

Reversible Control of Assembly and Disassembly of Interlocked Supermolecules

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Two kinds of interlocked supramolecular complexes that display stimulus-responsive assembly and disassembly have been described. One is a pseudorotaxane driven by hydrogen-bonding interactions between rings **2a** and **2b** and rods **1a** and **1b**. The rods contain a binding site for the ring as well as a stimulus-responsive diazo group, both of which are conformationally constrained in parallel by connecting them to a rigid xanthene skeleton. The trans isomer of **1a** bearing a rigid binding site cannot form the pseudorotaxanes with the rings **2a** and **2b** because the neighboring diazophenyl group sterically shields the binding site. However, when trans-1a was converted to the corresponding cis-1a by UV light, the pseudorotaxanes are immediately formed with association constants of 70 \pm 10 M⁻¹ and (1.1 \pm 0.1) \times 10³ M⁻¹ for **2a** and **2b**, respectively, in CDCl₃ at 24 \pm 1 °C. The pseudorotaxanes are completely disassembled into their molecular component when heated at 80-85 °C for 20 min. The assembly and disassembly processes can be reversibly cycled by repeating irradiation and heating alternatively. In the case of the rod 1b that possesses a flexible binding site, both cis and trans isomers can form the corresponding pseudorotaxanes with association constants of $(2.0 \pm 0.3) \times 10^2$ M⁻¹ for **2a** and *trans*-**1b** and of $(7.4 \pm 0.5) \times 10^2$ M⁻¹ for **2a** and *cis*-**1b** in CDCl₃ at 24 \pm 1 °C. In this system, therefore, external stimuli can modulate the relative distribution of the pseudorotaxane and its components. Finally, the work was extended to the construction of a kinetically more stable molecular machine based on a rotaxane-like complex 10. 11 between a metallocycle 11 and a dumbbell 10. In this system, the complex and its components showed separate sets of the signals, not the averaged, in ¹H NMR spectroscopy as expected by the increased kinetic stability.

Introduction

Interlocked supermolecules such as rotaxanes, catenanes, and pseudorotaxanes have attracted a great deal of attention in recent years because of their potential applications to molecular electronics in the future.¹ Rotaxanes and catenanes are mechanically interlocked supermolecules comprised of two distinct molecular components that cannot be separated without breaking a covalent bond. Two components may reversibly change their relative positions within the interlocked entities, so-called co-conformations,² to generate a thermodynamically stable state when an external stimulus is applied. On the other hand, the pseudorotaxane is a supramolecular complex, and its assembly and disassembly may be reversibly controlled at will. The switching capability of these supermolecules is one of the most important features required for construction of artificial molecularlevel machines.

The supramolecular states of the co-conformations (rotaxanes and catenanes) or the assembly/disassembly (pseudorotaxanes) can be controlled by modulation of noncovalent interactions. The most widely used method for this purpose is electro- and photochemical redox chemistry³ that alters effectively the strength of noncovalent interactions including hydrogen bonds and metal coordination. The other is the acid—base chemistry that induces the protonation and deprotonation at the recognition sites, thus greatly affecting the hydrogen-bonding capability.⁴ Light energy has been also used for operation

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of artificial molecular machines.^{5,6} In particular, in the molecular machines based on the diazo functionality, the trans isomer of the rod is nicely threaded but the cis isomer poorly fitted in the ring owing to its inherent bent shape.⁵

Herein we describe design, self-assembly, and properties of interlocked supramolecular complexes **1**·**2** that display stimulus-responsive assembly and disassembly and therefore function like a molecular machine (Figure 1).⁷ Reversible switching of two supramolecular states stems from trans-cis isomerization of the diazo functionality in the rod components **1a** and **1b**, which can be reversibly controlled by light and thermal stimulations. The working principle of new molecular machines is different from the previous diazo-based ones,⁵ and the

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FIGURE 1. Pseudorotaxane-based molecular machines.

efficiency in the regulation of the supramolecular states is one of the highest among light-driven molecular machines reported to date. A rotaxane-like complex **10**• **11** was also prepared from a metallocycle and a dumbbell and was proven to be a kinetically more stable molecular machine compared to the pseudorotaxane-based ones **1**• **2**.

Results and Discussion

Design Principle. The pseudorotaxane-based molecular machine designed here is shown schematically in Figure 1. A main driving force for the assembly of a ring and a rod is hydrogen-bonding interactions. In the trans isomer of the rod, the diazo group sterically interferes the ring encircling the binding site, and consequently, the pseudorotaxane cannot be formed. However, when UV light is applied, thus inducing isomersation into the cis isomer, the binding site is unlocked so that the ring can be threaded in it. For this purpose, a xanthene derivative has been found to be an ideal scaffold that places the binding site and the diazo unit in the proper positions.

Tetralactam macrocycles **2a** and **2b** were chosen as the ring component in this study because they are sufficiently soluble in noncompetitive solvents such as chloroform and 1,1,2,2-tetrachloroethane.⁸ On the basis of our previous studies,⁹ terephthalamido and adipamido functionalities that have strong hydrogen-binding affinities to **2a** and **2b** are utilized as the binding site in rods **1a** and **1b**.

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SCHEME 1. Synthesis of Rods 1a and 1b^a



^a Reaction conditions: (i) HNO_3/CH_3CO_2H , rt, 49%; (ii) Raney Ni, H₂, THF, rt, 93%; (iii) Br₂, Fe, CHCl₃, rt, 61%; (iv) *n*-BuLi(1.6 M in hexane), CO₂ gas, concd HCl, THF, 83%; (v) NaN₃, H₂SO₄, CHCl₃, 83%; (vi) nitrosobenzene, CH₃CO₂H, CHCl₃, 74%; (vii) Et₃N, CHCl₃, then Et₂NH, 26%; (viii) (CH₃)₃CCOCl, *i*-Pr₂NEt, CH₂Cl₂, 74%.

Synthesis and Isomerization. Tetralactam macrocycles **2a** and **2b** were synthesized according to literature procedures.¹⁰ Syntheses of rod molecules **1a** and **1b** containing diazo functionality are outlined in Scheme 1. A xanthenediamine **6** was synthesized in two different manners from 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene **(3)**, which was derived from xanthene-9-one following literature procedure.¹¹ The xanthenediamine **6** was first prepared by nitration(HNO₃/CH₃COOH, 49%) of **3**,¹²

followed by reduction (H₂–Raney Ni, 93%). Alternatively, bromination (Br₂/Fe, 61%) of **3** gave a dibromoxanthene which was converted into a dicarboxylic acid **5** (*n*-BuLi then CO₂, 83%)¹¹ and then treated with NaN₃/H₂SO₄ to give the xanthenediamine **6** in 83% yield.¹³ Condensation of **6** with 1 equiv of nitrosobenzene under acidic conditions gave azo compound **7** in 74% yield.¹⁴ The rod **1a** containing a rigid binding site was prepared in 26% yield from the reaction of terephthaloyl dichloride with 1 equiv each of **7** and diethylamine in one pot. Finally, the other rod **1b** was prepared in 74% yield in the presence of 2,2-dimethylpropionyl chloride by coupling of **7** and adipamide monoacid **8**.

The rods **1a** and **1b** exist as mixtures of the trans and cis isomers, and the former is a major component (96 \pm 2%) under ambient conditions based on the ¹H NMR spectra. The relative populations of the cis isomers increase up to $76 \pm 2\%$ based on the ¹H NMR integration when irradiated with UV light (365 nm)¹⁵ for approximately 10 min. The ¹H NMR spectra of trans and cis isomers are noticeably different from each other (Figure 2a). In particular, the signals for the aromatic hydrogens H^{d*} and H^{e*} of the diarylazo unit in the cis isomer were considerably upfield shifted ($\Delta \delta = 0.9-1.2$ ppm) relative to those in the trans isomer. These spectral behaviors are consistent with computer modeling (Figure 3),¹⁶ showing that two aryl planes of the diarylazo units stack together in the cis isomer, thus making the aromatic signals upfield shifted due to ring current effects. As shown in Figure 2b, the absorption band ($\lambda_{max} = 358$ nm), a characteristic band of the trans isomer, is greatly reduced in the UV-vis spectrum as expected for the trans-cis isomerization of the diarylazo functionality.¹⁷

Assembly and Disassembly of Pseudorotaxanes. The initial study for the pseudorotaxane-based machine was conducted with a rod **1a** and a ring **2a**. When thermally stable *trans*-**1a** was added to a solution of **2a** at room temperature, no change in the NH chemical shifts was observed in the ¹H NMR spectrum. However, the NH signal of the ring was moderately downfield shifted ($\Delta \delta = \sim 0.25$ ppm) when *trans*-**1a** was converted into *cis*-**1a** by UV irradiation (365 nm). The association constant between **2a** and *cis*-**1a** was calculated to be only $70 \pm 10 \text{ M}^{-1}$ in CDCl₃ at $24 \pm 1 \text{ °C}$ (Table 1).¹⁸ Although this system demonstrated that our new system was working as designed, the binding affinity between two

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⁽¹⁵⁾ The solution in a NMR tube or in a UV cuvette was directly irradiated with a UV light source (365 nm, 100 W long wave, UVP, Inc., B-100A).

⁽¹⁸⁾ The association constant was calculated by nonlinear leastsquares fitting of the titration curve, plotting NH chemical shifts of the ring vs equivalents of the rod. See: (a) Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375–378. (b) Fielding, L. *Tetrahedron* **2000**, *56*, 6151– 6169 and also see the Experimental Section for more details.



FIGURE 2. (a) Partial ¹H NMR spectra of **1a** before (bottom) and after (top) UV irradiation (10 min, *cis/trans* = 78:22) and (b) UV–vis spectral changes of **1a** (2.0×10^{-5} M in CHCl₃) upon irradiation for 0, 2, 4, 6, and 8 s.

components was too small for efficient assembly of the pseudorotaxane in solution.

To increase the binding affinity, we first modified the ring component. Recently, we reported that binding affinities between tetralactam macrocycles and diamide guests greatly increased when electron-withdrawing groups were introduced at the para position of the pyridine ring.¹⁹ A nitro-substituted tetralactam **2b** was therefore prepared and used as the ring for more efficient formation of the pseudorotaxane. The ¹H NMR spectra nicely illustrate a dramatic difference in the binding affinities of **2b** with two isomers, *trans*-**1a** and *cis*-**1a** (Figure 4).

When *trans*-**1a** (4 equiv) was added to a solution of the ring **2b** $(2.0 \times 10^{-3} \text{ M})$ in C₂D₂Cl₄ at room temperature



FIGURE 3. Energy-minimized structures of *trans*-**1a** and *cis*-**1a** using the MM2* force field implemented in MacroModel 7.1 program.

TABLE 1. Association Constants (K_a , M^{-1}) of the Rods and Rings at 24 \pm 1 °C in CDCl₃

		association con	association constant (K_a , M^{-1})	
rod	ring	trans rod	cis rod	
1a	2a	а	70 ± 10	
1a	2b	а	$(1.1\pm0.1) imes10^3$	
1b	2a	(2.0 \pm 0.3) $ imes$ 10 2	$(7.4\pm0.5) imes10^2$	
10	11	$(1.0\pm0.1) imes10^2$	$(3.0\pm0.2) imes10^2$	
^{<i>a</i>} Too small to determine the binding affinity ($K_a < 1 M^{-1}$).				

(Figure 4b), the chemical shift change of the ring NH signal is negligible ($\Delta \delta \sim 0.02$ ppm), implying that the trans isomer cannot form the pseudorotaxane complex as expected. However, the NH signal was considerably downfield shifted from 8.82 to 9.96 ppm on irradiation of the solution, which results in an increase of the cis-1a population up to approximately 78% (Figure 4c). The NH signal came back to the original position upon heating the solution at 80-85 °C for 20 min, a process which converted cis-1a to trans-1a (Figure 4d). As illustrated in Figure 4 (inset), the assembly and disassembly of the pseudorotaxane 1a·2b can be repeatedly cycled by alternating irradiation and heating. The association constant between **2b** and *cis*-**1a** was found to be $(1.1 \pm 0.1) \times 10^3$ M^{-1} in $CDCl_3$ at 24 ± 1 °C. 18 In addition, the association constant between **2b** and *cis*-**1a** was $(5.2 \pm 0.1) \times 10^3$ M^{-1} at 5 °C.

Another approach we examined to augment the binding affinity between two components is to modify the binding site in the rod into more flexible adipamide functionality as in the rod **1b**. In contrast to the rigid rod **1a**, addition of *trans*-**1b** to a $C_2D_2Cl_4$ solution of the ring **2a** induces the NH signal considerably downfield shifted ($\Delta \delta \sim 0.70$ ppm, Figure 5b). This result is not surprising because the binding site in *trans*-**1b** is flexible

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FIGURE 4. Partial ¹H NMR spectra in $C_2D_2Cl_4$ at 25 °C of (a) ring **2b** (2.0×10^{-3} M) (b) ring **2b** (2.0×10^{-3} M) + *trans*-1a (4 equiv) (c) after 10 min irradiation (365 nm, ~78% *cis*-1a) (d) after heating (80–85 °C) for 20 min. Inset: Plot of chemical shift changes by alternating irradiation (9.96 ppm) and heating (8.82 ppm).



FIGURE 5. Partial ¹H NMR spectra in $C_2D_2Cl_4$ at 25 °C of (a) **2a** (2.0 × 10⁻³ M), (b) **2a** (2.0 × 10⁻³ M) + *trans*-1b (4 equiv), (c) after 10 min irradiation (365 nm, ~76% *cis*-1b), and (d) after heating (80–85 °C) for 20 min. Inset: Plot of chemical shift changes by alternating irradiation (10.02 ppm) and heating (9.60 ppm).

enough to rotate away from the diazo blocker, thus minimizing the steric interference on the formation of the pseudorotaxane with the ring **2a**. Irradiation of the solution with UV light leads to further shift of the NH signal (Figure 5c), implying that *cis*-**1b** binds more strongly to the ring **2a** relative to *trans*-**1b**. Again, the NH signal moves back to the original position when *cis*-**1b** is transformed to the corresponding *trans*-**1b** by heating the solution (Figure 5d). The association constants of **2a** with *trans*-**1b** and *cis*-**1b** are determined to be $(2.0 \pm 0.3) \times 10^2 \text{ M}^{-1}$ and $(7.4 \pm 0.5) \times 10^2 \text{ M}^{-1}$, respectively, in CDCl₃ at 24 ± 1 °C. It is also worth mentioning that the binding affinity of *cis*-**1b** is 1 order of the magnitude higher than that of the *cis*-**1a** bearing a rigid binding site, terephthalamido functionality. Unlike in the rod **1a**, both isomers of the rod **1b** can form the corresponding pseudorotaxanes, and therefore external stimuli can modulate the relative distribution of the pseudorotaxane and its components.

Assembly and Disassembly of a Rotaxane-Like Complex. We have extended this work to the construction of a kinetically more stable machine based on a rotaxane-like complex²⁰ between a metallocycle and a stimulus-responsive dumbbell. We previously described self-assembly of a metallocycle **11** from a bispyridyl ligand^{9c} and Stang's palladium complex Pd(dppp)OTf₂²¹ and its application to the preparation of rotaxanes.²² In dumbbell **10**, the adipamide functionality was incorporated as the binding site for the metallocycle **11**, a diazoxanthene unit is attached to one end, and a bulky tritylphenoxy stopper is placed at the other to prevent the ring slipping off the dumbbell. The synthesis of dumbbell **10** is outlined in Scheme 2.

Because of the weak, reversible nature of Pd(II)-N coordinate bonds, a rotaxane-like complex is immediately formed when two components 10 and 11 were mixed together at room temperature. In the ¹H NMR spectrum, the complex 10.11 showed separate signals from its components 10 and 11 at room temperature in CDCl₃ owing to a slow exchange on the ¹H NMR time scale (Figure 6). This is direct evidence for that the rotaxanelike complex 10.11 is kinetically more stable, relative to the pseudorotaxanes 1.2, which showed time-averaged ¹H NMR signals as described above. Upon formation of the complex 10.11, two NH signals of metallocycle 11 are downfield shifted ($\Delta \delta = 1.1$ ppm) as a result of hydrogenbond formation. Moreover, the methylene $(-CH_2-)$ signals in the adipamido binding site in the dumbbell are upfield shifted ($\Delta \delta = 0.8 - 1.2$ ppm), suggesting that the ring encircles around the adipamide part. Relative intensities of the signals corresponding to the complex are increased upon irradiation of the solution containing 10 and **11** (Figure 6c). This result implies that *cis*-**10** binds more strongly than trans-10 does. Indeed, the association constants (K_a) of *trans*-10 and *cis*-10 were calculated to be (1.0 \pm 0.1) \times 10² M⁻¹ and (3.0 \pm 0.2) \times 10² M⁻¹, respectively, on the basis of the ¹H NMR integration in CDCl₃ at 25 °C.

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SCHEME 2. Synthesis of Dumbbell 10^{*a*} and Structure of Metallocycle 11^{*a*}



 a Reaction conditions: (i) (CH_3)_3CCOCl, $\emph{i-}Pr_2NEt,$ rt, CH_2Cl_2, 74%.

Conclusion

Reversible control of two supramolecular states that may impart different physical, electrochemical, or optical properties is a central feature for the construction of molecular-level switches, machines, and devices. We here describe interlocked supramolecular complexes that display stimulus-responsive assembly and disassembly driven by hydrogen-bonding interactions. In this system, reversible switching between two states is based on the transcis isomerism of diazo functionality induced by light and thermal energy, which leads to blocking and opening of the binding site in the rod component. The design principle and method applied in this study can be further extended to design and construction of new molecular machines using different pairs of molecular components.

Experimental Section

2,7-Di-*tert***-butyl-9,9-dimethyl-9***H***-xanthene-4,5-diamine (6).** The compound **6** was prepared by two different methods from 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene (**3**).

Method A. To a suspension of **3**¹¹ (2.7 g, 0.73 mol) in acetic acid (300 mL) was added dropwise a solution of fuming nitric acid (30 mL) in acetic acid (30 mL) over 1 h, and the solution was stirred for 42 h at room temperature. Precipitates were collected, washed with water and dried in a vacuum to yield 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-dinitro-9*H*-xanthene **4** as white solids (1.7 g, 49%): mp 296–298 °C; IR (KBr) 1600, 1265 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 2.4 Hz, 2H), 7.65 (d, J = 2.4 Hz, 2H), 1.67 (s, 6H), 1.36 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 147.7, 141.1, 139.3, 132.4, 127.5, 121.4, 35.8, 35.5, 32.6, 31.8. Anal. Calcd for C₂₃H₂₈N₂O₅: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.92; H, 6.87, N, 6.76.

To a solution of **4** (0.90 g, 2.4 mmol) in THF (50 mL) was added a catalytic amount of Raney Ni, and the solution was stirred under a H₂ balloon for 1 h. The catalyst was filtered, and the solvent was removed to give **6** as a white solid (0.71 g, 93%): mp 210–211 °C; IR (KBr) 3400 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.84 (s, 2H), 6.69 (s, 2H), 3.80 (s, 4H, NH₂), 1.61(s, 6H), 1.30 (s, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 135.6,



FIGURE 6. Partial ¹H NMR spectra (CDCl₃, 25 °C) of (a) **11** (5.0×10^{-3} M), (b) **11** (5.0×10^{-3} M) + *trans*-**10** (1 equiv), (c) after 10 min irradiation (365 nm, 74% of *cis*-**10**), and (d) after heating (80–85 °C) for 20 min. The NH signals for the free **11** (\bigcirc , \square) and the rotaxane complex (**0**, **I**) are indicated.

133.5, 127.5, 113.1, 111.8, 110.4, 35.8, 32.5, 32.0, 31.0. Anal. Calcd for $C_{23}H_{32}N_2O$: C, 78.36; H, 9.15; N, 7.95. Found: C, 78.35; H, 9.13, N, 7.94.

Method B. 2,7-Di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene-4,5dicarboxylic acid (**5**) was prepared from 2,7-di-*tert*-butyl-9,9dimethyl-9*H*-xanthene (**3**) according to literature procedures.¹¹ Compound **5** (0.60 g, 1.4 mmol) was dissolved in CHCl₃ (15 mL) containing fuming H₂SO₄ (0.10 mL), and NaN₃ (0.34 g, 5.8 mmol) was added. The solution was stirred for 1.5 h at room temperature, then for 1 h at 50–51 °C, and cooled to room temperature. The pH of the solution was adjusted to 12– 13 with 1 N aqueous KOH, and the organic layer was washed with water and brine. The solution was dried over anhydrous Na₂SO₄, filtered, and concentrated to give **6** in 83% yield, which gave the same physical and spectroscopic properties as those of the sample obtained from method A.

2,7-Di-*tert***-butyl-9,9-dimethyl-5-phenylazo-9***H***-xanthen-4-ylamine** (7). A solution of **6** (0.16 g, 0.45 mmol), nitrosobenzene (0.48 mg, 0.45 mmol), and two drops of acetic acid in CHCl₃ (6 mL) was stirred at room temperature under argon.¹⁴ After 12 h of stirring, the solution was diluted with CHCl₃ (20

mL), washed with saturated NaHCO₃ solution and brine, and dried over anhydrous MgSO₄. After concentration, the residue was purified by silica gel column chromatography (CH₂Cl₂/*n*-hexane = 1:1) to give 7 as a reddish solid (0.12 g, 61%): mp 180–182 °C; IR (KBr) 3390, 1480 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.97 (d, J = 6.7 Hz, 2H), 7.62–7.46 (m, 5H), 6.85 (d, J = 2.1 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 4.04 (s, 2H, NH₂), 1.69 (s, 6H), 1.34 (s, 9H), 1.32 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 146.7, 145.8, 140.6, 137.1, 135.6, 133.5, 133.0, 130.7, 129.2, 128.8, 127.0, 126.5, 123.4, 122.7, 116.6, 112.8, 112.1, 111.5, 35.1, 32.3, 32.2, 32.1. Anal. Calcd for C₂₉H₃₅N₃O: C, 78.87; H, 7.99; N, 9.52. Found: C, 78.87; H, 7.98; N, 9.51.

5-Diethylcarbamoylpentanoic Acid (8). A solution of adipoyl dichloride (1.0 g, 5.5 mol), benzyl alcohol (0.57 mL, 5.5 mmol), 4-(N,N-dimethylamino)pyridine (DMAP, 65 mg, 0.1 equiv), and Et₃N (1.5 mL, 11 mmol) in CH₂Cl₂ (15 mL) was stirred for 14 h at room temperature under nitrogen. After the solution was cooled to 0 °C (iced water bath), excess diethylamine (2.3 mL, 4 equiv) was added, and the solution was stirred for 1 h at room temperature. The mixture was washed with 1 N HCl, saturated NaHCO₃ solution, and brine and dried over anhydrous Na₂SO₄. After concentration, the residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 9:1) to yield 5-diethylcarbamoylpentanoic acid benzyl ester as a colorless oil (0.56 g, 35%). This benzyl ester was directly subjected to catalytic hydrogenolysis (H₂ balloon, 5% Pd/C, MeOH) to give quantitatively 8 as colorless oil: IR (thin film) 1729, 1606, 1281 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) & 3.37 (m, 2H), 3.30 (m, 2H), 2.40 (s, 2H), 2.34 (s, 2H), 1.71 (s, 4H), 1.18 (m, 3H), 1.11 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) & 177.7, 172.2, 42.1, 40.3, 33.9, 32.7, 24.7, 24.6, 14.3, 13.0. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96; O, 23.85. Found: C, 59.65; H, 9.55; N, 6.93.

Rod 1a. To a solution of terephthaloyl dichloride (0.11 g. 0.56 mmol) in CHCl₃ (35 mL) was added dropwise a solution of 7 (0.25 g, 0.56 mmol) in CHCl₃ (20 mL) containing triethylamine (0.20 mL, 1.1 mmol) over 2 h at 0 °C (iced water bath) under argon. After being stirred for 2.5 h at room temperature, the solution was cooled to 0 °C, and excess diethylamine (0.30 mL, 3.4 mmol) was added. After being stirred for 1 h at room temperature, the solution was washed with saturated NaHCO₃ solution and brine, dried over anhydrous MgSO₄, and concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give 1a as a reddish solid (90 mg, 26%): mp 238-240 °C; IR (KBr) 3287, 1640, 1480 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.98 (s, 1H, NH), 8.63 (s, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.79 (s, 2H), 7.62 (s, 1H), 7.55 (s, 1H), 7.50-7.41 (m, 3H), 7.24 (s, 1H), 7.09 (d, J = 7.8 Hz, 2H), 3.58 (m, 2H), 3.16 (m, 2H), 1.74 (s, 6H), 1.59 (s, 6H), 1.38 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 164.5, 152.5, 147.1, 146.3, 141.4, 140.4, 137.1, 135.3, 131.6, 130.1, 128.8, 127.6, 126.5, 125.2, 123.3, 122.7, 122.0, 117.6, 116.3, 114.9, 112.9, 40.8, 34.9, 31.9, 31.7, 31.5, 13.2; HRMS (FAB) m/z calcd for $C_{41}H_{49}N_4O_3$ 645.3805, found 645.3805. Anal. Calcd for $C_{41}H_{48}N_4O_3$: C, 76.37; H, 7.50; N, 8.69. Found: C, 76.36; H, 7.48; N, 8.68.

Rod 1b. To a solution of compound 8 (0.21 g, 0.86 mmol) in CH₂Cl₂ (15 mL) were added 2,2-dimethylpropionyl chloride (0.11 mL, 0.79 mmol) and N,N-diisopropylethylamine (0.44 mL, 2.2 mmol) at 0 °C. The solution was stirred under argon for 2 h at room temperature and cooled to 0 °C; 7 (0.32 g, 0.72 mmol) was then added. After being stirred for 24 h at room temperature, the mixture was washed with water and brine and dried over anhydrous Na₂SO₄. After concentration, the residue was purified by silica gel column chromatography $(CH_2Cl_2/EtOAc = 1:1)$ to give 1b as a reddish solid (0.33 g, 74%): mp 166-168 °C; IR (KBr) 3292, 1642, 1482 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.44 (s, 1H, NH), 8.19 (s,1H), 7.96 (d, J = 7.4 Hz, 2H), 7.65 (s, 1H), 7.60 (s, 1H), 7.57-7.51 (m, 3H), 7.16 (s, 1H), 3.38-3.34 (m, 2H), 3.26-3.22 (m, 2H), 2.46-2.43 (m, 2H), 2.29-2.26 (m, 2H), 1.77-1.74 (m, 4H), 1.70 (s, 6H), 1.38 (s, 9H), 1.36 (s, 9H), 1.13-1.09 (m, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 71.6, 170.9, 153.3, 146.4, 146.0, 145.4,

139.9, 137.0, 132.0, 131.2, 129.1, 126.5, 125.9, 122.6, 116.2, 115.3, 112.3, 41.9, 40.0, 37.8, 35.0, 34.9, 32.8, 31.5, 25.2, 25.0, 14.3, 13.1; HRMS (FAB) m/z calcd 625.4118 for $C_{39}H_{53}N_4O_3$, found 625.4118. Anal. Calcd for $C_{39}H_{52}N_4O_3$: C, 74.96; H, 8.39; N, 8.97; O, 7.68. Found: C, 74.99; H, 8.32; N, 8.93.

Dumbbell 10. To a solution of compound 9 (0.31 g, 0.55 mmol) in CH₂Cl₂ (15 mL) at 0 °C (iced water bath) were added 2,2-dimethylpropionyl chloride (0.06 mL, 0.50 mmol) and N,Ndiisopropylethylamine (0.24 mL, 1.4 mmol). The solution was stirred under argon for 1.5 h at room temperature, and 7 (0.20 g, 0.46 mmol) was added. After being stirred for 24 h at room temperature, the mixture was washed with saturated NaHCO₃ solution and brine and dried over anhydrous Na₂SO₄. After concentration, the residue was purified by silica gel column chromatography ($CH_2Cl_2/MeOH = 19:1$) to give **10** as a reddish solid (0.33 g, 73%): mp 83-85 °C; IR (KBr) 3300, 1640, 1480 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.42 (s, 1H, NH), 8.18 (s, 1H), 7.95 (d, J = 7.0 Hz, 2H), 7.65 (s, 1H), 7.60 (s, 1H), 7.55-7.51 (m, 3H), 7.26–7.17 (m, 16H), 7.07 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 5.61 (s, 1H, -NH), 3.91–3.89 (m, 2H), 3.23–3.22 (m, 2H), 2.44–2.43 (m, 2H), 2.15–2.14 (m, 2H), 1.74-1.70 (m, 12H), 1.55-1.33 (m, 24H); 13C NMR (126 MHz, CDCl₃) *b* 172.4, 170.9, 157.0, 153.3, 147.1, 146.4, 146.1, 145.4, 139.9, 138.7, 137.0, 132.1, 132.0, 131.1, 129.1, 127.4, 126.4, 125.9, 125.8, 122.6, 116.3, 115.3, 113.2, 112.4, 67.6, 39.4, 37.3, 36.3, 35.0, 34.9, 31.5, 29.6, 29.2, 26.7, 25.8, 25.1, 24.7; HRMS (FAB) m/z calcd for C₆₆H₇₅N₄O₄ 987.5788, found 987.5788. Anal. Calcd for C₆₆H₇₄N₄O₄: C, 80.29; H, 7.55; N, 5.67; O, 6.48. Found: C, 80.35; H, 7.40; N, 5.53.

¹H NMR Titrations and Calculation of Association **Constants.** Chloroform was stored over 4 Å molecular sieves and filtered through basic alumina prior to use. Two stock solutions of a ring (2.0 \times 10 $^{-3}$ M, e.g., 2a (1.90 mg) in 1.00 mL of CDCl₃) and a rod (2.0×10^{-2} M, e.g., **1a** (39.0 mg) in 3.00 mL of CDCl₃) were separately prepared at 24 ± 1 °C. The stock solutions of rods were covered with aluminum foil for minimum exposure to light. A 500 μ L portion of the ring solution was transferred to an NMR tube, and an initial NMR spectrum was taken to determine the initial chemical shift of the free ring. Aliquots of the rod solution (10 μ L initially, then 80– 100 μ L, and finally 300–700 μ L) were added to the NMR tube containing 500 μL of the ring solution. The spectrum was recorded after each addition, and 13-18 data points were obtained. This titration experiment generally took approximately 2 h, and before and after the titration, change in the cis and trans ratio of the stock solution was negligible on the basis of the ¹H NMR integration. The association constants were calculated to nonlinear least-squares fitting of the titration curves,¹⁸ plotting the chemical shift changes of the ring NH signal against the equivalent of the rod added. Titration experiments were at least duplicated, and errors in the association constants (K_a , M^{-1}) were found to be less than 15% in all cases.

As mentioned earlier, the rods **1a** and **1b** exist as mixtures of the trans and cis isomers. Here, the populations of the trans isomers can be increased >98% by heating at 80-85 °C for 20 min prior to the preparation of the stock solution for titration experiments. On the other hand, the ratios of the cis isomers were increased up to 76 \pm 2% upon irradiation of the stock solution, which were directly used for titration experiments. In the case of **1a** bearing a rigid binding site, the chemical shift changes of the ring NH are attributed only to complexation of the ring with cis-1a because the existing trans-1a $(\sim 22\%)$ could not bind at all. Therefore, the association constant can be calculated by simply correcting the concentrations of *cis*-1a. For 1b with a flexible binding site, the situation is more complicated because both isomers, trans-1b (24%) and *cis*-**1b** (76%), bind to the ring and induce the NH chemical shift changes under fast equilibrium. The association constant between cis-1b and 2a was calculated to solve the following equations simultaneously by an iterative procedure

$$\mathbf{H} + \mathbf{G}_{\mathsf{t}} = \mathbf{H}\mathbf{G}_{\mathsf{t}} \quad K_{\mathsf{t}} = \frac{[\mathbf{H}\mathbf{G}_{\mathsf{t}}]}{[\mathbf{H}][\mathbf{G}_{\mathsf{t}}]} \tag{1}$$

$$H + G_{c} = HG_{c} \quad K_{c} = \frac{[HG_{c}]}{[H][G_{c}]}$$
(2)

where H, G_t, G_c, and HG stand for a ring, trans and cis isomers, and a complex, respectively. The association constant *K*_t can be determined independently using the trans isomer, *trans*-**1b** (>98%). The observed chemical shift δ_{obs} at each titration point is a weighted average of free ring H and two complexes HG_t and HG_c that exist all in fast equilibrium under titration conditions.

$$\delta_{\text{obs}} = \delta_{\text{free}} \frac{[\text{H}_{\text{free}}]}{[\text{H}]_0} + \delta_{\text{HGt}} \frac{[\text{HG}_t]}{[\text{H}]_0} + \delta_{\text{HGc}} \frac{[\text{HG}_c]}{[\text{H}]_0}$$
(3)

Here, $\delta_{\rm free}$, $\delta_{\rm HGt}$, and $\delta_{\rm HGc}$ are the NH chemical shifts of free ring H and two complexes HG_t and HG_c, respectively. The concentration of two complexes, [HG_t] and [HG_c], can be calculated by iterating the following equations until [|[HG_t]_n - [HG_t]_{n-1}|]/[[HG_t]_n] $\leq \theta$, where *n* is the number of iteration and θ is an arbitrary small number. For the calculation, we

here fix
$$\theta = 1.0 \times 10^{-8}$$

$$\begin{split} [\mathrm{HG}_{\mathrm{t}}]_{n} &= 0.5 \times [([\mathrm{H}]_{0} + [\mathrm{G}_{\mathrm{t}}]_{0} + K_{\mathrm{t}}^{-1} - [\mathrm{HG}_{\mathrm{c}}]_{n-1}) - \\ \sqrt{([\mathrm{H}]_{0} + [\mathrm{G}_{\mathrm{t}}] + K_{\mathrm{t}}^{-1} - [\mathrm{HG}_{\mathrm{c}}]_{n-1})^{2} - 4[\mathrm{G}_{\mathrm{t}}]_{0}([\mathrm{H}]_{0} - [\mathrm{HG}_{\mathrm{c}}]_{n-1})}] \\ [\mathrm{HG}_{\mathrm{c}}]_{n} &= 0.5[([\mathrm{H}]_{0} + [\mathrm{G}_{\mathrm{c}}]_{0} + K_{\mathrm{c}}^{-1} - [\mathrm{HG}_{\mathrm{t}}]_{n}) - \\ \sqrt{([\mathrm{H}]_{0} + [\mathrm{G}_{\mathrm{c}}]_{0} + K_{\mathrm{c}}^{-1} - [\mathrm{HG}_{\mathrm{t}}]_{n})^{2} - 4[\mathrm{G}_{\mathrm{c}}]_{0}([\mathrm{H}]_{0} - [\mathrm{HG}_{\mathrm{t}}]_{n})}] \end{split}$$

Here, $[\]_0$ represents total concentration of the species in the bracket, and $[\]_{n-1}$ and $[\]_n$ are concentrations obtained from n-1th and nth iterations, respectively.

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Supporting Information Available: General experimental methods, ${}^{1}H{}^{-1}H$ NOESY of 1a, and ${}^{1}H$ NMR spectral changes of 1a,b and 10 upon irradiation and heating. This material is available free of charge via the Internet at http://pubs.acs.org.

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