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ANIONIC POLYMERIZATION OF L-LACTIDE EFFECT OF LITHIUM AND POTASSIUM AS COUNTERIONS

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SUMMARY

The polymerization of L-lactide was carried out with t-BuOK and t-BuOLi in the presence and absence of crown ethers. Each polymerization showed living nature only in the limited sense of having a decreasing amount of active species at high conversion. The initiator efficiency was low in each case because of the deprotonation reaction between the tert-butoxide ion and L-lactide. Although termination did not take place with lithium containing initiators to 90 % conversion, intra- and intermolecular transesterification was observed to a significant degree. With potassium containing initiators both termination and transesterification occurred.

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INTRODUCTION

Polylactides have been frequently applied for drug delivery systems as well as surgical materials because of their good biodegradation properties, biocompatibility, high mechanical strength and excellent shaping and moulding properties [1-3]. The most effective and most widely used initiators for the preparation of polylactides are complexation initiators, such as Sn(II)octoate and other tin compounds, Al isopropoxide, Zn, Pb, Sb salts, which initiate a chain growth via active covalent endgroups [4-9] .

Although anionic polymerization of L-lactide has been described in the literature, it is claimed to be of limited importance [10,11], and so, rarely studied. Its main drawbacks are the unavoidable racemization and transesterification. Interestingly enough, racemization occurs in molten phase to a great extent [12,13], but in solution it is strongly limited [14,15,18].

However, anionic polymerization has also advantages. It is very fast and the product does not contain heavy-metal contaminants, which is useful in pharmaceutical applications. The molecular mass is sensitive to the presence of crown ethers as was described in one of our papers [15]. In this connection, it has not been investigated so far, what is the role of the counterions and whether these polymerizations have really living character as was stated in some publications [14,15].

EXPERIMENTAL

Materials

L-lactide was prepared from L-lactic acid according to a described procedure

[19]. The crude monomer was purified by recrystallization from dry ethyl acetate and subsequently stored over P_4O_{10} in vacuum. $[\alpha]_D^{20} = -291.5°$ in benzene (literature datum is -298° [20]). Potassium tert-butoxide (Aldrich Chemical Co) was sublimed and distributed into glass ampules. Lithium tert-butoxide (Fluka product) was used as received. 18-crown-6 was purified by the acetonitrile method [17], 12-crown-4 (Aldrich product) was dried over P_4O_{10}. THF was refluxed and distilled over CaH_2 and subsequently over $LiAlH_4$ before use.

Polymerizations

Polymerizations were carried out under dry nitrogen atmosphere in a stainless steel dry box at ambient temperature. Thoroughly cleaned and dried round bottom flasks equipped with magnetic stirring bar served as reactors. 800 mg L-lactide was dissolved in absolute THF to amount to 3 mL solution (or according to the concentration indicated) and 140 μL 0.4 M initiator solution was added. The polymerization was terminated after different polymerization time by 4 mL CH_2Cl_2 and ~0.5 mL sample was withdrawn for SEC measurements.

Measurements

Size-exclusion chromatography (SEC) measurements were performed in CH_2Cl_2 on a Shimadzu LC-6A apparatus equipped with five Lichrogel columns (10 mm, PS 1, 20, 40, 400, 4000). The molecular masses were calculated by means of a calibration curve based on polystyrene standards. The yield was determined by the area of the monomer and the polymer. The difference of refractive index between L-lactide and poly(L-lactide) solution in CH_2Cl_2 is 3% . Optical rotations were measured on a Perkin Elmer 241 polarimeter. NMR spectra were taken using a BRUKER WP 200 SY spectrometer.

RESULTS AND DISCUSSION

Living character of the polymerization

Polymerizations are considered to be living if termination does not occur, that is, the ln $[M]_o/[M]_t$ versus time curve is linear and there is no chain transfer, which means linear $\overline{M}_n$ versus conversion function [16]. These functions can be constructed by measuring the composition of a given polymerization mixture at different time. Determining the polymer content after precipitation, which is usual practice in the literature [10,12,14,15], entails the risk of losing the low molecular mass components and so changing the molecular mass and its distribution. Therefore we measured these parameters directly in the polymerization mixture.

Figures 1 and 2 show that both termination and chain transfer occur by the polymerization with t-BuOK. The initiator efficiency is well below 100 %, i. e., the measured values of $\overline{M}_n$ are above the theoretical, $\overline{M}_n = M_{monomer} \cdot [M]_o/[I]_o$ line, indicating higher $\overline{M}_n$-s than expected from the feed.

The scattered pattern of measured values comes from the heterogeneity of the system. This is supported by the SEC chromatograms (fig. 3), where the peaks are bimodal. The molecular mass distribution decreases and becomes

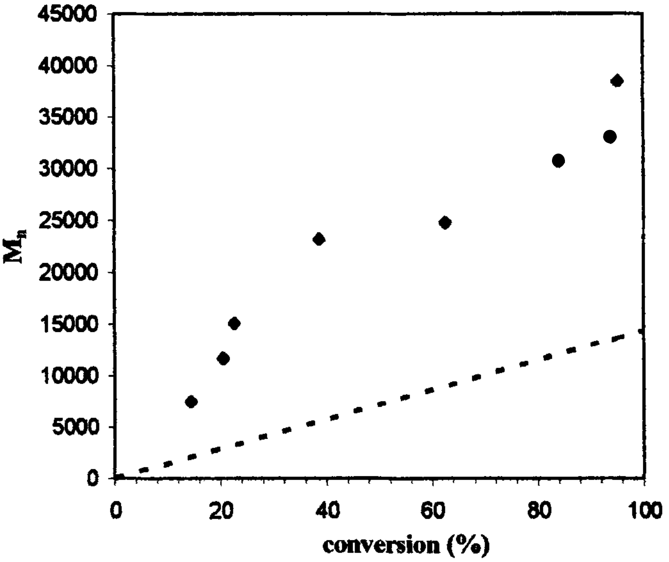


Fig. 1 Molecular mass versus conversion using t-BuOK initiator at ambient temperature. $[M]_o$=1.77 M, $[I]_o$=0.0178 M. ------ theoretical line.

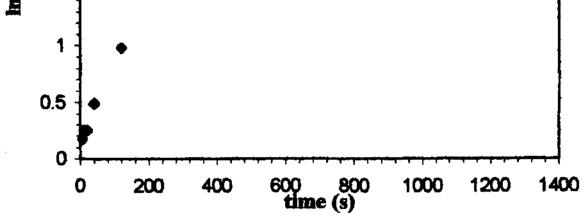


Fig. 2 $\ln[M]_o/[M]_t$ versus time using t-BuOK at ambient temperature. $[M]_o$=1.77 M, $[I]_o$=0.0178 M.

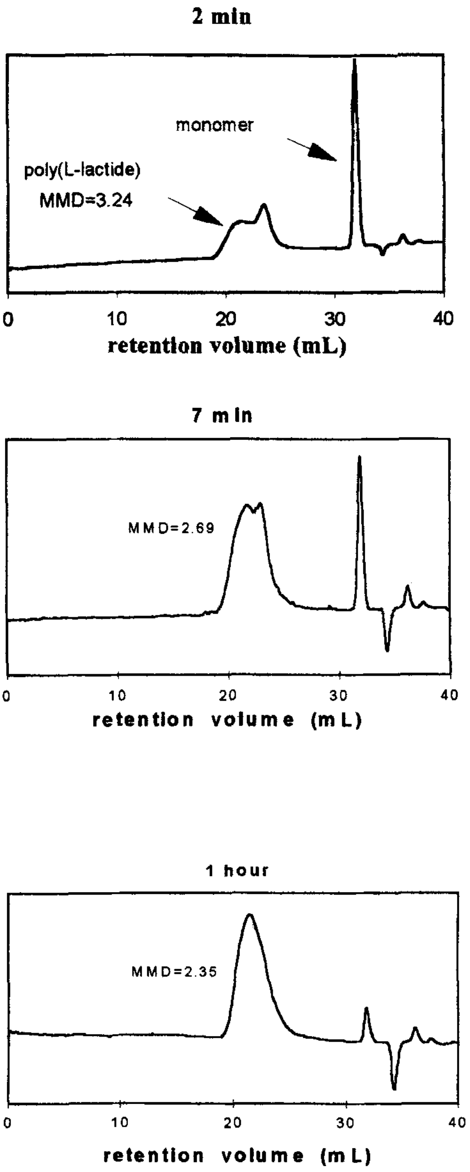


Fig. 3 SEC chromatograms of polymerization mixture after different polymerization time. The initiator is t-BuOK.

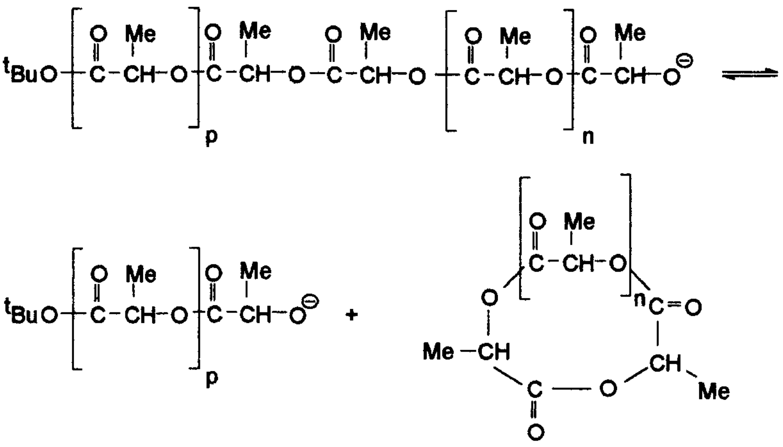
unimodal above 90 % conversion, which observation can be explained that mainly intermolecular transesterification occurs during the polymerization (Scheme 1).

Replacing potassium with lithium, the heterogeneity of the polymerization mixtures disappears (fig. 4).

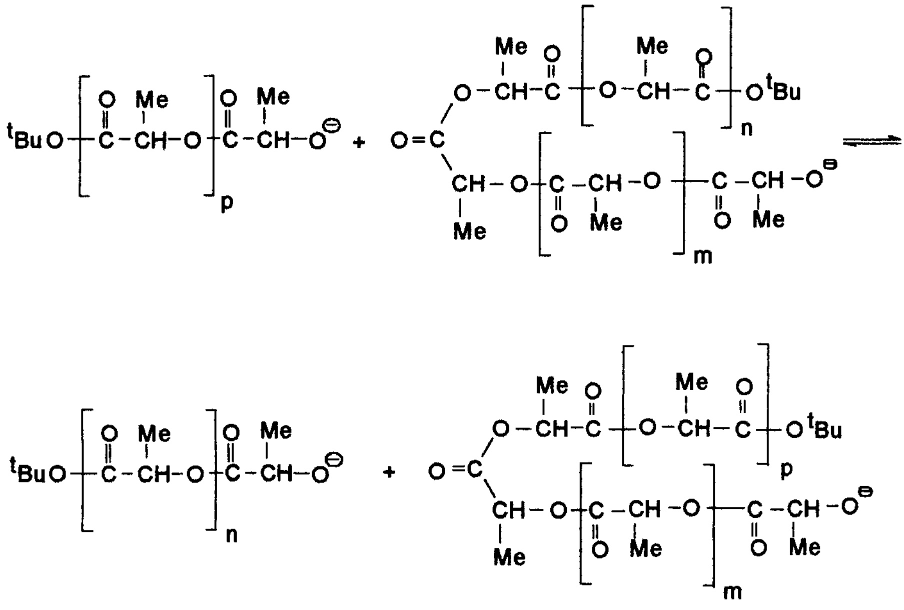
Inspite of this, the $\overline{M}_n$ versus conversion curve is not linear and exists above the theoretical values (fig. 5). The SEC traces are unimodal, but the molar mass distribution increases from 1.3-3.0. With increasing conversion, the amount of low molecular mass products increases as well, that is, transesterification also takes place. It follows from the optical rotation measurements, that in this case both intramolecular and intermolecular transesterification occur (see racemization section).
Although the number of molecules grows during the polymerization, the number of molecules with active chain end seems to be constant, which follows from the linear $\ln[M]_0/[M]_t$ versus time curve (fig. 6).

Independently, we tried to calculate the $\overline{M}_n$ from the integration ratio of methin quartet of monomeric units (δ=5.15) in the polymer chain and methin quartet of ultimate group (δ=4.36). Unfortunately, in the molecular range of $\overline{M}_n$ >10 kD this analysis does not give reliable results because of high noise/sign ratio.
The t-BuOK system can be made homogenous by adding 18-crown-6 in 1:1 molar ratio. In this case, the $\overline{M}_n$ versus conversion curve also runs above the theoretical line (fig. 7), but approaches that. Although the number of

Intramolecular transesterification (backbiting):



Intermolecular transesterification:



Scheme 1 Intra- and intermolecular transesterification of poly(L-lactide)

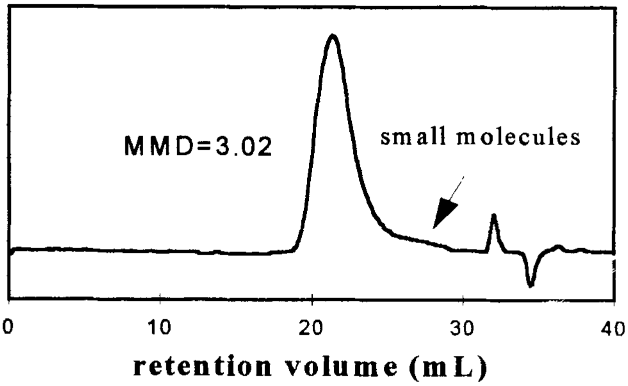


Fig. 4 SEC chromatogram of the polymerization mixture after 10 minutes using t-BuOLi initiator.

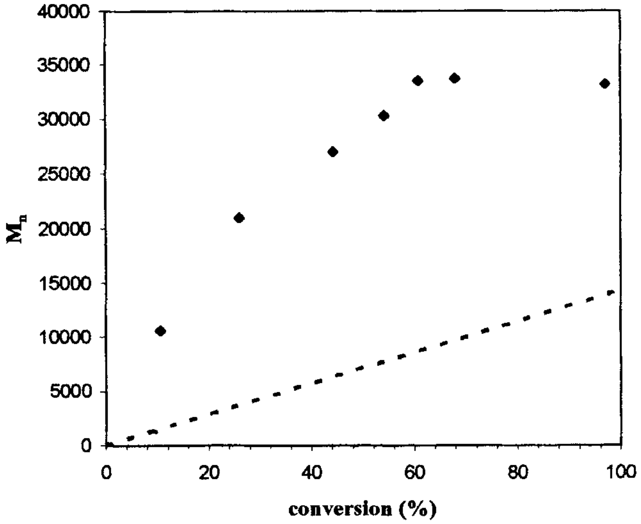


Fig. 5 $\overline{M}_n$ versus conversion using t-BuOLi initiator at ambient temperature. $[M]_o$=0.905 M, $[I]_o$=0.00905 M. ---- theoretical line.

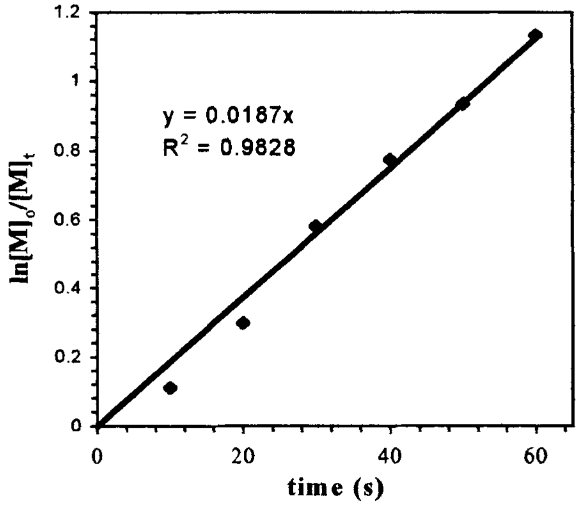


Fig. 6 $\ln[M]_o/[M]_t$ versus time curve using t-BuOLi initiator at ambient temperature. $[M]_o$=0.905 M, $[I]_o$=0.00905 M.

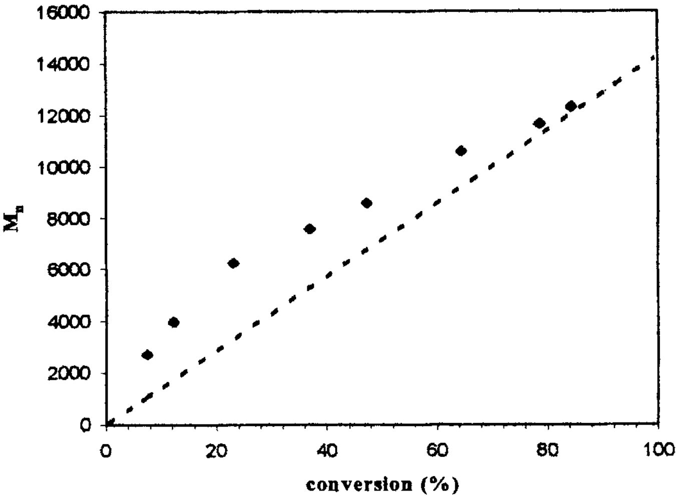


Fig. 7 $\overline{M}_n$ versus conversion using t-BuOK/18-crown-6 initiator at ambient temperature. $[M]_o$=1,76 M, $[I]_o$=0.0176 M. ----- theoretical line.

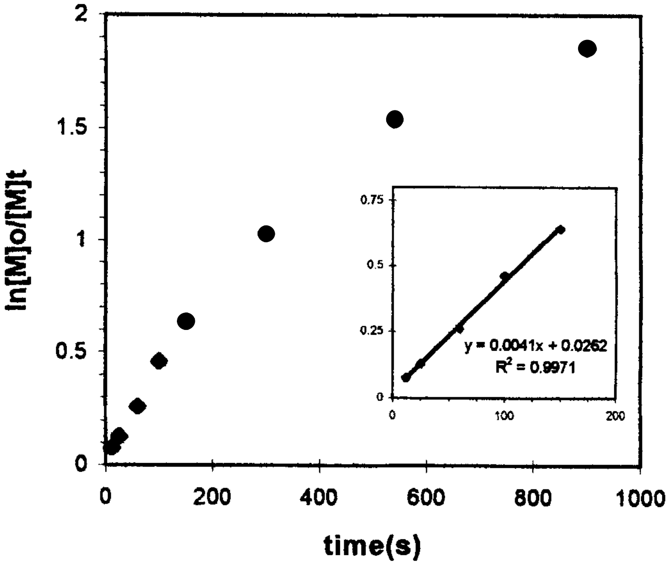


Fig. 8 ln$[M]_o/[M]_t$ versus time using t-BuOK/18-crown-6 initiator. $[M]_o$=1.76 M, $[I]_o$=0.0176 M.

molecules with active chain end decreases during the process, the termination is slow and for 150 s practically does not take place.

The presence of 12-crown-4 in t-BuOLi system does not cause changes to such an extent as 18-crown-6 does in the t-BuOK system .

Model experiments

For ^{1}H NMR spectroscopy, we mixed t-BuOLi with L-lactide in small molar ratio to locate the tert-butyl group after the initiation step. The spectrum of the mixture of t-BuOLi - lactide 2:1 shows two singlets of tert-butyl group, one at 1.44 ppm assigned as tert-butyl ester of lactic acid and one at 1.10 ppm

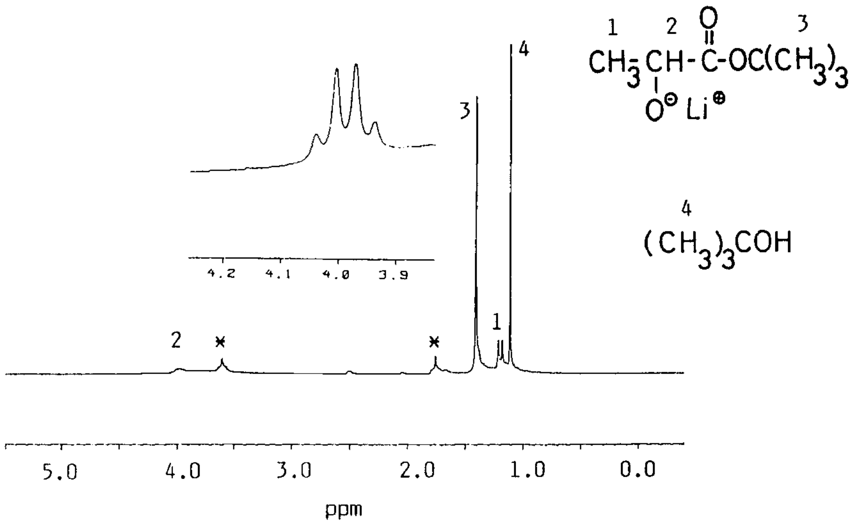


Fig. 9 ^{1}H NMR spectrum of t-BuOLi/L-lactide 2:1 mixture in deuterated DMSO. * THF impurity.

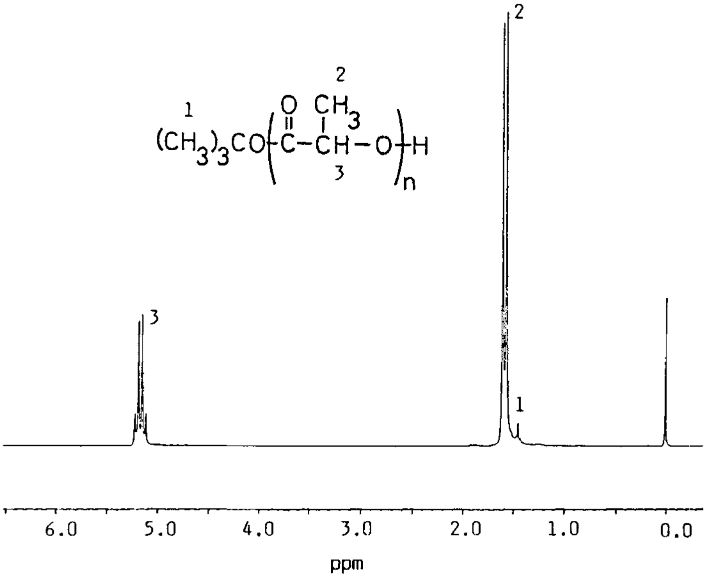


Fig. 10 ^{1}H NMR spectrum of polylactide prepared with t-BuOLi initiator. $\overline{M}_n$ = 27 600 by SEC.

Table 1 Change of specific optical rotation of the polymer in the course of the polymerization.

Initiator	Time	Conversion in %	$[\alpha]_D^{20}$ *
t-BuOK	40 s	32.6	- 131.9
t-BuOK	1 min	41.6	- 132.0
t-BuOK	5 mins	70.7	- 130.2
t-BuOK	10 mins	77.9	- 130.3
t-BuOK	1 h	89.7	- 131.8
t-BuOK+18-crown-6	150 s	47.3	- 133.2
t-BuOK+18-crown-6	5 mins	64.3	- 121.4
t-BuOK+18-crown-6	20 mins	84.2	- 114.0
t-BuOK+18-crown-6	1 h	91.5	- 109.5
t-BuOLi	10 s	44.9	- 146.8
t-BuOLi	20 s	68.8	- 149.6
t-BuOLi	40 s	88.3	- 150.6
t-BuOLi	60 s	93.6	- 153.8
t-BuOLi	5 mins	98.7	- 155.3
t-BuOLi	10 mins	99.5	- 154.0
t-BuOLi+12-crown-4	10 s	25.0	- 148.2
t-BuOLi+12-crown-4	20 s	52.6	- 152.9
t-BuOLi+12-crown-4	40 s	86.1	- 156.1
t-BuOLi+12-crown-4	60 s	93.0	- 157.5
t-BuOLi+12-crown-4	10 mins	97.2	- 155.5

*measured in CH_2Cl_2, in deg·dm^{-1}·g^{-1}·cm^3 unit.

assigned as tert-butanol (fig. 9). The ratio of the two peaks is approximately 1:1, but when the amount of L-lactide is increased, the amount of t-butanol increases as well.

In the case of polymers, we were able to identify the tert-butyl endgroups when the polymerization was initiated by t-BuOLi and its crown ether complex (fig. 10). In the polymers prepared with potassium containing initiators the endgroup was not significantly identified. This finding corroborates the earlier results of Kricheldorf [10].

Racemization

Although anionic mechanism is expected to cause racemization, the optical purity of the obtained polymers is quite high (table 1). We could practically measure the same values as the literature data for primary alcoholate initiators [15].

In the case of complexed K^+ couterion, the specific optical rotation decreases during the process owing to the racemization effect of alcoholate chain ends. However, when the system is heterogenous, i. e., in the case of t-BuOK, the specific optical rotation does not change significantly after the initiator is consumed. The risk of racemization is reduced in the case of Li^+ counterion. Slight increase of optical rotation can be spotted. Similarly to the observation and the explanation of Kricheldorf [10], we can explain this effect by the formation of cyclic oligomers due to backbiting, i. e., intramolecular transesterification, during the polymerization [scheme 1].

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