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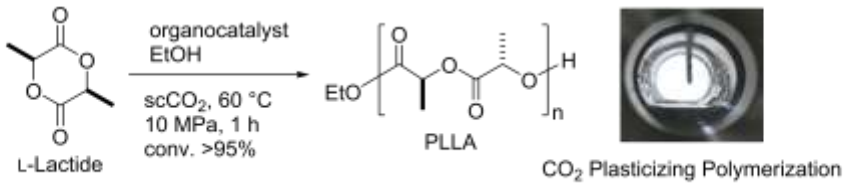

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Organocatalytic ring-opening polymerization of L-lactide in supercritical carbon dioxide under plasticizing conditions

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ABSTRACT

The synthesis of poly-L-lactide (PLLA) in supercritical carbon dioxide ($scCO_2$) was accomplished using an organocatalyst. The reaction proceeded smoothly under CO_2 plasticizing polymerization conditions at a lower temperature than those conventionally employed. This method allowed the formation of high-molecular-weight, pure PLLA, and therefore has the potential to reduce energy consumption and minimize production costs. Our method is non-toxic and efficient, affording a high-quality product while complying with volatile organic compound regulations. We can produce PLLA that meets the increasing standards (safety and high functionality) of the medical sector, while being applicable to full-scale industrial manufacturing and academic research.

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Introduction

Various biodegradable and biocompatible materials such as poly-L-lactide (PLLA, **1**), polyglycolide (PGA), and polycaprolactone (PCL) are widely used in daily life, which is why their importance has increased rapidly in the last few decades.[1,2,3] In particular, PLLA, PGA, and their copolymers have been studied extensively over other biodegradable polymers because they can be decomposed into harmless non-toxic compounds by in vivo hydrolysis of the ester group.[4] The resulting degradation products are excreted through the kidneys or decomposed into carbon dioxide and water via well-known biochemical pathways.[3] Furthermore, PLLA has diverse application in fibers, nonwoven fabrics, films, sheets, thermoformed packaging, paper coating, housing, three-dimensional printing, controlled drug release, bone fixation parts, and proppants.[5,6,7,8,9]

PLLA is generally synthesized by condensation polymerization (CP) from L-lactic acid (**2**) and/or ring-opening polymerization (ROP) of L-lactide (**3**) (Fig. 1).[6] Sufficient removal of water to suppress reverse hydrolysis is required for CP, otherwise the physical strength of PLLA may decrease due to the low molecular weight. Meanwhile, the ROP of L-lactide using tin(II) 2-ethylhexanoate as catalyst is used in practice to produce bulk PLLA in industry.[10] However, its application, for example, in medicine, is limited as traces of Sn catalyst remain in the polymer.[11,12,13] In addition, the presence of residual monomers due to the low reactivity of the Sn catalyst reduces the physical strength of PLLA. Avoiding a decrease in strength requires the introduction of a step to remove the residual monomers under reduced pressure. The CP and ROP reactions based on melt processing are energy consuming because they generally require high temperatures (above 200 °C) and extended reactions times. Furthermore, the color of the polymer by the Maillard reaction derived from plant components is sometimes problematic. The problem caused by the use of a metal catalyst was fundamentally solved when the metal-free organocatalytic solution polymerization of L-lactide was reported in 2001.[14,15,16,17] The polymerization proceeded smoothly under mild conditions at 35 °C, achieving narrowly dispersed PLLA (polydispersity index, PDI ≤ 1.2). However, a long reaction time (over 20 h at 35 °C) was required. In addition, the solubility of PLLA and L-lactide in conventional organic solvents is very low. Therefore, it is necessary to use toxic halogenated solvents such as chloroform and dichloromethane. This paper reports the organocatalytic polymerization of L-lactide in supercritical carbon dioxide ($scCO_2$) under mild conditions at 60 °C within 1 h, to afford PLLA free of metals, organic solvents,[18] and residual monomers.

Results and discussion

A supercritical fluid (SCF) such as $scCO_2$ is a characteristic fluid that combines the properties of both a liquid and a gas, thereby exhibiting excellent solubility and diffusibility,[19] which can be continuously controlled by adjusting the temperature and pressure, thereby allowing for the simple recovery of the gas. In particular, $scCO_2$ is inexpensive, safe, and nonflammable, and has low surface tension, low viscosity, and relatively mild critical temperature (T_c = 31.1 °C, P_c = 7.38 MPa).[20] Since the carbon atom of CO_2 is sandwiched between two electronegative oxygen

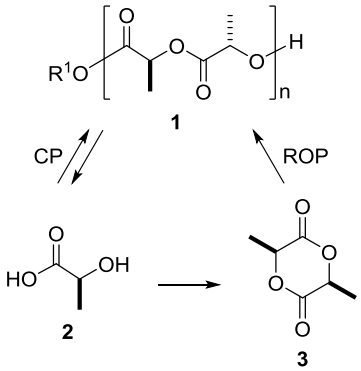

Fig. 1. Synthesis of PLLA as biodegradable and biocompatible materials

atoms, CO_2 can react with various nucleophiles. Therefore, despite the various advantages of $scCO_2$, an anionic polymerization reaction in $scCO_2$ is considered to be difficult.[21]

In the synthesis of PLLA, an organocatalyst such as 4-(dimethylamino)pyridine (DMAP) exhibited low reactivity due to the formation of a zwitterionic or anionic intermediate.[15,16,17] However, the ROP proceeded rapidly to give a high conversion (>95%, 1 h) in the presence of ethanol as the initiator, leading to the quantitative production of the resulting polymer (Fig. 2, Table 1, entry 1). Furthermore, the molecular weight of the synthesized PLLA was similar to the theoretical molecular weight (Mn = 4400), and narrowly dispersed PLLA was obtained (PDI = 1.10). Hence, we succeeded in preparing highly pure PLLA without metals, organic solvents, and residual monomers via a dry process.[22] Similarly, 4-pyrrolidinopyridine (PPY) and 9-azajulolidine (9-AJ) quantitatively afforded PLLA under $scCO_2$ conditions within 1 h (entries 2 and 3). In contrast, under solution polymerization conditions ($CHCl_3$ (3 M), 60 °C, 1 h), PLLA was obtained in 44% (DMAP), 80% (PPY), and >95% (9-AJ).[23] Reactions catalyzed by these 4-aminopyridine-based compounds were considered to proceed via nucleophilic[15,16,17] or bifunctional[24] catalytic mechanisms because the non-nucleophilic proton sponge® (pK_{BH} = 18.6 in MeCN)[25] with a similar basicity to DMAP (pK_{BH} = 18.0) produced only 10% PLLA. Highly basic nucleophilic amidine catalysts such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) also showed high reactivities, but with high PDI values (entries 4 and 5). In addition, highly basic non-nucleophilic guanidine catalysts, such as 1,1,3,3-tetramethylguanidine (TMG), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), gave similar results but via basic catalytic mechanisms (entries 6-8). All reaction conditions listed in Table 1 produced the resulting polymers in quantitative yields.

To elucidate the reason for high polymerization reactivity, the behavior of L-lactide and PLLA in $scCO_2$ was observed using a pressure vessel with a sapphire glass window at 60 °C, which is lower than the melting point of L-lactide (mp 98.6 °C). No significant change was observed up to the critical pressure (Pc = 7.38 MPa) (Fig. 3a), but the volume was apparently reduced at 10 MPa, which is the polymerization reaction pressure (Fig. 3b). When pressurized further, up to 12 MPa, the phase changed to the liquid state despite the temperature being below the L-lactide melting point (Fig. 3c). Finally, L-lactide was completely dissolved in $scCO_2$ at 26 MPa (Fig. 3d). Similarly, when PLLA was placed in $scCO_2$ at 60 °C and 10 MPa, solid PLLA changed to liquid (Fig. 3e). Under actual polymerization conditions, the polymerization mixture remained in the liquid phase (Fig. 3f). In addition, under $scCO_2$ conditions, the polymerization reaction was considered to proceed under high-concentration conditions, such as the bulk polymerization and uniform conditions used in solution polymerization. This method is referred to as the "CO_2 plasticizing polymerization" method (CPP method). Through this approach, $scCO_2$ dissolved L-lactide at low temperature, thereby allowing for various organocatalysts that are insensitive to CO_2 to selectively react with L-lactide.

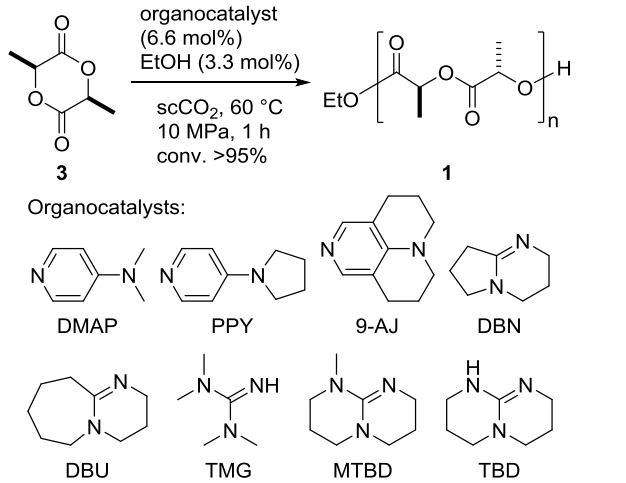

Fig. 2. Organocatalytic ROP in $scCO_2$

Table 1. Catalyst screening for organocatalytic ROP in $scCO_2$

Entry	Catalyst	Mn[a,b]	Mw[a]	PDI[c]
1	DMAP	4100 (2400)	4400	1.10
2	PPY	4500 (2600)	5600	1.27
3	9-AJ	4700 (2700)	6000	1.26
4	DBN	5600 (3200)	7600	1.37
5	DBU	5900 (3400)	8300	1.40
6	TMG	3400 (2000)	4500	1.32
7	MTBD	4600 (2700)	6400	1.39
8	TBD	5100 (3000)	7000	1.37

[a]Determined by GPC using polystyrene in $CHCl_3$ as a standard.
[b]Values in parentheses were calculated using a correction factor of 0.58.[26]
[c]Polydispersity index (PDI, Mw/Mn).

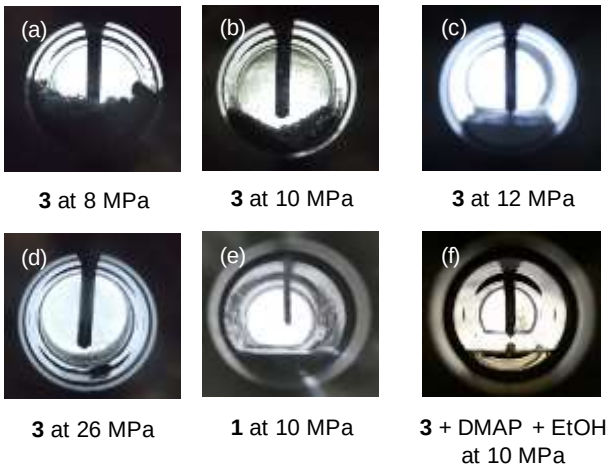

Fig. 3. Phase changes in $scCO_2$ at 60 °C detected using a pressure vessel with a sapphire glass window. The black bar inside the vessel is the temperature sensor.

This organocatalytic process would be expected to enable the synthesis of high-molecular-weight PLLA by controlling the equivalent amount of alcohol as the initiator. However, when the synthesis of PLLA with a theoretical molecular weight of over 10,000 was examined using DMAP, the obtained molecular weight was lower than the theoretical value (Fig. 4). We propose that insufficient catalytic activity to promote the propagation reaction (intermolecular esterification of polymer intermediate **4** with L-lactide **3**) suppresses the formation of linear PLLA **1**, and results in a reduction in molecular weight due to intramolecular esterification (back-biting of polymer intermediate(s) **4** and/or **5**), which forms cyclic PLLA **6** (Fig. 5).[27,28] Since the catalytic abilities of PPY and 9-AJ to accelerate polymerization are superior to that of DMAP, as mentioned above, the applicabilities of PPY and 9-AJ to the synthesis of high-molecular-weight PLLA were investigated. The use of PPY did not increase the molecular weight of the resulting PLLA, whereas the 9-AJ-mediated polymerization proceeded to afford experimental molecular weights that were in good agreement with theory (Fig. 4); hence PLLA (*M*n = 27,700) was synthesized in the presence of 0.5 mol% EtOH.[29] These results reveal that nucleophilicity[30] as well as steric hindrance on the pyridine ring play important roles in suppressing back-biting; hence substituents at the 3- and 5-positions of 9-AJ control intramolecular esterification.

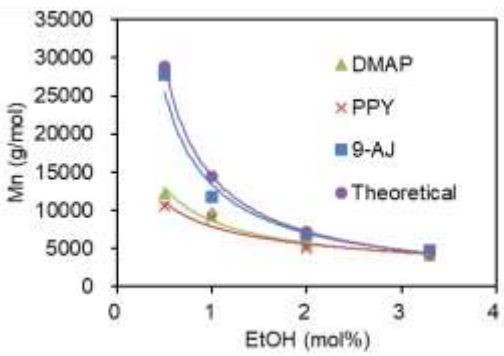

Fig. 4. Synthesis of high-molecular-weight PLLA. *M*n values were determined by GPC using polystyrene in $CHCl_3$ as a standard.

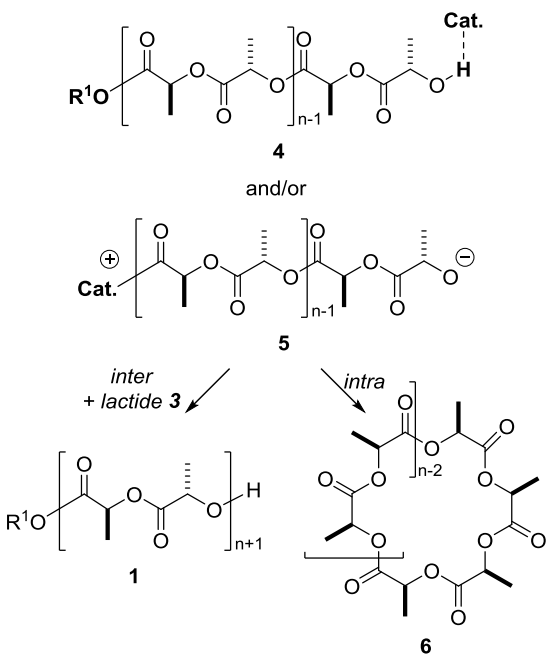

Fig. 5. Back-biting of polymer intermediates.

In order to further improve the purity of synthetic PLLA, the removal of the residual catalyst by $scCO_2$ extraction of the product was investigated because the solubility of PLLA in $scCO_2$ is lower than that of small molecules (Fig. 6). An examination of the extraction conditions indicated that the extraction efficiency improved at low temperature and high pressure (Fig. 7). At least 95% of the DMAP was removed from the polymer reaction mixture under the conditions employed (40 °C, 20 MPa, 5 h), thereby giving highly pure PLLA. Although it is difficult to completely remove the residual tin catalyst, the use of the organocatalytic method enabled the catalyst to be extracted without any remaining in the PLLA.

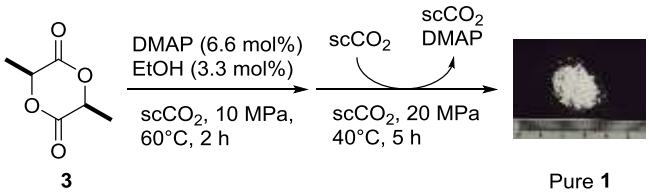

Fig. 6. Highly purified PLLA by $scCO_2$ extraction.

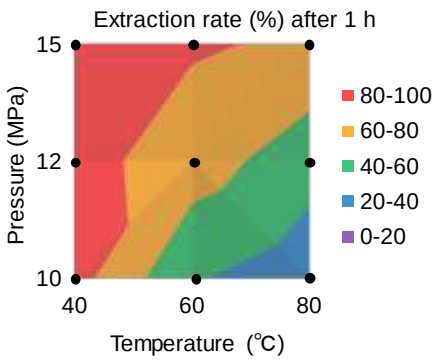

Fig. 7. Contour plot of the $scCO_2$ extraction efficiency of DMAP.

PLLA, which is a very hard polymer, is generally melted and processed into pellets for improved handling in industrial applications.[10] Thus, the addition of surfactants has been investigated in an attempt to achieve polymerization and granulation in a one-step and one-pot polymerization. Conventionally, a fluorochemical surfactant was used in $scCO_2$, but recently its toxicity has become a matter of concern.[31] Hence, in this study, the inexpensive and safe silicone surfactant **7** was used (Fig. 8). Notably, while bulk PLLA was obtained in the absence of surfactant **7** (Fig. 8a), in the presence of surfactant **7**, PLLA granules approximately 1 mm in diameter were formed (Fig. 8b). Since surfactant **7** contains carboxyl groups, the base catalyst may become inactivated through salt formation. However, while a longer reaction time was observed under CPP conditions, a polymer was still effectively obtained.[32] SEM images revealed that granular PLLA had a secondary particle structure (Fig. 8c). The shape of granular PLLA depended on the pressure and temperature. Powder PLLA particles with diameters in the 50–100 μm range were obtained at 10 MPa and 60 °C (Fig. 8d). The secondary particles in Fig. 8c are probably associated with this powdery PLLA. Granular PLLA with a smooth surface was obtained at 70 °C and 10 MPa (Fig. 8e). It was difficult to elucidate the formation mechanism of fine-powder PLLA under high-pressure conditions. However, when L-lactide and the surfactant were subjected to 12 MPa and 60 °C, the $scCO_2$ phase became cloudy (Fig. 8f) and micelles formed. Because granulation facilitated the removal of PLLA from the reaction vessel, simplification of the conventional post-treatment process is expected.

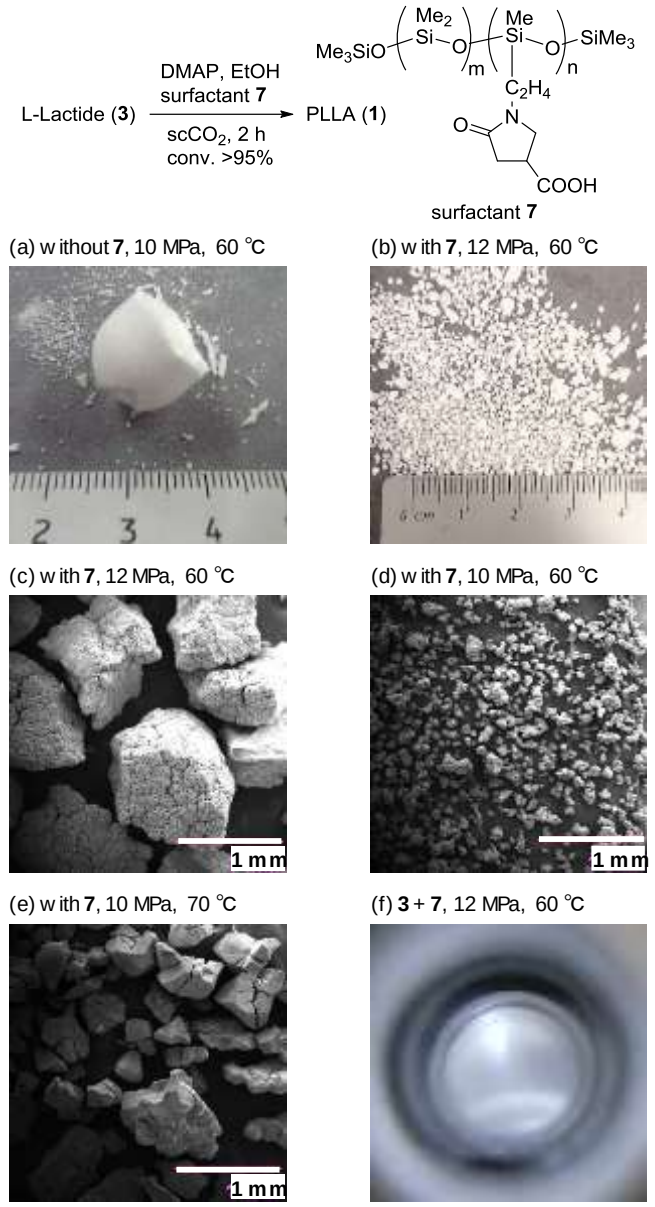

Fig. 8. One-pot polymerization and granulation.

Conclusion

In this study, we developed a synthetic method to produce highly pure linear PLLA without metals, organic solvents, and residual monomers under CPP conditions. This method is advantageous because of the reduced energy consumption, non-toxic nature, high product quality, efficiency, compliance with volatile organic compound (VOC) regulations, low cost, etc. Therefore, we believe that this approach opens new avenues for the development of PLLA in academic research and full-scale industrial manufacturing. The CPP method related to other organic transformations will be reported elsewhere.

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The authors declare no competing financial interest.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.XX

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