

L-Lactide Homopolymerization and Copolymerization with ϵ -Caprolactone by Tetrahydrosalen Stabilized Yttrium Borohydride Complex*

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Abstract L-lactide (LLA) homopolymerization and copolymerization with ϵ -caprolactone (CL) in toluene initiated by tetrahydrosalen-supported yttrium borohydride complex were systematically investigated. A possible mechanism of LLA homopolymerization was proposed according to the ^1H -NMR result. In addition, PCL-*b*-PLLA copolymers were synthesized by sequential addition of monomers and their structure was characterized by GPC, ^1H -NMR and ^{13}C -NMR.

Keywords: Yttrium borohydride complex; Homopolymerization; Block copolymer.

INTRODUCTION

Poly(L-lactide) (PLLA), poly(ϵ -caprolactone) (PCL) and their copolymers are most widely used polymeric materials in medical and pharmaceutical applications due to their biocompatibility and biodegradability^[1]. For example, they can be used for biodegradable sutures, artificial skin, resorbable prostheses and controlled drug release, since the aliphatic polyesters can be removed from the body *via* normal metabolic pathways^[2]. Furthermore, the rapid degradation of PLLA and the permeability of PCL in PLLA-PCL copolymers can be well controlled by adjusting the copolymerization procedure^[3]. So far, a large variety of metal complexes have successfully catalyzed the ring-opening polymerization (ROP) of cyclic esters, like organometallic compounds containing aluminum^[4], calcium^[5], zinc^[6], magnesium^[7] and stannous^[8]. Besides, rare-earth complex initiators in ROP polymerization are booming because of their low toxicity, high activity and good control over the molecular weight and molecular weight distribution.

The pioneering work by Guillaume *et al.* revealed that the lanthanide borohydride complex was an efficient catalytic system for synthesis of hydroxytelechelic poly(ϵ -caprolactone)s, which allow further functionalization and applications^[9–11]. Since then, great attention has been focused on the development of lanthanide monoborohydride complexes with various ancillary ligands as single site initiator in ROP of cyclic esters^[12–14]. Our group previously reported that salen ligand stabilized, *in situ* generated rare-earth borohydride complexes were efficient initiators for ROP of ϵ -caprolactone^[15–18]. Here we describe the characteristics and mechanism of L-lactide (LLA) homopolymerization and copolymerization with ϵ -caprolactone (CL) initiated by this rare-earth borohydride complex.

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EXPERIMENTAL

Materials

L-lactide (LLA) was prepared according to the literature^[19]. ϵ -Caprolactone (CL) was dried over CaH_2 for 48 h and distilled under reduced pressure. Dimethoxyethane (DME), toluene and hexane were refluxed over blue benzophenone-Na complex and distilled under nitrogen atmosphere. The catalyst yttrium borohydride complex stabilized by tetrahydrosalen ligand was synthesized as previously reported by our group^[15].

Polymerization

All the polymerizations were performed using standard Schlenk techniques under dried argon atmosphere. For the LLA homopolymerization, the monomer solution in toluene and catalyst solution were introduced into an ampoule by syringe. After that, the reaction was terminated with 5% *i*-PrOH/HCl and the mixture was poured into pure ethanol. The white product was thereafter filtered and dried under vacuum. For the typical block copolymerization of LLA with CL, CL was polymerized in toluene first, and LLA was following introduced. The following treatments of copolymers were similar to those of the homopolymer.

Measurements

The ^1H -NMR and ^{13}C -NMR spectra were obtained on a Bruker Avance DMX500 spectrometer using tetramethylsilane (TMS) as internal standard and CDCl_3 as solvent. The molecular weight and molecular weight distribution were determined by a gel permeation chromatography (GPC, Waters 1525/2414) using THF as eluent (1.0 mL/min). Polystyrene standards were used to generate a calibration curve.

RESULTS AND DISCUSSION

LLA Homopolymerization

The LLA homopolymerization initiated by yttrium borohydride was systematically investigated in this paper. The effects of monomer concentration and initiator amount on polymer yield, molecular weight and molecular weight distribution of PLLA were examined as shown in Table 1. The PLLA with a yield of 67.6% and weight-average molecular weight (M_w) of 7.55×10^3 Da was obtained at the LLA concentration ([LLA]) of 3 mol/L and the monomer/initiator ratio ([LLA]/[Y]) of 1500. However, the observed M_w s are generally lower than those of other polymerization systems^[20] and it seems that the catalyst was less efficient in the ROP of LLA than CL^[16]. This can be attributed to transesterification reactions frequently observed in the ROP of LLA or to a slow initiation step compared to propagation^[13]. Figure 1 indicated that the number-average molecular weight (M_n) linearly increased with [LLA]/[Y], while the M_w/M_n ratio (MWD) remained below 1.34, suggesting that the polymerization proceeded with some controllable characteristics. Table 2 exhibited the favorable polymerization temperature was 80 °C at the [LLA] of 3 mol/L and the [LLA]/[Y] of 1500. As shown from Run 5–7, the molecular weight increased and the molecular weight distribution remained in a narrow range (1.30–1.32) with an extended reaction time.

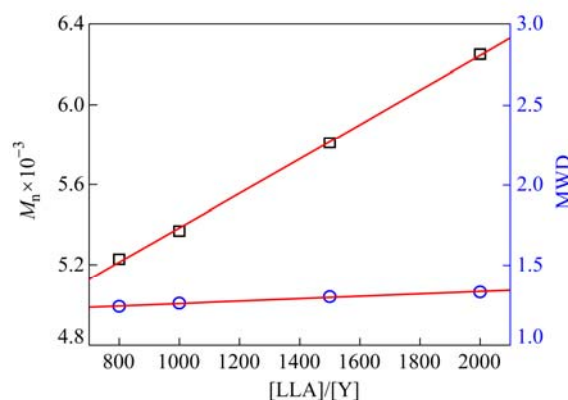


Fig. 1 Plots of M_n (□) and MWD (○) versus [LLA]/[Y] ([LLA] = 3 mol/L)

Table 1. Effects of monomer concentration and initiator amount on the polymerization

Run	[LLA] (mol/L)	[LLA]/[Y]	Yield (%)	$M_w \times 10^{-3}$	$M_n \times 10^{-3}$	MWD
1	2	1500	61.9	7.22	5.78	1.25
2	3	1500	67.6	7.55	5.81	1.30
3	4	1500	58.4	7.39	5.82	1.27
4	3	800	36.0	6.49	5.23	1.24
5	3	1000	44.0	6.77	5.37	1.26
6	3	2000	66.0	8.31	6.25	1.33

[LLA]: concentration of L-lactide; [Y]: concentration of yttrium borohydride complex

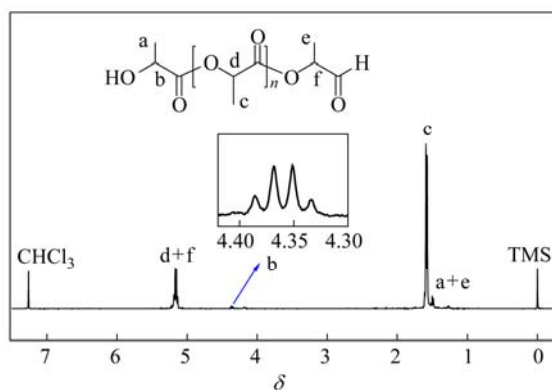
All the homopolymerizations were reacted in toluene for 4 h at 80 °C.

Table 2. Effects of temperature and time on the polymerization

Run	T (°C)	Time (h)	Yield (%)	$M_w \times 10^{-3}$	$M_n \times 10^{-3}$	MWD
1	70	4	56.9	7.89	6.16	1.28
2	80	4	67.6	7.55	5.81	1.30
3	90	4	68.6	6.98	5.37	1.30
4	100	4	60.0	6.74	5.27	1.28
5	80	3	68.0	7.71	5.89	1.31
6	80	5	71.0	8.56	6.53	1.31
7	80	6	73.5	8.77	6.64	1.32

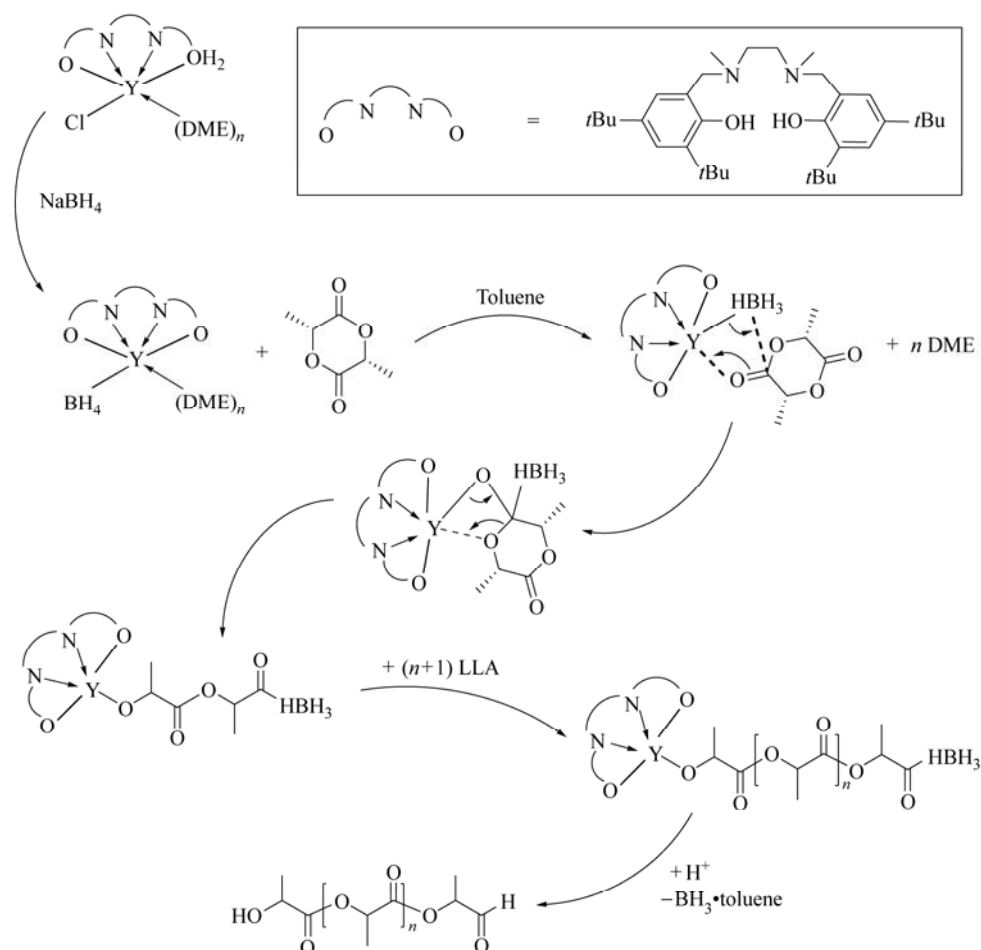
All the homopolymerizations were reacted in toluene at [LLA] of 3 mol/L and [LLA]/[Y] of 1500.

To determine the initiation mechanism of yttrium borohydride complex, a low molecular weight PLLA sample terminated by *i*-PrOH/HCl was prepared, and its ^1H -NMR spectrum is presented in Fig. 2. It can be observed from the spectrum that the signals at $\delta = 1.57$ and 5.15 should be assigned to the main chain protons ^cH and ^dH , respectively. No signal of the *i*-PrOC=O— end group was detected, suggesting that the mechanism was similar to the reported lanthanide borohydride initiating ring-opening polymerization of CL^[9]. Usually the ROP of cyclic esters with ligand-supported lanthanide borohydride complexes will provide α,ω -dihydroxytelechelic polymers^[21]. Indeed we could find the signal of terminal group HOCHMe— at $\delta = 4.36$, which was formed by hydrolysis of the metal-alkoxide bond. Whereas the other terminal group —CH₂OH generated from the reduction of the carbonyl group by BH_4^- could not be attested at $\delta = 3.65\text{--}3.85$ in the ^1H -NMR spectrum. Similar results were also presented in the ROP of LLA with other lanthanide borohydride initiators^[22, 23]. In our case, it seemed that the carbonyl group was not reduced and remained as an aldehyde in the end of the chain. And the signal of the aldehyde proton may be too weak to be observed since aldehyde protons relax particularly slowly^[24] and the integral would be underestimated in a big molecule.

**Fig. 2** ^1H -NMR spectrum of PLLA terminated by isopropanol (M_n (NMR) = 1.8×10^3)

Although the exact structure of the initiated-side end group could not be established unambiguously, a tentatively assumed polymerization mechanism of LLA can be depicted as shown in Scheme 1 according to the

above results. The Ln-BH_4 bond was generated from the salt-metathesis between yttrium complex and NaBH_4 . Then one molecule of LLA coordinated to the Ln center through the carbonyl group by substitution of DME, forming a real active Ln-O initiation species. Another LLA molecule was then inserted into the active Ln-O bond to trigger the polymerization. The repeated insertion and propagation process produced PLLA after the hydrolysis of Ln-O end group.



Scheme 1 Proposed mechanism of the initiation process of the polymerization of LLA

Copolymerization of LLA with CL

Table 3 illustrates the results of copolymerization of LLA with CL initiated by yttrium borohydride complex. It can be observed that the additive sequence of polymerization was of critical importance in synthesis of block copolymers of CL and LLA. The block copolymerization can be achieved only when CL was pre-polymerized, and subsequently initiated the next polymerization of LLA (Table 3, Run 1). Otherwise, only PLLA was obtained whether LLA was pre-polymerized or added with CL simultaneously. This result was similar to the copolymerization of CL with LLA by aluminum alkoxide and yttrium alkoxide^[25, 26].

The influences of initiator concentration, polymerization temperature and time on the copolymerization were summarized in Table 4 and Table 5. The PCL-*b*-PLLA copolymer can be prepared with a conversion of 86% and molecular weight of 1.81×10^4 Da within 90 min. Table 5 indicates that the second chain of PCL-*b*-PLLA got longer as the polymerization temperature increased with the MWDs in the range of 1.35–1.39, which differs from that there was a max M_w at 80 °C in the case of LLA homopolymerization. As shown from Run 4–8, the molecular weight increased with an extended reaction time, but decreased when the reaction time reached to

90 min (Run 8). This may be attributed to the growing degradation of PLLA since the MWD became wider and wider as the reaction time extended from 15 min to 90 min.

Table 3. Influences of the additive sequence on block copolymerization^a

Run	First-stage polymerization				Second-stage polymerization				Result		
	A	T_1 (°C)	t_1 (min)	Yield (%)	B	T_2 (°C)	t_2 (min)	Yield (%)	Polymer	$M_w \times 10^{-3}$	MWD
1	CL	80	30	83.3	LLA	100	60	85.6	Copolymer	18.14	1.39
2	LLA	100	180	86	CL	80	60	0	PLLA	4.50	1.14
3	CL+LLA ^b	100	180	40					PLLA	4.33	1.14

^a Polymerization conditions: [CL]/[Y] = 500, [LLA]/[CL] = 40/60;

^b LLA and CL were added simultaneously.

Table 4. Effects of catalyst concentration on the copolymerization

Run	[Y] (mmol/L)	Yield (%) ^a	$M_w \times 10^{-4}$	$M_n \times 10^{-4}$	MWD
1	3.0	74.0	1.48	1.15	1.29
2	4.0	78.1	1.61	1.20	1.34
3	5.0	85.6	1.81	1.30	1.39
4	6.0	85.1	1.74	1.23	1.42
5	7.0	76.8	1.52	1.02	1.49

The other polymerization conditions were the same as Run 1 in Table 3.

^a The total monomer conversion

Table 5. Influences of temperature and time on the copolymerization.

Run	T_2 (°C)	Time ^a (min)	Yield (%) ^b	$M_w \times 10^{-4}$	$M_n \times 10^{-4}$	MWD
1	70	60	67.8	1.50	1.11	1.35
2	80	60	76.0	1.54	1.12	1.37
3	90	60	87.4	1.70	1.24	1.37
4	100	60	85.6	1.81	1.30	1.39
5	100	15	65.2	1.15	0.88	1.30
6	100	30	68.0	1.24	0.93	1.34
7	100	45	70.2	1.40	1.04	1.35
8	100	90	84.0	1.53	1.08	1.42

The other polymerization conditions were the same as Run 1 in Table 3.

^a The second-stage polymerization time;

^b The total monomer conversion

The PCL-*b*-PLLA copolymers were characterized by GPC, ¹H-NMR and ¹³C-NMR. The GPC spectrum (Fig. 3) clearly shows that the peak of block copolymer (Curve B) shifted toward a higher molecular weight region compared to that of its original PCL pre-polymer (Curve A). Both of the curves A and B in the GPC analysis were unimodal, indicating the generation of a diblock copolymer rather than a mixture of two homopolymers of PCL and PLLA.

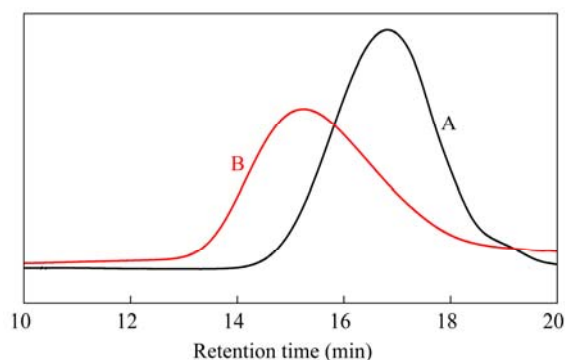


Fig. 3 GPC curves of PCL (A) and PCL-*b*-PLLA (B) (Table 3, Run 1)

Figure 4 illustrates the ^1H -NMR spectrum of PCL-*b*-PLLA copolymer terminated by ethanol/hydrochloric acid. Besides the typical signals of the main chain, the signal at $\delta = 3.75$ assigned to the methylene proton ($-\text{CH}_2\text{OH}$) was detected, which resulted from the reduction of the carbonyl group of CL by BH_4^- [21]. The ^{13}C -NMR spectrum (Fig. 4) shows that no peaks between the two carbonyls of PCL ($\delta = 173.4$) and PLLA ($\delta = 169.5$) were observed, indicating there was no transesterification in the copolymerization[27–29].

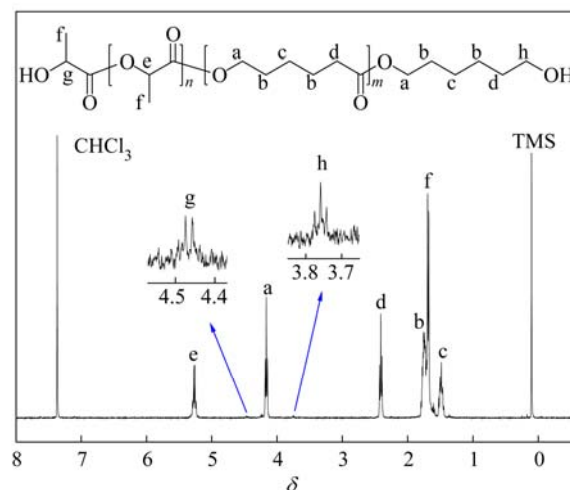


Fig. 3 ^1H -NMR spectrum of PCL-*b*-PLLA copolymer

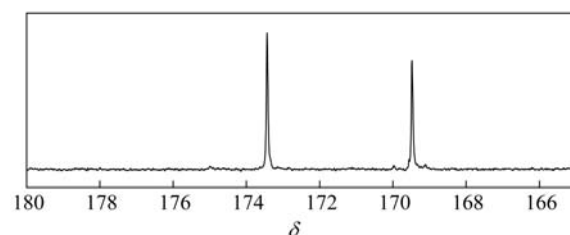


Fig. 4 ^{13}C -NMR spectrum of PCL-*b*-PLLA copolymer

CONCLUSIONS

In summary, the tetrahydrosalen-supported yttrium borohydride complex is an effective catalyst for LLA homopolymerization and its copolymerization with CL. Block copolymers PCL-*b*-PLLA can only be prepared when CL is first polymerized followed by the copolymerization of LLA. The diblock structure of the copolymer was ascertained by GPC, ^1H -NMR and ^{13}C -NMR.

REFERENCES

- 1 Okada, M., Prog. Polym. Sci., 2002, 27(1): 87
- 2 Darensbourg, D.J. and Karroonnirun, O., Macromolecules, 2010, 43(21): 8880
- 3 Song, C.X., Sun, H.F. and Feng, X.D., Polym. J., 1987, 19(5): 485
- 4 Ropson, N., Dubois, P., Jerome, R. and Teyssie, P., Macromolecules, 1995, 28(23): 7589
- 5 Zhong, Z.Y., Dijkstra, P.J., Birg, C., Westerhausen, M. and Feijen, J., Macromolecules, 2001, 34(12): 3863
- 6 Cheng, M., Attygalle, A.B., Lobkovsky, E.B. and Coates, G.W., J. Am. Chem. Soc., 1999, 121(49): 11583
- 7 Kricheldorf, H.R. and Lee, S.R., Polymer, 1995, 36(15): 2995
- 8 Kricheldorf, H.R., Kreiser-Saunders, I. and Stricker, A., Macromolecules, 2000, 33(3): 702

- 9 Guillaume, S.M., Schappacher, M. and Soum, A., *Macromolecules*, 2003, 36(1): 54
- 10 Guillaume, S.M., Schappacher, M., Scott, N.M. and Kempe, R., *J. Polym. Sci. Part A: Polym. Chem.*, 2007, 45(16): 3611
- 11 Schappacher, M., Fur, N. and Guillaume, S.M., *Macromolecules*, 2007, 40(25): 8887
- 12 Palard, I., Soum, A. and Guillaume, S.M., *Chem. Eur. J.*, 2004, 10(16): 4054
- 13 Bonnet, F., Cowley, A.R. and Mountford, P., *Inorg. Chem.*, 2005, 44(24): 9046
- 14 Zhang, X.M., Wang, C.Y., Xue, M.Q., Zhang, Y., Yao, Y.M. and Shen, Q., *J. Organomet. Chem.*, 2012, 713: 182
- 15 Wu, G.M., Sun, W.L. and Shen, Z.Q., *J. Appl. Polym. Sci.*, 2009, 112(1): 557
- 16 Huang, J., Yu, J.F., Wu, G.M., Sun, W.L. and Shen, Z.Q., *Chin. Chem. Lett.*, 2009, 20(11): 1357
- 17 Huang, J., Yu, J.F., Yu, H.J., Sun, W.L. and Shen, Z.Q., *Chinese J. Polym. Sci.*, 2011, 29(3): 390
- 18 Xiang, D., Yu, J.F. and Sun, W.L., *Chinese J. Polym. Sci.*, 2011, 29(3): 296
- 19 Kulkarni, R.K., Moore, E.G., Hegyeli, A.F. and Leonard, F., *J. Biomed. Mater. Res.*, 1971, 5(3): 169
- 20 Mehta, R., Kumar, V., Bhunia, H. and Upadhyay, S.N., *J. Macromol. Sci., Polym. Rev.*, 2005, 45(4): 325
- 21 Guillaume, S.M., *Eur. Polym. J.*, 2013, 49(4): 768
- 22 Skvortsov, G.G., Yakovenko, M.V., Castro, P.M., Fukin, G.K., Cherkasov, A.V., Carpentier, J.F. and Trifonov, A.A., *Eur. J. Inorg. Chem.*, 2007, 2007(20): 3260
- 23 Dyer, H.E., Huijser, S., Susperregui, N., Bonnet, F., Schwarz, A.D., Duchateau, R., Maron, L. and Mountford, P., *Organometallics*, 2010, 29(16): 3602
- 24 Simpson, J.H., "Organic structure determination using 2-D NMR spectroscopy: a problem-based approach", Science Press, Beijing, 2011, p. 73
- 25 Jacobs, C., Dubois, P., Jerome, R. and Teyssie, P., *Macromolecules*, 1991, 24(11): 3027
- 26 Stevels, W.M., Ankone, M.J.K., Dijkstra, P.J. and Feijen, J., *Macromolecules*, 1996, 29(9): 3332
- 27 Kasperczyk, J. and Bero, M., *Makromol. Chem.*, 1991, 192(8): 1777
- 28 Kasperczyk, J. and Bero, M., *Makromol. Chem.*, 1993, 194(3): 913
- 29 Bero, M. and Kasperczyk, J., *Macromol. Chem. Phys.*, 1996, 197(10): 3251