Synthesis of PEO-Based Materials for Biomedical Applications

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Summary: We have successfully carried out living anionic ring-opening polymerization of ethylene oxide in the mixture of benzene/dimethyl sulfoxide (DMSO) using authentic *n*-butyllithium with potassium *tert*-butoxide as the initiating system. The resulting poly(ethylene oxide) (PEO) used for biomedical applications could be readily modified by chain-end functionalizations. It was possible to control the molecular weight of PEO as well as to achieve quantitative chain-end functionalizations of PEO.

Keywords: biomedical applications; ethylene oxide; living anionic polymerization; ring-opening

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) 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] Especially, poly(ethylene glycol) was extensively used as not only PEO-conjugated prodrug chemically bonded to drug but also polymeric micelle for the physical entrapment of active drugs in drug delivery system.[9–11] The molecular weight as well as the chain-end reactivity of PEO will be extremely of importance to effect its properties in physiological media. In this respect, new development of the useful synthetic method to control the molecular weight as well as the chain-end functionality of PEO becomes very important subject in the polymer chemistry field.

Among many polymerization methods, controlled /'living' polymerizations of vinyl or cyclic monomers have been well known as the best way to control the molecular weight and the chain-end functionalization of the corresponding polymers.[12,13] Practically, we have investigated the convenient and cost-effective method to synthesize the useful PEOs carrying specific functional groups at the chain-ends and their utilizations for preparation of quantum dots including nano-sized gold for the biomedical application. We will report the results on this publication.

Experimental

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.[14,15] Trimellitic anhydride chloride (TMAC; Aldrich Chemical Co., 99%) was used without further purification. Ethylene

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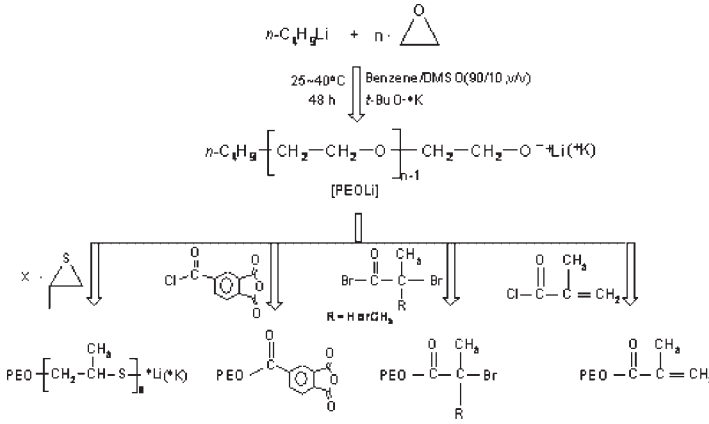
oxide (EO; Aldrich Chemical Co., 99.5+%) and propylene sulfide (PPS; Aldrich Chemical Co., 97%+) were purchased, followed by purification.[14,15] Methacryloyl chloride (Aldrich Chem. Co., 98%+) and 2-bromoisobutyryl bromide (Aldrich Chem. Co., 98%) were also purchased and used in the reactions without further purification. Potassium *tert*-butoxide (*t*-BuOK; Aldrich Chem. Co., 98%+) was also purchased and used. *n*-Butyllithium (*n*-BuLi; 1.6 M in hexane; Aldrich Chem. Co.) was used as an initiator after Gilman's titration using 1,2-dibromoethane.[16] Anionic ring-opening polymerization of ethylene oxide was performed in the mixture of benzene/dimethyl sulfoxide at 40 °C for 48 h; *n*-BuLi reacted with EO in the mixture solvent under high vacuum, followed by adding *t*-BuOK solution into the reactor ($[Li^+]/[K^+] = 1/1$, mol/mol) and standing the solution at 40 °C for 48 h. After the aliquots were taken, a TMAC solution was delivered into the remaining solution ([Li]/[TMAC] = 1/5, mol/mol) and the reaction solution was kept at room temperature for 24 h. The resulting solution was 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 containing lithium polymeric alkoxide was reacted with purified propylene sulfide under high vacuum. The resulting product was precipitated in diethyl ether. The purified products were characterized by the combination of ^{1}H NMR, SEC, and TLC analysis.

Results and Discussion

We have examined whether the chain end of alkoxide generated from *n*-butyllithium-initiated ring-opening polymerization of EO retains a living nature. The results for its livingness on the basis of the experimental criteria of living polymerization have been reported in the other literatures.[17,18] With these regards, the chain-end functionalized PEOs were able to be readily performed by following the reactions as shown in *Scheme* 1.

The most important point in this study is that our polymerization method of ethylene oxide (EO) can provide not only the control of the molecular weight of PEO but also the simple chain-end functionalizations. Practically, the functionalization yields were characterized by thin-layer chromatographic (TLC) analysis qualitatively and ^{1}H NMR spectroscopy analysis quantitatively. Among several functionalized polymers, Figure 1 shows comparison of ^{1}H NMR spectra of unfunctionalized PEO and the corresponding macroinitiator synthesized from the reaction of the polymeric alkoxide ([PEOLi]) with 2-bromoisobutyryl bromide (BIBB) ([PEOLi]/[BIBB] = 1/5, mol/mol).



Scheme 1.
Reaction routes.

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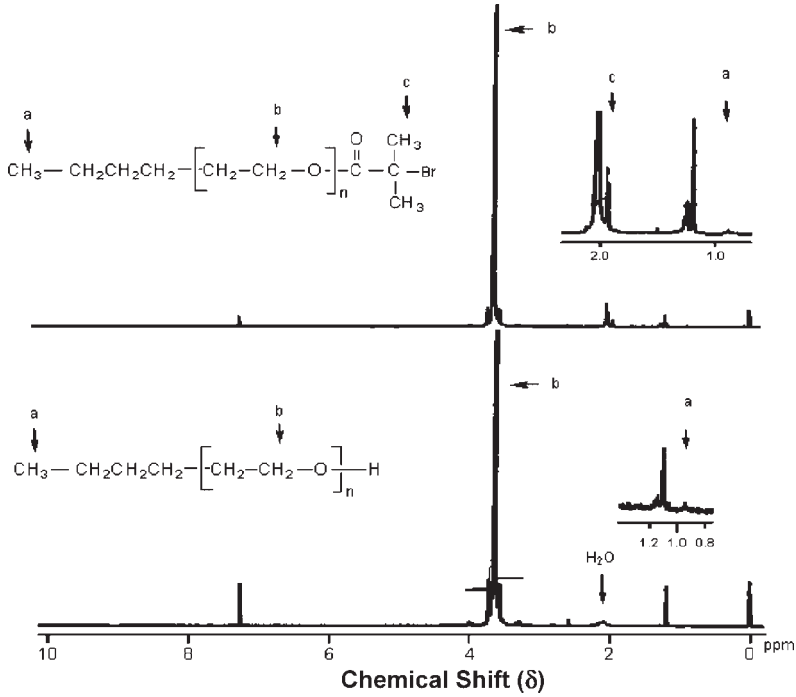

Figure 1.
Comparison of ^{1}H NMR spectra of unfunctionalized PEO and the corresponding ω-brominated PEO as a macroinitiator for ATRP.

The chemical shift at 1.9 ppm is assigned to the protons of methyl group on the isobutyryl unit. The functionalization yield calculated by comparing the integration area of the peaks was over 96 mol-%. The macroinitiator may be utilized for the synthesis of PEO-based block copolymers via atom transfer radical polymerization of vinyl monomers.

Recently, colloidal gold particles stabilized by ω-thiolated PEO has been reported to be utilized in tumor-targeted drug delivery.[19] Water-soluble gold nanoparticle is expected to play an important role in

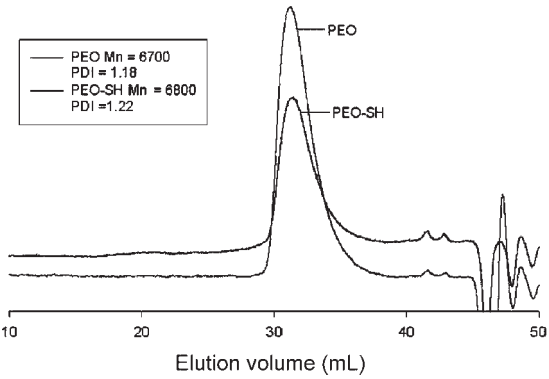

Figure 2.
The size exclusion chromatograms of poly(ethylene oxide) and the corresponding poly(ethylene oxide -*b*-propylene sulfide) (PEO-SH) synthesized from polymeric alkoxide-initiated polymerization of propylene sulfide.

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the biomedical application field. As described in the literature,[20] alkali metal alkoxide has been used in relatively polar solvent as an initiator for polymerization of propylene sulfide (PPS). We have successfully prepared ω-thiolated PEO from the reaction of lithium polymeric alkoxide with propylene sulfide ([Li]/[PPS] = 1/5) under high vacuum. The size exclusion chromatograms were shown in Figure 2. The chain-end thiolation seemed to be quantitative on the basis of ^{1}H NMR spectroscopic analysis.[18] Using the purified thiolated PEO, we prepared water-soluble nano-sized gold particles in tetrahydrofuran at room temperature by reduction of $HAuCl_4$/PEO using $NaBH_4$ as a reducing agent.

The optical properties of nano-sized transition metals are directly related to their surface plasomon resonances ascribing to a collective oscillation of the conduction electrons in response to optical excitation, which are strongly size-dependent.[21] For 10 nm gold sphere, the observed plasomon absorption transition occurs at ~520 nm (the Frőhlich frequency).[22] The typical UV/Visible spectra of nano-sized gold stabilized by ω-thiolated PEO (Au/PEO-SH) and PEO-SH itself in tetrahydrofuran (THF) are shown in Figure 3. The absorption maximum peak appearing at 530 nm indicates the formation of small-sized gold nanoparticles by complete reduction of Au(III) ions.[23] Especially, the appearance of the observed absorption maximum peak at $\lambda_{max} = 530$ nm

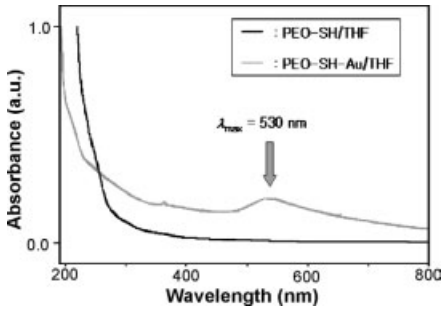

Figure 3.
UV/Visible spectra of PEO-SH-stabilized gold nanoparticles in tetrahydrofuran (PEO-SH/Au/THF) and the corresponding PEO-SH itself gold in THF (PEO-SH/THF).

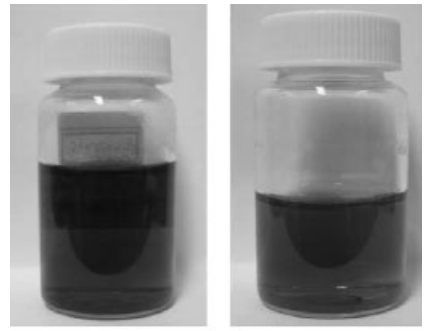

Figure 4.
Photos of gold nanoparticles dispersed in H_2O depending on particle size: Sample 1, 20~40 nm; Sample 2, 15~20 nm.

indicates that the particle sizes were greater than ~10 nm consistent with the optical absorption peak range of 520~545 nm corresponding to the particle size described above. The nano-sized gold powder was obtained from the precipitation of the synthesized-Au THF solution into an excess diethyl ether and drying, followed by re-dissolving in distilled H_2O. Figure 4 is the visual photos of PEO-SH-stabilized gold nanoparticles in H_2O with different sizes. In this experiment, the synthesized Au nanoparticles are also expected in the biomedical application field such as as already described in the literature.[22,24]

In addition, the most common characterization techniques of nanoclusters for the characterization of the size distribution are transmission electron microscopic (TEM) analysis.[25] The structure of the nanoclusters can be determined by their X-ray diffraction (XRD) and selected area electron diffraction (ED) patterns. Figure 5 shows the TEM photograph and the typical electron diffraction (ED) pattern of one of water-soluble gold nanoparticles in distilled water. Most particles are in the size range of 10~40 nm. As already expected in the UV/Visible absorption spectrum, the size greater than ~10 nm is consistent with the observed value from a broad surface plasmon absorption band at $\lambda_{max} = 530$ nm. The ED pattern informs that the gold

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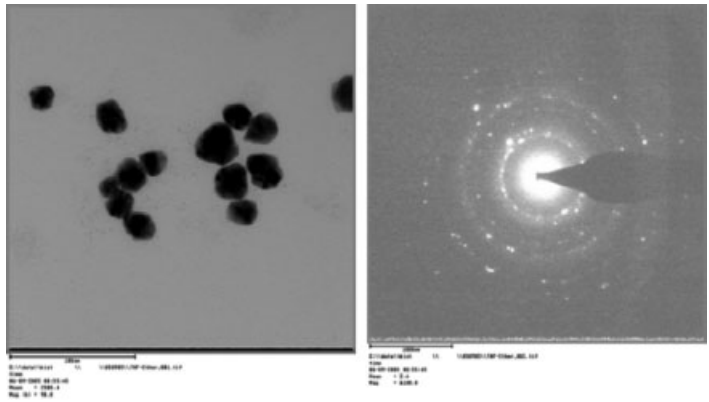

Figure 5.
TEM image and the ED pattern of Sample 1 in Figure 4 (scale bar; 100 nm).

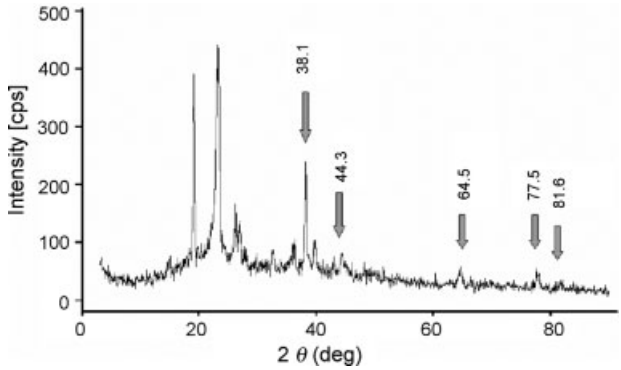

Figure 6.
XRD pattern of water-soluble gold nanoparticles.

nanoparticles must retain a crystalline structure. The X-ray diffraction pattern of the water-soluble gold nanoparticles is shown in Figure 6.

The XRD pattern of the water-soluble Au nanoparticles stabilized by ω-thiolated PEO showed five specific peaks at 38.1°, 44.3°, 64.5°, 77.5°, and 81.6°, which corresponded to the {111}, {200}, {220}, {311}, and {222} lattice planes of the face-centered cubic (fcc) lattice, respectively.[26] All the particles obtained from this experiment exhibited the similar lattice images to the above one. Therefore, the water-soluble gold nanoparticles stabilized by PEO-SH seem to be the same single crystallites with fcc structure as that of bulk Au.

Conclusion

We have successfully synthesized a living polymeric alkoxide in the mixture of benzene and dimethyl sulfoxide using an authentic alkyllithium initiator in the presence of potassium *tert*-butoxide under high vacuum. The resulting alkoxide was reacted simply with a variety of electrophiles as terminating agents producing the corresponding ω-functionalized PEOs. The macroinitiator such as ω-brominated PEO

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can be used for the synthesis of block copolymer via atom transfer radical polymerization for biomedical application. The ω-thiolated PEO was successfully utilized for the preparation of water-soluble gold nanoparticles with the range of 10∼40 nm size. The PEO-based materials carrying specific functional groups at the chain-ends are expected to be utilized for the synthesis of nanomaterials used in the biomedical field.

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