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Synthesis and Characterization of Poly(ethylene glycol) grafted Poly(ε-Caprolactone)

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Summary

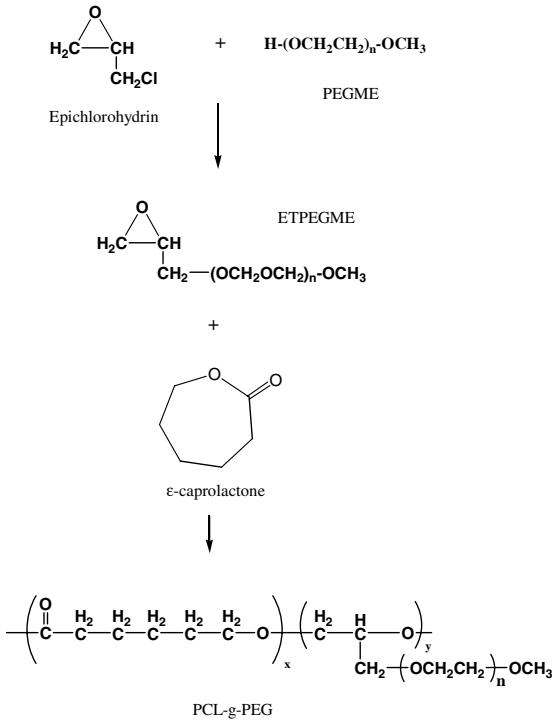
A new graft copolymer, poly(ε-caprolactone) (PCL) grafted with poly(ethylene glycol) (PEG), was prepared by one-pot synthesis of ε-caprolactone and modified PEG. Aluminium isopropoxide or potassium *tert*-butoxide was used as a catalyst for the ring-opening polymerization. Polymerization using potassium tert-butoxide as a catalyst showed very effective graft reaction of PEG onto poly(ε-caprolactone). A slight decrease in the melting temperature was observed with the increase of the PEG graft frequency. Interestingly, considerable changes were observed on the surface property by the introducing PEG side chains compared to that of PCL homopolymer. Measurements of water contact angle showed that the hydrophilic surface of the polymer could be obtained even at a low graft frequency of PEG.

Introduction

Poly(ε-caprolactone) (PCL) is one of the promising materials which can be applied for biomedical applications owing to its good biocompatibility, permeability and degradability [1]. However, its structure often needs to be modified for the taylor-made applications. Previous studies on the copolymerization based on ε-caprolactone showed a difference in degradation rate, mechanical and thermal properties, and drug release profile of the copolymers from the pure PCL [2-6].

Recently, copolymerization of both ε-caprolactone (ε-CL) and a hydrophilic unit is widely studied since it can produce an amphiphilic character of the final product [7,8]. Poly(ethylene glycol) (PEG) is an excellent hydrophilic candidate for biomaterials because of its good biocompatibility showing a resistance of the recognition by the immune system [9]. The copolymerization of ε-CL and PEG has been mainly focused on block copolymers [10-12], rather than graft copolymers. Recently, our group has reported on the preparation and application of novel biodegradable graft copolymers [13-15]. In this study the synthesis of the PEG

grafted PCL (PCL-g-PEG) is attempted by a ring opening polymerization. To understand the one-pot synthesis of the PCL-g-PEG from lactone and epoxide, the effect of catalyst on their copolymerization was also studied.



Reaction Scheme for the synthesis of PCL-g-PEG

Experimental Part

Materials

Poly(ethylene glycol)methyl ethers (PEGME, M_w= 350 and 550) (Aldrich Chemicals, Milwaukee, MO) were vacuum dried for 2days at 60°C before use. ε-Caprolactone (99+% purity) (Aldrich Chemicals) was used without further purification. Epichlorhydrin (99+%) (Aldrich Chemicals) was purified by anhydrous calcium oxide. Potassium *tert*-butoxide (98%) (Aros, USA) and aluminium isopropoxide (99.99+%) (Aldrich Chemicals) were used without further purification. Toluene and dichloromethane (Merck, Darmstadt, Germany) were purified by distillation. $CDCl_3$ (99.8 atom %D) for NMR measurements was purchased from Aldrich. All air and moisture-sensitive reagents and solvents were stored in a glove box (humidity: 0.0905 ppm by volume) under argon atmosphere.

Synthesis of PEGME grafted Poly(ε-caprolactone)

Preparation of the epoxy terminated PEGME is described elsewhere [13]. Synthesis of PEGME grafted poly(ε-caprolactone) was proceeded by a ring opening polymerization

of the epoxy terminated PEGME and ε-caprolactone. ε-Caprolactone was transferred into an argon purged 20ml ampule in a glove box and subsequently the epoxy terminated PEGME and catalyst were introduced. The ampule was sealed in a dry argon atmosphere and placed in a thermosetted oil bath for a preset time to proceed the ring opening polymerization reaction. Polymerization was stopped by adding an excess amount (relative to an initiator) of 1N HCl in methanol solution. The resulting mixture was precipitated into cold methanol or double distilled water to resolve a polymer product. The isolated polymer was washed with water three times and filtered followed by drying in vacuo. The synthesis scheme is shown above.

Measurements

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500 MHz using tetramehtylsilane (TMS) as an internal reference. The GPC analysis was performed using a Waters 660E liquid chromatography system. The sample dissolved in tetrahydrofuran (THF) was injected into the column at 30°C with THF as an eluent at a flow rate of 1.0 ml/min. The molecular weight and molecular weight distribution were calculated from a calibration curve obtained from polystyrene standards (Polysciences Inc, USA).

The thermal properties of the synthesized polymers were measured in hermetically-sealed pans using a differential scanning calorimeter (Du pont 2000 thermal analyzer instrument). Samples of 3-4mgs were loaded in hermetically-sealed cells and measurements were taken over a temperature range from -120 to 150°C at a heating rate of 10°C/min under nitrogen atmosphere.

PEG grafted poly(ε−caprolactone) was dissolved in dioxane and the solution was coated on the surface of a silicon wafer by using a spin coater equipped with teflon plate (1770 rpm, home-made) for 3min. Water contact angles of the coated samples were measured by the optical-bench contact angle goniometer (Model G-23; Krüss GmbH).

Π-A curves were recorded using a Langmuir-Blodgett apparatus (KSV Instruments, Finland, model LB5000) with computerized control at 25°C. A Pt-Wilhelmy balance was used as a surface pressure sensor. Poly(tetrafluoroethylene) (PTFE) trough with inside dimensions of 240 X 340mm was filled with water to its brim. Teflon-coated mobile barrier was used to control the surface area of the film. The precision of the surface pressure measurements was $\pm 0.1 mN \bullet m^{-1}$. Monolayers were spread from chloroform changing the volume of a 0.25mg/mL solution deposited between 60-100 μL. Film compression was started 5min after spreading and continued at a rate of 2.0 cm/min.

Results and Discussion

The copolymers synthesized were characterized by heteronuclear multiple quantum coherence (HMQC) spectroscopy, ^{1}H-^{1}H homo COSY and ^{13}C NMR spectra. Figure 1 shows the representative ^{1}H NMR spectrum of PCL-g-PEG (Entry 10) and the peak assignment.

The characteristic peaks of PCL (1.37, 1.64, 2.30, 4.06 ppm) and methoxy peak of PEGME (3.38 ppm) were clearly observed. The peaks appearing at 4.17 and 4.23 ppm correspond to methylene peaks of the epoxy group which is adjacent to the caprolactone unit. These indicate that PCL-g-PEGs were successfully synthesized.

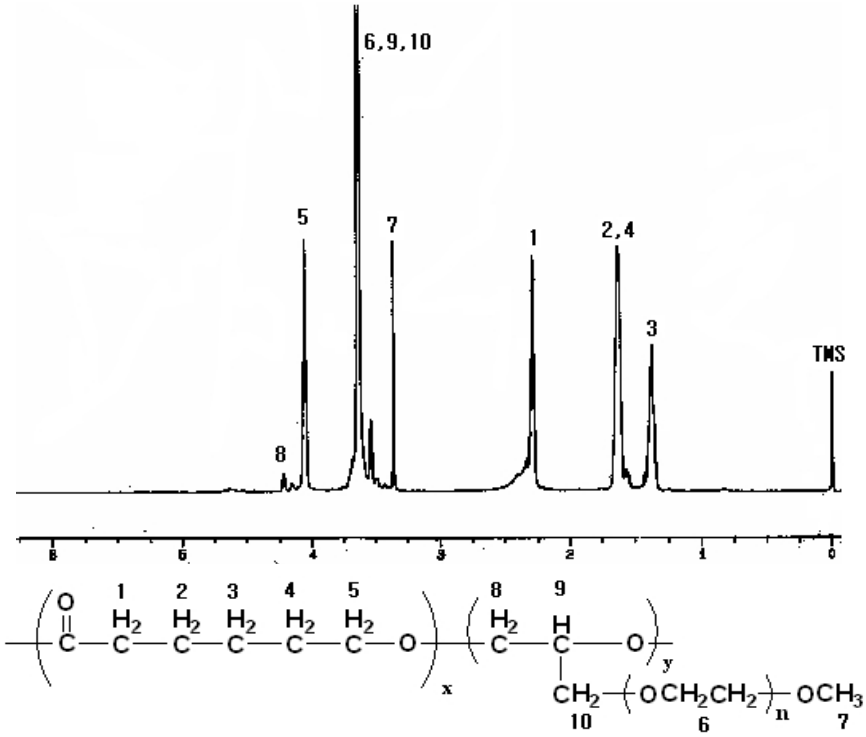


Figure 1. Representative ^{1}H NMR spectrum of PCL-g-PEG (Entry 10).

Table 1 shows the composition of the resulting polymers obtained from the copolymerization using aluminium isopropoxide as a ring-opening catalyst. The graft frequencies of the PEG in the copolymer is calculated with the following equation :

$$\text{Graft frequency} = I_{3.38ppm}/3 \div (I_{3.38ppm}/3 + I_{2.30ppm}/2) \quad (\mathbf{1})$$

where I represents the peak area in the NMR spectra.

Table 1. Bulk Polymerization of ε-caprolactone and the modified PEG initiated by aluminium isopropoxide.

Entry	F_{CL} : $F_{ETPEGME}$ a)	Graft frequency (mol%)	M_w X 10^{-4}	M_w/M_n	$[M]_0/[Al]$	Physical state
1	10 : 0	0	4.3	3.2	50	White powder
2	9 : 1	3.7	3.4	3.0	50	″
3	7 : 3	5.0	2.2	2.6	50	″
4	5 : 5	7.0	1.2	3.5	50	″
5	7 : 3	5.0	1.7	2.3	100	″
6	7 : 3	5.0	2.7	2.7	25	″

a) FCL and ETPEGME represents a mole fraction of ε-caprolactone and modified PEG (epoxy terminated PEGME) in the feed respectively.
* Reaction temperature = 120°C, Reaction Time = 3 hr, M_w of PEGME used is 350.

It is found from Table 1 that with increase of the relative fraction of the modified PEG in the feed up to 50 mol% results in an increase of the graft frequency and a decrease of the molecular weight. Though aluminium alkoxides were reported to be effective in promoting the living polymerization of lactones [16], the graft frequencies are found to be much lower than the fraction of modified PEG in the feed. It is thought that, because of the bulky character of modified PEG, coordination of aluminium alkoxide would be more difficult for the modified PEG than ε-caprolactone. Steric hindrance mechanism of the aluminium alkoxide was also proposed by other group [17].
Entry 3, 5, and 6 show the effect of catalyst amount on the polymerization reaction. The measured PEG graft frequencies are unchanged with catalyst concentration. However, variation of the catalyst concentration could affect the molecular weight of the PCL-g-PEG. The molecular weight increased with increase of the catalyst content in the range studied.
Table 2 shows water contact angle of the prepared polymer. It is found that the water contact angle decreases with increase of the PEG graft frequency. Even a small amount of graft PEG could contribute to producing a hydrophilic surface. This indicates that the advantage of graft structure, which has a high chain mobility due to its high free volume, is to effectively increase the surface hydrophilicity.
Table 3 summarizes the ring opening polymerization results of ε-caprolactone and the modified PEG initiated by potassium *tert*-butoxide. A higher graft yield was obtained when potassium *tert*-butoxide was used as a catalyst except for Entry 8. Entry 8 was prepared by solution polymerization in toluene and showed rather a low graft frequency. It represents that the bulk polymerization using potassium tert-butoxide is more efficient for enhancing the graft frequency. From these results, it is anticipated that the propagation reaction based on potassium *tert*-butoxide is different from that based on aluminium isopropoxide. Even when the longer modified PEG based on PEGME 550 was used for polymerization (Entry 10), the copolymerization of ε-caprolactone and modified PEG was very successful, indicating that potassium *tert*-butoxide makes the propagation reaction relatively free from steric hindrance of the bulky monomer group.

Table 2. Water contact angles for PCL-g-PEG.

	Entry 1	Entry 3	Entry 4
Graft frequencies	0	5.0	7.0
Contact angle (θ)	74^{o}	24^{o}	15^{o}

Figure 2 shows Π−A curves for PCL homopolymer (Tone® 787, Union Carbide) and PCL-g-PEGs. The same Π−A curves were obtained for the purchased PCL homopolymer and the synthesized PCL homopolymer (Entry 1). For comparison, the similar experimental conditions on Π-A to the previous works on poly(DL-lactic acid-co-glycolic acid) (PLGA) were chosen in this work [18]. The compressed monolayer of the synthesized PCL homopolymer is shown to collapse at the surface pressure of about 12 $mN \bullet m^{-1}$. PCL-g-PEG showed a similar pattern at the initial stage (region AB), however, from the point B it showed a plateau region (region BC) rather than a collapse. Considering the similarity in the appearance of plateau region between PCL-g-PEG and PLGA, the plateau region can be interpreted as a result of orientational changes of the polar groups of polymers at the interface between air and water phases [18].

Table 3. Ring opening polymerization of ε-caprolactone and modified PEG initiated by potassium tert-butoxide.

Entry	F_{CL} : $F_{ETPEGME}$	Graft frequency (mol%)	M_w X 10^{-4}	M_w/M_n	Physical state
7	7 : 3	23.0	0.4	2.2	Yellowish waxy-like powder
8 [a)]	7 : 3	5.0	1.8	1.7	Yellowish powder
9 [b)]	7 : 3	25.4	0.5	2.1	Yellowish waxy-like powder
10 [c)]	8 : 2	18.2	0.8	2.2	Yellowish wax

a) Reaction was conducted in toluene at 60°C.
b) Reaction Temperature was 150°C .
c) Modified PEG based on PEGME with molcular weight of 550 was used.
* General condition : Reaction temperature = 120°C, Reaction time = 10hr, M_w of PEGME used = 350, $[M]_0$/[catalyst]=50.

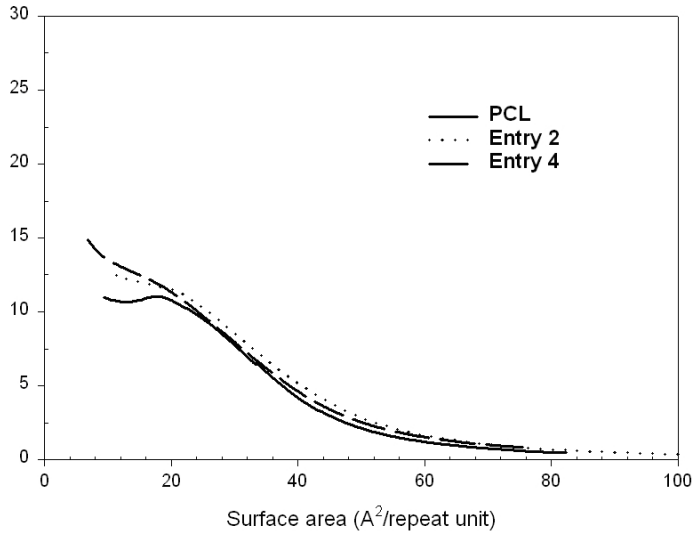


Figure 2. Π-A isotherms of PCL and PCL-g-PEG obtained at 25°C.

Figure 3 shows the typical DSC thermograms of PCL-g-PEGs, and the results are summarized in Table 4. With increase of the graft frequencies, the melting temperatures are found to decrease. However, this decrease in the melting temperature is not so significant as in the case of polylactide grafted with PEG [13]. Since five methylene units in the ε-caprolactone provide a higher hydrophobicity than the lactic group, PEG does not seem to effectively disrupt the PCL main chain crystalline phase, which can cause a different thermal behavior of PCL-g-PEG from the polylactide grafted with PEG which is previously reported by our group. The crystallinity of the PCL-g-PEG decreased with the increase of the graft frequency as in the case of melting temperatures. For the case of using longer modified PEG showed the melting endotherm of the grafted PEG (Entry 10) which is observed at 18°C as in Figure 3 [19].

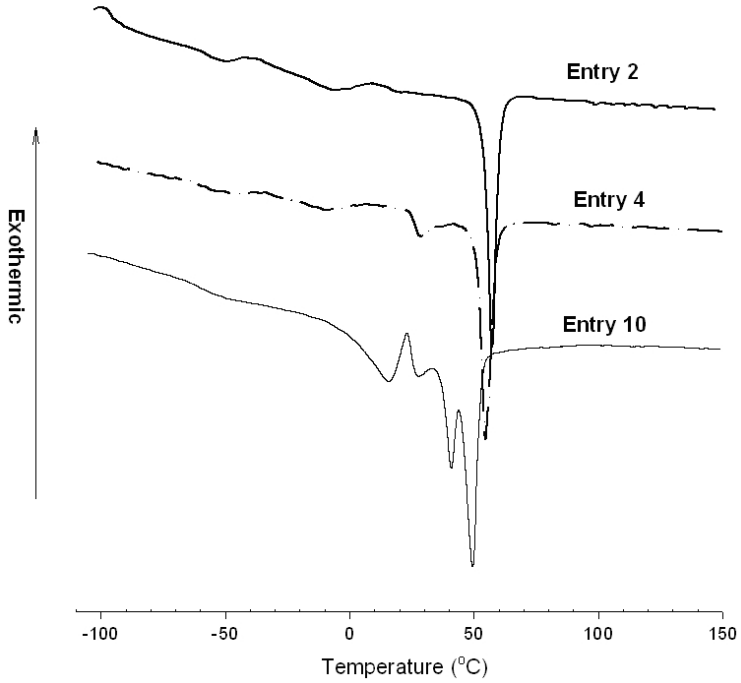


Figure 3. DSC Thermograms of PCL-g-PEG (Entry 2,4, and 10).

Table 4. Thermal properties of PCL-g-PEG.

Entry	1	2	3	4	5	6	7	8	9	10
T_m (°C)	63	63	58	56	58	58	53	57	53	48
[a)] X_c (%)	52.0	47.8	43.8	41.5	44.0	46.1	38.3	42.0	38.1	32.7

a) Represents the crystallinity of the PCL crystalline region. Crystallinity was calculated on the base of 139.5 J/g for 100% crystalline PCL [20]

Conclusions

The synthesis and characterization of PEG grafted PCL are successfully demonstrated. The PCL-g-PEG showed rather different thermal and surface characteristics from PCL and PLLA-g-PEG. A high graft frequency of PEG side chain could be obtained by using potassium tert-butoixde as a ring opening polymerization catalyst.
It can be suggested that our new amphiphilic graft structured polymer prepared from biocompatible monomeric unit can be a good candidate material for the application in the biomedical field.

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