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Stereoprogrammed Direct Synthesis of Calixarene-Based [3]Rotaxanes

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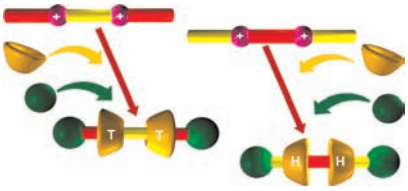
ABSTRACT



Directional calixarene wheels were threaded along a bis(benzylalkylammonium) axle in a stereoprogrammed way to obtain the first examples of calixarene-based [3]rotaxanes. The base/acid treatment demonstrated that these systems act as nanosized molecular shuttles. An unprecedented switching between the *tail-to-tail* and *head-to-head* relative orientation of the calix-wheels was observed.

The bottom-up[1] strategy relies on controlling the self-assembly[2] of molecular components with the aim to construct nanosized molecular devices able to store, process, and interpret information under appropriate external stimuli.[3] Among the possible candidates for a bottom-up approach, [*n*]rotaxanes[4] are particularly attractive because of their different, easily accessible coconformations that make them ideal bi- or multistable systems. In recent years, in addition to the fundamental studies concerning [2]rotaxanes, attention has been also devoted to longer [3]rotaxane systems, which can give rise to more complex functions for devising functional materials working at a larger scale length. Usually, flat or symmetrical wheels, such as crown ethers,[5] macrolactams,[6] or cucurbiturils,[7] have been used, whereas nonsymmetrical directional wheels still remain largely less exploited probably because of the inherent difficulty in controlling their relative orientation. In particular, a few examples of [3]rotaxane bearing two oriented cyclodextrin rings have been reported,[8] whereas no examples of calixarene-based [3]rotaxane are currently known.

Here, we wish to report the first examples of [3]rotaxanes in which two calix[6]arene wheels have a programmed relative orientation obtained through the rational choice of the threading element. Our approach is based on our recent observation that the *through-the-annulus* threading[9] of nonsymmetrical alkylbenzylammonium cations (e.g., **2a** in Figure 1) by hexaalkoxycalix[6]arene **1b** can be obtained with a marked preference for *endo*-alkyl complexation over the *endo*-benzyl one (see Figure 1), in the presence of the weakly coordinating TFPB[10,11] anion.

Obviously, the threading of bis(benzylalkylammonium) ions by two calix[6]arene wheels could give rise to three

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(1) Feymann, R. P. *Eng. Sci.* **1960**, *23*, 22. (b) Drexler, K. E. *Science* **1992**, *255*, 268.

(2) Amabilino, D. A.; Stoddart, J. F. *Chem. Rev.* **1995**, *35*, 1154.

(3) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines*, 2nd ed.; Wiley-VCH: Weinheim, 2008.

(4) *Molecular Catenanes, Rotaxanes and Knots: A Journey Through the World of Molecular Topology*; Sauvage, J. P., Dietrich-Buchecker, C., Eds.; Wiley-VCH: Weinheim, 1999.

(5) For recent examples of crown-based [3]rotaxane systems, see: (a) Chen, P.-N.; Lai, C.-C.; Chiu, S.-H. *Org. Lett.* **2011**, *13*, 4660. (b) Nakazono, K.; Takata, T. *Chem.—Eur. J.* **2010**, *16*, 13783. (c) Jiang, W.; Winkler, H. D. F.; Schalley, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 13852.

(6) For a recent example of macrolactam-based [3]rotaxane system, see: Fuller, A. M. L.; Leigh, D. A.; Lusby, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 4954.

(7) For recent examples of cucurbituril-based [3]rotaxane systems, see: Wittenberg, J. B.; Costales, M. G.; Zavalij, P. Y.; Isaacs, L. *Chem. Commun.* **2011**, *47*, 9420.

(8) Orientational isomers of a cyclodextrin [3]rotaxane have been obtained by linking two cyclodextrin pseudo[2]rotaxane units. Thus, all three possible diastereoisomers have been obtained in a statistical ratio: (a) Cheetham, A. G.; Claridge, T. D. W.; Anderson, H. L. *Org. Biomol. Chem.* **2007**, *5*, 457. A single directional isomer of a cyclodextrin-based pseudo[3]rotaxane was obtained under kinetic control: (b) Oshikiri, T.; Takashima, Y.; Yamaguchi, H.; Harada, A. *Chem.—Eur. J.* **2007**, *13*, 7091.

(9) Gaeta, C.; Troisi, F.; Neri, P. *Org. Lett.* **2010**, *12*, 2092.

10.1021/ol3011997

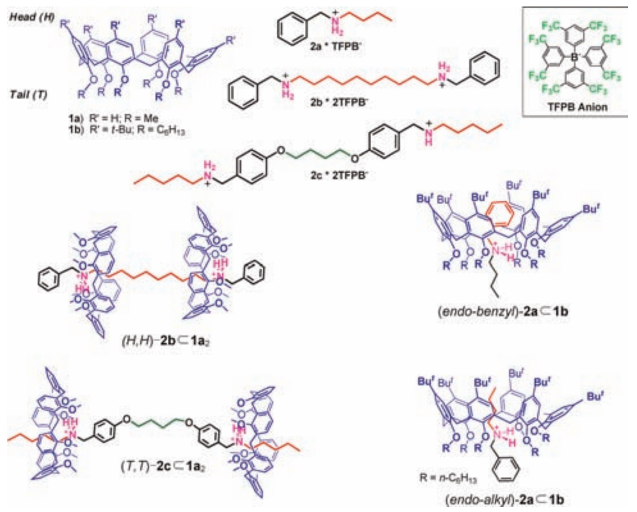


Figure 1. Structures of calix[6]arene wheels **1a**–**b**, alkylbenzylammonium axles **2a**–**c**, and their corresponding pseudorotaxanes.

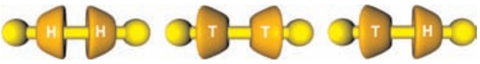
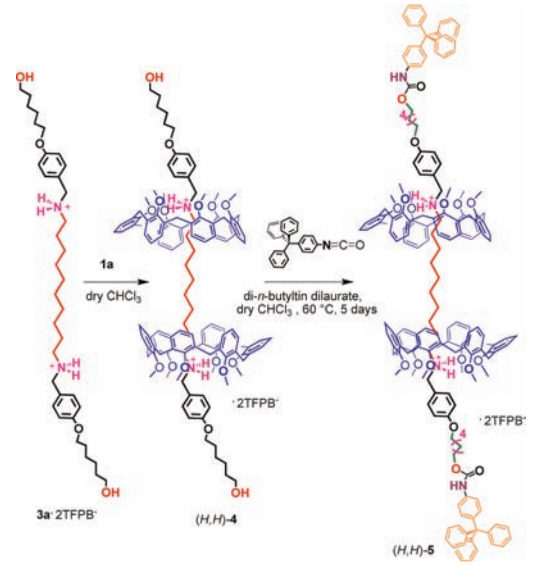


Figure 2. Sequence stereoisomerism in calixarene-based [3]rotaxane and pseudo[3]rotaxane structures.

stereoisomeric pseudo[3]rotaxane structures, which have been termed as *head-to-head* (*H,H*), *head-to-tail* (*H,T*), and *tail-to-tail* (*T,T*) and which can be considered as minimal sequence stereoisomers (Figure 2).[12]

Interestingly, we have very recently demonstrated[12] that the stereoselective self-assembly of each type of stereoisomer in Figure 2 is possible by exploiting the above-mentioned preference for the *endo*-alkyl complexation by calix[6]arene macrocycles **1a**–**b**. In this way, specific stereosequences, exemplified by pseudo[3]rotaxanes (*H,H*)-**2b**$\subset$**1a**$_2$ and (*T,T*)-**2c**$\subset$**1a**$_2$ (Figure 1), were obtained with rationally designed axles. On this basis, we expected that a suitable modification of this strategy, which allows the introduction of appropriate stoppers, would lead to [3]rotaxane structures with a programmed orientation of the calix-wheels.

Scheme 1



In particular, by considering axle **2b** (Figure 1) we designed and synthesized[13] its analogue **3a** bearing two internal alkylammonium and two terminal OH groups, which are derivatizable with a trityl-bearing isocyanate as the stoppering reagent (Scheme 1). In this instance, the above-mentioned preference of **1a** for the *endo*-alkyl stereochemistry (Figure 1) should lead to a *head-to-head* pseudo[3]rotaxane stereosequence.

Therefore, the TFPB salt of **3a** was equilibrated with hexamethoxycalix[6]arene **1a** to give pseudo[3]rotaxane **4** (Scheme 1).[13] The formation of pseudo[3]rotaxane **4** was confirmed by a prominent peak at 1014 m/z in the ESI(+) mass spectrum,[13] corresponding to the doubly charged supramolecular ion. The ^{1}H NMR spectrum[13] of a 1:2 mixture of TFPB salt of dicationic **3a** and hexamethoxy-*p*-*H*-calix[6]arene **1a** in CDCl$_3$ showed a typical signature at highfield and negative values (from 1.0 to -1.2 ppm) characteristic of an *endo*-complexation of the alkyl chains shielded by calixarene aromatic rings. This result and the absence of shielded benzylic resonances in the 4–6 ppm region, typical of *endo*-benzyl complexation, were a clear-cut proof that *head-to-head* pseudo[3]rotaxane (*H,H*)-**4** had been exclusively formed. The apparent total association constant ($K_{\text{tot}} = K_1 \cdot K_2 = (6.3 \pm 0.4) \times 10^6$ M^{-2}, percentage of formation 68%) for complex **4** was determined by integration of ^{1}H NMR spectra of its 1:2 titration mixture in CDCl$_3$ (concentration of **3a** and **1a**, 1.5 and 3.0 mM, respectively), which showed slowly exchanging signals for both the free and complexed guest.[13]

This pseudorotaxane was then stoppered by reaction with 4-tritylphenyl isocyanate to give the first example of calixarene-based [3]rotaxane **5** in 72% yield (Scheme 1).[13] The formation of **5** was confirmed by a prominent peak at

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(10) (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927. (b) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600. For recent examples on the use of TFPB superweak anion in supramolecular chemistry, see: (c) Gaeta, C.; Talotta, C.; Farina, F.; Camalli, M.; Campi, G.; Neri, P. *Chem.—Eur. J.* **2012**, *18*, 1219. For a review on counterion effects in supramolecular chemistry, see: (d) Gasa, T. B.; Valente, C.; Stoddart, J. F. *Chem. Soc. Rev.* **2011**, *40*, 57.

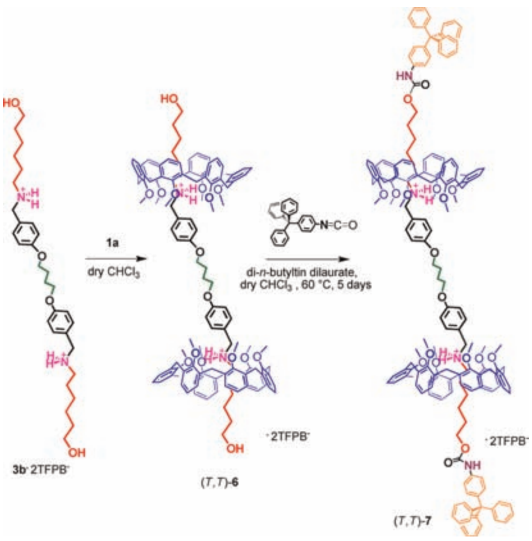
(11) We demonstrated that our "superweak anion" approach is a general mode to obtain *through-the-annulus threading* of scarcely efficient large calix[6]-[9] and -[7]arene[10c] hosts by exploiting the inducing effect of the weakly coordinating TFPB anion. Very recently, our conclusions have been corroborated by Chiu et al., who have shown that the TFPB anion is able to enhance the binding affinity between [24]-crown-8 hosts and dibenzylammonium guests: Chen, N.-C.; Chuang, C.-J.; Wang, L.-Y.; Lai, C.-C.; Chiu, S.-H. *Chem.—Eur. J.* **2012**, *18*, 1896.

(12) Talotta, C.; Gaeta, C.; Pierro, T.; Neri, P. *Org. Lett.* **2011**, *13*, 2098.

(13) See Supporting Information for further details.

1375 m/z in the ESI(+) mass spectrum, corresponding to the doubly charged supramolecular ion. The *head-to-head* stereosequence of the two calix-wheels in **4** was retained after the stoppering reaction as evidenced by the ^{1}H NMR spectrum of **5** in $CDCl_3$ (Figure S18), which showed a typical signature at highfield values (from 1.0 to −1.2 ppm) and no resonances in the 4−6 ppm region, similarly to that of (*H,H*)-**4**.

Scheme 2



In order to prepare a [3]rotaxane with a programmed *tail-to-tail* stereosequence, we designed thread **3b**,[13] the OH-bearing analogue of **2c**, characterized by external alkylammonium units (Scheme 2). Clearly, in this case the orientation of the calixarene cavity toward the exterior should be favored leading to a *tail-to-tail* stereochemistry. In fact, the ^{1}H NMR spectrum[13] of a 1:2 mixture of TFPB salt of **3b** and hexamethoxy-*p*-*H*-calix[6]arene **1a** in $CDCl_3$ showed again the presence of shielded alkyl resonances at negative values typical of *endo*-alkyl complexation and confirming the exclusive formation of *tail-to-tail* pseudo[3]rotaxane (*T,T*)-**6** (Scheme 2).

An apparent total association constant (K_{tot}) of $(5.4 \pm 0.3) \times 10^4$ M^{-2} in $CDCl_3$ (percentage of formation 53%, concentration of **3b** and **1a**, 1.5 and 3.0 mM, respectively) was determined for (*T,T*)-**6** by integration of ^{1}H NMR signals, which is significantly lower with respect to that obtained for pseudo[3]rotaxane (*H,H*)-**4** ($K_{tot} = 6.3 \times 10^6$ M^{-2}). Analogously to the synthesis of **5**, pseudo[3]rotaxane (*T,T*)-**6** was stoppered by the reaction with 4-tritylphenyl isocyanate to give the calixarene-based [3]rotaxane (*T,T*)-**7** in 52% yield (Scheme 2).[13] Again, the *tail-to-tail* stereochemistry of the two calix-wheels in **6** was retained after the stoppering reaction, as evidenced by the ^{1}H NMR spectrum of (*T,T*)-**7** in $CDCl_3$ (Figure S24).[13]

As expected from our previous studies,[9,12,14] molecular mechanics[15] calculations showed that in both [3]rotaxanes **5** and **7** the calix[6]arene wheels are anchored at the benzylalkylammonium centers of the thread by means of H-bonds between their ethereal OR atoms and the ammonium $^+NH_2$ groups (Figure 3).[13] In addition, these H-bondings contribute to fix the calix[6]arene macrocycles in a cone conformation as demonstrated by well-spaced AX systems for $ArCH_2Ar$ protons (Figures S18 and S24).[13] Finally, the space-filling CPK molecular models of **5** and **7** (Figure 3) clearly showed the nanosized dimension of these interlocked structures, which have estimated molecular lengths of 7.0 and 6.0 nm, respectively, in the 'straight' unfolded conformation.[13]

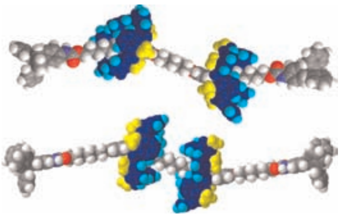
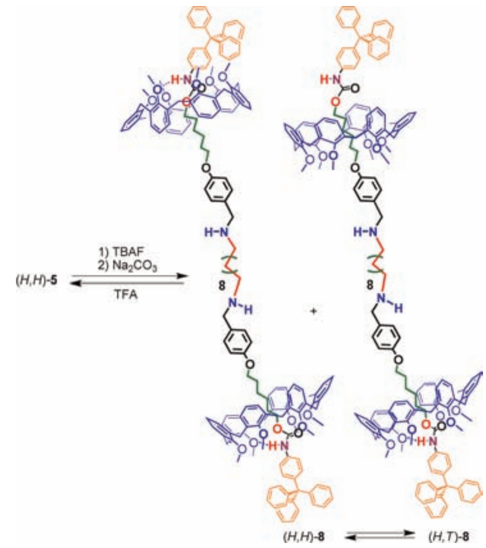


Figure 3. Lowest OPLS-energy structures of [3]rotaxane structures (*H,H*)-**5** (top) and (*T,T*)-**7** (bottom) obtained by Monte Carlo conformational searches.

To investigate the shuttling behavior of calix-wheels upon changing the protonation state of ammonium centers, we neutralized methoxy-bearing [3]rotaxane (*H,H*)-**5**, following the counteranion-exchange method reported by Takata et al.,[5b] to give neutral [3]rotaxane **8** in 86% yield (Scheme 3).

Scheme 3



Dynamic NMR studies[13] showed that upon deprotonation of **5** to give **8**, the calix-wheels move from the previous two alkylbenzylammonium stations to new positions in

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(14) Pierro, T.; Gaeta, C.; Talotta, C.; Casapullo, A.; Neri, P. *Org. Lett.* **2011**, *13*, 2650.

(15) MacroModel-9.0/Maestro-4.1 program: Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

which aliphatic chains are inside the calix-cavities. By considering the three different aliphatic sites along the axle and the three possible relative orientations of the two calix-wheels, this should lead to seven possible translational isomers.[13] A combined 2D NMR study (COSY-45, EXSY, and ROESY, in $CDCl_3$ at 253 K)[13] evidenced the presence of both (*H,H*)-**8** and (*H,T*)-**8** (Scheme 3) in a 6:4 ratio. Clearly, this implies a combined motion of translation followed by a *cone-to-cone* inversion, as previously demonstrated for similar [2]rotaxane systems.[14] In accordance with these conclusions, Monte Carlo conformational searches indicated a significant higher stability of (*H,H*)-**8** and (*H,T*)-**8** (0.00 and 0.72 kcal/mol relative OPLS-energy, respectively) with respect to the other possible coconformers,[13] as explained by the formation of two and one H-bond, respectively, between the urethane NH and the calixarene oxygen atoms.

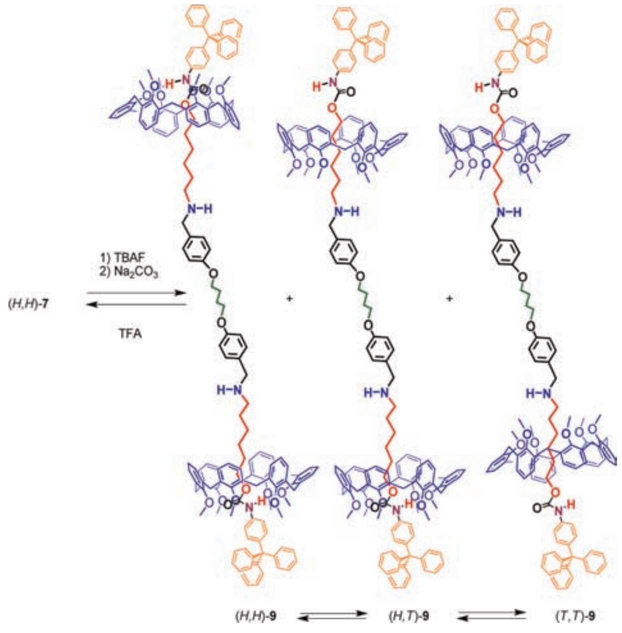
The shuttling behavior of the calix-wheels in [3]rotaxane **8** was also confirmed by a Molecular Dynamics (MD) simulation study. In fact, the data extracted from the simulation at 313 K clearly showed that the distance *d* (Å) between the two calix-wheels (Figure S37)[13] ranged from a minimum value of 8 Å to a maximum value of 35 Å, confirming the translation motion of the two wheels. Interestingly, about 60% of the coconformers sampled during the entire MD simulation (30 000 ps) showed a distance *d* in the 30–40 Å range (Figure S38),[13] thus revealing a clear tendency of the two calix-wheels to remain close to the urethane station.

This preference was also confirmed by monitoring the presence of CONH···OR H-bonds. In particular, variations were observed in the number of these interactions during the MD simulation (Figure S39),[13] but interestingly, ~76% of the sampled structures showed the presence of urethane H-bonds, thus confirming their decisive contribution to the stability of each supramolecular structure. Another aspect of the MD simulations is related to the *cone-to-cone* inversion of the wheels. In particular, simulations at 313 and 450 K (see Figure S40)[13] showed several inversions of calixarene aromatic rings, with the first one taking place after ~5000 ps.

The acidic treatment of neutral rotaxane **8** fully restored the original spectrum of (*H,H*)-**5** demonstrating that this system acts as a nanometer-sized molecular shuttle and that the original stereoprogramming is maintained when the system is back within its boundary conditions.

The shuttling behavior of the calix-wheels was also investigated for [3]rotaxane (*T,T*)-**7**, which was neutralized with the above counteranion-exchange method to give neutral [3]rotaxane **9** (Scheme 4).[13] In analogy to **8**, dynamic NMR studies on **9** evidenced again the movement of the calix-wheels from the original alkylbenzylammonium stations to new positions with shielded aliphatic chains. As above, a combined 2D NMR study (COSY-45, EXSY, and ROESY, in $CDCl_3$ at 253 K) evidenced the presence of translational isomers (*H,H*)-**9**, (*H,T*)-**9**, and (*T,T*)-**9** (Scheme 4) in a 55:25:20 ratio, respectively. In addition, Monte Carlo conformational searches confirmed their stability order with relative OPLS-energy values of 0.00, 0.54, and 0.76 kcal/mol, respectively, which were signficantly lower with respect to those of other coconformers.[13] It is worth pointing out that, in this instance, the two stabilizing CONH···OR H-bonds in (*H,H*)-**9** can only occur if the calix[6]arene wheels invert their original *tail-to-tail* orientation of **7** to a more suitable *head-to-head* one (Scheme 4).

Scheme 4



All these conclusions were confirmed by MD studies (10 000 ps, 313 K) that gave results very similar to those of **8**.[13] Finally, the acidic treatment of neutral rotaxane **9** fully restored the original spectrum of **7** demonstrating the complete reversibility of stereochemistry inversion of methoxy-bearing calix[6]arene wheels.

In conclusion, we have reported here a stereoprogrammed synthesis of the first examples of calixarene-based [3]rotaxane architectures. The base/acid treatment demonstrated that these systems act as molecular shuttles, which move on a nanometer scale level. An unprecedented switching between the relative orientation of the calix-wheels was observed in neutralized [3]rotaxanes, because of the small dimension of O-Me substituents, due to the formation of stabilizing H-bonds. In any case the original stereoprogramming was invariably reproduced when the cationic boundary conditions were restored. All these aspects represent interesting peculiar features of calixarene-based rotaxanes, which could be exploited to design molecular machines with new properties or functions.

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

The authors declare no competing financial interest.