Polymer Inclusion Complex Consisting of Poly(ϵ-lysine) and α-Cyclodextrin

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Received October 30, 2000

Revised Manuscript Received February 1, 2001

Introduction. The design of supramolecular structures organized by noncovalent interactions, especially host−guest interaction, has attracted much attention. Cyclodextrins (CDs) have been of interest as building blocks to construct such supramolecular structures due to water solubility and ability to accommodate various organic compounds in hydrophobic inner cavity.[1] Recently, with an increasing importance on macromolecular recognition, several polymers have been investigated as guest molecules to form inclusion complexes (ICs) with CDs.[2,3] Harada et al. have reported various kinds of polymer ICs with CDs and found there is a good correlation between the cross-sectional areas of the polymers and the size of the CDs.[2] Not only hydrophilic polymers such as poly(ethylene glycol), PEG, but also hydrophobic polymers such as polyisobutylene formed stoichiometric ICs with corresponding CDs.[3] Recently, they reported complex formation of poly(dimethylsiloxane) with β- and γ-CDs, which was the first observation for an inorganic polymer.[4] Tonelli et al. also have studied and investigated some unique properties of the included polymer placed in the confined environments, produced by the narrow channels formed in the crystalline matrices of the host clathrates.[5]

Our previous studies have focused on the design of biodegradable polyrotaxanes for biomedical applications such as supramolecular-structured drug carriers and tissue scaffolds.[6] We synthesized biodegradable polyrotaxanes in which α-CD molecules are threaded onto a poly(ethylene glycol) chain capped with bulky amino acids such as L-phenylalanine via peptide or ester linkage. The most attractive characteristic of such a polyrotaxane involves the control of drug release utilizing the dissociation of supramolecular structure. On the other hand, most polymers used to prepare ICs or (pseudo)polyrotaxanes were not biodegradable, while biodegradability of IC constituents would be preferred or required for biomedical applications. Only a few biodegradable polyesters such as poly(ϵ-caprolactone)[5,7] and poly(alkylene adipate)s[8] were studied for inclusion complexation.

A new polymer inclusion complex made up of a biodegradable and cationic poly(ϵ-lysine) (PL, M_n = 4090, M_w/M_n = 1.14) and α-CD is presented. PL is a natural polymer produced by a microorganism, *Streptomyces albulus*. It is a water-soluble and biodegradable polymer composed of 25−30 L-lysine residues connected via peptide linkages between α-carboxyl and ϵ-amino groups.[9] It has been used as a natural food preservative and a cationic surface active agent.[10] The preparation and characterization of the PL inclusion complex (PL-IC) with α-CD are presented here.

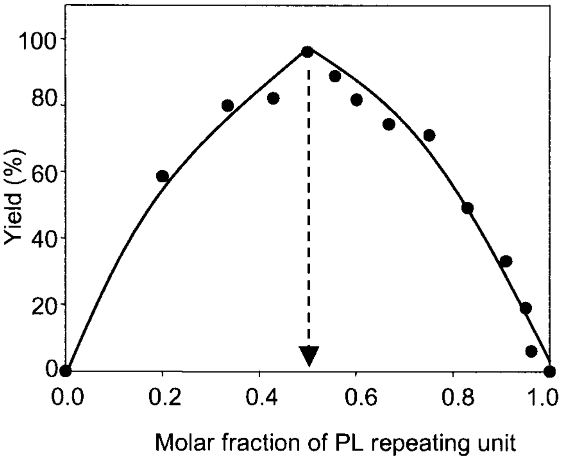

Figure 1. Yield dependence of the inclusion complexes on the feed amount of PL.

Results and Discussion. PL-IC formation was accomplished by simple mixing of two aqueous solutions of PL and α-CD with initial stirring for 30 min. After the aqueous solution of PL was added to the aqueous solution saturated with α-CD at room temperature, the solution became turbid within 30 min, and the complexes were formed as crystalline precipitates. The complexes were separated by centrifugation, washed with distilled water, and dried in vacuo for 24 h. We found that the β- and γ-CD could not form complexes with PL. Their cavity sizes are too large for steric fit with the polymer chain. In such cases, even if the polymeric guests form complexes with CDs for an instant, the complexes may dissociate easily.

Figure 1 represents a change in the yield of complexation as a function of the feed amount of PL. The yield of complexation was based on the ratio of PL amount in feed and IC products, of which composition was calculated from ^{1}H NMR characterization. The yield was significantly dependent on the feed ratio of α-CD and PL. It showed its maximum point corresponding to the molar feed ratio of 1:1 between α-CD and the repeating unit of PL. This indicates that the stoichiometry for complex formation is 1:1.

The stoichiometry of 1:1 was also confirmed by the peak integration of the ^{1}H NMR spectra of ICs. PL-IC became water-soluble with heating which results in dissociation of inclusion complexes. The composition of PL-IC could be obtained by comparison of the peak integrations for its constituents. The results were consistent with the stoichiometry of 1:1. Figure 2 shows the possible structure of PL-IC and a typical ^{1}H NMR spectrum of PL-IC dissolved in D_2O. Considering the unit height of CD molecules (about 8 Å) and the chain length of a PL repeating unit, the stoichiometry is reasonable.

Figure 3 shows the CP/MAS NMR spectra of a physical mixture of α-CD and PL with the same composition as PL-IC and PL-IC. The α-CD molecule is known to retain a less symmetrical cyclic conformation in the crystalline uncomplexed state, which is characterized by resolved C_1 and C_4 resonances of glucose units (Figure 3a). On the contrary, in the complexed state,

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10.1021/ma0018648 CCC: $20.00

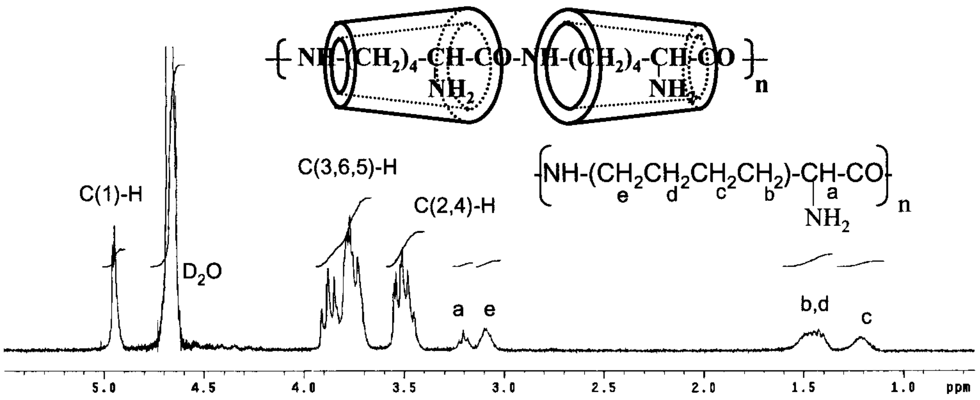

Figure 2. ^{1}H NMR spectrum of PL-IC in D_2O.

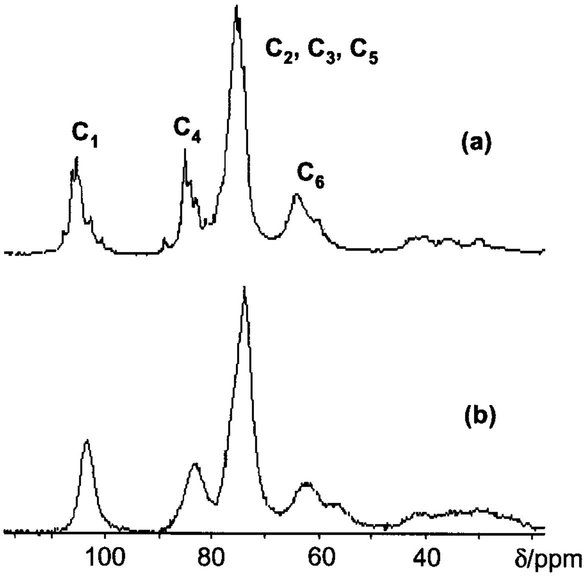

Figure 3. ^{13}C CP/MAS NMR spectra of a physical mixture of α-CD and poly(ε-lysine) (a) and PL-IC (b).

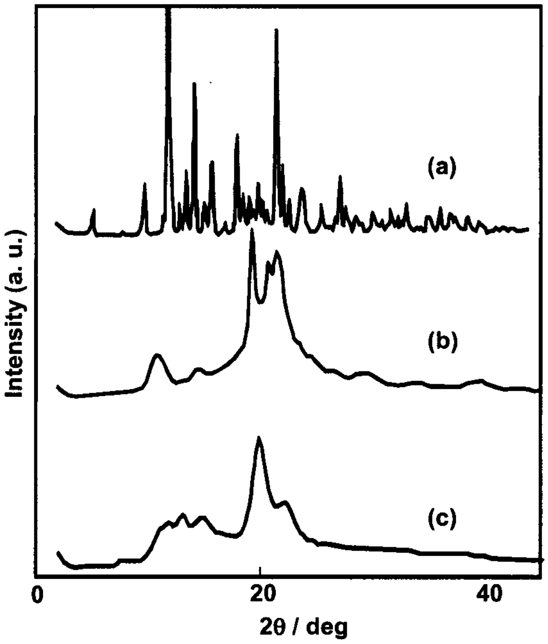

Figure 4. X-ray diffractograms of α-CD (a), PL (b), and PL-IC (c), measured with graphite-monochromatized Cu Kα radiation.

α-CD has a symmetrical cyclic conformation (Figure 3b). This result also can support the inclusion complexation between PL and α-CD.

Figure 4 shows wide-angle X-ray diffraction patterns of α-CD, PL, and their inclusion complex. The diffractogram of PL-IC showed a pattern quite different from those of α-CD and PL. This result suggests that the complex has a different crystalline structure. Reflections observed at $2\theta = 7.60°$ ($d = 11.6$ Å), 13.0° ($d = 6.80$ Å), and 20.0° ($d = 4.44$ Å) were explained by a hexagonal unit cell with lateral dimension $a = 13.6$ Å, which was the same as reported for PEG-IC.[11] These are assigned to be 100, 110, and 210 reflections, respectively. The strong {210} reflection is a typical peak of polymer inclusion complexes with α-CD,[2,3,5] suggesting the electron density distribution of the core of α-CD molecules with radius ~5 Å. It is a well-known fact that polymer ICs have a channel-type crystalline structure due to the long chain nature of guest molecules. The diffraction pattern of PL-IC is coincident with those observed for other polymer ICs, which have been previously proven to have channel-type structures.[3,5] As a result, PL-IC can be also considered to have the channel-type crystalline structure.

Thermal properties of PL-IC were observed by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). It was observed from TGA measurements that the decomposition temperature of PL-IC (313 °C) was not only much higher than α-CD (297 °C) but also higher than PL (306 °C). These results are due to the contribution of complex formation to thermal stability of both α-CD and PL. The melting properties of PL homopolymer and PL-IC were compared by DSC measurements. A large melting peak was observed around 165 °C for PL homopolymer. However, for PL-IC there was no corresponding melting peak, indicating that all PL chains participate in the formation of new channel-type crystalline structure together with α-CD molecules threaded along the polymer chain.

Acknowledgment. We thank Chisso Co., Japan, for supplying PL and CP/MAS-^{13}C NMR measurements. This study was financially supported by Grants-in-Aid for S. R. (B) (No. 851/09480253), from JSPS, Scientific Research for Priority Area "Molecular Synchronization for Construction of New Materials System" from MESSC, and from Micromachine Center, Japan.

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MA0018648