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PAPER

Novel ion-pair receptors based on hexahomotrioxacalix[3]arene derivatives†

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A series of novel heteroditopic hexahomotrioxacalix[3]arene triamide receptors capable of binding an anion and cation simultaneously in a cooperative fashion has been prepared. The lower rim functionalized *cone*-hexahomotrioxacalix[3]arene derivatives *cone*-**5a–5d** bearing three amide groups were synthesized from *cone*-**3** by a stepwise reaction. The crystal structures of **5c** and **5d** and ^{1}H NMR studies in nonpolar solvents strongly indicate that a number of interesting intramolecular hydrogen bonding interactions exist in these receptors. The binding abilities of these compounds towards *n*-butylammonium chloride and bromide salts have been investigated using ^{1}H NMR titration experiments in $CDCl_3$ solvent. Owing to the 'flattened cone' conformations and intramolecular hydrogen bonding involving the amide NH and neighbouring O atoms in *cone*-**5a–5d**, the affinities toward *n*-Bu_4NX (X = Cl^- and Br^-) were weakened. However, it should be noted that triamides *cone*-**5a–5d** show a single selectivity for halide anions in the presence of *n*-$BuNH_3^+$ through intermolecular hydrogen bonding with the amide NH hydrogen atoms in the receptors in $CDCl_3$ solution. Association constants were calculated from the chemical shift changes of the amide protons.

Introduction

Calixarenes are a class of macrocyclic compounds widely used in supramolecular chemistry for the construction of receptors capable of complexation of charged or neutral molecules.[1] As calixarenes have a cavity-shaped architecture, they can provide useful building blocks for host–guest type receptors through appropriate modification. Hexahomotrioxacalix[3]arene derivatives with C_3 symmetry can selectively bind ammonium ions, which play an important role in both chemistry and biology.[2] Recently, we reported the construction of C_3 symmetrically functionalized hexahomotrioxacalix[3]arenes, which selectively recognized primary ammonium ions.[3]

Anion recognition, complexation and transportation were recognized only recently as a very important part of supramolecular chemistry. There are several different strategies used for anion complexation. Basically, the receptors can be divided into two main groups: (i) charged systems exploiting electrostatic interactions with positively charged species (*e.g.* polyammonium[4] and guanidinium salts, quaternary ammonium salts); (ii) neutral systems[5] using other kinds of interactions, such as donor–acceptor interactions (receptors based on Lewis acids), hydrogen bonds, hydrophobic effects *etc.*

The design and application of new heteroditopic receptor systems capable of the simultaneous coordination of both anionic and cationic guest species have recently attracted a great deal of interest, as these systems have the potential to act as salt solubilisation, extraction, and membrane transport agents.[6] In earlier work in this area, a number of receptors in which an anion and cation are bound separately within the receptor have been synthesized.[7] In these systems, the cation may be bound using a variety of common motifs, while the anion is coordinated using Lewis acidic, electrostatic, or hydrogen bonding interactions.[8] As ion-pair chemistry has developed, more efficient cooperatively selective receptors have been reported.[9] For example, Beer *et al.* reported that a novel heteroditopic calix[4]diquinone receptor[10] was capable of binding an anion and cation simultaneously in a cooperative fashion. It was shown only to recognize halide anions in the presence of a suitable co-bound cationic guest species, and displayed affinity for certain ion-pairs where no affinity for either of the free ions was observed. More recently, Jabin and co-workers described a new class of heteroditopic receptors based on calix[6]arene, in which hosts can selectively encapsulate organic ion-pairs in a cooperative way. In particular the complexation of the chloride anion by the tris-ureas, while thiourea can act as an allosteric effector for organic cations through induced fit and allosterically controlled processes.[11] Accordingly, interest in a *contact* ion-pair binding approach, wherein the anion and cation are bound essentially as one moiety, is particularly noteworthy as it avoids the energetically unfavorable separation of the two

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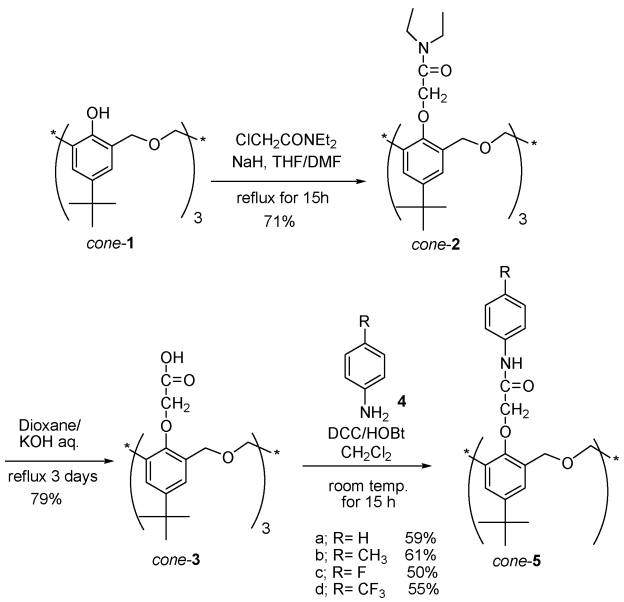
ions.[12] Importantly, the geometry of the ditopic receptor must be optimised so that the anion and cation binding sites are located in close proximity so as to enhance this interaction; incorrect orientation could lead to the ion-pair associating outside the receptor, or even to solvent-separated ion binding.

It is against this background that we describe herein the design, synthesis, crystal structure and binding properties of a series of ion-pair receptors, *cone*-**5a–5d**, based on hexahomotrioxacalix[3]arene, which demonstrate a dramatic enhancement of anion binding by a co-bound *n*-butylammonium ion.

Results and discussion

cone-[(*N*,*N*-Diethylaminocarbonyl)methoxy]hexahomotrioxacalix[3]arene, *cone*-**2**, was prepared by *O*-alkylation of **1** with *N*,*N*-diethylchloroacetamide in the presence of NaH in a refluxing solution of THF/DMF according to the reported procedures,[13] and *cone*-hexahomotrioxacalix[3]arene tricarboxylic acid, *cone*-**3**, was prepared by hydrolysis of *cone*-**2** with KOH aq. in a mixture of dioxane and water.[3c] *cone*-Hexahomotrioxacalix[3]arenetriamide derivatives (*cone*-**5a–5d**) were prepared by a condensation reaction of *cone*-**3** with the amino compounds (**4a–4d**) in the presence of DCC (dicyclohexylcarbodiimide) and HOBt (1-hydroxybenzotriazole) at room temperature for 15 h in CH_2Cl_2. The corresponding triamides *cone*-**5a–5d**, immobilised in the *cone* conformation, were obtained in 59, 61, 50 and 55% yields, respectively (Scheme 1).



Scheme 1

Conformation assignments for the new hexahomotrioxacalix[3]arene triamide derivatives *cone*-**5a–5d** are firmly established by the presence of the bridging methylene protons with a $\Delta\delta$ separation between H_{ax} and H_{eq} of $\Delta\delta$ 0.61, 0.59, 0.64 and 0.70 ppm respectively in the ^{1}H NMR spectra ($CDCl_3$). In the calix[4]arenes, the $\Delta\delta$ values of the $ArCH_2Ar$ protons have been correlated to the orientation of the adjacent aromatic rings.[14,15] The same findings were previously observed in homotrioxacalix[3]arenes.[16] Additionally, from the singlet peaks of the *tert*-butyl protons and calix aromatic protons for *cone*-**5a–5d**, it was established that the *cone* conformation was retained in the desired compounds. Thus, we can deduce that triamide derivatives of type *cone*-**5** prefer a flattened *cone* conformation, which might favor the formation of intramolecular hydrogen bonding between the NH and the neighboring O atoms of C=O groups.

Single crystal X-ray diffraction studies of the compounds *cone*-**5c** and *cone*-**5d** show very similar but rather deformed *cone* conformations (Fig. 1 and 2).† In the upper rim of *cone*-**5c**, the three *t*-Bu-phenyl rings are arranged with normals to the ring(b) and ring(c) rings only 25.6(8)° apart, and the third ring, of ring(a), lying at 67.8 and 57.0° to these. In the lower rim, the three phenyl rings are close to parallel and overlapping. This is achieved by considerable distortion from the potential C_3 symmetry and a very irregular 18-membered ring, through O(8a, 8b, 8c), around the centre of the calixarene system. Hydrogen bonding links each of the amide protons with the phenolic O-atoms of the same chain, *e.g.* H(13a)···O(1a), forming five-membered rings with N–H···O angles in the range 100.5–116.1°. Two of the NH groups make additional intramolecular hydrogen bonds, H(13b)···O(1c) and H(13c)···O(8b), in which the N–H···O angles are more acceptable at 154.1 and 175.9°.

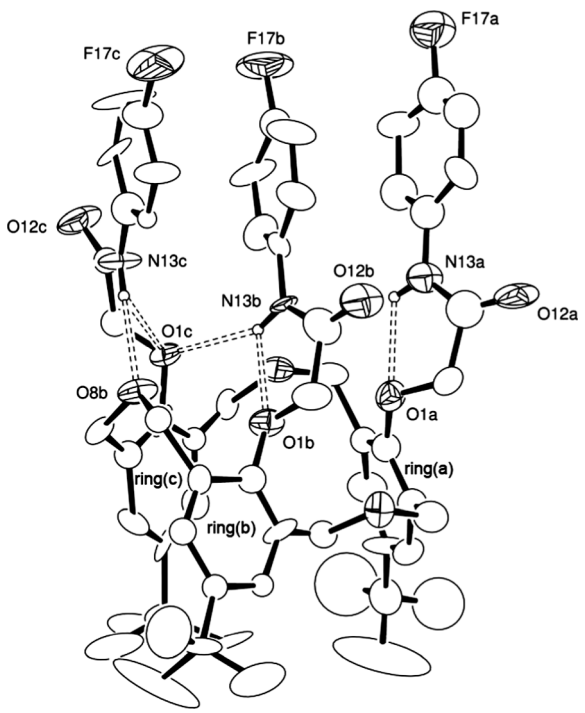


Fig. 1 X-Ray structure of compound *cone*-**5c**. The thermal ellipsoids are drawn at 50% probability; hydrogen atoms are omitted for clarity.

The 18-membered calixarene ring and the *t*-Bu-phenyl rings, *i.e.* the upper rim, in *cone*-**5d** have very similar conformations to those in *cone*-**5c**. The amide chains and fluoro-phenyl groups, however, have quite different orientations in the two crystals; the rings of ring(bl) and ring(cl) in *cone*-**5d** are close to parallel and slightly overlapping, but in a quite different orientation from those in *cone*-**5c**, and the ring(al) is rotated about 65° from them. Two of the NH groups in *cone*-**5d** form hydrogen bonds within the same chain, with five-membered rings, as in *cone*-**5c**. Both of these groups, and the third NH group, also form more linear hydrogen bonds, one

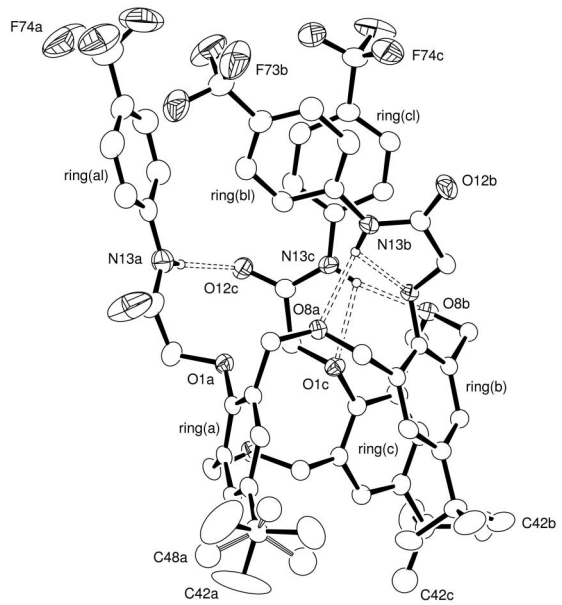


Fig. 2 X-Ray structure of compound *cone*-**5d**. The thermal ellipsoids are drawn at 50% probability; hydrogen atoms are omitted for clarity.

to a carbonyl O-atom and two to bridging ether O atoms; all are intramolecular. Based on these unequivocal results of the solid state structures of the receptors *cone*-**5c** and *cone*-**5d**, we believe that there might be two types of intramolecular hydrogen bonding systems in nonpolar solutions of *cone*-**5a–5d** (Fig. 3).

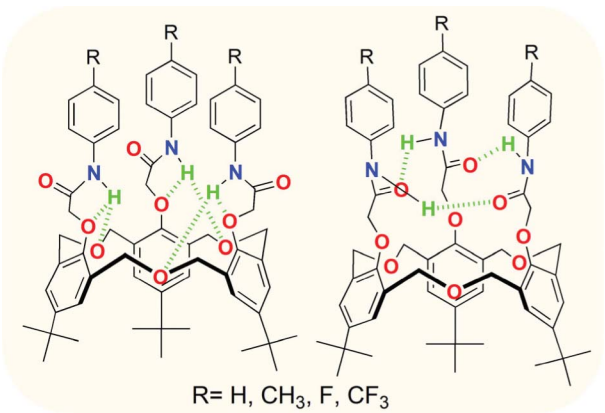


Fig. 3 Plausible intramolecular hydrogen bonding interactions of the receptors *cone*-**5a–5d** in $CHCl_3$ solution.

The artificial receptors, compounds *cone*-**5a–5d**, which have carbonyl amide groups in their structure, might form either intra- or inter-molecular hydrogen bonding, depending on the solvent. With hydrogen bonding acceptor solvents such as THF, dioxane, MeCN, and DMSO, the receptors can form intermolecular hydrogen bonding, whereas in nonpolar solvents such as $CHCl_3$, they form intramolecular hydrogen bonds (Fig. 3). When the concentration of compounds *cone*-**5a–5d** in $CDCl_3$ was diluted about 40 times, no changes in the chemical shifts were observed; this is attributed to the concentration-independent intramolecular hydrogen bonding formed in these compounds. However, in DMSO-d_6, the NH proton signals in compounds *cone*-**5a–5d** were shifted to lower field than in $CDCl_3$; this can be attributed to the intermolecular hydrogen bonding formed between the NH protons and solvent DMSO-d_6.

After adding an equivalent of *n*-$BuNH_3Cl$ or *n*-$BuNH_3Br$ to a solution of **5a–5d** (5×10^{-3} M) in $CDCl_3$ at 27 °C, the signals of the protons on the aromatic rings, ArCH_2O and ArOCH_2 were shifted dramatically to lower field (Fig. 4), and the NH proton signals of the encapsulated guest were shifted upfield, suggesting that binding of *n*-$BuNH_3^+$ occurred through the π-cavity formed by the three *t*-Bu-aromatic rings. This favourable binding is attributed to the π-effect of the aromatic rings (hydrophobic) and the driving force of H-bonds of *n*-$BuNH_3^+$ to the host due to both the host and the guest molecules having a suitable C_3-symmetrical structure. In order to achieve this symmetrical *cone* conformation, the intramolecular hydrogen bonding in the host is broken since such bonds would be impossible in this conformation (Scheme 2, middle). The change in conformation is evident from the downfield shift in the ^{1}H NMR spectra, for example the proton signal for the aromatic hydrogens shifts from δ = 6.90 ppm (Fig. 4a) to δ= 7.29 ppm (Fig. 4b). Generally, there are two modes for *cone*-**5a–5d** to bind with the *n*-butylammonium ion, *via* the lower rim through the substituent moieties **a–d** or *via* the upper rim through the π-cavity formed by the three *t*-Bu-aromatic rings. Also shown in Fig. 4, addition of *n*-$BuNH_3Cl$ or *n*-$BuNH_3Br$ to the solution of *cone*-**5d** (5×10^{-3} M) in $CDCl_3$ resulted in a significant downfield shift of the ^{1}H NMR signals of the NH protons on the receptor **5d**, from δ 9.71 ppm, Fig. 4(a), to δ 10.62 ppm, Fig. 4(b) and δ 10.23 ppm, Fig. 4(c), indicative that complexation of the halide guest was formed through hydrogen bonding.[17]

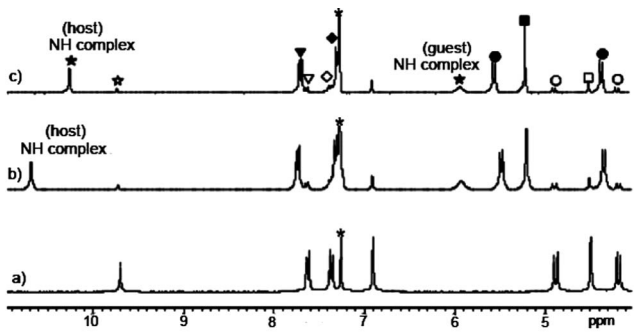
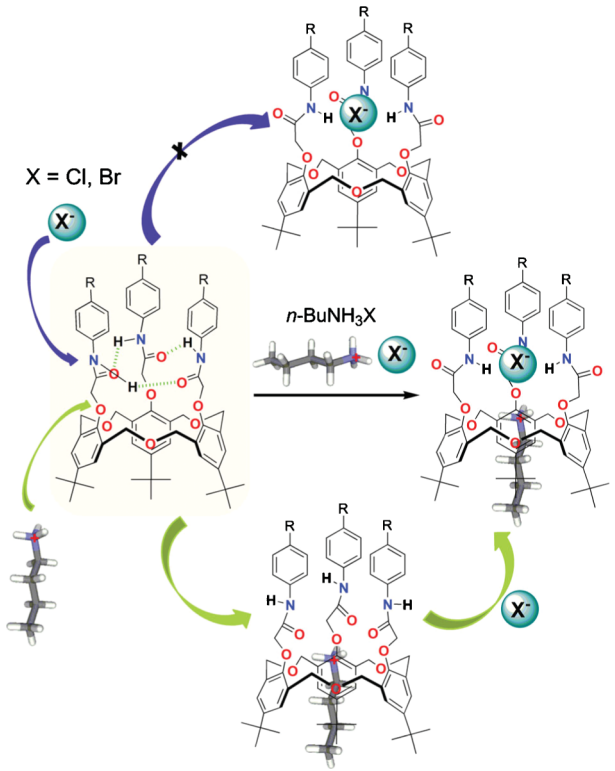


Fig. 4 Partial ^{1}H NMR spectra of *cone*-**5d** ($CDCl_3$, 5×10^{-3} M); (a) Free; (b) *cone*-**5d** ⊂ *n*-$BuNH_3Cl$; and (c) *cone*-**5d** ⊂ *n*-$BuNH_3Br$; * denotes the solvent peak; ★ ▼ ◆ ● and ■ denote the 'complexed' peaks; ☆ ▽ ◇ ○ and □ denote the 'uncomplexed' peaks.

However, upon addition of *n*-Bu_4NCl or *n*-Bu_4NBr to a 5×10^{-3} M solution of *cone*-**5a–5d** in $CDCl_3$, no complexation of halide anion was observed (Fig. 5b). This may be attributed to the intramolecular hydrogen bonding between the amide NH proton and the neighboring O atoms of C═O, O atoms of phenolic and bridging C–O–C moieties in *cone*-**5a–5d**, which distorts the geometry of the molecule greatly from C_3 symmetry and blocks the anion-binding site (Scheme 2, left and upper). Furthermore, the *n*-Bu_4N^+ ion, of course, cannot form hydrogen bonds with the host. Additionally, we have investigated host compounds of *cone*-**5a–5d** with *n*-Bu_4NCl in the presence of *n*-butylammonium picrate in $CDCl_3$ at 27 °C. For example, Fig. 5c shows the ^{1}H NMR spectrum of receptor *cone*-**5d** upon addition of 1.0 equiv. of



Scheme 2

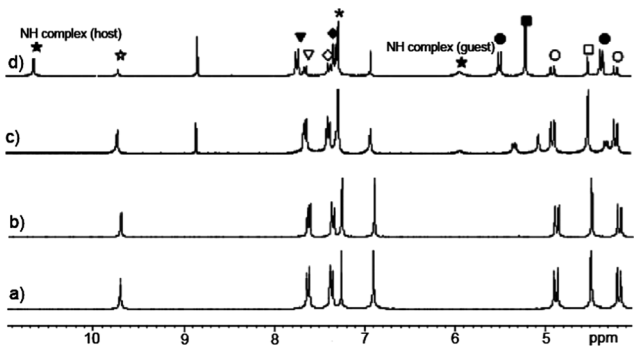


Fig. 5 Partial ^{1}H NMR spectra of *cone*-**5d** ($CDCl_3$, 5×10^{-3} M); (a) Free; (b) *cone*-**5d** ⊂ *n*-Bu_4NCl; (c) *cone*-**5d** ⊂ *n*-$BuNH_3Pic$; and (d) [*cone*-**5d** ⊂ *n*-$BuNH_3Pic$] ⊂ *n*-Bu_4NCl. * denotes the solvent peak; ★ ▼ ◆ ● and ■ denote the 'complexed' peaks; ☆ ▽ ◇ ○ and □ denote the 'uncomplexed' peaks.

n-butylammonium picrate in $CDCl_3$ solution; the spectral changes suggested that complexing between the host and guest occurred through the π-cavity (Scheme 2, lower). It also indicated that the intramolecular hydrogen bonding of the receptors *cone*-**5** was broken and the conformation changed to a C_3 symmetrical *cone* structure. This was evident from the downfield shift of the ^{1}H NMR signal for the aromatic hydrogens of receptor **5d** from $\delta = 6.93$ ppm (Fig. 5a) to $\delta = 7.29$ ppm (Fig. 5c). Interestingly, it should be noted that the addition of *n*-Bu_4NCl or *n*-Bu_4NBr to the (5×10^{-3} M) solution of the *cone*-**5d** ⊂ *n*-$BuNH_3^+$ resulted in a significant downfield shift of the ^{1}H NMR signals of the NH protons (Fig. 5d), indicating that complexation of the anionic guests with receptors occurred through hydrogen bonding.[16] These results suggested that *cone*-**5a–5d** can simultaneously complex *n*-$BuNH_3^+$ and Cl^- (or Br^-) anions, and that *n*-$BuNH_3^+$ cation complexation induces a structural change which is a prerequisite for anion complexation. This process resembles a heterotopic allosteric effect.[11]

Based on these observations, we investigated further the spectra of *cone*-**5a–5d** complexed with *n*-butylammonium halides, as shown in Fig. 4. With the addition of *n*-butylammonium halides, the proton peaks of *cone*-**5a–5d** were separated into 'complexed' and 'uncomplexed'. The integral intensity of proton peaks of the complex increased with an increasing amount of the *n*-butylammonium halide addition, and eventually changed completely to the complexed form. The downfield shift of NH protons can be attributed to their hydrogen bonding to the halide ion. As can be seen from Fig. 4, the chloride anion induces a larger downfield shift ($\Delta\delta = +0.97$ ppm) for the amide hydrogen of *cone*-**5** than the bromide anion ($\Delta\delta = +0.53$ ppm).

Furthermore, the 1 : 1 host–guest complexation process of *cone*-**5d** (host receptor, molecular weight R) with *n*-$BuNH_3Cl$ (guest, G) was investigated by electrospray ionization (ESI) mass spectrometry. The ESI MS spectrum produced by equivalent solutions of the receptor *cone*-**5d** and *n*-butylammonium chloride, Fig. 6, exhibited peaks corresponding to the 1 : 1 host–guest complex: [R + G – H – Cl=]$^+$, 1252.54, [R + G – Cl=]$^+$, 1253.54. Similar findings were also observed for the complexation of receptors *cone*-**5a–5c** with *n*-$BuNH_3X$ (X = Cl, Br and I). As the electronegativity of the halogen atom decreased along the series Cl, Br and I, the intensity of the hydrogen bonding formed between these anions and the NH protons should decrease in the same order. In fact, in the ^{1}H NMR spectrum of a mixture of *cone*-**5** and *n*-$BuNH_3X$, larger downfield chemical shifts in the complex of NH with Cl^- were observed compared with those seen with Br^- and I^-.

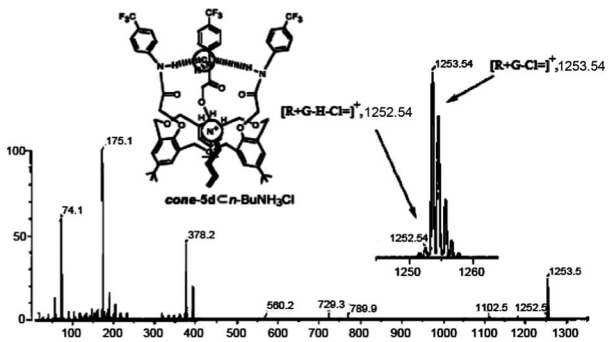


Fig. 6 Partial ESI mass spectra of *cone*-**5d** complex with *n*-$BuNH_3Cl$.

The chemical shifts of *cone*-**5a–5d** change on addition of the *n*-butylammonium ion, as shown in Fig. 7. For example, after adding an equivalent of *n*-$BuNH_3Cl$ to *cone*-**5d** in $CDCl_3$ at 27 °C, the methylene protons of $ArCH_2O$ and $ArOCH_2$ were dramatically shifted to lower field, indicating that the binding mode was occurring through the π cavity formed by the three *t*-Bu-aromatic rings. This binding is attributed to the π effect of the aromatic rings on the C–H protons of the alkyl groups, aided by the C_3-symmetric conformation of both the host and the guest moieties. With an excess of *n*-$BuNH_3Cl$, the free and encapsulated guest molecules were both clearly observed by ^{1}H NMR spectroscopy. The encapsulated guest signals were shifted upfield: CH_3 (0.95–0.33, $\Delta\delta = -0.62$ ppm), CH_3CH_2 (1.45–0.31, $\Delta\delta = -1.14$ ppm), $CH_3CH_2CH_2$ (1.77–0.27, $\Delta\delta = -1.5$ ppm), CH_2NH_3 (3.00–0.22, $\Delta\delta = -2.78$ ppm). The signals of the NH

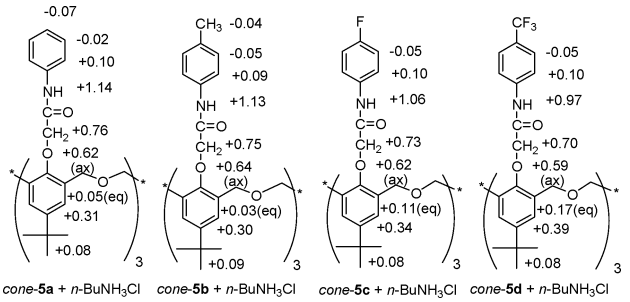


Fig. 7 Chemical shift changes ($\Delta\delta$) of *cone*-**5a–d** (5×10^{-3} M) induced in the presence of 1.0 equiv of *n*-$BuNH_3Cl$ (5×10^{-3} M) in $CDCl_3$ at 27 °C. A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (–) denotes a shift to higher magnetic field.

protons of the ammonium ion were also shifted upfield from δ = 8.79 ppm for the free ion to δ = 5.93 ppm on encapsulation ($\Delta\delta$ = –2.86 ppm), under the influence of the shielding resonance of the calix benzene rings.

As mentioned above, the $\Delta\delta$ difference between H_{ax} and H_{eq} of the $ArCH_2OCH_2Ar$ methylene protons in the calix[4]arene can serve as a measure of the tilt angle of the rings. This $\Delta\delta$ value increases from 0.70 to 1.12 ppm in *cone*-**5d** upon the binding of *n*-$BuNH_3X$ (X = Cl, Br). These findings imply that *cone*-**5d** 'pinches' into a more C_3 symmetrical shape when the guest is included because *n*-$BuNH_3Cl$ enters into the π cavity formed by the three aromatic rings and the Cl^- complexes with NH *via* hydrogen-bonding. Similar findings were observed in the case of *cone*-**5a–5c** and *n*-$BuNH_3Cl$ (the $\Delta\delta$ value increases from δ 0.61 to 1.18 ppm for *cone*-**5a**, from δ 0.59 to 1.20 ppm for *cone*-**5b** and from 0.64 to 1.15 ppm for *cone*-**5c**).

The association constants calculated from the changes in chemical shifts of the amide *NH* protons, are summarized in Table 1. The complexation constants are shown here to depend on the substituents present at the lower rim. The presence of the substituent groups in the receptors *cone*-**5b–5d** leads to an increase in the association constant compared with *cone*-**5a**. These results suggest that the substituents can also influence the enhancement of the amide complexation with anions. Receptors *cone*-**5a–5d** show a preference for Cl^- anion complexation over Br^- anion complexation, suggesting that the cavity formed by the three-fold amide moieties is more complementary to the size of Cl^- than to that of Br^-; the higher electronegativity of Cl^- is also beneficial. We note that in the case of tris(urea)-functionalized calix[6]arene, the anion complexation is preferred for Br^- anion because it has a large

Table 1 Association constants K_a (M^{-1})[a] and free energies of association ($-\Delta G°$, kJ mol^{-1}) of hosts *cone*-**5a–d** with halide anions[b]

	Cl^-		Br^-	
Hosts	K_a	$-\Delta G°$	K_a	$-\Delta G°$
cone-**5a**	8520 ± 510	22.6	1731 ± 122	18.0
cone-**5b**	8750 ± 534	22.8	1975 ± 195	19.0
cone-**5c**	10 655 ± 656	23.0	2450 ± 210	19.1
cone-**5d**	13 450 ± 9651	23.3	3120 ± 255	19.5

[a] Measured in $CDCl_3$ at 27 °C by the ^1H NMR titration method, noting the chemical shift change of the NH proton; host concentration was 5×10^{-3} M. [b] Anions were used as their *n*-butylammonium salts.

calix cavity and the three functionalized moieties in the 1, 3, and 5 positions of calix[6]arene[17a] are more complementary to the size of Br^- than that of Cl^-. Calix[5]arene derivatives were reported to complex with alkylammonium ions and display enzyme-like selectivity[18] towards biologically important ammonium substrates. Since hexahomotrioxacalix[3]arenes and their derivatives may adopt a C_3-symmetric conformation, it is expected that they can bind with primary ammonium ions and their derivatives, thus having a potential function not only in chemical but also in biological systems.

Conclusions

Novel ion-pair receptors *cone*-**5a–5d** have been synthesized and their binding with the *n*-butylammonium ion and the halide anions (Cl^-, Br^-) have been evaluated by ^1H NMR titration experiments. We have demonstrated that the properties of the ionophore hosts and their intramolecular hydrogen bonding patterns are related to distortion from a C_3-symmetric conformation. Owing to the intramolecular hydrogen bonding, the affinities of the ionophores *cone*-**5a–5d** to *n*-Bu_4NX (X = Cl^-, and Br^-) were weakened. It is clear that after complexation with *n*-$BuNH_3^+$ ion (Scheme 2 right, Fig. 4, and Fig. 5) the intramolecular hydrogen bonding was broken in receptors *cone*-**5a–5d**, and that a binding site was then available for complexation with halide anions (Cl^-, Br^-). These results led us to propose that the new ditopic receptors *cone*-**5a–5d** are capable of binding *n*-$BuNH_3X$ (X = Cl, Br) in nonpolar solvents, and that the complexation of the *n*-$BuNH_3^+$ unit is essential for anion complexation in the present system.

Experimental

General

All mps (Yanagimoto MP-S_1) are uncorrected. ^1H NMR spectra were determined 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets in a Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by Shimadzu 240 spectrophotometer. Elemental analyses were performed by Yanaco MT-5.

General procedure for the preparation of *cone*-hexahomotrioxacalix[3]arene derivatives *cone*-5a–5d

Materials. *cone*-Hexahomotrioxacalix[3]arene triacetic acid (*cone*-**3**) was prepared according to the previously reported procedure.[3c]

***cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(4-methylphenylaminocarbonyl)methoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-5b).** To a solution of *cone*-**3** (100 mg, 0.133 mmol), *p*-toluidine (130 mg, 1.17 mmol) and 1-hydroxybenzotriazole (HOBt) (26 mg, 0.17 mmol) in CH_2Cl_2 (12 mL) was added drop-wise a solution of dicyclohexylcarbodiimide (DCC) (190 mg; 0.92 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the mixture was stirred for 15 h at room temperature, it was condensed under reduced pressure. The residue was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with 10% citric acid (2 × 20 mL), 5% sodium bicarbonate (20 mL),

water (20 mL), saturated brine (20 mL), then dried (Na_2SO_4) and condensed under reduce pressure. The residue was recrystallized from methanol and gave *cone*-**5b** (83 mg, 61%) as colourless prisms. Mp: 234–236 °C. ν_{max} (KBr)/cm^{-1} 3298, 2959, 2863, 1689, 1604, 1532, 1481, 1406, 1362, 1310, 1198, 1069, 881, 817, 753, 661, 506. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.14 (27H, s, tBu), 2.25 (9H, s, Ph–CH_3), 4.27 (6H, d, J = 12.0, $ArCH_2O$), 4.38 (6H, s, $ArOCH_2$), 4.86 (6H, d, J = 12.0, $ArCH_2O$), 6.92 (6H, s, Ar–H), 6.94 (6H, d, J = 8.4, Ph–H_a), 7.43 (6H, d, J = 8.4, Ph–H_b) and 9.42 (3H, s, NH). MS m/z: 1018 (M^+). Anal. calcd. for $C_{63}H_{75}O_9N_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.52; H, 7.53; N, 4.30%.

Similarly, *cone*-**5a** and *cone*-**5c–d** were prepared as described above in 59, 50 and 55% yields, respectively.

***cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(phenylaminocarbonyl)methoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-5a).** Colourless prisms. Mp. 200–202 °C. ν_{max} (KBr)/cm^{-1} 3298, 2959, 2863, 1689, 1602, 1537, 1483, 1445, 1363, 1311, 1198, 1068, 879, 754, 693, 503. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (27H, s, tBu), 4.27 (6H, d, J = 12.0, $ArCH_2O$), 4.12 (6H, s, $ArOCH_2$), 4.88 (6H, d, J = 12.0, $ArCH_2O$), 6.92 (6H, s, ArH), 7.02(3H, t, J = 8.8, Ph–H_c), 7.15 (6H, t, Ph–H_b), 7.57 (6H, d, J = 8.8, Ph–H_a) and 9.52 (3H, s, NH). MS m/z: 976.51(M^+). Anal. calcd. for $C_{60}H_{69}O_9N_3$: C, 73.82; H, 7.12; N, 4.30, Found: C, 73.76; H, 7.12; N, 4.34%.

***cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(4-fluorophenylaminocarbonyl)methoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-5c).** Colourless prisms. Mp. 204–206 °C. ν_{max} (KBr)/cm^{-1} 3295, 2960, 2863, 1691, 1614, 1514, 1465, 1409, 1365, 1306, 1206, 1067, 881, 832, 661, 511, 504. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (27H, s, tBu), 4.22 (6H, d, J = 12.0, $ArCH_2O$), 4.42 (6H, s, $ArOCH_2$), 4.86 (6H, d, J = 12.0, $ArCH_2O$), 6.85 (6H, m, Ph–H_b), 6.90 (6H, s, ArH), 7.48 (6H, m, Ph–H_a) and 9.52 (3 H, s, NH). MS m/z: 1030 (M^+). Anal. calcd. for $C_{60}H_{66}F_3O_9N_3$: C, 69.95; H, 6.46; N, 4.08. Found: C, 69.95; H, 6.46; N, 4.01%.

***cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(4-trifluoromethylphenylaminocarbonyl)methoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-5d).** Colourless prisms. Mp. 198–200 °C. ν_{max} (KBr)/cm^{-1} 3284, 2961, 2870, 1695, 1606, 1539, 1484, 1413, 1327, 1256, 1165, 1123, 1068, 882, 843, 755, 687, 588, 506. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (27H, s, tBu), 4.18 (6H, d, J = 12.0, $ArCH_2O$), 4.49 (6H, s, $ArOCH_2$), 4.88 (6H, d, J = 12.0, $ArCH_2O$), 6.90 (6H, s, ArH), 7.37 (6H, d, J = 8.7, Ph–H_b), 7.63 (6H, d, J = 8.4, Ph–H_a) and 9.71 (3H, s, NH). MS m/z: 1180 (M^+). Anal. calcd. for $C_{63}H_{66}F_9O_9N_3$: C, 64.11; H, 5.64; N, 3.56. Found: C, 64.13; H, 5.62; N, 3.59%.

Determination of association constants

The measurements were performed by ^{1}H NMR titration experiments in a constant concentration of host receptors (5 ×10^{-3} M) and varying guest concentrations of (0–50) × 10^{-3} M. As a probe the chemical shift of the amide protons (NH) signal was used. The association constant values were calculated from the integral intensities of NH protons in the complex and in free host molecules according to literature methods.[19]

^{1}H NMR complexation experiments

To a $CDCl_3$ solution (490 μL, 5 × 10^{-3} M) of *cone*-**5** in the NMR tube was added a $CDCl_3$ solution (10 μL, 2.5 × 10^{-1} M) of *n*-Bu_4NCl, *n*-$BuNH_3Pic$ and/or *n*-$BuNH_3Cl$.[17] The spectrum for each was recorded after the addition and the temperature of the NMR probe was kept constant at 27 °C.

Crystallographic data for *cone*-5c and *cone*-5d

Crystal data for *cone*-**5c**: $C_{60}H_{66}F_3N_3O_9$, M = 1030.16. Triclinic, space group $P\bar{1}$ (no. 2), a = 11.411(4), b = 15.482(5), c = 16.504 (7) Å, α = 92.63(3), β = 97.69(3), γ = 106.65(3)°, V = 2757.3(18) Å^3. Z = 2, D_c = 1.241 g cm^{-3}, $F(000)$ = 1092, T = 293(1)K, μ(Mo-Kα) = 0.90 cm^{-1}, λ(Mo-Kα) = 0.71069 Å.

Crystals of *cone*-**5c** are white prisms which did not diffract well and showed a very streaky diffraction pattern. The data collection and reduction processes were as for *cone*-**5d** below, and yielded 10 289 reflections to θ_{max} = 20°; of these, 4076 were unique (R_{int} = 0.105) and 2772 'observed'. The molecular structure was determined eventually by direct methods in SHELXS. Refinement was, however, not satisfactory and was curtailed with wR_2 = 0.59 and R_1 = 0.30 for all reflections; for the 'observed' data, R_1 = 0.267. Several atoms, refined anisotropically, showed non-positive-definite thermal ellipsoids and were subsequently refined isotropically. Consequently, we are certain that the structure shown in Fig. 1 confirms the structural formula, but our results do not allow anything beyond a rough description of conformation and likely hydrogen bonding contacts.

Crystal data for *cone*-**5d**: $C_{63}H_{66}F_9N_3O_9$, M = 1180.2. Monoclinic, space group Cc (no. 9), a = 16.3465(11), b = 23.3116(18), c = 17.2917(13) Å, β = 116.247(7)°, V = 5909.8(8) Å^3. Z = 4, D_c = 1.326 g cm^{-3}, $F(000)$ = 2472, T = 293(1)K, μ(Mo-Kα) = 1.1 cm^{-1}, λ(Mo-Kα) = 0.71069 Å.

Crystals of *cone*-**5d** are large, beautiful, colourless blocks. One was cut down to *ca.* 0.87 × 0.73 × 0.51 mm, fixed on a glass fibre with epoxy resin, and mounted on an Oxford Diffraction Xcalibur-3 CCD diffractometer equipped with Mo-Kα radiation and graphite monochromator. Intensity data were measured by thin-slice ω- and φ-scans. Total no. of reflections recorded, to θ_{max} = 30°, was 42 557 of which 16 356 were unique (R_{int} = 0.025); 11 023 were 'observed' with $I > 2\sigma_I$.

Data were processed using the CrysAlis-CCD and -RED[20] programs. The structure was determined by the direct methods routines in the SHELXS program and refined by full-matrix least-squares methods, on F^2's, in SHELXL.[21] One *tert*-butyl group was disordered in two orientations. Except for the minor component C-atoms in the disordered group, the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealised positions and their U_{iso} values were set to ride on the U_{eq} values of the parent carbon atoms. At the conclusion of the refinement, wR_2 = 0.140 and R_1 = 0.085[21] for all 16 356 reflections weighted $w = [\sigma^2(F_o^2) + (0.0648P)^2 + 1.86P]^{-1}$ with $P = (F_o^2 + 2F_c^2)/3$; for the 'observed' data only, R_1 = 0.056. In the final difference map, the highest peak (*ca.* 0.24 e Å^{-3}) was close to O(12A).

For both structures, scattering factors for neutral atoms were taken from reference.[22] Computer programs used in this analysis have been noted above, and were run through WinGX[23] on a Dell Precision 370 PC at the University of East Anglia.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 816687 for *cone*-**5c** and 816686 for *cone*-**5d**.†

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