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Catenation of Calixarene Annulus

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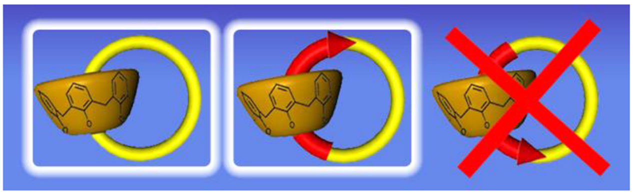
ABSTRACT



***Through-the-annulus*-catenated calixarenes have been obtained, for the first time, by exploiting the "superweak anion" approach that allows the threading of the calix cavity with functionalized dialkylammonium axles. In addition, the first example of a stereoprogrammed synthesis of a catenane orientational isomer (an oriented calix[2]catenane) has been obtained, after macrocyclization, by using a directional alkylbenzylammonium axle.**

In the last two decades, research interest in mechanically interlocked molecules (MIMs),[1] such as rotaxanes, catenanes, and knots, has increased dramatically thanks to their applications in nanotechnology[2] and as molecular machines[3] and sensors.[4] Among them, the catenanes, constituted by two or more mechanically interlocked rings, have attracted considerable attention as the basic component of switches,[5] unidirectional motors,[6] and electronic displays.[2] Various kinds of macrocycles, including crown-ethers,[2,7] azacyclophanes,[2,7] cyclodextrins,[8] cucurbiturils,[9] and macrolactams,[6,10] have been used as the basic macroring undergoing catenation, after threading with a complementary component and exploiting various preorganizing supramolecular interactions.

Regarding calixarene[11] macrocycles, only a few examples of catenanes have been reported in which the calixarene annulus is not catenated but simply acts as an "inert" scaffold on which a different kind of macrocycle is constructed, leaving the calix cavity completely unexploited (Figure 1A).[12] Consequently, to the best of our knowledge, no examples of *through-the-annulus*-catenated calixarene systems (calix-catenane, Figure 1B) are currently known. Here we describe the first examples of catenation through a calixarene annulus (i.e., a calix[6]arene) to give either a symmetrical system or a nonsymmetrical catenane with a stereoprogrammed orientation of the calix wheel.

The synthetic strategy undertaken to catenate the calix[6]arene macrocycle **1a** was based on the so-called

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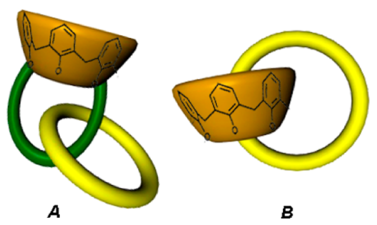


Figure 1. Schematic representation of the currently known prototypical examples of catenanes with unthreaded calix cavity (A) and the proposed calix[2]catenane with a *through-the-annulus* catenation (B).

"superweak anion" approach[13] that allows the *through-the-annulus* threading of such simple calix[6]arene hosts with dialkylammonium ions[13] by exploiting the inducing effect of the "superweak" tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (TFPB) anion (Figure 2).[14] The corresponding pseudorotaxane thus obtainable should then be cyclizable to a catenane form (clipping) if appropriate functional groups are present at the two terminations of the threading element.

Therefore, the TFPB salt of a dibenzylammonium cation bearing two terminal OH groups $\mathbf{2}^+\cdot$TFPB$^-$ (Figure 2)[13f] was equilibrated with hexamethoxy-*p*-*tert*-butylcalix[6]-arene **1a**, at 60 °C for 72 h, to give pseudo[2]rotaxane $[\mathbf{2}\subset\mathbf{1a}]^+\cdot$TFPB$^-$ (Scheme 1) (percentage of formation 23% and apparent association constant $K_{ass} = 90\ \mathrm{M}^{-1}$, as determined by integration of the slowly exchanging ^{1}H NMR signals). This pseudorotaxane is an ideal candidate to attempt the synthesis of a calix-threaded [2]catenane by [1 + 1] cyclocondensation clipping with appropriate diisocyanate derivatives. Initially, we attempted this cyclocondensation by using aliphatic diisocyanate **3a**[15] (Figure 2). However, under various conditions, the putative catenane could not be traced. To explain this unexpected result, we hypothesized that **3a** was not sufficiently preorganized to give the macroring closure.[16] Thus, we designed and synthesized diisocyanate **3b** (Scheme 1)[17] containing more rigid elements and meta-substituted aryl rings that should induce a certain favorable curvature.

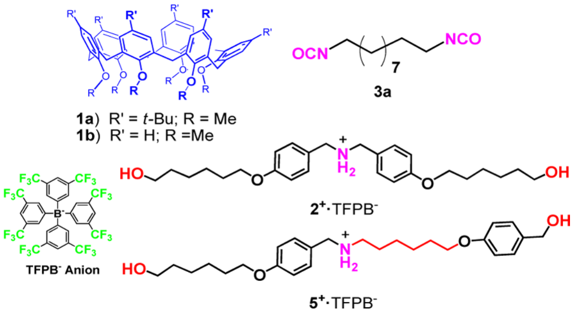
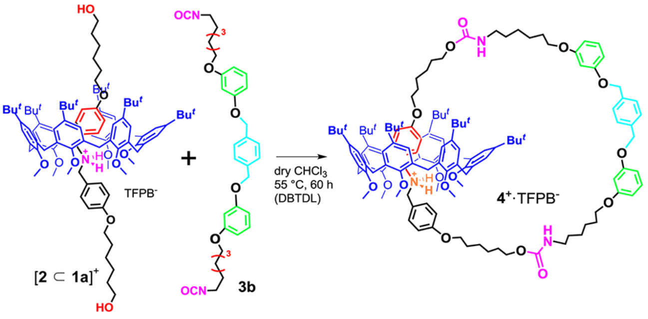


Figure 2. Structures of calix[6]arene wheels **1a**,**b**, alkylbenzylammonium axles $\mathbf{2}^+$ and $\mathbf{5}^+$, TFPB anion, and aliphatic diisocyanate **3a**.

Scheme 1



Therefore, pseudo[2]rotaxane $[\mathbf{2}\subset\mathbf{1a}]^+\cdot$TFPB$^-$, previously formed in a 6×10^{-3} M total concentration of each precursor in dry CHCl$_3$, and diisocyanate **3b** (6×10^{-3} M in dry CHCl$_3$) were added at a rate of 0.6 mL/min from two distinct dropping reservoirs to 2.0 mL of dry CHCl$_3$ under stirring in the presence of dibutyltin dilaurate (DBTDL) as the catalyst. Under these conditions, the first example of *through-the-annulus*-threaded calix[2]catenane $\mathbf{4}^+\cdot$TFPB$^-$ (Scheme 1) was formed and isolated by semipreparative HPLC in 30% yield.[17]

The ESI$^+$ MS spectrum of $\mathbf{4}^+\cdot$TFPB$^-$ gave sharp peaks centered at *m*/*z* 2060.21 [M]$^+$ (see Figure S11 in the Supporting Information) corresponding to the singly charged interlocked molecule. This [2]catenane nature was confirmed by the expected ^{1}H and ^{13}C NMR resonances of all components and by a typical upfield AX system at 5.08 and 4.50 ppm (d, $J = 8.3$ Hz, 2H each) (red signals in Figure 3) for ArH protons of the shielded endocavity benzylammonium unit of the axle,[17] similar to that observed for the related pseudorotaxane complex.[13] In addition, a 2D ROESY[17] experiment showed the presence of diagnostic cross-peaks between these shielded ArH protons of the axle and the calixarene ArH and *t*-Bu resonances at 7.16 and 1.12 ppm, respectively. These

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(12) For recent examples of calixarene-based catenane systems in which the calixarene annulus is unthreaded (type A in Figure 1), see: (a) Schlesier, T.; Metzroth, T.; Janshoff, A.; Gauss, J.; Diezemann, G. *J. Phys. Chem. B* **2011**, *115*, 6445. (b) Phipps, D. E.; Beer, P. D. *Tetrahedron Lett.* **2009**, *50*, 3454. (c) Li, Z.-T.; Zhao, X.; Shao, X.-B. In *Calixarenes in the Nanoworld*; Harrowfield, J., Vicens, J., Eds.; Springer: Dordrecht, The Netherlands, 2007; Chapter 3, pp 47–62 and references cited therein. (d) Wang, L.; Vysotsky, M. O.; Bogdan, A.; Bolte, M.; Böhmer, V. *Science* **2004**, *304*, 1312.

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(16) A similar reasoning also explained the unsatisfactory results obtained in some preliminary attempts using the more popular ring-closing metathesis (RCM) approach, which was not further pursued.

(17) See Supporting Information for further details.

data are a clear evidence that the calix[6]arene macrocycle is positioned around the benzylammonium center to whom it is bonded by hydrogen bonds between ethereal OMe atoms and the ammonium $^{+}NH_2$ group.

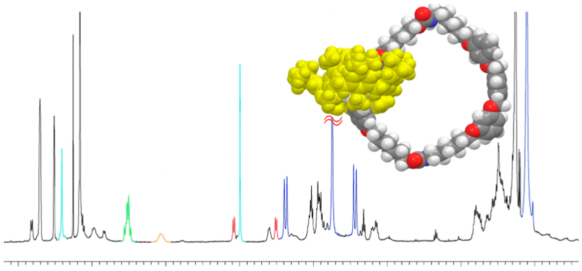

Figure 3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of **4**$^+\cdot$TFPB$^-$ and its B3LYP/6-31G* energy-minimized structure[18] (inset).

This location was fully confirmed by DFT calculations at the B3LYP/6-31G* level of theory,[18] which evidenced the two strongly stabilizing N–H···O hydrogen bonds (see inset in Figure 3). In addition, these interactions contribute to held the calix[6]arene macrocycle in a cone conformation as demonstrated by a well-spaced AX system at 3.44 and 4.38 ppm (d, J = 14.4 Hz, 6H each) for $ArCH_2Ar$ protons (Figure 3). Interestingly, all of these spectral features remained practically unaltered either by changing the temperature or by adding anions (Cl^-) or polar solvents (CH_3CN)[19] that usually led to decomplexation of the related pseudorotaxanes.[13a,20]

Because of the symmetrical nature of its constitutive components **2**$^+$ and **3b**, the newly formed macroring of catenane **4**$^+$ is also symmetrical, and consequently, no stereochemical problems are present here. Of course, a different situation would be obtained if one of the above components is constitutionally nonsymmetrical (oriented). In fact, this orientation coupled to the directional nature of the cone-shaped calixarene wheel would give rise to two possible catenane orientational isomers.[8b]

In this instance, it would be quite challenging to find a way to direct the synthesis specifically toward one of them in a stereoprogrammed mode. To the best of our knowledge, no examples of such stereoprogrammed synthesis of oriented catenane stereoisomers have been described in the chemical literature to date.[21] To address this issue, on the basis of previous work,[13a,b] we designed directional alkylbenzylammonium axle **5**$^+\cdot$TFPB$^-$ (Figure 2) having two different moieties attached to the ammonium center and bearing two terminal OH groups.[17]

As above, the new directional axle **5**$^+\cdot$TFPB$^-$ was equilibrated with hexamethoxy-*p*-*tert*-butylcalix[6]arene **1a** to obtain the corresponding pseudorotaxane.[17] However, ^{1}H NMR spectroscopy revealed no hint of threading of **5**$^+$ under various conditions. Therefore, we resorted to hexamethoxy-*p*-*H*-calix[6]arene **1b** (Figure 2) as an alternative wheel. In this instance (Figure 4), clear evidence of threading was observed in a 1:1 host/guest solution in $CDCl_3$ (9×10^{-3} M each) by NMR.[17] In fact, the complexation equilibrium was reached, at room temperature, within a few minutes with a percentage of formation of 25% and an apparent association constant $K_{ass} = 6.2 \times 10^2\ M^{-1}$ (determined by integration of the slowly exchanging ^{1}H NMR signals).

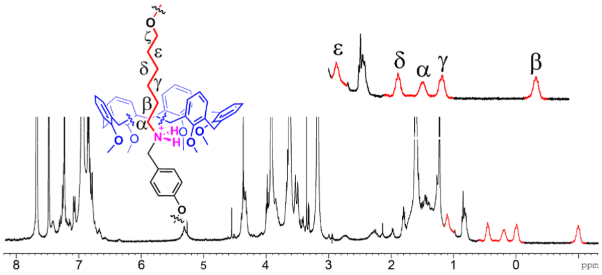

Figure 4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of an equimolar mixture (9×10^{-3} M) of **5**$^+\cdot$TFPB$^-$ and **1b**.

The relative orientation of the thread **5**$^+$ with respect to calixarene **1b** (see Scheme 2) was established by 1D and 2D NMR experiments.[17] In particular, the presence in the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 298 K) of [**5**⊂**1b**]$^+\cdot$TFPB$^-$ of a typical signature at high field or negative values (0.51, 0.25, 0.05, and −0.95 ppm; see Figure 4), characteristic of an *endo*-complexation of the alkyl chains shielded by calixarene aromatic rings, and the absence of shielded benzylic resonances in the 4–6 ppm region (Figure 4), typical of *endo*-benzyl complexation, was clear-cut proof that [(*endo*-alkyl)-**5**⊂**1b**]$^+\cdot$TFPB$^-$ pseudo[2]rotaxane (Scheme 2) had been formed in a stereocontrolled way. These conclusions were further confirmed by a COSY-45 spectrum[17] that allowed a complete confident assignment of all upfield shielded alkyl resonances of [(*endo*-alkyl)-**5**⊂**1b**]$^+\cdot$TFPB$^-$ pseudo[2]rotaxane. In the 2D ROESY spectrum[17] (400 MHz, $CDCl_3$, 298 K), the [(*endo*-alkyl)-**5**⊂**1b**]$^+\cdot$TFPB$^-$ complex gives rise to ROE correlations among the shielded α, β, γ, and δ signals and the host ArH at 6.99 ppm (d, J = 8.0 Hz, 6H).

In conclusion, the threading of *p*-*H*-calix[6]arene macrocycle **1b** with alkylbenzylammonium axle **5**$^+\cdot$TFPB$^-$ led

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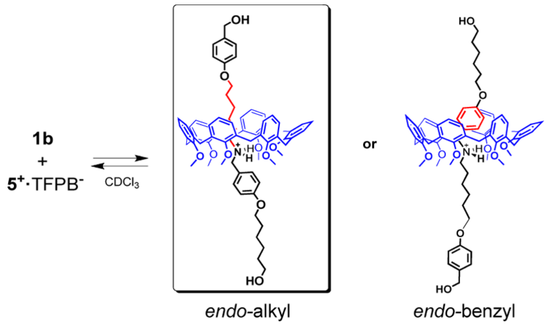
(18) DFT calculations were performed at the B3LYP level, using the 6-31G* basis set for the entire system (GAUSSIAN 09 Software Package, see page S43 in the Supporting Information for additional details).

(19) As previously reported in ref 13f, the addition of 10 equiv of n-$Bu_4N^+Cl^-$ is sufficient to give a complete dethreading of [**2**⊂**1a**]$^+$ pseudo[2]rotaxane, while [2]catenane **4**$^+$ retains its structure even after the addition of 30 equiv of n-$Bu_4N^+Cl^-$. Analogously, the addition of 300 equiv of CD_3CN leads to complete dethreading of [**2**⊂**1a**]$^+$,[13f] while **4**$^+$ retains its structure even after the addition of 700 equiv of CD_3CN.

(20) To investigate the behavior of [2]catenane **4**$^+$ upon deprotonation of its ammonium center, it was neutralized using phosphazene base P1-*t*-Bu to give the corresponding neutral [2]catenane **4**. The ^{1}H NMR spectrum of **4** ($CDCl_3$, 233 K) evidenced the presence of signals at negative values characteristic of an *endo*-alkyl inclusion.[17] Thus, upon deprotonation, the calix[6]arene wheel moves from the original dibenzylammonium site to new positions in which aliphatic chains are inside the calix cavity. On the basis of previous results,[13b,f] the most favored one is very likely that stabilized by H-bonds between calixarene OR atoms and urethane NH group.[17]

Scheme 2

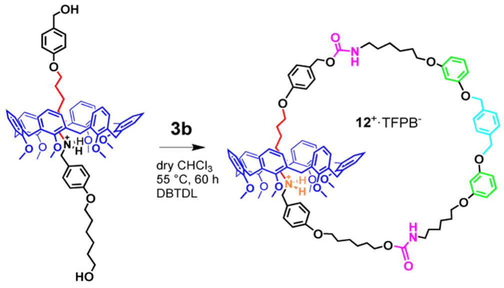


exclusively to the *endo*-alkyl orientational isomer, while no trace of the *endo*-benzyl one could be detected by ^{1}H NMR spectroscopy even after heating at 50 °C for 48 h. In good accord, DFT calculations (Figure S30) at the B3LYP/6-31G* level of the theory indicated that [(*endo*-alkyl)-$\mathbf{5}\subset\mathbf{1b}]^{+}\cdot$TFPB^{-} stereoisomer was more stable than the *endo*-benzyl one by 3.5 kcal/mol.[18,22]

Thus, having secured the stereocontrol of intermediate pseudo[2]rotaxane $[\mathbf{5}\subset\mathbf{1b}]^{+}\cdot$TFPB^{-}, we decided to test the [1 + 1] cyclocondensation with diisocyanate derivative **3b**, under the same conditions used above to obtain calix[2]catenane $\mathbf{4}^{+}\cdot$TFPB^{-}.[17] Unexpectedly, no traces of the putative catenane could be detected, under these conditions, with various analytical techniques. To explain this result, we reasoned that, very likely, the dilution caused by the slow dropping in a larger volume favored a quick dethreading process of the $[\mathbf{5}\subset\mathbf{1b}]^{+}\cdot$TFPB^{-} pseudo[2]rotaxane. On the other hand, the contrasting positive result obtained for $\mathbf{4}^{+}\cdot$TFPB^{-} can be rationalized by the slow kinetics of dethreading of $[\mathbf{2}\subset\mathbf{1a}]^{+}\cdot$TFPB^{-}, which requires more than 2 days to reach the new equilibrium.

Therefore, in a second experiment, diisocyanate derivative **3b** was added dropwise to a solution 6×10^{-3} M of pseudo[2]rotaxane [(*endo*-alkyl)-$\mathbf{5}\subset\mathbf{1b}]^{+}\cdot$TFPB^{-} in dry CHCl$_3$ at 55 °C, in the presence of dibutyltin dilaurate (DBTDL) as the catalyst.[17] Under these conditions, the first example of oriented calix[2]catenane $\mathbf{12}^{+}\cdot$TFPB^{-} was isolated in 23% yield (Scheme 3). The ESI^{+} MS spectrum of $\mathbf{12}^{+}\cdot$TFPB^{-} gave sharp peaks centered at m/z 1722.92 [M]$^{+}$ (Figure S31), confirming its catenane nature.[17] The *endo*-alkyl stereochemistry of the pseudorotaxane precursor $[\mathbf{5}\subset\mathbf{1b}]^{+}$ was retained after the macrocyclization reaction (Scheme 3) as evidenced by the ^{1}H NMR spectrum of $\mathbf{12}^{+}\cdot$TFPB^{-} in CDCl$_3$, which showed very similar spectral features in the pertinent diagnostic regions. As above, a COSY-45 spectrum[17] allowed a complete confident assignment of all upfield shielded alkyl resonances of $\mathbf{12}^{+}\cdot$TFPB^{-}. Also in this case, the 2D ROESY spectrum[17] (400 MHz, CDCl$_3$, 298 K) of $\mathbf{12}^{+}\cdot$TFPB^{-}

Scheme 3



confirmed the *endo*-alkyl stereochemistry by giving ROE correlations among the shielded α, β, γ, and δ signals and the calix ArH protons (Figure S35).

DFT calculations at the B3LYP/6-31G* level of theory were in good accordance with this result, indicating that (*endo*-alkyl)-$\mathbf{12}^{+}\cdot$TFPB^{-} stereoisomer was more stable than the *endo*-benzyl one by 3.1 kcal/mol (Figure 5).[18]

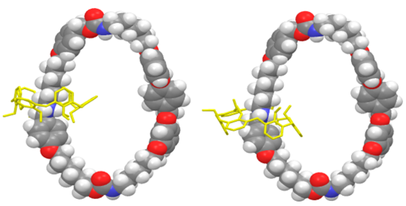


Figure 5. Energy-minimized structures of (*endo*-alkyl) (left) and (*endo*-benzyl) (right) orientational isomers of calix-threaded [2]catenane $\mathbf{12}^{+}$ (B3LYP DFT calculations using the 6-31G* basis set).

In conclusion, the first examples of *through-the-annulus*-catenated calixarenes (calix[2]catenanes) have been obtained by exploiting the "superweak anion" approach that allows the threading of the calix cavity with functionalized dialkylammonium axles. In addition, we have shown that directional alkylbenzylammonium axles can be threaded in a stereoprogrammed way to give, after macrocyclization, the first example of oriented calix-catenane. Considering the current enormous interest in mechanically interlocked molecules[1] and the large variety of shapes and dimensions obtainable with calix[*n*]arene macrocycles, it is conceivable that our approach to calixarene-based MIMs will pave the way to a quickly expanding new area of research.

Supporting Information Available. Synthetic details, 1D and 2D NMR spectra, and details on molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Oriented [2]catenane stereoisomers have been reported[8b] in which a constitutionally asymmetrical diamine was threaded through a constitutionally asymmetrical cyclodextrin. In this case, the two possible diastereoisomers were obtained in a statistical ratio and no stereocontrol could be evidenced.[8b]

(22) For possible explanations on this higher stability, see ref 13a.

The authors declare no competing financial interest.