Synthesis of Covalently-Linked *exo*-Calix[4]arenes

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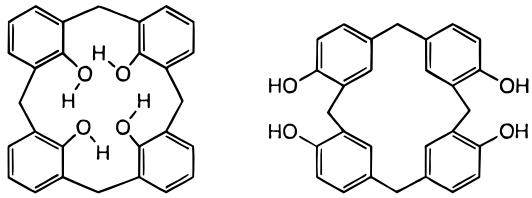
Calix[4]arenes, or *endo*-calix[4]arenes, **1** have been extensively studied for the past several decades,[1] but *exo*-calix[4]arenes **2** have only recently attracted much attention.[2−4] With respect to structure, an *exo*-calixarene, having the OH groups on the "upper rim" of the bowl-shaped molecules, is actually more similar to a resorcinarene (**3a**)[5] or cavitand (**3b**)[5] than to the corresponding *endo*-isomer. We report here the preparation of a tetra-(propyl-substituted) *exo*-calix[4]arene and a study of the conformational properties of it and some covalently-linked derivatives.



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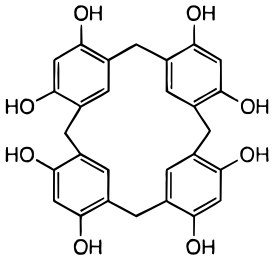
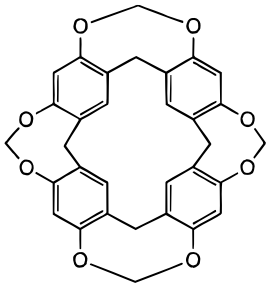


3a



3b

Experimental Section

General. All reagents used were analytical grade. DMF, CH_2Cl_2, and $CHCl_3$ were distilled from CaH_2. ^1H NMR spectra were recorded on a Varian VXR 300 MHz or on a Varian XL400 spectrometer. Mass spectra and high-resolution mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at the North Carolina State University in Raleigh. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

2,2-Bis[4′-(allyloxy)phenyl]propane (4b). Bisphenol A (235 g, 1.00 mol), allyl chloride (330 mL, 4.00 mol), potassium carbonate (276 g, 2.00 mol), sodium iodide (6.00 g, 0.040 mol), and absolute ethanol (1.50 L) were added to a 3 L three-necked round-bottomed flask. The mixture was allowed to reflux for 24 h under argon, cooled to ambient temperature, and filtered to remove solid material. The solvent was evaporated under reduced pressure to give a brown liquid (301 g, 98%). ^1H NMR ($CDCl_3$): δ 7.12 (dd, 4H, J = 7.8, 1.0 Hz); 6.81 (dd, 4H, J = 7.8, 1.0 Hz); 6.10−5.98 (m, 2H); 5.39 (dt, 2H, J = 17.4, 1.2 Hz); 5.26 (dt, 2H, J = 10.8, 1.2 Hz); 4.49 (d, 4H, J = 4.5 Hz); 1.62 (s, 6H).

2,2-Bis[3′-allyl-4′-hydroxyphenyl]propane (5). The crude compound **4b** (31 g, 0.10 mol) was heated to 160−180 °C for 4 h under argon and then cooled to ambient temperature to give a brown oil (30 g, 95%). ^1H NMR ($CDCl_3$): δ 6.95 (d, 2H, J = 7.8 Hz); 6.94 (s, 2H); 6.69 (d, 2H, J = 7.8 Hz); 5.98 (m, 2H); 5.11 (dt, 4H, J = 9.9, 1.2 Hz); 4.82 (bs, 2H, OH); 3.25 (d, 4H, J = 6.3 Hz); 1.59 (s, 6H).

2,2-Bis[3′-propyl-4′-hydroxyphenyl]propane (6). The crude compound **5** (62 g, 0.20 mol) was dissolved in methanol (1 L), and to this solution was added 5% Pd/C (5 g). The solution was degassed by purging with argon, and then hydrogen gas was bubbled through the solution for 24 h. The solution was filtered through Celite to remove the Pd/C, and the solvent was evaporated under reduced pressure to give an orange oil (60 g, 98%). ^1H NMR ($CDCl_3$): δ 6.93 (s, 2H); 6.91 (d, 2H, J = 7.6 Hz); 6.63 (d, 2H, J = 7.6 Hz); 4.58 (s, 2H); 2.51 (t, 4H, J = 7.6 Hz); 1.59 (s, 6H); 1.55 (m, 2H); 0.91 (t, 6H, J = 7.3 Hz).

2,2,14,14-Tetramethyl-8,11,17,23-tetrapropyl-6,10,18,22-tetrahydroxycalix[4]arene (7). The crude compound **6** (3.12 g, 10 mmol) and paraformaldehyde (0.38 g, 12 mmol) were dissolved in dried methylene chloride (1 L). The solution was degassed by purging with argon, and then $BF_3{\cdot}OEt_2$ (1.30 mL, 10 mmol) was added by syringe. The solution turned green after several minutes, and it was stirred at ambient temperature for 12 h. Water (200 mL) was added to quench the reaction and the methylene chloride solution was washed with two 200 mL portions of water and two 200 mL portions of brine and dried over Mg_2SO_4. The solvent was then evaporated under reduced pressure to give a yellow solid. The product was purified by chromatography on silica gel column using hexane−ethyl acetate (4:1). The second component was collected by combining appropriate fractions, and the solvent was evaporated under reduced pressure. The residue was crystallized from $CHCl_3$−hexanes to yield a white solid (712 mg, 22%). Mp: 213 °C. ^1H NMR ($CDCl_3$): δ 7.02 (d, 4H, J = 2.4 Hz); 6.62 (d, 4H, J = 2.4 Hz); 5.82 (s, 4H); 3.71 (s, 4H); 2.53 (t, 8H, J = 7.8 Hz); 1.67−1.55 (m, 20H); 0.96 (t, 12H, J = 7.5 Hz). MS {EI} *m*/*e*: calcd 648.42, found 648.42. Anal. Calcd for $C_{44}H_{56}O_4{\cdot}H_2O$: C, 79.3; H, 8.77. Found: C, 79.4, H, 8.70.

Mono- and Bis(methylene-linked)-2,2,14,14-tetramethyl-8,11,17,23-tetrapropyl-6,10,18,22-tetrahydroxycalix[4]-arene (8a and 9a). A solution of calixarene **7** (312 mg, 0.500 mmol) and K_2CO_3 (690 mg, 5.00 mmol) in 200 mL of DMF was degassed by purging with argon; CH_2BrCl (0.66 mL, 1.20 mmol) was then added. The solution was heated at reflux for 48 h under argon. After that, the solution was filtered; and the DMF was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and this solution was washed with two 100 mL portions of dilute hydrochloric acid, two 100 mL portions of brine and dried over $MgSO_4$. Evaporation of the solvent gave a yellow solid, which was purified by chromatography on silica gel column using hexane−ethyl acetate (9:1). The first component was collected, and the solvent was evaporated under reduced pressure. The residue was crystallized from $CHCl_3$−hexanes to yield a white solid, **9a** (25 mg, 15%). Mp: >300 °C. ^1H NMR ($CDCl_3$): δ 7.13 (d, 4H, J = 2.1 Hz); 6.66 (d, 4H, J = 2.1 Hz); 6.02 (d, 2H, J = 7.2 Hz); 4.65 (d, 2H, J = 7.2 Hz); 4.45 (d, 2H, J = 12 Hz); 3.05 (d, 2H, J = 12 Hz); 2.61−2.50 (m, 8H); 1.68−1.50 (m, 20H); 0.97 (t, 12H, J = 7.5 Hz). Anal. Calcd for $C_{46}H_{56}O_4{\cdot}H_2O$: C, 80.1; H, 8.47. Found: C, 80.0; H, 8.38. MS {EI} *m*/*e*: calcd 672.42, found 672.42.

The second component was also collected, and the solvent was evaporated under reduced pressure. The residue was crystallized from $CHCl_3$−hexanes to yield a white solid, **8a** (135 mg, 41%). Mp: 203 °C. ^1H NMR ($CDCl_3$): δ 7.11 (d, 2H, J = 2.7 Hz); 7.03 (d, 2H, J = 2.7 Hz); 6.77 (d, 2H, J = 2.7 Hz); 6.48 (d, 2H, J = 2.7 Hz); 6.01 (s, 2H), 5.98 (d, 1H, J = 6.8 Hz); 4.57 (d, 1H, J = 6.8 Hz); 4.51 (d, 1H, J = 12 Hz); 4.08 (d, 1H, J = 14.7

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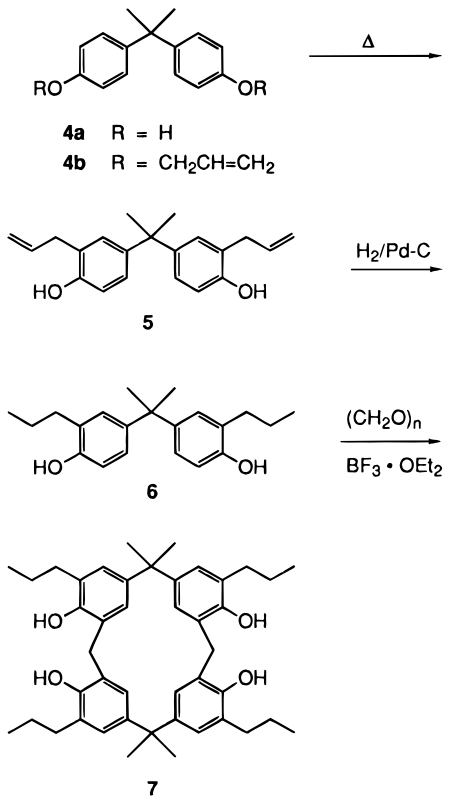
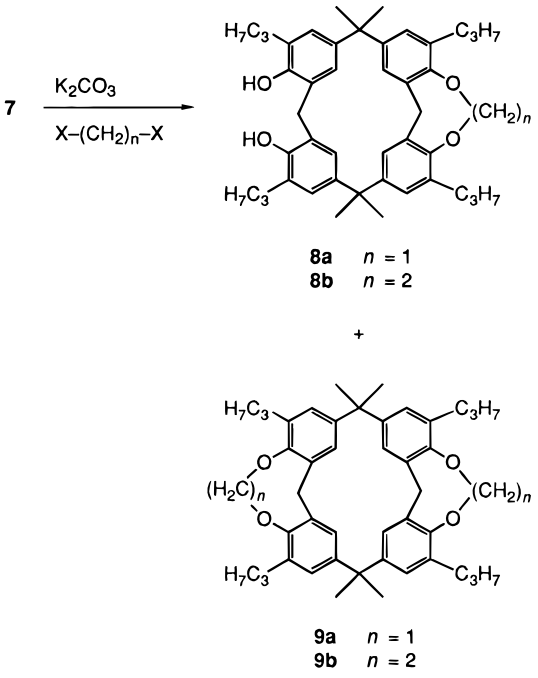
S0022-3263(96)01815-4 CCC: $14.00

Scheme 1



Scheme 2



Hz); 3.22 (d, 2H, J = 14.7 Hz); 3.12 (d, 1H, J = 12 Hz); 2.62−2.36 (m, 8H); 1.68−1.50 (m, 20H); 1.02−0.91 (m, 12H). MS {EI} *m/e*: calcd 660.42, found 660.42. Anal. Calcd for $C_{45}H_{56}O_4 \cdot 0.5H_2O$: C, 80.7; H, 8.58. Found: C, 80.5; H, 8.41.

Bis(ethylene-linked)-2,2,14,14-tetramethyl-8,11,17,23-tetrapropyl-6,10,18,22-tetrahydroxycalix[4]arene (9b). A solution of calixarene **7** (312 mg, 0.500 mmol) and K_2CO_3 (690 mg, 5.00 mmol) in 200 mL of DMF was degassed by purging with argon; ethylene distosylate (465 mg, 1.20 mmol) was then added. The solution was heated at reflux for 48 h under argon and then worked up as described for **9a** to yield **9b** (215 mg, 61%). Mp: 206 °C. ^{1}H NMR ($CDCl_3$): δ 7.07 (d, 4H, J = 2.7 Hz); 6.65 (d, 4H, J = 2.7 Hz); 4.75 (d, 2H, J = 12.9 Hz); 4.34 (m, 4H); 3.86 (m, 4H); 2.95 (d, 2H, J = 12.9 Hz); 2.67 (m, 4H); 2.45 (m, 4H); 1.67−1.55 (m, 20H); 0.94 (t, 12H, J = 7.5 Hz). Anal. Calcd for $C_{48}H_{60}O_4 \cdot H_2O$: C, 81.3; H, 8.66. Found: C, 81.5; H, 8.69.

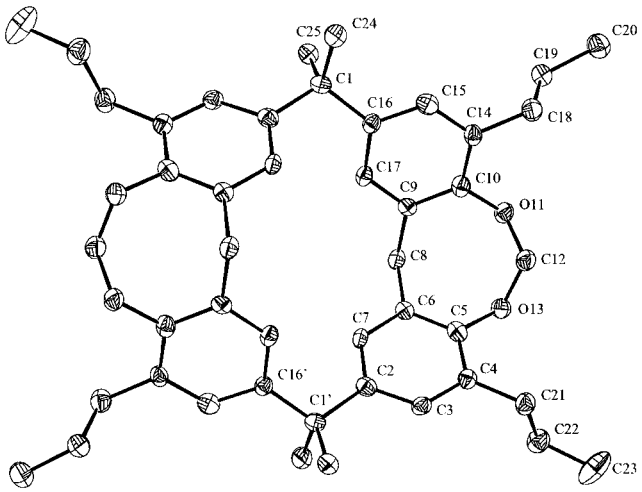


Figure 1. Top view of the molecular structure of bis-(methylene-linked)-2,2,14,14-tetramethyl-8,11,17,23-tetrapropyl-6,10,18,22-tetrahydroxycalix[4]arene (**9a**) showing the atom numbering scheme. Selected distances in Å (the prime marks denote the symmetry related atom): C6−C9, 2.531(3); C6−C9′, 5.483(3); C5−C10, 3.528(3); C5−C10′, 7.451(3); C4−C14, 5.812(3); C4−C14′, 7.401(3); C3−C15, 7.098(3); C3−C15′, 5.037(3).

Mono(ethylene-linked)-2,2,14,14-tetramethyl-8,11,17,23-tetrapropyl-6,10,18,22-tetrahydroxycalix[4]arene (8b). A solution of calixarene **7** (312 mg, 0.500 mmol) and K_2CO_3 (690 mg, 5.00 mmol) in 200 mL of DMF was degassed by purging with argon; ethylene distosylate (235 mg, 0.600 mmol) was then added. The solution was heated at reflux for 48 h under argon and then worked up as described for **8a**. The second component from chromatography was crystallized from CH_2Cl_2−hexanes to yield a light yellow solid (35 mg, 12%). Mp: 168−169 °C. ^{1}H NMR ($CDCl_3$): δ 7.04 (m, 4H); 6.72 (d, 2H, J = 2.4 Hz); 6.63 (d, 2H, J = 2.4 Hz); 5.82 (s, 2H); 4.72 (d, 1H, J = 12.9 Hz); 4.31 (m, 2H); 4.14 (d, 1H, J = 14.7 Hz); 3.79 (m, 4H); 3.37 (d, 1H, J = 14.7 Hz); 2.96 (d, 1H, J = 12.9 Hz); 2.71−2.30 (m, 8H); 1.68−1.50 (m, 20H); 1.02−0.91 (m, 12H). Anal. Calcd for $C_{46}H_{58}O_4 \cdot H_2O$: C, 79.8; H, 8.73. Found: C, 79.8; H, 8.66.

X-ray Crystal Structure Determination of Mono(methylene-linked)-2,2,14,14-tetramethyl-8,11,17,23-tetrapropyl-6,10,18,22-tetrahydroxycalix[4]arene (9a). Crystals of compound **9a** suitable for single-crystal X-ray diffraction were grown by layering a $CHCl_3$ solution of **9a** with hexane. Measurements were carried out on a colorless crystal with use of a Rigaku AFC-6S diffractometer. The structure was refined using full-matrix least-squares techniques.[6] Calculations were performed using the NRCVAX system. No correction was made for absorption.[10]

Results and Discussion

Tetrapropyl *exo*-calixarene **7** could be obtained in four steps starting with bisphenol A (Scheme 1). Thus, treating **4a** with allyl chloride gives 2,2-bis[4′-(allyloxy)-phenyl]propane (**4b**), which undergoes Claisen rearrangement to 2,2-bis(3′-allyl-4′-hydroxyphenyl)propane (**5**) upon heating at 180 °C. Hydrogenation of **5** yields 2,2-bis(3′-propyl-4′-hydroxyphenyl)propane (**6**). Condensation of **6** with paraformaldehyde in the presence of $BF_3 \cdot OEt_2$ affords the *exo*-calixarene **7** in 22% yield.

Like its *tert*-butyl analog,[3] compound **7** is conformationally mobile in solution as determined by NMR analysis. The ^{1}H NMR spectrum of **7** at 293 K exhibits two doublets at δ 7.02 and 6.62 ppm (J = 2.4 Hz) for the aromatic protons and a singlet at 3.71 ppm for the

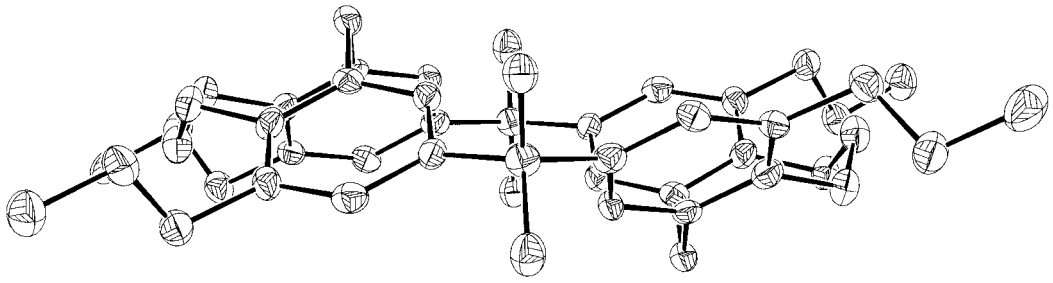
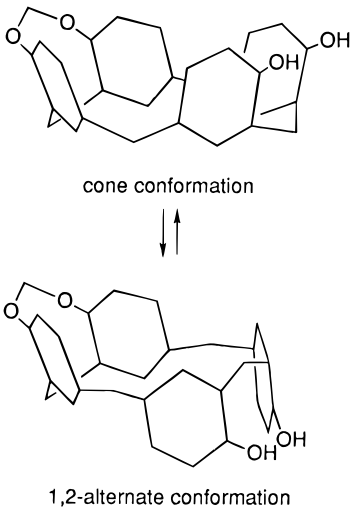


Figure 2. Side view of **9a** showing the flattened 1,2-alternate conformation.

methylene protons. No appreciable changes in the appearance of these signals are observed over the temperature range 185−323 K.

Calixarene **7** reacts with bromochloromethane or with ethylene ditosylate in the presence of potassium carbonate, producing a mixture of mono- and bis-linked calixarenes (**8** and **9**) that can be separated by chromatography (Scheme 2). These covalently-linked molecules have a lower conformational mobility than **7**; in fact, the bis-linked compounds are conformationally locked. Mono(methylene-linked) calixarene **8a** at 293 K exhibits four doublets in the aromatic region (δ 7.11, 7.03, 6.77, and 6.48; J = 2.7 Hz), two pairs of doublets in the methylene region (δ 4.51 and 3.12; J = 12 Hz; δ 4.08 and 3.22; J = 14.7 Hz), and a pair of doublets for the $-OCH_2O-$ group at δ 5.98 and 4.57 (J = 6.8 Hz). As the temperature is lowered, the peaks at δ 6.77, 6.48, 4.08, and 3.22 broaden, reaching coalescence at 216 K, indicating that **8a** undergoes a conformational inversion at 216 K. Line-shape analysis experiments,[7] subsequently performed on a Varian XL400 spectrometer using acetone-d_6 as the solvent, were applied to determine the rate constant and energy barrier for this process. The DNMR3[8] program used to simulate the peak shapes gave values of k = 64 s^{-1} and $\Delta G^{\ddagger}$ = 10.7 kcal mol^{-1} for the conformational change. These values are consistent with those reported for a related compound.[3a] Mono(ethylene-linked) calixarene **8b** shows similar behavior in its NMR spectra as the temperature is lowered. These results are consistent with the notion that the cone and 1,2-alternate conformations of these mono-linked species can be frozen at low temperatures.



Bis(methylene-linked) calixarene **9a** at 293 K shows two doublets in the aromatic region (δ 7.13 and 6.66; J = 2.7 Hz), one pair of doublets in the methylene region (δ 4.45 and 3.05, J = 12 Hz), and a pair of doublets for the two $-OCH_2O-$ groups at δ 6.02 and 4.65 (J = 7.2 Hz). The NMR spectra do not show any significant change over the temperature range from 185 to 323K. CPK models show that these species are locked into either the cone or the 1,2-alternate conformation, and the two cannot be interconverted without breaking a bond.

The molecular structure of **9a**, shown in Figures 1 and 2, has been determined by single-crystal X-ray diffraction, and it represents the first structurally-characterized example of the 1,2-alternate conformation of an *exo*-calix[4]arene. Distances and angles between bonded atoms are unexceptional, and the molecule sits on an inversion center. It is notable that the compound is flattened from the idealized 1,2-alternate conformation that has been described previously.[3] This flattening may be the result of crystal packing forces. The two unique phenyl rings are pitched at angles of 37.28° and 36.78° relative to the horizontal plane defined by atoms C1, C2′, and C16, and several distances between the sets of phenyl rings are given in the caption to Figure 1. The methylene linkages between the adjacent oxygen atoms are *anti* to the methylene bridges between the phenyl rings. This is undoubtedly a result of unfavorable steric interactions that would result if the two pairs of methylene groups were *syn*.

Although the parent *exo*-calixarene **7** readily interconverts between the cone and 1,2-alternate conformations at ambient temperature, the bis-linked compounds **9** are not able to switch between those two forms. Unfortunately, we have not been able to obtain crystals of the isomer of **9a** having the cone conformation. We assume that it must exist in the product mixture because of the ready interconversion of the conformers of monolinked **8a**, its immediate precursor.[9] If these two conformers are present, then the cone and 1,2-alternate conformers of **9** must have indistinguishable ^1H NMR resonances because we only observe one set of peaks. Further work is in progress to utilize these new *exo*-calixarene derivatives for the construction of supramolecular assemblies.

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(9) It seems unlikely that *only* the 1,2-alternate conformation is generated when the adjacent pair of hydroxy groups in **8** is covalently linked to produce **9**.

(10) The author has deposited atomic coordinates for **9a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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