Inclusion Complexes of Multiarm Poly(ethylene glycol) with Cyclodextrins

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Introduction

Cyclodextrins (CDs) are a series of cyclic oligosaccharides composed of six, seven, and eight glucose units linked by α-1,4 linkage, which are called α-, β-, and γ-CD, respectively. They form inclusion complexes with a wide range of low molecular weight compounds.[1,2] In recent years, extensive studies have been made on inclusion complexes (ICs) of polymers with CDs.[3−33] The inclusion complex of poly(ethylene glycol) (PEG) and α-CD is the first example of stoichiometric inclusion complexes between CD and polymers.[3] Harada et al. also reported double-stranded inclusion complexes of γ-CD threaded on end-modified PEGs.[5]

To our knowledge, there has been no study dealing with the inclusion complexes between star-shaped polymers and CDs. The column structure of linear polymer−CD ICs is caused by the long-chain nature of the polymer.[15] It is therefore of interest to investigate whether a star-shaped polymer can form crystalline inclusion complexes with CDs. Here we report our study on inclusion complexation between multiarm PEGs and CDs. A three-arm PEG glycerol ethoxylate (GE), a four-arm PEG (4A-PEG), and a six-arm PEG (6A-PEG) were used in the study. Interestingly, the three multiarm PEGs form stoichiometric crystalline inclusion complexes with both α-CD and γ-CD, but not with β-CD.

Experimental Section

Materials. PEG was obtained from Aldrich; its number-average molecular weight (M_n) is 2200. GE ($M_n = 1000$) was supplied by Aldrich. 4A-PEG ($M_n = 7400$, $M_w/M_n = 1.06$) and 6A-PEG ($M_n = 7200$, $M_w/M_n = 1.07$) were obtained from Polymer Source, Inc. The molecular structures of GE, 4A-PEG, and 6A-PEG are shown in Scheme 1. α-CD and γ-CD were obtained from Tokyo Kasei, Tokyo; β-CD was supplied by Acros Organics. All CDs were dried at 80 °C in vacuo for at least 12 h before use. D_2O, the solvent for NMR measurements, was supplied by Aldrich.

Preparation of Inclusion Complexes. An aqueous polymer solution (10% w/v) was mixed with a saturated aqueous solution of CD at room temperature, and the mixture was stirred at room temperature for 2 days. A feed ratio of 2:1 (ethylene glycol unit:CD) was used for all systems. The inclusion complex in a form of precipitate was isolated by centrifugation, washed with water, and dried in vacuo at 60 °C for 2 days. The yields of the complexes are calculated on the basis of a stoichiometry of 2:1 (ethylene glycol unit:CD) for α-CD ICs and 4:1 for γ-CD ICs.

Measurements. XRD patterns of the complexes were recorded on a Siemens D5005 X-ray powder diffractometer with Cu Kα (1.540 51 Å) radiation (40 kV, 40 mA). Powder samples were mounted on a sample holder and scanned with a step size of $2\theta = 0.01°$ between $2\theta = 3°$ and 50°.

Thermogravimetric analyses (TGA) were made with a TA Instruments SDT 2960 simultaneous DTA−TGA. Samples were heated at 20 °C/min from room temperature to 800 °C in a dynamic nitrogen atmosphere (flow rate = 70 mL/min).

^{1}H NMR spectra of the complexes were recorded at 300 MHz on a Bruker DPX-300 NMR spectrometer. Chemical shifts of the complexes were referenced to $\delta = 4.70$ ppm for HOD. ^{13}C CP/MAS NMR spectra were acquired on a Bruker DRX-400 NMR spectrometer with a sample spinning rate of 8.0 kHz at room temperature. The spectra were acquired with a 2.75 μs proton 90° pulse, a 3 ms contact time, and a 3 s repetition time.

Table 1. Yields and Stoichiometry (Ethylene Glycol Unit:CD) of Inclusion Complexes

complex	yield (%)	stoichiometry
α-CD/GE	10	2.7:1
γ-CD/GE	57	3.8:1
α-CD/4A-PEG	70	2.2:1
γ-CD/4A-PEG	97	4.0:1
α-CD/6A-PEG	69	2.4:1
γ-CD/6A-PEG	94	4.1:1

Results and Discussion

Interestingly, GE, 4A-PEG, and 6A-PEG are able to form inclusion complexes with both α-CD and γ-CD. Turbidity developed when solutions of polymer and CD were mixed, indicating the formation of crystalline inclusion complexes.[3,4] The mixture was then continuously stirred at room temperature for 2 days. The IC formed was separated by centrifugation, washed with water, and finally dried in vacuo at 60 °C for 2 days. All the complexes can dissolve in water by heating. Table 1 lists the yields and stoichiometry of the complexes wherein the results of the stoichiometry were established by ^{1}H NMR measurements. Similar to their linear chain analogues, the multiarm PEGs cannot form inclusion complexes with β-CD.

Inclusion complexes between PEG and CDs have been studied.[3−5] A stoichiometry (ethylene glycol unit:CD) of 2:1 for α-CD/PEG[3] and 4:1 for γ-CD/PEG[5] was established in which the γ-CD/PEG complex contains two side-by-side PEG chains in each γ-CD channel.[5] Harada et al. also found a good correlation between the cross-sectional areas of the polymers and the cavity size of the CDs.[7] As shown in Table 1, a stoichiometry of ca. 4:1 is established for all the γ-CD/multiarm PEG ICs. It is believed that each of the present γ-CD/multiarm PEG ICs also contains two side-by-side PEG chains in each γ-CD channel.

Figure 1 shows the XRD patterns of α-CD/PEG, α-CD/GE, α-CD/4A-PEG, and α-CD/6A-PEG ICs. The diffraction patterns of the four complexes are very similar. They are also similar to those of the inclusion complexes of α-CD and poly(oxytrimethylene)[6] as well as poly(ϵ-caprolactone).[9,15] The peak at 20.0° ($d = 4.44$ Å) is typical for α-CD−polymer ICs.[6,9,15,25] Since a column structure has been established in those inclusion complexes, the present XRD results suggest that the α-CD/multiarm PEG ICs also possess a column structure.

As shown in Figure 2, the XRD patterns of γ-CD/PEG, γ-CD/GE, γ-CD/4A-PEG, and γ-CD/6A-PEG ICs are quite similar. The patterns are also similar to those of other polymer/γ-CD complexes[8,10] which are known to possess a column structure. Furthermore, the fingerprint peak for the column structure of γ-CD-IC at ca.

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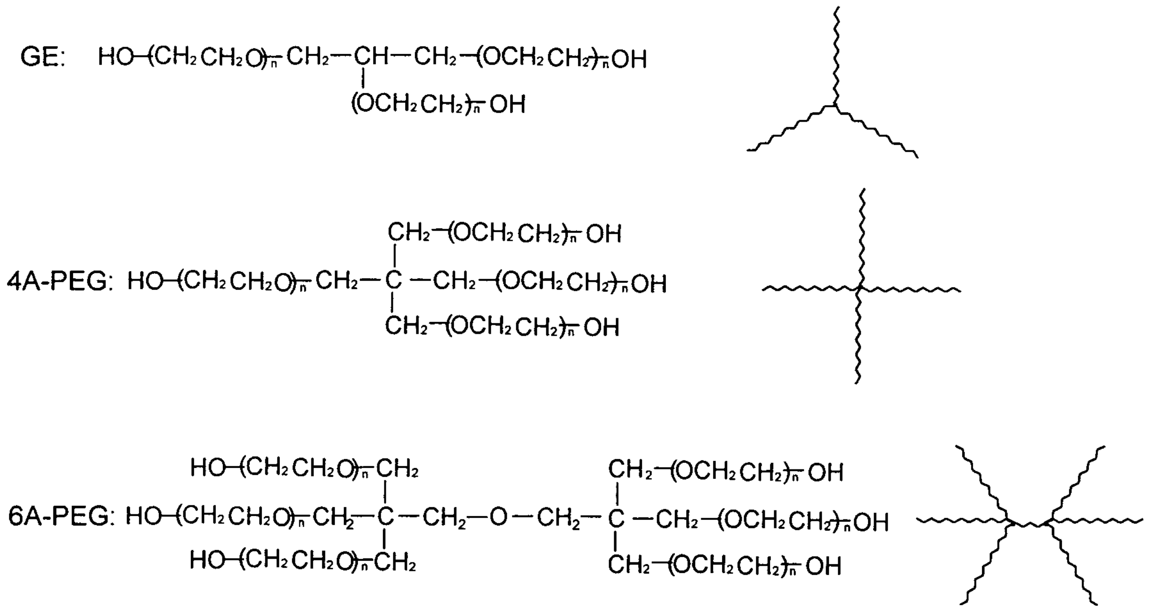
Scheme 1. Structures of Three Multiarm PEGs



$$\mathrm{GE{:}\ HO\!-\!(CH_2CH_2O)_{\bar{n}}\!-\!CH_2\!-\!\underset{\displaystyle (OCH_2CH_2)_{\bar{n}}OH}{\underset{|}{CH}}\!-\!CH_2\!-\!(OCH_2CH_2)_{\bar{n}}OH}$$

$$\mathrm{4A\text{-}PEG{:}\ HO\!-\!(CH_2CH_2O)_{\bar{n}}\!-\!CH_2\!-\!\overset{\displaystyle CH_2\!-\!(OCH_2CH_2)_{\bar{n}}OH}{\underset{\displaystyle CH_2\!-\!(OCH_2CH_2)_{\bar{n}}OH}{\overset{|}{\underset{|}{C}}}}\!-\!CH_2\!-\!(OCH_2CH_2)_{\bar{n}}OH}$$

$$\mathrm{6A\text{-}PEG{:}\ HO\!-\!(CH_2CH_2O)_{\bar{n}}\!-\!CH_2\!-\!\overset{\displaystyle HO\!-\!(CH_2CH_2O)_{\bar{n}}\!-\!CH_2}{\underset{\displaystyle HO\!-\!(CH_2CH_2O)_{\bar{n}}\!-\!CH_2}{\overset{|}{\underset{|}{C}}}}\!-\!CH_2\!-\!O\!-\!CH_2\!-\!\overset{\displaystyle CH_2\!-\!(OCH_2CH_2)_{\bar{n}}OH}{\underset{\displaystyle CH_2\!-\!(OCH_2CH_2)_{\bar{n}}OH}{\overset{|}{\underset{|}{C}}}}\!-\!CH_2\!-\!(OCH_2CH_2)_{\bar{n}}OH}$$

8.0° is present in all the present γ-CD complexes, suggesting that the three complexes also have a column structure.

Figure 3 shows the ^{13}C CP/MAS NMR spectra of α-CD and α-CD/4A-PEG IC. The spectrum of α-CD shows resolved carbon resonances from each of the glucose units while the spectrum of the inclusion complex shows unresolved carbon resonances. Thus, the formation of inclusion complexes in the present study is further supported by the ^{13}C CP/MAS NMR measurements. The PEG peaks in CD/multiarm PEG ICs are difficult to observe by solid-state NMR.

The thermal properties of the CD/multiarm PEG complexes were investigated by TGA. Figure 4 shows the TGA curves of α-CD and two inclusion complexes. The initial decomposition temperatures of complexes are higher than those of CDs (about 298 °C). The better thermal stability of ICs as compared to the CDs has been observed in a number of polymer–CD ICs.[15,21,25,30,31]

In contrast to their linear chain analogues, multiarm PEGs have star-shaped contours. It is well-known that the long-chain nature of linear polymers gives rise to the column structure of polymer–CD ICs.[15] Interestingly, the present study shows that the multiarm PEGs form inclusion complexes with α-CD, and the complexes also possess a column structure. It is envisaged that a few ethylene glycol units near the linking point in the multiarm PEGs are difficult to be included by α-CDs, which will lead to a stoichiometry higher than 2:1 especially when the molecular weight of the polymer is low. This "linking point" effect can be seen in Table 1 wherein the α-CD/GE IC has a much higher stoichiometry than the other α-CD ICs.

Rather unexpectedly, multiarm PEGs are able to form stoichiometric inclusion complexes with γ-CD. As discussed earlier, each of the γ-CD/multiarm PEG ICs is believed to contain two side-by-side PEG chains in each γ-CD channel. A cross-linked network is expected for a

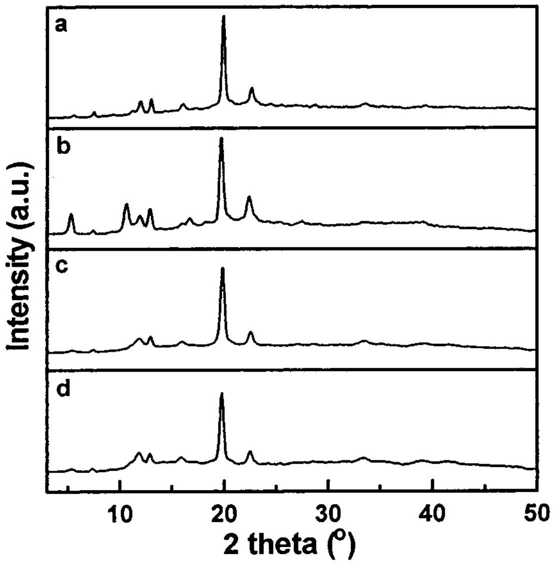


Figure 1. X-ray diffraction patterns for α-CD/PEG IC (a), α-CD/GE IC (b), α-CD/4A-PEG IC (c), and α-CD/6A-PEG IC (d).

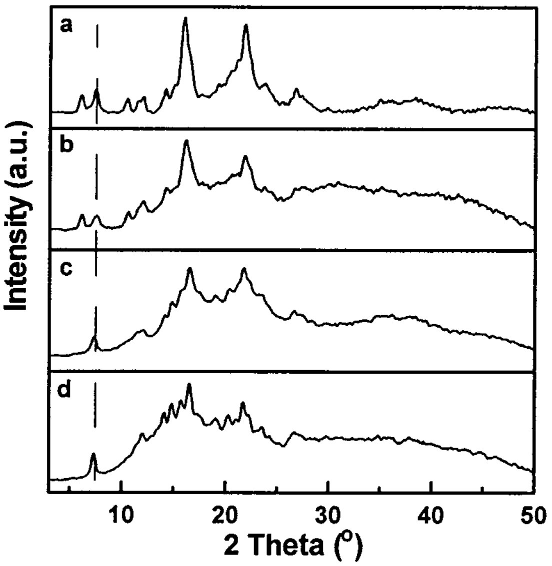


Figure 2. X-ray diffraction patterns for γ-CD/PEG IC (a), γ-CD/GE IC (b), γ-CD/4A-PEG IC (c), and γ-CD/6A-PEG IC (d).

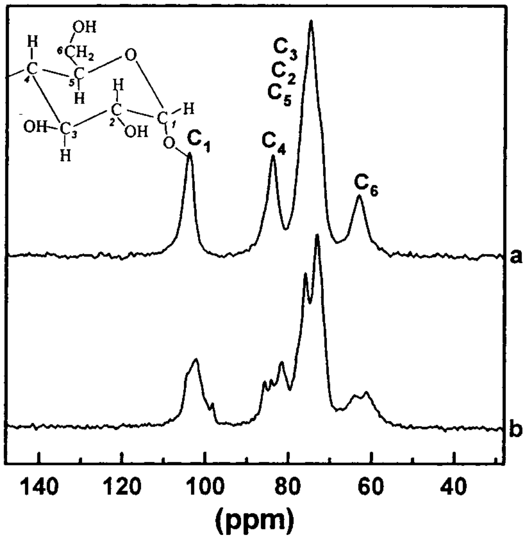


Figure 3. ^{13}C CP/MAS NMR spectra of the α-CD (b) and α-CD/4A-PEG complex (a).

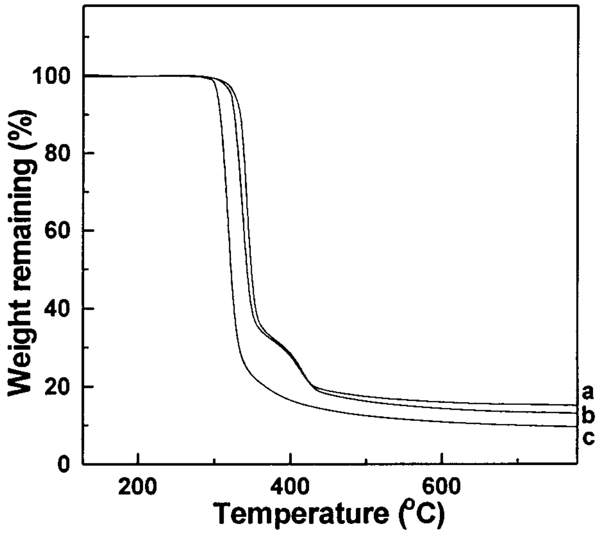
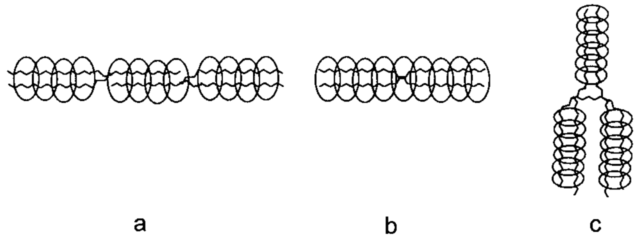


Figure 4. TGA curves of γ-CD/4A-PEG IC (a), α-CD/4A-PEG IC (b), and α-CD (c).

Scheme 2. Possible Structures for γ-CD/GE IC (a), γ-CD/4A-PEG IC (b), and γ-CD/6A-PEG IC (c)



double-stranded IC between γ-CD and a multiarm PEG unless the two side-by-side PEG chains in each γ-CD channel happen to belong to the same multiarm PEG molecule.[34] The present study shows that stoichiometric crystalline inclusion complexes in the form of precipitates in aqueous solutions are formed between γ-CD and multiarm PEGs. Thus, during the formation of γ-CD/multiarm PEG ICs, two PEG arms from the same molecule could "recognize" each other and thread across the same γ-CD cavity together. Scheme 2 illustrates possible structures for γ-CD/GE, γ-CD/4A-PEG, and γ-CD/6A-PEG ICs.

Conclusion

Star-shaped PEG with 3, 4, or 6 arms is able to form stoichiometric crystalline inclusion complexes with α-CD and γ-CD, but not with β-CD. A stoichiometry (ethylene glycol unit:CD) of ca. 2:1 for α-CD/multiarm PEG and ca. 4:1 for γ-CD/multiarm PEG is established by ^{1}H NMR measurements. The γ-CD/multiarm PEG complexes are believed to contain two side-by-side PEG chains in each γ-CD channel. XRD measurements show that all the complexes possess a column structure. For the γ-CD/multiarm PEG complexes, it is suggested that two PEG arms from the same molecule could "recognize" each other and thread across the same γ-CD cavity together.

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(34) A reviewer suggested that the inclusion of arms from different multiarm PEGs in the same γ-CD-IC column might not necessarily produce a network that would be easily recognized, because the “linking points” would be the only uncomplexed material between CD-IC crystalline cross-links and so would not be expected to produce a rubbery network.

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