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Formation of Inclusion Complexes of Oligoethylene and Its Derivatives with α-Cyclodextrin

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Oligoethylene (OE) was found to form inclusion complexes with α-cyclodextrin (α-CD) not only from aqueous solutions of α-CD but also from DMF solutions of α-CD to give stoichiometric compounds in a crystalline state in high yields. The yields depend on the oligomeric degree (n) of OE when DMF was used as solvent. OE of n less than 6 did not form complexes with α-CD in DMF solution. The complexes were characterized by IR, ^{1}H NMR, ^{13}C NMR, and ^{13}C CP/MAS and PST/MAS NMR spectra, X-ray (powder), and elemental analysis. The continuous variation plots for the complex formation and the ^{1}H NMR spectra of the complexes show that the stoichiometry of the crystalline complexes is 3 : 1 (ethylene unit–α-CD). The X-ray powder pattern of α-CD–OE complexes and the solid state ^{13}C CP/MAS, PST/MAS NMR spectra suggest that the OE chain is included in the channel formed by α-CD molecules and that the OE backbone in the complexes is more flexible than that in uncomplexed state (OE crystal) due to being included in the cavities of α-CD. Derivatives of OE(6) with small end groups, such as hydroxyl, carboxyl and amino groups, formed crystalline complexes with α-CD, but OE(6) carrying large end groups, such as 2,4-dinitrophenyl and 2,4,6-trinitrophenyl groups, did not form complexes with α-CD. However, it is found that derivatives of OE(6) with charged end groups, such as ammonio or carboxylato groups, do not form crystalline complexes with α-CD, but can form 1 : 1 (guest molecule–α-CD) complexes which are in equilibrium in aqueous solution. The complexation of diammoniohexaethylene cation (DAHE cation) with α-CD in aqueous solution was discussed by using ^{1}H NMR and 2D NOESY NMR spectra.

Cyclodextrins (CDs) are a series of cyclic oligosaccharides composed of six, seven, and eight D(+)-glucopyranose units linked by α-1,4-linkages: They are named α-, β-, and γ-CD, respectively. The geometry of CDs gives doughnut-shaped hydrophobic cavities having a depth of ca. 7.0 Å, and an internal diameter of ca. 4.5 Å for α-, ca. 7.0 Å for β-, and ca. 8.5 Å for γ-CD, respectively.[1)] The most characteristic feature of CDs is the ability to bind various low molecular weight compounds to form inclusion complexes with these guest molecules. Therefore, CDs have been studied extensively as models for enzyme active sites to mimic enzyme activity and to understand the mechanism of molecular recognition,[1,2)] while a great number of inclusion complexes of CDs with low molecular weight compounds, both organic[3)] and inorganic,[4)] were prepared and characterized.

However, except for a few examples in which a monomer was polymerized in situ within a CD complex[5)] and a few reports which suggest interactions between CDs and some polymers in aqueous solution,[6)] there were no reports on the complex formation between CDs and polymers when we started our research on the inclusion complexes of CDs with polymers.[7)]

Previously, we reported that poly(ethylene glycol) (PEG), a hydrophilic water-soluble polymer, selectively formed inclusion complexes with α-CD to give crystalline complexes; these complexes were proposed to take a necklacelike structure constructed by the PEG chain and many threaded α-CD molecules.[7,8)] We also reported that another two hydrophilic polymers, poly(propylene glycol) and poly(vinyl methyl ether), selectively formed crystalline complexes with β-CD and γ-CD.[9)] Furthermore, we reported the preparation of the polyrotaxanes in which many α-CDs are threaded on a PEG chain by capping the ends with bulky substituents and the preparation of the tubular polymer of α-CD.[10)] Wenz et al. also reported α-CDs threaded on a polyimine chain.[11)] Recently, we reported that polyisobutylene (PIB) (liquid), a hydrophobic polymer, formed complexes with β-CD and γ-CD, and that the chain-length selectivities between β-CD and γ-CD are reversed.[12)] All of the complexes described in the above references were formed from aqueous solutions of CDs.

Now we found that oligoethylene (OE), a crystalline hydrophobic oligomer, of oligomeric degree (n) up to 25 selectively formed inclusion complexes with α-CD from aqueous solution of α-CD as well as from DMF solution of α-CD to give crystalline complexes in high yields, but OE did not form any complex with β-CD or γ-CD. This is the first observation that α-CD forms solid-state complexes with a crystalline hydrophobic polymer/oligomer. Yenemura et al.,[13)] Saito et al.,[14)] and Watanabe et al.[15)] reported complexation between α-CD and some charged derivatives of OE, but the complexation was limited to form 1 : 1 (guest molecule–α-CD) complexes in aqueous solution and it did not give any crystalline complex. In this paper, we describe the formation of crystalline complexes of OE and some derivatives of OE(6) with α-CD, and make a comparison among OE, squalane, and PIB in complex formation with CDs. We also discuss the complexation between diammoniohexaethylene cation (DAHE cation) and α-CD in aqueous solution, with a comparison with Refs. 13, 14, and 15. The structures of the polymers/oligomers discussed in this paper are shown in Chart 1.

Experimental

Materials. α-CD, β-CD, and γ-CD were obtained from Nacalai Tesque Inc. and used after drying at 80 °C under vacuum. OEs of oligomeric degrees (*n*) 6, 9, 12 were purchased from Nacalai Tesque Inc.; those of 16, 20, 25 were from Tokyo Kasei Inc. α,ω-Diaminohexaethylene (DAHE) was obtained from Tokyo Kasei Inc., α,ω-Dihydroxyhexaethylene (DHHE) and α,ω-Dicarboxyhexaethylene (DCHE) were from Nacalai Tesque Inc. Hexane was purchased from Nacalai Tesque Inc. Squalane was obtained from Tokyo Kasei Inc. 2,6-Di-*O*-methyl-α-cyclodextrin (DM-α-CD) was kindly supplied by Nihon Shokuhin Kako Co., Ltd. Diaminohexaethylene dihydrochloride (DAHE·2HCl) was prepared by neutralization of DAHE with hydrochloric acid. 2,4-Dinitro-1-fluorobenzene (DNFB) was obtained from Nacalai Tesque Inc. 2,4,6-Trinitrobenzenesulfonic acid sodium salt dihydrate (TNBS) was obtained from Wako Pure Chemical Industries, Ltd. *N*,*N*-Dimethylformamide (DMF) (Nacalai Tesque Inc.) was purified with reduced pressure distillation from molecular sieves (4A) under nitrogen atmosphere. DMSO-d_6, DMF-d_7, and D_2O used as solvents in the NMR measurements were obtained from Aldrich.

***N*,*N*′-Bis(2,4-dinitrophenyl)–DAHE.** (DAHE–DNP$_2$) was prepared by treatment of DAHE with 2,4-dinitro-1-fluorobenzene in DMF according to a way reported previously.[16] Yield 82%. The product showed absorption at 360 nm, which indicated the compound was substituted with 2,4-dinitrophenylamino group; ^{1}H NMR (DMSO-d_6, 270 MHz) δ=8.86 (d, 2H, meta H of phenyl), 8.81 (m, 2H, H of ph-NH–), 8.24 (d, 2H, meta H of phenyl), 7.22 (d, 2H, ortho H of phenyl), 3.46 (m, 4H, H$_\alpha$ of hexaethylene chain), 1.63 (m, 4H, H$_\beta$ of hexaethylene chain), 1.11—1.39 (m, 4H×4, hexaethylene backbone). Found: C, 53.82; H, 6.01; N, 15.44%. Calcd for $C_{24}H_{32}N_6O_8$: C, 54.13; H, 6.06; N, 15.78%.

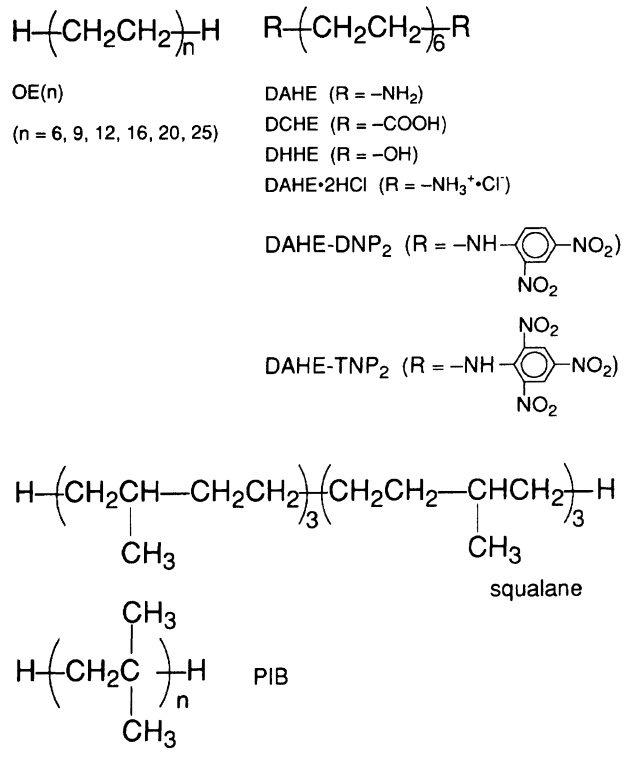


Chart 1.

***N*,*N*′-Bis(2,4,6-trinitrophenyl)–DAHE.** (DAHE–TNP$_2$) was prepared by the reaction of DAHE with TNBS according to a way reported previously.[17] Yield 78%. The product showed absorptions at 417 and 347 nm, indicating that 2,4,6-trinitrophenyl groups were substituted on the compound; ^{1}H NMR (DMSO-d_6, 270 MHz) δ=8.96 (s, 4H, metho H of phenyl), 8.79 (t, 2H, H of ph-NH–), 3.04 (m, 4H, H$_\alpha$ of hexaethylene chain), 1.66 (m, 4H, H$_\beta$ of hexaethylene chain), 1.18 (m, 4H×4, hexaethylene backbone). Found: C, 45.84; H, 4.78; N, 17.71%. Calcd for $C_{24}H_{30}N_8O_{12}$: C, 46.30; H, 4.86; N, 18.00%.

Preparation of Crystalline Complexes of OE with α-CD. (a) Complexes Formed from α-CD Aqueous Solution. OEs (75 mg) were added to a saturated aqueous solution of α-CD (5.0 ml) containing 0.725 g (0.745 mmol) α-CD; this was followed by heating to above the melting points of OEs. The mixtures were ultrasonically agitated for 10 min, then allowed to stand overnight at room temperature. After the unreacted OEs were removed, the complexes which precipitated were collected by centrifugation, washed with water, then dried under vacuum up to 80 °C to give the α-CD–OE complexes. The yields were calculated based on α-CD.

(b) Complexes Formed from α-CD DMF Solution. OEs (15 mg) were added to a DMF solution of α-CD (4.5 ml) containing 0.171 g (0.18 mmol) α-CD and followed by heating to above the melting points of OEs. The mixtures were ultrasonically agitated for 10 min, then allowed to stand overnight at room temperature. After the unreacted OEs were removed, the complexes which precipitated were collected by centrifugation, washed with water, then dried under vacuum up to 80 °C to give the α-CD–OE complexes. The yields were calculated based on α-CD.

α-CD–OE(6) Complex. Yield: 65% (from aqueous solution). Mp 300—305 °C (decomp); ^{1}H NMR (DMF-d_7, 270 MHz) δ=5.42 (m, 12H×2, C(2)OH and C(3)OH of α-CD), 4.90 (d, 6H×2, C(1)H of α-CD), 4.38 (t, 6H×2, C(6)-OH of α-CD), 3.74—3.89 (m, 24H×2, C(3)H, C(6)H, and C(5)H of α-CD), 3.53 (t, 6H×2, C(2)H of α-CD), 3.41 (m, 6H×2, C(4)H of α-CD), 1.29 (s, 4H×5, OE backbone), 0.87 (t, 3H×2, methyl ends of OE); ^{13}C NMR (DMF-d_7, 67.8 MHz) δ=103.24 (C(1) of α-CD), 83.16 (C(4) of α-CD), 74.68 (C(3) of α-CD), 73.56 (C(2) of α-CD), 73.44 (C(5) of α-CD), 61.42 (C(6) of α-CD), 34.84 (C of OE); IR (KBr) 3380 (O–H), 2926 (C–H), 1153, 1078, 1036 (C–O), 575 cm^{-1}. Found: C, 44.56; H, 6.99%. Calcd for $C_{12}H_{26}\cdot 2C_{36}H_{60}O_{30}\cdot 7H_2O$: C, 45.00; H, 7.19%.

α-CD–OE(9) Complex. Yield: 61% (from aqueous solution) and 41% (from DMF solution). Mp 300—305 °C (decomp); ^{1}H NMR (DMF-d_7, 270 MHz) δ=5.43 (m, 12H×3, C(2)OH and C(3)OH of α-CD), 4.91 (d, 6H×3, C(1)H of α-CD), 4.37 (t, 6H×3, C(6)OH of α-CD), 3.75—3.88 (m, 24H×3, C(3)H, C(6)H, and C(5)H of α-CD), 3.52 (t, 6H×4, C(2)H of α-CD), 3.41 (m, 6H×3, C(4)H of α-CD), 1.28 (s, 4H×8, OE backbone), 0.86 (t, 3H×2, methyl ends of OE); ^{13}C NMR (DMF-d_7, 67.8 MHz) δ=103.27 (C(1) of α-CD), 83.16 (C(4) of α-CD), 74.69 (C(3) of α-CD), 73.56 (C(2) of α-CD), 73.45 (C(5) of α-CD), 61.40 (C(6) of α-CD), 34.81 (C of OE); IR (KBr) 3377 (O–H), 2926 (C–H), 1152, 1076, 1030 (C–O), 575 cm^{-1}. Found: C, 46.35; H, 6.96%. Calcd for $C_{18}H_{38}\cdot 3C_{36}H_{60}O_{30}\cdot 6H_2O$: C, 46.12; H, 7.07%.

α-CD–OE(12) Complex. Yield: 59% (from aqueous solution) and 34% (from DMF solution). Mp 300—305 °C (decomp); ^{1}H NMR (DMF-d_7, 270 MHz): δ=5.43 (m, 12H×4, C(2)OH and C(3)OH of α-CD), 4.90 (d, 6H×4, C(1)H of α-CD), 4.37 (t, 6H×4, C(6)OH of α-CD), 3.75—3.89 (m, 24H×4, C(3)H, C(6)H, and C(5)H of α-CD), 3.53 (t, 6H×4, C(2)H of α-CD), 3.41 (m, 6H×4, C(4)H of α-CD), 1.28 (s, 4H×11, OE backbone), 0.87 (t, 3H×2, methyl ends of OE); ^{13}C NMR (DMF-d_7, 67.8 MHz) δ=103.25 (C(1) of α-CD), 83.16 (C(4) of α-CD), 74.68 (C(3) of α-CD), 73.56 (C(2) of α-CD), 73.44 (C(5) of α-CD), 61.40 (C(6) of α-CD), 34.82 (C of OE); IR (KBr) 3387 (O–H), 2924 (C–H), 1153, 1077, 1032 (C–O), 575 cm^{-1}. Found: C, 45.85; H, 7.12%. Calcd for $C_{24}H_{50}\cdot 4C_{36}H_{60}O_{30}\cdot 8H_2O$: C, 46.13; H, 7.05%.

α-CD–OE(16) Complex. Yield: 67% (from aqueous solution) and 33% (from DMF solution). Mp 300—305 °C (decomp); ^{1}H NMR (DMF-d_7, 270 MHz) δ=5.43 (m, 12H×5, C(2)OH and C(3)OH of α-CD), 4.89 (d, 6H×5, C(1)H of α-CD), 4.39 (t, 6H×5, C(6)OH of α-CD), 3.72—3.89 (m, 24H×5, C(3)H, C(6)H, and C(5)H of α-CD), 3.53 (t, 6H×5, C(2)H of α-CD), 3.41 (m, 6H×5, C(4)H of α-CD), 1.28 (s, 4H×15, OE backbone), 0.87 (t, 3H×2, methyl ends of OE); ^{13}C NMR (DMF-d_7, 67.8 MHz) δ=103.27 (C(1) of α-CD), 83.16 (C(4) of α-CD), 74.66 (C(3) of α-CD), 73.56 (C(2) of α-CD), 73.43 (C(5) of α-CD), 61.40 (C(6) of α-CD), 34.84 (C of OE); IR (KBr) 3395 (O–H), 2924 (C–H), 1152, 1077, 1033 (C–O), 575 cm^{-1}. Found: C, 46.62; H, 7.07%. Calcd for $C_{32}H_{66}\cdot 5C_{36}H_{60}O_{30}\cdot 15H_2O$: C, 45.59; H, 7.15%.

α-CD–OE(20) Complex. Yield: 65% (from aqueous solution) and 19% (from DMF solution). Mp 300—305 °C (decomp); ^{1}H NMR (DMF-d_7, 270 MHz) δ=5.43 (m, 12H×6, C(2)OH and C(3)OH of α-CD), 4.92 (d, 6H×6, C(1)H of α-CD), 4.37 (t, 6H×6, C(6)OH of α-CD), 3.74—3.87 (m, 24H×6, C(3)H, C(6)H, and C(5)H of α-CD), 3.53 (t, 6H×6, C(2)H of α-CD), 3.43 (m, 6H×6, C(4)H of α-CD), 1.28 (s, 4H×19, OE backbone), 0.87 (t, 3H×2, methyl ends of OE); ^{13}C NMR (DMF-d_7, 67.8 MHz) δ=103.23 (C(1) of α-CD), 83.19 (C(4) of α-CD), 74.68 (C(3) of α-CD), 73.52 (C(2) of α-CD), 73.42 (C(5) of α-CD), 61.40 (C(6) of α-CD), 34.85 (C of OE); IR (KBr) 3349 (O–H), 2925 (C–H), 1152, 1077, 1039 (C–O), 574 cm^{-1}. Found: C, 45.68; H, 7.10%. Calcd for $C_{40}H_{82}\cdot 6C_{36}H_{60}O_{30}\cdot 18H_2O$: C, 45.72; H, 7.16%.

α-CD–OE(25) Complex. Yield: 67% (from aqueous solution) and 15% (from DMF solution). Mp 300—305 °C (decomp); ^{1}H NMR (DMF-d_7, 270 MHz) δ=5.45 (m, 12H×8, C(2)OH and C(3)OH of α-CD), 4.91 (d, 6H×8, C(1)H of α-CD), 4.37 (t, 6H×8, C(6)OH of α-CD), 3.76—3.91 (m, 24H×8, C(3)H, C(6)H, and C(5)H of α-CD), 3.53 (t, 6H×8, C(2)H of α-CD), 3.40 (m, 6H×8, C(4)H of α-CD), 1.28 (s, 4H×24, OE backbone), 0.87 (t, 3H×2, methyl ends of OE); ^{13}C NMR (DMF-d_7, 67.8 MHz) δ=103.27 (C(1) of α-CD), 83.16 (C(4) of α-CD), 74.63 (C(3) of α-CD), 73.58 (C(2) of α-CD), 73.44 (C(5) of α-CD), 61.42 (C(6) of α-CD), 34.82 (C of OE); IR (KBr) 3383 (O–H), 2921 (C–H), 1152, 1076, 1031 (C–O), 575 cm^{-1}. Found: C, 46.76; H, 7.30%. Calcd for $C_{50}H_{102}\cdot 8C_{36}H_{60}O_{30}\cdot 16H_2O$: C, 46.27; H, 7.05%.

Preparation of Crystalline Complexes of Derivatives of OE(6) with α-CD. The derivatives of OE(6) (0.298 mmol) were dissolved in methanol (0.6 ml). A saturated aqueous solution of α-CD (4.8 ml) containing 0.697 g (0.715 mmol) α-CD was added and the mixtures were ultrasonically agitated for 10 min, then allowed to stand overnight at room temperature. The complexes which precipitated were collected by centrifugation, washed with water and methanol, then dried under vacuum up to 80 °C to give the target complexes. The yields were calculated based on the derivatives of OE(6).

α-CD–DAHE Complex. Yield: 85%. Mp 300—305 °C (decomp); ^{1}H NMR (D_2O, 270 MHz) δ=5.06 (m, 6H×2, C(1)H of α-CD), 3.96 (m, 6H×2, C(3)H of α-CD), 3.86 (m, 12H×2, C(6)H of α-CD), 3.81 (m, 6H×2, C(5)H of α-CD), 3.66 (m, 6H×2, C(2)H of α-CD), 3.56 (m, 6H×2, C(4)H of α-CD), 2.99 (m, 4H, H_α of DAHE), 1.68 (m, 4H, H_β of DAHE), 1.23—1.48 (m, 4H×4, H of DAHE backbone); ^{1}H NMR (DMSO-d_6, 270 MHz) δ=5.35 (s, broad, 12H×2, C(2)OH and C(3)OH of α-CD), 4.81 (d, 6H×2, C(1)H of α-CD), 4.33 (s, broad, 6H×2, C(6)OH of α-CD), 3.79 (t, 6H×2, C(3)H of α-CD), 3.58—3.67 (m, 18H×2, C(6)H and C(5)H of α-CD), 3.39 (t, 6H×2, C(2)H of α-CD), 3.29 (m, 6H×2, C(4)H of α-CD), 2.54 (t, 2H×2, H_α of DAHE), 1.25—1.36 (m, 4H×5, DAHE backbone); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ=101.78 (C(1) of α-CD), 81.93 (C(4) of α-CD), 73.08 (C(3) of α-CD), 71.99 (C(2) and C(5) of α-CD), 59.88 (C(6) of α-CD), 33.07 (C_α of DAHE), 28.79 (DAHE backbone), 26.19 (C_β of DAHE); IR (KBr) 3358 (O–H and N–H), 2928 (C–H), 1153, 1079, 1032 (C–O), 575 cm^{-1}. Found: C, 45.19; H, 7.07; N, 1.32%. Calcd for $C_{12}H_{28}N_2\cdot 2C_{36}H_{60}O_{30}\cdot 4H_2O$: C, 45.49; H, 7.09; N, 1.26%.

α-CD–DHHE Complex. Yield: 89%. Mp 300—305 °C (decomp); ^{1}H NMR (DMSO-d_6, 270 MHz) δ=5.38 (m, 12H×2, C(2)OH and C(3)OH of α-CD), 4.81 (d, 6H×2, C(1)H of α-CD), 4.34 (t, 6H×2, C(6)OH of α-CD), 4.18 (s, 2H, –OH of DHHE), 3.79 (t, 6H×2, C(3)H of α-CD), 3.58—3.67 (m, 18H×2, C(6)H and C(5)H of α-CD), 3.39 (t, 6H×2, C(2)H of α-CD), 3.29 (m, 6H×2, C(4)H of α-CD), 1.41 (t, 2H×2, H_α of DHHE), 1.26 (s, 4H×5, DHHE backbone); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ=101.78 (C(1) of α-CD), 81.94 (C(4) of α-CD), 73.10 (C(3) of α-CD), 72.02 (C(2) and C(5) of α-CD), 59.91 (C(6) of α-CD), 32.33 (C_α of DHHE), 28.73 (DHHE backbone); IR (KBr) 3388 (O–H), 2926 (C–H), 1154, 1079, 1033 (C–O), 573 cm^{-1}. Found: C, 44.80; H, 7.00%. Calcd for $C_{12}H_{26}O_2\cdot 2C_{36}H_{60}O_{30}\cdot 5H_2O$: C, 45.08; H, 7.03%.

α-CD–DCHE Complex. Yield: 84%. Mp 300–305 °C (decomp); ^{1}H NMR (DMSO-d_6, 270 MHz) δ=5.38 (m, 12H×2, C(2)OH and C(3)OH of α-CD), 4.81 (d, 6H×2, C(1)H of α-CD), 4.34 (t, 6H×2, C(6)OH of α-CD), 3.79 (t, 6H×2, C(3)H of α-CD), 3.58—3.67 (m, 18H×2, C(6)H and C(5)H of α-CD), 3.39 (t, 6H×2, C(2)H of α-CD), 3.29 (m, 6H×2, C(4)H of α-CD), 2.18 (t, 2H×2, H_α of DCHE), 1.50 (t, 2H×2, H_β of DCHE), 1.25 (s, 4H×4, DCHE backbone); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ=101.78 (C(1) of α-CD), 81.94 (C(4) of α-CD), 73.08 (C(3) of α-CD), 72.01 (C(2) and C(5) of α-CD), 59.90 (C(6) of α-CD), 33.48 (C_α of DCHE), 28.30—28.68 (DCHE backbone), 24.26 (C_β of DCHE); IR (KBr) 3379 (O–H), 2927 (C–H), 1710 (C=O), 1153, 1078, 1031 (C–O), 574 cm^{-1}. Found: C, 45.17; H, 6.67%. Calcd for $C_{14}H_{26}O_4\cdot 2C_{36}H_{60}O_{30}\cdot 4H_2O$: C, 45.38; H, 6.82%.

Influence of the Amount of PEG Added. The saturated aqueous solution of α-CD was held constant at

5.5 ml (containing 0.798 g α-CD), while the amounts of OE added were successively increased. The complexes which precipitated were collected and dried, then the yields were calculated based on α-CD.

Continuous Variation Method. The total amount of α-CD and ethylene units of OE was fixed in 1.04×10^{-3} mol, while the molar fractions of α-CD were varied from 0 to 1.0. The complexes which precipitated were collected and dried.

Measurements. Absorption spectra were recorded on a Shimadzu UV-2001 spectrophotometer. ^{1}H NMR spectra of the complexes were recorded at 270 MHz on a JEOL JNM EX-270 NMR spectrometer. Chemical shifts were referred to the solvent values ($\delta=2.50$ for DMSO, $\delta=8.00$ for DMF, and $\delta=4.70$ for HOD). ^{13}C NMR spectra of the complexes were recorded at 67.8 MHz on a JEOL JNM EX-270 NMR spectrometer. Chemical shifts were referred to the solvent values ($\delta=39.5$ for DMSO-d_6 and $\delta=162.7$ for DMF-d_7). 2D NOESY experiments were obtained at 400 MHz with D_2O as the solvent at 30 °C on a JEOL JNM GSX-400 NMR spectrometer. The 2048 experiments were performed with 8 scans per experiment. Solid state ^{13}C CP/MAS and PST/MAS NMR spectra were measured at 100 MHz on a JEOL JNM GSX-400 NMR spectrometer with a sample spinning rate of 5.5 kHz at room temperature. Chemical shifts were referred 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 $K\alpha$ radiation with Rigaku RAD-ROC X-ray diffractometer. (voltage, 40 kV; current, 40 mA; scanning speed, 3° min^{-1}).

Results and Discussion

Formation of Crystalline Complexes of OEs with α-CD. (a) Preparation and Properties. We reported that α-CD forms complexes with water-soluble hydrophilic PEG.[7,8] A good fit between the cross sectional area of PEG and the diameter of α-CD cavity plays an important role in the complex formation. Oligoethylene (OE), a hydrophobic oligomer, is insoluble in water and exists as crystals at room temperature, except for the cases that the oligomeric degrees (n) are less than 6 (liquid). OE has a similar cross sectional area to that of PEG. However, when we added the crystalline OE into a saturated aqueous solution or DMF solution of α-CD at room temperature followed by sonication, no complexes were obtained. When the aqueous solution of α-CD with OE was heated to above the melting points of OEs, followed by sonication, the solutions became turbid and the complexes were formed. When the DMF solution of α-CD was heated with OE, then followed by sonication, the solution became turbid and the complexes were formed as well. The α-CD–OE complexes were obtained as a white precipitate, while the unreacted OE floated on the solution when the reaction mixtures were allowed to cool to room temperature. After the unreacted OEs were removed, the complexes were isolated by filtration or centrifugation, washed with water, and dried.

Table 1 shows a comparison between three kinds of guest compounds, the polymers/oligomers composed of saturated hydrocarbon with various cross sectional area, in the formation of solid-state complexes with cyclodextrins. OE, which has the smallest sectional area, selectively formed a complex with α-CD (diameter of the cavity: ca. 4.5 Å) in high yield; while squalane, which has the larger sectional area due to the side methyl groups, selectively formed a complex with β-CD (diameter of the cavity: ca. 7.0 Å) in high yield; and polyisobutylene (PIB), which has the largest sectional area, selectively formed a complex with γ-CD (diameter of the cavity: ca. 8.5 Å) in high yield. The results indicate that the relationship between the section area of the polymers/oligomers and the diameters of the cavities of cyclodextrins is important in complex formation with hydrophobic polymers/oligomers as well as with hydrophilic[7—10,12] ones.

Figure 1 shows the yields of the complexes of α-CD with OEs of various oligomeric degrees (n). The yields are calculated on the basis of 3 : 1 (ethylene unit–α-CD) stoichiometry, which will be mentioned in the next section. The yields of the complexes of α-CD with OEs of various n are similar in the case of complex formation in α-CD aqueous solution. On the other hand, when DMF was used as solvent, α-CD did not form complexes with OEs of n less than 6. α-CD forms complexes with OEs of n of 9 and higher. The yields increase with the increase in the n of OEs, and show a maximum at $n=12$; then the yields decrease slightly with the increase in the n of OEs. The result is perhaps due to the fact that the higher molecular weight OEs are so difficult to dissolve in DMF and that the OE chains can not effectively diffuse into the α-CD cavities. The yields of the complexes in DMF are lower than those in aqueous solution. This is due to the fact that the α-CD–OE complexes partly dissolve in DMF. Figure 1 demonstrates that a minimum chain length of OE is required for the formation of solid-state complexes in DMF but such is not required in aqueous solution. This is thought to be the characteristic of the complex formation between hydrophobic

Table 1. Formation of Solid-State Complexes between Cyclodextrins and Hydrophobic Polymers/Oligomers with Various Chain Sectional Area

Polymer/Oligomer	Molecular weight	Yield[c)]/% α-CD	β-CD	γ-CD
OE(20)[a)]	563	63	0	0
Squalane[a)]	423	0	62	24
PIB[b)]	ca. 800	0	8	90

a) This work. b) Data from Ref. 12. c) Polymer/oligomer 75 mg, CD saturated aqueous solution with 0.745 mmol CD, heating over melting points of the polymer/oligomer and followed by sonication. Yields were calculated based on CD.

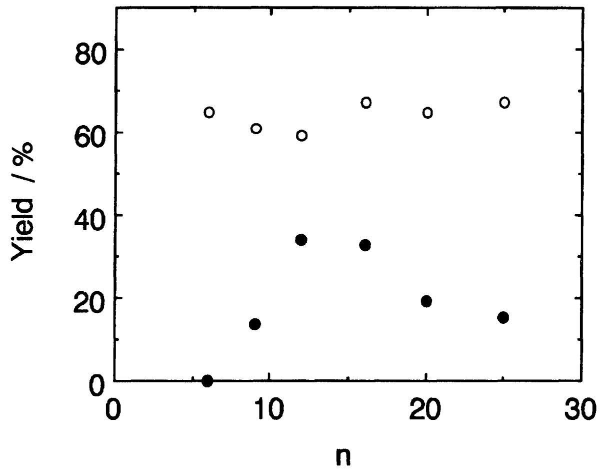


Fig. 1. Yields of the complexes of OEs with α-CD as a function of the oligomeric degree of OEs: (○) complexes formed from aqueous solution of α-CD; (●) complexes formed from DMF solution of α-CD.

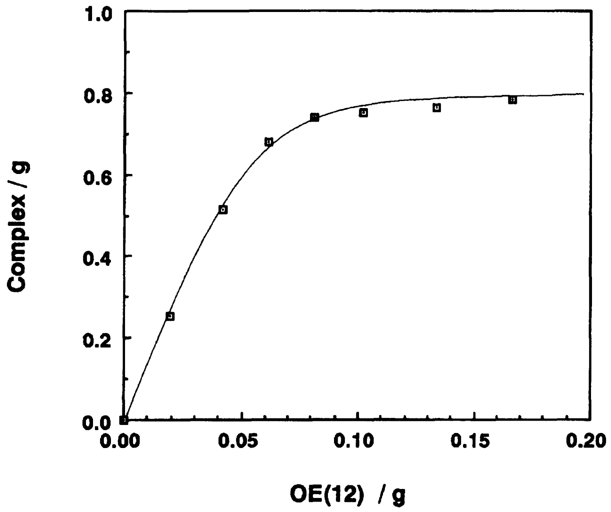


Fig. 2. Amount of α-CD–OE(12) complex as a function of added OE(12). Saturated aqueous solutions of α-CD (5.5 ml, containing 0.798 g α-CD) was used.

polymers/oligomers and α-CD, since a minimum chain length is required for the complex formation between the hydrophilic PEG and α-CD in aqueous solution. The present finding shows the importance of cooperation in the complex formation between OE and α-CD in DMF solution. The cooperation is thought to result from the fact that a single polymer/oligomer chain interacts with many CD molecules, i.e., a single polymer/oligomer chain has many binding sites which are included by CD molecules; and that the neighboring CD molecules bound on a polymer/oligomer chain interact with each other by forming hydrogen bonds.

The solubility of α-CD–OE complexes is quite different from that of α-CD–PEG complexes. The α-CD–OE complexes could not be dissolved in water at all even by heating. The α-CD–OE complexes were also insoluble in most organic solvents except for DMF. The solubility of the complexes in DMF is very low and increases as the temperature increases. This property enabled us to determine the NMR spectra of the complexes in DMF-d_7. The complexes dissociate into each component in hot DMSO. The insoluble OE separated out when the DMSO solution cooled to room temperature.

The addition of urea, which is thought to affect hydrogen bonds, to the suspension of the α-CD–OE complexes resulted in decomposition into α-CD and insoluble OE. The results indicate that hydrogen bonds play an important role in formation of the complexes, which is similar to the case of complex formation of α-CD with PEG.[7,8] The hydrogen bonds seem to be formed between α-cyclodextrins since 2,6-di-*O*-methyl-α-cyclodextrin, which lacks hydroxyl groups, does not form complexes with OE in solid state.

(b) Stoichiometry. The complex formation of α-CD with OE was studied quantitatively. Figure 2 shows the plots of the amount of the obtained complex versus OE(12) added. The amounts of the complex formed increase with the increase of OE(12) added to the α-CD aqueous solution, and a saturation was observed. The saturation shows that the complex formation is stoichiometric. Figure 3 shows the continuous variation plots for the complex formation between α-CD and OE(12). The plots show a maximum at the molar fraction of 0.25 (α-CD), suggesting that the stoichiometry of the complexes are 3 : 1 (ethylene unit–α-CD).

The stoichiometry was confirmed by the ^{1}H NMR spectra of the complexes. Figure 4 shows the ^{1}H NMR spectra of α-CD and the α-CD–OE(12) complex in DMF-d_7. In Fig. 4b, a comparison between the integral of the peaks of OE(12) and that of the peaks of α-CD gives the ratio of 3 : 1 (ethylene unit–α-CD). It should be noted that the stoichiometry of the complex

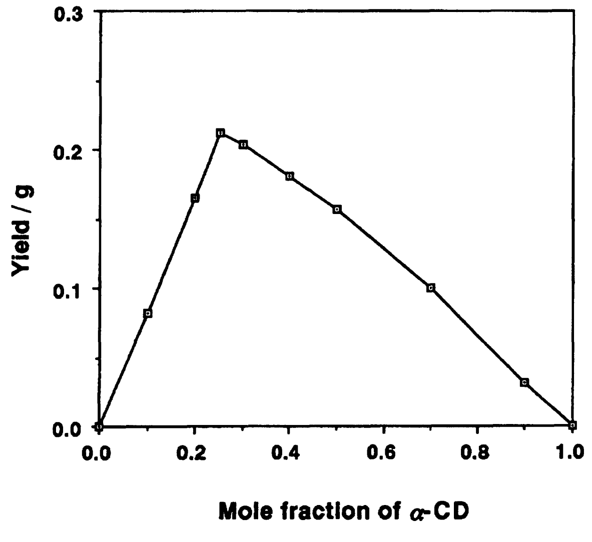


Fig. 3. Continuous variation plots for the complex formation between α-CD and OE(12). The sum of the amount of α-CD and ethylene units of OE(12) was fixed at 1.04×10^{-3} mol.

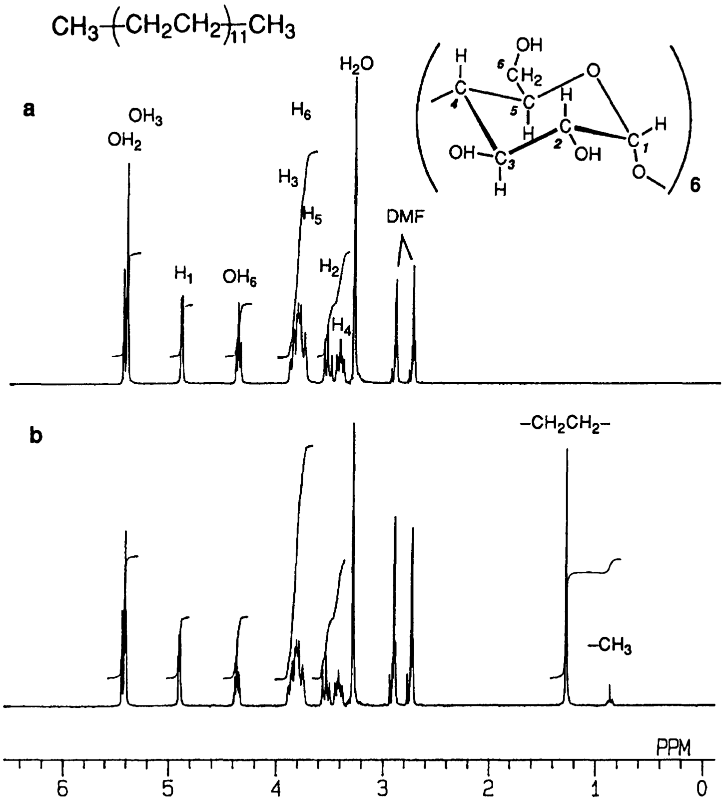


Fig. 4. 270 MHz ^{1}H NMR spectra of α-CD (a), and α-CD–OE(12) complex (b) in DMF-d_7.

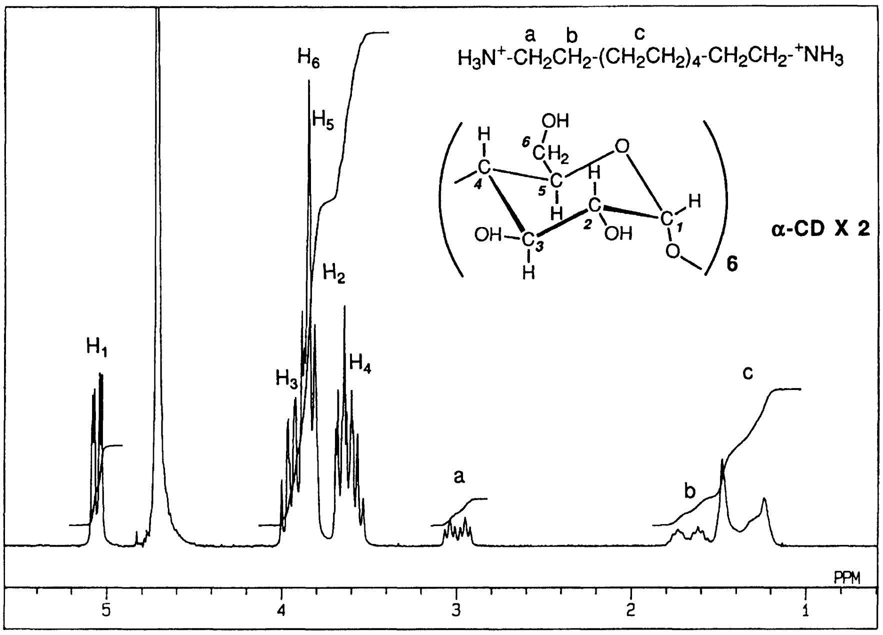


Fig. 5. 270 MHz ^{1}H NMR spectrum of α-CD–DAHE complex in D_2O+HCl.

formation is always 3 : 1 even if α-CD and OE are allowed to react in any ratio. The crystalline complexes between α-CD and some derivatives of OE(6), such as DAHE, DHHE, and DCHE, were also prepared. The ^{1}H NMR spectrum of α-CD–DAHE complex is shown in Fig. 5. The spectrum of α-CD–DAHE complex gives the ratio of two α-CD molecules per DAHE molecule. The n of DAHE is 6, indicating that the stoichiometry of α-CD–DAHE complex is 3 : 1 (ethylene unit–α-CD) as well. The crystalline complexes of α-CD with DHHE and DCHE were found to have the same stoichiometry of 3 : 1 (ethylene unit–α-CD). The X-ray studies of single crystals of polyethylene show that the ethylene units take a planar zigzag conformation and the length of a ethylene unit is 2.534 Å.[18] The length of three ethylene units (ca. 7.6 Å) corresponds to the depth of the cavity of α-CD (ca. 7.0 Å).

(c) Inclusion Mode. Figure 6 shows the X-ray powder patterns of the complexes of α-CD with OE(12) and other low molecular weight compounds. Saenger et al. reported that the structures of the inclusion compounds can be classified by two groups: One is cage type, and the other is channel type.[19] The X-ray powder pattern of the α-CD–OE complexes shows that the complexes are crystalline, and the pattern is very similar to that of the complex of α-CD with valeric acid, which has been reported to have the extended column structure, and totally different from that of the complex of α-CD with propionic acid, which has been reported to have the cage type structure. These results indicate that the α-CD–OE complexes are isomorphous with those of channel type structure rather than with those of the so-called cage type structure. By comparing Fig. 6c with the X-ray powder pattern of α-CD–PEG complexes,[7,8] we know that the two complexes show the same pattern, indicating that the α-CD molecules in the crystals of the two complexes take the same structure, even though the polymer/oligomer chains included in the cavities are different.

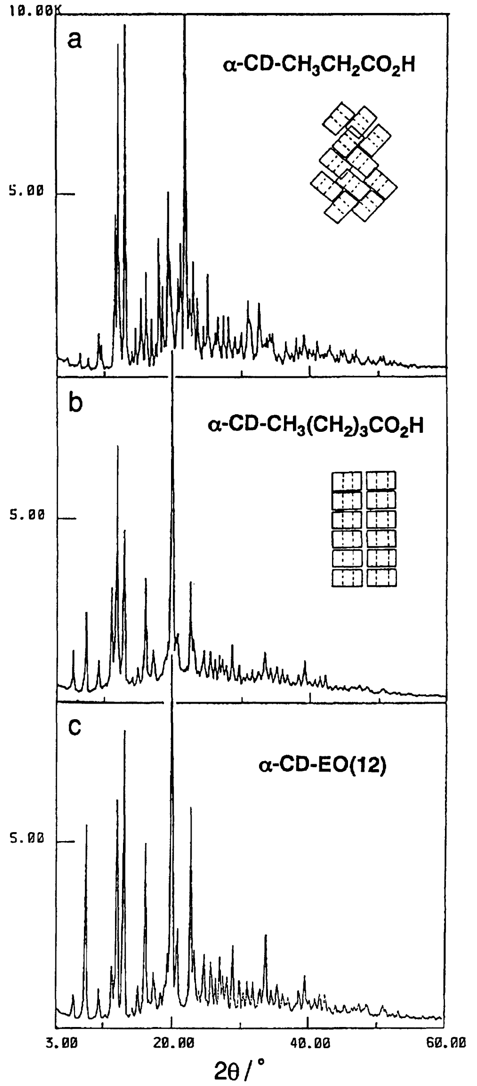


Fig. 6. X-Ray diffraction patterns for α-CD complexes: (a) α-CD–propionic acid complex; (b) α-CD–valeric acid complex; and (c) α-CD–OE(12) complex.

Molecular models show that OE chains are able to penetrate the α-CD cavity, while the squalane chain can not pass through the α-CD cavity. These views are in accordance with our results that α-CD formed complexes with OE but not with squalane. β-CD and γ-CD did not form complexes with OE. An OE chain is too thin to fit in the cavities of β-CD and γ-CD. Instead β-CD and γ-CD form complexes with squalane and PIB.

Figure 7 shows the ^{13}C CP/MAS NMR spectra of α-CD and the α-CD–OE(12) complex. α-CD assumes a less symmetrical conformation in the crystal when it does not include a guest in the cavity.[20] 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 78.3 and 98.8 ppm, respectively. On the other hand, in the spectrum of the α-CD–OE(12) the peaks at 78.3 and 98.8 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 α-CD in the complex 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

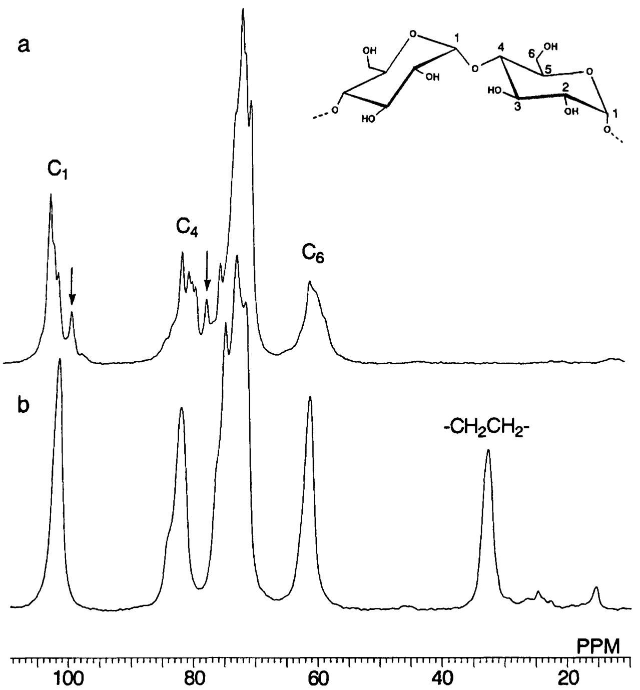


Fig. 7. ^{13}C CP/MAS NMR spectra of α-CD (a), and α-CD–OE(12) complex (b).

include guests in the cavity and α-CD adopts a symmetrical conformation when it includes guests in the cavities.[19] The CP/MAS NMR spectra of complexed and uncomplexed CDs are consistent with the results by X-ray studies. Accordingly, an OE chain is thought to be included in the cavities of α-CD.

The signals of OE appear in high field and separate from those of α-CD in the solid state ^{13}C NMR spectra, which enabled us to obtain much information about the OE chain included in the α-CD cavities from the spectrometric methods. We could not observe such separated peaks in our previous papers[7,8] because of the overlap of the signals of PEG and those of α-CD. Figure 8 shows the ^{13}C PST/MAS NMR spectrum of the physical mixture of α-CD and OE(12), and that of the α-CD–OE(12) complex. ^{13}C PST/MAS is known as a solid state NMR method which gives stronger signals of relatively flexible carbons of the sample than ^{13}C CP/MAS.[21] The spectrum of the physical mixture of α-CD–OE(12) shows that the relative intensity of the peak of the methyl ends of OE(12) is considerably stronger than that of the ethylene backbone of OE(12) (Fig. 8a). This may be explained as follows. In uncomplexed OE(12), the ethylene backbone is rigid, due to being restricted in the crystal lattice, but the methyl groups are relatively flexible, due to being in the chain ends. In Fig. 8b, each carbon of glucose of α-CD can also be observed in a single peak, which is similar to the CP/MAS spectrum. Figure 8b shows that the relative intensity of the peak of ethylene backbone of OE(12) is much stronger than that of the methyl ends of OE(12), which indicates that the ethylene backbone in the complex is much more flexible than that in the uncomplexed state (OE crystal). Furthermore, the intensity ratios of the peak of ethylene backbone to those of α-CD are much different between Figs. 8b and 7b. The ratios in Fig. 8b are higher than that in Fig. 7b, indicating that, in the complex, the ethylene backbone is not so rigid as α-CD is. These results are consistent with the views that the α-CDs form a channel, which constructs the crystal frame of the complex; and the OE chain is included in the channel.

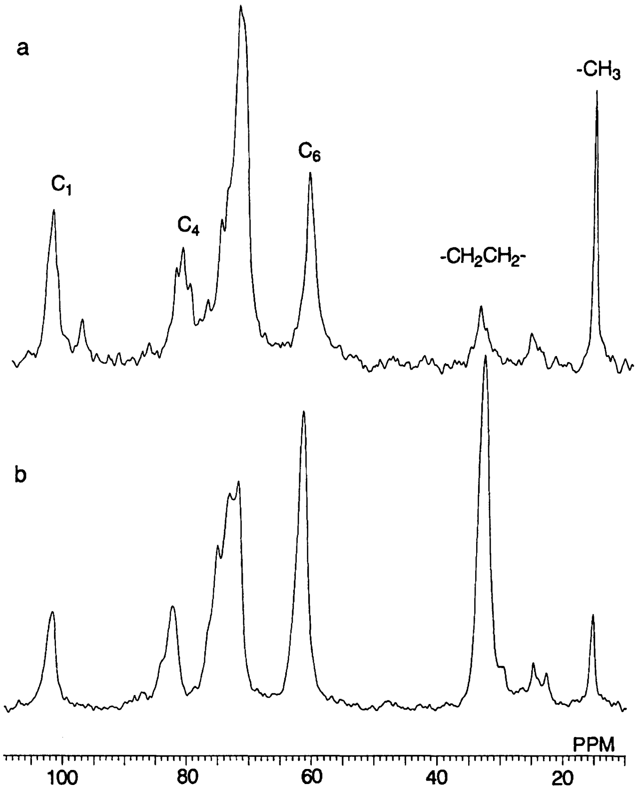
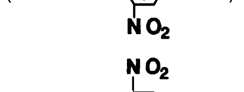
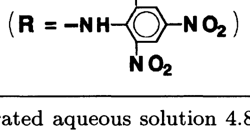


Fig. 8. ^{13}C PST/MAS NMR spectra for α-CD–OE(12): (a) physical mixture of 3 : 1 mole ratio (ethylene unit–α-CD); (b) complex.

Table 2 shows results of complex formation between α-CD and some derivatives of OE(6), the OE(6) with various end groups. First, OE(6) carrying bulky substituents such as 2,4,6-trinitrophenyl and 2,4-dinitrophenyl group at both ends, which do not fit or pass through the cavity of α-CD,[22] do not form any complex with α-CD. On the other hand, OE(6) with small end groups, such as methyl (OE as it is), hydroxyl, carboxyl, and amino groups form complexes with α-CD in high yields. The stoichiometry of all the solid complexes is 3 : 1 (ethylene unit–α-CD). The OE chain is thought to penetrate the cavities of α-CD from the ends and the molecular chains are included stoichiometrically in the cavities of α-CD to form the complexes.

Complexation between α-CD and DAHE Cation in Aqueous Solution. Although DAHE·2HCl did not form a solid complex with α-CD, DAHE cation was found to form an inclusion complex with α-CD in aqueous solution. The complexation was confirmed by the ^{1}H NMR and 2D NOESY ^{1}H NMR spectra. Figure 9 shows the ^{1}H NMR spectra of α-CD with various concentrations of DAHE cation in D_2O.

Table 2. Complex Formation between OE(6) of Various End Groups with CDs

Guest compound		Yield/%	
$R\{CH_2CH_2\}_6R$		α-CD[a]	β-CD[b]
OE(6)	(R=–H)	65	0
DAHE	(R=–NH_2)	85	0
DHHE	(R=–OH)	89	0
DCHE	(R=–COOH)	84	0
DAHE–DNP$_2$		0	0
DAHE–TNP$_2$		0	0

a) α-CD saturated aqueous solution 4.8 ml; derivatives of OE(6), 0.298 mmol; yields on the basis of derivatives of OE(6). b) β-CD saturated aqueous solution 10 ml; derivatives of OE(6), 0.068 mmol; yields on the basis of derivatives of OE(6).

Some new signals for α-CD as well as some shifts of the peaks of α-CD were observed when DAHE·2HCl was added into the solution. Figure 10 shows the ^{1}H NMR spectra of DAHE cation with various concentrations of α-CD in D_2O. The addition of α-CD to the solution gives some new signals for ethylene units of DAHE cation and makes the symmetric DAHE cation become unsymmetric. The intensities of these new signals in Figs. 9 and 10 increase with the increases in the concentrations of DAHE cation and α-CD, respectively. The results indicate that these new signals are assigned to the contribution from the complexed species of DAHE cation and α-CD, and that the lifetime of the complexed species is sufficiently long to give separated signals apart from the uncomplexed one on the NMR time scale. From the ^{1}H NMR spectra, the association constant K for the complexation between α-CD and DAHE cation was evaluated to be 7.4×10^3 $\mathrm{dm^3\,mol^{-1}}$.

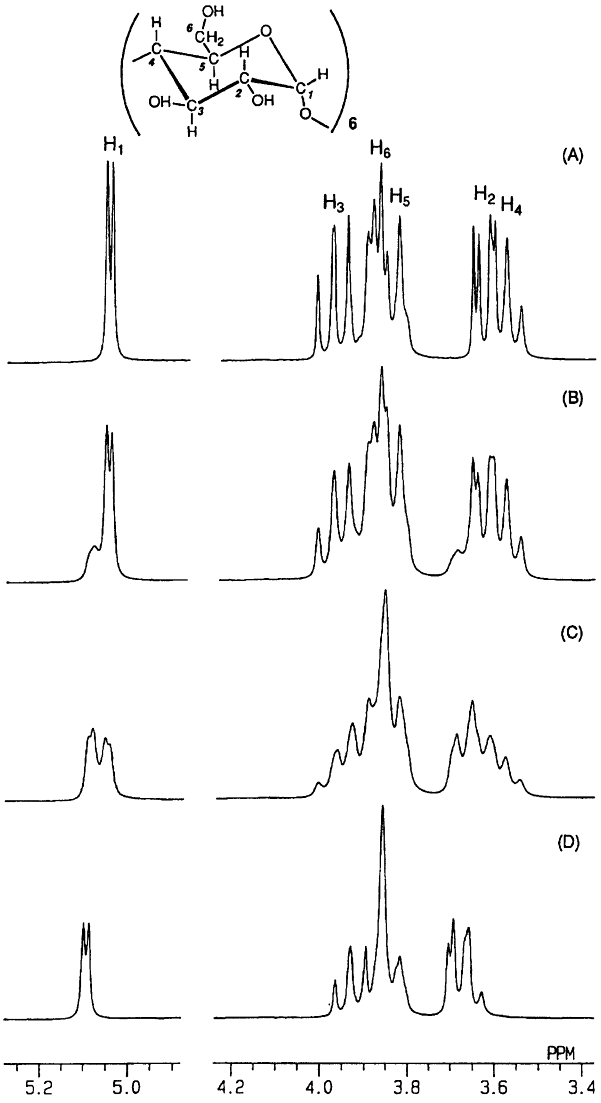


Fig. 9. 270 MHz ^{1}H NMR spectrum of α-CD (114 mM) in D_2O at 30 °C: (A) without DAHE·2HCl; (B) with DAHE·2HCl (30 mM); (C) with DAHE·2HCl (60 mM); (D) with DAHE·2HCl (120 mM). 1 M=1 mol dm^{-3}.

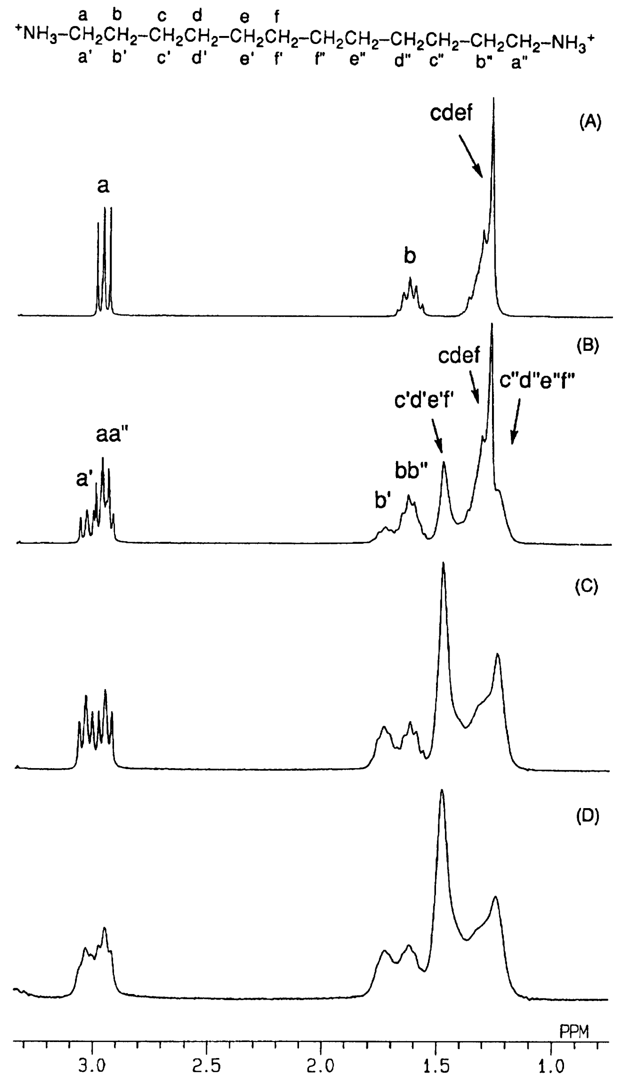


Fig. 10. 270 MHz ^{1}H NMR spectrum of DAHE·2HCl (30 mM) in D_2O at 30 °C: (A) without α-CD; (B) with α-CD (15 mM); (C) with α-CD (55 mM); (D) with α-CD (160 mM). 1 M=1 mol dm^{-3}.

In Figs. 9 and 10, the increase in the intensities of the signals of the complexed species reaches a saturation when the molar ratio between α-CD and DAHE cation becomes 1 : 1, indicating a 1 : 1 complexation between α-CD and DAHE cation in aqueous solution. The unsymmetric structure of 1 : 1 complex of DAHE cation with α-CD also corresponds to the ^{1}H NMR spectra shown in Fig. 10. These results are in agreement with Refs. 13, 14, and 15, in which oligoethylene compounds of oligomeric degrees up to 6 terminated with a positively charged group, such as viologen or pyridinium, or terminated with a negatively charged group, such as carboxylate, were reported to form statically and dynamically stable complexes with α-CD in aqueous solution.

Further evidence for complexation between α-CD and

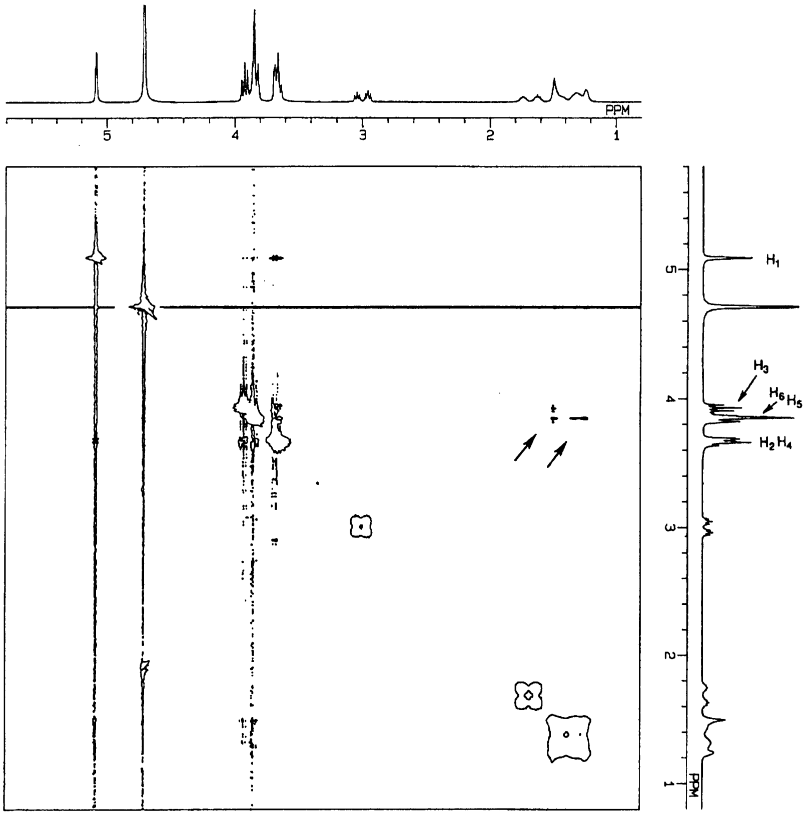


Fig. 11. 2D NOESY NMR spectrum of α-CD and DAHE•2HCl (1 : 1 mole ratio) in D_2O at 30 °C. The correlation peaks of ethylene protons with H-3 and H-5 of α-CD are shown with arrows.

DAHE cation was obtained from the NOESY ^{1}H NMR spectrum of α-CD and DAHE•2HCl in D_2O, as shown in Fig. 11. NOE correlation peaks of ethylene protons in the near central parts of DAHE cation with H-3 and H-5 of α-CD, which are oriented towards the interior of the cavity of α-CD, were clearly observed in the NOESY spectrum. In contrast, no NOE correlation peak of ethylene protons with H-1, H-2, and H-4 of α-CD, which are located on the exterior of the cavity of α-CD, was observed in Fig. 11. The results indicate that DAHE cation is included in the hydrophobic cavity of α-CD, and the binding position is near the central part of the chain of the DAHE cation.

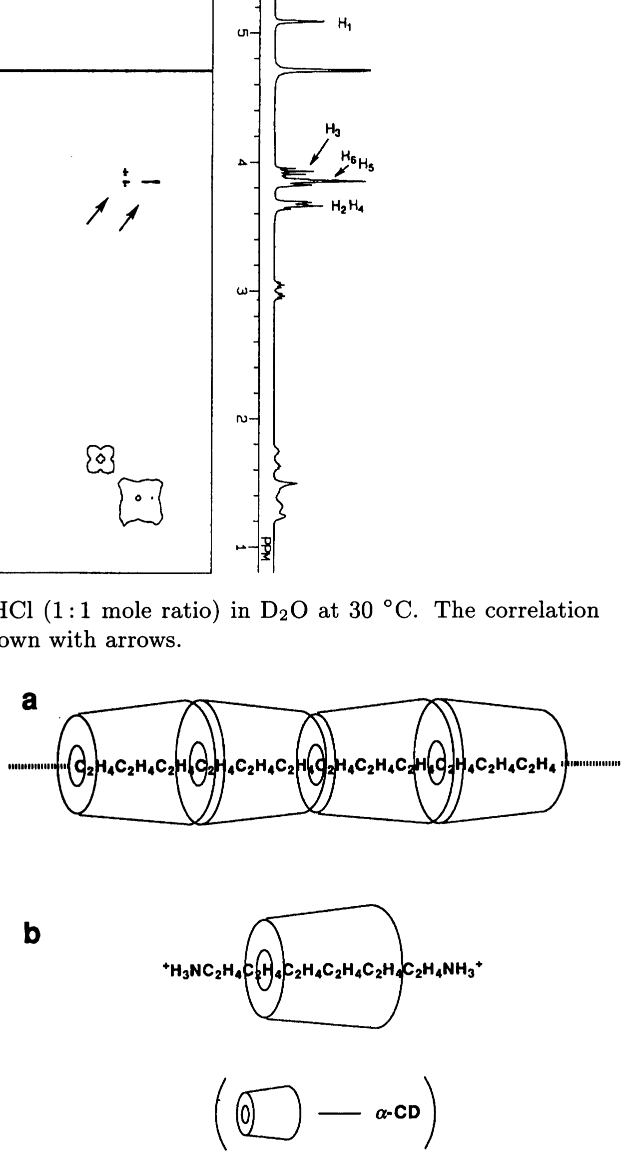


Fig. 12. Proposed structures of α-CD–OE complexes (a), and α-CD–DAHE cation complex (b).

Conclusions

Oligoethylenes of oligomeric degrees of 6 and larger and derivatives of OE(6) with small end groups, such as amino and hydroxyl groups, form complexes with α-CD in the stoichiometry of 3 : 1 (ethylene unit–α-CD) to give crystalline complexes in high yields. The crystalline complexes are proposed to take the necklace-like structure, which is shown in Fig. 12a. The formation of hydrogen bonds between cyclodextrins is thought to be the primary driving force in the inclusion complexation. The head-to-head and tail-to-tail arrangement, which results in a more effective formation of hydrogen bonds between α-CDs, is assumed to be the most probable structure. The results that the yields of the complexes formed in DMF solution depend on the oligomeric degree of OEs demonstrate that the chain length strongly affects the complexation. It is extremely distinctive that the sectional area as well as the length of the molecular chain plays a very important role in the formation of crystalline complexes between CDs and polymers/oligomers.

On the other hand, DAHE cation did not form crystalline complex with α-CD; the reason is assumed to be the effect of the positively charged ammonio groups in the ends, since the neutral DAHE forms a crystalline complex with α-CD in high yield. However, DAHE cation forms the statically and dynamically stable complex with α-CD in aqueous solution. A proposed structure of 1 : 1 α-CD–DAHE cation complex is shown in Fig. 12b. The hydrophobic interaction between α-CD cavity and ethylene units is thought to be very important in the complexation in aqueous solution.

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