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Acid–Base Controllable Recognition Properties of a Highly Versatile Calix[6]crypturea

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Abstract: Versatile concave receptors with binding properties that can be controlled by external stimuli are rare. Herein, we report on a calix[6]crypturea (**1**) that features two different binding sites in close proximity, that is, a tris(2-aminoethyl)amine (tren)-based tris-ureido cap that provides convergent hydrogen-bond-donor sites and a hydrophobic cavity suitable for the inclusion of organic guests. The binding properties of this heteroditopic receptor have been evaluated by NMR spectroscopic studies. Compound **1** behaves as a remarkably versatile host that strongly binds neutral molecules, anions, or contact ion pairs. Within each family of guests, compound **1** is able to discriminate between different guests with a high degree of selectivity. Indeed, neutral molecules that possess hydrogen-bond donor and acceptor groups, chloride anions, and linear ammonium ions associated to F^- or Cl^- are particularly well recognized. In comparison with all the related receptors, compound **1** displays several unique features: 1) charged or neutral species are also recognized in polar or protic solvents, 2) thanks to the flexibility of the calixarene structure, induced-fit processes allow the binding of large, biologically relevant ammonium salts such as neurotransmitters, and 3) the protonation of the basic cap leads to a positively charged receptor, **1**·H^+, which is reluctant to host anions and in which host properties are now governed by strong charge–dipole interactions with the guests. In other words, compound **1** presents an acid–base controllable tris-ureido recognition site protected by a hydrophobic corridor that can select guests through induced-fit processes. Thus, its versatile host properties can be allosterically controlled by protonation and selective guest-switching processes are possible. To illustrate all these remarkable features, a sophisticated three-pole supramolecular switch, based on the interconversion of host–guest systems displaying either charged or neutral guests, is described.

Keywords: calixarenes · host–guest systems · ion pairs · molecular switches · supramolecular chemistry

Introduction

The design and study of novel synthetic receptors for charged or neutral species is a major objective in supramolecular chemistry.[1] Indeed, these receptors can find potential applications in many areas, such as sensing, catalysis, nanoscience, biomimetism, drug delivery, and separation science. A classical strategy for the elaboration of efficient receptors consists of using bowl-shaped macrocycles displaying a hydrophobic cavity. In this regard, readily available molecular platforms such as cyclodextrins,[2] cucurbiturils,[3] resorcinarenes,[4] cyclotriveratrilenes,[5] and calixarenes[6] have been extensively studied. However, most artificial hosts described so far have been designed with the aim of being highly specific for a particular guest or family of guests (i.e., metal or ammonium ions,[1c] anions,[7] ion pairs,[7a–c] or neutral molecules[4a]). With the exception of the well-known azacryptands,[8] which do not possess a hydrophobic cavity, only few examples of versatile receptors have been reported.[9] Such receptors are particularly attractive because the control of their binding properties by an external stimulus can be exploited for the construction of unique switchable systems.[9b–d]

In this context, we have previously described molecular receptors consisting of a *p*-*t*Bu-calix[6]arene framework, constrained in a cone conformation by an azacryptand cap.[10] The grid-like nitrogenous cap closes the receptacle at the narrow rim leaving a single entrance controlled by the flexible *t*Bu door. One of them, calix[6]tris(2-aminoethyl)-

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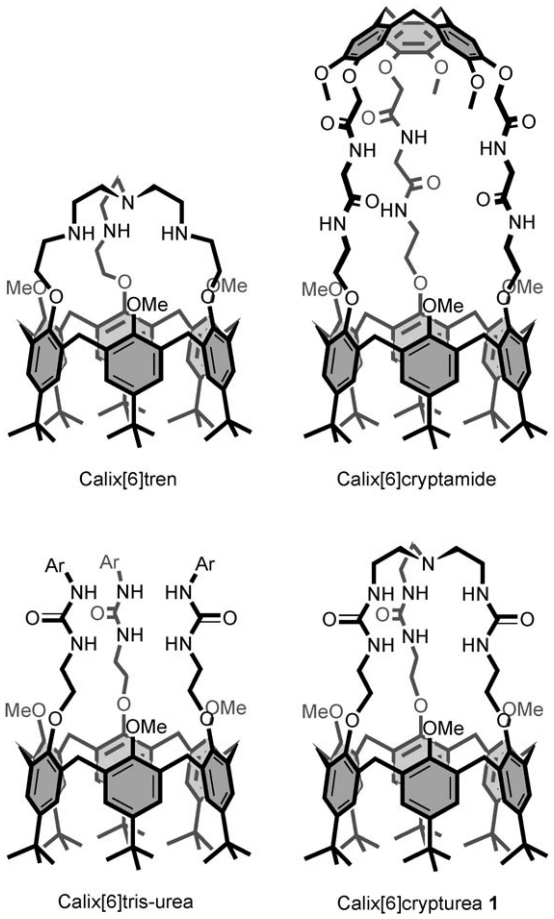
amine (calix[6]tren, Scheme 1), exhibited remarkably versatile host–guest properties toward polar, neutral molecules, or cationic species (ammonium and metal ions) and it was



Scheme 1.

shown that these binding properties can be tuned by the environment (more or less acid, presence of metal ions, etc.).[11] Replacing the basic polyamino cap by a cryptamide moiety led to heteroditopic receptors, the so-called calix[6]-cryptamides (Scheme 1), able to complex neutral guests or contact organic ion pairs in a cooperative way.[12] It is noteworthy that examples of metal-free complexation of contact ion pairs are still rare.[13] Very recently, it was shown that calix[6]tris-ureas (Scheme 1) can strongly bind a wide range of anions[14] through induced-fit processes, but can also behave as unique heteroditopic receptors for organic ion pairs[15] with a remarkable positive cooperativity in the complexation process, the anion acting as an allosteric effector.[16,17] However, a major drawback of these calix[6]tris-ureas was their lack of selectivity toward anions due, in great part, to their high flexibility. In the course of designing versatile calixarene-based receptors, in which the host properties can be controlled by external stimuli, a calix[6]arene bearing a tripodal ureido cap derived from a tris(2-aminoethyl)amine (tren) moiety, that is, calix[6]crypturea (**1**), was synthesized.[19] Indeed, such a heteroditopic receptor was expected to possess unique recognition properties, notably toward anions and contact ion pairs, because of the close proximity of two different binding sites; that is, a cap presenting three convergent ureido groups[20] and a hydrophobic cavity. In addition, similarly to calix[6]tren, we envisaged that the implementation of a proton-sensitive site at the level of the cap could lead to an acid–base control of the binding properties of the receptor.[21,22]

Herein, we report the binding properties of **1** that prove to be highly versatile and chemically controllable through the addition of acid or base to the medium. Remarkably, it was possible to exploit these properties for the elaboration of a unique three-pole supramolecular switch.[23]

Results and Discussion

NMR conformational analysis of calix[6]crypturea (1) and 1·H$^+$: ^{1}H NMR spectra of **1** recorded in either $CDCl_3$, CD_3OD, or CD_3CN show similar C_{3v} symmetrical patterns characteristic of averaged straight-cone conformations with the methoxy groups directed outside of the cavity[10a] ($\Delta\delta t_{Bu} < 0.21$ ppm and $\delta_{OMe} > 3.10$ ppm in all cases) (see Figure 1a for the spectrum in $CDCl_3$).[24] However, with $CDCl_3$ as the solvent, the chemical shifts of most of the signals were found to be dependent on the amount of residual water. In particular, progressive upfield shifts of the OMe and CH_2N signals, as well as downfield shifts of the CH_2O and NH signals, were observed upon the addition of traces of water. Similar shifts were obtained by lowering the temperature of recording from 328 to 258 K ($\Delta\delta_{OMe} = 0.35$ ppm).[24] All these data show that host **1** can bind water in apolar solvents, such as $CDCl_3$, through a complexation process that is fast on the NMR spectroscopy timescale. The upfield shift of the OMe signal observed upon the addition of water seems to indicate that these groups fill the cavity of the complex. Thus, water is likely to be recognized through hydrogen bonding between the convergent ureido groups of the cap. Such a result is highly compatible with what was observed on the parent calix[6]tren receptor.[11]

The protonated derivative, **1·H$^+$**, was obtained quantitatively after the addition of picric acid (PicH; 1 equiv) to a solution of **1** in $CDCl_3$. Its broad NMR pattern at room temperature became sharp at high temperature (328 K), showing a C_{3v} symmetrical cone conformation with the methoxy groups directed outside the cavity ($\delta_{OMe} = 3.48$ ppm[25]).[24] The protonation of the bridging tertiary amine was clearly evidenced by the impressive chemical shift of the NCH_2 protons (**1**: $\delta_{NCH2} = 2.52$ ppm versus **1·H$^+$**: $\delta_{NCH2} = 3.42$ ppm[25]).

Similarly to related tris-ureido cryptands,[20b] it is assumed that the nitrogen lone pair of **1** and the NH^+ proton of **1·H$^+$** are directed toward the inside of the cap to interact through intramolecular hydrogen bonding with the ureido groups.

Neutral molecule recognition: The ability of **1** to bind neutral guests (G) was first investigated by ^{1}H NMR spectrosco-

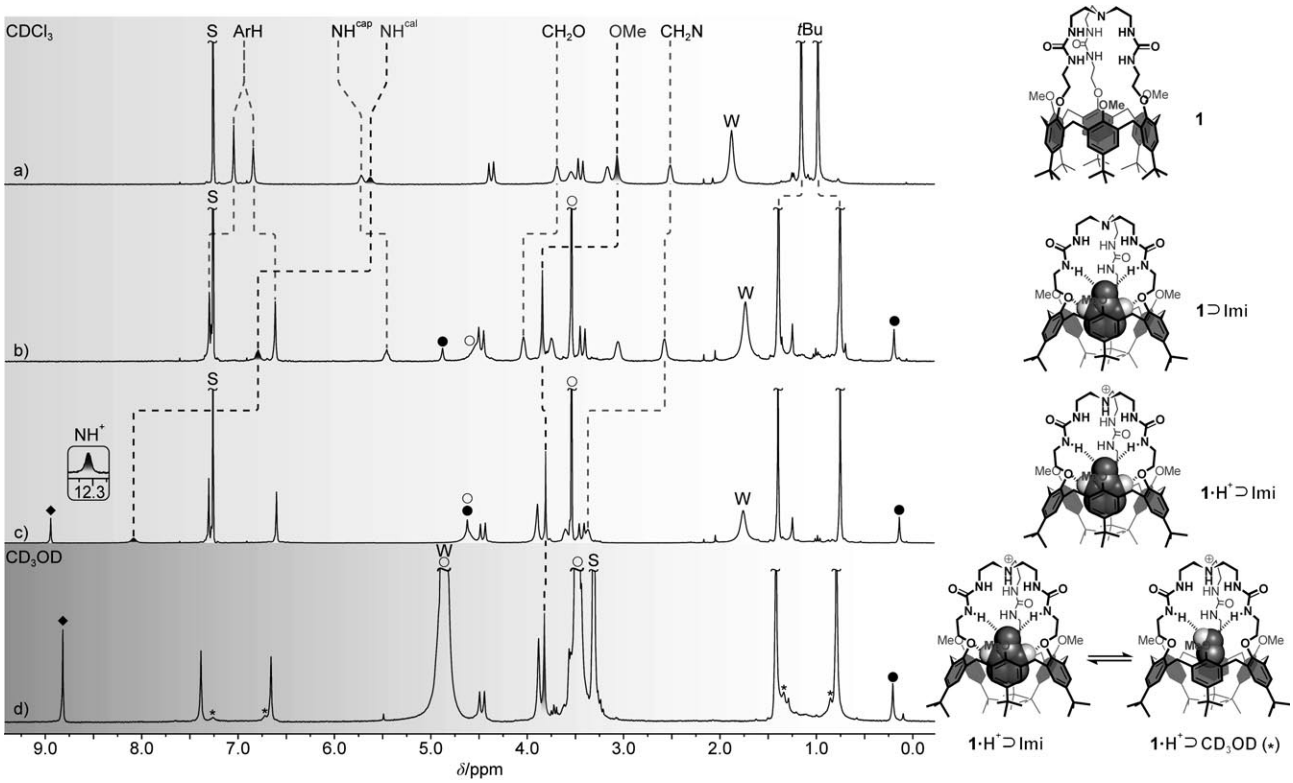
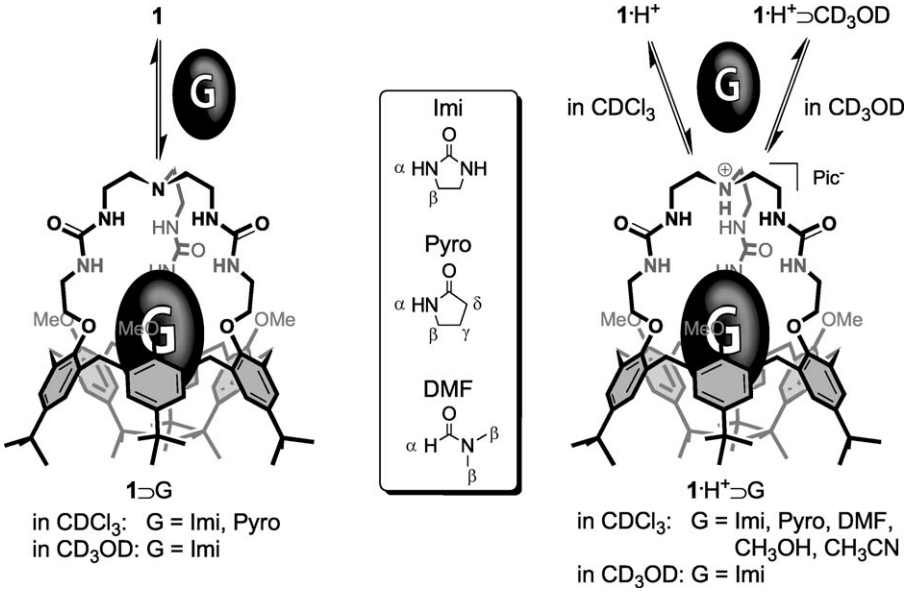


Figure 1. ^{1}H NMR spectra (300 MHz, 298 K) of a) **1** in $CDCl_3$; b) after addition of Imi (5 equiv) to **1**; c) **1**·H$^+$⊃Imi in $CDCl_3$ obtained after addition of Imi (5 equiv) to **1**·H$^+$; d) mixture of **1**·H$^+$⊃Imi and **1**·H$^+$⊃CD_3OD in CD_3OD obtained after addition of 86 equiv of Imi to **1**·H$^+$. ●: Imi included; ○: free Imi; ◆: Pic^-; ∗: **1**·H$^+$⊃CD_3OD; W: water; S: residual solvent.

py in $CDCl_3$. Thus, addition of approximately 5 equiv of imidazolidin-2-one (Imi) to **1** gave rise to the host–guest complex **1**⊃Imi exclusively ($K_a > 10^3\,M^{-1}$) (Scheme 2).[26] This complex displays a C_{3v} symmetrical flattened cone conformation with the methoxy groups outside of the cavity ($\delta_{OMe} = 3.84$ ppm) and a high-field singlet at $\delta = 0.20$ ppm corresponding to one equiv of included Imi (Figure 1b). The complexation induced shift (CIS) of the CH_2 protons of the guest, that is, $\delta = -3.35$ ppm, is typical of a positioning in the heart of the hydrophobic cavity (Table 1).[12] Interestingly, at the level of the cap, only the protons of the NH groups in close proximity to the cavity undergo a significant downfield shift upon complexation ($\Delta\delta_{NH} = 1.34$ ppm).[27] Moreover, the NH protons of the guest are shifted downfield despite the shielding of the cavity (Table 1). These data are fully consistent with a recognition process involving a four hydrogen-bonding system (see the structure displayed in Figure 1b) besides the favorable CH–π interactions with the aromatic walls of the host.[28] Among the other neutral guests tested, such as pyrrolidin-2-one (Pyro), CH_3CN, MeOH, DMF, and DMSO, only the inclusion of Pyro was detected (Table 1).



Scheme 2. Host–guest properties of **1**, **1**·H$^+$, and **1**·H$^+$⊃CD_3OD toward neutral guests in $CDCl_3$ and CD_3OD.

Table 1. Complexation induced shifts (CIS), relative affinities ($K_{G/Pyro}$) and association constants (K_a and K_{app}) of the neutral guests (G) in the case of **1**⊃G and **1**·H$^+$⊃G.

	1⊃G in $CDCl_3$		**1**⊃G in CD_3OD		**1**·H$^+$⊃G in $CDCl_3$		**1**·H$^+$⊃G in CD_3OD	
Guest	$K_{G/Pyro}$[a]	CIS[b]	K_a [M^{-1}][c]	CIS[b]	$K_{G/Pyro}$[a]	CIS[b]	K_{app} [M^{-1}][d]	CIS[b]
Imi	52	+0.36 (α) −3.35 (β)	0.6	−3.20 (β)	55	+0.05 (α) −3.40 (β)	10	−3.28 (β)
Pyro[f]	1	−3.61 (β) −3.17 (γ)	nd[e]	nd[e]	1	+0.66 (α) −3.71 (β) −3.14 (γ)	nd[e]	nd[e]
DMF	nd[e]	nd[e]	nd[e]	nd[e]	0.03	−3.01 (β)[g]	nd[e]	nd[e]

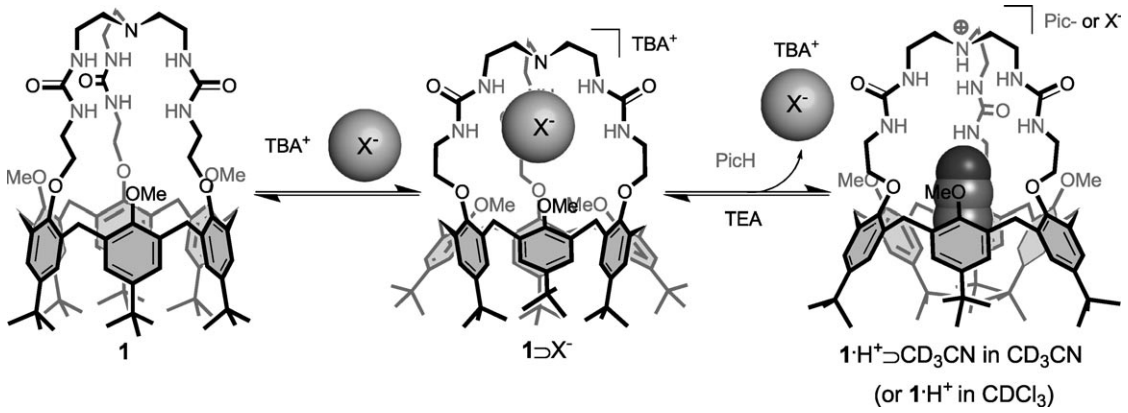
[a] Relative affinity calculated at 293 K and defined as $([G_{in}]\times[Pyro_{free}])/([G_{free}]\times[Pyro_{in}])$; the subscript "in" stands for "included"; errors estimated at ±10%. [b] CIS calculated at 293 K and defined as $\Delta\delta=\delta$(complexed G)−δ(free G). [c] K_a was determined at 293 K by integration of the different species in equilibrium; K_a is defined as $K_a=[\mathbf{1}\supset G]/([\mathbf{1}]\times[G])$; error estimated at ±10%. [d] K_{app} was determined at 293 K by integration of the different species in equilibrium; K_{app} is defined as $K_{app}=[\mathbf{1}\cdot H^+\supset G]/([\mathbf{1}\cdot H^+\supset CD_3OD]\times[G])$; error estimated at ±10%. [e] Not detected. [f] The CIS of the CH_2CO group (δ) was not determined because of signal overlapping. [g] Average value of the two inequivalent methyl groups.

Thus, similarly to the parent calix[6]cryptamide receptor, host **1** can specifically bind polar, neutral molecules that possess hydrogen-bond donor and acceptor groups such as amides or ureas. A ^{1}H NMR spectroscopy competitive binding experiment showed that the relative affinity of Imi toward host **1** is 52 times higher than that of Pyro (Table 1). This result emphasizes the remarkable complementarity between Imi and the calixarene core in terms of size, shape, and electronic structure. Compared to **1**, the protonated receptor **1**·H$^+$ displayed similar strong binding properties toward Imi and Pyro[24] ($K_a>5\times10^4$ and 10^3 M^{-1}, respectively) (Table 1, Figure 1c for **1**·H$^+$⊃Imi), Again, the NH protons in close proximity to the cavity experienced an impressive downfield shift upon complexation, showing the presence of similar hydrogen-bonding interactions.[27] However, complex **1**·H$^+$ was also able to bind DMF with a relative affinity three orders of magnitude lower than Imi (Table 1). The complexation of CH_3OH and CH_3CN was also evidenced, but, in both cases, the host–guest process was fast on the NMR spectroscopy timescale, even at low T (243 K). This substantial increase in affinity with respect to **1** is likely to be due to a stronger stabilization of the polar guests through an additional charge–dipole interaction with the protonated cap.

The next step was to evaluate the host–guest behavior of **1** and **1**·H$^+$ toward neutral guests in a protic solvent. Therefore, the addition of a large excess of Imi (40 equiv) to a solution of **1** in CD_3OD afforded approximately a 1:1 mixture of **1** and the expected complex **1**⊃Imi, the exchange process between the two species being slow on the NMR spectroscopy timescale. No guests other than Imi could be detected under similar conditions. Despite the weak association constant ($K_a=0.6$ M^{-1}), the *endo*-complexation of Imi constitutes a rare example of a cavitand-based neutral receptor accommodating a neutral guest through hydrogen bonding in a protic solvent.[29] In the case of host **1**·H$^+$ the solvent (CD_3OD) was a significant competitor for the calixarene cavity. Nevertheless, upon the addition of an excess of Imi (86 equiv), the complex **1**·H$^+$⊃Imi was obtained almost quantitatively, besides traces of the starting complex **1**·H$^+$⊃CD_3OD (Figure 1d).[30] Despite the competitive process with the solvent, the apparent association constant for Imi ($K_{app}=10$ M^{-1}) is more than one order of magnitude higher than the "true" association constant, K_a, determined with the neutral host **1**. Again, the enhancement of the host affinity obtained with the protonated receptor **1**·H$^+$ stems from the supplementary charge–dipole interaction.

Anion recognition: The binding behavior of host **1** toward anions (X^-) was first evaluated by ^{1}H NMR spectroscopy in $CDCl_3$ through the progressive addition of the corresponding tetra-*n*-butylammonium salts (TBA^+X^-). Whereas the initial spectrum remained unchanged in the presence of I^-, HSO_4^-, and $H_2PO_4^-$, the complexation of F^-, Cl^-, Br^-, CN^-, $CH_3CO_2^-$ (AcO^-), N_3^-, and NO_3^- through hydrogen-bonding interactions was clearly evidenced by the substantial downfield shift of the ureido protons. Moreover, a concomitant downfield shift of the CH_2O protons and an upfield shift of the OMe signal was observed. In all cases, the exchange process between **1** and **1**⊃**X**$^-$ was found to be fast on the NMR spectroscopy timescale and a conformational flip of the aromatic unit was apparent because the tBu$_{in}$ and tBu$_{out}$, as well as the ArH$_{in}$ and ArH$_{out}$, interchange their positions.[24] Thus, receptor **1** recognizes the anions at the level of the crypturea cap through an induced-fit process that involves the highly favorable filling of the cavity by the methoxy groups and the spreading of the ureido arms (Scheme 3). In CD_3CN, the complexation of anions led to similar conformational changes of the calixarene core, however, broad spectra were obtained upon the addition of less than 1 equiv of Cl^-, Br^-, CN^-, and AcO^-. When 1 equiv of Cl^- was added, a sharp signature in the NMR spectra corresponding to quantitative formation of the complex **1**⊃Cl^- was observed (Figure 2).[31] Interestingly, at 243 K, the complexation process was found to be slow on the NMR spectroscopy timescale for several anions (Cl^-, Br^-, CN^-, and AcO^-).[24] In these cases, the association constants, K_a, were determined through integration of the appropriate signals (i.e., those of **1**⊃X^- and **1**) (Table 2).[32] In the other cases (N_3^- and NO_3^-), it was achieved through ^{1}H NMR spectroscopic titration by monitoring the CISs of either the CH_2O or H_{ax} protons of host **1**.[24] Indeed, these protons displayed significant shift upon complexation and no overlapping region.[33]

First, the relative affinity of Cl^- towards host **1** is at least 25 times higher than all the other anions tested. The association constants displayed in Table 2 indicate that the binding discrimination is mostly based on the size of the anions. This is well illustrated with the halide series (entries 1–3)[34] but



Scheme 3. Host–guest properties of **1** toward anions in CD_3CN or $CDCl_3$ and acid–base controlled guest switch.

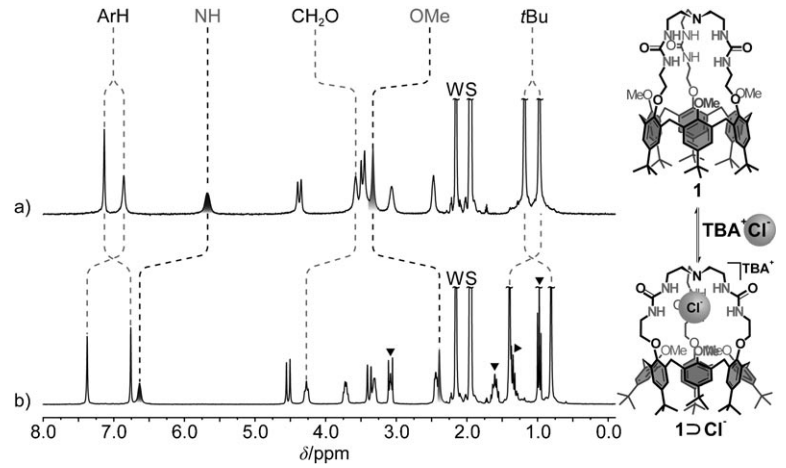


Figure 2. ^1H NMR spectra (CD_3CN, 300 MHz, 298 K) of a) **1**; b) after addition of TBA^+Cl^- (1 equiv) to **1**. ▼: TBA^+; W: water; S: residual solvent.

Table 2. Association constants (K_a) of calix[6]crypturea (**1**) toward anions X^- in CD_3CN.

Entry	Anion, X^-[a]	Geometry of X^-	K_a [M^{-1}][b]
1	Cl^-[c]	spherical	48300[d]
2	Br^-	spherical	1930
3	I^-	spherical	nd[e]
4	CN^-	linear	640
5	N_3^-	linear	215[f]
6	AcO^-	V shaped	160
7	NO_3^-	trigonal	98[f]

[a] TBA^+ salts. [b] K_a determined at 243 K and defined as $K_a = [1\supset X^-]/([1]\times[X^-])$; errors estimated at ±10%. [c] Hydrate salt. [d] Determined through a ^1H NMR competitive binding experiment with Br^-. [e] Not detected. [f] Determined at 298 K.

also by the fact that the most basic anions (i.e., AcO^- or CN^-) as well as trigonal anions (i.e., NO_3^-) are poorly recognized by **1** as compared to Cl^- (entries 4, 6, 7 vs. 1). This selectivity for the smaller chloride anion was further confirmed by ESI-MS competitive experiments. Indeed, injection of an equimolar mixture of **1** and five TBA^+ salts of anions (i.e., Cl^-, Br^-, CN^-, AcO^-, and N_3^-) in either $CHCl_3$ or CH_3CN afforded in both cases only one ion (m/z = 1402.7) corresponding to $[\mathbf{1}+Cl]^-$.[24]

All these results strongly differ with what was previously reported for the C_{3v} symmetrical calix[6]tris-urea derivatives that lack the covalent cap between the ureido arms (Scheme 1).[16] Indeed, these flexible receptors were able to adjust their tris-ureido recognition site to the size of the anion and, thus, the stronger affinities were observed toward the most basic anions (e.g., AcO^-) as well as anions possessing acidic hydrogen atoms (e.g., HSO_4^-),[35] large anions such as I^- also being recognized. In the case of **1**, the higher preorganization of the covalent tris-ureido cap ensures an impressive selectivity toward the smaller anions. The role of the cap was further evidenced through the binding of Cl^- in a protic solvent ($K_a = 20 \pm 2\,M^{-1}$ at 298 K in CD_3OD).[24] This remarkable result highlights the fact that neutral receptors can bind anions in protic solvents provided that they possess a highly preorganized recognition site,[36] isolated from the solvent.

Finally, the effect of the protonation of the cap toward anion recognition was evaluated. While one might have expected a reinforcement of the anion coordination with the positively charged receptor, the addition of PicH (1 equiv) to the complex $\mathbf{1}\supset Cl^-$ in either $CDCl_3$ or CD_3CN led to the quantitative formation of $\mathbf{1}\cdot H^+$ or $\mathbf{1}\cdot H^+\supset CD_3CN$, respectively, showing a complete release of the anion (Scheme 3).[24] The expulsion of the anion can be reasonably explained by a steric repulsion with the introverted NH^+ proton. Interestingly, the successive addition of a base, such as triethylamine (TEA, 1.5 equiv), restored the initial host–guest complex $\mathbf{1}\supset Cl^-$.[24] This interconversion between $\mathbf{1}\supset Cl^-$ and $\mathbf{1}\cdot H^+$ or $\mathbf{1}\cdot H^+\supset CD_3CN$ can be achieved several times in the same

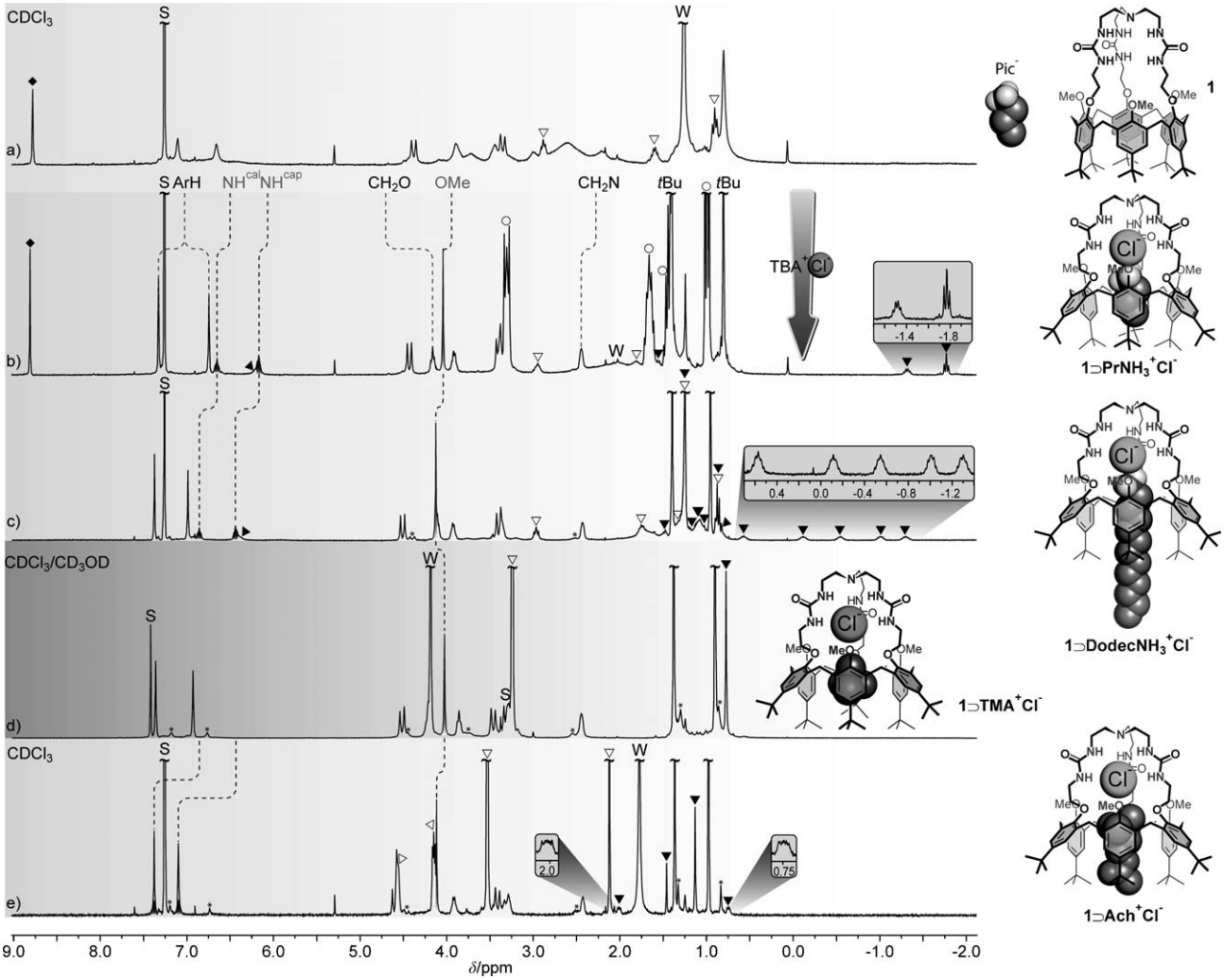
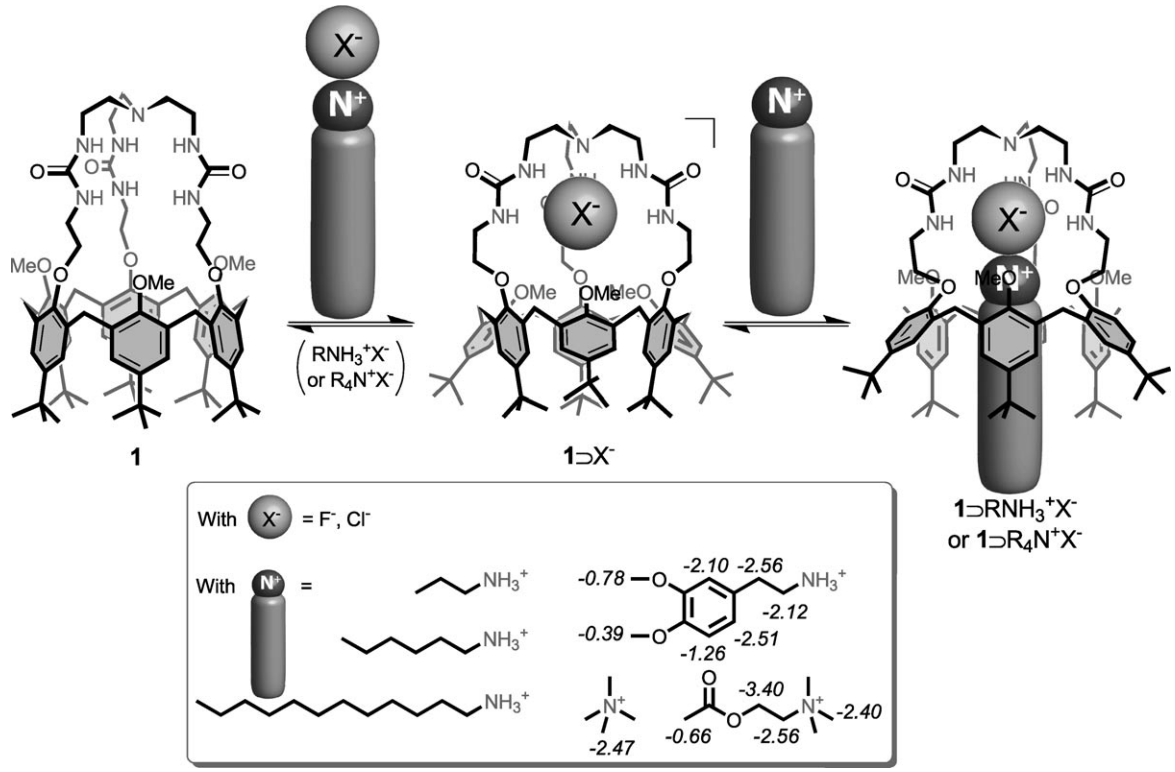


Figure 3. ^{1}H NMR spectra (300 MHz, 298 K) of a) **1** and 2 equiv of $PrNH_3^+Pic^-$ in $CDCl_3$; b) after addition of TBA^+Cl^- (5 equiv); c) **1**⊃$DodecNH_3^+Cl^-$ in $CDCl_3$ obtained after addition of $DodecNH_3^+Cl^-$ (ca. 3 equiv) to **1**; d) **1**⊃TMA^+Cl^- in $CDCl_3/CD_3OD$ (4:1) obtained after addition of TMA^+Cl^- (5 equiv) to **1**; e) **1**⊃ACh^+Cl^- in $CDCl_3$ obtained after addition of ACh^+Cl^- (7 equiv) to **1**. ▼: included ammonium; ▽: free ammonium; ○: TBA^+; ◆: Pic^-; ∗: **1**⊃Cl^-; W: water; S: residual solvent.

NMR tube without any observable degradation of the different species.[37] Thus, the anion complexation can be controlled by the addition of acids or bases to the external medium, allowing reversible guest switches between neutral molecules and anions.

Ion-pair recognition: The addition of an excess (2 equiv) of propylammonium picrate ($PrNH_3^+Pic^-$) to a solution of host **1** in $CDCl_3$ afforded a complex ^{1}H NMR spectrum displaying broad signals (Figure 3a). At 258 K, multiple high-field signals ($\delta < 0$ ppm) of low intensity were visible, attesting to the intracavity complexation of the ammonium ion. The further addition of PicH led to an ill-resolved NMR pattern with a reduced number of high-field signals, but still in very small proportions compared with the calixarene species. These data seem to indicate a weak binding of $PrNH_3^+$ by hosts **1** and **1**·H^+. In contrast, upon the addition of TBA^+Cl^- (5 equiv) to a solution of **1** in $CDCl_3$ containing $PrNH_3^+Pic^-$ (2 equiv), a unique species displaying sharp signals characteristic of a C_{3v} symmetrical flattened-cone conformation was obtained (Figure 3b). The presence of high-field signals resulting from the inclusion of 1 equiv of $PrNH_3^+$ ($\delta = -1.31$ and -1.77 ppm), as well as the downfield shift experienced by the NH protons of the ureido groups, and the expulsion of the OMe groups from the cavity ($\delta_{OMe} = 4.04$ ppm) attested to the formation of the host–guest complex **1**⊃$PrNH_3^+Cl^-$ (Scheme 4). The association constant[38] for both $PrNH_3^+$ and Cl^- was estimated to be $> 1.6 \times 10^9\,M^{-2}$ through the exclusive formation of **1**⊃$PrNH_3^+Cl^-$, obtained by the addition of 1 equiv of $PrNH_3^+Cl^-$.[24]

This result denotes that the complexation of the ammonium ion is greatly reinforced when the anion is bound in the tris-ureido cap. This positive cooperativity is clearly due to the close proximity between the two complexed ions and consequently to their strong electrostatic interaction. Thus, in analogy with the parent calix[6]tris-ureas[16] and calix[6]-



Scheme 4. Host–guest properties of **1** toward contact ion pairs and CISs observed for TMA^+ and the biologically relevant ammonium ions.

cryptamide,[12] host **1** behaves as a heteroditopic receptor that can bind contact organic ion pairs. However, compared with the former receptors, major improvements of the host–guest properties were observed with host **1**.

First, host **1** was also able to accommodate the ion pair $PrNH_3^+Cl^-$ in the presence of a large amount of protic solvent ($CD_3OD/CDCl_3$; 1:1), as well as $PrNH_3^+F^-$ in polar solvent (CD_3CN).[39] This result clearly illustrates the high complementarity between the three partners and denotes exceptional stability of the ternary complexes $\mathbf{1}\supset PrNH_3^+X^-$. It is noteworthy that besides these complexes, the intermediate complexes $\mathbf{1}\supset X^-$ were also observed in such solvents.

In contrast with the parent receptors, the strong binding of large ammoniums salts was also achieved with **1**. Indeed, introduction of either hexyl (Hex) or dodecylammonium ($DodecNH_3^+$) chloride salts (ca. 3 equiv) in a solution of **1** in $CDCl_3$ led, almost quantitatively,[40] to the corresponding complexes $\mathbf{1}\supset HexNH_3^+Cl^-$ and $\mathbf{1}\supset DodecNH_3^+Cl^-$, as indicated by the high-field signals belonging to the included ammonium ions (Scheme 4 and Figure 3c).[41] Remarkably, in both cases, all the methylene protons of the included alkyl chains appeared as well-separated resonances.[42] The CISs of the included ammonium chains of $PrNH_3^+$, $HexNH_3^+$, and $DodecNH_3^+$ were determined and an excellent correlation was obtained with their position relative to the ammonium group (Figure 4). Hence, whereas the α, δ, and ε methylene protons undergo a medium shielding effect ($\delta = -1.37$ to -1.52 ppm), the β and γ methylene protons are strongly affected ($\delta = -2.63$ to -3.13 ppm), suggesting a location in

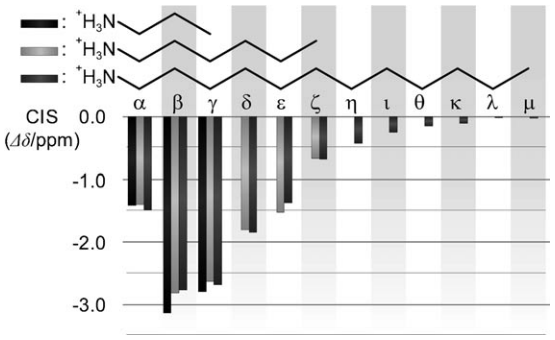


Figure 4. CISs of the included alkylammonium chains in the case of the ternary complexes $\mathbf{1}\supset RNH_3^+Cl^-$ (with R = Pr, Hex, Dodec).

the heart of the aromatic cavity. Moreover, the CISs decrease dramatically from the ζ methylene protons, indicating that the dodecyl chain protrudes out of the cavity. Finally, it is noteworthy that the *t*Bu, ArH, and OMe signals of the anisole moieties of $\mathbf{1}\supset HexNH_3^+Cl^-$ and $\mathbf{1}\supset DodecNH_3^+Cl^-$ experience a downfield shift compared with those of host–guest complexes obtained with smaller guests (see Figure 3b versus 3c). Indeed, these aromatic units have to adopt a straighter conformation, more parallel to the C_3 axis, since their *t*Bu groups are expelled from the cavity by the alkyl chain of the included ammonium ion.

It is important to note that the inclusion of guests possessing an alkyl chain longer than propyl is generally precluded with *p*-*t*Bu-calix[6]arene-based receptors because it leads to

a steric clash with the introverted *t*Bu groups that close the cavity of the host. However, the binding of large amino guests was observed with metal complexes of *p*-*t*Bu-calix[6]-arenes thanks to the strong coordination link to the metal center that allows the spreading of the *t*Bu groups from the C_3 axis and thus extension of the cavity size.[11,43] In the case of receptor **1**, this conformational energy penalty resulting from the repulsion of the *t*Bu groups is largely compensated by the strong electrostatic attraction that prevails in the contact ion pair.

All these findings prompted us to investigate the binding of quaternary ammonium salts and, to this end, tetramethylammonium chloride (TMA^+Cl^-) was added to a solution of **1** in $CDCl_3$. Despite the extremely poor solubility of TMA^+Cl^- in $CDCl_3$, a significant amount was extracted since a new species corresponding to the complex $\mathbf{1}\supset TMA^+Cl^-$ ($\delta_{TMA+in}=0.78$ ppm) was clearly apparent in addition to the signals of the free host **1**.[24] No free TMA^+Cl^- was observed showing a high affinity of the ion pair toward host **1** ($K_a > 2.3\times10^6\,M^{-2}$). In $CD_3OD/CDCl_3$ (1:4), a 9:1 mixture of $\mathbf{1}\supset TMA^+Cl^-$ and $\mathbf{1}\supset Cl^-$ was observed upon the addition of an excess of TMA^+Cl^- (5 equiv) (Figure 3d).[44] This result underscores the remarkable ability of **1** to host bulky ammonium ion pairs, even in the presence of protic solvents.

The next challenge was to test the inclusion of bulky, biologically relevant ammonium salts with either primary ammonium groups, such as 3,4-*O*-dimethyldopamine hydrochloride ($Me_2DOPAH^+Cl^-$) and 5-*O*-methylserotonine hydrochloride ($MeSEROH^+Cl^-$), or quaternary ammonium groups, such as acetylcholine chloride (ACh^+Cl^-).[45] To our delight, receptor **1** presented a strong affinity for the neurotransmitter acetylcholine chloride and the ternary complex $\mathbf{1}\supset Ach^+Cl^-$ was obtained almost quantitatively (>90%) upon the addition of an excess of ACh^+Cl^- (7 equiv) (Figure 3e).[46] In addition, the complex was still visible in a mixture of $CD_3OD/CDCl_3$ (4:1), highlighting a remarkable stabilization of the contact ion pair by **1**. Introduction of $Me_2DOPAH^+Cl^-$ (1 equiv) to a solution of **1** in $CDCl_3$ led to a small proportion (ca. 25%) of the desired contact ion pair complex $\mathbf{1}\supset Me_2DOPAH^+Cl^-$,[47] together with the chloride complex $\mathbf{1}\supset Cl^-$ in fast exchange with the free host **1**. Increasing the amount of $Me_2DOPAH^+Cl^-$ (6 equiv) mostly favored the chloride complex to the detriment of the free host. In contrast, $MeSEROH^+Cl^-$ was too sterically demanding to yield a stable adduct, either in $CDCl_3$ or after the subsequent addition of CD_3OD to solubilize a larger amount of salt. All these data show that the binding process is highly sensitive to the geometry of the guest. Indeed, the channel-like cavity obtained upon the spreading of the *t*Bu groups seems to be selective for the most linear guests.

Acid–base control of the host properties: In addition to the acid–base controlled switch between anions and neutral molecules described above, the unique versatility of **1** was further illustrated by the facile and reversible transformation of three different host–guest complexes ($\mathbf{1}\cdot H^+\supset$Imi, $\mathbf{1}\supset PrNH_3^+Cl^-$, and $\mathbf{1}\supset TMA^+Cl^-$) in solution. The guest-switching cycle started with a mixture of $\mathbf{1}\cdot H^+$ and three competing guests, that is, TMA^+Cl^- (2.5 equiv), $PrNH_3^+Cl^-$ (15 equiv), and Imi (2.5 equiv), in $CDCl_3/CD_3OD$ (98:2). The ^1H NMR spectrum of this complex initial mixture only showed the host–guest complex $\mathbf{1}\cdot H^+\supset$Imi (Figure 5, inset a). Addition of diaza(1,3)bicyclo[5.4.0]undecene (DBU) (2 equiv)[18] gave rise, exclusively, to the complex $\mathbf{1}\supset PrNH_3^+Cl^-$ through the deprotonation of the cap (Figure 5, inset b). The subsequent addition of a large excess of DBU led to the deprotonation of the propylammonium and, therefore, to the quantitative formation of the ternary complex $\mathbf{1}\supset TMA^+Cl^-$ (Figure 5, inset c). The full reversibility of the switching processes was demonstrated through the progressive addition of PicH, restoring cleanly, first the complex $\mathbf{1}\supset PrNH_3^+Cl^-$, and then the initial species $\mathbf{1}\cdot H^+\supset$Imi

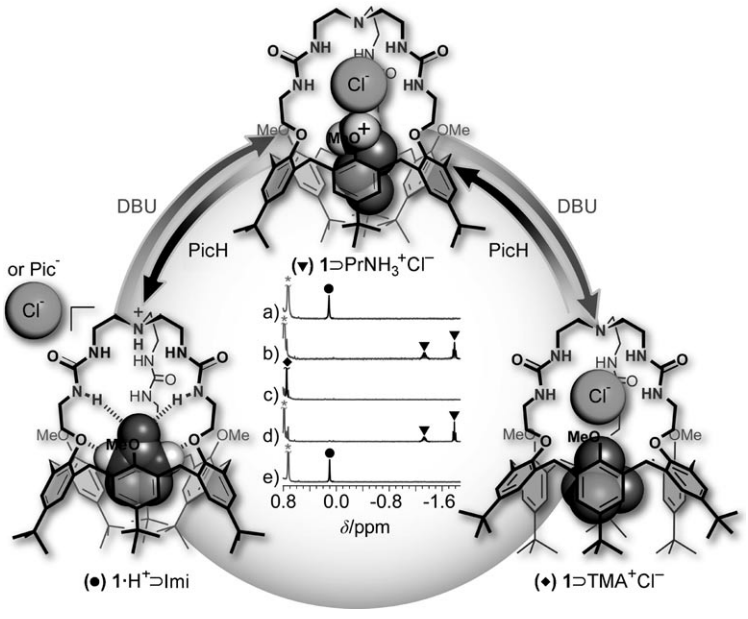


Figure 5. Reversible guest switches between $\mathbf{1}\cdot H^+\supset$Imi, $\mathbf{1}\supset PrNH_3^+Cl^-$, and $\mathbf{1}\supset TMA^+Cl^-$ triggered by the addition of acid or base and monitored by ^1H NMR in $CDCl_3/CD_3OD$ (98:2). Inset: ^1H NMR spectra (400 MHz, 298 K, high-field region) of a) mixture of $\mathbf{1}\cdot H^+$, TMA^+Cl^- (2.5 equiv), $PrNH_3^+Cl^-$ (15 equiv), and Imi (2.5 equiv); b) after addition of DBU (2 equiv); c) after addition of DBU (25 equiv); d) after addition of PicH (12 equiv); e) after addition of PicH (22 equiv). ●: included Imi; ▼: included $PrNH_3^+$; ◆: included TMA^+; ∗: *t*Bu group of the calixarene.

(Figure 5, insets d and e). These results constitute an unprecedented example of a three-pole supramolecular switch based on host–guest complexes that differ by the nature of the guests (i.e., neutral molecules or contact ion pairs). It was also possible to achieve an acid–base-controlled guest-switching process (e.g., between $\mathbf{1}\cdot H^+\supset$Imi and $\mathbf{1}\supset PrNH_3^+Cl^-$) by replacing PicH and DBU by trifluoroacetic acid (TFA) and TEA, respectively.[24]

All these reversible interconversions triggered by the addition of acid or base demonstrate the possible tuning of the binding properties of **1** by the environment. The versatility of the system is, in part, due to the protonation of the cap, which, 1) polarizes the receptor and thus favors the complexation of polar, neutral guests through charge–dipole interactions, and 2) causes anion release through steric repulsion. Thus, to some extent, the proton present on the charged nitrogen of the cap acts as an allosteric effector because it allows the switch from one mode of recognition to another and a remarkable guest selection from a complex mixture. In other words, host **1** illustrates how the host properties of a hydrophobic cavity can be tuned by an allosteric effector, which is reminiscent of natural systems and their propensity to undergo allosteric control.

Conclusion

All these results show that calix[6]arenes are superb molecular platforms for the elaboration of sophisticated host–guest systems. The key features of the unique host properties of calix[6]crypturea **1** are as follows:

1) The combination of two different binding sites in close proximity, that is, a tris-ureido cap and a hydrophobic cavity suitable for the inclusion of organic guests. This unusual association leads to multiple neighboring binding centers that can operate cooperatively. Indeed, the tris-ureido cap provides convergent hydrogen-bond-donor sites, whereas the calixarene core offers hydrogen-bond-acceptor sites, in addition to electron-rich aromatic walls favoring CH–π interactions. Furthermore, the hydrophobic channel-like cavity controls the access to the tris-ureido recognition site, protecting the bound guest from the external medium. All these structural features give rise to a heteroditopic receptor displaying high affinities for neutral guests, anions, and ion pairs, most of the host–guest complexes are even stable in polar or protic solvents. Despite its versatility, this multipoint recognition system shows a remarkable selectivity that is dominated by the presence of complementary hydrogen-bond donor and acceptor groups in the case of neutral guests, the size in the case of anions, and a good geometrical fit in the case of ammonium salts. Finally, the strong complexation of ammonium salts in apolar or protic solvents stresses the importance of the proximity of the two binding sites. Indeed, these guests are accommodated as contact ion pairs and thus the highly energetically unfavorable dissociation of the ion pair is avoided.
2) The high, but controlled, flexibility of the calixarene framework proves to be a major advantage. Indeed, the cavity of **1** can adapt its size and geometry to the guest for an optimized host–guest binding energy. Hence, impressive conformational reorganizations of the calixarene cavity have been evidenced upon the binding of anions and ion pairs. Remarkably, this flexibility allows the inclusion of small ammonium salts as well as large, biologically relevant ammonium salts, such as neurotransmitters, thanks to an induced-fit process involving the spreading of the anisole units. Such host properties based on interactive processes stand in contrast to rigid concave receptors, which exhibit strong binding only when there is a good fit between the size of the guest and of the cavity.
3) The implementation of an acid–base control for guest binding at the level of the tris-ureido cap. The protonation of the cap leads to a positively charged receptor $\mathbf{1}\cdot H^+$, in which the host properties are governed by strong charge–dipole interactions with the guest. First, in the case of neutral guests, a significant increase in binding strength is observed with the polarization of the receptor. Second, anion release results from the protonation of the host, making possible the reversible interconversion of different modes of recognition. This allosterically controlled binding system can lead to highly selective guest exchanges from complex mixtures. In particular, three-way supramolecular switches, based on the interconversion of host–guest systems displaying either charged or neutral guests, are possible.

Hence, host **1** displays 1) a tunable recognition site, protected by a hydrophobic corridor, that can adapt its conformation to the size of the guest through induced-fit processes, 2) versatile host properties that can be allosterically controlled by protonation, and 3) a high selectivity based on the electronic, geometric, or size complementarity with the guest. In other words, host **1** behaves as a remarkable biomimetic receptor and current efforts are now being directed toward the grafting of water-soluble groups to develop various applications, such as the sensing or the vectorization of biologically relevant species, as well as the design of acid–base controllable artificial molecular machines.

Experimental Section

General: ^{1}H NMR spectra were recorded either at 300, 400, or 600 MHz. Traces of residual solvent were used as internal standards and $CDCl_3$ was filtered over a short column of basic alumina to remove traces of HCl. Mass spectra were recorded on an ESIMS 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: −15 V, tube lens offset voltage: −30 V.

Estimation of the K_a values in $CDCl_3$: Association constants, K_a, for the host–guest systems in $CDCl_3$ were estimated according to the following

procedure: suitable aliquots of a solution of G (G = Imi, Pyo) or G_1G_2 ($G_1 = PrNH_3^+$, TMA^+, and $G_2 = Cl^-$) in $CDCl_3$were added to a solution of receptor H (**1** or **1**·H^+, 1×10^{-3}–4×10^{-3} M) in $CDCl_3$ in such a way that the corresponding ^{1}H NMR spectra recorded at 298 K revealed the total disappearance of the free host H (the equilibria were reached instantaneously) except in the case of TMA^+Cl^-, which is limited by its poor solubility in $CDCl_3$. The concentration of the undetectable species (H and in some cases G or G_1 and G_2) and the concentration of H⊃G or H⊃G_1G_2 were estimated to be 5 and 95% of the starting host concentration, respectively. K_a values were estimated according to the following equations: $K_a > [H\supset G]/([H][G])$ or $K_a > [H\supset G_1G_2]/([H][G_1][G_2])$.

The relative affinities of the neutral molecules, $K_{G/Pyro}$, in the case of **1** and **1**·H^+ were determined through ^{1}H NMR spectroscopic competitive binding studies in $CDCl_3$: Pyro (>1 equiv) and a second guest G (>1 equiv) were added successively to a solution of **1** or **1**·H^+ (3×10^{-3} M) in $CDCl_3$ in such a ratio that a ^{1}H NMR spectrum recorded at RT showed the resonances of both *endo*-complexes **1**⊃Pyro and **1**⊃G or **1**·H^+⊃Pyro and **1**·H^+⊃G, in addition to the signals corresponding to the free guests (Pyro and G). Integration of the signals of the included guests, $Pyro_{in}$ and G_{in}, and of the free guests, $Pyro_{free}$ and G_{free}, allowed the calculation of the relative affinity, $K_{G/Pyro}$, defined as $([G_{in}][Pyro_{free}])/([G_{free}][Pyro_{in}])$ (errors estimated at ±10%).

Determination of the K_a values of 1 toward anions X^- in CD_3CN: In the cases of Br^-, CN^-, and AcO^-, the association constants, K_a, were determined according to the following procedure: suitable aliquots of a solution of the TBA^+ salt of the anion (X^-) in CD_3CN were added to a solution of receptor **1** (ca. 10^{-3} M) in CD_3CN in such a way that the corresponding ^{1}H NMR spectra recorded at 243 K revealed the presence of all partners in slow exchange on the NMR spectroscopy timescale, thus allowing the determination of the constant K_a (the equilibria were reached instantaneously). Hence, the concentrations of **1**, X^-, and **1**⊃X^- at equilibrium were determined by integration of suitable signals. Thus, association constants were calculated according to the following equation: $K_a = [\mathbf{1}\supset X^-]/([\mathbf{1}][X^-])$. In the case of Cl^-, the association constant was determined through a competitive experiment with Br^-: suitable aliquots of a solution of TBA^+Br^- salt in CD_3CN were added to a solution of the complex **1**⊃Cl^-,TBA^+ in CD_3CN (10^{-3} M) in such a way that the corresponding ^{1}H NMR spectra recorded at 243 K revealed the presence of the two host–guest complexes (**1**⊃Cl^- and **1**⊃Br^-) in slow exchange on the NMR spectroscopy timescale, thus allowing the determination of the association constant through their relative affinity (the equilibria were reached instantaneously). Hence, the concentrations of Cl^-, Br^-, **1**⊃Cl^-, and **1**⊃Br^- were determined through integration of the TBA^+ signals and the characteristic NH signals. The association constant was then determined with the following equation: $K_{a(Cl-)} = K_{a(Br-)} \times ([\mathbf{1}\supset Cl^-][Br^-])/([\mathbf{1}\supset Br^-][Cl^-])$.

Acknowledgements

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[30] The starting complex $\mathbf{1}\cdot H^+\supset CD_3OD$ displays a classical C_{3v} symmetrical, flattened-cone conformation ($\Delta\delta t_{Bu} = 0.49$ ppm and $\Delta\delta_{ArH} = 0.55$ ppm) with the methoxy groups outside the cavity ($\delta_{OMe} = 3.65$ ppm), showing the inclusion of CD_3OD (see the Supporting Information).

[31] The addition of an excess of TBA^+X^- ($X^- = Cl^-$ or Br^-) did not affect the signals of $\mathbf{1}\supset X^-$, showing a 1:1 stoichiometry for the host–guest complexes.

[32] Cl^- was coordinated too strongly by **1** to allow the binding constant to be determined accurately by this method, since no free **1** was observed upon the addition of TBA^+Cl^- (1 equiv). Thus, the association constant for Cl^- was determined through a ^1H NMR spectroscopy competitive binding experiment with Br^- (see the Supporting Information).

[33] The binding of F^- was also studied in CD_3CN through a ^1H NMR spectroscopic titration with TBA^+F^-. While a strong recognition was apparent, the accurate determination of the association constant was not possible, since an abnormal looking titration curve was obtained (see the Supporting Information).

[34] In this case the decreasing charge density also contributes to the observed sequence of affinities, that is, $Cl^- > Br^- > I^-$.

[35] Such anions can be stabilized though an additional hydrogen-bonding interaction with an ether oxygen atom of the calixarene core.

[36] For a leading example of neutral receptor complexing anions in protic solvents, see: S. Kubik, R. Goddard, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5127–5132.

[37] Only a broadening of the NMR signals of $\mathbf{1}\supset Cl^-$ was observed (see the Supporting Information).

[38] Defined as $K_a = [\mathbf{1}\supset PrNH_3^+Cl^-]/([\mathbf{1}][X^-][PrNH_3^+])$.

[39] The addition of $PrNH_3^+Cl^-$ to **1** in CD_3CN led to the precipitation of the calixarene species.

[40] In both cases, a minor species (ca. 10%) corresponding to the host–guest complex $\mathbf{1}\supset Cl^-$ was observed.

[41] Similarly, the formation of $\mathbf{1}\supset HexNH_3^+F^-$ was achieved through the addition of $HexNH_3^+Pic^-$ (2 equiv) and TBAF (3 equiv) to a solution of **1** in $CDCl_3$. Interestingly, the CISs of the included alkyl chain were quite different from those of the complex $\mathbf{1}\supset HexNH_3^+Cl^-$ (see the Supporting Information), confirming the contact ion pairing of the two guests.

[42] Their assignment was made by 1D TOCSY and COSY experiments (see the Supporting Information).

[43] O. Sénèque, M. N. Rager, M. Giorgi, O. Reinaud, *J. Am. Chem. Soc.* **2000**, *122*, 6183–6189.

[44] With 1 equiv of TMA^+Cl^-, an approximately 7:3 mixture of $\mathbf{1}\supset TMA^+Cl^-$ and $\mathbf{1}\supset Cl^-$ (the latter being in fast exchange with **1**) was observed.

[45] For references dealing with the intracavity complexation of biologically relevant ammonium ions, see: a) K. N. Koh, K. Araki, A. Ikeda, H. Otsuka, S. Shinkai, *J. Am. Chem. Soc.* **1996**, *118*, 755–758; b) F. P. Ballistreri, A. Notti, S. Pappalardo, M. F. Parisi, I. Pisagatti, *Org. Lett.* **2003**, *5*, 1071–1074; c) S. M. Biros, E. C. Ullrich, F. Hof, L. Trembleau, J. Rebek, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 2870–2876; d) J. K. Kim, B. Raman, K. H. Ahn, *J. Org. Chem.* **2006**, *71*, 38–45; e) S. Le Gac, M. Giorgi, I. Jabin, *Supramol. Chem.* **2007**, *19*, 185–197.

[46] The minor species (<10%) corresponds to the chloride complex $\mathbf{1}\supset Cl^-$. All of the signals were assigned with the aid of 2D NMR spectra (see the Supporting Information).

[47] All the signals of the inclusion complex $\mathbf{1}\supset Me_2DOPAH^+Cl^-$ were assigned by COSY and HSQC experiments (see the Supporting Information).

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