



Structure of insoluble complex formed by a block copolymer of 2-ethyl-2-oxazoline and ethylene oxide and poly(methacrylic acid)

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ABSTRACT

Complexes that were insoluble in water were formed by mixing aqueous solutions of a block copolymer of 2-ethyl-2-oxazoline (EOX) and ethylene oxide (EO) and those of poly(methacrylic acid) (PMAA). The structures of these complexes were investigated by the results obtained mainly by infrared spectroscopy, X-ray diffraction, and differential scanning calorimetry. The molar ratio of MAA in the complexes was also estimated by analyzing the infrared spectra. Whereas homopolymers of EOX and EO formed nearly equimolar complexes with PMAA irrespective of the feed molar ratio, the molar ratio of MAA in the complexes formed by the block copolymer and PMAA depended on the feed molar ratio. Although the infrared spectra indicated structural differences between the homopolymer of EOX and EOX in the block copolymer before forming complexes, the spectra obtained for the complexes formed by the homopolymer and the block copolymer were similar to each other.

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1. Introduction

Intermolecular interactions between polymer chains sometimes induce the formation of polymer complexes. Whereas complexes formed by strong interactions can be used to increase stability against mechanical or thermal stresses, those formed by relatively weak interactions can be utilized for their flexible association-dissociation behavior. Polymer complexes can be formed between proton-donating polymers and proton-accepting polymers by the formation of hydrogen bonds, and these complexes have the potential to be used in various applications such as drug delivery systems (DDS) which require polymers to associate and dissociate under specific circumstances.

Poly(2-ethyl-2-oxazoline) is one of the promising polymers for application in DDS because it forms complexes with poly(methacrylic acid) (PMAA) and poly(acrylic acid) (PAA), and exhibits excellent biocompatibility [1,2]. Since Kwon et al. [3] reported the formation of a complex between PEOX and PMAA and proposed the potential application of this complex in DDS, there have been many studies on this complex. Kwon et al. [4] synthesized block

copolymers of EOX and ϵ -caprolactone (CL) for potential formation of complexes with PMAA or PAA. Some grafted copolymers of EOX were also synthesized, and their complexation behaviors with PMAA were investigated [5].

Although there have been some studies on the basic solution properties of PEOX in water [6,7], alcohols [7], and tetrahydrofuran [8], the number of studies on the basic properties of the complexes formed by PEOX is limited. We prepared complexes of PEOX and PMAA with a wide range of concentrations and investigated the structures of the complexes that were prepared from dilute solutions and dissolved in water and that of the complexes that were prepared from relatively concentrated solutions and obtained as precipitates [9]. The results of viscometry and dynamic light scattering indicated the formation of complexes with high polymer chain density and their growth in solutions. The molar ratio of MAA in the complexes was estimated to be approximately 0.5 and nearly independent of the molar ratio in the feed solutions. The dependence of the intrinsic viscosity and that of the molar ratio of MAA could be calculated assuming a single model.

To apply PEOX as a DDS carrier, there have also been researches on block copolymers of PEOX. Hsiue et al. prepared block copolymers of EOX and L-lactic acid [10] or aspartic acid [11] and investigated their behavior in releasing of drug molecules. Lee et al. [4] prepared micelles formed by block copolymers of EOX and CL

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including some solvents in the micelles. By utilizing the poorer solubility to water of poly(2-isopropyl-2-oxazoline) which has a chemical structure similar to that of PEOX, the micellation behavior of these block copolymers has also attracted the interest of many researchers [12,13].

In this study, we investigated the effect of block copolymerization on the complexation behavior of EOX to apply the results obtained in our previous study to a situation which is more similar to that encountered in DDS. Ethylene oxide (EO) was used as a block copolymerized with EOX because PEO is a typical hydrophilic polymer and is widely used for medical purposes and cosmetics due to its high biocompatibility. PEO is also reported to form complexes with PMAA or PAA, and the complexation behavior has been studied by infrared spectroscopy, solid state-NMR, light scattering measurements, and viscometry. Experimental results suggest that PEO and PMAA or PAA tend to form equimolar complexes irrespective of the molar ratio of the feed solutions [14–27]. To investigate the structure of EO blocks in the complexes of the block copolymer of EOX and EO (PEOX-*b*-EO) and PMAA, we also carried out some experiments on the complexes formed by PEO and PMAA.

2. Experimental

2.1. Materials

A block copolymer of EOX and EO and homopolymers of EO, MAA, and EOX were used in this study. Chemical structures of PEOX, PMAA, and PEO are shown in Fig. 1. A PEOX-*b*-EO sample was purchased from Polymersource and purified by filtering in aqueous solution through filters composed of hydrophilic polytetrafluoroethylene with a pore size of 0.45 μm . After removing the water from the filtered solution, the sample was dissolved in *tert*-butyl alcohol purchased from Wako Pure Chemical Industries, and a white powder was obtained by freeze-drying. The number-average molecular weights of the EOX block and EO block in PEOX-*b*-EO were reported to be 6500 and 5000 by the supplier. The molecular weight of PEOX-*b*-EO was also estimated by size exclusion online multi-angle light scattering (SEC-MALS) using *N,N*-dimethylformamide containing 0.01 M of LiBr as an eluent under the same conditions employed in our previous work [9]. The refractive index increment which is necessary for light scattering analysis was measured to be 0.0714 $\text{cm}^3 \text{g}^{-1}$ with the same instrument used in our previous work [9]. This value is very similar to the refractive index increment of PEOX (0.0877 $\text{cm}^3 \text{g}^{-1}$) [9], which suggests that the refractive index increments of the two blocks are similar to each other. We did not correct for the effect caused by the composition distribution of the copolymer to calculate the molecular weight from the data obtained by light scattering [28]. The weight-average molecular weight and polydispersity index determined by SEC-MALS were 9.38×10^3 and 1.25, respectively. The molecular weight determined by SEC-MALS was comparable to that reported by the supplier, which confirmed the accuracy of the molecular weight determined by SEC-MALS. The small value of the

polydispersity index indicates that the polymerization reaction well controlled the structure of the copolymer. The molar fraction of the monomers in the copolymer was calculated from the molecular weight reported by the supplier in the following discussions. (EOX:EO = 1:1.73).

The PEO sample used in this study was purchased from Wako Pure Chemical Industries and used without further purification. The molecular weight and polydispersity index of this sample were determined by SEC with an HPLC-8020 system (Tohso) using methanol as the eluent. Two TSK gel α -M columns and a TSK gel guardcolumn α (Tohso) were connected directly to separate the sample. The molecular weight was calculated using standard PEO purchased from Tohso, and the elution of the samples was detected with an RI-8020 refractometer (Tohso). The weight-average molecular weight and polydispersity index were 2.21×10^4 and 1.09, respectively.

The PMAA and PEOX samples used in our previous study [9] were also used in this study, and the weight-average molecular weights were 2.78×10^5 and 4.40×10^4 , respectively. The PEOX sample had a wide polydispersity, and the polydispersity index of the PMAA sample was 1.59.

2.2. Sample preparation

“Complex” samples were prepared by mixing aqueous solutions of PEOX-*b*-EO or PEO, and those of PMAA and collecting the precipitate by centrifugation. The concentration of the EOX block in PEOX-*b*-EO, and the concentrations of PEO and PMAA were fixed to 0.035 g cm^{-3} . “Mixture” samples were prepared by mixing a powder of PEOX-*b*-EO, or PEO, and a powder of PMAA in a mortar to compare with the complex samples. The details of the sample preparations are described in our previous paper [9].

“Cast” samples were prepared by a procedure similar to that proposed by Jeon et al. [21]. Aqueous solutions of PEOX-*b*-EO, or PEO, and those of PMAA were prepared, and the two solutions were mixed to obtain a suspension containing the complexes. The concentration of the PEOX block in PEOX-*b*-EO and the concentrations of PEO and PMAA were fixed to 0.035 g cm^{-3} , and the molar ratio of the monomers in the suspensions was controlled by changing the volumes of the mixed solutions. The suspension was dropped on an aluminum plate and dried in vacuo for more than three days. To distinguish from cast samples, the precipitated complexes collected by centrifugation are referred to as “precipitated” samples.

To compare the abilities of PEOX and PEO to form complexes with PMAA, complexes formed by PEOX or PEO and PMAA were prepared as follows. An aqueous solution dissolving both PEOX and PEO, and an aqueous solution of PMAA were prepared. The molar concentrations of EOX and EO of the former solution was 0.175 M (0.0173 g cm^{-3}) and 0.306 M (0.0135 g cm^{-3}), respectively. The molar ratio of EO to EOX was 1.75, which was approximately the same as that in PEOX-*b*-EO. The molar concentration of MAA in the aqueous solution was 0.353 M (0.0304 g cm^{-3}). The two solutions were mixed to obtain precipitates containing complexes formed by PEOX and PMAA and those formed by PEO and PMAA. The procedure used to collect and wash the precipitates was same as that used to obtain complex precipitates in our previous study [9].

2.3. Measurements

Infrared (IR) spectroscopy was carried out to investigate the structures and the molar fractions of the monomers in the complexes, and the experimental conditions in this study were the same as those used in our previous study [9]. The molar fraction of the monomers in the feed solutions and that in complexes were evaluated by using x_{MAA}° and x_{MAA} , which are defined as follow,

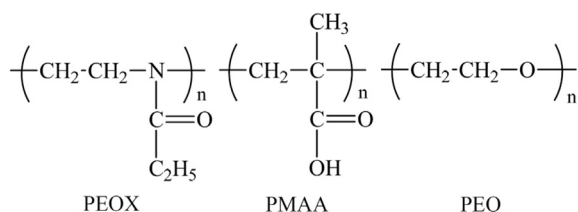


Fig. 1. Chemical structures of PEOX, PMAA, and PEO.

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