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Ph_2BiOEt-Initiated Copolymerizations of ε-Caprolactone and Glycolide

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ε-Caprolactone and glycolide were copolymerized in bulk at 100, 120 or 140°C. When tetra(ethylene glycol) was used as coinitiator, a preferential formation of alternating triads was observed. This tendency was surprisingly favored at the higher temperature, and thus, cannot be explained by a general equilibration (transesterification) process. In the absence of a coinitiator the tendency towards alternating sequences was less pronounced. The polymerization mechanism is discussed.

Keywords: ring-opening polymerization; biodegradable polyesters; ε-caprolactone; glycolide

1. Introduction

Syntheses of copolymers are a long known and extremely successful approach to a systematic variation of the properties of polymeric materials. In the field of biodegradable polyesters, this approach has intensively been used to vary the degree of crystallinity, glass-transition temperature (T_g) and rate of hydrolytic degradation. A particularly interesting monomer combination is ε-caprolactone (εCL) and glycolide (GG). Polyglycolide possesses a relatively high T_g ($\sim$30°C) and melting temperature ($T_m \approx 225°C$), whereas, poly(εCL) possesses a low T_g ($\sim -60°C$) and low T_m (60–65°C). Furthermore, glycolide sequences hydrolyze much faster than those of εCL and are also more hydrophilic due to the higher frequency of polar CO groups. Ring-opening copolymerizations of εCL and GG were studied by several research groups over the past thirty years (1–9) and a broad variety of metal salts and complexes was tested as catalysts (or initiators). In addition to binary copolymers, ternary random copolymers and block-copolymers containing εCL and glycolide were studied by numerous research groups (10–19). Quite recently, it was reported by Kricheldorf and coworkers (8, 9) that simple bismuth(III) salts as the n-hexanoate ($BiHex_3$) or the commercial subsalicylate (BiSS), also catalyze copolymerizations of εCL and GG. These copolymerizations are of particular interest for two reasons. First, it is well documented in the literature (20–22) that bismuth(III) salts such as BiSS and Bi-subcitrate have a long tradition as internal and external drug. The enormous body of information available on the toxicity of Bi-salts suggest that bismuth is the least toxic heavy metal. The low quantities of Bi^{3+} ions needed as catalysts or initiators for the preparation of biodegradable polyesters are far below the toxicity level. This aspect is important when biomedical applications of such polyesters are taken into account. Second, the sequences of εCL and G-units obtained with Bi-catalysts are unusual and differ from those obtained with tin(II) 2-ethylhexanoate ($SnOct_2$), because the formation of alternating triads (εCL-G-εCL) is favored. A predominance of these triads has the consequences that the copolymers are perfectly amorphous, the solubility does not depend on the blockiness of individual chains and the rate of hydrolytic degradation (and resorption) is homogeneous throughout a sample.

In the present work, Ph_2BiOEt-initiated copolymerizations of εCL and GG were studied for two reasons. Firstly, it was recently shown for homopolymerizations that Ph_2BiOEt yield higher molecular weights and a better control of the molecular weights (via the monomer-initiator ratio, M/I, than Bi(III) salts). Secondly, the validity of the speculative reaction mechanism published for the formation of alternating triads should be checked.

2. Experimental

2.1 Materials

Phenylmagnesium chloride (2 M in tetrahydrofuran), bismuth(III)chloride and bismuth(III)bromide were purchased

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from Aldrich Co. (Milwaukee, WI) and used as received. Ph_2BiOEt was prepared from Ph_2BiBr (synthesized from Phe_3Bi) according to the literature (22–25). ε-Caprolactone (εCL) was purchased from ACROS Organics (Geel, Belgium) and distilled over CaH_2 *in vacuo*. Glycolide was kindly supplied by Boehringer (Ingelheim/Rhein, Germany), twice recrystallized from ethyl acetate and stored over P_4O_{10}.

2.2 *Polymerization (No. 1, Table 1)*

In an atmosphere of dry argon ε-caprolactone (40 mmol), glycolide (20 mmol) and Ph_2BiOEt (0.06 mmol) were weighed into a 25 mL Erlenmeyer flask having silanized glass walls. TEG (1.5 mmol) was injected in the form of a 0.5 M solution in toluene. The reaction vessel was closed with a glass stopper and steel spring and immersed into an oil bath preheated to 100°C, and the temperature was rapidly raised to 140°C. Small samples were removed in certain time intervals to determine the conversion. Since the polymerization of glycolide was faster than that of εCL, the polymerization was stopped when the conversion of εCL had reached ≥97%. The virgin reaction products were characterized.

All other polymerizations listed in Tables 1–3 were performed analogously.

2.3 *Measurement*

The inherent viscosities were measured in DMSO with an automated Ubbelohde viscometer thermostated at 30°C. The 400 MHz ^{1}H-NMR spectra and the 100.4 MHz ^{13}C-NMR spectra were recorded on a Bruker "Avance 400" FT spectrometer in 5 mm o.d. sample tubes. DMSO-d_6 or $CDCl_3$ containing TMS served as solvents.

3. Results and Discussion

3.1 *Copolymerizations with TEG as Coinitiator*

Nearly or perfectly random copolymers of εCL and GG are amorphous and possess glass transition temperatures (T_gs) that may vary from +30/+35°C to −65/−70°C with increasing content of εCL. Therefore, these random copolyesters are not suited as engineering plastics, but they may be useful as soft segments in block copolymers. For such an application, a telechelic structure with two OH endgroups is particularly useful. Therefore, TEG was used as coinitiator in previous studies dealing with Bi(III) as initiators (8, 9). In these previous studies, the copolymerizations were conducted in bulk at temperatures of 120 or 140°C. To facilitate comparisons, these reaction conditions were also used in the present work.

Table 1. TEG-coinitiated copolymerizations of εCL and GG (2:1) at 140°C in bulk with constant monomer-initiator ratio (M/I = 1000/1) and variation of the monomer/TEG ratio

						^{1}H-NMR/ εCL		^{13}C-NMR/ εCL		^{1}H-NMR/G		^{13}C-NMR/G	
Expt. no.	Initiator	Mon.[a]/ TEG	Time (h)	Conv. (%)	εCL/G (found)	L_{CL}	% alt.	L_{CL}	% alt.	L_G	% alt.	L_G	% alt.
1	Ph_2BiOEt	40/1	5.0	96.5	0.95/1.0	1.24	81	1.24	81	1.30	76	1.31	76
2	Ph_2BiOEt	200/1	6.0	96.5	1.0/1.0	1.32	76	1.40	73	1.30	77	1.28	77
3	Ph_2BiOEt	1000/1	7.0	97.0	1.0/1.0	1.36	73	1.40	73	1.36	74	1.40	73
4	$SnOct_2$	40/1	2.0	95.5	1.0/1.0	1.49	67	1.46	69	1.48	68	1.45	70
5	$SnOct_2$	200/1	2.0	98.0	1.0/1.0	2.10	50	2.15	50	—	—	—	—
6	$SnOct_2$	1000/1	2.0	98.0	1.0/1.0	2.50	39	2.62	38	2.57	39	2.55	39
7	Ph_3Bi	40/1	24.0	96.0	0.90/1.0	1.35	75	1.35	78	1.25	80	1.23	80

[a] Sum of both monomers.

Table 2. TEG-coinitiated copolymerizations of εCL and GG (2:1) at 100°C in bulk with Ph_2BiOEt-initiator (M/I = 1000/1) and variation of mon./TEG ratio

					^{1}H-NMR/εCL		^{13}C-NMR/ εCL		^{1}H-NMR/G		^{13}C-NMR/G	
Expt. no.	Mon.[a]/TEG	Time (h)	Conv. (%)	εCL/G (found)	L_{CL}	% alt.	L_{CL}	% alt.	L_G	% alt.	L_G	% alt.
1	40/1	55	97.0	1.0/1.0	1.55	65	1.60	62	1.60	62	1.52	66
2	200/1	65	96.5	1.0/1.0	2.20	42	2.20	46	2.45	40	2.50	40
3	1000/1	55	97.0	1.2/1.0	2.50	45	2.40	42	2.80	35	2.75	36

[a] Sum of both monomers.

Table 3. Ph_2BiOEt-initiated copolymerization of εCL and GG (2:1) in bulk at 120°C

Expt. no.	Temp. (°C)	Mon./Init.	Conv. (%)	Time (h)	$\eta_{inh}{}^{a}$ (dL/g)	εCL/G^{b} (found)	^{1}H-NMR/ εCL		^{13}C-NMR/ εCL		^{1}H NMR/G		^{13}C NMR/G	
							$L_{CL}{}^{c}$	% alt.^{d}	$L_{CL}{}^{c}$	% alt.^{d}	$L_{G}{}^{c}$	% alt.^{d}	L_{G}^{c}	% alt.^{d}
1	140	40/1	99	25	0.30	1.00/1.0	1.44	70	1.38	73	1.44	70	1.37	71
2	140	1000/1	98	25	0.74	0.97/1.0	1.57	64	1.59	63	1.50	66	1.47	68
3	120	40/1	98	25	0.31	0.86/1.0	1.73	58	1.80	55	—	—	—	—
4	120	200/1	97	25	0.63	0.85/1.0	2.05	50	2.00	52	2.05	52	2.10	49
5	120	600/1	96	77	0.57	0.96/1.0	2.20	46	2.15	47	2.30	42	2.35	41

[a] Measured at 20°C with $c = 2$ g/L in CH_2Cl_2.
[b] Determined by ^{1}H-NMR spectroscopy.
[c] Average block lengths of εCL or G units.
[d] Percentage of alternating triads εCL-G-εCL.

All copolymerizations performed with TEG in bulk at 140°C were compiled in Table 1. To avoid fractionation the reaction products were not precipitated and the virgin copolyesters were characterized by ^{1}H- and ^{13}C-NMR spectroscopy. Both types of NMR spectra were evaluated with regard to the average block lengths of εCL and G units and with regard to the percentage of alternating triads εCL-G-εCL and G-εCL-G, respectively. Figures 1(A, B), and 2(A, B) present characteristic examples of such ^{1}H- and ^{13}C-NMR spectra. The comparison of these data listed in Table 1 revealed the following interesting trends. First, when the monomer/TEG ratio was varied from 40/1 to 1000/1, the percentage of alternating triads slightly decreased and the average of block lengths somewhat increased, if Ph_2BiOEt served as initiator (Nos. 1–3). In the optimum case, the percentage of alternating triads was as high as 81%. Second, the same trend was also observed for $SnOct_2$ as initiator (Nos. 4–6), but it was more pronounced. For the monomer/TEG ratio 1000/1 even a predominance of blocky sequences and alternating triads below 50% was found. Third, quite analogous to our previous studies, the Bi-initiator (here Ph_2BiOEt) yielded a higher percentage of alternating triads than $SnOct_2$ a difference which was particularly conspicuous for high monomer/TEG ratios. Fourth, Ph_3Bi was somewhat less effective in the formation of alternating triads than Ph_2BiOEt.

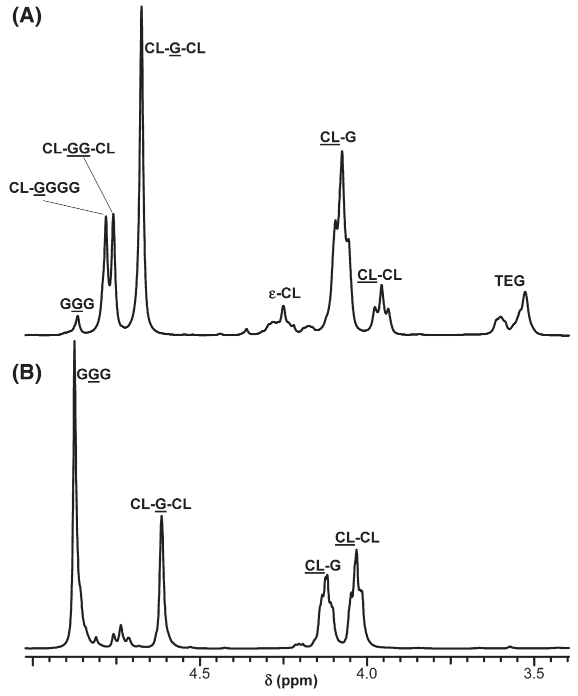


Fig. 1. 400 MHz ^{1}H NMR spectra of: (A) copolyester No. 1, Table 1, initiated by Ph_2BiOEt and measured in $CDCl_3$; (B) copolyester No. 3, Table 2 measured in DMSO-d_6.

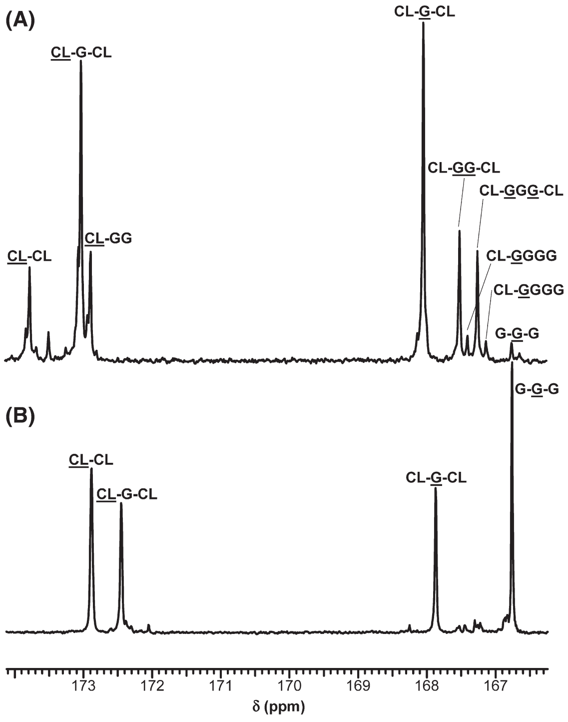
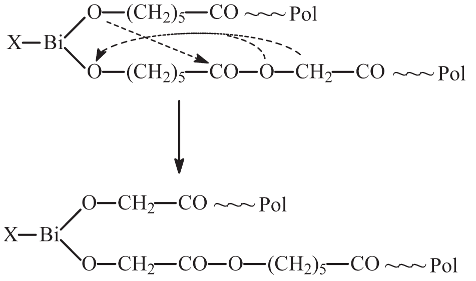


Fig. 2. 100.4 MHz ^{13}C NMR spectra of: (A) copolyester No. 1, Table 1, initiated by Ph_2BiOEt and measured in $CDCl_3$; (B) copolyester No. 3, Table 2 measured in DMSO-d_6.

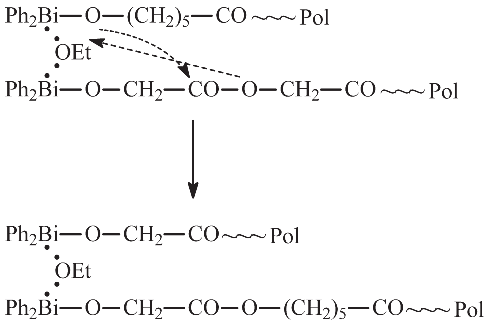
Using Ph_2BiOEt as initiator, three copolymerizations were repeated at 100°C and revealed the following tendencies. First, the percentage of alternating triads decreased considerably at higher monomer/TEG ratios, so that even blocky sequences were favored at mon./TEG ratios $\geq 200/1$. In other words, these results confirmed that the presence of TEG is highly favorable for a preferential formation of alternating triads. Second, the content of alternating triads was significantly lower (and the block lengths higher) than those found at 140°C. Quite analogous to our previous studies, this finding means that higher temperatures favor the formation of alternating triads (as illustrated in Figures 1 and 2). These results also confirm that the formation of alternating triads is based on a a special reaction mechanism and not on a general equilibration and transesterification process.

A third small series of polymerizations was conducted in such a way that neat Ph_2BiOEt was used as initiator without the addition of TEG. Two experiments were performed at 140°C with a variation of the monomer-initiator ratio (M/I) (Nos. 1 + 2, Table 3). In the absence of TEG, a significantly longer reaction time was needed to reach $\geq 97\%$ conversion of εCL. The percentage of alternating triads was somewhat lower and correspondingly, the block lengths were somewhat higher when the M/I ratio increased. This trend was also found and even more pronounced in the three copolymerizations conducted at 120°C (Nos. 3–5, Table 3). In this series, the sequences even changed from preferentially alternating to slightly blocky. Another conspicuous result is the considerably lower level of alternating triads, although the temperature was merely lowered by 20°C. Anyway, this trend parallels the same trend observed upon comparison of Table 1 and Table 2. Since even short blocks of G-units have a high tendency to crystallize copolyesters with a blocky sequence turn insoluble in many common organic solvents, so that further modification (e.g. syntheses of block copolymers) and characterization are difficult. It was found for the copolyesters of this work that with regard to solubilities these copolyesters may be subdivided into two groups. Copolyesters having average block lengths of glycolide (and ε-CL) units below 1.65 were completely soluble in $CHCl_3$, whereas all copolyesters with longer glycolide blocks required DMSO (or acidic solvents) for complete dissolution. Therefore, the "A spectra" in Figures 1 and 2 were recorded in $CDCl_3$ and the "B-spectra" in DMSO-d_6. Therefore, Ph_2BiOEt proved to be advantageous for the preparation of completely amorphous easily soluble copoly(glycolide/lactide)s.

The results of this work are also of interest from the view point of polymerization mechanisms. In previous studies of Bi^{3+}-initiated copolymerizations with GG or L-lactide, it was speculatively formulated that the formation of an alternating εCL-G-εCL triad begins with an intramolecular transesterification between two polymer chains attached to the same Bi-ion (Eq. (1)). This mechanism has at least the advantage that it can explain why the transesterification step responsible for the cleavage of a G-G bond is not a consequence of a general intermolecular transesterification and equilibration process. However, this mechanism cannot explain the results of this work based on Ph_2BiOEt unless one assumes that the true initiator is a dimeric species combining two Bi-atoms via a μ-oxo bridge (Eq. (2)). In a previous paper, evidence was presented (e.g. by crystal structure analysis) that such μ-oxo bridges indeed exist in Ph_2BiOEt, However, such a dimeric complex should be more stable at lower temperatures, whereas the experiments of this work demonstrate that formation of alternating triads are favored by higher temperatures. Another hypothesis is based on the assumption that Ph_2BiOEt partially decomposes at temperatures above 100°C (mentioned in Ref. (15)), so that two chains can indeed grow out from one Bi ion according to Eq. (1). The positive influence of higher temperatures and a positive influence of TEG which may help to cleave a Ph-Bi bond fit in with this hypothesis. None the less, all these hypotheses are highly speculative and a convincing explanation of all observed trends cannot be offered at this time.



(1)



(2)

4. Conclusions

The two main conclusions which may be drawn from this work concern a preparative and a mechanistic aspect. First, Ph_2BiOEt-initiated copolymerizations preferentially yield amorphous copolyesters which are easy to modify and process from solution or from the melt. With TEG as coinitiator, these copolyesters have a telechelic structure and allow for chain extension at both ends. Second, Ph_2BiOEt favors soft sequences under certain conditions and the mechanism speculatively proposed in previous publications for $Bi^{\oplus}$-initiated copolymerizations cannot explain these results. Furthermore, the following trends are worth noting. Alternating triads are favored by higher temperatures, by the addition of TEG and by lower M/I ratios. A satisfactory explanation for these trends is not available at this time.

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