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Second Generation of Calix[6]aza-Cryptands: Synthesis of Heteroditopic Receptors for Organic Ion Pairs

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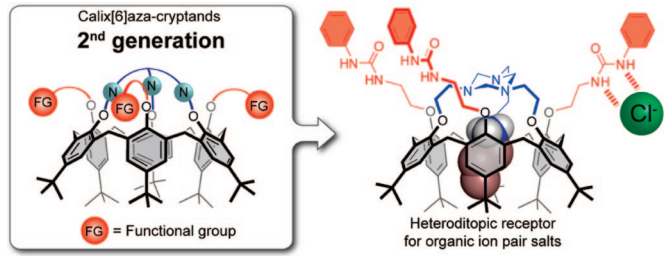
ABSTRACT



The efficient syntheses of calix[6]azacryptands decorated with anion-binding groups on the narrow rim have been achieved from an 1,3,5-tris-protected calix[6]hexa-amine. These heteroditopic receptors can bind ammonium ions or organic ion pair salts with a positive cooperativity. In regard to their functionalization at the 1,3,5-phenolic positions, these compounds constitute the first examples of a second generation of C_{3v} symmetrical calix[6]azacryptands.

The design of molecular receptors from concave macrocyclic compounds is particularly attractive. Indeed, these artificial hosts can find applications in various areas such as sensing, modeling of enzyme-active sites, catalysis, drug delivery, and separation science.[1] Due to their hydrophobic cavity that is well-adapted for the encapsulation of organic guests, calix[6]arenes[2] constitute an ideal platform for the design of such receptors.[3] In this context, we have developed a family of C_{3v} symmetrical calix[6]arene-based receptors, namely the calix[6]azacryptands, bearing a tripodal nitrogenous cap on the narrow rim (Figure 1).[4] The azacryptand cap constrains the calixarene in a cone conformation and constitutes a tunable binding site for either neutral or charged species (i.e., neutral molecules, anions, ammonium ions, organic ion pairs or metal ions), allowing versatile host−guest processes that can be controlled by the environment (presence of metal ions, acids, or bases).[5] Despite these remarkable properties, this first generation of receptors is limited by the lack of efficient methodologies for their selective functionalization. Indeed, chemical modifications at the level either of the nitrogenous binding site or of the wide rim alter the

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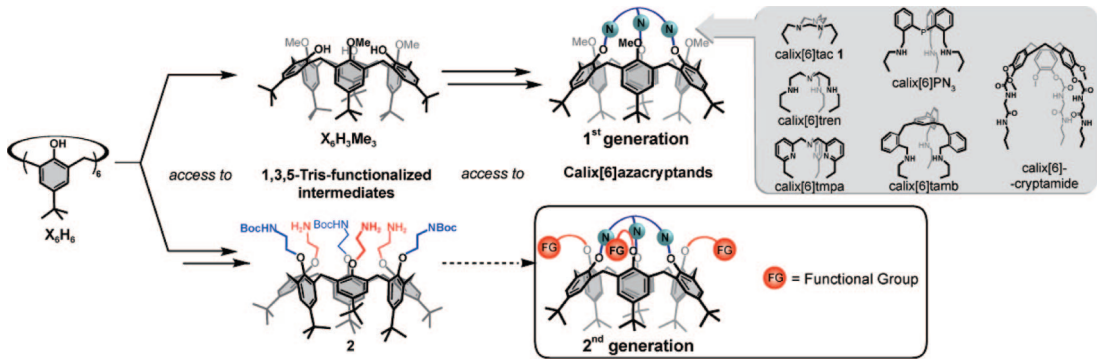
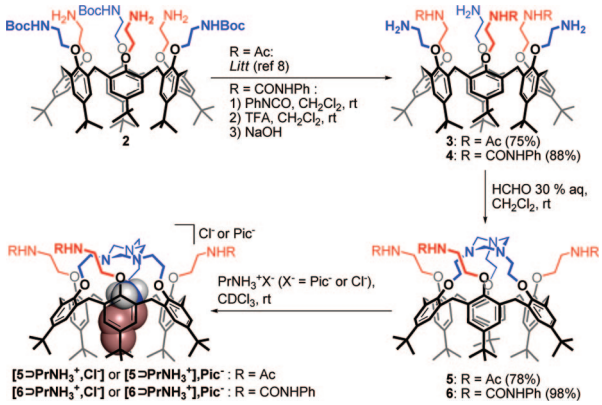


Figure 1. First and second generation of calix[6]azacryptands.

Scheme 1. Syntheses and Host−Guest Properties of 1,3,5-Tris-functionalized Calix[6]tacs **5**[8] and **6**



binding event. In addition, the selective removal of the methyl groups at the 1,3,5-phenolic positions remains challenging.[6] Until now, the 1,3,5-tris-methoxy-calix[6]arene ($X_6H_3Me_3$) intermediate was the only readily available calixarene-based building block displaying a 1,3,5-substitution pattern.[7] However, we have recently described an efficient strategy for the selective 1,3,5-tris-protection of a hexa-aminocalix[6]arene, yielding the molecular platform **2** (Figure 1).[8] This calix[6]arene possesses three alternating free amino groups accessible for a chemical transformation and thus constitutes an interesting alternative to the use of $X_6H_3Me_3$ since functionalized calix[6]cryptands could be easily obtained through macrocyclization reactions.

Among the different calix[6]azacryptands, calix[6]tac **1** (tac = 1,3,5-triazacyclohexane) has shown a remarkable ability to bind small ammonium ions inside its cavity.[9] Thus, we were interested in introducing anion-coordinating groups (i.e., amido or urea groups) on the calix[6]tac skeleton in order to obtain neutral heteroditopic receptors for organic ion pairs. Such receptors capable of simultaneous binding of cations and anions are intensively studied since they can lead to cooperative processes and present the advantage of avoiding the competitive ion-pairing of the guest salt.[10]

Herein, we report on the use of compound **2** for the synthesis of the first members of a second generation of calix[6]azacryptands based on the calix[6]tac skeleton.

The synthesis of the 1,3,5-tris-acetyl-calix[6]hexa-amine **3** was previously reported in an efficient two step sequence from the C_{3v} molecular platform **2** (75% overall yield) (Scheme 1).[8] Addition of an excess of phenylisocyanate (6 equiv) to a solution of **2** in CH_2Cl_2 led to the intermediate 1,3,5-tris-Boc-2,4,6-tris-phenylurea-calix[6]hexa-amine which was purified by flash chromatography.[11] The subsequent removal of the Boc groups by acidic treatment (TFA) afforded the C_{3v} symmetrical 1,3,5-tris-phenylurea-calix[6]hexa-amine **4**[12] in 88% overall yield from **2**. Finally, the [1 + 3] macrocyclization reaction of compounds **3** or **4** with aqueous HCHO in CH_2Cl_2 gave the expected 1,3,5-tris-acetamido-

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(11) The ^{1}H NMR spectrum of this compound showed a complex mixture of conformers even at high temperature (CD_3OD, 330 K) (see the Supporting Information).

(12) See the Supporting Information for the conformational properties of **4**.

Table 1. Selected Complexation Induced Shifts (CISs) of the Calixarene Hosts **1**, **5**, and **6** and Guest $PrNH_3^+$.

		guest $PrNH_3^+$ ($\Delta\delta$/ppm)[a]			host ($\Delta\delta$/ppm)[a]	
entry	host−guest complex	CH_3CH_2	CH_3CH_2	CH_2N	PhN*H*CO	CH_2NHCO
1	**[1⊃PrNH$_3^+$],Pic$^-$**	−2.33[b]	−2.96[b]	−2.43[b]		
2	**[1⊃PrNH$_3^+$],Cl$^-$**	−2.38	−3.05	−2.44		
3	**[5⊃PrNH$_3^+$],Pic$^-$**	−2.35	−3.09	−2.44		−0.18
4	**[5⊃PrNH$_3^+$,Cl$^-$]**	−2.34	−3.07	nd[c]		+0.65
5	**[6⊃PrNH$_3^+$],Pic$^-$**	−2.41	−3.15	−2.54	+0.16	+0.23
6	**[6⊃PrNH$_3^+$,Cl$^-$]**	−2.46	−3.08	−2.45	+1.34	+0.53

[a] CISs calculated at 294 K in $CDCl_3$ and defined as $\Delta\delta = \delta$(host−guest complex) − δ (free). [b] Determined in $CDCl_3/CD_3OD$ 92:8. [c] nd = not determined.

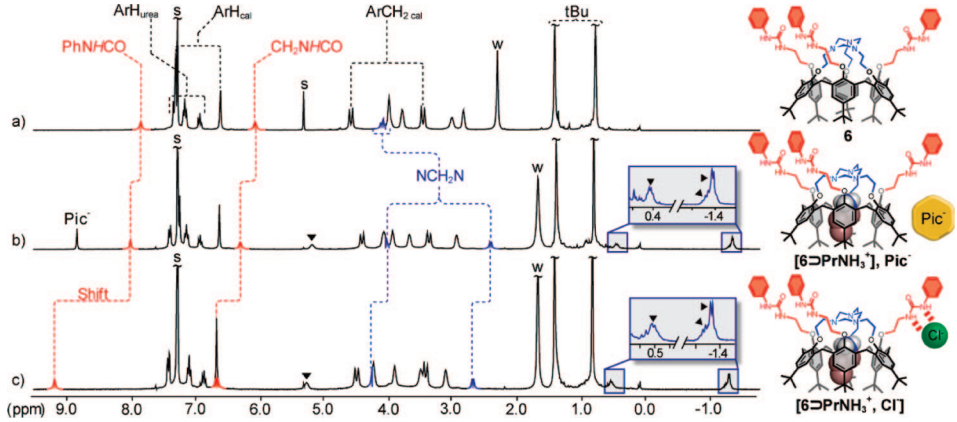

Figure 2. ^{1}H NMR spectra ($CDCl_3$, 294 K) of (a) **6**; (b) **6** + 1 equiv of $PrNH_3^+$,Pic$^-$; (c) **6** + 1 equiv of $PrNH_3^+Cl^-$. ▼: included $PrNH_3^+$. S = solvents ($CHCl_3$, CH_2Cl_2), W = water.

calix[6]tac **5** and 1,3,5-tris-phenylurea-calix[6]tac **6** in remarkably high yields (78% and 98% yield, respectively).

All the signals of the ^{1}H NMR spectra of calix[6]arenes **5** and **6** recorded in $CDCl_3$ (294 K) were assigned through 2D NMR analyses (COSY, HMQC, HMBC). It is noteworthy that the ^{1}H signals belonging either to the calixarene core or to the *tac* cap of **5** and **6** were found close to those reported for the parent calix[6]tac **1**, indicating very similar conformational properties for these three rigidified calix[6]arenes. Thus, **5** and **6** stand in a C_{3v} symmetrical flattened cone conformation ($\Delta\delta_{ArH}$ and $\Delta\delta_{tBu}$ > 0.6 ppm, see Figure 2a for **6**)[4a] with the bulky urea or amido arms directed toward the outside of the cavity (see the structures displayed in Scheme 1), the cone−cone inversion being prevented thanks to the presence of the *tac* cap. Hence, the 1,3,5-tris-functionalized calix[6]tac **5** and **6** possess a well-defined cavity suitable for guest inclusion.

The host−guest properties of receptors **5** and **6** toward the picrate and chloride salts of propylammonium ion were studied by ^{1}H NMR spectroscopy at rt. Thus, addition of 1 equiv of $PrNH_3^+Pic^-$ to $CDCl_3$ solutions of **5** or **6** led to the quantitative formation of the corresponding endocomplexes **[5⊃PrNH$_3^+$],Pic$^-$** and **[6⊃PrNH$_3^+$],Pic$^-$** (Scheme 1), as indicated by the presence of high-field signals corresponding to the inclusion of 1 equiv of $PrNH_3^+$, with a slow *in* and *out* exchange process on the NMR time scale (see Figure 2b for **[6⊃PrNH$_3^+$],Pic$^-$**).

The spectra of these host−guest complexes are quasi-superposable to the one observed in the case of the parent calix[6]tac (i.e., **[1⊃PrNH$_3^+$],Pic$^-$**), and in particular, the complexation induced shifts (CISs) of the included $PrNH_3^+$ are close in all cases (Table 1, entries 1, 3, and 5).[13] This shows a similar positioning of the ammonium ion in the cavity and thus a priori a similar way of binding, i.e. a combination of H-bonding, CH−π, and cation−π interactions between $PrNH_3^+$ and its host.[14]

Very interestingly, while the NH chemical shifts of the amido and urea groups of the host−guest complexes **[5⊃PrNH$_3^+$],Pic$^-$** and **[6⊃PrNH$_3^+$],Pic$^-$** were only slightly different from those of the free hosts (Figure 2b), a strong downfield shift of these protons was observed when $PrNH_3^+Cl^-$ was used in place of the picrate salt (Table 1, entries 3 vs 4 and 5 vs 6) (Figure 2c for **[6⊃PrNH$_3^+$,Cl$^-$]**). This clearly indicates that, in the presence of an appropriate coordinating anion such as Cl^-, calix[6]tac **5** and **6** can

(13) Moreover, HMQC spectra allowed us to determine the carbon resonances of the included $PrNH_3^+$. For **[5⊃PrNH$_3^+$],Pic$^-$**: δ (ppm) CH_3 = 10.6, CH_2 = 17.5, CH_2N = 38.0; for **[6⊃PrNH$_3^+$,Cl$^-$]**: δ (ppm) CH_3 = 10.8, CH_2 = 18.0, CH_2N = 38.2.

(14) These interactions have been evidenced in the case of the complex **[1⊃PrNH$_3^+$],Pic$^-$** thanks to an X-ray structure; see ref 9.

behave as heteroditopic receptors able to simultaneously encapsulate the ammonium ion in the cavity and bind its counteranion at the level of the amido or urea moieties through H bonding interactions (see the structure depicted in Figure 2c). It is noteworthy that differentiated signals for the free host **6** and for the complex **[6⊃PrNH$_3^+$,Cl$^-$]** were observed when less than 1 equiv of PrNH$_3^+$Cl$^-$ was added. Upon the progressive addition of PrNH$_3^+$Cl$^-$ (from 0 to 12 equiv), the chemical shifts of the downfield-shifted N*H*CO signals of **[6⊃PrNH$_3^+$,Cl$^-$]** were not affected and no species other than the free host and **[6⊃PrNH$_3^+$,Cl$^-$]** were observed (see the Supporting Information). These NMR data indicate a strong complexation of the Cl$^-$ at the level of the ureas and are highly consistent with a 1:1 calixarene/Cl$^-$ binding stoichiometry. Moreover, in comparison to **[6⊃PrNH$_3^+$],Pic$^-$**, the NC*H*$_2$N and C*H*$_2$N protons of the cap of **[6⊃PrNH$_3^+$,Cl$^-$]** are significantly downfield shifted (see Figure 2c vs 2b), the other protons of the receptor being weakly affected. This may indicate that the chloride stands in close proximity to the *tac* cap when this anion is simultaneously coordinated by the ureas. All these results taken together may support a cooperative complexation of the Cl$^-$ by the ureas of the endocomplex **[6⊃PrNH$_3^+$]**.[15]

The interaction of PrNH$_3^+$ and Cl$^-$ with both **5** and **6** was also investigated by mass spectrometry. ESI-MS spectra of **5** or **6** in the presence of 10 equiv of PrNH$_3^+$Pic$^-$ displayed ion peaks at *m*/*z* = 1453.3 and 1684.1 corresponding, respectively, to [**5**+PrNH$_3$]$^+$ and [**6**+PrNH$_3$]$^+$.[16] When the analyses were carried out under the same conditions with bulkier ammonium picrate salts (phenylethylammonium and hexylammonium) unable to be accommodated into the cavity of **5** and **6**, only protonated species [**5**+H]$^+$ and [**6**+H]$^+$ were observed. This indicates the presence of specific interactions between PrNH$_3^+$ and the receptors **5** and **6** which are likely due to the inclusion of the ammonium ion. A different complexation behavior toward Cl$^-$ was observed between **5** and **6** (using 10 equiv of TBACl). Indeed, while the [**6**+Cl]$^-$ ion peak at *m*/*z* = 1658.9 was detected as the major signal, the peak corresponding to [**5**+Cl]$^-$ was not observed. This result shows the weaker coordination properties of the amido groups toward anions.

Finally, a competitive NMR experiment between receptor **6** and the parent calix[6]tac **1** toward the complexation of PrNH$_3^+$X$^-$ (with X = Pic$^-$ and Cl$^-$) has been performed to see whether the coordination of the anion could enhance the binding of PrNH$_3^+$.[17] In both cases, progressive addition of the ammonium salt (up to 1 equiv/calix total) to a 1:1 solution of **1** and **6** in CDCl$_3$ led to a mixture of the corresponding endocomplexes.[18] With X = Pic$^-$, **[1⊃PrNH$_3^+$],Pic$^-$** and **[6⊃PrNH$_3^+$],Pic$^-$** were formed in equal amounts in all cases, indicating a similar binding constant. This result is highly compatible with the low affinity of the picrate anion for the urea groups. In contrast, with X = Cl$^-$, in comparison with **[1⊃PrNH$_3^+$],Cl$^-$**, a much larger amount of **[6⊃PrNH$_3^+$,Cl$^-$]** was produced with less than 1 equiv of PrNH$_3^+$Cl$^-$ (Figure 3). This highlights that the simultaneous binding of the anion by the urea groups of the ditopic receptor **6** enhances the endocomplexation of the ammonium ion.

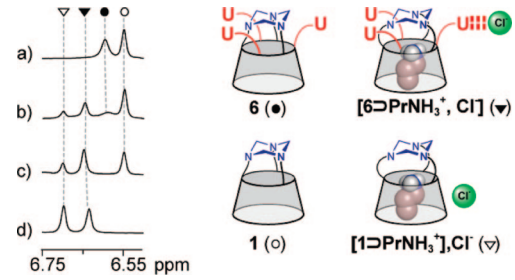

Figure 3. Competitive ^{1}H NMR study conducted with **1** and **6** toward the complexation of PrNH$_3^+$Cl$^-$ (CDCl$_3$, 294 K, ArH$_{in}$ region): 1:1 mixture of **1** and **6** before (a) and after addition of 0.6 equiv (b), 1.4 equiv (c) and 2 equiv (d) of PrNH$_3^+$Cl$^-$.

In conclusion, the selective introduction of anion binding groups on the narrow rim of a calix[6]azacryptand has led to heteroditopic receptors able to bind either ammonium ions or organic ion pair salts with a positive cooperativity. Thus, the 1,3,5-tris-protected-calix[6]hexa-amine **2** constitutes a promising intermediate for the preparation of sophisticated calix[6]cryptand based receptors.

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Supporting Information Available: General experimental methods; 1D, 2D NMR spectra of **4**−**6**, and ESI-MS spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) At 263 K, only one resonance was observed for the three N*H*Ph^{urea} protons of **[6⊃PrNH$_3^+$,Cl$^-$]** (see the Supporting Information). The chloride ion may be either simultaneously bound by the three urea groups or by two of the ureas with an overall fast exchange process on the NMR time scale even at low temperature.

(16) See the Supporting Information for the experimental conditions of the ESI-MS analyses.

(17) Because of strong association constants (K > 10^6 M^{-1}, see ref 9), accurate determination of the affinity of **6** toward PrNH$_3^+$X$^-$ was not possible by NMR spectroscopy.

(18) The ArH$_{in}$ region of the NMR spectra was well appropriate for the observation of the different species.