97, δ 134.72, δ 144.45, δ 146.04, δ 146.09, δ 152.39, δ 153.92, δ 155.44. IR (KBr): ν(OH) 3370 cm^{-1}.

General Procedure for the Preparation of 2-Hydroxyethoxy-Substituted Calixarenes.[13] A solution of the corresponding ethyl calixarylacetate (1 mmol) in 40 mL of dry THF was added dropwise to a stirred suspension of 95% $LiAlH_4$ (1.3 molar excess in respect to the corresponding stoichiometric ratio) in 40 mL of dry THF. The reaction mixture was stirred for 30 min in an inert atmosphere. The excess of $LiAlH_4$ was then destroyed by careful addition of water and the solvent evaporated under reduced pressure. The residue was taken up in chloroform and washed successively with dilute sulfuric acid and water. The organic phase was dried over magnesium sulfate, filtered, and evaporated to give the calixaryl alcohols in almost quantitative yields. The octols **12** and **13** were treated with chloroform and dilute sulfuric acid as described above, and the resulting suspension was filtered, washed with water, vacuum dried, and combined with the small residue from the organic phase.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis(2-hydroxyethoxy)calix[4]arene (8). Compound **8** was obtained from the corresponding tetraester and recrystallized from EtOH. Yield: 85%. Mp 283–285 °C. Anal. Calcd for $C_{52}H_{72}O_8 \cdot C_2H_5OH$: C, 74.4; H, 8.95. Found: C, 74.4; H, 9.15. ^1H NMR ($CDCl_3$): δ 1.13 (s, 36H), δ 3.26 (d, 4H, J = 12.8 Hz), δ 4.03 (m, 16H), δ 4.38 (d, 4H, J = 12.8 Hz), δ 5.18 (t, 4H, J = 5.6, (D_2O exchangeable)), δ 6.89 (s, 8H). ^{13}C NMR ($CDCl_3$): δ 30.36 (t, ^1J(CH) = 126.0 Hz), δ 31.36 (q, ^1J(CH) = 125.8 Hz), δ 33.90 (s), δ 61.63 (t, ^1J(CH) = 140.6 Hz), δ 77.77 (t, ^1J(CH) = 144.3 Hz), δ 125.48 (d, ^1J(CH) = 148.0 Hz), δ 133.49 and δ 145.63 (s), δ 152.25 (s). IR (KBr): ν (OH) 3428 cm^{-1}.

25,26,27,28-Tetra(2-hydroxyethoxy)calix[4]arene (9). Compound **9** was obtained from the corresponding tetraester and recrystallized from a mixture of $CHCl_3$ and MeOH. Yield: 90%. Mp: 263–265 °C. Anal. Calcd for $C_{36}H_{40}O_8$: C, 72.0; H, 6.70. Found: C, 72.2; H, 6.91. FAB mass spectrum: m/z 601 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ 3.25 (d, 4H, J = 14.8 Hz), δ 3.96 (s, 8H), δ 4.02 (s, 8H), δ 4.38 (d, 4H, J = 14.8 Hz), δ 4.98 (s, 4H, (D_2O exchangeable)), δ 6.68 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 30.29 (t, ^1J(CH) = 129.5 Hz), δ 61.55 (t, ^1J(CH) = 144.3 Hz), δ 77.88 (t, ^1J(CH) = 144.3 Hz), δ 123.20 (d, ^1J(CH) = 162.8 Hz), δ 128.79 (d, ^1J(CH) = 162.8 Hz), δ 134.60 (s), δ 155.05 (s). IR (KBr): ν (OH) 3416 cm^{-1}.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexakis(2-hydroxyethoxy)calix[6]arene (10). Compound **10** was obtained from the corresponding hexaester and recrystallized from a mixture of $CHCl_3$ and EtOH. Yield: 94%. Mp: 285–287 °C. Anal. Calcd for $C_{78}H_{108}O_{12} \cdot 0.5CHCl_3$: C, 72.7; H, 8.43. Found: C, 72.8; H, 8.83. ^1H NMR ($CDCl_3$): δ 1.16 (brs, 54 H), δ 3.67 (brs, 36 H), δ 4.62 (brs, 6 H, (D_2O exchangeable)), δ 7.03 (brs, 12 H). ^{13}C NMR ($CDCl_3$): δ 30.12 (t, ^1J(CH) = 125.9 Hz), δ 31.57 (q of sept, ^1J(CH) = 125.6, ^3J(CH) = 4.7 Hz), δ 34.18 (m, ^2J(CH) = 3.5 Hz), δ 61.66 (t, ^1J(CH) = 142.0 Hz), δ 75.26 (t, ^1J(CH) = 142.6 Hz), δ 125.97 (d, ^1J(CH) = 146.7 Hz), δ 133.07 and δ 145.8 (s), δ 151.98 (s). IR (KBr): ν(OH) 3391 cm^{-1}.

37,38,39,40,41,42-Hexakis(2-hydroxyethoxy)calix[6]-arene (11). Compound **11** was obtained from the corresponding hexaester and recrystallized from a mixture of $CHCl_3$ and EtOH. Yield: 96%. Mp: 330° dec without melting. Anal. Calcd for $C_{54}H_{60}O_{12} \cdot 0.6CHCl_3$: C, 67.4; H, 6.28. Found: C, 67.0; H, 6.80. ^1H NMR (DMSO): δ 3.39, δ 3.56, and δ 3.94 (brs, each 12H), δ 4.66 (t, J = 5.4 Hz, (D_2O exchangeable)), δ 6.70 (brs, 18 H), δ 8.30 (s, 0.6 H). ^{13}C NMR (DMSO): δ 29.96 (t, ^1J(CH) = 129.0 Hz), δ 60.52 (t, ^1J(CH) = 138.8 Hz), δ 74.79 (t, ^1J(CH) = 142.2 Hz), δ 79.22 (d, ^1J(CH) = 217.7 Hz), δ 123.12 (d, ^1J(CH) = 158.9 Hz), δ 128.34 (d, ^1J(CH) = 155.5 Hz), δ 133.89 (s), δ 155.22 (s). IR (KBr): ν (OH) 3325 cm^{-1}.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,-55,56-octakis(2-hydroxyethoxy)calix[8]arene (12). Compound **12** was obtained from the corresponding octaester, dissolved in DMSO, and precipitated with acetone. Yield: 65%. Mp 287 °C dec without melting. Anal. Calcd for $C_{104}H_{144}O_{16} \cdot 2(CH_3)_2SO$: C, 71.7; H, 8.94. Found: C, 71.7; H, 8.63. ^1H NMR ($CDCl_3$): δ 1.15 (s, 72H), δ 3.50–4.10 (m, 56H, 8H, (D_2O exchangeable)), δ 9.97 (s, 16H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.57 (t, ^1J(CH) = 125.8 Hz), δ 31.29 (q, ^1J(CH) = 125.8 Hz), δ 34.13 (s), δ 61.42 (t, ^1J(CH) = 144.3 Hz), δ 75.10 (t, ^1J(CH) = 148.0 Hz), δ 125.89 (d, ^1J(CH) = 155.4 Hz), δ 133.36 and δ 146.08 (s), δ 151.75 (s). IR (KBr): ν (OH) 3432 cm^{-1}.

49,50,51,52,53,54,55,56-Octakis(2-hydroxyethoxy)calix-[8]arene (13). Compound **13** was obtained from the corresponding octaester which could not be isolated in pure crystalline form. Instead an oil-like residue, obtained according to the procedure described for the preparation of calixaryl esters, was further used in the reduction step.[12] The compound, which was dissolved in pyridine and precipitated with MeOH, was obtained in 45% yield based on the starting calix-[8]arene. Mp 295–297 °C. Anal. Calcd for $C_{72}H_{80}O_{16}$: C, 72.0; H, 6.70. Found: C, 71.6; H, 6.95. FAB mass spectrum: m/z 1202 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ 3.50–3.80 (m, 32H), δ 4.03 (s, 16H), δ 4.54 (s, 8H (D_2O exchangeable)), δ 6.90–7.10 (m, 24H). ^{13}C NMR (DMSO): δ 29.12 (t, ^1J(CH) = 129.5 Hz), δ 60.39 (t, ^1J(CH) = 139.1 Hz), δ 73.63 (t, ^1J(CH) = 136.9 Hz), δ 123.76 (d, ^1J(CH) = 155.4 Hz), δ 128.62 (d, ^1J(CH) = 155.4 Hz), δ 134.17 (s), δ 155.06 (s). IR (KBr): ν (OH) 3453 cm^{-1}.

X-ray Data Collections and Structure Determinations. Crystals were grown by slow evaporation. Compounds **2**, **4**,

(13) Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J. G.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573–82.

and **5** were grown from a mixture of methanol and chloroform, **9** from toluene, and **10** from a mixture of ethanol and ethyl acetate. Cell constants and an orientation matrix for the data collection were obtained from the diffractometer routines from approximately 25 reflections. Equivalent reflections were merged, and data were corrected for Lorentz and polarization factors. Structures were solved using previously described techniques.[14-18] Crystallographic details are as follows: Compound **2** crystallizes in the triclinic space group $P1^-$ with a = 11.48(9) Å, b = 12.38(9) Å, c = 15.91(7) Å, α = 107.7(3)°, β = 91.1(1)°, γ = 107.6(3)°, V = 2037.90(2)° Å^3, and Z = 2. Compound **4** crystallizes in the monoclinic space group $C2/c$ with a = 18.635(1) Å, b = 20.839(2) Å, c = 37.451(3) Å, β = 98.38(1)°, V = 14388(2) Å^3, and Z = 8. Compound **5** crystallizes in the monoclinic space group, $P2_1/c$ with a = 16.745(4) Å, b = 20.772(4) Å, c = 27.951(3) Å, β = 98.45(1)°, V = 9591-(1) Å^3, and Z = 8. Compound **9** crystallizes in the triclinic space group $P1^-$ with a = 16.499(2) Å, b = 17.685(2) Å, c =11.664(2) Å, α = 90.82(1)°, β = 95.34(1)°, γ = 77.803(9)°, V = 3311.8(8) Å^3, and Z = 4. Compound **10** crystallizes in the monoclinic space group $P2_1/c$ with a = 19.628(3) Å, b = 14.701-(3) Å, c = 30.164(7) Å, β = 101.01(2)°, V = 8544(2) Å^3, and Z = 4.[37]

Computational Details. Molecular mechanics calculations for compounds **8**–**13** were carried out with the Insight II, Version 2.1.1 molecular modeling package[19] utilizing the CVFF force field.[20] This force field was originally developed to reproduce the structural features of peptides and proteins, and it has then been extended to more general systems that have hydrophilic functional groups.

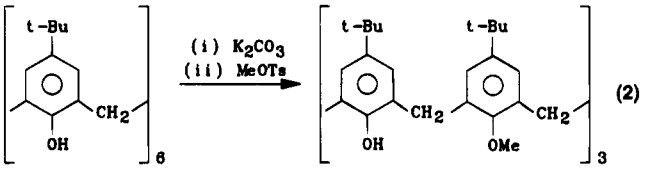
The initial geometries were constructed manually using the BUILDER mode of the program. From the optimized cone conformations of the corresponding calix[4]arenes **8** and **9**, and the pinched cone conformations of the calix[6]arenes **10** and **11**, the other basic conformations of the calixarene ring systems were derived by reinsertion of certain numbers of monomeric units in inverted positions, followed by energy minimization. The pleated loop analogue conformations of the calix[8]arenes **12** and **13** were derived by fusing together two cone conformers of the corresponding calix[4]arenes **8** or **9** with subsequent energy minimization. The other basic conformations of these two calix[8]arenes **12** and **13** were obtained from the corresponding pleated loop analogue conformations as already described for **8**–**11**. No special attempts have been made to find the most favorable positions of the *tert*-butyl groups in **9**, **11**, and **13** since it has been already demonstrated that these energy differences are typically very small (<0.1 kcal/mol).[21]

Lowest energy minima for a given basic conformation of the calixarene core fragment were sought by various rotations about the single C–O and C–C bonds of the 2-hydroxyethoxy substituents on the lower rim of compounds **8**–**13**. The effect of a different force field on the energies and conformations was studied for compound **9** with the QUANTA Version 3.3 program using the CHARMm force field.[22] All conformations were minimized until the root mean square (rms) of the first derivative of the energy was less than 0.001 kcal/mol Å. These conformers were ascertained to correspond to energy minima on the potential energy surface by computing their vibrational frequencies.

Results and Discussion

We have used two approaches to control the number of alcohol functionalities that can be introduced on to the lower rim. The first approach is to use calix[*n*]arenes with different values for *n*, thereby changing the number of phenolic residues in the molecule that can be functionalized. The second approach is to introduce blocking groups onto selected positions of the calixarenes, thereby controlling the number of free phenolic groups that are available for functionalization. Our approach to introducing blocking groups is to partially methoxylate the phenolic groups on the lower rim of the calixarene. The remaining phenolic groups can then be derivatized with 3-hydroxypropoxy functionalities.

Partially Methoxylated Calixarenes. When 5,11,-17,23-tetra-*tert*-butylcalix[4]arene is treated sequentially with potassium carbonate and then with methyl *p*-toluenesulfonate, the symmetrically dimethoxylated compound 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxy calix[4]arene is formed.[23,24] This compound is characterized by an ^{1}H NMR shift for the methoxy group at δ 3.90. We and others have now carried out a similar two-step synthetic procedure with the analogous compound 5,11,17,23,29,35-hexa-*tert*-butyl calix[6]arene and have obtained the symmetrically trimethoxylated compound 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trihydroxy-38,40,42-trimethoxycalix[6]arene **1** (equation 2).[23,25] The compound is characterized in the ^{1}H NMR



(2)

1

spectrum by a resonance for the methoxy protons at δ 3.46 and two resonances of equal intensity at δ 1.10 and δ 1.19 for the *tert*-butyl protons *para* to the hydroxy and methoxy groups on the upper rim. The ^{13}C{^{1}H} NMR spectrum of **1** shows two resonances for the methyl carbons of the *tert*-butyl groups at δ 31.19 and δ 31.52. The quaternary carbons of the *tert*-butyl groups appear as two singlets at δ 33.88 and δ 34.08. The bridging methylenes appear as a single resonance at δ 31.01. The methyl carbon of the methoxy groups appears as a single resonance at δ 61.04. The carbons of the calix[6]arene phenyl rings are observed as a set of seven resonances over the chemical shift range of δ 125–155.

By contrast with the compound 5,11,17,23,29,35-*tert*-butylcalix[6]arene, the calix[6]arene analogue that has hydrogens rather than *tertiary* butyl groups in the *para* positions of the upper rim undergoes methylation to give

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(16) Burla, M. C.; Camalli, M.; Cascarano, G.; Polidori, G., Spagana, R.; Viterbo, D. *J. Appl. Crystallogr.* **1989**, *22*, 389–93.
(17) MolEN, An Interactive Structure Solution Procedure, Enraf-Nonius, Delft, The Netherlands, 1990.
(18) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; DeClerq, J. P.; Woolfson, M. M. MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures form X-ray Diffraction Data, University of York, England, 1980.
(19) Insight II User Guide, version 2.1.0, Biosym Technologies, San Diego, 1992.
(20) Dauber-Osguthrope, P.; Roberts, V. A.; Osguthrope, D. J.; Wolf, J.; Genest, M.; Hagler, A. T. *Proteins: Struct., Funct. Genet.* **1988**, *4*, 31–47 and references cited therein.
(21) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165–76.
(22) QUANTA 3.3 released March 1992 by Molecular Simulations Inc.
(23) For a preliminary communication see: Moran, J. K.; Roundhill D. M. *Inorg. Chem.* **1992**, *31*, 4213–5.
(24) Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567–75.
(25) Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413–4. Otsuka, H.; Araki, K.; Shinkai, S. *Workshop on Calixarenes and Related Compounds*, June, 1993, PS/B-42.

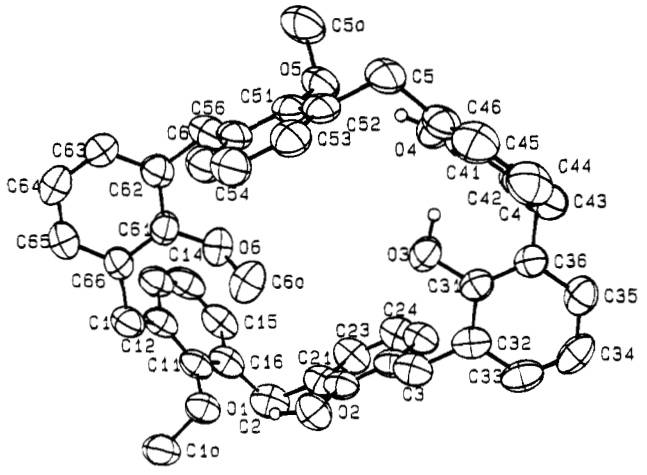


Figure 1.

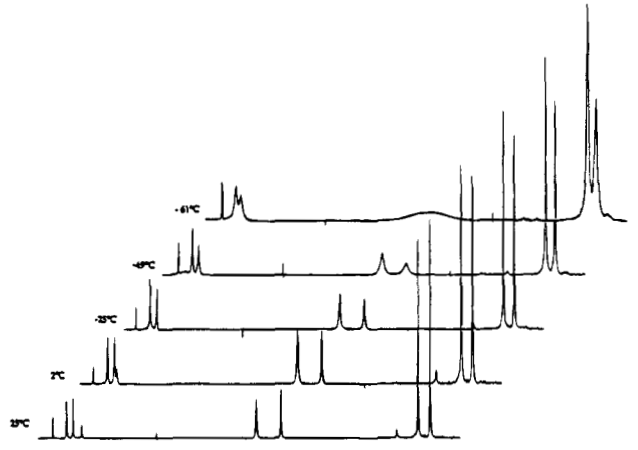
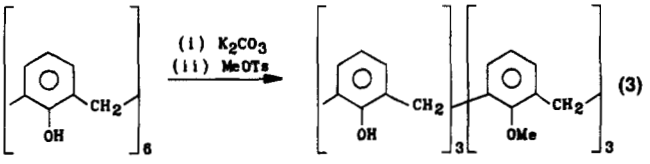


Figure 2.

37,38,39-trihydroxy-40,41,42-trimethoxycalix[6]arene, **2** (eq 3). Compound **2** differs from **1** in that now the



2

hydroxy and methoxy groups are in adjacent rather than in alternating positions around the lower rim (Figure 1). Compound **2** is characterized in the ^{1}H NMR spectrum by resonances for the methoxy protons at δ 3.29 and δ 3.98 in a ratio of 1:2. The ^{13}C{^{1}H} NMR of **2** shows two separate resonances for the methoxy carbons at δ 60.56 and δ 61.79.

The substitution patterns in these methoxylation reactions, along with the differences between compounds having hydrogen or *tertiary* butyl groups in the *para* positions, provides examples of site selective substitutions on the lower rim of calixarenes. For the dimethoxylation of the 5,11,17,23-tetra-*tert*-butyl-substituted calix[4]arene it has been postulated that methoxylation does not proceed beyond this stage because a conformation is adopted with the methoxy groups pointed inside the lower rim and the methoxy oxygens are hydrogen bonded to the two remaining phenolic hydrogens.[23] A similar situation may occur for **1**, where again the alternate hydroxy groups can be selectively methylated. For the calix[6]arene that has hydrogens in the *para* positions, the methoxylation of adjacent positions on the lower rim is unprecedented. The absence of *tert*-butyl groups on the lower rim will lead to an increased distance between the groups on the lower rim, thereby decreasing the hydrogen bonding. Furthermore, the compound with hydrogens in the *para* positions will be conformationally more labile, thereby allowing adjacent substitution to occur *via* conformations other than the cone.

Low-Temperature NMR Spectrum of 1. A feature of the ^{1}H NMR spectrum of **1** is that the bridging methylenes appear as a sharp singlet at room temperature in $CDCl_3$. This observation indicates that **1** is conformationally mobile at ambient temperature in solution. By comparison, 5,11,17,23,29,35-hexa-*tert*-butylcalix[6]arene, which contains six hydroxy groups, shows a very broad resonance at room temperature in $CDCl_3$ for the bridging methylenes. When 5,11,17,23,29,35-hexa-*tert*-butylcalix[6]arene is cooled down to −50 °C, the bridging methylenes can be resolved into three sets of overlapping quartets.[26] By contrast, the bridging methylenes for **1** just start to broaden out at −50 °C (Figure 2), and the fully methoxylated compound 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41,38,40,42-hexamethoxycalix[6]arene shows a sharp singlet for the bridging methylenes even at −50 °C.[27,28] These differences in coalescence temperatures indicate that the fully methoxylated compound is even more conformationally mobile than is **1** in solution. This increase in conformational mobility can be explained in terms of the decrease in hydrogen bonding, since as the degree of methoxylation is increased the amount of hydrogen bonding in the calix[6]arenes is decreased and the calix[6]arenes become conformationally more mobile.

A further consequence of the decrease in hydrogen bonding is seen in the shifts of the hydroxy resonances in the ^{1}H NMR spectrum. In 5,11,17,23,29,35-hexa-*tert*-butylcalix[6]arene, the hydroxy resonance is observed at δ 10.5, while in **1** this resonance appears at δ 6.77, which corresponds to an upfield shift of almost 4 ppm. Additionally, the variable-temperature ^{1}H NMR spectrum shows that there is a change in the chemical shift of the hydroxy resonance as the temperature of the solution is lowered. At ambient temperature the hydroxy resonance for **1** appears at δ 6.77. At −50 °C the peak appears as a broad resonance as δ 7.13. In **1** the hydroxy groups are separated by methoxy groups, and in solution at room temperature the molecule is conformationally mobile. At lower temperature the calix[6]arene becomes less conformationally mobile which allows for the hydroxy groups to hydrogen bond better. This resulting increase in hydrogen bonding results in a downfield shift of the hydroxy resonance.

Introduction of Hydroxyalkoxy Substituents onto the Lower Rim. In this paper we report two different synthetic routes for the introduction of an aliphatic hydroxyalkoxy substituent onto the lower rim of the calix[*n*]arene. One method involves converting the hydroxy groups of the lower rim into allyloxy groups, which are then converted into 3-hydroxypropoxy groups *via* a hydroboration and oxidation sequence. The other method,

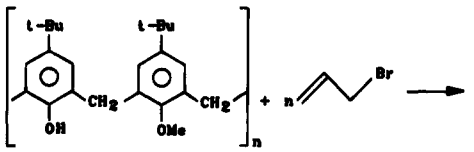
(26) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052–9.

(27) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409–26.

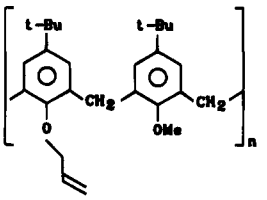
(28) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6059–63.

which results in the introduction of 2-hydroxyethoxy groups onto the lower rim, involves the reduction of an intermediate ethyl acetato-substituted calixarene with lithium aluminum hydride. The introduction of 3-hydroxypropoxy groups by the oxidative hydroboration approach can be used with the compounds **1** and **3**. This method is unsuccessful for the unsubstituted calixarenes where complete hydroboration of all the allyloxy groups cannot be accomplished. The introduction of the 2-hydroxyethoxy groups *via* the ethyl acetato intermediate can, however, be used to fully substitute all the lower rim positions.

Methoxy Allyloxy-Substituted Calixarenes. The compounds **1** and **3** have been converted into 5,11,17,-23,29,35-hexa-*tert*-butyl-37,39,41-tris(3-hydroxypropoxy)-38,40,42-trimethoxycalix[6]arene, **6**, and 5,11,17,23-tetra-*tert*-butyl-25,27-bis(3-hydroxypropoxy)-26,28-dimethoxycalix[4]arene, **7**. This conversion has been achieved by a sequence of reactions where **1** and **3** are first reacted with allyl bromide under basic reaction conditions to give the allyloxy derivatives 5,11,17,23,29,-35-hexa-*tert*-butyl-37,39,41-tris(allyloxy)-38,40,42-trimethoxycalix[6]arene, **4**, and 5,11,17,23-tetra-*tert*-butyl-25,27-bis(allyloxy)-26,28-dimethoxycalix[6] arene, **5** (eq 4). These allyoxy compounds are characterized in the ^{1}H



(n = 3, **4**, n = 2, **5**)



(4)

NMR spectrum by the presence of resonances due to the methoxy protons at δ 2.52 for **4** and at δ 3.19 and δ 3.93 for **5**, resonances due to the respective allyloxy protons CH_2, -CH, and =CH_2 at δ 4.16, δ 5.92, and a pair of =CH_2 resonances at δ 5.05 and δ 5.23 for **4** and at δ 3.71, δ 6.3, and δ 5.35 for **5**. The corresponding peaks for these different functional groups are also present in the ^{13}C-{^{1}H} NMR spectra of these compounds.

An ORTEP representation of **5** in Figure 3 shows that this molecule adopts the partial cone conformation in the crystalline state with one of the aromatic rings bearing methoxy group on the lower rim being in the "down" position. The conformation in the crystalline state of **4** can be described as 1, 2, 3 "up" 4, 5, 6 "down" as shown in the PLUTO drawing (Figure 4). A common feature in the crystal structures of these two calixarenes **4** and **5** is the contraction of the C=C bond between the terminal carbon atoms of the allyloxy groups. A similar contraction of the bond lengths between the terminal carbons in the allyloxy fragments has been recently reported for another calix[4]arene molecule,[29] which implies that this is possibly a common trend for allyloxy-substituted calixarenes.

(29) Georgiev, E. M.; Mague, J. T. ; Roundhill, D. M. *Supramol. Chem.* **1993**, *2*, 53–60.

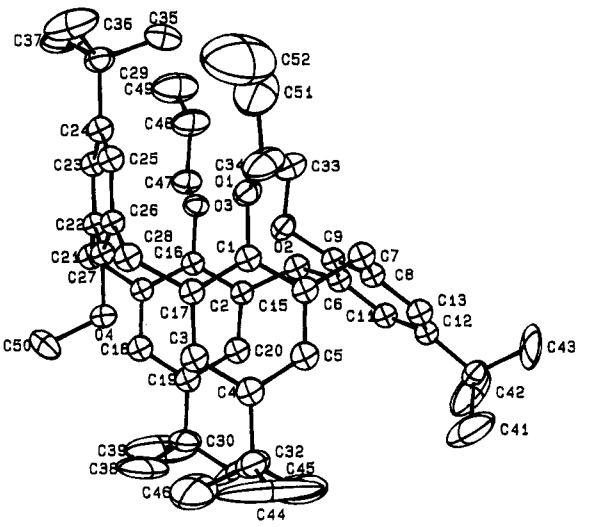
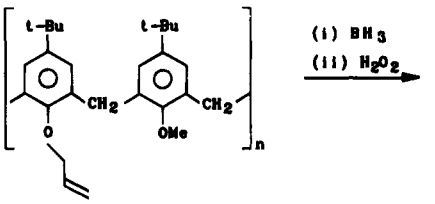
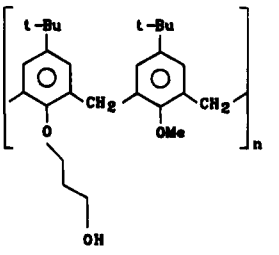


Figure 3.

Methoxy 3-Hydroxypropoxy-Substituted Calixarenes. Treatment of the allyloxy derivatives **4** and **5** with borane under hydroboration conditions, followed by cleavage of the intermediate borane with hydrogen peroxide, results in the formation of the 3-hydroxypropoxy derivatives **6** and **7** in yields of approximately 20% (eq 5). These 3-hydroxypropoxy compounds are charac-



(n = 3, **6**, n = 2, **7**)



(5)

terized in the ^{1}H NMR spectrum by resonances due to the methoxy and methylenic hydrogens. For **6** these resonances occur as a multiplet at δ 3.60. For **7** the methoxy resonances are observed at δ 3.67 and δ 3.88 and the hydroxypropoxy resonances for $OCH_2CH_2CH_2$-OH, $OCH_2CH_2CH_2OH$, and $OCH_2CH_2CH_2OH$ at δ 1.83, δ 4.01, and δ 3.69, respectively. The corresponding ^{13}C-{^{1}H} NMR spectra show resonances for the 3-hydroxypropoxy carbons at δ 32.62, δ 60.22, and δ 71.79 for **6** and at δ 39.41, δ 60.44, and δ 72.16 for **7**.

The analogous 3-hydroxypropoxy derivatives of the fully hydroxylated calixarenes cannot be prepared by this procedure because the hydroboration step fails. It appears that cross-coupling reactions occur between the alkylboranes that are formed and the double bonds of the remaining allyloxy groups. The presence of alkyborane and allyloxy substituents in adjacent positions apparently leads to a facile intramolecular reaction between the borane and alkene bonds.

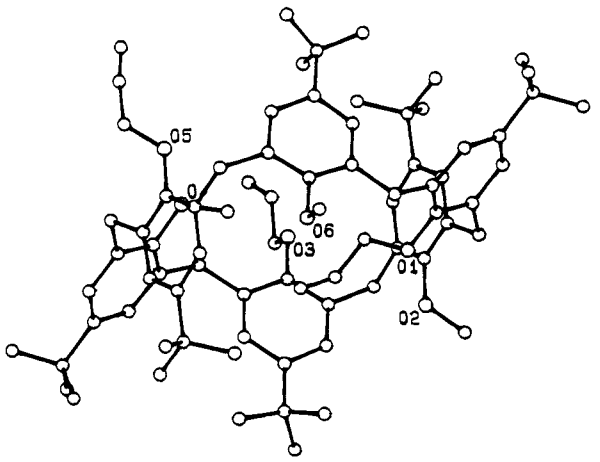
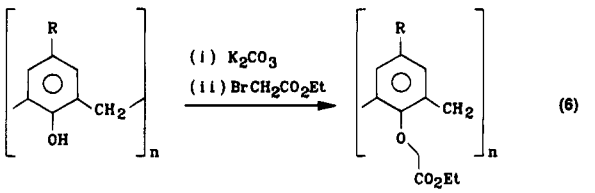


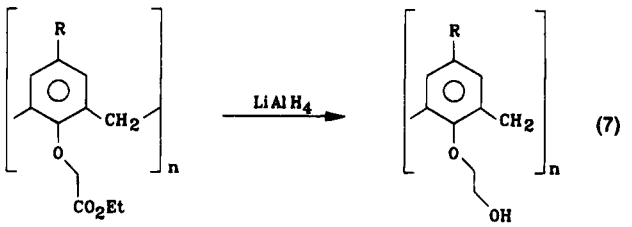
Figure 4.

2-Hydroxyethoxy-Substituted Calixarenes. The 2-hydroxethoxy group can be attached to the lower rim of a calix[4]arene, calix[6]arene, and calix[8]arene to give a tetrol, a hexol, and an octol, respectively. These compounds have been obtained by treating the corresponding calixarene first with potassium carbonate and then with ethyl bromoacetate to give the calixarene having ethyl acetato groups substituted on each of the lower rim positions (eq 6).[12] Subsequent reduction of this



(n = 4, 6, 8; R = H, *tert*-Bu)

intermediate ester with lithium aluminum hydride gives the 2-hydroxyethoxy-substituted calixarene (eq 7). This



(R = *tert*-Bu; n = 4, **8**; n = 6, **10**; n = 8, **12**)
(R = H; n = 4, **9**; n = 6, **11**; n = 8, **13**)

method has been used to prepare compounds **8**–**13**. These 2-hydroxyethoxy-substituted calix[*n*]arenes (*n* = 4, 6, and 8) have either a *tert*-butyl group or a hydrogen atom in the *para* position of the calixarene. Both the *tert*-butyl- and hydrogen-substituted compounds show resonances in the ^{1}H NMR spectrum due to ring ArCH_2 protons in the vicinity of δ 3.25 and δ 4.38 and to hydroxy O*H* protons in the δ 4–5 range. The assignment of the O*H* resonances has been confirmed by the observed disappearance of the resonance when D_2O is added to the solution. The *tert*-butyl-substituted calixarenes show additional resonances due to $C(CH_3)_3$ protons in the region of δ 1.13–1.16. The 2-hydroxyethoxy group is identified in the ^{1}H NMR spectrum by OCH_2 resonances in the δ 3.95–4.05 range. The structures of **9** and **10** have been confirmed by single crystal X-ray crystallography.

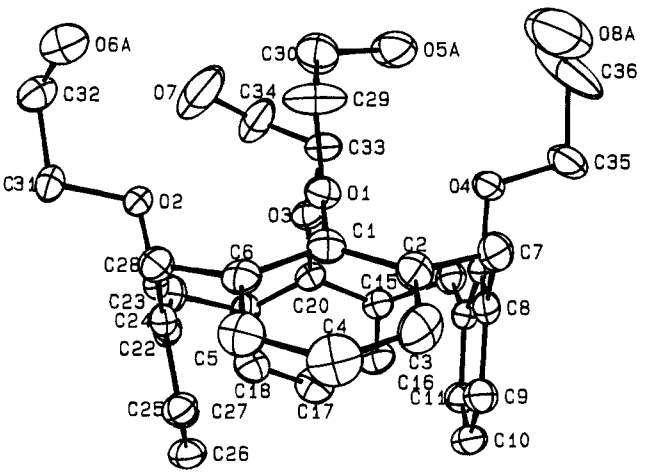


Figure 5.

Compound **9** crystallizes in the cone conformation (Figure 5). Toluene solvent molecules are occluded within the crystal lattice. These toluene molecules are incorporated into the gaps between the bulky calixarene molecules, and they do not form an inclusion complex as was found for toluene in *tert*-butylcalix[4]arene.[30] The cone conformation of **9** is additionally stabilized by multiple hydrogen bonds. An interesting structural feature of **9** is the alternating values of the inclination angles of the aromatic rings with respect to the best plane defined by the four bridging methylene carbons.[31] In the absence of the bulky *tert*-butyl substituents on the upper calixarene rim the inclination angles of the aromatic rings for the cone conformation should be totally dependent on the type of interactions between the substituents on the lower rim.[32] The interaction of the 2-hydroxyethoxy groups in **9** is defined by the attraction of the terminal hydroxy groups due to the hydrogen bond formation, counteracted by repulsion between the alkoxy fragments on the substituents. As a result of these two opposing factors the inclination angles for the sequential aromatic groups in **9** are 141.4(2)°, 82.8(1)°, 135.6(1)°, and 81.8(1)° for molecule 1 in the lattice. Thus, the two opposite aromatic rings have inclination angles that are either greater than 120° because of stronger hydrogen bonding between the substituents on the upper rim or have inclination angles less than 90° because of prevailing steric repulsion. We believe that this structure is the first example of a nonbridged calix[4]arene crystallizing in the cone conformation with inclination angles of two opposite aromatic rings being below 90°.

The hexol **10** crystallizes in the pinched cone conformation (Figure 6). The compound forms a 1:1 inclusion complex in the solid state with an ethanol solvent molecule.[33] The orientation of this occluded ethanol molecule and the conformation of the host are stabilized by two hydrogen bonds that the ethanol guest molecule forms with its host. This is one of the few examples of a

(30) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005–7.
(31) For a definition of the inclination angles in the cone conformation of calix[4]arenes see: Böhmer, V.; Vicens, J. In *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic Publishers: London, 1991; pp 54–7.
(32) Ugozzoli, F.; Andreetti, G. D. *J. Incl. Phenom. Mol. Recogn.* **1992**, *13*, 337–48.
(33) For an example of a calixarene with an occluded ethanol molecule see: Bugge, K.-E.; Verboom, W.; Reinhoudt, D. N. *Acta Crystallogr.* **1992**, *C48*, 1848–51.

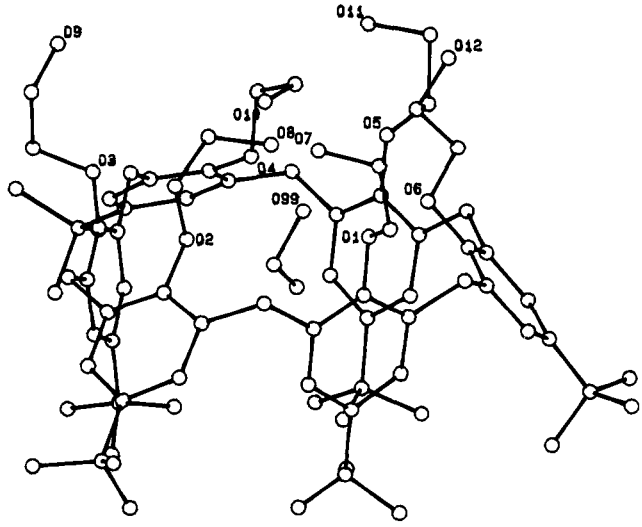
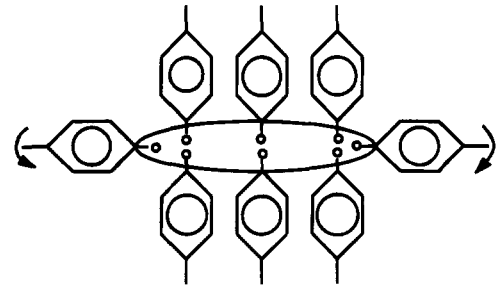


Figure 6.

hydrogen-bonded ethanol molecule occluded within a calixarene host.[34] The molecular (1:1) complex of **10** and ethanol has unique character since the ethanol molecule is sitting entirely in the calixarene cavity with its aliphatic end pointed inward toward the hydrophobic pocket and its hydroxy group forming two hydrogen bonds with the hydroxy and ether functionalities of the hydrophilic part of the calixarene host.

Molecular Mechanics Calculations. Molecular mechanics of the conformers of the 2-hydroxyethoxy-substituted calixarenes **8**–**13** provides information about the influence of both ring size and *para* substituent on the conformational properties. The different conformers are described in terms of the notation introduced recently by Gutsche.[35] This notation employs descriptors of the type "u" (up), "d" (down), and "o" (out) as well as their modifications "uo" (up and out), "ui" (up and in), "do" (down and out) and "di" (down and in) in order to describe the orientation of the aryl groups of the calixarene ring relative to the average plane of the molecule as determined by its bridging methylene groups.

The computational results for the four conformers of **9** with both CVFF and CHARMm force fields predict that the cone conformer **9a** is the global minimum structure, which agrees with the X-ray structural data. The relative energy of the partial cone conformer **9b** is the highest with both CVFF and CHARMm force fields, whereas for the conformers **9c** (1,3 alternate) and **9d** (1,2 alternate) different orderings have been obtained for the relative energies with the two force fields. A comparison of the optimized structures for the cone conformer **9a** from both CVFF and CHARMm force fields with the X-ray analysis data for this compound reveals that only the CVFF calculations reproduce a qualitatively correct set for the inclination angles of the four aromatic rings. The values for these angles calculated with the CVFF force field are 79.82°, 134.31°, 74.80°, and 130.57°, which differ only slightly from the values of 82.81(1)°, 141.4(2)°, 81.8(1)°, and 135.1(1)° obtained experimentally from the X-ray crystal structure data. By contrast, the CHARMm force field calculations for the cone conformation of **9** provide a set of inclination angles having all values larger than 90°, namely 98.33°, 133.60°, 98.49°, and 139.50°. Thus, the CVFF force field appears to better reproduce the experimental geometries than does the CHARMm force field.



o.u.u.u.o.d.d.d

Figure 7.

Introduction of a bulky *tert*-butyl substituent onto the *para* positions of the upper rim of **9a** leads to an increase in the inclination angles in the cone conformation. These angles all become larger than 90° as a result of steric repulsion between the *tert*-butyl groups. The values found for **8a** are 96.78°, 123.10°, 95.12°, and 136.04°. Moreover, these calculations predict that the cone conformation of **8** has the highest energy with the 1,2 alternate conformation **8d** having the lowest energy.

From the pinched cone conformers of hexamers **10a** and **11a**, calculation of the inclination angles by the use of a set of two reference planes proved unsuccessful because the deviation of the bridging methylene carbons from one of these two best planes is always unacceptably large (0.4 Å).[36] Molecular mechanics calculations do not predict the pinched cone conformer **10a** as that having the lowest energy. Possibly **10** crystallizes in the pinched cone conformation because of the stabilizing effect of the ethanol guest molecule, which forms two hydrogen bonds with its calixarene host.

The computed conformers of octamers **12** and **13** have a large number of aryl groups (up to 4) in an "o" (out) position, probably because of the increased conformational mobility of these two large macrocycles. In some of these "out" orientations half of the aryl groups are above and half are below the average plane of the molecule (Figure 7). Characteristic for such a particular orientation of the aryl group is that whereas its inclination angle varies from 0° to 90°, the axis that passes through the phenyl oxygen, and the *ipso* and *para* carbons, remains parallel to the average plane of the molecule. Possibly the conformational notations of the aryl groups in calixarenes can be better applied using the orientation of the O–C–C_{para} axis toward the average plane of the molecule instead of the inclination angles.[35]

Optimized structures of 2-hydroxyethoxy-substituted calix[8]arenes such as the *tert*-butyl substituted homologue **12** form a reversed "micro micelle" type of structure. In the majority of the computed conformers for **12** the hydrophilic 2-hydroxyethyloxy functionalities are positioned inside the calixarene cavity (head to head-type

(34) The hydrogen atoms participating in this hydrogen bonding were located from the difference Fourier map.

(35) Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572–9.

(36) Perrin, M.; Oehler, D. In *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Bohmer, V., Eds.; Kluwer Academic Publishers: London, 1991; pp 75–80.

(37) The author has deposited atomic coordinates for **2**, **4**, **5**, **9**, and **10** 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.

interaction) and are connected by multiple hydrogen bonds. By contrast, the hydrophobic *tert*-butyl groups (tails) are pointed away from the cavity. In all the "o" (out) orientations of the aryl groups we found no examples of the hydrophobic *tert*-butyl group being oriented inside the calixarene cavity. This result is not entirely surprising since calixarenes **8**–**13** represent examples of molecules bearing hydrophilic and hydrophobic functionalities on their lower and upper rims, respectively. A consequence of the increased conformational mobility in the larger macrocycles **12** and **13** is that the hydrophobic/hydrophilic interactions govern to a greater extent the conformational properties of these compounds, resulting in the formation of hydrophilic cavity and a hydrophobic zone on the periphery of the calixarene molecule.

Acknowledgment. We thank the Center for Bioenvironmental Research for financial support. We thank Dr. F. Fronczek (LSU) for the crystallographic data collection for compound **4**.

Supplementary Material Available: Tables of crystal data positional parameters, bond angles, bond distances, and general displacement parameter expressions along with values of 10* F_{obs} and 10* F_{calc} for **2**, **4**, **5**, **9**, and **10**. Tables of NMR assignments. Figures of possible conformers for the unsubstituted 2-hydroxyethoxy calixarenes and a table of calculated energies in kcal/mol for the conformers of calixarene alcohols **8**–**13** obtained by Molecular Mechanics calculations (109 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.