Tetrahedron 66 (2010) 4987–4993

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Calix[5]crown-3-based heteroditopic receptors for *n*-butylammonium halides

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ARTICLE INFO

Article history:
Received 15 January 2010
Received in revised form
28 March 2010
Accepted 10 May 2010
Available online 13 May 2010

Keywords:
Calixarenes
Heteroditopic receptors
Ion pair complexation
X-ray
Urea

ABSTRACT

(1,3)-Calix[5]arene-crown-3 derivatives **1a** and **1b**, bearing either three *n*-butylureido or 1-naphthylureido moieties at the lower rim, respectively, have been synthesised. Their cationic and anionic binding domains have been investigated by a combination of 1D- and 2D-NMR, UV/vis absorption and fluorescence and ESIMS techniques. Complexation data show that the attachment of 1-naphthyl groups at the lower rim of calix[5]crown-3 **1b** dramatically increases its anion-binding ability over the *n*-butyl-bearing derivative **1a**. Overall, both **1a** and **1b** act as highly efficient heteroditopic receptors for *n*-butylammonium halides and in so doing bind these salt species—as spatially-separated ions—much more effectively than the single ionic components. The X-ray crystal structure of the pivotal tris-[2-(2-chloroethoxy) ethoxy]-calixcrown precursor **2** is also reported.

1. Introduction

Neutral receptors, when confronted with the task of binding a charged substrate, need to override the natural tendency of the target ion to form an ion pair with its counterion, especially when this competition takes place in low polarity organic solvents.[1] Supramolecular chemists have, therefore, begun to concentrate a great deal of their energy on the design of receptors capable of simultaneously recognizing and synergically binding both ions of a given salt species, in an attempt to minimise the drawback of ion pairing effects. Hence, ion pair recognition[2] has revolved around two different strategic approaches (as depicted in cartoon fashion in Fig. 1): (i) supramolecular systems, which employ selected combinations of anion and cation receptors[3] and (ii) molecular systems, where binding sites with opposite affinity are suitably arranged on a single molecular scaffold.

As far as the latter systems are concerned, the same goal can be attained either by chiselling receptors that can bind the ion paired salt (or multiple ions in a cascade fashion)[4] such that the ions are in contact, so as to avoid Coulombic energy penalties resulting from the separation of the ion pair,[5] or by aiming at the concomitant but independent complexation of both ions as a spatially-separated ion pair[6] that, despite their relative distance, may still contribute to the stabilisation of the entire complex as a result of an overall charge neutrality and long-range electrostatic attraction effects.

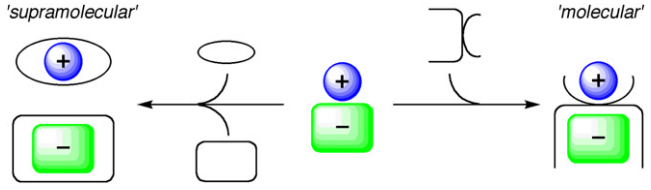

Figure 1. Cartoon representation of 'supramolecular' (binary host) and 'molecular' (heteroditopic host) ion pair receptors.

Whichever the design and nature of the system of choice, all the reported studies have demonstrated that the complexation of both ionic partners confers real advantages in terms of substrate solubilisation, extraction or transport under interfacial conditions.[4,6] Whether or not these receptors truly act with positive cooperativity is still a matter of debate. Indeed, very recent studies have shown that competition between complexation and ion pairing, in some cases, may result in a decrease, rather than an increase, of the binding ability of a given ditopic receptor, or even operate in opposite directions for the two ionic counterparts of a salt.[7]

Although the final outcome is not predictable in advance, the challenge of designing and synthesising tailor-made receptors for specific target salts can hardly be turned down. To date, heteroditopic architectures have been constructed by using the most diverse

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0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.05.021

families of cation[8] and anion[9] receptors, even though these studies have mainly been targeted at inorganic salts. Calixarenes[8a] have often been selected as convenient molecular building blocks for the construction of this type of receptor.[10] Our attention has, in this context, been focused on the development of a number of calix[5]arene-based heteroditopic[11] and -tetratopic[12] receptors capable of binding organic salts derived from biologically relevant amines (2-phenylethylamine, cadaverine, γ-aminobutanoic acid (GABA), lysine methyl ester).

As an extension of these studies we report herein a full account of the structural features and the binding properties of two heteroditopic receptors belonging to a new calix[5]crown-3 family very recently reported.[11b]

2. Results and discussion

2.1. Synthesis and structural elucidation

Earlier, we have reported on the reaction of calix[5]arenes with 2-(2-chloroethoxy)ethyl tosylate, which results in the formation of doubly- or mono-crown-3-bridged derivatives.[13] These compounds bear either one or three chloroalkyl pendant groups (as in the case of **2**, vide infra), respectively, and as a result they represent excellent precursors for the synthesis of novel lower-rim functionalised calix[5]crowns. Our initial findings included ^{1}H NMR and computational data, which, along with the independent synthesis of some key intermediate products, allowed us to propose a preferential route for the regioselective formation of such derivatives, and to postulate the exact regiochemistry of the final products. Definitive evidence confirming this structural assignment is now provided by the solid-state structure of pentakis(methyl)-31,33,34-tris[2-(2-chloroethoxy)ethoxy]calix[5]arene-crown-3 (**2**).

Single crystals suitable for an X-ray investigation were obtained from CH_3CN. The crystal structure of **2** reveals the presence of a calix[5]crown molecule in the asymmetric unit of the monoclinic unit cell (Fig. 2). The macrocycle adopts a *cone-in*[14] conformation, with one of the five aryl rings (ring A) tilted significantly towards the interior of the cavity, and the two crown-3-bridged rings leaning outwards. The dihedral angles between the aromatic rings and the mean plane generated by the bridging methylene groups of the calixarene are 47.5(1)°, 152.4(1)°, 104.8(1)°, 86.0(1)° and 152.9(1)° (rings A–E, respectively).[15] The two $-OCH_2CH_2O-$ portions of the polyether bridge adopt *gauche* conformations (dihedral angles 57.1(5)° and 82.1(4)°). As a direct consequence, the methylene group closest to the *p*-tolyloxy ring E points towards the interior of the cavity, whereas the central oxygen atom[16] points away from it.

(1,3)-Bridged calix[5]arene-crown-3 **2** was used as the starting material for the synthesis of both heteroditopic receptors **1a** and **1b** (Scheme 1). According to the procedure previously employed for the synthesis of **1a**,[11b] conversion of **2** (via tris-phthalimido derivative **3**) into tris-amine compound **4**, followed by reaction with 1-naphthylisocyanate in $CHCl_3$, afforded tris-naphthylureido-calix[5]crown **1b** in a 16% isolated yield. The latter was characterised by NMR, ESIMS and elemental analysis.

In agreement with their C_s-symmetric *cone-in* conformations, calixcrowns **1a** and **1b** display the following characteristic ^{1}H and ^{13}C NMR features: (i) three diagnostically important AX systems (ratio 2:1:2) for the hydrogen atoms of the bridging methylene groups and resonances for the relevant carbons in the range 28–32 ppm[17] and (ii) high-field resonances for the hydrogen atoms of the *p*-tolyl ring A (δ=6.15–6.33 (2H) and 1.67–1.71 (3H) ppm, respectively), consistent with the leaning of this ring towards the interior of the cavity (self-filling).[18]

2.2. ^{1}H NMR binding studies

The binding properties of tris-*N*-substituted ureido-calix[5]arene-crown-3 derivatives **1a** and **1b** as heteroditopic receptors were investigated by means of ^{1}H NMR titration experiments, using *n*-butylammonium halides as substrates. Furthermore, to demonstrate that the concomitant binding of both ionic partners is more efficient than that of the single ions, the affinity of the two receptors for the cation (i.e., *n*-$BuNH_3^+$) and the anions (i.e., Cl^-, Br^- and I^-) were independently assessed in the presence of model substrates with weakly coordinating counterions (i.e., *n*-butylammonium hexafluorophosphate on the one hand, and tetra-*n*-butylammonium halides on the other).[19] The results of these studies are summarised in Table 1.

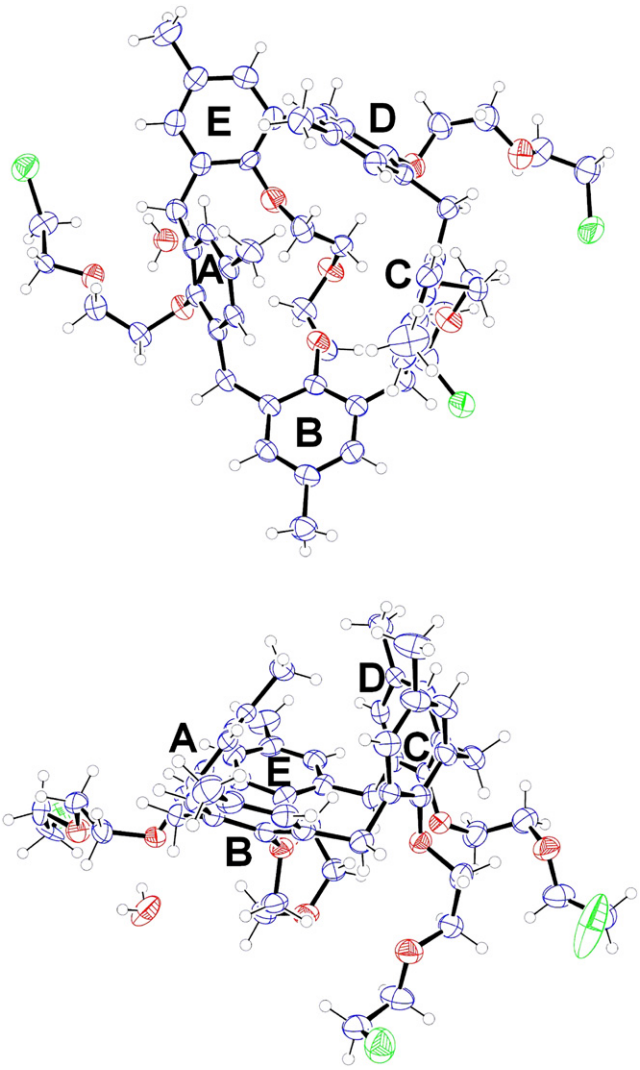
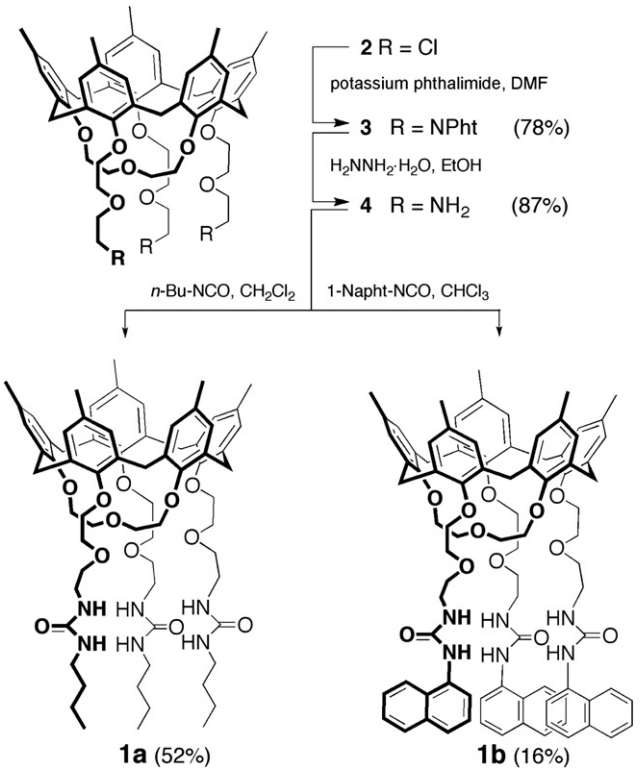


Figure 2. Orthogonal views of the asymmetric unit of the crystal, containing the calix[5]crown **2** and a water molecule in a site with 50% of statistical occupancy. Probability of the ORTEP ellipsoids is set to 50%. For the sake of clarity, only one of the two disordered conformations of the chloroethoxy moiety appended to ring A is shown.

Binding studies were routinely carried out by adding increasing amounts of the appropriate salt to a 1 mM solution of receptor (**1a** or **1b**) in CD_2Cl_2, so as to reach a 1:1 host/guest ratio. In the case of *n*-$BuNH_3^+PF_6^-$, host-guest complexation/decomplexation was judged to be slow on the NMR time scale on the basis of preliminary titration experiments, which, in the presence of [host]>[guest], revealed doubling of the calixcrown peaks (i.e., free and complexed). *endo*-Cavity inclusion of the target *n*-$BuNH_3^+$ cation was revealed by the appearance of high-field resonances (0.2 to −1.8 ppm) for the included *n*-butyl chain,[20] as a result of the shielding effect of the calixarene *p*-tolyl units. Furthermore, upon *n*-$BuNH_3^+$ binding, the peak assigned to the aromatic hydrogen atoms of the isolated *p*-tolyl unit



Scheme 1. Synthesis of the heteroditopic receptors **1a**,**b**.

A underwent a significant down-field complexation induced shift (CIS) (from 6.20 to 6.51 ppm for **1a** and from 6.11 to 6.45 ppm for **1b**, respectively), indicating that the cavity was 'opening-up' to make room for the incoming cationic guest. This behaviour is consistent with the *cone-in*/*cone-out* conformational rearrangement needed to reorganise the cavity upon *endo*-complexation.[21] For the two calix [5]crown-3 receptors under study (**1a**,**b**), cation binding was found to proceed with high conditional association constants (K_a=5.3±0.3×10^3 and 2.1±0.1×10^4 M^{-1}, corresponding to 65% and 70% complexation, respectively).

Compared to the *n*-BuNH$_3^+$ cation, the halide anion affinity for **1a**,**b** was found to be much lower (K_as in the range <5 to

Table 1
Conditional binding constants for receptors **1a**,**b** determined by ^{1}H NMR titration experiments (500 MHz, CD_2Cl_2, 298 K, [**1a**]=[**1b**]=1 mM)[a]

	1a	1b
n-BuNH$_3^+$[b]	5.3±0.3×10^3 M^{-1}	2.1±0.1×10^4 M^{-1}
Cl$^-$[c]	39±14 M^{-1}	577±66 M^{-1}
Br$^-$[c]	7±5 M^{-1}	178±15 M^{-1}
I$^-$[c]	<5 M^{-1}	27±2 M^{-1}
n-BuNH$_3$Cl	>10^{10} M^{-2}	>10^{10} M^{-2}
n-BuNH$_3$Br	>10^{10} M^{-2}	>10^{10} M^{-2}
n-BuNH$_3$I	>10^{10} M^{-2}	>10^{10} M^{-2}

[a] Values derived from the average of three independent measurements.
[b] Added as the PF_6^- salt.
[c] Added as the *n*-Bu$_4$N$^+$ salt.

577±66 M^{-1}) and, in all instances, complex formation/dissociation proceeded on a fast exchange regime on the NMR time scale. Anion binding appears to depend on: (i) the size and charge density of the halide ion (Cl$^-$>Br$^-$>I$^-$) and (ii) the nature of the substituents attached to the ureido binding site of the receptor. In line with the known behaviour of disubstituted ureas,[22] which accounts for *N*-aryl-*N*′-alkylureas being better anion receptors than *N*,*N*′-dialkylureas, tris-naphthylureido derivative **1b** turned out to bind halide anions more efficiently than tris-butylureido derivative **1a**.

When the three *n*-butylammonium halides were in turn added to the solutions of heteroditopic receptors **1a**,**b** (Figs. 3, S3 and S4, see Supplementary data) the differences in anion binding abilities levelled out. All the salts tested were bound with association constants higher than 10^{10} M^{-2} (corresponding to >95% complexation of both the cation and the anion). This outcome can easily be explained: once the *n*-BuNH$_3^+$ cation is included inside the calixarene cavity, each anion, freed from its counterion, becomes more readily available and consequently binds more efficiently to the ureido-bearing pendant chains. Likewise, the trapping of the anion facilitates the inclusion of the cation. Unlike 1:1 halide anion complexation/decomplexation (i.e., in the presence of *n*-Bu$_4$N$^+$X$^-$), which, as mentioned above, showed a fast exchanging profile on the NMR time scale, binding of the same anions upon ternary complex formation (i.e., in the presence of *n*-BuNH$_3^+$X$^-$) turned out to be slow. Accordingly, the spectra recorded in the presence of an excess of receptors **1a** and **1b** displayed distinct resonances for the NHs belonging to the free and complexed species. Table 2 shows the chemical shifts for the urea hydrogen atoms engaged in the

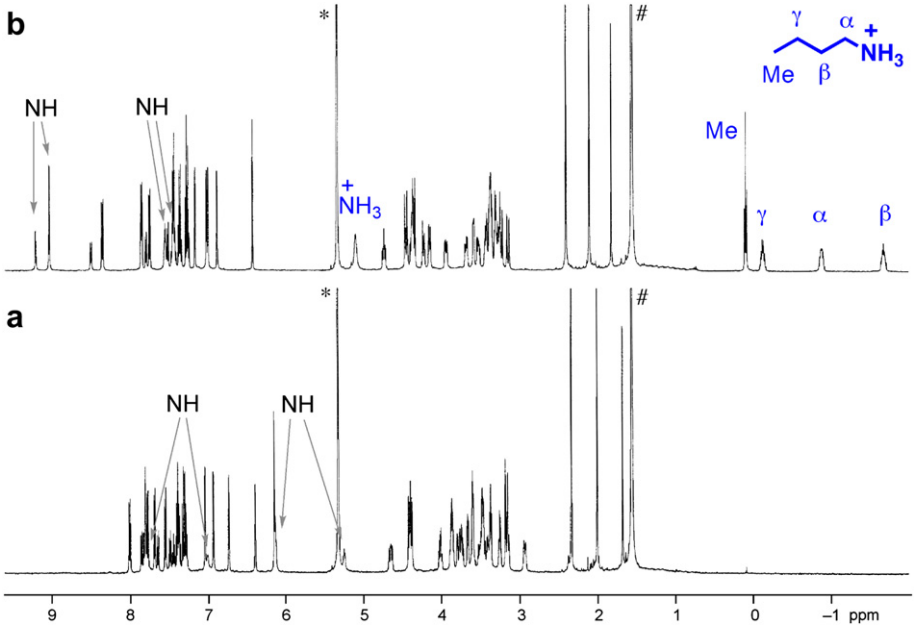


Figure 3. ^{1}H NMR spectra (500 MHz, CD_2Cl_2, 298 K, 1 mM) of: (a) **1b**; (b) [Cl$^-$⊂**1b**⊃*n*-BuNH$_3^+$]. *Residual solvent peaks. #H$_2$O.

Table 2
Chemical shifts (ppm) of the ureido NH resonances of the free receptors **1a**,**b** and their ternary complexes with *n*-$BuNH_3$+X^- (500 MHz, CD_2Cl_2, 298 K, 1 mM)

	δ (ppm)			
1a	5.50	5.30	4.93	4.77
[Cl^-⊂**1a**⊃*n*-$BuNH_3^+$]	6.71	6.51	6.46	6.13
[Br^-⊂**1a**⊃*n*-$BuNH_3^+$]	6.52	6.35	6.28	5.96
[I^-⊂**1a**⊃*n*-$BuNH_3^+$]	6.26	6.11	6.06	5.74
1b	7.82	7.04	6.18	5.46
[Cl^-⊂**1b**⊃*n*-$BuNH_3^+$]	9.19	9.02	7.82–7.86[a]	7.48–7.56[a]
[Br^-⊂**1b**⊃*n*-$BuNH_3^+$]	8.79	8.78	7.22–7.48[a]	7.06
[I^-⊂**1b**⊃*n*-$BuNH_3^+$]	8.55	8.40	7.03–7.08[a]	6.67

[a] Overlapping with the peaks of the naphthyl moieties. See Supplementary data for additional spectroscopic data on the ternary complexes.

formation of these ternary ion pair complexes. Interestingly, the CISs of these resonances decrease on going from chloride to iodide, mirroring the trend observed for the binding constant of these anions.

Qualitative evidence on the remarkable stability of these ternary ion pair complexes, as opposed to a 1:1 calix[5]crown/cation complex, came from positive mode ESIMS experiments (Fig. 4 and Fig. S7). Where [**1b**⊃*n*-$BuNH_3^+$]PF_6^- gave an intense peak at *m*/*z* 1512.3, corresponding to the **1b**⊃*n*-$BuNH_3^+$ ion, under similar conditions [Cl^-⊂**1b**⊃*n*-$BuNH_3^+$] did not produce any peak consistent with the presence of the above-mentioned 1:1 cationic complex, confirming that the overall-neutral ternary complex does not disassemble via the loss of a chloride ion under ESI experimental conditions.

2D ROESY experiments carried out on [Cl^-⊂**1a**⊃*n*-$BuNH_3^+$] and [Cl^-⊂**1b**⊃*n*-$BuNH_3^+$] provided additional information on the structural features of these ternary ion pair complexes (Fig. 5, Figs. S5 and S6). ROE correlations were observed among the hydrogen atoms of the *n*-butyl chain of the included guest and the *p*-tolyl moieties A, C and D. On the contrary, no through-space interactions

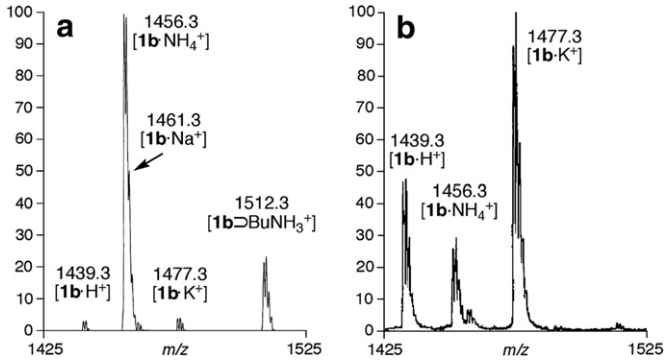


Figure 4. Sections of the ESIMS spectra of (a) [**1b**⊃*n*-$BuNH_3^+$]PF_6^-; (b) [Cl^-⊂**1b**⊃*n*-$BuNH_3^+$].

were detected for rings B and E, which are forced to lean outwards by the connecting crown-3 loop. Other correlations were observed between the cavity-included NH_3^+ group and the oxymethylene groups of the ethereal bridging chain. Upon complex formation, the NH_3^+ resonance experiences a larger CIS (i.e., stronger shielding) compared to that commonly observed for other calix[5]arene/alkylammonium complexes.[3f,23] Presumably, this upfield shift increase (from >7.5 ppm to 5.16±0.06 ppm, instead of 5.4–5.6 ppm) is associated with the ethereal loop occluding the bottom of the cavity of **1a**,**b** and in so doing preventing the *n*-$BuNH_3^+$ cation from reaching its normal position.

2.3. Absorption and fluorescence binding studies

The binding properties of receptor **1b** towards chloride and *n*-butylammonium ions were also investigated by absorption and fluorescence spectroscopy,[24] by taking advantage of the

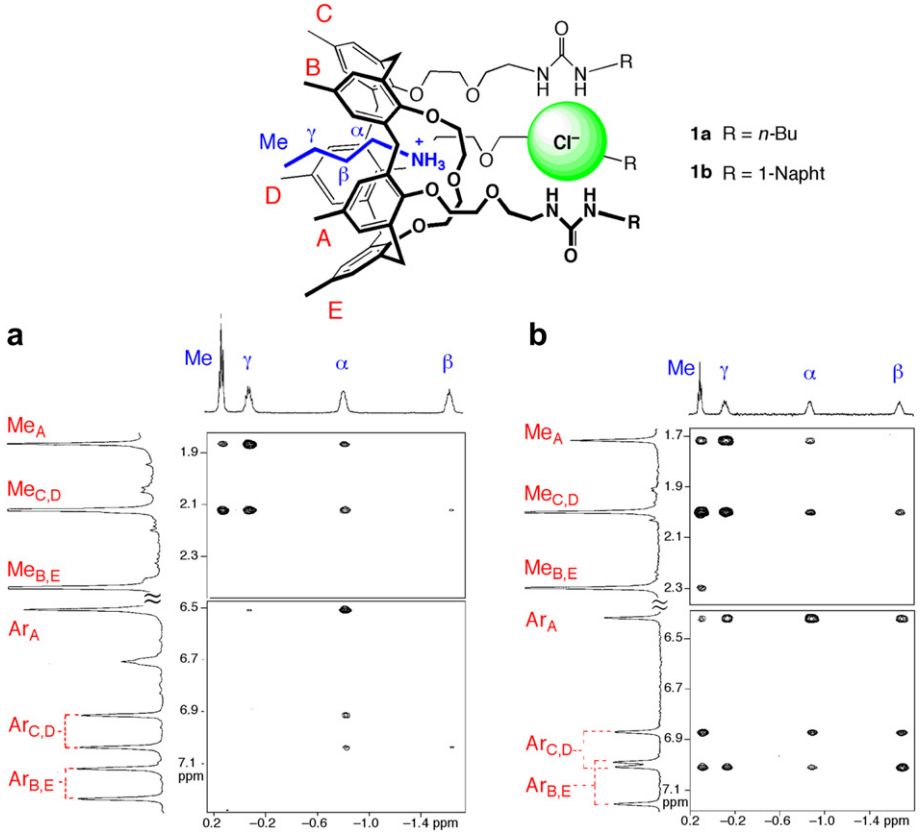


Figure 5. Sections of the 2D ROESY spectra (500 MHz, 298 K, CD_2Cl_2, 1 mM) of (a) [Cl^-⊂**1a**⊃*n*-$BuNH_3^+$]; (b) [Cl^-⊂**1b**⊃*n*-$BuNH_3^+$].

naphthalene moieties present at the lower rim of this calix[5] crown. The absorption spectrum of **1b** (Fig. 6A, trace a) is characteristic of a naphthylureido-containing species,[25] and in line with this, **1b** displays in emission (Fig. 6B, trace a) a strong band at 380 nm (τ=1.2 ns and ϕ=0.016). According to the fluorescence spectrum, the naphthyl pendant groups of **1b** are not engaged in $\pi-\pi^*$ stacking[26] and, as a result, no intramolecular excimer is observed.

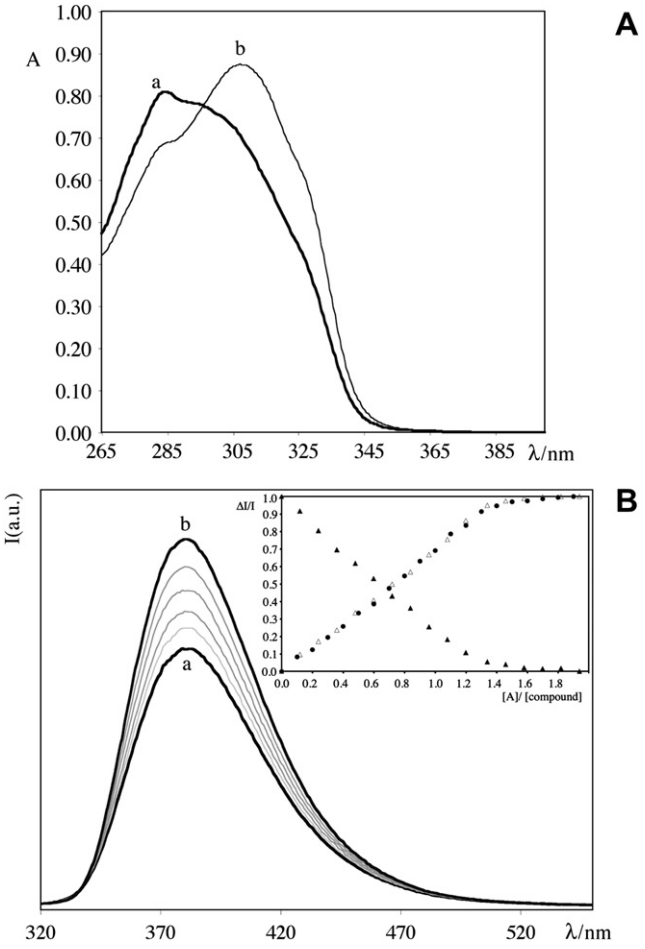


Figure 6. Absorption (top) and emission (bottom) spectra of **1b** (traces a, 0.04 mM in CH_2Cl_2) and corresponding spectra of **1b** in the course of and at the end (traces b) of the titration with *n*-$BuNH_3^+PF_6^-$. Inset: normalised titration curves obtained for **1b** from absorption and emission (excitation at 296 nm) measurements upon addition of *n*-$BuNH_3^+PF_6^-$ (in CH_2Cl_2, 298 K). Absorption values at 283 nm (full triangles) and 307 nm (open triangles); emission intensity values at 380 nm (full circles).

Absorption and emission titration experiments were performed in CH_2Cl_2, by adding successive aliquots of either chloride or *n*-butylammonium ions (in the form of *n*-$Bu_4N^+Cl^-$ or *n*-$BuNH_3^+PF_6^-$, respectively) to a 0.04 mM solution of **1b** up to a 2:1 M ratio. Addition of 2.0 equiv of Cl^- ions did not significantly modify either the absorption or the emission spectrum of **1b**, whereas, addition of the same amount of *n*-$BuNH_3^+$ ions caused substantial spectral changes (see Fig. 6). In particular, the absorption band centred at 284 nm decreased in intensity and concomitantly a new band at 307 nm appeared (Fig. 6A, trace b). The emission band centred at 380 nm underwent a half-fold increase in intensity and its excited state lifetime and quantum yield also varied (τ=1.8 ns and ϕ=0.02, respectively), suggesting that both radiative and non-radiative constants were affected. These spectral changes likely depend on a series of electronic effects caused by the conformational change of the host molecule upon substrate binding and/or the interaction of the *n*-butylammonium cation with the oxygen atoms of the calixcrown.

The normalised titration curves relative to the binding of *n*-$BuNH_3^+$ ions to receptor **1b**, obtained from the absorption and emission measurements (excitation at 296 nm), are shown in the inset to Figure 6B. Fitting of the absorption and emission data gave values of $7.9\pm0.2\times10^5$ and $3.16\pm0.4\times10^6$ M^{-1}, respectively, for the conditional binding constant of [**1b**$\supset$*n*-$BuNH_3^+$].[27] The apparent discrepancy observed between the values of the conditional binding constants determined by ^1H NMR and UV/fluorescence studies can be explained by taking into account the different concentration range in which the two sets of measurements were carried out (1 mM for NMR vs 0.04 mM for UV/fluorescence). Given that even alkylammonium salts with weakly coordinating anions are ion paired to some extent in non-polar organic solvents, it is evident that the more diluted solutions employed in the UV/fluorescence studies favoured the dissociation of the substrate (by providing a higher concentration of butylammonium ions available for complexation) and, as a result, conditional binding constants turned out to be higher.[1,23]

3. Conclusions

A new family of heteroditopic receptors, built around the calix[5]crown-3 framework and incorporating either alkyl- or aryl-substituted ureas, has been described and shown to complex, with high efficiency, alkylammonium halide salts. Such receptors act by placing each ion into its specific binding site, i.e., *n*-butylammonium cation into the calixarene cavity, and the halide anion into the pocket generated by the ureido-bearing pendant chains. ^1H NMR studies have provided clear-cut evidence that the binding of the entire salt species by these heteroditopic receptors is more efficient than that observed for the single ions. Furthermore, the presence of naphthyl groups allows for UV and fluorescence detection of the included guest(s). Future studies will be directed at the fine-tuning of these systems, with the aim of generating sensors for biologically relevant alkylammonium-bearing analytes.

4. Experimental section

4.1. General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or CD_2Cl_2, at 500 and 125 MHz, respectively, using the residual solvent peak as an internal standard. ^1H NMR peak assignments follow from 2D-COSY, 2D-TOCSY and C–H correlation experiments. ^{13}C NMR spectra were acquired with the attached proton test (APT) technique. Two-dimensional adiabatic ROESY spectra in CD_2Cl_2 were acquired with a standard pulse sequence over a sweep width of 6510 Hz using 1954 data points in the t_2 dimension and 256 increments in the t_1 dimension for different mixing times of τ_m=580 ms and 130 ms at 298 K. A total of 32 scans were collected for each t_1 increment with an acquisition time of 0.15 s followed by an additional relaxation delay of 2.5 s. ESI mass spectra were acquired on a Mariner ESI-TOF instrument (resolution >7,000) using $CHCl_3$/MeOH 4:1 (positive ion mode). CH_2Cl_2 was dried by standard methods prior to use; other chemicals were reagent grade and were used without further purification. Column chromatography was performed on silica gel (Merck, 230–400 mesh). All reactions were carried out under an argon atmosphere.

*4.1.1. 5,11,17,23,29-Pentakis(methyl)-31,33,34-tris-(2-(2-N-(N′-1-naphthylureido)ethoxy)ethoxy)-32,35-crown-3-calix[5]arene (**1b**).*

A solution of tris-aminocalix[5]arene-crown-3 **4** (226 mg, 0.24 mmol) and 1-naphthylisocyanate (136 mg, 0.80 mmol) in dry CH_2Cl_2 (20 mL) was stirred at room temperature under nitrogen for 3 h. The solvent was then evaporated, to give the crude product, which was purified by flash chromatography (AcOEt/CH_2Cl_2 5:1 v/v, then AcOEt) to give tris-ureidocalix[5]arene-crown-3 **1b** (54 mg, 16%) as a white solid; [Found: C, 73.94; H, 6.60; N, 5.81. $C_{89}H_{94}N_6O_{12}$ requires C, 74.25; H, 6.58; N, 5.84%]; δ_H ($CDCl_3$) 1.67, 2.01, 2.34 (s, ratio 1:2:2, C*H*$_3$, 15H), 2.86–2.95 (m, *bridge*-OC*H*$_2$, 2H), 3.11 and 4.34 (AX system, J=15.0 Hz, ArC*H*$_2$Ar, 4H), 3.11 and 4.36 (AX system, J=13.7 Hz, ArC*H*$_2$Ar, 2H), 3.14 and 4.38 (AX system, J=14.4 Hz, ArC*H*$_2$Ar, 4H), 3.23 (t, J=5.3, NC*H*$_2$, 2H), 3.28 (br t, OC*H*$_2$CH$_2$N, 2H), 3.32–3.48 (m, OC*H*$_2$, *bridge*-OC*H*$_2$ and NC*H*$_2$, 8H), 3.48–3.54 (br t, OC*H*$_2$CH$_2$N, 4H), 3.55–3.59 (br t, OC*H*$_2$, 2H), 3.65–3.72 (m, OC*H*$_2$ and *bridge*-OC*H*$_2$, 4H), 3.74–3.80 and 3.80–3.86 (2×m, OC*H*$_2$, 4H), 3.96–4.02 (m, OC*H*$_2$, 2H), 4.54–4.62 (m, *bridge*-OC*H*$_2$, 2H), 5.46 (br t, CH$_2$N*H*, 1H), 6.11 (s, Ar, 2H), 6.15–6.21 (m, CH$_2$N*H*, 2H), 6.33 (d, J=1.7 Hz, Ar, 2H), 6.67 (d, J=1.7 Hz, Ar, 2H), 6.88 (d, J=2.0 Hz, Ar, 2H), 7.00 (d, J=2.0 Hz, Ar, 2H), 7.14–7.28 (m, Napht and N*H*, 5H), 7.29–7.35 (m, Napht, 2H), 7.38 (br t, Napht, 1H), 7.46–7.51 (m, Napht, 3H), 7.57 (d, J=8.0 Hz, Napht, 1H), 7.63 (d, J=7.3 Hz, Napht, 2H), 7.71 (d, J=8.1 Hz, Napht, 2H), 7.75 (d, J=8.3 Hz, Napht, 1H), 7.80 (br s, N*H*, 2H), 7.85 (d, J=8.3 Hz, Napht, 1H), 7.94 (d, J=8.3 Hz, Napht, 2H); δ_C ($CDCl_3$) 20.6, 20.9, 21.1, 28.9, 29.1, 30.4, 40.0 (×2), 40.1, 68.5, 69.8 (×2), 70.3, 70.4 (×2), 71.8, 72.4, 72.9 (×2), 120.4 (×2), 121.9, 122.1 (×3), 124.4 (×2), 125.5, 125.7 (×10), 125.9, 126.0, 127.2 (×2), 127.8 (×2), 128.1 (×2), 128.2 (×3), 128.3 (×2), 128.9, 129.1 (×2), 131.3 (×2), 131.6 (×2), 132.4 (×2), 132.5, 132.7 (×2), 133.4 (×2), 133.6 (×3), 133.7 (×2), 133.8, 134.1 (×3), 134.2 (×3), 134.5 (×2), 134.8 (×2), 151.4 (×2), 151.6, 153.4 (×2), 157.0, 157.2 (×2); m/z (ESI) 1439.3 (100%, M·H$^+$), 1456.3 (69%, M·NH$_4^+$), 1477.3 (61%, M·K$^+$); mp: 142–145 °C (from AcOEt).

4.2. Complexation experiments

All spectra were recorded at 500 MHz and at 298 K. Percentages of complexation (required for the calculation of the corresponding conditional association constants, K_a) for the complexes of **1a**, **b** with n-BuNH$_3^+$X$^-$ salts (X$^-$=PF$_6^-$, Cl$^-$, Br$^-$, I$^-$) were determined by direct ^{1}H NMR analysis of the peak (host: ArH and NH; guests: α- and β-CH$_2$) intensity ratio of equimolar host/guest solutions. When the percentages of complexation found were higher than 95% (standard error ≤5%), K_a values for the ternary complexes were estimated to be >10^{10} M^{-2}. Samples were prepared by mixing together aliquots of stock solutions of host and guest; the resulting solutions were evaporated to dryness, and the residue redissolved in CD_2Cl_2, to obtain a final equimolar host/guest solution (1 mM in each). The following stock solutions were used: [calixarene]=[organic salt]=10 mM in $CHCl_3$/CH_3OH (1:1, v/v).

K_a values for the complexation of **1a**,**b** with n-Bu$_4$N$^+$X$^-$ (X$^-$=Cl$^-$, Br$^-$, I$^-$) were assessed by nonlinear treatment of the data obtained from ^{1}H NMR titration experiments. Samples were prepared by adding to a 0.5 mL solution of the host (6.6 mM in CD_2Cl_2) successive aliquots of a stock solution of the guest (58 mM in CD_2Cl_2) to a final volume of 1.0 mL. Eight values of δ_{obs} for the NH resonances were collected by keeping the [host] to [guest] ratio in the 1/0.45–1/8.8 interval. Nonlinear regression analysis of δ_{obs} vs [guest], using the WinEQNMR for Windows software package,[28] provided the K_a value.

Absorption and emission titrations experiments were performed on a solution of **1b** (CH_2Cl_2, 0.04 mM) by adding successive aliquots of n-BuNH$_3^+$PF$_6^-$ (CH_2Cl_2, 3 mM), to determine the affinity for n-butylammonium cations, or n-Bu$_4$N$^+$Cl$^-$ (CH_2Cl_2, 3 mM), to test the anion-binding domain. K_a values are averaged values obtained by fitting the data to conventional log K_a transitions by using SPECFIT.[27]

4.3. Crystal structure of 2

Crystals of **2** were obtained from a CH_3CN solution by slow evaporation of the solvent. They were protected by addition of Paratone before freezing at 100 K by a nitrogen stream. X-ray diffraction data collection was performed on a Bruker Nonius KappaCCD diffractometer using a copper rotating anode (λ=1.5418 Å) as the X-ray source and a CCD detector. Diffraction data were indexed and integrated using DENZO[29] and scaled with SCALEPACK.[29] The crystal has a monoclinic unit cell (space group: $P2_1/c$). Cell parameters and statistics of the scaling procedure are reported in Table S1.

The structure was solved by direct methods using SHELXS.[30] In the asymmetric unit, a calix[5]crown-3 molecule is present. Moreover, additional electron density in the asymmetric unit is due to the presence of a water molecule with an occupancy factor of 50%. A 2-chloroethyl group was found to be disordered over two different positions, each with occupancy factors of 50%. The structure was refined by full-matrix least-squares methods on F^2, using SHELX-97.[31] All non-hydrogen atoms were treated anisotropically. In the final refinement, hydrogen atoms were included at calculated positions, with the torsion angle of the methyl groups free to refine. The software XABS[32] was used to apply an empirical correction to the experimental intensities, in order to correct data for X-ray absorption. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 751118. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The authors are grateful to Dr. D. Garozzo and Dr. A. Messina (CNR–ICTP, Catania, Italy) for ESIMS spectra, and to Dr. G. Cafeo (Università di Messina, Italy), for her helpful advice.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.05.021. These data include MOL files and InChiKeys of the most important compounds described in this article.

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