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An Oriented Handcuff Rotaxane

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ABSTRACT

The first example of an oriented handcuff rotaxane has been obtained by *through-the-annulus* threading of a double-calix[6]arene system with a bis-ammonium axle. The relative orientation of the two calix-wheels can be predefined by exploiting the "*endo*-alkyl rule" which controls the directionality of the threading of alkylbenzylammonium axles with calixarene macrocycles.

Macrocyclic hosts with multiple cavities and/or multiple recognition sites have attracted increasing attention thanks to their usefulness for developing nontrivial interlocked architectures.[1] In this regard, interpenetrated systems in which two rings are linked to one another in a handcuff-like fashion have represented a significant synthetic challenge.[2] Based on the template-directed threading[1,3] of linear axles through such double-macrocycles, beautiful handcuff-like architectures have been reported to date, which shows interesting properties and functions.

The first example dates back to 1993 when Stoddart et al.[4a] reported the handcuff architecture **A** (Figure 1), which was followed by similar [2]catenane polymers **B**.[4b] Successively, Becher[5] reported an example of architecture **C**, in which the two connected rings are threaded through the same large ring to form a handcuff [2]catenane. A similar topology was built in 2005 by Sauvage,[6,2b] through the template effect of Cu(I), and more recently by Beer,[7] through the templation of the chloride anion. In 2000 Vögtle et al.[8] reported a molecular "pretzelane" **D** in which the two connected rings are mutually interpenetrated to give a [1]catenane.

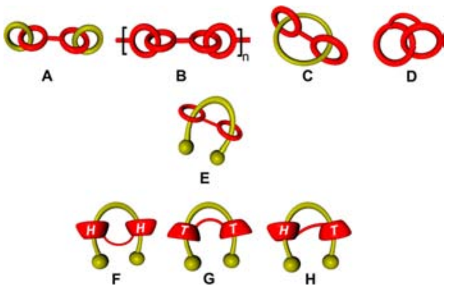

Figure 1. Schematic representation of the currently known prototypical examples of handcuff-derived architectures (**A**−**E**) and the proposed stereoisomeric oriented handcuff (pseudo)-[2]rotaxanes (**F**−**H**).

Regarding rotaxane architectures such as **E** (Figure 1), only very recently an example has been reported[2a] in which two flat crown-rings, rigidly linked to one another, were

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

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(7) Evans, N. H.; Serpell, C. J.; Beer, P. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 2507.

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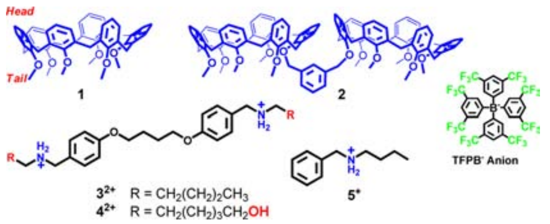


Figure 2. Structures of calix[6]arene wheels **1** and **2**, bis(alkylbenzylammonium) axles **3**$^{2+}$ and **4**$^{2+}$, TFPB anion, and alkylbenzylammonium axle **5**$^{+}$.

threaded with a bis-ammonium axle to mimic a double-leg elevator. To the best of our knowledge, this is the only example of handcuff rotaxane so far reported.

With respect to the use of flat macrocycles in **E** (Figure 1), a further synthetic challenge is represented by the use of three-dimensional nonsymmetrical rings (directional wheels), such as in double-calixarene **2** (Figure 2),[9] because of the inherent difficulty in controlling their relative orientation within the entire system.[10] In fact, the threading of **2** with a bis-ammonium axle (e.g., **3**$^{2+}$) could give rise to three stereoisomeric handcuff pseudo[2]rotaxane structures, in which the two calix-wheels could show three different relative orientations, *head-to-head* (*H,H*), *tail-to-tail* (*T,T*), and *head-to-tail* (*H,T*), respectively represented by **F**−**H** in Figure 1. Based on these considerations, the following questions arise: which stereochemistry (**F**, **G**, or **H**) of the handcuff pseudo[2]rotaxane formed between **2** and thread **3**$^{2+}$or **4**$^{2+}$ can be expected? Are we able to deliberately form only one of them?

Recently,[11] we have shown that the threading of a directional alkylbenzylammonium cation (e.g., **5**$^{+}$, Figure 2) by a calix[6]arene (e.g., **1**) leads to a preference for the *endo*-alkyl stereoisomer **6**$^{+}$ over the *endo*-benzyl one (Figure 3).[12] Successively, we showed that by encoding the appropriate alkylbenzyl sequence along bis-ammonium axles it was possible to obtain a specific stereosequence (e.g., *H*,*H* or *H*,*T*, Figure 3) of the two calix-wheels in pseudo[3]rotaxane architectures **7**$^{2+}$ and **8**$^{2+}$.[10] Analogously, the stereoprogrammed synthesis of a calix[2]catenane orientational isomer **9**$^{+}$ was obtained by macrocyclization, upon using a directional alkylbenzylammonium axle.[13]

From these studies we have generalized the following stereochemical "*endo*-alkyl rule" (Figure 3): threading of a directional alkylbenzylammonium axle (e.g., **5**$^{2+}$) through a non-*tert*-butylated hexaalkoxycalix[6]arene (e.g., **1**) occurs with an *endo*-alkyl preference.[14]

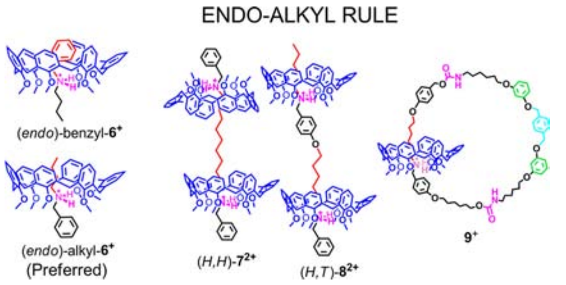
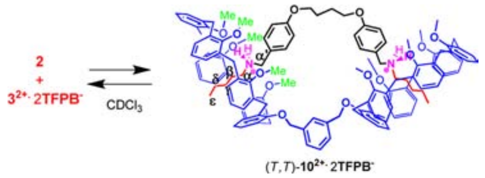


Figure 3. The "*endo*-alkyl rule"[14] and some related examples of oriented interpenetrated architectures reported.[10,13]

Scheme 1. Handcuff Threading of **2** with **3**$^{2+}$



On the basis of this "*endo*-alkyl rule",[14] we envisioned that the appropriate encoding of a sequence of alkylbenzylammonium binding sites along a bis-ammonium thread could allow the stereoprogrammed preparation of a given oriental isomer **F**, **G**, or **H** of a calixarene-based handcuff pseudorotaxane.

Naturally, the presence of the short *m*-xylylene spacer between the two wheels in **2** could favor a different anomalous stereochemistry with respect to that predicted by the "*endo*-alkyl rule". Prompted by these considerations, we decided to study the threading properties of double-calix[6]arene[15] **2** with bis-ammonium axles **3**$^{2+}$ and **4**$^{2+}$ and we wish to report here the results of our studies.

As a first step we decided to use thread **3**$^{2+}$ in which two alkylbenzylammonium moieties are connected by the benzyl ends to expose the alkyl chains at the terminations (Figure 2). On the basis of the above *endo*-alkyl rule, the threading of **2** with **3**$^{2+}$ should result in a *tail-to-tail* oriented handcuff pseudo[2]rotaxane such as **G**. To verify this prediction, the TFPB[16] salt of **3**$^{2+}$ was equilibrated

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[9] Gutsche, C. D. *Calixarenes, An Introduction*; Royal Society of Chemistry: Cambridge, U.K., 2008.

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[12] Analogously, the threading of a directional alkylbenzylammonium cation by calix[8]arene lead to a preference for the *endo*-alkyl stereoisomer over the *endo*-benzyl one: Gaeta, C.; Talotta, C.; Margarucci, L.; Casapullo, A.; Neri, P. *J. Org. Chem.* **2013**, *78*, 7627.

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[15] Saadioui, M.; Böhmer, V. In *Calixarenes*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; pp 130−154 and references cited therein.

[16] As reported by us,[11,12] the *through-the-annulus* threading of scarcely efficient calix[6−8]arene hosts with dialkylammonium axles can only be obtained through the inducing effect of the superweak anion TFPB (**T**etrakis[3,5-bis(tri**F**luoromethyl)**P**henyl]**B**orate). For a review on superweak anion TFPB^{-}, see: (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927. For recent examples on the use of the TFPB superweak anion in supramolecular chemistry, see (b) Pierro, T.; Gaeta, C.; Talotta, C.; Casapullo, A.; Neri, P. *Org. Lett.* **2011**, *13*, 2650. (c) Li, C.; Shu, X.; Li, J.; Fan, J.; Chen, Z.; Weng, L.; Jia, X. *Org. Lett.* **2012**, *14*, 4126. (d) Gaeta, C.; Talotta, C.; Farina, F.; Camalli, M.; Campi, G.; Neri, P. *Chem.—Eur. J.* **2012**, *18*, 1219. (e) Gaeta, C.; Talotta, C.; Farina, F.; Teixeira, F. A.; Marcos, P. A.; Ascenso, J. R.; Neri, P. *J. Org. Chem.* **2012**, *77*, 10285.

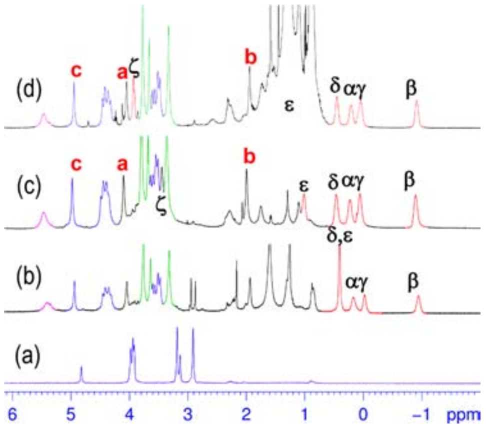

Figure 4. Portions of the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) **2**, (b) an equimolar mixture (3 mM) of **2** and $\mathbf{3}^{2+}\cdot 2TFPB^-$, (c) an equimolar mixture (3 mM) of **2** and $\mathbf{4}^{2+}\cdot 2TFPB^-$, and (d) handcuff [2]rotaxane (*T,T*)-$\mathbf{12}^{2+}$.

with double-calix[6]arene **2**[17] (Scheme 1) and the resulting solution was investigated by 1D and 2D NMR spectroscopy and ESI(+) mass spectrometry.

In particular, the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 298 K) of the 1:1 mixture (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 and indicative of the formation of pseudorotaxane (*T,T*)-$\mathbf{10}^{2+}$. This result and the absence of shielded benzylic resonances in the 4−6 ppm region, typical of *endo*-benzyl complexation,[10−14] were a clear-cut proof that the *tail-to-tail* isomer **G** of handcuff-pseudo[2]rotaxane (*T,T*)-$\mathbf{10}^{2+}$ (Scheme 1) had been stereoselectively formed. An apparent total association constant (K_{tot}) of $1.6 \pm 0.3 \times 10^3$ M^{-1} in $CDCl_3$ (percentage of formation 58%) was determined for (*T,T*)-$\mathbf{10}^{2+}$ by integration of the slowly exchanging ^{1}H NMR signals. These results show that the presence of the short *m*-xylylene spacer between the two calix-wheels of **2** does not generate any anomalous stereopreference with respect to the *endo*-alkyl rule.

Certainly, the presence of the typical highfield signature in Figure 4b could also be compatible with a cyclic or square-type[18] supramolecular architecture **I** or an undefined supramolecular oligomer or polymer **J** (see ref 18). The formation of handcuff pseudo[2]rotaxane $\mathbf{10}^{2+}$ was unequivocally confirmed by the base peak at *m*/*z* 979.83 in the ESI(+) mass spectrum (Figure 5). In fact, the Δ spacing of 0.5 *m*/*z* between the peaks in the isotopic envelop (Figure 5, inset) solely accounts for a doubly charged species of **10**, excluding architectures with higher charges such as **I** or **J** represented in ref 18.

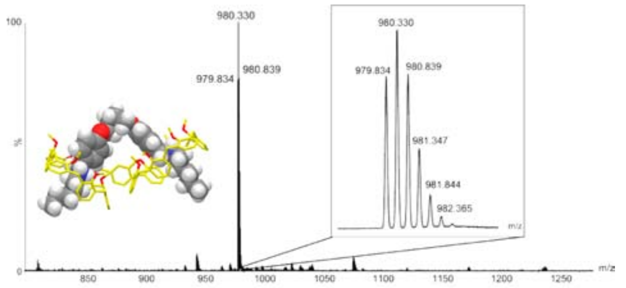

Figure 5. ESI(+) mass spectrum of (*T,T*)-$\mathbf{10}^{2+}$ and its AMBER energy-minimized structure (inset).

A COSY-45 spectrum[17] ($CDCl_3$, 400 MHz, 298 K) of the 1:1 mixture of thread $\mathbf{3}^{2+}$ and double-calix[6]arene **2** allowed a complete confident assignment of all shielded alkyl resonances. Thus, α-protons at 0.17 ppm show a coupling with the *β*-methylene group at −0.96 ppm, which presents a cross-peak with *γ*-protons at −0.03 ppm, finally coupled with *δ* CH_2 at 0.39 ppm, which was coupled with *ε*-protons at 0.40 ppm. In addition, the $ArCH_2Ar$ region (3−5 ppm) revealed the presence of three AX systems[19] at 4.43/3.58, 4.38/3.49, and 4.31/3.49 ppm relative to three $ArCH_2Ar$ groups. On the other hand, the ^{1}H NMR spectrum showed three singlets in a 2:1:2 ratio at 3.77, 3.63, and 3.33 ppm relative to OMe groups and a singlet at 4.95 ppm relative to OCH_2 groups of the *m*-xylylene bridge. These data indicate the presence of a symmetry plane bisecting the *m*-xylylene bridge and the 1,4-diphenoxybutane chain, which is perfectly compatible with a handcuff threading of **2**.

Molecular mechanics calculations revealed that a folding of the thread $\mathbf{3}^{2+}$ is required to simultaneously thread the two calixarene-wheels of **2**. Thus, the folded conformation adopted by $\mathbf{3}^{2+}$ in handcuff pseudo[2]rotaxane (*T,T*)-$\mathbf{10}^{2+}$ was characterized by unfavorable gauche conformations around C(1)−C(2) and C(2)−C(3) bonds (dihedral angles of 45° and 55°, respectively, Figure 6) of the central 1,4-diphenoxybutane fragment.[17] Simulated Annealing (SA) experiments[17] clearly evidenced that ~75% of the coconformers in the 4 kcal/mol lowest energy window (200 independent annealing experiments) showed a dihedral angle in the 42°−87° range around the C(1)−C(2) bond. Analogously, ~85% of the same structures gave a C(2)−C(3) dihedral angle in the 50°−75° range (Figure S15). This situation

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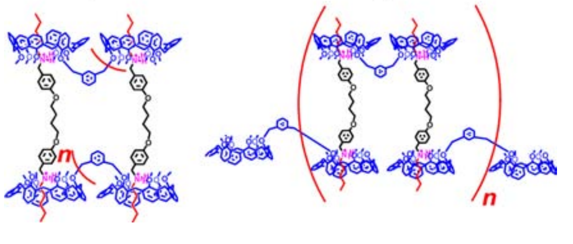
(17) See Supporting Information for further details.

(18) Structures **I** and **J**.



(19) The presence of well-defined AX systems for $ArCH_2Ar$ groups in the COSY-45 spectrum is a clear indication that the thread $\mathbf{3a}^+$ gave a handcuff-*through-the-annulus*-threading with double-calix[6]arene **2** in $CDCl_3$. In fact, the $ArCH_2Ar$ protons appear as singlets for the conformationally mobile free host **2** (see ^{1}H NMR spectrum of **2** in Figure 3a), whereas each of them gives rise to a couple of doublets (AX system) when the wheel is conformationally blocked by pseudorotaxane formation.

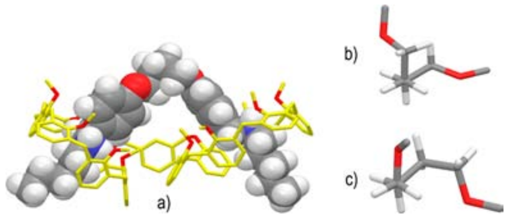


Figure 6. (a) Lowest energy structure of handcuff pseudo[2]rotaxane (T,T)-$\mathbf{10}^{2+}$ found by Monte Carlo search associated with Simulated Annealing experiments (MacroModel V. 9.0, AMBER force field). (b and c) Newman projections along the C(2)−C(3) and C(1)−C(2) bonds, respectively, showing the unfavorable gauche conformations.

resembles those observed by Rebek[20] in the encapsulation of long alkanes in a coiled form inside a self-assembled capsule and recently by us[16e] in the *endo*-complexation of large di-*n*-alkylammonium cations inside the narrow cavity of the 18-membered dihomooxacalix[4]arene ring. In analogy to those complexes, in the present case the energy loss due to the unfavorable folding of the thread is counterbalanced by the gain in H-bonding energy due to the double threading of the two calix[6] cavities.

In order to permanently trap the above handcuff [2]rotaxane architecture, we decided to investigate the threading of **2** with axle $\mathbf{4}^{2+}$ encoding again the external alkyl chains, which are now terminated by two easily stopperable OH groups (Scheme 2). Therefore, 1 equiv of the TFPB salt of $\mathbf{4}^{2+}$ was equilibrated with 1 equiv of double-calix[6]arene **2** in $CDCl_3$ to give handcuff pseudo[2]rotaxane (T,T)-$\mathbf{11}^{2+}$ (Scheme 2). The ^{1}H NMR spectrum of this mixture (Figure 4c) 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* handcuff pseudo[2]rotaxane (T,T)-$\mathbf{11}^{2+}$. Thus, the validity of the above *endo*-alkyl rule was again confirmed. An apparent total association constant (K_{tot}) of $1.7 \pm 0.3 \times 10^5$ M^{-1} in $CDCl_3$ (percentage of formation 84%) was determined for (T,T)-$\mathbf{11}^{2+}$ by integration of the slowly exchanging ^{1}H NMR signals. Pseudorotaxane (T,T)-$\mathbf{11}^{2+}$ was then stoppered by a reaction with 4-tritylphenyl isocyanate to give the first example of predefined orientational handcuff [2]rotaxane (T,T)-$\mathbf{12}^{2+}$ in 28% yield (Scheme 2). Its formation was confirmed by a prominent peak at 1370.1 *m*/*z* in the ESI(+) mass spectrum (Figure 7), corresponding to the doubly charged interlocked ion. As above, a combined 1D and 2D NMR study confirmed the *tail*-*to*-*tail* stereosequence of the two calix-wheels in handcuff [2]rotaxane (T,T)-$\mathbf{12}^{2+}$. Also in this case molecular mechanics calculations (AMBER force field, $CHCl_3$, GB/SA model solvent) indicated a folded conformation of the thread (Figure 6).

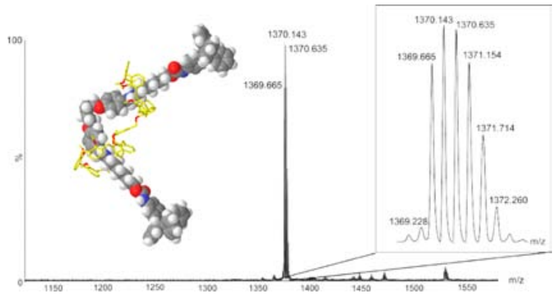
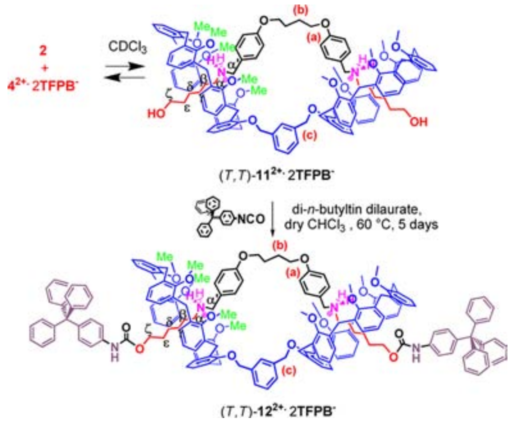


Figure 7. ESI(+) mass spectrum of (T,T)-$\mathbf{12}^{2+}$ and its AMBER energy-minimized structure (inset).

Scheme 2. Synthesis of Handcuff [2]Rotaxane (T,T)-$\mathbf{12}^{2+}$



Analogously to pseudorotaxane (T,T)-$\mathbf{10}^{2+}$, SA experiments clearly evidenced that ~65% of the coconformers in the 4 kcal/mol lowest energy window (200 independent experiments) showed a dihedral angle in the 45°−70° range around the C(1)−C(2) bond (Figure S16). Analogously, ~50% of the same structures gave a C(2)−C(3) dihedral angle in the 59°−84° range (Figure S16).

In conclusion, we have reported here the first examples of calixarene-based handcuff pseudorotaxane and rotaxane architectures. In addition, we have showed the possibility to control the threading directionality by exploiting the "*endo*-alkyl rule" to give a predefined orientational isomer. Therefore, it is conceivable that the extension of this approach could lead to novel mechanically interlocked architectures with high-order topologies.

Acknowledgment. We thank the Italian MIUR (PRIN 20109Z2XRJ_006) for financial support.

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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