Lactic Acid and Ricinoleic Acid Based Copolyesters

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ABSTRACT: Copolyesters based on purified ricinoleic (RA) and lactic (LA) acids with different RA:LA ratios were synthesized by thermal polycondensation and by transesterification of high molecular weight poly(lactic acid) (PLA) with ricinoleic acid and repolyesterification. Thermal polycondensation resulted in random P(LA–RA) copolyesters of molecular weights between 2000 and 8000 with the polymers containing 20% or more RA were liquid at room temperature. Transesterification of high molecular weight PLA with pure ricinoleic acid and repolymerization of those oligomers by condensation resulted in multiblock P(PLA–RA) copolyesters of molecular weights between 6000 and 14000. Polymers containing 50% RA were liquid at room temperature. ¹H NMR spectroscopy analysis coupled with information from DSC allowed determination of the polymer structure. Polymers prepared by thermal polycondensation are random copolymers (h > 1), while the copolymers prepared by transesterification have a multiblock character (h < 1). The LA number-average sequence length (L_{LA}) decreased from 12 to 4 for the LA–RA 9:1 and 5:5 copolymers prepared by thermal polycondensation. Thermal analysis by DSC revealed crystalline structure for polyester synthesized by transesterification. For polyesters synthesized by random condensation only P(LA–RA) 90:10 w/w contained crystalline domains.

1. Introduction

Biodegradable polyesters are useful materials for controlled drug delivery.^{1,2} They hydrolyze to hydroxy acid monomers when placed in aqueous medium.³⁻⁵ The biodegradable polymers that have been most intensively investigated are aliphatic polyesters of both natural and synthetic origins. Polyesters can be synthesized by polycondensation of hydroxy acids or by ring-opening polymerization of cyclic esters (lactones). A wide range of monomers have been used to produce biodegradable polyesters. Their polymerizations can be carried out either in the bulk or in solution. The most useful monomers used for polycondensation are lactic, glycolic, hydroxybutyric, and hydroxycaproic acids. Polyesters of glycolic and lactic acids are the main group of interest due to their long history of safety.⁵⁻⁸

Lactic acid based polymers have been prepared by direct polycondensation, ring-opening polymerization (ROP), grafting, chain extension, or transesterification.⁹ Lactic acid can be condensed with other hydroxy acids such as 6-hydroxycaproic acid, glycolic acid, and hydroxybutyric acid or in the presence of diols, diacids, and diamine. Direct condensation usually resulted in low molecular weight copolymers that can then be further linked to yield high molecular weight polymers. In the second step, linking molecules such as diisocyanates, bis(amino-ethers), phosgene, phosphate, and anhydrides takes place.¹⁰⁻¹²

Enantiomerically pure PLA is a semicrystalline polymer with $T_{\rm g}$ of about 55 °C and $T_{\rm m}$ of about 180 °C. The degree of crystallinity and melting temperature of PLA polymers can be reduced by random copolymerization with other comonomers, leading to the incorporation of units disturbing the crystallization ability of the PLA segments. For example, glycolide, ϵ -caprolactone, δ -valerolactone, 1,5-dioxepan-2-one (DXO) and trimethylene carbonate (TMC) are frequently used as comonomers in order to change thermal properties of resulting PLA copolymers. The $T_{\rm g}$ of PLA copolymer consisting of 28% DXO was reduced by 35 °C compared to a pure PLLA, and the crystallinity was also significantly lower. A linear decrease in $T_{\rm g}$ was also found for copolymers with more then 10% w/w TMC. A 50/50 copolymer of L-lactide and ϵ -caprolactone has been shown to have $T_{\rm g} = -15$ °C indicating a continuous amorphous phase.¹³⁻¹⁶

Fatty acids are suitable candidates for the preparation of biodegradable polymers, 2,3,17,18 as they are natural body components and they are hydrophobic, and thus they may retain an encapsulated drug for longer time periods when used as drug carriers. However, most fatty acids are monofunctional and cannot serve as monomers for polymerization. Ricinoleic acid is a common C18 fatty acid with a cis-configured double bond in the ninth position and a hydroxyl group in the 12th position (*cis*-12-hydroxyoctadeca-9-enoic acid). It is produced from the hydrolysis of castor oil.¹⁹

The objective of this study is to incorporate ricinoleic acid in lactide based polymers for the purpose of altering its physical properties. The bifunctionality of ricinoleic acid allows its polymerization without any modifications. Copolymerization of PLA with ricinoleic acid may result in polymers with desired properties such as pliability, hydrophobicity and softness. Ricinoleic acid hydrocarbon chain, cis configuration, and side chain may result in steric hindrance of the polymer to yield soft or even liquid polymers. In addition, the presence of a double bond in ricinoleic acid provides additional synthetic opportunities including cross-linking, hydroxylation, bromination, and other common modifications of double bonds.

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Previous studies in our laboratory focused on the synthesis of ricinoleic acid based polyanhydrides.^{18,20} Polyanhydrides synthesized from ricinoleic acid maleate or succinate and sebacic acid possessed desired physicochemical properties such as low melting temperature, hydrophobicity, and pliability, in addition to biocompatibility and biodegradability. The polymers were synthesized by melt condensation to yield film-forming polymers with molecular weights exceeding 100 000. In another study, fatty acid esters of ricinoleic acid were used as chain terminators of polyanhydrides based on sebacic acid.³

In our previous article we reported on the synthesis of ricinoleic acid lactones and their homopolymerization and copolymerization with lactide by ring-opening polymerization. A systematic study on the synthesis and characterization of ricinoleic acid lactones and ricinoleic acid-*co*-lactic acid polyesters was reported.²¹

The present study is a continuation of our efforts to synthesize new biodegradable polymers based on ricinoleic acid. The purpose of this study has been to synthesize ricinoleic acid based copolyesters with lactic acid using different polymerization techniques and determine the copolymer chain structure as a function of ricinoleic acid content and method of synthesis.

Various techniques have previously been used to study and characterize polyesters and polyanhydrides.²² Yet, quantitative correlation between physical properties and the ¹H NMR spectroscopy was reported mainly for polyanhydrides.²³ A systematic study on the synthesis and characterization of ricinoleic acid-*co*-lactic acid polyesters is reported.

2. Experimental Section

2.1. Materials. Crude ricinoleic acid was purchased from Acros (85% pure) (Geel, Belgium), L-Lactic acid (L-LA) and DL-lactic acid (DL-LA) were purchased from J. T. Baker (Deventer, The Netherlands). D-Lactic acid was prepared from the hydrolysis of D-lactide in water; D-lactide was purchased from Purac Biochem (Gorinchem, The Netherlands). CDCl₃, for NMR, was purchased from Sigma-Aldrich (Rehovot, Israel). All solvents and salts were analytical grade from Aldrich or Biolab (Jerusalem, Israel).

2.2. Instrumentation. IR spectra were performed on monomer and polymer samples cast on NaCl plates from CH2-Cl₂ solutions on Bruker (Vector 22 System FT-IR). UV spectra were taken on a Kontron Instruments Uvicon model 930 (Msscientific, Berlin, Germany). Thermal analysis was determined on a Mettler TA 4000-DSC differential scanning calorimeter (Mettler-Toledo. Schwerzzenbach, Switzerland), calibrated with Zn and In standards, at a heating rate of 10°C/ min under nitrogen atmosphere. Melting temperatures of the co-polyesters was determined also by Fisher Scientific melting point apparatus. Molecular weights of the co-polyesters were estimated on a gel permeation chromatography (GPC) system consisting of a Waters 1515 Isocratic HPLC Pump, with 2410 Refractive Index detector (RI) (Waters, MA), a Rheodyne (Coatati, CA) injection valve with a 20 μ L loop. Samples were eluted with chloroform through a linear Styrogel column, 500 Å-pore size (Waters, MA) at a flow rate of 1 mL/min. The molecular weights were determined relative to polystyrene standards (Polyscience, Warrington, PA) with a molecular weight range of 500 to 20 000 using BREEZE 3.20 version, copyright 2000 Waters corporation computer program. The lactic and ricinoleic acids release was determined by HPLC using C18 reverse-phase column (LichroCart 250-4, Lichrospher 100, 5μ m). Lactic acid was eluted with a solution of 0.1% H₃PO₄ in DDW at a flow rate of 1 mL/min and UV detection at 210 nm. Ricinoleic acid was eluted with a solution of acetonitrile:0.1% H_3PO_4 in DDW 65:35 v/v, at flow rate of 1.4 mL/min and UV detection at 210 nm. The hydrolysis was

conducted in 0.1 M phosphate buffer (pH 7.4) at 37 °C with a constant shaking of 100 rpm. ¹H NMR and ¹³C NMR spectra (in CDCl₃) were recorded on a Varian 300 and 500 MHz spectrometers using TMS as internal standard (Varian Inc., Palo Alto, CA). Optical rotations of polymers were determined by Optical Activity LTD polarimeter (Cambridgeshire, England) in 10 mg/mL polymer in CHCl₃ solution. Viscometry of the polymers in dichloromethane was measured in Cannon-Ubbelohde 75 μ m dilution viscometer. Afflux times were measured at four concentrations at 25 °C; the data were analyzed by standard methods.

2.3. Ricinoleic Acid Purification. Crude ricinoleic acid (100 g) was converted to ricinoleic acid methyl ester by bubbling gaseous HCl, throw methanol solution of ricinoleic acid at 0 °C. Ricinoleic acid methyl ester was extracted with hexanes, washed with DDW and with 10% (w/v) NaHCO₃, treated with anhydrous MgSO₄, filtered and evaporated to dryness. Yield = 102 g of ricinoleic acid methyl ester (\sim 97%). TLC (10% acetone in hexanes) showed two major spots: 1. $R_{\rm f}$ = 0.75; methyl esters of non-hydroxy fatty acids (i.e., oleic, linoleic, stearic, etc.), and 2. $R_{\rm f} = 0.375$; methyl ester of ricinoleic acid. The crude ricinoleic acid methyl ester was diluted with hexanes and purified by silica gel chromatography. Ricinoleic acid methyl ester was eluted with solution of 10% acetone in hexanes. Fractions containing different products were separately combined and evaporated to dryness under reduced pressure. A 55 g sample of pure ricinoleic acid methyl ester $[\alpha]^{20}_{D} = +3.4^{\circ}$ was collected.

 $^1\mathrm{H}$ NMR (CDCl₃, #16–#25): 5.59–5.37 (2H, m, C9–10, –CH=CH–), 3.62 (3H, s, –CO₂CH₃), 3.599 (1H, m, C12 HC–O–), 2.322 (2H, t, C2–CH₂), 2.202 (2H, t, C11–CH₂), 2.053 (2H, m, C8–CH₂), 1.59 (2H, m, C3–CH₂), 1.438 (2H, m, C13–CH₂), 1.296 (16H, m, C4–7 and C14–17), and 0.854 (3H, t, C18–CH₃) ppm.

To obtain pure ricinoleic acid, ricinoleic acid methyl ester was hydrolyzed in alkaline water: methanol 1:1 solution. Then the mixture was diluted with DDW and acidified with concentrated HCl solution to a final pH of 2. Pure ricinoleic acid was extracted with ethyl acetate, treated with anhydrous MgSO₄, filtered and evaporated to dryness, $[\alpha]^{20}_{D} = +3.8^{\circ}$.

 1 H NMR (CDCl₃) showed the disappearance of the peak at 3.62 which confirmed the complete removal of the methyl ester protecting group.

¹H NMR (CDCl₃, pure ricinoleic acid): 5.57-5.38 (2H, m, C9-10, -CH=CH-), 3.609 (1H, m, C12 HC-O-), 2.309 (2H, t, C2 $-CH_2$), 2.194 (2H, t, C11 $-CH_2$), 2.01 (2H, m, C8 $-CH_2$), 1.603 (2H, m, C3 $-CH_2$), 1.446 (2H, m, C13 $-CH_2$), 1.291 (16H, m, C4-7 and C14-17), and 0.862 (3H, t, C18 $-CH_3$) ppm.

2.4. Copolymer Synthesis by Thermal Polycondensation. Low molecular weight polyesters, PRA, L- and D-PLA, P(L-LA:RA), P(D-LA:RA) with different LA:RA (w/w) ratios were prepared by two-step thermal polycondensation according to the following procedure.

First, a 250 mL round-bottomed flask, equipped with a Dean–Stark reflux condenser and $CaCl_2$ drying tube, was charged with pure ricinoleic acid and lyophilized lactic acid in appropriate ratios (total amount of both acids was 20 g) and 150 mL of toluene.

The acid mixture was dried overnight with refluxing toluene to remove water traces, then toluene was removed and the temperature was raised gradually to 180 °C. The acids were condensed for 3 h. In the second step, the temperature was decreased back to 150 °C and the reaction flask was connected to an oil pump where the condensation was continued under a vacuum of 0.3 mmHg for additional 12 h. Each step was followed by GPC analysis of samples to determine the molecular weight of the forming polymers at each time period. All polymers were characterized by GPC, ¹H NMR, IR, DSC, mp, a Cannon-Ubbelohde 75 dilution viscometer, and specific optical rotation.

¹H NMR (CDCl₃, P(LA–RA) 60:40, δ): 5.45–5.30 (2H, m, C9–10, –CH=CH–), 5.20–5.02 (1H, q, CH–CH3, LA), 4.94–4.86 (1H, m, C12 HC–O–), 2.38–2.24 (2H, m, C2 –CH₂, and 2H, m, C11 –CH₂), 2.01 (2H, m, C8 –CH₂), 1.68–1.50 (2H,

Table 1. Physical Properties of RA-LA Copolyesters, Synthesized by Random Polycondensation of the Acids^a

					$\mathrm{mol}~\mathrm{wt}^g$			
polymer ^{b} P(LA:RA),	lactic	${ m specific} { m optical} { m rotation,}^d$	$\operatorname{melting}_{temp^e}$	intrinsic viscosity, ^f	3 h polycondensation at 180 °C		overnight polycondensation in a vacuum	
w/w	$acid^c$	$[\alpha]^{20}D$	t,°Ĉ	dL/g	$M_{ m n}$	$M_{ m w}$	M _n	$M_{ m w}$
99:1	L	-139.5	98	0.14	900	1500	2000	2700
97:3	L	-135	88	0.18	970	1200	3100	4500
94:6	L	-131.5	85	0.21	1100	1200	4200	6200
90:10	L	-131	80	0.19	1040	1140	4100	5800
85:15	L	-117.5	55	0.18	1000	1100	4000	5600
80:20	L	-106	h	0.11	770	800	2500	3200
70:30	L	-94	h	0.16	950	1100	5800	7800
60:40	L	-93	h	0.13	850	950	4200	5500
50:50	L	-88	h	0.13	1000	1200	3500	4500
100% PRA	-	+25	h	0.10	1100	1700	4300	5600
100% L-PLA	L	-140	158	0.18	1300	1600	4400	5600
100% d-PLA	D	+150	163	0.27	1600	1900	$11\ 000$	$13\ 000$

^{*a*} RA and LA acids were condensed at 180 °C for 3 h. ^{*b*} w/w ratio of the monomers used for copolymerization. ^{*c*} Lactic acid type. ^{*d*} Optical rotations of polymers determined by an Optical Activity LTD polarimeter in a 10 mg/mL polymer solution in CHCl₃. ^{*e*} Melting temperature of the copolymers measured by a Fisher apparatus. ^{*f*} Intrinsic viscosity of the polymers in dichloromethane measured in Cannon-Ubbelohde 75 dilution viscometer. ^{*g*} Molecular weight determined by GPC. ^{*h*} Liquid at room temperature.

m, C3 -CH₂, 2H, m, C13 -CH₂, and 3H, d, -CH₃, LA), 1.34-1.25 (16H, m, C4-7 and C14-17), and 0.868 (3H, t, C18 -CH₃) ppm.

 $^1\mathrm{H}$ NMR (CDCl₃, 100% PRA, δ): 5.44–5.30 (2H, m, C9–10, –CH=CH–), 4.873 (1H, m, C12 HC–O–), 2.309 (2H, t, C2 –CH₂), 2.194 (2H, t, C11–CH₂), 2.01 (2H, m, C8–CH₂), 1.603 (2H, m, C3–CH₂), 1.446 (2H, m, C13–CH₂), 1.291 (16H, m, C4–7 and C14–17), and 0.862 (3H, t, C18–CH₃) ppm.

 $^1\mathrm{H}$ NMR (CDCl₃, PLA, δ): 5.16–5.15 (1H, q, CH–CH3) and 1.58–1.56 (3H, d, –CH3, LA) ppm.

2.5. Copolymer Synthesis by Transesterification and Repolymerization by Polycondensation. Transesterification of PLA with ricinoleic acid was conducted as follows: 250 mL round-bottomed flask, equipped with a Dean-Stark reflux condenser and CaCl2 drying tube, was charged with pure ricinoleic acid and PLA (L-PLA: $Mn = 41\ 000;\ M_w = 91\ 000$) in the desired ratios (w/w total amount of both compounds was 10 g) and 100 mL of toluene. The ingredients were dried overnight by refluxing toluene to remove water traces, and then toluene was removed and in bulk transesterification was proceeded for 12 h at 150 °C, followed by GPC and ¹H NMR analysis. The reaction was stopped as soon as the product achieved minimal constant molecular weight. Repolymerization was carried out by thermal polycondensation. The reaction flask was connected to an oil pump and heated to 150 °C under a vacuum of 0.3 mmHg for additional 10 h, followed by GPC.

¹H NMR (P(LA–RA) 60:40, δ): 5.47–5.29 (2H, m, C9–10, –CH=CH–), 5.20–5.00 (1H, q, CH–CH3, LA), 4.90–4.87 (1H, m, C12 HC–O–), 2.38–2.24 (2H, m, C2 –CH₂, and 2H, m, C11 –CH₂), 1.99 (2H, m, C8 –CH₂), 1.66–1.40 (2H, m, C3 –CH₂, 2H, m, C13 –CH₂, and 3H, d, –CH3, LA), 1.30–1.24 (16H, m, C4–7 and C14–17), and 0.866 (3H, t, C18 –CH₃).

3. Results and Discussion

Thermal Polycondensation. Copolyester Synthesis. Biodegradable copolyesters of lactic and ricinoleic acids at various w/w ratios from 99:1 to 50:50, were synthesized by thermal polycondensation to yield solid and liquid-viscous materials (Scheme. 1). The solid polymers P(LA:RA) 99:1-85:15 had an off-white color and melted at temperatures between 55 and 98 °C. All viscous polymers-P(LA:RA) 8:2 to 5:5-were clear yellow liquids at room temperature that became yellow to brown as the content of RA content in the copolymer increased.

Polymers with molecular weights in the range 2000 to 11000 were obtained. All polymers possess typical IR absorption at 1748 cm⁻¹ corresponding to the ester

carbonyl stretching bands. ¹H NMR spectra of the polymers fit their composition. The molecular weights, thermal properties, specific optical rotation of the polymers, and their intrinsic viscosity are summarized in Table 1. Copolymerization process did not affect the optical purity of PLAs. There is a correlation between intrinsic viscosity and P(LA–RA)s molecular weight and content. All the liquid polymers had an intrinsic viscosity (in dichloromethane) between 0.10 and 0.16 dL/g (Table 1). Solid polymers found to be more viscous in the same conditions. All P(LA:RA)s with up to 20% RA w/w had an intrinsic viscosity between 0.14 and 0.27 dL/g.

Polymerization of pure RA by thermal polycondensation was confirmed by ¹H NMR (Figure 1). The proton on C12 is relocated to lower field as a result of ester bond formation. It was not the only change. Double bond protons were slightly shifted to upper field upon the polymerization. It can be explained by long-range deshielding/shielding effects. The protons close to electronegative groups, such as hydroxyl, experience a lower density of shielding electrons and absorb at lower frequency (deshielding). On the other hand, the protons distant from such groups, as next to ester bond that was created during polymerization, absorb at a higher frequency (all expressed in relation to tetramethylsilane). This ¹H NMR analysis allows the determination of unreacted monomer left in the polymer sample.

Transesterification. Copolyester Synthesis. Copolyesters of lactic and ricinoleic acids at 9:1 to 5:5 w/w ratios were synthesized by transesterification, followed by repolymerization by thermal polycondensation, to yield solid and viscous materials (Scheme 1). The solid polymers P(PLA:RA) 9:1–80:20 had an off-white to yellow brown color, depending on RA content, and melted at temperatures between 93 and 140 °C. The viscous polymer P(LA:RA) 5:5 was a yellowish viscous liquid at room temperature.

Polymers with molecular weights in the range 5000– 11000 were obtained. All polymers possess typical IR absorption at 1748 cm⁻¹ which corresponds to the ester carbonyl stretching bands. ¹H NMR spectra of the polymers fit their composition. The physical properties of the polyesters are summarized in Table 2. Copolymerization process did not affect the optical purity of



Figure 1. ¹H NMR spectra: (A) pure ricinoleic acid, with peaks at (a) 5.54, (b) 5.40, and (c) 3.63 ppm; (B) PRA, with peaks at (a) 5.45, (b) 5.31, and (c) 4.87 ppm in chloroform- d_1 .

Scheme 1. Synthesis of Poly (RA–LA) by (A) Random Condensation of LA and RA Acids or (B) Transesterification of PLA with RA and Repolyesterification



Table 2. Properties of Polymers Synthesized by Transesterification^a

					mol wt ^f			
polymer P(l-PLA:RA), ^b	specific optical rotation. ^c	$\operatorname{melting}_{\mathbf{range}^d}$	intrinsic viscosity. ^e	12 h transesterification 150 °C		10 h repolymerization 150 °C, 0.3 mmHg		
w/w	$[\alpha]_D^{25}$	t,°Č	dL/g	$M_{ m n}$	$M_{ m w}$	$M_{ m n}$	$M_{ m w}$	
90:10	-130.5	147	0.24	3200	4700	11 000	$14\ 000$	
80:20	-106	142	0.14	1800	4000	5000	8000	
70:30	-81	111	0.15	1500	2600	5500	8100	
60:40	-68	93	0.13	1300	2200	5000	7000	
50:50	-38	g	0.15	1200	2000	5600	8200	
100% PRA	+25.5	g	0.10	1400	2000	4300	5600	

^{*a*} Polymers synthesized by transesterification of L-PLA $M_w = 91000$ with RA at 150 °C and repolymerization. ^{*b*} w/w ratio of the monomers used for copolymerization. ^{*c*} Optical rotations of polymers determined by an Optical Activity LTD polarimeter in a 10 mg/mL polymer solution in CHCl₃. ^{*d*} Melting temperature of the copolymers measured by Fisher apparatus. ^{*e*} Intrinsic viscosity of the polymers in dichloromethane measured in Cannon-Ubbelohde 75 dilution viscometer. ^{*f*} Molecular weight determined by GPC. ^{*g*} Liquid at room temperature.

PLAs. There is a correlation between intrinsic viscosity and the P(LA-RA)s molecular weight.

Transesterification and Repolymerization Kinetics. RA was incorporated in the PLA by a transes-



experimental — calculated

Figure 2. Monitoring the molecular weight by GPC during the transesterification as a function of the RA content. The data are compared to the calculated molecular weight. Polymers were obtained from the reaction between PLA ($M_w =$ 91 000) and RA (99% pure) at 150 °C for 12 h. The PLA-RA ratio is weight to weight.

terification reaction (Scheme 1). The hydroxyl group of RA attacked ester group of L-PLA ($M_n = 41\ 000, M_w = 91\ 000$), to form new ester bonds. As the result of transesterification, RA (B) terminated PLA (A) blocks were created (AAAAB—first 12 h—transesterification reaction). The reaction between RA and PLA was continued until a constant molecular weight close to the calculated value was obtained (Figure 2). The calculated molecular weight assumed that pure ricinoleic acid was reacted with PLA of an $M_w = 91\ 000$.

Figure 3 shows the change in the molecular weight of P(PLA-RA) during transesterification and repolymerization processes. The molecular weight after 12 h of transesterification fit the expected molecular weight reduction. At this stage, the system was connected to a high vacuum oil pump and repolymerization process started. The repolymerization condensation was continued until no additional increase in polymer's molecular weight was observed. It was found that for all PLA: RA ratio AAAAB blocks were connected during repolymerization reaction. The molecular weights and melting temperatures of the P(PLA-RA) are shown in Table 2. Transesterification kinetics was also followed by ¹H NMR (Figure 4). As we previously showed (Figure 1), there are detectable difference in the location of double bond protons of RA monomer and polymerized RA. During the transesterification reaction, samples were withdrawn from the reaction flask and analyzed by GPC and by ¹H NMR. From the integration of ¹H NMR spectra from different transesterification stages (3,7 and 12 h) we can calculate the ratio between reacted and unreacted RA. According to those calculations, 46% monomer was left after 3 h of transesterification and only 13% after 7 h, and no traces of monomer were found after 12 h of transesterification.

GPC was used to follow the transesterification reaction. RA monomer (MW = 298), is easily detectable by GPC and also was well separated from other detectable molecular weights. The peak area ratio of monomer and copolymer fit their relative quantities during the transesterification reaction. From this ratio, the percentage of reacted RA monomer was calculated. The data calculated from GPC were compared to data that were obtained from ¹H NMR (Figure 5), and a good correlation was found.

Determination of Polymer Structure. Two series of P(LA–RA)s were synthesized by two different concepts. As it was summarized in Tables 1 and 2, copolyesters synthesized by polycondensation and by transesterification resulted in different physical properties for the corresponding copolymers.

These physical differences indicate different polymer structure: comonomer sequences and degrees of crystallinity. Those two parameters were determined using ¹H NMR and DSC. Whereas NMR spectroscopy could identify statistical segments in the polymeric chain, DSC was used to determine the thermal properties and degree of crystallinity.²⁴

Copolymer composition was verified by ¹H NMR by the integration ratio of the peaks at 5.15 ppm (one proton of PLA) and the peaks at 4.87 ppm one proton (C12) of PRA. The copolymer composition in the polymers was identical with the comonomer ratio in the weighted amounts. The relative degree of crystallinity of the copolymers depends directly on PLA block size – degree of randomness. To correlate the NMR spectra



Figure 3. Molecular weight change during the P(PLA–RA)s preparation by transesterification. The reaction was monitored by GPC during the transesterification and repolymerization reactions between PLA and RA as a function of time (see Scheme 1). Area A shows transesterification, while area B shows repolymerization.



Figure 4. ¹H NMR spectra: (a) pure ricinoleic acid monomer; (b) 3 h of transesterification reaction, PLA–RA 60:40 w/w, 46% monomer left; (c) 7 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, 13% monomer left; (d) 12 h of transesterification reaction, PLA–RA 60:40 w/w, no monomer left. All spectra performed in ¹H NMR 500 MHz with chloroform- d_1 as solvent. Calculations performed according to peak integration.



Table 3. Structure of NMR Checked Comonomer Units

Block type	Molecular Structure	Connection type
PLA -AAAA-	€ Las	[LA-LA]
PRA -BBBB-		[RA-RA]
P(LA-RA) -AAAB-	tothe him	[LA-RA]
P(LA-RA) -BAAA-	for H H H H H H H	[RA-LA]

Figure 5. Transesterification reaction progress as a function of the reacted RA content and reaction time as monitored by GPC and ¹H NMR.

to the composition and the frequency of occurrence of specific comonomer sequences and to determine the degree of randomness and the number-average sequence mathematical models was used. If the copolymer is not strictly alternating or blocklike, a randomly selected pair of comonomer units in the polymer chain may be represented as follows: RA–RA, RA–LA, LA–RA, LA– LA. To simplify the calculations, only the last three options were considered. The structures of those comonomer units are summarized in Table 3.

An examination of the ¹H NMR spectra of P(LA–RA)s (Figure 6) revealed three well separated quartets at 5.17, 5.10, and 5.05 ppm (one α -proton of PLA). The separation of the PRA proton peaks (4.87 ppm) was less pronounced. The PLA homopolymer has only one quartet at 5.15 ppm (Figure 6a). These additional peaks in

the copolymers' NMR spectra are attributed to longrange deshielding/shielding interactions. The LA–LA interactions are known from the pure PLA's NMR spectra. Ester bonds on both sides (LA–LA) cause the deshielding effect and the proton absorbs at a lower frequency. If we compare LA–RA and RA–LA, in the case of (AAAB) LA–RA, the α -proton of LA is located closer to the RA double bond and experiences a lower density of shielding electrons and absorbs at lower frequency (deshielding). For (BAAA) RA–LA, the α -proton distant from such groups, such as that next to the –CH₂– chain, absorbs at a higher frequency (all expressed in relation to tetramethylsilane).

As the w/w ratio and preparation method of the copolymers varied, the integration ratios of these peaks changed. Figure 6 represents the relevant peaks for P(LA:RA)s 60:40 w/w, synthesized by condensation and by transesterification. The integration data of the ¹H



Figure 6. ¹H NMR spectra: (a) PLA; (b) PRA; (c) P(LA–RA) 60:40 w/w synthesized by thermal polycondensation; (d) P(LA–RA) 60:40 w/w synthesized by transesterification followed by condensation; (e) P(LA–RA) 60:40 w/w synthesized by ROP. Spectra performed on a Varian NMR 500 MHz in chloroform-*d*₁. Calculations performed using peak integration.

NMR spectra of P(LA-RA)s 90:10 to 50:50 w/w, synthesized by both methods, were calculated in the following manner.

1. Unconditional Probability. [p(LA) and p(RA)] are the probabilities of a randomly selected monomer unit in the polymeric chain to be either LA or RA. This could be determined by the overall integration ratio of LA to RA.

$$p(LA) + p(RA) = 1 \tag{1}$$

2. Probability. [p(LA-LA), p(LA-RA), and <math>p(RA-LA)] are the probabilities that the randomly selected connection was either (LA-LA), (LA-RA), or (RA-LA). This probability could be determined from the integration ratios of the relevant peaks, as presented in Figure 6.

From these probabilities and the feed ratios it is possible to calculate the following:

I. Degree of Randomness (h) of the Formed Polymer

$$h = p(\text{LA}-\text{RA})/p(\text{LA})p(\text{RA})$$
(2)

h < 1 means block character of the copolymer; h = 1 means the polymer takes a random distribution; h > 1 means alternating tendency; and h = 2 means a full alternating copolymer.

II. Number-Average Sequence Length of a Monomer Sequence (L_n)

$$L_{\rm LA} = 1/p(\rm RA-LA) \tag{3}$$

For the P(LA-RA)s synthesized by thermal polycondensation and by transesterification with w/w ratios from 9:1 to 5:5, the results are presented in Table 4. Obtained results can be summarized in the following way. Polymers prepared by thermal polycondensation have alternating tendency (h > 1), [AABABABBAAA-BABB]. Polymers prepared by transesterification obtain block character (h < 1), [AAABAAABAABB] apart from P(PLA:RA) 50:50 w/w. Its alternating tendency is a result of the relatively high RA content. The numberaverage sequence length (L_{LA}) of lactic acid decreased from 12 to 4 for P(LA-RA)s from 9:1 to 5:5, respectively. The number-average sequence length (L_{LA}) of lactic acid decreased from 50 to 17 for P(LA-RA)s prepared by transesterification from 9:1 to 5:5, respectively. Sequence length is an additional evidence to random and block character of the polymers prepared by random polymerization vs transesterification, respectively.

The same calculations were performed on previously studied RA based copolyesters synthesized by ringopening polymerization (ROP).²¹ The results are given in Table 4. RA based polyesters synthesized by ROP had a block character (h < 1). Actually they obtain a

feed ratio of LA–RA in the polymer, ^b p(LA)	probability of finding the [LA–LA] unit, p(LA–LA)	probability of finding the [LA-RA] unit, p(LA-RA)	probability of finding the [RA-LA unit, p(RA-LA)	$\mathrm{av}\ \mathrm{block}\ \mathrm{length},^{d}\ L_{\mathrm{LA}}$	degree of randomness, ^c h				
Condensation									
0.9	0.80	0.12	0.08	12.5	1.33				
0.8	0.70	0.17	0.13	7.7	1.06				
0.7	0.53	0.36	0.11	9	1.71				
0.6	0.48	0.40	0.12	8.3	1.67				
0.5	0.40	0.35	0.25	4	1.4				
		Transester	ification ^e						
0.9	0.90	0.08	0.02	50	0.89				
0.8	0.82	0.14	0.04	25	0.87				
0.7	0.77	0.20	0.03	33.3	0.95				
0.6	0.76	0.20	0.04	25	0.83				
0.5	0.64	0.30	0.06	16.7	1.2				
Ring Opening Polymerization (ROP)									
0.9	0.99	0.01	0	f	0.11				
0.8	0.96	0.04	0	f	0.25				
0.7	0.97	0.03	0	f	0.14				
0.6	0.92	0.08	0	f	0.33				
0.5	0.94	0.06	0	f	0.24				

Table 4. Comonomer Sequence Distribution of the P(LA-RA)s^a

^{*a*} Probability, degree of randomness, and LA average block length were calculated based on LA:RA (w/w) feed ratios (9:1 to 5:5), according to eqs 1, 2, and 3 as presented in the text.²³ It was assumed that ricinoleic acid is pure and PLA molecular weight $M_w = 91\ 000$. ^{*b*} Equation 1. ^{*c*} Equation 2. ^{*d*} Equation 3. ^{*e*} PLA. ^{*f*} Limited only by molecular weight; polymer with AAABBB structure.



Figure 7. Thermal properties of P(LA–RA)s as determined by DSC. Column 1. P(LA-RA)s synthesized by transesterification followed by repolymerization by condensation. Column 2. P(LA-RA)s synthesized by direct polycondensation of RA + LA acids, and Column 3: P(LA-RA)s synthesized by ring-opening polymerization (ROP).²¹ The P(LA-RA) copolymer compositions were as follows: (a) 100:0; (b) 90:10; (c) 80:20; (d) 70:30; (e) 60:40; (f) 50:50 w/w of LA:RA.

[AAAABB] diblock structure. Such a structure is the result of the low reactivity of the sterically hindered RA lactone. ¹H NMR analysis of those polyesters confirms the diblock structure (Figure 6e). No [RA–LA] connections were found. The polyester contained only a small amount of [LA–RA] connections.

DSC revealed a crystalline structure for polyesters synthesized by transesterification and by ROP (Figure 7). For polyesters synthesized by random condensation only P(LA–RA) 90:10 w/w contained crystalline areas. This information is correlated with the ¹H NMR analysis where polymers containing relatively long LA blocks obtain crystalline areas. In P(LA–RA)s, only LA blocks are able to crystallize. Ricinoleic acid structure is sterically hindered where RA blocks formed noncrystal-

line brushlike domains along the polymer chain, thus increasing the RA content decreased the melting point and the crystallinity of the polymers. Figure 7 shows that polymers (Figure 7(1,3)) possessing a long enough LA block form detectable crystalline domains in the polymer where copolymers (Figure 7(2c-f)), with 20% and higher RA content do not have LA blocks long enough to form a detectable crystalline area in the polymer.

1. P(LA-RA)s are synthesized by transesterification followed by repolymerization by condensation.

2. P(LA–RA)s are synthesized by direct polycondensation of RA + LA acids.

3. P(LA-RA)s are synthesized by ring-opening polymerization (ROP).²¹

The copolymer compositions were as follows: (a) 100% PLA; (b) P(LA-RA) 90:10 w/w; (c) P(LA-RA) 80:20 w/w; (d) P(LA-RA) 70:30 w/w; (e) P(LA-RA) 60:40 w/w; (f) P(LA-RA) 50:50 w/w.

Conclusions

Copolymers of lactic acid (LA) and ricinoleic acid (RA) were synthesized by random condensation of RA and LA or by transesterification and repolymerization to yield random and multiblock copolymers, respectively. Copolymers prepared by ring opening copolymerization reported recently resulted in an AB diblock LA–RA copolymer.²¹ The copolymers of similar RA–LA composition and molecular weights showed significant differences in thermal properties, where viscous liquids at room temperature with RA content as low as 20%. These polymers, particularly the liquid polymers, may have use as sealants and as injectable carriers of drugs.

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