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PAPER

Acid–base modulation of a versatile heteroditopic calix[6]arene based receptor†

Damien Cornut,[a] Jérôme Marrot,[b] Johan Wouters[c] and Ivan Jabin*[a]

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A new calix[6]crypturea (**3**) has been efficiently synthesized through a domino Staudinger/aza-Wittig reaction followed by a [1 + 1] macrocyclization step. In comparison to the previously reported tren-based calix[6]crypturea, this heteroditopic receptor **3** displays a more flexible and larger tris-ureido cap. Due to this structural alteration, **3** exhibits unique host–guest properties: (i) the protonation of its basic cap leads to a rigidification of the whole structure and, thus, allosteric control of the binding properties and selective guest switching processes are possible, (ii) its versatility is unprecedented in the literature since it can bind either neutral molecules, anions, primary/secondary ammonium ions, quaternary ammonium ions or contact ion pairs according to different modes of recognition and with a remarkable selectivity within each family of guest, (iii) cascade complexes even stable in a protic environment can be obtained. These remarkable features are nicely illustrated by the fact that, according to the nature of its counterion, an ammonium ion $R^1R^2NH_2^+$ can be accommodated into the cavity either as an independent guest, as a contact ion-pair or as a cascade complex. All these results are reminiscent of biological receptors and validate the strategy that consists of designing receptors presenting a high flexibility that can be controlled by an external stimulus.

1 Introduction

The design of efficient molecular receptors for charged or neutral species is a major objective in supramolecular chemistry.[1] Indeed, such receptors can find many applications in various areas, such as sensing, catalysis, nanoscience, biomimicry, drug delivery and separation science. A classical strategy for the elaboration of artificial hosts consists of using concave macrocyclic structures displaying a hydrophobic cavity such as cyclodextrins[2] or cavitands[3] (*e.g.* resorcinarenes,[4] cyclotriveratrylenes,[5] or calixarenes[6]). In this context, versatile receptors, *i.e.* receptors capable of recognizing different families of guests, are particularly attractive since the control of their binding properties by an external stimulus can be notably exploited for the construction of unique switchable systems.[7] However, most receptors described so far are highly specific for a particular guest or family of guests (*i.e.* metal or ammonium ions,[1c] anions,[8] ion pairs[9] or neutral molecules[4a]). Thus, only few examples of versatile cavity-based receptors have been reported.[7,10] A possible explanation lies in their high conformational rigidity, indeed rigid receptors are usually more selective but less versatile. As a consequence, using rather flexible macrocyclic structures for the building of versatile receptors appears as an appealing strategy, the challenge being, however, to control their flexibility in order to reach high selectivity. In this regard, different families of bio-inspired receptors that combine a donor or acceptor polyaza-binding site in close proximity to a hydrophobic cavity have been built from the highly flexible calix[6]arene skeleton.[11] It was shown that the flexibility of their calix[6]arene subunit can be restricted either through coordination to a metal ion,[12] an anion[13] or even through ion-pairing[14] and covalent capping.[15] All these calix[6]arenes based-systems are constrained in the cone conformation and thus present a concave cavity suitable to include an organic guest. Moreover, flexibility of the calix[6]arene core turned out to be an advantage as the cavity size can adapt to the guest.[16] Such induced-fit phenomena (*i.e.* shaping the cone through guest binding) have been notably exploited for the elaboration of allosterically coupled multi-receptors.[14b,e] One of these families of receptors, *i.e.* the calix[6]tris-ureas (Fig. 1),[13,17] has been found to strongly bind either anions or organic contact-ion pairs in a cooperative way.[18,19] Indeed, the converging three ureido groups allow strong binding to anions, which, in turn, allows strong binding of an ion-paired ammonium accommodated into the calixarene cavity. Recently, an even more versatile and sophisticated heteroditopic receptor has been obtained through the grafting of a covalent tren-based tris-ureido cap on the narrow rim of the calix[6]arene cavity (Fig. 1).[20]

[a]*Laboratoire de Chimie Organique, Université Libre de Bruxelles (U.L.B.), Av. F. D. Roosevelt 50, CP160/06, B-1050 Brussels, Belgium. E-mail: ijabin@ulb.ac.be; Fax: (+) 32-2-650-27-98; Tel: (+) 32-2-650-35-37*

[b]*Institut Lavoisier, UMR CNRS 8180, Université de Versailles St-Quentin en Yvelines, 45 av. des Etats-Unis, 78035 Versailles cedex, France*

[c]*Département de Chimie, Université de Namur (FUNDP), Rue de Bruxelles 61, B5-5000 Namur, Belgium*

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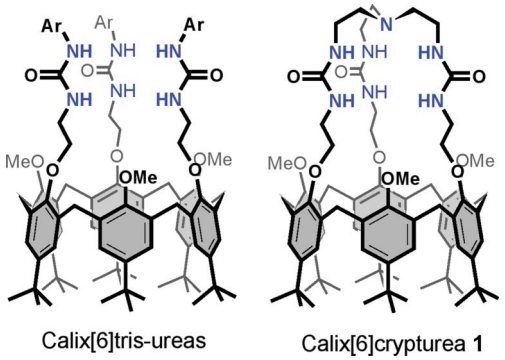


Fig. 1 Structures of the calix[6]tris-ureas, calix[6]crypturea **1**.

This calix[6]crypturea (**1**) exhibits unique host–guest properties toward polar neutral molecules, anions, or contact organic ion pairs and it has been shown that these versatile host properties can be controlled by protonation of the apical nitrogen of the capping tren moiety. Indeed, due to a steric repulsion with the introverted NH^+ proton, anion release was observed upon protonation of the basic cap of **1**.[21,22] Thus, sophisticated three-way supramolecular switches based on the interconversion of host–guest systems have been reported with this receptor.[23] Moreover, thanks to the flexibility of the calixarene framework, the intra-cavity binding of large biologically relevant ammonium salts was evidenced through induced fit processes that involve the spreading of the anisole units.

In the course of designing readily available calixarene based receptors whose host properties can be controlled by external stimuli, a related calix[6]crypturea bearing an additional methylene group that moves the proton sensitive site away from the tris-ureido binding site has been envisaged. Indeed, with this receptor, the complexation of an anion sandwiched between the positively charged NH^+ of the cap and a co-bound ammonium ion into the cavity was expected. Examples of such cascade complexes made of organic cations are extremely rare in the literature.[24] Besides, we wanted to see if the higher flexibility of this new receptor could be controlled through protonation and, thus, if allosteric regulation and molecular switches could be achieved.

Here, we report the synthesis of this new calix[6]crypturea (**3**) and its remarkably versatile binding properties toward either neutral or charged species, with major differences being observed in comparison with what was reported for the parent receptor **1**.

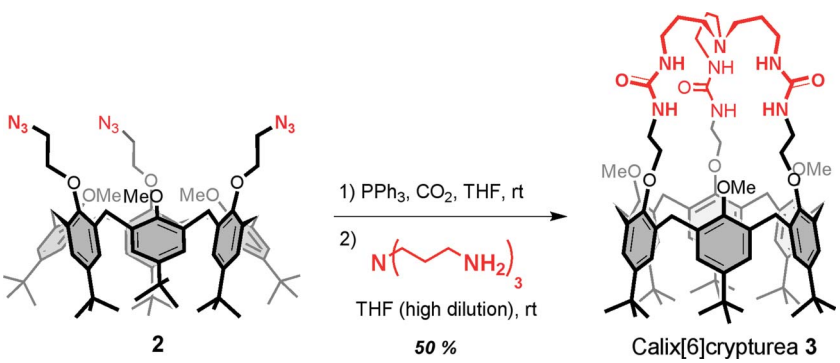
2 Results and discussion

2.1 Synthesis and characterization by NMR spectroscopy and XRD analysis of calix[6]crypturea 3

Calix[6]crypturea **3** was obtained from the known[20] calix[6]tris-azide **2** and the commercially available tris(3-aminopropyl)amine through a domino Staudinger/aza-Wittig reaction followed by a [1 + 1] macrocyclization step. More precisely, the reaction of calix[6]tris-azide **2** with PPh_3/CO_2 led *in situ* to the reactive intermediate calix[6]tris-isocyanate which was immediately reacted with the tris-amine under high dilution conditions. Flash chromatography purification of the crude mixture led to the desired calix[6]crypturea **3** in an overall 50% yield from **2** (Scheme 1).

Calix[6]crypturea **3** was characterized by ^{1}H NMR spectroscopy at 298 K and all the signals were assigned through 2D NMR analyses.[25] Thus, the ^{1}H NMR spectra recorded in either $CDCl_3$, $CD_3CN/CDCl_3$ (7 : 3) or $CD_3OD/CDCl_3$ (7 : 3) show very similar C_{3v} symmetrical patterns characteristic of averaged cone conformations (see Fig. 2a for the spectrum in $CDCl_3$).[25] In contrast to the parent receptor **1**, the NMR spectrum of **3** in an apolar solvent such as $CDCl_3$ was weakly sensitive to the addition of water or to the temperature (from 258 K to 328 K).[25] In all solvents, the downfield chemical shift of the three methoxy groups may result from a fast self-inclusion of one of these groups that averages three dissymmetrical but equivalent conformations (2.88 ppm $< \delta_{OMe} <$ 3.24 ppm).[26] Such an hypothesis was confirmed by an X-ray structure† obtained by slow diffusion of Et_2O into a cold (4 °C) $CHCl_3/CH_3CN$ solution of calix[6]crypturea **3** (Fig. 3, left). Indeed, the calixarene core stands in a pinched cone conformation with one methoxy group deeply included into the cavity. In addition, the flexible tris-ureido cap displays a distorted conformation with one introverted ureido arm that establishes strong hydrogen bonding interactions with the two NH of a second ureido group [d(N···O) = 2.748 and 2.843 Å]. Additional intermolecular hydrogen bonding interactions that involve these two ureido groups are also observable in the lattice, leading to a linear H-bonding network (Fig. 3, right).

The protonated derivative **3**·H^+ was obtained quantitatively after the addition of 1 equiv. of picric acid (PicH) to a solution of **3** in either $CDCl_3$, $CD_3CN/CDCl_3$ (7 : 3) or $CD_3OD/CDCl_3$ (7 : 3).[25] In all cases, a notable downfield shift of the NCH_2CH_2 protons clearly indicated the protonation of the bridging tertiary amine ($\Delta\delta_{NCH2}$ >0.74 ppm and $\Delta\delta_{NCH2CH2}$ >0.29 ppm).[27] It is noteworthy



Scheme 1 Synthesis of calix[6]crypturea **3**.

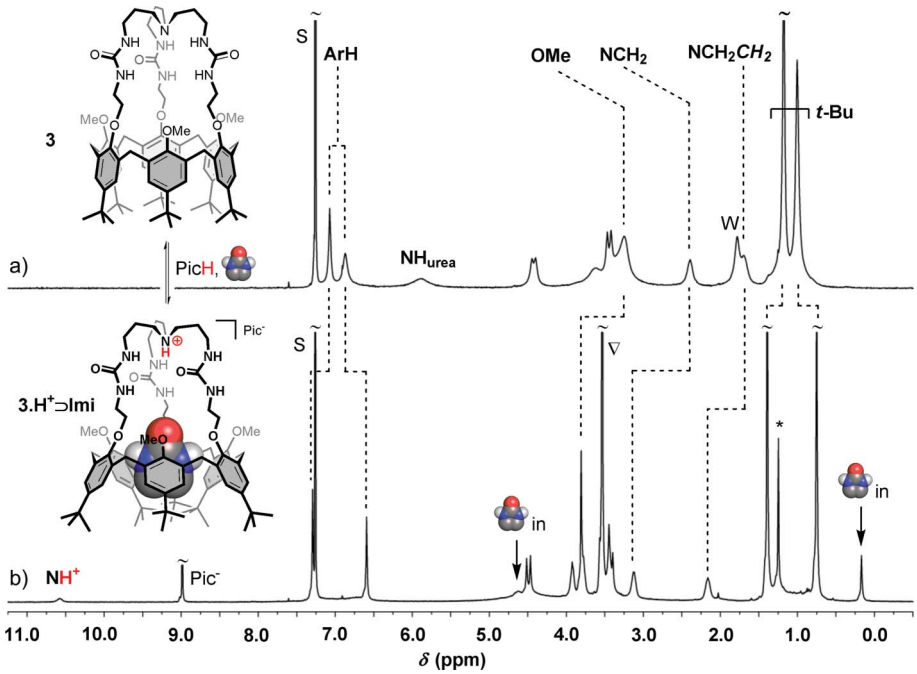


Fig. 2 ^{1}H NMR spectra (300 MHz, 298 K) of a) **3** in $CDCl_3$; b) **3**·**H**$^+$⊃**Imi** in $CDCl_3$; ∇: free Imi; W: water; S: residual solvent; *: residual grease.

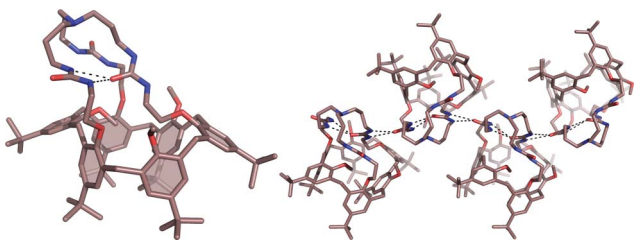
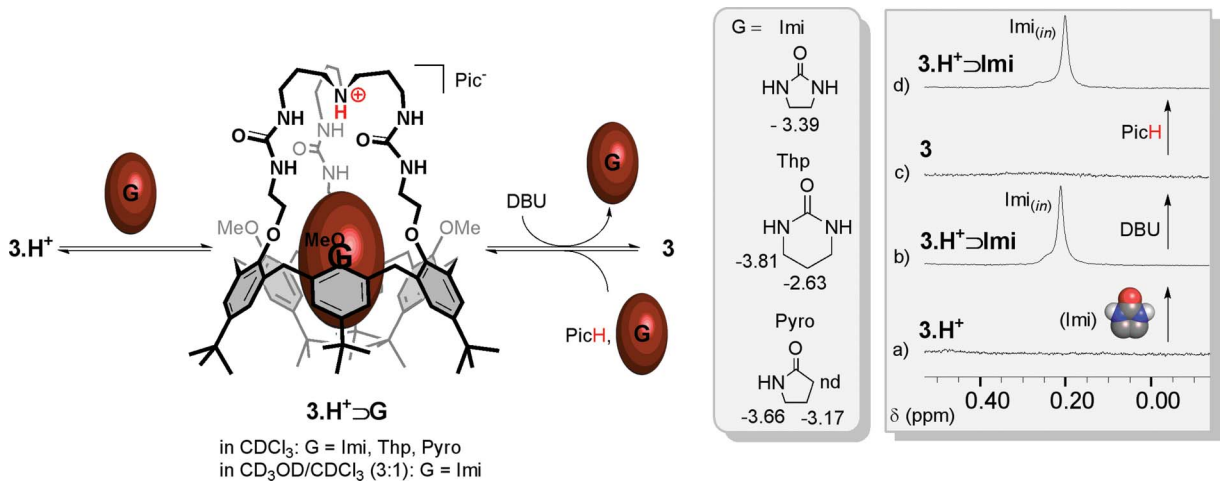


Fig. 3 Left: X-ray structure of calix[6]crypturea **3**. Selected distances: d(N···O) = 2.748 and 2.843 Å. Right: X-ray structures of **3** displaying the inter- and intramolecular H-bond interactions within the unit cell.

that, in $CDCl_3$ and $CD_3CN/CDCl_3$ (7 : 3), the NH^+ proton is clearly apparent at 10.73 and 10.07 ppm respectively.

2.2 Neutral molecule recognition

The host properties of calix[6]crypturea **3** toward polar neutral guests (G) were first investigated at 298 K by NMR spectroscopy in $CDCl_3$. Thus, the addition of an excess of imidazolidin-2-one (Imi), tetrahydropyrimidin-2(1*H*)-one (Thp), pyrrolidin-2-one (Pyro) or DMSO did not affect the NMR spectrum of **3**. The reluctance of **3** for such neutral guests differs from what was observed with the parent receptor **1** and can be rationalized by the higher flexibility and thus the weaker preorganization of the tris-ureido binding site of **3**. However, while the binding of small alcohols, DMF or propionamide could not be evidenced with the protonated derivative **3**·**H**$^+$, the selective inclusion of Imi, Thp and Pyro was detected (Scheme 2). The resulting complexes



Scheme 2 Host–guest properties of calix[6]crypturea **3**·**H**$^+$ toward neutral guests and reversible base-triggered release of these guests. Left inset: CISs of the neutral guests. Right inset: high-field region of the ^{1}H NMR spectra ($CDCl_3$, 300 MHz, 298 K) of a) **3**·**H**$^+$; b) +IMI (8 equiv.); c) +DBU (2 equiv.); d) +PicH (7 equiv.). nd: not determined because of signal overlapping.

Table 1 Relative affinities ($K_{G/Pyro}$) and association constant (K_a) of the neutral guests (G) in the case of **3·H⁺⊃G**

Entry	Guest	$K_{G/Pyro}$[a] in $CDCl_3$	K_a (M^{-1})[b] in $CD_3OD/CDCl_3$ (1 : 2)
1	Imi	17	18
2	Thp	2	—
3	Pyro	1	—

[a] Relative affinity determined at 298 K and defined as ($[G_{in}]\times[Pyro_{free}]$)/($[G_{free}]\times[Pyro_{in}]$) where the subscript "in" stands for "included". Errors estimated ±10%; [b] K_a was determined at 298 K by integration of the different species in equilibrium. K_a is defined as: $K_a = [\mathbf{3}\cdot\mathbf{H}^+\supset\mathbf{G}]/([\mathbf{3}\cdot\mathbf{H}^+]\times[G])$. Error estimated ±10%.

3·H⁺⊃G display well defined NMR spectra characteristic of C_{3v} symmetrical flattened cone conformation with the OMe groups expelled from the cavity (δ_{OMe} >3.78 ppm) (Fig. 2b). In all cases, the host–guest exchanges between **3·H⁺** and **3·H⁺⊃G** were found to be slow on the NMR time scale and integration of the high-field signals belonging to the included guest indicate a 1 : 1 host–guest stoichiometry. The complexation induced shifts (CISs) clearly indicate a positioning of the guests in the heart of the cavity (left inset, Scheme 2). These CISs are similar to those reported for the protonated **1·H⁺**, suggesting a comparable mode of recognition, *i.e.* hydrogen bonding interactions between the NH ureido groups of the cap and the carbonyl oxygen atom of the guests as well as between the NH(s) group(s) of the guests and the phenoxy oxygen atom(s) of the calixarene core. In addition, a ^{1}H NMR competitive binding experiment showed that the relative affinity of Imi toward host **3·H⁺** is one order of magnitude higher than that of Thp and Pyro (Table 1, entry 1 *vs.* entries 2 and 3).[28] Such a selectivity for ureido guests has been already described with closely related calix[6]arene based systems and has been rationalized thanks to an X-ray structure which revealed a four H bonding recognition process.[14b] Compared with **3**, the better recognition ability of **3·H⁺** could be due to an additional charge–dipole interaction between the protonated cap and the polar guests. In addition, a rigidification of the protonated cap could arise from a strong hydrogen bonding interaction between the NH^+ and an introverted ureido group (δ_{NH+} = *ca.* 10.55 ppm in all cases) (see structure of **3·H⁺⊃G** displayed in Scheme 2).[29] In such a case, the proton acts as an effector that favours the binding of neutral guests through a deep conformational reorganization of the tris-ureido binding site. All these considerations were corroborated with an optimized structure of **3·H⁺⊃Imi** obtained through computer modelling (Fig. 4, left).[30] Indeed, the position of the guest, the mode of recognition and the conformation of receptor **3·H⁺** obtained after energy minimization are highly compatible with what was deduced from the NMR data. Notably, a complementary DAAD-ADDA[31] quadruple H-bonding array between the ureido guest and **3·H⁺** as well as the presence of an introverted ureido arm can be observed. All in all, the optimized host–guest edifice is stabilized through seven H-bonding interactions. In a protic environment, *i.e.* $CD_3OD/CDCl_3$ (1 : 2), it was still possible to observe the complexation of Imi but with a weak association constant (Table 1).[25,32] Finally, taking advantage of the reluctance of **3** for neutral guests, a highly selective switching process between **3** and **3·H⁺⊃Imi** was achieved (right inset, Scheme 2). Indeed, the progressive addition of a base, *i.e.* diaza(1,3)bicyclo[5.4.0]undecene (DBU) to the host–guest complex **3·H⁺⊃Imi** led solely to the formation of **3**, while the further addition of PicH restored cleanly the complex **3·H⁺⊃Imi**. This switching process clearly illustrates that the complexation of neutral guests by host **3** can be controlled by an external stimulus, *i.e.* the addition of acids or bases to the medium.

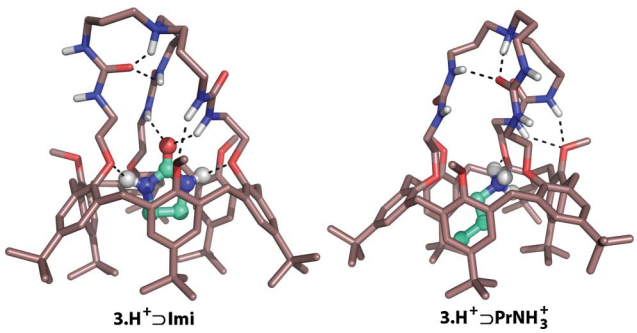


Fig. 4 Energy minimized structures of **3·H⁺⊃Imi** (left) and **3·H⁺⊃PrNH₃⁺** (right). With the exception of the N*H*, all the hydrogen atoms are omitted for clarity. Selected distances (Å) for **3·H⁺⊃Imi**: N(host)–O(Imi): 2.77 and 3.04; N(Imi)–O(host): 2.68 and 2.79; N^+–O(ureido): 2.44; N(ureido)–O(ureido): 2.82; N(ureido)–O(methoxy): 3.15. For **3·H⁺⊃PrNH₃⁺**: N^+(guest)–O(host): 2.76; N^+(host)–O(ureido): 2.84; N(ureido)–O(ureido): 2.91; N(ureido)–O(methoxy): 3.07 and 3.13.

2.3 Anion recognition

The binding of various anions (X^{n-}, with n = 1 or 2) by calix[6]crypturea **3** was investigated by NMR spectroscopy in $CD_3CN/CDCl_3$ (7 : 3) through the progressive addition of the corresponding tetra-*n*-butylammonium salts (nTBA$^+$X^{n-}). In all cases, only one set of signals was apparent over the course of the titration, showing fast host–guest exchanges on the NMR time scale. The complexation of Cl^-, Br^-, AcO^-, NO_3^-, $H_2PO_4^-$ and SO_4^{2-} through hydrogen bonding interactions was clearly evidenced by the significant downfield shift of the ureido protons.[33] A concomitant downfield shift of the C*H*$_2$O protons as well as an upfield shift of the OMe signal were observed. Moreover, the whole calixarene framework experiences a dramatic conformational change upon complexation of the anion since the tBu$_{in}$ and tBu$_{out}$ as well as the ArH$_{in}$ and ArH$_{out}$ interchange their positions (Fig. 5 for **3⊃SO₄²⁻**). Thus, similarly to **1**, receptor **3** recognizes the anions at the level of the crypturea cap through an induced fit process that involves the highly favourable filling of the cavity by the methoxy groups and the spreading of the ureido arms (Scheme 3).

The association constants K_a were estimated by monitoring the CISs of appropriate signals of calix[6]crypturea **3**, *i.e.* signals displaying significant shift upon complexation and no overlapping region (*i.e.* C*H*$_2$O or Ar*H* protons).[25] The data obtained for receptor **3** as well as those reported for the parent compound **1** (in CD_3CN) are given in Table 2. First, the affinity of SO_4^{2-} toward host **3** is *ca.* two to three orders of magnitude higher

Table 2 Comparison of the association constants K_a of calix[6]cryptureas **1** and **3** toward anions X^{n-} (with $n = 1$ or 2)

Entry	Anion X^{n-}[a]	Geometry of X^{n-}	K_a (M^{-1})[b]	
			1 (in CD_3CN)	**3** [in $CD_3CN/CDCl_3$ (7 : 3)]
1	Cl^-[c]	spherical	48 300[d]	58
2	Br^-	spherical	1930[d]	22
3	AcO^-	V-shaped	160[d]	300
4	NO_3^-	trigonal	98	48
5	$H_2PO_4^-$	tetrahedral	—	300
6	SO_4^{2-}	tetrahedral	nd[e]	16 300

[a] TBA^+ counterion was used in all cases; [b] K_a determined at 298 K and defined as: $K_a = [\mathbf{1}\supset X^-]/([\mathbf{1}]\times[X^-])$. Initial host concentration $[\mathbf{1}]i = 10^{-3}$ to 4.10^{-3} M and $[\mathbf{3}]i = 10^{-3}$ M. Errors estimated ±10%; [c] hydrate salt; [d] determined at 243 K; [e] not determined because a weak complexation and an abnormal looking titration curve were observed. This latter could result from an *exo*-complexation of the anion.

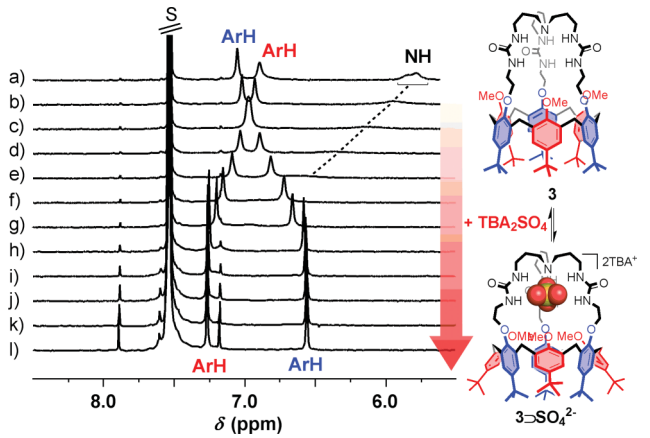
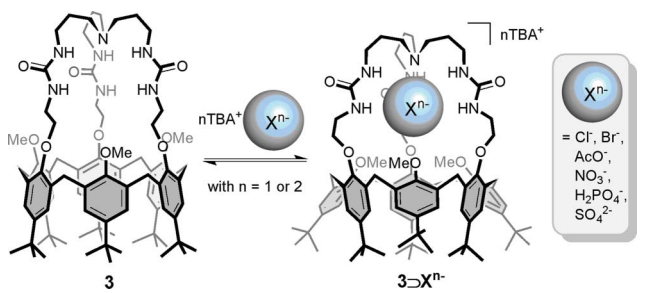


Fig. 5 a–l) ^1H NMR spectra (300 MHz, 298 K) in $CD_3CN/CDCl_3$ (7 : 3) obtained upon the progressive addition of $(TBA^+)_2SO_4^{2-}$ (from 0 to 9.5 equiv) to calix[6]crypturea **3**. S: residual solvent.

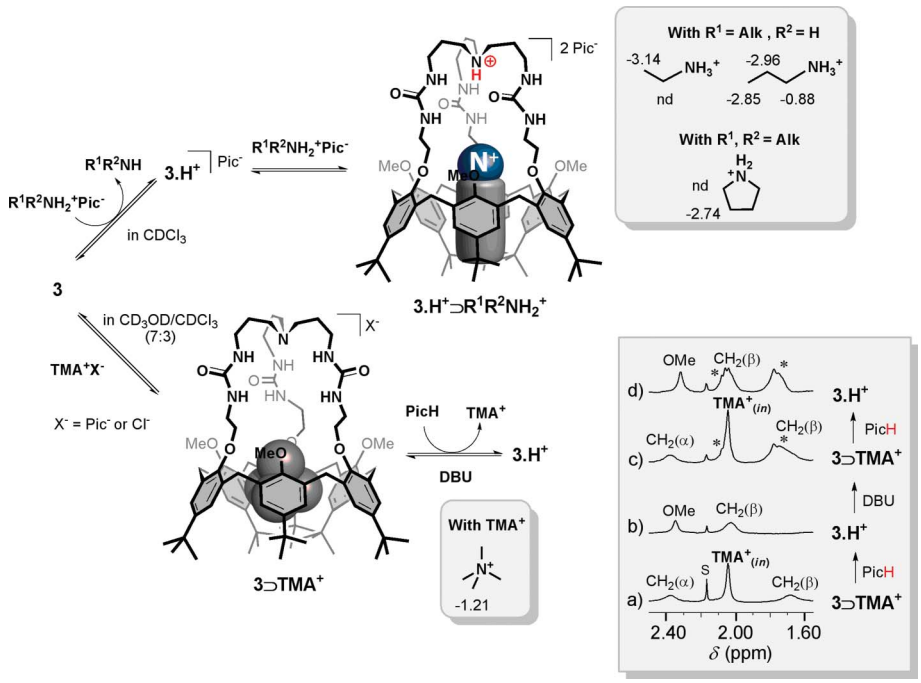


Scheme 3 Host–guest properties of calix[6]crypturea **3** toward anions in $CD_3CN/CDCl_3$ (7 : 3).

than those obtained with the other anions (Table 2, entry 6 *vs.* entries 1–5). This high selectivity for the sulfate anion strongly differs from what was observed with **1**. Indeed, in the case of the more rigid receptor **1**, the smallness of the pocket delimited by the tris-ureido cap and the introverted methoxy groups led to a binding discrimination which was mostly based on the size of the anions and thus a high selectivity was observed for the smaller chloride anion (Table 2, entry 1). In contrast, Cl^- is only poorly recognized by **3** as compared either to the more basic acetate or to the tetrahedral anions (Table 2, entries 1 *vs.* 3, 5 and 6). Moreover, if the binding of Cl^- by **1** was evidenced in a protic solvent (*i.e.* in CD_3OD), the NMR spectrum of **3** remained unchanged upon the addition of $(TBA^+)_2SO_4^{2-}$ in $CD_3OD/CDCl_3$ (7 : 3). In other words, host **1** possesses a preorganized tris-ureido recognition site of reduced size that can ensure a strong and selective binding of small anions even in a protic solvent while **3** shows a strong affinity for the bicharged sulfate anion but the higher flexibility of its binding site weakens its complexation ability in protic solvents. Finally, when the titration experiment was conducted with $(TBA^+)_2SO_4^{2-}$ and **3**·H^+ (obtained from **3** and 1 equiv. of PicH), a deprotonation of the receptor by the sulfate anion was observed over the course of the titration.[25] Thus, similarly to what was observed with **1**·H^+ which was reluctant to bind anions, this result seems to indicate that the binding ability of **3** toward anions is not reinforced through its protonation.

2.4 Ammonium ion recognition

Upon the progressive addition of picrate salts of primary or secondary ammonium ions $R^1R^2NH_2^+Pic^-$ (with R^1 = alkyl and R^2 = H or alkyl, Scheme 4) to a solution of calix[6]crypturea **3** in $CDCl_3$, increasing sharp signals corresponding to a new C_{3v} symmetrical calixarene species were apparent.[25,34] In all cases, the new species display a flattened cone conformation with the OMe groups expelled from the cavity (δ_{OMe} >3.84 ppm), down-field NH ureido signals and high-field signals (<0 ppm) corresponding to the inclusion of 1 equiv. of the ammonium ion into the cavity (Fig. 6a). The CISs of the alkyl chain of the ammonium ions indicate a positioning of these guests in the heart of the cavity (top inset, Scheme 4). Moreover, in all cases, the presence of a down-field NH^+ signal (δ_{NH+} >at 10 ppm) as well as a significant down-field shift of the NCH_2CH_2 protons attest to the protonation of the bridging tertiary amine. Addition of PicH to these host–guest complexes did not affect their NMR spectrum and superimposable NMR patterns were obtained upon the addition of the ammonium salts to **3**·H^+.[25] All these NMR data clearly indicate the selective formation of the dicationic host–guest complexes **3**·$H^+\supset R^1R^2NH_2^+$ (Scheme 4).[35] Interestingly, no *endo*-complex other than this dicationic complex was observable upon the progressive addition of even an excess of the free amine $R^1R^2NH_2$ to **3**·H^+. Thus, while parent receptors **1** or **1**·H^+ were insensitive to ammonium picrate salts, calix[6]crypturea **3** can accommodate ammonium ions but the prior protonation of the cap is mandatory (Scheme 4). The energy minimized structure of **3**·$H^+\supset PrNH_3^+$ shows that the NH^+ proton is hydrogen bonded with an introverted ureido arm of the cap (Fig. 4, right), the ammonium ion sitting in the cavity and being stabilized through



Scheme 4 Host–guest properties of calix[6]cryptureas **3** and **3**·**H**$^+$ toward ammonium ions. Insets: CISs of the ammonium ions and selected regions of the ^{1}H NMR spectra [$CD_3OD/CDCl_3$ (7 : 3), 300 MHz, 298 K] of a) **3**⊃**TMA**$^+$; b) +PicH (1.5 equiv.); c) +DBU (1.5 equiv.); d) +PicH (3.5 equiv.). nd: not determined because of signal overlapping. S: residual solvent; *: DBU. $CH_2(\alpha)$ and $CH_2(\beta)$ stand respectively for NCH_2 and NCH_2CH_2.

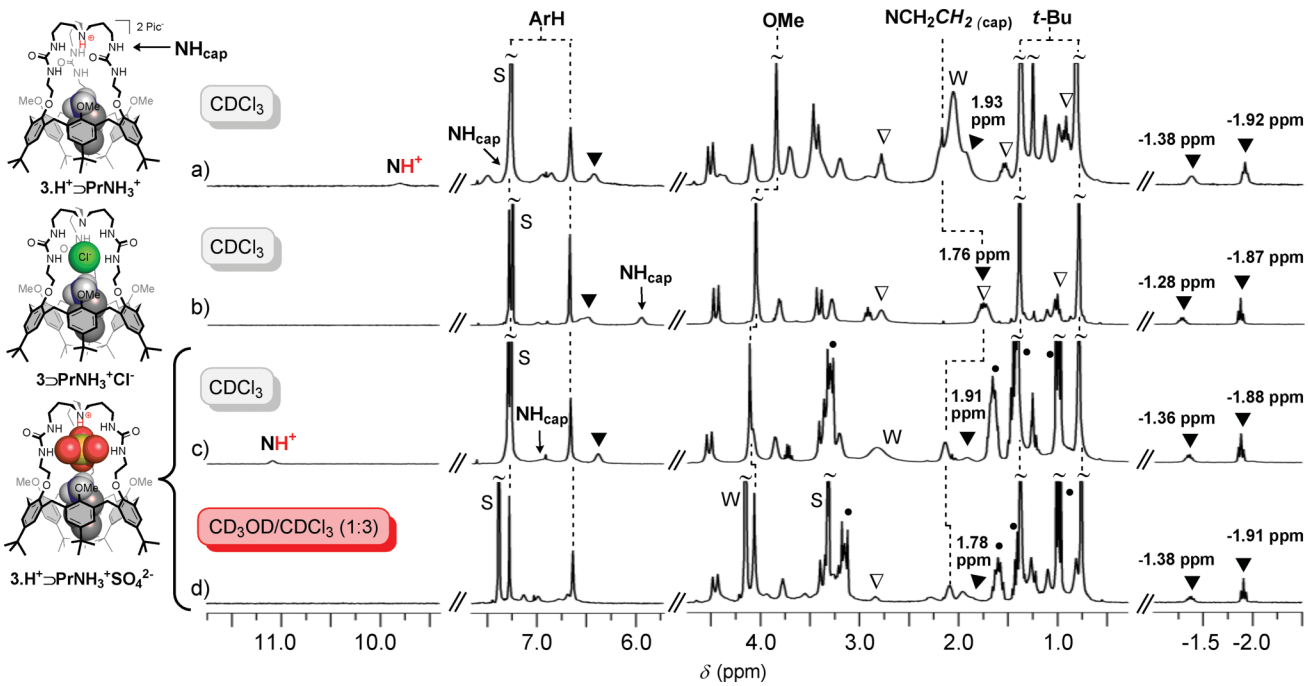


Fig. 6 ^{1}H NMR spectra (300 MHz, 298 K) of a) **3**·**H**$^+$⊃**PrNH**$_3^+$ in $CDCl_3$; b) **3**⊃**PrNH**$_3^+$**Cl**$^-$ in $CDCl_3$; c) **3**·**H**$^+$⊃**PrNH**$_3^+$**SO**$_4^{2-}$ in $CDCl_3$; d) **3**·**H**$^+$⊃**PrNH**$_3^+$**SO**$_4^{2-}$ in $CD_3OD/CDCl_3$ (1 : 3); ∇: free $PrNH_3^+$; ▼: $PrNH_3^+$ included; ●: TBA^+; W: water; S: residual solvent.

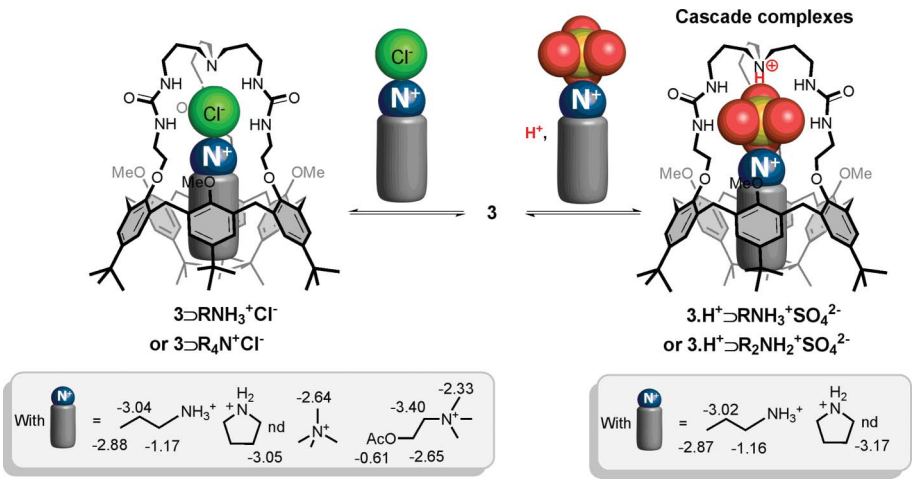
a H-bonding interaction with a phenoxy oxygen atom of the calixarene framework.[30] Additional intramolecular H-bonding interactions between the tris-ureido cap and the calixarene can be observed on the optimized structure. Since the ammonium ion and the NH$^+$ proton are on distinct binding sites, in this case, the NH$^+$ proton can be considered as an heterotropic allosteric activator that triggers the binding of the ammonium ions through a rigidification of the tris-ureido cap and, as a consequence, of the whole receptor. To our knowledge, these results constitute a rare case of *endo*-complexation of ammonium ions by a cationic receptor. Besides, no inclusion of the larger ammonium salt $HexNH_3^+Pic^-$ could be detected, showing that the calixarene cavity

controls the size of the guest. In $CD_3OD/CDCl_3$ (7 : 3), no binding of various primary, secondary or tertiary ammonium ions was observed even after a subsequent addition of PicH. However, to our delight, the *endo*-complexation of the tetramethylammonium ion (TMA^+) was clearly apparent in this protic environment (K_a = 28 M^{-1}) (Scheme 4). Moreover, in strong contrast with what was observed with primary or secondary ammonium ions, addition of PicH to the host–guest complex **3⊃TMA⁺** led to the release of the TMA^+ ion and to the formation of **3·H⁺**.[25] These observations show that quaternary ammonium ions are bound according to a different mode of recognition, and in this case, an inactive form of the receptor results from the protonation of the cap. These acid–base controllable properties of the receptor were again exemplified by a selective host–guest switching process between **3·H⁺** and **3⊃TMA⁺** through the alternating addition of PicH and DBU (right bottom inset, Scheme 4).[25]

2.5 Ion-pair recognition

The simultaneous complexation of an ammonium ion into the cavity and an anion at the level of the tris-ureido cap was then investigated by NMR spectroscopy in $CDCl_3$. Thus, the progressive addition of $PrNH_3^+Cl^-$ to **3** led to the selective formation of a new C_{3v} symmetrical NMR pattern characteristic of the ternary complex **3⊃PrNH₃⁺Cl⁻** (Scheme 5).[36] Indeed, this complex displays a flattened cone conformation with the OMe groups ejected from the cavity (δ_{OMe} = 4.06 ppm) and high-field signals belonging to the included propylammonium (Fig. 6b). In comparison with **3·H⁺⊃PrNH₃⁺**, the upfield chemical shift of the NCH_2CH_2 protons and the absence of signal above 7.5 ppm attest that the bridging tertiary amine is not protonated (Fig. 6a *vs.* 6b). Interestingly, while the protonated complex **3·H⁺⊃PrNH₃⁺** was the only observable species upon the addition of $PrNH_3^+Pic^-$ even in sub-stoichiometric quantity (*vide supra*), the addition of an excess of $PrNH_3^+Cl^-$ (*i.e.* 2 equiv.) did not lead to the protonation of **3⊃PrNH₃⁺Cl⁻** whose NMR spectrum remained unaffected. Moreover, in contrast to **3·H⁺⊃PrNH₃⁺**, the neutral complex **3⊃PrNH₃⁺Cl⁻** was still visible in the presence of a small amount of a protic solvent, *i.e.* $CD_3OD/CDCl_3$ (1 : 9).[25] These strong differences between the two host–guest complexes show the crucial role played by the anion. Indeed, in analogy with the parent receptor **1**, these observations denote that $PrNH_3^+Cl^-$ is recognized as a contact ion pair thanks to the close proximity between the two binding sites of **3** (*i.e.* the calixarene cavity and the three facing ureido groups). Due to the strong electrostatic interaction between the two partners of the associated ion-pair, the complexation of each partner is greatly reinforced when the other is simultaneously recognized and this mutual positive cooperativity increases the stability of the ternary complex in a protic environment. In $CDCl_3$, the cumulative formation constant β_2 for the simultaneous complexation of $PrNH_3^+$ and Cl^- was estimated to be $>7.2 \times 10^9$ M^{-2}, while in $CD_3OD/CDCl_3$ (1 : 9), a much lower constant was found (Table 3, entry 1). A weaker binding of the bulkier pyrrolidinium chloride ($PyrNH_2^+Cl^-$) was also observed (Scheme 5, Table 3). Despite the extremely poor solubility of TMA^+Cl^- in $CDCl_3$, host **3** was able to extract a significant amount of this salt,[25] and the absence of free TMA^+Cl^- suggested a strong binding of the ion-pair (Table 3, entry 3). However, when the spectrum was recorded in $CD_3OD/CDCl_3$ (7 : 3), a NMR pattern superimposable to that obtained with TMA^+Pic^- was observed, indicating the selective formation of the host–guest complex **3⊃TMA⁺** (Scheme 4). Interestingly, drastically different CISs were observed for the methyl groups of the TMA^+Cl^- salt in $CDCl_3$ and $CD_3OD/CDCl_3$ (7 : 3) (–2.57 ppm and –1.21 ppm respectively), attesting to a completely different binding mode for the cationic guest.[25] Such NMR data provides additional support for the co-binding of the chloride anion in pure $CDCl_3$. Finally, to our delight, the binding of the neurotransmitter acetylcholine chloride (Ach^+Cl^-) was also clearly detected (Scheme 5) (Table 3, entry 4).[25]

Compared with the former receptor **1**, major improvements in the ion-pairs' binding properties were observed with host **3**. Indeed, while the protonation of the ternary complex **1⊃PrNH₃⁺Cl⁻** led to the exclusive formation of **1·H⁺**, the addition of PicH to **3⊃PrNH₃⁺Cl⁻** in $CDCl_3$ afforded the cascade complex **3·H⁺⊃PrNH₃⁺Cl⁻** (*i.e.* high-field signals below 0 ppm belonging to the included ammonium ion and the presence of a NH^+ signal) with a cumulative formation constant β_2 of 2.2×10^5 M^{-2} (Table 4,



Scheme 5 Host–guest properties of calix[6]cryptureas **3** and **3·H⁺** toward ion-pairs. Insets: CISs of the ammonium ions. nd: not determined because of signal overlapping.

Table 3 Cumulative formation constants β_2 of the ion-pairs in the case of **3**

			β_2 (M^{-2})[a]
Entry	Guest	in $CDCl_3$	in $CD_3OD/CDCl_3$ (1 : 9)
1	$PrNH_3^+Cl^-$	$>7.2 \times 10^9$	1.2×10^4
2	$PyrNH_2^+Cl^-$	2860	—
3	TMA^+Cl^-	$>9.2 \times 10^6$	—
4	Ach^+Cl^-	140	—

[a] β_2 determined at 298 K by integration of the different species in equilibrium. β_2 is defined as $[\mathbf{3}\supset\mathbf{R^1R^2NH_2^+Cl^-}]/([\mathbf{3}]\times[R^1R^2NH_2^+]\times[Cl^-])$. Initial host concentration [**3**]i = 0.7 10^{-3} to 4.7 10^{-3} M. Error estimated ± 10%.

Table 4 Cumulative formation constants β_2 of the ion-pairs in the case of $\mathbf{3\cdot H^+}$

			β_2 (M^{-2})[b]
Entry	Guest[a]	in $CDCl_3$	in $CD_3OD/CDCl_3$ (1 : 3)
1	$PrNH_3^+Cl^-$	2.2×10^5	—
2	$PrNH_3^+SO_4^{2-}$	$>8.6 \times 10^8$	1.0×10^6
3	$PyrNH_2^+SO_4^{2-}$	—	6.5×10^5

[a] TBA^+ counterion was used in the case of the sulfate anion; [b] β_2 determined at 298 K by integration of the different species in equilibrium. β_2 is defined as $[\mathbf{3\cdot H^+}\supset\mathbf{R^1R^2NH_2^+}X^{n-}]/([\mathbf{3\cdot H^+}]\times[\mathbf{R^1R^2NH_2^+}]\times[X^{n-}])$. Initial host concentration [$\mathbf{3\cdot H^+}$]i = 2.4 10^{-3} to 3 10^{-3} M. Error estimated ± 10%.

entry 1). This finding prompted us to investigate the use of the sulfate anion, since such a bicharged anion would lead to more favourable neutral cascade complexes. Thus, the addition of a few equivalents of PicH/$PrNH_3^+TBA^+SO_4^{2-}$ to **3** in $CDCl_3$ led selectively to the formation of the complex $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$ (Scheme 5) with a remarkably high β_2 (Table 4, entry 2). In strong contrast, it was not possible to obtain the cascade complex $\mathbf{1\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$ under similar conditions, the only observable species being $\mathbf{1\cdot H^+}$ with this receptor. As shown in Fig. 6c, the NMR pattern of the cascade complex $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$ differs from those of the host–guest complexes $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+}$, $\mathbf{3}\supset\mathbf{PrNH_3^+Cl^-}$, and $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+Cl^-}$.[37] In particular, larger down-field shifts are observed for the NH^+ proton of the cap (if compared with $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+}$ and $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+Cl^-}$) and for the ureido protons (if compared with $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+Cl^-}$), in good agreement with stronger H-bonding interactions with the co-bound bicharged sulfate anion. Moreover, the chemical shifts of the included ammonium ion of $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$ are slightly different from those of $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+Cl^-}$ and $\mathbf{3}\supset\mathbf{PrNH_3^+Cl^-}$, indicating a close proximity between the cationic guest and its counterion (Fig. 6b *vs.* 6c). Very interestingly, the cascade complex $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$ proved to be remarkably resistant in a markedly protic solvent since its NMR spectrum in $CDCl_3$ was not affected by the addition of one third of CD_3OD (Table 4, entry 2).[25]

The role of the different partners of this unique cascade complex was evaluated through a series of NMR binding studies in $CD_3OD/CDCl_3$ (1 : 3). In this mixture of solvents, no inclusion of the ammonium ion was detected upon the addition of $PrNH_3^+Pic^-$ (1 equiv.) or $PrNH_3^+Cl^-$ (2 equiv.)/PicH (1 equiv.). However, the subsequent addition of respectively $TBA^+HSO_4^-$ (1 equiv.) or $(TBA^+)_2SO_4^{2-}$ (2 equiv.) afforded the quantitative formation of $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$.[25] Moreover, addition of $(PrNH_3^+)_2SO_4^{2-}$ (2 equiv.) to **3** led to the formation of $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$ showing that the propylammonium ion can act as the proton source for the elaboration of the cascade complex.[25] All these results indicate a highly cooperative and selective host–guest process. Indeed, there are two requirements that must be met for the *endo*-complexation of ammonium ions in this protic environment: (i) the receptor needs to be activated through protonation and (ii) a sandwiched bicharged anion that can equilibrate the charges and stabilize the cationic guest has to be present. Along these lines, the remarkable versatility of the receptor **3** was also illustrated by the formation of the cascade complex $\mathbf{3\cdot H^+}\supset\mathbf{PrNH_3^+SO_4^{2-}}$ upon the addition of $(TBA^+)_2SO_4^{2-}$ to a $CDCl_3$ solution of a mixture of $\mathbf{3}\supset\mathbf{PrNH_3^+Cl^-}$ and 1 equiv. of free $PrNH_3^+Cl^-$. Thus, the addition of a basic species, *i.e.* $(TBA^+)_2SO_4^{2-}$, can induce the protonation of the receptor, the driving force being the formation of the favourable neutral cascade complex.[25] Finally, the binding of $PyrNH_2^+SO_4^{2-}$ was also achieved in $CD_3OD/CDCl_3$ (1 : 3) (Scheme 5).[25] The cumulative formation constants β_2 for the simultaneous complexation of the ammonium ions and either the chloride or the sulfate anion by $\mathbf{3\cdot H^+}$ are summarized in Table 4. These data indicate a binding discrimination in favour of the smaller propylammonium ion associated to the bicharged SO_4^{2-} anion (Table 4, entry 2 *vs.* entries 1 and 3).

3 Conclusion

The synthesis of a new calix[6]crypturea (**3**) was efficiently achieved through a domino Staudinger/aza-Wittig reaction followed by a [1 + 1] macrocyclization step. As far as we know, the versatility of this heteroditopic receptor is unique since it can either recognize neutral molecules, anions, ammonium ions and contact ion pairs with a remarkable selectivity within each family of guest. Similarly to what was observed with the former calix[6]crypturea **1**, the present work also underscores the remarkable ability of **3** to strongly bind contact organic ion-pairs, the closeness of the two binding sites being crucial in the recognition process since it avoids the unfavourable separation of the co-bound ions. However, in comparison with **1**, the tripodal cap of **3** includes an additional methylene group that moves the proton sensitive site away from the tris-ureido binding site. This small structural alteration leads to drastic differences between the host–guest properties of these two receptors:

- **3** possesses a more flexible and larger tris-ureido cap and, thus, (i) is unable to bind neutral guests unless protonated, (ii) exhibits weaker recognition ability toward anions, (iii) displays a selectivity toward bigger anions such as SO_4^{2-}, (iv) is more versatile than **1**.
- the protonation of **3** leads to the rigidification of the tripodal cap probably thanks to the establishment of H bond interactions with an introverted ureido arm. This rigidification is transmitted to the whole calixarene cavity and, as a result, the more preorganized protonated form $\mathbf{3\cdot H^+}$ can now host neutral guests and, very surprisingly, primary or secondary ammonium ions. In this latter case, the NH^+ proton can be considered as an allosteric effector that permits the binding of ammonium ions into the cavity through a deep conformational alteration of the tris-ureido cap. This result constitutes a rare case of *endo*-complexation of ammonium ions by a cationic receptor. It is noteworthy that **1** or $\mathbf{1\cdot H^+}$ are unable to recognize ammonium ions.

• the greater distance between the proton sensitive site and the tris-ureido binding site of **3** allows the formation of cascade complexes $\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{R}^{1}\mathbf{R}^{2}\mathbf{NH}_{2}^{+}\mathbf{X}^{n-}$ with an anion bound between the convergent ureido groups and sandwiched between the NH^{+} proton and an ammonium ion accommodated into the cavity. Remarkably, with a bicharged anion such as SO_4^{2-}, these cascade complexes are even stable in a protic environment. As a reminder, when protonated, **1** was inert toward anions or ion pairs because of the too short distance between the capping tertiary nitrogen and the ureido groups.

All in all, when an ammonium ion $R^1R^2NH_2^+$ is added to the calix[6]crypturea **3**, three different types of host–guest system can be selectively obtained depending on the nature of the counterion. With a poorly coordinating anion such as Pic^-, the dicationic complex $\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{R}^{1}\mathbf{R}^{2}\mathbf{NH}_{2}^{+}$ is observed, while with coordinating monocharged X^- (*e.g.* Cl^-) and bicharged anions X^{2-} (*e.g.* SO_4^{2-}), neutral complexes $\mathbf{3}\supset\mathbf{R}^{1}\mathbf{R}^{2}\mathbf{NH}_{2}^{+}\mathbf{X}^{-}$ and cascade complexes $\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{R}^{1}\mathbf{R}^{2}\mathbf{NH}_{2}^{+}\mathbf{X}^{2-}$ are respectively formed. This strong dependence of the protonation state of the receptor on the nature of the anion present in solution nicely illustrates the unique and sophisticated host properties displayed by **3**.

All these results validate the strategy that consists of designing receptors presenting a high flexibility that can be controlled by an external stimulus. Indeed, as illustrated in the present work, allosteric control and selective guest switching processes can be achieved with such receptors. It is noteworthy that most of the biological receptors are based on rather flexible systems (*e.g.* protein scaffolds) and the function of some is allosterically regulated or pH dependent. Thus, besides its structure that reminds us of biological receptors, *i.e.* a tunable recognition site protected by a hydrophobic corridor that can adapt its conformation to the size of the guest, receptor **3** is highly reminiscent of what is encountered in natural systems. Current efforts are now being directed toward the synthesis and study of water-soluble related receptors.

Experimental section

General procedures

All reactions were performed under an inert atmosphere. Anhydrous THF was obtained through distillation over Na/benzophenone. Silica gel (230–400 mesh) was used for flash chromatography purifications. ^{1}H NMR spectra were recorded at 600, 400 or 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts are expressed in ppm. Traces of residual solvent were used as internal standard and $CDCl_3$ was filtered over a short column of basic alumina to remove traces of DCl. Most of the ^{1}H NMR spectra signals were attributed through 2D NMR analyses (COSY, HSQC, HMBC). Mass spectra were recorded on an ESI-MS apparatus equipped with an ion-trap using the following settings: flow rate: 10 μL min^{-1}, spray voltage: 5 kV, capillary temperature: 160 °C, capillary voltage: –15V, tube lens offset voltage: –30V. The calix[6]tris-azide **2** was prepared as previously described.[20]

Calix[6]crypturea 3

To a solution of calix[6]tris-azide **2** (401 mg, 328 μmol) in anhydrous THF (10 mL) was added triphenylphosphine (518 mg, 1.975 mmol). Then, CO_2 was bubbled through the solution for 5 min and the reaction mixture was stirred at room temperature under CO_2 atmosphere overnight. Subsequently, the reaction medium was drained with argon, placed in a syringe and the volume was adjusted to 10 mL with anhydrous THF. Afterwards, a second 10 mL syringe containing a solution of tris(3-aminopropyl)amine (65 μL, 328 μmol) in anhydrous THF (10 mL) was prepared. Then, the two solutions were simultaneously introduced at room temperature *via* a syringe pump (4.8 mL h^{-1}) into a stirred solution of anhydrous THF (140 mL) under argon atmosphere and the resulting solution was stirred one additional hour. The reaction mixture was evaporated to dryness and the crude solid was purified over silica gel (CH_2Cl_2/MeOH/25% aqueous NH_4OH; 88 : 12 : 0.6) to give the corresponding calix[6]crypturea **3** (230 mg, 50%) as a white solid. M.p. 262 °C (*dec*); IR (KBr) ν_{max} 3350, 2960, 1652, 1558, 1481 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3CN (3 : 7), 298 K) δ (ppm) 1.00 (s, 27H, *t*Bu), 1.12 (s, 27H, *t*Bu), 1.65 (s_b, 6H, NCH_2CH_2), 2.38 (s_b, 6H, NCH_2), 3.15 (m, 15H, OCH_3, $NHCH_2$), 3.30–3.49 (m, 12H, J = 15 Hz, CH^{eq}, $NHCH_2$), 3.61 (s_b, 6H, OCH_2), 4.43 (d, J = 15 Hz, 6H, CH^{ax}), 5.83 (s_b, 3H, $CH_2CH_2CH_2NH$), 5.91 (s_b, 3H, OCH_2CH_2NH), 6.90 (s, 6H, ArH), 7.05 (s, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3CN (3 : 7), 298 K) δ (ppm) 28.0 ($NCH_2CH_2CH_2NH$),[38] 30.6 ($ArCH_2$), 32.1 (CH_3^{tBu}), 35.0 (C_q^{tBu}), 35.1 (C_q^{tBu}), 39.7 ($NCH_2CH_2CH_2NH$), 41.5 (OCH_2CH_2NH), 52.7 ($NCH_2CH_2CH_2NH$), 61.6 (CH_3O), 73.7 (OCH_2CH_2NH), 126.9 (CH^{Ar}), 127.0 (CH^{Ar}), 134.0 (C^{Ar}-CH_2), 134.44 (C^{Ar}-CH_2), 146.6 (C^{Ar}-*t*Bu), 147.0 (C^{Ar}-*t*Bu), 153.2 (C^{Ar}-O), 154.7 (C^{Ar}-O), 160.1 (CO). HRMS calc. for $C_{87}H_{124}N_7O_9$: 1410.9461, found: 1410.9468.

Determination of the relative affinities of the neutral molecules $K_{G/Pyro}$ in the case of $3\cdot H^+$ through ^{1}H NMR competitive binding studies in $CDCl_3$

To a $CDCl_3$ solution containing $\mathbf{3}\cdot\mathbf{H}^{+}$ (4×10^{-3} to 5×10^{-3} M) were successively added Pyro (>1 equiv.) and a second guest G (>1 equiv.) in such a ratio that a ^{1}H NMR spectrum recorded at 298 K showed the resonances of both complexes $\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{Pyro}$ and $\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{G}$ besides the signals corresponding to the free guests (Pyro and G). Integration of the signals of the included guests, *i.e.* $Pyro_{in}$ and G_{in}, and of the free guests, *i.e.* $Pyro_{free}$ and G_{free}, allowed us to calculate the relative affinity $K_{G/Pyro}$, defined as $([G_{in}] \times [Pyro_{free}])/([G_{free}] \times [Pyro_{in}])$.

Determination of the association constant K_a of $3\cdot H^+$ toward Imi in $CD_3OD/CDCl_3$ (1 : 2)

To a 1 : 2 $CD_3OD/CDCl_3$ solution containing $\mathbf{3}\cdot\mathbf{H}^{+}$ (2.3×10^{-3} M) was added Imi in such a ratio that a ^{1}H NMR spectrum recorded at 298 K showed the resonances of both calixarene species $\mathbf{3}\cdot\mathbf{H}^{+}$ and $\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{Imi}$ besides the signals corresponding to the free guest (Imi). Integration of the signals of the calixarene species $\mathbf{3}\cdot\mathbf{H}^{+}$ and $\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{Imi}$ and of the free guest (Imi) allowed us to calculate the association constant K_a according to the following equation: $K_a = [\mathbf{3}\cdot\mathbf{H}^{+}\supset\mathbf{Imi}]/([\mathbf{3}\cdot\mathbf{H}^{+}] \times [\mathrm{Imi}])$.

Determination of the association constant K_a of 3 toward TMA^+ in $CD_3OD/CDCl_3$ (7 : 3)

To a 7 : 3 $CD_3OD/CDCl_3$ solution containing **3** (3.3×10^{-3} M) was added TMA^+Pic^- in such a ratio that a ^{1}H NMR spectrum

recorded at 298 K showed the resonances of both calixarene species **3** and **3**⊃**TMA**$^+$ besides the signals corresponding to the free guest (TMA^+). Integration of the signals of the calixarene species **3** and **3**⊃**TMA**$^+$ and of the free guest (TMA^+) allowed us to calculate the association constant K_a according to the following equation: $K_a = [\mathbf{3}\supset\mathbf{TMA}^+]/([\mathbf{3}] \times [TMA^+])$.

Determination of the association constants K_a of 3 toward anions X^{n-} in $CD_3CN/CDCl_3$ (7 : 3)

The association constants K_a were determined according to the following procedure: a solution of calix[6]crypturea **3** (1×10^{-3} to 3×10^{-3} M) in $CD_3CN/CDCl_3$ (7 : 3) was prepared. This solution was divided in two solutions (*i.e.* A and B) and the anion salt (nTBA$^+$X^{n-}) was added to the solution A. Suitable aliquots of solution A were added to solution B. The corresponding ^{1}H NMR spectra recorded at 298 K revealed one set of signals for the complex **3**⊃$\mathbf{X}^{n-}$ and for the free receptor **3** in fast exchange on the NMR time scale. Thus, the association constants K_a were determined by nonlinear least-square-fitting of 1 : 1 binding profile to the chemical shift of either the OCH_2 or the ArH protons. The error on the association constant was estimated as the standard deviation of the association constant values provided by the fitting (10%).

Estimation of the cumulative formation constant β_2 of 3 toward $PrNH_3^+Cl^-$ in $CDCl_3$.

Cumulative formation constant β_2 was estimated according to the following procedure: suitable aliquots of a solution of $PrNH_3^+Cl^-$ were added to a solution of receptor **3** (0.7×10^{-3} M) in such a way that the corresponding ^{1}H NMR spectrum recorded at 298 K revealed the total disappearance of the free receptor **3**. The concentration of the undetectable species (*i.e.* **3**) and the concentration of the ternary complex were estimated to be respectively 5% and 95% of the starting host concentration. Cumulative formation constant β_2 was estimated according to the following equation: $\beta_2 > [\mathbf{3}\supset\mathbf{PrNH_3^+Cl^-}]/([\mathbf{3}] \times [PrNH_3^+] \times [Cl^-])$.

Estimation of the cumulative formation constant β_2 of 3 toward TMA^+Cl^- in $CDCl_3$

Cumulative formation constant β_2 was estimated according to the following procedure: suitable aliquots of a solution of TMA^+Cl^- were added to a solution of receptor **3** (4.7×10^{-3} M) in such a way that a ^{1}H NMR spectrum recorded at 298 K showed the resonances of both calixarene species **3** and **3**⊃**TMA**$^+$**Cl**$^-$. The concentration of the undetectable species (*i.e.* free **TMA**$^+$**Cl**$^-$) was estimated to be 5% of the starting host concentration. Cumulative formation constant β_2 was estimated according to the following equation: $\beta_2 > [\mathbf{3}\supset\mathbf{TMA^+Cl^-}]/([\mathbf{3}] \times [TMA^+] \times [Cl^-])$.

Determination of the cumulative formation constants β_2 of 3 toward either Ach^+Cl^- or $PyrNH_2^+Cl^-$ in $CDCl_3$

To a $CDCl_3$ solution containing **3** (*ca.* 4×10^{-3} M) was added the ammonium salt in such a ratio that a ^{1}H NMR spectrum recorded at 298 K showed the resonances of both calixarene species **3** and **3**⊃**Ach**$^+$**Cl**$^-$ or **3**⊃**PyrNH**$_2^+$**Cl**$^-$ besides the signals corresponding to the free salts. Integration of the signals of the calixarene species **3** and **3**⊃**Ach**$^+$**Cl**$^-$ or **3**⊃**PyrNH**$_2^+$**Cl**$^-$ and of the free salts allowed us to calculate the cumulative formation constants β_2 according to the following equation: $\beta_2 = [\mathbf{3}\supset\mathbf{Ach^+Cl^-}]/([\mathbf{3}] \times [Ach^+] \times [Cl^-])$ or $\beta_2 = [\mathbf{3}\supset\mathbf{PyrNH_2^+Cl^-}]/([\mathbf{3}] \times [PyrNH_2^+] \times [Cl^-])$.

Determination of the cumulative formation constants β_2 of 3·H$^+$ toward $PrNH_3^+Cl$ in $CDCl_3$

To a $CDCl_3$ solution containing **3**·**H**$^+$ (2.4×10^{-3} M) was added $PrNH_3^+Cl^-$ in such a ratio that a ^{1}H NMR spectrum recorded at 298 K showed the resonances of both calixarene species **3**·**H**$^+$ and **3**·**H**$^+$⊃**PrNH**$_3^+$**Cl**$^-$ besides the signals corresponding to the free salt. Integration of the signals of the calixarene species **3**·**H**$^+$ and **3**·**H**$^+$⊃**PrNH**$_3^+$**Cl**$^-$ and of the free salts allowed us to calculate the overall binding constant β_2 according to the following equation: $\beta_2 = [\mathbf{3}\cdot\mathbf{H}^+\supset\mathbf{PrNH_3^+Cl^-}]/([\mathbf{3}\cdot\mathbf{H}^+] \times [PrNH_3^+] \times [Cl^-])$.

Estimation of the cumulative formation constants β_2 of 3·H$^+$ toward $PrNH_3^+SO_4^{2-}$ in $CDCl_3$

Cumulative formation constants β_2 were estimated according to the following procedure: the ammonium salt ($PrNH_3^+TBA^+$) SO_4^{2-} were added to a solution of receptor **3**·**H**$^+$ (*ca* 3×10^{-3} M) in such a way that the corresponding ^{1}H NMR spectra recorded at 298 K revealed the total disappearance of the free receptor **3**·**H**$^+$. The concentration of the undetectable species (*i.e.* **3**·**H**$^+$) and the concentration of the ternary complex were estimated to be respectively 5% and 95% of the starting host concentration. Cumulative formation constants β_2 were estimated according to the following equation: $\beta_2 > [\mathbf{3}\cdot\mathbf{H}^+\supset\mathbf{PrNH_3^+SO_4^{2-}}]/([\mathbf{3}\cdot\mathbf{H}^+] \times [PrNH_3^+] \times [SO_4^{2-}])$.

Determination of the cumulative formation constants β_2 of 3·H$^+$ toward $PrNH_3^+SO_4^{2-}$ and $PyrNH_2^+SO_4^{2-}$ in $CD_3OD/CDCl_3$ (1 : 3)

To a $CD_3OD/CDCl_3$ (1 : 3) solution containing **3** (2.9×10^{-3} M) was added $PrNH_3^+$ Pic^- or $PyrNH_2^+$ $Pic^-$and TBA^+ HSO_4^- in such a ratio that a ^{1}H NMR spectrum recorded at 298 K showed the resonances of both calixarene species **3**·**H**$^+$ and **3**·**H**$^+$⊃**PrNH**$_3^+$**SO**$_4^{2-}$ or **3**·**H**$^+$⊃**PyrNH**$_2^+$**SO**$_4^{2-}$ besides the signals corresponding to the free salts. Integration of the signals of the calixarene species **3**·**H**$^+$ and **3**·**H**$^+$⊃**PrNH**$_3^+$**SO**$_4^-$ or **3**·**H**$^+$⊃**PyrNH**$_2^+$**SO**$_4^{2-}$ and of the free salts allowed us to calculate the overall binding constant β_2 according to the following equation: $\beta_2 = [\mathbf{3}\cdot\mathbf{H}^+\supset\mathbf{PrNH_3^+SO_4^{2-}}]/([\mathbf{3}\cdot\mathbf{H}^+] \times [PrNH_3^+] \times [SO_4^{2-}])$ or $\beta_2 = [\mathbf{3}\cdot\mathbf{H}^+\supset\mathbf{PyrNH_2^+SO_4^{2-}}]/([\mathbf{3}\cdot\mathbf{H}^+] \times [PyrNH_2^+] \times [SO_4^{2-}])$.

Crystal data of calix[6]crypturea 3

Crystal data: $C_{87}H_{123}N_7O_9$, $M_w = 1410.92$, monoclinic, space group $P2_1/c$; dimensions: a = 16.1331(14) Å, b = 37.634(3) Å, c = 17.1581(15) Å, β = 98.715(2)°, V = 10297.4(15) Å^3; Z = 4; μ = 0.059 mm^{-1}; 123747 reflections measured at 100 K; independent reflections: 18406 [8840 Fo >4σ (Fo)]; data were collected up to a 2θmax value of 50.42° (99.1% coverage). Number of variables: 925; $R_1 = 0.0822$, w$R_2 = 0.2253$, S = 1.048; highest residual electron density 0.738 e.Å^{-3} (all data $R_1 = 0.1499$, w$R_2 = 0.2463$). Several disordered solvent molecules were initially modelled as discrete acetonitrile molecules but they were ultimately removed from the

structure. The data set was corrected for a disordered solvent with the program PLATON/SQUEEZE.[39] CCDC 820544 contains the supplementary crystallographic data for this paper.†

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25 See the Electronic Supporting Information (ESI†).

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27 In pure $CDCl_3$, **3**·**H**$^+$ displayed a broad NMR spectrum and the protonation process was slow on the NMR scale. In contrast, in $CD_3CN/CDCl_3$ (7 : 3) and $CD_3OD/CDCl_3$ (7 : 3), well defined spectra and fast proton transfers were observed. Surprisingly, in these polar solvents, two conformations differing by the chemical shift of the OMe groups were visible (see the ESI†). In both cases, one of the conformations is very close to that observed in the case of **3** and the other one corresponds to a C_{3v} symmetrical flattened cone conformation with the three OMe groups included into the cavity (δ_{OMe} <2.18 ppm).

28 Addition of 1.5 equiv. of Imi to **3**·**H**$^+$ led to a mixture of **3**·**H**$^+$⊃**Imi** and **3**·**H**$^+$ in slow exchange on the NMR timescale (see the ESI†). However, accurate determination of the association constant, *Ka* (*Ka* = [**3**·**H**$^+$⊃**Imi**]/([**3**·**H**$^+$]×[Imi]) from the integrations of the different species was not possible because of the weak competitive binding of water. This competitive binding was checked by NMR spectroscopy through the addition of aliquots of water to the above mixture of **3**·**H**$^+$⊃**Imi** and **3**·**H**$^+$ (see the ESI†). For a reference on the effects of water on hydrogen-bonding-based hosts in chloroform, see: J. C. Adrian, Jr. and C. S. Wilcox, *J. Am. Chem. Soc.*, 1991, **113**, 678–680.

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31 D and A stand for hydrogen-bond donors and acceptors respectively.
32 In the case of calixcrypturea **1**·$\mathbf{H^+}$, the protic solvent (*i.e.* CD_3OD) was a significant competitor for the calixarene cavity. However, despite this competitive process with the solvent, an apparent association constant of *ca.* 10 M^{-1} was determined for Imi.
33 In the case of the titration with $(TBA^+)_2SO_4^{2-}$, the NH ureido signals became extremely broad over the course of the titration (see Fig. 5) and, thus, it was not possible to determine precisely their chemical shift.
34 The complexation of the tetramethylammonium salt TMA^+Pic^- was also evaluated in $CDCl_3$. However, host **3** was not able to extract this insoluble quaternary ammonium salt.
35 Note that in all cases, a minor species that does not display high-field signals below 0 ppm was observed. Given the broadness of its NMR signals, it was not possible to conclude whether the cap is protonated or not. Since the proportion of this species did not change upon the addition of a large excess of ammonium salts, this minor compound could result from an *exo*-complexation of the ammonium ion.
36 Note that the host–guest exchange is slow on the NMR timescale.
37 See the ESI† for the comparison between **3**·$\mathbf{H^+}$⊃$\mathbf{PrNH_3^+SO_4^{2-}}$ and **3**·$\mathbf{H^+}$⊃$\mathbf{PrNH_3^+Cl^-}$.
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