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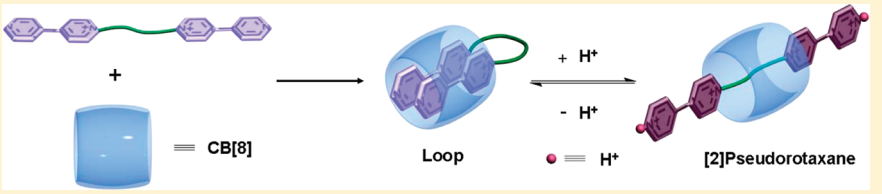
# Controlled Molecular Self-Assembly Behaviors between Cucurbituril and Bispyridinium Derivatives

Zhi-Jun Zhang, Ying-Ming Zhang, and Yu Liu*

Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

Supporting Information

**ABSTRACT:**




Two stable supramolecular loops (**1** and **2**) were successfully constructed by the molecular recognition of cucurbit[8]uril (CB[8]) and the homoditopic bispyridinium derivatives (**3** and **4**). Interestingly, the interconversion of molecular loops and [2]pseudorotaxanes could be reversibly switched under neutral and acidic condition, exhibiting the controlled electrochemical and spectroscopic behaviors.



Supramolecular self-assemblies are currently attracting great interest because of the practical applications in construction of artificial molecular machinery based on the precisely controlled association and dissociation of different isomers or components in response to external stimuli.[1] Modulated by external stimuli, including a change of pH, light input, temperature, or redox potential, a wide variety of nanosupramolecular architectures, such as pseudorotaxanes,[2] rotaxanes,[3] catenanes,[4] foldamers,[5] polymers,[6] and amphiphiles,[7] have been endowed with switchable properties. In particular, in external stimuli-responsive host−guest supramolecular systems, cucurbit[*n*]uril (CB[*n*]), a class of macrocycles with 5−10 glycoluril units linked by methylene groups, is one of the most widely employed host compounds for such systems because of its remarkable binding abilities to form 1:1, 1:2, or 1:1:1 ternary complexes with different substrates.[8] Kim and Inoue et al.[9] have reported the interconversion between a twin-axial [3]pseudorotaxane and a single-axial [4]pseudorotaxane in the presence of CB[6] and spermine, exhibiting a chemically controlled switching between two supramolecular species in solution. Moreover, triggered by the electrochemical and photochemical stimuli, a [2]pseudorotaxane-based molecular machine was successfully constructed, implementing the reversible formation of loop structures.[10] Nevertheless, the controlled interconversion between a stable molecular loop and its linear structure is still rare. In the present work, we report two stable molecular loops **1** {**3**⊂CB[8]} and **2** {**4**⊂CB[8]} constructed by the noncovalent interactions between CB[8] and the homoditopic bispyridinium derivatives **3** and **4**, in which the reversibility of molecular loops and [2]pseudorotaxane was conveniently achieved upon the addition of acid and base (Scheme 1). The controllable molecular self-assembly behaviors were comprehensively investigated by NMR, UV/vis, cyclic voltammetry, mass spectrometry, and computational methods.

A series of bispyridinium derivatives (**3**, **4**, and **5** in Chart 1) with different linkers were synthesized by the reaction of dihalides and 4,4′-bipyridine in a moderate yield. Subsequently, $^1$H NMR experiments were carried out to quantitatively investigate the binding process between the guest molecules and CB[8]. It is well-documented that the proton signals of guest molecules shift to higher field when it is incorporated into the cavity of CB[8], whereas the ones outside the cavity exhibit downfield shifts.[8a] As discerned from Figure 1A ,B, the proton signals ($H_d$, $H_a$, $H_c$, and $H_b$) of the aromatic moiety in **3** underwent an obvious complexation-induced upfield shift of 0.12, 0.72, 0.76, and 1.22 ppm, respectively, while those of aliphatic linkers showed a slight upfield shift upon continuous addition of CB[8]. Moreover, no obvious changes could be observed in the presence of excess CB[8] (Figure 1C,D), which jointly indicates that loop **1** was the predominant species in solution. The sizable chemical shifts may be attributed to the encapsulation of CB[8] and the shielding effect of bispyridinium units to each other. Further analysis of $^1$H NMR spectra could provide more detailed structural information of loop **1**. Besides the proton signals of the bispyridinium derivative, it is noteworthy that the $H_\alpha$ and $H_\beta$ of CB[8] on the exterior portals were also shifted upfield and split into two groups (Figure 1C). These observations indicate that the two portals of CB[8] were located in magnetically different environments and the unsymmetrical structures of the guest-pair inside the cavity.

In addition, the complex stoichiometry between **3** and CB[8] was explored by the titration method using $^1$H NMR (Figure S7, Supporting Information). As shown in Figure 1B, because of the *slow exchange* equilibrium, both free and bound guest molecule **3**

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**Scheme 1. Schematic Representation of Controlled Interconversion Process between the Loops 1 {3⊂CB[8]} or 2 {4⊂CB[8])} and the Corresponding [2]Pseudorotaxane Structures 1H {3H⊂CB[8]} or 2H {4H⊂CB[8]}**

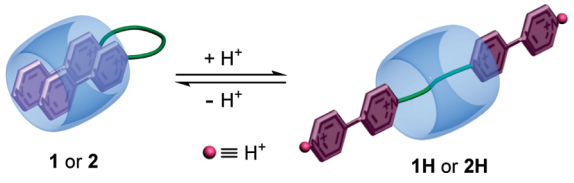
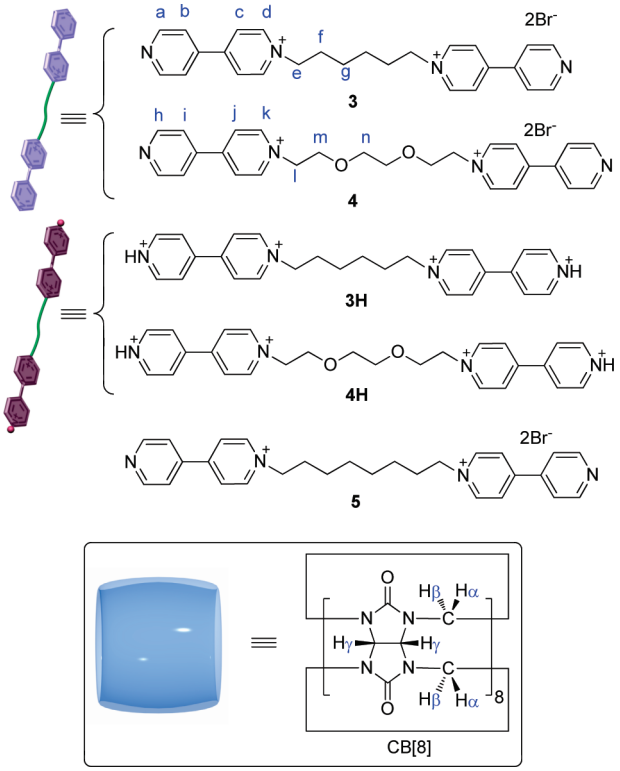



**Chart 1. Molecular Structures of 3, 4, 3H, 4H, 5, and CB[8]**




(defined as $\mathbf{3}_{free}$ and $\mathbf{3}_{bound}$, respectively) could be distinguished on the $^1$H NMR time scale. The ratio curve of $[\mathbf{3}_{free}]/[\mathbf{3}_{bound}]$ versus $[CB[8]]/[\mathbf{3}]$ showed an inflection point at 1.0, implying the formation of 1:1 host−guest complex. Combined with the NMR analysis, it is suggested that the two bispyridinium units are encapsulated into the cavity of CB[8] to form the molecular loop **1**. After validation of the 1:1 binding stoichiometry, the lower limit of the complex formation constant ($K_S$) could be estimated as $1.62 \times 10^5$ $M^{-1}$ from $^1$H NMR integration, indicating the high affinity of the bispyridinium moieties and CB[8] (Figure S8, Supporting Information).

Compared to **3** and **3H**, the absorbance in the range of 310−350 nm was increased in the presence of 1.0 equiv of CB[8] (Figure S9, Supporting Information), indicative of the inclusion complexation of guests by CB[8]. Significantly, α-cyclodextrin (α-CD) was added to the solution of **1** to examine the stability of the molecular loop (Figure S10, Supporting Information). The 2D NMR spectrum showed no NOE correlations between the aliphatic linkers and the interior protons of

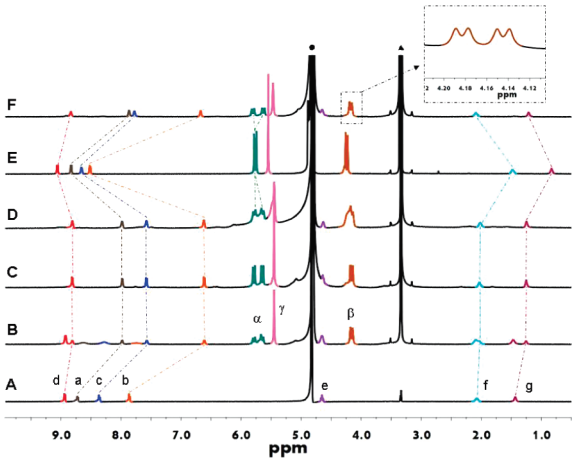



**Figure 1.** $^1$H NMR spectra: (A) **3** (1.0 mM), (B) **3** + 0.4 equiv of CB[8], (C) **3** + 1.0 equiv of CB[8] (1), (D) **3** + 2.0 equiv of CB[8], (E) **1** + 27 equiv of DCl (**1H**), (F) **1H** + 27 equiv of NaOD ($D_2O$, 400 MHz, 298K). Inset: the amplified area of $H_\beta$ of CB[8]. The solvent and MeOH are denoted as symbols ● and ▲, respectively.

α-CD cavity (Figure S11 and S12, Supporting Information), and ESI-MS experiment could not provide any evidence for the CD's complexation, indicating that the loop structure formed by CB[8] and the bispyridinium moiety at this state could be considered a stable one. As expected, the formation of loop **1** was further confirmed by ESI-MS. The peak at 862.9 could be assigned to $[\mathbf{1} - 2Br]^{2+}$ (Figure S13, Supporting Information). Furthermore, the energy-minimized structure of **1** obtained by the molecular mechanics and molecular dynamics simulation methods is congruent with the proposed loop structures containing two positive terminals in close proximity around the portal of CB[8] (Figure 2A).

Interestingly, when excess hydrochloric acid was added to afford **1H**, both 4-pyridyl groups in **3** were protonated with another positive charge (Figure S14, Supporting Information). As shown in Figure 1E, the characteristic peaks for the protons on the aliphatic linkers of axle molecule **3** shifted to higher field under the acidic conditions; that is, the protons $H_f$ and $H_g$ displayed large complexation-induced shifts of 0.63 and 0.66 ppm, respectively. The changes of chemical shifts discussed above demonstrate that acidified **3** (**3H**) facilitates the nonaromatic linkers into the cavity of CB[8] to form a [2]pseudorotaxane structure (Figure 2B).[11] In contrast, the proton $H_\alpha$ on the portal of CB[8] showed only one group of peaks, corresponding to the symmetrical structure in [2]pseudorotaxane **1H**. Furthermore, it is significant to note that the original loop structure could be restored by the addition of NaOD because the axle molecule **3H** was deprotonated to **3** in neutral solution (Figure 1F).

Moreover, the switching behaviors under neutral and acidic condition were studied by cyclic voltammetry. In the presence of CB[8], the first reduction peak of **3** exhibited a moderate positive shift, whereas the second one showed a large negative shift (Figure 3), which is indicative of a pair of the bispyridinium moieties inside CB[8].[10] As judged from Figure S17 (Supporting Information), the bispyridinium units in acidified **3** were not included and stabilized by CB[8] because both of the reduction peaks were positively shifted after complexation with CB[8].

More direct evidence for the interconversion process of loop and [2]pseudorotaxane was obtained from the diffusion-ordered spectroscopy (DOSY) experiment[12] (Figures S18 and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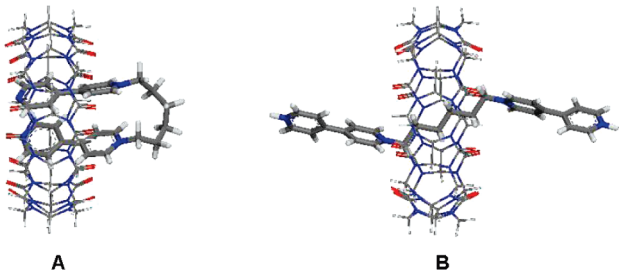


**Figure 2.** Molecular energy minimization of (A) molecular loop **1** and (B) [2]pseudorotaxane **1H**. The geometries were optimized by the molecular mechanics method with Dreiding force field.

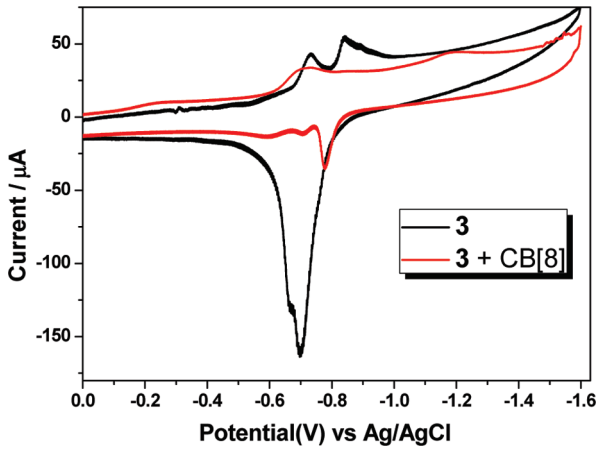


**Figure 3.** Cyclic voltammetric curves of **3** (1.0 mM in pH 7.0 phosphate buffer solution) in the absence and presence of 1.0 equiv of CB[8] at 100 mV $s^{-1}$.

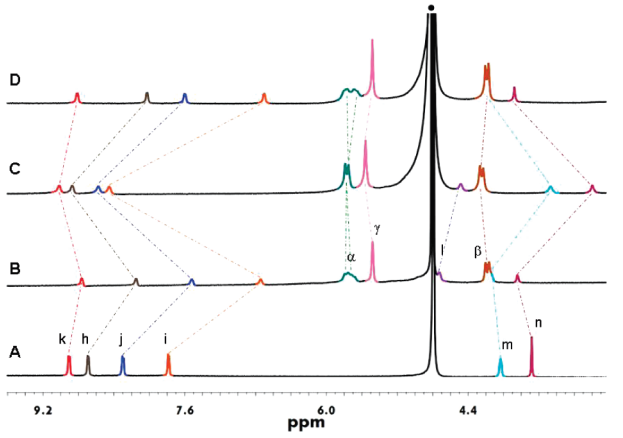


**Figure 4.** $^1$H NMR spectra: (A) **4** (1.0 mM), (B) **4** + 1.0 equiv of CB[8] (**2**), (C) **2** + 27 equiv of DCl (**2H**), (D) **2H** + 27 equiv of NaOD ($D_2O$, 400 MHz, 298K). The solvent and MeOH are denoted as symbols ● and ▲, respectively.

S19, Supporting Information). When acid was added to the solution of **1**, the measured diffusion coefficient was decreased from 2.67 × $10^{-10}$ to 2.47 × $10^{-10}$ $m^2$ $s^{-1}$, indicating that the average size was increased by 1.3 times upon acidification. Moreover, the hydrodynamic volumes of **1** and **1H** were estimated to be 1.7 and 2.2 times larger than that of free CB[8], respectively. These results reasonably exclude the possibility of 2:2 complex or *n*:*n* polymeric species (Figure S21, Supporting Information)[13] and confirm the interconversion of two supramolecular species (loop and [2]pseudorotaxane) by acid/base stimulation.

To examine the hydrophilic property and length of the linkers on the binding mode, the complexation of CB[8] with bispyridinium derivatives **4** and **5** was also investigated by means of $^1$H NMR titration. As seen in Figure 4A,B, the protons $H_k$, $H_h$, $H_j$, and $H_i$ underwent a large complexation-induced shift upfield 0.16, 0.54, 0.79, and 1.06 ppm, respectively, and the bispyridinium moiety was included in the cavity of CB[8] to form the molecular loop **2**. In comparison, the characteristic signals of $H_l$, $H_m$, and $H_n$ assigned to the triethylene glycol bridges shifted to higher field in the presence of acid (Figure 4C), revealing the movement of CB[8] toward the more hydrophilic triethylene glycol linkers. All the phenomena described above are indicative of the similar pH-switchable behaviors in **3**/CB[8] and **4**/CB[8] complexes (Figure 4D and Figures S22−25 in the Supporting Information). On the contrary, it was found that CB[8] favored the linker rather than the bispyridinium moiety in **5** (Figure S26, Supporting Information), mainly due to the more stronger hydrophobic interaction between CB[8] and the axle molecule possessing a longer aliphatic linker with eight methylene units.

The loop structures of **1** and **2** reveal that the two positively charged nitrogen terminals resided outside the cavity of CB[8] in the same direction.[14] One possible explanation for the stability ($K_S$ up to $10^5$ $M^{-1}$) should be attributed to the strong inclusion ability of CB hosts toward the guests possessing the hydrophobic units and positive charged terminals.[15] The polymerization of **1** and **2** is thermodynamically inhibited, mainly due to the large entropic losses of conformational freedom upon host−guest complexation and the relative instability of the polymeric species.[16] Instead, the conformation was changed from molecular loop to [2]pseudorotaxane in the presence of acid as a result of the disruption of CB[8]-induced homoguest pairs and the high affinity of CB[8] and the linkers in this state.

In summary, we presented a simple method to construct a reversible switching process between the molecular loops and [2]pseudorotaxanes based on the noncovalent interactions between CB[8] and bispyridinium derivatives. It is significant that the conformational changes could be reversibly adjusted by the protonation and deprotonation of nitrogen atoms on 4-pyridyl moiety as reactive donors. The ion−dipole and hydrophobic interactions play critical roles in controlling the conformational changes of supramolecular complexes. Consequently, the obtained results will pave a noncovalent and reversible way to efficiently control the molecular conformations of more sophisticated and functional systems.

## EXPERIMENTAL SECTION

**General Synthetic Procedure Exemplified by the Synthesis of Bispyridinium Derivative 3.** 1,6-Dibromohexane (1.8 g, 8.3 mmol) in 20 mL of $CH_3CN$ was added dropwise during 6 h to a refluxing solution of 4,4′-bipyridine (5.0 g, 32 mmol) in $CH_3CN$ (50 mL) The reaction mixture was maintained under reflux for a further 24 h. A produced precipitate was filtered and washed with $CH_3CN$ and then recrystallized from water to afford the product as a solid (2.1 g, 45%): $^1$H NMR (400 MHz, $D_2O$) $\delta$ 8.86 (d, $J$ = 5.3 Hz, 4H), 8.61 (m, 4H), 8.26 (d, $J$ = 5.5 Hz, 4H), 7.76 (d, $J$ = 1.6 Hz, 4H), 4.57 (t, $J$ = 6.9 Hz, 4H), 1.99 (m, 4H), 1.35 (s, 4H); $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 153.5,


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149.9, 144.7, 142.3, 125.9, 122.3, 61.4, 30.2, 24.8; HRMS (ESI) $m/z$ M calcd for $C_{26}H_{28}N_4^{2+}$ 198.1151, found 198.1150; mp 99−101 °C.

**Bispyridinium derivative 4:** yield 45%; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.24 (s, 4H), 8.84 (s, 4H), 8.69 (s, 4H), 8.05 (s, 4H), 4.89 (s, 4H), 3.95 (s, 4H), 3.56 (s, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 152.4, 150.9, 145.7, 140.7, 125.0, 121.9, 69.4, 68.7, 59.7; HRMS (ESI) $m/z$ $M^{2+}$ calcd for $C_{26}H_{28}N_4O_2^{2+}$ 214.1101, found 214.1103; $[M + Br]^+$ calcd for $C_{26}H_{28}BrN_4O_2^+$ 507.1390, found 507.1377; mp 68−70 °C.

**Bispyridinium derivative 5:** yield 52%; $^1$H NMR (400 MHz, $D_2O$) $\delta$ 8.84 (d, $J$ = 4.8 Hz, 4H), 8.69 − 8.55 (m, 4H), 8.26 (d, $J$ = 6.6 Hz, 4H), 7.76 (m, 4H), 4.55 (m, 4H), 1.94 (m, 4H), 1.26 (s, 8H). $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 153.4, 149.9, 144.7, 142.4, 125.9, 122.4, 61.6, 30.4, 27.8, 25.0; HRMS (ESI) $m/z$ M calcd for $C_{28}H_{32}N_4^{2+}$ 212.1308, found 212.1307; mp 125−127 °C.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures and characterization data for compounds **3**, **4**, and **5**; 1D, 2D NMR, and DOSY spectra; UV/vis spectra and cyclic voltammetry curves of **3** in the presence of acid and CB[8]; ESI-MS spectra of loops **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Author**
*E-mail: yuliu@nankai.edu.cn.

## ■ ACKNOWLEDGMENT

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(13) If there was a 2:2 complex or $n$:$n$ polymeric species in the aqueous solution, there should be more than one species in the DOSY spectra and the size of the complex formed by **3** and CB[8] should be more than 2 times larger than the one of free CB[8]. See Figure S21 in the Supporting Information for the possible structure of the 2:2 complex and $n$:$n$ polymeric species.

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