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ORIGINAL CONTRIBUTION

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Mechanism of dispersion polymerization of L-lactide initiated with 2,2-dibutyl-2-stanna-1,3-dioxepane

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Abstract Biodegradable polyester microspheres were synthesized directly by ring-opening polymerization of L-lactide initiated with 2,2-dibutyl-2-stanna-1,3-dioxepane. The polymerizations were carried out at 95 °C in a mixture of organic solvents (heptane/1,4–dioxane 4:1 v:v), in the presence of poly(dodecyl acrylate)-*g*-poly(ε-caprolactone) used as a surface-active agent. Under these conditions the poly(L-lactide) synthesized was shaped into microspheres. The absence of new particles in the polymerizations with multistep monomer addition indicated that after the formation of particle seeds the propagation proceeds exclusively inside the microspheres. The mean volume of these microspheres was proportional to the monomer conversion. It was found that regardless of the initiator concentration the average number of poly(L-lactide) macromolecules in one microsphere was 1.84×10^8. Matrix-assisted laser desorption ionization time of flight spectroscopy of poly(L-lactide) in the microspheres indicated that the propagation in the particles was accompanied by intra- and intermolecular transesterification side reactions, resulting in reshuffling of the polymer segments and the formation of cyclic oligomers.

Keywords L-Lactide · Dispersion polymerization · Formation of microspheres

Introduction

Biodegradable polyesters [often polylactides, poly(ε-caprolactone), poly(lactide-*co*-glycolide)] formulated into microspheres and other particulate materials were used as carriers of antibiotics, antimicrobial agents, steroids, polypeptides (vaccination), and other bioactive compounds [1–5]. The microspheres were obtained from presynthesized polymers, mainly by precipitation–evaporation methods [6]. The diameters of the microspheres obtained in this way were controlled in a range from 5 to 400 μm; however, the diameter distributions were very high (typically the coefficient of variation was close to 30%). For controlled targeting microspheres with narrow diameter distributions are needed [4]. Two of us (S.S. and S.S.) found methods of synthesis of polylactide and poly(ε-caprolactone) microspheres with low diameter polydispersity [7–10]. The kinetics and the mechanism of particle formation were investigated for dispersion polymerization of ε-caprolactone [9–12]. However, very little was known on dispersion polymerization of lactides. In our earlier studies we used tin(II) 2-ethylhexanoate as an initiator. This compound, often used to initiate polymerizations of lactides in bulk and in solution, also found application in industrially important processes. Unfortunately, it was difficult to control the molecular weight and the molecular-weight distributions of the polylactides obtained in polymerizations of lactides initiated with tin(II) 2-ethylhexanoate. Recently, it has been established that protic compounds (water or alcohols present in trace amounts or added deliberately) act as cocatalysts in the polymerizations of lactides initiated with tin(II) 2-ethylhexanoate and true active species with –Sn–O*R* groups propagate by

monomer insertion mechanism [13–15]. In polymerizations initiated with tin alkoxides [$>Sn(OR)_2$ and $Sn(OR)_2$] the alkoxide active centers are present from the very beginning, allowing much better control of the molecular weight and the molecular-weight distribution of the polymers obtained [16–18]. Thus, for studies of the dispersion polymerization of L-lactide we chose 2,2-dibutyl-2-stanna-1,3-dioxepane (DSD) as an initiator; this has been used in polymerizations of lactides and lactones in solution [16, 19, 20].

Experimental

Syntheses

DSD used as an initiator was synthesized as described previously [21]. The purification of the monomer, the solvents, and the processes of the dispersion polymerizations were described in detail earlier [8–10]. Briefly, 4.0 g L-lactide and 0.16 g poly(dodecyl acrylate)-*g*-poly(ε-caprolactone) [poly(DA-CL), a surface-active agent; $\overline{M}_n = 62000$, weight fraction of poly(ε-caprolactone) 0.26, $\overline{M}_n$ of poly(ε-caprolactone) grafts 6,500] were dissolved in a boiled mixture of 70 ml *n*-heptane and 20 ml 1,4-dioxane. Then, a solution of DSD in 10 ml heptane was added and polymerization was carried out with stirring (60 rpm) at 95 °C for 2 h. All the reagents and solvents were handled under argon. The polymerizations were also carried out under argon. After polymerization the mixture was left at room temperature for cooling. Thereafter, 100 ml heptane was added to the mixture and the remaining monomer crystals were removed by fractional sedimentation. The monomer conversion varied from 94% to more than 99% for DSD concentrations from 2×10^{-3} to 1×10^{-2} mol/l. The yield of the microspheres was above 85%. In one experiment samples of the reaction mixture were withdrawn before completion of the polymerization. The monomer conversion, the number and the diameters of the microspheres in each sample were determined.

Analyses

The molecular weight and the molecular-weight distribution of polylactides constituting the microspheres were determined using a gel permeation chromatography (GPC) setup combining an LKB 2150 pump (LKB-Pharmacia, Sweden), a Rheodyne 7125 injector with a 200-μl sample loop (Rheodyne, USA), a set of TSKgel G4000HXL and TSKgel G2000HXL columns (TosoHaas, Gemany), a light scattering detector (Dawn F MALS, Wyatt, USA), and an IR detector (Optilab 903 Interferometric Refractometer, Wyatt, USA). Dichloromethane was used as an eluant with a flow rate 0.8 ml/min. The absolute molecular weights of the polymers were calculated using Aurora 4.7 software. The values of the refractive index increments in dichloromethane [dn/dc equal to 2.56×10^{-2} and 3.10×10^{-2} ml/g for poly(L-lactide) and L-lactide, respectively] were determined according to the procedure recommended by Wyatt Inc.

The conversion of the monomer was determined using GPC and ^{1}H NMR spectroscopy methods as described earlier [22]. ^{1}H NMR spectra were recorded in $CDCl_3$ using a Bruker AC 200 spectrometer operating at 200 MHz.

Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrograms were registered using a Voyager Elite mass spectrometer (PerSeptive Biosystems, USA) equipped with a N_2 laser (337 nm, 4-ns pulse width) and a time-delayed extraction ion source. For these analyses isolated poly(L-lactide) microspheres were dissolved in chloroform containing 2,5-dihydroxybenzoic acid (DHB) and NaI. Subsequently, chloroform was evaporated in air. Spectra (256 scans were averaged per spectrum) were recorded in linear and reflector modes. Some additional analyses were made using 2-cyano-3-(4-hydroxyphenyl)propenic acid (αCHCA) and 2-(4-hydroxyphenylazo)benzoic acid (HABA) as matrices, KCl as an ionization promoter, and citric acid as a cation complexing agent.

The diameters of the microspheres were determined from scanning electron microscopy microphotographs recorded using a JEOL 35C (Japan) apparatus. The microphotographs were analyzed using Multiscan 6.08 software (Computer Scanning System, Poland). The diameters for at least 700 microspheres were measured for each sample.

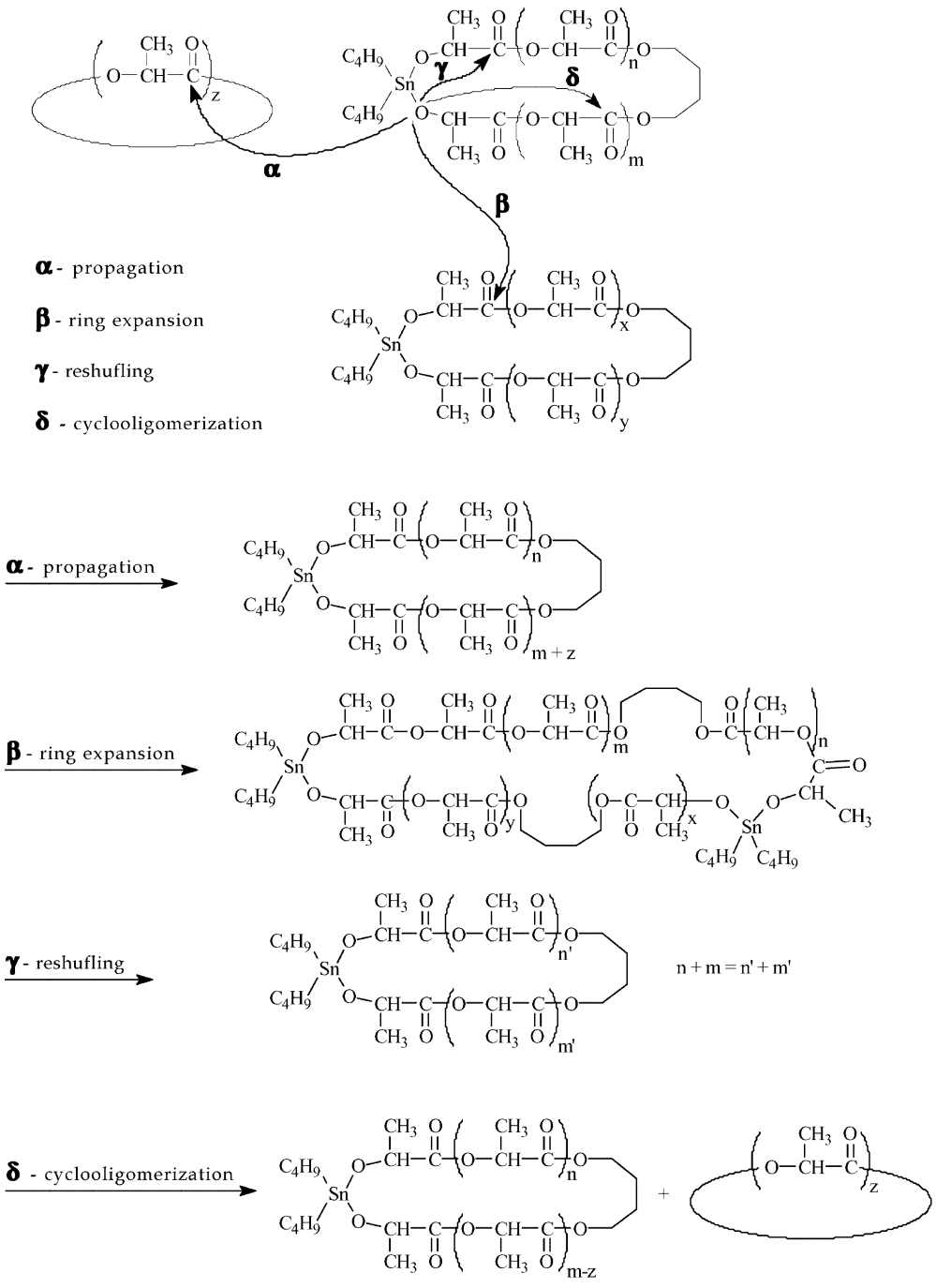
The concentration of the microspheres in the suspension was determined by counting their number on Bürker plate (Superior, Germany) cells using an optical microscope (PZO, Poland). These cells had known volumes (4×10^{-3} μl). The spheres in three randomly chosen cells on the plate were counted and an average number of microspheres per cell was calculated. Then, the counts were repeated (for three randomly chosen cells) with a fresh sample of suspension and a new average number of microspheres per cell was calculated by combining the data from all the counts. This procedure was repeated until the new average differed less than 2% from the old one. This method for the determination of averages from the probe has been described in detail by Allen [23]. It is known that standard deviation for the difference of the average of a random variable from a probe (e.g. an average for n cells) and the average of this variable for the whole population (e.g. by placing all microspheres on Bürker plates) is $\sigma/\sqrt{n}$, where σ denotes the standard deviation for the whole population and n number of elements (e.g. analyzed cells) in the probe [24]. It is also known that standard deviation for the difference of an average from two probes is $\sigma\sqrt{(n_1+n_2)/n_1n_2}$. For $n_1 \approx n_2 = n \gg 1$ this standard deviation is $\sigma\sqrt{2}/\sqrt{n}$ and could be considered as a good approximation for the standard deviation of the difference between the average from the probe and the average for the whole population [24]. Thus, the determination of the average number of microspheres per cell, performed as described earlier, $\left[\left(\sigma\sqrt{2}/\sqrt{n}\right)100\% = 2\%\right]$, allows the average value to be obtained from the probe differing from the average characterizing all the microspheres by about $(\sigma/\sqrt{n})\,100 \approx 1.4\%$.

Results and discussion

The well-established mechanism of propagation on $Sn(OR)_2$ and/or $>Sn(OR)_2$ active centers, proceeding by monomer insertion, and transesterification reactions involving these species [17, 18] suggest that for analysis of the polymers obtained in the polymerization of L-lactide initiated with DSD the set of reactions indicated in Scheme 1 should be taken into account.

Scheme 1 comprises propagation (α) involving monomer and cyclic oligomers (if formed during polymerization), intermolecular transesterification (β) leading to cyclic compounds with more than one active center, and two kinds of intermolecular transesterifications resulting in changes in the microstructure of growing macromolecules (γ) and in the formation of cyclic oligomers (δ). The latter has been not observed yet for polymerizations in solution; however, it is possible that the contribution of particular

Scheme 1



reactions to the whole process may be different for dispersion and solution polymerization.

The transesterification reaction (δ) affects the molecular weight, whereas reactions β, γ, and δ increase the molecular-weight polydispersity of the polymers obtained. Thus, the analysis of the molecular weight and the molecular-weight distribution is important for better knowledge of the dispersion polymerization process.

Molecular weights and molecular-weight distributions of poly(L-lactide) in the microspheres

The data in Table 1 indicate that for a monomer conversion below 90% the molecular-weight distributions were relatively narrow, $\left(\overline{M}_w/\overline{M}_n < 1.15\right)$. For higher monomer conversion, polymers with $\overline{M}_w/\overline{M}_n$ up to 1.44 were obtained. A similar increase in the

Table 1 Molecular weights and molecular-weight distributions of poly(L-lactide) in microspheres obtained by dispersion polymerization of L-lactide. Initial monomer concentration: 3.50×10^{-1} mol/l

Number	$[I]_o \times 10^3$ (mol/l)	Time (min)	Conversion[a]	M_n (calc.)	M_n	M_w/M_n
1	10.2	120	>0.99	4,070	6,600	1.44
2	3.83	120	0.98	10,200	8,600	1.37
3	2.06	120	0.94	18,400	22,400	1.21
4[b]	2.06	180	0.86	34,000	34,800	1.13
5	0.80	30	0.31	15,700	18,500	1.03
6	0.80	60	0.71	35,500	29,900	1.10
7	0.80	90	0.90	45,100	31,500	1.15
8	0.80	120	0.90	45,100	29,500	1.24

[a] Mean value from gel permeation chromatography and ^{1}H NMR measurements
[b] Addition of monomer to polymerization 3, total concentration of introduced monomer 5.64×10^{-1} mol/l

molecular-weight polydispersity with monomer conversion was observed earlier for polymerization initiated with tin(II) butoxide and carried out in solution [17]. It was found that this was due to the intermolecular transesterification reaction characterized by a rate constant significantly (about 150 times) lower than the corresponding rate constant of propagation [17]. Apparently, intermolecular transesterification was also important for dispersion polymerization of L-lactide.

The dependence of $\overline{M}_n$ on the monomer conversion is illustrated in Fig. 1. It is worth noting that when the monomer conversion reaches about 90% $\overline{M}_n$ decreases slightly with time.

For polymerizations proceeding according to Scheme 1 $\overline{M}_n$ can be described by

$$\overline{M}_n = \frac{Fw}{[DSD]_0}\left([Lc]_0 - [Lc]\right) \quad (1)$$

(in which Fw denotes the molecular weight of lactide, $[DSD]_0$ and $[Lc]_0$ are the initial concentrations of initiator and monomer, and [Lc] is the actual monomer concentration) only when the transesterification on route δ does not occur. Thus, the deviation from proportionality between $\overline{M}_n$ and the monomer conversion indicated that the transesterification with the formation of cyclic poly(L-lactide) oligomers did occur; however, the presence of these oligomers should be confirmed by other, desirably, direct analytical methods.

MALDI-TOF spectra of poly(L-lactide) from the microspheres

MALDI-TOF spectrograms were recorded in linear and reflector modes for all the samples of the microspheres using DHB as a matrix and NaI as an ionization promoter. The intensities of the spectra obtained with αCHCA and HABA matrices with and without ionization promoters were weaker and the spectra could be recorded only in the linear mode.

The MALDI-TOF spectrum (DHB matrix) of poly(L-lactide) synthesized in dispersion polymerization initiated with DSD is illustrated in Fig. 2.

The spectrum recorded in the linear mode was composed of a series of three signals. The central one was repeated with an interval of 72.02, corresponding to one –OCH(CH$_3$)C(O)– unit (basic unit, BU) and was assigned to macromolecules without $(C_4H_9)_2Sn <$

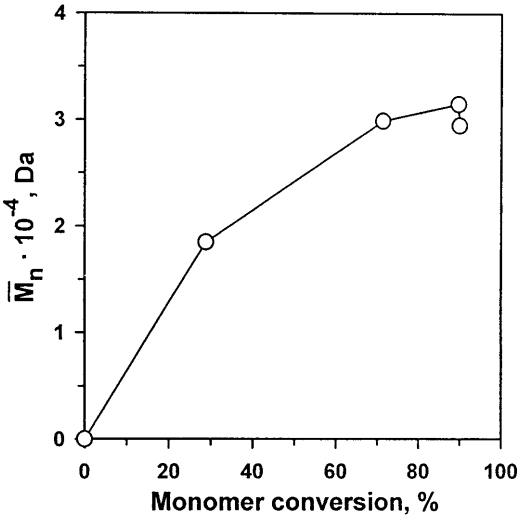


Fig. 1 Dependence of the number-average molecular weight on monomer conversion in dispersion polymerization of L-lactide initiated by 2,2-dibutyl-2-stanna-1,3-dioxepane (*DSD*). Initial concentrations: [L-lactide]$_0 = 3.50 \times 10^{-1}$ mol/l, $[DSD]_0 = 8.0 \times 10^{-4}$ mol/l

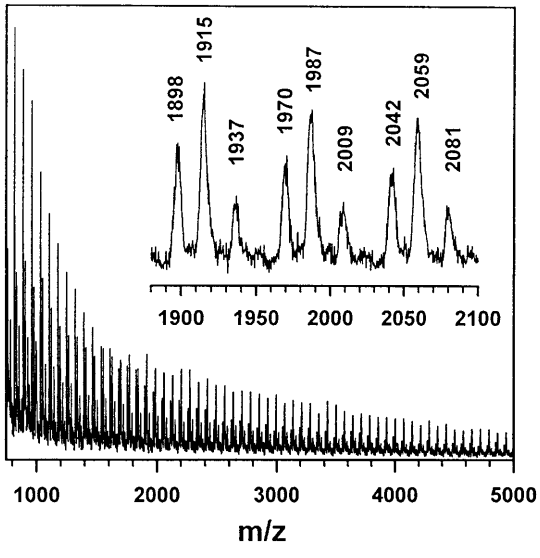
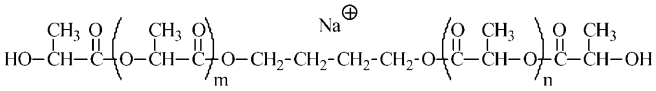


Fig. 2 Matrix-assisted laser desorption ionization time of flight (*MALDI-TOF*) spectrum of poly(L-lactide) in microspheres (sample 2 in Table 1) recorded in linear mode



Scheme 2

groups from active centers but bearing Na^+ cations from added NaI ionization promoter. Each macromolecule contained $-OCH_2CH_2CH_2CH_2O-$ from the initiator. The structures of these compounds and the formula describing their positions are given in Scheme 2 and Eq. (2), respectively.

$$m/z = 113.11 + 72.02N, \quad N = m + n + 2 \tag{2}$$

From the MALDI-TOF spectra it followed that owing to the transesterification reactions the polymer macromolecules were composed of even and odd numbers of BU. Without transesterification the macromolecules should contain an even number of BU because each addition of a monomer molecule introduces two of them.

The series of signals placed to the left of the series corresponding to poly(L-lactide) shown in Scheme 2 was related to the cyclic poly(L-lactide) oligomers (cf. Scheme 1); however, we noticed that the difference between the main series and the series corresponding to cyclics gradually decreased from 18 to 16 m/z units. Therefore, we assumed that there were signals of other species very close to the signals of the cyclic oligomers. In effect, in the low-resolution MALDI-TOF spectra the signals of the unknown species and of the cyclic oligomers partially overlapped and owing to changes in their proportions the observed gradual shift of the resulting signal did occur. With the purpose to verify this hypothesis and to determine the structure of the unknown compound we recorded spectra in a reflector mode providing much better resolution. Examples of these spectra are shown in Figs. 3 and 4.

We noticed that the exact assignment of all the signals was possible when in addition to the cyclic oligomers and the linear poly(L-lactide) , with the structures shown in Schemes 1 and 2, respectively, the products of the polymer hydrolysis and the transesterification in the reaction involving the DHB matrix were present. The structures of these compounds corresponding to the fragment of the MALDI-TOF spectrum shown in Fig. 4 are collected in Table 2. Apparently DHB facilitates hydrolysis and transesterification of polylactide samples prepared for MALDI-TOF analysis.

It is worth noting that for the αCHCA and HABA matrices the signals that for the DHB matrix were assigned to species 2, 3, 4, and 7 and their analogues with higher number of $-CH(CH_3)COO-$ units (Table 2) were absent. The spectra were also recorded without any ionization promoter and with promoters such as KCl and NaI and citric acid. It is important to stress that in the

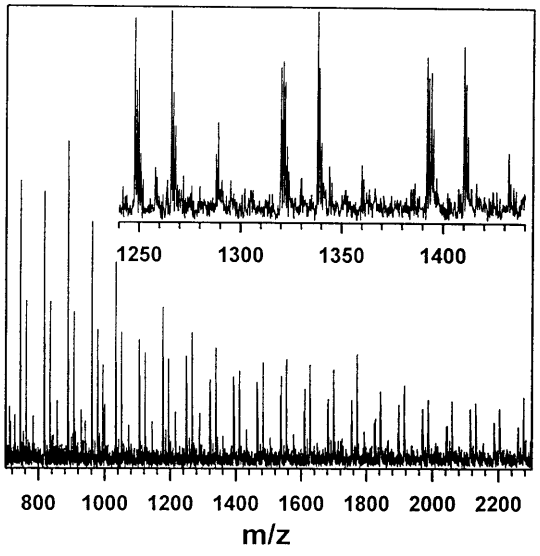


Fig. 3 MALDI-TOF spectrum of poly(L-lactide) in microspheres (sample 2 in Table 1) recorded in reflector mode

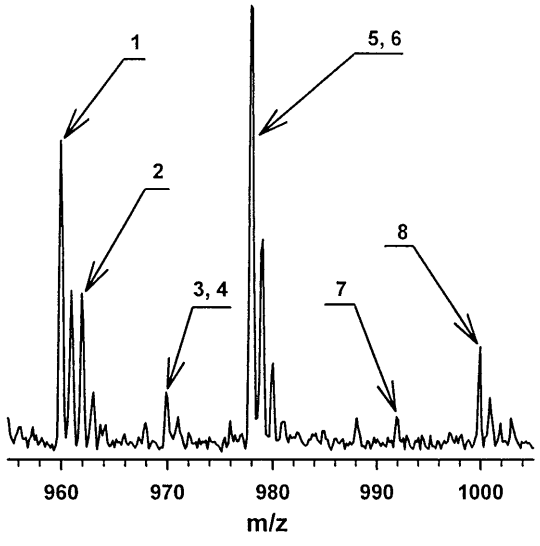
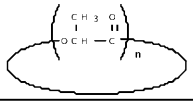
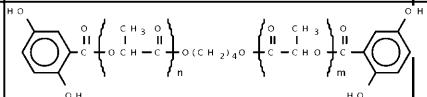
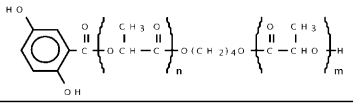
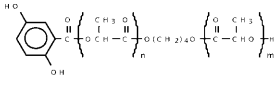
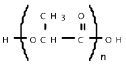
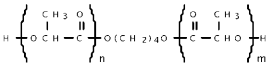
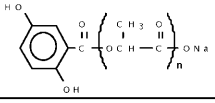
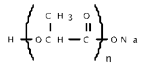


Fig. 4 Fragment of the MALDI-TOF spectrum of poly(L-lactide) in microspheres (sample 2 in Table 1) recorded in reflector mode. The compounds corresponding to these signals are denoted by *numbers* and their chemical structures are shown in Table 2

spectra without added ionization promoter the signals of compounds $H-[OCH(CH_3)C(O)]_nONa$ (species 8 in Table 2) were absent. The signals of these compounds were also absent when citric acid was added to the system (apparently, citric acid captures efficiently Na^+ cations). In the spectra with KCl added as the ionization promoter the signals of $H-[OCH(CH_3)C(O)]nONa$ were not present but we noticed new ones in positions corresponding to $H-[OCH(CH_3)C(O)]_nOK$. It is worth noting that

Table 2 Structures assigned to signals in Matrix-assisted laser desorption ionization time of flight spectra of poly (L-lactide)

No	Structure	m+n	m/z
1		13	959.8117
2		8	961.8359
3		11	969.8124
4		10	969.8560
5		13	977.8326
6		12	977.8762
7		11	991.7942
8		13	999.8144

analogous compounds were also observed in the MALDI TOF spectra of poly(ε-caprolactones) [25].

Lee et al. [26] observed products of hydrolysis of polylactides in MALDI-TOF spectra recorded with DHB; however, the authors assumed that hydrolysis occurred during polymer storage. We did not notice any change in the molecular weight of our samples after more than 2 years. Thus, reactions involving the DHB matrix seem to be more probable. It also has to be noted that Kowalski et al. [13] did not notice in the MALDI-TOF spectra any products of the DHB reaction with poly(ε-caprolactone), a polymer also prone to hydrolysis and transesterification. However, these spectra were recorded for samples obtained without prior isolation of polymer from a polymerizing mixture and were prepared under high-vacuum conditions.

With the purpose of verifying that the signals at m/z from 23 + 72.02n to 29 + 72.02n (an example is given in Fig. 5 for $n = 13$, i.e. for a signal ranging from 959 to 965) contribute these from cyclic poly(L-lactide) oligomers we attempted to fit to the experimental signal simulated signals of cyclics and linear poly(L-lactide) with end groups from DHB. For signals of these compounds we took into account the natural abundance of the ^{13}C isotope. The results of this fitting shown in Fig. 5 indicate that the spectrum was approximated by the fitting procedure with good accuracy. Good fitting was also observed for other signals of this series (at least for n from 10 to 22).

Scission of polymer chains during sample preparation for the MALDI-TOF experiments (reactions involving DHB matrix) resulted in lower values of $\overline{M}_n$ determined from MALDI-TOF spectra than values from GPC. For example, for the sample with $\overline{M}_n = 8600$ determined by GPC, the analysis of the MALDI-TOF spectrum yielded $\overline{M}_n \approx 6000$. Thus, unfortunately, the MALDI-TOF spectra of polylactides recorded with the DHB matrix can be used for confirmation of the presence of some species (e.g. cyclics) but not for characterization of the molecular masses of the original samples.

Mechanism of particle formation and characteristics of the microspheres

For every dispersion polymerization process it is important to learn how the particles are formed. Thus, we wanted to find out whether in the polymerization of L-lactide all the particles were nucleated in the initial stage or new microspheres were created continuously during the whole polymerization. Previously we found that in the polymerization initiated with tin(II) 2-ethylhexanoate about 15 min after initiation all the particles were nucleated and propagation proceeded within the microspheres formed [12]. We wanted to check whether in the polymerization initiated with DSD the microspheres were formed in a similar manner. The dependence of the concentration of the microspheres (number of particles per 1 l suspension) on the time of polymerization is shown in Fig. 6.

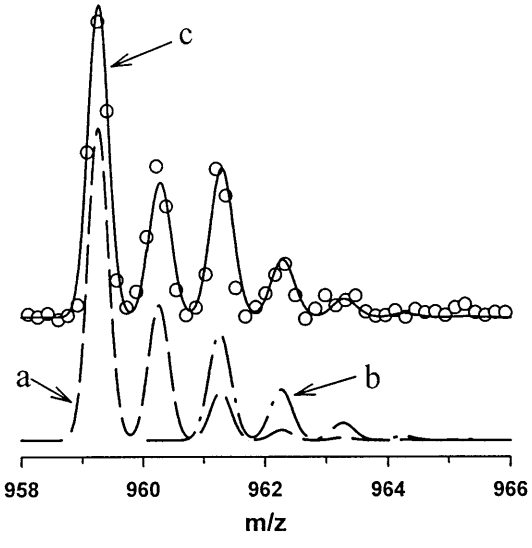


Fig. 5 Fitting of spectra of **a** cyclic poly(L-lactide) oligomers and of **b** linear poly(L-lactide) with end-groups from DHB to experimental spectrum (*points*). **c** The final fit

The plot in Fig. 6 indicates that also in the polymerization initiated with DSD all the microspheres were nucleated in the initial stage. It is worth noting that within the time period from 30 to 120 min, when the concentrations of the particles were measured, the monomer conversion varied from 30 to 90%.

The addition of a new monomer portion to the dispersion of the microspheres containing all active centers should result in polymerization without a change in the particle concentration, resulting in microspheres with larger diameters. With the purpose to verify this hypothesis we carried out a two-stage polymerization. In the first step L-lactide was polymerized for 120 min. The initial monomer and DSD concentrations were 3.50×10^{-1} and 2.06×10^{-3} mol/l, respectively. After 120 min we took a sample of the polymerizing mixture for analysis, added a new monomer portion to the mixture (combined concentration of monomer introduced to the polymerizing mixture was 5.64×10^{-1} mol/l), and continued the polymerization for an additional 60 min. After the first stage the monomer conversion was 94% and the number-average diameter and the number-average volume of the microspheres were 1.96 μm and 4.92 μm^3, respectively. After the second step the overall monomer conversion was 86%, the number-average diameter of the microspheres increased to 2.34 μm, and the number-average volume of the microspheres increased to 8.32 μm^3. However, it was assumed that at both stages the concentration of the microspheres was essentially the same, 4.17×10^{12} l^{-1} after the first step and 4.03×10^{12} l^{-1} after the second one.

In our earlier studies of L-lactide polymerization initiated with tin(II) 2-ethylhexanoate we determined the relations between the diameters of the microspheres synthesized and the monomer and surface agent [poly(DA-CL)] concentrations [9, 27, 28]. Briefly, it was found that polymerizations with a lower concentration of poly(DA-CL) yielded poly(L-lactide) with a higher fraction of polymer in the form of a shapeless coagulum; however, the diameters of the particles in microsphere fraction were not affected, whereas the increased monomer concentration led to microspheres with larger diameters. Unfortunately, in polymerizations initiated with tin(II) 2-ethylhexanoate we could not investigate the relations between the diameters of the microspheres and the concentration of the propagating macromolecules. As stated in the Introduction the true initiating species are produced in the reaction of tin(II) 2-ethylhexanoate with water or alcohol present in ill-controlled trace amounts and thus it was difficult to control the concentrations of the growing polymer chains. In this work such studies were possible because tin alkoxides are known to initiate polymerization of lactides producing one growing center per –SnO*R* group.

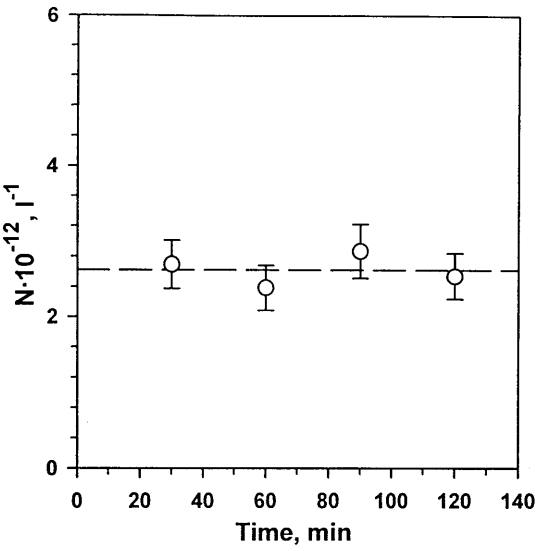


Fig. 6 Dependence of the concentration of microspheres (number of microspheres in 1 l suspension) on the time of polymerization. Polymerization conditions: $[\text{L-lactide}]_0 = 3.50 \times 10^{-1}$, $[\text{DSD}]_0 = 8.0 \times 10^{-4}$ mol/l

The dependence of the diameters on DSD concentration is illustrated in Table 3. The data collected indicate that in polymerizations with lower concentrations of DSD microspheres with larger number-average diameters, $(\overline{D}_n)$, were obtained.

For each sample of the microspheres we also determined the number-average volume of the particles. Taking the density of poly(L-lactide) to be 1.25 g/cm^3 we calculated the number-average mass of the microspheres. Figure 7 shows the relation between the number-average mass of the microspheres, $(\overline{mM}_n)$, and the molecular mass of poly(L-lactide) per mole of growing chains, i.e. to $\overline{M}_n$(calc), the latter is equal to the average mass of the polymer per growing chain divided by Avogadro's number. Thus, the average number of growing chains per microsphere is

$$\left[\overline{mM}_n/\overline{M}_n(\text{calc})\right] N_A \qquad (3)$$

For all experimental points in Fig. 7 the dependence of $\overline{mM}_n$ on $\overline{M}_n$(calc) was approximated with good accuracy by a straight line passing through the origin of the ordinates. This means that the average number of moles of propagating linear macromolecules in one microsphere was the same for all syntheses and was 2.98×10^{-16}, i.e. that the average microsphere contained 1.8×10^8 propagating macromolecules.

It is worth noting the broader distribution of masses for larger microspheres (larger error bars for larger microspheres in Fig. 7). Apparently, the particles that are larger at the beginning (owing to some size distribution of the nuclei of the microspheres) contain more growing species (all particles are formed

Table 3 Initial inititator concentrations, times of polymerizations, conversions, molecular weights, diameters, diameter distributions, and concentrations of particles in dispersion

Number	$[I]_o \times 10^3$ (mol/l)	Time (min)	Conversion[a]	M_n (calc.)	D_n (μm)	D_w/D_n	V (μm^3)	$N \times 10^{-12}$ (1/l)[d]
1	10.2	120	> 0.99	4,070	1.14	1.36	1.11	27.4
2	3.83	120	0.98	10,200	1.55	1.25	2.51	12.0
3	2.06	120	0.94	18,400	1.96	1.24	4.92	5.88 4.17[c]
4[b]	2.06	180	0.86	34,000	2.34	1.23	8.32	6.36 4.03[c]
5	0.80	30	0.31	15,700	1.76	1.21	3.54	2.69
6	0.80	60	0.71	35,500	2.37	1.27	9.16	2.38
7	0.80	90	0.90	45,100	2.42	1.26	9.65	2.87
8	0.80	120	0.90	45,100	2.55	1.23	10.90	2.54

[a] Mean value from gel permeation chromatography and ^{1}H NMR measurements
[b] Addition of monomer to polymerization 3, total concentration of introduced monomer 5.64×10^{-1} mol/l
[c] Counted on Bürker plate
[d] Calculated as the ratio of the average mass of particle (Vd, where $d = 1.25$ gcm^{-3} density of amorphous polylactide) and the average mass of polymer per growing chain, $\left[\overline{M}_n(\text{calc})/N_A\right]$

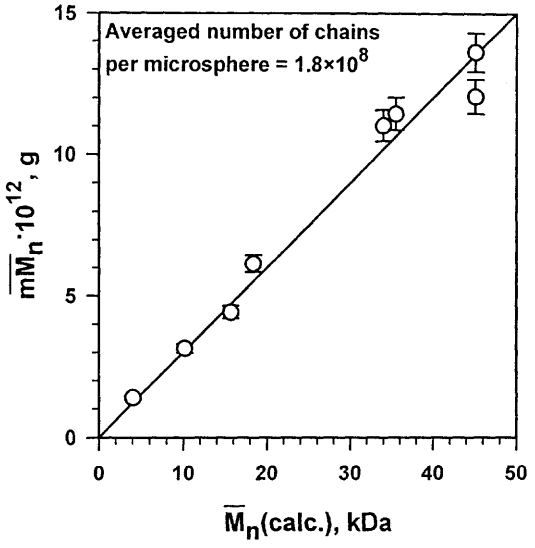


Fig. 7 Number-average mass of microspheres, $\left(\overline{mM}_n\right)$, as a function of the molecular mass of poly(L-lactide) per mole of growing chains

when propagating chains have similar lengths). Thus, the larger the particles the greater the number of growing chains they contain. Therefore, the larger particles grow faster. As a result, with time and with increased monomer conversion particle diameter the distributions and the particle masses become broader.

The formation of microspheres containing the same number of growing macromolecules, regardless of the initial concentration of initiator, could be explained in the following way. Initially the polymerizing mixture was homogeneous. The initiation and the first propagation steps proceed in solution. When the growing chains reached the critical length apparently a phase separation occurred and microspheres, very small at this stage, were formed. The size of these initial microspheres was determined by the composition of the suspending medium (composition of heptane/1,4-dioxane mixture, monomer concentration at the moment of phase separation, concentration of surface-active agent). In separate experiments we found that only very short poly(L-lactide) molecules, $\left(\overline{M}_n < 800\right)$, could be dissolved in the heptane/1,4-dioxane/monomer mixture with the same composition as used for the polymerization. Thus, it was reasonable to assume that in all the polymerizations phase separation occurred at a very low monomer conversion when the compositions of the polymerizing mixture did not differ significantly from the initial ones and, thus, were almost the same in all the syntheses. Thus, regardless of the initial concentrations of the initiator, the initial microspheres were formed from growing chains of the same length in media of almost identical composition and, therefore, their diameters were the same. In subsequent polymerization steps the growth of the microspheres was possible owing to diffusion of the monomer inside the microspheres, which could be considered as microreactors. Sufficient stabilization of the microspheres with poly(DA-CL) eliminated their coagulation, allowing gradual growth.

Conclusions

Polymerization of L-lactide initiated with DSD and carried out in a mixture of organic solvents (heptane/1,4-dioxane 4:1 v:v) in the presence of poly(DA-CL)used as a surface-active compound yields polymer in the form

of microspheres with relatively low diameter polydispersity. All the microspheres are nucleated in the early step of polymerization and they do not coalesce in the later stages of this process. Regardless of the initial concentration of the initiator the average number of macromolecules per microsphere is constant, suggesting the formation of primary microspheres in the phase-separation process. In the dispersion polymerization of L-lactide initiated with DSD the propagation was accompanied by transesterification reactions leading to the formation of cyclic oligomers.

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