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Optically Pure Calix[6]tris-ammoniums: Syntheses and Host−Guest Properties toward Neutral Guests

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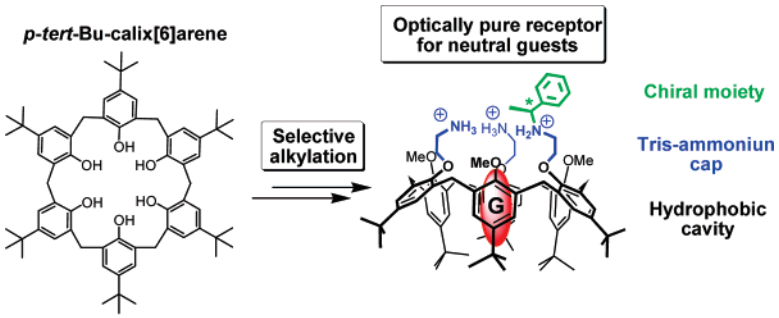

Optically pure calix[6]arenes bearing chiral amino arms **4**, **7**, and **10** have been synthesized in high yields from the known symmetrically 1,3,5-trismethylated calix[6]arene. For both compounds **7** and **10**, the key step consists of an efficient selective alkylation on the narrow rim of the calix[6]arene with $Ba(OH)_2$ as the base. All of these chiral calix[6]tris-amines possess a similar flattened cone conformation with the cavity occupied by the methoxy groups. In contrast to **4** and **7**, upon protonation, the enantiopure calix[6]arene **10** can switch to the opposite flattened cone conformation through self-assembly of its ammonium arms in an ion-paired cap which closes the cavity. As shown by NMR host−guest studies and an X-ray structure, the obtained polarized host (**10·3H**$^+$) behaves as a remarkable endo-receptor for small polar neutral molecules. Thanks to the tris-cationic chiral binding site of **10·3H**$^+$, it was shown that the guests experience a chiral environment upon inclusion. Finally, the first example of enantioselective molecular recognition inside the cavity of a calix[6]arene has been evidenced with a racemic 1,2-diol guest.

Introduction

There is a growing interest in the design and study of chiral synthetic receptors.[1] Such receptors can find applications in enantioselective catalysis and in the separation and analysis of enantiomers.[2] They can also contribute to a better understanding of the biological systems since chiral recognition processes play an essential role in the regulation of life functions. A good way to obtain a molecular receptor consists of mimicking the structural key features of the biological systems, thus associating a well-organized binding site to a hydrophobic cavity able to surround a guest molecule.[3] In this regard, calixarenes appear to be ideal platforms for the elaboration of enantioselective receptors with such host−guest properties.[4] Numerous syntheses of optically pure calix[4]arenes have been reported.[5] However, the cavity of

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calix[4]arenes is not large enough for the inclusion of organic molecules. Thus, their use was limited either to the preorganization of a chiral binding site outside of the cavity[6] or to the formation of chiral self-assembled capsules.[7] In contrast, calix[6]arenes[8] possess a hydrophobic cavity well adapted for the inclusion of organic molecules. Surprisingly, only a very few examples of either calix[6]arenes functionalized by chiral groups[9] or inherently chiral calix[6]arenes[10] have been reported. Moreover, to our knowledge, a chiral discrimination process inside the cavity of a calix[6]arene has not been described yet. This is mainly due to the fact that calix[6]arenes possess a high degree of conformational flexibility, and thus, they have first to be rigidified in order to display host−guest properties.[11] For this, we have developed a new class of calix[6]arenes bearing a covalent tripodal aza cap on the narrow rim.[12] The so-called calix[6]azacryptands exhibit outstanding host−guest properties toward either ammoniums, metal ions, or neutral molecules. This work has clearly demonstrated that the polarization of a hydrophobic cavity is an efficient strategy for the design of molecular receptors.[13] Recently,

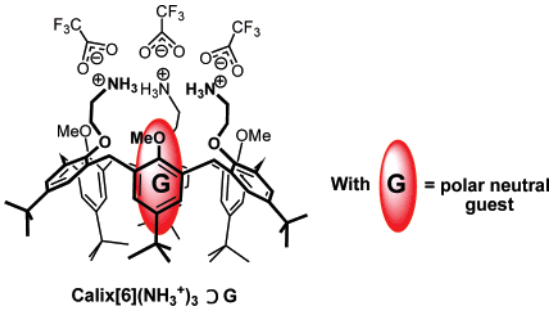

FIGURE 1. An efficient calix[6]tris-ammonium receptor for polar neutral guests (G).

we have shown that a calix[6]tris-ammonium can be also rigidified trough an ion-paired cap formed by the self-assembly of its ammonium arms and their counteranions (Figure 1).[14] This simple polarized host displays original endo-complexation properties toward neutral polar molecules thanks to its tris-cationic binding site. The efficiency of the receptor results from the combination of a strong charge-dipole interaction between the polarized guest and the tris-cationic cap, stabilizing CH−π interactions inside the calixarene cavity and hydrogen bonding in the cap. To elaborate enantiopure endo-receptors useful for a chiral discrimination between enantiomers of neutral molecules, we wanted to design and study calix[6]tris-ammoniums bearing chiral moieties close to the tris-cationic binding site. The present paper describes the syntheses, conformational properties, and host−guest behavior of optically pure calix[6]tris-ammoniums bearing, respectively, either one, two, or three chiral arms on the narrow rim.

Results and Discussion

Syntheses of the Optically Pure Calix[6]arenes 4, 7, and 10. The calix[6]arene bearing three chiral amino arms **4** has been obtained according to an efficient two-step sequence starting from the symmetrically 1,3,5-tris-methylated calix[6]arene, namely $X_6H_3Me_3$[15] **1** (Scheme 1). First, alkylation of $X_6H_3Me_3$ **1** with *S*-(−)-2-bromo-*N*-(1-phenylethyl)acetamide **2**,[16] in the presence of NaH, provided the corresponding chiral calix-tris-amide **3** in 80% yield after flash chromatography (FC) purification. A subsequent reduction by a large excess of BH_3/THF gave the desired C_3-symmetrical calix[6]tris-amine **4** in 85% yield.

For the preparation of the chiral calix[6]arenes **7** and **10**, it was necessary to develop efficient pathways for the introduction of only one or two chiral arms on the narrow rim. Selective alkylations of $X_6H_3Me_3$ **1** are very rare in

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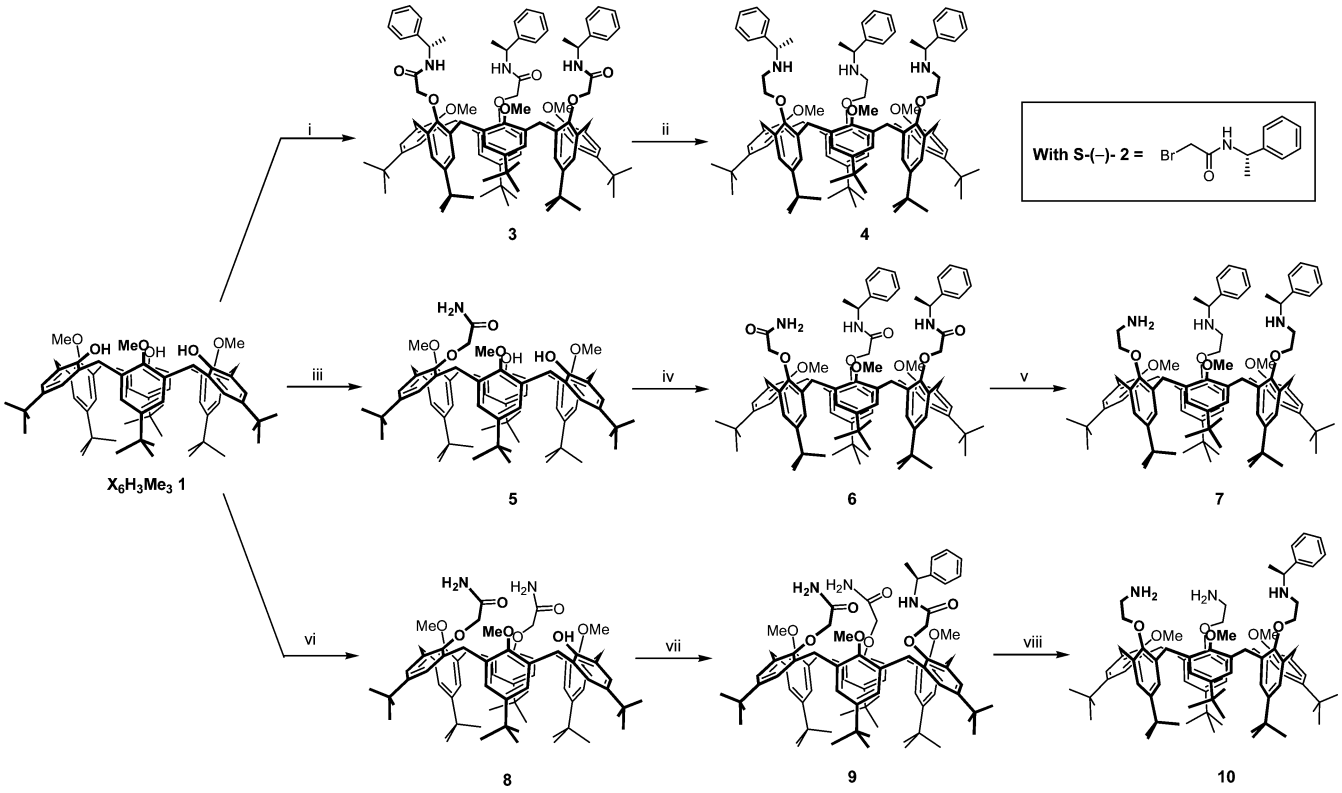
SCHEME 1. Syntheses of the Chiral Azacalix[6]ligands[a]



[a] Key: (i) NaH (4 equiv), (*S*)-(−)-2 (4 equiv), THF, reflux, 80%; (ii) BH_3/THF reflux, then EtOH reflux, 85%; (iii) $Ba(OH)_2$ (3.3 equiv), $BrCH_2CONH_2$ (1.3 equiv), DMF, rt, 60 %; (iv) NaH (2.2 equiv), (*S*)-(−)-2 (2.4 equiv), THF, reflux, 57 %; (v) BH_3/THF reflux, then EtOH reflux, 99%; (vi) $Ba(OH)_2$ (6 equiv), $BrCH_2CONH_2$ (3 equiv), DMF, 80 °C, 51%; (vii) NaH (1.1 equiv), (*S*)-(−)-2 (1.2 equiv), THF reflux, 76%; (viii) BH_3/THF reflux, then EtOH reflux, 99%.

the literature. Only two examples of mono-alkylation have been described to date. They deal with the introduction of bromoethylene[17] and protected aminoethylene arms.[18] We decided to investigate the feasibility of the mono- and di-alkylation of $X_6H_3Me_3$ **1** with bromoacetamide. Thus, various solvents (THF, DMF, acetone) and bases [NaH, K_2CO_3, $Ba(OH)_2$] were tested upon different reaction conditions (amount of bromoacetamide, temperature, reaction time), and the crude reaction mixtures were analyzed by ^{1}H NMR. This study showed that the nature of the base was crucial. Indeed, with NaH, the compound resulting from the tris-alkylation of $X_6H_3Me_3$ **1** was observed predominantly in all cases. In contrast, even the mono-alkylation reaction was revealed to be extremely slow with the weaker base K_2CO_3. Finally, under the reaction conditions (temperature, amounts of base and bromoacetamide), the use of $Ba(OH)_2$ allowed us to isolate in good yields either the mono-amide **5** (60%) or the bis-amide **8** (51%)[19] (Scheme 1).

Very interestingly, in the case of **5**, the ^{1}H NMR spectrum of the crude reaction mixture[20] was quite different from the one of the isolated compound (Figure 2a). A similar NMR spectrum was obtained when **5** was reacted with $Ba(OH)_2$ in DMF at room temperature (Figure 2b), while the subsequent addition of trifluoroacetic acid (TFA) in the NMR tube restored the NMR signals of **5**. All of these results indicate that the NMR spectrum displayed in Figure 2b corresponds to the barium complex **11** (see the proposed structure displayed in Figure 2b). This intermediate complex **11** may rationalize the remarkable selectivity, since its formation during the process should make the second alkylation slower. It is noteworthy that similar results have been described with the selective alkylation of calix[4]arenes through the in situ formation of stable sodium[21] or barium[22] complexes.

Finally, a two-step sequence, similar to the one used for **4**, led to the desired chiral calix[6]tris-amines **7** and **10** in 56% and 75% overall yields from **5** and **8**, respectively.

^{1}H NMR Conformational Study of the Chiral Calix[6]arenes 4, 7, and 10. All of the new compounds **3**−**10** were characterized by ^{1}H NMR spectroscopy in $CDCl_3$, and the signals were attributed through 2D-NMR analyses (HMQC, HMBC, COSY). The ^{1}H NMR spectrum of **4** is characteristic of a C_3-symmetrical species. In contrast, compounds **7** and **10** display dissymmetrical ^{1}H NMR patterns assignable to the presence of, respectively,

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(19) In both cases, compounds **5** and **8** were purified by flash chromatography and it was possible to recover some starting material, i.e., $X_6H_3Me_3$ **1**. Thus, **5** and **8** were obtained in 80% and 53% yields, taking into account, respectively, the 76% and 97% of conversion of $X_6H_3Me_3$ **1**.

(20) This ^{1}H NMR spectrum was obtained before any aqueous washing of the reaction mixture.

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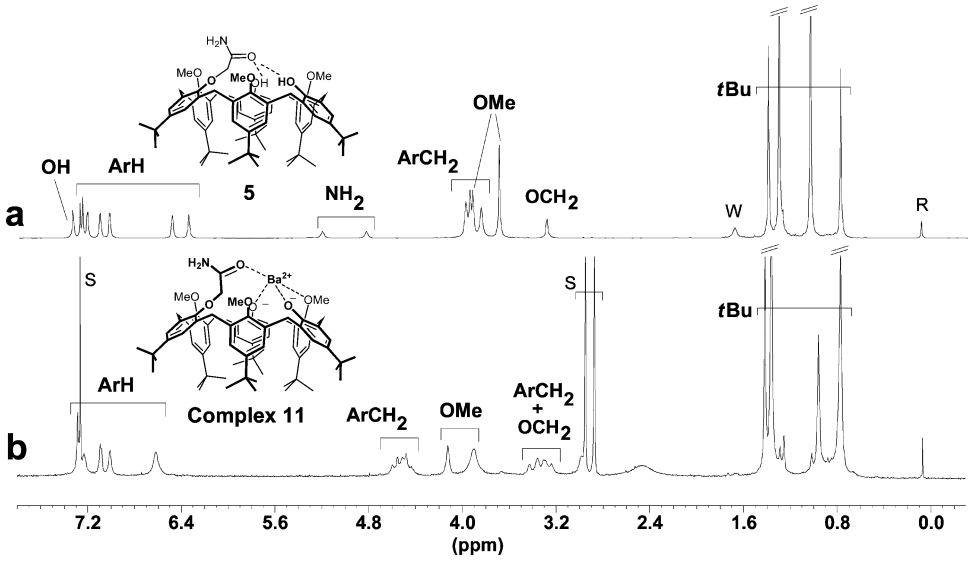
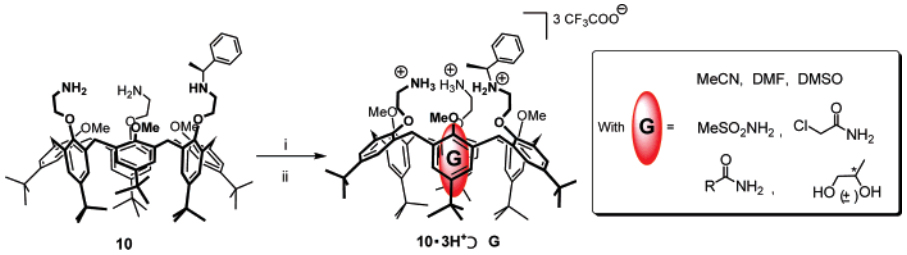


FIGURE 2. ^{1}H NMR spectra ($CDCl_3$, 293 K) of: (a) **5**; (b) complex **11**. Residual solvents, water, and reference are labeled S, W, and R, respectively.

SCHEME 2. Synthesis and Host−Guest Properties of the Chiral Calix[6]tris-ammonium 10·3H$^+$ [a]



[a] Key: (i) TFA, CH_2Cl_2; (ii) G, 81% overall yield from **10** (with G = CH_3CN).

two and one chiral arms. However, compounds **4**, **7**, and **10** possess some similar conformational properties:

(i) Their methoxy groups are projected toward the inside of the cavity as indicated by their high-field resonances (δ_{OMe} = 2.23 ppm for **4** and δ_{OMe} < 2.56 ppm for **7** and **10**), whereas the bulkier amino arms are rejected outside (see the structures of **4**, **7**, and **10** displayed in Scheme 1). This is characteristic of a flattened cone conformation with the cavity partially filled by the methoxy groups.

(ii) Their axial and equatorial ArCH_2Ar protons give differentiated doublets attesting that the cone−cone inversion is slower than the NMR time scale.

(iii) In all cases, 2D-NOESY spectra revealed strong interactions between the Ar*H* borne by the aromatic moieties in *in* and *out* positions, while the ^{13}C NMR signals for the ArCH_2Ar methylene carbons fall at 30.0 ± 0.5 ppm. These NMR data show that these compounds adopt a classical cone conformation.[23]

In contrast to **3**, **4**, **6**, **7**, and **10**, the methoxy groups of **9** and of the C_s-symmetrical compounds **5** and **8** possess a quasi-normal resonance (δ_{OMe} > 3.41 ppm in all cases), while their OCH_2CONH_2 resonances are highfield shifted (3.29, 3.90 and <4 ppm for **5**, **8**, and **9**, respectively) (see Figure 2a for **5**). These data indicate that the bulky amido arms of **5**, **8**, and **9** are directed toward the inside of the cavity. Thus, in comparison to all of the other calix[6]-arenes displayed in Scheme 1, compounds **5**, **8**, and **9** possess the opposite flattened cone conformation. In the case of **5** and **8**, this different conformational behavior may be due to the establishment of intramolecular hydrogen bonds between the carbonyl groups and the phenolic protons (see structure of **5** displayed in Figure 2a).[24]

Synthesis and Characterization in the Solid State of a Host−Guest Complex 10·3H$^+$⊃CH_3CN. Addition of an excess of TFA to a solution of calix[6]tris-amine **10** in dichloromethane led to the corresponding tris-ammonium salt **10·3H$^+$**. Upon slow diffusion of Et_2O into a solution of **10·3H$^+$** in acetonitrile, the corresponding endo-complex **10·3H$^+$⊃CH_3CN** was isolated in 81% overall yield (Scheme 2).

Crystals suitable for X-ray analysis of the endo-complex **10·3H$^+$⊃CH_3CN** were obtained according to this procedure (Figure 3). The calixarene host stands in a flattened cone conformation with the three ethylammonium arms directed toward the inside of the cavity. These cationic arms cap the narrow rim of the calixarene thanks to a hydrogen-bonding network between the ammonium groups, the trifluoroacetate anions, and the methoxy

(23) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1994**, *59*, 3871−3879.

(24) Such a conformationnal behavior has already been observed on a closely related calix[6]arene bearing a protected aminoethylene arm on the narrow rim: Sénèque, O.; Reinaud, O. *Tetrahedron* **2003**, *59*, 5563−5568.

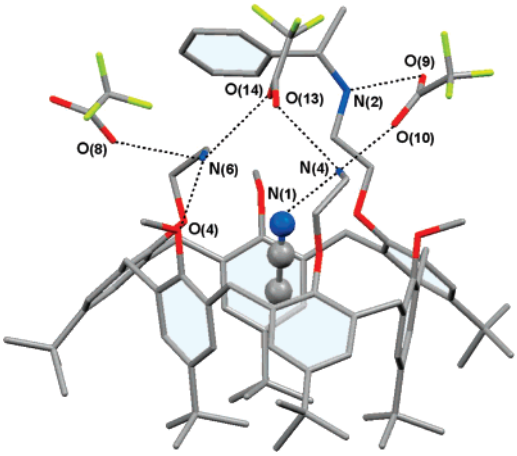


FIGURE 3. Crystal structure of **10·3H**$^+$⊃**CH$_3$CN**. Hydrogen atoms and some crystallization solvent molecules have been omitted for clarity. Hydrogen bond distances (Å): N(1)···(4) = 2.976, N(4)···O(13) = 2.866, N(4)···O(10) = 2.742, N(2)···O(9) = 2.764, N(6)···O(4) = 3.050, N(6)···O(8) = 2.746, N(6)···O(14) = 2.810.

groups of an anisole moiety. As previously described with the parent calix[6](NH$_3^+$)$_3$ receptor (Figure 1),[14] this ion-paired cap rigidifies the whole structure and allows the formation of a well-defined cavity for the inclusion of neutral polar molecules. It is noteworthy that the chain bearing the secondary ammonium group adopts a zigzag conformation in order to prevent steric interactions between the bulky chiral moiety and the hydrogen-bonded cap. The methoxy and the OCH$_2$ groups of the arms are in *out* position, thereby optimizing the space left for guest inclusion. Indeed, a guest molecule of MeCN is deeply buried in the heart of the calixarene cavity and is hydrogen bonded to an ammonium group of the cap [*d*(N1···N4) = 2.976 Å]. As shown on closely related endo-complexes,[25] the guest is further stabilized by a CH−π interaction between its methyl group and an aromatic ring of the calixarene [*d*(C···C=C) = ca. 3.5 Å]. Finally, additional intermolecular hydrogen bonding involving the ammonium and trifluoroacetate groups are observable in the lattice (see the Supporting Information).

Host−Guest Behavior, in Solution, of the Chiral Tris-ammonium Salts 4·3H$^+$, 7·3H$^+$, and 10·3H$^+$. First, the conformational behavior of the protonated derivatives of **4**, **7**, and **10** was studied by ^{1}H NMR spectroscopy. Upon addition of an excess (ca. 5 equiv) of TFA to a CDCl$_3$ solution of **4**, **7**, or **10**, new NMR signals corresponding to the tris-ammoniums salts **4·3H**$^+$, **7·3H**$^+$, and **10·3H**$^+$ were obtained.[26] Compounds **4·3H**$^+$ and **7·3H**$^+$ possess a conformation with the methoxy groups and the bulky ammonium arms in *in* and *out* positions, respectively (δ_{OMe} = 1.7 ppm and <2.5 ppm for **4·3H**$^+$ and **7·3H**$^+$, respectively). In contrast, the quasi-normal OMe resonances of **10·3H**$^+$ (3.1 ppm < δ_{OMe} < 3.8 ppm) indicated that, upon protonation, compound **10** switched from a flattened cone conformation to the opposite one with the methoxy groups being expulsed from the calixarene cavity. A similar conformational behavior in solution was observed with the parent calix[6](NH$_3^+$)$_3$ receptor.[14] This result is in accordance with the X-ray structure described above and suggests that, in chloroform, the ammonium arms of **10·3H**$^+$ are assembled with the counteranions in an ion-paired cap that closes the calixarene narrow rim.

Afterward, an ^{1}H NMR study of the host−guest behavior of **4·3H**$^+$, **7·3H**$^+$**,** and **10·3H**$^+$ was undertaken in CDCl$_3$. Unsurprisingly, upon the addition of small polar neutral molecules such as EtOH, DMF, and DMSO to a solution of **4·3H**$^+$ or **7·3H**$^+$, the ^{1}H NMR spectra remained unchanged and no endo-complexation was detected even at low temperature (223 K). This result clearly demonstrates that the permanent filling of the cavity by the OMe groups prevents the inclusion of neutral guests. In contrast, when DMSO (ca. 10 equiv) was added into a solution of **10·3H**$^+$, its NMR signals decreased in intensity and broadened. Moreover, a new dissymmetrical species which was associated with high-field signals (two singlets at −0.28 and −0.38 ppm) was observed (Figure 4a,b). NOESY experiments indicated that these high-field resonances belong to the unequivalent methyl groups of a guest DMSO molecule deeply included in the calixarene cavity (endo-complex **10·3H**$^+$⊃**DMSO**, Scheme 2). It is noteworthy that the methyl groups of this guest DMSO molecule are diastereotopic since they sense the chiral environment provided by the host. Moreover, the slow *in* and *out* exchange process of DMSO at room temperature, compared to the NMR time scale, emphasizes its strong binding by **10·3H**$^+$. Lowering the temperature had the following consequences: (i) all the resonances sharpened, (ii) the guest DMSO methyl signals experienced an upfield shift and a better splitting, and (iii) the proportion of the host−guest adduct **10·3H**$^+$⊃**DMSO** increased and finally became the only observable species at 223 K (Figure 4c). In comparison to **10·3H**$^+$, the larger splitting of the ArH and *t*-Bu signals of **10·3H**$^+$⊃**DMSO** indicates that the calixarene host adopts a flatter conformation upon complexation. The NMR resonances of the diastereotopic secondary ammonium protons are lower field than the primary ones (δ_{NH3+} = 8.30 and 8.65 ppm, δ_{NH2+} = 10.0 and 11.1 ppm). This result is in accordance with the X-ray structure of the endo-complex **10·3H**$^+$⊃**CH$_3$CN**, which has shown that the secondary ammonium protons are less directed toward the inside of the cavity.

These results prompted us to study, by NMR, the host−guest properties of **10·3H**$^+$ toward other small neutral polar molecules. Thus, a typical experiment consisted of dissolving pure **10·3H**$^+$ in CDCl$_3$ and by adding a few molar equivalents of a potential guest in the tube. NMR analyses (^{1}H, NOESY) were undertaken at low temperature and showed the complexation of primary amides, methanesulfonamide, 1,2-diol, and DMF (Scheme 2, Table 1). On the other hand, no endo-complexation was observed for compounds of low polarity (i.e., CH$_2$Cl$_2$, CHCl$_3$, Et$_2$O). Indeed, it was already shown with the parent calix[6](NH$_3^+$)$_3$ receptor that the crucial charge-dipole interaction between the tris-cationic cap and the guest molecule cannot take place with such apolar compounds. The relative affinities of some guests toward host **10·3H**$^+$ were determined at 263 K through ^{1}H NMR competitive binding experiments (see the Experimental Section, Table 1). Similar to the parent calix-

(25) Sénèque, O.; Giorgi, M.; Reinaud, O. *Supramol. Chem.* **2003**, *15*, 573−580. See ref 14.

(26) All the ^{1}H NMR signals of **4·3H**$^+$, **7·3H**$^+$, and **10·3H**$^+$ were assigned through HMQC analyses.

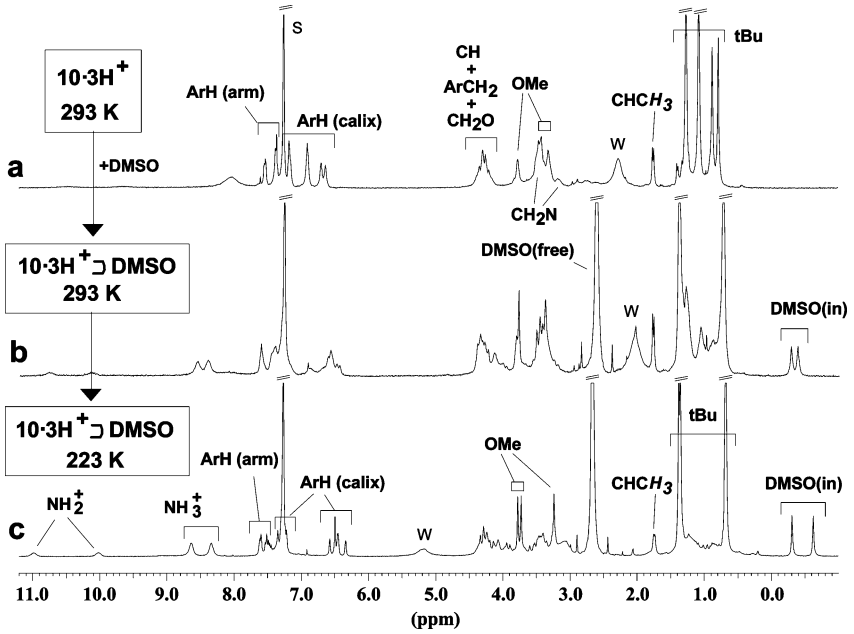


FIGURE 4. ^{1}H NMR spectra ($CDCl_3$): (a) **10·3H$^+$** at 293 K; (b) **10·3H$^+$⊃DMSO** at 293 K; (c) **10·3H$^+$⊃DMSO** at 223 K. Residual solvents and water are labeled S and W, respectively.

TABLE 1. Relative Affinities of Neutral Guests (G) toward Host 10·3H$^+$ and Observed NMR Complexation Induced Upfield Shifts (CIS)

			CIS[b] (ppm)		
entry	G	relative affinity[a]	α	β	γ
1	DMF	1	−1.41		−3.36[c]
2	DMSO	2.96		−3.15[c]	
3	(±)-propane-1,2-diol	0.92	−2.25[d,e]	−2.01[d,e]	−3.29[d,e]
4	CH_3CONH_2	28.3		−2.84[d]	
5	$EtCONH_2$	0.90		−2.11	−3.09
6	$ClCH_2CONH_2$	–		−2.18[d]	
7	$CH_3SO_2NH_2$	14.8		−3.34[d]	

[a] Calculated in $CDCl_3$ at 263 K and defined as $[G_{in}]/[DMF_{in}] \times [DMF_T]/G_T]$ where indexes "in" and "T" stand for "included" and "total amount", respectively. Errors estimated ±10%. [b] CIS calculated in $CDCl_3$ at 223 K and defined as $\Delta\delta = \delta$(complexed G) − δ(free G). α, β, and γ refer to the relative position of the protons to the oxygen atom. In the case of the guest propane-1,2-diol molecule, it refers to the position to the primary alcohol group. [c] Average value of the two unequivalent methyl groups. [d] Determined at 263 K. [e] Average value of the signals of the two diastereomers determined through a NOESY experiment.

[6]$(NH_3^+)_3$ receptor, acetamide displays the highest relative affinity (entry 4) since it combines a small size, a high dipolar moment (μ = 3.7 D), and the possibility to establish hydrogen bonds with the oxygen atoms of the calixarene core. In all cases (entries 1−7), the oxygen atom of the polar guest should be involved in the hydrogen-bonding network that caps the host structure.[27] The protons in the γ-position of this oxygen atom sit in the center of the hydrophobic cavity since they possess the highest shift values (see the complexation-induced shifts (CIS) of the guest proton resonances, Table 1, entries 1, 3, and 5).

Very interestingly, with the prochiral guests $ClCH_2CONH_2$ and $EtCONH_2$, a splitting of the resonances of their diastereotopic methylene protons was observed at low temperature. Similar to the case of the guest DMSO, it shows that the asymmetry of the chiral moiety is efficiently transmitted to the calixarene host and finally experienced by these guests. These promising results clearly demonstrate that a chiral recognition process is possible in the cavity of **10·3H$^+$**. Thus, the endo-complexation of chiral racemic molecules was tested at low temperature (223 K) in order to observe an eventual chiral discrimination between their two enantiomers. To our delight, the addition of (±)-propane-1,2-diol to **10·3H$^+$** led to a mixture of the two diastereomeric endo-complexes with a ca. 6:4 ratio in favor of **10·3H$^+$⊃(+)-propane-1,2-diol**.[28] Indeed, the methyl group of the included diol guest displayed two unequivalent doublets at δ_{CH3} = −2.24 and −2.28 ppm corresponding, respectively, to the two diastereomers **10·3H$^+$⊃(−)-propane-1,2-diol** and **10·3H$^+$⊃(+)-propane-1,2-diol** (see the Supporting Information).[29] To our knowledge, this result constitutes the first case of enantiomeric discrimination inside the cavity of an enantiopure calix[6]arene. With bulkier chiral racemic amides (lactamide, 2-chloropropanamide) or diols (butane-1,2-diol, butane-1,3-diol), no endo-complexation was detected even at low temperature. This indicates that the presence of the *t*-Bu groups of the anisole moieties at the entrance of the cavity ensures a severe size selectivity.

(27) In the case of propane-1,2-diol, the strong upfield shift of the γ-methyl protons (i.e., −3.29 ppm, Table 1) indicates this is likely the oxygen atom of the less bulky primary alcohol group which is hydrogen bonded to the ammonium groups. The secondary alcohol group may establish a supplementary hydrogen bond with an oxygen atom of the calixarene core.

(28) The complexity of the whole ^{1}H NMR spectrum and the overlapping of the CH_3 signals of the included diol guests prevented us from determining a very precise value for the diastereomeric excess (see the Supporting Information).

(29) A similar NMR host−guest study was undertaken with the enantiopure *R*-(−)-propane-1,2-diol, which allowed us to attribute the signals of the methyl group of each enantiomeric guest (see the Supporting Information).

Conclusion

The optically pure calix[6]arenes bearing chiral amino arms **4**, **7**, and **10** have been synthesized in high yields. An efficient selective alkylation pathway of the 1,3,5-tris-methylated calix[6]arene has been developed thanks to the use of $Ba(OH)_2$ as the base. An NMR conformational study has shown that these chiral calix[6]N_3 derivatives possess a flattened cone conformation with their methoxy groups being directed toward the inside of the cavity. Upon protonation, the two chiral calix[6]arenes **4** and **7** are not able to direct their ammonium arms toward the inside of the cavity because of the bulkiness of the chiral moiety. In contrast, the chiral derivative bearing only one chiral arm, i.e., **10**, undergoes a conformational change with the three ammonium arms forming a tris-cationic chiral binding site which caps the cavity. This leads to an efficient polarized host (**10**·**3H**$^+$) for small polar neutral molecules as illustrated by NMR host−guest studies and an X-ray structure. We have shown that prochiral guests can sense the asymmetry of this optically pure molecular receptor. The first example of enantioselective molecular recognition inside the cavity of a calix[6]arene has been even evidenced with a racemic guest. We are currently working toward the design of derivatives of **10** possessing an open cavity for the inclusion of larger guests. Moreover, the host−guest chemistry of the metal complexes of **4**, **7**, and **10** has to be explored. All this work should be helpful for the design of chiral calixarene receptors useful for applications in the fields of enantioselective catalysis and analysis.

Experimental Section

Chiral Calix[6]tris-amide 3. $X_6H_3Me_3$ **1** (0.501 g, 0.49 mmol) was added to a solution of NaH (60 wt % in oil, 0.076 g, 1.97 mmol) in anhydrous THF (20 mL). The reaction mixture was refluxed for 15 min, and a solution of *S*-(−)-2-bromo-*N*-(1-phenylethyl)acetamide **2** (0.476 g, 1.97 mmol) in 10 mL of anhydrous THF was slowly introduced. After 2 h of refluxing, the reaction mixture was cooled at 0 °C, and ethanol was slowly added until the gas liberation ceased. The solvent was removed under reduced pressure, and the resulting residue was dissolved in dichloromethane (50 mL) and washed with aqueous 0.1 N HCl (2 × 25 mL). After dichloromethane extraction, drying, filtration, and solvent evaporation, the resulting crude compound was purified by flash chromatography (ethyl acetate/dichloromethane; 15:85) giving pure calix[6]tris-amide **3** (0.590 g, 80%) as a white solid: mp 137 °C dec; $[\alpha]^{20}_D$ = + 3 (*c* 1.0, $CHCl_3$); IR (KBr) ν 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81 (s, 27H, *t*-Bu), 1.40 (s, 27H, *t*-Bu), 1.56 (d, J = 7 Hz, 9H, CHC*H*$_3$), 2.30 (s, 9H, OCH_3), 3.41 (d, J = 15 Hz, 3H, ArC*H*$_{eq}$), 3.51 (d, J = 15 Hz, 3H, ArC*H*$_{eq}$), 4.35 (d, J = 15 Hz, 3H, ArC*H*$_{ax}$), 4.41 (d, J = 15 Hz, 3H, ArC*H*$_{ax}$), 4. 44 (d, J = 15 Hz, 3H, OCH_2), 4.56 (d, J = 15 Hz, 3H, OCH_2), 5.19 (dq, $J_1 \approx J_2 \approx$ 8 Hz, 3H, C*H*CH$_3$), 6.66 (s, 3H, ArH_{calix}), 6.68 (s, 3H, ArH_{calix}), 7.15−7.35 (m, 21H, ArH_{calix} + ArH_{phe}), 7.62 (d, J = 8 Hz, 3H, NH); ^{13}C NMR ($CDCl_3$) δ 22.3, 30.0, 30.2, 31.0, 31.6, 34.0, 34.3, 48.5, 60.2, 71.7, 124.0, 124.2, 126.1, 127.3, 128.0, 128.2, 128.6, 128.9, 132.4, 132.8, 133.2, 133.3, 143.0, 146.4, 146.9, 150.7, 154.3, 167.8. Anal. Calcd for $C_{99}H_{123}N_3O_9$·H_2O: C, 78.38; H, 8.31; N, 2.77. Found: C, 78.11; H, 8.21; N, 2.63.

Chiral Calix[6]tris-amine 4. A solution of BH_3/THF (8.8 mL, 8.8 mmol) was slowly added to calix[6]tris-amide **3** (0.440 g, 0.29 mmol), and the reaction mixture was refluxed for 24 h. Ethanol was slowly added at 0 °C until the gas liberation ceased. After removal of the solvent under reduced pressure, 10 mL of anhydrous ethanol was added to the resulting residue, and the reaction mixture was refluxed for 48 h. Ethanol was evaporated under reduced pressure, and the resulting viscous compound was dried overnight under vacuum (0.1 mmHg) at 50 °C yielding calix[6]tris-amine **4** as a white solid. This latter was dissolved in dichloromethane (10 mL) and washed with an aqueous NaOH solution (5 mL, 1 M). After removal under reduced pressure of the solvent, calix[6]tris-amine **4** (0.363 g, 85%) was obtained pure as a white solid: mp 102 °C dec; $[\alpha]^{20}_D$ = −11 (*c* 1.0, $CHCl_3$); IR (KBr) ν = 3423, 2956 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 27H, *t*-Bu), 1.41 (s_b, 36H, *t*-Bu + CHC*H*$_3$), 2.23 (s, 9H, OC*H*$_3$), 2.86−3.03 (m, 6H, CH_2N), 3.42 (d, J = 15 Hz, 6H, ArC*H*$_{2eq}$), 3.93 (q, J = 6 Hz, 3H, C*H*CH$_3$), 3.96−4.05 (m, 6H, OCH_2), 4.59 (d, J = 15 Hz, 6H, ArC*H*$_{2ax}$), 6.66 (s, 6H, ArH_{calix}), 7.22−7.41 (m, 21H, ArH_{calix} + ArH_{phe}); ^{13}C NMR ($CDCl_3$) δ 24.6, 29.7, 31.1, 31.7, 33.9, 34.2, 47.9, 58.3, 60.2, 72.3, 123.5, 126.8, 126.9, 128.0, 128.1, 128.4, 133.2, 133.5, 145.6, 145.7, 151.7, 154.5. Anal. Calcd for $C_{99}H_{129}N_3O_6$·2 H_2O: C, 79.64; H, 8.98; N, 2.81. Found: C, 79.71; H, 8.98; N, 2.67.

Calix[6]mono-amide 5. Anhydrous DMF (6 mL) was added to a mixture of $X_6H_3Me_3$ **1** (0.150 g, 0.148 mmol), Ba-$(OH)_2$·$8H_2O$ (0.152 g, 0.482 mmol), and bromoacetamide (26.5 mg, 0.192 mmol). The reaction mixture was stirred at room temperature for 2 h and then was poured into water (25 mL) and vigorously stirred. The resulting precipitate was isolated by centrifugation, dissolved in dichloromethane, and washed with water. The organic layer was separated and dried over $MgSO_4$, and the solvent was removed under low pressure. The crude product was chromatographed (acetone/dichloromethane; 2:98 then 10:90), giving starting material (i.e., $X_6H_3Me_3$ **1**, 36 mg, 24%) and pure calix[6]monoamide **5** (96 mg, 60%) as a white solid: mp 172 °C dec; IR (KBr) ν = 3489, 3379, 2956, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (s, 9H, *t*-Bu), 1.04 (s, 18H, *t*-Bu), 1.31 (s, 18H, *t*-Bu), 1.40 (s, 9H, *t*-Bu), 3.29 (s, 2H, OCH_2-CO), 3.70 (s, 6H, OCH_3), 3.85 (s, 4H, ArC*H*$_2$), 3.92 (s, 3H, OCH_3), 3.95 (s, 4H, ArC*H*$_2$), 3.98 (s, 4H, ArC*H*$_2$), 4.83 (s, 1H, $CONH_2$), 5.21 (s, 1H, $CONH_2$), 6.35 (s, 2H, ArH), 6.49 (s, 2H, ArH), 7.02 (d, 2H, J = 2 Hz, ArH), 7.10 (d, 2H, J = 2 Hz, ArH), 7.21 (d, 2H, J = 2 Hz, ArH), 7.25 (s, 2H, ArH), 7.34 (s, 2H, ArO*H*); ^{13}C NMR ($CDCl_3$) δ 30.4, 30.6, 31.0, 31.2, 31.5, 31.6, 33.9, 34.1, 34.3, 59.9, 60.7, 71.0, 124.0, 125.4, 125.7, 127.0, 127.1, 128.2, 132.4, 132.7, 132.9, 133.7, 142.2, 146.1, 147.0, 147.1, 150.3, 151.8, 152.6, 153.5, 172.0; Anal. Calcd for $C_{71}H_{93}$-NO_7·$0.5H_2O$: C, 78.85; H, 8.76; N, 1.30. Found: C, 78.97; H, 8.79; N, 1.26.

Chiral Calix[6]tris-amide 6. Calix[6]mono-amide **5** (1.10 g, 1.03 mmol) was added to a solution of NaH (60 wt % in oil, 0.090 g, 2.26 mmol) in anhydrous THF (40 mL). The reaction mixture was refluxed for 15 min, and a solution of *S*-(−)-2-bromo-*N*-(1-phenylethyl)acetamide **2** (0.596 g, 2.46 mmol) in 10 mL of anhydrous THF was slowly introduced. After 16 h of refluxing, ethanol was slowly added at 0 °C until the gas liberation ceased. The solvent was removed under reduced pressure, and the resulting residue was dissolved in dichloromethane (50 mL) and washed with water (50 mL). After dichloromethane extraction, drying, filtration, and solvent evaporation, the resulting crude compound was purified by flash chromatography (ethyl acetate/dichloromethane; 1:4) giving pure calix[6]tris-amide **6** (0.815 g, 57%) as a white solid: mp 167 °C dec; $[\alpha]^{20}_D$ = +23 (*c* 1.0, $CHCl_3$); IR (KBr) ν = 3478, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 330 K) δ 0.92 (s, 9H, *t*-Bu), 0.95 (s, 9H, *t*-Bu), 1.10 (s, 9H, *t*-Bu), 1.24 (s, 9H, *t*-Bu), 1.26 (s, 9H, *t*-Bu), 1.37 (s, 9H, *t*-Bu), 1.51−1.59 (m, 6H, CHC*H*$_3$), 2.73 (s, 3H, OCH_3), 2.75 (s, 3H, OCH_3), 2.82 (s, 3H, OCH_3), 3.35−3.72 (m, 6H, ArC*H*$_2$), 4.08−4.55 (m, 12H, OCH_2 + ArC*H*$_2$), 5.20−5.40 (s_b + dq, $J_1 \approx J_2 \approx$ 7 Hz, 4H, NH_2 + C*H*CH$_3$), 6.72 (s, 2H, ArH), 6.83 (s, 1H, ArH), 6.86 (s, 1H, ArH), 6.97 (s, 2H, ArH), 7.00 (s, 1H, ArH), 7.04 (s, 1H, ArH), 7.18−7.28 (m, 8H, ArH), 7.38−7.40 (m, 6H, ArH), 7.64 (d, J = 8 Hz, 1H, NH), 7.79 (d, J = 8 Hz, 1H, NH). Anal. Calcd for $C_{91}H_{115}N_3O_9$·H_2O: C, 77.36; H, 8.35; N, 2.97. Found: C, 77.51; H, 8.06; N, 3.13.

Chiral Calix[6]tris-amine 7. A solution of BH_3/THF (15.07 mL, 15.07 mmol) was slowly added to calix-tris-amide **6** (0.730 g, 0.502 mmol), and the reaction mixture was refluxed for 24 h. Ethanol was slowly added at 0 °C until gas liberation ceased. After removal of the solvent under reduced pressure, 20 mL of anhydrous ethanol was added to the resulting residue, and the reaction mixture was refluxed for 48 h. Ethanol was evaporated under reduced pressure, and the resulting viscous compound was dried overnight under vacuum (0.1 mmHg) at 50 °C, yielding calix[6]tris-amine **7** as a white solid. This latter was dissolved in dichloromethane (20 mL) and washed with an aqueous NaOH solution (2 × 20 mL, 1 M). After removal of the solvent under reduced pressure, calix[6]tris-amine **7** (0.704 g, 99%) was obtained pure as a white solid: mp 205 °C dec; $[\alpha]^{20}_D = -19$ (*c* 1.0, $CHCl_3$); IR (KBr) $\nu = 3390, 2962, 1482\ cm^{-1}$; ^1H NMR ($CDCl_3$, 330 K) δ 0.83 (s, 9H, *t*-Bu), 0.87 (s, 9H, *t*-Bu), 0.91 (s, 9H, *t*-Bu), 1.37−1.42 (m, 33H, *t*-Bu + CHC*H*$_3$), 2.24−2.37 (m, 6H, OCH_3), 2.44 (s, 3H, OCH_3), 2.84−3.11 (m, 6H, CH_2N), 3.39−3.61 (m, 6H, ArC*H*$_2$*eq*), 3.81 (t, J = 6 Hz, 2H, OCH_2), 3.86−4.10 (m, 6H, OCH_2 + C*H*CH_3), 4.42−4.61 (m, 6H, ArC*H*$_2$*ax*), 6.67−6.80 (m, 6H, ArH_{calix}), 7.18−7.44 (m, 16H, ArH_{calix} + ArH_{phe}). Anal. Calcd for $C_{91}H_{121}N_3O_6 \cdot 3.5H_2O$: C, 77.19; H, 9.11; N, 2.97. Found: C, 77.10; H, 8.86; N, 2.83.

Calix[6]diamide 8. Anhydrous DMF (20 mL) was added to a mixture of $X_6H_3Me_3$ **1** (0.500 g, 0.490 mmol), $Ba(OH)_2 \cdot 8H_2O$ (0.928 g, 2.94 mmol), and bromoacetamide (0.199 mg, 1.47 mmol). The reaction mixture was stirred at 80 °C for 30 min and then was poured into water (100 mL) and vigorously stirred. The resulting precipitate was isolated by centrifugation, dissolved in dichloromethane, and washed with water. The organic layer was separated and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was chromatographed (acetone/dichloromethane; 10:90) giving starting material (i.e., $X_6H_3Me_3$ **1**, 15 mg, 3%) and pure calix[6]diamide **8** (0.282 g, 51%) as a white solid: mp 164 °C dec; IR (KBr) $\nu = 3484, 3374, 2956, 1685\ cm^{-1}$; ^1H NMR ($CDCl_3$) δ 0.88 (s_b, 18H, *t*-Bu), 1.04 (s, 9H, *t*-Bu), 1.33 (s, 9H, *t*-Bu), 1.35 (s_b, 18H, *t*-Bu), 3.54 (s, 3H, OCH_3), 3.85 (s_b, 6H, OCH_3), 3.94 (s_b, 16H, ArC*H*$_2$ + OCH_2), 5.08 (s_b, 4H, $CONH_2$), 6.26 (s, 2H, ArH), 6.58 (s_b, 2H, ArH), 6.80 (s_b, 2H, ArH), 7.12 (s, 2H, ArH), 7.15 (s, 2H, ArH), 7.30 (d, 2H, J = 2 Hz, ArH), 7.35 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 31.1, 31.2, 31.3, 31.5, 31.6, 34.0, 34.2, 58.9, 60.6, 71.6, 124.2, 124.8, 126.3, 127.6, 128.1, 131.3, 132.3, 133.4, 133.6, 142.7, 146.1, 147.0, 149.4, 153.0, 153.6, 171.3; Anal. Calcd for $C_{73}H_{96}N_2O_8 \cdot 0.5H_2O$: C, 77.01; H, 8.59; N, 2.46. Found: C, 77.05; H, 8.96; N, 2.28.

Chiral Calix[6]tris-amide 9. Calix[6]diamide **8** (1.80 g, 1.59 mmol) was added to a solution of NaH (60 wt % in oil, 0.070 g, 1.75 mmol) in anhydrous THF (40 mL). The reaction mixture was refluxed for 15 min, and a solution of *S*-(−)-2-bromo-*N*-(1-phenylethyl)acetamide **2** (0.436 g, 1.91 mmol) in 10 mL of anhydrous THF was slowly introduced. After 16 h of refluxing, ethanol was slowly added at 0 °C until the gas liberation ceased. The solvent was removed under reduced pressure, and the resulting residue was dissolved in dichloromethane (50 mL) and washed with water (50 mL). After dichloromethane extraction, drying, filtration, and solvent evaporation, the resulting crude compound was purified by flash chromatography (ethyl acetate/dichloromethane; 2:3) giving pure calix[6]tris-amide **9** (1.55 g, 76%) as a white solid: mp 177 °C dec; $[\alpha]^{20}_D = +26$ (*c* 1.0, $CHCl_3$); IR (KBr) $\nu = 3484, 1685\ cm^{-1}$; ^1H NMR ($CDCl_3$, 330 K) δ 1.04 (s, 9H, *t*-Bu), 1.06 (s, 9H, *t*-Bu), 1.10 (s, 9H, *t*-Bu), 1.19 (s, 9H, *t*-Bu), 1.32 (s, 9H, *t*-Bu), 1.34 (s, 9H, *t*-Bu), 1.50 (d, J = 7 Hz, 3H, CHC*H*$_3$), 3.41 (s, 6H, OCH_3), 3.59 (s, 3H, OCH_3), 3.52−4.00 (m, 12H, OCH_2 + ArC*H*$_2$), 4.11 (d, J = 17 Hz, 2H, ArC*H*$_2$), 4.31 (d, $J \approx 14$ Hz, 1H, ArC*H*$_2$), 4.36 (d, $J \approx 14$ Hz, 1H, ArC*H*$_2$), 4.45 (s, 2H, OCH_2), 4.83 (s_b, 4H, $CONH_2$), 5.26 (dq, $J_1 \approx J_2 \approx 8$ Hz, 1H, C*H*CH_3), 6.54 (s, 1H, ArH), 6.57 (s, 1H, ArH), 6.78 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.87 (s, 2H, ArH), 7.05 (s, 2H, ArH), 7.12 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.23−7.38 (m, 7H, ArH), 7.81 (s_b, 1H, N*H*CH). Anal. Calcd for $C_{83}H_{107}N_3O_9 \cdot H_2O$: C, 76.17; H, 8.39; N, 3.21. Found: C, 76.02; H, 8.14; N, 3.32.

Chiral Calix[6]tris-amine 10. A solution of BH_3/THF (36.03 mL, 36.03 mmol) was slowly added to calix[6]tris-amide **6** (1.55 g, 1.201 mmol), and the reaction mixture was refluxed for 24 h. Ethanol was slowly added at 0 °C until the gas liberation ceased. After removal of the solvent under reduced pressure, 35 mL of anhydrous ethanol was added to the resulting residue, and the reaction mixture was refluxed for 48 h. Ethanol was evaporated under reduced pressure, and the resulting viscous compound was dried overnight under vacuum (0.1 mmHg) at 50 °C yielding calix[6]tris-amine **10** as a white solid. This latter was dissolved in dichloromethane (30 mL) and washed with an aqueous NaOH solution (2 × 30 mL, 1 M). After removal under reduced pressure of the solvent, calix[6]tris-amine **10** (1.477 g, 99%) was obtained pure as a white solid: mp 199 °C dec; $[\alpha]^{20}_D = -16$ (*c* 1.0, $CHCl_3$); IR (KBr) $\nu = 3390, 2962, 1481\ cm^{-1}$; ^1H NMR ($CDCl_3$) δ 0.92 (s, 9H, *t*-Bu), 0.98 (s, 18H, *t*-Bu), 1.31 (s, 9H, *t*-Bu), 1.33 (s, 18H, *t*-Bu), 1.41 (d, J = 6 Hz, 3H, CHC*H*$_3$), 2.45 (s_b, 6H, OCH_3), 2.56 (s, 3H, OCH_3), 2.81−3.03 (m, 6H, CH_2N), 3.45 (d, J = 15 Hz, 2H, ArC*H*$_2$*eq*), 3.57−3.76 (m, 8H, CH_2O + ArC*H*$_2$*eq*), 3.91 (q, J = 6 Hz, 1H, C*H*CH_3), 3.97 (s_b, 2H, CH_2O), 4.21−4.40 (m, 4H, ArC*H*$_2$*ax*), 4.47 (d, J = 15 Hz, 2H, ArC*H*$_2$*ax*), 6.74 (s, 2H, ArH_{calix}), 6.80 (s, 2H, ArH_{calix}), 6.83 (s, 2H, ArH_{calix}), 7.14−7.44 (m, 11H, ArH_{calix} + ArH_{phe}). Anal. Calcd for $C_{83}H_{113}N_3O_6 \cdot 2.5H_2O$: C, 77.05; H, 9.19; N, 3.25. Found: C, 77.03; H, 8.85; N, 2.91.

Host−Guest Complex 10·3H$^+$⊃CH$_3$CN. Trifluoroacetic acid (225 μL, 2.94 mmol) was added to a solution of calix[6]-tris-amine **10** (111 mg, 0.089 mmol) in dichloromethane (1.0 mL), and the resulting solution was stirred at room temperature for 15 min. After removal of the solvent under reduced pressure, acetonitrile (1.0 mL) was added, and the solution was placed upon a slow diffusion of ether at 4 °C. After 7 days, pure chiral host **10·3H$^+$⊃CH$_3$CN** (0.115 g, 81%) was obtained as crystals suitable for X-ray analysis. Crystals were isolated by centrifugation and dried under vacuum: mp 206 °C dec. Anal. Calcd for $C_{83}H_{113}N_3O_6 \cdot 3CF_3COOH \cdot CH_3CN \cdot H_2O$: C, 66.24; H, 7.39; N, 3.40. Found: C, 66.03; H, 7.17; N, 3.02.

Determination of the Relative Affinities of the Neutral Guests G toward Host 10·3H$^+$ through ^{1}H NMR Competitive Binding Studies. In a typical procedure, DMF (60 equiv) and DMSO (50 equiv) were successively added in a $CDCl_3$ solution (0.60 mL) containing **10·3H$^+$** (5 mg, 3 μmol). An ^1H NMR spectrum recorded at 263 K showed the guest resonances of both endo-complexes **10·3H$^+$⊃DMF** and **10·3H$^+$⊃DMSO** besides the signals corresponding to the free DMF and DMSO. The integrations of the methyl group of the free guests and of the included guests were used to calculate the relative affinity defined as $[G_{in}]/[DMF_{in}] \times [DMF_T]/[G_T]$ (errors estimated ±10%). Ratio of neutral molecules G used for the other NMR competitive experiment: DMF/$EtCONH_2$ = 1.00; DMF/(±)-propane-1,2-diol = 0.48; DMF/$AcNH_2$ = 12.1; DMF/$CH_3SO_2NH_2$ = 9.07.

X-ray Structure Determination of Complex 10·3H$^+$⊃CH$_3$CN. X-ray quality crystals of complex **10·3H$^+$⊃CH$_3$CN** were grown as described above. Crystal data: $M_w = 1667.96$, orthorhombic, colorless crystal (0.4 × 0.3 × 0.2 mm^3), a = 18.9165(2) Å, b = 19.0923(3) Å, c = 26.6298(5) Å, V = 9617.8(3) Å^3, space group $P2_12_12_1$, $Z = 4$, $\rho = 1.152\ g\ cm^{-3}$, μ(Mo Kα) = 0.87 cm^{-1}, 18795 reflections measured at 223 K (Bruker-Nonius KappaCCD diffractometer[30]) in the 0.76−22.63° θ range, 6599 unique, 1087 parameters refined on F^2 [Shelxl][31] to final indices R[6053 refl: $F^2 > 4\sigma F^2$] = 0.0971, wR[6599 refl] = 0.2513 [$w = 1/[\sigma^2(F_o^2) + (0.1759P)^2 + 5.7794P]$ where $P = (F_o^2 + 2F_c^2)/3$]. Refinement details: complex **10·3H$^+$⊃CH$_3$CN** cocrystallized with three molecules of trifluoroacetate

(30) Bruker-Nonius 1998. Kappa CCD Reference Manual. Nonius, B. V., P.O. Box 811, 2600 Av, Delft, The Netherlands.

(31) Sheldrick, G. M. *SHELXL97. Program for the refinement of crystal structures*; University of Gottingen: Germany, 1997.

and a half molecule of diethyl ether. One CF_3COO^- and the Et_2O were found to be disordered and refined on several sites. One *tert*-butyl group showed severe disorder that prevented us to determine the position of the three carbon atoms. Restraints were applied to the disordered *tert*-butyl in order to get bond lengths with chemically reasonable values. All hydrogen atoms except those of the ammoniums and the disordered carbon atoms were introduced in geometric position, included in the calculations but not refined. The last residual Fourier positive and negative peaks were equal to 0.539 and −0.268, respectively. The CIF file for the X-ray structure of **10·3H$^+$⊃CH$_3$CN** has been submitted to the CCDC with entry number CCDC 278198.

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Supporting Information Available: Crystallographic data of **10·3H$^+$⊃CH$_3$CN**; ^{1}H NMR spectra of **3**, **4**, **6**−**10**, **10·3H$^+$⊃(−)-propane-1,2-diol**, **10·3H$^+$⊃(±)-propane-1,2-diol**; ^{13}C NMR spectra of **3**−**5** and **8**; HMQC spectra of **3**−**5** and **7**−**10**; HMBC spectra of **7**, **9**, and **10**; COSY spectra of **3**, **4**, **6**, **7**, **9**, and **10**; NOESY spectra of **10** and **10·3H$^+$⊃DMSO**; crystal structure of **10·3H$^+$⊃CH$_3$CN** displaying the main intermolecular H-bond interactions within the unit cell; general experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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