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Construction of supramolecular structures from cyclodextrins and polymers

Akira Harada

Department of Macromolecular Science, Faculty of Science, Osaka University, Toyonaka, Osaka, 560 Japan

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Cyclodextrins (CDs) have been found to form inclusion complexes with various polymers with high specificity to give stoichiometric compounds in crystalline states. In these complexes, polymer chains were threaded into cyclodextrins and recognized by the host. For example, α-cyclodextrin (α-CD) formed complexes with poly(ethylene glycol) (PEG) of molecular weight higher than 200, although β-CD did not form complexes with PEG of any molecular weight. However, β-CD formed complexes with poly(propylene glycol) (PPG) of various molecular weights with which α-CD did not form complexes. γ-CD formed complexes with poly(methyl vinyl ether) (PMVE), though α- and β-CD did not form complexes with PMVE. α-CD formed complexes with oligoethylene, but only γ-CD formed complexes with polyisobutylene of molecular weight over 500. The structures and properties of the complexes have been studied by spectroscopic methods. Polyrotaxanes in which many CDs are threaded on a single chain were prepared by capping the chain ends with bulky groups. Copyright © 1997 Elsevier Science Ltd. All rights reserved

INTRODUCTION

Cyclodextrins are cyclic molecules consisting of 6 to 8 glucose units linking through α-1,4 linkages (Fig. 1). They are known to form inclusion complexes with a large number of low-molecular-weight compounds, ranging from nonpolar molecules such as hydrocarbons and rare gases to polar compounds such as carboxylic acids and amines (Bender and Komiyama, 1978; Szejtli, 1982). However, there were no reports on the formation of inclusion complexes of cyclodextrins with polymers when we started our project on the cyclodextrin–polymer complex formation in the early 1980s. Therefore, we have studied interactions of cyclodextrins with various polymers and found that cyclodextrins form complexes with some polymers with high selectivities (Harada, 1993; Harada *et al.*, 1993a, 1994b, 1994e). There are some examples that suggest some interactions between cyclodextrins and polymers in solutions. For example, Kitano and Okubo (1977) reported that critical micelle concentrations of some surfactant molecules change on addition of cyclodextrin. Iijima *et al.* (1978) reported that diffusion constants of poly(vinyl alcohol) change on addition of cyclodextrin.

We have prepared polyrotaxanes in which many cyclodextrins are threaded onto a polymer chain by capping the end groups of the polymer chain in the complex of cyclodextrins with polymers.

COMPLEX FORMATION OF CYCLODEXTRINS WITH HYDROPHILIC POLYMERS

Aqueous solutions of some non-ionic polymers were added to saturated aqueous solutions of cyclodextrins to see whether cyclodextrins would form solid state complexes with polymers. Table 1 shows the results of the complex formation of cyclodextrins with some non-ionic polymers. When aqueous solutions of poly(ethylene glycol) (PEG) were added to aqueous solutions of α-cyclodextrin at room temperature with stirring, the solutions became turbid, and the complexes were formed as crystalline precipitates when the average molecular weights of PEG were higher than 200 (Harada and Kamachi, 1990a; Harada *et al.*, 1993b, 1994b). The rate of complex formation depends on the molecular weight. PEG of molecular weight 1000 formed complexes most rapidly. The rates decrease as the molecular weight increases when the

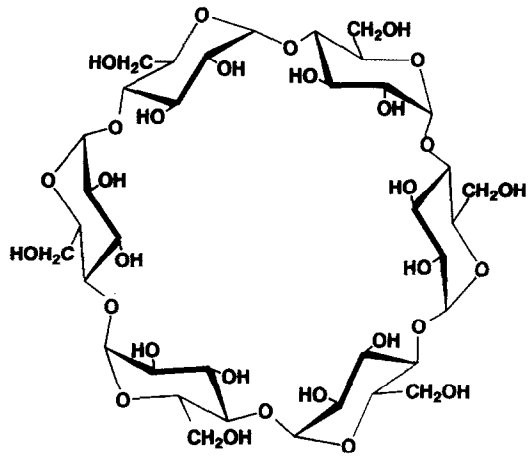


Fig. 1. α-Cyclodextrin.

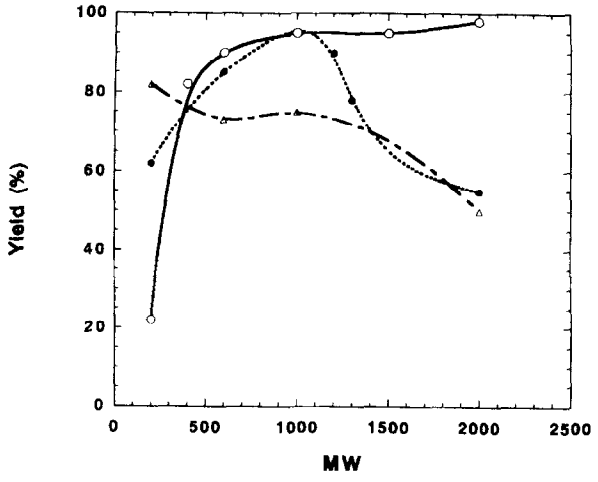


Fig. 2. Yields of the complexes of α-CD with PEG (○), POT (●), and PTHF (△) as a function of the molecular weight of polymer.

molecular weight is higher than 1000. The β-CD did not form complexes with PEG of any molecular weights. However, β-CD formed complexes with poly(propylene glycol) (PPG), which has methyl groups as side chains, although α-CD did not form complexes with PPG of any molecular weights (Harada and Kamachi, 1990b; Harada *et al.*, 1995a). γ-CD formed complexes with poly(methyl vinyl ether) (PMVE) which has the same composition as that of PPG but has a methoxy group as a side chain, although α-CD and β-CD did not form complexes with PMVE (Harada *et al.*, 1993c). There is a good correlation between the cross-sectional areas of these polymers and the sizes of cyclodextrin cavities. α-CD was found to form inclusion complexes not only with PEG but also with poly(oxytrimethylene) (POT) (Harada *et al.*, 1995b, c), and poly(tetrahydrofuran) (PTHF) (Harada *et al.*, 1995d).

EFFECTS OF THE MOLECULAR WEIGHTS OF POLYMERS ON COMPLEX FORMATION

Figure 2 shows the effects of the molecular weight on the complex formation of PEG, POT, and PTHF with α-CD. The yields of the complex of PEG with α-CD increased with increase in the molecular weight of the polymer and reached saturation at about molecular weight 1000. The yields are based upon weight of isolated complex. However, in the case of POT, the yields increased with increase in the molecular weight, reached a maximum at about molecular weight 1000, and then decreased with increased molecular weight (Harada *et al.*, 1995b, c). In contrast, the yields of the complexes with PTHF decreased with increase in the molecular weight, with a slight increase in the yields at molecular weight 1000 (Harada *et al.*, 1995d). These results indicate that the stability of the complexes with hydrophilic polymers increased with increase in the molecular weight of the polymer, and reached a maximum at about molecular weight 1000. However, as polymers become more hydrophobic, it becomes more difficult for cyclodextrins to include such polymer chains completely.

STOICHIOMETRIES

Figure 3 shows continuous variation plots for the complex formation of α-CD with PEG, POT, and PTHF. The plots show maxima at 0.33 for PEG, 0.37 for POT and 0.4 for PTHF, respectively. These results indicate that a PEG complex is 2:1 (two monomer units per CD), a POT complex is 1.7:1, and a PTHF complex 1.5:1. The length of two ethylene glycol units,

Table 1. Complex formation between CDs and polymers

	Polymer	M_W	Yield (%)		
			α-CD	β-CD	γ-CD
PEG	-(CH_2CH2OO)-	1000	92	0	Trace
POT	-(CH_2CH_2)-	563	63	0	0
PPG	-(CH_2)$_3$O)-	700	87	520	0
	CH_3-(CH_2CH0)-	1000	0	96	80
PIB	CH_3-(CH_2C-)-CH_3	1350	0	Trace	94
PMVE	CH_3-(CH_2C-)-OCH_3	2000	0	0	80

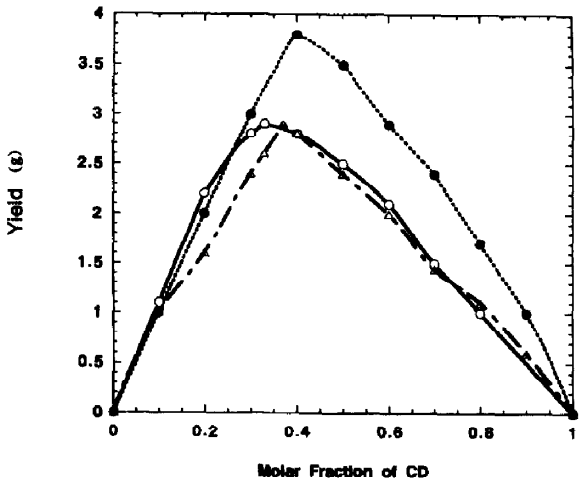


Fig. 3. Continuous variation plots for complex formation between α-CD and PEG (o), POT (△), and PTHF (•). Stock solutions of α-CD (7.2 g per 50 ml) are mixed with various concentrations of polymer solutions. The yields are arbitrary.

1.7 oxytrimethylene unit, and 1.5 tetrahydrofuran unit corresponds to the depth of the CD cavity (7 Å). Stoichiometries were confirmed by measurements of the ^{1}H NMR spectra of the complexes isolated. By the comparison of the integral of the CD with that of PEG, for example, two ethylene glycol units were found to be bound to a single α-CD. It is noteworthy that the stoichiometries are always 2:1 (units:CD) even if the polymer and CD were added to each other in any ratio. The stoichiometries were confirmed in the same way with POT and PTHF. These results indicate that complex formation is stoichiometric. CDs are close packed from end to end of a polymer chain.

INCLUSION MODES

Figure 4 shows the X-ray powder diffraction patterns of (a) α-CD and of the complexes of α-CD with (b) octanol and (c) PTHF. The patterns show that all of the complexes are crystalline, and the pattern of the PTHF complex is similar to that of the complex with octanol, which has been reported to have a channel structure (Saenger, 1976), and different from that of α-CD, which has been proven to have a cage structure by single crystal X-ray studies (Saenger, 1972). Therefore, these results indicate that the polymer complexes have channel-type structures rather than cage-type structures.

Figure 5 shows the ^{13}C CP/MAS NMR spectra of the complex of α-CD with PTHF and a mixture of α-CD and PTHF. The spectrum of α-CD in the mixture shows resolved C-1, C-4, and C-6 resonances, because α-CD assumes a less symmetrical conformation in the crystal when it does not include a guest in the cavity. C-1 and C-4 adjacent to a conformationally strained glycosidic linkage are observed at 98 and 78 ppm, respectively. In the spectrum of the α-CD-PTHF

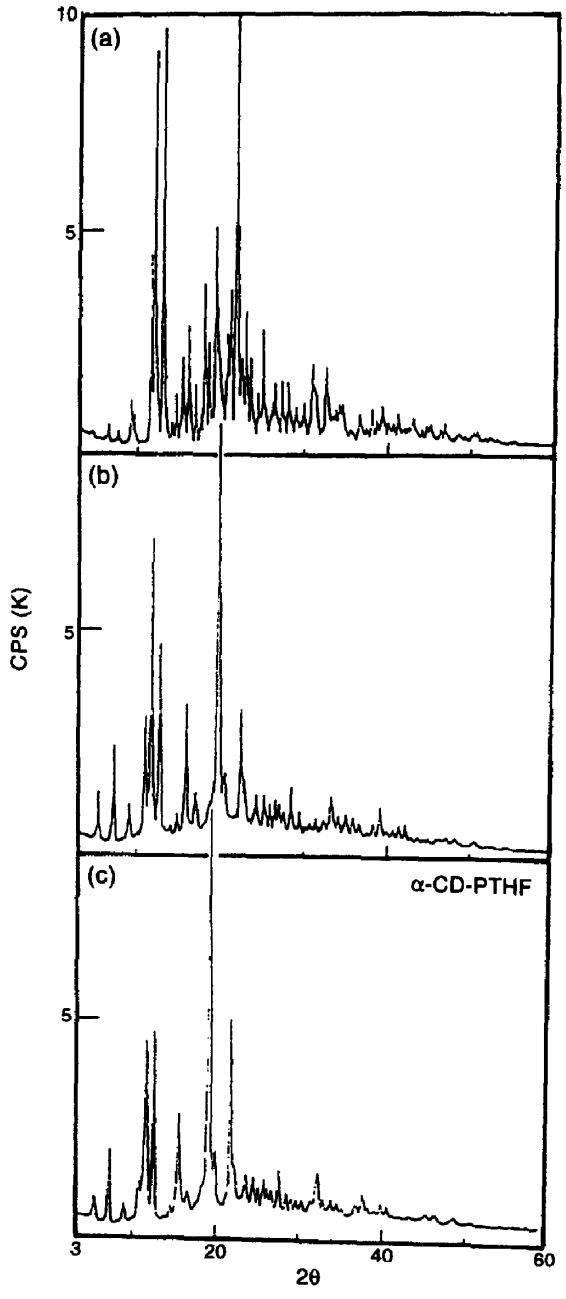


Fig 4. X-ray powder patterns of (a) the complex between α-CD and PTHF, (b) the complex between α-CD and octanol, and (c) α-CD.

complex the peaks at 78 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 with a polymer chain included in a tunnel formed by CDs. A stronger Ca carbon (internal ethylene units of PTHF) peak of PTHF in the complex than in the mixture indicates that a PTHF chain is more rigid than in the mixture.

Molecular model studies show that PEG, POT, and PTHF chains are able to penetrate α-CD cavities and that the single cavity accommodates two ethylene glycol units, 1.6 oxytrimethylene unit, and 1.4

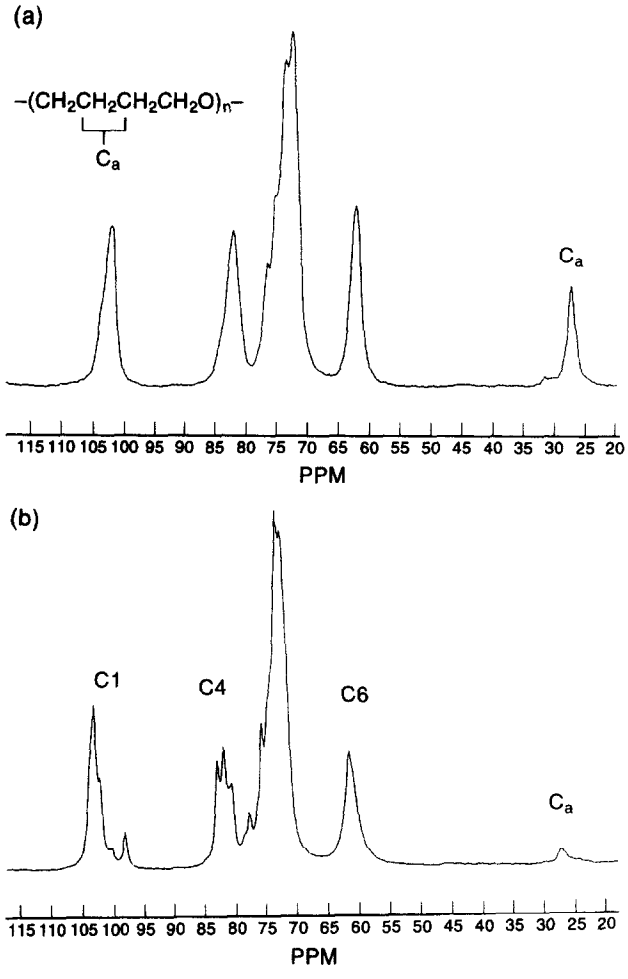


Fig. 5. ^{13}C CP/MAS NMR spectra of the complex of (a) α-CD with PTHF and (b) the mixture of α-CD and PTHF. The proportions of the two mixture components are the same as for the complex (CD : monomer unit = 1:1.5).

tetrahydrofuran unit, respectively. These results are consistent with those of the continuous variation studies of complex formation and with the ^1H NMR studies of the complexes.

The inclusion complex formation of polymers with cyclodextrins is entropically unfavorable. However, the formation of the complexes is thought to be promoted by hydrogen bond formation between CDs. Therefore, the head-to-head and tail-to-tail arrangement, which results in a more effective formation of hydrogen bonds between CDs, is thought to be the most probable structure. (Fig. 6)

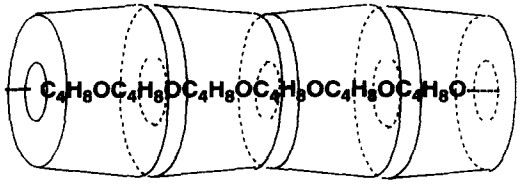


Fig. 6. Proposed structure of α-CD-PTHF complex.

COMPLEX FORMATION WITH HYDROPHOBIC POLYMERS

Recently, we found that cyclodextrins form complexes not only with hydrophilic polymers but also with hydrophobic polymers. In this case, sonication is effective for complex formation. For example, α-CD formed complexes with oligoethylene, although β-CD and γ-CD did not form complexes with oligoethylene under the same conditions (Li *et al.*, 1994). In contrast, β-CD and γ-CD formed complexes with polyisobutylene (PIB), although α-CD did not form complexes with PIB at all (Harada *et al.*, 1993d, 1996a) Again, there is a good relationship between the thickness of the polymer chain and the size of the cyclodextrin cavity. The yields of the complexes of β-CD with PIB decrease with increase in the molecular weight of PIB, whereas the yields of the complexes with γ-CD increase with increase in the molecular weight. The chain-length selectivities are totally reversed.

COMPLEX FORMATION WITH IONIC POLYMERS

More recently, we found that α-CD formed complexes with some polyesters and ionic polymers. α-CD was found to form inclusion complexes with viologen polymers (VP) having octamethylene groups, [poly(paraquat-octamethylene)], and longer methylene chains in aqueous solution (Harada *et al.*, 1996b). It took longer to reach equilibrium as the number of methylene groups increased. β-CD formed complexes with VP having decamethylene groups and longer methylene chains. The complex formation of β-CD with VPs is much faster than that of α-CD with VP. γ-CD formed complexes with such ionene polymers, poly[(dimethylimino)alkylene] dibromide, as 3,6-ionene and 6,8-ionene to give compounds in the solid state (Fig. 7).

PREPARATION OF POLYROTAXANES

In recent years, rotaxanes in which a ring molecule is threaded onto a linear molecule and both ends are blocked by bulky substituents have attracted renewed interest in the field of supramolecular science because of their unique structures and properties. Recently, CDs have been used as beads of rotaxanes. Both

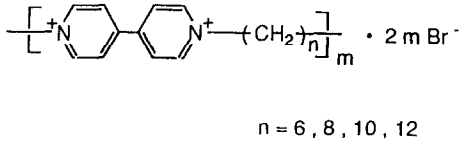


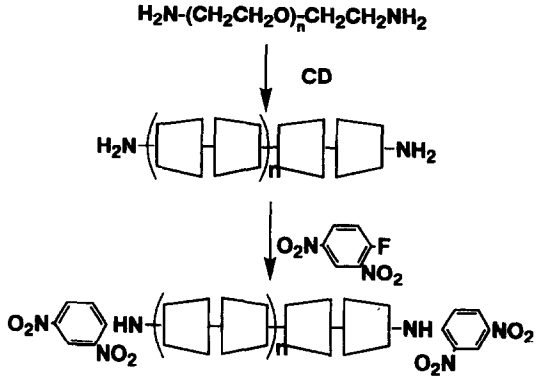
Fig. 7. Viologen polymers.

symmetric and unsymmetric ionic rotaxanes containing α-CDs have been reported (Ogino, 1981; Manka and Lawrence, 1990; Rao and Lawrence, 1990; Isnin and Kaifer, 1991). As mentioned above, we have found that α-CD forms complexes with PEG and that a PEG chain is included in a tunnel formed by CDs. We have prepared compounds in which many cyclodextrins are threaded onto a PEG chain and are trapped by capping the chain ends with bulky groups as shown in Scheme 1 (Harada *et al.*, 1992, 1993e, f, 1994a)

The inclusion complexes of α-CD with PEG bisamine (PEГ-BA) were prepared by adding an aqueous solution of PEГ-BA to a saturated aqueous solution of α-CD at room temperature, by use of a method similar to that used to prepare complexes of α-CD with PEG. The resulting complex was allowed to react with an excess of 2,4-dinitrofluorobenzene, which is bulky enough to prevent dethreading.

The products are insoluble in water and dimethylformamide, but they are soluble in dimethylsulfoxide and in 0.1 N NaOH. The products were characterized by UV–vis, X-ray diffraction, ^{1}H NMR, ^{13}CNMR, ^{13}CCP/MAS NMR and 2D NOESY NMR spectra. The ^{1}H NMR spectrum of the product shows that the product is composed of α-CD, PEG-BA, and dinitrophenyl groups, and the peaks of CD, PEG, and dinitrophenyl groups are broadened, which suggests that α-CDs are difficult to move on a PEG chain. 2D NOESY NMR spectra show that the signals of H-3 and H-5 protons of α-CD, which are directed toward the inside of the cavity, correlate with the resonance of the CH_2 of PEG, but the H-1, H-2, and H-4 protons, which are located outside the cavity, do not correlate with PEG. These results indicate that a PEG chain is included in α-CD cavities. (Wenz and Keller, 1992) prepared polyrotaxanes containing polyamines.

We have prepared some kinds of polyrotaxanes starting from PEGs of different molecular weights. The number of CDs increases with an increase in the molecular weight. A polyrotaxane prepared from PEG (M_W = 3350) has 20–23 CDs on a PEG chain. This corresponds to the molar ratio of ethylene glycol units to α-CDs of 3.9. More than half of the polymer chain is covered with α-CDs. A polyrotaxane prepared from PEG of molecualr weight 1450 has 15 α-CDs on a PEG chain. The molar ratio of ethylene glycol units to α-CD is 2.3. The ratio indicates that the molar ratio is almost stoichiometric; that is, CDs are almost close packed from end to end of the polymer chain.



Scheme 1. Preparation of polyrotaxane.

Polyrotaxanes consisting of monodispersed PEG have been prepared starting from α-CD and pure oligomers of PEG.

CONCLUSION

Cyclodextrins have been found to form inclusion complexes not only with low-molecular-weight compounds but also with various polymers. α-CD forms complexes with both hydrophilic and hydrophobic polymers having small cross-sectional area (such as PEG, POT, PTHF, and oligoethylene) to give crystalline complexes. β-CD formed complexes with PPG. γ-CD formed complexes with polymers having large cross-sectional areas, such as poly(methyl vinyl ether) and polyisobutylene. There is good correlation between cross-sectional areas and the sizes of CD cavities. Polymer chains have been found to be included in the cavities of CDs. Polyrotaxanes in which many CDs are threaded onto a polymer chain have been prepared. These kinds of synthesis may provide a new method to create new molecular architectures and functions (Harada *et al.*, 1993g, 1994b, 1995d, 1996)

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