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Synthesis and Study of Calix[6]cryptamides: A New Class of Heteroditopic Receptors that Display Versatile Host–Guest Properties Toward Neutral Species and Organic Associated Ion-Pair Salts

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Abstract: The synthesis of a new family of molecular receptors, namely the calix[6]cryptamides, was achieved through an original [1+1] macrocyclization step that consists of a peptide-coupling reaction between tripodal tris-carboxylic acids and a calix[6]trisamine subunit. Several C_3- or C_{3v}-symmetrical calix[6]arene-based compounds capped by a trisamido cryptand unit on the narrow rim have been obtained, with the more flexible partners leading to the best yields. These calix[6]cryptamides exhibit two favorably positioned binding sites for the complexation of organic-associated ion pairs in close proximity: a well-defined calix[6]arene cavity suitable for the inclusion of ammonium ions and a cryptamide unit for the coordination of anions. We demonstrate one example, chiral calix[6]cryptamide **12**, that constitutes a heteroditopic receptor capable of cooperatively binding both a primary ammonium ion and its chloride counterion, thanks to a combination of polarization and induced-fit effects. In addition, the hydrophobic calixarene cavity of **12** can strongly bind neutral guests through hydrogen bonding and is capable of discriminating between different enantiomers. All these versatile host–guest properties differ greatly from those observed in the parent calix[6]azacryptands.

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

Introduction

There is a growing interest in the design of synthetic receptors that are able to recognize neutral molecules or charged species through specific interactions.[1] These receptors can find potential applications in many areas, such as sensing, modeling of enzymic active sites, catalysis, nanoscience, drug delivery and separation science. Readily available calixarenes have emerged as very attractive building blocks for the development of such host–guest systems.[2] Of the different oligomers, calix[4]arenes have been extensively studied, since control of their conformational mobility and their selective functionalization can be more easily achieved. However, calix[4]arenes suffer from the smallness of their hydrophobic cavity and consequently they have mostly been used as molecular platforms for the preorganization of a binding site outside the cavity.[2,3] The larger calix[6]arenes display a cavity size that is well adapted for the inclusion of organic guests[4], but usually their high conformational flexibility needs to be restricted first. To do this, different strategies such as self-assembly,[5] metal-ion coordination,[6] and grafting of covalent bridges have been developed.[7] We have synthesized calix[6]arenes bearing a tripodal azacryptand cap on the narrow rim.[8] These calix[6]azacryptands exhibit remarkable host–guest properties toward polar neutral molecules or cationic species (ammonium and metal ions), thanks to the presence of the basic azacryptand cap that preorganizes the cavity and provides a tunable binding site.[9] In the course of designing versatile calixarene based *endo*-receptors for organic guests, we wanted to test the feasibility of grafting a tripodal amido cap (that is, a cryptamide unit) onto a calix[6]arene core. So far, only calix[6]arenes that have intramolecular dipodal amido bridges have been described.[10,11] Apart from the synthetic challenge, the

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target calix[6]cryptamides were particularly attractive, since they were predicted to possess both an ammonium ion binding site in the form of the hydrophobic cavity, and an anion binding site in the form of the tripodal arrangement of the amide groups.[12] Neutral heteroditopic receptors capable of simultaneously binding cations and anions are currently being intensively studied since they present the advantage of avoiding the competitive ion-pairing of the guest salt.[13] In this regard, heteroditopic calix[4]arene-based receptors that possess amido or urea groups have been already produced.[14] However, owing to the smallness of their cavity they are mostly used for the complexation of metal ions and their counterions.[15] With the larger calix[5,6]arenes, the introduction of urea moieties led to receptors capable of recognizing organic ion-pair salts, but only a few examples have been reported so far.[16–18]

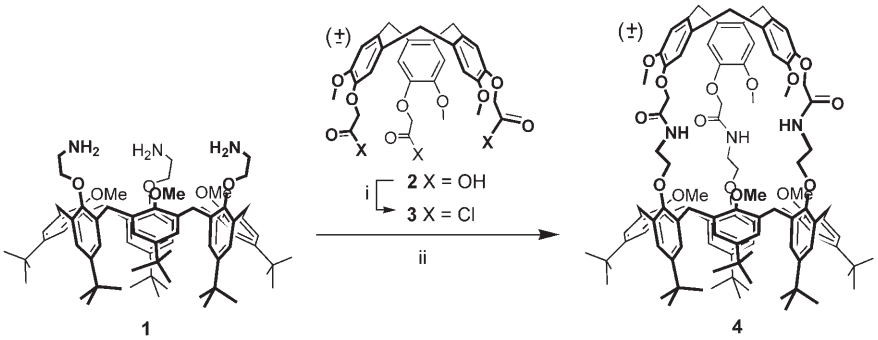
Here we describe an efficient synthesis of calix[6]cryptamides, a new class of bifunctional receptors, and also the NMR spectroscopic host–guest studies of chiral calix[6]cryptamide **12**. This versatile heteroditopic receptor exhibits unique host properties towards both organic-associated ion pair salts and neutral guests.

Results and Discussion

Synthesis of calix[6]cryptamide 4: For the key step of the synthesis of calix[6]cryptamides, we chose a [1+1] macrocyclization reaction between two tripodal subunits, since this strategy has proved its efficiency with the parent calix[6]azacryptands.[8] The reaction conditions for the macrocyclization step were first tested and optimized with calix[6]-trisamine **1** and well-preorganized tris-electrophilic partners **2** and **3** derived from a cyclotriveratrylene (CTV) skeleton. In addition, we were interested in producing a multitopic receptor that displayed two concave subunits linked by a trisamido binding site.[19]

The preparation of calix[6]trisamine **1** from the C_{3v} symmetrical 1,3,5-tris-*O*-methylated *t*Bu-calix[6]arene has already been reported by us. The synthesis is an efficient three-step sequence: *per*-alkylation with ethylbromoacetate in presence of a strong base (NaH), reaction with ammonia in MeOH, and subsequent reduction of the obtained amide groups by BH_3/THF (79% overall yield).[8g] (±)-CTV tris-carboxylic acid derivative **2** was synthesized according to the procedure described in the literature.[20]

First, the [1+1] macrocyclization reaction between calixarene **1** and trisacyl chloride **3** was tested under classical high dilution conditions (trisacyl chloride **3** was prepared quantitatively from CTV **2** and oxalyl chloride in dichloromethane).[21] The desired calix[6]cryptamide **4** (15%) was isolated after purification by flash chromatography (FC) (Scheme 1, entry 1 of Table 1).



Scheme 1. Synthesis of calix[6]cryptamide **4**; i) $(COCl)_2$, CH_2Cl_2; ii) see Table 1.

Table 1. Synthesis of calix[6]cryptamide **4** through reaction between calix[6]trisamine **1** and CTV derivatives **2** or **3**.

Entry	CTV derivative	Solvent	Conc.[M][a]	Reaction conditions[b]	Yield[%][c]
1	**3**	toluene	2.6×10^{-3}	TEA, 0°C then RT, 15 h	15
2	**2**	$CHCl_3/CH_3NO_2$; 4:1	1.0×10^{-2}	PyBOP, 50°C, 2 h	46
3	**2**	$CHCl_3/CH_3NO_2$; 4:1	1.0×10^{-2}	HBTU, 50°C, 2 h	42
4	**2**	$CHCl_3$/DMF; 2:1	1.0×10^{-2}	HBTU, 50°C, 2 h	41
5	**2**	$CHCl_3/CH_3NO_2$; 4:1	1.0×10^{-1}	PyBOP, 50°C, 15 h	10
6	**2**	$CHCl_3/CH_3NO_2$; 4:1	4.0×10^{-4}	HBTU, 50°C, 15 h	<5[d]

[a] Concentration of **1** and CTV derivative. [b] Reactions with HBTU and PyBOP were performed by the slow addition of a mixture of the coupling reagent and TEA (6 equiv each; see the Experimental Section). [c] The yields correspond to the isolated compound **4** after purification by flash chromatography. [d] This yield was estimated by using an NMR spectrum of the crude reaction mixture.

With the aim of improving the yield of the macrocyclization reaction, we decided to test the direct reaction between calix[6]trisamine **1** and CTV-trisacid **2** in the presence of peptide-coupling reagents such as HBTU or PyBOP.[22] Mixtures of solvents such as $CHCl_3/CH_3NO_2$ or $CHCl_3$/DMF were used to solubilize the two tripodal partners and the coupling reagent.[23] In addition, the influence of the concentration of subunits **1** and **2** was studied (entries 2–6, Table 1). The highest yield for **4** (46%) was obtained when subunits **1** and **2** were reacted at 50°C and at a concentration of 10^{-2} M in a 4:1 mixture of $CHCl_3/CH_3NO_2$, with PyBOP as the coupling reagent (entry 2, Table 1).[24] It is worth noting that the nature of the coupling reagent and the solvent have little influence on the yield (41–46%) (entries 3 vs. 2 and 4 vs. 3, respectively, Table 1). In contrast, high concentration (10^{-1} M) or high dilution ($4\ 10^{-4}$ M) of the

two subunits led to low yields (entries 5 and 6, Table 1). The ^{1}H NMR spectra of the crude reaction mixture show in both cases the presence of multiple species displaying ill-defined resonances.[25]

This first set of experiments shows that the peptide-coupling reaction can constitute an efficient strategy for [1+1] macrocyclization reactions between tripodal units[26] and thus we decided to test these reaction conditions for the synthesis of various calix[6]cryptamides.

Table 2. Reaction conditions for the synthesis of calix[6]cryptamides **10**–**13**.

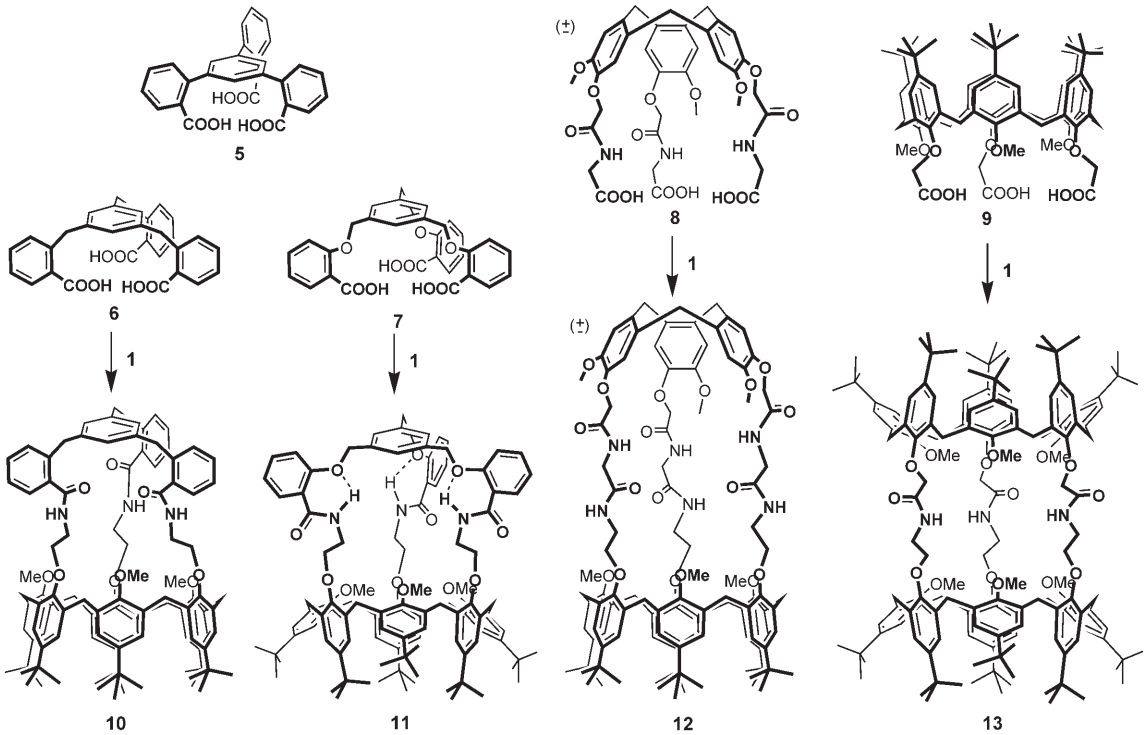
Entry	Trisamine	Trisacid	Solvent	Coupling reagent	Product	Yield[%][a]
1	**1**	**5**	$CHCl_3/CH_3NO_2$; 4:1	HBTU or PyBOP	–	–
2	**1**	**6**	$CHCl_3/CH_3NO_2$; 4:1	HBTU	**10**	13[b]
3	**1**	**7**	$CHCl_3/CH_3NO_2$; 4:1	HBTU	**11**	21
4	**1**	**8**	$CHCl_3$/DMF; 4:1	HBTU	**12**	33
5	**1**	**9**	$CHCl_3/CH_3NO_2$; 4:1	PyBOP	**13**	58

[a] The yields correspond to the isolated compounds after purification by flash chromatography. [b] The yield was calculated while taking into account the presence of about 1 equiv of 1,1,3,3-tetramethylurea in the final product (^{1}H NMR estimation).

Synthesis of calix[6]cryptamides 10–13: Calix[6]trisamine **1** was reacted with triscarboxylic acid derivatives **5**–**9**, which display different degrees of flexibility[27] (Scheme 2). All the reactions were performed under the optimal conditions determined for **2** (50 °C, 6 equiv of TEA, 6 equiv of coupling reagent, 10^{-2} M in a 4:1 mixture of $CHCl_3/CH_3NO_2$ or $CHCl_3$/DMF; Table 2). The choice of coupling reagent was governed by purification considerations. The reactions were monitored by ^{1}H NMR spectroscopy and the obtained calix[6]cryptamides were purified by flash chromatography. In the case of triscarboxylic acid **5**, a complex mixture of calixarene derivatives that displayed broad NMR resonances was obtained. However, the use of triscarboxylic acids **6**–**9** led to the corresponding calix[6]cryptamides **10**–**13** in moderate to good yields (13–58 %, Table 2, entries 2–5). Surprisingly, the efficiency of the macrocyclization reaction augments with increasing flexibility of the tripodal carboxylic acid. This can be rationalized if one considers that the bulkiness of the intermediate benzotriazole ester groups disfavors the [1+1] macrocyclization pathway in the case of rigid partners.

All these results show that the use of the peptide-coupling reaction for the [1+1] macrocyclization step can be extended to structurally different tripodal partners and gives access to original calixarene based compounds that are either closed at the narrow rim by a grid-like amido cap (**4**, **10**–**12**) or possessing a calix[6]tube skeleton (**13**).

NMR spectroscopic study of the conformational properties of calix[6]cryptamides 4 and 10–13: The conformational properties of calix[6]cryptamides **4** and **10**–**13** were investigated through extensive NMR studies in $CDCl_3$. All the resonances of the ^{1}H NMR spectra were attributed by means



Scheme 2. Syntheses of calix[6]cryptamides **10**–**13**; see Table 2 for the reaction conditions. The calix[6]cryptamides are shown in their major conformation, which has been deduced from NMR spectroscopic studies (see below).

of 2D NMR experiments (COSY, HMQC, HMBC). Due to their C_3 (compound **4**) or C_{3v} (compounds **10**, **11,** and **13**) symmetry, calix[6]cryptamides display simple ^{1}H NMR patterns. In the case of **12**, a minor dissymmetric conformer with a *t*Bu group included in the calixarene cavity was observed; however, recording the spectrum at 330 K in a 3:1 mixture of $CDCl_3/CD_3OD$ led to a unique C_3-symmetrical NMR signature (see the Supporting Information). The minor conformer observed in $CDCl_3$ is probably due to a dissymmetrical arrangement of the cap, induced by an intramolecular hydrogen-bonding network between the amido arms. Interestingly, the chirality of the CTV cap of **4** and **12** is transmitted to the calixarene core as shown by the diastereotopy of the $ArCH_2$ and ArH protons (see Figure 1a for **4**). It is worth noting that in the case of the tail-to-tail biscalix[6]arene **13**, both calixarene frameworks are differentiated as attested to by the two sets of signals displayed by the OMe groups and the $ArCH_2$ protons (Figure 1b).

Typical ^{1}H resonances of the calixarene subunits of calix[6]cryptamides **4** and **10–13** at 294 K are summarized in Table 3. From these NMR spectroscopic data, it is possible to deduce the following conformational features:

1) For all the calix[6]cryptamides, the $ArCH_2$ protons of the calixarene moiety display well-defined differentiated signals and, when the spectra are recorded at high temperature (330 K), these resonances are not affected. This clearly indicates an inhibition of the cone–cone inversion of the calixarene core due to the presence of the tripodal covalent cap on the narrow rim.
2) The large $\Delta\delta_{ArH}$ and $\Delta\delta_{tBu}$ values of **4**, **11,** and **13** indicate that their calixarene subunit adopts a flattened cone conformation, whereas a straighter cone is observed for **10** and **12** (see the structures displayed in Schemes 1 and 2).[28]
3) In compounds **4**, **11,** and **13**, which have a calixarene core in a flattened cone conformation, the highfield resonances of the OMe groups is due to their location in the calixarene cavity (Table 3, entries 1, 3, and 5). The methoxy groups of **12** are less directed toward the inside of the cavity since these compounds display a straighter conformation (Table 3, entry 4). In the case of **10**, the close proximity of the aromatic rings of the cap should be responsible, to some extent, for the high-field shift of the methoxy groups (Table 3, entry 2).
4) Compared with all the other calix[6]cryptamides, compound **11** displays a strong downfield resonance for the NHCO protons (Table 3, entry 3). This clearly indicates the presence of stable six-membered intramolecular hydrogen-bonded rings with the oxygen atoms in *ortho* positions (see Scheme 2).

This NMR spectroscopic conformational study shows that, thanks to their covalent tripodal cap, calix[6]cryptamides possess a well-defined cavity ideally preorganized for host–guest applications. Binding studies of charged or neutral species were conducted with each calix[6]cryptamide and results concerning the unique host–guest properties of calix[6]cryptamide **12** are described below.

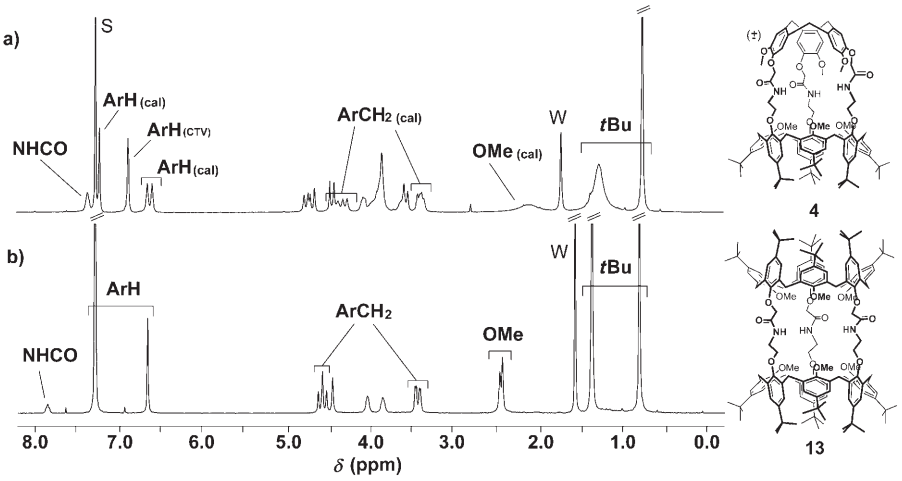


Figure 1. ^{1}H NMR spectra ($CDCl_3$, 294 K) of: a) calix[6]cryptamide **4**; b) calix[6]cryptamide **13**. S: solvent ($CHCl_3$); W: water; "cal" and "CTV" represent the calixarene and cyclotriveratrylene subunits, respectively.

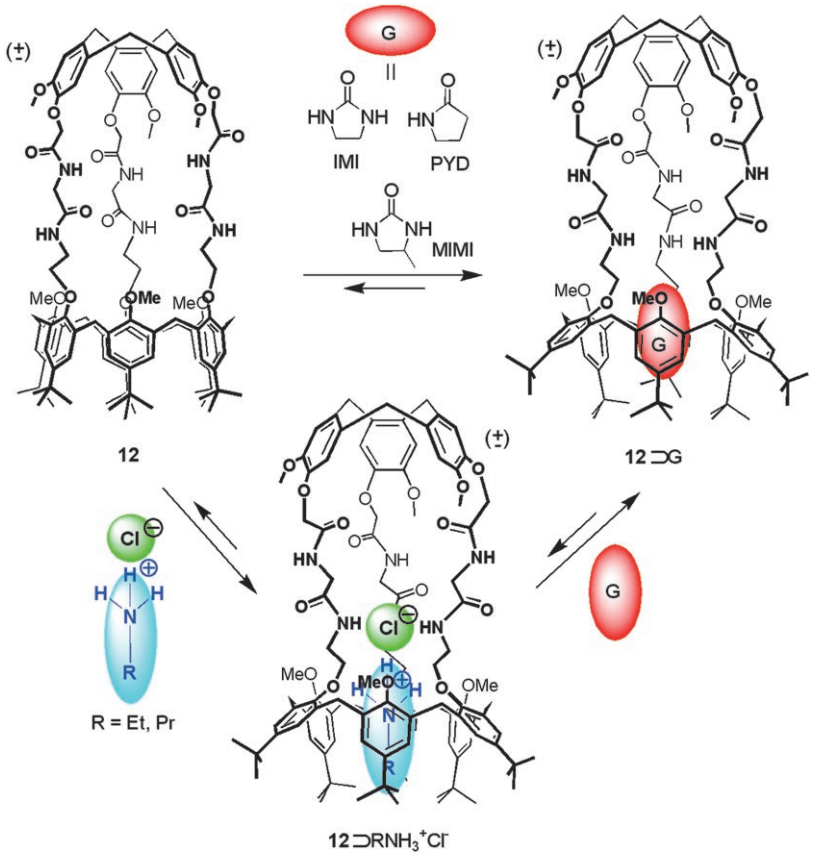
Table 3. Selected chemical shifts [ppm] of the calixarene subunit protons of calix[6]cryptamides **4** and **10–13** ($CDCl_3$, 294 K).

Entry	Compound	δ_{NHCO}	$\Delta\delta_{ArH}$	$\Delta\delta_{tBu}$	$\delta_{ArCH2ax}$	$\delta_{ArCH2eq}$	δ_{OMe}
1	**4**[a]	7.31	0.59	0.52	4.33	3.39	2.10
2	**10**	6.67	0.31	0.36	4.37	3.34	2.24
3	**11**	9.11	0.63	0.63	4.58	3.38	1.66
4	**12**[a,b]	–	0.32	0.35	4.43	3.45	2.60
5	**13**	7.81	0.61/0.62	0.55/0.57	4.55/4.60	3.44/3.45	2.45/2.48

[a] Average value due to the diastereotopy. [b] The ^{1}H NMR spectrum was recorded at 330 K in $CDCl_3/CD_3OD$ (3:1).

Study of the host–guest properties of calix[6]cryptamide 12:First, the host–guest properties of calix[6]cryptamide **12** toward neutral molecules G were evaluated by ^{1}H NMR spectroscopy. No inclusion was observed, even at low temperature (263 K), upon the addition of an excess (> 20 equiv) of EtOH, DMSO, or apolar molecules such as CH_2Cl_2 or Et_2O to a solution of **12** in $CDCl_3$. In contrast, calix[6]-cryptamide **12** was found to be a remarkably efficient host for the *endo*-complexation of amide or urea type guests such as pyrrolidin-2-one (PYD),

imidazolidin-2-one (IMI) or (±)-4-methylimidazolidin-2-one (MIMI)[29] (Scheme 3). Indeed, in each case the addition of a few equivalents (2 to 10 equiv) of these polar molecules (G) led to new C_3-symmetrical NMR spectroscopic patterns (Figure 2a, b for G = IMI at 263 K) displaying high-field signals, which have been assigned to the included guests through NOESY experiments (see the Supporting Information). These NMR data show unambiguously that the new species correspond to the host–guest complexes **12**⊃G. In all cases, the *in* and *out* exchange process of the guest within the cavity of **12** was slower than the NMR spectroscopic timescale. The NMR complexation-induced upfield shifts (CIS, see Table 4, entries 1–3) were quasi-similar to those obtained with the closely related protonated calix[6]azacryptands.[8d,g] Moreover, in the case of IMI,



Scheme 3. Host–guest properties of calix[6]cryptamide **12** toward neutral or charged species in $CDCl_3$.

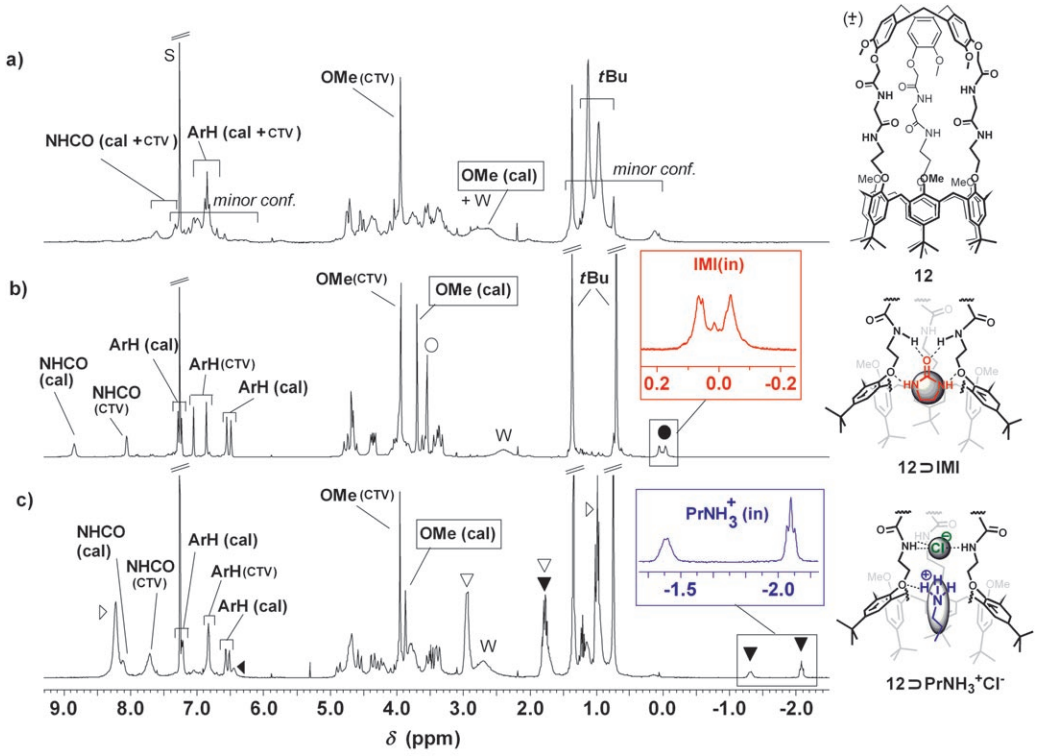
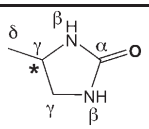
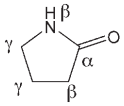
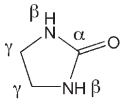
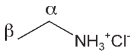
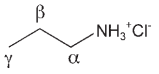


Figure 2. ^{1}H NMR spectra ($CDCl_3$, 263 K): a) **12**; b) **12**+2.6 equiv of IMI; c) **12**+15 equiv of $PrNH_3^+Cl^-$. ○: IMI (free); ●: IMI (in); ▽: $PrNH_3^+$ (free), ▼: $PrNH_3^+$ (in). S: solvent ($CHCl_3$); W: water; "cal" and "CTV" represent the calixarene and cyclotriveratrylene subunits respectively.

Table 4. Complexation-induced upfield shifts (CIS) and association constants (K) of the guests G and $RNH_3^+Cl^-$ in the case of **12**⊃G and **12**⊃$RNH_3^+Cl^-$.

Entry	G or $RNH_3^+Cl^-$	K [M^{-1}][a]	CIS[ppm][b] α	β	γ	δ
1		nd[c]	–	–	$-3.43_{(CH2N)}$[d,e] $-2.71_{(CHN)}$[d] $-3.60_{(CH2N)}$[f,e] $-2.71_{(CHN)}$[f]	-3.16[d] -3.26[f]
2		250	–	$-0.81_{(CH2CO)}$ $+0.74_{(NH)}$	$-3.82_{(CH2)}$ $-3.32_{(CH2N)}$	–
3		12 800	–	–	−3.47	–
4		nd[c]	nd[c]	−2.92	–	–
5		230	−1.20	−3.09	−3.07	–

[a] K calculated at 263 K and defined as: $K=[\mathbf{12}\supset G]/([\mathbf{12}]\times[G])$ or $K=[\mathbf{12}\supset RNH_3^+Cl^-]/([\mathbf{12}]\times[RNH_3^+Cl^-])$; errors estimated ±15%. [b] CIS calculated at 263 K and defined as $\Delta\delta=\delta_{complexed\ G}-\delta_{free\ G}$. [c] nd: not determined. [d] Major diastereomer. [e] Average value of the diastereotopic protons. [f] Minor diastereomer.

NOE effects were observed between the methylene protons of the guest and the ArH protons of the aromatic rings that are directed toward the inside of the calixarene cavity (see the Supporting Information).[30] These results demonstrate that the neutral guests are accommodated in the calixarene cavity and not in the CTV one. Interestingly, the host undergoes a significant conformational rearrangement upon complexation; the calixarene subunit adopts a flattened cone conformation ($\Delta\delta_{ArH}$ and $\Delta\delta_{tBu}\geq 0.6$ ppm) with the methoxy groups expelled from the cavity ($\delta_{OMe}\geq 3.7$ ppm). Such an induced-fit process has already been evidenced with one of the parent calix[6]azacryptands.[8g] A significant downfield shift of the NHCO resonances of the calixarene upon inclusion of the guests G ($\Delta\delta_{NHCO(cal)}\geq 1.2$ ppm, see Figure 2a,b for G = IMI at 263 K) indicates a stabilization of the guests through hydrogen-bonding. In addition, as shown by the positive CIS of the NH of the included PYD (entry 2, Table 4), the guests are probably stabilized through strong hydrogen-bonding interactions with the phenolic oxygen atoms of the host (see structure displayed in Figure 2 for G = IMI). These observations rationalize the specific recognition by receptor **12** of neutral molecules that possess hydrogen-bond donor and acceptor groups such as amides and ureas. In strong contrast with all previous host–guest calix[6]arene-based systems, the polarization of the calixarene cavity through metal-ion complexation[9a] or protonation[9b] is not a requirement for the efficient *endo*-complexation of neutral guests by a calix[6]cryptamide host. In other words, these results constitute the first example of intracavity recognition of neutral molecules by a neutral calix[6]arene-based receptor.

Interestingly, we also found that C_3 symmetrical calix[6]-cryptamide host **12** is able to perform intracavity chiral recognition. In fact, the host–guest study undertaken with (±)-MIMI indicated the formation of two diastereomeric *endo*-complexes. A diastereomeric excess of 44% was determined at 263 K through integration of well-resolved signals corresponding to the included MIMI guest of each diastereomer (Figure 3). This remarkable result constitutes a rare and leading example of enantioselective discrimination in the heart of the cavity of a chiral calixarene based receptor.[5d–g,8d]

In a second set of NMR spectroscopic experiments, the ability of calix[6]cryptamide **12** to accommodate organic charged species was investigated at 263 K. Addition of an excess (up to 15 equiv) of ammonium salts $RNH_3^+Cl^-$ (R = Et or Pr) to a solution of **12** in $CDCl_3$ produced the corresponding *endo*-complexes **12**⊃$RNH_3^+Cl^-$ (Scheme 3) with, in both cases, high-field signals characteristic of the presence of the alkyl chain of the ammonium ions in the heart of the calixarene cavity (Figure 2c for R = Pr).[31] As observed with neutral guests, the *in* and *out* guest exchange was slower than the NMR timescale, and involved an induced fit process with the expulsion of methoxy groups from the calixarene cavity. As expected, it was shown that **12** behaves as a heteroditopic receptor, since in addition to the *endo*-complexation of the ammonium ion RNH_3^+, the simultaneous binding of the chloride counterion by the amide groups of the host was clearly evidenced. Indeed, the resonances of the NHCO protons close to the calixarene subunit experienced a significant downfield shift (>0.5 ppm at 263 K, see Figure 2c for R = Pr) indicating a strong hydrogen-bonding interaction with the counter anion. Moreover, the CIS of the CH_2N protons of the $PrNH_3^+$ guest was found to be abnormally low compared to those at the β or γ position of the ammonium group (Table 4,

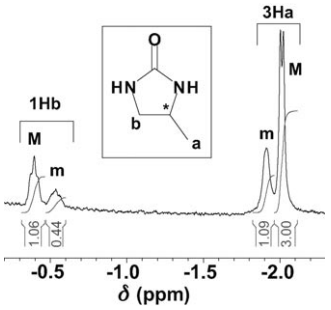


Figure 3. High-field region of the ^1H NMR spectrum ($CDCl_3$, 263 K) of **12**⊃MIMI. "M" and "m" represent "major diastereomer" and "minor diastereomer", respectively.

entry 5). This is in contrast with previously reported host–guest systems involving calix[6]arene-based receptors and ammonium ions, which all display high CIS for protons at the α, β, or γ position of the ammonium group (that is, −2.0 to −3.2 ppm). These NMR data are compatible with the specific coordination of the chloride anion in close proximity to the cationic ammonium group, through a convergent arrangement of hydrogen-bonding NH groups (see Figure 2c). Concerning the ammonium ion, in addition to the electrostatic interaction with its counterion, it is probably stabilized through a combination of CH–π interactions and hydrogen bonding to the ethereal oxygen atoms that have the amido arms, as this has been already observed on several XRD structures of closely related *endo*-complexes.[5f,8b] Interestingly, the use of low-coordinating counterions (picrate and tetrabutylammonium) demonstrated the remarkable cooperative binding of the associated ion pair. When a large excess (about 30 equiv) of $n\mathrm{Bu_4N^+Cl^-}$ was added to a solution of **12** in $CDCl_3$, the NMR spectrum of the receptor remained quasi-unchanged and only a tiny downfield perturbation of its NHCO protons was observed ($\Delta\delta = 0.06$ ppm at 263 K). On the other hand, when the bulkier and less densely charged picrate anion was used in place of the chloride anion, no inclusion of the propylammonium ion was detected even after a prolonged time.[32] Thus, the complexation of the chloride anion can only proceed when an ammonium ion is present in the calixarene cavity and conversely, without Cl^-, host **12** is inefficient at binding the ammonium ion. This remarkable positive cooperativity is probably due to both structural and electronic alterations of the receptor: on one hand each partner of the associated ion pair polarizes the receptor and on the other hand, the anion coordination contributes to the preorganization of the binding site of its counterion through an induced fit process. Indeed, the binding of Cl^- induces the expulsion of the OMe groups from the cavity and brings the oxygen atoms of the ammonium binding site closer. Only a few examples of such metal-free allosteric controls of the complexation of an associated ion-pair salt have been reported.[15,18,33]

Lastly, it was also possible to estimate the association constants (K) of PYD, IMI, and $\mathrm{PrNH_3^+Cl^-}$ for the receptor **12** (Table 4) from the ratio of the peak intensities of the host–guest complex and free partners.[34] A strong preference was found for IMI with respect to the two other guests. This emphasizes the remarkable complementary fit between IMI and the calixarene core in terms of size, shape, and electronic structure.[35] As a result, it was possible to release the ammonium salt quantitatively from the *endo*-complex **12**⊃$\mathrm{PrNH_3^+Cl^-}$ by the addition of a slight excess of IMI, resulting in the formation of the *endo*-complex **12**⊃IMI (Scheme 3).

Conclusion

In summary, we have shown that the peptide-coupling reaction constitutes a valuable strategy for [1+1] macrocyclization reactions between tripodal partners. The obtained C_3- or C_{3v}-symmetrical calix[6]cryptamides exhibit two distinct well-preorganized binding sites in close proximity. As revealed through NMR spectroscopic studies, the chiral calix[6]cryptamide **12** behaves as a heteroditopic receptor with unique host–guest properties, since it can accommodate neutral molecules in the heart of the calixarene cavity, perform intracavity chiral recognition, or cooperatively bind organic-associated ion-paired salts. These results contrast with the host–guest properties of the parent calix[6]azacryptands and constitute a remarkable example of the synergistic combination of a polyamide site and a calix[6]arene structure. Current work is directed toward studying the host–guest properties of this promising class of molecular receptors, with a focus on the design of multitopic anion sensors.

Experimental Section

General procedures: All reactions were performed under an inert atmosphere. CH_2Cl_2 and CH_3NO_2 were distilled over CaH_2 under argon. Toluene and $CHCl_3$ were distilled over P_2O_5 under argon. DMF was distilled over a mixture of $MgSO_4$ and silica gel under argon. Silica gel (230–400 mesh) was used for flash chromatography purifications. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are expressed in ppm. Traces of residual solvent or poly(dimethylsiloxane) were used as internal standard. All the ^1H NMR spectra signals were attributed through 2D NMR analyses (COSY, HMQC, HMBC).

Calix[6]cryptamide 4*Method A*: In a sealed tube, oxalyl chloride (100 μL, 1.153 mmol) was added to CTV derivative **2** (67 mg, 0.115 mmol) in anhydrous CH_2Cl_2 (2 mL). The mixture was heated for 3 h at 50 °C (a clear solution was obtained after about 30 min), then concentrated under reduced pressure yielding CTV derivative **3** as a white solid.

At 0 °C, a solution of crude compound **3** (0.115 mmol) in anhydrous toluene (10 mL) and a solution of calix[6]trisamine **1** (120 mg, 0.105 mmol) and TEA (54 μL, 0.388 mmol) in anhydrous toluene (10 mL) were simultaneously added to toluene (20 mL) over a period of 30 min. The mixture was stirred 15 h at room temperature and the solvent was then removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with an aqueous NaOH solution (1 M, 20 mL). The aqueous layer was then extracted with CH_2Cl_2 (1×10 mL) and the combined organic layers were evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt; 50:50), yielding calix[6]cryptamide **4** as a white solid (25 mg, 15 %).

Method B: Anhydrous $CHCl_3$ (10 mL) and anhydrous CH_3NO_2 (2.5 mL) were added to calix[6]trisamine **1** (100 mg, 0.0874 mmol) and CTV derivative **2** (51 mg, 0.0874 mmol). The mixture was heated at 50 °C until a clear solution was obtained (about 2 h), then a solution of PyBOP (273 mg, 0.524 mmol) and TEA (75 μL, 0.524 mmol) in anhydrous CH_3NO_2 (3 mL) was slowly added at 50 °C (0.5 mL every 30 min). The reaction mixture was stirred for 2 h at 50 °C and then the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL) and washed with H_2O (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (2×5 mL) and the combined organic layers were evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/AcOEt; 50:50), yielding calix[6]cryptamide **4** as a white solid (67 mg, 46 %). M.p.: 210 °C (decomp); ^1H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 27 H; *t*Bu), 1.27 (s_b, 27 H; *t*Bu), 2.10 (s_b, 9 H; OMe_{cal}), 3.38 (d, J = 14 Hz, 3 H; $ArCH_{eqcal}$), 3.41 (d, J = 15 Hz, 3 H; $ArCH_{eqcal}$), 3.57 (d, J = 14 Hz, 3 H; $ArCH_{eqCTV}$), 3.52–3.69 (m, 3 H; OCH_2CH_2N), 3.86 (s, 9 H; OMe_{CTV}), 3.90 (d, J = 8 Hz, 3 H; OCH_2CH_2N), 3.90–4.03 (m, 3 H; OCH_2CH_2N), 4.06 (d, J = 7 Hz, 3 H; OCH_2CH_2N), 4.30 (d, J = 15 Hz, 3 H; $ArCH_{axcal}$), 4.37 (d, J = 15 Hz, 3 H;

ArC$H_{ax\text{cal}}$), 4.45 (d, J=15 Hz, 3H; OCH_2CO), 4.68 (d, J=15 Hz, 3H; OCH_2CO), 4.76 (d, J=14 Hz, 3H; ArC$H_{ax\text{CTV}}$), 6.59 (s, 3H; ArH_{cal}), 6.64 (s, 3H; ArH_{cal}), 6.87 (s, 3H; ArH_{CTV}), 6.88 (s, 3H; ArH_{CTV}), 7.21 (s, 6H; ArH_{cal}), 7.31 ppm (s_b, 3H; NHCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 31.3, 31.6, 34.1, 34.3, 36.3, 40.2, 56.8, 60.7, 70.4, 71.9, 114.7, 117.1, 123.8, 124.0, 127.8, 128.1, 132.2, 132.8, 133.5, 134.3, 146.0(9), 146.1(5), 146.8, 148.9, 151.9, 154.7, 169.5 ppm; IR (KBr): $\tilde{\nu}$=3700–3120, 2961, 1682, 1520, 1464, 1264, 1197 cm^{-1}; elemental analysis calcd (%) for $C_{105}H_{129}N_3O_{15}\cdot 7H_2O$: C 70.09, H 8.01, N 2.34, found: C 69.77, H 7.93, N 2.33.

Calix[6]cryptamide 10: The procedure described for the preparation of **4** (Method B) was applied to calix[6]trisamine **1** (100 mg, 0.0874 mmol) and compound **6** (42 mg, 0.0874 mmol). HBTU was used instead of PyBop and the reaction time was 15 h. The crude mixture was washed with an aqueous NaOH solution (1 M, 20 mL) and the flash chromatography eluent was CH_2Cl_2/acetone (90:10). Calix[6]cryptamide **10** was isolated as a white solid (20 mg, 13%). The yield was calculated taking into account the presence of about 1 equiv of 1,1,3,3-tetramethylurea in the final product (^{1}H NMR estimation). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (s, 27H; *t*Bu), 1.25 (s, 27H; *t*Bu), 2.24 (s, 9H; OMe), 3.34 (d, J=15 Hz, 6H; ArCH_{eq}), 3.72 (s_b, 6H; OCH_2CH_2N), 3.98 (s_b, 6H; OCH_2CH_2N), 4.14 (s, 6H; ArCH_2Ar), 4.37 (d, J=14 Hz, 6H; ArCH_{ax}), 6.67 (s_b, 3H; NHCO), 6.80 (s, 6H; ArH_{cal}), 7.05 (t, J=7 Hz, 3H; ArH_{cap}), 7.11 (s, 6H; ArH_{cal}), 7.20–7.45 ppm (m, 12H; ArH_{cap}); HRMS (ESI-TOF): m/z calcd for $C_{105}H_{123}N_3O_9$ $[M+Na]^+$: 1592.9191; found: 1592.9157.

Calix[6]cryptamide 11: The procedure described for the preparation of **4** (Method B) was applied to calix[6]trisamine **1** (100 mg, 0.0874 mmol) and compound **7** (46 mg, 0.0874 mmol). HBTU was used instead of PyBop and the reaction time was 15 h. The crude mixture was washed with an aqueous NaOH solution (1 M, 15 mL) and the flash chromatography eluent was CH_2Cl_2/acetone (90:10). Calix[6]cryptamide **11** was isolated as a white solid (30 mg, 21%). M.p.: 200°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.73 (s, 27H; *t*Bu), 1.36 (s, 27H; *t*Bu), 1.66 (s, 9H; OMe), 3.38 (d, J=15 Hz, 6H; ArCH_{eq}), 4.12 (s_b, 6H; OCH_2CH_2N), 4.15 (s_b, 6H; OCH_2CH_2N), 4.58 (d, J=15 Hz, 6H; ArCH_{ax}), 5.66 (s, 6H; ArCH_2O), 6.59 (s, 6H; ArH_{cal}), 6.97 (d, J=8 Hz, 3H; ArH_{cap}), 7.07 (t, J=8 Hz, 3H; ArH_{cap}), 7.22 (s, 6H; ArH_{cal}), 7.38 (t, J=8 Hz, 3H; ArH_{cap}), 7.50 (s, 3H; ArH_{cap}), 8.28 (d, J=8 Hz, 3H; ArH_{cap}), 9.11 ppm (s_b, 3H; NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.6, 31.2, 31.8, 34.2, 34.4, 40.7, 60.4, 69.4, 72.1, 112.8, 120.9, 121.7, 121.8, 123.7, 128.2, 132.7, 132.8, 133.2, 133.6, 138.9, 146.3, 146.4, 151.4, 154.5, 156.4, 165.9 ppm; IR (KBr): $\tilde{\nu}$=3700–3115, 2961, 1661, 1599, 1528, 1483, 1298, 1210 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{105}H_{123}N_3O_{12}$ $[M+Na]^+$: 1640.9004; found: 1640.9047.

Calix[6]cryptamide 12: The procedure described for the preparation of **4** (Method B) was applied to calix[6]trisamine **1** (100 mg, 0.0874 mmol) and CTV derivative **8** (66 mg, 0.0874 mmol). HBTU was used instead of PyBop and DMF instead of CH_3NO_2. The crude mixture was washed with an aqueous HCl solution (1 M, 15 mL) and the flash chromatography eluent was CH_2Cl_2/acetone (55:45). After washing with diethyl ether, calix[6]cryptamide **12** was isolated as a white solid (53 mg, 33%). M.p.: 244°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ 3:1, 330 K): δ= 0.94 (s, 27H; *t*Bu), 1.29 (s_b, 27H; *t*Bu), 2.60 (s_b, 9H; OMe_{cal}), 3.32–3.70 (m, 6H; OCH_2CH_2N), 3.44 (d, J=14 Hz, 3H; ArC$H_{eq\text{cal}}$), 3.46 (d, J= 15 Hz, 3H; ArC$H_{eq\text{cal}}$), 3.61 (d, J=14 Hz, 3H; ArC$H_{eq\text{CTV}}$), 3.74–4.02 (m, 12H; NHCH_2CO, OCH_2CH_2N), 3.95 (s, 9H; OMe_{CTV}), 4.42 (d, J=14 Hz, 3H; ArC$H_{ax\text{cal}}$), 4.45 (d, J=15 Hz, 3H; ArC$H_{ax\text{cal}}$), 4.58 (d, J=15 Hz, 3H; OCH_2CO), 4.67 (d, J=15 Hz, 3H; OCH_2CO), 4.77 (d, J=14 Hz, 3H; ArC$H_{ax\text{CTV}}$), 6.79 (s, 3H; ArH_{cal}), 6.80 (s, 3H; ArH_{cal}), 6.96 (s, 3H; ArH_{CTV}), 7.00 (s, 3H; ArH_{CTV}), 7.12 ppm (s, 6H; ArH_{cal}); ^{13}C NMR (75 MHz, $CDCl_3$): complex spectrum due to the presence of two conformations (see the text); IR (KBr): $\tilde{\nu}$=3725–3125, 2960, 1663, 1513, 1481, 1265 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{111}H_{138}N_6O_{18}$ $[M+Na]^+$: 1865.9965; found: 1865.9952.

Calix[6]cryptamide 13: The procedure described for the preparation of **4** (Method B) was applied to calix[6]trisamine **1** (100 mg, 0.0874 mmol) and calix[6]trisacid **9** (104 mg, 0.0874 mmol). The reaction time was 15 h and the flash chromatography eluent was CH_2Cl_2/AcOEt (98:2). Calix[6]-cryptamide **13** was isolated as a white solid (117 mg, 58%). M.p.: 245°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82 (s, 54H; *t*Bu), 1.37 (s, 27H; *t*Bu), 1.39 (s, 27H; *t*Bu), 2.45 (s, 9H; OMe), 2.48 (s, 9H; OMe), 3.44 (d, J=16 Hz, 6H; ArCH_{eq}), 3.45 (d, J=15 Hz, 6H; ArCH_{eq}), 3.86 (s_b, 6H; OCH_2CH_2N), 4.04 (s_b, 6H; OCH_2CH_2N), 4.45 (s, 6H; OCH_2CO), 4.55 (d, J=15 Hz, 6H; ArCH_{ax}), 4.60 (d, J=15 Hz, 6H; ArCH_{ax}), 6.64 (s, 12H; ArH), 7.25 (s, 6H; ArH), 7.26 (s, 6H; ArH), 7.81 ppm (s_b, 3H; NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.3, 30.4, 31.3, 31.4, 31.8, 34.1(7), 34.2(2), 34.4, 34.5, 40.9, 53.6, 60.6(0), 60.6(1), 72.9, 123.9, 124.1, 128.1, 128.3, 132.8, 133.2, 133.3, 133.6, 146.0, 146.1, 146.3, 146.7, 152.5, 152.7, 154.9, 155.1, 169.9 ppm; IR (KBr): $\tilde{\nu}$=3715 to 3090, 2962, 1682, 1481, 1201, 1122 cm^{-1}; elemental analysis calcd (%) for $C_{150}H_{195}N_3O_{15}\cdot 3H_2O$: C 77.18, H 8.68, N 1.80, found: C 77.09, H 8.67, N 1.76.

Host–guest complex 12⊃IMI: IMI (2 equiv) was added to a solution of calix[6]cryptamide **12** (4.0 mg, 2.17 μmol) in $CDCl_3$ (500 μL) leading, after sonication, to the host–guest complex **12⊃IMI** as a unique species. ^{1}H NMR (300 MHz, $CDCl_3$, 263 K): δ=−0.10–0.14 (m, 4H; $CH_{2\text{IMI}in}$), 0.70 (s, 27H; *t*Bu), 1.37 (s, 27H; *t*Bu), 3.34 (d, J=15 Hz, 3H; ArC$H_{eq\text{cal}}$), 3.42 (d, J=15 Hz, 3H; ArC$H_{eq\text{cal}}$), 3.35–3.45 (m, 6H; OCH_2CH_2N), 3.59 (d, J=14 Hz, 3H; ArC$H_{eq\text{CTV}}$), 3.70 (s, 9H; OMe_{cal}), 3.80–4.10 (m, 12H; OCH_2CH_2N + NHCH_2CO), 3.94 (s, 9H; OMe_{CTV}), 4.35 (d, J=15 Hz, 3H; ArC$H_{ax\text{cal}}$), 4.37 (d, J=15 Hz, 3H; ArC$H_{ax\text{cal}}$), 4.60–4.72 (m, 6H; OCH_2CO), 4.77 (d, J=14 Hz, 3H; ArC$H_{ax\text{CTV}}$), 6.49 (s, 3H; ArH_{cal}), 6.55 (s, 3H; ArH_{cal}), 6.86 (s, 3H; ArH_{CTV}), 7.05 (s, 3H; ArH_{CTV}), 7.24 (s, 3H; ArH_{cal}), 7.29 (s, 3H; ArH_{cal}), 8.05 (s_b, 3H; $NHCO_{CTV}$), 8.84 ppm (s_b, 3H; $NHCO_{cal}$).

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[19] It is worth noting that syntheses of calix[6]arenes covalently linked through polyoxyethylene spacers to cyclotriveratrylene subunits have been already described according to a different synthetic strategy; the host–guest properties of the resulting capped compounds were not investigated; see: R. G. Janssen, W. Verboom, J. P. M. van Duynhoven, E. J. J. van Velzen, D. N. Reinhoudt, *Tetrahedron Lett.* **1994**, *35*, 6555–6558.

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[22] HBTU: *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; PyBOP: (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; for recent reviews on such peptide-coupling reagents, see: a) S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447–2467; b) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827–10852.

[23] HBTU and PYBOP have a low solubility in $CHCl_3$.

[24] When the reaction was conducted at room temperature for 2 h, it led to a quasi-similar ^{1}H NMR pattern of the crude mixture; as a result, all the reactions were conducted at 50 °C to be sure that they ran to completion.

[25] The coupling reaction was also performed in presence of imidazolidin-2-one (IMI) as a neutral template molecule; it was shown that this polar molecule can arrange the two tripodal partners **1** and **2** in a [1+1] ion-paired self-assembled structure (see reference [5g]) and additionally, IMI can be encapsulated by calix[6]cryptamides (see below); however, no improvement of the yield was observed when 10 equivalents of IMI were added to the initial reaction mixture (reaction conditions: $CHCl_3$/DMF (4:1), HBTU (6 equiv), TEA (6 equiv), 50 °C).

[26] To our knowledge, only a few examples of triple linkage with a peptide-coupling reagent have been described and in all cases the yields were very low (<15%), see: Z. Zhong, A. Ikeda, S. Shinkai, *J. Am. Chem. Soc.* **1999**, *121*, 11906–11907; R. D. Ionescu, T. Frejd, *Chem. Commun.* **2001**, 1088–1089.

[27] For the synthesis of trisacids **5**–**8**, see reference [5g]. For the synthesis of **9**, see: A. Castani, P. Minari, A. Pochini, R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1991**, 1413–1414.

[28] It is worth noting that, in the case of **4**, some of the signals of its anisole moieties were broad at room temperature (see Figure 1a), but sharpened at low or high temperature.

[29] For the preparation of this compound, see: S. Cortes, H. Kohn, *J. Org. Chem.* **1983**, *48*, 2246–2254.

[30] Moreover, the HMQC spectrum allowed us to determine the methylenic carbon resonance of the included IMI at 38.2 ppm (see the Supporting Information).

[31] Moreover, a 1:1 host–guest stoichiometry was observed through integration of the appropriate resonances.

[32] Such behavior differs significantly from what has been observed with the closely related calix[6]azacryptands, which all display remarkable host–guest properties toward picrate salts of ammonium ions in $CDCl_3$.

[33] For a review on synthetic allosteric receptors, see: L. Kovbasyuk, R. Krämer, *Chem. Rev.* **2004**, *104*, 3161–3187.

[34] Association constants K were calculated from the ^{1}H NMR spectra of **12** in the presence of a slight excess of PYD, IMI or $PrNH_3^+Cl^-$ (see the Supporting Information for the detailed procedure); in all cases, equilibria were reached instantaneously.

[35] Such a calix[6]arene/IMI complementarity has been rationalized by using an XRD structure of a closely related host–guest complex; see reference [5f] for details.

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