Synthesis and Characterization of Biodegradable Crosslinked Polymers from 5-Hydroxylevulinic Acid and α,ω-Diols

Yan Zhang,* Linbo Wu, Bo-Geng Li

State Key Laboratory of Chemical Engineering, Department of Chemical and Biochemical Engineering, Zhejiang University, Hangzhou 310027, China

Received 13 April 2009; accepted 17 July 2009
DOI 10.1002/app.31139
Published online 6 May 2010 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Novel biodegradable chemically crosslinked polymers, poly(5-hydroxylevulinic acid-*co*-α,ω-diol)s (PHLA-diols), were synthesized from 5-hydroxylevulinic acid and α,ω-diols and characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, thermogravimetric analysis, and dynamic mechanical analysis. The gel content, swelling ratio, tensile properties, and hydrolytic degradation behaviors were also measured and assessed. The glass-transition temperature of the PHLA-diols could be adjusted within a wide range (−50 to 30°C) by the type and feed ratio of the diol. Because of the low glass-transition temperature and crosslink structure, they exhibited certain elastic properties. The tensile modulus, strength, and elongation at break measured at 37°C were 1.4–6.3 MPa, 0.8–1.6 MPa, and 10–25%, respectively. These polymers could be hydrolytically degraded. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 3315–3321, 2010

Key words: biodegradable; crosslinking; polycondensation; polyesters

INTRODUCTION

Chemically crosslinked polymers are usually synthesized via the step growth or addition polymerization of multifunctional monomer systems and are widely used as thermosetting polymers, elastomers, coatings, adhesives, and so on. Recently, biodegradable crosslinked elastic polymers have attracted much attention[1–4] because they mimic tissue better and, therefore, are more advantageous than their rigid counterparts in some biomedical applications, such as surgical implants and tissue engineering scaffolds.[1,2] They can be synthesized via the polycondensation of multifunctional aliphatic acid/alcohol monomer systems[1–5] and via the ring-opening polymerization of a special lactone monomer.[6] Poly(glycerol sebacate) synthesized from glycerol and sebacic acid[1] and poly(1,8-octanediol-*co*-citric acid) synthesized from 1,8-octanediol and citric acid[2] are typical biodegradable crosslinked elastomers. These materials are biodegradable and biocompatible and have been assessed as tissue engineering scaffolds.[1,2,7–11]

In our previous work,[12,13] we prepared 5-hydroxylevulinic acid (5-HLA) and its low-molecular-weight polymer, poly(5-hydroxylevulinic acid) (PHLA), from levulinic acid, a biomass-derived platform chemical. PHLA exhibits a glass-transition temperature (T_g) that is much higher than those of ordinary aliphatic polyesters, although its molecular weight is low. Interestingly, we found in further study that 5-HLA can react with α,ω-diols to generate new biodegradable crosslinked polymers called *poly(5-hydroxylevulinic acid-co-α,ω-diol)s* (PHLA-diols). The synthesis and properties of such polymers are reported in this article.

EXPERIMENTAL

Materials

5-HLA was synthesized as previously described.[12,13] Ethylene glycol (EG), 1,4-butanediol (BDO), 1,6-hexanediol (HDO), poly(ethylene glycol) with a molecular weight of 200 (PEG200), poly(ethylene glycol) with a molecular weight of 400 (PEG400), stannous chloride dihydrate ($SnCl_2 \cdot H_2O$), and *p*-toluene sulfonic acid were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). 1,3-

**Present address:* Ningbo Institute of Technology, Zhejiang University, Ningbo 315100, China.
Correspondence to: L. Wu (wulinbo@zju.edu.cn).
Contract grant sponsor: National Science Foundation of China; contract grant numbers: 20304012, 20674067, and 20406018.
Contract grant sponsor: Prior Special Fund for the 973 Program of China; contract grant number: 2004CCA05500.
Contract grant sponsor: National Science Foundation of China of Zhejiang Province; contract grant number: Y404084.

Propanediol (PDO) and poly(ethylene glycol) with a molecular weight of 300 (PEG300) were purchased from Sigma-Aldrich (Shanghai, China) and Haltermann (Hamburg, Germany), respectively. Tetrahydrofuran (THF) was used as received.

Synthesis

The polymerization was conducted in two steps. First, a mixture of 5-HLA and a diol was dehydrated at 120°C under atmospheric pressure for 1.5 h and then under a pressure of about 2000 Pa for another 1.5 h. Then, $SnCl_2 \cdot H_2O$ and *p*-toluene sulfonic acid (molar ratio = 1 : 1, 0.5–0.9 wt % $SnCl_2 \cdot H_2O$ based on total monomer) were added to the resultant viscous prepolymer, and a curing or postpolycondensation reaction was carried out under atmospheric pressure at a given temperature up to a constant value of the gel content (ϕ_{gel}). To prepare samples for mechanical testing, the curing reaction was conducted in Teflon molds with dumbbell-like or rectangular caves. To prevent the formation of bubbles as a result of the escape of byproduct water, the reaction was carried out slowly via a gradual increase in the curing reaction temperature from 50 to 120°C.

Characterization

A crude sample with weight W_0 was extracted with boiling THF in a Soxhlet extractor for 24 h. The fully extracted and swollen sol-free sample was weighed (W_1) and then dried to a constant weight (W_2) *in vacuo* at 40°C. The gel content (ϕ_{gel}) of the crude sample was defined as W_2/W_0, and the swelling ratio (r_s) of the gel was defined as W_1/W_2.

Fourier transform infrared (FTIR) spectra of the PHLA-diols were recorded with a Nicolet 560 infrared spectrometer (Waltham, MA). Differential scanning calorimetry (DSC) analysis was performed with a differential scanning calorimeter (PerkinElmer DSC7, Waltham, MA) at a heating rate of 10°C/min and with scanning from −100 to 150°C. Samples before and after THF extraction were both used for DSC measurement. Thermogravimetric analysis was performed with PerkinElmer Pyris 1 thermogravimetric analyzer (Waltham, MA) at a heating rate of 20°C/min in nitrogen.

Mechanical testing

Specimens with high ϕ_{gel} values (without THF extraction) were used for mechanical tests. Tensile testing was carried out with a Zwick/Roell Z020 universal testing machine (Ulm, Germany) at 37°C with a crosshead separation speed of 50 mm/min. For each polymer, at least five dumbbell-like specimens were tested. Dynamic mechanical behavior was measured with a DMA Q800 (TA Instrument, New Castle, DE) with rectangular samples. The specimens were measured in single-cantilever mode from −60 to 100°C at a heating rate of 2°C/min with a frequency of 1 Hz.

Hydrolytic degradation

The hydrolytic degradation was conducted in deionized water at 37°C and in phosphate-buffered saline (PBS; pH 7.4) at 60°C, respectively. Dry specimens were placed in a tube containing 30 mL of liquid and stayed thermostatically for a predetermined time. After degradation, the samples were washed with deionized water and dried at 30°C for 48 h *in vacuo*. The normalized weight (W/W_0, where W_0 and W are the dry weights before and after degradation, respectively) was used to characterize the degradation.

RESULTS AND DISCUSSION

Synthesis

The reaction between 5-HLA and a diol was conducted in two stages. First, 5-HLA and a diol were mixed and polycondensed to produce a viscous prepolymer; then, a binary catalyst was added, and a curing reaction occurred, which produced the final product. The prepolymer was soluble in THF. After catalyst addition, the viscosity of the reaction mixture increased gradually, and the final product was no longer soluble but swollen in THF; this indicated the formation of crosslinks. For simplicity, the polymer of 5-HLA and the diol is called a PHLA-diol.

The α,ω-diols used in this study included EG, PDO, BDO, HDO, PEG200, PEG300, and PEG400. The diol type had a clear effect on the postpolycondensation reaction, as shown in Figure 1. The molar fraction of the diol in the monomer feed (ϕ_{diol}) was 0.5. ϕ_{gel} increased rapidly for BDO, PDO, and HDO. However, the crosslinking rate was reduced for EG and the PEGs, and there appeared an induction period. The reaction rate and final gel content ($\phi_{gel,f}$) decreased in the order BDO > PDO > HDO > EG > PEG200 > PEG300 > PEG400. $\phi_{gel,f}$ reached 0.38–0.98 in 0.5–5 h, depending on the diol used.

Figures 2 and 3 show the ϕ_{gel}–time curves of the HLA–BDO system [BDO molar fraction in the monomer feed (ϕ_{BDO}) = 0.5] at various catalyst concentrations (0.5–0.9 wt %) and temperatures (130–170°C) at the second reaction stage, respectively. The effects of the reaction conditions on $\phi_{gel,f}$ were weak, and almost the same $\phi_{gel,f}$, as high as 95–99%, was reached under all of these reaction conditions. However, the effects on the reaction rate were significant. At higher catalyst concentrations and higher temperatures, ϕ_{gel} increased more rapidly, and it took a shorter time to reach $\phi_{gel,f}$. ϕ_{gel} increased steadily with time and reached a $\phi_{gel,f}$ of 0.96 in about 100

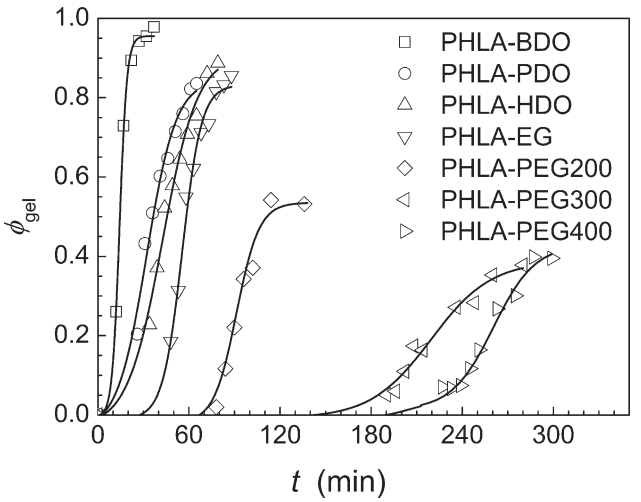


Figure 1 ϕ_{gel}–time (t) curves of crude PHLA-diols during the postpolycondensation of 5-HLA and diols (reaction conditions: ϕ_{diol} = 0.5, $SnCl_2{\cdot}H_2O$ concentration = 0.7 wt %, temperature = 150°C).

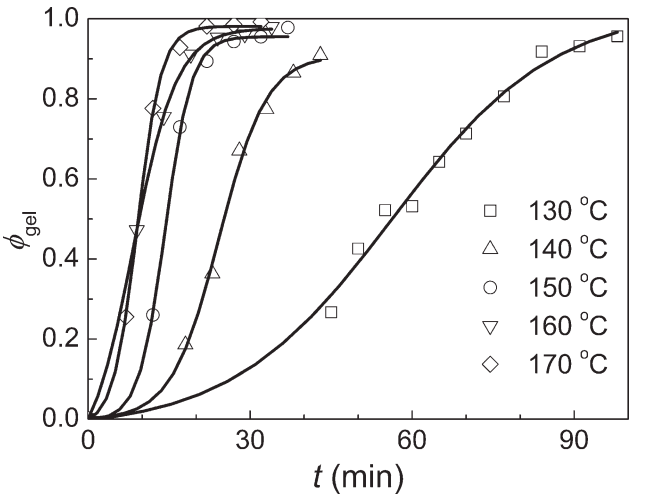


Figure 3 ϕ_{gel}–time (t) curves of crude PHLA–BDO during the postpolycondensation of 5-HLA and BDO at various temperatures (reaction conditions: ϕ_{BDO} = 0.5, $SnCl_2{\cdot}H_2O$ concentration = 0.7 wt %).

min at 130°C. The reaction sped up significantly when the temperature was raised to 140–150°C. However, its effect leveled off at higher temperatures, 160–170°C. At such high temperatures, the byproduct, water, was produced rapidly during the curing stage and in the polycondensation stage. As a result, bubbles were readily formed in the product. To obtain a dense product, the reaction rate had to be slowed down through elaborate adjustment of the temperature (<120°C) and/or catalyst concentration.

Crosslinked PHLA-diols could be obtained in a wide range of monomer feed ratios. For the 5-HLA–BDO system, ϕ_{BDO} influenced not only the reaction rate but also $\phi_{gel,f}$. As shown in Figure 4(A), a weakly crosslinked PHLA–BDO ($\phi_{gel,f}$ = 0.4) was obtained when 5% BDO was introduced into the monomer feed. The reaction accelerated and $\phi_{gel,f}$ increased continually with increasing ϕ_{BDO}. The highest $\phi_{gel,f}$ values were reached at ϕ_{BDO} values ranging from 0.25 to 0.55. $\phi_{gel,f}$ was higher than 0.92 in this ϕ_{BDO} range. At higher ϕ_{BDO} values, the reaction rate slowed, and $\phi_{gel,f}$ decreased again. Crosslinked polymers could no longer be synthesized when ϕ_{BDO} exceeded 0.85. On the contrary, r_s first decreased clearly with ϕ_{BDO}, leveled off at a ϕ_{BDO} value of 0.25–0.55, and then increased again. This implied that the polymer network was more dense as ϕ_{gel} increased. According to the changes in $\phi_{gel,f}$

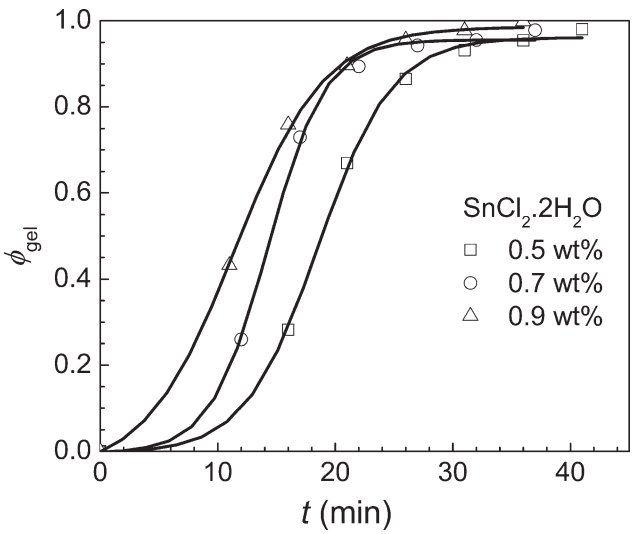


Figure 2 ϕ_{gel}–time (t) curves of crude PHLA–BDO during the postpolycondensation of 5-HLA and BDO with various amounts of the catalyst (reaction conditions: ϕ_{BDO} = 0.5, temperature = 150°C).

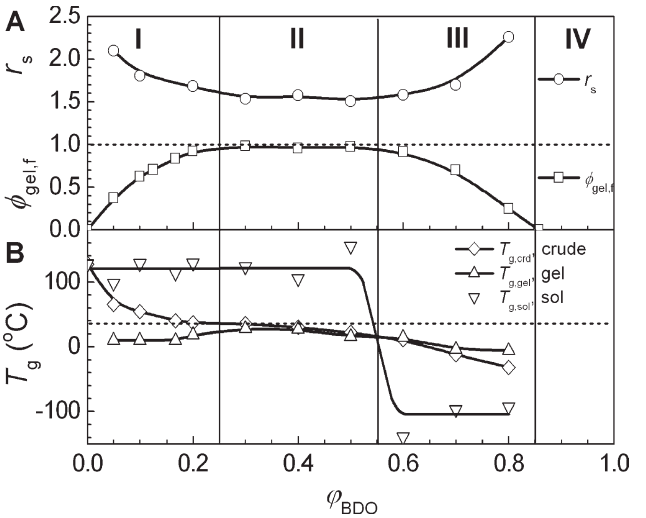
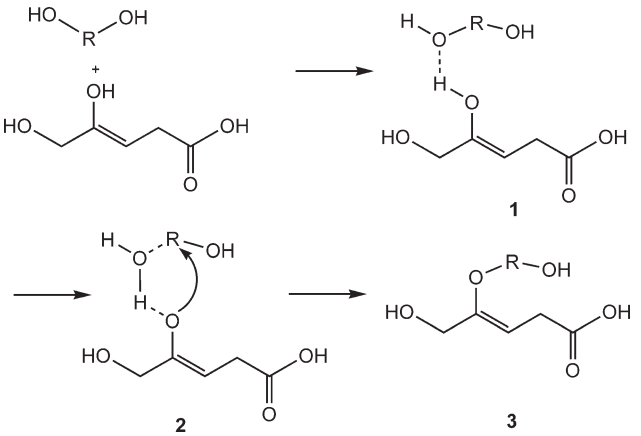


Figure 4 (A) $\phi_{gel,f}$ of crude PHLA–BDO and r_s of PHLA–BDO gel as functions of ϕ_{BDO}. (B) $T_{g,crd}$, $T_{g,gel}$, and $T_{g,sol}$ [estimated from eq. (1)] as functions of ϕ_{BDO} (reaction conditions: $SnCl_2{\cdot}H_2O$ concentration = 0.7 wt %, temperature 150°C).

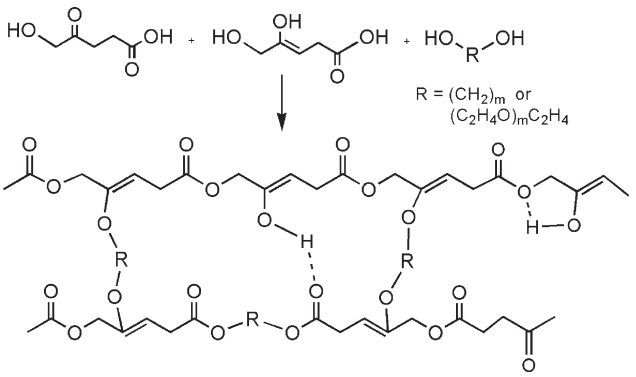


Scheme 1 Etherification reaction between the enol form of 5-HLA and the diol.

and r_s with ϕ_{BDO}, the ϕ_{BDO} range was divided into four regions: I, II, III, and IV at $\phi_{BDO} < 0.25$, $\phi_{BDO} = 0.25$–0.55, $\phi_{BDO} = 0.55$–0.85, and $\phi_{BDO} > 0.85$, respectively.

Although the crosslinking reaction between 5-HLA and a diol took place easily, the reaction mechanism involved was still not very clear. At first glance, it seems impossible to crosslink 5-HLA and a diol. However, because there is a keto–enol tautomerism equilibrium in 5-HLA[13] and the enol hydroxyl can react with alcohol hydroxyl to form an olefinic ether bond,[14] we speculate that an etherification reaction (Scheme 1) might have occurred between the enol hydroxyl and the diol hydroxyl. In brief, a hydrogen bond was first formed between the H atom of the enol and the O atom of the diol hydroxyl, and complex **1** was thus formed. Then, the H atom transferred to the O atom to form complex **2**. Last, compound **3,** with an olefinic ether structure, formed after dehydration. Therefore, in a 5-HLA/diol system, the esterifications between the carboxyls of 5-HLA and alcohol hydroxyls of both 5-HLA and the diols led to chain growth, and the etherification between the enol hydroxyls and the diol hydroxyls resulted in olefinic ether bonds, which acted as crosslinking points. Scheme 2 shows the possible crosslinking mechanism.

The FTIR and solid-state cross-polarization/magic angle spinning ^{13}C-NMR analyses of the PHLA–BDO gel ($\phi_{BDO} = 0.5$) provided some evidence for the crosslinking mechanism supposed here. In the FTIR spectrum shown in Figure 5, absorptions of enol double bonds at 1612–1616 cm^{-1} and olefinic ether bonds at 1255 cm^{-1} were observed. The solid cross-polarization/magic angle spinning ^{13}C-NMR spectrum also indicated chemical shifts of keto, ester, olefinic ether, and enol, but the spectrum looked a little messy; this suggested that the microstructure of the polymer may have been more complicated than that supposed in Scheme 1. So it was still a challenge to elucidate the crosslinking mechanism and the microstructure of the polymers.



Scheme 2 Possible crosslinking mechanism and microstructure of PHLA-diols.

Thermal properties

PHLA-diols are amorphous polymers, and T_g depends on the type and feed ratio of the diol used. Table I shows the T_g values of various crude PHLA-diols prepared at $\phi_{diol} = 0.5$. The T_g values of crude PHLA–EG, PHLA–PDO, PHLA–BDO, and PHLA–HDO with comparable ϕ_{gel} values (0.86, 0.89, 0.84, and 0.86) were 32.8, 17.0, 1.9, and − 15.6°C, respectively. No clear T_g change was found after extraction. PHLA–PEGs possessed lower T_g values, from − 30.6 to − 48.8°C. Clearly, T_g depended on the chain length or the flexibility of the diols.

Figure 4(B) shows the dependence of the T_g of PHLA–BDO on ϕ_{BDO}. For the crude PHLA–BDO product, the glass-transition temperature of the crude product ($T_{g,crd}$) decreased remarkably from

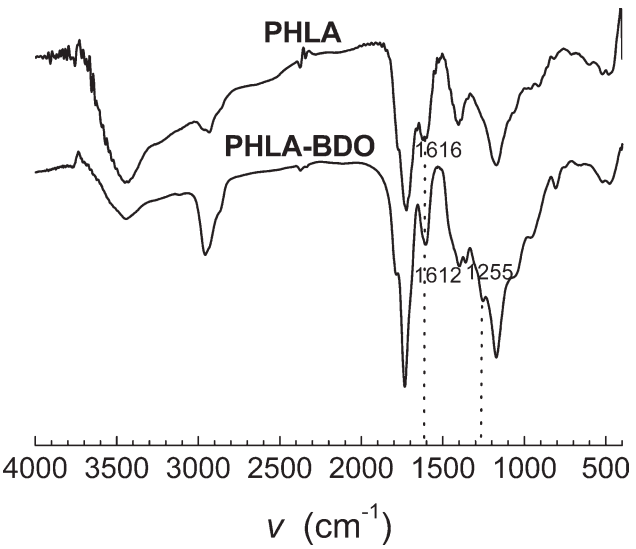


Figure 5 FTIR spectra of PHLA–BDO gel ($\phi_{BDO} = 0.5$) and PHLA.

TABLE I
T_g Values of Various PHLA-Diols

Run	PHLA-diol[a]	N_C[b]	ϕ_{gel}	$T_{g,crd}$ (°C)	$T_{g,gel}$ (°C)
1	PHLA–EG	2	0.86	32.8	30.8
2	PHLA–PDO	3	0.89	17.0	15.5
3	PHLA–BDO	4	0.84	1.9	2.8
4	PHLA–HDO	6	0.86	−15.6	−17.8
5	PHLA–PEG200	8.3	0.53	−30.6	—
6	PHLA–PEG300	12.8	0.38	−46.3	—
7	PHLA–PEG400	17.4	0.39	−48.8	—

[a] $\phi_{diol} = 0.5$.
[b] Number of carbon atoms in the diol.

greater than 100°C to about 37°C in region I, then decreased slowly from 37 to 10°C in region II, and decreased clearly again in region III. It reached −31.6°C when 80% BDO was introduced.

When the crude PHLA–BDOs were extracted with THF and the resultant dry gel was measured with DSC again, a significant difference was observed between the glass-transition temperature of the gel ($T_{g,gel}$) and $T_{g,crd}$. $T_{g,gel}$ was 55°C lower than $T_{g,crd}$ at a ϕ_{BDO} value of 0.05, but the difference gradually diminished as ϕ_{BDO} increased. $T_{g,gel}$ became close to or slightly lower than $T_{g,crd}$ in region II, but it became higher than $T_{g,crd}$ in region III instead. In the whole ϕ_{BDO} range, $T_{g,gel}$ was lower than 30°C and only exhibited a weak dependence on ϕ_{BDO}.

The crude product was composed of crosslinked gel and noncrosslinked sol. After extraction, the sol was removed, and only the gel remained. Obviously, the change in T_g after extraction mainly occurred because the sol had a different structure and, consequently, a different T_g from the gel. In our previous study, we found that PHLA itself had an unordinarily high T_g (≈ 120°C) because of the formation of hydrogen bonds between the carbonyls and enol hydroxyls. However, the formation of crosslinking in the PHLA-diol destroyed, at least partially, the hydrogen bonds. Therefore, the PHLA–BDO gels had much lower T_g values than PHLA. The glass-transition temperature of the sol ($T_{g,sol}$) could be roughly estimated with eq. (1). The results are also plotted in Figure 6. In regions I and II, the sols had high and constant $T_{g,sol}$ values, being of the same magnitude of the PHLA homopolymer,[13] and therefore, this indicated that the crude product was composed of PHLA-rich sol with a high $T_{g,sol}$ and a crosslinked PHLA–BDO gel with a low $T_{g,gel}$. As a result, T_g decreased remarkably in region I after extraction because of its high sol content, and it decreased slightly or remained unchanged in region II because of its low sol content. In contrast, the sol was BDO-rich and had a lower $T_{g,sol}$ than the PHLA–BDO gel in region III. Therefore, T_g increased again after extraction:

$$T_g = \phi_{gel} T_{g,gel} + (1 - \phi_{gel}) T_{g,sol} \quad (1)$$

$$T_g - T_{g,gel} = (T_{g,sol} - T_{g,gel}) - (T_{g,sol} - T_{g,gel})\phi_{gel} \quad (2)$$

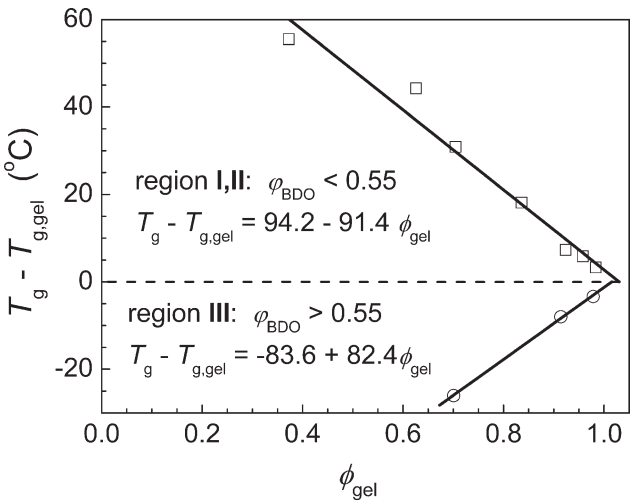


Figure 6 Dependence of the T_g difference between crude PHLA–BDO and PHLA–BDO gel ($T_g - T_{g,gel}$) on ϕ_{gel} in crude PHLA–BDO.

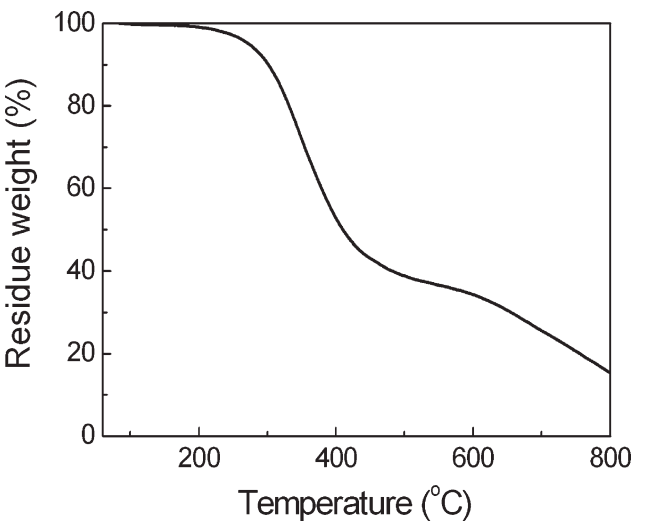


Figure 7 Thermogravimetric analysis of PHLA–BDO ($\phi_{BDO} = 0.5$).

TABLE II
Mechanical Properties of the PHLA-Diols

PHLA-diol[a]	ϕ_{gel}	Tensile modulus (MPa)	Tensile stress at break (MPa)	Elongation at break (%)
PHLA–EG	0.84	6.3 ± 0.3	1.6 ± 0.2	25.4 ± 1.7
PHLA–BDO	0.97	8.8 ± 1.2	1.1 ± 0.2	15.5 ± 1.9
PHLA–HDO	0.89	1.4 ± 0.2	0.8 ± 0.1	10.8 ± 1.3

[a] $\phi_{diol} = 0.5$.

Equation (1) is rearranged in eq. (2). The difference in T_g ($T_g - T_{g,gel}$) was plotted against ϕ_{gel} of the crude product, as shown later in Figure 8. The T_g difference decreased linearly with ϕ_{gel} in regions I and II but increased linearly in region III. These linear relationships indicated that the difference in T_g was due to the removal of the sols.

In addition, the thermogravimetric analysis indicated that the PHLA-diols had acceptable thermal stabilities. Figure 7 shows that PHLA–BDO ($\phi_{BDO} = 0.5$) was stable to 200°C. The temperatures for 5% weight loss and the fastest weight loss were 245 and 340°C, respectively. The stability was comparable to that of ordinary aliphatic polyesters, such as poly (lactic acid).

Mechanical properties

The static and dynamic mechanical properties of PHLA–EG, PHLA–PDO, and PHLA–BDO were measured, and the results are shown in Table II and Figure 8. The tensile modulus, strength, and elongation at break measured at 37°C were 1.4–6.3 MPa, 0.8–1.6 MPa, and 10–25%, respectively. The modulus and strength were over 1 magnitude higher than those of poly(glycerol sebacate) (0.3 and 0.5 MPa)[1] but 1–2 magnitudes lower than those of P4HB (250 and 10 MPa).[15] The elongation at break was close to that of P4HB (11%)[15] but much smaller than that of poly(glycerol sebacate) (270%).[1] So, the PHLA-diols appeared to be soft materials with perceptible but not high elasticity. The flexibility/elasticity resulted from the low T_g and the chemical crosslinking structure. The stiff PHLA chain moieties may have limited the elasticity, although the diol moieties were flexible.

As shown by the dynamic mechanical measurements, the storage moduli of PHLA–EG ($\phi_{gel} = 0.84$), PHLA–BDO ($\phi_{gel} = 0.98$), and PHLA–HDO ($\phi_{gel} = 0.89$) decreased remarkably and fell to rubberlike plateaus after the respective glass transitions. This result suggests the elasticity of the PHLA-diols, too. The storage moduli at a rubbery state were comparable to those obtained from the tensile tests. The T_g values read from the tangent of the loss angle basically agreed with those obtained from the DSC measurements.

Hydrolytic degradation

Aliphatic polyesters are biodegradable mainly via the hydrolysis of ester bonds in aqueous media.[16–18] PHLA-diols can be regarded as biodegradable

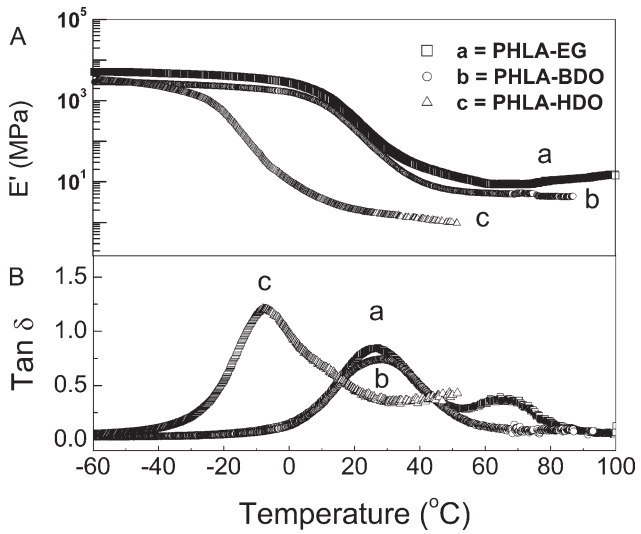


Figure 8 Storage modulus (E') and tangent of the loss angle (tan δ) of PHLA-diols as functions of temperature.

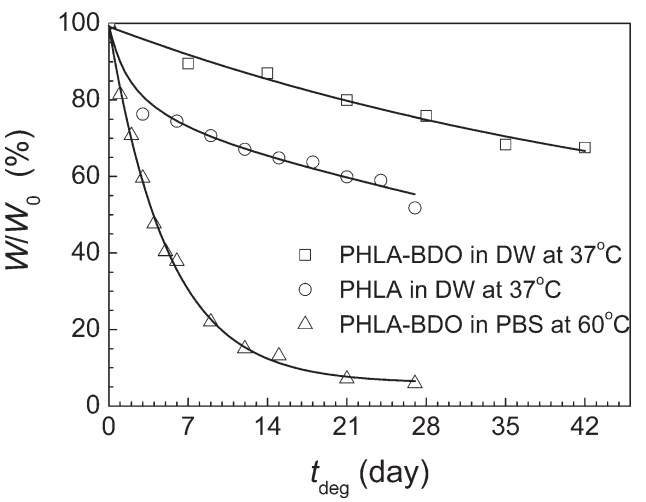


Figure 9 W/W_0–t_{deg} curves of PHLA–BDO ($\phi_{BDO} = 0.5$, $\phi_{gel} = 0.98$) and PHLA during degradation in deionized water (DW) at 37°C and in PBS at 60°C.

crosslinked aliphatic polyesters, although nonbiodegradable olefinic ether bonds are also present in the polymer structure. The hydrolytic degradation of PHLA–BDO (ϕ_{BDO} 0.5) with $\phi_{gel} = 0.98$ was conducted under two different conditions. The changes in W/W_0 of the samples as functions of the degradation time (t_{deg}) are shown in Figure 9.

In a previous article,[13] we reported the hydrolytic degradation of PHLA in deionized water because PHLA samples degraded in PBS were no longer soluble in THF so that it was impossible to determine the molecular weight of the degradation products. So the degradation of PHLA–BDO was first conducted in deionized water at 37°C to compare its degradation rate with PHLA under the same conditions. It experienced weight loss from the beginning of the degradation but degraded more slowly than the linear PHLA counterpart. It took 6 weeks for PHLA–BDO to lose 30% of its weight but only 2 weeks for PHLA to do the same. The crosslinked structure was mainly responsible for the slower degradation rate because the polymer network could not be completely destroyed by the cleavage of partial ester bonds.

To clarify if the polymer could be degraded completely, the degradation experiment was carried out in PBS at 60°C. Obviously, PHLA–BDO degraded more rapidly, and the degradation was nearly complete after 4 weeks. However, the degradation of PHLA-diols may be more complicated than that of existing polyesters because biodegradable ester bonds and nondegradable olefinic ether bonds are both present in the polymer network. Thorough studies are still needed.

CONCLUSIONS

Novel biodegradable crosslinked polymers, PHLA-diols, were synthesized from 5-HLA and α,ω-diols for the first time. The crosslinking structure may have resulted from simultaneous etherification and esterification reactions: the etherification between the enol hydroxyl in 5-HLA and the diol hydroxyl resulted in olefinic ether bonds that acted as crosslinking points, and the esterifications between the carboxyls of 5-HLA and the alcohol hydroxyls of both 5-HLA and the diols led to chain growth. The reaction rate depended on the diol type and feed ratio, catalyst concentration, and temperature, and $\phi_{gel,f}$ depended on the diol type and feed ratio. PHLA–BDO with ϕ_{gel} values as high as 98% was obtained at BDO feed ratios of 0.25–0.55. The T_g values of the PHLA-diols could be tuned in a wide range by the diol type and monomer feed ratio. Because of the low T_g and crosslink structure, the PHLA-diols exhibited certain elastic properties. For PHLA–BDO, the tensile modulus, strength, and elongation at break measured at 37°C were 1.4–6.3 MPa, 0.8–1.6 MPa, and 10–25%, respectively. These materials can be degraded via hydrolysis.

References

1. Wang, Y. D.; Ameer, G. A.; Sheppard, B. J.; Langer, R. Nat Biotechnol 2002, 20, 602.
2. Yang, J.; Webb, A. R.; Ameer, G. A. Adv Mater 2004, 16, 511.
3. Liu, Q. Y.; Tian, M.; Ding, T.; Shi, R.; Zhang, L. Q. J Appl Polym Sci 2005, 98, 2033.
4. Ding, T.; Liu, Q. Y.; Shi, R.; Tian, M.; Yang, J.; Zhang, L. Q. Polym Degrad Stab 2006, 91, 733.
5. Nagata, M.; Tanabe, T.; Sakai, W.; Tsutsumi, N. Polymer 2008, 49, 1506.
6. Younes, H. M.; Bravo-Grimaldo, E.; Amsden, B. G. Biomaterials 2004, 25, 5261.
7. Wang, Y. D.; Kim, Y. M.; Langer, R. J Biomed Mater Res A 2003, 66, 192.
8. Yang, J.; Webb, A. R.; Pickerill, S. J.; Hageman, G.; Ameer, G. A. Biomaterials 2006, 27, 1889.
9. Bettinger, C. J.; Weinberg, E. J.; Kulig, K. M.; Vacanti, J. P.; Wang, Y. D.; Borenstein, J. T.; Langer, R. Adv Mater 2006, 18, 165.
10. Bettinger, C. J.; Orrick, B.; Misra, A.; Langer, R.; Borenstein, J. T. Biomaterials 2006, 27, 2558.
11. Kang, Y.; Yang, J.; Khan, S.; Anissian, L.; Ameer, G. A. J Biomed Mater Res A 2006, 77, 331.
12. Zhang, Y.; Wu, L. B.; Li, F.; Bu, Z. Y.; Li, B. G. J Zhejiang Univ Eng Sci (in Chinese) 2006, 40, 1895.
13. Wu, L. B.; Zhang, Y.; Li, B. G. J Polym Environ 2008, 16, 68.
14. van der Rest, G.; Chamot-Rooke, J.; Mourgues, P.; McMahon, T. B.; Audier, H. E. J Am Soc Mass Spectrom 2001, 12, 938.
15. Poirier, Y.; Nawrath, C.; Somerville, C. Biotechnology 1995, 13, 142.
16. Göpferich, A. Biomaterials 1996, 17, 103.
17. Li, S. M.; McCarthy, S. Biomaterials 1999, 20, 35.
18. Wu, L. B.; Ding, J. D. Biomaterials 2004, 25, 5821.