An allosteric heteroditopic receptor for neutral guests and contact ion pairs with a remarkable selectivity for ammonium fluoride salts†

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Received 4th June 2010, Accepted 30th June 2010
DOI: 10.1039/c0ob00211a

Two novel calix[6]cryptamides bearing a tren-based cap have been synthesized and their host–guest properties have been investigated by ^{1}H and ^{19}F NMR spectroscopy. One of them behaves as a remarkable heteroditopic receptor toward either polar neutral guests, anions or contact ion pairs. It has been shown that only F^- can be encapsulated into the tris-amido cap of this host. Moreover, the fluoride anion acts as an allosteric activator by favoring the inclusion of ammonium ions into the calixarene cavity. The ammonium fluoride salts are bound as contact ion pairs and, remarkably, the calix[6]cryptamide host is reluctant to other ammonium salts. To our knowledge, such an highly cooperative and selective process toward contact ammonium fluoride salts is unique in the literature. Allosteric regulation of all the host–guest systems can also be achieved through protonation of the aza-cap. Indeed, guest release can be triggered by addition of various acids. In comparison to related calixarene-based receptors, all these unique properties are due to the smallness and the higher preorganization of the binding site provided by the convergent hydrogen bond donor groups of the tris-amido cap.

1 Introduction

The design of new multitopic receptors capable of binding target species with a high selectivity is an important goal in supramolecular chemistry.[1] Indeed, the simultaneous binding of multiple guests with an allosteric regulation of the recognition processes is a key issue for the construction of sophisticated devices.[2] A biomimetic approach for the elaboration of multitopic receptors consists of using bowl-shaped macrocycles displaying a hydrophobic cavity associated to a polyfunctional subunit that can recognize particular guests through specific interactions. The tripodal tris(2-aminoethyl)amine (tren) provides an attractive platform for the elaboration of such subunits. Thus, tren-based receptors displaying either cyclotriveratrilene (CTV),[3] aza-calixarene[4] or calixarene[5] scaffolds have been notably described and some of them have shown interesting host–guest properties toward either anions[4,5a] or neutral guests.[6] Besides, since the seminal work of Lehn,[7] many examples of aza-cryptands[8] or acyclic receptors[9] containing a tren moiety have been reported. In particular, polyamido tren-based cryptands have been used for the selective recognition of anions[10] and especially fluoride.[11] One interesting feature of the tren-based receptors is the possibility of controlling their binding properties through the protonation of the tertiary amino group. This acid–base control can be notably exploited for the construction of switchable systems.[12]

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 aza-cryptand cap.[5c,5d,13] 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]crypturea (Fig. 1),[14] behaves as an heteroditopic receptor that exhibits unique host–guest properties toward polar neutral molecules, anions[15,16] or contact organic ion pairs.[17,18] It has been shown that these versatile host properties can be allosterically controlled by protonation of the capping tren moiety and sophisticated three-way supramolecular switches based on the interconversion of host–guest systems have been reported. Replacing the crypturea cap by a cryptamide moiety led to the so-called calix[6]cryptamides (as a representative example, see calix[6]CTVamide depicted Fig. 1), also able to complex neutral guests or contact organic ion pairs in a cooperative way.[19,20] The

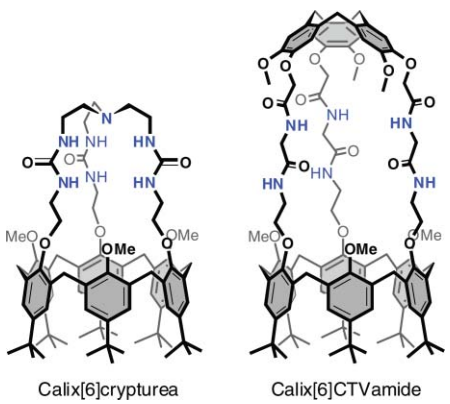

Fig. 1 Calix[6]crypturea and calix[6]CTVamide.

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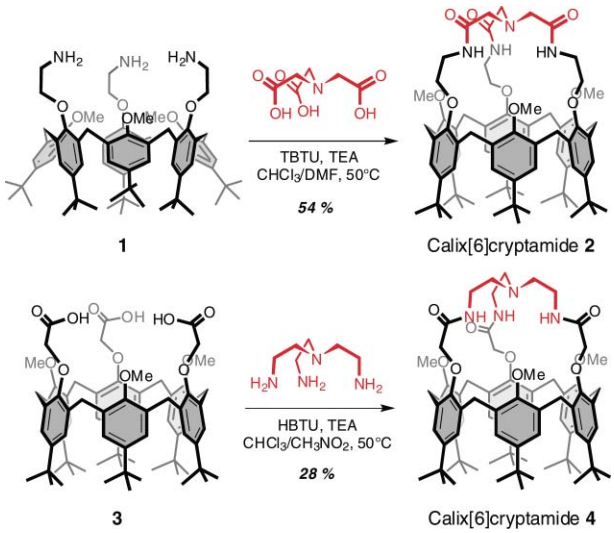
† Electronic supplementary information (ESI) available: NMR and ESI-MS spectra. See DOI: 10.1039/c0ob00211a

remarkable properties of these two families of receptors are due to the combination in close proximity of two different binding sites, *i.e.* a tris-ureido or tris-amido cap that offers convergent hydrogen bond donor sites and a hydrophobic cavity suitable for the inclusion of organic guests.

In the course of designing readily available calixarene-based receptors whose host properties can be allosterically controlled by external stimuli,[21] calix[6]arenes bearing a more rigid and smaller tris-amido tren moiety have been envisaged. Indeed, thanks to the higher preorganization of their binding site, such heteroditopic receptors were expected to possess reinforced and more selective recognition properties than the parent receptors.

Herein, we describe the straightforward syntheses and unique host–guest properties of two novel calix[6]cryptamides (*i.e.* **2** and **4**) that differ by the position of the carbonyl group on the tren-based cap.



Scheme 1 Syntheses of calix[6]cryptamides **2** and **4**.

2 Results and discussion

2.1 Syntheses and NMR conformational analysis of calix[6]cryptamides 2 and 4

Both calix[6]cryptamides **2** and **4** were synthesized through [1 + 1] macrocyclization reactions between tris-carboxylic acids and tris-amines (Scheme 1). The known C_{3v} symmetrical calixarene subunits (*i.e.* **1** and **3**)[22] were obtained in a few steps from 1,3,5-tris-methoxycalix[6]arene and the macrocyclization reactions were performed under conditions which were reported as optimal for the synthesis of various closely related calix[6]cryptamides.[19] Thus, calix[6]tris-amine **1** and calix[6]tris-acid **3** were reacted respectively with nitrilotriacetic acid and tris-(2-aminoethyl)amine (tren) in the presence of an excess of coupling agent (HBTU or TBTU) and TEA at 50 °C. The reactions were monitored by ^{1}H NMR spectroscopy and the obtained calix[6]cryptamides were purified by flash chromatography (FC). While calix[6]cryptamide **2** was isolated in 54% yield, calix[6]cryptamide **4** was only obtained in moderate yield (*i.e.* 28%).

Calix[6]cryptamides **2** and **4** were characterized by ^{1}H NMR spectroscopy in $CDCl_3$ at 298 K and all the signals were assigned through 2D NMR analyses. Both compounds display C_{3v} symmetrical patterns characteristic of averaged straight cone conformations ($\Delta\delta_{tBu} < 0.26$ ppm[5c]) (see Fig. 2a for the ^{1}H NMR spectrum of **2**). In both cases, the average chemical shift of the three methoxy groups (δ_{OMe} = 2.96 and 3.15 ppm for **2** and **4**, respectively) may result from the self-inclusion of one of these groups.[14] In contrast with **4**, the chemical shifts of most of the signals of calix[6]cryptamide **2** were found to be slightly dependent on the amount of residual water. In particular, progressive upfield

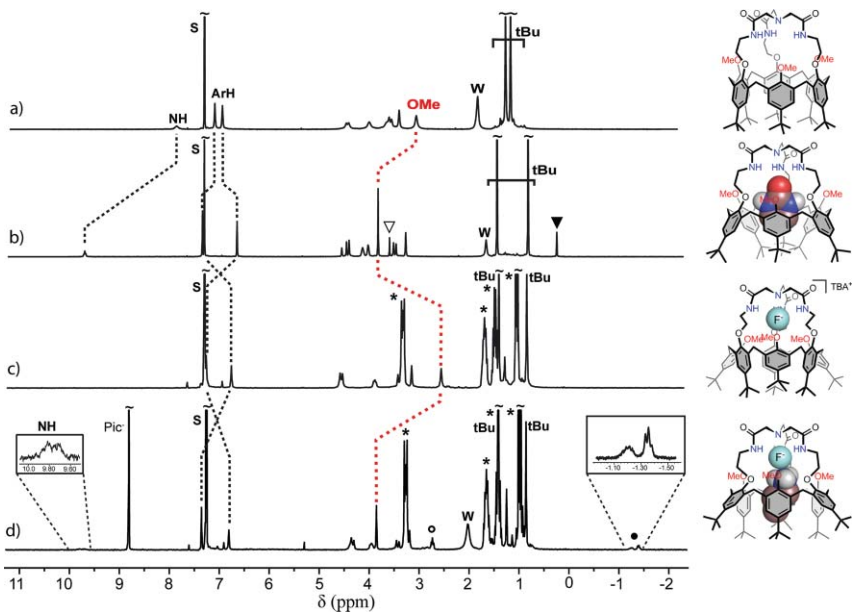
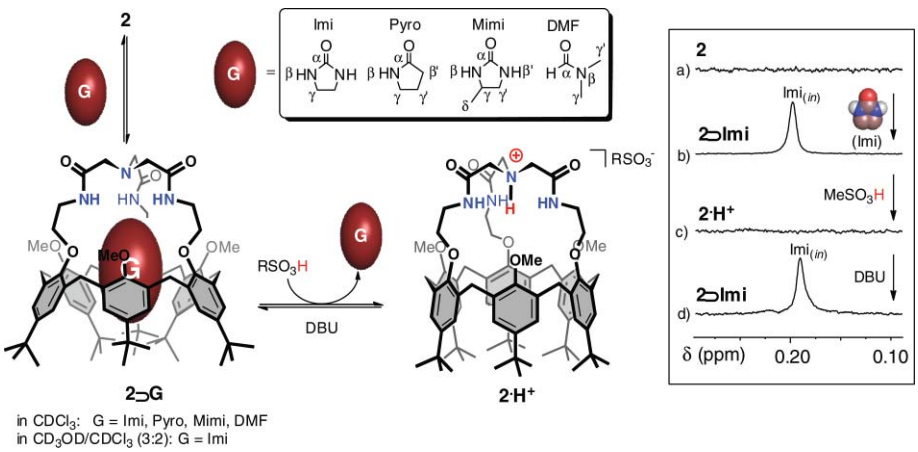


Fig. 2 ^{1}H NMR spectra (300 MHz, 298 K) of (a) **2** in $CDCl_3$; (b) **2**⊃**Imi** in $CDCl_3$ obtained after addition of 1.25 equiv. of Imi to **2**; (c) **2**⊃**F**$^-$ in $CDCl_3$ obtained after addition of 7.1 equiv. of TBA^+F^- to **2**; (d) **2**⊃**PrNH$_3^+$F**$^-$ in $CDCl_3$ obtained after addition of 4 equiv. of both $PrNH_3^+Pic^-$ and TBA^+F^- to **2**. ▽: free Imi; ▼: Imi included; *: TBA^+; ○: free $PrNH_3^+$; ●: $PrNH_3^+$ included. W: water; S: residual solvent.

shift of the OMe as well as downfield shift of the NH signals were observed upon the addition of traces of water. Similar shifts were obtained by lowering the temperature from 308 K to 263 K ($\Delta\delta_{NH}$ = 0.63 ppm).[23,24] Similarly to what was observed with the parent calix[6]crypturea, these data indicate that **2**, in apolar solvents such as $CDCl_3$, is able to weakly bind water through H-bonding interactions at the level of its cryptamide cap. When the spectra were recorded in $CD_3CN/CDCl_3$ (1 : 2),[25] more flattened averaged cone conformations as well as a downfield shift of the OMe signals were observed in both cases (δ_{OMe} = 3.60 and 3.51 ppm for **2** and **4**, respectively).[23] These conformational changes are due to the complexation of CD_3CN inside the cavity with a fast host–guest exchange on the NMR time scale (*vide infra*). In contrast, in the presence of a protic solvent (*i.e.* $CD_3OD/CDCl_3$; 3 : 2), calix[6]cryptamide **2** adopts a flattened cone conformation with the hydrophobic cavity filled by the introverted OMe groups (δ_{OMe} = 2.53 ppm).[23] Finally, the protonated derivatives **2**·$\mathbf{H^+}$ and **4**·$\mathbf{H^+}$ were obtained quantitatively after the addition of $MeSO_3H$ (>1 equiv.) to a solution of **2** or **4** in $CDCl_3$. The protonation of the bridging tertiary amine was clearly apparent through the strong chemical shift of the NCH_2 protons.[23] In contrast with **4**, when TFA or PTSA were used for the protonation of **2**, different C_{3v} symmetrical NMR patterns were obtained in each case, notably at the level of the ArH and OMe signals. Also, the NMR spectrum of **2** remained quasi-unchanged upon the addition of a large excess (*ca.* 20 equiv.) of picric acid (PicH).[26] Thus, in contrast with **4** or related calix[6]arene receptors,[6b,14] the protonation of **2** in an apolar solvent such as $CDCl_3$ is highly dependent on the strength of the resulting *exo*-interaction between **2**·$\mathbf{H^+}$ and its tightly associated counteranion, the protonation being extremely difficult with the low coordinating picrate anion. It may be rationalized by the establishment of a stable five-membered intramolecular hydrogen-bonded ring between NH^+ and an introverted carbonyl group, the anion being recognized by the resulting NH amido group directed toward the outside of the tris-amido cap.

2.2 Neutral molecule recognition

First, the host properties of calix[6]cryptamide **2** toward polar neutral guests (G) were investigated at 298 K by NMR spectroscopy in $CDCl_3$. While host **2** was reluctant to small alcohols (*i.e.* MeOH, EtOH) or amines (*i.e.* $PrNH_2$), the inclusion of ureas and amides such as imidazolidin-2-one (Imi), pyrrolidin-2-one (Pyro), (±)-4-methylimidazolidin-2-one (Mimi)[27] and DMF was observed (Scheme 2, Fig. 2b for **2**⊃**Imi**). In all cases, the host–guest exchanges are slow on the NMR time scale and integration of the high-field signals corresponding to the included guest indicate a 1 : 1 host–guest stoichiometry. The complexes **2**⊃**G** display C_{3v} symmetrical flattened cone conformation with the OMe groups expelled from the cavity (δ_{OMe} > 3.76 ppm) and the complexation-induced shifts (CISs) indicate a positioning of the guest in the heart of the cavity (Table 1). Impressive downfield shifts of the NH protons of the cryptamide cap were observed upon complexation ($\Delta\delta_{NH}$ > 1.4 ppm), suggesting strong hydrogen bonding interactions with the carbonyl oxygen atom of the guest. All these NMR data show that, similarly to the parent receptors (Fig. 1), host **2** can selectively bind polar neutral guests that can interact through hydrogen bonding interactions with the NH groups of the cap as well as through CH–π interactions with the aromatic walls of the host. One can note that, in the case of the chiral complex **2**⊃**Mimi**, the NMR pattern of the $ArH_{anisole}$ and $ArCH_{ax}$ protons strongly suggests that these diastereotopic protons are in close proximity to the chiral center of the guest.[23] In the case of Imi, the association constant K_a was estimated to be $>1 \times 10^5$ M^{-1}. In addition, a ^1H NMR competitive binding experiment showed that the relative affinity of Imi toward host **2** is from one to three orders of magnitude higher than the other ones (Table 1). Such a high selectivity for Imi 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.[28] This efficient mode of recognition has been confirmed with an optimized structure of **2**⊃**Imi** obtained through computer modeling (Fig. 3, top left).[29] The position of the guest and the conformation of calix[6]cryptamide **2** obtained after energy minimization are highly compatible with what was observed in solution by NMR spectroscopy. As mentioned above, it was also possible to detect a weak complexation of CH_3CN through its progressive addition to **2** in $CDCl_3$ (Table 1).[30] To our delight, neutral host **2** was also capable of binding Imi even in the presence of a large amount of CD_3OD (*i.e.* $CD_3OD/CDCl_3$;



Scheme 2 Host–guest properties of calix[6]cryptamide **2** toward neutral guests and reversible acid-triggered release of these guests. Inset: high-field region of the ^1H NMR spectra ($CDCl_3$, 300 MHz, 298 K) of a) **2**; b) +IMI (1.25 equiv.); c) +$MeSO_3H$ (6.2 equiv.); d) +DBU (26 equiv.).

Table 1 ^{1}H NMR complexation-induced shifts (CISs), relative affinities ($K_{G/DMF}$) and association constant (K_a) of the neutral guests (G) in the case of **2⊃G**

2⊃G in $CDCl_3$						
		CIS (ppm)[b]			**2⊃G** in $CD_3OD/CDCl_3$ 3 : 2	
Guest	$K_{G/DMF}$[a]	β	γ	δ	K_a/M^{-1}[c]	CIS (ppm)[b]
Imi	1070[d]	+0.06	−3.35	—	430	−3.24 (Hγ)
Pyro	63	−1.00 ($H_{\beta'}$)	−3.54 (H_γ) −3.19 ($H_{\gamma'}$)	—	nd[e]	nd[e]
Mimi	5	+0.10[f]	−3.40[f]	−2.94	nd[e]	nd[e]
DMF	1	—	−2.93[f]	—	nd[e]	nd[e]
MeCN	0.04[g]	−3.13[g]	—	—	nd[e]	nd[e]

[a] Relative affinity determined at 298 K and defined as $([G_{in}] \times [DMF_{free}])/([G_{free}] \times [DMF_{in}])$ where the subscript "in" stands for "included". Errors estimated ±15%. [b] CIS measured at 298 K and defined as $\Delta\delta = \delta$(complexed G) − δ (free G). The β, γ and δ positions are defined in Scheme 2. [c] K_a was determined at 298 K by integration of the different species in equilibrium. K_a is defined as: $K_a = [\mathbf{1}\supset\mathbf{G}]/([\mathbf{1}] \times [G])$. Error estimated ± 15%. [d] Determined through a competitive experiment with Pyro. [e] Not detected. [f] Average value of the different signals (H_β and $H_{\beta'}$ or H_γ and $H_{\gamma'}$). [g] Determined at 253 K.

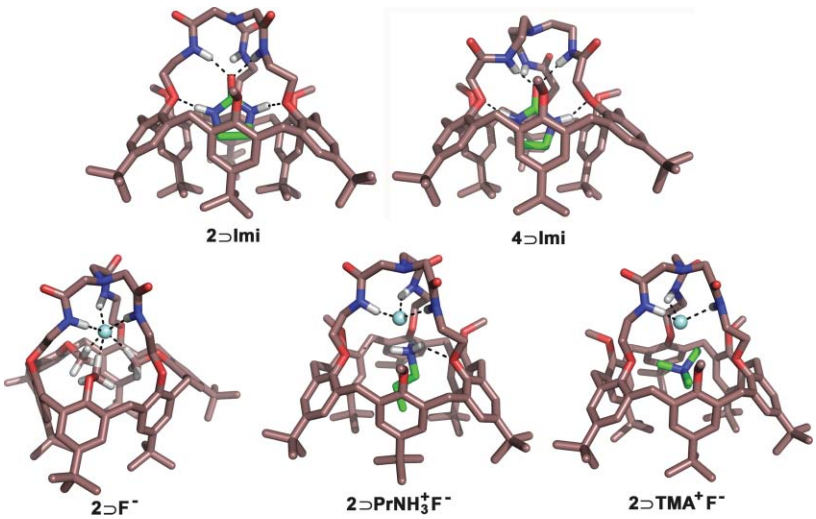
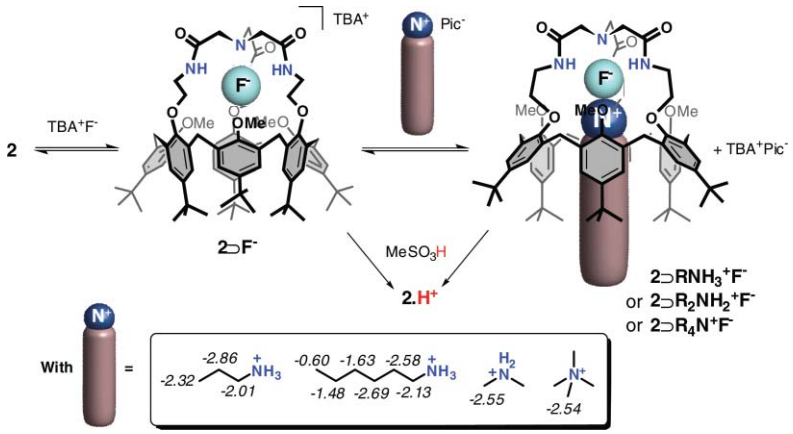


Fig. 3 Energy minimized structures of **2⊃Imi** (top left), **4⊃Imi** (top right), **2⊃F**$^-$ (bottom left), **2⊃PrNH$_3^+$F**$^-$ (bottom middle) and **2⊃TMA$^+$F**$^-$ (bottom right). Most of the hydrogen atoms are omitted for clarity. Selected distances (Å) for **2⊃Imi**: N(host)–O(Imi): 2.84 and 2.86; N(Imi)–O(host): 2.80 and 2.82. For **4⊃Imi** N(host)–O(Imi): 2.95 and 2.98; N(Imi)–O(host): 2.77 and 2.81. For **2⊃F**$^-$: N(host)–F$^-$: 2.89, 3.03 and 3.11; C(host)–F$^-$: 2.98, 3.12 and 3.14. For **2⊃ PrNH$_3^+$F**$^-$: N(host)–F$^-$: 2.78, 2.80 and 2.99; N$^+$(guest)–O(host): 2.96; N$^+$(guest)–F$^-$: 2.08. For **2⊃TMA$^+$F**$^-$: N(host)–F$^-$: 2.77, 2.81 and 2.87; N$^+$(guest)–F$^-$: 3.28.

3 : 2).[23] The association constant (K_a = 430 M^{-1}) is much higher than the one determined with the parent calix[6]crypturea under the same conditions (*i.e.* K_a = 10 M^{-1}), highlighting the better complementarity between Imi and the more rigid tripodal cap of **2**. Interestingly, the progressive addition of $MeSO_3H$ or PTSA to the host–guest complexes **2⊃G** led solely to the formation of the protonated derivative **2·H$^+$**, the exchange between the two calixarene species being slow on the NMR time scale (Scheme 2). Once **2·H$^+$** was obtained quantitatively, it was possible to restore the complexes **2⊃G** through the further addition of a base, *i.e.* diaza(1,3)bicyclo[5.4.0]undecene (DBU) (see inset Scheme 2). This switching process shows that the complexation of neutral guests by **2** can be controlled by an external stimulus, *i.e.* the addition of acids or bases to the external medium. The reluctance of **2·H$^+$** toward polar neutral guests is particularly unusual since, with all the closely related receptors, the protonation of the cap led to a significant enhancement of the recognition properties thanks to an additional charge–dipole interaction.[6b,13,14] A plausible explanation may lie in the competing formation of the stable five-membered intramolecular hydrogen-bonded ring discussed above (*i.e.* between NH$^+$ and an introverted C=O) together with an *exo*-complexation of the $MeSO_3^-$ counteranion. On the basis of this interpretation, the NH$^+$ proton can be considered as an allosteric inhibitor that induces a conformational reorganization of the tris-amido recognition site into an insensitive form of the receptor.

In contrast with **2**, calix[6]cryptamide **4** displays poor recognition properties toward neutral guests. Indeed, only the complexation of Imi was observed in $CDCl_3$ with an extremely weak association constant (K_a < 10 M^{-1}, CIS_{CH_2} = −3.18 ppm). In comparison to **2⊃Imi**, the energy minimized structure of **4⊃Imi** revealed that the cryptamide cap has to adopt a more distorted and flattened conformation in order to establish the hydrogen bonding interactions with the guest (Fig. 3, top right). As a result, the Imi molecule occupies a slightly different position in the cavity, closer to the bulky *t*Bu groups directed toward the C_3 axis. These conformational differences may explain the higher heat



Scheme 3 Host–guest properties of calix[6]cryptamide **2** toward either fluoride or contact ion pairs and acid-triggered release of these guests. The reported values correspond to the ^{1}H NMR CISs observed for the ammonium ions.

of formation obtained for **4⊃Imi** (–1755.5 kJ mol^{-1} *vs.* –1824.8 kJ mol^{-1} in the case of **2⊃Imi**).

2.3 Anion recognition

In a second set of experiments, the aptitude of calix[6]cryptamides **2** and **4** to bind various anions (X^-) in $CDCl_3$ was investigated by NMR spectroscopy through the progressive addition of the corresponding tetra-*n*-butylammonium (TBA^+X^-) salts. First, the NMR spectrum of **4** remained unchanged upon the addition of a large excess of either F^-, Cl^- or AcO^-, confirming the poor binding properties of host **4**. In contrast, when TBA^+ salts of F^-, Cl^-, AcO^-, $MeSO_3^-$ or NO_3^- were gradually added to a solution of **2**, a downfield shift of the C*H*$_2$O, C*H*$_2$NH and amido protons as well as an upfield shift of the OMe signal were observed. 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. Interestingly, the whole calixarene framework experiences a deep conformational change upon complexation of X^- since the *t*-Bu as well as the ArH signals interchange their position (Fig. 2c for **2⊃F**$^-$). All these NMR data are compatible with (i) a binding of the anions at the level of the cryptamide cap through hydrogen bonding interactions with the amido groups, (ii) a concomitant induced fit process that involves the self-inclusion of the OMe groups (Scheme 3 for **2⊃F**$^-$). However, strong differences were observed between fluoride and all the other tested anions (*i.e.* Cl^-, AcO^-, $MeSO_3^-$ and NO_3^-):

(i) The association constants K_a were estimated through ^{1}H NMR titrations by monitoring the CISs of appropriate signals of host **2**, *i.e.* signals displaying significant shifts upon complexation and no overlapping region.[23,31] Despite the low K_a in $CDCl_3$ estimated in all cases, a high selectivity was observed for fluoride (K_a = *ca.* 300 M^{-1}) in comparison to all the other anions tested (K_a < 25 M^{-1} in the case of Cl^-, AcO^-, $MeSO_3^-$ or NO_3^-).[32,33]

(ii) ESI-MS competitive experiments showed a similar binding discrimination for fluoride. Indeed, injection of an equimolar mixture of **2** and five TBA^+ salts of anions (*i.e.* F^-, Cl^-, Br^-, AcO^- and NO_3^-) in either $CHCl_3$ or CH_3CN afforded quasi-exclusively the ion (m/z = 1299) corresponding to [**2** + F]$^-$ besides [**2** – H]$^-$ and traces of other species.[23]

(iii) The signal of the amido NH protons became extremely broad over the course of the titration with F^-. However, the exchange process between **2** and **2⊃F**$^-$ was found to be slow on the NMR time scale when the titration experiment was conducted at low T (243 K) (K_a = *ca.* 600 M^{-1}) and, thus, an increasing broad signal corresponding to the amido NH protons was observed at 12.55 ppm.[23] This corresponds to a downfield shift ($\Delta\delta_{NH}$ = 4.05 ppm) which is much more pronounced than that observed for the other anions ($\Delta\delta_{NH}$ < 0.79 ppm). One can note that the apparent broadness of the NH signal can be due to a scalar coupling with the bound fluoride anion combined to a partial deuteriation of the amido groups (*vide infra*). Such NH–F couplings have already been observed with other receptors devoted to fluoride complexation.[34]

Taken together, these results suggest a different mode of recognition for F^- in comparison to the other anions. Indeed, given the reduced size of the binding site formed by the three convergent NH amido groups, it seems that only the small fluoride anion can be accommodated within the cryptamide cap. All the other anions are likely recognized outside of the cap through H-bonding interactions with *a priori* only one amido group, explaining their low affinity for the receptor and the weak downfield shift of the NH amido protons. Besides, the *endo*-complexation of F^- *vs.* the *exo*-complexation of all the other anions was clearly confirmed by the results obtained in the case of the ion pairs (*vide infra*).

Interestingly, the energy-minimized structure of **2⊃F**$^-$ shows an encapsulation of the anion inside a pocket delimited by the trisamido cap and the introverted methoxy groups (Fig. 3, bottom left). The average $N_{(amido)} \cdots F^-$ distance is 3.01 Å and the hydrogen atoms of the amido groups surround the fluoride with N–H $\cdots$ F^- angles ranging from 146.03° to 164.96°, indicating strong hydrogen bonding interactions. The calculated $C_{(OMe)} \cdots F^-$ distances may suggest that the methoxy groups participate in the anion stabilization through weak CH $\cdots$ F^- interactions.[35] It is noteworthy that the binding of F^- was not observed in the presence of a large amount of protic solvent (*i.e.* $CD_3OD/CDCl_3$; 3 : 2). Finally, while one might have expected a reinforcement of the anion coordination with a positively charged receptor, similar to what was obtained with neutral guests, a negative cooperativity was observed through the protonation of **2⊃F**$^-$ with $MeSO_3H$. Indeed, it led to the release of the encapsulated fluoride anion and to the formation of **2·H**$^+$.[23]

2.4 Ion pair recognition

The intra-cavity complexation of an ammonium ion simultaneously to the anion was then investigated by NMR spectroscopy in $CDCl_3$. First, the addition of an excess of $PrNH_3^+$ associated to either a low-coordinating anion (*i.e.* picrate, Pic^-), or to Cl^-, AcO^-, $MeSO_3^-$, NO_3^- or SO_4^{2-}, did not affect the NMR pattern of calix[6]cryptamide **2**.[36] However, the addition of $PrNH_3^+Pic^-$ (4 equiv.) and TBA^+F^- (4 equiv.) gave rise to the quantitative formation of a new C_{3v} symmetrical species corresponding to **2⊃PrNH$_3^+$F$^-$** . This ternary complex displays high-field signals corresponding to the inclusion of 1 equiv. of $PrNH_3^+$ and a flattened cone conformation with the OMe groups pointing outside the cavity (δ_{OMe} = 3.85 ppm, Fig. 2d). Moreover, the significant high-field shift of the amido NH protons ($\Delta\delta_{NH}$ = 1.30 ppm) attests of the strong hydrogen bonding interactions with the fluoride. The energy-minimized structure of **2⊃PrNH$_3^+$F$^-$** is depicted in Fig. 3 (bottom middle).[37] The very short distance between the fluoride and the charged nitrogen of the ammonium ion ($d_{N^+\cdots F^-}$ = 2.08 Å) confirms the presence of a strong electrostatic interaction at the level of the ion pair. The ammonium ion is further stabilized by the calixarene host through a combination of CH–π interactions with the aromatic walls ($d_{C\cdots C=C}$ = *ca.* 3.8 Å) and H-bonding interaction with a phenoxy oxygen. Such interactions between an ammonium ion and a calix[6]arene skeleton have already been observed on several XRD structures of related *endo*-complexes.[13a,28] Besides its strong interaction with the cation, as expected, the anion is coordinated to the convergent hydrogen bond-donor NH groups, the average $N_{(amido)}\cdots F^-$ distance being 2.86 Å.

Thus, similarly to the parent receptors, **2** can act as a heteroditopic receptor able to recognize a contact ion pair through a highly cooperative two-step binding process (Scheme 3). The cumulative formation constant β_2 for the simultaneous complexation of $PrNH_3^+$ and F^- was estimated to be $>6.3\times10^5$ M^{-2}. Interestingly, the strong complexation of secondary and quaternary ammonium salts, *i.e.* dimethyl- and tetramethylammonium fluoride ($Me_2NH_2^+F^-$ and TMA^+F^-, respectively), was also detected in $CDCl_3$ ($\beta_2 > 4.9\times10^4$ and 3.2×10^5 M^{-2}, respectively).[23] In both cases, the ^{1}H CISs indicate a deep inclusion of the ammonium ions inside the cavity (Scheme 3). The binding of the longer linear primary ammonium salt $HexNH_3^+F^-$ was also clearly observed, the overall binding constant (β_2 = 1550 M^{-2}) being, however, lower than for $PrNH_3^+F^-$.[23] It is noteworthy that the inclusion of guests possessing an alkyl chain longer than propyl is generally precluded with *p*-*t*Bu-calix[6]arene-based receptors since it leads to a steric clash with the introverted *t*Bu groups that close the cavity of the host. In the case of **2⊃HexNH$_3^+$F$^-$**, the conformational energy penalty resulting from the spreading of the *t*Bu groups from the C_3 axis is largely compensated by the strong electrostatic attraction that prevails at the level of the contact ion pair.[38] In contrast, the complexation of large primary ammonium fluoride salts derived from 3,4-*O*-dimethyldopamine or tryptamine was not observed even in the presence of a large excess of these compounds. Altogether, these results show that, similarly to the parent calix[6]crypturea, the recognition process is highly sensitive to the geometry of the ammonium ion, the calixarene cavity being selective for the smaller and most linear ones.

However, a major difference exists between host **2** and all the previously reported receptors since, in the case of **2**, the binding of contact ion pairs can exclusively proceed with F^- as the anionic partner. Again, this remarkable selectivity is clearly due to the smallness of the binding site provided by the convergent NH groups of the cryptamide cap. Indeed, the tested ammonium ions can be accommodated into the cavity only if the highly energetically unfavorable dissociation of the ion pair is avoided, thus, if an anion is bound in close proximity at the level of the tris-amido cap. As shown above, only the small fluoride anion can be encapsulated inside the cap and thus can be at a suitable distance for the crucial electrostatic interaction with the ammonium ion. In other words, the fluoride acts as an allosteric activator that regulates the binding properties of the calixarene cavity.[39] To our knowledge, such selectivity for ammonium fluoride salts has no precedent in the literature.

In addition, similarly to what was obtained with $PrNH_3^+Pic^-$ (*vide supra*), the intra-cavity binding of the ammonium ion was not detected with the picrate salts of $Me_2NH_2^+$, $HexNH_3^+$ and TMA^+. This shows that the complexation of these ammonium ions can not proceed with a low-coordinating anion such as picrate, thus confirming the cooperative two-step binding process depicted in Scheme 3.

Besides, it was observed that the amido NH protons of **2⊃TMA$^+$F$^-$** resonate at a much higher chemical shift than the amido protons of the other ternary complexes (δ_{NH} = 12.34 ppm, 9.73 ppm, 10.50 ppm and *ca.* 9.79 ppm, for **2⊃TMA$^+$F$^-$**, **2⊃PrNH$_3^+$F$^-$**, **2 ⊃ HexNH$_3^+$F$^-$** and **2⊃Me$_2$NH$_2^+$F$^-$**, respectively). This is compatible with stronger hydrogen bonding interactions with the fluoride anion in **2⊃TMA$^+$F$^-$**, which in turn are likely to be due to a weaker contribution of the electrostatic interaction in the stabilization of the anion. Indeed, the distance between the fluoride anion and the charged nitrogen atom is expected to be larger with the quaternary TMA^+ ion. This hypothesis was confirmed by an energy-minimized structure of **2⊃TMA$^+$F$^-$** which shows a much longer $d_{N^+\cdots F^-}$ distance of 3.28 Å (Fig. 3, bottom right).[37] In other words, the chemical shift experienced by the amido protons of the host upon complexation reflects the tightness of the ion pair.

Interestingly, complicated ^{1}H NMR signal patterns were observed for the amido NH groups of the different ternary complexes. As a representative example, the amido NH region for the complex **2⊃TMA$^+$F$^-$** is depicted in Fig. 4a. When the ^{1}H NMR spectrum was recorded with ^{19}F broad-band decoupling, a simpler pattern displaying three singlets of different intensities was obtained (Fig. 4b). Similarly, the ^{19}F NMR spectrum of **2⊃TMA$^+$F$^-$** shows a series of multiplets and one singlet around –90 ppm (Fig. 4e) while, with ^{1}H decoupling, four singlets were observed (Fig. 4f). These double resonance experiments reveal significant scalar couplings between the NH amido protons and the F^- anion of the ternary complexes, *i.e.* ^{1h}J scalar couplings across $N–H\cdots F^-$ hydrogen bonds, and thus provide further confirmation that the anion is located between these convergent NH groups. Besides, the complicated patterns observed for the NH amido groups (^{1}H NMR spectra) and for the F^- anion (^{19}F NMR spectra) in **2⊃TMA$^+$F$^-$** can be clearly attributed to a deuteriation of the exchangeable NH amido protons.[40] Such a deuteriation process of amido-based receptors facilitated by fluoride has been already reported by Bowman-James *et al.*[11] Indeed, F^- is basic enough to deprotonate even weakly acidic solvents such as chloroform or DMSO. In our case, the different patterns fit with the presence of the expected complex **2⊃TMA$^+$F$^-$** together with the three possible deuteriated species

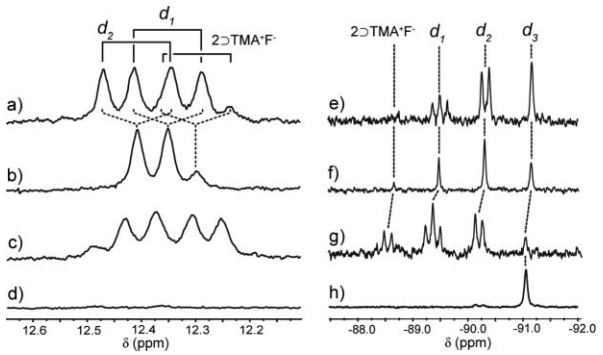


Fig. 4 NMR spectra (298 K) of **2⊃TMA⁺F⁻** in $CDCl_3$: (a) amido NH region of the ^1H NMR spectrum (400 MHz); (b) with ^{19}F inverse-gated broad-band decoupling; (c) after addition of *ca.* 100 equiv. of MeOH; (d) after 16 h; (e) ^{19}F NMR spectrum (376 MHz); (f) with ^1H inverse-gated broad-band decoupling; (g) after addition of *ca.* 100 equiv. of MeOH; (h) after 16 h. d_1, d_2 and d_3 refer to **2⊃TMA⁺F⁻-*d*$_1$**, **2⊃TMA⁺F⁻-*d*$_2$** and **2⊃TMA⁺F⁻-*d*$_3$**, respectively.

(*i.e.* the mono-, di- or tris-deuteriated complexes: respectively **2⊃TMA⁺F⁻-*d*$_1$**, **2⊃TMA⁺F⁻-*d*$_2$** and **2⊃TMA⁺F⁻-*d*$_3$**). On the basis of this interpretation, the assignment of the different species is given in Fig. 4. This rationalization was confirmed through the addition of an excess of MeOH (*ca.* 100 equiv.) which led in both cases (^1H and ^{19}F NMR spectra) to a reduction of the signals of the more deuteriated species to the benefit of the more protonated ones (Fig. 4c,g). After 16 h, a quasi-total deuteriation was apparent (Fig. 4d) and, as a result, only the singlet signal of the complex **2⊃TMA⁺F⁻-*d*$_3$** was observed in the ^{19}F NMR spectrum (Fig. 4h). ^1H–^{19}F ^{1h}J coupling constants of 50 Hz and 30 Hz were measured at 298 K for **2⊃TMA⁺F⁻** and **2⊃PrNH$_3$⁺F⁻**, respectively. These values are in good agreement with corresponding data for the F^- complexes of related calix[4]pyrrole or poly-amido receptors.[34a,41] The larger coupling observed for **2⊃TMA⁺F⁻** agrees with stronger hydrogen bonding interactions with the fluoride anion in this complex, as discussed above.

Interestingly, at low T in $CDCl_3$, it was also possible to observe the ^1H–^{19}F coupling between the NH_3^+ of the included ammonium ion and the fluoride anion of the complex **2⊃PrNH$_3$⁺F⁻** (coupling constant of *ca.* 30 Hz).[23,42] This scalar coupling confirms unambiguously that the ammonium fluoride salts are complexed as contact ion pairs.

Again, it was possible to trigger the release of the ion pair through the protonation of the cap of **2⊃PrNH$_3$⁺F⁻** with $MeSO_3H$. However, maybe because of the large amount of $MeSO_3H$ which was necessary to displace the equilibrium toward **2·H⁺** (24 equiv.), only a trace of the ternary complex was restored through the further addition of a large excess of DBU.[23] It is noteworthy that the ternary complex **2⊃PrNH$_3$⁺F⁻** survived to the presence of only a modest amount of a protic solvent (*i.e.* $CDCl_3/CD_3OD$; 12 : 1) but was stable in a 2 : 1 mixture of $CDCl_3/CD_3CN$.

Finally, similar NMR studies were undertaken with the calix[6]cryptamide **4** in place of **2**. Whereas a high selectivity was also observed for ammonium fluoride salts,[43] only a very small proportion of the ternary complex **4⊃PrNH$_3$⁺F⁻** was detected even in the presence of a large excess of $PrNH_3^+Pic^-$ and TBA^+F^-. This result is consistent with the reduced ability of **4** to bind F^-.

3 Conclusion

The readily available calix[6]cryptamide **2** behaves as a heteroditopic receptor that displays versatile host–guest properties toward either charged or neutral species. Similarly to the parent calix[6]crypturea, these properties are due to the combination of two distinct binding sites, that is, a tren-based cap and a hydrophobic cavity suitable for the inclusion of organic guests. The common key features of these two receptors are: (i) a close proximity of the two binding sites that allows highly cooperative processes such as the binding of contact ion pairs, (ii) induced-fit recognition processes that involve impressive conformational reorganization of the flexible calixarene cavity, (iii) a proton-sensitive site at the level of the cap that permits acid–base control of the binding properties of the receptor. However, in comparison to all the previously studied calixarene hosts, calix[6]cryptamide **2** possesses a smaller and less flexible tripodal aza-cap. This structural difference leads to a reinforced chelate effect toward anions and a higher preorganization of the binding site provided by the convergent hydrogen bond-donor groups. As a consequence, **2** displays several unique features:

· Compared with the parent receptors, a much stronger binding of neutral guests is observed in markedly protic solvents.

· Fluoride is the only anion that can be encapsulated into the small pocket delimited by the convergent hydrogen bond donor groups of the tris-amido binding site. As a result, the tested ammonium ions were detected in the calixarene cavity only when a fluoride anion is present into the cap. To our knowledge, calix[6]cryptamide **2** is the first receptor that exhibits such a remarkable selectivity toward contact ammonium fluoride salts. It is important to underline that these results have been clearly confirmed through ^{19}F NMR spectroscopy studies.

· The protonation of the aza-cap leads to a positively charged receptor **2·H⁺** which is insensitive toward either neutral molecules or charged species. This contrasts with the parent receptors whose binding properties toward neutral guests are strongly reinforced upon the protonation of the cap. This difference of behavior can be rationalized by an intramolecular hydrogen bonding interaction at the level of the tris-amido cap that "turns off" the binding properties of **2·H⁺**. This acid–base control of the recognition properties can be advantageously exploited for guest release processes.

From a biomimetic point of view, **2** can be seen as a receptor that displays (i) a preorganized recognition site protected by a hydrophobic corridor that can adapt its conformation to the size of the guest through induced fit processes, (ii) an allosteric regulation of the recognition processes (the fluoride anion and the NH^+ proton can be considered respectively as an allosteric activator and allosteric inhibitor), (iii) a high selectivity based either on the electronic, geometric or size complementarity with the guest.

Finally, despite their strong structural similarity, the host–guest properties of calix[6]cryptamides **2** and **4** are very different, **4** possessing an extremely poor recognition ability toward either neutral or charged species. This comparison nicely illustrates how a slight structural difference at the level of the recognition site can drastically modify the host properties of a receptor.

Current efforts are now directed toward the design of water-soluble calix[6]cryptamides decorated with fluorophores in order to develop applications such as the sensing of anions or ion pairs.

Experimental section

General procedures

All reactions were performed under an inert atmosphere. Anhydrous $CHCl_3$ and CH_3NO_2 were obtained through distillation, respectively over P_2O_5 and CaH_2 under argon. Anhydrous DMF was obtained through distillation over a mixture of $MgSO_4$, 4 Å molecular sieves and silica gel under argon. Silica gel (230–400 mesh) was used for flash chromatography purifications. ^{1}H NMR spectra were recorded at either 600, 400 or 300 MHz, ^{19}F NMR spectra were recorded at 376 MHz and ^{13}C NMR spectra were recorded at either 150, 100 or 75 MHz. Chemical shifts are expressed in ppm. Traces of residual solvent were used as internal standard in the case of ^{1}H and ^{13}C NMR spectra. $CFCl_3$ was used as internal standard in the case of ^{19}F NMR spectra. In all cases, $CDCl_3$ was filtered over a short column of basic alumina in order to remove traces of HCl. Most of the ^{1}H NMR spectra signals were attributed through 2D NMR analyses (COSY, HSQC, HMQC, 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: 10 V, tube lens offset voltage: −5V. The calix[6]tris-amine **1** and calix[6]tris-acid **3** were prepared as previously described.[22]

Calix[6]cryptamide 2

Anhydrous $CHCl_3$ (10 mL) and anhydrous DMF (5 mL) were added to calix[6]trisamine **1** (166 mg, 0.145 mmol) and nitrilotriacetic acid (28 mg, 0.145 mmol). A solution of TBTU (280 mg, 0.871 mmol) and TEA (116 µL, 0.871 mmol) in anhydrous DMF (5 mL) was then added. The reaction mixture was stirred for 15 h at 50 °C and then the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous NH_4OH solution (5%, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with H_2O (2 × 10 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2–MeOH; 95 : 5) yielding calix[6]cryptamide **2** (101 mg, 54%) as a white solid. m.p. 170 °C (*dec*); IR (KBr): ν 3675 to 3115, 2962, 1675, 1540, 1482, 1362, 1202, 1119, 1006 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.05 (s, 27H, tBu), 1.16 (s, 27H, tBu), 2.96 (s, 9H, OMe), 3.31 (s, 6H, NCH_2CONH), 3.49 (d, 6H, ArCH_2), 3.56 (s_b, 6H, NCH_2), 3.91 (s_b, 6H, OCH_2), 4.35 (d, 6H, ArCH_2), 6.89 (s, 6H, ArH), 7.05 (s, 6H, ArH), 7.85 (s_b, 3H, CONH); δ_C (75 MHz, $CDCl_3$) 30.9, 31.4, 31.5, 34.2, 34.3, 39.8, 60.8 (2C), 72.1, 125.9, 126.2, 132.8, 133.4, 145.9, 146.5, 154.0, 170.4; HRMS (ESI-TOF) calcd for $C_{81}H_{109}N_4O_9$ (M+H$^+$) 1281.8195, found 1281.8199.

Calix[6]cryptamide 4

Anhydrous $CHCl_3$ (15 mL) and anhydrous CH_3NO_2 (4 mL) were added to calix[6]trisacid **3** (150 mg, 0.126 mmol) and tris(2-aminoethyl)amine (19 µL, 0.126 mmol). The mixture was heated at 50 °C and then a solution of HBTU (287 mg, 0.757 mmol) and TEA (105 µL, 0.757 mmol) in anhydrous CH_3NO_2 (4.5 mL) was slowly added (0.5 mL every 30 min). The reaction mixture was stirred for 15 h at 50 °C and then the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous NaOH solution (1M, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (10 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2–MeOH; 95 : 5) yielding calix[6]cryptamide **4** (46 mg, 28%) as a white solid. m.p. 175 °C (*dec*); IR (KBr): ν 3710 to 3110, 2962, 1679, 1534, 1481, 1201 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.97 (s, 27H, *t*Bu), 1.22 (s, 27H, *t*Bu), 2.81 (s_b, 6H, NCH_2CH$_2$NCO), 3.15 (s, 9H, OMe), 3.40 (s_b, 6H, NCH$_2$CH_2NCO), 3.43 (d, J = 15 Hz, 6H, ArCH_{eq}), 4.34 (s, 6H, OCH_2), 4.41 (d, J = 15 Hz, 6H, ArCH_{ax}), 6.90 (s, 6H, ArH), 7.20 (s, 6H, ArH), 7.70 (s_b, 3H, NHCO); δ_C (75 MHz, $CDCl_3$) 29.6, 31.4, 31.5, 34.2, 34.4, 39.6, 57.2, 61.5, 71.9, 126.0, 126.3, 133.0, 133.1, 146.1, 147.1, 151.3, 154.2, 169.7; HRMS (ESI-TOF) calcd for $C_{81}H_{109}N_4O_9$ (M+H$^+$) 1281.8195, found 1281.8196.

Estimation of the association constant K_a of 2 toward Imi in $CDCl_3$

The association constant K_a for the host–guest system in $CDCl_3$ was estimated according to the following procedure: suitable aliquots of a $CDCl_3$ solution of Imi were added to a solution of receptor **2** (2×10^{-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 **2**. The concentration of the undetectable species and the concentration of **2⊃Imi** were estimated to be 2% and 98%, respectively, of the starting host concentration. The association constants K_a was estimated according to the following equation: $K_a > [\mathbf{2}\supset\mathbf{Imi}]/([\mathbf{2}] \times [\mathrm{Imi}])$.

Estimation of the overall binding constants β_2 of 2 toward ion pairs in $CDCl_3$

Overall binding constants β_2 in $CDCl_3$ were estimated according to the following procedure: suitable aliquots of a $CDCl_3$ solution of G_1G_2 ($G_1 = F^-$ and $G_2 = PrNH_3^+$, $Me_2NH_2^+$ or TMA^+) were added to a solution of receptor **2** (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 **2**. The concentration of the undetectable species and the concentration of **2⊃G$_1$G$_2$** were estimated to be 5% and 95%, respectively, of the starting host concentration. Overall binding constants β_2 were estimated according to the following equation: $K_a > [\mathbf{2}\supset\mathbf{G_1G_2}]/([\mathbf{2}]\times[G_1] \times [G_2])$.

Determination of the overall binding constant β_2 of 2 toward $HexNH_3^+F^-$ in $CDCl_3$

To a $CDCl_3$ solution containing **2** (2×10^{-3} M) was added an equimolar solution of TBAF and $HexNH_3Pic$ in such a ratio that a ^{1}H NMR spectrum recorded at 298 K showed the resonances of both calixarene species **2** and **2⊃HexNH$_3^+$F$^-$** as well as the signals corresponding to the free salts (*i.e.* TBA^+ and $HexNH_3^+Pic^-$). Integration of the signals of the calixarene species **2** and **2⊃HexNH$_3^+$F$^-$** and of the free salts allowed us to calculate the overall binding constant β_2 according to the following equation: $\beta_2 = [\mathbf{2}\supset\mathbf{HexNH_3^+F^-}]/([\mathbf{2}] \times [HexNH_3^+] \times [F^-])$.

Determination of the association constant K_a of 2 toward Imi in $CD_3OD/CDCl_3$ (3 : 2)

To a 3 : 2 $CD_3OD/CDCl_3$ solution containing **2** (4×10^{-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 **2** and **2**⊃**Imi** as well as the signals corresponding to the free guest (Imi). Integration of the signals of the calixarene species **2** and **2**⊃**Imi** and of the free guest (Imi) allowed us to calculate the association constant K_a according to the following equation: $K_a = [\mathbf{2}\supset\mathbf{Imi}]/([\mathbf{2}] \times [\mathrm{Imi}])$.

Determination of the relative affinities of the neutral molecules $K_{G/DMF}$ in the case of 2 through ^{1}H NMR competitive binding studies in $CDCl_3$

To a $CDCl_3$ solution containing **2** (3×10^{-3} to 5×10^{-3} M) were successively added DMF (> 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 **2**⊃**DMF** and **2**⊃**G** besides the signals corresponding to the free guests (DMF and G). Integration of the signals of the included guests, *i.e.* DMF_{in} and G_{in}, and of the free guests, *i.e.* DMF_{free} and G_{free}, allowed us to calculate the relative affinity $K_{G/DMF}$, defined as $([G_{in}] \times [DMF_{free}])/([G_{free}] \times [DMF_{in}])$.

Determination of the association constants K_a of 2 toward anions X^- in $CDCl_3$

The association constants K_a were determined according to the following procedure: suitable aliquots of a $CDCl_3$ solution containing the anion salt (TBA^+X^-) were added to a solution of cryptamide **2** (3×10^{-3} to 5×10^{-3} M). The corresponding ^{1}H NMR spectra recorded at 298 K revealed one set of signals for the complex **2**⊃X^- and for the free receptor **2** in fast exchange on the NMR time scale. Thus, the association constants K_a were determined by nonlinear least-squares-fitting of the 1 : 1 binding profile to the chemical shift of either the OMe 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%).

Determination of the association constant K_a of 2 toward F^- in $CDCl_3$ at 243 K

The association constant K_a was determined according to the following procedure: suitable aliquots of a $CDCl_3$ solution containing the anion salt (TBA^+F^-) were added to a solution of cryptamide **2** (2×10^{-3} M) in $CDCl_3$ in such a way that the corresponding ^{1}H NMR spectrum recorded at 243 K revealed the presence of all partners in slow exchange on the NMR time scale. The association constant K_a was calculated according to the following equation: $K_a = [\mathbf{2}\supset\mathbf{F}^-]/([\mathbf{2}] \times [F^-])$.

Acknowledgements

This research was supported by the Université Libre de Bruxelles (U.L.B.). We thank Rita D'Orazio for her help in the recording of several NMR spectra.

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37 In order to achieve convergence of the geometry optimization to chemically reasonable structures, H atoms of the amides were fixed. Similarly, position of the F^- was forced to stay inside the tripodal cap of the receptor.

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43 The complexation of $PrNH_3^+Cl^-$ or $PrNH_3^+Br^-$ by cryptamide **4** was not observed in $CDCl_3$.

