Macromolecules **2005,** *38,* 5017−5024

Bismuth(III) *n*-Hexanoate and Tin(II) 2-Ethylhexanoate Initiated Copolymerizations of ϵ-Caprolactone and L-Lactide

Hans R. Kricheldorf,* Kirstin Bornhorst, and Heiko Hachmann-Thiessen

Institut für Technische und Makromolekulare Chemie, Bundesstr. 45, D-20146 Hamburg, Germany

Received October 14, 2004; Revised Manuscript Received April 14, 2005

ABSTRACT: Using bismuth(III) hexanoate ($BiHex_3$) as initiator and tetraethylene glycol as co-initiator, ϵ-caprolactone (ϵCL) and L-lactide (LLA) were copolymerized in bulk. Whereas monomer/initiator and monomer/co-initiator ratios were kept constant, the temperature was varied from 100 to 140 °C. Amorphous copolyesters having a perfectly random sequence were found under all circumstances when $BiHex_3$ was used as initiator. In contrast, parallel experiments with tin(II) 2-ethylhexanoate ($SnOct_2$) as initiator yielded crystalline copolyesters with a blocky sequence. From kinetic measurements of homopolymerizations and from MALDI−TOF spectra of homopolyesters, it was learned that $BiHex_3$ is less efficient as initiator and transesterification catalyst than $SnOct_2$. Therefore, the formation of cycles by "backbiting degradation" is reduced, and the formation of random copolymers involves a special intramolecular transesterification mechanism. These results and the extremely low toxicity of Bi salts render $BiHex_3$ a particular useful initiator for biomedical applications of polylactones.

Introduction

Poly(ϵ-caprolactone), PϵCL, polylactides, PLAs, polyglycolide, PGL, and their copolymers are the most intensively studied and most widely used biodegradable polyesters.[1−5] The properties of the homopolyesters can be varied over a broad range via copolyesters, which may also include additional comonomers.

Two groups of copolyesters proved to be particularly useful and interesting, namely copolyesters having a nearly random sequence and copolyesters consisting of longer blocks. The random copolyesters are amorphous and transparent. Their glass-transition temperatures (T_g's) may vary between the extremes of −60/−65 °C characteristic for poly(ϵ-caprolactone), PϵCL, and 50−55 °C typical for polylactides. Amorphous copolyesters may be useful for the production of transparent films, as matrices for drug-delivery systems, or as soft segments in block copolymers. In the case of block copolymers the melting temperatures (T_m's) may vary between the values of 60−62 °C for PϵCL, 170−180 °C typical for poly(L-lactide)s, PLAs, and 220−225 °C for polyglycolide. Block copolyesters may be useful as medical sutures, thermoplastic elastomers, or engineering plastics.

Tin alkoxides and tin carboxylates are most widely used as initiators for the polymerization of lactones and cyclic diesters and thus for the production of biodegradable homo- and copolyesters. However, most tin compounds including the known initiators have the disadvantage of a significant cytotoxicity. Their application as antifouling agents in food and paints is based on their broad toxicity for most microorganisms. In recent publications,[6−9] we have demonstrated the usefulness of bismuth(III) salts as initiators for homopolymerizations of ϵCL and L-lactide, LLA, or DL-lactide, DLLA. Bismuth salts have a long tradition as drugs, and from toxicity studies it is known[10] that they possess a particularly low toxicity against kidney tubuli. Therefore, it may be said that bismuth has the lowest toxicity of all heavy metals. Therefore, it is worth to study the usefulness of bismuth salts and complexes as initiators or catalysts for syntheses of biodegradable polyesters in more detail. In this context the present work had the purpose to study copolymerizations of ϵCL with LLA initiated by bismuth(III) *n*-hexanoate ($BiHex_3$) or tin(II) 2-ethylhexanoate ($SnOct_2$) to allow for a comparison of both initiators. Bismuth(III) *n*-hexanoate was used instead of the previously used commercial acetate because the *n*-hexanoate is soluble in all lactones and in a broad variety of inert organic solvents quite analogous to $SnOct_2$. Finally, it should be mentioned that syntheses and NMR spectra sequence analyses of copolyesters derived from ϵCL and LLA were reported by several authors.[11−18]

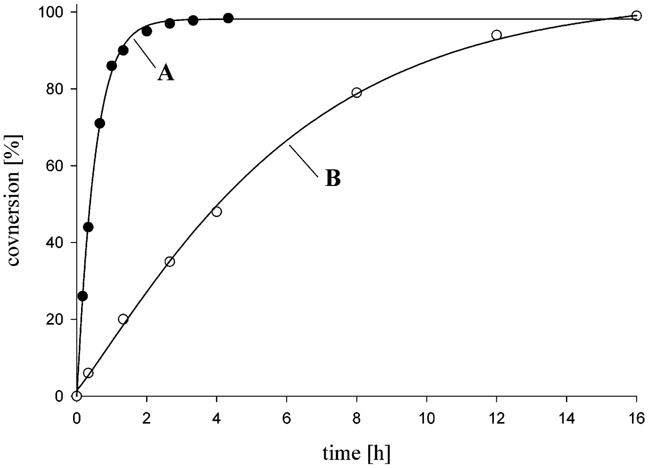


Figure 1. Time−conversion curves of $SnOct_2$ (A) and $BiHex_3$-initiated (B) polymerizations of ϵCL in bulk at 120 °C (M/I = 1000/1 and M/benzyl alcohol = 50/1).

Experimental Section

Materials. ϵ-Caprolactone (ϵCL) was purchased from Aldrich Co. (Milwaukee, WI) and distilled over freshly powdered calcium hydride. L-Lactide (LLA, S-grade) was kindly supplied by Boehringer KG (Ingelheim, Germany). It was recrystallized twice from ethyl acetate and stored in a desiccator over P_4O_{10}. Tetra(ethylene glycol), TEG, was azeotropically dried with toluene and distilled in vacuo over a short path apparatus. $BiHex_3$ was prepared from Bi(III) acetate (Aldrich Co.) and hexanoic acid as described in the literature.[19] $SnOct_2$ was purchased from Aldrich Co. and purified as described previously.[20] Benzyl alcohol (Aldrich Co.) was fractionated in vacuo prior to use. Chlorobenzene was distilled over P_4O_{10} prior to the preparation of initiator solutions.

10.1021/ma047873o CCC: $30.25

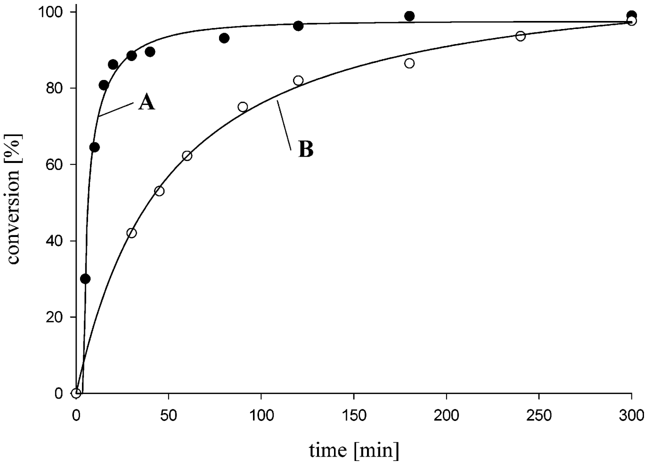


Figure 2. Time−conversion curves of $SnOct_2$ (A) and $BiHex_3$-initiated (B) polymerizations of LLA in bulk at 120°C (M/I = 1000/1 and M/benzyl alcohol = 50/1).

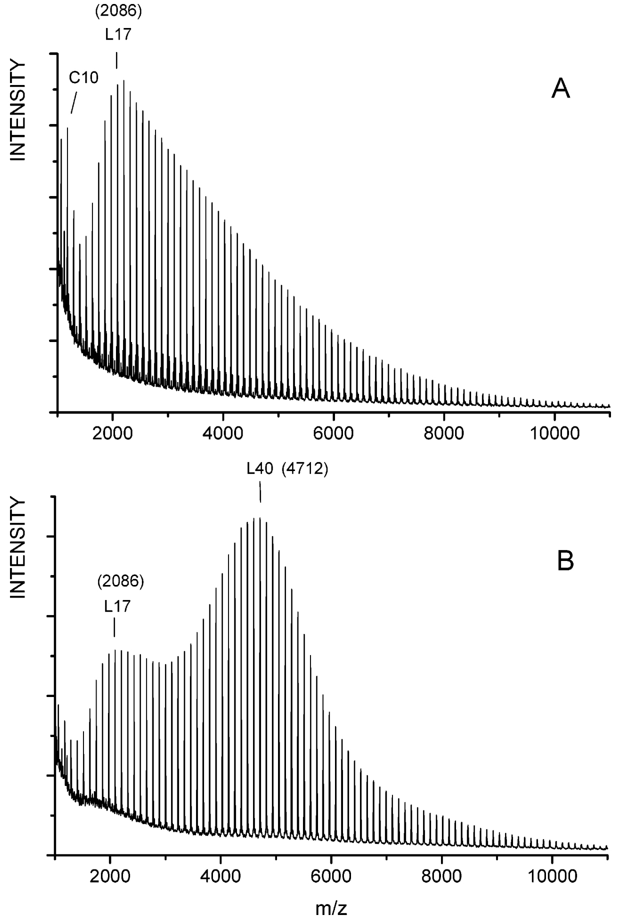


Figure 3. MALDI−TOF mass spectra of PϵCL co-initiated with benzyl alcohol at 120 °C: (A) initiated with $BiHex_3$ (no. 2, Table 1); (B) initiated with $SnOct_2$ (no. 1, Table 1).

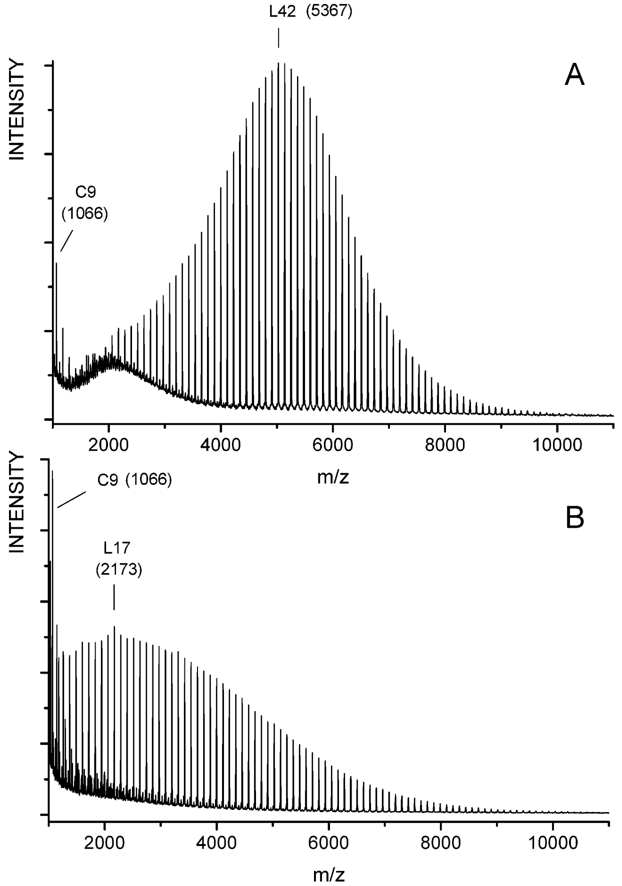


Figure 4. MALDI−TOF mass spectra of PϵCL co-initiated with TEG at 120 °C: (A) initiated with $BiHex_3$ (M/I = 500/1); (B) initiated with $SnOct_2$ (M/I = 1000/1).

Table 1. Homopolymerization of ϵCL and LLA in Bulk at 120 °C (M/I = 1000/1, M/Benzyl Alcohol = 50/1)

polym no.	monomer	initiator	time (h)	yield (%)	$\overline{DP}^a$	η_{inh}^b (dL/g)	$[\alpha]_D^c$ (deg)
1a	ϵCL	$Sn(Oct)_2$	3	87	54	0.24	
1b	ϵCL	$Sn(Oct)_2$	3	88	55	0.25	
2a	ϵCL	$BiHex_3$	16	85	52	0.25	
2b	ϵCL	$BiHex_3$	16	85	52	0.25	
3	LLA	$Sn(Oct)_2$	3	92	52	0.18	158
4	LLA	$Sn(Oct)_2$	5	90	51	0.18	156
5a	LLA	$BiHex_3$	5	92	52	0.17	156
5b	LLA	$BiHex_3$	5	90	51	0.18	156

[a] From ^1H NMR spectroscopy via the signals of $-CH(CH_3)-OH$ or $-CH_2OH$ end groups. [b] Measured at 20 °C with *c* = 2 g/L in CH_2Cl_2. [c] Measured at 25 °C with 10 g/L in CH_2Cl_2.

Homopolymerizations of ϵCL. *Time−Conversion Curves (Figure 1).* ϵ-Caprolactone (50 mmol) and benzyl alcohol (1 mmol) were weighed into a 50 mL Erlenmeyer flask having silanized glass walls. The reaction vessel was closed with a glass stopper and steel spring and immersed into an oil bath preheated to 120 °C. After homogenization, 0.1 mL of a 0.5 M $BiHex_3$ solution in chlorobenzene was injected, and the closed reaction vessel was thermostated at 120 °C. A small sample of the reaction mixture was removed from time to time under an atmosphere of dry nitrogen and analyzed by ^1H NMR spectroscopy. An analogous experiment was performed with $SnOct_2$ (0.5 M in chlorobenzene) as initiator. For initiation with $SnOct_2$ a rate constant of 1.9 h^{-1} was found and for $BiHex_3$ 0.16 h^{-1}. The times required for 50% conversion were 0.35 and 4.05 h, respectively.

Two homopolymerizations of ϵCL were performed in such a way that TEG was used as co-initiator (M/TEG = 50:1) and $SnOct_2$ or $BiHex_3$ as initiators at a M/I ratio of 500:1 in analogy to the copolymerizations described below. The MALDI−TOF MS presented in Figure 4 were taken from the virgin polymerization products.

Preparative Polymerizations (Table 1). ϵ-Caprolactone (50 mmol) was polymerized at 120 °C in bulk with benzyl alcohol (1 mmol) and $BiHex_3$ or $SnOct_2$ (0.1 mL of a 0.5 M solution in chlorobenzene). After 3 or 16 h (see Tables 2 and 3) the reaction mixture was cooled, dissolved in dichloromethane (30 mL), and precipitated into cold diethyl ether (400 mL).

Homopolymerizations of LLA. *Time−Conversion Curves (Figure 2).* L-Lactide (40 mmol) and benzyl alcohol (0.8 mmol) were weighed into a 50 mL Erlenmeyer flask having silanized glass walls. The closed reaction vessel was immersed into an

Table 2. Copolymerization of ϵCL and LLA in Bulk (Feed Ratio 2:1) Co-Initiated with TEG (M/C = 200/1) and Initiated with $SnOct_2$ or $BiHex_3$ (M/I = 500/1)

						SEC original data[b]		corrected data[c]		
copolym no.	initiator	temp (°C)	time (h)	yield (%)	η_{inh}[a] (dL/g)	M_n (Da)	M_w (Da)	M_n (Da)	M_w (Da)	PD
1	$Sn(Oct)_2$	100	24	77	0.57	45 000	64 000	27 000	38 500	1.41
2	$BiHex_3$	100	48	57	0.48	37 000	52 000	22 000	31 000	1.40
3	$Sn(Oct)_2$	120	16	51	0.52	43 000	57 000	26 000	34 000	1.35
4	$BiHex_3$	120	16	41	0.45	36 000	50 000	21 500	30 000	1.35
5	$Sn(Oct)_2$	140	2	53	0.51	44 000	57 000	36 500	34 000	1.30
6	$Sn(Oct)_2$	140	6	53	0.48	37 000	52 000	22 000	31 000	1.44
7	$BiHex_3$	140	6	31	0.33	33 000	47 000	20 000	28 000	1.40

[a] Measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [b] Direct calibration with polystyrene standards. [c] Original SEC data corrected with the factor 0.60. The M_n calculated for 100% conversion of both monomers amounts to 25 000 Da.

Table 3. Copolymerization of ϵCL and LLA in Bulk (Feed Ratio 2:1) Co-Initiated with TEG (M/C = 200/1) and Initiated with $SnOct_2$ or $BiHex_3$ (M/I = 500/1)

copolym no.	initiator	ϵCL/lactyl[a]	$\bar{L}_{CL}$[b] (^1H NMR)	$\bar{L}_{CL}$[c] (^{13}C NMR)	$\bar{L}_{LA}$[d] (^{13}C NMR)	altern[e] dyads (%)	T_g[f] (°C)	T_m[f] (°C)	morphology
1	$Sn(Oct)_2$	1.1	5.4	5.2	5.1	18	−29	+49	crystalline
2	$BiHex_3$	1.0	2.0	1.9	2.0	51	−30		amorphous
3	$Sn(Oct)_2$	1.1	3.5	3.4	3.3	29	−29	+41	crystalline
4	$BiHex_3$	1.1	2.0	1.9	1.9	51	−31		amorphous
5	$Sn(Oct)_2$	1.1	3.3	3.2	3.1	31	−31	+41	crystalline
6	$Sn(Oct)_2$	1.1	3.2	3.0	3.0	31	−31	+40	crystalline
7	$BiHex_3$	1.1	2.0	1.8	1.9	51	−31		amorphous

[a] Molar composition determined by ^1H NMR spectroscopy for O−CHMe−CO (lactyl) units. [b] Average block lengths of ϵCL calculated from the dyad splitting of ^1H NMR CH_2CO signal. [c] Average block lengths of ϵCL units calculated from the dyad splitting of ^{13}C NMR CO signals. [d] Average block lengths of lactyl units calculated from the triad splitting of the ^{13}C NMR CO signals. [e] Determined by ^1H NMR spectroscopy of ϵCL signals c and c′ in Figure 5. [f] From DSC measurements with a heating rate of 10°C/min.

Table 4. Copolymerizations of ϵCL and LLA in Bulk (Feed Ratio 1:1) Co-Initiated with TEG (M/C = 200/1) and Initiated with $SnOct_2$ or $BiHex_3$ (M/I = 500/1)

copolym no.	initiator	temp (°C)	time (h)	yield (%)	η_{inh}[a] (dL/g)	ϵCL/lactyl[b]	$\bar{L}_{CL}$[c] (^1H NMR)	$\bar{L}_{CL}$[d] (^{13}C NMR)	$\bar{L}_{LA}$[e] (^{13}C NMR)	altern[f] dyads (%)	morphology
1	$Sn(Oct)_2$	100	21	81	0.52	0.50	5.2	5.4	12.2	19	crystalline
2	$BiHex_3$	100	48	68	0.44	0.50	1.5	1.5	2.3	65	amorphous
3	$Sn(Oct)_2$	120	14	71	0.50	0.52	2.8	2.9	5.2	36	crystalline
4	$BiHex_3$	120	24	48	0.42	0.51	1.5	1.5	2.7	68	amorphous
5	$Sn(Oct)_2$	140	2	70	0.51	0.49	2.6	2.6	5.3	38	crystalline
6	$BiHex_3$	140	6	36	0.42	0.49	1.4	1.5	2.4	68	amorphous

[a] Measured at 20 °C with $c = 2$ g/L in CH_2Cl_2. [b] Molar composition determined by ^1H NMR spectroscopy for O−CHMe−CO (lactyl) units. [c] Average block lengths of ϵCL calculated from the ^1H NMR CH_2CO signal. [d] Average block lengths of ϵCL calculated from ^{13}C NMR signals. [e] Average block lengths calculated from ^{13}C NMR signals of lactyl units. [f] Calculated from ^1H NMR ($-CH_2CO-$) signals of ϵCL units (c and c′ in Figure 5).

oil bath preheated to 120 °C and stirred with a magnetic bar until a homogeneous solution was obtained (1−2 min). 0.08 mL of a $SnOct_2$ or $BiHex_3$ solution in chlorobenzene (0.5 M) was then injected by means of a syringe. From time to time a small sample of the reaction product was removed under an atmosphere of dry nitrogen, and a 400 MHz ^1H NMR spectrum was recorded immediately (in $CDCl_3$/benzene-d_6/TMS). For initiation with $SnOct_2$ a rate constant of 6.1 h^{-1} was found and for $BiHex_3$, 1.0 h^{-1}. The times required for 50% conversion were 0.11 and 0.66 h, respectively.

Preparative Polymerizations (Table 1). L-Lactide (40 mmol) was polymerized at 120 °C in bulk with benzyl alcohol (0.8 mmol) and $BiHex_3$ (0.08 mL of a 0.5 M solution in chlorobenzene). The reaction vessel was closed and thermostated for a period of 5 h. After cooling, the product was dissolved in dichloromethane (30 mL) and precipitated into cold diethyl ether (400 mL). The isolated polylactide was dried at 20 °C in vacuo. Analogous polymerizations (3 and 5 h) were conducted with $SnOct_2$.

Copolymerizations: Variation of the Temperature. *ϵCL/LLA 2:1 (Tables 2 and 3).* ϵ-Caprolactone (30 mmol), L-lactide (15 mmol), and tetra(ethylene glycol) (0.225 mmol) were weighed into a silanized 50 mL Erlenmeyer flask.

$BiHex_3$ or $SnOct_2$ (0.09 mmol as 0.5 M solution in chlorobenzene) was injected, and the closed reaction vessel was thermostated at 100 °C. Small samples were removed from time to time for ^1H NMR spectroscopic measurements to determine the time needed for 98% conversion of ϵCL. In parallel experiments the reaction vessel was kept closed until 98% conversion was achieved. Finally, the cold product was dissolved in dichloromethane and precipitated into cold diethyl ether. Analogous copolymerizations were conducted at 120 and 140 °C.

ϵCL/LLA 1:1 (Table 4). ϵCL (20 mmol), LLA (20 mmol), and TEG (0.2 mmol) were polymerized with $BiHex_3$ or $SnOct_2$ (0.08 mmol) at 100, 120, or 140 °C, as described above.

Copolymerizations: Variation of Time (Tables **5 and 6).** ϵCL and LLA (molar ratio 2:1) were copolymerized at 140 °C with TEG as co-initiator and $SnOct_2$ or $BiHex_3$ as initiators as described above. From time to time samples were removed from the reaction mixture, and ^{13}C NMR spectra were recorded immediately.

Transesterification Studies (Table 7**).** LLA (15 mmol) was polymerized in bulk at 120 °C/24 h with TEG (0.075 mmol) and $BiHex_3$ (0.03 mmol). In another Erlenmeyer flask ϵCL (30 mmol) was polymerized at 120 °C/24 h with TEG (0.15 mmol) and $BiHex_3$ (0.06 mmol). Both virgin polymers were dissolved together in dry 1-chloronaphthalene (30 mL) and heated to 140 °C (in a closed Erlenmeyer flask). Small samples were removed for ^1H NMR measurements after 1, 2, 3, 4, and 7 days.

An analogous experiment was conducted with $SnOct_2$ as initiator.

Table 5. Copolymerization of ϵCL and LLA (2:1) at 140 °C in Bulk Co-Initiated with TEG (M/Coi = 200/1) and Initiated by $SnOct_2$ (M/I = 500/1)

copolym no.	time (min)	conversion LLA (%)	conversion ϵCL (%)	ϵCL/lactyl[a]	altern dyads ϵCL (%)	$\bar{L}_{CL}$	altern dyads LA (%)	$\bar{L}_{LA}$
1	10	98	54	0.55	41	2.42	14	7.08
2	20	99	82	0.83	32	3.17	18	5.51
3	40	>99	96	0.96	30	3.40	24	4.12
4	60	>99	97	0.97	29	3.46	26	3.78
5	120	>99	>99	1.00	29	3.49	28	3.58
6	360	>99	>99	1.00	31	3.35	30	3.40

[a] Molar composition determined by ^1H NMR spectroscopy for lactyl units (O−CHMe−CO).

Table 6. Copolymerization of ϵCL and LLA (2:1) at 140 °C in Bulk Co-Initiated with TEG (M/Coi = 200/1) and Initiated with $BiHex_3$ (M/I = 500/1)

copolym no.	time (min)	conversion LLA (%)	conversion ϵCL (%)	ϵCL/lactyl[a]	altern dyads ϵCL (%)	$\bar{L}_{CL}$	altern dyads LA (%)	$\bar{L}_{LA}$
1	20	65	19	0.29	91	1.10	16	6.08
2	40	90	35	0.39	84	1.19	21	4.76
3	60	98	44	0.45	76	1.32	25	3.98
4	90	>99	66	0.66	63	1.59	28	3.56
5	120	>99	78	0.79	57	1.76	32	3.14
6	240	>99	94	0.94	51	1.95	42	2.37
7	360	>99	98	0.98	51	1.97	47	2.10

[a] Molar composition as determined by ^1H NMR spectroscopy for lactyl units (O−CHMe−CO).

Table 7. Equilibration of PolyϵCl[a] and Poly(LLA)[a] in 1-Chloronaphthalene at 140 °C

	average block lengths of ϵCL units[c]				
catalyst[b]	1 day	2 days	3 days	4 days	7 days
$SnOct_2$	155	101	77	65	47
$BiHex_3$	156	103	80	66	45

[a] Prepared at 120 °C/24 h with TEG as co-initiator (M/Coi = 200/1). [b] Molar ratio of repeat units/catalyst = 500/1. [c] Determined by ^1H NMR spectroscopy.

Measurements. The inherent viscosities were measured in CH_2Cl_2 with an automated Ubbelohde viscometer thermostated at 20 °C. The 400 MHz ^1H NMR spectra and the 100.4 MHz ^{13}C NMR spectra were recorded on a Bruker Avance 400 FT NMR spectrometer in 5 mm o.d. samples tubes. $CDCl_3$ containing TMS served as solvent and shift reference. A mixture of $CDCl_3$/benzene-d_6 (volume ratio 7:3) was used for the elaboration of the time−conversion curves of LLA.

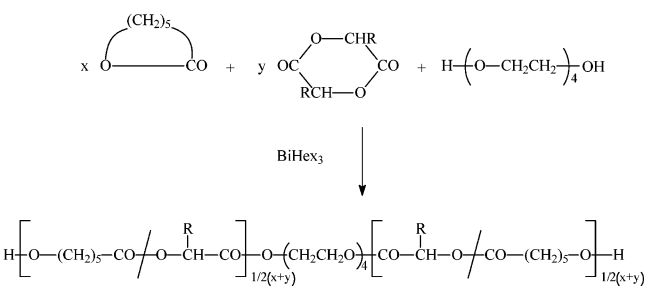
The MALDI−TOF mass spectra were measured with a Bruker Biflex III mass spectrometer equipped with a nitrogen laser (λ = 337 nm). All mass spectra were measured in the reflection mode at an acceleration voltage of 20 kV. The irradiation targets were prepared from $CHCl_3$ solutions using dithranol as matrix and K-trifluoroacetate as dopant. The SEC measurements were performed with an apparatus of Polymer Laboratories containing a RI detector "Shodex RI 101". A combination of three PL mixed bed columns was used with chloroform as eluent (flow rate 1.0 mL/min). Commercial polystyrene standards served for calibration. The optical rotations were measured in CH_2Cl_2 on a Perkin-Elmer polarimeter Md 341 in 1 mL sample tubes using a concentration of 10 g/L. The DSC measurements were performed on a Perkin-Elmer DSC-7 in aluminum pans with a heating rate of 10 °C/min.

Results and Discussion

Homopolymerizations. Although copolymerizations of ϵCL and LLA were the object of this study, homopolymerizations of both monomers were also conducted to achieve a better understanding of the reactivities of $BiHex_3$ relative to $SnOct_2$ and of ϵCL relative to LLA. These homopolymerizations were performed under the conditions used for copolymerizations. Therefore, all homopolymerizations were conducted in bulk at 120 °C. Two series of homopolymerizations had the purpose to elaborate time−conversion curves, which were presented in Figures 1 and 2. For these polymerizations benzyl alcohol served as co-initiator with a M/C ratio of 50/1. Both initiators were added at a monomer/initiator ratio (M/I) of 1000/1 to reduce the rates of polymerization to a level easy to monitor by ^1H NMR spectroscopy. The rate constants thus obtained were listed in the experimental part. From these rate constants and from the times required for 50% conversion, it may be calculated that the $BiHex_3$-initiated polymerizations of ϵCL is about 11 times slower than the $SnOct_2$-initiated polymerization. In the case of LLA, the polymerization initiated with $BiHex_3$ is slower by a factor around 6. Furthermore, the polymerizations of LLA proved to be faster by a factor around 4 ($SnOct_2$) or 6 ($BiHex_3$) than the homopolymerizations of ϵCL. Hence, these time−conversion measurements indicate that $BiHex_3$ is somewhat less reactive as initiator and transesterification catalyst than $SnOct_2$.

Finally, a few preparative polymerizations were performed with a M/I ratio of 1000 corresponding to the copolymerizations. These additional homopolymerizations summarized in Table 1 served two purposes. First, it should be elucidated if the average degrees of polymerization ($\overline{DP}$s) of the isolated polyesters agree with the feed ratios. Second, the optical purity of the polylactides should be checked. The $\overline{DP}$s determined by ^1H NMR via the −CH−(CH_3)−OH and −CH_2−OH end groups were slightly higher than the M/C ratio due to fractionation upon precipitation into diethyl ether. Considering this fractionation, the agreement was satisfactory. Again satisfactory were the optical rotation data of PLLA, indicating 98−99% optical purity. These homopolyesters were also subjected to MALDI−TOF mass spectrometry to find out whether cyclic oligo- and polyesters were formed. In the case of polylactides no cycles were found above 1300 Da regardless of the initiator. At lower masses the poor signal-to-noise ratio and matrix signals presented a clear-cut identification of reaction products. In the case of poly(ϵCL) a small fraction of cyclic oligolactones (presumably ≤1 wt %) was found in all three samples for masses below 1500 Da (Figure 3). These mass spectra also revealed that

Scheme 1



the frequency distributions of the PϵCL samples prepared with BiHex$_3$, on one hand, and SnOct$_2$, on the other, were different. The SnOct$_2$-initiated PϵCL had a bimodal distribution (Figure 3B) which cannot be explained at this time. Both polymerizations of ϵCL and the mass spectroscopy were repeated, and their reproducibility was confirmed.

The unexpected frequency distributions found for the benzyl alcohol-co-initiated polymerizations of ϵCL (Figure 3) prompted us to repeat these homopolymerizations with TEG as co-initiator because TEG was also used for all copolymerizations (see Tables 2−6). Interestingly, the MALDI−TOF MS looked different, as illustrated by Figure 4. The different frequency distributions obtained for co-initiation with benzyl alcohol and TEG may be a consequence of the fact that TEG may act as ligand. A complexation of Bi and Sn cations may prevent association of initiators and may prevent complexation of the cations at the active chain end by complexation of the cations at the active chain end by neighboring ester groups of the growing chain. With TEG both initiators yielded monomodal frequency distributions, but the distribution curve obtained from BiHex was narrower (Figure 4A). SEC measurements yielded a polydispersity (PD) of 1.15 for initiation with BiHex$_3$ and a PD of 1.45 for SnOct$_2$. Furthermore, more cyclic oligomers were found in the SnOct$_2$-initiated samples. Therefore, these MS confirm that under the conditions of these ring-opening polymerizations BiHex$_3$ is somewhat less active as transesterification catalyst.

Copolymerizations. All copolymerizations of ϵCL and LLA were conducted in bulk with tetra(ethylene glycol) as co-initiator (Scheme 1). This diol was selected as co-initiator for several reasons. It is inexpensive and easy to purify, and it may serve as a model for longer polydisperse poly(ethylene glycol)s. Furthermore, its proton signals are easy to detect in the ^{1}H NMR spectra of all copolyesters and thus facilitate the determination of the average degree of polymerization ($\overline{DP}$) by ^{1}H NMR spectroscopy. In parallel, polymerization experiments SnOct$_2$ were also used as initiator for comparison because SnOct$_2$ is the most widely used initiator in fundamental research and in the technical production of polylactides and other biodegradable polyesters.

Two series of copolymerizations were performed which differ by the molar ratio of ϵCL and LLA. The first series, the data of which were compiled in Tables 2 and 3, is based on a molar ratio 2:1, which means that the ratio of ϵCL and lactic acid (lactyl) units (LA) after complete conversion should be 1:1. For the second series (Table 4) a monomer ratio of 1:1 was selected, so that the molar ratio of ϵCL and LA units in the isolated copolyesters should amount to 1:2 after complete conversion. In both series the temperature was varied from 100 to 120 and 140 °C to study its influence on the sequences. The lowest temperature was 100 °C because in previous studies[5,6] dealing with homopolymerizations of ϵCL or LLA this temperature was found to be the minimum for high conversions in a reasonable time. To find the minimum time needed for roughly 97% conversion of both monomers small samples were taken from reaction mixture in certain time intervals and examined by ^{1}H NMR spectroscopy. In this way the quasi-nonsystematic series of reaction times listed in Tables 2 and 4 were determined.

The characterization of the isolated copolyester gave the following results. The yields of the copolyesters prepared with 2:1 feed ratio (2:1 copolyesters) were particularly low when compared to those of the homopolyesters (Table 1) or 1:1 copolyesters (Table 4). The reason for this phenomenon is the lower level of crystallinity, resulting in a more efficient fractionation upon precipitation into diethyl ether. Another consequence of this fractionation is the molecular weight, which may be higher than expected from the M/C ratio and 100% conversion of both monomers (see footnote *c* of Table 2). It is known from the work of five research groups[21−25] that direct calibration of SEC measurements with commercial polystyrene standards (PS) overestimates the real molecular weights of aliphatic polyesters by 50−80% (depending on structure and molecular weight). Therefore, the original data and molecular weights (number-average M_n and weight-average M_w) corrected with the factor 0.60 are listed in Table 2 (factors of 0.56 and 0.58 were given for polyϵCL or polyLA in refs 24 and 25). In the case of SnOct$_2$-initiated copolyesters, the experimentally corrected M_ns are in satisfactory agreement with the calculated theoretical value, whereas lower M_ns were obtained from the BiHex$_3$-initiated copolyesters.

The molar compositions were evaluated by ^{1}H NMR spectroscopy. The ϵCL/lactyl ratios agreed well with the feed ratio (Table 2), as expected from the high conversions of both monomers. This finding also indicates that the fractionation resulting from the precipitation is mainly based on different molecular weights and not on variations of the chemical composition. This conclusion was confirmed by repetition of the copolymerizations 3−6 of Tables 2 and 3. The molar compositions of the copolyesters were compared before and after precipitation, and no significant differences were found.

The average lengths of the homogeneous blocks of both monomers ($\bar{L}_{CL}$ and $\bar{L}_{LA}$) were determined from both ^{1}H and ^{13}C NMR spectra via eqs 1 and 2. The signal

$$\bar{L}_{CL} = \frac{I_{CL\text{-}CL}}{I_{CL\text{-}LA}} + 1 \tag{1}$$

$$\bar{L}_{LA} = \frac{I_{LA\text{-}LA}}{I_{LA\text{-}CL}} + 1 \tag{2}$$

$I_{CL\text{-}CL}$, $I_{LA\text{-}LA}$: intensities of dyads reflecting the εCL-εCL or LA-LA bonds

$I_{CL\text{-}LA}$, $I_{LA\text{-}CL}$: intensity of signals representing the crossover steps

assignments of dyads and triads underlying these calculations are presented in Figures 5 and 6. In the case of ^{13}C NMR spectroscopy, the CO signals were used for these calculations. ^{13}C NMR sequence analyses of copolyesters based on CO signals were first reported by Kricheldorf et al.[11,26] and later refined and extended to ^{1}H NMR spectroscopy by Kasperczyk and Bero.[14,15] The

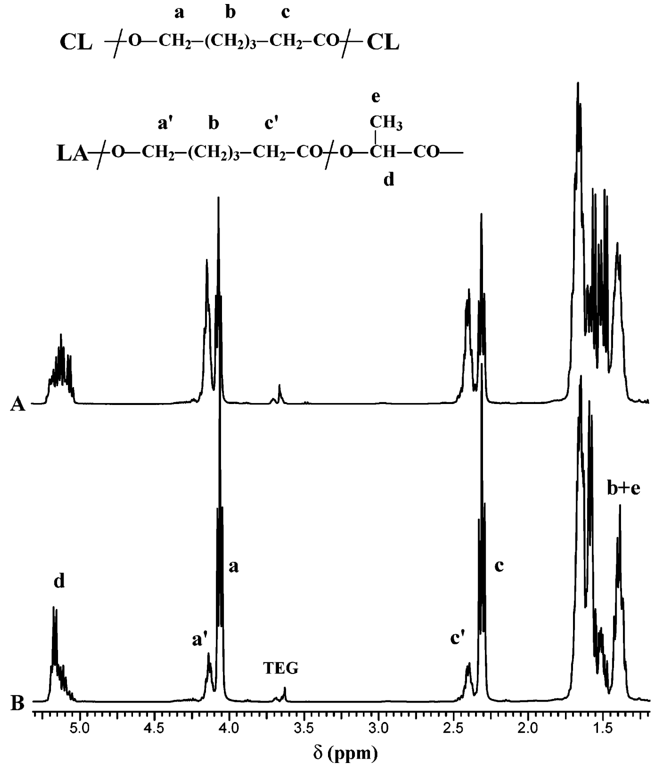


Figure 5. 400 MHz ^{1}H NMR spectrum of the copolyester: (A) no. 2, Table 2 (initiation with BiHex$_3$); (B) no. 1, Table 2 (initiation with SnOct$_2$).

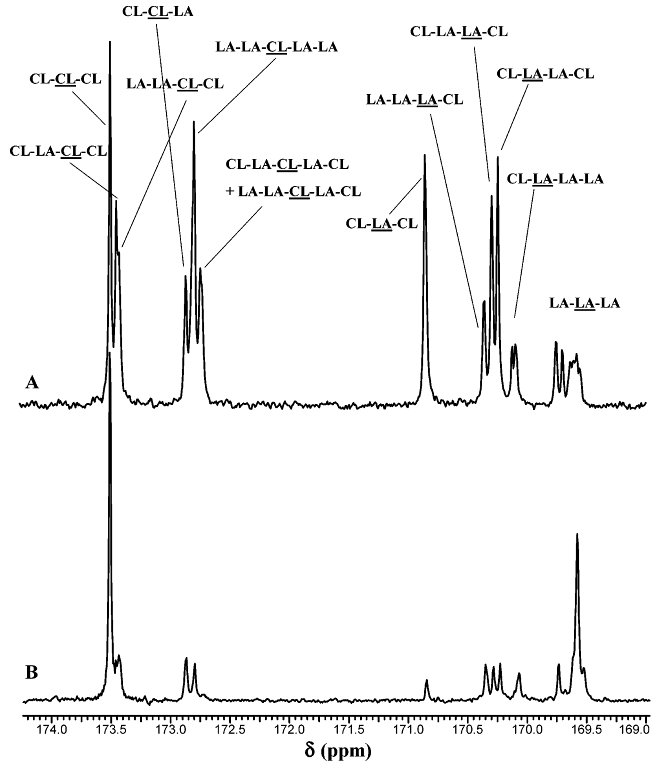


Figure 6. 100.4 MHz ^{13}C NMR spectrum (CO signals only) of the copolyester; (A) no. 2, Table 2 (initiation with BiHex$_3$); (B) no. 1, Table 2 (initiation with SnOct$_2$).

block lengths compiled in Table 3 demonstrate two interesting trends. The first and most important point is the blockiness of the sequences obtained from SnOct$_2$-initiated copolymerization. A block length of 2.0 corresponds to a random sequence, and such values were found for the BiHex$_3$-initiated copolymers. The second trend is the decrease of blockiness of the SnOct$_2$-initiated copolymers with higher temperatures. When the sequences were compared before and after precipitation (studied by repetition of copolymerizations 3−6, Tables 2 and 3), no significant difference was found for samples initiated with BiHex$_3$. When initiated by SnOct$_2$, the blockiness of the virgin reaction products was 5−10% higher than that of the copolyesters characterized after precipitation. The difference between the sequences obtained from SnOct$_2$- and BiHex$_3$-initiated copolymerizations is also reflected in the percentages of alternating dyads (calculated relative to the sum of both dyads from ^{1}H NMR signals). A percentage around 50% suggests randomness, whereas lower values indicate blockiness. Therefore, all sequence data listed in Table 3 together indicate that the copolyesters obtained with BiHex$_3$ as initiator had almost perfectly random sequences.

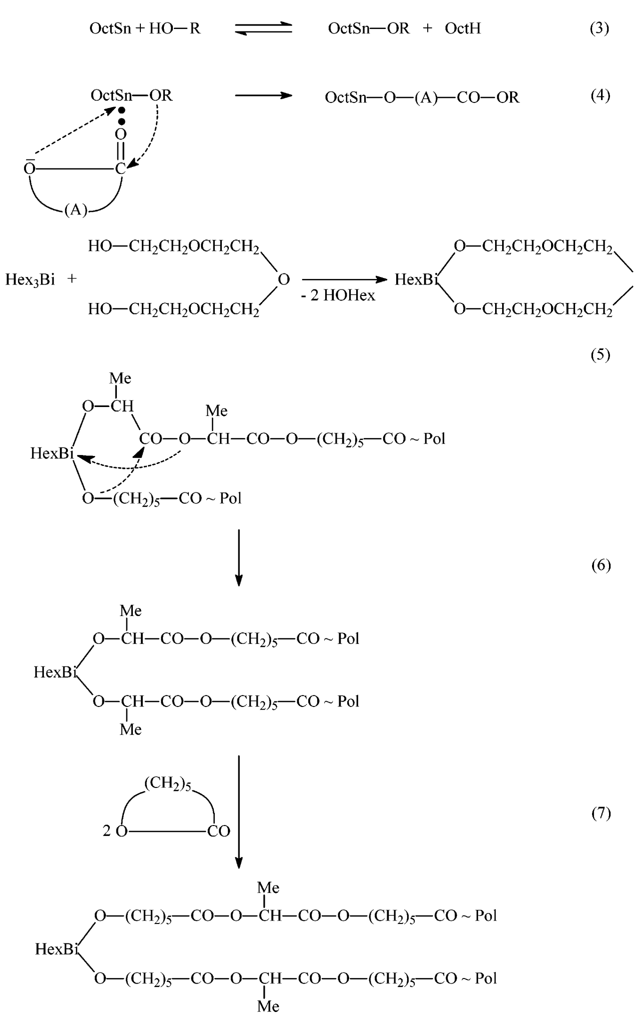
The different degrees of blockiness observed for SnOct$_2$- and BiHex$_3$-initiated copolyesters have the expected consequences for the morphology. DSC measurements revealed that the "SnOct$_2$ copolymers" possess one melting endotherm due to crystallized blocks of ϵCL units. Both the melting temperature (T_ms) and the melting enthalpies are, of course, lower than those of the homopolyesters because crystallites consisting of short blocks are smaller and less perfect than those formed by homopolymers. The different morphologies are directly evident to the naked eye. Whereas the "SnOct$_2$ copolyesters" are white and turbid, as expected for a semicrystalline material, the amorphous "Bi copolyesters" are transparent.

A second series of copolymerizations were conducted in such a way that a 1:1 feed ratio of ϵCL and LLA was used, whereas all other experimental parameters were kept constant (Table 4). Relatively high yields were found for the SnOct$_2$-initiated copolyesters and low yields for the "Bi copolyesters". This trend was also observed for the first series of copolymers (Table 2), but it was more pronounced in the second series. Since the conversions of both monomers were above 97%, the different yields are not a consequence of higher or lower conversions. The yields reflect the different solubilities in diethyl ether which was used for the precipitation of all copolyesters. Since the "Sn copolyesters" were crystalline in contrast to the amorphous "Bi copolyesters", their solubility is considerably lower. The molar composition of the isolated copolyesters were determined by ^{1}H NMR spectroscopy, and a satisfactory agreement with the feed ratio was found in all cases. This means, in turn, that the fractionation resulting from the precipitation into diethyl ether was based on different molecular weights and not on different compositions of the copolyester.

Because of the different feed ratio, the block lengths of the lactyl (LA) units were now roughly twice as long as those of the first series and the block lengths of the ϵCL units were correspondingly shorter. Again, the block lengths of the SnOct$_2$-initiated copolyesters decrease with higher temperatures due to transesterification. However, the most interesting result is the finding that the BiHex$_3$-initiated copolyesters possessed nearly random sequences, regardless of the temperature. Despite the high content of LA units, all "Bi copolyesters" were amorphous and transparent. Therefore, this second series of copolymerizations confirms again that the Bi initiator is particularly useful for the preparation of nearly random completely amorphous copolyesters.

Mechanistic Discussion. The polymerizations described above provided two seemingly disagreeing results. The homopolymerizations indicated, on one hand, that $BiHex_3$ is a poorer transesterification catalyst than $SnOct_2$. The sequence analyses of the copolyesters suggested, on the other hand, that $BiHex_3$ produces random sequences by efficient transesterification, whereas $SnOct_2$ yielded blocky sequences due to insufficient transesterification. To shed more light on this problem, two more series of copolymerizations were conducted with variation of the time. The changes of molar composition and average block lengths with time were determined and listed in Table 5 (initiation with $SnOct_2$) and Table 6 (initiation with $BiHex_3$). In agreement with the homopolymerizations, the incorporation of LLA was faster than that of ϵCL. The initially high block length of the LA units decreased, whereas that of ϵCL slightly increased, so that both block lengths leveled off at a value around 3.40 when $SnOct_2$ was used as initiator. These values were determined for virgin reaction products and thus were slightly higher than those of the precipitated copolyesters listed in Table 3.

23



With $BiHex_3$, the incorporation of LLA was again much faster, and the initially high block length continuously decreased with time until a value around 2.1 was achieved (no. 7, Table 1). Yet, in contrast to $SnOct_2$, the initial block length of ϵCL was extremely low (1.4), which means that La−CL−LA triads were initially dominating. In contrast, all $\bar{L}_{Cl}$ values obtained with $SnOct_2$ were above 2.4. Finally, the block lengths of both LA and ϵCL units approach a value around 2. In other words, when the active chain end was an ϵCL−Sn combination, the probability of an incorporation of another ϵCL unit was relatively high. Yet, in the case of an ϵCL−Bi end group, the incorporation of LLA was faster than that of ϵCL, so that alternating dyads were preferentially formed. However, this course of the copolymerization does not explain yet the high content of ϵCL−LA−ϵCL triads with a single lactic acid (lactyl) unit in the middle. This finding requires either an intensive transesterification with total equilibration or a special intramolecular transesterification mechanism as discussed below. To obtain more information about the intermolecular transesterification, a mixture of polyϵCL and polyLLA was treated with $SnOct_2$ or $BiHex_3$ in concentrated chloronaphthalene solution at 140 °C. From time to time the average block length of ϵCL was determined by ^1H NMR spectroscopy. As demonstrated by the $\bar{L}_{Cl}$ values of Table 7, both $SnOct_2$ and $BiHex_3$ showed equal transesterification activities, and even after 7 days the sequence was far from randomness. Therefore, no indication was found that $BiHex_3$ is reactive enough to generate a random copolyester just by intermolecular transesterification and backbiting. This situation and the previously published results obtained from copolymerizations of ϵCL and glycolide[27,28] suggested the existence of a special intramolecular mechanism as origin of the ϵCL−LA−ϵCL triads.

The polymerization mechanism initiated by $SnOct_2$ has recently been elucidated by two research groups.[20,29] The $SnOct_2$ undergoes an equilibration with the alcohol added as co-initiator, so that one (eq 3) or two Sn alkoxides are formed. These alkoxide groups are the active species and initiate a normal coordination−insertion mechanism (eq 4). From $Bu_2Sn(OMe)_2$ and other metal alkoxides it is known[30] that two or more chains grow from one metal atom. Furthermore, we have demonstrated that various metals form cyclic or spirocyclic alkoxides when reacted with oligo(ethylene glycol)s.[31,32] Therefore, it is rather obvious to assume that $BiHex_3$ forms two or three alkoxide bonds with an excess of TEG. Part of these reaction products will be cycles (eq 5). The bismuth bis- or tris-alkoxides can, in turn, initiate polymerizations of two or three chains.

When at least two chains grow out of one Bi group, the intramolecular transesterification formulated in eq 6 may take place. This transesterification is kinetically and thermodynamically favorable for two reasons. First, the most reactive type of ester groups reacts with the most nucleophilic alkoxide group of this system. Second, the five-membered cyclic transition state is entropically advantageous over that of an intermolecular transesterification.

This mechanistic concept is supported by the observation that $BiHex_3$-initiated copolymerizations of ϵCL and glycolide yield much higher fractions of alternating triads (ϵCL−O−CH_2CO−ϵCL), in agreement with a higher electrophilicity of glycolide relative to lactide ester groups. Furthermore, a preferential formation of alternating triads was also observed for $Al(OiPr)_3$-initiated copolymerizations of ϵCL and glycolide at 100

°C.[21] Under these conditions, no intermolecular or backbiting type of transesterification occurs. Therefore, a special energetically favorable intramolecular transesterification is a necessary assumption. Moreover, it was proven that $Al(OiPr)_3$ initiates three polyester chains at 100 °C.

In summary, the mechanistic concept outlined in eqs 6 and 7 agrees with all experimental observations presented in this work and previous publications.

Conclusions

In this work a couple of surprising results were obtained. Whereas blocky sequences of ϵCL and LA units were formed with $SnOct_2$ as initiator, $BiHex_3$ yielded random copolymers. By comparison with homopolymerization experiments, it may be concluded that $BiHex_3$ is somewhat less efficient as transesterification catalyst, so that the random sequences are either a consequence of equal rates of incorporation of ϵCL and LLA or a consequence of a special intramolecular transesterification mechanism. Time−conversion curves of homopolymerizations and copolymerizations clearly indicate that the polymerization (and thus, incorporation) of LLA is much faster than that of ϵCL. This observation and the predominance of ϵCL−O−CH(CH_3)−CO−ϵCL triads documented in the ^{1}H and ^{13}C NMR spectra prove that a special intramolecular transesterification mechanism is operating, which is different from the normal transesterification mechanisms. The normal intermolecular transesterification and the “backbiting equilibration” have a higher energy of activation and are responsible for randomization of the sequences at high temperatures and long times. The predominantly alternating sequences generated by $BiHex_3$ are advantageous for various applications because of a homogeneous amorphous morphology and because the rates of hydrolytic degradation are more uniform throughout the bulk of sample compared to the blocky sequences obtained by $SnOct_2$. Therefore, $BiHex_3$-initiated copolyesters are particularly useful as matrices for controlled drug release, as films for wound dressing as biodegradable adhesives, and as soft segments in biodegradable networks and (multi)block copolymers.

Acknowledgment. We thank Doz. Dr. Ch. Friedrich (University of Freiburg e.Br.) for the DSC measurements.

References and Notes

(1) Khraras, G. B.; Sanchez-Riera, F.; Severson, D. K. Polymers of Lactic Acid. In *Plastics from Micros*; Mobley, D. P., Ed.; Hanser Publishers: München, 1994.
(2) *Biomaterials in Surgery*; G. Thieme Publishers: Stuttgart, 1998.
(3) *Degradable Polymers*; Albertsson, A. C., Karlsson, S., Eds.; *Macromol. Symp.* **1998**, *130*.
(4) Kricheldorf, H. R. *Chemosphere* **2001**, *43*, 49.
(5) Ikada, Y.; Tsuji, H. *Macromol. Rapid Commun.* **2000**, *21*, 117.
(6) Kricheldorf, H. R.; Serra, A. *Polym. Bull. (Berlin)* **1985**, *14*, 497.
(7) Kricheldorf, H. R.; Boettcher, C. *J. Macromol. Sci., Pure Appl. Chem.* **1993**, *A30*, 441.
(8) Kricheldorf, H. R.; Hachmann-Thiessen, H.; Schwarz, G. *Biomacromolecules* **2004**, *5*, 492.
(9) Kricheldorf, H. R.; Hachmann-Thiessen, H.; Schwarz, G. *Macromolecules* **2004**, *37*, 6340.
(10) Rodilla, V.; Miles, A. T.; Jenner, W.; Harcksworth, G. M. *Chem. Biol. Interact.* **1998**, *115*, 71.
(11) Kricheldorf, H. R.; Jonté, J. M.; Berl, M. *Makromol. Chem.* **1985**, *Suppl. 12*, 25.
(12) Kricheldorf, H. R.; Kreiser-Saunders, I. *J. Macromol. Sci., Chem.* **1987**, *A24*, 1345.
(13) Grijpma, D. W.; Pennings, A. J. *Polym. Bull. (Berlin)* **1991**, *25*, 335.
(14) Kasperczyk, J.; Bero, M. *Makromol. Chem.* **1991**, *192*, 1777.
(15) Kasperczyk, J.; Bero, M. *Makromol. Chem.* **1993**, *194*, 913.
(16) Dobrzynski, P. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 3129.
(17) de Castro, M. L.; Wang, S. H. *Polym. Bull. (Berlin)* **2003**, *51*, 151.
(18) Kricheldorf, H. R.; Ahrensdorf, K.; Rost, S. *Macromol. Chem. Phys.* **2004**, *205*, 1602.
(19) Koch, T. R.; Wickham, P. P. *J. Org. Chem.* **1979**, *44*, 157.
(20) Kricheldorf, H. R.; Kreiser-Saunders, I.; Stricker, A. *Macromolecules* **2000**, *33*, 702.
(21) McLain, S. J.; Drysdale, N. E. *Polym. Prepr., ACS Polym. Div.* **1992**, *33* (1), 174.
(22) Pasch, H.; Rhode, K. *J. Chromatogr. A* **1995**, *699*, 24.
(23) Kricheldorf, H. R.; Eggerstedt, S. *Macromol. Chem. Phys.* **1998**, *199*, 283.
(24) Kowalski, A.; Duda, A.; Penczek, S. *Macromolecules* **1998**, *31*, 2114.
(25) Save, M.; Schappacher, M.; Soum, A. *Macromol. Chem. Phys.* **2002**, *203*, 889.
(26) Kricheldorf, H. R.; Mang, T.; Jonté, J. M. *Macromolecules* **1984**, *17*, 2173.
(27) Kricheldorf, H. R.; Rost, S. *Biomacromolecules*, in press.
(28) Kricheldorf, H. R.; Hachmann-Thiessen, H. *J. Polym. Sci., Part A: Polym. Chem.*, in press.
(29) Kowalski, A.; Duda, A.; Penczek, S. *Macromolecules* **2000**, *33*, 7359.
(30) Kricheldorf, H. R.; Berl, M.; Scharnagl, N. *Macromolecules* **1988**, *21*, 286.
(31) Kricheldorf, H. R.; Rost, S. *Polymer* **2004**, *45*, 3205.
(32) Kricheldorf, H. R.; Rost, S. *Macromolecules* **2004**, *37*, 7955.

MA047873O