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# Calix[6]tris(thio)ureas: Heteroditopic Receptors for the Cooperative Binding of Organic Ion Pairs

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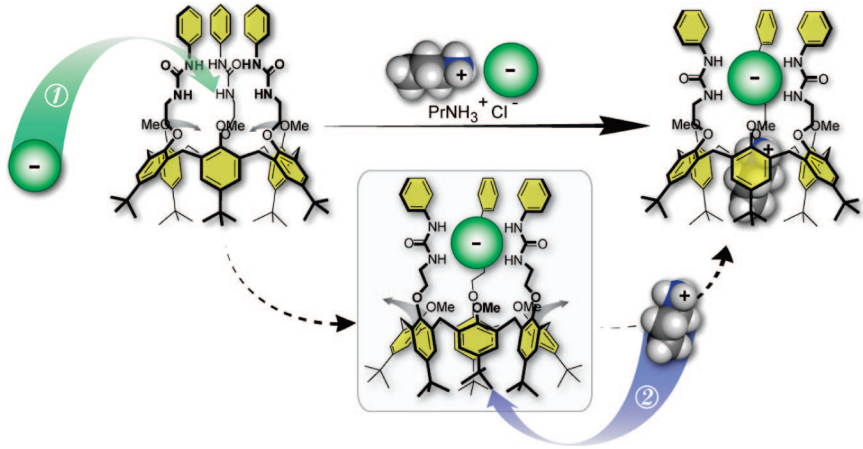


The straightforward syntheses of $C_{3v}$ symmetrical calix[6]trisureas and -thiourea have been achieved. NMR studies have shown that these flexible compounds possess a major cone conformation. While these neutral hosts can strongly bind anions such as $AcO^-$ or $HSO_4^-$ through induced fit processes, they can also behave as unique heteroditopic receptors for organic ion pairs with a remarkable positive cooperativity in the complexation process, the anion acting as an allosteric effector.

## Introduction

There is a growing interest in the design of efficient neutral receptors able to bind anions solely through hydrogen bonding interactions.[1] In this context, calix[4 or 6]arenes bearing multiple amido or (thio)urea groups on either the narrow or the wide rim have been shown to recognize various anions in organic media.[2] Calixarenes also constitute very attractive building blocks for the elaboration of bifunctional hosts capable of simultaneous complexation of cations and anions.[3] Thus, several neutral ditopic receptors binding cooperatively metal ions and their counterions have been developed from calix[4]arenes.[4] However, partly because of the smallness of their cavity,

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(1) (a) Sessler, J. L.; Gale, A. P.; Cho, W.-S. *Anion Receptor Chemistry*; The Royal Society of Chemistry: Cambridge, 2006; pp 171−226. (b) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516. (c) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882–7894.

(2) Matthews, S. E.; Beer, P. D. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001; pp 421−439.

(3) For a review on receptors for ion pairs, see: (a) Sessler, J. L.; Gale, A. P.; Cho, W.-S. *Anion Receptor Chemistry*; The Royal Society of Chemistry: Cambridge, 2006; pp 259−293.

(4) (a) Scheerder, J.; van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1090–1093. (b) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307–1311. (c) Tumcharern, G.; Tuntulani, T.; Coles, S. J.; Hursthouse, M. B.; Kilburn, J. D. *Org. Lett.* **2003**, *5*, 4971–4974. (d) Tongraung, P.; Chantarasiri, N.; Tuntulani, T. *Tetrahedron Lett.* **2003**, *44*, 29–32. (e) Webber, P. R. A.; Beer, P. D. *Dalton Trans.* **2003**, 2249–2252. (f) Nabeshima, T.; Saiki, T.; Iwabuchi, J.; Akine, S. *J. Am. Chem. Soc.* **2005**, *127*, 5507–5511.

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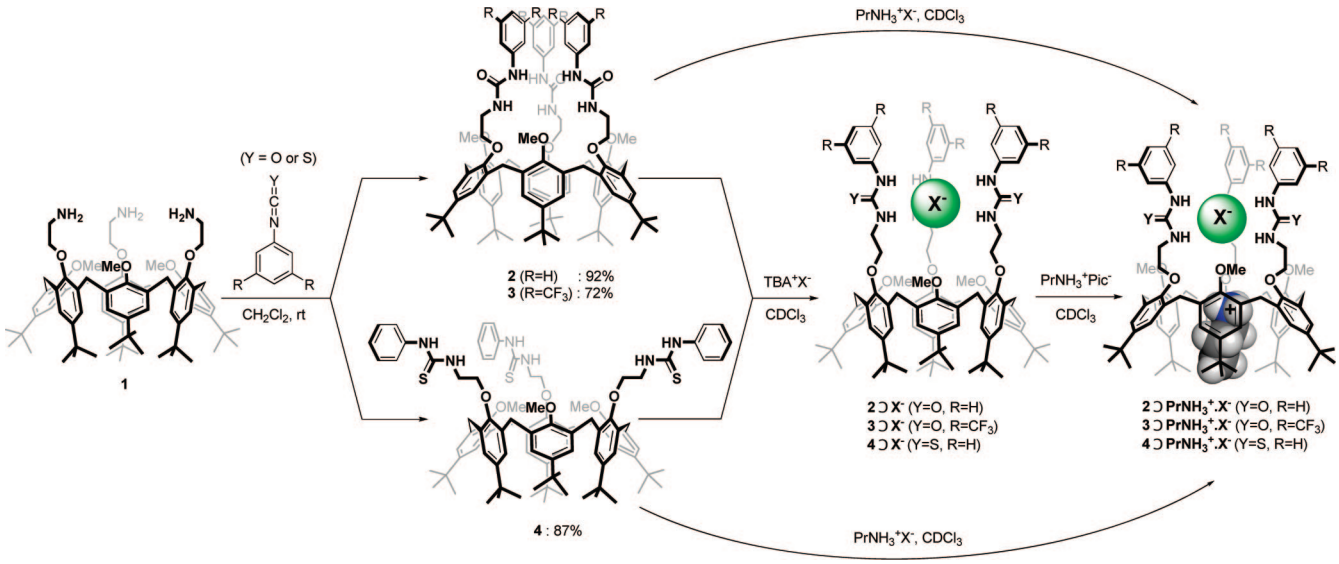
**SCHEME 1. Synthesis and Recognition Properties of Calix[6]trisureas 2, 3, and -Thiourea 4**




examples of calix[4]arene-based receptors aimed at complexing organic ion pairs (e.g., ammonium salts) are extremely rare.[5] The less studied calix[6]arenes possess a larger hydrophobic cavity that is more appropriate for the inclusion of organic guests,[6] and it was shown that the introduction of urea moieties on the wide rim can lead to pseudorotaxanes through organic ion-pair recognition processes.[7] Recently, we have described a new class of heteroditopic receptors (i.e., the calix[6]cryptamides) that can selectively encapsulate ammonium chloride salts in a cooperative way.[8] The complexation of the chloride anion by the trisamido cap of these receptors can only proceed when an ammonium ion is present in the calixarene cavity, and conversely, without $Cl^-$, no binding of the cation was detected. We were interested in developing related heteroditopic hosts but displaying a higher conformational flexibility and bearing stronger coordinating groups than amides. Thus, we envisaged the synthesis of calix[6]arenes functionalized on the narrow rim by three urea or thiourea groups arranged around a $C_3$ axis of symmetry and in close proximity from the cavity. Such receptors should possess two properly positioned binding sites for the complexation of organic associated ion pairs: a well-defined calixarene cavity suitable for the inclusion of ammonium ions and closed by six convergent (thio)urea hydrogen bond donors that can bind anions.[9]

Herein, we describe the synthesis of both calix[6]trisureas and calix[6]tristhiourea and their coordination behavior toward anions and organic ion pairs.

## Results and Discussion

Reaction of calix[6]trisamine **1**[10] with commercially available phenylisocyanate, 3,5-bis(trifluoromethyl)phenylisocyanate, or phenylisothiocyanate afforded calix[6]trisureas **2**, **3**, and calix[6]tristhiourea **4** in good yields (72−92%) (Scheme 1). The conformational properties of **2**, **3**, and **4** were investigated by NMR spectroscopy. First, $^1$H NMR spectra of trisurea compounds **2** and **3** recorded in $CDCl_3$ or $Cl_2CDCDCl_2$ at rt showed broad $C_{3v}$ symmetrical patterns that became sharper at high $T$.[11] These spectra are characteristic of a major flattened cone conformation[12] with the methoxy and the urea groups directed, respectively, toward the outside ($\delta_{OMe}$ > 3.46 ppm) and the inside of the cavity (see Figure 1a for **2** and structures displayed in Scheme 1). While these spectra remained unchanged upon dilution in $CDCl_3$,[11] $^1$H spectra recorded in competing solvents ($CD_3OD$ or acetone-$d_6$) showed narrower signals and were characteristic of a $C_{3v}$ symmetrical major flattened cone conformation with the methoxy groups pointing inside the cavity ($\delta_{OMe}$ < 2.5 ppm), indicating a conformational flip.[11] These results are highly compatible with the presence of an intramolecular hydrogen bonding network between the urea groups of compounds **2** and **3** in apolar solvents. In contrast, a $C_{3v}$ symmetrical flattened cone conformation with the thiourea moieties ejected outside of the cavity was observed for the compound **4** regardless of the nature of solvents (i.e., $CDCl_3$ and acetone-$d_6$).[13] The absence of self-associative intramolecular interactions for **4** is likely due to the weaker hydrogen bond accepting ability of sulfur as compared to oxygen. Finally, no coalescence of the signals of the $ArCH_2$ protons of receptors **2**−**4** was observed even at high $T$ (378 K in $Cl_2CDCDCl_2$),

(5) (a) Arduini, A.; Giorgi, G.; Pochini, A.; Secchi, A.; Ugozzoli, F. *J. Org. Chem.* **2001**, *66*, 8302–8308. (b) Arduini, A.; Brindani, E.; Giorgi, G.; Pochini, A.; Secchi, A. *J. Org. Chem.* **2002**, *67*, 6188–6194. (c) Lankshear, M. D.; Evans, N. H.; Bayly, S. R.; Beer, P. D. *Chem. Eur. J.* **2007**, *13*, 3861–3870. See also for an example with a calix[5]arene: (d) Garozzo, D.; Gattuso, G.; Notti, A.; Pappalardo, A.; Pappalardo, S.; Parisi, M. F.; Perez, M.; Pisagatti, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 4892–4896.

(6) Darbost, U.; Rager, M-.N.; Petit, S.; Jabin, I.; Reinaud, O. *J. Am. Chem. Soc.* **2005**, *127*, 8517–8525.

(7) (a) Arduini, A.; Ferdani, R.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3453–3456. (b) Arduini, A.; Calzavacca, F.; Pochini, A.; Secchi, A. *Chem. Eur. J.* **2003**, *9*, 793–799. (c) Credi, A.; Dumas, S.; Silvi, S.; Venturi, M.; Arduini, A.; Pochini, A.; Secchi, A. *J. Org. Chem.* **2004**, *69*, 5881–5887.

(8) Le Gac, S.; Jabin, I. *Chem. Eur. J.* **2008**, *14*, 548–557.

(9) Calix[6]arenes bearing three long (thio)urea arms have already been described, but in this case, the calixarene framework was only used as a molecular platform for the preorganization of a binding site for anions far away from the cavity. See: Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448–6454.

(10) Le Gac, S.; Zeng, X.; Girardot, C.; Jabin, I. *J. Org. Chem.* **2006**, *71*, 9233–9236.

(11) See the Supporting Information.

(12) In $CDCl_3$, trisureas **2** and **3** display a straighter conformation than **4** as indicated by the difference between the $^1$H chemical shift of the *t*Bu groups ($\Delta\delta_{tBu}$ = 0.18, 0.38, and 0.52 ppm for **2**, **3**, and **4**, respectively).

(13) One can note that a minor species with a dissymmetrical NMR pattern that likely corresponds to the 1,2,3-alternate conformer was also observed in all cases (compounds **2**, **3**, and **4** in $CDCl_3$ or acetone-$d_6$). Such a minor conformer has been already observed in many related cases, i.e., derivatives of the 1,3,5-trismethoxy-calix[6]arene functionalized by bulky groups on the narrow rim. See: (a) van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken, S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 5814–5822.

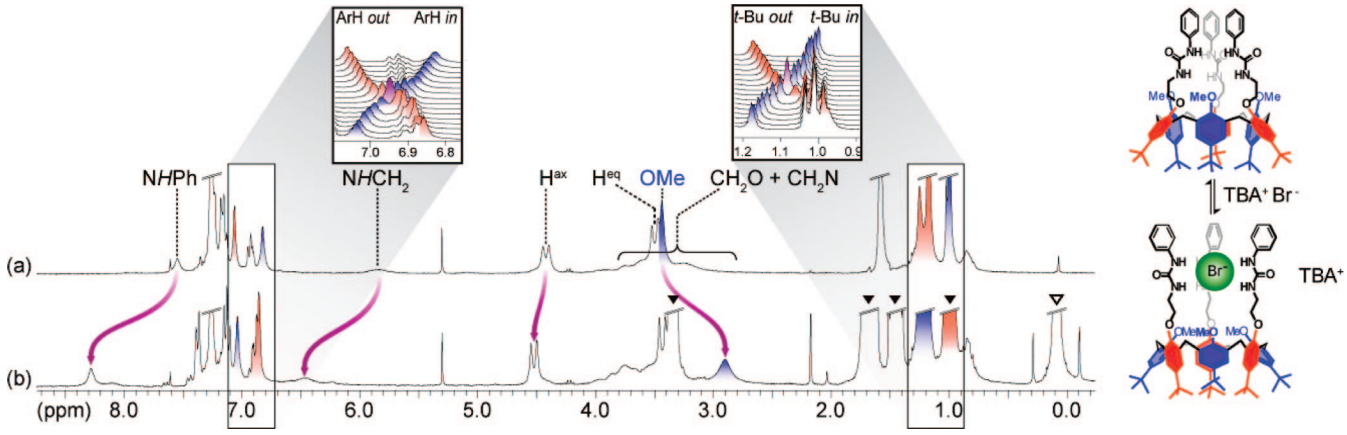



**FIGURE 1.** $^1$H NMR ($CDCl_3$, 300 MHz, 298 K) of (a) **2**; (b) after addition of 30 equiv of $TBA^+Br^-$. Insets: stack plots of calixarene's ArH and *t*Bu protons obtained upon the progressive addition of $TBA^+Br^-$ (from 0 to 9 equiv). ▼: $TBA^+$; ▽: octamethylcyclotetrasiloxane (internal reference).

showing that these compounds exhibit a high cone−cone interconversion barrier (>73 kJ mol$^{-1}$) due to the steric hindrance of the urea and thiourea moieties.[11]

Complexation abilities of **2**, **3**, and **4** toward anions $X^-$ of various geometries (i.e., $Cl^-$, $Br^-$, $I^-$, $HSO_4^-$, $AcO^-$, $ClO_4^-$, and $PF_6^-$) were investigated in $CDCl_3$ through $^1$H NMR titration with tetra-*n*-butylammonium salts ($TBA^+X^-$). In the case of $Cl^-$, $Br^-$, $I^-$, $HSO_4^-$, and $AcO^-$, hydrogen bonding interactions between these anions and the urea or thiourea groups of **2**, **3**, and **4** were clearly evidenced by the strong downfield shift of the NH protons (see Figure 1b for **2**⊃**Br**$^-$). In contrast, a very poor host−guest interaction was observed between host **2** and $ClO_4^-$ or $PF_6^-$ since the NMR pattern of the host remained quasi-unchanged upon the addition of these anions.

In all cases, only one set of signals was observed for the complex and for the free receptor, showing fast host−guest exchanges on the NMR time scale. After the addition of an excess (>4 equiv) of $TBA^+X^-$, all the resulting host−guest complexes **2**−**4**⊃**X**$^-$ displayed a flattened cone conformation with the OMe groups inside the cavity (Scheme 1). Thus, in the case of the trisurea receptors **2** and **3**, their whole calixarene skeleton undergoes a deep conformational change upon complexation since the *t*-Bu(in) and the *t*-Bu(out) as well as the ArH(in) and the ArH(out) signals interchange their position (see insets in Figure 1). This induced fit process is likely due to the separation of the urea groups for the binding of the anion and to the highly favorable filling of the cavity by the OMe groups.[14] In the case of the spherical anions, it is noteworthy that the flatness of the calixarene cavity of **2**⊃**X**$^-$ (with $X^- = Cl^-$, $Br^-$, or $I^-$) gradually augments with the decreasing size of the halide [maximum values of the $\Delta\delta_{t\mathrm{Bu}}$ observed for the host−guest complexes **2**⊃**X**$^-$: $\Delta\delta_{t\mathrm{Bu}(Cl^-)} = 0.43$ ppm, $\Delta\delta_{t\mathrm{Bu}(Br^-)} = 0.17$ ppm, $\Delta\delta_{t\mathrm{Bu}(I^-)} = 0.09$ ppm]. This trend supports a high flexibility of the calixarene skeleton, which can indeed easily adjust its conformation to the size of the anion.

Since the NH proton signal of the host−guest complexes became broad upon addition of the TBA salts, the binding constant *K* was determined through the monitoring of the complexation induced shifts (CISs) of the $ArCH_2$(ax) protons of the receptors. Indeed, in all cases, these protons displayed significant shifts, sharp signals, and no overlaping region (Table 1).[15] For all the anions, Job's plot experiments suggest a 1:1 binding stoichiometry.[11,16] However, in the case of $Cl^-$, a broadening of the whole $^1$H NMR spectra was observed upon the addition of ca. 0.2−0.3 equiv of anion. This may indicate the formation of transient host−guest species of 2:1 binding stoichiometry, and thus, accurate determination of the 1:1 binding constant was not possible.

**TABLE 1. Binding constants *K* of Trisureas 2, 3, and -Thiourea 4 toward Anions ($CDCl_3$, 298 K)**

| | | | log $K^b$ | | |
|---|---|---|---|---|---|
| entry | anion[a] | geometry | **2** | **3** | **4** |
| 1 | $Br^-$ | spherical | 2.2 | 3.3 | 1.4 |
| 2 | $I^-$ | spherical | <2 | 3.1 | <1 |
| 3 | $AcO^-$ | V-shaped | 3.9 | >5 | 3.6 |
| 4 | $HSO_4^-$ | tetrahedral | 4.3 | >5 | 3.4 |

[a] $TBA^+$ counterion was used in all cases. [b] *K* was determined with the CIS of the $ArCH_2$(ax) protons. *K* defined as: $K = [\mathbf{2}-\mathbf{4}\supset\mathbf{X}^-]/([\mathbf{2}-\mathbf{4}] \times [\mathbf{X}^-])$. Error estimated = 10%.

Trisurea **3** displayed much greater complexation affinities than **2** and **4**, a behavior that is likely due to the higher acidity of its urea protons. Surprisingly, despite the absence of competitive intramolecular hydrogen bonding network, the host properties of tristhiourea **4** are weaker than those of trisurea **2**.[17] A similar result was reported with calix[4 or 6]arenes bearing either multiple urea or thiourea groups on the narrow rim.[9,18] This may be due to a lower preorganization of the thiourea group as compared with the urea one. Indeed, it is known that steric interactions between the large sulfur atom and the C−H of the phenyl ring destabilize the *cis* geometry and thus the convergent array of hydrogen bonds.[19] The most basic anion (i.e., $AcO^-$) was particularly well coordinated by all the receptors **2**−**4** (Table

(14) It is well known that the OMe groups of 1,3,5-trismethoxy-calix[6]arene derivatives have a high tendency to fill the cavity in order to establish CH−$\pi$ interactions with the aromatic moieties; see ref 13.

(15) In the case of the complexation of $Br^-$ by **2**, it was possible to check that the value of *K* determined from the chemical shift change of the NH of the calixarene is in good agreement: log $K_{NH} = 2.2$. Moreover, a titration experiment in reverse mode (i.e., through the addition of the host **2** solution to the $TBA^+Br^-$ solution) has led to a similar binding constant: log $K = 2.4$.

(16) Job, A. *Ann. Chim.* **1928**, *9*, 113.

(17) Moreover, in comparison to trisurea **2**, a higher acidity is expected for the NH protons of tristhiourea **4**. Indeed, p$K_a$ values of 21.0 and 26.9 have been described for thiourea and urea, respectively. See Bordwell, E.; Algrim, D. J.; Harrelson, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 5903–5904.

(18) Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815–7820.

(19) (a) Bryantsev, V. S.; Hay, B. P. *J. Phys. Chem. A* **2006**, *110*, 4678–4688. (b) Brooks, S. J.; Edwards, P. R.; Gale, P. A.; Light, M. E. *New J. Chem.* **2006**, *30*, 65–70.

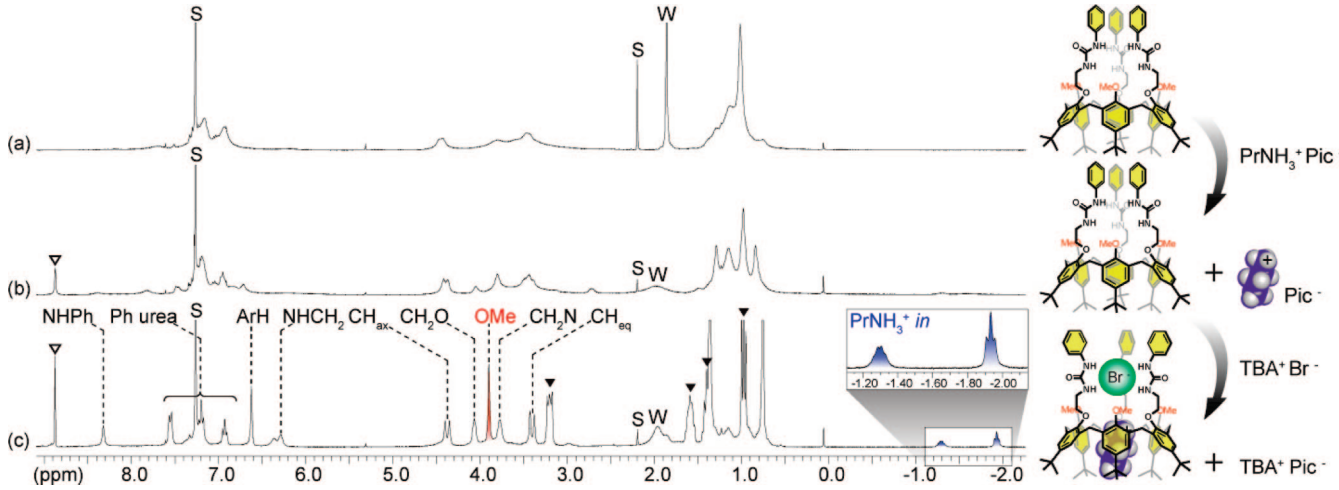



**FIGURE 2.** $^1$H NMR ($CDCl_3$, 300 MHz, 263 K) of (a) **2**; (b and c) with a sequential addition of 1 equiv of $PrNH_3^+Pic^-$ and 1 equiv of $TBA^+Br^-$. ▼: $TBA^+$; ▽: $Pic^-$; S: solvent ($CHCl_3$ and acetone); W: water.

1, entry 3). Moreover, a strong affinity was also observed for $HSO_4^-$ (Table 1, entry 4), most likely arising from a hydrogen bond between the acidic hydrogen atom of the anion and an oxygen ether of the calixarene structure. Such a dual mode of recognition of $HSO_4^-$ has already been described with a calix[4]arene bearing urea moieties on the narrow rim.[20] Interestingly, these two anions (i.e., $AcO^-$ and $HSO_4^-$) were coordinated too strongly by **3** to allow the binding constant to be determined accurately.

The intracavity complexation of an ammonium ion simultaneously to the anion was then investigated at 263 K. Thus, upon the addition of 1 equiv of propylammonium chloride to a $CDCl_3$ solution of either calix[6]trisureas **2**, **3**, or -thiourea **4**, high-field signals corresponding to the encapsulation of 1 equiv of ammonium ion in the calixarene cavity were observed (signals of the included propylammonium ion: $\delta_{(CH3CH2)}$ and $\delta_{(CH3)}$: −1.29 and −1.94 ppm for **2**; −1.26 and −1.92 ppm for **3**; −1.28 and −2.02 ppm for **4**). In all cases, the *in* and *out* exchange of the cation was slow on the NMR spectral time scale and the simultaneous binding of the choride by the urea or thiourea groups was clearly observed through the strong downfield shift of their NH signals. In addition, the resulting host−guest complexes **2**−**4**⊃$\mathbf{PrNH_3^+ \cdot Cl^-}$ possess a $C_{3v}$ symmetrical flattened cone conformation with the methoxy groups pointing outside the cavity ($\delta_{OMe} > 3.9$ ppm). Hence, compounds **2**, **3**, and **4** can act as heteroditopic receptors able to accommodate an organic associated ion pair (Scheme 1). It is noteworthy that NMR competitive experiments between urea versus thiourea receptors for the complexation of propylammonium chloride showed a better recognition of the ion pair by the urea receptors.

Very interestingly, when a low coordinating anion, such as picrate ($Pic^-$), was used in place of the chloride, only a trace of ammonium ion was detected in the cavity (see Figure 2a,b in the case of **2**).[21] The further addition of 1 equiv of $TBA^+Br^-$ salt led to the quasi-quantitative formation of the host−guest complexes **2**−**4**⊃$\mathbf{PrNH_3^+ \cdot Br^-}$ (see Figure 2c in the case of **2**). These results denote that the inclusion of the ammonium ion is directed by a highly cooperative two-step binding process with the anion playing the role of an allosteric effector.

Indeed, as demonstrated above and in contrast to the previously described calix[6]cryptamides, the coordination of the anion can proceed without the presence of the ammonium ion in the cavity since the self-inclusion of the OMe groups can stabilize the calixarene cavity through CH−$\pi$ interactions. On the contrary, the recognition of the ammonium ion can occur only if its binding site has been first preorganized by an anion coordinated to the urea or thiourea groups. The role of the anion is thus to structure the calixarene into a cone conformation with a well-defined cavity as well as to polarize the receptor.[22] It is noteworthy that this prerequisite in the binding process has been already observed in the case of the funnel complexes developed by Reinaud,[23] with however a metal ion in place of the anion. The second step of the complexation consists of the inclusion of the ammonium ion through an induced fit process (expulsion of the OMe groups) and its stabilization thanks to an electrostatic interaction with the anion as well as probable hydrogen bonding and CH−$\pi$ interactions with the calixarene structure.[24] Thus, this allosterically controlled complexation of the contact ion pair is made possible by the unique structures of the calix[6]arene-based receptors **2**, **3**, and **4** that (i) are sufficiently flexible to allow induced fit processes and (ii) display in close proximity a hydrophobic cavity and a binding site for anions.

Lastly, the influence of the nature of the anion on the endocomplexation of the ammonium ion was investigated. For this, $^1$H NMR spectra ($CDCl_3$, 263 K) obtained upon the addition of either $Br^-$ or $AcO^-$ $TBA^+$ salts (1 equiv) and $PrNH_3^+Pic^-$ (1 equiv) to the receptor **2** were compared. In particular, the fraction of included ammonium ion was found to be 86 and 28% for $Br^-$ and $AcO^-$, respectively.[25] This result was quite surprising since it does not correlate with the relative binding affinities of **2** for these anions (see Table 1). It may be explained

(20) Nam, K. C.; Kang, S. O.; Jeong, H. S.; Jeon, S. *Tetrahedron Lett.* **1999**, *40*, 7343–7346.

(21) This trace of included ammonium ion can be due to the presence of traces of $Cl^-$ in $CDCl_3$.

(22) The importance of the polarization of a cavity shaped receptor has been underlined; see refs 6 and 8.

(23) See for example: Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183–6189.

(24) Such interactions between included ammonium ions and calix[6]arenes have been observed in related cases. See: (a) Darbost, U.; Giorgi, M.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 4879–4884. (b) Zeng, X.; Hucher, N.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 6886–6889. (c) Zeng, X.; Coquière, D.; Alenda, A.; Garrier, E.; Prangé, T.; Li, Y.; Reinaud, O.; Jabin, I. *Chem. Eur. J.* **2006**, *12*, 6393–6402. (d) Le Gac, S.; Marrot, J.; Reinaud, O.; Jabin, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3123–3126.

(25) These percentages correspond to the ratio $PrNH_3^+$(included)/$PrNH_3^+$(total) determined from the integration of the signal of the methyl group of the included ammonium ion and the integration of the $Pic^-$ signal.

by an anion size effect or by the fact that stronger is the interaction of the anion with the urea moieties, weaker is its charge density and thus its electrostatic interaction with the included counterion.

## Conclusion

$C_{3v}$ symmetrical calix[6]trisureas **2**, **3**, and -thiourea **4** can act as unique heteroditopic receptor toward either anions or associated ion pairs through induced fit and allosterically controlled processes. These remarkable host−guest properties greatly differ from those of the more rigid calix[6]cryptamides which were a priori unable to bind anions without the presence of an ammonium ion in the calixarene cavity. This work opens interesting perspectives for the design of efficient calix[6]arene-based sensors for anions or organic ion pairs.

## Experimental Section

**General Procedure for the Preparation of Calix[6]tris(thio)ureas 2, 3, and 4.** In a sealed tube, phenylisocyanate, 3,5-bis(trifluoromethyl)phenylisocyanate, or phenylisothiocyanate (3.5 equiv) was added to calix[6]trisamine **1** (1 equiv) in anhydrous $CH_2Cl_2$ (0.17 M). The reaction mixture was stirred at rt for 5 h and then concentrated under reduced pressure. The crude residue was triturated with ethanol, and the resulting white precipitate was collected by centrifugation. The obtained solid was triturated with pentane and dried under vacuum to give the corresponding calix[6](thio)urea **2**, **3**, or **4** as a white powder.

**Calix[6]trisphenylurea 2:** 115 mg (92%); mp 182 °C (dec); $^1$H NMR (300 MHz, acetone-$d_6$, 298 K) $\delta$ (ppm) 0.88 (s, 27H, *t*Bu), 1.35 (s, 27H, *t*Bu), 2.44 (s, 9H, OMe), 3.48 (d, $J$ = 15 Hz, 6H, $ArCH_2^{eq}$), 3.65−3.68 (m, 6H, $CH_2N$), 4.01 (t, $J$ = 5 Hz, 6H, $OCH_2$), 4.59 (d, $J$ = 15 Hz, 6H, $ArCH_2^{ax}$), 6.27 (t, $J$ = 5 Hz, 3H, $NHCH_2$), 6.78 (s, 6H, $ArH^{cal}$), 6.89 (t, $J$ = 7 Hz, 3H, $ArH^{Ph}$), 7.18 (t, $J$ = 7 Hz, 6H, $ArH^{Ph}$), 7.30 (s, 6H, $ArH^{cal}$), 7.44 (d, $J$ = 7 Hz, 6H, $ArH^{Ph}$), 8.15 (s, 3H, NHPh); $^{13}$C NMR (75 MHz, acetone-$d_6$, 298 K) $\delta$ (ppm) 31.2(5) ($ArCH_2$), 31.2(7) ($ArCH_2$), 32.7 ($CH_3$), 32.9 ($CH_3$), 35.7 ($C(CH_3)$), 35.8 ($C(CH_3)$), 42.1 ($NCH_2$), 62.0 ($OCH_3$), 74.1 ($OCH_2$), 120.3 ($CH^{Ph}$), 123.3 ($CH^{Ph}$), 125.8 ($CH^{cal}$), 129.6 ($CH^{cal}$), 130.4 ($CH^{Ph}$), 135.0 (C), 135.4 (C), 142.5 (C), 147.4 (C), 147.6 (C), 153.7 (C), 156.2 (C), 157.5 (NCO). Anal. Calcd for $C_{96}H_{120}N_6O_9 \cdot 0.5H_2O$: C, 76.31; H, 8.07; N, 5.56. Found: C, 76.37; H, 8.22; N, 5.55.

**Calix[6]tris[3,5-bis(trifluoromethyl)]phenylurea 3:** 114 mg (72%); mp 187 °C (dec); $^1$H NMR (300 MHz, acetone-$d_6$, 298 K) $\delta$ (ppm) 0.85 (s, 27H, *t*Bu), 1.36 (s, 27H, *t*Bu), 2.34 (s, 9H, OMe), 3.46 (d, $J$ = 15 Hz, 6H, $ArCH_2^{eq}$), 3.75 (q, $J$ = 5 Hz, 6H, $CH_2NH$), 4.07 (t, $J$ = 5 Hz, 6H, $CH_2O$), 4.59 (d, $J$ = 15 Hz, 6H, $ArCH_2^{ax}$), 6.52 (t, $J$ = 5 Hz, 3H, $NHCH_2$), 6.74 (s, 6H, $ArH^{cal}$), 7.31 (s, 6H, $ArH^{cal}$), 7.46 (s, 3H, ArH), 8.09 (s, 6H, ArH), 8.80 (s, 3H, NHPh); $^{13}$C NMR (75 MHz, acetone-$d_6$, 298 K) $\delta$ (ppm) 31.1(0) ($ArCH_2$), 31.1(1) ($ArCH_2$), 32.7 ($CH_3$), 32.9 ($CH_3$), 35.7 ($C(CH_3)$), 35.8 ($C(CH_3)$), 42.1 ($NCH_2$), 61.9 ($OCH_3$), 73.6 ($OCH_2$), 115.8 ($CH^{Ph}$), 119.4 ($CH^{Ph}$), 125.5 (q, $J$ = 270 Hz, $CF_3$), 125.6 ($CH^{cal}$), 129.8 ($CH^{cal}$), 133.3 (q, $J$ = 33 Hz, $C(CF_3)$), 134.9 (C), 135.4 (C), 144.4(C), 147.5 (C), 147.6 (C), 153.5 (C), 156.2 (C), 156.8 (NCO). Anal. Calcd for $C_{102}H_{116}F_{18}N_6O_{10} \cdot H_2O$: C, 63.54; H, 6.06; N, 4.36. Found: C, 63.48; H, 5.89; N, 4.21.

**Calix[6]trisphenylthiourea 4:** 112 mg (87%); mp 188 °C (dec); $^1$H NMR (300 MHz, acetone-$d_6$, 298 K) $\delta$ (ppm) 0.83 (s, 27H, *t*Bu), 1.42 (s, 27H, *t*Bu), 2.20 (s, 9H, OMe), 3.46 (d, $J$ = 15 Hz, 6H, $ArCH_2^{eq}$), 4.11−4.25 (m, 12H, $CH_2N + CH_2O$), 4.57 (d, $J$ = 15 Hz, 6H, $ArCH_2^{ax}$), 6.72 (s, 6H, $ArH^{cal}$), 7.13−7.20 (m, 3H, $ArH^{Ph}$), 7.27−7.47 (m, 18H, $ArH^{Ph} + ArH^{cal}$), 8.97 (s, 3H, NHPh); $^{13}$C NMR (75 MHz, acetone-$d_6$, 298 K) $\delta$ (ppm) 31.1(9) ($ArCH_2$), 31.2(0) ($ArCH_2$), 32.7 ($CH_3$), 33.0 ($CH_3$), 35.7 ($C(CH_3)$), 35.9 ($C(CH_3)$), 46.9 ($NCH_2$), 61.8 ($OCH_3$), 72.6 ($OCH_2$), 125.4 ($CH^{cal}$), 126.4 ($CH^{cal}$), 127.4 ($CH^{Ph}$), 130.0 ($CH^{Ph}$), 131.1 ($CH^{Ph}$), 134.9 (C), 135.5 (C), 140.2 (C), 147.5 (C), 147.6 (C), 153.3 (C), 156.4 (C), 183.7 (NCS). Anal. Calcd for $C_{96}H_{122}N_6O_7S_3 \cdot 2H_2O$: C, 72.62; H, 7.76; N, 5.35. Found: C, 72.66; H, 7.56; N, 5.13.

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**Supporting Information Available:** General experimental methods; 1D, 2D NMR spectra, and variable temperature studies of **2**−**4**; $^1$H NMR dilution studies of **2** and **3**; the lower bound of the interconversion barrier of hosts **2**−**4**; Job's plot analysis of the association between host **2** and $Br^-$; the general procedure for the determination of the association constants $K$. This material is available free of charge via the Internet at http://pubs.acs.org.

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