

Synthesis of New pH-Sensitive Poly(ethylene oxide-*b*-maleic acid) from Modification of Poly(ethylene oxide-*b*-*N*-phenylmaleimide)

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Abstract: A new and useful poly(ethylene oxide)-based pH-sensitive block copolymer is introduced. Poly(ethylene oxide-*b*-*N*-phenylmaleimide) was first synthesized by anionic polymerization of *N*-phenylmaleimide (*N*-PMI) using mixed alkali metal polymeric alkoxide by sequential monomer addition method in the mixture of benzene/THF/DMSO (10/5/3, v/v/v) at room temperature. Reductive deimidation of the resulting block copolymer was performed using hydrazine monohydrate leading to the formation of the corresponding pH-sensitive poly(ethylene oxide-*b*-maleic acid).

Keywords: pH-sensitive block copolymer, poly(ethylene oxide-*b*-maleic acid), anionic polymerization, modification.

Introduction

Particle uptake by macrophages of the mononuclear phagocytic system in intravenous drug targeting arising from opsonic proteins adsorbing onto the particles should be overcome.¹ Specifically, poly(ethylene glycol) (PEG)-grafted nanoparticles have been described as potential intravenously injectable, long-circulating drug carriers. Poly(ethylene oxide) having the same architecture as PEG is well known as a widely used biomaterial which is not only soluble in water but also non-toxic and exhibits a rapid clearance from body.² We have found new facile synthetic route of poly(ethylene oxide) (PEO) with well-defined structure such as controlled molecular weight and a quantitative chain end functionality.³ The growing species in *n*-butyllithium-initiated ring opening polymerization of ethylene oxide in the mixture of benzene and dimethyl sulfoxide (DMSO) with potassium *tert*-butoxide were found to be mixed alkali metal polymeric alkoxide consisting of lithium and potassium as counter-ion exhibiting a living nature.³

A variety of polymerizations of *N*-PMI via several mechanisms have been reported by several groups.⁴⁻⁷ Especially,

a mixed alkoxide initiating system was found to be effective to polymerize *N*-PMI in toluene.⁷ The poly(*N*-PMI) was reported to be soluble in tetrahydrofuran (THF), dimethylsulfoxide (DMSO), dimethylformamide (DMF), and dichloromethane. Furthermore, it was found that organolithium-initiated polymerization of *N*-PMI in THF produced the THF-insoluble poly(*N*-PMI) fraction in the yield range of 20~38%.⁸ The insoluble fraction had to arise from a stereoregular architecture of the formed polymer.^{9,10}

In this note, we report the result for the synthesis of poly(ethylene oxide-*b*-maleic acid) exhibiting a pH-sensitive phase transition behavior obtained from reductive deimidation of poly(ethylene oxide-*b*-*N*-PMI).

Experimental

Materials. Benzene (DAEJUNG Chem. Co., reagent grade), tetrahydrofuran (DAEJUNG Chem. Co., reagent grade), and dimethyl sulfoxide (DMSO; DAEJUNG Chem. Co., reagent grade) were purified by following the modified procedures described in the literature.³ Chloroform (CHCl₃; DAEJUNG Chem. Co., 99.5%+) and diethyl ether (DAEJUNG Chem. Co., 99.0%+) were used without further purification. *n*-Butyllithium (*n*-BuLi; Aldrich Chem. Co., 1.6 M in

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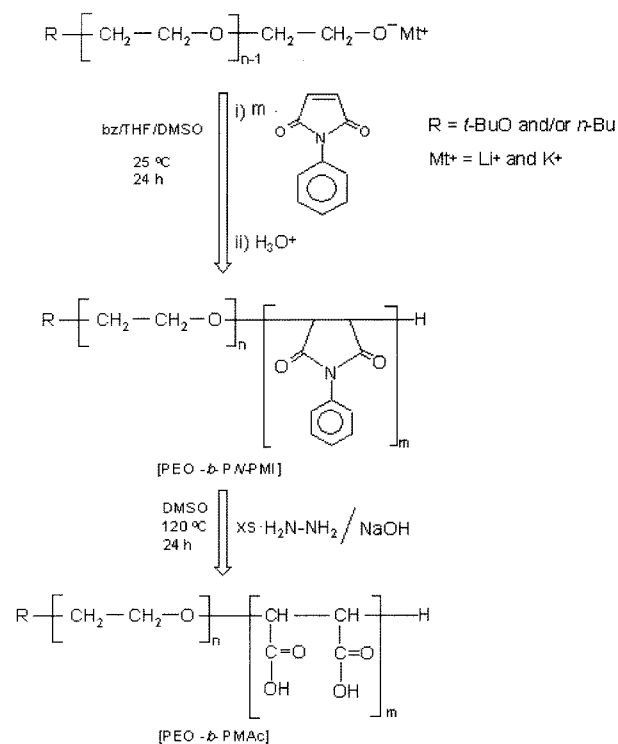
hexane) was used without further purification. Ethylene oxide (EO; Aldrich Chemical Co., 99.5%+) was used after purification followed by the procedures described in the literature.³ Potassium *tert*-butoxide (*t*-BuOK; Aldrich Chem. Co., 98%+) and *N*-phenylmaleimide (*N*-PMI; TCI, >97%) were also purchased and used without further purification.

Synthesis of PEO-*b*-Poly(maleic acid). Living polymeric alkoxide was first synthesized by *n*-BuLi-initiated ring-opening polymerization of ethylene oxide in the mixture of benzene and DMSO as described in the literatures.³ Poly(ethylene oxide-*b*-*N*-PMI) was then prepared by the polymeric alkoxide ([POMt])-initiated polymerization of *N*-phenylmaleimide (*N*-PMI) via sequential monomer addition method. The resulting block copolymer was deimidated by using hydrazine monohydrate with NaOH in DMSO at 120 °C for 24 h, followed by precipitated in diethyl ether. All the products were dried in vacuum oven at room temperature for at least 48 h prior to use and characterization.

Characterization. All of the products including PEO and the PEO-*b*-poly(maleic acid) were characterized by the combination of ¹H- & ¹³C-NMR and size exclusion chromatographic analysis. Size exclusion chromatographic (SEC) analysis was performed at a flow rate of 0.6 mL/min in an aqueous eluent consisting of 0.2 vol% HCl (0.1 M) and 4.0 vol% NH₄OH (0.05 M) at 30 °C using the Waters 515 HPLC component system with three Ultrastaygel[®], columns (500 Å, 250 Å, 120 Å) equipped with a Water 2410 Refractometer Index Detector system. ¹H- & ¹³C-NMR spectroscopic analyses were performed using a Bruker spectrometer (Model; Avance 400 (400 MHz)) in deuterated DMSO at 25 °C.

Results and Discussion

It was found that mixed alkali metal polymeric alkoxide consisting of lithium and potassium was effective to polymerize *N*-PMI *via* anionic mechanism resulting in the production of the corresponding poly(ethylene oxide-*b*-*N*-PMI). Especially, deimidation of the block copolymer using hydrazine monohydrate with 5% NaOH produced new pH-sensitive amphiphilic poly(ethylene oxide-*b*-maleic acid)s. The synthetic route of the block copolymer is shown in Scheme I. The precursor of the block copolymer, poly(ethylene oxide-*b*-*N*-PMI), was readily able to be synthesized by sequential monomer addition method following the same manner as in living anionic block copolymerization.¹¹ However, it was difficult to measure the relative molecular weights of the block copolymers by gel permeation chromatographic analysis because of some fraction of insolubility for tetrahydrofuran (THF) or H₂O at room temperature. Deimidation of the poly(*N*-PMI) fragment using hydrazine monohydrate in the presence of NaOH in DMSO led to a quantitative production of aniline resulting in the formation of poly(ethylene oxide-*b*-maleic acid)s. There are two dif-



Scheme I. Synthetic route.

ferent molecular weights of poly(ethylene oxide-*b*-maleic acid)s because of two different block copolymers, i.e., THF-soluble block copolymer and THF-insoluble block copolymer generated in the same reactor. Size exclusion chromatograms (SECs) of poly(ethylene oxide) and the corresponding poly(ethylene oxide-*b*-maleic acid)s run by using aqueous

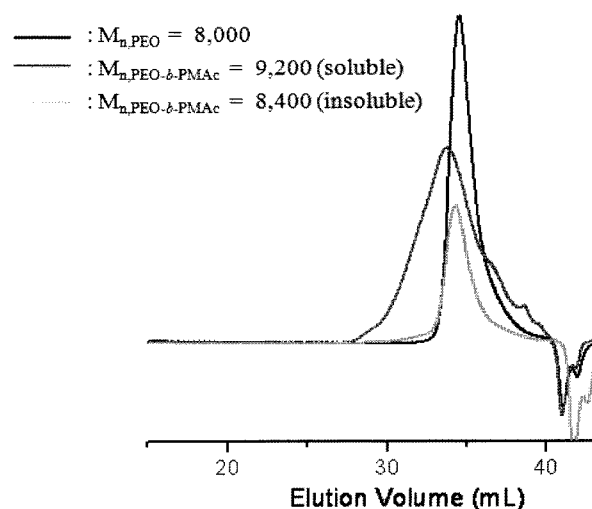


Figure 1. Comparison of size exclusion chromatograms of poly(ethylene oxide) and the corresponding poly(ethylene oxide-*b*-maleic acid)s obtained from deimidation of THF-soluble and THF-insoluble poly(ethylene oxide-*b*-*N*-PMI)s run by using the aqueous eluent consisting of 0.2 vol% HCl (0.1 M) and 4.0 vol% NH₄OH (0.05 M) at room temperature.

medium as an eluent consisting of 0.2 vol% HCl (0.1 M) and 4.0 vol% NH₄OH (0.05 M) are shown in Figure 1. These molecular weights were in a good agreement with those observed from ¹H NMR spectroscopic analysis ($M_{n,PEO} = 8,000$ g/mol). The molecular weight of poly(ethylene oxide-*b*-maleic acid) corresponding to the THF-insoluble poly(ethylene oxide-*b*-*N*-PMI) ($M_{n,N-PMI} = 900$ g/mol) must

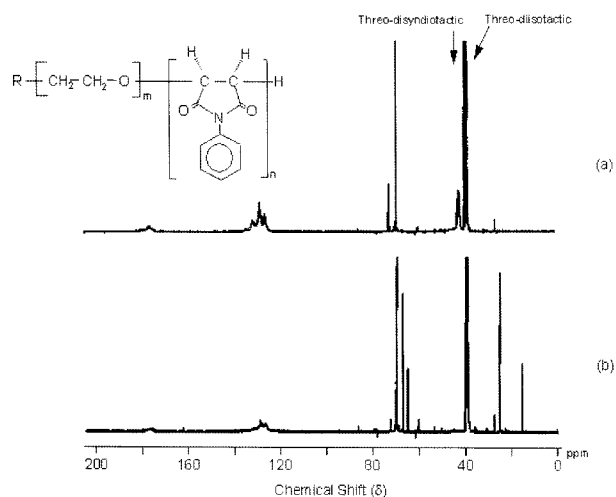


Figure 2. ¹³C-NMR spectra of poly(ethylene oxide-*b*-*N*-PMI) soluble in THF (a) and poly(ethylene oxide-*b*-*N*-PMI) insoluble in THF (b) in deuterated DMSO.

be smaller than that of the THF-soluble poly(ethylene oxide-*b*-*N*-PMI) ($M_{n,N-PMI} = 2,500$ g/mol). The rationale must be due to no further growth arising from the inhomogeneity of the active species with crystalline structure (including threo-diisotactic configuration). The THF-insoluble fraction must arise from the generation of the stereoregular architecture of the poly(*N*-PMI) fragments such as threo-diisotactic trans-addition structure leading to a helix structure decreasing the solubility to THF.¹⁰ Figure 2 shows the ¹³C NMR spectra of the THF-soluble fraction and the THF-insoluble fraction of poly(ethylene oxide-*b*-*N*-PMI). The cis-addition mode of *N*-PMI monomer may lead to the production of *erythro*-configurational stereoisomers. However, the chemical shift at $\delta = 38$ ppm corresponds to the threo-diisotactic trans-addition methine carbon on the *N*-PMI group, while the chemical shift at $\delta = 42$ ppm is assigned to the carbon on the threo-disyndiotactic configuration in Figure 2(a), which must arise from its trans-addition mode. Presumably, high threo-disyndiotactic stereoregular structure may affect the increase of THF solubility of poly(ethylene oxide-*b*-*N*-PMI) compared with block copolymer with high threo-diisotactic architecture synthesized under our experimental condition.

Figure 3 represents ¹H NMR spectra of poly(ethylene oxide), poly(ethylene oxide-*b*-*N*-PMI) soluble in THF, and the corresponding poly(ethylene oxide-*b*-maleic acid). In Figure 3(a) and 3(b), the chemical shifts in the range of 6.2~7.8 ppm are assigned to the protons on the phenyl ring

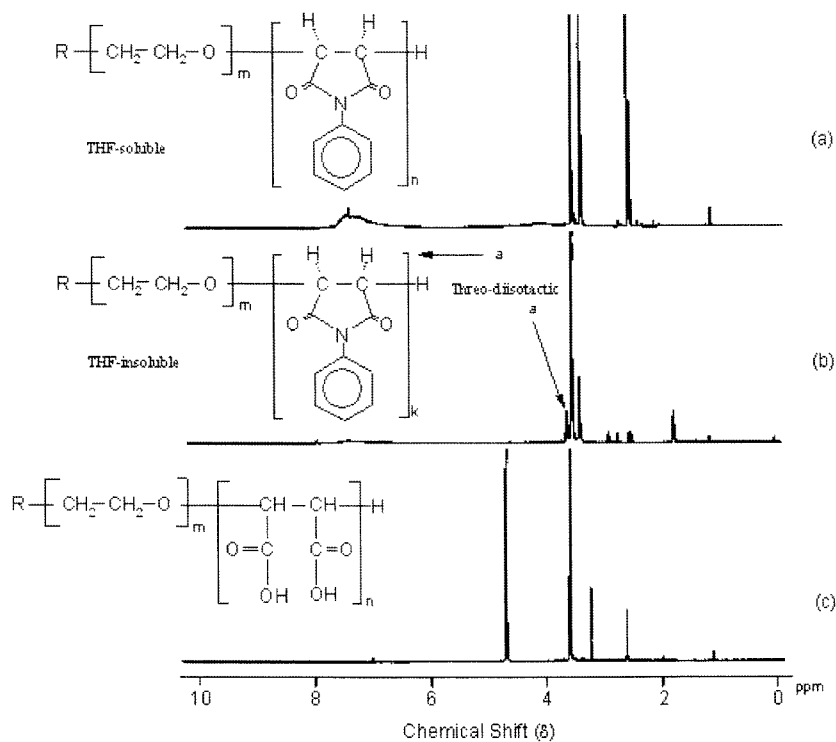


Figure 3. ¹H NMR spectra of poly(ethylene oxide-*b*-*N*-PMI) soluble in THF (a), poly(ethylene oxide-*b*-*N*-PMI) insoluble in THF (b), and the corresponding poly(ethylene oxide-*b*-maleic acid) in deuterated DMSO.



Figure 4. Photo image change of poly(ethylene oxide-*b*-maleic acid) obtained from the THF-insoluble fraction in aqueous media with pH (3.7 wt%).

of the *N*-PMI unit. Clearly, the deimidation of the poly(*N*-PMI) fragment using hydrazine monohydrate on the basis of the disappearance of the chemical shift in the range of 6.2–7.8 ppm provides the corresponding poly(ethylene oxide-*b*-maleic acid). The resulting block copolymer is expected to exhibit a pH-sensitive phase transition. Figure 4 is the photo images of the phase transition behavior depending on the pH change. The pH-sensitive phase transition behavior of the resulting block copolymer seems to be controlled with both the molecular weight and the fractional concentration of the poly(maleic acid) fragment.

Conclusions

Poly(ethylene oxide-*b*-*N*-PMI) was successfully synthesized by living anionic block polymerization of ethylene oxide and *N*-PMI using mixed alkoxide consisting of lithium hexanoate and potassium *t*-butoxide in the mixture of benzene and DMSO. New pH-sensitive poly(ethylene oxide-*b*-maleic acid) applicable for the biomedical field was successfully synthesized from deimidation of poly(ethylene oxide-*b*-*N*-PMI) using hydrazine monohydrate in the presence of NaOH. The resulting block copolymer exhibits pH-sensitive phase transition behavior.

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