Application of Calcium Acetylacetonate to the Polymerization of Glycolide and Copolymerization of Glycolide with ϵ-Caprolactone and L-Lactide

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Received December 22, 1998
Revised Manuscript Received May 10, 1999

Introduction. Biodegradable polymer-based implants, particularly those prepared from polyglycolide and glycolide/lactide copolymers, are widely used in medicine. The screws, nails, or other such implantable items find a broad range of applications in surgical operations, including treating bone fractures[1,2] or injuries of some internal organs.[3−5]

These copolymers also have applications in many therapeutic processes such as controlled drug release carriers in forms of films, microspheres, nanospheres, etc.[6]

In practice, almost all glycolide copolymers commercially used, and polyglycolide as well, are prepared via polymerizations conducted in the presence of tin initiators.[5,7−9]

It is practically impossible to entirely remove the tin compounds from the obtained polymers. This is a concern, since the tin compounds (in particular organometallic ones) are characterized by high toxicity. They are particularly dangerous for the health of young children.[10]

Also, chelate complexes, most often those of tin and aluminum, were used as the initiators of lactide polymerization.[11−14]

Much less toxic is the metallic zinc-based catalysts used to prepare soluble copolymers of lactide with glycolide.[15,16] Kricheldorf also conducted the copolymerization of glycolide with ϵ-caprolactone and lactide in the presence of zinc lactate.[17] Nevertheless, it is essential to search for initiators containing metals which are not harmful for the human organism, especially those taking part in metabolic processes, such as Ca, Mg, and Fe. Kricheldorf performed the copolymerization of glycolide with ϵ-caprolactone in the presence of iron compounds.[18] Brown et al.[19] polymerized glycolide using a series of typical anionic initiators in solution of sulfolane at 120 °C to afford low molecular weight polymers.[19]

With the use of typical nonmetallic anionic initiators for the copolymerization of glycolide with ϵ-caprolactone, only homopolymerization of glycolide was found to occur.[18] So far, calcium compounds, such as calcium carbonate or calcium oxide[20] have been used exclusively to polymerize lactide. However, only low molecular weight polymers in low yields were obtained. Calcium hydride has also been used to synthesize polylactide/poly(ethylene glycol)/polylactide block terpolymer.[21]

Unexpectedly, the use of calcium acetylacetonate has allowed us to obtain a high molecular weight homopolymer of glycolide, as well as copolymers of glycolide with lactide and with ϵ-caprolactone. The reactions were conducted at 150 and 200 °C. When the process was performed at the higher temperature, the materials obtained were yellow.

Due to the high melting temperature of polyglycolide blocks, the copolymerization reactions proceeded in many cases in a heterogeneous system: liquid monomer−suspension of polymer.

Experimental Section. Monomers and Initiators. Glycolide (Boehringer Ingelheim, Germany) and L-lactide (Aldrich Corp., Germany) were used as supplied with no additional purification; ϵ-caprolactone (Fluka, Buchs, Switzerland) was dried and distilled under argon prior to use.

Anhydrous calcium acetylacetonate was used as a commercial product (Fluka, Buchs, Switzerland).

A Procedure for Polymerization and Copolymerization. The polymerizations of glycolide and copolymerization of glycolide with lactide and ϵ-caprolactone were performed in bulk at 150 and 200 °C by conventional methods, using a vacuum line for degassing and sealing the ampules. The copolymers were ground and shaken with methyl alcohol in order to remove the unreacted monomers, followed by drying under vacuum at 50 °C.

Measurements. The viscosity numbers were determined in 1,1,1,3,3,3-hexafluoro 2-propanol (HFIP) at 25 °C using the Ubbelohde viscometer. The concentration of the solution was 2 g/dm^3.

The ^{1}H NMR spectra of the copolymers were recorded at 300 MHz using a Varian Unity Inova spectrometer and 5 mm sample tubes. Dried DMSO-d_6 was used as solvent. The spectra were obtained at 100 °C with 32 scans, 3.74 s acquisition time, and 7 μs pulse width.

The ^{13}C NMR spectra (75 MHz) were performed on a Varian Unity Inova spectrometer using 5 mm sample tubes and dried DMSO-d_6: measurement temperature 100 °C, 3000 scans, acquisition time 1.8 s, pulse width 9 μs, and delay of 3 s between pulses.

The copolymer chain microstructure and the transesterification process were studied by means of ^{1}H and ^{13}C NMR spectroscopy.[14,18,22]

Thermal properties, such as glass transition temperatures and heats of melting, were determined by differential scanning calorimetry using a DSC Du Pont 1090B apparatus, calibrated with galium and indium. The heating rate was 20 deg/min.

The yields of reactions were observed by weighing washed copolymers and by NMR.

Results and Discussion. The results of our study on the polymerization of glycolide and its copolymers with L-lactide are summarized in Table 1.

After 1 h reaction time the polyglycolide obtained (Table 1, nos. 1C and 1D) was insoluble in HFIP at 25 °C due to its high molecular weight. In contrast, a reaction time $\leq {}^1/_2$ h produced a soluble polymer (Table 1, nos. 1A and 1B). As polyglycolide is known to be soluble in this solvent when its number-average molecular weight is below 40 000, the M_n of the obtained polymer can be expected to exceed this value.

The high molecular weight of the polyglycolide was confirmed by differential scanning calorimetry. The DSC trace presented in Figure 1a is characteristic for a polyglycolide with high molecular weight.[23] This thermogram exhibits only the endothermic peak at 225 °C due to melting, whereas the glass transition tempera-

10.1021/ma981969z CCC: $18.00
Published on Web 06/18/1999

Table 1. Polymerization of Glycolide and Copolymerization of Glycolide with L-Lactide[a]

no.	f_{GG} (%)	time	yield (%)	F_{GG} (%)	l_{GG}	l_{LL}	η_{inh} (dL/g)	M_v
1A	100	10 min	15	100	∞	0	0.24	
1B	100	30 min	28	100	∞	0	0.64	
1C	100	1 h	42	100	∞	0	insoluble	
1D	100	1 day	85	100	∞	0	insoluble	
2	100	6 h	88	100	∞	0	insoluble	
3	80	4 days	89	85	8.8	1.6	0.75	39800
4A	50	1.5 h	24	71	17.0	6.9	0.25	9900
4B	50	1 day	70	60	6.2	4.1	0.62	31300
4C	50	3 days	82	55	5.0	4.1	0.78	41800
4D	50	9 days	96	52	4.1	3.8	0.84	45900
5	15	9 days	90	16	2.7	14.2	0.52	25000

[a] Polymerization in bulk. Temperature: 150 °C (no. 2, temperature 200 °C). f_{GG}, initial content of glycolide in monomers mixture (mole percent). F_{GG}, contents of glycolide in copolymer (mole percent). l_{GG}, average length of glycolidyl blocks in copolymer chains. l_{LL}, average length of caproyl blocks. η_{inh}, inherent viscosities (dL/g). M_v, viscosity average molecular weight; calculated in [24].

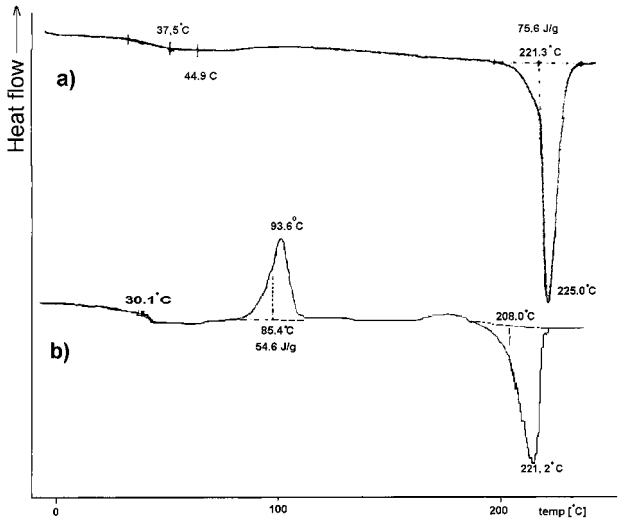

Figure 1. DSC thermograms of glycolide polymer: (A) conversion 15% (Table 1, no. 1A); (B) conversion 85% (Table 1, no. 1D).

ture is above 34 °C. In the case of low molecular weight polyglycolide the additional, an exothermic peak of crystallization is clearly visible (Figure 1b), being consistent with earlier observations by Cohn.[23]

When polymerization was carried out at 200 °C a higher conversion degree in a shorter period was observed (Table 1, No 2). However, the resulting product was brown due to thermal degradation processes.

Table 1 also provides the results of our investigations on copolymerization of glycolide with L-lactide (Table 1, nos. 3, 4A−D, and 5). A series of copolymers with various contents of glycolidyl units were obtained in high yields.

From the presented data, it follows that in the initial step of the reaction mainly glycolide is added to the growing chain, resulting in the formation of the copolymer containing long glycolide blocks (Table 1, no. 4A, Figure 2). Then the chain growth is accompanied by a decrease in the average block length, as well as by an increase in the content in lactyl units (Table 1, nos. 4B−D, Figure 2). After 9 days of the reaction the copolymer obtained in nearly 100% yield is characterized by the inherent viscosity of η_{inh}= 0,84 dL/g (measured in HFIP solution), which according to the calculations previously

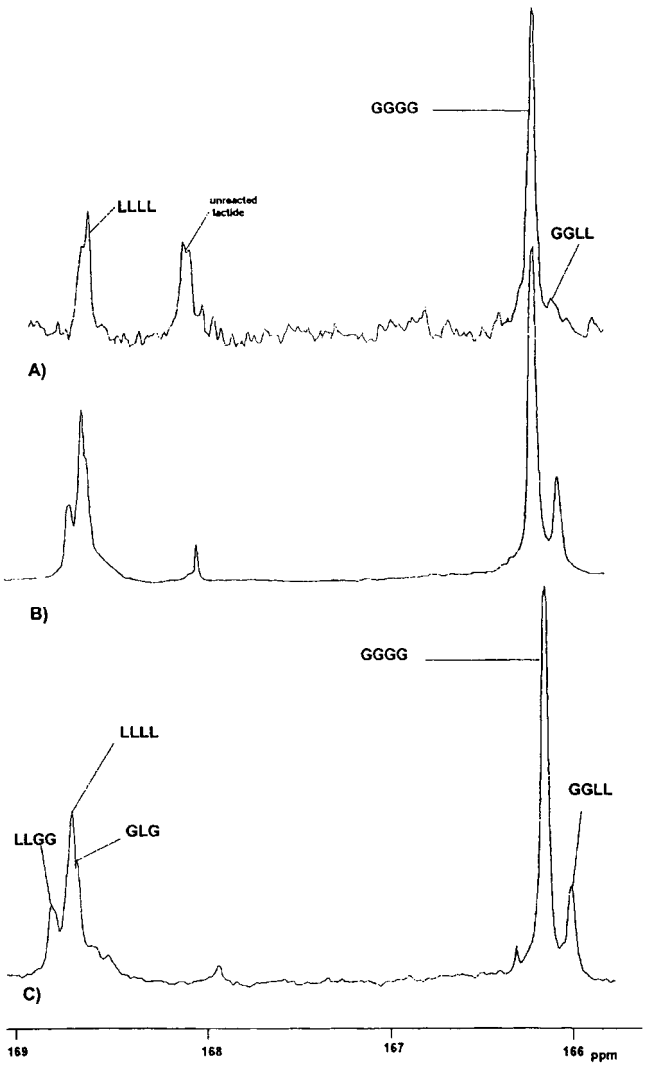

Figure 2. ^{13}C NMR spectra of glycolide/L-lactide copolymers obtained at different conversion: (A) conversion 24% (Table 2, no. 4A); (B) conversion 70% (Table 2, no. 4C); (C) conversion 96% (Table 2, no. 4D).

Table 2. Copolymerization of Glycolide with ϵ-Caprolactone at 150 °C[a]

no.	f_{GG} (%)	time	yield (%)	F_{GG} (%)	l_{GG}	l_{Cap}	η_{inh} (dL/g)
1	80	1 day	92	82	6.24	1.37	0.75
2A	30	1/2 h	30	31	1.28	2.85	
2B	30	1 h	40	27	1.16	3.13	
2C	30	8 h	50	29	1.27	3.10	0.52
2D	30	3 days	75	28	1.15	2.95	0.79
2E	30	10 days	97	31	1.25	2.78	1.1

[a] f_{GG}, initial content of glycolide in monomers mixture (mole percent). F_{GG}, contents of glycolide in copolymer (mole percentage). l_{GG}, average length of glycolidyl blocks in copolymer chains. l_{Cap}, average length of caproyl blocks. η_{inh}, inherent viscosities.

made by Kenley[24] corresponds to the viscosity average molecular weight of M_v = 45 900 (Table 2, no. 4D). The above values are comparable with the values of viscosity obtained by Kricheldorf for copolymerization of glycolide with lactide initiated by zinc lactate.[17]

The average lengths of lactidyl and glycolidyl blocks are close to those of respective blocks in the copolymer prepared under similar conditions in the presence of zinc lactate.[17] However they were nearly two times higher as compared with the corresponding blocks of the copolymer obtained when using tin octoate.[14] It suggests a lower degree of transesterification achieved during

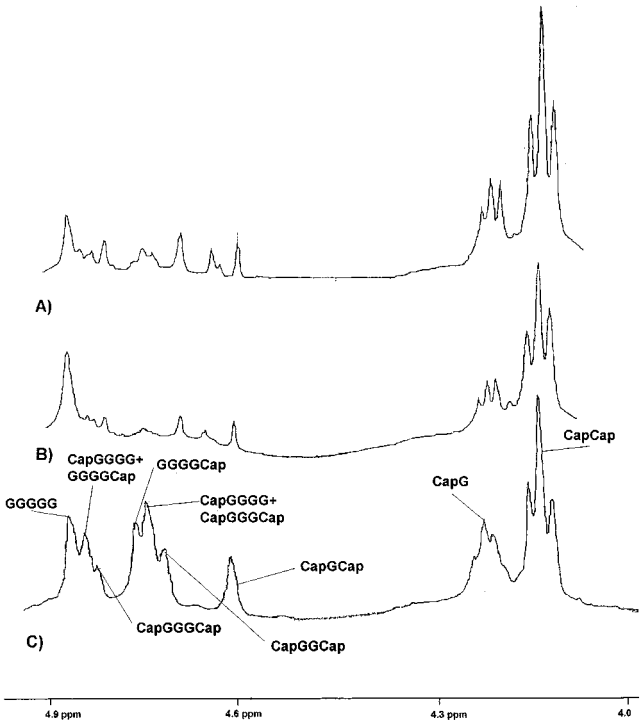

Figure 3. ^{1}H NMR spectra of glycolide/ϵ-caprolactone copolymers obtained at different conversions: (A) conversion 30% (Table 3, no. 2A); (B) conversion 75% (Table 3, no. 2D); (C) conversion 97% (Table 3, no. 2E).

copolymerization in the presence of calcium acetonate than in the presence of tin compounds. Nevertheless the ^{13}C NMR spectra exhibit the lines due to the −GLG− sequences showing the intermolecular transesterification processes (Figure 2).

The results concerning copolymerization of glycolide with caprolactone are presented in Table 2. High conversion degrees and viscosities similar to those observed in the copolymerization with lactide were obtained.

During the progress of the reaction, the composition of the forming copolymer was constant and was the same as the feed composition of the mixture of comonomers. This is a surprising observation, since in the copolymerization processes of glycolide with caprolactone with coordinating initiators described up to now[18,22] glycolide was added to the active chain preferentially. Also the lengths of the glycolidyl and caproyl blocks remain practically unaltered (Table 2, no. 2A−D).

During copolymerization, in the copolymer chain a high content of the segments of the −CapGCap− type is observed (Figure 3), formed as a result of the cleavage of glycolidyl units (GG). The average lengths of blocks in the obtained copolymer are shorter than those found in analogous copolymer synthesized in the presence of zinc lactate,[17] whereas their length is close to those observed in the copolymer obtained with tin compounds,[18,22] the latter being strong transesterification agents. It suggests a strong intermolecular transesterification effect on the course of the reaction.

High yields indicate the lack or low contribution of intramolecular transesterification reaction ("back-biting") during the copolymerization conducted.

A possibility of obtaining homopolymers of glycolide with high molecular weights, as well as random copolymers of glycolide with caprolactone, clearly shows the process described by us to differ considerably from the typical anionic polymerization reported in earlier works.[18,19]

Acknowledgment. The study has been supported by the research program (Project 3T09B09513 of the Commitee of Scientific Research in Poland).

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