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Calix[5]arene-Based Heteroditopic Receptor for 2-Phenylethylamine Hydrochloride

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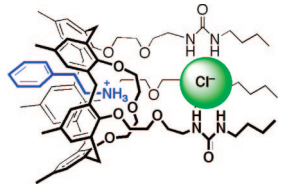
Received December 19, 2008



Novel (1,2-3,5)-calix[5]arene-bis-crown-3 and (1,3)-calix-[5]arene-crown-3 derivatives, bearing one or three ureido moieties at the lower rim, respectively, have been synthesized and investigated as heteroditopic receptors for inorganic and organic salts. Tris-ureido-calix[5]arene-crown-3 **10**, in particular, efficiently binds 2-phenylethylamine hydrochloride (PEA·HCl) as a spatially separated ion pair.

Host−guest interaction of a charged species with a neutral receptor is a complex event, which is regulated by several concurrent equilibria,[1] the main (opposed) ones being the complexation of the target ionic substrate by the neutral host and the concomitant association/dissociation of that substrate with its counterion, that is, ion pairing.[2] In these cases, the counterion implicitly acts as a competing receptor, limiting or even completely inhibiting complexation.[1b−e] To overcome this adverse effect, it has been common practice, when dealing with the selective recognition of a given cation or anion, to employ "non-coordinating" counterions, so as to make negligible the effect of ion pairing.[3]

The alternative approach to the selective complexation of a single ionic species is reliant on the design and construction of supramolecular[4] or molecular[5] systems capable of simultaneously binding both ionic counterparts. The former generally rely upon the synergic action of two independent receptors—one for the cation, the other for the anion—which ultimately produces separation of the ion pair. The latter, on the other hand, makes use of the knowledge gained over the past 30 years in the still-growing field of host−guest chemistry, combining the structural features of both cationic and anionic receptors to produce tailor-made heteroditopic receptors capable of selectively recognizing a target salt. By following this approach, a wide variety of heteroditopic host molecules have been constructed, combining most of the known cationic and anionic receptor motifs. Crown ethers,[6] cryptands,[7] and calixarenes[8] have all been extensively harnessed as cation-segregating moieties, whereas ureas,[9] polyamides,[10] and calixpyrroles[11] are among the most commonly employed anionic receptors. To date, however, examples of heteroditopic receptors for organic salts are still scarce.[12]

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10.1021/jo802777v CCC: $40.75
Published on Web 05/07/2009

As part of our ongoing research in the area of ion-pair complexation, we have shown in the past few years how suitably modified calixarenes can be used for the segregation and separation of alkali metals or linear alkyl(di)ammonium halides, either by exploiting the "binary host" approach (in tandem with calix[6]pyrrole[13] or diiodoperfluoroalkanes[14] as complementary anionic receptors) or by attaching ureido moieties to the upper rim, to produce heteroditopic[12g] or -tetratopic[12e] receptors.

Bearing in mind that alkylammonium moieties are ubiquitous in compounds of biological interest,[15] we have now undertaken the synthesis of new calixarene derivatives with the aim of developing versatile receptors for biogenic amines or trace amines[16] (as their hydrochlorides) in the form of a spatially separated ion pair.[17] In this paper we focus on calix[5]arene-(bis)crown-3 derivatives bearing ureido group(s) at the lower rim and describe their binding properties toward inorganic and organic salts.

We have just reported[18] that calix[5]arenes **1a**−**c** react with 2-(2-chloroethoxy)ethyl tosylate **2**, to produce derivatives **3** and **7a**,**b**, originating from the formation of either two or one intramolecular crown ether bridging loop(s) (see Scheme S1 of Supporting Information). Specifically, the reaction of *p*-H-calix[5]arene **1a**[19] and *p*-methylcalix[5]arene **1b**[20] with an excess of **2** and K_2CO_3 (10 equiv each) in refluxing CH_3CN gave (1,3)-bridged 2,4,5-tris[2-(2-chloroethoxy)ethoxy]calix[5]arene-crown-3 derivatives **7a** and **7b**, respectively, whereas the reaction of *p-tert*-butylcalix[5]arene **1c**[21] and **2**, under the very same conditions, produced (1,2-3,5)-bridged 4-[2-(2-chloroethoxy)ethoxy]calix[5]arene-bis-crown-3 **3**.

Compound **3**, in a preliminary investigation in the gas phase (ESI-MS),[18] showed interesting ionophoric properties toward alkali metal cations, with a marked preference for the larger ones (K^+ to Cs^+) over Na^+. These initial findings have now been confirmed by a series of ^{1}H NMR titration experiments (Supporting Information, Figures S3 and S4), which indicate that in all instances host−guest complexation is slow on the NMR time scale. Cesium, rubidium, and potassium ions, as picrate salts, were all taken up quantitatively in $CDCl_3/CD_3OD$ 4:1 solutions ($K_a > 10^6$ M^{-1}), while sodium was complexed less effectively ($K_a = 4.3 \times 10^3$ M^{-1}).[22,23] Furthermore, a closer look at the complexation-induced shifts experienced by the resonances (Ar and *t*-Bu) of the *p-tert*-butylphenyl ring bearing the 2-(2-chloroethoxy)ethoxy pendant chain suggests that the cation is likely being nested into the pocket generated by this pendant moiety and the ethereal bridge(s). On the other hand, when (1,2-3,5)-calix[5]arene-bis-crown-3 **3** was exposed to *n*-butylammonium picrate (which is known to undergo endo-cavity inclusion with a wide range of *p-tert*-butylcalix[5]arene derivatives),[24] no complexation was observed. This behavior was then ascribed to the cone-in conformation adopted by **3**, where the aryl moiety bearing the pendant group is tilted inward in a self-filling fashion.[18] The presence at the lower rim of two short bridging crown ether chains hampers the rearrangement to a regular cone conformation,[25] which is required to allow the *n*-$BuNH_3^+$ ion to enter the cavity. No evidence of ammonium interaction with the ethereal moieties was observed.

Conversion of **3** into a potential heteroditopic receptor for ion-pair recognition was carried out by derivatization of the 2-chloroethoxy terminal moiety present at the lower rim (Scheme 1). To this end, calix[5]arene **3** was reacted under standard Gabriel conditions with potassium phthalimide in DMF, to give calixarene **4** in 78% yield, which was then converted by treatment with hydrazine into the amino-derivative **5** (87% yield).[26] Amino-calixarene **5** was finally turned into the ureido derivative **6** by reaction with *n*-butylisocyanate in CH_2Cl_2 (52% yield).

Similarly to its chloro-precursor **3**, ureido-calix[5]arene-bis-crown-3 **6** displayed by ^{1}H NMR (Supporting Information, Figures S5 and S6; see also Figure S1, trace a, for ESI-MS

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(22) K_a values were derived from the average of at least three independent measurements (standard error ±15%).

(23) Lithium picrate was also tested, but only trace amounts of complex were detected ($K_a = 70$ M^{-1} in 4:1 $CDCl_3/CD_3OD$).

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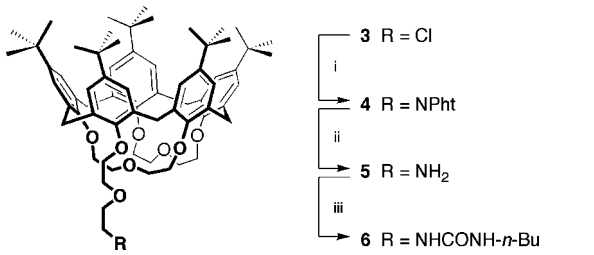
SCHEME 1. Synthesis of the Ureido-calix[5]arene-bis-crown-3 6[a]



[a] Reagents and conditions: (i) potassium phthalimide (KNPht), DMF (78%); (ii) $H_2N-NH_2 \cdot H_2O$, EtOH (87%); (iii) $CH_3(CH_2)_3NCO$, CH_2Cl_2 (52%).

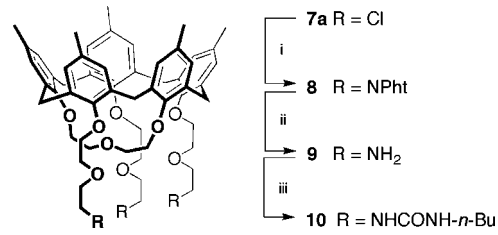
data) a strong affinity[27] for large cations (K^+ to Cs^+) of the alkali metal picrate series. Moreover, no apparent enhancement of the cation-binding constant was detected by ^1H NMR, under the same experimental conditions ($CDCl_3/CD_3OD$ 4:1, 1 mM), when the picrate was replaced by anions likely to be recognized by the ureido moiety (e.g., chloride, iodide, acetate, or benzoate).

Calix[5]arene-crown-3 **7a** was then tested as an ionophore and found to be equally efficient in the binding of sodium, potassium, rubidium, and cesium picrate ($K_a > 10^6$ M^{-1} in $CDCl_3/CD_3OD$ 4:1), giving slow-exchanging complexes on the NMR time scale[28] (Supporting Information, Figures S7 and S8; see also Figure S1, trace b, for ESI-MS data). In addition, calixcrown **7a**, contrary to the case of **3** and in agreement with its less pronounced structural rigidity (one polyether bridge instead of two) and more accessible cavity (methyl instead of *tert*-butyl groups at the upper rim), was able to form endo-cavity complexes with *n*-butylammonium picrate in $CDCl_3$ ($K_a > 10^6$ M^{-1}).[29] *n*-$BuNH_3^+$ inclusion in *p*-methylcalix[5]arene derivatives is unprecedented, and in analogy with the better known behavior of the *p-tert*-butylcalix[5]arene analogues,[24] this process is slow on the NMR time scale and gives rise to high field resonances ($\delta = 0.2$ to -1.8 ppm) for the cavity-included methylene/methyl groups (Supporting Information, Figure S9, trace b). Interestingly, however, when the more tightly ion-paired *n*-$BuNH_3^+Cl^-$ salt was added to a $CDCl_3$ solution of **7a**, the ^1H NMR spectrum showed a general broadening of the peaks, but no evidence of endo-cavity complexation was detected (Supporting Information, Figure S9, trace c).

Calix[5]arene-crown-3 **7a** was converted (via tris-phthalimido derivative **8** and tris-amino-calixarene **9**) into tris-ureido-calix-[5]arene-crown-3 **10** by applying the same synthetic strategy previously described for **6** (Scheme 2).

In analogy with **3**, **6**, and **7a**, tris-ureido-calixarene **10** forms stable complexes with the cations of alkali metal picrates ($K_a > 10^6$ M^{-1} for Na^+,[28] K^+, Rb^+, and Cs^+ in 4:1 $CDCl_3/CD_3OD$; Supporting Information, Figures S10 and S11; see also Figure S1, trace c, for ESI-MS data), but in addition it can also solubilize and bind very effectively alkali metal chloride salts

SCHEME 2. Synthesis of the Tris-ureido-calix[5]arene-crown-3 10[a]



[a] Reagents and conditions: (i) potassium phthalimide (KNPht), DMF (37%); (ii) $H_2N-NH_2 \cdot H_2O$, EtOH (89%); (iii) $CH_3(CH_2)_3NCO$, CH_2Cl_2 (74%).

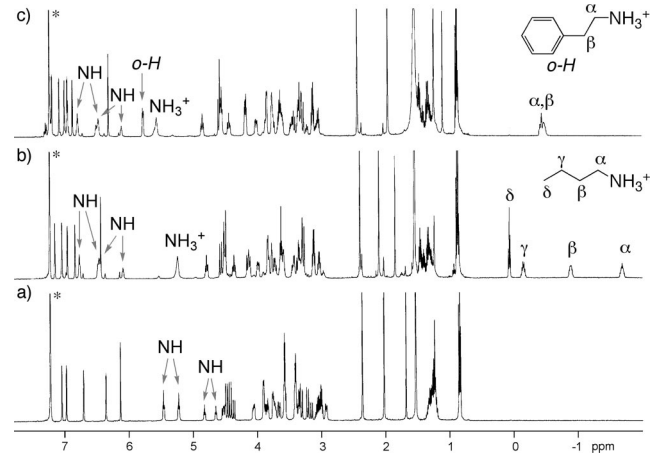


FIGURE 1. ^1H NMR spectra (500 MHz; $CDCl_3$; 300 K) of (a) [**10**] = 1 mM; (b) [**10**] = [*n*-$BuNH_3^+Cl^-$] = 1 mM; and (c) [**10**] = [PEA·HCl] = 1 mM. *Residual solvent peak.

(K_a's $> 10^6$ M^{-1})[28] in the same solvent mixture (Supporting Information, Figure S12; see also Figure S1, trace d, for ESI-MS data). These latter findings suggest that the three ureido moieties, present at the lower rim of **10**, are involved in the uptake of the chloride counterion, although no direct ^1H NMR proof of NHs···Cl^- interaction could be detected under the experimental conditions used.[30]

Clear-cut evidence of the cooperative role played by the three pendant ureido groups of **10** to act as an anion-binding site came from ^1H NMR experiments carried out in the presence of *n*-$BuNH_3^+Cl^-$, in neat $CDCl_3$ (Figure 1, trace b; see also Supporting Information, Figure S2, trace c, for ESI-MS data). In this case, salt complexation ($K_a = 7.35 \times 10^4$ M^{-1},[22] for both cation and anion) is incontrovertibly indicated by the appearance of high field peaks ($\delta = -1.75$ to 0.10 ppm) for the cavity-included *n*-$BuNH_3^+$ ion and the downfield shift ($\Delta\delta = 1.22-1.38$ ppm) experienced by the ureido NH resonances upon chloride binding.[31] The ureido-containing chains of **10**, absent in the trichloro-precursor **7a**, facilitate the separation of the ion-paired salt and, in so doing, permit the inclusion of the "naked" *n*-$BuNH_3^+$ ion. Anion binding by the ureido moieties of **10** was additionally confirmed by a separate ^1H NMR experiment with *n*-$Bu_4N^+Cl^-$. The cation of this salt is far too big to enter the cavity of **10**; however, because of a relatively

(27) In every case, binding of all cations to **6** was found to be slow on the NMR time scale: $K_a > 10^6$ M^{-1} for K^+, Rb^+, and Cs^+ and $K_a = 1.8 \times 10^3$ M^{-1} for Na^+.

(28) Peaks in ^1H NMR spectra for [$Na^+ \subset$**3a**] and [$Na^+ \subset$**10**] complexes were found to be broad, as a result of a faster exchange rate with respect to the other cations. Addition of an excess of sodium picrate resulted, however, in a sharpening of the peaks. This is not the first example observed for calixcrowns, see: Arnaud-Neu, F.; Ferguson, G.; Fuangswasdi, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Petringa, A. *J. Org. Chem.* **1998**, *63*, 7770–7779.

(29) ^1H NMR complexation experiments in the presence of organic salts were carried out in neat $CDCl_3$ to be able to observe the NH resonances and maximize, at the same time, the anion−ureido binding interactions.

(30) The NH groups of **10** undergo proton exchange in 4:1 $CDCl_3/CD_3OD$, and consequently their resonances are not observable.

(31) Host−guest complexation was judged to take place with a 1:1 stoichiometry on the basis of the fact that the addition of an excess of guest salt (2 equiv) to **10** (1 equiv) caused the disappearance of all the resonances accounting for the free host and did not induce any detectable chemical shift variation on those referring to the complexed species.

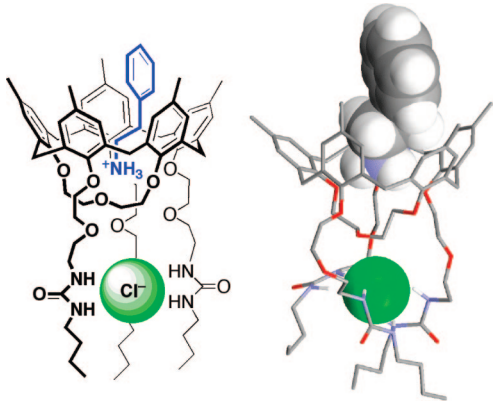


FIGURE 2. Equilibrium geometry for the [Cl^-⊂**10**⊃PEA·H^+] complex obtained from semiempirical calculations at the PM3 level.

loose ion pairing with its chloride counterion in $CDCl_3$, the latter is complexed by the ureido NH groups, though the binding constant is very small ($K_a = 17\ M^{-1}$).[22,32] These findings, taken together, demonstrate the power of the heteroditopic approach to the binding of salt species. In the case of **10** and *n*-$BuNH_3^+Cl^-$, the "weak" ureido−chloride interactions are sufficient to permit the complexation of *n*-$BuNH_3^+$ thanks to the ion-pair separation performed by the synergic action of the two binding sites. In turn, the chloride ion, "freed" from its organic counterion, is complexed by the ureido moieties with a much higher binding constant ($K_a = 7.35 \times 10^4\ M^{-1}$).[13a]

Tris-ureido-calix[5]arene-crown-3 **10** was finally set the task of binding 2-phenylethylamine[16,33] hydrochloride (PEA·HCl). Unlike its trichloro-precursor **7a**, **10** was able to bind this biologically relevant salt with an association constant ($K_a = 1.89 \times 10^5\ M^{-1}$,[22] for both cation and anion) even higher than the one detected for *n*-$BuNH_3^+Cl^-$. In the ^1H NMR spectrum of this complex (Cl^-⊂**10**⊃PEA·H^+), the NH resonances of the tripodal ureido chains undergo substantial downfield shifts ($\Delta\delta = 1.23-1.67$ ppm) upon chloride binding, whereas the peaks of the portion of the 2-phenylethylammonium ion residing within the calixarene cavity (*o*-H, α,*β*-CH_2's, and NH_3^+) are seen at unusually high field (5.78−5.83, −0.52/−0.39, and 5.60 ppm, respectively) (Figure 1, trace c; see also Supporting Information, Figure S2, trace d, for ESI-MS data).[31]

Semiempirical calculations[34] performed at the PM3 level on the Cl^-⊂**10**⊃PEA·H^+ complex showed that the cation is, as expected, embedded in the calix[5]arene cavity, whereas the chloride anion is encircled by the tentacle-like ureido-containing chains, which effectively encapsulate the ion (Figure 2). The two ions are physically separated by the crown-3 bridging loop, and the $^+N\cdots Cl^-$ distance is 7.17 Å. The geometry of the complex is in excellent agreement with the spectroscopic data. The included *o*-H and α,*β*-CH_2 groups of PEA·HCl are placed in the shielding cone of the *π*-rich aromatic cavity of **10**, and at the same time the ammonium group is situated in an optimal position to form tripodal hydrogen bonding with three of the phenolic oxygen atoms.

In conclusion, we have demonstrated that suitable chemical alteration of a readily available building block (i.e., placement of ureido moieties at the lower rim of a calix[5]arene-crown-3) may turn a potential host molecule (i.e., **7a**) into a powerful heteroditopic receptor (i.e., **10**) for organic salts. Our results also show that fine-tuning of the calix[5]arene upper rim (i.e., replacement of *tert*-butyl with methyl groups) has now permitted the recognition and binding of a prototype alkylarylamine of biological relevance (as its hydrochloride). Future studies will be targeted toward the design of *p*-methylcalix[5]arene-based receptors for biogenic/trace amines (e.g., dopamine and tyramine) structurally related to PEA.

Experimental Section

General Procedure for Phthalimido-calix[5]arenes 4 and 8. A stirred mixture of chloro-calix[5]arene[18] **3** or **7a** (0.246 mmol) and potassium phthalimide (3 equiv for each chloroethoxy chain) in anhydrous DMF (30 mL) was kept at 110 °C for 24 h under N_2. The solvent was evaporated under reduced pressure, and the residue was partitioned between chloroform (30 mL) and water (30 mL). The organic layer was washed with water (2 × 30 mL), dried ($MgSO_4$), and concentrated.

General Procedure for Amino-calix[5]arenes 5 and 9. A stirred mixture of phthalimido-calix[5]arene **4** or **8** (0.19 mmol) and hydrazine monohydrate (10 equiv for each phtalimide) in EtOH (25 mL) was refluxed overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and the solution obtained washed with aqueous NaOH (5% w/w, 2 × 30 mL), dried ($MgSO_4$), and then evaporated to dryness.

General Procedure for Ureido-calix[5]arenes 6 and 10. A solution of aminocalix[5]arene **5** or **9** (0.151 mmol) and *n*-butylisocyanate (2 equiv for each amino group) in dry CH_2Cl_2 (10 mL) was stirred at room temperature under nitrogen for 3 h. The solvent was then evaporated, to give the crude product.

Acknowledgment. We thank Dr. D. Garozzo (CNR, ICTP Catania) for mass spectra. We are also grateful to MiUR (PRIN-2006 project) for financial support of this work.

Supporting Information Available: General experimental methods, molecular modeling protocol, purification and characterization data for compounds **4**−**6** and **8**−**10**, ^1H NMR and ESI-MS spectra, and procedures for all the complexation experiments described, together with the ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802777V

(32) It is interesting to observe that complexation of chloride from *n*-$Bu_4N^+Cl^-$ is fast on the NMR time scale, while it becomes slow in the Cl^-⊂**10**⊃PEA·H^+ complex.

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