

## Living ring-opening polymerization of L,L-lactide initiated with potassium *t*-butoxide and its 18-crown-6 complex

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### Summary

Living polymerization of L,L-lactide initiated by potassium *t*-butoxide and its 18-crown-6 complex was investigated in THF solution at room temperature. The results support a reversible polymerization mechanism consisting of first order in monomer propagation and of unimolecular depropagation. The presence of 18-crown-6 has a strong MWD narrowing effect ( $M_w/M_n < 1.2$ ), slows down the overall rate of polymerization and gives rise to slow initiation. The polymerizations yield optically pure polymers both in the presence and absence of 18-crown-6.

### Introduction

The poly(L-lactide) and copolyesters of L-lactic acid possess extremely low toxicity and low immunogenicity, therefore, they are useful materials for various pharmaceutical and medical applications. In numerous patents and scientific papers dealing with the polymerization, various compounds are claimed as potential initiators [1-5]. These polymerizations are carried out almost exclusively in bulk at high temperatures and the conditions do not allow sufficient polymerization control as shown by unpredictable molecular weights and broad molecular weight distributions ( $M_w/M_n > 2$ ) [2,7]. These processes often bring about racemization.

On the other hand, when heavy metals are used as initiators, the poly(L-lactides) designated for medical or pharmaceutical purposes need to be purified from the poisonous catalysts.

Because of the above reasons, in this work we tried to achieve controlled polymerizations of L,L-lactide by using potassium salts as initiators in solution at room temperature.

Potassium salts of carboxylate anions, e.g. potassium acetate do not initiate the polymerization under these conditions even in the presence of 18-crown-6, although they initiate  $\beta$ -propiolactone [7] or oxirane [8] polymerizations.

As to our knowledge, potassium alkoxides have not been investigated so far. Therefore, we chose the potassium tert-butoxide and its 18-crown-6 complex in THF.

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## Experimental

Monomer: L,L-lactide was prepared from L-lactic acid according to the described procedure [9]. The crude monomer was purified twice by recrystallization from dry ethyl acetate and subsequently by sublimation in vacuo before use ( $80^{\circ}\text{C}$ ,  $\sim 10^{-2}$  mbar).  $[\alpha]_{\text{D}}^{25} = -279^{\circ}$ .

Initiator: Potassium tert-butoxide (Aldrich Chemical Co) was sublimed and distributed into glass ampules. 18-crown-6 was purified by the acetonitrile method [10].

Solvent: THF was distilled over  $\text{CaH}_2$  and subsequently over  $\text{LiAlH}_4$  before use.

## Polymerizations

Polymerizations were carried out under dry nitrogen atmosphere in a stainless steel dry box. Thoroughly cleaned and dried round bottom flasks equipped with magnetic stirring bar served as reactors. The reactors were charged by 10 mL solution of 2.88 g L,L-lactide and the polymerizations were started by fast introduction of 1 mL 0.2 M THF solution of t-BuOK or 1 mL 0.2 M THF solution of 18-Crown-6 and t-BuOK. For kinetic investigations 1 mL samples were drawn and terminated by 20 mL  $\text{CH}_3\text{OH}$ . The polymer was filtered, washed and dried.

## Measurements

GPC measurements were performed by means of a Shimadzu RID-6A apparatus equipped with five 10  $\mu\text{m}$  Lichrogel columns. The molecular weights were calculated by means of a universal calibration curve based on polystyrene standards.

The optical rotations were measured on a Bendix NPL 143 D automatic polarimeter.

## Preliminary Experiments

Potassium solutions, e.g. the THF solution of potassium/18-crown-6, are well known initiators of living ring-opening polymerizations [11]. However, according to our knowledge, no report appeared in the literature to claim the ring-opening polymerization of L,L-lactide initiated by K/18-crown-6/THF system. As Table 1 shows, this solution initiated the lactide polymerization but we were not able to define experimental conditions to achieve reproducible results. Since the potassium reacts with 18-crown-6 to yield the potassium salt of triethylene glycol [12], we have run polymerization using this salt as initiator. Unfortunately, the salt is only poorly soluble in THF, thus the concentration of the initiating species could not be maintained properly. This was the reason why we turned our attention toward the potassium tert-butoxide which is well soluble in THF.

## Results and Discussion

L,L-lactide can be polymerized with t-BuOK in THF solu-

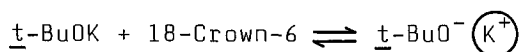
tion at room temperature (Table 2). The reaction is fast even at room temperature (Fig.1). As can be seen, the conversion approaches to a limiting value ( $\sim 83\%$ ) indicating that the polymerization is reversible. This finding corroborates earlier investigations [13]. The molecular weight distributions were, however, broader than expected for a living system.

To filter out the possible side reactions, i.e., to reduce the reactivity of the propagating species, we used 18-crown-6 to complex the gegenion. The presence of 18-crown-6 narrows the molecular weight distribution (Table 3) and slows down the polymerization (Fig. 1). The equilibrium concentration of L,L-lactide was significantly lower in the presence of 18-crown-6 than in its absence, indicating that the stabilizing effect of the gegenion is different in respect of the propagation and depropagation. (Table 4)

The living L,L-lactide polymerization thus involves the following elementary steps:

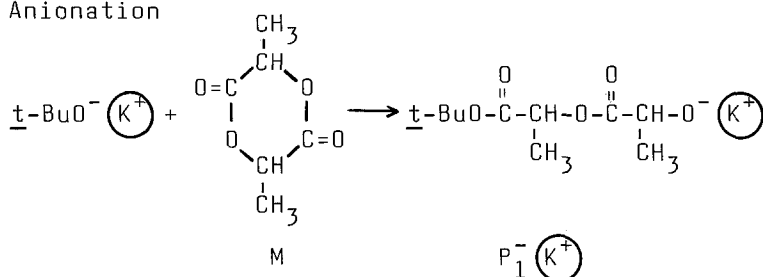
### Initiation

Ion generation

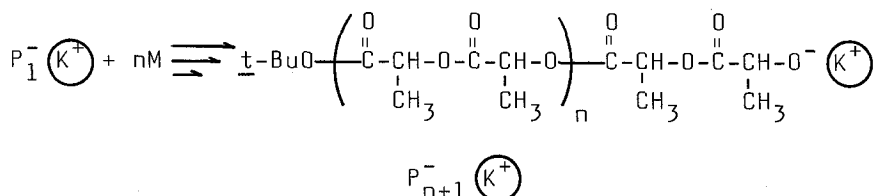


where  $(\text{K}^+)$  stands for the 18-Crown-6-complex of  $\text{K}^+$

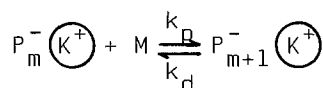
Anionation



### Propagation



Since the propagation is reversible



the rate of monomer consumption can be expressed as follows:

$$-\frac{d[M]}{dt} = k_p [P_m^- (K^+)] [M] - k_d [P_{m+1}^- (K^+)]$$

where  $k_p$  and  $k_d$  are the rate constants of propagation and depropagation, respectively.

Equilibrium state is reached when

$$k_p [P_m^- (K^+)] [M]_\infty = k_d [P_{m+1}^- (K^+)]$$

$$[M]_\infty = \frac{k_d}{k_p} \frac{[P_{m+1}^- (K^+)]}{[P_m^- (K^+)]} \approx \frac{k_d}{k_p}$$

If the initiation is fast

$$\sum [P_m^- (K^+)] = I_0 \quad \text{thus} \quad -\frac{d[M]}{dt} = k_p I_0 ([M] - [M]_\infty)$$

After integrating with the conditions  $t=0$ ,  $[M] = [M]_0$

we obtain

$$\ln([M] - [M]_\infty) = -k_p I_0 t + \ln([M]_0 - [M]_\infty)$$

The proposed mechanism is valid also for the uncomplexed  $t$ -BuOK but in this case the gegenion is  $K^+$ .

Since experimentally the L,L-lactide concentration was maintained much higher than the initiator concentration, we expected a straight line when plotting  $\ln([M] - [M]_\infty)$  versus  $t$ .

Indeed, the plot obtained was a straight line, supporting the above mechanism (Fig.2).

Plotting the  $\bar{M}_n$  values as a function of conversion, we obtained linear increase showing the living character of the L,L-lactide polymerization (Fig.3).

The slope of the  $\ln([M] - [M]_\infty)$  versus  $t$  straight line gives for the complexed case  $k_p = 5.3 \cdot 10^{-4} M^{-1} s^{-1}$ . The corresponding value for the uncomplexed case is  $k_p = 5.9 \cdot 10^{-3} M^{-1} s^{-1}$ , i.e., the propagation has been slowed down by a factor of 11 as a result of complexation. Using these constants,  $k_d$  values can be calculated from the  $[M]_\infty = k_d/k_p$  limiting concentrations:  $k_d = 2.37 \cdot 10^{-4} s^{-1}$  for the complexed and  $k_d = 1.45 \cdot 10^{-3} s^{-1}$  for the uncomplexed case. The slowing down factor is only 6 for the depropagation.

The calculated rate constants are only approximate values because the suggested mechanism is also only a rough approximation. This is especially the case when crown-ether-complexation was used: the assumption of fast initiation is not valid anymore. This fact can be well seen from the  $\bar{M}_n$  versus conversion plot of this system.

Although the  $\bar{M}_n$  increases with the conversion also in this case (Fig. 3),<sup>n</sup> the plot runs higher than in the absence of 18-crown-6. This means that the complexation gives rise to slow initiation.

Despite the living character of the system, the molecular weight can not be changed by the monomer/initiator ratio (Table 5).

### Optical Rotation

The poly(L-lactides) obtained by living polymerization initiated with *t*-BuOK or with *t*-BuOK + 18-crown-6 show optical activity, indicating that during the ring opening no racemization occurs. The value of the specific optical rotation is  $-146 \pm 1$ <sup>o</sup> which is close to the literature data (e.g.  $[\alpha]_D^{20} = -150$ <sup>o</sup> [1]). This means that the polymerization method described in this article yields almost optically pure poly(L-lactide).

Table 1: Polymerization with K/18-crown-6/THF system. The concentration of monomer  $C_M = 1.5$  M.

M/I	Time (h)	Yield %	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$
320	1	7.6	14000	1.43
160	1	21.6	13500	1.48
91	1	71.9	10300	1.53
64	1	56.0	5700	1.50

Table 2: Polymerization with *t*-BuOK.  $C_M = 1.45$  M, M/I = 100.

Time	Yield %	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$
1 min	37.7	10600	1.52
5 min	65.7	18200	1.47
10 min	68.4	18900	1.44
15 min	70.8	19900	1.43
25 min	76.4	20000	1.45
50 min	76.8	21600	1.42
120 min	74.4	22600	1.42
22 h	83.3	21800	1.45

Table 3: The effect of the  
 $\underline{t}$ -BuOK: 18-crown-6  
 Ratio on the MWD.  
 $C_M = 1.5 \text{ M}$ ,  $M/I = 100$ .

$\underline{t}$ -BuOK : 18-crown-6	$\bar{M}_w/\bar{M}_n$
1 : 0	1.42
1 : 0.5	1.32
1 : 1	1.17
1 : 2	1.16

Table 4: Polymerization with  $\underline{t}$ BuOK:  
 18-crown-6 = 1:1 complex  
 $C_M = 1.6 \text{ M}$ ,  $M/I = 100$ .

Time	Yield (%)	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$
5 min	11.7	8550	1.14
8 min	16.9	9900	1.11
14 min	28.8	11100	1.11
19 min	31.4	11350	1.16
25 min	38.3	12500	1.16
37 min	54.0	13270	1.15
75 min	63.0	13000	1.16
135 min	72.7	12650	1.20
22 h	72.2	14900	1.18
27 h	72.0	15000	1.17

Table 5: The effect of M/I on  
 the  $\bar{M}_n$ . Initiator:  
 $\underline{t}$ -BuOK + 18-crown-6  
 $C_M = 1.5 \text{ M}$

M/I	$\bar{M}_n$
166	13100
111	15700
83.3	18800
66.6	16500

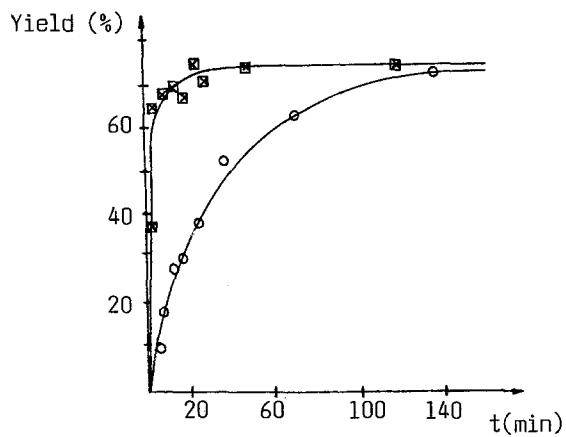


Fig.1. Yield of poly(L-lactide) during polymerization. (O)-complexed and (⊠)=uncomplexed case.

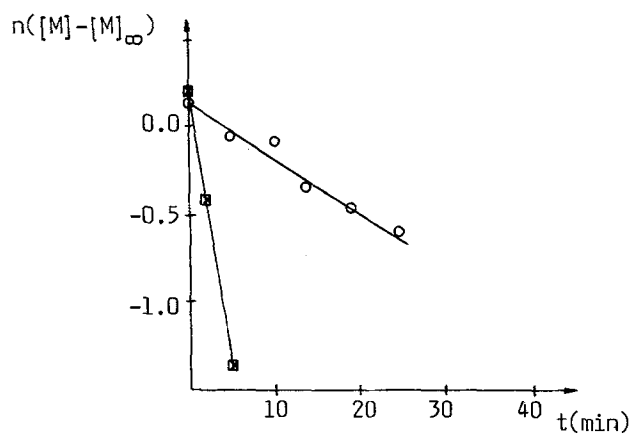


Fig.2. Dependence of  $\ln([M]-[M]_{\infty})$  on time, in the (O)=complexed and (⊠)=uncomplexed case.

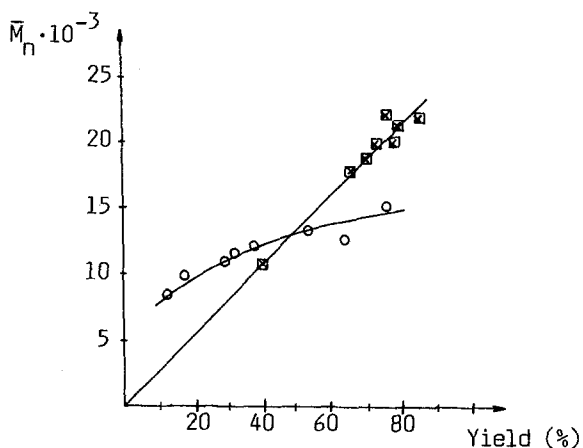


Fig.3. Dependence of  $\bar{M}_n$  on yield of polymer.  
(O)=complexed and (⊠)=uncomplexed case.

### References

1. J. Kleine and H.-H. Kleine, *Makromol. Chem.* **30** 23 (1959)
2. F. Chabor, M. Vert, S. Chapelle and P. Granger, *Polymer* **24** 53 (1983)
3. H.R. Kricheldorf and A. Serra, *Polym. Bull.* **14** 497 (1985)
4. R. Dunsing and H.R. Kricheldorf, *Polym. Bull.* **14** 491 (1985)
5. F.E. Kohn, J.G. von Ommen and J. Feijen, *Eur. Polym. J.* **19** 1081 (1983)
6. J. Rak, J.L. Ford, C. Rostron and V. Walters, *Pharm. Acta Helv.* **60** (5) 162 (1985)
7. S. Słomkowski and S. Penczek, *Macromolecules* **9** 367 (1976)
8. H. Koinuma, K. Naito and H. Hirai, *Makromol. Chem.* **183** 1383 (1982)
9. R. Dietzel and R. Krug, *Berichte* **58** 1313 (1925)
10. G. W. Gokel and D. J. Cram, *J. Org. Chem.* **39** 2445 (1974)
11. Z. Jedlinski, P. Kurcok and M. Kowalczyk, *Makromolecules* **18** 2679 (1985)
12. Z. Jedlinski, A. Stolarzewicz and Z. Grobelny, *Makromol. Chem.* **187** 795 (1986)
13. A. Duda and S. Penczek, *Macromolecules* **23** 1636 (1990)