Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5539–5544

TETRAHEDRON

The first synthesis and characterisation of elusive cone 1,2-diformyl tetralkoxycalix[4]arenes and their derivatives

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Received 11 March 2003; revised 2 May 2003; accepted 22 May 2003

Abstract—The synthesis and isolation of elusive tetralkoxycalix[4]arenes **2** in the cone conformation and bearing two formyl groups in proximal (1,2) positions at the upper rim are described for the first time. They were obtained as a mixture with the distal (1,3) regioisomers **3** by optimizing the Gross formylation reaction on the tetralkoxycalix[4]arenes **1**. After reduction to the corresponding alcohols, compounds **4** could be isolated and oxidized to 1,2-diformyl (**2**) and 1,2-diacid (**6**) tetralkoxycalix[4]arenes. These 1,2-difunctionalized derivatives are useful intermediates for the synthesis of calixarene-based molecular receptors having proximal binding groups.

1. Introduction

Calixarenes[1,2] and particularly calix[4]arenes are widely used as scaffolds for the synthesis of receptors for cations,[3,4] anions[5] and neutral molecules.[6] The main reason for the increasing importance of calixarenes in supramolecular and bioorganic chemistry is the possibility to functionalize them at both the lower (phenolic oxygens) and the upper (aromatic *p*-positions) rims.[7] One of the most useful methods of functionalization of the upper rim, which allows the synthesis of a large variety of host molecules, is (selective) formylation. The reaction is usually carried out using hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA)[8] if exhaustive functionalization is required or through the Gross formylation ($TiCl_4$ or $SnCl_4/Cl_2$-$CHOCH_3$)[9] which allows a certain degree of regioselective control. The selective diametral (1,3) diformylation of upper rim calix[4]arene 1,3-diethers can be easily achieved using the Gross method,[10] since in this case the phenolic aromatic nuclei are more reactive than the corresponding ethers (transfer of selectivity from the lower to the upper rim). More difficult is the regio control of the calix[4]arene tetraethers, although in selected cases good yields of upper rim diametral diformylated calix[4]arene tetraethers have been obtained.[11–13] Using the 1,3-diformylated calix[4]-arene tetraethers in the cone conformation as starting materials, Reinhoudt and co-workers synthesized a series of calix[4]arenes functionalized at the upper rim with 2,6-bis[(dimethylamino)methyl]pyridine units which complex Zn(II) ions and catalyse the hydrolysis of phosphodiester bonds,[14] showing a cooperative effect of the two metallic centres. In a continuation of these studies we are interested in evaluating the catalytic activity of Zn(II) complexes in proximal (1,2) positions. For this purpose we needed 1,2-diformyl tetralkoxycalix[4]arene derivatives in the cone conformation. This class of compounds is unknown, in line with the general difficulty encountered in calix[4]arene chemistry to obtain proximal upper rim difunctionalized derivatives. In fact, only the dibromo,[15,16] dinitro[17–21] and bischloromethyl[22] proximal derivatives have been described. A very recent report on the Gross formylation of calix[4]arene tetraethers in a variety of conditions[13] has confirmed the earlier observations[11] of a preference for diametral difunctionalized compounds over the proximal regioisomers, which therefore were not isolated and characterized.

We herein report the first examples of 1,2-diformylated tetralkoxycalix[4]arenes, which can be considered as very useful intermediates in the synthesis of novel calixarene-based molecular receptors having proximal binding groups.

Keywords: calixarenes; selective upper rim functionalization; formylation reaction; proximal functionalization; dialcohols; diacids; NMR spectroscopy.

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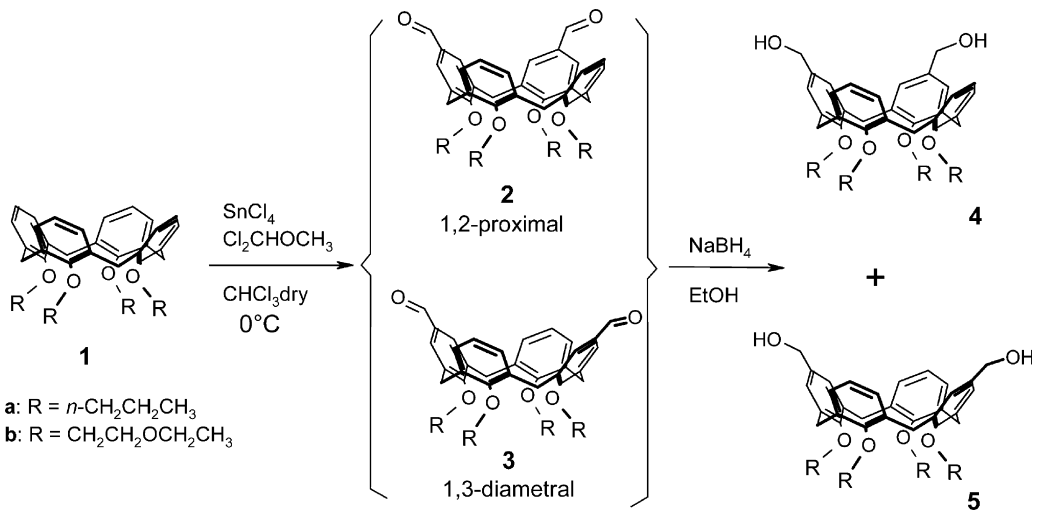
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00808-1



Scheme 1.

2. Results and discussion

The synthesis of calix[4]arenes 1,2-difunctionalized at the upper rim could potentially be carried out through a method which exploits the transfer of selectivity from the lower rim or by direct selective upper rim functionalization of calix[4]arene tetraethers. The first method would, however, require the synthesis of calix[4]arenes 1,2-dialkylated at the lower rim but these compounds can only be obtained in moderate yields.[23] Moreover, the subsequent *O*-alkylation of compounds bearing in the *para*-positions sensitive substituents, such as the formyl groups, may give rise to stability problems for these functional groups in the very basic conditions which are required for obtaining the cone conformation (NaH, DMF) and to problems in the stereochemical outcome of the reaction, since electron-withdrawing groups tend to favour the non-cone isomers. We therefore decided to reinvestigate the direct formylation of specific tetralkoxycalix[4]arenes in the cone structure, in order to find the best conditions for obtaining 1,2-diformylated derivatives.

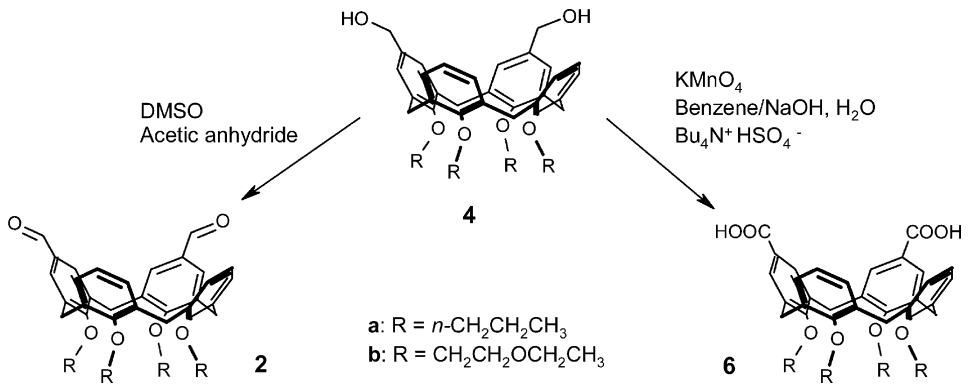
We have found that reacting **1b** at 0°C with 15 equiv. of $SnCl_4$ and Cl_2CHOCH_3 (see Scheme 1), the more classical 1,3 regioselectivity of the formylation reaction is somewhat decreased and the 1,2-diformylated derivative **2b** is formed in substantial amounts. By integration of the signals of the formyl protons of compounds **2b** (δ=9.65) and **3b** (δ=9.59) it was possible to calculate the ratio (40/60) of the two isomers (entry 1, Table 1). The reaction of tetrapropoxy-calix[4]arene **1a** under the same conditions (entry 2, Table 1) afforded a large amount of tri- and tetraformylated calixarenes. Decreasing the equivalents of $SnCl_4$ and Cl_2CHOCH_3 to 3 (entry 3, Table 1) gave a statistical mixture of distal and proximal diformyls **2a/3a** (65/35) in 30% yield. A similar reduction of formylating agents on **1b** (entry 4, Table 1) causes a drop in reactivity, since only 40% of reagent was converted to monoformyl calixarene. This seems to indicate that the Lewis acid is bound to the more coordinating ethoxy-ethyl chains at the lower rim of calixarene **1b**, thus decreasing the reactivity and influencing the regiochemistry of the reaction.[11] On the other hand, the propoxy chains of **1a** do not significantly coordinate to $SnCl_4$ and a statistical ratio of **2a/3a** is obtained. Further increase in the reaction temperature or moving to Duff formylation conditions[27] (entry 5, Table 1) gave only an increase of polysubstituted (tri- and tetraformylated) compounds and a decrease in the **2/3** ratio.

All attempts to separate **2** from **3** by chromatography failed. However, reduction of the mixture with $NaBH_4$ in ethanol quantitatively afforded the dialcohols **4** and **5**, which could be separated by column chromatography. Swern oxidation of the purified dialcohols **4a** and **4b** gave the

Table 1. Formylation of tetralkoxycalix[4]arenes **1** with $SnCl_4$ and Cl_2HCOCH_3 at 0°C in dry $CHCl_3$

Entry	Calix[4]arene	$SnCl_4/Cl_2HCOCH_3$[a] (equiv.)	Yield (%)				Relative ratio **2/3** (%)
			Mono[11,24]	Tri[11,25]	Tetra[11,26]	(**2**+**3**)	
1	**1b**	15/15	30	5	0	48	40/60
2	**1a**	15/15	0	30	65	5	[b]
3	**1a**	3/3	40	15	0	30	65/35
4	**1b**	3/3	40[c]	0	0	0	NA
5	**1b**	[d]	0	70	5	20	15/85

NA=not applicable.
[a] With respect to 1 equiv. of **1a**,**b**.
[b] Not determined.
[c] 60% of **1b** was also recovered.
[d] 10 equiv. of HMTA in CF_3COOH at 50°C for 15 h.



Scheme 2.

1,2-diformylated derivatives **2a**,**b** in 85–88% yield. Oxidation with $KMnO_4$ under phase transfer conditions gave the carboxylic acids **6a**,**b** in 85–90% yield (Scheme 2).

The ^{1}H NMR spectra of the two diformyl derivatives **2a**,**b** resulted to be very useful to establish, without ambiguity, the substitution in proximal position, especially thanks to the signals of the methylene bridges that are diagnostic of the calix[4]arene symmetry. As a result of the plane of symmetry in the molecule we see three doublets for the axial protons, three for the equatorial protons of the methylene bridges and two with a meta-coupling for the aromatic protons of the substituted rings (Fig. 1). A similar ^{1}H NMR pattern is also exhibited by the 1,2-diacids **6a**,**b**. In the case of dialcohols **4a** and **4b** we observed only one doublet for each of the protons of the methylene bridges, instead of three as expected. The main difference with the analogous compounds substituted in 1,3 positions are in the aromatic region. As observed in similar compounds,[28] the alcoholic functions in distal position can form intramolecular hydrogen bonds in apolar solvents such as $CDCl_3$, constraining the calixarene skeleton in a closed flattened cone conformation. In this structure the substituted aromatic rings are almost parallel and their protons are in the shielding cone of the two flattened unsubstituted aromatic rings. Therefore, there are two groups of signals for the aromatic protons of **5a** and **5b**. A singlet for the substituted ring at higher field (δ=6.4) and a doublet and a triplet at lower field ($\delta\approx$6.9 and 6.8). In the case of the 1,2 difunctionalized calix[4]arenes the distance between the two alcoholic groups does not allow the formation of intramolecular hydrogen bonds and the calix[4]arenes assume a more regular cone conformation. As a result the aromatic signals have similar chemical shifts giving a multiplet between 6.65 and 6.55 ppm. The lack of intramolecular hydrogen bonds is also confirmed by chemical shift of the singlet of ArCH_2OH. In the case of the proximal 1,2 disubstituted dialcohols this is 0.15 ppm downfield compared to the corresponding distal 1,3 disubstituted compounds.

3. Conclusions

By varying the reaction temperature and the ratio of reagents and catalyst in the Gross formylation, conditions have been found which give reasonable amounts of 1,2-diformylated tetralkoxycalix[4]arenes. This allowed, for the first time, their isolation in pure form and their characterisation together with the corresponding 1,2-dialcohols and 1,2-diacids. These compounds are important calix[4]arene intermediates for the synthesis of more complex receptors and catalysts with functions in proximal positions.

4. Experimental

4.1. General information

All moisture sensitive reactions were carried out under

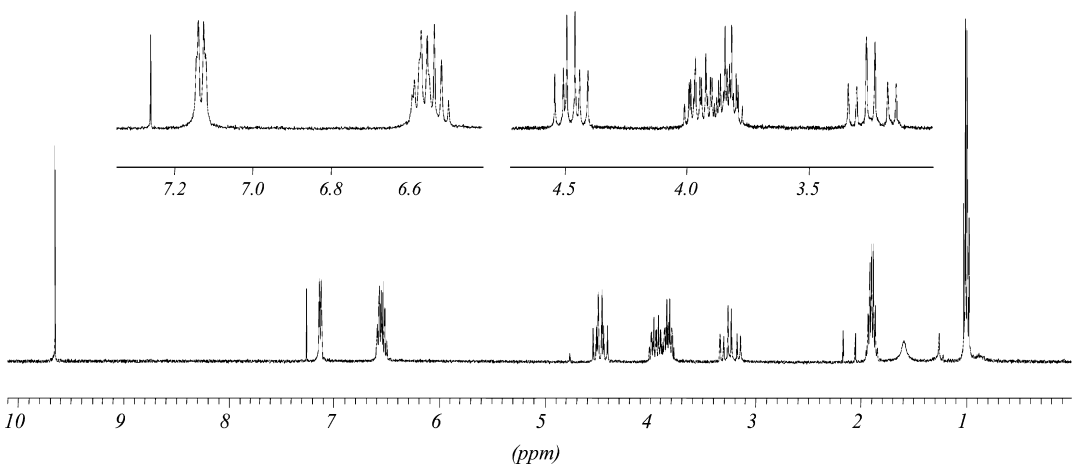


Figure 1. ^{1}H NMR spectrum of compound **2a** in $CDCl_3$ (400 MHz, 300 K).

nitrogen atmosphere. Most of the solvents and all reagents were commercial and used without further purification. All dry solvents were prepared according to standard procedures and stored over molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC300 and Bruker AMX400 spectrometers at 300 K. Spectra are reported in ppm downfield from TMS as internal standard. Mass spectra by electrospray ionization (ESI) and chemical ionization (CI) methods were recorded on a Micromass ZMD and on a Finnigan Mat SSQ710 spectrometer, respectively. FAB-MS spectra were recorded with a Finnigan MAT 90 spectrometer using *m*-NBA as a matrix. Analytical TLC was performed using Merck prepared plates (silica gel 60 F-254 on aluminium). Merck silica gel (40–63 μm) was used for flash chromatography. Melting points were determined in under nitrogen sealed capillaries with an Electrothermal apparatus.

4.2. Synthesis

4.2.1. Formylation procedure for obtaining 1,2 derivatives. The calix[4]arene tetraethers **1a**,**b** (2 g) were dissolved in 100 mL of dry chloroform and the solution, kept under N_2, was cooled to 0°C with an ice bath. After 15 min Cl_2CHOCH_3 and $SnCl_4$ (3 equiv. for **1a**; 15 equiv. for **1b**) were added to the vigorously stirred solution. After 1.5 h the reaction mixture was poured into 300 mL of 1 M HCl and the solution was stirred for 2 h. After the addition of 150 mL of CH_2Cl_2 to the solution, the organic phase was separated and washed twice with water, dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the mixture of **2** and **3** was obtained after purification by column chromatography (eluent: hex/EtOAc 8.8:1.2 for **1a**; hex/EtOAc 7:3 for **1b**).

4.2.2. 5,11-Bis-hydroxymethyl-25,26,27,28-tetrapropoxycalix[4]arene (4a). 0.45 g (0.691 mmol) of the mixture containing 1,3- and 1,2-diformyl tetrapropoxycalix[4]arene were dissolved in absolute EtOH. $NaBH_4$ (79 mg, 2.07 mmol) was added and the solution was stirred for 3 h. The solvent was evaporated under reduced pressure and the solid was dissolved in CH_2Cl_2 (100 mL) and washed with water (2×100 mL). The solvent was removed under vacuum and the residue was submitted to column chromatography (CH_2Cl_2/EtOAc/hex, 2:2:3) obtaining the 1,3-dialcohol (R_f=0.32; 151 mg) and 1,2-dialcohol **4a** (R_f=0.23; 257 mg) derivatives. Mp (of **4a**)=139–140°C. Yield 90%; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.65–6.56 (m, 10H, Ar*H*); 4.45 (d, 4H, ArCH_2Ar ax, J=13.4 Hz); 4.33 (s, 4H, ArCH_2OH); 3.85 (t, 4H, ArOCH_2, J=7.6 Hz); 3.84 (t, 4H, ArOCH_2, J=7.4 Hz); 3.14 (d, 4H, ArCH_2Ar eq., J=13.4 Hz); 1.95–1.87 (m, 8H, ArOCH$_2$CH_2); 1.00 (t, 6H, CH$_2$CH_3, J=7.5 Hz); 0.99 (t, 6H, CH$_2$CH_3, J=7.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 156.7, 156.3, 135.2, 135.1, 134.4, 128.2, 127.4, 127.3, 121.6, 76.7, 65.2, 31.0, 23.3, 10.3; MS (CI) *m*/*z* (%): 652.3 (100) $[M]^+$. Anal. calcd for $C_{42}H_{52}O_6$ (652.87): C, 77.27; H, 8.03. Found: C, 77.15; H, 8.19.

4.2.3. 5,11-Bis-hydroxymethyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (4b). Compound **4b** was obtained by the same procedure used for **4a** from the mixture of the two diformyl tetraethoxyethyl derivatives. The residue was submitted to column chromatography (CH_2Cl_2/EtOAc/hex, 5:5:2) obtaining the 1,3-dialcohol (R_f=0.35; 448 mg) and 1,2-dialcohol **4b** (R_f=0.24; 290 mg) derivatives. Compound **4b** is a colourless oil. Yield 90%; ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.58–6.47 (m, 10H, Ar*H*); 4.43 (d, 4H, ArCH_2Ar ax, J=13.5 Hz); 4.24 (s, 4H, ArCH_2OH); 4.04 (t, 8H, ArOCH_2, J=6.0 Hz); 3.76 (t, 8H, ArOCH$_2$CH_2, J=6.0 Hz); 3.47 (q, 8H, ROCH_2CH$_3$, J=6.9 Hz); 3.07 (d, 4H, ArCH_2Ar eq., J=13.5 Hz); 1.12 (t, 12H, ROCH$_2$CH_3, J=6.9 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 156.4, 156.1, 135.2, 135.1, 135.0, 134.5, 128.2, 127.3, 121.9, 73.2, 69.6, 66.3, 65.2, 30.8, 29.7, 15.3; MS (FAB+VE) *m*/*z* (%): 773.0 (100) $[M+H]^+$. Anal. calcd for $C_{46}H_{60}O_{10}$ (772.98): C, 71.48; H, 7.82. Found: C, 71.34; H, 7.94.

4.2.4. 5,11-Diformyl-25,26,27,28-tetrapropoxycalix[4]-arene (2a). Acetic anhydride (65 μL, 0.68 mmol) was added to a solution of 1,2-dialcohol calix[4]arene **4a** (21 mg, 0.0327 mmol) in 1 mL of dry DMSO. The reaction mixture was stirred for 20 h at room temperature and then poured in 15 mL of 1 M NaOH aqueous solution. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the combined organic phases were collected, dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hex/EtOAc, 9/1; R_f=0.19) obtaining colourless oil. Yield 88%; ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.65 (s, 2H, ArC*H*O); 7.14 (d, 2H, Ar*H*CHO, J_m=1.76 Hz); 7.12 (d, 2H, Ar*H*CHO, J_m=1.76 Hz); 6.60–6.50 (m, 6H, Ar*H*); 4.52 (d, 1H, ArCH_2Ar ax, J=13.7 Hz); 4.47 (d, 2H, ArCH_2Ar ax, J=13.4 Hz); 4.42 (d, 1H, ArCH_2Ar ax, J=13.4 Hz); 3.98 (dt, 1H, ArOCH_AH$_B$, J^2=10.2 Hz, J^3=7.6 Hz); 3.91 (dt, 1H, ArOCH$_A$$H_B$, J^2=10.2 Hz, J^3=7.3 Hz); 3.87 (dt, 1H, ArOCH_CH$_D$, J^2=10.2 Hz, J^3=7.3 Hz); 3.804 (dt, 1H, ArOCH$_C$$H_D$, J^2=10.2 Hz, J^3=7.3 Hz); 3.32 (d, 1H, ArCH_2Ar equiv., J=13.7 Hz); 3.24 (d, 2H, ArCH_2Ar eq., J=13.4 Hz); 3.16 (d, 1H, ArCH_2Ar eq., J=13.4 Hz); 1.93–1.86 (m, 8H, ArOCH$_2$CH_2); 1.07 (t, 6H, CH$_2$CH_3, J=7.6 Hz); 0.99 (t, 6H, CH$_2$CH_3, J=7.6 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 191.4, 162.2, 156.4, 136.5, 135.4, 135.2, 134.1, 131.0, 130.5, 129.8, 128.5, 128.0, 122.1, 76.7, 30.9, 23.3, 23.2, 10.2, 10.1; MS (ESI+) *m*/*z* (%): 671.3 (100) $[M+Na]^+$. Anal. calcd for $C_{42}H_{48}O_6$ (648.84): C, 77.75; H, 7.46. Found: C, 77.63; H, 7.59.

4.2.5. 5,11-Diformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (2b). Compound **2b** was obtained by the same procedure used for **2a** from the dialcohol **4b**. The residue was purified by column chromatography (hex/EtOAc, 7:3; R_f=0.23). Compound **2b** is a colourless oil. Yield 85%; ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.65 (s, 2H, ArC*H*O); 7.17–7.13 (m, 4H, Ar*H*); 6.61–6.50 (m, 6H, Ar*H*); 4.64 (d, 1H, ArCH_2Ar ax, J=13.8 Hz); 4.55 (d, 2H, ArCH_2Ar ax, J=13.7 Hz); 4.46 (d, 1H, ArCH_2Ar ax, J=13.6 Hz); 4.24–4.07 (m, 8H, ArOCH_2); 3.84–3.77 (m, 8H, ArOCH$_2$CH_2); 3.56–3.48 (m, 8H, ROCH_2CH$_3$); 3.30 (d, 1H, ArCH_2Ar eq., J=13.8 Hz); 3.24 (d, 2H, ArCH_2Ar eq., J=13.7 Hz); 3.15 (d, 1H, ArCH_2Ar eq., J=13.6 Hz); 1.26–1.15 (m, 12H, CH_3R); ^{13}C NMR (75 MHz; $CDCl_3$): δ 191.5, 162.1, 156.2, 136.5, 135.6, 135.2, 134.2, 131.2, 130.6, 129.9, 128.6, 128.2, 122.5, 73.6, 73.2, 69.8, 69.6, 66.4, 30.8, 15.3, 15.2; MS (CI) *m*/*z* (%): 768.8 (100) $[M]^+$.

Anal. calcd for $C_{46}H_{56}O_{10}$ (768.95): C, 71.85; H, 7.34. Found: C, 71.97; H, 7.45.

4.2.6. 5,11-Dicarboxy-25,26,27,28-tetrapropoxycalix[4]-arene (6a). To a solution of dialcohol calix[4]arene **4a** (30 mg 0.037 mmol) in benzene (4 mL) were added potassium permanganate (58 mg, 0.37 mmol), 8 mL of 6% NaOH aqueous solution and a catalytic amount of tetrabutylammonium hydrogen sulphate (2 mg, 0.006 mmol) as phase transfer agent. The mixture was vigorously stirred at room temperature overnight. EtOAc (80 mL) and 1 M HCl (80 mL) were added. The organic layer was separated, washed with water (80 mL) and dried over Na_2SO_4. Then it was evaporated under reduced pressure obtaining a white solid. Yield: 85%. Mp>300°C; ^{1}H NMR (300 MHz; CD_3COCD_3): δ 7.41 (d, 2H, Ar*H*, J_m=2.3 Hz); 7.40 (d, 2H, Ar*H*, J_m=2.3 Hz); 6.67–6.62 (m, 4H, Ar*H*); 6.55 (dd, 2H, Ar*H*, J_1=7.6 Hz, J_2=6.8 Hz); 4.58 (d, 1H, ArCH_2Ar ax, J=13.6 Hz); 4.55 (d, 2H, ArCH_2Ar ax, J=13.5 Hz); 4.52 (d, 1H, ArCH_2Ar ax, J=13.5 Hz); 4.05–3.99 (m, 4H, ArOCH_2); 3.95–3.90 (m, 4H, ArOCH_2); 3.42 (d, 1H, ArCH_2Ar eq., J=13.6 Hz); 3.32 (d, 2H, ArCH_2Ar eq., J=13.5 Hz); 3.23 (d, 1H, ArCH_2Ar eq., J= 13.5 Hz); 2.05–1.95 (m, 8H, ArOCH$_2$CH_2); 1.09 (t, 6H, CH$_2$CH_3, J=7.3 Hz); 1.08 (t, 6H, CH$_2$CH_3, J=7.3 Hz); ^{13}C NMR (75 MHz; CD_3COCD_3): δ 166.8, 160.9, 156.7, 135.7, 135.4, 135.1, 134.7, 130.4, 130.1, 128.5, 128.1, 124.3, 122.1, 76.9, 76.7, 30.7, 23.4, 23.3, 9.9; MS (ESI-) *m/z* (%): 679.5 (100) $[M-H]^-$; 339 (50) $[M-2H]^{2-}$. Anal. calcd for $C_{42}H_{48}O_8$ (680.84): C, 74.09; H, 7.11. Found: C, 73.95; H, 7.24.

4.2.7. 5,11-Dicarboxy-25,26,27,28-tetrakis(2-ethoxy-ethoxy)calix[4]arene (6b). Compound **6b** was obtained as a white solid by the same procedure used for **6a** from the dialcohol **4b**. Yield: 90%. Mp=178°C; ^{1}H NMR (300 MHz; CD_3OD): δ 7.34 (s, 4H, Ar*H*); 6.62–6.50 (m, 6H, Ar*H*); 4.64 (d, 1H, ArCH_2Ar ax, J=13.8 Hz); 4.60 (d, 2H, ArCH_2Ar ax, J=14.0 Hz); 4.55 (d, 1H, ArCH_2Ar ax, J=14.1 Hz); 4.25–4.17 (m, 4H, ArOCH_2); 4.15–4.08 (m, 4H, ArOCH_2); 3.90–3.86 (m, 8H, ArOCH$_2$CH_2); 3.62–3.53 (m, 8H, ROCH_2CH$_3$); 3.29 (d, 1H, ArCH_2Ar eq., J=13.8 Hz); 3.23 (d, 2H, ArCH_2Ar eq., J=14.0 Hz); 3.16 (d, 1H, ArCH_2Ar eq., J=14.1 Hz); 1.24–1.17 (m, 12H, ROCH$_2$CH_3); ^{13}C NMR (75 MHz; CD_3OD): δ 162.6, 158.0, 137.2, 136.7, 136.6, 136.1, 131.9, 131.5, 129.9, 129.6, 123.7, 75.1, 74.8, 71.5, 71.4, 67.7, 32.2, 16.0; MS (CI) *m/z* (%): 800.8 (100) $[M]^+$. Anal. calcd for $C_{46}H_{56}O_{12}$ (800.95): C, 68.98; H, 7.05. Found: C, 68.86; H, 7.20.

Acknowledgements

We thank MIUR (COFIN2001 Projects: 'Supramolecular Devices') and the CNR (Agenzia 2000 Project) for financial support. The Centro Interfacoltà di Misure (CIM) of the University of Parma is also acknowledged for the use of NMR and Mass facilities.

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