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Copolymerizations of Glycolide and L-Lactide Initiated with Bismuth(III)n-Hexanoate or Bismuth Subsalicylate

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Equimolar copolymerizations of glycolide and L-lactide were conducted in bulk in the temperature range from 100 to 160°C. The catalytic efficiency of tin(II)2-ethylhexanoate ($SnOct_2$) and bismuth(III)n-hexanoate ($BiHex_3$) were compared under identical conditions. Furthermore, four copolymerizations were conducted with bismuth subsalicylate as initiator/catalyst. The isolated copolyesters were characterized by viscosity and SEC measurements, by ^{1}H-NMR spectroscopy with regard to their composition and with ^{13}C-NMR spectroscopy with regard to their sequences. $BiHex_3$ proved to be nearly as efficient as initiator as $SnOct_2$ and the sequences were somewhat closer to randomness than those obtained from $SnOct_2$. All copolyesters were amorphous materials soluble in a variety of organic solvents. Chain extension with diisocyanates raised the molecular weights by a factor of 5–7.

Keywords: glycolide; lactide; copolymerization; bismuth catalysts

1 Introduction

Homo- and copolyesters of L-lactide are the most widely used and most intensively studied biodegradable polyesters at this time. The 1:1 copolyester of glycolide and L-lactide is particularly important for pharmaceutical applications because it is the most frequently used matrix material of drug-delivery systems. The technical production of most homo- and copolylactides is based on ring-opening polymerizations of L,L-lactide (LA) initiated by tin(II)2-ethylhexanoate ($SnOct_2$) in combination with a coinitiator. The reasons why $SnOct_2$ serves as the standard initiator are threefold. First, it is an efficient and versatile initiator, enabling syntheses of various homo- and copolyesters. Second, it allows for a racemization-free polymerization of LA in the melt at temperatures up to 180°C. Third, it has been approved by the American FDA as food additive. However, this approval is not based on its low toxicity, on the contrary, it is due to its broad cytotoxicity which makes it useful as an anti-fouling agent.

For biomedical applications, the cytotoxicity of $SnOct_2$ and other tin compounds is a serious disadvantage and purification of biodegradable polyesters from tin compounds is expensive and time-consuming. Therefore, metal salts and complexes showing a similarly good performance as initiator or catalyst as $SnOct_2$ in combination with a much lower toxicity are highly desirable. Among the potential alternatives, bismuth salts or complexes are outstanding for their low toxicity. For instance, Bi-salts are for many decades used as components of ointments (designed for skin care and burn wounds) such as Dermatol, Xeroform and Noviform (European trademarks). Furthermore, Bi-salts such as the subsalicylate (BiSS) or the subcitrate are used for at least one hundred years as drugs against gastro-intestinal complaints, such as diarrhea, nausea, heart burn, indigestion etc. (1–4). Therefore, numerous studies concerning syntheses, structure, medical application, metabolism and toxicity of bismuth compounds have been published (4, 5). Particularly noteworthy is a recent study (6) dealing with the poisoning of kidney tubuli by heavy metals. Bi^{3+} showed the lowest toxicity and performed even better than Zn^{2+}, although Zn^{2+} belongs to the metabolism of the human body. With this background in mind, we have recently launched a broader study (7–14) of the usefulness of Bi-salts and complexes as initiators (or catalysts) for homo- and copolymerizations of lactones and lactides. An interesting and unexpected result was the finding that the copolyesters of ε-caprolactone and LA (11) or ε − caprolactone and glycolide (GL) (12) possess sequences with a lower degree of blockiness than those copolylactones prepared with $SnOct_2$ under identical conditions. A lower degree of blockiness improves the solubility in organic solvents and allows for a more homogeneous hydrolytic degradation. In this context, it was the purpose of

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the present work to study 1:1 copolymerizations of glycolide and LA-initiated by bismuth(III)n-hexanoate ($BiHex_3$) or BiSS (Eq. (1)).

2 Experimental

2.1 *Materials*

Glycolide (S-grade) and L-lactide (S-grade) were kindly supplied by Boehringer KG (Ingelheim, Germany). They were recrystallized from dry ethylacetate (with the portionwise addition of ligroin) and dried over P_4O_{10} *in vacuo*. $SnOct_2$ was purchased from Aldrich Co. (Milwaukee, WI) and purified as described previously (15). BiSS was also purchased from Aldrich Co. and used as received. $BiHex_3$ was prepared from commercial Bi(III)acetate (Aldrich Co.) and n-hexanoic acid as mentioned previously (11, 16) and described below. Tetra(ethylene glycol) (TEG) and 1,12-dodecanediol were also purchased from Aldrich Co. They were azeotropically dried with toluene and distilled at 10^2 mbar over a short-path apparatus.

2.2 *Bismuth Hexanoate*

Bismuth(II)acetate and dry n-hexanoic acid (10 mol% excess) dissolved in 150 mL of dry toluene were heated to 125°C and water was azeotropically distilled off over 6 h. 150 mL dry toluene was added and again distilled over 6 h. Afterwards, it was stirred for 6 h in vacuum (0.1 mbar) at 50°C. It was then slowly heated to 140°C in vacuum (over a period of 6 h) and maintained for 4 more hours at 140°C.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 0.89$ (3H, m); 1.31 (4H, m); 1.62 (2H, m); 2.29 (2H, t) ppm.

2.3 *Copolymerizations*

Glycolide (20 mmol), and L-lactide (20 mmol) were weighed under dry nitrogen into a 50 mL Erlenmeyer flask having silanized glass walls. TEG (0.4 mmol) was added and this mixture was homogenized at 100°C for 1 min. Afterwards, 0.04 mL of a 0.5 M solution of $SnOct_2$ or $BiHex_3$ in dry chlorobenzene were injected. The reaction vessel was closed with glass-stopper and steel spring and thermostated at 100°C (or at 120, 140, and 160°C). When the conversion of L-lactide was above 95% (checked by ^{1}H-NMR spectroscopy), the reaction mixture was cooled and characterized.

In analogous experiments, the chain lengths of the copolyesters were varied, using TEG in amounts of 0.67, 0.20, or 0.10 mmol.

2.4 *Chain Extension*

Glycolide (20 mmol) and L-lactide (20 mmol) weighed under dry nitrogen into a 100 mL Erlenmeyer flask and 2 mL of a 0.5 M solution of TEG in toluene was added. The closed Erlenmeyer flask was immersed into an oil bath preheated to 120°C and shaken several times until a homogeneous melt was obtained. BiHex3 (0.04 mmol) was injected as 0.5 M solution in toluene. After 24 h at 120°C, the temperature was lowered to 80°C and dry 1,2-dichloroethane (5 mL) were added. The resulting solution was divided into two parts, 1,6-hexamethylene diisocyanate (HMDI, 0.52 mmol) was added to one part of the reaction mixture as 1 M solution in 1,2-dichloroethane.

4,4′-Diisocyanate diphenyl methane (MDI, 0.52 mmol) was added as 1 M solution in 1,2-dichloroethane to the second part of the reaction mixture. After 5 h at 80°C, both reaction mixtures were precipitated into methanol. Yields of 95% (with HMDI) or 97% (with MDI) were obtained.

2.5 *Measurements*

The inherent viscosities were measured in $CDCl_3$/TFA (4:1 by volume) using an automated Ubbelohde viscometer thermostated at 20°C.

The 400 MHz ^{1}H-NMR spectra were recorded with a Bruker Avance 400 NMR spectrometer in 5 mm o.d. sample tubes. $CDCl_3$ containing trifluoroacetic acid (volume ratio 4:1) or hexafluoroisopropanol containing C_6D_6 (volume ratio 9:1) served as solvents with internal TMS for shift referencing. The 100.4 MHz ^{13}C-NMR spectra were recorded on the same NMR spectrometer in 5 mm o.d. sample tubes, when normal broad band decoupling was used. For measurements with inverse-gated decoupling 10 mm o.d. sample tubes were used.

The DSC measurements were conducted on a Mettler "Toledo DSC 821 e" under nitrogen in aluminum pans with a heating rate of 10°C/min. The SEC measurements were performed on an appatus of Polymer Laboratories equipped with 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.

3 Results and Discussion

3.1 *Initiation with $BiHex_3$-Variation of the Temperature*

In previous studies dealing with copolymerizations of ε-caprolactone with glycolide or L-lactide, it was found that the temperature has a significant influence on the monomer sequences. Therefore, a first series of copolymerizations was conducted in such a way that the equimolar mixture of GL and LA was copolymerized at four different temperatures in the range of 100 to 160°C (Table 1). TEG was used as a coinitiator at a feed ratio of 50/50/1. In addition to $BiHex_3$, $SnOct_2$ was used as an initiator (at a monomer/initiator ratio of 1000/1) to allow for comparison of the new "Bi-initiator" with the standard initiator. The conversions were monitored by ^{1}H-NMR spectroscopy and the

Table 1. Comparison of the copolymerizations of lactide and glycolide in bulk-initiated by SnOct$_2$[a] and BiHex$_3$[a]. Variation of the temperature

Copol. no.	Initiator[a]	Molar feed ratio	Temp. (°C)	Time (h)	LA/GL/ TEG[b] (^{1}H NMR)	$\bar{L}_{GL}$[c]	Altern. dyads (%) GL-LA	$\bar{L}_{LA}$[d]	Altern. dyads (%) LA-GL	η_{inh}[e] (dL/g)	M_n[f] (Da)	M_w[f]/ M_n	M_n[g] (Da)
1	SnOct$_2$	51/51/1	100	48	46/48/1	4.88	20	4.72	21	0.41	13,973	1.83	12,400
2	BiHex$_3$	48/49/1	100	48	51/49/1	4.45	22	4.64	22	0.36	11,345	1.90	13,200
3	SnOct$_2$	46/46/1	120	4	55/61/1	4.48	22	4.17	24	0.40	17,683	1.84	15,200
4	BiHex$_3$	48/49/1	120	4	47/48/1	4.03	25	4.09	25	0.39	15,637	1.91	12,500
5	SnOct$_2$	102/103/1	120	4	113/119/1	4.28	23	4.19	24	0.33	—	—	30,300
6	BiHex$_3$	98/98/1	120	6.6	95/99/1	3.88	26	4.13	24	0.39	—	—	25,400
7	SnOct$_2$	49/49/1	140	2	50/49/1	4.03	25	3.99	25	0.45	17,051	1.78	13,100
8	BiHex$_3$	49/49/1	140	2	52/52/1	3.45	29	3.68	28	0.48	17,940	1.84	13,200
9	SnOct$_2$	90/91/1	140	2	101/102/1	4.23	24	4.33	23	0.31	—	—	26,600
10	BiHex$_3$	98/98/1	140	2	106/107/1	3.59	28	3.50	29	0.32	—	—	27,900
11	SnOct$_2$	51/51/1	160	0.5	50/50/1	3.56	28	3.55	28	0.42	13,712	2.10	13,200
12	BiHex$_3$	49/49/1	160	0.5	50/49/1	3.29	30	3.41	29	0.43	13,991	1.84	13,100
13	SnOct$_2$	105/106/1	160	0.5	96/103/1	3.81	26	4.05	25	0.46	—	—	25,900
14	BiHex$_3$	91/90/1	160	0.5	84/86/1	3.82	26	3.64	27	0.41	—	—	21,700

[a] Monomer initiator ratio (M/I = 1000/1).

[b] Molar composition.

[c] Average lengths of the homogeneous blocks calculated according to Eq. (1) from the CO-signals ^{13}C NMR.

[d] Average lengths of the homogeneous blocks calculated according to Eq. (2) from the CO-signals ^{13}C NMR.

[e] Measured at 20°C with $c = 2$ g/L in CHCl$_3$/TFA (6:1).

[f] From polystyrene-calibrated SEC measurements in chloroform corrected with the factor 0.67.

[g] Calculated from the composition as determined by ^{1}H NMR spectroscopy.

copolymerizations were stopped when the conversion of LA reached >95%.

The virgin reaction products were characterized to avoid any influence of fractionation (by precipitation) on the results. Yet, in this way it was not feasible to define and to determine yields. The molar compositions were determined by ^{1}H-NMR spectroscopy and it was found that the incorporation of GL was faster than that of LA as expected from its higher reactivity. When the conversion of LA had reached >95%, the molar compositions of the copolyesters were, of course, almost identical with the feed ratio. However, an unexpected result was obtained when the times required for completion of the copolymerizations were compared. With BiHex$_3$, initiated copolymerizations were only slightly slower than those initiated with SnOct$_2$. This finding was unexpected, because previous studies of BiHex$_3$- or BiSS-initiated homo- and copolymerizations of ε-caprolactone had shown that their reaction rates were 6–12 times lower than those achieved with SnOct$_2$ under identical conditions.

Due to the slightly slower copolymerizations of GL and LA initiated by BiHex$_3$ the molecular weights (and inherent viscosities) of the resulting copolyesters were slightly lower than those of SnOct$_2$-initiated copolyesters when identical reaction times were applied. Another slight difference found for BiHex$_3$ and SnOct$_2$-initiated copolymerizations concerns the polydispersities which were slightly higher for initiation with BiHex$_3$ (Table 1). Regarding the number average molecular weights (M_ns) listed in Table 1, it should be mentioned that the original values obtained by calibration with polystyrene were corrected by multiplication with the factor 0.67, whereby a satisfactory agreement with the value of 13,000 Da calculated for 100% conversion of both monomers was obtained. The correction factor is based on the work of four research groups (17–20) which found by different analytical approaches that polystyrene calculated SEC measurements overestimate the real molecular weights of aliphatic homo- and copolyesters by at least 50%.

The sequences were characterized by ^{13}C-NMR spectroscopy using the dyad splitting of the CO-signals (examplarily illustrated in Figure 1) which have been shown (21–23) for numerous copolyesters to be particularly sensitive to sequence effects. The average lengths of the homogeneous blocks ($\bar{L}_{GL}$ and $\bar{L}_{LA}$ in Table 1) were determined from the signal intensities of the dyad signals via Equation (2). The values listed in Table 1 indicate two trends. First, average lengths of the both GL-blocks and LA blocks decrease with higher reaction temperatures. Second, the block lengths of the BiHex$_3$-initiated copolyesters were slightly lower than those obtained with SnOct$_2$. The same trends were found when the percentage of alternating dyads were calculated relative to the sum of both dyads. The lower blockiness of Bi-initiated sequences is a small effect, but it must be seen in correlation to the considerably reduced blockiness of Bi-initiated copolyesters derived from εCL and GL or εCL and LA. The temperature dependence of the average block lengths resulting from BiHex$_3$ or SnOCt$_2$-initiated

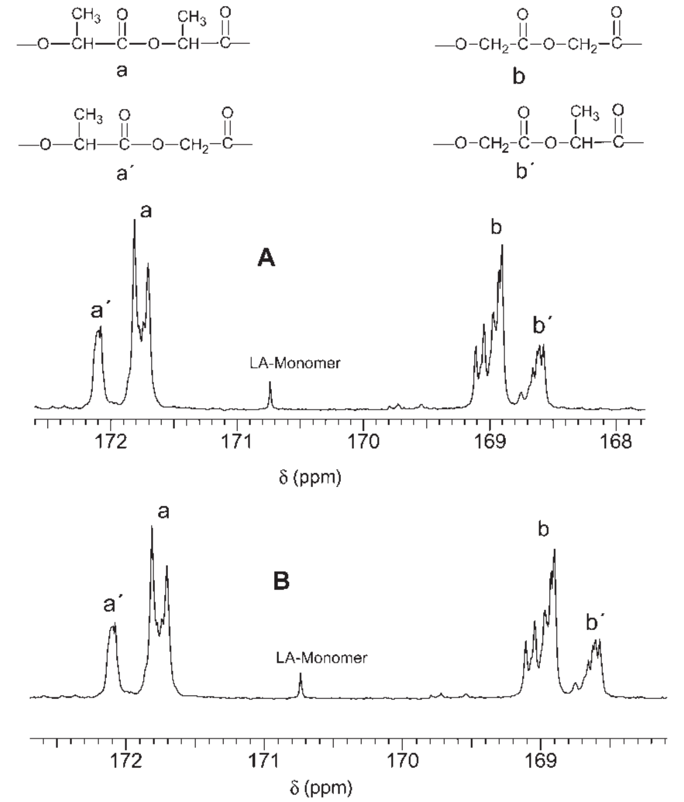

Fig. 1. 100.4 MHz ^{13}C NMR spectra (CO-signals only) of: A) copolyester prepared with $SnOct_2$ at 140°C and B) with $BiHex_3$ at 140°C (Nos. 7 and 8, Table 1).

polymerizations is illustrated in Figures 2 and 3.

$$\overline{L}_{GL} = \frac{I_{GL-GL}}{I_{GL-LA}} + 1; \quad \overline{L}_{LA} = \frac{I_{LA-LA}}{I_{LA-GL}} + 1 \qquad (1)$$

$I_{GL-GL}, I_{LA-LA}, I_{GL-LA}, I_{LA-GL}$ = intensities of the dyad peaks of ^{13}C NMR CO-signals (see Fig. 1)

3.2 Variation of the Monomer-Coinitiator Ratio

A second series of $BiHex_3$-initiated copolymerizations was conducted at 140 and 160°C with variation of the monomer/TEG ratio. The molar compositions determined by ^{1}H NMR spectroscopy were in good agreement with the feed ratios so far the GL/LA ratios were concerned (Table 2). A somewhat broader scattering was found for the monomer TEG ratios. Particular noteworthy are the relatively high monomer/TEG ratios found for the lowest feed ratios (30/30/1). The higher composition values suggest the chain growth was slightly faster than the initiation steps, so that a small amount of TEG had not reacted. However, the most interesting and unexpected result was found, when the ^{13}C-NMR spectra were evaluated. The average block lengths of both monomers systematically increased with higher monomer/TEG ratios. Respectively, the percentages of alternating dyads decreased. Since, the monomer/$BiHex_3$ ratio was kept constant in all those experiments, we cannot offer a straightforward explanation of this observation.

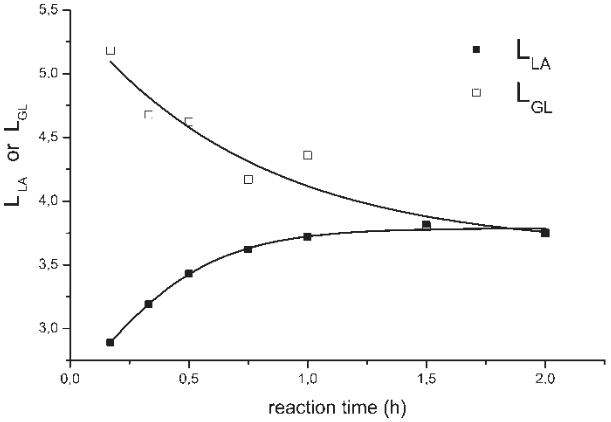

Fig. 2. Dependence of the average block lengths of: $SnOct_2$-initiated copolymerizations at 140°C (in bulk).

3.3 Initiation with BiSS

A few copolymerizations were performed with BiSS instead of $BiHex_3$ (and TEG as coinitiator) to elucidate the usefulness of this commercial drug as initiator (Table 3). Structure and properties of $BiHex_3$ and BiSS are largely different, and thus, justify a separate study. Whereas $BiHex_3$ is a monomeric species soluble in numerous polar solvents including lactones, BiSS has a complex polymeric structure and is insoluble in all organic solvents. Consequently, it did not dissolve in the melt of glycolide and lactide and in the course of the copolymerization only a minor fraction of BiSS seemingly dissolved in the reaction mixture. Nonetheless, the times required for almost complete conversions of both monomers were similar to those determined for $BiHex_3$. The GL/LA ratios of the copolyesters were close to the feed ratios. Yet at 120 and 160°C, the monomer/TEG ratios were higher than the feed, possibly to incomplete conversion of TEG. The average block lengths

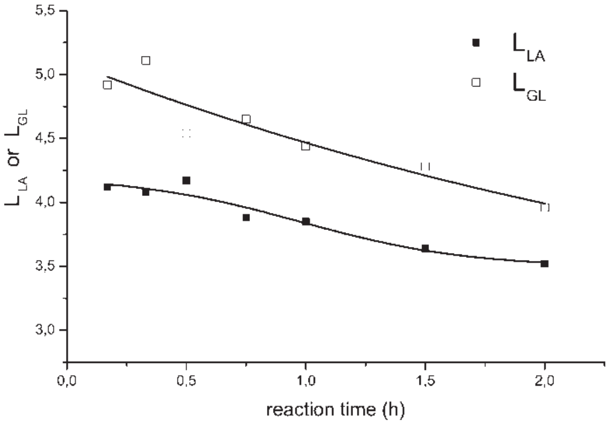

Fig. 3. Dependence of the average block lengths of: $BiHex_3$-initiated copolymerizations at 140°C (in bulk).

Table 2. Copolymerizations of lactide and glycolide in bulk-initiated by $BiHex_3$[a]. Variation of the block length

Copol. no.	Initiator[a]	Molar feed ratio	Temp. (°C)	Time (h)	LA/GL/ TEG[b] (^{1}H NMR)	$\bar{L}_{GL}$[c]	Altern. dyads (%) GL-LA	$\bar{L}_{LA}$[d]	Altern. dyads (%) LA-GL	DSC: T_g (°C)
1	$BiHex_3$	30/30/1	140	2	28/28/1	3.43	29	3.49	29	36.5
2	$BiHex_3$	49/49/1	140	2	52/52/1	3.55	29	3.68	28	41.0
3	$BiHex_3$	98/98/1	140	2	106/107/1	3.59	28	3.50	29	41.5
4	$BiHex_3$	177/177/1	140	2	178/184/1	4.64	22	3.56	28	43.0
5	$BiHex_3$	30/30/1	160	0.5	34/33/1	3.23	31	3.34	30	36.5
6	$BiHex_3$	49/49/1	160	0.5	50/49/1	3.39	30	3.41	29	37.5
7	$BiHex_3$	91/90/1	160	0.5	84/86/1	3.82	26	3.64	27	42.0
8	$BiHex_3$	186/186/1	160	0.5	209/212/1	4.33	23	3.59	28	40.5

[a] Monomer initiator ratio ($M/I = 1000/1$).
[b] Molar composition.
[c] Average lengths of the homogeneous blocks calculated according to Eq. (1) from the CO-signals ^{13}C NMR.
[d] Average lengths of the homogeneous blocks calculated according to Eq. (2) from the CO-signals ^{13}C NMR.

of both GL and LA units are also similar to those obtained with $BiHex_3$.

Finally, one experiment conducted with 1,12-dodecane diol as coinitiator should be mentioned (No. 4, Table 3). Furthermore, three copolymerizations were performed at 160°C with variation of the monomer/BiSS ratio (not described here in detail). The reason for these additional copolymerizations concerned the color of the copolyesters. While $SnOct_2$ imparted a yellow color to transparent molten mass, the bismuth salts imparted a greyish color. It was found that the intensity of this color decreased with lower reaction temperatures with lower concentration of Bi-salts, and it was reduced when 1,12-dodecane diol was used as coinitiator instead of TEG. Regardless of the reaction conditions all copolyesters yielded white powders upon precipitation from cold diethyl ether.

3.4 *Chain Extension of Telechelic Copolyesters*

The coinitiators of the copolymerizations of GL and LA with TEG had the consequence that copolyesters having two OH-endgroups were obtained. The existence of CH_2OH and CH-OH endgroups was confirmed by ^{1}H-NMR spectroscopy. In previous studies dealing with Bi(III)acetate of $BiHex_3$-initiated homopolymerizations of ε-caprolactone and LA the existence of CH_2OH or CH-OH endgroups was also confirmed by MALDI-TOF mass spectroscopy. Unfortunately, the MALDI-TOF mass spectra of the copolyesters prepared in this work were complex due to the random sequences of LA and GL and had low signal-to-noise ratios, so that they did not represent the main fraction of the samples. The existence of two OH endgroups should allow for a chain extension with diisocyanates. In two previous publications (13, 14), it was demonstrated that Bi salts also catalyze the addition of alcohols onto isocyanates. Therefore, two chain extension experiments were performed in the following way.

A telechelic copolyester was prepared from a LA/GL/TEG ratio of 20/20/1 under the conditions of experiment No. 1, Table 2. The crude copolyester was dissolved in dry 1,2-dichloroethane and this solution was subdivided into two equal parts. An equimolar amount (relativ to TEG) of 1,6-hexamethylene diisocyanate was added to one part of the copolyester solution and 4,4′-diisocyanato diphenylmethane (MDI)

Table 3. Copolymerizations of lactide and glycolide in bulk-initiated by BiSS[a]. Variation of temperature and time

Copol. no.	Initiator[a]	Molar feed ratio	Temp. (°C)	Time (h)	LA/GL/ TEG[b] (^{1}H NMR)	$\bar{L}_{GL}$[c]	Altern. dyads (%) GL-LA	$\bar{L}_{LA}$[d]	Altern. dyads (%) LA-GL	n_{inh}[e] (dL/g)
1	BiSS	51/50/1	120	7.3	58/58/1	4.34	30	3.34	31	0.37
2	BiSS	48/48/1	140	2	44/45/1	3.94	25	3.60	28	0.30
3	BiSS	51/52/1	160	1	58/59/1	3.46	29	3.26	31	0.39
4	BiSS	49/49/1	160	0.5	DDD[f]	3.39	29	3.44	29	0.43

[a] Monomer initiator ratio ($M/I = 1000/1$).
[b] Molar composition.
[c] Average lengths of the homogeneous blocks calculated according to Eq. (1) from the CO-signals ^{13}C-NMR.
[d] Average lengths of the homogeneous blocks calculated according to Eq. (2) from the CO-signals ^{13}C-NMR.
[e] Measured at 20°C with $c = 2$ g/L in $CHCl_3$.
[f] Coinitiator 1,12-dodecandiol, molar feed ratio 49/49/1.

was added to the second half. After 5 h at 80°C, the IR spectra indicated the disappearance of the characteristic isocyanate band at 2271 cm^{-1}. The reaction products isolated after precipitation into methanol were subjected to SEC measurements and compared to the SEC curves measured from the parent copolyester before addition of diisocyanates. It was found that the molecular weight (telechelic oligoester: $M_n \approx 2600$ Da) had increased by a factor of 5 in the case of the aliphytic diisocyanate and by a factor of 7 in the case of MDI. Almost the same chain extension factors were found in other chain extension experiments (13, 24, 25), and in the case of the homopolymer polysarcosine (24) the MALDI-TOF mass spectra were good enough to prove that the chain growth was mainly limited by cyclization. This result is not unusual, it is a quite normal consequence of our recently published theory of step-growth polymerizations (26) which postulates that cyclization competes with chain growth at any concentration and at any stage of a polymerization. Therefore, it may be concluded that the low chain extension factors found in this work are also predominantly a consequence of cyclization reactions.

4 Conclusions

The results of this work allow the conclusion that bismuth salts such as $BiHex_3$ and BiSS are useful initiators for copolymerizations of glycolide and lactide. The rates of the monomer incorporation are somewhat lower than those observed for $SnOct_2$, but the resulting monomer sequences are somewhat closer to randomness, when $BiHex_3$ is used as initiator. In summary, the performance of $BiHex_3$ (and BiSS) is quite similar to that of $SnOct_2$, but it is achieved on a much lower level of toxicity. The small amounts of Bi^{3+} ions needed as initiators do not need to be removed from (co)polylactones and (co)polylactides designed for pharmaceutical and other biomedical applications, because the non-toxic dose of BiSS in chewable Pepto-Bismol® tablets is in the range of 1.5–4.5 per day.

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