Well defined block copolymers of ε-caprolactone and L-lactide using $Y_5(\mu\text{-}O)(O^iPr)_{13}$[a] as an initiator

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SUMMARY:

Diblock copolymers composed of poly(ε-caprolactone) and poly(L-lactide) were synthesized via sequential living ring-opening polymerization of ε-caprolactone and L-lactide in dichloromethane initiated by $Y_5(\mu\text{-}O)(O^iPr)_{13}$ (yttrium isopropoxide). A series of diblock copolymers was synthesized with ε-caprolactone blocks of constant length (DP = 70) and lactide blocks of varying length (DP = 5–80), with polydispersities of 1,18–1,27. Molecular weights were close to theoretical values. ^{13}C NMR spectroscopy shows the absence of transesterification reactions and racemization. The thermal properties of the block copolymers were studied using differential scanning calorimetry. The block copolymers show a certain degree of phase mixing depending on the length of the poly(L-lactide) blocks. Crystallization of L-lactide sequences did not occur when the block length consisted of less than 40 L-lactic acid residues.

Introduction

Polymers based on L-lactide and ε-caprolactone are interesting materials for the use in biomedical applications such as drug delivery devices[1]. In this respect the phase behaviour of polymers consisting of a highly crystalline block and a block with a rubbery character is of interest, because the permeability of the individual components for drugs can differ widely[2]. This offers the opportunity to generate a desired release profile. The synthesis of block copolymers of poly(L-lactide) and poly(ε-caprolactone) could afford materials with properties to be used in matrices or reservoir devices, like hollow fibres, of drug delivery systems[3]. Furthermore, such block copolymers can be used as compatibilizers in blends of homopolymers[4].

Several efforts for the synthesis of these block copolymers have been reported. The use of stannous octoate as a catalyst in the melt polymerization of a mixture of ε-caprolactone and L-lactide leads to polymers with blocky structures[5]. If aluminium triisopropoxide is used for the block copolymerization in solution, careful control of the reaction conditions is necessary to prevent homopolymerization of lactide[6]. Homopolymerization of L-lactide occurs because not every isopropoxide group initiates the polymerization of ε-caprolactone. Recently the synthesis of poly(ester)s via ring-opening polymerization of lactones using yttrium and lanthanum alkoxide catalysts was reported[7,8].

Polymerizations carried out with these catalysts were shown to be living and very fast even at room temperature. Low polydispersities indicated the absence of transesterification reactions. Up to now only one block copolymerization of ε-caprolactone and L-

[a] Yttrium isopropoxide.

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lactide using $Y(OCH_2CH_2NMe_2)_3$ as a catalyst has been mentioned[7b]. The structure of this catalyst is unknown, and the stoichiometry not unambiguously determined. The number of active polymerization sites for the polymerization of ε-caprolactone was not determined. For the polymerization of L-lactide only two of three alkoxide groups were found to be active. This was attributed to an intrinsic lack of reactivity or catalyst deactivation by contaminations.

In this paper we describe the synthesis of poly(ε-caprolactone)-*block*-poly(L-lactide) via sequential polymerization of ε-caprolactone and L-lactide in dichloromethane using yttrium isopropoxide as an initiator. The block copolymers were characterized by NMR spectroscopy and gel-permeation chromatography, and their phase behaviour was investigated as a function of the poly(L-lactide) block length.

Experimental part

Reagents

L(−)-lactide (Purac Biochem b. v., the Netherlands) was used as received. ε-Caprolactone (Merck-Schuchardt, Darmstadt, Germany) was dried over calciumhydride and distilled prior to use. Yttrium isopropoxide (Aldrich, Brussels, Belgium) was washed with toluene and filtered to remove insolubles and dried for 48 h at 35 °C *in vacuo* and stored in a dry-box under nitrogen. Toluene was distilled from sodium benzophenoneketyl, and dichloromethane was distilled from calciumhydride prior to use. All manipulations were carried out in an inert nitrogen or argon atmosphere.

Block copolymerizations of ε-caprolactone and L-lactide

Polymerizations were carried out in a Braun 150 GI dry-box. To a solution of 4,28 g (37,5 mmol) ε-caprolactone in 40 mL of dichloromethane 5,0 mL of a 0,05 M solution of yttrium isopropoxide in toluene was added, corresponding to a mole ratio of monomer to initiator ([M]/[I]) of 150. Polymerization commenced at once and after 4 min a sample was taken for characterization of the prepolymer followed by the addition of an appropriate amount of a 0,1 M solution of L-lactide in dichloromethane. The conversion of L-lactide in time was followed by ^1H NMR spectroscopy. To limit the reaction time the polymerization was quenched at 75% conversion by the addition of an equal volume of a 0,1 M HCl solution. The organic phase was collected, solvents were removed under reduced pressure and the product was dried (70 °C) *in vacuo*. The white solid obtained was dissolved in chloroform and precipitated in a 10 fold excess of cold methanol and dried again.

Characterization

The number-average degree of polymerization of ε-caprolactone and L-lactide was determined by ^1H NMR end group analysis. ^1H NMR spectra were recorded on a Bruker AC 250 operating at 250 MHz (^1H) or 62,5 MHz (^{13}C). Gel-permeation chromatography (GPC) was used to determine molecular weights and molecular weight distributions ($\bar{M}_w/\bar{M}_n$). A Waters 6000A GPC apparatus equipped with three Waters μStyragel (10^3, 10^4, 10^5 Å pore diameter) columns was used, combined with a H502 viscometer detector (Viscotek Corp.) for determination of absolute values of molecular weights. Polymers were dissolved in tetrahydrofuran (1,0 wt.-%) and elution was performed at 25 °C at a flow rate of 2,0 mL/min using tetrahydrofuran (THF) as eluent.

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 220 °C at a heating rate of 20 °C/min, annealed for 1 min and slowly cooled to 20 °C, whereafter a second heating curve was recorded.

Results and discussion

For the successful synthesis of block copolymers of ε-caprolactone and L-lactide there are two important requirements[9]. The ε-caprolactone block has to be synthesized first for reasons of mutual reactivity. If the L-lactide block is synthesized first either transesterification reactions occur or no further polymerization takes place. This reactivity pattern was established for coordination type catalysts containing various metals such as Al[6,10], Y[7] and Sn[11]. The same seems to hold for a typical anionic type of catalyst, LiO^{t}Bu[12]. Furthermore, the reaction time for the complete conversion of ε-caprolactone must be known. Incomplete conversion of ε-caprolactone may result in a more or less random incorporation of monomers in the chain or failure to reach expected degrees of polymerization. On the other hand prolonged polymerization times could result in a broadening of the molecular weight distribution by transesterification[7,13]. Secondly, the number of active catalyst sites should not be different for both monomers. In the case of Al(O^{i}Pr)$_3$ this resulted in the formation of a poly(L-lactide) homopolymer[6].

The feasibility of the synthesis of a block copolymer using yttrium isopropoxide was established with regard to the above mentioned requirements. The reaction time for ε-caprolactone to reach >95% conversion was determined by following the reaction by means of ^{1}H NMR spectroscopy. The time required appeared approximately 4,5 min (Fig. 1). After quenching with diluted hydrochloric acid to deactivate the catalyst, the identity of the end groups was determined. The chemical shifts of the end groups (δ = 1,18 (C<u>H</u>$_3$)$_2$CHO—, 4,94 (CH$_3$)$_2$C<u>H</u>O—, 3,57 —C<u>H</u>$_2$OH) are in good aggreement with those reported by Kricheldorf et al. for poly(ε-caprolactone)s synthesized using Al(O^{i}Pr)$_3$ as an initiator[14]. A representative spectrum is shown in Fig. 2. Signals for

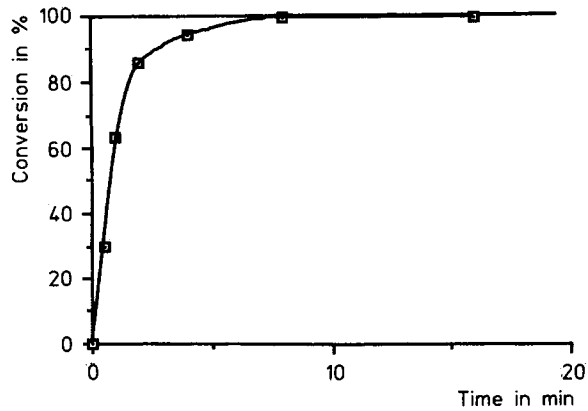

Fig. 1. Conversion as a function of time for the yttrium isopropoxide (**1**) initiated polymerization of ε-caprolactone in CH_2Cl_2 at 22 °C

the isopropoxycarbonyl and —CH$_2$OH end groups are clearly discerned. Only poly(ε-caprolactone)s with isopropoxycarbonyl end groups were obtained, which reveals that the polymerization of ε-caprolactone proceeds only through acyl-oxygen cleavage. The number of active catalyst sites was determined by studying the degree of polymerization as a function of the monomer-to-initiator ratio. The stoichiometry of

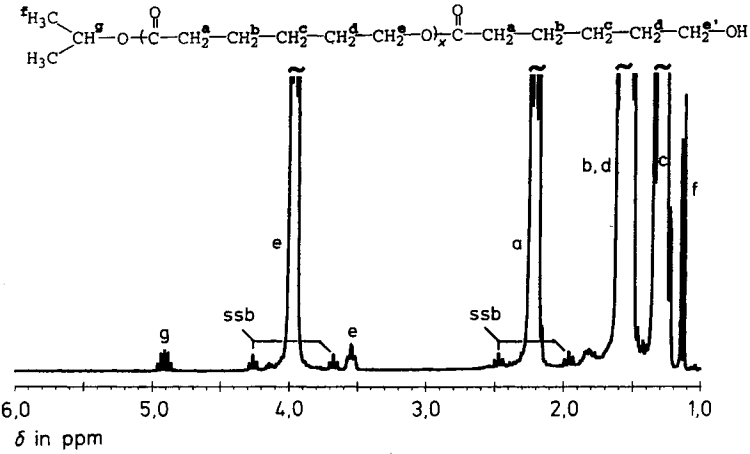

Fig. 2. ^{1}H NMR spectrum ($CDCl_3$) of the poly(ε-caprolactone) prepolymer prepared using **1**

the cluster compound yttrium isopropoxide was recently determined to be $Y_5(\mu\text{-}O)(O^iPr)_{13}$ (**1**)[15]. Hence, the average number of possible polymerization sites/Y (13/5) is 2,6. A linear relation between the degree of polymerization and the molar monomer-to-initiator ratio was found (Fig. 3). The line through the origin has a slope of 0,41, close to the theoretical value of 0,38 (1/2,6). It was concluded that all isopropoxide groups are active as initiators in the polymerization of ε-caprolactone and the polymerization proceeds in a living manner.

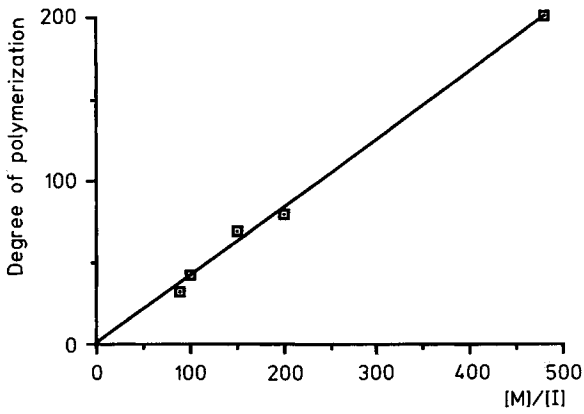

Fig. 3. Degree of polymerization as determined by ^{1}H NMR end group analysis as a function of the monomer-to-initiator ratio for the polymerization of ε-caprolactone using **1**

L-lactide homopolymerization using **1** as an initiator was also studied. The conversion of L-lactide in time is slow compared to ε-caprolactone (Fig. 4). The end groups are a isopropoxycarbonyl group and a —$CH(CH_3)OH$ alcohol end group (δ = 4,30 —C<u>H</u>$(CH_3)OH$, 2,8 —$CH(CH_3)O$<u>H</u>). Number-average molecular weights

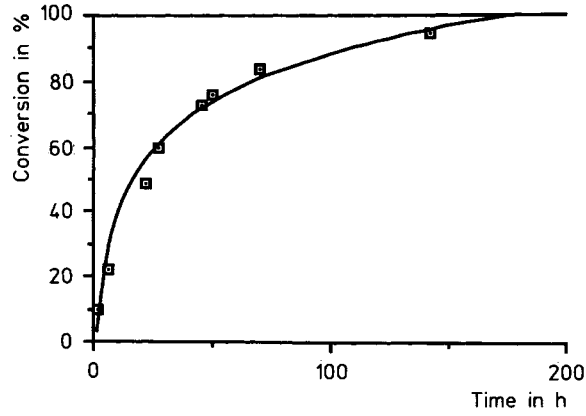

Fig. 4. Conversion as a function of time for the **1**-initiated polymerization of L-lactide in CH_2Cl_2 at 22 °C

($\overline{M}_n$) are close to calculated values if every isopropoxide ligand is active as initiator. In general, the polymerization characteristics of the polymerization of ε-caprolactone and L-lactide using **1** as an initiator are similar.

Block copolymers were synthesized by adding an appropriate amount of a L-lactide solution in dichloromethane to a living poly(ε-caprolactone) solution. The polymers were characterized with ^1H and ^{13}C NMR spectroscopy and gel-permeation chromatography. Results are presented in Tab. 1.

The ^1H NMR spectrum shows that the signal belonging to the $—CH_2OH$ ε-caprolactone end group (δ = 3,57) has disappeared and that signals attributable to a $—CH(CH)_3OH$ (δ = 4,30, 2,8) lactide end group have appeared. All chains formed in the first step are therefore active as initiators in the second step of the polymerization reaction. To ensure the identity of the —OH end groups of the lower molecular weight polymers (CLL1, CLL2, CLL3) the hydroxyl end groups were reacted with trifluoroacetic anhydride. The formation of the trifluoro acetic ester end group causes a downfield shift for the methine proton of the acylated lactate end group from δ = 4,30 to 5,15 ppm (Fig. 5). Also, the broad doublet assigned to the terminal alcohol proton (δ = 2,8) disappears and a signal for the carboxylic acid proton of trifluoro acetic acid appears (δ = 11,7) (not shown). The intensity of the end group signals in the higher molecular weight polymers CLL4 and CLL5 is too low for a direct, accurate determination of $\overline{M}_n$. The derivatization reaction with trifluoro acetic anhydride was not carried out for these polymers.

The ^{13}C NMR spectra of polymers CLL1 to CLL5 show no signals attributable to transesterification and confirm the diblock character of these polymers. A representative spectrum of the characteristic carbonyl region is shown in Fig. 6. For the lower molecular weight polymers the carbonyl signals belonging to the transition sequence (LLC and CCL at respectively δ = 170,1 and 173,4) as well as those of the end groups (δ = 172,9 $^iPrOCO—$, 175,0 $—COCH(Me)OH$) can be discerned[16]. The carbonyl signal of the L-lactide block is a sharp singlet indicating that racemization is absent.

GPC traces are monomodal, symmetric and show that the polymers have a polydispersity of around 1,2. No low molecular weight fractions are detected. This

Tab. 1. Results of block copolymerization of ε-caprolactone (CL) and L-lactide (LLA) in dichloromethane using yttrium isopropoxide as a catalyst

No.	PCL block [CL]/[I]	Conv. in %	PLLA block [LLA]/[I]	Reaction time in d	Conv. in %	Block copolymer $\bar{M}_{n,\,calc}$ [a] · 10^{-3} g/mol	$\bar{M}_{n,\,NMR}$ [b] · 10^{-3} g/mol	$\bar{M}_{n,\,GPC}$ [c] · 10^{-3} g/mol	$\bar{M}_w/\bar{M}_n$
CLL1	150	100	15	0,8	85	7,3	9,8	11,4	1,20
CLL2	150	100	30	2,0	77	7,9	11,3	12,8	1,18
CLL3	150	100	75	6,8	84	10,1	12,6	13,2	1,25
CLL4	150	100	150	7,5	73	12,7	15,7	15,2	1,27
CLL5	150	100	300	18,0	76	19,2	18,8	18,4	1,26

a) $\bar{M}_{n\,calc}$ was calculated as follows: $\bar{M}_{n,\,calc} = (cv_{CL} \cdot Fw_{CL} \cdot [CL] + cv_{LLA} \cdot Fw_{L\text{-}LA} \cdot [LLA])/(2{,}6 \cdot [I])$ where cv is the conversion and Fw is the molecular weight of the corresponding repeating unit.

b) Determined by ^1H NMR end group analysis.

c) Determined by GPC analysis.

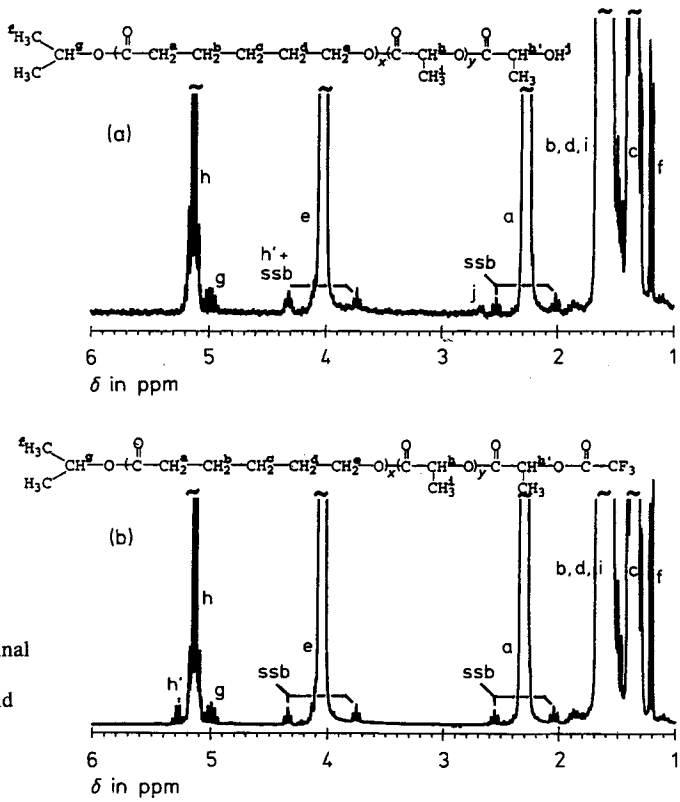

Fig. 5. ^{1}H NMR spectrum ($CDCl_3$) of polymer CLL2; (a) final block copolymer; (b) trifluoroacetic acid ester derivative

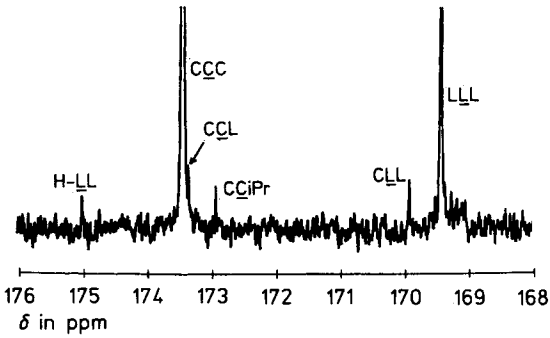

Fig. 6. Carbonyl region of the ^{13}C NMR spectrum of polymer CLL2 showing transition and end group carbonyl signals

confirms the conclusion that all poly(ε-caprolactone) chains are effective in initiating the L-lactide polymerization. Moreover, when number-average molecular weights are compared the GPC and NMR results are in good agreement and correspond to calculated values. In all, the use of **1** offers the possibility to synthesize very well defined block copolymers of poly(ε-caprolactone) and poly(L-lactide) in a convenient way.

The thermal properties of the synthesized block copolymers were determined by DSC. Melting temperatures and melting enthalpies are presented in Tab. 2. Second heating curves of the polymers studied are presented in Fig. 7. Glass transition temperatures are not detected because the T_g of poly(L-lactide) coincides with the

Tab. 2. Composition, melting temperatures and melting enthalpies of the block copolymers CLL1 to CLL5[a)]

No.	PLLA content in wt.-%	$T_{m,PCL}$ °C	$T_{m,PLLA}$ °C	ΔH_{PCL} J/g	ΔH_{PLLA} J/g	Crystallinity$_{PLLA}$[b)] in %
CLL1	11	61	—	81	—	—
CLL2	22	59	—	96	—	—
CLL3	45	58	130	85	37	26
CLL4	59	54	144	102	45	32
CLL5	72	54	156	69	53	37

a) Properties bearing a PLLA subscript relate to the poly(L-lactide) phase, a PCL subscript relates to the poly(ε-caprolactone) phase.
b) A value of 143 J/g was assumed for ΔH_∞ [17].

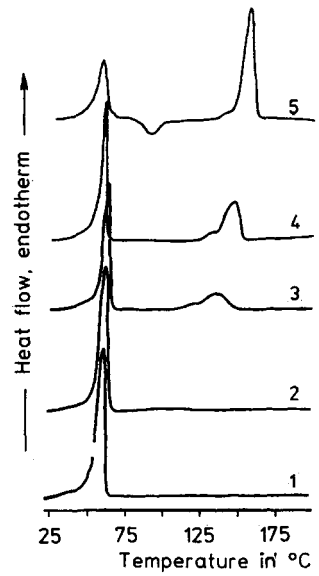

Fig. 7. DSC traces of polymers CLL1 to CLL5 numbered 1 to 5 (second heating curves)

melting peak of poly(ε-caprolactone) and the T_g of poly(ε-caprolactone) is below the temperature range studied. Both melting enthalpy and melting temperature increased with increasing L-lactide content, but the T_m (156 °C) of the poly(L-lactide) block in the polymer having the highest $\bar{M}_n$ (CLL5) is still considerably lower than that of the corresponding homopolymer (170 °C). This could indicate imperfect crystallization or

formation of smaller crystallites due to incorporation of poly(ε-caprolactone) segments or amorphous polylactide regions in the lattice. A more extensive phase characterization using X-ray scattering techniques will be presented in a following paper.

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Note added in proof
It was shown recently by A. Duda and S. Penczek [18] that the problems with block copolymerizations of ε-caprolactone and L-lactide using aluminium triisopropoxide are due to the different initiation rates of trimeric and tetrameric aggregates, which are in slow equilibrium at temperatures commonly used in the solution polymerization of these monomers.