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Photocontrolled Size Changes of Doubly-threaded Dimer Based on an α-Cyclodextrin Derivative with Two Recognition Sites

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The hydrodynamic size of a doubly-threaded dimer of an α-cyclodextrin (α-CD) derivative bearing two recognition sites, azobenzene (Azo) and heptamethylene moieties (C_7), linked with an oligo(ethylene glycol) chain was controlled by photoisomerization of the Azo moiety.

In biological systems, molecular machines and motors, such as dynein, myosin, and kinesin, play an essential role in maintaining bioactivities.[1] To mimic muscle fibers, the artificial molecular-based muscles and motors, which can convert chemical, electrochemical, and photochemical energies into mechanical motion, have attracted much attention.[2] Since muscle fibers utilize sliding of the components, doubly-threaded dimers are one of promising building blocks for artificial molecular-based muscles. Some attempts to mimic muscle fibers have been reported utilizing bistable doubly-threaded supramolecular dimers of crown ethers[3] or cyclodextrins (CDs).[4] In these previous studies, since the two recognition sites for the host rings are close to each other, it was not possible to observe large size changes. A large size change requires a long linker connecting two recognition sites. In this study, we have thus designed and synthesized an α-CD derivative bearing two recognition sites linked with an oligo(ethylene glycol) (OEG) chain, and observed directly a photocontrolled size change by pulse field gradient spin echo (PGSE) NMR spectroscopy.

The structure of the α-CD derivative **1** designed in this study is shown in Figure 1. Azobenzene (Azo) and heptamethylene (C_7) moieties have been chosen as photoresponsive and nonresponsive recognition sites, respectively. We have chosen these two moieties because the association constant of α-CD for *trans*-Azo is larger than that for C_7 (*trans*-Azo, $K_a = 1 \times 10^4\,M^{-1}$;[5] C_7, $K_a = 100\,M^{-1}$ (Figure S1)),[6] and α-CD does not interact or interacts very weakly with *cis*-Azo,[5] so the recognition site of the α-CD moiety would be switched by photoisomerization of the Azo moiety in **1**. These two recognition sites are connected with a long linker, i.e., OEG with a number-average molecular weight of 1000. These units have been coupled through amide bonds in turn because of the ease of synthesis and the stability of bonding (Scheme S1). As described in Supporting Information, **1** was synthesized in a reasonable total yield (3.3%), and well characterized by ^1H NMR and MALDI-TOF-MS.

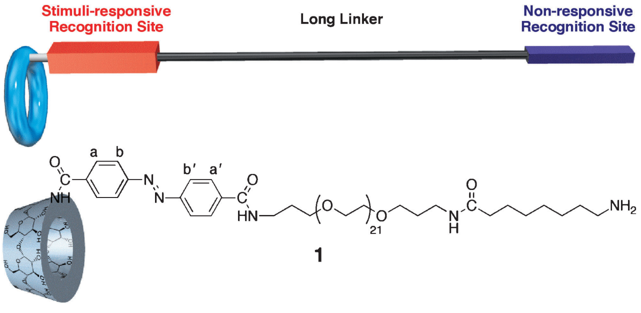

Figure 1. Molecular design and structure of **1**.

As demonstrated in the ROESY spectrum for *trans*-**1** (Figure 2a), the α-CD inner protons show correlation signals with protons of the *trans*-Azo moiety but not with protons of the C_7 moiety. An expanded ROESY spectrum exhibits correlation signals between the C3 protons in α-CD moiety and b proton in the *trans*-Azo moiety and also between the C5 protons in α-CD moiety and b′ proton in the *trans*-Azo moiety (Figure S2).[6] These spectra indicate that the α-CD moiety includes the *trans*-Azo

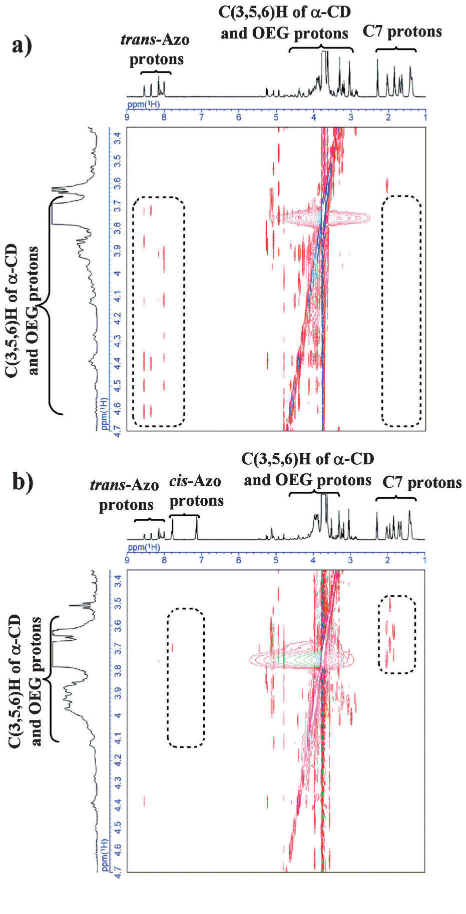

Figure 2. Partial ROESY NMR spectra for *trans*-**1** (a) and *cis*-**1** (b) measured in D_2O at 3.0 mM at 30 °C ($\tau_m = 200$ ms).

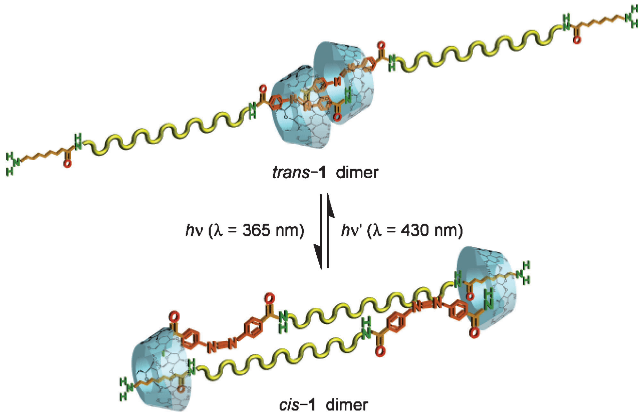

Figure 3. Conceptual illustration of photoresponsive structural change for the doubly-threaded dimer of **1**.

moiety from the secondary hydroxy side, i.e., from the wider rim. The ^{1}H NMR spectra for **1** measured at varying concentrations in D_2O did not show any shifts for the signals with increasing the concentration (Figure S3),[6] ruling out the formation of linear supramolecular oligomers. As discussed in detail later, the self-diffusion coefficient (D) of *trans*-**1** was determined to be $1.5 \times 10^{-10}\,m^2\,s^{-1}$ by PGSE NMR, consistent with the formation of dimer. On the basis of these data, we conclude that *trans*-**1** forms a doubly-threaded dimer in aqueous media (Figure 3).

Trans-**1** was isomerized to *cis*-**1** upon photoirradiation with UV light (365 nm). The *trans*-to-*cis* photoisomerization rate constant was determined to be $8.1 \times 10^{-3}\,s^{-1}$ using absorption spectra under the conditions used (Figures S4 and S5).[6,7] For the sample that reached the photostationary state, ^{1}H NMR spectrum indicated that more than 70% of *trans*-**1** molecules were isomerized to *cis*-**1**. It was also confirmed that *cis*-**1** molecules were also isomerized back to *trans*-**1** upon photoirradiation with visible light (430 nm). These *trans*-to-*cis* and *cis*-to-*trans* photoisomerizations showed a high reversibility as can be seen in Figure S6.[6]

The dimer structure of *cis*-**1** was also investigated by ROESY. The ROESY spectrum for *cis*-**1** indicates that the α-CD inner protons show correlation signals with the C_7 moiety but not with the *cis*-Azo moiety (Figure 2b). These ROESY data led us to conclude that the recognition site of the α-CD moiety is switched by photoisomerization of the Azo moiety in **1**: the α-CD moiety includes the Azo moiety for the dimer of *trans*-**1** whereas the α-CD moiety includes the C_7 moiety for the dimer of *cis*-**1** (Figure 3). This structural change of dimer has been also confirmed by circular dichroism spectroscopy (Figure S7).[6]

The size change between the dimers of *trans*-**1** and *cis*-**1** was confirmed by PGSE NMR. Figure 4 shows the self-diffusion coefficient D as a function of the concentration for **1**. Here the concentration of **1** is the total concentration, and the content of *cis*-**1** was practically constant at ca. 0.7 for all the samples photoirradiated. For both the *trans*-**1** and *cis*-**1**, D exhibits a concentration dependency similar to that for D of poly(ethylene glycol),[8] indicative of no significant dissociation of dimers in this concentration range. By extrapolation of D to zero concentration, D values at zero concentration (D_0) were determined to be 1.5×10^{-10} and $2.0 \times 10^{-10}\,m^2\,s^{-1}$ for the dimers of *trans*-**1** and *cis*-**1**, respectively. Using the D_0 values and the Einstein–Stokes equation,[9] the hydrodynamic radii (R_H) were determined to be 1.6 and 1.2 nm for the dimers of *trans*-**1** and *cis*-**1**, respectively, indicative of a considerable size change. The size change is smaller than the ideal one (ca. 50%) because of the flexibility of the OEG linker but roughly the same as that for natural muscles (ca. 27%).

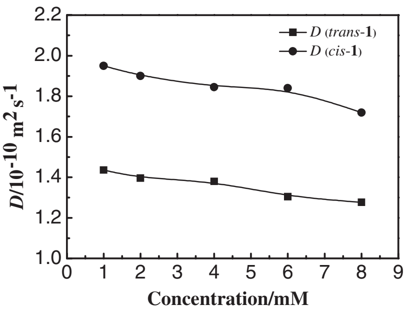

Figure 4. Self-diffusion coefficient (D) as a function of the concentration (1, 2, 4, 6, and 8 mM) for *trans*-**1** and *cis*-**1** measured in D_2O at 30 °C.

In summary, with the aim of constructing a molecular muscle caused by a large size change in a dimer, **1** bearing two recognition sites, the Azo and C_7 sites, connected with an OEG linker was designed and synthesized. Various characterization techniques demonstrated that the recognition site of the α-CD moiety was switched by photoisomerization of the Azo moiety in **1**, causing a considerable change in R_H for the doubly-threaded dimer. Polymer formation and polymer reaction utilizing the terminal amine moieties of **1** are in progress to construct molecular muscle showing macroscopic size changes.

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6 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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9 Hydrodynamic radius (R_H) was estimated by the following equation: $R_H = k_B T/6\pi\eta D$ where η is the viscosity coefficient and k_B is the Boltzmann constant.