Notes

Calix[4]arenes Blocked in a Rigid Cone Conformation by Selective Functionalization at the Lower Rim

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Introduction

Calix[4]arenes are very useful building blocks for receptors of cations,[1] anions,[2] and neutral molecules.[3] The introduction of bulky substituents at the lower rim of the calix prevents the interconversion among the four possible stereoisomers (cone, partial cone, 1,3-alternate, and 1,2-alternate). By choosing the reaction conditions, the control of the stereochemistry has been achieved expecially in alkylation reactions.

Most of the symmetrically substituted calix[4]arene cone isomers, which are extensively used as such or as molecular platforms for the synthesis of more complex receptors,[4] adopt a "flattened cone" (or pinched cone)[5] conformation in the solid state,[6] showing a C_{2v} symmetry. This conformation has been also shown to be the more stable by molecular modeling.[7] In solution, the ring inversion process is blocked when the substituents are bulkier then ethyl,[8] but some conformational flexibility still exists, and the C_{4v} symmetry, usually observed in the ^{1}H NMR spectra of these compounds, is considered to be a transition state for the interconversion between two C_{2v} structures[7a] (Figure 1).

Evidence for this interconversion has been obtained by Regen *et al.*[9] in the upper rim tetracarboxylic acid of a "cone" calix[4]arene derivative and has been attributed

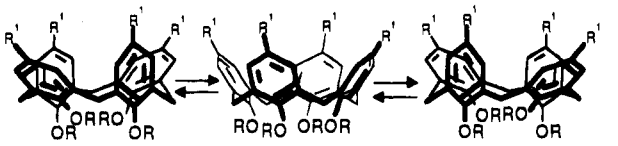

Figure 1. Dynamic stereochemistry of tetraalkoxycalix[4]-arenes in the cone conformation.

to the formation of "internal hydrogen bonds between alternate pendant groups". For most of the uses of calix-[4]arene cone isomers, this more subtle conformational interconversion is usually neglected. However, we haverecently observed that the gas phase complexation ability of calix[4]arenes cone isomers toward neutral organic molecules is strongly dependent on the rigidity of the host and on its residual flexibility which can cause the destruction of the apolar cavity.[10] Furthermore, this flexibility influences the reactivity of functional groups introduced at the upper rim, expecially in the diametrical (1,3) position, often favouring intramolecular processes.[11]

We present herein new synthetic procedures of lower rim selective functionalization which afford conformationally very rigid calix[4]arenes where the interconversion between two flattened cone conformations is inhibited.

Results and Discussion

Initially we collected further experimental evidence on the occurrence of the conformational process in solution by studying the temperature and solvent dependence of ^{1}H NMR (300 MHz) spectra of the "cone" tetrakis(n-octyloxy)calix[4]arene **1b**[9] and of the diametrical dicarboxylic acid **5b**, synthesized through the following reaction scheme (Scheme 1).

The main features of the room temperature ^{1}H NMR spectrum of **1b** taken in CD_2Cl_2 are a multiplet for the 12 aromatic protons centered at δ = 6.60, a pair of doublets at δ = 4.45 and 3.14 due to the bridging methylenes, and a triplet for the OCH_2 of the alkyl chain at δ = 3.89. Decreasing the temperature to 213 K the spectrum changes giving two distinct groups of signals for the two different type of aromatic nuclei at δ = 7.10 and 6.15[12] and two signals for the OCH_2 protons at δ = 3.90 and 3.75, while the bridging methylenes experience a AB quartet with no significant changes (Figure 2).

These changes clearly show the freezing of the molecular motion into a flattened cone conformation. A coalescence temperature, T_c, of 216 K and a $\Delta\nu$ = 111 Hz observed for the OCH_2 protons allows calculation of a barrier for the $C_{2v} \rightleftharpoons C_{2v}$ interconversion of $\Delta G^{\ddagger}$ = 10.2 kcal mol^{-1}.

The acid **5b** shows a flattened cone structure even at room temperature in $CDCl_3$. In fact the protons of the

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(10) (a) Arduini, A.; Cantoni, M.; Graviani, E.; Pochini, A.; Secchi, A.; Sicuri, A. R.; Ungaro, R.; Vincenti, M. *Tetrahedron*, in press. (b) Arduini A.; Pochini A.; Secchi, A.; Ungaro, R.; Vincenti, M. Unpublished results.

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(12) For the effect of flattened cone conformation on the chemical shift of the aromatic protons see: Goldmann, H.; Vögt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811.

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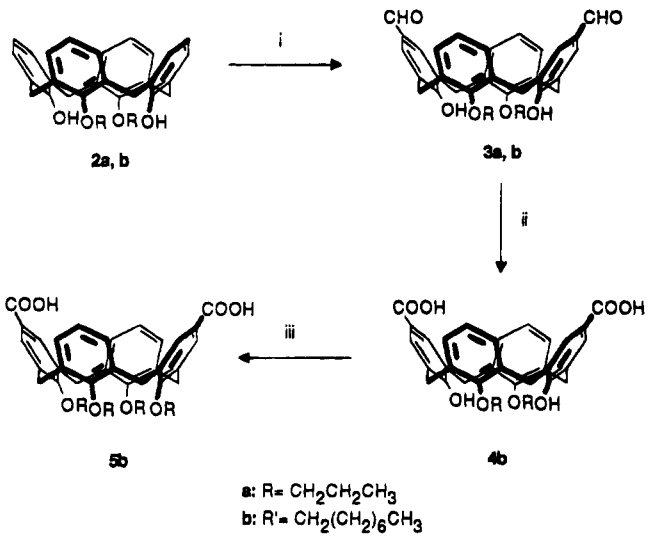
Scheme 1[a]



[a] (i) $SnCl_4$, Cl_2CHOCH_3, $CHCl_3$, $T = -15$ °C; (ii) H_2NSO_3H, $NaClO_2$, acetone/$CHCl_3$; (iii) NaH, n-$C_8H_{17}I$, DMF, $T = 80$ °C.

aromatic rings bearing the carboxylic functions absorb at an unusually high field ($\delta = 6.69$), while those of the unsubstituted ones give an AX_2 system at $\delta = 7.36$ and 6.95, and the OCH_2 protons show two distinct triplets at δ 3.95 and 3.61. Interestingly the NMR spectrum of **5b** is solvent dependent and in the polar CD_3OD (see Experimental Section) it indicates a conformationally mobile situation. From these data it appears that in $CDCl_3$ the flattened cone conformation is imposed by hydrogen bonding between the carboxylic acid functions. To check if this interaction occurred intra- or intermolecularly, we determined the osmometric molecular weight of compound **5b** in chloroform, which indicates a dimeric structure. It is therefore likely to assume that, because of stereoelectronic requirements,[13] the H-bonds take place between the carboxylic functions of two different calixarenes. In order to maximize hydrogen bonding the two aromatic units involved in the intermolecular interaction adopt a parallel orientation forcing the other two to become more flattened.

To avoid these phenomena and to enforce the cavity, we introduced rigidifying units on the lower rim, keeping the upper rim available for further functionalization. Two general synthetic strategies, based on our previous studies[14,15] on the selective lower rim functionalization of calix[4]arenes, were devised. First, by reacting calix[4]arene **1a** or **1c** in DMF with diethylene glycol ditosylate in the presence of an excess of NaH,[15] the proximal bis crowns **6a** and **6c** were obtained in 55 and 30% yield, respectively (Scheme 2). The temperature independent ^1H NMR spectra indicate that these compounds have an almost immobile cone structure, imposed by bridges.

In the second and complementary strategy we linked the two opposite free OH groups of the funtionalized

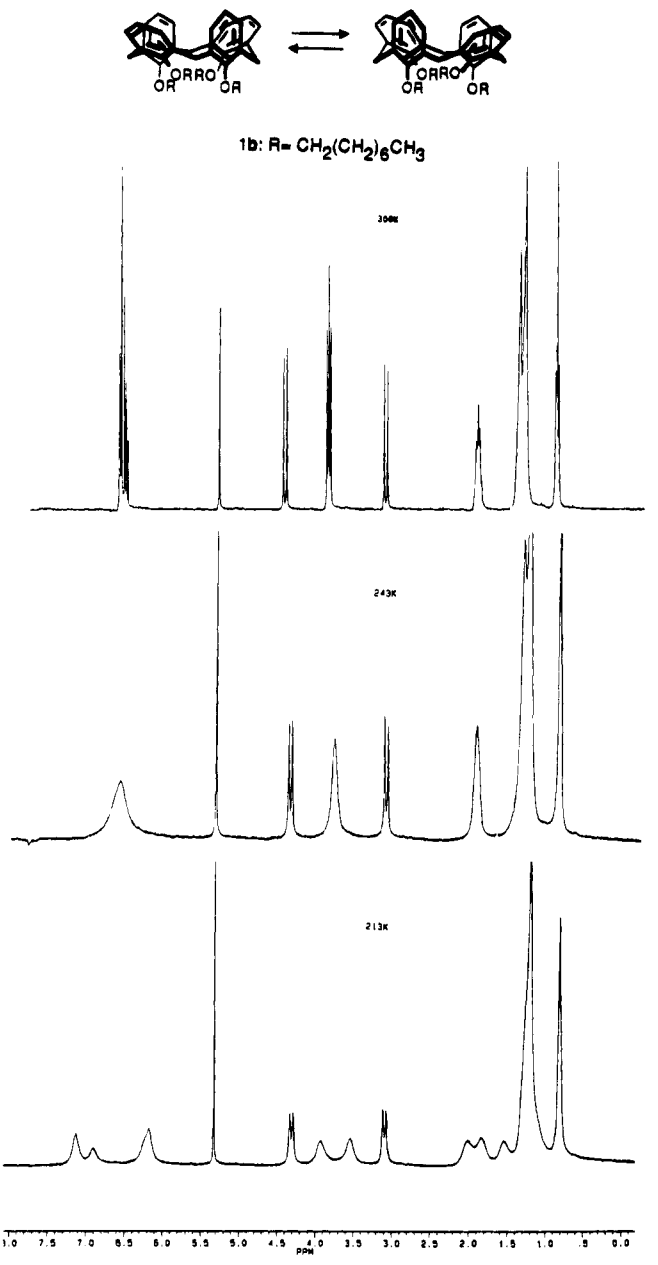
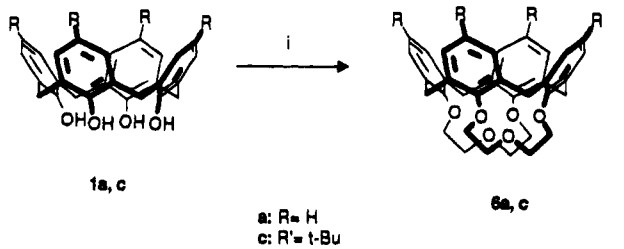


Figure 2. ^1H NMR (300 MHz) spectrum of **1b** in CD_2Cl_2 at different temperatures.

Scheme 2[a]



[a] (i) NaH, $(TsOCH_2CH_2)_2O$, DMF, $T = 80$ °C.

phenolic nuclei present in the 1,3-dialkoxy-calix[4]arene derivative **3a**, synthesized according with Scheme 1,[14] with a short diethylene glycol bridge, obtaining the crown ether **7** in good yield (Scheme 3).

Oxidation of the dialdehyde **7** yielded the diacid **8**. The ^1H NMR spectrum of compound **8** is substantially different from that shown by the diacid **5b**. In particular

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(14) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

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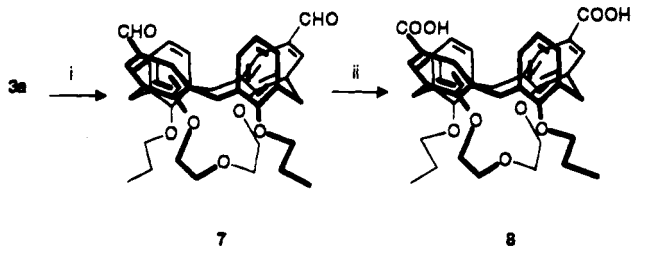
(16) The solubility of compound **8** in $CHCl_3$ is below 10^{-2} M hence preventing the obtainment of reliable osmometric measurements. This is an indirect evidence that **8** forms higher aggregates.

Scheme 3[a]



[a] (i) $(ICH_2CH_2)_2O$, NaH, DMF; (ii) H_2NSO_3H, $NaClO_2$, acetone/$CHCl_3$.

in $CDCl_3$ the protons adjacent to the carboxylic functions absorb at the expected value of $\delta = 7.88$, whereas the AX_2 system for the two unsubstituted aromatic nuclei appears at $\delta = 6.10$ and 5.93. Moreover this spectrum and that of the corresponding dialdehyde **7** is substantially insensitive to temperature (in the range 328 to 243 K) and solvent variations.

These data clearly indicate that the compounds **7** and **8** adopt a more rigid structure in solution, where the two upper rim-functionalized aromatic nuclei diverge from the cavity and the other two nuclei tend to be parallel to each other. This situation is exactly the opposite of that observed for compound **5b** where dimerization through intermolecular hydrogen bonding take place.

In conclusion the 1,2-double bridged calix[4]arenes **6a** and **6c** and the 1,3-monobridged derivatives **7** and **8**, are rigidified calix[4]arenes in which the interconversion between two flattened (or pinched) cone conformations is inhibited. These may be useful synthetic tools in supramolecular chemistry. The new compounds synthesized have either the upper rim available for further functionalizations (**6a**, **6c**) or are functionalized in diametrical position (**7** and **8**) providing more complex and rigid receptors. These new findings can be used to influence self aggregation and complex formation in calix[4]arene receptors, together with the reactivity of functional groups introduced at the upper rim. Studies in these directions are in progress in our laboratories.

Experimental Section

General. All reactions were carried out under nitrogen, and all solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use whereas all other reagents were reagent grade quality obtained from commercial supplies and used without further purification. ^1H NMR spectra were recorded at 300 and 400 MHz. ^{13}C NMR were recorded at 25 and 75 MHz. Chemical shifts (δ) are expressed in ppm from the internal reference tetramethylsilane. Mass spectra were recorded in the CI mode (CH_4).

Analytical thin layer chromatography was performed on precoated silica gel plates (Merck, 60 F_{254}), and column chromatography was performed with silica gel (Merck, particle size 0.040–0.063 mm). Osmometric measurements were carried out in chloroform at 37 °C using a vapor pressure osmometer. Calibration curves were obtained using compound **1b**. The molecular weight determination of compound **5b** was performed in three separate series of measurements and gave a molecular weight value of 1970 ± 40 D (calculated for a dimer 1922 D).[16]

As verified also by other authors,[17] the elemental analysis of calixarenes are very often incorrect; nevertheless, the identity of the compounds reported has been proven by their spectral data. Compounds **1a**,[1a] **1b**,[9] and **1c**[1a] were synthesized according to literature procedures.

25,27-Dihydroxy-26,28-di-n-propoxycalix[4]arene (2a). To a suspension of **1a** (3.0 g, 7.1 mmol) in CH_3CN (200 mL) were added 1-iodopropane (4.8 g, 28.2 mmol) and K_2CO_3 (3.9 g, 28.2 mmol), and the reaction mixture was refluxed with stirring for 24 h. The solvent was evaporated, the residue taken up with CH_2Cl_2 (100 mL), and the organic phase separated and washed twice with HCl (10%) and then with water. Evaporation of the organic phase afforded a solid which was recrystallized (CH_2Cl_2–MeOH) and gave 64% yield of **2a** as white crystals: mp 268–270 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 2H), 7.10 and 6.95 (2d, $J = 7.51$ Hz, 8H), 6.78 and 6.70 (2t, $J = 7.51$ Hz, 4H), 4.38 (d, $J = 12.90$ Hz, 4H), 4.02 (t, $J = 6.20$ Hz, 4H), 3.43 (d, $J = 12.90$ Hz, 4H), 2.13 (m, 4H), 1.36 (t, $J = 7.32$ Hz, 6H); ^{13}C NMR, ($CDCl_3$, 75 MHz), δ 153.3, 151.9, 133.4, 128.9, 128.4, 128.1, 125.2, 78.2, 31.4, 23.4, 10.8; MS m/e 509 ($M + H^+$).

25,27-Dihydroxy-26,28-bis(n-octyloxy)calix[4]arene (2b). To a suspension of **1a** (5.0 g, 11.6 mmol) and K_2CO_3 (3.7 g, 26.7 mmol) in CH_3CN (250 mL) 1-iodooctane (6.2 g, 25.8 mmol), was added and the reaction mixture was refluxed with stirring for 5 days. The solvent was then evaporated at reduced pressure and the residue taken up with HCl (10%, 100 mL) and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to dryness. Recrystallization from hexane gave 3.9 g of **2b** as colorless crystals (52% yield): mp 115–117 °C; ^1H NMR ($CDCl_3$, 400 MHz), δ 8.25 (s, 2H), 7.06 (d, $J = 7.44$ Hz, 4H), 6.92 (d, 4H, $J = 5.90$ Hz, 4H), 6.74 (m, 2H), 6.65 (m, 2H), 4.33 (d, $J = 13.14$ Hz, 4H), 4.00 (t, $J = 6.62$ Hz, 4H), 3.38 (d, $J = 13.14$ Hz, 4H), 1.3–2.0 (m, 24H), 0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.6, 152.6, 119.2, 125.5, 128.5, 128.7, 129.1, 133.0, 77.3, 32.2, 31.7, 30.3, 29.8, 29.6, 26.3, 23.0, 14.4; MS m/e 649 ($M + H^+$).

11,23-Diformyl-26,28-dialkoxy-25,27-dihydroxycalix[4]-arenes 3a and 3b. The appropriate dialkoxycalix[4]arene (**2a,b**) (1.5 mmol) was dissolved in chloroform (25 mL), the solution was cooled at −15 °C, and then $SnCl_4$ (4.0 g, 15.4 mmol) and 1,1-dichlorodimethyl ether (0.44 g, 3.9 mmol) were rapidly added. The reaction mixture was then stirred at room temperature for 30 min and quenched with water. The organic layer was separated, washed twice with water, and evaporated. The purple oily residue was purified by column chromatography. **3a:**[18] eluent hexane/ethyl acetate = 7/3, white solid, yield 95%, mp >320 °C. **3b:** eluent hexane/ethyl acetate = 4/1, white solid, 90% yield, mp 172–173 °C; ^1H NMR ($CDCl_3$, 100 MHz) δ 9.78 (s, 2H), 9.22 (s, 2H), 7.64 (s, 4H), 6.7–7.0 (m, 6H), 4.31 (d, $J = 13.20$ Hz, 4H), 4.04 (t, $J = 6.15$ Hz, 4H), 3.50 (d, $J = 13.20$ Hz, 4H), 1.4–1.2 (m, 24H), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 191.1, 159.9, 152.1, 132.7, 131.2, 129.7, 129.0, 125.9, 77.4, 32.2, 31.6, 30.3, 29.8, 29.6, 26.3, 23.0, 14.4; MS m/e (EI) 705 (M^+).

11,23-Dicarboxy-25,27-dihydroxy-26,28-bis(n-octyloxy)-calix[4]arene (4b). Compound **3b** (0.50 g, 0.71 mmol) was dissolved in a mixture of chloroform (50 mL) and acetone (50 mL), and then sulfamic acid (0.27 g, 2.8 mmol) and $NaClO_2$ (0.22 g, 2.4 mmol) dissolved in 3 mL of water were added with stirring; after 3 h the solvents were completely evaporated, the white solid was taken up with HCl (10%) and filtered to afford a quantitative yield of **4b**: mp 240 °C dec; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.4 (s, 2H), 9.13 (s, 2H), 7.82 (s, 4H), 7.2–6.7 (m, 6H), 4.2–3.2 (m, 12H), 1.9–0.88 (m, 30H); ^{13}C NMR (DMSO-d_6, 25 MHz) δ 167.1, 157.0, 151.7, 133.0, 130.3, 129.1, 127.7, 125.4, 121.5, 76.6, 31.3, 30.4, 29.5, 28.8, 28.7, 25.4, 22.0, 13.8; MS m/e 737 ($M + H^+$).

11,23-Dicarboxy-25,26,27,28-tetrakis(n-octyloxy)calix[4]-arene (5b). Compound **4b** (0.20 g, 0.26 mmol) and 1-iodooctane (0.63 g, 2.6 mmol) were dissolved in DMF (50 mL), and then NaH (55% in oil, 0.30 g, 6.9 mmol) was added. The reaction mixture was stirred at room temperature for 48 h and then quenched with HCl (10%, 10 mL, caution!), the solvent was evaporated to reduced pressure, and the oily residue was then taken up with ethanol (100 mL) containing 1.0 g of KOH dissolved in 10 mL of water and refluxed for 24 h. The solvent was evaporated and the solid residue dissolved in CH_2Cl_2 and precipitated with CH_3OH. After filtration 50% yield of **5b** was

(17) (a) Böhmer, V.; Jung, K.; Schön, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790. (b) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527.

(18) A similar reaction has recently been reported by Reinhoudt et. al.[19] in which the use of $TiCl_4$ as the catalyst afforded 55% yield of compound **3a**.

(19) Werboom, W.; Dotta, S.; Asfari, Z.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 5394.

obtained as white powder; mp 110 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.83 (s, 2H), 7.09 (d, J = 7.36 Hz, 4H), 6.95 (t, 2H), 6.69 (s, 4H), 4.33 (d, J = 13.64 Hz, 4H), 3.95 and 3.61 (2t, J = 8.16 and 6.32 Hz, 8H), 3.06 (d, J = 13.64 Hz, 4H), 1.87–1.18 (m, 48H), 0.81 (m, 12H); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.47 (s, 4H), 6.46 (s, 6H), 4.47 (d, J = 13.51 Hz, 4H), 4.03 and 3.85 (t, J = 7.20 Hz, 8H), 3.21 (d, J = 13.51 Hz, 4H), 1.92 (m, 8H), 1.4–1.33 (m, 40H), 0.91 (t, J = 6.81 Hz, 12H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 172.3, 160.1, 157.9, 136.9, 133.9, 130.0, 129.7, 123.5, 123.1, 75.5, 75.3, 32.2, 31.2, 30.8, 30.3, 30.0, 29.7, 26.9, 26.3, 23.0, 14.4; MS m/e 962 ($M + H^+$).

Synthesis of Calix[4]arene–Biscrown-3 (6a,c). NaH (55% in oil, 1.7 g, 38.0 mmol) was added to a solution containing the appropriate calix[4]arene (**1a,c**) (4.7 mmol) and dissolved in DMF (500 mL), the mixture heated at 80 °C, and then diethylene glycol ditosylate (4.9 g, 11.8 mmol) dissolved in 5 mL of DMF added. The reaction was stirred for 4 h at room temperature and evaporated to dryness and the residue taken up with HCl (10%, caution!) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and purified by column chromatography. **6a**: eluent hexane/ethyl acetate = 3/2, 55% yield, mp 265–268 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01–6.98 (m, 8H), 6.73 (t, J = 7.5 Hz, 4H), 5.05 and 4.49 (2d, J = 12.12 and 12.08 Hz, 4H), 4.31–3.84 (m, 16H), 3.26 and 3.21 (2d, J = 12.12 and 12.08 Hz, 4H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 135.6, 135.5, 129.0, 128.1, 123.7, 76.3, 74.8, 30.7, 29.8; MS m/e 565 ($M + H^+$); **6c**: eluent hexane/ethyl acetate = 7/3, yield 30%, mp 273–275 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93 and 6.88 (2d, J = 2.40 Hz, 8H), 5.03 and 4.45 (2d, J = 12.36 and 12.12 Hz, 4H), 4.33–3.39 (m, 16H), 3.16 and 3.13 (2d, J = 12.36 and 12.12 Hz, 4H), 1.09 (s, 36H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 153.2, 145.4, 135.2, 134.7, 126.0, 125.8, 76.2, 74.5, 34.3, 32.0, 31.8, 30.5; MS m/e 789 ($M + H^+$).

11,23-Diformyl-26,28-di-n-propoxycalix[4]arene-25,27-crown-3 (7). To 400 mL of DMF were added the dialdehyde **3a** (1.0 g, 1.8 mmol) and anhydrous Na_2CO_3 (5.0 g, 47.2 mmol) at room temperature and stirred for 30 min, and then 2-iodoethyl ether (1.1 g, 3.4 mmol) was added. The reaction mixture was heated at 80 °C for 24 h and then evaporated to dryness, the residue was dissolved in ethyl acetate and washed twice with water, and the organic phase evaporated to afford a brown oil which was purified by preparative chromatography (hexane/ethyl acetate = 75/25) and gave 40% yield of **7** as white solid: mp 216–218 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.98 (s, 2H), 7.71 (s, 4H), 6.20 (t, J = 7.75 Hz, 2H), 5.97 (d, J = 7.75 Hz, 4H), 4.43 (d, J = 13.69 Hz, 4H), 4.1–4.2 (m, 8H), 3.68 (t, J = 6.72 Hz, 4H), 3.32 (d, J = 13.69 Hz, 4H), 1.85 (m, 4H), 1.10 (t, J = 7.37 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.5, 164.2, 154.8, 138.0, 132.3, 131.1, 122.5, 77.5, 73.4, 70.5, 31.1, 23.9, 11.3; MS m/e 635 ($M + H^+$).

11,23-Dicarboxy-26,28-di-n-propoxycalix[4]arene-25,27-crown-3 (8). Compound **8** was obtained from the oxidation of compound **7** using the procedure for compound **4b**: 90% yield, white solid mp 335 °C dec; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (s, 4H), 6.18 (t, J = 7.58 Hz, 2H), 6.00 (d, J = 7.58 Hz, 4H), 4.42 (d, J = 13.45 Hz, 4H), 4.2–4.1 (m, 8H), 3.68 (t, J = 6.55 Hz, 4H), 3.30 (d, J = 13.45 Hz, 4H), 1.84 (m, 8H), 1.11 (t, J = 7.40 Hz, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.5, 167.5, 162.2, 136.6, 130.9, 126.9, 121.8, 76.6, 72.7, 69.6, 29.9, 23.0, 10.9; MS m/e 667 ($M + H^+$).

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Supplementary Material Available: ^{1}H NMR spectra of all new compounds **3b**, **4b**, **5b**, **6a**, **6c**, **7**, and **8** (9 pages). This material is contined in libraries on microfiches, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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