

Stereocomplex formation in ABA triblock copolymers of poly(lactide) (A) and poly(ethylene glycol) (B)

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(Received: February 16, 1995; revised manuscript of March 22, 1995)

SUMMARY:

Two series of triblock copolymers of poly(ethylene glycol) (PEG, number-average molecular weight $\bar{M}_n = 6000$) and poly(L-lactide) (PLLA) or poly(D-lactide) (PDLA) were prepared by ring-opening polymerization of lactide initiated by PEG end groups using stannous octoate as a catalyst, either in refluxing toluene or in the melt at 175 °C. The weight percentage of PLA in the polymers varied between 15 and 75 wt.-%. Blends of polymers containing blocks of opposite chirality were prepared by co-precipitation from homogeneous solutions. The melting temperatures of the crystalline PEG and PLA phases strongly depended on the composition of the polymers. The melting temperature of the PLA phase in the blends was approximately 40 °C higher than that of the single block copolymers. Stereocomplex formation between blocks of enantiomeric poly(lactides) in PEG/PLA block copolymers was established for the first time. Water uptake of polymeric films prepared by solution casting was solely determined by the PEG content of the film.

Introduction

Block copolymers of poly(lactide) and poly(ethylene glycol) have attracted much attention because they offer a unique combination of biodegradability and hydrophilicity. Poly(lactide)s and random or block copolyesters based on poly(lactide)s have found applications as drug delivery systems and medical sutures^{1,2}. Toxicity of these polymers is intrinsically low because metabolic pathways exist for the main degradation product of these polymers, lactic acid. Poly(ethylene glycol) is a water soluble polymer, which is accepted in most countries as a food or drug additive.

Recently it was shown that biodegradable hydrogels based on photopolymerized poly[(ethylene glycol)-*co*-lactide] diacrylate macromers have great potential as wound covering material³. Block copolymers based on PEG/PLA could provide a biodegradable alternative to PEG/poly(ethylene terephthalate) copolymers as a material for the use in surgery⁴.

Co-crystallization of enantiomeric poly(lactide)s in a *racemic* lattice, also called stereocomplex formation, leads to materials with higher melting points and lower critical gelation concentrations in solution compared to the optically pure polymers^{5,6,7}. These phenomena have been described extensively⁸. Stereocomplex formation in block copolymers of poly(L-lactide)-*block*-poly(D-lactide) was shown for the first time by our group and later by others^{9,10}.

The concepts of PEG/PLLA block copolymers and stereocomplex formation in PLA have now been combined by the preparation of binary blends of PEG/PLLA and PEG/PDLA block copolymers. A series of triblock copolymers was prepared by ring-

opening polymerization of lactide initiated by PEG end groups in refluxing toluene using stannous octoate as a catalyst. A similar series of polymers was also prepared in the melt at 175 °C. The polymers were characterized using NMR (^1H , ^{13}C) spectroscopy and gel-permeation chromatography. Thermal properties were studied by differential scanning calorimetry (DSC). The relative water uptake was determined gravimetrically by immersing films of 300 μm thickness in water.

Experimental part

L-(–)-lactide and D-(+)-lactide (Purac Biochem b.v., the Netherlands) were used as received. Poly(ethylene glycol) 6000 (PEG6000, $\overline{M}_w/\overline{M}_n = 1.05$) (Merck-Schuchardt, Darmstadt Germany) was dried under reduced pressure before use. Stannous^{II} octoate (stannous^{II} 2-ethylhexanoate) (Sigma Chem. Co., St. Louis, USA) was used as received. Toluene was distilled from sodium benzophenoneketyl prior to use. All glassware was dried before use and reactions were carried out in an argon atmosphere. A 0.05 M stock solution of $\text{Sn}(\text{Oct})_2$ in toluene was prepared in a Braun 150 GI drybox.

Solution polymerizations

In a typical experiment a total amount of 10 g of starting material (PEG6000 and L- or D-lactide) was dissolved in 50 mL toluene at 70 °C and an appropriate amount of $\text{Sn}(\text{Oct})_2$ solution (1 wt.-% of lactide amount) was added. After refluxing for 24 h, the reaction mixture was cooled, the solvent removed under reduced pressure and the polymer was dried overnight at 40 °C *in vacuo*. Before further work-up a sample was taken for NMR and gel-permeation chromatography (GPC) analysis. The polymer was dissolved in 40 mL of chloroform and precipitated in a five fold excess of cold diethyl ether and dried again.

Melt polymerizations

In a typical experiment a total amount of 10 g of starting material (PEG6000 and L- or D-lactide) was mixed with an appropriate amount of $\text{Sn}(\text{Oct})_2$ solution (10 mol.-% relative to PEG—OH end groups). The mixture was heated to 175 °C and after 4 h the reaction mixture was cooled and dissolved in 40 mL of chloroform. A sample was taken for NMR and GPC analysis. The polymer was precipitated in a five fold excess of cold, diethyl ether and dried overnight at 40 °C *in vacuo*.

Blend- and film preparation

A chloroform solution containing equal amounts of PLLA/PEG and PDLA/PEG polymers (10 wt.-%) was stirred for 72 h. The mixture was precipitated in a ten fold excess of well stirred hexane and the polymer thus obtained dried overnight *in vacuo*. Films were prepared by solution casting of 10 wt.-% chloroform solutions of the polymer onto silanized dishes. The relative water uptake, defined as the difference between dry and wet weight divided by the dry weight, was determined gravimetrically by immersing films of 300 μm thickness in water.

Characterization

The number-average degree of polymerization of the poly(lactide) blocks was determined from ^1H NMR spectra by end group analysis and by comparison to the PEG backbone

signal. ^1H NMR spectra were recorded on a Bruker AC 250 operating at 250 MHz (^1H) or 62.5 MHz (^{13}C) in chloroform- d_1 . Crude polymers and starting PEG were reacted with trifluoroacetic anhydride to be able to distinguish between reacted and unreacted PEG—OH end groups. To quantitate the number of —OH groups in the starting PEG a spectrum in DMSO- d_6 was recorded. Gel-permeation chromatography (GPC) was used to determine molecular weights and molecular weight distributions ($\overline{M}_w/\overline{M}_n$). GPC measurements were carried out with tetrahydrofuran (THF) as the eluent (2.0 mL/min) using a Waters 510 pump, a HP 1050 autosampler, four Waters μ Styragel columns (10^5 , 10^4 , 10^3 , 5×10^2) in series, a Waters 410 differential refractometer, and a Viscotek Viscometer Detector H502. The columns were calibrated with polystyrene standards using the universal calibration technique.

Thermal analysis of polymers was carried out with a Perkin-Elmer DSC7 differential scanning calorimeter calibrated with pure indium. The polymers were heated from -20°C to 200°C (homopolymers) or 250°C (blends) at a heating rate of $20^\circ\text{C}/\text{min}$, annealed for 1 min and cooled to -20°C at a cooling rate of $5^\circ\text{C}/\text{min}$ and a second heating curve was recorded.

Results and discussion

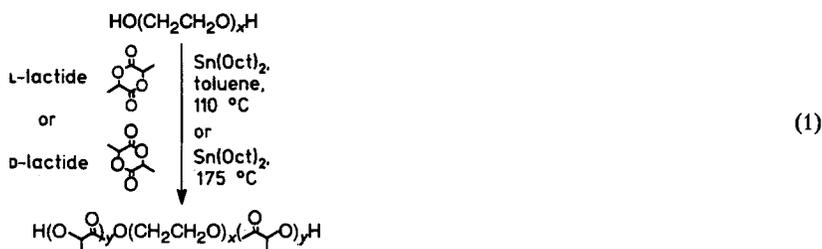
Synthesis and characterization

Various ways of preparing ABA triblock copolymers of PEG (B) and PLLA (A) have been established. In one study, polymers were prepared by polycondensating lactic acid in the presence of —OH terminated PEG, but no information on the molecular weight or molecular weight distribution was presented¹¹. Rather well defined polymers are prepared by reaction of $\text{Al}(\text{O}^i\text{Pr})_3$ or Na with —OH terminated PEG, followed by polymerization of L-lactide^{12,13}. In the latter case some racemization of L-lactide was observed. The polymers can even be prepared in the absence of any catalyst, but this requires long reaction times and extremely pure starting materials¹⁴. In this case the presence of diblock copolymers was not investigated.

However, the simplest way of preparing well defined triblock copolymers of PEG and PLLA is by using $\text{Sn}(\text{Oct})_2$ as a catalyst^{15,16}. $\text{Sn}(\text{Oct})_2$ is well known as a catalyst in homopolymerization of lactide and is widely accepted as a food additive or contaminant in PLA for pharmaceutical applications. Therefore, we used this method for the preparation of the ABA block copolymers. If polymers were prepared at 130°C in bulk, yields were low, presumably due to fractionation during the purification steps. The GPC trace of such a reaction mixture shows a bimodal distribution, with one of the peaks at an elution volume just above that of the starting PEG. After derivatization with trifluoroacetic anhydride, no peak assignable to a trifluoroacetic ester derivative of a PEG—OH end group can be discerned in the ^1H NMR spectrum. It seems that despite the bimodal molecular weight distribution all PEG—OH end groups have initiated lactide polymerization. Probably, phase separation occurs during the synthesis in a PLA/lactide rich and a PEG rich phase, enhancing further chain growth of the longer PLA chains. Previously it was shown that the use of $\text{Sn}(\text{Oct})_2$ in xylene allowed the synthesis of poly(D,L-lactide) at temperatures below the melting temperature of the monomer D,L-lactide¹⁷. Therefore, two simple laboratory procedures

which suppress phase separation were investigated. Reactions were carried out in refluxing toluene and in bulk at 175 °C (Eq. (1)) and results are shown in Tab. 1.

The NMR analysis of the ABA triblock copolymers of PLLA and PEG was described by other authors and will not be discussed in detail here^{12,15}. The general features of the NMR spectra do not differ from literature data. No unreacted PEG—OH end groups remained after reaction, as shown by ¹H NMR spectroscopy after preparation of the trifluoroacetic ester derivative of the polymers. Thus, all PEG—OH end groups have initiated polymerization and no diblock copolymer is present in the reaction mixture. The signal for the carbonyl oxygen atom in the PLA blocks is a sharp singlet, indicating absence of racemization.



Tab. 1. Results of the polymerization reactions carried out in bulk (175 °C) or in refluxing toluene

Code ^{a)}	PEG con- tent in feed in wt.-%	Conv. ^{b)} in %	Isolated yield in %	PEG con- tent ^{c)} in wt.-%	$10^{-3} \cdot \bar{M}_{n,\text{NMR}}$ g · mol ⁻¹	$10^{-3} \cdot \bar{M}_{n,\text{GPC}}$ ^{d)} g · mol ⁻¹	\bar{M}_w/\bar{M}_n
LAB1	75	99	82	86	6.9	8.2	1.08
LAB2	50	89	84	56	10.1	9.5	1.21
LAB3	25	98	82	27	23.5	16.1	1.55
DAB1	75	86	83	85	6.7	8.6	1.09
DAB2	50	96	82	47	10.3	9.7	1.22
DAB3	25	96	82	28	17.7	13.2	1.50
LAS1	75	87	92	82	6.9	8.8	1.09
LAS2	50	99	91	55	10.8	12.2	1.20
LAS3	25	>99	85	28	20.5	23.1	1.41
DAS1	75	89	90	83	6.8	8.8	1.08
DAS2	50	99	90	55	10.8	11.6	1.17
DAS3	25	>99	89	28	20.4	18.4	1.41

a) LA or DA in a code name refers to L- or D-lactide monomer, B or S refers to polymers prepared in bulk or in solution.

b) Conversion of lactide as determined by ¹H NMR spectroscopy.

c) PEG content in the polymer after purification as determined by ¹H NMR spectroscopy.

d) Calibrated with polystyrene standards using the universal calibration technique.

GPC traces for unpurified and purified polymers are similar and show symmetric, unimolecular weight distributions. The polydispersities increase with increasing molecular weight and range between 1.09 and 1.55. No low molecular weight fractions are detected, confirming efficient initiation of the lactide polymerization by the PEG—OH end groups. Number average molecular weights determined by GPC and ^1H NMR spectroscopy are in good agreement.

Polymers prepared by bulk polymerization at 175 °C appeared pale yellow in color as reported previously¹⁶⁾, while polymers prepared in solution were white. Conversion of lactide was generally high, as were yields, especially for the polymers prepared in solution. The PEG content in the purified polymers did not differ largely from the expected content from the monomer/PEG feed ratio. The agreement was best for the polymers containing longer poly(lactide) blocks. For polymers containing short poly(lactide) blocks the agreement was better for polymers prepared in solution than for those prepared in bulk. In all, well defined triblock copolymers were prepared by both methods. Solution polymerization has the advantage of yielding polymers, at a low polymerization temperature with a composition close to the composition expected from the feed contents, without discoloration.

Thermal properties

Melting points and melting enthalpies of polymers and blends determined by differential scanning calorimetry are presented in Tab. 2. Second heating curves of polymers with a crystalline poly(lactide) phase are shown in Fig. 1. Glass transition temperatures are not detected because the T_g of the PLA phase coincides with the melting peak of the PEG phase and the T_g of the PEG phase is below the temperature range studied. Attempts to determine glass transition temperatures by dynamic mechanical analysis were hampered by the brittleness of most of the test specimens

Tab. 2. Thermal properties^{a)} (melting temperatures and melting enthalpies) as determined by DSC of the polymers LAS1–3, DAS1–3, and the blends LDAS1–3

	PEG content in wt.-%	$T_{m,PEG}$ °C	$\Delta H_{m,PEG}$ J/g	$T_{m,PLA}$ °C	ΔH_{PLA} J/g
PEG6000	100	64	217		
LAS1	82	54	150		
LAS2	55	44	104	146	34
LAS3	28	42	27	164	47
DAS1	83	57	158		
DAS2	55	44	107	142	28
DAS3	28	40	16	159	43
LDAS1	83	53	136		
LDAS2	55	41	95	182	17
LDAS3	28	44	46	204	63

^{a)} Second heating curves, heating rate 20 °C/min.

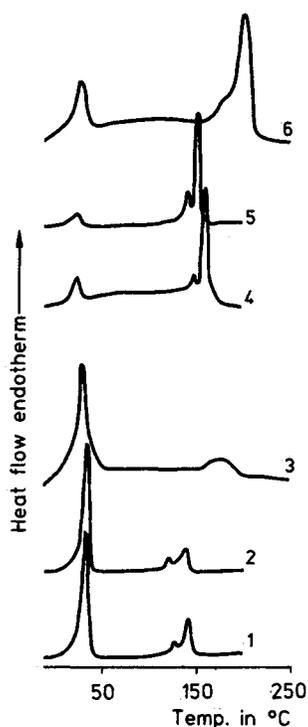


Fig. 1. Second heating curves of the polymers LAS2 (1), DAS2 (2), LDAS2 (3), LAS3 (4), DAS3 (5) and LDAS3 (6) (precipitated material)

prepared by compression moulding. As can be expected for a block copolymer, two melting peaks, each for one polymer phase, are detected. The data for each pair of L- and D-polymers are very similar, and small differences may reflect slight differences in composition or are within the accuracy of the measurement. Crystallization of the PEG phase occurs in all polymers studied after slow cooling of the block copolymers from the melt, and melting temperature and melting enthalpy decrease with decreasing PEG content. The T_m and ΔH_m of the polymers having the highest PEG contents (LAS1, DAS1) are still considerably lower than those of the PEG homopolymer, indicating that the presence of a second phase influences the crystallization behaviour to a large extent. Crystallization of the PLA phase does not occur in polymers containing less than 20 wt.-% PLA, which in this case corresponds to about 14 lactyl units. In poly(ϵ -caprolactone)-*block*-poly(L-lactide) polymers of comparable molecular weight the minimum poly(L-lactide) block length for crystallization was found to be around 40 lactyl units¹⁸. Polymers containing 60 lactyl units (LAS2 and DAS2) showed crystallinity of the PLA phase. The polymers which contain a crystalline PLA phase, show increasing T_m and ΔH_m with increasing PLA content.

The DSC traces of the blends differ largely from those of the separate block copolymers. The melting point of the PLA phase is increased by approximately 40 °C, independent of the composition of the polymers. The sharp increase in melting

temperature has been shown to be related to the crystallization of the PLA blocks in a *racemic* lattice, or stereocomplex formation⁵). Interestingly, the stereocomplex formation has no pronounced effect on the melting enthalpy in line with observations on blends of PLLA and PDLA⁶). The higher melting point of the crystals in the PLA phase can be attributed to a lower entropy of fusion. Also, the phase behaviour of the PEG phase seems to be unaffected by the stereocomplex formation.

The thermal properties of films prepared by solution casting were determined as well. The results are shown in Tab. 3. The curves of precipitated and solution casted material were very similar when first heating curves are considered. In polymers containing only 28 wt.-% PEG, no melting endotherm of a PEG phase was detected in the first heating curves of precipitated material or films. In these polymers crystallinity of the PEG phase is completely inhibited by fast crystallization of a continuous PLA phase. Again, high melting *racemic* crystallites were observed. In all materials studied the melting point of these crystallites was lowered when recording a second heating curve, in contrast to the PLA phase in the unmixed polymers. No satisfactory explanation for this phenomenon can be given presently.

Tab. 3. Thermal properties of films of 300 μm thickness compared with precipitated material

	PEG content in wt.-%	Precipitated materials				Films	
		$T_{m,PLA}$ °C second ^{a)}	$T_{m,PLA}$ °C first ^{a)}	ΔH_{PLA} J/g second	ΔH_{PLA} J/g first	$T_{m,PLA}$ °C first	ΔH_{PLA} J/g
LAS2	55	146	150	34	36	147	36
DAS2	55	142	145	28	38	143	24
LDAS2	55	182	199	17	47	205	61
LAS3	28	164	164	47	44	164	50
DAS3	28	159	160	43	44	160	50
LDAS3	28	204	219	63	85	220	35

^{a)} First and second refer to first and second heating curves.

Water uptake measurements

Films were prepared by solution casting of 10 wt.-% chloroform solutions of the polymer onto silanized dishes. The relative water uptake, defined as the difference between dry and wet weight divided by the dry weight, was determined gravimetrically after immersing films of 300 μm thickness in water. Equilibrium readings were obtained within ten minutes. No further significant water uptake was found after 24 h. The water uptake of the polymers LAS1 and DAS1 was not determined, because these polymers, having a PEG content of 82 wt.-%, were found to be soluble in water at low concentrations. For the blend LDAS2 only a few data points could be collected, because the samples had a tendency to fracture after swelling. Water uptake was solely

determined by the PEG content of the polymer and equilibrium readings of 35 and 125 wt.-% water uptake, with a maximum error margin of 10 percent of the value, were obtained for polymers containing 28 and 55 wt.-% PEG blocks, respectively.

Conclusions

Well defined ABA triblock copolymers of PEG (B) and PLLA (A) copolymers were prepared by polymerization of L-lactide in refluxing toluene using Sn(Oct)₂ as a catalyst and the —OH end groups of PEG6000 as macroinitiators. Solution polymerization has the advantage of yielding polymers with a composition close to the composition expected from the feed contents, without discoloration at a low polymerization temperature and unimodal molecular weight distributions. Stereocomplex formation of poly(lactides) occurs readily in blends of these ABA block copolymers, but does not alter the water uptake properties of these polymers.

These investigations were supported by the *Netherlands Foundation for Chemical Research* with financial aid from the *Netherlands' Technology Foundation*.

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