

Synthesis of Poly(lactic acid) by Direct Polycondensation of Lactic Acid Using 1,1'-Carbonyldiimidazole, *N,N,N',N'*-Tetramethylchloroformamidinium Chloride, and *N,N'*-Dicyclohexylcarbodiimide as Condensing Agents

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ABSTRACT: The direct polycondensation of racemic lactic acid using condensing agents, such as 1,1'-carbonyldiimidazole (CDI), *N,N,N',N'*-tetramethylchloroformamidinium chloride (TMCFCAC), and *N,N'*-dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP), was investigated. Reactions using CDI proceeded slightly. Polycondensation using TMCFCAC with pyridine gave a polymer in 83% yield, but the number-average molecular weight (\bar{M}_n) was 3700. Thus, TMCFCAC is not effective in the direct polycondensation of lactic acid. However, DCC/DMAP is effective, and polycondensation in dichloromethane at room temperature for 24 h afforded poly(lactic acid) having \bar{M}_n of 15400 in 89% yield.

KEY WORDS Poly(lactic acid) / Condensing Agent / *N,N'*-Dicyclohexylcarbodiimide / Direct Polycondensation /

Poly(lactic acid) has attracted much attention as a biodegradable material,^{1,2} and has been used in various fields. However, it is difficult to synthesize poly(lactic acid) from lactic acid by a one-step procedure. Therefore, poly(lactic acid), having high molecular weight, has been synthesized by the two-step procedure: the cyclized dimer (lactide) is prepared from lactic acid through oligo(lactic acid), followed by the ring-opening polymerization of lactide.³⁻⁷ As other methods of the poly(lactic acid) synthesis, the polycondensations of 2-halogenopropoates⁸⁻¹³ and transesterification of methyl lactate¹⁴ are known. But, the successful direct polycondensation of lactic acid is slight, and it was reported by Ajioka and his co-workers only.¹⁵⁻¹⁷ The reasons are that oligo(lactic acid) is unstable at high temperature to depolymerize to lactide,^{18,19} and a hydroxyl group coexists with a carboxyl group in the structure of lactic acid, and monomeric lactic acid contains water as stabilizer. The latter two factors prevent condensing agents from activating the carboxyl group selectively owing to the deactivation by the hydroxyl group or water.

In this article, direct polycondensation of lactic acid at mild conditions using various condensing agents, such as 1,1'-carbonyldiimidazole (CDI),^{20,21} *N,N,N',N'*-tetramethylchloroformamidinium chloride (TMCFCAC),²² and *N,N'*-dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP),²³ effective in esterification, was investigated as shown in Scheme 1.

RESULTS AND DISCUSSION

Polycondensations Using CDI

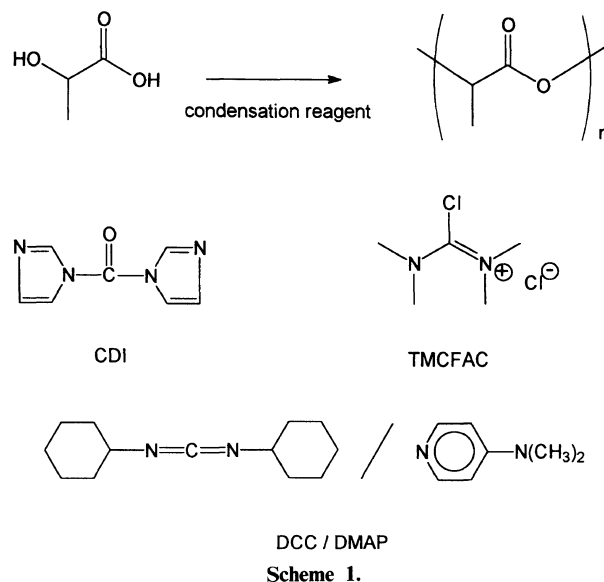
Water, contained in monomeric lactic acid as a stabilizer, was removed by azeotropic distillation with benzene. Then, tetrahydrofuran (THF) and CDI were

added to the residual mixture of lactic acid with benzene, and the polymerization was carried out at room temperature for 24 h. When the concentration of CDI was 0.86 mol l⁻¹ and that of monomer was 0.82 mol l⁻¹, the product was a clear viscous oil, of which number-average molecular weight (\bar{M}_n) and yield were 670 and 16%, respectively.

When the concentration of the monomer was not changed and the concentration of the catalyst increased to 1.23 mol l⁻¹, the product was a clear oil, of which \bar{M}_n and yield were 400 and 25%, respectively. Probably, CDI reacted with a hydroxyl group in lactic acid before activation of a carboxyl group.

Polycondensations Using TMCFCAC

Fujisawa *et al.* demonstrated that, even if a hydroxyl group coexists with a carboxyl group, TMCFCAC ac-



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tivates a carboxyl group selectively.²² After removal of water by the azeotropic distillation with benzene, the residual mixture of lactic acid with benzene was added to the mixture of TMCFAC, 1,2-dichloroethane, and pyridine as a hydrogen-chloride acceptor. A molar ratio of lactic acid/TMCFAC/pyridine was fixed as 1 : 1.1 : 1.1. The reaction was conducted at room temperature for 2 h. But, the product was a brown viscous oil, resulting in \bar{M}_n of 4000 and 89% yield.

The polymerization was carried out as reaction time increased to 24 h, but \bar{M}_n and yield of the polymer were 3700 and 83%, respectively. In these polycondensations, a precipitate formed during the polymerization. Although the molar ratio of TMCFAC/pyridine was 1 : 1.5, precipitation occurred during polymerization, and \bar{M}_n and yield changed slightly. When pyridine was not added, the reaction proceeded homogeneously, but \bar{M}_n and yield decreased to 870 and 11%, respectively. Thus, the effect of TMCFAC is not satisfactory.

Polycondensations Using DCC/DMAP

It is known that, even if a hydroxyl group coexists with a carboxyl group, DCC/DMAP also activates a carboxyl group selectively to form the complex, and that the activated complex reacts with a hydroxyl group to produce an ester linkage as well as *N,N'*-dicyclohexylurea (DCU).²³ Since DCU is insoluble in the common organic solvent, it can be removed easily. After removal of water by the azeotropic distillation with dichloromethane, the polymerization was carried out at room temperature for 24 h. A molar ratio of lactic acid/DCC/DMAP was fixed as 1 : 1.5 : 0.08. The product was a white powdery solid, and identified as poly(lactic acid) by spectroscopic data and elemental analysis. Each peak of NMR spectra showed the complex signals. It has been already clear that ¹H and ¹³C NMR spectra of racemic poly(lactic acid) give complex signals for each hydrogen atom or carbon atom.²⁴⁻²⁶ The yield of poly(lactic acid) was 89%, and \bar{M}_n was improved remarkably, the value was 15400 (run 1). The results are summarized in Table I.

Since the azeotropic composition of water with dichloromethane is low, the polymerization was performed using toluene as the azeotropic solvent to remove water and the reaction solvent (run 2). But, the product was a clear oil, and yield and \bar{M}_n decreased. When benzene was used as the azeotropic solvent to remove water and the mixture of benzene with dichloromethane was used as

the solvent for polymerization, yield was 86%, but \bar{M}_n decreased to 7400 (run 3). Nonpolar benzene in the reaction system may possibly lower the reactivity. Thus, dichloromethane is more suitable for the azeotropic solvent and the reaction solvent.

When the monomer increased to 3.4 mol l⁻¹ (run 5), \bar{M}_n of the polymer did not change and yield increased somewhat compared with run 1. However, further increase of the monomer to 4.5 mol l⁻¹ led \bar{M}_n of the obtained polymer to decrease to 11000 (run 6). In run 6, much higher viscosity of the reaction system during the polymerization was observed, caused by the precipitate of DCU. This is why \bar{M}_n decreased. When the monomer and catalysts decreased (run 4), the viscosity of the reaction system became lower, but yield and \bar{M}_n decreased. The decrease of monomer and catalysts may lower the efficiency. Prolonged polymerization time over 24 h almost did not affect yield and \bar{M}_n of the polymer (runs 7 and 8). Thus, the reaction condition in run 5 is suitable for the direct polycondensation of lactic acid using DCC/DMAP.

Discussion

CDI has high reactivity with a hydroxyl group due to two polar imidazole groups. CDI is thus deactivated by reaction with a hydroxyl group before activation of carboxylic acid. Stadler demonstrated that the mechanism of the activation of carboxylic acid using TMCFAC is the formation of the activated complex by substitution of a carboxylate for a chloro group in TMCFAC.²⁷ Due to the steric effect, TMCFAC indicated lower reactivity with a hydroxyl group than CDI. It can activate a carboxylic acid in lactic acid, but the efficiency is not enough. Since DCC has two nonpolar cyclohexyl groups, there is much lower reactivity with a hydroxyl group than TMCFAC. Thus, DCC activates carboxylic acid in lactic acid selectively, and polycondensation proceeds smoothly under mild conditions.

EXPERIMENTAL

Materials

90-wt% racemic lactic acid, containing 10-wt% water as a stabilizer, was obtained from Musashino Chemical Laboratory, Ltd., and used as received. CDI, oxalyl dichloride, *N,N,N',N'*-tetramethylurea, DCC, and DMAP were obtained commercially (Tokyo Kasei Kogyo Co., Ltd.), and used as received.

Table I. Direct polycondensation of lactic acid using DCC/DMAP^a

Run	Azeotropic solvent with water ^b	Solvent ^c	[M]	Time	Poly(lactic acid)		
			mol l ⁻¹	h	Yield/%	Properties	\bar{M}_n ^d
1	CH ₂ Cl ₂	CH ₂ Cl ₂	2.3	24	89	White powder	15400
2	Toluene	Toluene	2.3	24	52	Clear oil	4600
3	Benzene	CH ₂ Cl ₂	2.3	24	86	White powder	7400
4	CH ₂ Cl ₂	CH ₂ Cl ₂	1.1	24	51	White powder	10900
5	CH ₂ Cl ₂	CH ₂ Cl ₂	3.4	24	94	White powder	15400
6	CH ₂ Cl ₂	CH ₂ Cl ₂	4.5	24	94	White powder	11100
7	CH ₂ Cl ₂	CH ₂ Cl ₂	2.3	48	90	White powder	15800
8	CH ₂ Cl ₂	CH ₂ Cl ₂	2.3	72	90	White powder	15700

^a Polymerization was carried out with 45 mmol lactic acid, 68 mmol DCC, and 3.6 mmol DMAP. ^b Azeotropic solvent to remove water in lactic acid. ^c Solvent for polymerization. ^d Number-average molecular weight, measured by GPC.

Direct Polycondensation Using CDI

A typical procedure is as follows: 1.8 g (18 mmol) of 90-wt% racemic lactic acid and 20 ml of benzene were placed in a flask equipped with a Dean–Stark trap and reflux condenser. The mixture was heated to 90°C for 2 h under a Dean–Stark trap to remove water by azeotropic distillation. 4.4 g (27 mmol) of CDI and 22 ml of THF were added, and the mixture was stirred at room temperature for 24 h. 1 ml of water was added to quench excess CDI, and the solvent was evaporated off. The product was dissolved in dichloromethane, washed three times with water, and dried with anhydrous sodium sulfate. The solvent was evaporated off, and the product was dried under reduced pressure to afford a clear oil (\bar{M}_n , 400). Yield 25%.

Direct Polycondensation Using TMCFCAC

A typical procedure is as follows: 2.0 g (20 mmol) of 90-wt% racemic lactic acid and 20 ml of benzene were added to a flask equipped with a Dean–Stark trap and reflux condenser. After removal of water, 30 ml 1,2-dichloroethane and 4.0 ml pyridine were added, and the mixture was poured into a dropping funnel. In another flask equipped with a reflux condenser, 30 ml 1,2-dichloroethane, 2.8 g (22 mmol) oxalyl dichloride, and 4.6 g (40 mmol) of *N,N,N',N'*-tetramethylurea were added, and the mixture was heated at 65°C for 2 h, cooled to room temperature. Then, the reflux condenser was taken off, and the dropping funnel was attached. Lactic-acid solution was added dropwise for 2 h, and the mixture was stirred at room temperature for 24 h. After 30 ml of 2 M HCl were added, the reaction mixture was washed with water, neutralized with 0.5 M NaOH, and washed with water. The organic layer was dried with anhydrous sodium sulfate, and the solvents were evaporated off. The product was dried under reduced pressure to obtain a brown oil (\bar{M}_n , 3700). Yield 83%.

Direct Polycondensation Using DCC

A typical procedure (run 1) is as follows: 4.5 g (45 mmol) of 90-wt% racemic lactic acid and 140 ml of dichloromethane were placed in a flask equipped with a Dean–Stark trap and reflux condenser. After removal of water, 0.44 g (3.6 mmol) of DMAP were added, and the mixture was cooled to 0°C. 14.0 g (67.9 mmol) of DCC were added for 5 min, and the mixture was stirred at room temperature for 24 h. After removal of a white precipitate (DCU) by filtration, the reaction mixture was washed twice with 0.5 M HCl, twice with water, and dried with anhydrous sodium sulfate. The solvent was evaporated off. The product was dried under reduced pressure and purified by reprecipitation (chloroform/hexane) to give a white powder (\bar{M}_n , 15400). Yield 89 %.

¹H NMR (400 MHz, 50°C, CDCl₃): δ = 1.53–1.62 (m, 3H, –CH₃), 5.13–5.22 (m, 1H, –CH(CH₃)COO–). ¹³C NMR (125 MHz, 50°C CDCl₃): δ = 16.6–16.9 (m, –CH₃), 69.0–69.2 (m, –CH(CH₃)COO–), 169.5–169.6 (m, C=O). IR (KBr, disk) 1754 (C=O), 1190, 1090 (C–O) cm⁻¹. Anal. Calcd for (C₃H₄O₂)_n (56.06)_n: C,

50.00%; H, 5.59%. Found: C, 49.56%; H, 5.57%.

Measurements

IR spectra were recorded on a Hitachi 270-30 spectrophotometer. NMR spectra were obtained with FT-NMR spectrometer (JEOL JNM-LA 400 or JNM-LA 500). GPC-measurements were performed on a TOSOH HLC-802UR high performance liquid chromatography using polystyrene gel columns (solvent, tetrahydrofuran; calibration, narrow dispersity polystyrene standards).

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