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Synthesis of "Two-Story" Calix[6]aza-Cryptands

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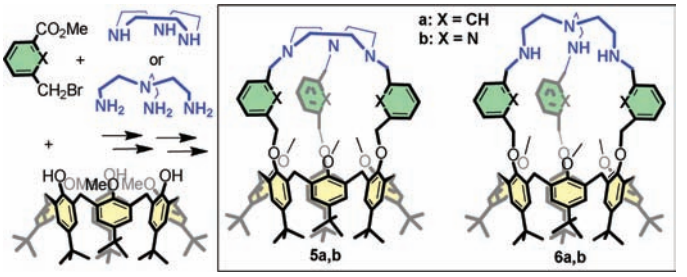
ABSTRACT



The first four members of a new family of C_{3v}-symmetrical "two-story" calix[6]aza-cryptands have been synthesized. These large funnel shaped aza-ligands are formed through introduction of three aromatic arms as spacers onto the small rim of a calix[6]arene and subsequently capped with the tripodal aza caps tacn [1,3,5-triazacyclononane] or tren [tris(aminoethyl)amine]. A key feature for an efficient final 1:1 macrocyclization appears to be an adequate geometrical fit between the extended calixarene scaffold and the aza caps.

Calix[6]arenes are useful building blocks for obtaining molecular receptors.[1] A prerequisite, however, for their use as a host is their rigidification into a cone conformation. Indeed these large macrocycles are highly flexible and easily undergo flipping of the aromatic walls through the annulus. We have developed strategies to close the small rim and constrain the calixarene core into a cone. The first one is based on coordination chemistry and led to the so-called "funnel" complexes.[2,3] The second one makes use of covalent linkages to yield calix[6]aza-cryptands.[4] These compounds, as illustrated in Figure 1, provide a hydrophobic cavity defined by the six aromatic units that is open at the large rim for guest hosting. Once coordinated in the aza cap, a metal ion has not only a distinct first coordination sphere but also a second coordination sphere well-defined by the oxygen-rich calix small rim separated by a two-atom linkage from the aza donors. Wanting to increase the size of the hydrophobic funnel and vary the second coordination core around the metal ions, we thought of inserting a spacer between the aza cap and the macrocycle. From a synthetic point of view, the spacer must be not only flexible enough to allow the aza cap to geometrically fit onto the small rim of the cone but also rigid enough to take advantage of the preorganization provided by the calixarene scaffold during the capping-macrocyclization. Indeed, one particularity of the so-called calix[6]aza-cryptands is that they cannot be purified by standard chromatographical methods. Therefore, a prerequisite for their isolation is a good yield in the final step. Here, we report the synthesis of the first members of such "two-story" calix[6]aza-cryptands based on the same

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synthetic strategy. The spacers are either *meta*-xylene or 2,6-dimethyl-pyridine units and the aza-caps are tacn [1,3,5-triazacyclononane] or tren [tris-(aminoethyl)amine], well-known ligands in coordination chemistry.

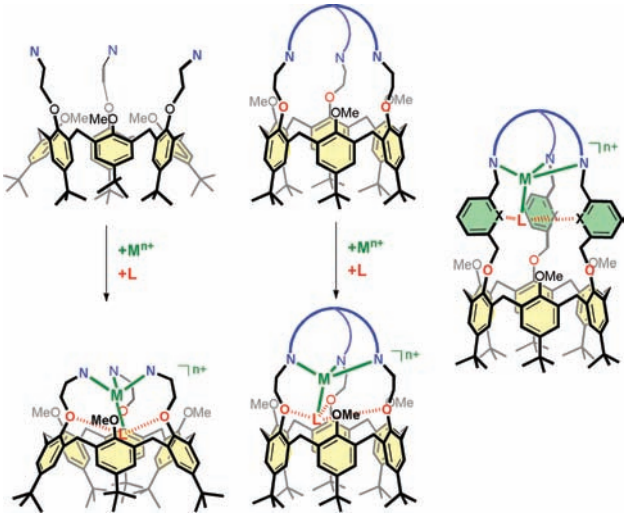

Figure 1. Left and center: funnel complexes obtained with calix-[6]aza-ligands with a two-atom spacer; right: a putative complex based on a "two-story" calix[6]aza-cryptand. The dashed lines highlight the second coordination sphere of the embedded metal ion.

Covalent capping of the calix-macrocycle has been successfully obtained either through the reaction of a nucleophilic cap with a calixarene prefunctionalized with electrophilic arms[4b,d,5] or, conversely, through the condensation of a nucleophilic calix-derivative with an electrophilic tripodal cap.[4a,c,d,6] Here, we chose the first option, and the multistep syntheses are depicted in Scheme 1.

The initial step is the introduction of three spacer arms bearing a function that will be subsequently transformed into a good electrophile. 1,3,5-Tris-*O*-methylated calix-[6]arene **1** was thus first reacted with either methyl 3-(bromomethyl)benzoate or methyl 6-(bromomethyl)picolinate in the presence of sodium hydride. The corresponding xyl-derivative **2a** and pyr-derivative **2b**[4d] were obtained in good yields. Although both molecules differ only in the phenyl vs pyridine groups, differences were observed in their chemical behavior. Xyl-ester **2a** revealed to be very sensitive to hydrolysis giving rise to carboxylic acid derivatives, whereas pyr-ester **2b** was fully stable in the presence of water.

The triester cores were then reduced into alcohols. Whereas the reaction proceeded smoothly and in high yield using $LiAlH_4$ for the xyl-derivative **2a**, reaction of triester **2b** with this metal hydride salt often led to the loss

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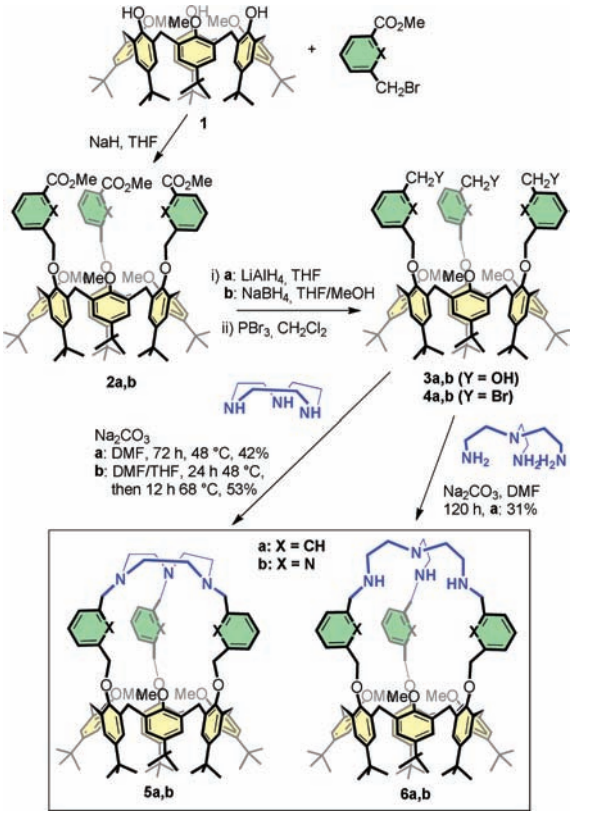
Scheme 1. Synthesis of Calix[6]xyl-tacn **5a**, Calix[6]pyr-tacn **5b**, Calix[6]xyl-tren **6a**, and Calix[6]pyr-tren **6b**[a]



[a] Overall yields from compound **1**: **5a**: 22%, **5b**: 44%, **6a**: 16%.

of pyridyl arms. Indeed, in the **b** case the methylene link between the phenoxyl units and the pyr group is very sensitive to nucleophilic attack. The smoother reducing reagent $NaBH_4$ was then advantageously used instead. Transforming the alcohol functions into electrophilic centers was carried out with PBr_3 to give the tris(bromo) derivatives **4a** and **4b**.

For all these intermediates, the ^1H NMR analyses indicate that the calixarene macrocycle adopts a flattened cone conformation as schematized in Scheme 1. Indeed, the chemical shift of the methoxy protons is situated around 2.3 ppm, indicating the position of the OMe groups close to the C_{3v} axis, while the bulkier free spacer arms are directed toward the outside of the cavity. For all compounds also, the two resonances of the *t*Bu groups and those corresponding to the aromatic protons of the calixarene skeleton display comparable chemical shift differences ($\Delta\delta_{tBu} \approx 0.5$ ppm and $\Delta\delta_{HAr} \approx 0.55$ ppm) indicating the similar alternate *in* and *out* positions of these aromatic units relative to the cavity.

The last step was the 1:1 macrocyclization of the bromo-derivatives **4a,b** with the nitrogen caps tacn and tren. All reactions were performed with a 1:1 calix/tripodal amine stoichiometry in the presence of sodium carbonate under reasonably diluted conditions (ca. 2×10^{-3} mol.L^{-1}) in either pure DMF (for compounds **5a**, **6a**, **6b**) or a

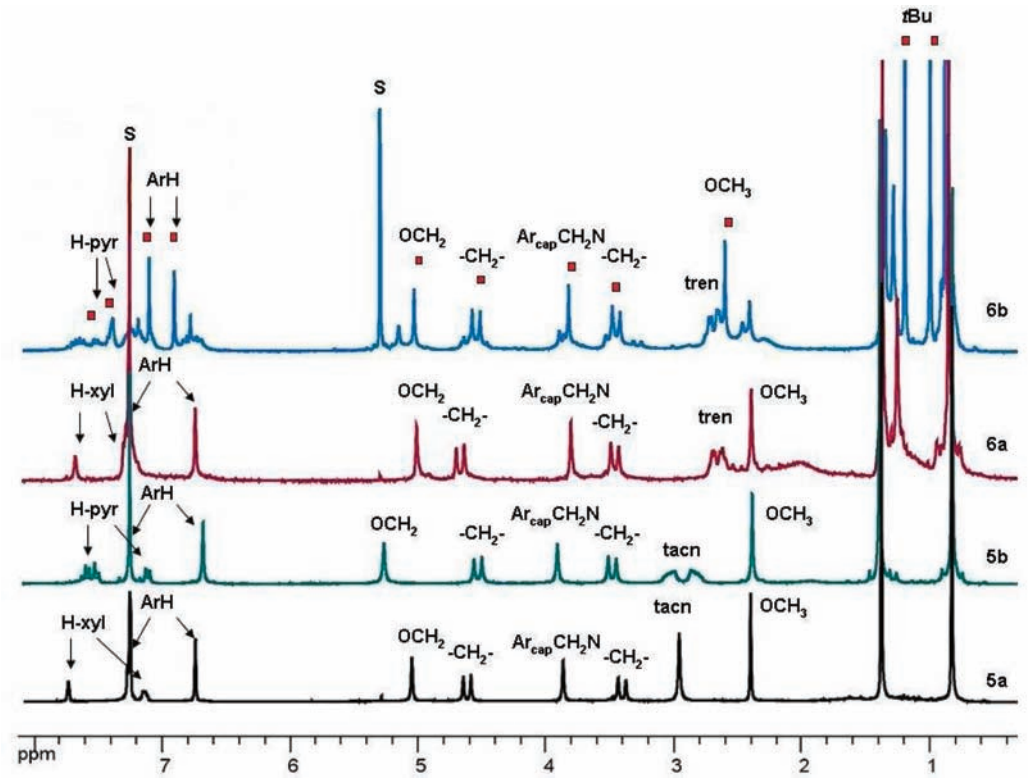


Figure 2. ^{1}H NMR spectra of calix[6]xyl-tacn **5a**, calix[6]pyr-tacn **5b**, calix[6]xyl-tren **6a**, and calix[6]pyr-tren **6b** (250 MHz, 300 K, $CDCl_3$ for **5a**, **5b**, **6a** and 250 MHz, 300 K, CD_2Cl_2 for **6b**). The red squares denote the resonances of **6b**. S denotes the solvent resonances.

DMF/THF mixture (for **5b**). After trituration in ether, the tacn ligands were isolated as pure compounds in 42% (X = CH, **5a**) and 53% (X = N, **5b**) yields. The same purification procedure afforded the tren ligand **6a** (X = CH) as a pure compound. The yield (31%) obtained for this tren ligand is a little lower than that for the corresponding tacn ones, which might be due to the higher flexibility of the tren cap. In the case of the N_7 derivative **6b**, we have never been able to isolate one single species. Indeed, the ^{1}H NMR spectrum of the isolated compound always indicated the presence of several species. One of these shows a C_{3v} symmetry which does correspond to the desired ligand **6b**, as described below.

These new cryptands were characterized by NMR spectroscopy. For compounds **5a**, **5b**, **6a**, the ^{1}H NMR signatures displayed in Figure 2 unambiguously attest to a C_{3v} symmetry. The resonances characteristic of the calix core have similar shifts, and hence the conformation is comparable in all three cases. The methylene groups bridging the aromatic units are split into two sets of diastereotopic protons, one signal for the axial and one for the equatorial position. Contrarily to precursors **2**–**4**, for compounds **5** and **6** this splitting was not affected by an increase of temperature, in agreement with the inhibition of the cone–cone inversion due to the covalent capping of their small rims. The pairs of *t*Bu and aromatic H_{Ar} resonances of the calixarene moiety are well separated in the case of compounds **5a,b** and **6a** [$\Delta\delta \cong 0.5$ to 0.6 ppm, for both sets of resonances], which shows that the aromatic units adopt alternate *in* an *out* positions relative to the center of the cavity and evidences a flattened cone conformation.[2c,4d] Finally, the high-field shift of the methoxy protons (around 2.4 ppm) indicate that they remain partially included in the calix-cone, very similar to the case of uncapped compounds **2**–**4**. Hence, the overall conformation adopted by the calixarene scaffold has been minimally affected by the capping step as schematized in Scheme 1. This stands in contrast to calix[6]arenes that have been capped with a small 2-atom spacer (Figure 1, center). For example, when the small and rigid 1,3,5-triazacyclohexane unit caps the same calix macrocycle through an ethyl spacer, the methoxy groups exhibit a proton resonance at 3.75 ppm, indicating that they have been totally expulsed from the cone.[4b] Likewise, with the more flexible tren cap and ethyl spacers, the methoxy δ shift is 3.05 ppm,[4a] which also attests to their relative projection away from the cavity, but to a lesser extent. It therefore seems that the aromatic spacers between the calixarene moiety and the aza cap offer sufficient flexibility for the capped calix-cryptand to keep a similar conformation before and after the final macrocyclization step.

In the case of **5a** and **6a**, one resonance belonging to the xyl-aromatic spacer is shifted to low field ($\delta \cong 7.8$ ppm), which must be due to the deshielding effect one aromatic

arm has on the others and suggests the spatial proximity of these three arms. Differences are observed for the signals of the tacn cap. For calix[6]xyl-tacn **5a**, the tacn protons appear as a single signal, while, in the case of calix[6]pyr-tacn **5b**, the protons of the cap are split. This suggests that the mobility of the cap depends on the nature of the aromatic linkers (xylyl or pyridyl).

In the case of **6b**, the resonances denoted in Figure 2 attest to the presence of calix[6]pyr-tren **6b** as a major compound. This was fully confirmed by 2D NMR experiments together with mass spectrometry. Although the resonances in the 2 to 5 ppm area are very similar to its xyl-analog **6a**, the peaks corresponding to the calix-aromatic units and their *t*Bu substituents show a smaller splitting, indicating a more straight conformation, which is confirmed by the lower-field shifted methoxy groups at 2.60 ppm.

The fact that the **b** case did not work as well as the **a** case for the tren derived ligand highlights the sensitivity of the key capping step to small variations of the reactants (calix-xyl vs calix-pyr and tren cap vs tacn cap). In addition, we wanted to check the geometrical factors that may play a role in the efficiency of the macrocylization step. We therefore synthesized the analogue of compound **4a** starting from the *para*-xylenyl spacer instead of the *meta* derivative following the same experimental procedure as described above. However, all attempts to isolate a capped compound analogous to **5a** were unsuccessful, the capping step resulting in the formation of products difficult to analyze, possibly polymers. This shows that an adequate geometrical fit is one of the key features for the successful final macrocyclization reaction in spite of the high flexibility of the calix[6]arene macrocycle.

In conclusion, we have described the synthesis of the first members of a novel family of funnel shaped aza-ligands. They are based on a calix[6]arene that has been extended at the small rim by three aromatic arms covalently assembled to a tripodal poly aza cap. The resulting "two-story" aza-cryptands maintain a C_{3v}-symmetrical structure in solution. Part of the success in the synthesis stems from the choice of the spacer used to connect the aza cap to the calixarene. Indeed, whereas the 1:1 final condensation proceeds with relatively good yields with both *meta*-xylenyl or 2,6-dimethylpyridyl spacers, with the corresponding *para*-xylenyl groups, no cryptand could be isolated. Hence, the *meta*-substitution pattern seems to be necessary to correctly orient the electrophilic arms to react three times with the nucleophilic tripode. This underlines the importance of a good geometrical fit between the cap and the three arms grafted on the calix[6]arene scaffold in spite of its high flexibility and conformational mobility. Interestingly also, these aromatic spacers open a new way for introducing additional functionalities to the system, through their nucleus substitution. Exploration of the coordination properties and host–guest behavior of these "two-story" funnel-like ligands is currently underway.

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Supporting Information Available. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.