

# **L-Lactide polymerization catalysed by Tin(II) 2-ethyl-hexanoate. A deeper look at chain transfer reactions.**

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## **Electronic Supplementary Information**

Reagents, syntheses, and analytical procedures	Page 1
<sup>1</sup> H NMR spectrum	Page 4
Size Exclusion Chromatography	Page 5
MALDI-ToF mass spectra	Page 7
Samples characterization (Table S1)	Page 8
Modelling procedure	Page 8
Interpretation of MALDI-ToF spectra	Page 12
Kinetic equations	Page 17

## **Experimental**

### *Reagents*

Methanol (analytical grade, Chempur, Poland) was used as received. Benzyl alcohol (BzOH) (analytical grade, POCH, Poland) was distilled under atmospheric pressure, and then on the high vacuum line (at 10<sup>-3</sup> mbar) into glass ampoules with break-seals. Tetrahydrofuran (POCH, Poland) was kept for several days over KOH, fractionally distilled from sodium metal chips, and then distilled in vacuum into glass ampoule with sodium/potassium alloy. Just before use it was distilled in vacuum into the reaction vessel. 2-propanol (analytical grade, Chempur, Poland) was dried by fractional distillation from over sodium metal chips. L-lactide (LL) (Boehringer-Ingelheim, Germany) was crystallized from dry 2-propanol, sublimed in vacuum, distributed into glass ampoules with break-seals, dried and sealed off. Sn(2-ethylhexanoate)<sub>2</sub> (SnOct<sub>2</sub>) (95%, Aldrich, USA) was distilled twice (10<sup>-3</sup> mbar, 413 K) - first into a glass ampoule with Rotaflo® stopcock and finally distributed in vacuum into a

glass ampoules with break-seals. Our earlier studies indicate that in this treatment water and other impurities are removed and ~99% purity of SnOct<sub>2</sub> can be achieved.

### *Polymerization*

The PLA samples were synthesized as follows: break-seals containing LL (3.0578 g, 21.22 mmol), SnOct<sub>2</sub> (0.0418 g, 0.1032 mmol), and BzOH (0.0331 g, 0.3065mmol) were attached to the reaction vessel equipped with ampoules for collecting samples. Tetrahydrofuran (18.2 ml) was distilled into it under vacuum and the reaction vessel was sealed off. Then the break-seals were broken, reagents were mixed at room temperature and the resulting solution was distributed into the sample ampoules. Ampoules were sealed off and placed in the thermostatic bath (353 K). At the suitable monomer conversions the selected ampoule was cooled to room temperature, opened, quenched by acetic acid, and finally dried in vacuum to the constant weight.

### *Size Exclusion Chromatography (SEC)*

SEC equipment comprised an Agilent Pump 1100 Series (preceded by an Agilent G1379A Degaser), Agilent 1100 Series Injector, and a set of two PLGel 5 $\mu$  MIXED–C thermostatted columns. Wyatt Optilab Rex differential refractometer and Dawn Eos (Wyatt Technology Corporation) multi angle laser photometer were used as detectors. Dichloromethane was used as eluent at flow rate of 0.8 ml·min<sup>-1</sup>. Value of refractive index increment (dn/dc) equal to 0.035 ml·g<sup>-1</sup> was determined according to Wyatt recommendations and used in calculations of mass average molar masses and dispersity of PLA samples by Astra 5.1 software.

### *MALDI-ToF spectroscopy*

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<sub>2</sub> laser (337 nm, 4-ns pulse width) and a time-delayed extraction ion source.

For these analyses isolated poly(L-Lactide) (PLA) samples were dissolved in 1 ml of methylene chloride containing 10 mg of ditranol and 1 mg of lithium iodide. Subsequently, 10  $\mu$ l of the solution was evaporated in air. Spectra (100 scans were averaged per spectrum) were recorded in linear mode.

#### *<sup>1</sup>H Nuclear Magnetic Resonance (NMR)*

Spectra of PLA samples dissolved in C<sub>6</sub>D<sub>6</sub> were acquired on Bruker AV III 500 spectrometer.

<sup>1</sup>H NMR (500 MHz, 298 K, C<sub>6</sub>D<sub>6</sub>):  $\delta$  = 7.25-7.35 (m, Ar), 4.97 (q, polymer CHOCO), 4.79 (m, PhCH<sub>2</sub>O), 4.71 (q, monomer CHOCO), 4.51 (q, CHOH), 1.28 (d, polymer CH<sub>3</sub>), 1.11 (d, monomer CH<sub>3</sub>), 0.84-0.73 (3 d, CH<sub>3</sub> end groups). The spectra confirms expected structure of PLA samples.

## Characterization of synthesized PLA samples

### NMR

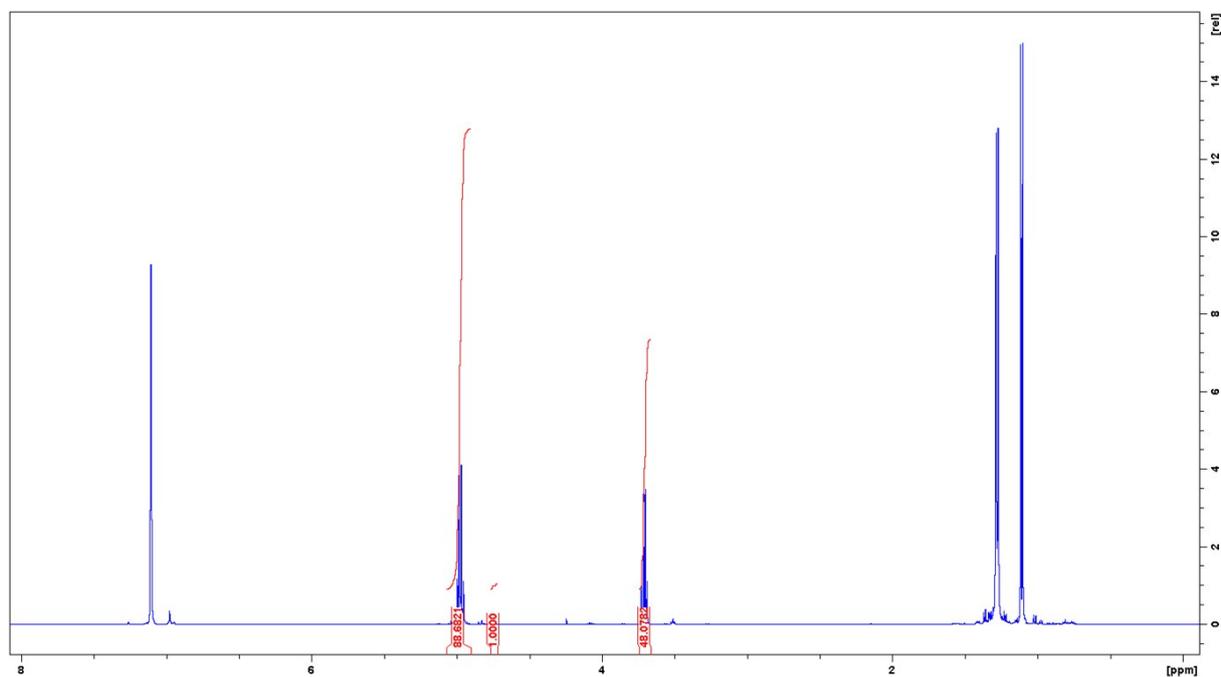


Figure S1. <sup>1</sup>H NMR spectrum of PLA sample C.

Integrations: I1 - polymer methine protons in range 5.07-4.90 ppm; I2 – monomer methine protons in range 3.74-3.66 ppm; I3 - benzyl end group methylene protons (right doublet) in range 4.77-4.72 ppm

Calculation of conversion:  $\text{conversion} = I1/(I1+I2)$

Calculation of number averaged molar mass:  $M_n = 72.0625 \times I1/I3 + 108.1378$

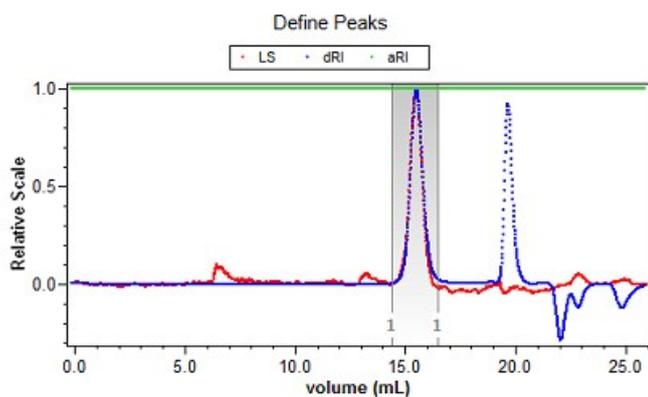
SEC

An example of original report from SEC analysis of Sample C is given below (Figure S2):

ASTRA 6 Report RESH-1-3M



File Name: D:\Wyatt Installation\LEWINSKI\RESH-1-3M.afe6  
Collection Operator: GPC\Eclipse (Eclipse)  
Processing Operator: GPC\Eclipse (Eclipse)  
Sample: RESH-1-3M



Configuration

Concentration Source: RI  
Flow Rate: 0.800 mL/min  
Light Scattering Instrument: HELEOS  
Cell Type: Fused Silica  
Wavelength: 664.1 nm  
Calibration Constant:  $3.1038 \times 10^{-5}$  1/(V cm)  
RI Instrument: rEX  
Solvent: methylene chloride  
Temperature Correction Enabled: no  
Refractive Index: 1.424

Processing

Collection Time: Friday March 27, 2015 11:20:07 AM Central European Daylight Time  
Processing time: Friday March 27, 2015 12:07:24.301 PM Central European Daylight Time

Peak settings:

Peak Name	Peak 1
Peak Limits (mL)	14.360 - 16.483
Light Scattering Model	Zimm
Fit Degree	1
dn/dc (mL/g)	0.0350

dn/dc (mL/g)	0.0350
A2 (mol mL/g <sup>2</sup> )	0.000
UV Ext. Coef. (mL/(mg cm))	0.000

**Results Fitting Procedure:**

Data	Fit Model	Degree	R <sup>2</sup>	Extrapolation
Molar Mass	none	n/a	n/a	none
rms radius	none	n/a	n/a	none
mean square radius	none	n/a	n/a	none

**Results****Peak Results**

Peak 1	
<b>Masses</b>	
Injected Mass (µg)	570.00
Calculated Mass (µg)	436.03
Mass Recovery (%)	76.5
Mass Fraction (%)	100.0
<b>Molar mass moments (g/mol)</b>	
Mn	7.525×10 <sup>3</sup> (±3.364%)
Mp	7.248×10 <sup>3</sup> (±1.935%)
Mv	n/a
Mw	7.941×10 <sup>3</sup> (±6.724%)
Mz	9.361×10 <sup>3</sup> (±32.134%)
<b>Polydispersity</b>	
Mw/Mn	1.055 (±7.518%)
Mz/Mn	1.244 (±32.310%)
<b>rms radius moments (nm)</b>	
Rn	21.5 (±29.6%)
Rw	28.1 (±26.5%)
Rz	46.0 (±23.8%)

Figure S2. Example report from SEC analysis of sample C.

RI traces of SEC chromatograms are collected in Figure S3.

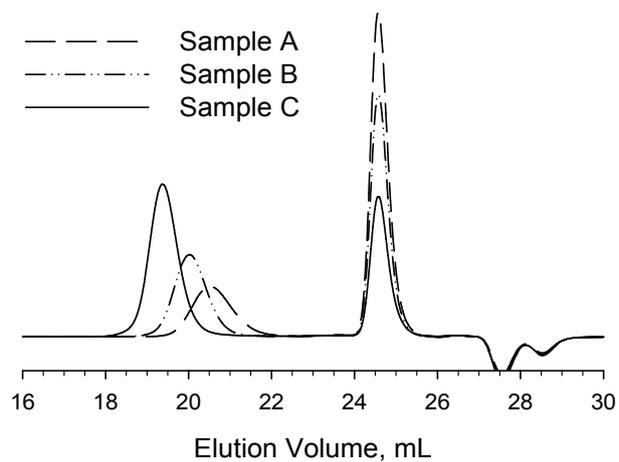


Figure S3. RI traces of SEC chromatograms of the synthesized PLA samples.

*MALDI-ToF*

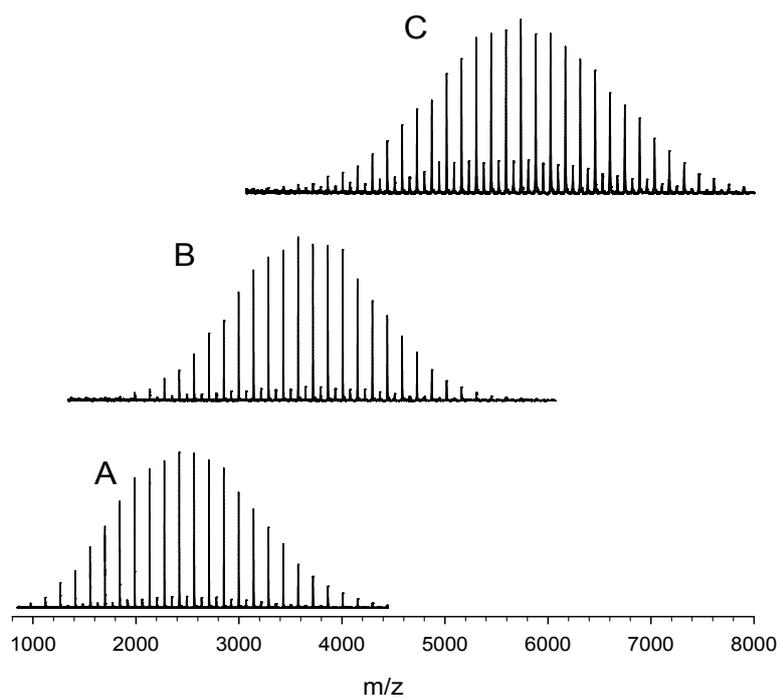


Figure S4. Collected MALDI-TOF mass spectra of synthesized PLA samples

Table S1. Polymerization time, conversion, molar masses, and dispersity of PLA samples.

ID	time min	conv. <sup>a)</sup> NMR	$M_n$ <sup>b)</sup> NMR	$M_n$ SEC	$M_n$ MALDI	$M_w$ SEC	$M_w$ MALDI	$\bar{D}$ SEC	$\bar{D}$ MALDI	Odd/Even <sup>c</sup>
A	69	0.26	2700	4000	2700	4200	2800	1.05	1.05	0.0602
B	118	0.41	4200	4900	3700	5200	3900	1.05	1.03	0.0870
C	192	0.65	6600	7500	5800	7900	6000	1.06	1.02	0.1908

a) from integrations of monomer and polymer methine protons

b) from ratio of monomer methine protons to  $-\text{CH}_2\text{O}-$  benzyl protons integrations and molar mass of the benzyl alcohol end group

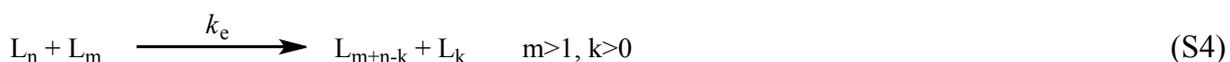
c) ratio of total fractions of chains with odd and even number of lactoyl units

Table S1 presents molar masses and dispersity of synthesized PLA samples.

## Modelling

### *Assumed scheme of the process*

It was assumed that the polymerization consists of few reactions: irreversible initiation (S1), reversible propagation (S2), and two reactions of segmental exchange. The first - specific redistribution - consist of an attack of active centres on the lactoyl unit closest to propagation centre in another chain (S3), and the second – nonspecific redistribution - proceeding by attack active centre of a chain on any lactoyl unit in another chain (S4).



Scheme S1. Reactions included in the model of the process of homopolymerization of L-Lactide initiated by alcohol/SnOct<sub>2</sub> system.

The initiation, propagation, and depropagation reactions yield only chains with even number of lactoyl units. The segmental exchange reactions give also chains with odd number of lactoyl units. According to the scheme we will consistently use  $n$  for designation of the number of the constitutive lactoyl units (not the monomeric units) in chain.

In our reaction set we intentionally ignored reaction of equilibration between active and inactive forms of chain ends, e.g. between inactive hydroxyl ends and active tin alkoxylates, really present in processes initiated by alcohol/SnOct<sub>2</sub> systems (S5).



As the equilibrium establishes rapidly comparing to rate of other reactions in the system it can be omitted without risk of an error. At the beginning of the process, the equilibrium concentrations of both forms of chain ends are fixed and remain constant at later stages.<sup>S1-S3,S5</sup> Very often a large excess of alcohol is used (3-fold in our experiments) yielding nearly complete shift of the equilibrium toward RO-SnOct. In consequence of the assumption, all rate constants used in the scheme, related to concentration of the added alcohol, have to be understood as the apparent rate constants. However, an approximated concentration of both forms of chain ends can be calculated from initial concentrations of reagents used and data presented in literature, making estimation of true rate constants possible.<sup>S5</sup>

One of the features of processes permitting the intermolecular segmental exchange reactions, especially ROP processes, is the presence of intramolecular reactions yielding cyclic products. These reactions could affect rate of broadening of molecular weight distribution significantly.<sup>S4,S5</sup> Fortunately, the intramolecular segmental exchange reactions can be also discarded, because cyclic products were not observed in case of discussed systems at a moderate temperature.<sup>S1-S3</sup>

Simplifications of the polymerization model allow better understanding of relations between experimental data and adjustable rate constants. Despite of the simplifications, the proposed reaction set gives a good reproduction all the features observed in experimental MALDI-ToF spectra and SEC chromatograms.

#### *Algorithm and data structure*

Data are organized in several arrays allowing a high speed of modelling, due to some degree of redundancy of stored information. Each lactoyl unit in the system is represented by a record consisting of the number of the chain being a host for the unit and the number describing position in the chain that particular unit occupies. Records are numbered and the numbers are stored in a supporting array allowing a random selection of any record. Analogously chains were stored as records containing length of the chain and the number of the record representing the lactoyl unit being an active centre of the chain. Chains records are also numbered and their numbers are stored in a separate supporting array. Additionally, there is a rectangular array which retains sequences of units in chains (sequence of number of records). Each row of the array represents a single chain. Such redundant data structures allow an easy and direct access to a random component of the system and identification of neighbours of any unit in any chain. Having this information it is easy to execute transfer of any fragment of chain from one chain to another. More details on the used data structure are given elsewhere.<sup>S6</sup>

The polymerization was modelled using a variant of kinetic Monte Carlo method invented by Gillespie.<sup>S7</sup> The variant was elaborated by Szymanski and described in detail elsewhere.<sup>S8</sup> In this variant the total reaction time is divided into a large number of small intervals, for which it can be assumed that concentrations of all reagents are constant. Within each interval all chains are permitted to react sequentially, according to the Gillespie algorithm, until cumulative time of reactions of a selected chain is shorter than the interval. Otherwise a next

chain is selected. After each reaction concentrations of reagents and chain lengths are modified to reflect changes of the system state. When each chain is reacted within the given time interval the loop for next time interval is started. After assumed total time of the process is attained, the simulation stops.

An executable program is attached as supporting material together with the sets of parameters defining all modelling experiments presented in the paper. The Mersenne-Twister pseudo random number generator was implemented in the program in order to get sufficiently long series of random numbers.<sup>S9</sup> The program runs under Windows® operating system. Even though its interface should be intuitive, the full documentation can be accessed elsewhere.<sup>S10</sup> The program shows a number of results e.g. distribution of degrees of polymerization (*DP*), approximate SEC chromatogram, MALDI-TOF spectrum and some other related plots, at any moment of the modelled process. User can carry on modelling using his own set of parameters.

### *Simulation experiments*

For all conducted simulation experiments only two parameters varied: rate constant of specific redistribution (S3)  $k_{e0}$  and rate constant of non-specific redistribution (S4)  $k_e$ . Other parameters were kept fixed:  $[BzOH]_0 = 1.438 \cdot 10^{-2} \text{ mol} \cdot \text{l}^{-1}$ ,  $[LL]_0 = 0.9998 \text{ mol} \cdot \text{l}^{-1}$ , rate constants of initiation and propagation were equal  $k_1 = k_p = 0.0067 \text{ l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ ,  $k_d = 0.0002 \text{ s}^{-1}$ . All these rate constants should be considered as the apparent ones and were adjusted for best reproduction of monomer conversion. 130 thousands of chains were modelled in each experiment. Table S2 contains list of experiments and used values of the rate constants.

Table S2. Rate constants of specific and non-specific redistribution reactions used in modelling.

Experiments	$k_{e0}^a$ $l \cdot mol^{-1} \cdot s^{-1}$	$k_e^b$ $l \cdot mol^{-1} \cdot s^{-1}$
E1a	0	$3 \cdot 10^{-6}$
E1b	0	$1 \cdot 10^{-5}$
E1c	0	$3 \cdot 10^{-5}$
E1d	0	$1 \cdot 10^{-4}$
E1e	0	$3 \cdot 10^{-4}$
E2a	$1 \cdot 10^{-4}$	0
E2b	$3 \cdot 10^{-4}$	0
E2c	$1 \cdot 10^{-3}$	0
E2d	$3 \cdot 10^{-3}$	0
E2e	$1 \cdot 10^{-2}$	0
Fit_nonspec <sup>c</sup>	0	$2.2 \cdot 10^{-4}$
Fit_spec <sup>c</sup>	$1.22 \cdot 10^{-3}$	0
Fit_best <sup>c</sup>	$1.05 \cdot 10^{-3}$	$2.6 \cdot 10^{-6}$

a) Specific redistribution. b) nonspecific redistribution. c) combination of rates giving best fit to experimental data

It should be clear, that if the rate constant of non-specific segmental exchange reaction  $k_e$  differs from zero, then the attack on the last unit in chain is also allowed with the same probability as attacks on any other unit in a chain. If  $k_{e0} \neq 0$  then probability of the attack on the last unit in chain is in fact proportional to sum of rate constants  $k_{e0}$  and  $k_e$ .

### Interpretation of MALDI-ToF spectra.

Figure S4 presents MALDI-ToF spectra of PLA samples for different moments of polymerization process. On each spectrum one can distinguish two series of signals with the bell-shaped distribution of intensities, both centred around the same maximal value of  $m/z$ . For all samples signals of higher intensity were ascribed to chains with even number of lactoyl units (later called shortly even chains) and signals of lower intensity placed between them with odd number of lactoyl units (called odd chains, respectively). Number averaged molar masses  $M_n$  and dispersities  $D$  determined by SEC, NMR, and MALDI-ToF are coherent

(cf. Table S1). Some noticeable differences between these parameters can be ascribed to experimental errors (for example the known suppression of signal intensity of high molar masses in MALDI-ToF spectra). As seen, the progress of the polymerization significantly increases  $M_n$  and contribution of the odd chains, together with negligible change of dispersity, which confirms results obtained by Prud'homme.<sup>S3</sup>

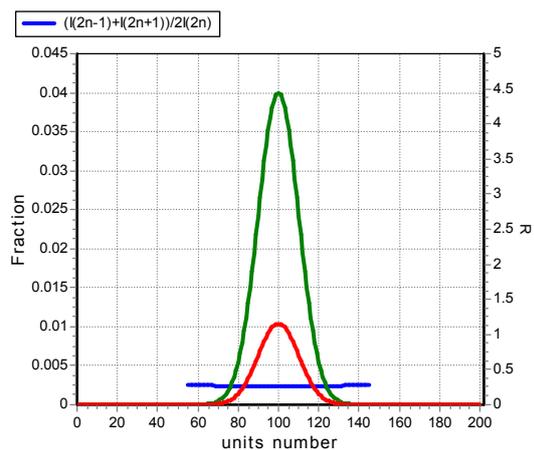


Figure S5A. Shape or  $R$  for two distributions with equal widths and centres.

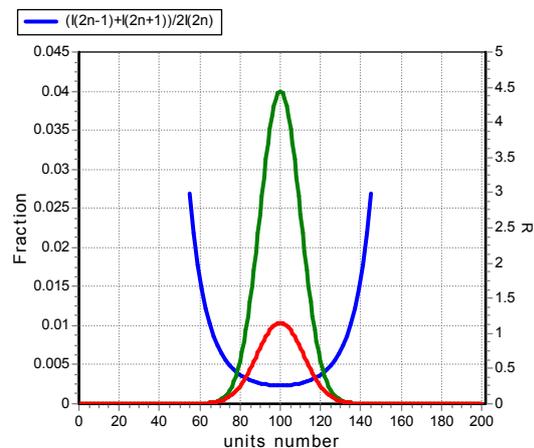


Figure S5B. Shape or  $R$  for two distributions with non-equal widths and equal centres

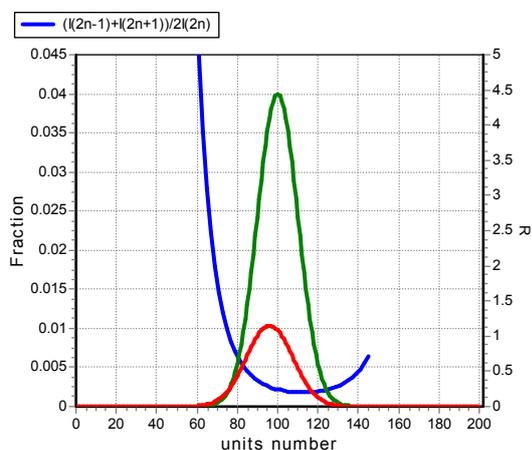


Figure S5C. Shape or  $R$  for two distributions with non-equal widths and centres

As in case of polymerization of L-lactide initiation, propagation, and depropagation reactions yield only even chains, the presence of the odd chains in a PLA sample is a proof of presence of segmental exchange reactions.

Starting discussion of observed phenomenon we introduce the parameter allowing a quantitative interpretation of MALDI-ToF spectra. Prud'homme et al. measured progress of redistribution reaction using a ratio of the intensity of the highest even chain signal to intensity of its closest odd chain placed on its right side. The ratio can grow from 0 at beginning of the process to approximately 1 when redistribution is advanced.<sup>S3</sup> In our studies we will follow the way proposed by Prud'homme and use of similar ratio  $R$  as function of number of lactoyl units in a chain (see equation 2 in the main text). Such form of equation 2, applied to analysis of two normal or Gaussian distributions, possess a few interesting features (cf. Figure S5). It is a horizontal straight line when distributions of odd and even chains have the same standard deviations and centres. When standard deviations differ the line is concave or convex, but symmetric, and if distribution centres do not match then the line is skewed. For different intensities of distributions all the mentioned properties are conserved. A simple program allowing exploration of behaviour of the equation 2 is included in the ESI. The proposed function also compensates a possible error coming from suppression of high molar masses in MALDI-ToF spectroscopy as it relates peaks ascribed to entities with very close molar masses.

It should be stressed that in spite of advanced segmental exchange reactions indicated by the  $R$  value, there are no effects of segmental exchange visible on SEC chromatograms presented in Figure S2. The chromatographic peaks remain very narrow without any shoulders or tails.

### Consequences of segmental exchange reactions

Let us imagine an uniform population of PLA chains with a number of lactoyl units equal to  $2n$  and two possible routes of segmental exchange reactions (the specific and the non-specific ones) between them (c.f. Figure S6).  $x$  is a position of lactoyl unit in a chain, counted from the initiator moiety.

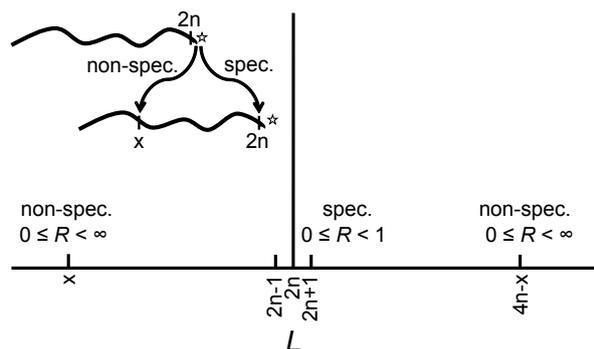


Figure S6. Changes of MWD caused by specific and non-specific redistribution reactions at the beginning of the process.

The non-specific reaction, commonly accepted for explanation of MWD broadening in polymerization of lactides, initially produces chains with length  $L$  (expressed as number of lactoyl units) spreading over range from 1 to  $4n-1$ . Due to very low abundance of chains with  $L \neq 2n$  at beginning of the process, values of ratios  $R$  could initially vary from 0 to infinity and would be very noisy. As the polymerization proceeds  $R$  become smoother due to continuously increase of number of reacted chains. Finally, when the equilibrium MWD is attained, the ratio stabilizes at level close to 1, as expected for the most probable (geometric) distribution.

Transferring this analysis to system composed of only even chains with the Poisson (or normal) distribution one could expect similar changes of chain's length though with broader distribution. For chain lengths close to the mean length of initial population  $R$  will form a smooth, V-shaped function adopting low values. With progress of the exchange reactions

these values grow gradually, however without any linear part observed in the experimental curves (cf. Figure 3 in main text).

Changes of dispersity  $\mathcal{D}$  can be also qualitatively predicted on basis of the Figure S6. At the very beginning of the process, when only even chains are present in the system, the reaction of nonspecific distribution yields odd chains only in case of 50% of attacks. Remaining 50 % of attacks do not change the odd/even chains ratio. Lengths of newly formed chains should be distributed broadly between  $L=1$  and  $L=4n-1$ . Therefore the non-specific redistribution causes a large increase of dispersity of the sample (c.f. Figure 5 in the main text). This indicates that standard deviation of the odd chains length distribution is larger than the even chains lengths distribution. All these attributes show that the non-specific reaction alone cannot fully explain all experimental findings of the discussed process.

Another picture appears from analysis of the specific redistribution reaction (cf. Figure S6). In this case, at the beginning of the polymerization process, every attack on the last unit in another chain produces two odd chains, so the reaction change the ratio odd/even chains twice as efficiently as the nonspecific redistribution. Lengths of products of the reaction differ from substrates only by one unit and increase of dispersity is minimal, in reality difficult to detect or measure. The Figure 5 in the main text shows evolution of dispersity vs. time for various rate constants in process with only the specific redistribution reaction. Dispersity remains practically unchanged, even when the rate constant is increased by two orders of magnitude. It is worth to note that since the depropagation decreases chain lengths by two lactoyl units it affects value of  $\mathcal{D}$  a lot more efficiently than the specific redistribution reaction.

Figure 4 in the main text shows changes of the ratio  $R$ . A several features of plots can be noticed, which confirms expectation derived in analysis of Figure S6. The first is the narrow range of lengths of chains appearing in the system in comparison to the broad range observed

for non-specific redistribution and large noises on both borders due to a low number of chains with the limiting lengths. Next, dependencies have horizontal linear segments, with its level increasing with rate constants  $k_{e0}$ , analogously to experimental results shown in Figure 3. The shapes indicate that widths and maxima of the even and odd chain lengths distributions are very close. This characteristic attribute suggests that, indeed, the specific redistribution reaction have to be considered as a crucial element for interpretation and understanding of our MALDI-ToF spectra.

We do not show a plot representing this process at the stage close to the equilibrium. Simply, the equilibrium would require unlikely high value of  $k_{e0}$  exceeding the propagation rate constant. Thus, in the real systems, the specific redistribution reaction changes MWD too slowly and the non-specific segmental exchange reaction is responsible broadening of MWD observed at late stage of the process.

### Kinetic equations

Rate  $r_{e0}$  of formation of the odd chains and disappearance of the even chains in the specific intermolecular exchange reaction is given by equation S6.

$$r_{e0} = \frac{d[O]}{dt} = -\frac{d[E]}{dt} = k_{e0} [E][E] - k_{e0} [O][O] \quad (S6)$$

Where [O] and [E] mean concentrations of the odd and even chains, respectively. At the very beginning of polymerization process, when  $DP_n \geq 2$  and still no odd chains exists ( $[O] = 0$ ), concentration of even chains [E] is equal to concentration of used alcohol. Thus the initial rate of the specific redistribution  $r_{e0}(0)$  is equal:

$$r_{e0}(0) = \frac{d[O]}{dt} = -\frac{d[E]}{dt} = k_{e0} ([ROH]_0)^2 \quad (S7)$$

It is clear that the specific redistribution is 2<sup>nd</sup> order reaction in respect to alcohol and its rate should be very sensitive to alcohol concentration.

Initial rate of propagation at start of polymerization  $r_p(0)$  is equal:

$$r_p(0) = \frac{d[\text{LL}]}{dt} = -k_p [\text{ROH}]_0 [\text{LL}]_0 \quad (\text{S8})$$

Where  $[\text{LA}]_0$  is initial concentration of L-Lactide.

After dividing (S7) by (S8) we get:

$$\frac{r_{e0}(0)}{r_p(0)} = \frac{k_{e0} [\text{ROH}]_0}{k_p [\text{LL}]_0} = \frac{k_{e0}}{k_p DP_n} \quad (\text{S9})$$

where  $DP_n$  is the number averaged degree of polymerization calculated for complete monomer conversion.

Thus, the ratio of odd chains formation to propagation rates should be inversely proportional to average polymerization degree, what was indeed observed by Prud'homme et al. (cf. Figure 9 in the ref. S3). Therefore, the kinetic analysis and experimental findings confirm important role of the specific redistribution in the system.

For the nonspecific intermolecular exchange reaction we have:

$$\begin{aligned} r_e &= \frac{d[\text{O}]}{dt} = -\frac{d[\text{E}]}{dt} = \frac{1}{2}k_e 2[\text{E}](\text{[LL]}_0 - \text{[LL]}) - \frac{1}{2}k_e 2[\text{O}](\text{[LL]}_0 - \text{[LL]}) = \\ &= k_e ([\text{E}] - [\text{O}])(\text{[LL]}_0 - \text{[LL]}) \end{aligned} \quad (\text{S10})$$

where factors 1/2 stem from the fact that half of lactoyl constitutional units is placed on even positions in the chain and the second half occupies odd positions. Concentration of the lactoyl constitutional units in polymer is expressed by the difference between initial and current monomer concentration multiplied by 2, i.e.  $2*([\text{LL}]_0 - [\text{LL}]_t)$ .

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