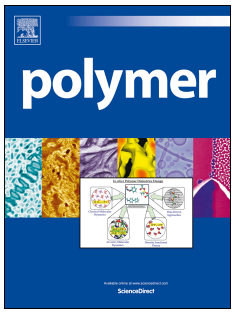
Accepted Manuscript



Synthesis of poly(L-lactide-*co*-5-amino-5-methyl-1,3-dioxan-2-ones)[P(*L*-LA-*co*-TAc)] containing amino groups via organocatalysis and post-polymerization functionalization

Peng Dong, Hao Sun, Daping Quan

PII: S0032-3861(16)30463-3

DOI: 10.1016/j.polymer.2016.05.064

Reference: JPOL 18725

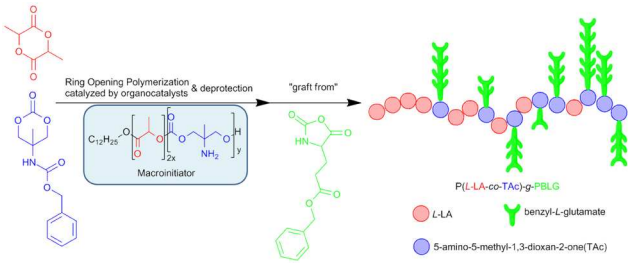
To appear in: *Polymer*

Received Date: 7 March 2016

Revised Date: 21 May 2016

Accepted Date: 24 May 2016

Please cite this article as: Dong P, Sun H, Quan D, Synthesis of poly(L-lactide-*co*-5-amino-5-methyl-1,3-dioxan-2-ones)[P(*L*-LA-*co*-TAc)] containing amino groups via organocatalysis and post-polymerization functionalization, *Polymer* (2016), doi: 10.1016/j.polymer.2016.05.064.



Synthesis of poly(*L*-lactide-*co*-5-amino-5-methyl-1,3-dioxan-2-ones)[P(*L*-LA-*co*-TAc)] containing amino groups via organocatalysis and post-polymerization functionalization

*Peng Dong, Hao Sun and Daping Quan**

PCFM Lab, GD HPPC Lab, School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, China

*To whom correspondence should be addressed.

TEL (86) 020-84114030

FAX (86) 020-84112245

E-mail: cesqdp@mail.sysu.edu.cn

Abstract

Poly(*L*-lactide-*co*-5-benzyloxycarbonylamino-5-methyl-1,3-dioxan-2-ones) (P(*L*-LA-*co*-TMAc)) containing amino groups were synthesized by the ring-opening polymerization of *L*-lactide(*L*-LA) and 5-benzyloxycarbonylamino-5-methyl-1,3-dioxan-2-one (TMAc), which was catalysed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in solution or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in bulk. Followed by deprotection under acidic conditions, deprotected copolymer poly(*L*-lactide-*co*-5-amino-5-methyl-1,3-dioxan-2-ones)[P(*L*-LA-*co*-TAc)] was prepared. Compared to polymerization reactions catalysed by stannous octoate ($Sn(Oct)_2$), a metallic catalyst, organocatalysts showed precise control over the composition and polydispersity index of the copolymers. Proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR), gel permeation chromatography (GPC) and differential scanning calorimetry (DSC) analyses confirmed the polymeric structure and sequence distribution of the product, which indicated that *L*-LA and TMAc formed random copolymers. Relatively longer P*L*LA segments were incorporated into the copolymer during the initial polymerization period due to differences in the reactivity of the two monomers, especially in the DBU-catalysed system. And copolymers with gradient property were obtained. The amino bearing deprotected copolymers served as macro-initiator of the subsequent ROP of benzyl-*L*-glutamate-N-carboxyanhydride(BLG-NCA). Finally, the multi-composite graft copolymer P(*L*-LA-*co*-TAc)-*g*-PBLG was obtained through post-polymerization functionalization.

Introduction

Traditional aliphatic polyesters based on *L*-lactic acid are widely used as drug delivery carriers

and tissue engineering scaffolds due to their excellent biocompatibility and mechanical properties[1,2]. However, these types of polyesters do not contain reactive groups for further modification. To introduce functional groups into polyesters, post modification procedures must be conducted, or functionalization must be performed at the beginning of the synthetic procedure. Regarding post modification, polyesters can be treated with a plasma after moulding to generate reactive groups[3,4] or can be coated with the desired functional material[5]. However, limited functional groups were incorporated, depending on the strength of the plasma[6–8], and the chemical groups distributed only on the surface of the material. In addition, the coating layer may peel off, especially in cell culture environments. To introduce functionality in the beginning of the synthetic procedure, the ring-opening polymerization (ROP) of lactides or glycolides can be performed using cyclic monomers with reactive functional groups[9–11]. The content and distribution of reactive groups in the copolymer chain can be conveniently controlled by changing the feed ratio of the co-monomers. The chain sequences and topography of the copolymer can also be designed and fabricated beforehand.

For functionalization of polyesters, cyclic carbonate monomers bearing reactive groups are generally adopted to copolymerize *D*,*L*/*L*-lactide and ε-caprolactone (ε-CL) due to their ease of preparation[12,13]. Various poly(ester-carbonate)s containing functional groups such as acryloyl[14], azido[15], halogen[16,17], propargyl[18,19], hydroxyl[20,21], carboxyl[22], amino[23,24] and vinyl-sulfone[25] moieties have been designed and synthesized. Xiuli Hu started with serinol to prepared cyclic carbonate bearing amino groups. And the monomer was copolymerized with *L*-lactide by catalysis of unstable diethyl zinc. RGD peptide was conjugated

to deprotected copolymer facilitating better cell performance[23]. Jinliang Yan used trans-4-aminocyclohexanol to prepare lactone containing amino groups. The functional lactone copolymerized with ε-caprolactone(ε-CL) by catalysis of $Sn(Oct)_2$. After deprotection, biotin was attached to the copolymer[24]. Compared to complex synthetic routes for the formation of functionalized lactones[9,26], such as morpholine-2,5-dione derivatives[27,28], simpler synthetic procedures and superior controllability of the polymerization reaction are achieved in the functionalization of cyclic carbonates. Thus, the polymerization of functionalized carbonates has received significant attention in recent years [29,30].

Stannous octoate ($Sn(Oct)_2$) is a general catalyst approved by the FDA for use in ROP. Several functionalized poly(ester-carbonate)s have been synthesized using $Sn(Oct)_2$ as a catalyst at high temperatures (>100 ^{o}C) and long reaction times (>24 h), either in bulk or in solution. The incorporated carbonate monomer ratios were closely aligned with the feed ratios, especially carbonate monomers containing stable and unprotected reactive groups, such as acryloyl[14] or azido[31]groups. However, cyclic carbonate monomers with benzyl- and benzoic-protected groups showed poor tolerance for the required high temperatures and long reaction times. Because side reactions such as transesterification or cross-linking could occur under the conditions. As a consequence, composition of the functional copolymer could derivated far form feed ratio[32]. Moreover, trace amounts of tin might be harmful for applications in biomedical fields[33]. Thus, a suitable catalyst system must be selected to synthesize functional poly(ester-carbonate)s.

The development of organocatalysts used in ROP provides more options for controlling the

copolymerization of functional cyclic carbonates and lactones under mild conditions[34,35]. Organocatalysts such as pyridine bases[36], N-Heterocyclic carbenes (NHCs)[37,38], amidines[15], guanidines[39] and organic acids[40] have shown excellent catalytic activity and can be easily removed from the system. One of the key issues for organocatalysts used in ROP is their controllability to synthesize copolymer with composition similar to feed ratio. Recently, Aline et al.[40] studied the sequential and simultaneous copolymerization of ε-caprolactone (ε-CL) and trimethylene carbonate (TMC) using methanesulfonic acid as catalyst. They proposed formation of gradient copolymers (P*CL-co*-PTMC). In fact, in the preparation of poly(ester-carbonate)s via an organocatalyst, the reactivity ratio of cyclic carbonate monomers was significantly different from that of the lactone, and statistically random poly(ester-carbonate) copolymers were difficult to produce. Moreover, differences in the microstructure have a significant impact on the thermal and mechanical properties of copolymers.And the heterogeneous distribution of reactive groups along the main polymer chain also affect modification of fucntinal groups. However, until now, in-depth studies on these important attributes have been not performed.

Thus, in the present investigation, we aimed to optimize the polymeric system applying 1,8-diazabicyclo undec-5-ene (DBU) and 1,5,7-triazabicyclo [4.4.0] dec-5-ene (TBD) as organocatalysts. Our work included the selection of the catalysts, exploring the microstructure and determining their effects on the copolymers of *L*-lactide (*L*-LA) and 5-benzyloxycarbonylamino-5-methyl-1, 3-dioxan-2-one (TMAc). Our purpose was synthesis of a series of amino-containing poly(ester-carbonate) copolymers with well-defined sequences through

simultaneous and sequential copolymerization from *L*-LA/TMAc. Based on the proposed system, post-polymerization functionalization was carried out by grafting poly(*γ*-benzyl-*L*-glutamates) (PBLG) onto amino-containing macro-initiator P(*L*-LA-*co*-TAc). The post-functionalization was carried out in a 'graft from' method by ROP of benzyl-*L*-glutamate-N-carboxyanhydrides (BLG-NCA). Finally, a comb-like copolymer was obtained, which exhibited interesting behaviour in different solvents.

Experimental sections

Materials

Benzyl chloroformate (≥99.5%), 2-amino-2-methyl-1,3-propanediol (AMPD, ≥99.0%) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) were purchased from Acros. Stannous octoate ($Sn(Oct)_2$ 96%) was purchased from Alfa Aesar, and ethyl chloroformate (≥99.5%) was purchased from Energy Chemical, Shanghai. The above-mentioned reagents were used as received. *L*-Lactide(*L*-LA) was purchased from Foryou Medical Devices Co., LTD, Huizhou, and was recrystallized twice from dry ethyl acetate. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 99%) was purchased from Acros and distilled under vacuum over CaH_2. Dodecanol (97%) was purchased from Alfa Aesar and was dried using 4 Å molecular sieves. Sodium bicarbonate, anhydrous magnesium sulfate and sodium chloride were obtained from Guangzhou, a chemical reagent manufacturer. Ethyl acetate, anhydrous diethyl ether and n-hexane were purchased from Fuyu chemical, Tianjin. Tetrahydrofuran (THF) was distilled in the presence of calcium hydride prior to use. Triethylamine (Et_3N) was sequentially distilled over phthalic anhydride and calcium hydride. Toluene and dichloromethane (DCM) were distilled with calcium hydride and were stored in the

presence of 4 Å molecular sieves.

Measurements

^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained in deuterated chloroform ($CDCl_3$, 99.5 atom % D with 0.03% v/v TMS), DMSO-d_6 (D, 99.9%+0.03% v/v TMS) or a mixture of deuterated chloroform and trifluoroacetic acid-d (for graft copolymers, v/v=90/10) using a Mercury-Plus 300 spectrometer (Varian, Inc. America).

Gel permeation chromatography (GPC) measurements were performed on a Waters 1525 binary high pressure liquid chromatography (HPLC) pump equipped with 3 Ultra Styragel columns and a Waters 2414 refractive index detector (Waters Alliance GPC2000, Waters Corporation, America). To characterize the copolymers, THF was used as an eluent at a flow rate of 1 mL/min at 40^{o}C. The number-averaged molecular weight (M_n) and polydispersity index (PDI) were calculated using Waters GPC Software, and narrowly dispersed polystyrenes were employed as calibration standards. To characterize the graft copolymers, DMF containing 0.5% LiBr was used as an eluent at a flow rate of 1 mL/min at 40℃. The number-averaged molecular weight (M_n) and polydispersity index (PDI) were calculated using Waters GPC Software, and narrowly dispersed polyethylene oxide (PEO) was employed as calibration standards.

The thermal properties of the polymers were determined on a TA Instruments Q10 Differential Scanning Calorimeter (DSC). The enthalpy (cell constant) and temperature were calibrated by running high-purity indium and gallium standards under conditions identical to those used to measure the samples.

Monomer synthesis. 5-Benzylcarbonylamino-5-methyl-1,3-dioxan-2-one (TMAc) was prepared in two steps, according to the method of Xiabing Jing and coworkers, with several modifications[41]. Briefly, benzyl chloroformate (16.2 mL, 104 mmol) was dissolved in THF, and the resulting solution was added dropwise into a 1 M sodium bicarbonate solution of AMPD (10 g, 95 mmol). The mixture was stirred for one day at room temperature. Subsequently, the THF was removed by rotary evaporation under vacuum, and the residues were extracted with ethyl acetate (3×200 mL). The organic phase was collected to afford the crude product, which was recrystallized from ethyl acetate/n-hexane to obtain the product as white crystals (AMPD-Cbz, 18.6 g, 77.8 % yield): ^{1}H NMR(300 MHs, $CDCl_3$): δ =7.35-7.40（s, -$CH_2C_6\mathbf{H}_5$, 5H）, 5.05-5.10 (s, -C$\mathbf{H}_2C_6H_5$, 2H), 3.6-3.7 (d, HOC$\mathbf{H}_2$C[CH_3]-, 2H), 3.75-3.85 (d, HOC$\mathbf{H}_2$C[CH_3]-, 2H), 1.20 (s, $HOCH_2C$[C$\mathbf{H}_3$]-, 3H) ppm.

Dried Et_3N (14.46 mL, 40 mmol) in 50 mL of anhydrous THF was added dropwise to a solution of ethyl chloroformate (8.74 mL, 40 mmol) and AMPD-Cbz (10 g, 37.7 mmol) over 2 hours in an ice bath. The reaction was performed at room temperature for another 8 hours after Et_3N addition. Next, the mixture was filtered, and the filtrate was concentrated. The crude product was recrystallized twice from THF/diethyl ether to obtain the product as pale white crystals (7.9 g, 71.3 % yield). ^{1}H NMR (300 MHs, $CDCl_3$): δ =7.35 (s, -$CH_2C_6\mathbf{H}_5$, 5H), 5.13-5.23 (br, -C[CH_3]N**H**CO, 1H), 5.09 (s, -C$\mathbf{H}_2C_6H_5$, 2H), 4.63 (d, -COOC$\mathbf{H}_2$C[CH_3]-, 2H), 4.19 (d, -COOC$\mathbf{H}_2$C[CH_3]-, 2H), 1.43 (m, -C[C$\mathbf{H}_3$]NHCO-, 3H) ppm.

Typical Procedure for the random copolymerization of *L*-LA and TMAc catalysed by DBU in DCM. The random copolymerization of *L*-LA and TMAc was conducted in DCM. Specifically, 0.206 g of TMAc (0.74 mmol), 1.0 g of *L*-LA (6.94 mmol) and 17.4 μL of dodecanol (7.68×10^{-2} mmol) were dissolved in 3.6 mL of solvent to maintain a monomer concentration of 1 M. After the monomers were completely dissolved, 561 μL of a solution of DBU (10 μL/mL in DCM, 7.68×10^{-2} mmol) was added to the system. The polymerization was conducted at 25 °C and was terminated by adding acetic acid after 4 hours. The polymer was precipitated by adding 100 mL of anhydrous diethyl ether twice to remove unreacted monomers. The final precipitate was dried in a vacuum oven for 48 hours to yield approximately 1.103 g of white polymer (91.4 % yield).

Typical procedure for the block copolymerization of *L*-LA and TMAc catalysed by DBU in DCM. Sequential polymerization was performed to obtain block copolymers of *L*-LA and TMAc. In a typical synthesis of P*L*-LA-*b*-PTMAc ([TMAc]/[*L*-LA]=10/90], 1.0 g of *L*-LA (6.94 mmol) and 17.45 μL of dodecanol (7.68×10^{-2} mmol) were dissolved in 3.6 mL of anhydrous DCM to maintain a monomer concentration of 1 M. After the monomers were completely dissolved, 561 μL of DBU (10 μL/mL in DCM) was added. The polymerization was performed for 4 hours, then 0.206 g of TMAc (0.74 mmol) was added under argon. The polymerization was continued for another 4 hours and was terminated by adding acetic acid. The polymer was purified as described above, providing 1.192 g of white polymer (98.8 % yield).

Typical procedure for the random copolymerization of *L*-LA and TMAc catalysed by $Sn(Oct)_2$ in toluene. To 4 mL of anhydrous toluene, 0.206 g of TMAc (0.74 mmol), 1.0 g of *L*-LA

(6.94 mmol) and 5.4 μL of dodecanol (2.38×10^{-2} mmol) were added and were dissolved completely. After the dissolution of the monomers was complete, 1.24 mL of $Sn(Oct)_2$ in toluene (10 μL/mL in toluene, 3.84×10^{-2} mmol) was added to the system. The polymerization was conducted for 48 hours at 100°C and was terminated by immersing the system in an ice bath. Finally, the polymer was purified as described above.

Typical procedure for the random copolymerization of *L*-LA and TMAc catalysed by TBD in the bulk state. To a vial that was subsequently sealed under vacuum, 0.204 g of TMAc (0.77 mmol), 1 g of *L*-LA (6.94 mmol), 16.1 mg of TBD (0.115 mmol) and 17 μL of 1-dodecanol (7.5×10^{-2} mmol) were added. The polymerization was conducted at 110 °C for 2 hours and was terminated by adding acetic acid. The polymer was purified twice in accordance with the previously described procedure.

Typical deprotection procedure for P(*L*-LA-*co*-TMAc). To 10 mL of trifluoroacetic acid (TFA), 0.5 g of P(*L*-LA-*co*-TMAc7.5%) (0.056 mmol) was added, and the mixture was stirred until complete dissolution was achieved. Subsequently, 10 mL of 33 % HBr in acetic acid was added, and the deprotection reaction was performed for 2 hours. Upon completion, diethyl ether was added to precipitate the product. The deprotected copolymers were dissolved in CH_2Cl_2, and triethylamine (TEA) was added to the neutralize acid used in the deprotection reaction. After filtering off the TEA salts, diethyl ether was added to the solution. The resulting precipitate was collected and dried in a vacuum oven for 48 hours.

Typical procedure for the ROP of BLG-NCA. To dry DMF, 0.05 g of P(*L*-LA-*co*-TAc6.2%) ($5.6x10^{-3}$ mmol) was added, followed by addition of 0.741 g BLG-NCA (2.8 mmol). After complete dissolution, the polymerization reaction was conducted under vacuum. After 4 hours, diethyl ether was added to terminate the reaction. The precipitate was collected and dried in a vacuum oven for 48 hours.

Results and discussions

Kinetics of the DBU-catalysed ring-opening copolymerization of *L*-LA and TMAc

DBU has been used to catalyse the ROP of *L*-LA and many other carbonate monomers under mild conditions[42]. To investigate the copolymerization behaviour of *L*-LA and TMAc, equal concentration of the monomers ([TMAc]/[*L*-LA] =50:50) was polymerized in DCM using dodecanol as an initiator at a monomers/initiator/catalyst ratio of ([TMAc]/[*L*-LA]/[dodecanol]/[DBU])=50:50:1:1. The polymerization kinetics of *L*-LA and TMAc were monitored by ^{1}H NMR, and the results are shown in Figure 1. After 15 minutes, the conversion of *L*-LA reached 49%, while only 30% TMAc conversion was observed. These results were directly obtained from the ^{1}H NMR spectra of aliquots of the copolymerization mixture in $CDCl_3$. At a reaction time of 65 minutes, the conversion rates of the two monomers were nearly the same. As the reaction time increased continuously, the polymerization rate of TMAc increased. Specifically, after 3 hours, the conversion of TMAc reached 80%, while the conversion of *L*-LA was only 71%. In the beginning of the reaction (<15 minutes), the polymerization rate of *L*-LA was faster than that of TMAc, and it reversed later. Therefore, poly(*L*-lactide-*co*-5-benzyloxycarbonylamino-5-methyl-1,3-dioxan-2-one) (P(*L*-LA-*co*-TMAc))

copolymers with gradient distributions were formed, possessing higher *L*-LA contents at beginning near initiator and higher TMAc contents at the end. The reactivity ratio of *L*-LA and TMAc ($\gamma_{L\text{-LA}}$, and γ_{TMAc}) was determined using the K-T method[43] which required conversions of the monomers were less than 10%. The conversion, feed ratio (f) and composition (F) of the monomers were converted to K-T parameters[44], including G, F', α, η and ξ, as shown in Figure S1. Based on the intercept and slope of the figure, we got $\gamma_{L\text{-LA}}$=0.95, and γ_{TMAc}=0.073. The reactivity ratio of *L*-LA and TMAc suggested they could form random copolymers. The relatively longer P*L*LA segment may have been incorporated into the copolymer during the initial polymerization period (scheme 1) due to differences in the copolymerization activities of the monomers.

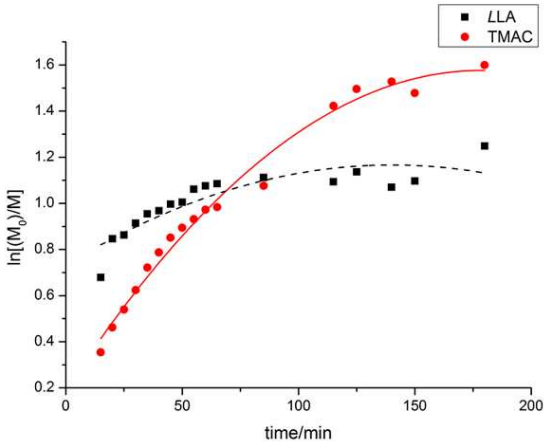
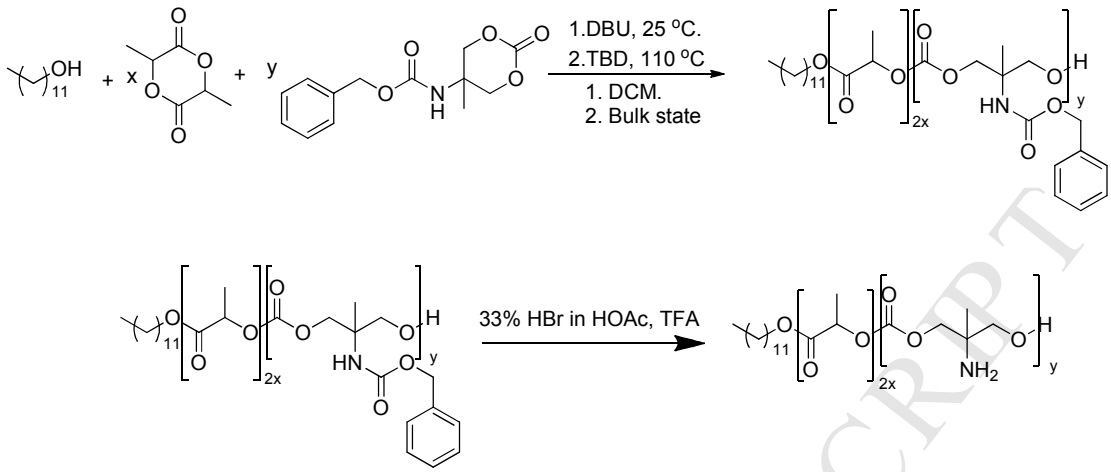


Figure 1. Consumption of *L*-LA and TMAC versus reaction time which was catalysed by DBU, the red line and dash line were guidance of monomer consumption.



Scheme 1. Synthesis of P(*L*-LA-*co*-TMAc) catalysed by either DBU in solution or TBD in bulk. And deprotection of P(*L*-LA-*co*-TMAc) via combination of 33% hydrobromic acid in acetic acid and trifluoroacetic acid.

Copolymerization of *L*-LA and TMAc catalysed by DBU in DCM

To investigate the controllability of the copolymerization of *L*-LA and TMAc, we carried out the simultaneous copolymerization of *L*-LA and TMAc in a single step. DBU served as the catalyst and [TMAc]/[*L*-LA] feed ratios were set of 10/90, 20/80 and 50/50 in DCM at 25°C (Table 1, entry 1-3). *n*-Dodecanol was used as an initiator. The reaction time was set to 4 h because the conversion of *L*-LA and TMAc exceeded 90 % and 81-84 %, respectively. The obtained P(*L*-LA-*co*-TMAc) copolymer was terminated by adding acetic acid after 4 hours. The copolymer was precipitated by adding 100 mL of anhydrous diethyl ether twice to remove unreacted monomers. The signal corresponding to the methyl group of *n*-dodecanol was observed in the ^{1}H NMR spectra of all of the copolymers. It was used to determine the composition and the molecular weight ($M_{n,NMR}$) of the copolymers. Moreover, the presence of the methyl signal confirmed the fidelity of the end group.

As shown in Table 1, the number-averaged molecular weight ($M_{n,NMR}$) of the resulting copolymer, which was estimated from the ^{1}H NMR data, decreased with an increase in the monomer feed ratios of [TMAc]/[*L*-LA]. It deviated from the theoretical number-averaged molecular weight ($M_{n,theo}$), which was calculated from the initial ratio of [M]/[initiator]. The corresponding GPC curves (Figure 2) were unimodal, but the molecular weight distributions were slightly broader than that of the DBU-catalysed system reported in the literature[42]. However, upon changing [TMAc]/[*L*-LA] during the simultaneous copolymerization catalysed by DBU indicated in Table 1(run 1-3), the copolymer composition matched well. Whereas, for the system applying $Sn(Oct)_2$ as catalyst, the content of incorporated TMAc units was less than 10%, even though the monomer feed ratios of [TMAc]/[*L*-LA] reached 50/50 (Table 1, entry 4-6). For DBU, the final molecular weights of the obtained copolymers did not perfectly match the targeted values only for entry with a high TMAc content. However, the composition of the copolymers matched the feed ratios well regardless of TMAc contents. In these cases, the situation was quite different from what $Sn(Oct)_2$ did. Both molecular weight and functional monomer ratio of the copolymer catalysed by $Sn(Oct)_2$ were derivative from the feed.

Table 1. Copolymerization results catalysed by DBU, $Sn(Oct)_2$ and TBD

group	entry	f/%[1]	[TMAc]/[*L*-LA]/[I]/[C][2]	$C_{L\text{-}LA}$/%[3]	C_{TMAc}/%[3]	T/°C[4]	Time/h[5]	M_n/(kg mol^{-1})[6]	M_n/(kg mol^{-1})[7]	PDI[8]	T_g/°C[9]	T_m/°C[9]
DBU random copolymerization	1	10.0	10/90/1/1	>90	82	25.0	4	14.0	14.7	1.36	43.6	133.3
	2	19.8	20/80/1/1	>90	81	25.0	4	14.8	9.33	1.36	27.9	109.9
	3	49.6	50/50/1/1	>90	84	25.0	4	17.8	6.67	1.34	3.90	NA
$Sn(Oct)_2$ random copolymerization	4	3.71	10/90/1/0.1	>87	42	100	48	12.6	13.4	1.33	48.7	144.6
	5	5.73	20/80/1/0.1	>90	38	100	48	12.6	8.41	1.25	47.3	139.1
	6	8.20	50/50/1/0.1	>85	30	100	48	10.3	6.74	1.22	39.8	131.1
DBU block copolymerization	7	10.0	10/90/1/1	>90	85	25.0	8	14.1	11.7	1.31	38.3	138.4
	8	18.2	20/80/1/1	>90	82	25.0	8	14.9	9.30	1.24	49.4	136.3
TBD random copolymerization	9	7.50	10/90/1/1.5	>90	84	110	2	15.5	13.9	1.34	45.2	158.8
	10	17.1	20/80/1/1.5	>90	70	110	2	16.6	10.4	1.30	42.6	NA
	11	30.5	50/50/1/1.5	>90	73	110	2	20.6	3.01	1.10	-9.90	NA
	12	100	100/0/1/1.5	/	80	110	2	26.7	1.30	1.01	-32.4	NA

1.TMAc ratio in copolymers; 2.Feed ratio of TMAc, *L*-LA, initiator and catalyst. The amount of catalyst has been optimized by pre-experiment; 3. Conversion of *L*-LA and TMAc was determined by ^{1}H NMR; 4. Temperature of polymerization conducted; 5. Polymerization time; 6. Theoretical molecular weight calculated via $186+144\times(1-f)\times C_{L\text{-}LA}+265\times f\times C_{TMAc}$; 7. Molecular weight characterized by ^{1}H NMR via $I_{1.9\ ppm}/3\times186+I_{5.2\ ppm}/2\times144+I_{7.3\ ppm}/5\times265$; 8. Molecular weight distribution characterized by GPC; 9. Glass transition temperature and melting temperature determined by DSC.

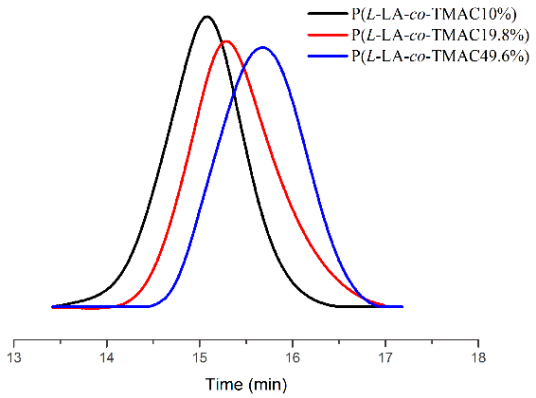


Figure 2. GPC traces of P(*L*-LA-*co*-TMAc10.0%), P(*L*-LA-*co*-TMAc19.8%) and P(*L*-LA-*co*-TMAc49.6%) using THF as eluant at 313K.

The chemical structure of P(*L*-LA-*co*-TMAc) was confirmed by ^{1}H NMR and ^{13}C NMR analyses. The ^{1}H NMR spectrum of P(*L*-LA-*co*-TMAc49.6%)(Figure 3, Table 1, entry 3) revealed the distinct peaks of the methyl and methylene group of the P*L*-LA segment, which were observed in the range of 1.56 ppm and 5.6 ppm. The peaks corresponding to phenyl and benzylic protons, as well as the methylene protons adjacent to the carbonate linkage and the methyl group of TMAc residual segments, appeared between 7.3 ppm and 7.5 ppm, 5.0 ppm, 4.2 ppm and 4.4 ppm and 1.3 ppm, respectively. In addition, the peak due to the methyl protons adjacent to the α-chain end of the initiator was also clearly observed at 0.9 ppm, indicating that *n*-dodecanol successfully initiated the ring-opening copolymerization of *L*-LA with TMAc.

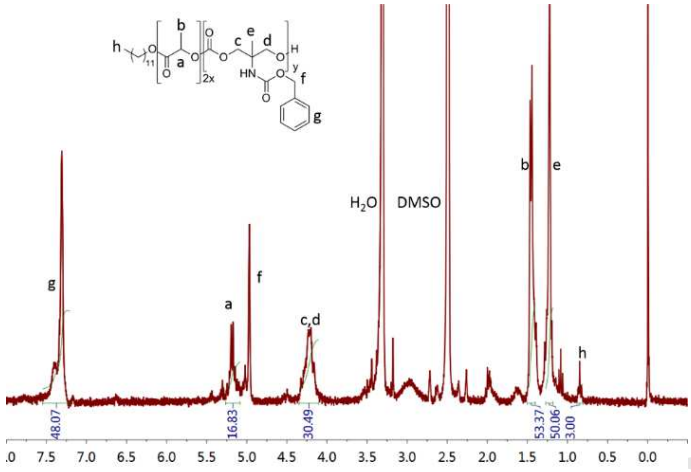


Figure 3. ^{1}H NMR spectrum of P(*L*-LA-*co*-TMAc49.6%) using DMSO-d6 as solvent at 298K. 49.6% means TMAc ratio in the copolymer.

Further details of the sequence distribution were obtained from the ^{13}C NMR spectrum (Figure 4, Table 1, entry 1). The carbonyl group in both the carbonate and ester bonds showed the expected shifts due to the presence of the predicted triad sequences of *L*-LA units (L) and TMAc units (T), including LLL, TTT, LLT, LTL, TLL, TTL, TLT and LTT. Therefore, upon enlarging the carbonyl region of the spectrum, five resonance signals were observed (168.9, 168.7, 168.6, 154.4, 153.2 ppm) and were assigned to the carbonyl group of the copolymer. Compared to homopolymers of P*L*-LA and PTMAc, the strong signal at 168.9 ppm was attributed to the LLL triad, and the signals at 168.7 ppm and 168.6 ppm were assigned to the LLT and TLL triad, respectively. The observed shift in the latter two peaks was due to the incorporation of TMAc blocks. The signal at 154.4 ppm was assigned to the LTL triad, and the peak at 153.2 ppm was attributed to the LTT or TTL triad. The TTT triad was not detected because the average length of the TMAc units (L_{TMAc}) was 1.2 (Table S1) for run 2, and the content of the TTT triad in the chain was low, as shown in the ^{13}C NMR spectrum. Conversely, the average length of *L*-LA units ($L_{L\text{-}LA}$) was 11.2 for run 1 and 4.8

for run 2; thus, LLL was clearly obtained. Moreover, differential scanning calorimetry (DSC, Figure S2a) showed a melting point associated with a relatively longer P*L*LA segment for run 1-2 and a fully amorphous copolymer for run 3, which is in accordance with the sequence distribution observed in the ^{13}C NMR spectrum. In addition, as the amount of TMAc increased from 10 to 50 percent, only one glass transition temperature (T_g) was observed (microphase separation did not occur) (Figure S2b), which decreased from 43.6 to 3.9 °C due to the lower chemical regularity of the polymer chains, as well as the lower molecular weight. Further, the ^{13}C NMR spectra (Figure 5, Table 1, entry 7) of the P*L*-LA-*b*-PTMAc block copolymer synthesized according to the method shown in Scheme S1. It possessed a similar composition and molecular weight compared to the aforementioned gradient copolymer. For the block copolymer, only two sequences of LLL (169.7 ppm) and TTT (155.2 ppm) were detected, and the DSC curve (Figure S2c) showed that the T_g of block copolymers was higher than that of random copolymers with the same composition due to their semi-crystalline characteristics.

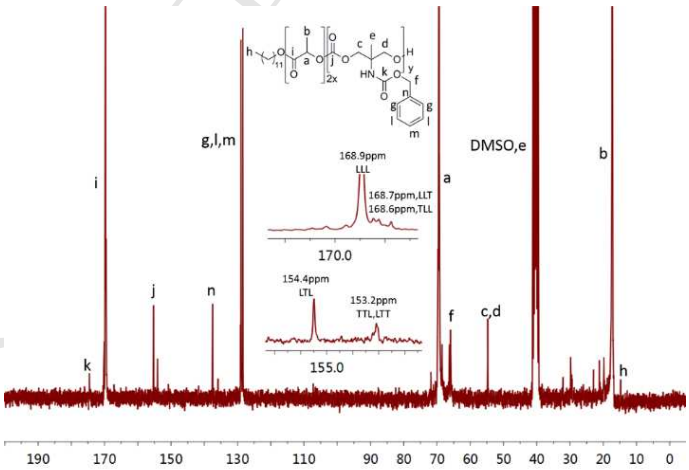


Figure 4. ^{13}C NMR spectrum of P(*L*-LA-*co*-TMAc10.0%) using DMSO-d6 as solvent at 298K. Inserted graph showed traid signals of carbonyl groups in the copolymer. 10.0% means TMAc ratio in the copolymer.

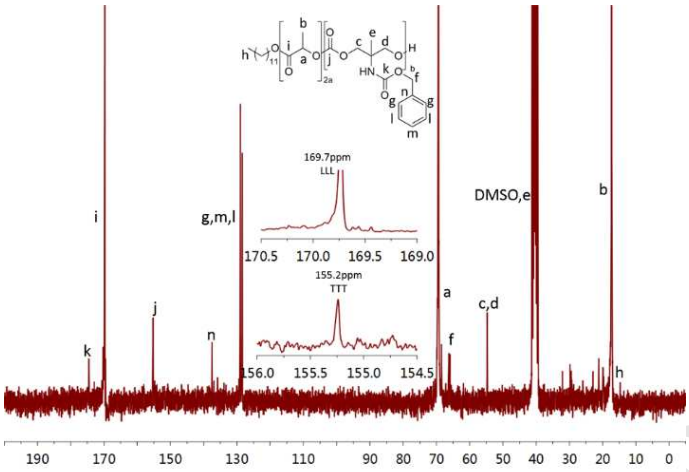


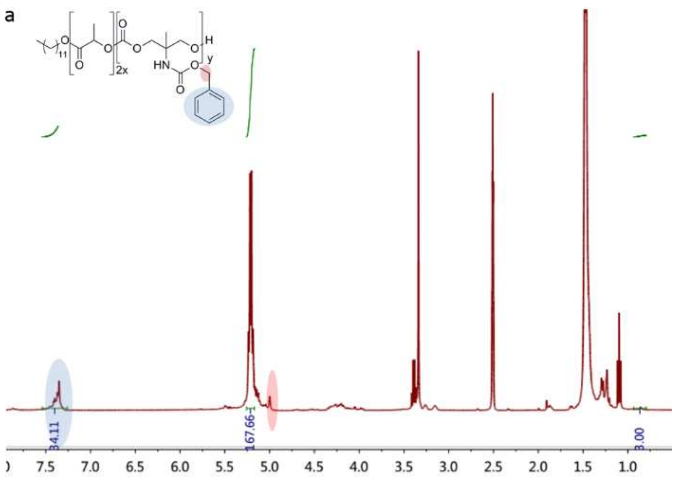
Figure 5. ^{13}C NMR spectrum of P*L*-LA-*b*-PTMAc10.0% using DMSO-d6 as solvent at 298K. Inserted graph showed traid signals of carbonyl groups in the copolymer.

Copolymerization of *L*-LA and TMAc catalysed by TBD in the bulk and deprotection

Considering that the proposed method is an environmentally friendly and easy procedure for industrial processes, we hoped that the copolymerization of *L*-LA and TMAc could be conducted during bulk polymerization. Hence, we conducted the ROP copolymerization of *L*-LA and TMAc catalysed by TBD in the bulk. TBD effectively catalysed the ROP copolymerization of *L*-LA and TMAc in 2 hours at 110 °C. But the same reaction failed using the DBU catalysis system, even after 24 hours. As shown in Table 1 (run 9-12), the molecular weight of the copolymer was less than the theoretical value for the TBD-catalysed system, but the resulting composite was similar to the feed ratios, and the distribution of the molecular weight was narrow, especially for the copolymer with a higher TMAc ratio. Considering that the reactivity ratio of *L*-LA and TMAc catalysed by TBD in bulk was $\gamma_{L\text{-LA}}$=1.396 and γ_{TMAc}=0.017, respectively (Figure S3), and the average length of *L*-LA units ($L_{L\text{-LA}}$) was 5.12 for run 9 and 3.3 for run 10, as determined by ^{13}C NMR, transesterification likely occurred during the copolymerization process, which increased the

random orientation of the polymer chains compared to the DBU system.

To produce free amino groups in the copolymers, hydrobromic acid combined with trifluoroacetic acid was used to remove carbobenzoxy groups[45,46]. Residual acid can be easily removed by neutralization after deprotection (scheme 1). Copolymer P(*L*-LA-*co*-TMAc7.5%)(Table 1, entry 9) was used to removed the carbobenzoxy group. The ^{1}H NMR spectra showed that the signals of the phenyl protons (7.3-7.5 ppm) and methylene protons present in benzyl groups (5.0 ppm) were nearly gone after 2 hours, as shown in Figure 6a and 6b. The molecular weight of P(*L*-LA-*co*-TAc) decreased from 13.9 kg/mol to 10.3 kg/mol when the carbobenzoxy groups were removed, and the degradation occurred during this process both indicated in ^{1}H NMR spectra and GPC curves(Figure 6). Free amino groups did not cause obvious depolymerization, which was illustrated by a unimodal peak of P(*L*-LA-*co*-TAc). Besides, amino groups were protonated in the acidic condition, transesterification caused by the amino groups could be reduced. And the strong acidic condition was responsible for the degradation. Moreover, the Degradation of P(*L*-LA-*co*-TAc) can be suppressed when the deprotection was carefully conducted in ice bath in dicated by GPC traces (Figure S4).



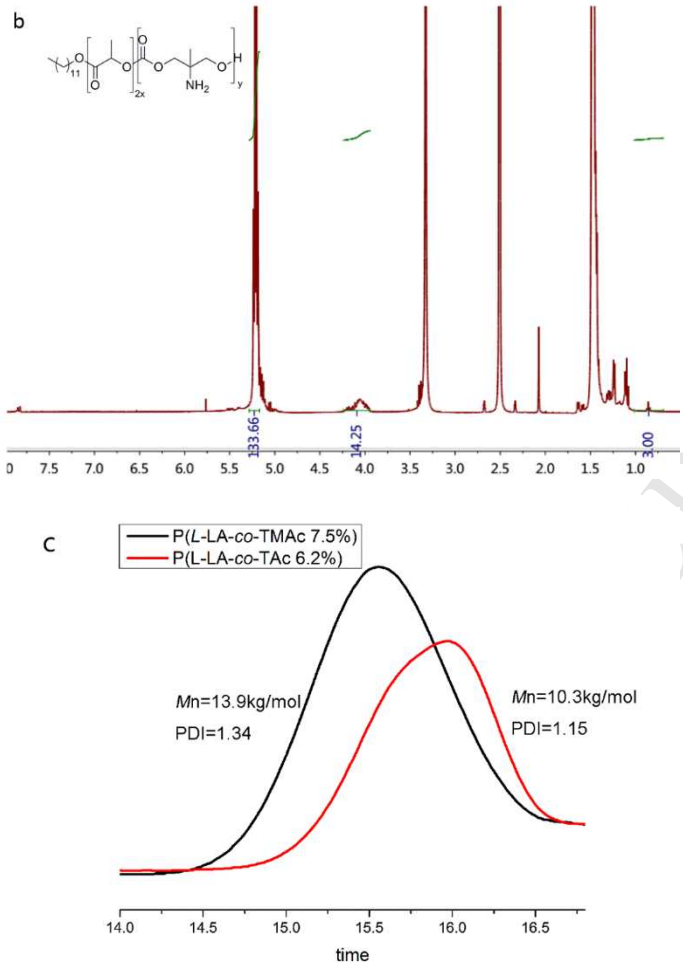


Figure 6. a) ^{1}H NMR spectrum of P(*L*-LA-*co*-TMAc7.5%). Circles indicated signal of phenyl proton (blue) and methylene of benzyl proton (red). b) ^{1}H NMR spectrum of P(*L*-LA-*co*-TMAc6.2%). c) GPC traces of P(*L*-LA-*co*-TMAc7.5%) and P(*L*-LA-*co*-TAc6.2%) using THF as eluant at 313K.

Post-polymerization functionalization of P(*L*-LA-*co*-TAc)

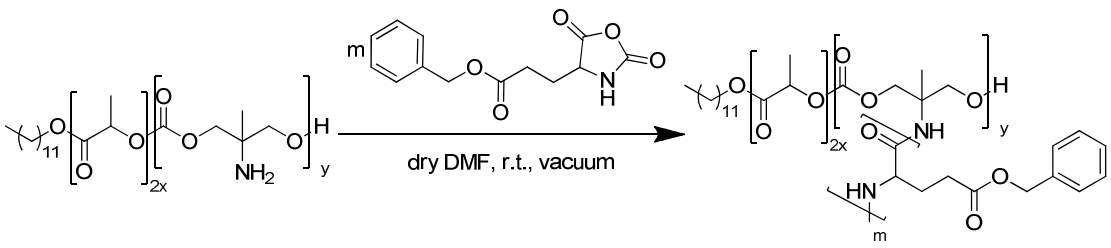
The pendent amino groups in P(*L*-LA-*co*-TAc) copolymer can act as anchor sites for further functionalization. A typical example is the ROP of α-amino acid N-carboxyanhydrides (NCA) initiated by the primary amines in the copolymer for the synthesis of P(*L*-LA-*co*-TAc)-grafted peptide copolymers (Scheme 2). Following the 'graft from' method, the multi-composite graft copolymer of P(*L*-LA-*co*-TAc)-grafted poly(γ-benzyl-*L*-glutamate) [P(*L*-LA-*co*-TAc)-*g*-PBLG] was produced under vacuum[50] for 2 or 4 hours. Results of the copolymerization were shown in

Table 3. In order to decrease the possible degradation of the precopolymers, the ROP reaction of NCA was carried out under vacuum to accelerate the ROP reaction. For the entry 3, 4 hours reaction time was selected considering the high amount of NCA monomer. It was also found that the final degrees of polymerization were similar to the feed ratios, indicating the good controllability of the ROP polymerization of NCA by the prepolymers bearing primary amino groups.

Gel permeation chromatography (GPC) was used to confirm successful synthesis of the [P(*L*-LA-*co*-TAc)-*g*-PBLG]. The GPC curve of P(*L*-LA-*co*-TAc) (Fig. 7 b) disappeared, and elution curve for the PBLG-modified P(*L*-LA-*co*-TAc) copolymers (Fig. 7 b) appeared at an earlier time in a monomodal manner. Shift of GPC trace indicated efficient ROP of NCA. However, the molecular weights obtained from the GPC and NMR was quite different (Table 3). Inherent structure difference of P(*L*-LA-*co*-TAc)-*g*-PBLG and PEO, a standard calibration used in GPC, should be responsible for the M_n difference in Table 3. After graft polymerization, the polydispersity index of the grafting copolymer increased.

In the ^{1}H NMR spectrum (Figure 7 a, Table 3, entry 3), the peaks at 7.21 ppm, 5.03 ppm, 4.10 ppm and 2.00-2.75 ppm were assigned to the hydrogen in the benzene ring, methylene hydrogen of benzyl, methine and methylene hydrogen of PBLG. The DP of the PBLG was calculated based on methine of lactide and methylene of benzyl group on grafted PBLG, $DP_{PBLG}=0.5\times I_{5.03\ ppm}/5.0$, 5.0 was average number of amino groups on deprotected copolymer P(*L*-LA-*co*-TAc6.2%).

Thus we revealed that DBU and TBD were efficient organocatalysts for the ROP of *L*-LA and TMAc in solvent and in bulk respectively, affording higher content of amino groups to synthesis well-defined P(*L*-LA-*co*-TAC)-*g*-PBLG. In other words, a multi-composite grafting copolymer can be obtained through post-polymerization functionalization.

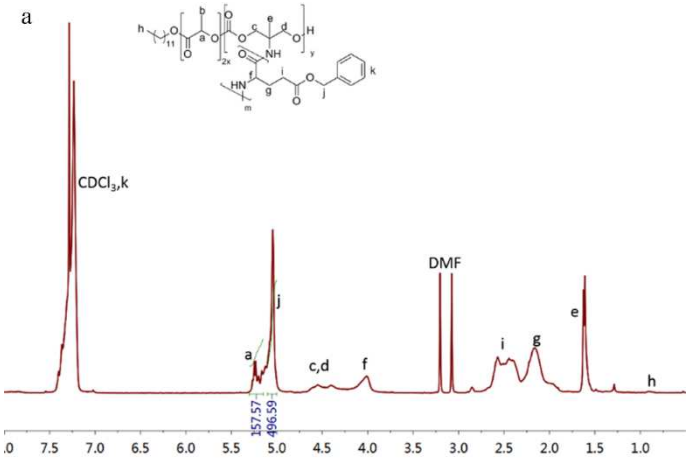


Scheme 2. Synthesis of P(*L*-LA-*co*-TAc)-*g*-PBLG via "graft from" method.

Table 3. Grafting PBLG to P(*L*-LA-*co*-TAc6.2%) via "graft from" method

Entry	Time/h	[BLG-NCA]/[-NH_2][1]	DP of PBLG[2]	M_n/ (kg mol^{-1})[3]	M_n/(kg mol^{-1})[4]	M_w/M_n [4]
1	2	5.0	4.50	16.3	14.1	1.34
2	2	20	20.0	35.9	27.0	1.30
3	4	50	49.8	71.5	38.7	1.40

Where 1 was feed ratio of BLG-NCA to amino groups in deprotected copolymer; 2 was calculated based on methyne of lactide and methylene of benzyl group on grafted PBLG. $DP_{PBLG}=0.5\times I_{5.03\ ppm}/5.0$, 5.0 was average number of amino groups on deprotected copolymers P(*L*-LA-*co*-TAc6.2%) 3. molecular weight characterized by H NMR, $Mn=0.5\times I_{5.0\ ppm}/N\times 264+M_{n,\ main\ chain}$; 4. characterized by GPC, mobile phase was DMF containing 0.5%(m/v) LiBr



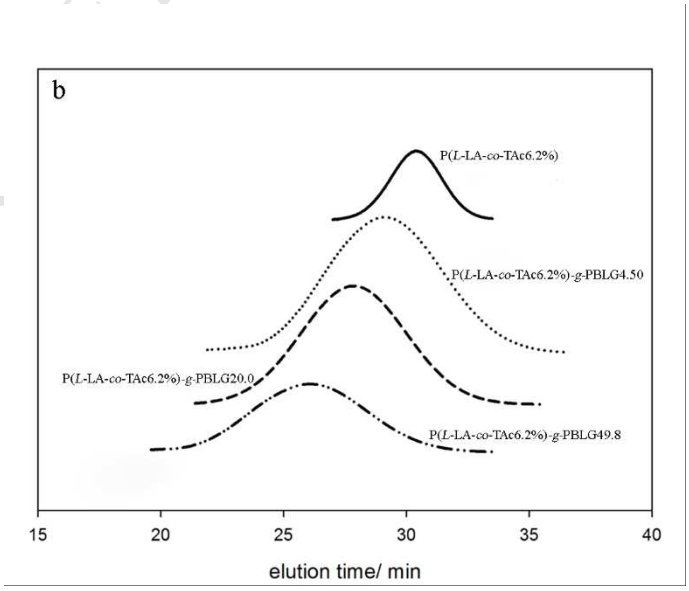


Figure 7. a) ^{1}H NMR spectrum of P(*L*-LA-*co*-TAc6.2%)-*g*-PBLG49.8. 49.8 means degree of polymerization(DP) of PBLG. b) GPC traces of P(*L*-LA-*co*-TAc6.2%) and P(*L*-LA-*co*-TAc6.2%)-*g*-PBLGx (x is DP of PBLG) using DMF containing 0.5%(w/v) LiBr as eluant at 313K..

Conclusions

Amino bearing poly(ester-carbonate)s were synthesized using DBU (in solvent) and TBD (in bulk) as organocatalysts. *L*-LA and TMAc formed random copolymers, but relatively longer P*L*LA segments were likely incorporated into the copolymer in the initial polymerization period (scheme 1) due to differences in the copolymerizing activity of the comonomer, especially in the DBU system. However, compared to the $Sn(Oct)_2$ system, which can be used to initiate NCA, highly functionalized groups were incorporated into the copolymer. Finally, P(*L*-LA-*co*-TAc)-*g*-PBLG, a multi-composite grafted copolymer, was obtained via post-polymerization functionalization.

Acknowledgements

The authors acknowledge financial support from the National Natural Science Foundation of China (Grant No. 5107378 and U1134007), Guangdong Natural Science Foundation (2015A030311025) and the Major Project of Health and Medical Collaborative Innovation of Guangzhou (201508020251)

References

[1] S. Bose, M. Roy, A. Bandyopadhyay, Recent advances in bone tissue engineering scaffolds, Trends in Biotechnology. 30 (2012) 546–554.

[2] L. He, Y. Zhang, X. Zeng, D. Quan, S. Liao, Y. Zeng, et al., Fabrication and characterization of poly(l-lactic acid) 3D nanofibrous scaffolds with controlled architecture by liquid-liquid phase separation from a ternary polymer-solvent system, Polymer. 50 (2009) 4128–4138.

[3] W. Liu, J. Zhan, Y. Su, T. Wu, C. Wu, S. Ramakrishna, et al., Effects of plasma treatment to

nanofibers on initial cell adhesion and cell morphology, Colloids and Surfaces B: Biointerfaces. 113 (2014) 101–106.

[4] L.S. Dolci, S.D. Quiroga, M. Gherardi, R. Laurita, A. Liguori, P. Sanibondi, et al., Carboxyl Surface Functionalization of Poly(<scp>L</scp> -lactic acid) Electrospun Nanofibers through Atmospheric Non-Thermal Plasma Affects Fibroblast Morphology, Plasma Processes and Polymers. 11 (2014) 203–213.

[5] G. Wu, P. Li, H. Feng, X. Zhang, P.K. Chu, Engineering and functionalization of biomaterials via surface modification, J. Mater. Chem. B. 3 (2015) 2024–2042.

[6] Z. Kolská, A. Řezníčková, M. Nagyová, N. Slepičková Kasálková, P. Sajdl, P. Slepička, et al., Plasma activated polymers grafted with cysteamine improving surfaces cytocompatibility, Polymer Degradation and Stability. 101 (2014) 1–9.

[7] S. Sarapirom, L.D. Yu, D. Boonyawan, C. Chaiwong, Effect of surface modification of poly(lactic acid) by low-pressure ammonia plasma on adsorption of human serum albumin, Applied Surface Science. 310 (2014) 42–50.

[8] S. Rimpelová, L. Peterková, N.S. Kasálková, P. Slepička, V. Švorčík, T. Ruml, Surface Modification of Biodegradable Poly(*L* -Lactic Acid) by Argon Plasma: Fibroblasts and Keratinocytes in the Spotlight, Plasma Processes and Polymers. 11 (2014) 1057–1067.

[9] W.W. Gerhardt, D.E. Noga, K.I. Hardcastle, A.J. García, D.M. Collard, M. Weck, Functional lactide monomers: methodology and polymerization., Biomacromolecules. 7 (2006) 1735–42.

[10] M. Trollsås, V.Y. Lee, D. Mecerreyes, P. Löwenhielm, M. Möller, R.D. Miller, et al., Hydrophilic aliphatic polyesters: design, synthesis, and ring-opening polymerization of functional cyclic esters, Macromolecules. 33 (2000) 4619–4627.

[11] A.M. Fischer, R. Thiermann, M. Maskos, H. Frey, One-pot synthesis of poly(l-lactide) multi-arm star copolymers based on a polyester polyol macroinitiator, Polymer. 54 (2013) 1993–2000.

[12] S. Daniel P., F. Kazuki, C. Daniel J., N. Alshakim, F. Masaki, Y. Manabu, et al., A Simple and Efficient Synthesis of Functionalized Cyclic Carbonate Monomers Using a Versatile Pentafluorophenyl Ester Intermediate, J. Am. Chem. Soc. 132 (2010) 14724–14726.

[13] J. Undin, P. Olsén, J. Godfrey, K. Odelius, A.-C. Albertsson, Controlled copolymerization of the non-homopolymerizable, functional monomer α-bromo-γ-butyrolactone via selective organocatalysis, Polymer. 87 (2015).

[14] W. Chen, H. Yang, R. Wang, R. Cheng, F. Meng, W. Wei, et al., Versatile synthesis of functional biodegradable polymers by combining ring-opening polymerization and postpolymerization modification via michael-type addition reaction, Macromolecules. 43 (2010) 201–207.

[15] J. Xu, F. Prifti, J. Song, A Versatile Monomer for Preparing Well-Defined Functional Polycarbonates and Poly(ester-carbonates)., Macromolecules. 44 (2011) 2660–2667.

[16] S. El Habnouni, V. Darcos, J. Coudane, Synthesis and Ring Opening Polymerization of a New Functional Lactone, α-Iodo-ε-caprolactone: A Novel Route to Functionalized Aliphatic Polyesters., Macromolecular Rapid Communications. 30 (2009) 165–9.

[17] J. Mindemark, T. Bowden, Synthesis and polymerization of alkyl halide-functional cyclic carbonates, Polymer. 52 (2011) 5716–5722.

[18] B. Parrish, R.B. Breitenkamp, T. Emrick, PEG- and Peptide-Grafted Aliphatic Polyesters by Click Chemistry PEG- and Peptide-Grafted Aliphatic Polyesters by Click Chemistry,

Biomaterials. 127 (2005) 7404–7410.

[19] A. Vora, K. Singh, D.C. Webster, A new approach to 3-miktoarm star polymers using a combination of reversible addition-fragmentation chain transfer (RAFT) and ring opening polymerization (ROP) via “Click” chemistry, Polymer. 50 (2009) 2768–2774.

[20] Z. Xie, C. Lu, X. Chen, L.I. Chen, Y.U. Wang, X. Hu, Synthesis and Characterization of Novel Poly (ester carbonate) s Based on Pentaerythritol, J. Polym. Sci. Part A: Polym. Chem. 45 (2007) 1737–1745.

[21] R.H. Lambeth, T.J. Henderson, Organocatalytic synthesis of (poly)hydroxyurethanes from cyclic carbonates and amines, Polymer. 54 (2013) 5568–5573.

[22] W.Y. Seow, Y.Y. Yang, Functional polycarbonates and their self-assemblies as promising non-viral vectors., Journal of Controlled Release. 139 (2009) 40–7.

[23] H. XIULI, C. XUESI, X. ZHIGANG, C. HAIBO, J. XIABIN, Anionic Amphiphilic End-Linked Conetworks by the Combination of Quasiliving Carbocationic and Group Transfer Polymerizations, J. Polym. Sci. Part A: Polym. Chem. 46 (2008) 7022–7032.

[24] J. Yan, Y. Zhang, Y. Xiao, Y. Zhang, M. Lang, Novel poly(ε-caprolactone)s bearing amino groups: Synthesis, characterization and biotinylation, Reactive and Functional Polymers. 70 (2010) 400–407.

[25] R. Wang, W. Chen, F. Meng, R. Cheng, C. Deng, J. Feijen, et al., Unprecedented Access to Functional Biodegradable Polymers and Coatings, Chemical Engineering. (2011) 6009–6016.

[26] M. Liu, N. Vladimirov, J.M.J. Fre, A New Approach to Hyperbranched Polymers, Macromolecules. 2 (1999) 6881–6884.

[27] N. Qiang, W. Yang, L. Li, P. Dong, J. Zhu, T. Wang, et al., Synthesis of pendent carboxyl-containing poly(ε-caprolactone-co-β-malic acid)-block-poly(l-lactide) copolymers for fabrication of nano-fibrous scaffolds, Polymer. 53 (2012) 4993–5001.

[28] Z. Xie, H. Guan, X. Chen, C. Lu, L. Chen, X. Hu, et al., A novel polymer–paclitaxel conjugate based on amphiphilic triblock copolymer, Journal of Controlled Release. 117 (2007) 210–216.

[29] C. Jérôme, P. Lecomte, Recent advances in the synthesis of aliphatic polyesters by ring-opening polymerization., Advanced Drug Delivery Reviews. 60 (2008) 1056–76.

[30] J. Feng, R.-X. Zhuo, X.-Z. Zhang, Construction of functional aliphatic polycarbonates for biomedical applications, Progress in Polymer Science. 37 (2012) 211–236.

[31] X. Zhang, Z. Zhong, R. Zhuo, Preparation of Azido Polycarbonates and Their Functionalization via Click Chemistry, Macromolecules. 44 (2011) 1755–1759.

[32] P. Olsén, J. Undin, K. Odelius, A.-C. Albertsson, Establishing α-bromo-γ-butyrolactone as a platform for synthesis of functional aliphatic polyesters – bridging the gap between ROP and SET-LRP, Polymer Chemistry. 5 (2014) 3847.

[33] M. Tanzi, P. Verderio, M. Lampugnani, M. Resnati, E. Dejana, E. Sturani, Cytotoxicity of some catalysts commonly used in the synthesis of copolymers for biomedical use, Journal of Materials Science: Materials in Medicine. 5 (1994) 393396.

[34] M.K. Kiesewetter, E.J. Shin, J.L. Hedrick, R.M. Waymouth, Organocatalysis: Opportunities and Challenges for Polymer Synthesis, Macromolecules. 43 (2010) 2093–2107.

[35] F. Suriano, O. Coulembier, J.L. Hedrick, P. Dubois, Functionalized cyclic carbonates: from synthesis and metal-free catalyzed ring-opening polymerization to applications, Polymer Chemistry. 2 (2011) 528.

[36] Y.C. Yu, S.J. Shin, K.D. Ko, W.R. Yu, J.H. Youk, One-pot synthesis of poly(vinyl

alcohol)-based biocompatible block copolymers using a dual initiator for ROP and RAFT polymerization, Polymer. 54 (2013) 5595–5600.

[37] A.P. Dove, R.C. Pratt, B.G.G. Lohmeijer, D.A. Culkin, E.C. Hagberg, G.W. Nyce, et al., N-Heterocyclic carbenes: Effective organic catalysts for living polymerization, Polymer. 47 (2006) 4018–4025.

[38] N.E. Kamber, W. Jeong, S. Gonzalez, J.L. Hedrick, R.M. Waymouth, N-Heterocyclic Carbenes for the Organocatalytic Ring-Opening Polymerization of ε-Caprolactone, Macromolecules. 42 (2009) 1634–1639.

[39] L. Simón, J.M. Goodman, The mechanism of TBD-catalyzed ring-opening polymerization of cyclic esters., The Journal of Organic Chemistry. 72 (2007) 9656–62.

[40] A. Couffin, D. Delcroix, B. Martín-Vaca, D. Bourissou, C. Navarro, Mild and efficient preparation of block and gradient copolymers by methanesulfonic acid catalyzed ring-opening polymerization of caprolactone and trimethylene carbonate, Macromolecules. 46 (2013) 4354–4360.

[41] X. Hu, X. Chen, Z. Xie, H. Cheng, X. Jing, Aliphatic Poly (ester-carbonate) s Bearing Amino Groups and Its RGD Peptide Grafting, Polymer. (2008) 7–9.

[42] B.G.G. Lohmeijer, R.C. Pratt, F. Leibfarth, J.W. Logan, D.A. Long, A.P. Dove, et al., Guanidine and amidine organocatalysts for ring-opening polymerization of cyclic esters, Macromolecules. 39 (2006) 8574–8583.

[43] K. Makiguchi, C. Asakura, K. Yanai, T. Satoh, T. Kakuchi, Diphenyl Phosphate-Catalyzed Ring-Opening Polymerization of 1,5-Dioxepan-2-one, Macromolecular Symposia. 349 (2015) 74–84.

[44] T. Kelen, K. Tüdõs, Analysis of the Linear Methods for Determining Copolymerization Reactivity Ratios. I. A New Improved Linear Graphic Method, Journal of Macromolecular Science: Part A - Chemistry. 9 (1975) 1–27.

[45] C. Deng, X. Chen, H. Yu, J. Sun, T. Lu, X. Jing, A biodegradable triblock copolymer poly(ethylene glycol)-b-poly(l-lactide)-b-poly(l-lysine): Synthesis, self-assembly, and RGD peptide modification, Polymer. 48 (2007) 139–149.

[46] C.D. Vacogne, S.M. Brosnan, A. Masic, H. Schlaad, Fibrillar gels via the self-assembly of poly(l-glutamate)-based statistical copolymers, Polym. Chem. 6 (2015) 5040–5052.

[47] Y.S. Nam, T.G. Park, Biodegradable polymeric microcellular foams by modified thermally induced phase separation method., Biomaterials. 20 (1999) 1783–1790.

[48] F.J. Hua, G.E. Kim, J.D. Lee, Y.K. Son, D.S. Lee, Macroporous poly(L-lactide) scaffold 1. Preparation of a macroporous scaffold by liquid-liquid phase separation of a PLLA-dioxane-water system, Journal of Biomedical Materials Research. 63 (2002) 161–167.

[49] A. Niehoff, A. Mantion, R. McAloney, A. Huber, J. Falkenhagen, C.M. Goh, et al., Elucidation of the structure of poly(γ-benzyl-l-glutamate) nanofibers and gel networks in a helicogenic solvent, Colloid and Polymer Science. 291 (2013) 1353–1363.

[50] R.A. Kowtoniuk, T. Pei, C.M. DeAngelo, J.H. Waldman, E.N. Guidry, J.M. Williams, et al., Optimization of an α-(Amino acid)- N -carboxyanhydride polymerization using the high vacuum technique: Examining the effects of monomer concentration, polymerization kinetics, polymer molecular weight, and monomer purity, J. Polym. Sci., Part A: Polym. Chem. 52 (2014) 1385–1391.

- High amount of functional cyclic carbonate, TMAc, was incorprated into poly(ester-carbonate)s by organocatalysts in a short period of 2 to 4 hours.
- Gradient poly(ester-carbonate)s was formed during the copolymerization.
- Free amino groups was achieved by deprotection in acidic environment.
- Poly(γ-benzyl-L-glutamate)(PBLG) was introduced to the amino bearing macro-initiators via "graft from" method with high control.