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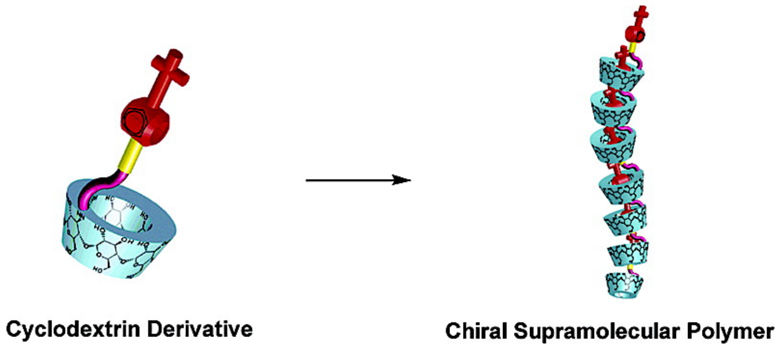

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Chiral Supramolecular Polymers Formed by Host−Guest Interactions

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Abstract: α-Cyclodextrin with a *p-t*-butoxyaminocinnamoylamino group in the 3-position (3-*p*-^{t}BocCiNH-α-CD) has been found to form a supramolecular polymer in an aqueous solution. The degree of polymerization of the supramolecular polymer is higher than 15 at 20 mM, as proved by VPO (vapor pressure osmometry) measurements and turbo ion spray TOF MS measurements. The existence of substitution/substitution interactions between adjacent monomers of the supramolecular polymer have been confirmed by the observation of positive and negative Cotton bands in circular dichroism spectra. The mechanism for the induction of the chirality was confirmed using model compounds. The substituents were found to exist as a left-handed anti configuration in supramolecular polymers. The supramolecular polymer was found to take a helical structure. The structure of the supramolecular polymer was observed by STM measurements.

Introduction

Supramolecular polymers are ubiquitous in nature, especially in biological systems. Microtubules, microfilaments, and flagella are helical supramolecular polymers formed by proteins. In recent years, much attention has been focused on supramolecular polymers formed by synthetic molecules because of their unique structures and properties.[1] Supramolecular oligomers formed by hydrogen bonds were reported for the first time by Lehn et al.[2] Supramolecular polymers formed by four hydrogen bonds for each unit were reported by Meijer et al.[3] Furthermore, Meijer et al. reported chiral supramolecular polymers formed by hydrogen bonding.[4] Rehahn et al. reported supramolecular polymers formed by metal coordination.[5] However, there are few reports on the formation of supramolecular polymers by host−guest interactions, although the formation of supramolecular polymers by these interactions is important within biological systems. To design such supramolecular polymers, we have to incorporate a host part and a guest part in a single molecule. Previously, we found and reported that 6-cinnamoyl-α-cyclodextrin (6-CiO-α-CD) formed supramolecular dimers and trimers.[6] When they were stabilized by attaching bulky substituents (trinitrophenyl group), a cyclic daisy chain was obtained, in which a guest part was included in the CD cavity of the other molecule from its primary hydroxyl side. To obtain linear supramolecular polymers, the formation of cyclic oligomers should be avoided. To avoid the formation of cyclic supramolecular structures, a guest part should be attached to the secondary hydroxyl side. 3-Cinnamoyl CD amide (3-CiNH-α-CD) was found to form longer supramolecular polymers.[7] The degree of polymerization reached almost to 12 in high concentrated aqueous solution (60 mM). However, we could not observe that the supramolecular polymers were helical. We then found that 3-*p*-^{t}BocCiNH-α-CD formed helical supramolecular polymers in aqueous solutions. We report herein for the first time the formation of helical supramolecular polymers by a cyclodextrin-based host−guest system.

Experimental Procedures

General. The ^{1}H NMR spectra were recorded at 400 MHz on a JEOL GSX-400 spectrometer at 30 °C. Chemical shifts were referenced to the external standard in the solvent (δ = 1.96 ppm for acetonitrile in D_2O). 2-D ROESY NMR and pulsed gradient NMR experiments (PFG NMR) were obtained with D_2O as the solvent at 60 °C at 500 MHz on a JEOL JNM LA-500 NMR spectrometer and 600 MHz on a VARIAN−UNITY PLUS-600 NMR spectrometer, respectively. WETBPPSTE pulse sequence was applied for PFG NMR measurements, and the pulsed gradients were increased from 0.30 to 25.0 G cm^{-1}. The time separation between pulsed field gradients and their duration were applied the values of 100 ms and 1.1 ms. FT-IR measurements were performed on a JASCO FT/IR-410 spectrometer. KBr was used as a dispersant. The analytical size

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exclusion chromatography and preparative size exclusion chromatography were carried out with TOHSO CCP&8010 system (column: TSKgel α-2500 and TSKgel α-3000; elution: methanol/water = 40:60). Circular dichroism spectra and UV spectra were recorded on a JASCO J820 spectrometer with 0.1 cm cell at room temperature. Positive-ion matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry experiments were performed by using a Shimadzu/KRATOS Axima CFR V2.2.1 mass spectrometer. α-Cyano-4-hydroxycinnamic acid and insulin were used as the standard materials. Ion spray TOF mass spectrometry experiments were performed by using an Applied Biosystems QSTAR XL system mass spectrometer. Vapor pressure osmometry measurements were carried out by a KNAUER No. A0280 vapor osmometer at 40 °C in water. NaCl aqueous solution and α-CD were used as standards. Solution viscosities were measured using Ubbelohde viscometers in a water bath at 30 °C. STM measurements were taken on a Nanoscope IIIa (Digital Instruments, Santa Barbara, CA). The sample was prepared by slow evaporation of a dilute aqueous solution of 3-*p*-^{t}BocCiNH-α-CD on MoS_2 overnight at room temperature. The STM image was obtained under the conditions of the sample bias voltage +315 mV, tunneling current 1.038 nA, and Scan rate 6.1 Hz.

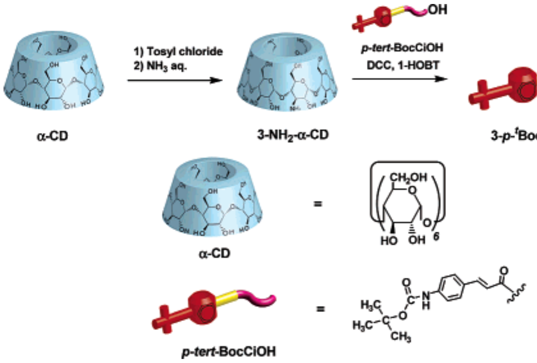
Materials. α-CD, tetramethylammonium chloride (TMA), and NaOH were obtained from Nacalai Tesque, Inc. *trans*-*p*-Aminocinnamic acid was obtained from Tokyo Kasei Kogyo, CO., Ltd. Di-*t*-butyl dicarbonate was obtained from Aldrich. Dimethyl sulfoxide (DMSO)-d_6 was obtained from Euriso top. D_2O was purchased from Silantes.

***p*-*t*-Butoxycinnamic Acid (*p*-^{t}BocCiOH).** *trans*-*p*-Aminocinnamic acid (1.63 g, 1.0×10^{-2} mol) in dioxane (10 mL) was added to 0.5 M NaOH aqueous solution (10 mL). Di-*t*-butyl dicarbonate (2.37 g, 1.2×10^{-2} mol) was added to the solution at 0 °C. The reaction was carried out with stirring for 6 h at 0 °C. Then, to the solution was added citric acid and ethyl acetate (30 mL). After being extracted three times, the ethyl acetate was dried with sodium sulfate and evaporated under vacuum to give 2.80 g of the desired product. (Yield, 98%). ^{1}H NMR (DMSO-d_6, 270 MHz): δ 9.54 (s, 1H), 7.56 (d, 1H, J = 8.78), 7.48 (d, 1H, J = 8.78), 7.48 (d, 1H, J = 15.86), 6.36 (d, 1H, J = 15.86), 1.47 (s, 1H). M.p. 204 °C.

Mono-3-deoxy-amino-α-CD (3-NH_2-α-CD). This compound was prepared according to the literature previously reported.[8]

3-*p*-^{t}BocCiNH-α-CD. To a solution of 3-NH_2-α-CD (591.0 mg, 6.08×10^{-4} mol) in 50 mL of DMF was added *p*-*t*-BocCiOH (548.0 mg, 2.08×10^{-3} mol). After the solution was cooled below 0 °C, *N*,*N*′-dicyclohexyl carbodiimide (171.0 mg, 8.29×10^{-4} mol) and 1-hydroxybenzotriazole (112.0 mg, 8.29×10^{-4} mol) was added. The resulting mixture was stirred at room temperature for 5 days. After the removal of insoluble materials by filtration, we poured the filtrate into acetone (1 L) and then collected and washed the precipitate with acetone. The crude product was purified by preparative reversed phase chromatography (elution: water/methanol =100:0 to 50:50). After the concentration of the solution containing 40% of methanol under vacuum, the residue was separated with preparative size-exclusion chromatography (Scheme 1). Yield, 46%. Positive ion MALDI-TOF Mass *m*/*z* 1240.25 (M + Na^+); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.47 (s, 1H), 8.07 (d, 1H, J = 8.79), 7.52−7.46 (q, 4H, J = 8.55), 7.31 (d, 1H, J = 15.63), 6.41 (d, 1H, J = 15.59), 5.90−5.17 (m, 11H), 4.86−4.64 (m, 6H), 4.52−4.49 (m, 6H), 3.93−3.29 (m, overlaps with HOD), 1.45 (s, 9H). IR (KBr, cm^{-1}): 1702 (vs, $^{\nu}$C═O, urethane), 1658 (vs, $^{\nu}$C═O, amide). Anal. Calcd for $C_{50}H_{76}N_2O_{32}{\cdot}7H_2O$: C, 44.71; H, 6.75; N, 2.09. Found: C, 44.97; H, 6.63; N, 2.18.

Scheme 1. Synthesis of 3-*p*-^{t}BocCiNH-α-CD



Results and Discussion

Formation of Supramolecular Polymers. When a guest group is covalently attached to a CD, the molecule may form intra-[9] or intermolecular complexes[10] in aqueous solutions. Supramolecular polymers would be formed by the formation of consecutive intermolecular complexes through host−guest interactions. 3-*p*-^{t}BocCiNH-α-CD is highly soluble in water. When the guest part of 3-*p*-^{t}BocCiNH-α-CD is included in another CD cavity in D_2O solution, the ^{1}H NMR spectra may show peak shifts. Figure 1a shows the ^{1}H NMR spectra of 3-*p*-^{t}BocCiNH-α-CD as a function of concentrations in D_2O solutions. As the concentration of 3-*p*-^{t}BocCiNH-α-CD increased within the range from 1 to 40 mM, remarkable peak shifts were observed in the protons of the substitution region. (The peak shifts of the ^{t}Boc part were also observed, but those data are shown in Figure S2). This result indicates that 3-*p*-^{t}BocCiNH-α-CD forms intermolecular complexes in D_2O solutions. In particular, the peak e drastically shifted upfield about 0.35 ppm at 40 mM (Figure 1b). The data were analyzed quantitatively with double reciprocal plots. This result indicates that the consecutive inclusion of 3-*p*-^{t}BocCiNH-α-CD gives rise

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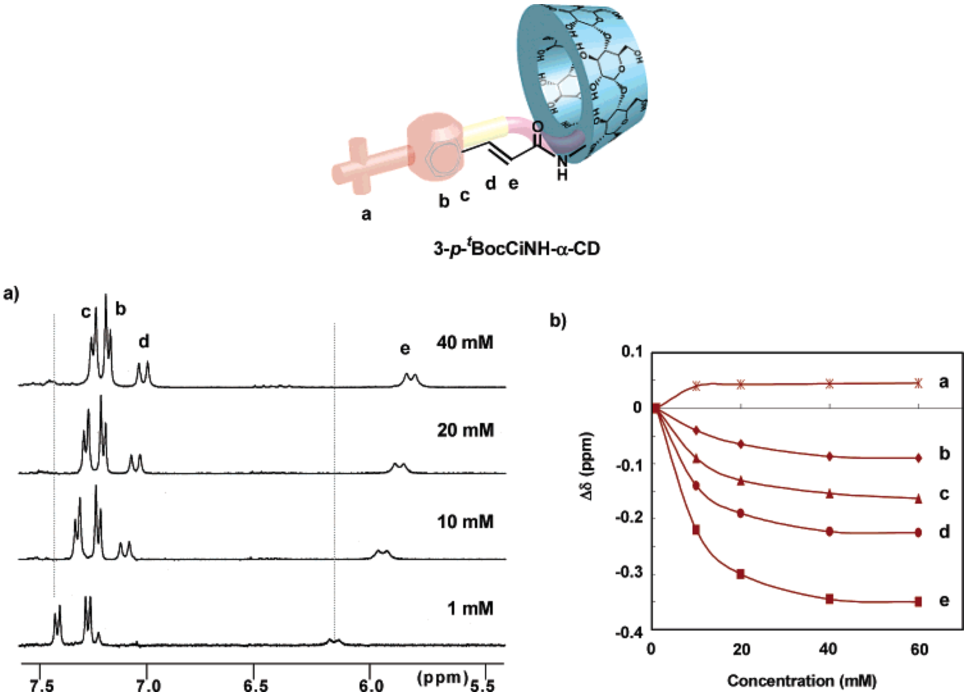

Figure 1. ^{1}H NMR spectra (400 MHz) of 3-*p*-^{t}BocCiNH-α-CD at various concentrations in D_2O (a) and plots of $\Delta\delta$ (a−e) as a function of concentrations (*b*).

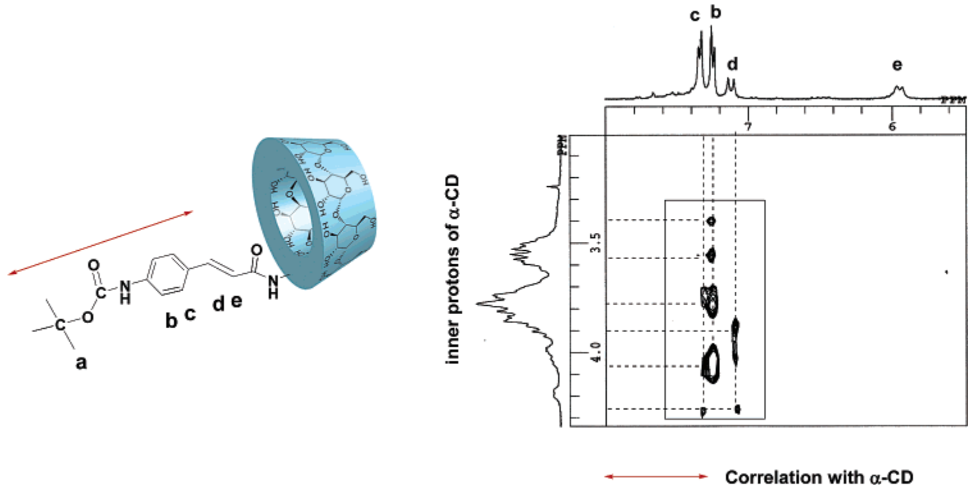

Figure 2. 500 MHz 2-D ROESY NMR spectrum of 3-*p*-^{t}BocCiNH-α-CD in D_2O.

to the formation of supramolecular polymers with an increase in the concentration.

Figure 2 shows the 2-D ROESY NMR spectrum of 3-*p*-^{t}BocCiNH-α-CD in D_2O solution. Rotational nuclear overhauser effects (ROEs) can be obviously observed between the substituent parts (b−d) and the inner protons of the CD part (the NOEs for a are also observed, and the data is shown in Figure S3), which indicates that the ^{t}Boc part is deeply included in another CD cavity.

It is difficult to estimate the size of supramolecular polymers by NMR measurements because the formation and dissociation of intermolecular complexes formed by 3-*p*-^{t}BocCiNH-α-CD are too fast on the NMR time scale. Figure 3 shows the results of VPO measurements of 3-*p*-^{t}BocCiNH-α-CD and native α-CD at various concentrations at 40 °C in H_2O. Although α-CD showed no concentration dependence on the molecular weight (MW), the MW of 3-*p*-^{t}BocCiNH-α-CD increased as the concentration increased from 0.5 to 15 mM. From the results

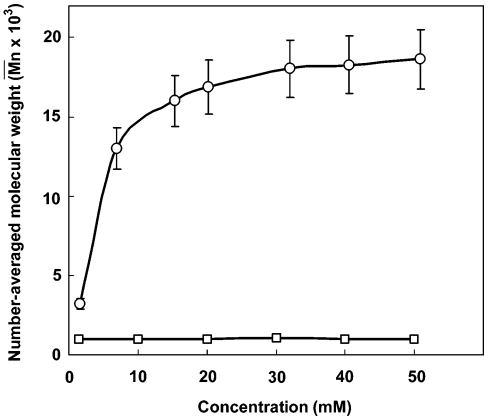

Figure 3. Effects of the concentrations on the molecular weight of 3-*p*-^{t}BocCiNH-α-CD (○) and α-CD (□) observed by VPO in water at 40 °C.

of NMR measurements in Figure 1, the peak shift of 3-*p*-^{t}BocCiNH-α-CD is remarkable in the range up to 10 mM. In

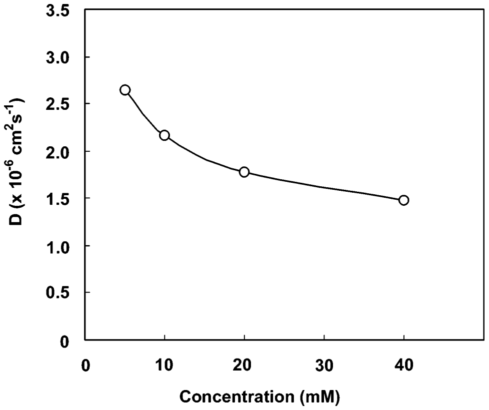

Figure 4. Plots of diffusion coefficients (*D*) of 3-*p*-^{t}BocCiNH-α-CD obtained by PFG NMR measurements as a function of concentrations at 30 °C.

the concentration range from 15 to 40 mM, the molecular weights are slightly increased from 16 000 to 20 000, which is also in good agreement with the NMR data. These results indicate that 3-*p*-^{t}BocCiNH-α-CD forms water-soluble supramolecular polymers at higher concentrations.

The self-diffusion coefficients of 3-*p*-^{t}BocCiNH-α-CD are also determined by the utilization of a pulsed field gradient (PFG) NMR measurement in D_2O solutions.[11] According to the Stejskal and Tanner's reports,[12] when ln I/I_0 versus g^2 was plotted, where I and g are the echo intensity and (pulsed) gradient strength, respectively, the slope of the line is given by $D/(\Delta - \delta/3)\gamma^2\delta^2$ (Figure S6). Here, δ, γ, and Δ are the duration, gyromagnetic ratio, and time interval, respectively, between the magnetic field gradient pulses. Figure 4 shows the plots of the diffusion coefficients derived from the attenuation of proton signals of 3-*p*-^{t}BocCiNH-α-CD (*D*) in D_2O solutions as a function of concentrations. The diffusion coefficients decreased with an increase in the concentration (5.0 mM: 2.65×10^{-6} cm s^{-1} and 40 mM: 1.57×10^{-6} cm s^{-1}). The results show that the sizes of intermolecular complexes formed by 3-*p*-^{t}BocCiNH-α-CD increased with an increase in the concentration in D_2O solutions.

Turbo ion spray TOF mass spectrum provides direct evidence supporting the formation of supramolecular polymers. Figure 5 shows the representative positive turbo ion spray-TOF mass spectra of 3-*p*-^{t}BocCiNH-α-CD with $AcONH_4$ at 10 mM in aqueous solutions. The signals can clearly be assigned as the supramolecular polymers. The number average molecular weight of the polymer was up to 18 000 formed by 3-*p*-^{t}BocCiNH-α-CD. The intervals of signals correspond to the molecular weight of 3-*p*-^{t}BocCiNH-α-CD. These data are in good agreement with the VPO data.

We could not observe cycle formation in this system, although 6-CiO-α-CD formed a cyclic trimer and dimer, and 6-CiNH-α-CD formed a cyclic dimer. The guest part of 3-CiNH-α-CD is attached to =C(3)−NH_2 of α-CD directly by amide bond, so that the direction of the guest part relative to α-CD is rather fixed so as not to form cyclic dimers. The insertion of the guest part from the secondary OH side of CD is thought to be disfavored.

Circular Dichroism Spectra of 3-*p*-^{t}BocCiNH-α-CD. Figure 6a (blue line) shows the circular dichroism spectrum of the complex of *p*-*t*-BocCiOH with α-CD in water. The spectrum shows an induced positive band around 250−380 nm, corresponding to the ^1L_a transition band of *p*-*t*-BocCiOH. The observed positive circular dichroism bands in 220−380 nm can be assigned to the bands induced by the inclusion of *p*-^{t}BocCiOH with α-CD. According to the theoretical treatment by Kodaka et al.,[13] a positive Cotton band is produced by the electronic transition moment being nearly parallel to the molecular axis

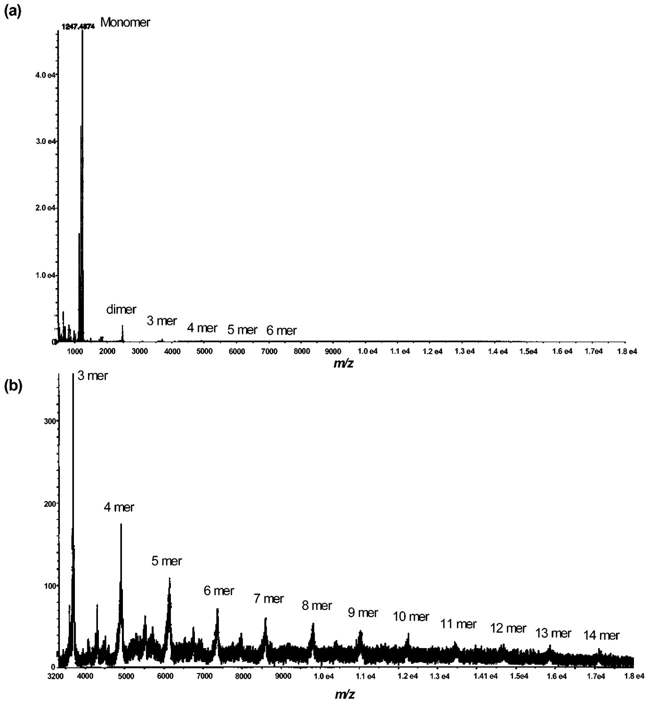

Figure 5. Positive turbo ion spray TOF mass spectra of 3-*p*-^{t}BocCiNH-α-CD with $AcONH_4$ in the range of 0−18 000 (a) and 3200−18 000 (b).

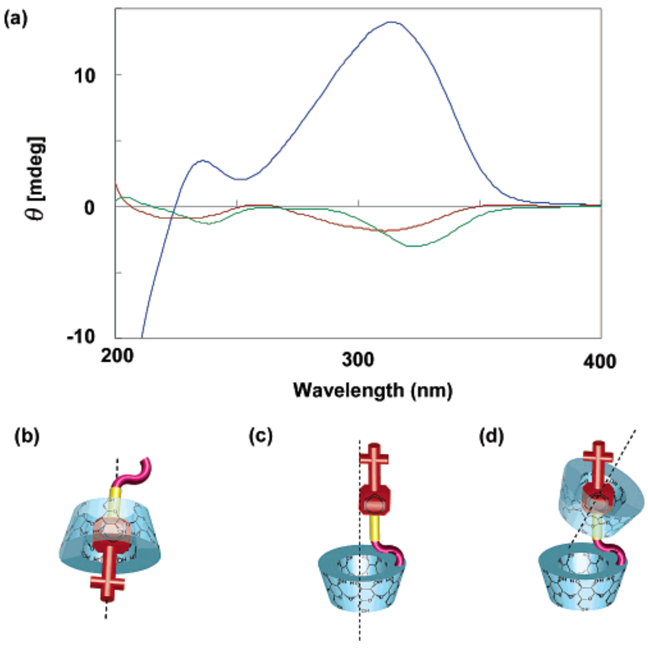

Figure 6. Circular dichroism spectra of *p*-^{t}BocCiOH with α-CD (blue line), 3-*p*-^{t}BocCiNH-α-CD at 0.25 mM (green line), and 3-*p*-^{t}BocCiNH-α-CD + native α-CD (brown line) in water (a); schematic structure of *p*-^{t}BocCiOH-α-CD complex (b); monomeric structure of 3-*p*-^{t}BocCiNH-α-CD (c); and heterodimeric structure of 3-*p*-^{t}BocCiNH-α-CD + native α-CD complexes (d).

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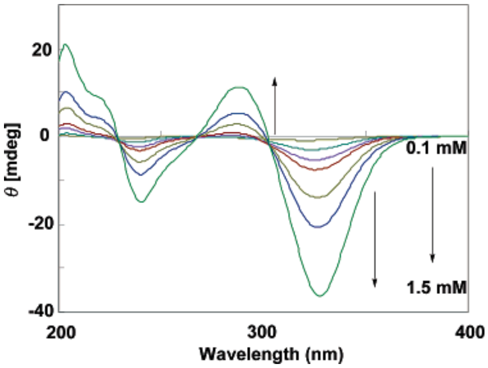

Figure 7. Circular dichroism spectra of 3-*p*-^{t}BocCiNH-α-CD at the concentration range from 0.1, 0.25, 0.38, 0.5, 0.75, 1.0, and 1.5 mM in water.

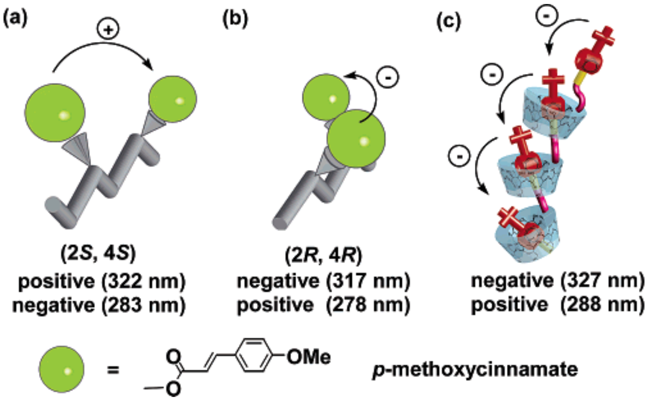

Figure 8. Schematic structures and signs of the observed Cotton bands of (2*S*,4*S*)-2,4-*anti*-hexanediol bis-*p*-methoxycinnamates (a), (2*R*,4*R*)-2,4-*anti*-pentanediol bis-*p*-methoxycinnamates (b), and 3-*p*-^{t}BocCiNH-α-CD (c).

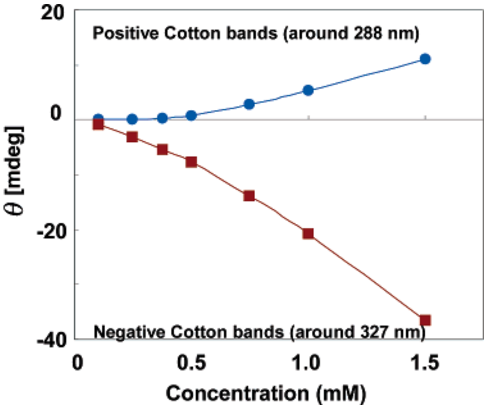

Figure 9. Plots of the observed Cotton band intensities as a function of concentrations.

of α-CD. The result of the induced circular dichroism indicates an axial inclusion in which the ^1L_a axis of *p*-^{t}BocCiOH is parallel to the axis of α-CD (Figure 6b).[14] The circular dichroism spectrum of 3-*p*-^{t}BocCiNH-α-CD at 0.25 mM is also shown in Figure 6a (green line). The observed negative Cotton band at 323 nm indicates that the *p*-^{t}BocCi part exists parallel to its own CD axis in monomeric structure without the formation of supramolecular complexes since the concentration (0.25 mM) is too low to form intermolecular complexes in aqueous solutions (Figure 6c). Interestingly, when an excess amount of α-CD was added to this solution of 3-*p*-^{t}BocCiNH-α-CD, the negative Cotton band shifted to 311 nm with some weakening in the intensity (Figure 6a, brown line). This result indicates that the ^{t}BocCi part is incorporated into the native α-CD cavity in a slantwise state to form 3-*p*-^{t}BocCiNH-α-CD-native α-CD heterodimer (Figure 6d).

Figure 7 shows the circular dichroism spectra of 3-*p*-^{t}BocCiNH-α-CD at concentrations ranging from 0.1 to 1.5 mM in water because the upper limit of the concentration detectable by the circular dichroism spectra is 1.5 mM. The induced circular dichroism bands in 3-*p*-^{t}BocCiNH-α-CD at higher than 0.25 mM are extremely different from those of the complex of *p*-^{t}BocCiOH with α-CD and 3-*p*-^{t}BocCiNH-α-CD at lower concentrations. As the concentration increased, the observed negative Cotton band around 323 nm at 0.25 mM is gradually separated to form a negative and a positive band, which shifted to 327 and 288 nm, respectively. Nakanishi et al. previously reported that the (2*S*,4*S*)-2,4-*anti*-hexanediol bis-*p*-methoxycinnamates gave rise to the splitting positive and negative Cotton bands around 322 and 283 nm, respectively, in the ^1L_a transition (Figure 8a).[15] (2*R*,4*R*)-2,4-*anti*-Pentanediol-bis-*p*-methoxycinnamates also showed the splitting Cotton bands with the opposite signs (Figure 8b). These observations show the existence of the pairwise exciton-coupling interactions (cinnamate/cinnamate interactions) in the compound and the rotational configuration effects on the sign of induced circular dichroism bands. According to this paper, the rotational configurations of cinnamates attached to a compound such as a polymer could be distinguished. This method is also applicable to the supramolecular polymer system possessing cinnamate groups. The splitting Cotton bands shown in Figure 7 also indicate the existence of substitution/substitution interactions between the adjacent 3-*p*-^{t}BocCiNH-α-CD units. Additionally, the substitution part of 3-*p*-^{t}BocCiNH-α-CD can be assigned to the existence of the left-handed anti configuration (Figure 8c). These data indicate the formation of helical supramolecular polymer constructed by 3-*p*-^{t}BocCiNH-α-CD in aqueous solution.

The plots of the observed circular dichroism are shown in Figure 9. The observed intensities (ellipticity, θ) obviously increased with nonlinearity as the concentration increased. These data indicate that 3-*p*-^{t}BocCiNH-α-CD forms the left-handed helical supramolecular polymer cooperatively.

Figure 10 shows the circular dichroism spectrum of 1.5 mM aqueous solution of 3-*p*-^{t}BocCiNH-α-CD with additions of excess amounts of α-CD (0.1 to 48 mM). The positive (288 nm) and negative (327 nm) Cotton bands originally observed at 1.5 mM were gradually decreased to unite into one negative Cotton effect band around 320 nm, indicating the disappearance of the substitution/substitution transition. The native α-CD competitively inhibited the formation of intermolecular complexes formed by 3-*p*-^{t}BocCiNH-α-CD to bear a 3-*p*-^{t}BocCiNH-α-CD-native α-CD heterodimer. The ultimate observed negative Cotton band is compatible with the slantwise inclusion of the ^{t}BocCi part with native α-CD, as shown in Figure 6d.

Viscosity Measurements of Supramolecular Polymer Solutions. To obtain the physical evidence of formation of the

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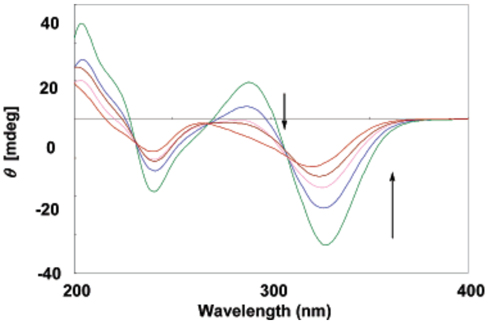

Figure 10. Circular dichroism spectra of 3-*p*-^{t}BocCiNH-α-CD (1.5 mM) on addition of α-CD (1.0, 6.0, 12, 24, and 48 mM) in water.

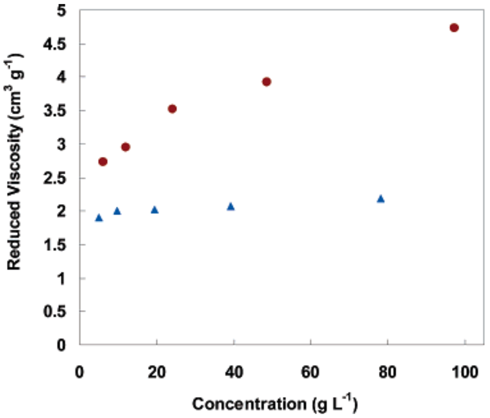

Figure 11. Reduced viscosity of 3-*p*-^{t}BocCiNH-α-CD (●) and native α-CD (▲) as a function of the concentrations in aqueous solutions.

supramolecular polymer, the viscosity titration of 3-*p*-^{t}BocCiNH-α-CD was performed in aqueous solution.[16] Figure 11 shows the reduced viscosity of 3-*p*-^{t}BocCiNH-α-CD and native α-CD aqueous solution, respectively, as a function of concentrations. Although the native α-CD solution showed a slight increase in the viscosity, the 3-*p*-^{t}BocCiNH-α-CD solution showed large concentration dependence. In particular, for the two highest concentrations, the 3-*p*-^{t}BocCiNH-α-CD solution showed a much higher viscosity than the α-CD solution. These results obviously indicate that the formation of the supramolecular polymer affects the viscosity of the aqueous solution.

STM Measurement of Supramolecular Polymers Constructed by 3-*p*-^{t}BocCiNH-α-CD. STM measurement was carried out to investigate the detailed structure of the 3-*p*-^{t}BocCiNH-α-CD in solid state under ambient conditions. Figure 12 shows a typical 3-D STM image of the 3-*p*-^{t}BocCiNH-α-CD prepared from its aqueous solutions (5.0×10^{-9} M). The image shows clearly a long chain with a helical structure, corresponding to the supramolecular polymer constructed by 3-*p*-^{t}BocCiNH-α-CD (>20 nm). It is difficult to discuss the period of the helicity because the supramolecular structures of the samples concentrated on a substrate are not necessarily consistent with the helical structure in an aqueous solution. However, the height of an object obviously corresponds to that of a CD ring in the 3-*p*-^{t}BocCiNH-α-CD (~2 nm).

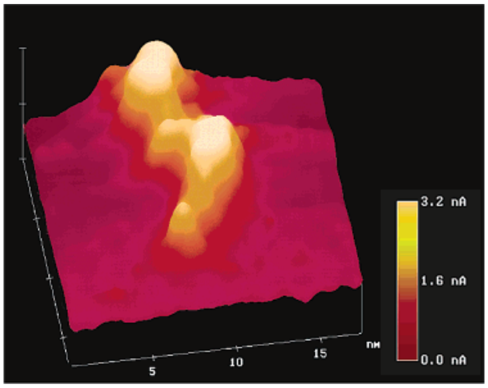

Figure 12. STM image of the 3-*p*-^{t}BocCiNH-α-CD prepared from its concentrated aqueous solution on MoS_2 substrate.

Conclusions

We have investigated the formation of cyclodextrin-based supramolecular polymers formed in an aqueous solution and in a solid state. α-Cyclodextrin with a *p*-*t*-butoxyaminocinnamoylamino group in the 3-position forms a supramolecular polymer of higher than a 15 mer, which was proved by VPO measurements and turbo ion spray TOF MS measurements in aqueous solution. The existence of substitution/substitution interactions shown among the adjacent monomers of the supramolecular polymer are proved by the observation of positive and negative Cotton bands in circular dichroism spectra. The mechanism for the induction of the chirality was also confirmed with model compounds. The substitution part of 3-*p*-^{t}BocCiNH-α-CD is incorporated into a CD cavity of an adjacent monomer in a slantwise state. The substituents exist as a left-handed anti configuration in supramolecular polymers. This is the first observation of CD-based helical supramolecular polymers formed in aqueous solutions. The formation of a helical supramolecular polymer with some cooperativity is shown by the increasing intensities of Cotton effect peaks with increase in the concentrations. These results remind us that microtubules, microfilaments, and flagella are helical supramolecular polymers formed by host−guest cooperative interactions in the biological system. We could also achieve the visualization of the supramolecular polymers by using STM measurements under ambient conditions. The length of the supramolecular polymer is observed more than 20 nm, and the helical structure is also confirmed on the substrate.

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Supporting Information Available: ^{1}H NMR spectra, 2-D ROESY NMR spectra, circular dichroism spectra, diffusion coefficients, and relative viscosity of 3-*p*-^{t}BocCiNH-α-CD. This material is available free of charge via the Internet at http://pubs.acs.org.

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