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

New Tetrafunctionalized *Cone* Calix[4]arenes as Neutral Hosts for Anion Recognition

Alessandro Casnati[a]; Laura Pirondini[a]; Nicola Pelizzi[a]; Rocco Ungaro[a]
[a] Dipartimento di Chimica Organica e Industriale, dell' Università, Parma, Italy

To cite this Article Casnati, Alessandro , Pirondini, Laura , Pelizzi, Nicola and Ungaro, Rocco(2000) 'New Tetrafunctionalized *Cone* Calix[4]arenes as Neutral Hosts for Anion Recognition', Supramolecular Chemistry, 12: 1, 53 — 65
To link to this Article: DOI: 10.1080/10610270008029804
URL: http://dx.doi.org/10.1080/10610270008029804

SUPRAMOLECULAR CHEMISTRY, Vol. 12, pp. 53-65
Reprints available directly from the publisher
Photocopying permitted by license only

New Tetrafunctionalized *Cone* Calix[4]arenes as Neutral Hosts for Anion Recognition

ALESSANDRO CASNATI, LAURA PIRONDINI, NICOLA PELIZZI and ROCCO UNGARO*

Dipartimento di Chimica Organica e Industriale dell'Università, Parco Area delle Scienze 17/A, 43100-Parma (Italy)

The synthesis and anion binding properties of several new *cone* calix[4]arenes having different flexibility and tetrafunctionalized at the upper rim with various type of hydrogen bonding donor groups such as thioureas (**1–3**), trifluoroacetamides (**4, 5**) and perfluorinated alcohols (**6**) are reported. The results obtained show that thiourea receptors are the most effective in the complexation of all anions and that the *rigid cone* compound **2** is more efficient than the *mobile cone* analog **1** in the binding of spherical anions, whereas the reverse is true for the complexation of tetrahedral $H_2PO_4^-$ anion.

Keywords: calix[4]arene, anion recognition, hydrogen bond, thiourea, trifluoroacetamide, perfluorinated alcohol

INTRODUCTION

Anion recognition is becoming an important research topic in Supramolecular Chemistry.[1] This is due to the important role played by anions in Biology and to the need of developing devices for separation and sensing of anions of enviromental concern such as nitrate, phosphate, etc. Most of the organic synthetic receptors for anions are charged species or contain a metal center which is directly coordinated to the anion or increases the binding ability of other functional groups. Natural receptors (*e.g.* Sulfate[2] or Phosphate[3] Binding Proteins) usually achieve selectivity by exploiting the high directionality of hydrogen bonding donor groups. In order to mimic the natural receptors, chemists have used mainly amides and (thio)ureas or a combination of the two for the synthesis of electroneutral anion receptors.[1] In several cases also calixarenes have been used as platforms for the obtainment of anion receptors. Calix[4]arenes functionalized at the lower rim with urea groups are selective for halide anions,[4] whereas larger calix[6]arenes having these groups in the 1,3,5 positions at the lower rim show a sharp selectivity for the complementary trianion of the 1,3,5-benzentricarboxylic acid.[5] One or two thioureas, which are better hydrogen bonding donor groups than ureas, have been introduced also at the upper rim of calix[4]arenes giving receptors selective for the Y-shaped carboxylate anions.[6] More recently, Reinhoudt *et al.* have synthesized resorc[4]arene cavitands bearing four (thio)ureas at the upper rim and found that they strongly complex halide anions in chloroform solution.[7] Activated amide groups have been also introduced on calix[4]arenes in order to obtain anion receptors.[1e,8,9]

Finally, very recently we have shown that also perfluorinated alcohols at the upper rim of calix[4]arenes can act as anion binding sites.[10]

* Proofs to: Professor Rocco Ungaro, Dipartimento di Chimica Organica e Industriale, Università degli Studi di Parma, Parco Area delle Scienze 17/A, 43100 Parma, Italy. phone: +39 521 905412, fax: +39 521 905472, e-mail: ungaro@ipruniv.cce.unipr.it

In this paper, we report the synthesis and anion binding properties of several new calix[4]arenes in the *cone* conformation, tetrafunctionalized at the upper rim with various type of hydrogen bonding donor groups such as thioureas, trifluoroacetamides or perfluorinated alcohols. We have also investigated the role of subtle conformational changes on anion binding by analysing the behaviour of *mobile cone* tetrapropoxycalix[4]arene derivatives **1**, **4** and **6**, and that of *rigid cone* biscrown-3-calix[4]arene derivatives **2** and **3**.

SYNTHESIS OF THE LIGANDS

Our first target was the tetraphenylthioureamethyl compound (**1**) which required the synthesis of the tetraminomethyl intermediate (**11**) in the *cone* conformation. Recently, Nagasaki *et al.*[11] reported the synthesis of the *1,3-alternate* isomer of **11** by chloromethylation of the tetrapropoxycalix[4]arene in the *1,3-alternate* structure, followed by substitution with potassium phthalimide and deprotection with hydrazine.

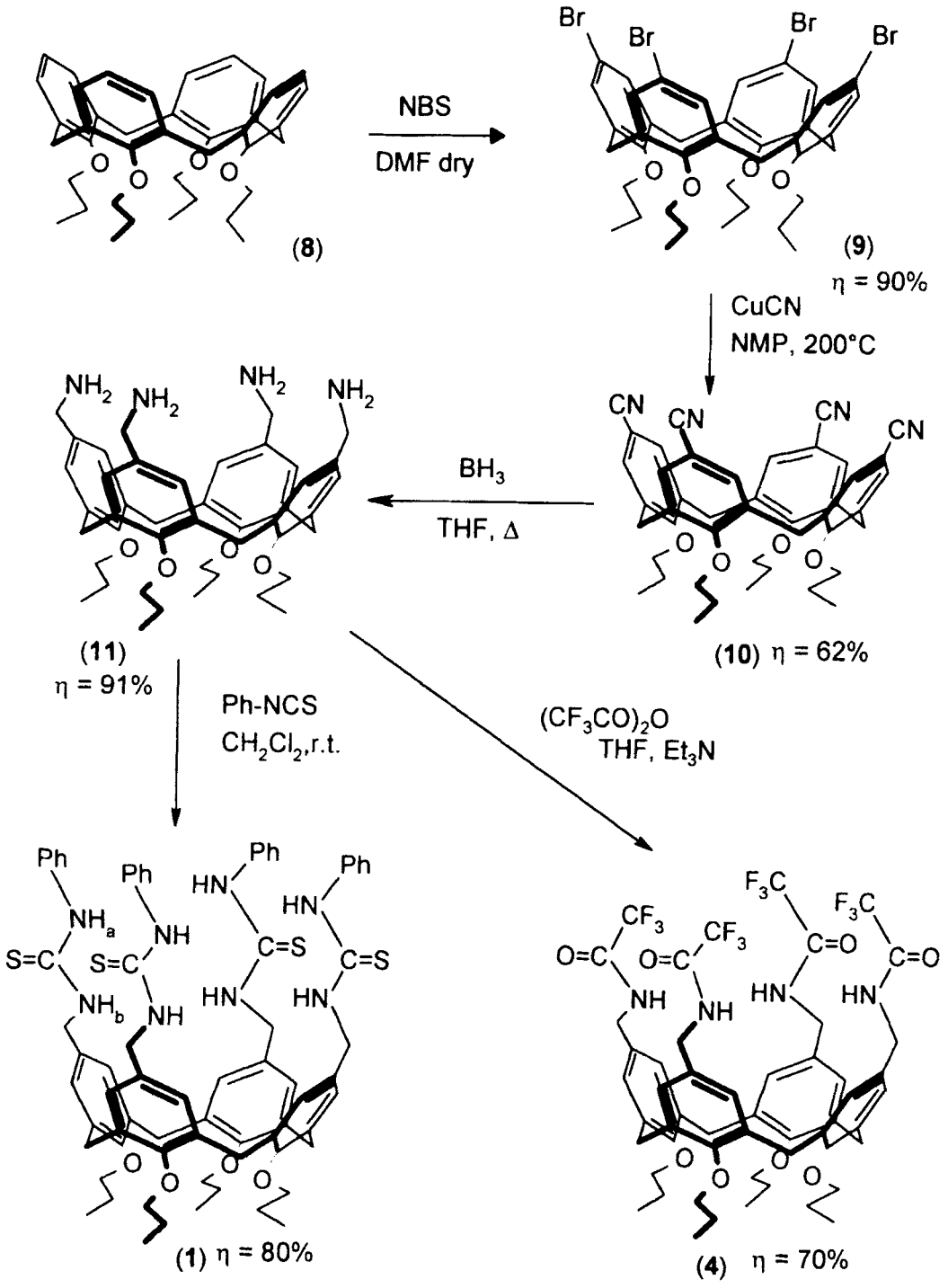
We used a different reaction sequence as depicted in Scheme 1, starting from tetrapropoxycalix[4]arene (**8**) blocked in the *cone* conformation, which was first brominated with NBS under conditions similar to those reported by Larsen *et al.*,[12] but using DMF instead of 2-butanone (MEK), to give compound **9** in 90% yield.

The reaction of **9** with CuCN at 200°C, gave tetracyano derivative **10**, which was easily reduced to tetraminomethyl calix[4]arene (**11**) with borane in dry THF. The reaction of **11** with phenylisothiocyanate gave **1** in 80% yield and with $(CF_3CO)_2O$ in dry THF afforded the tetramide derivative **4** in 70% yield. Following the same reaction sequence, but starting from calix[4]arene-biscrown-3 (**12**), it was possible to obtain the tetrathiourea (**2**) and the tetramide (**5**) in satisfactory yields.

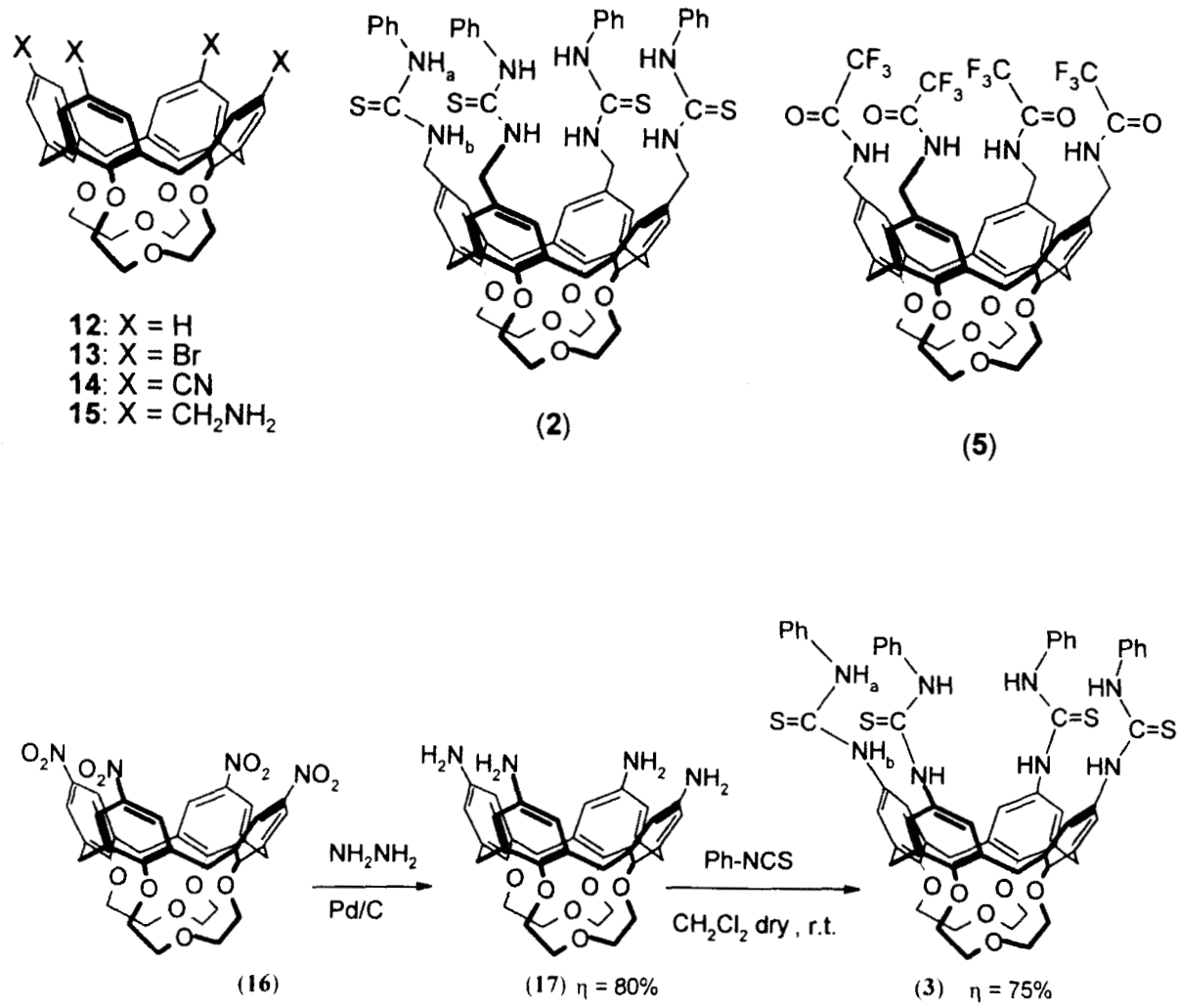
The only difference consists in the fact that, due to solubility problems of the tetramino-biscrown-3 (**15**) in THF, the synthesis of the trifluoroacetamido derivative **5** was performed in dry DMF. The *rigid cone* tetrathiourea derivative (**3**) was obtained through the reaction Scheme 2.

All thioureas **1–3** show very broad NMR spectra in $CDCl_3$, presumably due to *self*-association phenomena as observed by Rebek[13] and Böhmer[14] on similar systems. However, in DMSO-d_6 all three compounds show sharp peaks in the NMR spectra, which clearly indicate that their structure is monomeric. NH_a and NH_b protons of both hosts **1** and **2** resonate at $\delta = 9.5$ and $\delta = 7.40$, respectively, as expected from the fact that the former hydrogen is more acidic than the latter. The NH groups of compound **3**, which are all directly linked to an aromatic nucleus, give two singlets at $\delta = 9.58$ and $\delta = 9.25$ (NH_a and NH_b respectively). The presence of the trifluoroacetyl groups in compound **4** is clearly indicated by the presence of a quartet ($^1J_{C\text{-}F} = 290$ Hz) at 116 ppm due to CF_3 in the ^{13}C NMR spectrum and by the appearance of a triplet ($^3J_{H\text{-}H} = 5.7$ Hz) for the NH at $\delta = 6.97$ in the ^1H NMR spectrum. Compound **5** is completely insoluble in $CDCl_3$ probably due to extensive *self*-association and to its reduced flexibility and therefore all NMR spectra were recorded in DMSO-d_6. The triplet ($^3J_{H\text{-}H} = 5.5$ Hz) due to the NH protons is at δ 9.65 for compound **5** in DMSO-d_6, which is at lower field with respect to the NH of compound **4** in $CDCl_3$. However this is mainly a solvent effect, since it is known that going from chloroform to dimethylsulfoxide the urea NH protons are highly deshielded. Finally we synthesized (Scheme 3) two new *mobile cone* calix[4]arene tetrols **6** and **7**, the former bearing pefluorinated groups and the latter simple alkyl chains.

We first synthesized compound 7, in almost quantitative yields, by the reaction of the tetraester **19** with *n*-BuLi in dry THF. However, a similar procedure using organometallic compounds prepared *in situ* from $CF_3CF_2CF_2I$ and Mg, Li or

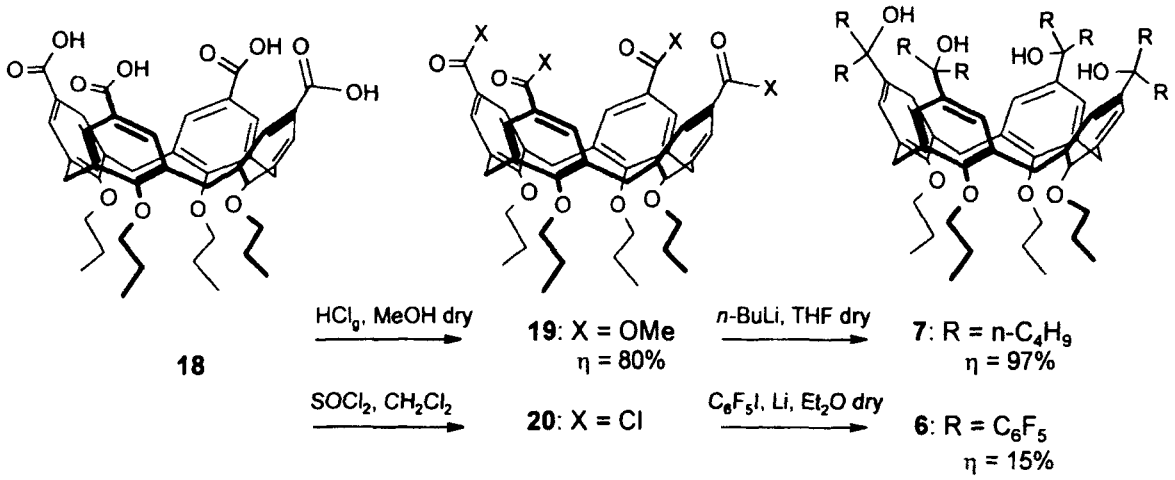


SCHEME 1



SCHEME 2

t-BuLi in diethyl ether,[15] gave no reaction. This behaviour can be explained considering the lower reactivity of these perfluorinated organometallic compounds in addition reactions to carbonyl groups compared with alkyl and aryl organolithium derivatives.[16] On the other hand, the reactivity of pentafluorophenyl lithium is much closer to that of simple organolithium compounds, since it easily reacts with acyl chlorides,[17] esters,[18] aldehydes[19] and ketones.[20] We first reacted C_6F_5Li[21] with tetraester **19** but without success. Only from the reaction with the tetrachloride **20** in dry Et_2O at –78°C, we could isolate compound **6**, although in low yields (15%). The obtainment of compound **6** was confirmed by mass spectrometry ($M^+ = 2040$) and by the presence of three doublets ($^1J_{C\text{-}F} = 240$ Hz) for the C_6F_5 carbons in the ^{13}C NMR spectrum.



SCHEME 3

TABLE I Association constants (Kass, M^{-1}) of hosts **1–4** and **6–7** towards anions of tetrabutylammonium salts at T = 300K

Ligand	*Solvent*	Cl^-	Br^-	I^-	CH_3COO^-	$PhCOO^-$	$H_2PO_4^-$
1	DMSO-d_6	90	a	n.t.	270	70	300
2	DMSO-d_6	120	30	n.t.	270	100	150
3	DMSO-d_6	35	a	a	b	b	b
4	$CDCl_3$	170	110	n.t.	190	580	n.t.
6	$CDCl_3$	130	480	20	90	n.t.	n.t.
7	$CDCl_3$	a	a	n.t.	a	n.t.	n.t.

a. No significant shifts observed.
b. Only broadening of the NH signals are observed; n.t. = not tested.

COMPLEXATION STUDIES

The complexation properties of ligands **1–7** towards spherical (Cl^-, Br^- and I^-), Y-shaped (CH_3COO^-, $PhCOO^-$) or tetrahedral anions (as tetra-*n*-butylammonium salts) were evaluated using ^1H NMR titrations in DMSO-d_6 or $CDCl_3$. To a solution of host ($5x10^{-2}M$), increasing amounts of guest ($4.4x10^{-2}M$) were added in order to have a host/guest ratio between 0.5 and 9. Usually the most sensitive signals to complexation are the NH protons for urea- and trifluoroacetamide-based receptors **1–5** or the OH protons for host **6**, which experience downfield shifts upon complexation with the anion. However, we also used other probes such as the ArH or the $ArCH_2NH$ protons. Non-linear regressions of the observed chemical shifts, at different host and guest concentrations,[22] allowed to determine the association constants (Kass) reported in Table I.

Due to serious *self*-association phenomena,[13,14] the urea receptors **1–3** were studied only in DMSO-d_6 (*vide supra*). The trifluoracetamido derivatives **4** and **5** or the alcohols **6** and **7** do not show any significant shifts in DMSO-d_6 upon addition of tetrabutylammonium halides or acetate, indicating that these receptors are not

able to complex anions in such a competing solvent. These data clearly show that thioureas are much stronger binding groups for anions than activated amides or alcohols. The comparison between hosts **1** and **2** allows to evaluate the effect of rigidity of the calixarene platform on anion binding. Both compounds are in the *cone* conformation but, as demonstrated by previous studies, tetrapropoxy derivatives experience a residual conformational mobility between two C_{2v} conformers in a flattened cone structure, while the biscrowns-3 are conformationally rigid.[23,24] Non-linear regression analyses of the data obtained with these derivatives show always a good fit with the 1:1 model for all anions except carboxylates. For the latter, the Job plots show some deviations from the ideal bell-shaped curve expecially in the region with molar fraction of guest (X_G) higher than 0.5, indicating the possible existence of a 1:2 (H/G) complex. However a preliminary calculation of the 1:1 and 1:2 Kass shows that the latter is at least one order of magnitude lower than the former, and is therefore not taken into account in the present work. The comparison between binding properties of the *mobile cone* tetraurea receptor **1** with those of the *rigid cone* analog **2** shows that rigidification of the calix has a modest positive effect in the binding of spherical anions such as Cl^- and Br^- and a slightly negative effect on the binding of the tetrahedral anion, $H_2PO_4^-$. Even more surprising are the (negative) results obtained with the tetrathiourea *rigid cone* derivative **3** which is able to complex only Cl^- among the monovalent anions tested, in spite of the better hydrogen-bond donating ability of the urea units directly connected to the calixarene aromatic rings, which has been verified in similar systems.[6b] The overall picture which emerges from all these data is that, differently from what observed in the apolar complexation of neutral molecules in organic media,[24] a rigid host is not a better anion binder than a *mobile one*. This is probably due to the high directionality of the hydrogen bonds which are involved in the complexation of anions by these neutral hosts. In the case of host **3** there could be the additional effect of the extended conjugation involving the phenyl-thioureido-calixarene moieties which increases the acidity of NHs but also tends to keep the system planar. As a consequence, not all NH groups could be convergent and available to bind the anion inside the cavity. However, host **3** is able to bind the more complementary tetranion of piromellitic (1,2,4,5-benzentetracarboxylic) acid, showing a Kass = 160 M^{-1} in DMSO-d_6.

The binding properties of hosts **4**, **6** and **7** were studied in $CDCl_3$, where they are not extensively associated since their ^1H NMR spectra are sharp and do not show any changes upon dilution from 10^{-2} to 10^{-4} M. The trifluoroacetamidocalix[4]arenebiscrown-3 (**5**) is not soluble at all in $CDCl_3$ and its binding properties could not be studied. The tetrapropoxy derivative **4** shows Kass higher than 100 M^{-1} for all the anions tested, with a selectivity for the Y-shaped anions and in particular for benzoate. On the contrary, the perfluorinated alcohol **6** is selective for halide anions and the binding constants for Cl^-, Br^- and I^- show an unusual peak selectivity for the bromide anion. This behaviour can be explained considering a better size complementarity between Br^- and the calix[4]arene cavity which allows the cooperative action of all four OH binding groups. Probably only two OH groups are in close contact with the smaller chloride anion. No complexation is shown by the alcohol derivative **7** which clearly demonstrates that the presence of perfluorinated aromatic nuclei strongly activate the hydrogen-bonding abilities of the alcoholic function. At present it is not completely clear if compound **6** is complexing anions just through hydrogen bonding with the OH groups or if also the electron poor aromatic rings act as additional binding sites through anion -π interaction.[25]

CONCLUSIONS

Six new anion receptors derived from calix[4]arenes tetrafunctionalized at the upper rim with hydrogen bonding groups have been synthesized. The association constants determined with several anions allow to compare the effect of the type of binding group used and of the different conformational mobility of the calixarene structure. Thiourea groups show the highest efficiency in the complexation of anions, compared with trifluoroacetamides or perfluorinated alcohols. The enhanced rigidity of the calixarene platform in ligands **2** and **3** with respect to **1** causes a decrease in the binding affinity towards tetrahedral $H_2PO_4^-$ anion. The very rigid receptor **3** binds spherical anions only slightly but interacts more strongly with the tetranion of piromellitic acid. A good selectivity in the recognition of benzoate anion is observed for the activated amide derivative **4**, whereas the perfluorinated alcohol derivative **6** binds more strongly bromide anion.

EXPERIMENTAL SECTION

Melting points were determined with an Electrothermal melting point apparatus in a capillary sealed under nitrogen. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker AMX400 (^1H: 400 MHz), AC300 (^1H: 300 MHz, ^{13}C: 75 MHz) spectrometers of the Centro Interdipartimentale di Misure (C.I.M.) of the University of Parma using Me_4Si as internal standard. Mass spectra were obtained with a Finnigan MAT SSQ710 spectrometer (DCI, methane as ionizing gas). Analytical TLC were performed on precoated silica gel plates (SiO_2, Merck, 60 F_{254}), while silica gel 60 (SiO_2, Merck, particle size 0.040–0.063 mm, 230–240 mesh) was used for preparative column chromatography. Tetrapropoxycalix[4]arene (**8**),[26] biscrown-3-calix[4]arene (**12**),[24] tetranitro-biscrown-3-calix[4]arene (**16**),[27] tetramino-biscrown-3-calix[4]arene (**17**)[27] and tetrapropoxycalix[4]arene-tetracid (**18**)[28] were prepared as described in the literature.

In NMR spectra, the "Ar" notation indicates the aromatic nuclei of the calixarene backbone, considering the phenol oxygen as main substituent, whom the ipso, ortho, meta and para position refer to. For compounds **1**, **2**, **3** and **6** the "Ph" notation refers to the aromatic nuclei on urea or perfluorinated alcohol functions.

Association constants (Kass) were determined by ^1H NMR titration experiments in $CDCl_3$ or DMSO-d_6; stock solutions of host ($5x10^{-3}$M) and tetrabutylammonium salt ($4.4x10^{-2}$M) were prepared and mixed together in the NMR tube in various molar ratios (H/G = 0.5, 0.7, 1, 1.6, 2.5, 4, 6, 9). For each addition, the ^1H NMR spectrum was recorded at 300 K and the chemical shift of some protons was plotted *versus* guest concentration. Non-linear regression analyses allowed the determination of Kass (accuracy ±10%).

General procedure for the synthesis of tetrabromo calixarenes 9 and 13

To a stirring solution of 1.7 mmol of compound **8** or **12** in 30 mL of DMF, NBS (8.4 mmol for **8** and 14 mmol for **12**) was added. After 24 h at room temperature, the reaction mixture was quenched by addition of 50 mL of a 1M HCl solution. The resulting solid was filtered on a Buchner funnel and recrystallized from methanol.

5,11,17,23-Tetrabromo-25,26,27,28-tetra-n-propoxycalix[4]arene (9)

Yield: 90%. M.p.: 278–280°C. ^1H NMR (300MHz; 300K; $CDCl_3$): δ 6.78 (s, 8H, ArH); 4.33 (d, 4H, ArCH*H*axAr, J = 13.5 Hz); 3.78 (t, 8H, OCH_2, J = 7.5 Hz); 3.07 (d, 4H, ArCH*H*eqAr, J = 13.5 Hz); 1.85 (m, 8H, $OCH_2CH_2CH_3$, J = 7.5 Hz); 0.94 (t, 12H, CH_3, J = 7.5 Hz). ^{13}C NMR (25MHz; 300K; $CDCl_3$): δ 155.6 (s, Ar ipso); 136.6 (s, Ar ortho); 131.3 (d, Ar meta); 115.4 (s, Ar para); 77.3 (t, OCH_2); 31.0 (t, $ArCH_2Ar$); 23.3 (t,

$OCH_2CH_2CH_3$); 10.4 (q, CH_3). MS (CI) m/e: 912 $(M+8)^+$ 20%; 910 $(M+6)^+$ 70%; 908 $(M+4)^+$ 100%; 906 $(M+2)^+$ 70%; 904 $(M)^+$ 20%.

5,11,17,23-Tetrabromo- 25,26–27,28-biscrown-3-calix[4]arene (13)

Yield: 95%. M.p.: >320°C. ^1H NMR (300MHz; 300K; $CDCl_3$): δ 7.15 (d, 4H, ArH, J = 2.4 Hz); 7.13 (d, 4H, ArH, J = 2.4 Hz); 4.96 (d, 2H, ArCH-*H*axAr, J = 12.1 Hz); 4.37 (d, 2H, ArCH*H*axAr, J = 12 Hz); 4.33 (d, 4H, OC*H*H, J = 11.6 Hz); 4.21, 4.08 (m, 8H, OCH_2); 3.82 (dd, 4H, OC*H*H, J = 11.6 Hz); 3.33 (d, 2H, ArCH*H*eqAr; J = 12.2 Hz); 3.28 (d, 2H, ArCH*H*eqAr, J = 12.1 Hz). ^{13}C NMR (75MHz; 300K; $CDCl_3$): δ 154.7 (s, Ar ipso); 137.2, 137.0 (d, Ar ortho); 132.3, 131.3 (s, Ar meta); 116.6 (s, Ar para); 75.9, 74.7 (t, OCH_2); 30.5, 29.7 (t, $ArCH_2Ar$). MS (CI) m/e: 884 $(M+8)^+$ 20%; 882 $(M+6)^+$ 70%; 880 $(M+4)^+$ 100%; 878 $(M+2)^+$ 70%; 876 $(M)^+$ 20%.

General Procedure for the synthesis of tetracyano calixarenes 10 and 14

To a stirring solution of tetrabromo calixarenes **9** and **13** (1 mmol) in 30 mL of N-methyl pyrrolidinone (NMP), CuCN (0.62 g, 7 mmol) was added, and the reaction mixture heated under nitrogen at 200°C for 24 h. After cooling the solution to 50°C, a solution of $FeCl_3$ (1.80 g, 11.2 mmol) in 30 mL of 1N HCl (CAUTION!, HCN may develop) was added and the mixture stirred for an additional 0.5 h. The resulting solid was filtered on a Buchner funnel and compounds **10** or **14** purified by column chromatography.

5,11,17,23-Tetracyano 25,26,27,28-tetra-n-propoxycalix[4]arene (10)

The product was purified from the crude by column chromatography (SiO_2: CH_2Cl_2/AcOEt = 3:1 as eluent) and subsequently triturated with hexane. Yield: 62%. M.p.: > 330°C. ^1H NMR (300 MHz; 300K; $CDCl_3$): δ 6.99 (s, 8H, ArH); 4.44 (d, 4H, ArCH*H*axAr, J = 11.5 Hz); 3.90 (t, 8H, OCH_2, J = 6.2 Hz); 3.25 (d, 4H, ArCH*H*eqAr, J = 11.5 Hz); 1.88 (sext, 8H, $OCH_2CH_2CH_3$, J = 6.2 Hz); 0.99 (t, 12H, CH_2CH_3, J = 6.2 Hz). ^{13}C NMR (75MHz; 300K; $CDCl_3$); δ 154.8 (s, Ar ipso); 135.8 (s, Ar ortho); 132.7 (d, Ar meta); 116.2 (s, C≡N); 107.3 (s, Ar para); 77.6 (t, OCH_2CH_2); 30.6 (t, $ArCH_2Ar$); 23.4 (t, OCH_2CH_2); 10.3 (q, CH_3). IR (KBr): 2225 cm^{-1}(ν, C≡N). MS (CI) m/e: 693 $(M-1)^+$ 100%.

5,11,17,23-Tetracyano-25,26–27,28-biscrown-3 calix[4]arene (14)

The product was obtained pure after column chromatography (SiO_2: CH_2Cl_2/AcOEt = 4:1 as eluent).

Yield: 32%. M.p.: >330°C. ^1H NMR (300MHz; 300K; $CDCl_3$): δ 7.82 (d, 4H, ArH, J = 1.8 Hz); 7.77 (d, 4H, ArH, J = 1.8 Hz); 5.02 (d, 2H, ArCH-*H*axAr, J = 12.1 Hz); 4.38 (d, 2H, ArCH*H*axAr, J = 12.2 Hz); 4.33 (t, 4H, OCH_2, J = 9.2 Hz); 4.21–4.08 (m, 8H, OCH_2); 3.82 (t, 4H, OCH_2, J = 9.8 Hz); 3.33 (d, 2H, ArCH*H*eqAr, J = 12.2 Hz); 3.28 (d, 2H, ArCH*H*eqAr, J = 12.1 Hz). ^{13}C NMR (75MHz; 300K; $CDCl_3$): δ 158.3 (s, Ar ipso); 136.0, 135.8 (2s, Ar ortho); 134.4, 133.2 (d, Ar meta); 119.0 (s, CN); 108.0 (s, Ar para); 76.8, 74.7 (t, OCH_2); 29.3, 28.6 (t, $ArCH_2Ar$). IR (KBr): 2220 cm^{-1}(υ CN). MS (CI) m/e: 665 $(M+1)^+$ 100%.

General procedure for the synthesis of tetramino calixarenes 11 and 15

To a stirring solution of tetracyano calixarene **10** or **14** (0.70 mmol) in 60 mL of dry THF at 0°C, 19.6 mL (19.6 mmol) of a BH_3 solution (1M in dry THF). The reaction mixture was refluxed under nitrogen for 24 h. Then 5 mL of MeOH and 15 mL of 1N HCl were added (CAUTION!) and the mixture heated at 50°C for 0.5 h. THF was removed under reduced pressure and the tetramino derivatives isolated as follows.

5,11,17,23-Tetraminomethyl-25,26,27,28-tetra-n-propoxycalix[4]arene, tetrachlorohydrate (11*4HCl)

After removal of THF a white solid precipitated from water solution, which was filtered and washed with 5 mL of CH_2Cl_2 on a Buchner funnel.

Yield: 91%. M.p.: 290°C (dec.). ^{1}H NMR (300MHz; 300K; CD_3OD): δ 6.87 (s, 8H, ArH); 4.49 (d, 4H, ArCH*H*axAr, J = 13.2 Hz); 3.88 (t, 8H, OCH_2, J = 5.3 Hz); 3.82 (s, 8H, NH_2); 3.30 (bs, 8H, $ArCH_2NH_2$); 3.26 (d, 4H, $ArCHH_{eq}Ar$, J = 13.2 Hz); 1.94 (m, 8H, $OCH_2CH_2CH_3$, J = 7.4 Hz); 1.02 (t, 12H, CH_3, J = 7.4 Hz). ^{13}C NMR (75MHz; 300K; CD_3OD): δ 158.4 (s, Ar ipso); 136.7 (s, Ar ortho); 130.5 (d, Ar meta); 128.3 (s, Ar para); 78.1 (t, OCH_2); 44.0 (t, CH_2NH_2); 31.7 (t, $ArCH_2Ar$); 24.4 (t, CH_2CH_3); 10.7 (q, CH_3). IR (KBr): 3421 cm^{-1} (bs, υ N-H). MS (CI) m/e: 707 $(M\text{-}4^*HCl\text{-}1)^+$ 100%; 708 $(M\text{-}4^*HCl)^+$ 75%.

Compound **11**, in its basic form, can be obtained by extraction in CH_2Cl_2 from 1N NaOH aqueous solution.

5,11,17,23-Tetraminomethyl-25,26–27,28-biscrown-3-calix[4]arene (15)

The aqueous solution obtained after removal of THF, was added of 10 mL of 1N HCl and washed with CH_2Cl_2 (3x15 mL). To the aqueous layer were slowly added pellets of NaOH till basic pH and the white product filtered on a Buchner.

Yield: 95%. M.p.: >330°C. ^{1}H NMR (300MHz; 300K; $CDCl_3$): δ 6.93 (s, 8H, ArH); 4.92 (d, 2H, ArCH*H*axAr, J = 12.8 Hz); 4.40 (d, 2H, ArCH-*H*axAr, J = 12.7 Hz); 4.23–4.14 (m, 8H, OCH_2); 3.80, 3.73 (m, 8H, OCH_2); 3.56 (s, 8H, CH_2N); 3.21 (d, 2H, ArCH*H*eqAr, J = 12.7 Hz); 3.15 (d, 2H, ArCH*H*eqAr, J = 12.8 Hz); 2.85 (bs, 8H, NH_2). ^{13}C NMR (75MHz; 300K; $CDCl_3$): δ 155.4 (s, Ar ipso); 136.7 (s, Ar para); 135.4 (s, Ar ortho); 129.7, 128.8 (d, Ar meta); 77.4, 75.7 (t, OCH_2); 55.4 (t, CH_2N); 30.5 (t, $ArCH_2Ar$). IR (KBr): 3425 cm^{-1} (υ -NH_2, b.s.). MS (CI) m/e: 680 (M^+) 100%.

General procedure for the preparation of thioureas 1, 2 and 3

To a stirring solution of tetramino derivatives **11**, **15** or **17** (0.4 mmol) dissolved in 30 mL of dry CH_2Cl_2, 0.19 mL (1.64 mmol) of phenylisothiocyanate was added under nitrogen. After 6 h, the solvent was removed under reduced pressure and pure compounds **1–3** obtained as follows.

5,11,17,23-Tetrakis[(N'-phenylthioureido)methyl]-25,26,27,28-tetrapropoxycalix[4]arene (1)

Pure compound **1** was obtained by column chromatography (Reverse phase RP18: MeOH/Acetone = 9:1 as eluent).

Yield: 80%. M.p.: 150–151°C. ^{1}H NMR (300MHz; 300K; DMSO-d_6): δ 9.60 (s, 4H, PhN*H*); 7.9 (s, 4H, $ArCH_2NH$); 7.47 (d, 8H, o-Ph, J = 8.0 Hz); 7.27 (t, 8H, m-Ph, J = 7.6 Hz); 7.05 (t, 4H, p-Ph, J = 8.0 Hz); 6.78 (s, 8H, ArH); 4.40 (s, 8H, $ArCH_2NH$); 4.37 (d, 4H, ArCH*H*axAr, J = 13 Hz); 3.80 (t, 8H, OCH_2, J = 7.4 Hz); 3.18 (d, 4H, $ArCHH_{eq}Ar$, J = 13 Hz); 1.89 (m, 8H, $OCH_2CH_2CH_3$, J = 7.2 Hz); 0.98 (t, 12H, CH_3, J = 7.1 Hz). ^{13}C NMR (75MHz; 300K; DMSO-d_6): δ 180.2 (s, C=S); 155.3 (s, Ar ipso); 139.3 (s, PhCNH); 134.3 (s, Ar ortho); 131.8 (d, m-Ph); 128.5 (d, Ar meta); 127.7 (d, p-Ph); 124.0 (s, Ar para); 122.9 (d, o-Ph); 76.4 (t, OCH_2); 47.3 (t, CH_2NH); 30.3 (t, $ArCH_2Ar$); 22.7 (t, CH_2CH_3); 10.1 (q, CH_3). IR (KBr): 3390 cm^{-1} (ν N-H). MS (CI) m/e: 733 [M – 4Ph-NH – 2C(S)-NH-CH2]$^+$ 100%.

5,11,17,23-Tetrakis[(N'-phenylthioureido) methyl]-25,26–27,28-biscrown-3-calix[4]arene (2)

Pure compound **2** was obtained by column chromatography (SiO_2: CH_2Cl_2/AcOEt = 3:1 as eluent).

Yield: 40%. M.p.: 190–191°C. ^{1}H NMR (300MHz; 300K; DMSO-d_6): δ 9.42 (s, 4H, PhN*H*); 7.90 (s, 4H, $ArCH_2NH$); 7.46 (d, 8H, o-Ph, J = 9.8 Hz); 7.28 (t, 8H, m-Ph, J = 7.5 Hz); 7.15 (s, 8H, ArH); 7.06 (t, 4H, p-Ph, J = 7.2 Hz); 4.94 (d, 2H, ArCH*H*axAr, J = 12.7 Hz); 4.44, 4.17 (m, 14H, ArCH*H*axAr, OCH_2); 3.66 (m, 6H,

OCH_2, ArCH*H*eqAr); 3.30 (s, 8H, ArCH_2NH); 3.20 (d, 2H, ArCH*H*eqAr, J = 12.7 Hz). ^{13}C NMR (75MHz; 300K; DMSO-d_6): δ 180.3 (s, C=S); 154.3 (s, Ar ipso); 139.2 (s, PhCNH); 135.2, 133.3 (s, Ar ortho); 128.6 (d, m-Ph); 128.3 (d, Ar meta); 127.8 (d, p-Ph); 123.9 (s, Ar para); 122.9 (d, o-Ph); 76.4, 74.2 (t, OCH_2); 47.2 (t, ArCH_2N); 31.3 (t, ArCH_2Ar). IR (KBr): 3350 cm^{-1} (υ NH); 1610 cm^{-1} (υ C=S). MS (CI) m/e: 706 (M- 4Ph-NH – 2 C(S)-NH-CH_2)$^+$ 100%.

5,11,17,23-Tetrakis(N′-phenylthioureido)-25,26-27,28-biscrown-3-calix[4]arene (3)

The product was crystallized from isopropyl ether.

Yield: 75%. M.p.: 280°C (dec.). ^{1}H NMR (300MHz; 300K; DMSO-d_6): δ 9.58 (s, 4H, PhNH); 9.24 (s, 4H, ArNH); 7.44 (d, 8H, o-Ph, J = 7.5 Hz); 7.26 (t, 8H, m-Ph, J = 7.5 Hz); 7.16 (m, 8H, ArH); 7.06 (t, 4H, p-Ph, J = 7.1 Hz); 4.95 (d, 2H, ArCH*H*axAr, J = 11.3); 4.42 (d, 2H, ArCH-*H*axAr, J = 12.1 Hz); 4.26–4.22 (bs, 12H, OCH_2); 3.68 (bs, 4H, OCH_2); 3.60 (d, 2H, ArCH*H*eqAr, J = 12.1 Hz); 3.18 (d, 2H, ArCH*H*eqAr, J = 11.3 Hz). ^{13}C NMR (75MHz; 300K; DMSO-d_6): δ 179.5 (s, C=S); 153.1 (s, Ar ipso); 140.0 (s, PhNH); 135.4, 134.7 (s, Ar ortho); 128.7 (d, Ar meta); 125.4, 124.0, 123.7 (3d, 1s, p-Ph, m-Ph, o-Ph, Ar para); 76.9, 74.6 (t, OCH_2); 31.1 (t, ArCH_2Ar). IR (KBr): 3358 cm^{-1} (υ N-H); 1530 cm^{-1} (υ C=S). MS (CI) m/e: 749 [M – 4Ph-NH – C(S)]$^+$ 90%; 707 [M–4Ph-NH – 2C(S)]$^+$ 100%; 666 [M – 4Ph-NH – 3C(S) + 1]$^+$ 50%.

General procedure for the synthesis of trifluoroacetyl derivatives 4 and 5

To a solution of 0.15 mmol of compound **11** in 30 mL of dry THF or of compound **15** in 30 mL of dry DMF was added triethylamine (0.90 mmol) under nitrogen. After cooling to 0°C, was added trifluoroacetic anhydride (0.90 mmol) and the reaction mixture stirred at room temperature for 6 h. Then the solvent was removed under reduced pressure and CH_2Cl_2 (30 mL) added to the residue. This organic layer was washed with water (30 mL), 10% aqueous NaOH (30 mL) and again water (30 mL). After drying over $MgSO_4$, CH_2Cl_2 was distilled off and pure product obtained as follows.

5,11,17,23-Tetrakis[(trifluoroacetamido)methyl]-25,26,27,28-tetra-n-propoxycalix[4]arene (4)

Pure compound **4** was obtained by recrystallization from hexane of the crude reaction mixture.

Yield: 70%. M.p.: 226–228°C. ^{1}H NMR (300 MHz; 300K; $CDCl_3$): δ 7.18 (bs, 4H, NH); 6.55 (s, 8H, ArH); 4.41 (d, 4H, ArCHH_{ax}Ar, J = 13.2 Hz); 4.19 (d, 8H, ArCH_2NH, J = 5.7 Hz); 3.82 (t, 8H, $OCH_2CH_2CH_3$, J = 7.5 Hz); 3.11 (d, 4H, ArCHH_{eq}Ar, J = 13.2 Hz); 1.99–1.87 (m, 8H, $OCH_2CH_2CH_3$); 1.00 (t, 12H, $OCH_2CH_2CH_3$, J = 7.4 Hz). ^{13}C NMR (75 MHz; 300K; $CDCl_3$): δ 179.0 (q, $COCF_3$, $J_{C\text{-}C\text{-}F}$ = 34 Hz); 155.9 (s, Ar ipso); 135.0 (s, Ar ortho); 129.8 (s, Ar para); 127.5 (d, Ar meta); 116.0 (q, $COCF_3$, $J_{C\text{-}F}$ = 290 Hz); 76.9 (t, $OCH_2CH_2CH_3$); 49.7 (t, ArCH_2NH); 30.6 (t, ArCH_2Ar); 23.1 (t, $OCH_2CH_2CH_3$); 10.1 (q, $OCH_2CH_2CH_3$). MS (CI) m/e: 1092 (M)$^+$ 65%; 980 (M-CF_3CONH)$^+$ 100%. IR (liquid film): 3283 cm^{-1} (ν N-H); 1700 cm^{-1}(ν C=O).

5,11,17,23-Tetrakis[(trifluoroacetamido)methy]-25,26,27,28-biscrown-3-calix[4]arene (5)

The crude reaction mixture was submitted to flash chromatography (SiO_2: CH_2Cl_2-AcOEt = 12:1 as eluent).

Yield: 30%. M.p.: 268–270°C. ^{1}H NMR (300 MHz; 300K; CD_3OD): δ 7.02 (s, 8H, ArH); 5.04 (d, 2H, ArCHH_{ax}Ar, J = 11.9 Hz); 4.51 (d, 2H, ArCH-H_{ax}Ar, J = 12.1 Hz); 4.31–4.21 (m, 20H, CH_2N and OCH_2); 3.75 (t, 4H, OCH_2, J = 9.0 Hz); 3.26 (d, 2H, ArCHH_{eq}Ar, J = 12.1 Hz); 3.18 (d, 2H, ArCHH_{eq}Ar, J = 11.9 Hz). ^{1}H NMR (300 MHz; 300K; DMSO-d_6): δ 9.65 (t, 4H, NH, J = 5.5 Hz); 7.03 (s, 8H, ArH); 4.92 (d, 2H, ArCHH_{ax}Ar, J = 11.8 Hz); 4.41 (d, 2H, ArCHH_{ax}Ar, J = 11.9 Hz); 4.26–4.16 (m, 12H, OCH_2); 4.13 (d, 8H, CH_2N, J = 5.5 Hz); 3.65 (t, 4H, OCH_2, J = 8.6 Hz); 3.26 (d, 2H, ArCHH_{eq}Ar, J = 11.9 Hz); 3.19 (d, 2H,

ArCHH_{eq}Ar, J = 11.8 Hz). ^{13}C NMR (75MHz; 300K; CD_3OD): δ 158.8 (q, $COCF_3$, $J_{C\text{-}C\text{-}F}$ = 37 Hz); 156.1 (s, Ar ipso); 137.2, 137.1 (s, Ar ortho); 133.2 (s Ar para), 129.6, 128.7 (d, Ar meta); 117.5 (q, $COCF_3$, $J_{C\text{-}F}$ = 286 Hz); 77.6, 75.86 (t, OCH_2); 43.9 (t, $ArCH_2NH$), 31.4, 30.5 (t, $ArCH_2Ar$). MS (CI) m/e: 1065 $(M+1)^+$ 25%; 1064 $(M)^+$ 20%; 953 $(M\text{-}CF_3CONH)^+$ 100%.

Synthesis of 5,11,17,23-tetrakis (metoxycarbonyl)-25,26,27,28-tetra-n-propoxycalix[4]arene (19)

After 1 h bubbling of $HCl_{(g)}$ in a round-bottomed flask containing 30ml of MeOH at 0°C, a sample of 0.47g (0.6 mmol) of tetracarboxy-tetrapropoxycalix[4]arene (**18**) dissolved in 10 mL of dry CH_2Cl_2 was added and the reaction mixture heated at 80°C for 12h. Then the solvent was removed under reduced pressure, the residue was quenched with 1N HCl (50mL) and the precipitate filtered on a Buchner funnel. This white solid was recrystallized from MeOH.

Yield: 80%. M.p.: 286–287°C. ^{1}H NMR (300MHz; 300K; $CDCl_3$): δ 7.31 (s, 8H, ArH); 4.43 (d, 4H, ArCHH_{ax}Ar, J = 13.6 Hz); 3.87 (t, 8H, $OCH_2CH_2CH_3$, J = 7.1 Hz); 3.79 (s, 12H, $C(O)OCH_3$); 3.24 (d, 4H, ArCHH_{eq}Ar, J = 13.6 Hz); 1.91–1.77 (m, 8H, $OCH_2CH_2CH_3$); 0.98 (t, $OCH_2CH_2CH_3$, J = 7.1 Hz). ^{13}C NMR (75MHz; 300K; $CDCl_3$): δ 166.6 (s, $ArC(O)OCH_3$); 160.5 (s, Ar ipso); 134.6 (s, Ar ortho); 130.1 (d, Ar meta); 124.3 (s, Ar para); 76.3 (t, $OCH_2CH_2CH_3$); 51.7 (q, $ArC(O)OCH_3$); 31.0 (t, $ArCH_2Ar$); 23.2 (t, $OCH_2CH_2CH_3$); 10.2 (q, $OCH_2CH_2CH_3$). MS (CI) m/e: 824 $(M)^+$ 60%; 793 $(M\text{-}2CH_3)^+$ 100%.

Synthesis of 5,11,17,23-tetrakis[1,1-(bispentafluorophenyl)methanol]-25,26,27,28-tetra-n-propoxycalix[4]arene (6)

A sample of 0.10g (0.13 mmol) of tetraacid (**18**) dissolved in 5mL of dry CH_2Cl_2 and 5 mL (68.7 mmol) of thionyl chloride, was heated to 40°C under nitrogen for 2 h. The vsolvent was removed under reduced pressure and the residue carefully dried at the vacuum pump. Then 20mL of dry ether were added and the reaction mixture cooled to - 78°C under Argon. Iodopentafluorobenzene (0.26 mL, 2mmol) and Li metallic (0.014 g, 2 mmol) were added and the reaction stirred at –78°C for 3h. After this period the cooling bath was removed, the reaction stirred for an additional 12 h period and then quenched with 1N HCl. This water layer was extracted with CH_2Cl_2(50ml), the organic phase separated and washed with water (2x50mL). The product was purified by column chromatography (SiO_2: hexane-ethyl acetate = 9:1 as eluent).

Yield: 15%. M.p.: 168–170°C. ^{1}H NMR (300MHz; 300K; $CDCl_3$): δ 6.64 (s, 8H, ArH); 4.52 (d, 4H, ArCHH_{ax}Ar, J = 13.0 Hz); 3.95 (t, 8H, $OCH_2CH_2CH_3$, J = 7.6 Hz); 3.90 (bs, 4H, OH); 3.15 (d, 4H, ArCHH_{eq}Ar, J = 13.0 Hz); 1.99–1.92 (m, 8H, $OCH_2CH_2CH_3$); 1.02 (t, 12H, $OCH_2CH_2CH_3$, J = 7.5 Hz). ^{13}C NMR (75MHz; 300K; $CDCl_3$): δ 156.9 (s, Ar ipso); 144.6 (d, Ph ortho, $J_{C\text{-}F}$ = 241 Hz); 141.0 (d, Ph para, $J_{C\text{-}F}$= 240 Hz); 137.6 (d, Ph meta, $J_{C\text{-}F}$ = 241 Hz); 135.9 (s, Ar para); 134.4 (s, Ar ortho); 126.1 (d, Ar meta); 118.0 (s, Ph ipso); 77.8 (t, $OCH_2CH_2CH_3$); 31.3 (t, $ArCH_2Ar$); 22.9 (t, $OCH_2CH_2CH_3$); 10.1 (q, $OCH_2CH_2CH_3$). MS (CI) m/e: 2040 $(M)^+$ 50%; 2022 $(M\text{-}H_2O)$ 100%.

Synthesis of 5,11,17,23-tetrakis(1-n-butyl-pentanol)-25,26,27,28-tetra-n-propoxycalix[4]arene (7)

A solution of 0.05g (0.07 mmol) of tetramethyl ester (**19**) in 10ml dry THF was carefully deoxygenated usig the freeze-pump-thaw method and Argon. The reaction mixture was cooled to –80°C, and 0.38mL (0.6 mmol) of a 1.6M solution of n-BuLi was added under Argon atmosphere. The cooling bath was removed and after 1h quenched (CAUTION!) with 50 mL of a 1N HCl solution. This water layer was extracted with ethyl acetate (50ml), the organic phase separated

and washed twice with water (2x50ml). Removal of the solvent yields pure compound **7**.

Yield: 97%. M.p.: 103–104°C. ^{1}H NMR (300MHz; 300K; $CDCl_3$): δ 6.73 (s, 8H, ArH); 4.44 (d, 4H, ArCHH_{ax}Ar, J = 12.8 Hz); 3.85 (t, 8H, $OCH_2CH_2CH_3$, J = 6.9 Hz); 3.13 (d, 4H, ArCH-H_{eq}Ar, J = 12.8 Hz); 1.94 (q, 8H, $OCH_2CH_2CH_3$, J = 7.4 Hz); 2.00–1.86 (m, 16H, $C(OH)CH_2CH_2CH_2CH_3$); 1.64–1.53 (m, 16H, $C(OH)CH_2CH_2CH_2CH_3$); 1.24–1.20 (m, 16H, $C(OH)CH_2CH_2CH_2CH_3$); 0.98 (t, 12H, $OCH_2CH_2CH_3$, J = 7.4 Hz); 0.85 (t, 24H, $C(OH)CH_2CH_2CH_2CH_3$, J = 7.2 Hz). ^{13}C NMR (75MHz; 300K; $CDCl_3$): δ 154.9 (s, Ar ipso); 140.7 (s, Ar ortho); 134.0 (d, Ar para); 125.0 (s, Ar meta); 76.5 (t, $C(OH)Bu_2$); 75.5 (t, $OCH_2CH_2CH_3$); 39.7 (t, $C(OH)CH_2CH_2CH_2CH_3$); 31.4 (t, $ArCH_2Ar$); 25.8 (t, $C(OH)CH_2CH_2CH_2CH_3$); 23.1 (t, $OCH_2CH_2CH_3$); 14.0 (q, $C(OH)CH_2CH_2CH_2CH_3$); 10.2 (q, $OCH_2CH_2CH_3$). MS (CI) m/e: 1090 (M-4xH_2O+H) 100%.

Acknowledgements

This research was supported by MURST (Project: "Dispositivi Supramolecolari") and by CNR (Project: "Agenti di Contrasto, di Shift e Sonde Luminescenti"). We also thank C.I.M. (Centro Interdipartimentale Misure) for the use of the NMR and mass spectrometry instruments.

References

1. a) *Supramolecular Chemistry of Anions*, ed. Bianchi, A.; Bowman-James, K.; Garcia-España, E. Eds; Wiley, New York, 1997.
   b) Beer, P.D.; Schmitt, P.; *Curr. Opin. Chem. Biol.* **1997**, *1*, 475.
   c) Schmidtchen, F.P.; Berger, M.; *Chem. Rev.* **1997**, *97*, 1609.
   d) Antonisse, M.M.G.; Reinhoudt, D.N.; *Chem. Commun.* **1998**, 443.
   e) Stibor, I.; Hafeed, D.S.M.; Lhoták, P.; Hodacová, J.; Koca, J.; Cajan, M.; *Gazz. Chim. Ital.* **1997**, *127*, 673.
2. a) Plugrath, J.W.; Quiocho, F.A.; *Nature* **1985**, *314*, 257.
   b) He, F.A.; Quiocho, F.A.; *Science* **1991**, *251*, 1479.
3. a) Christianson, D.W.; *J. Biol. Chem.* **1991**, *266*, 4264.
   b) Luecke, H.; Quiocho, F. A. *Nature* **1990**, *347*, 402.
4. Scheerder, J.; Fochi, M.; Engbersen, J.F.J.; Reinhoudt, D.N.; *J. Org. Chem.* **1994**, *59*, 7815.
5. Scheerder, J.; Engbersen, J.F.J.; Casnati A.; Ungaro, R.; Reinhoudt, D.N.; *J. Org. Chem.* **1995**, *60*, 6448.
6. Casnati, A.; Fochi, C.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R.; Reinhoudt, D.N.; *Gazz. Chim. Ital.* **1996**, *126*, 99. b) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R.; *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307.
7. a) Boerrigter, H.; Grave, L.; Nissink, J.W.M.; Chrisstoffels, L.A.J.; van der Maas, J.H.; Verboom, W.; de Jong, F.; Reinhoudt, D.N.; *J. Org. Chem.* **1998**, *63*, 4174.
   b) Nissink, J.W.M.; Boerrigter, H.; Verboom, W.; Reinhoudt, D.N.; van der Maas, J.H.; *J. Chem. Soc., Perkin Trans. 2* **1998**, 1671.
   c) Nissink, J.W.M.; Boerrigter, H.; Verboom, W.; Reinhoudt, D.N.; van der Maas, J.H.; *J. Chem. Soc., Perkin Trans. 2* **1998**, 2541.
8. Cameron, B.R.; Loeb, S.J.; *Chem. Commun.*, **1997**, 573.
9. a) Beer, P.D.; Drew, M.G.B.; Hazlewood, C.; Hesek, D.; Hodacova, J.; Stokes, S.E.; *J. Chem. Soc., Chem. Commun.* **1993**, 229.
   b) Beer, P.D.; Drew, M.G.B.; Hesek, D.; Shade, M.; Szemes, F.; *Chem. Commun.* **1996**, 2161.
   c) Beer, P.D.; Drew, M.G.B.; Hesek, D.; Nam, K.C.; *Chem. Commun.* **1997**, 107.
10. Pelizzi, N.; Casnati, A.; Ungaro R.; *Chem. Commun.* **1998**, 2607.
11. Nagasaki, T.; Noguchi, A.; Matsumoto, T.; Tamagaki, S.; Ogino, K.; *An. Quim.* **1997**, *93*, 341.
12. Larsen, M.; Jørgensen M.; *J. Org. Chem.* **1996**, *61*, 6651.
13. Hamann, B.C.; Shimizu, K.D.; Rebek, J. Jr.; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326. Castellano, R.K.; Rudkevich, D.M.; Rebek, J. Jr.; *J. Am. Chem. Soc.* **1996**, *118*, 10002.
14. Mogck, O.; Böhmer, V.; Thondorf, I.; Vogt, W.; *Tetrahedron* **1996**, *52*, 8489.
15. Beek J.A.; Clark, H.C.; Whyman, D.; *J. Chem. Soc.* **1962**, 4423.
16. Pierce, O.R.; McBee, E.T.; Judd, G.F.; *J. Am. Chem. Soc.* **1954**, *76*, 474.
17. Chang, I.S.; Price, J.T.; Tomlinson, A.J.; Willis, C.J.; *Can. J. Chem.* **1972**, *50*, 512. Dua, S.S.; Jukes, A.E.; Gilman, H.; *Organometal. Chem. Synth.* **1970–71**, *1*, 87–92.
18. Hafner, A.; Duthaler, R.O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F.; *J. Am. Chem. Soc.* **1992**, *114*, 2321.
19. Coe, P.L.; Stephens, R.; Tatlow, J.C.; *J. Chem. Soc.* **1962**, 3227.
20. Stickley, S.M.; Martin, J.C.; *Tetrahedron Lett.* **1995**, *36*, 9117.
21. CAUTION! May detonate above –20°C: Chernega, A.N.; Graham, A.J.; Green, M.L.H.; Haggit, J.; Lloyd, J.; Mehnert, C.P.; Metzler, N.; Souter, J.; *J. Chem. Soc., Dalton Trans.* **1997**, 2293.
22. For a comprehensive review on the NMR titration method applied to Molecular Recognition, see Wilcox, C.S. in « Frontiers in Supramolecular Chemistry and Photochemistry », Schneider, H.-J.; Durr, H. Eds., VCH, Weinheim (1991), p. 123.
23. Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R.; *J. Org. Chem.* **1995**, *60*, 1454.
24. Arduini, A.; McGregor, W.M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R.; *J. Chem. Soc., Perkin Trans. 2*, **1996**, 839.
25. Alkorta, I.; Rozas, I.; Elguero, J.; *J. Org. Chem.* **1997**, *62*, 4687.

26. Dondoni, A.; Marra, A.; Scherrmann, M.-C.; Casnati, A.; Sansone F.; Ungaro, R.; *Chem. Eur. J.* **1997**, *3*, 1774.
27. Arduini, A.; Mirone, L.; Paganuzzi, D.; Pinalli, A.; Pochini, A.; Secchi, A.; Secchi, A.; Ungaro, R.; *Tetrahedron* **1996**, *52*, 6011.
28. Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R.; *Eur. J. Org. Chem.*, **1998**, 897.