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Synthesizing [2]Rotaxanes and [2]Catenanes through Na^+-Templated Clipping of Macrocycles around Oligo(ethylene glycol) Units

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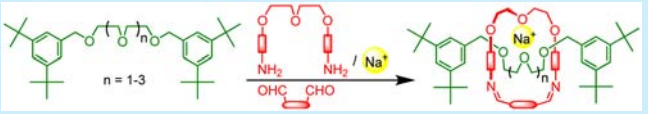
Supporting Information

ABSTRACT: Di-, tri-, and tetra(ethylene glycol) units in both dumbbell-shaped and macrocyclic molecules can be used as primary recognition units for the clipping of macrocycles in the presence of templating Na^+ ions to form corresponding [2]rotaxanes and [2]catenanes. One such tri(ethylene glycol)-containing [2]catenane behaves as a Na^+ ion-controllable molecular switch.



The strong chemical resistance, high organic solubility, and potential cationic binding ability of oligo(ethylene glycol)s have made them motifs found frequently in the structures of many functional organic molecules.[1] Nevertheless, their relatively high structural flexibility and solvation energy in organic solvents has meant that they have rarely been used as primary recognition units for the encircling of macrocyclic hosts in the synthesis of interlocked molecules. Recently, we demonstrated that the threading of oligo(ethylene glycol) units through the cavity of bis-*p*-xylyl[26]crown-6 (BPX26C6) is possible in the presence of a Na^+ ion template under solvent-free conditions.[2] A limitation of the "threading followed by stoppering"[3] approach for synthesizing rotaxanes is, however, that it can require new synthetic designs to facilitate the final stoppering reactions of known linearly shaped guest molecules; in contrast, the "clipping"[4] approach can be applied directly to dumbbell-shaped or macrocyclic molecules to afford the corresponding rotaxanes or catenanes, respectively, without concern for the procedures used to synthesize these precursor components (Figure 1). Therefore, if we could develop a macrocycle that could be "clipped" around an oligo(ethylene glycol) unit present in a functional molecule, derivatization into interlocked structures should become trivial and, thus, accelerate the development and discovery of new and practical applications for interlocked molecules. Herein, we report a macrocycle, generated from a diamine and a dialdehyde, that can be "clipped" around di-, tri-, and tetra(ethylene glycol)-containing dumbbell-shaped and cyclic guests through the templating effect of Na^+ ions. Using this approach, we have prepared a tri(ethylene glycol)-containing [2]catenane for which switching of the interlocked amino macrocycle can be triggered through the addition and removal of Na^+ ions.

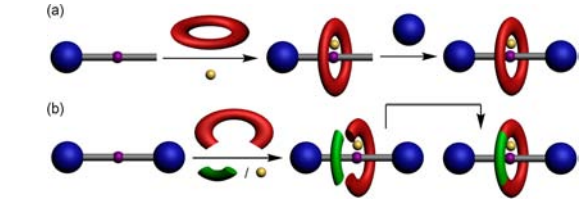
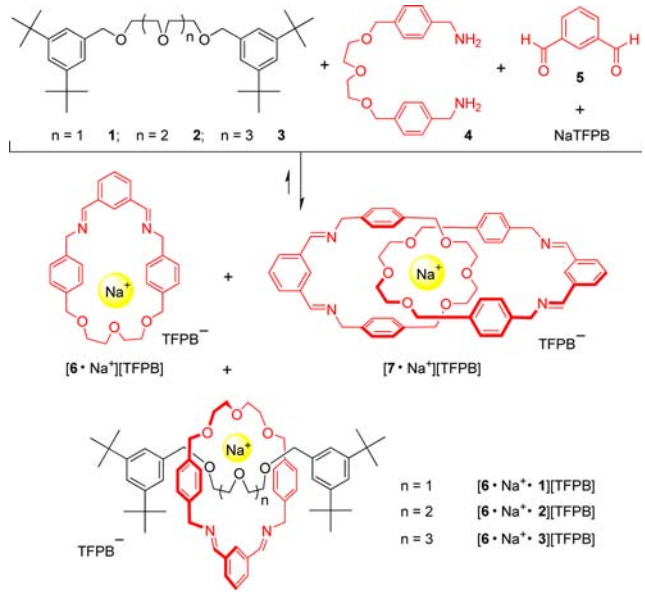


Figure 1. Cartoon representation of the (a) "threading followed by stoppering" and (b) "clipping" strategies.

We prepared the dumbbell-shaped guests **1**−**3** through alkylation of di-, tri-, and tetra(ethylene glycol), respectively, with 3,5-di-*tert*-butylbenzyl bromide under basic conditions (Scheme 1). Previously, we reported that heating an equimolar

Scheme 1. Clipping Synthesis of Imino[2]rotaxanes from Oligo(ethylene glycol)-Containing Dumbbell-Shaped Guests



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solution of the diamine **4**, the dialdehyde **5**, and NaTFPB in $CDCl_3$ at 323 K would result predominantly in the formation of the Na^+ ion-complexed imino macrocycle [**6**·Na^+], whereas the addition of further equivalents of **4** and **5** into the solution yielded the [2]catenane [**7**·Na^+] as the major product.[5] Thus, we anticipated that the macrocycle [**6**·Na^+] might favor hosting the orthogonally aligned oligo(ethylene glycol) units of the dumbbell-shaped guests **1**–**3** to generate corresponding [2]-rotaxanes as a means of stabilizing its templating metal ion.

An equimolar (10 mM) mixture of the di(ethylene glycol)-containing dumbbell-shaped molecule **1**, the diamine **4**, the dialdehyde **5**, and NaTFPB in $CDCl_3$ reached equilibrium after heating at 323 K for 52 h; the ^{1}H NMR spectrum of the resulting solution displayed three sets of signals that we assign to the Na^+ ion-complexed macrocycle [**6**·Na^+], the [2]catenane [**7**·Na^+], and the [2]rotaxane [**6**·Na^+·**1**], respectively (Figure 2). We infer

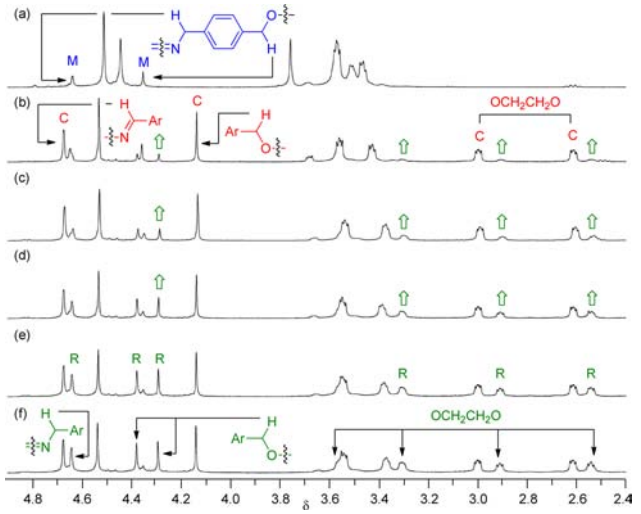


Figure 2. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of an equimolar (10 mM) mixture of the di(ethylene glycol)-containing dumbbell-shaped molecule **1**, the diamine **4**, the dialdehyde **5**, and NaTFPB after heating at 323 K for (a) 0, (b) 2, (c) 8, (d) 25, (e) 52, and (f) 70 h. Signals of the macrocycle [**6**·Na^+], the [2]catenane [**7**·Na^+], and the [2]rotaxane [**6**·Na^+·**1**] are labeled M, C, and R, respectively.

that the macrocycle [**6**·Na^+] (with characteristic signals for its benzylic protons at δ 4.35 and 4.64) was generated very rapidly, whereas the [2]catenane [**7**·Na^+] [with characteristic signals for its benzylic protons at δ 4.68 and 4.14 and its di(ethylene glycol) protons at δ 3.00 and 2.62] became the predominant species after 2 h. Relative to the [2]catenane [**7**·Na^+], the [2]rotaxane [**6**·Na^+·**1**] (with characteristic signals for the protons of its benzylic units at δ 4.64, 4.38, and 4.29 and its ethylene glycol units at δ 3.57, 3.31, 2.91, and 2.54) formed slowly in this equilibrium process, possibly because the [2]rotaxane could not be generated through a threading pathway (unlike the [2]catenane) or because its relatively flexible di(ethylene glycol) unit made the transition state for the Na^+ ion-templated clipping reaction less preorganized than that for the [2]catenane. On the basis of the integrated signals in the ^{1}H NMR spectrum of the equilibrium mixture, the ratio of the yields for the macrocycle [**6**·Na^+], the catenane [**7**·Na^+], and the [2]rotaxane [**6**·Na^+·**1**] was approximately 1:3.4:2.3.[6]

When we applied similar reaction conditions to the tri(ethylene glycol)-containing dumbbell-shaped molecule **2**, equilibrium was established after 52 h with the yields of the macrocycle [**6**·Na^+], the catenane [**7**·Na^+], and the [2]rotaxane [**6**·Na^+·**2**] in a ratio of 1:4.7:3.4 (Figure 3b). Thus, the relative

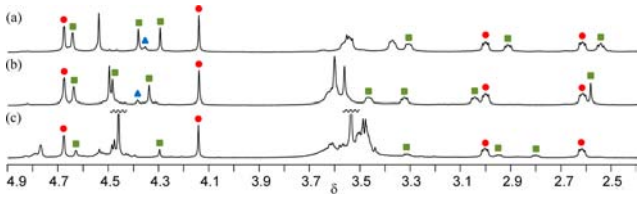
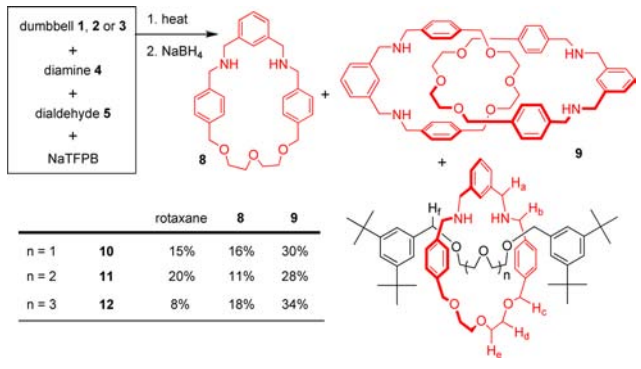


Figure 3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of equimolar (10 mM) mixtures of the diamine **4**, the dialdehyde **5**, NaTFPB, and the dumbbell-shaped molecules (a) **1**, (b) **2**, and (c) **3** that had been heated at 323 K for 52 h. Signal assignments: (■) Na^+-complexed [2]rotaxanes **10**–**12**; (●) [2]catenane [**7**·Na^+]; (▲) macrocycle [**6**·Na^+].

yield of the [2]rotaxane [**6**·Na^+·**2**] in the solution at equilibrium was slightly higher than that formed when the dumbbell-shaped molecule **1** was used as a component. We suspect that although the tri(ethylene glycol) unit in **2** is more flexible than the di(ethylene glycol) unit in **1** and, thus, the formation of its corresponding [2]rotaxane is entropically less favorable, its extra oxygen atom may overcome these drawbacks enthalpically, resulting in slightly more of its [2]rotaxane being present in the equilibrium mixture. In contrast, the ^{1}H NMR spectrum of the tetra(ethylene glycol)-containing dumbbell-shaped molecule **3** featured less pronounced signals for its [2]rotaxane [**6**·Na^+·**3**] at the equilibrium of its clipping reaction under otherwise identical conditions (Figure 3c). We suspect that the relatively higher flexibility (greater entropic cost) in the tetra(ethylene glycol) unit of **3** was responsible for the relatively lower amount of its [2]rotaxane [**6**·Na^+·**3**] in the reaction medium. Nevertheless, these results indicate that clipping the macrocycle **6**, formed from the diamine **4** and the dialdehyde **5**, around di-, tri-, and tetra(ethylene glycol)-containing dumbbell-shaped guests, under the templating effect of Na^+ ions, is a feasible approach for the preparation of corresponding [2]rotaxanes, although the efficiency is limited by the competitive pathway for the formation of the [2]catenane [**7**·Na^+].

To prove unambiguously that these [2]rotaxanes had formed in solution, we added $NaBH_4$ to the equilibrated mixtures to transform their labile imino bonds into thermodynamically stable amino bonds, isolating the corresponding macrocycle **8**, the [2]catenane **9**, and the [2]rotaxanes **10**–**12** (Scheme 2).[7] Consistent with the ^{1}H NMR spectra in Figure 2, the

Scheme 2. Clipping Synthesis of Oligo(ethylene glycol)-Containing Amino[2]rotaxanes



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[2]catenane **9** was the major isolated product in each case, with a yield (ca. 30%) that did not deviate much upon varying the ethylene glycol-containing dumbbell-shaped molecule. The isolated yields of the ethylene glycol-containing amino [2]-rotaxanes **10**−**12** (15, 20, and 8%, respectively) supported the notion that the clipping reactions were more effective when a di- or tri(ethylene glycol) unit was present in the dumbbell-shaped component.

The absence of any signals for the TFPB counteranions in the ^{1}H NMR spectra of the purified amino [2]rotaxanes **10**−**12** suggested the loss of the Na^+ ion templates during the aqueous extraction and chromatography processes.[8] Without a Na^+ ion present, we suspected that the two interlocked components in each of the amino [2]rotaxanes **10**−**12** would interact mainly through [N−H···O] hydrogen bonds between the oxygen atoms of the oligo(ethylene glycol) unit of the dumbbell-shaped component and the secondary amino groups of the macrocyclic component. Indeed, we observed significant downfield shifts for the benzylic protons H_f and the adjacent ethylene protons of the dumbbell-shaped component and for the protons H_a and H_b adjacent to the amino groups of the macrocyclic component when we decreased the number of ethylene glycol units in the dumbbell-shaped component of the [2]rotaxanes **10**−**12** from four to two, consistent with a shorter oligo(ethylene glycol) chain restraining these protons to reside in the shielding zones of the aromatic rings (Figure 4).

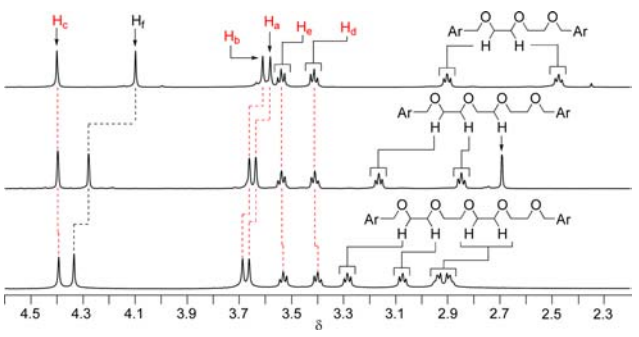
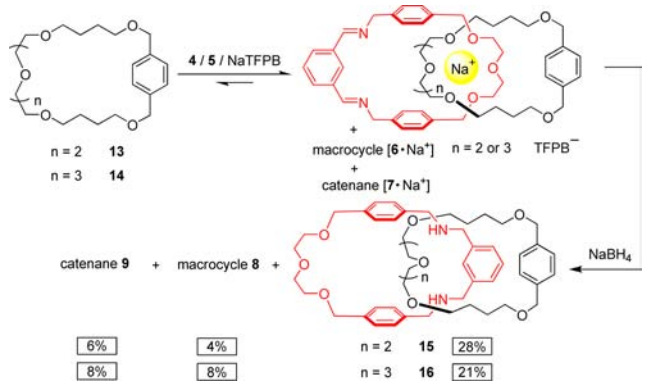


Figure 4. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of the [2]rotaxanes (a) **10**, (b) **11**, and (c) **12**.

Next, we turned our attention to the synthesis of [2]catenanes; using a similar approach, we synthesized the macrocycles **13** and **14** (see the Supporting Information).

The ^{1}H NMR spectrum of an equimolar (20 mM) mixture of the macrocycle **13**, the diamine **4**, the dialdehyde **5**, and NaTFPB in $CDCl_3$ displayed three sets of signals for macrocyclic entities, namely, the macrocycle [**6**·Na^+] and the two [2]catenanes [**7**·Na^+] and [**6**·Na^+·**13**]. In contrast to the situation in the syntheses of the [2]rotaxanes, integration of the signals in the ^{1}H NMR spectrum revealed that the [2]catenane [**6**·Na^+·**13**] was the major product at equilibrium, where the ratio of the yields of the macrocycle [**6**·Na^+] and the [2]catenanes [**7**·Na^+] and [**6**·Na^+·**13**] was 1:1:3. Subsequent $NaBH_4$-mediated reduction of the imino bonds in these reaction products allowed us to isolate, after chromatographic purification, the macrocycle **8** and the [2]catenanes **9** and **15** in yields of 6, 4, and 28%, respectively (Scheme 3). The higher efficiencies for the formation of both the imino and amino [2]catenanes [**6**·Na^+·**13**] and **15**, respectively, relative to those for the [2]rotaxanes [**6**·Na^+·**2**] and **11**, respectively, were likely due to the tri(ethylene glycol) unit in the crown ether **13** being less flexible and better preorganized for

Scheme 3. "Clipping" Synthesis of the Amino[2]catenanes 15 and 16



this Na^+ ion-templated "clipping" reaction than was the tri(ethylene glycol) unit in the dumbbell-shaped molecule **2**. We performed corresponding experiments to clip the macrocyclic component **8** onto the tetra(ethylene glycol)-containing macrocycle **14**; after reduction of the imino bonds, we isolated the macrocycle **8** and the [2]catenanes **9** and **16** in yields of 8, 8, and 21%, respectively. The significant increase in efficiency when clipping the macrocycle **8** onto the tetra(ethylene glycol)-containing macrocycle, relative to that around the dumbbell-shaped molecule **3**, supports the existence of a "macrocyclic effect," with the tetra(ethylene glycol) unit being conformationally more restricted and better preorganized for the clipping reaction in the case of the macrocyclic substrate.

The significant upfield shifts of the signals of the protons of the tri(ethylene glycol) CH_2 (H_1; from δ 3.60 to 2.95) and *n*-butyl (H_4; from ca. δ 3.40 to 2.92) groups in the macrocyclic component **13** after interlocking in the [2]catenane **15** suggested that these protons were shielded simultaneously by the aromatic units of the macrocyclic component **8**. The preferred conformation proposed in Figure 5 was supported by the

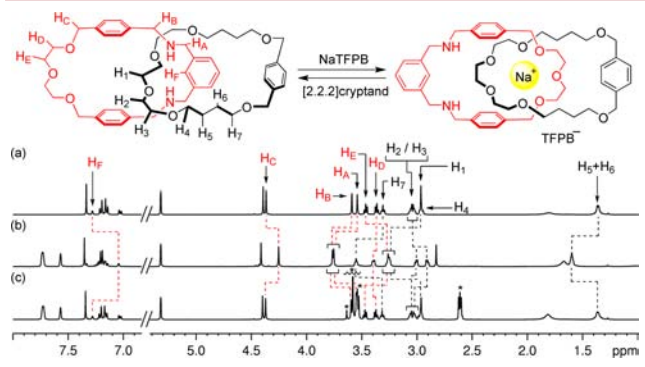


Figure 5. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) the [2]catenane **15**, (b) the solution in (a) after addition of 1 equiv of NaTFPB, and (c) the solution in (b) after the addition of 1 equiv of [2.2.2]cryptand. Asterisks: Signals representing the Na^+-complexed [2.2.2]cryptand.

observation of cross-signals for the NH-adjacent benzylic protons (H_A, H_B) and the aromatic proton (H_F) of the *m*-xylene units of the macrocyclic component **8** to the central CH_2 protons of the *n*-butyl groups (H_5, H_6) and the central protons (H_1) of the tri(ethylene glycol) units of the macrocyclic component **13**, respectively. The upfield shifts of the signals of the di(ethylene glycol) protons (H_{C-E}) of the macrocycle **8** after formation of

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the [2]catenane **15**[9] suggest that hydrogen bonding between the tri(ethylene glycol) unit and the secondary amino groups of the two interlocked components is relatively weak and that circumrotation of the macrocycle **13** around the macrocycle **8** is reasonably rapid. The addition of 1 equiv of NaTFPB to the solution of the [2]catenane **15** shifted the signals of the benzylic protons adjacent to the NH units (H_A, H_B) of the macrocyclic component **8** toward their positions in the free state, suggesting that the addition of Na^+ ions caused the interlocked macrocyclic component **13** to circumrotate to encircle the di(ethylene glycol) unit of the macrocycle **8** for collaborative complexation of the Na^+ ion by the two oligo(ethylene glycol) units. In the 2D NOESY spectrum of the [2]catenane **15**, the observation of strong cross-signals between the central CH_2 protons of the *n*-butyl groups (H_5, H_6) and the di(ethylene glycol) protons (H_D, H_E) was consistent with the proposed conformational change. Subsequent addition of 1 equiv of [2.2.2]cryptand, a very strong Na^+ ion binder, to the solution of [**15**·Na^+] removed the metal ions from the [2]catenane, regenerating the original state of **15** in solution by positioning the NH units back within the cavity of the macrocyclic component **13**, as evidenced by the signals in the ^1H NMR spectrum reverting back to their positions prior to the addition of Na^+ ions. Thus, compound **15** behaves as a metal ion-controllable catenane-based molecular switch that operates through the macrocyclic component **13** selectively positioning either the di(ethylene glycol) or diamine motif of the interlocked macrocyclic component **8** within its cavity upon the addition or removal of Na^+ ions.

We have demonstrated that di-, tri-, and tetra(ethylene glycol) units in both dumbbell-shaped and macrocyclic molecules can act as primary recognition units for the clipping of macrocycles in the presence of templating Na^+ ions to form corresponding [2]rotaxanes and [2]catenanes. One such tri(ethylene glycol)-containing [2]catenane behaves as a Na^+ ion-controllable molecular switch. This approach should allow the introduction of such macrocycles around the oligo(ethylene glycol) units of many widely applied functional molecules, facilitating the development of novel interlocked structures and switches.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and characterization data for the [2]-rotaxanes and [2]catenanes. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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(3) For recent examples, see: (a) De Bo, G.; Kuschel, S.; Leigh, D. A.; Lewandowski, B.; Papmeyer, M.; Ward, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 5811. (b) Akae, Y.; Koyama, Y.; Kuwata, S.; Takata, T. *Chem.—Eur. J.* **2014**, *20*, 17132. (c) Ma, Y.-X.; Meng, Z.; Chen, C.-F. *Org. Lett.* **2014**, *16*, 1860. (d) Lee, S.; Chen, C.-H.; Flood, A. H. *Nat. Chem.* **2013**, *5*, 704.

(4) For recent examples, see: (a) Langton, M. J.; Robinson, S. W.; Marques, I.; Felix, V.; Beer, P. D. *Nat. Chem.* **2014**, *6*, 1039. (b) Avestro, A.-J.; Gardner, D. M.; Vermeulen, N. A.; Wilson, E. A.; Schneebeli, S. T.; Whalley, A. C.; Belowich, M. E.; Carmieli, R.; Wasielewski, M. R.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 4442.

(5) Tung, S.-T.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 13269.

(6) The ^1H NMR spectrum of an equimolar (10 mM) mixture of the dumbbell-shaped molecule **1**, the diamine **4**, and the dialdehyde **5** heated at 323 K for 52 h featured broad and complex signals, none of which was characteristic of either the macrocycle [**6**·Na^+] or its interlocked molecules, suggesting the necessity of the Na^+ ion template in the formation of the [2]rotaxane.

(7) Similar reduction conditions have been used to synthesize rotaxanes through clipping of macrocycles around amide and urea functionalities; see: Ho, T.-H.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Chem.—Eur. J.* **2014**, *20*, 4563.

(8) Lin, Y.-H.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 10231.

(9) After TFA was added to the $CDCl_3$ solution of [2]catenane **15** to "lock" the macrocyclic component **13** around the newly formed diammonium station, these signals shifted downfield toward their positions in the free state, consistent with rapid circumrotation of the two interlocked macrocyclic components.

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