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# Synthesis and characterization of novel functionalized polylactides with pendent hydroxyl arms

Liang Wang, Xiaohua Jia, Zhi Yuan*

*Key Laboratory of Functional Polymer Materials, Ministry of Education, Institute of Polymer Chemistry, Nankai University, Tianjin 300071, China*

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**Abstract**

A class of polyesters have been synthesized by the ring-opening copolymerization of DL-lactide (DLLA) and *RS*-benzyloxyethyl-β-malolactonate (MABE) using different monomer feeding doses. The compositions and structures of poly(DL-lactide-*co*-*RS*-benzyloxyethyl-β-malolactonate) (poly(DLLA-*co*-MABE)) were determined by $^{1}H$ and $^{13}C$ NMR measurements. GPC measurement showed that the molecular weight of the copolymers decreased as the MABE content increases. After catalytic hydrogenation of the benzyl ether functions, the desired copolymers with pendent hydroxyl arms, poly(DL-lactide-*co*-*RS*-hydroxyethyl-β-malolactonate) (poly(DLLA-*co*-MAHE)), were recovered. Thermal properties of poly(DLLA-*co*-MABE) and poly(DLLA-*co*-MAHE) copolymers were examined by differential scanning calorimetry (DSC) measurement. Single glass transition temperature appeared in the DSC spectra, which confirmed that the copolymers were true copolymers and not blends. The hydrophilicity of poly(DLLA-*co*-MAHE) copolymer was tunable, which increased with the increase in MAHE content. Furthermore, the hydrolytic degradation of poly(DLLA-*co*-MAHE) material was investigated and the results showed that faster degradation was observed in the copolymer film containing more MAHE content.


*Keywords:* DL-Lactide; *RS*-Benzyloxyethyl-β-malolactonate; Poly(DL-lactide-*co*-*RS*-hydroxyethyl-β-malolactonate)

## 1. Introduction

As one of the most important class of synthetic biodegradable polymers, aliphatic polyesters are generally considered to be well-suited for applications as polymer-based biomaterials due to their good biocompatibility and biodegradability [1]. Biodegradable α-hydroxy polyesters, such as poly(L-lactic acid) (PLLA) and poly(lactic-*co*-glycolic acid) (PLGA), have been investigated as scaffolds for tissue engineered skin and cartilage [2,3]. These polymers are considered to be biocompatible, and can be fabricated into scaffolds with a variety of shapes and forms, and degrade in a controlled manner [4–9]. Polymeric materials based on lactide and glycolide are limited in scope due to their hydrophobic property and the absence of functionality on the polymer backbone, which could otherwise be used for tailoring physical properties and introducing bioactive substances [10].

To improve the cell affinity of aliphatic polyesters, many efforts have been directed to modify their surface. Plasma treatment, although very popular [11–14], appears unable to penetrate more than a few millimeters into the pores of a scaffold. Surface entrapment [15–17], while apparently promising for 2-dimensional applications, leads to collapse of the thin walls of a soft tissue scaffold during the swelling step. Partial surface hydrolysis by acid or base treatment [18–20] may cause the degradation of the aliphatic polyesters' scaffold. Numerous examples of chain-end functionalized aliphatic polyesters have also been reported, and most of them were prepared by the use of functional nucleophiles to initiate ring-opening lactone polymerization [21–23]. Amphiphilic block copolymers such as PEG-*b*-PLA were applicable not only in drug delivery system, but also has been utilized for the preparation

* Corresponding author. Tel.: +86 22 2350 1164; fax: +86 22 2350 3510.
*E-mail address:* zhiy@nankai.edu.cn (Z. Yuan).

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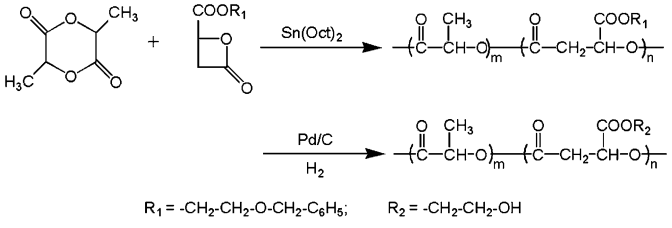
of nanoreactors and nanocontainers [24,25]. However, pendent functionalization provides a unique opportunity to alter physical and chemical properties by distributing functionality along the polymer backbone. This imparts a structural homogeneity that is distinct from other materials including block copolymers.

Functionalization of aliphatic polyesters can be achieved by polymerization of functionalized lactones. Polyesters with pendent carboxylic and amino functional groups, such as poly(malic acid) [26–29] and poly(L-serine ester) [30], have been synthesized. Polydepsipeptides with carboxylic, amino or thiol groups have also been reported [31]. A number of aliphatic polycarbonates or their copolymers such as poly(ethylene carbonate) [32] and poly(trimethylene carbonate) [33] were also reported to be degradable. Wang et al. have reported the preparation and degradation of poly(L-lactide-*co*-*RS*-β-malic acid) [34]. After 1 week, the malic acid units degraded completely; it might be the result of autocatalysis of carboxylic side groups [35].

For the linear biodegradable polyesters, the presence of lateral functionality such as hydroxyl groups could bring many benefits as follows: (i) it can easily adjust hydrophilic/hydrophobic balance of a material via regulating the hydrophilic lateral group and the hydrophobic chain backbone [36], (ii) the functional sites could be further modified by bioactive molecule, (iii) via cross-linking of the pendent functionalities, new biodegradable polymer network could be synthesized as tissue engineer carrier, (iv) a further living/controlled ring-opening polymerization of reactive cyclic monomer grafted at the reactive hydroxyl sites could construct a functional brush- or comb-type polymer architecture through controlling the graft density and length [37]. If the polylactides were functionalized with pendent hydroxy arms, the reactivity of the hydroxyl groups would be improved remarkably by the increasing flexibility of the side chain and the decreasing stereohindrance of the backbone, so that the post modification, cross-linking and polymerization could be achieved more easily. To our knowledge there were few related previous works focused on the synthesis of functionalized polylactide with hydroxy arms.

In this paper, a class of functionalized polylactides, poly(DL-lactide-*co*-*RS*-hydroxyethyl-β-malolactonate), with pendent hydroxy arms were synthesized by a two-step reaction. Firstly, two different monomers (DLLA and MABE) were copolymerized via the ring-opening polymerization using $Sn(Oct)_2$ as catalyst. After hydrogenation, the benzyl protective groups were removed and the hydroxyl arms were recovered. The configurational structure, hydrophilicity, molecular weight, thermal property and degradability of these copolymers were characterized. The biological responses of these new materials will be the subject of our forthcoming work. The synthetic root is shown in Scheme 1.




Scheme 1. Synthetic route of poly(DL-lactide-*co*-*RS*-hydroxyethyl-β-malolactonate).

## 2. Experimental

### 2.1. Materials

Stannous octoate, trifluoroacetic acid anhydride (TFAA) and palladium on charcoal (Pd/C, 10%) were purchased from Aldrich and used without further purification. Solvents such as tetrahydrofuran (THF), 1,4-dioxane and ethyl ether were dried with sodium and distilled. Dichloromethane was dried with $CaH_2$ and distilled. Acetic acid was dried with acetic acid anhydride and distilled. DL-Lactide was purchased from Beijing Chemical Reagent Company and recrystallized twice in acetyl acetate. Other reagents were of AR grade.

### 2.2. Instruments

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DMX-300 with tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. GPC was performed on Waters 515 with Polymer Standards Service Columns. Samples were measured at 35 °C with THF as eluent at a flow rate of 1.0 ml $min^{-1}$. The molecular weight was calibrated relative to polystyrene standards. The contact angle of the samples to water was measured in air using a FACE CA-D type Contact Angle Meter (Kyowa Kaimenkagaku Co., Ltd). Differential scanning calorimetry thermograms were registered with a Netzsch DSC 204 instrument, the heating rate being 10.0 K $min^{-1}$.

### 2.3. Synthesis of benzyloxyethanol

Sodium of 8.0 g was added into 15 ml of glycol, and then 25 ml of benzyl chloride was added dropwise. The system was stirred for 5 h at 60 °C and dissolved in 60 ml of ethyl ether. The organic phase was washed with 3 × 50 ml of water and 50 ml of saturated brine dried over $MgSO_4$. After filtration, the solvent was stripped out to give a yellow oil. This crude product was purified by distillation under vacuum and 32 g of purified benzyloxyethanol (72%) was obtained. $C_9H_{12}O_2$ (152.2): calcd C 71.01%, H 7.91%, O 21.08%; found C 71.03%, H 7.95%, O 21.03%. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.79 (s, 1H, O*H*), 3.57–3.60 (t, 2H, Bz–O–C$H_2$–), 3.72–3.77 (t, 2H, –$CH_2$–C$H_2$–OH), 4.56 (s, 2H, Ph–C$H_2$–), 7.33–7.35 (m, 5H, $C_6H_5$–).

### 2.4. Synthesis of the monoester mixture

*RS*-Bromosuccinic acid was prepared from DL-aspartic acid according to the literature [38]. Diacid of 5.0 g was dissolved in 10 ml of THF under $N_2$ atmosphere. The mixture was kept at −5 °C and 5.0 ml of TFAA were added. Then, the system

was stirred for 2 h at room temperature under $N_2$ atmosphere. THF, trifluoroacetic acid formed and the excess TFAA were evaporated leading to a pale brown oil, and then 3.4 ml of benzyloxyethanol was added. The mixture was stirred under $N_2$ atmosphere at 45 °C for 12 h. The product was dissolved into 30 ml of ethyl ether, washed with $3 \times 30$ ml of water and dried over $MgSO_4$/decolorizing charcoal for 2 h. After filtration, the solvent was stripped out to give 7.8 g of colourless oil (93%). $C_{13}H_{15}BrO_5$ (331.2): calcd C 46.97%, H 4.65%, Br 23.56%, O 24.82%; found C 47.15%, H 4.57%, Br 24.13%, O 24.16%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 2.99–3.37 (m, 2H, –CH–C$H_2$–), 3.65–3.72 (m, 2H, Bz–O–C$H_2$–$CH_2$–), 4.27–4.31 (t, 2H, Bz–O–$CH_2$–C$H_2$–, 25% of non-lactonizable monoester), 4.35–4.39 (t, 2H, Bz–O–$CH_2$–C$H_2$–, 75% of lactonizable monoester), 4.49–4.61 (m, 3H, Br–C*H*, Ph–C$H_2$–), 7.25–7.38 (m, 5H, $C_6H_5$–).

### 2.5. Synthesis of RS-benzyloxyethyl-β-malolactonate

Monoester mixture of 2.5 g was put in a beaker. Then, 5.0 ml of ethyl ether and 10 ml of water were added. This suspension was vigorously stirred and kept in ice bath. A solution of 2 mol $l^{-1}$ NaOH was added gradually to adjust pH to 7.2. The aqueous phase was added over 30 ml of dichloromethane at 40 °C, and then, the mixture was vigorously stirred at 40 °C for 4 h. After decantation, the organic phase was washed with $3 \times 30$ ml of water and 30 ml of saturated brine and dried over $NaSO_4$. After filtration, the dichloromethane was eliminated to give the crude monomer. Purified monomer of 0.6 g (24%) was obtained by chromatography performed twice on silica gel (eluent: dichloromethane). $C_{13}H_{14}O_5$ (250.2): calcd C 74.25%, H 7.38%, O 18.37%; found C 74.29%, H 7.39%, O 18.33%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 3.55–3.81 (m, 4H, Bz–O–C$H_2$–, CH–C$H_2$–), 4.41–4.44 (t, 2H, Bz–O–$CH_2$–C$H_2$–), 4.56 (s, 2H, Ph–C$H_2$–), 4.85–4.89 (t, 1H, C*H*–$CH_2$–), 7.31–7.36 (m, 5H, $C_6H_5$–).

### 2.6. Copolymerization

A certain amount of DLLA, MABE and 0.1 wt% stannous octoate was put into polymerization tubes. These tubes were filled with nitrogen and heated to 80 °C under vacuum to remove oxygen and trace water, and then the polymerization tubes were sealed under vacuum and placed into an oil bath. After copolymerization, the copolymers were dissolved in ethyl acetate and precipitated into a large amount of ethyl ether. The white poly(DLLA-*co*-MABE) copolymers were dried under vacuum for 2 days at 45 °C.

### 2.7. Removal of benzyl ether protective groups

In a round-bottom flask, 1.5 g of poly(DLLA-*co*-MABE) was dissolved into a mixture of solution (200 ml of 1,4-dioxane and 50 ml of anhydrous acetic acid) at room temperature and then added with 0.2 g of Pd/C. Hydrogen gas was bubbled into the solution for 6 h. After filtration, a clear copolymer solution was obtained. The solvent was removed under reduced pressure and the viscous solution was poured into large amount of ethyl ether, white precipitate was obtained. The de-protected copolymers: poly(DLLA-*co*-MAHE) were recovered by extensive drying at 40 °C under reduced pressure.

### 2.8. Preparation of the de-protected copolymer films

A 10 wt% solution of poly(DLLA-*co*-MAHE) in 1,4-dioxane was cast onto a glass plate. Polymeric films were obtained after the solvent was evaporated in air and further dried under vacuum.

### 2.9. Water uptake experiments

The dried films of known weight were immersed in distilled water. After each set time the films were taken out, wiped with filter paper and weighed. The amount of water absorbed by each copolymer film was calculated by the following equation:

$$\text{Water content}\ (\%) = \left(\frac{W_t - W_0}{W_0}\right)$$

where $W_0$ is the initial weight of the dry film; $W_t$ is the weight of the film after each set time in distilled water.

### 2.10. Water contact angle experiments

Water was pumped onto the surface of the film through a stainless steel needle at a rate of 2 μl $s^{-1}$ until the drop diameter was greater than 4 times the diameter of the needle. At this point, the drop was allowed to stand for 20 s before measuring the contact angle. Ten independent determinations at different sites of each sample were averaged. Deionized water was used for the measurement.

### 2.11. In vitro degradation experiments

De-protected copolymer (200 mg) was dissolved in 2.0 ml of acetone in a 15 mm internal diameter glass vial. After the solvent was evaporated, 10 ml of 0.2 mol $l^{-1}$ phosphate buffer solution (PBS, pH 7.4) was added. And then the flasks were kept at $37.0 \pm 0.5$ °C in a shaking bath (80 r $min^{-1}$) for predetermined periods of time. After each degradation period, the specimens were washed with distilled water, dried in a vacuum oven at 40 °C for 24 h and weighed. The weight loss percentage of the specimen was calculated from the dried weight obtained before and after degradation.

## 3. Results and discussion

### 3.1. Copolymerization

Two monomers of MABE and DLLA were copolymerized by ring-opening polymerization using stannous octoate as initiator. All of the copolymers obtained were white solid, except for the copolymer F which was soft and sticky at room temperature. The benzyloxyethyl protective groups could be removed

Table 1
Molecular weight of poly(DLLA-*co*-MABE) copolymers with the monomer feed variation[a]

| Copolymer | MABE content (mol %) | | | Molecular weight[c] | | |
|---|---|---|---|---|---|---|
| | Feeding | Polymer[b] | Yield (%) | $M_n$ | $M_w$ | $M_w/M_n$ |
| A | 0 | 0 | 85 | 224,500 | 411,000 | 1.83 |
| B | 5 | 5 | 79 | 70,100 | 100,000 | 1.42 |
| C | 10 | 9 | 77 | 47,300 | 74,200 | 1.56 |
| D | 15 | 14 | 71 | 31,400 | 50,300 | 1.60 |
| E | 20 | 17 | 65 | 16,300 | 26,400 | 1.62 |
| F | 35 | 28 | 60 | 9200 | 14,900 | 1.61 |

[a] Copolymerized at 130 °C for 48 h with 0.1 wt% catalyst.
[b] Calculated from $^1$H NMR.
[c] Determined by GPC.

by hydrogenolysis using Pd/C as catalyst, and the amount of functional groups in the copolymers can be controlled by adjusting the feeding dose of MABE. Compared to the previous route to functionalized PLA with hydroxyl groups [39], this new synthetic method has some advantages, such as simple reaction procedure, relative long hydroxyl arms and relative high content of functional groups found in the copolymer.

With the temperature maintained at 130 °C for 48 h, copolymerization was conducted with various monomer ratios. Table 1 shows that, upon increasing MABE content in the feed, the yield and the molecular weight decreased, while the content of MABE units in the copolymer increased. It could be seen that when MABE feeding was changed from 5.0% to 20%, the yield and $M_w$ decreased from 69% to 55% and from 100,000 to 26,400, respectively. It was due to transesterification, which commonly occurs in ring-opening polymerization [1]. The transesterification in this copolymerization system would be discussed in Section 3.2.

### 3.2. Structural characterization

$^1$H and $^{13}$C NMR spectral data were used to characterize the proportion and structure of poly(DLLA-*co*-MABE). Fig. 1 displays the $^1$H NMR spectrum of the copolymer D. Compared with the spectrum of PLA homopolymer [40], the signals at 5.19 and 1.57 ppm were due to the C*H* (b) and C$H_3$ (a) protons of DLLA repeat unit, respectively. According to the spectrum of poly(benzyl-β-malolactonate) which was previously published in the literature [27], the signals at 5.53 and 3.00 ppm were assigned to the C*H* (d) and C$H_2$ (c) protons of the MABE repeat unit in the copolymer main chain and the signals at 7.31, 4.51, 4.30 and 3.65 ppm were attributed to C$_6H_5$ (h), C$H_2$ (g), C$H_2$ (e) and C$H_2$ (f) in the benzyloxyethyl pendent groups. As a low content component in the copolymer, MABE segments were separated by large amount of DLLA repeat units, so the proton signals of MABE were relatively wide. By integration of bands (b) and (d), the MABE content in the copolymer was calculated and the results are summarized in Table 1.

The full $^{13}$C NMR spectra of samples A and E are shown in Fig. 2. Assignments of the major resonances were based on the spectrum of PDLLA (sample A) and PMA homopolymer [41]. The signals at 16.7, 69.1, and 169.3 ppm were assigned to the *C*H$_3$ (c), *C*H (b), and *C*O (a) of the DLLA repeat units. The signals at 35.5, 68.5 and 168.0 ppm were assigned to the *C*H$_2$ (e), *C*H (f) and *C*O (d) of MABE in the copolymer main chain. The signals at 67.6, 64.9, 73.1 and 167.9 ppm were attributed to the *C*H$_2$ (i), *C*H$_2$ (h), *C*H$_2$ (j) and *C*O (g) in the pendent groups. The peaks appeared at 137.8 and 127.7 ppm were due to the benzene ring.

To get an insight into the microstructures of the copolymer, the signals in the carbonyl regions and the signals assigned to the pendent benzyloxyethyl are enlarged and shown in Fig. 3. On the basis of a comparison to the $^{13}$C NMR spectrum of homopolymer A′ (PDLLA sample initiated by 2-benzyloxyethanol), the intense multi-peak at 169.3 ppm was assigned to L*L*L sequences (L was an LA unit with directionality −O−CH−(CH$_3$)−CO−) and the new arisen peak at 169.0 ppm in the spectra C and E was most likely due to the sequence effect of L*L*M (M was an MABE unit). From the analysis of $^{13}$C NMR spectra of copolymers C and E it was found that the strength of both signals at 168.1 and 167.9 ppm increased with the increase in MABE content. As a result, the signals at 168.1 and 167.9 ppm were assigned to *C*O (g) and *C*O (d) in

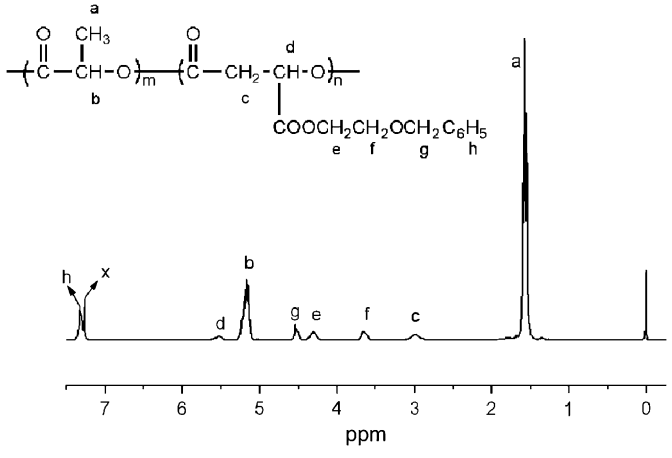



Fig. 1. $^1$H NMR spectrum of the copolymer D (solvent = $CDCl_3$). The peak (*x*) is the solvent signal.

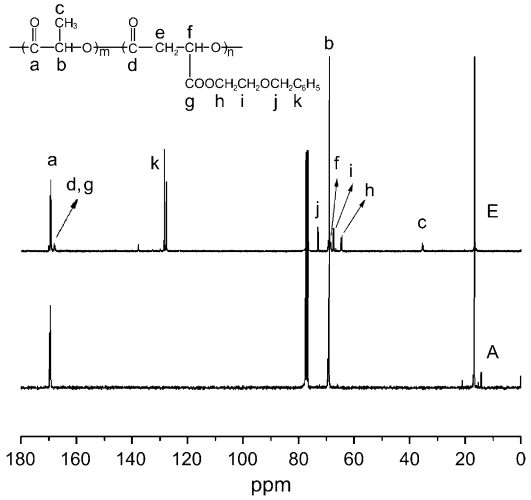



Fig. 2. $^{13}$C NMR spectra of copolymers A and E (solvent = $CDCl_3$).

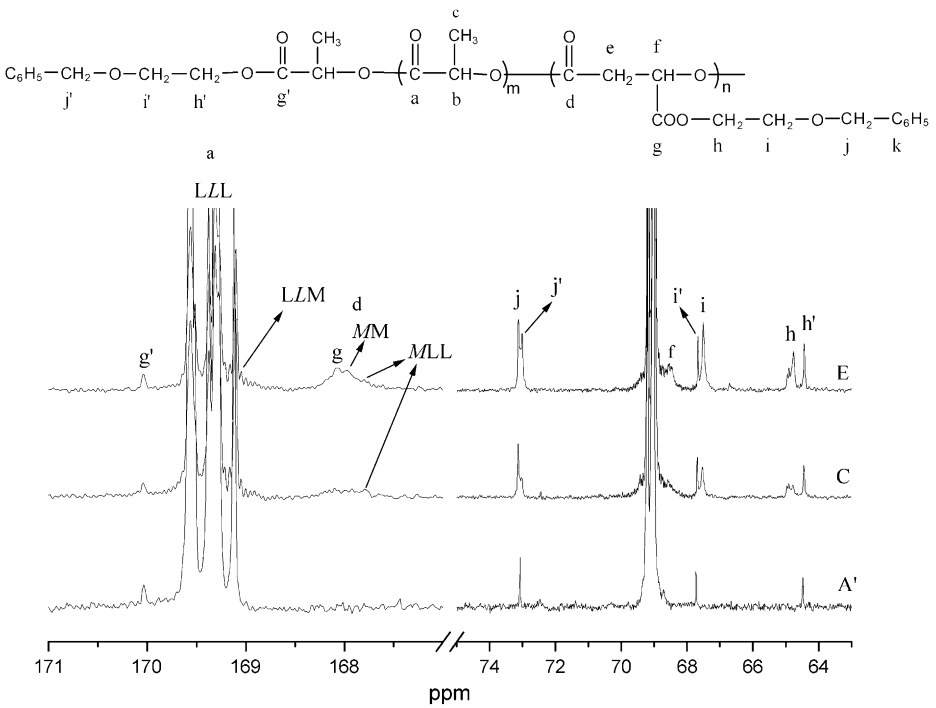



Fig. 3. Enlarged $^{13}$C NMR spectra of the carbonyl and the pendent benzyloxyethyl regions of polymers A′, C and E (solvent = $CDCl_3$).

the MABE units, respectively. The *C*O peaks in MABE units were extremely broad, which indicated that the MABE units were separated by large amount of DLLA repeat units. So, the signals at 167.9 and 167.7 ppm might be attributed to the *C*O (d) with *M*M and *M*LL sequences. The assignments of sequence effect further confirmed that MABE and DLLA units were linked by covalent bond and the polymer samples were true copolymer.

Commonly, in such coordination–insertion polymerizations initiated by $Sn(Oct)_2$, the molecular weight depends not only on the ratio of monomer/initiator, but also on the extent of transesterification side reactions. Many literatures have reported that these transesterification reactions can occur both intramolecularly (backbiting leading to macrocyclic structures and shorter chains) and intermolecularly (chain redistributions). But in our work, it is difficult for the backbiting and chain redistribution reactions to happen in the copolymerization of MABE and DLLA due to their high steric hindrance effect. From Table 1, it can be seen that as the MABE content increases the $M_w/M_n$ increased and $M_w$ decreased. This strongly suggested that the transesterification reactions occurred in the copolymerization process, and these side reactions related to the MABE monomer.

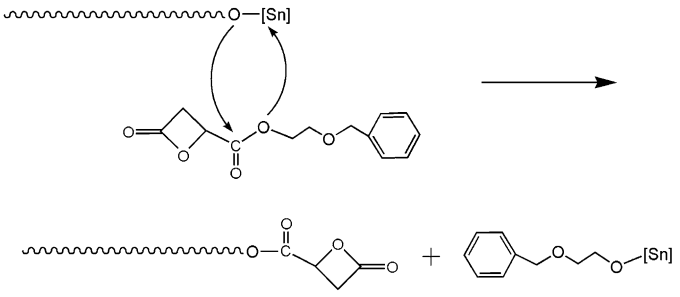
So, we firstly suppose the transesterification reaction as shown in Scheme 2 occurred in this copolymerization system.

The initially activated center reacted with the protective groups to produce a copolymer chain ended with a four member cyclic lactone and a new activated center of 2-benzyloxyethoxy-[Sn]. If such transesterification reaction really occurred in the copolymerization of MABE and DLLA, some polymer chains must have the 2-benzyloxyethyloxycarbonyl extremity. To prove our supposal, we prepared a new PDLLA sample (A′) using 2-benzyloxyethanol as initiator. This polymer definitely contained the 2-benzyloxyethyloxycarbonyl extremity.

By the comparison between the $^{13}$C NMR spectra of sample A′ and the copolymer samples C and E, it can be concluded that there were 2-benzyloxyethyloxycarbonyl extremity signals in the $^{13}$C NMR spectra of samples C and E. This NMR result strongly supported our supposal. The transesterification as shown in Scheme 2 occurred in the copolymerization of the two monomers, and it causes the molecular weight to decrease and $M_w/M_n$ to increase with the increase in MABE content.

### 3.3. Deprotection

Pd/C, which was a useful and mild catalyst for the removal of the benzyl ether group, was employed to hydrogenate the copolymers. Work was performed to select a suitable solvent for this reaction. A series of solvents with different polarities,




Scheme 2. Predicted mechanism of transesterification in the copolymerization of MAHE and DLLA.

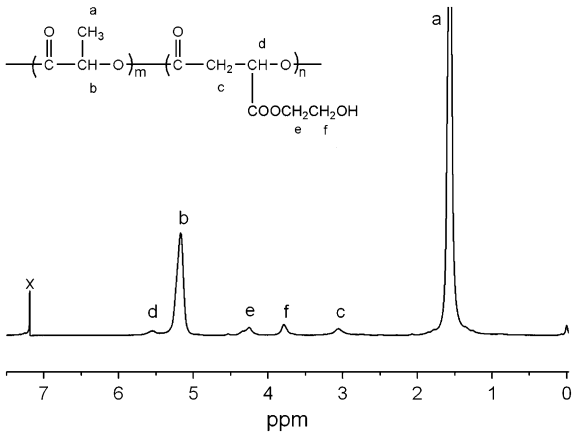



Fig. 4. $^1$H NMR spectrum of the de-protected copolymer D (solvent = $CDCl_3$). The peak (*x*) is the solvent signal.

including toluene, 1,4-dioxane, acetone, THF and acetic acid were examined. The hydrogenation in acetic acid was successful, while it was unsuccessful in the other solvents. Unfortunately, in this acidic solvent the degradation of the copolymers proceeded together with the hydrogenation and the $M_w$ decreased by nearly 20%. To solve this problem, the mixed solvents of 1,4-dioxane and acetic acid with different v/v ratios were tested. It was found that with the content of the acetic acid increasing the degrees of both hydrogenation and degradation increased. An optimum mixture of solvent was obtained as the v/v ratio of 1,4-dioxane and acetic acid being 4/1, in which a high extend of debenzylation and a low degradation degree were achieved in 6 h. $^1$H NMR spectrum of the de-protected copolymer D (d-D) is shown in Fig. 4.

After hydrogenation, the signals of $CH_2$ (g) and $C_6H_5$ (h) were extremely weakened and the peak center of $CH_2$ (f) moved from 3.65 to 3.79 ppm towards the low field. These results indicated the removal of benzyl protective groups and the formation of pendent hydroxy groups. The degree of debenzylation was calculated by monitoring the extent of decrease of the protons $CH_2$ (g) at 4.51 ppm relative to proton $CH$ (d) at 5.53 ppm. For example, copolymer D was debenzylated in the mixture solvent using Pd/C as catalyst at room temperature for 6 h and was isolated in quantitative yield as a white solid. The de-protected copolymer D had $M_w$ 46,500, $M_w/M_n$ 1.44 and a degree of benzyl ether removal of 93%.

### 3.4. Thermal properties of poly(DLLA-co-MABE) and poly(DLLA-co-MAHE)

The thermal properties of poly(DLLA-*co*-MABE) and poly(DLLA-*co*-MAHE) were determined by DSC and shown in Fig. 5. The amorphous copolymers were obtained by the copolymerization of two racemic monomers and no crystal-melting peaks were found in all DSC thermograms. In Fig. 5(a), the glass transition temperature ($T_g$) of the protected copolymers decreased as the MABE content increases. The copolymer F had a glass transition temperature as low as 20.4 °C, so it was soft and sticky at room temperature. The $T_g$'s of the de-protected copolymers as shown in Fig. 5(b) seemed irregular. This investigation can be explained like this: after hydrogenation, the hydroxyl pendent groups were recovered and the hydrogen bonds were formed between the hydroxyl groups and the carbonyl groups; the $T_g$'s of the de-protected copolymers were influenced by both molecular weight and hydrogen bonds; for the samples d-B, d-C and d-D, the hydrogen bonds were relatively weak and the $T_g$'s of these samples decreased with the decrease in molecular weight; with the MAHE content increasing, the effect of hydrogen bonds was enhanced, so that the $T_g$ of the sample d-E was higher than that of the sample d-D, which should be lower if only the molecular weight was taken into account. Only one $T_g$ was observed in all of the DSC thermograms which further confirmed that the copolymers were true copolymers and not just a mixture of PDLLA and PMAHE homopolymers.

### 3.5. Hydrophilicity measurements

The hydrophilicity of the de-protected copolymers was evaluated by water uptake and water contact angle measurements.

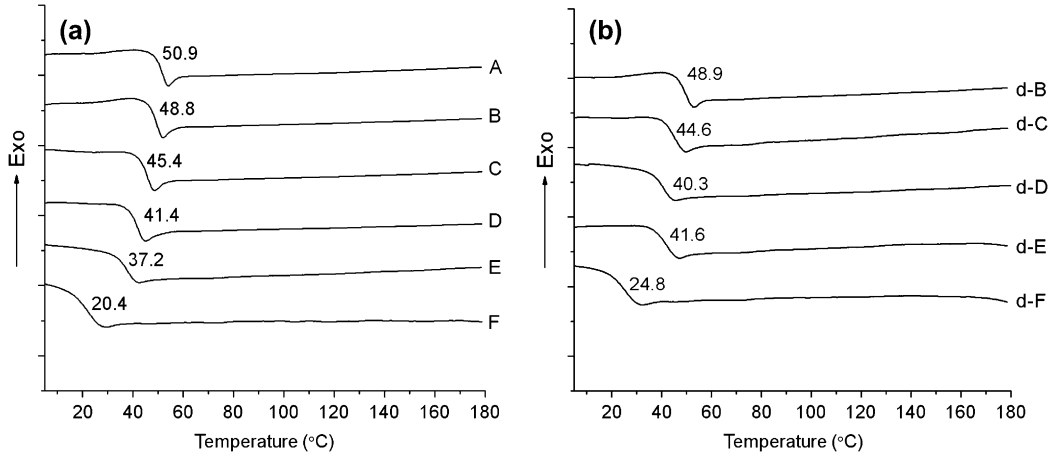



Fig. 5. DSC thermograms of the protected and de-protected copolymers: (a) poly(DL-lactide-*co*-*RS*-benzyloxyethyl-β-malolactonate); (b) poly(DL-lactide-*co*-*RS*-hydroxyethyl-β-malolactonate).

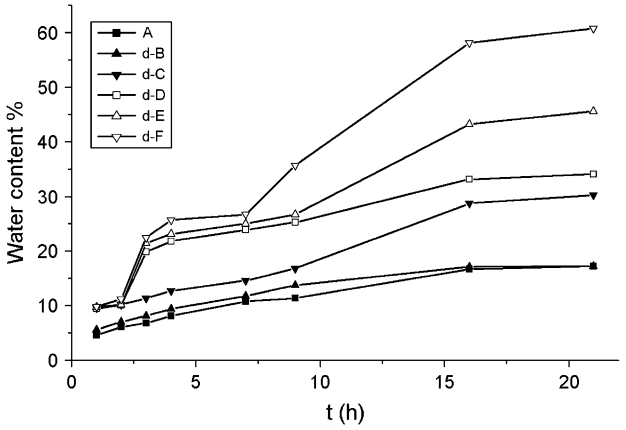



Fig. 6. Water uptake of the PDLLA homopolymer and the de-protected copolymers (from d-B to d-F).

The influence of MAHE content on the water uptake is illustrated in Fig. 6. The water content of all the copolymer films increased over time and faster water uptake rate was discovered in the film which contains more MAHE content. After 22 h, more water was taken by the films with more MAHE content.

The water contact angles of PDLLA homopolymer and the de-protected copolymers are shown in Fig. 7. The water contact angle decreased from 81 to 48° as the MAHE content increased from 0% to 17%. It suggested that the hydrophilicity was improved greatly by the introduction of hydroxyl arms into the polylactide backbone and it increased with increase in MAHE content.

### 3.6. In vitro degradation experiments

Fig. 8 shows the weight loss of the PDLLA and poly(DLLA-*co*-MAHE) copolymers according to the degradation time. Although the degradation of PDLLA had been described in the previous literature [16] and it was known that PDLLA had a lower degradation rate due to its hydrophobicity, the weight loss of PDLLA was also studied as a comparable

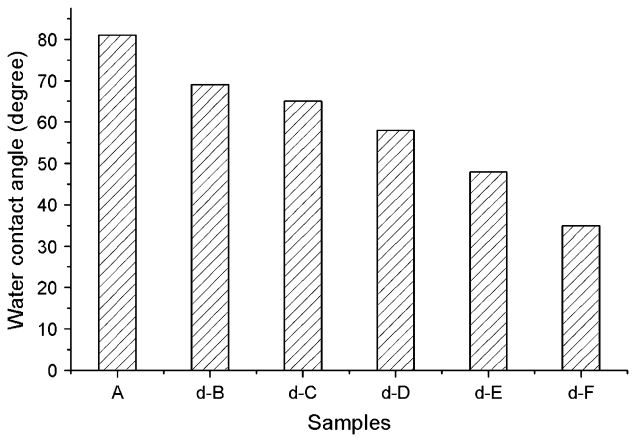



Fig. 7. Water contact angles of the PDLLA homopolymer and the de-protected copolymers (from d-B to d-F).

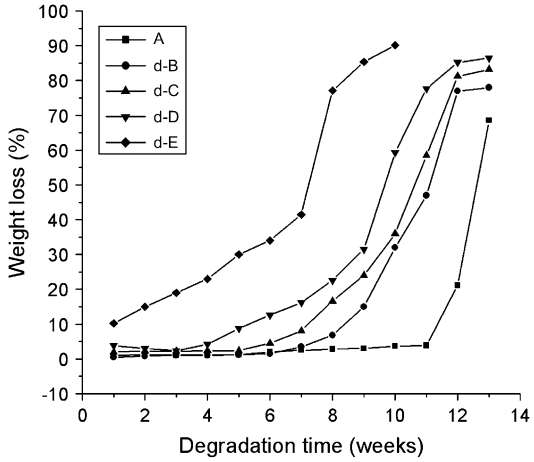



Fig. 8. The weight loss of the PDLLA homopolymer and the de-protected copolymers (from d-B to d-E) according to the degradation time.

data in this paper. As expected, the degradation rates of the copolymers increased with increasing content of MAHE. The weight loss percentage of the sample d-E was about 40% after 7 weeks, while significant weight loss of the sample A was found after 12 weeks. There was very little weight loss of the samples d-B, d-C and d-D in the first 7 weeks. Between 8 and 12 weeks, the weight loss of these three samples burst up to 77%, 81% and 85%, respectively, corresponding to the release of internal oligomers.

In order to get detail information about the degradation of these de-protected copolymers, the degradation process of the sample d-D was traced by $^{1}$H NMR. The $^{1}$H NMR spectra of the sample d-D after 1, 3, 5 and 7 weeks of degradation are shown in Fig. 9. It was found that after 7 weeks the $^{1}$H NMR signals assigned to MAHE units were extremely weakened. It indicated that the degradation rate of the MAHE units was faster than that of the DLLA units. The hydrophilic hydroxyl side groups of the MAHE units made it easy for water to diffuse into MAHE segments, so the MAHE units could degrade

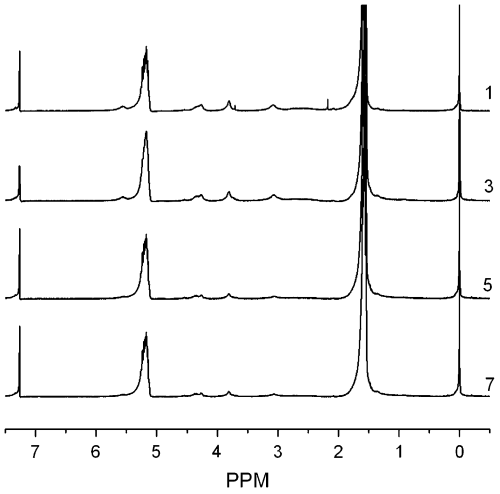



Fig. 9. $^{1}$H NMR spectra of the sample d-D after 1, 3, 5 and 7 weeks of degradation.

faster than the DLLA units. The degradation of MAHE units caused the scission of the copolymer main chain; this also accelerated the degradation of the copolymers. On the other hand, the component of sample d-D was very stable in the first 3 weeks; this stability would be beneficial for the further application in tissue engineering area.

## 4. Conclusions

The main conclusions from this paper can be summarized as follows:

1. Novel poly(DLLA-*co*-MAHE) copolymers with pendent hydroxyl arms were synthesized by the copolymerization of DLLA and MABE. These copolymers were random copolymers, which were proved by NMR measurement.
2. The hydrophilicity and water-swollen property of the film prepared by the de-protected copolymer could be adjusted by the MAHE content which was equal to the MABE content. Thus, films with various hydrophilicities and water-swollen properties can be designed via regulating the feeding dose of MABE.
3. In the degradation experiments faster degradation rate was discovered with the films containing higher MAHE content. In the first 3 weeks of degradation, all of the samples d-B, d-C and d-D were very stable; nearly no weight loss and composition changes were observed.

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## References

[1] Albertsson AC, Varma IK. Biomacromolecules 2003;4:1466–86.
[2] Holy CE, Cheng C, Davies JE, Shoichet MS. Biomaterials 2001;22:25–31.
[3] Busby W, Cameron NR, Jahoda CAB. Polym Int 2002;51:871–81.
[4] Harris LD, Kim BS, Mooney DJ. J Biomed Mater Res 1998;42:396–402.
[5] Kim WS, Vacanti JP, Cima L, Mooney D, Upton J, Puelacher WC, et al. Plast Reconstr Surg 1994;94:233–41.
[6] Mooney DJ, Mazzoni CL, Breuer C, McNamara K, Hern D, Vacanti JP, et al. Biomaterials 1996;17:115–24.
[7] Mikos AG, Thorsen AJ, Czerwonka LA, Bao Y, Langer R, Winslow DN, et al. Polymer 1994;35:1068–77.
[8] Çatiker E, Gümüsderelioglu M, Güner A. Polym Int 2000;49:728–34.
[9] Li S, McCarthy S. Biomaterials 1999;20:35–44.
[10] Cai K, Yao K, Cui Y, Yang Z, Li X, Xie H, et al. Biomaterials 2002;23:1603–11.
[11] Nitschke M, Schmack G, Janke A, Simon F, Pleul D, Werner C. J Biomed Mater Res 2002;59:632–8.
[12] Chu PK, Chen JY, Wang LP, Huang N. Mater Sci Eng R 2002;36:143–206.
[13] Dai L, St John HAW, Bi J, Zientek P, Chatelier RC, Griesser HJ. Surf Interface Anal 2000;29:46–55.
[14] Yang J, Bei J, Wang SG. Biomaterials 2002;23:2607–14.
[15] Quirk RA, Davies MC, Tendler SJB, Shakesheff KM. Macromolecules 2000;33:258–60.
[16] Quirk RA, Davies MC, Tendler SJB, Chan WC, Shakesheff KM. Langmuir 2001;17:2817–20.
[17] Zhu H, Ji J, Lin R, Gao C, Feng L, Shen J. J Biomed Mater Res 2002;62:532–9.
[18] Lee JY, Nam SH, Im SY, Park YJ, Lee YM, Seol YJ, et al. J Controlled Release 2002;78(1–3):187–97.
[19] Lee SJ, Khang G, Lee YM, Lee HB. J Biomater Sci Polym Ed 2002;13(2):197–212.
[20] Khang G, Jeon JH, Cho JC, Rhee JM, Lee HB. Polymer Korea 1999;23(6):861–8.
[21] Mizutani M, Arnold SC, Matsuda T. Biomacromolecules 2002;3:668–75.
[22] Nederberg F, Bowden T, Hilborn J. Macromolecules 2004;37:954–65.
[23] Cordova A, Iversen T, Hult K. Polymer 1999;40:6709–21.
[24] Kita-Tokarczyk K, Grumelard J, Haefele T, Meier W. Polymer 2005;46(11):3540–63.
[25] del Río C, Jurado JR, Acosta JL. Polymer 2005;46(12):3975–85.
[26] Ouchi T, Fujino A. Makromol Chem 1989;190:1523–30.
[27] Vert M, Fournier P, Boustta M, Domurado D, Guerin P, Braud C, et al. Macromol Rep 1994;A31:723–30.
[28] Bizzarri R, Chiellini F, Solaro R, Chiellini E, Cammas-Marion S, Guerin P. Macromolecules 2002;35:1215–23.
[29] Coulembier O, Degee P, Gerbaux P, Wantier P, Barbaud C, Flammang R, et al. Macromolecules 2005;38:3141–50.
[30] Zhou QX, Kohn J. Macromolecules 1990;23:3399–406.
[31] In't Veld PJA, Dijkstra PJ, Feijen J. Makromol Chem 1992;193:2713–30.
[32] Nishida H, Tokiwa Y. Chem Lett 1994;3:421–5.
[33] Zhu KJ, Hendren RW, Jensen K, Pitt CG. Macromolecules 1991;24:1736–40.
[34] He B, Bei J, Wang S. Polymer 2003;44:989–94.
[35] He B, Bei J, Wang S. Polym Adv Technol 2003;14(9):645–52.
[36] Gohy JF, Lohmeijer BGG, Schubert US. Macromol Rapid Commun 2002;23:555–60.
[37] Tasaka F, Miyazaki H, Ohya Y, Ouchi T. Macromolecules 1999;32:6386–9.
[38] Cammas S, Renard I, Langlois V, Guerin P. Polymer 1996;37:4215–20.
[39] Kumar R, Gao W, Gross RA. Macromolecules 2002;35:6835–44.
[40] Penczek S, Duda A, Szymanski R. Macromol Symp 1998;132:441–5.
[41] Boutalt K, Cammas S, Huet F, Guerin P. Macromolecules 1995;28:3516–20.