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An Efficient Method for Synthesis of PEO-Based Macromonomer and Macroinitiator

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Abstract: The *n*-butyllithium-initiated ring-opening polymerization of ethylene oxide, in a mixture of benzene and dimethylsulfoxide (DMSO), between 25-45 °C, with potassium *tert*-butoxide, is a useful and powerful method to control the molecular weight as well as achieve a quantitative chain-end functionalization yield of the resulting polymeric alkoxide *via* a one pot synthesis. The molecular weight of the product could be controlled by adjusting the ratio of grams of monomer to moles of initiators, such as *n*-butyllithium ([*n*-BuLi]) and potassium *t*-butoxide ([*t*-BuOK]). The yields for the macromonomer and ω-brominated poly(ethylene oxide) (PEO) were quantitative in relation to the chain-end functionalizations of the polymeric alkoxide formed. The resulting products were characterized by a combination of ^{1}H-NMR spectroscopic and size exclusion chromatographic analyses.

Keywords: poly(ethylene oxide), molecular weight control, chain-end functionalizations, macromonomer, macroinitiator.

Introduction

Poly(ethylene oxide) (PEO) has been well known as a basic polymer used in a variety of application fields such as lithium-ion battery[1-5] and biomedical field.[6-8] Poly(ethylene glycol) (PEG) exhibiting the same architecture as PEO with relatively low molecular weight (depending on the synthetic condition) in biomedical application field has been employed for a long time because it is cheap, water-soluble and biocompatible.[9] PEG was extensively used as not only PEG-conjugated prodrug chemically bonded to drug but also a steric stabilizing moiety in polymeric micelles for the physical entrapment of active drugs in the drug delivery system.[9-11] In addition, the molecular weight as well as the chain-end functionality of PEO will be of extreme importance to affect its properties in physiological media.

It has been well known for a long time that controlled 'living' polymerization of vinyl or cyclic monomers is the best method to control both molecular weight and chain-end functionalities of the corresponding polymers.[12,13] Anionic ring-opening polymerizations of ethylene oxide were carried out in highly polar solvents using the initiators having sodium or potassium alkali metal counterion.[14,15] The difficulty on the preparation of these initiating systems under high vacuum or inert gas has made a limitation to perform anionic ring-opening polymerizations of ethylene oxide to produce the corresponding polymers with controlled molecular weights. In spite of its importance and usefulness, not only no easy and useful synthetic process using authentic initiators but also no versatile and simple chain-end functionalization process of PEO has been reported on a commercial scale for a long time. New process for the preparation of PEO should be cost-effective and simple. In this respect, the use of authentic initiators such as organolithium compounds without other complex preparation processes may provide cost-effective and simple polymerization method. However, organolithium-initiated ring-opening polymerization of ethylene oxide even in highly polar solvents or in the presence of highly basic phosphazene has been reported to provide no quantitative conversion of EO.[15-17] Although the possibility for ring-opening polymerization using alkyllithium in the presence of potassium *t*-butoxide in the mixture of benzene and dimethyl sulfoxide (2/1, v/v) was suggested by one of the authors,[18,19] no quantitative conversion (70% for ethylene oxide) was obtained and the molecular weight of PEO obtained could not be controlled due to a side reaction even for a long reaction time (2-8 days).[15] In this publication, we want to report the results of a quantitative

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conversion by *n*-butyllithium-initiated polymerization of EO leading to both the control of the molecular weight of PEO and the quantitative synthesis of ω-functionalized PEO such as PEO-based macromonomer or macroinitiator.

Experimental

Materials. Benzene (Aldrich Chem. Co., anhydrous, 99.8%), dimethyl sulfoxide (DMSO; Aldrich Chemical Co., reagent grade), and tetrahydrofuran (THF; DAEJUNG, 99%) were purified by following the modified procedures described in the literatures.[20,21] Ethylene oxide (EO; Aldrich Chemical Co., 99.5+%) and propylene sulfide (PPS; Aldrich Chemical Co., 96+%) were purchased, followed by the purification procedures as described in the literatures.[20,21] Methacryloyl chloride (Aldrich Chem. Co., 98%+) was used as received. Potassium *tert*-butoxide (*t*-BuOK; Aldrich Chem. Co., 1.0 M solution in tetrahydrofuran) was used as received. 2-Bromoisobutyryl bromide (Aldrich Chem. Co., 98%+) was used as purchased. *n*-Butyllithium (*n*-BuLi; 1.6 M in hexane; Aldrich Chem. Co.) was used as an initiator after titration by Gilman's method using 1,2-dibromoethane.[22]

Polymerization and Functionalization. Anionic ring-opening polymerization of ethylene oxide was performed in the mixture of benzene/dimethyl sulfoxide at 40 °C for 48 h under high vacuum; first, *n*-BuLi (8.0×10^{-3} mol) reacted with purified EO (30 mL; $d = 0.882$) in 400 mL of the mixture of benzene/THF (99/1, v/v) for 6 h, followed by adding *t*-BuOK solution ($[K^+]/[Li^+] = 0.5/1$ mol/mol) and 50 mL of purified DMSO into the reactor and standing the solution with stirring at 40 °C with intermittently cooling down to 0 °C and heating to 40 °C for 48 h. After 200 mL of aliquot (total 500 mL solution) was taken, 30 mL of the EO purified was again delivered into the remained solution of the reactor via the break-seal technique to investigate whether further polymerization of EO by polymeric alkoxide proceeded and the further reaction was carried out for 48 h. Another aliquot (100 mL) was taken, 1 mL of propylene sulfide ($d = 0.946$) purified prior to use was delivered into the main reactor and the further reaction was performed at room temperature ion for 24 h. Analogously, *n*-BuLi-initiated ring-opening polymerization of ethylene oxide was also performed in the presence of *t*-BuOK ([Li]/[K] = 1/1, mol/mol) to obtain a 4,900 g/mol of calculated molecular weight, followed by taking an aliquot and a calculated amount of methacryloyl chloride was delivered into the PEO solution of one of the aliquot and reacted at room temperature for 48 h under high vacuum ([Reagent]/[Li] = 5/1, mol/mol). All the resulting solutions were poured into excess diethyl ether and cooled. The precipitate was filtered and dried in vacuum oven at room temperature prior to analysis. The other aliquot solution was reacted with 5 equivalent 2-bromoisobutyryl bromide dissolved in benzene at room temperature under high vacuum. After completion of the reaction, the resulting solution was poured into excess diethyl ether and cooled. The resulting products were dried at room temperature in vacuum oven for 48 h prior to analysis.

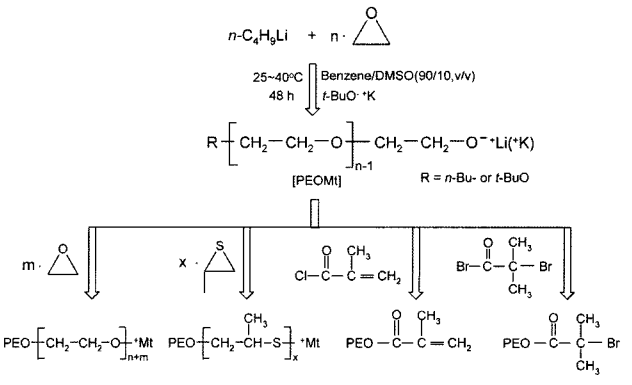
Characterization. Size exclusion chromatograms using a refractive index (RI) detector (Wyatt Technology mini DAWN and OPTILAB DSP Interferometric Refractometer) and a UV/Visible detector (Waters 490E Programmable Multiwavelength Detector) were obtained at a flow rate of 1.0 mL/min in THF at 30 °C using a Dionex P680 HPLC component system equipped with a five ultra-μ-Styragel columns (two 10^5, and one each of 10^4, 10^3, and 500 Å) after calibration with standard PS and PEO samples (Polymer Laboratories). Size exclusion chromatograms using a refractive index (RI) detector (Waters 410 Differential Refractometer) were obtained at a flow rate of 0.6 mL/min in distilled water at 25 °C using a Waters HPLC component system equipped with three ultra hydrogel columns (one each of 120, 250, and 500 Å) after calibration with standard PEO samples (Polymer Laboratories). ^{1}H-NMR spectroscopic analyses were performed using a Varian spectrometer (model; Gemini 200 (200 MHz)) and a Bruker spectrometer (Model; Avance 400 (400 MHz)) in $CDCl_3$ at 25 °C. Thin layer chromatographic (TLC) analyses were performed for qualitative determination of functionalization yield using toluene and ethyl acetate as eluents at room temperature.

Results and Discussion

A possibility for development of a useful and powerful method of PEO with well-defined molecular weight and structure has been investigated through *n*-BuLi-initiated ring-opening polymerization of EO via one pot synthesis. Practically, the reactivity of chain-end of polymeric alkoxide can be confirmed by the results for the experimental criteria observed from the chain extension reactions of polymeric alkoxide described in the literature.[15] The reaction diagrams are shown in Scheme I.

First, after complete consumption of monomer (48 h), fur-

Scheme I



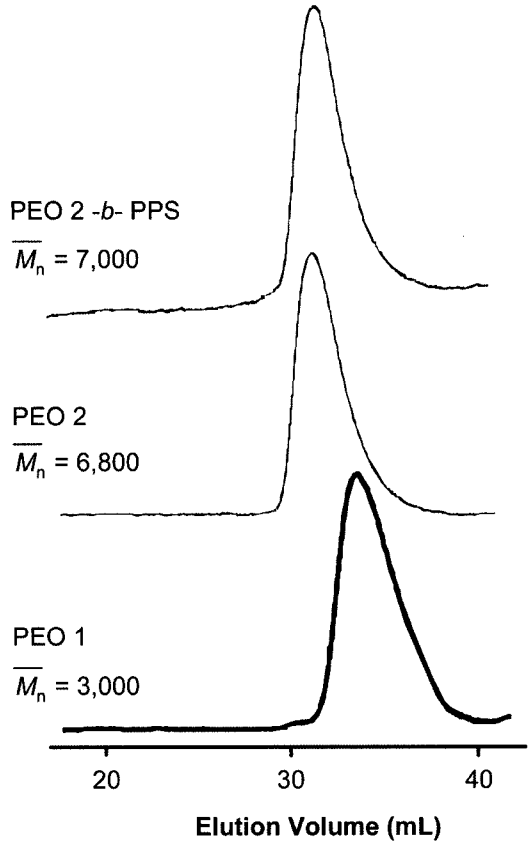


Figure 1. Size exclusion chromatograms of poly(ethylene oxide) synthesized incipiently (PEO 1), polymer by further polymerization from a sequential monomer addition into the PEO 1 solution (PEO 2), and block copolymer (PEO 2-*b*-PPS) prepared by the reaction of PEO 2 with propylene sulfide (using a Dionex P680 HPLC component system in THF at 30 °C).

ther addition of monomer will increase linearly the molecular weight of the formed polymer and addition of the other monomer such as PPS will produce the corresponding block copolymer. Size exclusion chromatograms (SEC) of the resulting poly(ethylene oxide) ([PEOMt]) with 3,000 g/mol, the PEO obtained from further proceeding polymerization by sequential addition of EO, and poly(ethylene oxide-*b*-propylene sulfide) are represented in Figure 1. The observed molecular weight (3,000 g/mol) of PEO is relatively smaller compared with calculated one (4,000 g/mol) on the basis of the ratio of amount of monomer to moles of initiator. This situation will be discussed in more detail later.

In addition, ^{1}H-NMR spectra of PEO and the corresponding poly(ethylene oxide-*b*-propylene sulfide) informs clearly the formation of block copolymer as shown in Figure 2. The chemical shift in the range δ= 1.35-1.45 ppm of thiolated PEO is assigned as the protons on the methyl group of the PPS unit (~PEO-CH_2-CH(CH_3)-S-).[23] The integration result informed that the number of PPS unit was in the range of 3-5 well matched to the theoretical value ([PPS]/[Li] = 5,

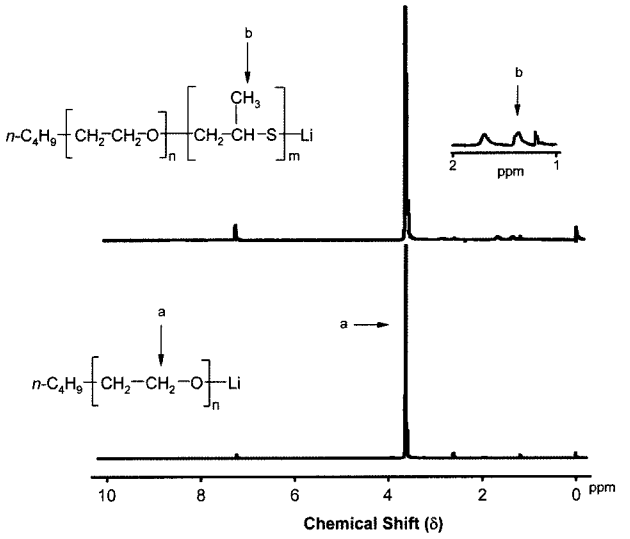


Figure 2. ^{1}H-NMR spectra of poly(ethylene oxide) (PEO 2) and the corresponding block copolymer (PEO 2-*b*-PPS) using $CDCl_3$ as solvent.

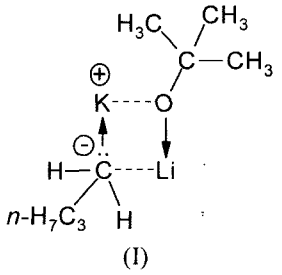
mol/mol). In addition, the R_f values using toluene of PEO and poly(ethylene oxide-*b*- propylene sulfide) were 0.6 and 0.2, respectively. The qualitative TLC results informed that all the growing alkoxides were converted to thiolate resulting in formation of poly(ethylene oxide-*b*-propylene sulfide).

These observed results indicates that two of seven experimental criteria for the living polymerization were satisfied irrespective of monomer conversion.

As already described in the literature,[24] organolithium-initiated polymerization of EO in hydrocarbon at room temperature under high vacuum is ineffective because of strong aggregation of lithium alkoxide. As already mentioned in the previous section, we have suggested a new process to polymerize EO by employing alkyllithium/potassium salts in the mixture of benzene/DMSO.[18,19] In those processes, the concentration of potassium *t*-butoxide ([Li]/[K] = 1/0.1-1/1.1, mol/mol) added and dimethyl sulfoxide ([benzene]/[DMSO] = 2/1, v/v) seemed to provide not a key factor for the quantitative conversion of EO to make the polymeric alkoxide proceed polymerization of ethylene oxide resulting in the production of corresponding poly(styrene-*b*-ethylene oxide) copolymers.[18,19]

Futhermore, because of the unreactivity arising from so strong association of polymeric lithium alkoxide without potassium salt even upon addition of DMSO,[18] a more effective dissociation process is required for further polymerization of EO by polymeric lithium alkoxide. In this respect, we originally utilized other alkali metal alkoxides such as potassium alkoxide exhibiting less association number in aprotic solvents.[25,26] The observation for an exchange reaction between counterions of potassium alkoxide and *n*-butyllithium even in benzene via the formation of the fol-

lowing complex (I) has been reported for a long time.[27,28]



(I)

No generation of the complex (I) is expected in this polymerization system because the reaction solution consists of lithium hexanoate and potassium *t*-butoxide. Presumably, potassium alkoxide effects the reduction of a number of strong association of lithium alkoxide even in aprotic solvent.[18] In this reaction, potassium alkoxide must play an important role to decrease a strong association of the lithium hexanoate formed by the *n*-BuLi-initiation of EO in benzene via cross-association between lithium alkoxide and potassium alkoxide:

$$(POLi)_n + m\cdot RO^-K^+ \rightleftarrows [(POLi)_x(ROK)_y] \rightleftarrows x\cdot POLi\cdot y\cdot ROK$$

A more specific process was proposed in the literature in detail.[18] In that polymerization, both PS-*block*-PEO and PEO were obtained. The production of PEO itself had to arise from polymerization of EO after initiation of potassium *t*-butoxide in the mixture of benzene and DMSO at relatively high temperature described in the literatures.[29,30] Furthermore, the reactivity of the growing species formed from the polymerization system seemed to be greatly dependent of the reaction condition such as the volume of DMSO used as well as a kind of added salts.[18] As shown in the above equilibrium state, all the growing species (PEOMt) in the final state must retain a reactivity based on featuring not only the linear increase of molecular weight but also the production of block copolymer by the alkoxide-initiated polymerization of EO and block copolymerization of PPS.

Anyway, the initiating system consisting of *n*-BuLi and *t*-BuOK must be effective to control the molecular weight of PEO although a predicted molecular weight could not be determined simply by the ratio of monomer to alkyllithium. In spite of a little complicated process, this proposed polymerization of EO in the mixture of benzene/DMSO with potassium *t*-butoxide seems to provide a powerful and useful tool for more cost-effective polymerization using authentic initiator compared with alkyllithium-initiated ring-opening polymerization of EO in the presence of the phosphazene.[17] No formation of dimsyl anion by the reaction of DMSO with alkyllithium was observed after complete conversion of *n*-BuLi to lithium *n*-hexanoate by the reaction with EO because of smaller chain transfer rate constant of polymeric alkoxide to DMSO compared with the propagating rate constant.[30] Furthermore, the livingness of the growing polymeric alkoxide can lead to the possibility for controlling the molecular weight of polymeric alkoxide as shown in the eq. (1).[31]

$$\frac{\text{Monomer (g)}}{\{x\cdot[n\text{-BuLi}] + y\cdot[t\text{-BuOK}]\}(\text{moL})} \quad (1)$$

The SEC results shown in Figure 1 inform that there is no chain transfer of the growing alkoxide because the molecular weight of PEO with a monomodal distribution is the same as the calculated one based on the eq. (1) arising from the dissociation state shown in the above equilibrium state. We found that there was no frequency of S=O absorption band originated from dimsyl anion in the FT-IR spectral analysis (at 1350-1300 and 1160-1120 cm^{-1}).

Analogously, we prepared polymeric alkoxide with 3,500 g/mol of molecular weight which was designed as 4,900 g/mol based on the moles of *n*-BuLi. This smaller molecular weight must arise from participation of *t*-BuOK in propagation of EO resulting in formation of PEO. The chemical shifts at 1.2 and 0.9 ppm are corresponding to the protons on the methyl groups of *t*-butoxy ($(CH_3)_3C$-O) and the protons on the methyl group of *n*-hexyl group (CH_3-$(CH_2)_5$-O) as shown in Figure 3 (bottom spectrum), respectively. On the basis of these results, the molecular weights of PEOs were not easily able to be controlled. However, all the chain-ends are expected to be still active. PEO-based mac-

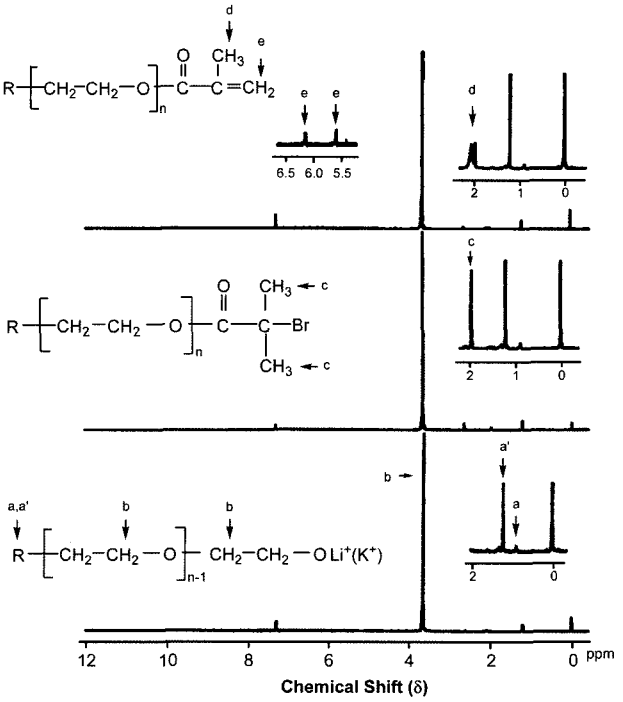


Figure 3. ^{1}H-NMR spectra of poly(ethylene oxide), the corresponding ω-brominated PEO (macroinitiator), and the corresponding PEO-based macromonomer using $CDCl_3$ as solvent.

Supporting data

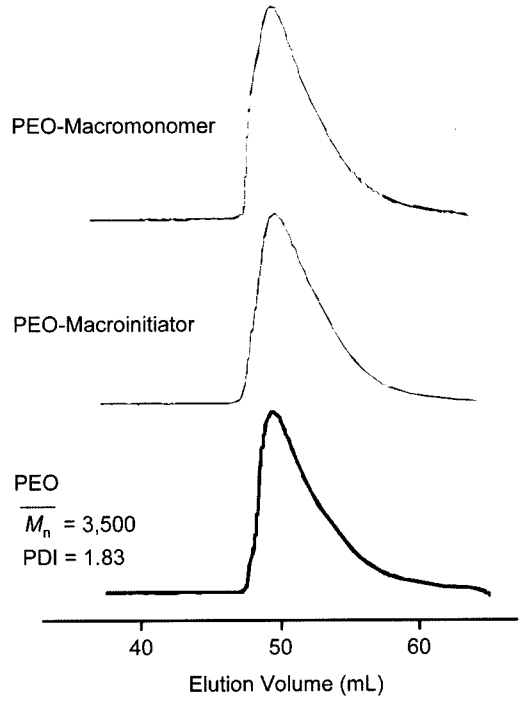


Figure. SEC results for polymers shown in Figure 3.

romonomer and ω-brominated PEO as a macroinitiator for atom transfer radical polymerization (ATRP) were prepared by the chain-end functionalizations of the polymeric alkoxide via the reactions of methacryloyl chloride and 2-bromoisobutyryl bromide. Figure 3 represents ^{1}H-NMR spectra of unfunctionalized PEO, PEO-based macromonomer and PEO-based macroinitiator for radical polymerization (ATRP) carrying the vinyl group and bromide atom at the chain-end, respectively. As already mentioned, the chemical shifts at δ= 0.9 and 1.2 ppm are assigned as the protons on methyl groups (-CH_3) of the *n*-hexyl and *t*-butoxy initiating fragment and the ratio of the integration area in the chemical shift range δ= 3.2-3.8 ppm (-O-CH_2CH_2-O-) to those of the chemical shifts at 1.2 and 0.9 ppm informs a relative molecular weight of PEO. The chemical shifts in the range δ= 5.6-6.2 ppm are assigned as the protons on the methylene group (CH_2=) of the vinyl group. The chemical shift at 1.95 ppm is corresponding to the protons on the methyl groups of the isobutyryl group at the chain-end. Both functionalization yields were over 98 mol% on the basis of comparison of the molecular weight calculated by the peak intensity at the chemical shift related to the isobutyryl group and the observed one by the eq. (1).

Based on all the observed results, the ring-opening polymerization of EO using the proposed initiating system in this study must be a useful and powerful method to obtain a quantitative conversion of EO leading to an easy control of molecular weight of PEO as well as a quantitiative yield from the synthesis of functionalized PEO.

Conclusions

We have developed a useful and powerful method to control the molecular weight of PEO as well as to achieve a quantitative chain-end functionalization yield *via* an anionic mechanism. Specifically, the cost-effective authentic alkyllithium-initiated ring-opening polymerization of EO can produce the corresponding polymer with a predicted molecular weight calculated from the ratio of grams of monomer to moles of initiator in the presence of potassium salt. A fraction of potassium salt was found to affect the control of molecular weight (M_n = monomer(g)/{x·[BuLi] + y·[*t*-BuOK]}) though further detail study should be carried out for control of molecular weight. Because all the growing species were active, the functionalization yields in the synthesis of PEO-based macromonomer and macroinitiator were over 98 mol%. A quantitative chain-end functionalization of the resulting PEO for applications in nanotechnology field as well as biotechnology field may be achieved under a relatively mild reaction condition. The development of their applications is our future task.

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