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Racemization-free Synthesis of Lactide Using an Onium Salt Catalyst

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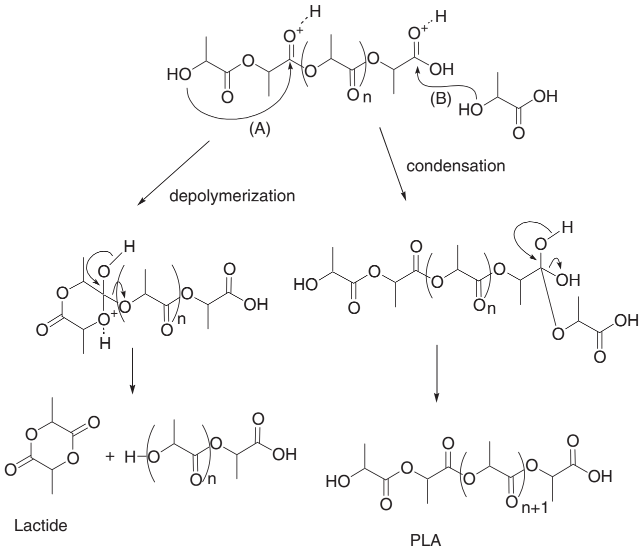
Synthesis of LL-lactide with high chemical, diastereomeric, and enantiomeric purities was achieved by depolymerization of oligo(lactic acid) in the presence of an onium salt catalyst.

LL-Lactide is a valuable precursor of poly(lactic acid), which now widely attracts attention as s promising biobased material. LL-Lactide, a cyclic dimer of L-lactic acid, is usually synthesized by thermal depolymerization of poly(or oligo) (lactic acid) in the presence of a catalyst, such as tin-, antimony-, or other metal-based compounds.[1] Among them, tin-based catalysts are frequently used as a practical catalyst due to their high activity and ready availability. Most of the existing procedures, however, suffer from difficulties of racemization during depoymerization, and accordingly recrystallization is necessary to obtain diastereomerically and enantiomerically pure lactide for poly(lactic acid) synthesis. During the course of our studies of the onium salt catalysis of poly(lactic acid) synthesis,[2] we observed formation of lactide under polycondensation conditions in a bulk state. Both condensation of lactic acid and lactide formation from oligo(lactic acid) proceed through a similar mechanism under the onium salt catalysis (Scheme 1). The former had been shown to proceed without racemization.[2] Thus, application of the onium salt catalysis to the depolymerization of poly(lactic acid) would afford lactide without racemization. Herein, procedures for the synthesis of LL-lactide with high chemical, diastereomeric, and enantiomeric purities are described.



Scheme 1. Acid-catalyzed polycondensation and depolymerization.

Heating a mixture of oligo(lactic acid) of average degree of polymerization 9 (DP = 9) and triphenylphosphonium triflate (TPP-T), 3-chloropyridinium triflate (Cl-Py-T), or pyridinium triflate (Py-T) at predetermined temperature under vacuum afforded lactide as a crystalline distillate. Reaction conditions and lactide yield are summarized in Table 1.

Below 3 mmHg, the reaction pressure did not affect the depolymerization reaction very much. Higher reaction temperature gave better yield (Entries 1–3). TPP-T, the best catalyst for the polycondensation of lactic acid, has lower thermal stability and the reaction temperature was restricted not higher than 140 °C. At 180 °C, Cl-Py-T gave comparable yields to Py-T (Entry 6). At higher reaction temperatures, depolymerization was accompanied by decomposition of the oligo(lactic acid) to give alkene side products, which was ascertained by comparison of the ratio of hydroxy and carboxylic terminus of the residual oligo(lactic acid).[3] When larger oligo(lactic acid)s were used, the

Table 1. Depolymerization of oligo(lactic acid) with onium salt catalyst

Entry	DP[a]	Catalyst /mol %[b]	Temp /°C	Time[c] /h	Yield /%
1[d]	9	Py-T (1.0)	180	1	20
	(30)			2	37
	(50)			3	41
	(100)			20	56
2[e]	9	Py-T (1.0)	160	1	13
	(15)			2	18
	(26)			3	22
3[e]	9	Py-T (1.0)	140	1	8
	(17)			2	10
	(23)			3	13
4[e]	9	TPP-T (0.5)	140	3	23
				5	24
				20	35
5[d]	9	Cl-Py-T (1.0)	180	1	21
	(34)			2	33
	(55)			3	39
6[d]	50	Py-T (1.0)	180	3	25
	(220)			20	33
7[d]	200	Py-T (1.0)	180	3	7
	(390)			20	19
8[d]	9	No cat	180	3	12

[a] DP of the starting oligo(lactic acid). Numbers in parentheses: DP of the oligo(lactic acid) when the reaction was resumed. [b] mol % of lactic acid in the oligomer. [c] At the indicated times, the lactide distillate was weighed and the reaction was resumed. [d] Reaction pressure 3 mmHg. [e] Reaction pressure 0.2 mmHg.

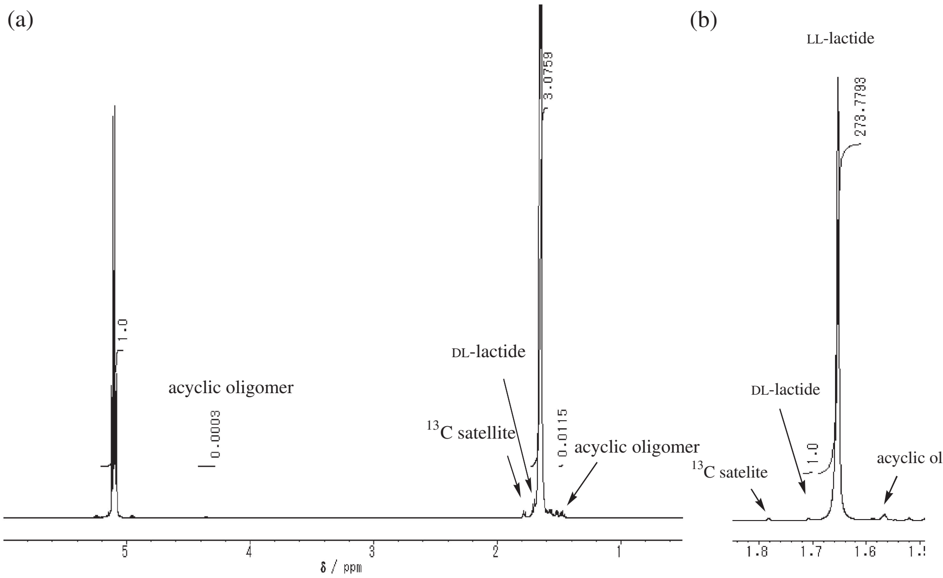


Figure 1. (a) ^{1}H NMR spectrum of crude distillate obtained from oligo(lactic acid). (b) ^{1}H homodecoupling spectrum of LL-lactide crude distillate (Table 1, Entry 1).

yield of lactide decreased significantly (compare Entries 1, 6, and 7). This unique DP dependence should be attributed, in part, to decrease of the concentration of the hydroxy terminus in the reaction mixture by condensation. With smaller (e.g., DP < 6) oligo(lactic acid), the distillate was contaminated by lactic acid oligomers. From Table 1, pyridinium triflate gave the best yield at 180 °C, but the prolonged depolymerization did not improve the yield of lactide very much.

In all cases in Table 1, pure lactide was obtained in good to moderate yield. The purity of the distillate solid was determined by ^{1}H NMR (Figure 1). The lactide was free from other impurities ($<0.1\%$) (Figure 1a), such as lactic acid or oligo(lactic acid) of smaller DP, and the ratio of diastereomeric lactides was determined to be >200:1 (Figure 1b). From this value, the enantiomeric excess of the LL-lactide was calculated to be >99.99%ee.[4]

The reiterative lactide synthesis was realized. In this lactide synthesis, depolymerization was carried out at 160 °C with Py-T as a catalyst (Table 1, Entry 2). When Cl-Py-T was used (Table 1, Entry 5), the residual poly(lactic acid) was contaminated with dilactilic acid, and with Py-T at 180 °C (Table 1, Entry 1), elimination reaction produced alkene side products in a significant amount. Thus, a mixture of lactic acid (90%) and Py-T (1 mol %) was heated at 150 °C at 25 mmHg for 4 h to afford oligo(lactic acid) of DP ≈ 9. The depolymerization at 160 °C at 1 mmHg afforded pure lactide in 25% yield (based on the oligo(lactic acid)) leaving poly(lactic acid) of DP $= 32$ as a distillation residue, which was hydrolyzed with aqueous lactic acid at 130 °C for 15 h to regenerate monomeric lactic acid (DP < 2). The amount of the added lactic acid is sufficient to replenish the isolated lactide, and the amount of water is 1.1 equivalent to hydrolyze the poly(lactic acid) to monomeric lactic acid. Then, the oligomerization–depolymerization–hydrolysis sequence was reiterated. The lactide synthesis proceeded as efficiently as the first run to give pure lactide, which exemplifies that the catalyst is stable under the reaction conditions and the side reactions such as elimination or formation of the ether derivatives did not occur during depolymerization. The lactide production cycle could be reiterated at least 5 times without loss of the yield of pure lactide (Table 2). It should be mentioned that, in this process, although the yield based on the oligo(lactic acid) in each run is moderate, the yield calculated on the basis of the replenished lactic acid after the second run reached 86–92%, which shows the practical usefulness of the present procedure.

Table 2. Reiterative production of L-lactide

	Reiteration				
	1	2	3	4	5
Condensation step					
OLA/mmol[a]	436	423	424	417	410
Depolymerization step					
Lactide/mmol[a]	112	101	99	105	108
Yield based on OLA/%	25	24	23	25	20
Yield based on LA replenished/%	—	86	87	92	89
Hydrolysis step					
LA replenished/mmol[a]	117	114	114	121	—

[a]As lactic acid unit.

Nonetheless, in order to improve the efficiency of the procedure, protection of the carboxylic acid group was examined to suppress elongation of oligo(lactic acid) by condensation. Inhibition of the condensation reaction during the depolymerization would increase the yield of the lactide. Eventually, depolymerization of docosyl ester[5] of oligo(lactic acid) of DP ≈ 9,[6] which was prepared by polycondensation of lactic acid with docosanol (1/9 mol equiv) in the presence of Cl-Py-T (1 mol % of lactic acid) at 140 °C at 25 mmHg for 7 h,[7] afforded 99.5 wt % LL-lactide with >99.5%de and >99.99%ee in 80% yield[8] by similar depolymerization at 160 °C, 1 mmHg for 3 h.

In summary, we have developed practical methods for synthesis of pure lactide using an onium salt catalyst. This procedure would contribute to simplify the synthetic process of enantiomerically pure lactide for PLLA synthesis.

References and Notes

1 a) M. Noda, H. Okuyama, *Chem. Pharm. Bull.* **1999**, *47*, 467. b) D. K. Yoo, D. Kim, D. S. Lee, *Macromol. Res.* **2006**, *14*, 510.

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3 E.g., with pyridinium triflate at 180 °C (Table 1, Entry 3), OH:COOH = 0.83:1 (3 h), 0.20:1 (20 h).

4 From the ratio of lactide diastereomers (a:b), enantiomeric excess of the major diastereomer can be calculated as
$\%\mathrm{ee} = (4a^2 - b^2)/(4a^2 + b^2) \times 100$.
See Supporting Information for detailed discussion of the calculation.[9]

5 When the ester of lower alcohols, such as methyl or cetyl alcohol, was involved, the lactide distillate was contaminated by methyl lactate or hexadecenes, respectively.

6 Esters of longer oligo(lactic acid) also gave lower yields of lactide upon depolymerization.

7 Cl-Py-T showed higher activity for the synthesis of oligo(lactic acid) esters. The oligo(lactic acid) docosyl ester appeared DP = 7–9, containing ca. 10% of the docosyl ether of oligo(lactic acid).

8 Analysis of the residue showed that 2-docosene, didocosyl ether, and docosyl ester of docosyl (oligo)-lactic acid are build up during the reaction. The structures of these compounds were determined after methanolysis (K_2CO_3, MeOH), as 2-docosene, didocosyl ether, and methyl 2-docosyloxypropionate. Depending on the purity of docosanol, which was distilled to remove lower alcohols, the lactide distillate could be contaminated with olefinic impurities derived from lower alcohols.

9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.