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Synthesis of [*n*]Rotaxanes by Template-Directed Clipping: The Role of the Dialkylammonium Recognition Sites

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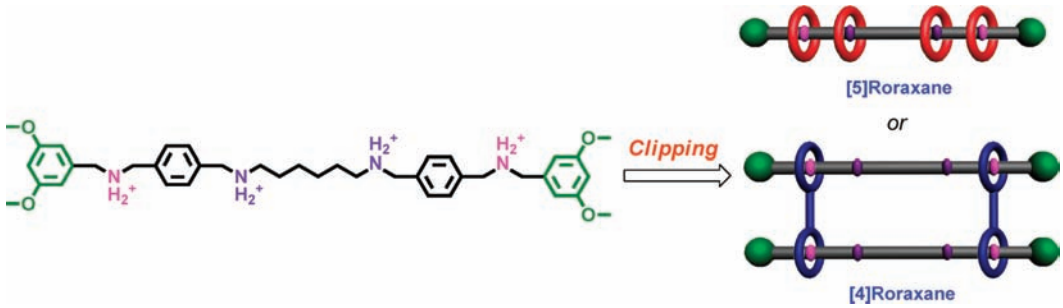
ABSTRACT



Linear and rectangular [*n*]rotaxanes were synthesized by template-directed clipping of heterocrown ether components onto the dumbbell-shaped molecules containing different dialkylammonium recognition sites. The effect of the structure of the dialkylammonium sites on the clipping efficiency was investigated, and selective clipping led to formation of a rectangular [4]rotaxane.

Interlocked molecules based on rotaxanes, catenanes, molecular knots, and molecular necklaces[1] have been widely developed due to their potential application in molecular-scale functional devices.[2] For example, rotaxanes have been used as molecular switches within nanoelectronics,[3] artificial muscles,[4] macroscopic liquid transport,[5] and mesoporous silica-mounted nanovalves.[6] Therefore, there have been a large number of rotaxanes synthesized by diversified approaches such as clipping, slipping, capping, active templates, and others.[7] In the clipping approach, a dumbbell-shaped component recognizes and binds the macrocyclic precursors and simultaneously templates the formation of the macrocycles around recognition sites. For example, Stoddart's group[8] reported efficient synthesis of [*n*]rotaxanes by clipping two components of a 24-crown-8 heterocrown ether, the 2,6-

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pyridinedicarboxaldehyde **4** and the tetraethylene glycol bis(2-aminophenyl)ether **5** (Figure 1), onto dumbbell-shaped

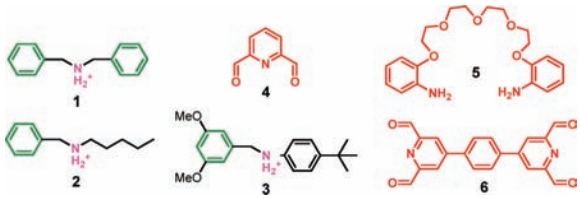


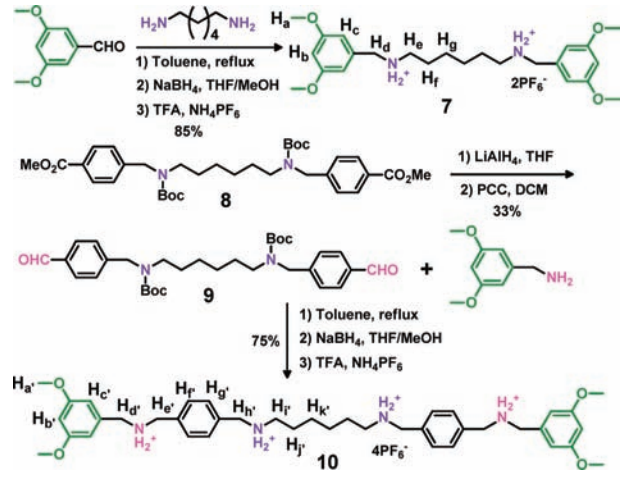
Figure 1

molecules containing dialkylammonium sites, and a similar method was also adopted by other groups.[9]

In all these cases, the recognition sites have a common dibenzylammonium moiety (i.e., in **1**). However, no one has studied the effect of different dialkylammonium structures, e.g., a benzyl-aliphatic alkylammonium (**2**) or an arylbenzylammonium (**3**), on the efficiency of the clipping reaction. Herein, dumbbell-shaped molecules **3**, **7**, and **10** with different ammonium structures were prepared, and their clipping was investigated in detail. Synthesis of some new supramolecular architectures by selective clipping was also exploited.

Scheme 1 outlines the synthesis of dumbbell-shaped ammoniums **7** and **10**. Condensation of 1,6-hexanediamine with 3,5-dimethoxybenzaldehyde gave the corresponding

Scheme 1



reversible dynamic imine, which was reduced by $NaBH_4$ in the solution of THF and MeOH to give the kinetically stable amine (C-NH). Protonation of the free amine with excess of TFA and subsequent counterion exchange with saturated NH_4PF_6 solution afforded the unsymmetrical dialkylammoniums **7** in 85% yield for three steps. The compound **10** with dibenzylammonium and unsymmetrical benzyl-aliphatic alkylammonium units was synthesized through a similar method. The diester **8**[10] with Boc-protected alkyldiamines was reduced by $LiAlH_4$, and the obtained alcohol was oxidized by pyridinium chlorochromate (PCC) to give the desired dialdehyde **9**, which was then treated with 3,5-dimethoxybenzylamine to afford the desired imine. After reduction with $NaBH_4$, the Boc protective groups were deprotected with excess TFA, and the as-formed amines were simultaneously protonated. Subsequent counterion exchange with saturated NH_4PF_6 afforded **10** in 75% yield for three steps. Similarly, compound **3** was prepared in 92% yield by condensation of 4-*tert*-butylaniline and 3,5-dimethoxybenzaldehyde followed by reduction, protonation, and counterion exchange.

The clipping reaction was first tested for **3** by mixing together equimolar amounts of **3**−**5** in CD_3CN, and the clipping process was followed by ^1H NMR spectroscopy. A complicated mixture containing the oligomers (Schiff base) of the condensation product of **4** and **5** was observed after 1 day, but there was no evidence that a [2]rotaxane was formed. In contrast, the clipping reaction of dibenzylammonium type molecules (e.g., **1**) under similar conditions gave the respective rotaxanes in nearly quantitative yield.[8] We then tested the clipping reaction of **7** with 2 equiv each of **4** and **5** in CD_3CN. Based on ^1H NMR spectroscopic analysis, a dynamic[8] [3]rotaxane was formed together with some uncomplexed and partially complexed dumbbell compounds and imine oligomers. The mixture was treated with BH_3·THF to reduce the dynamic imine bond into the kinetically stable C−NH bond, and

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then the [3]rotaxane **11** was separated by column chromatography in 86% yield. The ^{1}H NMR spectrum of the pure [3]rotaxane **11** is shown in Figure 2B, and compared

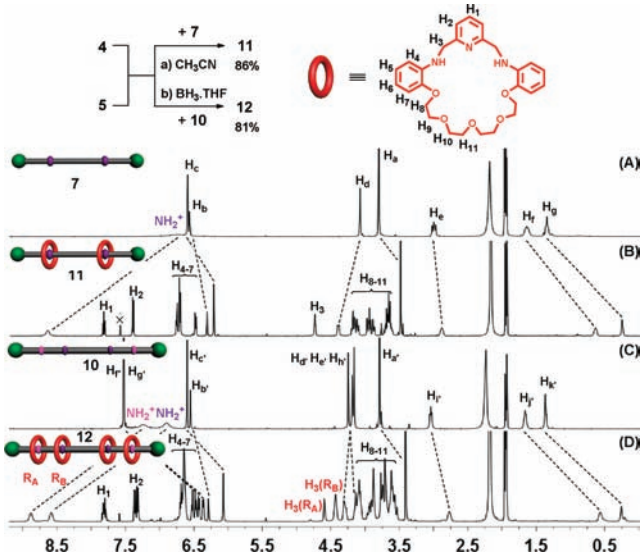

Figure 2. ^{1}H NMR spectra (500 MHz in CD_3CN at rt) of **7** (A); [3]rotaxane **11** (B); **10** (C); and [5]rotaxane **12** (D). (Resonance protons are labeled in Scheme 1.)

with the spectrum of template **7** (Figure 2A), the resonance of the protons on the stopper units (H_a, H_b and H_c) showed an obvious upfield shift while the ammonium ($-NH_2^+$) displayed a downfield shift. In addition, the resonances for the central alkyl chain (H_e, H_f, and H_g) also shifted upfield due to the shielding effect of the encircling crown ethers. The structure of **11** was further proved by the ESI mass spectrometry (Figure 3A).

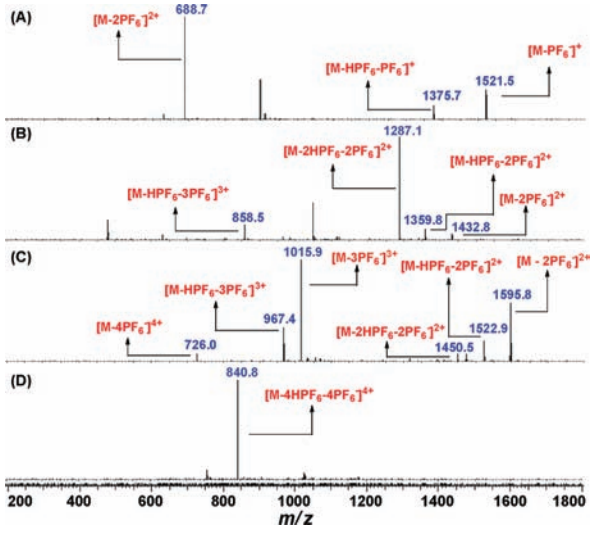

Figure 3. ESI mass spectra of [3]rotaxane **11** (A); [5]rotaxane **12** (B); [4]rotaxane **13** (C); and the dynamic [4]rotaxane **14** (D).

The above experiments also indicated that efficiency of the clipping reaction on different types of ammoniums followed a priority sequence of **1** > **2** > **3**, which is similar to the studies of threading crown ethers onto different ammonium sites.[11] To exploit the possible self-sorting clipping, the template **10** containing two different types of ammonium units was submitted for similar clipping reaction. A complicated mixture containing various dynamic [*n*]rotaxanes with the crown ether rings randomly located at different ammonium sites were formed when the ratio of compounds **4**, **5**, and **10** was 2:2:1, suggesting that there was no obvious selectivity between the two types of ammonium sites. Addition of an additional 2 equiv each of compounds **4** and **5** led to the formation of a dynamic [5]rotaxane together with some uncomplexed and partially complexed dumbbell molecules and imine olgiomers. Again, the pure kinetically stable [5]rotaxane **12** was separated after reduction of the as-formed dynamic rotaxanes. Compared with the ^{1}H NMR spectrum of **10** (Figure 2C), the resonances of two ammoniums ($-NH_2^+$) displayed similar downfield shifts in the pure [5]rotaxane **12** (Figure 2D). In addition, the other resonances such as $H_{a'}$, $H_{b'}$, $H_{c'}$, $H_{i'}$, $H_{j'}$, and $H_{k'}$ of **10** showed similar upfield shifts. Furthermore, the four crown ether rings have two different chemical environments (R_A and R_B) and as results, some resonances for the protons on crown ethers (e.g., H_3) can be easily distinguished. The structures of the [5]rotaxane **12** were also confirmed by ESI mass spectrometry (Figure 3B). So, although there was less selectivity on the clipping reaction, the dumbbell **10** containing different dialkylammonium sites still could be used to construct a complex hetero[5]rotaxane **12** in which four same macrocylces encircle onto two different types of recognition sites.

To further exploit the possibility of using these building blocks to build up new supramolecular architectures, the component **4** was replaced by tetraaldehyde **6**.[8c] The clipping reaction by using compounds **5**−**7** with the molar ratio of 2:1:1 was conducted. Due to the very poor solubility of **6**, the mixture became nearly clear only after stirring for 15 days at room temperature. A rectangular dynamic [4]rotaxane was formed as proved by the ^{1}H NMR spectroscopy (Figure 4A) which was in agreement with Stoddart's study by using dibenzylammonium sites.[8c] A characteristic resonance peak (H_3) at 8.31 ppm assigned to imine protons was observed. Compared with **7**, the resonances of ammoniums ($-NH_2^+$) in the dynamic [4]rotaxane displayed an obvious downfield shift. Some resonances assigned to the uncomplexed **5** and **7** were also observed because even after a long time stirring, there was still some insoluble **6** in the solution. After reduction by BH_3·THF, the pure kinetically stable, rectangular [4]rotaxane **13** was separated in 67% yield. The well-resolved ^{1}H NMR spectrum of **13** clearly proved its structure (Figure 4B). The ammonium resonances in **13** underwent an upfield shift along with disappearance of imine protons (H_3). Moreover, the resonance peaks of stopper units (H_b and H_c) displayed crossed upfield and downfield shift. The structure

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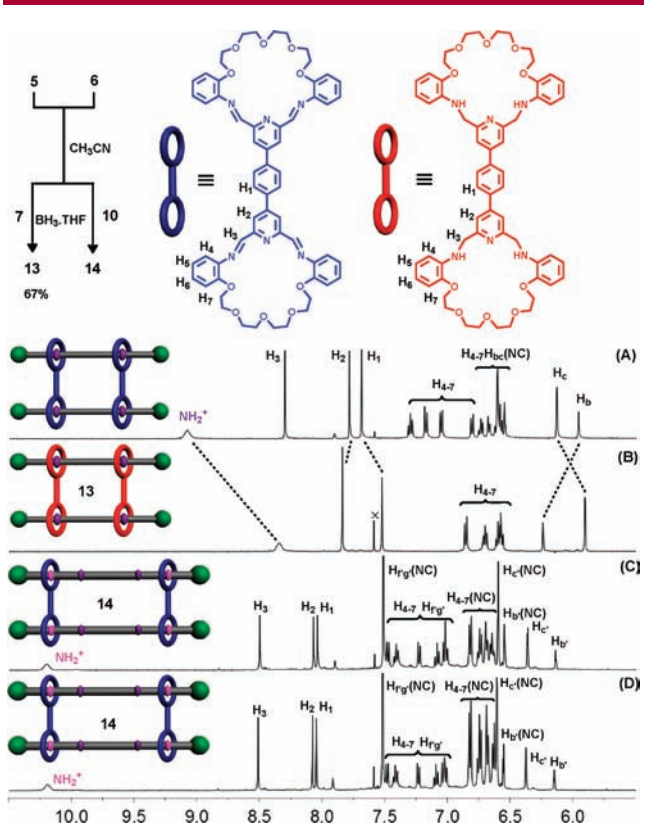

Figure 4. Partial ^{1}H NMR spectra (500 MHz in CD_3CN at rt) of the rectangular dynamic [4]rotaxane based on **7** (A); the kinetically stable [4]rotaxane **13** (B); the dynamic [4]rotaxane **14** when the ratio of **5**/**6**/**10** = 2:1:1 (C); and the dynamic [4]rotaxane **14** when the ratio of **5**/**6**/**10** = 4:2:1 (D). (NC indicates noncomplexed components.)

of [4]rotaxane **13** was further confirmed by ESI mass spectrometry (Figure 3C).

Subsequently, we studied the clipping reaction by mixing **10** together with 2 equiv of **5** and 1 equiv of **6** in CD_3CN. Surprisingly, a regioselective clipping reaction was observed, and a rectangular dynamic [4]rotaxane **14** in which the crown ether macrocycles selectively encircled onto the dibenzylammonium sites was formed. As shown in Figure 4C, a characteristic resonance peak (H_3) for imine bonds at 8.51 ppm was observed. Moreover, a more downfield shifted peak at 10.21 ppm for the complexed $-NH_2^+$ close to the stopper units was clearly observed; however, the other ammoniums ($-NH_2^+$) close to the hexyl unit did not display any obvious resonance at about 9.00 ppm like the dynamic [4]rotaxane from **7** (Figure 4A), indicating that the clipping reaction selectively took place at the dibenzylammonium sites! Compared with **10**, the upfield shift of the resonances ($H_{b'}$ and $H_{c'}$) on the stopper units further confirmed that the clipping reaction only happened at the dibenzyl ammonium sites. A detailed 2D ^{1}H$-^1$H COSY and ^{1}H$-^1$H NOSEY NMR spectroscopic analysis is given in the Supporting Information. ESI mass spectrometry also supported the existence of the dynamic rectangular [4]rotaxane **14**, and a single peak at m/z = 840.8 for $[M - 4PF_6^- - 4HPF_6]^{4+}$ was observed (Figure 3D). Again, due to the poor solubility of **6**, some resonances for uncomplexed **5** and **10** were found (Figure 4C). These results also indicated an amplified regioselectivity in a rectangle-shaped macrocycle under a thermodynamic control. When additional amounts of **5** and **6** were added with the molar ratio of **5**/**6**/**10** = 4:2:1, no obvious changes were observed in the ^{1}H NMR spectrum of the mixture after stirring for 18 days except that the relative intensity of the uncomplexed component increased (Figure 4D), which indicated that such clipping reaction only selectively took place at the $-NH_2^+$ sites close to the stopper units. The further clipping reaction on the central ammonium sites was forbidden likely due to steric hindrance when the crown ether components enter the middle of the as-formed rectangular macrocycle as well as the poor solubility of **6**. The dynamic rotaxane was also reduced by BH_3·THF, however, the poor solubility of the product limited the separation of the kinetically stable [4]rotaxane in pure form.

In conclusion, a detailed study on the clipping reaction based on different dialkylammonium templates was reported, and these new building blocks have been used for efficient synthesis of several linear and rectangular [*n*]rotaxanes. In particular, a regioselective formation of a rectangular [4]rotaxane **14** was observed for the first time. Our studies also indicated possible self-sorting clipping of different macrocycles onto different (but similar) recognition sites to form well-defined heterorotaxanes in the future.

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Supporting Information Available: Details on the synthesis and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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