Studies on Thermal Degradation of Hydroxyl-Terminated Poly(L-Lactic Acid) Oligomer

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Thermal degradation of poly(L-lactic acid) (PLLA) oligomers into L-lactide (LA) with different oligomer terminal groups were studied. The thermal degradation behaviours of these oligomers were compared at 210-220 ºC under 0.3-0.5 kPa and the yield is as follows: OLLAPOH > OLLA > OLLACOOH. The results showed that poly-hydroxyl-terminated OLLA (OLLAPOH) has a 10-20 % higher yield than pure PLLA oligomer (OLLA) and two-carboxylic acid-terminated OLLA (OLLACOOH). It was considered that hydroxyl ends of the chains induce the reaction. OLLAPOH simultaneously starts depolymerization from each hydroxyl end to speed up the reaction, to shorten the time the substance remains at high temperature and to reduce the byproducts. This results in an increased L-lactide yield. A practical approach for L-lactide production by thermal degradation of OLLAPOH is adopted by using a degradation mechanism, which is an unzipping reaction beginning from the hydroxyl ends of the chains.

Key Words: L-Lactide, Thermal degradation, Hydroxyl-terminated poly(L-lactic acid) oligomer, Carboxylic acid-terminated poly (L-lactic acid)oligomer, Poly(L-lactic acid) oligomer.

INTRODUCTION

Poly(L-lactic acid) (PLLA), a well-known biodegradable and bio-based plastic, is a promising substitute for non-biodegradable petrochemical-based polymers in industries, medicine and packaging[1-3]. Poly(L-lactide) (PLA) can be prepared in two ways, condensation of aqueous lactic acid or by the ring opening polymerization of the dimmer of lactic acid, L-lactide (LA). First approach is relatively simple and inexpensive, but the molecular weight, the molecular weight distribution and the endgroups are difficult to control and syntheses of copolyesters with controlled sequences are not possible. Therefore, PLA is conventionally produced by a ring-opening polymerization reaction of highly optically pure L-lactide, which is synthesized by metal-catalyzed thermal degradation of poly(L-lactic acid) oligomer[4] in a solvent free, continuous process. Byproducts, such as higher cyclic oligomers, meso-lactide and D-lactide, are also produced by inter-molecular transesterification, *cis*-elimination or enolization[5,6]. The low yield and high cost of L-lactide preparation limit its large-scale commercial application[7].

Many factors regulate thermal degradation in favour of a desired product. These include adopting a catalyst[8,9] to enhance the rate and selectivity of a reaction using an inert solvent to inhibit side reactions, which are favoured at high temperatures[10-12] and using an inert gas at normal pressure to remove products, which shortens the time of the reaction at high temperature and reduces oxidation[13,14]. McNeill and Leiper[5,15] protected the hydroxyl groups of poly(lactic acid) (PLA) by acetylation and proved that end-protection can improve the thermal stability of PLA. They proposed that the dominant thermal degradation process of PLA to lactide is a non-radical, backbiting ester interchange reaction at the hydroxyl end group[5]. This mechanism was adopted to explain lactide formation through the thermal degradation of PLA in various catalytic systems, such as alkali earth metal oxides MgO/CaO[2,8], $Al(OH)_3$[16] and $Sn(Oct)_2$[6,7]. Nishida *et al.*[17], studied the effect of $Sn(Oct)_2$ on the thermal degradation of PLLA. They proposed a widely accepted mechanism wherein the thermal degradation of PLLA is considered an unzipping reaction. In this process, the binding of a Sn atom on the hydroxyl end is assumed to be a fundamental reaction. The Sn atom attacks the penultimate carbonyl oxygen and then lactide is formed by cleavage of the acyl-oxygen bond of oligomers (Fig. 1). Although the thermal depolymerization mechanism is widely accepted, no report on the use of this mechanism for lactide production has yet been published. This paper investigates the relationship between the chain ends and lactide formation.
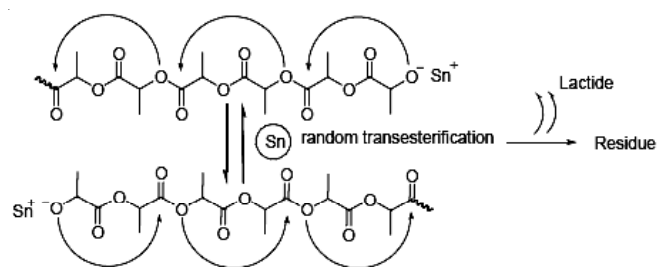
Fig. 1. Possible mechanism of Sn-catalyzed PLLA to lactide

EXPERIMENTAL

L-Lactic acid (88 % aq) was purchased from Anhui Fengyuan Company. Stannous octoate [Sn(Oct)$_2$] was purchased from Sigma-Aldrich. All other reagents were from Tianjin Fuchen Chemical Reagent Company and used as received.

Preparation of pure PLLA oligomer samples with different end groups: Pure PLLA oligomer (OLLA) was prepared by mixing L-lactic acid solution (30 g) and Sn(Oct)$_2$ (0.16 g) in a three-necked flask. The mixture was heated to 100 ºC to remove free water. The temperature was then gradually increased from 100-180 ºC for condensation polymerization under vacuum (5.5-7.5 kPa). A polyfunctional substance, such as the 1,4-butanediol, pentaerythritol, or succinic acid, was added to the mixture at the beginning and the same method was used to produce poly-hydroxyl-terminated OLLA (OLLAPOH, *e.g.*, OLLAOH and OLLATOH) or two-carboxylic acid-terminated OLLA (OLLACOOH).

Synthesis and purification of L-lactide: OLLA, OLLAPOH or OLLACOOH was heated and distilled at 210-220 ºC while stirring under a reduced pressure (0.3-0.5 kPa)[18]. The distillate was collected and recrystallized with ethanol, ethyl acetate and ethanol, respectively[19,20], resulting in a refined needle-like product. ^{1}H NMR spectra were obtained by a Varian Inova-400 spectrometer at room temperature with CDCl$_3$ as the solvent and TMS as the internal reference. The viscosity-average molecular weight of the oligomers was measured using an Ubbelohde viscometer (THF, 37 ± 0.1 ºC, [η] = 1.04 × 10^{-4} M η$_{0.75}$)[21].

RESULTS AND DISCUSSION

Synthesis and characterization of oligomer samples: According to the mechanism wherein hydroxyl chain ends induce thermal degradation, oligomer samples with different ends were prepared. OLLA (Fig. 2-1) was prepared by a continuous condensation polymerization reaction of aqueous L-lactic acid. OLLAOH (Fig. 2-2), OLLACOOH (Fig. 2-3) and OLLATOH (Fig. 2-4) were prepared from L-lactic acid by adding different polyfunctional substances[22]. The structures of the products were analyzed by ^{1}H NMR.

In the ^{1}H MNR spectra of the four oligomers (Fig. 3), two weak peaks are observed at 1.49 ppm (a) and 4.38 ppm (b). The main peaks are at 1.58 ppm (c) and 5.18 ppm (d), which are attributed to -CH(CH$_3$)OCO- and -CH(CH$_3$)OCO- on the main chain [1]. In Fig. 2-2, the weak peaks at 1.75 ppm (e) and 4.17 ppm (f) are assigned to -OCH$_2$CH$_2$CH$_2$CH$_2$O-[23] and -OCH$_2$CH$_2$CH$_2$CH$_2$O-[24]. No peak is observed at 3.66 ppm, which belongs to the OH-terminated group of 1,4-butanediol[24].
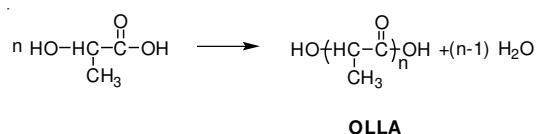

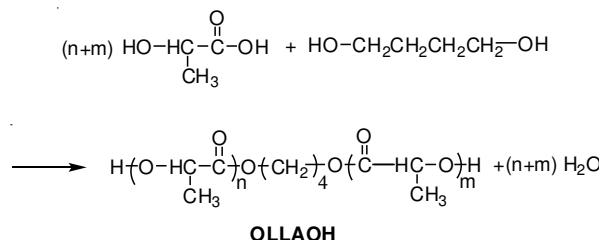Fig. 2-1. Pure lactic acid oligomer (OLLA)

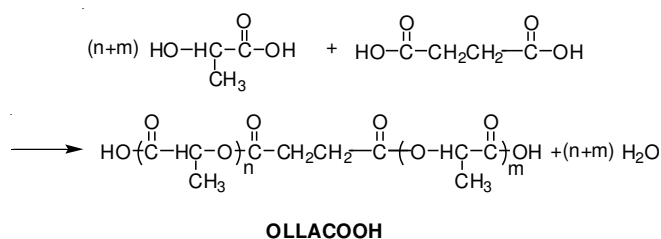Fig. 2-2. Lactic acid oligomer with two OH-terminated groups (OLLAOH)

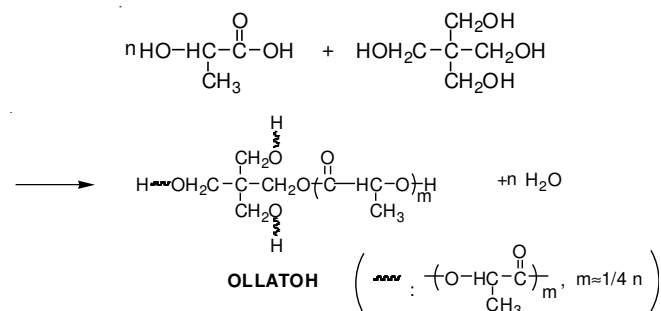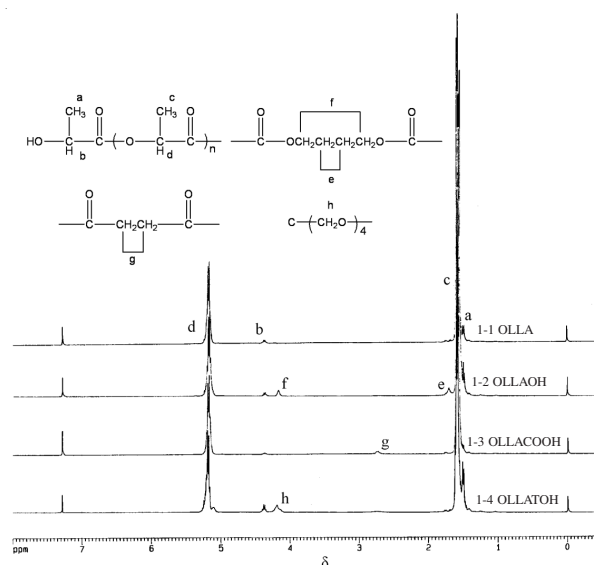Fig. 2-3. Lactic acid oligomer with two COOH-terminated groups (OLLACOOH)

Fig. 2-4. Lactic acid oligomer with four OH-terminated groups (OLLATOH)

Fig. 2. Lactic acid oligomers with the different terminated groups

Fig. 3. ^{1}H NMR spectra of the oligomers with different ends

In Fig. 2-3, the weak peak at 2.73 ppm (g) is assigned to -COCH$_2$CH$_2$CO-[25], while in Fig. 2-4, the weak peak at 4.18 ppm (h) is assigned to -CCH$_2$O-[26]. Equal moles of the reactive end groups can produce a high molecular weight polymer through condensation polymerization. In addition, the direct condensation polymerization of L-lactic acid is an equilibrium reaction and difficulties in removing trace water in the late stages of the reaction generally limit the molecular weight of OLLA. Therefore, OLLA samples with different Mη were prepared by controlling the reaction time and the amount of polyfunctional substances (Fig. 4).
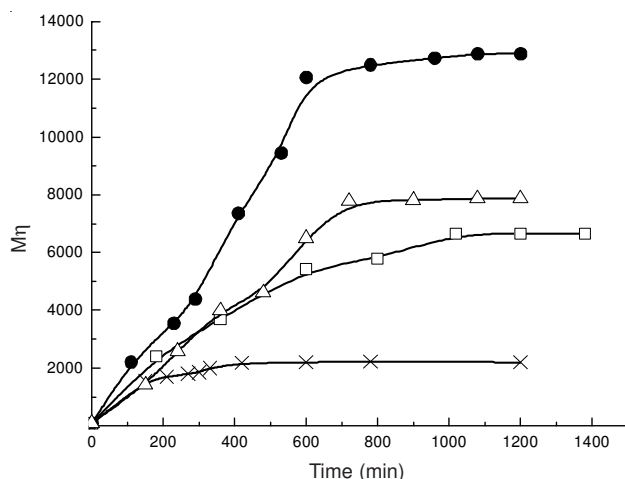

Fig. 4. Effects of time and amount of polyfunctional substance on Mη of oligomers; OLLA (•); OLLACOOH (Mol LA: Succinic acid = 45:1) (△); OLLAOH-1 (Mol LA: butanediol = 50:1) (□); OLLAOH-2 (Mol LA: but-anediol = 5:1) (×)

Thermal degradation of oligomer samples with different ends: To clarify the relationship between the chain end and lactide formation, four oligomer samples were thermally depolymerized to prepare L-lactide. The effect of the amount of hydroxyl end groups on degradation was studied. Byproducts interfere with the results. Therefore, the recrystallization yield of L-lactide was the scale on which the reaction was evaluated (Fig. 5).
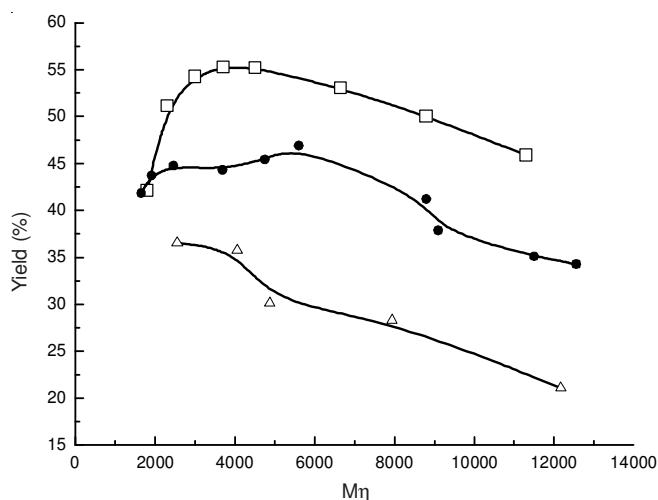

Fig. 5. L-Lactide formation from the thermal degradation of oligomer samples with different chain ends; OLLAOH (□); OLLA (•); OLLACOOH (△)

Fig. 5 shows that with the same Mη, OLLAOH has a 10-20 % higher degradation yield of L-lactide than OLLA and OLLACOOH, with the latter having the lowest yield. The degradation rates of oligomers with the same Mη are listed in Table-1. When Mη is about 2,400 Da, these oligomers have the same degradation rates. However, when Mη increases to 5,000 Da, the degradation rate of OLLAOH is the highest among the three and its yield is the best.

TABLE-1 RESULTS OF LACTIDE OBTAINED FROM DIFFERENT LACTIC ACID OLIGOMERS					
	Sample 1			Sample 2	
	Mη	Yield (%)	Time (min)	Mη	Yield (%)	Time (min)
OLLAOH	2300	42.12	40	4500	55.25	45
OLLA	2464	43.75	35	4754	45.44	60
OLLACOOH	2560	36.55	45	4880	30.14	80

The results in Table-1 and Fig. 5 indicate that thermal degradation can simultaneously start the unzipping reaction from the two hydroxyl ends of the chain to accelerate the reaction. Therefore, the degradation rate of OLLAOH is higher than both that of OLLA and OLLACOOH. At the same time, OLLACOOH and OLLA suffer from more random degradation processes at the carboxylic end, such as *cis*-elimination and nucleophilic attack, generating new chain ends and hydroxyl, carboxyl and acyl groups[1]. These additional reactions may slow down the degradation process at the beginning. Subsequently, the new hydroxyl end forms into an alkoxide with Sn and the alkoxy anion induces an unzipping reaction to produce L-lactide. However, as more side reactions occur, the yield of the L-lactide decreases.

Moreover, the thermal degradation of oligomers into L-lactide occurs at 220 ºC. In this high temperature, oligomers with higher Mη make the reactant more viscous. As a result, the products remain in the reactant and are not quickly distilled out. In this case, L-lactide suffers from more oxidation reactions and results in more byproducts. Of the oligomers, OLLACOOH has the lowest yield because the two carboxyl ends of the chains results in more oxidation reactions and longer reaction time. OLLAOH with two hydroxyl ends start and accelerate the unzipping reaction to give the best yield in the shortest reaction time.

Effect of Mη on thermal degradation: The molecular weight of OLLA is limited in the thermal degradation of OLLA into L-lactide. Ray *et al.*[27] and Bendix[28] described the optimal range of oligomer molecular weight as 5,000 and 500-2,000 Da, respectively. Hitoml[29], in his patent, discussed that the molecular weight of the oligomer, which was between 400 and 2,000 Da, is preferably between 1,000 and 2,000 Da.

As in Fig. 5, the best Mη of OLLA is from 1,600-6,000 Da and the L-lactide yield increases gradually and is stable at 40-46 %. However, the yield drops from 46-30 % when Mη increases from 6,000-12,000 Da and the colour of the products change from white to yellow and even brown. The higher Mη of OLLA makes the reactant more viscous and causes the products to remain at high temperature for a longer time, which increases the side reactions and reduces L-lactide yield. However, when the Mη of OLLA becomes lower (< 1,600 Da), the

content of carboxylic acid ends increase and this results in more random degradations. Moreover, oligomers with sufficiently low Mη are evaporated directly from the reactant in the molten state without any cyclization[6]. Therefore, both higher and lower Mη can cause more side reactions. In conclusion, the molecular weight of OLLA is a key factor in L-lactide production.

The negative effect of a higher molecular weight on the reaction is also observed in OLLAOH degradation. OLLAOH simultaneously starts its degradation from two hydroxyl ends to shorten the reaction time, which can reduce side reactions. Therefore, OLLAOH with higher Mη (> 4,000 Da) still performs its degradation process (Table-1) and the Mη range of OLLAOH is wider than OLLA.

With a lower Mη of about 2,400 Da, OLLAOH shows no evident predominance in the reaction rate compared to other OLLA samples (*i.e.*, OLLA, OLLAOH and OLLACOOH). All oligomers can finish their thermal degradation in a shorter time to avoid oxidation. However, the importance of the different chain ends is gradually exhibited increase with Mη. When the three OLLA samples have the same Mη (Mη ≈ 12,000 Da), OLLAOH results in a 45 % yield of L-lactide, which is higher than OLLAOH (35 %) and OLLACOOH (21 %). It is even equal to the best yield of OLLA with an Mη of 6,000 Da.

In summary, introducing hydroxyl ends to oligomer chains for thermal degradation counteracts the negative effect of a high molecular weight on L-lactide yield. This technique can be applied in L-lactide industrial production and obtain better yield in a shorter reaction time. In contrast, the mutual interaction of long reaction time and OLLACOOH chain structure causes more side reactions, resulting in worse yield.

In addition, the thermal degradation of OLLA (Mη ≈ 4,400 Da) mixed with 1,4-butanediol was done to obtain an L-lactide yield of 32 % with a lower reaction rate. This indicates that the hydroxyl ends are fundamental to inducing degradation, but the hydroxyl group from the external solution is an impurity that breaks the equilibrium reaction and results in poor yield.

The crude yield of L-lactide has been reported reach to 90 %, but the refined yield by recrystallization is still lower than 50 %[30]. We studied the thermal degradation of PLLA oligomers according to the mechanism of L-lactide formation, which is an unzipping reaction from the hydroxyl ends of the chains. The introduction of hydroxyl ends to OLLA raises the refined yield of L-lactide up to 55 % with a melting point at 95-96 ℃[19]. The purified L-lactide polymerized into PLLA with an Mη of 30×10^5 Da[31].

Pentaerythritol used as a polyfunctional substance to prepare OLLATOH (Fig. 2-4) with an Mη of 12,000 Da. The reaction time and L-lactide yield of OLLA, OLLAOH and OLLATOH with the same Mη of 11,000-12,000 Da are listed in Table-2, showing that OLLATOH has the best result.

TABLE-2
RESULTS OF LACTIDE OBTAINED FROM DIFFERENT LACTIC ACID OLIGOMERS

	Sample 3		
	Mη	Yield (%)	Time (min)
OLLATOH	12100	51.22	45
OLLAOH	11293	45.9	50
OLLA	11500	35.13	70

Conclusion

According to the thermal degradation mechanism, L-lactide formation from PLLA oligomer occurs through a non-radical, backbiting ester interchange reaction beginning from the hydroxyl ends of the chains. Modifying the PLLA oligomer by introducing hydroxyl ends results in a higher L-lactide yield and a shorter reaction time. The thermal degradation of OLLAOH and OLLATOH shows that the hydroxyl ends not only accelerated degradation and increased L-lactide yield but also extended the optimal molecular weight range. In contrast, because of the carboxyl ends, OLLACOOH suffers from side reactions, which produce more byproducts. Introducing hydroxyl ends may prevent additional side reactions during the process of large-scale L-lactide production.

REFERENCES

1. Y. Fan, H. Nishida, Y. Shirai and T. Endo, *Polym. Degrad. Stab.*, **84**, 143 (2004).
2. T. Motoyama, T. Tsukegi, Y. Shirai, H. Nishida and T. Endo, *Polym. Degrad. Stab.*, **92**, 1350 (2007).
3. D.W. Grijpma, G.J. Zonderva and A.J. Pennings, *Polym. Bull.*, **25**, 327 (1991).
4. E.T.H.Vink, K.R. Rabago, D. Glassner and P.R. Gruber, *Polym. Degrad. Stab.*, **80**, 403 (2003).
5. I.C. McNeill and H.A. Leiper, *Polym. Degrad. Stab.*, **11**, 309 (1985).
6. E.D. Kopinke, M. Remmler, K. Mackenzie, M. Moder and O. Wachsen, *Polym. Degrad. Stab.*, **53**, 329 (1996).
7. M. Noda and H. Okuyama, *Chem. Pharm. Bull.*, **47**, 467 (1999).
8. Y. Fan, Y. Nishida, T. Mori, Y. Shirai and T. Endo, *Polymer*, **45**, 1197 (2004).
9. H. Abe, N. Takahashi, K. J. Kim, M. Mochizuki and Y. Doi, *Biomacromolecules*, **5**, 1606 (2004).
10. N. Li, W.F. Jiang, J.B. Zhao and W.T. Yang, *Petrochem. Technol.*, **32**, 1073 (2003) In Chinese.
11. C.B. Hu, J.D. Chen, F. Wang, Z.G. Zhou and J.G. Ji, *J. Chongqing Univ. (Nat. Sci. Ed.)*, **30**, 108 (2007).
12. H. Sterzel, DE Patent 4407036 (1995).
13. K.K. Bhatia, US Patent, 4835293 (1989); 5091544 (1992).
14. C.E. Loew and N.Y. Buffalo, US Patent 2668162 (1954).
15. I.C. McNeill and H.A. Leiper, *Polym. Degrad. Stab.*, **11**, 267 (1985).
16. H. Nishida, Y. Fan, T. Mori, N. Oyagi, Y. Shirai and T. Endo, *Ind. Eng. Chem. Res.*, **44**, 1433 (2005).
17. H. Nishida, T. Mori, S. Hoshihara, Y. Fan, Y. Shirai and T. Endo, *Polym. Degrad. Stab.*, **81**, 515 (2003).
18. R.K. Kulkarni, K.C. Pani, C. Neuman and F. Leonard, *Arch. Surg.*, **93**, 839 (1966).
19. X.N. Liu, R.Q. Wei, Y. Liu and J. Wei, CN Patent 100343247C (2007).
20. X.N. Liu, R.Q. Wei, J. Wei and Y.Liu, CN Patent 100343246C (2007).
21. Drug Carriers in Biology and Medicine, D.L. Wise, T.D. Fellmann, J.E. Sanderson and R.L. Wentworth, London Academic Press, London, p. 237 (1979).
22. K. Hiltunen , M. Harkonen, J.V. Seppala and T. Vaananen, *Macromolecules*, **29**, 8677 (1996).
23. I. Barakat, P.H. Dubois, R. Jérôme and P.H. Teyssié, *J. Polym. Sci. Pol. Chem.*, **31**, 505 (1993).
24. N.Y. Huang, S.C. Tang, Z.J. Xu and Q.H. Wang, *J. Functional Polym.*, **17**, 285(2004) In Chinese.
25. B.H. Guo, H.G. Ding, X.L. Xu, J. Xu and Y.B. Sun, *Chem. J. Chin. Univ.*, **24**, 2312 (2003) In Chinese.
26. S.H. Lee, S.H. Kim, Y.K. Han and Y.H. Kim, *J. Polym. Sci. Polym. Chem.*, **39**, 973 (2001).
27. E.D. Ray, R.G. Patrick and E.H. David, *Adv. Mater.*, **12**, 1841 (2000).
28. D. Bendix, *Polym. Degrad. Stab.*, **59**, 129 (1998).
29. O. Hitoml and O. Makoto, US Patent 5801255 (1998).
30. J.J. Zhu, Y.L. Wang, X.J. Quan, J. Xin and R. Wang, *Chem. World*, **3**, 173 (2005) In Chinese.
31. H.R. Kricheldorf, I. Kreiser-Saunders and C. Boettcher, *Polymer*, **36**, 1253 (1995).