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A DFT study on a calix[5]crown-based heteroditopic receptor

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The structures and binding energies of complexes formed between tris-ureido-calix[5]crown **1** and *n*-butylammonium chloride and 2-phenylethylammonium chloride have been determined by density functional calculations. Density functional theory analysis shows that the heteroditopic receptor **1** binds organic salt species with positive cooperativity.

Keywords: calixarene; alkylammonium ions; ion-pair complexation; heteroditopic receptor; DFT

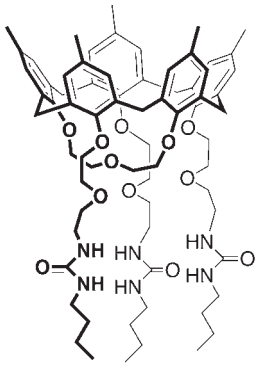
1. Introduction

Complexation of charged substrates by means of neutral receptors was one of the earliest goals of supramolecular chemistry, and considerable effort is still being put into the development of new or improved host molecules for the efficient and selective recognition of both cationic and anionic guests (*1*). For many years, the complexation of these species has been investigated disregarding the role played by the counterion of the target ionic substrate, implicitly circumventing the influence of ion-pairing effects (*2*) on the strength and selectivity of complexation by employing the so-called 'weakly coordinating' counterions (*3*).

The counterion, however, does indeed play a determinant role, acting in many ways as a competing receptor for the substrate (*4*). Recently, a new approach has been developed, reliant on the use of hetero(poly)topic receptors, capable of simultaneously – and, allegedly, cooperatively – recognising and sequestering both cationic and anionic counterparts of a given salt species (*5*).

Heteroditopic receptors have often been described as more efficient than their parent monotopic receptors, on the basis of transport and/or binding experiments. In many of these examples, efficiency and cooperativity have been deduced by fitting data as 1:1 complexation events. In a very recent paper, however, Roelens and co-workers (*6*) raised some fundamental questions on the applicability of a 1:1 association model to the interpretation of binding data relative to the complexation of ionic species, demonstrating that ion-pairing equilibria cannot be ignored even in the presence of weakly coordinating counterions. In a following report, the same authors showed that, upon binding of a salt species to a heteroditopic receptor, the 'cooperativity principle is neither general nor predictable' (*7*).

Over the past few years, we have been actively involved in the design, synthesis and study of heteroditopic (*8*) and -tetratopic (*9*) receptors, along with 'binary host' systems based on calix[4]- (*10*) or calix[5]arenes (*11*) for the binding of ion pairs. In an attempt to verify whether or not theoretical methods, which have become a powerful tool in supramolecular chemistry (*12*), are able to predict the cooperativity effects in the binding of organic salts (*13*), we have undertaken a study on our most recent heteroditopic receptor, 5,11,17,23,29-pentakis(methyl)-31,33,34-tris-(2-(2-*N*-(*N*′-butylureido)ethoxy)ethoxy)-32,35-crown-3-calix[5]arene (**1**) (*8a*), and its affinity towards *n*-butylammonium chloride (**2**·HCl) or 2-phenylethylammonium chloride (**3**·HCl).



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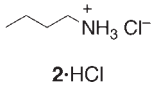
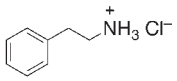


2·HCl



3·HCl

2. Results and discussion

Based on previous studies by Choe and co-workers (*14*), who have extensively investigated the binding of alkylammonium ions (*15*) to monotopic calix[5]arene

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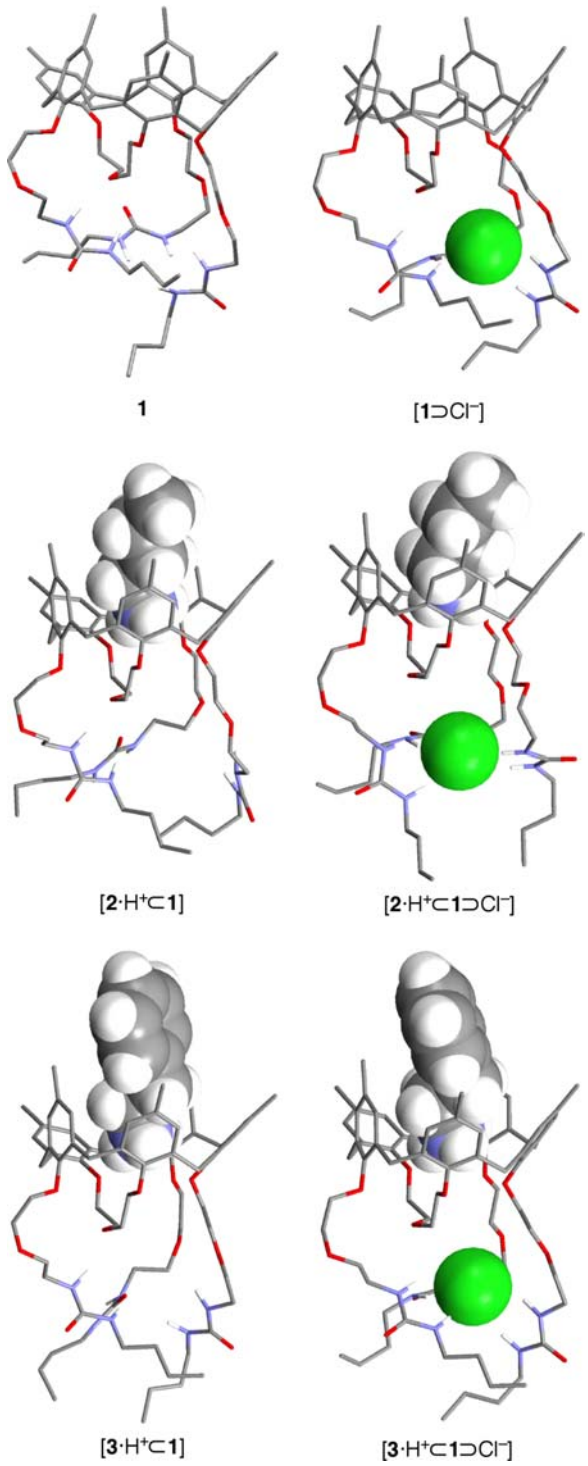

Figure 1. Optimised B3LYP/6-31G(d) geometries for calix[5]crown **1** and its complexes with **2**·H^+, **3**·H^+, Cl^-, **2**·HCl and **3**·HCl.

receptors, we decided to employ a density functional B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) protocol.

The molecular geometries of complexes formed by calix[5]crown **1** with (aryl)alkylammonium cations **2**·H^+ and **3**·H^+, Cl^- ion, as well as **2**·HCl and **3**·HCl salts, were initially optimised at the PM3 level in vacuum, and the conformations obtained were then used as a starting point for a full unconstrained reoptimisation at the B3LYP/6-31G(d) level of theory (Figure 1). Single-point energy calculations were then carried out at the B3LYP/6-311++G(d,p) level, to add polarisation functions for hydrogen atoms and diffuse functions for both hydrogen and heavy (non-hydrogen) atoms, in order to gain a more accurate picture of the hydrogen bonding interactions involved in the complexation of the anionic guest (*16*). In addition, single-point energy calculations were also carried out for the conformations (depicted in cartoon fashion in Figure 2) of the host molecule, the host–guest complexes and the host (and host–guest) structures obtained upon progressive *in silico* removal of the guest(s). All calculations were carried out in vacuum and results are summarised in Table S1 (see the Supporting Information, available online).

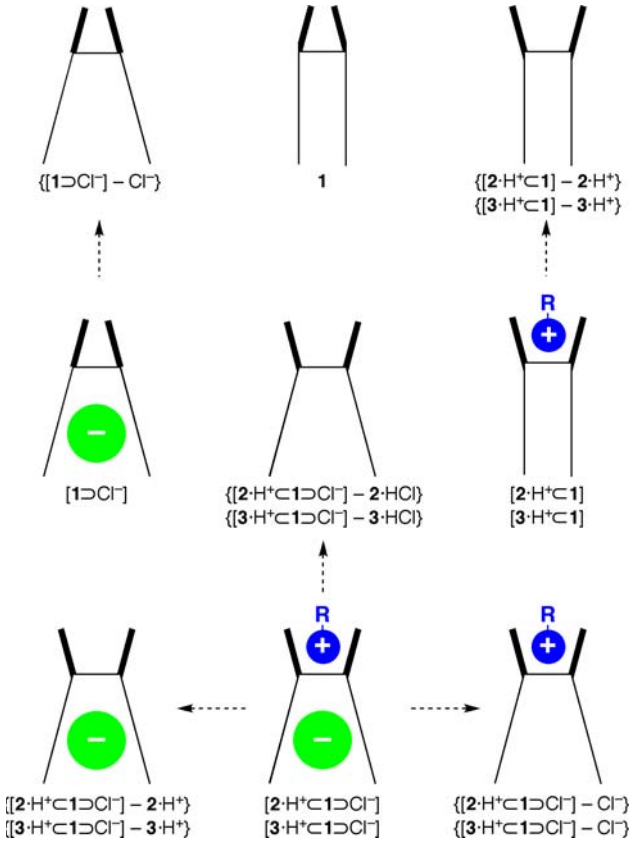

Figure 2. Cartoon representation of the complexes of calix[5]crown **1** with the cationic and/or anionic guest(s) described in this paper. Dashed arrows indicate *in silico* guest removal. R = *n*-$BuNH_3^+$(**2**·H^+) or $PhCH_2CH_2NH_3^+$(**3**·H^+).

Calixcrown (*17*) receptor **1** is capable of simultaneously binding an arylalkyl- or alkylammonium cation and its chloride counterion. The (aryl)alkylammonium guest penetrates the π-rich aromatic cavity of **1**, where it is

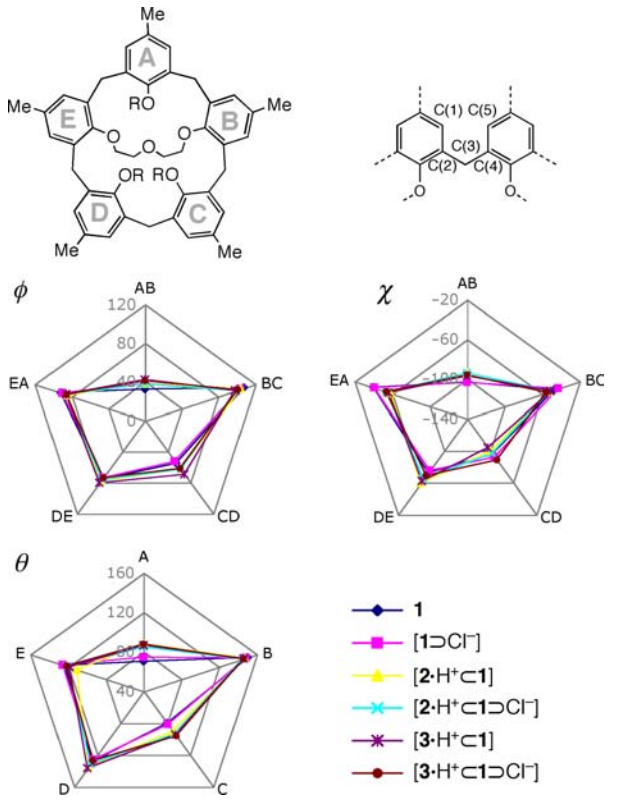

Figure 3. Radial plots comparing tilt angles (θ) and torsion angles ϕ and χ for free calix[5]crown **1** and its complexes with **2**·H^+, **3**·H^+, Cl^-, **2**·HCl and **3**·HCl.

tightly held by $^+$NH···O hydrogen bonds and CH–π interactions (*18*). At the same time, the chloride anion binds to the pocket generated by the ureido hydrogen atoms (*8a*).

In all calculated structures, calix[5]crown **1** was found to adopt a distorted C_s *cone-out* conformation (*19*), with one of the aryl groups bearing the crown-3 chain (ring B) leaning outwards with respect to the mean plane generated by the bridging methylene units, and the isolated aryl ring A tilted towards the interior of the cavity (Figure 3). The tilting of the latter ring is much more pronounced in the 'free' receptor **1**.

Despite this self-filling effect, calixarene **1** turns out to be a highly preorganised molecule for the complexation of organic cations. In the presence of an (aryl)alkylammonium ion, the cavity of **1** needs to widen only marginally to accommodate the incoming guest and to bring its ammonium group within hydrogen bonding distance of the phenolic oxygen atoms. Rings A and C 'open up' (their tilt angle θ increases by only *ca.* 10°–20°, *vide infra*), whereas rings B and E, the ones connected by the crown-3 ethereal bridge, do not significantly modify their orientation.

This type of guest-induced motion was also observed in the ^{1}H NMR spectra of such complexes in $CDCl_3$. A comparison of the chemical shifts of the ArH singlet in the different host–guest complexes indicates that the deeper the aryl group A is inserted into the cavity, the higher its upfield shift, as a result of an increasing shielding effect induced by the remaining aryl rings (Table 1) (*20*).

Table 1. Comparison between the tilt angle of ring A and the chemical shift (*23*) of its aromatic hydrogen atoms ($CDCl_3$, 1 mM, 500 MHz, 25°C).

Calculated	Tilt angle, θ (°)	Experimental	ArH δ (ppm)
1	69.9	**1**	6.17
[**1** ⊃ Cl^-]	74.4	[**1** ⊃ Cl^-]*n*-Bu_4N^+[a]	6.10[b]
[**2**·H^+ ⊂ **1**]	87.7	[**2**·H^+ ⊂ **1**]Pic^- [a]	6.43
[**2**·H^+ ⊂ **1** ⊃ Cl^-]	84.8	[**2**·H^+ ⊂ **1** ⊃ Cl^-]	6.46
[**3**·H^+ ⊂ **1**]	86.5	[**3**·H^+ ⊂ **1**]Pic^- [a]	6.31
[**3**·H^+ ⊂ **1** ⊃ Cl^-]	87.6	[**3**·H^+ ⊂ **1** ⊃ Cl^-]	6.35

[a] Tetra-*n*-butylammonium and picrate (Pic^-) were employed as weakly coordinating counterions.[1]
[b] Estimated from the Benesi–Hildebrandt linearisation of titration experiments.

Figure 3 provides a graphical summary of the calculated conformational changes the calixarene cavity undergoes upon cation, anion or ion-pair complexation. The conformational parameters ϕ and χ (*21*), which are defined as the dihedral angles generated by C(1)—C(2)—C(3)—C(4) and C(2)—C(3)—C(4)—C(5), respectively, present the +/− alternating sequence typical of a cone conformation and their values, being overall quite similar, indicate comparable structural features. The tilt angles (θ) of the aryl groups, measured with respect to the mean plane generated by the bridging methylene carbon atoms, are convenient descriptors of the overall conformation assumed by the calixarene cavity.

(Aryl)alkylammonium cations **2**·H^+ and **3**·H^+ sit inside the calixarene cavity, held in place mainly by a single (or two, in the cases of [**2**·H^+ ⊂ **1** ⊃ Cl^-] and [**3**·H^+ ⊂ **1** ⊃ Cl^-]) hydrogen bond to the phenolic oxygen atom(s) ($^+$NH···O = 1.9 ± 0.1 Å, see Figure S1 of the Supporting Information, available online). The inability of the ammonium moiety to form tripodal hydrogen bonding is due to the presence of the crown-3 bridge. The latter adopts in all structures a *trans–gauche* conformation, closing the bottom of the cavity, and thus preventing the (aryl)alkylammonium ion from reaching a more favourable position. In this regard, solid state (*18*), density functional theory (DFT) B3LYP/6-31G(d,p) (*14c*) and HF/6-31G data (*14d*) on different calix[5]arenes show that the nitrogen ammonium atom must be roughly 1.0–1.1 Å above the mean plane generated by the phenolic oxygen atoms to be able to fully interact with them. In the present cases, the nitrogen atom lies 2.1 ± 0.1 Å above that plane.

The ureido-bearing substituents show, as expected, a much higher degree of disorder, their spatial arrangement mainly being driven by C═O···HN hydrogen bonds. However, some common features keep recurring in all the

Table 2. DFT B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) calculated binding, complexation and preorganisation energies (kcal/mol) for the complexes of calix[5]crown **1** and **2**·H^+, **3**·H^+, Cl^-, **2**·HCl and **3**·HCl.

Species	$\Delta E_{preorg(H)}$	$\Delta E_{preorg(G)}$ [a]	ΔE_{compl}	$\Delta E_{binding}$
1 + Cl^-	9.4	–	−62.8	−53.4
1 + **2**·H^+	9.7	0.3	−41.1	−31.1
[**1** ⊃ Cl^-] + **2**·H^+	10.4	1.2	−81.3	−69.7
[**2**·H^+ ⊂ **1**] + Cl^-	17.3	0.9	−109.3	−91.2
1 + **2**·H^+ + Cl^-	27.0	1.2	−151.3	−123.1
1 + **3**·H^+	7.3	0.7	−38.4	−30.4
[**1** ⊃ Cl^-] + **3**·H^+	8.4	0.7	−77.3	−68.2
[**3**·H^+ ⊂ **1**] + Cl^-	15.2	0.0	−106.5	−91.3
1 + **3**·H^+ + Cl^-	20.5	0.7	−142.8	−121.6

[a] Relative to the cationic guest, as for Cl^- $\Delta E_{preorg(G)} = 0$.

geometry-optimised structures. The free calixarene **1** presents, in its minimum energy conformation, an intramolecular hydrogen bond between a ureido NH hydrogen atom (belonging to the pendant chain attached to ring A) and the central ethereal oxygen atom of the bridging chain (NH···O = 2.0 Å) (*22*). This hydrogen bonding interaction is not lost upon complexation with either of the two cationic guests (NH···O = 2.1 Å in both [**2**·H^+ ⊂ **1**] and [**3**·H^+ ⊂ **1**]), as the ethereal oxygen atom does not participate in the complexation of the (aryl)alkylammonium ions.

Inclusion of either **2**·H^+ or **3**·H^+ induces a widening of the calixarene cavity, but does not substantially influence the conformational freedom of the lower rim substituents. Even the complexation of chloride ions does not preclude the formation of a weaker hydrogen bond, although in [**1** ⊃ Cl^-], [**2**·H^+ ⊂ **1** ⊃ Cl^-] and [**3**·H^+ ⊂ **1** ⊃ Cl^-] the NH···O distances are somewhat longer (2.7 ± 0.3 Å). Interestingly, in the ion-pair complexes [**2**·H^+ ⊂ **1** ⊃ Cl^-] and [**3**·H^+ ⊂ **1** ⊃ Cl^-], this ureido hydrogen atom forms a bifurcated hydrogen bond, which also involves the chloride ion (NH···Cl^- = 2.8 ± 0.1 Å). All the remaining ureido hydrogen atoms are involved in NH···Cl^- hydrogen bonds (2.5 ± 0.1 Å).

Further insight into the binding behaviour of **1** was gained by conveniently analysing the energies of binding, preorganisation and complexation, determined according to the following equations (*24*):

$$\Delta E_{binding} = E_{(HG)} - E_{(H)} - E_{(G)}, \quad (1)$$

$$\Delta E_{preorg(H)} = E_{complexed(H)} - E_{(H)}, \quad (2)$$

$$\Delta E_{preorg(G)} = E_{complexed(G)} - E_{(G)}, \quad (3)$$

$$\Delta E_{compl} = E_{(HG)} - E_{complexed(H)} - E_{complexed(G)}, \quad (4)$$

$$\Delta E_{binding} = \Delta E_{compl} + \Delta E_{preorg(H)} + \Delta E_{preorg(G)}. \quad (5)$$

$\Delta E_{binding}$ represents the combination of the contribution of the stabilising interactions (ΔE_{compl}), and the energy spent by the host and the guest(s) ($\Delta E_{preorg(H)}$, $\Delta E_{preorg(G)}$) to rearrange their conformations prior to the actual complexation event. Results derived from B3LYP/6-311++G(d,p) energy calculations are reported in Table 2.

Complexation of the salt species by calix[5]crown **1** can be dissected into a series of discrete events: (1) conformational rearrangement of **1** to accommodate the first ion (either the cation or the anion); (2) conformational rearrangement of the first ion; (3) positioning of the first ion into its binding site; (4) conformational rearrangement of the resulting 1:1 complex to preorganise the second binding site for the incoming counterion; (5) conformational rearrangement of the counterion and (6) positioning of the counterion into the second binding site.

According to this type of fragmented contribution analysis, data in Table 2 suggest that binding of **2**·HCl and **3**·HCl to **1** takes place with a positive cooperativity. In all instances, binding of a given ion to the free receptor **1** is energetically less favoured than that of the same ion to the 1:1 complex (e.g. $\Delta E_{binding} = -31.1$ and −69.7 kcal/mol for **1** + **2**·H^+ → [**2**·H^+ ⊂ **1**] and [**1** ⊃ Cl^-] + **2**·H^+ → [**2**·H^+ ⊂ **1** ⊃ Cl^-], respectively). Similarly, a comparison between the binding energies calculated for either of the two salts and those obtained from the sum of the single ions forming that salt ($\Delta\Delta E_{binding} = -38.6$ and −37.8 kcal/mol for **2**·HCl and **3**·HCl, respectively)[2] reveals that ion-pair complexation is significantly favoured, and proceeds with a stabilisation greater than that obtained from the mere sum of the contributions of the two 1:1 binding events. These estimates can be explained by taking into account the stabilising contribution provided by the electrostatic attraction between the two ions included in the binding sites of the heteroditopic receptor ($^+$N···Cl^- = 7.3 and 7.0 Å for [**2**·H^+ ⊂ **1** ⊃ Cl^-] and [**3**·H^+ ⊂ **1** ⊃ Cl^-], respectively).

As far as the conformational rearrangement of the host is concerned, different trends are observed upon sequential ion binding. The first binding event proceeds with similar preorganisation energies for both anions and cations

($\Delta E_{preorg(H)} = 7.3–9.7$ kcal/mol), indicating that comparable energy penalties are paid for the 'opening' of the cavity and the 'unravelling' of the ureido-bearing chains. Once the anionic complex ([**1** ⊃ Cl^-]) is formed, preorganisation of the calixarene cavity to receive either of the two incoming cations (**2**·H^+ or **3**·H^+) requires an energy contribution similar to that calculated for the free receptor ($\Delta E_{preorg(H)} = 8.4–10.4$ vs. 7.3–9.7 kcal/mol). Conversely, preorganisation of the anionic binding site of both cationic complexes ([**2**·H^+ ⊂ **1**] and [**3**·H^+ ⊂ **1**]) to host the chloride ion suffers from a negative allosteric effect (*25*) with respect to the direct binding of Cl^- to **1** ($\Delta E_{preorg(H)} = 15.2–17.3$ vs. 9.4 kcal/mol). In other words, the energy gap involved in the conformational rearrangement of the three ureido pendant groups is higher when the cation guest is held inside the calixarene cavity.

$\Delta E_{binding}$ values from Table 2 suggest that receptor **1** displays significant preference neither for **2**·H^+ over **3**·H^+ ($\Delta E_{binding} = -31.1$ vs. -30.4 kcal/mol) nor for **2**·HCl over **3**·HCl ($\Delta E_{binding} = -123.1$ vs. -121.6 kcal/mol). Chloride ions, on the other hand, seem to bind to receptor **1** more tightly than (aryl)alkylammonium ions ($\Delta E_{binding} = -53.4$, -31.1 and -30.4 kcal/mol for [**1** ⊃ Cl^-], [**2**·H^+ ⊂ **1**] and [**3**·H^+ ⊂ **1**], respectively). This last finding may appear surprising when related to the very modest value for the conditional binding constant ($K_a = 17\ M^{-1}$) previously determined (*8a*) by ^{1}H NMR on the model *n*-Bu_4NCl salt in chloroform. The discrepancy, however, can be explained by taking into account ion-pairing and solvent effects occurring in solution. It is well known (*6*, *7*, *26*) that, in non-polar organic solvents, tetraalkylammonium salts are significantly ion-paired. This greatly reduces the availability of naked chloride ions, so that percentages of complexation are depressed. Moreover, chloroform is a mildly solvating solvent for anions. Calculations in vacuum provide a simplified picture, giving binding energies derived from multi-point interactions between ideally isolated species, devoid of all the influences of concomitant processes.

3. Conclusions

DFT B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) calculations have shown that ion-pair complexation of *n*-butylammonium or 2-phenylethylammonium chloride to the two binding sites of a calix[5]arene-based receptor takes place with positive cooperativity. A remarkable agreement between experimental ^{1}H NMR and calculated data on the binding geometries of both single ion and salt species to this receptor has also been found. Overall, our findings demonstrate that DFT studies can be used as a valuable tool for predicting the binding energies and structural features of heteroditopic receptors involved in ion-pair complexation of organic salt species.

4. Experimental

4.1 Molecular modelling

The conformational analysis of calix[5]crown **1** and complexes [**1** ⊃ Cl^-], [**2**·H^+ ⊂ **1**], [**2**·H^+ ⊂ **1** ⊃ Cl^-], [**3**·H^+ ⊂ **1**] and [**3**·H^+ ⊂ **1** ⊃ Cl^-] was carried out with the classical molecular mechanics force field using the Monte Carlo method to randomly sample the conformational space. The equilibrium geometries were first refined at the PM3 level, and the resulting conformations were used as input for the calculations at the density functional level of theory (DFT, B3LYP functional) using the 6-31G(d) basis set. Single-point energy calculations were performed at the DFT B3LYP/6-311++G(d,p) level of theory. All quantum mechanical calculations were performed using Spartan'08 (Wavefunction, Inc., Irvine, CA, USA) on a Macintosh equipped with Intel Dual Quad Core CPUs at 3.2 GHz.

4.2 ^{1}H NMR experiments

^{1}H NMR spectra were recorded at room temperature in $CDCl_3$, at 500 MHz, using the residual solvent signal as the internal standard. All spectra were recorded on equimolar solutions of host and guest (1 mM). The following stock solutions were used: [**1**] = 10 mM in $CDCl_3$; [(aryl)alkylammonium picrate] = 10 mM in CD_3OD. Complexes of calix[5]crown **1** with picrate salts were prepared by adding 70 μl of stock solutions of each component, evaporating the solvents to dryness and redissolving the residue in $CDCl_3$ to a final volume of 700 μl, for a final concentration of host and guest of 1 mM.

Acknowledgement

We are indebted to Prof. G. Bruno (Università di Messina) for some stimulating discussions and for his helpful advice.

Supporting Information

Additional figures, calculated energies and coordinates for all geometry-optimised structures are available online.

Notes

1. Neither picrate nor tetra-*n*-butylammonium ions bind to calix[5]crown **1**. They were therefore used as weakly coordinating counterions in order to gather structural information on the 1:1 complexes ([**1** ⊃ Cl^-], [**2**·H^+ ⊂ **1**] and [**3**·H^+ ⊂ **1**]) by ^{1}H NMR.
2. $\Delta\Delta E_{binding}$ is defined as follows: $\Delta\Delta E_{binding}$[**2**·HCl] = $\Delta E_{binding}$[**2**·H^+ ⊂ **1** ⊃ Cl^-] − $\Delta E_{binding}$[**2**·H^+ ⊂ **1**] − $\Delta E_{binding}$[**1** ⊃ Cl^-] for **2**·HCl, and $\Delta\Delta E_{binding}$[**3**·HCl] = $\Delta E_{binding}$[**3**·H^+ ⊂ **1** ⊃ Cl^-] − $\Delta E_{binding}$[**3**·H^+ ⊂ **1**] − $\Delta E_{binding}$[**1** ⊃ Cl^-] for **3**·HCl.

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