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Calix[6]arene-Based Cascade Complexes of Organic Ion Triplets Stable in a Protic Solvent

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Abstract: Herein we report a D_{3h}-symmetric tail-to-tail bis-calix[6]arene **3** featuring two divergent cavities triply connected by ureido linkages. This calix[6]tube was synthesized by a domino Staudinger/aza-Wittig reaction followed by a macrocyclization reaction. This process also afforded a C_{2h}-symmetric isomer that represents a rare example of a self-threaded rotaxane based on calix[6]arene subunits. The binding properties of **3** have been evaluated by NMR studies. Thus, bis-calix[6]arene **3** is able to bind simultaneously two neutral ureido guests through an induced-fit process. The guests are located in the cavities and are recognized through multiple hydrogen-bonding interactions with the ureido bridges. Host **3** can also simultaneously bind multiple ions and is especially efficient for the complexation of organic ion triplets. The anion is recognized through hydrogen-bonding interactions at the ureido binding site and is thus located between the two ammonium ions accommodated in the cavities. The resulting [1+1+2] quaternary complexes represent rare examples of cascade complexes with organic cations. These complexes are unique: 1) They are stable even in a markedly protic solvent, 2) the recognition of the ion triplets proceeds in a cooperative way through an induced-fit process and with a high selectivity, linear cations and doubly charged anions being particularly well recognized, 3) the ions are bound as contact ion triplets thanks to the closeness of the three binding sites, 4) the cationic guests can be exchanged and thus mixed [1+1+1+1] complexes can be obtained, 5) the ureido linkers wrapped around the anion adopt a helical shape and the resulting chirality is sensed by the cations. In other words, bis-calix[6]arene **3** presents a selective inner tunnel in which multiple guests such as organic ion triplets can be aligned in a cooperative way through induced-fit processes.

Keywords: calixarenes · cascade complexes · ion triplets · molecular recognition · supramolecular chemistry

Introduction

There is a growing interest in the design of molecular receptors featuring multiple concave hydrophobic cavities. Indeed, depending on the nature of the concave subunits and on the way they are linked, structures of different topologies such as capsules[1] or organic nanotubes[2] can be obtained. In this context, readily available calixarenes have emerged as very attractive building blocks.[3] Calix[4]arene subunits linked in a 1,3-alternate conformation have led to nanotubes that can be used for cation transport[4] or as nanomaterials for the storage of gases.[5] Head-to-head bis-calix[4]arenes have served as stoppers in rotaxanes[6] and the self-assembly of tetraureido-calix[4]arenes has led to head-to-head dimeric capsules that can be exploited for the elaboration of sophisticated molecular objects.[7] Supramolecular polymers[8] and selective ionophores[9] from bis-calix[4]- or -[5]arenes covalently connected in a tail-to-tail fashion have been reported, whereas head-to-head bis-calix[5]arenes bridged by a ureido spacer have been shown to recognize long-chain ammonium salts.[10] However, so far, only a few examples of double- or multi-calix[6]arenes have been described.[11] This is mainly attributable to the high flexibility of the calix[6]arene subunits, which makes the control of their linkage more difficult.

We have previously shown that calix[6]arene-based heteroditopic receptors decorated with ureido groups on the narrow rim can display versatile host–guest properties towards charged or neutral species. Indeed, calix[6]trisureas[12] and calix[6]crypturea[13] can strongly bind a wide

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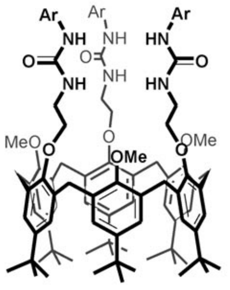
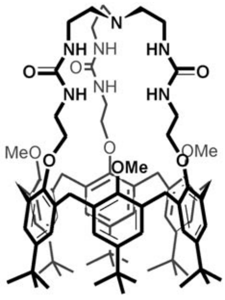
range of anions through induced-fit processes, but can also behave as unique receptors for organic contact ion pairs[14] with a positive cooperativity in the complexation process, the anion acting as an allosteric effector. It has also been shown that the calix[6]crypturea host is able to complex neutral guests and its binding properties can be chemically controlled by an external stimulus (addition of acid or base to the medium). In the course of developing multitopic, versatile calix[6]arene-based receptors, we became interested in the synthesis of a tubular tail-to-tail bis-calix[6]arene possessing a well-defined inner tunnel able to complex simultaneously multiple-charged or neutral species. This calix[6]tube was designed in such a way that it should display two divergent hydrophobic cavities triply connected by short ureido linkages.[15] Indeed, such a heterotritopic receptor was expected to possess unique recognition properties, notably towards tight ion triplets,[16] as a result of the original combination of the three different binding sites in close proximity, that is, the convergent hydrogen-bonding donor ureido groups (anion-binding site) located between the two cavities (ammonium ion binding sites). Furthermore, this calix[6]tube was also particularly attractive because it has been shown that the simultaneous binding of multiple guests in a tubular structure could provide allosteric regulation of the recognition process.[17]



Calix[6]tris-ureas



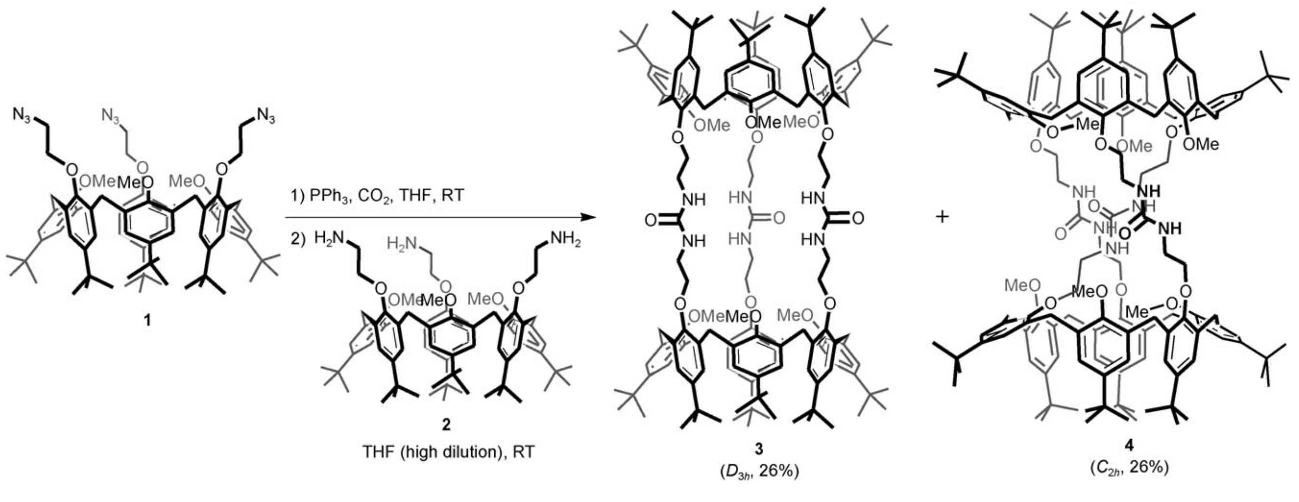
Calix[6]crypturea

Herein we report the synthesis and binding properties of the first tail-to-tail bis-calix[6]arene featuring a tris-ureido recognition site. This calix[6]tube can strongly bind organic ion triplets even in the presence of a protic solvent, leading to rare examples of metal-free cascade complexes.[18]

Results and Discussion

Synthesis and characterization of the calix[6]tube: The desired tail-to-tail bis-calix[6]arene **3** was obtained from the known[19] calix[6]tris-azide **1** and calix[6]tris-amine **2** by a domino Staudinger/aza-Wittig reaction followed by a [1+1] macrocyclization step. Indeed, the reaction of calix[6]tris-azide **1** with PPh_3/CO_2 led in situ to the reactive intermediate calix[6]tris-isocyanate, which immediately reacted with calix[6]tris-amine **2** under high dilution conditions. Purification of the crude mixture by flash chromatography led to a 1:1 mixture of the D_{3h}-symmetric bis-calix[6]arene **3** and its unexpected C_{2h}-symmetric isomer **4** (Scheme 1).[20] These two compounds were easily separated as a result of their highly different solubility in EtOH. Thus, both **3** and **4** were obtained in an overall yield of 26 % from **1**. The formation of these two isomers originates from the existence of two possible patterns for the formation of the macrocycle after the first two linkages (i.e., *syn* and *anti* patterns[21]). Note that the tail-to-tail bis-calix[6]arene **4** represents a rare example of a self-threaded rotaxane based on calix[6]arene subunits.[22]

The tail-to-tail bis-calix[6]arenes **3** and **4** were characterized by NMR spectroscopy in $CDCl_3$. The isomer **4** displays a complex ^1H NMR pattern in agreement with a C_{2h}-symmetrical structure with 1) one ureido linkage threading through the macrocycle formed by the other two and 2) both calixarene cavities filled by an inward methoxy group ($\delta_{OMe} = 1.76$ ppm compared with $\delta_{OMe} = 3.72$ ppm for the outward OMe groups; Scheme 1).[23] The bis-calix[6]arene **3** exhibits a broad NMR signature that can be ascribed



Scheme 1. Synthesis of D_{3h}- and C_{2h}-symmetric tail-to-tail bis-calix[6]arenes **3** and **4**.

to the intramolecular self-association of the ureido groups.[24] However, a well-resolved NMR pattern indicative of a D_{3h}-symmetric structure was observed at 330 K, which confirms the tubular architecture of this compound.[23] At this high temperature (*T*), the signals of the calixarene subunits of **3** are characteristic of an averaged straight cone conformation ($\Delta\delta_{tBu} = 0.14$ ppm, $\delta_{OMe} = 3.02$ ppm).[25] In the presence of a protic solvent [i.e., $CD_3OD/CDCl_3$ (3:1)],[26] the NH ureido protons of **3** experience a downfield shift ($\delta_{NH} = 6.49$ vs. 6.13 ppm in $CDCl_3$) and its calixarene subunits adopt a flattened averaged cone conformation with the hydrophobic cavity filled by the OMe groups ($\delta_{OMe} = 2.30$ ppm; Figure 1a, Scheme 1).

Neutral molecule recognition: The binding properties of the bis-calix[6]arenes **3** and **4** were investigated by NMR spectroscopy. As expected given its self-threaded structure, **4** did not exhibit any host properties towards either neutral or charged guests (anions or ion pairs). In the case of **3**, no evidence was obtained for the *endo* complexation of either small alcohols (i.e., MeOH, EtOH), amides (i.e., DMF), or apolar molecules (i.e., CH_2Cl_2) in $CDCl_3$. However, upon the progressive addition of imidazolidin-2-one (Imi), increasing NMR signals corresponding to a new D_{3h}-symmetric species were observed. When the titration was performed at low *T* (263 K), a highfield signal at 0.20 ppm showing the intracavity inclusion of Imi was clearly apparent.[23] Integration of this highfield signal indicated a 1:2 host–guest association, which attests to the formation of the ternary complex[$\mathbf{3}\supset(\text{Imi})_2$ (Scheme 2).[27] Over the course of the titration, slight shifts of the signals of the free host **3** were observed in addition to the separate peaks corresponding to[$\mathbf{3}\supset(\text{Imi})_2$. These shifts are likely due to the formation of the intermediate complex $\mathbf{3}\supset$Imi experiencing fast host–guest exchange on the NMR timescale with **3**. The complex $\mathbf{3}\supset(\text{Imi})_2$ displays a flattened cone conformation with the OMe groups expelled from the cavity ($\delta_{OMe} = 3.92$ ppm). The complexation-induced shift (CIS) of the methylenic protons of the included Imi ($\text{CIS}_{CH2} = -3.34$ ppm) indicates a positioning of this guest in the heart of the cavity.[28] Thus, host **3** is able to complex simultaneously two neutral ureido guests, one in each cavity, through an induced-fit process that ejects the OMe groups from the cavities. The overall binding constant β_2 for the formation of $\mathbf{3}\supset(\text{Imi})_2$ was estimated to be $>1.1\times10^4\,\text{M}^{-2}$ (see the Experimental Section). The high selectivity for Imi can be rationalized by a four hydrogen-bond recognition

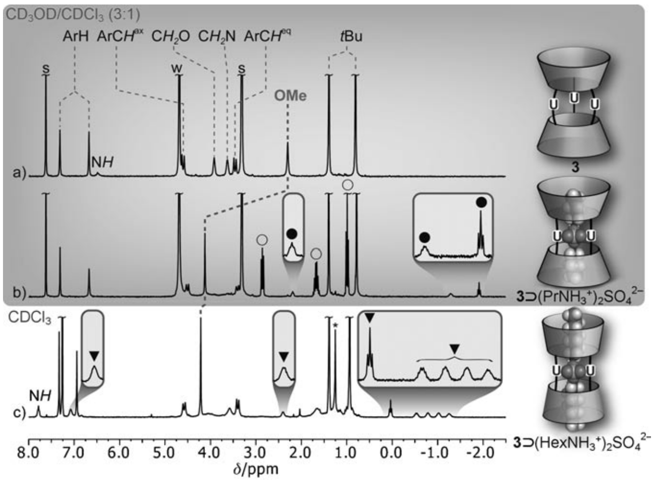
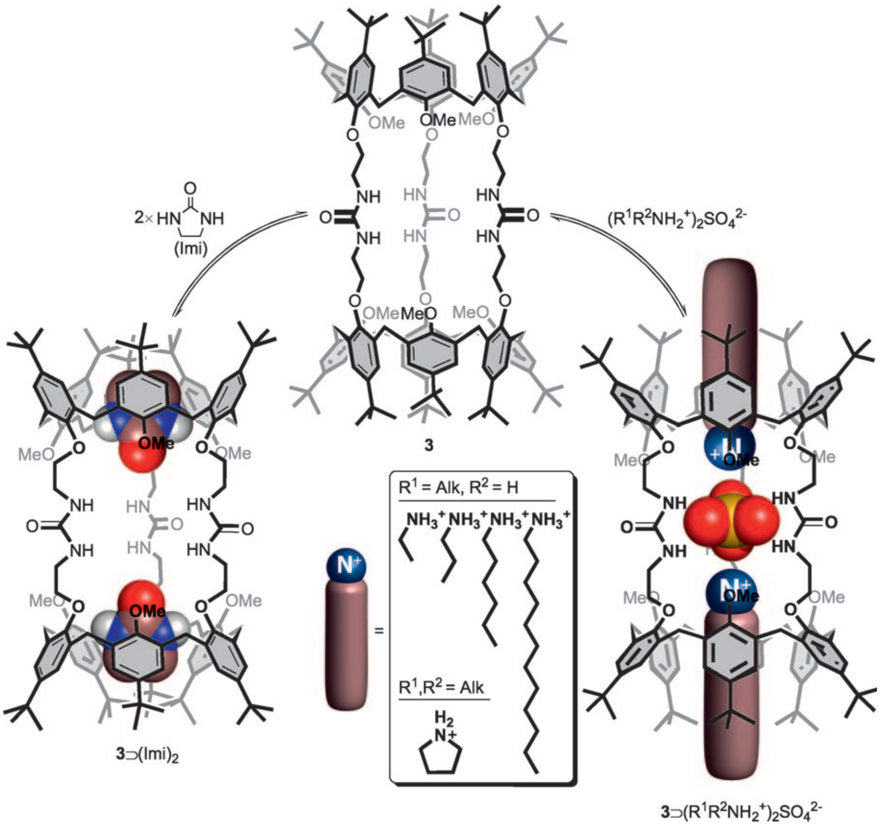


Figure 1. ^{1}H NMR spectra (300 MHz, 298 K) of a) **3** in $CD_3OD/CDCl_3$ (3:1); b) $\mathbf{3}\supset(PrNH_3^+)_2SO_4^{2-}$ in $CD_3OD/CDCl_3$ (3:1) obtained after the addition of 6 equiv of $(PrNH_3^+)_2SO_4^{2-}$ to **3**; c) $\mathbf{3}\supset(HexNH_3^+)_2SO_4^{2-}$ in $CDCl_3$ obtained after extraction of 1 equiv of $(HexNH_3^+)_2SO_4^{2-}$ by **3**. ●: $PrNH_3^+$ in; ○: $PrNH_3^+$ out; ▼: $HexNH_3^+$ in; W: water; S: residual solvent; *: residual grease.



Scheme 2. Host–guest properties of the calix[6]tube **3** towards neutral guests and ion triplets.

process between each guest and its calixarene subunit, as well as CH–π interactions between the methylenic protons of Imi and the aromatic walls of the host. Such an efficient mode of recognition for Imi has already been described for closely related calix[6]arene-based systems[29] and has been rationalized by an X-ray structure analysis.[30] Finally, upon the addition of 2% of CD_3OD, only 25% of the complex $\mathbf{3}\supset(\mathrm{Imi})_2$ survived. For comparison, the parent calix[6]crypturea receptor was able to complex Imi in pure CD_3OD, whereas calix[6]tris-ureas were insensitive to neutral guests. The intermediate host–guest behavior of **3** is likely due to the intermediate preorganization of its tris-ureido binding site in terms of flexibility.

Anion recognition: The progressive addition of tetra-*n*-butylammonium salts of various anions (i.e., TBA^+X^- with $X^- = Cl^-$, Br^-, I^-, CN^-, N_3^-, HSO_4^-, SO_4^{2-}, AcO^-, or NO_3^-) to **3** in $CDCl_3$ in some cases (i.e., $X^- = Cl^-$ and AcO^-) only caused tiny shifts of the signals and in particular of the ureido NH protons. The association constants K_a for all these anions were estimated by ^{1}H NMR titrations to be $< 1\,\mathrm{M}^{-1}$.[31] Again, if compared with the calix[6]crypturea receptor, the poor ability of **3** to coordinate anions can be rationalized by the large size of the macrocycles formed by the ureido linkages. Indeed, this structural difference results in a much greater flexibility of the tris-ureido recognition site as well as a lack of the chelate effect. Concerning the parent calix[6]tris-ureas, the higher acidity of their ureido protons contributes largely to their better efficiency in the recognition of anions.

Ion-triplet recognition: It was found that calix[6]tube **3** behaves as a remarkable receptor for the simultaneous complexation of ammonium ions and anions even in a markedly protic solvent. Indeed, the addition of a few equivalents of an ammonium sulfate salt $(RNH_3^+)_2SO_4^{2-}$ (with R = Et or Pr) to **3** in $CD_3OD/CDCl_3$ (3:1) led quantitatively to the D_{3h}-symmetric complex $\mathbf{3}\supset(RNH_3^+)_2SO_4^{2-}$ (Scheme 2).[23] Upon the progressive addition of the ammonium salts, only signals belonging to **3** and the [1+1+2] quaternary complexes were observed, which suggests a much lower stability of the intermediate complexes.[23] In both cases, the quaternary complexes were characterized by highfield signals (i.e., −1.5 ppm) corresponding to the alkyl chain of the ammonium ion deeply included inside the cavity. The CISs of the included ammonium ions are displayed in Table 1. As a representative example, the ^{1}H NMR spectrum of $\mathbf{3}\supset(PrNH_3^+)_2SO_4^{2-}$ is displayed in Figure 1b. The "normal" chemical shifts of the OMe of both complexes ($\delta_{OMe} >$ 4 ppm) reveal an induced-fit recognition process, the alternating aromatic units having interchanged their in and out positions upon complexation (see the structures depicted in Scheme 2).

Note that the resonances of the methylenic protons of the ureido bridges are very broad and also a variable-temperature NMR study undertaken with $\mathbf{3}\supset(PrNH_3^+)_2SO_4^{2-}$ showed a coalescence phenomenon for other resonances of the complex in the 293–263 K temperature range (Figure 2). At 243 K, a large splitting of the ArH and CH_2 resonances of the host was observed together with a splitting of the methylenic resonances of the guest.[23] Similarly to previous results,[32] this phenomenon can be attributed to the freezing of the helical twisting of the three ureido linkages. Indeed, the host–guest complex exists as a pair of D_3-symmetric helical enantiomers that are in conformational equilibrium (see

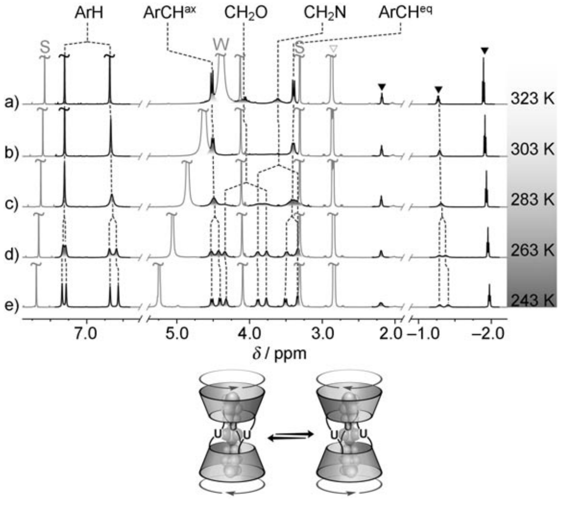


Figure 2. Variable-temperature ^{1}H NMR spectra (600 MHz) of $\mathbf{3}\supset(PrNH_3^+)_2SO_4^{2-}$ in $CD_3OD/CDCl_3$ (3:1) at a) 323, b) 303, c) 283, d) 263, and e) 243 K. ▼: $PrNH_3^+$ in; ▽: $PrNH_3^+$ out; S: Solvent; W: Water.

Table 1. Complexation-induced shifts (CISs) and cumulative formation constants β_3 of the ion-triplets in the case of $\mathbf{3}\supset(RNH_3^+)_2X^{n-}$ or $\mathbf{3}\supset(PyrNH_2^+)_2SO_4^{2-}$.

Guest ion-triplet	CIS [ppm][a]								β_3 [M^{-3}] in $CD_3OD/CDCl_3$ (v/v)[b]		
	α	β	γ	δ	ε	ζ	η	θ to μ	0:1	1:10	3:1
$(EtNH_3^+)_2SO_4^{2-}$	−1.13[c]	−3.02	–	–	–	–		–	$>3.2\times10^{13}$	$>3.4\times10^{13}$	9.5×10^{9}
$(PrNH_3^+)_2SO_4^{2-}$	−0.67[c]	−2.97	−2.90	–	–	–		–	$>3.2\times10^{13}$	$>1.2\times10^{14}$	1.3×10^{9}
$(PrNH_3^+)_2Cl^-$	−0.57[d]	−2.85	−3.03	–	–	–		–	$>1.5\times10^{9}$	4.6×10^{4}	nd[e]
$(HexNH_3^+)_2SO_4^{2-}$	−0.59[d]	−2.79	−2.65	−2.10	−1.85	−0.84		–	$>9.5\times10^{12}$	no inclusion	nd[e]
$(DodecNH_3^+)_2SO_4^{2-}$	−0.60[d]	−2.79	−2.50	−2.06	−1.70	−0.84	−0.50	< −0.45	$>2.4\times10^{12}$	no inclusion	nd[e]
$(PyrNH_2^+)_2SO_4^{2-}$	−1.34[d]	−3.04	–	–	–	–		–	$>1.0\times10^{10}$	67	nd[e]

[a] CIS is defined as $\Delta\delta = \delta$(complexed ammonium ion)$-\delta$(free ammonium ion). [b] β_3 determined at 298 K by integration of the different species in equilibrium. β_3 is defined as $[\mathbf{3}\supset(RNH_3^+)_2X^{n-}]/([\mathbf{3}][RNH_3^+]^2[X^{n-}])$ or $[\mathbf{3}\supset(PyrNH_2^+)_2SO_4^{2-}]/([\mathbf{3}][PyrNH_2^+]^2[SO_4^{2-}])$ in the case of $(PyrNH_2^+)_2SO_4^{2-}$. Initial host concentration $[\mathbf{3}]_i = 1.7–2.5\times10^{-3}\,\mathrm{M}$; error estimated to be ±15%. [c] CIS calculated at 298 K in $CD_3OD/CDCl_3$ (3:1). [d] CIS calculated at 298 K in $CDCl_3$. [e] Not determined.

the structures depicted in Figure 2). At low temperature, this equilibrium is slow on the NMR timescale and thus the diastereotopic aromatic and methylenic protons of the whole edifice are differentiated. In other words, the guest ammonium ions sense the helical chirality of the host. Note that an enantiomerization barrier of 57.5(1) kJ mol^{-1} was determined for the coalescence processes.[23]

Altogether, these results show that calix[6]tube **3** can act as a heterotritopic receptor able to recognize efficiently a contact ion triplet through a cooperative three-step binding process. Remarkably, high cumulative constants β_3 were found for the formation of the two complexes **3**$\supset$(RNH$_3^+$)$_2$SO$_4^{2-}$ (with R = Et or Pr; Table 1). By reducing the amount of CD$_3$OD [i.e., CD$_3$OD/CDCl$_3$ (1:10)], it was possible to observe the complexation of the pyrrolidinium sulfate salt (PyrNH$_2^+$)$_2$SO$_4^{2-}$, but with a low cumulative formation constant (Table 1). However, in this solvent mixture, the calix[6]tube **3** was not sensitive to the addition of larger ammonium salts, that is, (HexNH$_3^+$)$_2$SO$_4^{2-}$ or (DodecNH$_3^+$)$_2$SO$_4^{2-}$. Such selectivity for the smaller ammonium salts can be rationalized by the important steric hindrance generated by the introverted *t*Bu groups closing the cavities. Very interestingly, when propylammonium picrate (PrNH$_3^+$Pic$^-$, 2 equiv) and several TBA$^+$X$^-$ salts of monocharged anions (X$^-$ = F$^-$, Cl$^-$, AcO$^-$, or NO$_3^-$, ca. 1.5 equiv) were subsequently added to **3**, only a trace of PrNH$_3^+$ was detected in the calixarene cavity.[33] However, the subsequent addition of 1 equiv of (TBA$^+$)$_2$SO$_4^{2-}$ to this complex mixture gave rise to the selective and quasi-quantitative formation of the quaternary complex **3**$\supset$(PrNH$_3^+$)$_2$SO$_4^{2-}$.[23] Thus, in a protic solvent, the complexation of the sulfate anion can only proceed efficiently when ammonium ions are present in the calixarene cavities (see above) and conversely, without SO$_4^{2-}$, host **3** is inefficient at binding the two ammonium ions. This allosterically coupled binding process is made possible by the unique structure of **3** that 1) is sufficiently flexible to allow induced-fit processes and 2) displays two hydrophobic cavities and a recognition site for anions in close proximity, which favors a high cooperativity. Indeed, the closeness of the three binding sites is crucial in the recognition process because it avoids the unfavorable separation of the complexed ions.

These results represent a rare example of cascade complexes involving organic cations in place of classical metal ions.[34] Moreover, there is a big difference between **3** and the previously described cascade receptors. These latter usually coordinate two metal ions and then the anionic species form a bridge between the metal centers. Thus, whereas these dimetallic receptors are highly efficient for the recognition of anions in water, in contrast to **3**, they do not display a specific binding site for anions in the absence of the cations.

The possibility of making mixed [1+1+1+1] quaternary complexes such as **3**$\supset$(EtNH$_3^+$)(PrNH$_3^+$)SO$_4^{2-}$ was also studied through a competitive NMR experiment between (EtNH$_3^+$)$_2$SO$_4^{2-}$ and (PrNH$_3^+$)$_2$SO$_4^{2-}$. First, the complex **3**$\supset$(PrNH$_3^+$)$_2$SO$_4^{2-}$ was prepared by the addition of an excess (2 equiv) of (PrNH$_3^+$)$_2$SO$_4^{2-}$ to **3** in CD$_3$OD/CDCl$_3$ (3:1). Upon the subsequent and progressive addition of (EtNH$_3^+$)$_2$SO$_4^{2-}$, guest-exchange occurred as evidenced by increasing signals corresponding to the cascade complexes **3**$\supset$(EtNH$_3^+$)(PrNH$_3^+$)SO$_4^{2-}$ and **3**$\supset$(EtNH$_3^+$)$_2$SO$_4^{2-}$.[23] Owing to the overlapping of signals, it was not possible to determine precisely the proportions of the different species, but neither of the two different types of quaternary complexes (i.e., [1+1+1+1] vs. [1+1+2]) seemed to be favored. Nonetheless, this result shows that the included ammonium ions can be displaced by others and mixed [1+1+1+1] cascade complexes can be easily obtained.

Interestingly, despite the insolubility of ammonium sulfate salts in pure CDCl$_3$, cascade complexes of various ammonium sulfate salts as large as (PyrNH$_2^+$)$_2$SO$_4^{2-}$, (HexNH$_3^+$)$_2$SO$_4^{2-}$, or (DodecNH$_3^+$)$_2$SO$_4^{2-}$ were identified in this solvent (Figure 1c).[23] In all cases, the CISs indicate a deep inclusion of the ammonium ions inside the cavity (Table 1) and the signals of the NH$_3^+$ protons of these bound ions are clearly apparent at around 7 ppm. Moreover, the significant downfield shifts of the ureido NH protons ($\Delta\delta > 1.4$ ppm) are in good agreement with the coordination of SO$_4^{2-}$ through hydrogen-bonding interactions with the ureido linkages. In the case of the primary ammonium ions, prolonged heating (> 6 h) was necessary for the complexation to be completed and no trace of the free salt was observed in solution.[35] These highly efficient solid–liquid extractions denote a strong binding process. In addition, it is known that, with *p*-*t*Bu-calix[6]arene-based receptors, the complexation of guests possessing an alkyl chain longer than propyl can only be observed in the case of host–guest systems that display very high association constants. Indeed, in all cases, remarkably high estimated cumulative formation constants β_3 were found, even for the dodecylammonium ion, the alkyl chain of which protrudes out of the cavity (Table 1). Note that the complexation of the sulfate salt prepared from 2-(3,4-dimethoxyphenyl)ethylamine was not observed, which indicates a high selectivity for linear ammonium ions.

Finally, the complexation of an ammonium ion associated with a monocharged anion, that is, PrNH$_3^+$Cl$^-$, was also studied by NMR spectroscopy. In CDCl$_3$, signals corresponding to the intermediate C_{3v}-symmetric ternary complex **3**$\supset$PrNH$_3^+$Cl$^-$ were clearly apparent upon the addition of 0.5 equiv of PrNH$_3^+$Cl$^-$ to **3**.[23] The two calixarene subunits of this ternary complex exhibit separate signals, one of the calixarene cavities being filled by the methoxy groups ($\delta_{\mathrm{OMe}} = 2.46$ ppm), the other hosting the ammonium ion with CISs slightly different to those of the quaternary complex **3**$\supset$(PrNH$_3^+$)$_2$Cl$^-$.[23] This latter was obtained quantitatively through the further addition of an excess (4 equiv) of PrNH$_3^+$Cl$^-$. Note that a similar NMR signature was obtained quantitatively on addition of 1 equiv of PrNH$_3^+$Cl$^-$ and 1 equiv of PrNH$_3^+$Pic$^-$ to **3**, which indicates the presence of only one Cl$^-$ bound to the tris-ureido binding site.[23] Interestingly, notable differences can be observed in the NMR spectra of the two cascade complexes **3**$\supset$(PrNH$_3^+$)$_2$Cl$^-$ and **3**$\supset$(PrNH$_3^+$)$_2$SO$_4^{2-}$ in CDCl$_3$. In particular, the protons of the ureido groups and of the included ammonium ions (only those that are close to the anion, that is, $\mathrm{CH_2CH_2NH_3^+}$ protons) display different resonances (Table 1).[23] Furthermore, the signals of the ureido bridges are much broader in the case of $\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{SO_4^{2-}}$. Again, all these NMR data confirm the coordination of the anion to the tris-ureido recognition site and the high proximity between the anion and the ammonium ions accommodated inside the cavity. A strong cumulative formation constant was estimated for $\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{Cl^-}$, but, as one might have expected, in the presence of a small amount of a protic solvent [$\mathrm{CD_3OD/CDCl_3}$ (1:10)], the formation of this quaternary complex was less favorable although still observed (Table 1). Interestingly, a variable-temperature NMR study in $\mathrm{CDCl_3}$ undertaken in the presence of 1 equiv of $\mathrm{PrNH_3^+Cl^-}$ showed that the equilibrium was displaced in favor of the ternary complex $\mathbf{3}\supset\mathrm{PrNH_3^+Cl^-}$ when the temperature was lowered.[23] In addition, ^{1}H NMR competitive binding studies between $\mathrm{Cl^-}$ and $\mathrm{SO_4^{2-}}$ were performed either in $\mathrm{CDCl_3}$ or $\mathrm{CD_3OD/CDCl_3}$ (1:10) to estimate the importance of the charge of the anion on complex stability. Thus, in both cases, only the complex $\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{SO_4^{2-}}$ was detected upon the addition of 1 equiv of $(\mathrm{PrNH_3^+})_2\mathrm{SO_4^{2-}}$ and a large excess of $\mathrm{TBA^+Cl^-}$ (>110 equiv) to **3**, thereby showing a remarkable selectivity for the bicharged anion ($K_{\mathrm{SO_4^{2-}/Cl^-}} > 10^4$ in both cases).[23] All in all, these results show that the formation of cascade complexes from calix[6]tube **3** is also possible with monocharged anions, however, in comparison with the sulfate anion, the required ion-pair dissociation and the weaker electrostatic interactions make this process more difficult, especially in a protic solvent.

Conclusion

The straightforward synthesis of the first tail-to-tail bis-calix[6]arene **3** that incorporates two divergent hydrophobic cavities linked by ureido groups has been achieved. Although the *endo* complexation of neutral guests has been evidenced, it has been shown that this heterotritopic receptor is especially efficient for the cooperative binding of organic ion triplets. The recognition process takes advantage of the flexibility of the calix[6]arene platform and leads to a high selectivity for linear ammonium ions associated with doubly charged anions. The remarkable robustness of the cascade complexes in the presence of a protic solvent stresses the importance of the proximity of the three binding sites. Indeed, the charged guests are accommodated as tight ion triplets and thus the highly energetically unfavorable dissociation of the ions is avoided. Therefore this work illustrates well the synergistic effect of combining two hydrophobic pockets connected by a recognition site. Another remarkable feature of these cascade complexes is their chirality due to the helical arrangement of the ureido linkers that surround the anion. This helicity is efficiently transmitted to the calixarene cavities, which hence provide a chiral environment for the guest ammonium ions. We do believe that these examples of cascade complexes, made of organic cations strongly bound in two divergent cavities, open new perspectives for the elaboration of sophisticated self-assembled systems such as supramolecular polymers. Further research in our laboratory will be directed towards the complexation of other dicharged anions, quaternary or ditopic ammonium ions, as well as towards the grafting of water-soluble groups onto the calixtube.

Experimental Section

General: All reactions were performed under an inert atmosphere. THF was distilled over Na/benzophenone. Silica gel (230–400 mesh) was used for flash chromatography purification. ^{1}H NMR spectra were recorded at 600, 400, or 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts are expressed in ppm. Traces of residual solvent were used as the internal standard and $\mathrm{CDCl_3}$ was filtered through a short column of basic alumina to remove traces of HCl. Most of the ^{1}H NMR signals were assigned on the basis of 2D NMR analyses (COSY, HSQC, HMBC). Mass spectra were recorded with an ESI-MS apparatus equipped with an ion-trap using the following settings: Flow rate: 10 μL min^{-1}, spray voltage: 5 kV, capillary temperature: 160 °C, capillary voltage: −15 V, tube lens offset voltage: −30 V. The calix[6]tris-azide **1** and calix[6]tris-amine **2** were prepared as previously described.[19] NMR spectra were recorded on Bruker Avance 300 MHz and Varian Unity 600 MHz spectrometers, IR spectra were recorded on a Bruker IFS 25 spectrometer, and HRMS spectra were recorded with a Water Q-TOF 2 spectrometer (at the University Mons-Hainaut, Belgium).

Bis-calix[6]arenes 3 and 4: Triphenylphosphine (322 mg, 1.23 mmol) as added to a solution of calix[6]tris-azide **1** (250 mg, 0.20 mmol) in anhydrous THF (5 mL). Then $\mathrm{CO_2}$ was bubbled into the solution for 2 min and the reaction mixture was stirred at room temperature under $\mathrm{CO_2}$ overnight. The reaction medium was drained with argon, placed in a syringe and the volume was adjusted to 10 mL with anhydrous THF. A second syringe containing calix[6]tris-amine **2** (234 mg, 0.20 mmol) in anhydrous THF (10 mL) was prepared. The two solutions were simultaneously added dropwise through a syringe pump (0.793 mL h^{-1}) to anhydrous THF (100 mL) and the resulting solution was stirred at room temperature overnight. After evaporation of the solvent to remove $\mathrm{Ph_3PO}$, the resulting solid was suspended in a 1:1 ethanol/water mixture (150 mL), sonicated for 20 min, heated at reflux for 20 min, filtered, and dried under vacuum. Flash chromatography ($\mathrm{CH_2Cl_2}$/AcOEt, 80:20) of the resulting solid afforded a white solid corresponding to a 1:1 mixture of **3** and **4**. This solid was suspended in EtOH, sonicated, and centrifuged. The white solid was dried under vacuum to afford **3** (124 mg, 26 %) and the supernatant was evaporated to dryness to give **4** (126 mg, 26 %) as a white solid.

Compound 3: M.p. ca. 260 °C (dec.); IR (KBr): $\tilde{\nu}$= 3400, 1659 cm^{-1}; ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$, 298 K): δ=1.00 (s, 54 H, *t*Bu), 1.14 (s, 54 H, *t*Bu), 2.95 (br s, 18 H, $\mathrm{OCH_3}$), 3.37 (d, J=15 Hz, 12 H, $\mathrm{ArCH_2}$), 3.59 (br s, 12 H, $\mathrm{CH_2N}$), 3.71 (br s, 12 H, $\mathrm{OCH_2}$), 4.50 (d, J=15 Hz, 12 H, $\mathrm{ArCH_2}$), 6.09 (br s, 6 H, NH), 6.83 (s, 12 H, ArH), 7.02 ppm (s, 12 H, ArH); ^{1}H NMR (300 MHz, $\mathrm{CDCl_3/CD_3OD}$, 3:1, 298 K): δ= 0.60 (s, 54 H, *t*Bu), 1.19 (s, 54 H, *t*Bu), 2.08 (s, 18 H, $\mathrm{OCH_3}$), 3.25 (d, J=15 Hz, 12 H, $\mathrm{ArCH_2}$), 3.41 (br s, 12 H, $\mathrm{CH_2N}$), 3.71 (br s, 12 H, $\mathrm{OCH_2}$), 4.39 (d, J=15 Hz, 12 H, $\mathrm{ArCH_2}$), 6.17 (br s, 6 H, NH), 6.45 (s, 12 H, ArH), 7.10 ppm (s, 12 H, ArH); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3/CD_3OD}$, 3:1, 298 K): δ=29.2, 30.8, 31.2, 33.7, 34.0, 40.3, 60.0, 72.3, 123.4, 128.0, 132.7, 133.0, 145.9, 146.3, 149.2, 151.4, 153.7 ppm;[36] HRMS: calcd for $\mathrm{C_{153}H_{204}N_6O_{15}Na}$: 2388.5282; found: 2388.5332.

Compound 4: M.p. ca. 260 °C (dec.); IR (KBr): $\tilde{\nu}$=3382, 1659 cm^{-1}; ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$, 298 K): δ=0.75 (s, 36 H, *t*Bu), 1.04 (s, 36 H, *t*Bu), 1.34 (s, 18 H, *t*Bu), 1.39 (s, 18 H, *t*Bu), 1.76 (s, 6 H, $\mathrm{OCH_3}$), 3.11 (d, J=15 Hz, 4 H, $\mathrm{ArCH_2}$), 3.20–3.32 (m, 8 H, $\mathrm{ArCH_2+OCH_2}$), 3.37 (d, J=

15 Hz, 4H, ArCH$_2$), 3.44 (brs, 4H, CH$_2$N), 3.72 (brs, 20H, OCH$_3$+CH$_2$N), 3.95 (brs, 4H, OCH$_2$), 4.03 (brs, 4H, OCH$_2$), 4.28 (d, J=15 Hz, 4H, ArCH$_2$), 4.39 (d, J=15 Hz, 4H, ArCH$_2$), 4.47 (d, J=13 Hz, 4H, ArCH$_2$), 5.27 (brs, 2H, NH), 6.42 (brs, 4H, ArH), 6.51 (brs, 4H, NH), 6.75 (s, 4H, ArH), 6.81 (s, 4H, ArH), 7.06 (s, 4H, ArH), 7.09 (s, 4H, ArH), 7.10 ppm (s, 4H, ArH); HRMS: calcd for $C_{153}H_{204}N_6O_{15}Na$: 2388.5282; found: 2388.5264.

Estimation of the cumulative formation constant β_2 of 3 towards Imi in $CDCl_3$: The cumulative formation constant β_2 in $CDCl_3$ was estimated according to the following procedure: Suitable aliquots of a solution of Imi were added to a solution of receptor **3** (2.5×10^{-3} M) in such a way that the corresponding ^{1}H NMR spectra recorded at 263 K revealed the total disappearance of the free receptor **3**. The concentration of the undetectable species (i.e., **3**) and the concentration of $\mathbf{3}\supset(\mathrm{Imi})_2$ were estimated to be 5 and 95% of the starting host concentration, respectively. The cumulative formation constant β_2 was estimated according to the following equation: $\beta_2 > [\mathbf{3}\supset(\mathrm{Imi})_2]/([\mathbf{3}][\mathrm{Imi}]^2)$.

Estimation of the cumulative formation constants β_3 of 3 towards $(RNH_3^+)_2X^{n-}$ or $(PyrNH_2^+)_2SO_4^{2-}$ in $CDCl_3$ or $CD_3OD/CDCl_3$ (1:10): The cumulative formation constants β_3 were estimated according to the following procedure: Suitable aliquots of a solution of the chloride or sulfate salt were added to a solution of receptor **3** ($1.7–2.5\times10^{-3}$ M) in such a way that the corresponding ^{1}H NMR spectra recorded at 298 K revealed the total disappearance of the free receptor **3**. The concentration of the undetectable species (i.e., **3**) and the concentration of the quaternary complex were estimated to be 5 and 95% of the starting host concentration, respectively. The cumulative formation constants β_3 were estimated according to the following equation: $\beta_3 > [\mathbf{3}\supset(\mathrm{RNH_3^+})_2\mathrm{X}^{n-}]/([\mathbf{3}][\mathrm{RNH_3^+}]^2[\mathrm{X}^{n-}])$ or $[\mathbf{3}\supset(\mathrm{PyrNH_2^+})_2\mathrm{SO_4^{2-}}]/([\mathbf{3}][\mathrm{PyrNH_2^+}]^2[\mathrm{SO_4^{2-}}])$.

Determination of the cumulative formation constants β_3 of 3 towards $(PyrNH_2^+)_2SO_4^{2-}$ in $CD_3OD/CDCl_3$ (1:10) or $(EtNH_3^+)_2SO_4^{2-}$ and $(PrNH_3^+)_2SO_4^{2-}$ in $CD_3OD/CDCl_3$ (3:1): A solution containing the sulfate salt was added to **3** ($1.7–2.5\times10^{-3}$ M) in such a way that the ^{1}H NMR spectrum recorded at room temperature showed the resonances of both species (**3** and the corresponding quaternary complex) in addition to the signals corresponding to the free ammonium ion. Integration of the signals of the different species (i.e., **3**, the corresponding quaternary complex, and the free ammonium ion) allowed us to calculate the cumulative formation constants β_3 according to the following equation: $\beta_3 = [\mathbf{3}\supset(\mathrm{RNH_3^+})_2\mathrm{SO_4^{2-}}]/([\mathbf{3}][\mathrm{RNH_3^+}]^2[\mathrm{SO_4^{2-}}])$ or $[\mathbf{3}\supset(\mathrm{PyrNH_2^+})_2\mathrm{SO_4^{2-}}]/([\mathbf{3}][\mathrm{PyrNH_2^+}]^2[\mathrm{SO_4^{2-}}]$.

Determination of the cumulative formation constant β_3 of 3 towards $(PrNH_3^+)_2Cl^-$ in $CD_3OD/CDCl_3$ (1:10): A solution containing $PrNH_3^+Cl^-$ was added to **3** (1.7×10^{-3} M) in such a way that the ^{1}H NMR spectrum recorded at room temperature showed the resonances corresponding to **3** and the ternary complex $\mathbf{3}\supset\mathrm{PrNH_3^+Cl^-}$ in addition to the signals of the free ammonium ion. Integration of the signals of the different species (i.e., **3**, $\mathbf{3}\supset\mathrm{PrNH_3^+Cl^-}$, and the free ammonium ion) allowed us to calculate the cumulative formation constants β_2 according to the following equation: $\beta_2 = [\mathbf{3}\supset\mathrm{PrNH_3^+Cl^-}]/([\mathbf{3}][\mathrm{PrNH_3^+}][\mathrm{Cl^-}])$. Upon a subsequent addition of the solution containing $PrNH_3^+Cl^-$, the ^{1}H NMR spectrum showed only the resonances of $\mathbf{3}\supset\mathrm{PrNH_3^+Cl^-}$ and $\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{Cl^-}$ in addition to the signals corresponding to the free ammonium ion. Integration of the signals of the different species allowed us to calculate the association constants K_a according to the following equation: $K_a = [\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{Cl^-}]/([\mathbf{3}\supset\mathrm{PrNH_3^+Cl^-}][\mathrm{PrNH_3^+}])$. The cumulative formation constants β_3 was thus defined as $\beta_3 = \beta_2 K_a$.

Estimation of the relative affinity $K_{SO_4^{2-}/Cl^-}$ in the case of $3\supset(PrNH_3^+)_2X^-$ through ^{1}H NMR competitive binding studies in $CDCl_3$ or $CDCl_3/CD_3OD$ (10:1) at 298 K: $(PrNH_3^+)_2SO_4^{2-}$ (1 equiv) was added to a $CDCl_3$ or $CDCl_3/CD_3OD$ (10:1) solution containing **3** (1.7×10^{-3} M) leading to the quantitative formation of $\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{SO_4^{2-}}$. Then a large excess of TBA^+Cl^- (113–238 equiv) was added to the solution. The concentration of the undetectable species (i.e., $\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{Cl^-}$ and $SO_4^{2-}{}_{\mathrm{free}}$) and the concentration of the other species (i.e., $\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{SO_4^{2-}}$ and $Cl^-{}_{\mathrm{free}}$) were estimated to be 5 and 95% of the starting host concentration, respectively. The relative affinity $K_{SO_4^{2-}/Cl^-}$ was estimated according to the following equation: $K_{SO_4^{2-}/Cl^-}[\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{SO_4^{2-}}][\mathrm{Cl^-}]/([\mathbf{3}\supset(\mathrm{PrNH_3^+})_2\mathrm{Cl^-}][\mathrm{SO_4^{2-}}])$.

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[23] See the Supporting Information.

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[28] Owing to the broadness of most of the signals even at low T, the signal corresponding to the NH ureido protons of $\mathbf{3}\supset(\text{Imi})_2$ was not clearly identified.

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[35] In the case of $(DodecNH_3^+)_2SO_4^{2-}$, only 0.6 equiv of the salt was extracted even after prolonged heating (see the Supporting Information).

[36] The signal of C=O was not clearly identified.

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