Supramolecular Polymers Formed from β-Cyclodextrins Dimer Linked by Poly(ethylene glycol) and Guest Dimers

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ABSTRACT: Novel supramolecular polymers have been prepared from a β-cyclodextrin dimer and a ditopic guest dimer having adamantyl groups. β-Cyclodextrins were bound to poly(ethylene glycol) (PEG, M_n 600). Adamantyl groups were also bound to PEG (M_n 600). The ROESY NMR spectrum of a 1:1 mixture of the β-cyclodextrin dimer and the ditopic adamantane guest dimer showed ROE correlations between the protons of adamantyl substituents and the inner protons of β-cyclodextrin. Molecular weights and molecular sizes of the supramolecular polymer constructed by the mixture of the β-cyclodextrin dimer and the ditopic adamantane guest dimer were investigated by the pulse field gradient spin echo (PFGSE) NMR and by vapor pressure osmometry (VPO). The results have shown that the mixture of the β-cyclodextrin host dimer and the adamantane guest dimer gave linear supramolecular polymers with high molecular weight (M_n = 100 000).

Introduction

Recently, design and synthesis of supramolecular polymers have developed into an area of enormous interest for a wide variety of scientific and technological fields,[1,2] because biological macromolecules, such as DNA and protein, are also formed by noncovalent bond assemblies. The most important feature is that the supramolecular polymer is formed by a polymeric array of monomer units which gives the inherent reversibility associated with intermolecular self-assemblies. Several papers described the assembly of supramolecular structures based on exo ditopic host molecules and guest molecules. [3−10] Previously, we reported preparation and structures of cyclodextrins (CDs) having a hydrocinnamoyl group (6-HyCiO-CD) or a cinnamoyl group (6-CiO-CD) as a guest part.[11] Although HyCiO-β-CD was found to form intramolecular complexes, 6-CiO-α-CD gave intermolecular complexes to give supramolecular oligomers of the degree of polymerization up to three. When the supramolecular complexes were stabilized by attaching bulky stoppers, cyclic tri[2]rotaxanes, daisy chain necklaces, were obtained.[12] Meanwhile, there are many papers on the cooperative binding of guests by CD dimers,[13] but there are few on the formation of intermolecular complexes of CD dimers with guest dimers.[14,15] Although the synthesis of supramolecular complexes using the β-CD random polymer and the adamantane dimer has been reported, it is difficult to define the structure of the supramolecular complex because the β-CD polymer has random structures.[16,17] More recently, while we were preparing for this manuscript, Liu et al. reported intermolecular complexes of CD dimers with fullerene.[18] However, the association constant of the complex between the β-CD and fullerene is too low to form the supramolecular polymers with high molecular weight. To obtain larger supramolecular polymers, we have decided to study the formation of supramolecular polymers between β-CD linked by poly(ethylene glycol) and ditopic guest molecules, poly(ethylene glycol) with adamantyl moieties at both ends.

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Experimental Section

General Procedures. All manipulations were carried out by the use of standard Schlenk techniques under an argon atmosphere. THF was dried and deoxygenated by the distillation over sodium benzophenone ketyl under an argon atmosphere. DMF was dried and deoxygenated by distilling from BaO under the reduced pressure. β-CD, *p*-toluenesulfonyl chloride, sodium hydroxide, sodium azide, 28% ammonium solution, triphenylphosphine, *N,N′*-dicyclohexylcarbodiimide (DCC), and 1-hydroxybenzotriazole (HOBT) were obtained from Nacalai Tesque Inc. Poly(ethylene glycol) diacid (PEG-diacid, M_n = 600) was obtained from Furuka Inc. 1-Adamantanamine was obtained from Aldrich Chem. Co. 1,1′-Carbonylbis-1*H*-imidazole (CDI) and 1-adamantanamine hydrochloride were obtained from Tokyo Kasei Inc. 6-Amino-β-CD was prepared according to the literature.[19]

Measurements. The ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz on a JEOL-GSX 400 spectrometer. Chemical shifts were referenced to the solvent values (δ 2.50 ppm for DMSO-d_6 and δ 4.70 ppm for HOD). The 2D NMR (NOESY, ROESY) experiments was recorded at 600 MHz in D_2O on a VARIAN UNITY plus NMR spectrometer at 30.0 °C. Vapor pressure osmometry measurements were used KNAUER No. A0280 vapor osmometer at 40 °C in water. NaCl aqueous solution and α-CD were used as the instruments standard. The positive-ion matrix assisted laser desorption ionization time-of-flight (MALDI−TOF) mass spectra measurements were performed on a Shimadzu/KRATOS AXIMA-CFR spectrometer with DHBA as a matrix.

Determination of Diffusion Coefficient and Hydrodynamic Radius. The pulse field gradient spin−echo (PFGSE) NMR spectra were recorded at 600 MHz in D_2O on a VARIAN UNITY plus NMR spectrometer at 30.0 °C. A WETBPPSTE pulse sequence was applied for PFGSE NMR measurements, and the pulsed field gradient strength was increased from 0.30 to 25.0 G/cm.[20] For the time separation between pulsed field gradients and their duration were applied the values of 0.10 and 1.10×10^{-3} s, respectively. A WETBPPSTE pulse sequence was applied for PFGSE NMR measurements, and the pulsed field gradient strength was increased from 0.30 to 25.0 G/cm.

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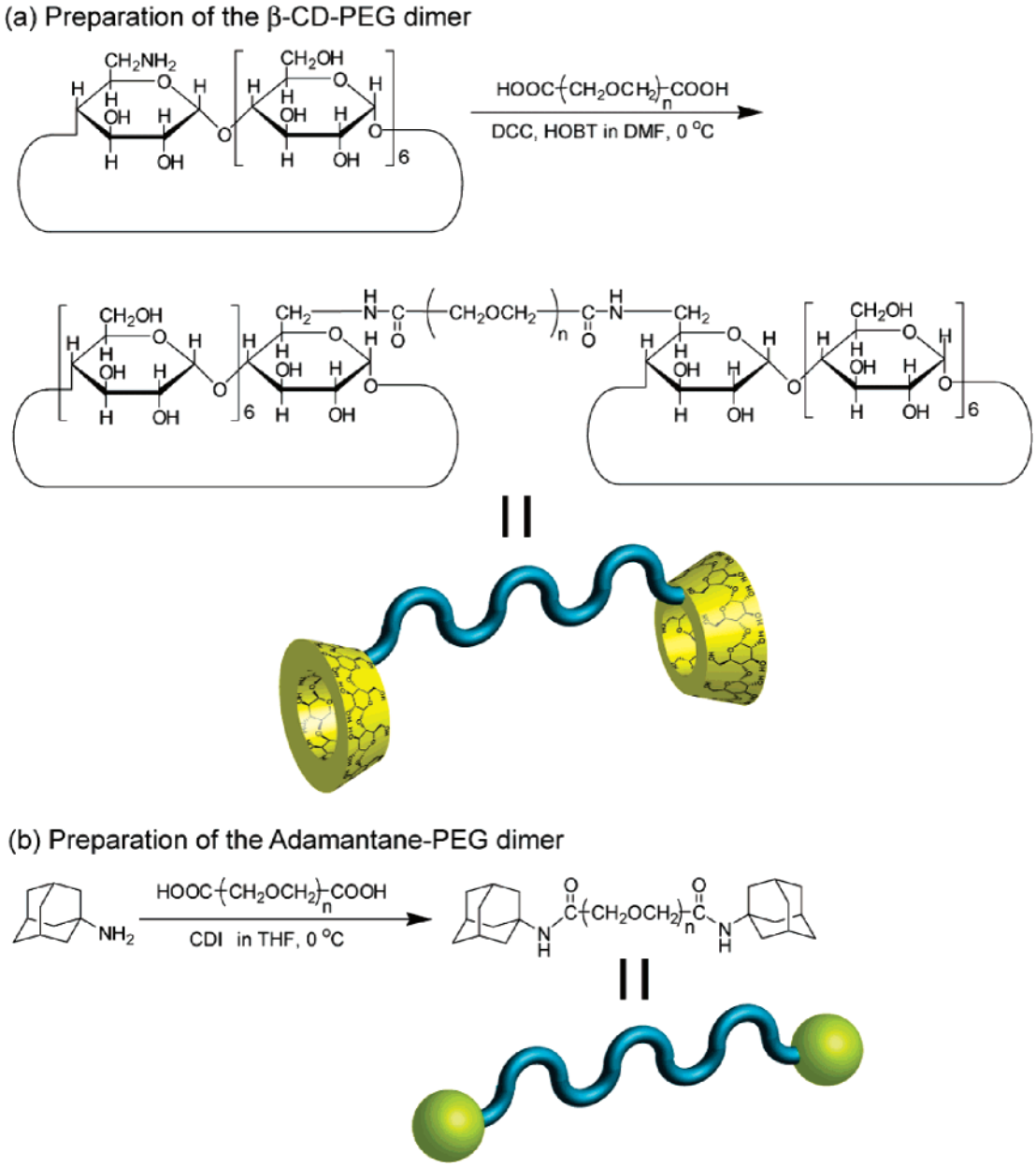
Scheme 1



The time separation between pulsed field gradients and their duration were applied the value of 0.10 and 1.10 × 10^{-3} s. According to the Stejskal and Ranner's reports,[21] when ln I/I_0 vs g^2 were plotted, where I and g are the echo intensity and (pulsed) gradient strength, respectively, the slope of the line given by $D/(\Delta - \delta/3)\gamma^2\delta^2$. Here, δ, γ, and Δ are the duration, gyromagnetic ratio, and the time separation, respectively, between the magnetic field gradient pulses. The hydrodynamic radius (R_h) was estimated by eq 1

$$R_h = \frac{k_B T}{6\pi\eta D} \tag{1}$$

where η is the viscosity coefficient and k_B is the Boltzmann constant.

Determination of Association Constants. The determination of the association constants of the complex between the β-CD-PEG dimer and the Ad-PEG dimer were carried out by measuring the difference between the chemical shifts of the Ad-PEG dimer alone and the same guest with increasing the concentration of β-CD-PEG dimer. For the systems of 1:1 inclusion complex between guest and host, equilibrium constants (K_c) were estimated by a modification of the Benesi–Hildebrand equation,[22] using eq 2:

$$\frac{1}{\Delta H_z} = \frac{1}{K_c} \cdot \frac{1}{[R]_0 \Delta\delta} \cdot \frac{1}{[\beta\text{-CD}]} + \frac{1}{[R]_0 \Delta\delta} \tag{2}$$

The association constant can be calculated from the slope of the straight line obtained by plotting $1/\Delta H_z$ vs $1/[\beta$-CD].

β-Cyclodextrin—Poly(ethylene glycol) (β-CD-PEG) Dimer. A solution of PEG-diacid 0.56 g (0.93 mmol) in DMF (15 mL) was added to a solution of DCC 1.7 g (8.2 mmol) and HOBT 1.2 g (8.9 mmol) in DMF (15 mL) at 0 °C. After 1 h, a solution of 6-NH_2-β-CD 3.0 g (2.6 mmol) in DMF (25 mL) was added to the reaction mixture, and the mixture was stirred at 0 °C for 2 h. It was allowed to warm to room temperature and stirred overnight. Insoluble materials were removed by filtration, and the filtrate was poured into acetone (400 mL). The precipitate was collected and washed with acetone, and then the crude product was purified by a Sephadex G-25 column chromatography (eluted with water). Yield: 373 mg (15%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.38 (s, 2H, −N*H*−), 5.71 (m, 28H, O(2)*H* and O(3)*H* of β-CD), 4.88 (m, 14H, C(1)*H* of β-CD), 4.47−4.25 (m, 12H, O(6)*H* of β-CD), 3.64−3.40 (m, 110H, C(2)*H*, C(3)*H*, C(4)*H*, C(5)*H*, C(6)*H* of β-CD and −CH_2−

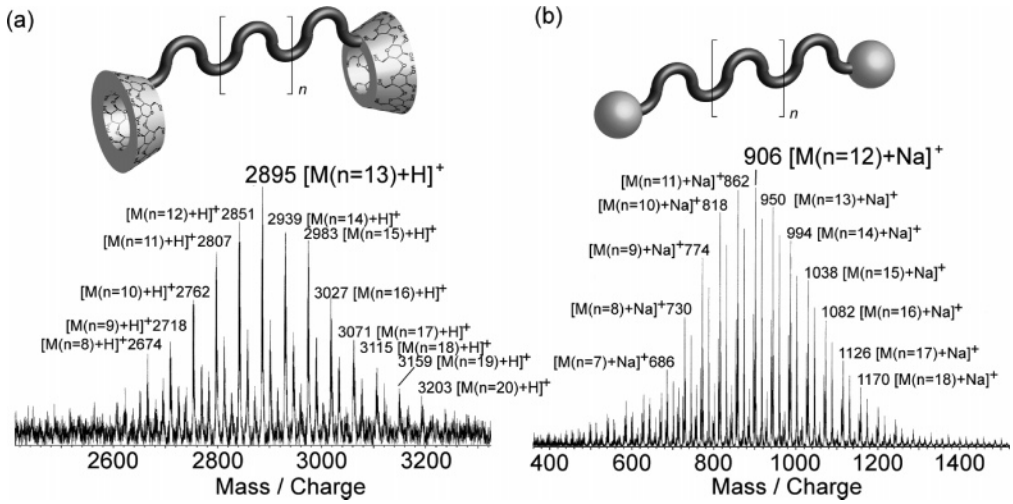


Figure 1. MALDI−TOF mass spectra of the β-CD-PEG dimer (a) and the Ad-PEG dimer (b).

of PEG). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.1 (*C*=O), 102.5 (*C*(1) of β-CD), 81.5 (*C*(4) of β-CD), 73.8 (*C*(3) of β-CD), 72.6 (*C*(2) of β-CD), 72.3 (*C*(5) of β-CD), 70.8 (*C*(5′) of β-CD), 70.4 (*C*(6′) of β-CD), 70.1 (-CH_2− of PEG), 60.6 (*C*(6) of β-CD). MALDI−TOF MS (*n*; ethylene glycol unit number in PEG): 2674 [β-CD dimer (n = 8) + H]$^+$, 2718 [β-CD dimer (n = 9) + H]$^+$, 2762 [β-CD dimer (n = 10) + H]$^+$, 2807 [β-CD dimer (n = 11) + H]$^+$, 2851 [β-CD dimer (n = 12) + H] $^+$, 2895 [β-CD dimer (n = 13) + H]$^+$, 2939 [β-CD dimer (n = 14) + H]$^+$, 2983 [β-CD dimer (n = 15) + H]$^+$, 3027 [β-CD dimer (n = 16) + H]$^+$, 3071 [β-CD dimer (n = 17) + H]$^+$, 3115 [β-CD dimer (n = 18) + H]$^+$, 3159 [β-CD dimer (n = 19) + H]$^+$, 3203 [β-CD dimer (n = 20) + H]$^+$.

Bisadamantane—Poly(ethylene glycol) (Ad-PEG) dimer. A THF solution of PEG-diacid 2.4 g (3.8 mmol) in 40 mL was added to CDI 2.4 g (15 mmol) and stirred at 0 °C for 1 h. The resulting solution was added dropwise to the solution of 1-adamantanamine (2.9 g, 19 mmol) in THF (50 mL) and stirred at 0 °C for 1 h. It was allowed to warm to room temperature and stirred overnight. The resulting solution was poured into water (1 L), and the precipitate was separated by filtration. The filtrate was evaporated and the residue was purified by silica gel chromatography (eluent THF). Yield: 13.4 g (98%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.76 (s, 2H, −N*H*−), 3.74 (s, 4H, −CO−CH_2−O− of PEG), 3.55−3.49 (m, 40H, −CH_2− of PEG), 2.00 (s, 6H, C*H* of adamantyl), 1.94 (s, 12H, −NH−C−CH_2− of adamantyl), 1.62 (s, 12H, −CH−CH_2−CH− of adamantyl). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9 (C=O), 69.7 (methylene of PEG), 50.5 (adamantyl), 40.9 (adamantyl), 35.9 (adamantyl), 28.8 (adamantyl). MALDI−TOF MS (*n*; ethylene glycol unit number in PEG): 686 [M (n = 7) + Na]$^+$, 730 [M (n = 8) + Na]$^+$, 774 [M (n = 9) + Na]$^+$, 818 [M (n = 10) + Na]$^+$, 862 [M (n = 11) + Na]$^+$, 906 [M (n = 12) + Na]$^+$, 950 [M (n = 13) + Na]$^+$, 994 [M (n = 14) + Na]$^+$, 1038 M (n = 15) + Na]$^+$, 1082 [M (n = 16) + Na]$^+$, 1126 [M (n = 17) + Na]$^+$, 1170 [M (n = 18) + Na]$^+$.

Results and Discussion

Preparation of β-CD-PEG Dimer and Ad-PEG Dimer. The β-CD-PEG dimer was prepared by the reaction of PEG-dicarboxylic acid with 2 equiv of 6-amino-β-CD using DCC and HOBT in DMF.[9] (Scheme 1a) We chose an adamantyl moiety as a guest part, because adamantane derivatives are known to be included in a β-CD cavity strongly. The Ad-PEG dimer was similarly prepared by the reaction of PEG-dicarboxylic acid with 2 equiv of 1-adamantanamine (Scheme 1b).

Figure 1 shows the MALDI−TOF mass spectra of the β-CD-PEG dimer (a) and the Ad-PEG dimer (b), respectively. The signal (m/z = 2895) can be assigned as proton cation adducts of the β-CD-PEG dimer. The other signals were also assigned as the β-CD-PEG dimers based on the poly dispersity of PEG. (Figure 1a) The Ad-PEG dimers were detected as monosodium cation adducts. The Ad-PEG dimer also shows the polydispersity of PEG (m/z = 686−1170). (Figure 1b) The other series of peaks of the β-CD-PEG dimer and the Ad-PEG dimer were also assigned as sodium and potassium adducts of the dimers.

Association Constants. Figure 2a shows the ^{1}H NMR spectra of the mixture of the β-CD-PEG dimer and the Ad-PEG dimer. The signals of methylene and methine protons of the adamantyl group on the Ad-PEG dimer were shifted toward downfield with an increase in the concentration of the β-CD-PEG dimer. The association constant K_c of the complex between the β-CD-PEG dimer and the Ad-PEG dimer was determined using the Benesi−Hildebrand plots based on the chemical shifts of methine proton of adamantane with various concentrations of the β-CD-PEG dimer. Figure 2b shows the Benesi−Hildebrand plots, which gave linear relation between the reciprocal of the concentration of the β-CD-PEG dimer and that of the shift, giving the association constant of 1.21×10^4 M^{-1}. The association constant between adamantane carboxylate and β-CD was reported to be 3.98×10^4 M^{-1}.[23] The associate constant of the complex between the β-CD-PEG dimer and the Ad-PEG dimer is similar to that of the complex between adamantane carboxylate and native β-CD.

NMR Measurements. To study the structure of the inclusion complex of the β-CD-PEG dimer with the Ad-PEG dimer, the ROESY NMR measurement was carried out. Figure 3 shows the ROESY NMR spectrum of the mixture of the β-CD-PEG dimer (5 mM) and the Ad-PEG dimer (5 mM). The peak of methine (H_a) proton of the adamantyl group was correlating well with inner protons (C(3)−*H*) of β-CD, and the peak of methine (H_b) and methylene (H_c) protons were correlating with inner protons (C(3)−*H*, C(5)−*H*) of β-CD, indicating that an adamantyl moiety inserts from the end of the secondary hydroxyl group side of β-CD. Moreover, there are cross-peaks between H_a/H_b and C(3)−*H,* indicating that the adamantyl moiety is deeply included in a cavity of β-CD.

Diffusion Coefficients by PFGSE NMR. The pulsed field gradient spin−echo (PFGSE) NMR technique was used to determine diffusion coefficients of the supramo-

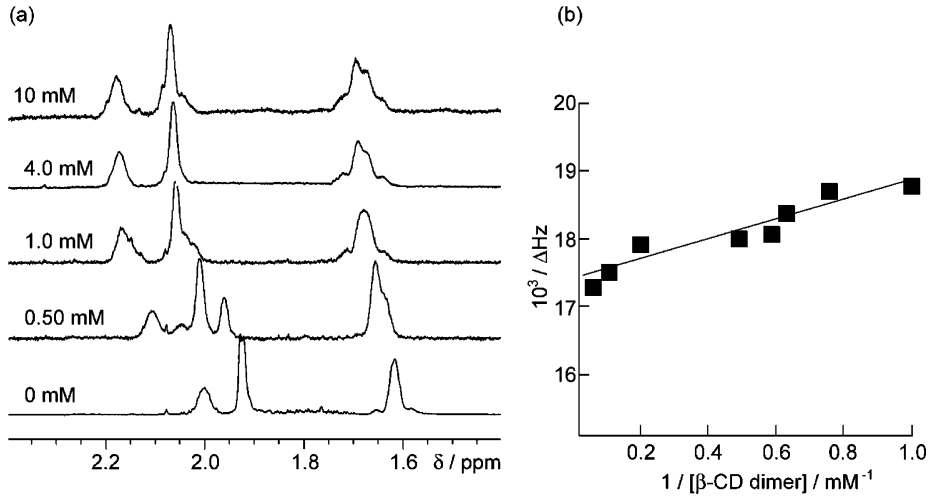


Figure 2. ^{1}H NMR spectra of the Ad-PEG dimer (1.0 mM) in the presence of the β-CD-PEG dimer in D_2O at 30 °C (a) and the Benesi−Hildebrand plots of the β-CD-PEG dimer−Ad-PEG dimer system (b).

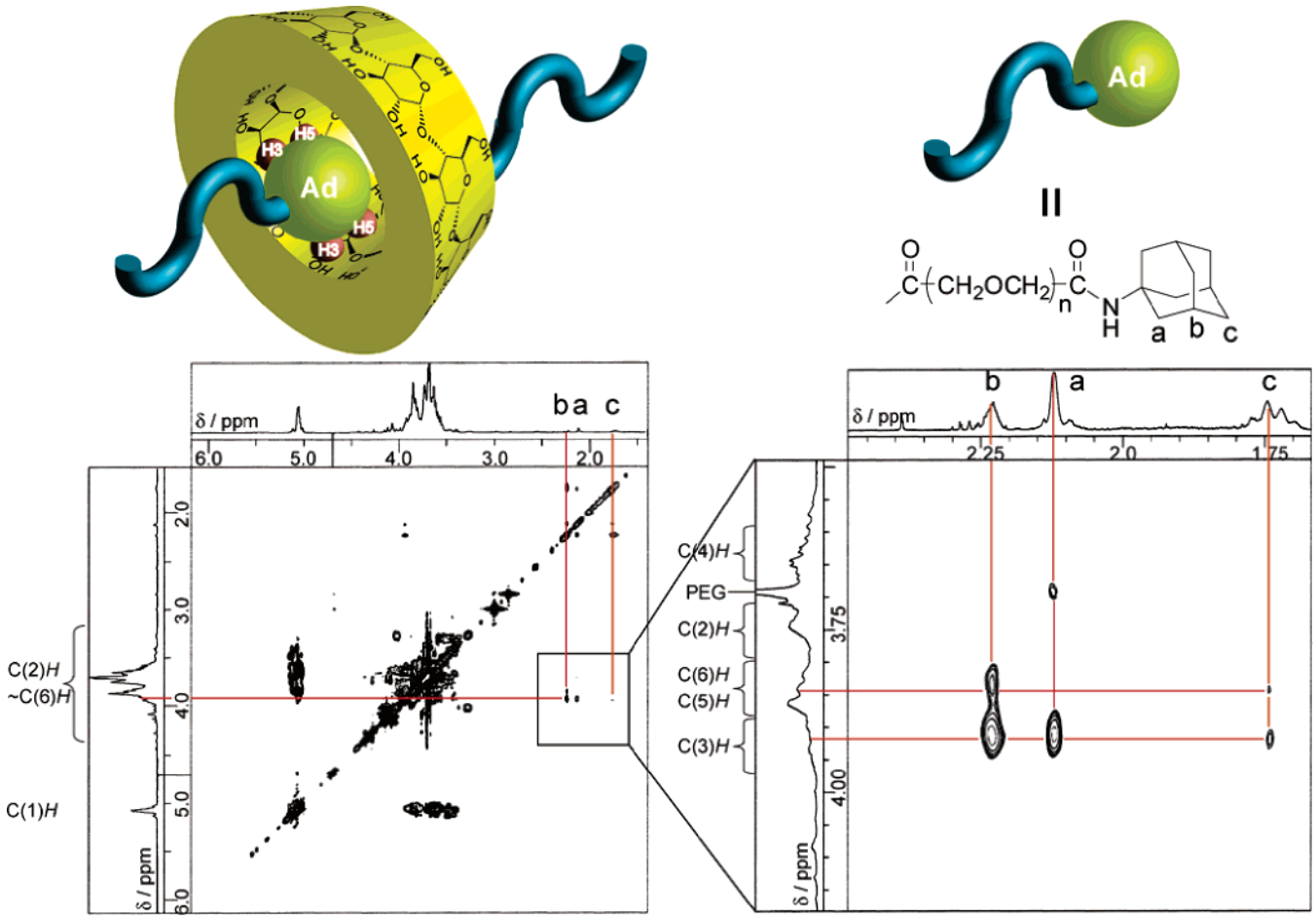


Figure 3. The 600 MHz ROESY NMR spectrum of a 1:1 mixture of the β-CD-PEG dimer and the Ad-PEG dimer in D_2O at 30 °C.

lecular polymer between the β-CD-PEG dimer and the Ad-PEG dimer. It is difficult to characterize supramolecules, such as the cyclodextrin supramolecular complex, by mass spectrometry et al. because of their dynamic nature. Recently, there are some papers on the NMR diffusion measurements to probe polymer solutions and supramolecular complexes.[24−29] This technique provides a direct measure of diffusion coefficients, the size of the particle, from the infinite dilution value. The light-scattering methods are important to determine the size of the thermodynamic supramolecular polymers. However, since the β-CD-PEG dimer and the Ad-PEG dimer did not have satisfactory solubility in water, it is difficult to determine the diffusion coefficients of the supramolecular polymer between the β-CD-PEG dimer and the Ad-PEG dimer by light scattering. Figure 4a shows the apparent diffusion coefficients for the supramolecular polymer between the β-CD-PEG dimer and the Ad-PEG dimer at various concentrations with 1:1 ratio of [β-CD-PEG dimer]:[Ad-PEG dimer]. The hydrodynamic radius values (R_h) determined at an infinite dilute of the mixture are

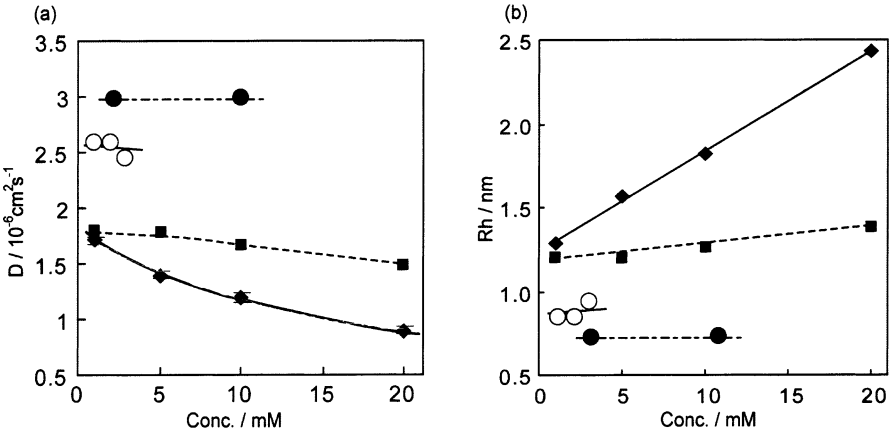


Figure 4. Concentration dependence of (a) diffusion coefficient values (D) and (b) hydrodynamic radius values (R_h) of supramolecular polymers formed between the β-CD-PEG dimer and the Ad-PEG dimer (filled rhombus), the β-CD-PEG dimer (filled square), the Ad-PEG dimer (open circle), and α-CD (filled circle) in D_2O at 30 °C by NMR.

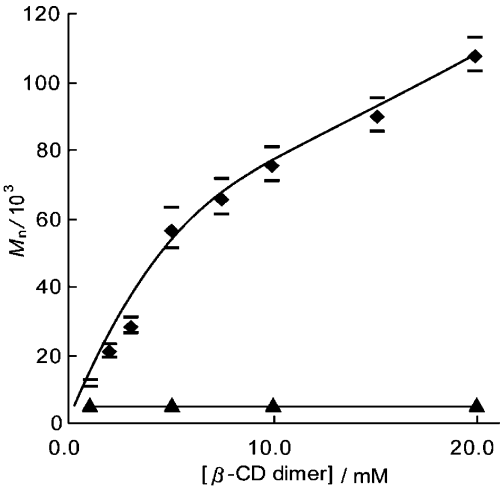
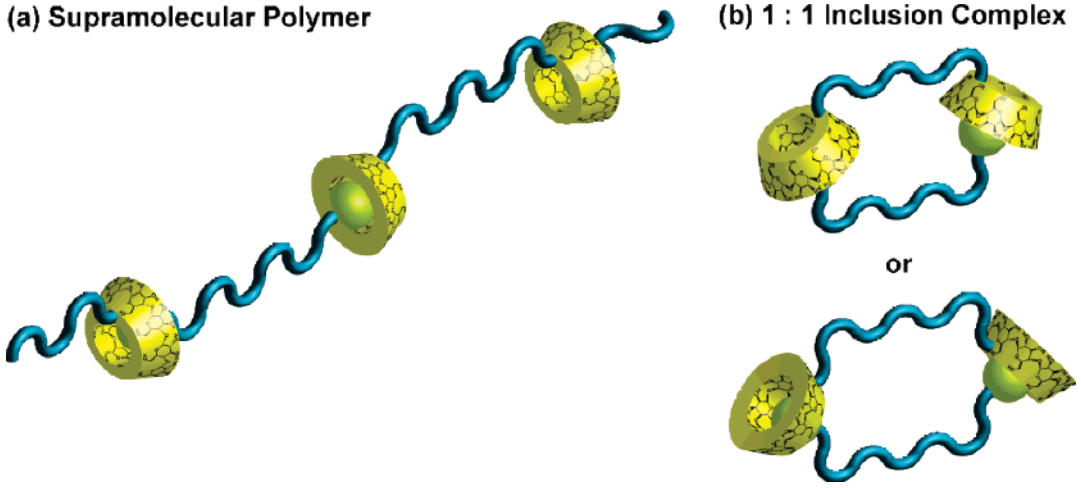


Figure 5. Concentration dependence of number-average molecular weights (M_n) for 1:1 mixtures of the β-CD-PEG dimer and the Ad-PEG dimer (rhombus). The triangle plots showed the concentration dependence of M_n of the β-CD-PEG dimer in aqueous solutions at 40 °C by VPO measurements.

shown as a function of moles mixture in Figure 4b. Diffusion coefficients (D) of the supramolecular polymer constructed from the mixture of the β-CD-PEG dimer and the Ad-PEG dimer decrease with increasing concentration; however, only the β-CD-PEG dimer and the Ad-PEG dimer still remained in any concentrations. The values of R_h of the supramolecular polymer increase with increasing concentrations from 1.22 to 2.4 nm. On the other hand, the R_h value of the β-CD −PEG dimer and α-CD did not change at any concentration. These results indicate that the mixture of the β-CD-PEG dimer and the Ad-PEG dimer formed supramolecular polymers. However, the D and R_h values of the supramolecular polymer were smaller than those of a theoretical model polymer. There are some reasons that the D value of the supramolecular polymer was estimated smaller than that of the theoretical model of the supramolecular species. The supramolecular polymer between the β-CD-PEG dimer and the Ad-PEG dimer was formed by the hydrophobic interaction. The β-CD-PEG dimer and the Ad-PEG dimer exchange each other much faster than the NMR time scale. Therefore, during diffusion, they dissociate and associate frequently. So the supramolecular species can be seen much smaller than the real size (supramolecular size) like the M_n measured by static methods like VPO. Actually, we could not detect the end group of the supramolecular polymer by the ^1H NMR measurements, because it is too fast to detect individual species on the NMR time scale. Another possibility is that the supramolecular polymer gave more compact forms than the some of each component, because connecting points might put together each other by some intermolecular interactions. In conclusion, when the β-CD-PEG dimer and the Ad-PEG dimer formed the supramolecular polymer, the molecular sizes

Scheme 2



might be estimated to be smaller by the PFG NMR than by the theoretical model.

Vapor Pressure Osmometry Measurements. The technique of vapor pressure osmometry (VPO) has been used to estimate association constants of supramolecular complexes.[30] We measured the molecular weight (M_n) of a 1:1 mixture of the β-CD-PEG dimer and Ad-PEG dimer by VPO measurements at 40 °C and estimated molecular weight of supramolecular polymers. The observed molecular weight (M_n) was found to increase with increasing 1:1 mixtures of the concentration, which shows dependence on the concentration. However, molecular weights of the β-CD-PEG dimer are almost independent of the concentration. The M_n for the β-CD-PEG dimer and the Ad-PEG dimer at 5 mM gave higher than 60 000 and reached about 100 000 at 20 mM. These results indicate that the β-CD-PEG dimer and the Ad-PEG dimer formed the supramolecular polymers of high molecular weight at high concentrations.

Previously, β-CD epichlorohydrin bridged polymer was reported to have interactions with the PEO bridged adamantane dimer.[16a,17] However, it is difficult to observe the correlations of the inclusion complex because of broad signals of β-CD epichlorohydrin bridged polymer. In their paper, the adamantyl group of the polymer was described to insert from the side of primary hydroxyl groups at the narrower rim of β-CD.[17] These results are in contrast to our results. In our study, two plausible possibilities for the formation of intermolecular inclusion complexes, a 1:1 complex and intermolecular supramolecular polymers, are illustrated in Scheme 2. The 1:1 complex was supposed to prevent further shifts of the signals for adamantyl moieties as the concentration of the β-CD-PEG dimer increases because all the β-CD cavities were blocked with adamantyl groups. (Scheme 2b) In addition to the lower field shifts of the signals for adamantyl moieties in Figure 2a, the value of the hydrodynamic radius and the molecular weight by VPO suggest the formation of the self-organized intermolecular supramolecular polymers with increasing the concentration of the β-CD-PEG dimer. (Scheme 2a).

Conclusion

We have prepared the novel β-cyclodextrin host dimer and the adamantane guest dimer bound by poly(ethylene glycol). The β-cyclodextrin−PEG dimer has been shown to bind the adamantane−PEG dimer with the association constant of 1.21×10^4 M^{-1}. A 1:1 mixture of the β-cyclodextrin−PEG dimer and the adamantane−PEG dimer showed ROE correlations between the protons of adamantyl groups and the inner protons of β-cyclodextrin, indicating the formation of the inclusion complex of between the β-cyclodextrin−PEG dimer and the adamantane−PEG dimer. The mixture of the β-cyclodextrin dimer and the ditopic adamantane guest dimer was investigated in water by the pulse field gradient spin echo NMR. Diffusion coefficients decrease with increasing the concentration. These results show the formation of the self-organized intermolecular supramolecular polymer. The mixture of the β-cyclodextrin host dimer and the ditopic adamantane guest dimer formed supramolecular polymers of high molecular weight (M_n > 100 000) measured by vapor pressure osmometry. Now we are studying the dynamic aspects and properties of the supramolecular polymers.

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