Polymer Bulletin 42, 131–139 (1999)

Polymer Bulletin

Application of zirconium (IV) acetylacetonate to the copolymerization of glycolide with ε-caprolactone and lactide

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Received: 13 October 1998/Revised version: 4 January 1999/Accepted: 4 January 1999

Summary

A study on the copolymerization of glycolide with lactide and glycolide with ε-caprolactone was performed in the presence of zirconium (IV) acetylacetonate at moderate temperatures (100° and 150°C).

Zirconium acetylacetonate appeared to be an efficient initiator of copolymerization. The obtained polymers were characterized by high molecular weights. Considerable influence of transesterification on the polymer chain microstructure was found.

Introduction

In several recent years a growing interest has been focused on biodegradable copolymers such poly(glycolide-co-lactide) and poly(glycolide-co-ε-caprolactone). The screws, plates and other implants made of such materials are applied in medicine during surgical operations when treating the bone fracture[1-3] or injury of some internal organs, like bladder, stomach, etc.[4-7]. The copolymers are also widely used as the materials for the drug carriers (films, microspheres, nanospheres, etc.) used in the process of the controlled drug release[8].

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Practically all these polymers, including commercial polyglycolide Dexon® [9-10], copolymer of glycolide with lactide - Vicryl® [11] or segmented copolymer of glycolide with ε-caprolactone - Monocryl® [7,12] are obtained by polymerization carried out in the presence of tin initiators.

A complete removal of the tin compounds from the obtained polymers is not possible. On the other hand the tin compounds (especially the organic ones) and tin complexes are known to be highly toxic. They are particularly dangerous to the health of babies and young children[13]. Antigenic activity of the tin organic compounds and complexes was also observed. It is augmented by their cumulation in the lung tissue and brain[14].

Zirconium compounds may be considered as initiators which are tens times less toxic than analogous tin compounds[13]. The drugs and cosmetics containing zirconium compounds are under the control and admitted by FDA (Food and Drug Administration) for use[13].

Up to date zirconium compounds have not been widely used to initiate the polymerization of lactones and lactides. An attempt to polymerize LL-lactide was made using zirconium (IV) n-propoxylate as the initiator[15]. The polymerization was carried out at 100°C to afford polylactide with the molecular weight below 17 000 in 89-97% yield.

The polymerization of ε-caprolactone was also performed in the presence of zirconium (IV) propoxylate [15] and zircocene complex [16].

In our work we present the results of a study on the copolymerization of glycolide with ε-caprolactone and glycolide with LL-lactide as well as homopolymerization of LL-lactide in the presence of zirconium (IV) acetylacetonate. The copolymerization was conducted at moderate temperatures (100°-150°C). Under these conditions the transesterification process was found to occur, and the influence of transesterification on the chain microstructure was determined. In most cases due to a high melting temperature of polyglycolide blocks the copolymerization proceeded in heterogeneous system of liquid monomer/suspension of polymer. The copolymer chain microstructure and the influence of transesterification were examined by means of ^{1}H and ^{13}C NMR spectroscopy, the utility of which was demonstrated in our earlier works [17-19].

In our previous work concerning the copolymerization of lactide with ε-caprolactone[17] we defined two basic modes of transesterification. In the first transesterification mode a cleavage of polylactide block occurs between lactidyl units (LL) originating from the monomer molecules (dilactide). The second mode of transesterification involved also a cleavage of lactidyl groups leading to the formation of

Cap-L-Cap chain sequences, where L designates the lactyl group, and Cap stands for the caproyl group.

The same definition of the second mode of transesterification can be applied for the copolymerization of glycolide with ε-caprolactone. In our earlier works we introduced a parameter describing the extent of the second transesterification mode [18].

According to the previously accepted definition [18,19]:

$T_{II} = [L\text{-}G\text{-}L]/[L\text{-}G\text{-}L]_R$, $T_{II} = [G\text{-}L\text{-}G]/[G\text{-}L\text{-}G]_R$

or $T_{II} = [Cap\text{-}G\text{-}Cap]/[Cap\text{-}G\text{-}Cap]_R$

where:

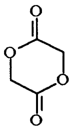
[L-G-L], [G-L-G] or [Cap-G-Cap] - the relative amount of the sequences in the copolymer chain;

$[L\text{-}G\text{-}L]_R$, $[Cap\text{-}G\text{-}Cap]_R$ or $[Cap\text{-}G\text{-}Cap]_R$ - the relative amount of the sequences calculated on the basis of Bernoullian statistics.

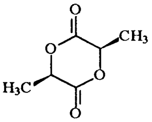
Experimental

Monomers and initiators

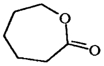
Glycolide (Boehringer Ingelheim, Germany) and LL-lactide (Aldrich Corp., Germany) were used as supplied with no additional purification; ε-caprolactone (Fluka, Buchs, Switzerland) was dried and distilled under argon prior to use.



glycolide



L-lactide



ε-caprolactone

Zirconium (IV) acetylacetonate was used as a commercial product (Aldrich Corp., Germany).

A procedure of copolymerization

The copolymerizations of glycolide with lactide and glycolide with ε-caprolactone were performed in bulk at 100°-150°C by conventional method using a vacuum line for degassing and sealing of the ampoules. The obtained copolymers were ground and shaken with hexane and methyl alcohol in order to remove the unreacted monomers, followed by drying under vacuum in the temperature of 50°C.

Measurements

The molecular weights of the resulting copolymers were determined by means of liquid chromatography method using a Waters ALC/GPC 3M apparatus. Tetrahydrofuran (THF) or hexafluoroisopropanol (HFIP) were used as eluent and polystyrene standards served for calibration.

The GPC experiments were conducted in THF or HFIP solution at 35°C (flow rate 1 mL/min.) using a Spectra-Physics SP 8800 gel permeation chromatograph equipped with IR detector. The column configuration consisted of two styragel-packed columns 500 Å (Polymer Laboratories). The number-average molecular weight (M_n) and the polydispersity index (M_w/M_n) were estimated according to the polystyrene calibration curve.

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

The ^1H NMR spectra of the copolymers were recorded at 300 MHz resonance frequency on a Varian Unity Inova spectrometer in 5 mm sample tubes. Dried DMSO-d_6 was used as a 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 obtained on a Varian Unity Inova spectrometer in 5 mm sample tubes in DMSO-d_6; measurement temperature 100°C, 3000 scans, acquisition time 1.8 s, pulse width 9 µs and deley of 3 s between pulses.

Results and discussion

Table 1 presents the results concerning the copolymerization of glycolide with LL-lactide as a function of the initial contents of the comonomers.

The copolymerization reaction in the presence of $Zr(acac)_4$ used as the initiator proceeded in nearly 100% yield. The copolymers obtained are characterized by high molecular weight. In the chain microstructure the lactidyl and glycolidyl microblocks can be distinguished (Fig 1, Table 1 No.3). In the polymer chain a large number of G-L-G sequences are observed. They result from the second transesterification mode. Sequences L-G-L also exist, although their amount is low.

Table 2 provides the results of a study on the copolymerization and the influence of copolymer composition and reaction temperature on the chain microstructure of glycolide/ε-caprolactone copolymer. Also in this case the high yields, close to 100%, and high molecular weights of the copolymers were obtained.

Table 1. Copolymerization of glycolide with LL- lactide.

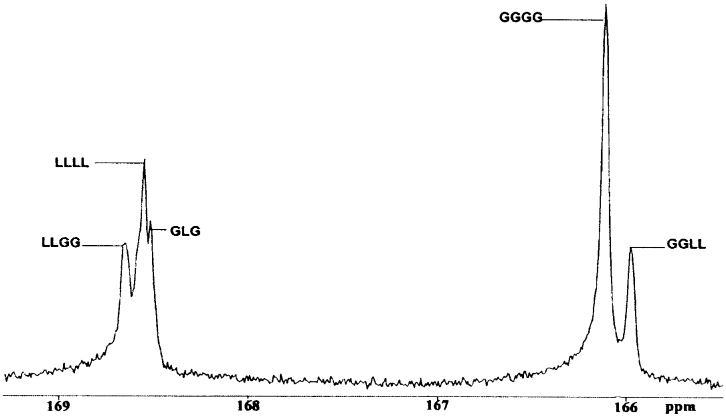
No	N^o_G %	temp ^oC	Y %	N_G %	l_{GG}	l_{LL}	T_{II} [LGL]	T_{II} [GLG]	η_{inh}	M_v $x10^{-3}$
1	100	150	92	100	∞	0.0	---	---	not soluble	---
2	80	100	98	85			not observed		3.5	277
3	50	100	98	53	4.1	3.8	0.3	1.4	2.2	154
4	15	100	93	19			0.2		1.5	95
5	0	100	96	0	0.0	∞	---	---	2.0	137

Polymerization in bulk. Molar ratio of initiator to monomer 1.2 $x10^{-3}$.

Reaction time: 120 h (No 2, 3, 4, 5) and 48 h (No 1)

N^o_G - initial content of glycolide in the mixture of monomers (molar percentage)
N_G - contents of glycolide in copolymer (molar percentage)
Y - total conversion of the reaction
l_{GG} - average length of glycolidyl blocks in copolymer chains
l_{LL} - average length of lactidyl blocks
T_{II}[LGL] - yield of the second mode of transesterification (sequences LGL)
T_{II}[GLG] - yield of the second mode of transesterification (sequences GLG)
η_{inh} - inherent viscosity (dL/g)
M_v - viscosity-average molecular weight; calculated in [20]

Figure 1. ^{13}C NMR (75 MHz) spectra of poly(glycolide-*co*-LL lactide) (Tab.1, pos No3) obtained in the presence of $Zr(acac)_4$ (carbonyl region).



An increase in the reaction temperature leads to a general shortening of the average length of glycolidyl and caproyl microblocks. It is accompanied by an increase in the relative amount of Cap-G-Cap segments formed as a result of the bond cleavage in glycolide segments (the second mode of transesterification, Table 2, Fig. 2). This observation indicates a large extent of transesterification when the reaction is performed at higher temperatures. When the initial amount of glycolide is less than 10% the copolymerization affords the copolymers soluble in THF. In this case it was possible to determine their molecular weights and polydispersity (Table 2, No. 3A, 3B). The molecular weights of the copolymers obtained in the temperature of 100°C are close to those calculated theoretically, when only one acetyloacetonate group was assumed to take part in the initiation reaction.

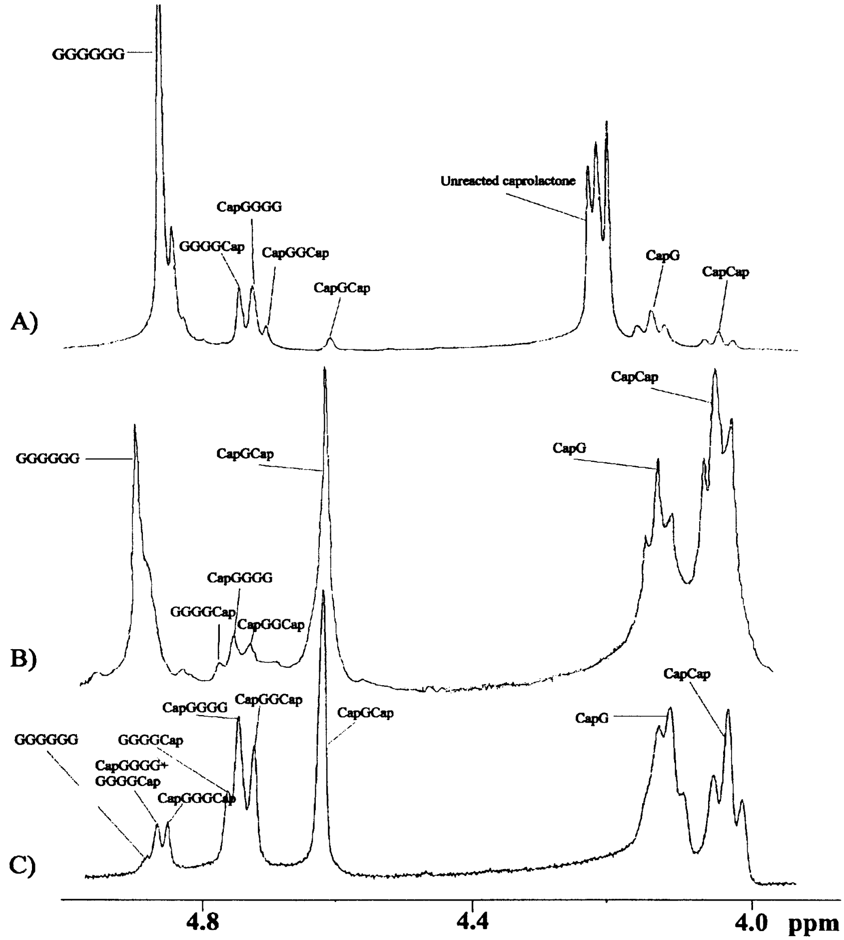
Table 2. Influence of composition and reaction temperature on the chain microstructure of poly[(glycolide)-co-(ε-caprolactone)]

No	N^o_G %	temp ^oC	Y %	N_G %	η_{inh}	M_n x10^{-3}	M_w/M_n	l_{GG}	l_{Cap}	T_{II}
1	80	100	97	80	3.1			6.7	1.8	0.86
2A	30	100	35	95	0.7			23.7	1.3	
2B	30	100	95	30	2.6	70 .2	1.9	0.9	2.7	0.96
2C	30	150	96	30	1.2	36	2.6	0.7	1.9	1.2
3A	10	100	96	11	3.4	89	2.1	0.44	4	0.92
3B	10	150	97	10	2.7	67.3	2.2	0.35	3.4	1.0

Polymerization in bulk. Molar ratio of initiator to the monomer 1.2x10^{-3}.
Reaction time: 120 h (No. 1, 2B, 3A), 3 h (No. 2A)
and 48 h (No. 2C, 3B)

N^o_G - initial content of glycolide in the mixture of comonomers (molar percentage)
N_G - contents of glycolide in copolymer (molar percentage)
Y - total conversion of the reaction
l_{GG} - average length of glycolidyl blocks in copolymer chains
l_{cap} - average length of caproyl blocks
T_{II} - yield of the second mode of transesterification
η_{inh} - inherent viscosity (dL/g)
M_n - number - average molecular weight
M_w/M_n - molecular weight distribution

Figure 2. ^{1}H NMR (300 MHz) spectra of poly[(glycolide)-*co*-(ε-caprolactone)] obtained in the presence of Zr(acac)$_4$.
A) conversion 35% (Table 2, pos. No. 2A)
B) polymerization at 100°C (Table 2, pos. No. 2B)
C) polymerization at 150°C (Table 2, pos. No. 2C)



An increase in the temperature of the process leads to the reduction in molecular weight. At considerable excess of caprolactone in the initial mixture the length of glycolide microblocks in the chain of the obtained copolymer was found to be considerably less than that of a whole glycolide unit. This observation indicates practically total cleavage of glycolide units to glycolyl subunits.

Zirconium acetylacetonate is a strong transesterificating agent, particularly in copolymerization of glycolide with ε-caprolactone at 150°C.

It is worthnoting that aside from of a high content of glycolidyl blocks in the copolymer chain, there also exist a large number of Cap-G-Cap units (Fig. 2B), accompanied by relatively low content of other types of the chain sequences.

On the basis of the presented data one can conclude that zirconium acetylacetonate is an efficient initiator of the copolymerization reactions involving glycolide, lactide and ε -caprolactone.

From the obtained results it follows that incorporating of glycolide units into the copolymer chain is favoured when copolymerizing glycolide with ε-caprolactone (Table 2 No. 2A). According to the previous studies of Kricheldorf 21) it is characterisitic for the coordination initiators.

The study has been supported by the research program (project 3TO 9B09513 of the Committee of Scientific Research in Poland).

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