Synthesis and properties of new calixarene-based ditopic receptors for the simultaneous complexation of cations and carboxylate anions

Nicola Pelizzi, Alessandro Casnati, Arianna Friggeri and Rocco Ungaro *

Dipartimento di Chimica Organica e Industriale dell'Universita', Viale delle Scienze, 43100-Parma, Italy

Calix[4]arene tetramide mono(thio)urea derivatives 5a,b and 9 are able to solubilize solid sodium salts of different anions in $CDCl_3$ thanks to their ability to complex simultaneously the cation at the lower rim and the anion at the upper rim. Therefore they behave as ditopic receptors. Binding studies in [$^2H_6$]DMSO performed only on the thiourea derivatives allowed us to establish that these receptors complex carboxylates better than spherical anions and that receptor 9 having the thiourea group directly connected to the aromatic nucleus is more efficient than 5a, which has a CH_2 spacer between the two units; in the latter case good selectivity for the acetate anion is observed. Complexation of sodium ion by the amide groups at the lower rim causes an increase in the anion binding properties of receptor 9 and has little effect on receptor 5a. This is explained by the effects of the cation encapsulation on the hydrogen bonding ability of the thiourea units in the two receptors.

Introduction

Calixarenes have been widely used in the last two decades as building blocks for the synthesis of receptors for cations and neutral molecules.[1] More recently, following a growing general interest in anion recognition,[2] several authors introduced hydrogen bonding donor groups or Lewis acid centers on calixarenes in order to complex negatively charged species.[3] Thiourea and urea units are powerful hydrogen bond donors and are able to efficiently coordinate anions.[4] These units have been already linked to calix[4]- and calix[6]-arenes obtaining receptors for different anions depending on the number and position of the (thio)urea units. Reinhoudt and co-workers showed that the introduction of four (thio)urea moieties at the lower rim of calix[4]arene gives selective receptors for halide anions,[5] whereas three of these binding groups at the lower rim of calix[6]arene in the 1,3,5-positions afforded a receptor particularly selective for the trianion of benzene-1,3,5-tricarboxylic acid.[6] They also reported several examples of ditopic calix[4]arene receptors containing, in the same molecule, binding groups for anions and for cations which show selectivity for NaH_2PO_4,[7] NaX (X = Cl, Br)[8] and CsCl.[9] In this context, our own work was focused on the use of mono- and di-(thio)urea upper rim derivatives of calix[4]arenes as anion receptors. This has allowed us to study the effect of the calix[4]arene apolar cavity on the selective binding of anions which occurs through a 'two point' interaction with the receptors. Selectivity for carboxylate anions with respect to spherical and tetrahedral anions was observed and evidence was collected that the cavity of the macrocycle might contribute to stabilize the complexes with attractive CH_3–π or π–π interactions.[10]

In this paper we report the synthesis and recognition properties of new ditopic calix[4]arene receptors **5a**,**b** and **9** containing one (thio)urea unit at the upper rim and four amide groups at the lower rim. The presence of four or two urea units at the upper rim of calix[4]arenes causes, especially in apolar solvents, the formation of intra- or inter-molecular hydrogen bonds, which strongly decreases the anion coordination properties of these receptors. Shimizu and Rebek first[11] and subsequently Böhmer and co-workers[12] reported that tetraureidocalix[4]arenes form dimeric molecular capsules in $CDCl_3$. More recently this phenomenon was also proven by X-ray crystallography.[13] On the other hand Scheerder *et al*. showed that 1,3-diureidocalix[4]arenes are blocked in a pinched cone conformation due to intramolecular hydrogen bonds.[14] The presence of four amide groups instead of esters, as reported previously in other systems,[8] should ensure a much stronger cation binding at the lower rim.[1]

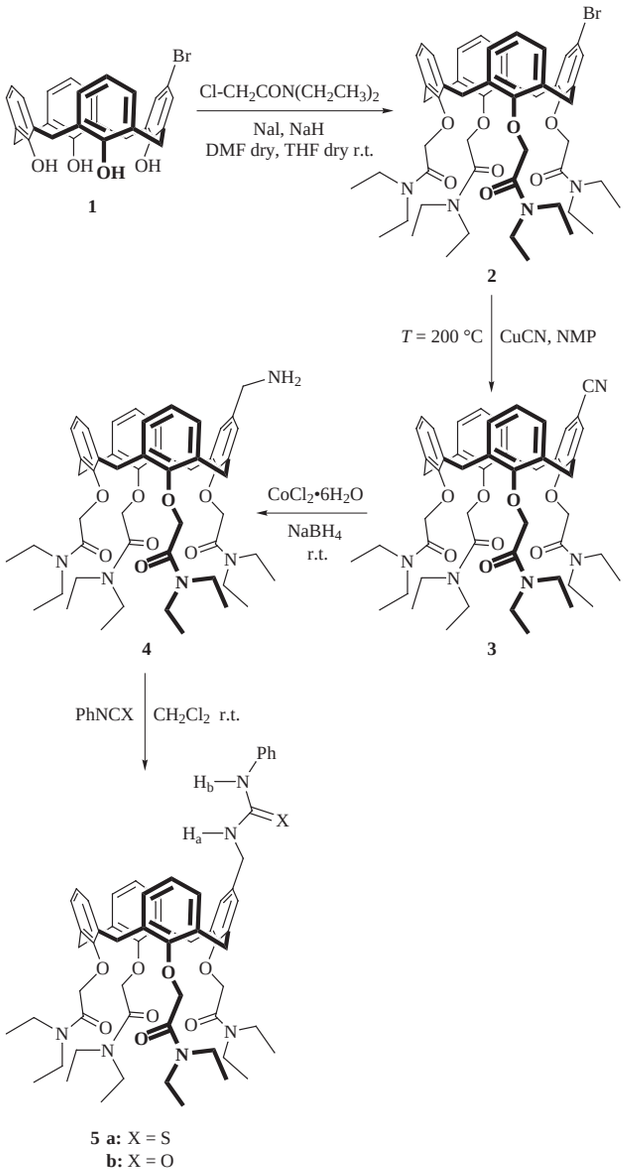
Results and discussion

Synthesis and conformational properties of the receptors 5 and 9

The synthesis of receptors **5a**,**b** was performed through the reaction sequence depicted in Scheme 1 starting from the previously reported monobromocalix[4]arene (**1**).[10] The reaction of **1** with α-chloro-*N*,*N*-diethylacetamide and NaH in THF–DMF gave compound **2** fixed in the cone conformation. The Br/CN exchange was performed with CuCN at 200 °C in *N*-methylpyrrolidinone (NMP) giving compound **3** which was subsequently reduced to the monoamino derivative **4** using $NaBH_4$ in the presence of $CoCl_2$, a methodology which allows the reduction of nitriles in the presence of amide groups.[15] The monothiourea receptors **5a**,**b** were obtained in nearly quantitative yields by reacting **4** with phenylisothiocyanate or phenylisocyanate and purified using reversed phase column chromatography (C18, eluent methanol). The ^1H NMR spectra of **5a**,**b** in $CDCl_3$ or in [$^2H_6$]DMSO, clearly show a cone conformation and a pattern typical of monosubstituted derivatives (two AX system for the $ArCH_2Ar$ protons, two doublets and two singlets for the OCH_2CO groups). Moreover, they are concentration independent in both solvents, strongly suggesting that these compounds are monomeric in solution. The NH protons of receptor **5a** give a singlet at $\delta = 7.53$ ppm and a triplet at $\delta = 5.94$ ppm in $CDCl_3$, which are shifted to 9.46 and 7.85 ppm in [$^2H_6$]DMSO. The low field signal is attributed to the NH near the phenyl substituent (NH_b in Scheme 1), while the high field triplet is correlated, in the COSY spectrum, with the $ArCH_2$ doublet and is attributed to NH_a.

We also synthesized the monothiourea tetramide **9** having the anion binding group directly linked to the aromatic nucleus (Scheme 2). The tetra(diethylamide)calix[4]arene **6**[16] was selectively mononitrated under mild conditions to give **7** which was reduced to the monoamino derivative **8** with $SnCl_2$ in ethanol. Reaction of **8** with phenylisothiocyanate gave the monothiourea receptor **9** in good yields.

The ^1H NMR spectrum of **9** in [$^2H_6$]DMSO shows two signals at $\delta = 9.30$ and 9.07 ppm corresponding to the NH protons. The



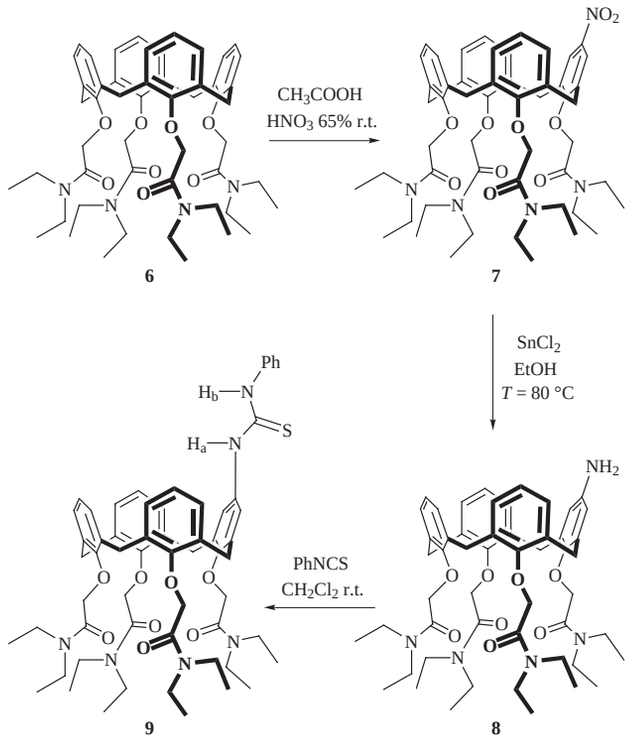
Scheme 1 Synthesis of compounds **5a**,**b**

absence of a methylene spacer between the calixarene and the thiourea gives a similar acid strength and hydrogen bonding properties to the two NH protons and, consequently, their signals are very close in the NMR spectrum. They were assigned through a two-dimensional NOESY spectrum which clearly indicates that the signal at $\delta = 9.30$ ppm (NH_a) correlates with the singlet of the calixarene aromatic proton, while the signal at $\delta = 9.07$ ppm (NH_b) correlates with the doublet of the *ortho* aromatic protons of the phenyl substituent.

Complexation studies

Since receptors **5a**,**b** and **9** were designed for the simultaneous complexation of cations and anions and should improve the extraction and transport of salts through liquid membranes, we initially tested their ability to dissolve solid salts in $CDCl_3$. Stoichiometric amounts of solid sodium salts (chloride, dihydrogenphosphate, acetate and β-naphtholate) were easily dissolved in $CDCl_3$ upon stirring with a 10^{-3} M solution of ligands **5** and **9**.

Several signals of the ligands were shifted upon complexation: in particular those of the methylene protons α to the amide groups (OCH_2CONR_2) moved to higher field and those of the thiourea groups were shifted downfield. On the basis of previous results on other systems[8,17] these data were taken as evidence that both the cation and anion coordination sites are



Scheme 2 Synthesis of compound **9**

involved in complexation and that compounds **5** and **9** behave as ditopic receptors. This binding is strong enough to compensate for the unfavorable cation–anion separation, which presumably takes place in our, as well as in other,[8] ditopic receptors.

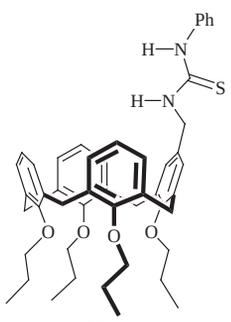
To obtain more quantitative data on the recognition properties of receptors **5** and **9** towards anions (especially carboxylates) we performed NMR titration experiments in [$^2H_6$]DMSO solution. The first titration was made by adding variable amounts of $NaBPh_4$ to a solution of hosts **5** and **9** in [$^2H_6$]-DMSO. In all cases no shift of the (thio)urea NH protons was observed indicating that the large BPh_4^- anion is not bound. On the other hand, two sets of signals for the protons of the host (in particular for the aromatic, the $ArCH_2Ar$ and the OCH_2CONR_2 protons) are visible until the host : guest ratio reaches the 1 : 1 value, when only the signals of the complex are visible. This indicates that the sodium ion is encapsulated at the lower rim and that the complex is in low exchange with the free ligand on the NMR timescale, as previously observed in other cases.[17] This observation allowed us also to study the effect of sodium ion complexation on the anion binding since it was possible to saturate the cationic binding site, by adding one equivalent of $NaBPh_4$, and then evaluate the association constants with anions by adding variable amounts of tetrabutylammonium salts (TBA). These titration experiments were repeated also on the free ligands **5a** and **9** and in all cases the downfield shifts of the urea NH protons induced by complexation were analyzed. In agreement with the reported lower hydrogen bonding ability of the urea group compared with thiourea,[18] very small shifts were observed in the titration of receptor **5b** with a few anions; therefore host **5b** was not investigated further. For **5a** and TBA acetate the 1 : 1 binding stoichiometry was verified by the continuous variation method (Job plot). The association constants were determined by a non-linear regression analysis of the titration data and are reported in Table 1, together with the literature pK_a values of carboxylic acids in DMSO.[19]

The association constants obtained with uncomplexed hosts **5a** and **9** are of the same order of magnitude of those reported previously[10] for the monotopic receptor **10**. The K_a values are in most cases $<10^3$ M^{-1}, but we have to consider that they are

Table 1 Association constants (K_a/M^{-1})[a] from ^{1}H NMR titration experiments in [$^2H_6$]DMSO at 300 K

		Host				
Anion[b]	pK_a[c]	**10**[d]	**5a**	**Na$^+$⊂5a**	**9**	**Na$^+$⊂9**
Br^-	—	<5	<5	*e*	<5	*e*
Cl^-	—	<5	160	*e*	10	*e*
Benzoate	10.90	170	175	190	250	1100
Formate	10.26	*e*	*e*	*e*	230	*f*
Acetate	12.60	92	470	330	940	1200
Propionate	*g*	*e*	280	215	250	1000
n-Butyrate	12.8	339	220	100	*e*	*e*
Isobutyrate	*g*	*e*	400	200	260	800

[a] Average of at least three independent experiments (accuracy ±10%). [b] As tetrabutylammonium salt. [c] Of the corresponding carboxylic acids in DMSO, data from ref. 19. [d] Data from ref. 10. [e] Values not determined. [f] A substantial broadening of the NH signals was observed. [g] Data not available.



10

determined in DMSO, a very competitive solvent for host : guest interactions based on hydrogen bonding. However the differences between the carboxylate anions are, in some cases, significant and worth discussing. The influence of the calixarene apolar cavity on anion binding seems to be more pronounced with the previously synthesized host **10**, which shows selectivity for benzoate and isobutyrate over acetate. With the new hosts **5a** and **9** the association constants roughly follow the anion basicity order (acetate > benzoate) revealed by the pK_a values of the corresponding carboxylic acids in DMSO (Table 1).[19] Probably, in hosts **5a** and **9** the repulsion between the four amide groups at the lower rim of the calixarene reduces the size of the apolar cavity, compared with ligand **10**, and then is not able to accommodate the aromatic nucleus of the guest. Therefore in this case, only the interaction between the urea NHs and the bidentate carboxylate anion stabilizes the complex, whereas the calixarene moiety exerts a negative steric effect. This is indicated by the lower value of the association constant found for alkanoates having a longer aliphatic chain, compared with acetate. With the exception of isobutyrate, higher values of the association constants were found for receptor **9** which has one NH of the thiourea unit directly linked to the aromatic nucleus. This is in agreement with the higher hydrogen bonding ability of aromatic thioureas compared with aliphatic ones.[18] Interestingly peak selectivity is found in the case of monothiourea **9** and acetate anion which seems to take advantage both of the reduced dimension of the cavity and of the higher acidity of the thiourea NH groups.

The complexation of sodium ion at the lower rim induces a different behaviour on the anion coordination properties of hosts **5a** and **9**. A small decrease in the association constants for all the anions is observed in the case of **Na$^+$⊂5a** compared with free **5a**, whereas the complexation of sodium ion causes a substantial increase in the association constants of all anions with **Na$^+$⊂9** compared with free ligand **9**. A corresponding decrease in the selectivity for acetate anion is also observed in this case. The complexation of sodium ion by the four amide groups at the lower rim of the calix has two general effects. One is to rigidify the calix[4]arene apolar cavity[20] and the second one is to induce a small electron-withdrawing effect on the thiourea group at the upper rim. A methylene group inserted between the aromatic nucleus and the thiourea unit in the host **5a** prevents the electron-withdrawing effect being 'felt' by NH protons and the anion binding properties of this complexed host do not change substantially with respect to the free ligand **5a**. On the other hand, in the case of host **9** the complexation of the sodium ion at the lower rim causes an increase in the hydrogen bonding ability of the urea NH group directly bound at one aromatic nucleus, causing an increase in the association constants with all carboxylate anions. This phenomenon is similar to the enhanced carboxylate binding recently observed in urea amide-based receptors with internal Lewis acid coordination,[21] although in our case the coordination of the hard sodium cation does not occur at the soft thiocarbonyl groups of the urea, but to the amide groups at the lower rim of the calix.

Conclusions

In conclusion, in this paper we have synthesized three novel ditopic receptors by introducing selectively a (thio)urea unit at the upper rim of calix[4]arene sodium-selective tetramide ligands in the cone conformation. They are able to complex simultaneously sodium ion at the lower and anions at the upper rim which greatly improves the solubility of sodium carboxylates in apolar solvents. Quantitative binding studies in [$^2H_6$]-DMSO solution performed on the thiourea derivatives allowed us to evaluate the effect of cation complexation on anion binding. It was found that if the urea unit is linked directly to the aromatic nucleus, the sodium complexation increases the efficiency but decreases the selectivity in anion binding, whereas little effect is observed when a CH_2 spacer is introduced between the urea unit and the calixarene aromatic nucleus. The new ligand synthesized could be useful for the efficient extraction and transport of carboxylate salts through liquid membranes.

Experimental

General

Melting points were determined on an Electrothermal apparatus in sealed capillaries under nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AMX400 (^{1}H : 400 MHz) and AC300 (^{1}H : 300 MHz, ^{13}C : 75 MHz) spectrometers using TMS as internal standard. δ Values are given in ppm; *J* values are given in Hz. IR spectra were recorded on a Perkin-Elmer 298 spectrometer. Mass spectra were obtained in EI or CI (CH_4) modes on a Finnigan Mat SSQ710 spectrometer. TLC was performed on precoated silica gel plates Merck 60 F_{254}, while silica gel Merck 60 (230–240 mesh) was used for preparative column chromatography. All solvents were purified with standard procedure; dry solvents were obtained by literature methods and stored over molecular sieves. All the reactions were carried out under nitrogen atmosphere.

5-Bromo-25,26,27,28-tetrahydroxycalix[4]arene (**1**)[10] and 25,26,27,28-tetra[(*N*,*N*-diethylaminocarbonyl)methoxy]calix-[4]arene (**6**)[16] were synthesized as described in the literature.

As verified also by other authors,[22] the elemental analysis of calixarenes are very often incorrect because of inclusion of solvent molecules and cannot be considered an appropriate criterion of purity; nevertheless, the identity of the compounds reported has been proven by their spectral data.

5-Bromo-25,26,27,28-tetrakis[(*N*,*N*-diethylaminocarbonyl)-methoxy]calix[4]arene (2).† A solution of 0.7 ml (5.4 mmol) of 2-chloro-*N*,*N*-diethylacetamide and 0.8 g (5.4 mmol) of NaI

† As an example of the IUPAC nomenclature of the calixarenes described in this paper, compound **2** would be named 1^5-bromo-1^2,3^2,5^2,7^2-tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy]-1,3,5,7(1,3)-tetrabenzacyclooctaphane.

was stirred under nitrogen in dry DMF (2 ml) and dry THF (10 ml) at reflux temperature for 1 h. After cooling to room temperature 0.3 g (0.6 mmol) of monobromocalix[4]arene (**1**) and 0.2 g (7.1 mmol, 50% suspension in oil) of NaH were added and the reaction mixture was stirred for 15 h. The reaction was quenched adding 60 ml of 1 M HCl (CAUTION!) and the precipitate filtered under reduced pressure. Pure product **2** (0.23 g, 41%) was obtained by chromatography (silica gel : ethylacetate–triethylamine 9 : 1).

Mp 144–146 °C; ν_{max}/cm^{-1} 1659 (C=O) and 1466 (C–N); δ_H(300 MHz; $CDCl_3$) 1.13 (24 H, m, NCH_2CH_3), 3.18 (2 H, d, *J* 13.7, $ArCH_{eq}Ar$), 3.25 (2 H, d, *J* 13.7, $ArCH_{eq}Ar$), 3.32 (16 H, m, NCH_2CH_3), 4.83 (2 H, s, OCH_2CO), 4.85 (2 H, s, OCH_2CO), 4.87 (2 H, d, *J* 15.5, OCH_2CO), 4.95 (2 H, d, *J* 15.5, OCH_2CO), 5.20 (2 H, d, *J* 13.7, $ArCH_{ax}Ar$), 5.23 (2 H, d, *J* 13.7, $ArCH_{ax}Ar$), 6.50 (2 H, d, *J* 7.5, ArH), 6.60 (2 H, s, ArH) and 6.62–6.74 (7 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 12.9, 14.1 (q, NCH_2CH_3), 31.7 (t, $ArCH_2Ar$), 39.7, 40.7 (t, NCH_2CH_3), 71.2, 71.4, 71.6 (t, OCH_2CO), 114.8 (s, *p*-Br-Ar), 122.2, 122.4 (d, *p*-Ar), 128.2, 128.4, 128.9, 130.7 (d, *m*-Ar), 134.4, 135.1, 136.8 (s, *o*-Ar), 156.3, 156.6 (s, *ipso*-Ar) and 168.2, 168.5 (s, CO); *m*/*z* 957 (100%, M + 2) and 955 (95, M).

5-Cyano-25,26,27,28-tetrakis[(*N*,*N*-diethylaminocarbonyl)-methoxy]calix[4]arene (3). CuCN (0.1 g, 1.3 mmol) was added to a solution of **2** (0.6 g, 0.7 mmol) in 5 ml of *N*-methyl-2-pyrrolidinone (NMP) and the reaction was stirred at 200 °C under nitrogen for 20 h. After cooling below 80 °C, the reaction was quenched (CAUTION!) by addition of a $FeCl_3$ solution (0.2 g, 1.3 mmol) in 12 ml of 3 M HCl. The mixture was stirred at room temperature for 1 h, then the precipitate was collected on a Buchner funnel under reduced pressure. The pure product (0.29 g, 51%) was obtained by chromatography (silica gel : ethylacetate–triethylamine 9 : 1).

Mp 171–174 °C; ν_{max}/cm^{-1} 2220 (CN); δ_H(300 MHz; $CDCl_3$) 1.12 (24 H, m, NCH_2CH_3), 3.20 (2 H, d, *J* 13.7, $ArCH_{eq}Ar$), 3.23 (2 H, d, *J* 13.8, $ArCH_{eq}Ar$), 3.33 (16 H, m, NCH_2CH_3), 4.80 (2 H, s, OCH_2CO), 4.89 (2 H, d, *J* 15.5, OCH_2CO), 4.95 (2 H, s, OCH_2CO), 5.03 (2 H, d, *J* 15.5, OCH_2CO), 5.13 (2 H, d, *J* 13.7, $ArCH_{ax}Ar$), 5.29 (2 H, d, *J* 13.8, $ArCH_{ax}Ar$), 6.47 (2 H, d, *J* 7.6, ArH), 6.73 (2 H, s, ArH), 6.74–6.78 (5 H, m, ArH) and 6.84 (2 H, dd, *J* 2.3, 7.1, ArH); δ_C(75 MHz; $CDCl_3$) 12.9, 14.1 (q, NCH_2CH_3), 31.6 (t, $ArCH_2Ar$), 40.0, 40.9 (t, NCH_2CH_3), 71.2, 71.6, 71.7 (t, OCH_2CO), 106.8 (s, CN), 122.6, 122.8 (d, *p*-Ar), 128.2, 128.5, 129.3 (d, *m*-Ar), 134.0, 134.3, 135.4, 136 (s, *o*-Ar), 156.4 (s, *ipso*-Ar) and 167.8, 168.1, 168.6 (s, CO); *m*/*z* 902 (100%, M).

5-Aminomethyl-25,26,27,28-tetrakis[(*N*,*N*-diethylamino-carbonyl)methoxy]calix[4]arene (4). To a stirring solution of monocyanocalix[4]arene **3** (1.5 g, 1.7 mmol) dissolved in 125 ml of methanol were added 0.8 g (3.3 mmol) of $CoCl_2 \cdot 6H_2O$ and 0.1 g (3.6 mmol) of $NaBH_4$. The reaction mixture was stirred at room temperature under nitrogen for 5 h, then quenched with 50 ml of NH_4OH solution (30%) and extracted with CH_2Cl_2 (3 × 75 ml). The combined extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford pure compound **4** (1.21 g, 80%).

Mp 92–94 °C; ν_{max}/cm^{-1} 3430 (NH); δ_H(300 MHz; $CDCl_3$) 1.08 (24 H, m, NCH_2CH_3), 3.20 (4 H, d, *J* 13.6, $ArCH_{eq}Ar$), 3.30 (16 H, m, NCH_2CH_3), 4.49 (2 H, s, CH_2NH_2), 4.82 (2 H, s, OCH_2CO), 4.90–4.85 (4 H, m, OCH_2CO), 4.93 (2 H, s, OCH_2CO), 5.19 (2 H, d, *J* 13.6, $ArCH_{ax}Ar$), 5.20 (2 H, d, *J* 13.6, $ArCH_{ax}Ar$), 6.37 (2 H, s, ArH) and 6.46–6.72 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 12.9, 14.2 (q, NCH_2CH_3), 31.8 (t, $ArCH_2Ar$), 39.7, 40.7 (t, NCH_2CH_3), 45.9 (t, CH_2NH_2), 71.2, 71.5 (t, OCH_2CO), 121.8, 122.0 (d, *p*-Ar), 126.8, 128.1, 128.4, 128.5 (d, *m*-Ar), 134.4 (s, *p*-NH_2CH_2Ar), 134.5, 134.5, 134.7, 135.0 (s, *o*-Ar), 155.3 and 156.5 (s, *ipso*-Ar) and 168.3, 168.6 (s, CO); *m*/*z* 907 (100%, M).

5-Nitro-25,26,27,28-tetrakis[(*N*,*N*-diethylaminocarbonyl)-methoxy]calix[4]arene (7). To a stirring solution of tetra-[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[4]arene **6** (0.2 g, 0.2 mmol) in 20 ml of CH_2Cl_2 was slowly added a mixture of 65% HNO_3 (0.4 ml, 9.2 mmol) and glacial acetic acid (0.3 ml, 5 mmol). The reaction mixture was stirred at room temperature under nitrogen for 24 h. Then the solution was poured into 30 ml of water and extracted with 30 ml of CH_2Cl_2. The organic layer was washed with water (3 × 40 ml) and the solvent was removed under reduced pressure. Pure compound **7** (0.09 g, 41%) was purified by chromatography (silica gel : ethylacetate–triethylamine 9 : 1).

Mp 85–87 °C; δ_H(300 MHz; $CDCl_3$) 1.11 (24 H, m, NCH_2CH_3), 3.25 (4 H, d, *J* 14.0, $ArCH_{eq}Ar$), 3.32 (16 H, m, NCH_2CH_3), 4.81 (2 H, s, OCH_2CO), 4.82 (2 H, d, *J* 11.5, OCH_2CO), 4.98 (2 H, d, *J* 11.5, OCH_2CO), 5.04 (2 H, s, OCH_2CO), 5.16 (2 H, d, *J* 14.0, $ArCH_{ax}Ar$), 5.32 (2 H, d, *J* 14.0, $ArCH_{ax}Ar$), 6.41 (1 H, t, *J* 7.5, ArH), 6.46 (2 H, d, *J* 7.5, ArH), 6.70 (2 H, t, *J* 7.3, ArH), 6.76 (4 H, dd, *J* 2.2, *J* 7.3, ArH) and 7.35 (2 H, s, ArH); δ_C(75 MHz; $CDCl_3$) 12.9, 14.2 (q, NCH_2CH_3), 31.6, 32.0 (t, $ArCH_2Ar$), 39.7, 40.7 (t, NCH_2CH_3), 71.2, 71.4, 71.7 (t, OCH_2CO), 122.2, 122.6, 123.6, 124.0 (d, *p*-Ar), 128.3, 128.5, 129.2, 129.6 (d, *m*-Ar), 134.0, 134.3, 135.2, 135.9 (s, *o*-Ar), 142.3 (s, *p*-NO_2-Ar), 156.4 (s, *ipso*-Ar) and 167.6, 168.3 (s, CO); *m*/*z* 922 (100%, M).

5-Amino-25,26,27,28-tetrakis[(*N*,*N*-diethylaminocarbonyl)-methoxy]calix[4]arene (8). To a stirring solution of mononitro-derivative **7** (0.2 g, 0.2 mmol) in 30 ml of ethanol were added 0.4 g (1.7 mmol) of $SnCl_2 \cdot 2H_2O$. The reaction mixture was heated under nitrogen for 6 h and then quenched by pouring it into 50 ml of ice–water. A 1 M KOH solution was added until pH 9 and then the aqueous phase was extracted with chloroform (2 × 30 ml). The combined organic layers were washed with H_2O (3 × 50 ml) and dried over $MgSO_4$. Compound **8** (0.13 g, 69%) was isolated by evaporation of the solvent under reduced pressure and used without further purification.

Mp 83–85 °C; δ_H(300 MHz; $CDCl_3$) 1.10 (24 H, m, NCH_2CH_3), 3.11 (2 H, d, *J* 13.6, $ArCH_{eq}Ar$), 3.24 (2 H, d, *J* 13.6, $ArCH_{eq}Ar$), 3.30–3.35 (16 H, m, NCH_2CH_3), 4.76 (2 H, s, OCH_2CO), 4.90 (6 H, m, OCH_2CO), 5.13 (2 H, d, *J* 13.6, $ArCH_{ax}Ar$), 5.23 (2 H, d, 13.6, $ArCH_{ax}Ar$), 5.91 (2 H, s, ArH) and 6.55–6.68 (9 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 12.9, 14.2 (q, NCH_2CH_3), 31.8 (t, $ArCH_2Ar$), 39.7, 40.7 (t, NCH_2CH_3), 71.3, 71.6 (t, OCH_2CO), 115.5 (s, *p*-NH_2-Ar), 121.7, 121.9 (d, *p*-Ar), 128.2, 128.3 (d, *m*-Ar), 134.7, 134.9, 135.2 (s, *o*-Ar), 140.5 (s, *ipso*-$ArNH_2$), 149.7, 156.5 (s, *ipso*-Ar) and 168.5 (s, CO); *m*/*z* 893 (100%, M).

General procedure for the synthesis of (thio)urea receptors 5a,b and 9

To a stirred solution of monoamino derivative (**4** or **8**) (0.3 mmol) in 60 ml of dry CH_2Cl_2 was added phenyl isocyanate or phenyl isothiocyanate (0.3 mmol). The reaction mixture was stirred at room temperature under nitrogen for 2 h, then the solvent was removed and the crude compound was purified by C_{18} reversed-phase column chromatography (using methanol eluent).

5-[(*N*′-Phenylthioureido)methyl]-25,26,27,28-tetrakis-[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[4]arene (5a). (Yield 91%); mp 95–97 °C; ν_{max}/cm^{-1} 3300 (NH) and 1660 (CO); δ_H(300 MHz; $CDCl_3$) 1.10 (24 H, m, NCH_2CH_3), 3.18 (2 H, d, *J* 13.7, $ArCH_{eq}Ar$), 3.21 (2 H, d, *J* 13.5, $ArCH_{eq}Ar$), 3.31 (16 H, m, NCH_2CH_3), 4.49 (2 H, d, *J* 4.8, $ArCH_2NHCS$), 4.82–4.90 (8 H, m, OCH_2CO), 5.21 (2 H, d, *J* 13.5, $ArCH_{ax}Ar$), 5.22 (2 H, d, *J* 13.7, $ArCH_{ax}Ar$), 5.94 (1 H, bs, $ArCH_2NHCS$), 6.42 (2 H, s, ArH), 6.44–6.67 (9 H, m, ArH), 7.16 (2 H, d, *J* 7.5, *o*-PhH), 7.27 (1 H, t, *J* 7.5, *p*-PhH), 7.41 (2 H, t, *J* 7.5, *m*-PhH) and 7.53 (1 H, s, CSNHPh); δ_H(300 MHz; [$^2H_6$]DMSO) 1.01 (24 H, m, NCH_2CH_3), 3.14 (2 H, d, *J* 13.4, $ArCH_{eq}Ar$), 3.16 (2 H, d, *J* 13.4, $ArCH_{eq}Ar$), 3.27 (16 H, m, NCH_2CH_3), 4.44 (2 H, d, *J* 4.5, $ArCH_2NHCS$), 4.83 (4 H, s, OCH_2CO), 4.91 (4 H, s, OCH_2CO), 5.08 (2 H, *J* 13.4, $ArCH_{ax}Ar$), 5.10 (2 H, d, *J* 13.4,

$ArCH_{ax}Ar$), 6.43–6.47 (11 H, m, ArH), 7.11 (1 H, t, *J* 7.8, *p*-PhH), 7.31 (2 H, t, *J* 7.8, *m*-PhH), 7.42 (2 H, d, *J* 7.8, *o*-PhH), 7.85 (1 H, bs, $ArCH_2NHCS$) and 9.46 (1 H, s, CSNHPh); δ_C(75 MHz; [$^2H_6$]DMSO) 12.9, 14.1 (q, NCH_2CH_3), 31.3, 31.4 (t, $ArCH_2Ar$), 47.2 (t, $ArCH_2NHCS$), 71.3, 71.7 (t, OCH_2CO), 121.9 (d, *p*-Ar), 123.1 (d, *o*-Ph), 124.1 (d, *p*-Ph), 127.7, 128.0, 128.3 (d, *m*-Ar), 128.5 (d, *m*-Ph), 131.5 (s, *m*-Ph), 134.0, 134.5, 134.8, 135.0 (s, *o*-Ar), 139.3 (s, *ipso*-Ph), 142.3 (s, *p*-$NHCH_2Ar$), 155.7, 156.2, 156.6 (s, *ipso*-Ar), 167.6, 167.9 (s, CO) and 180.4 (s, CS); *m*/*z* 906 (100%, M-PhNCS).

5-[(*N*′-Phenylureido)methyl]-25,26,27,28-tetrakis-[(*N*,*N*-diethylaminocarbonyl)methoxy]calix[4]arene (5b). (Yield 95%); mp 110 °C; ν_{max}/cm^{-1} 3300 (NH) and 1660 (CO); δ_H(400 MHz; [$^2H_6$]DMSO) 1.02 (12 H, m, NCH_2CH_3), 1.10 (12 H, m, NCH_2CH_3), 3.13 (2 H, d, *J* 13.2, $ArCH_{eq}Ar$), 3.16 (2 H, d, *J* 13.2, $ArCH_{eq}Ar$), 3.30 (16 H, m, NCH_2CH_3), 4.02 (2 H, d, *J* 5.6, $ArCH_2NHCS$), 4.77 (4 H, s, OCH_2CO), 4.91 (2 H, s, OCH_2CO), 4.92 (2 H, s, OCH_2CO), 5.08 (4 H, d, *J* 13.2, $ArCH_{ax}Ar$), 6.32 (1 H, t, *J* 6.0, ArH), 6.46 (2 H, t, *J* 7.2, ArH), 6.50 (2 H, s, ArH), 6.62–6.68 (5 H, m, ArH), 6.75 (2 H, d, *J* 7.3, ArH), 6.89 (1 H, t, 7.0, *p*-PhH), 7.22 (2 H, t, *J* 7.0, *m*-Ph), 7.38 (2 H, d, *J* 7.0, *o*-PhH), 8.39 (1 H, bs, $ArCH_2NHCS$) and 8.63 (1 H, s, CSNHPh); δ_C(75 MHz; [$^2H_6$]DMSO) 12.9, 14.1 (q, NCH_2CH_3), 31.4 (t, $ArCH_2Ar$), 39.5 (t, NCH_2CH_3), 71.4, 71.7 (t, OCH_2CO), 117.7 (d, *o*-Ph), 118.2 (d, *p*-Ph), 121.0, 121.9 (d, *m*-Ar), 127.5, 128.1, 128.3, 128.7 (d, *p*-Ar), 133 (d, *m*-Ph), 134.1, 134.2, 134.9, 135.1 (s, *o*-Ar), 140.5 (s, *ipso*-Ph), 155.1, 155.6, 156.3, 156.7 (s, *ipso*-Ar) and 167.7, 168.1 (s, CO); *m*/*z* 1025 (16%, M) and 906 (100, M-PhNCO).

5-(*N*′-Phenylthioureido)-25,26,27,28-tetrakis[(*N*,*N*-diethyl-aminocarbonyl)methoxy]calix[4]arene (9). (Yield 61%); mp 130–132 °C; δ_H(400 MHz; [$^2H_6$]DMSO) 1.03 (12 H, t, *J* 6.1, NCH_2CH_3), 1.11 (12 H, t, *J* 6.8, NCH_2CH_3), 3.14 (2 H, d, *J* 13.2, $ArCH_{eq}Ar$), 3.16 (2 H, d, *J* 13.3, $ArCH_{eq}Ar$), 3.28 (16 H, m, NCH_2CH_3), 4.82 (2 H, s, OCH_2CO), 4.84 (2 H, s, OCH_2CO), 4.88 (4 H, s, OCH_2CO), 5.10 (2 H, d, *J* 13.3, $ArCH_{ax}Ar$), 5.13 (2 H, d, *J* 13.2, $ArCH_{ax}Ar$), 6.45 (1 H, t, *J* 7.3, ArH), 6.53 (2 H, d, *J* 7.3, ArH), 6.59 (2 H, t, *J* 7.4, ArH), 6.66 (2 H, m, ArH), 6.70 (4 H, m, ArH), 7.12 (2 H, t, *J* 7.5, *p*-PhH), 7.32 (2 H, t, *J* 7.5, *m*-PhH), 7.41 (2 H, d, *J* 7.5, *o*-PhH), 9.07 (1 H, s, PhNH) and 9.30 (1 H, s, ArNH); δ_C(75 MHz; [$^2H_6$]DMSO) 12.9, 14.1 (q, NCH_2CH_3), 31.3 (t, $ArCH_2Ar$), 39.7 (t, NCH_2CH_3), 71.4, 71.6 (t, OCH_2CO), 121.9 (d, *o*-Ph), 123.7, 123.8, 124.3 (d, *p*-Ar), 125.9 (d, *p*-Ph), 128.0, 128.3 (d, *m*-Ar), 132.6 (d, *m*-Ph), 134.4, 134.6, 134.7 (s, *o*-Ar), 139.3 (s, *ipso*-Ph), 153.8, 156.3, 156.4 (s, *ipso*-Ar), 167.7, 167.8 (s, CO) and 178.9 (s, CS); *m*/*z* 934 (60%, M-PhNH) and 892 (100, M-PhNHCS).

Determination of association constants

Association constants (K_a) were measured by ^{1}H NMR titration experiments. Receptors $Na^+\subset$**5a** and $Na^+\subset$**9**, used for the titration experiments, were obtained by mixing directly in [$^2H_6$]DMSO **5a** or **9** and an equimolar amount of $NaBPh_4$. Stock solutions of host and guest in [$^2H_6$]DMSO at different concentrations were prepared and mixed together in the NMR tube in various molar ratios. ^{1}H NMR spectra were recorded at 300 K and the chemical shift of the NH protons were plotted against guest concentration. Non-linear regression analyses allowed the determination of K_a.

Acknowledgements

Financial contributions from MURST and from CNR are acknowledged. We also thank CIM (Centro Interdipartimentale Misure) for the use of the NMR and mass spectrometry instruments.

References

1 For recent review articles on calixarenes, see V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713; A. Pochini and R. Ungaro, in *Comprehensive Supramolecular Chemistry*, ed. F. Vögtle, Elsevier, Oxford, 1996, vol. 2, pp. 103–142.
2 F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 1609; P. D. Beer and P. Schmitt, *Curr. Opin. Chem. Biol.*, 1997, **1**, 475; M. M. G. Antonisse and D. N. Reinhoudt, *Chem. Commun.*, 1998, 443.
3 J. L. Atwood, K. T. Holman and J. W. Steed, *Chem. Commun.*, 1996, 1401; P. D. Beer, *Chem. Commun.*, 1996, 68; J. Scheerder, J. F. J. Engbersen and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bays*, 1996, **115**, 307.
4 E. Fan, S. A. Van Arman, S. Kincaid and A. D. Hamilton, *J. Am. Chem. Soc.*, 1993, **115**, 370; B. C. Haman, N. R. Branda and J. Rebek, Jr., *Tetrahedron Lett.*, 1993, **34**, 6837; S. Nishizawa, P. Buhlmann, M. Iwao and Y. Umezawa, *Tetrahedron Lett.*, 995, **36**, 6483; P. Buhlmann, S. Nishizawa, K. P. Xiao and Y. Umezawa, *Tetrahedron*, 1997, **53**, 1647.
5 J. Scheerder, M. Fochi, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 7815.
6 J. Scheerder, J. F. J. Engbersen, A. Casnati, R. Ungaro and D. N. Reinhoudt, *J. Org. Chem.*, 1995, **60**, 6448.
7 D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 3683.
8 J. Scheerder, J. P. M. van Duynhoven, J. F. J. Engbersen and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1090.
9 D. M. Rudkevich, J. D. Mercer-Chalmers, W. Verboom, R. Ungaro, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1995, **117**, 6124.
10 A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro and D. N. Reinhoudt, *Gazz. Chim. Ital.*, 1996, **126**, 99.
11 K. D. Shimizu and J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA*, 1995, **92**, 12 403.
12 O. Mogck, V. Böhmer and W. Vogt, *Tetrahedron*, 1996, **52**, 8489.
13 O. Mogck, E. F. Paulus, V. Böhmer, I. Thondorf and W. Vogt, *Chem. Commun.*, 1996, 2533.
14 J. Scheerder, R. Vreekamp, J. F. J. Engbersen, W. Verboom, J. P. M. van Duynhoven and D. N. Reinhoudt, *J. Org. Chem.*, 1996, **61**, 3476.
15 T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji and Z. Imai, *Tetrahedron Lett.*, 1969, **52**, 4555.
16 A. Casnati, Y. Ting, D. Berti, M. Fabbi, A. Pochini, R. Ungaro, D. Sciotto and G. G. Lombardo, *Tetrahedron*, 1993, **49**, 9815.
17 A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, G. D. Andreetti, G. Calestani and F. Ugozzoli, *J. Incl. Phenom. Mol. Recogn.*, 1988, **6**, 119.
18 F. G. Bordwell, D. J. Algrim, J. A. Harrelson, *J. Am. Chem. Soc.*, 1988, **110**, 5903.
19 K. Izutsu, *Acid-Base Dissociation Constants in Dipolar Aprotic Solvents*, Blackwell Scientific Publications, Oxford, 1990.
20 A. Arduini, W. M. McGregor, D. Paganuzzi, A. Pochini, A. Secchi, F. Ugozzoli and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, 1996, 839.
21 M. P. Hughes and B. D. Smith, *J. Org. Chem.*, 1997, **62**, 4492.
22 V. Böhmer, K. Jung, M. Schön and A. Wolff, *J. Org. Chem.*, 1992, **57**, 790; C. D. Gutsche and K. A. See, *J. Org. Chem.*, 1992, **57**, 4527.

Paper 8/01762J
Received 3rd *March* 1998
Accepted 6th *April* 1998