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First enantiopure calix[6]aza-cryptand: synthesis and chiral recognition properties towards neutral molecules

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Abstract—The synthesis of the first enantiopure calix[6]aza-cryptand was achieved in five steps from the known 1,3,5-tris-O-methylated calix[6]arene. A ^{1}H NMR spectroscopic study has shown that the chiral tren cap constrains the calixarene core in a straight cone conformation ideal for host–guest chemistry applications. As a result, the tetra-protonated derivative displays remarkable host properties towards polar neutral molecules and enantioselective recognition processes have been evidenced with chiral guests.

1. Introduction

The design of chiral synthetic receptors[1] is useful for the understanding of the chiral recognition processes, which occur in biological systems. Moreover, artificial hosts displaying chiral recognition ability towards neutral molecules can find applications in enantioselective catalysis and in the separation and analysis of enantiomers.[2] For this, chiral organic macrocycles presenting a cavity able to surround a guest molecule, such as cyclodextrins,[3] have been extensively studied.[4] Readily available calix[6]arenes could also constitute as ideal platforms for the design of such enantioselective *endo*-receptors.[5,6] Indeed, their cavity is large enough for the deep inclusion of organic molecules. Surprisingly, examples of enantiomerically pure calix[6]arenes are rare[7] and their host–guest properties towards chiral guests have not been investigated. This is mainly due to the fact that calix[6]-arenes suffer from their reputation as highly flexible molecules, which is not compatible with efficient syntheses and good host properties. However, three main strategies (i.e., the grafting of covalent bridges,[8] the coordination to a metal ion[9] and the use of self-assembly[10]) have been described for the rigidification of calix[6]arenes in the cone conformation, which is required for the *endo*-complexation of molecules. In this regard, we have recently developed a new class of calix[6]arenes bearing a tripodal aza-cap on the small rim.[11] The so called calix[6]aza-cryptand display a well defined cavity and an inhibited cone–cone inversion, thanks to the covalent cap. These compounds behave as remarkable molecular receptors towards neutral or charged species. For example, calix[6]tren **1** (Fig. 1, left) can bind either ammoniums, metal ions or neutral molecules according to

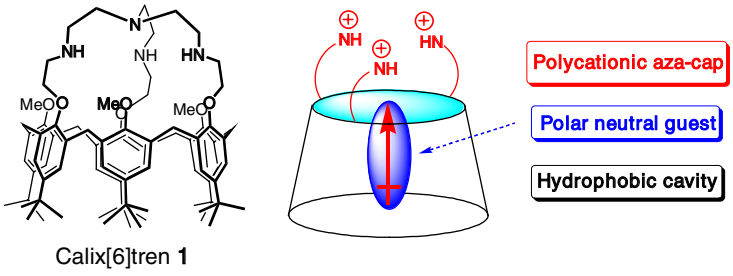

Figure 1. Left: calix[6]tren **1**; right: polarized calix[6]poly-ammonium receptors for neutral species.

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the way the receptor is polarized.[12] In particular, when the tren unit is fully protonated, it has been shown that the tetra-cationic aza-cap offers a strong binding site for polar neutral guests, thanks to hydrogen bonding and charge–dipole interactions. In addition, the guests are stabilized by CH–π interactions with the aromatic walls of the cavity. It is noteworthy that similar host–guest results have been obtained with a calix[6]arene lacking covalent bridges between the ammonium arms.[13] Thus, the polarization of a hydrophobic cavity with a polyammonium site is an efficient and general strategy for the design of receptors for polar neutral molecules (Fig. 1, right).

The next challenge was to synthesize enantiopure derivatives of the calix[6]aza-cryptands. Indeed, such receptors were expected to perform chiral recognition processes inside the heart of the hydrophobic cavity. Herein we report the synthesis and the conformational and host–guest properties of the first enantiopure calix[6]aza-cryptand.

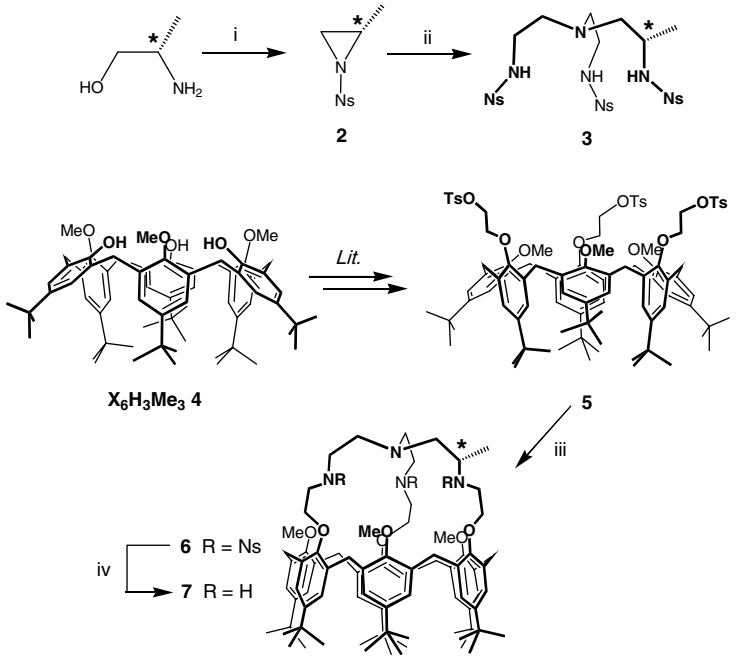
2. Results and discussion

2.1. Synthesis of the enantiopure calix[6]aza-cryptand 7

Calix[6]tren **1** was synthesized in five steps from the known 1,3,5-tris-O-methylated calix[6]arene **4** (X_6H_3-Me_3),[14] the key-step consisting of a [1+1] macrocyclization reaction between the 1,3,5-tris-tosylated calix[6]-arene **5** and a tren unit bearing 2-nitrobenzenesulfonyl groups (i.e., nosyl groups = Ns).[15] We chose to use a similar synthetic pathway for the preparation of the chiral calix[6]aza-cryptand **7**. For this, the chiral tren derivative **3** was synthesized in a two step sequence. First, according to a procedure described on closely related compounds,[16] the reaction of the (*S*)-2-aminopropan-1-ol with 3 equiv of NsCl in the presence of pyridine led to the expected aziridine **2**[17] in 74% yield after flash chromatography (FC) purification. Subsequent nucleophilic ring-opening of **2** by the known N-dinosylated tris-amine[18] [i.e., $HN(CH_2CH_2NHNs)_2$] afforded the tren derivative **3**[19] in 74% yield. The crucial [1+1] macrocyclization reaction between **3** and **5** was performed in presence of a Cs_2CO_3/K_2CO_3 mixture (0.5 and 3 equiv, respectively).[20] Under these basic conditions, the triply bridged calix[6]arene **6**[21] was then isolated by FC in 26% yield. Finally, the removal of the Ns groups under classical conditions gave the desired enantiopure calix[6]aza-cryptand **7**[22] in high yield (Scheme 1).

2.2. Conformational properties of the calix[6]aza-cryptand 7

Compound **7** was characterized by ^1H NMR spectroscopy in $CDCl_3$ (Fig. 2a) and the signals attributed through 2D NMR analyses (COSY, HMQC, HMBC). Compound **7** possesses a dissymmetrical NMR pattern since it displays, for example, three OMe resonances ($\delta_{OMe} = 2.83$, 3.00 and 3.06 ppm). This result is attributable to the presence of the stereogenic centre and it shows that the asymmetry of the cap is efficiently transmitted to the aromatic cavity. The presence of sharp and differentiated signals for the axial and equatorial ArCH_2 protons attests to the inhibition of the cone–cone interconversion thanks to the capping by the chiral tren unit. A variable NMR temperature study showed that the ^1H NMR spectrum of **7** was barely affected in the whole temperature range (from 262 to 330 K) with only some



Scheme 1. Reagents and conditions: (i) NsCl (3 equiv), pyridine (anhyd), CH_2Cl_2 (anhyd), 74%; (ii) $HN(CH_2CH_2NHNs)_2$ (1 equiv), MeOH, reflux, 74%; (iii) **3** (1 equiv), K_2CO_3 (3 equiv), Cs_2CO_3 (0.5 equiv), DMF (anhyd), 90 °C, 26%; (iv) PhSH (8 equiv), Na_2CO_3 (16 equiv); DMF (anhyd), 50 °C, 95%.

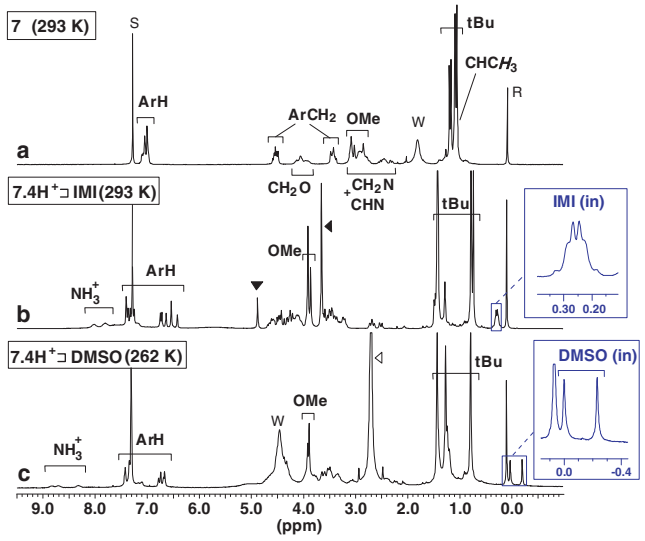


Figure 2. ^{1}H NMR spectra (300 MHz, $CDCl_3$): (a) **7** (293 K); (b) after addition of TFA (4 equiv) and IMI (ca. 2 equiv) (293 K); (c) after addition of TFA (4 equiv) and DMSO (ca. 35 equiv) (262 K). In the case of spectra b and c, some NH_3^+ signals above 9.5 ppm are not shown. (▼) signals of free IMI. (▽) signal of free DMSO. Residual solvents, water and reference have been labelled 'S', 'W' and 'R', respectively.

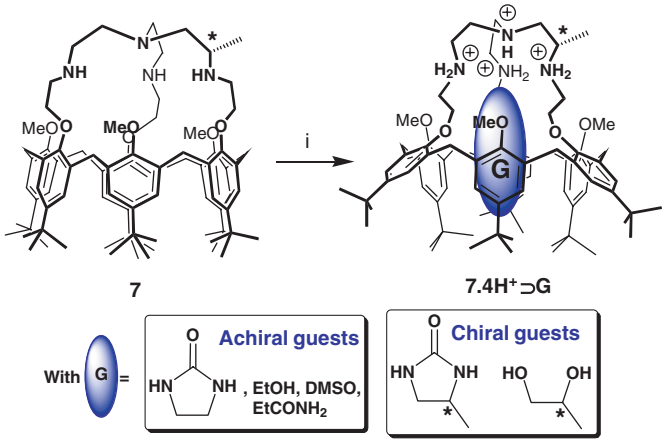
slight broadening of the spectra taking place at low temperature. As for the parent calix[6]tren **1**, the moderate high-field shift of the methoxy groups ($2.83 < \delta_{OMe} < 3.06$ ppm) and the small difference of resonance between the *t*Bu signals ($\Delta\delta_{tBu} = 0.14$ ppm) show that **7** adopts a straight and regular cone conformation with the OMe groups slightly included in the cavity (see the structure displayed on Scheme 1). This conformational behaviour is likely due to the presence of a hydrogen bonding network between the amino groups and the oxygen atoms of the calixarene core.

2.3. NMR study of the host–guest properties of 7.4H$^+$ towards achiral neutral molecules

The ability of compound **7** to act as a molecular receptor was investigated by ^{1}H NMR spectroscopy through its fully protonated derivative. Thus, the addition of 4 equiv of trifluoroacetic acid (TFA) to a solution of **7** in $CDCl_3$ led to the corresponding tetra-ammonium salt **7.4H**$^+$. This latter displayed an ill-defined NMR signature, which broadened at low temperature (262 K) indicating an empty cavity. However, upon the subsequent addition of polar neutral molecules such as imidazolidin-2-one (IMI), DMSO, $EtCONH_2$ or EtOH, new dissymmetrical NMR patterns, which were associated with high-field signals were observed (see Fig. 2b–c for IMI and DMSO at 293 and 262 K, respectively). NOESY experiments indicated that these high-field resonances belong to 1 equiv of the polar guest molecules deeply included in the calixarene cavity (*endo*-complex **7.4H**$^+ \supset$ **G**, Scheme 2).[23,24] In all cases, the normal resonances of the OMe groups of the anisole units ($\delta_{OMe} > 3.7$ ppm) attest that these groups have been expelled from the cavity upon complexation. In comparison with **7**, the larger difference of resonance between the *t*Bu signals ($\Delta\delta_{tBu} > 0.64$ ppm in all cases) shows that the cavity of **7.4H**$^+ \supset$ **G** adopts a flatter cone conformation (Scheme 2). It is also noteworthy that at rt, the *in* and *out* exchange process of IMI is slower than the NMR time scale. Moreover, a NMR competitive binding experiment conducted at 260 K showed that the affinity of IMI for **7.4H**$^+$ was at least 1360 times higher than the one of DMSO.[25] These results highlight the strong binding of IMI and its remarkable complementarity with the host **7.4H**$^+$. This is likely due to the fact that IMI possesses donor and acceptor hydrogen bonding groups ideally located for the establishment of multiple strong interactions with the ammoniums groups and the oxygen atoms of the calixarene core. Interestingly, diastereotopic signals were observed for the included DMSO and IMI molecules (DMSO: two methyl signals at −0.02 and −0.26 ppm; IMI: a broad multiplet at 0.26 ppm). This clearly shows that these guests can sense the chiral environment provided by the host.

2.4. Enantioselective recognition of chiral neutral molecules

In a second set of experiments, the host–guest properties of **7.4H**$^+$ towards chiral neutral molecules was evaluated by NMR. Thus, similarly to the previous study, **7.4H**$^+$



Scheme 2. Host–guest properties of the enantiomerically pure calix[6]aza-cryptand **7.4H**$^+$. (i) TFA (4 equiv), G.

was first generated in situ by the addition of TFA to **7**. The subsequent addition of chiral racemic guests [i.e., (±)-propane-1,2-diol (PPD) or (±)-4-methylimidazolidin-2-one (MIMI)[26]] led, in both cases, to a ca. 2:1 mixture of two diastereomeric *endo*-complexes (Fig. 3a and b). Indeed, the methyl group of the included guests displayed two unequivalent doublets corresponding to the two diastereomers **7.4H$^+$ ⊃ (−)-MIMI** and **7.4H$^+$ ⊃ (+)-MIMI** or **7.4H$^+$ ⊃ (−)-PPD** and **7.4H$^+$ ⊃ (+)-PPD**. In the case of (±)-PPD, the subsequent addition of the enantiopure (*R*)-(−)-PPD in the same NMR tube led to an inversion of the ratio, allowing us to attribute the signals of the methyl group of each enantiomeric guests (Fig. 3b and c). All these results clearly show a discrimination process between two enantiomers in the hydrophobic cavity of the host **7.4H$^+$**. This study constitutes a rare and may indeed be the first case of enantioselective recognition in the heart of the cavity of an enantiopure calix[6]arene.[27]

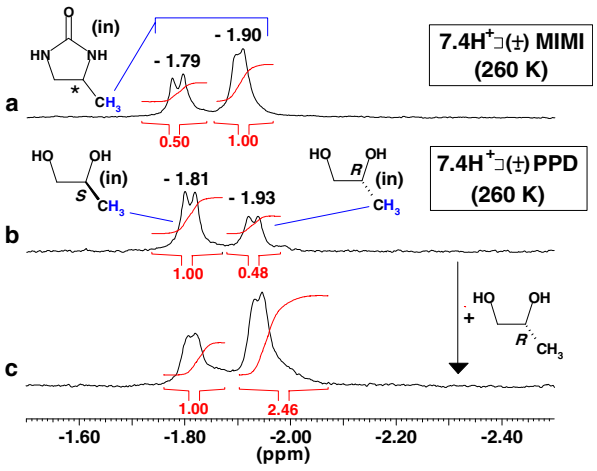


Figure 3. ^{1}H NMR spectra (guest region) (300 MHz, $CDCl_3$, 260 K): (a) 1:2 mixture of the two diastereomeric *endo*-complexes obtained upon the addition of (±)-MIMI (ca. 9 equiv) to **7.4H$^+$**; (b) 2:1 mixture of the two diastereomeric *endo*-complexes obtained upon the addition of (±)-PPD (ca. 17 equiv) to **7.4H$^+$**; (c) after the subsequent addition of *R*-(−)-PPD (ca. 23 equiv) to the previous mixture.

3. Conclusion

The first chiral calix[6]aza-cryptand **7** was prepared in five steps from the known $X_6H_3Me_3$ **4**. The chiral aza-cryptand cap prevents ring inversion, constraining the calixarene cavity to a straight cone conformation ideal for host–guest chemistry. Hence, NMR studies showed that the fully protonated derivative **7.4H$^+$** presents remarkable host–guest properties towards polar neutral molecules thanks to the tetra-cationic cap that provides an efficient binding site. Diastereotopic signals were observed with prochiral guests, indicating that the asymmetry of the molecular receptor can be experienced by the guests. Very originally, enantioselective molecular recognition processes inside the cavity of the molecular receptor **7.4H$^+$** have been evidenced with two structurally different racemic guests (i.e., a chiral 1,2-diol and a chiral imidazolidin-2-one). This work highlights the efficiency of an enantiopure polarized calix[6]arene to behave as an enantioselective molecular receptor. In order to develop applications in the field of enantioselective catalysis, we are now investigating the host–guest properties of the metal-complexes of **7**.

Acknowledgement

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17. Selected data for **2**: colourless oil, $[\alpha]_D^{20} = +109$ (*c* 0.7, $CHCl_3$). IR (neat): 1539, 1334, 1163, 852 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, $J = 6$ Hz, 3H), 2.27 (d, $J = 5$ Hz, 1H), 2.91 (d, $J = 7$ Hz, 1H), 3.11 (tq, $J_1 \approx J_2 \approx 6$ Hz, 1H), 7.71–7.80 (m, 3H), 8.19–8.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.15, 37.00, 38.86, 124.5, 131.3, 132.4, 132.7, 134.5.
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22. Selected data for **7**: Colourless solid, mp = 246 °C (dec), $[\alpha]_D^{20} = +16$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 3312, 2962, 1482, 1362 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.01–1.11 (m, 39H), 1.15 (s, 9H), 1.18 (s, 9H), 2.29 (d, $J = 11$ Hz, 1H), 2.36–2.48 (m, 2H), 2.52 (d, $J = 12$ Hz, 1H), 2.66–3.19 (m, 13H), 2.83 (s, 3H), 3.00 (s, 3H), 3.06 (s, 3H), 3.31–3.53 (m, 6H), 3.78–4.19 (m, 6H), 4.41–4.62 (m, 6H), 6.91–7.13 (m, 12H).
23. In the case of $\mathbf{7.4H^+} \supset \mathbf{IMI}$, the ^1H NMR signals were attributed through 2D NMR experiments (COSY, HMQC).
24. NMR chemical induced upfield shifts (in ppm) observed through the *endo*-complexation of the guests G. With G = IMI (293 K): −3.38 (CH_2); with G = DMSO (260 K): −2.80 (average value of the two unequivalent CH_3 groups); with G = $EtCONH_2$ (223 K): −3.33 (CH_3); with G = EtOH (223 K): −3.04 (CH_3).
25. Procedure for the determination of the relative affinities of the neutral guests (IMI and DMSO) towards host $\mathbf{7.4H^+}$ through a ^1H NMR competitive binding study: DMSO (143 equiv) and IMI (2 equiv) were added in a $CDCl_3$ solution (0.60 mL) containing $\mathbf{7.4H^+}$ (3 mg, 1.9 μmol). A ^1H NMR spectrum recorded at 260 K showed only the guest resonances of the *endo*-complex $\mathbf{7.4H^+} \supset \mathbf{IMI}$ besides the signals corresponding to the free DMF and IMI. Thus, the ratio of the included guests, that is, $IMI_{in}/DMSO_{in}$, was estimated to be at least 95:5 and the relative affinity $K_{IMI/DMF}$, defined as $[IMI_{in}]/[DMF_{in}] \times [DMF_T]/[IMI_T]$, was found to be at least 1360 (errors estimated ±10%).
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