Notes

Efficient Synthesis of Cyclic Poly(oxyethylene) by Electrostatic Self-Assembly and Covalent Fixation with Telechelic Precursor Having Cyclic Ammonium Salt Groups

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Introduction

Precise control in polymer architectures including single and multicyclic units has gained an increasing interest from both polymer science and technology.[1−3] Poly(oxyethylene), POE, is a unique class of polymer resources, extending its application toward innovative fields such as biomedical (targeted drug delivery) and electronic (ion-conducting) materials.[4,5] Hence, the tailored design of the polymer architecture will offer additional opportunities to improve the properties of POE-based polymers in these applications.

A cyclic POE is regarded as a polymer homologue of crown ethers.[6] In particular, medium size cyclic POE's such as 24-crown-8, 30-crown-10, and 60-crown-20 were used extensively to synthesize rotaxanes through threading by a linear chain.[7] Noncovalent interactions such as hydrogen bonding and ion−dipole interactions involving crown ether components have been exploited to construct these supramolecular architectures. Larger cyclic POE's such as 81-crown-27 and those with the molecular weights up to 10 000 were also prepared through a pseudo-high-dilution processes involving a telechelic POE having tosylate groups and KOH in excess.[8,9] Alternatively, a pseudo-high-dilution reaction of a telechelic POE having hydroxy groups with dichloromethane in the presence of KOH was performed to give a cyclic POE with an acetal linkage.[10] High cyclization yields were claimed in these studies,[9,10] and the isolated products exhibited distinct properties from their linear analogues both in solution and in bulk.[6,11] POE-based cyclic block copolymers having a short hydrophobic segment were also prepared to study their association behavior in water.[12] Nevertheless, these stepwise or bimolecular cyclization processes inherently produce linear side products which are not easy to identify or separate by conventional chromatographic means.[13]

We have recently developed an "electrostatic self-assembly and covalent fixation" process as a remarkably efficient means to construct a variety of unusual macromolecular topologies, including single and multicyclic architectures.[14,15] In this process, telechelic polymer precursors having moderately strained cyclic onium salt groups, carrying plurifunctional carboxylate counteranions, have been prepared as a key polymeric intermediate. As an extension of the preceding studies, we report here an effective synthesis of a cyclic POE using a telechelic POE having cyclic ammonium, i.e., quinuclidinium, salt groups. The isolated cyclic POE was unequivocally characterized by ^{1}H NMR, SEC, and TOF-MASS techniques.

Exprimental Section

Materials. A telechelic POE having tosylate groups (**1**) was prepared according to the reported method[16] from poly(ethylene glycol) (Nacalai Tesque Co., Ltd., #4000, $M_n = 2.8$K and PDI = 1.05). Quinuclidine (Aldrich, 97%), *p*-toluenesulfonyl (tosyl) chloride (Aldrich, 99+%), adipic acid (Tokyo Kasei Kogyo Co., Ltd., >99%), and propionic acid (Tokyo Kasei Kogyo Co., Ltd., >99.0%) were used without further purification. Tetra-*n*-butylammonium hydroxide (Tokyo Kasei Kogyo Co., Ltd., 10% in methanol, titrated) was used as received. Acetone (Nacalai tesque Co., Ltd., >99.5%) was reagent grade. Triethylamine (Wako Pure Chemical Industry Co., Ltd., 99+ %), dichloromethane (Kanto Chemical Co., Ltd., >99.0%), and toluene (Kanto Chemical Co., Ltd., >99.5%) were distilled over CaH_2.

Synthesis of Telechelic POE Having Quinuclidunium Salt Groups (2). POE, **1** (1.00 g, 3.2×10^{-4} mol), was dissolved in 15 mL of toluene, and excess quinuclidine (1.02 g, 9.0×10^{-3} mol) was added under a nitrogen atmosphere. The reaction solution was stirred at 90 °C for 4 h, and the solution was evaporated to dryness. The product (**2**) was isolated in a good yield (0.99 g, 99%) after precipitation into cold acetone (−78 °C).

1. ^{1}H NMR: δ 2.44 (s, 6H, CH_3−Ar), 3.58−3.70 (m, CH_2O), 4.16 (t, $J = 4.8$ Hz, 4H, CH_2OSO$_2$), 7.34 (d, $J = 8.4$ Hz, 4H, Ar−*H meta* to CO$_2$), 7.80 (d, $J = 8.4$ Hz, 4H, Ar−*H ortho* to CO$_2$).

2. ^{1}H NMR: Figure 1 (top); δ 1.97−2.03 (m, 12H, NCH$_2$CH_2-CH), 2.13−2.18 (m, 2H, NCH$_2$CH$_2$CH), 2.33 (s, 6H, CH_3−Ar), 3.91−3.97 (m, 4H, OCH$_2$CH_2N), 7.13 (d, $J = 8.0$ Hz, 4H, Ar−*H meta* to SO$_3$), 7.80 (d, $J = 8.0$ Hz, 4H, Ar−*H ortho* to SO$_3$).

Ion-Exchange and Ring-Opening Reactions of 2. The ion-exchange reaction of **2** was conducted by a process where the ion-exchange product could precipitate from an acetone solution containing an excess amount of the desired carboxylate anions in their tetra-*n*-butylammonium salt form. Thus, first, ammonium salts of adipic acid and of propionic acid, both are soluble in acetone, were prepared by the reaction with an equimolar quantity of tetra-*n*-butylammonium hydroxide in methanol (typically 0.53 g of adipic acid and 23.5 mL of methanolic solution of tetra-*n*-butylammonium hydroxide) by stirring for 1 h under a nitrogen atmosphere. The corresponding ammonium salts were isolated as white solids (2.61 g) after evaporating the solvent and finally dried in vacuo. Then, 0.21 g of **2** and a 10 mol equiv of tetra-*n*-butylammonium adipate (0.056 g) were dissolved in 3 mL of acetone and added dropwise

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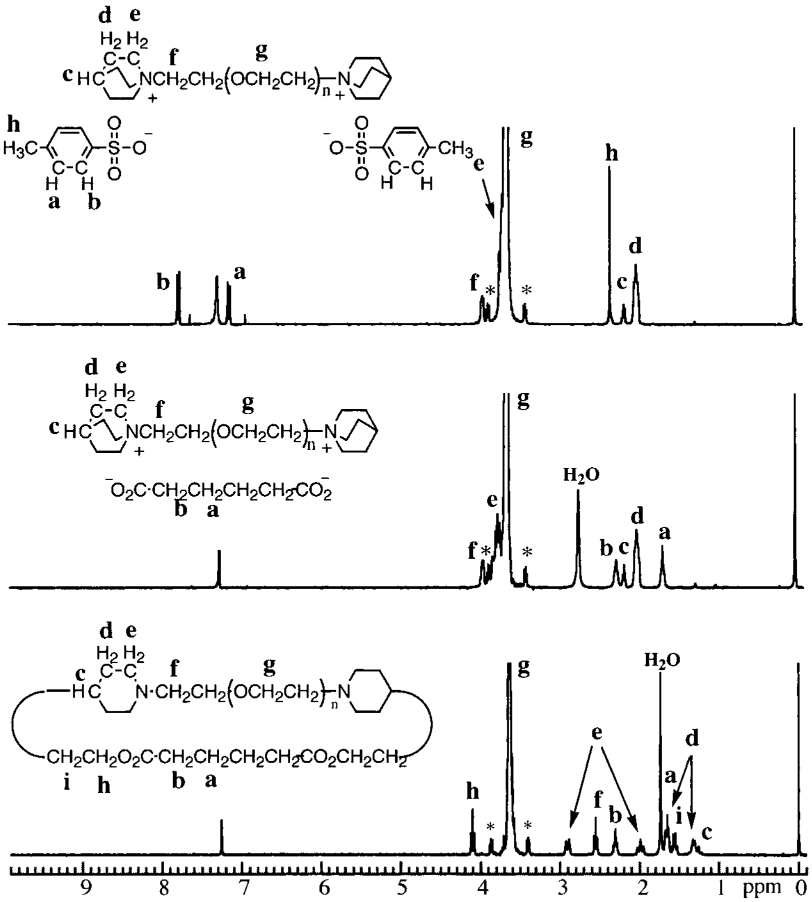


Figure 1. The 300 MHz ^{1}H NMR spectra of a telechelic POE having quinuclidinium salt groups (**2**; top) and the ion-exchange product with adipate before (**3**; middle) and after (**4**; bottom) the heat treatment ($CDCl_3$, 40 °C; * = satellite signal).

into 200 mL of acetone at 0 °C. The precipitated polymer product was filtered after stirring for 0.5 h and washed once with cold acetone and then twice with diethyl ether. The product was finally dried in vacuo to give an ion-exchange product (**3**) in a quantitative yield (0.20 g, 99%). For the ion-exchange reaction of **2** with propionate, an acetone solution of **2** and tetra-*n*-butylammonium propionate salt was added dropwise into acetone cooled at −15 °C, in place of 0 °C for adipate, to recover the ion-exchange product quantitatively.

A telechelic POE having quinuclidinium salt groups carrying an adipate anion, **3**, was then dissolved in toluene at various concentrations (0.70−5.0 g/L). The solution (typically 0.103 g of **3** in 160 mL of toluene) was warmed at 50 °C for 0.5 h under stirring to form a totally homogenious solution and subsequently heated to reflux (bath temperature: 130 °C) for 30 h. The crude reaction product was recovered quantitatively (0.10 g) after evaporating the solvent, and further purified, if required, by means of a preparative SEC fractionation techique. A stabilizer for the SEC eluent, i.e., 2,6-di-*tert*-butyl-4-methylphenol, was removed by precipitation of the product into acetone cooled at −78 °C.

3. ^{1}H NMR: Figure 1 (middle); δ 1.64−1.70 (m, 4H, $C\mathit{H}_2CH_2CO_2$), 1.97−2.03 (m, 12H, $NCH_2C\mathit{H}_2CH$), 2.13−2.18 (m, 2H, $NCH_2CH_2C\mathit{H}$), 2.22−2.28 (m, 4H, $CH_2C\mathit{H}_2CO_2$), 3.89−3.99 (m, 4H, $OCH_2C\mathit{H}_2N$), IR: 1560 cm^{-1} (carboxylate anion).

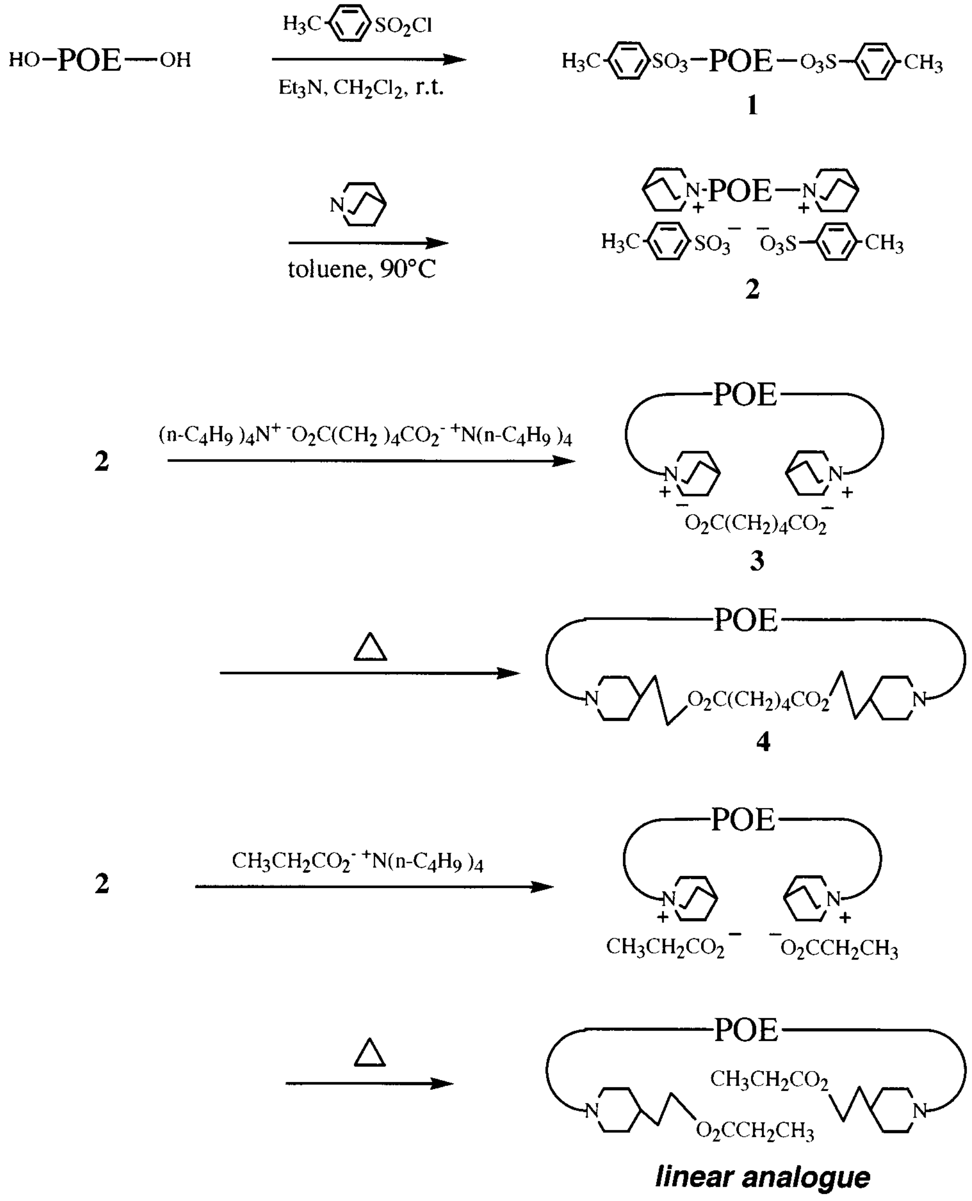
4. ^{1}H NMR: Figure 1 (bottom); δ 1.24−1.28 (m, 2H, $NCH_2CH_2C\mathit{H}$), 1.28−1.36 (m, 4H, $NCH_2C\mathit{H}_2CH$), 1.52−1.60 (m, 4H, $CO_2CH_2C\mathit{H}_2$), 1.62−1.68 (m, 4H, $NCH_2C\mathit{H}_2CH$), 1.65−1.69 (m, 4H, $C\mathit{H}_2CH_2CO_2$), 1.95−2.03 (m, 4H, $NC\mathit{H}_2CH_2CH$), 2.29−2.33 (m, 4H, $CH_2C\mathit{H}_2CO_2$), 2.55 (t, *J* = 6.2 Hz, 4H, $OCH_2C\mathit{H}_2N$), 2.88−2.94 (m, 4H, $NC\mathit{H}_2CH_2CH$), 4.10 (t, *J* = 6.8 Hz, 4H, $CO_2C\mathit{H}_2$), IR: 1730 cm^{-1} (ester carbonyl).

Measurements. SEC measurements were performed using a Tosoh model CCPS equipped with a refractive index detector model RI 8020 with a column of TSK G3000HXL (300 mm × 7.8 mm i.d., 5 μm average particle size) at 40 °C, calibrated with poly(ethylene glycol) standard samples from Polymer Laboratory Ltd. The eluent was THF at a flow rate of 1.0 mL/min. SEC fractionation was carried out using a JAI model LC-908W CCPS apparatus with a refractive index detector model RI-5 and with a column set of JAIGEL-2H-AF (300 mm × 20 mm i.d., exclusion molecular weight of 5K for polystyrene) and JAIGEL-3H-AF (300 mm × 20 mm i.d., exclusion molecular weight of 70K for polystyrene). The sample solution (3 mL containing 0.18 g of the crude product) was injected and recycled before fractionation. The eluent was THF at a flow rate of 3.5 mL/min. IR spectra were taken on a JASCO FT/IR-410 infrared spectrometer by casting the sample from chloroform solution on a NaCl plate. ^{1}H NMR spectra were recorded with a JEOL JNM-AL 300 apparatus in $CDCl_3$ at 40 °C. Chemical shift values are referenced relative to tetramethylsilane. MALDI−TOF MASS spectra were taken on a Shimadzu AXIMA-CFR mass spectrometer. The spectrometer was equipped with a nitrogen laser (λ = 337 nm) and with pulsed ion extraction. The operation was performed at an accelerating potential of 20 kV, in linear-positive ion mode. A 0.5 μL portion of the mixture consisting of polymer solutions (20 μL, 1 g/L, in THF) and matrix, 9*H*-pyrido[3,4-*b*] indole (norharman, Sigma), solution (100 μL, 10 g/L, in THF) was deposited onto a sample target plate and allowed to dry in air at room temperature. Mass values were calibrated with insulin β at 3496.66.

Results and Discussion

Telechelic poly(oxyethylene), POE, having quinuclidinium salt groups, carrying an adipate counteranion, **3**, was prepared through the sequential derivatization of poly(ethylene glycol) (MW of 2.8K and PDI of 1.03) by the tosylation, quaternization, and ion-exchamge reactions as in the previous polystyrene system[17] (Scheme

Scheme 1



1). The nearly quantitative end group derivatization was confirmed by ^{1}H NMR spectroscopy as shown in Figure 1 (top). The subsequent ion-exchange reaction from tosylate to carboxylate anions like adipate and propionate proceeded quantitatively by the following procedure. Since telechelic POE's are soluble in water, an acetone solution of the telechelic POE precursor **2** was added dropwise into cooled acetone solution (0 °C for adipate and −15 °C for propionate), where an excess of tetra-*n*-butylammonium carboxylate salt was included. The ion-exchange product was then recovered quantitatively. The ^{1}H NMR spectra of the products [Figure 1 (middle) for **3** and S-Figure 1 (top) (Supporting Information) for the precursor with propionate counteranions] showed the complete ion-exchange reaction by the signals at 1.65 (for adipate) and 1.14 ppm (for propionate) and by the absence of tosylate protons.

The polymer cyclization of **3** was performed in a toluene solution at reflux using different concentrations. Soluble products were recovered quantitatively irrespective of the polymer precursor concentration. The ^{1}H NMR spectra of the products after the heating [Figure 1 (bottom) for **4** and S-Figure 1 (bottom) (Supporting Information) for the corresponding linear analogue] confirmed that the quinuclidinium groups ring-opened almost quantitatively by nucleophilic attack of the adipate and the propionate counteranions. Thus, the signals due to the quinuclidinium salt group are replaced by those due to the amino−ester group typically visible at 4.10 ppm after heating. IR spectra (not shown) also showed the ring-opened structure by the ester carbonyl absorption at 1730 cm^{-1}, visible after the heating by replacing carboxylate absorption at 1560 cm^{-1}.

SEC profiles of products obtained under different concentrations are shown in Figure 2. The relative content of a lower molecular weight fraction with narrow size distribution increases with dilution, while that of a noticeable higher molecular weight fraction with a broader size distribution diminishes. This agrees with the poly(THF) and polystyrene systems reported previously.[14,17] The crude product was subjected to a preparative SEC fractionation to give a purified cyclic POE (PDI = 1.05), **4**, in 63% yield (Figure 2d). The SEC

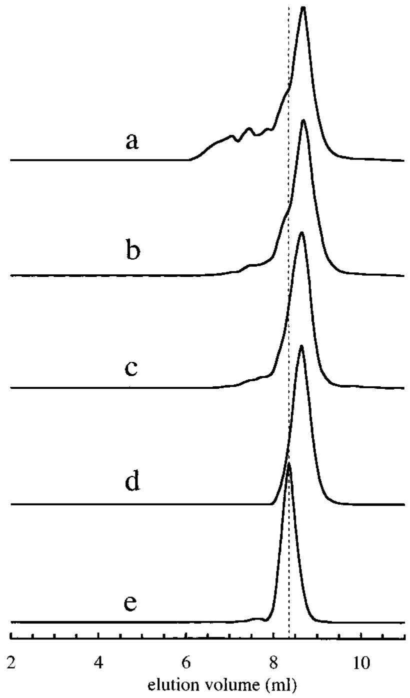


Figure 2. SEC traces (RI) of the quantitatively recovered product after the heat treatment of **3** (a−c), of the purified cyclic POE **4** (d) by the preparative SEC fractionation, and of the linear analogue (e). Concentration of the **3** in toluene: (a) 5.0, (b) 1.0, and (c) 0.7 g/L (TSK G3000HXL, eluent: THF, 1 mL/min).

profile of the cyclic polymer product from **3** was compared with its linear analogue prepared from the identical precursor but carrying propionate counteranions. The size of the cyclic product estimated by their apparent molecular weights was notably smaller than that of the linear counterpart. The estimated hydrodynamic volume ratio of cyclic/linear POE's was 0.76, in good agreement with the other cyclic/linear polymer systems.[18−22]

The cyclic POE, **4**, and its linear analogue were examined by a MALDI−TOF MASS spectroscopy (Figure 3). The cyclic polymer product, **4**, showed a uniform series of peaks corresponding to POE (peak interval of 44 mass units); each peak corresponds exactly to the molar mass summing up the linking structure produced by the ring-opening reaction of the quinuclidinium group by an adipate anion. As an example, the peak (assumed to be the adduct with H^+) at 3434.9 corresponds to the product with the DP_n of 70 plus H^+ as 3435.229. The linear product, obtained from the identical POE precursor but carrying propionate counteranions, also showed a major series of the peaks corresponding to the proton adduct. Thus, the peak (assumed to be the adduct with H^+) at 3436.7 corresponds to the product with the DP_n of 70 plus H^+ as 3437.245. A minor series of peaks having smaller molecular weights were observed in the linear product, presumably corresponding to chains with decomposed end groups. Since both cyclic and linear POE's are produced from the identical precursor **2**, after the ion-exchange either by an adipate or two propionate counteranions, their molecular weights differ by just 2 mass units. This was confirmed by the two TOF−MASS spectra shown in Figure 3. The DP_n of the strongest peak for cyclic and linear products differs slightly presumably due to the different ionization effeciency for cyclic and linear POEs of the same DP_n.

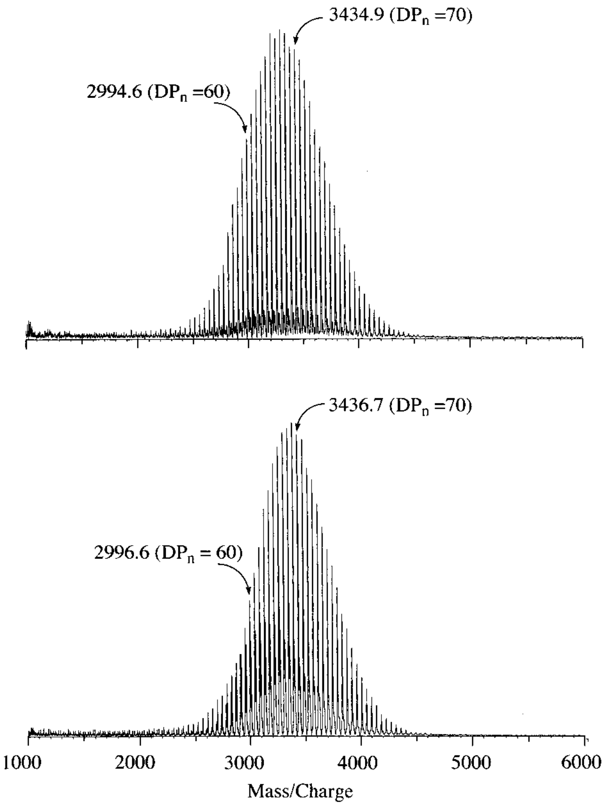


Figure 3. MALDI−TOF−MASS spectra of the cyclic POE (**4**, top) and of the linear analogue (bottom) (linear mode, matrix: norharman).

To conclude, the polymer cyclization process by the electrostatic self-assembly and covalent fixation technique effectively produced a cyclic POE. The telechelic precursor comprising a single polymer unit is predominantly formed under appropriate dilution, causing the deassembly of the aggregated form in bulk, and the subsequent covalent conversion in balancing the charges between cations and anions effectively leads to the cyclic product. A further application of the process to prepare cyclic POE having functional groups and to construct amphiphilic (hydrophilic−hydrophobic) copolymers of both cyclic units or of cyclic and linear units is now in progress in our laboratory.

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Supporting Information Available: The 300 MHz ^1H NMR spectra of a telechelic POE having quinuclidinium salt groups carrying propionate counteranions before (top) and after (bottom) the heat treatment ($CDCl_3$, 40 °C). This material is available free of charge via the Internet at http://pubs.acs.org.

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