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# Lactic and Ricinoleic Acid Based Copolyesters Stereocomplexation

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ABSTRACT: A systematic study of the synthesis and stereocomplexation of L-lactic acid and ricinoleic acid based copolyesters is reported. L-lactic acid and ricinoleic acid based copolyesters were synthesized by melt condensation and transesterification of high-molecular-weight poly(lactic acid) (PLA) with ricinoleic acid and repolymerization by condensation to yield random and block copolymers of molecular weights between 3000 and 5000. To correlate between the copolyesters synthesized by polycondensation and transesterification, P(LA-RA)s with different PLA blocks were synthesized. The relative degree of crystallinity of those copolyesters depends directly on PLA block size, which is the only difference between the corresponding polymers. $^1$H NMR spectroscopy analysis coupled with information from DSC allowed correlation between the degree of crystallinity and PLA block size. P(L-LA-RA)s and enantiomeric D-PLA were mixed together in acetonitrile solution to form stereocomplexes. Stereocomplex formation was dependent on the size of PLA block in the P(L-LA-RA)s, at least a block length of 10 LA units is required to form a stereocomplex. The formed stereocomplexes exhibited higher melting temperature than the enantiomeric polymers, indicating stereocomplex formulation.

## Introduction

Polyesters are useful bioabsorbable materials for controlled drug release. They hydrolyze to hydroxy acid monomers when placed in aqueous medium. It has been reported that drug release and degradation of polyesters can be altered by using various composites of hydrophobic and hydrophilic monomers.[1] D-, L-, and DL-poly(lactic acid) are good candidates for the preparation of biodegradable copolymers with polyanhydrides.

It was discovered in recent years that polyesters of D and L enantiomers of lactic acid form stable stereocomplexes, with physical and chemical properties different from the original polymers. Stereocomplexes were formed from the interaction between chemically identical polymers with different chiral configurations, forming a physical complex with altered physical properties compared to the parent compounds. Syndiotactic and isotactic poly(methyl methacrylate) were the first reported pair of polymers to form a stereocomplex in acetone or tetrahydrofuran (THF).[2] Lacking possibilities for electrostatic interactions or hydrogen bridge formation, the main force favoring the complexation was thought to come forth from stereospecific van der Waals interactions[3]. The discovery of the stereocomplex formation between D- and L-poly(lactic acid) (D- and L-PLA) is significant, as these polymers are widely used in various medical applications.[4] Stereocomplexes are also formed upon mixing di- and triblock copolymers if the stereoregular lactic acid sequences are of sufficient length.[5,6] Lactic acid based polymers have been prepared by direct polycondensation, ring opening polymerization (ROP), grafting, chain extension, or transesterification.[7] Lactic acid can be condensed with other hydroxy acids such as 6-hydroxycaproic acid, glycolic acid, and hydroxybutyric acid and the presence of diols, diacids, and diamines. 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(aminoethers), phosgene, phosphate, and anhydrides have been used.[8−10]

Enantiomerically pure PLA is a semicrystalline polymer with $T_g$ of about 55 °C and $T_m$ 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, $\epsilon$-caprolactone, $\delta$-valerolactone, 1,5-dioxepan-2-one (DXO), and trimethylene carbonate (TMC) are frequently used in the synthesis of PLA copolymers of different properties.[11−14] Fatty acids are suitable candidates for the preparation of biodegradable polymers,[15−19] as they are natural body components and they are hydrophobic and thus 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 9th position and a hydroxyl group in the 12th position (*cis*-12-hydroxyoctadeca-9-enoic acid). It is produced from the hydrolysis of castor oil.[20]

Previous studies in our laboratory focused on the synthesis of ricinoleic acid based polyanhydrides.[18,21] 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 on the basis of sebacic acid.[15] In addition, a systematic study

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on the synthesis and characterization of ricinoleic acid lactones, their homopolymerization, and ricinoleic acid-*co*-lactic acid polyesters synthesized by ring-opening polymerization was reported.[22]

In a previous article, we reported on the copolymerization of PLA with ricinoleic acid using different polymerization techniques that resulted in pliable, soft, or even liquid polymers influenced by the ricinoleic acid content.[23] The purpose of this study is to investigate the physical properties and stereocomplexation of P(LA-RA) with a focus on the correlation between copolymer sequence, PLA block length, and stereocomplexation.

## Experimental Section

**Materials.** Crude ricinoleic acid was purchased from Acros (85% pure) (Geel, Belgium), L-lactic acid (L-LA) was purchased from J. T. Baker (Deventer, Netherlands). D-Lactic acid was prepared from the hydrolysis of D-lactide in water and D-lactide was purchased from Purac Biochem (Gorinchem, Netherlands). $CDCl_3$, for NMR, was purchased from Sigma-Aldrich (Rehovot, Israel). All solvents and salts were analytical grade from Aldrich or Biolab (Jerusalem, Israel).

**Instrumentation.** IR spectra were performed on monomer and polymer samples cast on NaCl plates from $CH_2Cl_2$ solution on a Bruker Vector 22 System FT-IR. 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 copolyesters were determined also by a Fisher Scientific melting point apparatus. Molecular weights of the copolyesters 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 $\mu$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 500−20 000 using BREEZE version 3.20, copyright 2000 Waters Corporation computer program. Optical rotations of polymers were determined on an optical activity LTD polarimeter (Cambridgeshire, England) using 10 mg/mL polymer in $CHCl_3$ solution. Viscosity of the polymers in dichloromethane was measured in a Cannon Ubbelohde 75 micrometer dilution viscometer. Afflux times were measured for four concentrations at 25 °C, the data were analyzed for viscosity data by standard methods.

Scanning electron microscopy (SEM) was conducted using Quanta 2000 SEM (30 kV) after dried stereocomplex microparticles were fixed on a stub and gold-coated using a Polarone E5100.

**PLA Synthesis by Ring Opening Polymerization.** High-molecular-weight PLA was prepared by ring-opening polymerization (ROP) according to the following procedure: a 250-mL round-bottomed flask, equipped with a Dean−Stark reflux condenser and $CaCl_2$ tube, was charged with 50 g L-lactide and 100 mL toluene. The L-lactide was dried by evaporating the toluene over 4 h. During the evaporation, initiator benzyl alcohol was added. The quantity of initiator was calculated according to the required molecular weight of PLA (1 molecule of initiator per polymer chain). Sn(Oct) (60 mg) was added as catalyst, after evaporation of most of the toluene, and the solution was left to react at 135 °C. The reaction was followed by molecular weight determination with GPC and stopped after required molecular weight was received.

**Copolymer Synthesis by Transesterification and Repolymerization by Polycondensation.** Transesterification of PLA with ricinoleic acid was conducted as described elsewhere.[23] Briefly, a round-bottomed flask was charged with pure ricinoleic acid and PLA (L-PLA: $M_n$ = 41 000; $M_w$ = 91 000) in desired ratios (w/w, total amount of both compounds was 10 g) and 100 mL toluene. The ingredients were dried with toluene, and bulk transesterification was performed for 12 h at 150 °C, followed by GPC and $^1$H NMR analysis. The reaction was stopped as soon as the product achieved minimal constant molecular weight. Repolymerization was carried out by thermal polycondensation followed by GPC.

$^1$H NMR (P(LA-RA) 60:40, $\delta$): 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 $-CH_2$ and 2H, m, C11 $-CH_2$), 1.99 (2H, m, C8 $-CH_2$), 1.66−1.40 (2H, m, C3 $-CH_2$, 2H, m, C13 $-CH_2$, and 3H, d, −CH3, LA), 1.30−1.24 (16H, m, C4−7 and C14−17) and 0.866 (3H, t, C18 $-CH_3$).

**Copolymer Synthesis by Thermal Polycondensation.** Low-molecular-weight polyesters, PRA, L-, D-, and DL- PLA, P(L-LA:RA), P(D-LA:RA), and P(DL-LA:RA) with different LA:RA (w/w) ratios were prepared by thermal polycondensation as previously described.[23] Briefly, a round-bottomed flask was charged with pure ricinoleic acid and lyophilized lactic acid in appropriate ratios (total amount of both acids was 20 g) and 150 mL 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, then the reaction flask was connected to an oil pump where the condensation was continued under a vacuum of 0.3 mmHg for an 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, $^1$H NMR, IR, DSC, m.p., Cannon Ubbelohde 75 dilution viscometer, and specific optical rotation.

$^1$H NMR ($CDCl_3$, P(LA-RA) 60:40, $\delta$): 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 $-CH_2$ and 2H, m, C11 $-CH_2$), 2.01 (2H, m, C8 $-CH_2$), 1.68−1.50 (2H, m, C3 $-CH_2$, 2H, m, C13 $-CH_2$, and 3H, d, *−CH3, LA*), 1.34−1.25 (16H, m, C4−7 and C14−17) and 0.868 (3H, t, C18 $-CH_3$)-ppm.

$^1$H NMR ($CDCl_3$, 100% PRA, $\delta$): 5.44−5.30 (2H, m, C9−10, −CH═CH−), 4.873 (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.

$^1$H NMR ($CDCl_3$, PLA, $\delta$): 5.16−5.15 (1H, q, CH−CH3), 1.58−1.56 (3H, d, −CH3, LA) ppm.

**Copolymer Synthesis by Thermal Polycondensation with Different PLA Chain Length Prepared by Lactic Acid Polycondensation.** Low-molecular-weight polyesters, P(L-LA:RA) 80:20 with different size, and time-dependent LA blocks were prepared by two-step thermal polycondensation according to the following procedure.

To a 250-mL round-bottomed flask, equipped with a Dean−Stark apparatus, reflux condenser, and $CaCl_2$ drying tube, 16 g lyophilized L-lactic acid and 150 mL toluene was charged. The lactic acid solution was dried overnight with refluxing toluene to remove water traces, then the toluene was removed and the temperature was raised gradually to 180 °C. The reaction was continued for 0.5, 1.5, and 3 h to obtain different size PLA blocks. The process was followed by GPC. In the second step, 4 g of pure and dry ricinoleic acid was dissolved in 50 mL toluene and was added to the PLA flasks. Toluene was removed, and the temperature was raised gradually to 180 °C. The reaction was continued for 4 h and then connected to an oil pump, where the condensation was continued under a vacuum of 0.3 mm Hg for an additional 12 h. Each step was followed by GPC analysis of samples removed from the reaction flasks to determine the molecular weight of the forming polymers at each time period. All polymers were characterized by GPC, $^1$H NMR, IR, DSC, and specific optical rotation.

$^1$H NMR ($CDCl_3$, P(LA-RA) 1.5 h prepolymerization; 80:20, $\delta$): 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 $-CH_2$ and 2H, m, C11 $-CH_2$), 2.01 (2H, m, C8 $-CH_2$), 1.68−1.50 (2H, m, C3 $-CH_2$, 2H, m, C13 $-CH_2$, and 3H, d, *−CH3, LA*), 1.34−1.25 (16H, m, C4−7 and C14−17) and 0.868 (3H, t, C18 $-CH_3$) ppm.

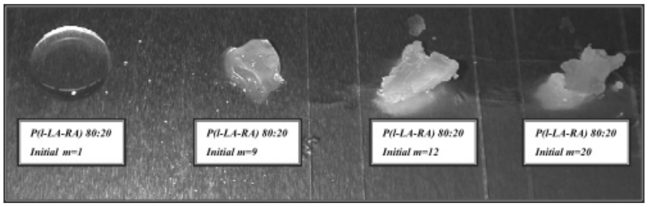
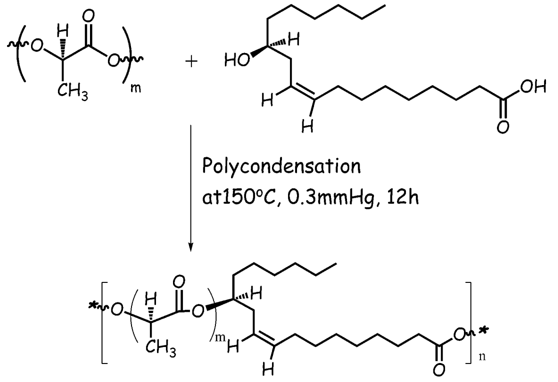


**Figure 1.** P(LA-RA)s 80:20 with time-dependent PLA blocks.

**Scheme 1. Synthesis of P(LA-RA)s 80:20 with Different PLA Chain Length ($m$ = 2−20)**



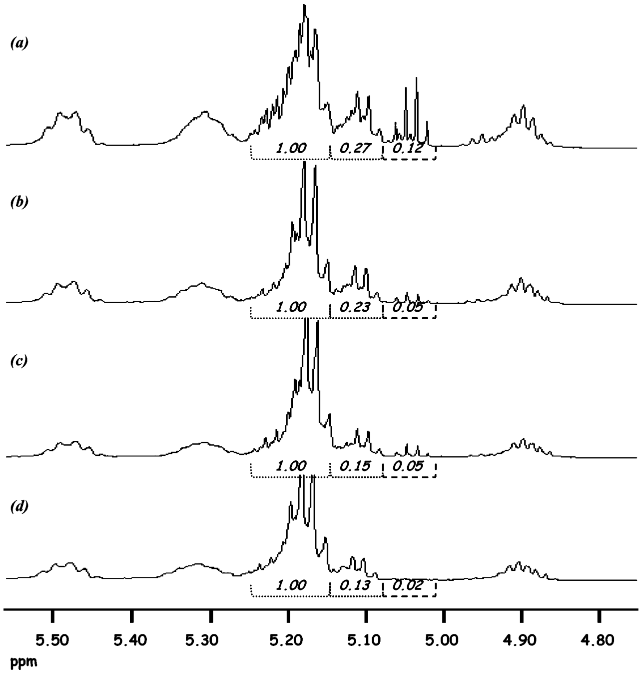


**Figure 2.** $^1$H NMR spectra of: (a) P(LA-RA) 80:20, $m$ = 1, random copolymerization of LA + RA; (b) P(LA-RA) 80:20, PLA block length $m$ = 9; (c) P(LA-RA) 80:20, PLA block length $m$ = 12; (d) P(LA-RA) 80:20, PLA block length $m$ = 20. Spectra performed on a Varian NMR 500 MHz in chloroform-$d_1$. Calculations performed using peak integration data.

**Stereocomplex Preparation.** Stereocomplexes were prepared by mixing acetonitrile solutions of the enantiomers and collecting the precipitated stereocomplexes. Noncomplexed polymers are well soluble in acetonitrile solution and remain in filtrate solution during collection of the stereocomplex powder. Stereocomplex formation was tested for all P(LA-RA)s synthesized by transesterification, polycondensation, and polycondensation with initial PLA blocks. In a typical experiment, P(L-LA-RA) 70:30 (500 mg) having a number-average molecular weight of 5800 and D-PLA (350 mg) (1:1 w/w ratio of PLAs) having a number-average molecular weight of 3000 were dissolved separately in acetonitrile (2 mL). The solutions were mixed together for 4 min by vortex apparatus, followed by mixing at 37 °C for an additional 4 h at 100 r/min. The solutions were left at room temperature without stirring overnight. The stereocomplex powder was collected by filtration. The filtrate was poured onto a glass Petri dish to allow solvent evaporation. The precipitates were characterized by DSC and SEM.

## Results and Discussion

**Copolymer Synthesis by Thermal Polycondensation with Different Chain Length.** P(LA-RA)s 80:20 with different PLA block lengths were synthesized by two-step polycondensation to yield liquid-viscous to viscous-semisolid materials (Scheme 1).

P(LA:RA) 80:20 with initial $m$ = 1 was a clear-yellow liquid at room temperature, where polymers with initial

**Table 1. Properties of Ricinoleic Acid-Lactic Acid Block Copolymers**[a]

| initial PLA block length | | | intrinsic viscosity[d] | specific optical rotation[e] | melting temperatures | melting range | heat of fusion[h] | molecular weight[b] | |
|---|---|---|---|---|---|---|---|---|---|
| molecular weight[b] | | | | | | | | | |
| $M_n$ | $M_w$ | $m$[c] | dL/g | $[\alpha]_D^{25}$ | Karl-Fischer[f] $t$ °C | DSC[g] $t$°C | $\Delta H$ $J/g$ | $M_n$ | $M_w$ |
| 72 | 72 | 1 | 0.14 | −106 | liquid at room temperature | | | 2500 | 3200 |
| 550 | 650 | 9 | 0.15 | −109 | 55−60 | 90 | 4.73 | 2500 | 4900 |
| 730 | 850 | 12 | 0.14 | −111 | 65−70 | 105 | 8.65 | 1900 | 3600 |
| 1000 | 1400 | 20 | 0.16 | −118 | 75−80 | 110 | 13.71 | 3100 | 5300 |

[a] Polymers synthesized by polycondensation of RA with LA oligomers prepared by condensation of LA. [b] Molecular weight of initial LA oligomers and P(LA-RA) determined by GPC. [c] Initial PLA block length $m = M_{w(PLA)}/M_{w(LA)}$. [d] Intrinsic viscosity of the polymers in dichloromethane measured in Cannon Ubbelohde 75 dilution viscometer. [e] Optical rotation was determined by Optical Activity LTD polarimeter using 10 mg/mL polymer solution in chloroform. [f] Melting temperatures of the copolymers measured by Fischer apparatus. [g] Melting range of the copolymers measured by DSC. [h] Heat of fusion of the copolymers measured by DSC.

**Table 2. Comonomer Sequence Distribution of the P(LA-RA)s 80:20**

| two-step polycondensation | | | | | | |
|---|---|---|---|---|---|---|
| initial PLA $m$[a] | feed ratio of LA-RA in the polymer$^{(1)}$ $p$(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) | degree of randomness $h^{(2)}$ | PLA block length in P(LA-RA) $L_{(LA)}^{(3)}$ |
| 1 | 0.8 | 0.72 | 0.19 | 0.09 | 1.19 | 11 |
| 9 | 0.8 | 0.76 | 0.18 | 0.06 | 1.12 | 16 |
| 12 | 0.8 | 0.83 | 0.12 | 0.05 | 0.75 | 20 |
| 20 | 0.8 | 0.85 | 0.11 | 0.04 | 0.70 | 25 |

[a] $m$: Initial PLA block length, calculated as in Table 1; probability, degree of randomness, and LA average block length were calculated on the basis of LA:RA (w/w) feed ratios, according to eqs 1, 2, and 3 as previously described.[26]

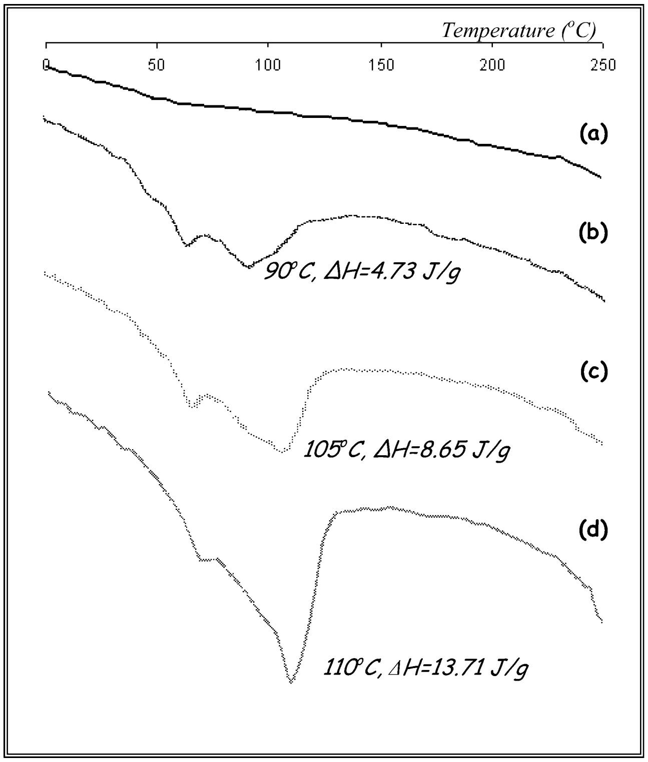


**Figure 3.** Thermal properties of P(LA-RA)s 80:20 with increased PLA blocks as determined by DSC: (a) P(LA-RA) 80:20, $m = 1$; (b) P(LA-RA) 80:20, $m = 9$; (c) P(LA-RA) 80:20, $m = 12$; (d) P(LA-RA) 80:20, $m = 20$; [Table 2].

$m = 9$ was viscous-yellow to off-white material ointmentlike at room temperature. Polymers with an initial PLA chain longer than 10 ($m > 10$) had an off-white color and melted at temperatures between 60 and 110 °C.

Polymers with molecular weights in the range of 3000−5000 were obtained. All polymers possess typical IR absorption at 1748 cm$^{-1}$, corresponding to the ester carbonyl stretching bands. $^1$H NMR spectra of the polymers fit their composition. The molecular weights, thermal properties, specific optical rotation of the polymers, and their intrinsic viscosity is summarized in Table 1. The copolymerization process did not affect the optical purity of PLAs. There was a correlation between the intrinsic viscosity and P(LA-RA)s molecular weight. The P(LA-RA)s 80:20 with different LA chain lengths had an intrinsic viscosity (in dichloromethane) between 0.14 and 0.16 dL/g (Table 1). Obtained polymers are visualized in Figure 1.

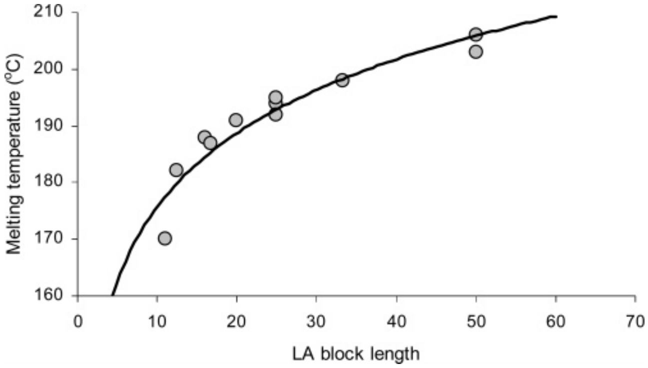


**Figure 4.** Correlation between the stereocomplex melting temperature and average LA block length in the copolymer.

**Correlation of Polymer Structure with Physical Differences.** Copolymer composition was verified by $^1$H NMR by the integration ratio of the peaks at 5.15 ppm (one proton of LA units) and the peak at 4.87 ppm (one proton at C12 of RA units). The composition of the RA-LA copolymers was identical to the polymerization entry comonomer ratio. The relative degree of crystallinity of the copolyesters as estimated from the heat absorption $\Delta H$ obtained by DSC depends directly on PLA block size, which is the only difference between the corresponding polymers.[24,25] The polymer composition, frequency of occurrence of specific comonomer sequences, degree of randomness, and the LA-RA sequence was determined by NMR.[23] If the copolymer is not strictly alternating or blocklike, a randomly selected pair of comonomer units in the polymer chain may be represented as

**Table 3. Stereocomplexes Formation and Properties**[a]

| percent of L-LA in the copolymer (% w/w) | percent of stereocomplex formation (%) | original polymer melting range (°C) | stereocomplex melting temperature (°C) | average LA block length(3) $L_{LA}$ | degree of randomness(2) $h$ |
|---|---|---|---|---|---|
| | | Condensation | | | |
| 90 | 89 (±5) | 80 | 182 | 12.5 | 1.33 |
| 80 | 35 (±5) | liquid at room temp. | 170 | 11 | 1.06 |
| 70 | clear solution | liquid at room temp. | | 9 | 1.71 |
| 60 | clear solution | liquid at room temp. | | 8.3 | 1.67 |
| 50 | clear solution | liquid at room temp. | | 4 | 1.4 |
| | | Transesterification[c] | | | |
| 90 | 91 (±5) | 147 | 203 | 50 | 0.89 |
| 80 | 76 (±5) | 142 | 193 | 25 | 0.87 |
| 70 | 71 (±5) | 111 | 198 | 33.3 | 0.95 |
| 60 | 46 (±5) | 93 | 194 | 25 | 0.83 |
| 50 | cloudy dispersion[b] | liquid at room temp. | ~187 | 16.7 | 1.2 |
| | | Two-Step Polycondensation[d] | | | |
| 80 | 35 (±5) | liquid at room temp. | 170 | 11 | 1.19 |
| 80 | 42 (±5) | 90 | 188 | 16 | 1.12 |
| 80 | 66 (±5) | 105 | 191 | 20 | 0.75 |
| 80 | 72 (±5) | 110 | 192 | 25 | 0.70 |
| 100% PLA | 95 (±5) | 158 | 206 | 50+ | 0 |

[a] Degree of randomness and LA average block length were calculated on the basis of LA:RA (w/w) feed ratios (9:1 to 5:5) and $^1$H NMR data, according to eqs 1, 2, and 3 as previously reported.[26] [b] Cloudy dispersion was obtained, fine particles were difficult to isolate, the solvent was evaporated. [c] It was assumed that ricinoleic acid is pure and PLA molecular weight $M_w$ = 91 000. [d] Polycondensation refers to P(LA-RA)s 80:20 with different initial PLA block (see Tables 1 and 2)

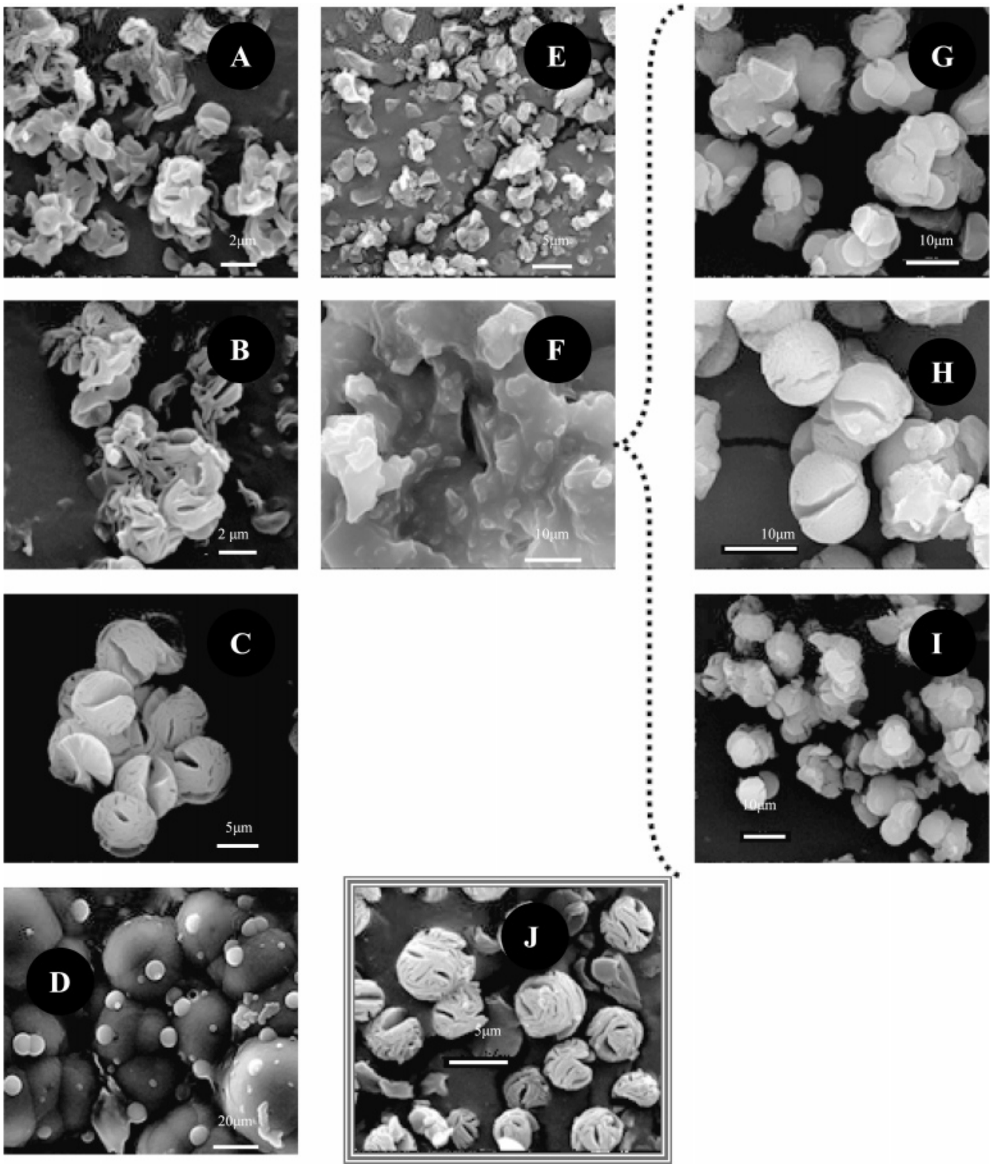


**Figure 5.** Scanning electron micrographs of microparticles prepared by stereocomplexation of: (A) P(LA-RA) 90:10 w/w synthesized by transesterification followed by condensation; (B) P(LA-RA) 80:20 w/w synthesized by transesterification followed by condensation; (C) P(LA-RA) 70:30 w/w synthesized by transesterification followed by condensation; (D) P(LA-RA) 60:40 w/w synthesized by transesterification followed by condensation; (E) P(LA-RA) 90:10 w/w synthesized by thermal polycondensation; (F) P(LA-RA) 80:20 w/w synthesized by thermal polycondensation; (G) P(LA-RA) 80:20 w/w, $m = 9$ synthesized by thermal polycondensation; (H) P(LA-RA) 80:20 w/w, $m = 12$ synthesized by thermal polycondensation; (I) P(LA-RA) 80:20 w/w, $m = 20$ synthesized by thermal polycondensation; (J) PLA synthesized by thermal polycondensation.

follows: RA-RA, RA-LA, LA-RA, LA-LA. To simplify the calculations, only the last three options were considered.

An examination of the $^1$H NMR spectra of P(LA-RA)s 80:20 (Figure 2) revealed three well-separated quartets at 5.17, 5.10, and 5.05 ppm (all are attributed to the $\alpha$-proton of PLA). The separation of the RA proton peaks (4.87 ppm) was less pronounced. The PLA homopolymer has only one quartet at 5.15 ppm. These additional peaks in the copolymers' NMR spectra are attributed to long-range deshielding/shielding interactions. The LA-LA interactions are known from the pure PLA's NMR spectra.

As the PLA block size of the copolymers varied, the integration ratios of these peaks changed. Figure 2 represents the relevant peaks for P(LA:RA)s 80:20 w/w, synthesized by condensation with different PLA block size. The integration data of the $^1$H NMR spectra of P(LA-RA) is summarized in Table 2. The probability of finding the particular sequences was calculated from $^1$H NMR data represented in Figure 2. Degree of randomness ($h$) of the formed polymers is calculated according following equation: $h = p(\mathrm{LA\text{-}RA})/p(\mathrm{LA})\mathrm{p}(\mathrm{RA})$. It is important to notify that $h < 1$ means the 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. The detailed description of calculations was previously described.[23,26]

Polymers prepared by thermal polycondensation, originally,[23] have an alternating tendency ($h > 1$), i.e.: [AABABABBAAABABB]. Polymers with a long enough initial PLA block obtain block character ($h < 1$), i.e.: [AAABAAABAAABB].

According to our previous report,[23] the number-average sequence length ($L_{\mathrm{LA}}$) of lactic acid decreased from 12 to 4 for P(LA-RA)s for 9:1 to 5:5 RA-LA copolymer, respectively. The number-average sequence length ($L_{\mathrm{LA}}$) of lactic acid decreased from 50 to 17 for

P(LA-RA)s prepared by transesterification of RA onto PLA 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 versus transesterification, respectively.

DSC revealed crystalline structure for P(LA-RA) 80:20 with initial PLA blocks (Figure 3). This information is correlated with the $^1$H NMR analysis, where polymers containing relatively long LA blocks possess crystalline domains. In P(LA-RA)s, only LA blocks are able to crystallize. Ricinoleic acid structure is sterically hindered where RA blocks formed noncrystalline brushlike domains along the polymer chain. Figure 2 shows that P(LA-RA)s 80:20 with even small, initial PLA blocks possess long enough LA blocks to form detectable crystalline domains in the polymer. P(LA-RA) 80:20 prepared by polycondensation of LA and RA do not have LA blocks long enough to form detectable crystalline domains in the polymer. According to the $\Delta H$, we can see that the longer the PLA block in the copolymer, the longer are the crystalline domains.[24,25]

**Stereocomplex Formation and Characterization.** Stereocomplexes were prepared by spontaneous precipitation from solution or by melt mixing. The stereocomplexes had different physical properties with respect to solubility, film forming properties, and melting temperature. The data for the starting polymers and resulting stereocomplexes is summarized in Table 3. The stereocomplexes are powdery crystalline materials formed spontaneously upon mixing in melt or solution and do not form films. Stereocomplex formation was tested for all P(LA-RA)s synthesized by transesterification and polycondensation with different initial PLA blocks.

Stereocomplex formation was dependent on the size of PLA blocks of the copolymer. Only polymers containing a long enough PLA block could form a stereocomplex. Percent of stereocomplex formation for each polymer was dependent on the relative ratio of such PLA blocks in the polymer.

According to results summarized in Table 3, we can conclude that a block length of a 10-unit LA sequence is required to form a stable stereocomplex. Good correlation was obtained between average LA block length of the stereocomplexes and their melting temperature (Figure 4).

Particle size and morphology is also dependent on PLA blocks length. Scanning electron micrographs of the powders are shown in Figure 5. Porous spherical particles were formed with a particle size of 2−7 $\mu$m depending on PLA block length and RA w/w content in the copolymer.

All stereocomplexes were insoluble in common organic solvents, such as chloroform, dichloromethane, acetonitrile, tetrahydrofuran, dioxane, dimethylformamide, and dimethyl sulfoxide in which the individual enantiomeric copolymers are highly soluble. Stereocomplexes possess a melting temperature that is significantly higher than the melting temperature of the corresponding enantiomers. As shown in Table 3, the stereocomplex segments melt at temperatures between 170 and 200 °C, which is about 50−150 °C above the melting temperature of the corresponding enantiomers.

## Conclusions

Stereocomplexes were formed from pasty copolymers of enantiomeric lactic (LA) and ricinoleic (RA) acid, having blocks of at least 10 enantiomeric lactic acid units. Stereocomplexes in the form of solid microparticles were formed by solvent mixing of copolymers of L-lactic acid with D-PLA.

This system can be used as carrier for drugs and polymeric scaffolds for tissue engineering.

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