Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

New artificial receptors from selectively functionalized calix[4]arenes

Arturo Arduini[a]; Alessandro Casnati[a]; Massimo Fabbi[a]; Patrizia Minari[a]; Andrea Pochini[a]; Anna Rita Sicuri[a]; Rocco Ungaro[a]
[a] Istituto di Chimica Organica dell' Università, Parma, Italy

To cite this Article Arduini, Arturo , Casnati, Alessandro , Fabbi, Massimo , Minari, Patrizia , Pochini, Andrea , Sicuri, Anna Rita and Ungaro, Rocco(1993) 'New artificial receptors from selectively functionalized calix[4]arenes', Supramolecular Chemistry, 1: 3, 235 — 246
To link to this Article: DOI: 10.1080/10610279308035166
URL: http://dx.doi.org/10.1080/10610279308035166

SUPRAMOLECULAR CHEMISTRY, Vol. 1, pp. 235–246
Reprints available directly from the publisher
Photocopying permitted by license only

New artificial receptors from selectively functionalized calix[4]arenes

ARTURO ARDUINI, ALESSANDRO CASNATI, MASSIMO FABBI, PATRIZIA MINARI, ANDREA POCHINI,* ANNA RITA SICURI and ROCCO UNGARO*

Istituto di Chimica Organica dell'Università, Viale delle Scienze, I-43100 Parma, Italy

(Received July 27, 1992)

The development of new synthetic methods for the monoalkylation of calix[4]arenes at the lower rim allows the synthesis of a new class of trihydroxamate siderophores. Three chelating hydroxamic acid units are introduced through a sequence of reactions which blocks the macrocycle in the cone conformation. The new ligands obtained form neutral 1:1 complexes (FeL) with iron (III), which are stable in EtOH/H_2O 9:1 at pH 2–7. Calix[4]arene bis-crown ethers are prepared by exploiting the selective 1,2-(proximal) functionalization of calix[4]arenes at the lower rim. These ligands are, however, less effective in complexing alkali metal cations compared with the 1,3-calix[4]arene crown-ethers which, in their partial cone structure, offer a better shielding for the complexed cations. Rigid upper rim-bridged calix[4]arenes potentially useful for the inclusion of neutral molecules are prepared by exploiting the selective 1,3-diformylation of calix[4]arene at the upper rim. Finally a new chloromethylation method for calix[4]arenes blocked in the cone conformation is described together with the synthesis of new cavitands.

INTRODUCTION

In the last 15 years calixarenes have been extensively used as building blocks for the construction of more complex receptors for ions and neutral molecules.[1,2]

In this context the most thoroughly studied macrocycles are the calix[4]arenes **1** and **2** (see diagram below) which have been functionalized at the lower rim (phenolic OH groups) or at the upper rim (aromatic nuclei). Particularly interesting are the ester and amide derivatives in the cone conformation which represent a new class of sodium and calcium selective receptors.[1,2]

The tetramide **3** is also able to encapsulate lanthanide ions giving luminescent complexes in water solution[3] and in the solid state.[4]

A second class of calixarene ionophores are the calixcrowns (e.g. **4**) which are probably the most selective synthetic ionophores for potassium ions known so far, and because of this they are extensively used in ion sensors[5,6] and supported liquid membranes.[7]

Finally, the calixspherands (e.g. **5**) represent an example of synthetic receptors able to form kinetically stable complexes with alkali metal ions, including rubidium, which opens interesting doorways into biomedical research.[8] The special features shown by calix[4]arene ligands are a consequence of a subtle combination of preorganization, nature of the donor groups and stereochemistry around the binding region which can be easily controlled. In order to extend the scope of calixarenes in supramolecular chemistry we and others have tackled the problem of their selective functionalization at both rims.

RESULTS AND DISCUSSION

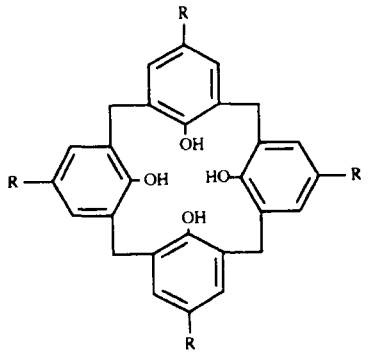
Metal ion ligands from selectively functionalized calix[4]arenes at the lower rim

The selective functionalization of calix[4]arenes at the lower rim has been extensively studied and methods have been developed that allow the selective monoalkylation,[9,10] the 1,3-(diametral)[11] and the 1,2-(proximal)-dialkylation.[12] By treating tetramethoxycalix[4]arenes **6a** and **6b** (Scheme 1) with three equivalents of iodotrimethylsilane in $CHCl_3$ the monomethoxycalix[4]arenes **7a** and **7b** are obtained in 85% and 65% yield, respectively.[9] The complementary direct methylation using CsF as a base produces **7a** in 67% and **7b** in 60% yield.[10]

The availability of good methods for the high yield synthesis of monomethoxycalix[4]arenes made attractive the design of calixarene-based siderophores.

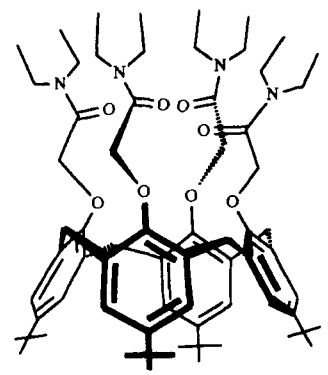
The natural siderophores bear three catecholate (e.g., **I**, see below) or hydroxamate (e.g. **II** and **III**) donor groups in acyclic, exocyclic and endocyclic

* To whom correspondence should be addressed.

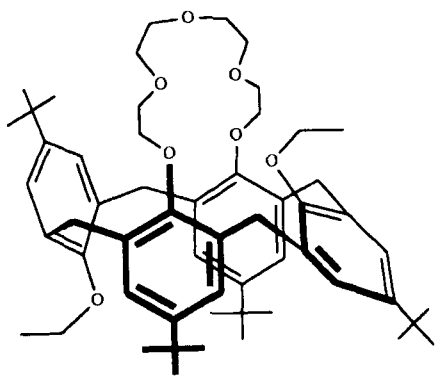


1: R = t-C_4H_9

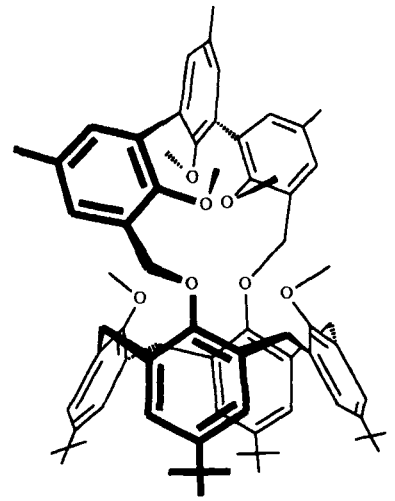
2: R = H



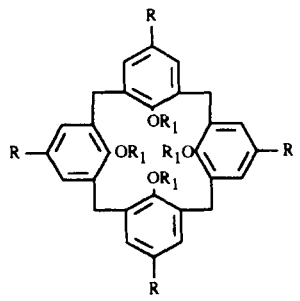
3



4



5

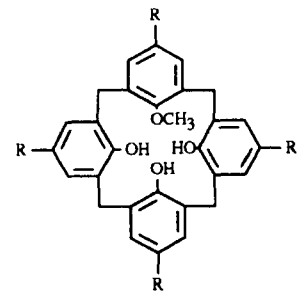


6a: R = t-C_4H_9; R_1 = CH_3

6b: R = H; R_1 = CH_3

3 eq $(CH_3)_3SiI$

$CHCl_3$



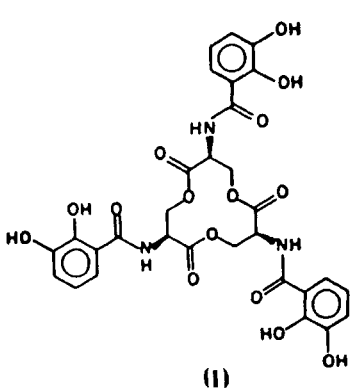
7a: R = t-C_4H_9

7b: R = H

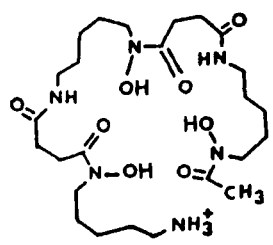
Scheme 1.

arrangements.[13] With the aim of developing new iron(III) chelators for clinical uses, several authors[14] have synthesized analogues of enterobactin (**I**), desferrioxamine B (**II**) and ferrichrome (**III**) having different degrees of flexibility of the backbone where the chelating groups are attached.

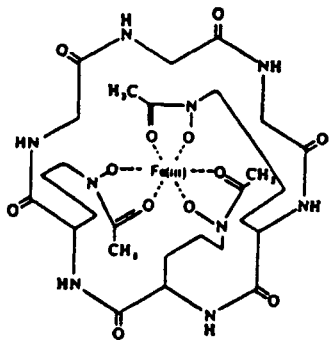
A tendency has emerged to synthesize trihydroxamate or tricathecholate siderophores with an increasing degree of preorganization.[15] Recently a macrobicyclic (cryptand) siderophore containing three endocyclic hydroxamate donor groups has been reported.[16] In order to be useful as a molecular platform for the synthesis of siderophores, the monomethoxycalix[4]arenes **7a** and **7b** had to be functionalized in



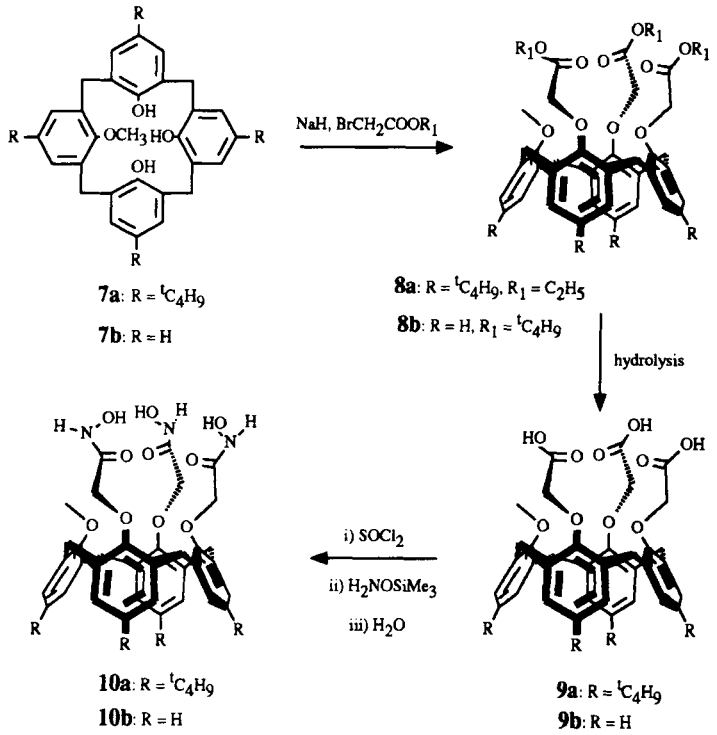
(I)
Enterobactin



(II)
Desferrioxamine B



(III)
Ferrichrome



7a: R = $^tC_4H_9$
7b: R = H

8a: R = $^tC_4H_9$, R_1 = C_2H_5
8b: R = H, R_1 = $^tC_4H_9$

10a: R = $^tC_4H_9$
10b: R = H

9a: R = $^tC_4H_9$
9b: R = H

Scheme 2

such a way that the three chelating chains introduced would form an octahedron around the complexed metal ion. Two hydroxamate siderophores **10a** and **10b** were synthesized in good yield through the sequence of reactions reported in Scheme 2.

The convergence of the three chelating chains in the trihydroxamates **10a** and **10b** as well as in their precursors **8** and **9** is clearly indicated by the ^{1}H-NMR spectra which show the typical AB system for the $ArCH_2Ar$ protons characteristic of the calix[4]arene in the cone conformation.

Compounds **10a** and **10b** form strong complexes *with iron(III)* in ethanol(EtOH)/water 9:1. Figure 1 shows the UV-visible spectra of the 1:1 complex between iron(III) and the trihydroxamate **10a** as a function of pH. The observed absorption maximum of this complex at $\lambda_{max} = 435$ nm is typical for the charge-transfer band between three hydroxamate groups co-ordinated in an octahedral fashion around the metal ion.[16,17]

The small changes in absorbance observed between pH 2.4 and 7.0 indicate that in this region the neutral complex (FeL) is fully formed and is rather stable. Due to the great stability of this complex in $EtOH/H_2O$ 9:1 only a preliminary evaluation of its formation constant ($\log \beta_{FeL} > 39$) could be made by direct potentiometric titration.[18]

The selective 1,3-dialkylation (diametral) of calix-[4]arenes is a well established method for the selective functionalization of these macrocycles and can be

easily accomplished by using two equivalents of an alkylating agent in the presence of one equivalent of K_2CO_3.[11] In these conditions only the two opposite OH groups (which are the most acidic[19]) are sequentially deprotonated and alkylated, whereas the base is too weak to ionize the formed 1,3-dialkoxycalix[4]arene because its mono anion cannot be stabilized by hydrogen bonds.

The use of strong bases completely changes the selectivity of the alkylation reaction. By treating calix[4]arenes with NaH in *N,N*-dimethylformamide or acetonitrile and 2.2 equivalents of an alkylating agent, the (proximal) 1,2-di-substituted calix[4]arenes can be obtained in 15–55% yield.[12]

This finding allowed a new and more direct synthesis of a calix[4]arene bis-crown-5[12] previously obtained via a four step alkylation-dealkylation procedure starting from *p-tert*-butylcalix[4]arene.[20] This compound could now be obtained in 16% yield in a two step synthesis (Scheme 3).

The selectivity in the first cyclization step which leads to **11** is very high (>95%) although the conversion is approximately 50%. Compound **12** is the first member of a new class of macrotricyclic compounds, the calix[4]arene-bis-crown ethers. The bis-crowns are of interest in the field of ion sensors because they show certain advantages over the simple crown ethers.[21] Table 1 reports the association constants and the binding free energies of alkali cation complexes of the bis-crown **12** in $CDCl_3$, determined according to the Cram's extraction method.[22]

Compared with the 1,3-dialkoxycalix[4]arene crown ethers synthesized previously and which represent the most efficient class of potassium selective synthetic receptors,[23] the calix[4]arene-bis-crown **12** is surprisingly much less efficient and selective.

This shows once again that in calixarene-based cation ligands very small changes in the geometry around the binding region often have a deep influence on their complexing properties.[2]

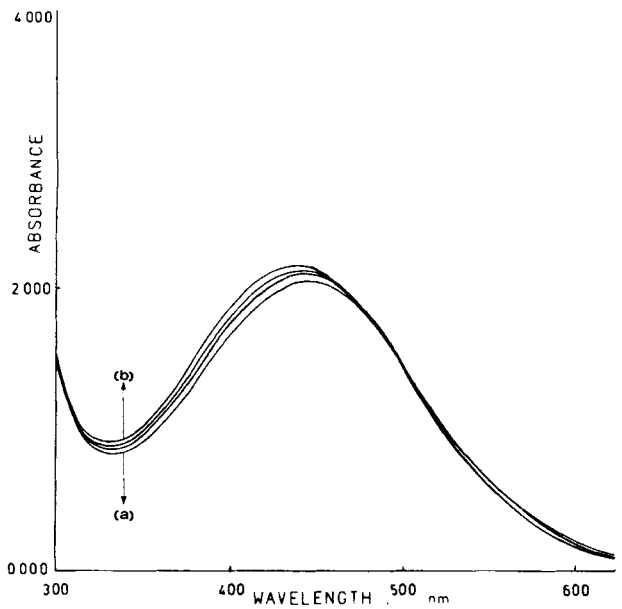


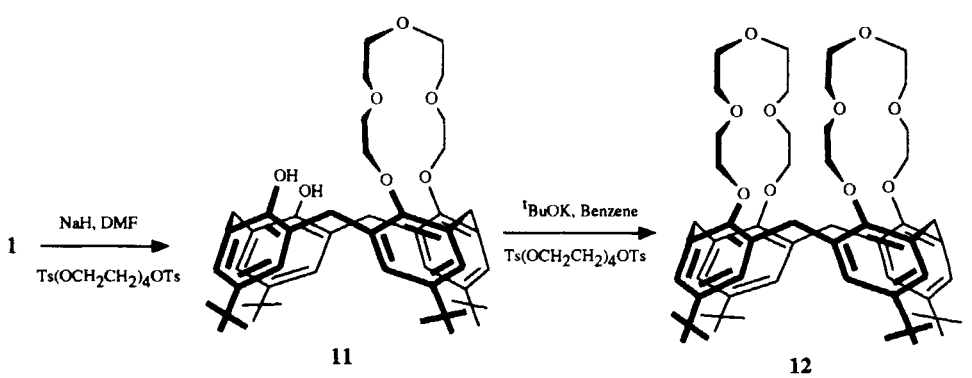
Figure 1 UV-visible spectra of Fe(III)·**10a**. Solutions measured as function of pH. Cell path = 0.1 cm, [FeL] = 1.1×10^{-3} M in C_2H_5OH/H_2O 9:1 (v/v), 25 °C. (a) pH = 2.4; (b) pH = 7.0.

Functionalization of calix[4]arenes at the upper rim and synthesis of new cavitands

Much evidence has been collected in previous studies of the inclusion of neutral molecules in the apolar cavity of calix[4]arenes in the solid state[2b] and in water solution.[24] Particularly attractive is the X-ray crystal structure (Fig 2) of the 2:1 complex between

Table 1 Association constant (K_a) and binding free energies ($-\Delta G°$) of complexes of host **12** with alkali picrates in $CDCl_3$ saturated with H_2O at 22 °C

Cation	Na^+	K^+	Rb^+	Cs^+
K_a (M^{-1})	9.0E04	8.9E05	8.2E05	3.6E04
$-\Delta G$ (*kcal/mol*)	6.7	8.1	8.0	6.2



Scheme 3.

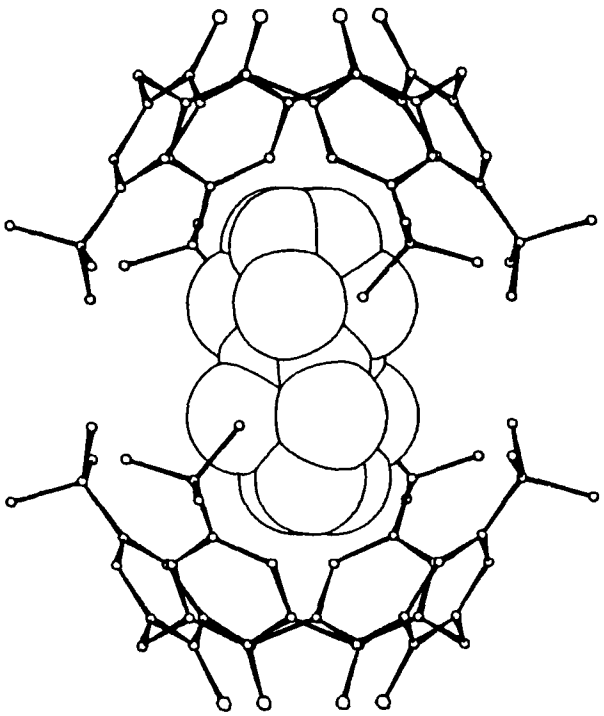
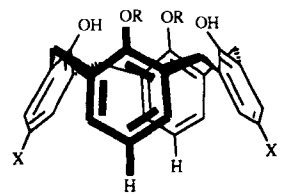


Figure 2 Molecular structure of the 2:1 complex between *p-tert*-butylcalix[4]arene (**1**) and anisole. The disordered anisole molecule is depicted by its van der Waals radius.

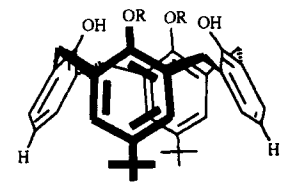
p-tert-butylcalix[4]arene **1** and anisole which shows that the guest molecule is held in a molecular capsule created by two host molecules which face each other by the upper rim.[25]

No evidence exists in the literature that inclusion of neutral molecules in calix[4]arenes occurs in organic media. With the aim of designing new receptor molecules based on calixarenes useful for studying molecular recognition in organic solvents we undertook a general project aimed at controlling the reactivity of calix[4]arenes at the upper rim.

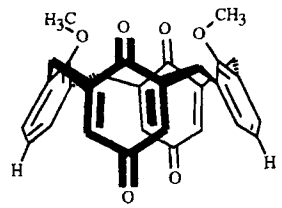
Several methods have been developed which allow the selective functionalization of the upper rim. Compounds like **13**–**16** have been synthesized by these methodologies which include direct substitution or selective removal of *tert*-butyl groups by transfer of regiocontrol from the lower to the upper rim.[11] In order to increase van der Waals interactions and to control the solvation of the host cavity we designed and synthesized new calix[4]arenes capped at the upper rim with bridges containing aromatic rings. The 1,3-diformyl cavitand **17a** was reduced to the corresponding dimethylol derivative **18** whose disodium salt was reacted with α,α′-dibromo-*p*-xylene under high dilution conditions to give in 30% yield



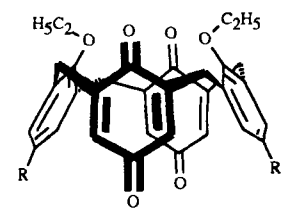
13: R = alkyl, X = Br, CHO, NO_2



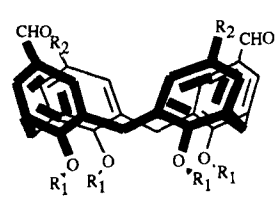
14



15

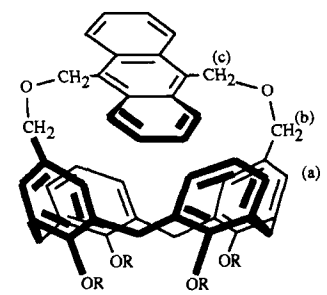


16: R = t-C_4H_9

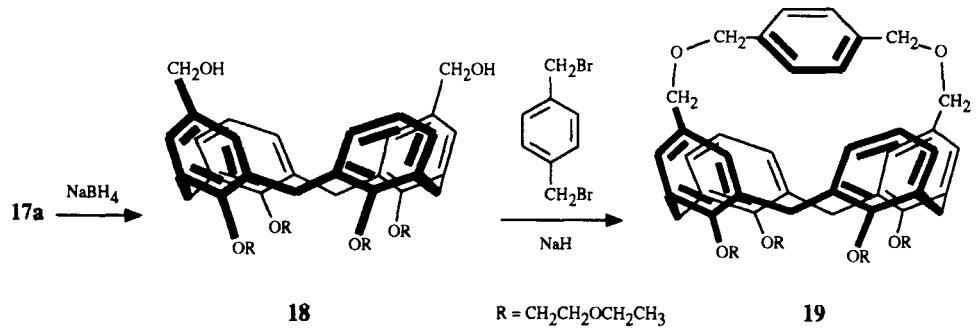


17a: $R_1 = C_2H_4OC_2H_5$; $R_2 = H$

17b: $R_1 = C_2H_4OC_2H_5$; R_2 = t-Bu

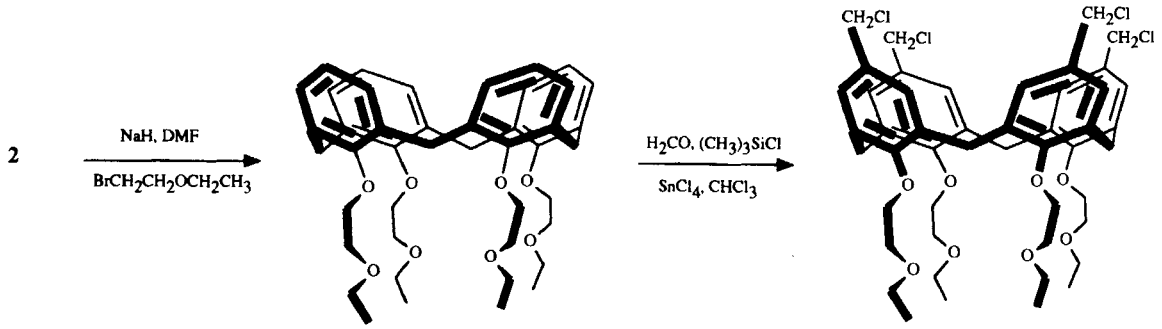


20: R = $CH_2CH_2OCH_2CH_3$



18 R = $CH_2CH_2OCH_2CH_3$ **19**

Scheme 4.



21 **22**

Scheme 5.

the desired calix[4]arene capped at the upper rim **19** (Scheme 4).

A more rigid compound **20** with a small but closed lipophilic cavity was obtained in 30% yield by reacting the dimethylol **18** with α,α'-dibromo-9,10-dimethylanthracene under the same conditions.

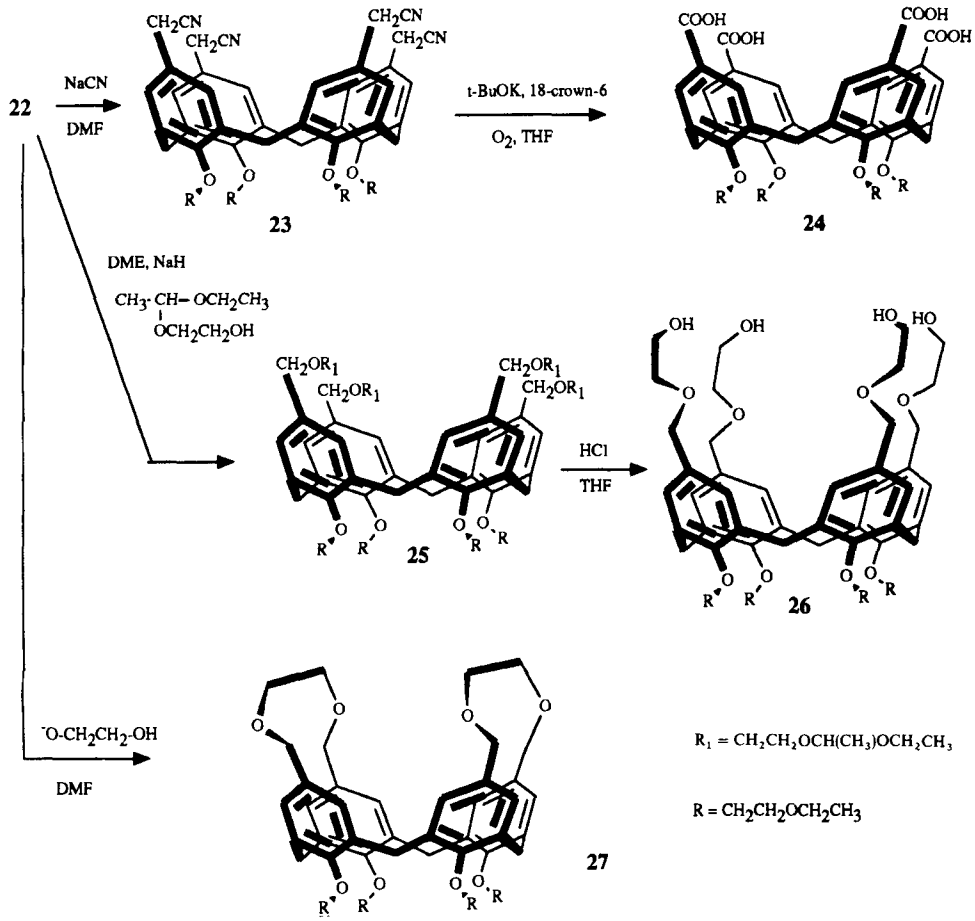
The ^{1}H-NMR spectrum of compound **20** is rather complex because of the strong anisotropic effects of the aromatic rings. The complete assignment of the structure was performed on the basis of two-dimensional COSY and NOESY experiments. Particularly affected by the anthracene nucleus is the upper rim region of the two calixarene rings which are connected by the bridge. The benzylic protons (b) are substantially high field shifted (*ca.* 2.7 ppm) whereas the aromatic protons of these two nuclei (a) absorb at *ca.* 5.8 δ. Moreover the anthryl benzylic protons (c) are shifted to low field (*ca.* 5.7 δ) by the anisotropic effects of calixarene ring.

Several methods have been developed previously for the tetrafunctionalization of calix[4]arenes at the upper rim.[1] A particularly useful reaction is the chloromethylation, which has been performed by us on calix[4]arene **2**[27] and by Shinkai *et al.*[28] on the flexible tetramethoxy derivative of **2**. No attempt has been made so far to chloromethylate calix[4]arene derivatives blocked in the cone conformation. By treating **2** with 2-bromoethoxy ethyl ether, in conditions where the tetra-alkylation produces almost exclusively compounds in the cone conformation,[12] the cavitand **21** was obtained in 72% yield. Chloromethylation of **21**, using a procedure recently developed for polymers,[29] produced the tetrachloromethylated compound **22** in 70% isolated yield (Scheme 5). **22** is a very useful intermediate for the introduction at the upper rim of calix[4]arenes of additional functional groups or more complex binding sites. As an example of the first case, the synthesis of the tetracarboxylic acid **24** via oxidation[30] of the cyano-derivative **23** is reported (Scheme 6).

Tetrachloromethylated calix[4]arenes **22** has been transformed into compound **25** by reaction with ethylene glycol monoprotected with ethyl vinyl ether[31] and, after hydrolysis, into the new cavitand **26**.

Attempts to synthesize **26** by the reaction of **22** with a large excess of the monosodium salt of ethylene glycol in different reaction conditions always produces the macrotricyclic compound **27**, whose structure has been assigned on the basis of ^{1}H-NMR data and COSY experiments.

The molecular inclusion properties of cavitands **26** and **27** are under investigation.



Scheme 6.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were recorded on Finnigan Mat SSQ710, while ^{1}H-NMR spectra (100 and 400 MHz) and ^{13}C-NMR (25 MHz) were recorded on a Bruker AC100 and on a Bruker AMX400 spectrometer of the Centro Interfacoltà di Misure of the University of Parma. Chemical shifts (δ) are expressed in ppm from Me_4Si. IR spectra were performed on a Perkin Elmer model 298 instrument. UV-visible spectra were recorded on a spectrophotometer Kontron Uvikon 860 driven by an IBM personal computer. Elemental analyses were carried out at the Istituto di Chimica Farmaceutica of the University of Parma. All solvents were purified by standard procedures. All reactions were carried out in a nitrogen atmosphere. 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. *p-tert*-Butylcalix[4]arene[32] (**1**) calix[4]arene[33] (**2**) and their monomethyl ethers[10] (**7**) were prepared as described in literature.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26,27-tris(ethoxycarbonylmethoxy)-28-methoxycalix[4]arene (8a)

The monomethyl ether of *p-tert*-butylcalix[4]arene **7a** (0.25 g, 0.38 mmol) was dissolved in MeCN (30 ml), K_2CO_3 (0.83 g, 6.03 mmol) and ethyl bromoacetate (0.51 ml, 3.0 mmol) was added. The reaction mixture was refluxed for 6 h, the solvent was removed under reduced pressure and the resulting solid was treated with CH_2Cl_2 (50 ml) and 2N HCl (50 ml). The organic phase was extracted twice with water (2 × 50 ml) and dichloromethane distilled off. Compound **8a** was recrystallized from EtOH: yield 63%; IR (KBr) ν_{max} 1760, 1470 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 0.89 (s, 18H, $C(CH_3)_3$), 1.20–1.30 (m, 27H, $C(CH_3)_3$ and CH_2CH_3), 3.20 (d, 4H, J = 12.9 Hz, H_{eq}), 4.10–4.70 (m, 19H, H_{ax}, OCH_3, CH_2CO and CH_2CH_3), 6.54 (s, 4H, ArH), 7.07 (s, 4H, ArH); ^{13}C-NMR ($CDCl_3$) δ

14.1 and 14.2 (q, CH_2CH_3), 31.1 and 31.6 (q, $C(CH_3)_3$), 31.9 (t, $ArCH_2Ar$), 33.6 and 34.0 (s, $C(CH_3)_3$), 59.0 and 60.0 (t, CH_2CH_3), 124.9 and 125.8 (d, Ar 4,6,10,12,16,18,22,24-C), 131.7 and 132.2 (s, Ar 1,3,7,9,13,15,19,21-C), 144.9 and 145.2 (s, Ar 5,11,17,23-C), 152.8 and 155.8 (s, Ar 25,26,27,28-C), 169.7 and 171.2 (s, C=O); mass spectrum (CI) 921.7 ($M^+ + 1$). Analysis calculated for $C_{57}H_{76}O_{10}$: C, 74.28; H, 8.31. Found: C, 74.05; H, 8.10.

25,26,27-Tris[(1,1-dimethylethoxy)carbonylmethoxy]-28-methoxycalix[4]arene (8b)

The monomethyl ether of calix[4]arene **7b** (0.30 g, 0.66 mmol) was dissolved in dry THF (40 ml) and dry DMF (10 ml). Then NaH (0.33 g, 13.9 mmol) and *tert*-butyl bromoacetate (7.7 g, 40 mmol) were added and the reaction mixture was heated at 80 °C for 5 h. THF was removed under reduced pressure and the resulting solid was treated with CH_2Cl_2 (40 ml) and 2N HCl (40 ml). The organic phase was separated, washed with water (2 × 50 ml) and evaporated to dryness. Compound **8b** was crystallized from MeOH: yield 61%; IR (KBr) ν_{max} 1760, 1470 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 1.48 (s, 9H, $C(CH_3)_3$), 1.58 (s, 27H, $C(CH_3)_3$), 3.22 (d, 4H, J = 13.6 Hz, H_{eq}), 3.93 (s, 3H, OCH_3), 4.30–4.90 (m, 10H, CH_2CO and H_{ax}), 6.29 (s, 3H, Ar 22,23,24-H), 6.60–7.11 (m, 9H, Ar 4,5,6,10,11,12,16,17,18-H). Analysis calculated for $C_{47}H_{56}O_{10}$: C, 72.28; H, 7.23. Found: C, 72.01; H, 7.35.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-26,27,28-tris(hydroxycarbonylmethoxy)-25-methoxycalix[4]arene (9a)

Compound **8a** (0.36 g, 0.4 mmol) was suspended in 80 ml of a 10% KOH solution in EtOH/H_2O 1:1. The reaction mixture was heated at 90 °C for 4 h, then ethanol was removed under reduced pressure. The water suspension was acidified with 3N HCl and the white precipitate was filtered and dried under vacuum: yield 95%; m.p. 243–245 °C; IR (KBr) ν_{max} 3600–2700, 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 0.88 (s, 18H, $C(CH_3)_3$), 1.30 (s, 18H, $C(CH_3)_3$), 3.27 (d, 4H, J = 12.8 Hz, H_{eq}), 3.82 (s, 3H, OCH_3), 4.5–4.8 (m, 10H, H_{ax} and CH_2CO), 6.67 (s, 4H, ArH), 7.15 (s, 4H, ArH) 9.87 (s, 3H, COOH); mass spectrum (CI) 837.5 ($M^+ + 1$). Analysis calculated for $C_{51}H_{64}O_{10}$: C, 73.18; H, 7.71. Found: C, 72.95; H, 7.90.

26,27,28-Tris(hydroxycarbonylmethoxy)-25-methoxycalix[4]arene (9b)

Compound **8b** (2.4 g, 3.1 mmol) was suspended in 11 ml of trifluoroacetic acid and stirred at room temperature for 5 h. Trifluoroacetic acid was removed using the rotavapour and the residue suspended in water. After filtration using a Buckner the product was recovered: yield 84%; m.p. 258–260 °C; IR (KBr) ν_{max} 3600–2800, 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 3.30 (d, 4H, J = 12.8 Hz, H_{eq}), 3.83 (s, 3H, OCH_3), 4.30–4.90 (m, 10H, CH_2CO and H_{ax}), 6.58 (s, 3H, ArH), 6.93–7.12 (m, 9H, ArH); mass spectrum (EI) 612 (M^+).

General procedure for the synthesis of hydroxamic acids 10a and 10b

A sample of carboxylic acids **9** was suspended in thionyl chloride (3 ml) and heated at 80 °C for 4 h. Thionyl chloride was then distilled off and the products carefully dried using the mechanical pump. In a three necked flask, hydroxylamine hydrochloride (0.13 g, 1.80 mmol) was dissolved in dry pyridine (5 ml) and cooled to −15 °C. Trimethylsilyl chloride (1.4 ml, 11 mmol) was added dropwise and the reaction mixture was stirred for 30 min at room temperature. After cooling to −15 °C, the acyl chloride, dissolved in CH_2Cl_2, was added. The reaction mixture was stirred at room temperature for approximately 20 h until a single spot, which appears violet upon spraying with $FeCl_3$, was formed on TLC (SiO_2, eluent EtOH/benzene/NH_3 5:2:1). After removal of the solvents under reduced pressure, the resulting solid was suspended in water, filtered using a Buckner flask and dried under vacuum.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-26,27,28-tris(*N*-hydroxyaminocarbonylmethoxy)-25-methoxycalix[4]arene (10a)

Yield 63%; m.p. 193–195 °C; IR (KBr) ν_{max} 3300–3100, 1680 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3, 100 MHz, 97 °C) δ 0.99 (s, 18H, $C(CH_3)_3$), 1.13 (s, 9H, $C(CH_3)_3$), 1.19 (s, 9H, $C(CH_3)_3$), 3.17 (d, 4H, J = 12.6 Hz, H_{eq}), 3.46 (s, 3H, OCH_3), 4.20–4.35 (m, 6H, OCH_2), 4.43 (d, 4H, H_{ax}), 6.75 (s, 4H, ArH), 6.98 (s, 2H, ArH), 7.04 (s, 2H, ArH); ^{13}C-NMR (CD_3SOCD_3) δ 31.9 (q, $C(CH_3)_3$), 32.5 (t, $ArCH_2Ar$), 34.9 (s, $C(CH_3)_3$), 73.8 (t, OCH_2CO), 127.0 (bs, Ar 4,6,10,12,16,18,22,24-C), 134.2 and 135.2 (s, Ar 1,3,7,9,13,15,19,21-C), 146.9 and 147.6 (s, Ar 5,11,17,23-C), 154.1 (s, Ar 25,26,27,28-C), 168.0 (s, C=O); mass spectrum (CI) 881.7 ($M^+ + 1$). Analysis calculated for $C_{51}H_{67}N_3O_{10}$: C, 69.44; H, 7.65; N, 4.76. Found: C, 69.24; H, 7.51; N, 4.93.

26,27,28-Tris(*N*-hydroxyaminocarbonylmethoxy)-25-methoxycalix[4]arene (10b)

Yield 74%; m.p. 168–170 °C; IR (KBr) ν_{max} 3500–2800, 1680 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3, 100 MHz) δ

3.3–3.6 (m, 7H, H_{eq} and OCH_3), 4.26 (s, 6H, OCH_2), 4.48 (d, 4H, J = 12.6 Hz, H_{ax}), 6.53 (s, 3H, Ar 22,23,24-H), 6.90 (m, 3H, Ar 5,11,17-H), 7.10 (m, 6H, Ar 4,6,10,12,16,18-H), 9.12 (s, 3H, NH), 10.80 (s, 3H, OH); mass spectrum (FAB) 658 ($M^+ + 1$). Analysis calculated for $C_{35}H_{35}N_3O_{10}$: C, 63.92; H, 5.36; N, 6.38. Found C, 63.71; H, 5.45; N, 6.71.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-dihydroxy-27,28-crown-5-calix[4]arene (11)

In a two-necked round-bottomed flask *p-tert*-butylcalix[4]arene (1 g, 0.15 mmol) was suspended in dry DMF (100 ml) and NaH (50% in oil, 0.43 g. 9.0 mmol) was added. The resulting homogeneous solution was stirred at room temperature for 30 min and a solution of tetraethylene glycol di-*p*-tosylate (0.76 g, 1.5 mmol) dissolved in dry DMF (30 ml) was added after 2 h. The reaction mixture was then stirred at room temperature for 48 h. The reaction was quenched by careful addition of 2N HCl (30 ml) and the solvent was evaporated. The resulting solid was dissolved in ethyl acetate (150 ml) and water (150 ml); after separation the organic layer was washed with water (2 × 100 ml) and the solvent evaporated to afford a solid, which was purified by column chromatography (SiO_2, hexane/ethyl acetate 6:4): yield 45%; m.p. 115–117 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 18H, $C(CH_3)_3$), 1.15 (s, 18H, $C(CH_3)_3$), 3.26, 3.29, 3.30 (d, 1H, 2H, 1H, J = 13.1, 13.0 and 12.5 Hz, H_{eq}), 3.65–4.51 (m, 14H, OCH_2 and H_{ax}), 6.92 (bs, 6H, ArH), 6.97 (d, 2H, J = 2.4 Hz, ArH), 8.17 (s, 2H, OH); ^{13}C-NMR ($CDCl_3$), δ 31.1, 34.1, 34.4 (t, $ArCH_2Ar$), 31.7 and 31.9 (q, $C(CH_3)_3$), 32.3 and 32.5 (s, $C(CH_3)_3$), 70.8, 71.1, 72.9 and 76.0 (t, OCH_2), 125.1, 125.5, 126.0 and 126.2 (d, Ar 4,6,10,12,16,18,22,24-C), 129.0, 129.3, 134.0, 134.1, 142.4, 146.8, 149.6, 151.9 (s, Ar 1,3,5,7,9,11,13,15,17,21,25,26,27,28-C) mass spectrum (CI) 808 ($M^+ + 1$).

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-27,28-bis-crown-5-calix[4]arene (12)

Compound **11** (0.26 g, 0.32 mmol) was dissolved in dry benzene (10 ml) and *t*-BuOK (0.11 g, 0.96 mmol) was added with stirring. After 30 min a solution of tetraethylene glycol di-*p*-tosylate (0.19 g, 0.32 mmol) dissolved in dry benzene (40 ml) was dripped in over 1 h. The reaction mixture was then heated at 80 °C for 4 days and quenched with 1N HCl (50 ml). The organic layer was separated and the solid obtained after evaporation of the solvent was chromatographed on preparative plates (SiO_2, 2 runs, CH_2Cl_2/THF 95:5) to afford compound **12**: yield 35%; m.p. 135–137 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 36H, $C(CH_3)_3$), 3.12, 3.21 (d, 2H, J = 13.0 Hz, H_{eq}), 3.76 (s, 16H, OCH_2), 4.0–4.3 (m, 16H, OCH_2), 4.38 and 4.59 (d, 2H, H_{ax}), 6.82 (s, 8H, ArH); ^{13}C-NMR ($CDCl_3$), δ 30.5 (t, $ArCH_2Ar$), 31.4 (q, $C(CH_3)_3$), 32.7 (s, $C(CH_3)_3$), 70.3, 70.5, 71.0 and 73.6 (t, OCH_2), 124.9, 125.0 (d, Ar 4,6,10,12,16,18,22,24-C), 133.5, 134.0, 144.5, 153.4 (s, Ar 1,3,5,7,9,11,13,15,17,21,25,26,27,28-C); mass spectrum (CI) 965 ($M^+ + 1$).

5,17-Bis-hydroxymethyl-25,26,27,28-tetraethoxyethylcalix[4]arene (18)

To a solution of 5,17-diformyl-25,26,27,28-tetraethoxyethylcalix[4]arene **17a** (1 g, 1.3 mmol) in 100 ml of absolute ethanol $NaBH_4$ (0.3 g, 7.8 mmol) was added. The mixture was stirred for 2 h at room temperature and then treated with a saturated solution of ammonium chloride until the acidic pH was reached. The solution was extracted with 100 ml of ethyl acetate and the organic layer was separated and washed twice with water. The solvent was evaporated under reduced pressure to give the product in quantitative yield: m.p. 97–98 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.18–1.26 (m, 12H, OCH_2CH_3), 3.15 (d, 4H, J = 13.3 Hz, H_{eq}), 3.51–3.60 (m, 8H, OCH_2CH_3), 3.82 (t, 4H, J = 5.4 Hz, $ArOCH_2CH_2O$), 3.90 (t, 4H, J = 6.4 Hz, $ArOCH_2CH_2O$), 4.01 (t, 4H, J = 5.4 Hz, $ArOCH_2$-CH_2O), 4.17 (s, 4H, $ArCH_2OH$), 4.26 (t, 4H, J = 6.4 Hz, $ArOCH_2CH_2O$), 4.52 (d, 4H, J = 13.3 Hz, H_{ax}), 6.40 (s, 4H, Ar 4,6,16,18-H), 6.79 (t, 2H, J = 7.3 Hz, Ar 11,23-H), 6.92 (d, 4H, J = 7.3 Hz, Ar 10,12,22,24-H); ^{13}C-NMR ($CDCl_3$) δ 15.4, 15.5 (q, CH_3CH_2O), 30.9 (t, $ArCH_2Ar$), 64.7, 66.3, 66.5, 69.7, 72.7, 73.7 (t, CH_3CH_2O, $ArOCH_2CH_2O$, $ArOCH_2CH_2O$ and $ArCH_2OH$), 122.4, 128.7 (d, Ar 11,23,4,6,10,12,16,18,22,24-C), 126.6, 134.2, 134.8, 135.8 (s, Ar 1,3,7,9,13,15,19,21,5,17-C), 156.1, 157.1 (s, Ar 25,26,27,28-C); mass spectrum (CI) 773 ($M^+ + 1$).

Synthesis of compound 19

A 100 ml round-bottomed flask, equipped with a N_2 inlet and stirring bar, was charged with compound **18** (0.15 g, 0.19 mmol), NaH (50% in oil, 0.018 g, 0.39 mmol) freed from protective oil by two hexane washings and α,α'-dibromo-*p*-xylene (0.056 g, 0.21 mmol) in DME dry (60.5 ml). The solution was stirred at room temperature for 48 h. The reaction was quenched with brine (caution!) and extracted with ethyl acetate. The organic layer was separated, washed twice with water and evaporated to afford a white solid which was further purified by column chromatography (SiO_2, eluent hexane/ethyl acetate 7:3): yield 30%; m.p. 58–60 °C (MeOH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.17–1.26 (m, 12H, OCH_2CH_3), 3.14 (d, 4H, J = 12.6 Hz, H_{eq}), 3.51–3.59 (m, 8H, OCH_2CH_3), 3.62 (s, 4H, $ArCH_2$Oxylyl), 3.74 (t, 4H, J = 5.4 Hz,

$ArOCH_2CH_2O$), 3.90 (t, 4H, J = 5.4 Hz, $ArOCH_2$-CH_2O), 4.02 (t, 4H, J = 6.5 Hz, $ArOCH_2CH_2O$), 4.35 (t, 4H, J = 6.5 Hz, $ArOCH_2CH_2O$), 4.47 (d, 4H, J = 12.6 Hz, H_{ax}), 4.56 (s, 4H, $ArCH_2OCH_2$), 6.40 (s, 4H, OCH_2ArHCH_2O), 6.92 (t, 2H, J = 7.4 Hz, Ar 11,23-H), 7.02 (s, 4H, Ar 4,6,16,18-H), 7.16 (d, 4H, J = 7.4 Hz, Ar 10,12,22,24-H); ^{13}C-NMR ($CDCl_3$) δ 15.2, 15.4 (q, CH_3CH_2O), 66.2, 66.5, 69.5, 69.7, 71.7, 72.2, 74.4, 75.5 (t, $ArOCH_2CH_2OCH_2$, $ArCH_2OCH_2$ and $ArCH_2$Oxylyl), 122.2, 122.4, 123.9, 128.0 (d, Ar 11,23,4,6,10,12,16,18,22,24-C and xylyl-C), 132.6, 132.9, 136.5, 137.9, 150.7, 152.8 (s, Ar 5,17,1,3,7,9, 13,15,19,21-C and xylyl-C), 157.2 (s, Ar 25,26,27,28-C); mass spectrum (CI) 875 ($M^+ + 1$).

Synthesis of compound 20

A 100 ml round-bottomed flask shielded from light and equipped with a N_2 inlet and stirring bar was charged with compound **18** (0.35 g, 0.45 mmol), α,α'-dibromo-9,10-dimethylanthracene (0.18 g, 0.50 mmol) and NaH (50% in oil, 0.04 g, 0.9 mmol and freed from protective oil by two hexane washings) in DME dry (120 ml). The reaction was stirred at room temperature for 8 h, and then quenched with 10% HCl until pH = 6 (caution!), and extracted with ethyl acetate. The organic layer was separated, washed twice with water, and evaporated to afford a yellow compound. Purification by column chromatography (SiO_2, hexane/ethyl acetate 60:40): yield 35%. Note: this compound has to be kept in the dark, because it decomposes quickly. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, 6H, J = 7.0 Hz, OCH_2CH_3), 1.29 (t, 6H, J = 7.3 Hz, OCH_2CH_3), 2.62 (s, 4H, $ArCH_2O$), 3.00 (d, 4H, J = 13.2 Hz, H_{eq}), 3.42 (q, 4H, J = 7.0 Hz, OCH_2CH_3), 3.51 (q, 4H, J = 7.3 Hz, OCH_2CH_3), 3.66 (t, 4H, J = 5.2 Hz, $ArOCH_2CH_2O$), 3.76 (t, 4H, J = 5.2 Hz, $ArOCH_2CH_2O$), 3.82 (t, 4H, J = 6.5 Hz, 4H, $ArOCH_2CH_2O$), 4.25 (t, 4H, J = 6.5 Hz, $ArOCH_2$ CH_2O), 4.32 (d, 4H, J = 13.2 Hz, H_{ax}), 5.73 (s, 4H, OCH_2-anthracene), 5.77 (s, 4H, Ar 4,6,16,18-H), 6.85 (t, 2H, J = 7.3 Hz, Ar 11,23-H), 6.90 (d, 4H, J = 7.3 Hz, Ar 10,12,22,24-H), 7.56–7.61 (m, 4H, anthracene 2,3,7,6-H), 8.38–8.41 (m, 4H, anthracene 1,4,5,8-H); ^{13}C-NMR ($CDCl_3$) δ 15.2, 15.3 (q, CH_3CH_2O), 30.8 (t, $ArCH_2Ar$), 63.6 (t, OCH_2-anthracene), 66.1, 66.4 (t, OCH_2CH_3), 67.2 (t, $ArCH_2O$), 69.4, 69.5 (t, $ArOCH_2CH_2O$), 72.1, 73.9 (t, $ArOCH_2CH_2O$), 122.7 (d, Ar 11,23-C), 124.4 (d, Ar 4,6,16,18-C), 124.7 (d, anthracene 1,8,5,4-C), 125.7 (d, anthracene 2,3,7,6-C), 128.5 (d, Ar 10,12,22,24-C), 130.3, 130.4, 132.2, 132.5, 136.1 (s, Ar 5,17,1,3,7,9,13,15,19,21-C and anthracene 9,10-C), 153.2, 157.3 (s, Ar 25,26,27,28-C); mass spectrum (FAB^+) 974 (M^+).

25,26,27,28-Tetraethoxyethylcalix[4]arene (21)

A solution of calix[4]arene **2** (4.24 g, 0.01 mol), 2-bromo-ethyl ethyl ether (0.96 g, 0.04 mol) and sodium hydride (50% in oil, 1.8 g, 0.04 mol, freed from protecting mineral oil by two hexane washings) in DMF (200 ml) was stirred at 80 °C for 2 h and the solvent evaporated under reduced pressure. The residue was mixed with ethyl acetate (200 ml) and water (200 ml). The organic layer, separated, washed twice with water and dried ($MgSO_4$), was evaporated under reduced pressure to give the crude product **21** recrystallized from methanol: yield 72%; m.p. 115–116 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 12H, J = 7.5 Hz, CH_3CH_2O), 3.14 (d, 4H, J = 13.4 Hz, H_{eq}), 3.54 (q, 8H, J = 7.5 Hz, CH_3CH_2O), 3.84 (t, 8H, J = 5.7 Hz, $ArOCH_2CH_2O$), 4.10 (t, 8H, J = 5.7 Hz, $ArOCH_2CH_2O$), 4.48 (d, 4H, J = 13.4 Hz, H_{ax}), 6.58–6.63 (m, 12H, ArH); ^{13}C-NMR ($CDCl_3$) δ 15.3 (q, CH_3CH_2O), 30.9 (t, $ArCH_2Ar$), 66.4 (t, CH_3CH_2O), 69.7 (t, $ArOCH_2CH_2O$), 73.1 (t, $ArOCH_2$-CH_2O), 122.2, 135.1 (d, Ar 4,6,10,12,16,18,22,24,5,11, 17,23-C), 128.2 (s, Ar 1,3,7,9,13,15,19,21-C), 156.5 (s, Ar 25,26,27,28-C); mass spectrum (CI) 713 ($M^+ + 1$).

5,11,17,23-Tetrachloromethyl-25,26,27,28-tetraethoxyethylcalix[4]arene (22)

A solution of compound **21** (1.0 g, 1.41 mmol), paraformaldehyde (0.32 g, 11.28 mmol) and trimethylchlorosilane (1.20 g, 11.28 mmol) in CH_2Cl_2 (120 ml) was stirred at −20 °C for 20 min and then $SnCl_4$ (2.87 g, 11.28 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and stirred until all starting material had disappeared (TLC, SiO_2, eluent hexane/ethyl acetate 7:3). After approximately 2 h, the reaction was quenched with 10% HCl. The organic layer was separated and washed twice with water, dried over Na_2SO_4 and evaporated to afford a yellow solid which was further purified by column chromatography (SiO_2, eluent hexane/ethyl acetate 7:3): yield 70%; m.p. 104–105 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, 12H, J = 7.1 Hz, OCH_2CH_3), 3.10 (*d, 4H, J = 13.5 Hz,* H_{eq}), 3.50 (q, 8H, J = 7.1 Hz, OCH_2CH_3), 3.80 (t, 8H, J = 5.5 Hz, $ArOCH_2CH_2O$), 4.10 (8H, J = 5.5 Hz, $ArOCH_2$-CH_2O), 4.30 (s, 8H, $ArCH_2Cl$), 4.50 (d, 4H, J = 13.5 Hz, H_{ax}), 6.66 (s, 8H, ArH); ^{13}C-NMR ($CDCl_3$) δ 15.3 (q, CH_3CH_2O), 30.8 (t, $ArCH_2Ar$), 46.6 (t, $ArCH_2Cl$), 66.4 (t, OCH_2CH_3), 69.6 (t, $ArOCH_2CH_2O$), 73.4 (t, $ArOCH_2CH_2O$), 128.6 (d, Ar 4,6,10,12,16,18,22,24-C), 131.2 and 135.1 (s, Ar 1,3,7,9,13,15,19,21,5,11,17,23-C), 156.6 (s, Ar 25,26,27,28-C); mass spectrum (CI) 905 ($M^+ + 1$).

5,11,17,23-Tetracyanomethyl-25,26,27,28-tetraethoxyethylcalix[4]arene (23)

A solution of compound **22** (0.4 g, 0.44 mmol) and sodium cyanide (0.10 g, 2.2 mmol) in DMSO (15 ml) was stirred at 130 °C for 24 h. The reaction was quenched with brine and extracted with ethyl acetate. The organic layer was separated and washed twice with water, dried over Na_2SO_4 and evaporated to afford a white solid which was further purified by column chromatography (SiO_2, eluent hexane/ethyl acetate 1:1): yield 80%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 12H, J = 7 Hz, OCH_2CH_3), 3.13 (d, 4H, J = 13.3 Hz, H_{eq}), 3.50–3.55 (m, 16H, $ArCH_2CN$ and OCH_2CH_3), 3.81 (t, 8H, J = 5.3 Hz, $ArOCH_2CH_2O$), 4.13 (t, 8H, J = 5.3 Hz, $ArOCH_2CH_2O$), 4.52 (d, 4H, J = 13.3 Hz, H_{ax}), 6.65 (s, 8H, ArH); ^{13}C-NMR ($CDCl_3$) δ 15.3 (q, CH_3CH_2O), 22.9 (t, $ArCH_2CN$), 30.8 (t, $ArCH_2Ar$), 66.4 (t, OCH_2CH_3), 69.6 (t, $ArOCH_2CH_2O$), 73.5 (t, $ArOCH_2CH_2O$), 111.64 (s, $ArCH_2CN$), 127.8 (d, Ar 4,6,10,12,16,18,22,24-C), 123.8 and 135.4 (s, Ar 1,3,7,9,13,15,19,21,5,11,17,23-C), 156.0 (s, Ar 25,26,27,28-C); mass spectrum (CI) 869 ($M^+ + 1$).

5,11,17,23-Tetracarboxy-25,26,27,28-tetraethoxyethylcalix[4]arene (24)

A 100 ml round-bottomed flask equipped with N_2 inlet and stirring bar was charged with compound **23** (0.5 g, 0.58 mmol), *t*-BuOK (1.3 g, 11.6 mmol), 18-crown-6 (0.03 g) in THF (50 ml) at room temperature. The solution was stirred for 5 min in N_2 atmosphere and then the oxidant (air) was vented through the solution for 24 h keeping the liquid volume constant. The solvent was evaporated under reduced pressure and the residue was quenched with 10% HCl. The precipitate was filtered and washed twice with water. Purification, when required, was accomplished by column chromatography (SiO_2, ethyl acetate/acetic acid 99:1) or by recrystallization from methanol: yield 95%; m.p. > 300 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 1.11 (t, 12H, J = 6.9 Hz, OCH_2CH_3), 3.36 (d, 4H, J = 13.0 Hz, H_{eq}), 3.48 (q, 8H, J = 6.9 Hz, OCH_2CH_3), 3.80 (t, 8H, J = 4.7 Hz, $ArOCH_2CH_2O$), 4.13 (t, 8H, J = 4.7 Hz, $ArOCH_2CH_2O$), 4.47 (d, 4H, J = 13.0 Hz, H_{ax}), 7.35 (s, 8H, ArH); ^{13}C-NMR (DMSO-d_6) δ 15.1 (q, CH_3CH_2O), 30.0 (t, $ArCH_2Ar$), 65.4 (t, OCH_2CH_3), 69.1 (t, $ArOCH_2CH_2O$), 73.4 (t, $ArOCH_2CH_2O$), 124.6 (d, Ar 4,6,10,12,16,18,22,24-C), 129.6, 134.4 (s, Ar 5,11,17,23,1,3,7,9,13,15,19,21-C), 159.9 (s, Ar 25,26,27,28-C), 166.8 (s, ArCOOH); mass spectrum (CI) 889 ($M^+ + 1$).

Synthesis of compound 27

A 100 ml round-bottomed flask equipped with N_2 inlet and stirring bar was charged with compound **22** (0.5 g, 0.55 mmol), ethylene glycol (1.02 g, 16.5 mmol) and sodium hydride (50% in oil, 0.8 g, 17.5 mmol, freed from protective mineral oil by two hexane washings) in DMF (50 ml). The reaction was stirred at room temperature for 12 h and then was quenched with H_2O (caution!) and 10% HCl and extracted with ethyl acetate. The organic layer was separated, washed twice with water and evaporate to afford a yellow solid. Purification by column chromatography (SiO_2, eluent hexane/ethyl acetate 6:4) gave pure compound **27**: yield 50%; m.p. 120–121 °C (MeOH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 12H, J = 7.7 Hz, CH_3CH_2O), 2.86 (m, 4H, $ArCH_2OCH_2CH_2OCH_2Ar$), 2.97 (d, 2H, J = 12.9 Hz, H_{eq}), 3.28 (m, 4H, $ArCH_2OCH_2CH_2OCH_2Ar$), 3.34 (d, 2H, J = 12.6 Hz, H_{eq}), 3.60 (q, 8H, J = 7.7 Hz, OCH_2CH_3), 3.90–3.94 (m, 12H, $ArCH_2O$, $ArOCH_2CH_2O$), 4.10–4.17 (m, 8H, $ArOCH_2CH_2O$), 4.45 (d, 2H, J = 12.9 Hz, H_{ax}), 4.48 (d, 2H, J = 12.6 Hz, H_{ax}), 4.68 (d, 4H, J = 13.4 Hz, $ArCH_2O$), 6.49 (d, 4H, J = 1.8 Hz, ArH), 7.08 (d, 4H, J = 1.8 Hz, ArH); ^{13}C-NMR ($CDCl_3$) δ 15.4 (q, CH_3CH_2O), 31.3 (t, $ArCH_2Ar$), 66.4, 68.5, 69.8, 73.3, 73.7 (t, $ArOCH_2CH_2OCH_2CH_3$, $ArCH_2OCH_2$ and $ArCH_2OCH_2CH_2O$), 126.7, 129.1 (d, Ar 4,6,10,12,16, 18,22,24-C), 131.9, 132.0, 134.6, 134.7, 136.1 (s, Ar 1,3,7,9,13,15,19,21,5,11,17,23-C), 155.3 (s, Ar 25,26,27, 28-C); mass spectrum (CI) 885 ($M^+ + 1$).

Synthesis of compound 25

A 100 ml round-bottomed flask equipped with N_2 inlet and stirring bar was charged with compound **22** (1 g, 1.10 mmol), $CH_3CH_2OCH(CH_3)OCH_2CH_2OH$[31] (2 g, 22.2 mmol) and sodium hydride (50% in oil, 1.0 g, 22.2 mmol, freed from protective oil by two hexane washings) in DME (20 ml). After 5 min NaI (0.05 g) was added and the reaction was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the residue was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed twice with water and evaporated to afford a yellow liquid compound. Purification by column chromatography (SiO_2, hexane/ethyl acetate 1:1) gave pure liquid **25**: yield 75%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.13–120 (m, 24H, OCH_2CH_3 and $OCH(CH_3)OCH_2CH_3$), 1.27 (d, 12H, J = 5.3 Hz, $OCH(CH_3)O$), 3.05 (d, 4H, J = 14 Hz, H_{eq}), 3.42–3.65 (m, 32H, $ArOCH_2CH_2OCH_2CH_3$, $ArCH_2OCH_2CH_2O$ and $OCH(CH_3)OCH_2CH_3$), 3.77 (t, 8H, J = 5.6 Hz, $ArOCH_2CH_2O$), 4.04 (t, 8H, J = 5.6 Hz, $ArOCH_2CH_2O$), 4.14 (s, 8H, $ArCH_2O$), 4.40 (d, 4H, J = 14 Hz, H_{ax}), 4.69 (q, 4H, J = 5.3 Hz, $OCH(CH_3)O$), 6.54 (s, 8H, ArH).

Synthesis of compound 26

A solution of compound **25** (1 g, 0.77 mmol) in THF (10 ml) was cooled to −10 °C. A solution of 0.5N HCl (10 ml) was added dropwise. The reaction was stirred for approximately 3 h, until all starting material had disappeared (HPLC, reversed phase C-18, mobil phase methanol). The reaction was neutralized with a saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed twice with water and evaporated to afford a yellow liquid compound: yield 95%; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, 12H, J = 6.8 Hz, OCH_2CH_3), 3.09 (d, 4H, J = 13.2 Hz, H_{eq}), 3.39 (t, 8H, J = 4.8 Hz, $ArCH_2OCH_2CH_2OH$ or $ArCH_2OCH_2CH_2OH$), 3.50 (q, 8H, J = 6.8 Hz, OCH_2CH_3), 3.60 (t, 8H, J = 4.8 Hz, $ArCH_2OCH_2$-CH_2OH or $ArCH_2OCH_2CH_2OH$), 3.81 (t, 8H, J = 5.5 Hz, $ArOCH_2CH_2O$), 4.08 (t, 8H, J = 5.5 Hz, $ArOCH_2CH_2O$), 4.19 (s, 8H, $ArCH_2O$), 4.45 (d, 8H, J = 13.2 Hz, H_{ax}), 6.33 (s, 8H, ArH); mass spectrum (CI) 1009 ($M^+ + 1$).

ACKNOWLEDGEMENTS

Financial support from the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica (M.U.R.S.T.), from GLAXO S.p.A., and from the E.E.C. Science Project (Contract SC1/0359) is gratefully acknowledged.

REFERENCES

1 (a) Gutsche, C.D.; in *Calixarenes* (Stoddart, J.F., ed.), The Royal Society of Chemistry, Cambridge, **1989**. (b) Vicens, J.; Bohmer, V.; eds. *Calixarene: a Versatile Class of Macrocyclic Compounds*, Kluwer, Dordrecht, **1992**.
2 (a) Ungaro, R.; Pochini, A.; in *Frontiers in Supramolecular Organic Chemistry and Photochemistry* (Schneider, H.-J. and Durr, H., eds.), VCH, Veinheim, **1981**, pp. 57–81. (b) Andreetti, G.D.; Ugozzoli, F.; Pochini, A.; Ungaro, R.; in *Inclusion Compounds*, Vol. 4 (Atwood, J.L., Davies, J.E.D. and MacNicol, D.D., eds.), Oxford University Press, Oxford, **1991**, pp. 64–125.
3 Sabbatini, N.; Guardigli, M.; Mecati, M.; Balzani, V.; Ungaro, R.; Ghidini, E.; Casnati, A.; Pochini, A.; *J. Chem. Soc., Chem. Commun.* **1990**, 878–879.
4 Hazenkamp, M.F.; Blasse, G.; Sabbatini, N.; Ungaro, R.; *Inorg. Chim. Acta.* **1990**, *172*, 93–95.
5 Sudhölter, E.J.R.; van der Waal, P.D.; Skowronska-Ptasinka, M.; van den Berg, A.; Bergveld, P.; Reinhoudt, D.N.; *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 222–225.
6 King, A.M.; Moore, C.P.; Sandanayake, K.R.A.S.; Sutherland, I.O.; *J. Chem. Soc., Chem. Commun.* **1992**, 582–584.
7 Nijenhuis, W.F.; Buitenhuis, E.G.; de Jong, F.; Sudhölter, E.J.R.; Reinhoudt, D.N.; *J. Amer. Chem. Soc.* **1991**, *113*, 7963–7968.
8 Dijkstra, P.J.; Brunink, J.A.; Bugge, K.-E.; Reinhoudt, D.N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E.; *J. Amer. Chem. Soc.* **1989**, *111*, 7567–7575.
9 Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; *Tetrahedron* **1991**, *47*, 2221–2228.
10 Groenen, L.C.; Ruël, B.H.M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D.N.; *Tetrahedron* **1991**, *47*, 8379–8384.
11 (a) van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G.J.; Harkema, S.; Reinhoudt, D.N.; *Tetrahedron Lett.* **1989**, *30*, 2681, 2684. (b) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D.N.; *J. Org. Chem.* **1990**, *55*, 5639–5646.
12 Groenen, L.C.; Ruël, B.H.M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D.N.; *Tetrahedron Lett.* **1991**, *32*, 2675–2678.
13 Raymond, K.N.; Müller, G.; Matzenke, B.F.; *Top. Curr. Chem.* **1984**, *123*, 49–102.
14 Nielands, J.B.; in *Development of Iron Chelators for Clinical Use* (Martell, A.E., Andersen, W.F. and Badman, D.G., eds.), Elsevier North Holland, New York, **1981**.
15 Ebmeyer, F.; Vögtle, F.; in *Inclusion Compounds*, Vol. 4, (Atwood, J.L., Davis, J.E.D. and McNicol, D.D. eds.), Oxford University Press, Oxford, **1991**, pp. 163–282.
16 Sun, Y.; Martell, A.E.; *J. Amer. Chem. Soc.* **1989**, *111*, 8023–8024.
17 Yuen, Ng.C.; Rodgers, S.J.; Raymond, K.N.; *Inorg. Chem.* **1989**, *28*, 2062–2066.
18 Casnati, A.; Arduini, A.; Pochini, A.; Ungaro, R.; *VI Int. Symposium on Molecular Recognition and Inclusion*, Berlin, **1990**, Abst. F14.
19 Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T.; *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3480–3485.
20 Arduini, A.; Casnati, A.; Dodi, L.; Pochini, A.; Ungaro, R.; *J. Chem. Soc., Chem. Commun.* **1990**, 1597–1599.
21 Kimura, K.; Shono, T.; in *Cation Binding by Macrocycles*, (Inoue, Y. and Gokel, G.W., eds.), Dekker, New York, **1990**, pp. 429–463.
22 Lein, G.M.; Cram, D.J.; *J. Amer. Chem. Soc.* **1985**, *107*, 448–455.
23 Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A.A.; Reinhoudt, D.N.; *J. Amer. Chem. Soc.* **1990**, *112*, 6979–6985.
24 Shinkai, S.; in *Calixarene: a Versatile Class of Macrocyclic Compounds* (Vicens, J. and Bohmer, V., eds.), Kluwer, Dordrecht, **1992**, pp. 173–198.
25 Ungaro, R.; Pochini, A.; Andreetti, G.D.; Domiano, P.; *J. Chem. Soc., Perkin Trans. II* **1985**, 197–201.
26 (a) Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A.R.; Ungaro, R.; *J. Chem. Soc., Chem. Commun.* **1991**, 936–937. (b) Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A.R.; Fanni, S.; Ungaro, R.; submitted for publication, **1992**.
27 (a) Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R.; *Tetrahedron* **1989**, *45*, 2177–2182. (b) Arduini, A.; Pochini, A.; Rizzi, A.; Sicuri, A.R.; Ugozzoli, F.; Ungaro, R.; *Tetrahedron* **1992**, *48*, 905–912.
28 Nagashi, T.; Sisido, K.; Arimura, T.; Shinkai, S.; *Tetrahedron* **1992**, *48*, 797–804.
29 Itsuno, S.; Uchikoshi, K.; Ito, K.; *J. Amer. Chem. Soc.* **1990**, *112*, 8187–8188.
30 DiBiase, S.A.; Wolak, R.P. Jr.; Dishong, D.M.; Gokel, G.W.; *J. Org. Chem.* **1980**, *45*, 3630–3634.
31 Shastakovkii, M.F.; Gershtein, N.A.; Volkova, Z.S.; *Izvest. Akad. Nauk S.S.S.R.*, Otdel, Khim. Nauk., **1952**, 671–681; (*C.A. ibid* **1953**, *47*, 10472f).
32 Gutsche, C.D.; *Org. Syntheses* **1989**, *68*, 233–246. White, J.D.; Ed.
33 Gutsche, C.D.; Lin, L.-G.; *Tetrahedron* **1986**, *42*, 1633–1640.