UPPER-RIM UREA-DERIVATIZED CALIX[4]ARENES AS NEUTRAL RECEPTORS FOR MONOCARBOXYLATE ANIONS (*) (**)

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Summary – Several new anion receptors have been synthesized by introducing one or two urea or thiourea units at the upper rim of calix[4]arenes, blocked in the *cone* conformation. The difunctionalized receptor **13** shows selectivity in the recognition of acetate anion, which interacts with the two urea units through four hydrogen bonds. The monofunctionalized receptors **21** and **22** complex more strongly aromatic carboxylates or butyrate anion since the primary hydrogen bonding contacts are strengthened by weak π/π or CH_3/π host-guest interactions.

The selective recognition of anions by synthetic receptors is a less developed area of research compared with metal ion complexation. Only recently the Supramolecular Chemistry of anions has been investigated more systematically with a variety of host molecules[1] including calixarene-based receptors[2]. The carboxylate group of the D-alanyl-D-alanine terminal part of cell wall peptidoglycan is selectively recognized by the binding pocket of vancomycin-type antibiotics[3], and di- and tricarboxylates are also components of several metabolic processes[4]. For these and other reasons the synthesis of selective receptors for mono- or polycarboxylate anions has been recently pursued in Supramolecular Chemistry[2b,5].

Recently, Hamilton *et al.* have shown[5c] that the use of urea units as hydrogen-bond donors in carboxylate complexes has the advantage of creating four favourable secondary hydrogen-bonding interactions[6], which result in the formation of strong complexes even in highly competing solvents, such as DMSO-d_6. Thiourea moieties have been also introduced at the lower rim of calix[4]arenes and the receptors synthesized have been shown to interact with halide anions through hydrogen bonding[2e]. More recently we have reported on the binding of halide and tricarboxylate anions by neutral urea-derivatized *p-tert*-butylcalix[6]arenes[5h]. In line with this research we here report the synthesis and anion recognition properties of calix[4]arenes in the *cone* conformation[7], having one or two urea and thiourea moieties at the upper rim (aromatic nuclei). These new cleft-like compounds allow one to evaluate the role of the apolar cavity of calix[4]arenes in the complexation of anions and particularly of carboxylates.

RESULTS AND DISCUSSION

SYNTHESIS AND CONFORMATIONAL PROPERTIES OF THE LIGANDS

A key intermediate in the synthesis of the difunctionalized urea-receptors is the diamino derivative **12**, which has been obtained *via* two different reaction pathways (*Routes A* and *B* in scheme 1).

Route A takes advantage of the possibility of obtaining the selective formylation of the diametrical position at the upper rim of 1,3-dipropoxycalix[4]arene, **2**. The diformylated compound **3** was oxidized to diacid **4** and subsequent alkylation with n-C_3H_7I and NaH in DMF afforded compound **5** fixed in the *cone* conformation. Reaction of the dichloride **7** with potassium phthalimide gave compound **8** which upon hydrazinolysis yielded the 1,3-diaminocalix[4]arene **12**. *Route B* exploits the possibility of selective bromination of the 1,3-dipropoxycalix[4]arene[8], **2**, at the *para* position of the phenolic nuclei to give compound **9** (76% yield) which was subsequently blocked in the *cone* conformation by propylation using n-C_3H_7I and NaH/DMF[9]. The dibromo compound **10** was transformed into the diamino derivative **12** *via* the dicyano compound **11**, in 56% yield. Reaction of **12** with phenyl isocyanate or isothiocyanate (scheme 2) gave the diametrically disubstituted urea derivatives **13** and **14** in nearly quantitative yields.

(*) Dedicated to Professor Fernando Montanari on the occasion of his 70th birthday.

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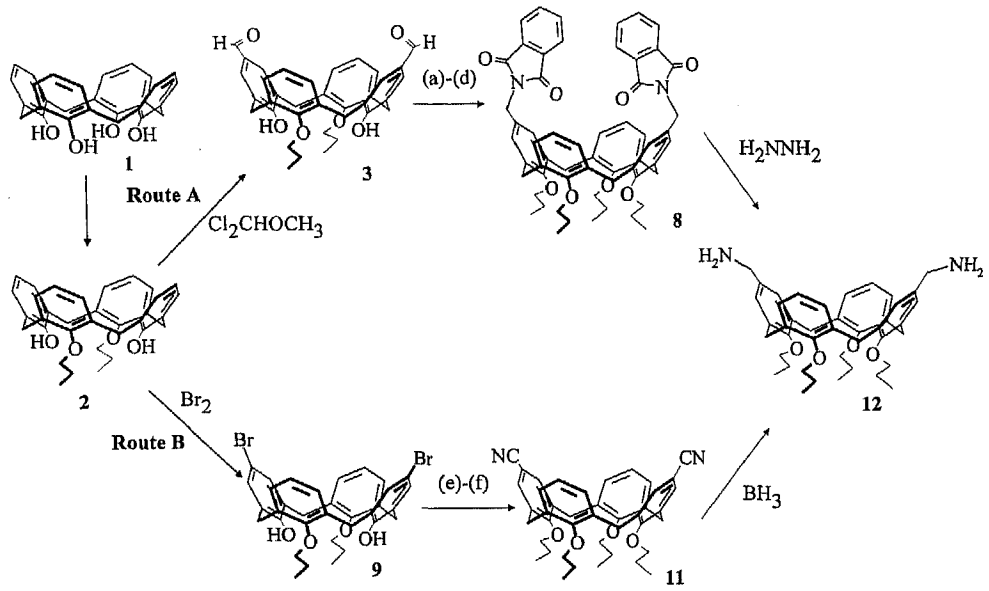
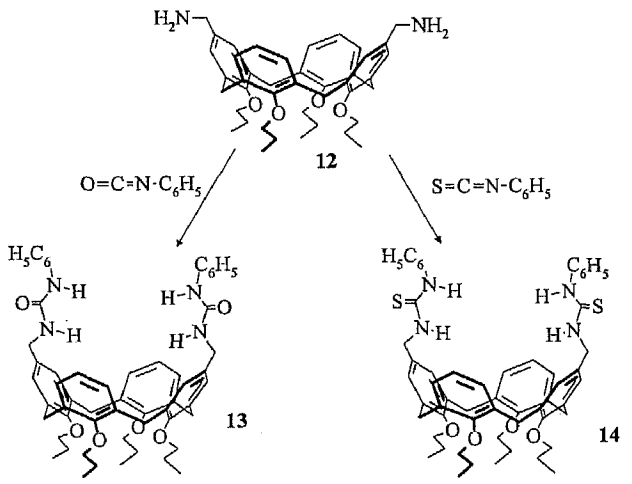
SCHEME 1



(a) $NaClO_2$, H_2NSO_3H; (b) C_3H_7I, NaH/DMF; (c) BH_3/THF, $SOCl_2$, $CHCl_3$; (d) KPhthalimide; (e) C_3H_7I, NaH/DMF; (f) CuCN, NMP, 200 °C.

SCHEME 2



The ^1H NMR spectrum of compounds **13** and **14** are rather broad in $CDCl_3$ thus indicating high degree of self-association in this solvent. In DMSO-d_6 the spectra are sharp and clearly show a *flattened cone* conformation for both compounds. In the case of **13**, for example (figure 1), the low-field singlet at 8.49 ppm has been attributed to the urea NH_a linked to the phenyl nucleus whereas the second NH_b gives a triplet (J=5.9 Hz) at δ=6.48 ppm which correlates, in the COSY spectrum, with the $ArCH_2$ doublet at δ=4.14 ppm. The six-proton high-field singlet at 6.34 ppm indicates that the two diametrical unfunctionalized aromatic rings are almost parallel each other and the two aromatics bearing the urea moieties are more open in the *flattened cone* conformation.

The monofunctionalized derivatives **21** and **22** were synthesized through the reaction sequence

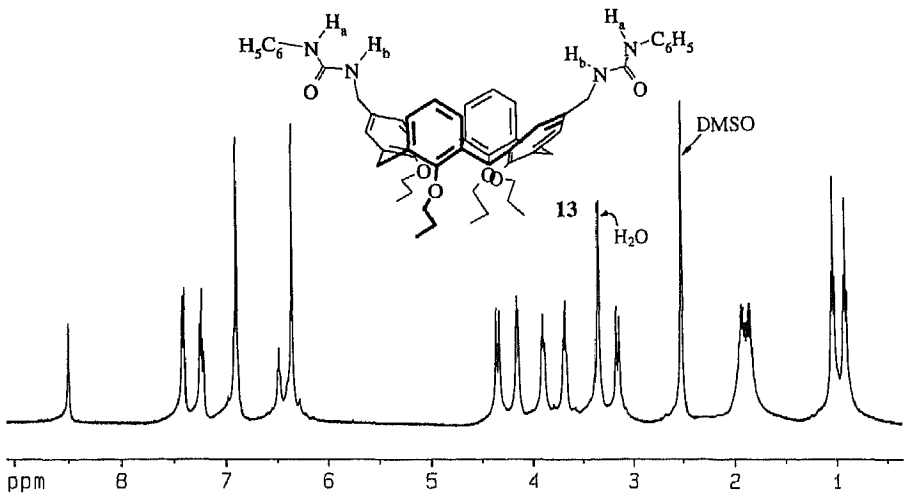


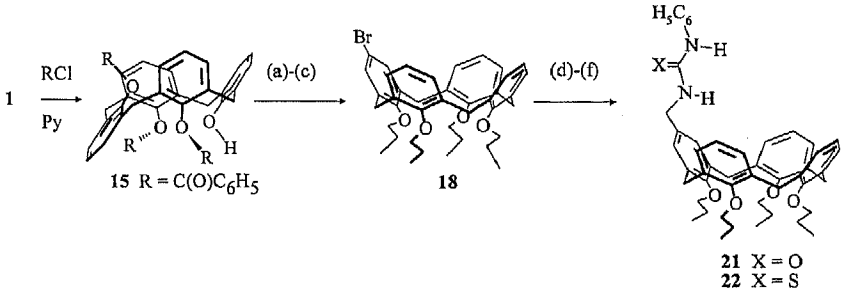
Fig. 1 – ^1H NMR spectrum of **13** in DMSO-d_6 (400 MHz).

depicted in scheme 3. Calix[4]arene was first transformed into the tribenzoate **15**[10], which assumes a *partial cone* structure. Compound **15** was then selectively brominated at the phenolic aromatic nucleus to give **16** which, after hydrolysis and propylation (NaH, DMF), was transformed into the monobromo derivative **18** in the *cone* conformation. Reaction of **18** with CuCN in *N*-methylpyrrolidinone (NMP) at 200 °C gave the cyano derivative **19**, which was reduced to the monoamino **20** by using BH_3 in dry THF.

monitoring the downfield shift of the urea NH_a signal upon the addition of variable amounts of tetrabutylammonium salts of different anions to a DMSO-d_6 solution of the host. The host concentration was kept between 5×10^{-4} and 5×10^{-3} *M* in the case of difunctionalized compound **13** in order to reduce the effect of self-association of the ligands, which was shown to be not negligible with this host even in DMSO-d_6 (K=300 M^{-1}).

In the case of the monofunctionalized receptors **21** and **22** no self-association phenomena were

SCHEME 3



(a) Br_2/CH_2Cl_2; (b) KOH; (c) C_3H_7I, NaH/DMF; (d) CuCN, NMP, 200 °C; (e) BH_3/THF; (f) X=C=N-C_6H_5.

The urea derivatives **21** and **22** were obtained in 70% and 98% overall yields, respectively, by treating amine **20** with the corresponding phenyl isocyanate. Their ^1H NMR and ^{13}C NMR spectra (see the *Experimental*) clearly indicate a *cone* conformation for both compounds **21** and **22** in solution. For all urea or thiourea derivatives synthesized we assume a *trans-trans* geometry as depicted in schemes 2 and 3 since this geometry has been shown by most *N,N'*-disubstituted urea derivatives both in solution[11] and in the solid state[12].

Anion binding studies

The interaction of anion species with hosts **13** and **21-22** was studied in DMSO-d_6 by ^1H NMR, detected by ^1H NMR, by diluting the samples in the concentration range 10^{-1}-10^{-3} *M* and therefore a higher concentration (~10^{-2} *M*) was used for these ligands in the binding studies.

Two typical titration curves obtained are depicted in figure 2. A good agreement between calculated and observed data is obtained assuming a 1:1 host/guest stoicheiometry in the non-linear regression analysis.

Table 1 reports the association constants (K_{ass}) obtained with the difunctionalized host **13**, and table 2 those obtained with monoureas **21** and **22**.

In all cases the spherical halide anions show no evidence of complexation with all hosts studied, in these conditions. On the other hand, carboxylate anions strongly interact with all urea receptors. In the case of the difunctionalized host **13** a strong

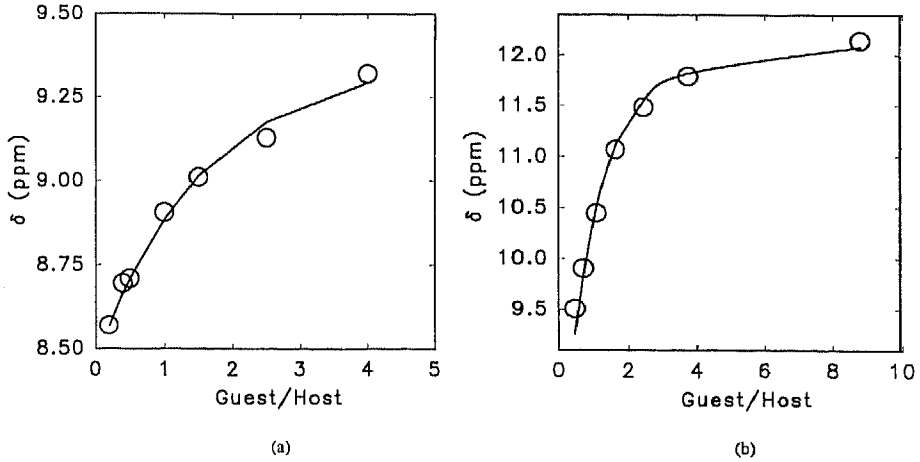


Fig. 2 – Titration plots of (a) acetate anion and diphenylurea **13** and (b) butyrate anion and monophenylthiourea **22**.

TABLE 1 - ASSOCIATION CONSTANTS OF THE ANIONS OF TETRABUTYLAMMONIUM SALTS WITH DIPHENYLUREA RECEPTOR **13** IN DMSO-d_6

Guest	K_{ass}, M^{-1}
Br^-, I^-, Cl^-	<10
Benzoate	290±50
Acetate	2200±500
Butyrate	133±56
o-Phthalate	300±150
m-Phthalate	230±50
p-Phthalate	200±100

TABLE 2 - ASSOCIATION CONSTANTS OF THE ANIONS OF TETRABUTYLAMMONIUM SALTS WITH MONOPHENYLUREA (**21**) AND MONOPHENYLTHIOUREA (**22**) DERIVATIVES IN DMSO-d_6

Guest	Host **21** K_{ass}, M^{-1}	Host **22** K_{ass}, M^{-1}
Br^-, I^-, Cl^-	<10	<10
$H_2PO_4^-$	<10	<10
Benzoate	118±32	170±17
Acetate	80±26	92±39
Butyrate	128±18	339±69
p-Nitrobenzoate	117±38	58±3
Phenylacetate	n.d.[a]	230±60
Lactate	54±30	<10

([a]) n.d.=not determined.

preference for acetate anion is observed, whereas aromatic carboxylates and butyrate form less stable complexes. The similar K_{ass} values observed for the benzoate and all phthalates suggest that only one carboxylate anion of the latter is interacting with the urea moieties of host **13**.

The interaction of carboxylate anion with one single *N,N'*-dialkylurea unit in DMSO-d_6 usually[5c,g] gives K_{ass} values of the order of 50-150 M^{-1}, much lower than those found with host **13**. This suggests that the possible geometry for carboxylate binding in receptor **13** is that shown in figure 3a, where the carboxylate anion interacts with all four urea NH groups, using both *syn* and *anti* oxygen lone pairs. A possible role of other weak interactions (CH_3/π) in the stabilization of the acetate complex cannot be ruled out, although we have no experimental proof of such interaction. The lower K_{ass} value found for the aromatic carboxylate anions compared with acetate can be explained on the basis of the lower basicity of the former.

behaviour has been also observed in the case of tricarboxylate binding to urea-derivatized *p-tert*-butylcalix[6]arenes. The available data allow us to draw some preliminary conclusions on the binding mode of carboxylate anions with receptors **13** and **21-22**, although a more extensive collection of experimental data appears to be necessary in order to generalize these results.

Differently from what observed with the diurea receptor **13**, the acetate anion shows the weakest binding with monourea derivative **21** (K_{ass}=80±20 M^{-1}). This value is very close to that observed with single ureas, thus indicating that binding occurs only *via* the formation of two hydrogen bonds (figure 3b). On the other hand, butyrate anion shows the highest value of K_{ass} with both receptors **21** and **22**. This can be explained by assuming that, beside hydrogen bonding, other weak

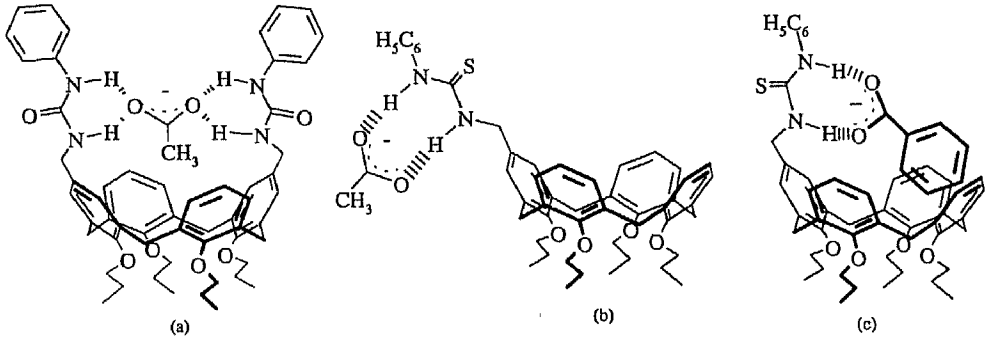


Fig. 3 – Suggested binding mode of carboxylate anions with urea-derivatized calix[4]arenes: (a) acetate with **13**, (b) acetate with **22**, (c) benzoate with **22**.

A possible positive role played by the apolar calix[4]arene cavity in the stabilization of carboxylate anion complexes is observed with the monofunctionalized receptors **21** and **22** (table 2). Here the thiourea derivative **22** generally shows higher values of association constants compared with the urea analogue **21**, which is in agreement with the higher acidity of thiourea compared with that of urea (p*K*a=23.0 and 26.9, respectively)[13]. A similar interactions such as CH_3/π are stabilizing the complex. A similar behaviour has been previously observed in the recognition of alcohols by resorc[4]arenes, which occurs *via* a combination of hydrogen bonding and CH_3/π interactions[14]. Also aromatic carboxylate anions are bound quite strongly to receptors **21** and **22**, thus indicating that π/π interactions (edge-to-face and/or face-to-face) can contribute to stabilize the complexes (figure 3c).

CONCLUSIONS

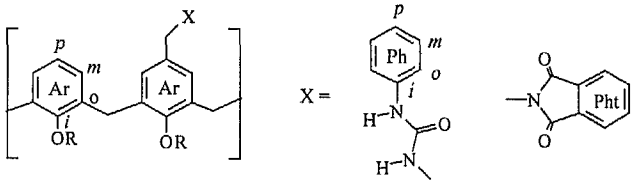
The main purpose of this work was to investigate if the presence of urea or thiourea binding groups anchored at the upper rim of calix[4]arenes, in the *cone* conformation, could provide neutral anion receptors with improved selectivity and efficiency. The diurea receptor **13** selectively binds acetate over other aliphatic and aromatic mono- and dicarboxylates, probably through a combination of hydrogen bonding and CH_3/π interactions, whereas the monoureas **21** and **22** show preference for aromatic carboxylates and for butyrate. In this case, the binding geometry, which exploits a primary interaction of two hydrogen bonds between the carboxylate anion and the urea unit, brings the aromatic nucleus or the longer aliphatic chain of the butyrate in close proximity with the apolar cavity of the calix[4]arene, thus allowing weak interactions (π/π or CH_3/π) to operate in stabilizing the complex. The results obtained suggest that the concept of multipoint interactions[15] is a useful tool to induce selectivity in the recognition of anions by synthetic macrocyclic receptors.

EXPERIMENTAL[a]

General

Melting points were determined on an Electrothermal apparatus in sealed capillary tubes and are uncorrected. Mass spectra (DCI, CH_4; FAB, NBA) were performed on a Finnigan MAT SSQ710 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker AMX400 (^1H: 400 MHz) and AC300 (^1H: 300 MHz, ^{13}C: 75 MHz) spectrometers of the Centro Interdipartimentale di Misure (C.I.M.) of the Università di Parma. Chemical shifts (δ) are expressed in ppm from $(CH_3)_4Si$. In NMR spectra, the Ar notation defines the aromatic nuclei of the calixarene backbone, considering the phenol oxygen as main substituent to which the *ipso, ortho, meta* and *para* positions refer, while the aromatic nuclei of phenyl ureas and phthalimide are indicated as Ph and Pht, respectively (see the chart).

CHART



IR spectra were taken on a Perkin-Elmer 298 spectrophotometer. All compounds gave satisfactory elemental analyses. All solvents were purified by standard procedures. Analytical TLC's 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. 25,26,27,28-tetrahydroxy-*p-tert*-butylcalix[4]arene[16], tetrahydroxycalix[4]arene, **1**[10], 25,27-bis(1-propyloxy)-calix[4]arene, **2**[8], 5,17-diformyl-25,27-bis(1-propyloxy)calix[4]arene, **3**[9], and 25,26,27-tribenzoyloxycalix[4]arene, **15**[10], were prepared as described in the literature.

([a]) The name calix[4]arene is used instead of the official CA name: pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol.

Determination of association constants

The measurements were performed by ^1H NMR titration experiments. Stock solutions of host (5×10^{-4}-10^{-3} *M* for host **13** and ~5×10^{-2} *M* for hosts **21** and **22**) and guest in DMSO-d_6 at different concentrations were prepared and mixed together in the NMR tube in various molar ratios. ^1H NMR spectra were recorded at 298 K and the chemical shift of the NH_a and/or NH_b proton was plotted against guest/host ratios. Non-linear regression analysis of these data allowed the determination of K_{ass}[17,18].

26,28-dihydroxy-25,27-bis(1-propoxy)calix[4]arene-5,17-dicarboxylic acid, 4

A stirred solution of diformylcalix[4]arene **3** (3.78 g, 6.69 mmol) in 50 ml of $CHCl_3$ and 50 ml of acetone was cooled at 0 °C. To this solution, sulphamic acid (2.60 g, 26.8 mmol) and sodium chlorite (2.12 g, 23.4 mmol) dissolved in a small amount of water were added dropwise. After 8 h the solvents were distilled off under reduced pressure and the residue suspended in 1 *N* HCl. The precipitate was filtered off and triturated with dichloromethane to afford a colourless solid (3.79 g, 6.36 mmol, 95% yield): m.p. 315-7 °C. ^1H NMR (DMSO-d_6), δ, ppm: 12.2 (2 H, s, COOH), 9.21 (2 H, s, OH), 7.81 (4 H, s, ArH), 7.08 (4 H, d, *J*=7 Hz, ArH), 6.88 (2 H, t, *J*=7 Hz, ArH), 4.18 (4 H, d, *J*=13 Hz, $ArCH_{ax}Ar$), 4.10 (4 H, t, *J*=7 Hz, $OCH_2CH_2CH_3$), 3.60 (4 H, d, *J*=13 Hz, $ArCH_{eq}Ar$), 2.03 (4 H, m, $OCH_2CH_2CH_3$), 1.30 (6 H, t, $OCH_2CH_2CH_3$); ^{13}C NMR (DMSO-d_6), δ, ppm: 167.2 (s, C=O), 157.1, 151.5 (s, Ar *ipso*), 133.1, 127.7 (d, Ar *meta*), 130.3, 129.1 (s, Ar *ortho*), 125.2, 121.2 (s, Ar *para*), 78.2 (t, $OCH_2CH_2CH_3$), 30.0 (t, $ArCH_2Ar$), 23.0 (t, $OCH_2CH_2CH_3$), 10.7 (q, $OCH_2CH_2CH_3$); IR (KBr): 3600-3200 (COOH), 1690 cm^{-1} (C=O); MS (DCI), *m/z*: 597 [$(M+H)^+$, 30%], 579 [$(M-H_2O)^+$, 100%].

25,26,27,28-tetrakis(1-propoxy)calix[4]arene-5,17-dicarboxylic acid, 5

To a stirred solution of compound **4** (1.25 g, 2.09 mmol) in 20 ml of dry DMF, 1-iodopropane (1.64 ml, 16.8 mmol) and NaH (50% dispersion in oil, 0.80 g, 16.8 mmol) were added. The reaction mixture was stirred at room temperature under nitrogen for 7 h and then quenched by addition of 40 ml of 1 *N* HCl (CAUTION!). The aqueous phase was extracted twice with dichloromethane (2×40 ml) and the combined organic layers were washed with water (2×40 ml), a 5% sodium thiosulphate solution (40 ml) and water (40 ml). Dichloromethane was removed under reduced pressure and the resulting solid suspended in 40 ml of a 10% NaOH solution in EtOH/H_2O, 1:1 (*v/v*). This solution was refluxed for 4 h, then ethanol was distilled off and the remaining basic solution acidified with 1 *N* HCl. The resulting colourless precipitate was filtered off and recrystallized from methanol (1.02 g, 1.50 mmol, 72% yield): m.p. 271-3 °C. ^1H NMR ($CDCl_3$), δ, ppm: 7.12 (6 H, m, ArH), 6.74 (4 H, s, ArH), 4.31 (4 H, d, *J*=13 Hz, $ArCH_{ax}Ar$), 3.98, 3.65 (4 H, t, *J*=7 Hz, $OCH_2CH_2CH_3$), 3.80 (4 H, d, *J*=13 Hz, $ArCH_{eq}Ar$), 1.84 (8 H, m, $OCH_2CH_2CH_3$), 1.08, 0.84 (6 H, t, *J*=7.2 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 172.2 (s, C=O), 157.9 (s, Ar *ipso*), 136.9, 133.4 (s, Ar *ortho*), 129.8 (d, Ar *meta*), 129.8 (d, Ar *para*), 122.8 (s, Ar *para*), 77.1 (t, $OCH_2CH_2CH_3$), 31.2 (t, $ArCH_2Ar$), 23.8, 23.2 (t, $OCH_2CH_2CH_3$), 11.1, 10.0 (t, $OCH_2CH_2CH_3$); IR (KBr): 3300-2900 (COOH), 1690 cm^{-1} (C=O); MS (DCI), *m/z*: 681 [$(M+H)^+$, 65%], 663 [$(M-OH)^+$, 100%].

5,17-bis(hydroxymethyl)-25,26,27,28-tetrakis(1-propyloxy)calix[4]arene, 6

A solution of compound **5** (1.15 g, 1.70 mmol) in 23 ml of dry THF was cooled with an ice-bath. Then BH_3 (1 *M* in THF, 23.7 ml, 23.7 mmol) was added dropwise under nitrogen. The reaction mixture was heated at 80 °C for 8 h and then quenched by careful addition of 22 ml of methanol. The product was isolated by evaporation of the solvents (1.05 g, 1.60 mmol, 95% yield). An analytically pure sample was obtained by recrystallization from hexane: m.p. 199-200 °C. ^1H NMR (DMSO-d_6), δ, ppm: 6.82 (4 H, s, ArH), 6.38 (6 H, s, ArH), 4.95 (2 H, t, *J*=5.0 Hz, OH), 4.33 (4 H, d, *J*=13.0 Hz, $ArCH_{ax}Ar$), 4.28 (4 H, d, *J*=5.0 Hz, $ArCH_2OH$), 3.86 (4 H, t, *J*=7.7 Hz, $OCH_2CH_2CH_3$), 3.69 (4 H, t, *J*=7.0 Hz, $OCH_2CH_2CH_3$), 3.13 (4 H, d, *J*=13.0 Hz, $ArCH_{eq}Ar$), 1.94-1.82 (8 H, m, $OCH_2CH_2CH_3$),

1.02 (6 H, t, J=7.3 Hz, $OCH_2CH_2C\underline{H}_3$), 0.91 (6 H, t, J=7.4 Hz, $OCH_2CH_2C\underline{H}_3$); ^{1}H NMR ($CDCl_3$), δ, ppm 6.92 (4 H, d, J=7.4 Hz, ArH *meta*), 6.78 (2 H, t, J=7.4 Hz, ArH *para*), 6.37 (4 H, s, ArH), 4.45 (4 H, d, J=13.2 Hz, $ArC\underline{H}_{ax}Ar$), 4.16 (4 H, s, $ArC\underline{H}_2OH$), 3.97, 3.73 (4 H, t, J=7.9 Hz, $OC\underline{H}_2CH_2CH_3$), 3.14 (4 H, d, J=13.2 Hz, $ArC\underline{H}_{eq}Ar$), 2.0-1.86 (8 H, m, $OCH_2C\underline{H}_2CH_3$), 1.05, 0.93 (6 H, t, J=7.4 Hz, $OCH_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 157.6, 156.9 (s, Ar *ipso*), 136.0, 134.2 (s, Ar *ortho*), 134.2 (s, Ar *para*), 128.8, 126.4 (d, Ar *meta*), 122.2 (d, Ar *para*), 77.2, 76.6 (t, $O\underline{C}H_2CH_2CH_3$), 64.9 (t, $ArC\underline{H}_2OH$), 31.0 (t, $ArC\underline{H}_2Ar$), 23.4, 23.1 (t, $OCH_2\underline{C}H_2CH_3$), 10.7, 10.0 (q, $OCH_2CH_2\underline{C}H_3$); IR (KBr): 3600-3200 cm^{-1} (OH); MS (DCI), *m/z*: 653 [$(M+H)^+$, 20%], 634 [$(M-H_2O)^+$, 100%].

5,17-BIS(CHLOROMETHYL)-25,26,27,28-TETRAKIS(1-PROPYLOXY)-CALIX[4]ARENE, 7

A solution of dialcohol **6** (0.947 g, 1.45 mmol) in 15 ml of dry chloroform was treated with thionyl chloride (0.27 ml, 3.67 mmol). The reaction mixture was stirred for 4 h under nitrogen at room temperature. The product was isolated by evaporation of the solvent under reduced pressure (0.95 g, 1.38 mmol, 95% yield): m.p. 153 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 6.68 (6 H, s, ArH), 6.60 (4 H, s, ArH), 4.45 (4 H, d, J=13.5 Hz, $ArC\underline{H}_{ax}Ar$), 4.25 (4 H, s, $ArC\underline{H}_2Cl$), 3.88 (4 H, t, J=7.2 Hz, $OC\underline{H}_2CH_2CH_3$), 3.83 (4 H, t, J=6.9 Hz, $OC\underline{H}_2CH_2CH_3$), 3.16 (4 H, d, J=13.5 Hz, $ArC\underline{H}_{eq}Ar$), 1.96-1.83 (8 H, m, $OCH_2C\underline{H}_2CH_3$), 1.01 (6 H, t, J=7.5 Hz, $OCH_2CH_2C\underline{H}_3$), 0.98 (6 H, t, J=7.4 Hz, $OCH_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 156.8, 156.6 (s, Ar *ipso*), 135.3, 134.9 (s, Ar *ortho*), 131.0 (s, Ar *para*), 128.4 (d, Ar *meta*), 122.3 (d, Ar *para*), 76.9, 76.7 (t, $O\underline{C}H_2CH_2CH_3$), 46.7 (t, $ArC\underline{H}_2Cl$), 31.0 (t, $ArC\underline{H}_2Ar$), 23.3, 23.2 (t, $OCH_2\underline{C}H_2CH_3$), 10.4, 10.3 (q, $OCH_2CH_2\underline{C}H_3$); MS (DCI), *m/z*: 688 [M^+, 40%], 653 [$(M-Cl)^+$, 100%].

5,17-BIS(PHTHALIMIDOMETHYL)-25,26,27,28-TETRAKIS(1-PROPYLOXY)CALIX[4]ARENE, 8

Potassium phthalimide (0.54 g, 3.0 mmol) and a catalytic amount of NaI were added to a solution of the bis(chloromethyl) derivative **7** (1.03 g, 1.5 mmol) in 80 ml of dry toluene. The reaction mixture was stirred for 48 h in a Schlenk tube heating at 110 °C under dinitrogen, then cooled and quenched with 30 ml of 1 *N* HCl and the organic layer washed with a 5% $Na_2S_2O_3$ solution (100 ml) and water (2×100 ml). After evaporation of the solvent under reduced pressure, the product was recrystallized from dichloromethane/methanol (0.68 g, 0.75 mmol, 50% yield): m.p. 304-5 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 7.88-7.84 (4 H, m, PhtH), 7.73-7.70 (4 H, m, PhtH), 7.02 (4 H, s, ArH), 6.33 (2 H, t, J=7.4 Hz, ArH *para*), 6.25 (4 H, d, J=7.4 Hz, ArH *meta*), 4.74 (4 H, s, $ArC\underline{H}_2N$), 4.37 (4 H, d, J=13.6 Hz, $ArC\underline{H}_{ax}Ar$), 3.87 (4 H, t, J=7.8 Hz, $OC\underline{H}_2CH_2CH_3$), 3.68 (4 H, t, J=7.2 Hz, $OC\underline{H}_2CH_2CH_3$), 3.11 (4 H, d, J=13.6 Hz, $ArC\underline{H}_{eq}Ar$), 1.94-1.81 (8 H, m, $OCH_2C\underline{H}_2CH_3$), 1.02 (6 H, t, J=7.2 Hz, $OCH_2CH_2C\underline{H}_3$), 0.85 (6 H, t, J=7.6 Hz, $OCH_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 168.1 (s, CO), 157.3 (s, Ar *ipso*), 136.5 (s, Ar *ortho*), 133.9 (d, Pht), 133.6 (s, Ar *para*), 129.5 (s, Pht), 129.0 (d, Ar *meta*), 127.6 (d, Pht), 123.3 (d, Ar *meta*), 122.1 (d, Ar *para*), 76.8 and 76.5 (t, $O\underline{C}H_2CH_2CH_3$), 41.5 (t, $ArC\underline{H}_2N$), 30.9 (t, $ArC\underline{H}_2Ar$), 23.4, 23.0 (t, $OCH_2\underline{C}H_2CH_3$), 10.6, 9.9 (q, $OCH_2CH_2\underline{C}H_3$); MS (DCI), *m/z*: 911 [$(M+H)^+$, 100%), 765 [$(M-Pht)^+$, 30%].

5,17-DIBROMO-26,28-DIHYDROXY-25,27-BIS(1-PROPYLOXY)CALIX-[4]ARENE (3), 9

A solution of Br_2 (0.76 ml) in 40 ml of dry dichloromethane was added dropwise, at room temperature, to a stirred solution of dipropyloxycalix[4]arene **2** (3.0 g, 5.90 mmol) in 140 ml of dry dichloromethane. After 0.5 h the colourless precipitate formed was filtered off and washed with dichloromethane to yield pure compound **9** (3.26 g, 4.90 mmol, 83% yield): m.p. > 300 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 8.36 (2 H, s, OH), 7.16 (4 H, s, ArH), 6.93 (4 H, d, J=7.0 Hz, ArH), 6.80 (2 H, t, J=7.0 Hz, ArH), 4.25 (4 H, d, J=13.1 Hz, $ArC\underline{H}_{ax}Ar$), 3.95 (4 H, t, J=6.8 Hz, $OC\underline{H}_2CH_2CH_3$), 3.32 (4 H, d, J=13 Hz, $ArC\underline{H}_{eq}Ar$), 2.06 (4 H, m, $OCH_2C\underline{H}_2CH_3$), 1.29 (6 H, t, J=7.4 Hz, $OCH_2CH_2C\underline{H}_3$); IR (KBr): 3400-3100 cm^{-1} (OH); MS (FAB), *m/z*: 666 [$(M+2)^+$, 100%], 664 [M^+, 50%], 585 [$(M-Br)^+$, 20%].

5,17-DIBROMO-25,26,27,28-TETRAKIS(1-PROPYLOXY)CALIX[4]-ARENE (4), 10

To a suspension of compound **9** (3.35 g, 5.03 mmol) in 150 ml of dry DMF, NaH (50% dispersion in oil, 1.21 g, 50.3 mmol) previously washed with petroleum ether, and 1-iodopropane (3.9 ml, 40.26 mmol) were added at room temperature. The reaction mixture was then heated at 90 °C for 24 h and then quenched with 1 *N* HCl (100 ml) and the resulting solid was filtered off under reduced pressure. Compound **10** was obtained upon trituration with methanol (2.87 g, 3.82 mmol, 76% yield): m.p. 246-7 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 6.73 (4 H, s, ArH), 6.61 (6 H, s, ArH), 4.37 (4 H, d, J=13.1 Hz, $ArC\underline{H}_{ax}Ar$), 3.86-3.71 (8 H, m, $OC\underline{H}_2CH_2CH_3$), 3.07 (4 H, d, J=13.1 Hz, $ArC\underline{H}_{eq}Ar$), 1.95-1.74 (8 H, m, $OCH_2C\underline{H}_2CH_3$), 1.01-0.87 (12 H, m, $OCH_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 156.4, 155.7 (s, Ar *ipso*), 137.2, 134.4 (s, Ar *ortho*), 130.7, 128.4 (d, Ar *meta*), 122.5 (d, Ar *para*), 114.7 (s, Ar *para*), 76.8 (t, $O\underline{C}H_2CH_2CH_3$), 30.9 (t, $ArC\underline{H}_2Ar$), 23.2 (t, $OCH_2\underline{C}H_2CH_3$), 10.3 (q, $OCH_2CH_2\underline{C}H_3$); MS (FAB), *m/z*: 750 [$(M+2)^+$, 100%], 748 [M^+, 50%].

5,17-DICYANO-25,26,27,28-TETRAKIS(1-PROPYLOXY)CALIX[4]-ARENE (5), 11

CuCN (0.95 g, 10.66 mmol) was added to a solution of compound **10** (2.0 g, 2.66 mmol) in 55 ml of *N*-methyl-2-pyrrolidinone (NMP) and the reaction mixture was heated at 200 °C under dinitrogen for 12 h. Then it was quenched by careful addition, at 100 °C, of a solution of $FeCl_3$ (1.73 g, 10.6 mmol) in 50 ml of 3 *N* HCl and stirred for 2 h at room temperature. The precipitate was filtered off under reduced pressure. From this crude, pure compound **11** was isolated by chromatography on silica gel eluting with 9:1, CH_2Cl_2/hexane; yield: 0.96 g, 1.49 mmol, 56%; m.p. 266-7 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 6.76 (4 H, s, ArH), 6.68 (6 H, s, ArH), 4.36 (4 H, d, J=13.5 Hz, $ArC\underline{H}_{ax}Ar$), 3.80 (4 H, t, J=6.9 Hz, $OC\underline{H}_2CH_2CH_3$), 3.77 (4 H, t, J=7.2 Hz, $OC\underline{H}_2CH_2CH_3$), 3.10 (4 H, d, J=13.5 Hz, $ArC\underline{H}_{eq}Ar$), 1.81-1.78 (8 H, m, $OCH_2C\underline{H}_2CH_3$), 0.92, 0.98 (6 H, t, J=7.5 Hz, $OCH_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 158.1, 156.7 (s, Ar *ipso*), 136.2, 134.6 (s, Ar *ortho*), 132.0, 128.9 (d, Ar *meta*), 123.0 (d, Ar *para*), 119.1 (s, $\underline{C}N$), 116.4 (s, Ar *para*), 77.3, 76.8 (t, $O\underline{C}H_2CH_2CH_3$), 30.7 (t, $ArC\underline{H}_2Ar$), 23.4, 23.1 (t, $OCH_2\underline{C}H_2CH_3$), 10.4, 10.1 (q, $OCH_2CH_2\underline{C}H_3$); IR (KBr): 2230 cm^{-1} (CN); MS (DCI), *m/z*: 643 [$(M+H)^+$, 100%].

5,17-BIS(AMINOMETHYL)-25,26,27,28-TETRAKIS(1-PROPYLOXY)-CALIX[4]ARENE (6), 12

Method A – To a suspension of diphthalimidomethylcalix[4]arene **8** (1.36 g, 1.5 mmol) in 135 ml of dry methanol, hydrazine monohydrate (2.25 g, 45 mmol) was added. The reaction mixture was heated at reflux under dinitrogen for 12 h. After evaporation of the methanol under reduced pressure the residue was taken up with dichloromethane (50 ml) and washed with a 5% aqueous NaOH solution (25 ml) and water (30 ml). The organic layer was concentrated to a volume of 10 ml and diethyl ether added (15 ml). Compound **12** crystallized in 50% yield from this solution.

Method B – A solution of the dicyano derivative **11** (0.62 g, 0.97 mmol) in 75 ml of dry THF was cooled with an ice-bath and then BH_3 (1 *M* in THF, 19.5 ml, 19.5 mmol) was added dropwise under dinitrogen. The reaction mixture was then heated at 80 °C for 8 h. After cooling it was quenched with 20 ml of 1 *N* HCl (CAUTION!) and stirred for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (30 ml) and extracted with 1 *N* HCl (30 ml). The aqueous phase was made basic with an NaOH solution and extracted with dichloromethane (2×50 ml). The combined organic extracts were dried over $MgSO_4$, the solvent evaporated under reduced pressure and the pure compound **12** obtained by trituration with hexane (0.38 g, 0.58 mmol, 60% yield): m.p. 290 °C (dec). ^{1}H NMR ($CDCl_3$), δ, ppm: 6.55 (10 H, bs, ArH), 4.44 (4 H, d, J = 13.2 Hz, $ArC\underline{H}_{ax}Ar$), 3.84 (8 H, t, J=6.8 Hz, $OC\underline{H}_2CH_2CH_3$), 3.52 (4 H, s, $C\underline{H}_2NH_2$), 3.13 (4 H, d, J=13.2 Hz, $ArC\underline{H}_{eq}Ar$), 1.95-1.82 (8 H, m, $OCH_2C\underline{H}_2CH_3$), 0.98 (12 H, t, J=7.1 Hz, $OCH_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 157.5, 156.5 (s, Ar *ipso*), 136.0 (s, Ar *para*), 135.6, 134.6 (s, Ar *ortho*), 128.5, 126.9 (d, Ar *meta*), 122.3 (d, Ar *para*), 76.6, 76.8

(t, $OCH_2CH_2CH_3$), 44.6 (t, CH_2NH_2), 31.0 (t, $ArCH_2Ar$), 23.3, 23.1 (t, $OCH_2CH_2CH_3$), 10.5, 10.1 (q, $OCH_2CH_2CH_3$); IR (KBr): 3480-3340 cm^{-1} (NH); MS (DCI), *m/z*: 651 [$(M+H)^+$, 100%], 634 [$(M-NH_2)^+$, 60%].

25,26,27-TRIBENZOYLOXY-5-BROMO-28-HYDROXYCALIX[4]-ARENE, **16**

A solution of Br_2 (0.08 ml, 1.65 mmol) in 10 ml of dichloromethane was slowly added dropwise to tribenzoyloxycalix[4]arene **15** (1.02 g, 1.38 mmol) previously dissolved in 9 ml of dichloromethane. The reaction mixture was stirred for 18 h under a dinitrogen atmosphere at room temperature Then the dichloromethane solution was transferred into a separatory funnel and washed with a 5% aqueous solution of sodium thiosulphate (25 ml) and water (2×25 ml). The organic phase was evaporated and the product recrystallized from dichloromethane/methanol (1.05 g, 1.17 mmol, 85% yield): m.p. 335 °C (dec.). ^1H NMR ($CDCl_3$), δ, ppm: 8.02 (4 H, d, *J*=7.4 Hz, ArH), 7.75 (2 H, t, *J*=7.1 Hz, ArH), 7.56 (5 H, m, ArH), 7.32 (3 H, bs, ArH), 7.07 (4 H, bs, ArH), 6.84 (3 H, d, *J*=7.4 Hz, ArH), 6.62 (5 H, bs, ArH), 5.24 (1 H, s, OH), 3.77 (4 H, bd, $ArCH_2Ar$), 3.66 (2 H, d, *J*=15.3 Hz, $ArCH_2Ar$), 3.51 (2 H, d, *J*=14.4 Hz, $ArCH_2Ar$); ^{13}C NMR ($CDCl_3$), δ, ppm: 164.4, 164.2 (s, CO), 151.6, 146.2, 133.8 (s, Ar), 133.7 (d, Ar), 133.4, 133.2, 132.0 (s, Ar), 131.6, 131.4, 130.9, 129.8, 129.6, 128.9, 127.9, 126.1, 125.1 (d, Ar), 112.0 (s, Ar), 37.3, 33.1 (t, $ArCH_2Ar$); IR (KBr): 3540 (OH), 1745 cm^{-1} (CO). MS (DCI), *m/z*: 818 [$(M+2)^+$, 40%], 816 [M^+, 100%].

5-BROMO-25,26,27,28-TETRAHYDROXYCALIX[4]ARENE, **17**

Compound **16** (0.850 g, 1.04 mmol) was suspended in a 10% KOH solution in 1:1 (*v/v*) ethanol-water and stirred under dinitrogen for 4 h. Then the solvents were evaporated under reduced pressure and 30 ml of a 5% aqueous KOH solution was added. The resulting solid was filtered off, washed first with 1 *N* HCl (30 ml) and then with H_2O (100 ml) to neutrality dried, and recrystallized from dichloromethane/hexane (0.48 g, 0.95 mmol, 91% yield): m.p. 330 °C (dec.). ^1H NMR ($CDCl_3$, 270 K), δ, ppm: 10.07 (4 H, s, OH), 7.16 (2 H, s, ArH), 7.10 (2 H, dd, *J*=7.6, 1.5 Hz, ArH *meta*), 7.07 (2 H, d, *J*=7.6 Hz, ArH *meta*), 7.06 (2 H, dd, *J*=7.6, 1.5 Hz, ArH *meta*), 6.78 (2 H, t, *J*=7.6 Hz, ArH *para*), 6.75 (1 H, t, *J*=7.6 Hz, ArH *para*), 4.26, 4.22 (2 H, d, *J*=13.9 Hz, $ArCH_{ax}Ar$), 3.56, 3.49 (2 H, t, *J*=13.9 Hz, $ArCH_{eq}Ar$); ^{13}C NMR ($CDCl_3$), δ, ppm: 148.6, 148.5, 148.3 (s, Ar *ipso*), 131.3, 130.2, 129.1 (s, Ar *ortho*), 128.9, 128.2, 127.2 (d, Ar *meta*), 122.2 (d, Ar *para*), 113.6 (s, Ar *para*), 31.5, 31.4 (t, $ArCH_2Ar$); IR (KBr): 3400-3100 cm^{-1} (OH); MS (DCI), *m/z*: 504 [$(M+2)^+$, 80%], 502 [M^+, 100%].

5-BROMO-25,26,27,28-TETRAKIS(1-PROPYLOXY)CALIX[4]ARENE, **18**

NaH (50% suspension in oil, 0.439 g, 9.1 mmol) and 1-iodopropane (0.9 ml, 9.12 mmol) were added to a solution of compound **17** (0.480 g, 0.95 mmol) in 35 ml of dry DMF. The reaction mixture was stirred for 6 h under dinitrogen at room temperature, and then DMF was removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane (20 ml) and washed with 1 *N* HCl (15 ml), 5% $Na_2S_2O_3$ solution (15 ml) and water (2×20 ml) in that order. The organic solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using 7:3 hexane/ethyl acetate as eluent to give **18** (0.58 g, 0.86 mmol, 90% yield). An analytically pure sample was obtained by recrystallization from methanol: m.p. 108-10 °C. ^1H NMR ($CDCl_3$), δ, ppm: 6.81 (2 H, d, *J*=7.5, 2.1 Hz, ArH), 6.78 (2 H, d, *J*=7.5, 2.1 Hz, ArH), 6.72 (2 H, t, *J*=7.5 Hz, ArH), 6.61 (1 H, t, *J*=7.2 Hz, ArH), 6.50 (2 H, s, ArH), 6.42 (2 H, d, *J*=7.5 Hz, ArH), 4.46 and 4.41 (2 H, d, *J*=13.6 Hz, $ArCH_{ax}Ar$), 3.90 and 3.75 (4 H, m, $OCH_2CH_2CH_3$), 3.18 and 3.10 (2 H, d, *J*=13.6 Hz, $ArCH_{eq}Ar$), 1.93-1.84 (8 H, m, $OCH_2CH_2CH_3$), 1.06 and 1.05 (3 H, t, *J*=7.3 Hz, $OCH_2CH_2CH_3$), 0.93 (6 H, t, *J*=7.5 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 157.1, 156.0, 155.7 (s, Ar *ipso*), 136.9 136.1, 135.0, 134.4 (s, Ar *ortho*), 130.5 128.9 128.3, 127.8 (d, Ar *meta*), 122.1 (d, Ar *para*), 114.7 (s, Ar *para*), 76.8, 76.7 (t, $OCH_2CH_2CH_3$), 30.9 (t, $ArCH_2Ar$), 23.4, 23.3 (t, $OCH_2CH_2CH_3$), 10.6, 10.5 (q, $OCH_2CH_2CH_3$); MS (DCI), *m/z*: 672 [$(M+2)^+$, 100%), 670 [M^+, 80%].

5-CYANO-25,26,27,28-TETRAKIS(1-PROPYLOXY)CALIX[4]ARENE, **19**

The same procedure as for the preparation of the dicyano compound **11** was followed using 2 equivalents of CuCN. Pure compound **19** was isolated by chromatography on silica gel using 9:1 CH_2Cl_2/hexane, as eluent: (50% yield): m.p. 169-70 °C. ^1H NMR ($CDCl_3$), δ, ppm: 7.05-6.80 (6 H, m, ArH), 6.49 (3 H, m, ArH), 6.28 (2 H, d, *J*=8.0 Hz, ArH), 4.42 (4 H, d, *J*=13.6 Hz, $ArCH_{ax}Ar$), 3.94-3.64 (8 H, m, $OCH_2CH_2CH_3$), 3.21 (2 H, d, *J*=13.6 Hz, $ArCH_{eq}Ar$), 3.08 (2 H, d, *J*=13.6 Hz, $ArCH_{eq}Ar$), 1.95-1.73 (8 H, m, $OCH_2CH_2CH_3$), 1.12-0.81 (12 H, m, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 159.6, 157.4 (s, Ar *ipso*), 136.8, 135.9, 135.2, 133.8 (s, Ar *ortho*), 131.7, 129.5, 128.5, 127.9 (d, Ar *meta*), 122.3 (d, Ar *para*), 122.2 (s, Ar *para*), 120.2 (s, CN), 77.7, 77.6 (t, $OCH_2CH_2CH_3$), 31.0, 30.8 (t, $ArCH_2Ar$), 23.4, 23.0 (t, $OCH_2CH_2CH_3$), 10.6, 10.0 (q, $OCH_2CH_2CH_3$); IR (KBr): 2200 cm^{-1} (CN); MS (DCI), *m/z*: 618 [$(M+H)^+$, 100%].

5-AMINOMETHYL-25,26,27,28-TETRAKIS(1-PROPYLOXY)CALIX[4]-ARENE, **20**

The same procedure as for the preparation of the diamino derivative **12** (*Method B*) was followed using 10 ml of BH_3 solution (1 *M* in THF, 10 mmol) for each mmol of monocyano compound **19**. Yield: 60%; m.p. 166-8 °C. ^1H NMR ($CDCl_3$), δ, ppm: 6.76 (4 H, d, *J*=6.8 Hz, ArH), 6.67 (2 H, t, *J*=6.8 Hz, ArH), 6.52-6.48 (3 H, m, ArH), 6.38 (2 H, s, ArH), 4.47, 4.46 (2 H, d, *J*=13.3 Hz, $ArCH_{ax}Ar$), 3.93 (4 H, t, *J*=7.5 Hz, $OCH_2CH_2CH_3$), 3.80 (4 H, t, *J*=7.3 Hz, $OCH_2CH_2CH_3$), 3.42 (2 H, s, $ArCH_2NH_2$), 3.16, 3.15 (2 H, d, *J*=13.3 Hz, $ArCH_{eq}Ar$), 1.99-1.89 (8 H, m, $OCH_2CH_2CH_3$), 1.07-0.95 (12 H, m, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 157.0, 156.6, 155.1 (s, Ar *ipso*), 136.2 (s, Ar *para*), 135.7, 134.9, 134.7 (s, Ar *ortho*), 128.4, 127.9, 127.7, 126.6 (d, Ar *meta*), 121.9, 121.6 (d, Ar *para*), 76.8, 76.6 (t, $OCH_2CH_2CH_3$), 45.9 (t, $ArCH_2NH_2$), 31.0, 30.4 (t, $ArCH_2Ar$), 23.5, 23.2 (t, $OCH_2CH_2CH_3$), 10.5, 10.2 (q, $OCH_2CH_2CH_3$); MS (DCI), *m/z*: 621 [M^+, 100%], 605 [$(M-NH_2)^+$, 50%].

GENERAL PROCEDURE FOR THE SYNTHESIS OF UREA RECEPTORS **13, 14** AND **21, 22**

Phenyl isocyanate or phenyl isothiocyanate (1.1 mmol for the synthesis of **13, 14**, 2.2 mmol for **21, 22**) was added, under dinitrogen, to a solution of aminomethylcalixarenes **12** or **20** (1 mmol) in 25 ml of dry dichloromethane. The reaction mixtures were stirred for 2 h at room temperature, the solvent was removed under reduced pressure and the crude products purified as described below.

5,17-bis[(N'-phenylureido)methyl]-25,26,27,28-tetrakis(1-propyloxy)calix[4]arene, ***13*** – Recrystallized from cold ethanol (83% yield). An analytically pure sample was obtained by C_{18} reverse-phase column chromatography using methanol as eluent: m.p. 218 °C (dec.). ^1H NMR (DMSO-d_6), δ, ppm: 8.49 (2 H, s, CONHPh), 7.40 (4 H, d, *J*=8.4 Hz, PhH *ortho*), 7.22 (4 H, t, *J*=7.6 Hz, PhH *meta*), 6.91-6.88 (6 H, m, ArH and PhH *para*), 6.48 (2 H, t, *J*=5.9 Hz, CH_2NHCO), 6.34 (6 H, s, ArH), 4.34 (4 H, d, *J*=12.8 Hz, $ArCH_{ax}Ar$), 4.14 (4 H, d, *J*=5.9 Hz, $ArCH_2NH$), 3.89 (4 H, t, *J*=7.7 Hz, $OCH_2CH_2CH_3$), 3.67 (4 H, t, *J*=6.8 Hz, $OCH_2CH_2CH_3$), 3.15 (4 H, d, *J*=12.8 Hz, $ArCH_{eq}Ar$), 1.93-1.86 (4 H, m, $OCH_2CH_2CH_3$), 1.03 (6 H, t, *J*=7.4 Hz, $OCH_2CH_2CH_3$), 0.91 (6 H, t, *J*=7.4 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 157.6 (s, CO), 156.6, 154.2 (s, Ar *ipso*), 139.1 (s, Ph *ipso*), 136.5, 133.4 (s, Ar *ortho*), 132.2 (s, Ar *para*), 128.9 (d, Ph *meta*), 125.3 (d, Ar *para*), 122.8, 122.0 (d, Ar *meta*), 120.2 (d, Ph *para*), 119.9 (d, Ph *ortho*), 77.1, 76.5 (t, $OCH_2CH_2CH_3$), 42.5 (t, $ArCH_2NH$), 31.0 (t, $ArCH_2Ar$), 23.5, 23.0 (t, $OCH_2CH_2CH_3$), 10.8, 10.0 (q, $OCH_2CH_2CH_3$); IR (KBr): 3400-3210 (NH), 1655 cm^{-1} (CO). MS (DCI), *m/z*: 890 [$(M+H)^+$, 20%], 770 [$(M-PhNHCO)^+$, 100%], 651 [$(M-2\cdot PhNHCO)^+$, 90%].

5,17-bis[(N'-phenyl(thio)ureido)methyl]-25,26,27,28-tetrakis(1-propyloxy)calix[4]arene, ***14*** – Purified by C_{18} reverse-phase chromatography (98% yield): m.p. > 300 °C. ^1H NMR (DMSO-d_6): δ, ppm: 9.62 (2 H, s, CSNHPh), 8.13 (2 H, s, CH_2NHCS), 7.46 (4 H, m, PhH *ortho*), 7.31 (4 H, t, *J*=7.4 Hz, PhH *meta*), 7.10 (2 H, t, *J*=7.1 Hz, PhH *para*), 7.00 (4 H, s, ArH), 6.30 (6 H,

bs, ArH), 4.61 (4 H, s, $ArCH_2N$), 4.35 (4 H, d, J=12.9 Hz, $ArCH_{ax}Ar$), 3.92 (4 H, t, J=7.2 Hz, $OCH_2CH_2CH_3$), 3.66 (4 H, t, J=6.3 Hz, $OCH_2CH_2CH_3$), 3.15 (4 H, d, J=12.9 Hz, $ArCH_{eq}Ar$), 1.94-1.83 (8 H, m, $OCH_2CH_2CH_3$), 1.05 (6 H, t, J=7.2 Hz, $OCH_2CH_2CH_3$), 0.90 (6 H, t, J=7.2 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 180.2 (s, CS), 156.8, 156.2 (s, Ar *ipso*), 136.9 (s, Ph *ipso*), 136.0, 134.5 (s, Ar *ortho*), 130.0 (d, Ph *meta*), 129.6 (s, Ar *para*), 128.0, 127.5 (d, Ar *meta*), 126.9 (d, Ph *para*), 125.3 (d, Ar *para*), 122.2 (d, Ph *ortho*), 76.8 (t, $OCH_2CH_2CH_3$), 49.1 (t, $ArCH_2NH$), 31.0 (t, $ArCH_2Ar$), 23.3 (t, $OCH_2CH_2CH_3$), 10.5, 10.3 (q, $OCH_2CH_2CH_3$); IR (KBr): 3400-3200 (NH), 1500 cm^{-1} (CS). MS (DCI), *m/z*: 920 [M^+, 20%], 770 [(M–PhNHC-SNH)$^+$, 100%].

5-[(N'-phenylureido)methyl]-25,26,27,28-tetrakis(1-propyl-oxy)calix[4]arene, 21 – Precipitated with cold methanol (70% yield): m.p. 236-8 °C. ^1H NMR (DMSO-d_6), δ, ppm: 8.40 (1 H, s, CONHPh), 7.37 (2 H, d, J=7.4 Hz, PhH *ortho*), 7.21 (2 H, d, J=7.5 Hz, PhH *meta*), 6.88 (1 H, t, J=7.5 Hz, PhH *para*), 6.73 (2 H, t, J=7.1 Hz, ArH), 6.65 (2 H, s, ArH), 6.63 (1 H, t, J=7.1 Hz, ArH), 6.50-6.44 (6 H, m, ArH), 6.35 (1 H, t, J=5.6 Hz, $ArCH_2NHCO$), 4.34 and 4.33 (2 H, d, J=13.1 Hz, $ArCH_{ax}Ar$), 4.02 (2 H, d, J=5.6 Hz, $ArCH_2NH$), 3.86-3.80 (4 H, m, $OCH_2CH_2CH_3$), 3.73 (4 H, t, J=7.1 Hz, $OCH_2CH_2CH_3$), 3.14 and 3.11 (2 H, d, J=13.1 Hz, $ArCH_{eq}Ar$), 1.92-1.80 (8 H, m, $OCH_2CH_2CH_3$), 1.04-0.93 (12 H, m, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 156.9 (s, CO), 156.4, 156.2 (s, Ar *ipso*), 139.3 (s, Ph *ipso*), 135.5, 135.4, 134.9, 134.7 (s, Ar *ortho*), 129.3 (s, Ar *para*), 128.9 (d, Ph *meta*), 128.4, 127.9, 127.1 (d, Ar *para*), 122.0, 121.1, 120.3, 118.7 (d, Ar *meta*), 120.2 (d, Ph *para*), 119.9 (d, Ph *ortho*), 76.8, 75.7 (t, $OCH_2CH_2CH_3$), 44.3 (t, $ArCH_2NH$), 31.0 (t, $ArCH_2Ar$), 23.3, 23.25 (t, $OCH_2CH_2CH_3$), 10.4, 10.3 (q, $OCH_2CH_2CH_3$); IR (KBr): 3400-3210 (NH), 1655 cm^{-1} (CO); MS (DCI), *m/z*: 741 [(M+H)$^+$, 100%], 621 [(M–PhNHCO)$^+$, 60%].

5-[[N'-phenyl(thio)ureido]methyl]-25,26,27,28-tetrakis(1-propyl-oxy)calix[4]arene, 22 – Purified by C_{18} reverse-phase column chromatography using methanol as eluent to give **22** (98% yield): m.p. 126-8 °C. ^1H NMR (DMSO-d_6), δ, ppm: 9.48 (1 H, s, CSNHPh), 7.84 (1 H, t, $ArCH_2NHCS$), 7.43 (2 H, d, J = 7.5 Hz, PhH *ortho*), 7.31 (2 H, t, J = 7.6 Hz, PhH *meta*), 7.10 (1 H, t, J = 7.3 Hz, ArH *para*), 6.72-6.43 (11 H, m, ArH), 4.43, 4.42 (2 H, d, J = 13.1 Hz, $ArCH_{ax}Ar$), 3.87 (4 H, t, J = 7.2 Hz, $OCH_2CH_2CH_3$), 3.78 (4 H, t, J = 7.0 Hz, $OCH_2CH_2CH_3$), 3.57 (2 H, t, J = 6.2 Hz, $ArCH_2NH$), 3.13, 3.10 (2 H, d, J = 13.1 Hz, $ArCH_{eq}Ar$), 1.93-1.80 (8 H, m, $OCH_2CH_2CH_3$), 1.02-0.93 (12 H, m, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$), δ, ppm: 180.2 (s, CS), 156.8, 150.6 (s, Ar *ipso*), 136.5 (s, Ph *ipso*), 135.5, 135.1, 135.0, 134.6 (s, Ar *ortho*), 130.0 (d, Ar *meta*), 128.3 (s, Ar *para*), 128.1, 127.7, 126.9, 126.7 (d, Ar *meta*), 124.9 (d, Ph *para*), 122.0, 121.8 (d, Ar *para*), 121.2 (d, Ph *ortho*), 76.6, 76.5 (t, $OCH_2CH_2CH_3$), 49.2 (t, $ArCH_2NH$), 31.0 (t, $ArCH_2Ar$), 23.2, 23.0 (t, $OCH_2CH_2CH_3$), 10.3, 10.1 (q, $OCH_2CH_2CH_3$); IR (KBr): 3100-2900 (NH), 1500 cm^{-1} (CS); MS (DCI), *m/z*: 757 [(M+H)$^+$, 20%], 621 [(M–PhNHCS)$^+$, 90%)], 606 [(M–PhNHCSNH)$^+$, 100%].

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