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Light-Switchable Janus [2]Rotaxanes Based on α-Cyclodextrin Derivatives Bearing Two Recognition Sites Linked with Oligo(ethylene glycol)

Shujing Li,[a] Daisuke Taura,[a] Akihito Hashidzume,[a] and Akira Harada*[a, b]

Abstract: Two Janus [2]rotaxanes, **5a** and **5b**, with α-cyclodextrin (α-CD) derivatives substituted on the 6-position with two recognition sites (azobenzene and heptamethylene (C7)) that were linked with linkers of different lengths (oligo(ethylene glycol) with a degree of polymerization equal to 2 or approximately 21) were synthesized and characterized. 2D ROESY NMR spectroscopy and circular dichroism (cd) spectra demonstrated that the recognition site of the α-CD moiety was switched by photoisomerization of the azobenzene moiety in **5a** and **5b**. The different size changes of **5a** and **5b** in hydrodynamic radius (R_H) owing to the different length of linker between two recognition sites were observed by pulse-field-gradient spin-echo NMR spectroscopy. The kinetic results indicated that the different length of linker had no or a weak effect for the photoisomerization process of **5a** and **5b**.

Keywords: cyclodextrins · molecular muscles · photochemistry · rotaxanes · supramolecular chemistry

Introduction

Biological systems utilize well-defined supramolecular assemblies formed from macromolecules, for example, nucleic acids and proteins, as molecular machines to maintain living activities.[1] These biological supramolecular machines have been inspiring a number of research groups to make their efforts for construction of highly-functional artificial supramolecular machines.[2] One of the most important challenges toward artificial supramolecular machines is artificial muscles that undergo expansion and contraction as a response to external stimuli, mimicking the movement of muscle fibers that utilize sliding of the components.[3]

An important structural unit of artificial muscles is Janus [2]rotaxanes in which the location of the rotor moiety is switched by external stimuli. A stimuli-responsive Janus [2]rotaxane was first reported by Sauvage et al.[4] They synthesized a Janus [2]rotaxane based on a crown ether moiety containing two Cu^I metals and demonstrated switching of the location of the crown ether moiety by extraction of Cu^I with KCN and by remetalation with Zn^{II}. Stoddart and co-workers[5] have synthesized a Janus [2]rotaxane from crown ether and ammonium moieties and observed that the location of the crown ether moiety was switched by changing the pH value. Stoddart and co-workers[6] also have extended their Janus [2]rotaxane to a polymeric one by Huisgen [3+2] cycloaddition by using dangling alkyne groups at both ends and a diazide. More recently, Grubbs and co-workers[7] have synthesized a Janus [2]rotaxane carrying azide moieties by ring-closing metathesis and formed polymers of the Janus [2]rotaxane units by Huisgen [3+2] cycloaddition with a dialkyne. They directly observed a pH-responsive change in the radius of gyration of the polymer obtained by multi-angle, laser-light scattering.

An important rotor moiety, apart from crown ethers, is cyclodextrin (CD). The advantage of CDs is their molecular-recognition ability in aqueous media. Janus [2]rotaxanes containing CD as a rotor have been reported independently by Kaneda and co-workers[8] and our group.[9] A photoresponsive Janus [2]rotaxane has been reported by Easton and co-workers.[10] They utilized a stilbene moiety as a photoresponsive moiety and demonstrated photoresponsive switching of the location of the α-CD moiety through spectroscopic analysis. We have also previously synthesized a Janus [2]rotaxane containing α-CD, successfully switched the location

[a] S. Li, D. Taura, A. Hashidzume, Prof. A. Harada
Department of Macromolecular Science
Graduate School of Science
Osaka University
1-1 Machikaneyama, Toyonaka, Osaka 560-0043 (Japan)
Fax: (+81) 6-6850-5445
E-mail: harada@chem.sci.osaka-u.ac.jp

[b] Prof. A. Harada
Core Research for Evolutional Science and Technology (CREST)
(Japan) Science and Technology Agency (JST)
5 Sanbancho, Chiyoda-ku, Tokyo 102-0075 (Japan)

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of the α-CD moiety by changing the media, and observed a change in the hydrodynamic radius R_H of the Janus [2]rotaxane as determined by pulse-field-gradient spin-echo (PGSE) NMR spectroscopy.[11]

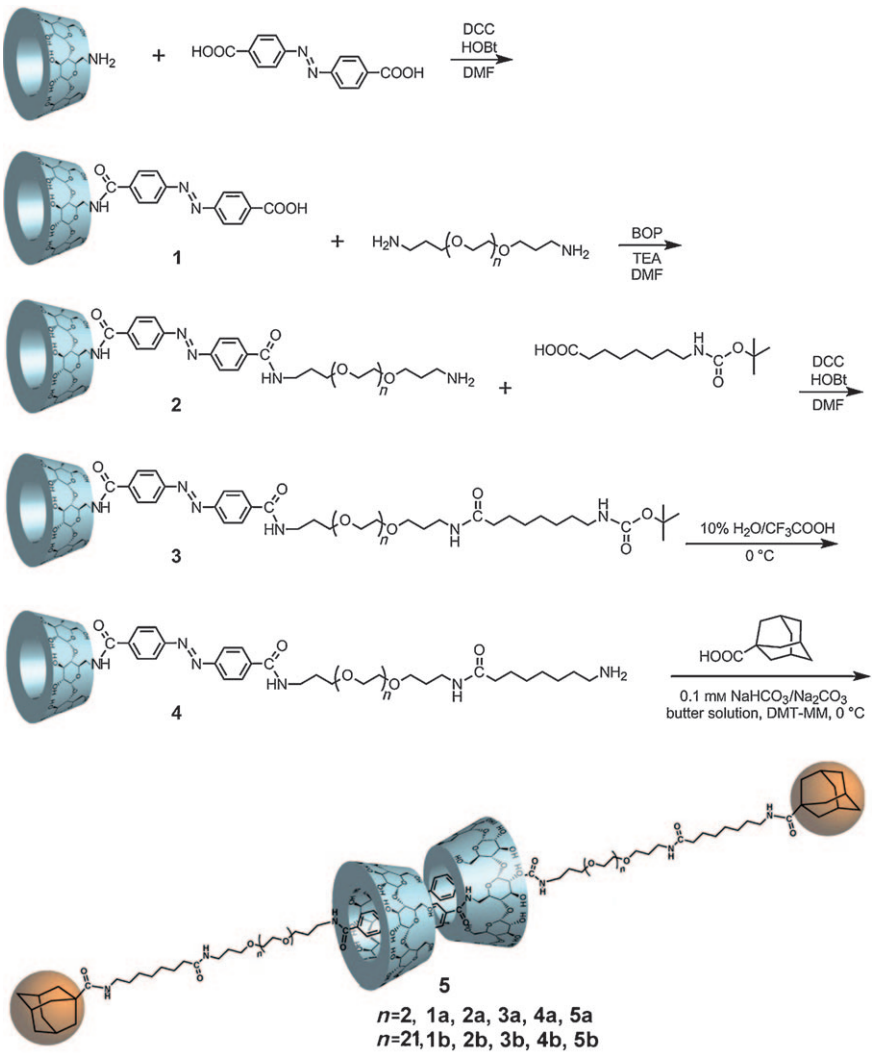
These previous studies have utilized two recognition sites close to each other. To realize a large size change, a longer linker between the two recognition sites is necessary. In the preceding study, we have synthesized an α-CD derivative substituted on its 3-position with azobenzene (Azo) and heptamethylene (C7) moieties as photoresponsive and nonresponsive recognition sites, respectively, connected by a longer linker, oligo(ethylene glycol) (OEG; degree of polymerization (DP) = ~21).[12] We have characterized a doubly threaded dimer formed from the 3-substituted α-CD derivative in water by several techniques and observed a photoresponsive R_H change of the dimer by PGSE NMR spectroscopy.[12] However, it was not possible to cap both ends of the doubly threaded dimer with bulky stoppers to obtain a Janus [2]rotaxane. Thus, in this study, we have successfully synthesized Janus [2]rotaxanes by using α-CD derivatives substituted on the 6-position with Azo and C7 moieties linked with OEG linkers of DP = 2 and approximately 21. Herein, we describe the synthesis of the Janus [2]rotaxanes, their photoresponsive R_H change, and the effect of the linker length.

Results and Discussion

Synthesis of Janus [2]Rotaxanes (5a and 5b)

In this study, the Janus [2]rotaxanes were synthesized according to Scheme 1, which is similar to the previous 3-substituted analogue. An Azo group and a C7 moiety have been chosen as the photoresponsive part and nonresponsive recognition site, respectively. It is well known that the Azo moiety is isomerized from the *trans* form to the *cis* form under irradiation with UV light and from the *cis* form to the *trans* form under irradiation with visible light.[13] It is also known that α-CD includes a *trans*-Azo moiety with an association constant as high as $10^4\,M^{-1}$, but it does not interact with the *cis*-Azo moiety.[14] On the other hand, α-CD includes the C7 moiety with an association constant of $10^2\,M^{-1}$. Preliminary ROESY experiments for model compounds indicated that the signals owing to the C3 and C5 protons inside the cavity of α-CD showed correlation signals not only owing to the *trans*-Azo moiety but also with signals owing to octamethylene or longer oligomethylene moieties. This is indicative of the lower selectivity of α-CD (data not shown).

Mono(6-amino-6-deoxy)-α-CD[15] (6-NH_2-α-CD) was coupled with azobenzene-4,4′-dicarboxylic acid by using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) to give **1**. Compound **1** was allowed to react with excess OEG (DP = 2 or ~21) carrying amino groups on both ends by using (benzotriazol-1-yloxy)-tris(dimethylamino) phosphonium hexafluorophosphate (BOP) to give **2**. Compound **2** was allowed to react with *tert*-butoxycarbonyl-8-aminooctanoic acid (Boc-Aoc(8)-OH) by using DCC and HOBt to yield **3**. Without purification of **3**, the *tert*-butoxycarbonyl group was deprotected with trifluoroacetic acid (TFA) to produce **4**. Compound **4** was capped with 1-adamantanecarboxylic acid by using 4-(4,6-dimethoxy-1,3,5-tria-



Scheme 1. Synthesis of Janus [2]rotaxanes **5a**, **5b**.

zin-2-yl)-4-methylmorpholinium chloride (DMT-MM) at 0 °C in an aqueous $NaHCO_3/Na_2CO_3$ buffer solution in which **4** formed a doubly threaded dimer, to form the Janus [2]rotaxane, **5a** or **5b**. Compounds **1**, **2**, **4**, and **5** were purified by HPLC and obtained in reasonable yields (30–40% for each step).

The Janus [2]rotaxanes obtained, **5a** and **5b**, were fully characterized by matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF-MS), 1D NMR, 2D NMR (COSY, TOCSY, HMQC, HMBC, and ROESY), and circular dichroism (cd) spectroscopies. The MALDI-TOF-MS data showed signals ascribable to the Janus [2]rotaxanes, **5a** and **5b**, at $m/z = 3482.3$ and 4864.6–5571.1, respectively (see Figure S1 in the Supporting Information). The ^{1}H NMR spectra for **5a** and **5b** in D_2O exhibit well-resolved peaks and well-split peaks in the region of CD protons, indicating that the Azo moiety is included by the α-CD moiety (see Figures S2 and S3 in the Supporting Information). To understand the detailed inclusion fashion of **5a** and **5b**, signals of all the protons in the α-CD moiety were assigned by utilizing COSY, TOCSY, and ROESY NMR spectroscopy as can be seen in Figure 1. Drastic upfield and downfield shifts of signals owing to the inner C3 and C5 protons in the α-CD moiety were observed. This is indicative of strong shielding and deshielding effects induced by the tight inclusion of the *trans*-Azo moiety facing its π electron cloud to the B and E glucopyranose units in the α-CD moiety. The 2D ROESY NMR spectra of **5a** and **5b** show correlation signals between the inner protons of the α-CD moiety and the *trans*-Azo protons as shown in Figure 2. The spectra exhibit strong correlation signals between the C3 protons in the α-CD moiety and the *c* and *d* protons in the *trans*-Azo moiety and between the C5 protons in the α-CD moiety and the *b* proton in the *trans*-Azo moiety, respectively. However, the spectra do not show significant correlation signals between the inner protons in the α-CD moiety and the protons in the C7 moiety. These data indicate that the α-CD moiety selectively includes the *trans*-Azo moiety from the narrower rim to form a doubly threaded dimer conformation because of the higher association constant. The conformations of **5a** and **5b** were also investigated by cd spectroscopy, as can be seen in Figure 3. These spectra exhibit the negative- and positive-induced circular dichroism (icd) bands in the region of n–π* and π–π* transitions of the *trans*-Azo moiety. This indicates that α-CD includes the *trans*-Azo moiety and that the transition moments of n–π* and π–π* in the *trans*-Azo moiety are perpendicular and parallel to the axis of the α-CD moiety, respectively.[16]

In the preceding study, it was not possible to cap the doubly threaded dimer of the 3-substituted analogue with 1-adamantanecarboxylic acid under the same conditions. The ^{1}H NMR spectrum of the 3-substituted analogue showed weak but clear signals owing to the free monomer,[12] whereas the ^{1}H NMR spectra for **4a** and **4b** did not exhibit signals owing to the free monomer, indicating that the association constants of the dimerization for 6-substituted **4a** and **4b** were much higher than that for the 3-substituted analogue. This observation indicates that the higher association constant is necessary for efficient capping reaction of Janus [2]rotaxanes.

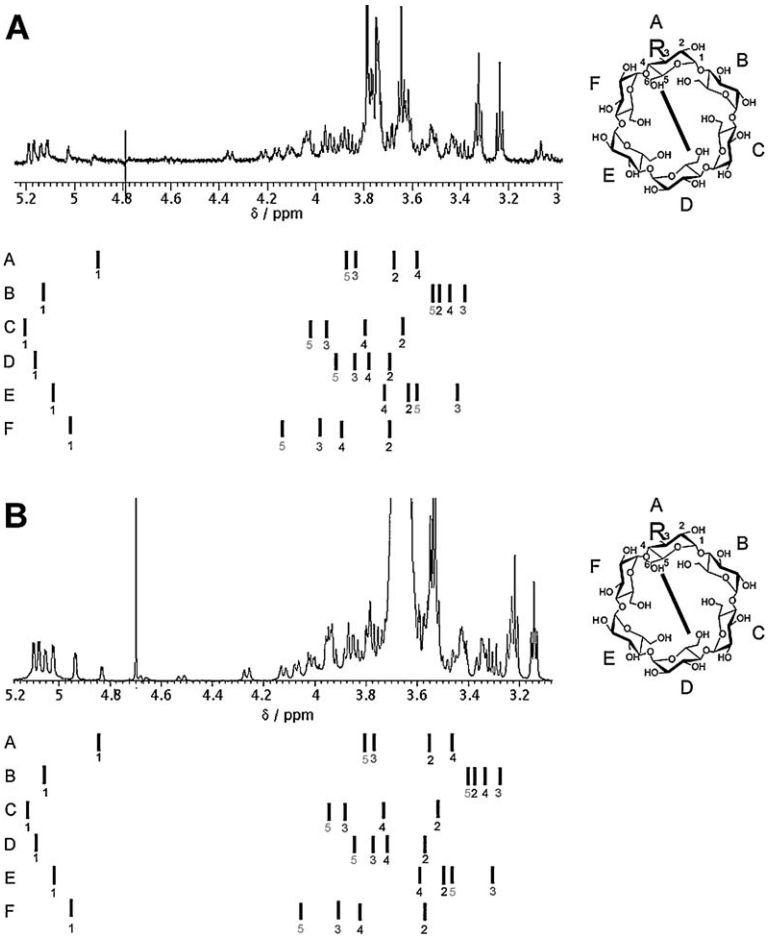


Figure 1. Assignments of **5a** (A) and **5b** (B) before UV irradiation based on COSY, TOCSY, ROESY, HMBC, and HMQC measurements (left) in D_2O, and proposed inclusion fashion of the Azo group (right). Sugar units are labeled clockwise from A to F (viewed from the wider rim), beginning with the altrose unit.

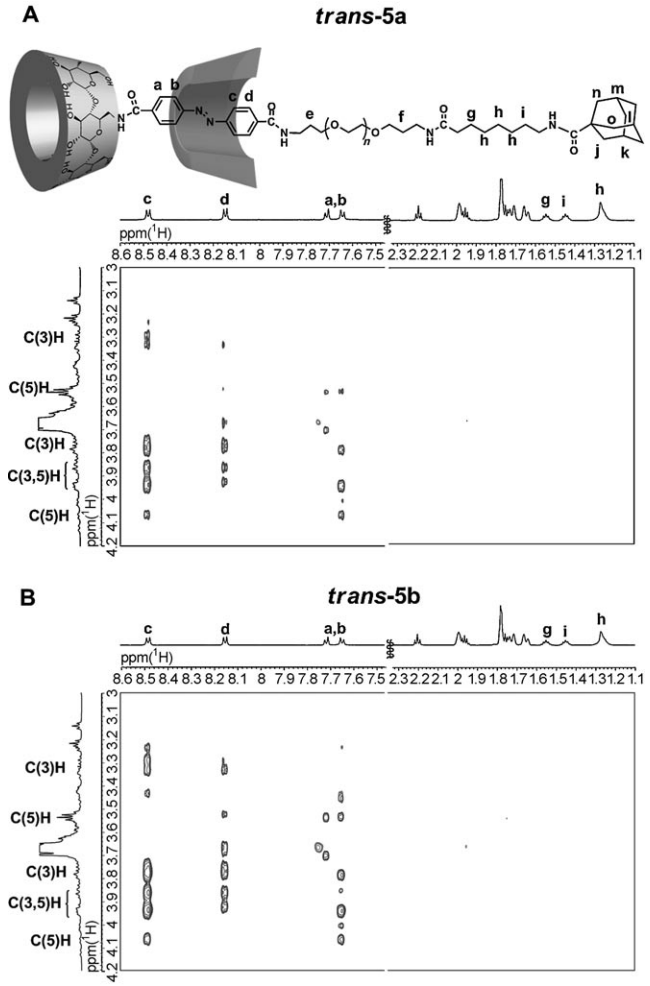


Figure 2. Partial ROESY NMR spectra for 3.0 mM **5a** (A) and **5b** (B) before UV irradiation measured in D_2O at 30 °C (the mixing time = 200 ms).

Photoisomerization of the Janus [2]Rotaxanes (5a and 5b)

Photoisomerization properties of the Janus [2]rotaxanes, **5a** and **5b**, were investigated in detail by UV/Vis absorption spectroscopy. Figure 4 A shows a typical example of time-dependent UV/Vis absorption spectra for **5a** and **5b** under irradiation with UV light at 365 nm. With elapse of irradiation time (t), the absorption band around 340 nm attributable to the *trans*-Azo moiety decreases, whereas the broad absorption band around 440 nm ascribable to the *cis*-Azo moiety increases. To understand the kinetics of *trans*-to-*cis* photoisomerization of **5a** and **5b**, $\ln[(A_0-A_{eq})/(A_t-A_{eq})]$ values were plotted against t as shown in Figure 5 A assuming a pseudo-first-order reaction[17] in which A_0, A_t, and A_{eq} are the initial absorbance, the absorbance at t, and the absorbance in the photostationary state of the Azo moiety at 340 nm, respectively. Figure 5 shows a good linear relationship, indicating that the *trans*-to-*cis* photoisomerization obeys the pseudo-first-order kinetics. From the slopes of the straight lines in Figure 5 A and Equation (1), the pseudo-first-order rate constants of *trans*-to-*cis* photoisomerization (k_{tc}) were determined to be 5.0×10^{-3} and $4.9\times10^{-3}\,s^{-1}$ for **5a** and **5b**, respectively, as listed in Table 1.

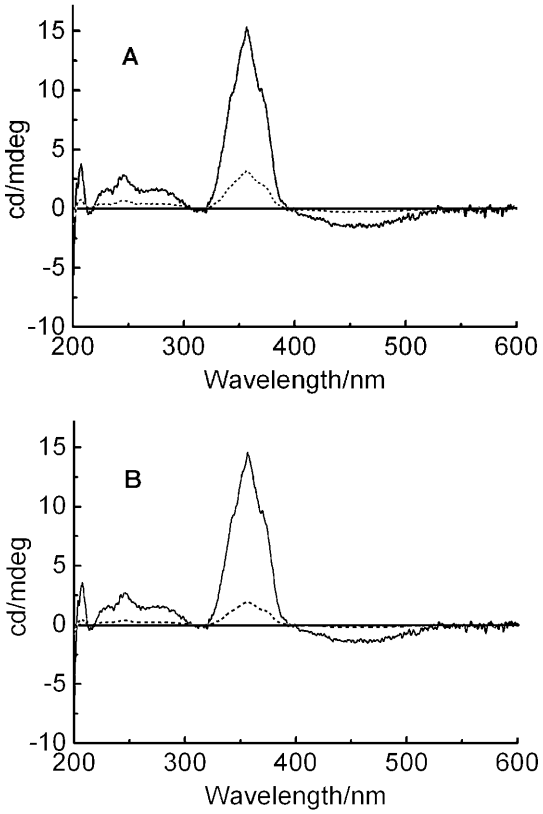


Figure 3. Circular dichroism spectra variations of 2×10^{-4} M **5a** (A) and **5b** (B) before (——) and after UV irradiation (•••••) in water.

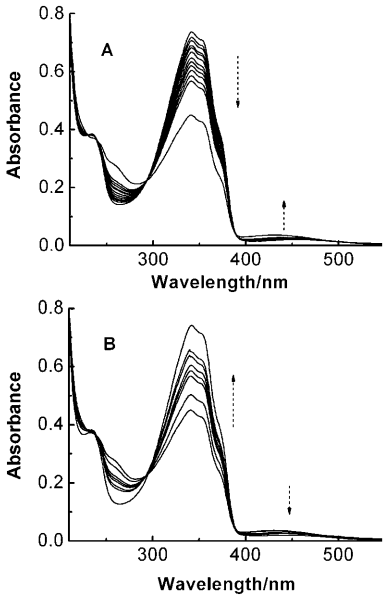


Figure 4. UV/Vis spectra variations of 2×10^{-5} M *trans*-to-*cis* of **5a** (A), and *cis*-to-*trans* of **5a** (B) in water under photoirradiation at 365 nm.

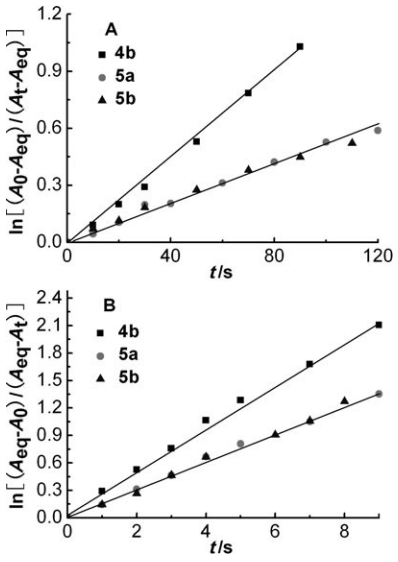


Figure 5. The pseudo-first-order plots for the *trans*-to-*cis* (A) and *cis*-to-*trans* photoisomerizations (B) of **5a**, **5b**, and **4b** in water.

Table 1. Pseudo-first-order rate constants of *trans*-to-*cis* and *cis*-to-*trans* photoisomerization (k_{tc} and k_{ct}) for **5a**, **5b** and **4b**.

Rate constant	5a	5b	4b
$k_{ts}\times10^{3}\ s^{-1}$	5.0	4.9	12
$k_{ct}\times10^{1}\ s^{-1}$	1.7	1.5	2.3

$$\ln\frac{(A_0-A_{eq})}{(A_t-A_{eq})}=k_{tc}t \quad (1)$$

These data are indicative of either no or a weak effect of the linker length. It is noteworthy that k_{tc} ($1.2\times10^{-2}\ s^{-1}$) for the stopper-free, doubly threaded dimer, **4b**, is considerably larger than those for **5a** and **5b**. This observation indicates that the restricted structure of the mechanically interlocked Janus [2]rotaxanes retards the *trans*-to-*cis* photoisomerization. Notably, the *cis* contents for **5a** and **5b** in the photostationary state (approximately 40%) were considerably lower than that for **4b** (approximately 80%), indicating that the mechanically interlocked structure makes the *cis* form less stable in water.

Similar kinetic studies on the *cis*-to-*trans* photoisomerization for the Azo moiety in **5a** and **5b** were also investigated upon irradiation with visible light at 430 nm, as can be seen in Figure 4B. Prior to the experiments, the solution was irradiated by UV light at 365 nm for 20 min to ensure that the sample had been in a photostationary state. Similar to the *trans*-to-*cis* photoisomerization, the plots in Figure 5B show good linear relationships, which is indicative of the pseudo-first-order kinetics. From the slopes of the straight lines in Figure 5B and the following Equation (2), the pseudo-first-order rate constants of *cis*-to-*trans* photoisomerization (k_{ct}) were determined to be 0.17 and 0.15 s^{-1} for **5a** and **5b**, respectively, as listed in Table 1.

$$\ln\frac{(A_{eq}-A_0)}{(A_{eq}-A_t)}=k_{ct}t \quad (2)$$

The k_{ct} values for **5a** and **5b** are almost the same, indicative of no or a weak effect of the linker length. It should be noted here that the k_{ct} values for **5a** and **5b** are smaller than that ($0.23\ s^{-1}$) for the reference, **4b**, indicating that the restricted structure inhibits the *cis*-to-*trans* photoisomerization. The similar result of *cis*-to-*trans* photoisomerization has been reported for restricted systems, for example, Langmuir–Blodgett membranes.[18] The excellent reversibility was confirmed as can be seen in Figure S4 in the Supporting Information.

In water, the *cis* content of the Janus [2]rotaxanes under the photostationary state was as low as 40%, presumably not only because of the restricted structure but also because of the stable inclusion complex of the α-CD and *trans*-Azo moieties. Thus, the *trans*-to-*cis* photoisomerization was carried out in methanol, in which the inclusion complex was less stable, to obtain the *cis* form in as high as approximately 85%. As we did not further purify the Janus [2]rotaxanes after UV irradiation, because the *cis*-Azo moiety would be thermally converted back to the *trans* isomer even in the dark,[19] the photoisomerization product should be a mixture of *cis–cis*, *cis–trans*, and *trans–trans* isomers. However, it may be possible to characterize the *cis–cis* isomer as the main component. In the following, the mixtures, which were recovered by evaporation of methanol followed by dissolution in water, were used for characterization of the *cis–cis* isomer of **5a** and **5b**.

Characterization of the *cis–cis* Isomer of the Janus [2]Rotaxane (5a and 5b)

The *cis–cis* isomers of **5a** and **5b** were also fully characterized by 1D NMR and 2D ROESY NMR and cd spectroscopy. The ^{1}H NMR spectra exhibited signals owing to protons in the *cis*-Azo moiety and new signals ascribable to protons in the C7 moiety, as can be seen in Figures S5 and S6 in the Supporting Information. Figure 6 shows the ROESY spectra for the *cis–cis* isomers of **5a** and **5b**. These spectra show strong correlation signals between the inner protons of the α-CD moiety and the protons in the C7 and adamantane moieties but do not show significant correlation signals between the inner protons of the α-CD moiety and the protons in the *cis*-Azo moiety. As shown in Figure 3, the cd spectra exhibit the very weak icd bands ascribable to the residual *trans*-Azo moiety in a complex, which is indicative of almost no interaction of the α-CD moiety with the *cis*-Azo moiety. These observations indicate that the location of the α-CD moiety is switched from the Azo moiety to the C7 moiety by *trans*-to-*cis* photoisomerization of the Azo moiety, as illustrated in Figure 7.

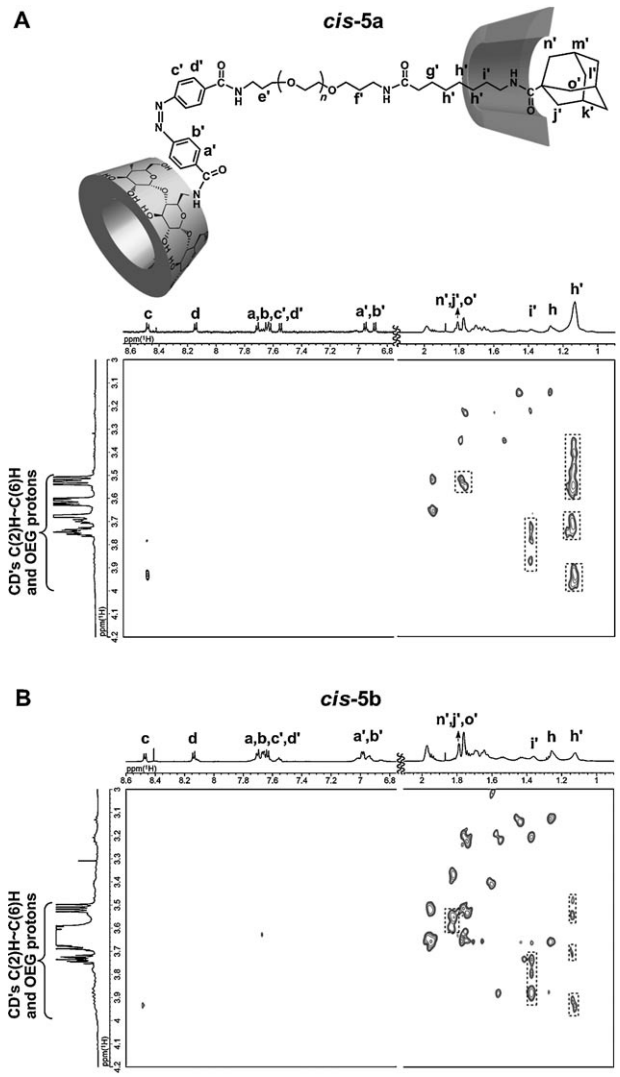


Figure 6. Partial ROESY NMR spectra for 3.0 mM **5a** (A) and **5b** (B) after UV irradiation measured in D_2O at 30 °C ($\tau_m = 200$ ms).

Comparison of the Hydrodynamic Radii for the *trans–trans* and *cis–cis* Isomers of the Janus [2]Rotaxanes (5a and 5b)

The *trans–trans* and *cis–cis* isomers of the Janus [2]rotaxanes, **5a** and **5b**, were characterized by PGSE NMR to estimate the R_H value in water. Figure 8 shows a typical example of the plots of the logarithm of the ratio of the observed spin-echo intensities with and without field gradients ($\ln(I/I_0)$) versus the square of the gradient strength (G^2) for the *trans–trans* and *cis–cis* isomers of **5a** and **5b**. Figure 8 indicates good linear relationships, which is indicative of unimodal relaxations. From the slopes of the straight lines and Equation (3), the self-diffusion coefficients (D) were determined, as listed in Table 2.

$$\ln\,(I/I_0) = \gamma^2 G^2 \delta^2 (\Delta - \delta/3 - \tau/2) D \qquad (3)$$

In Equation (3), γ is the gyromagnetic ratio, G the gradient strength, Δ the delay between the midpoints of the gradients, δ the gradient length, and τ the 90°–180° pulse distance. By using these D values and the Stokes–Einstein equation (shown in Equation (4)), R_H values were calculated as listed in Table 2.

$$R_H = k_B T / 6\pi\eta D \qquad (4)$$

In Equation (4), η is the viscosity coefficient and k_B is the Boltzmann constant. In both cases of **5a** and **5b**, R_H of the *trans–trans* isomer was larger than that of the *cis–cis* isomer by approximately 20% (3.0 and 2.6 nm for the *trans–trans* and *cis–cis* isomers of **5a**, respectively, and 4.4 and 3.6 nm for the *trans–trans* and *cis–cis* isomers of **5b**, respectively). The effect of the linker length on R_H is not so strong. This may be because the OEG linker is very flexible and the Janus [2]rotaxanes take a random-coil conformation. It is promising that dense accumulation of the Janus [2]rotaxane units make the linker more rigid, like polymer brushes.[20]

Conclusions

In summary, with the aim of constructing a molecular muscle caused by a different size change in the Janus [2]rotaxane, **5a** and **5b** with two recognition sites (the Azo and C7 site, linked with OEG; DP = 2 or approximately 21), were synthesized and characterized. 2D NMR spectroscopy, cd spectra, and PGSE NMR spectroscopy demonstrated that the recognition site of the α-CD moiety was switched by photoisomerization of the Azo moiety in **5a** and **5b**, causing a different size change in R_H owing to the different length of linker between the two recognition sites. Polymer formation and polymer reaction utilizing the terminal amine moieties of **4a** and **4b** are in progress to construct a molecular muscle showing macroscopic size changes.

Experimental Section

Materials

N,N-Dimethylformamide (DMF) was purified by using a GlassContour solvent dispensing system. Azobenzene-4,4′-dicarboxylic acid, BOP, 1-adamantanecarboxylic acid, and diethylene glycol bis(3-aminopropyl) ether (oligo(ethylene glycol) (OEG), DP = 2) were obtained from Tokyo Chemical Industry Co., Ltd. *p*-Toluenesulfonyl chloride, 28% ammonia solution, DCC, HOBt, and TFA were obtained from Nacalai Tesque Inc. (OEG, DP = ~21, number average molecular weight of 1.0×10^3) was obtained from NOF corporation. Boc-Aoc(8)-OH was obtained from Watanabe Chemical Industry Co., Ltd. DMT-MM was obtained from Wako Pure Chemical Industries. α-CD was obtained from Junsei Chemical Co., Ltd. These reagents were used without additional purification. 6-*p*-Toluenesulfonyl-α-CD[21] and 6-NH_2-α-CD[15] were prepared according to the literature.

*Synthesis of Janus [2]Rotaxanes, **5a** and **5b***

1: 6-NH_2-α-CD (0.49 g, 0.50 mmol) and azobenzene-4,4′-dicarboxylic acid (0.14 g, 0.50 mmol) were dissolved in DMF (50 mL). DCC (0.15 g, 0.75 mmol) and HOBt (0.10 g, 0.75 mmol) were added to the solution with cooling at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred at room temperature for an additional 8 h. The solvent was evaporated

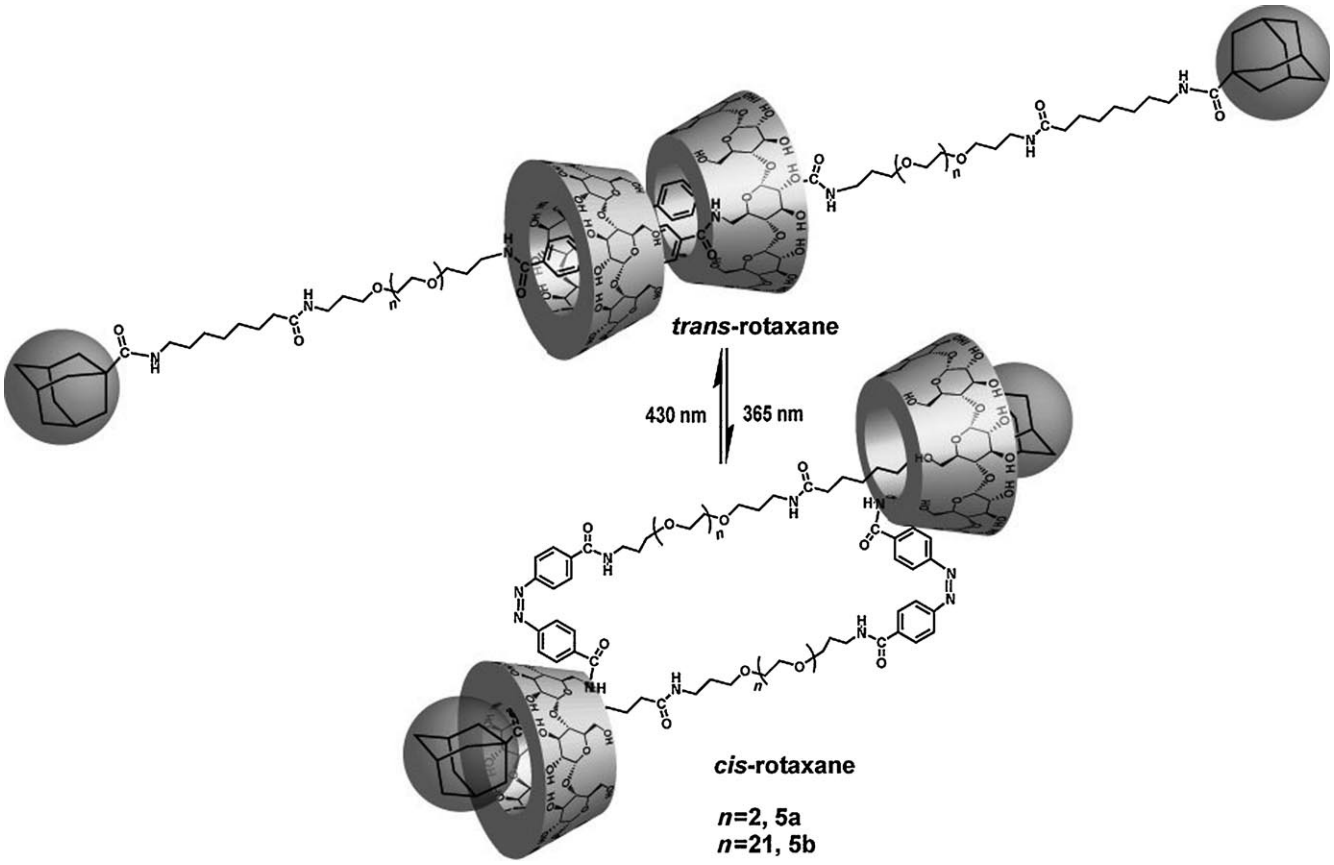


Figure 7. Conceptual illustration of photoresponsive structural changes for the Janus [2]rotaxane of **5a** and **5b**.

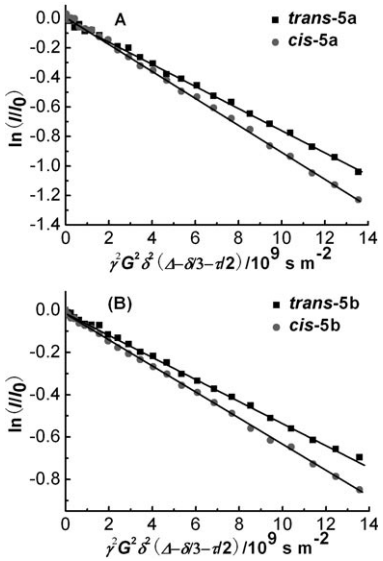


Figure 8. PGSE NMR spectroscopic data for 3.0 mM the *trans–trans* and the *cis–cis* isomers of **5a** (A) and **5b** (B) in D_2O at 30 °C.

and then the residue obtained was dissolved in water. The insoluble solid was filtered off and then the solvent was evaporated under reduced pressure to obtain the crude product. The product, **1**, was purified by liquid chromatography/mass spectrometry (LC/MS) by using a mixed solvent of water and methanol as eluent and recovered by evaporation of the solvent. Yield: 0.23 g, 38%. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 12.1 (s, 1H, COO*H*) 8.55 (t, *J* = 6.0 Hz, 1H, -N*H*-), 8.05 (d, *J* = 8.4 Hz, 2H, Azo-*H*), 7.97 (q, *J* = 6.0 Hz, 4H, Azo-*H*), 7.64 (d, *J* = 8.5 Hz, 2H, Azo-*H*), 5.58–5.40 (m, 12H, O*H* of CD), 4.97 (d, 1H, C(1)*H* of CD), 4.84–4.79 (m, 5H, C(1)*H* of CD), 4.60–4.55 (1H, O*H* of CD), 4.44–4.36 (m, 5H, O*H* of CD), 3.92–3.20 ppm (m, 30H, C*H* of CD). Positive ion MALDI-TOF-MS: *m*/*z* = 1248.6 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{50}H_{69}O_{32}N_3 \cdot 7H_2O$: C 44.48, H 6.20, N 3.11; found: C 44.32, H 6.12, N 3.07.

Table 2. The *D* and R_H values for the *trans–trans* and *cis–cis* isomers of **5a**, **5b**.

Sample	D [10^{-11} m^{2}s^{-1}]	R_H [nm]
trans–trans **5a**	7.5	3.0
cis–cis **5a**	8.7	2.6
trans–trans **5b**	5.1	4.4
cis–cis **5b**	6.2	3.6

2a and 2b: Compound **1** (0.49 g, 0.40 mmol), OEG (DP = 2, 0.2 mL, 2.0 mmol), or OEG (DP = 21, 2.0 g, 2.0 mmol), and BOP (0.50 g, 1.2 mmol) were dissolved in anhydrous DMF (30 mL). TEA (1.4 mL) was added into the solution and the mixture was stirred for 3 days. After evaporation of the solvent, the product, **2a** or **2b**, was purified by LC/MS by using a mixed solvent of water and methanol as eluent and recovered by evaporation of the solvent.

2a: Yield: 0.23 g, 40%. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.63 (t, *J* = 5.3 Hz, 1H, -Azo-N*H*-DEG-), 8.55 (t, *J* = 5.3 Hz, 1H, -CD-N*H*-Azo-), 8.06 (q, *J* = 8.6 Hz, 4H, Azo-*H*), 7.98 (q, *J* = 8.6 Hz, 4H, Azo-*H*), 7.55 (2H, -NH_2), 5.58–5.40 (m, 12H, O*H* of CD), 4.97 (d, 1H, C(1)*H* of CD), 4.84–4.79 (m, 5H, C(1)*H* of CD), 4.60–4.55 (1H, O*H* of CD), 4.44–4.36

(m, 5H, O*H* of CD), 3.92–3.20 (m, -O-CH_2- of DEG, C*H* of CD, -NH-CH_2-CH$_2$-, -CH$_2$-CH_2-NH-), 1.79 (m, J=6.7 Hz, 2H, -NH-CH$_2$-CH_2-), 1.60 ppm (m, J=6.7 Hz, 2H, -CH_2-CH$_2$-NH$_2$). Positive ion MALDI-TOF-MS: m/z=1426.3 $[M+H]^+$.

2b: Yield: 0.32 g 36%. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=8.63 (t, J=5.3 Hz, 1H, -Azo-N*H*-OEG-), 8.55 (t, J=5.3 Hz, 1H, -CD-N*H*-Azo-), 8.06 (q, J=8.6 Hz, 4H, Azo-*H*), 7.98 (q, J=8.6 Hz, 4H, Azo-*H*), 7.55 (2H, -NH_2), 5.58–5.40 (m, 12H, O*H* of CD), 4.97 (d, 1H, C(1)*H* of CD), 4.84–4.79 (m, 5H, C(1)*H* of CD), 4.60–4.55 (1H, O*H* of CD), 4.44–4.36 (m, 5H, O*H* of CD), 3.92–3.20 (m, -O-CH_2- of OEG, C*H* of CD, -NH-CH_2-CH$_2$-, -CH$_2$-CH_2-NH-), 1.79 (m, J=6.7 Hz, 2H, -NH-CH$_2$-CH_2-), 1.60 ppm (m, J=6.7 Hz, 2H, -CH_2-CH$_2$-NH$_2$). Positive ion MALDI-TOF MS (n: the number of ethylene glycol unit in OEG): m/z 2129.7 [M-(n=18)+H]$^+$, 2173.8 [M(n=19)+H]$^+$, 2217.4 [M(n=20)+H]$^+$, 2261.7 [M-(n=21)+H]$^+$, 2305.3 [M(n=22)+H]$^+$, 2349.4 [M(n=23)+H]$^+$, 2393.3 [M-(n=24)+H]$^+$, 2437.3 [M(n=25)+H]$^+$, 2481.1 [M(n=26)+H]$^+$).

4a and 4b: 2a (0.17 g, 0.13 mmol) or **2b** (0.28 g, 0.13 mmol) and Boc-Aoc(8)-OH (0.16 g, 0.60 mmol) were dissolved in DMF (10 mL). DCC (0.036 g, 0.17 mmol) and HOBt (0.024 g, 0.17 mmol) were added to the solution with cooling at 0°C. After stirring for 1 h at 0°C, the solution was stirred at room temperature for an additional 8 h. The solvent was evaporated and then the residue obtained was dissolved in water. The insoluble solid was filtered off and then the crude product, **3a** or **3b**, was recovered by lyophilization from the solution. The crude compound, **3a** or **3b**, was dissolved in an aqueous solution of TFA (H$_2$O/TFA, 1:9 (v/v), 6.0 mL) with cooling at 0°C and stirred for 30 min. The solvent was then evaporated to dryness under reduced pressure. The obtained residue was dissolved in water (10.0 mL), and was neutralized with 0.50 M ammonia solution. The product, **4a** or **4b**, was purified by LC/MS by using a mixed solvent of water and methanol as eluent and recovered by evaporation of the solvent.

4a. Yield: 0.075 g, 40%. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=8.63 (t, J=5.3 Hz, 1H, -Azo-N*H*-DEG-), 8.55 (t, J=5.3 Hz, 1H, -CD-N*H*-Azo-), 8.06 (q, J=8.6 Hz, 4H, Azo-*H*), 7.98 (q, J=8.6 Hz, 4H, Azo-*H*), 7.55 (t, J=5.3 Hz, 1H, -CH$_2$-N*H*-CO-), 5.58–5.40 (m, 12H, O*H* of CD), 4.97 (d, 1H, C(1)*H* of CD), 4.84–4.79 (m, 5H, C(1)*H* of CD), 4.60–4.55 (1H, O*H* of CD), 4.44–4.36 (m, 5H, O*H* of CD), 3.92–3.20 (m, -O-CH_2- of DEG, C*H* of CD, -NH-CH_2-CH$_2$-, -CH$_2$-CH_2-NH-, -(CH$_2$)$_6$-CH_2-NH$_2$), 2.03 (t, J=7.3 Hz, 2H, -CO-CH_2-(CH$_2$)$_6$-), 1.79 (m, J=6.7 Hz, 2H, -NH-CH$_2$-CH_2-), 1.60 (m, J=6.7 Hz, 2H, -CH_2-CH$_2$-NH-), 1.48 (m, J=6.9 Hz, 4H, -CH$_2$-CH_2-(CH$_2$)$_5$- and -(CH$_2$)$_5$-CH_2-CH$_2$-), 1.26 ppm (m, J=6.7 Hz, 6H, -CH$_2$-(CH_2)$_3$-CH$_2$-). Positive ion MALDI-TOF-MS: m/z=1567.6 $[M+H]^+$.

4b. Yield: 0.10 g 35%. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=8.63 (t, J=5.3 Hz, 1H, -Azo-N*H*-OEG-), 8.55 (t, J=5.3 Hz, 1H, -CD-N*H*-Azo-), 8.06 (q, J=8.6 Hz, 4H, Azo-*H*), 7.98 (q, J=8.6 Hz, 4H, Azo-*H*), 7.55 (t, J=5.3 Hz, 1H, -CH$_2$-N*H*-CO-), 5.58–5.40 (m, 12H, O*H* of CD), 4.97 (d, 1H, C(1)*H* of CD), 4.84–4.79 (m, 5H, C(1)*H* of CD), 4.60–4.55 (1H, O*H* of CD), 4.44–4.36 (m, 5H, O*H* of CD), 3.92–3.20 (m, -O-CH_2- of OEG, C*H* of CD, -NH-CH_2-CH$_2$-, -CH$_2$-CH_2-NH-, -(CH$_2$)$_6$-CH_2-NH$_2$), 2.03 (t, J=7.3 Hz, 2H, -CO-CH_2-(CH$_2$)$_6$-), 1.79 (m, J=6.7 Hz, 2H, -NH-CH$_2$-CH_2-), 1.60 (m, J=6.7 Hz, 2H, -CH_2-CH$_2$-NH-), 1.48 (m, J=6.9 Hz, 4H, -CH$_2$-CH_2-(CH$_2$)$_5$- and -(CH$_2$)$_5$-CH_2-CH$_2$-), 1.26 ppm (m, J=6.7 Hz, 6H, -CH$_2$-(CH_2)$_3$-CH$_2$-). Positive ion MALDI-TOF-MS (n: the number of ethylene glycol unit in OEG): m/z 2270.8 [M(n=18)+H]$^+$, 2314.9 [M-(n=19)+H]$^+$, 2358.5 [M(n=20)+H]$^+$, 2402.8 [M(n=21)+H]$^+$, 2446.4 [M-(n=22)+H]$^+$, 2490.5 [M(n=23)+H]$^+$, 2534.4 [M(n=24)+H]$^+$, 2578.4 [M-(n=25)+H]$^+$, 2622.2 [M(n=26)+H]$^+$).

5a and 5b: 4a (70 mg, 45 μmol) or **4b** (108 mg, 48 μmol) was dissolved in an Na$_2$CO$_3$/NaHCO$_3$ buffer solution (0.1 M, 5 mL) with cooling at 0°C and stirred for 1 h to form the doubly threaded dimer. 1-Adamantanecarboxylic acid (18 mg, 90 μmol) and the coupling reagent DMT-MM (25 mg, 90 μmol) were added to the solution. The solution was stirred at 0°C for an additional 8 h and then dialyzed by using a dialysis membrane of a molecular-weight cut off=500 against pure water for 3 days to remove the salt. The crude compound was recovered by freeze drying and the product, **5a** or **5b**, was purified by LC/MS by using a mixed solvent of methanol and water as eluent.

5a. Yield: 49 mg, 32%. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=8.39 (t, J=5.3 Hz, 1H, -Azo-N*H*-DEG-), 8.31 (t, J=5.3 Hz, 1H, -CD-N*H*-Azo-), 7.99 (t, J=7.45 Hz, 2H, Azo-*H*), 7.90 (q, J=7.45 Hz, 2H, Azo-*H*), 7.80 (t, J=6.2 Hz, 2H, Azo-*H*), 7.67 (t, J=6.2 Hz, 2H, Azo-*H*), 7.45 (t, J=5.3 Hz, 1H, -CH$_2$-N*H*-CO-), 7.25 (t, 1H, -CH$_2$-N*H*-CO-Ad), 5.58–5.40 (m, 12H, O*H* of CD), 4.97 (d, 1H, C(1)*H* of CD), 4.84–4.79 (m, 5H, C(1)*H* of CD), 4.60–4.55 (1H, O*H* of CD), 4.44–4.36 (m, 5H, O*H* of CD), 3.92–3.20 (m, -O-CH_2- of DEG, C*H* of CD, -NH-CH_2-CH$_2$-, -CH$_2$-CH_2-NH-, -(CH$_2$)$_6$-CH_2-NH-), 2.02 (t, J=7.3 Hz, 2H, -CO-CH_2-(CH$_2$)$_6$-), 1.95 (m, 3H, Ad-*H*), 1.86 (m, J=6.7 Hz, 2H, -NH-CH$_2$-CH_2-), 1.76–1.57 (m, 14H, Ad-*H*, -CH_2-CH$_2$-NH-), 1.47 (m, J=6.9 Hz, 2H, -CH$_2$-CH_2-(CH$_2$)$_5$-), 1.37 (m, J=6.9 Hz, 2H, -(CH$_2$)$_5$-CH_2-CH$_2$-), 1.23 ppm (m, 6H, -CH$_2$-(CH_2)$_3$-CH$_2$-). Positive ion MALDI-TOF MS: m/z=3482.3 $[M+Na]^+$.

5b. Yield: 69 mg, 30%. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=8.39 (t, J=5.3 Hz, 1H, -Azo-N*H*-OEG-), 8.31 (t, J=5.3 Hz, 1H, -CD-N*H*-Azo-), 7.99 (t, J=7.45 Hz, 2H, Azo-*H*), 7.90 (q, J=7.45 Hz, 2H, Azo-*H*), 7.80 (t, J=6.2 Hz, 2H, Azo-*H*), 7.67 (t, J=6.2 Hz, 2H, Azo-*H*), 7.45 (t, J=5.3 Hz, 1H, -CH$_2$-N*H*-CO-), 7.25 (t, 1H, -CH$_2$-N*H*-CO-Ad), 5.58–5.40 (m, 12H, O*H* of CD), 4.97 (d, 1H, C(1)*H* of CD), 4.84–4.79 (m, 5H, C(1)*H* of CD), 4.60–4.55 (1H, O*H* of CD), 4.44–4.36 (m, 5H, O*H* of CD), 3.92–3.20 (m, -O-CH_2- of OEG, C*H* of CD, -NH-CH_2-CH$_2$-, -CH$_2$-CH_2-NH-, -(CH$_2$)$_6$-CH_2-NH-), 2.02 (t, J=7.3 Hz, 2H, -CO-CH_2-(CH$_2$)$_6$-), 1.95 (m, 3H, Ad-*H*), 1.86 (m, J=6.7 Hz, 2H, -NH-CH$_2$-CH_2-), 1.76–1.57 (m, 14H, Ad-*H*, -CH_2-CH$_2$-NH-), 1.47 (m, J=6.9 Hz, 2H, -CH$_2$-CH_2-(CH$_2$)$_5$-), 1.37 (m, J=6.9 Hz, 2H, -(CH$_2$)$_5$-CH_2-CH$_2$-), 1.23 ppm (m, 6H, -CH$_2$-(CH_2)$_3$-CH$_2$-). Positive ion MALDI-TOF-MS (n: the number of ethylene glycol unit in OEG): m/z 4864.6 [M(n=18)+H]$^+$, 4952.6 [M-(n=19)+H]$^+$, 5039.9 [M(n=20)+H]$^+$, 5128.7 [M(n=21)+H]$^+$, 5217.3 [M-(n=22)+H]$^+$, 5304.1 [M(n=23)+H]$^+$, 5394.5 [M(n=24)+H]$^+$, 5480.7 [M-(n=25)+H]$^+$, 5571.1 [M(n=26)+H]$^+$).

Measurements

The ^{1}H NMR spectra were recorded on a JEOL ECA500 NMR spectrometer. Chemical shifts were referenced to the solvent values (2.49 ppm for DMSO or 4.70 ppm for HOD) at 30°C. 2D NMR (*g*-COSY, TOCSY, HMQC, HMBC, and ROESY) spectra were recorded on a VARIAN INOVA 600 NMR spectrometer at 30°C.

LC–MS experiments were carried out on Waters 2545 and Waters 515 as the binary and makeup pumps equipped with a SunFire Prep C18 OBD column (19×150 mm) by using the gradient program of water and methanol as eluent at a flow rate of 10 mL min^{-1}. Waters SFO and Waters 2767 were used as the switching valve and the injector/fraction collector. 3100 Mass Detector and Waters 2996 Photodiode Array Detector were also used as MS and UV detectors. The LC, MS, and mass-directed fraction collection were controlled by Masslynx version 4.1 with Fractionlynax.

The positive-ion MALDI-TOF-MS experiments were performed by using a Shimadzu/KRATOS Axima CFR Ver.2.2.3 mass spectrometer with dihydroxylbenzoic acid (DHBA) as a matrix.

UV/Vis absorption spectra were recorded on a JASCO V-650 spectrometer with a 1 cm quartz cell at room temperature.

Circular dichroism spectra were recorded on a JACSO J820 spectrometer with a 0.1 cm quartz cell at 30°C.

Photoisomerization

Solutions of compounds **4b**, **5a**, and **5b** were photoirradiated by an Asahi Spectra Compact Xenon Light Source MAX-301. HQBP 365 and HQBP 430 (Asahi Spectra Co.) band-pass filters were used for the wavelengths of 365±10 and 430±10 nm, respectively. The distance between the sample cell and the optical filter was fixed at 1.0 cm.

Determination of Self-Diffusion Coefficients

PGSE NMR spectra were recorded at 600 MHz in D$_2$O on a VARIAN INOVA 600 NMR spectrometer at 30°C. The bipolar pulse pair stimulated echo (BPPSTE) sequence was applied.[22] The strength of pulsed gradients was increased from 6.36×10^{-1} to 43.1 gauss cm^{-1}. The time separation of pulsed field gradients and their duration were 0.10 and 1.0×10^{-3} s,

respectively. The sample was not spun and the airflow was disconnected. The shape of the gradient pulse was rectangular, and its strength varied automatically during the course of the experiments.

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