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 hand-cuff-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, Becher⁵ 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

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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).

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.

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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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 $\mathbf{F}-\mathbf{H}$ 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 endoalkyl 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



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+}



a non-tert-butylated hexaalkoxycalix[6]arene (e.g., 1) occurs with an endo-alkyl preference.14

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 doublecalix[6]arene¹⁵ 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 TFPB¹⁶ salt of 3^{2+} was equilibrated

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⁽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 (Tetrakis[3,5-bis(triFluoromethyl)Phenyl]Borate). 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 ¹H NMR spectra (400 MHz, CDCl₃, 298 K) of (a) **2**, (b) an equimolar mixture (3 mM) of **2** and $3^{2+} \cdot 2\text{TFPB}^{-}$, (c) an equimolar mixture (3 mM) of **2** and $4^{2+} \cdot 2\text{TFPB}^{-}$, and (d) handcuff [2]rotaxane (*T*,*T*)-**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 ¹H NMR spectrum (CDCl₃, 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)-10²⁺. 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 handcuffpseudo[2]rotaxane (T,T)-10²⁺ (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 CDCl₃ (percentage of formation 58%) was determined for $(T,T)-10^{2+}$ by integration of the slowly exchanging ¹H 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-type¹⁸ supramolecular architecture **I** or an undefined supramolecular oligomer or polymer **J** (see ref 18). The formation of handcuff pseudo[2]rotaxane 10^{2+} was unequivocally confirmed by the base peak at m/z 979.83 in









Figure 5. ESI(+) mass spectrum of (T,T)-10²⁺ and its AMBER energy-minimized structure (inset).

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.

A COSY-45 spectrum¹⁷ (CDCl₃, 400 MHz, 298 K) of the 1:1 mixture of thread 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 CH₂ at 0.39 ppm, which was coupled with ε-protons at 0.40 ppm. In addition, the ArCH₂Ar region (3-5 ppm) revealed the presence of three AX systems¹⁹ at 4.43/3.58, 4.38/3.49, and 4.31/3.49 ppm relative to three ArCH₂Ar groups. On the other hand, the ¹H 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 OCH₂ groups of the *m*-xylvlene 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 3^{2+} is required to simultaneously thread the two calixarene-wheels of **2**. Thus, the folded conformation adopted by 3^{2+} in handcuff pseudo[2]rotaxane (*T*,*T*)- 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) experiments¹⁷ 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

⁽¹⁹⁾ The presence of well-defined AX systems for ArCH₂Ar groups in the COSY-45 spectrum is a clear indication that the thread $3a^+$ gave a handcuff-*through-the-annulus*-threading with double-calix[6]arene **2** in CDCl₃. In fact, the ArCH₂Ar protons appear as singlets for the conformationally mobile free host **2** (see ¹H 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)-10²⁺ 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 Rebek²⁰ 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 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 4^{2+} was equilibrated with 1 equiv of doublecalix[6]arene 2 in CDCl₃ to give handcuff pseudo[2]rotaxane (T,T)-11²⁺ (Scheme 2). The ¹H NMR spectrum of this mixture (Figure 4c) showed again the presence of shielded alkyl resonances at negative values typical of endoalkyl complexation and confirming the exclusive formation of *tail-to-tail* handcuff pseudo[2]rotaxane (T,T)- 11^{2+} . Thus, the validity of the above *endo*-alkyl rule was again confirmed. An apparent total association constant (\bar{K}_{tot}) of 1.7 \pm 0.3 \times $\hat{10}^5$ M⁻¹ in CDCl₃ (percentage of formation 84%) was determined for $(T,T)-11^{2+}$ by integration of the slowly exchanging ¹H NMR signals. Pseudorotaxane (T,T)-11²⁺ was then stoppered by a reaction with 4-tritylphenyl isocyanate to give the first example of predefined orientational handcuff [2]rotaxane $(T,T)-12^{2+}$ 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 (\hat{T},T) -12²⁺. Also in this case molecular mechanics calculations (AMBER force field, CHCl₃, GB/SA model solvent) indicated a folded conformation of the thread (Figure 6).



Figure 7. ESI(+) mass spectrum of (T,T)-12²⁺ and its AMBER energy-minimized structure (inset).





Analogously to pseudorotaxane (T,T)-10²⁺, 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.

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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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