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Novel Synthesis of Reactive Poly(ethylene glycol) grafted Poly(L-lactide) via Two Step Polymerizations

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Summary

Novel poly(L-lactide)-*graft*-poly(ethylene glycol) having reactive group at the end of grafted chain was prepared by two step polymerizations: ring-opening polymerization of L-lactide and 1,2-epoxy-5-hexene followed by radical polymerization of the product of ring-opening reaction and poly(ethylene glycol) methacrylate. $Al(Et)_3 \cdot 0.5H_2O$ and AIBN were used as catalyst and initiator for the two step polymerizations respectively. The structure of the synthesized polymers was also characterized.

Introduction

Poly(L-lactide) (PLLA), which is biocompatible and biodegradable polymer, has been mainly focused on its application to the matrix for the drug delivery system [1], tissue engineering [2], and medical sutures [3, 4]. It is well known that PLLA shows good biocompatibility and ready resorbance in living tissue [5, 6]. However, high crystalinity and low hydrophilicity of PLLA reduce its degradation rate and result in its poorer compatibility with soft tissue [7]. To overcome these problems, our group synthesized novel graft copolymer, which was mono methoxy poly(ethylene glycol) grafted poly(L-lactide) (PLLA-*g*-mPEG) [8]. However, there is still a need to give a reactivity to the chain end of this graft polymer in order that it can be used as a complexing agent of drugs in drug delivery systems.

One approach to give a reactive poly(ethylene glycol) (PEG) to PLLA is the reactive extrusion of PLLA with poly(ethylene glycol) methacrylate (PEGMA). The second one to introduce reactive PEG to PLLA is based on the protection of hydroxyl group contained in cyclic monomer [9, 10]. After ring-opening polymerization of lactide and the protected monomer, the deprotection of hydroxyl group is performed for further reaction with PEG derivatives. However, these processes have several drawbacks: In the first approach, PLLA chain may be degraded during the reactive extrusion. In the case of using the protected monomer, it is difficult to introduce the high content of the PEG in the PLLA, since only a single PEG unit can be grafted to each main chain [9, 10].

In this paper, we report on the novel synthesis of PLLA grafted with PEG having a reactive group, wherein the content of the reactive PEG can be easily controlled in a desired range possibly without degradation during radical polymerization process [11].

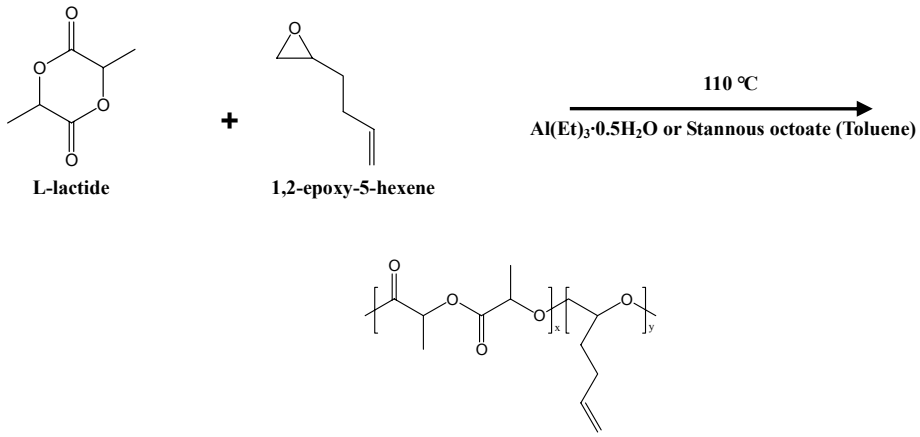
Experimental part

Preparation of materials

The catalyst, $Al(Et)_3 \cdot H_2O$ for the effective ring-opening copolymerization of L-lactide and 1,2-epoxy-5-hexene [12] was prepared as follows [13, 14]: 20 mmol triethyl-aluminium (in dry toluene, purchased from Aldrich) was transferred to a 20 ml vial. The solution was cooled in external methanol bath (-50 °C) followed by slow addition of a solution of 10 mmol of distilled water in 1,4-dioxane (1/9 v/v) with vigorous stirring. After 15 min of stirring, the bath was removed and the temperature was increased to ambient temperature with stirring for 10 h. A clear solution was formed and stored in the refrigerator (about 4 °C) before use. For reference catalyst, stannous octoate was purchased from Aldrich, and used as received.
L-lactide, 1,2-epoxy-5-hexene and poly(ethylene glycol) methacrylate (M_n=360) were purchased from Aldrich. L-lactide was purified by recrystallization, and 1,2-epoxy-5-hexene and poly(ethylene glycol) methacrylate were dried over sodium hydride for 48 h at room temperature prior to use. AIBN, initiator for radical polymerization was purchased from Kanto Chemical, and used as received. Tetrahydrofuran and toluene were purchased from Merck, and purified by distillation with sodium metal. All other chemicals were ultra high purity, and used without further purification.

Ring-opening polymerization

The scheme of ring-opening polymerization of L-lactide and 1,2-epoxy-5-hexene is shown below.

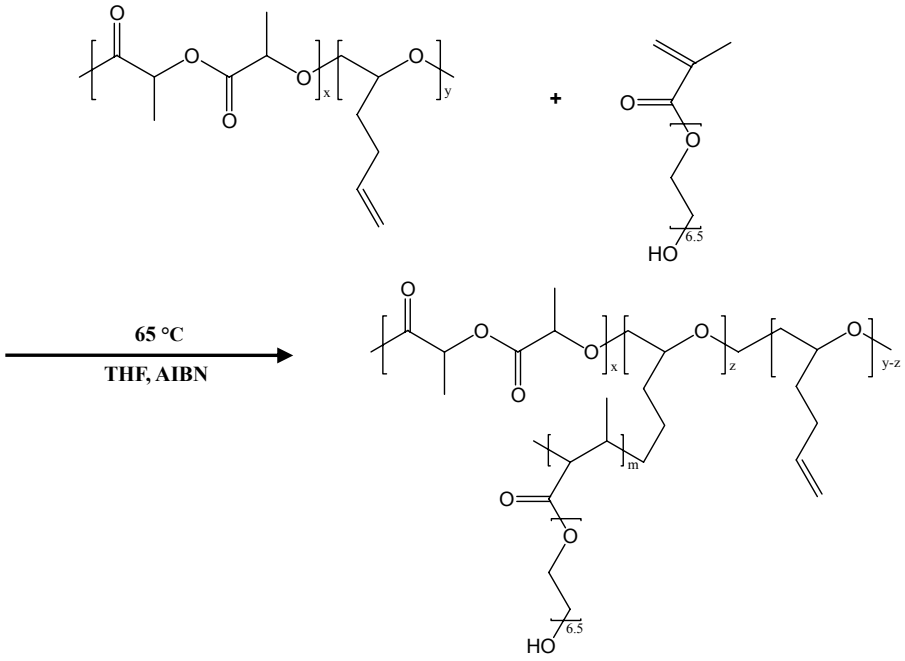


L-lactide and 1,2-epoxy-5-hexene dissolved in dry toluene were transferred into a 100 ml round bottomed flask in a glove box which was purged with dry argon and then catalyst dissolved in dry toluene were transferred into the flask. The round

bottomed flask was sealed under argon atmosphere and placed in a temperature-controlled oil bath. After the reaction with preset time, the product was precipitated and washed in diethyl ether three times, and the tetrahydrofuran was added to remove homopolymer of 1,2-epoxy-5-hexene. The solution was filtered and a clear solution was obtained. The polymer product in the solution was precipitated with diethylether, and the product was vacuum dried at 70 °C for 24 h to remove the residual solvent.

Radical polymerization

The radical polymerization reaction scheme is shown below.



The preformed polymer produced by ring-opening polymerization and poly(ethylene glycol) methacrylate dissolved in dry tetrahydrofuran were transferred into 100 ml round bottomed flask in the temperature-controlled oil bath with a preset temperature and dry nitrogen purging. AIBN dissolved in dry tetrahydrofuran was then transferred into the flask and the radical polymerization was processed for a preset time of reaction. The product was filtered to remove crosslinked polymer. The filtrate was precipitated and washed with methanol three times, and vacuum dried for 24 h to remove residual solvent.

Characterization

The structures of the synthesized copolymer were characterized using proton nuclear magnetic resonance spectroscopy (Bruker-AMX-500 NMR spectrometer, Bruker). For NMR experiment, the polymer solution (5 wt-%) was prepared with chloroform-d.

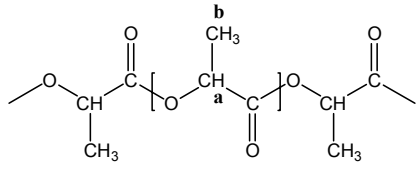
The molar ratio of L-lactide, 1,2-epoxy-5-hexene and PEGMA in the graft copolymer sample was determined from the peak area of the protons of each component in the ^{1}H NMR spectra.

Measurements of molecular weight of polymers were performed by gel permeation chromatography (Waters 410 differential refractometer, Waters^{TM} 600 pump). Ultrastyragel columns with HR1, HR2, HR4 were placed in a series. Tetrahydrofuran was used as the eluent at a flow rate of 1.0ml/min. The injection volume was 200µl, and sample concentration were normally ~0.5 % (w/v). Polystyrene standards with a low dispersity (Waters) were used to make a calibration curve.

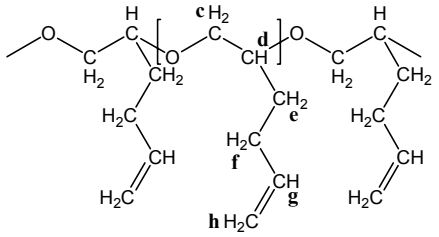
Results and Discussion

Structure of L-lactide, 1,2-epoxy-5-hexene Copolymers

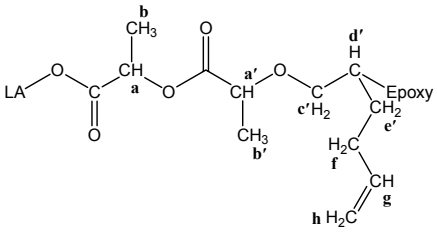
The copolymers obtained by ring-opening polymerization were characterized by ^{1}H NMR, ^{1}H-^{1}H NMR correlated spectroscopy. Figure 1 shows the 1D and 2D ^{1}H NMR spectrum and the assignments of each peak corresponding to the protons in L-lactide, 1,2-epoxy-5-hexene copolymer.



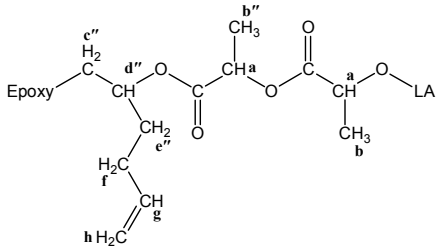
(a)



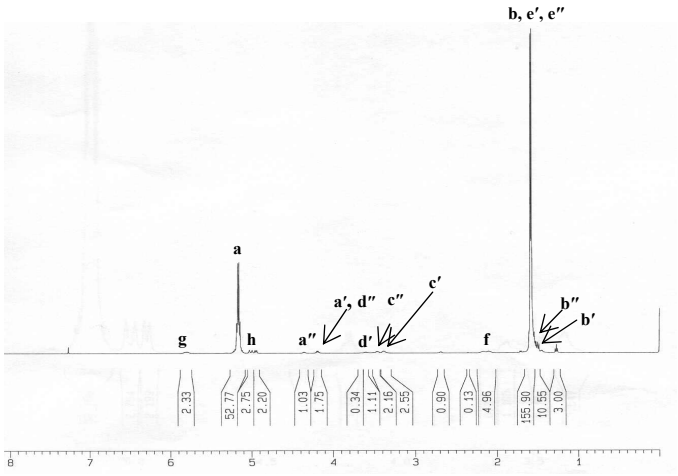
(b)



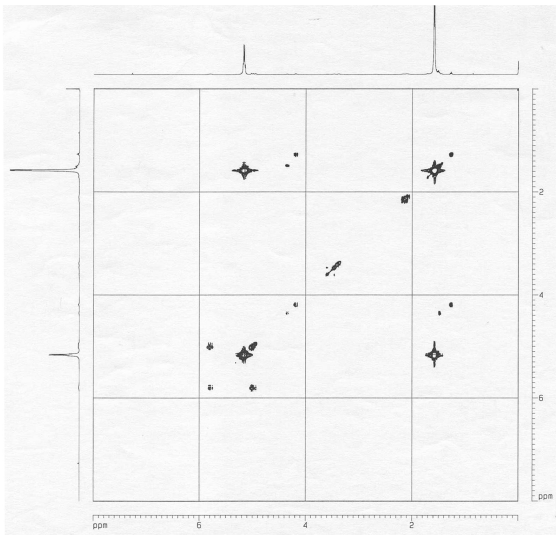
(c)



(d)



(e)



(f)

Figure 1. 500 MHz 1D and 2D ^{1}H NMR spectrum of poly(L-lactide-*co*-1,2-epoxy-5-hexene) and peak assignments.

The most intense ^{1}H-NMR signals at 5.21, 1.62 ppm were assigned (see Figure 1(a)) on the basis of previous work [10]. The relatively weak signals of c, d, e, f, g, h in Figure 1(b) were assigned from homopolymer of poly(1,2-epoxy-5-hexene). Assignments of protons a′(a″), b′(b″), c′(c″), d′(d″), e′(e″) shown in Figure 1(c), (d) were made on the basis of careful inspection of the ^{1}H-^{1}H COSY 2D NMR. Specifically, cross peaks were found as follows: (1.45, 4.38), (1.55, 4.15), (1.59, 4.38), (1.59, 3.38), (1.59, 3.61). The molar composition of 1,2-epoxy-5-hexene in the copolymers was determined by following equation:

$$Butene\ Content(mol-\%)=\frac{A_{4.99\sim5.02}/2}{A_{4.99\sim5.02}/2+A_{5.12\sim5.22}}\times100$$

To determine the effective catalyst for ring-opening polymerization of L-lactide and 1,2-epoxy-5-hexene, we performed the ring-opening polymerization with two different catalysts, $Al(Et)_3{\cdot}H_2O$ and stannous octoate. Table 1 shows the calculated molar composition of 1,2-epoxy-5-hexene and it is clear that $Al(Et)_3{\cdot}H_2O$ is more effective for introducing the epoxy-derivative unit into the copolymer and this result is good agreement with previous ones [8, 12]. $Al(Et)_3{\cdot}H_2O$ was thus used as a catalyst for performing a series of ring-opening polymerization in this work.

Table 1. Ring-opening copolymerization of L-lactide and 1,2-epoxy-5-hexene

Entry	Reaction Time [hr]	$F_l^{(a)}/F_e^{(b)}$	Butene Contents [mole-%]	M_n	PDI	T_g [°C]	T_m [°C]	Catalyst[(c)]
1	12	50/50	7.0	15500	2.5	52	146, 158	$AlEt_3{\cdot}0.5H_2O$
2	24	50/50	7.4	16000	2.6	52	145, 160	$AlEt_3{\cdot}0.5H_2O$
3	36	50/50	8.1	16200	2.7	51	141, 149	$AlEt_3{\cdot}0.5H_2O$
4	36	50/50	4.3	13800	2.1	52	143, 150	Stannous Octoate
5	36	70/30	4.0	17000	2.0	52	144, 151	$AlEt_3{\cdot}0.5H_2O$

(a) Feed mole of L-lactide, (b) Feed mole of 1,2-epoxy-5-hexene, (c) [monomer]/[catalyst]=100
* Reaction temperature: 110 °C

Structure of Poly(L-lactide)-g-poly(ethylene glycol)

The graft copolymers obtained by radical polymerization were characterized by ^{1}H-NMR. Since the PEGMA, 1,2-epoxy-5-hexene, and their homopolymers were soluble in methanol (non-solvent for poly(L-lactide-*co*-1,2-epoxy-5-hexene)), the precipitates of radical polymerization product in methanol must be a PEG containing aliphatic polyester (PLLA-*g*-PEG). Figure 2 shows the ^{1}H NMR spectrum of PLLA-*g*-PEG. The peak assignments of the PLLA-*g*-PEG were performed by comparison of the ^{1}H NMR spectrum of poly(L-lactide-*co*-1,2-epoxy-5-hexene) (PLLA-*g*-butene) with that of PLLA-*g*-PEG and previous works [8, 10]. The molar composition of PEGMA in the graft copolymers was determined by following equation:

$$PEG\ Content(mol-\%)=\frac{(A_{4.1}-0.0283\times A_{5.12\sim5.22}+A_{3.60\sim3.80})/26}{(A_{4.1}-0.0283\times A_{5.12\sim5.22}+A_{3.60\sim3.80})/26+A_{5.12\sim5.22}}\times100$$

The proton peaks of oxyethylene unit of PLLA-*g*-PEG are overlapped with proton peaks of methine unit of PLLA-*g*-butene. Thus, the separation of overlapped peak is needed to calculate the molar ratio of each proton. The terms in equation 2 is based on the peak fitting of the overlapped peaks. Table 2 shows the effect of the amount of initiator on the PEG content. The PEG content is found to increase with decrease in the AIBN content. This is due to the higher degree of radical polymerization at a lower AIBN content. It is also evidenced by the amount of unreacted butene unit. With an increasing initiator concentration, the unreacted butene unit is decreased.

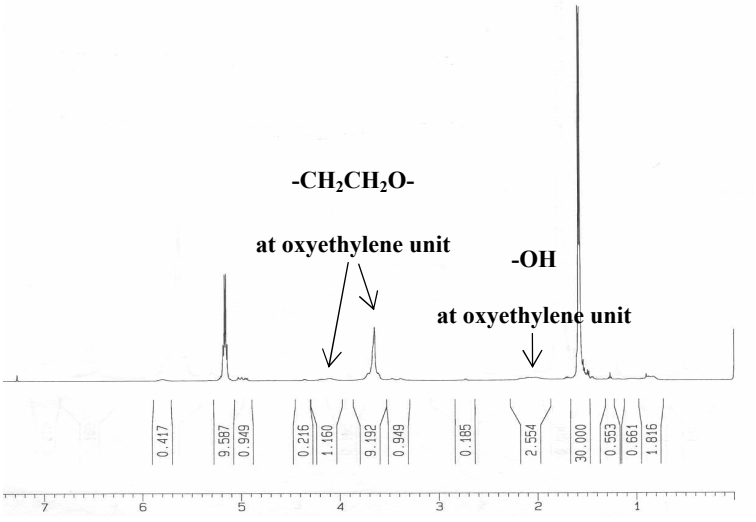


Figure 2. 500 MHz ^{1}H NMR spectrum of poly(L-lactide)-*graft*-poly(ethylene glycol) and peak assignments.

Table 2. Radical polymerization of poly(L-lactide-*co*-1,2-epoxy-5-hexene) and poly(ethylene glycol) methacrylate

Entry	Prepolymer [g]	PEGMA [g]	AIBN [mg]	Butene Remaining[a] [mol-%]	PEG Contents [mol-%]
7	0.5	1	2.2	83.8	18.0
8	0.5	1	7.3	74.3	5.2
9	0.5	1	22	69.8	4.6
10	0.5	1	33	67.0	4.1

a) Calculated from ^{1}H-NMR spectrum
* Reaction Time: 17 hr, * Reaction Temperature: 65 °C, * Prepolymer: Entry 5 [4mol-% butene]

Conclusion

The novel reactive poly(ethylene glycol) grafted poly(L-lactide) was successfully synthesized and the structure was completely characterized.
Two steps were introduced for the novel polymer synthesis: ring-opening and radical polymerization, which is relatively simple compared with another approaches to synthesize functionalized PLLA-*g*-PEG. It has also advantage that the PEG content in the copolymer can be controlled possibly without the decomposition of PLLA chain during radical polymerization.
The novel functionalized PLLA-*g*-PEG is expected to apply to the drug delivery systems based on chemical conjugation of drugs and also to the biodegradable functional substrate for the bioengineering filed.

Acknowledgements

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