Preparation and Properties of Inclusion Complexes of Poly(ethylene glycol) with α-Cyclodextrin

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ABSTRACT: α-Cyclodextrin (α-CD) was found to form inclusion complexes with poly(ethylene glycol) (PEG) of various molecular weights to give stoichiometric compounds in a crystalline state in high yields. α-CD does not form complexes with the low molecular weight analogs, ethylene glycol, diethylene glycol, and triethylene glycol. The rate of the complex formation depends on the molecular weight of PEG. PEG of molecular weight 1000 forms complexes most rapidly. The complexes were characterized by IR, ^{1}H NMR, ^{13}C NMR, and ^{13}C CP/MAS NMR spectra and X-ray (powder), thermal, and elemental analyses. The ^{1}H NMR spectra of the complexes show that the stoichiometry of the complexes is 2:1 (two ethylene glycol units and one α-CD). X-ray powder patterns of the PEG–α-CD complex show that α-CDs form channels. The ^{13}C CP/MAS NMR spectrum of the complex suggests that a PEG chain is included in the channel formed by α-CDs. α-CD formed complexes with PEG having small end groups, such as methyl, dimethyl, and amino groups, but did not form complexes with PEG carrying large substituents, such as 2,4-dinitrophenyl and 3,5-dinitrobenzoyl groups. β-CD did not form complexes with poly(ethylene glycol) of any molecular weight. The modes of the complexes are discussed.

Introduction

Cyclodextrins (CDs) are cyclic molecules consisting of six to eight glucose units linked through α-1,4-linkages. They are named α(6), β(7), and γ(8) cyclodextrins, respectively. The most characteristic feature of cyclodextrins is the ability to form inclusion complexes with various low molecular weight compounds.[1] Since cyclodextrins were discovered, there have been many reports on the complex formation of cyclodextrins with low molecular weight compounds of both organic[1] and inorganic[2] nature. Some of the complexes have been studied by an X-ray diffraction method, and all the guest molecules have been found to be included in the cavities of cyclodextrins.[3]

However, there were no reports on the formation of complexes between cyclodextrins and polymers when we started our project. There are some examples in which a monomer was polymerized in situ within a cyclodextrin complex. Ogata *et al.* prepared hexamethylenediamine complexes of β-CD. Polyamides were obtained by condensation of dibasic acid chlorides and the inclusion complexes of the diamine.[4] Maciejewski reported the polymerization and copolymerization of vinylidene chloride as adducts with β-CD.[5] There are some reports which suggest interactions between cyclodextrins and some polymers in aqueous solutions. Kitano *et al.* reported that cyclodextrins show some effects on the critical micelle concentrations of some micelle-forming surfactants.[6] Iijima *et al.* studied diffusion of cyclodextrin in the presence of poly(styrenesulfonate) in aqueous solutions and reported that there are some interactions between cyclodextrin and the polymer.[7]

We found that α-cyclodextrin forms complexes with poly(ethylene glycol) of various molecular weights to give stoichiometric complexes in high yields in a crystalline state. In a previous paper we reported briefly on the complex formation between α-CD and poly(ethylene glycol) as the first example of the complex formation of cyclodextrin with polymers in a crystalline state.[8] This paper describes the preparation and properties of the inclusion complexes of poly(ethylene glycol) with α-CD in detail, and the modes of the complexation are discussed.

Results and Discussion

Complex Formation between PEG and α-CD. Cyclodextrins are known to form inclusion complexes with water-soluble low molecular weight compounds when the aqueous solutions of low molecular weight compounds, such as propanol and propionic acid, were added to a saturated aqueous solution of cyclodextrin at room temperature. First, we tested whether cyclodextrins would form complexes with some water-soluble polymers or not. Table I shows the results of the formation of the complexes of cyclodextrins with some nonionic polymers. We found that cyclodextrins did not form complexes with some nonionic, water-soluble polymers, such as poly(vinyl alcohol) (PVA), polyacrylamide (PAAm), and poly(*N*-vinylpyrrolidone) (PVPo), by the same procedure as that for low molecular weight compounds. However, we found that α-CD forms complexes with poly(ethylene glycol) in high yields in a crystalline state. When aqueous solutions of PEG or bulk PEG were added to a saturated aqueous solution of α-CD at room temperature, the solution became turbid and the complexes were formed as precipitates when the average molecular weight of PEG was more than 200.

While we have been preparing the complexes of α-CD with PEG, we found that the rates of the complex formation depend on the molecular weight of PEG. The rates were followed by absorbance at 700 nm. Figure 1 shows the time course for the turbidity development after mixing the α-CD solution and PEG solution (15 mg/mL). There was almost no change of turbidity at molecular weight 200. Complexes were formed and the turbidity develops at molecular weight more than 300 after some induction period. At molecular weight 600–1000, the solution became turbid instantaneously. The rate decreases as the molecular weight increases at molecular weight over 1000. The figure clearly shows that PEG of molecular weight 1000 forms complexes most rapidly. This may be partly due to the fact that the number of end groups decreases as the molecular weight increases. Addition of the PEG

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Table I. Preparation of the Complexes between CD and Polymers[a]

polymer	yield (%) α-CD	yield (%) β-CD
PVA($\overline{DP}$500)	0	0
PVA($\overline{DP}$2000)	0	0
PAAm($\overline{MW}$10 000)	0	0
PVPo($\overline{MW}$10 000)	0	0
PEG($\overline{MW}$1000)	92	0
PPG($\overline{MW}$1000)	0	96

[a] CD saturated aqueous solution, 1 mL; polymers, 20 mg.

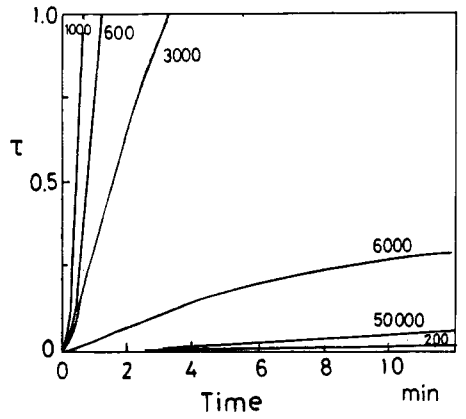

Figure 1. Time course for the turbidity development after mixing the α-CD solution and the PEG solution.

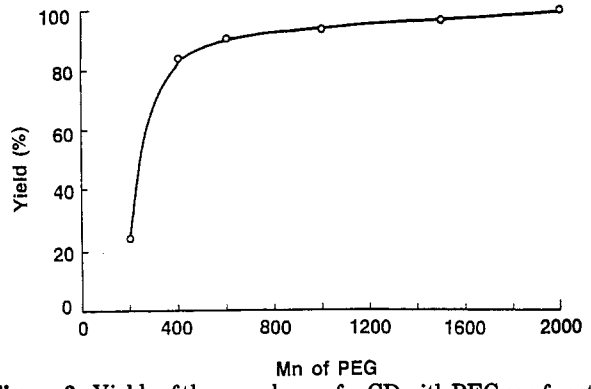

Figure 2. Yields of the complexes of α-CD with PEG as a function of the molecular weight of PEG.

solution to a saturated aqueous solution of β-CD did not cause any change in solution.

Preparation of Complexes. The complexes were isolated by filtration or centrifugation, washed with water, and dried. Figure 2 shows the yields of the complexes of α-CD with PEG of various molecular weights. The yields are calculated on the basis of 2:1 (ethylene glycol unit–α-CD) stoichiometry which will be mentioned in the next section. α-CD does not form complexes with the low molecular weight analogs, ethylene glycol,[9] diethylene glycol, and triethylene glycol. α-CD forms complexes with PEG of molecular weight more than 200. The yields increase with an increase in the molecular weight. The complexes were obtained almost quantitatively with PEG of molecular weight over 1000. β-CD did not form complexes with PEG of any molecular weight. Although PEG of molecular weight over 1000 formed complexes with α-CD slowly, they gave high yields (91–95%) after several hours.

The present finding that a minimum PEG length is required for the formation of stable cyclodextrin complexes shows the importance of cooperativity in complexation

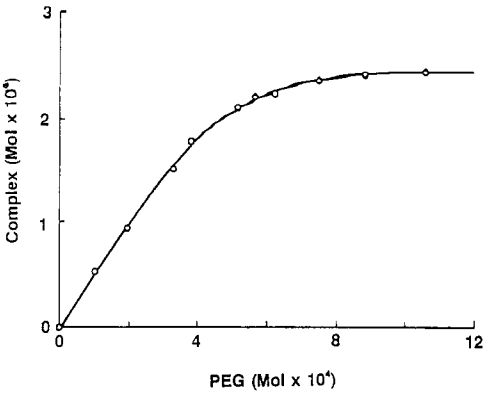

Figure 3. Amount of α-CD–PEG complex as a function of added PEG($\overline{MW}$ = 600). A total amount of 2 mL of saturated aqueous solution of α-CD (290 mg) was used.

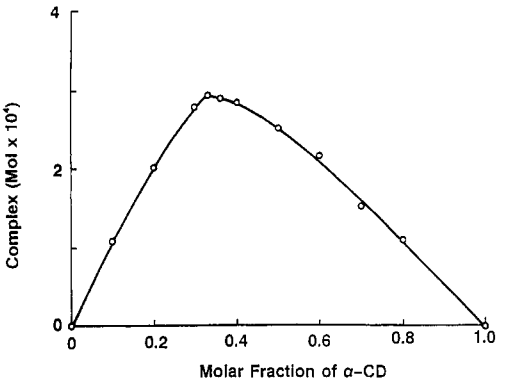

Figure 4. Continuous variation plots for the complex formation between α-CD and PEG($\overline{MW}$ = 1000). The sum of the initial concentration of α-CD and PEG was fixed at 1.13×10^{-3} M.

and is similar to the formation of PEG complexes with hydrogen-donor polymers such as poly(acrylic acid).[10]

Stoichiometry of the Complex. The complex formation of α-CD with PEG was studied quantitatively. Figure 3 shows plots of the amount of the complex obtained versus PEG added. The amounts of the complex formed increased with an increase of PEG added to the aqueous solution of α-CD, and saturation was observed. These results indicate that the complex formation is stoichiometric. The saturation values show that more than 90% of the α-CD was consumed by complex formation with PEG. Figure 4 shows the continuous variation plots for the complex formation between α-CD and PEG. The plots show the maximum at the molar ratio of 0.33 (α-CD), suggesting that the stoichiometries of the complexes are 2:1 (ethylene glycol unit–α-CD). The stoichiometries were confirmed by the ^{1}H NMR spectrum. Figure 5 shows the ^{1}H NMR spectrum of the complex of PEG-600 with α-CD. It should be noted that the stoichiometries of the complexes are always 2:1 even if α-CD and PEG are combined in other ratios. The length of two ethylene glycol units corresponds to the depth of the cavity of α-CD.

Carbohydrate polymers, such as dextran and pullulan, did not form insoluble complexes with PEG. Amylose and dextrin did not form insoluble complexes with PEG. Glucose, methyl glycoside, maltose, and maltotriose did not form complexes with PEG. Cyclodextrin derivatives, such as glucosyl-α-CD, maltosyl-α-CD, and soluble polymers of α-CD, did not form insoluble complexes with PEG.

Properties of the Complexes. The complexes of α-CD with PEG of low molecular weight (1000) are soluble in a large amount of water. The complexes of PEG of high molecular weight can be dissolved in water by heating. The addition of an excess amount of benzoic acid, which

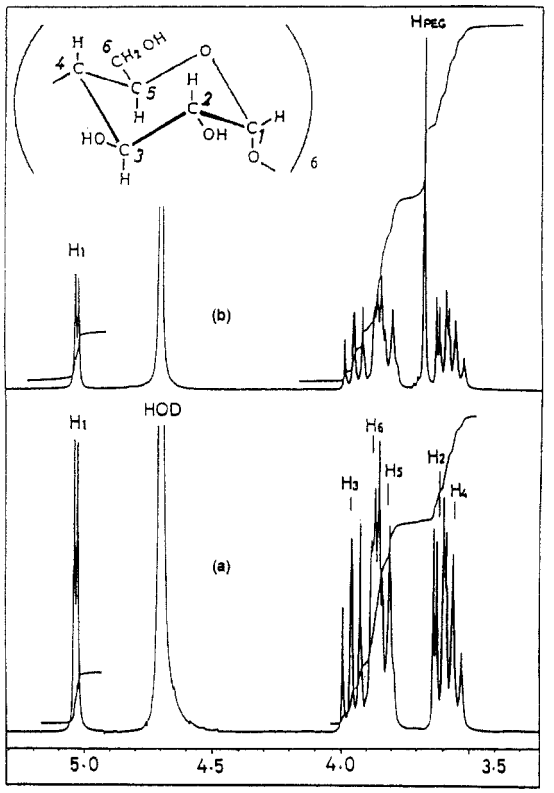

Figure 5. 270-MHz ^{1}H NMR spectra of the complexes of PEG($\overline{MW}$ = 600) with α-CD (a) and α-CD (b) in D_2O.

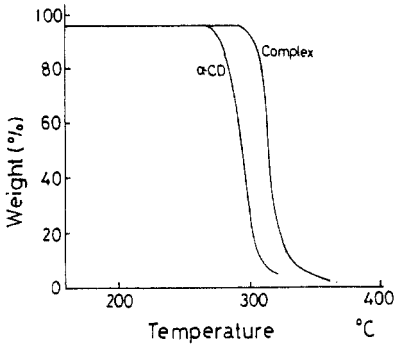

Figure 6. Thermogravimetric analysis of α-CD and the α-CD–PEG($\overline{MW}$ = 1000) complex.

is a low molecular weight guest,[11] to the suspension of the complex resulted in solubilization of the complex when the molecular weight of PEG is low (1000). The formation of the complex is evidently reversible. In solution, complexes are in equilibrium between the complex and its component. The addition of salts, such as NaCl and KCl, did not cause any change in the solubility of the complexes. This result indicates that there are no ionic interactions between α-CD and the polymer. The addition of urea, which is thought to affect hydrogen bonds, results in solubilization of the complexes. The results indicate that hydrogen bonding plays an important role in forming the complexes between PEG and α-CD.

The decomposition point of the complexes is a little higher than that of the cyclodextrin. Figure 6 shows that the complex of α-CD with PEG-1000 decomposes above 300 °C, whereas α-CD melts and decomposes below 300 °C. Thus, poly(ethylene glycol) stabilizes α-CD.

Binding Mode of the Complex. Figure 7 shows the X-ray powder patterns of the complex of α-CD with PEG and with other low molecular weight compounds. Saenger *et al.* reported that the structures of the inclusion complexes of CDs with low molecular weight compounds

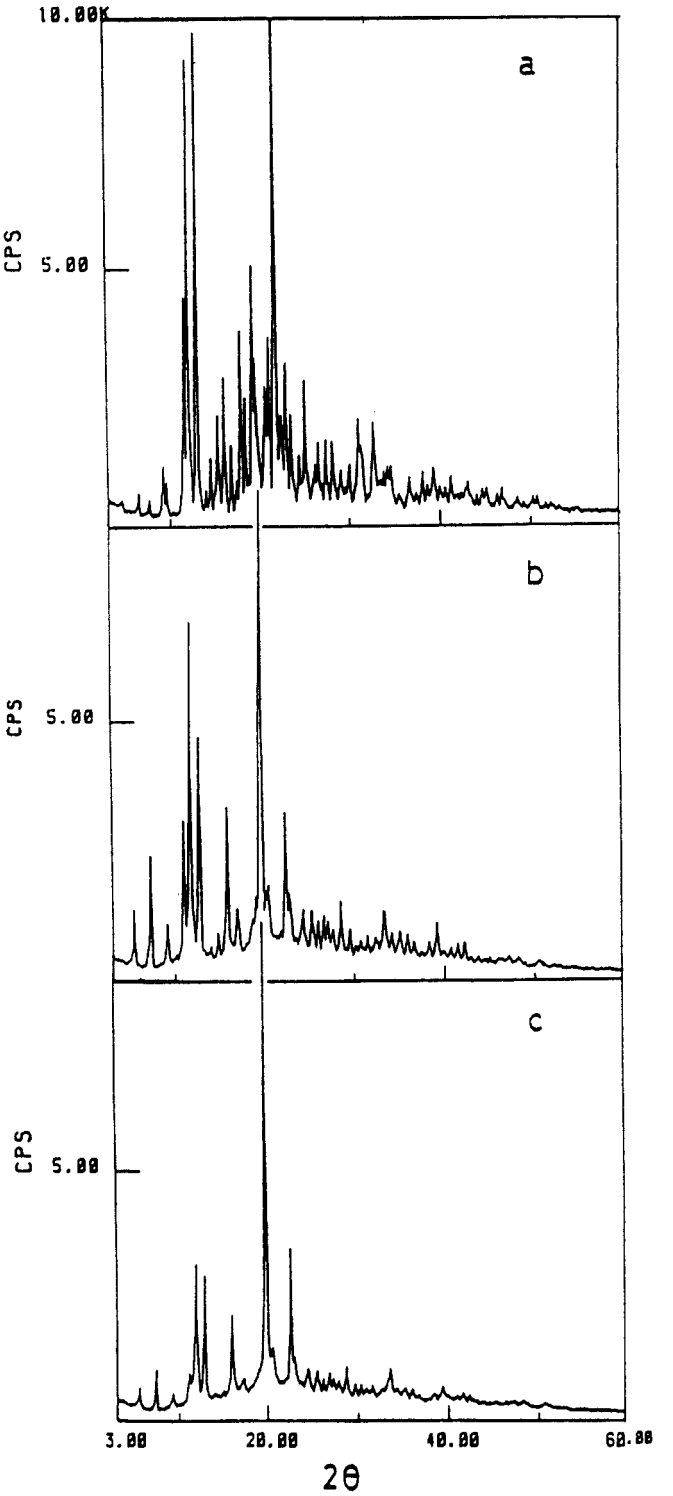

Figure 7. X-ray diffraction patterns for α-CD complexes: α-CD–propionic acid (a), α-CD–valeric acid (b), and α-CD–PEG($\overline{MW}$ = 1000) (c).

can be classified by two groups; one is "cage type", and the other is "channel type".[12] The X-ray powder pattern of the α-CD–PEG complex shows that the complexes are crystalline, and the patterns are very similar to those of the complex of α-CD with valeric acid or octanol, which have been reported to have extended column structure, and totally different from those of the complexes with small molecules, such as acetic acid, propionic acid, and propanol, which have a cage structure. These results indicate that the complexes of α-CD and PEG are isomorphous with those of channel type structure rather than the so-called "cage" type structure.

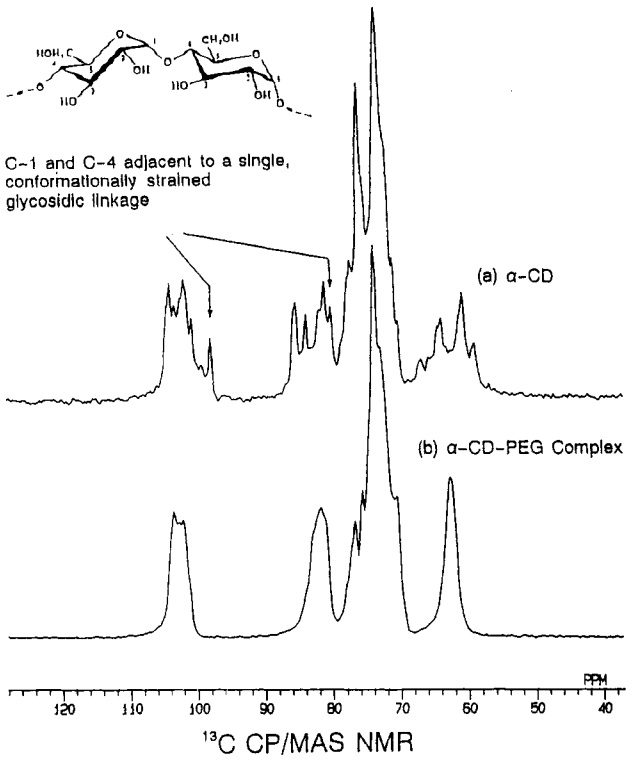

Figure 8. ^{13}C CP/MAS NMR spectra of α-CD (a) and the α-CD–PEG complex (b).

Molecular models show that PEG chains are able to penetrate α-CD cavities, while the poly(propylene glycol) chain cannot pass through the α-CD cavity. These views are in accordance with our results that α-CD formed complexes with PEG but not with poly(propylene glycol). β-CD did not form complexes with PEG. A PEG chain is too thin to fit in the β-CD cavity. Instead β-CD forms complexes with poly(propylene glycol) as we reported previously in another paper.[13] Model studies further indicate that the single cavity (depth 6.7 Å) accommodates two ethylene glycol units (6.6 Å) when ethylene glycol units assume a planar zigzag conformation.

Figure 8 shows the ^{13}C CP/MAS NMR spectra of α-CD and the α-CD–PEG complex. α-CD assumes a less symmetrical conformation in the crystal when it does not include a guest in the cavity.[14] In this case, the spectrum shows resolved C-1 and C-4 resonances from each of the six α-1,4-linked glucose residues. Especially C-1 and C-4 adjacent to a conformationally strained glycosidic linkage are observed at 80 and 98 ppm, respectively.[14] On the other hand, in the spectrum of the α-CD–PEG complex the peaks at 80 and 98 ppm disappeared. Each carbon of glucose can be observed in a single peak. These results indicate that α-CD adopts a symmetrical conformation, and each glucose unit of CD is in a similar environment. The X-ray studies of single crystals showed that α-CD assumes a less symmetrical conformation when it does not include guests in the cavity and α-CD adopts a symmetrical conformation when it includes guests in the cavities.[12] CP/MAS NMR spectra of complexed and uncomplexed CDs are consistent with the results by X-ray. So a PEG chain is though to be included in the cavities.

Table II shows results of complex formation between α-CD and PEG with various end groups. First, PEGs with small end groups, such as methyl, dimethyl, and amino groups, form complexes. The yields are rather higher than unmodified PEG. These results indicate that interactions (hydrogen bonds) between OH groups of PEG and OH groups of α-cyclodextrin are not the driving force for complex formation.

Table II. Complex Formation between CD and PEG with Various Small End Groups

$R(CH_2CH_2O)_nCH_2CH_2R'$			yield[a] (%)	
R	R′	MW	α-CD	β-CD
–OH	–OH	1000	90	0
$–NH_2$	$–NH_2$	1450	94	0
		2000	96	0
$–OCH_3$	$–OCH_3$	500	88	0
		1000	93	0
		2000	98	0
$–OCH_3$	–OH	750	89	0

[a] $R(CH_2CH_2O)_nCH_2CH_2R'$, 15 mg; CD saturated solution, 1 mL; sonication, 10 min; allowed to stand overnight at room temperature.

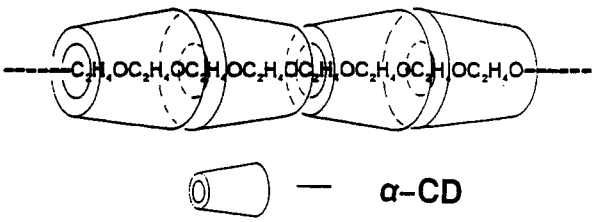

Figure 9. Proposed structure of the α-CD–PEG complex.

PEGs carrying bulky substituents such as a 3,5-dinitrobenzoyl group and a 2,4-dinitrophenyl group at both ends of the PEG, which do not fit or pass through the α-CD cavity,[15] do not form any complexes with α-CD.

Figure 9 shows a proposed structure of the complex of poly(ethylene glycol) with α-cyclodextrin. The inclusion complex formation of PEG in the α-CD channel is entropically unfavorable. However, formation of the complexes is thought to be promoted by hydrogen bond formation between cyclodextrins. Therefore, head-to-tail and tail-to-tail arrangement is thought to be the most probable structure.

In conclusion α-cyclodextrin forms complexes with poly(ethylene glycol) of various molecular weights to give crystalline complexes in high yields, although β-CD did not form complexes with PEG.

Experimental Section

Materials. α-Cyclodextrin and β-cyclodextrin were obtained from Nakarai Tesque Inc. and used after drying at 80 °C under vacuum. Poly(ethylene glycols)s of average molecular weights 200, 300, 400, 3000, and 8500 were purchased from Tokyo Kasei Inc., those of 600, 1000, 1450, and 2000 were from Nakarai Tesque Inc., that of 3350 was from Sigma, and that of 50 000 was from Wako Pure Chemical Industries, Ltd. Poly(ethylene glycol)–monomethyl ether of molecular weights 500, 1000, and 2000 were obtained from Fluka. Poly(ethylene glycol)–bisamine with average molecular weight 3350 was obtained from Sigma. The average molecular weights of the various PEG samples were found by GPC (gel permeation chromatography) to be within the specification given by the suppliers. Ethylene glycol and diethylene glycol were obtained from Nakarai Tesque Inc., and triethylene glycol was purchased from Tokyo Kasei Inc. Glucosyl-α-CD and maltosyl-α-CD were kindly supplied by Ensuikou Seitou Co., Inc. Pullulan, maltose, maltotriose, and amylose were obtained from Hayashibara Biochemical Research, and dextran was purchased from Wako Pure Chemical Industries, Ltd. Water-soluble α-CD polymer was prepared by the reaction of α-CD with epichlorohydrin.[16] 2,4-Dinitrofluorobenzene (DNFB) and *p*-toluenesulfonyl chloride were obtained from Nakarai Tesque Inc. Potassium phthalimide and hydrazine hydrate were obtained from Wako Pure Chemical Industries, Ltd. Dimethylformamide (DMF; Nakarai Tesque Inc.) was purified with reduced-pressure distillation from molecular sieves (4A) under a nitrogen atmosphere. Tetrahydrofuran (THF; Nakarai Tesque Inc.) was fractionally distilled from CaH_2 under a nitrogen atmosphere. DMSO-d_6, $CDCl_3$, and D_2O used as solvents in the NMR measurements were obtained from Aldrich.

Preparation of Modified PEG. PEG–bisamine (PEGBA) was prepared from PEG-1450 according to the method described by Pillai et al.[17]

PEGBA-1450 ($\overline{MW}$ = 1450). PEG–tosylate (4.6 g), which was prepared from PEG-1450 and *p*-toluenesulfonyl chloride, and potassium phthalimide (7.0 g) in DMF (60 mL) were heated under reflux in a nitrogen atmosphere for 5 h. The precipitate was then filtered off, and to the clear filtrate was added diethyl ether slowly with stirring, keeping it in an ice bath. The precipitate was filtered, washed with diethyl ether, and dried under vacuum to give PEG–phthalimide (3.3 g), yield 73%.

PEG–phthalimide (3.2 g) and hydrazine hydrate (6.0 mL) in ethanol (60 mL) were heated under reflux for 20 h. The product was precipitated from diethyl ether. The precipitate was filtered and redissolved in methylene chloride, and the insoluble impurities were removed by filtration. The filtrate was precipitated from diethyl ether. The precipitate was filtered, washed with diethyl ether, and dried under vacuum to give PEGBA-1450 (2.57 g, 94%). Anal. Calcd for $C_{64}H_{132}N_2O_{31}\cdot 2H_2O$: C, 52.59; H, 9.38; N, 1.92. Found: C, 52.57; H, 9.19; N, 1.54.

PEGBA-2000 ($\overline{MW}$ = 2000). Yield: 90%. Anal. Calcd for $C_{88}H_{180}N_2O_{43}\cdot 4H_2O$: C, 52.16; H, 9.35; N, 1.38. Found: C, 52.36; H, 9.04; N, 1.09.

PEG-bis(2,4-dinitrophenylamine) was prepared by treatment of PEG–bisamine ($\overline{MW}$ = 3350) with 2,4-dinitrofluorobenzene in DMF in a way similar to that described previously.[18] Yield: 80%. GPC analysis showed that the product had the same elution time and molecular weight distribution (M_w/M_n = 1.03) as those of the PEG-3350 and the product showed absorption at 360 nm which indicated the polymer was attached with a 2,4-dinitrophenylamine group. ^{1}H NMR (DMSO-d_6, 270 MHz): δ 8.86 (d, 2H, meta H of phenyl), 8.26 (m, 2H, H of –NH–), 7.44 (d, 2H, meta H of phenyl), 7.27 (d, 2H, ortho H of phenyl), 4.04 (d, 4H, H of $-CH_2N=$), 3.51 (m, 4H × 75, polymer backbone).

PEG–bis(3,5-dinitrobenzoate) was prepared by the reaction of PEG-600 with 3,5-dinitrobenzoyl chloride as described previously.[19] Yield: 48.5%. GPC analysis showed that the product had the same elution time and molecular weight distribution (M_w/M_n = 1.05) as those of the PEG-600 and the product showed absorption, indicating that 3,5-dinitrobenzoate groups were attached to the polymer. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 9.22 (t, 2H, para H of phenyl), 9.17 (d, 4H, ortho H of phenyl), 4.61 (t, 4H, of $-COOCH_2-$), 3.63–3.89 (m, 4H × 12, polymer backbone).

Reaction of Poly(ethylene glycol)s with α-CD. Preparation of the Inclusion Complexes. Poly(ethylene glycol)s or modified poly(ethylene glycol)s (15 mg) were dissolved in water (0.1 mL). A saturated aqueous solution of α-CD (1.0 mL) containing 145 mg of α-CD (0.15 M) was added at room temperature, and the mixtures were ultrasonically agitated for 10 min and then allowed to stand overnight at room temperature. The products precipitated were collected by centrifugation, washed with water, and then dried under vacuum up to 70 °C to give the α-CD–PEG complexes. The complexes can be recrystallized from water when the molecular weight of PEG is less than 2000.

α-CD–PEG-600. Yield: 90%. Mp: 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEG), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD). ^{13}C NMR (DMSO-d_6, 67.8 MHz): δ 101.87 (C(1) of α-CD), 82.02 (C(4) of α-CD), 73.17 (C(3) of α-CD), 72.09 (C(2) and C(5) of α-CD), 69.71 (CH_2 of PEG), 59.99 (C(6) of α-CD). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{280}H_{492}O_{232}$: C, 44.42; H, 6.55. Found: C, 44.62; H, 6.61.

α-CD–PEG-1000. Yield: 91%. Mp: 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEG), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD). ^{13}C NMR (DMSO-d_6, 67.8 MHz): δ 101.85 (C(1) of α-CD), 82.02 (C(4) of α-CD), 73.17 (C(3) of α-CD), 72.08 (C(2) and C(5) of α-CD), 69.71 (CH_2 of PEG), 59.99 (C(6) of α-CD). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{440}H_{772}O_{364}$: C, 44.46; H, 6.55. Found: C, 44.67; H, 6.71.

α-CD–PEGBA-1450. Yield: 94%. Mp: 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEGBA), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD). ^{13}C NMR (DMSO-d_5, 67.8 MHz): δ 101.84 (C(1) of α-CD), 81.99 (C(4) of α-CD), 73.14 (C(3) of α-CD), 72.04 (C(2) and C(5) of α-CD), 69.67 (CH_2 of PEGBA), 59.95 (C(6) of α-CD). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{640}H_{1220}N_2O_{575}$: C, 42.36; H, 6.78; N, 0.15. Found: C, 42.37; H, 6.75; N, 0.13.

α-CD–PEGBA-2000. Yield: 96%. Mp: 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEGBA), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD). ^{13}C NMR (DMSO-d_6, 67.8 MHz): δ 101.84 (C(1) of α-CD), 81.99 (C(4) of α-CD), 73.14 (C(3) of α-CD), 72.08 (C(2) and C(5) of α-CD), 69.67 (CH_2 of PEGBA), 59.95 (C(6) of α-CD). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{880}H_{1632}N_2O_{769}$: C, 43.06; H, 6.70; N, 0.11. Found: C, 42.10; H, 6.71; N, 0.16.

α-CD–PEGDME-500. Yield: 88%. Mp: 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEGDME), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD), 3.36 (s, $-OCH_3$ of PEGDME); ^{13}C NMR (DMSO-d_6, 67.8 MHz): δ 101.87 (C(1) of α-CD), 82.02 (C(4) of α-CD), 73.17 (C(3) of α-CD), 72.08 (C(2) and C(5) of α-CD), 69.71 (CH_2 of PEGDME), 59.99 (C(6) of α-CD), 57.94 ($-OCH_3$ of PEGDME). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{242}H_{438}O_{199}$: C, 44.50; H, 6.76. Found: C, 44.61; H, 6.67.

α-CD–PEGDME-1000. Yield: 93%. Mp: 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEGDME), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD), 3.36 (s, $-OCH_3$ of PEGDME). ^{13}C NMR (DMSO-d_6, 67.8 MHz): δ 101.85 (C(1) of α-CD), 82.02 (C(4) of α-CD), 73.19 (C(3) of α-CD), 72.08 (C(2) and C(5) of α-CD), 69.71 (CH_2 of PEGDME), 59.99 (C(6) of α-CD), 57.84 ($-OCH_3$ of PEGDME). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{442}H_{776}O_{364}$: C, 44.56; H, 6.56. Found: C, 44.43; H, 6.67.

α-CD–PEGDME-2000. Yield: 98%. Mp: 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEGDME), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD), 3.36 (s, $-OCH_3$ of PEGDME). ^{13}C NMR (DMSO-d_6, 67.8 MHz): δ 101.85 (C(1) of α-CD), 82.00 (C(4) of α-CD), 73.19 (C(3) of α-CD), 72.06 (C(2) and C(5) of α-CD), 69.69 (CH_2 of PEGDME), 59.97 (C(6) of α-CD), 57.84 ($-OCH_3$ of PEGDME). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{882}H_{1634}O_{771}$: C, 43.11; H, 6.70. Found: C, 44.31; H, 6.81.

α-CD–PEGMME-750. Yield: 89%. Mp 300–305 °C (dec). ^{1}H NMR (D_2O, 270 MHz): δ 5.03 (d, 6H, C(1)H of α-CD), 3.96 (t, 6H, C(3)H of α-CD), 3.85 (m, 12H, C(6)H of α-CD), 3.80 (m, 6H, C(5)H of α-CD), 3.68 (s, 8H, CH_2 of PEGMME), 3.61 (m, 6H, C(2)H of α-CD), 3.56 (t, 6H, C(4)H of α-CD), 3.36 (s, $-OCH_3$ of PEGDME). ^{13}C NMR (DMSO-d_6, 67.8 MHz): δ 101.85 (C(1) of α-CD), 82.02 (C(4) of α-CD), 73.19 (C(3) of α-CD), 72.08 (C(2) and C(5) of α-CD), 69.69 (CH_2 of PEGMME), 59.97 (C(6) of α-CD), 57.92 ($-OCH_3$ of PEGMME). IR (KBr, cm^{-1}): 3406 (vs, ν_{OH}), 2927 (s, ν_{CH}), 1154, 1078, 1031 (vs, ν_{CO}), 574. Anal. Calcd for $C_{321}H_{564}O_{265}$: C, 44.50; H, 6.56. Found: C, 44.26; H, 6.73.

Influence of the Amount of PEG Added. The saturated aqueous solution of α-CD was held constant at 2.0 mL, while the amounts of PEG added were successively increased. The products precipitated were collected and dried, and then the yields were calculated base on the α-CD.

Measurements. Gel permeation chromatographic (GPC) determination was carried out with a Tosoh CCP&8010 system (columns: G3000HXL and G2000HXL). Absorption spectra were recorded on a Shimadzu UV-2001 spectrophotometer. Proton NMR spectra of the complexes were recorded at 270 MHz

on a JEOL GSX-270 NMR spectrometer. Chemical shifts were referenced to the solvent values (2.50 ppm for DMSO, 7.26 ppm for $CHCl_3$, and 4.70 ppm for HOD). Solid-state ^{13}C CP/MAS NMR spectra were measured at 67.8 MHz on a JEOL EX-270 NMR spectrometer with a sample spinning rate of 5.5 kHz at room temperature. Chemical shifts were referenced to external standard TMS. CP spectra were acquired with a 4-ms proton 90° pulse, a 1-ms contact time, and a 5-s repetition time. Powder X-ray diffraction patterns were taken by using Cu Kα radiation with a Rigaku RAD-ROC X-ray diffractometer (voltage, 40 kV; current, 40 mA; scanning speed, 3°/min). Thermogravimetric measurements were performed on a Shimadzu DT-30 with a heating rate of 10 °C/min.

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