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Monodisperse Enantiomeric Lactic Acid Oligomers: Preparation, Characterization, and Stereocomplex Formation

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ABSTRACT: D- and L-lactic acid oligomers were synthesized by polymerization of D- or L-lactide using 2-(2-methoxyethoxy)ethanol (MEE) and stannous octoate as initiator and catalyst, respectively. The average degree of polymerization (DP_{av}) of the oligomers could be tailored by the monomer/initiator ratio. HPLC and GPC analysis showed that the oligomers had a M_w/M_n ratio of around 1.5. Mass spectroscopic analysis revealed that products contained besides MEE−(lactate)$_{n=2,4,6,etc.}$ also MEE−(lactate)$_{n=1,3,5,etc.}$. The latter products are most likely formed due to transesterification reactions. Monodisperse lactic acid oligomers (DP 1−16) were obtained from the polydisperse oligomers by preparative HPLC and characterized by NMR and mass spectrometry. DSC analysis showed that crystallinity was present in D- or L-oligomers with DP ≥ 11. On the other hand, in blends of D- and L-oligomers of lactic acid crystallinity (stereocomplexation) was observed at a DP ≥ 7.

Introduction

Because of its biodegradability and biocompatibility, poly(lactic acid) (PLA) is widely under investigation for pharmaceutical and biomedical applications.[1−3] PLLA and PDLA, polymers of L-lactic acid and D-lactic acid respectively, are semicrystalline materials. High molecular weight PLA has a melting temperature (T_m) of 170 °C, a melting enthalpy (ΔH_m) of 70 J/g, and a glass transition temperature (T_g) of 60 °C.[4] Interestingly, in blends of high molecular weight PDLA and PLLA a phase of a higher T_m (230 °C) is observed. This is attributed to the formation of racemic crystallites, also called stereocomplexes. This phenomenon was first described by Ikada et al.[5] and has been the subject of extensive investigation by the same[6−9] and other research groups.[10,11]

Formation of stereocomplexes is not limited to homopolymers of D- and L-lactic acid but has also been observed in blends of random copolymers of L-lactide/ϵ-caprolactone and D-lactide/ϵ-caprolactone,[12] blends of D-rich and L-rich PLA,[13] poly(D-lactide-*co*-glycolide), and poly(L-lactide-*co*-glycolide),[14] and triblock copolymers of poly(ethylene glycol) and PLLA or PDLA.[15] In addition, it was reported that stereoregular fragments are formed during hydrolytic degradation of intrinsically amorphous poly(D,L-lactide). These fragments showed a retarded degradation, thereby affecting the biocompatibility of the poly(D,L-lactide).[16,17] The critical D- and L-lactide unit length needed for stereocomplex formation is not clear yet. Tsuji et al. reported that the critical D- and L-lactide length needed for stereocomplex formation is smaller than that for homocrystallization. However, no quantitative data were given.[14] Loomis et al. estimated that about 10 lactate units are required.[12] In a recent study, it was shown that in a blend of D-16mer and L-16mer stereocomplex formation was observed.[23] In this paper we describe the preparation and characterization of polydisperse and monodisperse lactic acid oligomers and their ability to form stereocomplexes. This yields insight into the minimum lactate length required to form racemic crystallites, as well as for the formation of homocrystallites.

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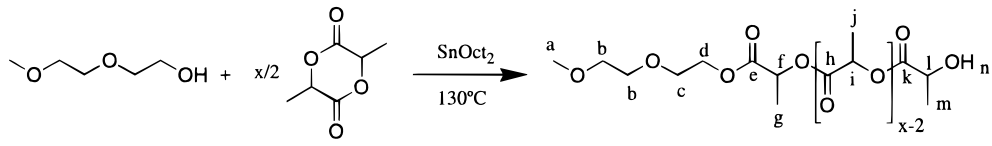

Figure 1. Reaction scheme of the synthesis of MEE-L-(or D-)lactic acid oligomer.

Experimental Section

Materials. L-Lactide ((3*S-cis*)-3,6-dimethyl-1,4-dioxane-2,5-dione, >99.5%) and D-lactide ((3*R-cis)*-3,6-dimethyl-1,4-dioxane-2,5-dione, >99.5%) were obtained from Purac Biochem BV (Gorinchem, The Netherlands) and used without further treatment. Stannous octoate (tin(II) bis(2-ethylhexanoate), $SnOct_2$, 95%) (Sigma Chemical Co., St. Louis, MO) was used as received. Toluene was purchased from Acros Chimica (Geel, Belgium), distilled from sodium/benzophenone, and stored on molecular sieves. Dichloromethane (Merck, Darmstadt, Germany) and 2-(2-methoxyethoxy)ethanol (Aldrich-Chemie, Steinheim, Germany) were used as received. Acetonitrile (HPLC−S, gradient grade) was purchased from Biosolve LTD (Valkenswaard, The Netherlands).

Mass Spectrometry. Fast atom bombardment mass spectra (FAB MS) (positive ion mode) were obtained with a JMS-SX/SX102A tandem mass spectrometer (BEBE) (JEOL, Tokyo, Japan) operating at a accelerating voltage of 10 kV. Glycerol was used as the matrix.

The electron spray (ESI) mass spectra were run with a VG-Platform Benchtop LC-MS (Micromass, Altrichem, U.K.). An electron spray interface was used to ionize the molecules (positive ion mode). The nebulizing gas had a flow of 25 L/h; the flow of the drying gas was 300 L/h. The voltage applied to the capillary was 4.2 kV, and the cone voltage was 35 V. The mass spectrometer was calibrated from 600 to 2200 Da with horse heart myoglobin (multiply charged).

Matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) mass spectra were acquired with a Micromass (former Fisons) Tofspec mass spectrometer in reflectron mode at Unilever Research Laboratory (Vlaardingen, The Netherlands). The spectrometer was equipped with a 100-cm flight tube and kept at a pressure of 1×10^{-7} mbar. The lactate oligomers were dispersed in water (0.2 mg/mL) and added to a layer of α-cyano-4-hydroxycinnamic acid, deposited by evaporation of an acetone solution. The weight ratio of lactate oligomer to matrix was 1:1000. Ions were formed by laser desorption at 337 nm (N_2 laser, pulse length 4 ns), accelerated by a 20 kV potential, and reflected by a 24 kV potential. At least 40 shots were averaged for a spectrum. A poly(ethylene glycol) mixture, consisting of PEG-600, −1450, and −4100 was used for calibration. Positive ions were detected.

NMR Spectroscopy. NMR spectra were recorded with a Gemini 300 MHz spectrometer (Varian Associates Inc. NMR Instruments, Palo Alto, CA). Approximately 30 mg of material was dissolved in 0.8 mL of deuteriochloroform (99.6+ % ^2H, Acros). For ^1H NMR, chloroform (at 7.26 ppm) was used as the reference line. A pulse length of 4.5 μs ($PW_{90} \approx 12$ μs) was used with a relaxation delay of 15 s. For the ^{13}C NMR spectra, the pulse length was set at 4.5 μs ($PW_{90} \approx 12$ μs), and the relaxation delay at 2 s. The central line in the chloroform triplet at 76.9 ppm was used as the reference line. The CH−COSY spectra were recorded by observing the ^{13}C signal; the relaxation delay was 2 s. A line broadening of 3 Hz was used.

High-Performance Liquid Chromatography. Monodisperse lactic acid oligomers were prepared by fractionation of polydisperse lactic acid oligomers by preparative HPLC (column: Econosphere C8, 10 μm, 250 × 22 mm; Alltech, IL) with an LC Module 1 plus system (Waters Associates Inc., Milford, MA). Oligomer (200 mg) was dissolved in 1.5 mL of acetonitrile, and the solution was injected onto the column. A gradient was run from 100% A (water/actonitrile 95:5) to 100% B (acetonitrile/water 95:5) in 50 min. The flow rate was 5.0 mL/min. The individual peaks, detected by UV ($\lambda = 195$ nm), were collected. After freeze-drying, the products were analyzed by ^1H NMR, mass spectrometry, and HPLC.

The polydisperse and monodisperse oligomers were analyzed by HPLC (analytical column, LiChrospher 100 RP-18 (5 μm, 125 × 4 mm i.d.) including an RP-18 guard column (4 × 4 mm) (Merck)). The compounds (10 mg) were dissolved in 50:50 acetonitrile:water (1 mL) and 100 μL of this solution was injected onto the column. A gradient was run from 100% A (water/actonitrile 95:5) to 100% B (acetonitrile/water 95:5) in 30 min; the flow rate was 1 mL/min. UV detection at a wavelength of 195 nm was applied. The chromatograms were analyzed with Millennium 2010 V. 2.15 software (Waters Associates Inc.).

(Modulated) Differential Scanning Calorimetry. The melting temperature (T_m), the melting enthalpy (ΔH_m), and glass transition temperature (T_g) of the D- and L-lactic acid oligomers and blends were determined by (modulated) differential scanning calorimetry ((M)DSC). (M)DSC measurements were carried out with a DSC 2920 differential scanning calorimeter (TA Instruments, New Castle, England). Temperature and heat flow calibration was performed with indium. Blends of enantiomeric lactic acid oligomers were prepared by dissolving equal weights of the D- and L-oligomer in dichloromethane. After evaporation of the organic solvent at ambient conditions, the remaining products, were analyzed by (M)DSC.

For the DSC measurements, the samples were cooled to −20 °C for 5 min and then heated to 100 °C, for the oligomers with DP = 1−9, or to 160 °C, for the oligomers with DP = 10−16, in a stream of helium. The heating rate was 5 °C/min. For the MDSC analysis, the samples were first cooled to −100 °C for 5 min and then heated to 100 °C, for the oligomers with DP = 1−9, or to 160 °C, for the oligomers with DP = 10−16, in a stream of helium. The heating rate was 2 °C/min, the amplitude 0.318 °C, and the period 60 s.

FTIR Spectroscopy. FTIR spectra were recorded with a Bio-Rad FTS-25 spectrometer (Bio-Rad Laboratories Inc., Cambridge, MA). Dry KBr powder was pressed into pellets under vacuum. A few drops of a solution of material in DCM was added to a pellet, and the organic solvent was allowed to evaporate. For each sample, 16 scans were recorded between 4000 and 450 cm^{-1}, with a resolution of 2 cm^{-1}.

Gel Permeation Chromatography. The molecular weights and molecular weight distributions of polydisperse MEE−lactic acid oligomers were determined by gel permeation chromatography (GPC) with a system consisting of a Model 510 HPLC pump, a Model 410 differential refractometer (Waters Associates Inc., Milford, MA), and three thermostated (35 °C) Shodex KF series columns (KF 800P 4.6 × 10 mm, precolumn; KF 80 m 8 × 300 mm, exclusion limit 2×10^7; KF 801 8 mm × 300 mm, exclusion limit 1.5×10^3; Showa Denko, Tokyo, Japan). Degassed chloroform was used as the mobile phase. The flow rate was 1.0 mL/min. The columns were calibrated with polystyrene standards of known molecular weight and narrow molecular weight distribution (TKS Standards, TOSOH Corp., Japan). The chromatograms were analyzed with Millennium 2010 V. 2.15 software (Waters Associates Inc.).

Synthesis of Polydisperse Methoxyethoxyethanol−Lactate (MEE−Lactate). Lactic acid oligomers with varying molecular weights were synthesized using 2-(2-methoxyethoxy)ethanol as initiator and stannous octoate as catalyst (Figure 1), in essentially the same way as previously reported for the synthesis of HEMA−lactic acid oligomers.[18] Oligomers

Table 1. Characteristics of the Polydisperse MEE−Lactic Acid Oligomers Determined by ^{1}H NMR, HPLC, and GPC

feed ratio lactide/MEE	DP[a] (^{1}H NMR)	DP[b] (HPLC)	M_n[c] (HPLC)	M_w[d] (HPLC)	M_w/M_n (HPLC)	M_n (GPC)	M_w (GPC)	M_w/M_n (GPC)
1	2.1	2.00	264	303	1.15	565	687	1.21
1.5	2.9	2.82	323	399	1.23	708	1227	1.73
2	3.9	4.04	411	510	1.24	837	1323	1.58
2.5	5.0	4.43	439	665	1.51	966	1406	1.45
3	6.0	5.49	516	743	1.44	1069	1663	1.56
4	7.9	8.32	719	888	1.23	*e*	*e*	*e*
5	9.8	*e*	*e*	*e*	*e*	1569	2794	1.78
10	19.0	*e*	*e*	*e*	*e*	2562	5005	1.95
15	29.5	*e*	*e*	*e*	*e*	4746	7754	1.63

[a] DP = degree of polymerization = the ratio of integrals of methine protons of lactide and the methyl protons of MEE, increased with one for the methine proton of the lactyl end group. [b] DP = degree of polymerization = $(M_n - M_{MEE}\ (=120))/M_{lactate\ unit}\ (=72)$. [c] $M_n = \sum w_i/\sum(w_i/M_i)$; w_i = weight fraction of oligomer with DP = i, M_i = molecular weight fraction of oligomers with DP = i, weight fractions were obtained from the HPLC chromatogram (Figure 4a). [d] $M_w = \sum w_i M_i$. [e] Not analyzed.

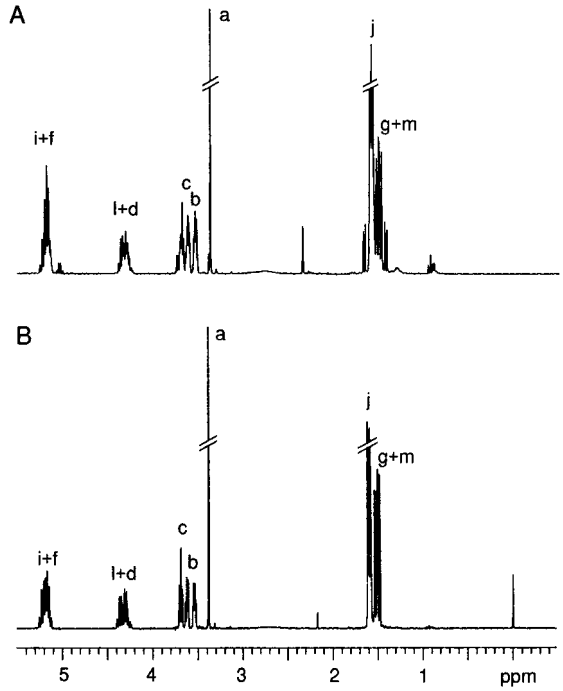

Figure 2. ^{1}H NMR spectrum of polydisperse MEE−lactate with $DP_{av} = 6$ (A) and monodisperse MEE−lactate with DP = 6 (B).

with different degrees of polymerization were obtained by varying the M/I (monomer/initiator) ratio. As an example, the synthesis of MEE−lactate with an average degree of polymerization (DP_{av}) of 10 is given. A mixture of L-lactide (or D-lactide) (10 g, 69.4 mmol) and 2-(2-methoxyethoxy)ethanol (1.67 g, 13.9 mmol) was stirred at 130 °C until the lactide was molten. Subsequently, stannous octoate (0.28 g, 0.69 mmol) in about 0.3 mL of toluene was added. The mixture was stirred for 4 h at 130 °C and allowed to cool to room temperature, to yield MEE-L-lactate (or MEE-D-lactate). The crude product was used for NMR analysis (Figure 2).

^{1}H NMR ($CDCl_3$): δ 7.15−7.24 (toluene), 5.16 (overlapping q, J = 7.2 Hz, H_{i+f}), 4.36 (q, J = 7.2 Hz, H_l), 4.32 (dt, J_{AB} = 12 Hz, J_{BX} = 4.8 Hz, H_{d1}), 4.28 (dt, J_{AB} = 12 Hz, J_{AX} = 4.8 Hz, H_{d2}), 3.69 (t, J = 4.8 Hz, H_c), 3.61 (m, H_{b1}), 3.53 (m, H_{b2}), 3.40 (s, H_a), 2.70 (bs, H_n + water), 2.34 (toluene), 1.61 (d, J = 7.2 Hz, H_j), 1.52 (d, J = 6.9 Hz, H_g), 1.49 (d, J = 6.9 Hz, H_m), 0.88−0.94 (stannous octoate).

^{13}C NMR ($CDCl_3$): δ 177 and 169.4 (C_e and C_k), 169.9 (C_h), 71.8 (C_b), 70.4 (C_b), 69.0 (C_f), 68.9 (C_i), 68.8 (C_c), 66.6 (C_l), 64.3 (C_d), 58.9 (C_a), 16.7 (C_m), 16.6 (C_g), 16.5 (C_j). Interpretation based on ATP (attached proton test) and CH−COSY.

FTIR (KBr in cm^{-1}): 3510 (w, ν_{O-H}), 2895 (w, ν_{O-Me}), 1757 (s, $\nu_{C=O}$), 1216 (s, ν_{CO-O}), 1184 (s, ν_{O-R}).

Results and Discussion

Synthesis and Characterization. To synthesize lactic acid oligomers from lactide, a compound with a primary hydroxyl group (2-(2-methoxyethoxy)ethanol (MEE)) was used as initiator and stannous octoate as catalyst (Figure 1). We selected MEE because it is nonvolatile and stable under the reaction conditions and has easily recognizable signals in ^{1}H NMR. Figure 2A shows the ^{1}H NMR spectrum of a MEE−D-lactate with an average degree of polymerization (DP_{av}) of 6. The degree of polymerization was determined from the ratio of integrals of methine protons (H_{i+f}) of lactide and the methyl protons (H_a) of MEE, increased with one for the methine proton (H_l) of the lactyl end group. The relative intensities of the methine quartets at 5.04 (lactide) and 5.16 ppm (lactic acid oligomer, H_{i+f} in Figure 2A) show that around 2−3% free lactide is present after polymerization, which corresponds with the equilibrium concentration at the selected temperature.[19] The molecular weight of the lactic acid oligomer can be tailored by varying the M/I ratio (Table 1), as previously demonstrated for the synthesis of HEMA−lactate oligomers.[18]

Figure 3a shows the ESI mass spectrum of the lactic acid oligomer with a DP_{av} of 6. A regular series of peaks is observed ranging from m/z 215 to about 1700. The insert shows that the spectrum is a repetition of a series of three peaks. The first peak (m/z 481) in the cluster corresponds with the protonated molecular ion, with five lactate units (72 Da per unit) plus 119 + 1 Da for the MEE and H of the hydroxyl end group. The next two peaks are the ammonium (m/z 498) and the sodium adduct (m/z 503), respectively. No peaks were observed for lactic acid oligomers without the MEE end group.

Interestingly, the repeating unit in the mass spectrum is 72 Da, corresponding with one lactate residue. However, since lactide was used in the polymerization, a repeating unit of 144 (two lactate units) was expected. The occurrence of the repeating unit of 72 was confirmed by MALDI TOF and FAB (results not shown). We therefore conclude that intermolecular transesterification occurs during polymerization. As a result, the polydisperse products consist of oligomers with both odd and even numbers of lactate units. Transesterification has been suggested to occur during the polymerization of PLA using stannous octoate[20] and aluminum-based compounds[21−23] as initiator, respectively.

Monodisperse Lactate Oligomers. Recently, the fractionation of poly(lactic acid) using packed column supercritical fluid chromatography has been described.[23] In our study monodisperse lactic acid oligomers were prepared by fractionation with HPLC. Figure 4A shows

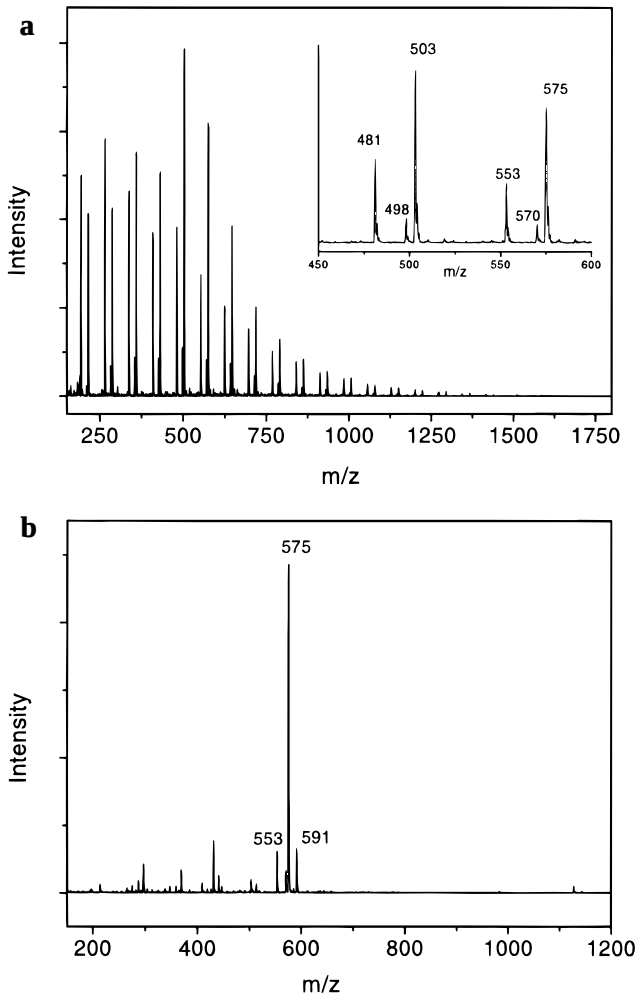

Figure 3. (a) Mass spectrum (ESI) of polydisperse lactic acid oligomer with $DP_{av} = 6$. (b) Mass spectrum (ESI) of monodisperse lactic acid oligomer with DP = 6.

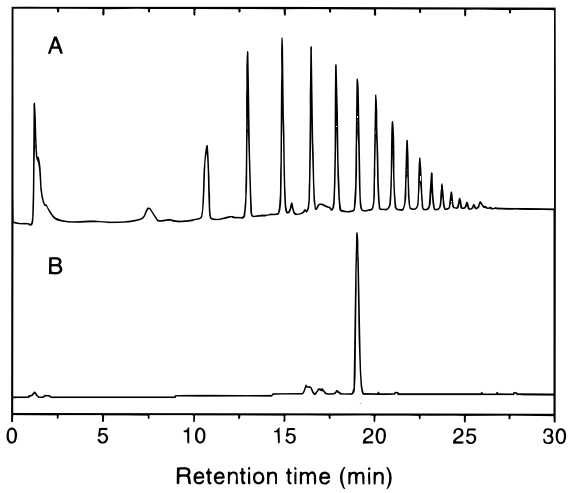

Figure 4. HPLC chromatogram of polydisperse lactic acid oligomer with $DP_{av} = 4$ (A) and monodisperse lactic acid oligomer with DP = 6 (B).

an HPLC chromatogram of a MEE−L-lactic acid oligomer with a DP_{av} of 4. The peak with retention time of 1 min is the void volume and the stannous octoate, whereas the signal at 8 min corresponds with unreacted lactide. At least 17 oligomers are observed with retention times ranging from 11 to 26 min. The individual peaks were collected and analyzed by ^{1}H NMR, MS, and

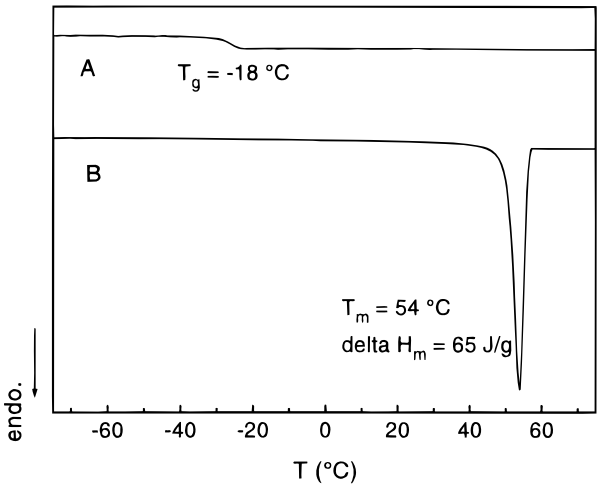

Figure 5. DSC thermograms of monodisperse MEE−L-lactic acid oligomer DP = 7 (A) and the corresponding blend of the L- and D-forms (B).

HPLC. Each peak in the HPLC chromatogram was shown to represent a lactic acid oligomer with a particular chain length, starting with a DP of 1 at a retention time of 11 min. Figure 2B shows the ^{1}H NMR spectrum, Figure 4B the HPLC chromatogram, and Figure 3b the ESI mass spectrum of the fraction with a degree of polymerization of 6. The most intense peak at *m*/*z* 575 (Figure 3b) corresponds with the mass of the sodium adduct of MEE−$(lactate)_6$. The peaks at *m*/*z* 553 and 591 correspond with the H^+ and K^+ adduct, respectively. Small peaks at *m*/*z* 503, 431, and 359 were also detected and correspond with oligomers with a DP of 5, 4, and 3, respectively. HPLC analysis also demonstrated that the MEE−$(lactate)_6$ was slightly contaminated with MEE−$(lactate)_{3-5}$. However, the overall purity was >90%. From the HPLC chromatograms of the polydisperse lactate oligomers the absolute molecular weights of the products were calculated and compared with the characteristics of the polydisperse lactic acid oligomers determined by ^{1}H NMR and GPC (Table 1). These data show a linear relationship between the M/I ratio of the feed and the DP_{av} of the obtained oligomer, as well as a good relationship between the HPLC and NMR data. The M_w and M_n determined by GPC deviates from those determined by HPLC, most likely because polystyrene standards were used for GPC calibration.

(M)DSC Analysis of the D- and L-Lactic Acid Oligomers and Their Blends. Figure 5 shows the thermograms of monodisperse MEE−$(L\text{-lactic acid})_7$ oligomer (A) and the blend of an equal weight of corresponding D- and L-product (B). It appears that the MEE−$(lactic\ acid)_7$ oligomer itself is completely amorphous ($T_g = -18$ °C), whereas in the blend a crystalline phase ($T_m = 54$ °C and $\Delta H_m = 65$ J/g) is detected. Since the enantiomeric oligomer is amorphous, the crystalline phase of the blend can be fully ascribed to stereocomplex formation between the D- and L-form. It should be noted that no T_g is detected in the blend. This indicates that the product is highly crystalline. The high crystallinity is also indicated by the sharp melting peak in the DSC thermogram.

Figure 6 shows the thermograms of monodisperse MEE−$(lactic\ acid)_{11}$ oligomer (A) and a blend of the corresponding D- and L-form (B). In both samples crystallinity is observed. However, both T_m and ΔH_m

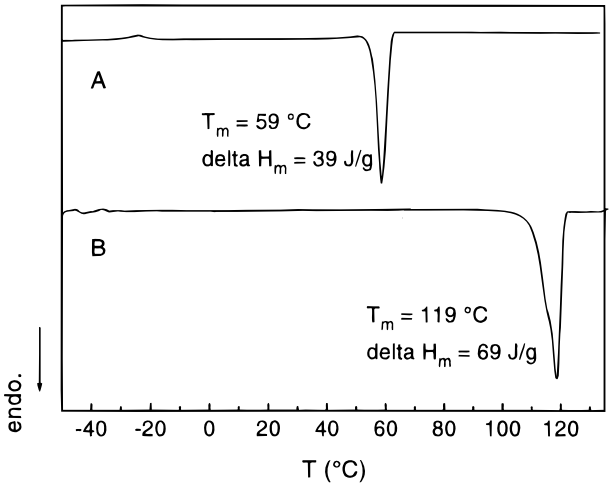

Figure 6. DSC thermograms of monodisperse MEE−L-lactic acid oligomer DP = 11 (A) and the corresponding blend of the L- and D-forms (B).

of the blend are higher than the T_m and ΔH_m for the enantiomeric oligomer. This again demonstrates that in the blend stereocomplexes are present. No T_g is detected in either sample, indicating that the products are highly crystalline.

Figure 7 shows the T_g and T_m for the enantiomeric oligomers (7a) and the blends (7b) as a function of the DP for the monodisperse lactic acid oligomers. From Figure 7a it can be concluded that enantiomeric oligomers can crystallize at DP ≥ 11. The melting temperature slightly increases with the degree of polymerization. On the other hand the products with a DP < 11 were completely amorphous. As expected, the T_g increases with DP. The melting enthalpy amounts to 40 ± 5 J/g. For 100% crystalline material, a ΔH_m of 93 J/g was reported.[24] Figure 7b shows the T_g and T_m for the blends of monodisperse oligomers. It appears that stereocomplexes are formed from DP ≥ 7. The T_m increases with increasing DP and could be fitted according to the following equation; $T_m = 234-1338/DP$ ($r^2 = 0.996$). For $DP_{infinite}$ a T_m of 239 °C is predicted, in excellent agreement with the T_m reported for a blend of equal amounts of high molecular weight PLLA and PDLA.[5] The ΔH_m is independent of the DP and amounted to 65 ± 5 J/g. For 100% crystalline material, values for ΔH_m of 84 and 142 J/g were reported.[6,12]

From Figure 7a,b it can be concluded that the minimum chain length for stereocomplex formation is 7, whereas individual enantiomeric lactic acid oligomers crystallize at a DP ≥ 11. This difference can be explained by the crystal structures of homopolymers and stereocomplexes. It has been reported that the crystals in the homopolymers of PLLA (or PDLA) have a 10_3 helix structure, whereas the stereocomplex forms a more compact 3_1 helix.[25,26] Obviously, one of the lactic acid end groups (most likely the group to which the MEE group is coupled) is not able to participate in the crystallite formation; as a result 11 units are required to form a 10_3 helix. To form the 3_1 helix seven lactic acid residues are sufficient. This indicates that for the more compact stereocomplex only two helix turns are required to form a crystal.

Conclusions

Polydisperse lactic acid oligomers were prepared in a controlled way, using MEE as initiator and stannous octoate as catalyst at 130 °C, and fully characterized. Mass spectrometry showed that transesterification occurs during the polymerization of lactide. Monodisperse oligomers were prepared by fractionation of polydisperse lactic acid oligomers by preparative HPLC. DSC analysis of monodisperse products showed that seven lactate groups are required for the formation of stereocomplexes from the blends of the oligomers, whereas for the individual enantiomeric lactic acid oligomers eleven lactate groups are needed for crystallization.

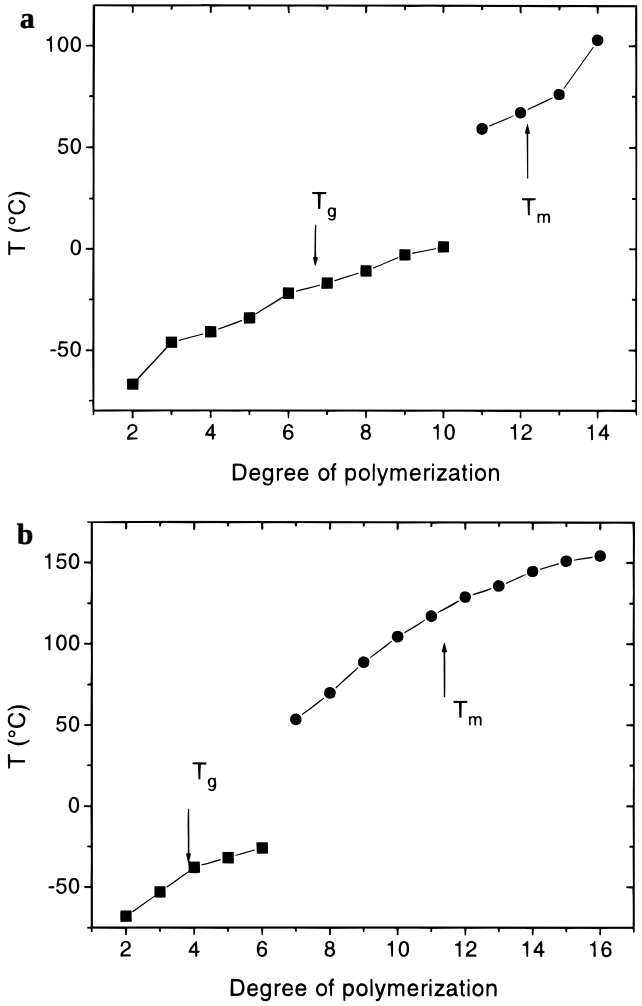

Figure 7. Melting temperature (T_m) and glass transition temperature (T_g) of the monodisperse lactic acid oligomers (a) and the blends of monodisperse lactic acid oligomers (L- and D-forms) (b) as a function of the degree of polymerization.

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