

Thermodynamic Analysis of Inclusion Complexation between α -Cyclodextrin-Based Molecular Tube and Poly(ethylene oxide)-*block*-poly(tetrahydrofuran)-*block*-poly(ethylene oxide) Triblock Copolymer

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Thermodynamic analysis of inclusion complexation between α -cyclodextrin-based molecular tube (MT) and poly(ethylene oxide)-*block*-poly(tetrahydrofuran)-*block*-poly(ethylene oxide) triblock copolymer (PEO-*b*-PTHF-*b*-PEO) was carried out in terms of isothermal titration calorimetry. As for the titration of MT to PEO in aqueous solution, no strong exothermic peak was observed. On the contrary, strong exothermic peaks were observed for the titration of MT to PEO-*b*-PTHF-*b*-PEO in aqueous solution, which is attributable to inclusion complexation between MT and the triblock copolymer. Thermodynamic parameters were obtained for the process of inclusion complexation between MT and PEO-*b*-PTHF-*b*-PEO by changing the molecular weight of MT and the temperature. The stoichiometry of inclusion complexation changes in relation to the molecular weight of MT. Interestingly, it was found that MT with a large molecular weight behaves as the host molecule having multibinding sites. Thermodynamic parameters suggested that van der Waals interaction, hydrophobic interaction, and hydrogen bond play an important role to determine the magnitude of ΔH . Some thermodynamic parameters clearly indicated that the dehydration of the triblock copolymer is a key factor in inclusion complexation between MT and PEO-*b*-PTHF-*b*-PEO. These results afford a deeper insight into the mechanism of the macromolecular recognition process.

Introduction

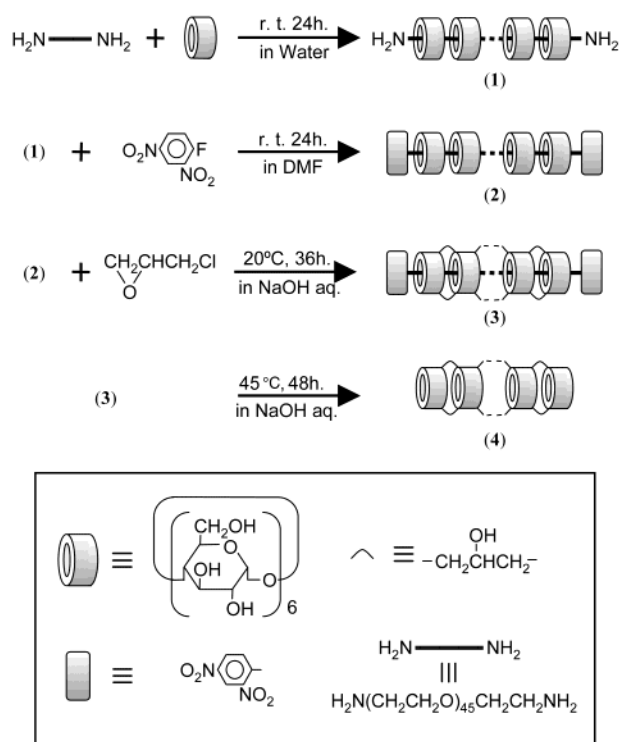
Cyclodextrin (CD) is a cyclic oligomer of α -D-glucose linked by α -1, 4-glycoside bonds.¹ The most familiar members are α -, β -, and γ -CDs consisting of six, seven and eight glucose units, respectively. CD has a hollow truncated cone-like structure, and the environment inside the cavity is hydrophobic due to C³H, C⁵H, and C⁶H hydrogens and O⁴ ether oxygen. Inclusion complexation of CDs has been studied for more than three decades.² Until the 1990s, the study of the molecular recognition by CD focused on inclusion complexation between CD and low molecular weight compounds. In the 1990s, Harada et al. reported macromolecular recognition by CD, namely CDs selectively form an inclusion complex with a linear polymer.³ When an aqueous solution of poly(ethylene oxide) (PEO) is added to an α -CD saturated aqueous solution, the solution becomes turbid within a few minutes. The inclusion complex consisting of α -CDs and PEO can be obtained as a white precipitate in high yield.⁴ Since the environment of the CD cavity is hydrophobic, CD has been known as the host molecule for hydrophobic compounds. Thus, it is quite interesting that a hydrophilic polymer such as PEO forms an inclusion complex with α -CD. Although thermodynamic analysis affords some insight into the mechanism for inclusion complexation, it is difficult to analyze the thermodynamics of macromolecular recognition by CD. This is because two processes may occur simultaneously in inclusion complexation between CD and a polymer, i.e. the formation of inclusion complex and the aggregation of the inclusion complex. Baglioni et al. discussed the kinetics of inclusion complexation between α -CDs and PEO,

assuming that the time when the turbidity changes depends on the rate of inclusion complexation.⁵

Based on the inclusion complex consisting of α -CDs and PEO, Harada et al. prepared α -CD-based polyrotaxane, in which many α -CD molecules are threaded onto a PEO capped with bulky blocking groups.⁶ Moreover, they successfully prepared a tubular conjugate, so-called "molecular tube (MT)", by cross-linking the hydroxyl groups of adjacent α -CDs in the polyrotaxane.⁷ MT also can form an inclusion complex with various kinds of low molecular weight compounds. In our previous study, the thermodynamics of inclusion complexation between MT and sodium alkyl sulfonate (C_nSO₃Na) was reported.⁸ From the results of this thermodynamic analysis, it was suggested that van der Waals interaction and hydrophobic interaction contribute to inclusion complexation. The most important characteristic of MT is that MT can form an inclusion complex with a linear polymer without the precipitation of the inclusion complex. The macromolecular recognition by MT is an attractive subject not only as a model for the macromolecular recognition process in biology but also in the theoretical aspect. Although polymeric chains exhibit random coil conformations in solution, the flexibility of a polymeric chain may be lost in the cavity of MT. Ito et al. studied theoretical aspects of inclusion complexation between MT and a linear polymer based on Flory–Huggins lattice theory.⁹

In the present study, the thermodynamics for inclusion complexation between MT and poly(ethylene oxide)-*block*-poly(tetrahydrofuran)-*block*-poly(ethylene oxide) triblock copolymer (PEO-*b*-PTHF-*b*-PEO) was analyzed by isothermal titration calorimetry (ITC). As far as we know, this is the first report of thermodynamic data associated with the macromolecular rec-

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SCHEME 1: Preparation of α -Cyclodextrin-Based Molecular Tube

ognition process by MT. ITC is the best method to investigate the thermodynamics, because it allows simultaneous determination of both the free energy and the enthalpy changes at a given temperature, as well as precise determination of the heat capacity change from measurements at different temperatures.¹⁰ PTHF is more hydrophobic than PEO due to a longer methylene moiety between the ether oxygen atoms, and the solubility of PTHF in water is very poor.¹¹ Thus, it is hard to analyze thermodynamics of inclusion complexation between MT and PTHF in aqueous media. The modification of the hydrophobic molecule by PEO drastically improves the solubility in water. Therefore, a nonionic amphiphile triblock copolymer PEO-*b*-PTHF-*b*-PEO was prepared and used for the thermodynamic analysis of the macromolecular recognition process by MT.

Experimental Section

Materials. PTHF ($M_n = 650$), potassium-*tert*-butoxide, ethyl bromoacetate, *p*-toluenesulfonyl chloride, potassium phthalimide, hydrazine monohydrate, Wakogel C200, thionyl chloride, 4-(dimethylamino)pyridine (DMAP), pyrene, and pure water were purchased from Wako Pure Chemical Ind. (Osaka, Japan). Poly(ethylene oxide) methyl ether ($M_n = 2000$) was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). *p*-Toluenesulfonyl chloride and ethyl bromoacetate were purified by the usual methods. Sephadex G-50 and Sephadex LH-60 (Amersham-Pharmacia Biotech. Inc.) were used for preparative purification. A refractive index detector Model 133 (Gilson, Inc.), a Peristaltic pump P-1, and two-channel recorder REC-112 (Amersham-Pharmacia Biotech. Inc.) were used for gel permeation chromatography (GPC) analysis. ¹H NMR spectra were measured with by a Gemini 300 ¹H NMR instrument (Varian Inc.).

Preparation of MTs with Different Number-Average Molecular Weights (4). MT was prepared according to the method described by Harada et al. (Scheme 1).⁷ The preparative conditions were described in our previous reports.^{8,12} To

minimize the polydispersity, the prepared MT was fractionated by GPC [column, Sephadex G-50 (5×80 cm); solvent, water]. The number-average molecular weight (M_n) of the fractionated MT was analyzed by GPC [column, Sephadex G-75 (1×20 cm); solvent, water]. MTs with M_n of 4400, 5900, 8200, and 10000 (MT_{4.4}, MT_{5.9}, MT_{8.2}, and MT_{10.0}) were used for thermodynamic analysis (Table 1).

Preparation of PEO-*b*-PTHF-*b*-PEO (8). PEO-*b*-PTHF-*b*-PEO was prepared according to Scheme 2. The preparation of **8** was confirmed by ¹H NMR and GPC (Supporting Information).

Determination of Critical Micelle Concentration (CMC). CMC for PEO-*b*-PTHF-*b*-PEO was determined based on the fluorescent probe technique developed by Wilhelm et al.¹³ All solutions were prepared by dissolving PEO-*b*-PTHF-*b*-PEO in pure water. The concentration of the triblock copolymer ranged from 1.0×10^{-6} to 1.0×10^{-3} mol L⁻¹. Pyrene was dissolved in acetone (4.8×10^{-4} mol L⁻¹), and 5 μ L of the pyrene solution was added to each triblock copolymer aqueous solution (4 mL). The prepared solutions were stirred at room temperature for 24h. Steady-state fluorescent spectra were measured using a FP-777 spectrofluorometer (Japan Spectroscopic Co., Ltd.) at 25 °C. The excitation spectrum was observed at 390 nm. From the change in I_{338}/I_{333} value in the excitation spectra, the micelle formation was examined. I_{333} and I_{338} denote the intensities in excitation spectra at 333 and 338 nm, respectively. CMC was determined to be 2.3×10^{-5} mol L⁻¹.

Isothermal Titration Calorimetry. The isothermal titration calorimetric experiments were carried out using an Omega isothermal titration calorimeter (MicroCal, Inc.). MT_{4.4}, MT_{5.9}, MT_{8.2}, and MT_{10.0} were used in this study. As for MT_{4.4}, MT_{8.2}, and MT_{10.0}, measurements were carried out at 298 K, and the measurements for MT_{5.9} were carried out at 288, 298, and 308 K. The reaction cell and an injection syringe were filled with triblock copolymer aqueous solution and MT aqueous solution, respectively. This arrangement minimized the contributions from the heat of dilution of the block copolymer. Pure water was used as a solvent throughout the work. Twenty portions, 10 μ L each, of the MT solution were injected into the triblock copolymer solution at 3 min intervals, and the binding heat was recorded at 298K. The blank measurements, i.e., pure water in the cell was titrated by MT aqueous solution in the syringe, were also carried out at 288, 298, and 308 K to correct the observed binding heats. The calorimetric data were processed by the computer program Origin for ITC, Version 2.9 (MicroCal, Inc.). As a reference, the PEO aqueous solution was also titrated by the MT aqueous solution. The experimental conditions are summarized in Table 1.

Results

Inclusion Complexation between MT and PEO. Figure 1a shows the signal of the isothermal titration for inclusion complexation between MT ($M_n = 5900$) and PEO ($M_n = 2000$). Unexpectedly, the exothermic peaks were very small. Since we could not obtain the appropriate titration curve from the ITC signal, it was impossible to analyze the thermodynamic parameters for inclusion complexation between MT and PEO.

Inclusion Complexation between MT and PEO-*b*-PTHF-*b*-PEO at 298 K. Parts b and c of Figure 1 show the signal of the isothermal titration and the binding isotherm for inclusion complexation between MT and PEO-*b*-PTHF-*b*-PEO at 298 K, respectively. Strong exothermic peaks were obtained. The enthalpy change ΔH , the association constant ($K_a = [\text{complex}]/[\text{MT}][\text{copolymer}]$), and the stoichiometric number n were

TABLE 1: Experimental Condition of ITC Measurement

| code | M_n of MT ^a | M_w/M_n^{-1} of MT ^a | concentration of MT, $\times 10^4$ mol L ⁻¹ | guest | concentration of guest, $\times 10^5$ mol L ⁻¹ | T , ^b K |
|------------------------------|--------------------------|-----------------------------------|--|------------------|---|----------------------|
| MT _{5,9} /PEO(298) | 5900 | 1.40 | 3.0 | PEO ^c | 2.0 | 298 |
| MT _{4,4} /TBC(298) | 4400 | 1.38 | 3.5 | TBC ^d | 2.0 | 298 |
| MT _{5,9} /TBC(288) | 5900 | 1.40 | 3.0 | TBC ^d | 2.0 | 288 |
| MT _{5,9} /TBC(298) | 5900 | 1.40 | 3.0 | TBC ^d | 2.0 | 298 |
| MT _{5,9} /TBC(308) | 5900 | 1.40 | 3.0 | TBC ^d | 2.0 | 308 |
| MT _{8,2} /TBC(298) | 8200 | 1.45 | 2.0 | TBC ^d | 2.0 | 298 |
| MT _{10,0} /TBC(298) | 10000 | 1.47 | 1.6 | TBC ^d | 2.0 | 298 |

^a M_n and M_w of MT are evaluated by GPC (column, Sephadex G75; solvent, water). ^b Temperature. ^c Poly(ethylene oxide). $M_n = 2000$. ^d Poly(ethylene oxide)-*block*-poly(tetrahydrofuran)-*block*-poly(ethylene oxide) triblock copolymer (PTHF segment $M_n = 650$; PEO segment $M_n = (2000 \times 2)$).

SCHEME 2: Preparation of Poly(ethylene oxide)-*block*-poly(tetrahydrofuran)-*block*-poly(ethylene oxide) Triblock Copolymer

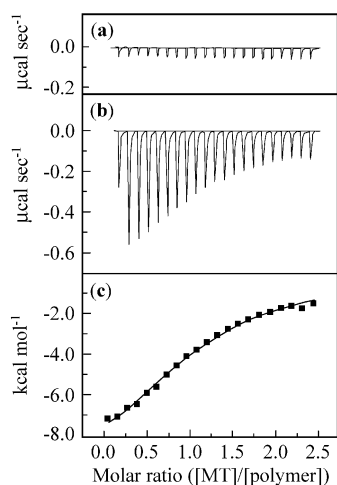
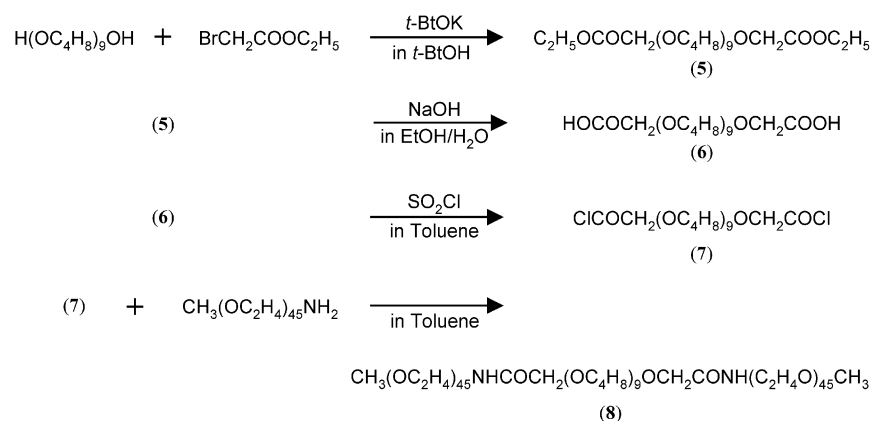


Figure 1. Signal of isothermal titration for inclusion complexation of a molecular tube ($M_n = 5900$) with (a) PEO ($M_n = 2000$) and (b) PEO-*b*-PTHF-*b*-PEO (PTHF segment $M_n = 650$, PEO segment $M_n = ((2000)(2))$). (c) Binding isotherm of (b). The concentrations of PEO and PEO-*b*-PTHF-*b*-PEO aqueous solutions in the cell are 2.0×10^{-5} mol L⁻¹. The concentration of MT aqueous solution in the syringe is 3.0×10^{-4} mol L⁻¹.

evaluated by the nonlinear regression fitting of the binding isotherm. Then, the free energy change ΔG and the entropy change ΔS were obtained from eqs 1 and 2.

$$\Delta G = -RT \ln K_a \quad (1)$$

$$\Delta G = \Delta H - T\Delta S \quad (2)$$

Table 2 summarizes the thermodynamic parameters for inclusion complexation between MT and PEO-*b*-PTHF-*b*-PEO

at 298 K. Figure 2 shows the thermodynamic parameters for inclusion complexation between MT and PEO-*b*-PTHF-*b*-PEO triblock copolymer at 298K as a function of M_n of MT ($M_{n\text{-MT}}$). It was found that ΔH was a large negative value in all systems. Although $T\Delta S$ was negative, $T\Delta S$ for MT_{4,4}/TBC(298) was almost zero. ΔH decreased with increasing $M_{n\text{-MT}}$. On the contrary, $-T\Delta S$ increased with $M_{n\text{-MT}}$. Although the changes of ΔH and $-T\Delta S$ were compensatory, ΔG slightly decreased with increasing $M_{n\text{-MT}}$. K_a increased with $M_{n\text{-MT}}$ from 5.73×10^4 to 1.64×10^5 mol⁻¹ L. The stoichiometric number n decreased with increasing $M_{n\text{-MT}}$ from 2.10 to 0.60.

Effect of Temperature on Inclusion Complexation between MT and PEO-*b*-PTHF-*b*-PEO. Table 3 summarizes the thermodynamic parameters for inclusion complexation between MT_{5,9} and PEO-*b*-PTHF-*b*-PEO triblock copolymer at 288, 298, and 308 K. Figure 3 shows the effect of the temperature on thermodynamic parameters for inclusion complexation between MT_{5,9} and PEO-*b*-PTHF-*b*-PEO triblock copolymer. ΔH was large and negative in all systems. Although $T\Delta S$ was negative at 298 and 308 K, it was positive at 288 K. It was found that ΔH and $-T\Delta S$ strongly depend on temperature. These changes were compensatory. ΔG decreased slightly with increasing temperature. The temperature coefficient of ΔH , i.e., the heat capacity change ΔC_p , was a large negative value (-3.2 kJ K⁻¹ mol⁻¹). K_a decreased with increasing temperature from 1.51×10^5 to 4.18×10^4 mol⁻¹ L. The stoichiometric numbers were almost independent of temperature.

Discussion

Inclusion Complexation between MT and PEO. As shown in Figure 1a, the exothermic peaks were too small to analyze the thermodynamics. Two possible explanations can be proposed for this result. (i) Although MT forms an inclusion complex

TABLE 2: Results of ITC Measurement for Inclusion Complexation between MT and PEO-*b*-PTHF-*b*-PEO Triblock Copolymer at 298 K (\pm SEM, $n = 4$)

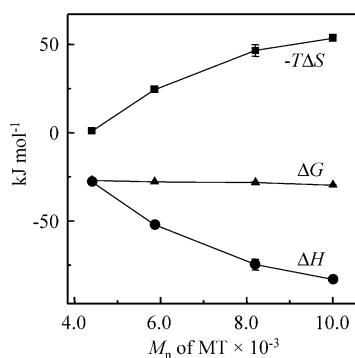
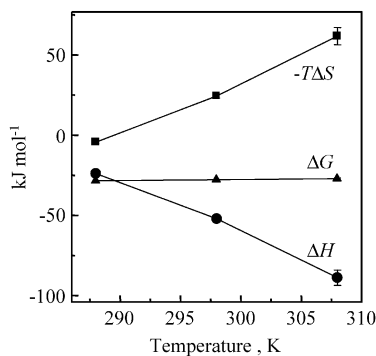
| code | T , K | $\Delta H^{a,f}$ kJ mol ⁻¹ | $T\Delta S^{b,f}$ kJ mol ⁻¹ | $\Delta G^{c,f}$ kJ mol ⁻¹ | $K_a^{a,d}$ $\times 10^{-4}$ mol ⁻¹ L | $n^{d,e}$ |
|------------------------------|---------|--|---|--|---|-----------|
| MT _{4.4} /TBC(298) | 298 | -27.8 \pm 0.8 | -0.7 \pm 1.0 | -27.1 \pm 0.2 | 5.73 \pm 0.50 | 2.10 |
| MT _{5.9} /TBC(298) | 298 | -52.2 \pm 1.1 | -24.3 \pm 1.2 | -27.9 \pm 0.1 | 7.92 \pm 0.22 | 1.07 |
| MT _{8.2} /TBC(298) | 298 | -74.7 \pm 3.1 | -46.5 \pm 3.3 | -28.2 \pm 0.3 | 8.94 \pm 1.03 | 0.74 |
| MT _{10.0} /TBC(298) | 298 | -83.1 \pm 1.1 | -53.4 \pm 1.2 | -29.7 \pm 0.2 | 16.4 \pm 1.2 | 0.60 |

^a ΔH , K_a , and n are evaluated directly from the titration data using the Origin software. ^b $-T\Delta S$ is calculated by the equation $\Delta G = \Delta H - T\Delta S$. ^c ΔG is calculated by the equation $\Delta G = -RT \ln K_a$. ^d Association constant $K_a = [\text{complex}]/[\text{MT}][\text{copolymer}]$. ^e Stoichiometric number (MT/copolymer ratio). ^f Thermodynamic parameters are calculated based on the mol. of molecular tube.

TABLE 3: Results of ITC Measurement for Inclusion Complexation between MT_{5.9} and PEO-*b*-PTHF-*b*-PEO Triblock Copolymer at 288, 298, and 308 K (\pm SEM, $n = 4$)

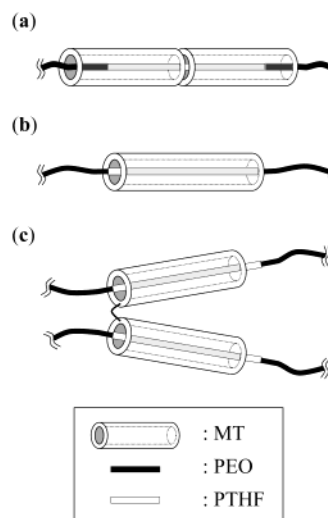
| code | T , K | $\Delta H^{a,f}$ kJ mol ⁻¹ | $T\Delta S^{b,f}$ kJ mol ⁻¹ | $\Delta G^{c,f}$ kJ mol ⁻¹ | $K_a^{a,d}$ $\times 10^{-4}$ mol ⁻¹ L | $n^{d,e}$ |
|-----------------------------|---------|--|---|--|---|-----------|
| MT _{5.9} /TBC(288) | 288 | -24.0 \pm 0.4 | 4.5 \pm 0.6 | -28.5 \pm 0.2 | 15.1 \pm 1.10 | 1.00 |
| MT _{5.9} /TBC(298) | 298 | -52.2 \pm 1.1 | -24.3 \pm 1.2 | -27.9 \pm 0.1 | 7.92 \pm 0.22 | 1.07 |
| MT _{5.9} /TBC(308) | 308 | -88.9 \pm 4.8 | -61.7 \pm 5.4 | -27.2 \pm 0.6 | 4.18 \pm 0.81 | 1.04 |

^a ΔH , K_a , and n are evaluated directly from the titration data using the Origin software. ^b $-T\Delta S$ is calculated by the equation $\Delta G = \Delta H - T\Delta S$. ^c ΔG is calculated by the equation $\Delta G = -RT \ln K_a$. ^d Association constant $K_a = [\text{complex}]/[\text{MT}][\text{copolymer}]$. ^e Stoichiometric number (MT/copolymer ratio). ^f Thermodynamic parameters are calculated based on the mol. of molecular tube.

**Figure 2.** Thermodynamic parameters for inclusion complexation between MT and PEO-*b*-PTHF-*b*-PEO triblock-copolymer at 298 K as a function of molecular weight of MT. ΔG (\blacktriangle), ΔH (\bullet), and $-T\Delta S$ (\blacksquare).**Figure 3.** Effect of temperature on thermodynamics for inclusion complexation between MT_{5.9} and PEO-*b*-PTHF-*b*-PEO triblock copolymer. ΔG (\blacktriangle), ΔH (\bullet), and $-T\Delta S$ (\blacksquare).

with PEO, the heat generation is small because of the small ΔH in the process of inclusion complexation. (ii) Since inclusion complexation between MT and PEO is not so favorable process, MT scarcely forms an inclusion complex under this condition. This will be discussed later.

Inclusion Complexation between MT and PEO-*b*-PTHF-*b*-PEO. In the titration of MT to the triblock copolymer, strong exothermic peaks were observed (Figure 1b). As shown in Figure 1a, the titration of MT to PEO shows small exothermic peaks. In addition, ITC measurement was carried out below the

**Figure 4.** Possible structures of inclusion complex between MT and PEO-*b*-PTHF-*b*-PEO: (a) 2:1, (b) 1:1, and (c) 1:2 inclusion complexes (MT: copolymer). MT in (c) has a kink point to include the two independent strands of the triblock copolymer.

CMC of the triblock copolymer to minimize the effect of micelle formation. Thus, the strong exothermic peaks in Figure 1b are attributable to the interaction between MT and the PTHF segment of the triblock copolymer. The ¹H NMR spectrum supported that MT forms an inclusion complex with the triblock copolymer, the peaks assigned to the methylene protons of PTHF shifted downfield and broadened in comparison with those of free triblock copolymer (data not shown). This result is consistent with that for inclusion complexation of α -CD¹⁴ or MT¹² with a guest molecule having an aliphatic moiety.

Stoichiometry of the Inclusion Complex between MT and PEO-*b*-PTHF-*b*-PEO. As shown in Table 2, n strongly depends on M_n -MT. As for MT_{4.4} and MT_{5.9}, n was found to be close to 2.0 and 1.0, respectively. Parts a and b of Figure 4 show the possible structures in 2:1 and 1:1 inclusion complexes (MT: copolymer). Interestingly, n was found to be below 1.0 for MT_{8.2} and MT_{10.0}. In these cases, MT behaves as the host molecule having multi binding sites. The α -CD cavity (diameter: 5 Å) is too narrow to accommodate two strands of PEO.¹⁵ Thus, it

is considered that MT has multi tubular structures to accommodate more than one triblock copolymer. Two possible explanations can be proposed. One is that MT with a large molecular weight is a dimer of two short MTs. Another is that MT has a kink point to include two strands of MT. The former possibility can be excluded, because the intramolecular cross-linked product of the polyrotaxane (**3**) was removed in the purification process.¹² As for the latter possibility, MALDI-TOF mass spectrum measurement revealed that the number of the cross-linkers between adjacent α -CDs in MT is 3 on average.¹² In addition, some cross-linker might not actually cross-link between adjacent α -CDs. Therefore, it is considered that the used MT contains some kink points cross-linked by only one cross-linker. If MT has one kink point around the middle part, such a MT can be bent as to include two independent triblock copolymers (Figure 4c). To confirm this hypothesis, other instrumental analysis, e.g., scanning probe microscopy, should be carried out.

These results can be examined from the lengths of MT and the PTHF segment. Based on the length of the two tetrahydrofuran units in zigzag conformation (12.1 Å),¹⁶ the average length of the PTHF segment (L_{PTHF}) is estimated to be 54.5 Å ($= (12.1 \times 9/2)$). The molecular weight of the repeating unit in MT is calculated to be 1140 ($= 972 + (56 \times 3)$). Thus, the average length of MT (L_{MT}) can be estimated from $M_{n-\text{MT}}$, assuming that the length of the α -CD torus and the distance between adjacent α -CDs are ca. 8¹⁷ and 2 Å, respectively.

$$L_{\text{MT}} = (M_{n-\text{MT}}/1140) \times 10 \text{ (Å)} \quad (3)$$

From eq 3, the lengths of MT_{4.4}, MT_{5.9}, MT_{8.2}, and MT_{10.0} are estimated to be 39, 52, 72, and 88 Å, respectively. Since the assumed L_{MT} for MT_{4.4} (39 Å) is much shorter than the PTHF segment (54.5 Å), MT may form the 2:1 inclusion complex. For MT_{5.9}, the assumed L_{MT} (52 Å) is almost the same as L_{PTHF} (54.5 Å). For MT_{8.2} and MT_{10.0}, the assumed L_{MT} s are larger than L_{PTHF} . If these MTs would form a 1:1 inclusion complex with the triblock copolymer, a large part of the MT cavity would be sacrificed for inclusion complexation with the PEO segment. Presumably, the 1:2 inclusion complex, in which only the PTHF segments may interact with MT, is more stable than the 1:1 inclusion complex. MT may change its conformation at the kink point to form the most stable inclusion complex in relation to the relative length of itself and the guest molecules.

Certainly, the observed stoichiometry is the mean value of all possible inclusion complexes in the system. In the polymer system, some types of inclusion complex may coexist due to the polydispersity of MT and the triblock copolymer. Especially, 1:1 and 1:2 inclusion complexes should coexist in the cases of MT_{8.2} and MT_{10.0}.

Relationship between Enthalpy and Entropy. Some research groups discussed the general trends of the relationship between enthalpy and entropy in chemical and biological supramolecular systems, and they proposed some factors to understand the inclusion complexation behavior.¹⁸

Figure 5 shows the enthalpy–entropy compensation plots based on this study (solid line) and our previous study (dotted line), i.e., inclusion complexation between MT and $\text{C}_n\text{SO}_3\text{Na}$. In the enthalpy–entropy compensation plot, it is considered that the slope (α) and the intercept at $\Delta H = 0$ ($T\Delta S_0$) are in relation to the degrees of conformational change and the desolvation in the process.¹⁸ As for $\text{C}_n\text{SO}_3\text{Na}$, α and $T\Delta S_0$ were calculated to be 0.83 and 14.8 kJ mol⁻¹, respectively. In the case of the triblock copolymer, α and $T\Delta S_0$ were calculated to be 0.96 and 25.9 kJ mol⁻¹, respectively. It was found that $T\Delta S_0$ for the

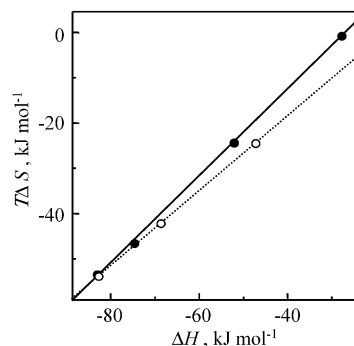


Figure 5. Enthalpy–entropy compensation plots for the system between MT and PEO-*b*-PTHF-*b*-PEO (solid line) and the system between MT and $\text{C}_n\text{SO}_3\text{Na}$ (dotted line). The line was obtained from the least-squares fit. All data were obtained by ITC measurement at 298K.

triblock copolymer is much larger than that for $\text{C}_n\text{SO}_3\text{Na}$. This result indicates that the dehydration process in inclusion complexation between MT and the copolymer should be a more important factor than that between MT and $\text{C}_n\text{SO}_3\text{Na}$. The larger α for the triblock copolymer than $\text{C}_n\text{SO}_3\text{Na}$ may arise from the conformational changes of the triblock copolymer and MT.

Factors Contributing to Inclusion Complexation. Over three decades, many research groups have reported thermodynamic analyses and proposed interpretation of the results.² These studies are useful for examining the factors contributing to inclusion complexation. Especially, the results in our previous study,⁸ i.e., inclusion complexation between MT and $\text{C}_n\text{SO}_3\text{Na}$, are comparable to those in this study. Similarly to inclusion complexation between MT and $\text{C}_n\text{SO}_3\text{Na}$, it is considered that van der Waals interaction contributes to the large negative value of ΔH . However, the obtained thermodynamic parameters indicated that the enthalpy gain for inclusion complexation of the triblock copolymer is much smaller than that for inclusion complexation of the alkyl chains. For instance, the interaction surface between MT_{5.9} and PTHF (all parts of the MT cavity) is much larger than that between MT_{6.4} and $\text{C}_{12}\text{SO}_3\text{Na}$ (only end parts of the MT cavity). However, the absolute value of ΔH for PTHF (52.2 ± 1.1 kJ mol⁻¹) is much smaller than that for $\text{C}_{12}\text{SO}_3\text{Na}$ (82.8 ± 7.4 kJ mol⁻¹).⁸ The difference between the PTHF backbone and the alkyl chain is whether ether oxygen atoms exist. In the process of inclusion complexation with MT, hydrogen bonds between the ether oxygen atoms and the hydrated water molecules must be broken. This dehydration process causes the decrease in the enthalpy gain. This interpretation is consistent with the result of the enthalpy–entropy compensation plot, which indicates that the dehydration process should affect the thermodynamic parameters for the triblock copolymer more significantly than that for $\text{C}_n\text{SO}_3\text{Na}$.

It was confirmed that ΔH strongly depends on temperature. This result indicates that some thermoresponsive interactions participate in the inclusion complexation process. The large negative value of ΔC_p was also reported in inclusion complexation between MT and $\text{C}_n\text{SO}_3\text{Na}$ (-1.0 kJ K⁻¹ mol⁻¹).⁸ In that case, the large negative value of ΔC_p was considered to be due to hydrophobic interaction. ΔC_p for the triblock copolymer (-3.2 kJ mol⁻¹) is much more negative value than that for $\text{C}_n\text{SO}_3\text{Na}$. This result is attributable to the additional factor in inclusion complexation between MT and the triblock copolymer, namely, hydrogen bond interaction between the ether oxygen atoms of PTHF and the hydrated water molecules.

$T\Delta S$ was large and negative in the case of MTs with a large molecular weight (MT_{5.8}, MT_{8.2}, and MT_{10.0}). It is considered

that the PTHF segment loses its mobility and conformational flexibility by inclusion complexation, which was supported by the broad ^1H NMR peaks of the included PTHF. This factor is likely to contribute to the entropy loss. As for $\text{MT}_{4.4}/\text{TBC}(298)$ and $\text{MT}_{5.9}/\text{TBC}(288)$, $T\Delta S$ was almost zero or positive. These results indicate that some factors compensate for the entropy loss. An entropy gain may arise from the release of the oriented water molecule around the PTHF segment. The entropy gain is often shown in the process involving hydrophobic interaction.¹⁹ In a model of hydrophobic interaction, the water molecules in the vicinity of the hydrophobic surface are oriented.²⁰ Recently, spectroscopic evidence on the orientation of water molecules at the $\text{CCl}_4/\text{H}_2\text{O}$ interface was reported.²¹ For PTHF, the tetramethylene moiety corresponds to the hydrophobic surface. In addition, the hydrated water molecules around the ether oxygen atoms of PTHF may be strongly oriented by hydrogen bonds. It is considered that these oriented water molecules around the PTHF segment are released by inclusion complexation with MT, and that this process contributes to the entropy gain. With increasing $M_{n-\text{MT}}$, the entropy loss becomes significant. This may be because the interaction of MT and the triblock copolymer becomes large with increasing $M_{n-\text{MT}}$.

In inclusion complexation between CD and low molecular weight compounds, CD tends to encapsulate only the hydrophobic moiety of the guest molecule. This may be because the enthalpy loss of the dehydration is larger than the enthalpy gain based on the molecular interaction between CD and the guest molecule. In the case of MT, the interaction surface between MT and the guest polymer is large. Thus, MT can earn enough enthalpy gain to compensate for the enthalpy loss of the dehydration. For PEO, the enthalpy loss of the dehydration is more serious than that for PTHF, because PEO has more ether oxygen atoms than PTHF. This may be a reason the titration of PEO to MT shows small exothermic peaks (Figure 1a). Interestingly, α -CDs can form a stable inclusion complex with PEO in aqueous media. As for the macromolecular recognition process by CDs, one of the important driving forces is considered to be the hydrogen bond between the hydroxyl groups of adjacent CDs.²² The crystal structure shows the hydrogen bond network between adjacent CDs.²³ For MT, the process of inclusion complexation does not involve the formation of a new hydrogen bond network. In addition, MT having tubular structure restricts the conformation of the included polymer more strongly than α -CD. These factors unfavorably contribute to stabilize the inclusion complex. However, it is unlikely that the inclusion complexation between MT and PEO is an unfavorable process, because MT forms an inclusion complex with the central PTHF segment via the terminal PEO segments in the copolymer. Since MT predominantly captures the PTHF segment, it is considered that the inclusion complex of MT with the PTHF segment is much more stable than that with the PEO segment. Presumably, the association constant for the inclusion complexation between MT and PEO may be just small.

Conclusions

Thermodynamic analysis for inclusion complexation between MT and PEO-*b*-PTHF-*b*-PEO triblock copolymer was carried

out in terms of ITC. The thermodynamic parameters suggest that van der Waals interaction, hydrophobic interaction, and hydrogen bond interaction participate in inclusion complexation. In addition, it is considered that the release of the oriented water molecules around the triblock copolymer and the conformational change of MT and the copolymer affect the stability of the inclusion complex via the entropy term. Some thermodynamic parameters clearly indicate that the dehydration process is a key factor in inclusion complexation between MT and the polymer. Also, one can recognize that hydrogen bond network formation is important in inclusion complexation between CD and the polymer. These results should be useful in many fields, e.g., surface science, physical chemistry, supramolecular science, and biological chemistry.

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Supporting Information Available: The detailed synthesis and characterization of PEO-*b*-PTHF-*b*-PEO, along with GPC data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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