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A Cyclodextrin-Based Molecular Shuttle Containing Energetically Favored and Disfavored Portions in Its Dumbbell Component

Yoshinori Kawaguchi and Akira Harada*

Department of Macromolecular Science, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

harada@chem.sci.osaka-u.ac.jp

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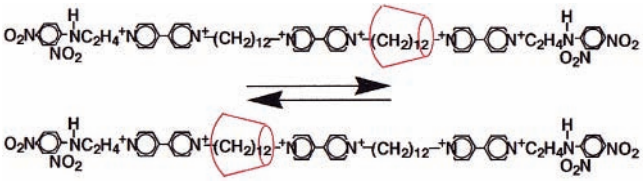
ABSTRACT



A molecular shuttle containing dodecamethylene units, 4,4′-bipyridinium units, and α-cyclodextrin (α-CD) has been prepared. Shuttling behavior is solvent- and temperature-sensitive and could be controlled by double interactions: hydrophobic interaction between a CD ring and a station and a repulsive interaction between a CD ring and a linker. This is a novel method to control the mobility of a bead in a molecular shuttle.

Recently, much attention has been focused on some interlocked molecules, such as rotaxanes, catenanes, and polyrotaxanes, because of their unique structures and properties.[1] One of the characteristic features is exemplified by a molecular shuttle, in which a cyclic molecule (bead) moves back and forth like a shuttle between two or more groups (stations) having noncovalent interactions with a bead. Stoddart and co-workers described the first report of a molecular shuttle.[2] Although there have been some reports on molecular shuttles thereafter,[3,4] those molecular shuttles have been constructed by using noncovalent interactions (π-donor—π-acceptor interactions, metal ion coordination, and hydrogen bonding) between a bead and a station. Here, we report the synthesis of a molecular shuttle containing α-cyclodextrin (α-CD)[5] as a bead and the control of its

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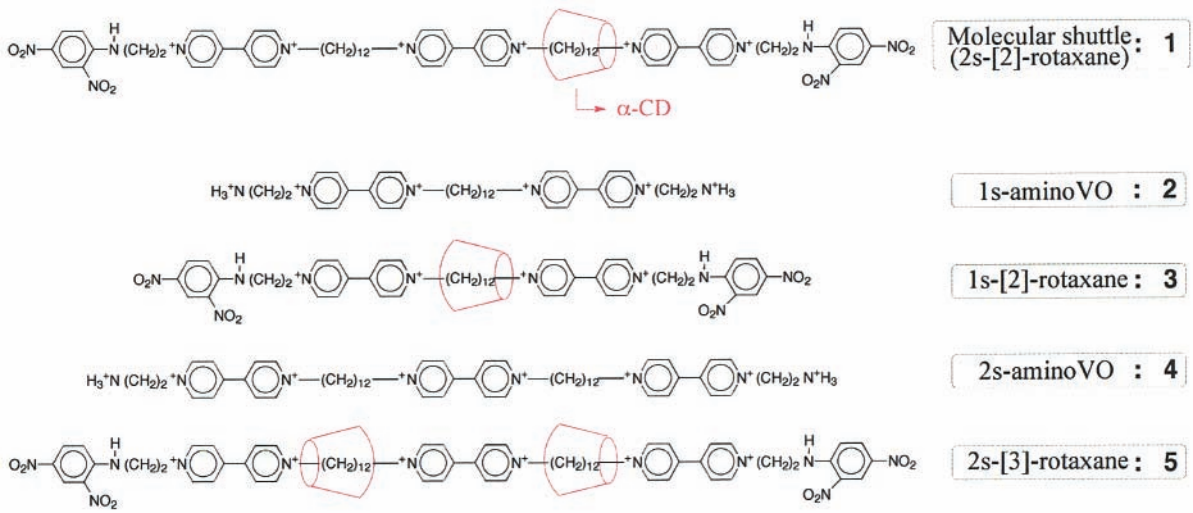


Figure 1. Structures of compounds.

movement by hydrophobic interaction between a CD ring and a station and by a repulsive interaction between a CD ring and a linker, which arises from the fact that cations disfavor a hydrophobic α-CD cavity.

The molecular shuttle **1** (Figure 1) consists of an α-CD ring (shuttle), two dodecamethylene chains (stations), three viologen groups (linkers), and two 2,4-dinitrophenyl groups (bulky end stoppers). First, we prepared a 1s-[2]-rotaxane **3** (here, *n* of *n*s-[2]-rotaxane shows the number of stations in a rotaxane), using inclusion complex formation between α-CD and the dodecamethylene part of end-aminated viologen oligomer (VO) **2** and capping the chain ends with 2,4-dinitro-1-fluorobenzene.[6]

The ^{1}H NMR spectrum of **3** in DMSO-d_6 shows splitting at the methylene region (Figure 2e). Similar spectral changes

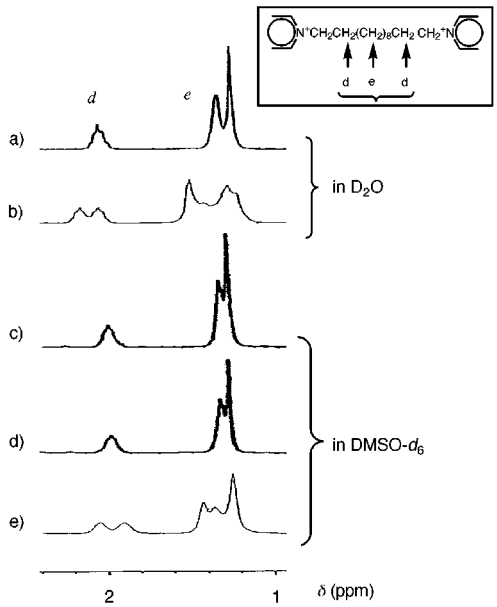


Figure 2. ^{1}H NMR spectra (270 MHz). 1s-AminoVO (**2**) in the absence (a) and presence (b) of α-CD in D_2O at 30 °C. 1s-AminoVO (**2**) in the absence (c) and presence (d) of α-CD in DMSO-d_6 at 30 °C. 1s-[2]-Rotaxane (**3**) in DMSO-d_6 at 30 °C (e).

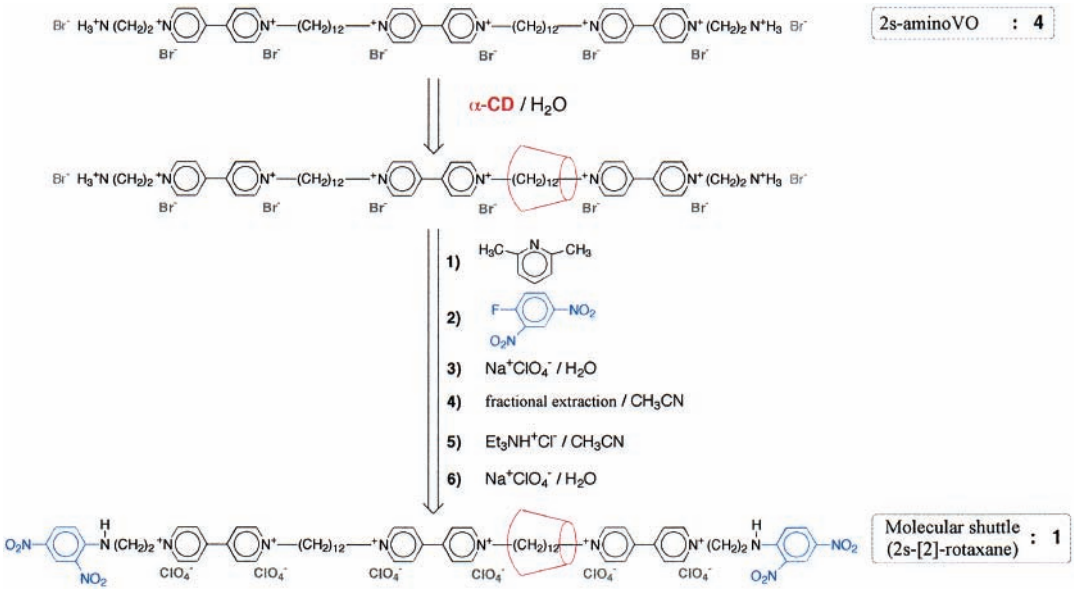
are observed on the addition of α-CD to non-end-capped guest molecule **2** in D_2O (Figure 2a,b), showing the formation of the stable pseudorotaxane containing α-CD and an ionic alkanediyl compound.[7,8] However, the change is not observed in DMSO-d_6 (Figure 2c,d), indicating the inability

(5) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978. (b) Harada, A. In *Large Ring Molecules*; Semlyen, J. A. Ed.; John Wiley & Sons Ltd: Chichester, U.K., 1996; pp 407−432.

(6) **Experimental Procedure.** 1s-AminoVO (**2**) (0.2 mmol) and α-CD (0.6 mmol) were dissolved in water (2 mL) and allowed to stand overnight at room temperature. After the addition of 2,6-dimethylpyridine (4 mmol) to the solution, 2,4-dinitro-1-fluorobenzene (2 mmol) was introduced, and the mixture was stirred for 5 h at room temperature. After the evaporation of this solvent, the residue was washed with diethyl ether and then dissolved in water (300 mL). The addition of an excess amount of sodium perchlorate to the solution caused a precipitate. After the removal of the solvent, the product was collected, washed with water, and dried under high vacuum to give the 1s-[2]-rotaxane (**3**). The yield based on compound **2** was 55%: mp 188−190 °C (dec); UV/vis (in H_2O/DMSO (v/v = 9:1), λ_{max}) 354, 261 nm; IR (KBr) 3317 (vs, ν_{OH}), 3124, 3063, 2929, 2859 (s, ν_{CH}), 1637, 1618, 1590, 1558, 1541, 1522, 1507, 1457, 1339, 1315 (s, m, $\nu_{C=C}$, $\nu_{C=N}$, $\nu_{N=O}$), 1148, 1120, 1108, 1087, 1030 (vs, ν_{C-O}, ν_{CH}) cm^{-1}; ^{1}H NMR (270 MHz, 30 °C, DMSO-d_6 δ 2.5 ppm) δ 9.35−9.24 (m, 8H, α aromatic H in viologen), 8.91−8.84 (m, 4H, amine H and one of phenyl H in stopper), 8.78−8.69 (m, 8H, β aromatic H in viologen), 8.33 (dd, 2H, one of phenyl H in stopper), 7.46 (dd, 2H, one of phenyl H in stopper), 5.79−5.55 (m, 12H, O(2)H and O(3)H of α-CD), 4.92 (br, 4H, α methylene H in ethylene spacer), 4.83 (d, 6H, C(1)H of α-CD), 4.71−4.63 (m, 4H, α methylene H in dodecamethylene station), 4.53 (br, 6H, O(6)H of α-CD), 4.19 (br, 4H, β methylene H in ethylene spacer), 3.82−3.66 (m, 24H, C(3)H, C(5)H and C(6)H of α-CD), 3.44−3.37 (m, 12H, C(2)H and C(4)H of α-CD), 2.05−1.91 (m, 4H, β methylene H in dodecamethylene station), 1.44−1.25 (m, 16H, γ, δ, and ϵ methylene H in dodecamethylene station).

(7) (a) Saito, H.; Yonemura, H.; Nakamura, H.; Matsuo, T. *Chem. Lett.* **1990**, 535−538. (b) Wylie, R. S.; Macartney, D. H. *Supramol. Chem.* **1993**, *3*, 29−35. (c) Gómez-Orellana, I.; Hallén, D.; Stödeman, M. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 3397−3400. (d) Castro, R.; Godínez, L. A.; Criss, C. M.; Kaifer, A. E. *J. Org. Chem.* **1997**, *62*, 4928−4935. (e) Herrmann, W.; Keller, B.; Wenz, G. *Macromolecules* **1997**, *30*, 4966−4972.

Scheme 1. Synthesis of Molecular Shuttle (2s-[2]-Rotaxane, **1**)



of α-CD to form complexes in organic solvents as a result of the lack of hydrophobic interaction. Thus, the splitting of the peaks of **3** in DMSO-d_6 shows that α-CD includes a dodecamethylene part even in organic solvents, indicating that α-CD cannot come out from the rotaxane structure due to the large end-capping groups.

Molecular shuttle (2s-[2]-rotaxane: **1**) was prepared by a method (Scheme 1) similar to that of **3** and purified by fractional extraction using CH_3CN.[9] The ^{1}H NMR spectrum of **1** (in D_2O[10] at 30 °C) (Figure 3a) shows an overlap of a nonincluded part and an included part (split), indicating that one of two dodecamethylene parts in **1** is included by α-CD and the site-exchange process is slow enough to be separately detected by NMR at room temperature. The splitting of the methylene region did not change in the ^{1}H NMR spectra in D_2O at higher temperatures[11] (Figure 3b,c), showing that an α-CD ring stays at one of the dodecamethylene parts on the NMR time scale. It is probably due to the strong hydrophobic interaction between α-CD and a dodecamethylene part.

The ^{1}H NMR spectrum of **1** at the methylene region in DMSO-d_6 at 30 °C also shows the splitting, despite the lack

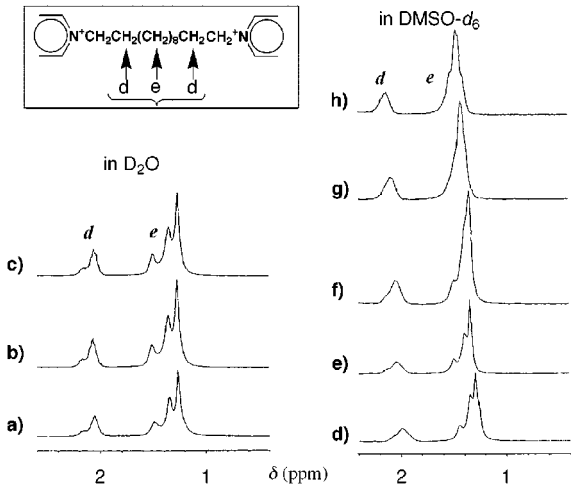


Figure 3. ^{1}H NMR spectra (270 MHz) of molecular shuttle **(1)** in D_2O at 30 (a), 60 (b), and 75 °C (c) and in DMSO-d_6 at 30 (d), 60 (e), 90 (f), 120 (g), and 150 °C (h).

(8) Harada, A.; Adachi, H.; Kawaguchi, Y.; Okada, M.; Kamachi, M. *Polym. J.* **1996**, *28*, 159−163.

(9) **Experimental Procedure.** 2s-AminoVO (**4**) (0.7 mmol) and α-CD (0.8 mmol) were dissolved in water (10 mL) and allowed to stand overnight at room temperature. After the addition of 2,6-dimethylpyridine (10 mmol) to the solution, 2,4-dinitro-1-fluorobenzene (7 mmol) was introduced, and the mixture was stirred for 5 h at room temperature. After the evaporation of the solvent, the residue was washed with diethyl ether and then dissolved in water (500 mL). The addition of an excess amount of sodium perchlorate to the solution caused a precipitate. After the removal of the solvent, the residue was collected and washed with water. It was purified by fractional extraction using acetonitrile. The addition of the excess amount of triethylamine hydrochloride to the acetonitrile solution caused a precipitate as a yellow solid. This product was dissolved in water (25 mL). The addition of an excess amount of sodium perchlorate to the aqueous solution caused a precipitate. After the removal of the solvent, the product was collected, washed with water, and dried under high vacuum to give the molecular shuttle 2s-[2]-rotaxane **1**. The yield based on compound **4** was 11%: mp 187−190 °C (dec); UV/vis (in H_2O/DMSO (v/v = 9:1), λ_{max}) 352, 262 nm; IR (KBr) 3337 (vs, ν_{OH}), 3124, 3063, 2928, 2857 (s, ν_{CH}), 1637, 1618, 1590, 1558, 1541, 1523, 1507, 1456, 1339, 1314 (s, m, $\nu_{C=C}$, $\nu_{C=N}$, $\nu_{N=O}$), 1149, 1120, 1109, 1087, 1031 (vs, ν_{C-O}, ν_{CH}) cm^{-1}; ^{1}H NMR (270 MHz, 30 °C, DMSO-d_6 δ 2.5 ppm) δ 9.36−9.25 (m, 12H, α aromatic H in viologen), 8.90−8.84 (m, 4H, amine H and one of phenyl H in stopper), 8.74 (br, 12H, β aromatic H in viologen), 8.31 (dd, 2H, one of phenyl H in stopper), 7.44 (dd, 2H, one of phenyl H in stopper), 5.79−5.55 (m, 12H, O(2)H and O(3)H of α-CD), 4.91 (br, 4H, α methylene H in ethylene spacer), 4.84 (br, 6H, C(1)H of α-CD), 4.70 (br, 8H, α methylene H in dodecamethylene station), 4.67 (br, 6H, O(6)H of α-CD), 4.19 (br, 4H, β methylene H in ethylene spacer), 3.82−3.66 (m, 24H, C(3)H, C(5)H and C(6)H of α-CD), 3.44−3.37 (m, 12H, C(2)H and C(4)H of α-CD), 2.06−1.92 (m, 8H, β methylene H in dodecamethylene station), 1.44−1.27 (m, 32H, γ, δ and ϵ methylene H in dodecamethylene station).

(10) Product **1** has poor solubility in water. To solubilize in water, we changed the counteranion from perchlorate anion to chloride anion and measured ^{1}H NMR spectra of **1** in D_2O.

(11) Chemical shifts were referenced to internal DMF (δ 2.85) at various temperatures.

of hydrophobic interactions (Figure 3d). The cationic viologen groups are thought to serve as an energy barrier to α-CD for moving because of energetically disfavorable interactions between α-CD and cationic groups. However, these methylene signals become simple at higher temperature[12] in DMSO-d_6 (Figure 3h). These simple signals are time-equilibrated between the two dodecamethylene parts, showing that α-CD quickly shuttles between them. We try to estimate the free energy of activation and the rate of this site-exchange process. It is known that the rate of this site-exchange process (k) at coalescence temperature (T_c) is given by the chemical shift difference between the target split signals ($\Delta\nu$) from[13]

$$k_c = \frac{\pi}{\sqrt{2}}\Delta\nu$$

The free energy of activation for the site-exchange process ($\Delta G^{\ddagger}$) is given by T_c and k_c (k at T_c) from the Eyring equation.[13] T_c is estimated to be 130 °C. From the $\Delta\nu$ values[14] of peak *d* on 1s-[2]-rotaxane **3** and 2s-[3]-rotaxane **5** (Figure 1), k_c is calculated to be about 80 s^{-1}. From the Eyring equation, $\Delta G^{\ddagger}$ is estimated to be about 20 kcal/mol, and k at 30 °C is calculated to be about 0.9 min^{-1}. These values of **1** are summarized in Figure 4. The rate of this site-exchange process in DMSO-d_6 is much slower than the rate of previously reported molecular shuttles[2,3] at room temperature despite the lack of hydrophobic interaction in DMSO-d_6. This is caused by a repulsive interaction between a bead and a linker. The rate of site exchange appears to be slower in D_2O than in DMSO-d_6. This is due to the additional hydrophobic interaction. This result is in agreement with the previously reported results of the viologen polymer/α-CD system.[8]

(12) Chemical shifts were referenced to the solvent value (δ 2.5) at various temperatures.

(13) Values of k_c were obtained by using the approximate expression (Sutherland, I. O. *Annu. Rep. NMR Spectrosc.* **1971**, 4, 71−235), and the Eyring equation

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was used to estimate the $\Delta G^{\ddagger}$ values at T_C and to extrapolate values of k at room temperature. We recognize that many approximations are involved in this semiquantitative treatment, and so the $\Delta G^{\ddagger}$ values should be viewed as having at least 10% error margins.

(14) The $\Delta\nu$ value of peak *d* on 1s-[2]-rotaxane **3** is 35.4 Hz, and that on 2s-[3]-rotaxane **5** is 37.6 Hz.

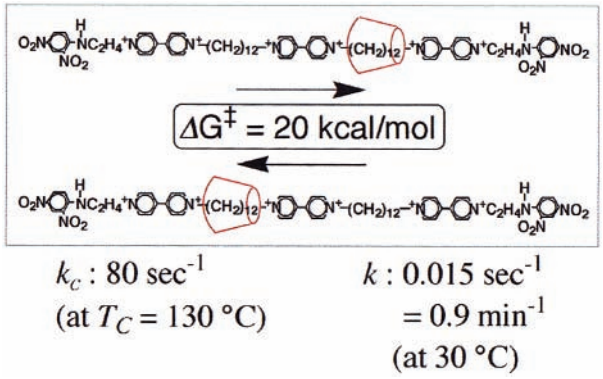

Figure 4. Movement of a bead in **1**.

In conclusion, we have prepared a molecular shuttle **1** based on the complex formation between α-CD and a viologen oligomer. This molecular shuttle is solvent- and temperature-sensitive. Shuttling behavior of **1** is slow as a result of the double interactions; positive interactions with the station and negative interactions with the linker. From these results, the mobility of beads on a molecular shuttle could be controlled by changing an intensity of various interactions between a bead and a linker. This is a novel method to control the mobility of a bead in a molecular shuttle.

Now, we are studying the mobility of a bead in this molecular shuttle and the effects of the counterions and linkers on the mobility of a bead. The details will be published later.

$$k_c = K\frac{k_B T_C}{h}\exp\left(\frac{-\Delta G^{\ddagger}}{RT}\right) \Rightarrow \Delta G^{\ddagger} = 4.57T_C(10.32 + \log(T_C) - \log(K_C))$$

Supporting Information Available: Detailed synthetic protocols for molecular shuttle (**1**) and 1s-[2]-rotaxane (**3**). This material is available free of charge via the Internet at http://pubs.acs.org.

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