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# Contraction of Supramolecular Double-Threaded Dimer Formed by α-Cyclodextrin with a Long Alkyl Chain

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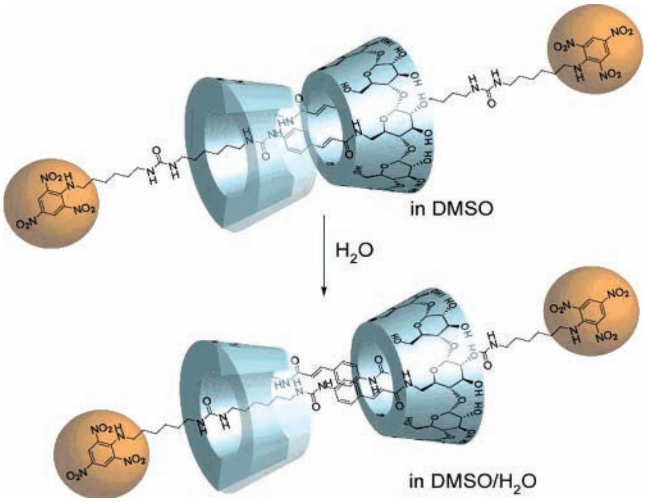
## ABSTRACT



**A double-threaded dimer bearing a long substituent part and a large stopper group has been prepared and showed a conformational change with increased solvent polarity.**

Molecular motors and machines in biological systems, such as dynein, flagellar, myosin, and kinesin, have highly precise structures and achieve controlled movements by external stimuli. Molecular motors in biological systems can be roughly categorized as either linear molecular motors[1] or rotary motors.[2] Recently, the subject of nanoscale artificial molecular muscles and motors has attracted much interest from researchers.[3−5] Sauvage reported that a linear molecular muscle based on transition metal templates showed expansive and contractive properties under the action of a chemical signal.[3] Other notable work concerning linear molecular

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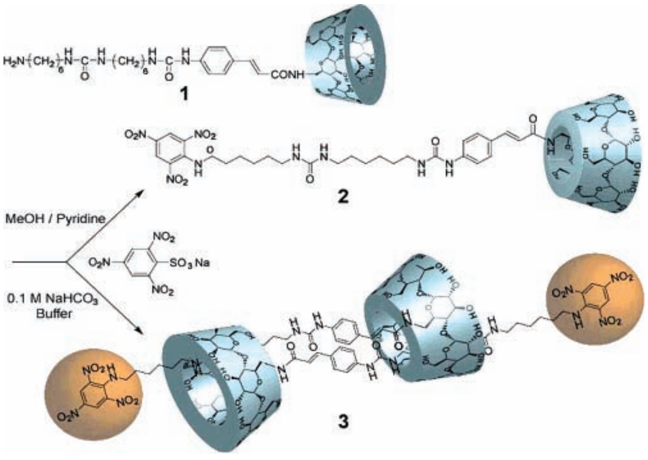
muscles was carried out by Stoddart et al. using palindromic [3]rotaxane with the redox-active tetrathiafulvalene unit and cyclobis(paraquat-*p*-phenylene).[4] These designs have been developed employing a double-threaded dimer, in which the actuation was inspired by natural muscle, such as that of the myosin−actin complex. We previously reported that 6-cinnamamide-α-CD and 6-aminocinnamate-α-CD formed a double-threaded dimer; however, substituent groups on α-CDs are too short to mimic the contraction and extension of skeletal muscle.[6] In this paper, we have prepared a modified 6-aminocinnamamide-α-CD and investigated the formation of the double-threaded dimer. We discuss the conformational change of the double-threaded dimer by increased solvent polarity.

The reaction of **1** with sodium 2,4,6-trinitrobenzene sulfonate (TNBS) in methanol/pyridine at room temperature afforded 6-[4-(6-(6-(2,4,6-trinitroanilino)hexylureido)hexylureido)cinnamamido]-α-CD (**2**) as a model compound in 85% yield because the interaction between the long alkyl chain and α-CD is very weak in organic solvents. The double-threaded dimer (**3**) was prepared in a sodium carbonate buffer at room temperature and confirmed by $^1$H NMR, 2D-ROESY, MALDI-TOF mass, and circular dichroism spectroscopies (Scheme 1).

**Scheme 1**



The $^1$H NMR spectrum of **1** is similar to that of **2**; however, the spectra of **2** and **3** are different in DMSO-$d_6$ (see Supporting Information, Figure S2). Comparing the $^1$H NMR spectra of **2** with that of **3**, the peaks of cinnamamide protons and alkyl protons of **3** shifted to higher magnetic fields (Figure S2c). Moreover, the chemical shift of the end group of **3** exhibited a single resonance, indicating formation of a symmetric supramolecular complex. The MALDI-TOF mass spectrum of **3** showed the dimer species (Figure S3, red line). The peaks of the supramolecular polymers having a degree of polymerization of more than two were not observed. Compounds **1** and **2** showed only the monomer species. On the basis of our $^1$H NMR and MALDI-TOF mass spectra, formation of a double-threaded dimer (**3**) is proposed.

The spectrum of **3** in DMSO-$d_6$ showed the ROE correlation between the protons of the cinnamamide group and protons of α-CD (O(6)-H) and between the hexyl group (the part of **i**) and inner protons of α-CD (C(3)-H and C(5)-H) (Figure 1a). Phenyl protons of the cinnamamide group were not correlated to inner protons of α-CD (C(3)-H and C(5)-H),[7] whereas hexyl protons (the part of **i**) were correlated to

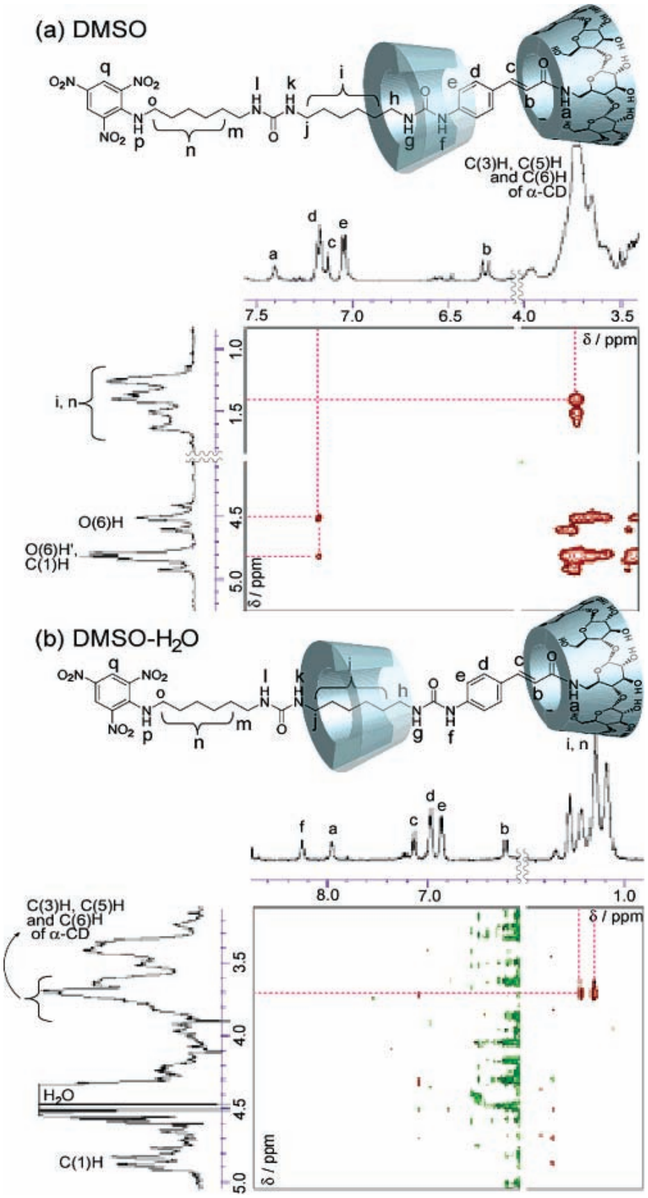


**Figure 1.** ROESY spectra of **3** in (a) DMSO-$d_6$ and (b) DMSO-$d_6$/$H_2O$. To clarify the illustration, another long alkyl chain was omitted.

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inner protons of α-CD in the ratio of $H_2O$/DMSO-$d_6$ = 1:1 (Figure 1b). These results indicate that α-CD moved from the site of the cinnamamide group to that of the hexyl group.

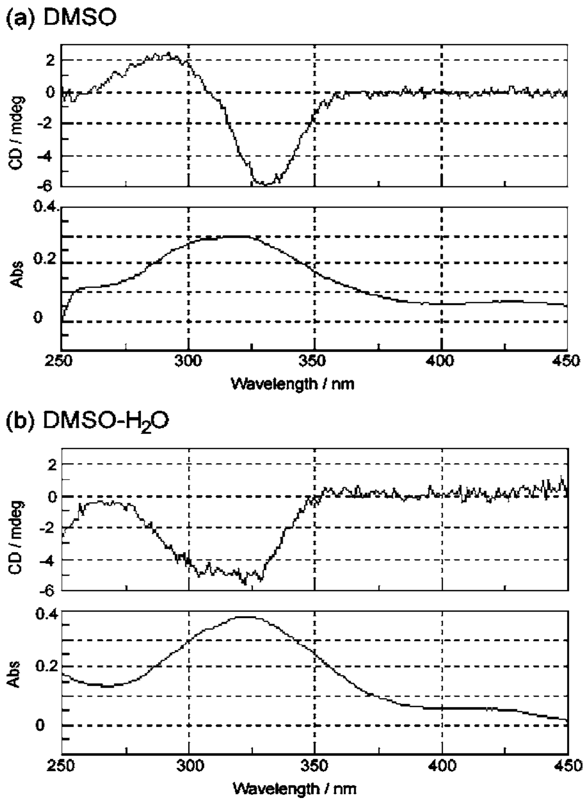

**Figure 2.** Circular dichroism spectra of **3** in (a) DMSO and (b) DMSO/$H_2O$ at 25 °C.

Double-threaded dimer **3** showed a negative exciton coupling at the maximum absorption wavelength of the cinnamamide group (331 nm) in DMSO (Figure 2a). The potential reason for this exciton coupling is that two cinnamamide groups are located in close proximity. However, double-threaded dimer **3** exhibited a negative induced circular dichroism band at 331 nm (no exciton coupling) in 1:1 $H_2O$/DMSO-$d_6$ (Figure 2b).[8] This result indicates that the cinnamamide moiety was located outside the α-CD cavity with an orientation perpendicular to α-CD.[9] The inclusion site of α-CD was found to change with the solvent polarity. Considering the results of our ROESY NMR and circular dichroism spectral data, α-CD of **3** moves to the hexyl site in the axle guest parts in 1:1 $H_2O$/DMSO-$d_6$.

To estimate the size of the double-threaded dimer **3** in DMSO-$d_6$ and $H_2O$/DMSO-$d_6$ (1:1), the pulse field gradient spin−echo (PFGSE) NMR technique was used and the diffusion coefficients ($D$) and hydrodynamic radii ($R_H$)[12,13] of the supramolecular complexes were determined. The apparent volume of double-threaded dimer **3** in DMSO-$d_6$ and $H_2O$/DMSO-$d_6$ (1:1) was 8.142 and 8.641 $nm^3$ in diluted solution (5 mM), respectively. The change of length of **3** is estimated to be about 0.66 nm calculated by molecular modeling. These results are conconsistent with the hydrodynamic radii and indicate that **3** forms a complex with a larger size or a stretched state in $H_2O$/DMSO-$d_6$.

In conclusion, double-threaded dimer **3** bearing a long substituent part and a large stopper group has been prepared. Upon addition of water to a solution of **3**, the conformation of **3** was found to change, as revealed by $^1H$ NMR, ROESY, and circular dichroism spectroscopies. Changes in molecular size as a function of solvent polarity have been demonstrated by PFGSE-NMR. As a general property of CDs, slightly apolar cavity of CD is substituted by nonpolar guest molecules in aqueous media, which are energetically favored.[10−11] On the basis of the characteristics of CDs, we have demonstrated that double-threaded CD dimer (**3**) undergoes a contractile motion when the solvent polarity is increased. We are currently expanding these studies to the synthesis of supramolecular polymers based on double threaded dimer units.

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**Supporting Information Available:** Selected NMR data (1D NMR and ROESY spectrum). This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] The $^1H$ NMR spectrum of (TNA-HUHU-CiNH-α-CD)$_2$ in $D_2O$ was not measured because the solubility of (TNA-HUHU-CiNH-α-CD)$_2$ in $D_2O$ is very low.

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[12] The viscosity of the DMSO/water mixture is necessary to determine the diffusion coefficient. The viscosity of the DMSO/water mixture refers to the following paper. Catalan, J.; Diaz, C.; Garcia-Blanco, F. *J. Org. Chem.* **2001**, *66*, 5846−5852.

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