Synthesis and Reactions of Calix[4]arene Bisanhydrides[1]

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The tetrabenzyl ether, tetra-*p*-bromobenzenesulfonate, and tetra-*p*-methylbenzenesulfonate of *p*-carboxymethylcalix[4]arene in the 1,3-alternate conformation have been converted to the corresponding bisanhydrides. Reactions of the bisanhydrides with alcohols or amines afford calix[4]arenes carrying two carboxymethyl and two carboalkoxymethyl or two amidomethyl groups on the upper rim positions. The substitution pattern that is established confers molecular chirality on the calixarenes.

Calixarenes are cavity-containing macrocyclic compounds[2] that are of interest, inter alia, for their potential to serve as catalysts when appropriately substituted on the lower and/or upper rims. Among the numerous methods that have been fashioned for effecting upper rim functionalization are those employing anhydride intermediates, the first example of which was reported by Xie and Gutsche for a calix[4]arene monoanhydride.[3] The present paper extends these studies to calix[4]arene bisanhydrides and provides compounds that are useful precursors to upper rim-substituted calix[4]arenes possessing molecular chirality.

The starting material for the present study is *p*-cyanomethylcalix[4]arene (**1**),[4] prepared from the readily available *p-tert*-butylcalix[4]arene[5] by removal of the *tert*-butyl groups followed by application of the *p*-quinonemethide reaction sequence[6] (amino-methylation with HCHO and R_2NH, methylation with MeI, and treatment with CN^-). Subsequent functional group alteration was then carried out by two routes, one involving hydrolysis of the cyano groups *before* O-functionalization (**1** → **2** → **3** → **4** → **5**) and the other involving hydrolysis of the cyano groups *after* O-functionalization (**1** → **6** → **7** → **5**). In the first route acid-catalyzed hydrolysis of the tetracyano compound **1** followed by esterification with MeOH produced the previously reported[7] tetraester **2** which was treated with benzyl bromide and a large excess of K_2CO_3 to afford the tetrabenzyl ether **3** in 83% yield. The appearance of a singlet at δ 3.63 in the ^{1}H NMR spectrum and a line at δ 37.48 in the ^{13}C NMR spectrum[8] established the conformation as 1,3-alternate, and this conformation is retained throughout the remaining transformations. Hydrolysis of **3** with aqueous alcoholic KOH gave the tetracarboxylic acid **4** which, however, resisted conversion to an anhydride upon treatment with $(COCl)_2$ or $SOCl_2$ in CH_2Cl_2. Prolonged treatment with refluxing Ac_2O did produce the desired bisanhydride **5a**, but in only 8% yield. Therefore, an alternative route to the bisanhydrides was sought which started with the conversion of **1** to an arylsulfonate by treatment with *p*-toluenesulfonyl chloride (tosylation) or *p*-bromobenzenesulfonyl chloride (brosylation) in the presence of 1-methylimidazole, producing the 1,3-alternate conformers of **6b** and **6a**. Acid-catalyzed hydrolysis of the arylsulfonates gave the tetraacids **7a** and **7b** which reacted with $(COCl)_2$ under high dilution conditions to afford the bisanhydrides **5b** and **5c** in 61% and 34% yields, respectively. (Scheme 1).

The bisanhydrides **5a**−**c** reacted with alcohols (MeOH, EtOH, n-PrOH, i-PrOH) to give the half esters **8a**−**h** and with amines ($PhCH_2CH_2NH_2$, Et_2NH, Me_2CHNH_2) and bis[(3,5-dimethyl-1-pyrazoyl)ethyl]amine to give the half amides **10a**−**d** in quantitative yields (Chart 1). The products of these reactions all possess molecular chirality, and as a consequence display rather complex ^{1}H NMR spectral patterns. When the half esters **8a**−**h** are converted to the corresponding tetraesters **9a**−**h**, however, the ^{1}HNMR spectra became much less complex as the result of the transformation from chiral to achiral molecules (Scheme 2). In like fashion, the complexity of the ^{1}H NMR spectra of the half amides **10b** and **12** were markedly reduced when converted to the tetraamides **11a** and **11b**, respectively. A representative example of the contrasting ^{1}H NMR spectra for the chiral and achiral molecules is shown in Figure 1. The half amide **10d** and the tetraamides **11b**,**c** are of interest in connection with our ongoing study of copper-containing calixarenes as oxidation catalysts.[9]

Experimental Section[10]

5,11,17,23-Tetrakis(carbomethoxymethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (3) (1,3-Alternate Conformer). A mixture of 54.0 g (0.4 M) of anhydrous K_2CO_3 and

(1) Paper 51 in a series entitled Calixarenes. For paper 50, cf.: Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* **1999**, *64*, 998−1003.

(2) (a) Gutsche, C. D. *Calixarenes Revisited*; Stoddart, F. J., Ed.; Monographs in Supramolecular Chemistry: The Royal Society of Chemistry, 1998. (b) Böhmer, V. Calixarene, Macrocycles with (Almost) Unlimited Possibilities. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745. (c) Gutsche, C. D. Calixarenes. *Aldrichimica Acta* **1995**, 28, 3−9. (d) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991. (e) Gutsche, C. D. *Calixarenes*; Stoddart, F. J., Ed.; Monographs in Supramolecular Chemistry: The Royal Society of Chemistry, 1989.

(3) Xie, D.; Gutsche, C. D. *J. Org. Chem.* **1997**. *62*, 2280.

(4) The term "calixarene" is variously employed in different contexts. In colloquial usage (as employed in the Discussion Section), it implies the presence of oxygens on the lower rim. In the more precise and complete specification of a compound (as used in the Experimental Section), it implies only the basic skeleton to which the substituents, including the O-containing groups, are attached at positions designated by appropriate numbers.

(5) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234.

(6) Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153.

(7) Sharma, S. K.; Kanamathareddy, S.; Gutsche, C. D. *Synthesis* **1997**, 1268.

(8) Jaime, C.; deMendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

(9) Xie, D.; Gutsche, C. D. *J. Org. Chem.* **1999**, *63*, 9270.

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Published on Web 04/24/1999

Scheme 1

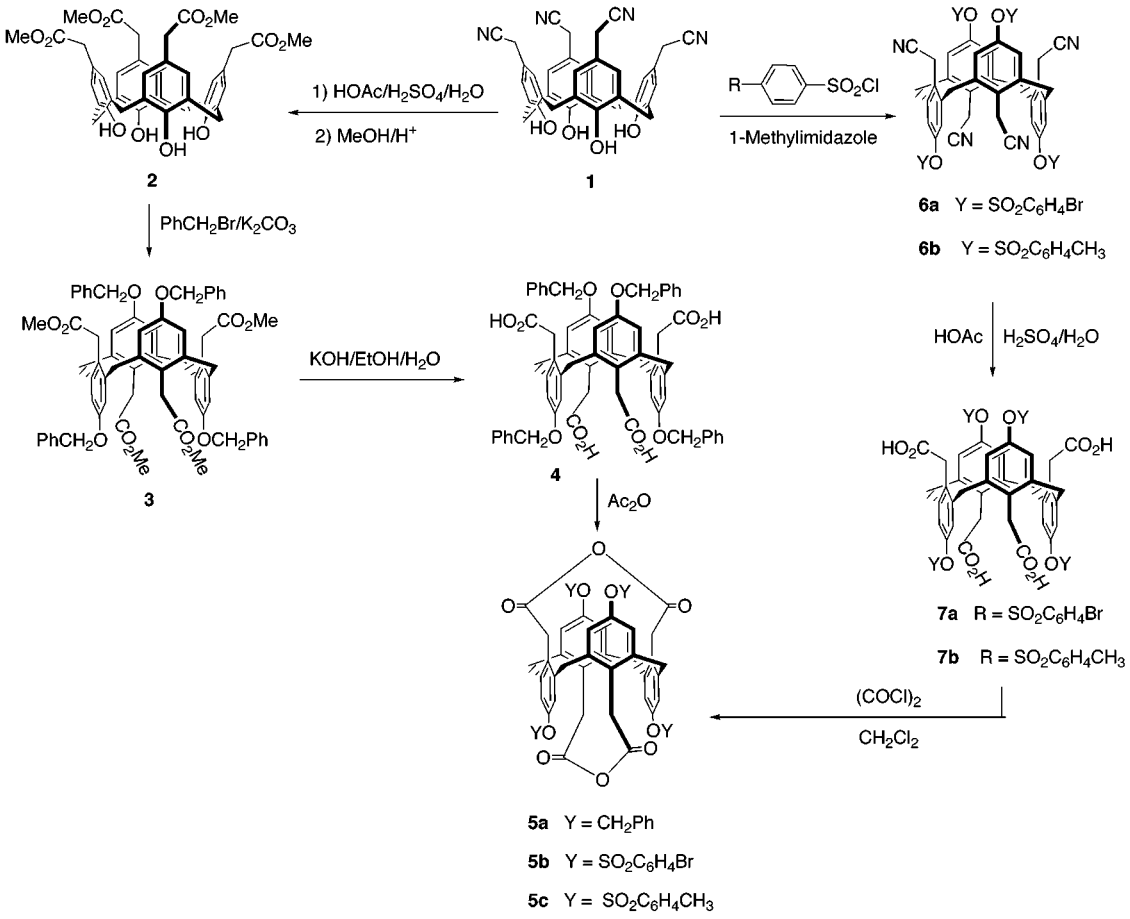
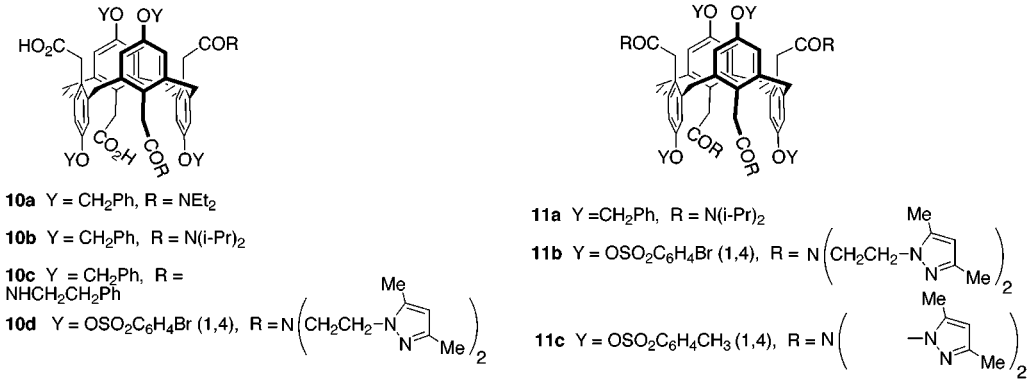


Chart 1



2.5 g of NaI was suspended in 200 mL of Me_2CO in a 500 mL round-bottomed flask, and 7.0 g (10 mmol) of the tetraester **2**[7] was added. The reaction mixture was stirred for 5 min, and 27.5 g (0.15 M) of benzyl bromide was added. The reaction mixture was stirred for 36 h at room temperature. The solvent was removed by evaporation, and the residue was poured into ice-cold water and neutralized with 20% HCl to give a light yellow precipitate. The precipitate was removed by filtration, and the product was purified by column chromatography (CH_2Cl_2 eluent) to give 8.90 g (83%) of the tetrabenzyl ether **3** as a white powder: mp 255−56 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (bs, 12), 7.08 (d, 8, J = 6.0 Hz), 6.57 (s, 8), 4.80 (s, 8), 3.63 (s, 8), 3.54 (s, 12), 2.89 (s, 8); ^{13}C NMR ($CDCl_3$) δ 172.57, 155.02, 138.32, 133.98, 131.90, 128.08, 127.34, 127.01, 126.36, 71.61, 51.73, 40.00, 37.48. Anal. Calcd for $C_{68}H_{64}O_{12}$: C, 76.10; H, 6.01. Found: C, 75.84; H, 6.03.

5,11,17,23-Tetrakis(carboxymethyl)-25,26,27,28-tetrakis-(benzyloxy)calix[4]arene (4) (1,3-Alternate Conformer). A mixture of 4.0 g (4 mmol) of tetraester **3**, 4.0 g (large excess) of KOH in 100 mL of EtOH, and 20 mL of H_2O was refluxed for 48 h, and progress of the reaction was monitored with ^{1}H NMR. After completion, most of the EtOH was removed under reduced pressure, and the residue was dissolved in ice-cold water and neutralized with 50% HCl to give a white precipitate. This was removed by filtraton, washed thoroughly with cold water, and dried at 80−90 °C for 2 days to give 2.71 g (72%) of the tetraacid **4**. An analytical sample was obtained by trituration with MeOH: mp 260−62 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.52−7.39 (m, 12), 7.10 (d, 8, J = 6.3 Hz), 6.57 (s, 8), 4.78 (s, 8H), 3.61 (s, 8H), 2.85 (s, 8); ^{13}C NMR ($CDCl_3$ + 1 drop DMSO-d_6) δ 174.27, 154.99, 138.35, 133.91, 132.14, 128.21, 128.03, 127.16, 126.61, 71.86, 40.37, 37.59. Anal. Calcd for $C_{64}H_{56}O_{12}\cdot H_2O$: C, 74.26; H, 5.65. Found: C, 74.36; H, 5.59.

Bisanhydride of 5,11,17,23-Tetrakis(carboxymethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (5a) (1,3-Alternate Conformer). A slurry of 3.5 g (3.5 mmol) of the tetraacid **4** in 200 mL ofAc_2O was stirred for 4 h at room temperature and then refluxed for 18 h in an oil bath at 135−

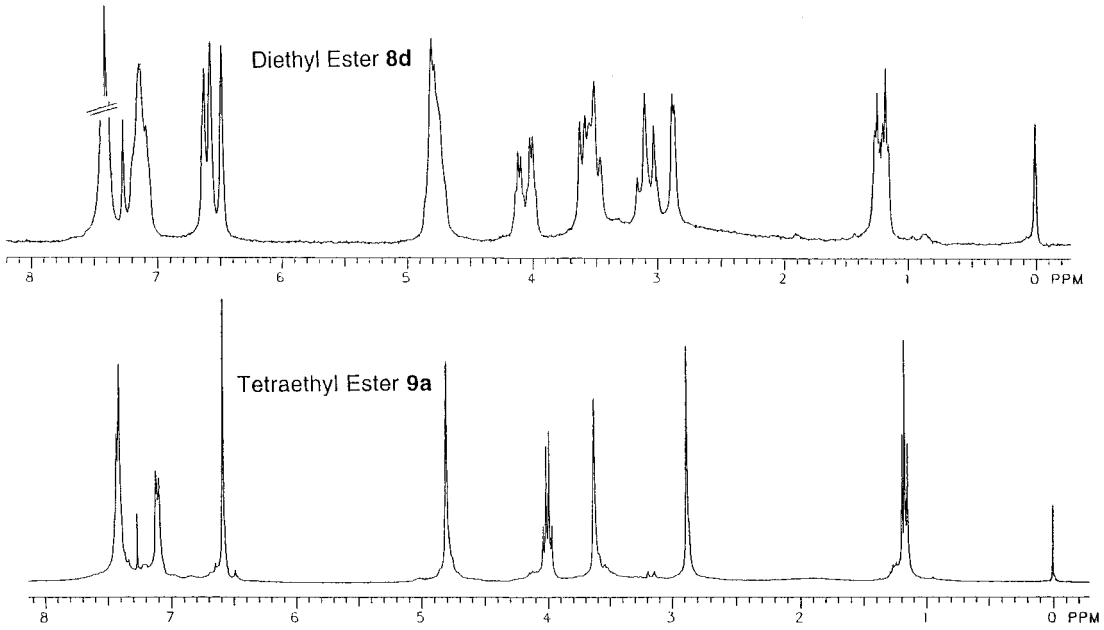
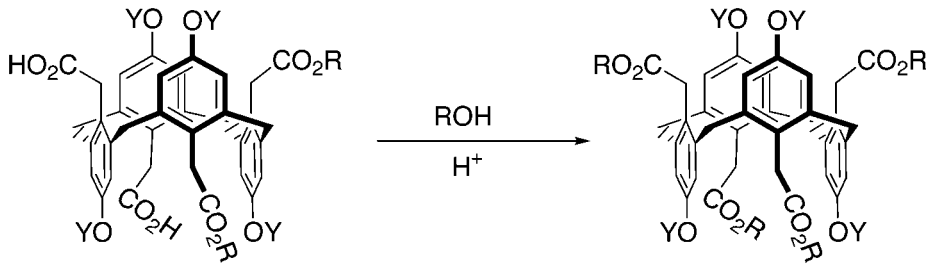


Figure 1. ^{1}H NMR spectra of the diethyl ester **8d** and tetraethyl ester **9a** of the tetrabenzyl ether of *p*-carboxymethylcalix[4]-arene.

Scheme 2



8a Y = CH_2Ph, R = Me
8b Y = $SO_2C_6H_4$(4-Br), R = Me
8c Y = $SO_2C_6H_4$(4-Me), R = Me
8d Y = CH_2Ph, R = Et
8e Y = $SO_2C_6H_4$(4-Br), R = Et
8f Y = $SO_2C_6H_4$(4-Me), R = Et
8g Y = CH_2Ph, R = n-Pr
8h Y = $SO_2C_6H_4$(4-Br), R = n-Pr

9a Y = CH_2Ph, R = Et
9b Y = $SO_2C_6H_4$(4-Br), R = Me
9c Y = $SO_2C_6H_4$(4-Me), R = Me
9d Y = $SO_2C_6H_4$(4-Br), R = Et
9e Y = $SO_2C_6H_4$(4-Me), R = Et
9f Y = $SO_2C_6H_4$(4-Br), R = n-Pr
9g Y = $SO_2C_6H_4$(4-Me), R = n-Pr
9h Y = $SO_2C_6H_4$(4-Br), R = i-Pr

40 °C. The reaction mixture was poured into cold water, and the yellow semisolid precipitate was extracted into CH_2Cl_2. The organic layer was separated, the solvent was removed under reduced pressure, and the residue was triturated with *n*-hexane. The hexane-insoluble material was the major product and proved to be starting material. Evaporation of the hexane produced a light yellow solid which was subjected to column chromatography ($CHCl_3$ eluent) to give 0.28 g (8%) of the bisanhydride **5a** as a white powder. An analytical sample was prepared by trituration with cold MeOH: mp 265−66 °C; ^{1}H NMR ($CDCl_3$) δ 7.47−7.40 (m, 20), 6.79 (s, 8), 4.82 (s, 8H), 3.53 (s, 8H), 3.13 (s, 8); ^{13}C NMR ($CDCl_3$) δ 167.54, 155.58, 138.15, 133.72, 131.46, 128.85, 128.37, 125.19, 75.29, 42.55, 35.46. Anal. Calcd for $C_{64}H_{52}O_{10}\cdot 0.5\ H_2O$: C, 77.64; H, 5.40. Found: C, 77.46; H, 5.33.

Bisanhydride of 5,11,17,23-Tetrakis(carboxymethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyl)calix[4]-arene (5b) (1,3-Alternate Conformer). A mixture of 2.0 g (1.33 mmol) of **7a** in 150 mL of HPLC grade dry CH_2Cl_2 containing 6 mL of $(COCl)_2$ was refluxed under N_2 for 6 h. Evaporation of the solvent and excess $(COCl)_2$ under vacuum gave a white solid which was stirred with *n*-hexane, and the insoluble material was removed by filtration and dried. The product was flash chromatographed (HPLC grade CH_2Cl_2 eluent) to give 1.2 g (61%)[12] of **5b** as a white powder: mp 270−72 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 8, J = 8.7 Hz), 7.84 (d, 8, J = 8.4 Hz), 6.70 (s, 8), 3.37 (s, 8), 3.30 (s, 8); ^{13}C NMR ($CDCl_3$) δ 166.24, 145.30, 135.74, 133.67, 133.36, 130.92, 130.59, 129.84, 129.63, 42.43, 34.31. Anal. Calcd for $C_{60}H_{40}S_4Br_4O_{18}$: C, 48.14; H, 2.69. Found: C, 47.77; H, 2.52.

Bisanhydride of 5,11,17,23-Tetrakis(carboxymethyl)-25,26,27,28-tetrakis(4′-methylbenzenesulfonyl)calix[4]arene (5c) (1,3-Alternate Conformer). A mixture of 4.0 g (4 mmol) of **7b** in 300 mL of dry CH_2Cl_2 containing 6 mL of $(COCl)_2$ was refluxed under N_2 for 10 h. The product was worked up and purified according to the procedure of **5b** as a white powder: yield 1.4 g (34%);[11] mp 287−88 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, 8, J = 8.4 Hz), 7.48 (d, 8, J = 8.1 Hz), 6.67 (s, 8), 3.51 (s, 8), 3.31 (s, 8), 2.52 (s, 12); ^{13}C NMR ($CDCl_3$) δ 166.45, 146.34, 145.41, 134.09, 133.80, 130.93, 130.49, 129.15, 128.34, 42.36, 34.23, 21.86. Anal. Calcd for $C_{64}H_{52}S_4O_{18}$: C, 62.12; H, 4.24. Found: C, 62.08; H, 4.54.

5,11,17,23-Tetrakis(cyanomethyl)-25,26,27,28-tetrakis-(4′-bromobenzenesulfonyl)calix[4]arene (6a) (1,3-Alternate Conformer). A slurry of 4.35 g (7.5 mmol) of *p*-cyanomethylcalix[4]arene (**1**) in 200 mL of anhydrous MeCN was treated, with stirring, with 15 mL of 1-methylimidazole (clear yellow solution) followed by portionwise addition of 25.0 g (0.1 mol) of 4-bromobenzenesulfonyl chloride. The reaction mixture was stirred at room temperature for 4 days (progress of the reaction monitored by ^{1}H NMR). After completion, it was poured into ice-cold H_2O and neutralized with 50% HCl to give a light yellow precipitate.This was separated by filtration and purified by column chromatography (CH_2Cl_2 eluent) to give 9.6 g (88%) of **6a** as a pale yellow powder. An analytical sample was obtained by trituration with MeOH: mp 273−274 °C (softening at 240 °C); ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 16), 6.87 (s, 8), 3.58 (s, 8), 3.36 (s, 8); ^{13}C NMR ($CDCl_3$) δ 146.24, 135.91, 134.23, 133.69, 130.92, 130.73, 130.06, 128.39, 118.27, 35.18, 23.02. Anal. Calcd for $C_{60}H_{40}N_4S_4Br_4O_{12}$: C, 49.47; H, 2.77. Found: C, 50.03; H, 2.48.

5,11,17,23-Tetrakis(cyanomethyl)-25,26,27,28-tetrakis-(4′-methylbenzenesulfonyl)calix[4]arene (6b) (1,3-Alternate Conformer). Following the procedure described above for **6a**, a 5.81 g (10 mmol) sample of **1** was converted (5 day reaction time) to 8.10 g (67%) of **6b** as an almost colorless powder from which an analytical sample was obtained by trituration from MeOH: mp 266−68 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 8, J = 8.4 Hz), 7.49 (d, 8, J = 8.4 Hz), 6.82 (s, 8), 3.46 (s, 8), 3.36 (s, 8), 2.54 (s, 12); ^{13}C NMR ($CDCl_3$) δ 146.74, 146.43, 134.44, 134.23, 130.84, 128.76, 128.55, 127.88, 118.21, 35.14, 22.92, 22.20. Anal. Calcd for $C_{64}H_{52}N_4S_4O_{12}$: C, 64.20; H, 4.38. Found: C, 65.04; H, 4.46.

5,11,17,23-Tetrakis(carboxymethyl)-25,26,27,28-tetrakis-(4′-bromobenzenesulfonyl)calix[4]arene (7a) (1,3-Alternate Conformer). A slurry of 7.32 g (5 mmol) of the tetraester **6a** in 150 mL of acetic acid was treated with 12 mL of H_2O and 12 mL of concentrated H_2SO_4 with careful stirring at room temperature. The reaction mixture was refluxed for 10 h, and the progress of the reaction was monitored with ^{1}H NMR. The reaction mixture was poured over 400 mL of ice-cold water to give a white precipitate which was removed by filtration and washed thoroughly with water to remove unreacted acid. The product was dried at 80−90 °C for 2 days to give 7.20 g (94%) of **7a** as a colorless powder. An analytical sample was obtained by triturating with MeOH: mp 156−57 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.79 (s, 16), 6.82 (s, 8), 3.38 (s, 8), 3.28 (s, 8); ^{13}C NMR ($CDCl_3$) δ 173.28, 144.90, 135.86, 134.58, 134.23, 133.41, 132.11, 131.25, 130.78, 40.56, 35.61. Anal. Calcd for $C_{60}H_{44}S_4Br_4O_{20}$: C, 47.01; H, 2.89. Found: C, 47.17; H, 2.76.

5,11,17,23-Tetrakis(carboxymethyl)-25,26,27,28-tetrakis-(4′-methylbenzenesulfonyl)calix[4]arene (7b) (1,3-Alternate Conformer). Following the procedure described above for the preparation of **7a**, a 0.6 g (5 mmol) sample of **6b** was converted to 5.8 g (93%) of **7b** which was obtained as a colorless solid after trituration with MeOH: mp 286−87 °C; ^{1}H NMR (DMSO-d_6)[11] δ 8.10 (d, 8, J = 8.4 Hz), 7.66 (d, 8, J = 8.1 Hz), 6.39 (s, 8), 3.53 (s, 8), 2.89 (s, 8), 2.51 (s, 12); ^{13}C NMR (DMSO-d_6) δ 172.39, 147.19, 144.05, 133.43, 133.34, 131.99, 131.24, 131.11, 128.48, 40.27, 34.23, 21.78. Anal. Calcd for $C_{64}H_{56}S_4O_{20}$: C, 60.37; H, 4.43. Found: C, 60.31; H, 4.56.

5,11-Bis(carboxymethyl)-17,23-bis(methoxycarbomethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (8a) (1,3-Alternate Conformer). A mixture of 80 mg (0.08 mmol) of the bisanhydride **5a** in 50 mL of HPLC grade MeOH was refluxed for 4 h under N_2. The MeOH was removed under reduced pressure, and the residue was triturated with *n*-hexane to leave a quantitative yield of **8a** as a white powder: mp 255−57 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.47−7.39(m, 12), 7.12 (b, 8). 6.61 (s,4), 6.49 (s, 4), 4.84−4.70 (m, 8), 3.70−3.47 (m, 14), 3.06 (s, 4), 3.00 (s, 4). Anal. Calcd for $C_{66}H_{60}O_{12}$·MeOH C, 74.70; H, 5.98. Found: C, 74.78; H, 5.73.

5,11-Bis(carboxymethyl)-17,23-bis(methoxycarbomethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyloxy)-calix[4]arene (8b) (1,3-alternate conformer) was obtained in quantitative yield as a white powder by refluxing l.0 g of **5b** with anhydrous MeOH and working up the reaction mixture as described above for **8a**: mp 140−41 °C (softening), 151−53 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.82−7.68 (m, 16), 6.84−6.63 (m, 8), 3.91−3.80 (m, 6), 3.52−3.20 (m, 16). Anal. Calcd for $C_{62}H_{48}S_4Br_4O_{20}$: C, 47.70; H, 3.10. Found: C, 47.63; H, 3.23.

5,11-Bis(carboxymethyl)-17,23-bis(methoxycarbomethyl)-25,26,27,28-tetrakis(4′-methylbenzenesulfonyloxy)-calix[4]arene (8c) (1,3-alternate conformer) was obtained in quantitative yield as a white powder from the reaction of l.1 g of **5c** with anhydrous MeOH: mp 240−42 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.89−7.80 (m, 8), 7.47−7.43 (m, 8), 6.83−6.57 (m, 8), 3.89−3.74 (m, 12), 3.51−3.10 (m, 16), 2.52 (m, 6). Anal. Calcd for $C_{66}H_{60}S_4O_{20}$: C, 60.91; H, 4.64. Found: C, 60.71; H, 4.46.

5,11-Bis(carboxymethyl)-17,23-bis(ethoxycarbomethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (8d) (1,3-alternate conformer) was prepared in quantitative yield by refluxing 50 mg of **5a** with absolute EtOH and was obtained as a white powder: mp 154−56 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.40 (bs, 12), 7.14−7.08 (m, 8). 6.62−6.48 (m, 8), 4.80−4.70 (m, 8), 4.11−3.99 (2q, 4), 3.62−3.46 (m, 8), 3.10−2.86 (m, 8), 1.26−1.15 (2t, 6). Anal. Calcd for $C_{68}H_{64}O_{12}$·H_2O: C, 74.84; H, 6.09. Found: C, 74.69; H, 5.75.

5,11-Bis(carboxymethyl)-17,23-bis(ethoxycarbomethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyloxy)calix-[4]arene (8e) (1,3-alternate conformer) was obtained in quantitative yield by refluxing 0.21 g of **5b** with absolute EtOH as a white powder: mp 159−61 °C; ^{1}H NMR ($CDCl_3$) δ 7.87−7.41 (m, 16), 6.83−6.52 (m, 8), 4.38−4.15 (m, 4), 3.62−2.98 (m, 16), 1.41−1.26 (m, 6). Anal. Calcd for $C_{64}H_{52}S_4Br_4O_{20}$: C, 48.37; H, 3.29. Found: C, 48.28; H, 3.48.

5,11-Bis(carboxymethyl)-17,23-bis(ethoxycarbomethyl)-25,26,27,28-tetrakis(4′-methylbenzenesulfonyloxy)calix-[4]arene (8f) (1,3-alternate conformer) was obtained in quantitative yield by refluxing 0.12 g of **5c** with absolute EtOH as a white powder: mp 265−67 °C (softening at 255−6 °C); ^{1}H NMR ($CDCl_3$)[11] δ 7.87−7.81 (m, 8), 7.46−7.42 (m, 8), 6.78−6.57 (m, 8), 4.36−4.18 (m, 4), 3.46−3.15 (m, 16), 2.5 (bs, 12), 1.39−1.32 (m, 6).

(10) Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. The HPLC grade of *N*,*N*-dimethylformamide (DMF), dichloromethane, acetonitrile, and acetone were used. Tetrahydrofuran (THF) was dried over benzophenone/Na and distilled before using. Column chromatography was carried out with Aldrich 70−230 mesh, 60 Å silica gel. Thin-layer chromatography (TLC) was performed on 250 μm silica gel plates containing a fluorescent indicator. Melting points were measured in sealed and evacuated capillary tubes on a MEL-Temp apparatus (Laboratory Devices, Cambridge, MA) using a 400 °C thermometer calibrated against a thermocouple and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer, and the chemical shifts are reported as δ values with units of parts per million (ppm). ^{1}H NMR spectra are referenced to tetramethylsilane (TMS) at 0.00 ppm as an internal standard and recorded at room temperature (20 ± 1 °C), and ^{13}C NMR spectra are referenced to $CDCl_3$ (77.00 ppm), DMSO-d_6 (40.0 ppm), or TMS (0.00 ppm) and also recorded at room temperature (20 ± 1 °C). Microanalytical samples were dried for at least 48−72 h at 111 °C (refluxing toluene) or at 140 °C (refluxing xylene) at 1−2 mm, and the analyses were carried out by Desert Laboratories, Tucson, AZ. In cases where the solvent of crystallization affected the elemental analysis, appropriate increments of the solvents were used to obtain the best fit between the observed and calculated values.

(11) The CO_2H resonances are not reported in the ^{1}H NMR spectra.

(12) Further elution gave a mixture of starting material and an unidentified intermediate from which additional bisanhydride can be obtained by retreatment with $(COCl)_2$ as described.

5,11-Bis(carboxymethyl)-17,23-bis(*n*-propoxycarbomethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (8g) (1,3-alternate conformer) was prepared in quantitative yield from 80 mg of **5a** and *n*-propanol as a white powder: mp 181−84 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.38 (b, 12), 7.11 (b, 8). 6.60 (s, 8), 4.77−4.74 (m, 8), 3.99−3.90 (m, 4), 3.60−3.49 (m, 8), 3.02 (s, 4), 2.94 (s, 4), 1.62−1.54 (m, 4), 0.90−0.86 (m, 6). Anal. Calcd for $C_{70}H_{68}O_{12}\cdot 3H_2O$: C, 72.77; H, 6.46. Found: C, 72.98; H, 6.55.

5,11-Bis(carboxymethyl)-17,23-bis(*n*-propoxycarbomethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyloxy)calix[4]arene (8h) (1,3-alternate conformer) was prepared in quantitative yield from 0.21 g of **5b** and 2-propanol as a white powder: mp. 118−19 °C; ^{1}H NMR ($CDCl_3$)[11] δ 7.87−7.62 (m, 16), 6.84−6.51 (m, 8), 4.29−4.09 (m, 4), 3.55−3.17 (m, 16), 1.78−1.70 (m, 4), 1.02−0.95 (m, 6). Anal. Calcd for $C_{66}H_{56}S_4Br_4O_{20}$: C, 49.02; H, 3.49. Found: C, 48.63; H, 3.34.

5,11,17,23-Tetrakis(carboethoxymethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (9a) (1,3-Alternate Conformer). A mixture of 0.20 g (0.2 mmol) of tetraacid **4** and 100 mL of absolute EtOH containing 2 drops of concentrated H_2SO_4 was refluxed for 4 h. After completion of the reaction (as revealed by TLC), the EtOH was removed under reduced pressure and the residue was poured over ice-cold water to give a white precipitate. The product was removed by filtration to give 0.22 g (100%) of a white powder which was purified by chromatography (CH_2Cl_2 eluent) followed by trituration with MeOH: mp 150−52 °C (softening at 118 °C); ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 12), 7.10 (m, 8), 6.58 (s, 8), 4.79 (s, 8), 4.00 (q, 8, J = 6.9 Hz), 3.62 (s, 8), 2.88 (s, 8), 1.16 (t, 12, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.53, 155.32, 138.69, 134.25, 132.18, 128.39, 127.82, 127.30, 126.76, 71.98, 60.79, 40.51, 37.82, 14.51. Anal. Calcd for $C_{72}H_{74}O_{12}$: C, 76.44; H, 6.59. Found: C, 76.23; H, 6.46. The tetraethyl ester **9a** was also obtained by refluxing **8a** with EtOH containing a drop of concentrated H_2SO_4.

5,11,17,23-Tetrakis(carbomethoxymethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyl)calix[4]arene (9b) (1,3-Alternate Conformer). A slurry of 0.20 g (0.13 mmol) of the dimethyl ester **8b** in 50 mL of anhydrous MeOH was treated wth 2 drops of concentrated H_2SO_4 with stirring at room temperature. The reaction mixture was refluxed (after 30 min clear solution) for 3 h and worked up as described above for **9a** to give **9b** in quantitative yield. An analytical sample was obtained by column chromatography (CH_2Cl_2 eluent): mp 216−18 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 8, J = 8.58 Hz), 7.45 (d, 8, J = 8.73 Hz), 6.82 (s, 8), 3.72 (s, 12), 3.60 (s, 8), 3.02 (s, 8); ^{13}C NMR ($CDCl_3$) δ 171.08, 145.52, 135.66, 134.01, 132.84, 132.39, 132.12, 129.66, 129.15, 52.24, 39.65, 35.96. Anal. Calcd for $C_{64}H_{52}S_4Br_4O_{20}$: C, 48.38; H, 3.30. Found: C, 48.57; H, 3.48.

5,11,17,23-Tetrakis(carbomethoxymethyl)-25,26,27,28-tetrakis(4′-methylbenzenesulfonyl)calix[4]arene (9c) (1,3-alternate conformer) was prepared as described above for **9a** using anhydrous MeOH to give a quantitative yield of **9c** as a white powder: mp 231−33 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 8, J = 8.31 Hz), 7.43 (d, 8, J = 8.04 Hz), 6.72 (s, 8), 3.74 (s, 12), 3.44 (s, 8), 3.09 (s, 8), 2.51 (s, 12); ^{13}C NMR ($CDCl_3$) δ 171.26, 145.82, 145.22, 133.93, 133.70, 131.54, 131.03, 130.19, 128.06, 52.12, 39.95, 34.99, 21.80. Anal. Calcd for $C_{68}H_{64}S_4O_{20}$: C, 61.43; H, 4.85. Found: C, 61.08; H, 4.95.

5,11,17,23-Tetrakis(carboethoxymethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyl)calix[4]arene (9d) (1,3-alternate conformer) was prepared as described above for **9a** using absolute EtOH to give a quantitative yield of **9d** as a white powder: mp 205−6 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 8, J = 8.70 Hz), 7.44 (d, 8, J = 8.70 Hz), 6.83 (s, 8), 4.16 (dd, 8, J = 7.0 Hz), 3.62 (s, 8), 2.99 (s, 8), 1.29 (t, 12, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.68, 145.47, 135.66, 134.03, 132.81, 132.29, 132.15, 129.60, 129.13, 61.05, 39.83, 36.00, 14.24. Anal. Calcd for $C_{68}H_{60}S_4Br_4O_{20}$: C, 49.64; H, 3.67. Found: C, 49.38; H, 3.83. The tetraethyl ester **9d** was also obtained by refluxing the diethyl ester **8e** with absolute EtOH containing a drop of concentrated H_2SO_4.

5,11,17,23-Tetrakis(carboethoxymethyl)-25,26,27,28-tetrakis(4′-methylbenzenesulfonyl)calix[4]arene (9e) (1,3-alternate conformer) was prepared as described above for **9a** using absolute EtOH to give a quantitative yield of **9e** as a white powder: mp 216−17 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 8, J = 8.3 Hz), 7.42 (d, 8, J = 8.3 Hz), 6.74 (s, 8), 4.07 (q, 8, J = 6.9 Hz), 3.45 (s, 8), 3.05 (s, 8), 2.51 (s, 12), 1.31 (t, 12, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 170.86, 145.73, 145.17, 133.93, 133.72, 131.56, 131.22, 130.16, 128.04, 60.90, 40.15, 35.00, 21.79, 14.27. Anal. Calcd for $C_{72}H_{72}S_4O_{20}\cdot H_2O$: C, 61.61; H, 5.31. Found: C, 61.68; H, 5.12. The tetraethyl ester **9e** was also obtained when the diethyl ester **8f** was refluxed with absolute EtOH containing a drop of concentrated H_2SO_4.

5,11,17,23-Tetrakis(carbo-*n*-propyloxymethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyl)calix[4]arene (9f) (1,3-alternate conformer) was prepared as described above for **9a** using anhydrous n-PrOH to give a quantitative yield of **9f** as a white powder: mp 155−57 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 8, J = 8.4 Hz), 7.42 (d, 8, J = 8.7 Hz), 6.84 (s, 8), 4.05 (t, 8, J = 6.6 and 6.9 Hz), 3.62 (s, 8), 2.99 (s, 8), 1.65 (m, 8), 0.94 (t, 12, J = 7.2 and 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.73, 145.48, 135.69, 134.04, 132.79, 132.35, 132.19, 129.57, 129.09, 66.60, 39.83, 36.01, 21.95, 10.38. Anal. Calcd for $C_{72}H_{68}S_4Br_4O_{20}$: C, 50.83; H, 4.04. Found: C, 50.52; H, 4.05. The tetra-*n*-propyl ester **9f** was also obtained when the di-*n*-propyl ester **8h** was refluxed with n-PrOH containing a drop of concentrated H_2SO_4.

5,11,17,23-Tetrakis(carbo-*n*-propyloxymethyl)-25,26,27,28-tetrakis(4′-methyl-benzenesulfonyl)calix[4]arene (9g) (1,3-alternate conformer) was prepared as described above for **9a** using anhydrous MeOH to give a 90% yield of **9g** as a white powder: mp 178−80 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 8, J = 8.4 Hz), 7.42 (d, 8, J = 7.8 Hz), 6.75 (s, 8), 4.08 (t, 8, J = 6.6 Hz), 3.45 (s, 8), 3.08 (s, 8), 2.51 (s, 12), 1.69 (m, 8), 0.95 (t, 12, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.91, 145.71, 145.16, 133.72, 131.59, 131.29, 130.13, 128.05, 66.49, 40.15, 35.00, 21.98, 21.79, 10.39. Anal. Calcd for $C_{76}H_{80}S_4O_{20}$: C, 63.31; H, 5.59. Found: C, 62.96; H, 5.49.

5,11,17,23-Tetrakis(carboisopropylmethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyl)calix[4]arene (9h) (1,3-alternate conformer) was prepared as described above for **9a** using anhydrous i-PrOH to give an 87% yield of **9h** as a white powder: mp 192−94 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 8, J = 6.9 Hz), 7.40 (d, 8, J = 6.6 Hz), 6.85 (s, 8), 5.02 (m, 4), 3.64 (s, 8), 2.94 (s, 8), 1.25 (d, 24, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 170.22, 145.47, 135.67, 134.08, 132.76, 132.54, 132.19, 68.44, 40.07, 36.07, 21.82. Anal. Calcd for $C_{72}H_{68}S_4Br_4O_{20}\cdot 0.5CH_2Cl_2$: C, 49.94; H, 3.94. Found: C, 49.95; H, 3.53.

5,11-Bis(carboxymethyl)-17,23-bis(*N*,*N*-diethylamidomethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (10a) (1,3-Alternate Conformer). A mixture of 0.2 g (0.2 mmol) of the bisanhydride **5a** and 0.11 g of diethylamine in 30 mL of CH_2Cl_2 was refluxed 3 h under N_2, and the reaction mixture was worked up to give 0.21 g (100%) of **10a** as a light yellow powder: mp 215−17 °C; ^{1}H NMR ($CDCl_3$) δ 7.39−7.24 (m, 20), 6.78 (d, 4, J = 6.6 Hz), 6.44 (d, 4, J = 6.0 Hz), 4.74−4.70 (m, 8), 3.57−3.48 (m, 8), 3.30 (s, 4), 3.09−3.00 (m, 12), 1.15 (t, 6, J = 7.0 Hz), 1.01 (t, 6, J = 6.6 Hz).

5,11-Bis(carboxymethyl)-17,23-bis(*N*,*N*-isopropylamidomethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (10b) (1,3-Alternate Conformer). A mixture of 50 mg (0.05 mmol) of **5a** and 40 mg of diisopropylamine in 20 mL of CH_2Cl_2 was refluxed 2 h under N_2, and the reaction mixture was worked up to give 54 mg (100%) of **10b** as a white powder: mp 156−58 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of DMSO-d_6) δ 7.52−7.33 (m, 12), 7.18−7.10 (m, 8), 6.56−6.31 (m, 8), 4.73 (m, 8), 3.56, 3.46−3.33 (m, 8), 2.98 (m, 8), 1.02(d, 48, J = 6.3 Hz). The diisopropylamide **10b** was converted to the tetraisopropyl amide **11** by using DCC/1-HOBt (vide infra).

5,11-Bis(carboxymethyl)-17,23-bis(*N*-phenylethylamidomethyl)-25,26,27,28-tetrakis(benzyloxy)calix[4]arene (10c) (1,3-Alternate Conformer). A mixture of 98 mg (0.99 mmol) of the bisanhydride **5a** and 0.2 g of 2-phenylethylamine in 40 mL of HPLC grade CH_2Cl_2 was refluxed for 2 h under N_2. After completion of the reaction, the CH_2Cl_2 was removed under reduced pressure, and the concentrated material was triturated with *n*-hexane to leave a light yellow precipitate which was removed by filtration and purified to

give 100 mg (100%)) of **10c** as a light yellow powder: mp 110−12 °C; ^{1}H NMR ($CDCl_3$)[13] δ 7.37−7.35 (m, 12), 7.29−7.20 (m, 6), 7.13−7.06 (m, 12), 6.60 (s, 4), 6.44 (s, 4), 5.45 (t, 2), 4.73−4.48 (m, 8), 3.45−3.38 (m, 12), 3.10 (s, 4), 3.01(s, 4), 2.77−2.72 (m, 4). Anal. Calcd for $C_{80}H_{74}N_2O_{10}\cdot 2H_2O$: C, 76.29; H, 6.24. Found: C, 76.22; H, 6.11.

5,11-Bis(carboxymethyl)-17,23-bis((bis[(3,5-dimethyl-1-pyrazoyl)ethyl]amidomethyl)-25,26,27,28-tetrakis(4-bromobenzenesulfonyloxy)calix[4]arene (10d) (1,3-Alternate Conformer). A mixture of 150 mg (0.01 mmol) of bisanhydride **5b** and 0.06 g of bis[(3,5-dimethyl-1-pyrazoyl)-ethyl]amine in 50 mL of CH_2Cl_2 was refluxed for 4 h under N_2. After completion of the reaction, the CH_2Cl_2 was removed under reduced pressure and the residue was triturated with *n*-hexane followed by MeOH to give 200 mg (100%) of **10d** as a white powder: mp 162−64 °C (softening at 152−54 °C); ^{1}H NMR ($CDCl_3$) δ 7.90−7.59 (m, 16), 6.83−6.54 (m, 8), 5.87 (s, 2), 5.78 (s, 2), 4.29 (m, 4), 4.10 (m, 4), 3.79−3.76 (m, 6), 3.55−3.22 (m, 16), 3.00−2.90 (m, 4), 2.33 (s, 6), 2.24 (s, 6), 2.21 (s, 6), 2.16 (s, 6). Anal. Calcd for $C_{88}H_{86}N_{10}S_4Br_4O_{18}$: C, 52.34; H, 4.29. Found: C, 51.50; H, 4.14.

5,11,17,23-Tetrakis(*N*,*N*-diisopropylamidomethyl)-25,-26,27,28-tetrakis(benzyloxy)calix[4]arene (11a) (1,3-Alternate Conformer). A mixture of 500 mg (0.5 mmol) of the tetraacid **4**, 0.4 g of isopropylamine, 0.5 g of dicyclohexylcarbodimide (DCC), and 0.1 g of 1-hydroxybenzotriazole (1-HOBT) in 60 mL of HPLC grade CH_2Cl_2 and 10 mL of THF was stirred at room temperature for 18 h and worked up to give 0.42 g (62%) of **11a** as a white powder: mp 265−67 °C (softening at 135 °C); ^{1}H NMR (DMSO-d_6) δ 7.41 (b, 12), 7.10 (bs, 8), 6.50 (s, 8), 4.70 (s, 8), 3.51 (s, 8), 3.05 (m, 8), 2.62 (s, 8), 1.12 (d, 48). Anal. Calcd for $C_{88}H_{108}N_4O_8\cdot CHCl_3$: C, 72.76; H, 7.48. Found: C, 72.93; H, 6.95.

5,11,17,23-Tetrakis(bis(3,5-dimethyl-1-pyrazoylethyl)amidomethyl)-25,26,27,28-tetrakis(4′-bromobenzenesulfonyloxy)calix[4]arene (11b) (1,3-Alternate Conformer). A mixture of 300 mg (0.05 mmol) of the bisanhydride **5b**, 0.50 g of bis[(3,5-dimethyl-1-pyrazoyl)ethyl]amine, 0.5 g of DCC, and 0.1 g of 1-HOBT in 100 mL of HPLC grade CH_2Cl_2 was stirred at room temperature for 2 days. The white precipitate of DCU and unreacted DCC was removed by filtration, and the filtrate was concentrated under reduced pressure and stirred with CH_2Cl_2. Again, the precipitate was removed by filtration, and this procedure repeated until the product was free of DCC and DCU. Further puricifation was effected by trituration with MeOH to give 280 mg (56%) of **11b** as a white powder: mp 99−101 °C (softening at 90−91 °C); ^{1}H NMR (DMSO-d_6) δ 7.88 (d, 8, J = 7.8 Hz), 7.43 (d, 8, J = 8.4 Hz), 6.72 (s, 8), 5.76 (s, 4), 5.74 (s, 4), 4.01 (bs, 8), 3.85 (bs, 8), 3.65 (bs, 8), 3.42 (bs, 16), 3.12 (bs, 8), 2.07 (s, 24), 2.05 (s, 12), 1.98 (s, 12). Anal. Calcd for $C_{116}H_{128}N_{20}S_4Br_4O_{16}$: C, 55.59; H, 5.14. Found: C, 55.64; H, 5.15.

5,11,17,23-Tetrakis(bis(3,5-dimethyl-1-pyrazoylethyl)amidomethyl)-25,26,27,28-tetrakis(4′-methylbenzenesulfonyloxy)calix[4]arene (11c) (1,3-Alternate Conformer). A mixture of 0.38 g (0.05 mmol) of bisanhydride **5c**, 0.50 g of bis[(3,5-dimethyl-1-pyrazoyl)ethyl]amine, 0.5 g of DCC, and 0.1 g of 1-HOBT in 90 mL of HPLC grade CH_2Cl_2 and 10 mL of THF was stirred at room temperature for 2 days and worked up to give 0.42 g (62%) of **11c** as white powder: mp 82−4 °C (softening at 71−2 °C); ^{1}H NMR (DMSO-d_6) δ 7.82 (d, 8, J = 8.1 Hz), 7.44 (d, 8, J = 7.5 Hz), 6.70 (s, 8), 5.80 (s, 4), 5.72 (s, 4), 3.99 (bs, 8), 3.81 (bs, 8), 3.56 (bs, 8), 3.43 (bs, 16), 3.09 (bs, 8), 2.44 (s, 12), 2.12 (s, 12), 2.07 (s, 24), 1.94 (s, 12). Anal. Calcd for $C_{120}H_{140}N_{20}S_4O_{16}\cdot 0.5CH_2Cl_2$: C, 62.33; H, 6.14. Found: C, 62.62; H, 6.51.

(13) The CO_2H and NH resonances are not reported in the ^{1}H NMR spectra.

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