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Bundling Two Polymeric Chains with γ-Cyclodextrin Cavity Contributing to Supramolecular Network Formation

Ryouji Kawabata, Ryo Katoono, Masayuki Yamaguchi, and Nobuhiko Yui*

School of Materials Science, Japan Advanced Institute of Science and Technology, Asahidai, Nomi, Ishikawa 923-1292, Japan

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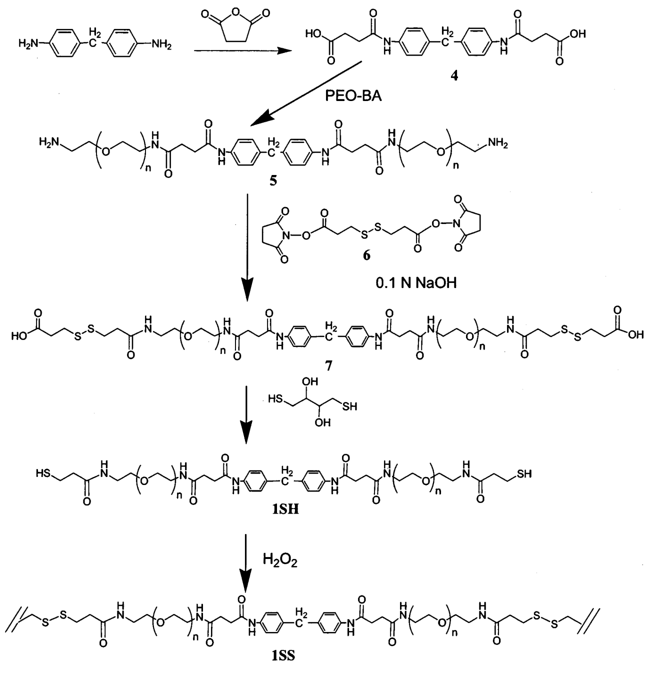
ABSTRACT: Poly(oxyethylene) (PEO) containing a 4,4′-diaminodiphenylmethane moiety with thiol groups at the terminals (**1SH**) and its inclusion complexes with γ- and β-cyclodextrins (γ- and β-CDs) (**2SH** and **3SH**) were prepared. ^{1}H NMR spectroscopy indicated that the two molecules of **1SH** were bundled with γ-CD through intermolecular interaction in **2SH** while the only one molecule was included with β-CD in **3SH**. The polymer **1SH** and the complexes **2SH** and **3SH** were chain-extended by disulfide linkage formation through oxidation reaction (**1SS**, **2SS**, and **3SS**, respectively). All of the complexes were confirmed by using gel permeation chromatography and viscosity measurement. Significant increases in the viscosity were observed for **2SH** and **2SS**, compared with **1SH**, **3SH** and **1SS**, **3SS**, respectively. It is suggested that the double-stranded inclusion complexation of the PEO chains by γ-CD like the bundling with its cavity acts as a cross-link and contributes to network formation.

Introduction

Supermolecules are molecular assemblies through noncovalent interactions such as van der Waals interaction, hydrogen bonding, electrostatic interaction, hydrophobic interaction, and coordination bonding.[1] A (pseudo)polyrotaxane is one form of these supramolecular polymers, in which two or more cyclic molecules are threaded onto a polymeric chain through intermolecular forces with (without) bulky end groups. For instance, a variety of polyrotaxane structures have been proposed in the past decade, since a pseudopolyrotaxane and a polyrotaxane consisting of cyclodextrins (CDs) and poly(oxyethylene) (PEO) were first reported by Harada et al.[2] Supramolecular structures seen in these polyrotaxanes have favorable characteristics on the mobility of cyclic compounds along the polymeric chain which is closely related to multivalent interaction with biological systems[3] and stimuli-responsive reversible changes.[4−8] On the other hand, many kinds of stimuli-responsive materials were reported in the field of supramolecular chemistry: for example, hydrogels,[5,9] other polymers,[10] molecular machines,[7] and electronic devices[8] have been interesting topics in recent years. In addition, hydrogels consisting of polyrotaxanes have been extensively studied in order to focus on controlling degradation rates suitable for tissue regeneration,[11] enhancing mechanical properties due to the sliding of cyclic compounds,[12] and reversively constructing microstructures of polyrotaxane aggregates as cross-links.[13] Previously, we have studied thermosensitive[5] and pH-dependent polyrotaxanes[6] consisting of CDs and some water-soluble polymers. If polyrotaxane structures could be controlled 2- or 3-dimentionally, these supramolecular materials should be promising candidates as actuators for artificial muscles. In the course of these studies, we have focused on the fact that γ-CDs form 1:2 inclusion complexes with some polymeric chains.[14,15] For instance, γ-CDs can include two polymeric chains (e.g., PEO, polyethylenimine, etc.) into their cavities. It is of our special interest that these double inclusion complexes of γ-CDs are effective to construct external stimuli-responsive networks.[16]

Scheme 1



Here we report on a supramolecular network formation via the inclusion complexation of PEO chains with γ-CDs. It is expected that such a 1:2 inclusion complex acts as a mobile cross-link in the network. We prepared inclusion complexes of PEO containing a 4,4′-diaminodiphenylmethane (DADP) moiety and thiol groups at the terminals (**1SH**) with γ-CD or β-CD, as shown in Schemes 1 and 2 (**2SH** and **3SH**), respectively. We assumed that one γ-CD molecule includes two chains of **1SH** at DADP moieties. The axial PEO chain could be chain-extended through oxidation reaction of the terminal thiol groups to disulfide bonds to form a network of PEO chains bundled with γ-CD cavities. The formation and deformation of the network could be reversible upon oxidation−reduction reaction between thiol groups and disulfide bonds.

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* Corresponding author. E-mail: yui@jaist.ac.jp.

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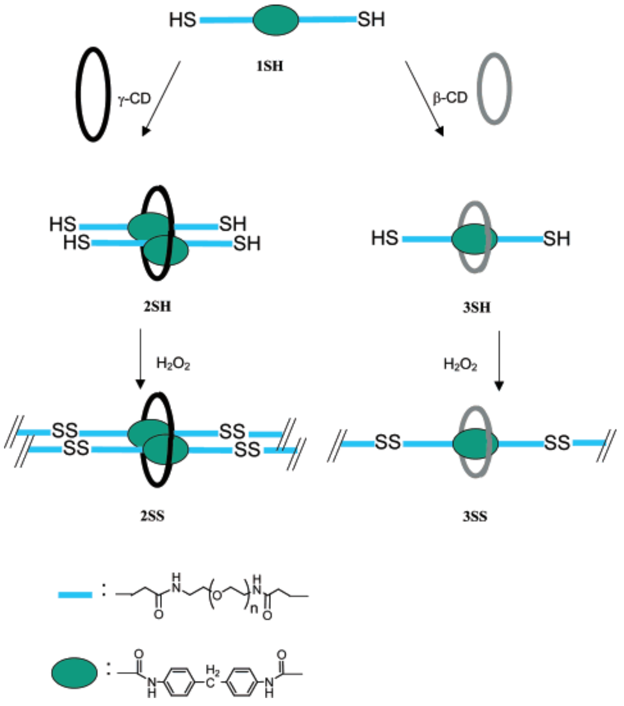
Scheme 2



Experimental Section

Materials. Poly(oxyethylene) bisamine (PEO-BA: $M_n = 3350$), DL-dithiothreitol (DTT), and 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) were purchased from Sigma Aldrich Inc. (St. Louis, MO). 3,3′-Dithiodipropionic acid (DTDP) and β-cyclodextrin (β-CD) were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). γ-Cyclodextrin (γ-CD) was purchased from Kanto Chemical Co., Ltd. (Tokyo, Japan). Benzotriazole-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) reagent was purchased from Kokusan Chemical Co., Ltd. (Tokyo, Japan). 1-Hydroxybenzotriazole (HOBt), *N*,*N*′-dicyclohexylcarbodiimide (DCC), and anhydrous *N*,*N*-dimethylacetamide (DMAc) were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). *N*-Diisopropylethylamine (DIEA) was purchased from Wako Pure Chemical Co., Ltd. (Osaka, Japan). *N*-Hydroxysuccinimide (HOSu) was purchased from Peptide Institute Inc. (Osaka, Japan).

Preparation of Dicarboxylic Acid 4.[17] To a solution of DADP (5.0 g, 25 mmol) in acetone (50 mL) was added succinyl anhydride (10 g, 100 mmol). The mixture was stirred for 2 h at room temperature. The resulting precipitates were collected by filtration to give **4** (9.2 g, 92%) as a white solid. ^{1}H NMR (D_2O, 300 MHz, 298 K) δ/ppm: 7.15 (4H, d, J = 7.6 Hz), 6.94 (4H, d, J = 7.6 Hz), 3.59 (2H, s), 2.60−2.43 (4H, m), 2.43−2.25 (4H, m).

Preparation of Poly(oxyethylene) Containing 4,4′-Diaminodiphenylmethane Moieties 5. To a solution of PEO-BA (3.0 g, 0.9 mmol) in DMAc (30 mL) were added **4** (60 mg, 0.4 mmol), BOP reagent (820 mg, 1.6 mmol), HOBt (250 mg, 1.6 mmol), and DIEA (320 μL, 1.6 mmol). The mixture was stirred for 24 h at room temperature, poured into 0.1 M HCl aqueous solution, and then extracted with dichloromethane. The organic layer was washed with 0.1 M NaOH aqueous solution and poured into diethyl ether. The resulting precipitate were collected by centrifugation to give **5** (2.5 g, 80%) as a white solid. ^{1}H NMR (D_2O, 300 MHz, 298 K) δ/ppm: 7.42−7.30 (4H, br), 7.22−7.10 (4H, br), 4.20−4.10 (4H, br), 4.10−4.00 (4H, br), 4.00−3.30 (582H, m), 3.30−3.18 (4H,

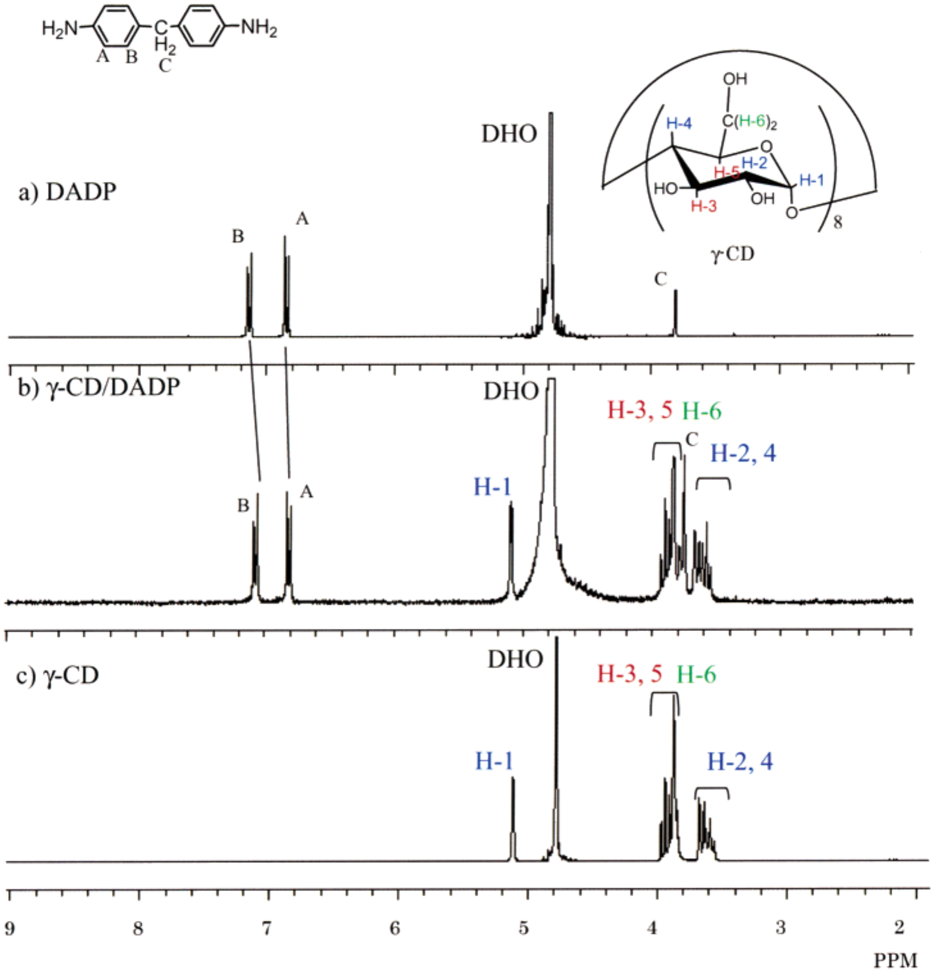


Figure 1. ^{1}H NMR spectra of DADP, γ-CD/DADP complex (1/2 molar ratio), and γ-CD in D_2O (0.1 M PBS, pH 6) ([γ-CD + DADP] = 5 mM).

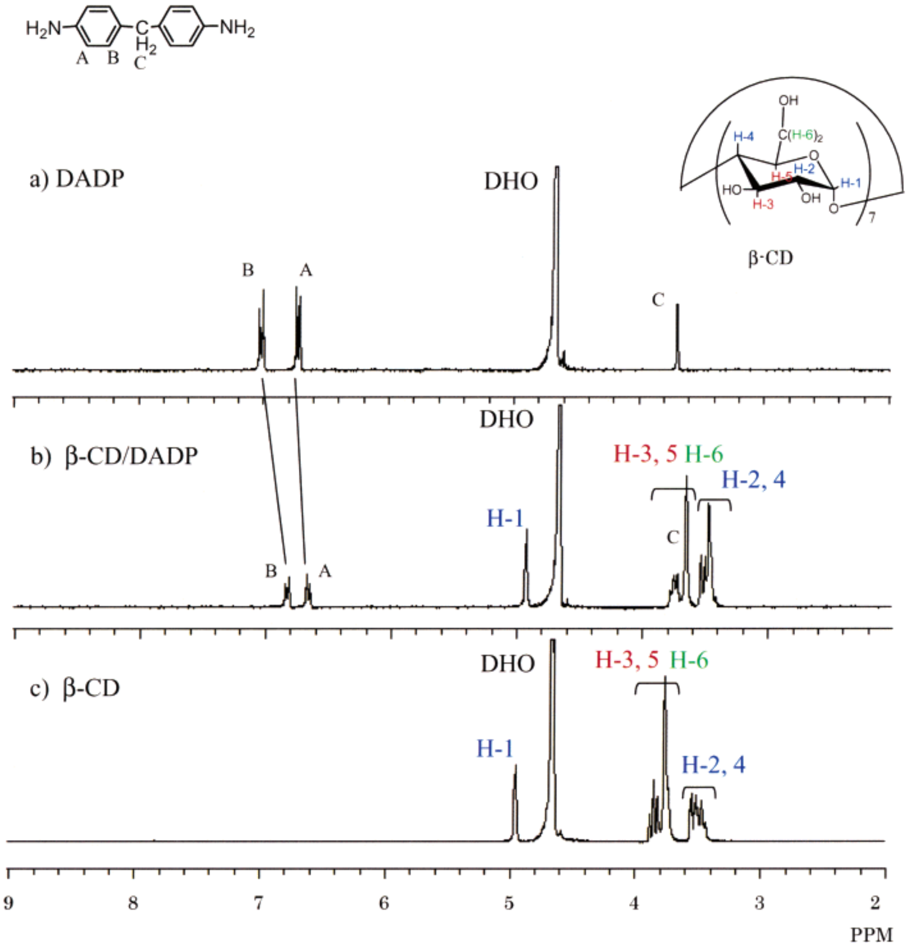


Figure 2. ^{1}H NMR spectra of DADP, β-CD/DADP complex (1/1 molar ratio), and β-CD in D_2O (0.1 M PBS, pH 6) ([β-CD + DADP] = 5 mM).

Table 1. Chemical Shifts (δ, ppm) of the Protons of γ- and β-CD with and without DADP in D_2O (0.1 M PBS, pH 6)

protons	γ-CD	β-CD	γ-CD/DADP 1/2 complex	β-CD/DADP 1/1 complex	$\Delta\delta$ (complex - free)
H-1 of γ-CD	5.116		5.099		−0.017
H-2, -4 of γ-CD	3.681−3.562		3.679−3.556		−0.002 to −0.004
H-3, -5, -6 of γ-CD	3.971−3.837		3.933−3.773		−0.038 to −0.064
H-1 of β-CD		4.960		4.932	−0.028
H-2, -4 of β-CD		3.562−3.442		3.546−3.452	−0.016 to −0.020
H-3, -5, -6 of β-CD		3.887−3.740		3.779−3.654	−0.108 to −0.086

br), 3.18−3.10 (4H, br), 3.10−3.0 (4H, br), 2.70−2.56 (4H, br), 2.56−2.44 (4H, br).

Preparation of 3,3′-Dithiodipropionic Acid Disuccinimidyl Ester 6.[18] To a solution of DTDP (2.1 g, 20 mmol) in 1,4-dioxane (90 mL) were added DCC (4.5 g, 22 mmol) and HOSu (2.5 g, 22 mmol). The mixture was stirred for 18 h at room temperature, and then the mixture was filtered. The filtrate was evaporated to dryness. The crude solid was recrystallized from 1,4-dioxane and hexane to give **6** (1.5 g, 40%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz, 298 K) δ/ppm: 3.16−3.07 (4H, m), 3.07−2.98 (4H, m), 2.81 (8H, s).

Preparation of 1SH. To a solution of **5** (2.5 g, 0.35 mmol) in dry DMAc (12.5 mL) was added **6** (390 mg, 1.05 mmol). The mixture was stirred for 24 h at room temperature and then poured into distilled water and extracted with dichloromethane. The solvent was evaporated to dryness to give **7** containing disulfide bonds with carboxyl groups at terminals as a white solid. The compound **7** was dissolved in PBS (0.1 M, pH 7, 50 mL) and added to a solution of DTT (200 mg, 1.3 mmol) in PBS (0.1 M, pH 7, 50 mL) and stirred for 5 h. The mixture was extracted with dichloromethane. The organic layer was washed with 0.1 M NaOH and saturated NaCl aqueous solutions and then poured into diethyl ether. The resulting precipitates were collected by centrifugation to give **1SH** (1.6 g, 64%) as a white solid. The contents of thiol groups in **1SH** were determined with DTNB method[19] by using the UV−vis spectroscopy, after **1SH** was dissolved with a 0.10 g/L of DTNB solution in 0.1 M pH 7.4 PBS. A molar absorptivity at 412 nm was used to quantify the 5-thio-3-nitrobenzoate anion (thiol groups 0.21 mmol/g). ^{1}H NMR (D_2O, 300 MHz, 298 K) δ/ppm: 7.43 (4H, d, J = 8.4 Hz), 7.35−7.20 (4H, br), 4.20−4.07 (4H, br), 4.07−4.00 (4H, m), 3.90−3.75 (8H, m), 3.75−3.40 (570H, br), 3.40−3.30 (4H, br), 3.30−3.15 (8H, br), 3.140 (4H, t, J = 10.2 Hz), 2.680 (4H, t, J = 13.5 Hz), 2.608 (4H, t, J = 13.5 Hz), 2.55−2.40 (8H, m).

^{1}H NMR Spectroscopy of γ- and β-CD/DADP. For each component of the complex, 5.0 mL solutions (0.1 M PBS at pH 6) of identical concentrations were prepared. The host solution of γ-CD was prepared by dissolving γ-CD (32.4 mg, 25 μmol) in D_2O (5.0 mL, 0.1 M PBS, pH 6). The guest solution of DADP was prepared by dissolving DADP (4.95 mg 25 μmol) in D_2O (5.0 mL, 0.1 M PBS pH 6). The two solutions were then combined to give a series of the samples with identical total concentration (5 mM) but containing different mole fractions (χ) of the two components. The ^{1}H NMR spectrum of each sample was then recorded, and these spectra were used to produce a graph of ($\Delta\delta\chi_{DADP}$) against χ shown as Job's plot ($\Delta\delta = \delta_{observed} - \Delta\delta_{c=1.0}$).[20] For the complex of β-CD and DADP, Job's plot was produced by the same method.

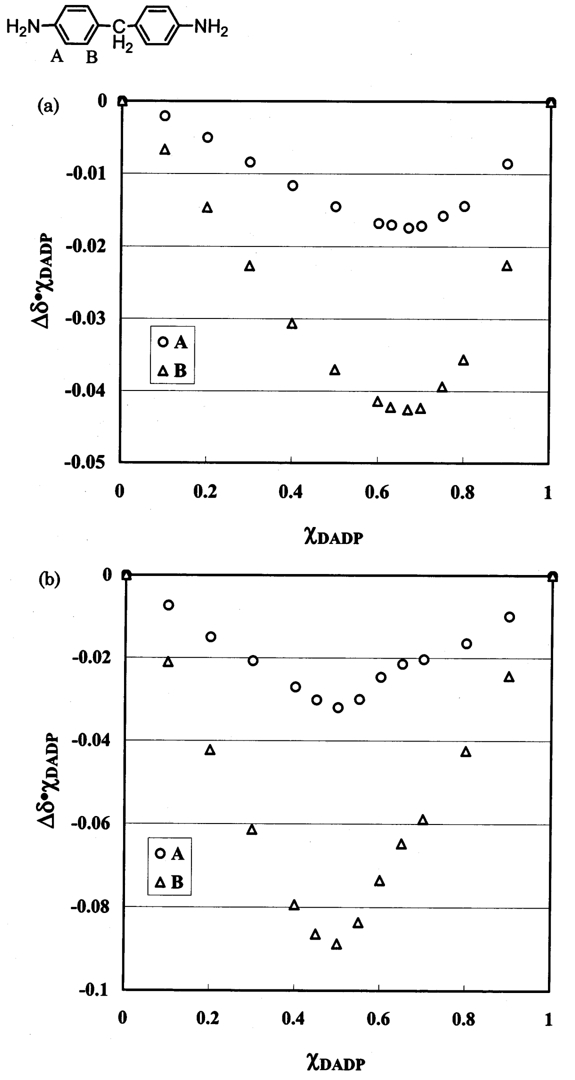


Figure 3. Job's plots for DADP complexation with γ-CD (a) and β-CD (b) in 0.1 M D_2O (0.1 M PBS, pH 6). χ_{DADP} denotes molar fraction of DADP.

Preparation of 2SH and 3SH and Their Oxidation. The inclusion complexes of **1SH** (500 mg, 70 μmol) with γ-CD (45 mg, 35 μmol), with β-CD (40 mg, 35 mmol), or without any CD were prepared by dissolving in PBS (1.0 mL, 0.1 M, pH 7.4). These solutions were sonicated for 1 h at 60 °C and then kept at room temperature for 24 h. These solutions (300 μL) were applied to the viscosity measurements. Hydrogen peroxide (6%, 40 μL) was added to each solution. After these solutions were stirred by a vortex mixer, the solutions (300 μL) were applied to the viscosity measurements. Oxidized samples of **1SH**, **2SH**, and **3SH** correspond to **1SS**, **2SS**, and **3SS**, respectively. All of the solutions were diluted with 0.1 M $NaNO_3$ aqueous solutions to ca. 50-fold volume and applied to GPC measurements.

Gel Permeation Chromatography (GPC) of the Complexes. The GPC measurements were conducted at 30 °C with a TOSOH HLC-8120GPC system containing a TSK-gel α-2500 and a TSK-gel α-4000 (TOSOH, Tokyo, Japan) calibrated by poly(oxyethylene) standards with RI detection. An aqueous solution of 0.1 M $NaNO_3$ was used as a mobile phase at 1.0 mL/min flow rate, and the injection volume was 30 μL.

Viscosity Measurements of the Complexes. The frequency dependence of oscillatory sheer viscosity was evaluated by a cone-and-plate rheometer at 25 °C. The diameter was 40 mm, and the cone angle was 1.996°. The viscosity measurements were conducted in a rheometer (Rheosol-G3000, UBM Ltd., Kyoto, Japan). The dynamic frequency sweep experiments were carried out in the range 0.63−10.1 rad/s.

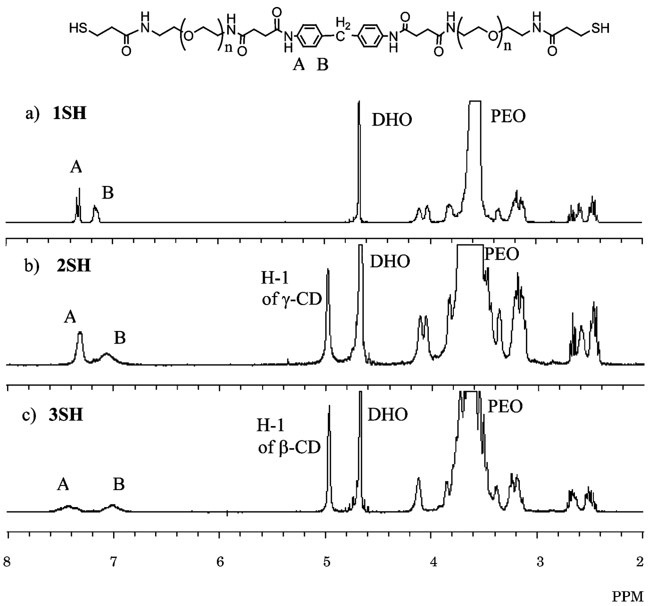


Figure 4. ^{1}H NMR spectra of **1SH** (a), **2SH** (b), and **3SH** (c) in D_2O (17 mM).

Results and Discussion

Preparation of Polymer 1 and Pseudo(poly)rotaxanes 2 and 3. The polymer **1** was prepared in four steps from DADP (Scheme 1). Treatment of DADP with succinic anhydride in acetone gave dicarboxylic acid **4**. Condensation of **4** with PEO-BA in DMAc gave the polymer **5** with amino groups at each terminal. The disulfide groups were introduced into **7** by reacting **5** with **6** in DMAc. Finally, cleavage reaction of the disulfide bonds in **7** by using DTT gave the polymer **1SH** containing a DADP moiety with thiol groups at both terminals. Compounds **4**−**7** were characterized by ^{1}H NMR spectroscopy (Experimental Section).

Pseudorotaxanes **2SH** and **3SH** were prepared by mixing the polymer **1SH** with γ- and β-CD in 0.1 M PBS at pH 7, respectively. Oxidation reaction of the pseudorotaxanes **2SH** and **3SH** with hydrogen peroxide gave the pseudopolyrotaxanes **2SS** and **3SS** with increasing their molecular weights, respectively (Scheme 2). The preparations of the polymers **1**−**3** were confirmed by ^{1}H NMR spectroscopy, GPC, and viscosity measurements.

^{1}H NMR Spectroscopy of γ- and β-CD/DADP. NMR spectroscopy provides one of the most powerful experimental tools for studying host−guest chemistry in solution.[21] When mixing CDs and DADP solutions in D_2O (0.1 M PBS, pH 6), the complexation-iduced shifts were observed at the aromatic protons of DADP in ^{1}H NMR spectroscopy (Figures 1 and 2). The chemical shifts for the H-3, H-5, and H-6 of γ- and β-CD shifted upfield higher than those for H-1, H-2, and H-4 (Table 1). The H-3 and H-5 atoms are directed toward the interior of the cavity of γ- and β-CD, whereas the H-1, H-2, and H-4 atoms are located on the exterior. These results indicate that DADP molecules are located in the cavities of γ- and β-CD. For γ-CD and DADP, the changes in $\Delta\delta\chi$ for the aromatic protons of DADP were plotted as a function of the mole fraction of DADP to give a peak at 0.67 (Figure 3a), indicating the formation of a 1:2 complex. For β-CD and DADP, the changes in $\Delta\delta\chi$ for the aromatic protons of DADP gave a peak at 0.50 (Figure 3b), indicating the formation of a 1:1 complex. Figure 4 shows the

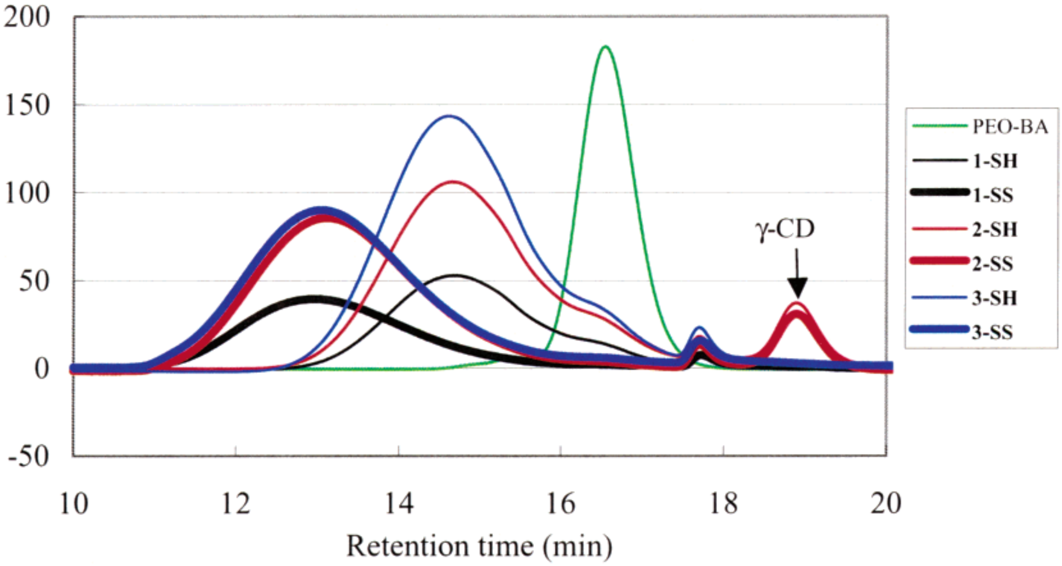


Figure 5. Gel permeation chromatograms of the complexes **1-3SH**, **1-3SS**, and PEO-BA. Each concentration was ca. 1.4 mM, and each injection volume was 30 μL.

Table 2. Molecular Weight of the Complexes Determined from Gel Permeation Chromatography

	retention time of peak top (min)	M_n (calcd from PEO)	M_w (calcd from PEO)
PEO-BA	16.5	2.4K	2.6K
1SH	14.7	8.0K	13K
1SS	13.0	31K	58K
2SH	14.7	6.5K	13K
2SS	13.1	25K	51K
3SH	14.6	6.8K	14K
3SS	13.1	27K	55K

^{1}H NMR spectra of **1-3SH**. The signals assigned to the aromatic group were shifted upfield as observed in the complex of CDs with DADP (B). However, these signals were broadened so that Job's plots could not be produced (A, B). This result suggests that the DADP moiety of **1SH** as well as PEO repeating units is also included into the cavity of γ- and β-CD. These results support our assumption that γ-CD includes two **1SH** chains at DADP moieties. These chemical shifts were observed at averaged states between free and fully complexed molecules in the NMR time scale. Each molecule of these inclusion complexes can be consistently exchanging each other. Therefore, it is considered that the junctions of γ-CD including DADP moieties can act as mobile cross-links in the following viscosity measurements.

GPC and Viscosity Measurements of the Complexes. Figure 5 shows GPC chromatogram for polymer **1**, complexes **2** and **3**, and PEO-BA. Here we confirmed that the extension reactions of the axial polymeric chains occurred through oxidation-reaction. It is imagined that the inclusion complex **2SH** was dissociated into γ-CD and **1SH** in the diluted GPC condition through approximately 50-fold volume as a mobile phase. Actually, the signal assigned to free γ-CD was observed in **2SH** and **2SS**, while any signal for free β-CD was not observed in the spectra of **3SH** and **3SS**. This result suggests that β-CD can be threaded onto **1SH** in **3SH** and **3SS**. We considered that the components of high molecular weight at GPC chromatogram are only axial polymeric chains in **2SH** and **2SS**. On the basis of these GPC results, the effect of CD inclusion on the viscosities of **1-3SS** can be comparably discussed later.

As compared among the spectra of **1-3SH**, the shapes and retention times of the peak tops (14.6−14.7 min) were almost the same as each other. According to the spectra of **1-3SS** compared with **1-3SH**, it is suggested that the complexes **2SH** and **3SH** were chain-extended through oxidation reaction as **1SH** because all of the retention times of signals from **1-3SS** were almost the same (13.0−13.1 min). As a consequence, it was confirmed that CDs could not inhibit extending reaction through

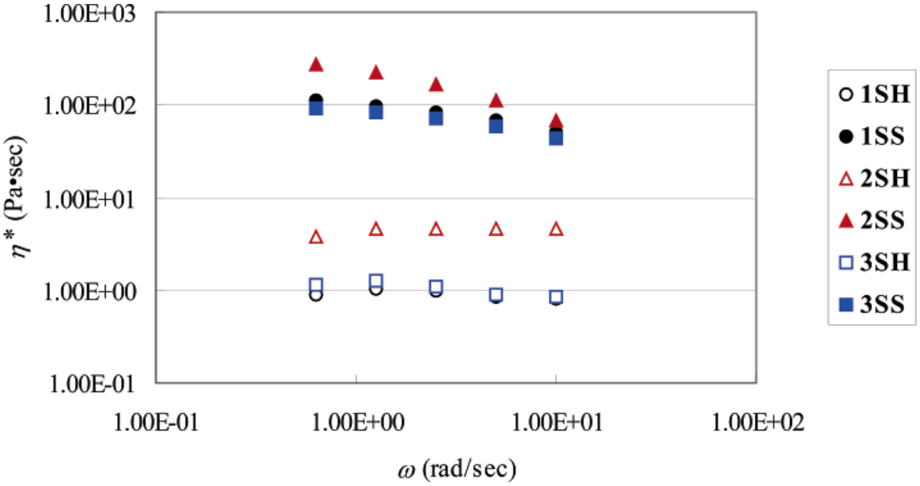


Figure 6. Viscosity of the complexes. Each concentration was 70 mM.

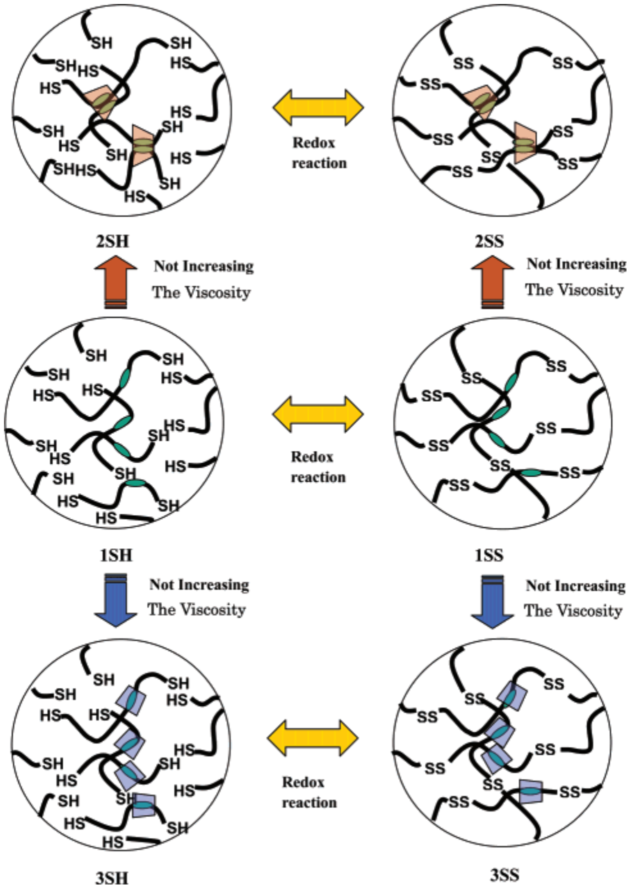


Figure 7. Schematic representation of **1-3SH** and **1-3SS**.

oxidation reaction. The content of thiol groups in **1SH** was 0.21 mmol/g from the DTNB method, while the terminal thiol content in **1SH** was calculated as 0.25 mmol/g from the GPC measurements (M_n was calculated as 8000). Therefore, it is obvious that the results of the GPC measurements are adequate. The average molecular weights and the retention times calculated from the GPC measurements are summarized in Table 2.

Figure 6 shows the angular frequency dependence of the absolute values of dynamic shear viscosities for the polymers. The viscosity of **1SS** was about 100-fold higher than **1SH**. It is considered that this increase in the viscosity is derived from extension of the polymer length through oxidation reaction.[22]

The complex **2SH** showed higher viscosity than **1SH** without adding hydrogen peroxide, while **3SH** was almost the same in the viscosity as **1SH**. Moreover, after oxidation reaction, the viscosity of **2SS** was also higher than those of **1SS** and **3SS**. In the presence of γ-CD, it is expected that two or more PEO chains are linked to each other by introducing two PEO chains into the γ-CD cavity. It is considered that apparent molecular weight increase is due to the formation of double-stranded inclusion. In the presence of β-CD, PEO chains cannot be linked to each other because β-CD includes only one polymeric chain in its cavity. Indeed, in the β-CD system, which is single-stranded inclusion complex, the viscosity change was scarce between with and without CDs. An outstanding feature in the viscosity measurements was observed for the double-stranded inclusion complex of γ-CD: the viscosity was significantly increased by adding γ-CDs into **1SH** and **1SS**. These results strongly suggest that apparent molecular weight (viscosity) of **2SH** increases due to the formation of mobile cross-links, as schematically illustrated in Figure 7.

Conclusion

Inclusion complexes of **1SH** with CDs were prepared (**2SH** and **3SH**). The results of ^{1}H NMR spectroscopy suggest that one γ-CD molecule can include two axial PEO chains at DADP moieties to act as a mobile cross-link. The viscosities of **1SH**, **2SH**, and **3SH** were investigated before and after the oxidation reaction (**1SS**, **2SS**, and **3SS**). It was confirmed that the axial PEO chains were chain-extended by oxidation reaction from the result of GPC and viscosity measurements. The complex **2SH** was higher in the viscosity than **3SH** and **1SH**, indicating the double inclusion complex of PEO chains into γ-CD cavity can act as a cross-link. A similar tendency was observed after the oxidation reaction, suggesting the important role of bundled polymeric chain within γ-CD cavity on network formation.

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