Complex Formation between Hydrophobic Polymers and Methylated Cyclodextrins. Oligo(ethylene) and Poly(propylene)

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ABSTRACT: We report here the complex formation between methylated cyclodextrins (CDs) and hydrophobic polymers, such as oligo(ethylene) (OE) and poly(propylene) (PP), in aqueous solutions. These polymers can be dissolved in water phases on addition of 2,6-di-*O*-methyl- β -CD (DM- β -CD). OE was found to be solubilized in water containing DM- α -CD. The ¹H-NMR experiments showed that the ¹H resonances of OE change on addition of DM- β -CD or DM- α -CD in D₂O at 25 °C. The ¹H signals of methyl protons of PP shifted upfield and broadened on addition of DM- β -CD. These phenomena indicate that OE and PP selectively form hydrophilic complexes with methylated CDs. The complex formation of methylated CDs depends on the length (molecular weight) of the hydrophobic polymers.

KEY WORDS Methylated Cyclodextrin / Inclusion Complex / Hydrophobic Polymer / Solubilization /

Previously, we reported the complex formations between cyclodextrins (CDs)¹ and hydrophilic polymers in aqueous solutions². Methylated CDs have been extensively used due to their higher solubility not only in water but also in most of organic solvents and to their stronger affinity to various compounds, in comparison with unmodified CDs. It is interesting that the binding modes between methylated CDs and guests often differ from those of native CDs. Recently, we found that some polymers, poly(propylene glycol)³ and poly(terahydrofuran)⁴ yielded inclusion complexes with methylated CDs. The solubilities of the polymers in water increase by interactions with 2,6-di-*O*-methyl- β -CD (DM- β -CD).

Matsuo et al.⁵ and Botsi et al.⁶ reported that hydrophilic oligo(ethylene) derivatives form hydrophilic complexes with CDs, but each complex consists of only one or two CDs and was not isolated. It is noticeable that native CDs give crystalline multiplet complexes with some hydrophobic polymers, such as poly(isobutylene)⁷, oligo(ethylene)⁸, and poly(propylene), in water phases. It was expected that hydrophobic polymers form multiplet complexes with methylated CDs in water to change the properties and structures. The present work is focused on the complex formation between methylated CDs and hydrophobic polymers in aqueous solutions. We found by turbidity and ¹H-NMR measurements that hydrophobic oligo(ethylene) (C(*n*)): “*n*” is the number of carbon atoms) and poly(propylene) (PP) interact with methylated CDs in aqueous solutions to form inclusion complexes.

RESULTS AND DISCUSSION

Oligo(ethylene)

When aqueous solution of α -CD was added to OE with heating and sonicating, the solution became turbid and complexes were formed as crystalline solids. However, addition of DM- α -CD or DM- β -CD caused an increase in solubility of C(15) in water to give a clear solution. Figure 1 shows the effects of methylated CDs on the transmittance of *n*-pentadecane (C(15)) in water. C(15) is hydrophobic, and the solubility is only about 0.1 (mg/1 mL water) at room

Figure 1. Effects of methylated CDs on the transmittance of C(15) in water at room temperature.

temperature. 2,3,6-Tri-*O*-methyl- β -CD (TM- β -CD) aqueous solutions at various concentrations did not solubilize C(15). The mixture became turbid to give a small amount of precipitate.

Figure 2. ¹H-NMR spectra of C(15) (a), DM- α -CD-C(15) (b), and DM- β -CD-C(15) (c) mixtures in D₂O at 25 °C. [DM- α -CD]/[C(15)]=10. [DM- β -CD]/[C(15)]=8

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Figure 2 shows the ^1H -NMR spectra of C(15), DM- α -CD-C(15), and DM- β -CD-C(15) mixtures in D_2O at 25 $^\circ\text{C}$. The ^1H resonance of methyl H of C(15) shifted downfield from 0.86 ppm to 0.96 (DM- α -CD) and 0.90 ppm (DM- β -CD) by addition of DM-CDs. Furthermore, the signal of methylene H of C(15) showed substantial splitting, and shifted downfield from $\delta = 1.25$ ppm to 1.38 and 1.29 ppm on addition of DM- α -CD and to 1.30 and 1.38 ppm by DM- β -CD addition, respectively. The turbidity and ^1H -NMR results suggested that C(15) forms inclusion complexes with hydrophilic DM- α -CD and DM- β -CD to be solubilized in water. The shifts of the ^1H signals of C(15) showed that the exchange rate of DM-CD-C(15) complex was faster than ^1H -NMR time scale.

Figure 3. ^1H -NMR spectra of C(15) at various concentrations of DM- β -CD in D_2O at 25 $^\circ\text{C}$.

Figure 4. Changes of the solubility of C(15) in water as a function of molar ratio of DM- β -CD to C(15).

We focused on the interaction between C(15) and DM- β -CD. Figure 3 gives the ^1H -NMR spectra of C(15) at various concentrations of DM- β -CD in D_2O . The degree of solubilized C(15) was calculated by comparison of the integral of methyl H of C(15) and C(1)H of DM- β -CD. Figure 4 shows the changes of the water solubility of C(15) as a function of molar ratio of DM- β -CD to C(15). The changes of chemical shifts of methylene H of C(15) are

plotted in Figure 5. The solubility and chemical shift of C(15) increase on addition of DM- β -CD, suggesting the formation of hydrophilic complexes. 500 MHz 2D ROESY

Figure 5. Changes of the ^1H chemical shifts of C(15) as a function of molar ratio of DM- β -CD to C(15).

NMR spectrum of DM- β -CD-C(15) in D_2O is shown in Figure 6. The NOE correlations were observed between the protons of C(15) and C(3)H at the inside shell of DM- β -CD. In addition, weak NOE correlations were observed between C(15) protons and C(5)H at the inside of DM- β -CD cavity, whereas cross peaks of C(15) resonances with C(1), C(2), and C(4) protons at the outside of CD pocket did not appear. These results showed that C(15) locates in the DM- β -CD cavity.

Figure 6. 2D ROESY NMR spectrum of DM- β -CD-C(15) in D_2O at 30 $^\circ\text{C}$. Arrows show the cross peaks between C(15) and C(3)H of DM- β -CD.

Figure 7 shows the ^1H -NMR spectra of C(n) ($n = 10, 12, 15$, and 18) with and without DM- β -CD in D_2O . Addition of DM- β -CD resulted in the downfield shift of the ^1H resonance of methylene H of C(10) with splitting into a set of equivalent signals (from $\delta = 1.25$ ppm to 1.33 and 1.40 ppm). We had observed similar NMR changes in the case of the complex formation between viologen polymer and CDs. Matsuo⁵ reported that the symmetric alkyl derivatives become asymmetric on the 1:1 complexation with α -CD, since an α -CD locates near the center of an alkyl chain to cause the different modifications of the NMR properties.

Probably, C(10) forms a 1:1 complex with DM- β -CD to give a set of equivalent signals of the methylene protons. On the contrary, the ^1H signal of methylene H of C(18) shifted upfield from $\delta = 1.21$ to 1.28 ppm without dispersion by addition of DM- β -CD. These phenomena suggested that C(18), with many binding sites, forms multiple ($1 \geq 2$) (C(18) : DM- β -CD) complexes with DM- β -CD. Longer C(n)s ($n = 18, 24, 32$, and 40) showed changes in NMR spectra similar to that of C(18). This dependence of the chain length also indicated that C(15) forms 1:1 and 1: n ($n \geq 2$) (C(15) : DM- β -CD) complexes. Molecular modeling studies showed that up to 4 DM- β -CD molecules can be threaded onto a C(15) chain. The 1:1 binding constant between DM- β -CD and C(15) was evaluated to be about 200 M^{-1} by the ^1H -NMR studies. Figure 8 shows the degrees of solubilized C(n)s which were evaluated from the ^1H -NMR spectra in D_2O . Figure 9 shows the effects of DM- β -CD on the transmittance of C(n). The two plots show a maximum at C(15). C(40) and longer poly(ethylene), which are solid at room temperature, interacted with DM- β -CD only slightly.

Figure 7. ^1H -NMR spectra of C(n) ($n = 10, 12, 15$, and 18) with and without DM- β -CD in D_2O at 25°C .

Figure 8. Effects of DM- β -CD on the water-solubility of C(n)s. Each degree of solubilized C(n) was evaluated from signals of C(1)H of DM- β -CD and methylene H of C(n) in the ^1H -NMR spectra of the mixed samples in D_2O at 25°C .

Figure 9. Effects of DM- β -CD on the transmittance of C(n) in water.

Figure 10. Effects of DM- β -CD on the transmittance of PPs in aqueous solutions.

Figure 11. Changes of the ^1H resonances of PP1600 on addition of DM- β -CD in D_2O at 25°C . $[\text{DM-}\beta\text{-CD}]/[\text{PP1600}] = 1.4$.

Figure 10 shows the effects of DM- β -CD on the transmittance of PPs in aqueous solutions. PP of the weight average molecular weight (M_w) of 1600 (PP1600) was found to be solubilized in DM- β -CD solutions. The turbidities of PPs of higher M_w s did not change by DM- β -CD. This is because PP of high M_w is too hydrophobic to interact effectively with DM- β -CD in water phases. The ^1H resonance of methyl H on PP1600 was broadened and

shifted downfield ($\Delta\delta = +0.09$ ppm) on addition of DM- β -CD in D₂O at 25°C (Figure 11). DM- α -CD and TM- β -CD did not affect the solubility of PP. Molecular modeling studies showed that a PP chain can penetrate a DM- β -CD cavity but cannot thread DM- α -CD and TM- β -CD, because of the large cross sectional area. These results showed that hydrophobic PP with many binding sites penetrates hydrophilic DM- β -CD rings to form hydrophilic multiplet complexes.

When PP was mixed with β -CD or γ -CD aqueous solution, the mixture became turbid to give complexes. α -CD neither produced complexes with PP nor changed the PP solubility in water. Poly(propylene glycol) is dissolved in water by DM- β -CD, and gives crystalline complexes with β -CD and γ -CD. The complexation phenomena of PP showed some similarities with that of poly(propylene glycol). Modeling studies showed that the sectional areas of PP and poly(propylene glycol) are identical. It is shown that there is a good correlation between the cross sectional areas of polymers and the sizes of CDs in the complex formation.

In conclusion, we found that the solubility of oligo(ethylene) or PP in water increased markedly due to the complex formation with methylated CDs. Oligo(ethylene) was shown to form multiplet hydrophilic complexes with DM- α -CD and DM- β -CD in aqueous solutions, and these complexes did not crystallize even after 6 months. PP is solubilized in a DM- β -CD aqueous solution. The complex formation between methylated CDs and hydrophobic polymers depends on the length (Mw) of the polymers, and demonstrates that the sectional area of the chain plays an important role. This report provided the first example that the solubilization of hydrophobic polymer in a water phase succeeded using the macromolecular recognition of methylated CDs.

EXPERIMENTAL

Materials

2,6-Di-*O*-methyl- β -CD (DM- β -CD) and 2,3,6-Tri-*O*-methyl- β -CD (TM- β -CD) were purchased from Nacalai Tesque Ltd. DM- α -CD was kindly supplied from Nippon Food Chemical Ltd. α -, β -, and γ -Cyclodextrin (CD) were obtained from Nacalai Tesque Ltd. *n*-Decane, *n*-dodecane, *n*-pentadecane, and *n*-octadecane were purchased from Nacalai Tesque Ltd. *n*-Dotriacontane, *n*-tetracontane, and *n*-pentacontane were purchased from Tokyo Kasei Kogyo Co., Ltd. Poly(ethylene)s (PEs) (high density, low density, and powder) were purchased from Aldrich. *atactic*-Polypropylene (PP) was purchased from Scientific Polymer Products, Inc. PP samples were fractionated using column chromatography on Sephadex LH-20 (eluent: THF). The weight average molecular weight (Mw) of PP was determined by GPC. The molecular dispersity of PP sample was less than 1.3. D₂O and DMSO-*d*₆ were obtained from Aldrich.

Measurements

Absorption spectra were recorded on a Shimadzu UV-2001 spectrometer at room temperature. ¹H-NMR experiments were carried out on a JEOL EX-270 NMR

spectrometer operating at 270 MHz. Chemical shifts of NMR spectra in D₂O at 25°C were referenced to the external standard, 3-(trimethylsilyl)propionic acid sodium salt (DSS) ($\delta = 0.00$ ppm). 2D ROESY NMR spectra were recorded in D₂O at 30 °C on a JNM-GX500 NMR spectrometer operating at 500 MHz for ¹H. HOD ($\delta = 4.70$ ppm) was used as an internal standard. GPC determination was carried out with a Tosoh CCP&8010 system (column: G3000HXL and G2000HXL, solvent: THF). The Mw values of samples were determined using a calibration curve derived from standard poly(styrene)s

Turbidimetric titration and NMR analysis of D₂O solutions

Methylated CD was dissolved in D₂O (2.00 mL). PE or PP (8.0 mg) was added to the D₂O solution, and then the mixture was vigorously stirred at room temperature. Turbidities of the mixed samples were measured by transmittance (%) at 800 nm using an absorption spectrometer. NMR measurements were carried out at 25 °C after bubbling the mixture with N₂ gas.

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