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Ring-opening polymerization of ε-caprolactone by poly(propyleneglycol) in the presence of a monomer activator

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ABSTRACT

The ring-opening polymerization of ε-caprolactone (CL) was induced by using polypropylene glycol (PPG) as an initiator in the presence of the monomer activator $HCl \cdot Et_2O$ to synthesize triblock copolymers composed of PPG and poly(ε-caprolactone) (PCL). The degree of CL conversion and the molecular weight of PCL increased linearly with the polymerization time or with the feed ratio of CL to PPG in the presence of $HCl \cdot Et_2O$ in CH_2Cl_2 at 25 °C. The PCLs obtained had molecular weights close to the theoretical values calculated from the CL:PPG molar ratios and exhibited monomodal GPC curves with narrow polydispersity indexes. The apparent rate constant (k_{app}) for the polymerization of CL activated by $HCl \cdot Et_2O$ was greatly affected by the ratio of $HCl \cdot Et_2O$/PPG. The activation energy for the polymerization of CL in this system was estimated to be 49.8 kJ/mol K. We successfully prepared PPG and PCL triblock copolymers using this activated monomer mechanism.

1. Introduction

Polyethyleneglycol (PEG) is a nonionic and biocompatible material with outstanding physicochemical and biological properties [1,2]. PEG is widely used in the areas of small-molecule encapsulation, drug formulation, pharmaceutical excipients, cosmetics, paint formulations, biomedical coatings, and so on. Nonionic and biocompatible polypropyleneglycol (PPG) derives from propyleneglycol (PG) monomers with a methyl substituent at the ethyleneglycol (EG) basic structure. Although PEG and PPG have similar polyether units, and are thought to be nontoxic, they have distinct properties and hence are used in different applications. PPGs are widely used in industry for the fabrication of lubricants, stabilizers, removers, paint formulations, chemical intermediates, or raw materials for polyurethane [3–6]. Despite these many industrial applications, little attention has been given to PPG-based biomaterials (PPG molecular weight of 400–2000 g/mol for biomedical application) [7,8].

For practical biomedical applications, PPG is mainly used in the form of block copolymers with PEG. The PPG block provides the molecule with its necessary hydrophobicity, whereas the PEG block gives it its hydrophilicity [9]. The PEG–PPG–PEG triblock copolymer is a well-known US Food and Drug Administration (FDA) approved polymer and has been applied in drug delivery systems as a thermogelling system [10–12].

Poly(ε-caprolactone) (PCL), a biodegradable polyester, is attracting growing interest as a biologically friendly synthetic biomaterial amenable to many practical applications in drug delivery systems and tissue engineering [13–15]. In the last few years, numerous studies have examined the preparation of PEG-based PCL block copolymers with a special focus on the ring-opening polymerization (ROP) of the ε-caprolactone (CL) monomer, in which the activated monomer mechanism (AMM) plays an important role [16–20]. ROP of CL by PEG via AMM should be proceeded by nucleophilic attack of the hydroxyl chain end of PEG to the CL monomer molecules bearing a activate charge. This AMM has the advantage of preventing the side reaction such as the formation of cyclic oligomers.

Block copolymers of PPG and PCL exhibit mechanical properties that are not shown by the individual homopolymers. Thus, the preparation of PPG and PCL block copolymers appears to be a promising approach for the development of interesting biomaterials. To the best of our knowledge, however, no previous study

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Table 1
Dependence of ROP of CL on time.[a]

Time (h)	Conv.[b] (%)	$M_{n,\ theor}$[c]	$M_{n,\ NMR}$[b]	M_w/M_n[d]
0	–	–	1000(PPG)	1.09
1	7.0	1080	1070	1.12
2	13.0	1190	1130	1.12
4	26.0	1300	1260	1.13
6	36.4	1410	1364	1.15
8	45.7	1520	1457	1.16
12	89.0	2010	1890	1.18
24	99.9	2140	1999	1.18

[a] Condition: [HCl]/[I] = 2, [CL]/[CH_2Cl_2] = 1 M, [CL]/[I] = 17.5, room temperature, 24 h.
[b] Determined by ^{1}H NMR.
[c] Calculated M_n from conversion of CL.
[d] Measured by gel permeation chromatography (based on standard polystyrene).

has examined the preparation of PPG/PCL block copolymers in the presence of a monomer activator. Monomer-activated ROP can easily yield PPG and PCL block copolymers in the presence of a monomer activator. In this article, we present the first approach to the synthesis of PPG/PCL block copolymers via monomer-activated ROP of CL by PPG in the presence of HCl solution in diethyl ether ($HCl\cdot Et_2O$) as a monomer activator.

2. Experimental

2.1. Materials

Polypropyleneglycol (PPG), 425, 1000, 2000 g/mol (Aldrich), and HCl (Aldrich; 1.0 M solution in diethyl ether) were used as-received. ε-caprolactone (ε-CL) was distilled over CaH_2 under reduced pressure. CH_2Cl_2 was distilled sequentially from $CaCl_2$ and CaH_2 under nitrogen before use.

2.2. Instrumentation

^{1}H NMR spectra were measured using Bruker 300 and 500 MHz instrument with $CDCl_3$ in the presence of tetramethylsilane as internal standard. Molecular weights and molecular weight distributions of PPG and PCL–PPG–PCL triblock copolymers were measured by Futecs At-4000 GPC system (Shodex RI-101 detector) using three columns (Shodex K-802, K-803, K-804 polystyrene gel column) at 40 °C, using $CHCl_3$ as an eluent with a flow rate of 0.8 mL/min by polystyrene calibration.

2.3. Synthesis of poly(ε-caprolactone)–poly(propyleneglycol)–poly(ε-caprolactone) triblock copolymers (PCL–PPG–PCL)

All glasses were dried by heating in vacuum and handled under a dry nitrogen stream. The typical process for the polymerization to give PCL–PPG–PCL with total PCL molecular weight (2000 g/mol) is as follows. PPG (1000 g/mol), (1 g, 1 mmol), and toluene (80 mL) were introduced into a flask. The PPG solution was distillated by azeotropic distillation to remove water. Toluene was then distilled off completely. To PPG was added the CH_2Cl_2 (20 mL), followed by the addition of CL (2 g, 17.5 mmol) using syringe. The polymerization was initiated by the addition of 1.0 M solution of HCl in diethyl ether (2 mL, 2 mmol) at 25 °C. After 24 h, the reaction mixture was poured into *n*-hexane to precipitate a polymer, which was separated from the supernatant by decantation. The obtained polymer was redissolved in CH_2Cl_2 and then filtered. The polymer solution was concentrated

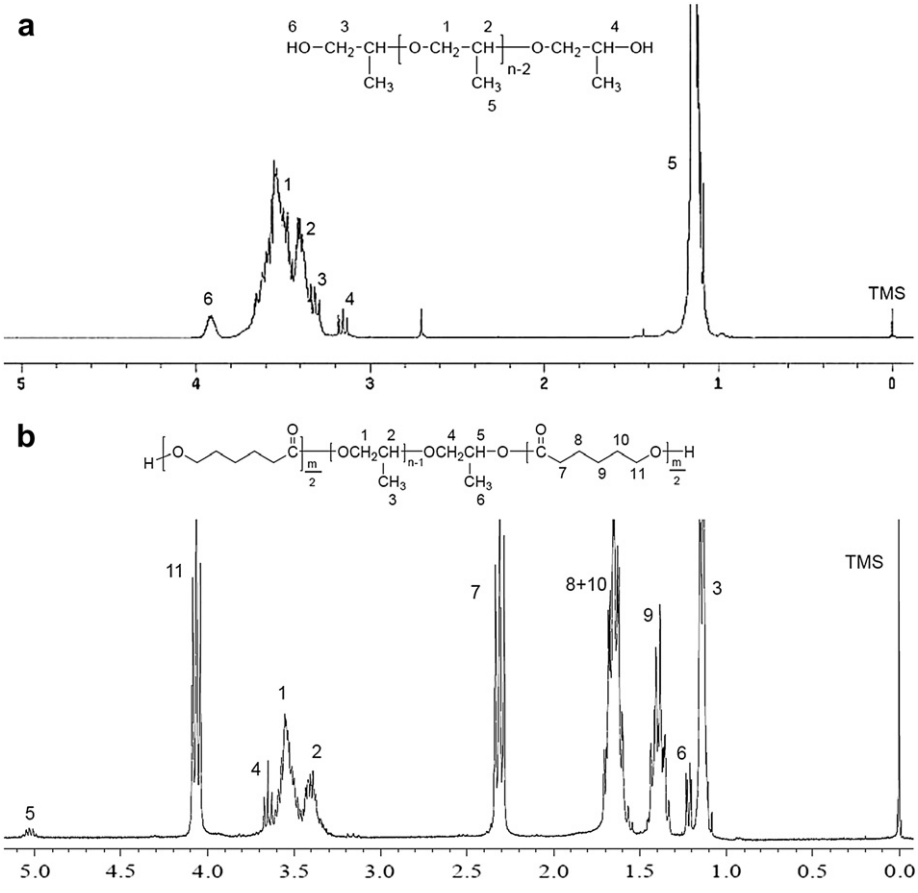


Fig. 1. ^{1}H NMR spectra of (a) PPG (1000 g/mol) and (b) PCL–PPG–PCL triblock copolymer (1000–1000–1000).

Table 2
Synthesis of PCL–PPG–PCL triblock copolymers.

Initiator[a] (I)	[CL]/[I]	$M_{n,\ theor}$ PCL–PPG–PCL	Yield[b] (%)	$M_{n,\ NMR}$[c] PCL–PPG–PCL	M_w/M_n[d]
PPG	8.8	500–425–500	97	550–425–550	1.19
($M_w = 425$)	13.2	750–425–750	98	720–425–720	1.22
	17.5	1000–425–1000	97	830–425–830	1.25
PPG	8.8	500–1000–500	95	500–1000–500	1.18
($M_w = 1000$)	11.0	625–1000–625	96	660–1000–660	1.22
	13.1	750–1000–750	94	750–1000–750	1.22
	17.5	1000–1000–1000	95	1000–1000–1000	1.24
	21.9	1250–1000–1250	96	1120–1000–1120	1.25
	26.3	1500–1000–1500	95	1410–1000–1410	1.28
	35.0	2000–1000–2000	93	1950–1000–1950	1.24
	52.6	3000–1000–3000	92	3100–1000–3100	1.28
	87.6	5000–1000–5000	90	4900–1000–4900	1.34
PPG	8.8	500–2000–500	96	1000–2000–1000	1.24
($M_w = 2000$)	13.1	750–2000–750	95	840–2000–840	1.24
	17.5	1000–2000–1000	93	1000–2000–1000	1.26
	21.9	1250–2000–1250	95	1250–2000–1250	1.28

Condition: [HCl]/[Initiator] = 2, [CL]/[CH_2Cl_2] = 1 M, room temperature, 24 h.
[a] PPG = 425 ($M_w/M_n = 1.08$), PPG = 1000 ($M_w/M_n = 1.09$), PPG = 2000 ($M_w/M_n = 1.10$).
[b] *n*-hexane insoluble part.
[c] Determined by ^{1}H NMR.
[d] Measured by gel permeation chromatography (based on standard polystyrene).

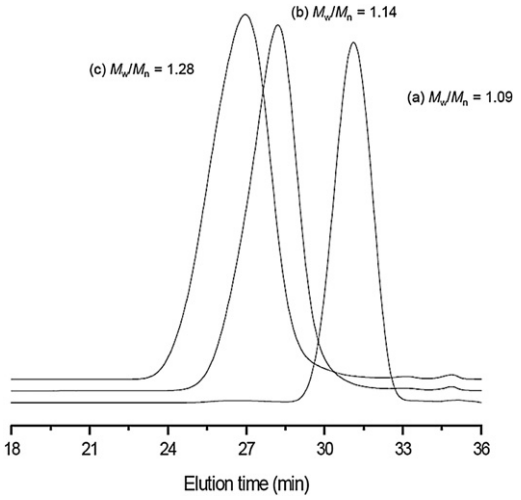


Fig. 2. GPC curves of polymers obtained by polymerization in the presence of HCl·Et_2O in CH_2Cl_2 at 25 °C: (a) PPG (1000 g/mol), (b) PCL–PPG–PCL (960–1000–960) triblock copolymer obtained from 8.8 equiv. of CL after 24 h, and (c) PCL–PPG–PCL (1000–1000–1000) triblock copolymer obtained after additional 24 h of polymerization (after further addition of 8 equiv. of CL).

by rotary evaporator and dried in vacuum to give a colorless polymer of quantitative yield. The CL monomer conversion into PCL was determined by ^{1}H NMR spectroscopy before precipitation with *n*-hexane.

3. Results and discussion

In the absence of HCl·Et_2O, the polymerization of CL using PPG as initiator does not proceed. To examine the ROP of CL as a function of time, we induced the CL polymerization using PPG as initiator in the presence of HCl·Et_2O in CH_2Cl_2 at 25 °C for 24 h. We found that both the extent of CL conversion and the PCL molecular weight increased linearly with the polymerization time (Table 1). After 24 h, a near-quantitative CL conversion was observed. The molecular weights (M_n values) determined by means of NMR studies were close to the theoretical values calculated from the CL conversion. The polydispersity index of the PCL–PPG–PCL triblock copolymers increased slightly with the polymerization time and reached a value of 1.18 after 24 h. This value is narrow compared to that of PPG (1.09), which was used as initiator. After 24 h of polymerization, colorless PCL–PPG–PCL triblock copolymers were obtained in near-quantitative yields after *n*-hexane precipitation.

Fig. 1 shows the ^{1}H NMR spectra of PPG and PCL–PPG–PCL triblock copolymer obtained by polymerization. The characteristic peaks of PPG are observed. For PCL–PPG–PCL triblock copolymer, signals due to the terminal methyl, methylene, and methine protons (6, 4, 5) of PPG (blocked by PCL) are observed at around 1.21, 3.65, and 5.03 ppm, respectively. This indicates that the terminal hydroxyl group of PPG serves as initiator in this polymerization system.

The change in molecular weight upon varying the feed ratio of CL to PPG (as initiator) was examined (see Table 2). The polymer yields were near-quantitative and the polydispersity indices of PCL–PPG–PCL triblock copolymers remained in the range of about 1.34. The molecular weights can be calculated by integration of the ^{1}H NMR spectra, that is, by calculating the ratio of the methylene oxide protons of the PPG main chain to the characteristic methylene protons of the PCL main chain (propylene oxide units/PCL units). The PCL molecular weights calculated based on ^{1}H NMR were in good agreement with the theoretical molecular weights calculated from the feed ratio of CL to PPG. These findings indicate that in the polymerization using HCl·Et_2O as monomer activator, the molecular weight of the PCL segment can be controlled well by varying the [PPG]/[CL monomer] ratio.

When the PCL–PPG–PCL triblock copolymers were kept under polymerization conditions for a further 24 h after completing the CL monomer conversion, neither M_n nor the polydispersity index of the polymer changed, which indicates that no chain-transfer processes, such as back-biting reactions of the PCL–PPG–PCL triblock copolymers, take place in the presence of HCl·Et_2O and absence of CL.

A second-feed experiment was carried out to confirm the living nature of the polymerization. After achieving quantitative monomer conversion after 24 h, 8 equiv. of CL were added to restart the polymerization. As shown in Fig. 2, the gel permeation chromatography (GPC) curve shifted completely to a higher M_n field and

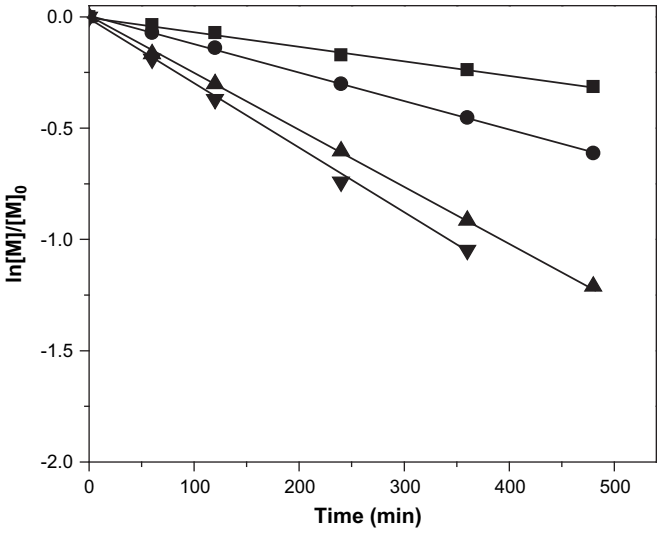
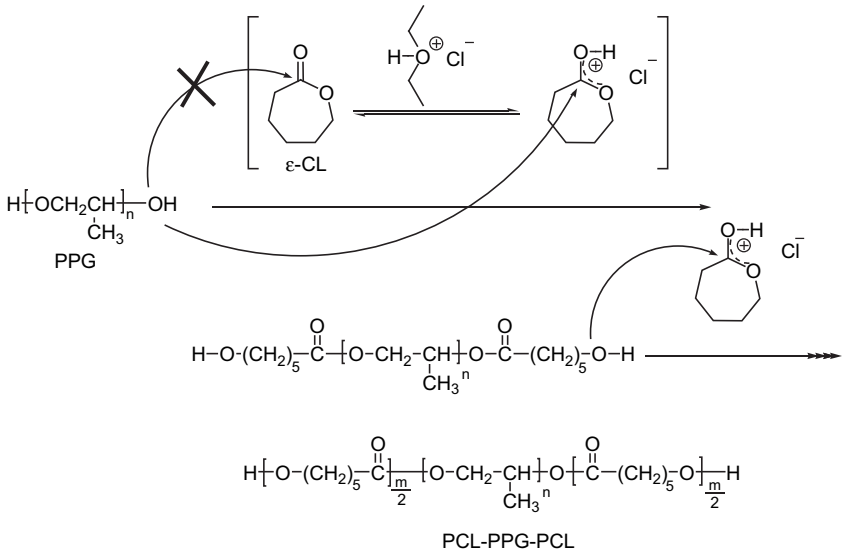


Fig. 3. Kinetics of the ROP of CL initiated by PPG ($M_n = 1000$ g/mol) in CH_2Cl_2 at 25 °C ([CL]/[CH_2Cl_2] = 1 M): (■) $[H^+]_o/[I]_o = 1$ and $k_{app} = 6.05 \times 10^{-4}\ s^{-1}$, (●) $[H^+]_o/[I]_o = 2$ and $k_{app} = 1.122 \times 10^{-3}\ s^{-1}$, (▲) $[H^+]_o/[I]_o = 4$ and $k_{app} = 2.25 \times 10^{-3}\ s^{-1}$, (▼) $[H^+]_o/[I]_o = 8$ and $k_{app} = 3.03 \times 10^{-3}\ s^{-1}$.



Scheme 1.

was monomodal in nature. The final polymer showed a slightly broad polydispersity index (1.28) compared to that of the PCL–PPG–PCL triblock copolymer obtained in the first-feed experiment (1.14). This clearly demonstrated the living nature of the system, even after all the monomer was completely polymerized, thus indicating a restarting of the polymerization process by the second addition of CL monomer to the system.

To investigate the effect of $HCl \cdot Et_2O$ as a monomer activator, the kinetics of CL polymerization were studied as a function of the concentration of $HCl \cdot Et_2O$. Fig. 3 shows kinetic plots obtained for the polymerization of CL at various $HCl \cdot Et_2O$ concentrations (1, 2, 4, and 8 equiv.) with respect to the PPG initiator in CH_2Cl_2 at 25 °C. The $\ln [M]/[M]_o$ versus time plots exhibited linear variations without induction. From the slope of the plots, the values of the apparent rate constant (k_{app}) for the polymerization of CL activated by $HCl \cdot Et_2O$ were estimated as follows: $k_{app} = 6.05 \times 10^{-4}$, 1.12×10^{-3}, 2.25×10^{-3}, and $3.03 \times 10^{-3}\ s^{-1}$, respectively. The value of k_{app} increased upon increasing the $[H^+]_o/[I]_o$ ratio, which indicates that the constant is greatly affected by this ratio. This result strongly indicates that HCl acts as an activator in the ROP of CL. As represented in the plausible polymerization mechanism of Scheme 1, $HCl \cdot Et_2O$ can participate in the carbonyl oxygen of CL. Thus, it was proposed that the polymerization should be proceeded by the nucleophilic attack of the hydroxyl end group to the carbonyl carbon of the protonated CL.

To explore the activation energies (E_a values), the ROP of CL was induced at −17, 0, and 25 °C. The k_{app} values obtained from the slopes of the kinetic plots for the CL polymerization at these temperatures were 7.71×10^{-5}, 1.95×10^{-4}, and $1.12 \times 10^{-3}\ s^{-1}$, respectively. From the linear slope of the $\ln k$ versus $1/T$ in an Arrhenius plot of apparent rate constants, the E_a for the CL polymerization was 49.8 kJ/mol K (Fig. 4).

In conclusion, we have examined the feasibility of ROP of CL by using PPG initiators in the presence of $HCl \cdot Et_2O$ as a monomer activator at room temperature. The PCLs obtained had molecular weights close to the theoretical values, calculated from the CL:PPG molar ratios, and no side reactions were observed. We believe that this ROP system may extend the use of PPG and PCL block copolymers in practical biomedical applications. Further studies to compare the physical properties of PPG/PCL and PEG/PCL block copolymers for practical biomedical applications such as carrier in drug delivery or matrix in tissue engineering are in progress.

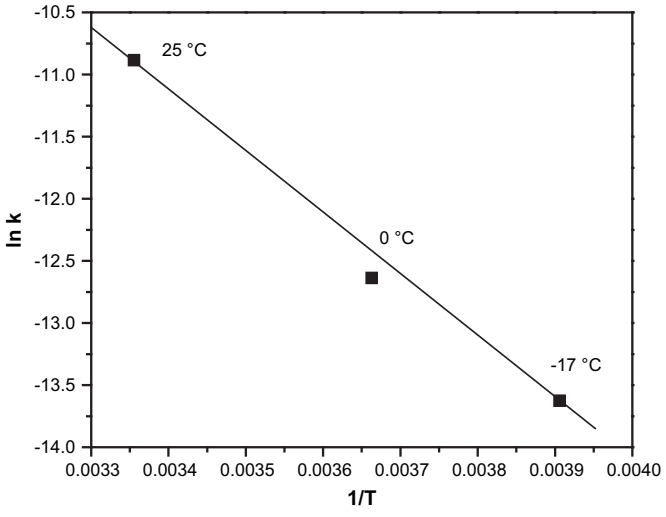


Fig. 4. Relationship between $\ln k$ and $1/T$ in the polymerizations of CL initiated by PPG ($M_n = 1000$ g/mol) in CH_2Cl_2 ($[CL]/[CH_2Cl_2] = 1$ M, $[H^+]_o/[I]_o = 2$; $E_a = 49.8$ kJ/mol K).

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