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Self-assembly via ionic interactions of calix[6]arene-based receptors displaying remarkable host–guest properties toward neutral guests

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Abstract—The association of a C_{3v}-symmetrical calix[6]tris-amine with different concave tris-carboxylic acids of various degrees of flexibility has been explored by ^{1}H NMR spectroscopy. In all cases, self-assembled structures directed by the selective inclusion of a neutral guest molecule were obtained, the more preorganized being stable in protic solvents. With a rigid C_3-symmetrical cap, chiral guest recognition in the calixarene cavity resulted. A large tris-acidic partner gave a unique molecular ditopic receptor that is able to simultaneously accommodate two neutral molecules in two distinct hydrophobic cavities with different binding processes.

1. Introduction

Self-assembly is the spontaneous and reversible association of subunits via non-covalent interactions into well-defined structures.[1] Thanks to error-correcting processes, it provides an efficient strategy for the formation of complex or highly ordered supramolecular structures.[2] As in biological systems, self-assembly has been exploited for the elaboration of receptors[3] and, for this, readily available, preorganized calix[4]arenes[4] have been shown to be powerful building blocks. They have provided systems such as capsules, rosettes, and numerous metal ion receptors.[5] In contrast, the larger calix[6]arenes have been scarcely studied in self-assembly,[6] although their cone conformation has a cavity size suited to the inclusion of a much broader range of organic guests. This limited use is mainly due to the difficulty of constraining calix[6]arenes into a well-defined cone conformation.[7] As a mean of constraint, the grafting of covalent bridges between the phenolic units has been studied[8] and, in this context, we have developed a new class of versatile and tunable molecular receptors, namely the calix[6]aza-cryptands.[9] These are rigidified into the required cone conformation by an aza-cryptand cap at the narrow rim. Recently, we have also shown that protonation of calix[6]tris-amines by a strong acid such as trifluoro acetic acid (TFA) (Fig. 1, left)[10] produces trications, which assemble with the counter anions to form a supramolecular ion-paired cap that locks the calixarene structure into the cone conformation. These very simple systems are good hosts for polar neutral molecules via H bonding, charge–dipole, and CH–π interactions. Ionic interactions between ammonium ions and a calix[6]arene bearing carboxylate groups at the narrow rim have also been shown to lead to remarkably stable self-assembled host–guest systems accommodating large and bioactive ammonium ions inside the calixarene cavity (Fig. 1, middle).[11] Recently, these two modes of supramolecular rigidification have been combined in a sophisticated ditopic receptor involving two complementary calix[6]arene subunits **1** and **2** (Fig. 1, right),[12] the [1+1+1+1] self-assembly of the quaternary adducts being obtained through an allosterically controlled process. Very interestingly, the ionic carboxylate–ammonium interactions provide to all these self-assembled structures a remarkable stability in polar protic solvents. This is in contrast to self-assembly based on hydrogen bonding between neutral donors and acceptors, which is usually disrupted by the addition of small amounts of polar solvent.[13] Seeking multitopic receptors for organic guests, we wished to develop new calixarene-based systems self-assembled through ionic interactions and having different hydrophobic cavities.[14] Thus, well-preorganized tripodal compounds of a concave geometry such as cyclotriveratrylene (CTV) derivatives were chosen as the complementary subunits.[15]

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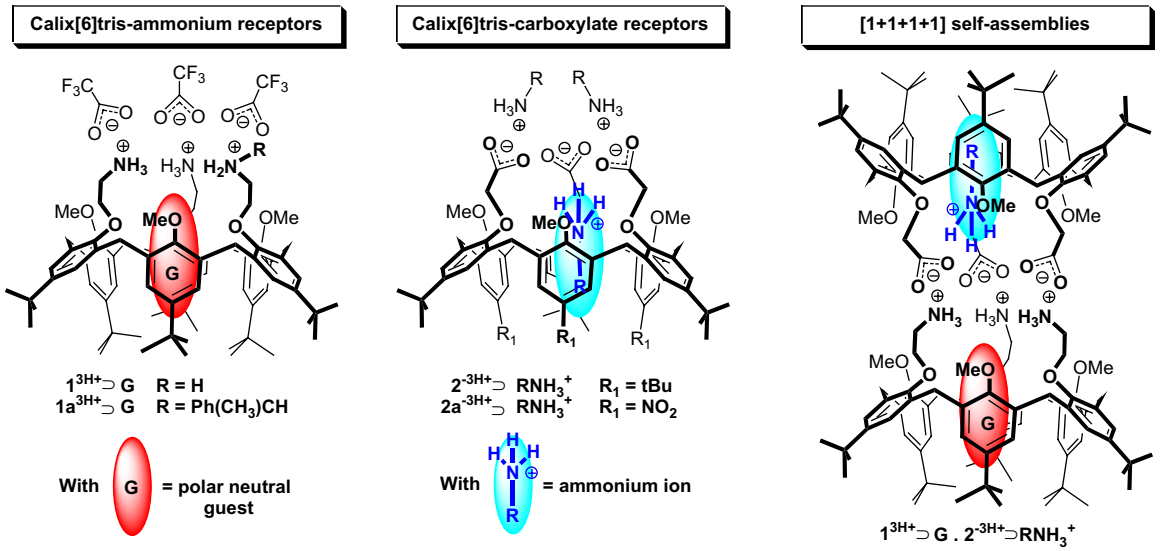


Figure 1. The use of ionic interactions for the elaboration of stable self-assembled calix[6]arene-based receptors.

Here, we report on the self-assembly of the C_{3v}-symmetrical calix[6]tris-amine **1** with preorganized C_3- or C_{3v}-symmetrical tris-carboxylic acid partners **3**, **5**, **7**, **9**, and **11** having various degrees of flexibility (Scheme 1). All the resulting self-assembled structures display efficient host–guest properties toward neutral molecules, the better preorganized being the more stable in protic solvents. One of them behaves as unique self-assembled molecular ditopic receptor since it can simultaneously accommodate two neutral molecules in two distinct hydrophobic cavities through different binding processes.

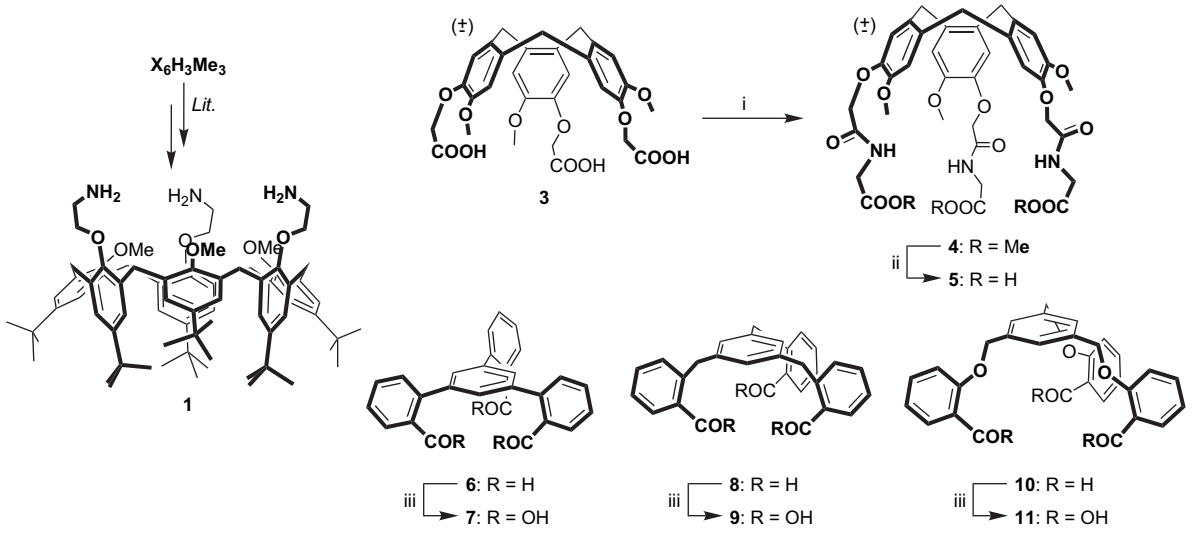
2. Results and discussion

2.1. Syntheses of the subunits

We have previously reported the synthesis of calix[6]tris-amine **1**. The efficient three-step sequence from the C_{3v} symmetrical tris-*O*-methylated *t*-Bu-calix[6]arene ($X_6H_3Me_3$, Scheme 1) involves its peralkylation with ethylbromoacetate in the presence of a strong base (NaH), reaction of the resulting tris-ester with ammonia in MeOH, and subsequent reduction of the amido groups by BH_3/THF (79% overall yield).[9g] The (±)-CTV tris-carboxylic acid derivative **3** was synthesized according to a procedure described in the literature.[16] Coupling, using HBTU,[17] to glycine methyl ester, followed by hydrolysis of the ester units, gave the CTV derivative **5** in 68% overall yield (Scheme 1). The tris-carboxylic acids **7**, **9**, and **11** were prepared in high yields (86–90%) by oxidation of the parent tris-aldehydes **6**,[18] **8**, and **10**[19] using sodium chlorite in an acidic buffer.[20]

2.2. Self-assembly of calix[6]tris-amine 1 with tris-carboxylic acid subunits 3, 7, 9, and 11

First, the self-assembly of calix[6]tris-amine **1** with (±)-CTV **3** was investigated through extensive NMR studies. Addition of 1 equiv of calix[6]tris-amine **1** (Fig. 2a) to



Scheme 1. (i) $MeOOCCH_2NH_2 \cdot HCl$ (4 equiv) HBTU (4 equiv), TEA (7 equiv), DMF, 50 °C, 72%; (ii) NaOH, MeOH, 0 °C then rt, 94%; (iii) $NaClO_2$ (8 equiv), NaH_2PO_4, DMSO/DCM/H_2O, rt; **7**: 86%, **9**: 90%, **11**: 90%.

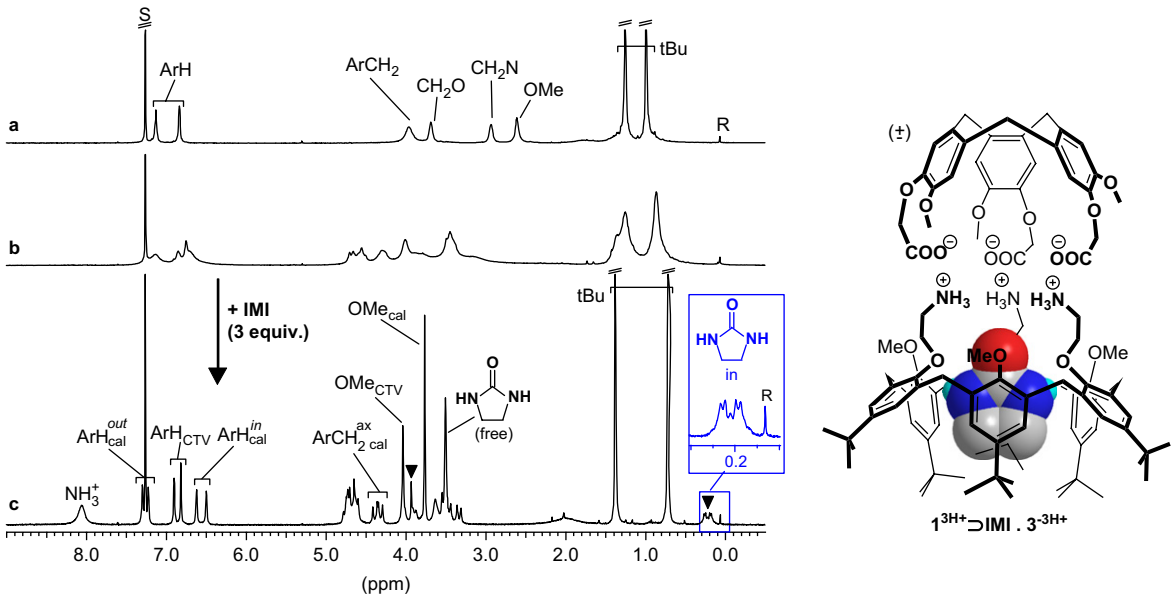


Figure 2. ^{1}H NMR spectra ($CDCl_3$, 293 K, 300 MHz) of: (a) **1**; (b) 1:1 mixture of **1** and **3**; (c) after addition of IMI (3 equiv). ▼: Included IMI. Residual solvent and reference have been labeled S and R, respectively. 'cal' and 'CTV' stand for 'calixarene' and 'cyclotriveratrylene', respectively.

a suspension of **3** in $CDCl_3$ led to complete dissolution[21] after sonication and heating for 15 h at 50 °C. The resulting NMR spectrum (Fig. 2b) was ill-resolved, even at low temperature (223 K) and at low concentration (0.9 mM), indicating the formation of various aggregated species. This lack of selectivity may be ascribed to the flexibility of the calix[6]arene structure. However, subsequent addition of 3 equiv of a neutral polar molecule, i.e., imidazolidin-2-one (IMI), to this 1:1 mixture led to a spectacular sharpening of the NMR spectrum (Fig. 2c). All the signals were attributed by 2D NMR spectroscopy (COSY, HMQC, HMBC, EXSY, see Supplementary data), leading to the following deductions.

(i) The ^{1}H NMR spectrum (Fig. 2c) displays sets of signals characteristic of one CTV and one calixarene subunit displaying C_3 symmetry, at rt. The signals of the calixarene core are very similar to those observed for other previously reported self-assembled calix[6]arenes (Fig. 1)[10b,12] but with a splitting of the methylene and aromatic protons. This is attributed to the formation of a discrete 1:1 adduct in which the chirality of the CTV core is transmitted to the calixarene skeleton, leading to the diastereodifferentiation of some of its protons.

(ii) The calixarene adopts a flattened cone conformation (both aromatic and *t*-Bu resonances are strongly differentiated, $\Delta\delta_{t\text{-Bu}}$=0.66 ppm and $\Delta\delta_{\text{ArH}}$=0.70 ppm,[22] respectively) with the OMe groups expelled from the cavity (δ_{OMe}=3.76 ppm). The HMBC spectrum shows that the *t*-Bu groups of the aromatic moieties bearing the amino arms are directed toward the outside of the cavity (see the structure in Fig. 2). These data are consistent with the capping of the narrow rim of the calixarene core by the nitrogenous arms.

(iii) The cone–cone inversion of the calixarene core is slow on the NMR time scale since sharp doublets are observed for its $ArCH_2$ protons ($\delta_{\text{ArCH}_2\text{ ax}}$ = 4.35 ppm and $\delta_{\text{ArCH}_2\text{ eq}}$ = 3.40 ppm).[22]

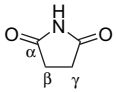
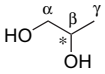
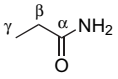
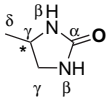
(iv) The down-field chemical shift of the CH_2N protons ($\delta_{\text{CH}_2\text{N}}$ = 3.63 ppm) as well as the broad signal at 8.05 ppm corresponding to NH_3^+ protons attest to the protonation of the amino groups.

(v) The EXSY spectrum revealed that the new high-field signal at δ=0.22 ppm corresponds to the inclusion of 1 equiv of IMI. The marked up-field complexation induced shift (CIS) of its methylenic protons clearly indicates its binding in the heart of the calixarene cavity (CIS=−3.30, see Table 1, entry 10).

(vi) The diastereotopic splitting of the guest IMI methylenic protons shows that the chirality of the self-assembled calixarene and CTV subunits is efficiently transmitted to the encapsulated guest (inset, Fig. 2c).[23]

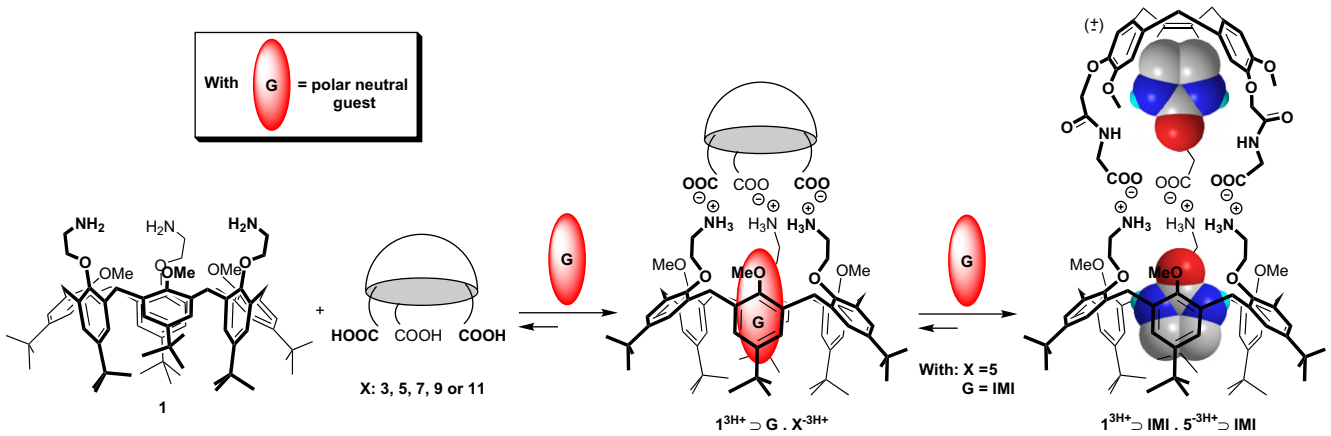
All these NMR data are consistent with the cooperative formation of a discrete [1+1+1] self-assembled ternary structure, namely $\mathbf{1^{3H+}\supset IMI\cdot 3^{-3H+}}$, composed of a calix[6]tris-ammonium-based host–guest complex capped by the CTV tris-carboxylate subunit (Scheme 2). This result constitutes the first example of an ion-paired self-assembly of calix[6]arene and CTV building blocks. Polar neutral molecules (G) other than IMI can be used.[24] Indeed, addition of few equivalents (1–10 equiv) of imides, alcohols, amides, sulfoxides, carbamates, or ureas (Table 1) led to sharp NMR spectra characteristic of the ternary assemblies $\mathbf{1^{3H+}\supset G\cdot 3^{-3H+}}$ with slow *in* and *out* guest exchanges on the NMR time scale. It is noteworthy that the presence of donor and/or acceptor H-bonding groups that are able to interact with the host is a common feature for all these guests. The observed CIS values (Table 1) are similar to those reported with the previously described calix[6]tris-ammonium receptors[9d,10b] indicating similar binding mechanisms for the guests, i.e., through H bonding, CH–π interactions with the aromatic walls, and charge–dipole interactions (the polar guests directing their dipole along the C_3 axis of the calixarene core, see the structure displayed in Fig. 2 for G=IMI). The relative affinities of the guests ($K_{\text{G/DMF}}$) were calculated through NMR competitive binding experiments (Table 1).

Table 1. Complexation induced up-field shifts (CIS) and relative affinities of the guests G in the case of $\mathbf{1}^{3H+}\supset\mathbf{G}\cdot\mathbf{3}^{-3H+}$

Entry	G	$K_{G/DMF}$[a]	CIS (ppm)[b]			
			α	β	γ	δ
1		0.2	—	−1.74, −1.99	−3.00	—
2		0.2	n.d.[c]	−3.04	—	—
3		0.8	n.d.[c]	n.d.[c]	−3.33	—
4		1.0	—	−2.00	−3.08	—
5		1	−1.35	—	−3.16	—
6		1.3	—	−2.73, −2.81	—	—
7		5.6	—	—	$-3.13_{(CH_2N)}$, $-3.58_{(CH_2O)}$	—
8		15	—	—	$-3.33_{(CH_2N)}$,[d] $-3.26_{(CH_2N)}$,[d] $-3.14_{(CHN)}$[d] $-3.35_{(CH_2N)}$,[e] $-3.50_{(CH_2N)}$,[e] $-2.94_{(CHN)}$[e]	−2.86[d] −2.82[e]
9		22	—	$-3.42_{(CH_2CO)}$	$-3.07_{(CH_2)}$, $-1.96_{(CH_2N)}$	—
10		430	—	—	−3.30	—

[a] Relative affinity calculated at 293 K and defined as $[G_{in}]/[DMF_{in}]\times[DMF_{free}]/[G_{free}]$ where the subscript '*in*' stands for 'included'. Errors estimated ±10%.
[b] CIS calculated at 293 K and defined as $\Delta\delta=\delta$(complexed G)−δ(free G). α, β, γ, and δ refer to the relative position of the protons to the oxygen atom.
[c] n.d.: not determined.
[d] Major diastereomer.
[e] Minor diastereomer.

Thus, IMI is the best guest since this molecule has the strongest complementarity in term of size, shape, and electronic structure with host $\mathbf{1}^{3H+}$, as previously found by XRD analysis of a closely related host–guest complex.[12] Its relative affinity compared to DMF is similar to that reported with $\mathbf{1}^{3H+},^{3TFA-}$ (i.e., $K_{IMI/DMF}$=430 vs 400, respectively), thus indicating that the host–guest affinity is essentially independent of the nature of the counter anions.



Scheme 2. Self-assembly of calix[6]tris-amine **1** with tris-carboxylic acids **3**, **5**, **7**, **9**, or **11** in the presence of a polar neutral molecule.

This first set of experiments clearly demonstrated that the self-assembly process is directed by the guest through an induced-fit process. Indeed, the inclusion of the guest leads to the expulsion of the methoxy groups, the rigidification of the calixarene core, and the preorganization of the ammonium arms that is necessary for the assembly of the discrete [1+1] ion-paired complex.

The use of the tris-carboxylic acids **7**, **9**, and **11** in place of CTV **3** led to similar self-assembly processes with the calix[6]tris-amine **1**. Indeed, the addition of a few equivalents of IMI was required to obtain well-defined ^{1}H NMR spectra consistent with the selective formation of C_{3v} symmetrical [1+1+1] self-assembled structures, i.e., $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{7}^{-3H+}$, $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{9}^{-3H+}$, and $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{11}^{-3H+}$ (Scheme 2) (see Supplementary data).[25] In all cases, the CIS of the guest and the conformational properties of the calixarene core were identical to what was observed in the case of CTV **3**. It is noteworthy that, in contrast to the other systems, the formation of the ternary complex $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{11}^{-3H+}$ was found to be slow at rt since, in this case, the equilibrium was only reached after several hours ($\approx$5 h, compared to less than 2 min in the other cases). Such behavior is probably due to the higher flexibility of the tris-acid **11** and emphasizes the importance of the preorganization of the subunits for a kinetically facile ion-paired assembly.

The stability of the self-assemblies was then evaluated with complexes $\mathbf{1}^{3H+}\supset\mathbf{G}\cdot\mathbf{3}^{-3H+}$ (G=DMF, DMSO, and IMI) and $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{7}^{-3H+}$. First, their ^{1}H NMR spectrum was not affected at high temperature (330 K), the *in* and *out* guest exchanges remaining slow on the NMR time scale and in the case of $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{3}^{-3H+}$, the chirality of the CTV cap still being sensed by the guest. Accurate determination of the equilibrium constants K for the formation of these ternary complexes was not possible since the 'free' subunits are partially aggregated. However, ignoring this aggregation, K values for $\mathbf{1}^{3H+}\supset\mathbf{G}\cdot\mathbf{3}^{-3H+}$ were estimated to be larger than 4.5×10^6 M^{-2} for G=DMF at rt and ca. 10^5 M^{-2} for G=DMSO at 330 K in $CDCl_3$.[26] Finally, the high stability of these [1+1+1] supramolecular structures was apparent in polar and protic solvents at millimolar concentrations. Half of the assembly $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{3}^{-3H+}$ was still present in 4:1 $CDCl_3$/DMSO-d_6 or 2:1 $CDCl_3$/CD_3OD mixtures,[27] and, remarkably, the complex $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{7}^{-3H+}$ remained stable in pure CD_3OD (See Supplementary data).[28] This latter result can be related to the high rigidity of the tris-acid **7**, which should lead to the tightest ion-pair binding. To the best of our knowledge, this result constitutes the first example of a self-assembly based on a calix[6]arene that is stable in a protic solvent. It highlights the efficiency of using ionic interactions in addition to H bonds for the construction of self-assemblies in protic solvents.

2. 3. NMR study of the chiral recognition ability of $\mathbf{1}^{3H+}\supset\mathbf{G}\cdot\mathbf{3}^{-3H+}$

Molecular receptors displaying chiral recognition of neutral molecules can find applications in enantioselective catalysis and in the separation and analysis of enantiomers.[29] In this context, examples of enantioselective recognition in the cavity of chiral calix[6]arenes are extremely rare in the literature.[9d,10a] As shown above, the chirality of the CTV cap in the self-assembled system $\mathbf{1}^{3H+}\supset\mathbf{G}\cdot\mathbf{3}^{-3H+}$ can be sensed by the guest, which suggests a possible chiral discrimination process inside the calixarene cavity. In our case, a challenge arose from the fact that the source of chirality was not covalently linked to the host.[30] Hence, a few equivalents of racemic polar neutral molecules, i.e., (±)-propan-1,2-diol (PPD), (±)-butan-1,2-diol (BTD), and (±)-4-methylimidazolidin-2-one (MIMI),[31] were added to a 1:1 $CDCl_3$ solution of **1** and **3**. In all cases, two C_3-symmetrical diastereomeric self-assemblies were observed at low temperature (220–260 K) and integration of the guest signals yielded the diastereomeric excesses (de) (see Fig. 3 in the case of $\mathbf{1}^{3H+}\supset\mathbf{MIMI}\cdot\mathbf{3}^{-3H+}$). Thus, with the two 1,2-diol guests, PPD and BTD, low de was observed ($\leq$10%).[32] However, the urea guest MIMI led to a chiral recognition process with a promising de of 30%. In the calix[6]arene field, this result constitutes the first example of enantioselective intra-cavity discrimination through an ion-paired transmission of the chirality.

2.4. Self-assembly of calix[6]tris-amine 1 with the CTV subunit 5

The use of building blocks **1** and **5** led to a ditopic receptor possessing unique host–guest properties. Indeed, the addition of 3.8 equiv of IMI to a 1:1 mixture of these two partners led to the quantitative formation of a new C_3-symmetrical species (Fig. 4a and b, $CDCl_3$).[33] This latter displays a well-defined spectrum in agreement with the formation of inclusion complex $\mathbf{1}^{3H+}\supset\mathbf{IMI}$ capped by the CTV tris-carboxylate $\mathbf{5}^{-3H+}$ (Scheme 2).[34] However, in this case an additional feature was observed in the NMR spectrum: besides the typical signals of 1 equiv of IMI included in the calixarene cavity ('▼', Fig. 4b), the signal corresponding to the CH_2 of the IMI in excess was observed with a high-field shift (δ=2.98 ppm, '▽', Fig. 4b)[35] compared to the normal resonance of the free molecule (δ=3.55 ppm at 298 K in $CDCl_3$). Furthermore, with increasing amount of IMI (5.8 equiv), this signal was shifted downfield (δ =3.16 ppm, '▽', Fig. 4c). These observations are in

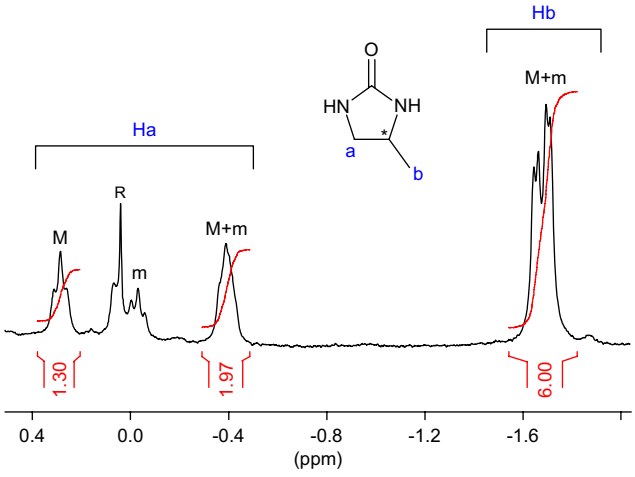


Figure 3. High-field area of the ^{1}H NMR spectrum ($CDCl_3$, 220 K) of $\mathbf{1}^{3H+}\supset\mathbf{MIMI}\cdot\mathbf{3}^{-3H+}$. 'M' and 'm' stand for 'major diastereomer' and 'minor diastereomer', respectively. R=reference.

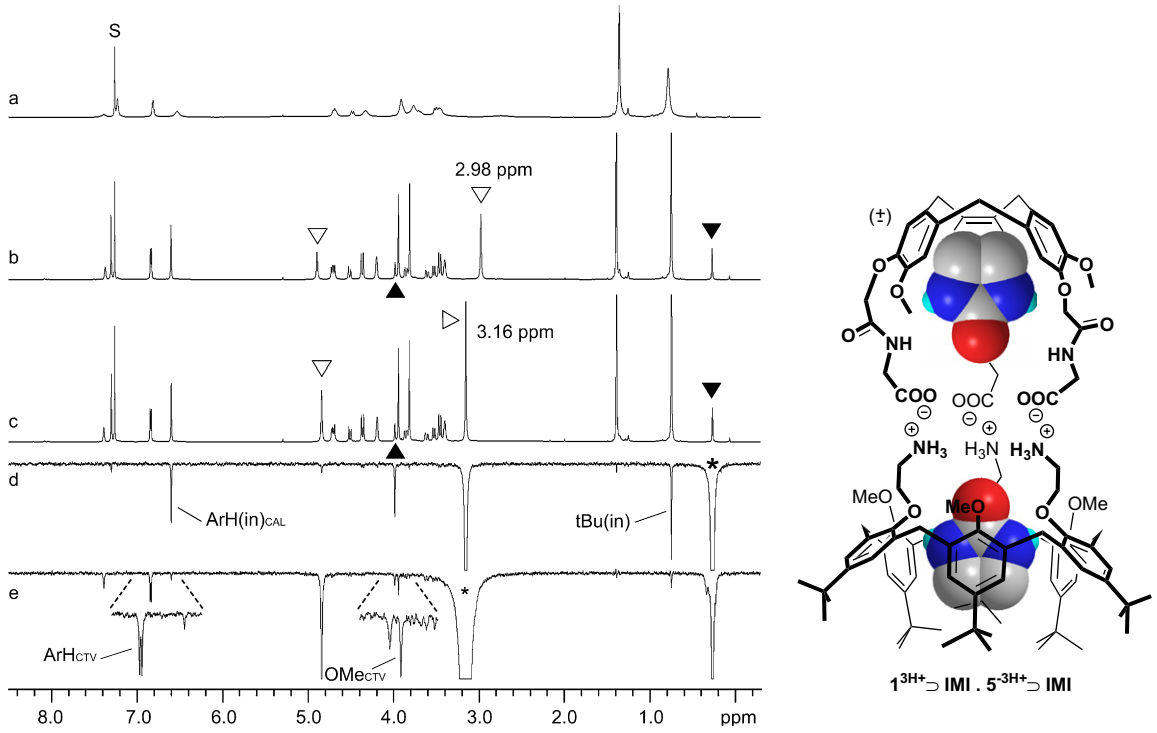


Figure 4. ^{1}H NMR spectra ($CDCl_3$, 298 K, 600 MHz) of: (a) a 1:1 mixture of **1** and **5**; (b) after the addition of 3.8 equiv of IMI; (c) after the addition of 5.8 equiv of IMI. 1D NOESY spectra ($CDCl_3$, 298 K, τ_m=800 ms) obtained with $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{5}^{-3H+}\supset\mathbf{IMI}$; (d) after selective excitation of the IMI signal at 0.27 ppm; (e) after selective excitation of the IMI signal at 3.16 ppm. ▼: IMI_{CAL}. ▽: IMI_{CTV}+IMI_{free}. *: Pulse excitation. Residual solvent has been labeled as S.

accordance with the formation of a self-assembled ditopic receptor, namely $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{5}^{-3H+}\supset\mathbf{IMI}$, that includes simultaneously two IMI molecules, one in the calixarene cavity (IMI_{CAL}) and one in the CTV cavity (IMI_{CTV}), the *in* and *out* guest exchanges of IMI_{CTV} being fast on the NMR time scale (Scheme 2). This was clearly confirmed by 1D NOESY experiments carried out in presence of IMI (Fig. 4d and e). Firstly, NOE effects were observed between the methylenic protons of IMI_{CAL} and the calixarene cavity (i.e., ArH_{in} and *t*-Bu_{in} protons) (selective pulse excitation at δ=0.27 ppm, Fig. 4d). These NOE effects are in good agreement with a classical positioning of an IMI molecule within the cavity of a calix[6]tris-ammonium receptor. Secondly, the CH_2 protons of IMI_{CTV} gave important NOE effects with some protons of the CTV cavity (i.e., OMe and ArH) (selective pulse excitation at δ=3.16 ppm, Fig. 4e).[36] Thus, IMI_{CTV} adopts a position with the methylenic protons directed toward the CTV aromatic walls, probably because of CH–π interactions (see the structure displayed in Fig. 4).

A series of NMR experiments were undertaken in order to compare the two binding processes operating with the ditopic receptor $\mathbf{1}^{3H+}\cdot\mathbf{5}^{-3H+}$. First, the ^{1}H NMR spectrum of a 1:1:1 mixture of **1**, **5**, and IMI recorded at 223 K indicated the exclusive formation of the ternary species $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{5}^{-3H+}$, which shows a weaker binding of IMI in the CTV cavity than in the calixarene one. The subsequent addition of different neutral guests G (G=EtOH, DMSO, and pyrrolidin-2-one) did not lead to their encapsulation in the CTV cavity, which seems to bind an IMI molecule with high specificity.[37]

The complex $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{5}^{-3H+}\supset\mathbf{IMI}$ was also investigated by DOSY NMR experiments with IMI concentrations of 3.8 and 5.8 equiv (Fig. 4b and c). In good agreement with the discrete nature of the structure, in both cases the same diffusion coefficients were found for IMI_{CAL}, the calixarene and the CTV subunits (Fig. 5) (see Supplementary data).[38] In the case of the signal of the IMI molecule in fast exchange *in* and *out* the CTV cavity, intermediate diffusion coefficients between those of free IMI[39] and IMI_{CTV}[40] were observed. This allowed us to determine the molar fraction of IMI_{CTV} for both concentrations. As a result, the binding CTV site was found to be occupied at 80[41,42] and 100% with 3.8 and 5.8 equiv of IMI, respectively (Fig. 4b and c). Thus, it was possible to deduce the chemical shift of IMI_{CTV} (δ=1.68 ppm, CIS=−1.87 ppm) as well as the apparent constants $K_1>10^4\ M^{-1}$ and $K_2=4.10^2\ M^{-1}$ defined by the following equation (see Supplementary data):

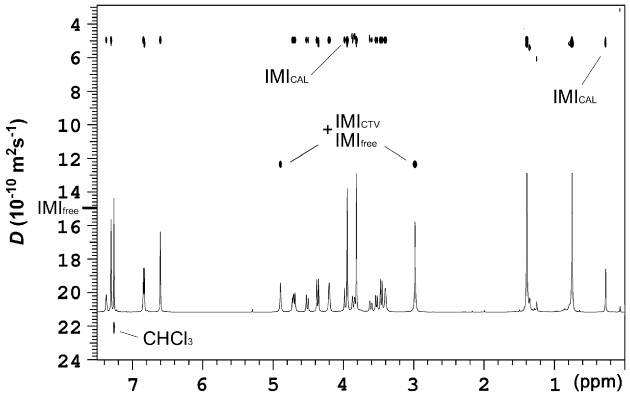


Figure 5. Diffusion coefficients determined through DOSY experiments ($CDCl_3$, 298 K, 600 MHz) with $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{5}^{-3H+}\supset\mathbf{IMI}$ (5.8 equiv of IMI). The diffusion coefficient for IMI_{free} was determined through other experiences.

$$\mathbf{1}^{3H+}\cdot\mathbf{5}^{-3H+} \overset{K_1}{\underset{\text{IMI}}{\rightleftharpoons}} \mathbf{1}^{3H+}\supset\text{IMI}\cdot\mathbf{5}^{-3H+} \overset{K_2}{\underset{\text{IMI}}{\rightleftharpoons}} \mathbf{1}^{3H+}\supset\text{IMI}\cdot\mathbf{5}^{-3H+}\supset\text{IMI}$$

Finally, kinetic data relative to the host–guest exchanges were determined through EXSY experiments. Thus, a residence time of ca. 4 s was determined for IMI_{CAL},[43] while it was estimated to be less than 10^{-3} s for IMI_{CTV}.[44]

All these results show that the ditopic self-assembled receptor $\mathbf{1}^{3H+}\cdot\mathbf{5}^{-3H+}$ displays two distinct recognition sites for polar organic guests.

(i) The calixarene cavity constitutes a polarized, hydrophobic binding site equipped with convergent hydrogen bonding donor and acceptor groups (i.e., the ammonium groups and the phenolic oxygen atoms, respectively). The flattened cone conformation adopted by the calixarene upon complexation produces the closure of the cavity by three of the *t*-Bu groups. As a consequence, the guests must collide with this molecular door before leaving the cavity.[45] All these recognition features lead to the strong and specific *endo*-complexation of various polar neutral guests, with a preference for molecules capable of multiple hydrogen bonding.

(ii) In comparison, the CTV cavity offers a weaker and more labile binding site, which can recognize an IMI molecule with high specificity. This can be rationalized if we consider that the CTV core has a higher rigidity, which prevents any conformational change of the binding site and has a wider opening that facilitates guest threading through the amido arms.

In summary, in contrast to the CTV subunit, the more flexible calixarene structure may undergo major conformational changes upon complexation and thus can better recognize polar neutral guests through induced-fit processes.

3. Conclusions

The self-assembly by ion-pairing between a calix[6]trisamine and tripodal tris-carboxylic acid partners with different degrees of preorganization has been shown to be a highly selective process. It leads to the formation of molecular receptors displaying a high affinity for polar neutral molecules. The self-assembly process is directed by the inclusion of a guest molecule that organizes the calixarene host, thus increasing the directionality of the interactions between the subunits. The use of tripodal caps has provided self-assembled calixarene-based receptors with unique host–guest properties: (i) with a concave CTV partner enlarged by amido arms, it produced a ditopic host that can simultaneously bind two neutral molecules in its two distinct cavities, the more flexible calixarene subunit leading to a better recognition due to induced-fit processes, (ii) with the best preorganized cap, the self-assembled structures were found to be stable in pure methanol, (iii) with a chiral cap, an enantioselective recognition process inside the calixarene cavity was possible through a supramolecular transmission of the chirality. All these results are an important contribution to a better understanding of the host–guest chemistry and are of particular interest for the construction of sophisticated molecular nano-size objects and devices.

4. Experimental section

4.1. General methods

DMF was distilled over $MgSO_4$ and silica gel under reduced pressure. Silica gel (230–400 mesh) was used for flash chromatographic separations. All the reactions were performed under an inert atmosphere. ^{1}H NMR spectra were recorded at either 600 MHz or 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts are expressed in parts per million. Traces of residual solvent or poly(dimethylsiloxane) (R) were used as internal standard. All the signals of the ^{1}H NMR spectra were attributed through 2D NMR analyses (COSY, HMQC, HMBC, NOESY). For all the host–guest NMR studies, $CDCl_3$ was previously neutralized with basic alumina.

4.2. (±)-CTVtris-ester 4

To a solution of CTV **3** (100 mg, 0.17 mmol) in anhydrous DMF (1 mL) were successively added triethylamine (0.167 mL, 1.20 mmol), glycinemethylester·HCl (86 mg, 0.69 mmol), and HBTU (261 mg, 0.69 mmol). The solution was stirred for 2 h at 50 °C and was then concentrated under reduced pressure. CH_2Cl_2 (20 mL) was added to the residue and the organic layer was washed with an aqueous solution of 1 M HCl (5 mL). The aqueous layer was then extracted with CH_2Cl_2 (2×5 mL) and the combined organic layers were washed with H_2O (5 mL) and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/acetone, 1:1), yielding pure compound **4** (98 mg, 72%) as a white solid. Mp: 88 °C. IR (KBr): ν 3720–3120, 1748, 1674, 1514, 1266, 1215 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (d, J=14 Hz, 3H, ArCH_{eq}), 3.67 (s, 9H, CO_2CH_3), 3.87 (s, 9H, ArOCH_3), 4.00 (dd, J_1=18 Hz, J_2=5 Hz, 3H, CHN), 4.14 (dd, J_1=18 Hz, J_2=5 Hz, 3H, CHN), 4.49 (d, J=15 Hz, 3H, OCHCO), 4.55 (d, J=15 Hz, 3H, OCHCO), 4.72 (d, J=14 Hz, 3H, ArCH_{ax}), 6.83 (s, 3H, ArH), 6.88 (s, 3H, ArH), 7.36 (t, J=5 Hz, 3H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.4, 40.9, 52.4, 56.2, 69.9, 113.6, 117.1, 131.8, 134.3, 146.0, 148.7, 169.3, 169.9. EIMS *m*/*z* (rel int) 795 (M^+, 31), 667 (37), 666 (base), 537 (40), 271 (46). Anal. Calcd for $C_{39}H_{45}N_3O_{15}\cdot 0.5CH_2Cl_2$: C, 56.60; H, 5.53; N, 5.01. Found: C, 56.92; H, 5.40; N, 5.35.

4.3. (±)-CTVtris-acid 5

To a solution of CTVtris-ester **4** (60 mg, 0.075 mmol) in methanol (2 mL) was added at 0 °C an aqueous solution of 1 M NaOH (0.5 mL, 0.50 mmol). The mixture was stirred at rt for 3 h. An aqueous solution of 1 M HCl (1 mL) was then added at 0 °C, leading to the formation of a white precipitate, and the mixture was concentrated under reduced pressure. The solid residue was washed with H_2O until pH=6, yielding compound **5** (53 mg, 94%) as a white solid. Mp: 225 °C (decomp.). IR (KBr): ν 3720–3040, 2934, 1734, 1654, 1515, 1385, 1266 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 330 K) δ 3.51 (d, J=14 Hz, 3H, ArCH_{eq}), 3.77 (s, 9H,

OCH_3), 3.83 (m, 6H, CH_2N), 4.45 (d, J=15 Hz, 3H, OCHCO), 4.47 (d, J=15 Hz, 3H, OCHCO), 4.70 (d, J=14 Hz, 3H, ArCH_{ax}), 7.06 (s, 3H, ArH), 7.16 (s, 3H, ArH), 8.01 (br s, 3H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.9, 55.8, 68.9, 113.7, 116.7, 131.7, 133.5, 145.7, 147.7, 168.5, 170.9. Anal. Calcd for $C_{36}H_{39}N_3O_{15}\cdot 3H_2O$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.59; H, 5.14; N, 5.06.

4.4. 1,3,5-Tri(2′-carboxyphenyl)benzene 7

To a solution of 1,3,5-tri(2′-formylphenyl)benzene[18] (70 mg, 0.18 mmol) in a 6:1 DMSO/CH_2Cl_2 mixture (7 mL) was added a solution of NaH_2PO_4 (105 mg, 0.76 mmol) in H_2O (1 mL). Then a solution of $NaClO_2\cdot H_2O$ (155 mg, 1.43 mmol) in H_2O (1 mL) was added very slowly (over 2 h) to the previous mixture. After the appearance of a yellow coloration, the mixture was stirred for 4 h. An aqueous solution of 1 M HCl (20 mL) was then added, the precipitate was isolated by filtration, and washed with H_2O until pH=6, yielding compound **7** (68 mg, 86%) as a white solid. IR (KBr): ν 1691, 1266 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.39 (s, 3H, ArH), 7.45–7.68 (m, 9H, ArH), 7.73 (d, J=7 Hz, 3H, ArH), 12.92 (br s, 3H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 127.4, 127.5, 129.1, 130.5, 130.9, 132.4, 139.9, 140.0, 169.9. EIMS m/z (rel int) 438 (M^+, 26), 420 (23), 375 (base), 357 (57). HRMS (EI) calcd for $C_{27}H_{18}O_6$ (M^+) 438.1103, found 438.1105.

4.5. 1,3,5-Tri(2′-carboxyphenylmethyl)benzene 9

1,3,5-Tri(2′-formylphenylmethyl)benzene[9g] (100 mg, 0.23 mmol) was reacted similarly to 1,3,5-tri(2′-formylphenyl)benzene in the case of the preparation of compound **7**, yielding compound **9** (100 mg, 90%) as a white solid. Mp: 230 °C (decomp.). IR (KBr): ν 3715–3130, 1687, 1599, 1385, 1267 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.22 (s, 6H, CH_2), 7.14 (d, J=7 Hz, 3H, ArH), 7.28 (t, J=7 Hz, 3H, ArH), 7.42 (d, J=7 Hz, 3H, ArH), 7.78 (d, J=7 Hz, 3H, ArH), 12.87 (br s, 3H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 38.3, 126.1, 127.0, 130.1, 130.5, 130.9, 131.6, 140.8, 141.4, 168.8. EIMS m/z (rel int) 480 (M^+, 2), 462 (35), 427 (34), 426 (base), 398 (37), 252 (39), 133 (57). Anal. Calcd for $C_{30}H_{24}O_6\cdot H_2O$: C, 72.28; H, 5.26. Found: C, 71.92; H, 5.03.

4.6. 1,3,5-Tri(2′-carboxyphenyloxamethyl)benzene 11

1,3,5-Tri(2′-formylphenyloxamethyl)benzene[9g] (100 mg, 0.21 mmol) was reacted similarly to 1,3,5-tri(2′-formylphenyl)benzene in the case of the preparation of compound **7**, yielding compound **11** (100 mg, 90%) as a white solid. Mp: 200 °C (decomp.). IR (KBr): ν 3710–3310, 3077, 2918, 1709, 1602, 1253 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.21 (s, 3H, CH_2), 7.03 (t, 3H, J=8 Hz, ArH), 7.21 (d, 3H, J=8 Hz, ArH), 7.50 (t, 3H, J=8 Hz, ArH), 7.67 (d, 3H, J=8 Hz, ArH), 12.65 (br s, 3H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 69.9, 114.1, 120.5, 121.9, 125.8, 130.7, 132.9, 137.4, 157.1, 167.3. Anal. Calcd for $C_{30}H_{24}O_9\cdot 0.6CH_2Cl_2$: C, 63.43; H, 4.38. Found: C, 63.37; H, 4.38.

4.7. Self-assembly $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{3}^{-3H+}$

IMI of 3 equiv was added to a mixture of calix[6]tris-amine **1** (6.0 mg, 5.24 μmol) and CTV **3** (3.0 mg, 5.15 μmol) in $CDCl_3$ (0.6 mL, neutralized on basic alumina). After sonication, the mixture was heated at 50 °C until a clear solution was obtained (≈15 h). ^{1}H NMR spectrum recorded at 294 K showed the presence of the self-assembled complex $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{3}^{-3H+}$ as the only observable species. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (m, 4H, CH_{2IMIin}), 0.72 (s, 27H, t-Bu), 1.38 (s, 27H, t-Bu), 3.33 (d, J=15 Hz, 3H, ArCH_{eqcal}), 3.46 (d, J=16 Hz, 3H, ArCH_{eqcal}), 3.52 (d, J=16 Hz, 3H, ArCH_{eqCTV}), 3.63 (s, 6H, OCH_2CH_2N), 3.76 (s, 9H, OMe_{cal}), 3.89 (d, J=12 Hz, 3H, OCH_2CH_2N), 3.93 (s, 2H, NH_{IMIin}), 4.03 (s, 9H, OMe_{CTV}), 4.31 (d, J=15 Hz, 3H, ArCH_{axcal}), 4.38 (d, J=15 Hz, 3H, ArCH_{axcal}), 4.54–4.83 (m, 12H, ArCH_{axCTV} [3H]+OCH_2CH_2N [3H]+OCH_2-COO [6H]), 6.50 (s, 3H, ArH_{cal}), 6.62 (s, 3H, ArH_{cal}), 6.82 (s, 3H, ArH_{CTV}), 6.90 (s, 3H, ArH_{CTV}), 7.22 (s, 3H, ArH_{cal}), 7.30 (s, 3H, ArH_{cal}), 8.05 (br s, 9H, NH_3^+). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4 (CH_2), 29.9 (CH_2), 31.2 (CH_3), 31.9 (CH_3), 34.3 (C), 34.6 (C), 36.2 (CH_2), 38.9 (CH_2), 40.6 (CH_2), 55.8 (CH_3), 60.9 (CH_3), 67.7 (CH_2), 72.8 (CH_2), 112.3 (CH), 113.6 (CH), 123.1 (CH), 124.1 (CH), 128.4 (CH), 128.9 (CH), 131.1 (C), 131.2 (C), 131.7 (C), 132.5 (C), 134.0 (C), 145.1 (C), 146.4 (C), 146.7 (C), 147.0 (C), 153.1 (C), 153.5 (C), 164.6 (C), 172.8 (C).

4.8. Self-assembly $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{5}^{-3H+}\supset\mathbf{IMI}$

A mixture of calix[6]tris-amine **1** (8.0 mg, 6.99 μmol) and CTV **5** (5.3 mg, 7.03 μmol) in $CDCl_3$ (1.4 mL, neutralized on basic alumina) was first sonicated and then heated at 50 °C in a 5 mm. Young tube until a clear solution was obtained (≈15 h). To 600 μL of this solution was added 5.8 equiv of IMI leading, after sonication, to the self-assembly $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{5}^{-3H+}\supset\mathbf{IMI}$ as a unique species. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.27 (s, 4H, $CH_{2IMIcal}$), 0.75 (s, 27H, t-Bu), 1.39 (s, 27H, t-Bu), 3.16 (s, $CH_{2IMICTV}$+$CH_{2IMIfree}$), 3.40 (br s, 6H, OCH_2CH_2N), 3.46 (d, J=15.0 Hz, 6H, ArCH_{eqcal}), 3.53 (d, J=13.8 Hz, 3H, ArCH_{eqCTV}), 3.61 (dd, J_1=3.6 Hz, J_2=17.4 Hz, 3H, $NHCH_2COO$), 3.82 (s, 9H, OMe_{cal}), 3.86 (dd, J_1=3.6 Hz, J_2=17.4 Hz, 3H, $NHCH_2COO$), 3.94 (s, 9H, OMe_{CTV}), 3.98 (s, 2H, NH_{IMIcal}), 4.19 (br s, 6H, OCH_2CH_2N), 4.36 (d, J=15.0 Hz, 6H, ArCH_{axcal}), 4.51 (d, J=15.6 Hz, 3H, OCH_2CO), 4.70 (d, J=15.0 Hz, 3H, OCH_2CO), 4.71 (d, J=13.8 Hz, 3H, ArCH_{axCTV}), 4.84 (s, NH_{IMICTV}+$NH_{IMIfree}$), 6.60 (s, 6H, ArH_{cal}), 6.83 (s, 3H, ArH_{CTV}), 6.85 (s, 3H, ArH_{CTV}), 7.30 (s, 6H, ArH_{cal}), 7.39 (br s, 3H, NHCO). Further addition of 200 μL of the parent 1:1 mixture of $\mathbf{1}^{3H+}$ and $\mathbf{5}^{-3H+}$ to the above solution led to a decrease in the IMI concentration down to 3.8 equiv.

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Supplementary data

The general procedure for the determination of the relative affinities of the neutral molecules in the case of $\mathbf{1}^{3H+}\supset\mathbf{G}\cdot\mathbf{3}^{-3H+}$, the procedure for the determination of

the association constant (K) for the self-assemblies $\mathbf{1}^{3H+}\supset\mathbf{G}\cdot\mathbf{3}^{-3H+}$, the ^{13}C NMR spectrum as well as the HMQC, COSY, HMBC, and NOESY spectra of the self-assembly $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{3}^{-3H+}$, the ^{1}H NMR spectra of $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{7}^{-3H+}$ in $CDCl_3$ and CD_3OD, the ^{1}H NMR spectra of $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{9}^{-3H+}$ and $\mathbf{1}^{3H+}\supset\mathbf{IMI}\cdot\mathbf{11}^{-3H+}$, the NOESY spectrum of $\mathbf{1}^{3H+}\supset\mathbf{DMF}\cdot\mathbf{3}^{-3H+}$, and full details concerning the NMR study of the inclusion of IMI by the self-assembly $\mathbf{1}^{3H+}\cdot\mathbf{5}^{-3H+}$. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.122.

References and notes

1. Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153–180; Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312–1319.
2. Lawrence, D. S.; Jiang, T. J.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229–2260; Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853–908; Sherrington, D. C.; Taskinen, K. A. *Chem. Soc. Rev.* **2001**, *30*, 83–93.
3. Linton, B.; Hamilton, A. D. *Chem. Rev.* **1997**, *97*, 1669–1680; Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647–1668; Fujita, M. *Chem. Soc. Rev.* **1998**, *27*, 417–425; Higler, I.; Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **1998**, 2689–2702; Johnston, M. R.; Latter, M. J. *Supramol. Chem.* **2005**, *17*, 595–607.
4. Gutsche, C. D. *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1998.
5. (a) Böhmer, V.; Shivanyuk, A. *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000; pp 203–240; (b) Rudkevich, D. M. *Calixarene 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 2001; pp 155–180.
6. Arduini, A.; Domiano, L.; Ogliosi, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1997**, *62*, 7866–7868; Gonzalez, J. J.; Ferdani, R.; Albertini, E.; Blasco, J. M.; Arduini, A.; Pochini, A.; Prados, P.; de Mendoza, J. *Chem.—Eur. J.* **2000**, *6*, 73–80; Rincon, A. M.; Prados, P.; de Mendoza, J. *Eur. J. Org. Chem.* **2002**, 640–644; Arduini, A.; Ferdani, R.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Sheldrick, G. M.; Prados, P.; González, J. J.; de Mendoza, J. *J. Supramol. Chem.* **2002**, *2*, 85–88; Zadmart, R.; Junkers, M.; Schrader, T.; Grawe, T.; Kraft, A. *J. Org. Chem.* **2003**, *68*, 6511–6521; For calix[6]arene-based rotaxanes, see also: Arduini, A.; Ferdani, R.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3453–3456; Arduini, A.; Ciesa, F.; Fragassi, M.; Pochini, A.; Secchi, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 278–281.
7. Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734.
8. (a) Lüning, U.; Löffler, F.; Eggert, J. *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 2001; pp 71–88; (b) Chen, Y.; Gong, S. *J. Incl. Phenom. Macrocycl. Chem.* **2003**, *45*, 165–184.
9. For the syntheses of calix[6]aza-cryptands, see: (a) Jabin, I.; Reinaud, O. *J. Org. Chem.* **2003**, *68*, 3416–3419; (b) Darbost, U.; Giorgi, M.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 4879–4884; (c) Zeng, X.; Hucher, N.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 6886–6889; (d) Garrier, E.; Le Gac, S.; Jabin, I. *Tetrahedron: Asymmetry* **2005**, *16*, 3767–3771; (e) Le Gac, S.; Zeng, X.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2005**, *70*, 1204–1210; (f) Zeng, X.; Coquière, D.; Alenda, A.; Garrier, E.; Prangé, T.; Li, Y.; Reinaud, O.; Jabin, I. *Chem.—Eur. J.* **2006**, *12*, 6393–6402; (g) Le Gac, S.; Zeng, X.; Girardot, C.; Jabin, I. *J. Org. Chem.* **2006**, *71*, 9233–9236 For the host–guest properties of calix[6]aza-cryptands, see: (h) Darbost, U.; Zeng, X.; Rager, M.-N.; Giorgi, M.; Jabin, I.; Reinaud, O. *Eur. J. Inorg. Chem.* **2004**, 4371–4374; (i) Darbost, U.; Rager, M.-.N.; Petit, S.; Jabin, I.; Reinaud, O. *J. Am. Chem. Soc.* **2005**, *127*, 8517–8525; (j) Izzet, G.; Douziech, B.; Prangé, T.; Tomas, A.; Jabin, I.; Le Mest, Y.; Reinaud, O. *Proc. Natl. Acad. Sci., U.S.A.* **2005**, *102*, 6831–6836; (k) Izzet, G.; Zeng, X.; Over, D.; Giorgi, M.; Jabin, I.; Le Mest, Y.; Reinaud, O. *Inorg. Chem.* **2007**, *46*, 375–377.
10. (a) Darbost, U.; Zeng, X.; Giorgi, M.; Jabin, I. *J. Org. Chem.* **2005**, *70*, 10552–10560; (b) Darbost, U.; Giorgi, M.; Hucher, N.; Jabin, I.; Reinaud, O. *Supramol. Chem.* **2005**, *17*, 243–250.
11. Le Gac, S.; Giorgi, M.; Jabin, I. *Supramol. Chem.* **2007**, *19*, 185–197.
12. Le Gac, S.; Marrot, J.; Reinaud, O.; Jabin, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3123–3126.
13. The fact that electrostatic interactions lead to increased bond strength over hydrogen bonds has been emphasized in various self-assembled systems. For leading examples, see: Lee, S. B.; Hong, J.-I. *Tetrahedron Lett.* **1996**, *37*, 8501–8504; Fiammengo, R.; Timmerman, P.; Huskens, J.; Versluis, K.; Heck, A. J. R.; Reinhoudt, D. N. *Tetrahedron* **2002**, *58*, 757–764; Corbellini, F.; Fiammengo, R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569–6575; Grawe, T.; Schrader, T.; Zadmard, R.; Kraft, A. *J. Org. Chem.* **2002**, *67*, 3755–3763; Zadmard, R.; Schrader, T.; Grawe, T.; Kraft, A. *Org. Lett.* **2002**, *4*, 1687–1690; Corbellini, F.; Di Costanzo, L.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946–9947; Botana, E.; Nattinen, K.; Prados, P.; Rissanen, K.; de Mendoza, J. *Org. Lett.* **2004**, *6*, 1091–1094; Sasine, J. S.; Brewster, R. E.; Caran, K. L.; Bentley, A. M.; Shuker, S. B. *Org. Lett.* **2006**, *8*, 2913–2915; Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *J. Am. Chem. Soc.* **2006**, *128*, 5270–5278.
14. For recent work on the syntheses and applications of multitopic calixarenes, see: *Calixarenes in the Nanoworld*; Vicens, J., Harrowfield, J., Eds.; Springer: London, 2006.
15. It is noteworthy that syntheses of calix[6]arenes covalently linked to cyclotriveratrylene subunits at the narrow rim have been reported but the host–guest properties of the resulting capped compounds were not investigated. See: Janssen, R. G.; Verboom, W.; van Duynhoven, J. P. M.; van Velzen, E. J. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, *35*, 6555–6558.
16. Vériot, G.; Dutasta, J.-P.; Matouzenko, G.; Collet, A. *Tetrahedron* **1995**, *51*, 389–400.
17. HBTU: *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.
18. Chardonnens, L.; Chardonnens, H. *Helv. Chim. Acta* **1968**, *51*, 1998–2005.
19. For the syntheses of **8** and **10**, see Ref. 9g.
20. For other examples on the use of this procedure, see: Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569.
21. Compound **3** is almost insoluble in $CDCl_3$.
22. Average value of the diastereotopic protons.
23. This diastereotopic splitting of the guest IMI methylenic protons is clearly due to the chirality of the CTV subunit since it was not observed when the achiral caps **7**, **9**, and **11** were used (see Scheme 2).

24. In contrast, the addition of molecules of low polarity such as acetone, THF, or CH_2Cl_2 did not affect the NMR pattern of the 1:1 mixture of $\mathbf{1}^{3H+}$+$\mathbf{3}^{-3H+}$.
25. In all cases, the sharpness of the ^1H NMR spectra at rt and the observed C_{3v} symmetry at low temperature (223 K) are in accordance with a [1+1] ion-paired complex rather than larger assemblies.
26. For detailed procedure on *K* determination, see Supplementary data.
27. The amount of $\mathbf{1}^{3H+} \supset \mathbf{IMI} \cdot \mathbf{3}^{-3H+}$ was measured by integration of the signal of the included IMI compared to an internal reference (1,1,2,2-tetrachloroethane). The dissociation of the self-assembly led to ill-defined species.
28. A second species displaying a quasi-similar NMR pattern to the one of $\mathbf{1}^{3H+} \supset \mathbf{IMI} \cdot \mathbf{7}^{-3H+}$, but which does not include the IMI guest, was also observed. Complementary studies have shown that this new species is due to the competitive binding of the solvent (CD_3OD) in the calixarene cavity and thus corresponds to the assembly $\mathbf{1}^{3H+} \supset \mathbf{CD_3OD} \cdot \mathbf{7}^{-3H+}$.
29. Chankvetadze, B.; Endresz, G.; Blaschke, G. *Chem. Soc. Rev.* **1996**, 141–153; Pu, L. *Chem. Rev.* **2004**, *104*, 1687–1716.
30. For examples of enantiopure anionic species in chiral recognition processes, see: Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373–382.
31. For the preparation of this compound, see: Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246–2254.
32. In the case of BTD, de=10%. With PPD, accurate value of the de could not be determined because of overlapping signals, but it seems negligible.
33. Compound **5**, which is insoluble in $CDCl_3$, was completely extracted after sonication and heating at 50 °C for 15 h.
34. In this case, the chirality of the CTV cap was sensed by the calixarene and by the guest only at low temperature (<263 K). This is likely due to the large distance of the calixarene host from the chiral source.
35. This signal was attributed to the methylenic protons of an IMI molecule through an EXSY experiment.
36. Minor NOE effects between the protons of IMI_{CTV} and the calixarene core (ArH_{in} and t-Bu_{in} protons) were also observed. This is likely due to the exchange, on the NMR time scale, of the IMI molecules between the two different binding sites.
37. Further addition of IMI resulted in similar NMR spectra than those displayed in Figure 4b and c.
38. All diffusion coefficients *D* were normalized, thanks to an internal reference ($CHCl_3$), and are average values of at least two experiments.
39. This diffusion coefficient was determined by independent experiences with NMR samples of IMI at different concentrations in $CDCl_3$ (internal reference: $CHCl_3$).
40. The diffusion coefficient of IMI_{CTV} was supposed identical to the one of the other partners of the self-assembly $\mathbf{1}^{3H+} \supset \mathbf{IMI} \cdot \mathbf{5}^{-3H+} \supset \mathbf{IMI}$.
41. It corresponds to a 4:1 ratio of $\mathbf{1}^{3H+} \supset \mathbf{IMI} \cdot \mathbf{5}^{-3H+} \supset \mathbf{IMI}$ and $\mathbf{1}^{3H+} \supset \mathbf{IMI} \cdot \mathbf{5}^{-3H+}$.
42. Average value determined through two different methods (thanks to the diffusion coefficients and the chemical shifts, see Supplementary data).
43. Average value of two experiments performed with 3.8 and 5.8 equiv of IMI (see Supplementary data).
44. Fast exchange implies that the residence time τ is shorter than the inverse of the CIS absolute value measured in hertz, thus $\tau < 1/(1.9 \times 600)$ s.
45. Rondelez, Y.; Rager, M.-N.; Duprat, A.; Reinaud, O. *J. Am. Chem. Soc.* **2002**, *124*, 1334–1340.