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Double-Threaded Dimer and Supramolecular Oligomer Formed by Stilbene Modified Cyclodextrin: Effect of Acyl Migration and Photostimuli

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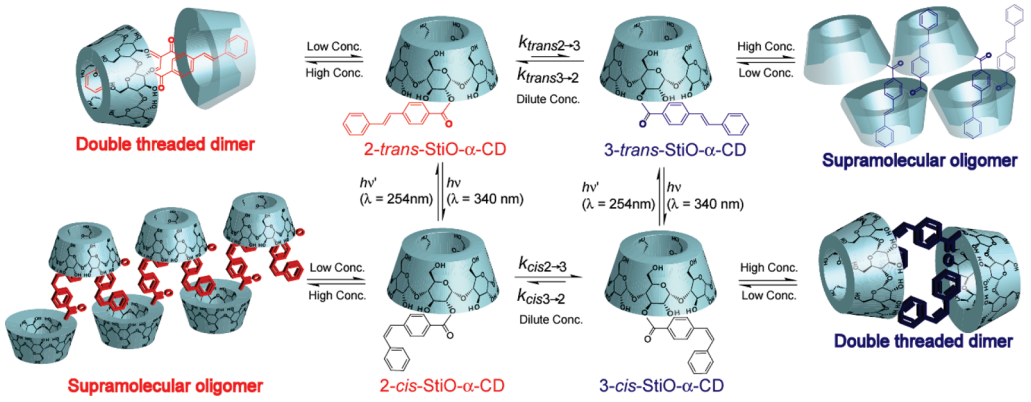

We observed changing supramolecular structures of stilbene-α-cyclodextrin (StiO-α-CD) by photoirradiation and migration. Stilbene derivatives show photoinduced isomerization under irradiation with $\lambda = 340$ nm to give 2-*cis*-StiO-α-CD and with $\lambda = 254$ nm to give 2-*trans*-StiO-α-CD. Photoisomerization of StiO-α-CD shows the photostationary state during 30 min. 2D NMR and diffusion coefficient studies revealed that 2-*trans*-StiO-α-CD forms a double-threaded dimer but 2-*cis*-StiO-α-CD changes to a supramolecular oligomer by photoirradiation. We found that the mutual migration of a stilbene group (StiO) on α-CD occurs under neutral conditions. The StiO group of α-CD (StiO-α-CD) moves between the C2 and C3 positions on the secondary hydroxyl group of StiO-α-CD (the wider rim of α-CD) to give 3-*trans*-StiO-α-CD. 3-*trans*-StiO-α-CD forms a supramolecular oligomer, whereas 3-*cis*-StiO-α-CD changes to a double-threaded dimer, indicating that 3-StiO-α-CDs gives the opposite results in the supramolecular structures of 2-StiO-α-CDs. The thermal isomerization (migration) is very slow. It takes about 300 h to reach the equilibrium state. Moreover, the migration rate constant ($k_{trans3\rightarrow2}$) of the *trans*-StiO group from the C3 position to the C2 position of α-CD is faster than $k_{trans2\rightarrow3}$ from the C2 position to the C3 position of α-CD. On the other hand, $k_{cis2\rightarrow3}$ of the *cis*-StiO group from the C2 position to the C3 position of α-CD is faster than $k_{cis3\rightarrow2}$ from the C3 position to the C2 position, meaning $k_{cis2\rightarrow3} > k_{cis3\rightarrow2}$, which is the opposite result for $k_{trans3\rightarrow2} > k_{trans2\rightarrow3}$. The formation of a stable double-threaded dimer would suppress the migration of the StiO group of StiO-α-CDs in aqueous solutions.

Introduction

External stimuli responsive supramolecular assemblies are expected to serve as remotely actuated nanomaterials[1−5] such as artificial molecular muscles,[6,7] drug delivery systems,[8] biosensors, and shape memory materials. Previously, stimuli responsive supramolecular assemblies[9] have been controlled by chemical,[10] electrical,[11] or photochemical

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stimuli,[12−16] but photostimuli have been widely exploited to modulate the conformation of supramolecular assemblies with photochromic chromophores. Photochromic chromophores can be classified into two types: thermally reversible and photochemically reversible.[17] We have focused on stilbene derivatives as photochemically reversible chromophores. Some stilbene derivatives represent thermally irreversible photochromic compounds, meaning that the geometry of the stilbene derivative depends on the wavelength. Previously, Janus [2]rotaxanes containing CD as a rotor have been reported independently by Kaneda,[18] Easton,[19] and our group.[20] A photoresponsive Janus [2]rotaxane has been reported by Easton and co-workers.[19] They utilized a stilbene moiety as a photoresponsive moiety and demonstrated photoresponsive switching of the location of the α-CD moiety. We have reported the preparation of a double-threaded dimer and supramolecular oligomers with cinnamoyl-α-cyclodextrins (2-CiO-α-CD and 3-CiO-α-CD).[21] However, these supramolecular complexes cannot change the structures by external stimuli. Although the stilbene amide α-CD (3-Sti-α-CDs) achieved the formation of a double-threaded dimer and that of nonthreaded supramolecular self-assembly by photoirradiation with an increase in the concentration,[22] it is still difficult to establish the controlling formation of a double-threaded dimer and supramolecular oligomers. The structure of the supramolecular polymers formed by the stilbene bis(β-CD) dimer with the adamantyl dimer is controlled by an external stimulus. The conformation of the stilbene bis(β-CD) dimer in aqueous solution is photochemically controlled. When the stilbene bis(β-CD) is in trans conformation, a supramolecular dimer is formed in aqueous solution, whereas in its cis conformation of the stilbene bis(β-CD) dimer, supramolecular linear polymers were observed.[23]

Herein, we investigate the reversible structural control of supramolecular complexes with cyclodextrin-stilbene derivatives by photoirradiation because the association constant of α-CD for *trans*-stilbene is larger than that for *cis*-stilbene (*trans*-stilbene, $K_a = 1260\ M^{-1}$; *cis*-stilbene, $K_a = 360\ M^{-1}$).[24] The stilbene (StiO) group was introduced into the secondary hydroxyl group of α-CD through an ester bond as a flexible linker (StiO-α-CDs). Unexpectedly, the StiO group on 2-StiO-α-CDs migrated between adjacent hydroxyl groups to give 3-StiO-α-CDs under neutral conditions. This paper reports the migration and formation of supramolecular complexes with the isomers of StiO-α-CDs (2-*trans*-StiO-α-CD, 3-*trans*-StiO-α-CD, 2-*cis*-StiO-α-CD, and 3-*cis*-StiO-α-CD).

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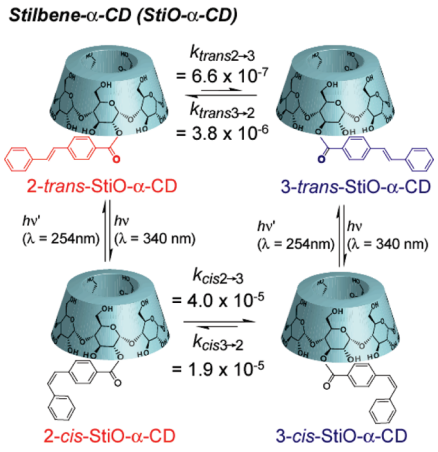

FIGURE 1. Schematic illustration of the isomerization of 2-*trans*-stilbene-α-CD (2-*trans*-StiO-α-CD) and 3-*trans*-StiO-α-CD. Photoirradiation isomerizes *trans*-StiO-α-CDs to *cis*-StiO-α-CDs. StiO groups migrate under neutral conditions. The kinetic rate (k) at 1 mM were described in the scheme.

Results and Discussion

Migration of Acyl-α-CD in D_2O. Figure 1 shows the chemical structure of α-CDs modified with stilbene groups (StiO-α-CD). α-CDs modified with stilbene (StiO) group on the secondary hydroxyl group was prepared by the reaction of succinimidyl-*N*-(4-stilbene carbonyl) with α-CD and sodium hydride in *N*,*N* dimethylformamide (DMF). These products were purified to give 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD (Figure 1), which were separated by reversed phase chromatography.[25] Photoirradiation at λ = 340 nm caused the *trans*-StiO group to isomerize into a *cis*-StiO group, and irradiation at 254 nm recovered from *cis*- to *trans*-forms. After photoirradiation with UV light (λ = 340 nm), 80% of *trans*-StiO-α-CD isomerized to *cis*-StiO-α-CD (*trans*/*cis* = 20:80). Photoisomerization of StiO-α-CD showed the photostationary state by 30 min at 2.1 mM. The mixed isomers were separated by preparative reversed phase HPLC. Figure 2a shows the changes in the ^{1}H NMR spectra of 3-*trans*-StiO-α-CD to 2-*trans*-StiO-α-CD in D_2O (1 mM) at 45 °C. The peak intensities of 3-*trans*-StiO-α-CD decreased with time, while those of 2-*trans*-StiO-α-CD increased to reach a ratio of 4:1 for 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD (Figure 2b). Observation of the migration of 2-*trans*-StiO-α-CD by ^{1}H NMR under the same conditions yielded a ratio of 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD 4:1. Although it is known that silyl groups such as *tert*-butyldimethylsilyl groups migrate between vicinal hydroxyl groups under strong basic conditions,[26−33] it is not known if the acyl groups migrated under neutral conditions. To the best of our knowledge, the mutual migration of an ester group under neutral conditions has yet to be reported.

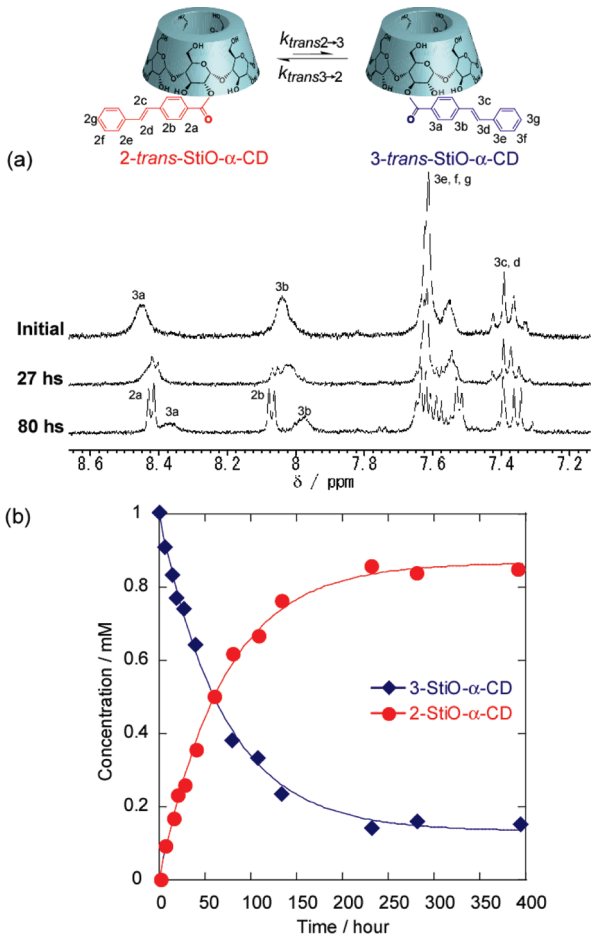

FIGURE 2. (a) Time course of the ^{1}H NMR spectra of the migration from 3-*trans*-StiO-α-CD to 2-*trans*-StiO-α-CD in D_2O (1 mM) at 45 °C. (b) Plots of rate of the StiO-α-CD contents vs time.

TABLE 1. Apparent Migration Rates (k) of StiO-α-CDs at 0.5 and 1.0 mM Aqueous Solutions at 45 °C

		rate constant/s^{-1}	
concentration/mM		*trans*-StiO-α-CD	*cis*-StiO-α-CD
0.5	$k_{2\to3}$	1.6×10^{-6}	-
	$k_{3\to2}$	1.1×10^{-5}	-
1.0	$k_{2\to3}$	6.6×10^{-7}	4.0×10^{-5}
	$k_{3\to2}$	3.8×10^{-6}	1.9×10^{-5}

Figure 1 shows the migration scheme of the StiO groups. Table 1 summarizes the migration rate constants (k) of the StiO group in D_2O, which were very slow. The migration rate constants ($k_{trans2\to3}$) of the *trans*-StiO group from the C2 position to the C3 position of α-CD decreased as the concentration of 2-*trans*-StiO-α-CD increased. The $k_{trans3\to2}$ of

(25) Although three kinds of StiO-α-CD (2-*trans*-StiO-α-CD, 3-*trans*-StiO-α-CD, and 6-*trans*-StiO-α-CD) are prepared by in the mixture of α-CD and Succinimidyl-*N*-(4-stilbene carboxylate), 6-*trans*-StiO-α-CD having the StiO group at the primary hydroxyl group forms little. Main product of the reaction gives 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD because the secondary hydroxyl group forms the hydrogen bond network to activate the nucleophilicity.

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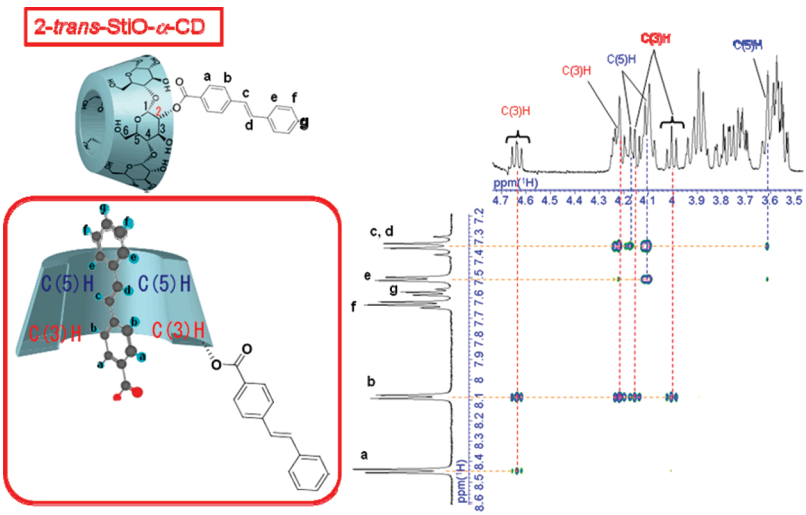

FIGURE 3. The 500 MHz ROESY spectrum of 2-*trans*-StiO-α-CD in D_2O at 25 °C (1 mM, mixing time = 200 ms).

the *trans*-StiO group from the C3 position to the C2 position of α-CD was faster than $k_{trans2\rightarrow3}$ ($k_{trans3\rightarrow2}$ (= 3.8×10^{-6}) > $k_{trans2\rightarrow3}$ (= 6.6×10^{-7})). On the other hand, the migration rate constant ($k_{cis2\rightarrow3}$) of the *cis*-StiO group from the C2 position to the C3 position of α-CD was faster than $k_{trans2\rightarrow3}$, meaning $k_{cis2\rightarrow3}$ (= 4.0×10^{-5}) > $k_{trans2\rightarrow3}$ (= 6.6×10^{-7}). It should be noted that $k_{cis2\rightarrow3}$ was faster than $k_{cis3\rightarrow2}$ of the *cis*-StiO group, meaning $k_{cis2\rightarrow3}$ (= 4.0×10^{-5}) > $k_{cis3\rightarrow2}$ (= 1.9×10^{-5}). The k_{cis} of *cis*-StiO-α-CDs led to the opposite order of k_{trans} of *trans*-StiO-α-CDs as shown in Figure 1.

As shown in Figure 2a, peaks of 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD showed a downfield shift and upfield shift, respectively. We hypothesized that the peak shifts are correlated with the formation of supramolecular complexes. which led to a decrease in the migration rates. The proton of the 2-StiO group showed downfield shift with the complex formation between the hydrophobic α-CD cavity and the StiO group, whereas those of the 3-StiO group showed upfield shift with the dissociation.

Formation of Supramolecular Complexes of *trans*-StiO-α-CDs. 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD were purified by preparative reversed phase HPLC to verify the supramolecular structures from StiO-α-CDs. The 2D ROESY NMR spectrum of 2-*trans*-StiO-α-CD in D_2O (1 mM) indicated that the stilbene proton peaks are correlated with the inner protons (C(3)-H and C(5)-H) of α-CD and the stilbene group is included from the secondary hydroxyl group side (wider rim) (Figure 3). The correlation peaks of the 2D ROESY spectrum of 3-*trans*-StiO-α-CD were similar to those of 2-*trans*-StiO-α-CD (Supporting Information Figure S11). These results confirmed the formation of supramolecular complexes.

The molecular size of the supramolecular complexes from *trans*-StiO-α-CDs was determined using the pulse field gradient spin−echo (PFG) NMR technique to give the diffusion coefficients (*D*). The apparent *D* of supramolecular complexes formed by 3-*trans*-StiO-α-CD (blue ▲) decreased as the concentration increased, and reached 1.7×10^{-10} m^2/s at 40 mM (Figure 4), indicating that 3-*trans*-StiO-α-CD forms a supramolecular oligomer at concentrations above 10 mM in aqueous solutions. Additionally, the molecular size of the supramolecular oligomer depends on the concentration. Our

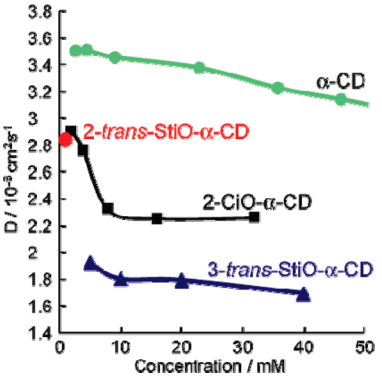

FIGURE 4. Plots of diffusion coefficients (*D*s) of 2-*trans*StiO-α-CD (red •), 3-*trans*StiO-α-CD (blue ▲), and α-CD (green •) in D_2O at 30 °C. Plot (■) shows 2-cinnamoyl-α-CD (2-CiO-α-CD), which formed a double threaded dimer above 10 mM.

previous study on a double-threaded dimer formed by 2-cinnamoyl-α-CD (2-CiO-α-CD; ■) showed a constant value above 10 mM, which reached 2.3×10^{-10} m^2/s at 32 mM.[21] The maximum degree of polymerization for the 3-*trans*-StiO-α-CD was calculated by the following equation, $n_{max} = (KC)^{1/2}$, where *K* is the association constant and *C* is the concentration.[34−40] The association constants (K_a) of α-CD with *trans*-stilbene carboxylic acid sodium salt and *cis*-stilbene carboxylic acid sodium salt as model compounds were estimated by modifying the Benesi−Hildebrand equation.[41] For systems with a 1:1 inclusion complex between the guest and host, α-CD exhibited $K_{tSti} = (1.6 \pm 0.2) \times 10^3$ M^{-1} for *trans*-stilbene carboxylic acid carboxylic acid sodium salt and $K_{cSti} = (2.5 \pm 1.0) \times 10^2$ M^{-1} for *cis*-stilbene carboxylic

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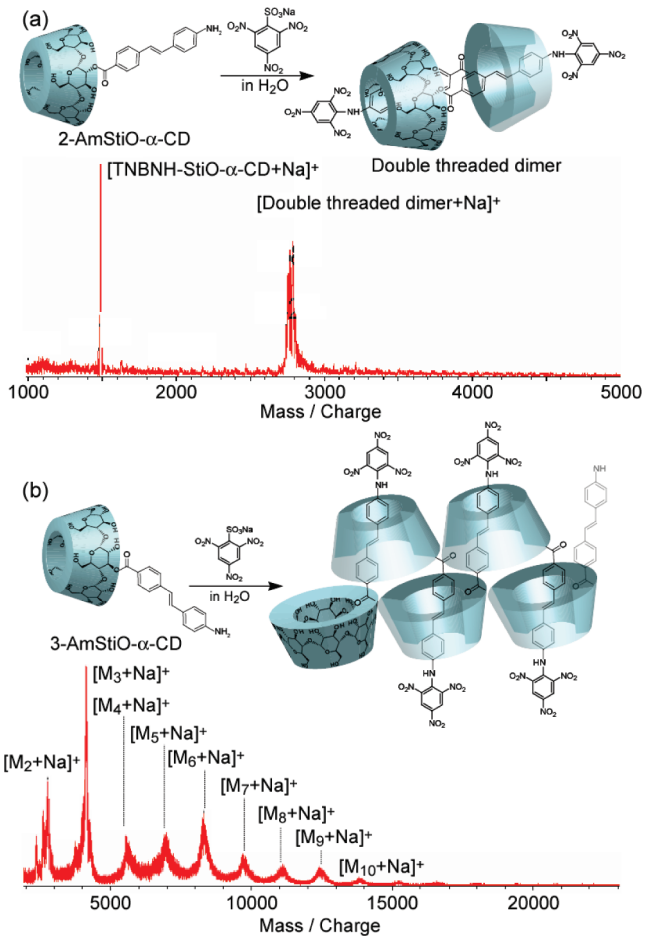


FIGURE 5. MALDI-TOF mass spectra of crude products reacted by (a) 2-AmStiO-α-CD with TNBS Na and (b) 3-AmStiO-α-CD with TNBS Na.

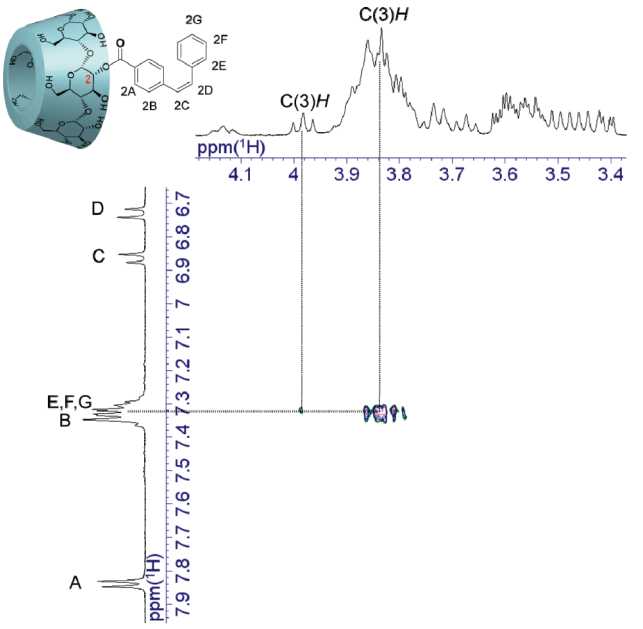


FIGURE 6. 2D ROESY NMR spectrum of 2-*cis*-StiO-α-CD (5 mM) at 20 °C. Spectrum shows the partial area between the inner protons of *cis*-StiO-α-CDs and the stilbene group.

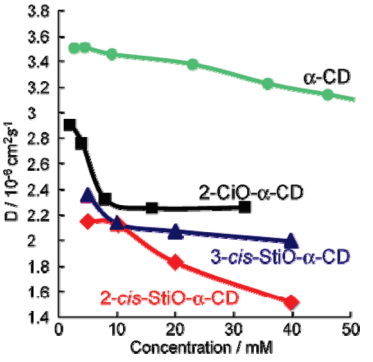


FIGURE 7. Plots of diffusion coefficients (D) of 2-*cis*-StiO-α-CD (red ♦), 3-*cis*-StiO-α-CD (blue ▲), and α-CD (green •) in D_2O at 30 °C. Plot (■) shows 2-cinnamoyl-α-CD (2-CiO-α-CD), which formed a double-threaded dimer above 10 mM.

acid carboxylic acid sodium salt (Figure S28). Using K_{tSti} based on $n_{max} = (KC)^{1/2}$, 3-*trans*-StiO-α-CD formed n_{max} = 8 at 40 mM. The apparent D of supramolecular complexes formed by 2-*trans*-StiO-α-CD was 2.7×10^{-10} m^2/s at 1 mM, whereas the concentration dependency of 2-*trans*-StiO-α-CD for D was not measured because 2-*trans*-StiO-α-CD (red •) was slightly soluble in water and immediately formed a powder crystal above 1.0 mM.

To elucidate the supramolecular structure of 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD in D_2O, we prepared *trans*-StiO-α-CD analogues (2-AmStiO-α-CD and 3-AmStiO-α-CD) with an amino group on the stilbene group, which was attached to the trinitrobenzene group (TNB) that served as a stopper. After the formation of supramolecular complexes with AmStiO-α-CDs in an aqueous solution, these supramolecular complexes were reacted with trinitrobenzene sulfonate sodium salt (TNBS Na) to prevent supramolecular complexes decomposition in organic media and by the laser impacts of MALDI-TOF mass spectrometry. The mass spectrum of 2-AmStiO-α-CD did not display polymeric species, but dimeric species, whereas that of 3-AmStiO-α-CD showed polymeric species (Figure 5). The peak intervals were av 1.4 kDa, which corresponds to the TNB-NH-StiO-α-CD unit. The ^1H NMR spectrum of the double-threaded dimer formed by 2-AmStiO-α-CD did not exhibit complicated peak splitting, indicating that a symmetric structure is formed. As shown above, 2-*trans*-StiO-α-CD and 3-*trans*-StiO-α-CD formed a double-threaded dimer and the supramolecular oligomer, respectively.

Formation of Supramolecular Complexes with *cis*-StiO-α-CDs. We thought that *cis*-StiO-α-CDs would not form supramolecular complexes in aqueous solutions because the association constant (K_{cSti}) of α-CD for *cis*-stilbene carboxylate is $K_{tSti} > K_{cSti}$. However, the 2D-ROESY NMR spectrum of *cis*-StiO-α-CDs in D_2O showed that the edge of *cis*-stilbene protons (E and F) are correlated with the inner protons (C(3)-H) of α-CD (Figure 6 and Supporting Information Figure S33), suggesting that the *cis*-StiO group is shallowly included in the α-CD cavity to form supramolecular complexes. The apparent D of the supramolecular complexes formed by 2-*cis*-StiO-α-CD decreased as the concentration increased, and reached 1.5×10^{-10} m^2/s at 40 mM (Figure 7), indicating that 2-*cis*-StiO-α-CD forms a

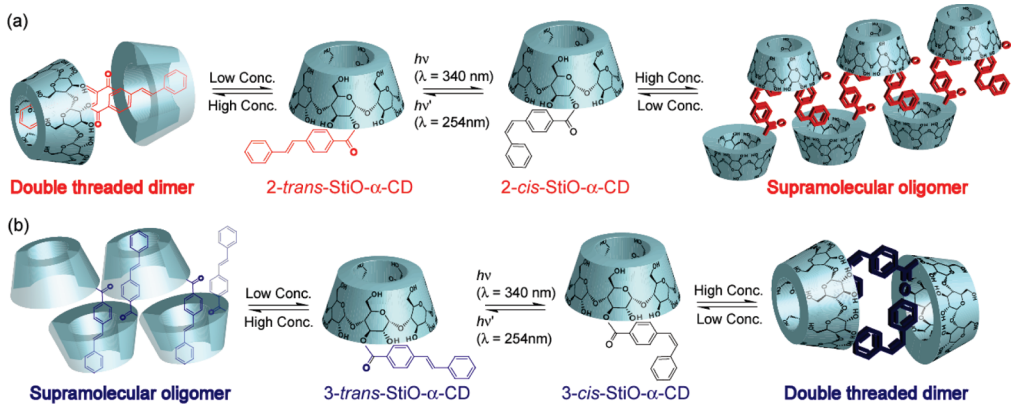


FIGURE 8. Illustration of the formation of supramolecular complexes using StiO-α-CDs.

supramolecular oligomer above 10 mM in aqueous solutions, similar to 3-*trans*-StiO-α-CD (Figure 8a). On the other hand, the apparent *D* of 3-*cis*-StiO-α-CD showed a constant value over 10 mM and reached 2.2×10^{-10} m^2/s at 40 mM, which is similar to the double-threaded dimer formed by 2-CiO-α-CD (Figure 8b). These results indicate that 2-*cis*-StiO-α-CD and 3-*cis*-StiO-α-CD form a supramolecular oligomer and a double-threaded dimer in aqueous solutions, respectively. (Figure 8)

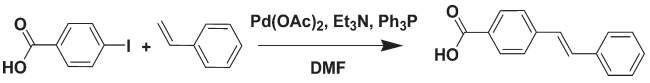
2D NMR and diffusion coefficient studies for StiO-α-CDs confirmed that 2-*trans*-StiO-α-CD forms a double-threaded dimer and 2-*cis*-StiO-α-CD formed a supramolecular oligomer with an increase in the concentration, whereas 3-*trans*-StiO-α-CD surprisingly formed a supramolecular oligomer and 3-*cis*-StiO-α-CD formed a double-threaded dimer, indicating that StiO-α-CDs recognize the structure of guest molecule and the substitutional position of a guest molecule on α-CD.

Conclusion

We successfully prepared a double-threaded dimer and supramolecular oligomer consisting of StiO-α-CDs. Although we initially speculated that 2-*cis*-StiO-α-CD would not form a supramolecular complex, it indeed formed a supramolecular oligomer even though the association constant of α-CD for the *cis*-StiO group is relatively small. The supramolecular oligomer formed by 2-*cis*-StiO-α-CD might be stabilized due to $\pi-\pi$ stacking interactions between the stilbene groups. Interestingly, 3-*trans*-StiO-α-CD formed a supramolecular oligomer, whereas 3-*cis*-StiO-α-CD formed a double-threaded dimer. 2-StiO-α-CD and 3-StiO-α-CD exhibited opposite behaviors in regards to the formation of supramolecular complexes. α-CD accurately recognized the substitution position of the StiO group on a glucopyranose unit as well as the structure of substituent groups. As described previously, $k_{cis2\rightarrow3}$ of the *cis*-StiO group was faster than $k_{trans2\rightarrow3}$ of the *trans*-StiO group, whereas the association constant (K_a) of α-CD for *trans*-stilbene carboxylic acid was larger than that of *cis*-stilbene carboxylic acid ($K_{tSti} > K_{cSti}$). Although $k_{trans3\rightarrow2} > k_{trans2\rightarrow3}$ for the *trans*-StiO group, $k_{cis2\rightarrow3} > k_{cis3\rightarrow2}$ for the *cis*-StiO group. StiO-α-CDs mostly form the monomer or the dimer at 1 mM. The formation of a double-threaded dimer would suppress the migration of the StiO group of StiO-α-CDs in aqueous solutions. Herein, we successfully observed the formation of supramolecular complexes with *cis*−*trans* isomers of StiO-α-CDs, and the acyl migration is intricately interrelated to the formation of supramolecular complexes.

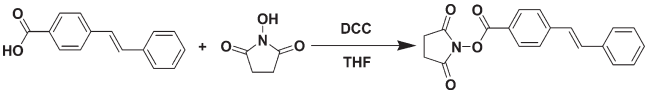
Experimental Section

Preparation of 4-Stilbene Carboxylic Acid.[42]



Styrene (1.7 g, 16 mmol) and 4-iodobenzoic acid (4.0 g, 11 mmol) were dissolved in *N*,*N*-dimethylformamide (DMF; 20 mL) and triethylamine (20 mL). The solution was refluxed in the presence of triphenylphosphine (94 mg, 0.36 mmol) and palladium(II) acetate (67 mg, 0.31 mmol) for 24 h. After removing the solvent, ethyl acetate (200 mL) was added, and the soluble part was washed with three portions of water (60 mL). The organic layer was reprecipitated in hexane (400 mL) to give 4-stilbene carboxylic acid (pale brown powder, 1.6 g, 44%). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 12.8 (br s, 1H, OH), 7.92−7.91 (d, J = 7.8 Hz, 2H, 3-position of stilbene), 7.69−7.67 (d, J = 7.8 Hz, 2H, 2-position of stilbene), 7.64−7.62 (d, J = 7.8 Hz, 2H, 2′-position of stilbene), 7.41−7.38 (t, J = 8.1 Hz, 2H, 3′-position of stilbene), 7.40−7.29 (d, J = 16 Hz, 2H, olefin of stilbene), 7.31−7.28 (m, J = 7.3 Hz, 1H, 4′-position of stilbene). TLC (ethyl acetate/hexane 1:1): R_f = 0.30 (relative to the solvent front). IR (KBr): 3300−2500 (O−H), 1680 (C=O), 1425 (O−H), 1290 (C−O) cm^{-1}. FAB-MS: m/z, 224 (M$^+$), 207, 178, 154, 135, 107. Mp: 254−255 °C. Anal. Calcd for $C_{15}H_{12}O_2 \cdot 0.17H_2O$: C, 79.26; H, 5.47. Found: C, 79.27; H, 5.49.

Preparation of Succinimidyl-*N*-(4-stilbene carbonyl).

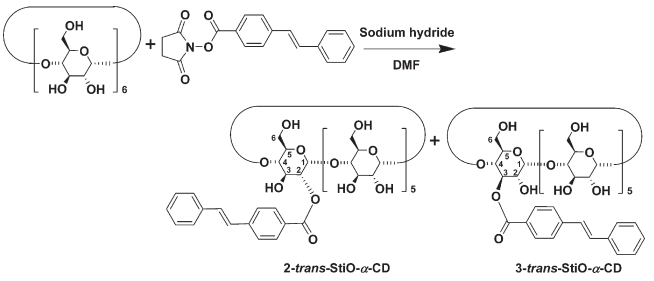


4-Stilbene carboxylic acid (5.1 g, 23 mmol) and *N*-hydroxyl succinimide (3.2 g, 24 mmol) were dissolved in tetrahydrofuran (THF; 150 mL). The solution was cooled to 0 °C, and then *N*,*N*′-dicyclohexyl carbodiimide (DCC; 5.8 g, 28 mmol) was added. The resulting solution was stirred for 24 h. The precipitate was removed via filtration, and the filtrate was evaporated under reduced pressure. The residue was washed with 2-propanol and purified by column chromatography (silica gel, $CHCl_3$) (3.0 g, 42%). ^{1}H NMR (500 MHz, DMSO-d_6, 30 °C) δ_H 8.08 (d, J = 8.5 Hz, 2H, 3-position of stilbene), 7.86 (d, J = 8.5 Hz, 2H, 2-position of stilbene), 7.68 (d, J = 7.4 Hz, 2H, 2′-position of

(42) Nishimura, D.; Oshikiri, T.; Takashima, Y.; Hashidzume, A.; Yamaguchi, H.; Harada, A. *J. Org. Chem.* **2008**, *73*, 2496.

stilbene), 7.53 (d, J = 16.5 Hz, 1H, −C*H*=CH-Ph), 7.40−7.43 (t, J = 7.4 Hz, 2H, 3′-position of stilbene), 7.38−7.42 (d, J = 16.5 Hz, 1H, −CH=C*H*-Ph), 7.33 (t, J = 7.4 Hz, 1H, 4′-position of stilbene), 2.89 (s, 4H, succinimidyl moiety). ^{13}C NMR (125 MHz, DMSO-d_6, 30 °C) δ 170.31 (*C*=O of succinimidyl moiety), 161.47 (−O−*C*=O), 144.02 (*1-Ph*), 136.33 (*1′-Ph*), 132.71 (*4-Ph*), 130.46 (*3-Ph*), 128.79 (*3′-Ph*), 128.54 (−CH=*C*H-Ph-(C=O)), 127.16 (*2′-Ph*), 127.04 (*2-Ph*), 126.87 (*4′-Ph*), 122.76 (−*C*H=CH-Ph-(C=O)), 25.51 (*C*H$_2$ of succinimidyl moiety). Anal. Calcd. for $C_{19}H_{15}NO_4 \cdot 0.04CHCl_3$: C, 70.13; H, 4.65; N, 4.30. Found: C, 70.08; H, 4.67; N 4.36. Mp: 267−268 °C.

Preparation of 4-Stilbene Carbonyl Modified α-Cyclodextrin (StiO-α-CD) at the Secondary Hydroxyl Groups.



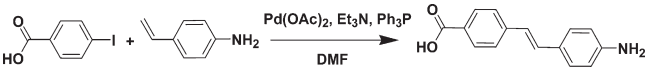
Dried α-CD (0.68 g, 0.70 mmol) was dissolved in 10 mL of dried DMF. Sodium hydride (60% in oil suspension; 29 mg, 0.73 mmol) was added to the solution, which was then stirred for 12 h at room temperature. Succinimidyl-*N*-(4-stilbene carbonyl) (0.24 g, 0.70 mmol) dissolved in 5 mL of dried DMF was gradually added to the α-CD solution while stirring. After 1 h, the solution was poured into acetone (200 mL). The precipitate, which contained two isomers of 4-stilbene carbonyl modified α-CD, was collected by centrifugation and washed with acetone twice. Reverse-phase preparative HPLC was performed to separate the isomers. The resulting precipitate was dissolved in 25 mL of distilled water, and an aliquot of the solution (5.0 mL) was injected onto the HPLC system. Lyophilization of each eluent gave 58 mg of Fraction 1 (the former peak of the two main peaks) and 28 mg of Fraction 2 (the latter peak of the two main peaks). Fractions 1 and 2 were identified as 3-StiO-α-CD and 2-StiO-α-CD, respectively, after characterizing by ^{1}H NMR, ^{13}C NMR, and various 2D NMR (COSY, TOCSY, and HBQC).

Characteristic Data of 2-*trans*-StiO-α-CD. ^{1}H NMR (D_2O, 25 °C, 1 mM, 500 MHz) δ_H 8.45 (d, J = 8.2 Hz, 2H, 3-position of stilbene), 8.08 (d, J = 8.2 Hz, 2H, 2-position of stilbene), 7.63 (t, J = 7.4 Hz, 2H, 3′-position of stilbene), 7.57 (t, J = 7.4 Hz, 1H, 4′-position of stilbene), 7.51 (d, J = 7.4 Hz, 1H, 2′-position of stilbene), 7.30−7.39 (d, 16.4 Hz, 2H, olefin of stilbene), 5.01−5.64 (m, 6H, C1*H* of CD). ^{1}H NMR (DMSO-d_6, 30 °C, 500 MHz) δ_H 8.08 (d, J = 8.5 Hz, 2H, 3-position of stilbene), 7.72 (d, J = 8.5 Hz, 2H, 2-position of stilbene), 7.65 (d, J = 7.4 Hz, 2H, 2′-position of stilbene), 7.38−7.44 (m, 3H, 3′-position and −C*H*=CH-Ph of stilbene), 7.29−7.36 (m, 2H, 4′-position and −CH=C*H*-Ph of stilbene), 5.40−5.70 (m, 11H, O(2, 3)*H* of CD), 4.75−5.14 (m, 6H, C(1)*H* of CD), 3.15−4.67 (m, overlaps with HOD, others of CD). ^{13}C NMR (DMSO-d_6, 30 °C, 125 MHz) δ 165.6 (−O−*C*=O), 141.6 (*1-Ph*), 136.6 (*1′-Ph*), 131.1 (*4-Ph*), 130.2 (−*C*H=CH-Ph), 128.7 (*3,5-Ph*), 128.4 (*3′, 5′-Ph*), 128.2 (4′-Ph), 127.4 (−CH=*C*H-Ph), 126.8, 126.3, 102.2, 102.0, 101.9, 101.8, 98.8, 82.4, 82.2, 82.1, 82.0, 73.7, 73.3, 73.2, 73.1, 72.5, 72.4, 72.2, 72.1, 72.0, 71.7, 69.6, 60.0−59.9 (C(1−6) of CD). MALDI-TOF MS: m/z = 1201.0 ($[C_{50}H_{70}O_{31} + Na]^+$ = 1201.4), 1217.1 ($[C_{50}H_{70}O_{31} + K]^+$ = 1217.1). Anal. Calcd for $C_{50}H_{70}O_{31}(H_2O)_{7.4}$: C, 46.18; H, 6.57. Found: C, 45.84; H, 6.22.

Characteristic Data of 3-*trans*-StiO-α-CD. ^{1}H NMR (D_2O, 25 °C, 5 mM, 500 MHz) δ_H 8.54 (br d, 2H, 3-position of stilbene), 8.09 (br d, 2H, 2-position of stilbene), 7.59 (t, J = 7.4 Hz, 2H, 2′-position of stilbene), 7.54−7.48 (m, 3H, 3′- and 4′-position of stilbene), 7.36 (d, J = 16.2 Hz, 1H, −CH=C*H*-Ph-(C=O)), 7.24 (d, J = 16.2 Hz, 1H, −C*H*=CH-Ph-(C=O)), 6.08 (br, 1H, C(3)*H* of CD), 5.26−4.86 (m, 6H, C(1)*H* of CD), 4.50−3.20 (m, others of CD).

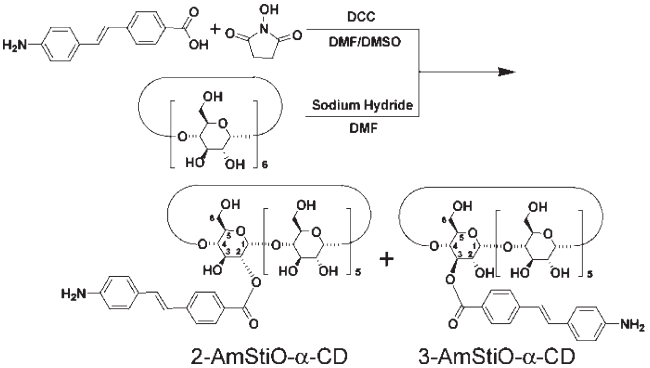
^{1}H NMR (DMSO-d_6, 30 °C, 500 MHz) δ_H 7.95 (d, J = 8.5 Hz, 2H, 3-position of stilbene), 7.69 (d, J = 8.5 Hz, 2H, 2-position of stilbene), 7.64 (d, J = 7.3 Hz, 2H, 2′-position of stilbene), 7.41−7.28 (m, 5H, 3′,4′-position and olefin of stilbene), 5.52−5.23 (m, 11H, O(2, 3)*H* of CD), 4.92−5.71 (m, 6H, C(1)*H* of CD), 4.52−4.42 (m, 6H, O(6)*H* of CD), 3.91−3.06 (m, overlaps with HOD, others of CD). ^{13}C NMR (DMSO-d_6, 30 °C, 125 MHz) δ 165.5 (−O−*C*=O), 140.9 (*1-Ph*), 136.7 (*1′-Ph*), 130.6 (−*C*H=CH-Ph-(C=O)), 130.0 (*4-Ph*), 129.9 (*3-Ph*), 128.8 (*3′-Ph*), 128.1 (*4′-Ph*), 127.6 (−CH=*C*H-Ph-(C=O)), 126.6 (*2′-Ph*) 126.02 (*2-Ph*), 102.2, 102.0, 101.9, 101.6, 82.6, 82.2, 82.1, 81.9, 79.2, 74.9, 73.2, 73.1, 72.8, 72.4, 72.3, 72.2, 72.1, 72.0, 71.9, 71.6, 71.1, 70.9, 60.1, 60.0 (*C*(1−6) of CD). MALDI-TOF MS: m/z = 1201.7 ($[C_{50}H_{70}O_{31} + Na]^+$ = 1201.4), 1217.7 ($[C_{50}H_{70}O_{31} + K]^+$ = 1217.1). Anal. Calcd for $C_{51}H_{70}O_{31}(H_2O)_{8.2}$: C, 46.17; H, 6.56. Found: C, 45.94; H, 6.26.

Preparation of 4-(4′-Aminostilbene) Carboxylic Acid.



4-Vinyl aniline 90% (0.59 g, 4.4 mmol) and 4-iodobenzoic acid (1.1 g, 4.4 mmol) were dissolved in DMF (6.0 mL) and triethylamine (6.0 mL). The solution was refluxed in the presence of triphenylphosphine (12 mg, 0.043 mmol) and palladium(II) acetate (9.9 mg, 0.043 mmol) for 48 h. After removing the solvent, ethyl acetate (100 mL) was added, and the soluble part was extracted with 2 M hydrochloric acid solution (100 mL × 3). Neutralizing the aqueous layer with an aqueous sodium hydroxide solution yielded a precipitate of 4′-aminostilbene-4-carboxylic acid (yellow powder, 0.17 g, 16%). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 12.6 (br s, 1H, OH), 7.87 (d, J = 8.3 Hz, 2H, 3-position of stilbene), 7.58 (d, J = 8.3 Hz, 2H, 2-position of stilbene), 7.31 (d, J = 8.5 Hz, 2H, 2′-position of stilbene), 7.20 (d, J = 16.3 Hz, 1H, −C*H*=CH-Ph-NH$_2$), 6.95 (d, J = 16.3 Hz, 1H, −CH=C*H*-Ph-NH$_2$), 5.44 (s, 2H, NH$_2$). Mp: 292−300 °C dec.

Preparation of 4-(4′-Aminostilbene) Carbonyl Modified α-Cyclodextrin (AmStiO-α-CD) at the Secondary Hydroxyl Groups.



Dried α-CD (0.30 g, 0.31 mmol) was dissolved in 5 mL of dried DMF. Sodium hydride (60% in oil suspension; 12 mg, 0.31 mmol) was added to the solution, which was stirred for 12 h at room temperature. 4-(4′-Aminostilbene) carboxylic acid (73 mg, 0.31 mmol) and *N*,*N*′-dicyclohexyl carbodiimide (DCC; 76 mg, 0.38 mmol) were dissolved in DMF/DMSO = 50/50 (5 mL) and stirred for 24 h at 0 °C. The solution was gradually added to the α-CD solution while stirring. After 3 h, the mixture solution was poured into acetone (150 mL). The precipitate was collected by

centrifugation and washed with acetone twice. Reverse-phase preparative HPLC was performed to separate the isomers. The resulting precipitate was dissolved in 25 mL of distilled water and an aliquot of the solution (5.0 mL) was injected onto the HPLC system. Lyophilization of each eluent gave 59 mg of Fraction 1 (the former peak of the two main peaks) and 27.6 mg of Fraction 2 (the latter peak of the two main peaks). Fractions 1 and 2 were identified as 3-AmStiO-α-CD and 2-AmStiO-α-CD, respectively, after characterization by ^{1}H NMR, ^{13}C NMR, and various 2D NMR (COSY, TOCSY, and HBQC).

Characteristic Data of 2-AmStiO-α-CD. ^{1}H NMR (DMSO-d_6, 30 °C, 500 MHz) δ_H 8.01 (d, J = 8.5 Hz, 2H, 3-position of stilbene), 7.59 (d, J=8.5, 2H, 2-position of stilbene), 7.32 (d, J = 8.6 Hz, 2H, 2′-position of stilbene), 7.22 (d, J = 16.3 Hz, 1H, −C*H*=CH-Ph-NH_2), 6.96 (d, J=16.3 Hz, 1H, −CH=C*H*-Ph-NH_2), 6.57 (d, J=8.6 Hz, 2H, 3′-position of stilbene), 5.69−5.38 (m, 11H, O(2, 3)*H* of CD), 5.12−4.75 (m, 6H, C(1)*H* of CD), 4.57−4.40 (m, 6H, O(6)*H* of CD), 4.65, 4.20, 4.08, 3.84−3.16 (m, overlaps with HOD, others of CD). ^{13}C NMR (DMSO-d_6, 30 °C, 125 MHz) δ 165.7 (−O−*C*=O), 149.3 (*4′-Ph*), 142.0 (*1-Ph*), 131.5 (*4-Ph*), 139.9 (*3-Ph*), 128.6 (−*C*H=CH-Ph-(C=O)), 128.1 (*2′-Ph*), 125.2 (*2-Ph*), 124.3 (*1′-Ph*), 121.7 (−CH=*C*H-Ph-(C=O)), 113.8 (*3′-Ph*), 102.2, 102.1, 102.0, 101.9, 101.6, 82.5, 82.2, 82.1, 81.9, 79.2, 73.2, 73.1, 72.9, 72.4, 72.3, 72.2, 72.1, 71.9, 71.8, 71.6, 71.1, 70.9, 60.1, 60.0, 59.9 (C(1−6) of CD). MALDI-TOF MS: m/z = 1219.5 ($[C_{50}H_{70}O_{31} + Na]^+$ = 1216.4), 1235.6 ($[C_{50}H_{70}O_{31} + K]^+$ = 1232.4). Anal. Calcd for $C_{51}H_{71}NO_{31}\cdot 9.9H_2O$: C, 44.63; H, 6.67; N, 1.02. Found: C, 44.38; H, 6.36; N 1.12.

Characteristic Data of 3-AmStiO-α-CD. ^{1}H NMR (DMSO-d_6, 30 °C, 500 MHz) δ_H 7.89 (d, J = 8.4 Hz, 2H, 3-position of stilbene), 7.56 (d, J = 8.4, 2H, 2-position of stilbene), 7.31 (d, J = 8.5 Hz, 2H, 2′-position of stilbene), 7.20 (d, J = 16.2 Hz, 1H, −C*H*=CH-Ph-NH_2), 6.96 (d, J = 16.2 Hz, 1H, −CH=C*H*-Ph-NH_2), 6.56 (d, J = 8.5 Hz, 2H, 3′-position of stilbene), 5.54−5.26 (m, 11H, O(2, 3)*H* of CD), 4.91−4.71 (m, 6H, C(1)*H* of CD), 4.53−4.42 (m, 6H, O(6)*H* of CD), 3.92−3.07 (m, overlaps with HOD, others of CD). ^{13}C NMR (DMSO-d_6, 30 °C, 125 MHz) δ 165.7 (−O−*C*=O), 149.3 (*4′-Ph*), 142.0 (*1-Ph*), 131.5 (*4-Ph*), 139.9 (*3-Ph*), 128.6 (−*C*H=CH-Ph-(C=O)), 128.1 (*2′-Ph*), 125.2 (*2-Ph*), 124.3 (*1′-Ph*), 121.7 (−CH=*C*H-Ph-(C=O)), 113.8 (*3′-Ph*), 102.2, 102.1, 102.0, 101.9, 101.6, 82.5, 82.2, 82.1, 81.9, 79.2, 73.2, 73.1, 72.9, 72.4, 72.3, 72.2, 72.1, 71.9, 71.8, 71.6, 71.1, 70.9, 60.1, 60.0, 59.9 (C(1−6) of CD). MALDI-TOF MS: m/z = 1217.4 ($[C_{50}H_{70}O_{31} + Na]^+$ = 1216.4), 1234.5 ($[C_{50}H_{70}O_{31} + K]^+$ = 1232.4). Anal. Calcd for $C_{51}H_{71}NO_{31}\cdot 10.6H_2O$: C, 44.23; H, 6.71; N, 1.01. Found: C, 43.91; H, 6.34; N 1.07.

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Supporting Information Available: Typical chromatograms, ^{1}H NMR spectra, ^{13}C NMR spectra, plots of diffusion coefficients, determination of pseudo-first-order rate constants, 2D ROESY NMR spectra, circular dichroism spectra, and determination of association constants. This material is available free of charge via the Internet at http://pubs.acs.org.