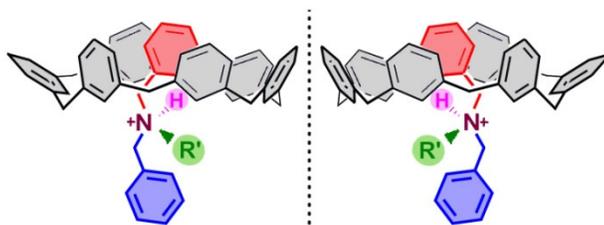


Calix[6]arene Threading with Weakly Interacting Tertiary Ammonium Axles: Generation of Chiral Pseudorotaxane Architectures

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Supporting Information Placeholder



ABSTRACT: The TFPB “superweak anion” effectively induces the threading of a scarcely preorganized calix[6]arene (**1**) with weakly interacting tertiary ammonium axles ($2^+–3^+$). The pseudorotaxanes ($4^+–5^+$) thus formed show an unexpected chirality due to an unprecedented formation of a threading-induced stereogenic ammonium center.

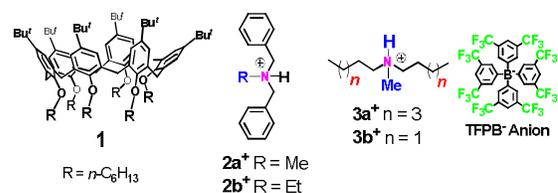
Among all the supramolecular entities, particular attention has been devoted to interpenetrated architectures, such as rotaxanes, catenanes, and knots,¹ thanks to their applications in nanotechnology² and as molecular machines³ and sensors.⁴ Interlocked architectures can be efficiently obtained through a template-directed⁵ synthesis by exploiting the threading of a linear axle through a macrocyclic wheel to form a pseudorotaxane complex,¹ which can be considered the most obvious precursor to both catenanes and rotaxanes.

In this regard, one of the most popular threading motifs is based on the interaction between dialkylammonium axles and crown-ether macrocycles mainly driven by H-bonds and ion-dipole interactions.¹ Consequently, ammonium/crown-based shuttles are among the most studied molecular machines³ because they are able to translocate the macrocyclic component (wheel) over two or more sites (“stations”) after deprotonation of the secondary ammonium centre.

Interestingly, it is known⁶ that the tertiarization of a *sec*-nitrogen axle facilitates the neutralization of ammonium rotaxanes,^{6a} and thus can ensure a more clean and clear switching process. On this basis, the study of new threading motifs based on weakly interacting⁷ tertiary ammonium axles could permit the synthesis of interlocked architectures with novel and intriguing properties.

Strangely, a survey of recent literature reveals that the threading of *tert*-ammonium axles has been scarcely investigated. Probably, this is due to the fact that tertiary ammonium axles form with crown ether macrocycles very labile pseudorotaxane complexes, as shown by Takata and coworkers, who reported the formation of a *tert*-ammonium/DB24C8 pseudo[2]rotaxane in very low yield (< 3%).^{6a} For this reason, the *tert*-ammonium site is often obtained by post-assembled nitrogen tertiarization in *sec*-ammonium/crown-based rotaxane.⁷

In 2010^{8a} we showed that scarcely preorganized calix[6]arene macrocycles (e.g.: **1**) were threaded by dialkylammonium axles only when the ammonium cation was coupled to the weakly coordinating Tetrakis[3,5-bis(triFluoromethyl)Phenyl]Borate (TFPB[−]) “superweak anion” (Scheme 1).^{8b–f} Two years later, a report showed that the TFPB anion was able to enhance the binding affinity between 24-crown-8 hosts and dibenzylammonium guests.⁹



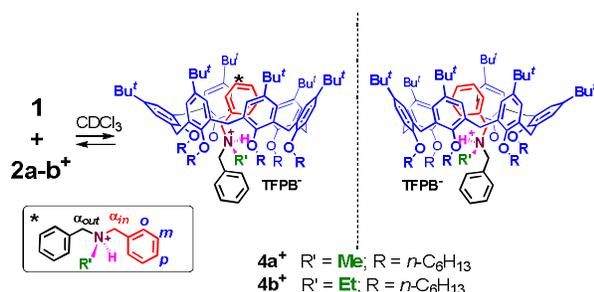
Scheme 1. Structures of calix[6]arene wheel **1**, and ammonium cations $2^+–3^+$, and TFPB[−] anion.

Prompted by these observations, we decided to evaluate if the inducing effect of the TFPB “superweak anion” is able to give an effective threading of calix[6]arene derivative **1** with weakly interacting tertiary ammonium cations ($2^+–3^+$).

As an initial study, we decided to investigate the complexing ability of hexahydroxycalix[6]arene **1** towards the tertiary *N*-methyl dibenzylammonium cation $2a^+$. As expected, the preliminary addition to a CDCl₃ solution of **1** of $2a^+$ as chloride, hexafluorophosphate, or tetraphenylborate salt gave no NMR evidences of appreciable interaction.¹⁰ Instead, when the TFPB salt of $2a^+$ was added to a CDCl₃ solution of **1** (Scheme 2) remarkable changes were observed in its ¹H NMR spectrum (Figure 1). The clearest ones were the sharpening of all signals and the appearance of a well-defined AX system at

4.52 and 3.48 ppm, ($J = 14.4$ Hz) for ArCH₂Ar groups (Figure 1), indicative of the formation of **4a**⁺ pseudo[2]rotaxane with a calix[6]arene-wheel **1** in a cone conformation (Scheme 2). The formation of **4a**⁺ was confirmed by the presence of cavity-shielded benzylic resonances at 4.32, 5.20, and 5.92 ppm for *ortho*-, *meta*-, and *para*-BnH (Figure 1), respectively, which are associated to those outside the calix cavity at normal value of chemical shift (*ortho*-, *meta*-, and *para*-BnH at 8.13, 7.61, and 7.77 ppm, respectively). Complex formation was also confirmed by the ESI(+) mass spectrum, which gave as the base peak a value of 1690 m/z corresponding to **4a**⁺ supramolecular ion. The presence of the *N*-benzyl group inside the calix cavity of **1** was proved by a 2D ROESY spectrum,¹⁰ where diagnostic cross-peaks were seen between the *t*-butyl groups of **1** at 1.11 ppm and the shielded benzyl resonances of the axle at 4.32, 5.20, and 5.92 ppm (Figure S13).

Interestingly, a close inspection of the COSY-45¹⁰ spectrum of **4a**⁺ complex revealed that the protons of benzylic methylene group of **2a**⁺ outside the calix cavity (α_{out}) (inset in Scheme 2) are diastereotopic since they form an AB system at 3.49/3.66 ppm (Figures S11-S12) which correlates in the HSQC spectrum with a CH₂ carbon at 59.6 ppm.¹⁰ In addition, a second AX system relative to a diastereotopic α_{in} group inside the calix cavity was present at 0.56/1.42 ppm ($\Delta\delta = 0.86$ ppm), which correlates in the HSQC spectrum with a CH₂ carbon at 60.1 ppm.¹⁰



Scheme 2. Formation of **4a**⁺ and **4b**⁺ pseudo[2]rotaxanes.

The presence of diastereotopic protons relative to both α_{out} and α_{in} (Scheme 2) methylene groups of **2a**⁺ is indicative of the presence of a nitrogen stereogenic center, which makes the entire **4a**⁺ pseudo[2]rotaxane chiral. Interestingly, this chirality was created by the directionality of the cone calixarene wheel, which upon threading with **2a**⁺ differentiates the two benzylic units around the ammonium center. Naturally, the induction of a nitrogen stereogenic center in **4a**⁺ is only possible with a directional non-flat wheel such as a cone calixarene and would not be possible with a flat wheel such as a crown macrocycle. At this regard, it is worthy to note that while in the literature there are beautiful examples of dissymmetric supramolecules obtained by assembly of achiral molecules,^{1,11} to the best of our knowledge, this is the first example of an asymmetric supramolecule in which the chirality is generated by a supramolecular stereogenic center. In fact, other examples of chiral interpenetrated systems devoid of covalent chirality are either *topologically chiral*^{1,12a} (with a chiral molecular graph) or *mechanically chiral*^{12b} (with directional non-symmetrical components).

Interestingly, the complexation equilibrium between *tert*-ammonium axle **2a**⁺ and **1** was reached, at room temperature,

within a few minutes with a percentage of formation of 60% and an apparent association constant $K_{ass} = 1.1 \pm 0.2 \times 10^3$ M⁻¹ (determined by integration of the slowly exchanging ¹H NMR signals).^{10,13} This value is significantly lower than that previously observed for the complexation of *sec*-dibenzylammonium·TFPB⁻ by **1** ($K_{ass} = 1.2 \times 10^5$ M⁻¹),^{8a} probably due to the lower number of H-bonding sites of the tertiary ammonium axle **2a**⁺.

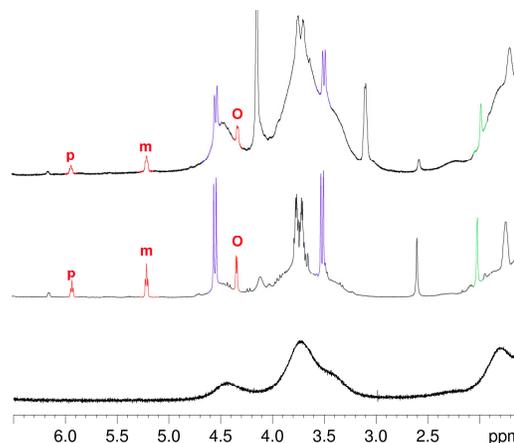


Figure 1. Significant portions of the ¹H NMR spectra (400 MHz, CDCl₃, 298 K) of (bottom) **1**; (middle) 1:1 mixture of **1** and **2a**⁺; (c) 1:1 mixture of **1** and **2b**⁺. The coloring of the signals corresponds to that used in the structure drawings reported in Scheme 2.

The presence of one fundamental stabilizing H-bond between the ⁺NH proton of **2a**⁺ and the ethereal oxygens of **1** was confirmed by the DFT-optimized structure (B3LYP/6-31G⁺ level of theory) of the **4a**⁺ complex (Figure 2, left), which evidenced a N⁺...O distance of 3.0 Å.¹⁰ Interestingly, a close inspection of this structure (Figure 2, right) revealed that the methyl group of **2a**⁺ is almost coplanar to the mean plane of the six calixarene O-atoms of **1** with a N⁺CH₃...O^{calix} distance ranging from 3.0 to 3.2 Å and N⁺C-H...O^{calix} angles over 130°, typical of the weak C-H...O hydrogen bonds.¹⁴ Finally, CH... π interactions were also evidenced between the CH₂- α_{in} protons of **2a**⁺ (magenta in Figure 2, right) and two Ar rings of **1**.

To evaluate the influence of a *N*-substituent larger than methyl, we decided to study the threading of *N*-ethyldibenzylammonium cation **2b**⁺. As above, the addition **2b**⁺·TFPB⁻ salt to a CDCl₃ solution of **1** caused ¹H NMR changes very similar to those discussed for **2a**⁺ and indicative of the formation of **4b**⁺ pseudo[2]rotaxane with a cone calix-wheel (Figure 1).¹⁰ An apparent association constant $K_{ass} = 250 \pm 20$ M⁻¹ was determined for pseudo[2]rotaxane **4b**⁺ by integration of the slowly exchanging ¹H NMR signals of the free and complexed guest. This value was significantly lower than that observed for *N*-methylated pseudo[2]rotaxane **4a**⁺ ($K_{ass} = 1.1 \times 10^3$ M⁻¹) probably because the ethyl group in **4b**⁺ is sterically more demanding than the methyl one in **4a**⁺. Analogously to **4a**⁺, the ¹H NMR spectrum of **4b**⁺ revealed the presence of two AB systems at 3.46/3.64 and 0.65/1.40 ppm (which correlated in the HSQC spectrum with CH₂ carbons at 60.8 and 60.9 ppm, respectively),¹⁰ relative to the α_{out} and α_{in} methylene groups

of $2b^+$ (Scheme 2). Again, this diastereotopicity is indicative of a chiral structure for pseudorotaxane $4b^+$.

These results clearly indicate that the superweak anion approach is quite effective to induce the calix[6]arene threading with weakly interacting tertiary *N*-alkyldibenzylammonium axles $2a-b^+$. To extend its validity we decided to test the threading of tertiary $3a-b^+$ axles bearing two aliphatic chains and one methyl group.

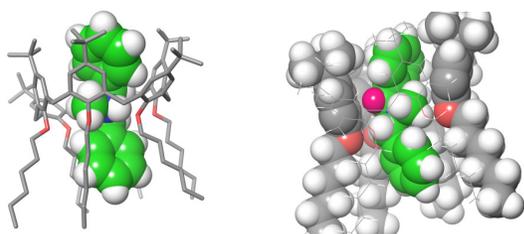
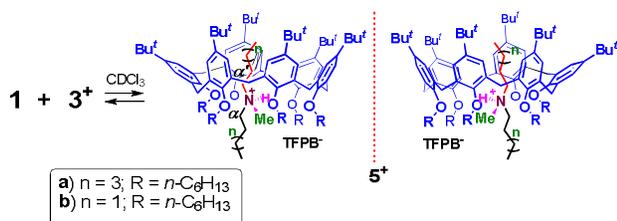


Figure 2. Optimized structure of the pseudo[2]rotaxane $4a^+$ (B3LYP DFT calculations using the 6-31G* basis set).

The 1H NMR spectrum in $CDCl_3$ of a 1:1 mixture of **1** and *N*-methylhexylammonium $3a^+$ ·TFPB $^-$ salt (Figure S22) provides a clear indication that the threading is also occurring in this instance to give pseudo[2]rotaxane $5a^+$ (Scheme 3). In fact, a typical signature at negative δ values can be seen, which corresponds to H-atoms of the hexyl chain of $3a^+$ shielded by the aromatic cavity of **1** (see also Figure 3).



Scheme 3. Formation of of $5a^+$ and $5b^+$ pseudo[2]rotaxanes

In analogy to $4a^+$, also in this case, the threading generates a supramolecular stereogenic center in pseudo[2]rotaxane $5a^+$. Its chirality was proven by the presence of AB or AX systems related to the diastereotopic protons of the shielded hexyl chain. In fact, an inspection of the COSY-45 spectrum (Figures S24-S25)¹⁰ of $5a^+$ complex revealed that the α_{in} methylene group of $3a^+$ forms an AX system at $-0.16/1.16$ ppm, with an impressive $\Delta\delta$ of 1.0 ppm, which correlates in the HSQC spectrum (Figure 3, top) with a CH_2 carbon at 57.4 ppm. Interestingly, each α_{in} -proton is *J*-coupled to the subsequent β protons (see inset in Figure 3, bottom), which also form an AB system at $-0.74/-1.05$ ppm ($\Delta\delta = 0.31$ ppm). The *J*-coupling continues (Figure 3, bottom) to diastereotopic γ protons (AB system at $-0.86/-1.26$ ppm, $\Delta\delta = 0.40$ ppm, HSQC at 24.1 ppm), which are coupled with δ protons (AB at $-0.02/0.10$ ppm, HSQC at 31.7 ppm), and extends to ϵ and ζ protons (at 0.51 and 1.17 ppm, respectively). A similar analysis can be extended to the hexyl chain outside the cavity,

which, inter alia, shows a $CH_2-\alpha_{out}$ AX system at 1.82/3.25 ppm with an impressive $\Delta\delta$ of 1.43 ppm (Figure 3, top).

A further analysis of the COSY-45 spectrum ($CDCl_3$, 400 MHz) of $5a^+$ pseudo[2]rotaxane (see pages S31-S33 in Supporting Information) showed the usual $ArCH_2Ar$ AX system at 3.46/4.56 ppm, which was HSQC-correlated with a CH_2 carbon at 27.9 ppm, in perfect agreement with a typical calix[6]arene-wheel **1** in a *cone* conformation.¹⁵ In addition to these features, the combined analysis of COSY-45 and HSQC spectra clearly evidenced the presence of three less abundant pseudo[2]rotaxane species in which the calix-wheel **1** adopts different conformations with *anti*-oriented Ar rings.

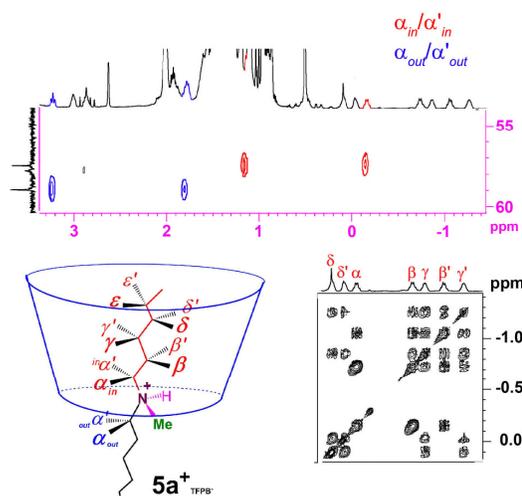


Figure 3. Expansion of the 2D HSQC (top) and COSY (bottom) spectra (600 MHz, $CDCl_3$, 298 K) of a 1:1 mixture of **1** and $3a^+$.

In fact, the COSY-45 spectrum (Figure S31) clearly evidenced a second conformer displaying an AX system at 3.52/4.48 ppm, with a relative intensity of 0.12 with respect to the cone one (1.00). Two additional minor conformers, with a relative abundance of 0.06 and 0.04, were also represented by AX systems at 4.39/3.44, 4.31/3.42, 4.41/3.71, and 4.34/3.49 ppm.¹⁰ In association with all these AX systems pertinent correlations were seen in the range 27-30 ppm of the HSQC spectrum, which also evidenced further three correlations at 33-35 ppm related to *anti* oriented Ar rings.¹⁰ A careful analysis of all these data allowed us to assign the following conformations to the threaded calix-wheel **1**, in order of decreasing abundance: *1,2,3-alternate* (0.12), *1,2-alternate* (0.06), and *partial-cone* (0.04). Therefore, the pseudo[2]rotaxanes ($5a^+$)^{cone}, ($5a^+$)^{1,2,3-alt}, ($5a^+$)^{1,2-alt}, and ($5a^+$)^{pc} (Figures S29 and S33) are present in solution in the 1.00:0.12:0.06:0.04 ratio.

In agreement with this conclusion, the optimization of each of the possible $5a^+$ conformers¹⁶ by DFT calculations at the B3LYP/6-31G(d,p) level of the theory using Grimme's dispersion corrections (IOp(3/124 = 3)),¹⁷ indicated the following stability order: ($5a^+$)^{cone} > ($5a^+$)^{1,2,3-alt} > ($5a^+$)^{1,2-alt} > ($5a^+$)^{pc} with the relative energies of 0.00, 1.90, 2.10, and 2.46 kcal/mol, in good agreement with their relative abundance in solution. In all these instances, the presence of one fundamental stabilizing H-bond between the 1NH proton of $3a^+$ and the

etheral oxygens of **1** was confirmed by the DFT-optimized structure (Figure 4). Interestingly, the four other possible conformations ($5a^+$)^{1,3-alt}, ($5a^+$)^{1,4-alt}, ($5a^+$)^{1,3,5-alt}, and ($5a^+$)^{1,2,4-alt} were found at energies higher than 7 kcal/mol (Figure S33) in agreement with their undetectability in solution.

The apparent association constant for the above described ($5a^+$)^{cone}, ($5a^+$)^{1,2,3-alt}, ($5a^+$)^{1,2-alt}, ($5a^+$)^{pc} complex were determined by quantitative ¹H NMR analysis¹⁸ of a 1:1 titration mixture of **1** and **3a**⁺ in CDCl₃, using 1,1,2,2-tetrachloroethane as the internal standard, to give a value of 2400±100 M⁻¹, 280±20 M⁻¹, 140±10 M⁻¹, and 95±15 M⁻¹, respectively.

The formation of pseudorotaxane structures with different conformations of the wheel has been already observed for cyclodextrins¹⁹ and pillarenes,²⁰ but is still unprecedented for calixarenes.

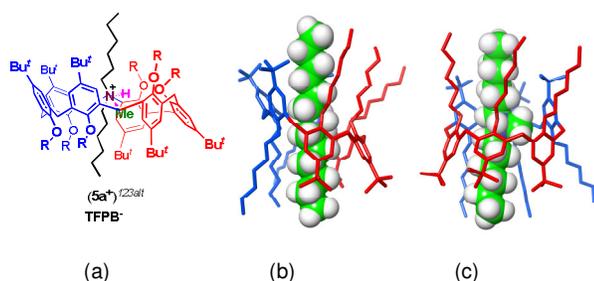


Figure 4. (a) Chemical drawing of pseudo[2]rotaxane ($5a^+$)^{1,2,3-alt} and (b) and (c) different views of its optimized structure (DFT calculations using B3LYP/6-31G(d,p) level of the theory and Grimme's dispersion corrections (IOP(3/124 = 3)).¹⁷

The extension of the threading studies to *N*-methylbutylammonium **3b**⁺·TFPB⁻ salt with **1** in CDCl₃ provided results were similar to those just described for **3a**⁺, with a strong prevalence of cone-wheel pseudo[2]rotaxane **5b**⁺ and only minor amounts of different conformations (see pages S35-S38 in Supporting Information). In particular, also in this instance the chiral nature of pseudo[2]rotaxane **5b**⁺ was proven by the presence of diastereotopic protons of the shielded butyl chain (α/α' , -0.03/1.11 ppm; β/β' , -0.03/-1.11 ppm; γ/γ' , -0.76/-1.26 ppm).¹⁰

In conclusion, we have shown that weakly interacting tertiary ammonium axes can be able to effectively thread scarcely preorganized calix[6]arene wheels when coupled with the “superweak” TFPB⁻ anion. Interestingly, chiral pseudorotaxanes were formed in which the chirality is due to an unprecedented example of threading-induced stereogenic ammonium center. These results could be considered of general interest in the field of supramolecular threading motifs and could allow the design of novel interpenetrated architectures with expanded properties or functions.

ASSOCIATED CONTENT

Supporting Information

Synthetic details, 1D and 2D NMR spectra, detailed results of the DFT calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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