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L-Lactide Polymerization Studied by ^{1}H NMR with Diffusion Ordered Spectroscopy (DOSY). "One NMR Tube Experiment" Providing: Conversion, Polymer Structure, M_n and M_w.

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Supplementary Information

Materials

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^{-3} 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 (LA) (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)$_2$ ($SnOct_2$) (95%, Aldrich, USA) was distilled twice (10^{-3} mbar, 413 K) into glass ampoule with Rotaflo® stopcock and finally distributed in vacuum into glass ampoules with break-seals. Our earlier studies

indicated that in this treatment water and other impurities are removed and ~ 99% purity of $SnOct_2$ can be achieved.[S1]

$CDCl_3$ (99.8%, Armar Chemicals, Switzerland) was stored over calcium hydride. C_6D_6 (99.5%, Armar Chemicals, Switzerland) for NMR spectroscopy was applied as received. Kinetic studies were conducted in the solvent dried over sodium/potassium alloy and stored in vacuum in ampoule Rotaflo® stopcock.

Preparation of well-defined PLA samples

The well-defined PLA samples used for determination of the relationship between mass-average molar masses M_w and diffusion coefficients (D) were synthesized as follows: break-seals containing LA (4.13 g, 28.7 mmol), $SnOct_2$ (0.0583 g, 0.14 mmol), and BzOH (0.0447 g, 0.41 mmol) were attached to the reaction vessel equipped with a polarimetric cell and three ampoules for collecting samples (Figure S1). Tetrahydrofuran (26.6 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 polarimetric cell and sample ampoules. Ampoules and the cell were sealed off and placed in the thermostatic bath (353 K). Conversions was determined from polarimetric measurements at room temperature, knowing that in this system racemization reactions are absent.[S1] At the suitable monomer conversions, as determined from polarimetry, the selected ampoule was cooled to room temperature, opened, quenched by acetic acid, and polymer was isolated by precipitation into cold methanol and finally dried in vacuum to the constant weight.

Analytical procedures

Size Exclusion Chromatography (SEC)

The mass average molar masses M_w's of PLA were determined by SEC using an Agilent Pump 1100 Series (preceded by an Agilent G1379A Degaser), Agilent 1100 Series Injector, and a set of two PLGel 5μ MIXED–C thermostatted columns. Wyatt Optilab Rex differential refractometer and a Dawn Eos (Wyatt Technology Corporation) multi angle laser photometer were used as detectors. Dichloromethane was used as eluent at a flow rate of 0.8 $mL \cdot min^{-1}$ at 303 K. Value of refractive index increment (dn/dc) equal to 0.035 $mL \cdot g^{-1}$ was determined according to Wyatt recommendations and used in calculations of M_w by Astra 5.1 software. Collected RI traces of all samples are shown in the Figure S1.

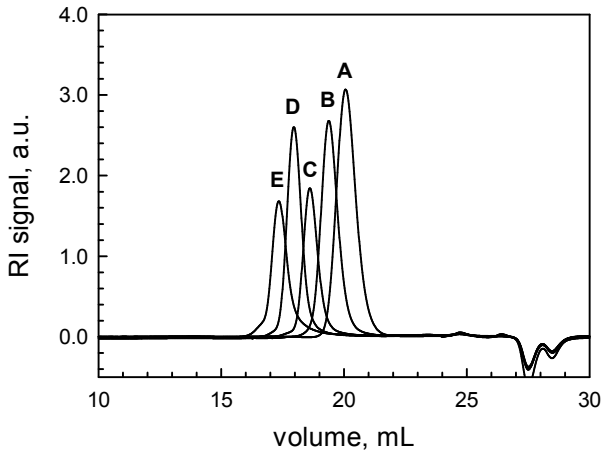


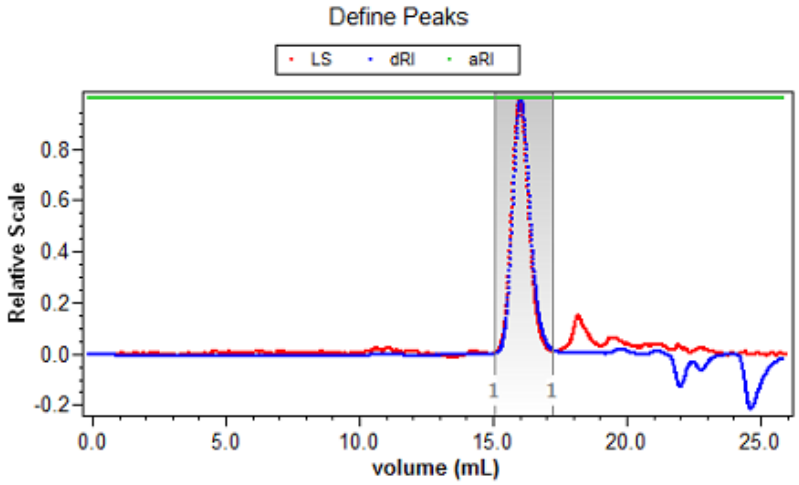
Figure S1. RI traces of PLA samples.

Next two pages present Astra report for SEC analysis of sample A.

ASTRA 6 Report PL-159-1b

File Name: D:\Wyatt Installation\LEWINSKI\PL-159-1b.afe6
Collection Operator: GPC\Eclipse (GPC\Eclipse (Eclipse))
Processing Operator: GPC\Eclipse (Eclipse)

Sample: PL-159-1



Configuration

Concentration Source: RI
Flow Rate: 0.800 mL/min

Light Scattering Instrument: HELEOS
Cell Type: Fused Silica
Wavelength: 664.1 nm
Calibration Constant: 3.1038×10^{-5} 1/(V cm)

RI Instrument: rEX

Solvent: methylene chloride
Temperature Correction Enabled: no
Refractive Index: 1.424

Processing

Collection Time: Thursday December 12, 2013 11:04:27 AM Central European Daylight Time
Processing time: Monday February 24, 2014 10:06:34.647 AM Central European Daylight Time

Peak settings:

Peak Name	Peak 1
Peak Limits (mL)	15.058 - 17.249
Light Scattering Model	Zimm
Fit Degree	1
dn/dc (mL/g)	0.0350

dn/dc (mL/g)	0.0350
A2 (mol mL/g²)	0.000
UV Ext. Coef. (mL/(mg cm))	0.000

Results Fitting Procedure:

Data	Fit Model	Degree	R^2	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
Masses	
Injected Mass (µg)	690.00
Calculated Mass (µg)	677.21
Mass Recovery (%)	98.1
Mass Fraction (%)	100.0
Molar mass moments (g/mol)	
Mn	4.120×10^3 (±2.079%)
Mp	4.184×10^3 (±1.573%)
Mv	n/a
Mw	4.244×10^3 (±2.184%)
Mz	4.413×10^3 (±5.839%)
Polydispersity	
Mw/Mn	1.030 (±3.015%)
Mz/Mn	1.071 (±6.198%)
rms radius moments (nm)	
Rn	n/a
Rw	n/a
Rz	n/a

[1]H NMR Spectroscopy

Spectra of PLA samples dissolved in C_6D_6 or $CDCl_3$ were acquired on Bruker AV III 500 spectrometer. ^{1}H NMR (500 MHz, 298 K, C_6D_6): δ = 7.25-7.35 (m, Ar), 5.12 (q, C*H*OCO, m, PhCH_2O), 4.32 (q, C*H*OH), 1.354 (d, CH_3), 1.43-1.49 (3 d, CH_3 end groups). In Figure S3 is presented the ^{1}H NMR spectrum of sample A. The spectrum confirms structure of the sample and the M_n = 4025 calculated from equation S1 is consisted with M_n determined from SEC.

$M_n = 72.06*(I(d,e,e',e'')-I(e'''))/I(e''') + 108.14$ (S1)

Where I(d,e,e',e'') is total integration of signals ascribed to protons **d, e, e', e''** and I(e''') is integration of signal ascribed to proton **e'''**.

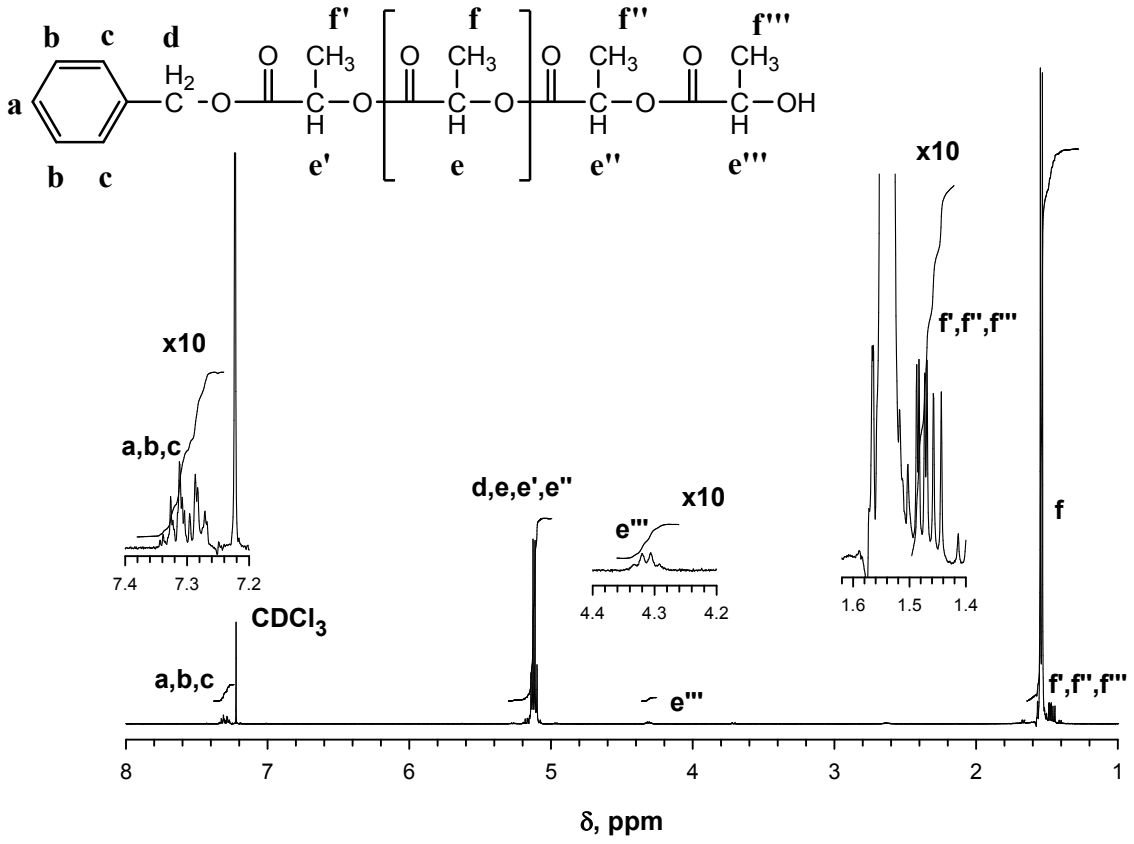


Figure S2. ^{1}H NMR 500 MHz spectrum of sample A in $CDCl_3$ solvent. Integrations (number of protons): I(e''')=1, I(d,e,e',e'')=53.4. The $SnOct_2$ moiety has been removed in the work-out of samples.

DOSY ^1H NMR

All measurements were performed in C_6D_6 solvent. Spectra were acquired following conditions applied by Grubbs.[S2] Bruker AV III 500 spectrometer equipped with 5 mm BBI probe head with z-gradients coil and GAB/2 gradient unit capable to produce B0 gradients with maximum strength of $5 \cdot 10^3$ $G \cdot m^{-1}$ was used. The BCU-05 cooling unit was used for temperature stabilization. All samples were thermostatted at 298 K for at least 5 minutes before data accumulation and the ^1H $\pi/2$ pulse length was checked and adjusted for each sample. The standard Bruker pulse program dstebpgp3s for diffusion measurement using double stimulated echo for convection compensation and LED (Longitudinal Eddy Current Delay) using bipolar gradient pulses for diffusion and 3 spoil gradients was exploited. Gradient pulse (small delta, δ) was set to 3.2 ms, diffusion time (big delta, Δ) was set for each sample separately between 100 and 350 ms. Gradient spoil pulse was 0.6 ms, the eddy current delay was set to 5.0 ms and delay for gradient recovery was set to 0.2 ms. DOSY experiments were run in pseudo 2D mode with 32 increments for gradient steps; gradients were changed exponentially between 5 and 95 percents of the maximum strength. Collected spectra were processed by TopSpin 3.1 software supplied by Bruker. The 1 Hz line broadening Lorenzian function was applied, dimension and each row was phased and baseline corrected before the Fourier transformation execution in F2 dimension. Diffusion coefficients for resolved ^1H signals were extracted from decay curves using the T1/T2 analyze module of the TopSpin program or the ITAMeD algorithm provided by Urbańczyk et al.[S3] In the ITAMeD the number of iterations was set to $5 \cdot 10^4$ and the sparsity-promoting norm l_1 to 0.01 for well-defined samples and l_1 was equal 0 for polymerizing mixtures. The signal decay curves are shown in Figure S3.

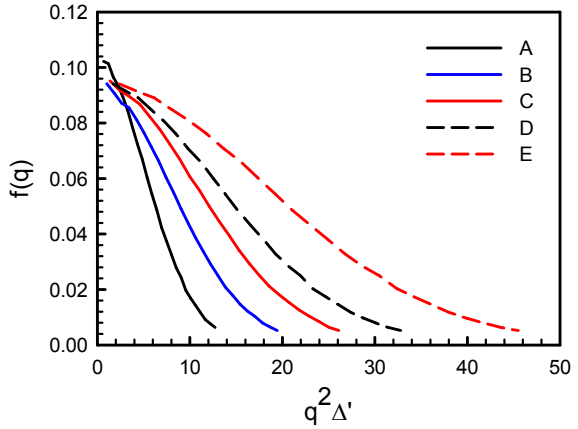


Figure S3. DOSY ^{1}H NMR signal decay curves for PLA samples. [PLA] = 0.5 g/L.

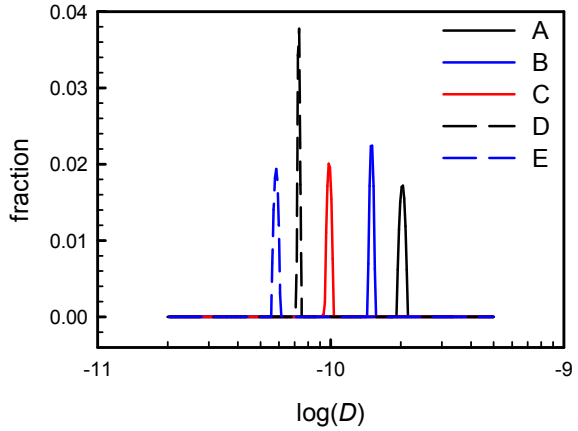


Figure S4. Distribution of diffusion coefficients *D* obtained using the ITAMeD algorithm.

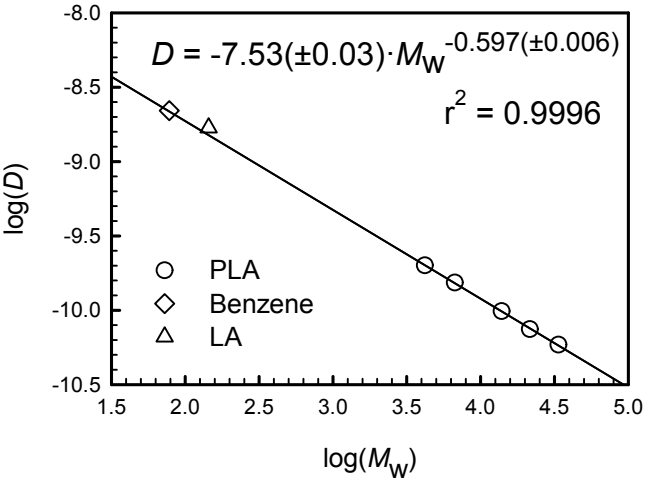


Figure S5. Dependence of M_w on *D* obtained from discrete diffusion coefficients *D* extracted by the T_1/T_2 module of TopSpin.

Determination of M_w at high solution concentrations

The diffusion coefficient is known to depend not only on the molecular mass, but also on the concentration of the polymer in the analyzed solution.[S4,S,5] The dependence is linear up to a some limiting concentration (usually up to 5-15%) and its slope weakly change with the molar mass of macromolecules.[S4] When polymer concentration is different from 0.5 g/L (at which the dependence was established) and vary due to the progress of polymerization process, then the diffusion coefficient determined for the selected experimental conditions has to be adjusted to the valid concentrations in order to properly determine M_w. Therefore diffusion coefficients at high concentration (30 g/L) in C_6D_6 were determined for PLA's samples A-E and, additionally, linearity of the dependence of D on polymer concentration was checked for one chosen sample B. The results are presented in Figure S6.

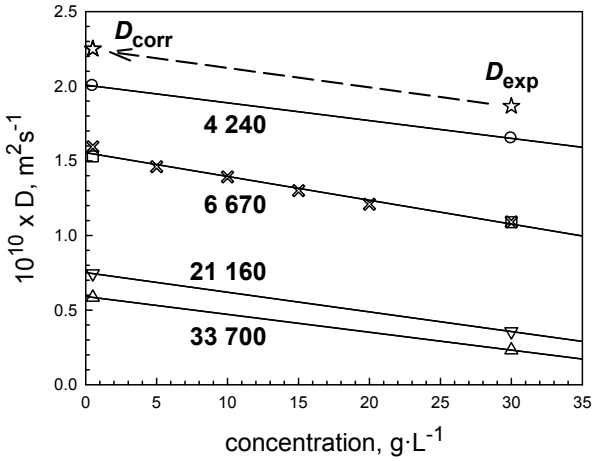


Figure S6. Dependence of the D on M_w and concentration of polymers. Open marks: data used for determination of plot slopes. Numbers indicate M_w of samples. The good linearity of the concentration dependence is confirmed by points marked by crosses. Stars illustrate a correction introduced by equation S2.

It follows that in the range of polymer concentrations up to 30 g/L the dependence is linear. Slopes of the determined plots do not depend on molar masses. Therefore it was assumed that the

mean value of the slope (S) is equal to $(1.3\pm0.2)\cdot10^{-12}$ m^2L/gs and is common for all molar masses, at least within the studied range. Thus, the value of diffusion coefficient corrected to the valid condition can be calculated from equation (S2):

$$D_{corr} = D_{exp} - S(c_{exp} - c_{corr}) \quad \text{(S2)}$$

Where: D means diffusion coefficient; S is the mean value of slope for all plots; c is concentration; indices "exp" and "corr" mean experimental and corrected value, respectively.

Finally the M_w were calculated from the D_{corr} values using Equation 3 given in the main text.

Dependence of D on polymer concentrations stems from: (a) non zero value of the second virial coefficient, (b) the partial specific volume of polymer in solution, (c) the frictional coefficient of polymer molecule (related to intrinsic viscosity).[S4] The second virial coefficient could vanish in theta temperature, however the partial specific volume is always different from zero and the frictional coefficient could be dependent on polymer concentration.

Kinetics of polymerization

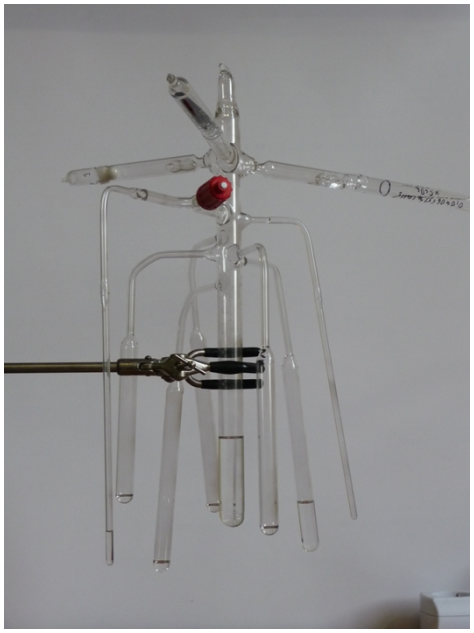


Figure S7. Reaction vessel used for studies of the living process.

Kinetic experiment with sampling of the polymerization mixture.

A mixture containing LA (1.0881 g, 0.0755 mol), $SnOct_2$ (0.0406 g, $1.00 \cdot 10^{-5}$ mol), BzOH (0.0108 g, $1.00 \cdot 10^{-5}$ mol), C_6D_6 (32.5 ml); $[LA]_0$ = 32.6 g/L (0.226 mol/L), $[BzOH]_0 = [SnOct_2]_0 = 2.99 \cdot 10^{-3}$ mol/L was prepared and distributed into four tubes in high vacuum conditions. Then the tubes were sealed-off and heated for predetermined times at 353 K. After that the tubes were opened and the polymerizing mixture was quenched with excess of acetic acid ("killed"). Obtained solutions were analyzed by the ^{1}H NMR/DOSY method and SEC with MALLS detector. Determined molar masses and diffusion coefficients are given in Table 2 in the main text and shown in Figure S8.

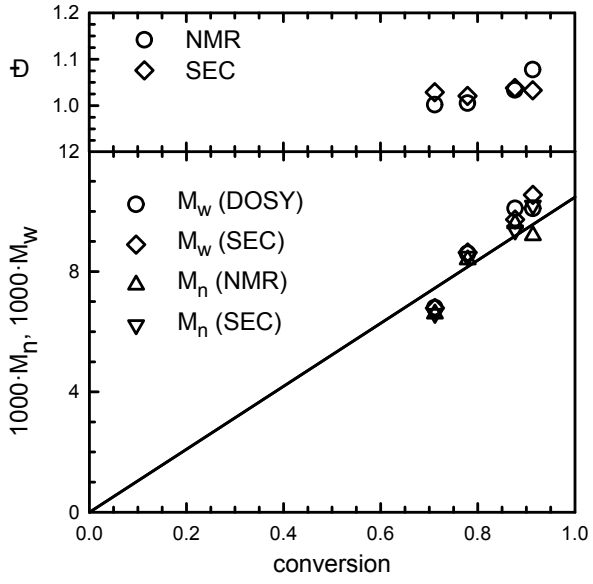


Figure S8. Dependence of M_n, M_w, and $Đ$ on conversion for "killed" PLA. Polymerization in C_6D_6 at 353 K, initiated with $SnOct_2$/BzOH system. Solid line is the least square fit to the M_n data.

As it follows from Figure S8 the M_w from DOSY and from SEC are almost identical, indicating that the determined earlier relationship is correct.

Moreover, for the dead macromolecules both DOSY and SEC give nearly the same values of M_n and M_w, and very low $Đ$, as expected for controlled/living processes. $Đ$ obtained from ^{1}H NMR/DOSY are more scattered than these from SEC, because M_n and M_w determined by NMR come from two independent procedures, each one possessing its own specific errors. In case of SEC, both M_n and M_w are determined by the same physical method.

Examples of polymerization process studied *in situ* ("One NMR Tube Experiment")

Two experiments were carried on in two different ranges of molecular weights (conditions are given below).

A) LA (1.0881 g, 0.0755 mol), $SnOct_2$ (0.0406 g, $1.00 \cdot 10^{-5}$ mol), BzOH (0.0108 g, $1.00 \cdot 10^{-5}$ mol), C_6D_6 (32.5 ml); $[LA]_0$ = 32.6 g/L (0.226 mol/L), $[BzOH]_0 = [SnOct_2]_0 = 2.99 \cdot 10^{-3}$ mol/L.

B) LA (0.18912 g, 1.312 mmol), $SnOct_2$ (0.0282 g, 0.0696 mmol), BzOH (0.0075 g, 0.0694 mmol), C_6D_6 (6.12 ml); $[LA]_0$ = 30 g/L (0.214 mol/L), $[BzOH]_0 = 1.134 \cdot 10^{-2}$ mole/L, $[SnOct_2]_0 = 1.131 \cdot 10^{-2}$ mol/L.

Break-seals containing LA, $SnOct_2$, and BzOH were attached to reaction vessel equipped with NMR tube. Dry C_6D_6 was distilled into it under high vacuum and the vessel was sealed off. Then the break-seals were broken, reagents were mixed at room temperature and solution was transferred into the NMR tube. Then the tube was sealed off and placed in thermostatic bath at 353 K. At predetermined time intervals the tube was cooled and NMR spectra were taken at 298 K. Measurements required ca. 20 minutes. During this time at 298 K conversion was negligible. Time of cooling from 353 K to 298 K was less than 30 s.

For two different concentrations of the initiating systems coherent results were obtained, illustrated in figures S9-S11.

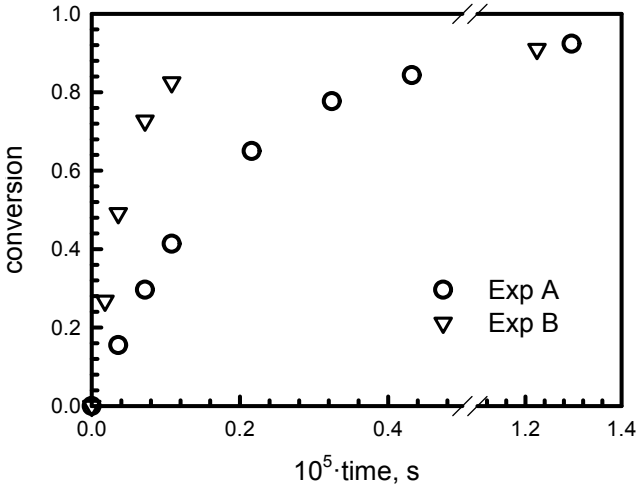


Figure S9. The monomer conversion in polymerization of LA in C_6D_6 at 353 K, initiated with $SnOct_2$/BzOH system. The last values on the plot were used for determination of the equilibrium concentration of L-lactide.

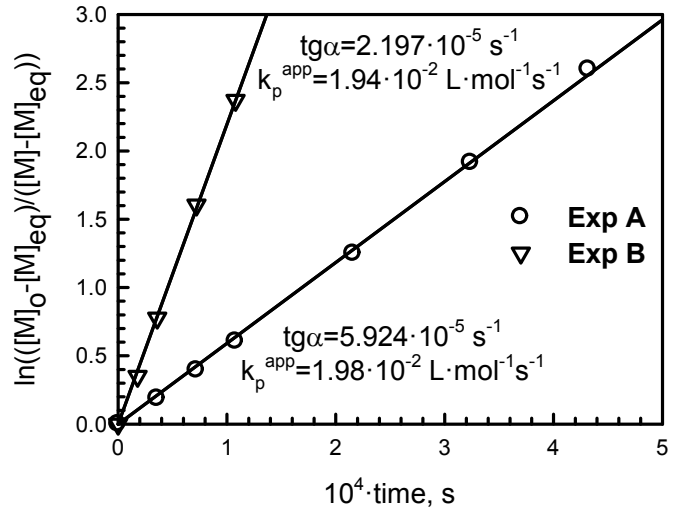


Figure S10. Semi-logarithmic kinetic plots for polymerization of LA in C_6D_6 at 353 K, initiated with $SnOct_2$/BzOH system. Apparent rate constants k_p^{app} = tgα/$[BzOH]_0$ are reported for both conducted experiments.

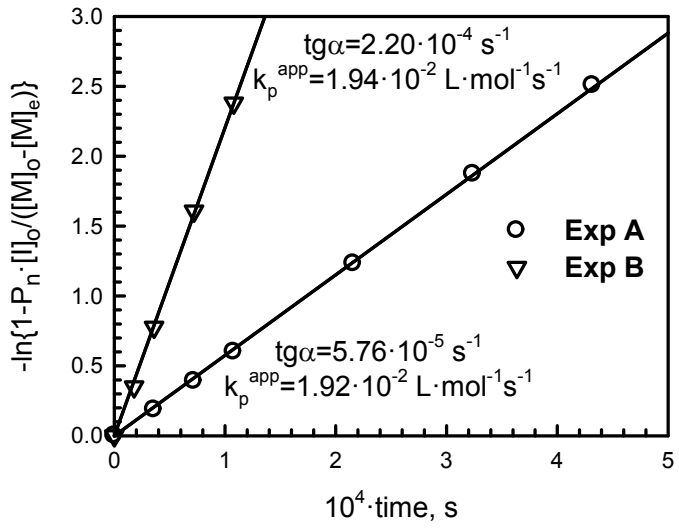


Figure S11. Plots of Equation 5 (from the main text) for polymerizations of LA in C_6D_6 at 353 K, initiated with $SnOct_2$/BzOH system. Apparent rate constants k_p^{app} = tgα/$[BzOH]_0$ are reported for both conducted experiments.

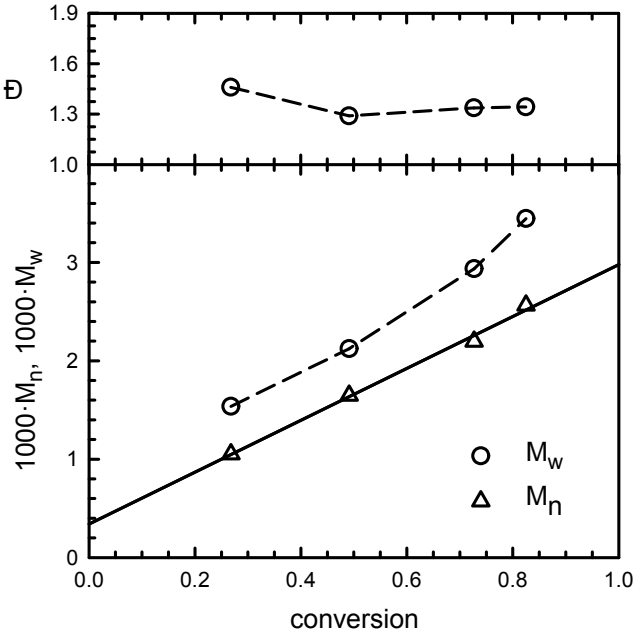


Figure S12. Dependence of M_n, M_w, and $Đ$ on conversion in controlled/living polymerization of LA in C_6D_6 at 353 K, initiated with $SnOct_2$/BzOH system (Experiment B). Solid line is the least square fit to the M_n data. Dashed lines illustrate evolution of M_w and $Đ$. The M_n plot does not hit "0" value, since at the zero time M_n was already equal to the molar mass of initiator.

High values of $Đ$ obtained from studies of the living process may indicate aggregation of the living macromolecules (compare Figures S8 for killed samples and Figures S12 and Figure 5 in the main text, for the living one).

Structure of active centers of propagation.

In the LA polymerization initiated by $SnOct_2$/BzOH the active form of catalyst results from reversible reaction:

$SnOct_2 + BzOH \rightleftharpoons BzO\text{-}SnOct + Oct\text{-}H$ (S3)

When initiation is over, then in the propagation step active and temporarily inactive chains centers of propagation are in equilibrium with inactive ones.[S1]

$PLAO\text{-}SnOct + Oct\text{-}H \rightleftharpoons PLAO\text{-}H + SnOct_2$ (S4)

Thus, concentration of the active centers is constant and is a function of the position of equilibrium. This equilibrium is responsible for broadening of the signal of methine proton ~CO-C(CH_3)**H**-O- of the ultimate lactoyl unit in the living polymerization mixture. Due to this broadening integration of the signal is not accurate. Acidification of the living polymer (killing) with acetic acid decomposes PLA-O-Sn- bond and transforms the broad signal into one regular quartet centered at 4.15 ppm, ascribed to protons of the end group -COC(CH_3)**H**-OH. Integration of the quartet is consistent with integration of the signal of methylene protons of the benzyl end group.

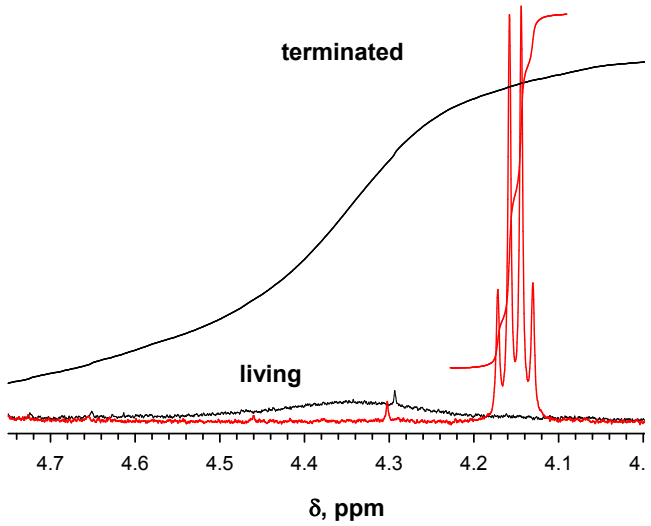


Figure S13. ^{1}H NMR 500 MHz spectrum of polymerization mixture in region of methine proton of the ultimate lactyoyl unit ~CO-C(CH_3)**H**-O- in C_6D_6. Experiment B. Reaction time = 3 h. Black line: living mixture, red line: terminated mixture. Integrations (number of protons): the quartet=1, the broad signal=0.93.

REFERENCES

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