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Sequence Stereoisomerism in Calixarene-Based Pseudo[3]rotaxanes

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ABSTRACT

Two calix[6]arene directional wheels can be ordered in the right stereosequence by their *through-the-annulus* threading with a rationally designed bis(benzylalkylammonium) axle. These stereoisomeric pseudo[3]rotaxanes can be considered as a minimal “informational system” because the “written information” on the thread is transferred to a specific sequence stereoisomer.

The most important and marvelous biological “informational systems”, such as DNA, RNA, and proteins, rely on the diverse and precise sequences of a limited set of covalently linked building blocks, which Leigh and coworkers have defined as a sort of “sequence isomerism”.[1] Obviously, in such biological systems control of the sequential order of the constitutive building blocks is crucial to the transmission and translation of genetic information. A conceptually comparable sequence isomerism can be obtained in the case of mechanically interlocked molecules, such as rotaxanes and catenanes,[2] if two or more different rings are in a different sequential order along the threading element (Figure 1), provided that their relative position is maintained by mechanical restrictions. This isomerism is of a stereochemical nature and can be related to conformational isomerism, which can be also maintained by intramolecular mechanical restrictions.

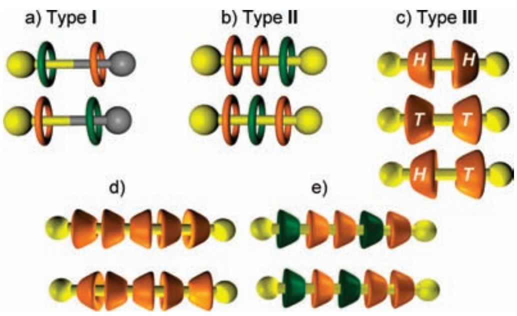

Figure 1. Sequence isomerism in rotaxane and pseudorotaxane structures.

In the case of rotaxanes or pseudorotaxanes the minimal structural requirements to observe a sequence stereoisomerism is to have two different rings and a directional (asymmetric) thread (type **I**, Figure 1a) or three rings of two different types and a symmetrical thread (type **II**, Figure 1b).[3] Another possibility is linked to the use of three-dimensional nonsymmetrical rings (directional wheels), which minimally requires only one type of ring, but in two different orientations (type **III**, Figure 1c). In this latter instance three different stereoisomers can be obtained, which could be termed as head-to-head (*H,H*), head-to-tail (*H,T*), and tail-to-tail (*T,T*) (Figure 1c).

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(1) Fuller, A.-M. L.; Leigh, D. A.; Lusby, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 4954.

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

(3) An example of sequence-specific formation of heteropseudo[3]rotaxane in which two different crown-ethers were threaded with a directional (asymmetric) thread was reported by Schalley: (a) Jiang, W.; Winkler, H. D. F.; Schalley, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 13852. Instead, examples have been reported in which two different wheels were threaded with a symmetrical thread and consequently no isomerism was displayed: (b) Amabilino, D. B.; Ashton, P. R.; Bělohradský, M.; Raymo, F. M.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1995**, 747. (c) Chen, L.; Zhao, X.; Chen, Y.; Zhao, C. X.; Jiang, X. K.; Li, Z. T. *J. Org. Chem.* **2003**, *68*, 2704.

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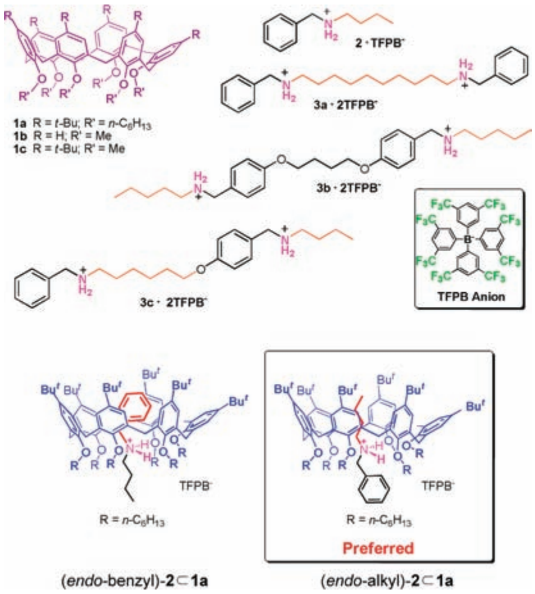

Figure 2. Structures of calix[6]arene wheels **1a**−**c** and alkylbenzylammonium axles **2** and **3a**−**c**.

More complex and more informative sequence stereoisomerism is obtained with longer sequences of identical or different directional wheels (Figure 1d−e). Obviously, for a larger number of identical wheels the sequence stereoisomerism will resemble the tacticity of polymers.[4]

Currently only a few examples of sequences of type I[1,3] have been described, whereas no instances of stereocontrolled directed synthesis of **II** and **III**[5] have been reported. Here, we wish to report some examples of sequence stereoisomerism of type **III**, in which the rational choice of the threading elements allows the stereocontrolled direct preparation of given sequence diastereoisomers of type **III** in Figure 1.

Our approach is based on our recent observation[6] that the *through-the-annulus* threading of simple calix[6]arene[7] hosts **1a**−**c** (Figure 2) can be obtained through the inducing effect of the weakly coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB) anion[8] that gives free "naked" dialkylammonium cations. In particular, we observed that the complexation of a nonsymmetrical alkylbenzylammonium cation (e.g., **2**) by hexaalkoxycalix[6]arenes (e.g., **1a**) can lead to a preference for the *endo*-alkyl stereoisomer (**2**$\subset$**1a**) over the *endo*-benzyl one up to a 30:1 ratio (Figure 2).[6a]

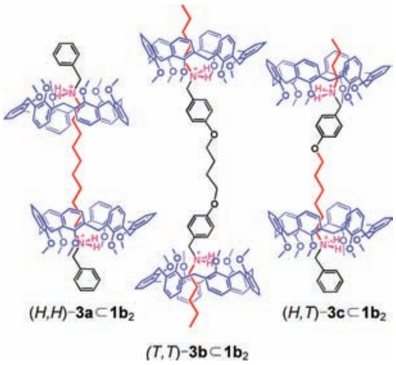

Figure 3. Structures of (*H,H*)-, (*T,T*)-, and (*H,T*)-pseudo[3]rotaxanes obtained by threading hexamethoxy-*p*-H-calix[6]arene **1b** with axles **3a**, **3b**, and **3c**, respectively.

On this basis we envisioned that the appropriate covalent linkage of two such alkylbenzylammonium recognition motifs could allow good control of the consequent sequence stereoisomerism.

As a first step we decided to connect two alkylbenzylammonium motifs by the alkyl ends to give a thread exposing benzyl units at the two extremities (**3a**).[9] We expected that the *endo*-alkyl stereochemistry should be favored at both ammonium centers resulting in a head-to-head pseudo[3]rotaxane (Figure 3). In accordance with this expectation, the ^{1}H NMR spectrum of a 1:2 mixture of the TFPB salt of dicationic thread **3a** and hexamethoxy-*p*-H-calix[6]arene **1b** in $CDCl_3$ (Figure 4b) showed a typical signature at highfield negative values (from 1.0 to −1.0 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 clear-cut proof that head-to-head pseudo[3]rotaxane (*H,H*)-**3a**$\subset$**1b**$_2$ (Figure 3) had been exclusively formed.

The formation of pseudo[3]rotaxane (*H,H*)-**3a**$\subset$**1b**$_2$ (Figure 3) was confirmed by a prominent peak at 898 *m*/*z* in the ESI(+) mass spectrum,[9] corresponding to the doubly charged supramolecular ion. The double *endo*-alkyl stereochemistry was fully confirmed by a 2D ROESY spectrum coupled to a full signal assignment by 2D COSY analysis.[9] In particular, diagnostic cross-peaks were

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(4) Young, R. J.; Lovell, P. A. *Introduction to Polymers*, 3rd ed.; CRC Press: Boca Raton, FL, 2011.

(5) 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. For other examples of orientational isomers of [3]rotaxane systems, see: (c) Saudan, C.; Dunand, F. A.; Abou-Hamdan, A.; Bugnon, P.; Lye, P. G.; Lincoln, S. F.; Merbach, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 10290. (d) Eliadou, K.; Yannakopoulou, K.; Rontoyianni, A.; Mavridis, I. M. *J. Org. Chem.* **1999**, *64*, 6217. (e) Qu, D. H.; Wang, Q. C.; Ma, X.; Tian, H. *Chem.—Eur. J.* **2005**, *11*, 5929. (f) Craig, M. R.; Claridge, T. D. W.; Hutchings, M. G.; Anderson, H. L. *Chem. Commun.* **1999**, 1537.

(6) (a) Gaeta, C.; Troisi, F.; Neri, P. *Org. Lett.* **2010**, *12*, 2092. (b) For the first examples of calixarene-based molecular shuttles obtained by using the same approach, see: Pierro, T.; Gaeta, C.; Talotta, C.; Casapullo, A.; Neri, P. *Submitted.*

(7) Gutsche, C. D. *Calixarenes, An Introduction*; Royal Society of Chemistry: Cambridge, UK, 2008.

(8) (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927. (b) For a review on counterion effects in supramolecular chemistry, see: Gasa, T. B.; Valente, C.; Stoddart, J. F. *Chem. Soc. Rev.* **2011**, *40*, 57.

(9) See Supporting Information for further details.

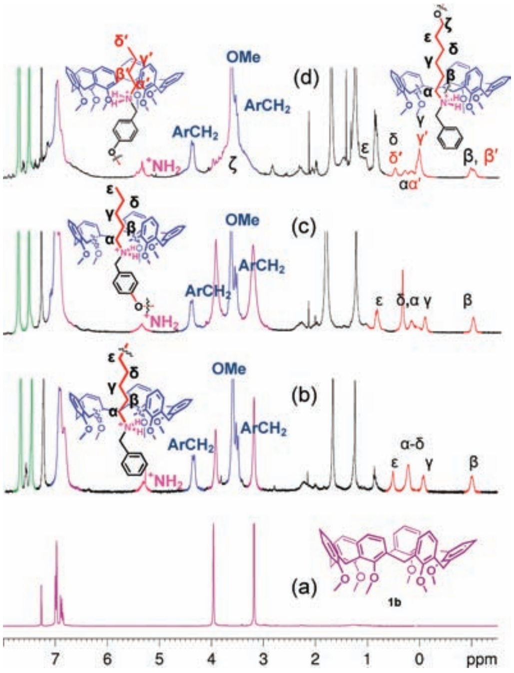

Figure 4. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) **1b**; (b) 1:2 mixture of **3a** and **1b**; (c) 1:2 mixture of **3b** and **1b**; and (d) 1:2 mixture of **3c** and **1b**. In some structure drawings an aromatic ring of the wheel has been removed for clarity.

present in the ROESY spectrum of (*H,H*)-**3a**$\subset$**1b**$_2$ (400 MHz, $CDCl_3$, 298 K) between the shielded aliphatic $\alpha-\varepsilon$ protons (Figure 4b) of the axle and ArH protons of the two equivalent calix-wheels. Another cross-peak indicative of the head-to-head orientation of the two calix-wheels was present at 3.60/7.59 ppm between OMe protons at the lower rim of calix[6]arene macrocycle and ArH protons of the benzyl units of the thread. The stereochemical preference was also confirmed by molecular mechanics calculations[10] (OPLS force field, $CHCl_3$, GB/SA model solvent), which indicated the (*H,H*) sequence isomer of **3a**$\subset$**1b**$_2$ as the lowest in energy with respect to (*H,T*) and (*T,T*) ones by 3.6 and 4.3 kcal/mol, respectively (see Figure S49 in the Supporting information).

It is interesting to point out that the formation of pseudo[3]rotaxane (*H,H*)-**3a**$\subset$**1b**$_2$ occurs with high efficiency and only a minimal amount of uncomplexed calix[6]arene host **1b** was present, while the singly threaded species was below the detection limit.

Under these conditions the association constant cannot be determined by simple integration methods; therefore we resorted to a dilution experiment of the 1:2 mixture of **3a** and **1b** in $CDCl_3$.[9] A nonlinear least-squares fitting[11] of the integration data led to a value of 16 923 ± 2599 and 342 ± 30 M^{-1} for the first (K_1) and the second (K_2) association constant, respectively, in good agreement with the previously reported monomeric 1:1 complexation constants.[6a]

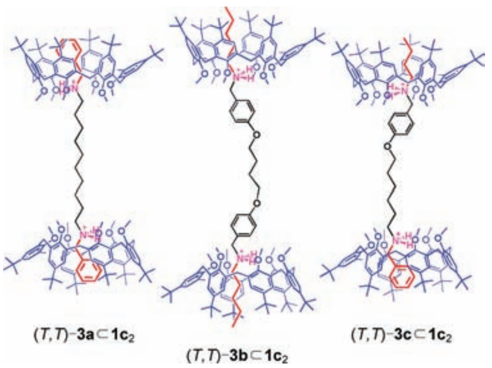

Figure 5. Structures of (*T,T*)-pseudo[3]rotaxanes obtained by threading hexamethoxy-*p*-*t*-Bu-calix[6]arene **1c** with axles **3a**, **3b**, and **3c**.

The logical extension of the above approach was the connection of two alkylbenzylammonium moieties by the benzyl ends to give a thread exposing alkyl chains at the terminations (**3b**). In this case the orientation of the calixarene cavity toward the exterior should be favored leading to a tail-to-tail pseudo[3]rotaxane (Figure 3). In fact, the ^{1}H NMR spectrum of a 1:2 mixture of the TFPB salt of **3b** and hexamethoxy-*p*-H-calix[6]arene **1b** in $CDCl_3$ (Figure 4c) showed again the presence of shielded alkyl resonances at negative values typical of *endo*-alkyl complexation. Also in this instance, no shielded benzylic signals could be traced confirming the exclusive formation of tail-to-tail pseudo[3]rotaxane (*T,T*)-**3b**$\subset$**1b**$_2$.

As above the structure of (*T,T*)-**3b**$\subset$**1b**$_2$ was fully confirmed by an ESI(+) MS spectrum, which showed a prominent peak at 942 *m*/*z* corresponding to the doubly charged supramolecular ion, and by a 2D COSY NMR spectrum.[9] In this instance the values of the single association constants (K_1 and K_2) could not be determined by dilution experiments and only the total binding constant ($K_{tot} = K_1 \cdot K_2$) could be evaluated by signal integration. A value of $7.4 \times 10^5\ M^{-2}$ was obtained for K_{tot} of (*T,T*)-**3b**$\subset$**1b**$_2$, which is lower than that calculated for (*H,H*)-**3a**$\subset$**1b**$_2$ ($5.8 \times 10^6\ M^{-2}$).

Finally, thread **3c** bearing an alkyl and a benzyl unit at the two extremities was synthesized in order to direct the calix[6]arene wheels **1b** in the head-to-tail stereosequence (Figure 3). As expected, the ^{1}H NMR spectrum of a 1:2 mixture of the TFPB salt of dicationic thread **3c** and hexamethoxy-*p*-H-calix[6]arene **1b** in $CDCl_3$ (Figure 4d) was indicative that head-to-tail pseudo[3]rotaxane (*H,T*)-**3c**$\subset$**1b**$_2$ had been exclusively formed.

In fact, it showed a typical signature at highfield negative values (from 1.0 to −1.0 ppm) characteristic of

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[10] 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.

[11] Elizarov, A. M.; Chiu, S.-H.; Glink, P. T.; Stoddart, J. F. *Org. Lett.* **2002**, *4*, 679.

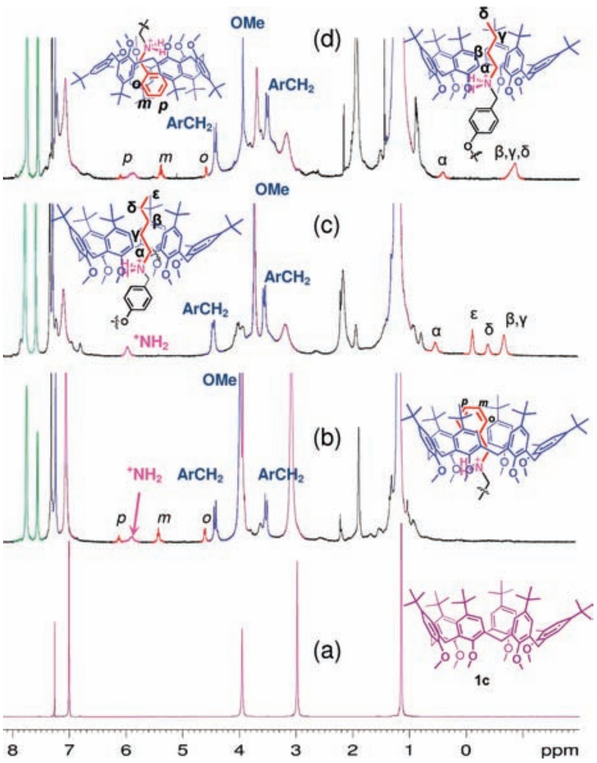

Figure 6. ^{1}H NMR spectra (400 MHz, CDCl$_3$, 298 K) of (a) **1c**; (b) 1:2 mixture of **3a** and **1c**; (c) 1:2 mixture of **3b** and **1c**; and (d) 1:2 mixture of **3c** and **1c**. In some structure drawings an aromatic ring of the wheel has been removed for clarity.

an *endo*-alkyl complexation. In addition, the absence of shielded *endo*-benzyl resonances in the 4−6 ppm region was a clear indication that head-to-head or tail-to-tail sequential isomers have not been formed. Again, the presence of pseudo[3]rotaxane $(H,T)\text{-}\mathbf{3c}\subset\mathbf{1b}_2$ was confirmed by a prominent peak at 906 m/z in the ESI(+) mass spectrum,[9] corresponding to the doubly charged supramolecular ion.

From the above three examples we can conclude that the rational choice of the axle allows preparation of all three possible (H,H)-, (T,T)-, and (H,T)-stereosequences of two threaded calix-wheels **1b**. In other words, the “information written” on the thread is transferred to a specific pseudorotaxane sequence stereoisomer, which can be considered as a minimal “informational system”.

In this regard it is interesting to examine how the structure of the calix-wheel could influence the transfer of the written information. In particular, we speculated that the presence of bulky groups on the wheel could alter the stereopreference of a given thread. Thus, we decided to study the complexation of hexamethoxycalix[6]arene **1c**, bearing *tert*-butyl groups at the upper rim, with the benzyl-exposing thread **3a**, which gives rise to a head-to-head stereosequence with hexamethoxycalix[6]arene **1b** bearing H-atoms at the upper rim. The ^{1}H NMR spectrum (Figure 6b) of a 1:2 mixture of the TFPB salt of **3a** and *p*-*t*-Bu-calix[6]-wheel **1c** in CDCl$_3$ revealed the presence of shielded benzylic resonances in the 4−6 ppm region, which was clear proof of a double *endo*-benzyl complexation of **3a**, to give tail-to-tail pseudo[3]rotaxane $(T,T)\text{-}\mathbf{3a}\subset\mathbf{1c}_2$ (Figure 5). As above, the formation of this pseudo[3]rotaxane was confirmed by the doubly charged supramolecular peak at 1235 m/z in the ESI(+) mass spectrum, while a total binding constant of 2.5×10^5 M^{-2} was evaluated by signal integration.[9]

Clearly, the change of thread **3a** from the head-to-head to the tail-to-tail stereosequence by replacing *p*-H-**1b** with *p*-*t*-Bu-calix[6]-wheel **1c** has to be attributed to the steric encumbrance of the *t*-Bu groups in **1c**. This conclusion was also confirmed by OPLS calculations (in CHCl$_3$, GB/SA model solvent), which favored $(T,T)\text{-}\mathbf{3a}\subset\mathbf{1c}_2$ with respect to the $(H,H)\text{-}\mathbf{3a}\subset\mathbf{1c}_2$ stereoisomer by an energy difference of 4 kcal/mol and evidenced a steric crowding between facing calixarene *t*-Bu groups in the latter (see Figure S50 in the Supporting Information).[9]

An analogous study with threads **3b** and **3c** evidenced that the tail-to-tail stereosequence is again preferred with *p*-*t*-Bu-calix[6]-wheel **1c** to give $(T,T)\text{-}\mathbf{3b}\subset\mathbf{1c}_2$ and $(T,T)\text{-}\mathbf{3c}\subset\mathbf{1c}_2$ (Figures 5 and 6), thus confirming the strong role played by the *t*-Bu groups on this wheel.

In conclusion, the first examples of calixarene-based pseudo[3]rotaxane systems have been obtained by the *through-the-annulus* threading of alkoxycalix[6]arene macrocycles with bis(benzylalkylammonium) ions coupled to the weakly coordinating TFPB anion. In addition, we have here reported the first example of rational control of the stereosequence of two threaded directional wheels, which can be considered as a minimal “informational system” whose “written information” on the thread is transferred to a specific pseudorotaxane sequence stereoisomer.

In analogy to natural informational systems, such as DNA, where the sequence of nucleic bases encodes the genetic information, control of the sequence (stereo)-isomerism in threaded structures, such as rotaxane and pseudorotaxane, could allow the design of “informational devices” in which each sequence isomer corresponds to a specific physical or chemical output. Further studies in this direction are in progress in our laboratory.

Acknowledgment. Thanks are due to Dr. Patrizia Iannece (Dipartimento di Chimica e Biologia, Università di Salerno) for ESI-MS measurements.

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