Novel [2]Pseudorotaxanes Containing Cucurbituril as a Molecular Bead: Unexpected Formation of a Kinetic Product Which Spontaneously Converts into a Thermodynamic Product by Translocation of the Bead†

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The construction of nanometer-scale devices such as molecular machines and switches from molecular components is of much interest in recent years.[1] Mechanically interlocked molecules such as rotaxanes and catenanes have great potential as such molecular devices because the relative positions of their components can be induced to change by external stimuli.[2] For example, in a [2]rotaxane, which is composed of a ring threaded on a linear chain terminated by bulky stoppers, the translocation of the ring along the linear component can be achieved by external chemical, electrochemical, or photochemical stimuli. In appropriately designed systems, such mechanical movements occur between two different well-defined states so that they behave as molecular machines or switches that are potentially useful in molecular-scale information storage and processing as well as sensor.

Cucurbituril (CB[6]) is a macrocycle comprising six glycoluril units with a hydrophobic cavity that is accessible through two identical carbonyl-fringed portals.[3,4] In the past several years, we have synthesized novel mechanically interlocked molecules such as rotaxanes, polyrotaxanes, and molecular necklaces by taking advantage of the strong tendency of CB[6] to form stable host-guest complexes with diaminoalkane derivatives.[5] For example, *N,N'*-bis(4-pyridylmethyl)-1,4-diaminobutane dihydrochloride and CB[6] readily form a pseudorotaxane which then reacts with a metal ion or complex to form a polyrotaxane or a molecular necklace. More recently, our efforts have been focused on molecular machines and switches based on [2]rotaxanes.[6] To realize molecular device, however, such molecular machines or switches need to be organized at an interface or on the surface of a solid to behave coherently.[7] Therefore, we initiated our efforts to anchor rotaxane-based molecular switches on a solid surface. As a preliminary work we designed and synthesized a (pseudo)rotaxane that can be attached on a surface by covalent bond. Here we report the synthesis of a novel [2]rotaxane by threading a molecular "bead" with a diaminoalkane-based "string" containing a pyridinemethyl terminal and an iminodicarboxylic acid terminal. Interestingly, the threading process first produces a kinetic product which then converts into a thermodynamic product by translocation of the molecular "bead" along the "string".

Experimental Section

General procedure for the preparation of tertiary amine 2. To a solution of primary amine **1** (4 mmol) and diisopropylethylamine (8.1 mmol) in CH_3CN (40 mL) in an ice bath was added methyl bromoacetate (8.8 mmol) and then the resulting solution was stirred for 20 h at room temperature. After the solvent was removed by evaporation and the residue was dissolved in dichloromethane (80 mL). The resulting solution was washed with aqueous $NaHCO_3$ solution, dried, and evaporated to give a crude product that was further purified by column chromatography using EtOAc/*n*-hexane as an eluent.

2a: 97% yield; ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 2H), 1.42 (m, 2H), 1.57 (m, 2H), 2.67 (t, J = 7.1 Hz, 2H), 3.23 (t, J = 6.9 Hz, 2H), 3.51 (s, 4H), 3.67 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 24.6, 27.8, 29.0, 51.7, 51.9, 54.5, 55.2, 172.0; MS (EI): *m/z* 273 [M^+].

2b: 98% yield; ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 4H), 1.49 (m, 2H), 1.60 (m, 2H), 2.70 (t, J = 7.3 Hz, 2H), 3.26 (t, J = 6.9 Hz, 2H), 3.55 (s, 4H), 3.71 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 26.9, 27.0, 28.1, 29.1, 51.7, 51.9, 54.6, 55.2, 172.1; MS (EI): *m/z* 287 [M^+].

General procedure for the preparation of (4-pyridylmethyl)aminoalkyliminodiacetic acid 3. A solution of **2** (2 mmol) in MeOH (20 mL) was stirred for 15 h at room temperature in the presence of Pd/C under H_2 atmosphere. The resulting solution was filtered through Celite and concentrated to give an amine intermediate which was then reacted *in situ* with 4-pyridylaldehyde (2 mmol) in MeOH (15 mL) in the presence of 4 Å molecular sieve for 20 h. To the resulting solution was treated with $NaBH_4$ and then stirred for 10 h. The reaction mixture was concentrated and dissolved with CH_2Cl_2. After washing with aqueous $NaHCO_3$ solution, the organic phase was dried and evaporated to afford a crude product. The crude product was dissolved in a mixture of THF (15 mL) and H_2O (15 mL) in the presence of

†Dedicated to the memory of Professor Sang Chul Shim, an outstanding scientist, teacher and administrator of our age

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$NaHCO_3$ (2 mmol). To the resulting solution was added CbzCl at 5 °C and the mixture was stirred for 2 h at the same temperature and 3 h at room temperature before EtOAc (60 mL) was added. The resulting mixture was washed with aqueous $NaHCO_3$ solution and the organic phase was separated, dried, and concentrated to give Cbz-protected aminodiester which was further purified by column chromatography. Finally, a solution of Cbz-protected aminodiester (1 mmol) in HBr-H_2O (10 mL) was stirred for 5 h at 80 °C before the solution was concentrated by evaporation. Addition of EtOAc to the solution produced a solid which was filtered, washed with ether extensively to afford **3**.

3a: 40% yield; ^{1}H NMR (D_2O) δ 1.48 (m, 2H), 1.82 (m, 4H), 3.24 (t, J = 7.7 Hz, 2H), 3.38 (t, J = 8.0 Hz, 2H), 4.17 (s, 4H), 4.63 (s, 2H), 8.19 (d, J = 6.5 Hz, 2H), 8.90 (d, J = 6.6 Hz, 2H); ^{13}C NMR (D_2O) δ 23.0, 23.4, 25.3, 48.3, 49.6, 55.6, 56.7, 127.8, 142.3, 152.0, 169.1; MS (EI): *m/z* 309 [M^+-3HBr], 471 [M^+-HBr].

3b: 38% yield; ^{1}H NMR (D_2O) δ 1.42 (m, 4H), 1.76 (m, 4H), 3.21 (t, J = 7.8 Hz, 2H), 3.35 (t, J = 8.1 Hz, 2H), 4.17 (s, 4H), 4.60 (s, 2H), 8.17 (d, J = 6.6 Hz, 2H), 8.88 (d, J = 6.8 Hz, 2H); ^{13}C NMR (D_2O) δ 23.5, 25.4, 25.5, 25.6, 48.6, 49.6, 55.3, 57.0, 127.8, 142.4, 152.0, 168.9; MS (EI): *m/z* 323 [M^+-3HBr].

General procedure for [2]pseudorotaxane 4. To a solution of **3** (0.3 mmol) in H_2O (30 mL) was added CB[6] (0.4 mmol) in small portions and the mixture was stirred for ~20 min at room temperature. Excess CB[6] was filtered out to provide a clear solution which was concentrated to 1 mL by evaporation. Addition of EtOH (30 mL) to the solution produced a precipitate which was filtered to afford **4** quantitatively.

4a: ^{1}H NMR (D_2O) δ 1.86 (m, 2H), 1.98 (m, 2H), 2.21 (m, 2H), 3.48 (m, 2H), 3.59 (t, J = 7.1 Hz, 2H), 4.07 (s, 4H), 4.34 (d, J = 16.0 Hz, 6H), 4.40 (d, J = 19.1 Hz, 6H), 4.72 (s, 2H), 5.60 (s, 12H), 5.72 (d, J = 6.7 Hz, 6H), 5.77 (d, J = 6.8 Hz, 6H), 7.01 (d, J = 6.6 Hz, 2H), 8.01 (d, J = 6.8 Hz, 2H); ESI-MS: *m/z* 310.3 ([M-CB + H]$^+$), 653.8 ([M + 2H]$^{2+}$); Elemental analysis (%) calcd for $C_{51}H_{62}Br_3N_{27}O_{16}\cdot 7H_2O$: C 36.57, H 4.57, N 22.58; found: C 36.55, H 4.67, N 22.94.

4b: ^{1}H NMR (D_2O) δ 1.60 (m, 2H), 1.77 (m, 2H), 1.90 (m, 2H), 2.17 (m, 2H), 3.43 (m, 2H), 3.56 (t, J = 7.4 Hz, 2H), 4.04 (s, 4H), 4.34 (d, J = 16.0 Hz, 6H), 4.40 (d, J = 19.8 Hz, 6H), 4.72 (s, 2H), 5.60 (s, 12H), 5.73 (distorted d, 6H), 5.78 (distorted d, 6H), 7.02 (d, J = 6.5 Hz, 2H), 8.07 (d, J = 6.7 Hz, 2H); ESI-MS: *m/z* 660.8 ([M + 2H]$^{2+}$), 671.8 ([M + H + Na]$^{2+}$), 680.8 ([M + H + Na + H_2O]$^{2+}$), 1037.3 ([CB + Na + H_2O]$^+$), 1320.3 ([M + H]$^+$); Elemental analysis (%) calcd for $C_{52}H_{64}Br_3N_{27}O_{16}\cdot H_2O$: C 39.50, H 4.21, N 23.92; found: C 39.22, H 4.55, N 23.61.

Formation of [2]pseudorotaxane 5. A solution of **4** in H_2O was stirred for several days at room temperature or a few minutes at 60-70 °C. The resulting solution was evaporated to dryness to afford **5** quantitatively.

5a: ^{1}H NMR (D_2O) δ 0.41 (m, 2H), 0.79 (m, 2H), 1.03 (m, 2H), 2.53 (t, J = 9.0 Hz, 2H), 3.53 (t, J = 8.1 Hz, 2H), 4.39 (d, J = 14.3 Hz, 6H), 4.44 (d, J = 14.4 Hz, 6H), 4.78 (s, 4H), 4.83 (s, 2H), 5.68 (s, 12H), 5.78 (d, J = 15.6 Hz, 6H), 5.87 (d, J = 15.5 Hz, 6H), 8.59 (d, J = 6.0 Hz, 2H), 9.01 (d, J = 6.2 Hz, 2H); ESI-MS: *m/z* 653.8 ([M + 2H]$^{2+}$); Elemental analysis (%) calcd for $C_{51}H_{62}Br_3N_{27}O_{16}$: C 39.55, H 4.03, N 24.42; found: C 39.33, H 4.47, N 24.72.

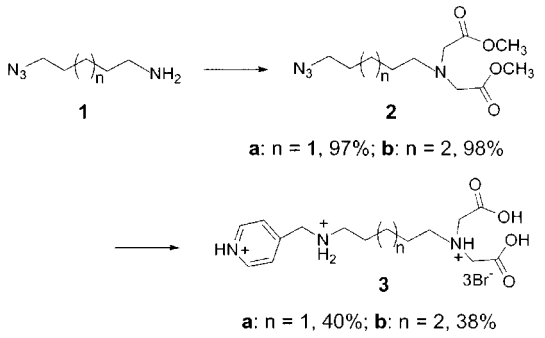
5b: ^{1}H NMR (D_2O) δ 0.45 (m, 4H), 0.76 (m, 2H), 1.34 (m, 2H), 2.85 (t, J = 9.2 Hz, 2H), 3.49 (t, J = 7.8 Hz, 2H), 4.33 (d, J = 14.6 Hz, 6H), 4.38 (d, J = 14.9 Hz, 6H), 4.50 (s, 2H), 4.62 (s, 2H), 4.82 (s, 2H), 5.61 (s, 12H), 5.76 (d, J = 15.6 Hz, 6H), 5.83 (d, J = 15.5 Hz, 6H), 8.50 (d, J = 6.7 Hz, 2H), 8.96 (d, J = 6.7 Hz, 2H); ESI-MS: *m/z* 660.8 ([M + 2H]$^{2+}$); Elemental analysis (%) calcd for $C_{52}H_{64}Br_3N_{27}O_{16}$: C 39.96, H 4.13, N 24.20; found: C 39.68, H 4.42, N 24.67.

X-Ray crystal structure determination of 7. Single crystals of **7** suitable for X-ray work were grown by slow evaporation. The data collection was performed at 223 K with a Siemens SMART diffractometer (MoK_α, λ = 0.71073 Å) equipped with a CCD area detector. An empirical absorption correction was applied (SADABS). The structure was solved by direct methods and refined initially by full-matrix least-squares method (SHELXTL). Crystal data for **7**: $[(C_{36}H_{36}N_{24}O_{12})\cdot(C_6H_{10}N_2)]\cdot 2Br\cdot 10H_2O$, M_r = 1447.03, monoclinic, $P2_1/n$, a = 11.8935(3) Å, b = 15.5261(4) Å, c = 14.8604(3) Å, β = 91.672(1)°, V = 2742.95(11) Å^3, Z = 2, ρ_{calcd} = 1.752 gcm^{-3}, μ = 1.59 cm^{-1}. Due to the inversion center located at the center of CB[6] the guest molecule is disordered over two sites. All the non-hydrogen atoms except for the disordered ones were refined anisotropically. Some water molecules were found to be disordered; they were refined with suitable disorder models. Final block-diagonal matrix least-squares refinement on F^2 with all 4281 reflections and 412 variables converged to $R1$ ($I > 2\sigma(I)$) = 0.0615, $\omega R2$ (all data) = 0.1644, and GOF = 1.081. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-182491). The data can be obtained free of charge *via http://www.ccdc.cam.ac.uk/perl/catreq/catreq.cgi* (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

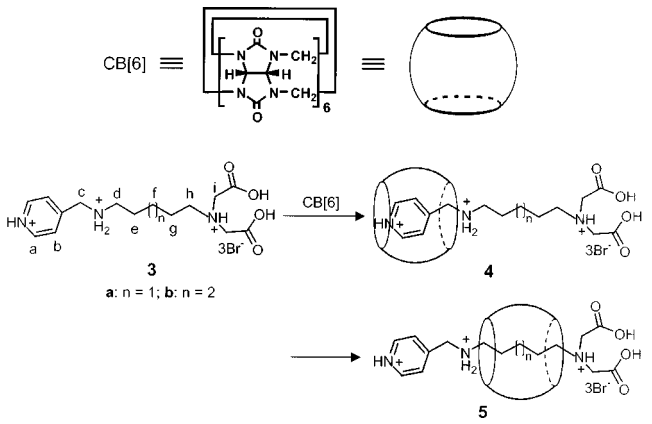
Results and Discussion

The synthesis of (4-pyridinylmethyl)aminoalkylimino diacetic acids is outlined in Scheme 1. Azidoalkyl amines **1**[8] were dialkylated with methyl bromoacetate to afford the tertiary amines **2** in high yields. The azido group in **2** was reduced into amine followed by reductive alkylation with 4-pyridinecarboxaldehyde and Cbz protection of the resulting secondary amine to afford Cbz-protected diesters in moderate yields. The Cbz group was deprotected and the ester group was hydrolyzed simultaneously using HBr-H_2O to give (pyridylmethyl)aminoalkyliminodiacetic acids **3**.

Threading of CB[6] with **3a** and **3b** followed by immediate isolation of the product gives [2]pseudorotaxane **4a** and **4b**, respectively (Scheme 2). To our surprise, the CB[6] bead in **4** resides exclusively at the pyridylmethyl unit as evidenced by ^{1}H-NMR spectroscopy.[4] For example, the ^{1}H-NMR spectrum of **4a** (Figure 1b) reveals that the signals (*a*, *b*, and



Scheme 1. Synthesis of the string **3**.



Scheme 2. Threading of CB[6] with the string **3** to form the kinetic product **4** and its conversion to the thermodynamic product **5**.

c) for the pyridylmethyl unit in **4a** are up-field-shifted relative to those in **3a**. For the better understanding of the unexpected result we attempted to grow single crystals of **4** suitable for X-ray crystallography but failed. Therefore, we decided to investigate the structure of the host-guest complex (**7**) between CB[6] and protonated pyridylmethylamine **6,** instead (Scheme 3). In the crystal structure of **7** (Figure 2) the guest molecule resides inside the cavity while disordered over two sites related to each other by the inversion center located at the center of the cavity. The disorder prevented us from locating the protons attached to nitrogen atoms, but the

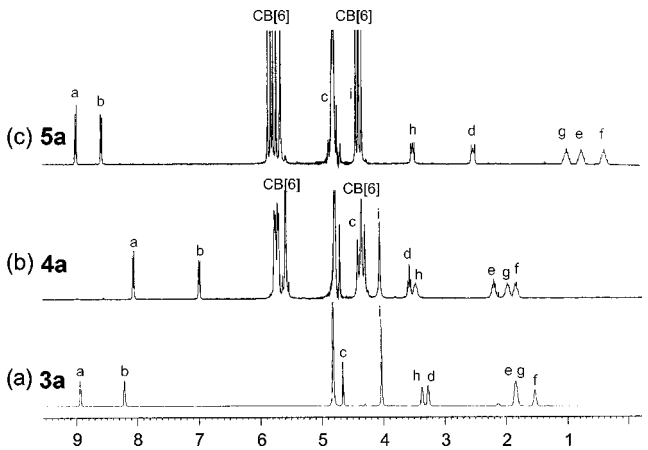
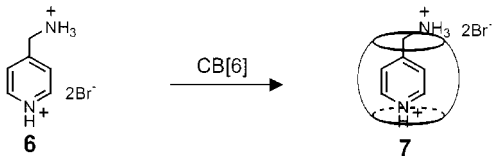


Figure 1. Comparison of the ^{1}H NMR spectra (in D_2O at 25 °C) of **3a** (a), **4a** (b), and **5a** (c).



Scheme 3. Host-guest complex **7** formed between CB[6] and protonated pyridylmethylamine **6**.

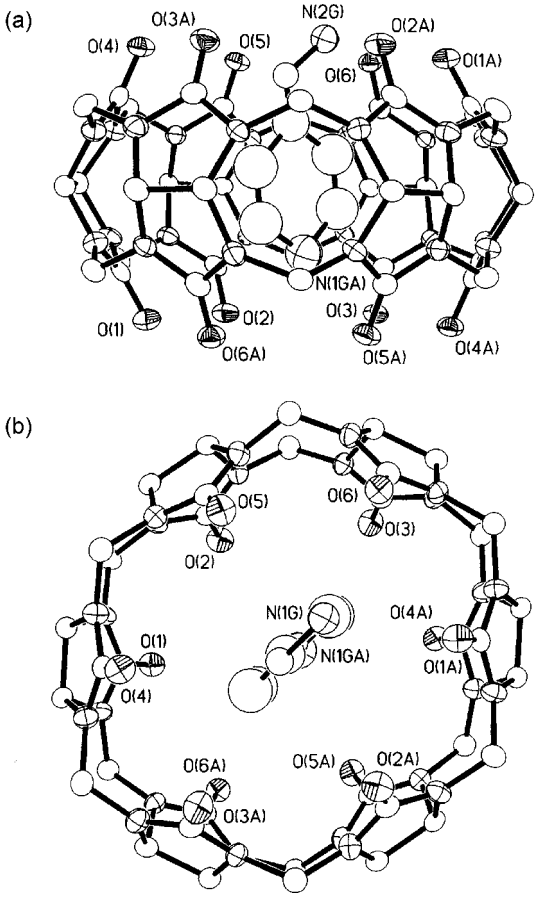


Figure 2. X-ray crystal structure of **7**: **(**a) side view and (b) top view. Hydrogen atoms, counter anions (Br^-), and solvent (H_2O) molecules are omitted for clarity. Hydrogen bonding interactions: N2G···O1A 2.79(1)Å, N2G···O5 3.05(1)Å, N2G···O6 2.88(1)Å.

existence of two Br^- ions in the lattice suggests that both amine and pyridine nitrogen atoms are protonated. The CB[6] host shows an ellipsoidal distortion to accommodate the guest molecule (Figure 2b). The major driving force for the inclusion of the guest in CB[6] appears to be the charge-dipole and hydrogen bonding interactions between the protonated amine group of the guest and the portal oxygen atoms as well as the hydrophobic interaction between the aromatic residue of the guest and the inside wall of the host. The charge-dipole interaction between the protonated pyridyl nitrogen atom of the guest and the portal oxygen atoms may also contribute to the stability of the complex.[9] Some important geometrical parameters showing the host-guest interactions are listed in the caption of Figure 2.

Upon standing in solution **4a** and **4b** slowly converts to **5a** and **5b**, respectively, as evidenced by ^{1}H NMR spectroscopy.

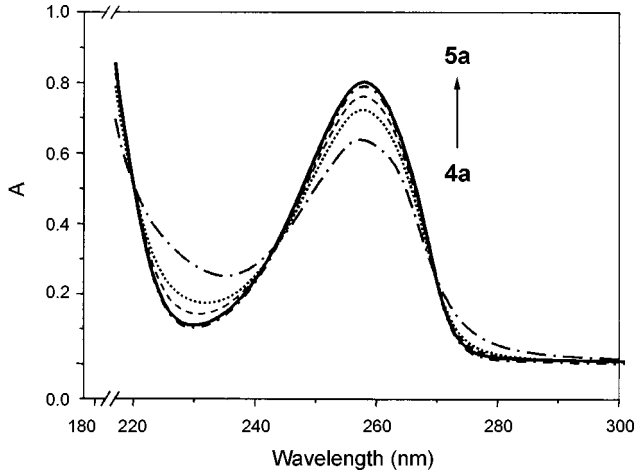


Figure 3. UV-visible spectral changes associated with the conversion **4a** to **5a** in H_2O at 25 °C. The absorption spectra were taken with a 0.23 mM solution.

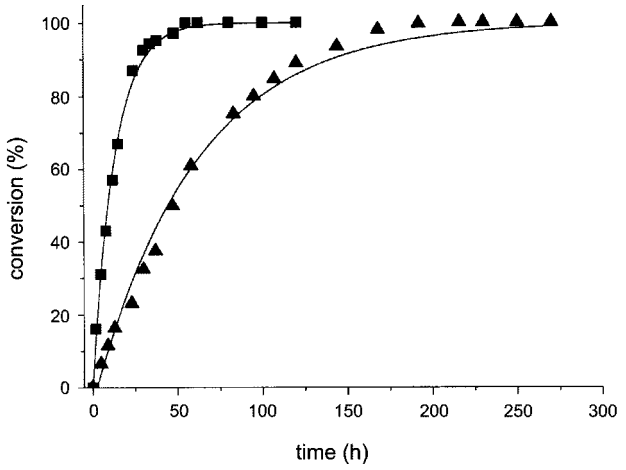


Figure 4. Plots of conversion from **4a** (■) and **4b** (▲) to **5a** and **5b**, respectively at 25 °C.

The conversion is very slow at room temperature but occurs rapidly and completely in a few minutes at 60-70 °C. The comparison of the ^{1}H-NMR spectra of **4a** and **5a** (Figure 1) reveals that the signals (*a*, *b*, and *c*) for the pyridylmethyl unit in **5a** are down-field-shifted while those (*d*, *e*, *f*, and *g*) for the alkyl unit are up-field-shifted relative to those in **4a**. In addition, the signal *i* in **5a** is down-field-shifted relative to that in **4a**. These observations are consistent with the *complete* and *irreversible* movement of the CB[6] bead from the pyridylmethyl site in **4a** to the alkyl site in **5a**. The conversion is also accompanied by change in UV-visible spectrum as shown in Figure 3.[10] The intensity of the band at 258 nm increases upon conversion from **4a** to **5a**. This spectral change must be associated with the movement of CB[6] from the pyridylmethyl site to the alkyl site but the exact nature of the change is unknown at present time.

The kinetics of the conversion from **4a** to **5a** and from **4b** to **5b** has been studied at 25 °C by ^{1}H-NMR spectroscopy. Figure 4 shows that the conversion follows a first order kinetics. The conversion from **4a** to **5a** occurs faster than that from **4b** to **5b**. The first order rate constants are calculated to be 2.1 (± 0.1) × 10^{-5} s^{-1} and 5.0 (± 0.3) × 10^{-6} s^{-1} for the conversion from **4a** to **5a** and that from **4b** to **5b**, respectively. The activation parameter $\Delta G^{\ddagger}$ is estimated to be 23.8 kcal/mol and 24.7 kcal/mol for the former and the latter conversion, respectively.

In summary, we synthesized novel [2]rotaxanes by reacting CB[6] and (4-pyridinylmethyl)aminoalkylimino diacetic acids. In the initial products, the CB[6] bead is threaded on the terminal pyridinylmethylamine unit. Upon standing in solution at room temperature, however, the bead translocates slowly but completely to the inner diaminoalkane unit to form thermodynamically more stable [2]rotaxanes. This unexpected result may provide an insight into the synthesis of other rotaxanes containing CB[6] by a slipping mechanism.[11] We are currently working on anchoring the [2]pseudorotaxanes on a surface by covalent modification.

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