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Branched supramolecular polymers formed by bifunctional cyclodextrin derivatives

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ABSTRACT

Branched supramolecular polymers have been prepared from the mixture of 3-cinnamamide-α-CD (**1**) and 3-N^{α}-cinnamamidehexancarbonyl-N^{ε}-cinnamamide-lysinamide-α-CD (**3**) and from the mixture of 3-cinnamamidehexanamide-α-CD (**2**) and **3**. Compounds **1** and **2** formed a linear supramolecular polymer, whereas compound **3** having two guest moieties formed a hyperbranched supramolecular polymer. Physical properties of these supramolecular polymers were studied by viscosity measurements in aqueous solutions. When compound **3** was added to the solution of compound **2**, the η_{sp}/C value of the mixture of **2** and **3** was found to be much higher than that of compound **2**. These results indicate that compound **3** functions as a branching moiety to increase the viscosity. Supramolecular polymers consisting of compound **2** or **3** did not show the viscosity increase, whereas the mixture of **2** and **3** gave highly viscous solutions and formed fibers from the concentrated aqueous solutions. It is caused by the branching of linear supramolecular polymers with compound **3** and hydrophobic and/or hydrogen bonding interactions between supramolecular polymers.

1. Introduction

Supramolecular polymers are ubiquitous in nature. They are used for the formation and the stabilization of more sophisticated supramolecular structures and are considered as key components of functional expression.[1] In recent years, many kinds of artificial supramolecular polymers linked by appropriate interactions including metal coordinations,[2–4] hydrogen bonds,[5–9] and/or hydrophobic interactions[10–12] have been reported by the efforts of synthetic chemists. Previously, we reported the preparation and structures of cyclic tri[2]rotaxanes (daisy chain necklaces)[11a] and linear supramolecular polymers,[10] formed by cyclodextrins (CDs) having a cinnamoyl group (6-CiO-α-CD) and a cinnamamide group (**1**, 3-CiNH-α-CD) as a guest part. However, the viscosity of supramolecular polymers is lower than that expected from the molecular weight of supramolecular polymers. It's considered that the introduction of branching units may lead to higher degree of polymerization and viscous supramolecular systems.[13] Herein, in order to improve the degree of polymerization and the physical properties, we report the preparation of 3-cinnamoylaminohexanamide-α-cyclodextrin (**2**, 3-CiHxNH-α-CD) bearing the hexyl group and 3-N^{α}-cinnamolyaminohexancarbonyl-N^{ε}-cinnamoyl-lysinamide-α-cyclodextrin (**3** 3-N^{α}-CiHxNH-N^{ε}-CiNH-lysNH-α-CD) bearing two guest parts, as shown in Figure 1. We found that the mixture of **3** with **1** and **3** with **2** gave highly viscous solution and formed fibers from the solution. This is the first example of the formation of fibrous materials from the CD-based supramolecular polymers.

2. Results and discussion

2.1. Preparation of 2 and 3

α-CD derivatives were prepared by the reaction of mono-3-deoxy-3-amino-α-CD (3-NH_2-α-CD) with cinnamoylaminohexanoic acid (CiHexOH) or N^{α}-cinnamoylaminohexancarbonyl-N^{ε}-cinnamoyl-lysine (N^{α}-CiHex-N^{ε}-CiNH-lysine) in dimethylformamide (DMF), respectively, using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (1-HOBt) (Scheme 1). Compound

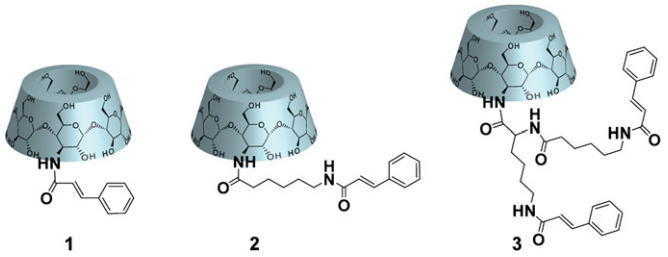

Figure 1. Chemical structures of 3-cinnamamide modified α-CDs.

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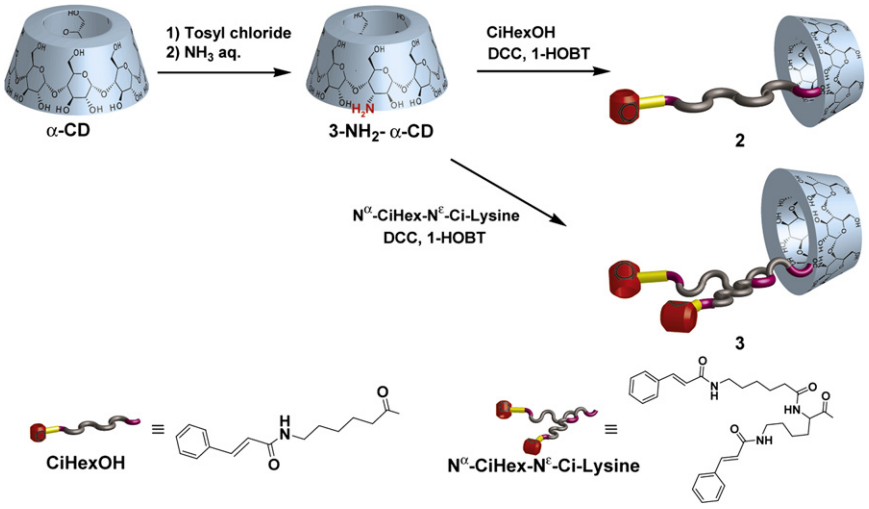

Scheme 1. Preparation of **2** and **3**.

2 has a cinnamamide moiety as a guest and a pentyl moiety as a spacer, whereas **3** has two cinnamamide moieties, which can be included by other α-CDs. Compound **1** was prepared according to the literature.[11c]

2.2. Formation of homo-supramolecular complex consisting of 2 or 3

Figure 2 shows ^{1}H NMR spectra of compounds **2** and **3** under various concentrations. Aromatic protons of the cinnamamide groups shifted upfield with an increase in the concentration, indicating that **2** and **3** formed intermolecular complexes. Figure 3 shows ROESY NMR spectra of compounds **2** and **3**. Cinnamamide protons correlated with inner protons (C(3)–*H* and C(5)–*H*) of α-CD. The inner proton C3(H) of α-CD, which is located in the secondary hydroxyl side (wider rim), showed the ROE correlations with aromatic protons (a, b, a′, and b′), whereas C3(H) did not show any correlation peaks with double bond protons (c, d, c′, and d′). On the other hand, the inner proton C5(H) of α-CD, which is located in the primary hydroxyl side (narrow rim), showed the ROE correlations with both aromatic protons and double bond protons. These observations suggested that cinnamamide groups were included in other α-CD cavities from the primary hydroxyl side to form the head to tail type supramolecular complexes.

Electrospray ionization (ESI) mass spectrometric measurement was also performed to make sure of intermolecular complexation and to investigate the molecular weight of supramolecular complexes. Figure 4 shows mass spectra of compounds **2**, **3**, and the

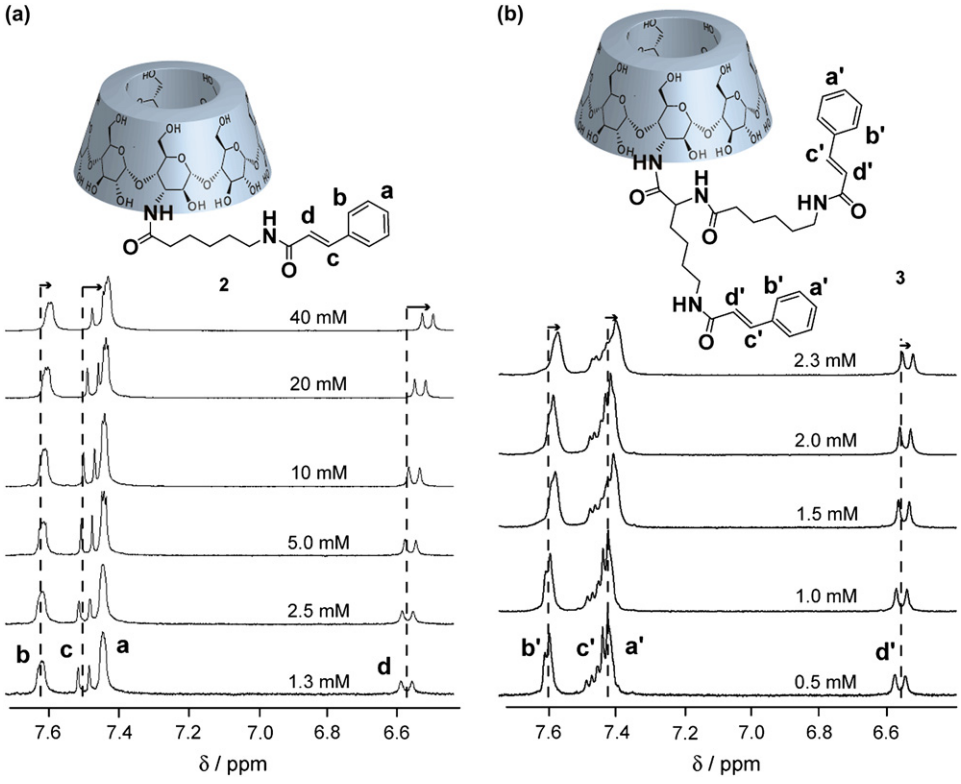

Figure 2. Partial ^{1}H NMR spectra of compounds **2** (a) and **3** (b) under various concentrations in D_2O.

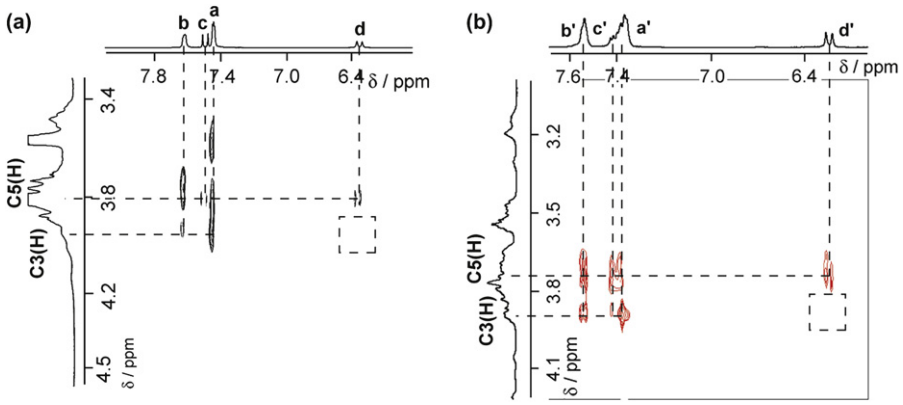

Figure 3. Partial ROESY spectra of compounds **2** (a) and **3** (b) in D_2O.

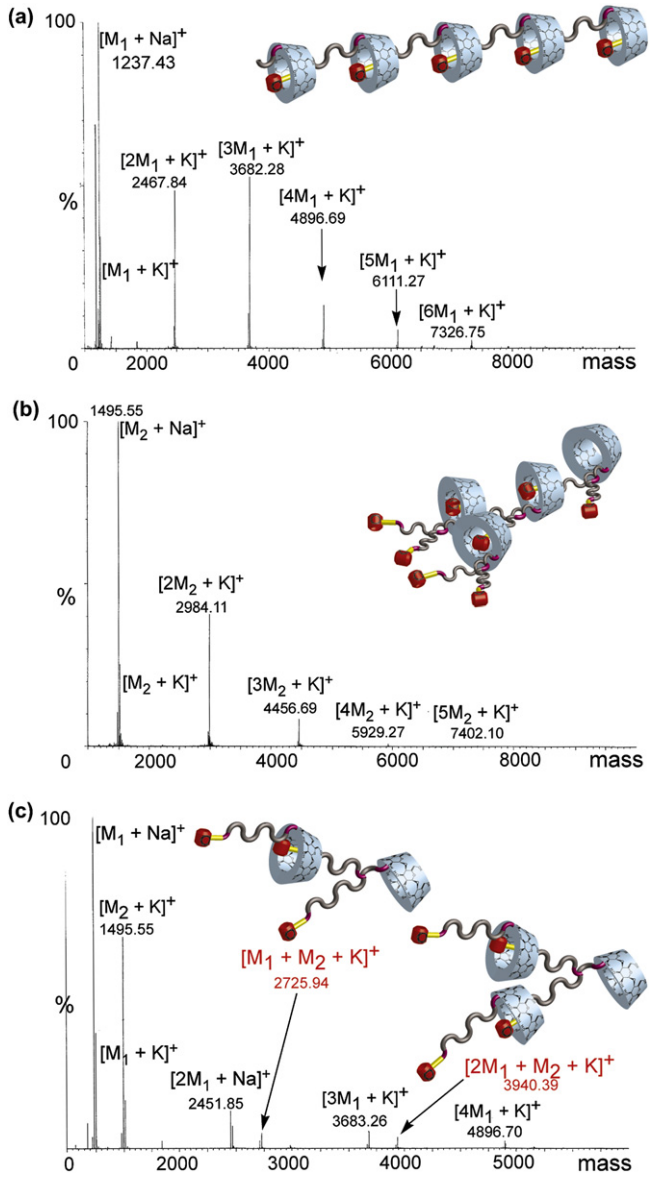

Figure 4. ESI-TOF mass spectra of compounds **2** (a), **3** (b), and the mixture of **2** and **3** (c).

mixture of **2** and **3**. Each signal was observed as the species of the potassium cation adducts. The spectra of compounds **2** and **3** showed polymeric species up to approximately 5-mer (Fig. 4a and b). The interval between signals corresponds to the molecular weight of each modified α-CD as a monomer unit. On the other hand, the spectrum of the mixture of **2** and **3** showed both homo-type and hetero-type complex signals ($[M_1+M_2+K]^+$ and $[2\,M_1+M_2+K]^+$) as shown in Figure 4c. Considering the chemical structures of compounds **2** and **3**, compound **2** formed linear-type supramolecular complex and compound **3** formed hyperbranched-type supramolecular complex. ESI-TOF mass spectrum of the mixture of **2** and **3** indicated the formation of hetero-type supramolecular complex.

2.3. Formation of hetero-supramolecular complex consisting of 2 and 3

The ^1H NMR spectra of the mixture of **2** and **3** showed that the protons of cinnamamide groups of compound **3** shifted upfield significantly with an increase in the molar ratio of compound **3** (Fig. 5). These results indicate that the mixture of **2** and **3** formed hetero-type supramolecular complexes in aqueous solutions.

2.4. Viscosity and molecular size of supramolecular polymers

The physical properties of the supramolecular polymers formed by 3-cinnamamide-α-CDs (**1**–**3**) were investigated by the viscosity measurement under semidilute conditions. The η_{sp}/C values of **1** and **2** moderately increased with an increase in the concentration and reached 2.6 $cm^3\,g^{-1}$ and 3.3 $cm^3\,g^{-1}$ at 53 mM, respectively, as shown in Figure 6. These results indicate that **1** and **2** formed linear supramolecular polymers at high concentrations. However, the η_{sp}/C value of compound **3** was too low to be measured[14] because of the low solubility in water. We suppose that the low solubility of **3** is caused not only by the effect of the hydrophobic guest group but also by the formation of the rigid supramolecular structure. It should be noted that compound **3** was easily solubilized in 20 mM aqueous solutions of compound **2**, which reached the saturated concentration at 14.1 mM. Mixtures of **2** and **3** showed a significant increase in the viscosity with an increase in the molar ratio of compound **3**. The η_{sp}/C value of the mixture of **2** and **3** (molar ratio, **3**/**2**=0.7) is 1.4 times larger than that of compound **2** at 34.1 mM. Compound **3** affects the elevation of viscosity of aqueous solutions, which was caused by the formation of hetero-type (branched) supramolecular complex. In a concentrated solution, the mixture exhibits the thread-forming property and freestanding fiber was formed by wet spinning. In contrast, compound **2** did not show such properties.

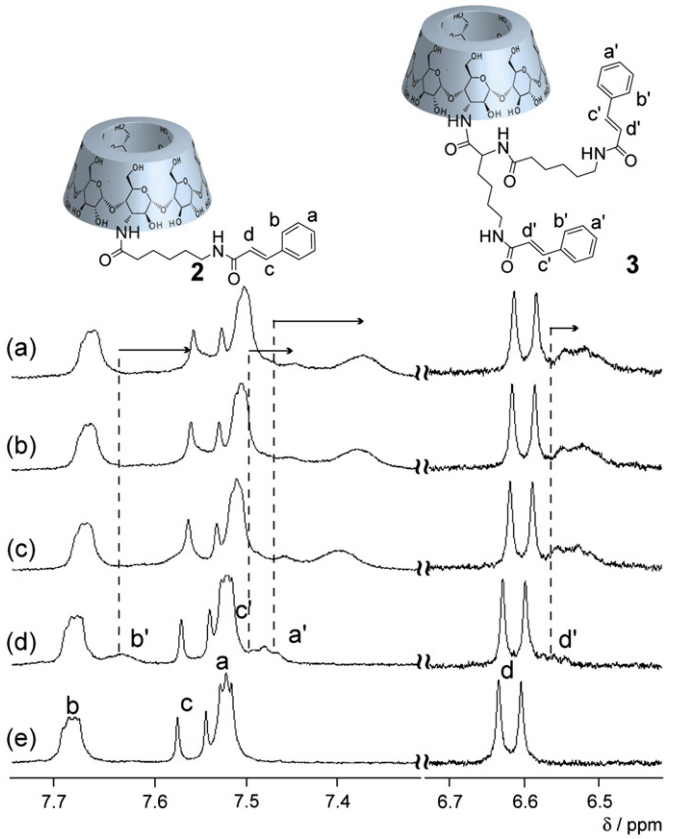

Figure 5. Partial ^{1}H NMR spectra of **2** (20 mM) with **3** at 14.1 mM (a), 11.7 mM (b), 7.1 mM (c), 2.4 mM (d), and 0 mM (e) in D_2O at 30 °C.

To estimate the hydrodynamic radius (R_h) of the supramolecular complex from **1** with **3**, and from **2** with **3**, pulsed field gradient (PFG) spin-echo NMR measurements were carried out.[15] The apparent diffusion coefficients (D_s) of the mixture significantly decreased with an increase in the molar ratio of **3**, reaching 1.8×10^{-6} cm^2 s^{-1} (R_h=1.3 nm) at 34 mM, while the D_s of **2** decreased slightly. It should be noted that the hydrodynamic volumes of supramolecular complexes from compound **2** with **3** are larger than that of the supramolecular complexes from compound **2**. These results are in agreement with the data of the viscosity measurements. Compound **3** plays an important role in the formation of larger supramolecular complexes as a branching point in the mixture of **2** and **3**.

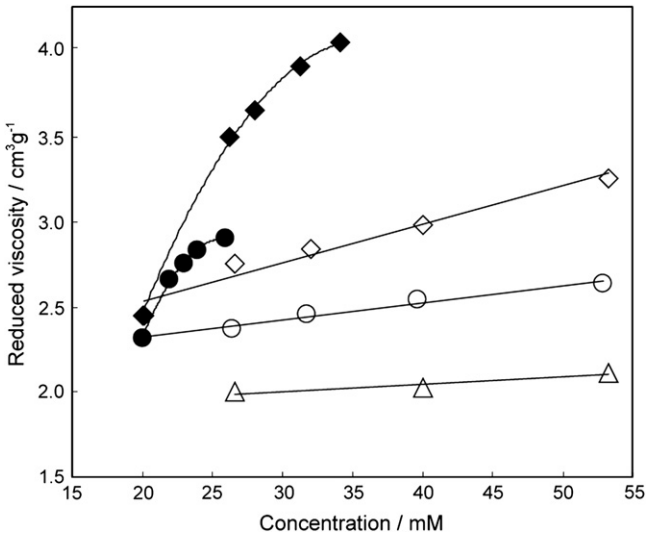

Figure 6. Reduced viscosities of α-CD (triangle), **1** (open circle), **2** (open rhombic), the mixture of **1** with **3** (filled circle), and the mixture of **2** with **3** (filled rhombic) in H_2O at 25 °C.

2.5. Formation mechanism of branched supramolecular polymers

The association constants (K) were determined by UV–vis absorption spectroscopy.[16] The model system of compounds **2** and **3** has K_{11}, K_{21}, and K_{22}, which were determined to be 5.7×10^2 M^{-1}, 5.8×10 M^{-2}, and 5.6 M^{-1}, respectively ($K_{11}>K_{21}$, K_{22}). These results suggest that the supramolecular complexes from the mixture of **2** and **3** mainly consist of compound **2**. Compound **3** was solubilized in the solution of compound **2**, and then compound **2** forms branched supramolecular complex including guest groups of compound **3**. It should be noted that the viscosity transcends the estimated results from association constants of model system.[17] These results suggest that the other interactions as well as inclusion effects of α-CD cavities have an influence on the formation of the supramolecular polymer. On the basis of these data, we represented the proposed structures of branched supramolecular polymer (Fig. 7). The size of the branched supramolecular polymer is larger than the expected value from assembly constants of model systems. We supposed that supramolecular polymer was formed not only through the formation of intermolecular inclusion complexes but also through aggregations by intermolecular interactions such as hydrophobic interactions and/or hydrogen bonds. Supramolecular

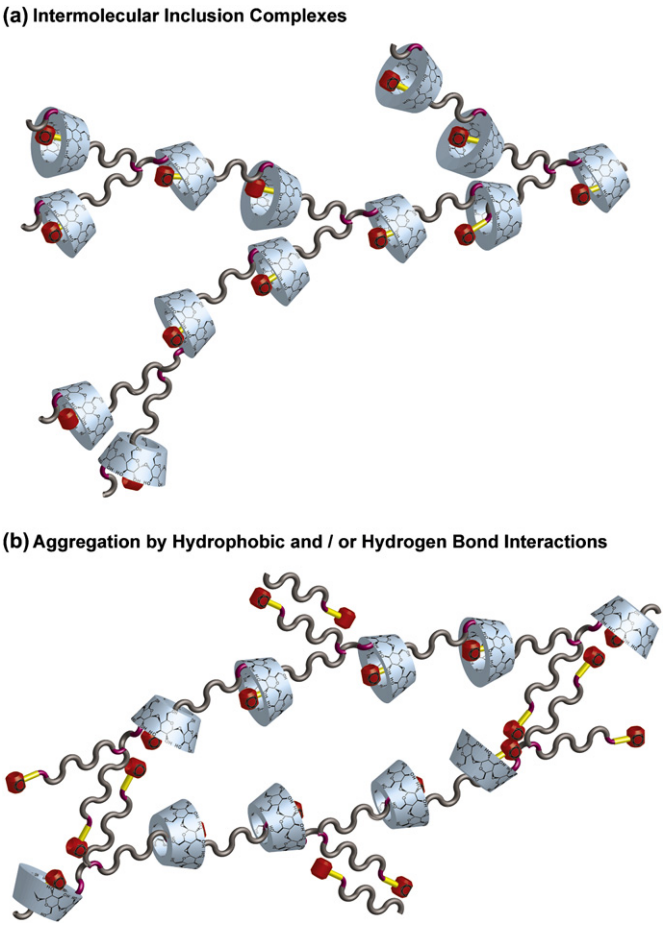

Figure 7. Schematic illustration of branched supramolecular polymers formed by **2**–**3** complexes in aqueous solutions.

complexes are able to interact with the other polymer chains through non-included guest parts in aqueous solutions, especially, at high concentrations since compound **3** consists of one host moiety and two guest moieties.

3. Conclusion

We investigated the formation behavior of branched supramolecular polymers consisting of the complex of **1**–**3**. Compounds **1**–**3** were found to form linear-type and hyperbranched-type supramolecular complexes in the aqueous solutions. The mixture of **1** and **3** and that of **2** and **3** formed viscous supramolecular polymers, which exhibit polymer-like properties in concentrated solution. Their properties were caused by branching of linear supramolecular polymer through the formation of hetero-type inclusion complex and hydrophobic interactions and/or hydrogen bond.

4. Experimental section

4.1. General

The ^{1}H NMR spectra were recorded on JEOL JNM EX-270 and JEOL JNM LA-500 NMR spectrometers at 30 °C. Chemical shifts were determined with reference to solvent values (δ 2.49 ppm for DMSO-d_6 and δ 6.45 ppm for D_2O). The 2D NMR and pulsed field gradient spin-echo (PFGSE) NMR experiments were performed with D_2O as the solvent at 30 °C on a VARIAN-INOVA-600 NMR spectrometer. The preparative reversed phase chromatography was carried out with a Waters Delta 600 system (column: SunFireTM Prep C18 19×150 mm). Positive-ion matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry experiments were performed using a Shimadzu/KRATOS Axima CFR Ver.2.2.3 mass spectrometer calibrated by α-cyano-4-hydroxycinnamic acid and insulin. Electrospray ionization mass spectrometric experiments were performed by using a JASCO Q-Tof Premier system mass spectrometer.

4.2. Materials

α-CD was obtained from Junsei Chemical Co., Ltd. *trans*-Cinnamoyl chloride, *N*-hydroxysuccinimide, palladium carbon, ammonium formate, 6-aminohexanoic acid, DCC, 1-HOBt, DMF, and sodium hydroxide were obtained from Nacalai Tesque Inc. *Z*-6-Aminohexanoic acid N^{ε}-*Z*-L-lysine benzyl ester hydrochloride was obtained from Novabiochem. DMSO-d_6 and D_2O used as solvents in the NMR measurements were obtained from Euriso-top. 3-NH_2-α-CD was prepared according to the method reported previously.[18]

4.3. Synthesis

*4.3.1. Mono-3-deoxy-3-cinnamamidehexanamide-α-CD (**2**)*

4.3.1.1. Cinnamoylaminohexanoic acid (CiHexOH). *trans*-Cinnamoyl chloride (1.0 g, 6.0 mmol) in THF (10 mL) was added to 1.27 N NaOH aqueous solution (30 mL) of 6-aminohexanoic acid (0.95 g, 7.2 mmol). The solution was stirred at 0 °C for 2 h. After the solution was adjusted at pH=3 with 1.0 M hydrochloric acid, the precipitate was collected and washed with ethyl acetate to give CiHexOH in 75% yield (1.19 g). ^{1}H NMR (DMSO-d_6, 270 MHz): δ 11.93 (s, 1H, –COO*H*), 8.05 (t, *J*=5.5 Hz, 1H, –CON*H*–), 7.54 (m, 3-H, *H* of Ph), 7.39–7.38 (m, 1H, Ph–C*H*═ and m, 5-H, *H* of Ph), 6.60 (d, *J*=15.8 Hz, 2H, ═C*H*–CONH), 3.15 (q, *J*=5.9, 6.8 Hz, 2H, –CH_2–NHCO), 2.20 (t, *J*=7.3 Hz, 2H, COOH–CH_2), 1.48 (m, 4H, –CH_2–), 1.30 (m, 2H, –CH_2–). Anal. Calcd for $C_{15}H_{19}NO_3\cdot 0.1H_2O$: C, 68.47; H, 7.35; N, 5.32. Found: C, 68.50; H, 7.32; N, 5.39. MALDI-TOF mass *m*/*z*=284 $[M+Na]^+$.

*4.3.1.2. Mono-3-deoxy-3-cinnamamidehexancarbonylamino-α-CD (**2**).* CiHexOH (0.39 g, 1.5 mmol), DCC (0.27 g, 1.3 mmol), and 1-HOBt (0.18 g, 1.3 mmol) were dissolved in distilled DMF (20 mL) under ice cooling and the solution was stirred for 2 h. 3-NH_2-α-CD (1.0 g, 1.0 mmol) in distilled DMF (10 mL) was added to the solution dropwise. The resulting mixture was stirred at room temperature for 5 days. After removal of insoluble materials by filtration, the filtrate was poured into acetone (500 mL). The precipitate was collected and washed with acetone. The crude product was purified by preparative size exclusion chromatography (elution: water) to give **2** in 45% yield (0.58 g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.05 (t, *J*=5.5 Hz, 1H, –CON*H*–CH_2–), 7.65 (d, *J*=8.9 Hz, 1H, –CON*H*–α-CD), 7.55 (m, 3-H, *H* of Ph), 7.40 (d, *J*=6.1 Hz, 1H, Ph–C*H*═), 7.38 (m, 2-H and 4-H, *H* of Ph), 6.61 (d, *J*=15.9 Hz, 1H, ═C*H*–CONH), 5.96–5.15 (m, 11H, O(2)*H* and O(3)*H* of α-CD), 4.91–4.83 (m, 6*H*, C(1)*H* of α-CD), 4.51–4.40 (m, 8*H*, O(6)*H* and C(6′)*H* of α-CD), 4.15–3.30 (m, overlaps with HOD), 3.15 (m, 2H, –CONH–CH_2–), 2.20 (t, *J*=7.3 Hz, 2H, –CH_2–CONH–), 1.48 (m, 4H, –CH_2–), 1.30 (m, 2H, –CH_2–). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.5 (–CH_2–NH*C*O), 165.5 (–CH_2–*C*═O), 139.1 (Ph–*C*H═), 135.7, 130.1, 129.6, 128.2 (*C* of Ph), 123.1 (Ph–CH═*C*H–), 105.5, 103.2, 103.0, 102.8, 102.3, 101.9 (*C*(1′) and *C*(1) of α-CD), 83.7, 82.6, 82.4, 81.5 (*C*(4′) and *C*(4) of α-CD), 74.4–72.4 (*C*(3′), *C*(3), *C*(2′), *C*(2), *C*(5′), and *C*(5) of α-CD), 61.0, 60.8 (*C*(6′) and *C*(6) of α-CD), 39.5, 36.5, 29.8, 27.1, 25.8 (–CH_2–). MALDI-TOF mass *m*/*z*=1238 $[M+Na]^+$. Anal. Calcd for $C_{51}H_{78}N_2O_{31}$: C, 47.50; H, 6.63; N, 2.33. Found: C, 47.59; H, 6.73; N, 2.18.

*4.3.2. Mono-3-deoxy-3-[N^{α}-cinnamoylaminohexancarbonyl-N^{ε}-cinnamoyl-lysinamide]-α-CD (**3**)*

4.3.2.1. Succinimidyl Z-6-aminohexanoate (Z-6-Hex-ONSu). *Z*-6-Aminohexanoic acid (2.0 g, 7.5 mmol), DCC (1.5 g, 7.5 mmol), and *N*-hydroxysuccinimide (ONSu) (0.87 g, 7.5 mmol) were added to THF (50 mL). The resulting mixture was stirred at room temperature for 2 days. After removal of insoluble materials by filtration, the filtrate was evaporated. Then, the residue was dissolved in ethyl acetate and washed with water. Ethyl acetate was dried over sodium sulfate and evaporated under vacuum to give *Z*-6-Hex-ONSu in 83% yield (2.1 g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.34 (m, 5H, *H* of Ph), 7.19 (t, *J*=5.5 Hz, 1H, –N*H*COO–), 4.99 (s, 2H, –OCH_2–Ph), 2.98 (q, *J*=6.6, 6.1 Hz, 2H, –CH_2–NHCOO–), 2.80 (s, 4H, *H* of ONSu), 2.63 (t, *J*=7.3 Hz, 2H, –OCO–CH_2–), 1.61 (m, 2H, –CH_2–), 1.38 (m, 4H, –CH_2–).

4.3.2.2. N^{α}-Z-Aminohexancarbonyl-N^{ε}-Z-lysine benzyl ester (N^{α}-Z-AmHex-N^{ε}-Z-lysine (OBzl)). To a solution of N^{ε}-*Z*-L-lysine benzyl ester hydrochloride (1.0 g, 2.5 mmol) in DMF was added excess triethylamine, and the reacting solution was allowed to stir at room temperature for 30 min. After removal of insoluble materials by centrifugal separation, to the supernatant was added *Z*-6-Hex-ONSu (0.9 g, 2.5 mmol) and allowed to stir at 100 °C for 3 days. After the reacting solution was poured into water, the precipitate was washed with water to collect N^{α}-*Z*-AmHex-N^{ε}-*Z*-lysine (OBzl) in yield 47% (1.2 g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.12 (d, *J*=7.5 Hz, 1H, –N*H*CO–CH–), 7.33 (m, 15H, *H* of Ph), 7.17 (m, 2H, –N*H*COO– (N^{α}) and –N*H*COO– (N^{ε})), 5.09 (s, 2H, –CH_2–Ph (*OBzl*)), 5.08 (s, 2H, –CH_2–Ph (N^{ε})), 4.99 (s, 2H, –CH_2–Ph (N^{α})), 4.22 (m, 2H, –CH_2–), 2.94 (m, 4H, –OCONH–CH_2 (N^{α}, N^{ε})), 2.09 (t, *J*=7.4 Hz, 2H, –NHCO–CH_2 (N^{α})), 1.60–1.21 (m, 12H, –CH_2–).

4.3.2.3. N^{α}-Aminohexancarbonyl-lysine (N^{α}-AmHex-lysine). To a solution of N^{α}-*Z*-HexNH-N^{ε}-*Z*-lysine (*OBzl*) (1.7 g, 2.7 mmol) and 10% palladium carbon (2.6 g) in methanol was added ammonium formate (2.1 g). The resulting mixture was stirred at room temperature for 2 h. After removal of 10% palladium carbon by filtration, the filtrate was evaporated under vacuum to give the crude N^{α}-AmHex-

lysine. The crude N^{α}-AmHex-lysine was used in the following reaction without further purification. ^{1}H NMR (D_2O, 500 MHz): δ 4.09 (d, J=8.2 Hz, 1H, –OCNH–C*H*–COOH), 2.91 (m, 4H, –C*H*$_2$–NH$_2$ (N^{α}, N^{ε})), 2.23 (t, J=7.3 Hz, 2H, –NHCO–C*H*$_2$–), 1.75–1.33 (m, 12H, –C*H*$_2$–).

4.3.2.4. N^{α}-Cinnamamidehexancarbonyl-N^{ε}-cinnamamide-lysine (N^{α}-CiHex-N^{ε}-CiNH-lysine). *trans*-Cinnamoyl chloride (1.8 g, 11 mmol) in THF (10 mL) was added to 1.0 N NaOH aqueous solution (20 mL) of N^{α}-AmHex-lysine. The solution was stirred at 0 °C for 2 h. After the solution was adjusted at pH=3 with 1.0 M hydrochloric acid, the precipitate was collected and washed with ethyl acetate to give N^{α}-CiHex-N^{ε}-CiNH-lysine in 78% yield (1.1 g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.08 (m, 2H, Ph–CH=CH–CON*H* (N^{α}, N^{ε})), 7.88 (d, J=7.7 Hz, 1H, –N*H*CO–), 7.54 (d, J=6.7 Hz, 3-H, *H* of Ph (N^{α}, N^{ε})), 7.42–7.34 (m, 2-H, *H* of Ph (N^{α}, N^{ε}), 4-H, *H* of Ph (N^{α}, N^{ε}), and 2H, Ph-C*H* (N^{α}, N^{ε})), 6.64–6.58 (d, J=15.8 Hz, 2H, C*H*–CONH– (N^{α}, N^{ε})), 4.06 (m, 1H, –CONH–C*H*–COOH), 3.14 (m, 4H, Ph–CH=CH–CONH–C*H*$_2$ (N^{α}, N^{ε})), 2.11 (m, 2H, –CONH–C*H*$_2$), 1.66–1.28 (m, 12H, –C*H*$_2$–). Anal. Calcd for $C_{30}H_{37}N_3O_5\cdot 1H_2O$: C, 67.24; H, 7.30; N, 7.84. Found: C, 67.00; H, 7.03; N, 7.75. MALDI-TOF mass m/z=542 $[M+Na]^+$.

*4.3.2.5. Mono-3-deoxy-3-[N^{α}-cinnamamidehexancarbonyl-N^{ε}-cinnamamide-lysinamide]-α-CD (**3**).* N^{α}-CiHex-N^{ε}-Ci-lysine (0.53 g, 1.0 mmol), DCC (0.28 g, 1.3 mmol), and 1-HOBt (0.18 g, 1.3 mmol) were dissolved in distilled DMF (20 mL) under ice cooling. The reacting solution was stirred for 2 h. 3-NH$_2$-α-CD (1.0 g, 1.0 mmol) in distilled DMF (10 mL) was added to the solution dropwise. The resulting mixture was stirred at room temperature for 5 days. After removal of insoluble materials by filtration, the filtrate was poured into acetone (500 mL). The precipitate was collected and washed with acetone. The crude product was purified by preparative reversed phase chromatography to give **3** in 46% yield (0.7 g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.04 (m, 2H, Ph–CH=CH–CON*H* (N^{α}, N^{ε})), 7.89 (d, J=8.9 Hz, 1H, –N*H*CO–), 7.78 (d, J=8.4 Hz, 1H, –N*H*CO–α-CD), 7.54–7.53 (m, 3-H, *H* of Ph (N^{α}, N^{ε})), 7.41–7.33 (m, 2-H, *H* of Ph (N^{α}, N^{ε}), 4-H, *H* of Ph (N^{α}, N^{ε}), and 2H, Ph–C*H*=(N^{α}, N^{ε})), 6.64–6.59 (d, J=15.8 Hz, 2H, =C*H*–CONH (N^{α}, N^{ε})), 5.89–5.21 (m, 11H, O(2)*H* and O(3)*H* of α-CD), 5.02–4.78 (m, 6H, C(1)*H* of α-CD), 4.51–4.40 (m, 8H, O(6)*H* and C(6′)*H* of α-CD), 4.28 (m, 1H, CONH–C*H*–CONH), 4.15–3.30 (m, overlaps with HOD), 3.14 (m, 4H, Ph–CH=CH–CONH–C*H*$_2$ (N^{α}, N^{ε})), 2.13 (m, 2H, CONH–C*H*$_2$), 1.66–1.25 (m, 12H, –C*H*$_2$–). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 175.5 (N^{α}–*C*=O–NH–), 172.6, 172.1 (N^{α}, N^{ε}–CH$_2$–NH–*C*=O), 165.5 (–*C*=O–NH–α-CD), 139.2 (N^{ε}–Ph–*C*H=), 139.1 (N^{α}–Ph–*C*H=), 135.7, 135.7, 130.1, 129.6, 128.2, 128.2 (*C* of Ph), 123.1 (N^{ε}–Ph–CH=*C*H–), 123.1 (N^{α}–Ph–CH=*C*H–), 103.3, 103.0, 102.8, 102.2, 101.8 (C(1′) and C(1) of α-CD), 83.8, 82.6, 81.7, 81.3, 80.6 (C(4′) and C(4) of α-CD), 74.5–71.1 (C(3′), C(3), C(2′), C(2), C(5′), and C(5) of α-CD), 60.7, 60.9, 90.9 (C(6′) and C(6) of α-CD), 63.0, 39.5, 39.3, 36.0, 29.8, 27.1, 25.9, 23.7 (–*C*H$_2$–). Positive-ion MALDI-TOF mass m/z=1495 $[M+Na]^+$. Anal. Calcd for $C_{66}H_{96}N_4O_{33}\cdot 5H_2O$: C, 50.64; H, 6.84; N, 3.58. Found: C, 50.57; H, 6.72; N, 3.66.

4.4. Measurements

The determination of association constants of the complex between host and guest was carried out by the solubility method. The solubility of guest compounds was measured at various concentrations of α-CD solutions. Equal amounts of guest compound were weighed into each of several 1.5 mL microtubes. To each microtube was added 1.0 mL of aqueous solutions of α-CD at various concentrations. After sonication, microtubes were rotated for a day and were allowed to stand for 30 min at room temperature. The heterogeneous solutions were centrifuged and the solubility of guest compound was measured by the absorbance of the supernatant. For the system of 1:1 inclusion complex between CiHexOH and α-CD, the association constant (K_1) was estimated by Eq. 1. On the other hand, for the system of 1:3 inclusion complex between N^{α}-CiHex-N^{ε}-Ci-lysine and α-CD, the association constants (K_{21} and K_{22}) were estimated by Eq. 2. Where S is a substrate, L is an α-CD ligand, S_t is a total molar concentration of the substrate, L_t is a total molar concentration of the α-CD ligand, and K is a stability constant.

$$\mathrm{S}+\mathrm{L}\rightarrow\mathrm{SL}\quad S_t = S_0 + K_1 S_0 L_t/(1+K_1 S_0),\ \text{slope} = (S_t - S_0)/L_t \tag{1}$$

$$\mathrm{S}+\mathrm{LL}\rightarrow\mathrm{L'L}\quad (S_t - S_0)/[\mathrm{L}] = K_1' S_0 + K_1' K_2' S_0[\mathrm{L}]$$

$$\mathrm{S}+\mathrm{L'L}\rightarrow\mathrm{L'L'}\quad L_t = [\mathrm{L}](1 + K_1' S_0 + 2K_1' K_2' S_0[\mathrm{L}]) \tag{2}$$

PFGSE NMR diffusion measurements were carried out by using the bipolar pulse pair stimulated echo (BPPSTE).[19] The pulsed gradients' strength 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. The D values, where D represents diffusion coefficient, were determined from the slope of the regression line $\ln(I/I_o)$ versus G^2, according to Eq. 3 in which I/I_0 is observed spin-echo intensity/intensity without gradients, G is gradient strength, Δ is delay between the midpoints of the gradients, δ is gradient length, and τ is 90–180° pulse distance. The calibration of gradients was carried out by a diffusion measurement of H_2O ($D_{H_2O} = 2.30\times10^{-9}$ m^2 s^{-1})[20] at 25 °C.

$$\ln(I/I_0) = -\gamma^2 G^2 \delta^2 (\Delta - \delta/3 - \tau/2) D \tag{3}$$

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.040.

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