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Synthesis of poly(L-lactic-*co*-glycolic acid) telechelic prepolymers by direct melt polycondensation, and their characterization

RAPID COMMUNICATION

Summary — A series of L-lactic/glycolic acid polymers (PLLGAc) differing in molar ratios of L-lactic (L-LAc) to glycolic (GAc) acid and of relatively low molecular weights [M_n(theor) = 4000] were synthesized by direct melt polycondensation in the presence of 1,4-butanediol and sulfuric acid as a molecular weight regulator and catalyst, respectively. The characterization experiments (FT-IR, ^{1}H NMR) demonstrated a good correlation between the polymer compositions and the ratios of L-LAc and GAc in the feed. The DSC studies of the prepolymers indicated that the melting point as well as degree of crystallinity of PLLGAc decreased with the increase in the molar fraction of GA units in the copolymer. The glass transition temperatures of the polymers varied from 29 to 45 °C, depending on the polymer composition. The alkaline hydrolyzability (0.1 M NaOH, 37 °C) of the polymers is strongly affected by GA content in PLLGAc. With increasing GA content in the prepolymer, weight loss of a sample becomes faster.

Key words: lactic acid, glycolic acid, prepolymer, polycondensation.

CHARAKTERYSTYKA TELECHELICZNYCH PREPOLIMERÓW POLI(KWAS-L-MLEKOWY-*ko*--GLIKOLOWY) ZSYNTETYZOWANYCH METODĄ BEZPOŚREDNIEJ POLIKONDENSACJI W FAZIE STOPIONEJ

Streszczenie — Zsyntetyzowano kopolimery kwasów L-mlekowego i glikolowego (PLLGAc) o zmiennych udziałach molowych monomerów i stałym ciężarze cząsteczkowym równym 4000. Jako związek regulujący ciężar cząsteczkowy prepolimerów zastosowano 1,4-butanodiol, a katalizatorem reakcji był kwas siarkowy. Strukturę chemiczną zsyntetyzowanych polimerów zbadano metodami spektroskopii FTIR (rys. 1) i ^{1}H NMR (rys. 2). Potwierdzono zależność pomiędzy składem chemicznym kopolimerów a wzajemnym udziałem monomerów użytych do syntezy (tab. 1). Analiza DSC (rys. 3 i 4) wykazała, że ze wzrostem udziału fragmentów glikolowych (GA) w PLLGAc temperatura topnienia polimeru obniża się, a stopień krystaliczności maleje. Temperatura zeszklenia polimerów zmienia się w zależności od składu komonomerów w zakresie od 29 do 45 °C. Degradację hydrolityczną uzyskanych poliestrów badano w środowisku zasadowym (0.1 M NaOH, w temp. 37 °C) i stwierdzono, że ubytek masy próbki wyraźnie zależy od składu polimeru (rys. 5). Im większa jest zawartość fragmentów GA w PLLGAc, tym większa podatność kopolimeru na hydrolizę zasadową i szybszy ubytek masy.

Słowa kluczowe: kwas mlekowy, kwas glikolowy, prepolimer, polikondensacja.

Polymers derived from α-hydroxyacids such as lactic acid (LAc) and glycolic acid (GAc) are biocompatible and biodegradable, and they have been widely used in various biomedical and pharmaceutical applications, such as absorbable sutures, bone fracture fixation devices, reconstructive implants, controlled drug release carriers and scaffolds in tissue engineering [1]. Poly(α-hydroxyacid)s degrade *in vivo* by random hydrolysis of the ester bonds to non-harmful compounds which are eliminated from the body *via* the Krebs cycle as carbon dioxide and water [2]. These polyesters can be produced either by condensation of LAc and GAc, or by ring-opening polymerization (ROP) of the related cyclic dimers, namely, lactide and glycolide [3, 4]. An expensive production of cyclic diesters and complex methods of their purification render the lactide- and glycolide-based

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polymers high-priced. In addition, their syntheses are generally carried out with the use of organometallic compounds as initiators, which are often harmful and toxic [5]. Taking above into consideration, a direct melt polycondensation of lactic and glycolic acids have recently been investigated extensively [6—9]. One of the methods of preparation of high molecular weight polymers is the synthesis of the prepolymers and subsequently chain extension with the use of the coupling agents such as diisocyanates, acid dichlorides, anhydrides or oxazolines. Recently, Seppälä and co-workers have reported the syntheses of telechelic lactic acid based polymers by the use of different functionalization agents, catalysts and by varying polycondensation conditions [10, 11]. The catalysts most widely used in the melt polycondensation of LAc and GAc as well as in the ROP of cyclic diesters include Lewis acids, primarily tin compounds [6, 10—14]. Regarding the biocompatibility of polymeric materials, several attempts have been made to use less toxic catalysts, mainly zinc [7, 15] and iron [16, 17] compounds, which are present in human body or can be easily removed in the purification step of polymer, namely protonic acids such as sulfuric acid [11]. Recently, there has been a growing interest in developing metal-free catalysts for ROP of cyclic diesters focusing mostly on tertiary amines [18], phosphines [19], *N*-heterocyclic carbenes [20], and sulfonic acids [21]. Accomplished with these compounds, the ROP of lactide demonstrate the living character and gives polymers of predictable molecular weight with narrow polydispersity in almost quantitative conversions.

In this article, we report on the synthesis and characterization of low-molecular weight copolymers of lactic and glycolic acids of different monomer ratios. To produce hydroxyl-terminated prepolymers showing constant molecular weight, 1,4-butanediol was used. The semicrystalline prepolymers may find their applications as hard segments in the preparation of thermoplastic elastomers, especially those exhibiting shape memory properties, for biomedical purposes.

EXPERIMENTAL

Materials

The pharmaceutical, heat stable L-lactic acid (L-LAc, 90 % aq, 99.9 % optically pure), was supplied by Purac, The Netherlands, and used as received.

The following products were used as received without further treatment:

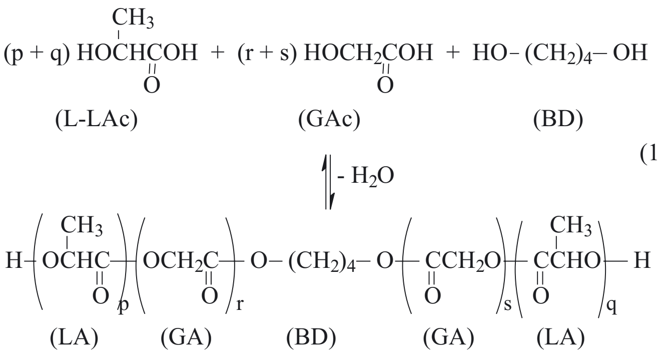
— glycolic acid (GAc, 70 % aq), tin (II) octoate (95 %), 1,4-butanediol (BD, 99 %) from Sigma-Aldrich;

— sulfuric acid (95 %), dichloromethane (99+ %), and methanol (99+ %) from POCH, Poland.

L-lactide (m.p. 97 °C by DSC) was obtained by depolymerization of L-LAc oligomers [22], purified [23] and dried under vacuum at 40 °C for a week before use.

Synthesis

Polymerization reaction is described by equation:



$$(p+q)\,\mathrm{HO}\overset{\mathrm{CH_3}}{\mathrm{CH}}\underset{\mathrm{O}}{\overset{}{\mathrm{C}}}\mathrm{OH} + (r+s)\,\mathrm{HOCH_2}\underset{\mathrm{O}}{\mathrm{C}}\mathrm{OH} + \mathrm{HO{-}(CH_2)_4{-}OH}$$

$$\text{(L-LAc)} \qquad \text{(GAc)} \qquad \text{(BD)}$$

$$\rightleftharpoons\ -\mathrm{H_2O} \tag{1}$$

$$\mathrm{H}\left(\mathrm{O}\overset{\mathrm{CH_3}}{\mathrm{CH}}\underset{\mathrm{O}}{\mathrm{C}}\right)_p\left(\mathrm{OCH_2}\underset{\mathrm{O}}{\mathrm{C}}\right)_r\mathrm{O{-}(CH_2)_4{-}O}\left(\underset{\mathrm{O}}{\mathrm{C}}\mathrm{CH_2O}\right)_s\left(\underset{\mathrm{O}}{\mathrm{C}}\overset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{O}\right)_q\mathrm{H}$$

$$\text{(LA)} \qquad \text{(GA)} \qquad \text{(BD)} \qquad \text{(GA)} \qquad \text{(LA)}$$

All syntheses were carried out in the melt, using rotary evaporator (RVO 200A, Ingos) operating at 120 rpm. In a typical experiment, 200 g of monomers were put into the flask. The excess water was distilled under reduced pressure at 120 °C for 3 h. Then, the continuous nitrogen sweep was applied, and accurately weighed amounts of 1,4-butanediol and sulfuric acid (in amount 0.1 wt %) were added. The temperature of the reaction mixture was raised to 200 °C and simultaneously the pressure was lowered from 100 to 3 kPa over a period of 8 h. The conditions were then kept constant for further 4 h. The products were purified by dissolution/precipitation method in dichloromethane-methanol (1:8 v/v) system in order to remove any residual monomer and catalyst. The powdered polymers were dried under reduced pressure at 40 °C to a constant weight before being subjected to analyses.

Poly(L-lactide), denoted here as PLLA and used as a reference, was synthesized by ROP in bulk [24] in the presence of 1,4-butanediol and tin octoate as an initiator and catalyst, respectively.

Methods of characterization

The 400 MHz ^{1}H NMR spectra were obtained by a Bruker DPX spectrometer using deuterated chloroform as a solvent and tetramethylsilane as a shift reference.

Fourier transform infrared spectra (FT-IR) were recorded using a Nexus spectrophotometer in 400—4000 cm^{-1} range with 32 scans per sample.

The number-average molecular weights ($\overline{M}_n$) of the selected polymers were determined by vapor pressure osmometry (VPO) using a Knauer A028 osmometer, in chloroform.

Thermal properties were examined by means of a DuPont 910 calorimeter at a heating rate of 10 °C/min. The polymer was melted and maintained at 160 °C for 5 minutes to remove the thermal history. Subsequently, the sample was cooled to 70 °C, crystallized for 1 hour, and allowed to cool to room temperature. Then, the thermogram was recorded in the temperature range from 25 to 160 °C. The degree of crystallinity, (χ) was calculated from the measured heat of melting (ΔH_m), assuming that the melting enthalpy of crystalline regions of poly(L-lactide) (PLLA) is $\Delta H_{m\,PLLA} = 135$ J/g [25] according to the equation:

$$\chi = \frac{\Delta H_m \cdot 100\,\%}{\Delta H_{m\,PLLA} \cdot W_{LA}} \qquad (2)$$

where: W_{LA} — *weight fraction of LA in polymer*.

The acid numbers were determined by standard titrimetric method (DIN 53 402), calculated from three titers and averaged.

The alkaline hydrolysis of the one-gram cylindrical samples (12 mm diameter and 8 mm length) was carried out in 0.1 M NaOH solution at 37 °C. To exclude the influence of polymer crystallinity on the rate of degradation, the amorphous samples were prepared by melt-quenching. Specimens were recovered in 12 h intervals, flushed with distilled water, dried, and then weighed to determine the weight loss. The hydrolysis medium was changed every 24 h.

RESULTS AND DISCUSSION

Characteristic of prepolymers

The characteristic of low-molecular weight telechelic polymers obtained by direct melt polycondensation of L-lactic and glycolic acids are presented in Table 1.

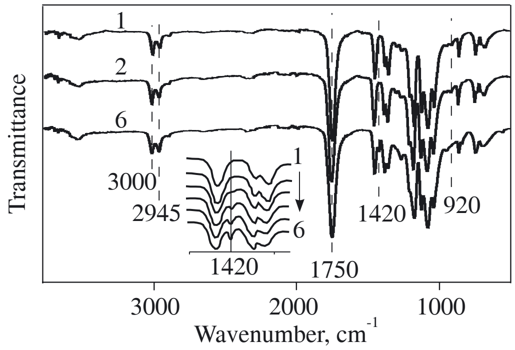


Fig. 1. FT-IR spectra of PLLA (1), PLLAc (2) and PLLGAc-80 (6)

The chemical structures of the oligomers were characterized by FT-IR and ^{1}H NMR spectroscopies. Figure 1 presents the FT-IR spectra for PLLA, PLLAc, and PLLGAc-80.

In all infrared spectra, the band of the strongest intensity is located at about 1750 cm^{-1} which is assigned to the ester carbonyl C=O stretching vibrations. As can be seen, the spectra of oligomers obtained by ROP of lactide (PLLA) and polycondensation of L-lactic acid (PLLAc) reveal many similarities. There are no distinct differences in the band intensities and wavenumbers in the whole infrared spectral region. On the other hand, the infrared spectra of PLLAc and PLLGAc yield some differences in two regions, which are sensitive to the structural changes of the L-LAc and GAc copolymers. The most important is the appearance of the 1420 cm^{-1} peak in the copolymers, which is absent in PLLAc. This new band is attributed to C-H deformational vibrations in the CH_2 groups in glycolic (GA) segments. The enlarged spectral region near 1420 cm^{-1} reveals the evolution of a new peak when the GA unit content in the copolymers changes. Obviously, with increasing molar content of GA moieties in the oligomers, the intensity of a peak increases. The two peaks at 2900—3000 cm^{-1} associated with the existence of stretching vibrations of the CH_3 group characteristic of lactic (LA) units are also considered to be sensitive to the structural changes taking

Table 1. Characterization of purified poly(L-lactic acid) and poly(L-lactic-*co*-glycolic acid) oligomers

Number of a sample	Symbol of oligomer	Molar composition, L-LAc/GAc		M_n[1)]	Acid number	Yield[2)], %	Appearance of a product crude/purified
		in feed, wt. %	in product[1)], wt. %				
1	PLLA	100/0	100/0	3740 (3580)	0.5	89	white/white
2	PLLAc	100/0	100/0	3940	2.8	66	yellowish/white
3	PLLGAc-95	95/5	94.4/5.6	4350	2.9	64	yellowish/white
4	PLLGAc-90	90/10	86.8/13.2	4050 (3990)	2.5	64	yellowish/white
5	PLLGAc-85	85/15	81.7/18.3	3820	2.6	63	yellowish/white
6	PLLGAc-80	80/20	77.9/22.1	3830	1.9	61	yellowish/white

[1)] determined by ^{1}H NMR (numbers in parentheses refer to $\overline{M}_n$ from VPO measurements).
[2)] weight of a purified product related to the weight of dehydrated monomers in feed.

Table 2. Thermal properties of the prepolymers

Number of a sample	Symbol of oligomer	T_g, °C	T_m, °C	χ, %
1	PLLA	45	141	40
2	PLLAc	43	140	34
3	PLLGAc-95	40	121	31
4	PLLGAc-90	35	92	18
5	PLLGAc-85	32	82	10
6	PLLGAc-80	29	n.d.[1)]	n.d.[1)]

[1)] n.d. means that value was not detected.

place during copolycondensation of lactic and glycolic acids. When the content of GA moieties in the polymer backbone increases, an increase in the intensity of the peak at 2945 cm^{-1} in relation to that of 3000 cm^{-1} can be noticed.

For all analyzed polymers, broad visible bands at 3400—3600 cm^{-1} for hydroxyl end groups, and no peaks assigned to carboxyl terminals in the 3000—3450 cm^{-1} region confirmed the structure of hydroxyl-terminated telechelic oligomers. The oligomers 1—5 also exhibit a crystalline peak at 920 cm^{-1}, which is absent in the oligomer 6, indicating that the polymer with the highest content of GA units is amorphous.

The typical ^1H NMR spectra of PLLAc (2) and PLLGAc-80 (6) are shown in Figure 2.

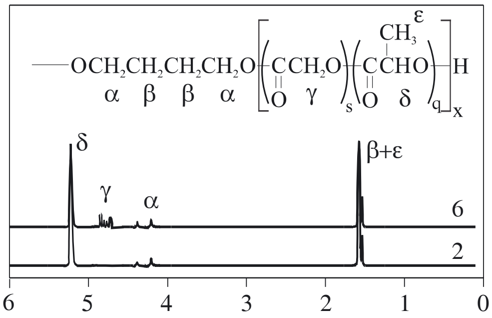


Fig. 2. ^1H NMR spectra of PLLAc (2) and PLLGAc-80 (6) oligomers

The spectra of homopolymers exhibit the bands at 1.59 ppm associated with $-CH_3$ of LA segments and $-O-CH_2-CH_2-$ of BD units, at 5.20 ppm assigned to $-CH-$ of LA segments as well as a peak at 4.17 ppm characteristic of $-O-CH_2-$ belonging to BD units. The copolymers show an additional multiplet near 4.85 ppm (4.60—4.90 ppm) assigned to $-CH_2-$ of GA fragments [15, 22, 26]. A small visible peak at 4.35 ppm can be attributed to the CH groups which are bonded to the hydroxyl terminals.

The molar compositions and number-average molecular weights of the oligomers were calculated from the ratios of the intensities of peaks at 5.20, 4.60—4.90, and 4.17 ppm. As can be seen in Table 1, the contents of GA units in the copolymers are higher than those in the feed. This phenomenon can be explained by a higher reactivity of the primary hydroxyl groups of GAc as compared with the secondary ones of L-LAc. The molecular weights of the two selected prepolymers, *i.e.* homopolymer (1) and copolymer (4), were additionally determined by vapor pressure osmometry. As expected, a good agreement is observed in M_n values obtained by both methods.

The DSC results of PLLA (1), PLLAc (2) and PLLGAc (3—6) oligomers are presented in Figure 3.

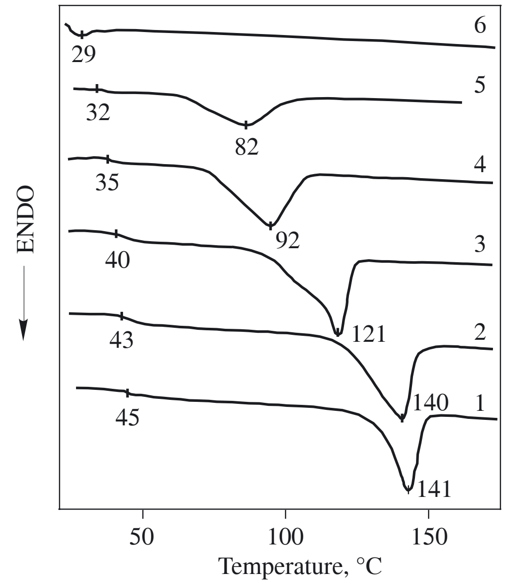


Fig. 3. DSC thermograms of PLLA (1), PLLAc (2) and PLLGAc (3—6) oligomers

The PLLA homopolymer (1) shows a sharp melting endotherm with a peak at 141 °C. The PLLAc oligomer (2) shows a thermal characteristics close to that of PLLA (1), with the exception that the melting endotherm of the former becomes broader. The differences in the thermogram shapes of both homopolymers may be explained by different polydispersities of the prepolymers. The polymers obtained by ROP typically show lower polydispersity indices than the condensation polymers. Higher concentration of low-molecular weight fractions in polycondensates results in the formation of less perfect crystalline structures as compared with the PLLA prepolymer. Furthermore, the glass transition temperature shifts to lower temperatures, from 45 °C for (1) to 43 °C for (2).

As compared with homopolymers, the copolymerization of L-LAc and GAc results in decreasing melting and glass transition temperatures, as well as the degree of crystallinity. In addition, the melting endotherm becomes less sharp and more flattened when the concen-

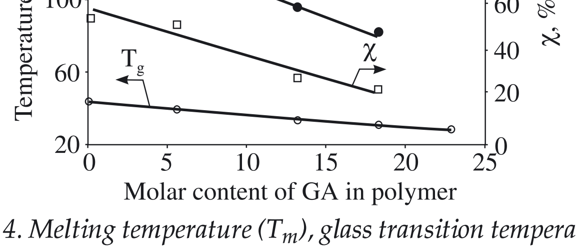


Fig. 4. Melting temperature (T_m), glass transition temperature (T_g) and degree of crystallinity (χ) determined by DSC as functions of molar content of GA in polymers

tration of GA moieties in the polymer increases. The copolymer 6, containing 22.1 % of GA, exhibits the characteristics of an amorphous polymer, and no melting peak can be detected. Dependence of the melting and glass transition temperatures, as well as degree of crystallinity of the oligomers on the copolymer composition is plotted in Figure 4.

The incorporation of GA segments into PLLAc backbone leads to a decrease in melting point of the crystalline phase from 140 °C to 82 °C. At the same time, the glass transition temperature lowers from 43 °C to 29 °C.

Hydrolysis

The *in vitro* degradation of a series of low-molecular weight L-LAc and GAc polymers was studied in alkaline solution (0.1 M NaOH) at 37 °C. The degradation behavior of all amorphous-made polymers investigated is similar following a linear-type profile which is characterized by a steady degradation (Fig. 5). The copolymers exhibit a faster increase in weight loss than LA homopolymers. The rate of weight loss clearly depends on the GA content in PLLGAc. With increasing amount of GA units in PLLGAc chain the degradation of the sample become faster.

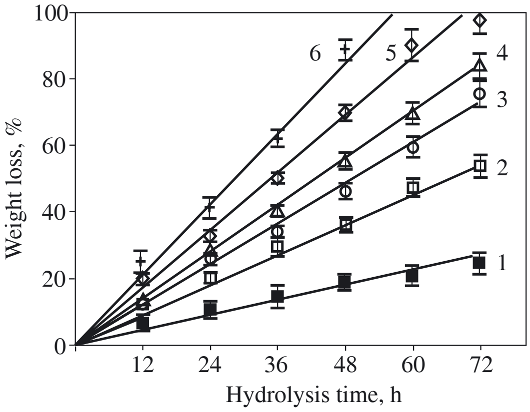


Fig. 5. Weight loss of PLLA (1), PLLAc (2) and PLLGAc (3—6) oligomers

The alkaline hydrolysis rate of biodegradable polyesters is thought to be dependent on their hydrophilicity [27, 28]. The incorporation of GA moieties into PLLAc chains results in higher susceptibility to attack of the hydroxide ions on the ester groups in the polymer backbone. Furthermore, the increasing GA unit content in the copolymer causes a reduction in the glass transition temperature of the material. For the oligomers 4—6, the temperature of the hydrolysis medium is above their T_g's, therefore the materials are in the rubbery state. The more chain mobility, the easier water penetration of the sample, and consequently, a more rapid hydrolysis. The rate of weight loss is the lowest, among the investigated polymers, for the PLLA homopolymer. The differences in the hydrolysis profiles of PLLA (1) and PLLAc (2) are likely due to their different polydispersity indices. The lower molecular weight species in polycondensates enhance the hydrophilicity of the polymer and, thus, the hydrolysis rate increases.

All the prepolymers were readily soluble in common solvents such as chloroform, dichloromethane, *N,N*-dimethylformamide, 1,4-dioxane and slightly soluble in acetone.

These preliminary results show that metal-free, semicrystalline telechelic copolymers of lactic and glycolic acids can be synthesized by direct melt polycondensation. Further investigations are being undertaken to determine the effects of various polymerization conditions on the properties of the products as well as the applicability of these polymeric materials in the syntheses of the shape-memory thermoplastic elastomers.

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