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A novel self-assembled supramolecular architecture involving cation, anion and a calix[4]arene heteroditopic receptor

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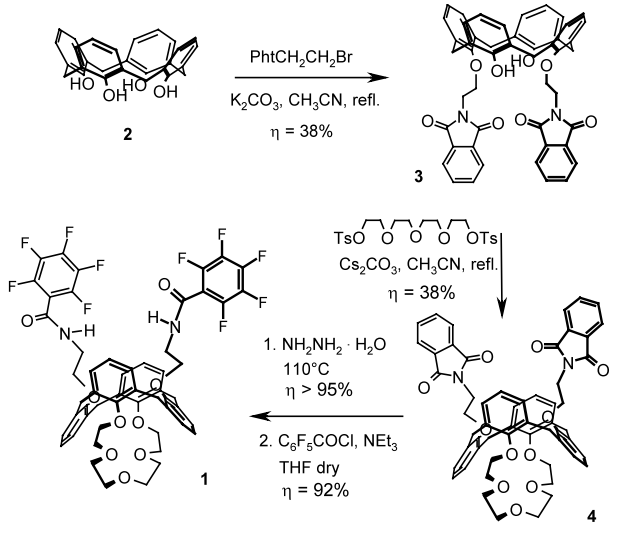
Abstract—In the presence of potassium acetate the heteroditopic calix[4]arene receptor **1**, in the *1,3-alternate* structure and bearing two pentafluorophenyl amide groups as anion binders and a crown-5 polyether for cation complexation, self-assembles in an unexpected 2:2:2 (calixarene:cation:anion) supramolecular structure, as shown by X-ray crystal structure.

Calix[4]arenes have been widely used in the past as building blocks for the synthesis of receptors for cations, which show remarkable selectivity toward sodium, potassium or cesium depending on the nature of binding groups and on the conformation of the macrocycle.[1] On the other hand, several binding groups such as (thio)urea,[2] amide[3a,b] and perfluorinated alcohol moieties[3c] have been used for the complexation of anions via hydrogen bonding.[4] A step forward in the field of ion complexation is the design and synthesis of heteroditopic receptors able to complex simultaneously cations and anions either as ion-pairs or as free ions.[3b,5] These kind of receptors can show interesting allosteric or co-operative effects[5a,6] which affect the selective extraction of salts in organic media or their transport through artificial membranes.[5c] Calixarene-based heteroditopic receptors are also known[2c,7] mostly involving *cone* calix[4]arenes. Continuing these studies we designed a new heteroditopic receptor **1**, based on a calix[4]arene in the *1,3-alternate* structure, which allows having a polyether loop on one side and two pentafluoro benzamide groups as anion binding units on the other side with respect to the calix[4]arene macrocyclic ring. This receptor indeed shows heteroditopic properties towards metal salts and, surprisingly, in the presence of potassium acetate it forms an unusual 2:2:2 (ligand:cation:anion) complex, whose structure has been elucidated by X-ray crystallography. The compound **1** was synthesised according to Scheme 1, starting from calix[4]arene **2** which was first diametrically alkylated at the lower rim with 2-bromoethylphthalimide to give compound **3** which reacted with tetra-



Scheme 1.

Keywords: calixcrowns; ditopic receptors; anion binding; acetate receptor; potassium selective ligands; cooperativity; self-assembly; X-ray.

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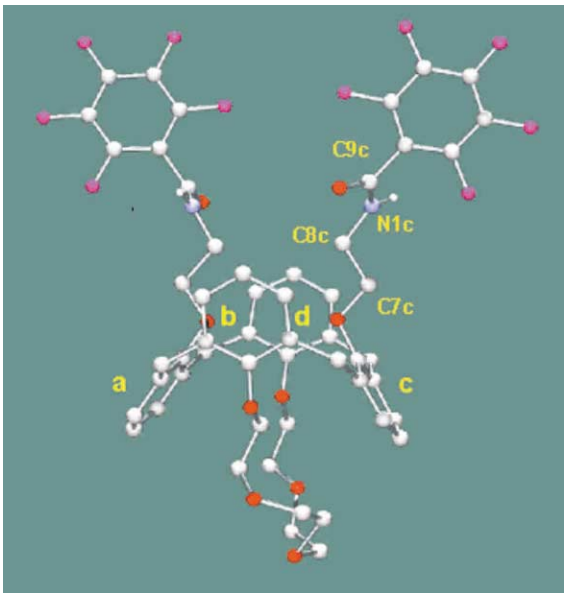

Figure 1. Perspective view of the free ligand **1** (colour key: carbon, white; oxygen, red; nitrogen, blue; hydrogen, white; fluorine, cyano).

ethylene glycol ditosylate in CH_3CN in the presence of Cs_2CO_3 to give the calix[4]arene-crown-5 derivative **4**, fixed in the *1,3-alternate* conformation. Hydrazinolysis of compound **4** gave the diamine **5** which was acylated with pentafluorobenzoyl chloride thus giving the heteroditopic receptor **1** in good overall yields.[8]

Crystals of the free ligand **1**, suitable for X-ray diffraction studies were obtained from CH_2Cl_2/CH_3OH (1/1).[9] Fig. 1 reports a perspective view of the ligand showing the calix[4]arene in a distorted *1,3-alternate* conformation ($\mathbf{a} \wedge \mathbf{c} = 61.1(2)°$, $\mathbf{b} \wedge \mathbf{d} = 56.4(2)°$), which can be indicated as C_1 ++, −−, ++, −− according to the symbolic representation devised for calix[4]arenes.[10] The crown ether loop shows the classical distortion at the level of the furthest oxygen atom O2* with respect to the calix, whereas the amide N–H groups are not involved in any *inter*- or *intramolecular* hydrogen bonding.

Initial anion binding studies were conducted by extracting solid salts in excess (3 equiv.) in the presence of 2 mM $CDCl_3$ solution of host **1**. In these conditions the ligand was saturated (>98% complexation) in all cases using potassium acetate, chloride and bromides as solid salts. The ^1H NMR spectrum changes profoundly in the region of the crown ether and amide protons, indicating that both cations and anions are simultaneously bound in the two regions of the heteroditopic receptors. Solid–liquid extraction experiments using a ligand/salt ratio = 2 allowed to establish that the crown ether protons are in slow exchanging regime on the ^1H NMR time scale, at room temperature, whereas the NH protons are fast exchanging. Both type of protons experience downfield shifts upon salt complexation, and the limiting shifts of the N–H protons is anion dependent ($\Delta\delta = 2.8$ ppm for CH_3COO^-, 2.16 ppm for Cl^- and 1.83 ppm for Br^-). ^1H NMR titration experiments were also performed in homogeneous solution using tetrabutyl ammonium acetate and bromide (Table 1). In both cases a 1:1 stoichiometry was verified by Job-plot analyses of data and an association constant $K_{ass} =$ 35 M^{-1} (CH_3COO^-) and 12 M^{-1} (Br^-) were calculated.

Interestingly, the acetate anion binding experiences a four-fold increase ($K_{ass} = 140$ M^{-1}) if the crown ether loop is first complexed with the potassium cation (using 1 equiv. of $KBPh_4$), which indicates a cooperative effect between the two binding sites. Even more interesting is the fact that, upon addition of 1 equiv. of potassium acetate to a $CDCl_3$ solution of ligand **1**, nice crystals suitable for X-ray diffractometric studies, formed.[11] The crystal structure shows the presence of a 2:2:2 (ligand:cation:anion) complex (Fig. 2) held together by the simultaneous contribution of several noncovalent interactions. The potassium cation is bound by the crown ether loop in a more regular fashion, in compari-

Table 1. Association constants (K_{ass}, M^{-1}) with different anions as tetrabutyl ammonium salts ($CDCl_3$, 300 K)[a]

Receptor	Anion	K_{ass} (M^{-1})
1	AcO^-	35
1	Br^-	12
1 × $KBPh_4$	AcO^-	140

[a] Errors within 10%.

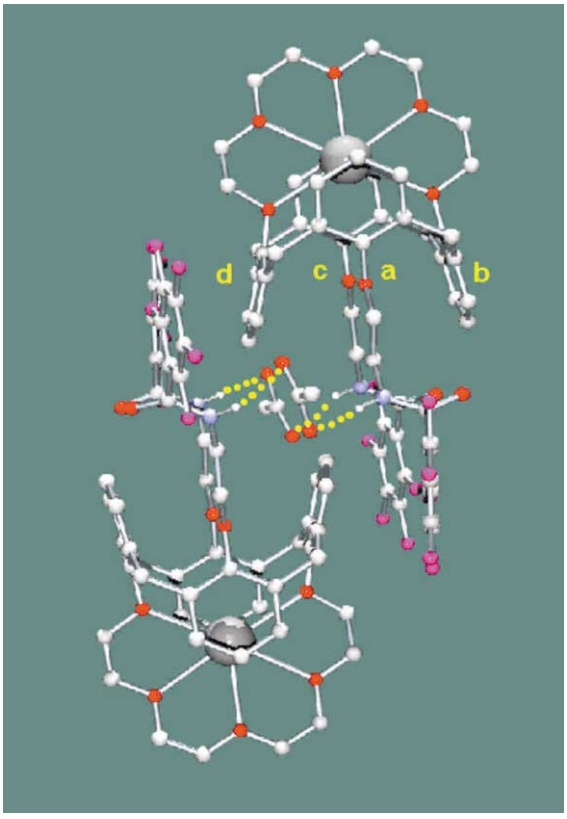

Figure 2. A self-assembled superstructure held by anion–ligand H-bonding (colour key: carbon, white; oxygen, red; nitrogen, blue; hydrogen, white; fluorine, cyano).

son to other calix[4]arene-crown-5 complexes,[12] since the K–O bond distances range from 2.760(3) to 2.814(4) Å. Two unsymmetrical $K^{+}\cdots\pi$[13] interactions involving the aromatic rings **a** and **c** contribute to stabilise the complex [K^{+}–$C_{aromatic}$ distances 3.446(6)–3.517(5) Å in **a** and 3.319(5)–3.518(4) Å in **c**: range found in the Cambridge Structural Database 3.195–3.515 Å] and are stronger than that documented in a previous work, with the *partial cone p-tert*-butylcalix[4]arene crown-5.[12] This is the first example of a solid state complex between a calix[4]arene-crown-5 derivative in the *1,3-alternate* conformation and potassium cation.

The free ligand undergoes a great conformational change upon complexation. In the amide chain at the unit **c** the torsion angle C_{7C}–C_{8C}–N_{1C}–C_{9C} changes from −100.0(6) to 100.1(5)° bringing the two amide groups of the complex in *syn* orientation. The two acetate anions, which lie almost on a plane containing the crystallographic centre of symmetry of the supermolecule, act as bridges, each one linking two N–H groups of two different macrocycles. In this way a centrosymmetric structure is obtained and the space occupancy is maximised. Although we have no definitive proof that this rather unusual supramolecular architecture exists also in solution, the fourfold increase in the acetate anion binding observed when ligand **1** is complexed with potassium ion, is an indication of the enhanced stability of the complexes when both binding units are simultaneously bound. This is the first example of a higher order superstructure formed by a heteroditopic calixarene receptor and can be a useful model to explain the unusual transport behaviour of similar systems.[7d] In fact, one can easily forecast that the diffusion of such 2:2:2 species through a supported liquid membrane should be quite slow. Studies to prove the generality of this finding in other ditopic receptors are in progress.

Acknowledgements

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8. **General**: Melting points were determined on a Electrothermal apparatus in capillaries sealed under nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded with Bruker spectrometers AC300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) using TMS as internal standard. Mass spectra were obtained in ESI mode on Micromass 4LCZ or in CI (CH_4) mode on Finnigan Mat SSQ710 spectrometers. All the reactions were carried out under nitrogen atmosphere.
25,27-Bis-(3-phthtalimidoethoxy)calix[4]arene (3). To a stirred solution of calix[4]arene **2** (1.0 g, 2.35 mmol) in 30 ml of dry acetonitrile were added *N*-(3-bromoethyl)-phthalimide (1.25 g, 4.94 mmol), K_2CO_3 (0.39 g, 2.82 mmol) and a catalytic amount of KI. The reaction mixture was refluxed under nitrogen for 60 h and then the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 ml) and this solution washed with a 1N NH_4Cl aqueous solution (3×30 ml). The organic phase was dried over $MgSO_4$, the solvent removed at the Rotavapor, and compound **3** obtained as a white powder by treatment with acetonitrile. Yield: 38%. ($C_{48}H_{38}N_2O_8$: MW 770.84. Found: C, 74.65; H, 5.02; N, 3.66%. $C_{48}H_{38}N_2O_8$ requires C, 74.79; H, 4.97; N, 3.63). δ_H (300 MHz; 300 K; $CDCl_3$) 7.94–7.92 (m, 4H, Phth-H); 7.69–7.67 (m, 4H, Phth-H); 6.99 (d, 4H, ArH meta, *J* 7.5 Hz); 6.79 (d, 4H, ArH meta, *J* 7.5 Hz); 6.67–6.58 (m, 4H, ArH *para*); 4.51 and 4.28 (2t, 4H each, OCH_2 and NCH_2, *J* 6.7 Hz); 4.22 (d, 4H, $ArCH_{ax}Ar$, *J* 13.1 Hz); 3.33 (d, 4H, $ArCH_{eq}Ar$, *J* 13.2 Hz). ν_{max}/cm^{-1} (NaCl, CH_2Cl_2) 3422 (OH), 1715 (C=O). *m*/*z* (CI) 770.6 [M^{+} 100].
25,27-Bis-(2-phthalimidoethoxy)calix[4]arene-crown-5 *in 1,3-alternate* ***(4)***. To a stirred solution of compound **3**

(0.90 g, 1.2 mmol) in 100 ml of acetonitrile were added tetraethylene glycol di-*p*-toluenesulfonate (0.66 g, 1.3 mmol) and Cs_2CO_3 (1.18 g, 6 mmol). The reaction mixture was refluxed for 5 days and subsequently the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 ml) and washed with 1N NH_4Cl (3×20 ml). The organic layer was dried over $MgSO_4$ and the solvent removed to yield a product which was purified by column chromatography (SiO_2: CH_2Cl_2/MeOH = 95:5). Yield: 38%. ($C_{56}H_{52}N_2O_{11}$: MW 929.04. Found: C, 72.34; H, 5.68; N, 3.09%. $C_{56}H_{52}N_2O_{11}$ requires C, 72.40; H, 5.64; N, 3.01). δ_H (300 MHz; 300 K; $CDCl_3$) 7.81 and 7.71 (2m, 8H, Phth-H); 7.40 (d, 4H, ArH *meta*, *J* 7.5 Hz); 7.11–7.09 (m, 6H, ArH *meta* and ArH *para*); 6.90 (t, 2H, ArH *para*); 3.91 (s, 8H, $ArCH_2Ar$); 3.69–3.39 (m, 20H, $ArOCH_2CH_2OCH_2CH_2$, OCH_2 and NCH_2); 3.21 (t, 4H, $ArOCH_2CH_2OCH_2CH_2$). ν_{max}/cm^{-1} (NaCl, CH_2Cl_2) 1716 (C=O). *m*/*z* (CI) 928.4 (M^+ 100).

25,27-Bis-(2-aminoethoxy)calix[4]arene-crown-5 *in 1,3-alternate* (***5***). A solution of compound **4** (0.5 g, 0.54 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.52 ml, 10.76 mmol) in EtOH (40 ml) was heated at 110°C in a Schlenk tube for 8 h. EtOH was removed under reduced pressure, the residue was taken with CH_2Cl_2 (30 ml) and washed with a 2N NaOH solution (3×15 ml), and then dried over $MgSO_4$. Removal of CH_2Cl_2 yield pure compound **5**. Yield >95%. ($C_{40}H_{48}N_2O_7$: MW 668.83. Found: C, 71.87; H, 7.15; N, 4.25%. $C_{40}H_{48}N_2O_7$ requires C, 71.83; H, 7.23; N, 4.18). δ_H (300 MHz; 300 K; $CDCl_3$) 7.10 (d, 4H, ArH *meta*, *J* 7.4 Hz); 7.05 (d, 4H, ArH *meta*, *J* 7.3 Hz); 6.93–6.84 (m, 4H, ArH *para*); 3.87 (s, 8H, $ArCH_2Ar$); 3.68–3.53 (m, 12H, $ArOCH_2CH_2OCH_2CH_2$ and $OCH_2CH_2NH_2$); 3.46 (t, 4H, $ArOCH_2CH_2OCH_2CH_2$, *J* 7.2 Hz); 3.01 (t, 4H, $ArOCH_2CH_2OCH_2CH_2$, *J* 7.1 Hz); 2.50 (bs, 4H, CH_2NH_2); 1.66 (bs, 4H, NH_2). ν_{max}/cm^{-1} (KBr) 3407 (bs, NH_2). *m*/*z* (CI) 669.4 [$(M+H)^+$ 100].

25,27 - Bis - [(2 - *N* - pentafluorobenzamido)ethoxy]calix[4] arene-crown-5 *in 1,3-alternate* (***1***). A solution of diamine **5** (0.2 g, 0.30 mmol) and triethylamine (0.084 ml, 0.60 mmol) in 30 ml of dry THF under an argon atmosphere was cooled to −40°C. Then was added dropwise a solution of pentafluorobenzoyl chloride (0.086 ml, 0.60 mmol) dissolved in 30 ml of dry THF. After 2 h at −40°C and 3 h at room temperature, THF was removed under reduced pressure. The residue, taken with CH_2Cl_2 (30 ml) was washed with H_2O (3×15 ml) and dried over $MgSO_4$. CH_2Cl_2 was removed and the resulting solid treated with hexane. A white solid, corresponding to compound **1** was filtered on a buchner funnel. Yield 92%. Mp 217°C. ($C_{54}H_{46}F_{10}N_2O_9$: MW 1056.95. Found: C, 61.28; H, 4.45; N, 2.73% $C_{54}H_{46}F_{10}N_2O_9$ requires C, 61.36; H, 4.39; N, 2.65). δ_H (300 MHz; 300 K; $CDCl_3$) 7.14 (d, 4H, ArH *meta*, *J* 7.4 Hz); 6.97 (d, 4H, ArH *meta*, *J* 7.5 Hz); 6.93 (t, 2H, ArH *para*, *J* 7.4 Hz); 6.71 (bs, 2H, NH); 6.40 (t, 2H, ArH *para*, *J* 7.4 Hz); 3.88, 3.81 (2d, 4H each, $ArCH_2Ar$, *J* 16.7 Hz); 3.64–3.48 (m, 16H, $ArOCH_2CH_2OCH_2CH_2$ and OCH_2); 3.27–3.21 (m, 4H, CH_2NH); 3.14 (t, 4H, $ArOCH_2CH_2OCH_2CH_2$). ν_{max}/cm^{-1} (NaCl, CH_2Cl_2) 3400 (bs, NH), 1659 (C=O). *m*/*z* (FAB) 1079.7 [$(M+Na)^+$ 100], 1057.8 [$(M+H)^+$ 8]. *m*/*z* (CI) 1056.1 (M^+ 10), 819.6 [$(M-F_5C_6CONHCH_2CH_2+H)^+$ 100].

9. *Crystal data for* ***1*** $C_{54}H_{46}F_{10}N_2O_9$, $M_r = 1033.96$, triclinic, space group $P\bar{1}$, $a = 13.633(3)$, $b = 17.307(4)$, $c = 10.693(2)$ Å, $\alpha = 97.26(2)$, $\beta = 93.83(2)$, $\gamma = 95.53(2)°$, $\rho_{calcd} = 1.383$ g cm^{-3}, $\mu = 0.112$ mm^{-1}, $Z = 2$, independent reflections: 9362 ($R_{int} = 0.04$), final *R* indices: $R_1 = 0.078$, $wR_2 = 0.261$. CCDC 172976.
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