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# Synthesis of Water Soluble Molecular Receptors from Calix[4]arenes Fixed in the Cone Conformation

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**Abstract:** New water soluble hosts have been synthesized in good yields from calix[4]arenes fixed in the cone conformation. They are preorganized ditopic receptors which can be used for the selective recognition of metal ions and neutral molecules in aqueous solution

## INTRODUCTION

In the last few years, a new class of very efficient and selective cation receptors has been synthesized by functionalization of the phenolic OH groups (bottom rim) of calix[4]arenes with ester, amide and carboxylic acid units[1].

These ligands show complexing properties comparable with those of cryptands[1] and have selectivity towards cations with high charge density such us $Na^+$, $Ca^{2+}$ and lanthanides[1,2].

Particularly interesting is the tetramide of p-*tert*-butylcalix[4]arene which encapsulates lanthanide ions and forms expecially with $Tb^{3+}$ highly luminescent complexes[3]

The properties of such calix[4]arene ligands are a consequence of the particular geometry which is generated after the functionalization of calix[4]arenes at the bottom rim, which blocks the macrocycle into the cone structure[4], where the four chelating chains are convergent and interact simultaneously with the complexed cation[1, 2]

All the calix[4]arene ligands of this type, known so far, are very lipophilic due to the calix[4]arene backbone and to the alkyl groups present in the para position of the aromatic nuclei.

For these reason the ligands have been studied in organic media and used in ion sensors[5], ion transport through liquid membranes[6] and metal extraction[1].

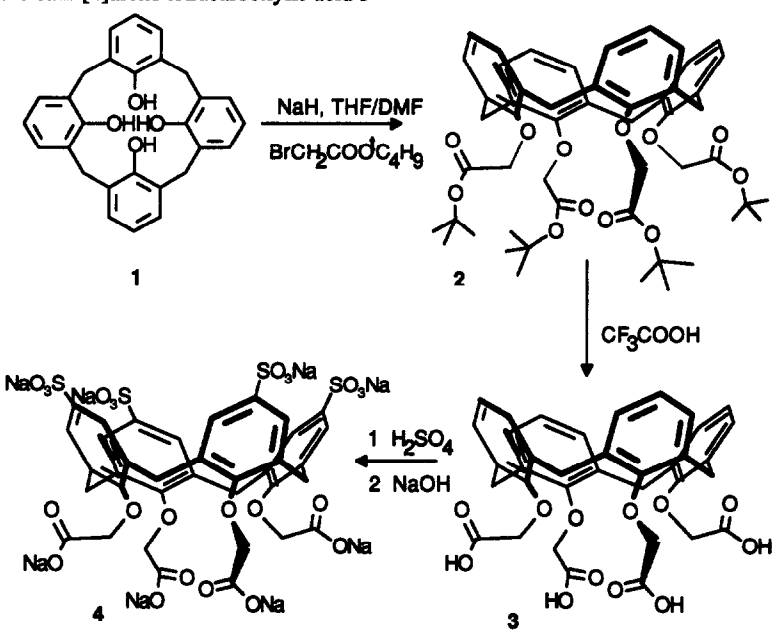
To test the potential of these calixarene ligands, and expecially of those forming luminescent complexes, in biomedical applications[7] it would be highly desirable to have them soluble in water and with the cone structure preserved

## RESULTS AND DISCUSSION

Shinkai et al have reported the synthesis of a water soluble calix[4]arene sulfonated at the upper rim[8]. When this compound was treated with chloroacetic acid in a mixture of DMSO/$H_2O$ a tetracarboxylic acid derivative was obtained which showed a $^1H$ NMR pattern in accord with a fixed 1,3-alternate structure[9], where the four chelating chains are not convergent.

In order to reach our goal we have reversed the synthetic strategy, first synthesizing the ligands in the fixed cone structure and then sulfonating them at the upper rim. The results of these studies are reported in this paper

By treating calix[4]arene **1** with NaH in THF/DMF = 5 v/v and tert-butyl monobromoacetate the tetraester **2** was obtained in 70% yield, which upon de-tert-butylation with trifluoracetic acid gave quantitatively the calix[4]arene tetracarboxylic acid **3**



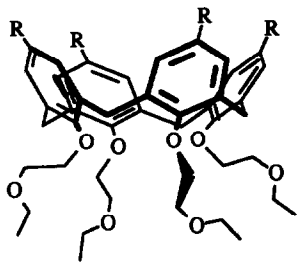

**1** **2** **3** **4**

Sulfonation of the tetraacid **3** with $H_2SO_4$ conc and subsequent neutralization to sodium salt afforded the water soluble tetracarboxylate tetrasulfonated calix[4]arene **4** in 68% yield.

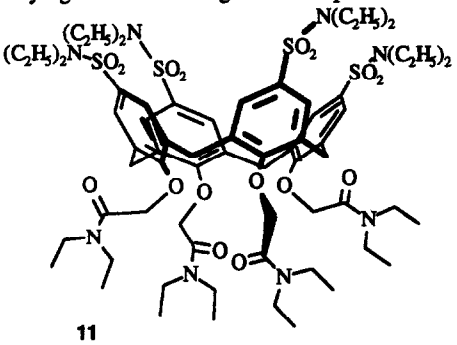
Compound **4** exists in a fixed cone structure as inferred from its NMR spectra which show a very simple pattern. The $^1H$ NMR shows two pairs of doublets for the $ArCH_2Ar$ protons (3.69 and 4 70 δ) and singlets for other protons, whereas the $^{13}C$ NMR shows only one absorption for the bridging methylene carbon at 32.0 ppm, which is typical for all *syn* oriented aromatic nuclei[10]. Interestingly compound **4**, isolated after precipitation with methanol strongly complexes this solvent molecule which is probably encapsulated into the apolar cavity of the calixarene as shown by the high field absorption at 2.8 δ in the $^1H$ NMR spectrum. The methanol molecule cannot be completely removed even after drying under vacuum suggesting that in this rigid and preorganized host molecule the binding of uncharged molecules should be stronger than in flexible

sulfonated calix[4]arene having free phenolic OH groups for which an association constant of 1000 $M^{-1}$ has been estimated[11]

Analogously to compound **3**, also the tetra(ethoxyethoxy)calix[4]arene **5** may be sulfonated at the upper rim by treatment with concentrated sulfuric acid and subsequent neutralization with $NaHCO_3$. Also in this case the freezing of the conformation in the first alkylation step allows to obtain another water-soluble calix[4]arene host **6** fixed in the cone structure, for studying molecular recognition in aqueous solvents

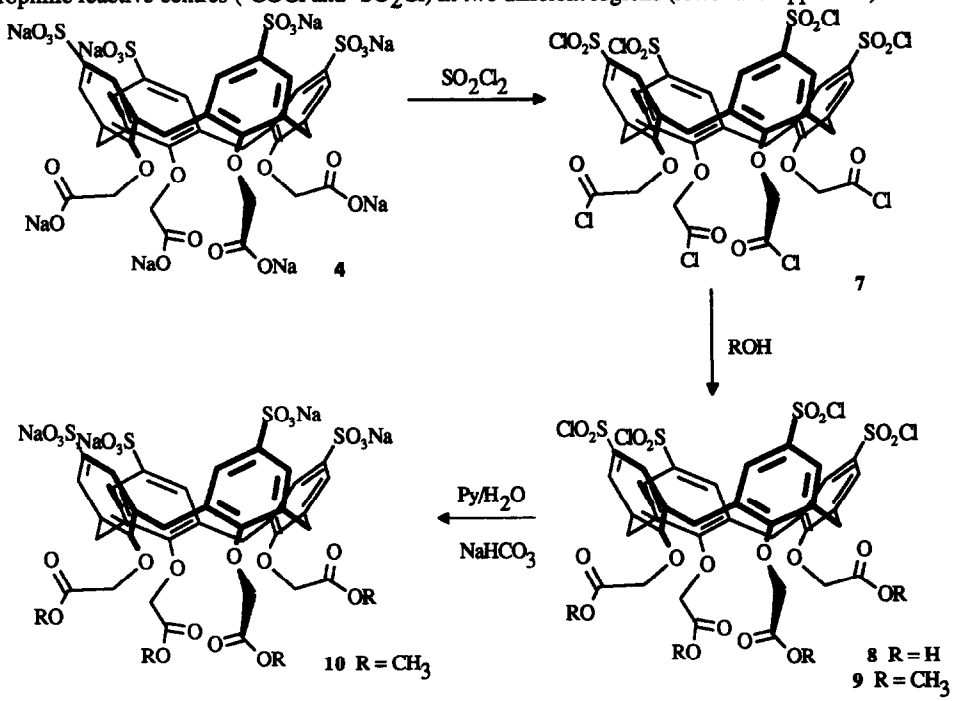


**5** R = H
**6** R = $SO_3Na$



**11**

By treating the tetracarboxylate-tetrasulfonate **4** in thionyl chloride with DMF as catalyst[12], the octachloride **7** was obtained, this compound represents a very interesting intermediate, since it offers two electrophilic reactive centres (-COCl and -$SO_2Cl$) in two different regions (lower and upper rim) of the calix




**4**
**7**
**8** R = H
**9** R = $CH_3$
**10** R = $CH_3$

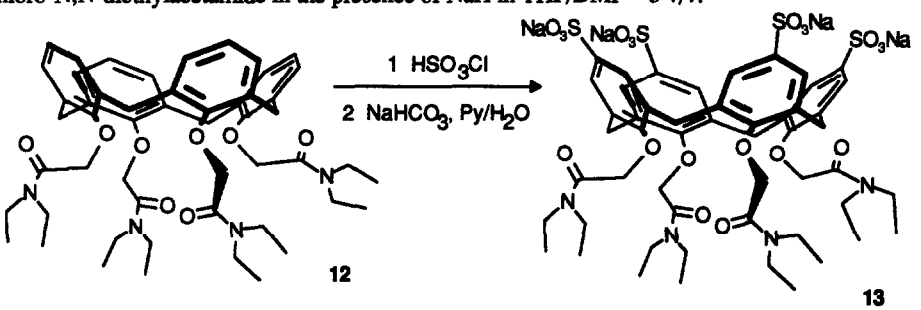
The different reactivities of these functions could be exploited to introduce chelating groups such as acids, esters, amides (at the lower rim) followed by the attachment of the ligands on complex matrices such as

polymers, sugars, peptides (via -$SO_2Cl$ groups at the upper rim). Moreover compound **7** is quite stable in the absence of bases since it can be purified by trituration with water!

Selective solvolysis of chlorocarbonyl moieties was achieved by treating **7** with acetone/water to afford the acid **8** or acetone/methanol to give the ester **9.**

The water-soluble ester **10**, was easily obtained by hydrolysis in pyridine-water of the chlorosulfonyl groups, followed by neutralization with $NaHCO_3$.

The reaction of the octachloride **7** with diethylamine gave quantitatively the octaamide **11**, preventing the synthesis through this route, of the water-soluble tetramide **13**, which however was synthesized by direct chlorosulfonation, followed by hydrolysis in pyridine-water, of compound **12** obtained from calix[4]arene **1** and 2-chloro-N,N-diethylacetamide in the presence of NaH in THF/DMF = 5 v/v.




**12** **13**

Compounds **4, 6, 10** and **13** represent an interesting class of ditopic water-soluble host molecules which can encapsulate metal ions at the lower rim and neutral molecules inside the apolar cavity of the calix The molecular recognition properties of these new macrocycles are under investigation.

## EXPERIMENTAL SECTION

Melting points were determined on a Electrothermal apparatus in a sealed capillary and are uncorrected Mass spectra were performed on spectrometer Varian CH-5 and VG 7070 EQ-HF. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker AC100 ($^1H$ NMR 100MHz, $^{13}C$ NMR 25MHz) and on a Bruker CXP200 ($^1H$ NMR 200 MHz) spectrometer of the Centro Interdipartimentale di Misure (C I.M.) of the University of Parma. Chemical shifts ($\delta$) are expressed in ppm from $Me_4Si$.

IR spectra were performed on a spectrophotometer Perkin-Elmer 298 Elemental analyses were carried out at the Istituto di Chimica Farmaceutica of the University of Parma.

Concentration of sodium cation was determined by atomic emission spectrometry on a Philips PU 7450 ICP Thermogravimetric analyses were carried out on a Perkin-Elmer TGA 7 apparatus.

All solvents were purified by standard procedures. Analytical TLC were performed on precoated silica gel plates ($SiO_2$, Merck, 60 $F_{254}$), while silica gel 60 (Merck, particle size 0.040-0.063 mm, 230-240 mesh) was used for preparative column chromatography.

Calix[4]arene **1** was prepared according to ref.[13] and compound **5** according to ref [14]

*25,26,27,28-Tetrakis(1,1-dimethylethoxycarbonylmethoxy)calix[4]arene (2)*

Under a nitrogen atmosphere calix[4]arene (2.12 g, 5 0 mmol) was dissolved in THF (120 mL) and DMF (30 ml) Then NaH (3 24 g, 81 mmol 60% in oil) was added, followed by an excess of tert-butyl monobromoacetate (29.3 g, 150 mmol) and the reaction mixture refluxed for 4 hours. THF and most of unreacted bromoacetate were removed in vacuo, then the residue was treated with 10% HCl and extracted

with $CH_2Cl_2$ (70 ml) The organic layer was washed with water and the solvent removed under reduced pressure. The yellow oily residue was crystallized with methanol to yield 3.52 g of product (80% yield): m.p. = 269-270°C; IR (KBr) $\nu_{max}$ 1750(s), 1160 $cm^{-1}$, $^1H$ NMR ($CDCl_3$) δ 1 46 (s, 36H, $C(CH_3)_3$), 3.22 (d, 4H, Heq, J = 13.7 Hz), 4.63 (s, 8H, $OCH_2CO$), 4.89 (d, 4H, Hax), 6.61 (s, 12H, ArH); $^{13}C$ NMR ($CDCl_3$) δ 28.2 (q, $C(\underline{C}H_3)_3$), 31 7 (t, $Ar\underline{C}H_2Ar$), 71 9 (t, $O\underline{C}H_2CO$), 81.0 (s, $\underline{C}(CH_3)_3$), 122.5 (d, Ar para), 128 4 (d, Ar meta), 134.8 (s, Ar ortho), 156 1 (s, Ar ipso), 169.3 (s, C=O); mass spectrum (EI), 881.0 ($M^+$, calcd 880 4) Anal calcd for $C_{52}H_{64}O_{12}$. C, 70 89, H, 7 32 Found· C, 70 55, H, 7 53.

*25,26,27,28-Tetrakis(hydroxycarbonylmethoxy)calix[4]arene (3)*

A sample of compound **2** (2 8 g, 3 18 mmol) was suspended in 11 mL of trifluoroacetic acid and stirred at room temperature for 5 hours. The solvent was then removed under reduced pressure and the residue was triturated with water and filtered to give 1.98 g of product (95% yield). m.p. = 263-265°C; IR (KBr) $\nu_{max}$ 3400-2800(bs), 1750(s) $cm^{-1}$, $^1H$ NMR ($CD_3COCD_3$) δ 3.37 (d, 4H, Heq, J = 13.0 Hz), 4.82 (s, 8H, $OCH_2CO$), 5.09 (d, 4H, Hax), 6 72 (t, 4H, ArH para, J= 7.5Hz), 6 98 (d, 8H, ArH meta, J = 7 5Hz), 7.77 (bs, 4H, OH); $^{13}C$ NMR ($CD_3COCD_3$) δ 31.6 (t, $ArCH_2Ar$), 72.7 (t, $O\underline{C}H_2CO$), 124 8 (d, Ar para), 129.8 (d, Ar meta), 135 5 (s, Ar ortho), 155.9 (s, Ar ipso), 171.2 (s, C=O); mass spectrum (EI), 656.8 (M+, calcd 656 25) Anal. calcd for $C_{36}H_{32}O_{12}$ C, 65.84, H, 4 91. Found: C, 65.75, H, 4.70.

*5,11,17,23-Tetrasulfonato-25,26,27,28-tetrakis(hydroxycarbonylmethoxy)calix[4]arene, octasodium salt (4)*

A sample of **3** ( 3 0 g, 4 57 mmol) was suspended in 13 mL of concentrated $H_2SO_4$ (96%). The reaction mixture was stirred for 5 hours at room temperature and then quenched with 25 mL of water. After cooling the precipitate was filtered on a frit, suspended in water and titrated with a solution of $Ba(OH)_2$ till pH= 4-5. $BaSO_4$ was filtered off and the pH of the solution was adjusted at pH = 8-9 by addition of a hot solution of $Na_2CO_3$ (0.4N). After the removal of the precipitate, the filtrate was concentrated on a rotary evaporator, $HNO_3$ 0 1N added till pH = 3 and the resulting solution was boiled for 4 hours in order to remove carbonates This solution was then concentrated under reduced pressure, cooled and filtered on a buchner. A white precipitate was recrystallized from HCl 6N, dissolved in a small amount of water and carefully titrated with a 1N solution of NaOH till neutrality. By addition of methanol a white precipitate formed which was collected and dried at 80°C for 6 hours under vacuum to afford 3 36g (60% yield) of octasodium salt m.p.>350°C; IR (KBr) $\nu_{max}$ 3700-3100(bs), 1610(s), 1200(s), 1050 $cm^{-1}$; $^1H$ NMR ($D_2O$) δ 3 69 (d, 4H, Heq, J = 12.7Hz), 4 48 (s, 8H, $O\underline{C}H_2CO$), 4 70 (d, 4H, Hax), 7 70 (s, 8H, ArH); $^{13}C$ NMR ($D_2O$) δ 32 0 (t, $ArCH_2Ar$), 77.6 (t, $O\underline{C}H_2CO$), 128 6 (d, Ar meta), 138.5 (s, Ar ortho), 141.8 (s, Ar para), 157 1 (s, Ar ipso), 170.6 (s, C=O). Anal calcd for $C_{36}H_{24}Na_8O_{24}S_4 \cdot 4H_2O$ C, 35.30; H, 2 63; Na, 15 02. Found: C, 35.76; H, 2 32; Na, 15.2.

*5,11,17,23-Tetrasulfonato-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene, tetrasodium salt (6)*

A sample of compound **5** (0.6 g, 0 85 mmol) was stirred in 3 mL concentrated $H_2SO_4$ (96%) for 2 hours The homogeneous reaction mixture was diluted with water (15 mL) and added of a 1.5N solution of barium acetate till pH = 4-5 The precipitate was filtered, collected and suspended in water . The pH was adjusted to 8-9 with a 0 1N solution of $Na_2CO_3$ and this heterogeneous solution was boiled for 1 hour After cooling the precipitate of inorganic salts was separated and the filtrate was mixed with the first one. This solution was concentrated under reduced pressure and titrated with a 0 1N solution of $Na_2CO_3$ till pH = 9 The resulting $BaCO_3$ was eliminated by filtration and the solution evaporated to dryness under reduced pressure This residue was first triturated with MeOH and then purified by crystallization from 25 mL of a 4.1 mixture n-butanol·water, to give 0 86 g (yield = 80%) m.p.>350°C; IR (KBr) $\nu_{max}$ 3650-3300(bs), 1195(s), 1055(s) $cm^{-1}$, $^1H$ NMR ($D_2O$) δ 1 17 (t, 12H, $OCH_2\underline{C}H_3$), 3 45 (d, 4H, Heq, J = 13.2Hz), 3.63 (q, 8H, $OC\underline{H}_2CH_3$), 4.02 (t, 8H, $ArOCH_2\underline{C}H_2$, J = 6.5Hz), 4.28 (t, 8H, $ArO\underline{C}H_2CH_2$, J = 6.5Hz), 4.58 (d, 4H, Hax), 7 34 (s, 8H, ArH), $^{13}C$ NMR ($D_2O$) δ 17.1 (q, $OCH_2\underline{C}H_3$), 33.5 (t, $ArCH_2Ar$), 69.2 (t, $O\underline{C}H_2CH_3$), 72 6 (t, $ArOCH_2\underline{C}H_2$), 75 8 (t, $ArO\underline{C}H_2CH_2$), 128 7 (d, Ar meta), 137 7 (s, Ar ortho), 139.9 (s, Ar para),

161.1 (s, Ar ipso) Anal calcd for $C_{44}H_{52}Na_4O_{20}S_4 \cdot 8H_2O$. C, 41 76, H, 5.42, Na, 7.27. Found C, 42.1; H, 5 28, Na, 7.48.

*5,11,17,23-Tetrakis(chlorosulfonyl)-25,26,27,28-tetrakis(chlorocarbonylmethoxy)calix[4]arene (7).*

A solution of compound **4** (1.0 g, 0 82 mmol) in 15 mL of thionyl chloride and 0.25 mL of DMF was refluxed (110°C) under nitrogen atmosphere for 60 hours Thionyl chloride was removed and the raw product dried carefully under vacuum. The product was purified by trituration in water and filtrated to obtain 0.9 g (yield = 98%) of a yellowish powder IR (KBr) $\nu_{max}$ 1820 and 1805(s), 1385 (s), 1170(s) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 3 55 (d, 4H, Heq, J = 13 0 Hz), 4.40 (d, 4H, Hax), 4 53 (s, 8H, $OCH_2CO$), 7 51 (s, 8H, ArH). Anal calcd for $C_{36}H_{24}Cl_8O_{16}S_4$. C, 38.57; H, 2.16. Found: C, 38.21; H, 2.89.

*5,11,17,23-Tetrakis(chlorosulfonyl)-25,26,27,28-tetrakis(hydroxycarbonylmethoxy)calix[4]arene (8).*

A sample of compound **7** (1 1 g, 0.98 mmol) was solubilized in 20 mL of acetone. After the addition of 5 mL of water, acetone was distilled off under reduced pressure and a white product precipitated. This product was filtered and 0.75g (73% yield) of compound **8** were recovered· m.p. = 188-190°C; IR (KBr) $\nu_{max}$ 3600-2800(bs), 1750(s), 1385, 1185(s) $cm^{-1}$; $^1H$ NMR ($CD_3COCD_3$) δ 3.94 (d, 4H, Heq, J = 14.0 Hz), 5 15 (s, 8H, $OCH_2CO$), 5 28 (d, 4H, Hax), 7 80 (s, 8H, ArH); $^{13}C$ NMR ($CD_3COCD_3$) δ 31 6 (t, $ArCH_2Ar$), 72 1 (t, $O\underline{C}H_2CO$), 128.9 (d, Ar meta), 137 1 (s, Ar ortho), 139.8 (s, Ar para), 162 3 (s, Ar ipso), 170.6 (s, C = O), mass spectrum (FAB-), 1048.5 (M+, calcd 1047.9). Anal. calcd for $C_{36}H_{28}Cl_4O_{20}S_4$ C, 41.23; H, 2 69, Cl, 13.49, S, 12 20. Found· C, 41.36; H, 2.75

*5,11,17,23-Tetrakis(chlorosulfonyl)-25,26,27,28-tetrakis(methoxycarbonylmethoxy) calix[4]arene (9).*

Compound **7** (1.0 g, 0 89 mmol) was suspended in 7.5 mL of dry acetone containing 2.5 mL (62 mmol) of dry MeOH The heterogeneuos reaction mixture was stirred for 75 minutes under nitrogen atmosphere. Then 5 mL of water were added and after the removal of acetone by distillation, a white precipitate was filtered and dried, thus obtaining 0.89 g (90% yield) of compound **9**: m.p. = 255-257°C; IR (KBr) $\nu_{max}$ 1770(s), 1380, 1175(s), $cm^{-1}$, $^1H$ NMR ($CD_3COCD_3$) δ 3.83 (s, 12H, $OCH_3$), 3.95 (d, 4H, Heq, J = 14.0 Hz), 5.13 (s, 8H, $OCH_2CO$), 5.34 (d, 4H, Hax), 7 81 (s, 8H, ArH), $^{13}C$ NMR ($CD_3COCD_3$) δ 31.5 (t, $ArCH_2Ar$), 52 2 (q, $OCH_3$), 72.3 (t, $O\underline{C}H_2CO$), 128.9 (d, Ar meta), 137.1 (s, Ar ortho), 139.9 (s, Ar para), 162.5 (s, Ar ipso), 170 2 (s, C=O); mass spectrum, 1105 ($M^+$, calcd 1104.3), 1069 (M-Cl). Anal. calcd for $C_{40}H_{36}S_4O_{20}Cl_4$ C, 43 41; H, 3 28 Found· C, 43 24, H, 3 16

*5,11,17,23-Tetrasulfonato-25,26,27,28-tetrakis(methoxycarbonylmethoxy)calix[4]arene (10)*

Compound **9** (0.9 g, 0 8 mmol) was first dissolved at room temperature in 4.0 mL of pyridine, then water (0 5 ml) was added and the reaction mixture stirred for 40 minutes. The solvent was distilled off under reduced pressure and the residue carefully titrated to neutrality with a solution of $NaHCO_3$. The solution was evaporated to dryness and a white solid 0 70 g (70% yield) obtained after crystallization from water-methanol· m.p. > 350°C; IR (KBr) $\nu_{max}$ 3650-3200(bs), 1755(s), 1050(s) $cm^{-1}$, $^1H$ NMR ($D_2O$) δ 3.46 (d, 4H, Heq, J = 14 0 Hz), 3 75 (s, 12H, $OCH_3$), 4 56 (d, 4H, Hax), 4 87 (s, 8H, $OCH_2CO$), 7 31 (s, 8H, ArH); $^{13}C$ NMR ($D_2O$) δ 33.2 (t, $ArCH_2Ar$), 54 8 (q, $OCH_3$), 73.7 (t, $O\underline{C}H_2CO$), 128.8 (d, Ar meta), 137 0 (s, Ar ortho), 140.6 (s, Ar para), 159.2 (s, Ar ipso), 174.6 (s, C=O) Anal. calcd for $C_{40}H_{36}Na_4O_{24}S_4 \cdot 8H_2O$. C, 38.00; H, 4.14. Found: C, 38 21; H, 4 09

*5,11,17,23-Tetrakis(N,N-diethylaminosulfonyl)-25,26,27,28-tetrakis(N,N-diethylaminocarbonylmethoxy) calix[4]arene (11)*

Compound **7** (0.15g, 0.133 mmol) was suspended in 2 5 ml of dry acetone and added of 110 μl of diethylamine (0.08 g, 1.07 mmol) The reaction mixture was stirred under nitrogen for 3 h, then quenched with 2.5 ml of water. After evaporation of acetone under reduced pressure, the white solid was filtered, washed

with water and carefully dry under vacuum, to afford 0 12 mg of compound **11** (65% yield): m.p = 230-232°C; IR (NaCl) $\nu_{max}$ 1650(s), 1340 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.92-1.22 (m, 48H, $NCH_2\underline{CH_3}$), 2.98 (q, 16H, S-$NCH_2CH_3$), 3.3-3.4 (m, 20H, C-$NCH_2CH_3$ and Heq), 5.11 (s, 8H, $OCH_2CO$), 5.56 (d, 4H, Hax, J = 13 9 Hz), 7.27 (s, 8H, ArH); $^{13}C$ NMR ($CDCl_3$) δ 13.1 and 14.4 (q, C-$NCH_2\underline{C}H_3$), 14.5 (q, S-$NCH_2\underline{C}H_3$), 32.1 (t, $ArCH_2Ar$), 40.1 and 40.8 (t, C-$N\underline{C}H_2CH_3$), 42.5 (t, S-$N\underline{C}H_2CH_3$), 72.3 (t, $OCH_2CO$), 127 9 (d, Ar meta), 134.8 (s, Ar ortho), 138 2 (s, Ar para), 159 7 (s, Ar ipso), 168.1 (s, C=O). Anal. calcd for $C_{68}H_{104}N_8O_{16}S_4$. C, 57 62; H, 7.39; N, 7 90 Found· C, 57.81; H, 7.24; N, 8 03

*25,26,27,28-Tetrakis(N,N-diethylaminocarbonylmethoxy)calix[4]arene (12)*

A solution of calix[4]arene **1** (1 0 g, 2.35 mmol) in 60 mL of a mixture of THF/DMF (5/1 v/v) was added of NaH (0 92 g, 23 mmol, 60% in oil) and of 2-chloro-N,N-diethylacetamide (2.82 g, 18.9 mmol) The reaction mixture was refluxed under nitrogen for 3 hours. Then THF was removed under reduced pressure and the reaction quenced with 10% HCl (50 mL) This phase was extracted with $CH_2Cl_2$ (70 mL), the organic phase separated and washed with water (3 X 80 mL) $CH_2Cl_2$ was evaporated and the residue treated with ethyl ether, from which white crystals of the sodium chloride complex were filtered. This product was dissolved in 100 mL of ethyl acetate and extracted with 10% HCl (2 X 75 mL) and water (3 X 75 mL). The organic phase was separated and the solvent distilled under vacuum to give 1.44 g (yield = 70%) of product **12**: m.p. = 212-214°C, IR (KBr) $\nu_{max}$ 1665(s), 1470(s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.08 (m, 24H, $NCH_2\underline{CH_3}$), 3.22 (d, 4H, Heq, J = 14.0 Hz), 3.30 (q, 16H, $N\underline{C}H_2CH_3$), 4.89 (s, 8H, $OCH_2CO$), 5.22 (d, 4H, Hax), 6.58 (s, 12H, ArH); $^{13}C$ NMR ($CDCl_3$) δ 13.1 and 14 4 (q, $NCH_2\underline{C}H_3$), 32.0 (t, $ArCH_2Ar$), 39.9 and 40 9 (t, $N\underline{C}H_2CH_3$), 71 5 (t, $O\underline{C}H_2CO$), 122 2 (d, Ar para), 128 4 (d, Ar meta), 134.9 (s, Ar ortho), 156.6 (s, Ar ipso), 168.6 (s, C=O), mass spectrum (EI), 876 0 ($M^+$, calcd 876.5). Anal. calcd for $C_{52}H_{68}N_4O_8$: C, 71 20; H, 7 81; N, 6.39 Found: C, 71 53; H, 7 74; N, 6.51.

*5,11,17,23-Tetrasulfonato-25,26,27,28-tetrakis(N,N-diethylaminocarbonyl-methoxy)calix[4]arene, tetra-sodium salt (13)*

A solution of 3.0 g of compound **12** (3 4 mmol) in 10 mL of chlorosulfonic acid and 50 mL $CH_2Cl_2$ was stirred for 48 hours at room temperature The reaction mixture was then poured in 50 mL of water and ice and extracted with (2 x 50 mL) $CH_2Cl_2$ The combined organic extracts were washed with a 10% solution of $NaHCO_3$ till the acqueous phase reached pH = 9 By evaporation of the organic phase a solid was obtained which was suspended and refluxed for 14 hours in a mixture of 40 mL acetone, 5 mL pyridine, 2 mL water The solvent was removed under reduced pressure, the resulting solid dissolved in water (5 mL) and carefully neutralized with a solution of $NaHCO_3$ After addition of n-butanol a white powder was obtained which was recrystallized from methanol to afford, after drying, 4.04 g (83% yield) of product **13** m.p. >350°C, IR (KBr) $\nu_{max}$ 3700-3200(s), 1660(s), 1460(s), 1215(s), 1060(s) $cm^{-1}$, $^1H$ NMR ($D_2O$) δ 1 05-1 18 (m, 24H, $NCH_2\underline{CH_3}$), 3 10-3 40 (q, 16H, $N\underline{C}H_2CH_3$), 3.65 (d, 4H, Heq, J = 14 0 Hz), 4.59 (d, 4H, Hax), 4 83 (s, 8H, $OCH_2CO$), 7 63 (s, 8H, ArH), $^{13}C$ NMR ($D_2O$) δ 14.6 and 15.4 (q, $NCH_2\underline{C}H_3$), 32 1 (t, $ArCH_2Ar$), 42.8 and 43 4 (t, $N\underline{C}H_2CH_3$), 75 9 (t, $OCH_2CO$), 128.9 (d, Ar meta), 138 2 (s, Ar ortho), 142 5 (s, Ar para), 157 0 (s, Ar ipso), 170.4 (s, C=O). Anal calcd for $C_{52}H_{64}N_4Na_4O_{20}S_4 \cdot 8H_2O$. C, 43.70, H, 5.64, N, 3 92 Na, 6.43. Found C, 43 51, H, 5 72, N, 4 07, Na, 6.58

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