

Threading the Calix[5]arene Annulus

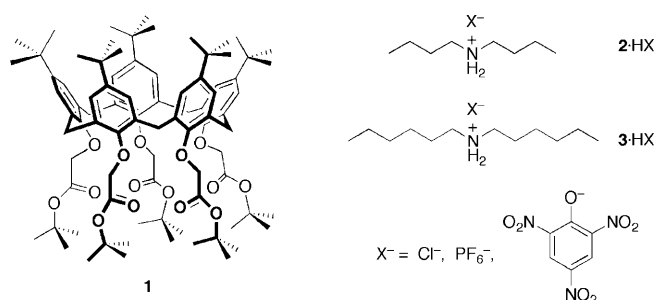
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Among the fast-expanding collection of molecular systems available for nanoscale applications, mechanically interlocked molecules,^[1] such as rotaxanes and catenanes, have already moved towards becoming technological realities.^[2] Rotaxanes (and their pseudorotaxane precursors), in particular, have been constructed by using the most diverse macrocyclic receptors as wheel components. Crown ethers,^[1,3] cyclodextrins,^[4] cyclic amides,^[5] and more recently cucurbiturils^[6] have all been threaded onto suitable complementary linear axle components. Calix[*n*]arenes,^[7] on the other hand, have received much less attention as building blocks for the construction of interlocked supermolecules,^[8] despite their tunable size, their versatility of derivatization (both at the wide and narrow rims), and their ready availability. The only notable exceptions are the findings of Arduini, Pochini, and co-workers, who have extensively investigated pseudorotaxanes and rotaxanes based on heterotopic calix[6]arene receptors adorned with ureido groups and viologen-derived linear components.^[9]

Leaving aside calix[4]arenes,^[10] the cavity of which is too small to be threaded by a linear guest, the slightly larger calix[5]arenes are the next potential candidates for pseudorotaxane formation. Although calix[5]arenes have previously been shown to efficiently perform a number of tasks, which range from the complexation of alkyl(di)ammonium ions^[11] and ion pairs^[12] to the self-assembly of supramolecular polymers,^[13] to the best of our knowledge, no studies have so far

been carried out to evaluate whether or not a linear thread can interpenetrate the calix[5]arene annulus. Herein we describe the first examples of [2]pseudorotaxanes derived from a calix[5]arene and linear secondary alkylammonium ions and we show that the ease of formation of these species is predominantly determined by salt ion-pairing effects, whereas the time course of the threading/dethreading process depends on the length of the cation alkylammonium chains.

Very recently we have reported the solid-state structure of a calix[5]arene/*n*-butylammonium *endo*-cavity complex.^[14] Inspection of this structure revealed that the spatial arrangement of the oxygen atoms around the nitrogen atom of the included guest is reminiscent of the oxygen array present in crown ether/secondary ammonium ion complexes.^[15] Even though the cavity size of a calix[5]arene (at its narrow rim) appears to be slightly smaller than that found in the solid-state structure of the dibenzo[24]crown-8 encircling the di-*n*-butylammonium ion (ca. 5 vs. 6 Å,^[16] respectively), calix[5]arenes were judged to be sufficiently flexible to allow for the inclusion of secondary alkylammonium cations. After a preliminary screening, penta-*tert*-butylpentakis(*tert*-butoxycarbonylmethoxy)calix[5]arene^[17] (**1**) was selected as the prototype wheel component, whereas di-*n*-butylammonium (2·H⁺) and di-*n*-hexylammonium (3·H⁺) were chosen as axle components. The axle components were all tested as chloride, picrate (Pic[−]), and hexafluorophosphate salts to evaluate the influence of ion pairing^[18] on the pseudorotaxane assembly process.



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Formation of the pseudorotaxanes was investigated by ^1H NMR spectroscopy. In a typical experiment, the appropriate amount of dialkylammonium salt was added to a 5 mM solution of **1** in $(\text{CDCl}_3)_2$, so as to reach a 1:1 host/guest ratio. Data on the threading experiments (Table 1)

Table 1. Percentages of formation^[a] and conditional binding constants^[19a] of pseudorotaxanes $[\mathbf{2}\cdot\text{H}^+\mathbf{1}]\text{X}^-$ and $[\mathbf{3}\cdot\text{H}^+\mathbf{1}]\text{X}^-$, determined by ^1H NMR spectroscopy (500 MHz, 25 °C, 5 mM, $(\text{CDCl}_3)_2$).

X^-	$\mathbf{2}\cdot\text{H}^+\mathbf{1}$ [%] ($[\text{M}^{-1}]$)	$\mathbf{3}\cdot\text{H}^+\mathbf{1}$ [%] ($[\text{M}^{-1}]$)
PF_6^- ^[b]	88 (1.2×10^4)	69 (1.4×10^3)
Pic^-	57 (6.1×10^2)	39 (2.1×10^2)
Cl^-	<5 (<10)	<5 (<10)

[a] Values derived from the average of three independent measurements. Standard error $\leq 10\%$. [b] Samples prepared as solutions in $(\text{CDCl}_3)_2/\text{CD}_3\text{OD}$ (9:1, v/v), evaporated to dryness and then taken up in $(\text{CDCl}_3)_2$ (see the Supporting Information). [c] Equilibration time 24 h.

show different behavior of the two cationic guests, along with a strong dependence on the ion-pairing tendency of the salts used.^[19] Addition of $\mathbf{2}\cdot\text{H}^+$ or $\mathbf{3}\cdot\text{H}^+$ to calix[5]arene **1** resulted in the formation of slow exchanging (on the NMR timescale), *endo*-cavity inclusion complexes, unambiguously confirmed by the appearance of high-field resonances ($\delta = -1.10$ to -2.65 and -0.14 to -2.50 ppm, respectively), for the methylene hydrogen atoms of the included dialkylammonium guest experiencing the shielding effects of the calixarene aromatic units (Figure 1).

Threading of $\mathbf{3}\cdot\text{H}^+$, at room temperature, was found to reach equilibrium after 24 h from the addition (Figure S9 in the Supporting Information),^[20] whereas $\mathbf{2}\cdot\text{H}^+$, was able to thread **1** within a few minutes. Most likely, the higher

degree of conformational freedom of $\mathbf{3}\cdot\text{H}^+$, with respect to the shorter $\mathbf{2}\cdot\text{H}^+$ guest, is responsible for the time-dependent process observed, which sees the former moving slowly into the cavity of calix[5]arene **1**.

Formation of the [2]pseudorotaxane $\mathbf{3}\cdot\text{H}^+\mathbf{1}$ is further corroborated by the ESIMS spectra (Figure S1 in the Supporting Information) and ROESY experiments. Under identical ROESY conditions, complexes $\mathbf{2}\cdot\text{H}^+\mathbf{1}$ and $\mathbf{3}\cdot\text{H}^+\mathbf{1}$ show different behavior. The $\mathbf{3}\cdot\text{H}^+\mathbf{1}$ pseudorotaxane gives rise to ROE correlations among the β - ϵ -methylenes (and the methyl end group) and the aromatic hydrogen atoms of the *tert*-butylphenoxy rings (Figure 2), as well as between the α -methylene and the axial hydrogen atoms of the bridging methylene units (Figure S5 in the Supporting Information). Conversely, the inclusion complex with the shorter di-*n*-butylammonium guest showed only negative cross-peaks that are indicative of chemical exchange between the included and the free guest species (Figure S4 in the Supporting Information).^[21] Assignment of the resonances belonging to the α - and α' - CH_2 groups of pseudorotaxane $\mathbf{3}\cdot\text{H}^+\mathbf{1}$ ($\delta = 2.45$ and 3.80 ppm, respectively) followed from a COSY spectrum. Interestingly, a comparison of the upfield complexation-induced shifts (CISS) experienced by the α -methylene hydrogen atoms of di-*n*-hexylammonium $\mathbf{3}\cdot\text{H}^+$ and *n*-hexylammonium $\mathbf{5}\cdot\text{H}^+$ ions, upon inclusion into **1** ($\Delta\delta = 0.61$ and 3.89 ppm, respectively), suggests that a di-*n*-alkylammonium cation is able to penetrate more deeply into the calixarene cavity with respect to an *n*-alkylammonium one (Table S1 in the Supporting Information). Data for $\mathbf{3}\cdot\text{H}^+\mathbf{1}$ are indeed consistent with the α - CH_2 group of the guest sitting at the periphery of the shielding cone of the aromatic moieties. Threading of $\mathbf{3}\cdot\text{H}^+$ into **1** is additionally substantiated by the opposite (downfield) CIS detected on the α' -

CH_2 resonance ($\Delta\delta = 0.74$ ppm with respect to the free guest), which indicates that the second *n*-alkyl chain of the guest (the *exo*-cavity one, residing among the narrow rim substituents) is placed in the deshielding region of the aromatic rings.

Additional evidence on the above-mentioned NMR spectroscopy structural assignment was provided by the comparison of the calculated equilibrium geometries^[22] of pseudorotaxane $\mathbf{3}\cdot\text{H}^+\mathbf{1}$ and the model complex $\mathbf{5}\cdot\text{H}^+\mathbf{1}$ obtained from **1** and $\mathbf{5}\cdot\text{H}^+$ (Figure 3). DFT calculations at the B3LYP/6-31G(d) level of theory showed that in $\mathbf{5}\cdot\text{H}^+\mathbf{1}$ ^[23] the calix[5]arene adopts a C_s symmetric conformation (Figures S13 and S14 in the Supporting Information), with one of the five aryl groups

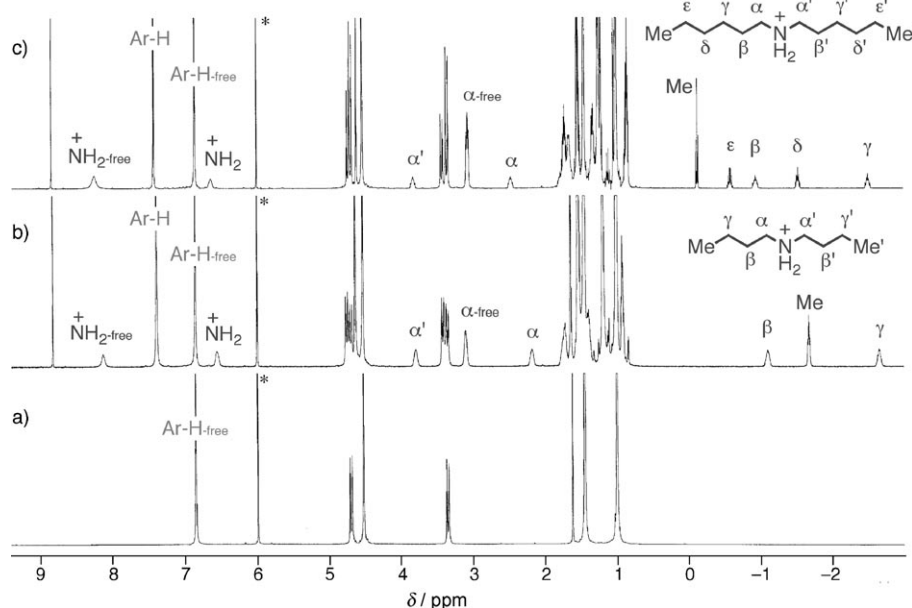


Figure 1. ^1H NMR Spectra (500 MHz, 25 °C, 5 mM, $(\text{CDCl}_3)_2$) of a) **1**; b) $[\mathbf{2}\cdot\text{H}^+\mathbf{1}]\text{Pic}^-$; c) $[\mathbf{3}\cdot\text{H}^+\mathbf{1}]\text{Pic}^-$. *Residual solvent peak.

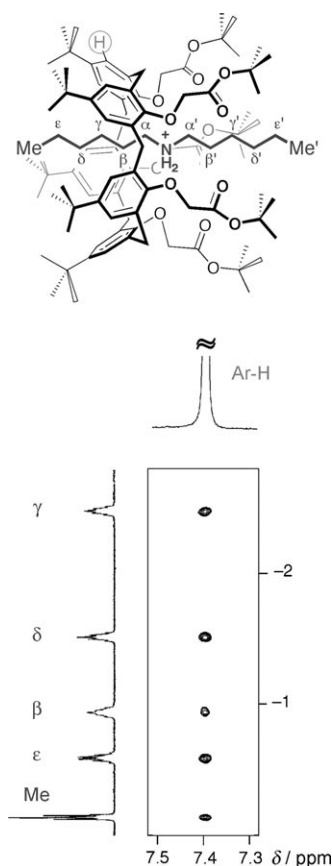


Figure 2. Section of the ROESY spectrum of $[3\cdot\text{H}^+\cdot\mathbf{1}]\text{Pic}^-$ (500 MHz, 25°C, 5 mm, $(\text{CDCl}_2)_2$).

tilted outwards to allow its pendant carbonyl group to hydrogen bond to the ammonium ion. In the pseudorotaxane $3\cdot\text{H}^+\cdot\mathbf{1}$, on the other hand, calix[5]arene $\mathbf{1}$ is forced to stand in a more regular C_{5v} conformation (Figures S13 and S14 in the Supporting Information), as a result of the presence of the second hexyl group filling the pocket created by the narrow rim ester substituents, thus preventing the formation of the additional $\text{C}=\text{O}\cdots\text{H}-\text{N}$ bond seen with $5\cdot\text{H}^+$. Furthermore, the NH_3^+ group of $5\cdot\text{H}^+$ lies above the mean plane generated by the phenolic oxygen atoms, whereas the secondary ammonium moiety of $3\cdot\text{H}^+$ is coplanar to the same plane, mirroring the behavior of ammonium ions/crown ether complexes.^[15] It is also worth noting that, when compared with $5\cdot\text{H}^+\cdot\mathbf{1}$, upon inclusion of $3\cdot\text{H}^+$ the narrow rim of the cavity of $\mathbf{1}$ opens up from approximately 5 to 6 Å.^[24]

The counterion chosen for the dialkylammonium components was found to play a significant role on the effectiveness of the threading process (Table 1). As predicted by theory,^[13b,18,19] ion-pairing effects hamper the complexation of a charged species by a neutral receptor. On going from PF_6^- , to Pic^- , and finally to Cl^- , a progressive decrease of the percentages of complexation was observed (from 69–88% to <5%, respectively), with a consequent drop of the conditional binding constant. Overall, efficiency was highest for

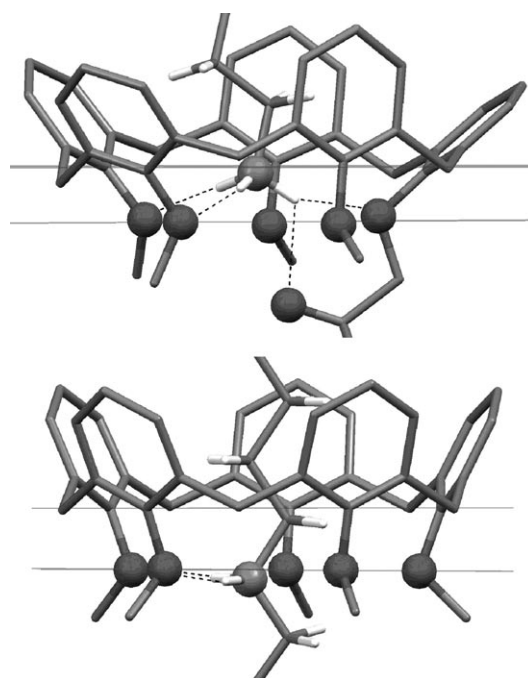


Figure 3. Details of the calculated structures of $5\cdot\text{H}^+\cdot\mathbf{1}$ (top) and $3\cdot\text{H}^+\cdot\mathbf{1}$ (bottom), highlighting the penetration of (di)alkylammonium ions into the cavity. The top and bottom lines represent the mean planes generated by the bridging methylene carbon atoms and the phenolic oxygen atoms, respectively. The oxygen atoms of the calixarene and the nitrogen atom of the guests are shown in ball style. Wide and narrow rim substituents not involved in complexation are omitted for clarity.

$2\cdot\text{HPF}_6$, which resulted in 88% complex formation ($K_a = 1.2 \times 10^4 \text{ M}^{-1}$ in $(\text{CDCl}_2)_2$).

Dethreading of the [2]pseudorotaxane $3\cdot\text{H}^+\cdot\mathbf{1}$ was achieved by applying a number of chemical stimuli of a different nature, acting either on the host (through addition of a competitive guest), on the guest (through a base) or on the counterion (through a tighter ion-pairing anion). In all instances, dethreading was found to proceed with slow kinetics, on a timescale similar to (or even slower than) that observed for the formation of the pseudorotaxane (Figure 4). This suggests that the rate-limiting event is the dethreading

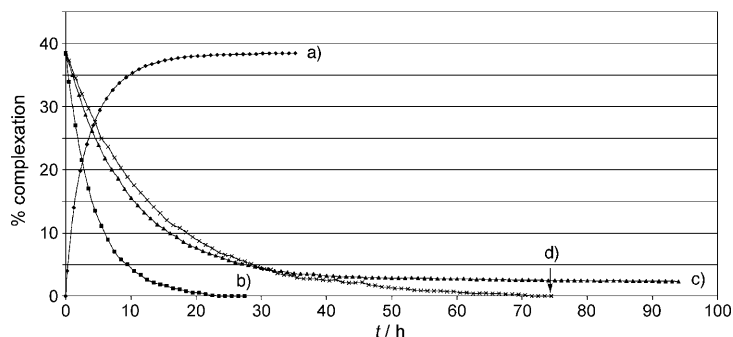


Figure 4. Time course of threading/dethreading for the [2]pseudorotaxane $3\cdot\text{H}^+\cdot\mathbf{1}$ determined by ^1H NMR (500 MHz, 25°C, $(\text{CDCl}_2)_2$). a) Formation of $[3\cdot\text{H}^+\cdot\mathbf{1}]\text{Pic}^-$; dethreading of $[3\cdot\text{H}^+\cdot\mathbf{1}]\text{Pic}^-$ upon addition of b) $n\text{Bu}_4\text{N}^+\text{Cl}^-$; c) Et_3N ; d) $n\text{BuNH}_3^+\text{Pic}^-$ (4HPic).

of the guest molecule and not any of the rapid chemical transformations the cation undergoes upon release from the calixarene (i.e., recombination of the original salt, deprotonation, or formation of a tighter ion-paired salt).

Typically, addition of 10 equiv of $n\text{Bu}_4\text{N}^+\text{Cl}^-$ to a 5 mM solution of the pseudorotaxane $[\mathbf{3}\cdot\text{H}^+\mathbf{1}]\text{Pic}^-$ in $(\text{CDCl}_3)_2$ results in complete decomplexation after 24 h (Figure S11 in the Supporting Information), as a consequence of the formation of a tighter ion pair between $\mathbf{3}\cdot\text{H}^+$ and the chloride ion.^[26] Similarly, the addition of 10 equiv of triethylamine to a solution of $[\mathbf{3}\cdot\text{H}^+\mathbf{1}]\text{Pic}^-$ produces deprotonation of the thread with consequent disassembly of the pseudorotaxane, although, in this case, the system was found to retain the presence of a minute amount (<3%) of the initial pseudorotaxane after equilibration for 4 days (Figure S10 in the Supporting Information). Lastly, the addition of 10 equiv of solid $n\text{BuNH}_3^+\text{Pic}^-$ ($\mathbf{4}\cdot\text{HPic}$) results in the complete replacement of the dialkylammonium guest over a 3 day period (Figure S12 in the Supporting Information). Dethreading was also carried out by physical methods: heating of a solution of $\mathbf{3}\cdot\text{H}^+\mathbf{1}$ in $(\text{CDCl}_3)_2$ causes the progressive extrusion of the di-*n*-hexylammonium thread from the calix[5]arene cavity, reaching complete decomplexation at 100°C (Figure S8 in the Supporting Information).

In conclusion, we have demonstrated that a suitably substituted calix[5]arene forms, in the presence of di-*n*-alkylammonium ions, a hitherto unknown family of [2]pseudorotaxanes. The kinetics of assembly and disassembly of these interpenetrated supermolecules are controlled by the length of the axle alkyl chains, whereas the extent of their formation (hence their thermodynamic stability) depends predominantly on the axle counterion. Our findings show that extrusion of a cationic axle out of its host can efficiently be accomplished by the addition of strongly associating anions (Cl^-). To the best of our knowledge, this is one of the rare examples^[26b] of ion pairing being used as an external stimulus to induce dethreading of a pseudorotaxane. These features, taken together, make calix[5]arene-based [2]pseudorotaxanes attractive for their potential applications as membrane transport agents, slow-release substrate delivery systems, and more generally as chemical devices.^[27] Future studies will be directed at the development of a synthetic strategy for the covalent linking of stoppering groups for the formation of rotaxanes.

Experimental Section

Calix[5]arene **1** was synthesized according to a literature procedure.^[17] Dialkylammonium salts ($\mathbf{2}\cdot\text{HX}$ and $\mathbf{3}\cdot\text{HX}$) were conveniently prepared by treating a solution of the amine (**2** or **3**) in MeOH with an equimolar aqueous solution of the appropriate acid (HCl, HPic, or HPPF_6). Routinely, residues obtained after solvent removal under reduced pressure were triturated with Et_2O to afford solid materials, which were then collected by suction filtration.

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Keywords: calixarenes • density functional calculations • ion pairs • NMR spectroscopy • pseudorotaxanes

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