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Anionic Polymerization of Lactones. 14. Anionic Block Copolymerization of δ-Valerolactone and L-Lactide Initiated with Potassium Methoxide

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ABSTRACT: The anionic block copolymerization of δ-valerolactone and L-lactide in the presence of potassium methoxide in THF at 20 °C yields "tailored" δ-valerolactone–L-lactide AB diblock copolymers exhibiting expected compositions and molecular weights. In the investigated process slight reacemization of L-lactide during polymerization occurs but transesterification and back-biting reactions do not take place. DSC measurements combined with optical microscopic observations indicate microphase separation of crystalline domains in these block copolymers.

Introduction

A growing interest in bioresorbable polymers and their biomedical and pharmaceutical applications has been observed in the past decade.[1-3] Especially, polylactide and polyglycolide constitute a very interesting group of nontoxic biomaterials[4-7] because the products of their biodegradation in living organisms are excreted in human metabolic processes.[7] Consequently they have found many applications as absorbable surgical sutures[8,9] and drug delivery systems.[10,11] However, high crystallinity[4,9,12] and low hydrophilicity[13] of these homopolymers worsen their drug permeability and compatibility with soft tissue. These problems can be overcome by block copolymerization of glycolide or lactide with ϵ-caprolactone[14-17] or poly(oxyalkylenes)[18-20] which possess good permeability and compatibility. Until now, except for Teyssie works,[21,22] the lactide block copolymers have been obtained in bulk at high temperature,[16-20] using coordinative catalysts, i.e., in conditions favoring side reactions such as transesterification or racemization. Teyssie et al.[21,22] have found recently that no transesterification reactions occur in block copolymerization of ϵ-caprolactne and L-lactide initiated with aluminum isopropoxide/isopropyl alcohol catalyst at temperatures up to 70 °C.

We have shown recently that anionic homopolymerization of a lactide initiated with potassium methoxide in THF solution at 20 °C leads to the respective polymer with a good yield.[23] In the present work we reported on the synthesis of AB type block copolymers obtained in the anionic polymerization of δ-valerolactone and L-lactide initiated with potassium methoxide carried out in THF solution at room temperature.

Experimental Section

Materials. L-Lactide was synthesized from L-lactic acid (from Fluka) according to the method described by Kulkarni et al.[24] The resulting lactide was then distilled (1 mmHg), three times recrystallized from dry ethyl acetate, and dried over P_2O_5 in vacuo. In addition, the obtained product was purified by sublimation (purity 99.95% by DSC, mp 95 °C); δ-valerolactone (from Aldrich) was distilled twice over calcium hydride in an atmosphere of dry argon. The fraction boiling at 89 °C (2 mmHg) was collected (99.8% by GC). Potassium methoxide was obtained by reaction of dry methanol with a potassium mirror. After evaporation of the excess methanol, the obtained product was heated at 60 °C in an ampule attached to the high-vacuum line (during 48 h). THF was purified according to the method described[25] and then was distilled over a sodium–potassium alloy in an atmosphere of dry argon.

Homopolymerization and Block Copolymerization. Polymerization experiments were conducted in THF solution, at 20 °C in a silanized glass apparatus. The δ-valerolactone monomer initial concentration was equal to 2.5 mol/L in each experiment. The initiator concentration was changed in the range of 1.92×10^{-2}–1.25×10^{-1} mol/L. After a definite period of prepolymerization time (ca. 5–10 min) the required amount of the second monomer (L-lactide) in a THF solution was added into the reaction mixture containing a THF solution of prepolymer. The course of homopolymerization and block copolymerization was monitored by GPC. After 15 min the block copolymerization was terminated by introduction of acetic acid (in ethyl ether) to the reaction mixture. Then the product was precipitated in methanol or a hexane/methanol mixture (volume ratio 10:1). The composition of block copolymers obtained was determined by ^{1}H NMR spectroscopy from the intensity ratio of the signals due to the prepolymer segment at $\delta = 4.08$ ppm (t, 2 H, OCH_2CH_2) and the poly(L-lactide) block at $\delta = 5.15$ ppm (q, 1 H, CH).

Measurements. ^{1}H and ^{13}C NMR spectra were run in $CDCl_3$ with TMS as internal standard using the Varian VXR-300 spectrometer. The ^{13}C NMR spectra were obtained at a temperature of 30 °C, with 30 000 scans, acquisition time 1.8 s, and

Table I
Results of Block Copolymerization of δ-Valerolactone (VL) and L-Lactide (LL) Initiated by Potassium Methoxide in THF at 25 °C[a]

sample no.	ratio of monomers in the reaction mixture (VL:LL), mol %	yield, %	mol wt of prepolym[b] M_n(calc)[c]	M_n[b]	copolym composn (mole ratio of units (VL:LL)	mol wt of block copolym M_n(calc)[c]	M_n[b]	M_w/M_n
1	80:20	98	13 000	12 700	81:19	17 160	16 200	1.39
2	58:42	99	12 500	12 200	57:43	24 900	23 500	1.40
3	51:49	98	11 900	11 600	50:50	25 000	23 900	1.41
4	39:61	97	7 900	8 000	38:62	25 200	24 900	1.45
5	20:80	99	3 600	3 500	19:81	23 600	22 100	1.40

[a] Prepolymerization of δ-valerolactone was initiated by potassium methoxide at the initial monomer concentration 2.5 mol/L in each experiment. The conversion of δ-valerolactone in the prepolymerization was higher than 99% after 5–10 min. The block copolymerization time was equal to 15 min. [b] Determined by the GPC technique in THF. [c] Calculated for 100% conversion.

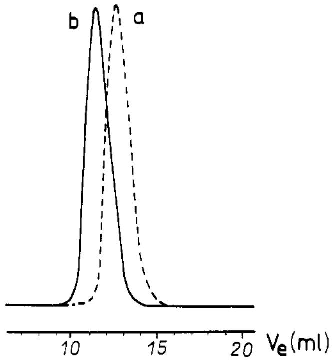


Figure 1. GPC traces of poly(δ-valerolactone-*block*-L-lactide) and its corresponding δ-valerolactone prepolymer; (a) prepolymer, M_n = 12 200; (b) block copolymer, M_n = 23 500.

pulse width 10 μs. The GPC experiments were conducted in THF (flow rate 1 mL/min), at 30 °C, by using the Spectra Physics 8800 gel permeation chromatograph. The column configuration consists of two PL gel-packed columns (10^3 and 500 Å). Molecular weights were estimated according to the PS calibration curve. Conversion of δ-valerolactone and L-lactide was measured by GPC using calibration curves for these monomers as described in ref 26. The melting behavior of homopolymers and block copolymers and that of poly(δ-valerolactone)/poly(L-lactide) blends were studied by differential scanning calorimetry. A DSC Du Pont 1090B (thermal analyzer) apparatus calibrated with indium was employed. The melting enthalpies, glass transition temperatures, and melting temperatures were determined using the Internal DSC Analysis Programme. All DSC measurements were performed with a heating rate of 20 °C/min. The thermogravimetric measurements were conducted in air by using a Q-1500-D derivatograph (MOM, Budapest). The microscopic observations were carried out by using an Axioplane optical microscope (Opton) equipped with a Mettler hot stage.

Results and Discussion

The alkali-metal alkoxides were found to act as initiators of δ-valerolactone[27,28] and L-lactide[23] homopolymerization. Therefore we performed experimental studies aimed at the synthesis of the block copolymers from the above-mentioned monomers carried out in the presence of potassium methoxide. At first δ-valerolactone prepolymer was obtained by anionic polymerization initiated with potassium methoxide. The prepolymerization yields "living" poly(δ-valerolactone) with an expected molecular weight (see Table I). When a THF solution of L-lactide was introduced into δ-valerolactone prepolymer solution, further reaction proceeded spontaneously, and after 15 minutes the L-lactide was almost entirely consumed. The obtained product shows a molecular weight higher than that of the prepolymer and a unimodal molecular weight distribution which indicate the formation of the block copolymer (Figure 1). The absence of signals due to cyclic oligomers in a GPC chromatogram of the reaction mixture suggests that no back-biting reaction takes place in the investigated process.

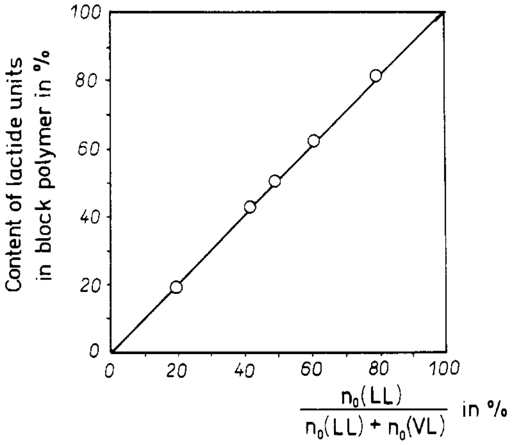


Figure 2. Relationship between the initial mole fraction of L-lactide and the content of lactide units in the various block copolymers obtained: n_0(LL) = initial amount of L-lactide (mol), n_0(VL) = initial amount of δ-valerolactone (mol).

The results of block copolymerization proceeding in THF solution at various ratios of δ-valerolactone prepolymer to L-lactide monomer are presented in Table I.

The above results indicate that poly(δ-valerolactone)–poly(L-lactide) block copolymers with expected molecular weights were obtained in good yields. The block copolymer compositions (i.e., the content of poly(δ-valerolactone) and poly(L-lactide) segments) were calculated from ^{1}H NMR spectra, as described in the Experimental Section. There exists a linear dependence between the content of lactide units in the block copolymer and the initial mole contribution of the L-lactide monomer in the reaction mixture (Figure 2).

In the ^{1}H NMR spectrum of low molecular weight δ-valerolactone-L-lactide block copolymer, besides signals characteristic of a polymer chain, signals attributed to methyl ester ($CH_3OC(O)$) and $C(O)CH(CH_3)OH$ end groups are also present (Figure 3).

The signals ratio of the hydroxyl and methine protons of the end group to the CH_3O group of the incorporated initiator was nearly 1:1:3. On the basis of these observations, the following mechanism of the anionic block copolymerization of δ-valerolactone and L-lactide initiated with potassium methoxide can be proposed (Scheme I).

The methoxide anion attacks the carbonyl carbon atom in the δ-valerolactone molecule with acyl–oxygen bond scission and formation of the methyl ester end group and the propagating alkoxide active species. Further polymerization proceeds via acyl–oxygen bond scission. When the second monomer is added to the "living" prepolymer, the block polymerization again occurs due to acyl–oxygen scission in the L-lactide molecule, leading to poly(δ-vale-

Table II
Thermal Properties of Homopolymers and Block Copolymers of δ-Valerolactone and L-Lactide[a]

sample no.	polym composn (mole ratio of units, VL:LL)	M_n (GPC)	T_d,[b] °C	melting temp, °C		melting enthalpy, J g^{-1}	
				T_{m1}	T_{m2}	ΔH_{m1}	ΔH_{m2}
1	100:0	20 900	310	55.3		97.3	
2	81:19	16 200	310	52.7		63.7	
3	57:43	23 500	315	52.1	135.7	46.4	17.7
4[c]	57:43			53.6	150.1	40.6	23.7
5	50:50	23 900	315	52.7	132.7	44.7	16.1
6	38:62	24 900	320	46.7	125.9	25.3	18.3
7	19:81	22 100	320		142.1		30.6
8	0:100	27 000	320		158.0		39.9

[a] DSC scan rate, 20 °C/min; T_m and ΔH_m, for original samples. [b] Thermal decomposition temperature determined in air for 10% mass loss of a sample. [c] Data obtained for the blend of homopolymers prepared by precipitation from a $CHCl_3$ solution of the poly(δ-valerolactone) and poly(L-lactide) mixture into cold methanol.

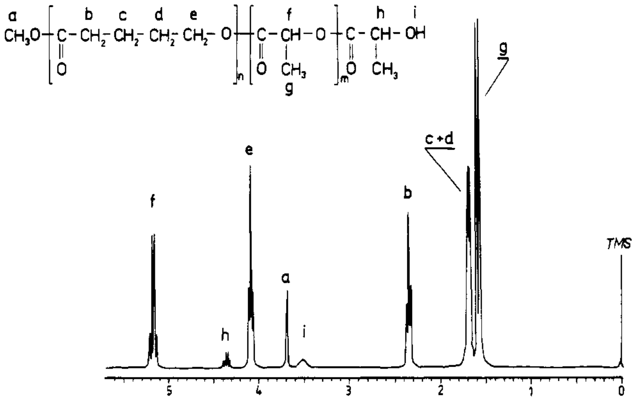
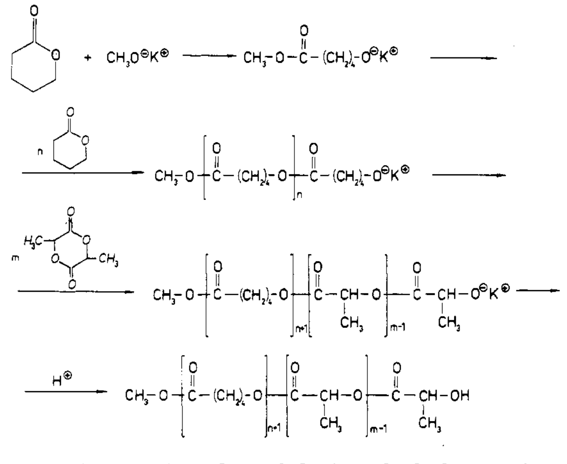


Figure 3. ^{1}H NMR (300-MHz) spectrum of poly(δ-valerolactone-*block*-L-lactide) obtained in the presence of potassium methoxide (M_n = 3200, VPO; composition VL:LL = 55:45).

Scheme I



rolactone-*block*-L-lactide) exhibiting alcoholate active centers. After termination with diluted acetic acid solution in ethyl ether, an AB type block copolymer possessing the methyl ester and hydroxyl end groups is obtained.

The ^{13}C NMR spectrum of the poly(δ-valerolactone-*block*-L-lactide) obtained in anionic polymerization initiated with potassium methoxide is presented in Figure 4. Signals characteristic of the poly(δ-valerolactone) (δ = 173.21 ppm) and poly(L-lactide) (δ = 169.05–169.70 ppm) block sequences are present in the spectrum as far as a carbonyl carbon region is concerned. In this region there are no signals of alternating valerolactone–lactide sequences,[17] thus indicating that in the investigated polymerization transesterification reaction does not occur. The polylactide carbonyl and methine carbon signals exhibit, besides lines characteristic for isotactic tetrads iii (δ = 169.56 and 69.04 ppm, respectively), several lines of slight intensities corresponding to other stereosequences.[29] The slight racemization of polylactide blocks proceeds probably by the reversible deprotonation of the monomer as proposed previously by Kricheldorf for anionic polymerization of L-lactide.[30,31] These results show that the anionic block copolymerization of δ-valerolactone and L-lactide initiated with potassium methoxide yields the poly(δ-valerolactone-*block*-L-lactide), the polylactide block having a high degree of tacticity. The above observations are consistent with those found for homopolymerization of L-lactide initiated by potassium methoxide.[23]

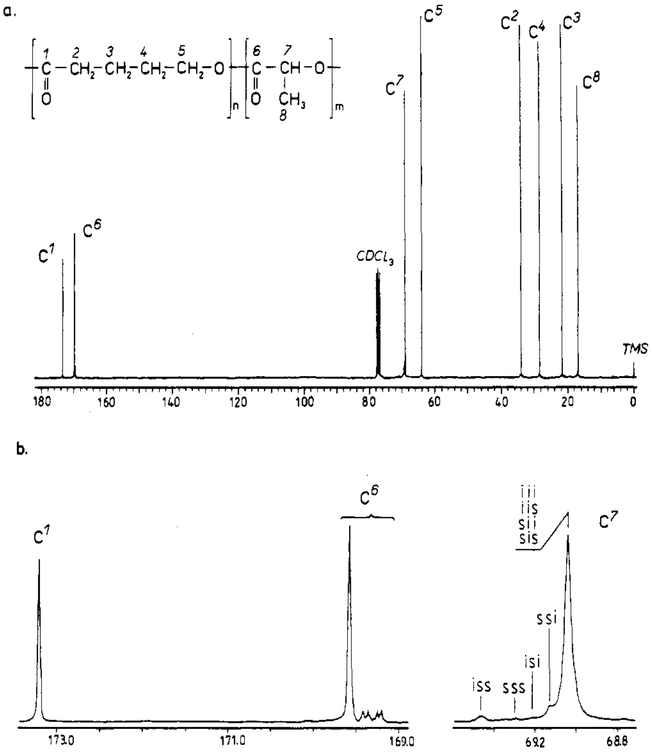


Figure 4. (a) ^{13}C NMR (75-MHz) spectrum of poly(δ-valerolactone-*block*-L-lactide) obtained in the presence of potassium methoxide (composition VL:LL = 57:43). (b) Expanded carbonyl carbons and methine carbon regions.

Thermal properties of obtained block copolymers are presented in Table II. Typical DSC traces for poly(δ-valerolactone-*block*-L-lactide) copolymers with different compositions are shown in Figure 5. Two melting endotherms observed in the case of the VL:LL = 57:43 copolymer (curve b, Figure 5) are characteristic of block copolymers with the lactide content in the range between 43 and 62 mol %.

The melting enthalpies of a given polymer depend clearly on the block copolymer composition. With the increase of the content of L-lactide units the melting enthalpy at lower temperature decreases and the melting enthalpy at

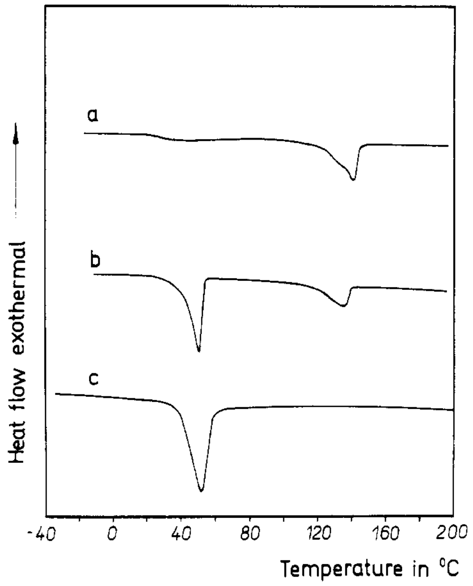


Figure 5. Typical DSC curves for original samples of block copolymers (a) VL:LL = 19:81. (b) VL:LL = 57:43. (c) VL:LL = 81:19.

higher temperature increases (Table II). For a higher content of a given monomer unit only one melting endotherm with the maximum at the temperature close to the melting point of the respective homopolymer is observed (curves a and c, Figure 5).

In order to explain the relation between the observed DSC behavior of block copolymers and their crystalline structure, the DSC analyses of the respective homopolymers and their blends were also performed. This study revealed both poly(δ-valerolactone) and poly(L-lactide) homopolymers to be crystalline materials (Table II); however, some differences in thermal properties of these homopolymers should be noted. The quenched sample of δ-valerolactone homopolymer exhibits a T_g at −66 °C and sharp, rapid recrystallization with an exotherm peak maximum at −52 °C followed by melting with an exotherm peak maximum at 52 °C. The quenched sample of poly(L-lactide) shows a T_g at 54 °C and a broad recrystallization exotherm above 100 °C with a maximum at 123 °C as well as a melting endotherm with two maxima at 151 and 158 °C (Figure 6a,b).

The DSC trace of a quenched sample of a 57/43 mol % poly(δ-valerolactone)/poly(L-lactide) blend (Figure 6d) is very similar to the DSC curve, being a simple superposition of DSC traces of respective homopolymers (Figure 6c). This fact points to the immiscibility of the homopolymer blend, a phenomenon which has been confirmed by optical microscopic observations of phase separation in this system.

The DSC trace of a quenched sample of a δ-valerolactone–L-lactide block copolymer with the same composition as the blend (VL:LL = 57:43) also exhibits two separate melting endotherms, related to δ-valerolactone and L-lactide blocks (Figure 6e). Although block copolymer is a homogeneous material, as revealed by optical microscopic observations, the DSC data indicate microphase separation of crystalline domains. Such behavior is also observed for poly(δ-valerolactone-*block*-L-lactides) with a L-lactide content between 62 and 43 mol %.

Conclusions

The anionic block copolymerization of δ-valerolactone and L-lactide initiated with potassium methoxide in THF solution leads to the respective AB type block copolymers with expected compositions and molecular weights. Block structure of the obtained copolymers is confirmed by GPC expriments as well as by DSC analysis. The polymerization is of "living" character and proceeds due to alkoxide active species formed via monomer acyl–oxygen bond cleavage. The ^{13}C NMR structural investigations on copolymers obtained indicate that a transesterification reaction does not take place in this polymerization system and that poly(δ-valerolactone-*block*-L-lactides) possessing slightly racemized polylactide blocks are formed.

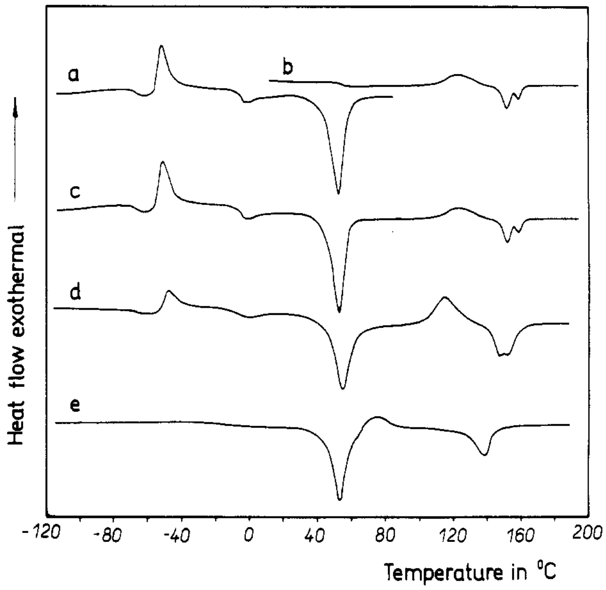


Figure 6. Typical DSC curves (heating run) of quenched samples of (a) poly(δ-valerolactone), (b) poly(L-lactide), (c) a superposition of a and b curves, (d) a blend of 57 mol % poly(δ-valerolactone) and 43 mol % poly(L-lactide), and (e) poly(δ-valerolactone-*block*-L-lactide) with composition VL:LL = 57:43 mol %.

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Registry No. δ-Valerolactone (homopolymer), 26354-94-9; L-lactide (homopolymer), 33135-50-1; (δ-valerolactone)(L-lactide) (block copolymer), 138540-50-8; L-lactide (SRU), 26161-42-2; δ-valerolactone (SRU), 26499-05-8.